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# **SAS/STAT<sup>®</sup> 12.1 User's Guide The NLMIXED Procedure (Chapter)**



This document is an individual chapter from *SAS/STAT® 12.1 User's Guide*.

The correct bibliographic citation for the complete manual is as follows: SAS Institute Inc. 2012. *SAS/STAT® 12.1 User's Guide*. Cary, NC: SAS Institute Inc.

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Electronic book 1, August 2012

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# Chapter 64

## The NLMIXED Procedure

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## Overview: NLMIXED Procedure

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### Introduction

The NLMIXED procedure fits nonlinear mixed models—that is, models in which both fixed and random effects enter nonlinearly. These models have a wide variety of applications, two of the most common being pharmacokinetics and overdispersed binomial data. PROC NLMIXED enables you to specify a conditional distribution for your data (given the random effects) having either a standard form (normal, binomial, Poisson) or a general distribution that you code using SAS programming statements.

PROC NLMIXED fits nonlinear mixed models by maximizing an approximation to the likelihood integrated over the random effects. Different integral approximations are available, the principal ones being adaptive Gaussian quadrature and a first-order Taylor series approximation. A variety of alternative optimization techniques are available to carry out the maximization; the default is a dual quasi-Newton algorithm.

Successful convergence of the optimization problem results in parameter estimates along with their approximate standard errors based on the second derivative matrix of the likelihood function. PROC NLMIXED enables you to use the estimated model to construct predictions of arbitrary functions by using empirical Bayes estimates of the random effects. You can also estimate arbitrary functions of the nonrandom parameters, and PROC NLMIXED computes their approximate standard errors by using the delta method.

### Literature on Nonlinear Mixed Models

---

Davidian and Giltinan (1995) and Vonesh and Chinchilli (1997) provide good overviews as well as general theoretical developments and examples of nonlinear mixed models. Pinheiro and Bates (1995) is a primary reference for the theory and computational techniques of PROC NLMIXED. They describe and compare several different integrated likelihood approximations and provide evidence that adaptive Gaussian quadrature is one of the best methods. Davidian and Gallant (1993) also use Gaussian quadrature for nonlinear mixed models, although the smooth nonparametric density they advocate for the random effects is currently not available in PROC NLMIXED.

Traditional approaches to fitting nonlinear mixed models involve Taylor series expansions, expanding around either zero or the empirical best linear unbiased predictions of the random effects. The former is the basis for the well-known first-order method (Beal and Sheiner 1982, 1988; Sheiner and Beal 1985),



and it is optionally available in PROC NLMIXED. The latter is the basis for the estimation method of Lindstrom and Bates (1990), and it is not available in PROC NLMIXED. However, the closely related Laplacian approximation is an option; it is equivalent to adaptive Gaussian quadrature with only one quadrature point. The Laplacian approximation and its relationship to the Lindstrom-Bates method are discussed by: Beal and Sheiner (1992); Wolfinger (1993); Vonesh (1992, 1996); Vonesh and Chinchilli (1997); Wolfinger and Lin (1997).

A parallel literature exists in the area of generalized linear mixed models, in which random effects appear as a part of the linear predictor inside a link function. Taylor-series methods similar to those just described are discussed in articles such as: Harville and Mee (1984); Stiratelli, Laird, and Ware (1984); Gilmour, Anderson, and Rae (1985); Goldstein (1991); Schall (1991); Engel and Keen (1992); Breslow and Clayton (1993); Wolfinger and O'Connell (1993); McGilchrist (1994), but such methods have not been implemented in PROC NLMIXED because they can produce biased results in certain binary data situations (Rodriguez and Goldman 1995; Lin and Breslow 1996). Instead, a numerical quadrature approach is available in PROC NLMIXED, as discussed in: Pierce and Sands (1975); Anderson and Aitkin (1985); Hedeker and Gibbons (1994); Crouch and Spiegelman (1990); Longford (1994); McCulloch (1994); Liu and Pierce (1994); Diggle, Liang, and Zeger (1994).

Nonlinear mixed models have important applications in pharmacokinetics, and Roe (1997) provides a wide-ranging comparison of many popular techniques. Yuh et al. (1994) provide an extensive bibliography on nonlinear mixed models and their use in pharmacokinetics.

---

## PROC NLMIXED Compared with Other SAS Procedures and Macros

The models fit by PROC NLMIXED can be viewed as generalizations of the random coefficient models fit by the MIXED procedure. This generalization allows the random coefficients to enter the model nonlinearly, whereas in PROC MIXED they enter linearly. With PROC MIXED you can perform both maximum likelihood and restricted maximum likelihood (REML) estimation, whereas PROC NLMIXED implements only maximum likelihood. This is because the analog to the REML method in PROC NLMIXED would involve a high-dimensional integral over all of the fixed-effects parameters, and this integral is typically not available in closed form. Finally, PROC MIXED assumes the data to be normally distributed, whereas PROC NLMIXED enables you to analyze data that are normal, binomial, or Poisson or that have any likelihood programmable with SAS statements.

PROC NLMIXED does not implement the same estimation techniques available with the NLINMIX macro or the default estimation method of the GLIMMIX procedure. These are based on the estimation methods of: Lindstrom and Bates (1990); Breslow and Clayton (1993); Wolfinger and O'Connell (1993), and they iteratively fit a set of generalized estimating equations (see Chapters 14 and 15 of Littell et al. 2006; Wolfinger 1997). In contrast, PROC NLMIXED directly maximizes an approximate integrated likelihood. This remark also applies to the SAS/IML macros MIXNLIN (Vonesh and Chinchilli 1997) and NLMEM (Galecki 1998).

The GLIMMIX procedure also fits mixed models for nonnormal data with nonlinearity in the conditional mean function. In contrast to the NLMIXED procedure, PROC GLIMMIX assumes that the model contains a linear predictor that links covariates to the conditional mean of the response. The NLMIXED procedure is designed to handle general conditional mean functions, whether they contain a linear component or not. As mentioned earlier, the GLIMMIX procedure by default estimates parameters in generalized linear mixed models by pseudo-likelihood techniques, whereas PROC NLMIXED by default performs maximum likeli-

hood estimation by adaptive Gauss-Hermite quadrature. This estimation method is also available with the GLIMMIX procedure (METHOD=QUAD in the PROC GLIMMIX statement).

PROC NLMIXED has close ties with the NLP procedure in SAS/OR software. PROC NLMIXED uses a subset of the optimization code underlying PROC NLP and has many of the same optimization-based options. Also, the programming statement functionality used by PROC NLMIXED is the same as that used by PROC NLP and the MODEL procedure in SAS/ETS software.

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## Getting Started: NLMIXED Procedure

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### Nonlinear Growth Curves with Gaussian Data

As an introductory example, consider the orange tree data of Draper and Smith (1981). These data consist of seven measurements of the trunk circumference (in millimeters) on each of five orange trees. You can input these data into a SAS data set as follows:

```
data tree;
    input tree day y;
    datalines;
1  118   30
1  484   58
1  664   87

... more lines ...

5 1582  177
;
```

Lindstrom and Bates (1990) and Pinheiro and Bates (1995) propose the following logistic nonlinear mixed model for these data:

$$y_{ij} = \frac{b_1 + u_{i1}}{1 + \exp[-(d_{ij} - b_2)/b_3]} + e_{ij}$$

Here,  $y_{ij}$  represents the  $j$ th measurement on the  $i$ th tree ( $i = 1, \dots, 5$ ;  $j = 1, \dots, 7$ ),  $d_{ij}$  is the corresponding day,  $b_1, b_2, b_3$  are the fixed-effects parameters,  $u_{i1}$  are the random-effect parameters assumed to be iid  $N(0, \sigma_u^2)$ , and  $e_{ij}$  are the residual errors assumed to be iid  $N(0, \sigma_e^2)$  and independent of the  $u_{i1}$ . This model has a logistic form, and the random-effect parameters  $u_{i1}$  enter the model linearly.

The statements to fit this nonlinear mixed model are as follows:

```
proc nlmixed data=tree;
    parms b1=190 b2=700 b3=350 s2u=1000 s2e=60;
    num = b1+u1;
    ex = exp(-(day-b2)/b3);
    den = 1 + ex;
    model y ~ normal(num/den, s2e);
    random u1 ~ normal(0, s2u) subject=tree;
run;
```

The **PROC NLMIXED** statement invokes the procedure and inputs the tree data set. The **PARMS** statement identifies the unknown parameters and their starting values. Here there are three fixed-effects parameters ( $b_1$ ,  $b_2$ ,  $b_3$ ) and two variance components ( $s^2_u$ ,  $s^2_e$ ).

