SAS/STAT® 14.2 User's Guide
The PHREG Procedure

This document is an individual chapter from *SAS/STAT® 14.2 User's Guide*.

The correct bibliographic citation for this manual is as follows: SAS Institute Inc. 2016. *SAS/STAT® 14.2 User's Guide*. Cary, NC: SAS Institute Inc.

SAS/STAT® 14.2 User's Guide

SAS Institute Inc., SAS Campus Drive, Cary, NC 27513-2414

November 2016

Chapter 86
The PHREG Procedure

Contents

Overview: PHREG Procedure

The analysis of survival data requires special techniques because the data are almost always incomplete and familiar parametric assumptions might be unjustifiable. Investigators follow subjects until they reach a prespecified endpoint (for example, death). However, subjects sometimes withdraw from a study, or the study is completed before the endpoint is reached. In these cases, the survival times (also known as failure times) are *censored*; subjects survived to a certain time beyond which their status is unknown. The uncensored survival times are sometimes referred to as *event* times. Methods of survival analysis must account for both censored and uncensored data.

Many types of models have been used for survival data. Two of the more popular types of models are the accelerated failure time model (Kalbfleisch and Prentice 1980) and the Cox proportional hazards model (Cox 1972). Each has its own assumptions about the underlying distribution of the survival times. Two closely related functions often used to describe the distribution of survival times are the survivor function and the hazard function. See the section "Failure Time Distribution" on page 6886 for definitions. The accelerated failure time model assumes a parametric form for the effects of the explanatory variables and usually assumes a parametric form for the underlying survivor function. The Cox proportional hazards model also assumes a parametric form for the effects of the explanatory variables, but it allows an unspecified form for the underlying survivor function.

The PHREG procedure performs regression analysis of survival data based on the Cox proportional hazards model. Cox's semiparametric model is widely used in the analysis of survival data to explain the effect of explanatory variables on hazard rates.

The survival time of each member of a population is assumed to follow its own hazard function, $\lambda_i(t)$, expressed as

$$\lambda_i(t) = \lambda(t;\mathbf{Z}_i) = \lambda_0(t)\exp(\mathbf{Z}_i'\boldsymbol{\beta})$$

where $\lambda_0(t)$ is an arbitrary and unspecified baseline hazard function, $\mathbf{Z}_i$ is the vector of explanatory variables for the ith individual, and $\boldsymbol{\beta}$ is the vector of unknown regression parameters that is associated with the explanatory variables. The vector $\boldsymbol{\beta}$ is assumed to be the same for all individuals. The survivor function can be expressed as

$$S(t;\mathbf{Z}_i) = [S_0(t)]^{\exp(\mathbf{Z}_i'\boldsymbol{\beta})}$$

where $S_0(t) = \exp(-\int_0^t \lambda_0(u)du)$ is the baseline survivor function. To estimate $\boldsymbol{\beta}$, Cox (1972, 1975) introduced the partial likelihood function, which eliminates the unknown baseline hazard $\lambda_0(t)$ and accounts for censored survival times.

The partial likelihood of Cox also allows time-dependent explanatory variables. An explanatory variable is time-dependent if its value for any given individual can change over time. Time-dependent variables have

many useful applications in survival analysis. You can use a time-dependent variable to model the effect of subjects changing treatment groups. Or you can include time-dependent variables such as blood pressure or blood chemistry measures that vary with time during the course of a study. You can also use time-dependent variables to test the validity of the proportional hazards model.

An alternative way to fit models with time-dependent explanatory variables is to use the counting process style of input. The counting process formulation enables PROC PHREG to fit a superset of the Cox model, known as the multiplicative hazards model. This extension also includes recurrent events data and left-truncation of failure times. The theory of these models is based on the counting process pioneered by Andersen and Gill (1982), and the model is often referred to as the Andersen-Gill model.

Multivariate failure-time data arise when each study subject can potentially experience several events (for example, multiple infections after surgery) or when there exists some natural or artificial clustering of subjects (for example, a litter of mice) that induces dependence among the failure times of the same cluster. Data in the former situation are referred to as multiple events data, which include recurrent events data as a special case; data in the latter situation are referred to as clustered data. You can use PROC PHREG to carry out various methods of analyzing these data.

The population under study can consist of a number of subpopulations, each of which has its own baseline hazard function. PROC PHREG performs a stratified analysis to adjust for such subpopulation differences. Under the stratified model, the hazard function for the *j*th individual in the *i*th stratum is expressed as

$$\lambda_{ij}(t) = \lambda_{i0}(t)\exp(\mathbf{Z}'_{ij}\boldsymbol{\beta})$$

where $\lambda_{i0}(t)$ is the baseline hazard function for the *i*th stratum and $\mathbf{Z}_{ij}$ is the vector of explanatory variables for the individual. The regression coefficients are assumed to be the same for all individuals across all strata.

Ties in the failure times can arise when the time scale is genuinely discrete or when survival times that are generated from the continuous-time model are grouped into coarser units. The PHREG procedure includes four methods of handling ties. The *discrete* logistic model is available for discrete time-scale data. The other three methods apply to continuous time-scale data. The *exact* method computes the exact conditional probability under the model that the set of observed tied event times occurs before all the censored times with the same value or before larger values. *Breslow* and *Efron* methods provide approximations to the exact method.

Variable selection is a typical exploratory exercise in multiple regression when the investigator is interested in identifying important prognostic factors from a large number of candidate variables. The PHREG procedure provides four selection methods: forward selection, backward elimination, stepwise selection, and best subset selection. The best subset selection method is based on the likelihood score statistic. This method identifies a specified number of best models that contain one, two, or three variables and so on, up to the single model that contains all of the explanatory variables.

The PHREG procedure also enables you to do the following: include an offset variable in the model; weight the observations in the input data; test linear hypotheses about the regression parameters; perform conditional logistic regression analysis for matched case-control studies; output survivor function estimates, residuals, and regression diagnostics; and estimate and plot the survivor function for a new set of covariates.

PROC PHREG can also be used to fit the multinomial logit choice model to discrete choice data. See `http://support.sas.com/resources/papers/tnote/tnote_marketresearch.html` for more information about discrete choice modeling and the multinomial logit model. Look for the "Discrete Choice" report.

The PHREG procedure uses ODS Graphics to create graphs as part of its output. For example, the ASSESS statement uses a graphical method that uses ODS Graphics to check the adequacy of the model. For general information about ODS Graphics, see Chapter 21, "Statistical Graphics Using ODS."

For both the BASELINE and OUTPUT statements, the default method of estimating a survivor function has changed to the Breslow (1972) estimator—that is, METHOD=CH. The option NOMEAN that was available in the BASELINE statement prior to SAS/STAT 9.2 has become obsolete—that is, requested statistics at the sample average values of the covariates are no longer computed and added to the OUT= data set. However, if the COVARIATES= data set is not specified, the requested statistics are computed and output for the covariate set that consists of the reference levels for the CLASS variables and sample averages for the continuous variable. In addition to the requested statistics, the OUT= data set also contains all variables in the COVARIATES= data set.

The remaining sections of this chapter contain information about how to use PROC PHREG, information about the underlying statistical methodology, and some sample applications of the procedure. The section "Getting Started: PHREG Procedure" on page 6813 introduces PROC PHREG with two examples. The section "Syntax: PHREG Procedure" on page 6821 describes the syntax of the procedure. The section "Details: PHREG Procedure" on page 6886 summarizes the statistical techniques used in PROC PHREG. The section "Examples: PHREG Procedure" on page 6973 includes eight additional examples of useful applications. Experienced SAS/STAT software users might decide to proceed to the "Syntax" section, while other users might choose to read both the "Getting Started" and "Examples" sections before proceeding to "Syntax" and "Details."

Getting Started: PHREG Procedure

This section uses the two-sample vaginal cancer mortality data from Kalbfleisch and Prentice (1980, p. 2) in two examples to illustrate some of the basic features of PROC PHREG. The first example carries out a classical Cox regression analysis and the second example performs a Bayesian analysis of the Cox model.

Two groups of rats received different pretreatment regimes and then were exposed to a carcinogen. Investigators recorded the survival times of the rats from exposure to mortality from vaginal cancer. Four rats died of other causes, so their survival times are censored. Interest lies in whether the survival curves differ between the two groups.

The following DATA step creates the data set Rats, which contains the variable Days (the survival time in days), the variable Status (the censoring indicator variable: 0 if censored and 1 if not censored), and the variable Group (the pretreatment group indicator).

```
data Rats;
   label Days  ='Days from Exposure to Death';
   input Days Status Group @@;
   datalines;
143 1 0   164 1 0   188 1 0   188 1 0
190 1 0   192 1 0   206 1 0   209 1 0
213 1 0   216 1 0   220 1 0   227 1 0
230 1 0   234 1 0   246 1 0   265 1 0
304 1 0   216 0 0   244 0 0   142 1 1
156 1 1   163 1 1   198 1 1   205 1 1
232 1 1   232 1 1   233 1 1   233 1 1
```

```
233 1 1   233 1 1   239 1 1   240 1 1
261 1 1   280 1 1   280 1 1   296 1 1
296 1 1   323 1 1   204 0 1   344 0 1
;
```

By using ODS Graphics, PROC PHREG allows you to plot the survival curve for Group=0 and the survival curve for Group=1, but first you must save these two covariate values in a SAS data set as in the following DATA step:

```
data Regimes;
   Group=0;
   output;
   Group=1;
   output;
run;
```

Classical Method of Maximum Likelihood

PROC PHREG fits the Cox model by maximizing the partial likelihood and computes the baseline survivor function by using the Breslow (1972) estimate. The following statements produce Figure 86.1 and Figure 86.2:

```
ods graphics on;
proc phreg data=Rats plot(overlay)=survival;
   model Days*Status(0)=Group;
   baseline covariates=regimes out=_null_;
run;
```

In the MODEL statement, the response variable, Days, is crossed with the censoring variable, Status, with the value that indicates censoring is enclosed in parentheses. The values of Days are considered censored if the value of Status is 0; otherwise, they are considered event times.

Graphs are produced when ODS Graphics is enabled. The survival curves for the two observations in the data set Regime, specified in the COVARIATES= option in the BASELINE statement, are requested through the PLOTS= option with the OVERLAY option for overlaying both survival curves in the same plot.

Figure 86.2 shows a typical printed output of a classical analysis. Since Group takes only two values, the null hypothesis for no difference between the two groups is identical to the null hypothesis that the regression coefficient for Group is 0. All three tests in the "Testing Global Null Hypothesis: BETA=0" table (see the section "Testing the Global Null Hypothesis" on page 6906) suggest that the survival curves for the two pretreatment groups might not be the same. In this model, the hazard ratio (or risk ratio) for Group, defined as the exponentiation of the regression coefficient for Group, is the ratio of the hazard functions between the two groups. The estimate is 0.551, implying that the hazard function for Group=1 is smaller than that for Group=0. In other words, rats in Group=1 lived longer than those in Group=0. This conclusion is also revealed in the plot of the survivor functions in Figure 86.2.

Figure 86.1 Comparison of Two Survival Curves

The PHREG Procedure

Model Information		
Data Set	WORK.RATS	
Dependent Variable	Days	Days from Exposure to Death
Censoring Variable	Status	
Censoring Value(s)	0	
Ties Handling	BRESLOW	

Number of Observations Read	40
Number of Observations Used	40

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
40	36	4	10.00

Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	204.317	201.438
AIC	204.317	203.438
SBC	204.317	205.022

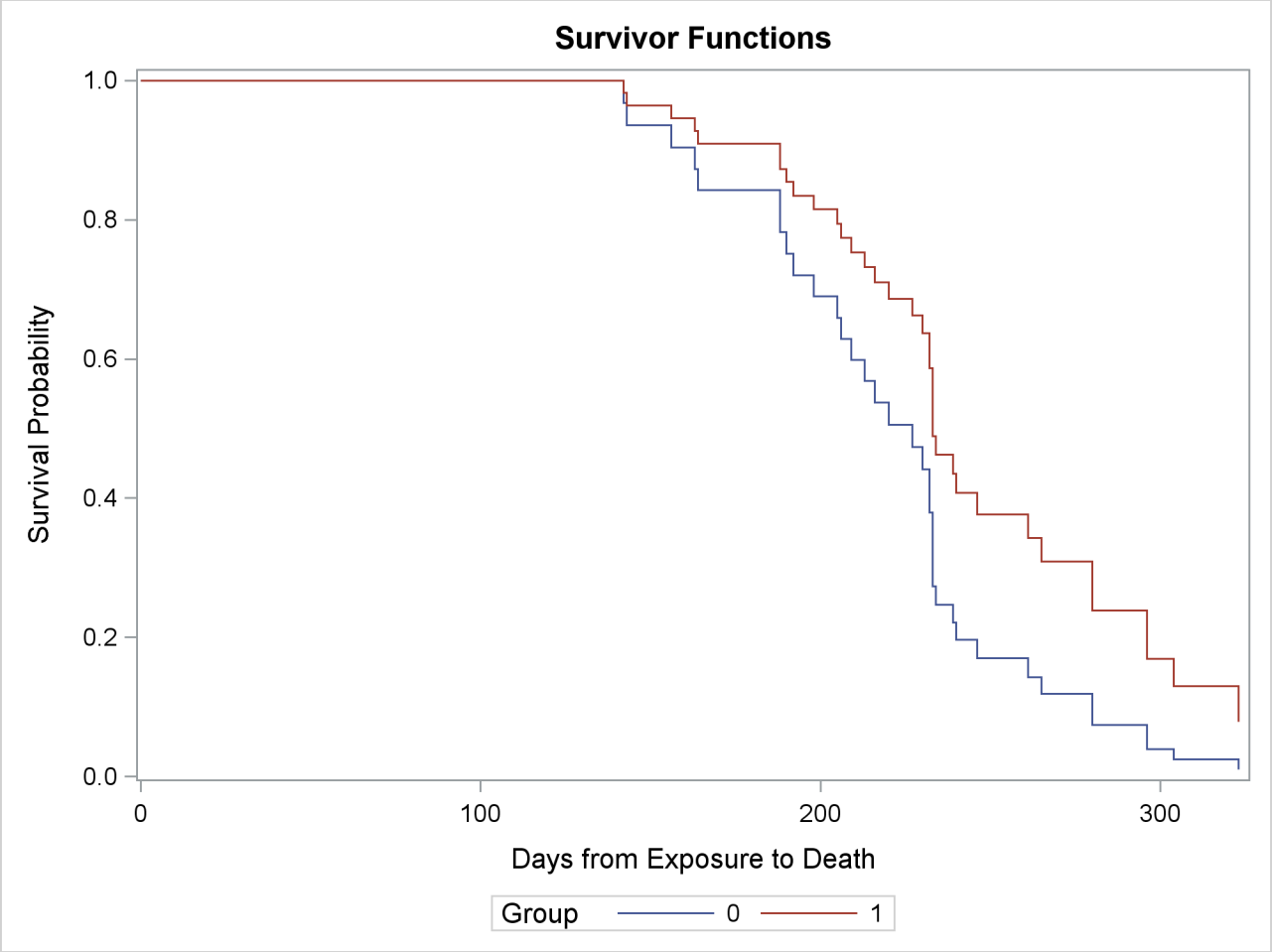
Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	2.8784	1	0.0898
Score	3.0001	1	0.0833
Wald	2.9254	1	0.0872

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Group	1	-0.59590	0.34840	2.9254	0.0872	0.551

Figure 86.2 Survivorship for the Two Pretreatment Regimes



In this example, the comparison of two survival curves is put in the form of a proportional hazards model. This approach is essentially the same as the log-rank (Mantel-Haenszel) test. In fact, if there are no ties in the survival times, the likelihood score test in the Cox regression analysis is identical to the log-rank test. The advantage of the Cox regression approach is the ability to adjust for the other variables by including them in the model. For example, the present model could be expanded by including a variable that contains the initial body weights of the rats.

Next, consider a simple test of the validity of the proportional hazards assumption. The proportional hazards model for comparing the two pretreatment groups is given by the following:

$$\lambda(t) = \begin{cases} \lambda_0(t) & \text{if GROUP} = 0 \\ \lambda_0(t)e^{\beta_1} & \text{if GROUP} = 1 \end{cases}$$

The ratio of hazards is e^{β_1}, which does not depend on time. If the hazard ratio changes with time, the proportional hazards model assumption is invalid. Simple forms of departure from the proportional hazards model can be investigated with the following time-dependent explanatory variable $x = x(t)$:

$$x(t) = \begin{cases} 0 & \text{if GROUP} = 0 \\ \log(t) - 5.4 & \text{if GROUP} = 1 \end{cases}$$

Here, $\log(t)$ is used instead of t to avoid numerical instability in the computation. The constant, 5.4, is the average of the logs of the survival times and is included to improve interpretability. The hazard ratio in the two groups then becomes $e^{\beta_1 - 5.4\beta_2} t^{\beta_2}$, where β_2 is the regression parameter for the time-dependent variable x. The term e^{β_1} represents the hazard ratio at the geometric mean of the survival times. A nonzero value of β_2 would imply an increasing ($\beta_2 > 0$) or decreasing ($\beta_2 < 0$) trend in the hazard ratio with time.

The following statements implement this simple test of the proportional hazards assumption. The MODEL statement includes the time-dependent explanatory variable X, which is defined subsequently by the programming statement. At each event time, subjects in the risk set (those alive just before the event time) have their X values changed accordingly.

```
proc phreg data=Rats;
   model Days*Status(0)=Group X;
   X=Group*(log(Days) - 5.4);
run;
```

The analysis of the parameter estimates is displayed in Figure 86.3. The Wald chi-square statistic for testing the null hypothesis that $\beta_2 = 0$ is 0.0158. The statistic is not statistically significant when compared to a chi-square distribution with one degree of freedom ($p = 0.8999$). Thus, you can conclude that there is no evidence of an increasing or decreasing trend over time in the hazard ratio.

Figure 86.3 A Simple Test of Trend in the Hazard Ratio

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Group	1	-0.59976	0.34837	2.9639	0.0851	0.549
X	1	-0.22952	1.82489	0.0158	0.8999	0.795

Bayesian Analysis

PROC PHREG uses the partial likelihood of the Cox model as the likelihood and generates a chain of posterior distribution samples by the Gibbs Sampler. Summary statistics, convergence diagnostics, and diagnostic plots are provided for each parameter. The following statements generate Figure 86.4–Figure 86.10:

```
ods graphics on;
proc phreg data=Rats;
   model Days*Status(0)=Group;
   bayes seed=1 outpost=Post;
run;
```

The BAYES statement invokes the Bayesian analysis. The SEED= option is specified to maintain reproducibility; the OUTPOST= option saves the posterior distribution samples in a SAS data set for post-processing; no other options are specified in the BAYES statement. By default, a uniform prior distribution is assumed on the regression coefficient Group. The uniform prior is a flat prior on the real line with a distribution that reflects ignorance of the location of the parameter, placing equal probability on all possible values the regression coefficient can take. Using the uniform prior in the following example, you would expect the Bayesian estimates to resemble the classical results of maximizing the likelihood. If you can elicit an informative prior on the regression coefficients, you should use the COEFFPRIOR= option to specify it.

You should make sure that the posterior distribution samples have achieved convergence before using them for Bayesian inference. PROC PHREG produces three convergence diagnostics by default. If ODS Graphics is enabled before calling PROC PHREG as in the preceding program, diagnostics plots are also displayed.

The results of this analysis are shown in the following figures.

The "Model Information" table in Figure 86.4 summarizes information about the model you fit and the size of the simulation.

Figure 86.4 Model Information

The PHREG Procedure

Bayesian Analysis

Model Information		
Data Set	WORK.RATS	
Dependent Variable	Days	Days from Exposure to Death
Censoring Variable	Status	
Censoring Value(s)	0	
Model	Cox	
Ties Handling	BRESLOW	
Sampling Algorithm	ARMS	
Burn-In Size	2000	
MC Sample Size	10000	
Thinning	1	

PROC PHREG first fits the Cox model by maximizing the partial likelihood. The only parameter in the model is the regression coefficient of Group. The maximum likelihood estimate (MLE) of the parameter and its 95% confidence interval are shown in Figure 86.5.

Figure 86.5 Classical Parameter Estimates

Maximum Likelihood Estimates					
Parameter	**DF**	**Estimate**	**Standard Error**	**95% Confidence Limits**	
Group	1	-0.5959	0.3484	-1.2788	0.0870

Since no prior is specified for the regression coefficient, the default uniform prior is used. This information is displayed in the "Uniform Prior for Regression Coefficients" table in Figure 86.6.

Figure 86.6 Coefficient Prior

Uniform Prior for Regression Coefficients	
Parameter	**Prior**
Group	Constant

The "Fit Statistics" table in Figure 86.7 lists information about the fitted model. The table displays the DIC (deviance information criterion) and pD (effective number of parameters). For more information, see the section "Fit Statistics" on page 6954.

Figure 86.7 Fit Statistics

Fit Statistics	
DIC (smaller is better)	203.444
pD (Effective Number of Parameters)	1.003

Summary statistics of the posterior samples are displayed in the "Posterior Summaries and Intervals" table in Figure 86.8. Note that the mean and standard deviation of the posterior samples are comparable to the MLE and its standard error, respectively, because of the use of the uniform prior.

Figure 86.8 Summary Statistics

The PHREG Procedure

Bayesian Analysis

Posterior Summaries and Intervals

Parameter	N	Mean	Standard Deviation	95% HPD Interval	
Group	10000	-0.5998	0.3511	-1.2984	0.0756

PROC PHREG provides diagnostics to assess the convergence of the generated Markov chain. Figure 86.9 shows the effective sample size diagnostic. There is no indication that the Markov chain has not reached convergence. For information about interpreting these diagnostics, see the section "Statistical Diagnostic Tests" on page 141 in Chapter 7, "Introduction to Bayesian Analysis Procedures."

Figure 86.9 Convergence Diagnostics

The PHREG Procedure

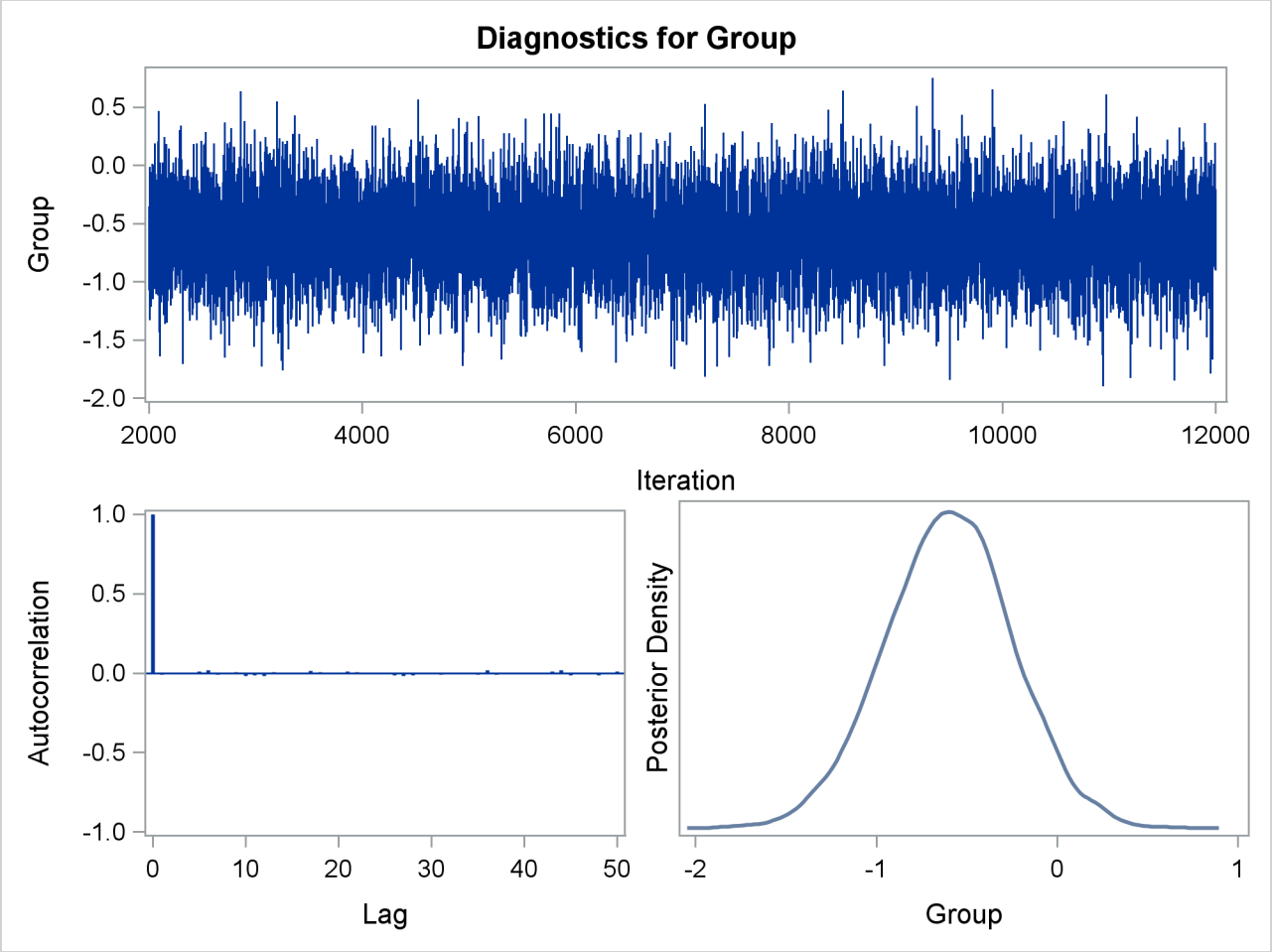
Bayesian Analysis

Effective Sample Sizes

Parameter	ESS	Autocorrelation Time	Efficiency
Group	10000.0	1.0000	1.0000

You can also assess the convergence of the generated Markov chain by examining the trace plot, the autocorrelation function plot, and the posterior density plot. Figure 86.10 displays a panel of these three plots for the parameter Group. This graphical display is automatically produced when ODS Graphics is enabled. Note that the trace of the samples centers on –0.6 with only small fluctuations, the autocorrelations are quite small, and the posterior density appears bell-shaped—all exemplifying the behavior of a converged Markov chain.

Figure 86.10 Diagnostic Plots



The proportional hazards model for comparing the two pretreatment groups is

$$\lambda(t) = \begin{cases} \lambda_0(t) & \text{if Group=0} \\ \lambda_0(t)\mathrm{e}^{\beta} & \text{if Group=1} \end{cases}$$

The probability that the hazard of Group=0 is greater than that of Group=1 is

$$\Pr(\lambda_0(t) > \lambda_0(t)\mathrm{e}^{\beta}) = \Pr(\beta < 0)$$

This probability can be enumerated from the posterior distribution samples by computing the fraction of samples with a coefficient less than 0. The following DATA step and PROC MEANS perform this calculation:

```
data New;
   set Post;
   Indicator=(Group < 0);
   label Indicator='Group < 0';
run;
proc means data=New(keep=Indicator) n mean;
run;
```

Figure 86.11 Prob(Hazard(Group=0) > Hazard(Group=1))

The MEANS Procedure

Analysis Variable : Indicator Group < 0	
N	Mean
10000	0.9581000

The PROC MEANS results are displayed in Figure 86.11. There is a 95.8% chance that the hazard rate of Group=0 is greater than that of Group=1. The result is consistent with the fact that the average survival time of Group=0 is less than that of Group=1.

Syntax: PHREG Procedure

The following statements are available in the PHREG procedure. Items within < > are optional.

PROC PHREG < *options* > ;
ASSESS *keyword* < / *options* > ;
BASELINE < **OUT=***SAS-data-set* > < **COVARIATES=***SAS-data-set* >
< *keyword*=*name* . . . *keyword*=*name* > < / *options* > ;
BAYES < *options* > ;
BY *variables* ;
CLASS *variable* < (*options*) > < . . . *variable* < (*options*) > > < / *options* > ;
CONTRAST < '*label*' > *effect values* < , . . . , *effect values* > < / *options* > ;
FREQ *variable* ;
EFFECT *name* = *effect-type* (*variables* < / *options* >) ;
ESTIMATE < '*label*' > *estimate-specification* < / *options* > ;
HAZARDRATIO < '*label*' > *variable* < / *options* > ;
ID *variables* ;
LSMEANS < *model-effects* > < / *options* > ;
LSMESTIMATE *model-effect lsmestimate-specification* < / *options* > ;
MODEL *response* < ∗ *censor*(*list*) > = < *effects* > < / *options* > ;
OUTPUT < **OUT=***SAS-data-set* > < *keyword*=*name* . . . *keyword*=*name* > < / *options* > ;
Programming statements ;
RANDOM *variable* < / *options* > ;
ROC < '*label*' > *specification* ;
SLICE *model-effect* < / *options* > ;
STORE < **OUT=** > *item-store-name* < / **LABEL=**'*label*' > ;
STRATA *variable* < (*list*) > < . . . *variable* < (*list*) > > < / *option* > ;
< *label*: > **TEST** *equation* < , . . . , *equation* > < / *options* > ;
WEIGHT *variable* < / *option* > ;

The PROC PHREG and MODEL statements are required. The CLASS statement, if present, must precede the MODEL statement, and the ASSESS or CONTRAST statement, if present, must come after the MODEL statement. The BAYES statement, that invokes a Bayesian analysis, is not compatible with the ASSESS,

CONTRAST, ID, OUTPUT, and TEST statements, as well as a number of options in the PROC PHREG and MODEL statements. For more information, see the section "Specifics for Bayesian Analysis" on page 6945.

The rest of this section provides detailed syntax information for each statement, beginning with the PROC PHREG statement. The remaining statements are covered in alphabetical order.

PROC PHREG Statement

PROC PHREG < *options* > **;**

The PROC PHREG statement invokes the PHREG procedure. Table 86.1 summarizes the *options* available in the PROC PHREG statement.

Table 86.1 PROC PHREG Statement Options

Option	Description
ALPHA=	Specifies the level of significance
ATRISK	Displays a table that contains the number of units and the corresponding number of events in the risk sets
CONCORDANCE	Computes concordance statistics
COVM	Uses the model-based covariance matrix in the analysis
COVOUT	Adds the estimated covariance matrix to the OUTEST= data set
COVSANDWICH	Requests the robust sandwich estimate for the covariance matrix
DATA=	Names the SAS data set to be analyzed
EV	Requests the Schemper-Henderson predictive measures
FAST	Uses a fast algorithm for large data with start/stop input
INEST=	Names the SAS data set that contains initial estimates
MULTIPASS	Recompiles the risk sets
NAMELEN=	Specifies the length of effect names
NOPRINT	Suppresses all displayed output
NOSUMMARY	Suppresses the summary display observation frequencies
OUTEST=	Creates an output SAS data set containing estimates of the regression coefficients
PLOTS=	Controls the plots that are produced through ODS Graphics
ROCOPTIONS	Specifies options for receiver operating characteristic analysis
SIMPLE	Displays simple descriptive statistics
TAU=	Specifies upper time limit for Uno's concordance statistic and the integrated area under the curve
ZPH	Requests diagnostics based on weighted residuals for checking the proportional hazards assumption

You can specify the following *options* in the PROC PHREG statement.

ALPHA=*number*

specifies the level of significance α for $100(1-\alpha)\%$ confidence intervals. The value *number* must be between 0 and 1; the default value is 0.05, which results in 95% intervals. This value is used as the default confidence level for limits computed by the BASELINE, BAYES, CONTRAST,

HAZARDRATIO, and MODEL statements. You can override this default by specifying the ALPHA= option in the separate statements.

ATRISK
displays a table that contains the number of units at risk at each event time and the corresponding number of events in the risk sets. For example, the following risk set information is displayed if the ATRISK option is specified in the example in the section "Getting Started: PHREG Procedure" on page 6813.

Risk Set Information		
	Number of Units	
Days	At Risk	Event
142	40	1
143	39	1
156	38	1
⋮	⋮	⋮
296	5	2
304	3	1
323	2	1

CONCORDANCE <=*method*<(*options*)>>
computes concordance statistics for the model specified in the MODEL statement (unless the NOFIT option is specified) and for each model specified in an ROC statement. For more information, see the section "Concordance Statistics" on page 6925. You can specify the following *methods*:

HARRELL <(SE)>
requests Harrell's concordance statistic (Harrell et al. 1984). The SE suboption, if specified, produces standard error for the concordance statistic by the method of Kang et al. (2015).

UNO <(*uno-options*)>
computes the concordance statistic of Uno et al. (2011). You can specify the following *uno-options*:

SE
computes the standard error for the concordance statistic by using the perturbation resampling approach as described in Uno et al. (2011).

SEED=*n*
specifies an integer seed for the random number generator to generate the perturbation samples.

ITER=*n*
specifies the number of perturbation samples to use.

ALPHA=*number*
specifies the significance level of the confidence interval for the concordance probability.

DIFF
calculates paired differences in the estimated concordance statistics among all identified ROC models. If the SE suboption is also specified, standard errors and confidence limits are also computed.

Specifying the CONCORDANCE option without any suboptions is equivalent to specifying CONCORDANCE=HARRELL.

COVOUT
adds the estimated covariance matrix of the parameter estimates to the OUTEST= data set. The COVOUT option has no effect unless the OUTEST= option is specified.

COVM
requests that the model-based covariance matrix (which is the inverse of the observed information matrix) be used in the analysis if the COVS option is also specified. The COVM option has no effect if the COVS option is not specified.

COVSANDWICH < (AGGREGATE) >
COVS < (AGGREGATE) >
requests the robust sandwich estimate of Lin and Wei (1989) for the covariance matrix. When this option is specified, this robust sandwich estimate is used in the Wald tests for testing the global null hypothesis, null hypotheses of individual parameters, and the hypotheses in the CONTRAST and TEST statements. In addition, a modified score test is computed in the testing of the global null hypothesis, and the parameter estimates table has an additional StdErrRatio column, which contains the ratios of the robust estimate of the standard error relative to the corresponding model-based estimate. Optionally, you can specify the keyword AGGREGATE enclosed in parentheses after the COVSANDWICH (or COVS) option, which requests a summing up of the score residuals for each distinct ID pattern in the computation of the robust sandwich covariance estimate. This AGGREGATE option has no effect if the ID statement is not specified.

DATA=*SAS-data-set*
names the SAS data set that contains the data to be analyzed. If you omit the DATA= option, the procedure uses the most recently created SAS data set.

EV
requests the Schemper-Henderson measure (Schemper and Henderson 2000) of the proportion of variation that is explained by a Cox regression. This measure of explained variation (EV) is the ratio of distance measures between the 1/0 survival processes and the fitted survival curves with and without covariates information. The distance measure is referred to as the predictive inaccuracy, because the smaller the predictive inaccuracy, the better the prediction. When you specify this option, PROC PHREG creates a table that has three columns: one presents the predictive inaccuracy without covariates (D); one presents the predictive inaccuracy with covariates (Dz); and one presents the EV measure, computed according to $100\frac{D-Dz}{Dz}\%$.

FAST
uses an alternative algorithm to speed up the fitting of the Cox regression for a large data set that has the counting process style of input. Simonsen (2014) has demonstrated the efficiency of this algorithm when the data set contains a large number of observations and many distinct event times. The algorithm requires only one pass through the data to compute the Breslow or Efron partial log-likelihood function and the corresponding gradient and Hessian. PROC PHREG ignores the FAST option if you specify a

TIES= option value other than BRESLOW or EFRON, or if you specify programming statements for time-varying covariates. You might not see much improvement in the optimization time if your data set has only a moderate number of observations.

INEST=*SAS-data-set*
names the SAS data set that contains initial estimates for all the parameters in the model. BY-group processing is allowed in setting up the INEST= data set. For more information, see the section "INEST= Input Data Set" on page 6957.

MULTIPASS
requests that, for each Newton-Raphson iteration, PROC PHREG recompile the risk sets that correspond to the event times for the (start,stop) style of response and recomputes the values of the time-dependent variables defined by the programming statements for each observation in the risk sets. If the MULTIPASS option is not specified, PROC PHREG computes all risk sets and all the variable values and saves them in a utility file. The MULTIPASS option decreases required disk space at the expense of increased execution time; however, for very large data, it might actually save time, because it is time-consuming to write and read large utility files. This option has an effect only when the (start,stop) style of response is used or when there are time-dependent explanatory variables.

NAMELEN=*n*
specifies the length of effect names in tables and output data sets to be *n* characters, where *n* is a value between 20 and 200. The default length is 20 characters.

NOPRINT
suppresses all displayed output. Note that this option temporarily disables the Output Delivery System (ODS); for more information about ODS, see Chapter 20, "Using the Output Delivery System."

NOSUMMARY
suppresses the summary display of the event and censored observation frequencies.

OUTEST=*SAS-data-set*
creates an output SAS data set that contains estimates of the regression coefficients. The data set also contains the convergence status and the log likelihood. If you use the COVOUT option, the data set also contains the estimated covariance matrix of the parameter estimators. For more information, see the section "OUTEST= Output Data Set" on page 6956.

PLOTS<(*global-plot-options***)> = ***plot-request*

PLOTS<(*global-plot-options***)> = (***plot-request* < . . . < *plot-request* > >**)**
controls the plots that are produced through ODS Graphics. Two types of plots can be produced: plots related to the receiver operating characteristic curves (such as AUC, AUCDIFF, and ROC) and the baseline function plots (such as CIF, CUMHAZ, MCF, and SURVIVAL).

For the baseline function plots, each observation in the COVARIATES= data set in the BASELINE statement represents a set of covariates for which a curve is produced for each *plot-request* and for each stratum. You can use the ROWID= option in the BASELINE statement to specify a variable in the COVARIATES= data set for identifying the curves that are produced for the covariate sets. If the ROWID= option is not specified, the produced curves are identified by the covariate values if there is only a single covariate or by the observation numbers of the COVARIATES= data set if the model has two or more covariates. If the COVARIATES= data set is not specified, a reference set of covariates that consists of the reference levels for the CLASS variables and the average values for the continuous

variables is used. For plotting more than one curve, you can use the OVERLAY= *global-plot-option* to group the curves in separate plots.

When you specify one *plot-request*, you can omit the parentheses around the plot request. Here are some examples:

```
plots=survival
plots=(survival auc)
```

ODS Graphics must be enabled before plots can be requested. For example:

```
ods graphics on;
proc phreg plots(cl)=survival;
   model Time*Status(0)=X1-X5;
   baseline covariates=One;
run;
```

For more information about enabling and disabling ODS Graphics, see the section "Enabling and Disabling ODS Graphics" on page 607 in Chapter 21, "Statistical Graphics Using ODS."

The *global-plot-options* include the following:

CL< =EQTAIL | HPD >
displays the pointwise interval limits for the specified curves. For the classical analysis, CL displays the confidence limits. For the Bayesian analysis, CL=EQTAIL displays the equal-tail credible limits and CL=HPD displays the HPD limits. Specifying just CL in a Bayesian analysis defaults to CL=HPD.

OVERLAY < =*overlay-option* **>**
specifies how the curves for the various strata and covariate sets are overlaid. If the STRATA statement is not specified, specifying OVERLAY without any option will overlay the curves for all the covariate sets. The available *overlay-options* are as follows:

BYGROUP

GROUP
overlays, for each stratum, all curves for the covariate sets that have the same GROUP= value in the COVARIATES= data set in the same plot.

INDIVIDUAL

IND
displays, for each stratum, a separate plot for each covariate set.

BYROW

ROW
displays, for each covariate set, a separate plot containing the curves for all the strata.

BYSTRATUM

STRATUM

displays, for each stratum, a separate plot containing the curves for all sets of covariates.

The default is OVERLAY=BYGROUP if the GROUP= option is specified in the BASELINE statement or if the COVARIATES= data set contains the _GROUP_ variable; otherwise the default is OVERLAY=INDIVIDUAL.

TIMERANGE=(< *min* > < *,max* >**)**

TIMERANGE=< *min* > < *,max* >

RANGE=(< *min* > < *,max* >**)**

RANGE=< *min* > < *,max* >

specifies the range of values on the time axis to clip the display. The *min* and *max* values are the lower and upper bounds of the range. By default, *min* is 0 and *max* is the largest event time.

You can specify the following *plot-requests*:

AUC

plots the time-dependent area under the curve (AUC) for each identified model. For a particular time *t*, the AUC is the area under the receiver operating characteristic (ROC) curve at *t*. This option is ignored if time points are specified in the AT= *suboption* in the ROCOPTIONS *option*.

AUCDIFF

plots the difference between two AUC curves for each pair of identified models. This option is ignored if time points are specified in the AT= *suboption* in the ROCOPTIONS *option*.

CIF

plots the estimated cumulative incidence function (CIF) for each set of covariates in the COVARIATES= data set in the BASELINE statement. If the COVARIATES= data set is not specified, the estimated CIF is plotted for the reference set of covariates, which consists of reference levels for the CLASS variables and average values for the continuous variables.

CUMHAZ

plots the estimated cumulative hazard function for each set of covariates in the COVARIATES= data set in the BASELINE statement. If the COVARIATES= data set is not specified, the estimated cumulative hazard function is plotted for the reference set of covariates, which consists of reference levels for the CLASS variables and average values for the continuous variables.

MCF

plots the estimated mean cumulative function for each set of covariates in the COVARIATES= data set in the BASELINE statement. If the COVARIATES= data set is not specified, the estimated mean cumulative function is plotted for the reference set of covariates, which consists of reference levels for the CLASS variables and average values for the continuous variables.

NONE

suppresses all the plots in the procedure. Specifying this option is equivalent to disabling ODS Graphics for the entire procedure.

ROC< (TICK) >
plots the time-dependent receiver operating characteristic (ROC) curves. You must specify the time points at which the ROC curves are calculated by using the AT= suboption in the ROCOPTIONS option. A plot is produced for each time point. Grid lines are displayed for both axes at 0.0, 0.2, 0.4, 0.6, 0.8, and 1.0. By default, the plots are displayed in panels, with each panel containing up to six plots. Tick values are not shown in the panel plots unless you specify the keyword TICK to show the tick values at the grid lines. You can specify the OVERLAY=INDIVIDUAL *global-plot-option* to display each plot individually.

SURVIVAL
plots the estimated survivor function for each set of covariates in the COVARIATES= data set in the BASELINE statement. If COVARIATES= data set is not specified, the estimated survivor function is plotted for the reference set of covariates, which consists of reference levels for the CLASS variables and average values for the continuous variables.

ROCOPTIONS (*options*)
specifies *options* that apply to the analysis of receiver operating characteristic (ROC) curves for the model that is specified in the MODEL statement (unless the NOFIT option is specified) and for each model specified in a ROC statement. You can specify the following *options*:

AT=*number-list*
specifies the list of time points at which the ROC curves are calculated. The *number-list* can be a list of numbers separated by blanks, or of the form 10 to 30 by 5, or a combination of both.

AUC
displays the area under the curve at time points specified in the AT= *suboption* or at the event times if the AT= *suboption* is not specified.

AUCDIFF
displays the differences between the AUC functions for each pair of identified models at the time points specified in the AT= *suboption* or at the event times if no time points are specified.

IAUC
displays the integrated area under the curve (IAUC), computed as a weighted average of the AUC values at all the event times if the TAU= option is not specified or at the event times less than or equal to the value specified in the TAU= option. The weights that are used are jumps of the Kaplan-Meier estimate of the survivor function.

METHOD=*method* < *(options)* >
specifies the method to calculate ROC curves and AUC statistics. For more information, see the section "Time-Dependent ROC Curves" on page 6928. You can specify the following *methods* along with any applicable *options*:

IPCW< *(ipcw-options)* >

UNO< *(ipcw-options)* >
uses the inverse probability of censoring weighting (IPCW) technique of Uno et al. (2007). Event observations are weighted according to their probabilities of being censored. The following *ipcw-options* apply only to AUC calculations:

CL
computes the pointwise confidence limits for the AUC based on perturbation resampling.

SEED=*n*
specifies an integer seed for the random number generator to generate perturbation samples.

ITER=*n*
specifies the number of perturbation samples.

ALPHA=*value*
specifies the significance level of the confidence interval for the AUC.

KM
uses the conditional Kaplan-Meier method of Heagerty, Lumley, and Pepe (2000).

NNE < *(nne-options)* **>**
uses the nearest neighbors technique of Heagerty, Lumley, and Pepe (2000). You can specify the following *nne-options*:

ASYM
uses asymmetric kernels in the estimation.

SPAN=*value*
specifies the proportion of observations to be used in deriving the bandwidth for the kernel-based estimation. By default, SPAN=0.05.

RECURSIVE
CHAMBLESS
uses the method of Chambless and Diao (2006). The calculation is recursive, and it is performed on the ordered event times sequentially from the smallest to the largest.

By default, METHOD=NNE.

OUTAUC=*SAS-data-set*
names the output data set to contain the data necessary to produce the AUC plot. Each curve is identified by the corresponding model label. For the list of variables in this data set, see the section "OUTAUC= Output Data Set in the ROCOPTIONS Option" on page 6958.

OUTROC=*SAS-data-set*
names the output data set to contain the data necessary to produce the ROC plots. Each ROC curve corresponds to a block of observations that are identified by a time point and a model label. For the list of variables in this data set, see the section "OUTROC= Output Data Set in the ROCOPTIONS Option" on page 6958.

SIMPLE
displays simple descriptive statistics (mean, standard deviation, minimum, and maximum) for each explanatory variable in the MODEL statement.

TAU=*value*

specifies the upper time limit for computing the integrated area under the curve (IAUC) statistic and Uno's concordance statistic. Only event times that do not exceed the specified *value* are used in the calculation. The default *value* is the largest event time.

ZPH<(*zph-options***)>**

requests diagnostics based on the weighted Schoenfeld residuals for checking the proportional hazards assumption (for more information, see the section "ZPH Diagnostics" on page 6924). For each predictor, PROC PHREG presents a plot of the time-varying coefficients in addition to a correlation test between the weighted residuals and failure times in a given scale. You can specify the following *zph-options*:

FIT=NONE | LOESS | SPLINE

displays a fitted smooth curve in a plot of time-varying coefficients. FIT=LOESS displays a loess curve. FIT=SPLINE fits a penalized B-spline curve. If you do not want to display a fitted curve, specify FIT=NONE. By default, FIT=SPLINE.

GLOBAL

computes the global correlation test.

NOPLOT

suppresses the plots of the time-varying coefficients $\beta(t)$.

NOTEST

suppresses the correlation tests.

OUT=*SAS-data-set*

names the output data set that contains the time-varying coefficients $\boldsymbol{\beta}(t)$, one row per event time. The variables that contain $\boldsymbol{\beta}(t)$ have the same names as the predictors. The data set also contains the transformed event times $g(t)$.

TRANSFORM=IDENTITY | KM | LOG | RANK

specifies how the failure times should be transformed in the diagnostic plots and correlation tests. You can choose from the following transformations:

IDENTITY	specify the identity transformation, $g(t) = t$.
KM	specifies the complement of the Kaplan-Meier estimate transformation, $g(t) = 1 - \mathrm{KM}(t)$.
LOG	specifies the log transformation, $g(t) = \log(t)$.
RANK	specifies the rank transformation, $g(t) = \mathrm{rank}(t)$.

ASSESS Statement

ASSESS <VAR=(*list***)> <PH> </** ***options*** **> ;**

The ASSESS statement performs the graphical and numerical methods of Lin, Wei, and Ying (1993) for checking the adequacy of the Cox regression model. The methods are derived from cumulative sums of martingale residuals over follow-up times or covariate values. You can assess the functional form of a

covariate or you can check the proportional hazards assumption for each covariate in the Cox model. PROC PHREG uses ODS Graphics for the graphical displays. You must specify at least one of the following *options* to create an analysis.

VAR=(*variable-list***)**
specifies the list of explanatory variables for which their functional forms are assessed. For each variable on the list, the observed cumulative martingale residuals are plotted against the values of the explanatory variable along with 20 (or *n* if NPATHS=*n* is specified) simulated residual patterns.

PROPORTIONALHAZARDS
PH
requests the checking of the proportional hazards assumption. For each explanatory variable in the model, the observed score process component is plotted against the follow-up time along with 20 (or *n* if NPATHS=*n* is specified) simulated patterns.

The following *options* can be specified after a slash (/):

NPATHS=*n*
specifies the number of simulated residual patterns to be displayed in a cumulative martingale residual plot or a score process plot. The default is *n*=20.

CRPANEL
requests that a plot with four panels, each containing the observed cumulative martingale residuals and two simulated residual patterns, be created.

RESAMPLE < =*n* **>**
requests that the Kolmogorov-type supremum test be computed on 1,000 simulated patterns or on *n* simulated patterns if *n* is specified.

SEED=*n*
specifies an integer seed for the random number generator used in creating simulated realizations for plots and for the Kolmogorov-type supremum tests. Specifying a seed enables you to reproduce identical graphs and *p*-values for the model assessments from the same PHREG specification. If the SEED= option is not specified, or if you specify a nonpositive seed, a random seed is derived from the time of day.

BASELINE Statement

BASELINE < **OUT=***SAS-data-set* > < **OUTDIFF=***SAS-data-set* > < **COVARIATES=***SAS-data-set* >
< **TIMELIST=***list* > < *keyword***=***name* . . . *keyword***=***name* > < / *options* > **;**

The BASELINE statement creates a SAS data set (named by the OUT= option) that contains the baseline function estimates at the event times of each stratum for every set of covariates in the COVARIATES= data set. If the COVARIATES= data set is not specified, a reference set of covariates consisting of the reference levels for the CLASS variables and the average values for the continuous variables is used. You can use the DIRADJ option to obtain the direct adjusted survival curve that averages the estimated survival curves for the observations in the COVARIATES= data set. No BASELINE data set is created if the model contains a time-dependent variable defined by means of programming statement.

Table 86.2 summarizes the *options* available in the BASELINE statement.

Table 86.2 BASELINE Statement Options

Option	Description
Data Set and Time List Options	
OUT=	Specifies the output BASELINE data set
OUTDIFF=	Specifies the output data set that contains differences of direct adjusted survival curves
COVARIATES=	Specifies the SAS data set that contains the explanatory variables
TIMELIST=	Specifies a list of time points for Bayesian computation of survival estimates.
Keyword Options	
CIF=	Specifies the cumulative incidence estimate
CMF=	Specifies the cumulative mean function estimate
CUMHAZ=	Specifies the cumulative hazard function estimate
LOGLOGS=	Specifies the log of the negative log of SURVIVAL
LOGSURV=	Specifies the log of SURVIVAL
LOWERCIF=	Specifies the lower pointwise confidence limit for CIF
LOWERCMF=	Specifies the lower pointwise confidence limit for CMF
LOWERCUMHAZ=	specifies the lower pointwise confidence limit for CUMHAZ
LOWERHPDCUMHAZ=	Specifies the lower limit of the HPD interval for CUMHAZ
LOWERHPD=	Specifies the lower limit of the HPD interval for SURVIVAL
LOWER=	Specifies the lower pointwise confidence limit for SURVIVAL
STDCIF=	Specifies the estimated standard error of CIF
STDCMF=	Specifies the estimated standard error of CMF
STDCUMHAZ=	Specifies the estimated standard error of CUMHAZ
STDERR=	Specifies the standard error of SURVIVAL
STDXBETA=	Specifies the estimated standard error of the linear predictor estimator
SURVIVAL=	Specifies the survivor function estimate
UPPERCIF=	Specifies the upper pointwise confidence limit for CIF
UPPERCMF=	Specifies the upper pointwise confidence limit for CMF
UPPERCUMHAZ=	Specifies the upper pointwise confidence limit for CUMHAZ
UPPERHPDCUMHAZ=	Specifies the upper limit of the HPD interval for CUMHAZ
UPPERHPD=	Specifies the upper limit of the HPD interval for SURVIVAL
UPPER=	Specifies the upper pointwise confidence limit for SURVIVAL
XBETA=	Specifies the estimate of the linear predictor $\mathbf{x}'\boldsymbol{\beta}$
Other Options	
ALPHA=	Specifies the significance level of the confidence interval for the survivor function
CLTYPE=	Specifies the transformation used to compute the confidence limits
DIRADJ	Computes direct adjusted survival curves
GROUP=	Names a variable whose values are used to identify or group the survival curves
METHOD=	Specifies the method used to compute the survivor function estimates

Table 86.2 *continued*

Options	Description
NORMALSAMPLE=	Specifies the number of normal random samples for CIF confidence limits
ROWID=	Names the variable in the COVARIATES= data set for identifying the baseline functions curves in the plots
SEED=	Specifies the random number generator seed

The following *options* are available in the BASELINE statement.

OUT=*SAS-data-set*
names the output BASELINE data set. If you omit the OUT= option, the data set is created and given a default name by using the DATA*n* convention. For more information, see the section "OUT= Output Data Set in the BASELINE Statement" on page 6958.

OUTDIFF=*SAS-data-set*
names the output data set that contains all pairwise differences of direct adjusted probabilities between groups if the GROUP= variable is specified, or between strata if the GROUP= variable is not specified. It is required that the DIRADJ option be specified to use the OUTDIFF= option.

COVARIATES=*SAS-data-set*
names the SAS data set that contains the sets of explanatory variable values for which the quantities of interest are estimated. All variables in the COVARIATES= data set are copied to the OUT= data set. Thus, any variable in the COVARIATES= data set can be used to identify the covariate sets in the OUT= data set.

TIMELIST=*list*
specifies a list of time points at which the survival function estimates and cumulative hazard function estimates are computed. The following specifications are equivalent:

```
timelist=5,20 to 50 by 10
timelist=5 20 30 40 50
```

If the TIMELIST= option is not specified, the default is to carry out the prediction at all event times and at time 0. This option can be used only for the Bayesian analysis.

keyword=name
specifies the statistics to be included in the OUT= data set and assigns names to the variables that contain these statistics. Specify a *keyword* for each desired statistic, an equal sign, and the name of the variable for the statistic. Not all *keywords* listed in Table 86.3 (and discussed in the text that follows) are appropriate for both the classical analysis and the Bayesian analysis; and the table summaries the choices for each analysis.

Table 86.3 Summary of the Keyword Choices

Keyword	Classical	Bayesian
Survivor Function		
SURVIVAL=	x	x
STDERR=	x	x
LOWER=	x	x
UPPER=	x	x
LOWERHPD=		x
UPPERHPD=		x
Cumulative Hazard Function		
CUMHAZ=	x	x
STDCUMHAZ=	x	x
LOWERCUMHAZ=	x	x
UPPERCUMHAZ=	x	x
LOWERHPDCUMHAZ=		x
UPPERHPDCUMHAZ=		x
Cumulative Incidence Function		
CIF=	x	
STDCIF=	x	
LOWERCIF=	x	
UPPERCIF=	x	
Cumulative Mean Function		
CMF=	x	
STDCMF=	x	
LOWERCMF=	x	
UPPERCMF=	x	
Others		
XBETA=	x	x
STDXBETA=	x	x
LOGSURV=	x	
LOGLOGS=	x	

You can specify the following *keywords*:

CIF=
specifies the cumulative incidence function estimate for competing risks data. Specifying CIF=_ALL_ is equivalent to specifying CIF=CIF, STDCIF=StdErrCIF, LOWERCIF=LowerCIF, and UPPERCIF=UpperCIF.

CMF=

MCF=

specifies the cumulative mean function estimate for recurrent events data. Specifying CMF=_ALL_ is equivalent to specifying CMF=CMF, STDCMF=StdErrCMF, LOWERCMF=LowerCMF, and UPPERCMF=UpperCMF. Nelson (2002) refers to the mean function estimate as MCF (mean cumulative function).

CUMHAZ=

specifies the cumulative hazard function estimate. Specifying CUMHAZ=_ALL_ is equivalent to specifying CUMHAZ=CumHaz, STDCUMHAZ=StdErrCumHaz, LOWERCUMHAZ=LowerCumHaz, and UPPERCUMHAZ=UpperCumHaz. For a Bayesian analysis, CUMHAZ=_ALL_ also includes LOWERHPDCUMHAZ=LowerHPDCumHaz and UpperHPDCUMHAZ=UpperHPDCumHaz.

LOGLOGS=

specifies the log of the negative log of SURVIVAL.

LOGSURV=

specifies the log of SURVIVAL.

LOWER=

L=

specifies the lower pointwise confidence limit for the survivor function. For a Bayesian analysis, this is the lower limit of the equal-tail credible interval for the survivor function. The confidence level is determined by the ALPHA= option.

LOWERCIF=

specifies the lower pointwise confidence limit for the cumulative incidence function. The confidence level is determined by the ALPHA= option.

LOWERCMF=

LOWERMCF=

specifies the lower pointwise confidence limit for the cumulative mean function. The confidence level is determined by the ALPHA= option.

LOWERHPD=

specifies the lower limit of the HPD interval for the survivor function. The confidence level is determined by the ALPHA= option.

LOWERHPDCUMHAZ=

specifies the lower limit of the HPD interval for the cumulative hazard function. The confidence level is determined by the ALPHA= option.

LOWERCUMHAZ=

specifies the lower pointwise confidence limit for the cumulative hazard function. For a Bayesian analysis, this is the lower limit of the equal-tail credible interval for the cumulative hazard function. The confidence level is determined by the ALPHA= option.

STDERR=
specifies the standard error of the survivor function estimator. For a Bayesian analysis, this is the standard deviation of the posterior distribution of the survivor function.

STDCIF=
specifies the estimated standard error of the cumulative incidence function estimator.

STDCMF=
STDMCF=
specifies the estimated standard error of the cumulative mean function estimator.

STDCUMHAZ=
specifies the estimated standard error of the cumulative hazard function estimator. For a Bayesian analysis, this is the standard deviation of the posterior distribution of the cumulative hazard function.

STDXBETA=
specifies the estimated standard error of the linear predictor estimator. For a Bayesian analysis, this is the standard deviation of the posterior distribution of the linear predictor.

SURVIVAL=
specifies the survivor function ($S(t) = [S_0(t)]^{\exp(\boldsymbol{\beta}'\mathbf{x})}$) estimate. Specifying SURVIVAL=_ALL_ is equivalent to specifying SURVIVAL=Survival, STDERR=StdErrSurvival, LOWER=LowerSurvival, and UPPER=UpperSurvival; and for a Bayesian analysis, SURVIVAL=_ALL_ also specifies LOWERHPD=LowerHPDSurvival and UPPERHPD=UpperHPDSurvival.

UPPER=
U=
specifies the upper pointwise confidence limit for the survivor function. For a Bayesian analysis, this is the upper limit of the equal-tail credible interval for the survivor function. The confidence level is determined by the ALPHA= option.

UPPERCIF=
specifies the upper pointwise confidence limit for the cumulative incidence function. The confidence level is determined by the ALPHA= option.

UPPERCMF=
UPPERMCF=
specifies the upper pointwise confidence limit for the cumulative mean function. The confidence level is determined by the ALPHA= option.

UPPERCUMHAZ=
specifies the upper pointwise confidence limit for the cumulative hazard function. For a Bayesian analysis, this is the upper limit of the equal-tail credible interval for the cumulative hazard function. The confidence level is determined by the ALPHA= option.

UPPERHPD=
specifies the upper limit of the equal-tail credible interval for the survivor function. The confidence level is determined by the ALPHA= option.

UPPERHPDCUMHAZ=
specifies the upper limit of the equal-tail credible interval for the cumulative hazard function. The confidence level is determined by the ALPHA= option.

XBETA=
specifies the estimate of the linear predictor $\mathbf{x}'\boldsymbol{\beta}$.

The following *options* can appear in the BASELINE statement after a slash (/). The METHOD= and CLTYPE= options apply only to the estimate of the survivor function in the classical analysis. For the Bayesian analysis, the survivor function is estimated by the Breslow (1972) method.

ALPHA=*value*
specifies the significance level of the confidence interval for the survivor function. The value must be between 0 and 1. The default is the value of the ALPHA= option in the PROC PHREG statement, or 0.05 if that option is not specified.

CLTYPE=*method*
specifies the transformation used to compute the confidence limits for $S(t,\mathbf{z})$, the survivor function for a subject with a fixed covariate vector $\mathbf{z}$ at event time t. The CLTYPE= option can take the following values:

LOG
specifies that the confidence limits for $\log(S(t,\mathbf{z}))$ be computed using the normal theory approximation. The confidence limits for $S(t,\mathbf{z})$ are obtained by back-transforming the confidence limits for $\log(S(t,\mathbf{z}))$. The default is CLTYPE=LOG.

LOGLOG
specifies that the confidence limits for the $\log(-\log(S(t,\mathbf{z})))$ be computed using normal theory approximation. The confidence limits for $S(t,\mathbf{z})$ are obtained by back-transforming the confidence limits for $\log(-\log(S(t,\mathbf{z})))$.

NORMAL
IDENTITY
specifies that the confidence limits for $S(t,\mathbf{z})$ be computed directly using normal theory approximation.

DIRADJ
computes direct adjusted survival curves (Makuch 1982; Gail and Byar 1986; Zhang et al. 2007) by averaging the estimated survival curves for the observations in the COVARIATES= data set. For more information about the adjusted survival curves, see the section "Direct Adjusted Survival Curves" on page 6935 and Example 86.8. If the COVARIATES= data set is not specified, the input data set specified in the DATA= option in the PROC PHREG statement is used instead. If you also specify the GROUP= option, PROC PHREG computes an adjusted survival curve for each value of the GROUP= variable.

GROUP=*variable*
names a variable whose values identify or group the estimated survival curves. The behavior of this option depends on whether you also specify the DIRADJ option:

- If you also specify the DIRADJ option, *variable* must be a CLASS variable in the model. A direct adjusted survival curve is computed for each value of *variable* in the input data. The *variable*

does not have to be a variable in the COVARIATES= data set. Each direct adjusted survival curve is the average of the survival curves of all individuals in the COVARIATES= data set with their value of *variable* set to a specific value.

- If you do not specify the DIRADJ option, *variable* is required to be a numeric variable in the COVARIATES= data set. Survival curves for the observations with the same value of the *variable* are overlaid in the same plot.

METHOD=*method*

specifies the method used to compute the survivor function estimates. For more information, see the section "Survivor Function Estimators" on page 6932. You can specify the following *methods*:

BRESLOW

CH

EMP

specifies that the Breslow (1972) estimator be used to compute the survivor function—that is, that the survivor function be estimated by exponentiating the negative empirical cumulative hazard function.

FH

specifies that the Fleming-Harrington (FH) estimates be computed. The FH estimator is a tie-breaking modification of the Breslow estimator. If there are no tied event times, this estimator is the same as the Breslow estimator.

PL

specifies that the product-limit estimates of the survivor function be computed. This estimator is not available if you use the model syntax that allows two time variables for counting process style of input; in such a case the Breslow estimator (METHOD=BRESLOW) is used instead.

The default is METHOD=BRESLOW.

NORMALSAMPLE=*n*

specifies the number of sets of normal random samples to simulate the Gaussian process in the estimation of the confidence limits for the cumulative incidence function. By default, NORMALSAMPLE=100.

ROWID=*variable*

ID=*variable*

ROW=*variable*

names a variable in the COVARIATES= data set for identifying the baseline function curves in the plots. This option has no effect if the PLOTS= option in the PROC PHREG statement is not specified. Values of this variable are used to label the curves for the corresponding rows in the COVARIATES= data set. You can specify ROWID=_OBS_ to use the observation numbers in the COVARIATES= data set for identification.

SEED=*n*

specifies an integer seed, ranging from 1 to $2^{31}-1$, to simulate the distribution of the Gaussian process in the estimation of the confidence limits for the cumulative incidence function. Specifying a seed enables you to reproduce identical confidence limits from the same PROC PHREG specification. If the SEED= option is not specified, or if you specify a nonpositive seed, a random seed is derived from the time of day on the computer's clock.

For recurrent events data, both CMF= and CUMHAZ= statistics are the Nelson estimators, but their standard error are not the same. Confidence limits for the cumulative mean function and cumulative hazard function are based on the log transform.

BAYES Statement

BAYES < *options* > **;**

The BAYES statement requests a Bayesian analysis of the regression model by using Gibbs sampling. The Bayesian posterior samples (also known as the chain) for the regression parameters can be output to a SAS data set. Table 86.4 summarizes the *options* available in the BAYES statement.

Table 86.4 BAYES Statement Options

Option	Description
Monte Carlo Options	
INITIAL=	Specifies initial values of the chain
NBI=	Specifies the number of burn-in iterations
NMC=	Specifies the number of iterations after burn-in
SAMPLING=	Specifies the sampling algorithm
SEED=	Specifies the random number generator seed
THINNING=	Controls the thinning of the Markov chain
Model and Prior Options	
COEFFPRIOR=	Specifies the prior of the regression coefficients
DISPERSIONPRIOR=	Specifies the prior of the dispersion parameter for frailties
PIECEWISE=	Specifies details of the piecewise exponential model
Summaries and Diagnostics of the Posterior Samples	
DIAGNOSTICS=	Displays convergence diagnostics
PLOTS=	Displays diagnostic plots
STATISTICS=	Displays summary statistics
Posterior Samples	
OUTPOST=	Names a SAS data set for the posterior samples

The following list describes these *options* and their *suboptions*.

COEFFPRIOR=UNIFORM | **NORMAL** < **(***normal-option***)** > | **ZELLNER** < **(***zellner-option***)** >

CPRIOR=UNIFORM | **NORMAL** < **(***normal-option***)** > | **ZELLNER** < **(***zellner-option***)** >

COEFF=UNIFORM | **NORMAL** < **(***normal-option***)** > | **ZELLNER** < **(***zellner-option***)** >

specifies the prior distribution for the regression coefficients. The default is COEFFPRIOR=UNIFORM. The following prior distributions are available:

UNIFORM
specifies a flat prior—that is, the prior that is proportional to a constant ($p(\beta_1, \ldots, \beta_k) \propto 1$ for all $-\infty < \beta_i < \infty$).

NORMAL< (*normal-option*) >
specifies a normal distribution. The *normal-options* include the following:

INPUT=*SAS-data-set*
specifies a SAS data set that contains the mean and covariance information of the normal prior. The data set must contain the _TYPE_ variable to identify the observation type, and it must contain a variable to represent each regression coefficient. If the data set also contains the _NAME_ variable, values of this variable are used to identify the covariances for the _TYPE_='COV' observations; otherwise, the _TYPE_='COV' observations are assumed to be in the same order as the explanatory variables in the MODEL statement. PROC PHREG reads the mean vector from the observation with _TYPE_='MEAN' and the covariance matrix from observations with _TYPE_='COV'. For an independent normal prior, the variances can be specified with _TYPE_='VAR'; alternatively, the precisions (inverse of the variances) can be specified with _TYPE_='PRECISION'.

RELVAR < =*c* >
specifies a normal prior $N(\mathbf{0}, c\mathbf{J})$, where $\mathbf{J}$ is a diagonal matrix with diagonal elements equal to the variances of the corresponding ML estimator. By default, *c*=1E6.

VAR=*c*
specifies the normal prior $N(\mathbf{0}, c\mathbf{I})$, where $\mathbf{I}$ is the identity matrix.

If you do not specify a *normal-option*, the normal prior $N(\mathbf{0}, 10^6\mathbf{I})$, where $\mathbf{I}$ is the identity matrix, is used. For more information, see the section "Normal Prior" on page 6950.

ZELLNER< (*zellner-option*) >
specifies the Zellner g-prior for the regression coefficients. The g-prior is a normal prior distribution with mean zero and covariance matrix equal to $(g\mathbf{X}'\mathbf{X})^{-1}$, where $\mathbf{X}$ is the design matrix and g can be a constant or a parameter with a gamma prior. The *zellner-options* include the following:

G=*number*
specifies a constant *number* for g.

GAMMA < (SHAPE=*a* ISCALE=*b*) >
specifies that g has a gamma prior distribution $G(a, b)$ with density $f(t) = \frac{b(bt)^{a-1}\mathrm{e}^{-bt}}{\Gamma(a)}$. By default, *a*=*b*=1E–4.

If you do not specify a *zellner-option*, the default is ZELLNER(g=1E–6).

DISPERSIONPRIOR=GAMMA< (*gamma-options*) > | IGAMMA< (*igamma-options*) > | IMPROPER
DPRIOR=GAMMA< (*gamma-options*) > | IGAMMA< (*igamma-options*) > | IMPROPER
specifies the prior distribution of the dispersion parameter. For gamma frailty, the dispersion parameter is the variance of the gamma frailty; for lognormal frailty, the dispersion parameter is the variance of the normal random component. The default is DISPERSIONPRIOR=IMPROPER.

You can specify the following values for this *option*:

GAMMA< (*gamma-options***) >**
specifies the gamma prior. A gamma prior $G(a, b)$ with hyperparameters a and b has density $f(\theta) = \frac{b^a \theta^{a-1} e^{-b\theta}}{\Gamma(a)}$, where a is the shape parameter and b is the inverse-scale parameter. You can use the following *gamma-options* enclosed in parentheses to specify the hyperparameters:

SHAPE=*a*
ISCALE=*b*
results in a $G(a, b)$ prior when both *gamma-options* are specified.

SHAPE=*c*
results in a $G(c, c)$ prior when specified alone.

ISCALE=*c*
results in a $G(c, c)$ prior when specify alone.

The default is SHAPE=1E–4 and ISCALE=1E–4.

IGAMMA< (*igamma-options***) >**
specifies the inverse-gamma prior. An inverse-gamma prior $IG(a, b)$ with hyperparameters a and b has a density $f(\theta) = \frac{b^a \theta^{-(a+1)} e^{-\frac{b}{\theta}}}{\Gamma(a)}$, where a is the shape parameter and b is the scale parameter. You can use the following *igamma-options* enclosed in parentheses to specify the hyperparameters:

SHAPE=*a*
SCALE=*b*
results in a $IG(a, b)$ prior when both *igamma-options* are specified.

SHAPE=*c*
results in a $IG(c, c)$ prior when specified alone.

SCALE=*c*
results in a $IG(c, c)$ prior when specified alone.

The default is SHAPE=2.001 AND SCALE=0.01.

IMPROPER
specifies the improper prior, which has a density $f(\theta)$ proportional to θ^{-1}.

DIAGNOSTICS=ALL | NONE | *keyword* | (*keyword-list*)
DIAG=ALL | NONE | *keyword* | (*keyword-list*)
controls the number of diagnostics produced. You can request all the diagnostics in the following list by specifying DIAGNOSTICS=ALL. If you do not want any of these diagnostics, you specify DIAGNOSTICS=NONE. If you want some but not all of the diagnostics, or if you want to change certain settings of these diagnostics, you specify a subset of the following *keywords*. The default is DIAGNOSTICS=(AUTOCORR GEWEKE ESS).

AUTOCORR < (LAGS= *numeric-list*) >
computes the autocorrelations of lags given by LAGS= list for each parameter. Elements in the list are truncated to integers and repeated values are removed. If the LAGS= option is not specified, autocorrelations of lags 1, 5, 10, and 50 are computed for each variable. For more information, see the section "Autocorrelations" on page 149 in Chapter 7, "Introduction to Bayesian Analysis Procedures."

ESS

computes the effective sample size of Kass et al. (1998), the correlation time, and the efficiency of the chain for each parameter. For more information, see the section "Effective Sample Size" on page 149 in Chapter 7, "Introduction to Bayesian Analysis Procedures."

MCSE

MCERROR

computes the Monte Carlo standard error for each parameter. The Monte Caro standard error, which measures the simulation accuracy, is the standard error of the posterior mean estimate and is calculated as the posterior standard deviation divided by the square root of the effective sample size. For more information. see the section "Standard Error of the Mean Estimate" on page 150 in Chapter 7, "Introduction to Bayesian Analysis Procedures."

HEIDELBERGER < (*heidel-options*) >

computes the Heidelberger and Welch tests for each parameter. For more information, see the section "Heidelberger and Welch Diagnostics" on page 145 in Chapter 7, "Introduction to Bayesian Analysis Procedures." The tests consist of a stationary test and a halfwidth test. The former tests the null hypothesis that the sample values form a stationary process. If the stationarity test is passed, a halfwidth test is then carried out. Optionally, you can specify one or more of the following *heidel-options*:

SALPHA=*value*

specifies the α level ($0 < \alpha < 1$) for the stationarity test. The default is the value of the ALPHA= option in the PROC PHREG statement, or 0.05 if that option is not specified.

HALPHA=*value*

specifies the α level ($0 < \alpha < 1$) for the halfwidth test. The default is the value of the ALPHA= option in the PROC PHREG statement, or 0.05 if that option is not specified.

EPS=*value*

specifies a small positive number ϵ such that if the halfwidth is less than ϵ times the sample mean of the retaining samples, the halfwidth test is passed.

GELMAN < (*gelman-options*) >

computes the Gelman and Rubin convergence diagnostics. For more information, see the section "Gelman and Rubin Diagnostics" on page 142 in Chapter 7, "Introduction to Bayesian Analysis Procedures." You can specify one or more of the following *gelman-options*:

NCHAIN=*number*

N=*number*

specifies the number of parallel chains used to compute the diagnostic and has to be 2 or larger. The default is NCHAIN=3. The NCHAIN= option is ignored when the INITIAL= option is specified in the BAYES statement, and in such a case, the number of parallel chains is determined by the number of valid observations in the INITIAL= data set.

ALPHA=*value*

specifies the significance level for the upper bound. The default is the value of the ALPHA= option in the PROC PHREG statement, or 0.05 if that option is not specified (resulting in a 97.5% bound).

GEWEKE < *geweke-options* >
computes the Geweke diagnostics. For more information, see the section "Geweke Diagnostics" on page 143 in Chapter 7, "Introduction to Bayesian Analysis Procedures." The diagnostic is essentially a two-sample t-test between the first f_1 portion and the last f_2 portion of the chain. The default is f_1=0.1 and f_2=0.5, but you can choose other fractions by using the following *geweke-options*:

FRAC1=*value*
specifies the early f_1 fraction of the Markov chain.

FRAC2=*value*
specifies the latter f_2 fraction of the Markov chain.

RAFTERY < (*raftery-options*) >
computes the Raftery and Lewis diagnostics. For more information, see the section "Raftery and Lewis Diagnostics" on page 146 in Chapter 7, "Introduction to Bayesian Analysis Procedures." The diagnostic evaluates the accuracy of the estimated quantile ($\hat{\theta}_Q$ for a given $Q \in (0, 1)$) of a chain. $\hat{\theta}_Q$ can achieve any degree of accuracy when the chain is allowed to run for a long time. A stopping criterion is when the estimated probability $\hat{P}_Q = \Pr(\theta \leq \hat{\theta}_Q)$ reaches within $\pm R$ of the value Q with probability S; that is, $\Pr(Q - R \leq \hat{P}_Q \leq Q + R) = S$. The following *raftery-options* enable you to specify Q, R, S, and a precision level ϵ for a stationary test.

QUANTILE=*value*

Q=*value*
specifies the order (a value between 0 and 1) of the quantile of interest. The default is 0.025.

ACCURACY=*value*

R=*value*
specifies a small positive number as the margin of error for measuring the accuracy of estimation of the quantile. The default is 0.005.

PROBABILITY=*value*

S=*value*
specifies the probability of attaining the accuracy of the estimation of the quantile. The default is 0.95.

EPSILON=*value*

EPS=*value*
specifies the tolerance level (a small positive number) for the test. The default is 0.001.

INITIAL=*SAS-data-set*
specifies the SAS data set that contains the initial values of the Markov chains. The INITIAL= data set must contain a variable for each parameter in the model. You can specify multiple rows as the initial values of the parallel chains for the Gelman-Rubin statistics, but posterior summary statistics, diagnostics, and plots are computed only for the first chain.

NBI=*number*
specifies the number of burn-in iterations before the chains are saved. The default is 2000.

NMC=*number*
specifies the number of iterations after the burn-in. The default is 10000.

OUTPOST=*SAS-data-set*
OUT=*SAS-data-set*
names the SAS data set that contains the posterior samples. For more information, see the section "OUTPOST= Output Data Set in the BAYES Statement" on page 6958. Alternatively, you can output the posterior samples into a data set, as shown in the following example in which the data set is named PostSamp.

```
ODS OUTPUT PosteriorSample = PostSamp;
```

PIECEWISE <=*keyword* **<(<NINTERVAL=***number***> <INTERVALS=(***numeric-list***)> <PRIOR=***option***>)>>**

specifies that the piecewise constant baseline hazard model be used in the Bayesian analysis. You can specify one of the following two *keywords*:

HAZARD
models the baseline hazard parameters in the original scale. The hazard parameters are named Lambda1, Lambda2, . . ., and so on.

LOGHAZARD
models the baseline hazard parameters in the log scale. The log-hazard parameters are named Alpha1, Alpha2, . . ., and so on.

Specifying PIECEWISE by itself is the same as specifying PIECEWISE=LOGHAZARD.

You can choose one of the following two options to specify the partition of the time axis into intervals of constant baseline hazards:

NINTERVAL=*number*
N=*number*
specifies the number of intervals with constant baseline hazard rates. PROC PHREG partitions the time axis into the given number of intervals with approximately equal number of events in each interval.

INTERVALS=(*numeric-list***)**
INTERVAL=(*numeric-list***)**
specifies the list of numbers that partition the time axis into disjoint intervals with constant baseline hazard in each interval. For example, INTERVALS=(100, 150, 200, 250, 300) specifies a model with a constant hazard in the intervals [0,100), [100,150), [150,200), [200,250), [250,300), and [300,∞). Each interval must contain at least one event; otherwise, the posterior distribution can be improper, and inferences cannot be derived from an improper posterior distribution.

If neither NINTERVAL= nor INTERVAL= is specified, the default is NINTERVAL=8.

To specify the prior for the baseline hazards $(\lambda_1, \ldots, \lambda_J)$ in the original scale, you specify the following:

PRIOR = IMPROPER | UNIFORM | GAMMA< (*gamma-option*) > | ARGAMMA< (*argamma-option*) >

The default is PRIOR=IMPROPER. The available prior options include the following:

IMPROPER
specifies the noninformative and improper prior $p(\lambda_1, \ldots, \lambda_J) \propto \prod_i {\lambda_i}^{-1}$ for all $\lambda_i > 0$.

UNIFORM
specifies a uniform prior on the real line; that is, $p(\lambda_i) \propto 1$ for all $\lambda_i > 0$.

GAMMA < (*gamma-option*) >
specifies an independent gamma prior $G(a, b)$ with density $f(t) = \frac{b(bt)^{a-1}\mathrm{e}^{-bt}}{\Gamma(a)}$, which can be followed by one of the following *gamma-options* enclosed in parentheses. The hyperparameters a and b are the shape and inverse-scale parameters of the gamma distribution, respectively. For more information, see the section "Independent Gamma Prior" on page 6949. The default is $G(10^{-4}, 10^{-4})$ for each λ_j, setting the prior mean to 1 with variance 1E4. This prior is proper and reasonably noninformative.

INPUT=*SAS-data-set*
specifies a data set containing the hyperparameters of the independent gamma prior. The data set must contain the _TYPE_ variable to identify the observation type, and it must contain the variables named Lambda1, Lambda2, ..., and so forth, to represent the hazard parameters. The observation with _TYPE_='SHAPE' identifies the shape parameters, and the observation with _TYPE_='ISCALE' identifies the inverse-scale parameters.

RELSHAPE< =*c* >
specifies independent $G(c\hat{\lambda}_j, c)$ distribution, where $\hat{\lambda}_j$'s are the MLEs of the hazard rates. This prior has mean $\hat{\lambda}_j$ and variance $\frac{\hat{\lambda}_j}{c}$. By default, *c*=1E–4.

SHAPE=*a* and ISCALE=*b*
together specify the $G(a, b)$ prior.

SHAPE=*c*
ISCALE=*c*
specifies the $G(c, c)$ prior.

ARGAMMA < (*argamma-option*) >
specifies an autoregressive gamma prior of order 1, which can be followed by one of the following *argamma-options*. For more information, see the section "AR1 Prior" on page 6949.

INPUT=*SAS-data-set*
specifies a data set containing the hyperparameters of the correlated gamma prior. The data set must contain the _TYPE_ variable to identify the observation type, and it must contain the variables named Lambda1, Lambda2, ..., and so forth, to represent the hazard parameters. The observation with _TYPE_='SHAPE' identifies the shape parameters, and the observation with _TYPE_='ISCALE' identifies the *relative* inverse-scale parameters; that is, if a_j and b_j are, respectively, the SHAPE and ISCALE values for $\lambda_j, 1 \le j \le J$, then $\lambda_1 \sim G(a_1, b_1)$, and $\lambda_j \sim G(a_j, b_j/\lambda_{j-1})$ for $2 \le j \le J$.

SHAPE=*a* and SCALE=*b*
together specify that $\lambda_1 \sim G(a, b)$ and $\lambda_j \sim G(a, b/\lambda_{j-1})$ for $2 \leq j \leq J$.

SHAPE=*c*
ISCALE=*c*
specifies that $\lambda_1 \sim G(c, c)$ and $\lambda_j \sim G(c, c/\lambda_{j-1})$ for $2 \leq j \leq J$.

To specify the prior for $\alpha_1, \ldots, \alpha_J$, the hazard parameters in the log scale, you specifying the following:

PRIOR=UNIFORM | NORMAL<(*normal-option*)>
specifies the prior for the loghazard parameters. The default is PRIOR=UNIFORM. The available PRIOR= options are as follows:

UNIFORM
specifies the uniform prior on the real line; that is, $\alpha_i \propto 1$ for all $-\infty < \alpha_i < \infty$.

NORMAL<(*normal-option*)>
specifies a normal prior distribution on the log-hazard parameters. The *normal-options* include the following. If you do not specify a *normal-option*, the normal prior $N(\mathbf{0}, 10^6\mathbf{I})$, where $\mathbf{I}$ is the identity matrix, is used.

INPUT=*SAS-data-set*
specifies a SAS data set containing the mean and covariance information of the normal prior. The data set must contain the _TYPE_ variable to identify the observation type, and it must contain variables named Alpha1, Alpha2, ..., and so forth, to represent the log-hazard parameters. If the data set also contains the _NAME_ variable, the value of this variable will be used to identify the covariances for the _TYPE_='COV' observations; otherwise, the _TYPE_='COV' observations are assumed to be in the same order as the explanatory variables in the MODEL statement. PROC PHREG reads the mean vector from the observation with _TYPE_='MEAN' and the covariance matrix from observations with _TYPE_='COV'. For more information, see the section "Normal Prior" on page 6950. For an independent normal prior, the variances can be specified with _TYPE_='VAR'; alternatively, the precisions (inverse of the variances) can be specified with _TYPE_='PRECISION'.

If you have a joint normal prior for the log-hazard parameters and the regression coefficients, specify the same data set containing the mean and covariance information of the multivariate normal distribution in both the COEFFPRIOR=NORMAL(INPUT=) and the PIECEWISE=LOGHAZARD(PRIOR=NORMAL(INPUT=)) options. For more information, see the section "Joint Multivariate Normal Prior for Log-Hazards and Regression Coefficients" on page 6950.

RELVAR<=*c*>
specifies the normal prior $N(\mathbf{0}, c\mathbf{J})$, where $\mathbf{J}$ is a diagonal matrix with diagonal elements equal to the variances of the corresponding ML estimator. By default, *c*=1E6.

VAR=*c*
specifies the normal prior $N(\mathbf{0}, c\mathbf{I})$, where $\mathbf{I}$ is the identity matrix.

PLOTS < (*global-plot-options*) **> =** *plot-request*

PLOTS < (*global-plot-options*) **> =** (*plot-requests*)

controls the diagnostic plots produced through ODS Graphics. Three types of plots can be requested: trace plots, autocorrelation function plots, and kernel density plots. By default, the plots are displayed in panels unless the global plot option UNPACK is specified. If you specify more than one type of plots, the plots are displayed by parameters unless the global plot option GROUPBY=TYPE is specified. When you specify only one plot request, you can omit the parentheses around the plot request. For example:

```
plots=none
plots(unpack)=trace
plots=(trace autocorr)
```

ODS Graphics must be enabled before plots can be requested. For example:

```
ods graphics on;
proc phreg;
   model y=x;
   bayes plots=trace;
run;
```

If ODS Graphics is enabled but you do not specify the PLOTS= option in the BAYES statement, then PROC PHREG produces, for each parameter, a panel that contains the trace plot, the autocorrelation function plot, and the density plot. This is equivalent to specifying **`plots=(trace autocorr density)`**.

The *global-plot-options* include the following:

FRINGE

creates a fringe plot on the X axis of the density plot.

GROUPBY = PARAMETER | TYPE

specifies how the plots are to be grouped when there is more than one type of plots. The choices are as follows:

TYPE

specifies that the plots be grouped by type.

PARAMETER

specifies that the plots be grouped by parameter.

GROUPBY=PARAMETER is the default.

SMOOTH

displays a fitted penalized B-spline curve each trace plot.

UNPACKPANEL

UNPACK

specifies that all paneled plots be unpacked, meaning that each plot in a panel is displayed separately.

The *plot-requests* include the following:

ALL
specifies all types of plots. PLOTS=ALL is equivalent to specifying PLOTS=(TRACE AUTOCORR DENSITY).

AUTOCORR
displays the autocorrelation function plots for the parameters.

DENSITY
displays the kernel density plots for the parameters.

NONE
suppresses all diagnostic plots.

TRACE
displays the trace plots for the parameters. For more information, see the section "Visual Analysis via Trace Plots" on page 137 in Chapter 7, "Introduction to Bayesian Analysis Procedures."

Consider a model with four parameters, X1–X4. Displays for various specification are depicted as follows.

1. PLOTS=(TRACE AUTOCORR) displays the trace and autocorrelation plots for each parameter side by side with two parameters per panel:

Display 1	Trace(X1)	Autocorr(X1)
	Trace(X2)	Autocorr(X2)
Display 2	Trace(X3)	Autocorr(X3)
	Trace(X4)	Autocorr(X4)

2. PLOTS(GROUPBY=TYPE)=(TRACE AUTOCORR) displays all the paneled trace plots, followed by panels of autocorrelation plots:

Display 1	Trace(X1)	
	Trace(X2)	
Display 2	Trace(X3)	
	Trace(X4)	
Display 3	Autocorr(X1)	Autocorr(X2)
	Autocorr(X3)	Autocorr(X4)

3. PLOTS(UNPACK)=(TRACE AUTOCORR) displays a separate trace plot and a separate correlation plot, parameter by parameter:

Display 1	Trace(X1)
Display 2	Autocorr(X1)
Display 3	Trace(X2)
Display 4	Autocorr(X2)
Display 5	Trace(X3)
Display 6	Autocorr(X3)
Display 7	Trace(X4)
Display 8	Autocorr(X4)

4. PLOTS(UNPACK GROUPBY=TYPE) = (TRACE AUTOCORR) displays all the separate trace plots followed by the separate autocorrelation plots:

Display 1	Trace(X1)
Display 2	Trace(X2)
Display 3	Trace(X3)
Display 4	Trace(X4)
Display 5	Autocorr(X1)
Display 6	Autocorr(X2)
Display 7	Autocorr(X3)
Display 8	Autocorr(X4)

SAMPLING=*keyword*

specifies the sampling algorithm used in the Markov chain Monte Carlo (MCMC) simulations. Two sampling algorithms are available:

ARMS

GIBBS

requests the use of the adaptive rejection Metropolis sampling (ARMS) algorithm to draw the Gibbs samples. ALGORITHM=ARMS is the default.

RWM
requests the use of the random walk Metropolis (RWM) algorithm to draw the samples.

For details about the MCMC sampling algorithms, see the section "Markov Chain Monte Carlo Method" on page 129 in Chapter 7, "Introduction to Bayesian Analysis Procedures."

SEED=*number*
specifies an integer seed ranging from 1 to $2^{31}-1$ for the random number generator in the simulation. Specifying a seed enables you to reproduce identical Markov chains for the same specification. If the SEED= option is not specified, or if you specify a nonpositive seed, a random seed is derived from the time of day.

STATISTICS <(*global-options***)> = ALL | NONE |** *keyword* **| (***keyword-list***)**

STATS <(*global-statoptions***)> = ALL | NONE |** *keyword* **| (***keyword-list***)**
controls the number of posterior statistics produced. Specifying STATISTICS=ALL is equivalent to specifying STATISTICS=(SUMMARY INTERVAL COV CORR). If you do not want any posterior statistics, you specify STATISTICS=NONE. The default is STATISTICS=(SUMMARY INTERVAL). For more information, see the section "Summary Statistics" on page 150 in Chapter 7, "Introduction to Bayesian Analysis Procedures." The *global-options* include the following:

ALPHA=*numeric-list*
controls the probabilities of the credible intervals. The ALPHA= values must be between 0 and 1. Each ALPHA= value produces a pair of 100(1–ALPHA)% equal-tail and HPD intervals for each parameters. The default is the value of the ALPHA= option in the PROC PHREG statement, or 0.05 if that option is not specified (yielding the 95% credible intervals for each parameter).

PERCENT=*numeric-list*
requests the percentile points of the posterior samples. The PERCENT= values must be between 0 and 100. The default is PERCENT= 25, 50, 75, which yield the 25th, 50th, and 75th percentile points for each parameter.

You can specify the following values for a *keyword* or as part of a *keyword-list*. To specify a list, place parentheses around multiple *keywords* that are separated by spaces.

CORR
produces the posterior correlation matrix.

COV
produces the posterior covariance matrix.

SUMMARY
produces the means, standard deviations, and percentile points for the posterior samples. The default is to produce the 25th, 50th, and 75th percentile points, but you can use the global PERCENT= option to request specific percentile points.

INTERVAL
produces equal-tail credible intervals and HPD intervals. The default is to produce the 95% equal-tail credible intervals and 95% HPD intervals, but you can use the global ALPHA= option to request intervals of any probabilities.

THINNING=*number*

THIN=*number*

controls the thinning of the Markov chain. Only one in every k samples is used when THINNING=k, and if NBI=n_0 and NMC=n, the number of samples kept is

$$\left[\frac{n_0+n}{k}\right]-\left[\frac{n_0}{k}\right]$$

where $[a]$ represents the integer part of the number a. The default is THINNING=1.

BY Statement

BY *variables* **;**

You can specify a BY statement with PROC PHREG to obtain separate analyses of observations in groups that are defined by the BY variables. When a BY statement appears, the procedure expects the input data set to be sorted in order of the BY variables. If you specify more than one BY statement, only the last one specified is used.

If your input data set is not sorted in ascending order, use one of the following alternatives:

- Sort the data by using the SORT procedure with a similar BY statement.
- Specify the NOTSORTED or DESCENDING option in the BY statement for the PHREG procedure. The NOTSORTED option does not mean that the data are unsorted but rather that the data are arranged in groups (according to values of the BY variables) and that these groups are not necessarily in alphabetical or increasing numeric order.
- Create an index on the BY variables by using the DATASETS procedure (in Base SAS software).

For more information about BY-group processing, see the discussion in *SAS Language Reference: Concepts*. For more information about the DATASETS procedure, see the discussion in the *Base SAS Procedures Guide*.

CLASS Statement

CLASS *variable* < **(***options***)** > *. . .* < *variable* < **(***options***)** > > < / *global-options* > **;**

The CLASS statement names the classification variables to be used as explanatory variables in the analysis. Response variables do not need to be specified in the CLASS statement.

The CLASS statement must precede the MODEL statement. Most options can be specified either as individual variable *options* or as *global-options*. You can specify *options* for each variable by enclosing the options in parentheses after the variable name. You can also specify *global-options* for the CLASS statement by placing them after a slash (/). *Global-options* are applied to all the variables specified in the CLASS statement. If you specify more than one CLASS statement, the *global-options* specified in any one CLASS statement apply to all CLASS statements. However, individual CLASS variable *options* override the *global-options*. You can specify the following values for either an *option* or a *global-option*:

CPREFIX=*n*

specifies that, at most, the first *n* characters of a CLASS variable name be used in creating names for the corresponding design variables. The default is $32 - \min(32, \max(2, f))$, where f is the formatted length of the CLASS variable.

DESCENDING

DESC

reverses the sort order of the classification variable. If both the DESCENDING and ORDER= options are specified, PROC PHREG orders the categories according to the ORDER= option and then reverses that order.

LPREFIX=*n*

specifies that, at most, the first *n* characters of a CLASS variable label be used in creating labels for the corresponding design variables. The default is $256 - \min(256, \max(2, f))$, where f is the formatted length of the CLASS variable.

MISSING

treats missing values (., ._, .A, . . . , .Z for numeric variables and blanks for character variables) as valid values for the CLASS variable.

ORDER=DATA | FORMATTED | FREQ | INTERNAL

specifies the sort order for the levels of classification variables. This ordering determines which parameters in the model correspond to each level in the data, so the ORDER= option can be useful when you use the CONTRAST statement. By default, ORDER=FORMATTED. For ORDER=FORMATTED and ORDER=INTERNAL, the sort order is machine-dependent. When ORDER=FORMATTED is in effect for numeric variables for which you have supplied no explicit format, the levels are ordered by their internal values.

The following table shows how PROC PHREG interprets values of the ORDER= option.

Value of ORDER=	Levels Sorted By
DATA	Order of appearance in the input data set
FORMATTED	External formatted values, except for numeric variables with no explicit format, which are sorted by their unformatted (internal) values
FREQ	Descending frequency count; levels with more observations come earlier in the order
INTERNAL	Unformatted value

For more information about sort order, see the chapter on the SORT procedure in the *Base SAS Procedures Guide* and the discussion of BY-group processing in *SAS Language Reference: Concepts*.

PARAM=*keyword*

specifies the parameterization method for the classification variable or variables. You can specify any of the *keywords* shown in the following table; ; the default is PARAM=REF. Design matrix columns are created from CLASS variables according to the corresponding coding schemes:

Value of PARAM=	Coding
EFFECT	Effect coding
GLM	Less-than-full-rank reference cell coding (this *keyword* can be used only in a global option)
ORDINAL **THERMOMETER**	Cumulative parameterization for an ordinal CLASS variable
POLYNOMIAL **POLY**	Polynomial coding
REFERENCE **REF**	Reference cell coding
ORTHEFFECT	Orthogonalizes PARAM=EFFECT coding
ORTHORDINAL **ORTHOTHERM**	Orthogonalizes PARAM=ORDINAL coding
ORTHPOLY	Orthogonalizes PARAM=POLYNOMIAL coding
ORTHREF	Orthogonalizes PARAM=REFERENCE coding

All parameterizations are full rank, except for the GLM parameterization. The REF= option in the CLASS statement determines the reference level for EFFECT and REFERENCE coding and for their orthogonal parameterizations. It also indirectly determines the reference level for a singular GLM parameterization through the order of levels.

If PARAM=ORTHPOLY or PARAM=POLY and the classification variable is numeric, then the ORDER= option in the CLASS statement is ignored, and the internal unformatted values are used. See the section "Other Parameterizations" on page 389 in Chapter 19, "Shared Concepts and Topics," for further details.

REF=*'level' | keyword*

specifies the reference level for PARAM=EFFECT, PARAM=REFERENCE, and their orthogonalizations. For PARAM=GLM, the REF= option specifies a level of the classification variable to be put at the end of the list of levels. This level thus corresponds to the reference level in the usual interpretation of the linear estimates with a singular parameterization.

For an individual variable REF= option (but not for a global REF= option), you can specify the *level* of the variable to use as the reference level. Specify the formatted value of the variable if a format is assigned. For a global or individual variable REF= option, you can use one of the following *keywords*. The default is REF=LAST.

FIRST designates the first ordered level as reference.

LAST designates the last ordered level as reference.

TRUNCATE< *=n* >

specifies the length *n* of CLASS variable values to use in determining CLASS variable levels. The default is to use the full formatted length of the CLASS variable. If you specify TRUNCATE without the length *n*, the first 16 characters of the formatted values are used. When formatted values are longer

than 16 characters, you can use this option to revert to the levels as determined in releases before SAS 9. The TRUNCATE option is available only as a global option.

Class Variable Naming Convention

Parameter names for a CLASS predictor variable are constructed by concatenating the CLASS variable name with the CLASS levels. However, for the POLYNOMIAL and orthogonal parameterizations, parameter names are formed by concatenating the CLASS variable name and keywords that reflect the parameterization. See the section "Other Parameterizations" on page 389 in Chapter 19, "Shared Concepts and Topics," for examples and further details.

Class Variable Parameterization with Unbalanced Designs

PROC PHREG initially parameterizes the CLASS variables by looking at the levels of the variables across the complete data set. If you have an *unbalanced* replication of levels across variables or BY groups, then the design matrix and the parameter interpretation might be different from what you expect. For instance, suppose you have a model with one CLASS variable A with three levels (1, 2, and 3), and another CLASS variable B with two levels (1 and 2). If the third level of A occurs only with the first level of B, if you use the EFFECT parameterization, and if your model contains the effect A(B) and an intercept, then the design for A within the second level of B is not a differential effect. In particular, the design looks like the following:

		Design Matrix			
		A(B=1)		A(B=2)	
B	A	A1	A2	A1	A2
1	1	1	0	0	0
1	2	0	1	0	0
1	3	–1	–1	0	0
2	1	0	0	1	0
2	2	0	0	0	1

PROC PHREG detects linear dependency among the last two design variables and sets the parameter for A2(B=2) to zero, resulting in an interpretation of these parameters as if they were reference- or dummy-coded. The REFERENCE or GLM parameterization might be more appropriate for such problems.

CONTRAST Statement

CONTRAST '*label*' *row-description* <**,** *. . . row-description*> </ *options*> **;**

The CONTRAST statement provides a mechanism for obtaining customized hypothesis tests. It is similar to the CONTRAST statement in PROC GLM and PROC CATMOD, depending on the coding schemes used with any categorical variables involved.

The CONTRAST statement enables you to specify a matrix, $\mathbf{L}$, for testing the hypothesis $\mathbf{L}\boldsymbol{\beta} = \mathbf{0}$. You must be familiar with the details of the model parameterization that PROC PHREG uses (for more information, see the PARAM= option in the section "CLASS Statement" on page 6851). Optionally, the CONTRAST statement enables you to estimate each row, $\boldsymbol{l}_i'\boldsymbol{\beta}$, of $\mathbf{L}\boldsymbol{\beta}$ and test the hypothesis $\boldsymbol{l}_i'\boldsymbol{\beta} = 0$. Computed statistics are based on the asymptotic chi-square distribution of the Wald statistic.

There is no limit to the number of CONTRAST statements that you can specify, but they must appear after the MODEL statement.

The syntax of a *row-description* is:

effect values <,. . . ,*effect values*>

The following parameters are specified in the CONTRAST statement:

label identifies the contrast on the output. A label is required for every contrast specified, and it must be enclosed in quotes.

effect identifies an effect that appears in the MODEL statement. You do not need to include all effects that are included in the MODEL statement.

values are constants that are elements of the **L** matrix associated with the effect. To correctly specify your contrast, it is crucial to know the ordering of parameters within each effect and the variable levels associated with any parameter. The "Class Level Information" table shows the ordering of levels within variables. The E option, described later in this section, enables you to verify the proper correspondence of *values* to parameters.

The rows of **L** are specified in order and are separated by commas. Multiple degree-of-freedom hypotheses can be tested by specifying multiple *row-descriptions*. For any of the full-rank parameterizations, if an effect is not specified in the CONTRAST statement, all of its coefficients in the **L** matrix are set to 0. If too many values are specified for an effect, the extra ones are ignored. If too few values are specified, the remaining ones are set to 0.

When you use effect coding (by specifying PARAM=EFFECT in the CLASS statement), all parameters are directly estimable (involve no other parameters). For example, suppose an effect coded CLASS variable A has four levels. Then there are three parameters $(\alpha_1, \alpha_2, \alpha_3)$ representing the first three levels, and the fourth parameter is represented by

$$-\alpha_1 - \alpha_2 - \alpha_3$$

To test the first versus the fourth level of A, you would test

$$\alpha_1 = -\alpha_1 - \alpha_2 - \alpha_3$$

or, equivalently,

$$2\alpha_1 + \alpha_2 + \alpha_3 = 0$$

which, in the form $\mathbf{L}\boldsymbol{\beta} = 0$, is

$$\begin{bmatrix} 2 & 1 & 1 \end{bmatrix} \begin{bmatrix} \alpha_1 \\ \alpha_2 \\ \alpha_3 \end{bmatrix} = 0$$

Therefore, you would use the following CONTRAST statement:

```
contrast '1 vs. 4' A 2 1 1;
```

To contrast the third level with the average of the first two levels, you would test

$$\frac{\alpha_1 + \alpha_2}{2} = \alpha_3$$

or, equivalently,

$$\alpha_1 + \alpha_2 - 2\alpha_3 = 0$$

Therefore, you would use the following CONTRAST statement:

```
contrast '1&2 vs. 3' A 1 1 -2;
```

Other CONTRAST statements involving classification variables with PARAM=EFFECT are constructed similarly. For example:

```
contrast '1 vs. 2    '  A  1 -1  0;
contrast '1&2 vs. 4  '  A  3  3  2;
contrast '1&2 vs. 3&4'  A  2  2  0;
contrast 'Main Effect'  A  1  0  0,
                        A  0  1  0,
                        A  0  0  1;
```

When you use the less-than-full-rank parameterization (by specifying PARAM=GLM in the CLASS statement), each row is checked for estimability. If PROC PHREG finds a contrast to be nonestimable, it displays missing values in corresponding rows in the results. PROC PHREG handles missing level combinations of categorical variables in the same manner as PROC GLM. Parameters corresponding to missing level combinations are not included in the model. This convention can affect the way in which you specify the **L** matrix in your CONTRAST statement. If the elements of **L** are not specified for an effect that contains a specified effect, then the elements of the specified effect are distributed over the levels of the higher-order effect just as the GLM procedure does for its CONTRAST and ESTIMATE statements. For example, suppose that the model contains effects A and B and their interaction A*B. If you specify a CONTRAST statement involving A alone, the **L** matrix contains nonzero terms for both A and A*B, since A*B contains A.

The Cox model contains no explicit intercept parameter, so it is not valid to specify one in the CONTRAST statement. As a consequence, you can test or estimate only homogeneous linear combinations (those with zero-intercept coefficients, such as contrasts that represent group differences) for the GLM parameterization.

The degrees of freedom are the number of linearly independent constraints implied by the CONTRAST statement—that is, the rank of **L**.

You can specify the following *options* after a slash (/).

ALPHA= *p*
: specifies the level of significance *p* for the $100(1-p)\%$ confidence interval for each contrast when the ESTIMATE option is specified. The value *p* must be between 0 and 1. By default, *p* is equal to the value of the ALPHA= option in the PROC PHREG statement, or 0.05 if that option is not specified.

E
: requests that the **L** matrix be displayed.

ESTIMATE=*keyword*
: requests that each individual contrast (that is, each row, $l_i'\boldsymbol{\beta}$, of $\mathbf{L}\boldsymbol{\beta}$) or exponentiated contrast ($\mathrm{e}^{l_i'\boldsymbol{\beta}}$) be estimated and tested. PROC PHREG displays the point estimate, its standard error, a Wald confidence interval, and a Wald chi-square test for each contrast. The significance level of the confidence interval is controlled by the ALPHA= option. You can estimate the contrast or the exponentiated contrast ($\mathrm{e}^{l_i'\boldsymbol{\beta}}$), or both, by specifying one of the following *keywords*:

PARM	specifies that the contrast itself be estimated.
EXP	specifies that the exponentiated contrast be estimated.
BOTH	specifies that both the contrast and the exponentiated contrast be estimated.

SINGULAR=*number*

tunes the estimability check. This option is ignored when the full-rank parameterization is used. If $\mathbf{v}$ is a vector, define ABS($\mathbf{v}$) to be the largest absolute value of the elements of $\mathbf{v}$. For a row vector $\boldsymbol{l}'$ of the contrast matrix $\mathbf{L}$, define c to be equal to ABS($\boldsymbol{l}$) if ABS($\boldsymbol{l}$) is greater than 0; otherwise, c equals 1. If ABS($\boldsymbol{l}' - \boldsymbol{l}'\mathbf{T}$) is greater than $c * \textit{number}$, then $\boldsymbol{l}$ is declared nonestimable. The $\mathbf{T}$ matrix is the Hermite form matrix $\mathbf{I}_0^-\mathbf{I}_0$, where $\mathbf{I}_0^-$ represents a generalized inverse of the information matrix $\mathbf{I}_0$ of the null model. The value for *number* must be between 0 and 1; the default value is 1E–4.

TEST<(*keywords***)>**

requests a Type 3 test for each contrast. The default is to use the Wald statistic, but you can requests other statistics by specifying one or more of the following *keywords*:

ALL

requests the likelihood ratio tests, the score tests, and the Wald tests. Specifying TEST(ALL) is equivalent to specifying TEST=(LR SCORE WALD).

NONE

suppresses the Type 3 analysis. Even if the TEST option is not specified, PROC PHREG displays the Wald test results for each model effect if a CLASS variable is involved in a MODEL effect. The NONE option can be used to suppress such display.

LR

requests the likelihood ratio tests. This request is not honored if the COVS option is also specified.

SCORE

requests the score tests. This request is not honored if the COVS option is also specified.

WALD

requests the Wald tests.

EFFECT Statement

EFFECT *name*=*effect-type* **(***variables* <**/** *options*>**) ;**

The EFFECT statement enables you to construct special collections of columns for design matrices. These collections are referred to as *constructed effects* to distinguish them from the usual model effects that are formed from continuous or classification variables, as discussed in the section "GLM Parameterization of Classification Variables and Effects" on page 385 in Chapter 19, "Shared Concepts and Topics."

You can specify the following *effect-types*:

COLLECTION specifies a collection effect that defines one or more variables as a single effect with multiple degrees of freedom. The variables in a collection are considered as a unit for estimation and inference.

LAG specifies a classification effect in which the level that is used for a particular period corresponds to the level in the preceding period.

MULTIMEMBER | MM specifies a multimember classification effect whose levels are determined by one or more variables that appear in a CLASS statement.

POLYNOMIAL | POLY specifies a multivariate polynomial effect in the specified numeric variables.

SPLINE specifies a regression spline effect whose columns are univariate spline expansions of one or more variables. A spline expansion replaces the original variable with an expanded or larger set of new variables.

Table 86.5 summarizes the *options* available in the EFFECT statement.

Table 86.5 EFFECT Statement Options

Option	Description
Collection Effects Options	
DETAILS	Displays the constituents of the collection effect
Lag Effects Options	
DESIGNROLE=	Names a variable that controls to which lag design an observation is assigned
DETAILS	Displays the lag design of the lag effect
NLAG=	Specifies the number of periods in the lag
PERIOD=	Names the variable that defines the period. This option is required.
WITHIN=	Names the variable or variables that define the group within which each period is defined. This option is required.
Multimember Effects Options	
NOEFFECT	Specifies that observations with all missing levels for the multimember variables should have zero values in the corresponding design matrix columns
WEIGHT=	Specifies the weight variable for the contributions of each of the classification effects
Polynomial Effects Options	
DEGREE=	Specifies the degree of the polynomial
MDEGREE=	Specifies the maximum degree of any variable in a term of the polynomial
STANDARDIZE=	Specifies centering and scaling suboptions for the variables that define the polynomial
Spline Effects Options	
BASIS=	Specifies the type of basis (B-spline basis or truncated power function basis) for the spline effect
DEGREE=	Specifies the degree of the spline effect
KNOTMETHOD=	Specifies how to construct the knots for the spline effect

For more information about the syntax of these *effect-types* and how columns of constructed effects are computed, see the section "EFFECT Statement" on page 395 in Chapter 19, "Shared Concepts and Topics."

ESTIMATE Statement

ESTIMATE < '*label*' > *estimate-specification* < **(***divisor***=***n***)** >
< **,** < '*label*' > *estimate-specification* < **(***divisor***=***n***)** > > < **,** . . . >
< / *options* > **;**

The ESTIMATE statement provides a mechanism for obtaining custom hypothesis tests. Estimates are formed as linear estimable functions of the form $\mathbf{L}\boldsymbol{\beta}$. You can perform hypothesis tests for the estimable functions, construct confidence limits, and obtain specific nonlinear transformations.

Table 86.6 summarizes *options* available in the ESTIMATE statement. If the BAYES statement is specified, the ADJUST=, STEPDOWN, TESTVALUE, LOWER, UPPER, and JOINT options are ignored. The PLOTS= option is not available for the maximum likelihood analysis. It is available only for the Bayesian analysis.

Table 86.6 ESTIMATE Statement Options

Option	Description
Construction and Computation of Estimable Functions	
DIVISOR=	Specifies a list of values to divide the coefficients
NOFILL	Suppresses the automatic fill-in of coefficients for higher-order effects
SINGULAR=	Tunes the estimability checking difference
Degrees of Freedom and *p*-values	
ADJUST=	Determines the method for multiple comparison adjustment of estimates
ALPHA=α	Determines the confidence level $(1-\alpha)$
LOWER	Performs one-sided, lower-tailed inference
STEPDOWN	Adjusts multiplicity-corrected *p*-values further in a step-down fashion
TESTVALUE=	Specifies values under the null hypothesis for tests
UPPER	Performs one-sided, upper-tailed inference
Statistical Output	
CL	Constructs confidence limits
CORR	Displays the correlation matrix of estimates
COV	Displays the covariance matrix of estimates
E	Prints the **L** matrix
JOINT	Produces a joint *F* or chi-square test for the estimable functions
PLOTS=	Requests ODS statistical graphics if the analysis is sampling-based
SEED=	Specifies the seed for computations that depend on random numbers
Generalized Linear Modeling	
CATEGORY=	Specifies how to construct estimable functions with multinomial data
EXP	Exponentiates and displays estimates

Table 86.6 *continued*

Option	Description
ILINK	Computes and displays estimates and standard errors on the inverse linked scale

For details about the syntax of the ESTIMATE statement, see the section "ESTIMATE Statement" on page 442 in Chapter 19, "Shared Concepts and Topics."

FREQ Statement

FREQ *variable* < / *option* > **;**

The FREQ statement identifies the *variable* (in the input data set) that contains the frequency of occurrence of each observation. PROC PHREG treats each observation as if it appears *n* times, where *n* is the value of the FREQ variable for the observation. If not an integer, the frequency value is truncated to an integer. If the frequency value is missing, the observation is not used in the estimation of the regression parameters.

The following *option* can be specified in the FREQ statement after a slash (/):

NOTRUNCATE

NOTRUNC

specifies that frequency values are not truncated to integers.

HAZARDRATIO Statement

HAZARDRATIO < '*label*' > *variable* < / *options* > **;**

The HAZARDRATIO statement enables you to request hazard ratios for any variable in the model at customized settings. For example, if the model contains the interaction of a CLASS variable A and a continuous variable X, the following specification displays a table of hazard ratios comparing the hazards of each pair of levels of A at X=3:

```
hazardratio A / at (X=3);
```

The HAZARDRATIO statement identifies the variable whose hazard ratios are to be evaluated. If the variable is a continuous variable, the hazard ratio compares the hazards for a given change (by default, a increase of 1 unit) in the variable. For a CLASS variable, a hazard ratio compares the hazards of two levels of the variable. More than one HAZARDRATIO statement can be specified, and an optional label (specified as a quoted string) helps identify the output.

Table 86.7 summarizes the *options* available in the HAZARDRATIO statement.

Table 86.7 HAZARDRATIO Statement Options

Option	Description
ALPHA=	Specifies the alpha level
AT	Specifies the variables that interact with the variable of interest
CL=	Specifies confidence limits
DIFF=	Specifies which differences to consider
E	Displays the log-hazard ratio
PLCONV=	Controls the convergence criterion
PLMAXIT=	Specifies the maximum number of iterations to achieve the convergence
PLSINGULAR=	Specifies the tolerance for testing the singularity
UNITS=	Specifies the units of change

Options for the HAZARDRATIO statement are as follows.

ALPHA=*number*

specifies the alpha level of the interval estimates for the hazard ratios. The value must be between 0 and 1. The default is the value of the ALPHA= option in the PROC PHREG statement, or 0.05 if that option is not specified.

AT (*variable***=ALL | REF |** *list* **< . . .** *variable***=ALL | REF |** *list* **>)**

specifies the variables that interact with the variable of interest and the corresponding values of the interacting variables. If the interacting variable is continuous and a numeric list is specified after the equal sign, hazard ratios are computed for each value in the list. If the interacting variable is a CLASS variable, you can specify, after the equal sign, a list of quoted strings corresponding to various levels of the CLASS variable, or you can specify the keyword ALL or REF. Hazard ratios are computed at each value of the list if the list is specified, or at each level of the interacting variable if ALL is specified, or at the reference level of the interacting variable if REF is specified.

If this option is not specified, PROC PHREG finds all the variables that interact with the variable of interest. If an interacting variable is a CLASS variable, *variable*= ALL is the default; if the interacting variable is continuous, *variable*=*m* is the default, where *m* is the average of all the sampled values of the continuous variable.

Suppose the model contains two interactions: an interaction A*B of CLASS variables A and B, and another interaction A*X of A with a continuous variable X. If 3.5 is the average of the sampled values of X, the following two HAZARDRATIO statements are equivalent:

```
hazardratio A;
hazardratio A / at (B=ALL X=3.5);
```

CL=WALD | PL | BOTH

specifies whether to create the Wald or profile-likelihood confidence limits, or both for the classical analysis. By default, Wald confidence limits are produced. This option is not applicable to a Bayesian analysis.

DIFF=*diff-request*

specifies which differences to consider for the level comparisons of a CLASS variable. This option is ignored in the estimation of hazard ratios for a continuous variable. The *diff-requests* include the following:

DISTINCT

DISTINCTPAIRS

ALL

requests all comparisons of only the distinct combinations of pairs

PAIRWISE

requests all possible pairwise comparisons of levels

REF

requests comparisons between the reference level and all other levels of the CLASS variable.

For example, let A be a CLASS variable with 3 levels (A1, A2, and A3), and A3 is specified as the reference level. The following table depicts the hazard ratios displayed for the three alternatives of the DIFF= option:

	Hazard Ratios Displayed					
DIFF=*option*	**A1 vs A2**	**A2 vs A1**	**A1 vs A3**	**A3 vs A1**	**A2 vs A3**	**A3 vs A2**
DISTINCT	√		√		√	
PAIRWISE	√	√	√	√	√	√
REF			√		√	

The default is DIFF=DISTINCT.

E

displays the vector $\mathbf{h}$ of linear coefficients such that $\mathbf{h}'\boldsymbol{\beta}$ is the log-hazard ratio, with $\boldsymbol{\beta}$ being the vector of regression coefficients.

PLCONV=*value*

controls the convergence criterion for the profile-likelihood confidence limits. The quantity *value* must be a positive number, with a default value of 1E–4. The PLCONV= option has no effect if profile-likelihood confidence intervals (CL=PL) are not requested.

PLMAXIT=*n*

specifies the maximum number of iterations to achieve the convergence of the profile-likelihood confidence limits. By default, PLMAXITER=25. If convergence is not attained in *n* iterations, the corresponding profile-likelihood confidence limit for the hazard ratio is set to missing. The PLMAXITER= option has no effect if profile-likelihood confidence intervals (CL=PL) are not requested.

PLSINGULAR=*value*

specifies the tolerance for testing the singularity of the Hessian matrix in the computation of the profile-likelihood confidence limits. The test requires that a pivot for sweeping this matrix be at least this number times a norm of the matrix. Values of the PLSINGULAR= option must be numeric. By default, *value* is the machine epsilon times 1E7, which is approximately 1E–9. The PLSINGULAR= option has no effect if profile-likelihood confidence intervals (CL=PL) are not requested.

UNITS=*value*
specifies the units of change in the continuous explanatory variable for which the customized hazard ratio is estimated. The default is UNITS=1. This option is ignored in the computation of the hazard ratios for a CLASS variable.

ID Statement

ID *variables* **;**

The ID statement specifies additional variables for identifying observations in the input data. These variables are placed in the OUT= data set created by the OUTPUT statement. In the computation of the COVSANDWICH estimate, you can aggregate over distinct values of these ID variables.

Only variables in the input data set can be included in the ID statement.

LSMEANS Statement

LSMEANS < *model-effects* > < / *options* > **;**

The LSMEANS statement compares least squares means (LS-means) of fixed effects. LS-means are *predicted population margins*—that is, they estimate the marginal means over a balanced population. In a sense, LS-means are to unbalanced designs as class and subclass arithmetic means are to balanced designs.

Table 86.8 summarizes the *options* available in the LSMEANS statement. If the BAYES statement is specified, the ADJUST=, STEPDOWN, and LINES options are ignored. The PLOTS= option is not available for the maximum likelihood analysis. It is available only for the Bayesian analysis.

Table 86.8 LSMEANS Statement Options

Option	Description
Construction and Computation of LS-Means	
AT	Modifies the covariate value in computing LS-means
BYLEVEL	Computes separate margins
DIFF	Requests differences of LS-means
OM=	Specifies the weighting scheme for LS-means computation as determined by the input data set
SINGULAR=	Tunes estimability checking
Degrees of Freedom and *p*-values	
ADJUST=	Determines the method for multiple-comparison adjustment of LS-means differences
ALPHA=α	Determines the confidence level ($1-\alpha$)
STEPDOWN	Adjusts multiple-comparison *p*-values further in a step-down fashion
Statistical Output	
CL	Constructs confidence limits for means and mean differences

Table 86.8 *continued*

Option	Description
CORR	Displays the correlation matrix of LS-means
COV	Displays the covariance matrix of LS-means
E	Prints the **L** matrix
LINES	Produces a "Lines" display for pairwise LS-means differences
MEANS	Prints the LS-means
PLOTS=	Requests graphs of means and mean comparisons
SEED=	Specifies the seed for computations that depend on random numbers
Generalized Linear Modeling	
EXP	Exponentiates and displays estimates of LS-means or LS-means differences
ILINK	Computes and displays estimates and standard errors of LS-means (but not differences) on the inverse linked scale
ODDSRATIO	Reports (simple) differences of least squares means in terms of odds ratios if permitted by the link function

For details about the syntax of the LSMEANS statement, see the section "LSMEANS Statement" on page 458 in Chapter 19, "Shared Concepts and Topics."

LSMESTIMATE Statement

LSMESTIMATE *model-effect* < '*label*' > *values* < *divisor*=*n* >
< , < '*label*' > *values* < *divisor*=*n* > > < , . . . >
< / *options* > ;

The LSMESTIMATE statement provides a mechanism for obtaining custom hypothesis tests among least squares means.

Table 86.9 summarizes the *options* available in the LSMESTIMATE statement. If the BAYES statement is specified, the ADJUST=, STEPDOWN, TESTVALUE, LOWER, UPPER, and JOINT options are ignored. The PLOTS= option is not available for the maximum likelihood analysis. It is available only for the Bayesian analysis.

Table 86.9 LSMESTIMATE Statement Options

Option	Description
Construction and Computation of LS-Means	
AT	Modifies covariate values in computing LS-means
BYLEVEL	Computes separate margins
DIVISOR=	Specifies a list of values to divide the coefficients
OM=	Specifies the weighting scheme for LS-means computation as determined by a data set

Table 86.9 *continued*

Option	Description
SINGULAR=	Tunes estimability checking
Degrees of Freedom and *p*-values	
ADJUST=	Determines the method for multiple-comparison adjustment of LS-means differences
ALPHA=α	Determines the confidence level ($1-\alpha$)
LOWER	Performs one-sided, lower-tailed inference
STEPDOWN	Adjusts multiple-comparison *p*-values further in a step-down fashion
TESTVALUE=	Specifies values under the null hypothesis for tests
UPPER	Performs one-sided, upper-tailed inference
Statistical Output	
CL	Constructs confidence limits for means and mean differences
CORR	Displays the correlation matrix of LS-means
COV	Displays the covariance matrix of LS-means
E	Prints the **L** matrix
ELSM	Prints the **K** matrix
JOINT	Produces a joint *F* or chi-square test for the LS-means and LS-means differences
PLOTS=	Requests graphs of means and mean comparisons
SEED=	Specifies the seed for computations that depend on random numbers
Generalized Linear Modeling	
CATEGORY=	Specifies how to construct estimable functions with multinomial data
EXP	Exponentiates and displays LS-means estimates
ILINK	Computes and displays estimates and standard errors of LS-means (but not differences) on the inverse linked scale

For details about the syntax of the LSMESTIMATE statement, see the section "LSMESTIMATE Statement" on page 477 in Chapter 19, "Shared Concepts and Topics."

MODEL Statement

MODEL *response* < ∗ *censor* **(***list***)** > **=** *effects* < / *options* > **;**

MODEL (*t1***,** *t2***)**< ∗ *censor***(***list***)** > **=** *effects* < / *options* > **;**

The MODEL statement identifies the variables to be used as the failure time variables, the optional censoring variable, and the explanatory effects, including covariates, main effects, interactions, nested effects; for more information, see the section "Specification of Effects" on page 3670 in Chapter 47, "The GLM Procedure."

A note of caution: specifying the effect T*A in the MODEL statement, where T is the time variable and A is a CLASS variable, does not make the effect time-dependent. For more information, see the section "Time and CLASS Variables Usage" on page 6886 for more information.

Two forms of MODEL syntax can be specified; the first form allows one time variable, and the second form allows two time variables for the counting process style of input (for more information, see the section "Counting Process Style of Input" on page 6892).

In the first MODEL statement, the name of the failure time variable precedes the equal sign. This name can optionally be followed by an asterisk, the name of the censoring variable, and a list of censoring values (separated by blanks or commas if there is more than one) enclosed in parentheses. If the censoring variable takes on one of these values, the corresponding failure time is considered to be censored. Following the equal sign are the explanatory effects (sometimes called independent variables or covariates) for the model.

Instead of a single failure-time variable, the second MODEL statement identifies a pair of failure-time variables. Their names are enclosed in parentheses, and they signify the endpoints of a semiclosed interval $(t1, t2]$ during which the subject is at risk. If the censoring variable takes on one of the censoring values, the time $t2$ is considered to be censored.

The censoring variable must be numeric and the failure-time variables must contain nonnegative values. Any observation with a negative failure time is excluded from the analysis, as is any observation with a missing value for any of the variables listed in the MODEL statement. Failure-time variables with a SAS date format are not recommended because the dates might be translated into negative numbers and consequently the corresponding observation would be discarded.

Table 86.10 summarizes the *options* available in the MODEL statement. These *options* can be specified after a slash (/). Four convergence criteria are allowed for the maximum likelihood optimization: ABSFCONV=, FCONV=, GCONV=, and XCONV=. If you specify more than one convergence criterion, the optimization is terminated as soon as one of the criteria is satisfied. If none of the criteria is specified, the default is GCONV=1E–8.

Table 86.10 MODEL Statement Options

Option	Description
Model Specification Options	
EVENTCODE=	Specific the code that represents the event of interest for competing-risks data
NOFIT	Suppresses model fitting
OFFSET=	Specifies offset variable
SELECTION=	Specifies effect selection method
Effect Selection Options	
BEST=	Controls the number of models displayed for best subset selection
DETAILS	Requests detailed results at each step
HIERARCHY=	Specifies whether and how hierarchy is maintained and whether a single effect or multiple effects are allowed to enter or leave the model per step
INCLUDE=	Specifies number of effects included in every model
MAXSTEP=	Specifies maximum number of steps for stepwise selection
SEQUENTIAL	Adds or deletes effects in sequential order

Table 86.10 *continued*

Option	Description
SLENTRY=	Specifies significance level for entering effects
SLSTAY=	Specifies significance level for removing effects
START=	Specifies number of variables in first model
STOP=	Specifies number of variables in final model
STOPRES	Adds or deletes variables by residual chi-square criterion
Maximum Likelihood Optimization Options	
ABSFCONV=	Specifies absolute function convergence criterion
FCONV=	Specifies relative function convergence criterion
FIRTH	Specifies Firth's penalized likelihood method
GCONV=	Specifies relative gradient convergence criterion
XCONV=	Specifies relative parameter convergence criterion
MAXITER=	Specifies maximum number of iterations
RIDGEINIT=	Specifies the initial ridging value
RIDGING=	Specifies the technique to improve the log likelihood function when its value is worse than that of the previous step
SINGULAR=	Specifies tolerance for testing singularity
Confidence Interval Options	
ALPHA=	Specifies α for the $100(1-\alpha)\%$ confidence intervals
PLCONV=	Specifies profile-likelihood convergence criterion
RISKLIMITS=	Computes confidence intervals for hazard ratios
Display Options	
CORRB	Displays correlation matrix
COVB	Displays covariance matrix
ITPRINT	Displays iteration history
NODUMMYPRINT	Suppresses "Class Level Information" table
TYPE1	Displays Type 1 analysis
TYPE3	Displays Type 3 tests or joint tests of effects
Miscellaneous Options	
ENTRYTIME=	Specifies the delayed entry time variable
ROCLABEL=	Specifies a label to identify the model that is specified in the MODEL statement model for an ROC analysis
TIES=	Specifies the method of handling ties in failure times

ALPHA=*value*

sets the significance level used for the confidence limits for the hazard ratios. The quantity *value* must be between 0 and 1. The default is the value of the ALPHA= option in the PROC PHREG statement, or 0.05 if that option is not specified. This option has no effect unless the RISKLIMITS option is specified.

ABSFCONV=*value*

CONVERGELIKE=*value*

specifies the absolute function convergence criterion. Termination requires a small change in the objective function (log partial likelihood function) in subsequent iterations,

$$|l_k - l_{k-1}| < value$$

where l_k is the value of the objective function at iteration k.

BEST=*n*

is used exclusively with the best subset selection (SELECTION=SCORE). The BEST=*n* option specifies that *n* models with the highest-score chi-square statistics are to be displayed for each model size. If the option is omitted and there are no more than 10 explanatory variables, then all possible models are listed for each model size. If the option is omitted and there are more than 10 explanatory variables, then the number of models selected for each model size is, at most, equal to the number of explanatory variables listed in the MODEL statement.

See Example 86.2 for an illustration of the best subset selection method and the BEST= option.

CORRB

displays the estimated correlation matrix of the parameter estimates.

COVB

displays the estimated covariance matrix of the parameter estimates.

DETAILS

produces a detailed display at each step of the model-building process. It produces an "Analysis of Variables Not in the Model" table before displaying the variable selected for entry for forward or stepwise selection. For each model fitted, it produces the "Analysis of Maximum Likelihood Estimates" table.

See Example 86.1 for a discussion of these tables.

ENTRYTIME=*variable*

ENTRY=*variable*

specifies the name of the variable that represents the left-truncation time. This option has no effect when the counting process style of input is specified. For more information, see the section "Left-Truncation of Failure Times" on page 6893.

EVENTCODE=*number*

FAILCODE=*number*

specifies the number that represents the event of interest for the competing-risks analysis of Fine and Gray (1999). For example:

```
model T*Status(0 1)= X1-X5 / eventcode=2;
```

This specifies that a subject whose Status value is 2 has the event of interest, a subject whose Status value is 0 or 1 is a censored observation, and a subject that has another value of the Status variable has a competing event.

FCONV=*value*

specifies the relative function convergence criterion. Termination requires a small relative change in the objective function (log partial likelihood function) in subsequent iterations,

$$\frac{|l_k - l_{k-1}|}{|l_{k-1}| + 1\mathrm{E}-6} < \textit{value}$$

where l_k is the value of the objective function at iteration k.

FIRTH

performs Firth's penalized maximum likelihood estimation to reduce bias in the parameter estimates (Heinze and Schemper 2001; Firth 1993). This method is useful when the likelihood is monotone—that is, the likelihood converges to finite value while at least one estimate diverges to infinity.

GCONV=*value*

specifies the relative gradient convergence criterion. Termination requires that the normalized prediction function reduction is small,

$$\frac{\mathbf{g}_k \mathbf{H}_k^{-1} \mathbf{g}_k}{|l_k| + 1\mathrm{E}-6} < \textit{value}$$

where l_k is the log partial likelihood, $\mathbf{g}_k$ is the gradient vector (first partial derivatives of the log partial likelihood), and $\mathbf{H}_k$ is the negative Hessian matrix (second partial derivatives of the log partial likelihood), all at iteration k.

HIERARCHY=*keyword*

HIER=*keyword*

specifies whether and how the model hierarchy requirement is applied and whether a single effect or multiple effects are allowed to enter or leave the model in one step. You can specify that only CLASS variable effects, or both CLASS and continuous variable effects, be subject to the hierarchy requirement. The HIERARCHY= option is ignored unless you also specify the forward, backward, or stepwise selection method.

Model hierarchy refers to the requirement that, for any term to be in the model, all effects contained in the term must be present in the model. For example, in order for the interaction A*B to enter the model, the main effects A and B must be in the model. Likewise, neither effect A nor B can leave the model while the interaction A*B is in the model.

You can specify any of the following *keywords* in the HIERARCHY= option:

NONE

indicates that the model hierarchy is not maintained. Any single effect can enter or leave the model at any given step of the selection process.

SINGLE

indicates that only one effect can enter or leave the model at one time, subject to the model hierarchy requirement. For example, suppose that you specify the main effects A and B and the interaction of A*B in the model. In the first step of the selection process, either A or B can enter the model. In the second step, the other main effect can enter the model. The interaction effect can enter the model only when both main effects have already been entered. Also, before A or B can be removed from the model, the A*B interaction must first be removed. All effects (CLASS and continuous variables) are subject to the hierarchy requirement.

SINGLECLASS
is the same as HIERARCHY=SINGLE except that only CLASS effects are subject to the hierarchy requirement.

MULTIPLE
indicates that more than one effect can enter or leave the model at one time, subject to the model hierarchy requirement. In a forward selection step, a single main effect can enter the model, or an interaction can enter the model together with all the effects that are contained in the interaction. In a backward elimination step, an interaction itself, or the interaction together with all the effects that the interaction contains, can be removed. All effects (CLASS and continuous variable) are subject to the hierarchy requirement.

MULTIPLECLASS
is the same as HIERARCHY=MULTIPLE except that only CLASS effects are subject to the hierarchy requirement.

The default value is HIERARCHY=SINGLE, which means that model hierarchy is to be maintained for all effects (that is, both CLASS and continuous variable effects) and that only a single effect can enter or leave the model at each step.

INCLUDE=*n*
includes the first *n* effects in the MODEL statement in every model. By default, INCLUDE=0. The INCLUDE= option has no effect when SELECTION=NONE.

ITPRINT
displays the iteration history, including the last evaluation of the gradient vector.

MAXITER=*n*
specifies the maximum number of iterations allowed. The default value for *n* is 25. If convergence is not attained in *n* iterations, the displayed output and all data sets created by PROC PHREG contain results that are based on the last maximum likelihood iteration.

MAXSTEP=*n*
specifies the maximum number of times the explanatory variables can move in and out of the model before the stepwise model-building process ends. The default value for *n* is twice the number of explanatory variables in the MODEL statement. The option has no effect for other model selection methods.

NODUMMYPRINT

NODESIGNPRINT

NODP
suppresses the "Class Level Information" table, which shows how the design matrix columns for the CLASS variables are coded.

NOFIT
performs the global score test, which tests the joint significance of all the explanatory variables in the MODEL statement. No parameters are estimated. If the NOFIT option is specified along with other MODEL statement options, NOFIT takes precedence, and all other options are ignored except the TIES= option.

OFFSET=*name*
specifies the name of an offset variable, which is an explanatory variable with a regression coefficient fixed as one. This option can be used to incorporate risk weights for the likelihood function.

PLCONV=*value*
controls the convergence criterion for confidence intervals based on the profile-likelihood function. The quantity *value* must be a positive number, with a default value of 1E–4. The PLCONV= option has no effect if profile-likelihood based confidence intervals are not requested.

RIDGING=*keyword*
specifies the technique to improve the log likelihood when its value is worse than that of the previous step. The available *keywords* are as follows:

ABSOLUTE
specifies that the diagonal elements of the negative (expected) Hessian be inflated by adding the ridge value.

RELATIVE
specifies that the diagonal elements be inflated by the factor equal to 1 plus the ridge value.

NONE
specifies the crude line-search method of taking half a step be used instead of ridging.

The default is RIDGING=RELATIVE.

RIDGEINIT=*value*
specifies the initial ridge value. The maximum ridge value is 2000 times the maximum of 1 and the initial ridge value. The initial ridge value is raised to 1E–4 if it is less than 1E–4. By default, RIDGEINIT=1E–4. This option has no effect for RIDGING=ABSOLUTE.

RISKLIMITS< =*keyword* **>**
RL< =*keyword* **>**
produces confidence intervals for hazard ratios of main effects not involved in interactions or nestings. Computation of these confidence intervals is based on the profile likelihood or based on individual Wald tests. The confidence coefficient can be specified with the ALPHA= option. You can specify one of the following *keywords*:

PL
requests profile-likelihood confidence limits.

WALD
requests confidence limits based on the Wald tests.

BOTH
request both profile-likelihood and Wald confidence limits.

Classification main effects that use parameterizations other than REF, EFFECT, or GLM are ignored. If you need to compute hazard ratios for an effect involved in interactions or nestings, or using some other parameterization, then you should specify a HAZARDRATIO statement for that effect.

ROCLABEL='*label***'**
specifies a label to identify the model that is specified in the MODEL statement (or the final model if a selection method is used) when a concordance analysis or an ROC analysis is conducted. By default, ROCLABEL='Model'.

SELECTION=*method*
specifies the method used to select the model. The *methods* available are as follows:

BACKWARD

B
requests backward elimination.

FORWARD

F
requests forward selection.

NONE

N
fits the complete model specified in the MODEL statement. This is the default value.

SCORE
requests best subset selection. It identifies a specified number of models with the highest-score chi-square statistic for all possible model sizes ranging from one explanatory variable to the total number of explanatory variables listed in the MODEL statement. This option is not allowed if an explanatory effect in the MODEL statement contains a CLASS variable.

STEPWISE

S
requests stepwise selection.

For more information, see the section "Effect Selection Methods" on page 6940.

SEQUENTIAL
forces variables to be added to the model in the order specified in the MODEL statement or to be eliminated from the model in the reverse order of that specified in the MODEL statement.

SINGULAR=*value*
specifies the singularity criterion for determining linear dependencies in the set of explanatory variables. The default value is 1E–12.

SLENTRY=*value*

SLE=*value*
specifies the significance level (a value between 0 and 1) for entering an explanatory variable into the model in the FORWARD or STEPWISE method. For all variables not in the model, the one with the smallest *p*-value is entered if the *p*-value is less than or equal to the specified significance level. The default value is 0.05.

SLSTAY=*value*

SLS=*value*

specifies the significance level (a value between 0 and 1) for removing an explanatory variable from the model in the BACKWARD or STEPWISE method. For all variables in the model, the one with the largest *p*-value is removed if the *p*-value exceeds the specified significance level. The default value is 0.05.

START=*n*

begins the FORWARD, BACKWARD, or STEPWISE selection process with the first *n* effects listed in the MODEL statement. The value of *n* ranges from 0 to *s*, where *s* is the total number of effects in the MODEL statement. The default value of *n* is *s* for the BACKWARD method and 0 for the FORWARD and STEPWISE methods. Note that START=*n* specifies only that the first *n* effects appear in the first model, while INCLUDE=*n* requires that the first *n* effects be included in every model. For the SCORE method, START=*n* specifies that the smallest models contain *n* effects, where *n* ranges from 1 to *s*; the default value is 1. The START= option has no effect when SELECTION=NONE.

STOP=*n*

specifies the maximum (FORWARD method) or minimum (BACKWARD method) number of effects to be included in the final model. The effect selection process is stopped when *n* effects are found. The value of *n* ranges from 0 to *s*, where *s* is the total number of effects in the MODEL statement. The default value of *n* is *s* for the FORWARD method and 0 for the BACKWARD method. For the SCORE method, STOP=*n* specifies that the smallest models contain *n* effects, where *n* ranges from 1 to *s*; the default value of *n* is *s*. The STOP= option has no effect when SELECTION=NONE or STEPWISE.

STOPRES

SR

specifies that the addition and deletion of variables be based on the result of the likelihood score test for testing the joint significance of variables not in the model. This score chi-square statistic is referred to as the residual chi-square. In the FORWARD method, the STOPRES option enters the explanatory variables into the model one at a time until the residual chi-square becomes insignificant (that is, until the *p*-value of the residual chi-square exceeds the SLENTRY= value). In the BACKWARD method, the STOPRES option removes variables from the model one at a time until the residual chi-square becomes significant (that is, until the *p*-value of the residual chi-square becomes less than the SLSTAY= value). The STOPRES option has no effect for the STEPWISE method.

TYPE1

requests that a Type 1 (sequential) analysis of likelihood ratio test be performed. This consists of sequentially fitting models, beginning with the null model and continuing up to the model specified in the MODEL statement. The likelihood ratio statistic for each successive pair of models is computed and displayed in a table.

TYPE3 < (*keywords***) >**

requests a Type 3 test or a joint test for each effect that is specified in the MODEL statement. For more information, see the section "Type 3 Tests and Joint Tests" on page 6907. The default is to use the Wald statistic, but you can requests other statistics by specifying one or more of the following *keywords*:

ALL

requests the likelihood ratio tests, the score tests, and the Wald tests. Specifying TYPE3(ALL) is equivalent to specifying TYPE3=(LR SCORE WALD).

NONE
suppresses the Type 3 analysis. Even if the TYPE3 option is not specified, PROC PHREG displays the Wald test results for each model effect if a CLASS variable is involved in a MODEL effect. The NONE option can be used to suppress such display.

LR
requests the likelihood ratio tests. This request is not honored if the COVS option is also specified.

SCORE
requests the score tests. This request is not honored if the COVS option is also specified.

WALD
requests the Wald tests.

TIES=*method*
specifies how to handle ties in the failure time. The following *methods* are available:

BRESLOW
uses the approximate likelihood of Breslow (1974). This is the default value.

DISCRETE
replaces the proportional hazards model by the discrete logistic model

$$\frac{\lambda(t;\mathbf{z})}{1-\lambda(t;\mathbf{z})} = \frac{\lambda_0(t)}{1-\lambda_0(t)}\exp(\mathbf{z}'\boldsymbol{\beta})$$

where $\lambda_0(t)$ and $h(t;\mathbf{z})$ are discrete hazard functions.

EFRON
uses the approximate likelihood of Efron (1977).

EXACT
computes the exact conditional probability under the proportional hazards assumption that all tied event times occur before censored times of the same value or before larger values. This is equivalent to summing all terms of the marginal likelihood for $\boldsymbol{\beta}$ that are consistent with the observed data (Kalbfleisch and Prentice 1980; DeLong, Guirguis, and So 1994).

TIES=EXACT can take a considerable amount of computer resources. If ties are not extensive, TIES=EFRON and TIES=BRESLOW methods provide satisfactory approximations to TIES=EXACT for the continuous time-scale model. In general, Efron's approximation gives results that are much closer to the exact method results than Breslow's approximation does. If the time scale is genuinely discrete, you should use TIES=DISCRETE. TIES=DISCRETE is also required in the analysis of case-control studies when there is more than one case in a matched set. If there are no ties, all four methods result in the same likelihood and yield identical estimates. The default, TIES=BRESLOW, is the most efficient method when there are no ties.

XCONV=*value*

CONVEREPARM=*value*
specifies the relative parameter convergence criterion. Termination requires a small relative parameter change in subsequent iterations,

$$\max_i |\delta_k^{(i)}| < value$$

where

$$\delta_k^{(i)} = \begin{cases} \theta_k^{(i)} - \theta_{k-1}^{(i)} & |\theta_{k-1}^{(i)}| < .01 \\ \frac{\theta_k^{(i)} - \theta_{k-1}^{(i)}}{\theta_{k-1}^{(i)}} & \text{otherwise} \end{cases}$$

where $\theta_k^{(i)}$ is the estimate of the ith parameter at iteration k.

OUTPUT Statement

OUTPUT < **OUT=***SAS-data-set*> < *keyword*=*name* . . . *keyword*=*name*> < / *option*> ;

The OUTPUT statement creates a new SAS data set that contains all the variables in the input data set and optionally contains variables for the estimated linear predictor and its standard error estimate, survival estimates, residuals, and influence statistics.

The estimated linear predictor and its standard error estimate are computed for all observations in which the explanatory variables have no missing values, even if the observed time is missing; if the observed time is not missing, the predicted probability is computed at the observed time. By adding observations that have a missing censoring indicator to the input data set, you can compute predicted probabilities for new observations or for settings of explanatory variables and observed times that are not present in the data without affecting the model. Alternatively, you can use the BASELINE statement to compute predicted survival probabilities for new observations.

No data set is created for the OUTPUT statement if the model contains any time-dependent variables that are defined by programming statements.

Table 86.11 summarizes the options available in the OUTPUT statement. The statistic and diagnostic *keywords* specify the statistics to be included in the output data set and name the new variables that contain the statistics.

Table 86.11 OUTPUT Statement Options

Option	Description
METHOD=	Specifies the method to use to estimate the survival probabilities
OUT=	Names the output data set
Statistic Keywords	
ATRISK=	Names the variable that contains the number of subjects at risk
CIF=	Names the variable that contains the cumulative incidence probability
LOGLOGS=	Names the variable that contains the log of the negative log of survival probability
LOGSURVS=	Names the variable that contains the log of survival probability
XBETA=	Names the variable that contains the linear predictor
STDXBETA=	Names the variable that contains standard error of the linear predictor
SURVIVAL=	Names the variable that contains the survival probability

Table 86.11 *continued*

Option	Description
Diagnostic Keywords	
DFBETA=	Requests the standardized deletion parameter differences
LD=	Names the variable that contains the likelihood displacement diagnostic
LMAX=	Names the variable that contains the relative influence diagnostic
RESDEV=	Names the variable that contains the deviance residuals
RESMART=	Names the variable that contains the martingale residuals
RESSCH=	Requests the Schoenfeld residuals
RESSCO=	Requests the score residuals
WTRESSCH=	Requests the weighted Schoenfeld residuals

OUT=*SAS-data-set*

names the output data set. If you omit the OUT= option, the OUTPUT data set is created and given a default name by using the DATA*n* convention. For more information, see the section "OUT= Output Data Set in the OUTPUT Statement" on page 6957.

METHOD=*method*

specifies the method used to compute the survivor function estimates. For more information, see the section "Survivor Function Estimators" on page 6932. This option appears in the OUTPUT statement after a slash (/). You can specify the following *methods*:

BRESLOW

CH

EMP

computes the cumulative hazard function estimate of the survivor function; that is, the survivor function is estimated by exponentiating the negative cumulative hazard function.

FH

computes the Fleming-Harrington (FH) estimates of the survivor function. The FH estimator is a tie-breaking modification of the Breslow estimator. If there are no tied event times, this estimator is the same as the Breslow estimator.

PL

computes the product-limit estimates of the survivor function. This estimator is not available if you use the model syntax that allows two time variables for the counting process style of input; in such a case, the Breslow estimator (METHOD=BRESLOW) is used instead.

By default, METHOD=BRESLOW.

The following list describes the statistic and diagnostic *keywords*:

ATRISK=*name*

names the variable that contains the number of subjects at risk at the observed time (or at the right endpoint of the at-risk interval when a counting-process specification is used in the MODEL statement, as described in the section "Counting Process Style of Input" on page 6892).

CIF=*name*
names the variable that contains the cumulative incidence probabilities at the observed times. For more information, see the section "Cumulative Incidence Prediction" on page 6900.

DFBETA=_ALL_ |*name-list*
requests the approximate changes in the parameter estimates ($\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}_{(j)}$) when the *j*th observation is omitted. These variables are a weighted transform of the score residual variables and are useful in assessing local influence and in computing robust variance estimates. You can specify this option in one of the following ways:

name-list specifies up to *s* variable names, where *s* is the number of regression parameters of the model that is specified in the MODEL statement. The first variable contains the changes in the first regression parameter, the second variable contains the changes for the second regression parameter, and so on.

ALL requests the changes for all parameters and names them DFBETA_*xxx*, where *xxx* is the name of the model regression parameter that is formed from the input variable names (concatenated with the appropriate categories if a classification variable is used). For example, suppose that the model contains a continuous variable X and a CLASS variable Gender with two levels ("Female" and "Male") and that Gender has a GLM parameterization. Three statistics are produced: DFBETA_X, DFBETA_GenderFemale, and DFBETA_GenderMale.

If an effect that is specified in the MODEL statement is not included in the final model, the corresponding statistics are set to missing. For more information, see the section "Diagnostics Based on Weighted Residuals" on page 6924.

LD=*name*
names the variable that contains the approximate likelihood displacement when the observation is left out. This diagnostic can be used to assess the impact of each observation on the overall fit of the model. For more information, see the section "Influence of Observations on Overall Fit of the Model" on page 6925.

LMAX=*name*
names the variable that contains the relative influence of observations on the overall fit of the model. This diagnostic is useful in assessing the sensitivity of the model's fit to each observation. For more information, see the section "Influence of Observations on Overall Fit of the Model" on page 6925.

LOGLOGS=*name*
names the variable that contains the log of the negative log of the variable named in the SURVIVAL= option.

LOGSURV=*name*
names the variable that contains the log of variable named in the SURVIVAL= option.

RESDEV=*name*
names the variable that contains the deviance residuals. This variable is a transform of the variable named in the RESMART= option and can achieve a more symmetric distribution. For more information, see the section "Residuals" on page 6921.

RESMART=*name*

names the variable that contains the martingale residuals. The martingale residual at the observed time t can be interpreted as the difference over $[0, t]$ in the observed number of events minus the expected number of events. For more information, see the section "Residuals" on page 6921.

RESSCH=_ALL_ | *name-list*

requests Schoenfeld residuals, which are useful in assessing the proportional hazards assumption. Schoenfeld residuals are computed only at uncensored times and are missing for censored times. You can specify this option in one of the following ways:

name-list specifies up to s variable names, where s is the number of regression parameters of the model that is specified in the MODEL statement. The first variable contains the Schoenfeld residuals for the first regression parameter, the second variable contains the Schoenfeld residuals for the second regression parameter, and so on.

ALL requests Schoenfeld residuals for all regression parameters and names them RESSCH_*xxx*, where *xxx* is the name of the model regression parameter that is formed from the input variable names (concatenated with the appropriate categories if a classification variable is used). For example, suppose that the model contains a continuous variable X and a CLASS variable Gender with two levels ("Female" and "Male") and that Gender has a GLM parameterization. Three statistics are produced: RESSCH_X, RESSCH_GenderFemale, and RESSCH_GenderMale.

If an effect in the MODEL statement is not included in the final model, the corresponding Schoenfeld residuals are set to missing. For more information, see the section "Residuals" on page 6921.

RESSCO=_ALL_ | *name-list*

requests the score residuals, which are a decomposition of the first partial derivative of the log likelihood. These residuals can be used to assess the leverage that is exerted by each subject in the parameter estimates. They are also useful in constructing robust sandwich variance estimates. You can specify this option in one of the following ways:

name-list specifies up to s variable names, where s is the number of regression parameters of the model that is specified in the MODEL statement. The first variable contains the score residuals for the first regression parameter, the second variable contains the score residuals for the second parameter, and so on.

ALL requests score residuals for all regression parameters and names them RESSCO_*xxx*, where *xxx* is the name of the model regression parameter that is formed from the input variable names (concatenated with the appropriate categories if a classification variable is used). For example, suppose that the model contains a continuous variable X and a CLASS variable Gender with two levels ("Female" and "Male") and that Gender has a GLM parameterization. Three statistics are produced: RESSCO_X, RESSCO_GenderFemale, and RESSCO_GenderMale.

If an effect in the MODEL statement is not included in the final model, the corresponding score residuals are set to missing. For more information, see the section "Residuals" on page 6921.

STDXBETA=*name*
names the variable that contains the standard error estimates of linear predictor that is specified in the XBETA= option.

SURVIVAL=*name*
names the variable that contains the predicted survival probabilities at the observed times. For more information, see the section "Survivor Function Estimators" on page 6932.

WTRESSCH=_ALL_ | *name-list*
requests the weighted Schoenfeld residuals, which are useful in investigating the nature of nonproportionality if the proportional hazard assumption does not hold. You can specify this option in one of the following ways:

name-list specifies up to *s* variable names, where *s* is the number of regression parameters of the model that is specified in the MODEL statement. The first variable contains the weighted Schoenfeld residuals for the first regression parameter, the second variable contains the weighted Schoenfeld residuals for the second regression parameter, and so on.

ALL requests weighted Schoenfeld residuals for all regression parameters and names them WTRESSCH_*xxx*, where *xxx* is the name of the model regression parameter that is formed from the input variable names (concatenated with the appropriate categories if a classification variable is used). For example, suppose that the model contains a continuous variable X and a CLASS variable Gender with two levels ("Female" and "Male") and that Gender has a GLM parameterization. Three statistics are produced: WTRESSCH_X, WTRESSCH_GenderFemale, and WTRESSCH_GenderMale.

If an effect in the MODEL statement is not included in the final model, the corresponding weighted Schoenfeld residuals are set to missing. For more information, see the section "Diagnostics Based on Weighted Residuals" on page 6924.

XBETA=*name*
names the variable that contains the estimates of the linear predictor.

Programming Statements

Programming statements are used to create or modify the values of the explanatory variables in the MODEL statement. They are especially useful in fitting models with time-dependent explanatory variables. Programming statements can also be used to create explanatory variables that are not time dependent. For example, you can create indicator variables from a categorical variable and incorporate them into the model. PROC PHREG programming statements cannot be used to create or modify the values of the response variable, the censoring variable, the frequency variable, or the strata variables.

The following DATA step statements are available in PROC PHREG:

ABORT;
ARRAY *arrayname* < **[** *dimensions* **]** > < **$** > < *variables-and-constants* >**;**
CALL *name* < **(***expression* < **,** *expression . . .* >**)** >**;**
DELETE;
DO < *variable* **=** *expression* < **TO** *expression* > < **BY** *expression* > >
    < **,** *expression* < **TO** *expression* > < **BY** *expression* > > . . .
    < **WHILE** *expression* > < **UNTIL** *expression* >**;**
END;
GOTO *statement-label***;**
IF *expression***;**
IF *expression* **THEN** *program-statement***;**
                ELSE *program-statement***;**
variable **=** *expression***;**
variable **+** *expression***;**
LINK *statement-label***;**
PUT < *variable* > < **=** > . . . **;**
RETURN;
SELECT < **(***expression***)** >**;**
STOP;
SUBSTR(*variable***,** *index***,** *length***)=** *expression***;**
WHEN (*expression***)***program-statement***;**
        OTHERWISE *program-statement***;**

By default, the PUT statement in PROC PHREG writes results to the Output window instead of the Log window. If you want the results of the PUT statements to go to the Log window, add the following statement before the PUT statements:

```
FILE LOG;
```

DATA step functions are also available. Use these programming statements the same way you use them in the DATA step. For detailed information, see *SAS Statements: Reference*.

Consider the following example of using programming statements in PROC PHREG. Suppose blood pressure is measured at multiple times during the course of a study investigating the effect of blood pressure on some survival time. By treating the blood pressure as a time-dependent explanatory variable, you are able to use the value of the most recent blood pressure at each specific point of time in the modeling process rather than using the initial blood pressure or the final blood pressure. The values of the following variables are recorded for each patient, if they are available. Otherwise, the variables contain missing values.

Time	survival time
Censor	censoring indicator (with 0 as the censoring value)
BP0	blood pressure on entry to the study
T1	time 1
BP1	blood pressure at T1
T2	time 2
BP2	blood pressure at T2

The following programming statements create a variable BP. At each time T, the value of BP is the blood pressure reading for that time, if available. Otherwise, it is the last blood pressure reading.

```
proc phreg;
   model Time*Censor(0)=BP;
   BP = BP0;
   if Time>=T1 and T1^=. then BP=BP1;
   if Time>=T2 and T2^=. then BP=BP2;
run;
```

For other illustrations of using programming statements, see the section "Classical Method of Maximum Likelihood" on page 6814 and Example 86.6.

RANDOM Statement

RANDOM *variable* < / *options* > **;**

The RANDOM statement enables you to fit a shared frailty model for clustered data. For more information about the frailty model, see the section "The Frailty Model" on page 6896. The *variable* that represents the clusters must be a CLASS variable (declared in the CLASS statement).

The following *options* can be specified in the RANDOM statement:

ABSPCONV=*r*

specifies an absolute variance estimate convergence criterion for the doubly iterative estimation process. The PHREG procedure applies this criterion to the variance parameter estimate of the random effects. Suppose $\hat{\theta}^{(j)}$ denotes the estimate of the variance parameter at the *j*th optimization. By default, PROC PHREG examines the relative change in the variance estimate between optimizations (see the PCONV= option). The purpose of the ABSPCONV= criterion is to stop the doubly iterative process when the absolute change $|\hat{\theta}^{(j)} - \hat{\theta}^{(j-1)}|$ is less than the tolerance criterion *r*. This convergence criterion does not affect the convergence criteria applied within any individual optimization. In order to change the convergence behavior within an individual optimization, you can use the ABSCONV=, ABSFCONV=, ABSGCONV=, ABSXCONV=, FCONV=, or GCONV= option in the NLOPTIONS statement.

ALPHA=*value*

specifies the α level of the confidence limits for the random effects. The default is the value of the ALPHA= option in the PROC PHREG statement, or 0.05 if that option is not specified. This option is ignored if the SOLUTION option is not also specified.

DIST=GAMMA | LOGNORMAL

specifies the distribution of the shared frailty. DIST=GAMMA specifies a gamma frailty model. DIST=LOGNORMAL specifies a lognormal frailty model; that is, the log-frailty random variable has a normal distribution with mean zero. The default is DIST=LOGNORMAL.

METHOD=REML | ML

specifies the estimation method for the variance parameter of the normal random effects. METHOD=REML performs the residual maximum likelihood; METHOD=ML performs maximum likelihood. This option is ignored for the gamma frailty model. The default is METHOD=REML.

NOCLPRINT

suppresses the display of the "Class Level Information for Random Effects" table.

PCONV=*r*

specifies the variance estimate convergence criterion for the doubly iterative estimation process. The PHREG procedure applies this criterion to the variance estimate of the random effects. Suppose $\hat{\theta}^{(j)}$ denotes the estimate of variance at the *j*th optimization. The procedure terminates the doubly iterative process if the relative change

$$2 \times \frac{|\hat{\theta}^{(j)} - \hat{\theta}^{(j-1)}|}{|\hat{\theta}^{(j)}| + |\hat{\theta}^{(j-1)}|}$$

is less than *r*. To check an absolute convergence criterion in addition, you can specify the ABSPCONV= option in the RANDOM statement. The default value for *r* is 1E–4. This convergence criterion does not affect the convergence criteria applied within any individual optimization. In order to change the convergence behavior within an individual optimization, you can use the ABSCONV=, ABSFCONV=, ABSGCONV=, ABSXCONV=, FCONV=, or GCONV= option in the NLOPTIONS statement.

SOLUTION <(*number-list***)>**

displays statistical measures of the random-effect parameters. The behavior of this option depends on whether you also specify the BAYES statement:

- When you do not specify a BAYES statement, this option displays point estimates and confidence intervals for the random components and for the frailties.
- When you also specify a BAYES statement, this option displays the summary statistics and diagnostics of the random-effect parameters. Optionally, you can specify a *number-list* of indices of the random-effect parameters for which the summary statistics and diagnostics are to be displayed. For example, to display the summary statistics and diagnostics for the second to the fifth random-effect parameters, specify

```
SOLUTION(2 to 5)
```

If you specify SOLUTION without a list, summary statistics and diagnostics are displayed for each random-effect parameter.

INITIALVARIANCE=*value*

INITIAL=*value*

specifies an initial value of the dispersion parameter. For the lognormal frailty model, the dispersion parameter represents the variance of the normal random effect; for the gamma frailty model, it represents the variance of the gamma frailty. The default is INITIAL=1.

ROC Statement

ROC <'*label*'> *specification* **;**

The ROC statement specifies a model to be used in the concordance analysis or ROC analysis. There is no limit to the number of ROC statements that you can have. You can specify a *label* in quotation marks to identify an ROC statement. If you do not specify a *label*, the model in the *i*th ROC statement is labeled "ROC*i*".

You can specify one of the following *specifications*:

effect-list
specifies a list of effects that have previously been specified in the MODEL statement.

PRED=*variable*
specifies a *variable* in the input data set. The *variable* does not have to be specified in the MODEL statement. For an example, see Example 86.16.

SOURCE=*item-store-name*
specifies a one- or two-level name of an existing item store.

The PRED= option and the SOURCE= option enable you to input a model that is produced outside PROC PHREG; for example, you can fit a parametric survival model by using PROC LIFEREG, save the model in an item store, and then specify the item-store name in the SOURCE= option in a ROC statement to produce an ROC analysis of the imported model.

STRATA Statement

STRATA *variable* < **(***list***)** > < *. . . variable* < **(***list***)** > > < */ option* > **;**

The proportional hazards assumption might not be realistic for all data. If so, it might still be reasonable to perform a stratified analysis. The STRATA statement names the variables that determine the stratification. Strata are formed according to the nonmissing values of the STRATA variables unless the MISSING option is specified. In the STRATA statement, *variable* is a variable with values that are used to determine the strata levels, and *list* is an optional list of values for a numeric variable. Multiple variables can appear in the STRATA statement.

The values for *variable* can be formatted or unformatted. If the variable is a character variable, or if the variable is numeric and no list appears, then the strata are defined by the unique values of the variable. If the variable is numeric and is followed by a list, then the levels for that variable correspond to the intervals defined by the list. The corresponding strata are formed by the combination of levels and unique values. The list can include numeric values separated by commas or blanks, *value* to *value* by *value* range specifications, or combinations of these.

For example, the specification

```
strata age (5, 10 to 40 by 10) sex;
```

indicates that the levels for age are to be less than 5, 5 to 10, 10 to 20, 20 to 30, 30 to 40, and greater than 40. (Note that observations with exactly the cutpoint value fall into the interval preceding the cutpoint.) Thus, with the sex variable, this STRATA statement specifies 12 strata altogether.

The following *option* can be specified in the STRATA statement after a slash (/):

MISSING
allows missing values (‘.’ for numeric variables and blanks for character variables) as valid STRATA variable values. Otherwise, observations with missing STRATA variable values are deleted from the analysis.

SLICE Statement

SLICE *model-effect* < / *options* > **;**

The SLICE statement provides a general mechanism for performing a partitioned analysis of the LS-means for an interaction. This analysis is also known as an analysis of simple effects.

The SLICE statement uses the same *options* as the LSMEANS statement, which are summarized in Table 19.21. For details about the syntax of the SLICE statement, see the section "SLICE Statement" on page 506 in Chapter 19, "Shared Concepts and Topics."

STORE Statement

STORE < **OUT=** >*item-store-name* < / **LABEL=**'*label*' > **;**

The STORE statement requests that the procedure save the context and results of the statistical analysis. The resulting item store has a binary file format that cannot be modified. The contents of the item store can be processed with the PLM procedure. For details about the syntax of the STORE statement, see the section "STORE Statement" on page 509 in Chapter 19, "Shared Concepts and Topics."

TEST Statement

< *label* **:** > **TEST** *equation* < **,** . . . **,** *equation* > < / *options* > **;**

The TEST statement tests linear hypotheses about the regression coefficients. PROC PHREG performs a Wald test for the joint hypothesis specified in a single TEST statement. Each equation specifies a linear hypothesis; multiple equations (rows of the joint hypothesis) are separated by commas. The *label*, which must be a valid SAS name, is used to identify the resulting output and should always be included. You can submit multiple TEST statements.

The form of an *equation* is as follows:

term < ± *term* . . . > <= < ± *term* < ± *term* . . . >>>

where *term* is a variable or a constant or a constant times a variable. The variable is any explanatory variable in the MODEL statement. When no equal sign appears, the expression is set to 0. The following program illustrates possible uses of the TEST statement:

```
proc phreg;
   model time= A1 A2 A3 A4;
   Test1: test A1, A2;
   Test2: test A1=0,A2=0;
   Test3: test A1=A2=A3;
   Test4: test A1=A2,A2=A3;
run;
```

Note that the first and second TEST statements are equivalent, as are the third and fourth TEST statements.

The following *options* can be specified in the TEST statement after a slash (/):

AVERAGE

enables you to assess the average effect of the variables in the given TEST statement. An overall estimate of the treatment effect is computed as a weighted average of the treatment coefficients as illustrated in the following statement:

```
TREATMENT: test trt1, trt2, trt3, trt4 / average;
```

Let β_1, β_2, β_3, and β_4 be corresponding parameters for trt1, trt2, trt3, and trt4, respectively. Let $\hat{\boldsymbol{\beta}} = (\hat{\beta}_1, \hat{\beta}_2, \hat{\beta}_3, \hat{\beta}_4)'$ be the estimated coefficient vector and let $\hat{\mathbf{V}}(\hat{\boldsymbol{\beta}})$ be the corresponding variance estimate. Assuming $\beta_1 = \beta_2 = \beta_3 = \beta_4$, let $\bar{\beta}$ be the average treatment effect. The effect is estimated by $\mathbf{c}'\hat{\boldsymbol{\beta}}$, where $\mathbf{c} = [\mathbf{1}_4'\hat{\mathbf{V}}^{-1}(\hat{\boldsymbol{\beta}})\mathbf{1}_4]^{-1}\hat{\mathbf{V}}^{-1}(\hat{\boldsymbol{\beta}})\mathbf{1}_4$ and $\mathbf{1}_4 = (1,1,1,1)'$. A test of the null hypothesis $H_0 : \bar{\beta} = 0$ is also included, which is more sensitive than the multivariate test for testing the null hypothesis $H_0 : \beta 1 = \beta 2 = \beta 3 = \beta 4 = 0$.

E

specifies that the linear coefficients and constants be printed. When the AVERAGE option is specified along with the E option, the optimal weights of the average effect are also printed in the same tables as the coefficients.

PRINT

displays intermediate calculations. This includes $\mathbf{L}\hat{\mathbf{V}}(\hat{\boldsymbol{\beta}})\mathbf{L}'$ bordered by $(\mathbf{L}\hat{\boldsymbol{\beta}} - \mathbf{c})$, and $[\mathbf{L}\hat{\mathbf{V}}(\hat{\boldsymbol{\beta}})\mathbf{L}']^{-1}$ bordered by $[\mathbf{L}\hat{\mathbf{V}}(\hat{\boldsymbol{\beta}})\mathbf{L}']^{-1}(\mathbf{L}\hat{\boldsymbol{\beta}} - \mathbf{c})$, where $\mathbf{L}$ is a matrix of linear coefficients and $\mathbf{c}$ is a vector of constants.

For more information, see the section "Using the TEST Statement to Test Linear Hypotheses" on page 6910.

WEIGHT Statement

WEIGHT *variable* < / *option* > **;**

The *variable* in the WEIGHT statement identifies the variable in the input data set that contains the case weights. When the WEIGHT statement appears, each observation in the input data set is weighted by the value of the WEIGHT variable. The WEIGHT values can be nonintegral and are not truncated. Observations with negative, zero, or missing values for the WEIGHT variable are not used in the model fitting. When the WEIGHT statement is not specified, each observation is assigned a weight of 1. The WEIGHT statement is available for TIES=BRESLOW and TIES=EFRON only.

The following *option* can be specified in the WEIGHT statement after a slash (/):

NORMALIZE

NORM

causes the weights specified by the WEIGHT *variable* to be normalized so that they add up the actual sample size. With this option, the estimated covariance matrix of the parameter estimators is invariant to the scale of the WEIGHT variable.

Details: PHREG Procedure

Failure Time Distribution

Let T be a nonnegative random variable representing the failure time of an individual from a homogeneous population. The survival distribution function (also known as the survivor function) of T is written as

$$S(t) = \Pr(T \geq t)$$

A mathematically equivalent way of specifying the distribution of T is through its hazard function. The hazard function $\lambda(t)$ specifies the instantaneous failure rate at t. If T is a continuous random variable, $\lambda(t)$ is expressed as

$$\lambda(t) = \lim_{\Delta t \to 0^+} \frac{\Pr(t \leq T < t + \Delta t \mid T \geq t)}{\Delta t} = \frac{f(t)}{S(t)}$$

where $f(t)$ is the probability density function of T. If T is discrete with masses at $x_1 < x_2 < \ldots$, then survivor function is given by

$$S(t) = \sum_{x_j \leq t} \Pr(T = x_j) = \sum_j \Pr(T = j)\delta(t - x_j)$$

where $\delta(u)$=0 if $u < 0$ and $\delta(u)$=1 otherwise. The discrete hazards are given by

$$\lambda_j = \Pr(T = x_j \mid T \geq x_j) = \frac{\Pr(T = x_j)}{S(x_j)}, \quad j = 1, 2, \ldots$$

Time and CLASS Variables Usage

The following DATA step creates an artificial data set, Test, to be used in this section. There are four variables in Test: the variable T contains the failure times; the variable Status is the censoring indicator variable with the value 1 for an uncensored failure time and the value 0 for a censored time; the variable A is a categorical variable with values 1, 2, and 3 representing three different categories; and the variable MirrorT is an exact copy of T.

```
data Test;
   input T Status A @@;
   MirrorT = T;
   datalines;
 23        1      1    7        0      1
 23        1      1   10        1      1
 20        0      1   13        0      1
 24        1      1   10        1      1
 18        1      2    6        1      2
 18        0      2    6        1      2
 13        0      2   13        1      2
```

```
  9        0       2    15        1       2
  8        1       3     6        1       3
 12        0       3     4        1       3
 11        1       3     8        1       1
  6        1       3     7        1       3
  7        1       3    12        1       3
  9        1       2    15        1       2
  3        1       2    14        0       3
  6        1       1    13        1       2
;
```

Time Variable on the Right Side of the MODEL Statement

When the time variable is explicitly used in an explanatory effect in the MODEL statement, the effect is *not* time-dependent. In the following specification, T is the time variable, but T does not play the role of the time variable in the explanatory effect T*A:

```
proc phreg data=Test;
   class A;
   model T*Status(0)=T*A;
run;
```

The parameter estimates of this model are shown in Figure 86.12.

Figure 86.12 T*A Effect

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
T*A	1	1	-0.16549	0.05042	10.7734	0.0010	.	A 1 * T
T*A	2	1	-0.11852	0.04181	8.0344	0.0046	.	A 2 * T

To verify that the effect T*A in the MODEL statement is not time-dependent, T is replaced by MirrorT, which is an exact copy of T, as in the following statements:

```
proc phreg data=Test;
   class A;
   model T*Status(0)=A*MirrorT;
run;
```

The results of fitting this model (Figure 86.13) are identical to those of the previous model (Figure 86.12), except for the parameter names and labels. The effect A*MirrorT is not time-dependent, so neither is A*T.

Figure 86.13 T*A Effect

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
MirrorT*A	1	1	-0.16549	0.05042	10.7734	0.0010	.	A 1 * MirrorT
MirrorT*A	2	1	-0.11852	0.04181	8.0344	0.0046	.	A 2 * MirrorT

CLASS Variables and Programming Statements

In PROC PHREG, the levels of CLASS variables are determined by the CLASS statement and the input data and are not affected by user-supplied programming statements. Consider the following statements, which produce the results in Figure 86.14. Variable A is declared as a CLASS variable in the CLASS statement. By default, the reference parameterization is used with A=3 as the reference level. Two regression coefficients are estimated for the two dummy variables of A.

```
proc phreg data=Test;
   class A;
   model T*Status(0)=A;
run;
```

Figure 86.14 shows the dummy variables of A and the regression coefficients estimates.

Figure 86.14 Design Variable and Regression Coefficient Estimates

The PHREG Procedure

Class Level Information

Class	Value	Design Variables	
A	1	1	0
	2	0	1
	3	0	0

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
A	1	1	-1.40925	0.64802	4.7293	0.0297	0.244	A 1
A	2	1	-0.65705	0.51764	1.6112	0.2043	0.518	A 2

Now consider the programming statement that attempts to change the value of the CLASS variable A as in the following specification:

```
proc phreg data=Test;
   class A;
   model T*Status(0)=A;
   if A=3 then A=2;
run;
```

Results of this analysis are shown in Figure 86.15 and are identical to those in Figure 86.14. The `if A=3 then A=2` programming statement has no effects on the design variables for A, which have already been determined.

Figure 86.15 Design Variable and Regression Coefficient Estimates

The PHREG Procedure

Class Level Information

Class	Value	Design Variables	
A	**1**	1	0
	2	0	1
	3	0	0

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
A	**1**	1	-1.40925	0.64802	4.7293	0.0297	0.244	A 1
A	**2**	1	-0.65705	0.51764	1.6112	0.2043	0.518	A 2

Additionally any variable used in a programming statement that has already been declared in the CLASS statement is *not* treated as a collection of the corresponding design variables. Consider the following statements:

```
proc phreg data=Test;
   class A;
   model T*Status(0)=A X;
   X=T*A;
run;
```

The CLASS variable A generates two design variables as explanatory variables. The variable X that is created by the **X=T*A** programming statement is a single time-dependent covariate whose values are evaluated using the exact values of A that exist in the data, not the dummy-coded values that represent the levels of A. In the Test data set, A assumes the values of 1, 2, and 3, and these are the exact values that are used in producing X. If A is a character variable, the programming statement converts the character value of A to numeric before carrying out the multiplication. If the values of A were Bird, Cat, and Dog, the programming statement X=T*A would produce an error for failing to convert the character values to numeric values.

Figure 86.16 Single Time-Dependent Variable X*A

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
A	**1**	1	0.15798	1.69338	0.0087	0.9257	1.171	A 1
A	**2**	1	0.00898	0.87573	0.0001	0.9918	1.009	A 2
X		1	0.09268	0.09535	0.9448	0.3311	1.097	

To generalize the simple test of proportional hazard assumption for the design variables of A (as in the section the "Classical Method of Maximum Likelihood" on page 6814), you specify the following statements, which are not the same as in the preceding program or as in the specification in the section "Time Variable on the Right Side of the MODEL Statement" on page 6887:

```
proc phreg data=Test;
   class A;
   model T*Status(0)=A X1 X2;
   X1= T*(A=1);
   X2= T*(A=2);
run;
```

The Boolean parenthetical expressions (A=1) and (A=2) resolve to a value of 1 or 0, depending on whether the expression is true or false, respectively.

Results of this test are shown in Figure 86.17.

Figure 86.17 Simple Test of Proportional Hazards Assumption

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
A	1	1	-0.00766	1.69435	0.0000	0.9964	0.992	A 1
A	2	1	-0.88132	1.64298	0.2877	0.5917	0.414	A 2
X1		1	-0.15522	0.20174	0.5920	0.4417	0.856	
X2		1	0.01155	0.18858	0.0037	0.9512	1.012	

In general, when your model contains a categorical explanatory variable that is time-dependent, it might be necessary to use hardcoded dummy variables to represent the categories of the categorical variable. Alternatively, you might consider using the counting-process style of input where you break up the covariate history of an individual into a number of records with nonoverlapping start and stop times and declare the categorical time-dependent variable in the CLASS statement.

Partial Likelihood Function for the Cox Model

Let $\mathbf{Z}_l(t)$ denote the vector explanatory variables for the lth individual at time t. Let $t_1 < t_2 < \ldots < t_k$ denote the k distinct, ordered event times. Let d_i denote the multiplicity of failures at t_i; that is, d_i is the size of the set $\mathcal{D}_i$ of individuals that fail at t_i. Let w_l be the weight associated with the lth individual. Using this notation, the likelihood functions used in PROC PHREG to estimate $\boldsymbol{\beta}$ are described in the following sections.

Continuous Time Scale

Let $\mathcal{R}_i$ denote the risk set just before the ith ordered event time t_i. Let $\mathcal{R}_i^*$ denote the set of individuals whose event or censored times exceed t_i or whose censored times are equal to t_i.