The next three statements are SAS programming statements specifying the logistic mixed model. A new variable  $u_1$  is included to identify the random effect. These statements are evaluated for every observation in the data set when the NLMIXED procedure computes the log likelihood function and its derivatives.

The **MODEL** statement defines the dependent variable and its conditional distribution given the random effects. Here a normal (Gaussian) conditional distribution is specified with mean  $\text{num}/\text{den}$  and variance  $s^2_e$ .

The **RANDOM** statement defines the single random effect to be  $u_1$ , and specifies that it follow a normal distribution with mean 0 and variance  $s^2_u$ . The **SUBJECT=** argument in the **RANDOM** statement defines a variable indicating when the random effect obtains new realizations; in this case, it changes according to the values of the *tree* variable. PROC NLMIXED assumes that the input data set is clustered according to the levels of the *tree* variable; that is, all observations from the same tree occur sequentially in the input data set.

The output from this analysis is as follows.

**Figure 64.1** Model Specifications

The NLMIXED Procedure	
Specifications	
Data Set	WORK.TREE
Dependent Variable	Y
Distribution for Dependent Variable	Normal
Random Effects	u1
Distribution for Random Effects	Normal
Subject Variable	tree
Optimization Technique	Dual Quasi-Newton
Integration Method	Adaptive Gaussian Quadrature

The “Specifications” table lists basic information about the nonlinear mixed model you have specified (Figure 64.1). Included are the input data set, the dependent and subject variables, the random effects, the relevant distributions, and the type of optimization. The “Dimensions” table lists various counts related to the model, including the number of observations, subjects, and parameters (Figure 64.2). These quantities are useful for checking that you have specified your data set and model correctly. Also listed is the number of quadrature points that PROC NLMIXED has selected based on the evaluation of the log likelihood at the starting values of the parameters. Here, only one quadrature point is necessary because the random-effect parameters  $u_{i1}$  enter the model linearly. (The Gauss-Hermite quadrature with a single quadrature point results in the Laplace approximation of the log likelihood.)

**Figure 64.2** Dimensions Table for Growth Curve Model

Dimensions	
Observations Used	35
Observations Not Used	0
Total Observations	35
Subjects	5
Max Obs Per Subject	7
Parameters	5
Quadrature Points	1

**Figure 64.3** Starting Values of Parameter Estimates and Negative Log Likelihood

Parameters					
b1	b2	b3	s2u	s2e	NegLogLike
190	700	350	1000	60	132.491787

The “Parameters” table lists the parameters to be estimated, their starting values, and the negative log likelihood evaluated at the starting values (Figure 64.3).

**Figure 64.4** Iteration History for Growth Curve Model

Iteration History					
Iter	Calls	NegLogLike	Diff	MaxGrad	Slope
1	4	131.686742	0.805045	0.010269	-0.633
2	6	131.64466	0.042082	0.014783	-0.0182
3	8	131.614077	0.030583	0.009809	-0.02796
4	10	131.572522	0.041555	0.001186	-0.01344
5	11	131.571895	0.000627	0.0002	-0.00121
6	13	131.571889	5.549E-6	0.000092	-7.68E-6
7	15	131.571888	1.096E-6	6.097E-6	-1.29E-6
NOTE: GCONV convergence criterion satisfied.					

The “Iteration History” table records the history of the minimization of the negative log likelihood (Figure 64.4). For each iteration of the quasi-Newton optimization, values are listed for the number of function calls, the value of the negative log likelihood, the difference from the previous iteration, the absolute value of the largest gradient, and the slope of the search direction. The note at the bottom of the table indicates that the algorithm has converged successfully according to the **GCONV** convergence criterion, a standard criterion computed using a quadratic form in the gradient and the inverse Hessian.

The final maximized value of the log likelihood as well as the information criterion of Akaike (AIC), its small sample bias corrected version (AICC), and the Bayesian information criterion (BIC) in the “smaller is better” form appear in the “Fit Statistics” table (Figure 64.5). These statistics can be used to compare different nonlinear mixed models.

**Figure 64.5** Fit Statistics for Growth Curve Model

Fit Statistics	
-2 Log Likelihood	263.1
AIC (smaller is better)	273.1
AICC (smaller is better)	275.2
BIC (smaller is better)	271.2

**Figure 64.6** Parameter Estimates at Convergence

Parameter Estimates							
Parameter	Estimate	Standard Error	DF	t Value	Pr >  t	Alpha	Lower
b1	192.05	15.6473	4	12.27	0.0003	0.05	148.61
b2	727.90	35.2472	4	20.65	<.0001	0.05	630.04
b3	348.07	27.0790	4	12.85	0.0002	0.05	272.88
s2u	999.88	647.44	4	1.54	0.1974	0.05	-797.70
s2e	61.5139	15.8831	4	3.87	0.0179	0.05	17.4153
Parameter Estimates							
	Parameter	Upper	Gradient				
	b1	235.50	1.154E-6				
	b2	825.76	5.289E-6				
	b3	423.25	-6.1E-6				
	s2u	2797.45	-3.84E-6				
	s2e	105.61	2.892E-6				

The maximum likelihood estimates of the five parameters and their approximate standard errors computed using the final Hessian matrix are displayed in the “Parameter Estimates” table (Figure 64.6). Approximate  $t$ -values and Wald-type confidence limits are also provided, with degrees of freedom equal to the number of subjects minus the number of random effects. You should interpret these statistics cautiously for variance parameters like s2u and s2e. The final column in the output shows the gradient vector at the optimization solution. Each element appears to be sufficiently small to indicate a stationary point.

Since the random-effect parameters  $u_{i1}$  enter the model linearly, you can obtain equivalent results by using the first-order method (specify **METHOD=FIRO** in the **PROC NL MIXED** statement).

## Logistic-Normal Model with Binomial Data

This example analyzes the data from Beitler and Landis (1985), which represent results from a multi-center clinical trial investigating the effectiveness of two topical cream treatments (active drug, control) in curing an infection. For each of eight clinics, the number of trials and favorable cures are recorded for each treatment. The SAS data set is as follows.

```
data infection;
    input clinic t x n;
    datalines;
1 1 11 36
1 0 10 37
2 1 16 20
2 0 22 32
3 1 14 19
3 0 7 19
4 1 2 16
4 0 1 17
5 1 6 17
5 0 0 12
6 1 1 11
6 0 0 10
7 1 1 5
7 0 1 9
8 1 4 6
8 0 6 7
;
```

Suppose  $n_{ij}$  denotes the number of trials for the  $i$ th clinic and the  $j$ th treatment ( $i = 1, \dots, 8; j = 0, 1$ ), and  $x_{ij}$  denotes the corresponding number of favorable cures. Then a reasonable model for the preceding data is the following logistic model with random effects:

$$x_{ij}|u_i \sim \text{Binomial}(n_{ij}, p_{ij})$$

and

$$\eta_{ij} = \log\left(\frac{p_{ij}}{1 - p_{ij}}\right) = \beta_0 + \beta_1 t_j + u_i$$

The notation  $t_j$  indicates the  $j$ th treatment, and the  $u_i$  are assumed to be iid  $N(0, \sigma_u^2)$ .

The PROC NLMIXED statements to fit this model are as follows:

```
proc nlmixed data=infection;
    parms beta0=-1 beta1=1 s2u=2;
    eta    = beta0 + beta1*t + u;
    expeta = exp(eta);
    p      = expeta/(1+expeta);
    model x ~ binomial(n,p);
    random u ~ normal(0,s2u) subject=clinic;
    predict eta out=eta;
    estimate '1/beta1' 1/beta1;
run;
```

The **PROC NLMIXED** statement invokes the procedure, and the **PARMS** statement defines the parameters and their starting values. The next three statements define  $p_{ij}$ , and the **MODEL** statement defines the conditional distribution of  $x_{ij}$  to be binomial. The **RANDOM** statement defines  $u$  to be the random effect with subjects defined by the clinic variable.

The **PREDICT** statement constructs predictions for each observation in the input data set. For this example, predictions of  $\eta_{ij}$  and approximate standard errors of prediction are output to a data set named eta. These predictions include empirical Bayes estimates of the random effects  $u_i$ .

The **ESTIMATE** statement requests an estimate of the reciprocal of  $\beta_1$ .

The output for this model is as follows.

**Figure 64.7** Model Information and Dimensions for Logistic-Normal Model

The NLMIXED Procedure	
Specifications	
Data Set	WORK.INFECTION
Dependent Variable	x
Distribution for Dependent Variable	Binomial
Random Effects	u
Distribution for Random Effects	Normal
Subject Variable	clinic
Optimization Technique	Dual Quasi-Newton
Integration Method	Adaptive Gaussian Quadrature
Dimensions	
Observations Used	16
Observations Not Used	0
Total Observations	16
Subjects	8
Max Obs Per Subject	2
Parameters	3
Quadrature Points	5

The “Specifications” table provides basic information about the nonlinear mixed model (Figure 64.7). For example, the distribution of the response variable, conditional on normally distributed random effects, is binomial. The “Dimensions” table provides counts of various variables. You should check this table to make sure the data set and model have been entered properly. PROC NLMIXED selects five quadrature points to achieve the default accuracy in the likelihood calculations.

**Figure 64.8** Starting Values of Parameter Estimates

Parameters			
beta0	beta1	s2u	NegLogLike
-1	1	2	37.5945925

The “Parameters” table lists the starting point of the optimization and the negative log likelihood at the starting values (Figure 64.8).

**Figure 64.9** Iteration History and Fit Statistics for Logistic-Normal Model

Iteration History					
Iter	Calls	NegLogLike	Diff	MaxGrad	Slope
1	2	37.3622692	0.232323	2.882077	-19.3762
2	3	37.1460375	0.216232	0.921926	-0.82852
3	5	37.0300936	0.115944	0.315897	-0.59175
4	6	37.0223017	0.007792	0.01906	-0.01615
5	7	37.0222472	0.000054	0.001743	-0.00011
6	9	37.0222466	6.57E-7	0.000091	-1.28E-6
7	11	37.0222466	5.38E-10	2.078E-6	-1.1E-9

NOTE: GCONV convergence criterion satisfied.

Fit Statistics	
-2 Log Likelihood	74.0
AIC (smaller is better)	80.0
AICC (smaller is better)	82.0
BIC (smaller is better)	80.3

The “Iteration History” table indicates successful convergence in seven iterations (Figure 64.9). The “Fit Statistics” table lists some useful statistics based on the maximized value of the log likelihood.

**Figure 64.10** Parameter Estimates for Logistic-Normal Model

Parameter Estimates							
Parameter	Estimate	Standard Error	DF	t Value	Pr >  t	Alpha	Lower
beta0	-1.1974	0.5561	7	-2.15	0.0683	0.05	-2.5123
beta1	0.7385	0.3004	7	2.46	0.0436	0.05	0.02806
s2u	1.9591	1.1903	7	1.65	0.1438	0.05	-0.8554

Parameter Estimates		
Parameter	Upper	Gradient
beta0	0.1175	-3.1E-7
beta1	1.4488	-2.08E-6
s2u	4.7736	-2.48E-7

The “Parameter Estimates” table indicates marginal significance of the two fixed-effects parameters (Figure 64.10). The positive value of the estimate of  $\beta_1$  indicates that the treatment significantly increases the chance of a favorable cure.



**Figure 64.11** Table of Additional Estimates

Additional Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr >  t	Alpha	Lower	Upper
1/beta1	1.3542	0.5509	7	2.46	0.0436	0.05	0.05146	2.6569

The “Additional Estimates” table displays results from the **ESTIMATE** statement (Figure 64.11). The estimate of  $1/\beta_1$  equals  $1/0.7385 = 1.3542$  and its standard error equals  $0.3004/0.7385^2 = 0.5509$  by the delta method (Billingsley 1986; Cox 1998). Note that this particular approximation produces a  $t$ -statistic identical to that for the estimate of  $\beta_1$ .

Not shown is the eta data set, which contains the original 16 observations and predictions of the  $\eta_{ij}$ .

---

## Syntax: NLMIXED Procedure

The following statements are available in the NLMIXED procedure:

```

PROC NLMIXED < options > ;
  ARRAY array-specification ;
  BOUNDS boundary-constraints ;
  BY variables ;
  CONTRAST 'label' expression < , expression > < options > ;
  ESTIMATE 'label' expression < options > ;
  ID names ;
  MODEL model-specification ;
  PARMS parameters-and-starting-values ;
  PREDICT expression OUT=SAS-data-set < options > ;
  RANDOM random-effects-specification ;
  REPLICATE variable ;
  Programming statements ;

```

The following sections provide a detailed description of each of these statements.

---

## PROC NLMIXED Statement

```

PROC NLMIXED < options > ;

```

The PROC NLMIXED statement invokes the NLMIXED procedure. Table 64.1 summarizes the options available in the PROC NLMIXED statement.

**Table 64.1** PROC NLMIXED Statement Options

Option	Description
<b>Basic Options</b>	
DATA=	Specifies the input data set
METHOD=	Specifies the integration method
<b>Displayed Output Specifications</b>	
ALPHA=	Specifies $\alpha$ for confidence limits
CORR	Requests the correlation matrix
COV	Requests the covariance matrix
DF=	Specifies the degrees of freedom for $p$ -values and confidence limits
ECORR	Requests the correlation matrix of additional estimates
ECOV	Requests the covariance matrix of additional estimates
EDER	Requests derivatives of additional estimates
EMPIRICAL	Requests the empirical (“sandwich”) estimator of covariance matrix
HESS	Requests the Hessian matrix
ITDETAILS	Requests iteration details
START	Specifies the gradient at starting values
<b>Debugging Output</b>	
FLOW	Displays the model execution messages
LISTCODE	Displays compiled model program
LISTDEP	Produces a model dependency listing
LISTDER	Displays the model derivatives
LIST	Displays the model program and variables
TRACE	Displays detailed model execution messages
XREF	Displays the model cross references
<b>Quadrature Options</b>	
NOADSCALE	Requests no adaptive scaling
NOAD	Requests no adaptive centering
OUTQ=	Displays output data set
QFAC=	Specifies the search factor
QMAX=	Specifies the maximum points
QPOINTS=	Specifies the number of points
QSCALEFAC=	Specifies the scale factor
QTOL=	Specifies the tolerance
<b>Empirical Bayes Options</b>	
EBOPT	Requests comprehensive optimization
EBSSFRAC=	Specifies the step-shortening fraction
EBSTOL=	Specifies the step-shortening tolerance
EBSTEPS=	Specifies the number of Newton steps
EBSUBSTEPS=	Specifies the number of substeps
EBTOL=	Specifies the convergence tolerance
EBZSTART	Requests zero as the starting values

Table 64.1 *continued*

Option	Description
<b>Optimization Specifications</b>	
HESCAL=	Specifies the type of Hessian scaling
INHESIAN<=>	Specifies the start for approximated Hessian
LINESEARCH=	Specifies the line-search method
LSPRECISION=	Specifies the line-search precision
OPTCHECK<=>	Checks optimality in a neighborhood
RESTART=	Specifies the iteration number for update restart
TECHNIQUE=	Specifies the minimization technique
UPDATE=	Specifies the update technique
<b>Derivatives Specifications</b>	
DIAHES	Uses only the diagonal of Hessian
FDHESSIAN<=>	Specifies the finite-difference second derivatives
FD<=>	Specifies the finite-difference derivatives
<b>Constraint Specifications</b>	
LCDEACT=	Specifies the Lagrange multiplier tolerance for deactivating
LCEPSILON=	Specifies the range for active constraints
LCSINGULAR=	Specifies the tolerance for dependent constraints
<b>Termination Criteria Specifications</b>	
ABSCONV=	Specifies the absolute function convergence criterion
ABSFCNV=	Specifies the absolute function difference convergence criterion
ABSGCONV=	Specifies the absolute gradient convergence criterion
ABSXCONV=	Specifies the absolute parameter convergence criterion
FCONV=	Specifies the relative function convergence criterion
FCONV2=	Specifies another relative function convergence criterion
FDIGITS=	Specifies the number accurate digits in objective function
FSIZE=	Specifies the FSIZE parameter of the relative function and relative gradient termination criteria
GCONV=	Specifies the relative gradient convergence criterion
MAXFUNC=	Specifies the maximum number of function calls
MAXITER=	Specifies the maximum number of iterations
MAXTIME=	Specifies the upper limit seconds of CPU time
MINITER=	Specifies the minimum number of iterations
XCONV=	Specifies the relative parameter convergence criterion
XSIZE=	Used in XCONV criterion
<b>Step Length Specifications</b>	
DAMPSTEP<=>	Specifies the damped steps in line search
INSTEP=	Specifies the initial trust-region radius
MAXSTEP=	Specifies the maximum trust-region radius
<b>Singularity Tolerances</b>	
SINGCHOL=	Specifies the tolerance for Cholesky roots