Exact Likelihood

$$L_1(\boldsymbol{\beta}) = \prod_{i=1}^{k} \left\{ \int_0^{\infty} \prod_{j \in \mathcal{D}_i} \left[1 - \exp\left(- \frac{e^{\boldsymbol{\beta}' \mathbf{Z}_j(t_i)}}{\sum_{l \in \mathcal{R}_i^*} e^{\boldsymbol{\beta}' \mathbf{Z}_l(t_i)}} t \right) \right] \exp(-t) dt \right\}$$

Breslow Likelihood

$$L_2(\boldsymbol{\beta}) = \prod_{i=1}^{k} \frac{e^{\boldsymbol{\beta}' \sum_{j \in \mathcal{D}_i} \mathbf{Z}_j(t_i)}}{\left[\sum_{l \in \mathcal{R}_i} e^{\boldsymbol{\beta}' \mathbf{Z}_l(t_i)} \right]^{d_i}}$$

Incorporating weights, the Breslow likelihood becomes

$$L_2(\boldsymbol{\beta}) = \prod_{i=1}^{k} \frac{e^{\boldsymbol{\beta}' \sum_{j \in \mathcal{D}_i} w_j \mathbf{Z}_j(t_i)}}{\left[\sum_{l \in \mathcal{R}_i} w_l e^{\boldsymbol{\beta}' \mathbf{Z}_l(t_i)} \right]^{\sum_{j \in \mathcal{D}_i} w_j}}$$

Efron Likelihood

$$L_3(\boldsymbol{\beta}) = \prod_{i=1}^{k} \frac{e^{\boldsymbol{\beta}' \sum_{j \in \mathcal{D}_i} \mathbf{Z}_j(t_i)}}{\prod_{j=1}^{d_i} \left(\sum_{l \in \mathcal{R}_i} e^{\boldsymbol{\beta}' \mathbf{Z}_l(t_i)} - \frac{j-1}{d_i} \sum_{l \in \mathcal{D}_i} e^{\boldsymbol{\beta}' \mathbf{Z}_l(t_i)} \right)}$$

Incorporating weights, the Efron likelihood becomes

$$L_3(\boldsymbol{\beta}) = \prod_{i=1}^{k} \frac{e^{\boldsymbol{\beta}' \sum_{j \in \mathcal{D}_i} w_j \mathbf{Z}_j(t_i)}}{\left[\prod_{j=1}^{d_i} \left(\sum_{l \in \mathcal{R}_i} w_l e^{\boldsymbol{\beta}' \mathbf{Z}_l(t_i)} - \frac{j-1}{d_i} \sum_{l \in \mathcal{D}_i} w_l e^{\boldsymbol{\beta}' \mathbf{Z}_l(t_i)} \right) \right]^{\frac{1}{d_i} \sum_{j \in \mathcal{D}_i} w_j}}$$

Discrete Time Scale

Let $\mathcal{Q}_i$ denote the set of all subsets of d_i individuals from the risk set $\mathcal{R}_i$. For each $\mathbf{q} \in \mathcal{Q}_i$, $\mathbf{q}$ is a d_i-tuple $(q_1, q_2, \ldots, q_{d_i})$ of individuals who might have failed at t_i.

Discrete Logistic Likelihood

$$L_4(\boldsymbol{\beta}) = \prod_{i=1}^{k} \frac{e^{\boldsymbol{\beta}' \sum_{j \in \mathcal{D}_i} \mathbf{Z}_j(t_i)}}{\sum_{\mathbf{q} \in \mathcal{Q}_i} e^{\boldsymbol{\beta}' \sum_{l=1}^{d_i} \mathbf{Z}_{q_l}(t_i)}}$$

The computation of $L_4(\boldsymbol{\beta})$ and its derivatives is based on an adaptation of the recurrence algorithm of Gail, Lubin, and Rubinstein (1981) to the logarithmic scale. When there are no ties on the event times (that is, $d_i \equiv 1$), all four likelihood functions $L_1(\boldsymbol{\beta})$, $L_2(\boldsymbol{\beta})$, $L_3(\boldsymbol{\beta})$, and $L_4(\boldsymbol{\beta})$ reduce to the same expression. In a stratified analysis, the partial likelihood is the product of the partial likelihood functions for the individual strata.

Counting Process Style of Input

In the counting process formulation, data for each subject are identified by a triple $\{N, Y, \mathbf{Z}\}$ of counting, at-risk, and covariate processes. Here, $N(t)$ indicates the number of events that the subject experiences over the time interval $(0, t]$; $Y(t)$ indicates whether the subject is at risk at time t (one if at risk and zero otherwise); and $\mathbf{Z}(t)$ is a vector of explanatory variables for the subject at time t. The sample path of N is a step function with jumps of size +1 at the event times, and $N(0) = 0$. Unless $\mathbf{Z}(t)$ changes continuously with time, the data for each subject can be represented by multiple observations, each identifying a semiclosed time interval $(t_1, t_2]$, the values of the explanatory variables over that interval, and the event status at t_2. The subject remains at risk during the interval $(t_1, t_2]$, and an event might occur at t_2. Values of the explanatory variables for the subject remain unchanged in the interval. This style of data input was originated by Therneau (1994).

For example, a patient has a tumor recurrence at weeks 3, 10, and 15 and is followed up to week 23. Consider three fixed explanatory variables Trt (treatment), Number (initial tumor number), and Size (initial tumor size), and one time-dependent covariate Z that represents a hormone level. The value of Z might change during the follow-up period. The data for this patient are represented by the following four observations:

T1	T2	Status	Trt	Number	Size	Z
0	3	1	1	1	3	12.3
3	10	1	1	1	3	14.7
10	15	1	1	1	3	13.8
15	23	0	1	1	3	15.5

Here (T1,T2] contains the at-risk intervals. The variable Status indicates whether a recurrence has occurred at T2; a value of 1 indicates a tumor recurrence, and a value of 0 indicates nonrecurrence. The following statements fit a multiplicative hazards model with baseline covariates Trt, Number, and Size, and a time-varying covariate Z.

```
proc phreg;
   model (T1,T2) * Status(0) = Trt Number Size Z;
run;
```

Another useful application of the counting process formulation is delayed entry of subjects into the risk set. For example, in studying the mortality of workers exposed to a carcinogen, the survival time is chosen to

be the worker's age at death by malignant neoplasm. Any worker joining the workplace at a later age than a given event failure time is not included in the corresponding risk set. The variables of a worker consist of Entry (age at which the worker entered the workplace), Age (age at death or age censored), Status (an indicator of whether the observation time is censored, with the value 0 identifying a censored time), and X1 and X2 (explanatory variables thought to be related to survival). The specification for such an application is as follows:

```
proc phreg;
   model (Entry, Age) * Status(0) = X1 X2;
run;
```

Alternatively, you can use a time-dependent variable to control the risk set, as illustrated in the following specification:

```
proc phreg;
   model Age * Status(0) = X1 X2;
   if Age < Entry then X1= .;
run;
```

Here, X1 becomes a time-dependent variable. At a given death time t, the value of X1 is reevaluated for each subject with Age $\geq t$; subjects with Entry $> t$ are given a missing value in X1 and are subsequently removed from the risk set. Computationally, this approach is not as efficient as the one that uses the counting process formulation.

Left-Truncation of Failure Times

Left-truncation occurs when individuals are not observed at the natural time origin of the phenomenon under study but come under observation at some known later time (called the left-truncation time). The risk set just prior to an event time does not include individuals whose left-truncation times exceed the given event time. Thus, any contribution to the likelihood must be conditional on the truncation limit having been exceeded.

You use the ENTRY= option to specify the variable that represents the left-truncation time. Suppose T1 and T2 represent the left-truncation time and the survival time, respectively. To account for left-truncation, you specify the following statements:

```
proc phreg;
   model T2*Dead(0)=X1-X10/entry=T1;
   title 'The ENTRY= option is Specified';
run;
```

Equivalently, you can use the counting process style of input for left-truncation:

```
proc phreg;
   model (T1,T2)*Dead(0)=X1-X10;
   title 'Counting Process Style of Input';
run;
```

Since the product-limit estimator of the survivor function is not available for the counting process style of input, you cannot use PROC PHREG to obtain the product-limit estimate of the survivor function if you have data with left-truncation times. In the preceding PROC PHREG calls, if you also specify METHOD=PL in a BASELINE statement or an OUTPUT statement, it is defaulted to METHOD=BRESLOW.

The Multiplicative Hazards Model

Consider a set of n subjects such that the counting process $N_i \equiv \{N_i(t), t \geq 0\}$ for the ith subject represents the number of observed events experienced over time t. The sample paths of the process N_i are step functions with jumps of size $+1$, with $N_i(0) = 0$. Let $\boldsymbol{\beta}$ denote the vector of unknown regression coefficients. The multiplicative hazards function $\Lambda(t, \mathbf{Z}_i(t))$ for N_i is given by

$$Y_i(t)d\Lambda(t, \mathbf{Z}_i(t)) = Y_i(t)\exp(\boldsymbol{\beta}'\mathbf{Z}_i(t))d\Lambda_0(t)$$

where

- $Y_i(t)$ indicates whether the ith subject is at risk at time t (specifically, $Y_i(t) = 1$ if at risk and $Y_i(t) = 0$ otherwise)
- $\mathbf{Z}_i(t)$ is the vector of explanatory variables for the ith subject at time t
- $\Lambda_0(t)$ is an unspecified baseline hazard function

See Fleming and Harrington (1991) and Andersen et al. (1992). The Cox model is a special case of this multiplicative hazards model, where $Y_i(t) = 1$ until the first event or censoring, and $Y_i(t) = 0$ thereafter.

The partial likelihood for n independent triplets $(N_i, Y_i, \mathbf{Z}_i), i = 1, \ldots, n$, has the form

$$\mathcal{L}(\boldsymbol{\beta}) = \prod_{i=1}^{n}\prod_{t\geq 0}\left\{\frac{Y_i(t)\exp(\boldsymbol{\beta}'\mathbf{Z}_i(t))}{\sum_{j=1}^{n} Y_j(t)\exp(\boldsymbol{\beta}'\mathbf{Z}_j(t))}\right\}^{\Delta N_i(t)}$$

where $\Delta N_i(t) = 1$ if $N_i(t) - N_i(t-) = 1$, and $\Delta N_i(t) = 0$ otherwise.

Proportional Rates/Means Models for Recurrent Events

Let $N(t)$ be the number of events experienced by a subject over the time interval $(0, t]$. Let $dN(t)$ be the increment of the counting process N over $[t, t + dt)$. The rate function is given by

$$d\mu_{\mathbf{Z}}(t) = E[dN(t)|Z(t)] = \mathrm{e}^{\boldsymbol{\beta}'\mathbf{Z}(t)}d\mu_0(t)$$

where $\mu_0(.)$ is an unknown continuous function. If the $\mathbf{Z}$ are time independent, the rate model is reduced to the mean model

$$\mu_Z(t) = \mathrm{e}^{\boldsymbol{\beta}'Z}\mu_0(t)$$

The partial likelihood for n independent triplets $(N_i, Y_i, \mathbf{Z}_i), i = 1, \ldots, n$, of counting, at-risk, and covariate processes is the same as that of the multiplicative hazards model. However, a robust sandwich estimate is used for the covariance matrix of the parameter estimator instead of the model-based estimate.

Let T_{ki} be the kth event time of the ith subject. Let C_i be the censoring time of the ith subject. The at-risk indicator and the failure indicator are, respectively,

$$Y_i(t) = I(C_i \geq t) \text{ and } \Delta_{ki} = I(T_{ki} \leq C_i)$$

Denote

$$S^{(0)}(\boldsymbol{\beta}, t) = \sum_{i=1}^{n} Y_i(t) \mathrm{e}^{\boldsymbol{\beta}' \mathbf{Z}_i(t)} \text{ and } \bar{\mathbf{Z}}(\boldsymbol{\beta}, t) = \frac{\sum_{i=1}^{n} Y_i(t) \mathrm{e}^{\boldsymbol{\beta}' \mathbf{Z}_i(t)} \mathbf{Z}_i(t)}{S^{(0)}(\boldsymbol{\beta}, t)}$$

Let $\hat{\boldsymbol{\beta}}$ be the maximum likelihood estimate of $\boldsymbol{\beta}$, and let $\mathcal{I}(\hat{\boldsymbol{\beta}})$ be the observed information matrix. The robust sandwich covariance matrix estimate is given by

$$\mathcal{I}^{-1}(\hat{\boldsymbol{\beta}}) \sum_{i=1}^{n} \left[W_i(\hat{\boldsymbol{\beta}}) W_i'(\hat{\boldsymbol{\beta}}) \right] \mathcal{I}^{-1}(\hat{\boldsymbol{\beta}})$$

where

$$\begin{aligned} W_i(\boldsymbol{\beta}) &= \sum_k \Delta_{ki} \left\{ Z_i(T_{ki}) - \bar{\mathbf{Z}}(\boldsymbol{\beta}, T_{ki}) \right\} - \\ &\quad \sum_{j=1}^{n} \sum_l \frac{\Delta_{lj} Y_i(T_{lj}) \mathrm{e}^{\boldsymbol{\beta}' \mathbf{Z}_i(T_{lj})}}{S^0(\boldsymbol{\beta}, T_{lj})} \left\{ Z_i(T_{lj}) - \bar{\mathbf{Z}}(\boldsymbol{\beta}, T_{lj}) \right\} \end{aligned}$$

For a given realization of the covariates $\boldsymbol{\xi}$, the Nelson estimator is used to predict the mean function

$$\hat{\mu}_{\boldsymbol{\xi}}(t) = \mathrm{e}^{\hat{\boldsymbol{\beta}}' \boldsymbol{\xi}} \sum_{i=1}^{n} \sum_k \frac{I(T_{ki} \le t) \Delta_{ki}}{S^{(0)}(\hat{\boldsymbol{\beta}}, T_{ki})}$$

with standard error estimate given by

$$\hat{\sigma}^2(\hat{\mu}_{\boldsymbol{\xi}}(t)) = \sum_{i=1}^{n} \left(\frac{1}{n} \hat{\Psi}_i(t, \boldsymbol{\xi}) \right)^2$$

where

$$\begin{aligned} \frac{1}{n} \hat{\Psi}_i(t, \boldsymbol{\xi}) &= \mathrm{e}^{\hat{\boldsymbol{\beta}}' \boldsymbol{\xi}} \left\{ \sum_k \frac{I(T_{ki} \le t) \Delta_{ki}}{S^{(0)}(\hat{\boldsymbol{\beta}}, T_{ki})} - \sum_{j=1}^{n} \sum_k \frac{Y_i(T_{kj}) \mathrm{e}^{\hat{\boldsymbol{\beta}}' \mathbf{Z}_i(T_{kj})} I(T_{kj} \le t) \Delta_{kj}}{[S^{(0)}(\hat{\boldsymbol{\beta}}, T_{kj})]^2} - \right. \\ &\quad \left[\sum_{i=1}^{n} \sum_k \frac{I(T_{ki} \le t) \Delta_{ki} [\bar{\mathbf{Z}}(\hat{\boldsymbol{\beta}}, T_{ki}) - \boldsymbol{\xi}]}{S^{(0)}(\hat{\boldsymbol{\beta}}, T_{ki})} \right] \\ &\quad \left. \times \mathcal{I}^{-1}(\hat{\boldsymbol{\beta}}) \int_0^{\tau} [\mathbf{Z}_i(u) - \bar{\mathbf{Z}}(\hat{\boldsymbol{\beta}}, u)] d\hat{M}_i(u) \right\} \end{aligned}$$

Since the cumulative mean function is always nonnegative, the log transform is used to compute confidence intervals. The $100(1-\alpha)\%$ pointwise confidence limits for $\mu_{\boldsymbol{\xi}}(t)$ are

$$\hat{\mu}_{\boldsymbol{\xi}}(t) \mathrm{e}^{\pm z_{\alpha/2} \frac{\hat{\sigma}(\hat{\mu}_{\boldsymbol{\xi}}(t))}{\hat{\mu}_{\boldsymbol{\xi}}(t)}}$$

where $z_{\alpha/2}$ is the upper $100\alpha/2$ percentage point of the standard normal distribution.

The Frailty Model

You can use the frailty model to model correlations between failures of the same cluster. The hazard rate for the *j*th individual in the *i*th cluster is

$$\lambda_{ij}(t) = \lambda_0(t)\mathrm{e}^{\boldsymbol{\beta}'\mathbf{Z}_{ij}(t)+\gamma_i}$$

where $\lambda_0(t)$ is an arbitrary baseline hazard rate, $\mathbf{Z}_{ij}$ is the vector of (fixed-effect) covariates, $\boldsymbol{\beta}$ is the vector of regression coefficients, and γ_i is the random effect for cluster i.

Frailties are the exponential transformations of the random components, and the frailty model can be written as

$$\lambda_{ij}(t) = \lambda_0(t)\mathrm{e}^{\gamma_i}\mathrm{e}^{\boldsymbol{\beta}'\mathbf{Z}_{ij}(t)}$$

The random components $\gamma_1, \ldots, \gamma_s$ (alternatively, the frailties $\mathrm{e}^{\gamma_1}, \ldots, \mathrm{e}^{\gamma_s}$) are assumed to be independent and identically distributed. Modeling is based on the random effects rather than on the frailties.

Two frailty distributions are available in PROC PHREG: gamma and lognormal. Use the DIST= option in the RANDOM statement to choose the distribution. Let θ be an unknown parameter. The frailty distributions are listed in Table 86.12.

Table 86.12 Frailty Distributions

Frailty Option	Distribution	Density f(γ_i)	Mean and Variance
DIST=GAMMA	$\mathrm{e}^{\gamma_i} \sim G\left(\frac{1}{\theta}, \frac{1}{\theta}\right)$	$\frac{\exp(\frac{\gamma_i}{\theta})\exp\left(-\frac{\exp(\gamma_i)}{\theta}\right)}{\theta^{\frac{1}{\theta}}\Gamma(\frac{1}{\theta})}$	E(e^{γ_i})=1, V(e^{γ_i})=θ
DIST=LOGNORMAL	$\gamma_i \sim N(0, \theta)$	$\frac{1}{\sqrt{(2\pi\theta)}}\exp\left(-\frac{\gamma_i^2}{2\theta}\right)$	E(γ_i)=0, V(γ_i)=θ

The unknown parameter θ is a dispersion parameter. Each frailty distribution has a central tendency of 1 (the gamma frailty has a mean of 1, and the lognormal frailty has a median of 1). Thus, you can infer that individuals in cluster i with frailty $\mathrm{e}^{\gamma_i} > 1$ (or $\mathrm{e}^{\gamma_i} < 1$) tend to fail at a faster (or slower) rate than they fail under an independence model.

PROC PHREG estimates the regression coefficients $\boldsymbol{\beta}$, the random effects $\gamma_1, \ldots, \gamma_s$, and the dispersion parameter θ. The RANDOM statement in PROC PHREG enables you to fit a shared frailty model by a penalized partial likelihood approach. For more information, see the section "The Penalized Partial Likelihood Approach for Fitting Frailty Models" on page 6943. If you also specify the BAYES statement, PROC PHREG performs a Bayesian analysis of the shared frailty model. For more information, see the section "Frailty Model" on page 6951.

If the RANDOM statement is specified, any ASSESS, BASELINE, and OUTPUT statements are ignored. Also ignored are the COVS options in the PROC PHREG statement and the following *options* in the MODEL statement: BEST=, DETAILS, HIERARCHY=, INCLUDE=, NOFIT, PLCONV=, SELECTION=, SEQUENTIAL, SLENTRY=, SLSTAY=, TYPE1, and TYPE3(ALL, LR, SCORE). Profile likelihood confidence intervals for the hazard ratios are not available for the frailty model analysis.

Proportional Subdistribution Hazards Model for Competing-Risks Data

Competing risks arise in the analysis of time-to-event data when the event of interest can be impeded by a prior event of a different type. For example, a leukemia patient's relapse might be unobservable because the patient dies before relapse is diagnosed. In the presence of competing risks, the Kaplan-Meier method of estimating the survivor function is biased, because you can no longer assume that a subject will experience the event of interest if the follow-up period is long enough. The cumulative incidence function (CIF), which is the marginal failure subdistribution of a given cause, is widely used in competing-risks analysis.

The proportional hazards model for the subdistribution that Fine and Gray (1999) propose aims at modeling the cumulative incidence of an event of interest. They define a subdistribution hazard,

$$\bar{\lambda}_k(t) = -\frac{d}{dt}\left(1 - F_k(t)\right)$$

where $F_k(t)$ is the cumulative incidence function for the failure of cause k, and they impose a proportional hazards assumption on the subdistribution hazards:

$$\bar{\lambda}_k(t|\mathbf{Z}) = \bar{\lambda}_{k,0}\exp(\boldsymbol{\beta}_k'\mathbf{Z})$$

The estimation of the regression coefficients is based on modified risk sets, where subjects that experience a competing event are retained after their event. The weight of those subjects that are artificially retained in the risk sets is gradually reduced according to the conditional probability of being under follow-up had the competing event not occurred.

You use PROC PHREG to fit the Fine and Gray (1999) model by specifying the EVENTCODE= option in the MODEL statement to indicate the event of interest. Maximum likelihood estimates of the regression coefficients are obtained by the Newton-Raphson algorithm. The covariance matrix of the parameter estimator is computed as a sandwich estimate. You can request the CIF curves for a given set of covariates by using the BASELINE statement. The PLOTS=CIF option in the PROC PHREG statement displays a plot of the curves. You can obtain Schoenfeld residuals and score residuals by using the OUTPUT statement.

To model the subdistribution hazards for clustered data (Zhou et al. 2012), you use the COVS(AGGREGATE) option in the PROC PHREG statement. You also have to specify the ID statement to identify the clusters. To model the subdistribution hazards for stratified data (Zhou et al. 2011), you use the STRATA statement. PROC PHREG handles only regular stratified data that have a small number of large subject groups.

When you specify the EVENTCODE= option in the MODEL statement, the ASSESS, BAYES, and RANDOM statements are ignored. The ATRISK and COVM options in the PROC PHREG statement are also ignored, as are the following options in the MODEL statement: BEST=, DETAILS, HIERARCHY=, INCLUDE=, NOFIT, PLCONV=, RISKLIMITS=PL, SELECTION=, SEQUENTIAL, SLENTRY=, SLSTAY=, TYPE1, and TYPE3(LR, SCORE). Profile likelihood confidence intervals for the hazard ratios are not available for the Fine and Gray competing-risks analysis.

Parameter Estimation

For the ith subject, $i = 1, \ldots, n$, let X_i, Δ_i, ϵ_i, and $\mathbf{Z}_i(t)$ be the observed time, event indicator, cause of failure, and covariate vector at time t, respectively. Assume that K causes of failure are observable ($\epsilon_i \in (1, \ldots, K)$). Consider failure from cause 1 to be the failure of interest, with failures of other causes as

competing events. Let

$$\begin{aligned} N_i(t) &= I(X_i \le t, \epsilon_i = 1) \\ Y_i(t) &= 1 - N_i(t-) \end{aligned}$$

Note that if $\epsilon_i = 1$, then $N_i(t) = I(X_i \le t)$ and $Y_i(t) = I(X_i \ge t)$; if $\epsilon_i \ne 1$, then $N_i(t) = 0$ and $Y_i(t) = 1$. Let

$$\begin{aligned} r_i(t) &= I(C_i \ge T_i \wedge t) \\ w_i(t) &= r_i(t)\frac{G(t)}{G(X_i \wedge t)} \end{aligned}$$

where $G(t)$ is the Kaplan-Meier estimate of the survivor function of the censoring variable, which is calculated using $\{X_i, 1-\Delta_i, i = 1, 2, \ldots, n\}$. If $\Delta_i = 0$, then $r_i(t) = 1$ when $t \le X_i$ and 0 otherwise; and if $\Delta_i = 1$, then $r_i(t) = 1$. Table 86.13 displays the weight of a subject at a function of time.

Table 86.13 Weight for the *i*th Subject

t, X_i	**Status**	$r_i(t)$	$Y_i(t)$	$w_i(t)$
$t \le X_i$	$\Delta_i = 0$	1	1	1
	$\Delta_i\epsilon_i = 1$	1	1	1
	$\Delta_i\epsilon_i \ne 1$	1	1	1
$t > X_i$	$\Delta_i = 0$	0	1	0
	$\Delta_i\epsilon_i = 1$	1	0	$G(t)/G(X_i)$
	$\Delta_i\epsilon_i \ne 1$	1	1	$G(t)/G(X_i)$

The regression coefficients $\boldsymbol{\beta}$ are estimated by maximizing the pseudo-likelihood $L(\boldsymbol{\beta})$ with respect to $\boldsymbol{\beta}$:

$$L(\boldsymbol{\beta}) = \prod_{i=1}^{n}\left(\frac{\exp(\boldsymbol{\beta}'\mathbf{Z}_i(X_i))}{\sum_{j=1}^{n} Y_j(X_i)w_j(X_i)\exp(\boldsymbol{\beta}'\mathbf{Z}_j(X_i))}\right)^{I(\Delta_i\epsilon_i=1)}$$

The variance-covariance matrix of the maximum likelihood estimator $\hat{\boldsymbol{\beta}}$ is approximated by a sandwich estimate.

With $\mathbf{a}^{(0)} = 1$, $\mathbf{a}^{(1)} = \mathbf{a}$, and $\mathbf{a}^{(2)} = \mathbf{a}\mathbf{a}'$, let

$$\begin{aligned} \mathbf{S}_2^{(r)}(\boldsymbol{\beta}, u) &= \sum_{j=1}^{n} w_j(u)Y_j(u)\mathbf{Z}_j(u)^{\otimes r}\exp(\boldsymbol{\beta}'\mathbf{Z}_j(u)), \quad r = 0, 1, 2 \\ \bar{\mathbf{Z}}(\boldsymbol{\beta}, u) &= \frac{\mathbf{S}_2^{(1)}(\boldsymbol{\beta}, u)}{S_2^{(0)}(\boldsymbol{\beta}, u)} \end{aligned}$$

The score function $\mathbf{U}_2(\boldsymbol{\beta})$ and the observed information matrix $\hat{\boldsymbol{\Omega}}$ are given by

$$\begin{aligned}\mathbf{U}_2(\hat{\boldsymbol{\beta}}) &= \sum_{i=1}^{n}\Big(\mathbf{Z}_i(X_i) - \bar{\mathbf{Z}}(\boldsymbol{\beta}, X_i)\Big) I(\Delta_i\epsilon_i = 1)\\ \hat{\boldsymbol{\Omega}} &= -\frac{\partial \mathbf{U}_2(\hat{\boldsymbol{\beta}})}{\partial \boldsymbol{\beta}} = \sum_{i=1}^{n}\left(\frac{\mathbf{S}_2^{(2)}(\hat{\boldsymbol{\beta}}, X_i)}{S_2^{(0)}(\hat{\boldsymbol{\beta}}, X_i)} - \bar{\mathbf{Z}}^{\otimes 2}(\hat{\boldsymbol{\beta}}, X_i)\right) I(\Delta_i\epsilon_i = 1)\end{aligned}$$

The sandwich variance estimate of $\hat{\boldsymbol{\beta}}$ is

$$\widehat{\mathrm{var}}(\hat{\boldsymbol{\beta}}) = \hat{\boldsymbol{\Omega}}^{-1}\hat{\boldsymbol{\Sigma}}\hat{\boldsymbol{\Omega}}^{-1}$$

where $\hat{\boldsymbol{\Sigma}}$ is the estimate of the variance-covariance matrix of $\mathbf{U}_2(\hat{\boldsymbol{\beta}})$ that is given by

$$\hat{\boldsymbol{\Sigma}} = \sum_{i=1}^{n}(\hat{\boldsymbol{\eta}}_i + \hat{\boldsymbol{\psi}}_i)^{\otimes 2}$$

where

$$\hat{\boldsymbol{\eta}}_i = \int_0^{\infty}\Big(\mathbf{Z}_i(u) - \bar{\mathbf{Z}}(\hat{\boldsymbol{\beta}}, u)\Big) w_i(u)\, d\hat{M}_i^1(u)$$

$$\hat{\boldsymbol{\psi}}_i = \int_0^{\infty}\frac{\hat{\mathbf{q}}(u)}{\pi(u)}\, d\hat{M}_i^c(u)$$

$$\hat{\mathbf{q}}(u) = -\sum_{i=1}^{n}\int_0^{\infty}\Big(\mathbf{Z}_i(s) - \bar{\mathbf{Z}}(\hat{\boldsymbol{\beta}}, s)\Big) w_i(s)\, d\hat{M}_i^1 I(s \geq u > X_i)$$

$$\pi(u) = \sum_j I(X_j \geq u)$$

$$\hat{M}_i^1(t) = N_i(t) - \int_0^t Y_i(s)\exp(\hat{\boldsymbol{\beta}}'\mathbf{Z}_i(s))\, d\hat{\Lambda}_{10}(s)$$

$$\hat{M}_i^c(t) = I(X_i \leq t, \Delta_i = 0) - \int_0^t I(X_i \geq u)\, d\hat{\Lambda}^c(u)$$

$$\hat{\Lambda}_{10}(t) = \sum_{i=1}^{n}\int_0^t \frac{1}{S_2^{(0)}(\hat{\boldsymbol{\beta}}, u)} w_i(u)\, dN_i(u)$$

$$\hat{\Lambda}^c(t) = \int_0^t \frac{\sum_i d\{I(X_i \leq u, \Delta_i = 0)\}}{\sum_i I(X_i \geq u)}$$

Residuals

You can use the OUTPUT statement to output Schoenfeld residuals and score residuals to a SAS data set.

Schoenfeld residuals:	$\mathbf{Z}_i(X_i) - \bar{\mathbf{Z}}(\hat{\boldsymbol{\beta}}, X_i), \Delta_i\epsilon_i = 1$	$1 \leq i \leq n$
Score residuals	$\hat{\boldsymbol{\eta}}_i + \hat{\boldsymbol{\psi}}_i$	$1 \leq i \leq n$

Cumulative Incidence Prediction

For an individual with covariates $\mathbf{Z} = \mathbf{z}_0$, the cumulative subdistribution hazard is estimated by

$$\hat{\Lambda}_1(t;\mathbf{z}_0) = \int_0^t \exp[\hat{\boldsymbol{\beta}}'\mathbf{z}_0]d\,\hat{\Lambda}_{10}(u)$$

and the predicted cumulative incidence is

$$\hat{F}_1(t;\mathbf{z}_0) = 1 - \exp[-\hat{\Lambda}_1(t;\mathbf{z}_0)]$$

To compute the confidence interval for the cumulative incidence, consider a monotone transformation $m(p)$ with first derivative $\dot{m}(p)$. Fine and Gray (1999, Section 5) give the following procedure to calculate pointwise confidence intervals. First, you generate B samples of normal random deviates $\{(A_{k1},\ldots,A_{kn}), 1 \le k \le B\}$. You can specify the value of B by using the NORMALSAMPLE= option in the BASELINE statement. Then, you compute the estimate of $\text{var}\{m[\hat{F}_1(t;\boldsymbol{z}_0)] - m[F_1(t;\boldsymbol{z}_0)]\}$ as

$$\hat{\sigma}^2(t;\boldsymbol{z}_0) = \frac{1}{B}\sum_{k=1}^{B}\hat{J}_{1k}^2(t;\boldsymbol{z}_0)$$

where

$$\begin{aligned}\hat{J}_{1k}(t;\boldsymbol{z}_0) &= \dot{m}[\hat{F}_1(t;\mathbf{z}_0)]\exp[-\hat{\Lambda}_1(t;\mathbf{z}_0)]\sum_{i=1}^{n}A_{ki}\left\{\int_0^t \frac{\exp(\hat{\boldsymbol{\beta}}'\boldsymbol{z}_0)}{S_2^{(0)}(\hat{\boldsymbol{\beta}},u)}w_i(u)d\,\hat{M}_i^1(u)\right.\\ &\quad \left. + \hat{\boldsymbol{h}}'(t;\boldsymbol{z}_0)\hat{\boldsymbol{\Omega}}^{-1}(\hat{\boldsymbol{\eta}}_i + \hat{\boldsymbol{\psi}}_i) + \int_0^\infty \frac{\hat{\boldsymbol{v}}(u,t,\boldsymbol{z}_0)}{\hat{\pi}(u)}d\,\hat{M}_i^c(u)\right\}\end{aligned}$$

$$\hat{\mathbf{h}}(t;\mathbf{z}_0) = \exp(\hat{\boldsymbol{\beta}}'\mathrm{z}_0)\left\{\hat{\Lambda}_{10}(t)\mathbf{z}_0 - \int_0^t \bar{\mathbf{Z}}(\hat{\boldsymbol{\beta}},u)d\,\hat{\Lambda}_{10}(u)\right\}$$

$$\hat{v}(u,t,\mathbf{z}_0) = -\exp(\hat{\boldsymbol{\beta}}'\mathrm{z}_0)\sum_{i=1}^{n}\int_0^t \frac{1}{S_2^{(0)}(\hat{\boldsymbol{\beta}},s)}w_i(s)d\,\hat{M}_i^1(s)I(s \ge u > X_i)$$

A 100(1–α)% confidence interval for $\hat{F}_1(t;\mathbf{z}_0)$ is given by

$$m^{-1}\left(m[\hat{F}_1(t;\mathbf{z}_0)] \pm z_\alpha\hat{\sigma}(t;\mathbf{z}_0)\right)$$

where z_α is the $100(1-\alpha/2)$th percentile of a standard normal distribution.

The CLTYPE option in the BASELINE statement enables you to choose the LOG transformation, the LOGLOG (log of negative log) transformation, or the IDENTITY transformation. You can also output the standard error of the cumulative incidence, which is approximated by the delta method as follows:

$$\hat{\sigma}^2(\hat{F}(t;\mathbf{z}_0)) = \left(\dot{m}[\hat{F}(t;\mathbf{z}_0)]\right)^{-2}\hat{\sigma}^2(t;\mathbf{z}_0)$$

Table 86.14 displays the variance estimator for each transformation that is available in PROC PHREG.

Table 86.14 Variance Estimate of the CIF Predictor

CLTYPE= *keyword*	**Transformation**	$\widehat{\mathrm{var}}(\hat{F}(t;\mathbf{z_0}))$
IDENTITY	$m(p) = p$	$\hat{\sigma}^2(t;\mathbf{z_0})$
LOG	$m(p) = \log(p)$	$\left(\hat{F}_1(t;\mathbf{z_0})\right)^2 \hat{\sigma}^2(t;\mathbf{z_0})$
LOGLOG	$m(p) = \log(-\log(p))$	$\left(\hat{F}(t;\mathbf{z_0})\log(\hat{F}(t;\mathbf{z_0}))\right)^2 \hat{\sigma}^2(t;\mathbf{z_0})$

Hazard Ratios

Consider a dichotomous risk factor variable X that takes the value 1 if the risk factor is present and 0 if the risk factor is absent. The log-hazard function is given by

$$\log[\lambda(t|X)] = \log[\lambda_0(t)] + \beta_1 X$$

where $\lambda_0(t)$ is the baseline hazard function.

The hazard ratio ψ is defined as the ratio of the hazard for those with the risk factor ($X = 1$) to the hazard without the risk factor ($X = 0$). The log of the hazard ratio is given by

$$\log(\psi) \equiv \log[\psi(X = 1, X = 0)] = \log[\lambda(t|X = 1)] - \log[\lambda(t|X = 0)] = \beta_1$$

In general, the hazard ratio can be computed by exponentiating the difference of the log-hazard between any two population profiles. This is the approach taken by the HAZARDRATIO statement, so the computations are available regardless of parameterization, interactions, and nestings. However, as shown in the preceding equation for $\log(\psi)$, hazard ratios of main effects can be computed as functions of the parameter estimates, and the remainder of this section is concerned with this methodology.

The parameter, β_1, associated with X represents the change in the log-hazard rate from $X = 0$ to $X = 1$. So the hazard ratio is obtained by simply exponentiating the value of the parameter associated with the risk factor. The hazard ratio indicates how the hazard change as you change X from 0 to 1. For instance, $\psi = 2$ means that the hazard when $X = 1$ is twice the hazard when $X = 0$.

Suppose the values of the dichotomous risk factor are coded as constants a and b instead of 0 and 1. The hazard when $X = a$ becomes $\lambda(t)\exp(a\beta_1)$, and the hazard when $X = b$ becomes $\lambda(t)\exp(b\beta_1)$. The hazard ratio corresponding to an increase in X from a to b is

$$\psi = \exp[(b-a)\beta_1] = [\exp(\beta_1)]^{b-a} \equiv [\exp(\beta_1)]^c$$

Note that for any a and b such that $c = b - a = 1$, $\psi = \exp(\beta_1)$. So the hazard ratio can be interpreted as the change in the hazard for any increase of one unit in the corresponding risk factor. However, the change in hazard for some amount other than one unit is often of greater interest. For example, a change of one pound in body weight might be too small to be considered important, while a change of 10 pounds might be more meaningful. The hazard ratio for a change in X from a to b is estimated by raising the hazard ratio estimate for a unit change in X to the power of $c = b - a$ as shown previously.

For a polytomous risk factor, the computation of hazard ratios depends on how the risk factor is parameterized. For illustration, suppose that Cell is a risk factor with four categories: Adeno, Large, Small, and Squamous.

For the effect parameterization scheme (PARAM=EFFECT) with Squamous as the reference group, the design variables for Cell are as follows:

	Design Variables		
Cell	X_1	X_2	X_3
Adeno	1	0	0
Large	0	1	0
Small	0	0	1
Squamous	–1	–1	–1

The log-hazard for Adeno is

$$\begin{aligned}\log[\lambda(t|\text{Adeno})] &= \log[\lambda_0(t)] + \beta_1(X_1 = 1) + \beta_2(X_2 = 0) + \beta_3(X_3 = 0) \\ &= \lambda_0(t) + \beta_1\end{aligned}$$

The log-hazard for Squamous is

$$\begin{aligned}\log[\lambda(t|\text{Squamous})] &= \log[\lambda_0(t)] + \beta_1(X_1 = -1) + \beta_2(X_2 = -1) + \beta_3(X_3 = -1)) \\ &= \log[\lambda_0(t)] - \beta_1 - \beta_2 - \beta_3\end{aligned}$$

Therefore, the log-hazard ratio of Adeno versus Squamous

$$\begin{aligned}\log[\psi(\text{Adeno, Squamous})] &= \log[\lambda(t|\text{Adeno})] - \log[\lambda(t|\text{Squamous})] \\ &= 2\beta_1 + \beta_2 + \beta_3\end{aligned}$$

For the reference cell parameterization scheme (PARAM=REF) with Squamous as the reference cell, the design variables for Cell are as follows:

	Design Variables		
Cell	X_1	X_2	X_3
Adeno	1	0	0
Large	0	1	0
Small	0	0	1
Squamous	0	0	0

The log-hazard ratio of Adeno versus Squamous is given by

$$\begin{aligned}&\log(\psi(\text{Adeno, Squamous})) \\ &= \log[\lambda(t|\text{Adeno})] - \log[\lambda(t|\text{Squamous})] \\ &= (\log[\lambda_0(t)] + \beta_1(X_1 = 1) + \beta_2(X_2 = 0) + \beta_3(X_3 = 0)) - \\ &\quad (\log[\lambda_0(t)] + \beta_1(X_1 = 0) + \beta_2(X_2 = 0) + \beta_3(X_3 = 0)) \\ &= \beta_1\end{aligned}$$

For the GLM parameterization scheme (PARAM=GLM), the design variables are as follows:

	Design Variables			
Cell	X_1	X_2	X_3	X_4
Adeno	1	0	0	0
Large	0	1	0	0
Small	0	0	1	0
Squamous	0	0	0	1

The log-hazard ratio of Adeno versus Squamous is

$$\begin{aligned}
&\log(\psi(\text{Adeno}, \text{Squamous})) \\
&\quad = \log[\lambda(t|\text{Adeno})] - \log[\lambda(t|\text{Squamous})] \\
&\quad = \log[\lambda_0(t)] + \beta_1(X_1 = 1) + \beta_2(X_2 = 0) + \beta_3(X_3 = 0) + \beta_4(X_4 = 0)) - \\
&\qquad (\log(\lambda_0(t)) + \beta_1(X_1 = 0) + \beta_2(X_2 = 0) + \beta_3(X_3 = 0) + \beta_4(X_4 = 1)) \\
&\quad = \beta_1 - \beta_4
\end{aligned}$$

Consider Cell as the only risk factor in the Cox regression in Example 86.3. The computation of hazard ratio of Adeno versus Squamous for various parameterization schemes is tabulated in Table 86.15.

Table 86.15 Hazard Ratio Comparing Adeno to Squamous

	Parameter Estimates				
PARAM=	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$	$\hat{\beta}_4$	**Hazard Ratio Estimates**
EFFECT	0.5772	–0.2115	0.2454		$\exp(2 \times 0.5772 - 0.2115 + 0.2454) = 3.281$
REF	1.8830	0.3996	0.8565		$\exp(1.8830) = 3.281$
GLM	1.8830	0.3996	0.8565	0.0000	$\exp(1.8830) = 3.281$

The fact that the log-hazard ratio ($\log(\psi)$) is a linear function of the parameters enables the HAZARDRATIO statement to compute the hazard ratio of the main effect even in the presence of interactions and nest effects. The section "Hazard Ratios" on page 6901 details the estimation of the hazard ratios in a classical analysis.

To customize hazard ratios for specific units of change for a continuous risk factor, you can use the UNITS= option in a HAZARDRATIO statement to specify a list of relevant units for each explanatory variable in the model. Estimates of these customized hazard ratios are given in a separate table. Let (L_j, U_j) be a confidence interval for $\log(\psi)$. The corresponding lower and upper confidence limits for the customized hazard ratio $\exp(c\beta_j)$ are $\exp(cL_j)$ and $\exp(cU_j)$, respectively (for $c > 0$), or $\exp(cU_j)$ and $\exp(cL_j)$, respectively (for $c < 0$).

Newton-Raphson Method

Let $L(\boldsymbol{\beta})$ be one of the likelihood functions described in the previous subsections. Let $l(\boldsymbol{\beta}) = \log L(\boldsymbol{\beta})$. Finding $\boldsymbol{\beta}$ such that $L(\boldsymbol{\beta})$ is maximized is equivalent to finding the solution $\hat{\boldsymbol{\beta}}$ to the likelihood equations

$$\frac{\partial l(\boldsymbol{\beta})}{\partial \boldsymbol{\beta}} = 0$$

With $\hat{\boldsymbol{\beta}}^0 = \mathbf{0}$ as the initial solution, the iterative scheme is expressed as

$$\hat{\boldsymbol{\beta}}^{j+1} = \hat{\boldsymbol{\beta}}^{j} - \left[\frac{\partial^2 l(\hat{\boldsymbol{\beta}}^{j})}{\partial \boldsymbol{\beta}^2}\right]^{-1} \frac{\partial l(\hat{\boldsymbol{\beta}}^{j})}{\partial \boldsymbol{\beta}}$$

The term after the minus sign is the Newton-Raphson step. If the likelihood function evaluated at $\hat{\boldsymbol{\beta}}^{j+1}$ is less than that evaluated at $\hat{\boldsymbol{\beta}}^{j}$, then $\hat{\boldsymbol{\beta}}^{j+1}$ is recomputed using half the step size. The iterative scheme continues until convergence is obtained—that is, until $\hat{\boldsymbol{\beta}}_{j+1}$ is sufficiently close to $\hat{\boldsymbol{\beta}}_{j}$. Then the maximum likelihood estimate of $\boldsymbol{\beta}$ is $\hat{\boldsymbol{\beta}} = \hat{\boldsymbol{\beta}}_{j+1}$.

The model-based variance estimate of $\hat{\boldsymbol{\beta}}$ is obtained by inverting the information matrix $\mathcal{I}(\hat{\boldsymbol{\beta}})$

$$\hat{\mathbf{V}}_m(\hat{\boldsymbol{\beta}}) = \mathcal{I}^{-1}(\hat{\boldsymbol{\beta}}) = -\left[\frac{\partial^2 l(\hat{\boldsymbol{\beta}})}{\partial \boldsymbol{\beta}^2}\right]^{-1}$$

Firth's Modification for Maximum Likelihood Estimation

In fitting a Cox model, the phenomenon of monotone likelihood is observed if the likelihood converges to a finite value while at least one parameter diverges (Heinze and Schemper 2001).

Let $\mathbf{x}_l(t)$ denote the vector explanatory variables for the lth individual at time t. Let $t_1 < t_2 < \ldots < t_m$ denote the k distinct, ordered event times. Let d_j denote the multiplicity of failures at t_j; that is, d_j is the size of the set $\mathcal{D}_j$ of individuals that fail at t_j. Let $\mathcal{R}_j$ denote the risk set just before t_j. Let $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_k)'$ be the vector of regression parameters. The Breslow log partial likelihood is given by

$$l(\boldsymbol{\beta}) = \log L(\boldsymbol{\beta}) = \sum_{j=1}^{m} \left\{ \boldsymbol{\beta}' \sum_{l \in \mathcal{D}_j} \mathbf{x}_l(t_j) - d_j \log \sum_{h \in \mathcal{R}j} \mathrm{e}^{\boldsymbol{\beta}' \mathbf{x}_h(t_j)} \right\}$$

Denote

$$\mathbf{S}_j^{(a)}(\boldsymbol{\beta}) = \sum_{h \in \mathcal{R}j} \mathrm{e}^{\boldsymbol{\beta}' \mathbf{x}_h(t_j)} [\mathbf{x}_h(t_j)]^{\otimes a} \qquad a = 0, 1, 2$$

Then the score function is given by

$$\begin{aligned} \mathbf{U}(\boldsymbol{\beta}) &\equiv (U(\beta_1), \ldots, U(\beta_k))' \\ &= \frac{\partial l(\boldsymbol{\beta})}{\partial \boldsymbol{\beta}} \\ &= \sum_{j=1}^{m} \left\{ \sum_{l \in \mathcal{D}j} \mathbf{x}_l(t_j) - d_j \frac{\mathbf{S}_j^{(1)}(\boldsymbol{\beta})}{S_j^0(\boldsymbol{\beta})} \right\} \end{aligned}$$

and the Fisher information matrix is given by

$$\begin{aligned}\mathcal{I}(\boldsymbol{\beta}) &= -\frac{\partial^2 l(\boldsymbol{\beta})}{\partial \boldsymbol{\beta}^2} \\ &= \sum_{j=1}^{m} d_j \left\{ \frac{\mathbf{S}_j^{(2)}(\boldsymbol{\beta})}{S_j^{(0)}(\boldsymbol{\beta})} - \left[\frac{\mathbf{S}_j^{(1)}(\boldsymbol{\beta})}{\mathbf{S}_j^{(0)}(\boldsymbol{\beta})}\right]\left[\frac{\mathbf{S}_j^{(1)}(\boldsymbol{\beta})}{\mathbf{S}_j^{(0)}(\boldsymbol{\beta})}\right]' \right\}\end{aligned}$$

Heinze (1999); Heinze and Schemper (2001) applied the idea of Firth (1993) by maximizing the penalized partial likelihood

$$l^*(\boldsymbol{\beta}) = l(\boldsymbol{\beta}) + 0.5 \log(|\mathcal{I}(\boldsymbol{\beta})|)$$

The score function $\mathbf{U}(\boldsymbol{\beta})$ is replaced by the modified score function by $\mathbf{U}^*(\boldsymbol{\beta}) \equiv (U^*(\beta_1), \ldots, U^*(\beta_k))'$, where

$$U^*(\beta_r) = U(\beta_r) + 0.5 \mathrm{tr}\left\{ \mathcal{I}^{-1}(\boldsymbol{\beta}) \frac{\partial \mathcal{I}(\boldsymbol{\beta})}{\partial \beta_r} \right\} \qquad r = 1, \ldots, k$$

The Firth estimate is obtained iteratively as

$$\boldsymbol{\beta}^{(s+1)} = \boldsymbol{\beta}^{(s)} + \mathcal{I}^{-1}(\boldsymbol{\beta}^{(s)}) \mathbf{U}^*(\boldsymbol{\beta}^{(s)})$$

The covariance matrix $\hat{\mathbf{V}}$ is computed as $\mathcal{I}^{-1}(\hat{\boldsymbol{\beta}})$, where $\hat{\boldsymbol{\beta}}$ is the maximum penalized partial likelihood estimate.

Explicit formulae for $\frac{\partial \mathcal{I}(\boldsymbol{\beta})}{\partial \beta_r}, r = 1, \ldots, k$

Denote

$$\begin{aligned}\mathbf{x}_h(t) &= (x_{h1}(t), \ldots, x_{hk}(t))' \\ \mathbf{Q}_{jr}^{(a)}(\boldsymbol{\beta}) &= \sum_{h \in \mathcal{R}j} \mathrm{e}^{\boldsymbol{\beta}' \mathbf{x}_h(t_j)} x_{hr}(t_j) [\mathbf{x}_h(t_j)]^{\otimes a} \qquad a = 0, 1, 2; r = 1, \ldots, k\end{aligned}$$

Then

$$\begin{aligned}\frac{\partial \mathcal{I}(\boldsymbol{\beta})}{\partial \beta_r} = \sum_{j=1}^{m} d_j \Bigg\{ &\left[\frac{\mathbf{Q}_{jr}^{(2)}(\boldsymbol{\beta})}{S_j^{(0)}(\boldsymbol{\beta})} - \frac{\mathbf{Q}_{jr}^{(0)}(\boldsymbol{\beta})}{S_j^{(0)}(\boldsymbol{\beta})} \frac{\mathbf{S}_j^{(2)}(\boldsymbol{\beta})}{S_j^{(0)}(\boldsymbol{\beta})}\right] - \\ &\left[\frac{\mathbf{Q}_{jr}^{(1)}(\boldsymbol{\beta})}{S_j^{(0)}(\boldsymbol{\beta})} - \frac{\mathbf{Q}_{jr}^{(0)}(\boldsymbol{\beta})}{S_j^{(0)}(\boldsymbol{\beta})} \frac{\mathbf{S}_j^{(1)}(\boldsymbol{\beta})}{S_j^{(0)}(\boldsymbol{\beta})}\right]\left[\frac{\mathbf{S}_j^{(1)}(\boldsymbol{\beta})}{S_j^{(0)}(\boldsymbol{\beta})}\right]' - \\ &\left[\frac{\mathbf{S}_j^{(1)}(\boldsymbol{\beta})}{S_j^{(0)}(\boldsymbol{\beta})}\right]\left[\frac{\mathbf{Q}_{jr}^{(1)}(\boldsymbol{\beta})}{S_j^{(0)}(\boldsymbol{\beta})} - \frac{\mathbf{Q}_{jr}^{(0)}(\boldsymbol{\beta})}{S_j^{(0)}(\boldsymbol{\beta})} \frac{\mathbf{S}_j^{(1)}(\boldsymbol{\beta})}{S_j^{(0)}(\boldsymbol{\beta})}\right]' \Bigg\} \qquad r = 1, \ldots, k\end{aligned}$$

Robust Sandwich Variance Estimate

For the ith subject, $i = 1, \ldots, n$, let X_i, w_i, and $\mathbf{Z}_i(t)$ be the observed time, weight, and the covariate vector at time t, respectively. Let Δ_i be the event indicator and let $Y_i(t) = I(X_i \geq t)$. Let

$$S^{(r)}(\boldsymbol{\beta}, t) = \sum_{j=1}^{n} w_j Y_j(t) \mathrm{e}^{\boldsymbol{\beta}' \mathbf{Z}_j(t)} \mathbf{Z}_j^{\otimes r}(t), r = 0, 1$$

Let $\bar{\mathbf{Z}}(\boldsymbol{\beta}, t) = \frac{S^{(1)}(\boldsymbol{\beta},t)}{S^{(0)}(\boldsymbol{\beta},t)}$. The score residual for the ith subject is

$$\mathbf{L}_i(\boldsymbol{\beta}) = \Delta_i \left\{ \mathbf{Z}_i(X_i) - \bar{\mathbf{Z}}(\beta, X_i) \right\} - \sum_{j=1}^{n} \Delta_j \frac{w_j Y_i(X_j) \mathrm{e}^{\boldsymbol{\beta}' \mathbf{Z}_i(X_j)}}{S^{(0)}(\boldsymbol{\beta}, X_j)} \left\{ \mathbf{Z}_i(X_j) - \bar{\mathbf{Z}}(\boldsymbol{\beta}, X_j) \right\}$$

For TIES=EFRON, the computation of the score residuals is modified to comply with the Efron partial likelihood. For more information, see the section "Residuals" on page 6921.

The robust sandwich variance estimate of $\hat{\boldsymbol{\beta}}$ derived by Binder (1992), who incorporated weights into the analysis, is

$$\hat{\mathbf{V}}_s(\hat{\boldsymbol{\beta}}) = \mathcal{I}^{-1}(\hat{\boldsymbol{\beta}}) \left[\sum_{j=1}^{n} (w_j \mathbf{L}_j(\hat{\boldsymbol{\beta}}))^{\otimes 2} \right] \mathcal{I}^{-1}(\hat{\boldsymbol{\beta}})$$

where $\mathcal{I}(\hat{\boldsymbol{\beta}})$ is the observed information matrix, and $\mathbf{a}^{\otimes 2} = \mathbf{a}\mathbf{a}'$. Note that when $w_i \equiv 1$,

$$\hat{\mathbf{V}}_s(\hat{\boldsymbol{\beta}}) = \mathbf{D}'\mathbf{D}$$

where $\mathbf{D}$ is the matrix of DFBETA residuals. This robust variance estimate was proposed by Lin and Wei (1989) and Reid and Crépeau (1985).

Testing the Global Null Hypothesis

The following statistics can be used to test the global null hypothesis $H_0: \boldsymbol{\beta} = \mathbf{0}$. Under mild assumptions, each statistic has an asymptotic chi-square distribution with p degrees of freedom given the null hypothesis. The value p is the dimension of $\boldsymbol{\beta}$. For clustered data, the likelihood ratio test, the score test, and the Wald test assume independence of observations within a cluster, while the robust Wald test and the robust score test do not need such an assumption.

Likelihood Ratio Test

$$\chi^2_{\mathrm{LR}} = 2 \left[l(\hat{\boldsymbol{\beta}}) - l(\mathbf{0}) \right]$$

Score Test

$$\chi^2_S = \left[\frac{\partial l(\mathbf{0})}{\partial \boldsymbol{\beta}}\right]' \left[-\frac{\partial^2 l(\mathbf{0})}{\partial \boldsymbol{\beta}^2}\right]^{-1} \left[\frac{\partial l(\mathbf{0})}{\partial \boldsymbol{\beta}}\right]$$

Wald's Test

$$\chi^2_W = \hat{\boldsymbol{\beta}}' \left[-\frac{\partial^2 l(\hat{\boldsymbol{\beta}})}{\partial \boldsymbol{\beta}^2}\right] \hat{\boldsymbol{\beta}}$$

Robust Score Test

$$\chi^2_{\mathrm{RS}} = \left[\sum_i \mathbf{L}_i^0\right]' \left[\sum_i \mathbf{L}_i^0 \mathbf{L}_i^{0\prime}\right]^{-1} \left[\sum_i \mathbf{L}_i^0\right]$$

where $\mathbf{L}_i^0$ is the score residual of the ith subject at $\boldsymbol{\beta} = \mathbf{0}$; that is, $\mathbf{L}_i^0 = \mathbf{L}_i(\mathbf{0}, \infty)$, where the score process $\mathbf{L}_i(\boldsymbol{\beta}, t)$ is defined in the section "Residuals" on page 6921.

Robust Wald's Test

$$\chi^2_{\mathrm{RW}} = \hat{\boldsymbol{\beta}}'[\hat{\mathbf{V}}_s(\hat{\boldsymbol{\beta}})]^{-1}\hat{\boldsymbol{\beta}}$$

where $\hat{\mathbf{V}}_s(\hat{\boldsymbol{\beta}})$ is the sandwich variance estimate. For more information, see the section "Robust Sandwich Variance Estimate" on page 6906.

Type 3 Tests and Joint Tests

For models that use less-than-full-rank parameterization (as specified by the PARAM=GLM option in the CLASS statement), a Type 3 test of an effect of interest (main effect or interaction) is a test of the Type III estimable functions that are defined for that effect. When the model contains no missing cells, the Type 3 test of a main effect corresponds to testing the hypothesis of equal marginal means. For more information about Type III estimable functions, see Chapter 47, "The GLM Procedure," and Chapter 15, "The Four Types of Estimable Functions." Also see Littell, Freund, and Spector (1991).

For models that use full-rank parameterization, all parameters are estimable when there are no missing cells, so it is unnecessary to define estimable functions. The standard test of an effect of interest in this case is the joint test that the values of the parameters associated with that effect are zero. For a model that uses effects parameterization (as specified by the PARAM=EFFECT option in the CLASS statement), the joint test for a main effect is equivalent to testing the equality of marginal means. For a model that uses reference parameterization (as specified by the PARAM=REF option in the CLASS statement), the joint test is equivalent to testing the equality of cell means at the reference level of the other model effects. For more information about the coding scheme and the associated interpretation of results, see Muller and Fetterman (2002, Chapter 14).

If there is no interaction term, the Type 3 test of an effect for a model that uses GLM parameterization is the same as the joint test of the effect for the model that uses full-rank parameterization. In this situation, the joint test is also called the Type 3 test. For a model that contains an interaction term and no missing cells,

the Type 3 test of a component main effect under GLM parameterization is the same as the joint test of the component main effect under effect parameterization. Both test the equality of cell means. But this Type 3 test differs from the joint test under reference parameterization, which tests the equality of cell means at the reference level of the other component main effect. If some cells are missing, you can obtain meaningful tests only by testing a Type III estimation function, so in this case you should use GLM parameterization.

The results of a Type 3 test or a joint test do not depend on the order in which you specify the terms in the MODEL statement.

The following statistics can be used to test the null hypothesis H_{0L}: $\mathbf{L}\boldsymbol{\beta} = \mathbf{0}$, where $\mathbf{L}$ is a matrix of known coefficients. Under mild assumptions, each of the following statistics has an asymptotic chi-square distribution with p degrees of freedom, where p is the rank of $\mathbf{L}$. Let $\tilde{\boldsymbol{\beta}}_{\mathbf{L}}$ be the maximum likelihood of $\boldsymbol{\beta}$ under the null hypothesis $H_{0\mathbf{L}}$; that is,

$$l(\tilde{\boldsymbol{\beta}}_{\mathbf{L}}) = \max_{\mathbf{L}\boldsymbol{\beta}=\mathbf{0}} l(\boldsymbol{\beta})$$

Likelihood Ratio Statistic

$$\chi^2_{\mathrm{LR}} = 2\left[l(\hat{\boldsymbol{\beta}}) - l(\tilde{\boldsymbol{\beta}}_{\mathbf{L}})\right]$$

Score Statistic

$$\chi^2_S = \left[\frac{\partial l(\tilde{\boldsymbol{\beta}}_{\mathbf{L}})}{\partial \boldsymbol{\beta}}\right]' \left[-\frac{\partial^2 l(\tilde{\boldsymbol{\beta}}_{\mathbf{L}})}{\partial \boldsymbol{\beta}^2}\right]^{-1} \left[\frac{\partial l(\tilde{\boldsymbol{\beta}}_{\mathbf{L}})}{\partial \boldsymbol{\beta}}\right]$$

Wald's Statistic

$$\chi^2_W = \left(\mathbf{L}\hat{\boldsymbol{\beta}}\right)' \left[\mathbf{L}\hat{\mathbf{V}}(\hat{\boldsymbol{\beta}})\mathbf{L}'\right]^{-1} \left(\mathbf{L}\hat{\boldsymbol{\beta}}\right)$$

where $\hat{\mathbf{V}}(\hat{\boldsymbol{\beta}})$ is the estimated covariance matrix, which can be the model-based covariance matrix $\left[-\frac{\partial^2 l(\hat{\boldsymbol{\beta}})}{\partial \boldsymbol{\beta}^2}\right]^{-1}$ or the sandwich covariance matrix $V_S(\hat{\boldsymbol{\beta}})$. For more information, see the section "Robust Sandwich Variance Estimate" on page 6906.

Confidence Limits for a Hazard Ratio

Let $\mathbf{e}_j$ be the jth unit vector—that is, the jth entry of the vector is 1 and all other entries are 0. The hazard ratio for the explanatory variable with regression coefficient $\beta_j = \mathbf{e}_j'\boldsymbol{\beta}$ is defined as $\exp(\beta_j)$. In general, a log-hazard ratio can be written as $\mathbf{h}'\boldsymbol{\beta}$, a linear combination of the regression coefficients, and the hazard ratio $\exp(\mathbf{h}'\boldsymbol{\beta})$ is obtained by replacing $\mathbf{e}_j$ with $\mathbf{h}$.

Point Estimate

The hazard ratio $\exp(\mathbf{e}_j'\boldsymbol{\beta})$ is estimated by $\exp(\mathbf{e}_j'\hat{\beta})$, where $\hat{\boldsymbol{\beta}}$ is the maximum likelihood estimate of the $\boldsymbol{\beta}$.

Wald's Confidence Limits

The $100(1-\alpha)\%$ confidence limits for the hazard ratio are calculated as

$$\exp\left(\mathbf{e}_j'\hat{\beta} \pm z_{\alpha/2}\sqrt{\mathbf{e}_j'\hat{\mathbf{V}}(\hat{\boldsymbol{\beta}})\mathbf{e}_j}\right)$$

where $\hat{\mathbf{V}}(\hat{\boldsymbol{\beta}})$ is estimated covariance matrix, and $z_{\alpha/2}$ is the $100(1-\alpha/2)$th percentile point of the standard normal distribution.

Profile-Likelihood Confidence Limits

The construction of the profile-likelihood-based confidence interval is derived from the asymptotic χ^2 distribution of the generalized likelihood ratio test of Venzon and Moolgavkar (1988). Suppose that the parameter vector is $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_k)'$ and you want to compute a confidence interval for β_j. The profile-likelihood function for $\beta_j = \gamma$ is defined as

$$l_j^*(\gamma) = \max_{\boldsymbol{\beta} \in \mathcal{B}_j(\gamma)} l(\boldsymbol{\beta})$$

where $\mathcal{B}_j(\gamma)$ is the set of all $\boldsymbol{\beta}$ with the jth element fixed at γ, and $l(\boldsymbol{\beta})$ is the log-likelihood function for $\boldsymbol{\beta}$. If $l_{\max} = l(\hat{\boldsymbol{\beta}})$ is the log likelihood evaluated at the maximum likelihood estimate $\hat{\boldsymbol{\beta}}$, then $2(l_{\max} - l_j^*(\beta_j))$ has a limiting chi-square distribution with one degree of freedom if β_j is the true parameter value. Let $l_0 = l_{\max} - 0.5\chi_1^2(1-\alpha)$, where $\chi_1^2(1-\alpha)$ is the $100(1-\alpha)$th percentile of the chi-square distribution with one degree of freedom. A $100(1-\alpha)\%$ confidence interval for β_j is

$$\{\gamma : l_j^*(\gamma) \geq l_0\}$$

The endpoints of the confidence interval are found by solving numerically for values of β_j that satisfy equality in the preceding relation. To obtain an iterative algorithm for computing the confidence limits, the log-likelihood function in a neighborhood of $\boldsymbol{\beta}$ is approximated by the quadratic function

$$\tilde{l}(\boldsymbol{\beta} + \boldsymbol{\delta}) = l(\boldsymbol{\beta}) + \boldsymbol{\delta}'\mathbf{g} + \frac{1}{2}\boldsymbol{\delta}'\mathbf{V}\boldsymbol{\delta}$$

where $\mathbf{g} = \mathbf{g}(\boldsymbol{\beta})$ is the gradient vector and $\mathbf{V} = \mathbf{V}(\boldsymbol{\beta})$ is the Hessian matrix. The increment $\boldsymbol{\delta}$ for the next iteration is obtained by solving the likelihood equations

$$\frac{d}{d\boldsymbol{\delta}}\{\tilde{l}(\boldsymbol{\beta} + \boldsymbol{\delta}) + \lambda(\mathbf{e}_j'\boldsymbol{\delta} - \gamma)\} = \mathbf{0}$$

where λ is the Lagrange multiplier, $\mathbf{e}_j$ is the jth unit vector, and γ is an unknown constant. The solution is

$$\boldsymbol{\delta} = -\mathbf{V}^{-1}(\mathbf{g} + \lambda\mathbf{e}_j)$$

By substituting this $\boldsymbol{\delta}$ into the equation $\tilde{l}(\boldsymbol{\beta} + \boldsymbol{\delta}) = l_0$, you can estimate λ as

$$\lambda = \pm\left(\frac{2(l_0 - l(\boldsymbol{\beta}) + \frac{1}{2}\mathbf{g}'\mathbf{V}^{-1}\mathbf{g})}{\mathbf{e}_j'\mathbf{V}^{-1}\mathbf{e}_j}\right)^{\frac{1}{2}}$$

The upper confidence limit for β_j is computed by starting at the maximum likelihood estimate of $\boldsymbol{\beta}$ and iterating with positive values of λ until convergence is attained. The process is repeated for the lower confidence limit, using negative values of λ.

Convergence is controlled by value ϵ specified with the PLCONV= option in the MODEL statement (the default value of ϵ is 1E–4). Convergence is declared on the current iteration if the following two conditions are satisfied:

$$|l(\boldsymbol{\beta}) - l_0| \leq \epsilon$$

and

$$(\mathbf{g} + \lambda \mathbf{e}_j)' \mathbf{V}^{-1} (\mathbf{g} + \lambda \mathbf{e}_j) \leq \epsilon$$

The profile-likelihood confidence limits for the hazard ratio $\exp(\mathbf{e}_j' \boldsymbol{\beta})$ are obtained by exponentiating these confidence limits.

Using the TEST Statement to Test Linear Hypotheses

Linear hypotheses for $\boldsymbol{\beta}$ are expressed in matrix form as

$$H_0: \mathbf{L}\boldsymbol{\beta} = \mathbf{c}$$

where $\mathbf{L}$ is a matrix of coefficients for the linear hypotheses, and $\mathbf{c}$ is a vector of constants. The Wald chi-square statistic for testing H_0 is computed as

$$\chi^2_W = \left(\mathbf{L}\hat{\boldsymbol{\beta}} - \mathbf{c}\right)' \left[\mathbf{L}\hat{\mathbf{V}}(\hat{\boldsymbol{\beta}})\mathbf{L}'\right]^{-1} \left(\mathbf{L}\hat{\boldsymbol{\beta}} - \mathbf{c}\right)$$

where $\hat{\mathbf{V}}(\hat{\boldsymbol{\beta}})$ is the estimated covariance matrix. Under H_0, χ^2_W has an asymptotic chi-square distribution with r degrees of freedom, where r is the rank of $\mathbf{L}$.

Optimal Weights for the AVERAGE option in the TEST Statement

Let $\boldsymbol{\beta}_0 = (\beta_{i_1}, \ldots, \beta_{i_s})'$, where $\{\beta_{i_1}, \ldots, \beta_{i_s}\}$ is a subset of s regression coefficients. For any vector $\mathbf{e} = (e_1, \ldots, e_s)'$ of length s,

$$\mathbf{e}'\hat{\boldsymbol{\beta}}_0 \sim N(\mathbf{e}'\boldsymbol{\beta}_0, \mathbf{e}'\hat{\mathbf{V}}(\hat{\boldsymbol{\beta}}_0)\mathbf{e})$$

To find $\mathbf{e}$ such that $\mathbf{e}'\hat{\boldsymbol{\beta}}_0$ has the minimum variance, it is necessary to minimize $\mathbf{e}'\hat{\mathbf{V}}(\hat{\boldsymbol{\beta}}_0)\mathbf{e}$ subject to $\sum_{i=1}^{k} e_i = 1$. Let $\mathbf{1}_s$ be a vector of 1's of length s. The expression to be minimized is

$$\mathbf{e}'\hat{\mathbf{V}}(\hat{\boldsymbol{\beta}}_0)\mathbf{e} - \lambda(\mathbf{e}'\mathbf{1}_s - 1)$$

where λ is the Lagrange multiplier. Differentiating with respect to $\mathbf{e}$ and λ, respectively, yields

$$\begin{aligned} \hat{\mathbf{V}}(\hat{\boldsymbol{\beta}}_0)\mathbf{e} - \lambda\mathbf{1}_s &= \mathbf{0} \\ \mathbf{e}'\mathbf{1}_s - 1 &= 0 \end{aligned}$$

Solving these equations gives

$$\mathbf{e} = [\mathbf{1}_s'\hat{\mathbf{V}}^{-1}(\hat{\boldsymbol{\beta}}_0)\mathbf{1}_s]^{-1}\hat{\mathbf{V}}^{-1}(\hat{\boldsymbol{\beta}}_0)\mathbf{1}_s$$

This provides a one degree-of-freedom test for testing the null hypothesis $H_0 : \beta_{i_1} = \ldots = \beta_{i_s} = 0$ with normal test statistic

$$Z = \frac{\mathbf{e}'\hat{\boldsymbol{\beta}}_0}{\sqrt{\mathbf{e}'\hat{\mathbf{V}}(\hat{\boldsymbol{\beta}}_0)\mathbf{e}}}$$

This test is more sensitive than the multivariate test specified by the TEST statement

```
Multivariate: test X1, ..., Xs;
```

where X1, ..., Xs are the variables with regression coefficients $\beta_{i_1}, \ldots, \beta_{i_s}$, respectively.

Analysis of Multivariate Failure Time Data

Multivariate failure time data arise when each study subject can potentially experience several events (for instance, multiple infections after surgery) or when there exists some natural or artificial clustering of subjects (for instance, a litter of mice) that induces dependence among the failure times of the same cluster. Data in the former situation are referred to as multiple events data, and data in the latter situation are referred to as clustered data. The multiple events data can be further classified into ordered and unordered data. For ordered data, there is a natural ordering of the multiple failures within a subject, which includes recurrent events data as a special case. For unordered data, the multiple event times result from several concurrent failure processes.

Multiple events data can be analyzed by the Wei, Lin, and Weissfeld (1989), or WLW, method based on the marginal Cox models. For the special case of recurrent events data, you can fit the intensity model (Andersen and Gill 1982), the proportional rates/means model (Pepe and Cai 1993; Lawless and Nadeau 1995; Lin et al. 2000), or the stratified models for total time and gap time proposed by Prentice, Williams, and Peterson (1981), or PWP. For clustered data, you can carry out the analysis of Lee, Wei, and Amato (1992) based on the marginal Cox model. To use PROC PHREG to perform these analyses correctly and effectively, you have to array your data in a specific way to produce the correct risk sets.

All examples described in this section can be found in the program *phrmult.sas* in the SAS/STAT sample library. Furthermore, the "Examples" section in this chapter contains two examples to illustrate the methods of analyzing recurrent events data and clustered data.

Marginal Cox Models for Multiple Events Data

Suppose there are n subjects and each subject can experience up to K potential events. Let $\mathbf{Z}_{ki}(.)$ be the covariate process associated with the kth event for the ith subject. The marginal Cox models are given by

$$\lambda_k(t;\mathbf{Z}_{ki}) = \lambda_{k0}e^{\boldsymbol{\beta}_k'\mathbf{Z}_{ki}(t)}, k = 1,\ldots,K; i = 1,\ldots,n$$

where $\lambda_{k0}(t)$ is the (event-specific) baseline hazard function for the kth event and $\boldsymbol{\beta}_k$ is the (event-specific) column vector of regression coefficients for the kth event. WLW estimates $\boldsymbol{\beta}_1,\ldots,\boldsymbol{\beta}_K$ by the maximum

partial likelihood estimates $\hat{\boldsymbol{\beta}}_1, \ldots, \hat{\boldsymbol{\beta}}_K$, respectively, and uses a robust sandwich covariance matrix estimate for $(\hat{\boldsymbol{\beta}}'_1, \ldots, \hat{\boldsymbol{\beta}}'_K)'$ to account for the dependence of the multiple failure times.

By using a properly prepared input data set, you can estimate the regression parameters for all the marginal Cox models and compute the robust sandwich covariance estimates in one PROC PHREG invocation. For convenience of discussion, suppose each subject can potentially experience $K = 3$ events and there are two explanatory variables Z1 and Z2. The event-specific parameters to be estimated are $\boldsymbol{\beta}_1 = (\beta_{11}, \beta_{21})'$ for the first marginal model, $\boldsymbol{\beta}_2 = (\beta_{12}, \beta_{22})'$ for the second marginal model, and $\boldsymbol{\beta}_3 = (\beta_{13}, \beta_{23})'$ for the third marginal model. Inference of these parameters is based on the robust sandwich covariance matrix estimate of the parameter estimators. It is necessary that each row of the input data set represent the data for a potential event of a subject. The input data set should contain the following:

- an ID variable for identifying the subject so that all observations of the same subject have the same ID value
- an Enum variable to index the multiple events. For example, Enum=1 for the first event, Enum=2 for the second event, and so on.
- a Time variable to represent the observed time from some time origin for the event. For recurrence events data, it is the time from the study entry to each recurrence.
- a Status variable to indicate whether the Time value is a censored or uncensored time. For example, Status=1 indicates an uncensored time and Status=0 indicates a censored time.
- independent variables (Z1 and Z2)

The WLW analysis can be carried out by specifying the following:

```
proc phreg covs(aggregate);
   model Time*Status(0)=Z11 Z12 Z13 Z21 Z22 Z23;
   strata Enum;
   id ID;
   Z11= Z1 * (Enum=1);
   Z12= Z1 * (Enum=2);
   Z13= Z1 * (Enum=3);
   Z21= Z2 * (Enum=1);
   Z22= Z2 * (Enum=2);
   Z23= Z2 * (Enum=3);
run;
```

The variable Enum is specified in the STRATA statement so that there is one marginal Cox model for each distinct value of Enum. The variables Z11, Z12, Z13, Z21, Z22, and Z23 in the MODEL statement are event-specific variables derived from the independent variables Z1 and Z2 by the given programming statements. In particular, the variables Z11, Z12, and Z13 are event-specific variables for the explanatory variable Z1; the variables Z21, Z22, and Z23 are event-specific variables for the explanatory variable Z2. For $j = 1, 2$, and $k = 1, 2, 3$, variable Zjk contains the same values as the explanatory variable Zj for the rows that correspond to kth marginal model and the value 0 for all other rows; as such, β_{jk} is the regression coefficient for Zjk. You can avoid using the programming statements in PROC PHREG if you create these event-specific variables in the input data set by using the same programming statements in a DATA step.

The option COVS(AGGREGATE) is specified in the PROC PHREG statement to obtain the robust sandwich estimate of the covariance matrix, and the score residuals used in computing the middle part of the sandwich

estimate are aggregated over identical ID values. You can also include TEST statements in the PROC PHREG code to test various linear hypotheses of the regression parameters based on the robust sandwich covariance matrix estimate.

Consider the AIDS study data in Wei, Lin, and Weissfeld (1989) from a randomized clinical trial to assess the antiretroviral capacity of ribavirin over time in AIDS patients. Blood samples were collected at weeks 4, 8, and 12 from each patient in three treatment groups (placebo, low dose of ribavirin, and high dose). For each serum sample, the failure time is the number of days before virus positivity was detected. If the sample was contaminated or it took a longer period of time than was achievable in the laboratory, the sample was censored. For example:

- Patient #1 in the placebo group has uncensored times 9, 6, and 7 days (that is, it took 9 days to detect viral positivity in the first blood sample, 6 days for the second blood sample, and 7 days for the third blood sample).
- Patient #14 in the low-dose group of ribavirin has uncensored times of 16 and 17 days for the first and second sample, respectively, and a censored time of 21 days for the third blood sample.
- Patient #28 in the high-dose group has an uncensored time of 21 days for the first sample, no measurement for the second blood sample, and a censored time of 25 days for the third sample.

For a full-rank parameterization, two design variables are sufficient to represent three treatment groups. Based on the reference coding with placebo as the reference, the values of the two dummy explanatory variables Z1 and Z2 representing the treatments are as follows:

Treatment Group	Z1	Z2
Placebo	0	0
Low dose ribavirin	1	0
High dose ribavirin	0	1

The bulk of the task in using PROC PHREG to perform the WLW analysis lies in the preparation of the input data set. As discussed earlier, the input data set should contain the ID, Enum, Time, and Status variables, and event-specific independent variables Z11, Z12, Z13, Z21, Z22, and Z23. Data for the three patients described earlier are arrayed as follows:

ID	Time	Status	Enum	Z1	Z2
1	9	1	1	0	0
1	6	1	2	0	0
1	7	1	3	0	0
14	16	1	1	1	0
14	17	1	2	1	0
14	21	0	3	1	0
28	21	1	1	0	1
28	25	0	3	0	1

The first three rows are data for Patient #1 with event times at 9, 6, and 7 days, one row for each event. The next three rows are data for Patient #14, who has an uncensored time of 16 days for the first serum sample, an uncensored time of 17 days for the second sample, and a censored time of 21 days for the third sample. The last two rows are data for Patient #28 of the high-dose group (Z1=0 and Z2=1). Since the patient did not have a second serum sample, there are only two rows of data.

To perform the WLW analysis, you specify the following statements:

```
proc phreg covs(aggregate);
   model Time*Status(0)=Z11 Z12 Z13 Z21 Z22 Z23;
   strata Enum;
   id ID;
   Z11= Z1 * (Enum=1);
   Z12= Z1 * (Enum=2);
   Z13= Z1 * (Enum=3);
   Z21= Z2 * (Enum=1);
   Z22= Z2 * (Enum=2);
   Z23= Z2 * (Enum=3);
   EqualLowDose: test Z11=Z12, Z12=Z23;
   AverageLow: test Z11,Z12,Z13 / e average;
run;
```

Two linear hypotheses are tested using the TEST statements. The specification

```
   EqualLowDose: test Z11=Z12, Z12=Z13;
```

tests the null hypothesis $\beta_{11} = \beta_{12} = \beta_{13}$ of identical low-dose effects across three marginal models. The specification

```
AverageLow: test Z11,Z12,Z13 / e average;
```

tests the null hypothesis of no low-dose effects (that is, $\beta_{11} = \beta_{12} = \beta_{13} = 0$). The AVERAGE option computes the optimal weights for estimating the average low-dose effect $\bar{\beta}_1 = \beta_{11} = \beta_{12} = \beta_{13}$ and performs a 1 DF test for testing the null hypothesis that $\bar{\beta}_1 = 0$. The E option displays the coefficients for the linear hypotheses, including the optimal weights.

Marginal Cox Models for Clustered Data

Suppose there are n clusters with K_i members in the ith cluster, $i = 1, \ldots, n$. Let $\mathbf{Z}_{ki}(.)$ be the covariate process associated with the kth member of the ith cluster. The marginal Cox model is given by

$$\lambda(t; \mathbf{Z}_{ki}) = \lambda_0(t) e^{\boldsymbol{\beta}' \mathbf{Z}_{ki}(t)} k = 1, \ldots, K_i; i = 1, \ldots, n$$

where $\lambda_0(t)$ is an arbitrary baseline hazard function and $\boldsymbol{\beta}$ is the vector of regression coefficients. Lee, Wei, and Amato (1992) estimate $\boldsymbol{\beta}$ by the maximum partial likelihood estimate $\hat{\boldsymbol{\beta}}$ under the independent working assumption, and use a robust sandwich covariance estimate to account for the intracluster dependence.

To use PROC PHREG to analyze the clustered data, each member of a cluster is represented by an observation in the input data set. The input data set to PROC PHREG should contain the following:

- an ID variable to identify the cluster so that members of the same cluster have the same ID value
- a Time variable to represent the observed survival time of a member of a cluster

- a Status variable to indicate whether the Time value is an uncensored or censored time. For example, Status=1 indicates an uncensored time and Status=0 indicates a censored time.
- the explanatory variables thought to be related to the failure time

Consider a tumor study in which one of three female rats of the same litter was randomly subjected to a drug treatment. The failure time is the time from randomization to the detection of tumor. If a rat died before the tumor was detected, the failure time was censored. For example:

- In litter #1, the drug-treated rat has an uncensored time of 101 days, one untreated rat has a censored time of 49 days, and the other untreated rat has a failure time of 104 days.
- In litter #3, the drug-treated rat has a censored time of 104 days, one untreated rat has a censored time of 102 days, and the other untreated rat has a censored time of 104 days.

In this example, a litter is a cluster and the rats of the same litter are members of the cluster. Let Trt be a 0-1 variable representing the treatment a rat received, with value 1 for drug treatment and 0 otherwise. Data for the two litters of rats described earlier contribute six observations to the input data set:

Litter	Time	Status	Trt
1	101	1	1
1	49	0	0
1	104	1	0
3	104	0	1
3	102	0	0
3	104	0	0

The analysis of Lee, Wei, and Amato (1992) can be performed by PROC PHREG as follows:

```
proc phreg covs(aggregate);
   model Time*Status(0)=Treatment;
   id Litter;
run;
```

Intensity and Rate/Mean Models for Recurrent Events Data

Suppose each subject experiences recurrences of the same phenomenon. Let $N(t)$ be the number of events a subject experiences over the interval $[0,t]$ and let $\mathbf{Z}(.)$ be the covariate process of the subject.

The intensity model (Andersen and Gill 1982) is given by

$$\lambda_{\mathbf{Z}}(t)dt = E\{dN(t)|\mathcal{F}_{t-}\} = \lambda_0(t)\mathrm{e}^{\boldsymbol{\beta}'\mathbf{Z}(t)}dt$$

where $\mathcal{F}_t$ represents all the information of the processes N and $\mathbf{Z}$ up to time t, $\lambda_0(t)$ is an arbitrary baseline intensity function, and $\boldsymbol{\beta}$ is the vector of regression coefficients. This model consists of two components: (1) all the influence of the prior events on future recurrences, if there is any, is mediated through the time-dependent covariates, and (2) the covariates have multiplicative effects on the instantaneous rate of the counting process. If the covariates are time invariant, the risk of recurrences is unaffected by the past events.

The proportional rates and means models (Pepe and Cai 1993; Lawless and Nadeau 1995; Lin et al. 2000) assume that the covariates have multiplicative effects on the mean and rate functions of the counting process. The rate function is given by

$$d\mu_{\mathbf{Z}}(t) = E\{dN(t)|\mathbf{Z}(t)\} = \mathrm{e}^{\boldsymbol{\beta}'\mathbf{Z}(t)} d\mu_0(t)$$

where $\mu_0(t)$ is an unknown continuous function and $\boldsymbol{\beta}$ is the vector of regression parameters. If $\mathbf{Z}$ is time invariant, the mean function is given by

$$\mu_{\mathbf{Z}}(t) = E\{N(t)|\mathbf{Z}\} = \mathrm{e}^{\boldsymbol{\beta}'\mathbf{Z}} \mu_0(t)$$

For both the intensity and the proportional rates/means models, estimates of the regression coefficients are obtained by solving the partial likelihood score function. However, the covariance matrix estimate for the intensity model is computed as the inverse of the observed information matrix, while that for the proportional rates/means model is given by a sandwich estimate. For a given pattern of fixed covariates, the Nelson estimate for the cumulative intensity function is the same for the cumulative mean function, but their standard errors are not the same.

To fit the intensity or rate/mean model by using PROC PHREG, the counting process style of input is needed. A subject with K events contributes $K + 1$ observations to the input data set. The kth observation of the subject identifies the time interval from the $(k - 1)$ event or time 0 (if $k = 1$) to the kth event, $k = 1, \ldots, K$. The $(K + 1)$ observation represents the time interval from the Kth event to time of censorship. The input data set should contain the following variables:

- a TStart variable to represent the $(k - 1)$ recurrence time or the value 0 if $k = 1$
- a TStop variable to represent the kth recurrence time or the follow-up time if $k = K + 1$
- a Status variable indicating whether the TStop time is a recurrence time or a censored time; for example, Status=1 for a recurrence time and Status=0 for censored time
- explanatory variables thought to be related to the recurrence times

If the rate/mean model is used, the input data should also contain an ID variable for identifying the subjects.

Consider the chronic granulomatous disease (CGD) data listed in Fleming and Harrington (1991). The disease is a rare disorder characterized by recurrent pyrogenic infections. The study is a placebo-controlled randomized clinical trial conducted by the International CGD Cooperative Study to assess the effect of gamma interferon to reduce the rate of infection. For each study patient the times of recurrent infections along with a number of prognostic factors were collected. For example:

- Patient #17404, age 38, in the gamma interferon group had a follow-up time of 293 without any infection.
- Patient #204001, age 12, in the placebo group had an infection at 219 days, a recurrent infection at 373 days, and was followed up to 414 days.

Let Trt be the variable representing the treatment status with value 1 for gamma interferon and value 2 for placebo. Let Age be a covariate representing the age of the CGD patient. Data for the two CGD patients described earlier are given in the following table.

ID	TStart	TStop	Status	Trt	Age
174054	0	293	0	1	38
204001	0	219	1	2	12
204001	219	373	1	2	12
204001	373	414	0	2	12

Since Patient #174054 had no infection through the end of the follow-up period (293 days), there is only one observation representing the period from time 0 to the end of the follow-up. Data for Patient #204001 are broken into three observations, since there are two infections. The first observation represents the period from time 0 to the first infection, the second observation represents the period from the first infection to the second infection, and the third time period represents the period from the second infection to the end of the follow-up.

The following specification fits the intensity model:

```
proc phreg;
   model (TStart,TStop)*Status(0)=Trt Age;
run;
```

You can predict the cumulative intensity function for a given pattern of fixed covariates by specifying the CUMHAZ= option in the BASELINE statement. Suppose you are interested in two fixed patterns, one for patients of age 30 in the gamma interferon group and the other for patients of age 1 in the placebo group. You first create the SAS data set as follows:

```
data Pattern;
   Trt=1; Age=30;
   output;
   Trt=2; Age=1;
   output;
run;
```

You then include the following BASELINE statement in the PROC PHREG specification. The CUMHAZ=_all_ option produces the cumulative hazard function estimates, the standard error estimates, and the lower and upper pointwise confidence limits.

```
baseline covariates=Pattern out=out1 cumhaz=_all_;
```

The following specification of PROC PHREG fits the mean model and predicts the cumulative mean function for the two patterns of covariates in the Pattern data set:

```
proc phreg covs(aggregate);
   model (Tstart,Tstop)*Status(0)=Trt Age;
   baseline covariates=Pattern out=out2 cmf=_all_;
   id ID;
run;
```

The COV(AGGREGATE) option, along with the ID statement, computes the robust sandwich covariance matrix estimate. The CMF=_ALL_ option adds the cumulative mean function estimates, the standard error estimates, and the lower and upper pointwise confidence limits to the OUT=Out2 data set.

PWP Models for Recurrent Events Data

Let $N(t)$ be the number of events a subject experiences by time t. Let $\mathbf{Z}(t)$ be the covariate vectors of the subject at time t. For a subject who has K events before censorship takes place, let $t_0 = 0$, let t_k be the kth recurrence time, $k = 1, \ldots, K$, and let t_{K+1} be the censored time. Prentice, Williams, and Peterson (1981) consider two time scales, a total time from the beginning of the study and a gap time from immediately preceding failure. The PWP models are stratified Cox-type models that allow the shape of the hazard function to depend on the number of preceding events and possibly on other characteristics of $\{N(t)$ and $\mathbf{Z}(t)\}$. The total time and gap time models are given, respectively, as follows:

$$\lambda(t|\mathcal{F}_{t-}) = \lambda_{0k}(t)e^{\boldsymbol{\beta}_k'\mathbf{Z}(t)}, \qquad t_{k-1} < t \leq t_k$$
$$\lambda(t|\mathcal{F}_{t-}) = \lambda_{0k}(t - t_{k-1})e^{\boldsymbol{\beta}_k'\mathbf{Z}(t)}, \qquad t_{k-1} < t \leq t_k$$

where λ_{0k} is an arbitrary baseline intensity functions, and $\boldsymbol{\beta}_k$ is a vector of stratum-specific regression coefficients. Here, a subject moves to the kth stratum immediately after his $(k - 1)$ recurrence time and remains there until the kth recurrence occurs or until censorship takes place. For instance, a subject who experiences only one event moves from the first stratum to the second stratum after the event occurs and remains in the second stratum until the end of the follow-up.

You can use PROC PHREG to carry out the analyses of the PWP models, but you have to prepare the input data set to provide the correct risk sets. The input data set for analyzing the total time is the same as the AG model with an additional variable to represent the stratum that the subject is in. A subject with K events contributes $K + 1$ observations to the input data set, one for each stratum that the subject moves to. The input data should contain the following variables:

- a TStart variable to represent the $(k - 1)$ recurrence time or the value 0 if $k = 1$
- a TStop variable to represent the kth recurrence time or the time of censorship if $k = K + 1$
- a Status variable with value 1 if the Time value is a recurrence time and value 0 if the Time value is a censored time
- an Enum variable representing the index of the stratum that the subject is in. For a subject who has only one event at t_1 and is followed to time t_c, Enum=1 for the first observation (where Time=t_1 and Status=1) and Enum=2 for the second observation (where Time=t_c and Status=0).
- explanatory variables thought to be related to the recurrence times

To analyze gap times, the input data set should also include a GapTime variable that is equal to (TStop – TStart).

Consider the data of two subjects in CGD data described in the previous section:

- Patients #174054, age 38, in the gamma interferon group had a follow-up time of 293 without any infection.
- Patient #204001, age 12, in the placebo group had an infection at 219 days, a recurrent infection at 373 days, and a follow-up time of 414 days.

To illustrate, suppose all subjects have at most two observed events. The data for the two subjects in the input data set are as follows:

ID	TStart	TStop	Gaptime	Status	Enum	Trt	Age
174054	0	293	293	0	1	1	38
204001	0	219	219	1	1	2	12
204001	219	373	154	1	2	2	12
204001	373	414	41	0	3	2	12

Subject #174054 contributes only one observation to the input data, since there is no observed event. Subject #204001 contributes three observations, since there are two observed events.

To fit the total time model of PWP with stratum-specific slopes, either you can create the stratum-specific explanatory variables (Trt1, Trt2, and Trt3 for Trt, and Age1, Age2, and Age3 for Age) in a DATA step, or you can specify them in PROC PHREG by using programming statements as follows:

```
proc phreg;
   model (TStart,TStop)*Status(0)=Trt1 Trt2 Trt3 Age1 Age2 Age3;
   strata Enum;
   Trt1= Trt * (Enum=1);
   Trt2= Trt * (Enum=2);
   Trt3= Trt * (Enum=3);
   Age1= Age * (Enum=1);
   Age2= Age * (Enum=2);
   Age3= Age * (Enum=3);
run;
```

To fit the total time model of PWP with the common regression coefficients, you specify the following:

```
proc phreg;
   model (TStart,TStop)*Status(0)=Trt Age;
   strata Enum;
run;
```

To fit the gap time model of PWP with stratum-specific regression coefficients, you specify the following:

```
proc phreg;
   model Gaptime*Status(0)=Trt1 Trt2 Trt3 Age1 Age2 Age3;
   strata Enum;
   Trt1= Trt * (Enum=1);
   Trt2= Trt * (Enum=2);
   Trt3= Trt * (Enum=3);
   Age1= Age * (Enum=1);
   Age2= Age * (Enum=2);
   Age3= Age * (Enum=3);
run;
```

To fit the gap time model of PWP with common regression coefficients, you specify the following:

```
proc phreg;
   model Gaptime*Status(0)=Trt Age;
   strata Enum;
run;
```

Model Fit Statistics

Suppose the model contains p regression parameters. The three statistics displayed by the PHREG procedure are calculated as follows:

- –2 log likelihood:

  $$-2 \text{ Log L} = -2\log(L_n(\hat{\boldsymbol{\beta}}))$$

  where $L_n(.)$ is a partial likelihood function for the corresponding TIES= option as described in the section "Partial Likelihood Function for the Cox Model" on page 6890, and $\hat{\boldsymbol{\beta}}$ is the maximum likelihood estimate of the regression parameter vector.

- Akaike's information criterion (AIC):

  $$\text{AIC} = -2 \text{ Log L} + 2p$$

- Schwarz Bayesian criterion (SBC):

  $$\text{SBC} = -2 \text{ Log L} + p\log(d)$$

  where d is the number of uncensored observations in the data (Volinsky and Raftery 2000). The SBC statistic is also known as the Bayesian information criterion (BIC).

The –2 log likelihood statistic has a chi-square distribution under the null hypothesis (that all the explanatory effects in the model are zero) and the procedure produces a p-value for this statistic. The AIC and SBC statistics offer two different ways of adjusting the –2 log likelihood statistic for the number of terms in the model and the number of observations used. It is recommended that you use these statistics when you compare different models for the same data (for example, when you use the METHOD=STEPWISE option in the MODEL statement); lower values of the statistic indicate a more desirable model.

Schemper-Henderson Predictive Measure

Measures of predictive accuracy of regression models quantify the extent to which covariates determine an individual outcome. Schemper and Henderson's (2000) proposed predictive accuracy measure is defined as the difference between individual processes and the fitted survivor function.

For the ith individual ($1 \le i \le n$), let l_i, X_i, Δ_i, and $\mathbf{Z}_i$ be the left-truncation time, observed time, event indicator (1 for death and 0 for censored), and covariate vector, respectively. If there is no delay entry, then $l_i = 0$. Let $t_{(1)} < \cdots < t_{(m)}$ be m distinct event times with d_j deaths at $t_{(j)}$. The survival process $Y_i(t)$ for the ith individual is

$$Y_i(t) = \begin{cases} 1 & l_i \le t < X_i \\ 0 & t \ge X_i \text{ and } \Delta_i = 1 \\ \text{undefined} & t \ge X_i \text{ and } \Delta_i = 0 \end{cases}$$

Let $\hat{S}(t)$ be the Kaplan-Meier estimate of the survivor function (assuming no covariates). Let $\hat{S}(t|\mathbf{Z})$ be the fitted survivor function with covariates $\mathbf{Z}$, and if you specify TIES=EFRON, then $\hat{S}(t|\mathbf{Z})$ is computed by the Efron method; otherwise, the Breslow estimate is used.

The predictive accuracy is defined as the difference between individual survival processes $Y_i(t)$ and the fitted survivor functions with ($\hat{S}(t|\mathbf{Z}_i)$) or without ($\hat{S}(t)$) covariates between 0 and τ, the largest observed time. For each death time $t_{(j)}$, define a mean absolute distance between the $Y_i(t)$ and the $\hat{S}(t)$ as

$$\begin{aligned}\hat{M}(t_{(j)}) &= \frac{1}{n_j}\sum_{i=1}^{n} I(l_i \le t_{(j)})\Big\{ I(X_i > t_{(j)} \ge l_i)(1-\hat{S}(t_{(j)})) + \Delta_i I(X_i \le t_{(j)})\hat{S}(t_{(j)}) \\ &\quad + (1-\Delta_i) I(X_i \le t_{(j)}) \left[(1-\hat{S}(t_{(j)}))\frac{\hat{S}(t_{(j)})}{\hat{S}(X_i)} + \hat{S}(t_{(j)})\left(1-\frac{\hat{S}(t_{(j)})}{\hat{S}(X_i)}\right)\right]\Big\}\end{aligned}$$

where $n_j = \sum_{i=1}^{n} I(l_i \le t_{(j)})$. Let $\hat{M}(t_{(j)}|\mathbf{Z})$ be defined similarly to $\hat{M}(t_{(j)})$, but with $\hat{S}(t_{(j)})$ replaced by $\hat{S}(t_{(j)}|\mathbf{Z}_i)$ and $\hat{S}(X_i)$ replaced by $\hat{S}(X_i|\mathbf{Z}_i)$. Let $\hat{G}(t)$ be the Kaplan-Meier estimate of the censoring or potential follow-up distribution, and let

$$w = \sum_{j=1}^{m} \frac{d_j}{\hat{G}(t_{(j)})}$$

The overall estimator of the predictive accuracy with ($\hat{D}_z$) and without ($\hat{D}$) covariates are weighted averages of $\hat{M}(t_{(j)}|\mathbf{Z})$ and $\hat{M}(t_{(j)})$, respectively, given by

$$\begin{aligned}\hat{D}_z &= \frac{1}{w}\sum_{j=1}^{m} \frac{d_j}{\hat{G}(t_{(j)})}\hat{M}(t_{(j)}|\mathbf{Z}) \\ \hat{D} &= \frac{1}{w}\sum_{j=1}^{m} \frac{d_j}{\hat{G}(t_{(j)})}\hat{M}(t_{(j)})\end{aligned}$$

The explained variation by the Cox regression is

$$V = 100\left(1-\frac{\hat{D}_z}{\hat{D}}\right)\%$$

Because the predictive accuracy measures $\hat{D}_z$ and $\hat{D}$ are based on differences between individual survival processes and fitted survivor functions, a smaller value indicates a better prediction. For this reason, $\hat{D}_z$ and $\hat{D}$ are also referred to as predictive inaccuracy measures.

Residuals

This section describes the computation of residuals (RESMART=, RESDEV=, RESSCH=, and RESSCO=) in the OUTPUT statement.

First, consider TIES=BRESLOW. Let

$$\begin{aligned} S^{(0)}(\boldsymbol{\beta},t) &= \sum_i Y_i(t)\mathrm{e}^{\boldsymbol{\beta}'\mathbf{Z}_i(t)} \\ S^{(1)}(\boldsymbol{\beta},t) &= \sum_i Y_i(t)\mathrm{e}^{\boldsymbol{\beta}'\mathbf{Z}_i(t)}\mathbf{Z}_i(t) \\ \bar{\mathbf{Z}}(\boldsymbol{\beta},t) &= \frac{S^{(1)}(\boldsymbol{\beta},t)}{S^{(0)}(\boldsymbol{\beta},t)} \\ d\Lambda_0(\boldsymbol{\beta},t) &= \sum_i \frac{dN_i(t)}{S^{(0)}(\boldsymbol{\beta},t)} \\ dM_i(\boldsymbol{\beta},t) &= dN_i(t) - Y_i(t)\mathrm{e}^{\boldsymbol{\beta}'\mathbf{Z}_i(t)}d\Lambda_0(\boldsymbol{\beta},t) \end{aligned}$$

The martingale residual at t is defined as

$$\hat{M}_i(t) = \int_0^t dM_i(\hat{\boldsymbol{\beta}},s) = N_i(t) - \int_0^t Y_i(s)\mathrm{e}^{\hat{\boldsymbol{\beta}}'\mathbf{Z}_i(s)}d\Lambda_0(\hat{\boldsymbol{\beta}},s)$$

Here $\hat{M}_i(t)$ estimates the difference over $(0,t]$ between the observed number of events for the ith subject and a conditional expected number of events. The quantity $\hat{M}_i \equiv \hat{M}_i(\infty)$ is referred to as the martingale residual for the ith subject. When the counting process MODEL specification is used, the RESMART= variable contains the component $(\hat{M}_i(t_2) - \hat{M}_i(t_1))$ instead of the martingale residual at t_2. The martingale residual for a subject can be obtained by summing up these component residuals within the subject. For the Cox model with no time-dependent explanatory variables, the martingale residual for the ith subject with observation time t_i and event status Δ_i is

$$\hat{M}_i = \Delta_i - \mathrm{e}^{\hat{\boldsymbol{\beta}}'\mathbf{Z}_i}\int_0^{t_i} d\Lambda_0(\hat{\boldsymbol{\beta}},s)$$

The deviance residuals D_i are a transform of the martingale residuals:

$$D_i = \mathrm{sign}(\hat{M}_i)\sqrt{2\left[-\hat{M}_i - N_i(\infty)\log\left(\frac{N_i(\infty)-\hat{M}_i}{N_i(\infty)}\right)\right]}$$

The square root shrinks large negative martingale residuals, while the logarithmic transformation expands martingale residuals that are close to unity. As such, the deviance residuals are more symmetrically distributed around zero than the martingale residuals. For the Cox model, the deviance residual reduces to the form

$$D_i = \mathrm{sign}(\hat{M}_i)\sqrt{2[-\hat{M}_i - \Delta_i\log(\Delta_i - \hat{M}_i)]}$$

When the counting process MODEL specification is used, values of the RESDEV= variable are set to missing because the deviance residuals can be calculated only on a per-subject basis.

The Schoenfeld (1982) residual vector is calculated on a per-event-time basis. At the jth event time t_{i_j} of the ith subject, the Schoenfeld residual

$$\hat{\mathbf{U}}_i(t_{i_j}) = \mathbf{Z}_i(t_{i_j}) - \bar{\mathbf{Z}}(\hat{\boldsymbol{\beta}},t_{i_j})$$

is the difference between the *i*th subject covariate vector at t_{i_j} and the average of the covariate vectors over the risk set at t_{i_j}. Under the proportional hazards assumption, the Schoenfeld residuals have the sample path of a random walk; therefore, they are useful in assessing time trend or lack of proportionality. Harrell (1986) proposed a z-transform of the Pearson correlation between these residuals and the rank order of the failure time as a test statistic for nonproportional hazards. Therneau, Grambsch, and Fleming (1990) considered a Kolmogorov-type test based on the cumulative sum of the residuals.

The score process for the *i*th subject at time t is

$$\mathbf{L}_i(\boldsymbol{\beta}, t) = \int_0^t [\mathbf{Z}_i(s) - \bar{\mathbf{Z}}(\boldsymbol{\beta}, s)] dM_i(\boldsymbol{\beta}, s)$$

The vector $\hat{\mathbf{L}}_i \equiv \mathbf{L}_i(\hat{\boldsymbol{\beta}}, \infty)$ is the score residual for the *i*th subject. When the counting process MODEL specification is used, the RESSCO= variables contain the components of $(\mathbf{L}_i(\hat{\boldsymbol{\beta}}, t_2) - \mathbf{L}_i(\hat{\boldsymbol{\beta}}, t_1))$ instead of the score process at t_2. The score residual for a subject can be obtained by summing up these component residuals within the subject.

The score residuals are a decomposition of the first partial derivative of the log likelihood. They are useful in assessing the influence of each subject on individual parameter estimates. They also play an important role in the computation of the robust sandwich variance estimators of Lin and Wei (1989) and Wei, Lin, and Weissfeld (1989).

For TIES=EFRON, the preceding computation is modified to comply with the Efron partial likelihood. For a given time t, let $\Delta_i(t)$=1 if the t is an event time of the *i*th subject and 0 otherwise. Let $d(t) = \sum_i \Delta_i(t)$, which is the number of subjects that have an event at t. For $1 \le k \le d(t)$, let

$$\begin{aligned}
S^{(0)}(\boldsymbol{\beta}, k, t) &= \sum_i Y_i(t)\left\{1 - \frac{k-1}{d(t)}\Delta_i(t)\right\} \mathrm{e}^{\boldsymbol{\beta}'\mathbf{Z}_i(t)} \\
S^{(1)}(\boldsymbol{\beta}, k, t) &= \sum_i Y_i(t)\left\{1 - \frac{k-1}{d(t)}\Delta_i(t)\right\} \mathrm{e}^{\boldsymbol{\beta}'\mathbf{Z}_i(t)}\mathbf{Z}_i(t) \\
\bar{\mathbf{Z}}(\boldsymbol{\beta}, k, t) &= \frac{S^{(1)}(\boldsymbol{\beta}, k, t)}{S^{(0)}(\boldsymbol{\beta}, k, t)} \\
d\Lambda_0(\boldsymbol{\beta}, k, t) &= \sum_i \frac{dN_i(t)}{S^{(0)}(\boldsymbol{\beta}, k, t)} \\
dM_i(\boldsymbol{\beta}, k, t) &= dN_i(t) - Y_i(t)\left(1 - \Delta_i(t)\frac{k-1}{d(t)}\right)\mathrm{e}^{\boldsymbol{\beta}'\mathbf{Z}_i(t)} d\Lambda_0(\boldsymbol{\beta}, k, t)
\end{aligned}$$

The martingale residual at t for the *i*th subject is defined as

$$\hat{M}_i(t) = \int_0^t \frac{1}{d(s)} \sum_{k=1}^{d(s)} dM_i(\hat{\boldsymbol{\beta}}, k, s) = N_i(t) - \int_0^t \frac{1}{d(s)} \sum_{k=1}^{d(s)} Y_i(s)\left(1 - \Delta_i(s)\frac{k-1}{d(s)}\right)\mathrm{e}^{\hat{\boldsymbol{\beta}}'\mathbf{Z}_i(s)} d\Lambda_0(\hat{\boldsymbol{\beta}}, k, s)$$

Deviance residuals are computed by using the same transform on the corresponding martingale residuals as in TIES=BRESLOW.

The Schoenfeld residual vector for the *i*th subject at event time t_{i_j} is

$$\hat{\mathbf{U}}_i(t_{i_j}) = \mathbf{Z}_i(t_{i_j}) - \frac{1}{d(t_{i_j})} \sum_{k=1}^{d(t_{i_j})} \bar{\mathbf{Z}}(\hat{\boldsymbol{\beta}}, k, t_{i_j})$$

The score process for the ith subject at time t is given by

$$\mathbf{L}_i(\boldsymbol{\beta}, t) = \int_0^t \frac{1}{d(s)} \sum_{k=1}^{d(s)} \Big(\mathbf{Z}_i(s) - \bar{\mathbf{Z}}(\boldsymbol{\beta}, k, s) \Big) dM_i(\boldsymbol{\beta}, k, s)$$

For TIES=DISCRETE or TIES=EXACT, it is difficult to come up with modifications that are consistent with the corresponding partial likelihood. Residuals for these TIES= methods are computed by using the same formulas as in TIES=BRESLOW.

Diagnostics Based on Weighted Residuals

ZPH Diagnostics

The vector of weighted Schoenfeld residuals, $\mathbf{r}_i$, is computed as

$$\mathbf{r}_i = n_e \mathcal{I}^{-1}(\hat{\boldsymbol{\beta}}) \hat{\mathbf{U}}_i(t_i)$$

where n_e is the total number of events and $\hat{\mathbf{U}}_i(t_i)$ is the vector of Schoenfeld residuals at event time t_i. The components of $\mathbf{r}_i$ are output to the WTRESSCH= variables in the OUTPUT statement.

The weighted Schoenfeld residuals are useful in assessing the proportional hazards assumption. The idea is that most of the common alternatives to the proportional hazards can be cast in terms of a time-varying coefficient model,

$$\lambda(t, \mathbf{Z}) = \lambda_0(t) \exp(\beta_1(t) Z_1 + \beta_2(t) Z_2 + \cdots)$$

where $\lambda(t, \mathbf{Z})$ and $\lambda_0(t)$ are hazard rates. Let $\hat{\beta}_j$ and r_{ij} be the jth component of $\hat{\boldsymbol{\beta}}$ and $\mathbf{r}_i$, respectively. Grambsch and Therneau (1994) suggest using a smoothed plot of $(\hat{\beta}_j + r_{ij})$ versus t_i to discover the functional form of the time-varying coefficient $\beta_j(t)$. A zero slope indicates that the coefficient does not vary with time.

DFBETA Diagnostics

The weighted score residuals are used more often than their unscaled counterparts in assessing local influence. Let $\hat{\boldsymbol{\beta}}_{(i)}$ be the estimate of $\boldsymbol{\beta}$ when the ith subject is left out, and let $\delta\hat{\boldsymbol{\beta}}_i = \hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}_{(i)}$. The jth component of $\delta\hat{\boldsymbol{\beta}}_i$ can be used to assess any untoward effect of the ith subject on $\hat{\beta}_j$. The exact computation of $\delta\hat{\boldsymbol{\beta}}_i$ involves refitting the model each time a subject is omitted. Cain and Lange (1984) derived the following approximation of $\boldsymbol{\Delta}_i$ as weighted score residuals:

$$\delta\hat{\boldsymbol{\beta}}_i = \mathcal{I}^{-1}(\hat{\boldsymbol{\beta}}) \hat{\mathbf{L}}_i$$

Here, $\hat{\mathbf{L}}_i$ is the vector of the score residuals for the ith subject. Values of $\delta\hat{\boldsymbol{\beta}}_i$ are output to the DFBETA= variables. Again, when the counting process MODEL specification is used, the DFBETA= variables contain the component $\mathcal{I}^{-1}(\hat{\boldsymbol{\beta}})(\mathbf{L}_i(\hat{\boldsymbol{\beta}}, t_2) - \mathbf{L}_i(\hat{\boldsymbol{\beta}}, t_1))$, where the score process $\mathbf{L}_i(\boldsymbol{\beta}, t)$ is defined in the section "Residuals" on page 6921. The vector $\delta\hat{\boldsymbol{\beta}}_i$ for the ith subject can be obtained by summing these components within the subject.

Note that these DFBETA statistics are a transform of the score residuals. In computing the robust sandwich variance estimators of Lin and Wei (1989) and Wei, Lin, and Weissfeld (1989), it is more convenient to use the DFBETA statistics than the score residuals (see Example 86.10).

Influence of Observations on Overall Fit of the Model

The LD statistic approximates the likelihood displacement, which is the amount by which minus twice the log likelihood ($-2\log L(\hat{\boldsymbol{\beta}})$), under a fitted model, changes when each subject in turn is left out. When the *i*th subject is omitted, the likelihood displacement is

$$2\log L(\hat{\boldsymbol{\beta}}) - 2\log L(\hat{\boldsymbol{\beta}}_{(i)})$$

where $\hat{\boldsymbol{\beta}}_{(i)}$ is the vector of parameter estimates obtained by fitting the model without the *i*th subject. Instead of refitting the model without the *i*th subject, Pettitt and Bin Daud (1989) propose that the likelihood displacement for the *i*th subject be approximated by

$$\mathrm{LD}_i = \hat{\mathbf{L}}_i' \mathcal{I}^{-1}(\hat{\boldsymbol{\beta}}) \hat{\mathbf{L}}_i$$

where $\hat{\mathbf{L}}_i$ is the score residual vector of the *i*th subject. This approximation is output to the LD= variable.

The LMAX statistic is another global influence statistic. This statistic is based on the symmetric matrix

$$\mathbf{B} = \mathbf{L}\mathcal{I}^{-1}(\hat{\boldsymbol{\beta}})\mathbf{L}'$$

where $\mathbf{L}$ is the matrix with rows that are the score residual vectors $\hat{\mathbf{L}}_i$. The elements of the eigenvector associated with the largest eigenvalue of the matrix $\mathbf{B}$, standardized to unit length, give a measure of the sensitivity of the fit of the model to each observation in the data. The influence of the *i*th subject on the global fit of the model is proportional to the magnitude of ζ_i, where ζ_i is the *i*th element of the vector $\boldsymbol{\zeta}$ that satisfies

$$\mathbf{B}\boldsymbol{\zeta} = \lambda_{\max}\boldsymbol{\zeta} \quad \text{and} \quad \boldsymbol{\zeta}'\boldsymbol{\zeta} = 1$$

with $\lambda_{\max}$ being the largest eigenvalue of $\mathbf{B}$. The sign of ζ_i is irrelevant, and its absolute value is output to the LMAX= variable.

When the counting process MODEL specification is used, the LD= and LMAX= variables are set to missing, because these two global influence statistics can be calculated on a per-subject basis only.

Concordance Statistics

The predictive accuracy of a statistical model can be measured by the agreement between observed and predicted outcomes. In the context of logistic regression with binary outcomes, the concordance statistic (also known as C-statistic) is the most commonly used measure of accuracy. The concept underlying concordance is that a subject who experiences a particular outcome has a higher predicted probability of that outcome than a subject who does not experience the outcome.

The C-statistic can be calculated as the proportion of pairs of subjects whose observed and predicted outcomes agree (are concordant) among all possible pairs in which one subject experiences the outcome of interest and the other one does not. The higher the C-statistic, the better the model can discriminate between subjects who do experience the outcome of interest and subjects who do not.

C-statistics can be formulated for any modeling approach that generates predicted values. In the context of survival analysis, various C-statistics have been formulated to deal with right-censored data. PROC PHREG provides concordance statistics that were introduced by Harrell (1986) and Uno et al. (2011). The following

subsections discuss these statistics. In these subsections, $\boldsymbol{\beta}$ denotes the true regression parameters, and for a pair of subjects whose covariate vectors are $\mathbf{Z}_1$ and $\mathbf{Z}_2$ the survival times are denoted as T_1 and T_2 and the censoring times are denoted as D_1 and D_2, respectively. For the ith individual ($1 \leq i \leq n$) in a sample, let X_i, Δ_i, and $\mathbf{Z}_i$ be the observed time, event indicator (1 for death and 0 for censored), and covariate vector, respectively. Let $\hat{\boldsymbol{\beta}}$ denote the maximum partial likelihood estimates of $\boldsymbol{\beta}$.

Harrell's Concordance Statistic

Harrell (1986) proposes the following definition of the concordance probability:

$$C_H = \Pr(\boldsymbol{\beta}'\mathbf{Z}_1 > \boldsymbol{\beta}'\mathbf{Z}_2 | T_1 < T_2, T_1 < \min(D_1, D_2))$$

Assuming no ties in the event times and the predictor scores, C_H can be estimated by

$$\hat{C}_H = \frac{\sum_{i \neq j} \Delta_i I(X_i < X_j) I(\hat{\boldsymbol{\beta}}'\mathbf{Z}_i > \hat{\boldsymbol{\beta}}'\mathbf{Z}_j)}{\sum_{i \neq j} \Delta_i I(X_i < X_j)}$$

When there are ties in the predictor scores, the preceding calculation can be adjusted to be

$$\hat{C}_H = \frac{\sum_{i \neq j} \Delta_i I(X_i < X_j) \left[I(\hat{\boldsymbol{\beta}}'\mathbf{Z}_i > \hat{\boldsymbol{\beta}}'\mathbf{Z}_j) + 0.5 I(\hat{\boldsymbol{\beta}}'\mathbf{Z}_i = \hat{\boldsymbol{\beta}}'\mathbf{Z}_j) \right]}{\sum_{i \neq j} \Delta_i I(X_i < X_j)}$$

Assuming that the censoring time is independent of the event time, Kang et al. (2015) derive the standard errors estimator by using the delta method. Note this derivation assumes that $\hat{\boldsymbol{\beta}}$ is fixed, so it does not account for the variability in estimating $\boldsymbol{\beta}$. In order to show this condition more explicitly, the linear predictor $\boldsymbol{\beta}'\mathbf{Z}$ is replaced by a single variable Y. For a pair of subjects i and j, define the following quantities:

$$\operatorname{sgn}(Y_i, Y_j) = I(Y_i \geq Y_j) - I(Y_i \leq Y_j)$$

$$\operatorname{csgn}(X_i, \Delta_i, X_j, \Delta_j) = I(X_i \geq X_j)\Delta_j - I(X_i \leq X_j)\Delta_i$$

Let $t_{ijXY} = \operatorname{csgn}(X_i, \Delta_i, X_j, \Delta_j) \operatorname{sgn}(Y_i, Y_j)$, $t^*_{ijXX} = \operatorname{csgn}(X_i, \Delta_i, X_j, \Delta_j)^2$. Further define the following quantities:

$$t_{XY} = \frac{1}{n(n-1)} \sum_{i \neq j} t_{ijXY}$$

$$t^*_{XX} = \frac{1}{n(n-1)} \sum_{i \neq j} t^*_{ijXX}$$

Harrell's estimator can be rewritten as

$$\hat{C}_H = \frac{1}{2}\left(\frac{t_{XY}}{t^*_{XX}} + 1\right)$$

Applying the delta method, the variance of Harrell's C-statistic can be estimated by

$$\widehat{\operatorname{var}}(\hat{C}_H) = \begin{bmatrix} \frac{1}{t^*_{XX}} & -\frac{t_{XY}}{t^{*2}_{XX}} \end{bmatrix} \begin{bmatrix} \widehat{\operatorname{var}}(t_{XY}) & \widehat{\operatorname{cov}}(t^*_{XX}, t_{XY}) \\ \widehat{\operatorname{cov}}(t^*_{XX}, t_{XY}) & \widehat{\operatorname{var}}(t^*_{XX}) \end{bmatrix} \begin{bmatrix} \frac{1}{t^*_{XX}} & -\frac{t_{XY}}{t^{*2}_{XX}} \end{bmatrix}'$$

where

$$\widehat{\text{var}}(t^*_{XX}) = \frac{4\sum_i \left(\sum_j t^*_{ijXX}\right)^2 - \sum_i \sum_j t^{*2}_{ijXX} - \frac{2(2n-3)}{n(n-1)} \left(\sum_i \sum_j t^{*2}_{ijXX}\right)^2}{n(n-1)(n-2)(n-3)}$$

$$\widehat{\text{var}}(t_{XY}) = \frac{4\sum_i \left(\sum_j t_{ijXY}\right)^2 - \sum_i \sum_j t_{ijXY} - \frac{2(2n-3)}{n(n-1)} \left(\sum_i \sum_j t_{ijXY}\right)^2}{n(n-1)(n-2)(n-3)}$$

$$\widehat{\text{cov}}(t^*_{XX}, t_{XY}) = \frac{4\sum_i \left(\sum_j t^*_{ijXX} \sum_{j'} t_{ij'XY}\right) - \sum_i \sum_j t^*_{ijXX} t_{ijXY} - \frac{2(2n-3)}{n(n-1)} \left(\sum_i \sum_j t^{*2}_{ijXX}\right) \left(\sum_i \sum_j t_{ijXY}\right)}{n(n-1)(n-2)(n-3)}$$

Uno's Concordance Statistic

Uno et al. (2011) propose the following method for estimating the concordance probability:

$$C_U = \Pr(\boldsymbol{\beta}'\mathbf{Z}_1 > \boldsymbol{\beta}'\mathbf{Z}_2 | T_1 < T_2)$$

If τ is a specified time point within the support of the censoring variable, Uno et al. (2011) also define a truncated version of the concordance probability as

$$C_U = \Pr(\boldsymbol{\beta}'\mathbf{Z}_1 > \boldsymbol{\beta}'\mathbf{Z}_2 | T_1 < T_2, T_1 < \tau)$$

You can specify a τ value in the TAU= option in the PROC PHREG statement. If the TAU= option is not specified, there is no truncation and the τ value is taken as the largest event time.

For the ith individual ($1 \le i \le n$), let X_i, Δ_i, and $\mathbf{Z}_i$ be the observed time, event indicator (1 for death and 0 for censored), and covariate vector, respectively. Let $\hat{G}(t)$ be the Kaplan-Meier estimate of the censoring distribution (assuming no covariates). C_U is consistently estimated by

$$\hat{C}_U = \frac{\sum_{i=1}^n \sum_{j=1}^n \Delta_i \hat{G}(X_i^-)^{-2} I(X_i < X_j, X_i < \tau) \left[I(\hat{\boldsymbol{\beta}}'\mathbf{Z}_i > \hat{\boldsymbol{\beta}}'\mathbf{Z}_j) + 0.5 * I(\hat{\boldsymbol{\beta}}'\mathbf{Z}_i = \hat{\boldsymbol{\beta}}'\mathbf{Z}_j) \right]}{\sum_{i=1}^n \sum_{j=1}^n \Delta_i \hat{G}(X_i^-)^{-2} I(X_i < X_j, X_i < \tau)}$$

Define $W = \sqrt{n}(\hat{C}_U - C_U)$. It can be shown that W is asymptotically distributed as a normal random variable with mean zero. The variance of W can be approximated by using the perturbation-resampling method. Specifically, let $\{\psi_i, i = 1, \ldots, n\}$ be a set of independent samples from an exponential distribution with mean of 1 and variance of 1. For a large n, W can be approximated by

$$\tilde{W} = \sum_{i<j} 0.5 * \left[\hat{V}_{ij}(\hat{\boldsymbol{\beta}}) + \hat{V}_{ji}(\hat{\boldsymbol{\beta}}) \right] \psi_i \psi_j + \left[\hat{K}(G^*) - \hat{K}(\hat{G}) \right] + \left[\hat{C}_U(\boldsymbol{\beta}^*) - \hat{C}_U(\hat{\boldsymbol{\beta}}) \right]$$

where

$$\hat{K}(G) = \frac{\sum_{i<j} G(X_i^-)^{-2} I(X_i < X_j, X_i < \tau) \Delta_i \left[I(\hat{\boldsymbol{\beta}}'\mathbf{Z}_i > \hat{\boldsymbol{\beta}}'\mathbf{Z}_j) + 0.5 * I(\hat{\boldsymbol{\beta}}'\mathbf{Z}_i = \hat{\boldsymbol{\beta}}'\mathbf{Z}_j) - \hat{C}_\tau(\hat{\boldsymbol{\beta}}) \right]}{\sum_{i<j} \hat{G}(X_i^-)^{-2} I(X_i < X_j, X_i < \tau) \Delta_i},$$

$$\hat{V}_{ij}(\hat{\boldsymbol{\beta}}) = \frac{G(X_i^-)^{-2} I(X_i < X_j, X_i < \tau) \Delta_i \left[I(\hat{\boldsymbol{\beta}}'\mathbf{Z}_i > \hat{\boldsymbol{\beta}}'\mathbf{Z}_j) + 0.5 * I(\hat{\boldsymbol{\beta}}'\mathbf{Z}_i = \hat{\boldsymbol{\beta}}'\mathbf{Z}_j) - \hat{C}_\tau(\hat{\boldsymbol{\beta}}) \right]}{\sum_{i<j} \hat{G}(X_i^-)^{-2} I(X_i < X_j, X_i < \tau) \Delta_i}$$

and $G^*(\cdot)$ and $\boldsymbol{\beta}^*$ are the perturbed versions of $\hat{G}$ and $\hat{\boldsymbol{\beta}}$. $G^*(\cdot)$ is calculated as

$$G^*(t) = \hat{G}(t) - \hat{G}(t)\frac{2}{n(n-1)}\sum_{i<j}\int_0^t \frac{1}{n^{-1}\sum_i I(X_i \geq u)}\left[d\hat{M}(u) + d\hat{M}(u)\right]\psi_i\psi_j/2$$

where $\hat{M}(t) = I(X_i \leq u, \Delta_i = 0) - \int_0^t I(X_i \geq u)d\hat{\Lambda}_C(u)$ and $\hat{\Lambda}_C(\cdot)$ is a consistent estimator of the cumulative hazard function for the censoring time variable. $\boldsymbol{\beta}^*$ is calculated as

$$\boldsymbol{\beta}^* = \hat{\boldsymbol{\beta}} + \frac{2}{n(n-1)}\sum_{i<j}\left\{\hat{H}(\hat{\boldsymbol{\beta}})\left[U_i(\hat{\boldsymbol{\beta}}) + U_j(\hat{\boldsymbol{\beta}})\right]/2\right\}\psi_i\psi_j$$

where $\hat{H}$ is the estimated variance-covariance matrix of $\hat{\boldsymbol{\beta}}$ divided by n and U_i is the contribution to the partial likelihood function from the ith individual. The third term of the formula for $\tilde{W}$ is dropped out if you use the PRED= option in an ROC statement to specify a variable that contains the prediction scores.

Suppose $\hat{\sigma}^2$ is the sample variance based on M realizations of $\tilde{W}$. The $100(1-\alpha)\%$ confidence limits for C_U are $\hat{C}_U \pm z_{\alpha/2}\hat{\sigma}$, where $z_{\alpha/2}$ is the upper $100\alpha/2$ percentile of the standard normal distribution.

Time-Dependent ROC Curves

In the context of logistic regression with binary outcomes, receiver operator characteristic (ROC) curves and AUC (area under the ROC curve) statistics are commonly used to assess the ability of the model to discriminate between the two outcomes. To adapt the concept of ROC curves to the survival setting, various definitions and estimators of time-dependent ROC curves and AUC functions have been proposed. See Blanche, Latouche, and Viallon (2013) for a comprehensive survey of different methods. Time-dependent ROC curves and AUC functions characterize how well the fitted model can distinguish between subjects who experience an event from subjects who are event-free.

Whereas C-statistics provide overall measures of predictive accuracy, time-dependent ROC curves and AUC functions summarize the predictive accuracy at specific times. In practice, it is common to use several time points within the support of the observed event times.

Let T denote the event-time variable, and let Y denote the continuous variable to be assessed. At time t, a binary outcome can be defined as follows:

$$D_t = I(T \leq t)$$

Suppose c denotes a specific value within the support of Y. The sensitivity (SE) and specificity (SP) can be defined as

$$\mathrm{SE}_t(c) = \Pr(Y > c | D_t = 1)$$

$$\mathrm{SP}_t(c) = \Pr(Y \leq c | D_t = 0)$$

The ROC curve at time t is defined to be

$$\mathrm{ROC}_t(c) = SE_t(c)\left[1 - SP_t^{-1}(c)\right]$$

This definition is often referred to as the "cumulative/dynamic" ROC curve in the literature. "Cumulative" means all events that occurred before time t are considered as "cases." Other types of time-dependent ROC curves are available in the literature—for example, in Heagerty and Zheng (2005).

The AUC statistic at time t is the area under the ROC curve at time t:

$$\mathrm{AUC}_t = \int \mathrm{ROC}_t(u)du$$

Let $\boldsymbol{\beta}$ denote the vector of regression parameters. For the ith individual ($1 \leq i \leq n$), let X_i, Δ_i, and $\mathbf{Z}_i$ be the observed time, event indicator (1 for death and 0 for censored), and covariate vector, respectively. Let $\hat{\boldsymbol{\beta}}$ denote the maximum partial likelihood estimates of $\boldsymbol{\beta}$. The estimated linear predictor for the ith individual is $Y_i = \boldsymbol{\beta}'\mathbf{Z}_i$. PROC PHREG supports the approaches that are described in the following sections for estimating time-dependent ROC curves.

Inverse Probability of Censoring Weighting Approach

Let $\hat{G}(t)$ be the Kaplan-Meier estimate of the censoring distribution (assuming no covariates). Assuming that the censoring distribution is independent of the failure time distribution, the sensitivity and specificity under a specific threshold value c can be consistently estimated by

$$\widehat{\mathrm{SE}}_t(c) = \frac{\sum_{i=1}^n \Delta_i I(\hat{\boldsymbol{\beta}}'\mathbf{Z}_i > c, X_i \leq t)/\hat{G}(X_i)}{\sum_{i=1}^n \Delta_i I(X_i \leq t)/\hat{G}(X_i)}$$

$$\widehat{\mathrm{SP}}_t(c) = \frac{\sum_{i=1}^n I(\hat{\boldsymbol{\beta}}'\mathbf{Z}_i \leq c, X_i > t)}{\sum_{i=1}^n I(X_i > t)}$$

$\mathrm{ROC}_t(c)$ can be estimated by substituting in these estimated sensitivities and specificities. The estimated AUC_t is calculated by using the trapezoidal rule to integrate the estimated $\mathrm{ROC}_t(c)$ curve.

Uno et al. (2007) propose estimating the standard errors of the AUC_t estimator by using the perturbation-resampling method. Let $\{\psi_i, i = 1, \ldots, n\}$ be a set of independent samples from an exponential distribution with mean of 1 and variance of 1. The perturbed versions of $\widehat{\mathrm{SE}}_t(c)$ and $\widehat{\mathrm{SP}}_t(c)$ are

$$\widehat{\mathrm{SE}}^*_t(c) = \frac{\sum_{i=1}^n \Delta_i I(\boldsymbol{\beta}^{*'}\mathbf{Z}_i > c, X_i \leq t)\psi_i/\hat{G}^*(X_i)}{\sum_{i=1}^n \Delta_i I(X_i \leq t)\psi_i/\hat{G}^*(X_i)}$$

$$\widehat{\mathrm{SP}}^*_t(c) = \frac{\sum_{i=1}^n I(\boldsymbol{\beta}^{*'}\mathbf{Z}_i \leq c, X_i > t)\psi_i}{\sum_{i=1}^n I(X_i > t)\psi_i}$$

where $G^*(\cdot)$ and $\boldsymbol{\beta}^*$ represent the perturbed versions of $\hat{G}(\cdot)$ and $\hat{\boldsymbol{\beta}}$. $G^*(\cdot)$ is calculated as

$$G^*(t) = \hat{G}(t) - \hat{G}(t)\frac{2}{n(n-1)}\sum_{i<j}\int_0^t \frac{1}{n^{-1}\sum_i I(X_i \geq u)}\left[d\hat{M}(u) + d\hat{M}(u)\right]\psi_i\psi_j/2$$

where $\hat{M}(t) = I(X_i \leq u, \Delta_i = 0) - \int_0^t I(X_i \geq u)d\hat{\Lambda}_C(u)$ and $\hat{\Lambda}_C(\cdot)$ is a consistent estimator of the cumulative hazard function for the censoring time variable. $\boldsymbol{\beta}^*$ is calculated as

$$\boldsymbol{\beta}^* = \hat{\boldsymbol{\beta}} + \frac{2}{n(n-1)}\sum_{i<j}\left\{\hat{H}(\hat{\boldsymbol{\beta}})\left[U_i(\hat{\boldsymbol{\beta}}) + U_j(\hat{\boldsymbol{\beta}})\right]/2\right\}\psi_i\psi_j$$

where $\hat{H}$ is the estimated variance-covariance matrix of $\hat{\boldsymbol{\beta}}$ divided by n and U_i is the partial likelihood contribution from the ith individual.

The perturbed AUC_t estimate is obtained by substituting in the perturbed sensitivities and specificities. Suppose $\hat{\sigma}^2$ is the sample variance based on M realizations of the perturbed AUC_t. The $100(1-\alpha)\%$ confidence limits for AUC_t are $\widehat{\mathrm{AUC}}_t \pm z_{\alpha/2}\hat{\sigma}$, where $\widehat{\mathrm{AUC}}_t$ is the estimated AUC_t and $z_{\alpha/2}$ is the upper $100\alpha/2$ percentile of the standard normal distribution.

To choose this method of computing the time-dependent ROC curve, specify METHOD=IPCW in the ROCOPTIONS option in the PROC PHREG statement.

NOTE: This perturbation approach of estimating the standard error of the AUC_t statistic does not apply to a model that is specified by the PRED= option or SOURCE= option in an ROC statement.

Conditional Kaplan-Meier Approach

By using Bayes' theorem, sensitivity and the specificity can be written as

$$\mathrm{SE}_t(c) = \Pr(Y > c | D_t = 1) = \frac{[1 - S(t|Y > c)]\Pr(Y > c)}{1 - S(t)}$$

$$\mathrm{SP}_t(c) = \Pr(Y \le c | D_t = 0) = \frac{S(t|Y \le c)\Pr(Y \le c)}{S(t)}$$

where $S(\cdot)$ is the survivor function and $S(\cdot|Y > c)$ is the conditional survivor function for $Y > c$.

Heagerty, Lumley, and Pepe (2000) use the Kaplan-Meier method to estimate the survivor function $S(.)$ and the conditional survivor function $S(.|Y > c)$. The latter was estimated using subjects where the condition $Y > c$ is met. The sensitivity and the specificity are estimated by

$$\widehat{\mathrm{SE}}_t(c) = \frac{\left[1 - \hat{S}_{KM}(t|Y > c)\right][1 - \hat{F}_Y(c)]}{1 - \hat{S}_{KM}(t)}$$

$$\widehat{\mathrm{SP}}_t(c) = \frac{\hat{S}_{KM}(t|Y \le c)\hat{F}_Y(c)}{\hat{S}_{KM}(t)}$$

where $\hat{S}_{KM}(\cdot)$ is the Kaplan-Meier estimator and $\hat{F}_Y(c) = \sum_i I(Y_i \le c)/n$.

To choose this method of computing ROC curves, specify METHOD=KM in the ROCOPTIONS in the PROC PHREG statement.

Nearest Neighbors Approach

Following Akritas (1994), the bivariate survival function, $S(c,t) = \Pr(Y > c, T > t)$, can be estimated by

$$\hat{S}_{b_n}(c,t) = \frac{1}{n}\sum_i \hat{S}_{b_n}(t|Y = Y_i)I(Y_i > c)$$

where $\hat{S}_{b_n}(t|Y = Y_i)$ is a smoothed estimate of the conditional survival function. Define the weighted Kaplan-Meier estimator as

$$\hat{S}_{b_n}(t|Y = Y_i) = \prod_{s \in \{X_i : i = 1,\cdots,n, \Delta_i = 1\}, s \le t} \left[1 - \frac{\sum_j K_{b_n}(Y_i, Y_j)I(X_i = s)\Delta_i}{\sum_j K_{b_n}(Y_i, Y_j)I(X_i = s)}\right]$$

where $K_{b_n}(Y_i, Y_j)$ is a kernel function that depends on the parameter b_n. Akritas (1994) uses the nearest neighbor kernel, $K_{b_n}(Y_i, Y_j) = I\{-b_n < \hat{F}_Y(Y_i) - \hat{F}_Y(Y_j) < b_n\}$, where $0 < 2b_n < 1$; this effectively

selects the nearest $2b_n$ proportion of observations in the neighborhood. The default value for b_n is 0.05. You can specify a different value by using the SPAN= suboption in METHOD=NNE in the ROCOPTIONS option in the PHREG statement.

The sensitivity and specificity can then be estimated as

$$\widehat{\mathrm{SE}}_t(c) = \frac{1 - \hat{F}_Y(c) - \hat{S}_{b_n}(c,t)}{1 - \hat{S}_{b_n}(t)}$$

$$\widehat{\mathrm{SP}}_t(c) = 1 - \frac{\hat{S}_{b_n}(c,t)}{\hat{S}_{b_n}(t)}$$

where $\hat{S}_{b_n}(t) = \hat{S}_{b_n}(-\infty, t)$. For more information, see Heagerty, Lumley, and Pepe (2000).

To choose this method of computing time-dependent ROC curves, specify METHOD=NNE in the ROCOPTIONS option in the PROC PHREG statement.

Recursive Approach

Chambless and Diao (2006) propose estimating time-dependent ROC curves by using a recursive approach akin to the Kaplan-Meier method. Let $t_1 < t_2 < \cdots < t_M$ be the distinct event times in the data. The area under the curve at time $t_m, 1 \le t_m \le M$, can be derived as

$$\mathrm{AUC}_{t_m} = \frac{\sum_{k=1}^{m} \gamma_k \lambda(t_k)(1 - \lambda(t_k))S(t_{k-1}) - \sum_{k=1}^{m} \tau_k \lambda(t_k)(1 - S(t_{k-1}))S(t_{k-1})}{S(t_m)(1 - S(t_m))}$$

where $S(\cdot)$ is the survivor function, $\lambda(\cdot)$ is the hazard function, $t_0 = 0$, $\tau_0 = 0$, and

$$\tau_k = \Pr(\boldsymbol{\beta}'\mathbf{Z}_i > \boldsymbol{\beta}'\mathbf{Z}_j | X_i = t_k, \Delta_i = 1, X_j > t_k)$$

$$\gamma_k = \Pr(\boldsymbol{\beta}'\mathbf{Z}_i > \boldsymbol{\beta}'\mathbf{Z}_j | X_i = t_{k-1}, \Delta_i = 1, X_j = t_k, \Delta_j = 1)$$

In a recursive fashion, the sensitivity and specificity at time t_m can be shown to be

$$\mathrm{SE}_{t_m}(c) = \sum_{k=1}^{m} \rho_k(c)\lambda(t_k)S(t_{k-1})/[1 - S(t_m)]$$

$$\mathrm{SP}_{t_m}(c) = \frac{\Pr(\boldsymbol{\beta}'\mathbf{Z}_i \le c) - \sum_{k=1}^{m}[1 - \rho_k(c)]\lambda(t_k)S(t_{k-1})}{S(t_m)}$$

where $\rho_k(c) = \Pr(\boldsymbol{\beta}'\mathbf{Z}_i > c | X_i = t_k, \Delta_i = 1)$.

Define $\mathcal{R}_k$ to be the risk set at time t_k, and let r_k be the number of subjects in $\mathcal{R}_k$. Let $\mathbf{Z}_{(k)}$ be the covariate vector for the subject whose event time is t_k. The unknown parameters τ_k, γ_k, and $\rho_k(c)$ can be estimated by

$$\hat{\tau}_k = \frac{1}{k-1} \sum_{i=1}^{k} I(\hat{\boldsymbol{\beta}}' Z_{(i)} > \hat{\boldsymbol{\beta}}' Z_{(k)})$$

$$\hat{\gamma}_k = \frac{1}{r_k - 1} \sum_{j \in \mathcal{R}_k} I(\hat{\boldsymbol{\beta}}' Z_{(k)} > \hat{\boldsymbol{\beta}}' Z_j)$$

$$\hat{\rho}_k(c) = I(\hat{\boldsymbol{\beta}}' Z_{(k)} > c)$$

When there is only one event at each event time, $\lambda(t_k)$ is estimated by $\hat{\lambda}(t_k) = 1/r_k$ and $S(t_k)$ is estimated by the Kaplan-Meier method as $\hat{S}(t_k) = \hat{S}(t_{k-1})[1 - \hat{\lambda}(t_{k-1})]$. In the case of a tie, the order of the events in the calculation is the same as the order of their appearance in the input data set.

To choose this method of computing time-dependent ROC curves, specify METHOD=RECURSIVE in the ROCOPTIONS option in the PROC PHREG statement.

Survivor Function Estimators

Three estimators of the survivor function are available: the Breslow (1972) estimator, which is based on the empirical cumulative hazard function, the Fleming and Harrington (1984) estimator, which is a tie-breaking modification of the Breslow estimator, and the product-limit estimator (Kalbfleisch and Prentice 1980, pp. 84–86).

Let $\{t_1 < \cdots < t_k\}$ be the distinct uncensored times of the survival data.

Breslow Estimator

To select this estimator, specify the METHOD=BRESLOW option in the BASELINE statement or OUTPUT statement. For the jth subject, let $\{(X_j, \Delta_j, \mathbf{Z}_j(.))\}$ represent the failure time, the event indicator, and the vector of covariate values, respectively. For $t \geq 0$, let

$$\begin{aligned} Y_j(t) &= I(X_j \geq t) \\ \Delta_j(t) &= \begin{cases} 1 & X_j = t \text{ and } \Delta_j = 1 \\ 0 & \text{otherwise} \end{cases} \\ d(t) &= \sum_j \Delta_j(t) \end{aligned}$$

Note that $d(t)$ is the number of subjects that have an event at t. Let

$$\begin{aligned} S^{(0)}(\boldsymbol{\beta}, t) &= \sum_j Y_j(t) \mathrm{e}^{\boldsymbol{\beta}' \mathbf{Z}_j(t)} \\ S^{(1)}(\boldsymbol{\beta}, t) &= \sum_j Y_j(t) \mathrm{e}^{\boldsymbol{\beta}' \mathbf{Z}_j(t)} \mathbf{Z}_j(t) \\ \bar{\mathbf{Z}}(\boldsymbol{\beta}, t) &= \frac{S^{(1)}(\boldsymbol{\beta}, t)}{S^{(0)}(\boldsymbol{\beta}, t)} \end{aligned}$$

For a given realization of the explanatory variables $\boldsymbol{\xi}$, the cumulative hazard function estimator at $\boldsymbol{\xi}$ is

$$\hat{\Lambda}_B(t, \boldsymbol{\xi}) = \mathrm{e}^{\hat{\boldsymbol{\beta}}' \boldsymbol{\xi}} \sum_{t_i \leq t} \frac{d(t_i)}{S^{(0)}(\hat{\boldsymbol{\beta}}, t_i)}$$

with variance estimated by

$$\hat{\sigma}^2(\hat{\Lambda}_B(t, \boldsymbol{\xi})) = \mathrm{e}^{2\hat{\boldsymbol{\beta}}' \boldsymbol{\xi}} \sum_{t_i \leq t} \frac{d(t_i)}{[S^{(0)}(\hat{\boldsymbol{\beta}}, t_i)]^2} + H(t, \boldsymbol{\xi})' [\mathcal{I}(\hat{\boldsymbol{\beta}})]^{-1} H(t, \boldsymbol{\xi})$$

where

$$H(t,\boldsymbol{\xi}) = \mathrm{e}^{\hat{\boldsymbol{\beta}}'\boldsymbol{\xi}} \sum_{t_i \le t} \frac{d(t_i)}{S^{(0)}(\hat{\boldsymbol{\beta}}, t_i)} \left(\bar{\mathbf{Z}}(\hat{\boldsymbol{\beta}}, t_i) - \boldsymbol{\xi} \right)$$

For the marginal model, the variance estimator computation follows Spiekerman and Lin (1998).

The Breslow estimate of the survivor function for $\mathbf{Z} = \boldsymbol{\xi}$ is

$$\hat{S}_B(t,\boldsymbol{\xi}) = \exp(-\hat{\Lambda}_B(t,\boldsymbol{\xi}))$$

By the delta method, the standard error of $\hat{S}_B(t,\boldsymbol{\xi})$ is approximated by

$$\hat{\sigma}(\hat{S}_B(t,\boldsymbol{\xi})) = \hat{S}_B(t,\boldsymbol{\xi})\hat{\sigma}(\hat{\Lambda}_B(t,\boldsymbol{\xi}))$$

Fleming-Harrington Estimator

To select this estimator, specify the METHOD=FH option in the BASELINE statement or OUTPUT statement. With $Y_j(t)$ and $d(t)$ as defined in the section "Breslow Estimator" on page 6932 and for $1 \le k \le d(t)$, let

$$\begin{aligned}
S_E^{(0)}(\boldsymbol{\beta}, k, t) &= \sum_j Y_j(t) \left\{ 1 - \frac{k-1}{d(t)} \Delta_j(t) \right\} \mathrm{e}^{\boldsymbol{\beta}'\mathbf{Z}_j(t)} \\
S_E^{(1)}(\boldsymbol{\beta}, k, t) &= \sum_j Y_j(t) \left\{ 1 - \frac{k-1}{d(t)} \Delta_j(t) \right\} \mathrm{e}^{\boldsymbol{\beta}'\mathbf{Z}_j(t)} \mathbf{Z}_j(t) \\
\bar{\mathbf{Z}}_E \boldsymbol{\beta}, k, t) &= \frac{S_E^{(1)}(\boldsymbol{\beta}, k, t)}{S_E^{(0)}(\boldsymbol{\beta}, k, t)}
\end{aligned}$$

For a given realization of the explanatory variables, the Fleming-Harrington adjustment of the cumulative hazard function is

$$\hat{\Lambda}_F(t,\boldsymbol{\xi}) = \mathrm{e}^{\hat{\boldsymbol{\beta}}'\boldsymbol{\xi}} \sum_{t_i \le t} \left\{ \sum_{k=1}^{d(t_i)} \frac{1}{S_E^{(0)}(\hat{\boldsymbol{\beta}}, k, t_i)} \right\}$$

with variance estimated by

$$\hat{\sigma}^2(\hat{\Lambda}_F(t,\boldsymbol{\xi})) = \mathrm{e}^{2\hat{\boldsymbol{\beta}}'\boldsymbol{\xi}} \sum_{t_i \le t} \left\{ \sum_{k=1}^{d(t_i)} \frac{1}{[S_E^{(0)}(\hat{\boldsymbol{\beta}}, k, t_i)]^2} \right\} + H_E(t,\boldsymbol{\xi})'[\mathcal{I}(\hat{\boldsymbol{\beta}})]^{-1} H_E(t,\boldsymbol{\xi})$$

where

$$H_E(t,\boldsymbol{\xi}) = \mathrm{e}^{\hat{\boldsymbol{\beta}}'\boldsymbol{\xi}} \left\{ \left[\sum_{t_i \le t} \sum_{k=1}^{d(t_i)} \frac{1}{S_E^{(0)}(\hat{\boldsymbol{\beta}}, k, t_i)} \bar{\mathbf{Z}}_E(\hat{\boldsymbol{\beta}}, k, t_i) \right] - \hat{\Lambda}_F(t,\mathbf{0})\boldsymbol{\xi} \right\}$$

The Fleming-Harrington estimate of the survivor function for $\mathbf{Z} = \boldsymbol{\xi}$ is

$$\hat{S}_F(t,\boldsymbol{\xi}) = \exp(-\hat{\Lambda}_F(t,\boldsymbol{\xi}))$$

By the delta method, the standard error of $\hat{S}_B(t,\boldsymbol{\xi})$ is approximated by

$$\hat{\sigma}(\hat{S}_F(t,\boldsymbol{\xi})) = \hat{S}_F(t,\boldsymbol{\xi})\hat{\sigma}(\hat{\Lambda}_F(t,\boldsymbol{\xi}))$$

Product-Limit Estimator

To select this estimator, specify the METHOD=PL option in the BASELINE statement or OUTPUT statement. Let $\mathcal{D}_i$ denote the set of individuals that fail at t_i. Let $\mathcal{C}_i$ denote the set of individuals that are censored in the half-open interval $[t_i, t_{i+1})$, where $t_0 = 0$ and $t_{k+1} = \infty$. Let γ_l denote the censoring times in $[t_i, t_{i+1})$, where l ranges over $\mathcal{C}_i$.

The likelihood function for all individuals is given by

$$\mathcal{L} = \prod_{i=0}^{k} \left\{ \prod_{l \in \mathcal{D}_i} \left([S_0(t_i)]^{\exp(\mathbf{Z}_l'\boldsymbol{\beta})} - [S_0(t_i + 0)]^{\exp(\mathbf{Z}_l'\boldsymbol{\beta})} \right) \prod_{l \in \mathcal{C}_i} [S_0(\gamma_l + 0)]^{\exp(\mathbf{Z}_l'\boldsymbol{\beta})} \right\}$$

where $\mathcal{D}_0$ is empty. The likelihood $\mathcal{L}$ is maximized by taking $S_0(t) = S_0(t_i + 0)$ for $t_i < t \leq t_{i+1}$ and allowing the probability mass to fall only on the observed event times $t_1, \ldots, t_k$. By considering a discrete model with hazard contribution $1 - \alpha_i$ at t_i, you take $S_0(t_i) = S_0(t_{i-1} + 0) = \prod_{j=0}^{i-1} \alpha_j$, where $\alpha_0 = 1$. Substitution into the likelihood function produces

$$\mathcal{L} = \prod_{i=0}^{k} \left\{ \prod_{j \in \mathcal{D}_i} \left(1 - \alpha_i^{\exp(\mathbf{Z}_j'\boldsymbol{\beta})} \right) \prod_{l \in \mathcal{R}_i - \mathcal{D}_i} \alpha_i^{\exp(\mathbf{z}_l'\boldsymbol{\beta})} \right\}$$

If you replace $\boldsymbol{\beta}$ with $\hat{\boldsymbol{\beta}}$ estimated from the partial likelihood function and then maximize with respect to $\alpha_1, \ldots, \alpha_k$, the maximum likelihood estimate $\hat{\alpha}_i$ of α_i becomes a solution of

$$\sum_{j \in \mathcal{D}_i} \frac{\exp(\mathbf{Z}_j'\hat{\boldsymbol{\beta}})}{1 - \hat{\alpha}_i^{\exp(\mathbf{Z}_j'\hat{\boldsymbol{\beta}})}} = \sum_{l \in \mathcal{R}_i} \exp(\mathbf{Z}_l'\hat{\boldsymbol{\beta}})$$

When only a single failure occurs at t_i, $\hat{\alpha}_i$ can be found explicitly. Otherwise, an iterative solution is obtained by the Newton method.

The baseline survival function is estimated by

$$\hat{S}_0(t) = \hat{S}_0(t_{i-1} + 0) = \prod_{j=0}^{i-1} \hat{\alpha}_j, t_{i-1} < t \leq t_i$$

For a given realization of the explanatory variables $\boldsymbol{\xi}$, the product-limit estimate of the survival function at $\mathbf{Z} = \boldsymbol{\xi}$ is

$$\hat{S}_P(t, \boldsymbol{\xi}) = [\hat{S}_0(t)]^{\exp(\boldsymbol{\beta}'\boldsymbol{\xi})}$$

Approximating the variance of $-\log(S_P(t, \boldsymbol{\xi}))$ by the variance estimate of the Breslow estimator of the cumulative hazard function, the variance of the product-limit estimator at $\mathbf{Z} = \boldsymbol{\xi}$ is given by

$$\hat{\sigma}(\hat{S}_P(t, \boldsymbol{\xi})) = \hat{S}_P(t, \boldsymbol{\xi}) \hat{\sigma}(\hat{\Lambda}_B(t, \boldsymbol{\xi}))$$

Direct Adjusted Survival Curves

Consider the Breslow estimator of the survival function. For $j = 1, \ldots, n$, let $\boldsymbol{\xi}_j$ represent the covariate set of the jth patient. The direct adjusted survival curve averages the estimated survival curves for each patient:

$$\bar{S}(t) = \frac{1}{n} \sum_{j=1}^{n} \hat{S}(t, \boldsymbol{\xi}_j)$$

The variance of $\bar{S}(t)$ can be estimated by

$$\hat{\sigma}^2(\bar{S}(t)) = \frac{1}{n^2}\left(V^{(1)}t) + V^{(2)}(t)\right)$$

where

$$\begin{aligned} V^{(1)}(t) &= \left(\sum_{j=1}^{n} \mathrm{e}^{\hat{\boldsymbol{\beta}}'\boldsymbol{\xi}_j} \hat{S}(t, \boldsymbol{\xi}_j)\right)^2 \sum_{t_i \le t} \frac{d(t_i)}{[S^{(0)}(\hat{\boldsymbol{\beta}}, t_i)]^2} \\ V^{(2)}(t) &= \left(\sum_{j=1}^{n} \hat{S}(t, \boldsymbol{\xi}_j) H(t, \boldsymbol{\xi}_j)\right)' \left[\mathcal{I}(\hat{\boldsymbol{\beta}})\right]^{-1} \left(\sum_{j=1}^{n} \hat{S}(t, \boldsymbol{\xi}_j) H(t, \boldsymbol{\xi}_j)\right) \end{aligned}$$

Comparison of Direct Adjusted Probabilities of Two Strata

For a stratified Cox model, let k index the strata. For the jth patient, let $\hat{S}_k(t, \boldsymbol{\xi}_j)$ and $H_k(t, \boldsymbol{\xi}_j)$ be the estimated survival function and the **H** vector for the kth stratum. The direct adjusted survival curve for the kth stratum is

$$\bar{S}_k(t) = \frac{1}{n} \sum_{j=1}^{n} \hat{S}_k(t, \boldsymbol{\xi}_j)$$

The variance of $\bar{S}_1(t) - \bar{S}_2(t)$ can be estimated by

$$\hat{\sigma}^2(\bar{S}_1(t) - \bar{S}_2(t)) = \frac{1}{n^2}\left(U_1^{(1)}(t) + U_2^{(1)} + U_{12}^{(2)}(t)\right)$$

where

$$\begin{aligned} U_k^{(1)}(t) &= \left(\sum_{j=1}^{n} \mathrm{e}^{\boldsymbol{\beta}'\boldsymbol{\xi}_j} \hat{S}_k(t, \boldsymbol{\xi}_j)\right)^2 \sum_{t_i \le t} \frac{d(t_i)}{[S^{(0)}(\hat{\boldsymbol{\beta}}, t_i)]^2}, \quad k = 1, 2 \\ U_{12}^{(2)}(t) &= \left\{\sum_{j=1}^{n} \left[\hat{S}_1(t, \boldsymbol{\xi}_j) H_1(t, \boldsymbol{\xi}_j) - \hat{S}_2(t, \boldsymbol{\xi}_j) H_2(t, \boldsymbol{\xi}_j)\right]\right\}' \mathcal{I}^{-1}(\hat{\boldsymbol{\beta}}) \\ &\quad \left\{\sum_{j=1}^{n} \left[\hat{S}_1(t, \boldsymbol{\xi}_j) H_2(t, \boldsymbol{\xi}_j) - \hat{S}_1(t, \boldsymbol{\xi}_j) H(_2t, \boldsymbol{\xi}_j)\right]\right\} \end{aligned}$$

Comparison of Direct Adjusted Survival Probabilities of Two Treatments

For $j = 1, \ldots, n$, let $\boldsymbol{\xi}_{jk}$ represent the covariate set of the jth patient with the kth treatment, $k = 1, 2$. The direct adjusted survival curve for the kth treatment is

$$\bar{S}_k(t) = \frac{1}{n} \sum_{i=j}^{n} \hat{S}(t, \boldsymbol{\xi}_{jk})$$

The variance of $\bar{S}_1(t) - \bar{S}_2(t)$ can be estimated by

$$\hat{\sigma}^2 \left(\bar{S}_1(t) - \bar{S}_2(t) \right) = \frac{1}{n^2} \left(V_{12}^{(1)}(t) + V_{12}^{(2)}(t) \right)$$

where

$$\begin{aligned} V_{12}^{(1)}(t) &= \left\{ \sum_{j=1}^{n} \left[\mathrm{e}^{\boldsymbol{\beta}' \boldsymbol{\xi}_{1j}} \hat{S}(t, \boldsymbol{\xi}_{1j}) - \mathrm{e}^{\boldsymbol{\beta}' \boldsymbol{\xi}_{2j}} \hat{S}(t, \boldsymbol{\xi}_{2j}) \right] \right\}^2 \sum_{t_i \le t} \frac{d(t_i)}{[S^{(0)}(\hat{\boldsymbol{\beta}}, t_i)]^2} \\ V_{12}^{(2)}(t) &= \left\{ \sum_{j=1}^{n} \left[\hat{S}(t, \boldsymbol{\xi}_{1j}) H(t, \boldsymbol{\xi}_{1j}) - \hat{S}(t, \boldsymbol{\xi}_{2j}) H(t, \boldsymbol{\xi}_{2j}) \right] \right\}' \mathcal{I}^{-1}(\hat{\boldsymbol{\beta}}) \\ &\quad \left\{ \sum_{j=1}^{n} \left[\hat{S}(t, \boldsymbol{\xi}_{1j}) H(t, \boldsymbol{\xi}_{1j}) - \hat{S}(t, \boldsymbol{\xi}_{2j}) H(t, \boldsymbol{\xi}_{2j}) \right] \right\} \end{aligned}$$

Confidence Intervals for the Survivor Function

When the computation of confidence limits for the survivor function $S(t)$ is based on the asymptotic normality of the survival estimator $\hat{S}(t)$—which can be the Breslow estimator $\hat{S}_B(t)$, the Fleming-Harrington estimator $\hat{S}_F(t)$, or the product-limit estimator $\hat{S}_P(t)$—the approximate confidence interval might include impossible values outside the range [0,1] at extreme values of t. This problem can be avoided by applying the asymptotic normality to a transformation of $S(t)$ for which the range is unrestricted. In addition, certain transformed confidence intervals for $S(t)$ perform better than the usual linear confidence intervals (Borgan and Liestøl 1990). The CLTYPE= option in the BASELINE statement enables you to choose one of the following transformations: the log-log function, the log function, and the linear function.

Let g be the transformation that is being applied to the survivor function $S(t)$. By the delta method, the standard error of $g(\hat{S}(t))$ is estimated by

$$\tau(t) = \hat{\sigma} \left[g(\hat{S}(t)) \right] = g' \left(\hat{S}(t) \right) \hat{\sigma}[\hat{S}(t)]$$

where g' is the first derivative of the function g. The 100(1–α)% confidence interval for $S(t)$ is given by

$$g^{-1} \left\{ g[\hat{S}(t)] \pm z_{\frac{\alpha}{2}} g'[\hat{S}(t)] \hat{\sigma}[\hat{S}(t)] \right\}$$

where g^{-1} is the inverse function of g. The choices for the transformation g are as follows:

- CLTYPE=NORMAL specifies linear transformation, which is the same as having no transformation in which g is the identity. The 100(1–α)% confidence interval for $S(t)$ is given by

$$\hat{S}(t) - z_{\frac{\alpha}{2}}\hat{\sigma}\left[\hat{S}(t)\right] \leq S(t) \leq \hat{S}(t) + z_{\frac{\alpha}{2}}\hat{\sigma}\left[\hat{S}(t)\right]$$

- CLTYPE=LOG specifies log transformation. The estimated variance of $\log(\hat{S}(t))$ is $\hat{\tau}^2(t) = \frac{\hat{\sigma}^2(\hat{S}(t))}{\hat{S}^2(t)}$. The 100(1–$\alpha$)% confidence interval for $S(t)$ is given by

$$\hat{S}(t)\exp\left(-z_{\frac{\alpha}{2}}\hat{\tau}(t)\right) \leq S(t) \leq \hat{S}(t)\exp\left(z_{\frac{\alpha}{2}}\hat{\tau}(t)\right)$$

- CLTYPE=LOGLOG specifies log-log transformation. The estimated variance of $\log(-\log(\hat{S}(t))$ is $\hat{\tau}^2(t) = \frac{\hat{\sigma}^2[\hat{S}(t)]}{[\hat{S}(t)\log(\hat{S}(t))]^2}$. The 100(1–$\alpha$)% confidence interval for $S(t)$ is given by

$$\left[\hat{S}(t)\right]^{\exp\left(z_{\frac{\alpha}{2}}\hat{\tau}(t)\right)} \leq S(t) \leq \left[\hat{S}(t)\right]^{\exp\left(-z_{\frac{\alpha}{2}}\hat{\tau}(t)\right)}$$

Caution about Using Survival Data with Left Truncation

The product-limit estimator is used in a number of instances in the PHREG procedure, such as to transform the time values in the ZPH option in the PROC PHREG statement. The product-limit estimator is also used to construct the weights in the inverse probability of censoring weighting (IPCW) techniques, which are adapted to fit the proportional subdistribution model of Fine and Gray (1999) for competing-risks data and to assess the predictive accuracy of a model (Schemper and Henderson 2000). Although the product-limit estimator is the gold standard for estimating the survivor function of right-censored data, it might not be meaningful for right-censored data with left-truncation, as illustrated by Example 4.3 in Klein and Moeschberger (2003). In their example, 94 men and 365 women passed through the Channing House Retirement Center between January 1964 and July 1975. The outcome is the time to death, using the natural metric of age (in months).

The following statements create the data set Channing, which contains the following variables:

- Gender: female or male
- Age_entry: age at entry, in months
- Age_exit: age at exit (death or last follow-up), in months
- Death: death indicator, with the value 1 for death and 0 for censoring

```
data Channing;
   input Gender$ Age_entry Age_exit Death @@;
   datalines;
Female  1042 1172  1  Female   921 1040  1  Female   885 1003  1
Female   901 1018  1  Female   808  932  1  Female   915 1004  1
Female   901 1023  1  Female   852  908  1  Female   828  868  1
Female   968  990  1  Female   936 1033  1  Female   977 1056  1
Female   929  999  1  Female   936 1064  1  Female  1016 1122  1
```

```
Female   910 1020  1  Female  1140 1200  1  Female  1015 1056  1
Female   850  940  1  Female   895  996  1  Female   854  969  1

   ... more lines ...

  Male   751  777  1    Male   906  966  1    Male   835  907  1
  Male   946 1031  1    Male   759  781  1    Male   909  914  0
  Male   962  998  1    Male   984 1022  1    Male   891  932  1
  Male   835  898  1    Male  1039 1060  1    Male  1010 1044  1
;
```

The following statements use the PHREG procedure to save the product-limit estimate of the survivor function for each gender in the data set Outs. For each gender, the number of subjects at risk and the number of deaths at each death time are captured in the data set Atrisk. By merging these two data sets, Outs and Atrisk, you can conveniently display side by side the number of subjects at risk, the number of deaths, and the product-limit survival estimate at each death time.

```
ods graphics on;
proc phreg data=Channing plots(overlay=row)=survival atrisk;
   model Age_exit*Death(0)= /entrytime=Age_entry;
   strata Gender;
   baseline out=Outs survival=Probability / method=pl;
   ods output RiskSetInfo=Atrisk;
run;

data Outs;
   set Outs;
   if Gender="Female" then StratumNumber=1;
   else                    StratumNumber=2;
run;
data Outs;
   merge atrisk outs;
   by StratumNumber Age_exit;
run;

proc print data=Outs;
   id Gender;
   var Age_exit Atrisk Event Probability;
run;
```

Figure 86.18 displays two product-limit survival curves, one for women and one for men. The survival probabilities are tabulated in Figure 86.19 for women and in Figure 86.20 for men. Although the survival curve for women does not appear unusual, the survival curve for men looks odd, because the curve drops to 0 at 781 months even though the majority of men survive beyond 781 months. At 781 months, the risk set consists of a single time to death, rendering the product-limit estimate as 0 at 781 months and thereafter. The product-limit curve for men for these data is meaningless. Klein and Moeschberger (2003) suggest using only those observations in which the value of Age_exit exceeds 781 months.

Figure 86.18 Product-Limit Estimates for Women and Men

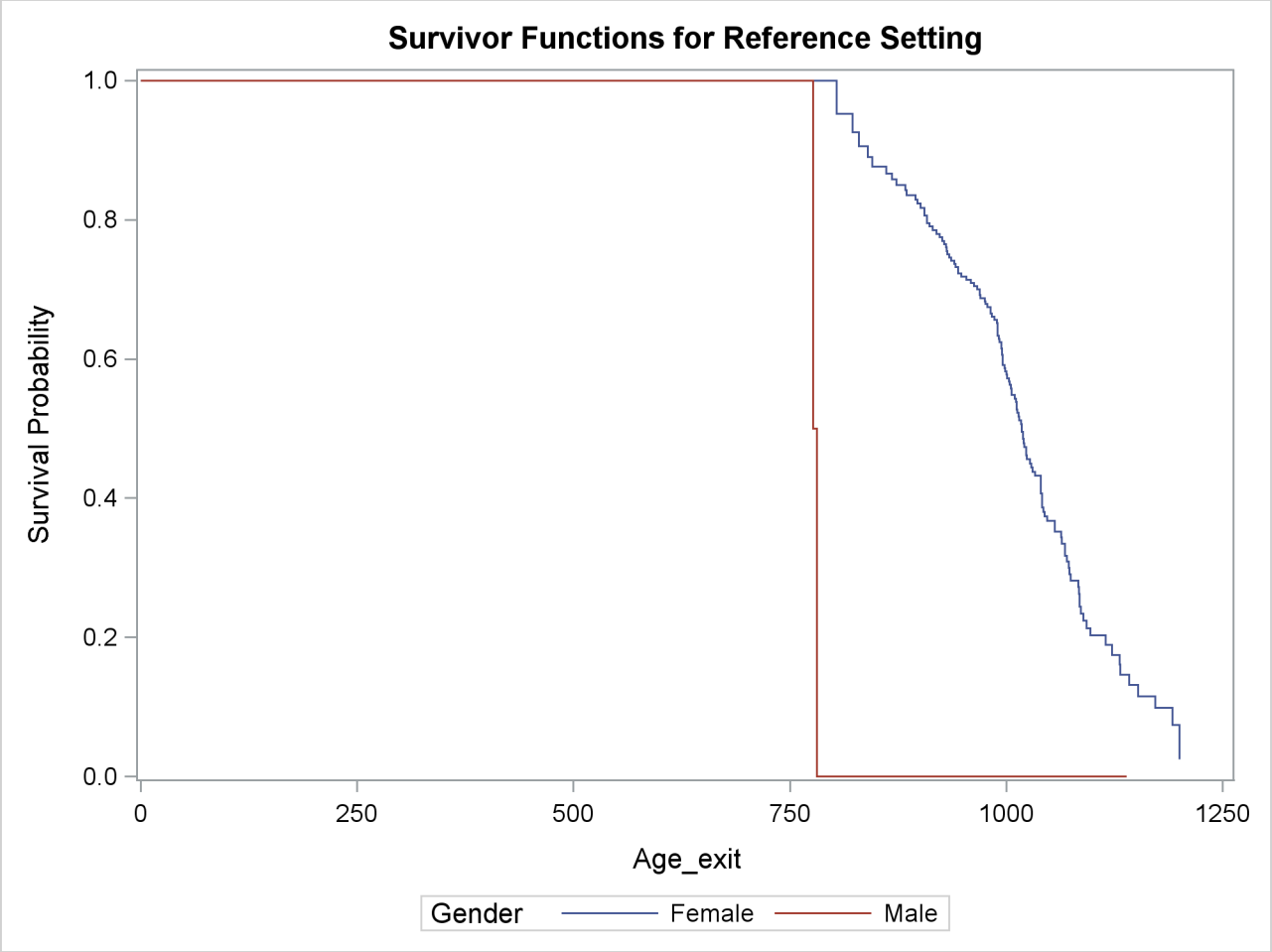


Figure 86.19 Product-Limit Survival Probabilities for Women

Gender	Age_exit	Atrisk	Event	Probability
Female	0	.	.	1.00000
Female	804	21	1	0.95238
Female	822	36	1	0.92593
Female	830	46	1	0.90580
Female	840	58	1	0.89018
Female	845	66	1	0.87669
Female	861	89	1	0.86684
	.	.	.	.
	.	.	.	.
	.	.	.	.
Female	1152	8	1	0.11493
Female	1172	7	1	0.09852
Female	1192	4	1	0.07389
Female	1200	3	2	0.02463

Figure 86.20 Product-Limit Survival Probabilities for Men

Gender	Age_exit	Atrisk	Event	Probability
Male	0	.	.	1.0
Male	777	2	1	0.5
Male	781	1	1	0.0
Male	869	24	1	0.0
Male	872	25	1	0.0
Male	876	25	1	0.0
Male	893	33	1	0.0
	.	.	.	.
	.	.	.	.
	.	.	.	.
Male	1085	10	1	0.0
Male	1094	8	2	0.0
Male	1128	3	1	0.0
Male	1139	2	1	0.0

PROC PHREG currently makes no attempt to circumvent the problem of the invalid product-limit estimator for left-truncated data.

Effect Selection Methods

Five effect selection methods are available. The simplest method (and the default) is SELECTION=NONE, for which PROC PHREG fits the complete model as specified in the MODEL statement. The other four methods are FORWARD for forward selection, BACKWARD for backward elimination, STEPWISE for stepwise selection, and SCORE for best subsets selection. These methods are specified with the SELECTION= option in the MODEL statement and are based on the score test or Wald test as described in the section "Type 3 Tests and Joint Tests" on page 6907.

When SELECTION=FORWARD, PROC PHREG first estimates parameters for effects that are forced into the model. These are the first n effects in the MODEL statement, where n is the number specified by the START= or INCLUDE= option in the MODEL statement (n is zero by default). Next, the procedure computes the score statistic for each effect that is not in the model. Each score statistic is the chi-square statistic of the score test for testing the null hypothesis that the corresponding effect that is not in the model is null. If the largest of these statistics is significant at the SLSENTRY= level, the effect with the largest score statistic is added to the model. After an effect is entered in the model, it is never removed from the model. The process is repeated until none of the remaining effects meet the specified level for entry or until the STOP= value is reached.

When SELECTION=BACKWARD, parameters for the complete model as specified in the MODEL statement are estimated unless the START= option is specified. In that case, only the parameters for the first n effects in the MODEL statement are estimated, where n is the number specified by the START= option. Next, the procedure computes the Wald statistic of each effect in the model. Each Wald's statistic is the chi-square statistic of the Wald test for testing the null hypothesis that the corresponding effect is null. If the smallest of these statistics is not significant at the SLSTAY= level, the effect with the smallest Wald statistic is removed. After an effect is removed from the model, it remains excluded. The process is repeated until no other variable in the model meets the specified level for removal or until the STOP= value is reached.

The SELECTION=STEPWISE option is similar to the SELECTION=FORWARD option except that effects already in the model do not necessarily remain. Effects are entered into and removed from the model in such a way that each forward selection step can be followed by one or more backward elimination steps. The stepwise selection process terminates if no further effect can be added to the model or if the effect just entered into the model is the only effect that is removed in the subsequent backward elimination.

For SELECTION=SCORE, PROC PHREG uses the branch-and-bound algorithm of Furnival and Wilson (1974) to find a specified number of models with the highest score (chi-square) statistic for all possible model sizes, from 1, 2, or 3 variables, and so on, up to the single model that contains all of the explanatory variables. The number of models displayed for each model size is controlled by the BEST= option. You can use the START= option to impose a minimum model size, and you can use the STOP= option to impose a maximum model size. For instance, with BEST=3, START=2, and STOP=5, the SCORE selection method displays the best three models (that is, the three models with the highest score chi-squares) that contain 2, 3, 4, and 5 variables. One of the limitations of the branch-and-bound algorithm is that it works only when each explanatory effect contains exactly one parameter—the SELECTION=SCORE option is not allowed when an explanatory effect in the MODEL statement contains a CLASS variable.

The SEQUENTIAL and STOPRES options can alter the default criteria for adding variables to or removing variables from the model when they are used with the FORWARD, BACKWARD, or STEPWISE selection method.

Assessment of the Proportional Hazards Model

The proportional hazards model specifies that the hazard function for the failure time T associated with a $p \times 1$ column covariate vector $\mathbf{Z}$ takes the form

$$\lambda(t;\mathbf{Z}) = \lambda_0(t)\mathrm{e}^{\boldsymbol{\beta}'\mathbf{Z}}$$

where $\lambda_0(.)$ is an unspecified baseline hazard function and $\boldsymbol{\beta}$ is a $p \times 1$ column vector of regression parameters. Lin, Wei, and Ying (1993) present graphical and numerical methods for model assessment based on the cumulative sums of martingale residuals and their transforms over certain coordinates (such as covariate values or follow-up times). The distributions of these stochastic processes under the assumed model can be approximated by the distributions of certain zero-mean Gaussian processes whose realizations can be generated by simulation. Each observed residual pattern can then be compared, both graphically and numerically, with a number of realizations from the null distribution. Such comparisons enable you to assess objectively whether the observed residual pattern reflects anything beyond random fluctuation. These procedures are useful in determining appropriate functional forms of covariates and assessing the proportional hazards assumption. You use the ASSESS statement to carry out these model-checking procedures.

For a sample of n subjects, let $(X_i, \Delta_i, \mathbf{Z}_i)$ be the data of the ith subject; that is, X_i represents the observed failure time, Δ_i has a value of 1 if X_i is an uncensored time and 0 otherwise, and $\mathbf{Z}_i = (Z_{1i}, \ldots, Z_{pi})'$ is a p-vector of covariates. Let $N_i(t) = \Delta_i I(X_i \leq t)$ and $Y_i(t) = I(X_i \geq t)$. Let

$$S^{(0)}(\boldsymbol{\beta}, t) = \sum_{i=1}^{n} Y_i(t)\mathrm{e}^{\boldsymbol{\beta}'\mathbf{Z}_i} \quad \text{and} \quad \mathbf{Z}(\boldsymbol{\beta}, t) = \frac{\sum_{i=1}^{n} Y_i(t)\mathrm{e}^{\boldsymbol{\beta}'\mathbf{Z}_i}\mathbf{Z}_i}{S^{(0)}(\boldsymbol{\beta}, t)}$$

Let $\hat{\boldsymbol{\beta}}$ be the maximum partial likelihood estimate of $\boldsymbol{\beta}$, and let $\mathcal{I}(\hat{\boldsymbol{\beta}})$ be the observed information matrix.

The martingale residuals are defined as

$$\hat{M}_i(t) = N_i(t) - \int_0^t Y_i(u)\mathrm{e}^{\hat{\boldsymbol{\beta}}'\mathbf{Z}_i}\, d\,\hat{\Lambda}_0(u), i = 1,\ldots,n$$

where $\hat{\Lambda}_0(t) = \int_0^t \frac{\sum_{i=1}^n dN_i(u)}{S^{(0)}(\hat{\boldsymbol{\beta}},u)}$.

The empirical score process $\mathbf{U}(\hat{\boldsymbol{\beta}},t) = (U_1(\hat{\boldsymbol{\beta}},t),\ldots,U_p(\hat{\boldsymbol{\beta}},t))'$ is a transform of the martingale residuals:

$$\mathbf{U}(\hat{\boldsymbol{\beta}},t) = \sum_{i=1}^n \mathbf{Z}_i \hat{M}_i(t)$$

Checking the Functional Form of a Covariate

To check the functional form of the *j*th covariate, consider the partial-sum process of $\hat{M}_i = \hat{M}_i(\infty)$:

$$W_j(z) = \sum_{i=1}^n I(Z_{ji} \le z)\hat{M}_i$$

Under that null hypothesis that the model holds, $W_j(z)$ can be approximated by the zero-mean Gaussian process

$$\begin{aligned}\hat{W}_j(z) \;=\; & \sum_{l=1}^n \Delta_l \left\{ I(Z_{jl} \le z) - \frac{\sum_{i=1}^n Y_i(X_l)\mathrm{e}^{\boldsymbol{\beta}'\mathbf{Z}_i} I(Z_{ij} \le z)}{S^{(0)}(\hat{\boldsymbol{\beta}}, X_l)} \right\} G_l - \\ & \sum_{k=1}^n \int_0^\infty Y_k(s)\mathrm{e}^{\hat{\boldsymbol{\beta}}'\mathbf{Z}_k} I(Z_{jk} \le z)[\mathbf{Z}_k - \bar{\mathbf{Z}}(\hat{\boldsymbol{\beta}}, s)]' d\,\hat{\Lambda}_0(s) \\ & \times \mathcal{I}^{-1}(\hat{\boldsymbol{\beta}}) \sum_{l=1}^n \Delta_l [\mathbf{Z}_l - \bar{\mathbf{Z}}(\hat{\boldsymbol{\beta}}, X_l)] G_l\end{aligned}$$

where $(G_1,\ldots,G_n)$ are independent standard normal variables that are independent of $(X_i, \Delta_i, \mathbf{Z}_i)$, $i = 1,\ldots,n$.

You can assess the functional form of the *j*th covariate by plotting a small number of realizations (the default is 20) of $\hat{W}_j(z)$ on the same graph as the observed $W_j(z)$ and visually comparing them to see how typical the observed pattern of $W_j(z)$ is of the null distribution samples. You can supplement the graphical inspection method with a Kolmogorov-type supremum test. Let s_j be the observed value of $S_j = \sup_z |W_j(z)|$ and let $\hat{S}_j = \sup_z |\hat{W}_j(z)|$. The *p*-value $\Pr(S_j \ge s_j)$ is approximated by $\Pr(\hat{S}_j \ge s_j)$, which in turn is approximated by generating a large number of realizations (1000 is the default) of $\hat{W}_j(.)$.