Table 64.1 *continued*

Option	Description
SINGHESS=	Specifies the tolerance for Hessian
SINGSWEEP=	Specifies the tolerance for sweep
SINGVAR=	Specifies the tolerance for variances
<b>Covariance Matrix Tolerances</b>	
ASINGULAR=	Specifies the absolute singularity for inertia
CFACTOR=	Specifies the multiplication factor for COV matrix
COVSING=	Specifies the tolerance for singular COV matrix
G4=	Specifies the threshold for Moore-Penrose inverse
MSINGULAR=	Specifies the relative M singularity for inertia
VSINGULAR=	Specifies the relative V singularity for inertia

These options are described in alphabetical order. For a description of the mathematical notation used in the following sections, see the section “[Modeling Assumptions and Notation](#)” on page 5383.

**ABSCONV=*r***

**ABSTOL=*r***

specifies an absolute function convergence criterion. For minimization, termination requires  $f(\boldsymbol{\theta}^{(k)}) \leq r$ . The default value of *r* is the negative square root of the largest double-precision value, which serves only as a protection against overflows.

**ABSFCNV=*r*<[*n*]>**

**ABSFTOL=*r*<[*n*]>**

specifies an absolute function difference convergence criterion. For all techniques except NMSIMP, termination requires a small change of the function value in successive iterations:

$$|f(\boldsymbol{\theta}^{(k-1)}) - f(\boldsymbol{\theta}^{(k)})| \leq r$$

The same formula is used for the NMSIMP technique, but  $\boldsymbol{\theta}^{(k)}$  is defined as the vertex with the lowest function value, and  $\boldsymbol{\theta}^{(k-1)}$  is defined as the vertex with the highest function value in the simplex. The default value is  $r = 0$ . The optional integer value *n* specifies the number of successive iterations for which the criterion must be satisfied before the process can be terminated.

**ABSGCONV=*r*<[*n*]>**

**ABSGTOL=*r*<[*n*]>**

specifies an absolute gradient convergence criterion. Termination requires the maximum absolute gradient element to be small:

$$\max_j |g_j(\boldsymbol{\theta}^{(k)})| \leq r$$

This criterion is not used by the NMSIMP technique. The default value is  $r = 1\text{E-}5$ . The optional integer value *n* specifies the number of successive iterations for which the criterion must be satisfied before the process can be terminated.

**ABSXCONV**= $r < [n] >$ **ABSXTOL**= $r < [n] >$ 

specifies an absolute parameter convergence criterion. For all techniques except NMSIMP, termination requires a small Euclidean distance between successive parameter vectors,

$$\| \boldsymbol{\theta}^{(k)} - \boldsymbol{\theta}^{(k-1)} \|_2 \leq r$$

For the NMSIMP technique, termination requires either a small length  $\alpha^{(k)}$  of the vertices of a restart simplex,

$$\alpha^{(k)} \leq r$$

or a small simplex size,

$$\delta^{(k)} \leq r$$

where the simplex size  $\delta^{(k)}$  is defined as the L1 distance from the simplex vertex  $\boldsymbol{\xi}^{(k)}$  with the smallest function value to the other  $n$  simplex points  $\boldsymbol{\theta}_l^{(k)} \neq \boldsymbol{\xi}^{(k)}$ :

$$\delta^{(k)} = \sum_{\boldsymbol{\theta}_l^{(k)} \neq \boldsymbol{\xi}^{(k)}} \| \boldsymbol{\theta}_l^{(k)} - \boldsymbol{\xi}^{(k)} \|_1$$

The default is  $r = 1\text{E-}8$  for the NMSIMP technique and  $r = 0$  otherwise. The optional integer value  $n$  specifies the number of successive iterations for which the criterion must be satisfied before the process can terminate.

**ALPHA**= $\alpha$ 

specifies the alpha level to be used in computing confidence limits. The default value is 0.05.

**ASINGULAR**= $r$ **ASING**= $r$ 

specifies an absolute singularity criterion for the computation of the inertia (number of positive, negative, and zero eigenvalues) of the Hessian and its projected forms. The default value is the square root of the smallest positive double-precision value.

**CFACTOR**= $f$ 

specifies a multiplication factor  $f$  for the estimated covariance matrix of the parameter estimates.

**COV**

requests the approximate covariance matrix for the parameter estimates.

**CORR**

requests the approximate correlation matrix for the parameter estimates.

**COVSING**= $r > 0$ 

specifies a nonnegative threshold that determines whether the eigenvalues of a singular Hessian matrix are considered to be zero.

**DAMPSTEP=<math>r>****DS=<math>r>**

specifies that the initial step-size value  $\alpha^{(0)}$  for each line search (used by the QUANEW, CONGRA, or NEWRAP technique) cannot be larger than  $r$  times the step-size value used in the former iteration. If you specify the DAMPSTEP option without factor  $r$ , the default value is  $r = 2$ . The DAMPSTEP= $r$  option can prevent the line-search algorithm from repeatedly stepping into regions where some objective functions are difficult to compute or where they could lead to floating-point overflows during the computation of objective functions and their derivatives. The DAMPSTEP= $r$  option can save time-costly function calls that result in very small step sizes  $\alpha$ . For more details on setting the start values of each line search, see the section “[Restricting the Step Length](#)” on page 5398.

**DATA=SAS-data-set**

specifies the input data set. Observations in this data set are used to compute the log likelihood function that you specify with PROC NLMIXED statements.

**NOTE:** If you are using a [RANDOM](#) statement, the input data set must be clustered according to the [SUBJECT=](#) variable. One easy way to accomplish this is to sort your data by the [SUBJECT=](#) variable prior to calling PROC NLMIXED. PROC NLMIXED does not sort the input data set for you.

**DF= $d$** 

specifies the degrees of freedom to be used in computing  $p$  values and confidence limits. The default value is the number of subjects minus the number of random effects for random effects models, and the number of observations otherwise.

**DIAHES**

specifies that only the diagonal of the Hessian is used.

**EBOPT**

requests that a more comprehensive optimization be carried out if the default empirical Bayes optimization fails to converge.

**EBSSFRAC= $r > 0$** 

specifies the step-shortening fraction to be used while computing empirical Bayes estimates of the random effects. The default value is 0.8.

**EBSTOL= $r \geq 0$** 

specifies the objective function tolerance for determining the cessation of step-shortening while computing empirical Bayes estimates of the random effects. The default value is  $r = 1\text{E}-8$ .

**EBSTEPS= $n \geq 0$** 

specifies the maximum number of Newton steps for computing empirical Bayes estimates of random effects. The default value is  $n = 50$ .

**EBSUBSTEPS= $n \geq 0$** 

specifies the maximum number of step-shortenings for computing empirical Bayes estimates of random effects. The default value is  $n = 20$ .

**EBTOL= $r \geq 0$** 

specifies the convergence tolerance for empirical Bayes estimation. The default value is  $r = \epsilon\text{E}4$ , where  $\epsilon$  is the machine precision. This default value equals approximately  $1\text{E}-12$  on most machines.

**EBZSTART**

requests that a zero be used as starting values during empirical Bayes estimation. By default, the starting values are set equal to the estimates from the previous iteration (or zero for the first iteration).

**ECOV**

requests the approximate covariance matrix for all expressions specified in [ESTIMATE](#) statements.

**ECORR**

requests the approximate correlation matrix for all expressions specified in [ESTIMATE](#) statements.

**EDER**

requests the derivatives of all expressions specified in [ESTIMATE](#) statements with respect to each of the model parameters.