Checking the Proportional Hazards Assumption

Consider the standardized empirical score process for the *j*th component of $\mathbf{Z}$

$$U_j^*(t) = [\mathcal{I}^{-1}(\hat{\boldsymbol{\beta}})_{jj}]^{\frac{1}{2}} U_j(\hat{\boldsymbol{\beta}},t),$$

Under the null hypothesis that the model holds, $U_j^*(t)$ can be approximated by

$$\begin{aligned}\hat{U}_j^*(t) &= [\mathcal{I}^{-1}(\hat{\boldsymbol{\beta}})_{jj}]^{\frac{1}{2}}\Bigg\{\sum_{l=1}^{n} I(X_l \le t)\Delta_l[Z_{jl} - \bar{Z}_j(\hat{\boldsymbol{\beta}}, t)]G_l - \\ &\sum_{k=1}^{n}\int_0^t Y_k(s)\mathrm{e}^{\hat{\boldsymbol{\beta}}'\mathbf{Z}_k} Z_{jk}[\mathbf{Z}_k - \bar{\mathbf{Z}}(\hat{\boldsymbol{\beta}}, s)]' d\,\hat{\Lambda}_0(s) \\ &\times\mathcal{I}^{-1}(\hat{\boldsymbol{\beta}})\sum_{l=1}^{n}\Delta_l[\mathbf{Z}_l - \bar{\mathbf{Z}}(\hat{\boldsymbol{\beta}}, X_l)]G_l\Bigg\}\end{aligned}$$

where $\bar{Z}_j(\hat{\boldsymbol{\beta}}, t)$ is the jth component of $\bar{\mathbf{Z}}(\hat{\boldsymbol{\beta}}, t)$, and $(G_1, \ldots, G_n)$ are independent standard normal variables that are independent of $(X_i, \Delta_i, \mathbf{Z}_i, (i = 1, \ldots, n)$.

You can assess the proportional hazards assumption for the jth covariate by plotting a few realizations of $\hat{U}_j^*(t)$ on the same graph as the observed $U_j^*(t)$ and visually comparing them to see how typical the observed pattern of $U_j^*(t)$ is of the null distribution samples. Again you can supplement the graphical inspection method with a Kolmogorov-type supremum test. Let s_j^* be the observed value of $S_j^* = \sup_t |U_j^*(t)|$ and let $\hat{S}_j^* = \sup_t |\hat{U}_j^*(t)|$. The p-value $\Pr[S_j^* \ge s_j^*]$ is approximated by $\Pr[\hat{S}_j^* \ge s_j^*]$, which in turn is approximated by generating a large number of realizations (1000 is the default) of $\hat{U}_j^*(.)$.

The Penalized Partial Likelihood Approach for Fitting Frailty Models

Let $\boldsymbol{\gamma} = (\gamma_1, \ldots, \gamma_s)'$ be the vector of random components for the s clusters.

Gamma Frailty Model

Assume each e^{γ_i} has an independent and identically distributed gamma distribution with mean 1 and a common unknown variance θ; that is, e^{γ_i} is iid $G\left(\frac{1}{\theta}, \frac{1}{\theta}\right)$. The penalty function is

$$-\frac{1}{\theta}\sum_{i=1}^{s}\left(\gamma_i - \mathrm{e}^{\gamma_i}\right)$$

plus a function of θ. The penalized partial log likelihood is given by

$$l_p(\boldsymbol{\beta}, \boldsymbol{\gamma}, \theta) = l_{\text{partial}}(\boldsymbol{\beta}, \boldsymbol{\gamma}) + \frac{1}{\theta}\sum_{i=1}^{s}\left(\gamma_i - \mathrm{e}^{\gamma_i}\right)$$

where $l_{\text{partial}}(\boldsymbol{\beta}, \boldsymbol{\gamma})$ is the log of any of the partial likelihoods in the sections "Partial Likelihood Function for the Cox Model" on page 6890 and "The Multiplicative Hazards Model" on page 6894.

The profile marginal log-likelihood of this shared frailty model (Therneau and Grambsch 2000, pp. 257–258) is

$$l_m(\theta) = l_p(\hat{\boldsymbol{\beta}}(\theta), \hat{\boldsymbol{\gamma}}(\theta), \theta) + \sum_{i=1}^{s}\left\{\theta^{-1} - (\theta^{-1} + d_i)\log\left[\theta^{-1} + d_i\right] + \theta^{-1}\log(\theta^{-1}) + \log\left[\frac{\Gamma(\theta^{-1} + d_i)}{\Gamma(\theta^{-1})}\right]\right\}$$

where d_i is the number of events in the ith cluster.

The maximization of this approximate likelihood is a doubly iterative process that alternates between the following two steps:

- For a provisional value of θ, the best linear unbiased predictors (BLUP) of $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$ are computed by maximizing the penalized partial log-likelihood $l_p(\boldsymbol{\beta}, \boldsymbol{\gamma}, \theta)$. The marginal likelihood is evaluated. This constitutes the inner loop.
- A new value of θ is obtained by the golden section search based on the marginal likelihood of all the previous iterations. This constitutes the outer loop.

The outer loop is iterated until the bracketing interval of θ is small.

Lognormal Frailty Model

With each γ_i having a zero-mean normal distribution and a common variance θ, the penalty function is

$$\frac{1}{2\theta}\boldsymbol{\gamma}'\boldsymbol{\gamma}$$

plus a function of θ. The penalized partial log likelihood is given by

$$l_p(\boldsymbol{\beta}, \boldsymbol{\gamma}, \theta) = l_{\text{partial}}(\boldsymbol{\beta}, \boldsymbol{\gamma}) - \frac{1}{2\theta}\boldsymbol{\gamma}'\boldsymbol{\gamma}$$

where $l_{\text{partial}}(\boldsymbol{\beta}, \boldsymbol{\gamma})$ is the log of any of the partial likelihoods in the sections "Partial Likelihood Function for the Cox Model" on page 6890 and "The Multiplicative Hazards Model" on page 6894.

For a given θ, let $\mathbf{H}$ be the negative Hessian of the penalized partial log likelihood $l_p(\boldsymbol{\beta}, \boldsymbol{\gamma}, \theta)$; that is,

$$\mathbf{H} = \mathbf{H}(\boldsymbol{\beta}, \boldsymbol{\gamma}) = \begin{bmatrix} \mathbf{H}_{11} & \mathbf{H}_{12} \\ \mathbf{H}_{21} & \mathbf{H}_{22} \end{bmatrix}$$

where $\mathbf{H}_{11} = -\frac{\partial^2 l_p(\boldsymbol{\beta},\boldsymbol{\gamma},\theta)}{\partial \boldsymbol{\beta}^2}$, $\mathbf{H}_{12} = \mathbf{H}'_{21} = -\frac{\partial^2 l_p(\boldsymbol{\beta},\boldsymbol{\gamma},\theta)}{\partial \boldsymbol{\beta}\partial \boldsymbol{\gamma}}$, and $\mathbf{H}_{22} = -\frac{\partial^2 l_p(\boldsymbol{\beta},\boldsymbol{\gamma},\theta)}{\partial \boldsymbol{\gamma}^2}$.

The marginal log likelihood of this shared frailty model is

$$l_m(\boldsymbol{\beta}, \theta) = -\frac{1}{2}\log(\theta^s) + \log\left[\int \mathrm{e}^{l_p(\boldsymbol{\beta},\boldsymbol{\gamma},\theta)} d\boldsymbol{\gamma}\right]$$

Using a Laplace approximation to the integral as in Breslow and Clayton (1993), an approximate marginal log likelihood (Ripatti and Palmgren 2000; Therneau and Grambsch 2000) is given by

$$l_m(\boldsymbol{\beta}, \theta) \approx -\frac{1}{2}\log(\theta^s) - \frac{1}{2}\log(|\mathbf{H}_{22}(\boldsymbol{\beta}, \tilde{\boldsymbol{\gamma}}, \theta)|) - l_p(\boldsymbol{\beta}, \tilde{\boldsymbol{\gamma}}, \theta)$$

The maximization of this approximate likelihood is a doubly iterative process that alternates between the following two steps:

- For a provisional value of θ, PROC PHREG computes the best linear unbiased predictors (BLUP) of $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$ by maximizing the penalized partial log likelihood $l_p(\boldsymbol{\beta}, \boldsymbol{\gamma}, \theta)$. This constitutes the inner loop.

- For $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$ fixed at the BLUP values, PROC PHREG estimates θ by maximizing the approximate marginal likelihood $l_m(\boldsymbol{\beta}, \theta)$. This constitutes the outer loop.

The outer loop is iterated until the difference between two successive estimates of θ is small.

The ML estimate of θ is

$$\hat{\theta} = \frac{\hat{\boldsymbol{\gamma}}'\hat{\boldsymbol{\gamma}} + \text{trace}(\mathbf{H}_{22}^{-1})}{s}$$

The variance for $\hat{\theta}$ is

$$\text{var}(\hat{\theta}) = 2\hat{\theta}\left[s + \frac{1}{\hat{\theta}^2}\text{trace}(\mathbf{H}_{22}^{-1}\mathbf{H}_{22}^{-1}) - \frac{2}{\hat{\theta}}\text{trace}(\mathbf{H}_{22}^{-1})\right]^{-1}$$

The REML estimation of θ is obtained by replacing $(\mathbf{H}_{22})^{-1}$ by $(\mathbf{H}^{-1})_{22}$.

The inverse of the final $\mathbf{H}$ matrix is used as the variance estimate of $(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\gamma}})'$.

The final BLUP estimates of the random components $\gamma_1, \ldots, \gamma_s$ can be displayed by using the SOLUTION option in the RANDOM statement. Also displayed are estimates of the lognormal frailties, which are the exponentiated estimates of the BLUP estimates.

Wald-Type Tests for Penalized Models

Let $\mathbf{I}$ be the negative Hessian of the partial log likelihood $l_{\text{partial}}(\boldsymbol{\beta}, \boldsymbol{\gamma})$:

$$\mathbf{I} = \begin{bmatrix} \mathbf{I}_{11} & \mathbf{I}_{12} \\ \mathbf{I}_{21} & \mathbf{I}_{22} \end{bmatrix}$$

where $\mathbf{I}_{11} = -\frac{\partial^2 l_{\text{partial}}(\boldsymbol{\beta},\boldsymbol{\gamma})}{\partial \boldsymbol{\beta}^2}$, $\mathbf{I}_{12} = \mathbf{I}_{21}' = -\frac{\partial^2 l_{\text{partial}}(\boldsymbol{\beta},\boldsymbol{\gamma})}{\partial \boldsymbol{\beta}\partial \boldsymbol{\gamma}}$, and $\mathbf{I}_{22} = -\frac{\partial^2 l_{\text{partial}}(\boldsymbol{\beta},\boldsymbol{\gamma})}{\partial \boldsymbol{\gamma}^2}$. Write $\boldsymbol{\tau}' = (\boldsymbol{\beta}', \boldsymbol{\gamma}')'$. The Wald-type chi-square statistic for testing $H_0 : \mathbf{C}\boldsymbol{\tau} = \mathbf{0}$ is

$$(\mathbf{C}\hat{\boldsymbol{\tau}})'(\mathbf{C}\mathbf{H}^{-1}\mathbf{C}')^{-1}(\mathbf{C}\hat{\boldsymbol{\tau}})$$

Let $\mathbf{H}$ be the negative Hessian of the penalized partial log likelihood $l_p(\boldsymbol{\beta}, \boldsymbol{\gamma}, \theta)$ at the ML estimate θ; that is, $\mathbf{H} = \frac{\partial^2}{\partial \boldsymbol{\beta}\partial \boldsymbol{\gamma}} l_p(\boldsymbol{\beta}, \boldsymbol{\gamma}, \hat{\theta})$. Let $\mathbf{V} = \mathbf{H}^{-1}\mathbf{I}\mathbf{H}^{-1}$. Gray (1992) recommends the following generalized degrees of freedom for the Wald test:

$$\text{DF} = \text{trace}[(\mathbf{C}\mathbf{H}^{-1}\mathbf{C}')^{-1}\mathbf{C}\mathbf{V}\mathbf{C}')]$$

See Therneau and Grambsch (2000, Section 5.8) for a discussion of this Wald-type test.

PROC PHREG uses the label "Adjusted DF" to represent this generalized degrees of freedom in the output.

Specifics for Bayesian Analysis

To request a Bayesian analysis, you specify the new BAYES statement in addition to the PROC PHREG statement and the MODEL statement. You include a CLASS statement if you have effects that involve categorical variables. The FREQ or WEIGHT statement can be included if you have a frequency or weight

variable, respectively, in the input data. The STRATA statement can be used to carry out a stratified analysis for the Cox model, but it is not allowed in the piecewise constant baseline hazard model. Programming statements can be used to create time-dependent covariates for the Cox model, but they are not allowed in the piecewise constant baseline hazard model. However, you can use the counting process style of input to accommodate time-dependent covariates that are not continuously changing with time for the piecewise constant baseline hazard model and the Cox model as well. The HAZARDRATIO statement enables you to request a hazard ratio analysis based on the posterior samples. The ASSESS, CONTRAST, ID, OUTPUT, and TEST statements, if specified, are ignored. Also ignored are the COVM and COVS options in the PROC PHREG statement and the following options in the MODEL statement: BEST=, CORRB, COVB, DETAILS, HIERARCHY=, INCLUDE=, MAXSTEP=, NOFIT, PLCONV=, SELECTION=, SEQUENTIAL, SLENTRY=, and SLSTAY=.

Piecewise Constant Baseline Hazard Model

Single Failure Time Variable

Let $\{(t_i, \mathbf{x}_i, \delta_i), i = 1, 2, \ldots, n\}$ be the observed data. Let $a_0 = 0 < a_1 < \ldots < a_{J-1} < a_J = \infty$ be a partition of the time axis.

Hazards in Original Scale The hazard function for subject i is

$$h(t|\mathbf{x}_i; \boldsymbol{\theta}) = h_0(t) \exp(\boldsymbol{\beta}'\mathbf{x}_i)$$

where

$$h_0(t) = \lambda_j \text{ if } a_{j-1} \le t < a_j, j = 1, \ldots, J$$

The baseline cumulative hazard function is

$$H_0(t) = \sum_{j=1}^{J} \lambda_j \Delta_j(t)$$

where

$$\Delta_j(t) = \begin{cases} 0 & t < a_{j-1} \\ t - a_{j-1} & a_{j-1} \le t < a_j \\ a_j - a_{j-1} & t \ge a_j \end{cases}$$

The log likelihood is given by

$$\begin{aligned} l(\boldsymbol{\lambda}, \boldsymbol{\beta}) &= \sum_{i=1}^{n} \delta_i \left[\sum_{j=1}^{J} I(a_{j-1} \le t_i < a_j) \log \lambda_j + \boldsymbol{\beta}'\mathbf{x}_i \right] - \sum_{i=1}^{n} \left[\sum_{j=1}^{J} \Delta_j(t_i)\lambda_j \right] \exp(\boldsymbol{\beta}'\mathbf{x}_i) \\ &= \sum_{j=1}^{J} d_j \log \lambda_j + \sum_{i=1}^{n} \delta_i \boldsymbol{\beta}'\mathbf{x}_i - \sum_{j=1}^{J} \lambda_j \left[\sum_{i=1}^{n} \Delta_j(t_i) \exp(\boldsymbol{\beta}'\mathbf{x}_i) \right] \end{aligned}$$

where $d_j = \sum_{i=1}^{n} \delta_i I(a_{j-1} \le t_i < a_j)$.

Note that for $1 \le j \le J$, the full conditional for λ_j is log-concave only when $d_j > 0$, but the full conditionals for the β's are always log-concave.

For a given $\boldsymbol{\beta}$, $\frac{\partial l}{\partial \boldsymbol{\lambda}} = 0$ gives

$$\tilde{\lambda}_j(\boldsymbol{\beta}) = \frac{d_j}{\sum_{i=1}^{n} \Delta_j(t_i) \exp(\boldsymbol{\beta}'\mathbf{x}_i)}, \quad j = 1, \ldots, J$$

Substituting these values into $l(\boldsymbol{\lambda}, \boldsymbol{\beta})$ gives the profile log likelihood for $\boldsymbol{\beta}$

$$l_p(\boldsymbol{\beta}) = \sum_{i=1}^{n} \delta_i \boldsymbol{\beta}' \mathbf{x}_i - \sum_{j=1}^{J} d_j \log\left[\sum_{l=1}^{n} \Delta_j(t_l) \exp(\boldsymbol{\beta}' \mathbf{x}_l)\right] + c$$

where $c = \sum_j (d_j \log d_j - d_j)$. Since the constant c does not depend on $\boldsymbol{\beta}$, it can be discarded from $l_p(\boldsymbol{\beta})$ in the optimization.

The MLE $\hat{\boldsymbol{\beta}}$ of $\boldsymbol{\beta}$ is obtained by maximizing

$$l_p(\boldsymbol{\beta}) = \sum_{i=1}^{n} \delta_i \boldsymbol{\beta}' \mathbf{x}_i - \sum_{j=1}^{J} d_j \log\left[\sum_{l=1}^{n} \Delta_j(t_l) \exp(\boldsymbol{\beta}' \mathbf{x}_l)\right]$$

with respect to $\boldsymbol{\beta}$, and the MLE $\hat{\boldsymbol{\lambda}}$ of $\boldsymbol{\lambda}$ is given by

$$\hat{\boldsymbol{\lambda}} = \tilde{\boldsymbol{\lambda}}(\hat{\boldsymbol{\beta}})$$

For $j = 1, \ldots, J$, let

$$\begin{aligned} \mathbf{S}_j^{(r)}(\boldsymbol{\beta}) &= \sum_{l=1}^{n} \Delta_j(t_l) \mathrm{e}^{\boldsymbol{\beta}' \mathbf{x}_l} \mathbf{x}_l^{\otimes r}, \quad r = 0, 1, 2 \\ \mathbf{E}_j(\boldsymbol{\beta}) &= \frac{\mathbf{S}_j^{(1)}(\boldsymbol{\beta})}{S_j^{(0)}(\boldsymbol{\beta})} \end{aligned}$$

The partial derivatives of $l_p(\boldsymbol{\beta})$ are

$$\begin{aligned} \frac{\partial l_p(\boldsymbol{\beta})}{\partial \boldsymbol{\beta}} &= \sum_{i=1}^{n} \delta_i \mathbf{x}_i - \sum_{j=1}^{J} d_j \mathbf{E}_j(\boldsymbol{\beta}) \\ -\frac{\partial^2 l_p(\boldsymbol{\beta})}{\partial \boldsymbol{\beta}^2} &= \sum_{j=1}^{J} d_j \left\{ \frac{\mathbf{S}_j^{(2)}(\boldsymbol{\beta})}{S_j^{(0)}(\boldsymbol{\beta})} - \left[\mathbf{E}_j(\boldsymbol{\beta})\right]\left[\mathbf{E}_j(\boldsymbol{\beta})\right]' \right\} \end{aligned}$$

The asymptotic covariance matrix for $(\hat{\boldsymbol{\lambda}}, \hat{\boldsymbol{\beta}})$ is obtained as the inverse of the information matrix given by

$$\begin{aligned} -\frac{\partial^2 l(\hat{\boldsymbol{\lambda}}, \hat{\boldsymbol{\beta}})}{\partial \boldsymbol{\lambda}^2} &= \mathcal{D}\left(\frac{d_1}{\hat{\lambda}_1^2}, \ldots, \frac{d_J}{\hat{\lambda}_J^2}\right) \\ -\frac{\partial^2 l(\hat{\boldsymbol{\lambda}}, \hat{\boldsymbol{\beta}})}{\partial \boldsymbol{\beta}^2} &= \sum_{j=1}^{J} \hat{\lambda}_j \mathbf{S}_j^{(2)}(\hat{\boldsymbol{\beta}}) \\ -\frac{\partial^2 l(\hat{\boldsymbol{\lambda}}, \hat{\boldsymbol{\beta}})}{\partial \boldsymbol{\lambda} \partial \boldsymbol{\beta}} &= (\mathbf{S}_1^{(1)}(\hat{\boldsymbol{\beta}}), \ldots, \mathbf{S}_J^{(1)}(\hat{\boldsymbol{\beta}})) \end{aligned}$$

See Example 6.5.1 in Lawless (2003) for details.

Hazards in Log Scale By letting

$$\alpha_j = \log(\lambda_j), \quad j = 1, \ldots, J$$

you can build a prior correlation among the λ_j's by using a correlated prior $\boldsymbol{\alpha} \sim N(\boldsymbol{\alpha}_0, \Sigma_\alpha)$, where $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_J)'$.

The log likelihood is given by

$$l(\boldsymbol{\alpha}, \boldsymbol{\beta}) = \sum_{j=1}^{J} d_j \alpha_j + \sum_{i=1}^{n} \delta_i \boldsymbol{\beta}' \mathbf{x}_i - \sum_{j=1}^{J} \mathrm{e}^{\alpha_j} S_j^{(0)}(\boldsymbol{\beta})$$

Then the MLE of λ_j is given by

$$\mathrm{e}^{\hat{\alpha}_j} = \hat{\lambda}_j = \frac{d_j}{S_j^0(\hat{\boldsymbol{\beta}})}$$

Note that the full conditionals for α's and β's are always log-concave.

The asymptotic covariance matrix for $(\hat{\boldsymbol{\alpha}}, \hat{\boldsymbol{\beta}})$ is obtained as the inverse of the information matrix formed by

$$\begin{aligned}
-\frac{\partial^2 l(\hat{\boldsymbol{\alpha}}, \hat{\boldsymbol{\beta}})}{\partial \boldsymbol{\alpha}^2} &= \mathcal{D}\left(\mathrm{e}^{\hat{\alpha}_j} S_j^0(\hat{\boldsymbol{\beta}}), \ldots, \mathrm{e}^{\hat{\alpha}_J} S_J^0(\hat{\boldsymbol{\beta}})\right) \\
-\frac{\partial^2 l(\hat{\boldsymbol{\alpha}}, \hat{\boldsymbol{\beta}})}{\partial \boldsymbol{\beta}^2} &= \sum_{j=1}^{J} \mathrm{e}^{\hat{\alpha}_j} \mathbf{S}_j^{(2)}(\hat{\boldsymbol{\beta}}) \\
-\frac{\partial^2 l(\hat{\boldsymbol{\alpha}}, \hat{\boldsymbol{\beta}})}{\partial \boldsymbol{\alpha} \partial \boldsymbol{\beta}} &= (\mathrm{e}^{\hat{\alpha}_j} \mathbf{S}_1^{(1)}(\hat{\boldsymbol{\beta}}), \ldots, \mathrm{e}^{\hat{\alpha}_j} \mathbf{S}_J^{(1)}(\hat{\boldsymbol{\beta}}))
\end{aligned}$$

Counting Process Style of Input

Let $\{((s_i, t_i], \mathbf{x}_i, \delta_i), i = 1, 2, \ldots, n\}$ be the observed data. Let $a_0 = 0 < a_1 < \ldots < a_k$ be a partition of the time axis, where $a_k > t_i$ for all $i = 1, 2, \ldots, n$.

Replacing $\Delta_j(t_i)$ with

$$\Delta_j((s_i, t_i]) = \begin{cases} 0 & t_i < a_{j-1} \vee s_i > a_j \\ t_i - \max(s_i, a_{j-1}) & a_{j-1} \le t_i < a_j \\ a_j - \max(s_i, a_{j-1}) & t_i \ge a_j \end{cases}$$

the formulation for the single failure time variable applies.

Priors for Model Parameters

For a Cox model, the model parameters are the regression coefficients. For a piecewise exponential model, the model parameters consist of the regression coefficients and the hazards or log-hazards. The priors for the hazards and the priors for the regression coefficients are assumed to be independent, while you can have a joint multivariate normal prior for the log-hazards and the regression coefficients.

Hazard Parameters

Let $\lambda_1, \ldots, \lambda_J$ be the constant baseline hazards.

Improper Prior The joint prior density is given by

$$p(\lambda_1, \ldots, \lambda_J) = \prod_{j=1}^{J} \frac{1}{\lambda_j} \text{ for all } \lambda_j > 0$$

This prior is improper (nonintegrable), but the posterior distribution is proper as long as there is at least one event time in each of the constant hazard intervals.

Uniform Prior The joint prior density is given by

$$p(\lambda_1, \ldots, \lambda_J) \propto 1 \text{ for all } \lambda_j > 0$$

This prior is improper (nonintegrable), but the posteriors are proper as long as there is at least one event time in each of the constant hazard intervals.

Gamma Prior The gamma distribution $G(a, b)$ has a PDF

$$f_{a,b}(t) = \frac{b(bt)^{a-1}\mathrm{e}^{-bt}}{\Gamma(a)}, t > 0$$

where a is the shape parameter and b^{-1} is the scale parameter. The mean is $\frac{a}{b}$ and the variance is $\frac{a}{b^2}$.

Independent Gamma Prior Suppose for $j = 1, \ldots, J$, λ_j has an independent $G(a_j, b_j)$ prior. The joint prior density is given by

$$p(\lambda_1, \ldots, \lambda_J) \propto \prod_{j=1}^{J} \left\{ \lambda_j^{a_j - 1} \mathrm{e}^{-b_j \lambda_j} \right\}, \forall \lambda_j > 0$$

AR1 Prior $\lambda_1, \ldots, \lambda_J$ are correlated as follows:

$$\begin{aligned}
\lambda_1 &\sim G(a_1, b_1) \\
\lambda_2 &\sim G\left(a_2, \frac{b_2}{\lambda_1}\right) \\
\ldots &\quad \ldots \\
\lambda_J &\sim G\left(a_J, \frac{b_J}{\lambda_{J-1}}\right)
\end{aligned}$$

The joint prior density is given by

$$p(\lambda_1, \ldots, \lambda_J) \propto \lambda_1^{a_1 - 1} \mathrm{e}^{-b_1 \lambda_1} \prod_{j=2}^{J} \left(\frac{b_j}{\lambda_{j-1}} \right)^{a_j} \lambda_j^{a_j - 1} \mathrm{e}^{-\frac{b_j}{\lambda_{j-1}} \lambda_j}$$

Log-Hazard Parameters

Write $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_J)' \equiv (\log\lambda_1, \ldots, \log\lambda_J)'$.

Uniform Prior The joint prior density is given by

$$p(\alpha_1 \ldots \alpha_J) \propto 1, \forall -\infty < \alpha_i < \infty$$

Note that the uniform prior for the log-hazards is the same as the improper prior for the hazards.

Normal Prior Assume $\boldsymbol{\alpha}$ has a multivariate normal prior with mean vector $\boldsymbol{\alpha}_0$ and covariance matrix $\boldsymbol{\Psi}_0$. The joint prior density is given by

$$p(\boldsymbol{\alpha}) \propto \mathrm{e}^{-\frac{1}{2}(\boldsymbol{\alpha}-\boldsymbol{\alpha}_0)'\boldsymbol{\Psi}_0^{-1}(\boldsymbol{\alpha}-\boldsymbol{\alpha}_0)}$$

Regression Coefficients

Let $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_k)'$ be the vector of regression coefficients.

Uniform Prior The joint prior density is given by

$$p(\beta_1, \ldots, \beta_k) \propto 1, \forall -\infty < \beta_i < \infty$$

This prior is improper, but the posterior distributions for $\boldsymbol{\beta}$ are proper.

Normal Prior Assume $\boldsymbol{\beta}$ has a multivariate normal prior with mean vector $\boldsymbol{\beta}_0$ and covariance matrix $\boldsymbol{\Sigma}_0$. The joint prior density is given by

$$p(\boldsymbol{\beta}) \propto \mathrm{e}^{-\frac{1}{2}(\boldsymbol{\beta}-\boldsymbol{\beta}_0)'\boldsymbol{\Sigma}_0^{-1}(\boldsymbol{\beta}-\boldsymbol{\beta}_0)}$$

Joint Multivariate Normal Prior for Log-Hazards and Regression Coefficients Assume $(\boldsymbol{\alpha}', \boldsymbol{\beta}')'$ has a multivariate normal prior with mean vector $(\boldsymbol{\alpha}_0', \boldsymbol{\beta}_0')'$ and covariance matrix $\boldsymbol{\Phi}_0$. The joint prior density is given by

$$p(\boldsymbol{\alpha}, \boldsymbol{\beta}) \propto \mathrm{e}^{-\frac{1}{2}[(\boldsymbol{\alpha}-\boldsymbol{\alpha}_0)',(\boldsymbol{\beta}-\boldsymbol{\beta}_0)']\boldsymbol{\Phi}_0^{-1}[(\boldsymbol{\alpha}-\boldsymbol{\alpha}_0)',(\boldsymbol{\beta}-\boldsymbol{\beta}_0)']'}$$

Zellner's g-Prior Assume $\boldsymbol{\beta}$ has a multivariate normal prior with mean vector $\mathbf{0}$ and covariance matrix $(g\mathbf{X}'\mathbf{X})^{-1}$, where $\mathbf{X}$ is the design matrix and g is either a constant or it follows a gamma prior with density $f(\tau) = \frac{b(b\tau)^{a-1}\mathrm{e}^{-b\tau}}{\Gamma(a)}$ where a and b are the SHAPE= and ISCALE= parameters. Let k be the rank of $\mathbf{X}$. The joint prior density with g being a constant c is given by

$$p(\boldsymbol{\beta}) \propto c^{\frac{k}{2}}\mathrm{e}^{-\frac{1}{2}\boldsymbol{\beta}'(c\mathbf{X}'\mathbf{X})^{-1}\boldsymbol{\beta}}$$

The joint prior density with g having a gamma prior is given by

$$p(\boldsymbol{\beta}, \tau) \propto \tau^{\frac{k}{2}}\mathrm{e}^{-\frac{1}{2}\boldsymbol{\beta}'(\tau\mathbf{X}'\mathbf{X})^{-1}\boldsymbol{\beta}}\frac{b(b\tau)^{a-1}\mathrm{e}^{-b\tau}}{\Gamma(a)}$$

Dispersion Parameter for Frailty Model

Improper Prior The density is

$$p(\theta) = \frac{1}{\theta}$$

Inverse Gamma Prior The inverse gamma distribution $IG(a, b)$ has a density

$$p(\theta|a, b) = \frac{b^a \theta^{-(a+1)} \mathrm{e}^{-\frac{b}{\theta}}}{\Gamma(a)}$$

where a and b are the SHAPE= and SCALE= parameters.

Gamma Prior The gamma distribution $G(a, b)$ has a density

$$p(\theta|a, b) = \frac{b^a \theta^{a-1} \mathrm{e}^{-b\theta}}{\Gamma(a)}$$

where a and b are the SHAPE= and ISCALE= parameters.

Posterior Distribution

Denote the observed data by D.

Cox Model

$$\pi(\boldsymbol{\beta}|D) \propto \underbrace{L(D|\boldsymbol{\beta})}_{\text{partial likelihood}} \overbrace{p(\boldsymbol{\beta})}^{\text{prior}}$$

Frailty Model

Based on the framework of Sargent (1998),

$$\pi(\boldsymbol{\beta}, \boldsymbol{\gamma}, \theta|D) \propto \underbrace{L(D|\boldsymbol{\beta}, \boldsymbol{\gamma})}_{\text{partial likelihood}} \overbrace{g(\boldsymbol{\gamma}|\theta)}^{\text{random effects}} \underbrace{p(\boldsymbol{\beta})p(\theta)}_{\text{priors}}$$

where the joint density of the random effects $\boldsymbol{\gamma} = (\gamma_1, \ldots, \gamma_s)'$ is given by

$$g(\boldsymbol{\gamma}|\theta) \propto \begin{cases} \prod_i \exp\left(\frac{\gamma_i}{\theta}\right) \exp\left(-\exp\left(\frac{\gamma_i}{\theta}\right)\right) & \text{gamma frailty} \\ \prod_i \exp\left(-\frac{\gamma_i^2}{2\theta}\right) & \text{lognormal frailty} \end{cases}$$

Piecewise Exponential Model

Hazard Parameters

$$\pi(\boldsymbol{\lambda}, \boldsymbol{\beta}|D) \propto L_H(D|\boldsymbol{\lambda}, \boldsymbol{\beta}) p(\boldsymbol{\lambda}) p(\boldsymbol{\beta})$$

where $L_H(D|\boldsymbol{\lambda}, \boldsymbol{\beta})$ is the likelihood function with hazards $\boldsymbol{\lambda}$ and regression coefficients $\boldsymbol{\beta}$ as parameters.

Log-Hazard Parameters

$$\pi(\boldsymbol{\alpha}, \boldsymbol{\beta}|D) \propto \begin{cases} L_{\mathrm{LH}}(D|\boldsymbol{\alpha}, \boldsymbol{\beta}) p(\boldsymbol{\alpha}, \boldsymbol{\beta}) & \text{if} \quad (\boldsymbol{\alpha}', \boldsymbol{\beta}')' \sim \mathrm{MVN} \\ L_{\mathrm{LH}}(D|\boldsymbol{\alpha}, \boldsymbol{\beta}) p(\boldsymbol{\alpha}) p(\boldsymbol{\beta}) & \text{otherwise} \end{cases}$$

where $L_{\mathrm{LH}}(D|\boldsymbol{\alpha}, \boldsymbol{\beta})$ is the likelihood function with log-hazards $\boldsymbol{\alpha}$ and regression coefficients $\boldsymbol{\beta}$ as parameters.

Sampling from the Posterior Distribution

For the Gibbs sampler, PROC PHREG uses the ARMS (adaptive rejection Metropolis sampling) algorithm of Gilks, Best, and Tan (1995) to sample from the full conditionals. This is the default sampling scheme. Alternatively, you can requests the random walk Metropolis (RWM) algorithm to sample an entire parameter vector from the posterior distribution. For a general discussion of these algorithms, see section "Markov Chain Monte Carlo Method" on page 129 in Chapter 7, "Introduction to Bayesian Analysis Procedures."

You can output these posterior samples into a SAS data set by using the OUTPOST= option in the BAYES statement, or you can use the following SAS statement to output the posterior samples into the SAS data set Post:

```
ods output PosteriorSample=Post;
```

The output data set also includes the variables LogLike and LogPost, which represent the log of the likelihood and the log of the posterior log density, respectively.

Let $\boldsymbol{\theta} = (\theta_1, \ldots, \theta_k)'$ be the parameter vector. For the Cox model, the θ_i's are the regression coefficients β_i's, and for the piecewise constant baseline hazard model, the θ_i's consist of the baseline hazards λ_i's (or log baseline hazards α_i's) and the regression coefficients β_j's. Let $L(D|\boldsymbol{\theta})$ be the likelihood function, where D is the observed data. Note that for the Cox model, the likelihood contains the infinite-dimensional baseline hazard function, and the gamma process is perhaps the most commonly used prior process (Ibrahim, Chen, and Sinha 2001). However, Sinha, Ibrahim, and Chen (2003) justify using the partial likelihood as the likelihood function for the Bayesian analysis. Let $p(\boldsymbol{\theta})$ be the prior distribution. The posterior $f\pi(\boldsymbol{\theta}|D)$ is proportional to the joint distribution $L(D|\boldsymbol{\theta}) p(\boldsymbol{\theta})$.

Gibbs Sampler

The full conditional distribution of θ_i is proportional to the joint distribution; that is,

$$\pi(\theta_i|\theta_j, i \neq j, D) \propto L(D|\boldsymbol{\theta}) p(\boldsymbol{\theta})$$

For example, the one-dimensional conditional distribution of θ_1, given $\theta_j = \theta_j^*, 2 \leq j \leq k$, is computed as

$$\pi(\theta_1|\theta_j = \theta_j^*, 2 \leq j \leq k, D) = L(D|\boldsymbol{\theta} = (\theta_1, \theta_2^*, \ldots, \theta_k^*)') p(\boldsymbol{\theta} = (\theta_1, \theta_2^*, \ldots, \theta_k^*)')$$

Suppose you have a set of arbitrary starting values $\{\theta_1^{(0)}, \ldots, \theta_k^{(0)}\}$. Using the ARMS algorithm, an iteration of the Gibbs sampler consists of the following:

- draw $\theta_1^{(1)}$ from $\pi(\theta_1|\theta_2^{(0)},\ldots,\theta_k^{(0)},D)$
- draw $\theta_2^{(1)}$ from $\pi(\theta_2|\theta_1^{(1)},\theta_3^{(0)},\ldots,\theta_k^{(0)},D)$
- $\vdots$
- draw $\theta_k^{(1)}$ from $\pi(\theta_k|\theta_1^{(1)},\ldots,\theta_{k-1}^{(1)},D)$

After one iteration, you have $\{\theta_1^{(1)},\ldots,\theta_k^{(1)}\}$. After n iterations, you have $\{\theta_1^{(n)},\ldots,\theta_k^{(n)}\}$. Cumulatively, a chain of n samples is obtained.

Random Walk Metropolis Algorithm

PROC PHREG uses a multivariate normal proposal distribution $q(.|\boldsymbol{\theta})$ centered at $\boldsymbol{\theta}$. With an initial parameter vector $\boldsymbol{\theta}^{(0)}$, a new sample $\boldsymbol{\theta}^{(1)}$ is obtained as follows:

- sample $\boldsymbol{\theta}^*$ from $q(.|\boldsymbol{\theta}^{(0)})$
- calculate the quantity $r = \min\left\{\frac{\pi(\boldsymbol{\theta}^*|D)}{\pi(\boldsymbol{\theta}^{(0)}|D)},1\right\}$
- sample u from the uniform distribution $U(0,1)$
- set $\boldsymbol{\theta}^{(1)} = \boldsymbol{\theta}^*$ if $u < r$; otherwise set $\boldsymbol{\theta}^{(1)} = \boldsymbol{\theta}^{(0)}$

With $\boldsymbol{\theta}^{(1)}$ taking the role of $\boldsymbol{\theta}^{(0)}$, the previous steps are repeated to generate the next sample $\boldsymbol{\theta}^{(2)}$. After n iterations, a chain of n samples $\{\boldsymbol{\theta}^{(1)},\ldots,\boldsymbol{\theta}^{(n)}\}$ is obtained.

Starting Values of the Markov Chains

When the BAYES statement is specified, PROC PHREG generates one Markov chain that contains the approximate posterior samples of the model parameters. Additional chains are produced when the Gelman-Rubin diagnostics are requested. Starting values (initial values) can be specified in the INITIAL= data set in the BAYES statement. If the INITIAL= option is not specified, PROC PHREG picks its own initial values for the chains based on the maximum likelihood estimates of $\boldsymbol{\theta}$ and the prior information of $\boldsymbol{\theta}$.

Denote $[x]$ as the integral value of x.

Constant Baseline Hazard Parameters λ_i's

For the first chain that the summary statistics and diagnostics are based on, the initial values are

$$\lambda_i^{(0)} = \hat{\lambda}_i$$

For subsequent chains, the starting values are picked in two different ways according to the total number of chains specified. If the total number of chains specified is less than or equal to 10, initial values of the rth chain ($2 \le r \le 10$) are given by

$$\lambda_i^{(0)} = \hat{\lambda}_i \mathrm{e}^{\pm\left([\frac{r}{2}]+2\right)\hat{s}(\hat{\lambda}_i)}$$

with the plus sign for odd r and minus sign for even r. If the total number of chains is greater than 10, initial values are picked at random over a wide range of values. Let u_i be a uniform random number between 0 and 1; the initial value for λ_i is given by

$$\lambda_i^{(0)} = \hat{\lambda}_i \mathrm{e}^{16(u_i - 0.5)\hat{s}(\hat{\lambda}_i)}$$

Regression Coefficients and Log-Hazard Parameters θ_i's

The θ_i's are the regression coefficients β_i's, and in the piecewise exponential model, include the log-hazard parameters α_i's. For the first chain that the summary statistics and regression diagnostics are based on, the initial values are

$$\theta_i^{(0)} = \hat{\theta}_i$$

If the number of chains requested is less than or equal to 10, initial values for the rth chain ($2 \leq r \leq 10$) are given by

$$\theta_i^{(0)} = \hat{\theta}_i \pm \left(2 + \left[\frac{r}{2}\right]\right)\hat{s}(\hat{\theta}_i)$$

with the plus sign for odd r and minus sign for even r. When there are more than 10 chains, the initial value for the θ_i is picked at random over the range $(\hat{\theta}_i - 8\hat{s}(\hat{\theta}_i), \hat{\theta}_i + 8\hat{s}(\hat{\theta}_i))$; that is,

$$\theta_i^{(0)} = \hat{\theta}_i + 16(u_i - 0.5)\hat{s}(\hat{\theta}_i)$$

where u_i is a uniform random number between 0 and 1.

Fit Statistics

Denote the observed data by D. Let $\boldsymbol{\theta}$ be the vector of parameters of length k. Let $L(D|\boldsymbol{\theta})$ be the likelihood. The deviance information criterion (DIC) proposed in Spiegelhalter et al. (2002) is a Bayesian model assessment tool. Let $\mathrm{Dev}(\boldsymbol{\theta}) = -2\log L(D|\boldsymbol{\theta})$. Let $\overline{\mathrm{Dev}(\theta)}$ and $\bar{\boldsymbol{\theta}}$ be the corresponding posterior means of $\mathrm{Dev}(\boldsymbol{\theta})$ and $\boldsymbol{\theta}$, respectively. The deviance information criterion is computed as

$$\mathrm{DIC} = 2\overline{\mathrm{Dev}(\boldsymbol{\theta})} - \mathrm{Dev}(\bar{\boldsymbol{\theta}})$$

Also computed is

$$pD = \overline{\mathrm{Dev}(\boldsymbol{\theta})} - \mathrm{Dev}(\bar{\boldsymbol{\theta}})$$

where pD is interpreted as the effective number of parameters.

Note that $\mathrm{Dev}(\boldsymbol{\theta})$ defined here does not have the standardizing term as in the section "Deviance Information Criterion (DIC)" on page 152 in Chapter 7, "Introduction to Bayesian Analysis Procedures." Nevertheless, the DIC calculated here is still useful for variable selection.

Posterior Distribution for Quantities of Interest

Let $\boldsymbol{\theta} = (\theta_1, \ldots, \theta_k)'$ be the parameter vector. For the Cox model, the θ_i's are the regression coefficients β_i's; for the piecewise constant baseline hazard model, the θ_i's consist of the baseline hazards λ_i's (or log

baseline hazards α_i's) and the regression coefficients β_j's. Let $\mathcal{S} = \{\boldsymbol{\theta}^{(r)}, r = 1, \ldots, N\}$ be the chain that represents the posterior distribution for $\boldsymbol{\theta}$.

Consider a quantity of interest τ that can be expressed as a function $f(\boldsymbol{\theta})$ of the parameter vector $\boldsymbol{\theta}$. You can construct the posterior distribution of τ by evaluating the function $f(\boldsymbol{\theta}^{(r)})$ for each $\boldsymbol{\theta}^{(r)}$ in $\mathcal{S}$. The posterior chain for τ is $\{f(\boldsymbol{\theta}^{(r)}), r = 1, \ldots, N\}$. Summary statistics such as mean, standard deviation, percentiles, and credible intervals are used to describe the posterior distribution of τ.

Hazard Ratio

As shown in the section "Hazard Ratios" on page 6901, a log-hazard ratio is a linear combination of the regression coefficients. Let $\mathbf{h}$ be the vector of linear coefficients. The posterior sample for this hazard ratio is the set $\{\exp(\mathrm{h}'\boldsymbol{\beta}^{(r)}), r = 1, \ldots, N\}$.

Survival Distribution

Let x be a covariate vector of interest.

Cox Model Let $\{(t_i, \mathbf{z}_i, \delta_i), i = 1, 2, \ldots, n\}$ be the observed data. Define

$$Y_i(t) = \begin{cases} 1 & t < t_i \\ 0 & \text{otherwise} \end{cases}$$

Consider the rth draw $\boldsymbol{\beta}^{(r)}$ of $\mathcal{S}$. The baseline cumulative hazard function at time t is given by

$$H_0(t|\boldsymbol{\beta}^{(r)}) = \sum_{i:t_i \le t} \frac{\delta_i}{\sum_{l=1}^{n} Y_l(t_i)\exp(\mathbf{z}_l'\boldsymbol{\beta}^{(r)})}$$

For the given covariate vector x, the cumulative hazard function at time t is

$$H(t; \mathbf{x}|\boldsymbol{\beta}^{(r)}) = H_0(t|\boldsymbol{\beta}^{(r)}) \exp(\mathbf{x}'\boldsymbol{\beta}^{(r)})$$

and the survival function at time t is

$$S(t; \mathbf{x}|\boldsymbol{\beta}^{(r)}) = \exp[-H^{(r)}(t; \mathbf{x}|\boldsymbol{\beta}^{(r)})]$$

Piecewise Exponential Model Let $0 = a_0 < a_1 < \ldots < a_J < \infty$ be a partition of the time axis. Consider the rth draw $\boldsymbol{\theta}^{(r)}$ in $\mathcal{S}$, where $\boldsymbol{\theta}^{(r)}$ consists of $\boldsymbol{\lambda}^{(r)} = (\lambda_1^{(r)}, \ldots, \lambda_J^{(r)})'$ and $\boldsymbol{\beta}^{(r)}$. The baseline cumulative hazard function at time t is

$$H_0(t|\boldsymbol{\lambda}^{(r)}) = \sum_{j=1}^{J} \lambda_j^{(r)} \Delta_j(t)$$

where

$$\Delta_j(t) = \begin{cases} 0 & t < a_{j-1} \\ t - a_{j-1} & a_{j-1} \le t < a_j \\ a_j - a_{j-1} & t \ge a_j \end{cases}$$

For the given covariate vector $\mathbf{x}$, the cumulative hazard function at time t is

$$H(t;\mathbf{x}|\boldsymbol{\lambda}^{(r)},\boldsymbol{\beta}^{(r)}) = H_0(t|\boldsymbol{\lambda}^{(r)})\exp(\mathbf{x}'\boldsymbol{\beta}^{(r)})$$

and the survival function at time t is

$$S(t;\mathbf{x}|\boldsymbol{\lambda}^{(r)},\boldsymbol{\beta}^{(r)}) = \exp[-H(t;\mathbf{x}|\boldsymbol{\lambda}^{(r)},\boldsymbol{\beta}^{(r)})]$$

Computational Resources

Let n be the number of observations in a BY group. Let p be the number of explanatory variables. The minimum working space (in bytes) needed to process the BY group is

$$\max\{12n, 24p^2 + 160p\}$$

Extra memory is needed for certain TIES= options. Let k be the maximum multiplicity of tied times. The TIES=DISCRETE option requires extra memory (in bytes) of

$$4k(p^2 + 4p)$$

The TIES=EXACT option requires extra memory (in bytes) of

$$24(k^2 + 5k)$$

If sufficient space is available, the input data are also kept in memory. Otherwise, the input data are reread from the utility file for each evaluation of the likelihood function and its derivatives, with the resulting execution time substantially increased.

Input and Output Data Sets

OUTEST= Output Data Set

The OUTEST= data set contains one observation for each BY group containing the maximum likelihood estimates of the regression coefficients. If you also use the COVOUT option in the PROC PHREG statement, there are additional observations containing the rows of the estimated covariance matrix. If you specify SELECTION=FORWARD, BACKWARD, or STEPWISE, only the estimates of the parameters and covariance matrix for the final model are output to the OUTEST= data set.

Variables in the OUTEST= Data Set

The OUTEST= data set contains the following variables:

- any BY variables specified
- _TIES_, a character variable of length 8 with four possible values: BRESLOW, DISCRETE, EFRON, and EXACT. These are the four values of the TIES= option in the MODEL statement.

- _TYPE_, a character variable of length 8 with two possible values: PARMS for parameter estimates or COV for covariance estimates. If both the COVM and COVSANDWICH options are specified in the PROC PHREG statement along with the COVOUT option, _TYPE_='COVM' for the model-based covariance estimates and _TYPE_='COVS' for the robust sandwich covariance estimates.
- _STATUS_, a character variable indicating whether the estimates have converged
- _NAME_, a character variable containing the name of the TIME variable for the row of parameter estimates and the name of each explanatory variable to label the rows of covariance estimates
- one variable for each regression coefficient and one variable for the offset variable if the OFFSET= option is specified. If an explanatory variable is not included in the final model in a variable selection process, the corresponding parameter estimates and covariances are set to missing.
- _LNLIKE_, a numeric variable containing the last computed value of the log likelihood

Parameter Names in the OUTEST= Data Set

For continuous explanatory variables, the names of the parameters are the same as the corresponding variables. For CLASS variables, the parameter names are obtained by concatenating the corresponding CLASS variable name with the CLASS category; see the PARAM= option in the CLASS statement for more details. For interaction and nested effects, the parameter names are created by concatenating the names of each component effect.

INEST= Input Data Set

You can specify starting values for the maximum likelihood iterative algorithm in the INEST= data set. The INEST= data set has the same structure as the OUTEST= data set but is not required to have all the variables or observations that appear in the OUTEST= data set.

The INEST= data set must contain variables that represent the regression coefficients of the model. If BY processing is used, the INEST= data set should also include the BY variables, and there must be one observation for each BY group. If the INEST= data set also contains the _TYPE_ variable, only observations with _TYPE_ value 'PARMS' are used as starting values.

OUT= Output Data Set in the ZPH Option

The OUT= data set in the ZPH option contains the variable of event times and the variables that represent the time-varying coefficients, one for each parameter. If the transformation that you specify in the ZPH option is not an identity, the OUT= data set also contains a variable that represents the transformed event times.

OUT= Output Data Set in the OUTPUT Statement

The OUT= data set in the OUTPUT statement contains all the variables in the input data set, along with statistics you request by specifying *keyword=name* options. The new variables contain a variety of diagnostics that are calculated for each observation in the input data set.

OUT= Output Data Set in the BASELINE Statement

The OUT= data set in the BASELINE statement contains all the variables in the COVARIATES= data set, along with statistics you request by specifying *keyword=name* options. For unstratified input data, there are 1 + n observations in the OUT= data set for each observation in the COVARIATES= data set, where n is the number of distinct event times in the input data. For input data that are stratified into k strata, with n_i distinct events in the ith stratum, $i = 1, \ldots, k$, there are 1+n_i observations for the ith stratum in the OUT= data set for each observation in the COVARIATES= data set.

OUTAUC= Output Data Set in the ROCOPTIONS Option

The OUTAUC= data set contains data necessary for producing the AUC (area under the curve) plot; it can be created by specifying the OUTAUC= suboption in the ROCOPTIONS option in the PROC PHREG statement. This data set has the following variables:

- any specified BY variables
- _ID_, the sequence number of the model
- _SOURCE_, the model label
- the time variable, which identifies time point t at which the AUC statistic is calculated
- _AUC_, the AUC statistic, which is the area under the time-dependent ROC curve at each event time
- _STDERR_, the standard error of the AUC statistic
- _LOWERAUC_, the lower confidence limit for the AUC
- _UPPERAUC_, the upper confidence limit for the AUC

OUTIDFF= Output Data Set in the BASELINE Statement

The OUTDIFF= data set contains the differences of the direct adjusted survival probabilities between two treatments or two strata and their standard errors.

OUTPOST= Output Data Set in the BAYES Statement

The OUTPOST= data set contains the generated posterior samples. There are 3+n variables, where n is the number of model parameters. The variable Iteration represents the iteration number, the variable LogLike contains the log-likelihood values, and the variable LogPost contains the log-posterior-density values. The other n variables represent the draws of the Markov chain for the model parameters.

OUTROC= Output Data Set in the ROCOPTIONS Option

The OUTROC= data set contains data necessary for producing the ROC plot; it can be created by specifying the OUTROC= suboption in the ROCOPTIONS option in the PROC PHREG statement. This data set has the following variables:

- any specified BY variables

- the time variable, which identifies the time point at which the ROC curve is calculated
- _ID_, the sequence number of the model
- _SOURCE_, the model label
- _CUTOFF_, the cutpoint for predicting the response. Any observation whose predicted value exceeds or equals to the cutpoint is predicted to be an event; otherwise, it is predicted to be a nonevent.
- _SENSITIVITY_, the sensitivity, which is the proportion of event observations that were predicted to have an event response
- _SPECIFICITY_, the specificity, which is the proportion of nonevent observations that were predicted to have a nonevent response

Displayed Output

If you use the NOPRINT option in the PROC PHREG statement, the procedure does not display any output. Otherwise, PROC PHREG displays results of the analysis in a collection of tables. The tables are listed separately for the maximum likelihood analysis and for the Bayesian analysis.

Maximum Likelihood Analysis Displayed Output

Model Information

The "Model Information" table displays the two-level name of the input data set, the name and label of the failure time variable, the name and label of the censoring variable and the values indicating censored times, the model (either the Cox model or the piecewise constant baseline hazard model), the name and label of the OFFSET variable, the name and label of the FREQ variable, the name and label of the WEIGHT variable, and the method of handling ties in the failure time for the Cox model. The ODS name of the "Model Information" table is ModelInfo.

Number of Observations

The "Number of Observations" table displays the number of observations read and used in the analysis. The ODS name of the "Number of Observations" is NObs.

Class Level Information

The "Class Level Information" table is displayed when there are CLASS variables in the model. The table lists the categories of every CLASS variable that is used in the model and the corresponding design variable values. The ODS name of the "Class Level Information" table is ClassLevelInfo.

Class Level Information for Random Effects

The "Class Level Information for Random Effects" table is displayed when the RANDOM statement is specified. The table lists the categories of the classification variable specified in the RANDOM statement. The ODS name of the "Class Level Information for Random Effects" table is ClassLevelInfoR.

Summary of the Number of Event and Censored Values

The "Summary of the Number of Event and Censored Values" table displays, for each stratum, the breakdown of the number of events and censored values. The ODS name of the "Summary of the Number of Event and Censored Values" table is CensoredSummary.

Risk Sets Information

The "Risk Sets Information" table is displayed if you specify the ATRISK option in the PROC PHREG statement. The table displays, for each event time, the number of units at-risk and the number of units that experience the event. The ODS name of the "Risk Sets Information" table is RiskSetInfo.

Descriptive Statistics for Continuous Explanatory Variables

The "Simple Statistics for Continuous Explanatory Variables" table is displayed when you specify the SIMPLE option in the PROC PHREG statement. The table contains, for each stratum, the mean, standard deviation, and minimum and maximum for each continuous explanatory variable in the MODEL statement. The ODS name of the "Descriptive Statistics for Continuous Explanatory Variables" table is SimpleStatistics.

Frequency Distribution of CLASS Variables

The "Frequency Distribution of CLASS Variables" table is displayed if you specify the SIMPLE option in the PROC PHREG statement and there are CLASS variables in the model. The table lists the frequency of the levels of the CLASS variables. The ODS name of the "Frequency Distribution of CLASS Variables" table is ClassLevelFreq.

Maximum Likelihood Iteration History

The "Maximum Likelihood Iteration History" table is displayed if you specify the ITPRINT option in the MODEL statement. The table contains the iteration number, ridge value or step size, log likelihood, and parameter estimates at each iteration. The ODS name of the "Maximum Likelihood Iteration History" table is IterHistory.

Gradient of Last Iteration

The "Gradient of Last Iteration" table is displayed if you specify the ITPRINT option in the MODEL statement. The ODS name of the "Gradient of Last Iteration" table is LastGradient.

Convergence Status

The "Convergence Status" table displays the convergence status of the Newton-Raphson maximization. The ODS name of the "Convergence Status" table is ConvergenceStatus.

Model Fit Statistics

The "Model Fit Statistics" table displays the values of –2 log likelihood for the null model and the fitted model, the AIC, and SBC. The ODS name of the "Model Fit Statistics" table is FitStatistics.

Covariance Parameter Estimates

The "Covariance Parameter Estimates" table displays the estimate of the variance parameter of the random effect and the standard error estimate of the variance parameter estimator. The ODS name of the "Covariance Parameter Estimates" table is CovParms.

Testing Global Null Hypothesis: BETA=0

The "Testing Global Null Hypothesis: BETA=0" table displays results of the likelihood ratio test, the score test, and the Wald test for testing the hypothesis that all parameters are zero. For the frailty model, the score test is not displayed and an adjusted degrees of freedom is used (for more information, see the section "Wald-Type Tests for Penalized Models" on page 6945). For ODS purpose, the name of the "Testing Global Null Hypothesis: BETA=0" table is GlobalTests.

Likelihood Ratio Statistics for Type 1 Analysis

The "Likelihood Ratio Statistics for Type 1 Analysis" table is displayed if the TYPE1 option is specified in the MODEL statement. The table displays the degrees of freedom, the likelihood ratio chi-square statistic, and the *p*-value for each effect in the model. The ODS name of "Likelihood Ratio Statistics for Type 1 Analysis" is Type1.

Type 3 Tests

The "Type 3 Tests" table is displayed if the model contains a CLASS variable or if the TYPE3 option is specified in the MODEL statement. The table displays, for each specified statistic, the Type 3 chi-square, the degrees of freedom, and the *p*-value for each effect in the model. For the frailty model, the table also displays the adjusted Wald-type test results (for more information, see the section "Wald-Type Tests for Penalized Models" on page 6945). The ODS name of "Type 3 Tests" is Type3.

Analysis of Maximum Likelihood Estimates

The "Analysis of Maximum Likelihood Estimates" table displays the maximum likelihood estimate of the parameter; the estimated standard error, computed as the square root of the corresponding diagonal element of the estimated covariance matrix; the ratio of the robust standard error estimate to the model-based standard error estimate if you specify the COVS option in the PROC PHREG statement; the Wald Chi-Square statistic, computed as the square of the parameter estimate divided by its standard error estimate; the degrees of freedom of the Wald chi-square statistic, which has a value of 1 unless the corresponding parameter is redundant or infinite, in which case the value is 0; the *p*-value of the Wald chi-square statistic with respect to a chi-square distribution with one degree of freedom; the hazard ratio estimate; and the confidence limits for the hazard ratio if you specified the RISKLIMITS option in the MODEL statement. The ODS name of the "Analysis of Maximum Likelihood Estimates" table is ParameterEstimates.

Solution for Random Effects

The "Solution for Random Effects" table displays the BLUP estimates of the random effects, the estimated standard errors, the confidence intervals for the random effects, the exponentiated values of the BLUP estimates, and confidence intervals for the exponentiated random effects. The ODS name of the "Solution for Random Effects" table is SolutionR.

Regression Models Selected by Score Criterion

The "Regression Models Selected by Score Criterion" table is displayed if you specify SELECTION=SCORE in the MODEL statement. The table contains the number of explanatory variables in each model, the score chi-square statistic, and the names of the variables included in the model. The ODS name of the "Regression Models Selected by Score Criterion" table is BestSubsets.

Analysis of Effects Eligible for Entry

The "Analysis of Effects Eligible for Entry" table is displayed if you use the FORWARD or STEPWISE selection method and you specify the DETAILS option in the MODEL statement. The table contains the

score chi-square statistic for testing the significance of each variable not in the model (after adjusting for the variables already in the model), and the *p*-value of the chi-square statistic with respect to a chi-square distribution with one degree of freedom. This table is produced before a variable is selected for entry in a forward selection step. The ODS name of the "Analysis of Effects Eligible for Entry" table is EffectsToEntry.

Analysis of Effects Eligible for Removal

The "Analysis of Effects Eligible for Removal" table is displayed if you use the BACKWARD or STEPWISE selection method and you specify the DETAILS option in the MODEL statement. The table contains the Wald chi-square statistic for testing the significance of each candidate effect for removal, the degrees of freedom of the Wald chi-square, and the corresponding *p*-value. This table is produced before an effect is selected for removal. The ODS name of the "Analysis of Effects Eligible for Removal" table is EffectsToRemoval.

Summary of Backward Elimination

The "Summary of Backward Elimination" table is displayed if you specify the SELECTION=BACKWARD option in the MODEL statement. The table contains the step number, the effects removed at each step, the corresponding chi-square statistic, the degrees of freedom, and the *p*-value. For ODS purpose, the name of the "Summary of Backward Elimination" table is ModelBuildingSummary.

Summary of Forward Selection

The "Summary of Forward Selection" table is displayed if you specify the SELECTION=FORWARD option in the MODEL statement. The table contains the step number, the effects entered at each step, the corresponding chi-square statistic, the degrees of freedom, and the *p*-value. For ODS purpose, the name of the "Summary of Forward Selection" table is ModelBuildingSummary.

Summary of Stepwise Selection

The "Summary of Stepwise Selection" table is displayed if you specify SELECTION=STEPWISE is specified in the MODEL statement. The table contains the step number, the effects entered or removed at each step, the corresponding chi-square statistic, the degrees of freedom, and the corresponding *p*-value. For ODS purpose, the name of the "Summary of Stepwise Selection" table is ModelBuildingSummary.

Covariance Matrix

The "Covariance Matrix" table is displayed if you specify the COVB option in the MODEL statement. The table contains the estimated covariance matrix for the parameter estimates. The ODS name of the "Covariance Matrix" table is CovB.

Correlation Matrix

The "Correlation Matrix" table is displayed if you specify the COVB option in the MODEL statement. The table contains the estimated correlation matrix for the parameter estimates. The ODS name of the "Correlation Matrix" table is CorrB.

Hazard Ratios for label

The "Hazard Ratios for *label*" table is displayed if you specify the HAZARDRATIO statement. The table displays the estimate and confidence limits for each hazard ratio. The ODS name of the "Hazard Ratios for *label*" table is HazardRatios.

Predictive Inaccuracy and Explained Variation

The "Predictive Inaccuracy and Explained Variation" table is displayed if you specify the EV option in the PROC PHREG statement. The table displays the predictive inaccuracy without covariates, the predictive inaccuracy with covariates, and the explained variation. If you specify the STRATA statement, the table also contains the stratum identification. The ODS name of the "Predictive Inaccuracy and Explained Variation" table is ExplainedVariation.

ZPH Tests of Nonproportional Hazards

The "ZPH Tests of Nonproportional Hazards" table is displayed if you specify the ZPH option in the PROC PHREG statement. For each parameter, the table displays the correlation between the time-varying coefficients and transformed times; the chi-square statistic and the corresponding p-value; and the t statistic and the corresponding p-value. The ODS name of the "ZPH Tests of Nonproportional Hazards" table is zphTest.

Coefficients of Contrast label

The "Coefficients of Contrast *label*" table is displayed if you specify the E option in the CONTRAST statement. The table displays the parameter names and the corresponding coefficients of each row of contrast *label*. The ODS name of the "Coefficients of Contrast *label*" table is ContrastCoeff.

Contrast Test Results

The "Contrast Test Results" table is displayed if you specify the CONTRAST statement. The table displays the degrees of freedom, test statistics, and the p-values for testing each contrast. The ODS name of the "Contrast Test Results" table is ContrastTest.

Contrast Estimation and Testing Results by Row

The "Contrast Estimation and Testing Results by Row" table is displayed if you specify the ESTIMATE option in the CONTRAST statement. The table displays, for each row, the estimate of the linear function of the coefficients, its standard error, and the confidence limits for the linear function. The ODS name of the "Contrast Estimation and Testing Results by Row" table is ContrastEstimate.

Linear Coefficients for label

The "Linear Coefficients *label*" table is displayed if you specify the E option in the TEST statement with *label* being the TEST statement label. The table contains the coefficients and constants of the linear hypothesis. The ODS name of the "Linear Coefficients for *label*" table is TestCoeff.

L[cov(b)]L' and Lb-c

The "L[cov(b)]L' and Lb-c" table is displayed if you specified the PRINT option in a TEST statement with *label* being the TEST statement label. The table displays the intermediate calculations of the Wald test. The ODS name of the "L[cov(b)]L' and Lb-c" table is TestPrint1.

Ginv(L[cov(b)]L') and Ginv(L[cov(b)]L')(Lb-c)

The "Ginv(L[cov(b)]L') and Ginv(L[cov(b)]L')(Lb-c)" table is displayed if you specified the PRINT option in a TEST statement with *label* being the TEST statement label. The table displays the intermediate calculations of the Wald test. The ODS name of the "Ginv(L[cov(b)]L') and Ginv(L[cov(b)]L')(Lb-c)" table is TestPrint2.

label Test Results

The "*label* Test Results" table is displayed if you specify a TEST statement with *label* being the TEST statement label. The table contains the Wald chi-square statistic, the degrees of freedom, and the *p*-value. The ODS name of "*label* Test Results" table is TestStmts.

Average Effect for label

The "Average Effect for *label*" table is displayed if the AVERAGE option is specified in a TEST statement with *label* being the TEST statement label. The table contains the weighted average of the parameter estimates for the variables in the TEST statement, the estimated standard error, the z-score, and the *p*-value. The ODS name of the "Average Effect for *label*" is TestAverage.

Reference Set of Covariates for Plotting

The "Reference Set of Covariates for Plotting" table is displayed if the PLOTS= option is requested without specifying the COVARIATES= data set in the BASELINE statement. The tables contains the values of the covariates for the reference set, where the reference levels are used for the CLASS variables and the sample averages for the continuous variables.

Harrell's Concordance Estimates

The "Harrell's Concordance Estimates" table is displayed if you specify CONCORDANCE=HARRELL in the PROC PHREG statement (or by default if you specify the CONCORDANCE option without specifying a method). The table displays the label of the identified model, the Harrell concordance estimate, the estimated standard error if the SE suboption is specified, the number of concordance pairs, the number of discordance pairs, the number of pairs that are tied in the predictor, and the number of pairs that are tied in time. The ODS name of the "Harrell's Concordance Estimates" table is Concordance.

Uno's Concordance Estimates

The "Uno's Concordance Estimates" table is displayed if you specify CONCORDANCE=UNO in the PROC PHREG statement. The table displays the label of the identified model, the Uno concordance estimate, and the estimated standard error if the SE suboption is specified. The ODS name of the "Uno's Concordance Estimates" table is Concordance.

Difference in Uno's Concordance Estimates

The "Difference in Uno's Concordance Estimates" table is displayed if you specify CONCORDANCE=UNO in the PROC PHREG statement and you specify both the SE and DIFF suboptions. The table identifies which pair of models is being compared and displays the difference of their concordance estimates, the estimated standard error of the difference, the Wald chi-square statistic (computed as the square of the difference divided by its standard error estimate), and the *p*-value of the Wald chi-square statistic with respect to a chi-square distribution with one degree of freedom. The ODS name of the "Difference in Uno's Concordance Estimates" table is ConcordanceDiff.

Time-Dependent Area under the Curve

The "Time-Dependent Area under the Curve" table is displayed if you specify the AUC suboption in the ROCOPTIONS option in the PROC PHREG statement. The table displays the label of the identified model, the time point at which the ROC curves are calculated, and the corresponding area under the ROC curve (AUC). If you specify METHOD=IPCW(CL) in the ROCOPTIONS option, the table also displays the estimated standard error and the confidence limits for the AUC. The ODS name of the "Time-Dependent Area under the Curve" table is AUC.

Differences in Time-Dependent Area under the Curve

The "Differences in Time-Dependent Area under the Curve" table is displayed if you specify the AUCDIFF suboption in the ROCOPTIONS option in the PROC PHREG statement. The table identifies which pair of models is being compared and displays the time point at which ROC curves are calculated and the difference in the AUC statistics. If you also specify METHOD=IPCW(CL) in ROCOPTIONS option, the table also displays the estimated standard error and the confidence limits for the difference in the AUC. The ODS name of the "Differences in Time-Dependent Area Under the Curve" table is AUCDiff.

Integrated Time-Dependent Area under the Curve

The "Integrated Time-Dependent Area under the Curve" table is displayed if you specify the IAUC suboption in the ROCOPTIONS option in the PROC PHREG statement. The table displays the label of the identified model and the integrated area under the curve (IAUC). The ODS name of the "Integrated Time-Dependent Area Under the Curve" table is IAUC.

Bayesian Analysis Displayed Output

Model Information

The "Model Information" table displays the two-level name of the input data set, the name and label of the failure time variable, the name and label of the censoring variable and the values indicating censored times, the model (either the Cox model or the piecewise constant baseline hazard model), the name and label of the OFFSET variable, the name and label of the FREQ variable, the name and label of the WEIGHT variable, the method of handling ties in the failure time, the number of burn-in iterations, the number of iterations after the burn-in, and the number of thinning iterations. The ODS name of the "Model Information" table is ModelInfo.

Number of Observations

The "Number of Observations" table displays the number of observations read and used in the analysis. The ODS name of the "Number of Observations" is NObs.

Summary of the Number of Event and Censored Values

The "Summary of the Number of Event and Censored Values" table displays, for each stratum, the breakdown of the number of events and censored values. This table is not produced if the NONSUMMARY option is specified in the PROC PHREG statement. The ODS name of the "Summary of the Number of Event and Censored Values" table is CensoredSummary.

Descriptive Statistics for Continuous Explanatory Variables

The "Simple Statistics for Continuous Explanatory Variables" table is displayed when you specify the SIMPLE option in the PROC PHREG statement. The table contains, for each stratum, the mean, standard deviation, and minimum and maximum for each continuous explanatory variable in the MODEL statement. The ODS name of the "Descriptive Statistics for Continuous Explanatory Variables" table is SimpleStatistics.

Class Level Information

The "Class Level Information" table is displayed if there are CLASS variables in the model. The table lists the categories of every CLASS variable in the model and the corresponding design variable values. The ODS name of the "Class Level Information" table is ClassLevelInfo.

Frequency Distribution of CLASS Variables

The "Frequency Distribution of CLASS Variables" table is displayed if you specify the SIMPLE option in the PROC PHREG statement and there are CLASS variables in the model. The table lists the frequency of the levels of the CLASS variables. The ODS name of the "Frequency Distribution of CLASS Variables" table is ClassLevelFreq.

Regression Parameter Information

The "Regression Parameter Information" table displays the names of the parameters and the corresponding level information of effects containing the CLASS variables. The ODS name of the "Regression Parameter Information" table is ParmInfo.

Constant Baseline Hazard Time Intervals

The "Constant Baseline Hazard Time Intervals" table displays the intervals of constant baseline hazard and the corresponding numbers of failure times and event times. This table is produced only if you specify the PIECEWISE option in the BAYES statement. The ODS name of the "Constant Baseline Hazard Time Intervals" table is Interval.

Maximum Likelihood Estimates

The "Maximum Likelihood Estimates" table displays, for each parameter, the maximum likelihood estimate, the estimated standard error, and the 95% confidence limits. The ODS name of the "Maximum Likelihood Estimates" table is ParameterEstimates.

Hazard Prior

The "Hazard Prior" table is displayed if you specify the PIECEWISE=HAZARD option in the BAYES statement. It describes the prior distribution of the hazard parameters. The ODS name of the "Hazard Prior" table is HazardPrior.

Log-Hazard Prior

The "Log-Hazard Prior" table is displayed if you specify the PIECEWISE=LOGHAZARD option in the BAYES statement. It describes the prior distribution of the log-hazard parameters. The ODS name of the "Log-Hazard Prior" table is HazardPrior.

Coefficient Prior

The "Coefficient Prior" table displays the prior distribution of the regression coefficients. The ODS name of the "Coefficient Prior" table is CoeffPrior.

Initial Values

The "Initial Values" table is displayed if you specify the INITIAL option in the BAYES statement. The table contains the initial values of the parameters for the Gibbs sampling. The ODS name of the "Initial Values" table is InitialValues.

Fit Statistics

The "Fit Statistics" table displays the DIC and pD statistics for each parameter. The ODS name of the "Fit Statistics" table is FitStatistics.

Posterior Summaries

The "Posterior Summaries" table displays the size of the posterior sample, the mean, the standard error, and the percentiles for each model parameter. The ODS name of the "Posterior Summaries" table is PostSummaries.

Posterior Intervals

The "Posterior Intervals" table displays the equal-tail interval and the HPD interval for each model parameter. The ODS name of the "Posterior Intervals" table is PostIntervals.

Posterior Covariance Matrix

The "Posterior Covariance Matrix" table is produced if you include COV in the SUMMARY= option in the BAYES statement. This tables displays the sample covariance of the posterior samples. The ODS name of the "Posterior Covariance Matrix" table is Cov.

Posterior Correlation Matrix

The "Posterior Correlation Matrix" table is displayed if you include CORR in the SUMMARY= option in the BAYES statement. The table contains the sample correlation of the posterior samples. The ODS name of the "Posterior Correlation Matrix" table is Corr.

Posterior Autocorrelations

The "Posterior Autocorrelations" table displays the lag 1, lag 5, lag 10, and lag 50 autocorrelations for each parameter. The ODS name of the "Posterior Autocorrelations" table is AutoCorr.

Gelman-Rubin Diagnostics

The "Gelman-Rubin Diagnostics" table is produced if you include GELMAN in the DIAGNOSTIC= option in the BAYES statement. This table displays the estimate of the potential scale reduction factor and its 97.5% upper confidence limit for each parameter. The ODS name of the "Gelman-Rubin Diagnostics" table is Gelman.

Geweke Diagnostics

The "Geweke Diagnostics" table displays the Geweke statistic and its p-value for each parameter. The ODS name of the "Geweke Diagnostics" table is Geweke.

Raftery-Lewis Diagnostics

The "Raftery-Lewis Diagnostics" tables is produced if you include RAFTERY in the DIAGNOSTIC= option in the BAYES statement. This table displays the Raftery and Lewis diagnostics for each variable. The ODS name of the "Raftery-Diagnostics" table is "Raftery."

Heidelberger-Welch Diagnostics

The "Heidelberger-Welch Diagnostics" table is displayed if you include HEIDELBERGER in the DIAGNOSTIC= option in the BAYES statement. This table describes the results of a stationary test and a halfwidth test for each parameter. The ODS name of the "Heidelberger-Welch Diagnostics" table is Heidelberger.

Effective Sample Sizes

The "Effective Sample Sizes" table displays, for each parameter, the effective sample size, the correlation time, and the efficiency. The ODS name of the "Effective Sample Sizes" table is ESS.

Hazard Ratios for label

The "Hazard Ratios for *label*" table is displayed if you specify the HAZARDRATIO statement. The table displays the posterior summary for each hazard ratio. The summary includes the mean, standard error, quartiles, and equal-tailed and HPD intervals. The ODS name of the "Hazard Ratios for *label*" table is HazardRatios.

Reference Set of Covariates for Plotting

The "Reference Set of Covariates for Plotting" table is displayed if the PLOTS= option is requested without specifying the COVARIATES= data set in the BASELINE statement. The table contains the values of the covariates for the reference set, where the reference levels are used for the CLASS variables and the sample averages for the continuous variables.

ODS Table Names

PROC PHREG assigns a name to each table it creates. You can use these names to reference the table when using the Output Delivery System (ODS) to select tables and create output data sets. These names are listed separately in Table 86.16 for the maximum likelihood analysis and in Table 86.17 for the Bayesian analysis. For more information about ODS, see Chapter 20, "Using the Output Delivery System."

Each of the EFFECT, ESTIMATE, LSMEANS, LSMESTIMATE, and SLICE statements creates ODS tables, which are not listed in Table 86.16 and Table 86.17. For information about these tables, see the corresponding sections of Chapter 19, "Shared Concepts and Topics."

Table 86.16 ODS Tables for a Maximum Likelihood Analysis Produced by PROC PHREG

ODS Table Name	Description	Statement / Option
AUC	Area under the ROC curve at specific time points	PROC / ROCOPTIONS(AUC)
AUCDiff	Differences in AUC between models	PROC / ROCOPTIONS(AUCDIFF)
BestSubsets	Best subset selection	MODEL / SELECTION=SCORE
CensoredSummary	Summary of event and censored observations	Default
ClassLevelFreq	Frequency distribution of CLASS variables	CLASS, PROC / SIMPLE
ClassLevelInfo	CLASS variable levels and design variables	CLASS
ClassLevelInfoR	Class levels for random effects	RANDOM
Concordance	Concordance statistics	PROC / CONCORDANCE=
ConcordanceDiff	Concordance differences between models	PROC / CONCORDANCE=UNO(DIFF)
ContrastCoeff	L matrix for contrasts	CONTRAST / E
ContrastEstimate	Individual contrast estimates	CONTRAST / ESTIMATE=
ContrastTest	Wald test for contrasts	CONTRAST
ConvergenceStatus	Convergence status	Default
CorrB	Estimated correlation matrix of parameter estimators	MODEL / CORRB

Table 86.16 *continued*

ODS Table Name	Description	Statement / Option
CovB	Estimated covariance matrix of parameter estimators	MODEL / COVB
CovParms	Variance estimates of the random effects	RANDOM
EffectsToEnter	Analysis of effects for entry	MODEL / SELECTION=F|S
EffectsToRemove	Analysis of effects for removal	MODEL / SELECTION=B|S
ExplainedVariation	Schemper-Henderson predictive accuracy and explained variation	PROC / EV
FitStatistics	Model fit statistics	Default
FunctionalFormSupTest	Supremum test for functional form	ASSESS / VAR=
GlobalScore	Global chi-square test	MODEL / NOFIT
GlobalTests	Tests of the global null hypothesis	Default
HazardRatios	Hazard ratios and confidence limits	HAZARDRATIO
IAUC	Integrated area under the curve	PROC / ROCOPTONS(IAUC)
IterHistory	Iteration history	MODEL /ITPRINT
LastGradient	Last evaluation of gradient	MODEL / ITPRINT
ModelBuildingSummary	Summary of model building	MODEL / SELECTION=B|F|S
ModelInfo	Model information	Default
NObs	Number of observations	Default
ParameterEstimates	Maximum likelihood estimates of model parameters	Default
ProportionalHazardsSupTest	Supremum test for proportional hazards assumption	ASSESS / PH
ResidualChiSq	Residual chi-square	MODEL / SELECTION=F|B
ReferenceSet	Reference set of covariates for plotting	PROC / PLOTS=
RiskSetInfo	Risk set information	PROC / ATRISK
SimpleStatistics	Summary statistics of input continuous explanatory variables	PROC / SIMPLE
SolutionR	Solutions for random effects	RANDOM / SOLUTION
TestAverage	Average effect for test	TEST / AVERAGE
TestCoeff	Coefficients for linear hypotheses	TEST / E
TestPrint1	**L**[cov(**b**)]**L**' and **Lb**-**c**	TEST / PRINT
TestPrint2	Ginv(**L**[cov(**b**)]**L**') and Ginv(**L**[cov(**b**)]**L**')(**Lb**-**c**)	TEST / PRINT
TestStmts	Linear hypotheses testing results	TEST
Type1	Type 1 likelihood ratio tests	MODEL / TYPE1
ModelANOVA	Type 3 tests or joint tests	MODEL / TYPE3 | CLASS
zphTest	Proportional hazards assumption tests based on scaled Schoenfeld residuals	PROC / ZPH

Table 86.17 ODS Table for a Bayesian Analysis Produced by PROC PHREG

ODS Table Name	Description	Statement / Option
AutoCorr	Autocorrelations of the posterior samples	BAYES
CensoredSummary	Numbers of the event and censored observations	PROC
ClassLevelFreq	Frequency distribution of CLASS variables	CLASS, PROC / SIMPLE
ClassLevelInfo	CLASS variable levels and design variables	CLASS
CoeffPrior	Prior distribution of the regression coefficients	BAYES
Corr	Posterior correlation matrix	BAYES / SUMMARY=CORR
Cov	Posterior covariance Matrix	BAYES / SUMMARY=COV
ESS	Effective sample sizes	BAYES / DIAGNOSTICS=ESS
FitStatistics	Fit statistics	BAYES
Gelman	Gelman-Rubin convergence diagnostics	BAYES / DIAGNOSTICS=GELMAN
Geweke	Geweke convergence diagnostics	BAYES
HazardPrior	Prior distribution of the baseline hazards	BAYES / PIECEWISE
HazardRatios	Posterior summary statistics for hazard ratios	HAZARDRATIO
Heidelberger	Heidelberger-Welch convergence diagnostics	BAYES / DIAGNOSTICS=HEIDELBERGER
InitialValues	Initial values of the Markov chains	BAYES
ModelInfo	Model information	Default
NObs	Number of observations	Default
MCError	Monte Carlo standard errors	BAYES / DIAGNOSTICS=MCERROR
ParameterEstimates	Maximum likelihood estimates of model parameters	Default
ParmInfo	Names of regression coefficients	CLASS,BAYES
Partition	Partition of constant baseline hazard intervals	BAYES / PIECEWISE
PostIntervals	Equal-tail and high probability density intervals of the posterior samples	BAYES
PosteriorSample	Posterior samples	BAYES / (for ODS output data set only)
PostSummaries	Summary statistics of the posterior samples	BAYES

Table 86.17 *continued*

ODS Table Name	Description	Statement / Option
Raftery	Raftery-Lewis convergence diagnostics	BAYES / DIAGNOSTICS=RAFTERY
ReferenceSet	Reference set of covariates for plotting	PROC / PLOTS=
SimpleStatistics	Summary statistics of input continuous explanatory variables	PROC / SIMPLE

ODS Graphics

Statistical procedures use ODS Graphics to create graphs as part of their output. ODS Graphics is described in detail in Chapter 21, "Statistical Graphics Using ODS."

Before you create graphs, ODS Graphics must be enabled (for example, by specifying the ODS GRAPHICS ON statement). For more information about enabling and disabling ODS Graphics, see the section "Enabling and Disabling ODS Graphics" on page 607 in Chapter 21, "Statistical Graphics Using ODS."

The overall appearance of graphs is controlled by ODS styles. Styles and other aspects of using ODS Graphics are discussed in the section "A Primer on ODS Statistical Graphics" on page 606 in Chapter 21, "Statistical Graphics Using ODS."

You can reference every graph produced through ODS Graphics with a name. The names of the graphs that PROC PHREG generates are listed separately in Table 86.18 for the maximum likelihood analysis and in Table 86.19 for the Bayesian analysis. When the ODS Graphics are in effect in a Bayesian analysis, each of the ESTIMATE, LSMEANS, LSMESTIMATE, and SLICE statements can produce plots associated with their analyses. For information of these plots, see the corresponding sections of Chapter 19, "Shared Concepts and Topics."

Table 86.18 Graphs for a Maximum Likelihood Analysis Produced by PROC PHREG

ODS Graph Name	Plot Description	Statement / Option
AUCPlot	Area under the curve plot	PROC / PLOTS=AUC
AUCDiffPlot	Area under the curve difference plot	PROC / PLOTS=AUCDIFF
CIFPLOT	Cumulative incidence function plot	PROC / PLOTS=CIF
CumhazPlot	Cumulative hazard function plot	PROC / PLOTS=CUMHAZ
CumulativeResiduals	Cumulative martingale residual plot	ASSESS / VAR=
CumResidPanel	Panel plot of cumulative martingale residuals	ASSESS / VAR= & CRPANEL
MCFPlot	Mean cumulative function plot	PROC / PLOTS=MCF
ROCPanel	Receiver operating characteristic plots in panels	PROC / PLOTS=ROC
ROCPlot	Receiver operating characteristic plot	PROC / PLOTS(OVERLAY=IND)=ROC
ScoreProcess	Standardized score process plot	ASSESS / PH
SurvivalPlot	Survivor function plot	PROC / PLOTS=SURVIVAL

Table 86.19 Graphs for a Bayesian Analysis Produced by PROC PHREG

ODS Graph Name	Plot Description	Statement / Option
ADPanel	Autocorrelation function and density panel	BAYES / PLOTS=(AUTOCORR DENSITY)
AutocorrPanel	Autocorrelation function panel	BAYES / PLOTS= AUTOCORR
AutocorrPlot	Autocorrelation function plot	BAYES / PLOTS(UNPACK)=AUTOCORR
CumhazPlot	Cumulative hazard function plot	PROC / PLOTS=CUMHAZ
DensityPanel	Density panel	BAYES / PLOTS=DENSITY
DensityPlot	Density plot	BAYES / PLOTS(UNPACK)=DENSITY
SurvivalPlot	Survivor function plot	PROC / PLOTS=SURVIVAL
TAPanel	Trace and autocorrelation function panel	BAYES / PLOTS=(TRACE AUTOCORR)
TADPanel	Trace, density, and autocorrelation function panel	BAYES / PLOTS=(TRACE AUTOCORR DENSITY)
TDPanel	Trace and density panel	BAYES / PLOTS=(TRACE DENSITY)
TracePanel	Trace panel	BAYES / PLOTS=TRACE
TracePlot	Trace plot	BAYES / PLOTS(UNPACK)=TRACE

Examples: PHREG Procedure

This section contains 16 examples of using PROC PHREG. Example 86.13 and Example 86.14 illustrate Bayesian methodology, and the other examples use the classical method of maximum likelihood.

Example 86.1: Stepwise Regression

Krall, Uthoff, and Harley (1975) analyzed data from a study on multiple myeloma in which researchers treated 65 patients with alkylating agents. Of those patients, 48 died during the study and 17 survived. The following DATA step creates the data set Myeloma. The variable Time represents the survival time in months from diagnosis. The variable VStatus consists of two values, 0 and 1, indicating whether the patient was alive or dead, respectively, at the end of the study. If the value of VStatus is 0, the corresponding value of Time is censored. The variables thought to be related to survival are LogBUN (log(BUN) at diagnosis), HGB (hemoglobin at diagnosis), Platelet (platelets at diagnosis: 0=abnormal, 1=normal), Age (age at diagnosis, in years), LogWBC (log(WBC) at diagnosis), Frac (fractures at diagnosis: 0=none, 1=present), LogPBM (log percentage of plasma cells in bone marrow), Protein (proteinuria at diagnosis), and SCalc (serum calcium at diagnosis). Interest lies in identifying important prognostic factors from these nine explanatory variables.

```
data Myeloma;
   input Time VStatus LogBUN HGB Platelet Age LogWBC Frac
         LogPBM Protein SCalc;
   label Time='Survival Time'
         VStatus='0=Alive 1=Dead';
   datalines;
 1.25  1  2.2175   9.4  1  67  3.6628  1  1.9542  12  10
 1.25  1  1.9395  12.0  1  38  3.9868  1  1.9542  20  18
 2.00  1  1.5185   9.8  1  81  3.8751  1  2.0000   2  15
 2.00  1  1.7482  11.3  0  75  3.8062  1  1.2553   0  12
 2.00  1  1.3010   5.1  0  57  3.7243  1  2.0000   3   9
 3.00  1  1.5441   6.7  1  46  4.4757  0  1.9345  12  10
 5.00  1  2.2355  10.1  1  50  4.9542  1  1.6628   4   9
 5.00  1  1.6812   6.5  1  74  3.7324  0  1.7324   5   9
 6.00  1  1.3617   9.0  1  77  3.5441  0  1.4624   1   8
 6.00  1  2.1139  10.2  0  70  3.5441  1  1.3617   1   8
 6.00  1  1.1139   9.7  1  60  3.5185  1  1.3979   0  10
 6.00  1  1.4150  10.4  1  67  3.9294  1  1.6902   0   8
 7.00  1  1.9777   9.5  1  48  3.3617  1  1.5682   5  10
 7.00  1  1.0414   5.1  0  61  3.7324  1  2.0000   1  10
 7.00  1  1.1761  11.4  1  53  3.7243  1  1.5185   1  13
 9.00  1  1.7243   8.2  1  55  3.7993  1  1.7404   0  12
11.00  1  1.1139  14.0  1  61  3.8808  1  1.2788   0  10
11.00  1  1.2304  12.0  1  43  3.7709  1  1.1761   1   9
11.00  1  1.3010  13.2  1  65  3.7993  1  1.8195   1  10
11.00  1  1.5682   7.5  1  70  3.8865  0  1.6721   0  12
11.00  1  1.0792   9.6  1  51  3.5051  1  1.9031   0   9
13.00  1  0.7782   5.5  0  60  3.5798  1  1.3979   2  10
14.00  1  1.3979  14.6  1  66  3.7243  1  1.2553   2  10
15.00  1  1.6021  10.6  1  70  3.6902  1  1.4314   0  11
16.00  1  1.3424   9.0  1  48  3.9345  1  2.0000   0  10
```

```
16.00  1  1.3222   8.8  1  62  3.6990  1  0.6990  17  10
17.00  1  1.2304  10.0  1  53  3.8808  1  1.4472   4   9
17.00  1  1.5911  11.2  1  68  3.4314  0  1.6128   1  10
18.00  1  1.4472   7.5  1  65  3.5682  0  0.9031   7   8
19.00  1  1.0792  14.4  1  51  3.9191  1  2.0000   6  15
19.00  1  1.2553   7.5  0  60  3.7924  1  1.9294   5   9
24.00  1  1.3010  14.6  1  56  4.0899  1  0.4771   0   9
25.00  1  1.0000  12.4  1  67  3.8195  1  1.6435   0  10
26.00  1  1.2304  11.2  1  49  3.6021  1  2.0000  27  11
32.00  1  1.3222  10.6  1  46  3.6990  1  1.6335   1   9
35.00  1  1.1139   7.0  0  48  3.6532  1  1.1761   4  10
37.00  1  1.6021  11.0  1  63  3.9542  0  1.2041   7   9
41.00  1  1.0000  10.2  1  69  3.4771  1  1.4771   6  10
41.00  1  1.1461   5.0  1  70  3.5185  1  1.3424   0   9
51.00  1  1.5682   7.7  0  74  3.4150  1  1.0414   4  13
52.00  1  1.0000  10.1  1  60  3.8573  1  1.6532   4  10
54.00  1  1.2553   9.0  1  49  3.7243  1  1.6990   2  10
58.00  1  1.2041  12.1  1  42  3.6990  1  1.5798  22  10
66.00  1  1.4472   6.6  1  59  3.7853  1  1.8195   0   9
67.00  1  1.3222  12.8  1  52  3.6435  1  1.0414   1  10
88.00  1  1.1761  10.6  1  47  3.5563  0  1.7559  21   9
89.00  1  1.3222  14.0  1  63  3.6532  1  1.6232   1   9
92.00  1  1.4314  11.0  1  58  4.0755  1  1.4150   4  11
 4.00  0  1.9542  10.2  1  59  4.0453  0  0.7782  12  10
 4.00  0  1.9243  10.0  1  49  3.9590  0  1.6232   0  13
 7.00  0  1.1139  12.4  1  48  3.7993  1  1.8573   0  10
 7.00  0  1.5315  10.2  1  81  3.5911  0  1.8808   0  11
 8.00  0  1.0792   9.9  1  57  3.8325  1  1.6532   0   8
12.00  0  1.1461  11.6  1  46  3.6435  0  1.1461   0   7
11.00  0  1.6128  14.0  1  60  3.7324  1  1.8451   3   9
12.00  0  1.3979   8.8  1  66  3.8388  1  1.3617   0   9
13.00  0  1.6628   4.9  0  71  3.6435  0  1.7924   0   9
16.00  0  1.1461  13.0  1  55  3.8573  0  0.9031   0   9
19.00  0  1.3222  13.0  1  59  3.7709  1  2.0000   1  10
19.00  0  1.3222  10.8  1  69  3.8808  1  1.5185   0  10
28.00  0  1.2304   7.3  1  82  3.7482  1  1.6721   0   9
41.00  0  1.7559  12.8  1  72  3.7243  1  1.4472   1   9
53.00  0  1.1139  12.0  1  66  3.6128  1  2.0000   1  11
57.00  0  1.2553  12.5  1  66  3.9685  0  1.9542   0  11
77.00  0  1.0792  14.0  1  60  3.6812  0  0.9542   0  12
;
```

The stepwise selection process consists of a series of alternating forward selection and backward elimination steps. The former adds variables to the model, while the latter removes variables from the model.

The following statements use PROC PHREG to produce a stepwise regression analysis. Stepwise selection is requested by specifying the SELECTION=STEPWISE option in the MODEL statement. The option SLENTRY=0.25 specifies that a variable has to be significant at the 0.25 level before it can be entered into the model, while the option SLSTAY=0.15 specifies that a variable in the model has to be significant at the 0.15 level for it to remain in the model. The DETAILS option requests detailed results for the variable selection process.

```
proc phreg data=Myeloma;
   model Time*VStatus(0)=LogBUN HGB Platelet Age LogWBC
                         Frac LogPBM Protein SCalc
                         / selection=stepwise slentry=0.25
                           slstay=0.15 details;
run;
```

Results of the stepwise regression analysis are displayed in Output 86.1.1 through Output 86.1.7.

Individual score tests are used to determine which of the nine explanatory variables is first selected into the model. In this case, the score test for each variable is the global score test for the model containing that variable as the only explanatory variable. Output 86.1.1 displays the chi-square statistics and the corresponding *p*-values. The variable LogBUN has the largest chi-square value (8.5164), and it is significant ($p = 0.0035$) at the SLENTRY=0.25 level. The variable LogBUN is thus entered into the model.

Output 86.1.1 Individual Score Test Results for All Variables

The PHREG Procedure

Model Information		
Data Set	WORK.MYELOMA	
Dependent Variable	Time	Survival Time
Censoring Variable	VStatus	0=Alive 1=Dead
Censoring Value(s)	0	
Ties Handling	BRESLOW	

Summary of the Number of Event and Censored Values			
Total	**Event**	**Censored**	**Percent Censored**
65	48	17	26.15

Analysis of Effects Eligible for Entry			
Effect	**DF**	**Score Chi-Square**	**Pr > ChiSq**
LogBUN	1	8.5164	0.0035
HGB	1	5.0664	0.0244
Platelet	1	3.1816	0.0745
Age	1	0.0183	0.8924
LogWBC	1	0.5658	0.4519
Frac	1	0.9151	0.3388
LogPBM	1	0.5846	0.4445
Protein	1	0.1466	0.7018
SCalc	1	1.1109	0.2919

Residual Chi-Square Test		
Chi-Square	**DF**	**Pr > ChiSq**
18.4550	9	0.0302

Output 86.1.2 displays the results of the first model. Since the Wald chi-square statistic is significant (p = 0.0039) at the SLSTAY=0.15 level, LogBUN stays in the model.

Output 86.1.2 First Model in the Stepwise Selection Process

Step 1. Effect LogBUN is entered. The model contains the following effects:

LogBUN

Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	309.716	301.959
AIC	309.716	303.959
SBC	309.716	305.830

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	7.7572	1	0.0053
Score	8.5164	1	0.0035
Wald	8.3392	1	0.0039

Analysis of Maximum Likelihood Estimates						
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
LogBUN	1	1.74595	0.60460	8.3392	0.0039	5.731

The next step consists of selecting another variable to add to the model. Output 86.1.3 displays the chi-square statistics and p-values of individual score tests (adjusted for LogBUN) for the remaining eight variables. The score chi-square for a given variable is the value of the likelihood score test for testing the significance of the variable in the presence of LogBUN. The variable HGB is selected because it has the highest chi-square value (4.3468), and it is significant (p = 0.0371) at the SLENTRY=0.25 level.

Output 86.1.3 Score Tests Adjusted for the Variable LogBUN

Analysis of Effects Eligible for Entry			
Effect	DF	Score Chi-Square	Pr > ChiSq
HGB	1	4.3468	0.0371
Platelet	1	2.0183	0.1554
Age	1	0.7159	0.3975
LogWBC	1	0.0704	0.7908
Frac	1	1.0354	0.3089
LogPBM	1	1.0334	0.3094
Protein	1	0.5214	0.4703
SCalc	1	1.4150	0.2342

Output 86.1.3 *continued*

Residual Chi-Square Test		
Chi-Square	**DF**	**Pr > ChiSq**
9.3164	8	0.3163

Output 86.1.4 displays the fitted model containing both LogBUN and HGB. Based on the Wald statistics, neither LogBUN nor HGB is removed from the model.

Output 86.1.4 Second Model in the Stepwise Selection Process

Step 2. Effect HGB is entered. The model contains the following effects:

LogBUN HGB

Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	**Without Covariates**	**With Covariates**
-2 LOG L	309.716	297.767
AIC	309.716	301.767
SBC	309.716	305.509

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	11.9493	2	0.0025
Score	12.7252	2	0.0017
Wald	12.1900	2	0.0023

Analysis of Maximum Likelihood Estimates						
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**
LogBUN	1	1.67440	0.61209	7.4833	0.0062	5.336
HGB	1	-0.11899	0.05751	4.2811	0.0385	0.888

Output 86.1.5 shows Step 3 of the selection process, in which the variable SCalc is added, resulting in the model with LogBUN, HGB, and SCalc as the explanatory variables. Note that SCalc has the smallest Wald chi-square statistic, and it is not significant ($p = 0.1782$) at the SLSTAY=0.15 level.

Output 86.1.5 Third Model in the Stepwise Regression

Step 3. Effect SCalc is entered. The model contains the following effects:

LogBUN HGB SCalc

Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Output 86.1.5 *continued*

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	309.716	296.078
AIC	309.716	302.078
SBC	309.716	307.692

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	13.6377	3	0.0034
Score	15.3053	3	0.0016
Wald	14.4542	3	0.0023

Analysis of Maximum Likelihood Estimates						
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
LogBUN	1	1.63593	0.62359	6.8822	0.0087	5.134
HGB	1	-0.12643	0.05868	4.6419	0.0312	0.881
SCalc	1	0.13286	0.09868	1.8127	0.1782	1.142

The variable SCalc is then removed from the model in a step-down phase in Step 4 (Output 86.1.6). The removal of SCalc brings the stepwise selection process to a stop in order to avoid repeatedly entering and removing the same variable.

Output 86.1.6 Final Model in the Stepwise Regression

Step 4. Effect SCalc is removed. The model contains the following effects:

LogBUN HGB

Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	309.716	297.767
AIC	309.716	301.767
SBC	309.716	305.509

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	11.9493	2	0.0025
Score	12.7252	2	0.0017
Wald	12.1900	2	0.0023

Output 86.1.6 *continued*

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
LogBUN	1	1.67440	0.61209	7.4833	0.0062	5.336
HGB	1	-0.11899	0.05751	4.2811	0.0385	0.888

Note: Model building terminates because the effect to be entered is the effect that was removed in the last step.

The procedure also displays a summary table of the steps in the stepwise selection process, as shown in Output 86.1.7.

Output 86.1.7 Model Selection Summary

Summary of Stepwise Selection

Step	Effect Entered	Effect Removed	DF	Number In	Score Chi-Square	Wald Chi-Square	Pr > ChiSq
1	LogBUN		1	1	8.5164		0.0035
2	HGB		1	2	4.3468		0.0371
3	SCalc		1	3	1.8225		0.1770
4		SCalc	1	2		1.8127	0.1782

The stepwise selection process results in a model with two explanatory variables, LogBUN and HGB.

Example 86.2: Best Subset Selection

An alternative to stepwise selection of variables is best subset selection. This method uses the branch-and-bound algorithm of Furnival and Wilson (1974) to find a specified number of best models containing one, two, or three variables, and so on, up to the single model containing all of the explanatory variables. The criterion used to determine the "best" subset is based on the global score chi-square statistic. For two models A and B, each having the same number of explanatory variables, model A is considered to be better than model B if the global score chi-square statistic for A exceeds that for B.

In the following statements, best subset selection analysis is requested by specifying the SELECTION=SCORE option in the MODEL statement. The BEST=3 option requests the procedure to identify only the three best models for each size. In other words, PROC PHREG will list the three models having the highest score statistics of all the models possible for a given number of covariates.

```
proc phreg data=Myeloma;
   model Time*VStatus(0)=LogBUN HGB Platelet Age LogWBC
                         Frac LogPBM Protein SCalc
                         / selection=score best=3;
run;
```

Output 86.2.1 displays the results of this analysis. The number of explanatory variables in the model is given in the first column, and the names of the variables are listed on the right. The models are listed in descending order of their score chi-square values within each model size. For example, among all models containing two explanatory variables, the model that contains the variables LogBUN and HGB has the largest score value

(12.7252), the model that contains the variables LogBUN and Platelet has the second-largest score value (11.1842), and the model that contains the variables LogBUN and SCalc has the third-largest score value (9.9962).

Output 86.2.1 Best Variable Combinations

The PHREG Procedure

Regression Models Selected by Score Criterion

Number of Variables	Score Chi-Square	Variables Included in Model
1	8.5164	LogBUN
1	5.0664	HGB
1	3.1816	Platelet
2	12.7252	LogBUN HGB
2	11.1842	LogBUN Platelet
2	9.9962	LogBUN SCalc
3	15.3053	LogBUN HGB SCalc
3	13.9911	LogBUN HGB Age
3	13.5788	LogBUN HGB Frac
4	16.9873	LogBUN HGB Age SCalc
4	16.0457	LogBUN HGB Frac SCalc
4	15.7619	LogBUN HGB LogPBM SCalc
5	17.6291	LogBUN HGB Age Frac SCalc
5	17.3519	LogBUN HGB Age LogPBM SCalc
5	17.1922	LogBUN HGB Age LogWBC SCalc
6	17.9120	LogBUN HGB Age Frac LogPBM SCalc
6	17.7947	LogBUN HGB Age LogWBC Frac SCalc
6	17.7744	LogBUN HGB Platelet Age Frac SCalc
7	18.1517	LogBUN HGB Platelet Age Frac LogPBM SCalc
7	18.0568	LogBUN HGB Age LogWBC Frac LogPBM SCalc
7	18.0223	LogBUN HGB Platelet Age LogWBC Frac SCalc
8	18.3925	LogBUN HGB Platelet Age LogWBC Frac LogPBM SCalc
8	18.1636	LogBUN HGB Platelet Age Frac LogPBM Protein SCalc
8	18.1309	LogBUN HGB Platelet Age LogWBC Frac Protein SCalc
9	18.4550	LogBUN HGB Platelet Age LogWBC Frac LogPBM Protein SCalc

Example 86.3: Modeling with Categorical Predictors

Consider the data for the Veterans Administration lung cancer trial presented in Appendix 1 of Kalbfleisch and Prentice (1980). In this trial, males with advanced inoperable lung cancer were randomized to a standard therapy and a test chemotherapy. The primary endpoint for the therapy comparison was time to death in days, represented by the variable Time. Negative values of Time are censored values. The data include information about a number of explanatory variables: Therapy (type of therapy: standard or test), Cell (type of tumor cell: adeno, large, small, or squamous), Prior (prior therapy: 0=no, 10=yes), Age (age, in years), Duration (months from diagnosis to randomization), and Kps (Karnofsky performance scale). A censoring indicator variable, Censor, is created from the data, with the value 1 indicating a censored time and the value 0 indicating an event time. The following DATA step saves the data in the data set VALung.

```
proc format;
   value yesno 0='no' 10='yes';
run;

data VALung;
   drop check m;
   retain Therapy Cell;
   infile cards column=column;
   length Check $ 1;
   label Time='time to death in days'
         Kps='Karnofsky performance scale'
         Duration='months from diagnosis to randomization'
         Age='age in years'
         Prior='prior therapy'
         Cell='cell type'
         Therapy='type of treatment';
   format Prior yesno.;
   M=Column;
   input Check $ @@;
   if M>Column then M=1;
   if Check='s'|Check='t' then do;
      input @M Therapy $ Cell $;
      delete;
   end;
   else do;
      input @M Time Kps Duration Age Prior @@;
      Status=(Time>0);
      Time=abs(Time);
   end;
   datalines;
standard squamous
 72 60  7 69  0   411 70  5 64 10   228 60  3 38  0   126 60  9 63 10
118 70 11 65 10    10 20  5 49  0    82 40 10 69 10   110 80 29 68  0
314 50 18 43  0  -100 70  6 70  0    42 60  4 81  0     8 40 58 63 10
144 30  4 63  0   -25 80  9 52 10    11 70 11 48 10
standard small
 30 60  3 61  0   384 60  9 42  0     4 40  2 35  0    54 80  4 63 10
 13 60  4 56  0  -123 40  3 55  0   -97 60  5 67  0   153 60 14 63 10
 59 30  2 65  0   117 80  3 46  0    16 30  4 53 10   151 50 12 69  0
 22 60  4 68  0    56 80 12 43 10    21 40  2 55 10    18 20 15 42  0
139 80  2 64  0    20 30  5 65  0    31 75  3 65  0    52 70  2 55  0
287 60 25 66 10    18 30  4 60  0    51 60  1 67  0   122 80 28 53  0
 27 60  8 62  0    54 70  1 67  0     7 50  7 72  0    63 50 11 48  0
392 40  4 68  0    10 40 23 67 10
standard adeno
  8 20 19 61 10    92 70 10 60  0    35 40  6 62  0   117 80  2 38  0
132 80  5 50  0    12 50  4 63 10   162 80  5 64  0     3 30  3 43  0
 95 80  4 34  0
standard large
177 50 16 66 10   162 80  5 62  0   216 50 15 52  0   553 70  2 47  0
278 60 12 63  0    12 40 12 68 10   260 80  5 45  0   200 80 12 41 10
156 70  2 66  0  -182 90  2 62  0   143 90  8 60  0   105 80 11 66  0
103 80  5 38  0   250 70  8 53 10   100 60 13 37 10
```

```
test squamous
999 90 12 54 10   112 80  6 60  0   -87 80  3 48  0  -231 50  8 52 10
242 50  1 70  0   991 70  7 50 10   111 70  3 62  0     1 20 21 65 10
587 60  3 58  0   389 90  2 62  0    33 30  6 64  0    25 20 36 63  0
357 70 13 58  0   467 90  2 64  0   201 80 28 52 10     1 50  7 35  0
 30 70 11 63  0    44 60 13 70 10   283 90  2 51  0    15 50 13 40 10
test small
 25 30  2 69  0  -103 70 22 36 10    21 20  4 71  0    13 30  2 62  0
 87 60  2 60  0     2 40 36 44 10    20 30  9 54 10     7 20 11 66  0
 24 60  8 49  0    99 70  3 72  0     8 80  2 68  0    99 85  4 62  0
 61 70  2 71  0    25 70  2 70  0    95 70  1 61  0    80 50 17 71  0
 51 30 87 59 10    29 40  8 67  0
test adeno
 24 40  2 60  0    18 40  5 69 10   -83 99  3 57  0    31 80  3 39  0
 51 60  5 62  0    90 60 22 50 10    52 60  3 43  0    73 60  3 70  0
  8 50  5 66  0    36 70  8 61  0    48 10  4 81  0     7 40  4 58  0
140 70  3 63  0   186 90  3 60  0    84 80  4 62 10    19 50 10 42  0
 45 40  3 69  0    80 40  4 63  0
test large
 52 60  4 45  0   164 70 15 68 10    19 30  4 39 10    53 60 12 66  0
 15 30  5 63  0    43 60 11 49 10   340 80 10 64 10   133 75  1 65  0
111 60  5 64  0   231 70 18 67 10   378 80  4 65  0    49 30  3 37  0
;
```

The following statements use the PHREG procedure to fit the Cox proportional hazards model to these data. The variables Prior, Cell, and Therapy, which are categorical variables, are declared in the CLASS statement. By default, PROC PHREG parameterizes the CLASS variables by using the reference coding with the last category as the reference category. However, you can explicitly specify the reference category of your choice. Here, Prior=no is chosen as the reference category for prior therapy, Cell=large is chosen as the reference category for type of tumor cell, and Therapy=standard is chosen as the reference category for the type of therapy. In the MODEL statement, the term Prior|Therapy is just another way of specifying the main effects Prior, Therapy, and the Prior*Therapy interaction.

```
proc phreg data=VALung;
   class Prior(ref='no') Cell(ref='large') Therapy(ref='standard');
   model Time*Status(0) = Kps Duration Age Cell Prior|Therapy;
run;
```

Coding of the CLASS variables is displayed in Output 86.3.1. There is one dummy variable for Prior and one for Therapy, since both variables are binary. The dummy variable has a value of 0 for the reference category (Prior=no, Therapy=standard). The variable Cell has four categories and is represented by three dummy variables. Note that the reference category, Cell=large, has a value of 0 for all three dummy variables.

Output 86.3.1 Reference Coding of CLASS Variables

The PHREG Procedure

Class Level Information				
Class	Value	Design Variables		
Prior	no	0		
	yes	1		
Cell	adeno	1	0	0
	large	0	0	0
	small	0	1	0
	squamous	0	0	1
Therapy	standard	0		
	test	1		

The test results of individual model effects are shown in Output 86.3.2. There is a strong prognostic effect of Kps on patient's survivorship ($p < 0.0001$), and the survival times for patients of different Cell types differ significantly ($p = 0.0003$). The Prior*Therapy interaction is marginally significant ($p = 0.0416$)—that is, prior therapy might play a role in whether one treatment is more effective than the other.

Output 86.3.2 Wald Tests of Individual Effects

Joint Tests			
Effect	DF	Wald Chi-Square	Pr > ChiSq
Kps	1	35.5051	<.0001
Duration	1	0.1159	0.7335
Age	1	1.9772	0.1597
Cell	3	18.5339	0.0003
Prior	1	2.5296	0.1117
Therapy	1	5.2349	0.0221
Prior*Therapy	1	4.1528	0.0416

Note: Under full-rank parameterizations, Type 3 effect tests are replaced by joint tests. The joint test for an effect is a test that all of the parameters associated with that effect are zero. Such joint tests might not be equivalent to Type 3 effect tests under GLM parameterization.

In the Cox proportional hazards model, the effects of the covariates are to act multiplicatively on the hazard of the survival time, and therefore it is a little easier to interpret the corresponding hazard ratios than the regression parameters. For a parameter that corresponds to a continuous variable, the hazard ratio is the ratio of hazard rates for a increase of one unit of the variable. From Output 86.3.3, the hazard ratio estimate for Kps is 0.968, meaning that an increase of 10 units in Karnofsky performance scale will shrink the hazard rate by $1 - (0.968)^{10}$=28%. For a CLASS variable parameter, the hazard ratio presented in the Output 86.3.3 is the ratio of the hazard rates between the given category and the reference category. The hazard rate of Cell=adeno is 219% that of Cell=large, the hazard rate of Cell=small is 162% that of Cell=large, and the hazard rate of Cell=squamous is only 66% that of Cell=large. Hazard ratios for Prior and Therapy are missing since the model contains the Prior*Therapy interaction. You can use the HAZARDRATIO statement to obtain the hazard ratios for a main effect in the presence of interaction as shown later in this example.

Output 86.3.3 Parameters Estimates with Reference Coding

Analysis of Maximum Likelihood Estimates

Parameter			DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
Kps			1	-0.03300	0.00554	35.5051	<.0001	0.968	Karnofsky performance scale
Duration			1	0.00323	0.00949	0.1159	0.7335	1.003	months from diagnosis to randomization
Age			1	-0.01353	0.00962	1.9772	0.1597	0.987	age in years
Cell	**adeno**		1	0.78356	0.30382	6.6512	0.0099	2.189	cell type adeno
Cell	**small**		1	0.48230	0.26537	3.3032	0.0691	1.620	cell type small
Cell	**squamous**		1	-0.40770	0.28363	2.0663	0.1506	0.665	cell type squamous
Prior	**yes**		1	0.45914	0.28868	2.5296	0.1117	.	prior therapy yes
Therapy	**test**		1	0.56662	0.24765	5.2349	0.0221	.	type of treatment test
Prior*Therapy	**yes**	**test**	1	-0.87579	0.42976	4.1528	0.0416	.	prior therapy yes * type of treatment test

The following PROC PHREG statements illustrate the use of the backward elimination process to identify the effects that affect the survivorship of the lung cancer patients. The option SELECTION=BACKWARD is specified to carry out the backward elimination. The option SLSTAY=0.1 specifies the significant level for retaining the effects in the model.

```
proc phreg data=VALung;
   class Prior(ref='no') Cell(ref='large') Therapy(ref='standard');
   model Time*Status(0) = Kps Duration Age Cell Prior|Therapy
         / selection=backward slstay=0.1;
run;
```

Results of the backward elimination process are summarized in Output 86.3.4. The effect Duration was eliminated first and was followed by Age.

Output 86.3.4 Effects Eliminated from the Model

The PHREG Procedure

Summary of Backward Elimination

Step	Effect Removed	DF	Number In	Wald Chi-Square	Pr > ChiSq	Effect Label
1	Duration	1	6	0.1159	0.7335	months from diagnosis to randomization
2	Age	1	5	2.0458	0.1526	age in years

Output 86.3.5 shows the Type 3 analysis of effects and the maximum likelihood estimates of the regression coefficients of the model. Without controlling for Age and Duration, KPS and Cell remain significant, but the Prior*Therapy interaction is less prominent than before ($p = 0.0871$) though still significant at 0.1 level.

Output 86.3.5 Type 3 Effects and Parameter Estimates for the Selected Model

Joint Tests

Effect	DF	Wald Chi-Square	Pr > ChiSq
Kps	1	35.9218	<.0001
Cell	3	17.4134	0.0006
Prior	1	2.3113	0.1284
Therapy	1	3.8030	0.0512
Prior*Therapy	1	2.9269	0.0871

Note: Under full-rank parameterizations, Type 3 effect tests are replaced by joint tests. The joint test for an effect is a test that all of the parameters associated with that effect are zero. Such joint tests might not be equivalent to Type 3 effect tests under GLM parameterization.

Analysis of Maximum Likelihood Estimates

Parameter			DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
Kps			1	-0.03111	0.00519	35.9218	<.0001	0.969	Karnofsky performance scale
Cell	**adeno**		1	0.74907	0.30465	6.0457	0.0139	2.115	cell type adeno
Cell	**small**		1	0.44265	0.26168	2.8614	0.0907	1.557	cell type small
Cell	**squamous**		1	-0.41145	0.28309	2.1125	0.1461	0.663	cell type squamous
Prior	**yes**		1	0.41755	0.27465	2.3113	0.1284	.	prior therapy yes
Therapy	**test**		1	0.45670	0.23419	3.8030	0.0512	.	type of treatment test
Prior*Therapy	**yes**	**test**	1	-0.69443	0.40590	2.9269	0.0871	.	prior therapy yes * type of treatment test

Finally, the following statements refit the previous model and computes hazard ratios at settings beyond those displayed in the "Analysis of Maximum Likelihood Estimates" table. You can use either the HAZARDRATIO statement or the CONTRAST statement to obtain hazard ratios. Using the CONTRAST statement to compute hazard ratios for CLASS variables can be a daunting task unless you are familiar with the parameterization schemes (see the section "Parameterization of Model Effects" on page 385 in Chapter 19, "Shared Concepts and Topics"), but you have control over which specific hazard ratios you want to compute. HAZARDRATIO statements, on the other hand, are designed specifically to provide hazard ratios. They are easy to use and you can also request both the Wald confidence limits and the profile-likelihood confidence limits; the latter is not available for the CONTRAST statements. Three HAZARDRATIO statements are specified; each has the CL=BOTH option to request both the Wald confidence limits and the profile-likelihood limits. The first HAZARDRATIO statement, labeled 'H1', estimates the hazard ratio for an increase of 10 units in the KPS; the UNITS= option specifies the number of units increase. The second HAZARDRATIO statement, labeled 'H2' computes the hazard ratios for comparing any pairs of tumor Cell types. The third HAZARDRATIO statement, labeled 'H3', compares the test therapy with the standard therapy. The DIFF=REF option specifies that each nonreference category is compared to the reference category. The purpose of using DIFF=REF here is to ensure that the hazard ratio is comparing the test therapy to the standard therapy instead of the other way around. Three CONTRAST statements, labeled 'C1', 'C2', and 'C3', parallel to the HAZARDRATIO statements 'H1', 'H2', and 'H3', respectively, are specified. The ESTIMATE=EXP option specifies that the linear predictors be estimated in the exponential scale, which are precisely the hazard ratios.

```
proc phreg data=VALung;
   class Prior(ref='no') Cell(ref='large') Therapy(ref='standard');
   model Time*Status(0) = Kps Cell Prior|Therapy;
   hazardratio 'H1' Kps / units=10 cl=both;
   hazardratio 'H2' Cell / cl=both;
   hazardratio 'H3' Therapy / diff=ref cl=both;
   contrast 'C1' Kps 10 / estimate=exp;
   contrast 'C2' cell 1  0  0, /* adeno vs large    */
                 cell 1 -1  0, /* adeno vs small    */
                 cell 1  0 -1, /* adeno vs squamous */
                 cell 0 -1  0, /* large vs small    */
                 cell 0  0 -1, /* large vs Squamous */
                 cell 0  1 -1  /* small vs squamous */
                  / estimate=exp;
   contrast 'C3' Prior 0 Therapy 1  Prior*Therapy 0,
                 Prior 0 Therapy 1  Prior*Therapy 1  / estimate=exp;
run;
```

Output 86.3.6 displays the results of the three HAZARDRATIO statements in separate tables. Results of the three CONTRAST statements are shown in one table in Output 86.3.7. However, point estimates and the Wald confidence limits for the hazard ratio agree in between the two outputs.

Output 86.3.6 Results from HAZARDRATIO Statements

The PHREG Procedure

H1: Hazard Ratios for Karnofsky performance scale

Description	Point Estimate	95% Wald Confidence Limits		95% Profile Likelihood Confidence Limits	
Kps Unit=10	0.733	0.662	0.811	0.662	0.811

H2: Hazard Ratios for cell type

Description	Point Estimate	95% Wald Confidence Limits		95% Profile Likelihood Confidence Limits	
Cell adeno vs large	2.115	1.164	3.843	1.162	3.855
Cell adeno vs small	1.359	0.798	2.312	0.791	2.301
Cell adeno vs squamous	3.192	1.773	5.746	1.770	5.768
Cell large vs small	0.642	0.385	1.073	0.380	1.065
Cell large vs squamous	1.509	0.866	2.628	0.863	2.634
Cell small vs squamous	2.349	1.387	3.980	1.399	4.030

Output 86.3.6 *continued*

H3: Hazard Ratios for type of treatment

Description	Point Estimate	95% Wald Confidence Limits		95% Profile Likelihood Confidence Limits	
Therapy test vs standard At Prior=no	1.579	0.998	2.499	0.998	2.506
Therapy test vs standard At Prior=yes	0.788	0.396	1.568	0.390	1.560

Output 86.3.7 Results from CONTRAST Statements

Contrast Estimation and Testing Results by Row

Contrast	Type	Row	Estimate	Standard Error	Alpha	Confidence Limits		Wald Chi-Square	Pr > ChiSq
C1	EXP	1	0.7326	0.0380	0.05	0.6618	0.8111	35.9218	<.0001
C2	EXP	1	2.1150	0.6443	0.05	1.1641	3.8427	6.0457	0.0139
C2	EXP	2	1.3586	0.3686	0.05	0.7982	2.3122	1.2755	0.2587
C2	EXP	3	3.1916	0.9575	0.05	1.7727	5.7462	14.9629	0.0001
C2	EXP	4	0.6423	0.1681	0.05	0.3846	1.0728	2.8614	0.0907
C2	EXP	5	1.5090	0.4272	0.05	0.8664	2.6282	2.1125	0.1461
C2	EXP	6	2.3493	0.6318	0.05	1.3868	3.9797	10.0858	0.0015
C3	EXP	1	1.5789	0.3698	0.05	0.9977	2.4985	3.8030	0.0512
C3	EXP	2	0.7884	0.2766	0.05	0.3964	1.5680	0.4593	0.4980

Example 86.4: Firth's Correction for Monotone Likelihood

In fitting the Cox regression model by maximizing the partial likelihood, the estimate of an explanatory variable X will be infinite if the value of X at each uncensored failure time is the largest of all the values of X in the risk set at that time (Tsiatis 1981; Bryson and Johnson 1981). You can exploit this information to artificially create a data set that has the condition of monotone likelihood for the Cox regression. The following DATA step modifies the Myeloma data in Example 86.1 to create a new explanatory variable, Contrived, which has the value 1 if the observed time is less than or equal to 65 and has the value 0 otherwise. The phenomenon of monotone likelihood will be demonstrated in the new data set Myeloma2.

```
data Myeloma2;
   set Myeloma;
   Contrived= (Time <= 65);
run;
```

For illustration purposes, consider a Cox model with three explanatory variables, one of which is the variable Contrived. The following statements invoke PROC PHREG to perform the Cox regression. The IPRINT option is specified in the MODEL statement to print the iteration history of the optimization.

```
proc phreg data=Myeloma2;
   model Time*Vstatus(0)=LOGbun HGB Contrived / itprint;
run;
```

The symptom of monotonicity is demonstrated in Output 86.4.1. The log likelihood converges to the value of –136.56 while the coefficient for Contrived diverges. Although the Newton-Raphson optimization process did not fail, it is obvious that convergence is questionable. A close examination of the standard errors in the "Analysis of Maximum Likelihood Estimates" table reveals a very large value for the coefficient of Contrived. This is very typical of a diverged estimate.

Output 86.4.1 Monotone Likelihood Behavior Displayed

The PHREG Procedure

Maximum Likelihood Iteration History

Iter	Ridge	Log Likelihood	LogBUN	HGB	Contrived
0	0	-154.8579914384	0.0000000000	0.000000000	0.000000000
1	0	-140.6934052686	1.9948819671	-0.084318519	1.466331269
2	0	-137.7841629416	1.6794678962	-0.109067888	2.778361123
3	0	-136.9711897754	1.7140611684	-0.111564202	3.938095086
4	0	-136.7078932606	1.7181735043	-0.112273248	5.003053568
5	0	-136.6164264879	1.7187547532	-0.112369756	6.027435769
6	0	-136.5835200895	1.7188294108	-0.112382079	7.036444978
7	0	-136.5715152788	1.7188392687	-0.112383700	8.039763533
8	0	-136.5671126045	1.7188405904	-0.112383917	9.040984886
9	0	-136.5654947987	1.7188407687	-0.112383947	10.041434266
10	0	-136.5648998913	1.7188407928	-0.112383950	11.041599592
11	0	-136.5646810709	1.7188407960	-0.112383951	12.041660414
12	0	-136.5646005760	1.7188407965	-0.112383951	13.041682789
13	0	-136.5645709642	1.7188407965	-0.112383951	14.041691020
14	0	-136.5645600707	1.7188407965	-0.112383951	15.041694049
15	0	-136.5645560632	1.7188407965	-0.112383951	16.041695162
16	0	-136.5645545889	1.7188407965	-0.112383951	17.041695572

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
LogBUN	1	1.71884	0.58376	8.6697	0.0032	5.578
HGB	1	-0.11238	0.06090	3.4053	0.0650	0.894
Contrived	1	17.04170	1080	0.0002	0.9874	25183399

Next, the Firth correction was applied as shown in the following statements. Also, the profile-likelihood confidence limits for the hazard ratios are requested by using the RISKLIMITS=PL option.

```
proc phreg data=Myeloma2;
   model Time*Vstatus(0)=LogBUN HGB Contrived /
      firth risklimits=pl itprint;
run;
```

PROC PHREG uses the penalized likelihood maximum to obtain a finite estimate for the coefficient of Contrived (Output 86.4.2). The much preferred profile-likelihood confidence limits, as shown in (Heinze and Schemper 2001), are also displayed.

Output 86.4.2 Convergence Obtained with the Firth Correction

The PHREG Procedure

Maximum Likelihood Iteration History

Iter	Ridge	Log Likelihood	LogBUN	HGB	Contrived
0	0	-150.7361197494	0.0000000000	0.000000000	0.0000000000
1	0	-136.9933949142	2.0262484120	-0.086519138	1.4338859318
2	0	-134.5796594364	1.6770836974	-0.109172604	2.6221444778
3	0	-134.1572923217	1.7163408994	-0.111166227	3.4458043289
4	0	-134.1229607193	1.7209210332	-0.112007726	3.7923555412
5	0	-134.1228364805	1.7219588214	-0.112178328	3.8174197804
6	0	-134.1228355256	1.7220081673	-0.112187764	3.8151642206

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Profile Likelihood Confidence Limits	
LogBUN	1	1.72201	0.58379	8.7008	0.0032	5.596	1.761	17.231
HGB	1	-0.11219	0.06059	3.4279	0.0641	0.894	0.794	1.007
Contrived	1	3.81516	1.55812	5.9955	0.0143	45.384	5.406	6005.404

Example 86.5: Conditional Logistic Regression for m:n Matching

Conditional logistic regression is used to investigate the relationship between an outcome and a set of prognostic factors in matched case-control studies. The outcome is whether the subject is a case or a control. If there is only one case and one control, the matching is 1:1. The *m:n* matching refers to the situation in which there is a varying number of cases and controls in the matched sets. You can perform conditional logistic regression with the PHREG procedure by using the discrete logistic model and forming a stratum for each matched set. In addition, you need to create dummy survival times so that all the cases in a matched set have the same event time value, and the corresponding controls are censored at later times.

Consider the following set of low infant birth-weight data extracted from Appendix 1 of Hosmer and Lemeshow (1989). These data represent 189 women, of whom 59 had low-birth-weight babies and 130 had normal-weight babies. Under investigation are the following risk factors: weight in pounds at the last menstrual period (LWT), presence of hypertension (HT), smoking status during pregnancy (Smoke), and presence of uterine irritability (UI). For HT, Smoke, and UI, a value of 1 indicates a "yes" and a value of 0 indicates a "no." The woman's age (Age) is used as the matching variable. The SAS data set LBW contains a subset of the data corresponding to women between the ages of 16 and 32.

```
data LBW;
   input id Age Low LWT Smoke HT UI @@;
   Time=2-Low;
   datalines;
 25  16   1   130   0  0  0    143  16   0   110   0  0  0
166  16   0   112   0  0  0    167  16   0   135   1  0  0
189  16   0   135   1  0  0    206  16   0   170   0  0  0
216  16   0    95   0  0  0     37  17   1   130   1  0  1
```

```
 45  17   1   110   1  0  0     68  17   1   120   1  0  0
 71  17   1   120   0  0  0     83  17   1   142   0  1  0
 93  17   0   103   0  0  0    113  17   0   122   1  0  0
116  17   0   113   0  0  0    117  17   0   113   0  0  0
147  17   0   119   0  0  0    148  17   0   119   0  0  0
180  17   0   120   1  0  0     49  18   1   148   0  0  0
 50  18   1   110   1  0  0     89  18   0   107   1  0  1
100  18   0   100   1  0  0    101  18   0   100   1  0  0
132  18   0    90   1  0  1    133  18   0    90   1  0  1
168  18   0   229   0  0  0    205  18   0   120   1  0  0
208  18   0   120   0  0  0     23  19   1    91   1  0  1
 33  19   1   102   0  0  0     34  19   1   112   1  0  1
 85  19   0   182   0  0  1     96  19   0    95   0  0  0
 97  19   0   150   0  0  0    124  19   0   138   1  0  0
129  19   0   189   0  0  0    135  19   0   132   0  0  0
142  19   0   115   0  0  0    181  19   0   105   0  0  0
187  19   0   235   1  1  0    192  19   0   147   1  0  0
193  19   0   147   1  0  0    197  19   0   184   1  1  0
224  19   0   120   1  0  0     27  20   1   150   1  0  0
 31  20   1   125   0  0  1     40  20   1   120   1  0  0
 44  20   1    80   1  0  1     47  20   1   109   0  0  0
 51  20   1   121   1  0  1     60  20   1   122   1  0  0
 76  20   1   105   0  0  0     87  20   0   105   1  0  0
104  20   0   120   0  0  1    146  20   0   103   0  0  0
155  20   0   169   0  0  1    160  20   0   141   0  0  1
172  20   0   121   1  0  0    177  20   0   127   0  0  0
201  20   0   120   0  0  0    211  20   0   170   1  0  0
217  20   0   158   0  0  0     20  21   1   165   1  1  0
 28  21   1   200   0  0  1     30  21   1   103   0  0  0
 52  21   1   100   0  0  0     84  21   1   130   1  1  0
 88  21   0   108   1  0  1     91  21   0   124   0  0  0
128  21   0   185   1  0  0    131  21   0   160   0  0  0
144  21   0   110   1  0  1    186  21   0   134   0  0  0
219  21   0   115   0  0  0     42  22   1   130   1  0  1
 67  22   1   130   1  0  0     92  22   0   118   0  0  0
 98  22   0    95   0  1  0    137  22   0    85   1  0  0
138  22   0   120   0  1  0    140  22   0   130   1  0  0
161  22   0   158   0  0  0    162  22   0   112   1  0  0
174  22   0   131   0  0  0    184  22   0   125   0  0  0
204  22   0   169   0  0  0    220  22   0   129   0  0  0
 17  23   1    97   0  0  1     59  23   1   187   1  0  0
 63  23   1   120   0  0  0     69  23   1   110   1  0  0
 82  23   1    94   1  0  0    130  23   0   130   0  0  0
139  23   0   128   0  0  0    149  23   0   119   0  0  0
164  23   0   115   1  0  0    173  23   0   190   0  0  0
179  23   0   123   0  0  0    182  23   0   130   0  0  0
200  23   0   110   0  0  0     18  24   1   128   0  0  0
 19  24   1   132   0  1  0     29  24   1   155   1  0  0
 36  24   1   138   0  0  0     61  24   1   105   1  0  0
118  24   0    90   1  0  0    136  24   0   115   0  0  0
150  24   0   110   0  0  0    156  24   0   115   0  0  0
185  24   0   133   0  0  0    196  24   0   110   0  0  0
199  24   0   110   0  0  0    225  24   0   116   0  0  0
 13  25   1   105   0  1  0     15  25   1    85   0  0  1
```

```
 24  25   1   115   0  0  0     26  25   1    92   1  0  0
 32  25   1    89   0  0  0     46  25   1   105   0  0  0
103  25   0   118   1  0  0    111  25   0   120   0  0  1
120  25   0   155   0  0  0    121  25   0   125   0  0  0
169  25   0   140   0  0  0    188  25   0    95   1  0  1
202  25   0   241   0  1  0    215  25   0   120   0  0  0
221  25   0   130   0  0  0     35  26   1   117   1  0  0
 54  26   1    96   0  0  0     75  26   1   154   0  1  0
 77  26   1   190   1  0  0     95  26   0   113   1  0  0
115  26   0   168   1  0  0    154  26   0   133   1  0  0
218  26   0   160   0  0  0     16  27   1   150   0  0  0
 43  27   1   130   0  0  1    125  27   0   124   1  0  0
  4  28   1   120   1  0  1     79  28   1    95   1  0  0
105  28   0   120   1  0  0    109  28   0   120   0  0  0
112  28   0   167   0  0  0    151  28   0   140   0  0  0
159  28   0   250   1  0  0    212  28   0   134   0  0  0
214  28   0   130   0  0  0     10  29   1   130   0  0  1
 94  29   0   123   1  0  0    114  29   0   150   0  0  0
123  29   0   140   1  0  0    190  29   0   135   0  0  0
191  29   0   154   0  0  0    209  29   0   130   1  0  0
 65  30   1   142   1  0  0     99  30   0   107   0  0  1
141  30   0    95   1  0  0    145  30   0   153   0  0  0
176  30   0   110   0  0  0    195  30   0   137   0  0  0
203  30   0   112   0  0  0     56  31   1   102   1  0  0
107  31   0   100   0  0  1    126  31   0   215   1  0  0
163  31   0   150   1  0  0    222  31   0   120   0  0  0
 22  32   1   105   1  0  0    106  32   0   121   0  0  0
134  32   0   132   0  0  0    170  32   0   134   1  0  0
175  32   0   170   0  0  0    207  32   0   186   0  0  0
;
```

The variable Low is used to determine whether the subject is a case (Low=1, low-birth-weight baby) or a control (Low=0, normal-weight baby). The dummy time variable Time takes the value 1 for cases and 2 for controls.

The following statements produce a conditional logistic regression analysis of the data. The variable Time is the response, and Low is the censoring variable. Note that the data set is created so that all the cases have the same event time and the controls have later censored times. The matching variable Age is used in the STRATA statement so that each unique age value defines a stratum. The variables LWT, Smoke, HT, and UI are specified as explanatory variables. The TIES=DISCRETE option requests the discrete logistic model.

```
proc phreg data=LBW;
   model Time*Low(0)= LWT Smoke HT UI / ties=discrete;
   strata Age;
run;
```

The procedure displays a summary of the number of event and censored observations for each stratum. These are the number of cases and controls for each matched set shown in Output 86.5.1.

Output 86.5.1 Summary of Number of Case and Controls

The PHREG Procedure

Model Information	
Data Set	WORK.LBW
Dependent Variable	Time
Censoring Variable	Low
Censoring Value(s)	0
Ties Handling	DISCRETE

Summary of the Number of Event and Censored Values

Stratum	Age	Total	Event	Censored	Percent Censored
1	16	7	1	6	85.71
2	17	12	5	7	58.33
3	18	10	2	8	80.00
4	19	16	3	13	81.25
5	20	18	8	10	55.56
6	21	12	5	7	58.33
7	22	13	2	11	84.62
8	23	13	5	8	61.54
9	24	13	5	8	61.54
10	25	15	6	9	60.00
11	26	8	4	4	50.00
12	27	3	2	1	33.33
13	28	9	2	7	77.78
14	29	7	1	6	85.71
15	30	7	1	6	85.71
16	31	5	1	4	80.00
17	32	6	1	5	83.33
Total		174	54	120	68.97

Results of the conditional logistic regression analysis are shown in Output 86.5.2. Based on the Wald test for individual variables, the variables LWT, Smoke, and HT are statistically significant while UI is marginal.

The hazard ratios, computed by exponentiating the parameter estimates, are useful in interpreting the results of the analysis. If the hazard ratio of a prognostic factor is larger than 1, an increment in the factor increases the hazard rate. If the hazard ratio is less than 1, an increment in the factor decreases the hazard rate. Results indicate that women were more likely to have low-birth-weight babies if they were underweight in the last menstrual cycle, were hypertensive, smoked during pregnancy, or suffered uterine irritability.

Output 86.5.2 Conditional Logistic Regression Analysis for the Low-Birth-Weight Study

Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Output 86.5.2 *continued*

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	159.069	141.108
AIC	159.069	149.108
SBC	159.069	157.064

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	17.9613	4	0.0013
Score	17.3152	4	0.0017
Wald	15.5577	4	0.0037

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
LWT	1	-0.01498	0.00706	4.5001	0.0339	0.985
Smoke	1	0.80805	0.36797	4.8221	0.0281	2.244
HT	1	1.75143	0.73932	5.6120	0.0178	5.763
UI	1	0.88341	0.48032	3.3827	0.0659	2.419

For matched case-control studies with one case per matched set (1:n matching), the likelihood function for the conditional logistic regression reduces to that of the Cox model for the continuous time scale. For this situation, you can use the default TIES=BRESLOW.

Example 86.6: Model Using Time-Dependent Explanatory Variables

Time-dependent variables can be used to model the effects of subjects transferring from one treatment group to another. One example of the need for such strategies is the Stanford heart transplant program. Patients are accepted if physicians judge them suitable for heart transplant. Then, when a donor becomes available, physicians choose transplant recipients according to various medical criteria. A patient's status can be changed during the study from waiting for a transplant to being a transplant recipient. Transplant status can be defined by the time-dependent covariate function $z = z(t)$ as

$$z(t) = \begin{cases} 0 & \text{if the patient has not received the transplant at time } t \\ 1 & \text{if the patient has received the transplant at time } t \end{cases}$$

The Stanford heart transplant data that appear in Crowley and Hu (1977) consist of 103 patients, 69 of whom received transplants. The data are saved in a SAS data set called Heart in the following DATA step. For each patient in the program, there is a birth date (Bir_Date), a date of acceptance (Acc_Date), and a date last seen (Ter_Date). The survival time (Time) in days is defined as Time = Ter_Date – Acc_Date. The survival time is said to be uncensored (Status=1) or censored (Status=0), depending on whether Ter_Date is the date of death or the closing date of the study. The age, in years, at acceptance into the program is Acc_Age = (Acc_Date – Bir_Date) / 365. Previous open-heart surgery for each patient is indicated by the variable PrevSurg. For each transplant recipient, there is a date of transplant (Xpl_Date) and three measures (NMismatch, Antigen, Mismatch) of tissue-type mismatching. The waiting period (WaitTime) in days for a transplant recipient is calculated as WaitTime = Xpl_Date – Acc_Date, and the age (in years) at transplant is Xpl_Age = (Xpl_Date –

Bir_Date) / 365. For those who do not receive heart transplants, the WaitTime, Xpl_Age, NMismatch, Antigen, and Mismatch variables contain missing values.

The input data contain dates that have a two-digit year representation. The SAS option YEARCUTOFF=1900 is specified to ensure that a two-digit year xx is year 19xx.

```
options yearcutoff=1900;
data Heart;
   input ID
         @5  Bir_Date mmddyy8.
         @14 Acc_Date mmddyy8.
         @23 Xpl_Date mmddyy8.
         @32 Ter_Date mmddyy8.
         @41 Status 1.
         @43 PrevSurg 1.
         @45 NMismatch 1.
         @47 Antigen 1.
         @49 Mismatch 4.
         @54 Reject 1.
         @56 NotTyped $1.;
   label Bir_Date ='Date of birth'
         Acc_Date ='Date of acceptance'
         Xpl_Date ='Date of transplant'
         Ter_Date ='Date last seen'
         Status   =  'Dead=1 Alive=0'
         PrevSurg ='Previous surgery'
         NMismatch= 'No of mismatches'
         Antigen  = 'HLA-A2 antigen'
         Mismatch ='Mismatch score'
         NotTyped = 'y=not tissue-typed';
   Time= Ter_Date - Acc_Date;
   Acc_Age=int( (Acc_Date - Bir_Date)/365 );
   if ( Xpl_Date ne .) then do;
      WaitTime= Xpl_Date - Acc_Date;
      Xpl_Age= int( (Xpl_Date - Bir_Date)/365 );
   end;
   datalines;
 1 01 10 37 11 15 67          01 03 68 1 0
 2 03 02 16 01 02 68          01 07 68 1 0
 3 09 19 13 01 06 68 01 06 68 01 21 68 1 0 2 0 1.11 0
 4 12 23 27 03 28 68 05 02 68 05 05 68 1 0 3 0 1.66 0
 5 07 28 47 05 10 68          05 27 68 1 0
 6 11 08 13 06 13 68          06 15 68 1 0
 7 08 29 17 07 12 68 08 31 68 05 17 70 1 0 4 0 1.32 1
 8 03 27 23 08 01 68          09 09 68 1 0
 9 06 11 21 08 09 68          11 01 68 1 0
10 02 09 26 08 11 68 08 22 68 10 07 68 1 0 2 0 0.61 1
11 08 22 20 08 15 68 09 09 68 01 14 69 1 0 1 0 0.36 0
12 07 09 15 09 17 68          09 24 68 1 0
13 02 22 14 09 19 68 10 05 68 12 08 68 1 0 3 0 1.89 1
14 09 16 14 09 20 68 10 26 68 07 07 72 1 0 1 0 0.87 1
15 12 04 14 09 27 68          09 27 68 1 1
16 05 16 19 10 26 68 11 22 68 08 29 69 1 0 2 0 1.12 1
17 06 29 48 10 28 68          12 02 68 1 0
```

```
18 12 27 11 11 01 68 11 20 68 12 13 68 1 0 3 0 2.05 0
19 10 04 09 11 18 68          12 24 68 1 0
20 10 19 13 01 29 69 02 15 69 02 25 69 1 0 3 1 2.76 1
21 09 29 25 02 01 69 02 08 69 11 29 71 1 0 2 0 1.13 1
22 06 05 26 03 18 69 03 29 69 05 07 69 1 0 3 0 1.38 1
23 12 02 10 04 11 69 04 13 69 04 13 71 1 0 3 0 0.96 1
24 07 07 17 04 25 69 07 16 69 11 29 69 1 0 3 1 1.62 1
25 02 06 36 04 28 69 05 22 69 04 01 74 0 0 2 0 1.06 0
26 10 18 38 05 01 69          03 01 73 0 0
27 07 21 60 05 04 69          01 21 70 1 0
28 05 30 15 06 07 69 08 16 69 08 17 69 1 0 2 0 0.47 0
29 02 06 19 07 14 69          08 17 69 1 0
30 09 20 24 08 19 69 09 03 69 12 18 71 1 0 4 0 1.58 1
31 10 04 14 08 23 69          09 07 69 1 0
32 04 02 05 08 29 69 09 14 69 11 13 69 1 0 4 0 0.69 1
33 01 01 21 11 27 69 01 16 70 04 01 74 0 0 3 0 0.91 0
34 05 24 29 12 12 69 01 03 70 04 01 74 0 0 2 0 0.38 0
35 08 04 26 01 21 70          02 01 70 1 0
36 05 01 21 04 04 70 05 19 70 07 12 70 1 0 2 0 2.09 1
37 10 24 08 04 25 70 05 13 70 06 29 70 1 0 3 1 0.87 1
38 11 14 28 05 05 70 05 09 70 05 09 70 1 0 3 0 0.87 0
39 11 12 19 05 20 70 05 21 70 07 11 70 1 0             y
40 11 30 21 05 25 70 07 04 70 04 01 74 0 1 4 0 0.75 0
41 04 30 25 08 19 70 10 15 70 04 01 74 0 1 2 0 0.98 0
42 03 13 34 08 21 70          08 23 70 1 0
43 06 01 27 10 22 70          10 23 70 1 1
44 05 02 28 11 30 70          01 08 71 1 1
45 10 30 34 01 05 71 01 05 71 02 18 71 1 0 1 0 0.0  0
46 06 01 22 01 10 71 01 11 71 10 01 73 1 1 2 0 0.81 1
47 12 28 23 02 02 71 02 22 71 04 14 71 1 0 3 0 1.38 1
48 01 23 15 02 05 71          02 13 71 1 0
49 06 21 34 02 15 71 03 22 71 04 01 74 0 1 4 0 1.35 0
50 03 28 25 02 15 71 05 08 71 10 21 73 1 1             y
51 06 29 22 03 24 71 04 24 71 01 02 72 1 0 4 1 1.08 1
52 01 24 30 04 25 71          08 04 71 1 0
53 02 27 24 07 02 71 08 11 71 01 05 72 1 0             y
54 09 16 23 07 02 71          07 04 71 1 0
55 02 24 19 08 09 71 08 18 71 10 08 71 1 0 2 0 1.51 1
56 12 05 32 09 03 71 11 08 71 04 01 74 0 0 4 0 0.98 0
57 06 08 30 09 13 71          02 08 72 1 0
58 09 17 23 09 23 71 10 13 71 08 30 72 1 1 2 1 1.82 1
59 05 12 30 09 29 71 12 15 71 04 01 74 0 1 2 0 0.19 0
60 10 29 22 11 18 71 11 20 71 01 24 72 1 0 3 0 0.66 1
61 05 12 19 12 04 71          12 05 71 1 0
62 08 01 32 12 09 71          02 15 72 1 0
63 04 15 39 12 12 71 01 07 72 04 01 74 0 0 3 1 1.93 0
64 04 09 23 02 01 72 03 04 72 09 06 73 1 1 1 0 0.12 0
65 11 19 20 03 06 72 03 17 72 05 22 72 1 0 2 0 1.12 1
66 01 02 19 03 20 72          04 20 72 1 0
67 09 03 52 03 23 72 05 18 72 01 01 73 1 0 3 0 1.02 0
68 01 10 27 04 07 72 04 09 72 06 13 72 1 0 3 1 1.68 1
69 06 05 24 06 01 72 06 10 72 04 01 74 0 0 2 0 1.20 0
70 06 17 19 06 17 72 06 21 72 07 16 72 1 0 3 1 1.68 1
71 02 22 25 07 21 72 08 20 72 04 01 74 0 0 3 0 0.97 0
```

```
 72 11 22 45 08 14 72 08 17 72 04 01 74 0 0 3 1 1.46 0
 73 05 13 16 09 11 72 10 07 72 12 09 72 1 0 3 1 2.16 1
 74 07 20 43 09 18 72 09 22 72 10 04 72 1 0 1 0 0.61 0
 75 07 25 20 09 29 72           09 30 72 1 0
 76 09 03 20 10 04 72 11 18 72 04 01 74 0 1 3 1 1.70 0
 77 08 27 31 10 06 72           10 26 72 1 0
 78 02 20 24 11 03 72 05 31 73 04 01 74 0 0 3 0 0.81 0
 79 02 18 19 11 30 72 02 04 73 03 05 73 1 0 2 0 1.08 1
 80 06 27 26 12 06 72 12 31 72 04 01 74 0 1 3 0 1.41 0
 81 02 21 20 01 12 73 01 17 73 04 01 74 0 0 4 1 1.94 0
 82 08 19 42 11 01 71           01 01 73 0 0
 83 10 04 19 01 24 73 02 24 73 04 13 73 1 0 4 0 3.05 0
 84 05 13 30 01 30 73 03 07 73 12 29 73 1 0 4 0 0.60 1
 85 02 13 25 02 06 73           02 10 73 1 0
 86 03 30 24 03 01 73 03 08 73 04 01 74 0 0 3 1 1.44 0
 87 12 19 26 03 21 73 05 19 73 07 08 73 1 0 2 0 2.25 1
 88 11 16 18 03 28 73 04 27 73 04 01 74 0 0 3 0 0.68 0
 89 03 19 22 04 05 73 08 21 73 10 28 73 1 0 4 1 1.33 1
 90 03 25 21 04 06 73 09 12 73 10 08 73 1 1 3 1 0.82 0
 91 09 08 25 04 13 73           03 18 74 1 0
 92 05 03 28 04 27 73 03 02 74 04 01 74 0 0 1 0 0.16 0
 93 10 10 25 07 11 73 08 07 73 04 01 74 0 0 2 0 0.33 0
 94 11 11 29 09 14 73 09 17 73 02 25 74 1 1 3 0 1.20 1
 95 06 11 33 09 22 73 09 23 73 10 07 73 1 0             y
 96 02 09 47 10 04 73 10 16 73 04 01 74 0 0 2 0 0.46 0
 97 04 11 50 11 22 73 12 12 73 04 01 74 0 0 3 1 1.78 0
 98 04 28 45 12 14 73 03 19 74 04 01 74 0 0 4 1 0.77 0
 99 02 24 24 12 25 73           01 14 74 1 0
100 01 31 39 02 22 74 03 31 74 04 01 74 0 1 3 0 0.67 0
101 08 25 24 03 02 74           04 01 74 0 0
102 10 30 33 03 22 74           04 01 74 0 0
103 05 20 28 09 13 67           09 18 67 1 0
;
```

Crowley and Hu (1977) have presented a number of analyses to assess the effects of various explanatory variables on the survival of patients. This example fits two of the models that they have considered.

The first model consists of two explanatory variables—the transplant status and the age at acceptance. The transplant status (XStatus) is a time-dependent variable defined by the programming statements between the MODEL statement and the RUN statement. The XStatus variable takes the value 1 or 0 at time t (measured from the date of acceptance), depending on whether or not the patient has received a transplant at that time. Note that the value of XStatus changes for subjects in each risk set (subjects still alive just before each distinct event time); therefore, the variable cannot be created in the DATA step. The variable Acc_Age, which is not time dependent, accounts for the possibility that pretransplant risks vary with age. The following statements fit this model:

```
proc phreg data= Heart;
   model Time*Status(0)= XStatus Acc_Age;
   if (WaitTime = . or Time < WaitTime) then XStatus=0.;
   else  XStatus= 1.0;
run;
```

Results of this analysis are shown in Output 86.6.1. Transplantation appears to be associated with a slight decrease in risk, although the effect is not significant ($p = 0.8261$). The age at acceptance as a pretransplant risk factor adds significantly to the model ($p = 0.0289$). The risk increases significantly with age at acceptance.

Output 86.6.1 Heart Transplant Study Analysis I

The PHREG Procedure

Model Information		
Data Set	WORK.HEART	
Dependent Variable	Time	
Censoring Variable	Status	Dead=1 Alive=0
Censoring Value(s)	0	
Ties Handling	BRESLOW	

Number of Observations Read	103
Number of Observations Used	103

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
103	75	28	27.18

Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	596.651	591.292
AIC	596.651	595.292
SBC	596.651	599.927

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	5.3593	2	0.0686
Score	4.8093	2	0.0903
Wald	4.7999	2	0.0907

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
XStatus	1	-0.06720	0.30594	0.0482	0.8261	0.935
Acc_Age	1	0.03158	0.01446	4.7711	0.0289	1.032

The second model consists of three explanatory variables—the transplant status, the transplant age, and the mismatch score. Four transplant recipients who were not typed have no Mismatch values; they are excluded from the analysis by the use of a WHERE clause. The transplant age (XAge) and the mismatch score (XScore) are also time dependent and are defined in a fashion similar to that of XStatus. While the patient is waiting for a transplant, XAge and XScore have a value of 0. After the patient has migrated to the recipient population, XAge takes on the value of Xpl_Age (transplant age for the recipient), and XScore takes on the value of Mismatch (a measure of the degree of dissimilarity between donor and recipient). The following statements fit this model:

```
proc phreg data= Heart;
   model Time*Status(0)= XStatus XAge XScore;
   where NotTyped ^= 'y';
   if (WaitTime = . or Time < WaitTime) then do;
      XStatus=0.;
      XAge=0.;
      XScore= 0.;
   end;
   else do;
      XStatus= 1.0;
      XAge= Xpl_Age;
      XScore= Mismatch;
   end;
run;
```

Results of the analysis are shown in Output 86.6.2. Note that only 99 patients are included in this analysis, instead of 103 patients as in the previous analysis, since four transplant recipients who were not typed are excluded. The variable XAge is statistically significant ($p = 0.0143$), with a hazard ratio exceeding 1. Therefore, patients who had a transplant at younger ages lived longer than those who received a transplant later in their lives. The variable XScore has only minimal effect on the survival ($p = 0.1121$).

Output 86.6.2 Heart Transplant Study Analysis II

The PHREG Procedure

Model Information		
Data Set	WORK.HEART	
Dependent Variable	Time	
Censoring Variable	Status	Dead=1 Alive=0
Censoring Value(s)	0	
Ties Handling	BRESLOW	

Number of Observations Read	99
Number of Observations Used	99

Summary of the Number of Event and Censored Values			
Total	Event	Censored	Percent Censored
99	71	28	28.28

Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	561.680	551.874
AIC	561.680	557.874
SBC	561.680	564.662

Output 86.6.2 *continued*

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	9.8059	3	0.0203
Score	9.0521	3	0.0286
Wald	9.0554	3	0.0286

Analysis of Maximum Likelihood Estimates						
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**
XStatus	1	-3.19837	1.18746	7.2547	0.0071	0.041
XAge	1	0.05544	0.02263	6.0019	0.0143	1.057
XScore	1	0.44490	0.28001	2.5245	0.1121	1.560

Example 86.7: Time-Dependent Repeated Measurements of a Covariate

Repeated determinations can be made during the course of a study of variables thought to be related to survival. Consider an experiment to study the dosing effect of a tumor-promoting agent. Forty-five rodents initially exposed to a carcinogen were randomly assigned to three dose groups. After the first death of an animal, the rodents were examined every week for the number of papillomas. Investigators were interested in determining the effects of dose on the carcinoma incidence after adjusting for the number of papillomas.

The input data set TUMOR consists of the following 19 variables:

- ID (subject identification)
- Time (survival time of the subject)
- Dead (censoring status where 1=dead and 0=censored)
- Dose (dose of the tumor-promoting agent)
- P1–P15 (number of papillomas at the 15 times that animals died. These 15 death times are weeks 27, 34, 37, 41, 43, 45, 46, 47, 49, 50, 51, 53, 65, 67, and 71. For instance, subject 1 died at week 47; it had no papilloma at week 27, five papillomas at week 34, six at week 37, eight at week 41, and 10 at weeks 43, 45, 46, and 47. For an animal that died before week 71, the number of papillomas is missing for those times beyond its death.)

The following SAS statements create the data set TUMOR:

```
data Tumor;
   infile datalines missover;
   input ID Time Dead Dose P1-P15;
   label ID='Subject ID';
   datalines;
 1 47 1  1.0  0  5  6  8 10 10 10 10
 2 71 1  1.0  0  0  0  0  0  0  0  0  1  1  1  1 1 1 1
 3 81 0  1.0  0  1  1  1  1  1  1  1  1  1  1  1 1 1 1
 4 81 0  1.0  0  0  0  0  0  0  0  0  0  0  0  0 0 0 0
 5 81 0  1.0  0  0  0  0  0  0  0  0  0  0  0  0 0 0 0
```

```
 6 65 1  1.0  0  0  0  1  1  1  1  1  1  1  1  1 1
 7 71 0  1.0  0  0  0  0  0  0  0  0  0  0  0  0 0 0 0
 8 69 0  1.0  0  0  0  0  0  0  0  0  0  0  0  0 0 0
 9 67 1  1.0  0  0  1  1  2  2  2  2  3  3  3  3 3 3
10 81 0  1.0  0  0  0  0  0  0  0  0  0  0  0  0 0 0 0
11 37 1  1.0  9  9  9
12 81 0  1.0  0  0  0  0  0  0  0  0  0  0  0  0 0 0 0
13 77 0  1.0  0  0  0  0  1  1  1  1  1  1  1  1 1 1 1
14 81 0  1.0  0  0  0  0  0  0  0  0  0  0  0  0 0 0 0
15 81 0  1.0  0  0  0  0  0  0  0  0  0  0  0  0 0 0 0
16 54 0  2.5  0  1  1  1  2  2  2  2  2  2  2  2
17 53 0  2.5  0  0  0  0  0  0  0  0  0  0  0  0
18 38 0  2.5  5 13 14
19 54 0  2.5  2  6  6  6  6  6  6  6  6  6  6  6
20 51 1  2.5 15 15 15 16 16 17 17 17 17 17 17
21 47 1  2.5 13 20 20 20 20 20 20 20
22 27 1  2.5 22
23 41 1  2.5  6 13 13 13
24 49 1  2.5  0  3  3  3  3  3  3  3  3
25 53 0  2.5  0  0  1  1  1  1  1  1  1  1  1  1
26 50 1  2.5  0  0  2  3  4  6  6  6  6  6
27 37 1  2.5  3 15 15
28 49 1  2.5  2  3  3  3  3  4  4  4  4
29 46 1  2.5  4  6  7  9  9  9  9
30 48 0  2.5 15 26 26 26 26 26 26 26
31 54 0 10.0 12 14 15 15 15 15 15 15 15 15 15 15
32 37 1 10.0 12 16 17
33 53 1 10.0  3  6  6  6  6  6  6  6  6  6  6  6
34 45 1 10.0  4 12 15 20 20 20
35 53 0 10.0  6 10 13 13 13 15 15 15 15 15 15 20
36 49 1 10.0  0  2  2  2  2  2  2  2  2
37 39 0 10.0  7  8  8
38 27 1 10.0 17
39 49 1 10.0  0  6  9 14 14 14 14 14 14
40 43 1 10.0 14 18 20 20 20
41 28 0 10.0  8
42 34 1 10.0 11 18
43 45 1 10.0 10 12 16 16 16 16
44 37 1 10.0  0  1  1
45 43 1 10.0  9 19 19 19 19
;
```

The number of papillomas (NPap) for each animal in the study was measured repeatedly over time. One way of handling time-dependent repeated measurements in the PHREG procedure is to use programming statements to capture the appropriate covariate values of the subjects in each risk set. In this example, NPap is a time-dependent explanatory variable with values that are calculated by means of the programming statements shown in the following SAS statements:

```
proc phreg data=Tumor;
   model Time*Dead(0)=Dose NPap;
   array pp{*} P1-P14;
   array tt{*} t1-t15;
   t1=27;  t2=34;  t3=37;  t4=41;  t5=43;
   t6=45;  t7=46;  t8=47;  t9=49; t10=50;
```

```
   t11=51; t12=53; t13=65; t14=67; t15=71;
   if Time <  tt[1]  then NPap=0;
   else if time >= tt[15] then NPap=P15;
   else do i=1 to dim(pp);
      if tt[i] <= Time < tt[i+1] then NPap= pp[i];
   end;
run;
```

At each death time, the NPap value of each subject in the risk set is recalculated to reflect the actual number of papillomas at the given death time. For instance, subject one in the data set Tumor was in the risk sets at weeks 27 and 34; at week 27, the animal had no papilloma, while at week 34, it had five papillomas. Results of the analysis are shown in Output 86.7.1. After the number of papillomas is adjusted for, the dose effect of the tumor-promoting agent is not statistically significant.

Output 86.7.1 Cox Regression Analysis on the Survival of Rodents

The PHREG Procedure

Model Information	
Data Set	WORK.TUMOR
Dependent Variable	Time
Censoring Variable	Dead
Censoring Value(s)	0
Ties Handling	BRESLOW

Number of Observations Read	45
Number of Observations Used	45

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
45	25	20	44.44

Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	166.793	143.269
AIC	166.793	147.269
SBC	166.793	149.707

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	23.5243	2	<.0001
Score	28.0498	2	<.0001
Wald	21.1646	2	<.0001

Output 86.7.1 *continued*

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Dose	1	0.06885	0.05620	1.5010	0.2205	1.071
NPap	1	0.11714	0.02998	15.2705	<.0001	1.124

Another way to handle time-dependent repeated measurements in the PHREG procedure is to use the counting process style of input. Multiple records are created for each subject, one record for each distinct pattern of the time-dependent measurements. Each record contains a T1 value and a T2 value representing the time interval (T1,T2] during which the values of the explanatory variables remain unchanged. Each record also contains the censoring status at T2.

One advantage of using the counting process formulation is that you can easily obtain various residuals and influence statistics that are not available when programming statements are used to compute the values of the time-dependent variables. On the other hand, creating multiple records for the counting process formulation requires extra effort in data manipulation.

Consider a counting process style of input data set named Tumor1. It contains multiple observations for each subject in the data set Tumor. In addition to variables ID, Time, Dead, and Dose, four new variables are generated:

- T1 (left endpoint of the risk interval)
- T2 (right endpoint of the risk interval)
- NPap (number of papillomas in the time interval (T1,T2])
- Status (censoring status at T2)

For example, five observations are generated for the rodent that died at week 47 and that had no papilloma at week 27, five papillomas at week 34, six at week 37, eight at week 41, and 10 at weeks 43, 45, 46, and 47. The values of T1, T2, NPap, and Status for these five observations are (0,27,0,0), (27,34,5,0), (34,37,6,0), (37,41,8,0), and (41,47,10,1). Note that the variables ID, Time, and Dead are not needed for the estimation of the regression parameters, but they are useful for plotting the residuals.

The following SAS statements create the data set Tumor1:

```
data Tumor1(keep=ID Time Dead Dose T1 T2 NPap Status);
   array pp{*} P1-P14;
   array qq{*} P2-P15;
   array tt{1:15} _temporary_
      (27 34 37 41 43 45 46 47 49 50 51 53 65 67 71);
   set Tumor;
   T1 = 0;
   T2 = 0;
   Status = 0;
   if ( Time = tt[1] ) then do;
      T2 = tt[1];
      NPap = p1;
      Status = Dead;
```

```
      output;
   end;
   else do _i_=1 to dim(pp);
      if ( tt[_i_] = Time ) then do;
         T2= Time;
         NPap = pp[_i_];
         Status = Dead;
         output;
      end;
      else if (tt[_i_]  < Time ) then do;
         if (pp[_i_]  ^= qq[_i_] ) then do;
            if qq[_i_]  = . then T2= Time;
            else                 T2= tt[_i_];
            NPap= pp[_i_];
            Status= 0;
            output;
            T1 = T2;
         end;
      end;
   end;
   if ( Time >= tt[15] ) then do;
      T2 = Time;
      NPap = P15;
      Status = Dead;
      output;
   end;
run;
```

In the following SAS statements, the counting process MODEL specification is used. The DFBETA statistics are output to a SAS data set named Out1. Note that Out1 contains multiple observations for each subject—that is, one observation for each risk interval (T1,T2].

```
proc phreg data=Tumor1 noprint;
   model (T1,T2)*Status(0)=Dose NPap;
   output out=Out1 resmart=Mart dfbeta=db1-db2;
   id ID Time Dead;
run;
```

The output from PROC PHREG (not shown) is identical to Output 86.7.1 except for the "Summary of the Number of Event and Censored Values" table. The number of event observations remains unchanged between the two specifications of PROC PHREG, but the number of censored observations differs due to the splitting of each subject's data into multiple observations for the counting process style of input.

Next, the MEANS procedure sums up the component statistics for each subject and outputs the results to a SAS data set named Out2:

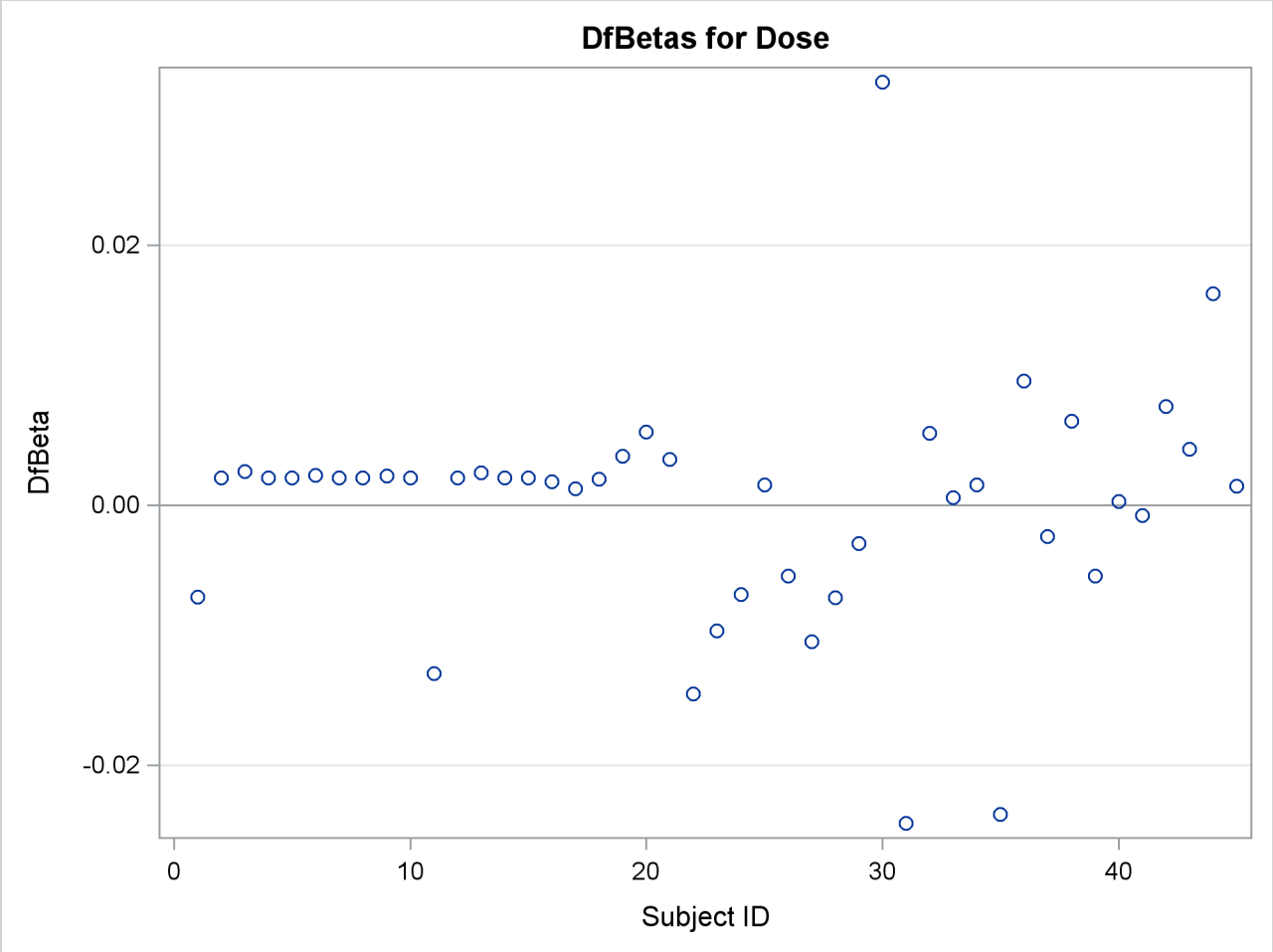
```
proc means data=Out1 noprint;
   by ID Time Dead;
   var Mart db1-db2;
   output out=Out2 sum=Mart db_Dose db_NPap;
run;
```

Finally, DFBETA statistics are plotted against subject ID for easy identification of influential points:

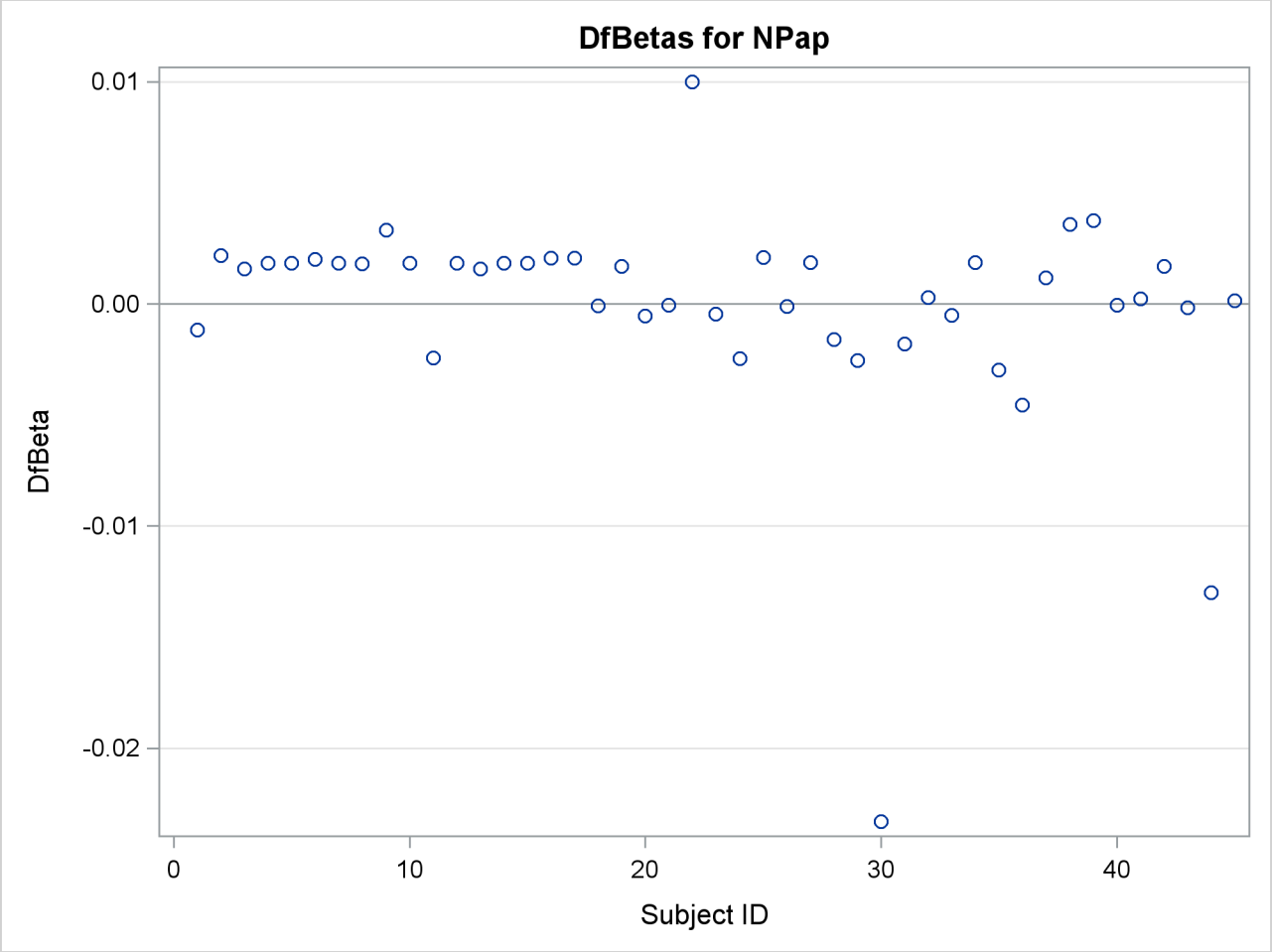
```
title 'DfBetas for Dose';
proc sgplot data=Out2;
   yaxis label="DfBeta" grid;
   refline 0 / axis=y;
   scatter y=db_Dose x=ID;
run;
title 'DfBetas for NPap';
proc sgplot data=Out2;
   yaxis label="DfBeta" grid;
   refline 0 / axis=y;
   scatter y=db_NPap x=ID;
run;
```

The plots of the DFBETA statistics are shown in Output 86.7.2 and Output 86.7.3. Subject 30 appears to have a large influence on both the Dose and NPap coefficients. Subjects 31 and 35 have considerable influences on the DOSE coefficient, while subjects 22 and 44 have rather large influences on the NPap coefficient.

Output 86.7.2 Plot of DFBETA Statistic for DOSE versus Subject Number



Output 86.7.3 Plot of DFBETA Statistic for NPAP versus Subject Number



Example 86.8: Survival Curves

You might want to use your regression analysis results to predict the survivorship of subjects of specific covariate values. The COVARIATES= data set in the BASELINE statement enables you to specify the sets of covariate values for the prediction. On the other hand, you might want to summarize the survival experience of an average patient for a given population. The DIRADJ option in the BASELINE statement computes the direct adjusted survival curve that averages the estimated survival curves for patients whose covariates are represented in the COVARIATES= data set. By using the PLOTS= option in the PROC PHREG statement, you can use ODS Graphics to display the predicted survival curves. You can elect to output the predicted survival curves in a SAS data set by optionally specifying the OUT= option in the BASELINE statement. This example illustrates how to obtain the covariate-specific survival curves and the direct adjusted survival curve by using the Myeloma data set in Example 86.1, where variables LogBUN and HGB were identified as the most important prognostic factors. Suppose you want to compute the predicted survival curves for two sets of covariate values: (LogBUN=1.0, HGB=10) and (LogBUN=1.8, HGB=12). These values are saved in the data set Inrisks in the following DATA step. Also created in this data set is the variable Id, whose values will be used in identifying the covariate sets in the survival plot.

```
data Inrisks;
   length Id $20;
   input LogBUN HGB Id $12-31;
   datalines;
1.00 10.0  logBUN=1.0 HGB=10
1.80 12.0  logBUN=1.8 HGB=12
;
```

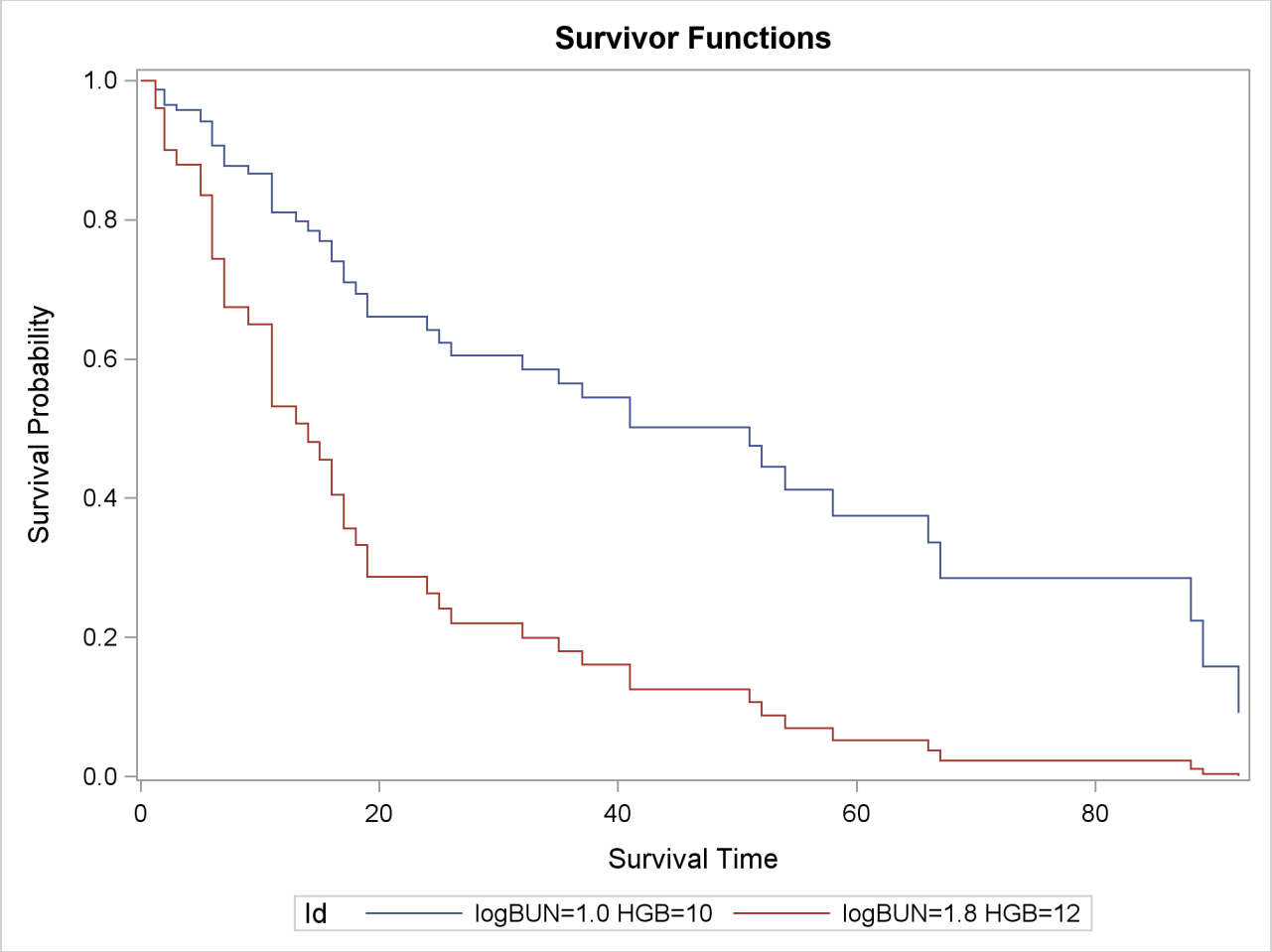
The following statements plot the survival functions in Output 86.8.1 and save the survival estimates in the data set Pred1:

```
ods graphics on;
proc phreg data=Myeloma plots(overlay)=survival;
   model Time*VStatus(0)=LogBUN HGB;
   baseline covariates=Inrisks out=Pred1 survival=_all_/rowid=Id;
run;
```

The COVARIATES= option in the BASELINE statement specifies the data set that contains the set of covariates of interest. The PLOTS= option in the PROC PHREG statement creates the survival plot. The OVERLAY suboption overlays the two curves in the same plot. If the OVERLAY suboption is not specified, each curve is displayed in a separate plot. The ROWID= option in the BASELINE statement specifies that the values of the variable Id in the COVARIATES= data set be used to identify the curves in the plot. The SURVIVAL=_ALL_ option in the BASELINE statement requests that the estimated survivor function, standard error, and lower and upper confidence limits for the survivor function be output into the SAS data set that is specified in the OUT= option.