**EMPIRICAL**

requests that the covariance matrix of the parameter estimates be computed as a likelihood-based empirical (“sandwich”) estimator (White 1982). If  $f(\boldsymbol{\theta}) = -\log\{m(\boldsymbol{\theta})\}$  is the objective function for the optimization and  $m(\boldsymbol{\theta})$  denotes the marginal log likelihood (see the section “[Modeling Assumptions and Notation](#)” on page 5383 for notation and further definitions) the empirical estimator is computed as

$$\mathbf{H}(\hat{\boldsymbol{\theta}})^{-1} \left( \sum_{i=1}^s \mathbf{g}_i(\hat{\boldsymbol{\theta}}) \mathbf{g}_i(\hat{\boldsymbol{\theta}})' \right) \mathbf{H}(\hat{\boldsymbol{\theta}})^{-1}$$

where  $\mathbf{H}$  is the second derivative matrix of  $f$  and  $\mathbf{g}_i$  is the first derivative of the contribution to  $f$  by the  $i$ th subject. If you choose the EMPIRICAL option, this estimator of the covariance matrix of the parameter estimates replaces the model-based estimator  $\mathbf{H}(\hat{\boldsymbol{\theta}})^{-1}$  in subsequent calculations. You can output the subject-specific gradients  $\mathbf{g}_i$  to a SAS data set with the [SUBGRADIENT](#) option in the [PROC NL MIXED](#) statement.

The EMPIRICAL option requires the presence of a [RANDOM](#) statement and is available for [METHOD=GAUSS](#) and [METHOD=ISAMP](#) only.

**FCONV=r<[n]>****FTOL=r<[n]>**

specifies a relative function convergence criterion. For all techniques except NMSIMP, termination requires a small relative change of the function value in successive iterations,

$$\frac{|f(\boldsymbol{\theta}^{(k)}) - f(\boldsymbol{\theta}^{(k-1)})|}{\max(|f(\boldsymbol{\theta}^{(k-1)})|, \text{FSIZE})} \leq r$$

where FSIZE is defined by the [FSIZE=](#) option. The same formula is used for the NMSIMP technique, but  $\boldsymbol{\theta}^{(k)}$  is defined as the vertex with the lowest function value, and  $\boldsymbol{\theta}^{(k-1)}$  is defined as the vertex with the highest function value in the simplex. The default is  $r = 10^{-\text{FDIGITS}}$ , where FDIGITS is the value of the [FDIGITS=](#) option. The optional integer value  $n$  specifies the number of successive iterations for which the criterion must be satisfied before the process can terminate.

**FCNV2= $r < [n] >$** **FTOL2= $r < [n] >$** 

specifies another function convergence criterion. For all techniques except NMSIMP, termination requires a small predicted reduction

$$df^{(k)} \approx f(\theta^{(k)}) - f(\theta^{(k)} + s^{(k)})$$

of the objective function. The predicted reduction

$$\begin{aligned} df^{(k)} &= -\mathbf{g}^{(k)'} \mathbf{s}^{(k)} - \frac{1}{2} \mathbf{s}^{(k)'} \mathbf{H}^{(k)} \mathbf{s}^{(k)} \\ &= -\frac{1}{2} \mathbf{s}^{(k)'} \mathbf{g}^{(k)} \\ &\leq r \end{aligned}$$

is computed by approximating the objective function  $f$  by the first two terms of the Taylor series and substituting the Newton step:

$$\mathbf{s}^{(k)} = -[\mathbf{H}^{(k)}]^{-1} \mathbf{g}^{(k)}$$

For the NMSIMP technique, termination requires a small standard deviation of the function values of the  $n + 1$  simplex vertices  $\theta_l^{(k)}$ ,  $l = 0, \dots, n$ ,

$$\sqrt{\frac{1}{n+1} \sum_l \left[ f(\theta_l^{(k)}) - \bar{f}(\theta^{(k)}) \right]^2} \leq r$$

where  $\bar{f}(\theta^{(k)}) = \frac{1}{n+1} \sum_l f(\theta_l^{(k)})$ . If there are  $n_{act}$  boundary constraints active at  $\theta^{(k)}$ , the mean and standard deviation are computed only for the  $n + 1 - n_{act}$  unconstrained vertices. The default value is  $r = 1\text{E-}6$  for the NMSIMP technique and  $r = 0$  otherwise. The optional integer value  $n$  specifies the number of successive iterations for which the criterion must be satisfied before the process can terminate.

**FD <= FORWARD | CENTRAL |  $r >$** 

specifies that all derivatives be computed using finite difference approximations. The following specifications are permitted:

FD is equivalent to FD=100.

FD=CENTRAL uses central differences.

FD=FORWARD uses forward differences.

FD= $r$  uses central differences for the initial and final evaluations of the gradient and for the Hessian. During iteration, start with forward differences and switch to a corresponding central-difference formula during the iteration process when one of the following two criteria is satisfied:

- The absolute maximum gradient element is less than or equal to  $r$  times the **ABSGCONV=** threshold.
- The normalized predicted function reduction (see the **GTOL** option) is less than or equal to  $\max(1\text{E-}6, r \times \text{GTOL})$ . The  $1\text{E-}6$  ensures that the switch is done, even if you set the GTOL threshold to zero.



Note that the FD and FDHESSIAN options cannot apply at the same time. The FDHESSIAN option is ignored when only first-order derivatives are used. See the section “[Finite-Difference Approximations of Derivatives](#)” on page 5393 for more information.

**FDHESSIAN**<=**FORWARD** | **CENTRAL**>

**FDHES**<=**FORWARD** | **CENTRAL**>

**FDH**<=**FORWARD** | **CENTRAL**>

specifies that second-order derivatives be computed using finite difference approximations based on evaluations of the gradients.

FDHESSIAN=FORWARD uses forward differences.

FDHESSIAN=CENTRAL uses central differences.

FDHESSIAN uses forward differences for the Hessian except for the initial and final output.

Note that the FD and FDHESSIAN options cannot apply at the same time. See the section “[Finite-Difference Approximations of Derivatives](#)” on page 5393 for more information.

**FDIGITS**=*r*

specifies the number of accurate digits in evaluations of the objective function. Fractional values such as FDIGITS=4.7 are allowed. The default value is  $r = -\log_{10} \epsilon$ , where  $\epsilon$  is the machine precision. The value of  $r$  is used to compute the interval size  $h$  for the computation of finite-difference approximations of the derivatives of the objective function and for the default value of the [FCONV](#)= option.

**FLOW**

displays a message for each statement in the model program as it is executed. This debugging option is very rarely needed and produces voluminous output.

**FSIZE**=*r*

specifies the FSIZE parameter of the relative function and relative gradient termination criteria. The default value is  $r = 0$ . For more details, see the [FCONV](#)= and [GCONV](#)= options.

**G4**= $n > 0$

specifies a dimension to determine the type of generalized inverse to use when the approximate covariance matrix of the parameter estimates is singular. The default value of  $n$  is 60. See the section “[Covariance Matrix](#)” on page 5402 for more information.

**GCONV**= $r < [n] >$

**GTOL**= $r < [n] >$

specifies a relative gradient convergence criterion. For all techniques except CONGRA and NMSIMP, termination requires that the normalized predicted function reduction is small,

$$\frac{\mathbf{g}(\boldsymbol{\theta}^{(k)})' [\mathbf{H}^{(k)}]^{-1} \mathbf{g}(\boldsymbol{\theta}^{(k)})}{\max(|f(\boldsymbol{\theta}^{(k)})|, \text{FSIZE})} \leq r$$

where FSIZE is defined by the FSIZE= option. For the CONGRA technique (where a reliable Hessian estimate  $H$  is not available), the following criterion is used:

$$\frac{\|\mathbf{g}(\boldsymbol{\theta}^{(k)})\|_2^2 \quad \|\mathbf{s}(\boldsymbol{\theta}^{(k)})\|_2}{\|\mathbf{g}(\boldsymbol{\theta}^{(k)}) - \mathbf{g}(\boldsymbol{\theta}^{(k-1)})\|_2 \max(|f(\boldsymbol{\theta}^{(k)})|, \text{FSIZE})} \leq r$$

This criterion is not used by the NMSIMP technique.

The default value is  $r = 1\text{E-}8$ . The optional integer value  $n$  specifies the number of successive iterations for which the criterion must be satisfied before the process can terminate.

**HESCAL=0|1|2|3**

**HS=0|1|2|3**

specifies the scaling version of the Hessian matrix used in NRRIDG, TRUREG, NEWRAP, or DBLDOG optimization.

If HS is not equal to 0, the first iteration and each restart iteration sets the diagonal scaling matrix  $\mathbf{D}^{(0)} = \text{diag}(d_i^{(0)})$ :

$$d_i^{(0)} = \sqrt{\max(|H_{i,i}^{(0)}|, \epsilon)}$$

where  $H_{i,i}^{(0)}$  are the diagonal elements of the Hessian. In every other iteration, the diagonal scaling matrix  $\mathbf{D}^{(0)} = \text{diag}(d_i^{(0)})$  is updated depending on the HS option:

HS=0 specifies that no scaling is done.

HS=1 specifies the Moré (1978) scaling update:

$$d_i^{(k+1)} = \max \left[ d_i^{(k)}, \sqrt{\max(|H_{i,i}^{(k)}|, \epsilon)} \right]$$

HS=2 specifies the Dennis, Gay, and Welsch (1981) scaling update:

$$d_i^{(k+1)} = \max \left[ 0.6 * d_i^{(k)}, \sqrt{\max(|H_{i,i}^{(k)}|, \epsilon)} \right]$$

HS=3 specifies that  $d_i$  is reset in each iteration:

$$d_i^{(k+1)} = \sqrt{\max(|H_{i,i}^{(k)}|, \epsilon)}$$

In each scaling update,  $\epsilon$  is the relative machine precision. The default value is HS=0. Scaling of the Hessian can be time-consuming in the case where general linear constraints are active.

## HESS

requests the display of the final Hessian matrix after optimization. If you also specify the [START](#) option, then the Hessian at the starting values is also printed.

**INHESIAN=<r>**

**INHES=<r>**

specifies how the initial estimate of the approximate Hessian is defined for the quasi-Newton techniques QUANEW and DBLDOG. There are two alternatives:

- If you do not use the  $r$  specification, the initial estimate of the approximate Hessian is set to the Hessian at  $\boldsymbol{\theta}^{(0)}$ .
- If you do use the  $r$  specification, the initial estimate of the approximate Hessian is set to the multiple of the identity matrix,  $r\mathbf{I}$ .

By default, if you do not specify the option INHESIAN= $r$ , the initial estimate of the approximate Hessian is set to the multiple of the identity matrix  $r\mathbf{I}$ , where the scalar  $r$  is computed from the magnitude of the initial gradient.

**INSTEP=*r***

reduces the length of the first trial step during the line search of the first iterations. For highly nonlinear objective functions, such as the EXP function, the default initial radius of the trust-region algorithm TRUREG or DBLDOG or the default step length of the line-search algorithms can result in arithmetic overflows. If this occurs, you should specify decreasing values of  $0 < r < 1$  such as INSTEP=1E-1, INSTEP=1E-2, INSTEP=1E-4, and so on, until the iteration starts successfully.

- For trust-region algorithms (TRUREG, DBLDOG), the INSTEP= option specifies a factor  $r > 0$  for the initial radius  $\Delta^{(0)}$  of the trust region. The default initial trust-region radius is the length of the scaled gradient. This step corresponds to the default radius factor of  $r = 1$ .
- For line-search algorithms (NEWRAP, CONGRA, QUANEW), the INSTEP= option specifies an upper bound for the initial step length for the line search during the first five iterations. The default initial step length is  $r = 1$ .
- For the Nelder-Mead simplex algorithm, using TECH=NMSIMP, the INSTEP=*r* option defines the size of the start simplex.

For more details, see the section “[Computational Problems](#)” on page 5399.

**ITDETAILS**

requests a more complete iteration history, including the current values of the parameter estimates, their gradients, and additional optimization statistics. For further details, see the section “[Iterations](#)” on page 5405.

**LCDEACT=*r*****LCD=*r***

specifies a threshold *r* for the Lagrange multiplier that determines whether an active inequality constraint remains active or can be deactivated. During minimization, an active inequality constraint can be deactivated only if its Lagrange multiplier is less than the threshold value  $r < 0$ . The default value is

$$r = -\min(0.01, \max(0.1 \times \text{ABSGCONV}, 0.001 \times \text{gmax}^{(k)}))$$

where ABSGCONV is the value of the absolute gradient criterion, and  $\text{gmax}^{(k)}$  is the maximum absolute element of the (projected) gradient  $\mathbf{g}^{(k)}$  or  $\mathbf{Z}'\mathbf{g}^{(k)}$ . (See the section “[Active Set Methods](#)” for a definition of  $\mathbf{Z}$ .)

**LCEPSILON=*r* > 0****LCEPS=*r* > 0****LCE=*r* > 0**

specifies the range for active and violated boundary constraints. The default value is  $r = 1\text{E}-8$ . During the optimization process, the introduction of rounding errors can force PROC NLMIXED to increase the value of *r* by a factor of 10, 100, . . . . If this happens, it is indicated by a message displayed in the log.

**LCSINGULAR= $r > 0$** **LCSING= $r > 0$** **LCS= $r > 0$** 

specifies a criterion  $r$ , used in the update of the QR decomposition, that determines whether an active constraint is linearly dependent on a set of other active constraints. The default value is  $r = 1\text{E-}8$ . The larger  $r$  becomes, the more the active constraints are recognized as being linearly dependent. If the value of  $r$  is larger than 0.1, it is reset to 0.1.

**LINESEARCH= $i$** **LIS= $i$** 

specifies the line-search method for the CONGRA, QUANEW, and NEWRAP optimization techniques. See Fletcher (1987) for an introduction to line-search techniques. The value of  $i$  can be  $1, \dots, 8$ . For CONGRA, QUANEW and NEWRAP, the default value is  $i = 2$ .

- |       |   |
|-------|---|
| LIS=1 | specifies a line-search method that needs the same number of function and gradient calls for cubic interpolation and cubic extrapolation; this method is similar to one used by the Harwell subroutine library.   |
| LIS=2 | specifies a line-search method that needs more function than gradient calls for quadratic and cubic interpolation and cubic extrapolation; this method is implemented as shown in Fletcher (1987) and can be modified to an exact line search by using the LSPRECISION= option. |
| LIS=3 | specifies a line-search method that needs the same number of function and gradient calls for cubic interpolation and cubic extrapolation; this method is implemented as shown in Fletcher (1987) and can be modified to an exact line search by using the LSPRECISION= option.  |
| LIS=4 | specifies a line-search method that needs the same number of function and gradient calls for stepwise extrapolation and cubic interpolation.  |
| LIS=5 | specifies a line-search method that is a modified version of LIS=4.   |
| LIS=6 | specifies golden section line search (Polak 1971), which uses only function values for linear approximation.  |
| LIS=7 | specifies bisection line search (Polak 1971), which uses only function values for linear approximation.   |
| LIS=8 | specifies the Armijo line-search technique (Polak 1971), which uses only function values for linear approximation.  |

**LIST**

displays the model program and variable lists. The LIST option is a debugging feature and is not normally needed.

**LISTCODE**

displays the derivative tables and the compiled program code. The LISTCODE option is a debugging feature and is not normally needed.

**LISTDEP**

produces a report that lists, for each variable in the program, the variables that depend on it and on which it depends. The LISTDEP option is a debugging feature and is not normally needed.

**LISTDER**

displays a table of derivatives. This table lists each nonzero derivative computed for the problem. The LISTDER option is a debugging feature and is not normally needed.

**LOGNOTE<=*n*>**

writes periodic notes to the log that describe the current status of computations. It is designed for use with analyses requiring extensive CPU resources. The optional integer value *n* specifies the desired level of reporting detail. The default is *n* = 1. Choosing *n* = 2 adds information about the objective function values at the end of each iteration. The most detail is obtained with *n* = 3, which also reports the results of function evaluations within iterations.

**LSPRECISION=*r*****LSP=*r***

specifies the degree of accuracy that should be obtained by the line-search algorithms LIS=2 and LIS=3. Usually an imprecise line search is inexpensive and successful. For more difficult optimization problems, a more precise and expensive line search might be necessary (Fletcher 1987). The second line-search method (which is the default for the NEWRAP, QUANEW, and CONGRA techniques) and the third line-search method approach exact line search for small LSPRECISION= values. If you have numerical problems, you should try to decrease the LSPRECISION= value to obtain a more precise line search. The default values are shown in the following table.

TECH=	UPDATE=	LSP default
QUANEW	DBFGS, BFGS	<i>r</i> = 0.4
QUANEW	DDFP, DFP	<i>r</i> = 0.06
CONGRA	all	<i>r</i> = 0.1
NEWRAP	no update	<i>r</i> = 0.9

For more details, see Fletcher (1987).