The survival Plot (Output 86.8.1) contains two curves, one for each of row of covariates in the data set Inrisks.

Output 86.8.1 Estimated Survivor Function Plot



The following statements print out the observations in the data set Pred1 for the realization LogBUN=1.00 and HGB=10.0:

```
proc print data=Pred1(where=(logBUN=1 and HGB=10));
run;
```

As shown in Output 86.8.2, 32 observations represent the survivor function for the realization LogBUN=1.00 and HGB=10.0. The first observation has survival time 0 and survivor function estimate 1.0. Each of the remaining 31 observations represents a distinct event time in the input data set Myeloma. These observations are presented in ascending order of the event times. Note that all the variables in the COVARIATES=lnRisks data set are included in the OUT=Pred1 data set. Likewise, you can print out the observations that represent the survivor function for the realization LogBUN=1.80 and HGB=12.0.

Output 86.8.2 Survivor Function Estimates for LogBUN=1.0 and HGB=10.0

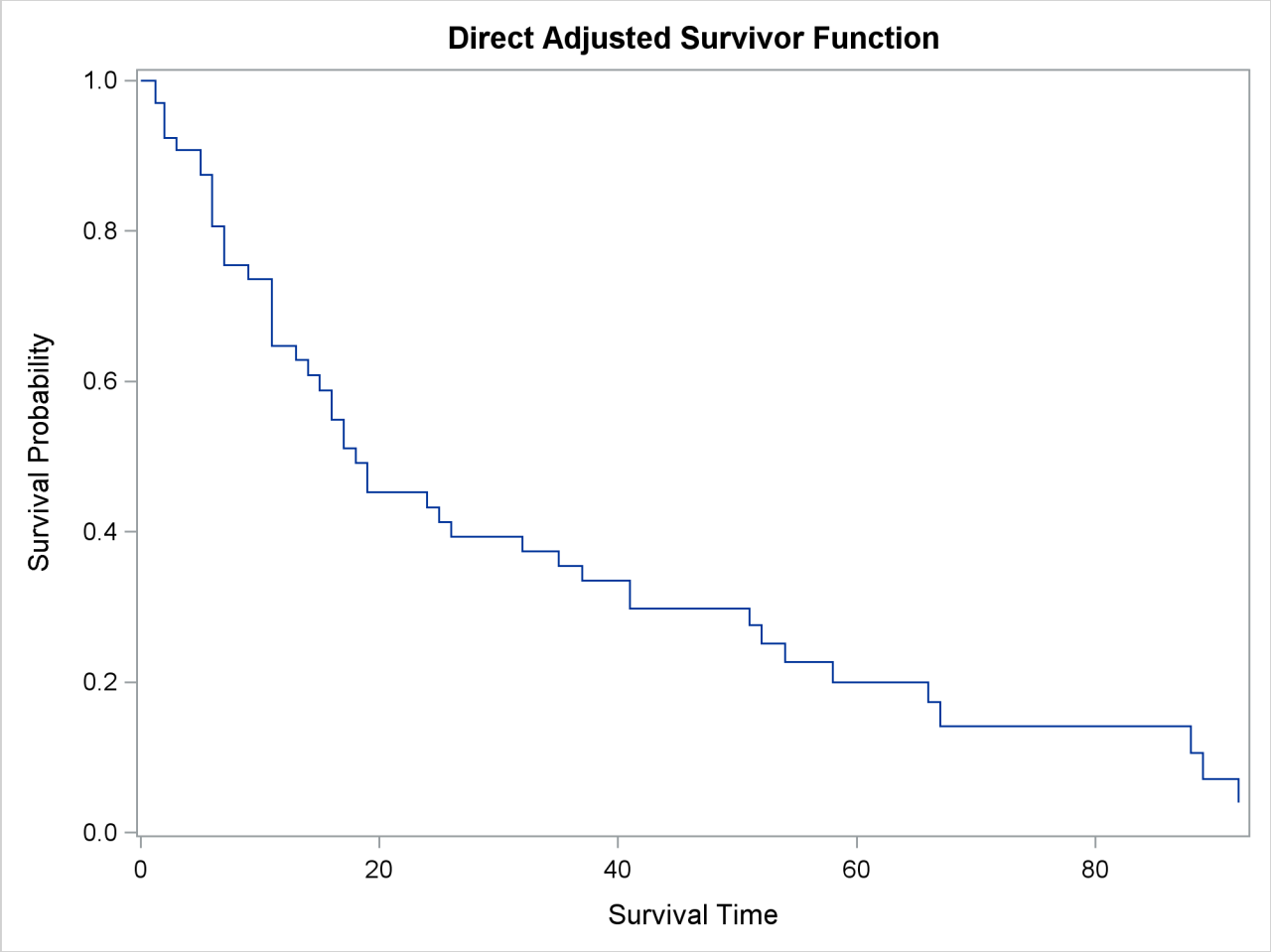
Obs	Id	LogBUN	HGB	Time	Survival	StdErrSurvival	LowerSurvival	UpperSurvival
1	logBUN=1.0 HGB=10	1	10	0.00	1.00000	.	.	.
2	logBUN=1.0 HGB=10	1	10	1.25	0.98678	0.01043	0.96655	1.00000
3	logBUN=1.0 HGB=10	1	10	2.00	0.96559	0.01907	0.92892	1.00000
4	logBUN=1.0 HGB=10	1	10	3.00	0.95818	0.02180	0.91638	1.00000
5	logBUN=1.0 HGB=10	1	10	5.00	0.94188	0.02747	0.88955	0.99729
6	logBUN=1.0 HGB=10	1	10	6.00	0.90635	0.03796	0.83492	0.98389
7	logBUN=1.0 HGB=10	1	10	7.00	0.87742	0.04535	0.79290	0.97096
8	logBUN=1.0 HGB=10	1	10	9.00	0.86646	0.04801	0.77729	0.96585
9	logBUN=1.0 HGB=10	1	10	11.00	0.81084	0.05976	0.70178	0.93686
10	logBUN=1.0 HGB=10	1	10	13.00	0.79800	0.06238	0.68464	0.93012
11	logBUN=1.0 HGB=10	1	10	14.00	0.78384	0.06515	0.66601	0.92251
12	logBUN=1.0 HGB=10	1	10	15.00	0.76965	0.06779	0.64762	0.91467
13	logBUN=1.0 HGB=10	1	10	16.00	0.74071	0.07269	0.61110	0.89781
14	logBUN=1.0 HGB=10	1	10	17.00	0.71005	0.07760	0.57315	0.87966
15	logBUN=1.0 HGB=10	1	10	18.00	0.69392	0.07998	0.55360	0.86980
16	logBUN=1.0 HGB=10	1	10	19.00	0.66062	0.08442	0.51425	0.84865
17	logBUN=1.0 HGB=10	1	10	24.00	0.64210	0.08691	0.49248	0.83717
18	logBUN=1.0 HGB=10	1	10	25.00	0.62360	0.08921	0.47112	0.82542
19	logBUN=1.0 HGB=10	1	10	26.00	0.60523	0.09136	0.45023	0.81359
20	logBUN=1.0 HGB=10	1	10	32.00	0.58549	0.09371	0.42784	0.80122
21	logBUN=1.0 HGB=10	1	10	35.00	0.56534	0.09593	0.40539	0.78840
22	logBUN=1.0 HGB=10	1	10	37.00	0.54465	0.09816	0.38257	0.77542
23	logBUN=1.0 HGB=10	1	10	41.00	0.50178	0.10166	0.33733	0.74639
24	logBUN=1.0 HGB=10	1	10	51.00	0.47546	0.10368	0.31009	0.72901
25	logBUN=1.0 HGB=10	1	10	52.00	0.44510	0.10522	0.28006	0.70741
26	logBUN=1.0 HGB=10	1	10	54.00	0.41266	0.10689	0.24837	0.68560
27	logBUN=1.0 HGB=10	1	10	58.00	0.37465	0.10891	0.21192	0.66232
28	logBUN=1.0 HGB=10	1	10	66.00	0.33626	0.10980	0.17731	0.63772
29	logBUN=1.0 HGB=10	1	10	67.00	0.28529	0.11029	0.13372	0.60864
30	logBUN=1.0 HGB=10	1	10	88.00	0.22412	0.10928	0.08619	0.58282
31	logBUN=1.0 HGB=10	1	10	89.00	0.15864	0.10317	0.04435	0.56750
32	logBUN=1.0 HGB=10	1	10	92.00	0.09180	0.08545	0.01481	0.56907

Next, the DIRADJ option in the BASELINE statement is used to request a survival curve that represents the survival experience of an average patient in the population in which the COVARIATES= data set is sampled. When the DIRADJ option is specified, PROC PHREG computes the direct adjusted survival function by averaging the predicted survival functions for the rows in the COVARIATES= data set. The following statements plot the direct adjusted survival function in Output 86.8.3.

```
proc phreg data=Myeloma plots=survival;
   model Time*VStatus(0)=LogBUN HGB;
   baseline covariates=Myeloma survival=_all_/diradj;
run;
```

When the DIRADJ option is specified in the BASELINE statement, the default COVARIATES= data set is the input data set. For clarity, the COVARIATES=MYELOMA is specified in the BASELINE statement in the preceding PROC PHREG call.

Output 86.8.3 Average Survival Function for the Myeloma Data



If neither the COVARIATES= data set nor the DIRADJ option is specified in the BASELINE statement, PROC PHREG computes a predicted survival curve based on $\bar{\mathbf{Z}}$, the average values of the covariate vectors in the input data (Neuberger et al. 1986). This curve represents the survival experience of a patient with an average prognostic index $\boldsymbol{\beta}'\bar{\mathbf{Z}}$ equal to the average prognostic index of all patients. This approach has a couple of drawbacks: it is possible that no patient could ever have such an average index, and it does not account for the variability in the prognostic factor from patient to patient.

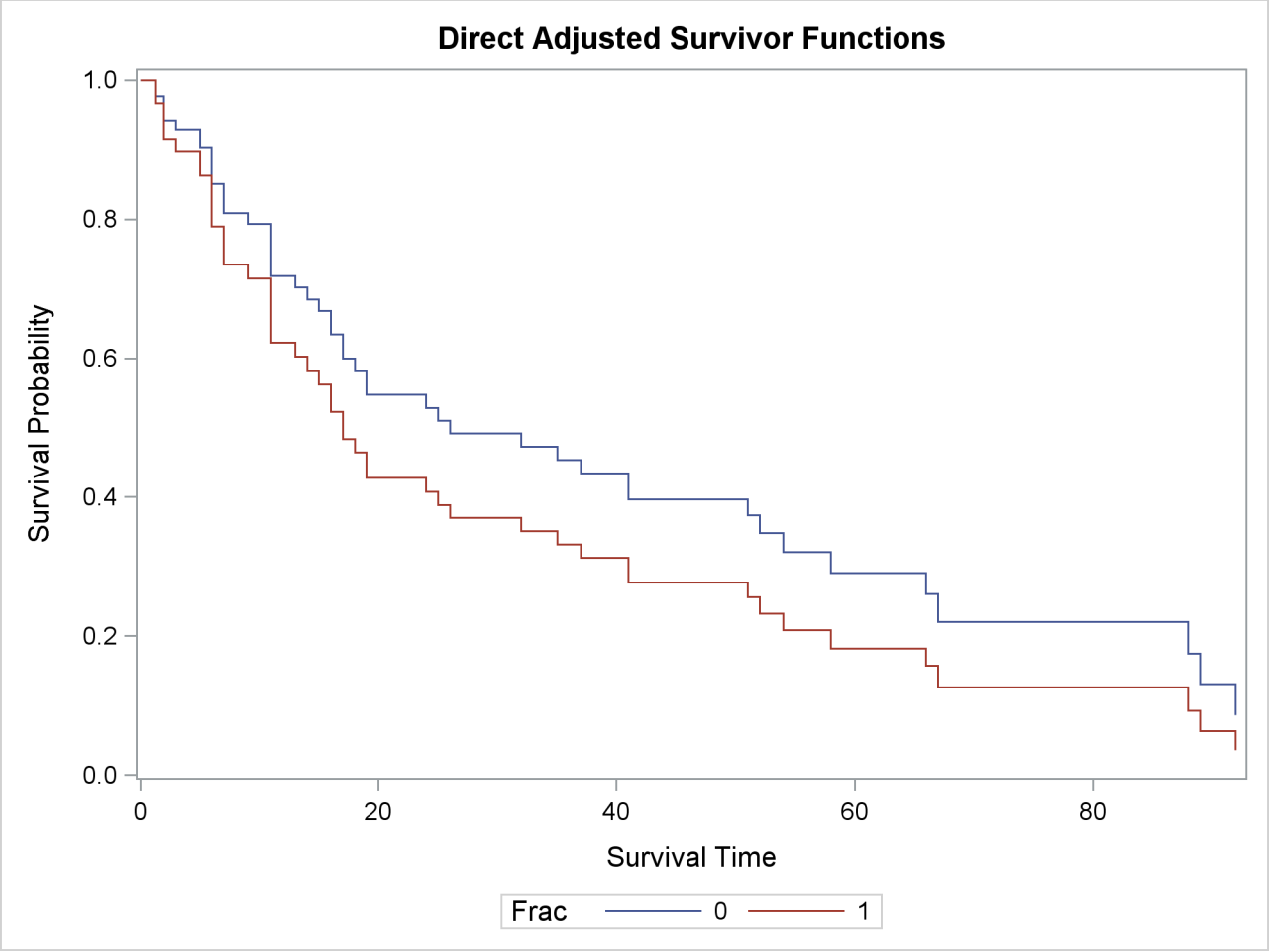
The DIRADJ option is particularly useful if the model contains a categorical explanatory variable that represents different treatments of interest. By specifying this categorical variable in the GROUP= option, you obtain a direct adjusted survival curve for each category of the variable. In addition, you can use the OUTDIFF= option to save all pairwise differences of these direct adjusted survival probabilities in a data set. For illustration, consider a model that also includes the categorical variable Frac, which has a value 0 if a patient did not have a fracture at diagnosis and 1 otherwise, as an explanatory variable. The following statements plot the adjusted survival curves in Output 86.8.4 and save the differences of the direct adjusted survival probabilities in the data set Diff1:

```
proc phreg data=Myeloma plots(overlay)=survival;
   class Frac;
   model Time*VStatus(0)=LogBUN HGB Frac;
   baseline covariates=Myeloma outdiff=Diff1 survival=_all_/diradj group=Frac;
run;
```

Because the CLASS variable Frac is specified as the GROUP= variable, a separate direct adjusted survival curve is computed for each value of the variable Frac. Each direct adjusted survival curve is the average of the predicted survival curves for all the patients in the entire Myeloma data set with their Frac value set to a specific constant. For example, the direct adjusted survival curve for Frac=0 (no fracture at diagnosis) is computed as follows:

1. The value of the variable Frac is set to 0 for all observations in the Myeloma data set.
2. The survival curve for each observation in the modified data set is computed.
3. All the survival curves computed in step 2 are averaged.

Output 86.8.4 Average Survival by Fracture Status



Output 86.8.4 shows that patients without fracture at diagnosis have better survival than those with fractures.

Differences in the survival probabilities and their standard errors are displayed in Output 86.8.5.

```
proc print data=Diff1;
run;
```

Output 86.8.5 Differences in the Survival between Fracture and Nonfracture

Obs	Frac	Frac2	Time	SurvDiff	StdErr
1	0	1	1.25	0.01074	0.01199
2	0	1	2.00	0.02653	0.02605
3	0	1	3.00	0.03165	0.03063
4	0	1	5.00	0.04191	0.03963
5	0	1	6.00	0.06115	0.05669
6	0	1	7.00	0.07416	0.06853
7	0	1	9.00	0.07854	0.07261
8	0	1	11.00	0.09669	0.09002
9	0	1	13.00	0.09998	0.09327
10	0	1	14.00	0.10319	0.09644
11	0	1	15.00	0.10611	0.09937
12	0	1	16.00	0.11117	0.10464
13	0	1	17.00	0.11532	0.10922
14	0	1	18.00	0.11704	0.11120
15	0	1	19.00	0.11969	0.11447
16	0	1	24.00	0.12072	0.11593
17	0	1	25.00	0.12145	0.11713
18	0	1	26.00	0.12189	0.11808
19	0	1	32.00	0.12208	0.11883
20	0	1	35.00	0.12197	0.11933
21	0	1	37.00	0.12155	0.11956
22	0	1	41.00	0.11983	0.11924
23	0	1	51.00	0.11821	0.11850
24	0	1	52.00	0.11580	0.11714
25	0	1	54.00	0.11262	0.11507
26	0	1	58.00	0.10824	0.11203
27	0	1	66.00	0.10301	0.10814
28	0	1	67.00	0.09451	0.10130
29	0	1	88.00	0.08248	0.09133
30	0	1	89.00	0.06847	0.08033
31	0	1	92.00	0.05038	0.06515

Example 86.9: Analysis of Residuals

Residuals are used to investigate the lack of fit of a model to a given subject. You can obtain martingale and deviance residuals for the Cox proportional hazards regression analysis by requesting that they be included in the OUTPUT data set. You can plot these statistics and look for outliers.

Consider the stepwise regression analysis performed in Example 86.1. The final model included variables LogBUN and HGB. You can generate residual statistics for this analysis by refitting the model containing those variables and including an OUTPUT statement as in the following invocation of PROC PHREG. The *keywords* XBETA, RESMART, and RESDEV identify new variables that contain the linear predictor scores $\mathbf{z}_j'\hat{\boldsymbol{\beta}}$, martingale residuals, and deviance residuals. These variables are xb, mart, and dev, respectively.

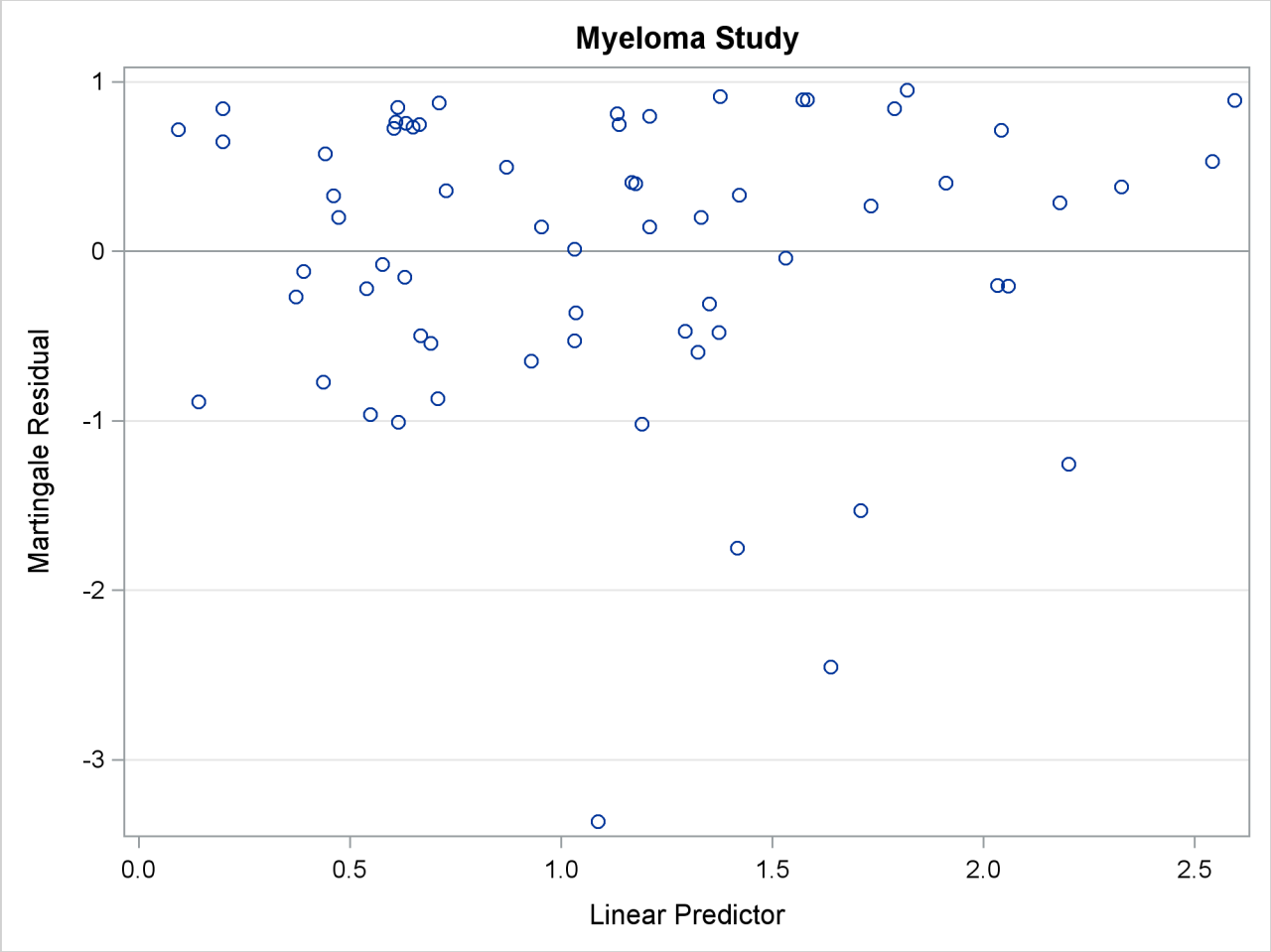
```
proc phreg data=Myeloma noprint;
   model Time*Vstatus(0)=LogBUN HGB;
   output out=Outp xbeta=Xb resmart=Mart resdev=Dev;
run;
```

The following statements plot the residuals against the linear predictor scores:

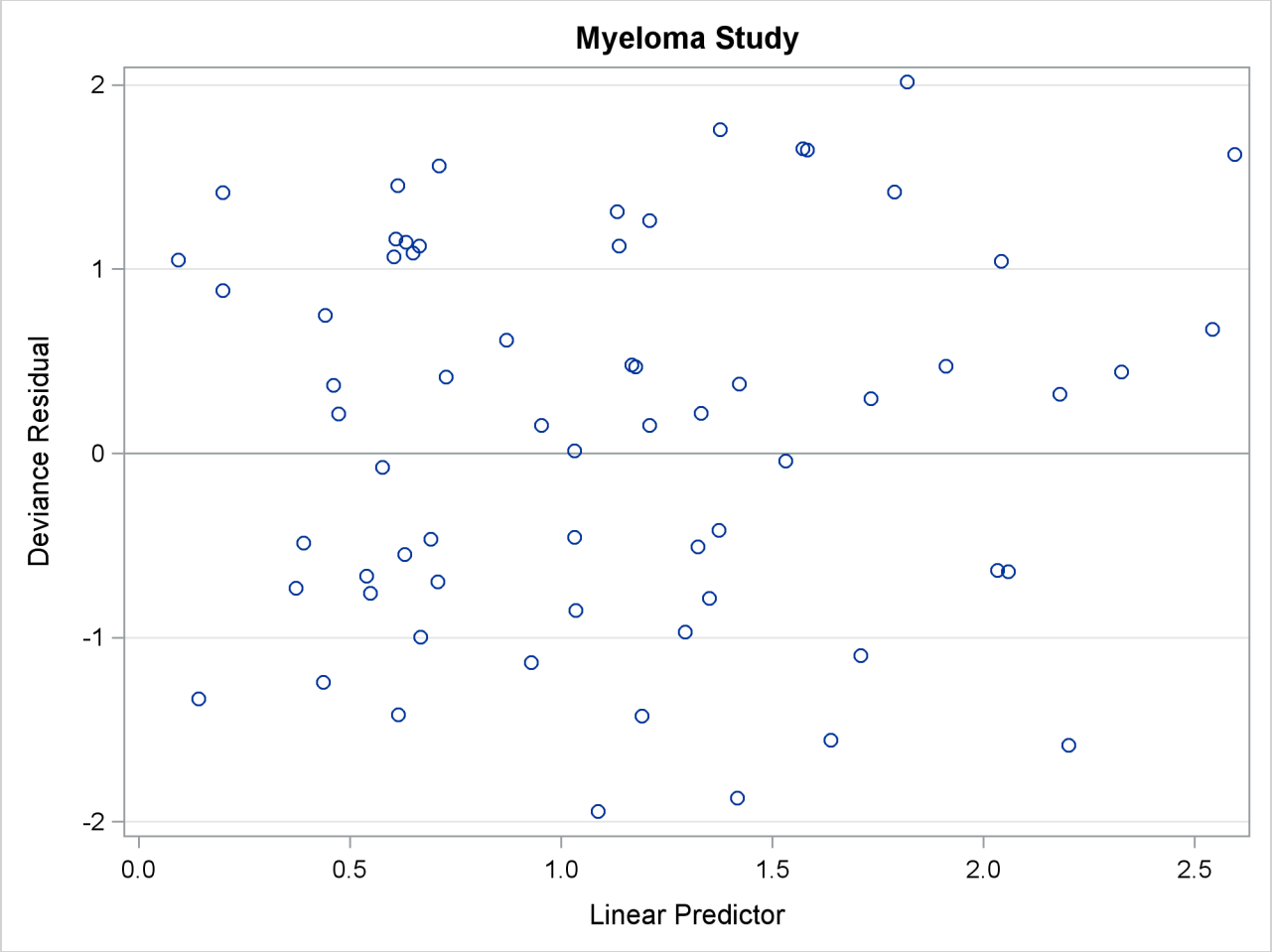
```
title "Myeloma Study";
proc sgplot data=Outp;
   yaxis grid;
   refline 0 / axis=y;
   scatter y=Mart x=Xb;
run;
proc sgplot data=Outp;
   yaxis grid;
   refline 0 / axis=y;
   scatter y=Dev x=Xb;
run;
```

The resulting plots are shown in Output 86.9.1 and Output 86.9.2. The martingale residuals are skewed because of the single event setting of the Cox model. The martingale residual plot shows an isolation point (with linear predictor score 1.09 and martingale residual –3.37), but this observation is no longer distinguishable in the deviance residual plot. In conclusion, there is no indication of a lack of fit of the model to individual observations.

Output 86.9.1 Martingale Residual Plot



Output 86.9.2 Deviance Residual Plot



Example 86.10: Analysis of Recurrent Events Data

Recurrent events data consist of times to a number of repeated events for each sample unit—for example, times of recurrent episodes of a disease in patients. Various ways of analyzing recurrent events data are described in the section "Analysis of Multivariate Failure Time Data" on page 6911. The bladder cancer data listed in Wei, Lin, and Weissfeld (1989) are used here to illustrate these methods.

The data consist of 86 patients with superficial bladder tumors, which were removed when the patients entered the study. Of these patients, 48 were randomized into the placebo group, and 38 were randomized into the group receiving thiotepa. Many patients had multiple recurrences of tumors during the study, and new tumors were removed at each visit. The data set contains the first four recurrences of the tumor for each patient, and each recurrence time was measured from the patient's entry time into the study.

The data consist of the following eight variables:

- Trt, treatment group (1=placebo and 2=thiotepa)
- Time, follow-up time

- Number, number of initial tumors
- Size, initial tumor size
- T1, T2, T3, and T4, times of the four potential recurrences of the bladder tumor. A patient with only two recurrences has missing values in T3 and T4.

In the data set Bladder, four observations are created for each patient, one for each of the four potential tumor recurrences. In addition to values of Trt, Number, and Size for the patient, each observation contains the following variables:

- ID, patient's identification (which is the sequence number of the subject)
- Visit, visit number (with value k for the kth potential tumor recurrence)
- TStart, time of the $(k-1)$ recurrence for Visit=k, or the entry time 0 if VISIT=1, or the follow-up time if the $(k-1)$ recurrence does not occur
- TStop, time of the kth recurrence if Visit=k or follow-up time if the kth recurrence does not occur
- Status, event status of TStop (1=recurrence and 0=censored)

For instance, a patient with only one recurrence time at month 6 who was followed until month 10 will have values for Visit, TStart, TStop, and Status of (1,0,6,1), (2,6,10,0), (3,10,10,0), and (4,10,10,0), respectively. The last two observations are redundant for the intensity model and the proportional means model, but they are important for the analysis of the marginal Cox models. If the follow-up time is beyond the time of the fourth tumor recurrence, it is tempting to create a fifth observation with the time of the fourth tumor recurrence as the TStart value, the follow-up time as the TStop value, and a Status value of 0. However, Therneau and Grambsch (2000, Section 8.5) have warned against incorporating such observations into the analysis.

The following SAS statements create the data set Bladder:

```
data Bladder;
   keep ID TStart TStop Status Trt Number Size Visit;
   retain ID TStart 0;
   array tt[4] T1-T4;
   infile datalines missover;
   input Trt Time Number Size T1-T4;
   ID + 1;
   TStart=0;
   do Visit=1 to 4;
      if tt[Visit] = . then do;
         TStop=Time;
         Status=0;
      end;
      else do;
         TStop=tt[Visit];
         Status=1;
      end;
      output;
      TStart=TStop;
```

```
   end;
   if (TStart < Time) then delete;
   datalines;
1       0       1     1
1       1       1     3
1       4       2     1
1       7       1     1
1       10      5     1
1       10      4     1   6
1       14      1     1
1       18      1     1
1       18      1     3   5
1       18      1     1   12  16
1       23      3     3
1       23      1     3   10  15
1       23      1     1   3   16  23
1       23      3     1   3   9   21
1       24      2     3   7   10  16  24
1       25      1     1   3   15  25
1       26      1     2
1       26      8     1   1
1       26      1     4   2   26
1       28      1     2   25
1       29      1     4
1       29      1     2
1       29      4     1
1       30      1     6   28  30
1       30      1     5   2   17  22
1       30      2     1   3   6   8   12
1       31      1     3   12  15  24
1       32      1     2
1       34      2     1
1       36      2     1
1       36      3     1   29
1       37      1     2
1       40      4     1   9   17  22  24
1       40      5     1   16  19  23  29
1       41      1     2
1       43      1     1   3
1       43      2     6   6
1       44      2     1   3   6   9
1       45      1     1   9   11  20  26
1       48      1     1   18
1       49      1     3
1       51      3     1   35
1       53      1     7   17
1       53      3     1   3   15  46  51
1       59      1     1
1       61      3     2   2   15  24  30
1       64      1     3   5   14  19  27
1       64      2     3   2   8   12  13
2       1       1     3
2       1       1     1
2       5       8     1   5
```

```
2       9       1     2
2       10      1     1
2       13      1     1
2       14      2     6   3
2       17      5     3   1   3   5   7
2       18      5     1
2       18      1     3   17
2       19      5     1   2
2       21      1     1   17  19
2       22      1     1
2       25      1     3
2       25      1     5
2       25      1     1
2       26      1     1   6   12  13
2       27      1     1   6
2       29      2     1   2
2       36      8     3   26  35
2       38      1     1
2       39      1     1   22  23  27  32
2       39      6     1   4   16  23  27
2       40      3     1   24  26  29  40
2       41      3     2
2       41      1     1
2       43      1     1   1   27
2       44      1     1
2       44      6     1   2   20  23  27
2       45      1     2
2       46      1     4   2
2       46      1     4
2       49      3     3
2       50      1     1
2       50      4     1   4   24  47
2       54      3     4
2       54      2     1   38
2       59      1     3
;
```

First, consider fitting the intensity model (Andersen and Gill 1982) and the proportional means model (Lin et al. 2000). The counting process style of input is used in the PROC PHREG specification. For the proportional means model, inference is based on the robust sandwich covariance estimate, which is requested by the COVS(AGGREGATE) option in the PROC PHREG statement. The COVM option is specified for the analysis of the intensity model to use the model-based covariance estimate. Note that some of the observations in the data set Bladder have a degenerated interval of risk. The presence of these observations does not affect the results of the analysis since none of these observations are included in any of the risk sets. However, the procedure will run more efficiently without these observations; consequently, in the following SAS statements, the WHERE clause is used to eliminate these redundant observations:

```
title 'Intensity Model and Proportional Means Model';
proc phreg data=Bladder covm covs(aggregate);
   model (TStart, TStop) * Status(0) = Trt Number Size;
   id id;
   where TStart < TStop;
run;
```

Results of fitting the intensity model and the proportional means model are shown in Output 86.10.1 and Output 86.10.2, respectively. The robust sandwich standard error estimate for Trt is larger than its model-based counterpart, rendering the effect of thiotepa less significant in the proportional means model ($p = 0.0747$) than in the intensity model ($p = 0.0215$).

Output 86.10.1 Analysis of the Intensity Model

Intensity Model and Proportional Means Model

The PHREG Procedure

Analysis of Maximum Likelihood Estimates with Model-Based Variance Estimate

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Trt	1	-0.45979	0.19996	5.2873	0.0215	0.631
Number	1	0.17165	0.04733	13.1541	0.0003	1.187
Size	1	-0.04256	0.06903	0.3801	0.5375	0.958

Output 86.10.2 Analysis of the Proportional Means Model

Analysis of Maximum Likelihood Estimates with Sandwich Variance Estimate

Parameter	DF	Parameter Estimate	Standard Error	StdErr Ratio	Chi-Square	Pr > ChiSq	Hazard Ratio
Trt	1	-0.45979	0.25801	1.290	3.1757	0.0747	0.631
Number	1	0.17165	0.06131	1.296	7.8373	0.0051	1.187
Size	1	-0.04256	0.07555	1.094	0.3174	0.5732	0.958

Next, consider the conditional models of Prentice, Williams, and Peterson (1981). In the PWP models, the risk set for the $(k + 1)$ recurrence is restricted to those patients who have experienced the first k recurrences. For example, a patient who experienced only one recurrence is an event observation for the first recurrence; this patient is a censored observation for the second recurrence and should not be included in the risk set for the third or fourth recurrence. The following DATA step eliminates those observations that should not be in the risk sets, forming a new input data set (named Bladder2) for fitting the PWP models. The variable Gaptime, representing the gap times between successive recurrences, is also created.

```
data Bladder2(drop=LastStatus);
   retain LastStatus;
   set Bladder;
   by ID;
   if first.id then LastStatus=1;
   if (Status=0 and LastStatus=0) then delete;
   LastStatus=Status;
   Gaptime=Tstop-Tstart;
run;
```

The following statements fit the PWP total time model. The variables Trt1, Trt2, Trt3, and Trt4 are visit-specific variables for Trt; the variables Number1, Number2, Numvber3, and Number4 are visit-specific variables for Number; and the variables Size1, Size2, Size3, and Size4 are visit-specific variables for Size.

```
title 'PWP Total Time Model with Noncommon Effects';
proc phreg data=Bladder2;
   model (TStart,Tstop) * Status(0) = Trt1-Trt4 Number1-Number4
                                      Size1-Size4;
   Trt1= Trt * (Visit=1);
   Trt2= Trt * (Visit=2);
   Trt3= Trt * (Visit=3);
   Trt4= Trt * (Visit=4);
   Number1= Number * (Visit=1);
   Number2= Number * (Visit=2);
   Number3= Number * (Visit=3);
   Number4= Number * (Visit=4);
   Size1= Size * (Visit=1);
   Size2= Size * (Visit=2);
   Size3= Size * (Visit=3);
   Size4= Size * (Visit=4);
   strata Visit;
run;
```

Results of the analysis of the PWP total time model are shown in Output 86.10.3. There is no significant treatment effect on the total time in any of the four tumor recurrences.

Output 86.10.3 Analysis of the PWP Total Time Model with Noncommon Effects

PWP Total Time Model with Noncommon Effects

The PHREG Procedure

Summary of the Number of Event and Censored Values

Stratum	Visit	Total	Event	Censored	Percent Censored
1	1	85	47	38	44.71
2	2	46	29	17	36.96
3	3	27	22	5	18.52
4	4	20	14	6	30.00
Total		178	112	66	37.08

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Trt1	1	-0.51757	0.31576	2.6868	0.1012	0.596
Trt2	1	-0.45967	0.40642	1.2792	0.2581	0.631
Trt3	1	0.11700	0.67183	0.0303	0.8617	1.124
Trt4	1	-0.04059	0.79251	0.0026	0.9592	0.960
Number1	1	0.23605	0.07607	9.6287	0.0019	1.266
Number2	1	-0.02044	0.09052	0.0510	0.8213	0.980
Number3	1	0.01219	0.18208	0.0045	0.9466	1.012
Number4	1	0.18915	0.24443	0.5989	0.4390	1.208
Size1	1	0.06790	0.10125	0.4498	0.5024	1.070
Size2	1	-0.15425	0.12300	1.5728	0.2098	0.857
Size3	1	0.14891	0.26299	0.3206	0.5713	1.161
Size4	1	0.0000732	0.34297	0.0000	0.9998	1.000

The following statements fit the PWP gap-time model:

```
title 'PWP Gap-Time Model with Noncommon Effects';
proc phreg data=Bladder2;
   model Gaptime * Status(0) = Trt1-Trt4 Number1-Number4
                               Size1-Size4;
   Trt1= Trt * (Visit=1);
   Trt2= Trt * (Visit=2);
   Trt3= Trt * (Visit=3);
   Trt4= Trt * (Visit=4);
   Number1= Number * (Visit=1);
   Number2= Number * (Visit=2);
   Number3= Number * (Visit=3);
   Number4= Number * (Visit=4);
   Size1= Size * (Visit=1);
   Size2= Size * (Visit=2);
   Size3= Size * (Visit=3);
   Size4= Size * (Visit=4);
   strata Visit;
run;
```

Results of the analysis of the PWP gap-time model are shown in Output 86.10.4. Note that the regression coefficients for the first tumor recurrence are the same as those of the total time model, since the total time and the gap time are the same for the first recurrence. There is no significant treatment effect on the gap times for any of the four tumor recurrences.

Output 86.10.4 Analysis of the PWP Gap-Time Model with Noncommon Effects

PWP Gap-Time Model with Noncommon Effects

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Trt1	1	-0.51757	0.31576	2.6868	0.1012	0.596
Trt2	1	-0.25911	0.40511	0.4091	0.5224	0.772
Trt3	1	0.22105	0.54909	0.1621	0.6873	1.247
Trt4	1	-0.19498	0.64184	0.0923	0.7613	0.823
Number1	1	0.23605	0.07607	9.6287	0.0019	1.266
Number2	1	-0.00571	0.09667	0.0035	0.9529	0.994
Number3	1	0.12935	0.15970	0.6561	0.4180	1.138
Number4	1	0.42079	0.19816	4.5091	0.0337	1.523
Size1	1	0.06790	0.10125	0.4498	0.5024	1.070
Size2	1	-0.11636	0.11924	0.9524	0.3291	0.890
Size3	1	0.24995	0.23113	1.1695	0.2795	1.284
Size4	1	0.03557	0.29043	0.0150	0.9025	1.036

You can fit the PWP total time model with common effects by using the following SAS statements. However, the analysis is not shown here.

```
title2 'PWP Total Time Model with Common Effects';
proc phreg data=Bladder2;
   model (tstart,tstop) * status(0) = Trt Number Size;
   strata Visit;
run;
```

You can fit the PWP gap-time model with common effects by using the following statements. Again, the analysis is not shown here.

```
title2 'PWP Gap Time Model with Common Effects';
proc phreg data=Bladder2;
   model Gaptime * Status(0) = Trt Number Size;
   strata Visit;
run;
```

Recurrent events data are a special case of multiple events data in which the recurrence times are regarded as multivariate failure times and the marginal approach of Wei, Lin, and Weissfeld (1989) can be used. WLW fits a Cox model to each of the component times and makes statistical inference of the regression parameters based on a robust sandwich covariance matrix estimate. No specific correlation structure is imposed on the multivariate failure times. For the kth marginal model, let $\boldsymbol{\beta}_k$ denote the row vector of regression parameters, let $\hat{\boldsymbol{\beta}}_k$ denote the maximum likelihood estimate of $\boldsymbol{\beta}_k$, let $\hat{\mathbf{A}}_k$ denote the covariance matrix obtained by inverting the observed information matrix, and let $\mathbf{R}_k$ denote the matrix of score residuals. WLW showed that the joint distribution of $(\hat{\boldsymbol{\beta}}_1, \ldots, \hat{\boldsymbol{\beta}}_4)'$ can be approximated by a multivariate normal distribution with mean vector $(\boldsymbol{\beta}_1, \ldots, \boldsymbol{\beta}_4)'$ and robust covariance matrix

$$\begin{pmatrix} \mathbf{V}_{11} & \mathbf{V}_{12} & \mathbf{V}_{13} & \mathbf{V}_{14} \\ \mathbf{V}_{21} & \mathbf{V}_{22} & \mathbf{V}_{23} & \mathbf{V}_{24} \\ \mathbf{V}_{31} & \mathbf{V}_{32} & \mathbf{V}_{33} & \mathbf{V}_{34} \\ \mathbf{V}_{41} & \mathbf{V}_{42} & \mathbf{V}_{43} & \mathbf{V}_{44} \end{pmatrix}$$

with the submatrix $\mathbf{V}_{ij}$ given by

$$\mathbf{V}_{ij} = \hat{\mathbf{A}}_i (\mathbf{R}_i' \mathbf{R}_j) \hat{\mathbf{A}}_j$$

In this example, there are four marginal proportional hazards models, one for each potential recurrence time. Instead of fitting one model at a time, you can fit all four marginal models in one analysis by using the STRATA statement and model-specific covariates as in the following statements. Using Visit as the STRATA variable on the input data set Bladder, PROC PHREG simultaneously fits all four marginal models, one for each Visit value. The COVS(AGGREGATE) option is specified to compute the robust sandwich variance estimate by summing up the score residuals for each distinct pattern of ID value. The TEST statement TREATMENT is used to perform the global test of no treatment effect for each tumor recurrence, the AVERAGE option is specified to estimate the parameter for the common treatment effect, and the E option displays the optimal weights for the common treatment effect.

```
title 'Wei-Lin-Weissfeld Model';
proc phreg data=Bladder covs(aggregate);
   model TStop*Status(0)=Trt1-Trt4 Number1-Number4 Size1-Size4;
   Trt1= Trt * (Visit=1);
   Trt2= Trt * (Visit=2);
   Trt3= Trt * (Visit=3);
```

```
    Trt4= Trt * (Visit=4);
    Number1= Number * (Visit=1);
    Number2= Number * (Visit=2);
    Number3= Number * (Visit=3);
    Number4= Number * (Visit=4);
    Size1= Size * (Visit=1);
    Size2= Size * (Visit=2);
    Size3= Size * (Visit=3);
    Size4= Size * (Visit=4);
    strata Visit;
    id ID;
    TREATMENT: test trt1,trt2,trt3,trt4/average e;
run;
```

Out of the 86 patients, 47 patients have only one tumor recurrence, 29 patients have two recurrences, 22 patients have three recurrences, and 14 patients have four recurrences (Output 86.10.5). Parameter estimates for the four marginal models are shown in Output 86.10.6. The 4 DF Wald test (Output 86.10.7) indicates a lack of evidence of a treatment effect in any of the four recurrences ($p = 0.4105$). The optimal weights for estimating the parameter of the common treatment effect are 0.67684, 0.25723, –0.07547, and 0.14140 for Trt1, Trt2, Trt3, and Trt4, respectively, which gives a parameter estimate of –0.5489 with a standard error estimate of 0.2853. A more sensitive test for a treatment effect is the 1 DF test based on this common parameter; however, there is still insufficient evidence for such effect at the 0.05 level ($p = 0.0543$).

Output 86.10.5 Summary of Bladder Tumor Recurrences in 86 Patients

Wei-Lin-Weissfeld Model

The PHREG Procedure

Summary of the Number of Event and Censored Values

Stratum	Visit	Total	Event	Censored	Percent Censored
1	1	86	47	39	45.35
2	2	86	29	57	66.28
3	3	86	22	64	74.42
4	4	86	14	72	83.72
Total		344	112	232	67.44

Output 86.10.6 Analysis of Marginal Cox Models

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	StdErr Ratio	Chi-Square	Pr > ChiSq	Hazard Ratio
Trt1	1	-0.51762	0.30750	0.974	2.8336	0.0923	0.596
Trt2	1	-0.61944	0.36391	0.926	2.8975	0.0887	0.538
Trt3	1	-0.69988	0.41516	0.903	2.8419	0.0918	0.497
Trt4	1	-0.65079	0.48971	0.848	1.7661	0.1839	0.522
Number1	1	0.23599	0.07208	0.947	10.7204	0.0011	1.266
Number2	1	0.13756	0.08690	0.946	2.5059	0.1134	1.147
Number3	1	0.16984	0.10356	0.984	2.6896	0.1010	1.185
Number4	1	0.32880	0.11382	0.909	8.3453	0.0039	1.389
Size1	1	0.06789	0.08529	0.842	0.6336	0.4260	1.070
Size2	1	-0.07612	0.11812	0.881	0.4153	0.5193	0.927
Size3	1	-0.21131	0.17198	0.943	1.5097	0.2192	0.810
Size4	1	-0.20317	0.19106	0.830	1.1308	0.2876	0.816

Output 86.10.7 Tests of Treatment Effects

Wei-Lin-Weissfeld Model

The PHREG Procedure

Linear Coefficients for Test TREATMENT

Parameter	Row 1	Row 2	Row 3	Row 4	Average Effect
Trt1	1	0	0	0	0.67684
Trt2	0	1	0	0	0.25723
Trt3	0	0	1	0	-0.07547
Trt4	0	0	0	1	0.14140
Number1	0	0	0	0	0.00000
Number2	0	0	0	0	0.00000
Number3	0	0	0	0	0.00000
Number4	0	0	0	0	0.00000
Size1	0	0	0	0	0.00000
Size2	0	0	0	0	0.00000
Size3	0	0	0	0	0.00000
Size4	0	0	0	0	0.00000
CONSTANT	0	0	0	0	0.00000

Test TREATMENT Results

Wald Chi-Square	DF	Pr > ChiSq
3.9668	4	0.4105

Average Effect for Test TREATMENT

Estimate	Standard Error	z-Score	Pr > |z|
-0.5489	0.2853	-1.9240	0.0543

Example 86.11: Analysis of Clustered Data

When experimental units are naturally or artificially clustered, failure times of experimental units within a cluster are correlated. Two approaches can be taken to adjust for the intracluster correlation. In the marginal Cox model approach, Lee, Wei, and Amato (1992) estimate the regression parameters in the Cox model by the maximum partial likelihood estimates under an independent working assumption and use a robust sandwich covariance matrix estimate to account for the intracluster dependence. Lin (1994) illustrates this methodology by using a subset of data from the Diabetic Retinopathy Study (DRS). An alternative approach to account for the within-cluster correlation is to use a shared frailty model where cluster effects are incorporated into the model as independent and identically distributed random variables.

The following DATA step creates the data set Blind that represents 197 diabetic patients who have a high risk of experiencing blindness in both eyes as defined by DRS criteria. One eye of each patient is treated with laser photocoagulation. The hypothesis of interest is whether the laser treatment delays the occurrence of blindness. Since juvenile and adult diabetes have very different courses, it is also desirable to examine how the age of onset of diabetes might affect the time of blindness. Since there are no biological differences between the left eye and the right eye, it is natural to assume a common baseline hazard function for the failure times of the left and right eyes.

Each patient is a cluster that contributes two observations to the input data set, one for each eye. The following variables are in the input data set Blind:

- ID, patient's identification
- Time, time to blindness
- Status, blindness indicator (0:censored and 1:blind)
- Treat, treatment received (Laser or Others)
- Type, type of diabetes (Juvenile: onset at age ≤ 20 or Adult: onset at age > 20)

```
proc format;
   value type 0='Juvenile' 1='Adult';
   value Rx  1='Laser' 0='Others';
run;

data Blind;
   input ID Time Status dty trt @@;
   Type= put(dty, type.);
   Treat= put(trt, Rx.);
   datalines;
   5 46.23 0 1 1    5 46.23 0 1 0   14 42.50 0 0 1   14 31.30 1 0 0
  16 42.27 0 0 1   16 42.27 0 0 0   25 20.60 0 0 1   25 20.60 0 0 0
  29 38.77 0 0 1   29  0.30 1 0 0   46 65.23 0 0 1   46 54.27 1 0 0

   ... more lines ...

1705  8.00 0 0 1 1705  8.00 0 0 0 1717 51.60 0 1 1 1717 42.33 1 1 0
1727 49.97 0 1 1 1727  2.90 1 1 0 1746 45.90 0 0 1 1746  1.43 1 0 0
1749 41.93 0 1 1 1749 41.93 0 1 0
;
```

As a preliminary analysis, PROC FREQ is used to summarize the number of eyes that developed blindness.

```
proc freq data=Blind;
   table Treat*Status;
run;
```

By the end of the study, 54 eyes treated with laser photocoagulation and 101 eyes treated by other means have developed blindness (Output 86.11.1).

Output 86.11.1 Distribution of Blindness

The FREQ Procedure

Frequency Percent Row Pct Col Pct	Table of Treat by Status		
	Status		
Treat	0	1	Total
Laser	143	54	197
	36.29	13.71	50.00
	72.59	27.41	
	59.83	34.84	
Others	96	101	197
	24.37	25.63	50.00
	48.73	51.27	
	40.17	65.16	
Total	239	155	394
	60.66	39.34	100.00

The following statements use PROC PHREG to carry out the analysis of Lee, Wei, and Amato (1992). The explanatory variables in this Cox model are Treat, Type, and the Treat × Type interaction. The COVS(AGGREGATE) option is specified to compute the robust sandwich covariance matrix estimate. The ID statement identifies the variable that represents the clusters. The HAZARDRATIO statement requests hazard ratios for the treatments be displayed.

```
proc phreg data=Blind covs(aggregate);
   class Treat Type;
   model Time*Status(0)=Treat|Type;
   id ID;
   hazardratio 'Marginal Model Analysis' Treat;
run;
```

Results of the marginal model analysis are displayed in Output 86.11.2. The robust standard error estimates are smaller than the model-based counterparts, since the ratio of the robust standard error estimate relative to the model-based estimate is less than 1 for each parameter. Laser photocoagulation appears to be effective ($p = 0.0217$) in delaying the occurrence of blindness, although there is also a significant interaction effect between treatment and type of diabetes ($p = 0.0053$).

Output 86.11.2 Inference Based on the Marginal Model

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Parameter			DF	Parameter Estimate	Standard Error	StdErr Ratio	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
Treat	Laser		1	-0.42467	0.18497	0.850	5.2713	0.0217	.	Treat Laser
Type	Adult		1	0.34084	0.19558	0.982	3.0371	0.0814	.	Type Adult
Treat*Type	Laser	Adult	1	-0.84566	0.30353	0.865	7.7622	0.0053	.	Treat Laser * Type Adult

Hazard ratio estimates of the laser treatment relative to nonlaser treatment are displayed in Output 86.11.3. For both types of diabetes, the 95% confidence interval for the hazard ratio lies below 1. This indicates that laser-photocoagulation treatment is more effective in delaying blindness regardless of the type of diabetes. However, the effect is more prominent for adult-onset diabetes than for juvenile-onset diabetes since the hazard ratio estimates for the former are less than those of the latter.

Output 86.11.3 Hazard Ratio Estimates for Marginal Model

Marginal Model Analysis: Hazard Ratios for Treat

Description	Point Estimate	95% Wald Robust Confidence Limits	
Treat Laser vs Others At Type=Adult	0.281	0.175	0.451
Treat Laser vs Others At Type=Juvenile	0.654	0.455	0.940

Next, you analyze the same data by using a shared frailty model. The following statements use PROC PHREG to fit a shared frailty model to the Blind data set. The RANDOM statement identifies the variable ID as the variable that represents the clusters. You must declare the cluster variable as a classification variable in the CLASS statement.

```
proc phreg data=Blind;
   class ID Treat Type;
   model Time*Status(0)=Treat|Type;
   random ID;
   hazardratio 'Frailty Model Analysis' Treat;
run;
```

Selected results of this analysis are displayed in Output 86.11.4 to Output 86.11.6.

The "Random Class Level Information" table in Output 86.11.4 displays the 197 ID values of the patients. You can suppress the display of this table by using the NOCLPRINT option in the RANDOM statement.

Output 86.11.4 Unique Cluster Identification Values

The PHREG Procedure

Class Level Information for Random Effects

Class	Levels	Values
ID	197	5 14 16 25 29 46 49 56 61 71 100 112 120 127 133 150 167 176 185 190 202 214 220 243 255 264 266 284 295 300 302 315 324 328 335 342 349 357 368 385 396 405 409 419 429 433 445 454 468 480 485 491 503 515 522 538 547 550 554 557 561 568 572 576 581 606 610 615 618 624 631 636 645 653 662 664 683 687 701 706 717 722 731 740 749 757 760 766 769 772 778 780 793 800 804 810 815 832 834 838 857 866 887 903 910 920 925 931 936 945 949 952 962 964 971 978 983 987 1002 1017 1029 1034 1037 1042 1069 1074 1098 1102 1112 1117 1126 1135 1145 1148 1167 1184 1191 1205 1213 1228 1247 1250 1253 1267 1281 1287 1293 1296 1309 1312 1317 1321 1333 1347 1361 1366 1373 1397 1410 1413 1425 1447 1461 1469 1480 1487 1491 1499 1503 1513 1524 1533 1537 1552 1554 1562 1572 1581 1585 1596 1600 1603 1619 1627 1636 1640 1643 1649 1666 1672 1683 1688 1705 1717 1727 1746 1749

The "Covariance Parameter Estimates" table in Output 86.11.5 displays the estimate and asymptotic estimated standard error of the common variance parameter of the normal random effects.

Output 86.11.5 Variance Estimate of the Normal Random Effects

Covariance Parameter Estimates

Cov Parm	REML Estimate	Standard Error
ID	0.8308	0.2145

Output 86.11.6 displays the Wald tests for both the fixed effects and the random effects. The random effects are statistically significant ($p = 0.0042$). Results of testing the fixed effects are very similar to those based on the robust variance estimates. Laser photocoagulation appears to be effective ($p = 0.0252$) in delaying the occurrence of blindness, although there is also a significant treatment by diabetes type interaction effect ($p = 0.0071$).

Output 86.11.6 Inference Based on the Frailty Model

Type 3 Tests

Effect	Wald Chi-Square	DF	Pr > ChiSq	Adjusted DF	Adjusted Pr > ChiSq
Treat	4.8961	1	0.0269	0.9587	0.0252
Type	2.6395	1	0.1042	0.6795	0.0629
Treat*Type	7.1349	1	0.0076	0.9644	0.0071
ID	110.3922	.	.	74.2788	0.0042

Analysis of Maximum Likelihood Estimates

Parameter			DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
Treat	Laser		1	-0.49848	0.22528	4.8961	0.0269	.	Treat Laser
Type	Adult		1	0.39788	0.24490	2.6395	0.1042	.	Type Adult
Treat*Type	Laser	Adult	1	-0.96540	0.36142	7.1349	0.0076	.	Treat Laser * Type Adult

Estimates of hazard ratios of the laser treatment relative to nonlaser treatment are displayed in Output 86.11.7. These estimates closely resemble those computed in analysis based on the marginal Cox model in Output 86.11.3, which leads to the same conclusion that laser photocoagulation is effective in delaying blindness for both types of diabetes, and more effective for the adult-onset diabetes than for juvenile-onset diabetes.

Output 86.11.7 Hazard Ratio Estimates for Frailty Model

Frailty Model Analysis: Hazard Ratios for Treat			
Description	Point Estimate	95% Wald Confidence Limits	
Treat Laser vs Others At Type=Adult	0.231	0.133	0.403
Treat Laser vs Others At Type=Juvenile	0.607	0.391	0.945

Example 86.12: Model Assessment Using Cumulative Sums of Martingale Residuals

The Mayo liver disease example of Lin, Wei, and Ying (1993) is reproduced here to illustrate the checking of the functional form of a covariate and the assessment of the proportional hazards assumption. The data represent 418 patients with primary biliary cirrhosis (PBC), among whom 161 had died as of the date of data listing. A subset of the variables is saved in the SAS data set Liver. The data set contains the following variables:

- Time, follow-up time, in years
- Status, event indicator with value 1 for death time and value 0 for censored time
- Age, age in years from birth to study registration
- Albumin, serum albumin level, in g/dl
- Bilirubin, serum bilirubin level, in mg/dl
- Edema, edema presence
- Protime, prothrombin time, in seconds

The following statements create the data set Liver:

```
data Liver;
   input Time Status Age Albumin Bilirubin Edema Protime @@;
   label Time="Follow-up Time in Years";
   Time= Time / 365.25;
   datalines;
  400 1 58.7652 2.60 14.5 1.0 12.2 4500 0 56.4463 4.14  1.1 0.0 10.6
 1012 1 70.0726 3.48  1.4 0.5 12.0 1925 1 54.7406 2.54  1.8 0.5 10.3
 1504 0 38.1054 3.53  3.4 0.0 10.9 2503 1 66.2587 3.98  0.8 0.0 11.0
 1832 0 55.5346 4.09  1.0 0.0  9.7 2466 1 53.0568 4.00  0.3 0.0 11.0
 2400 1 42.5079 3.08  3.2 0.0 11.0   51 1 70.5599 2.74 12.6 1.0 11.5
 3762 1 53.7139 4.16  1.4 0.0 12.0  304 1 59.1376 3.52  3.6 0.0 13.6
 3577 0 45.6893 3.85  0.7 0.0 10.6 1217 1 56.2218 2.27  0.8 1.0 11.0
 3584 1 64.6461 3.87  0.8 0.0 11.0 3672 0 40.4435 3.66  0.7 0.0 10.8

   ... more lines ...
```

```
  989 0 35.0000 3.23  0.7 0.0 10.8  681 1 67.0000 2.96  1.2 0.0 10.9
 1103 0 39.0000 3.83  0.9 0.0 11.2 1055 0 57.0000 3.42  1.6 0.0  9.9
  691 0 58.0000 3.75  0.8 0.0 10.4  976 0 53.0000 3.29  0.7 0.0 10.6
;
```

Consider fitting a Cox model for the survival time of the PCB patients with the covariates Bilirubin, log(Protime), log(Albumin), Age, and Edema. The log transform, which is often applied to blood chemistry measurements, is deliberately not employed for Bilirubin. It is of interest to assess the functional form of the variable Bilirubin in the Cox model. The specifications are as follows:

```
ods graphics on;
proc phreg data=Liver;
   model Time*Status(0)=Bilirubin logProtime logAlbumin Age Edema;
   logProtime=log(Protime);
   logAlbumin=log(Albumin);
   assess var=(Bilirubin) /  resample seed=7548;
run;
```

The ASSESS statement creates a plot of the cumulative martingale residuals against the values of the covariate Bilirubin, which is specified in the VAR= option. The RESAMPLE option computes the *p*-value of a Kolmogorov-type supremum test based on a sample of 1,000 simulated residual patterns.

Parameter estimates of the model fit are shown in Output 86.12.1. The plot in Output 86.12.2 displays the observed cumulative martingale residual process for Bilirubin together with 20 simulated realizations from the null distribution. When ODS Graphics is enabled, this graphical display is requested by specifying the ASSESS statement. It is obvious that the observed process is atypical compared to the simulated realizations. Also, none of the 1,000 simulated realizations has an absolute maximum exceeding that of the observed cumulative martingale residual process. Both the graphical and numerical results indicate that a transform is deemed necessary for Bilirubin in the model.

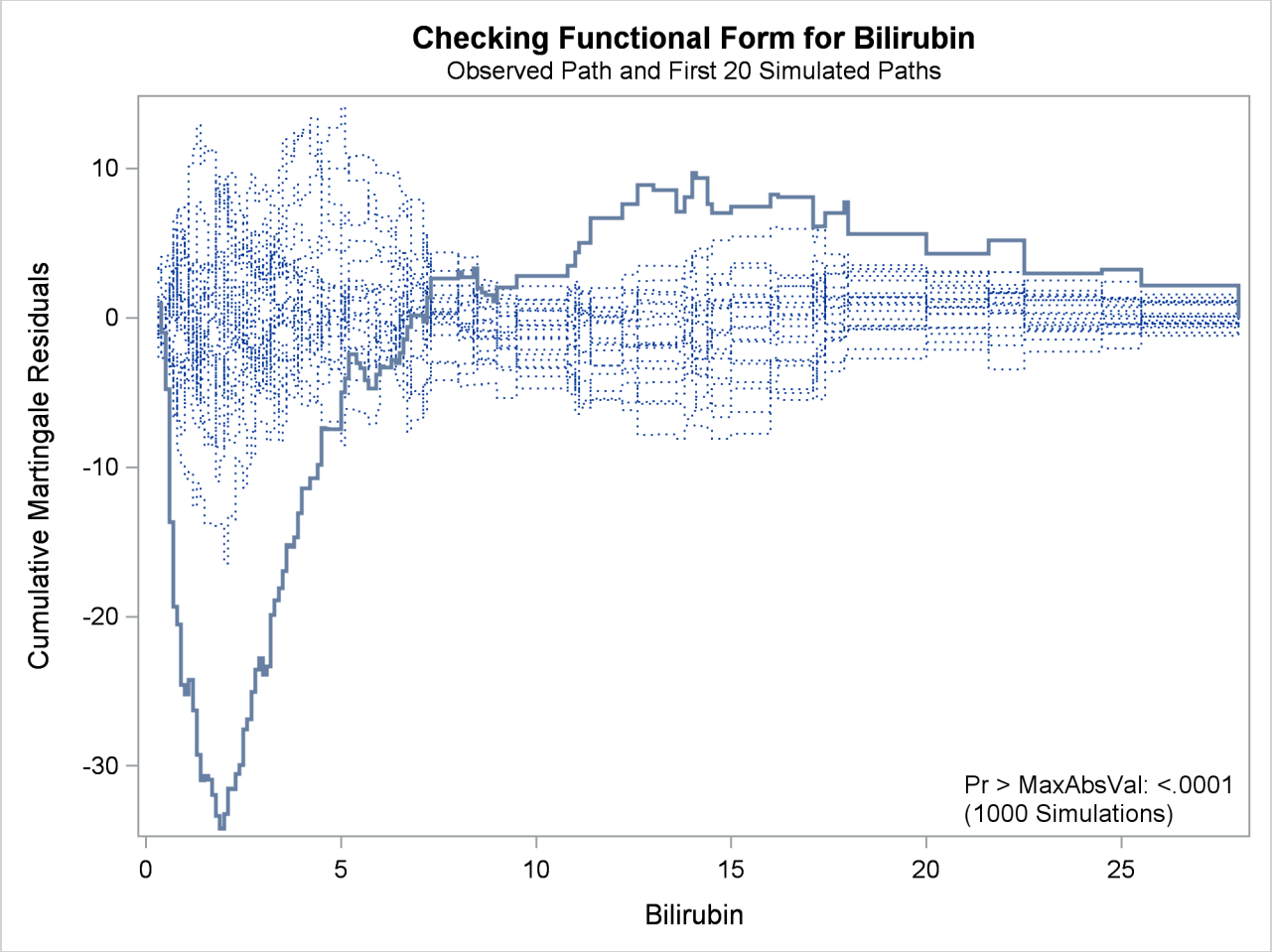
Output 86.12.1 Cox Model with Bilirubin as a Covariate

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Bilirubin	1	0.11733	0.01298	81.7567	<.0001	1.124
logProtime	1	2.77581	0.71482	15.0794	0.0001	16.052
logAlbumin	1	-3.17195	0.62945	25.3939	<.0001	0.042
Age	1	0.03779	0.00805	22.0288	<.0001	1.039
Edema	1	0.84772	0.28125	9.0850	0.0026	2.334

Output 86.12.2 Cumulative Martingale Residuals vs Bilirubin



The cumulative martingale residual plots in Output 86.12.3 provide guidance in suggesting a more appropriate functional form for a covariate. The four curves were created from simple forms of misspecification by using 10,000 simulated times from a exponential model with 20% censoring. The true and fitted models are shown in Table 86.20. The following statements produce Output 86.12.3.

```
data sim(drop=tmp);
   p = 1 / 91;
   seed = 1;
   do n = 1 to 10000;
      x1 = rantbl( seed, p, p, p, p, p, p, p, p, p, p,
                           p, p, p, p, p, p, p, p, p, p,
                           p, p, p, p, p, p, p, p, p, p,
                           p, p, p, p, p, p, p, p, p, p,
                           p, p, p, p, p, p, p, p, p, p,
                           p, p, p, p, p, p, p, p, p, p,
                           p, p, p, p, p, p, p, p, p, p,
                           p, p, p, p, p, p, p, p, p, p,
                           p, p, p, p, p, p, p, p, p, p );

      x1 = 1 + ( x1 - 1 ) / 10;
```

```
      x2= x1 * x1;
      x3= x1 * x2;
      status= rantbl(seed, .8);
      tmp= log(1-ranuni(seed));
      t1= -exp(-log(x1)) * tmp;
      t2= -exp(-.1*(x1+x2)) * tmp;
      t3= -exp(-.01*(x1+x2+x3)) * tmp;
      tt= -exp(-(x1>5)) * tmp;
      output;
   end;
run;


proc sort data=sim;
   by x1;
run;

proc phreg data=sim noprint;
   model t1*status(2)=x1;
   output out=out1 resmart=resmart;
run;

proc phreg data=sim noprint;
   model t2*status(2)=x1;
   output out=out2 resmart=resmart;
run;


proc phreg data=sim noprint;
   model t3*status(2)=x1 x2;
   output out=out3 resmart=resmart;
run;

proc phreg data=sim noprint;
   model tt*status(2)=x1;
   output out=out4 resmart=resmart;
run;

data out1(keep=x1 cresid1);
   retain cresid1 0;
   set out1;
   by x1;
   cresid1 + resmart;
   if last.x1  then output;
run;

data out2(keep=x1 cresid2);
   retain cresid2 0;
   set out2;
   by x1;
   cresid2 + resmart;
   if last.x1  then output;
run;
```

```
data out3(keep=x1 cresid3);
   retain cresid3 0;
   set out3;
   by x1;
   cresid3 + resmart;
   if last.x1  then output;
run;

data out4(keep=x1 cresid4);
   retain cresid4 0;
   set out4;
   by x1;
   cresid4 + resmart;
   if last.x1  then output;
run;

data all;
   set out1;
   set out2;
   set out3;
   set out4;
run;

proc template;
   define statgraph MisSpecification;
      BeginGraph;
         entrytitle "Covariate Misspecification";
         layout lattice / columns=2 rows=2 columndatarange=unionall;

            columnaxes;
               columnaxis / display=(ticks tickvalues label) label="x";
               columnaxis / display=(ticks tickvalues label) label="x";
            endcolumnaxes;

            cell;
               cellheader;
                  entry "(a) Data: log(X), Model: X";
               endcellheader;
               layout overlay / xaxisopts=(display=none)
                                yaxisopts=(label="Cumulative Residual");
                  seriesplot y=cresid1 x=x1 / lineattrs=GraphFit;
               endlayout;
            endcell;

            cell;
               cellheader;
                  entry "(b) Data: X*X, Model: X";
               endcellheader;
               layout overlay / xaxisopts=(display=none)
                                yaxisopts=(label=" ");
                  seriesplot y=cresid2 x=x1 / lineattrs=GraphFit;
               endlayout;
            endcell;
```

```
            cell;
               cellheader;
                  entry "(c) Data: X*X*X, Model: X*X";
               endcellheader;
               layout overlay / xaxisopts=(display=none)
                                yaxisopts=(label="Cumulative Residual");
                  seriesplot y=cresid3 x=x1 / lineattrs=GraphFit;
               endlayout;
            endcell;

            cell;
               cellheader;
                  entry "(d) Data: I(X>5), Model: X";
               endcellheader;
               layout overlay / xaxisopts=(display=none)
                                yaxisopts=(label=" ");
                  seriesplot y=cresid4 x=x1 / lineattrs=GraphFit;
               endlayout;
            endcell;

         endlayout;
      EndGraph;
   end;
run;

proc sgrender data=all template=MisSpecification;
run;
```

Output 86.12.3 Typical Cumulative Residual Plot Patterns

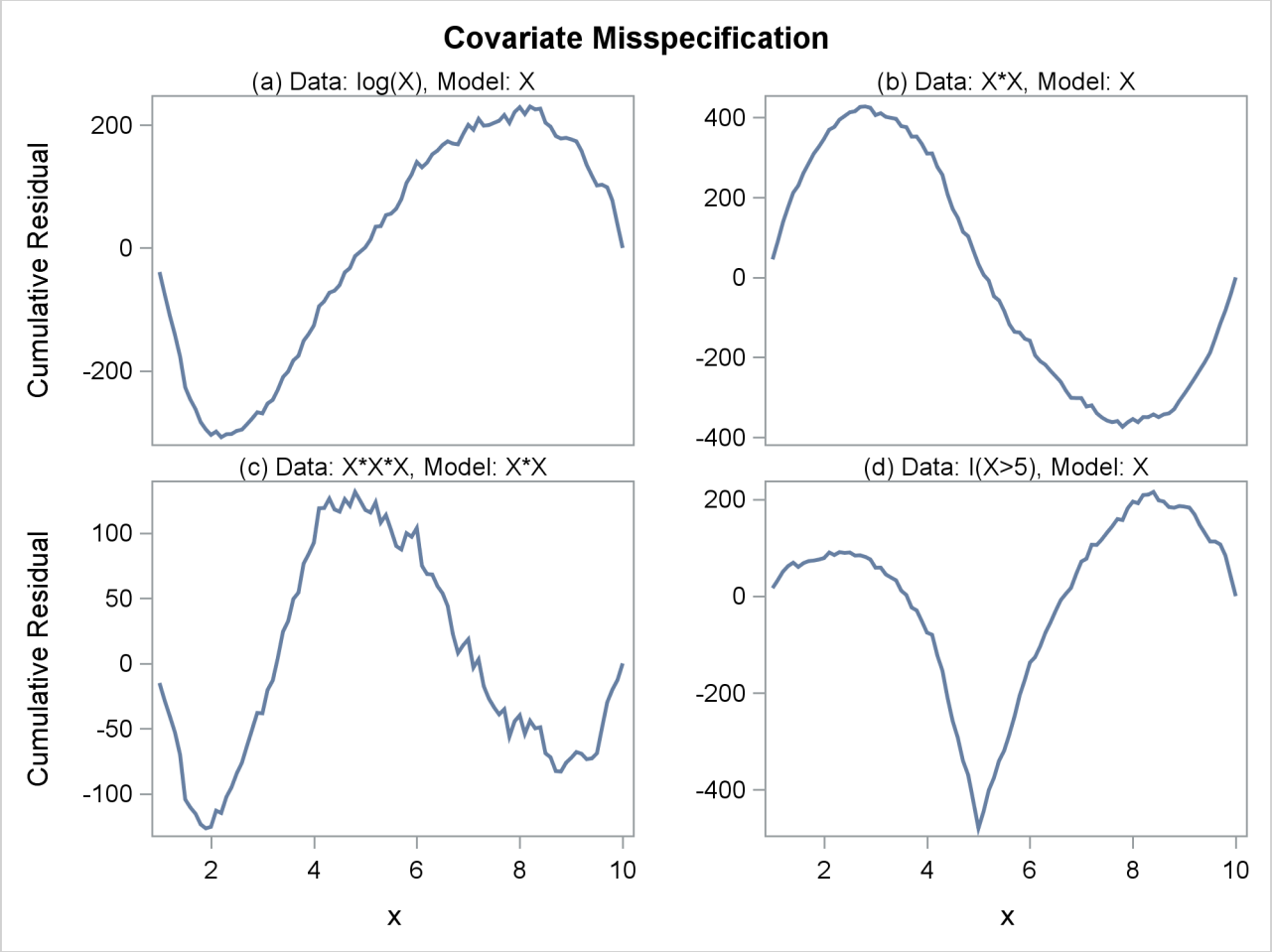


Table 86.20 Model Misspecifications

Plot	Data	Fitted Model
(a)	$\log(X)$	X
(b)	$\{X, X^2\}$	X
(c)	$\{X, X^2, X^3\}$	$\{X, X^2\}$
(d)	$I(X > 5)$	X

The curve of observed cumulative martingale residuals in Output 86.12.2 most resembles the behavior of the curve in plot (a) of Output 86.12.3, indicating that log(Bilirubin) might be a more appropriate term in the model than Bilirubin.

Next, the analysis of the natural history of the PBC is repeated with log(Bilirubin) replacing Bilirubin, and the functional form of log(Bilirubin) is assessed. Also assessed is the proportional hazards assumption for the Cox model. The analysis is carried out by the following statements:

```
proc phreg data=Liver;
   model Time*Status(0)=logBilirubin logProtime logAlbumin Age Edema;
   logBilirubin=log(Bilirubin);
   logProtime=log(Protime);
   logAlbumin=log(Albumin);
   assess var=(logBilirubin) ph / crpanel resample seed=19;
run;
```

The SEED= option specifies a integer seed for generating random numbers. The CRPANEL option in the ASSESS statement requests a panel of four plots. Each plot displays the observed cumulative martingale residual process along with two simulated realizations. The PH option checks the proportional hazards assumption of the model by plotting the observed standardized score process with 20 simulated realizations for each covariate in the model.

Output 86.12.4 displays the parameter estimates of the fitted model. The cumulative martingale residual plots in Output 86.12.5 and Output 86.12.6 show that the observed martingale residual process is more typical of the simulated realizations. The *p*-value for the Kolmogorov-type supremum test based on 1,000 simulations is 0.052, indicating that the log transform is a much improved functional form for Bilirubin.

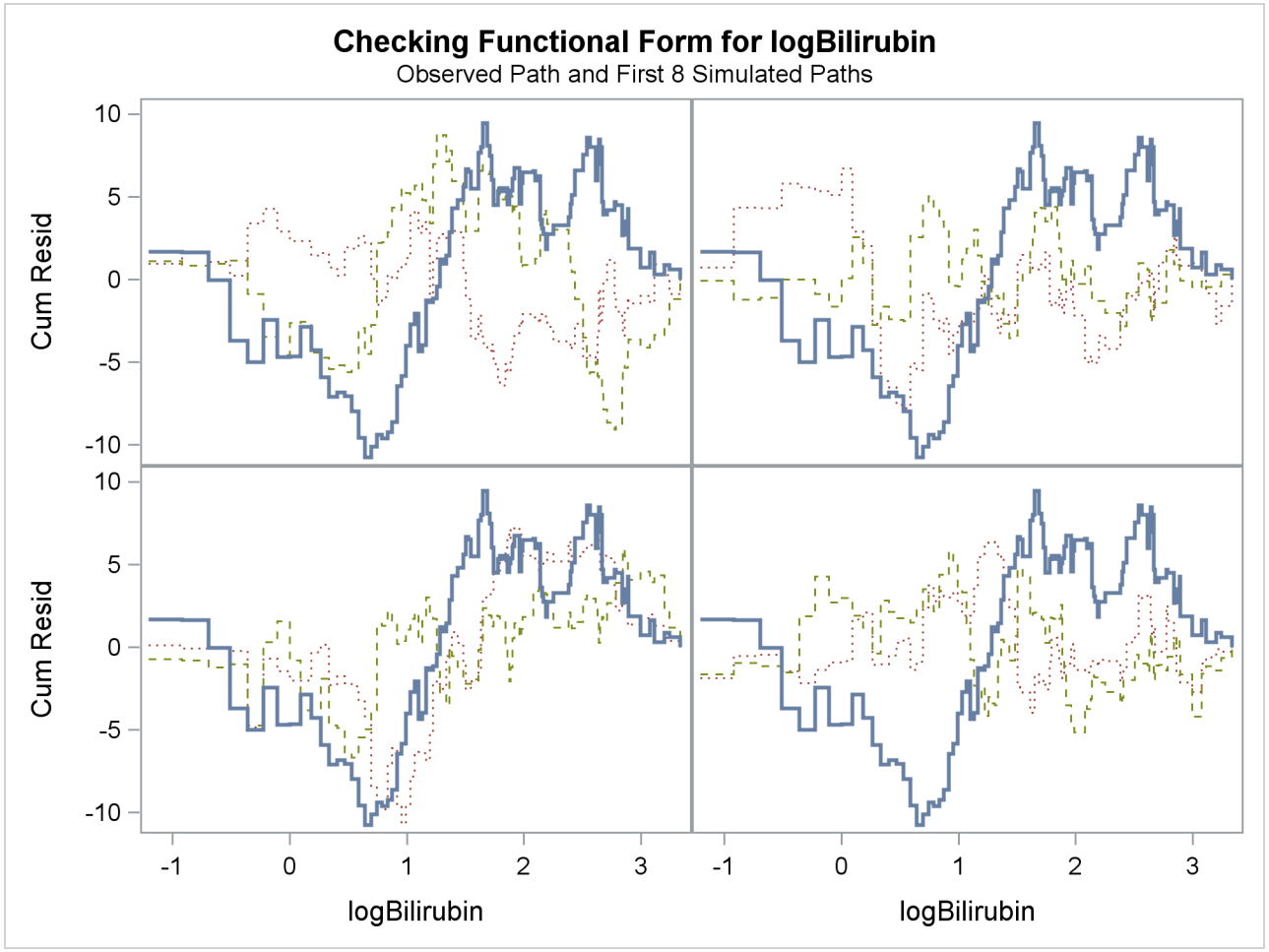
Output 86.12.4 Model with log(Bilirubin) as a Covariate

The PHREG Procedure

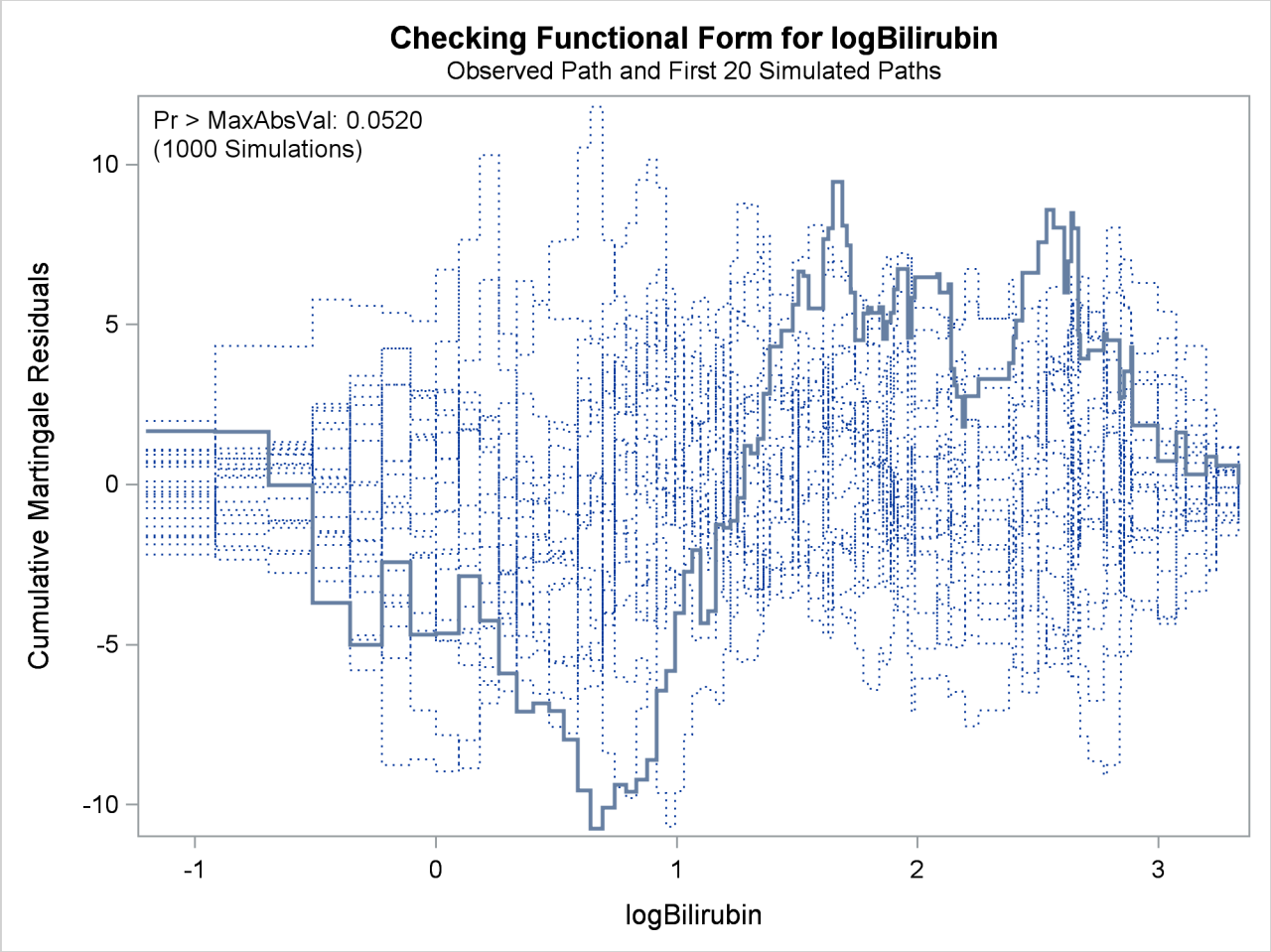
Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
logBilirubin	1	0.87072	0.08263	111.0484	<.0001	2.389
logProtime	1	2.37789	0.76674	9.6181	0.0019	10.782
logAlbumin	1	-2.53264	0.64819	15.2664	<.0001	0.079
Age	1	0.03940	0.00765	26.5306	<.0001	1.040
Edema	1	0.85934	0.27114	10.0447	0.0015	2.362

Output 86.12.5 Panel Plot of Cumulative Martingale Residuals versus log(Bilirubin)

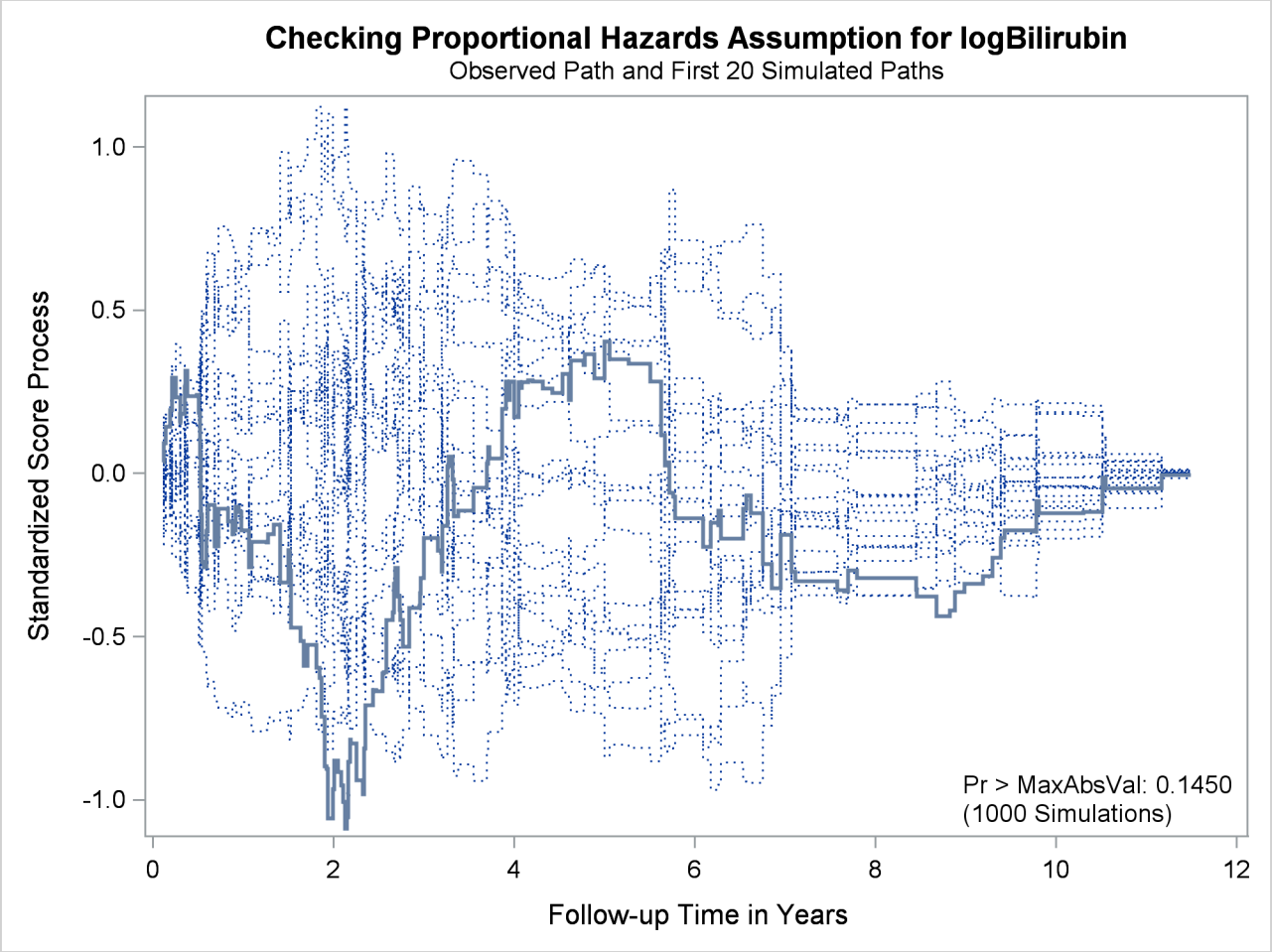


Output 86.12.6 Cumulative Martingale Residuals versus log(Bilirubin)



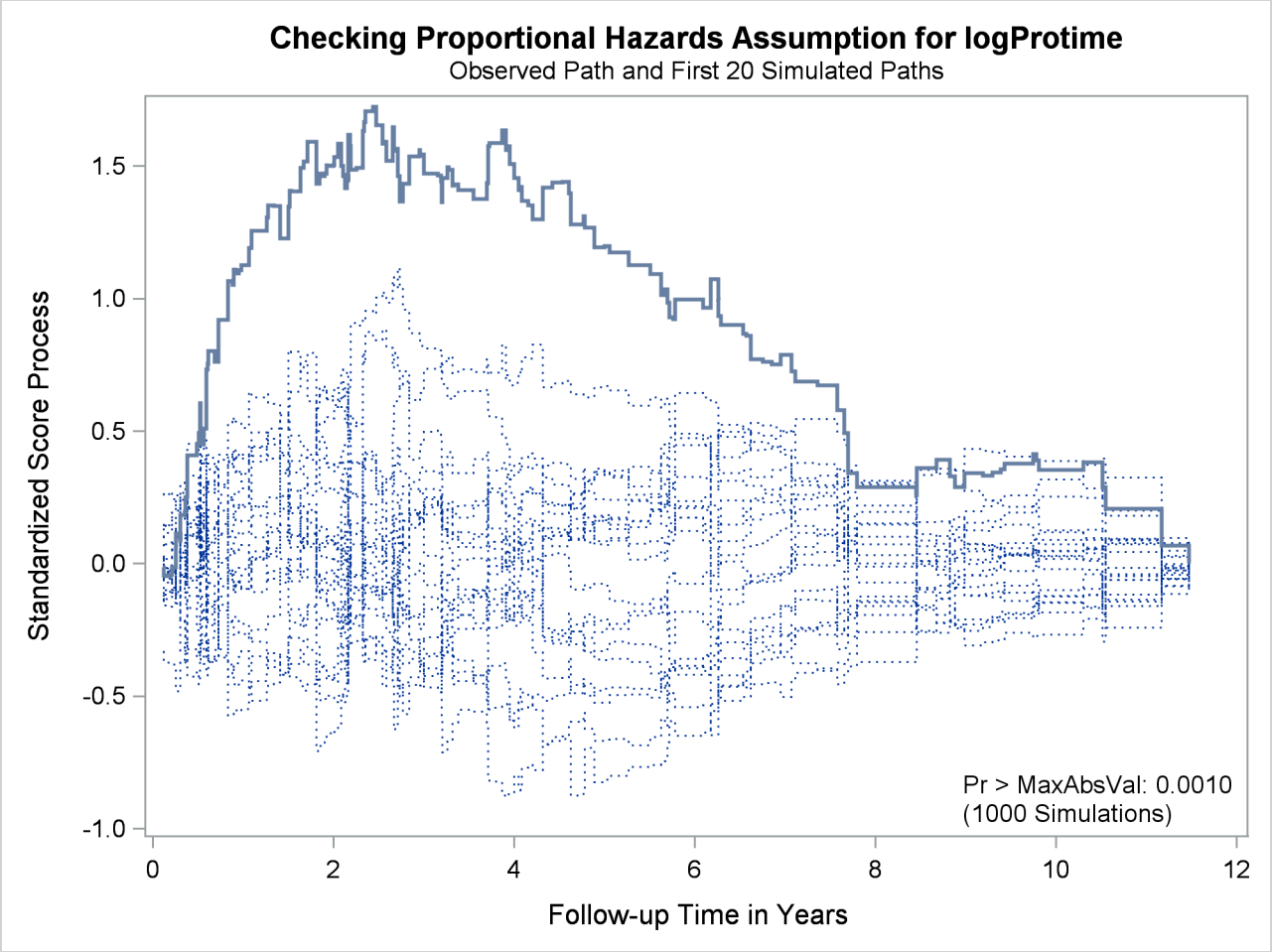
Output 86.12.7 and Output 86.12.8 display the results of proportional hazards assumption assessment for log(Bilirubin) and log(Protime), respectively. The latter plot reveals nonproportional hazards for log(Protime).