**MAXFUNC=*i*****MAXFU=*i***

specifies the maximum number *i* of function calls in the optimization process. The default values are as follows:

- TRUREG, NRRIDG, NEWRAP: 125
- QUANEW, DBLDOG: 500
- CONGRA: 1000
- NMSIMP: 3000

Note that the optimization can terminate only after completing a full iteration. Therefore, the number of function calls that is actually performed can exceed the number that is specified by the MAXFUNC= option.

**MAXITER=*i*****MAXIT=*i***

specifies the maximum number *i* of iterations in the optimization process. The default values are as follows:

- TRUREG, NRRIDG, NEWRAP: 50
- QUANEW, DBLDOG: 200
- CONGRA: 400
- NMSIMP: 1000

These default values are also valid when *i* is specified as a missing value.

**MAXSTEP=*r*<[*n*]>**

specifies an upper bound for the step length of the line-search algorithms during the first *n* iterations. By default, *r* is the largest double-precision value and *n* is the largest integer available. Setting this option can improve the speed of convergence for the CONGRA, QUANEW, and NEWRAP techniques.

**MAXTIME=*r***

specifies an upper limit of *r* seconds of CPU time for the optimization process. The default value is the largest floating-point double representation of your computer. Note that the time specified by the MAXTIME= option is checked only once at the end of each iteration. Therefore, the actual running time can be much longer than that specified by the MAXTIME= option. The actual running time includes the rest of the time needed to finish the iteration and the time needed to generate the output of the results.

**METHOD=*value***

specifies the method for approximating the integral of the likelihood over the random effects. Valid values are as follows:

**FIRO**

specifies the first-order method of Beal and Sheiner (1982). When using METHOD=FIRO, you must specify the NORMAL distribution in the **MODEL** statement and you must also specify a **RANDOM** statement.

**GAUSS**

specifies adaptive Gauss-Hermite quadrature (Pinheiro and Bates 1995). You can prevent the adaptation with the **NOAD** option or prevent adaptive scaling with the **NOADSCALE** option. This is the default integration method.

**HARDY**

specifies Hardy quadrature based on an adaptive trapezoidal rule. This method is available only for one-dimensional integrals; that is, you must specify only one random effect.

**ISAMP**

specifies adaptive importance sampling (Pinheiro and Bates 1995). You can prevent the adaptation with the **NOAD** option or prevent adaptive scaling with the **NOADSCALE** option. You can use the **SEED=** option to specify a starting seed for the random number generation used in the importance sampling. If you do not specify a seed, or if you specify a value less than or equal to zero, the seed is generated from reading the time of day from the computer clock.

**MINITER=*i*****MINIT=*i***

specifies the minimum number of iterations. The default value is 0. If you request more iterations than are actually needed for convergence to a stationary point, the optimization algorithms can behave strangely. For example, the effect of rounding errors can prevent the algorithm from continuing for the required number of iterations.

**MSINGULAR= $r > 0$** **MSING= $r > 0$** 

specifies a relative singularity criterion for the computation of the inertia (number of positive, negative, and zero eigenvalues) of the Hessian and its projected forms. The default value is  $1\text{E-}12$  if you do not specify the SINGHESS= option; otherwise, the default value is  $\max(10\epsilon, (1\text{E-}4) \times \text{SINGHESS})$ . See the section “[Covariance Matrix](#)” on page 5402 for more information.

**NOAD**

requests that the Gaussian quadrature be nonadaptive; that is, the quadrature points are centered at zero for each of the random effects and the current random-effects variance matrix is used as the scale matrix.

**NOADSCALE**

requests nonadaptive scaling for adaptive Gaussian quadrature; that is, the quadrature points are centered at the empirical Bayes estimates for the random effects, but the current random-effects variance matrix is used as the scale matrix. By default, the observed Hessian from the current empirical Bayes estimates is used as the scale matrix.

**OPTCHECK $\leq r > 0$** 

computes the function values  $f(\theta_l)$  of a grid of points  $\theta_l$  in a ball of radius of  $r$  about  $\theta^*$ . If you specify the OPTCHECK option without factor  $r$ , the default value is  $r = 0.1$  at the starting point and  $r = 0.01$  at the terminating point. If a point  $\theta_l^*$  is found with a better function value than  $f(\theta^*)$ , then optimization is restarted at  $\theta_l^*$ .

**OUTQ=SAS-data-set**

specifies an output data set containing the quadrature points used for numerical integration.

**QFAC= $r > 0$** 

specifies the additive factor used to adaptively search for the number of quadrature points. For **METHOD=GAUSS**, the search sequence is 1, 3, 5, 7, 9, 11,  $11 + r$ ,  $11 + 2r$ , ..., where the default value of  $r$  is 10. For **METHOD=ISAMP**, the search sequence is 10,  $10 + r$ ,  $10 + 2r$ , ..., where the default value of  $r$  is 50.

**QMAX= $r > 0$** 

specifies the maximum number of quadrature points permitted before the adaptive search is aborted. The default values are 31 for adaptive Gaussian quadrature, 61 for nonadaptive Gaussian quadrature, 160 for adaptive importance sampling, and 310 for nonadaptive importance sampling.

**QPOINTS= $n > 0$** 

specifies the number of quadrature points to be used during evaluation of integrals. For **METHOD=GAUSS**,  $n$  equals the number of points used in each dimension of the random effects, resulting in a total of  $n^r$  points, where  $r$  is the number of dimensions. For **METHOD=ISAMP**,  $n$  specifies the total number of quadrature points regardless of the dimension of the random effects.

By default, the number of quadrature points is selected adaptively, and this option disables the adaptive search.

**QSCALEFAC= $r > 0$**

specifies a multiplier for the scale matrix used during quadrature calculations. The default value is 1.0.

**QTOL= $r > 0$**

specifies the tolerance used to adaptively select the number of quadrature points. When the relative difference between two successive likelihood calculations is less than  $r$ , then the search terminates and the lesser number of quadrature points is used during the subsequent optimization process. The default value is 1E-4.

**RESTART= $i > 0$**

**REST= $i > 0$**

specifies that the QUANEW or CONGRA algorithm is restarted with a steepest descent/ascent search direction after, at most,  $i$  iterations. Default values are as follows:

- CONGRA: UPDATE=PB: restart is performed automatically,  $i$  is not used.
- CONGRA: UPDATE $\neq$ PB:  $i = \min(10n, 80)$ , where  $n$  is the number of parameters.
- QUANEW:  $i$  is the largest integer available.

**SEED= $i$**

specifies the random number seed for **METHOD=ISAMP**. If you do not specify a seed, or if you specify a value less than or equal to zero, the seed is generated from reading the time of day from the computer clock. The value must be less than  $2^{31} - 1$ .

**SINGCHOL= $r > 0$**

specifies the singularity criterion  $r$  for Cholesky roots of the random-effects variance matrix and scale matrix for adaptive Gaussian quadrature. The default value is 1E4 times the machine epsilon; this product is approximately 1E-12 on most computers.

**SINGHESS= $r > 0$**

specifies the singularity criterion  $r$  for the inversion of the Hessian matrix. The default value is 1E-8. See the ASINGULAR, MSINGULAR=, and VSINGULAR= options for more information.

**SINGSWEEP= $r > 0$**

specifies the singularity criterion  $r$  for inverting the variance matrix in the first-order method and the empirical Bayes Hessian matrix. The default value is 1E4 times the machine epsilon; this product is approximately 1E-12 on most computers.

**SINGVAR= $r > 0$**

specifies the singularity criterion  $r$  below which statistical variances are considered to equal zero. The default value is 1E4 times the machine epsilon; this product is approximately 1E-12 on most computers.

**START**

requests that the gradient of the log likelihood at the starting values be displayed. If you also specify the **HESS** option, then the starting Hessian is displayed as well.



**SUBGRADIENT=SAS-data-set**

**SUBGRAD=SAS-data-set**

specifies a SAS data set to save in models with **RANDOM** statement the subject-specific gradients of the integrated, marginal log-likelihood with respect to all parameters. The sum of the subject-specific gradients equals the gradient reported in the “Parameter Estimates” table. The data set contains a variable identifying the subjects.

In models without **RANDOM** statement the **SUBGRADIENT=** data set contains the observation-wise gradient. The variable identifying the **SUBJECT=** is then replaced with the **Observation**. This observation counter includes observations not used in the analysis and is reset in each **BY**-group.