Output 86.12.7 Standardized Score Process for log(Bilirubin)



[

Output 86.12.8 Standardized Score Process for log(Protime)



Plots for log(Albumin), Age, and Edema are not shown here. The Kolmogorov-type supremum test results for all the covariates are shown in Output 86.12.9. In addition to log(Protime), the proportional hazards assumption appears to be violated for Edema.

Output 86.12.9 Kolmogorov-Type Supremum Tests for Proportional Hazards Assumption

Supremum Test for Proportionals Hazards Assumption

Variable	Maximum Absolute Value	Replications	Seed	Pr > MaxAbsVal
logBilirubin	1.0880	1000	19	0.1450
logProtime	1.7243	1000	19	0.0010
logAlbumin	0.8443	1000	19	0.4330
Age	0.7387	1000	19	0.4620
Edema	1.4350	1000	19	0.0330

Example 86.13: Bayesian Analysis of the Cox Model

This example illustrates the use of an informative prior. Hazard ratios, which are transformations of the regression parameters, are useful for interpreting survival models. This example also demonstrates the use of the HAZARDRATIO statement to obtain customized hazard ratios.

Consider the VALung data set in Example 86.3. In this example, the Cox model is used for the Bayesian analysis. The parameters are the coefficients of the continuous explanatory variables (Kps, Duration, and Age) and the coefficients of the design variables for the categorical explanatory variables (Prior, Cell, and Therapy). You use the CLASS statement in PROC PHREG to specify the categorical variables and their reference levels. Using the default reference parameterization, the design variables for the categorical variables are Prioryes (for Prior with Prior='no' as reference), Celladeno, Cellsmall, Cellsquamous (for Cell with Cell='large' as reference), and Therapytest (for Therapy='standard' as reference).

Consider the explanatory variable Kps. The Karnofsky performance scale index enables patients to be classified according to their functional impairment. The scale can range from 0 to 100—0 for dead, and 100 for a normal, healthy person with no evidence of disease. Recall that a flat prior was used for the regression coefficient in the example in the section "Bayesian Analysis" on page 6817. A flat prior on the Kps coefficient implies that the coefficient is as likely to be 0.1 as it is to be –100000. A coefficient of –5 means that a decrease of 20 points in the scale increases the hazard by $e^{-20\times-5}$(=2.68 $\times 10^{43}$)-fold, which is a rather unreasonable and unrealistic expectation for the effect of the Karnofsky index, much less than the value of –100000. Suppose you have a more realistic expectation: the effect is somewhat small and is more likely to be negative than positive, and a decrease of 20 points in the Karnofsky index will change the hazard from 0.9-fold (some minor positive effect) to 4-fold (a large negative effect). You can convert this opinion to a more informative prior on the Kps coefficient $\boldsymbol{\beta}_1$. Mathematically,

$$0.9 < e^{-20\boldsymbol{\beta}_1} < 4$$

which is equivalent to

$$-0.0693 < \boldsymbol{\beta}_1 < 0.0053$$

This becomes the plausible range that you believe the Kps coefficient can take. Now you can find a normal distribution that best approximates this belief by placing the majority of the prior distribution mass within this range. Assuming this interval is $\mu \pm 2\sigma$, where μ and σ are the mean and standard deviation of the normal prior, respectively, the hyperparameters μ and σ are computed as follows:

$$\begin{aligned} \mu &= \frac{-0.0693 + 0.0053}{2} = -0.032 \\ \sigma &= \frac{0.0053 - (-0.0693)}{4} = 0.0186 \end{aligned}$$

Note that a normal prior distribution with mean –0.0320 and standard deviation 0.0186 indicates that you believe, before looking at the data, that a decrease of 20 points in the Karnofsky index will probably change the hazard rate by 0.9-fold to 4-fold. This does not rule out the possibility that the Kps coefficient can take a more extreme value such as –5, but the probability of having such extreme values is very small.

Assume the prior distributions are independent for all the parameters. For the coefficient of Kps, you use a normal prior distribution with mean –0.0320 and variance 0.0186^2(=0.00035). For other parameters, you resort to using a normal prior distribution with mean 0 and variance 1E6, which is fairly noninformative. Means and variances of these independent normal distributions are saved in the data set Prior as follows:

```
proc format;
   value yesno 0='no' 10='yes';
run;

data VALung;
   drop check m;
   retain Therapy Cell;
   infile cards column=column;
   length Check $ 1;
   label Time='time to death in days'
         Kps='Karnofsky performance scale'
         Duration='months from diagnosis to randomization'
         Age='age in years'
         Prior='prior therapy'
         Cell='cell type'
         Therapy='type of treatment';
   format Prior yesno.;
   M=Column;
   input Check $ @@;
   if M>Column then M=1;
   if Check='s'|Check='t' then do;
      input @M Therapy $ Cell $;
      delete;
   end;
   else do;
      input @M Time Kps Duration Age Prior @@;
      Status=(Time>0);
      Time=abs(Time);
   end;
   datalines;
standard squamous
 72 60  7 69  0   411 70  5 64 10   228 60  3 38  0   126 60  9 63 10
118 70 11 65 10    10 20  5 49  0    82 40 10 69 10   110 80 29 68  0
314 50 18 43  0  -100 70  6 70  0    42 60  4 81  0     8 40 58 63 10
144 30  4 63  0   -25 80  9 52 10    11 70 11 48 10
standard small
 30 60  3 61  0   384 60  9 42  0     4 40  2 35  0    54 80  4 63 10
 13 60  4 56  0  -123 40  3 55  0   -97 60  5 67  0   153 60 14 63 10
 59 30  2 65  0   117 80  3 46  0    16 30  4 53 10   151 50 12 69  0
 22 60  4 68  0    56 80 12 43 10    21 40  2 55 10    18 20 15 42  0
139 80  2 64  0    20 30  5 65  0    31 75  3 65  0    52 70  2 55  0
287 60 25 66 10    18 30  4 60  0    51 60  1 67  0   122 80 28 53  0
 27 60  8 62  0    54 70  1 67  0     7 50  7 72  0    63 50 11 48  0
392 40  4 68  0    10 40 23 67 10
standard adeno
  8 20 19 61 10    92 70 10 60  0    35 40  6 62  0   117 80  2 38  0
132 80  5 50  0    12 50  4 63 10   162 80  5 64  0     3 30  3 43  0
 95 80  4 34  0
standard large
177 50 16 66 10   162 80  5 62  0   216 50 15 52  0   553 70  2 47  0
278 60 12 63  0    12 40 12 68 10   260 80  5 45  0   200 80 12 41 10
156 70  2 66  0  -182 90  2 62  0   143 90  8 60  0   105 80 11 66  0
103 80  5 38  0   250 70  8 53 10   100 60 13 37 10
```

```
test squamous
999 90 12 54 10   112 80  6 60  0   -87 80  3 48  0  -231 50  8 52 10
242 50  1 70  0   991 70  7 50 10   111 70  3 62  0     1 20 21 65 10
587 60  3 58  0   389 90  2 62  0    33 30  6 64  0    25 20 36 63  0
357 70 13 58  0   467 90  2 64  0   201 80 28 52 10     1 50  7 35  0
 30 70 11 63  0    44 60 13 70 10   283 90  2 51  0    15 50 13 40 10
test small
 25 30  2 69  0  -103 70 22 36 10    21 20  4 71  0    13 30  2 62  0
 87 60  2 60  0     2 40 36 44 10    20 30  9 54 10     7 20 11 66  0
 24 60  8 49  0    99 70  3 72  0     8 80  2 68  0    99 85  4 62  0
 61 70  2 71  0    25 70  2 70  0    95 70  1 61  0    80 50 17 71  0
 51 30 87 59 10    29 40  8 67  0
test adeno
 24 40  2 60  0    18 40  5 69 10   -83 99  3 57  0    31 80  3 39  0
 51 60  5 62  0    90 60 22 50 10    52 60  3 43  0    73 60  3 70  0
  8 50  5 66  0    36 70  8 61  0    48 10  4 81  0     7 40  4 58  0
140 70  3 63  0   186 90  3 60  0    84 80  4 62 10    19 50 10 42  0
 45 40  3 69  0    80 40  4 63  0
test large
 52 60  4 45  0   164 70 15 68 10    19 30  4 39 10    53 60 12 66  0
 15 30  5 63  0    43 60 11 49 10   340 80 10 64 10   133 75  1 65  0
111 60  5 64  0   231 70 18 67 10   378 80  4 65  0    49 30  3 37  0
;

data Prior;
   input _TYPE_ $ Kps Duration Age Prioryes Celladeno Cellsmall
         Cellsquamous Therapytest;
   datalines;
   Mean -0.0320 0 0 0 0 0 0 0
   Var  0.00035 1e6 1e6 1e6 1e6 1e6 1e6 1e6
   run;
```

In the following BAYES statement, COEFFPRIOR=NORMAL(INPUT=PRIOR) specifies the normal prior distribution for the regression coefficients whose details are contained in the data set Prior. Posterior summaries (means, standard errors, and quantiles) and intervals (equal-tailed and HPD) are requested by the STATISTICS= option. Autocorrelations and effective sample sizes are requested by the DIAGNOSTICS= option as convergence diagnostics along with the trace plots (PLOTS= option) for visual analysis. For comparisons of hazards, three HAZARDRATIO statements are specified—one for the variable Therapy, one for the variable Age, and one for the variable Cell.

```
ods graphics on;
proc phreg data=VALung;
   class Prior(ref='no') Cell(ref='large') Therapy(ref='standard');
   model Time*Status(0) = Kps Duration Age Prior Cell Therapy;
   bayes seed=1 coeffprior=normal(input=Prior) statistics=(summary interval)
         diagnostics=(autocorr ess) plots=trace;
   hazardratio 'Hazard Ratio Statement 1' Therapy;
   hazardratio 'Hazard Ratio Statement 2' Age / unit=10;
   hazardratio 'Hazard Ratio Statement 3' Cell;
run;
```

This analysis generates a posterior chain of 10,000 iterations after 2,000 iterations of burn-in, as depicted in Output 86.13.1.

Output 86.13.1 Model Information

The PHREG Procedure

Bayesian Analysis

Model Information		
Data Set	WORK.VALUNG	
Dependent Variable	Time	time to death in days
Censoring Variable	Status	
Censoring Value(s)	0	
Model	Cox	
Ties Handling	BRESLOW	
Sampling Algorithm	ARMS	
Burn-In Size	2000	
MC Sample Size	10000	
Thinning	1	

Output 86.13.2 displays the names of the parameters and their corresponding effects and categories.

Output 86.13.2 Parameter Names

Regression Parameter Information				
Parameter	**Effect**	**Prior**	**Cell**	**Therapy**
Kps	**Kps**			
Duration	**Duration**			
Age	**Age**			
Prioryes	**Prior**	yes		
Celladeno	**Cell**		adeno	
Cellsmall	**Cell**		small	
Cellsquamous	**Cell**		squamous	
Therapytest	**Therapy**			test

PROC PHREG computes the maximum likelihood estimates of regression parameters (Output 86.13.3). These estimates are used as the starting values for the simulation of posterior samples.

Output 86.13.3 Parameter Estimates

Maximum Likelihood Estimates					
Parameter	**DF**	**Estimate**	**Standard Error**	**95% Confidence Limits**	
Kps	1	-0.0326	0.00551	-0.0434	-0.0218
Duration	1	-0.00009	0.00913	-0.0180	0.0178
Age	1	-0.00855	0.00930	-0.0268	0.00969
Prioryes	1	0.0723	0.2321	-0.3826	0.5273
Celladeno	1	0.7887	0.3027	0.1955	1.3819
Cellsmall	1	0.4569	0.2663	-0.0650	0.9787
Cellsquamous	1	-0.3996	0.2827	-0.9536	0.1544
Therapytest	1	0.2899	0.2072	-0.1162	0.6961

Output 86.13.4 displays the independent normal prior for the analysis.

Output 86.13.4 Coefficient Prior

Independent Normal Prior for Regression Coefficients		
Parameter	**Mean**	**Precision**
Kps	-0.032	2857.143
Duration	0	1E-6
Age	0	1E-6
Prioryes	0	1E-6
Celladeno	0	1E-6
Cellsmall	0	1E-6
Cellsquamous	0	1E-6
Therapytest	0	1E-6

Fit statistics are displayed in Output 86.13.5. These statistics are useful for variable selection.

Output 86.13.5 Fit Statistics

Fit Statistics	
DIC (smaller is better)	966.260
pD (Effective Number of Parameters)	7.934

Summary statistics of the posterior samples are shown in Output 86.13.6 and Output 86.13.7. These results are quite comparable to the classical results based on maximizing the likelihood as shown in Output 86.13.3, since the prior distribution for the regression coefficients is relatively flat.

Output 86.13.6 Summary Statistics

The PHREG Procedure

Bayesian Analysis

Posterior Summaries						
				Percentiles		
Parameter	**N**	**Mean**	**Standard Deviation**	**25%**	**50%**	**75%**
Kps	10000	-0.0326	0.00523	-0.0362	-0.0326	-0.0291
Duration	10000	-0.00159	0.00954	-0.00756	-0.00093	0.00504
Age	10000	-0.00844	0.00928	-0.0147	-0.00839	-0.00220
Prioryes	10000	0.0742	0.2348	-0.0812	0.0737	0.2337
Celladeno	10000	0.7881	0.3065	0.5839	0.7876	0.9933
Cellsmall	10000	0.4639	0.2709	0.2817	0.4581	0.6417
Cellsquamous	10000	-0.4024	0.2862	-0.5927	-0.4025	-0.2106
Therapytest	10000	0.2892	0.2038	0.1528	0.2893	0.4240

Output 86.13.7 Interval Statistics

Posterior Intervals

Parameter	Alpha	Equal-Tail Interval		HPD Interval	
Kps	0.050	-0.0429	-0.0222	-0.0433	-0.0226
Duration	0.050	-0.0220	0.0156	-0.0210	0.0164
Age	0.050	-0.0263	0.00963	-0.0265	0.00941
Prioryes	0.050	-0.3936	0.5308	-0.3832	0.5384
Celladeno	0.050	0.1879	1.3920	0.1764	1.3755
Cellsmall	0.050	-0.0571	1.0167	-0.0888	0.9806
Cellsquamous	0.050	-0.9687	0.1635	-0.9641	0.1667
Therapytest	0.050	-0.1083	0.6930	-0.1284	0.6710

With autocorrelations retreating quickly to 0 (Output 86.13.8) and large effective sample sizes (Output 86.13.9), both diagnostics indicate a reasonably good mixing of the Markov chain. The trace plots in Output 86.13.10 also confirm the convergence of the Markov chain.

Output 86.13.8 Autocorrelation Diagnostics

The PHREG Procedure

Bayesian Analysis

Posterior Autocorrelations

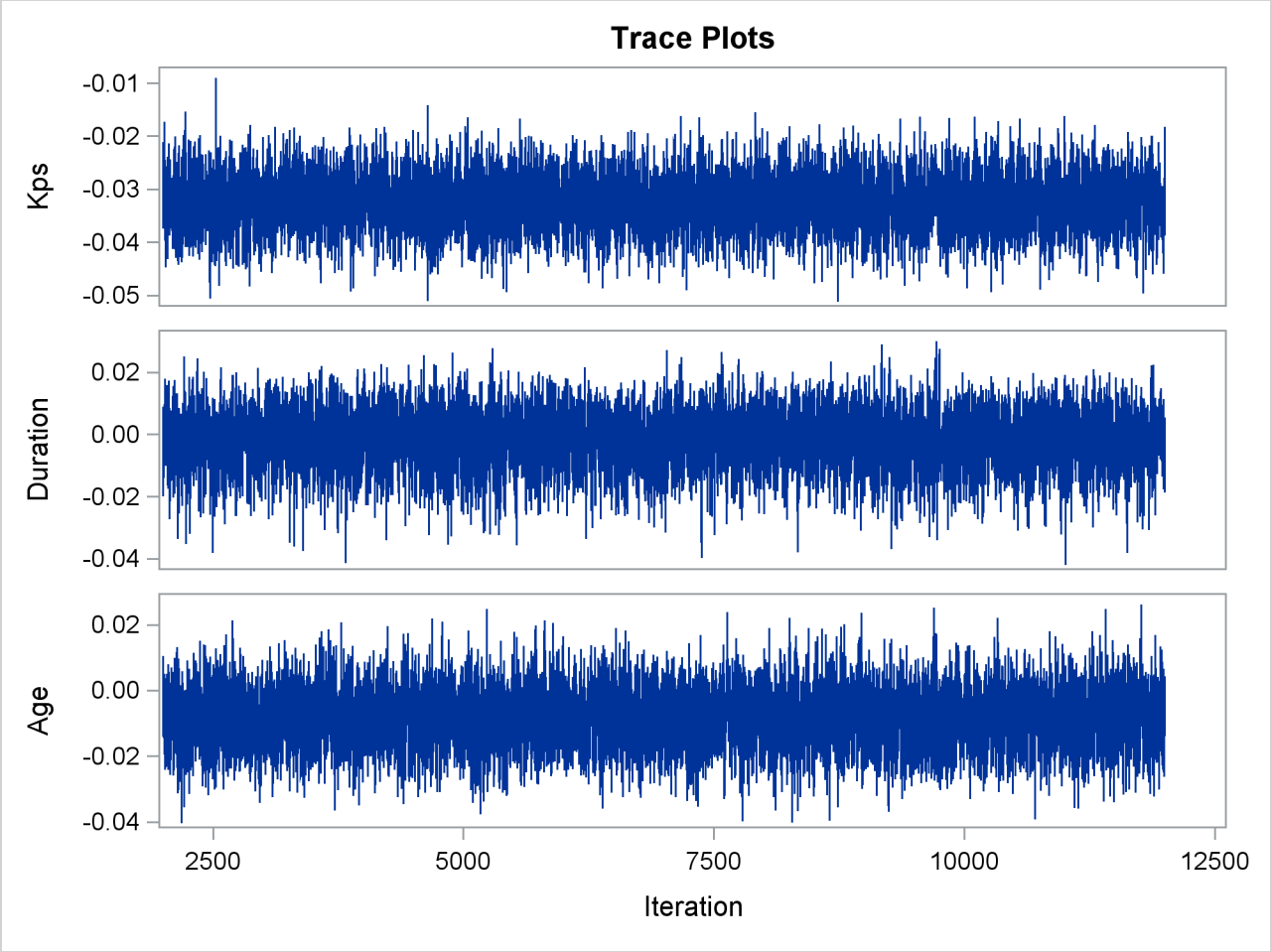
Parameter	Lag 1	Lag 5	Lag 10	Lag 50
Kps	0.1442	-0.0016	0.0096	-0.0013
Duration	0.2672	-0.0054	-0.0004	-0.0011
Age	0.1374	-0.0044	0.0129	0.0084
Prioryes	0.2507	-0.0271	-0.0012	0.0004
Celladeno	0.4160	0.0265	-0.0062	0.0190
Cellsmall	0.5055	0.0277	-0.0011	0.0271
Cellsquamous	0.3586	0.0252	-0.0044	0.0107
Therapytest	0.2063	0.0199	-0.0047	-0.0166

Output 86.13.9 Effective Sample Size Diagnostics

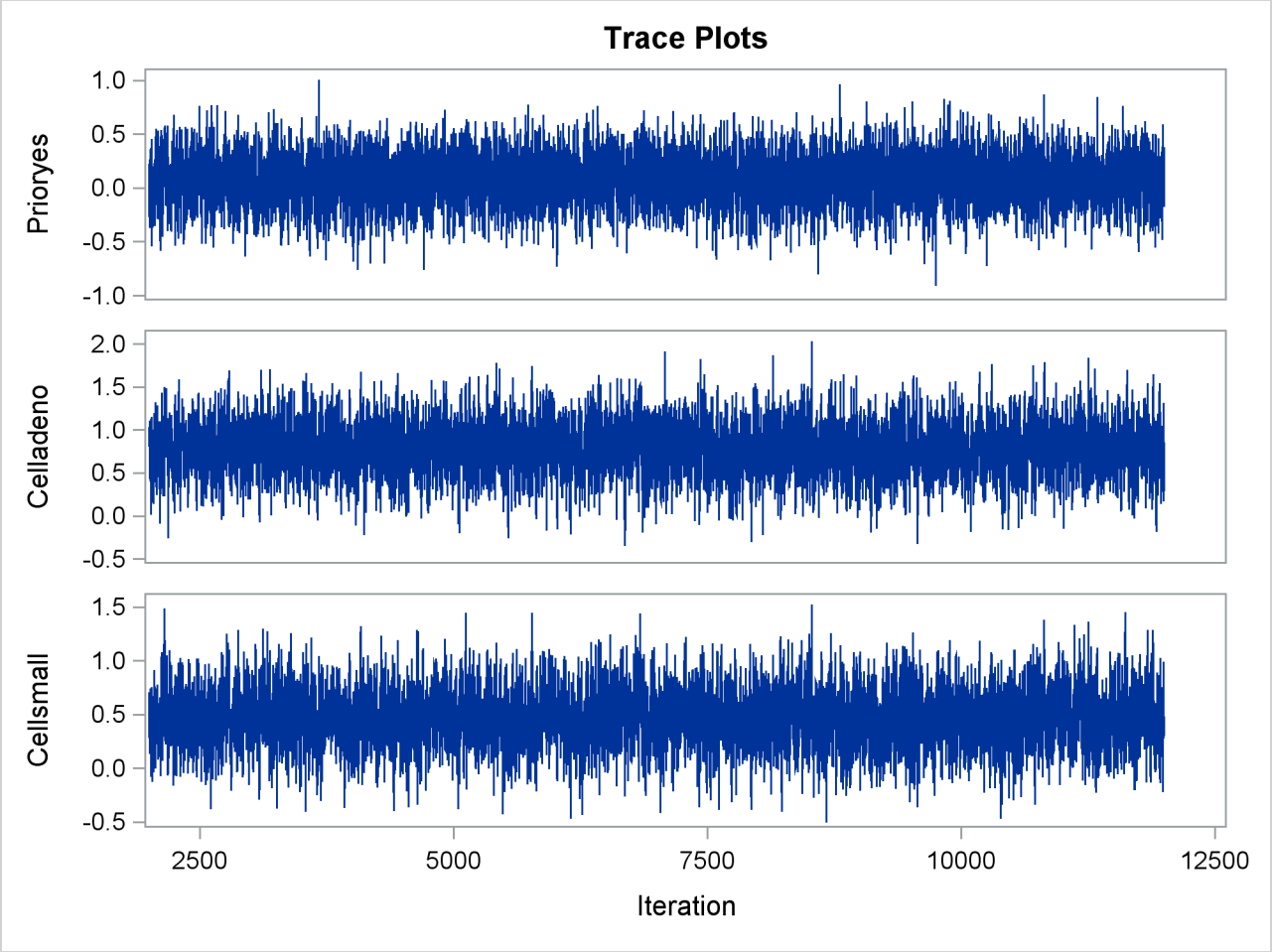
Effective Sample Sizes

Parameter	ESS	Autocorrelation Time	Efficiency
Kps	7046.7	1.4191	0.7047
Duration	5790.0	1.7271	0.5790
Age	7426.1	1.3466	0.7426
Prioryes	6102.2	1.6388	0.6102
Celladeno	3673.4	2.7223	0.3673
Cellsmall	3346.4	2.9883	0.3346
Cellsquamous	4052.8	2.4674	0.4053
Therapytest	6870.8	1.4554	0.6871

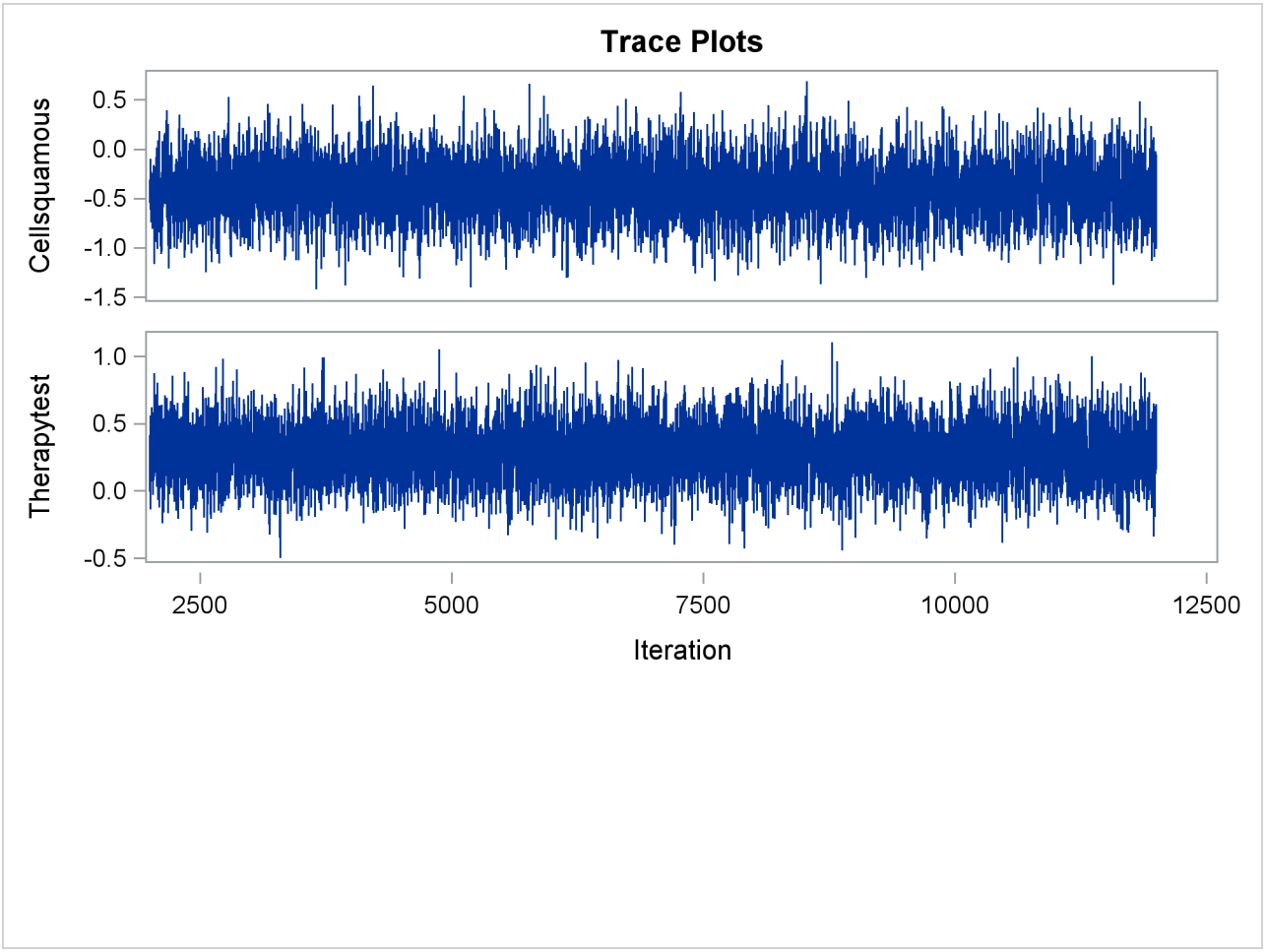
Output 86.13.10 Trace Plots



Output 86.13.10 *continued*



Output 86.13.10 *continued*



The first HAZARDRATIO statement compares the hazards between the standard therapy and the test therapy. Summaries of the posterior distribution of the corresponding hazard ratio are shown in Output 86.13.11. There is a 95% chance that the hazard ratio of standard therapy versus test therapy lies between 0.5 and 1.1.

Output 86.13.11 Hazard Ratio for Treatment

Hazard Ratio Statement 1: Hazard Ratios for type of treatment

				Quantiles						
Description	N	Mean	Standard Deviation	25%	50%	75%	95% Equal-Tail Interval		95% HPD Interval	
Therapy standard vs test	10000	0.7645	0.1573	0.6544	0.7488	0.8583	0.5001	1.1143	0.4788	1.0805

The second HAZARDRATIO statement assesses the change of hazards for an increase in Age of 10 years. Summaries of the posterior distribution of the corresponding hazard ratio are shown in Output 86.13.12.

Output 86.13.12 Hazard Ratio for Age

Hazard Ratio Statement 2: Hazard Ratios for age in years

				Quantiles						
Description	N	Mean	Standard Deviation	25%	50%	75%	95% Equal-Tail Interval		95% HPD Interval	
Age Unit=10	10000	0.9230	0.0859	0.8635	0.9195	0.9782	0.7685	1.1011	0.7650	1.0960

The third HAZARDRATIO statement compares the changes of hazards between two types of cells. For four types of cells, there are six different pairs of cell comparisons. The results are shown in Output 86.13.13.

Output 86.13.13 Hazard Ratios for Cell

Hazard Ratio Statement 3: Hazard Ratios for cell type

				Quantiles						
Description	N	Mean	Standard Deviation	25%	50%	75%	95% Equal-Tail Interval		95% HPD Interval	
Cell adeno vs large	10000	2.3048	0.7224	1.7929	2.1982	2.7000	1.2067	4.0227	1.0053	3.7057
Cell adeno vs small	10000	1.4377	0.4078	1.1522	1.3841	1.6704	0.7930	2.3999	0.7309	2.2662
Cell adeno vs squamous	10000	3.4449	1.0745	2.6789	3.2941	4.0397	1.8067	5.9727	1.6303	5.5946
Cell large vs small	10000	0.6521	0.1780	0.5264	0.6325	0.7545	0.3618	1.0588	0.3331	1.0041
Cell large vs squamous	10000	1.5579	0.4548	1.2344	1.4955	1.8089	0.8492	2.6346	0.7542	2.4575
Cell small vs squamous	10000	2.4728	0.7081	1.9620	2.3663	2.8684	1.3789	4.1561	1.2787	3.9263

Example 86.14: Bayesian Analysis of Piecewise Exponential Model

This example illustrates using a piecewise exponential model in a Bayesian analysis. Consider the Rats data set in the section "Getting Started: PHREG Procedure" on page 6813. In the following statements, PROC PHREG is used to carry out a Bayesian analysis for the piecewise exponential model. In the BAYES statement, the option PIECEWISE stipulates a piecewise exponential model, and PIECEWISE=HAZARD requests that the constant hazards be modeled in the original scale. By default, eight intervals of constant hazards are used, and the intervals are chosen such that each has roughly the same number of events.

```
data Rats;
   label Days  ='Days from Exposure to Death';
   input Days Status Group @@;
   datalines;
143 1 0   164 1 0   188 1 0   188 1 0
190 1 0   192 1 0   206 1 0   209 1 0
213 1 0   216 1 0   220 1 0   227 1 0
230 1 0   234 1 0   246 1 0   265 1 0
304 1 0   216 0 0   244 0 0   142 1 1
156 1 1   163 1 1   198 1 1   205 1 1
232 1 1   232 1 1   233 1 1   233 1 1
233 1 1   233 1 1   239 1 1   240 1 1
261 1 1   280 1 1   280 1 1   296 1 1
296 1 1   323 1 1   204 0 1   344 0 1
;
```

```
proc phreg data=Rats;
   model Days*Status(0)=Group;
   bayes seed=1 piecewise=hazard statistics=(summary interval)
         diagnostics=(autocorr geweke ess);
run;
```

The "Model Information" table in Output 86.14.1 shows that the piecewise exponential model is being used.

Output 86.14.1 Model Information

The PHREG Procedure

Bayesian Analysis

Model Information		
Data Set	WORK.RATS	
Dependent Variable	Days	Days from Exposure to Death
Censoring Variable	Status	
Censoring Value(s)	0	
Model	Piecewise Exponential	
Sampling Algorithm	ARMS	
Burn-In Size	2000	
MC Sample Size	10000	
Thinning	1	

By default the time axis is partitioned into eight intervals of constant hazard. Output 86.14.2 details the number of events and observations in each interval. Note that the constant hazard parameters are named Lambda1,..., Lambda8. You can supply your own partition by using the INTERVALS= suboption within the PIECEWISE=HAZARD option.

Output 86.14.2 Interval Partition

Constant Hazard Time Intervals				
Interval				
[Lower,	Upper)	N	Event	Hazard Parameter
0	176	5	5	Lambda1
176	201.5	5	5	Lambda2
201.5	218	7	5	Lambda3
218	232.5	5	5	Lambda4
232.5	233.5	4	4	Lambda5
233.5	253.5	5	4	Lambda6
253.5	288	4	4	Lambda7
288	Infty	5	4	Lambda8

The model parameters consist of the eight hazard parameters Lambda1, ..., Lambda8, and the regression coefficient Group. The maximum likelihood estimates are displayed in Output 86.14.3. Again, these estimates are used as the starting values for simulation of the posterior distribution.

Output 86.14.3 Maximum Likelihood Estimates

Maximum Likelihood Estimates

Parameter	DF	Estimate	Standard Error	95% Confidence Limits	
Lambda1	1	0.000953	0.000443	0.000084	0.00182
Lambda2	1	0.00794	0.00371	0.000672	0.0152
Lambda3	1	0.0156	0.00734	0.00120	0.0300
Lambda4	1	0.0236	0.0115	0.00112	0.0461
Lambda5	1	0.3669	0.1959	0	0.7509
Lambda6	1	0.0276	0.0148	0	0.0566
Lambda7	1	0.0262	0.0146	0	0.0548
Lambda8	1	0.0545	0.0310	0	0.1152
Group	1	-0.6223	0.3468	-1.3020	0.0573

Without using the PRIOR= suboption within the PIECEWISE=HAZARD option to specify the prior of the hazard parameters, the default is to use the noninformative and improper prior displayed in Output 86.14.4.

Output 86.14.4 Hazard Prior

Improper Prior for Hazards

Parameter	Prior
Lambda1	1 / Lambda1
Lambda2	1 / Lambda2
Lambda3	1 / Lambda3
Lambda4	1 / Lambda4
Lambda5	1 / Lambda5
Lambda6	1 / Lambda6
Lambda7	1 / Lambda7
Lambda8	1 / Lambda8

The noninformative uniform prior is used for the regression coefficient Group (Output 86.14.5), as in the section "Bayesian Analysis" on page 6817.

Output 86.14.5 Coefficient Prior

Uniform Prior for Regression Coefficients

Parameter	Prior
Group	Constant

Summary statistics for all model parameters are shown in Output 86.14.6 and Output 86.14.7.

Output 86.14.6 Summary Statistics

The PHREG Procedure

Bayesian Analysis

Posterior Summaries

Parameter	N	Mean	Standard Deviation	Percentiles 25%	50%	75%
Lambda1	10000	0.000945	0.000444	0.000624	0.000876	0.00118
Lambda2	10000	0.00782	0.00363	0.00519	0.00724	0.00979
Lambda3	10000	0.0155	0.00735	0.0102	0.0144	0.0195
Lambda4	10000	0.0236	0.0116	0.0152	0.0217	0.0297
Lambda5	10000	0.3634	0.1965	0.2186	0.3266	0.4685
Lambda6	10000	0.0278	0.0153	0.0166	0.0249	0.0356
Lambda7	10000	0.0265	0.0151	0.0157	0.0236	0.0338
Lambda8	10000	0.0558	0.0323	0.0322	0.0488	0.0721
Group	10000	-0.6154	0.3570	-0.8569	-0.6186	-0.3788

Output 86.14.7 Interval Statistics

Posterior Intervals

Parameter	Alpha	Equal-Tail Interval		HPD Interval	
Lambda1	0.050	0.000289	0.00199	0.000208	0.00182
Lambda2	0.050	0.00247	0.0165	0.00194	0.0152
Lambda3	0.050	0.00484	0.0331	0.00341	0.0301
Lambda4	0.050	0.00699	0.0515	0.00478	0.0462
Lambda5	0.050	0.0906	0.8325	0.0541	0.7469
Lambda6	0.050	0.00676	0.0654	0.00409	0.0580
Lambda7	0.050	0.00614	0.0648	0.00421	0.0569
Lambda8	0.050	0.0132	0.1368	0.00637	0.1207
Group	0.050	-1.3190	0.0893	-1.3379	0.0652

The requested diagnostics—namely, lag1, lag5, lag10, lag50 autocorrelations (Output 86.14.8), the Geweke diagnostics (Output 86.14.9), and the effective sample size diagnostics (Output 86.14.10)—show a good mixing of the Markov chain.

Output 86.14.8 Autocorrelations

The PHREG Procedure

Bayesian Analysis

Posterior Autocorrelations

Parameter	Lag 1	Lag 5	Lag 10	Lag 50
Lambda1	0.0705	0.0015	0.0017	-0.0076
Lambda2	0.0909	0.0206	-0.0013	-0.0039
Lambda3	0.0861	-0.0072	0.0011	0.0002
Lambda4	0.1447	-0.0023	0.0081	0.0082
Lambda5	0.1086	0.0072	-0.0038	-0.0028
Lambda6	0.1281	0.0049	-0.0036	0.0048
Lambda7	0.1925	-0.0011	0.0094	-0.0011
Lambda8	0.2128	0.0322	-0.0042	-0.0045
Group	0.5638	0.0410	-0.0003	-0.0071

Output 86.14.9 Geweke Diagnostics

Geweke Diagnostics

Parameter	z	Pr > |z|
Lambda1	-0.0705	0.9438
Lambda2	-0.4936	0.6216
Lambda3	0.5751	0.5652
Lambda4	1.0514	0.2931
Lambda5	0.8910	0.3729
Lambda6	0.2976	0.7660
Lambda7	1.6543	0.0981
Lambda8	0.6686	0.5038
Group	-1.2621	0.2069

Output 86.14.10 Effective Sample Size

Effective Sample Sizes

Parameter	ESS	Autocorrelation Time	Efficiency
Lambda1	7775.3	1.2861	0.7775
Lambda2	6874.8	1.4546	0.6875
Lambda3	7655.7	1.3062	0.7656
Lambda4	6337.1	1.5780	0.6337
Lambda5	6563.3	1.5236	0.6563
Lambda6	6720.8	1.4879	0.6721
Lambda7	5968.7	1.6754	0.5969
Lambda8	5137.2	1.9466	0.5137
Group	2980.4	3.3553	0.2980

Example 86.15: Analysis of Competing-Risks Data

Bone marrow transplant (BMT) is a standard treatment for acute leukemia. Klein and Moeschberger (1997) present a set of BMT data for 137 patients, grouped into three risk categories based on their status at the time of transplantation: acute lymphoblastic leukemia (ALL), acute myelocytic leukemia (AML) low-risk, and AML high-risk. During the follow-up period, some patients might relapse or some patients might die while in remission. Consider relapse to be the event of interest. Death is a competing risk because death impedes the occurrence of leukemia relapse. The Fine and Gray (1999) model is used to compare the risk categories on the disease-free survival.

The following DATA step creates the data set Bmt. The variable Disease represents the risk group of a patient, which is either ALL, AML-Low Risk, or AML-High Risk. The variable T represents the disease-free survival in days, which is the time to relapse, time to death, or censored. The variable Status has three values: 0 for censored observations, 1 for relapsed patients, and 2 for patients who die before experiencing a relapse.

```
proc format;
   value DiseaseGroup 1='ALL'
                      2='AML-Low Risk'
                      3='AML-High Risk';

data Bmt;
   input Disease T Status @@;
   label T='Disease-Free Survival in Days';
   format Disease DiseaseGroup.;
   datalines;
1   2081   0   1   1602   0   1   1496   0   1   1462   0   1   1433   0
1   1377   0   1   1330   0   1    996   0   1    226   0   1   1199   0
1   1111   0   1    530   0   1   1182   0   1   1167   0   1    418   2
1    383   1   1    276   2   1    104   1   1    609   1   1    172   2
1    487   2   1    662   1   1    194   2   1    230   1   1    526   2
1    122   2   1    129   1   1     74   1   1    122   1   1     86   2
1    466   2   1    192   1   1    109   1   1     55   1   1      1   2
1    107   2   1    110   1   1    332   2   2   2569   0   2   2506   0
2   2409   0   2   2218   0   2   1857   0   2   1829   0   2   1562   0
2   1470   0   2   1363   0   2   1030   0   2    860   0   2   1258   0
2   2246   0   2   1870   0   2   1799   0   2   1709   0   2   1674   0
2   1568   0   2   1527   0   2   1324   0   2    957   0   2    932   0
2    847   0   2    848   0   2   1850   0   2   1843   0   2   1535   0
2   1447   0   2   1384   0   2    414   2   2   2204   2   2   1063   2
2    481   2   2    105   2   2    641   2   2    390   2   2    288   2
2    421   1   2     79   2   2    748   1   2    486   1   2     48   2
2    272   1   2   1074   2   2    381   1   2     10   2   2     53   2
2     80   2   2     35   2   2    248   1   2    704   2   2    211   1
2    219   1   2    606   1   3   2640   0   3   2430   0   3   2252   0
3   2140   0   3   2133   0   3   1238   0   3   1631   0   3   2024   0
3   1345   0   3   1136   0   3    845   0   3    422   1   3    162   2
3     84   1   3    100   1   3      2   2   3     47   1   3    242   1
3    456   1   3    268   1   3    318   2   3     32   1   3    467   1
3     47   1   3    390   1   3    183   2   3    105   2   3    115   1
3    164   2   3     93   1   3    120   1   3     80   2   3    677   2
3     64   1   3    168   2   3     74   2   3     16   2   3    157   1
3    625   1   3     48   1   3    273   1   3     63   2   3     76   1
3    113   1   3    363   2
;
```

PROC PHREG enables you to plot the cumulative incidence function for each disease category, but first you must save these three Disease values in a SAS data set, as in the following DATA step:

```
data Risk;
   Disease=1; output;
   Disease=2; output;
   Disease=3; output;
   format Disease DiseaseGroup.;
   run;
```

The following statements use the PHREG procedure to fit the proportional subdistribution hazards model. To designate relapse (Status=1) as the event of interest, you specify EVENTCODE=1 in the MODEL statement. The HAZARDRATIO statement provides the hazard ratios for all pairs of disease groups. The COVARIATES= option in the BASELINE statement specifies the data set that contains the covariate settings for predicting cumulative incidence functions; and the OUT= option saves the prediction results in a SAS data set. The PLOTS= option in the PROC PHREG statement displays the cumulative incidence curves.

```
ods graphics on;
proc phreg data=Bmt plots(overlay=stratum)=cif;
   class Disease (order=internal ref=first);
   model T*Status(0)=Disease / eventcode=1;
   Hazardratio 'Pairwise' Disease / diff=pairwise;
   baseline covariates=Risk out=out1 cif=_all_ / seed=191;
run;
```

Output 86.15.1 displays the codes of different types of observations in the input data set. Relapse is the failure of interest with Status = 1, death is a competing failure with Status = 2, and censored observations are those with Status = 0. Out of the 137 transplant patients, 42 have a relapse, 41 die without experiencing a relapse, and 54 are censored (Output 86.15.2).

Output 86.15.1 Code for the Competing Failures and Censored Observations

The PHREG Procedure

Model Information		
Data Set	WORK.BMT	
Dependent Variable	T	Disease-Free Survival in Days
Status Variable	Status	
Event of Interest	1	
Competing Event	2	
Censored Value	0	

Output 86.15.2 Distribution of Events and Censored Observations

Summary of Failure Outcomes			
Total	**Event of Interest**	**Competing Event**	**Censored**
137	42	41	54

Output 86.15.3 shows a significant effect ($p = 0.0030$) of Disease on the disease-free survival. With the reference coding, the CLASS variable Disease is represented by two dummy variables. Parameter estimates and Wald tests for individual parameters are shown in Output 86.15.3.

Output 86.15.3 Wald Test of the Disease Effect

Type 3 Tests

Effect	DF	Wald Chi-Square	Pr > ChiSq
Disease	2	11.6406	0.0030

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
Disease	**AML-Low Risk**	1	-0.80340	0.42846	3.5160	0.0608	0.448	Disease AML-Low Risk
Disease	**AML-High Risk**	1	0.50849	0.36618	1.9283	0.1649	1.663	Disease AML-High Risk

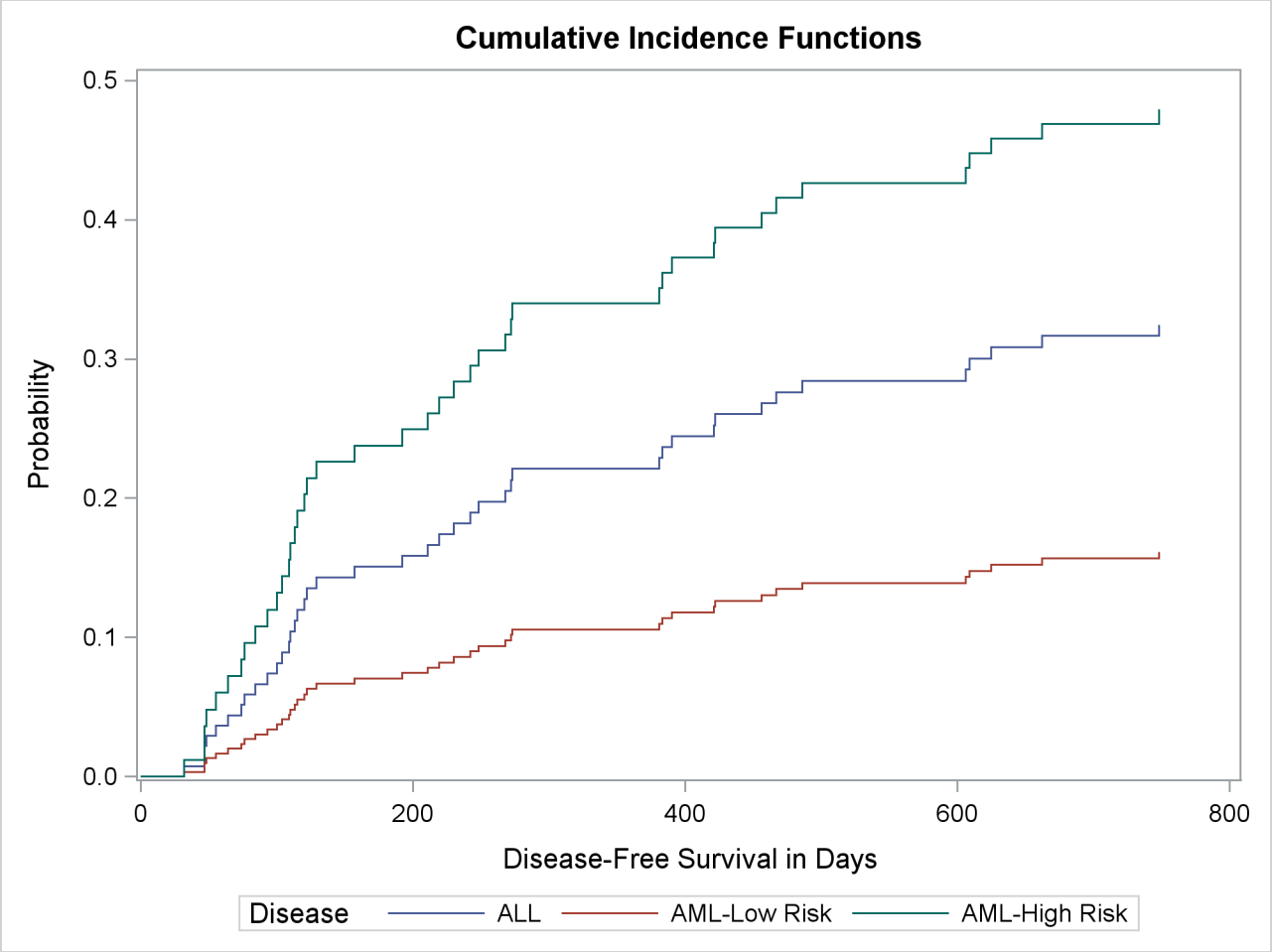
Hazard ratio estimates of one disease group relative to another disease group are displayed in Output 86.15.4. The hazard of relapse for the ALL patients is 2.2 times that for the AML-low risk patients, and the hazard for the AML-high risk patients is 1.7 times that for the ALL patients. It is expected that at any given time after the transplant, an AML high-risk patient is more likely to relapse than an ALL patient, and an ALL patient is more likely to relapse than an AML low-risk patient. Such ordering of probabilities is revealed in the plot of the cumulative incidence functions in Output 86.15.5.

Output 86.15.4 Pairwise Comparison of Disease Group

Pairwise: Hazard Ratios for Disease

Description	Point Estimate	95% Wald Confidence Limits	
Disease ALL vs AML-Low Risk	2.233	0.964	5.171
Disease AML-Low Risk vs ALL	0.448	0.193	1.037
Disease ALL vs AML-High Risk	0.601	0.293	1.233
Disease AML-High Risk vs ALL	1.663	0.811	3.408
Disease AML-Low Risk vs AML-High Risk	0.269	0.127	0.573
Disease AML-High Risk vs AML-Low Risk	3.713	1.745	7.900

Output 86.15.5 CIF of the Three Disease Groups



You use the following statements to display the cumulative incidence prediction for the ALL (Disease=1) risk group:

```
proc print data=Out1(where=(Disease=1));
   title 'CIF Estimates and 95% Confidence limits for the ALL Group';
run;
```

Output 86.15.6 Cumulative Incidence Prediction

CIF Estimates and 95% Confidence limits for the ALL Group

Obs	Disease	T	CIF	StdErrCIF	LowerCIF	UpperCIF
1	ALL	0	0.00000	.	.	.
2	ALL	32	0.00727	0.007237	0.00103	0.05114
3	ALL	47	0.02183	0.014323	0.00604	0.07898
4	ALL	48	0.02922	0.017822	0.00884	0.09657
5	ALL	55	0.03663	0.019106	0.01318	0.10181
6	ALL	64	0.04405	0.019259	0.01870	0.10378
7	ALL	74	0.05151	0.019951	0.02411	0.11005
8	ALL	76	0.05897	0.025533	0.02524	0.13778
9	ALL	84	0.06646	0.025378	0.03145	0.14048
10	ALL	93	0.07400	0.025092	0.03807	0.14383
11	ALL	100	0.08158	0.030460	0.03924	0.16959
12	ALL	104	0.08920	0.029038	0.04712	0.16883
13	ALL	109	0.09682	0.033564	0.04907	0.19100
14	ALL	110	0.10443	0.035734	0.05341	0.20422
15	ALL	113	0.11205	0.041176	0.05453	0.23026
16	ALL	115	0.11972	0.037619	0.06467	0.22163
17	ALL	120	0.12742	0.036521	0.07266	0.22347
18	ALL	122	0.13518	0.042929	0.07254	0.25190
19	ALL	129	0.14293	0.041747	0.08063	0.25336
20	ALL	157	0.15068	0.046376	0.08243	0.27545
21	ALL	192	0.15848	0.051406	0.08392	0.29928
22	ALL	211	0.16628	0.058106	0.08383	0.32983
23	ALL	219	0.17404	0.056257	0.09236	0.32794
24	ALL	230	0.18185	0.053563	0.10210	0.32392
25	ALL	242	0.18967	0.065355	0.09653	0.37265
26	ALL	248	0.19753	0.057829	0.11128	0.35062
27	ALL	268	0.20535	0.054765	0.12176	0.34634
28	ALL	272	0.21322	0.058189	0.12489	0.36402
29	ALL	273	0.22105	0.061340	0.12832	0.38080
30	ALL	381	0.22893	0.061228	0.13554	0.38669
31	ALL	383	0.23677	0.062212	0.14147	0.39626
32	ALL	390	0.24461	0.063708	0.14682	0.40754
33	ALL	421	0.25250	0.070833	0.14571	0.43757
34	ALL	422	0.26035	0.063694	0.16118	0.42053
35	ALL	456	0.26825	0.067518	0.16379	0.43932
36	ALL	467	0.27621	0.073253	0.16424	0.46450
37	ALL	486	0.28422	0.066216	0.18004	0.44871
38	ALL	606	0.29233	0.067521	0.18590	0.45971
39	ALL	609	0.30039	0.079301	0.17905	0.50396
40	ALL	625	0.30845	0.067182	0.20128	0.47270
41	ALL	662	0.31657	0.070668	0.20439	0.49033
42	ALL	748	0.32469	0.082845	0.19692	0.53537

Output 86.15.6 shows the point estimate and the confidence limits for the cumulative incidence at each distinct time when the event of interest occurred for the ALL patients. The predictions for the AML-low risk patients and AML-high risk patients are not shown.

Example 86.16: Concordance and ROC Curves

The concordance statistic and ROC curves are popular diagnostic tools for a logistic regression model. For a survival model, ROC curves are time-sensitive. That is, you might have different ROC curves at different time points. Two different ways of computing the concordance statistic are available. Each method estimates a different measure of concordance probability.

The data set Liver, presented in Example 86.12, is used in this example to illustrate the concordance statistic and time-dependent ROC curves. The data set consists of 418 patients who have primary biliary cirrhosis (PBC). In the data set, the variable Time represents the follow-up time in years (which is the time from registration to the earlier of liver transplantation, death, or study termination), the variable Status is the censoring indicator (1 for death and 0 for censored), and the explanatory variables are Age (age in years), Albumin (serum albumin level in g/dl), Bilirubin (serum bilirubin level in mg/dl), Edema (presence of edema), and Protime (prothrombin time in seconds).

The following statements use the PHREG procedure to fit the Cox regression model that uses Bilirubin, Age, and Edema as explanatory variables. The CONCORDANCE option in the PROC PHREG statement requests that Harrell's concordance statistics be displayed. The PLOTS=ROC option plots the time-dependent ROC curves at time points 2, 4, 6, 8, and 10 years, which are specified in the AT= suboption in the ROCOPTIONS option.

```
ods graphics on;
proc phreg data=Liver concordance plots=roc rocoptions(at=2 to 10 by 2);
   model Time*Status(0)=Bilirubin Age Edema;
run;
```

Results of the Harrell concordance statistics are shown in Output 86.16.1. There are 34,798 concordance pairs, 8,884 discordance pairs, 2 pairs that are tied in the linear predictor, and 5 pairs that are tied in the follow-up time, which gives a concordance estimate of 0.7966. You can specify CONCORDANCE=HARRELL(SE) to compute the standard error of Harrell's concordance statistic, or you can use specify CONCORDANCE=UNO for an alternative concordance measure.

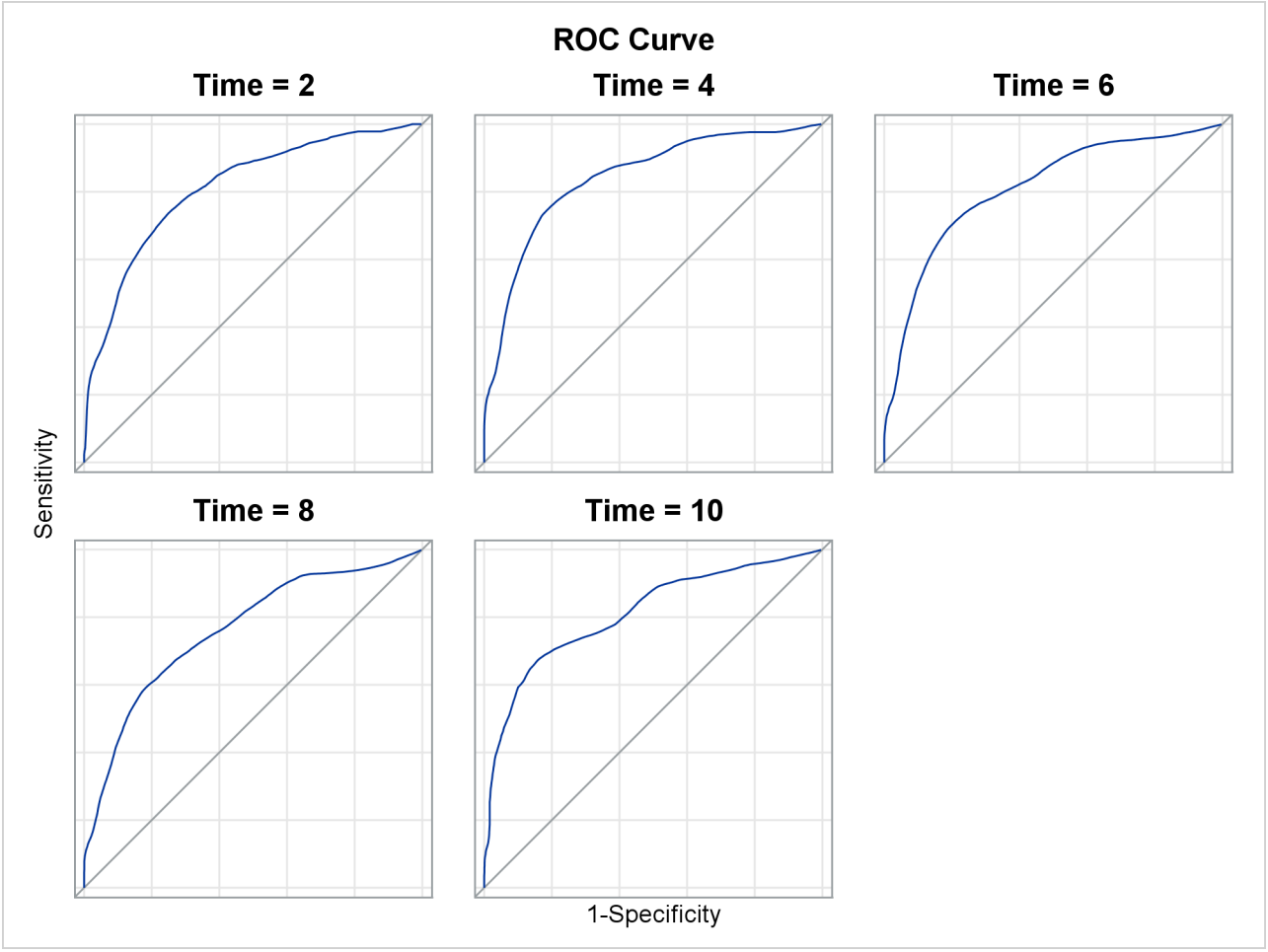
Output 86.16.1 Concordance Statistics

The PHREG Procedure

Harrell's Concordance Statistic					
		Comparable Pairs			
Source	Estimate	Concordance	Discordance	Tied in Predictor	Tied in Time
Model	0.7966	34798	8884	2	5

Output 86.16.2 shows the time-dependent ROC curves at the selected years. By default, these curves are computed by the nearest neighbors technique of Heagerty, Lumley, and Pepe (2000) and are displayed in a panel. It appears that among the five selected years, year 4 has the largest area under the curve (AUC), year 8 has the lowest AUC, and the others are in between. If you specify the OVERLAY=INDIVIDUAL global plot option to display individual plots, each plot also displays the area under the ROC curve.

Output 86.16.2 ROC Plot at Selected Time Points

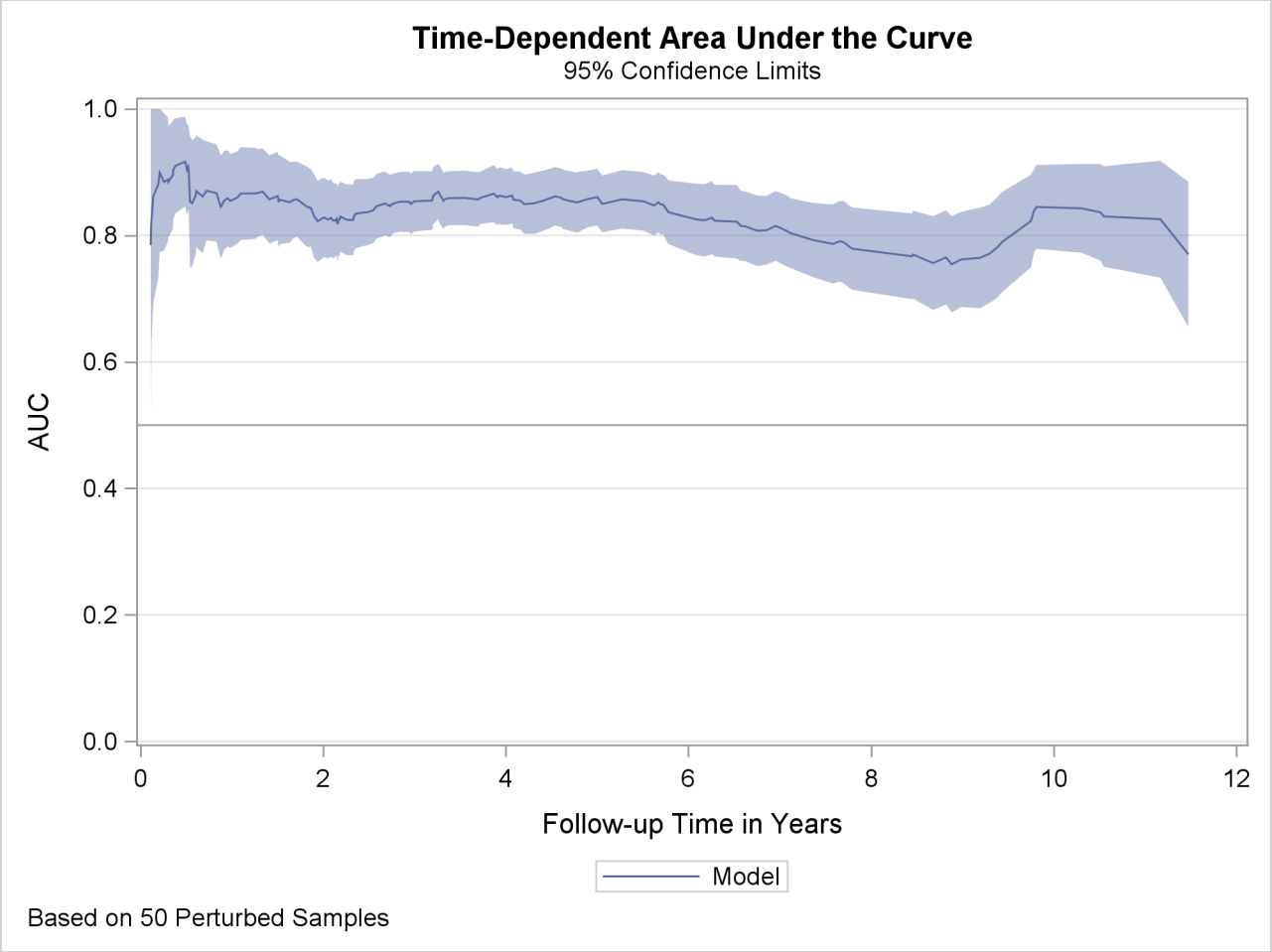


Time-dependent ROC curves change only at the distinct event times. You can examine the area under the curve at all distinct event times by plotting the curve of the AUC. The following statements plot the curve of the AUC of the fitted model and display the 95% pointwise confidence limits. The PLOTS=AUC option in the PROC PHREG statement plots the AUC curve. The ROCOPTIONS in the PROC PHREG statement enables you to specify the inverse probability of censoring weighting (IPCW) method to compute the ROC curves, and the CL suboption requests pointwise confidence limits for the AUC curve.

```
proc phreg data=Liver plots=auc rocoptions(method=ipcw(cl seed=1234));
   model Time*Status(0)=Bilirubin Age Edema;
run;
```

Output 86.16.3 displays the AUC curve and the 95% confidence limits for the fitted model. The AUC statistic reaches a high of 0.92 at Year 0.21 but mostly hovers around 0.8.

Output 86.16.3 AUC Plot with 95% Confidence Limits



Consider three submodels of the previously fitted Cox model, each of which contains two of the three covariates: Bilirubin, Age, and Edema. You can use the Uno et al. (2011) methodology to assess the difference of the concordance probabilities between any two submodels. In the following statements, three ROC statements are specified, one for each submodel. The DIFF suboption in CONCORDANCE=UNO in the PROC PHREG statement requests that all pairwise differences be calculated. The SE suboption requests that standard error be computed for each pairwise difference, based on 100 perturbation samples as specified by the ITER= suboption. The seed of the random generator for the perturbation resampling is set to be 1234. The NOFIT option is specified in the MODEL statement, because there is no need to fit the specified model.

```
proc phreg data=Liver concordance=uno(diff se seed=1234 iter=100);
   model Time*Status(0)=Bilirubin Age Edema / nofit;
   roc 'Bilirubin+Age' Bilirubin Age;
   roc 'Age+Edema' Age Edema;
   roc 'Bilirubin+Edema' Bilirubin Edema;
run;
```

Output 86.16.4 displays results of the concordance analysis. It appears that the two submodels that contain Bilirubin have a significantly larger concordance probability than the submodel without Bilirubin. In other words, the two submodels that contain Bilirubin predict the survival outcomes better than the model without Bilirubin.

Output 86.16.4 Comparing Uno's Concordance Estimates

The PHREG Procedure

Differences in Uno's Concordance Statistic

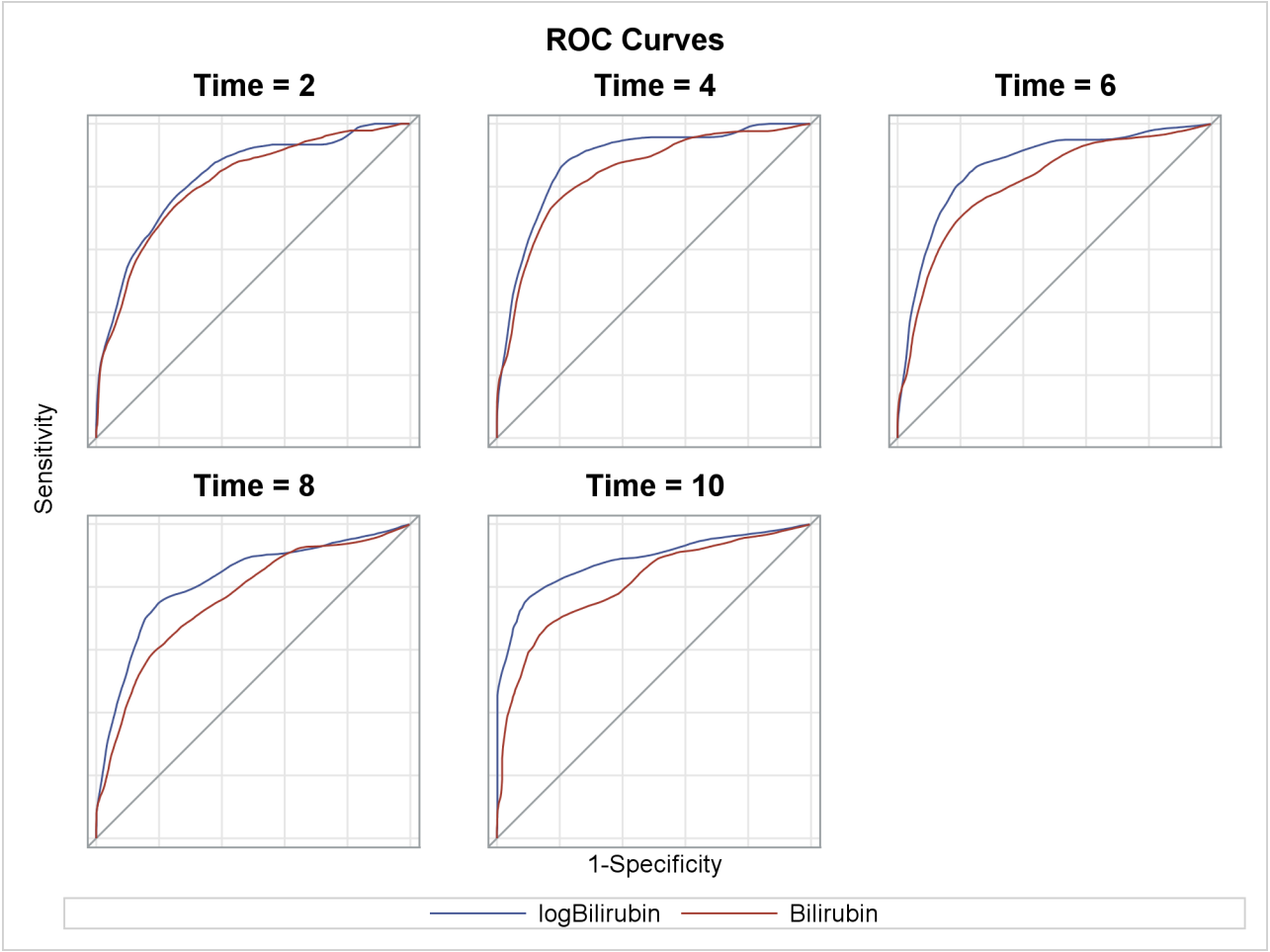
Source	_Source	Estimate	Standard Error	Chi-Square	Pr > ChiSq
Bilirubin+Age	Age+Edema	0.0972	0.0232	17.57	<.0001
Bilirubin+Age	Bilirubin+Edema	-0.0264	0.0231	1.31	0.2529
Age+Edema	Bilirubin+Edema	-0.1236	0.0287	18.51	<.0001

Example 86.12 demonstrated that the log transform is a much improved functional form for Bilirubin in a Cox regression model. It is expected that the model with Bilirubin in the log scale would have a better discriminating power than the model with Bilirubin in the original scale. In the following statements, PROC PHREG is used to fit the model with the log transform for Bilirubin. By using the OUTPUT statement, the linear predictor variable is saved as the variable Y in the output data set Liver2. With Liver2 as the input data set, PROC PHREG is called to fit the Cox model with Bilirubin in the original scale. The linear predictor variable Y is specified in the ROC statement as the PRED= variable.

```
proc phreg data=Liver;
   model Time*Status(0)=logBilirubin Age Edema;
   logBilirubin = log(Bilirubin);
   output out=Liver2 xbeta=Y;
run;
proc phreg data=Liver2 plots=roc rocoptions(at=2 to 10 by 2);
   model Time*Status(0)=Bilirubin Age Edema / roclabel='Bilirubin';
   roc 'logBilirubin' pred=Y;
run;
```

Output 86.16.5 displays the ROC curves of the two competing models. The ROC curve for the model with the log scale for Bilirubin essentially lies above that of its counterpart with the original scale for all the selected time points. This leads to the conclusion that the log transform for Bilirubin improves the predictive power of the model.

Output 86.16.5 ROC Plots to Evaluate the Log Transform for Bilirubin



References

Akritas, M. G. (1994). "Nearest Neighbor Estimation of a Bivariate Distribution under Random Censoring." *Annals of Statistics* 22:1299–1327.

Andersen, P. K., Borgan, Ø., Gill, R. D., and Keiding, N. (1992). *Statistical Models Based on Counting Processes*. New York: Springer-Verlag.

Andersen, P. K., and Gill, R. D. (1982). "Cox's Regression Model Counting Process: A Large Sample Study." *Annals of Statistics* 10:1100–1120.

Binder, D. A. (1992). "Fitting Cox's Proportional Hazards Models from Survey Data." *Biometrika* 79:139–147.

Blanche, P., Latouche, A., and Viallon, V. (2013). "Time-Dependent AUC with Right-Censored Data: A Survey." In *Risk Assessment and Evaluation of Predictions*, edited by M.-L. T. Lee, M. Gail, R. Pfeiffer, G. Satten, T. Cai, and A. Gandy, 239–251. New York: Springer.

Borgan, Ø., and Liestøl, K. (1990). "A Note on Confidence Interval and Bands for the Survival Curves Based on Transformations." *Scandinavian Journal of Statistics* 18:35–41.

Breslow, N. E. (1972). "Discussion of Professor Cox's Paper." *Journal of the Royal Statistical Society, Series B* 34:216–217.

Breslow, N. E. (1974). "Covariance Analysis of Censored Survival Data." *Biometrics* 30:89–99.

Breslow, N. E., and Clayton, D. G. (1993). "Approximate Inference in Generalized Linear Mixed Models." *Journal of the American Statistical Association* 88:9–25.

Bryson, M. C., and Johnson, M. E. (1981). "The Incidence of Monotone Likelihood in the Cox Model." *Technometrics* 23:381–383.

Cain, K. C., and Lange, N. T. (1984). "Approximate Case Influence for the Proportional Hazards Regression Model with Censored Data." *Biometrics* 40:493–499.

Chambless, L. E., and Diao, G. (2006). "Estimation of Time-Dependent Area under the ROC Curve for Long-Term Risk Prediction." *Statistics in Medicine* 25:3474–3486.

Cox, D. R. (1972). "Regression Models and Life Tables." *Journal of the Royal Statistical Society, Series B* 20:187–220. With discussion.

Cox, D. R. (1975). "Partial Likelihood." *Biometrika* 62:269–276.

Crowley, J., and Hu, M. (1977). "Covariance Analysis of Heart Transplant Survival Data." *Journal of the American Statistical Association* 72:27–36.

DeLong, D. M., Guirguis, G. H., and So, Y. C. (1994). "Efficient Computation of Subset Selection Probabilities with Application to Cox Regression." *Biometrika* 81:607–611.

Efron, B. (1977). "The Efficiency of Cox's Likelihood Function for Censored Data." *Journal of the American Statistical Association* 72:557–565.

Fine, J. P., and Gray, R. J. (1999). "A Proportional Hazards Model for the Subdistribution of a Competing Risk." *Journal of the American Statistical Association* 94:496–509.

Firth, D. (1993). "Bias Reduction of Maximum Likelihood Estimates." *Biometrika* 80:27–38.

Fleming, T. R., and Harrington, D. P. (1984). "Nonparametric Estimation of the Survival Distribution in Censored Data." *Communications in Statistics—Theory and Methods* 13:2469–2486.

Fleming, T. R., and Harrington, D. P. (1991). *Counting Processes and Survival Analysis*. New York: John Wiley & Sons.

Furnival, G. M., and Wilson, R. W. (1974). "Regression by Leaps and Bounds." *Technometrics* 16:499–511.

Gail, M. H., and Byar, D. P. (1986). "Variance Calculations for Direct Adjusted Survival Curves, with Applications to Testing for No Treatment Effect." *Biometrical Journal* 28:587–599.

Gail, M. H., Lubin, J. H., and Rubinstein, L. V. (1981). "Likelihood Calculations for Matched Case-Control Studies and Survival Studies with Tied Death Times." *Biometrika* 68:703–707.

Gilks, W. R., Best, N. G., and Tan, K. K. C. (1995). "Adaptive Rejection Metropolis Sampling within Gibbs Sampling." *Journal of the Royal Statistical Society, Series C* 44:455–472.

Grambsch, P. M., and Therneau, T. M. (1994). "Proportional Hazards Tests and Diagnostics Based on Weighted Residuals." *Biometrika* 81:515–526.

Gray, R. J. (1992). "Flexible Method for Analyzing Survival Data Using Splines, with Applications to Breast Cancer Prognosis." *Journal of the American Statistical Association* 87:942–951.

Harrell, F. E. (1986). "The PHGLM Procedure." In *SUGI Supplemental Library Guide, Version 5 Edition*. Cary, NC: SAS Institute Inc.

Harrell, F. E., Jr., Lee, K. L., Califf, R. M., Pryor, D. B., and Rosati, R. A. (1984). "Regression Modelling Strategies for Improved Prognostic Prediction." *Statistics in Medicine* 3:143–152.

Heagerty, P. J., Lumley, T., and Pepe, M. S. (2000). "Time-Dependent ROC Curves for Censored Survival Data and a Diagnostic Marker." *Biometrics* 56:337–344.

Heagerty, P. J., and Zheng, Y. (2005). "Survival Model Predictive Accuracy and ROC Curves." *Biometrics* 61:92–105.

Heinze, G. (1999). *The Application of Firth's Procedure to Cox and Logistic Regression*. Technical Report 10, updated January 2001, Department of Medical Computer Sciences, Section of Clinical Biometrics, University of Vienna.

Heinze, G., and Schemper, M. (2001). "A Solution to the Problem of Monotone Likelihood in Cox Regression." *Biometrics* 51:114–119.

Hosmer, D. W., Jr., and Lemeshow, S. (1989). *Applied Logistic Regression*. New York: John Wiley & Sons.

Ibrahim, J. G., Chen, M.-H., and Sinha, D. (2001). *Bayesian Survival Analysis*. New York: Springer-Verlag.

Kalbfleisch, J. D., and Prentice, R. L. (1980). *The Statistical Analysis of Failure Time Data*. New York: John Wiley & Sons.

Kang, L., Chen, W., Petrick, N. A., and Gallas, B. D. (2015). "Comparing Two Correlated C Indices with Right-Censored Survival Outcome: A One-Shot Nonparametric Approach." *Statistics in Medicine* 34:685–703.

Kass, R. E., Carlin, B. P., Gelman, A., and Neal, R. M. (1998). "Markov Chain Monte Carlo in Practice: A Roundtable Discussion." *American Statistician* 52:93–100.

Klein, J. P., and Moeschberger, M. L. (1997). *Survival Analysis: Techniques for Censored and Truncated Data*. New York: Springer-Verlag.

Klein, J. P., and Moeschberger, M. L. (2003). *Survival Analysis: Techniques for Censored and Truncated Data*. 2nd ed. New York: Springer-Verlag.

Krall, J. M., Uthoff, V. A., and Harley, J. B. (1975). "A Step-Up Procedure for Selecting Variables Associated with Survival." *Biometrics* 31:49–57.

Lawless, J. F. (2003). *Statistical Model and Methods for Lifetime Data*. 2nd ed. New York: John Wiley & Sons.

Lawless, J. F., and Nadeau, C. (1995). "Some Simple Robust Methods for the Analysis of Recurrent Events." *Technometrics* 37:158–168.

Lee, E. W., Wei, L. J., and Amato, D. A. (1992). "Cox-Type Regression Analysis for Large Numbers of Small Groups of Correlated Failure Time Observations." In *Survival Analysis: State of the Art*, edited by J. P. Klein and P. K. Goel, 237–247. Dordrecht, Netherlands: Kluwer Academic.

Lin, D. Y. (1994). "Cox Regression Analysis of Multivariate Failure Time Data: The Marginal Approach." *Statistics in Medicine* 13:2233–2247.

Lin, D. Y., and Wei, L. J. (1989). "The Robust Inference for the Proportional Hazards Model." *Journal of the American Statistical Association* 84:1074–1078.

Lin, D. Y., Wei, L. J., Yang, I., and Ying, Z. (2000). "Semiparametric Regression for the Mean and Rate Functions of Recurrent Events." *Journal of the Royal Statistical Society, Series B* 62:711–730.

Lin, D. Y., Wei, L. J., and Ying, Z. (1993). "Checking the Cox Model with Cumulative Sums of Martingale-Based Residuals." *Biometrika* 80:557–572.

Littell, R. C., Freund, R. J., and Spector, P. C. (1991). *SAS System for Linear Models*. 3rd ed. Cary, NC: SAS Institute Inc.

Makuch, R. W. (1982). "Adjusted Survival Curve Estimation Using Covariates." *Journal of Chronic Diseases* 35:437–443.

Muller, K. E., and Fetterman, B. A. (2002). *Regression and ANOVA: An Integrated Approach Using SAS Software*. Cary, NC: SAS Institute Inc.

Nelson, W. (2002). *Recurrent Events Data Analysis for Product Repairs, Disease Recurrences, and Other Applications*. Philadelphia: SIAM.

Neuberger, J., Altman, D. G., Christensen, E., Tygstrup, N., and Williams, R. (1986). "Use of a Prognostic Index in Evaluation of Liver Transplantation for Primary Biliary Cirrhosis." *Transplantation* 41:713–716.

Pepe, M. S., and Cai, J. (1993). "Some Graphical Displays and Marginal Regression Analyses for Recurrent Failure Times and Time Dependent Covariates." *Journal of the American Statistical Association* 88:811–820.

Pettitt, A. N., and Bin Daud, I. (1989). "Case-Weighted Measures of Influence for Proportional Hazards Regression." *Journal of the Royal Statistical Society, Series C* 38:313–329.

Prentice, R. L., Williams, B. J., and Peterson, A. V. (1981). "On the Regression Analysis of Multivariate Failure Time Data." *Biometrika* 68:373–379.

Reid, N., and Crépeau, H. (1985). "Influence Functions for Proportional Hazards Regression." *Biometrika* 72:1–9.

Ripatti, S., and Palmgren, J. (2000). "Estimation of Multivariate Frailty Models Using Penalized Partial Likelihood." *Biometrics* 56:1016–1022.

Sargent, D. J. (1998). "A General Framework for Random Effects Survival Analysis in the Cox Proportional Hazards Setting." *Biometrics* 54:1486–1497.

Schemper, M., and Henderson, R. (2000). "Predictive Accuracy and Explained Variation in Cox Regression." *Biometrics* 56:249–255.

Schoenfeld, D. A. (1982). "Partial Residuals for the Proportional Hazards Regression Model." *Biometrika* 69:239–241.

Simonsen, J. (2014). Statens Serum Institut, Copenhagen. Unpublished SAS macro.

Sinha, D., Ibrahim, J. G., and Chen, M.-H. (2003). "A Bayesian Justification of Cox's Partial Likelihood." *Biometrika* 90:629–641.

Spiegelhalter, D. J., Best, N. G., Carlin, B. P., and Van der Linde, A. (2002). "Bayesian Measures of Model Complexity and Fit." *Journal of the Royal Statistical Society, Series B* 64:583–616. With discussion.

Spiekerman, C. F., and Lin, D. Y. (1998). "Marginal Regression Models for Multivariate Failure Time Data." *Journal of the American Statistical Association* 93:1164–1175.

Therneau, T. M. (1994). *A Package for Survival Analysis in S*. Technical Report 53, Section of Biostatistics, Mayo Clinic, Rochester, MN.

Therneau, T. M., and Grambsch, P. M. (2000). *Modeling Survival Data: Extending the Cox Model*. New York: Springer-Verlag.

Therneau, T. M., Grambsch, P. M., and Fleming, T. R. (1990). "Martingale-Based Residuals and Survival Models." *Biometrika* 77:147–160.

Tsiatis, A. A. (1981). "A Large Sample Study of the Estimates for the Integrated Hazard Function in Cox's Regression Model for Survival Data." *Annals of Statistics* 9:93–108.

Uno, H., Cai, T., Pencina, M. J., D'Agostino, R. B., and Wei, L. J. (2011). "On the C-Statistics for Evaluating Overall Adequacy of Risk Prediction Procedures with Censored Survival Data." *Statistics in Medicine* 30:1105–1117.

Uno, H., Cai, T., Tian, L., and Wei, L. J. (2007). "Evaluating Prediction Rules for t-Year Survivors with Censored Regression Models." *Journal of the American Statistical Association* 102:527–537.

Venzon, D. J., and Moolgavkar, S. H. (1988). "A Method for Computing Profile-Likelihood-Based Confidence Intervals." *Journal of the Royal Statistical Society, Series C* 37:87–94.

Volinsky, C. T., and Raftery, A. E. (2000). "Bayesian Information Criterion for Censored Survival Models." *Biometrics* 56:256–262.

Wei, L. J., Lin, D. Y., and Weissfeld, L. (1989). "Regression Analysis of Multivariate Incomplete Failure Time Data by Modeling Marginal Distribution." *Journal of the American Statistical Association* 84:1065–1073.

Zhang, X., Loberiza, F. R., Klein, J. P., and Zhang, M. J. (2007). "A SAS Macro for Estimation of Direct Adjusted Survival Curves Based on a Stratified Cox Regression Model." *Computer Methods and Programs in Biomedicine* 88:95–111.

Zhou, B., Fine, J., Latouche, A., and Labopin, M. (2012). "Competing Risks Regression for Cluster Data." *Biostatistics* 13:371–383.

Zhou, B., Latouche, A., Rocha, V., and Fine, J. (2011). "Competing Risks Regression for Stratified Data." *Biometrics* 67:661–670.

Subject Index

Syntax Index