Saving disaggregated gradient information with the **SUBGRADIENT=** option requires **METHOD=GAUSS** or **METHOD=ISAMP**.

**TECHNIQUE=value**

**TECH=value**

specifies the optimization technique. By default, **TECH = QUANEW**. Valid values are as follows:

- **CONGRA**  
performs a conjugate-gradient optimization, which can be more precisely specified with the **UPDATE=** option and modified with the **LINESEARCH=** option. When you specify this option, **UPDATE=PB** by default.
- **DBLDOG**  
performs a version of double-dogleg optimization, which can be more precisely specified with the **UPDATE=** option. When you specify this option, **UPDATE=DBFGS** by default.
- **NMSIMP**  
performs a Nelder-Mead simplex optimization.
- **NONE**  
does not perform any optimization. This option can be used as follows:
  - to perform a grid search without optimization
  - to compute estimates and predictions that cannot be obtained efficiently with any of the optimization techniques
- **NEWRAP**  
performs a Newton-Raphson optimization combining a line-search algorithm with ridging. The line-search algorithm **LIS=2** is the default method.
- **NRRIDG**  
performs a Newton-Raphson optimization with ridging.
- **QUANEW**  
performs a quasi-Newton optimization, which can be defined more precisely with the **UPDATE=** option and modified with the **LINESEARCH=** option. This is the default estimation method.
- **TRUREG**  
performs a trust region optimization.

**TRACE**

displays the result of each operation in each statement in the model program as it is executed. This debugging option is very rarely needed, and it produces voluminous output.

**UPDATE=method****UPD=method**

specifies the update method for the quasi-Newton, double-dogleg, or conjugate-gradient optimization technique. Not every update method can be used with each optimizer. See the section “[Optimization Algorithms](#)” on page 5388 for more information.

Valid methods are as follows:

- **BFGS**  
performs the original Broyden, Fletcher, Goldfarb, and Shanno (BFGS) update of the inverse Hessian matrix.
- **DBFGS**  
performs the dual BFGS update of the Cholesky factor of the Hessian matrix. This is the default update method.
- **DDFP**  
performs the dual Davidon, Fletcher, and Powell (DFP) update of the Cholesky factor of the Hessian matrix.
- **DFP**  
performs the original DFP update of the inverse Hessian matrix.
- **PB**  
performs the automatic restart update method of Powell (1977) and Beale (1972).
- **FR**  
performs the Fletcher-Reeves update (Fletcher 1987).
- **PR**  
performs the Polak-Ribiere update (Fletcher 1987).
- **CD**  
performs a conjugate-descent update of Fletcher (1987).

**VSINGULAR= $r > 0$** **VSING= $r > 0$** 

specifies a relative singularity criterion for the computation of the inertia (number of positive, negative, and zero eigenvalues) of the Hessian and its projected forms. The default value is  $r = 1\text{E-}8$  if the **SINGHESS=** option is not specified, and it is the value of **SINGHESS=** option otherwise. See the section “[Covariance Matrix](#)” on page 5402 for more information.

**XCONV= $r < [n] >$** **XTOL= $r < [n] >$** 

specifies the relative parameter convergence criterion. For all techniques except NMSIMP, termination requires a small relative parameter change in subsequent iterations:

$$\frac{\max_j |\theta_j^{(k)} - \theta_j^{(k-1)}|}{\max(|\theta_j^{(k)}|, |\theta_j^{(k-1)}|, \text{XSIZE})} \leq r$$

For the NMSIMP technique, the same formula is used, but  $\theta^{(k)}$  is defined as the vertex with the lowest function value and  $\theta^{(k-1)}$  is defined as the vertex with the highest function value in the simplex.

The default value is  $r = 1\text{E-}8$  for the NMSIMP technique and  $r = 0$  otherwise. The optional integer value  $n$  specifies the number of successive iterations for which the criterion must be satisfied before the process can be terminated.

#### XREF

displays a cross-reference of the variables in the program showing where each variable is referenced or given a value. The XREF listing does not include derivative variables. This option is a debugging feature and is not normally needed.

#### XSIZE= $r > 0$

specifies the XSIZE parameter of the relative parameter termination criterion. The default value is  $r = 0$ . For more details, see the [XCONV=](#) option.

---

## ARRAY Statement

**ARRAY** *arrayname* [ *dimensions* ] <\$> <*variables-and-constants*> ;

The ARRAY statement is similar to, but not exactly the same as, the ARRAY statement in the SAS DATA step, and it is exactly the same as the ARRAY statements in the NLIN, NLP, and MODEL procedures. The ARRAY statement is used to associate a name (of no more than eight characters) with a list of variables and constants. The array name is used with subscripts in the program to refer to the array elements. The following statements illustrate this:

```
array r[8] r1-r8;

do i = 1 to 8;
    r[i] = 0;
end;
```

The ARRAY statement does not support all the features of the ARRAY statement in the DATA step. It cannot be used to assign initial values to array elements. Implicit indexing of variables cannot be used; all array references must have explicit subscript expressions. Only exact array dimensions are allowed; lower-bound specifications are not supported. A maximum of six dimensions is allowed.

On the other hand, the ARRAY statement does allow both variables and constants to be used as array elements. (Constant array elements cannot have values assigned to them.) Both dimension specification and the list of elements are optional, but at least one must be specified. When the list of elements is not specified or fewer elements than the size of the array are listed, array variables are created by suffixing element numbers to the array name to complete the element list.

## BOUNDS Statement

**BOUNDS** *b-con* <, *b-con* ... >;

where *b-con* :=      number *operator* parameter\_list *operator* number  
          or *b-con* :=      number *operator* parameter\_list  
          or *b-con* :=      parameter\_list *operator* number  
 and *operator* :=      <=, <, >=, or >

Boundary constraints are specified with a BOUNDS statement. One- or two-sided boundary constraints are allowed. The list of boundary constraints are separated by commas. For example:

```
bounds 0 <= a1-a9 x <= 1, -1 <= c2-c5;
bounds b1-b10 y >= 0;
```

You can specify more than one BOUNDS statement. If you specify more than one lower (upper) bound for the same parameter, the maximum (minimum) of these is taken.

If the maximum  $l_j$  of all lower bounds is larger than the minimum of all upper bounds  $u_j$  for the same parameter  $\theta_j$ , the boundary constraint is replaced by  $\theta_j := l_j := \min(u_j)$  defined by the minimum of all upper bounds specified for  $\theta_j$ .

## BY Statement

**BY** *variables* ;

You can specify a BY statement with PROC NLMIXED 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 NLMIXED 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).

An optimization problem is solved for each BY group separately unless the **TECH=NONE** option is specified.

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*.

---

## CONTRAST Statement

**CONTRAST** *'label' expression < , expression > < options > ;*

The CONTRAST statement enables you to conduct a statistical test that several expressions simultaneously equal zero. The expressions are typically contrasts—that is, differences whose expected values equal zero under the hypothesis of interest.

In the CONTRAST statement you must provide a quoted string to identify the contrast and then a list of valid SAS expressions separated by commas. Multiple CONTRAST statements are permitted, and results from all statements are listed in a common table. PROC NLMIXED constructs approximate  $F$  tests for each statement using the delta method (Cox 1998) to approximate the variance-covariance matrix of the constituent expressions.

The following option is available in the CONTRAST statement:

**DF=***d*

specifies the denominator degrees of freedom to be used in computing  $p$  values for the  $F$  statistics. The default value corresponds to the **DF=** option in the PROC NLMIXED statement.

---

## ESTIMATE Statement

**ESTIMATE** *'label' expression < options > ;*

The ESTIMATE statement enables you to compute an additional estimate that is a function of the parameter values. You must provide a quoted string to identify the estimate and then a valid SAS expression. Multiple ESTIMATE statements are permitted, and results from all statements are listed in a common table. PROC NLMIXED computes approximate standard errors for the estimates using the delta method (Billingsley 1986). It uses these standard errors to compute corresponding  $t$  statistics,  $p$ -values, and confidence limits.

The **ECOV** option in the PROC NLMIXED statement produces a table containing the approximate covariance matrix of all the additional estimates you specify. The **ECORR** option produces the corresponding correlation matrix. The **EDER** option produces a table of the derivatives of the additional estimates with respect to each of the model parameters.

The following options are available in the ESTIMATE statement:

**ALPHA=** $\alpha$

specifies the alpha level to be used in computing confidence limits. The default value corresponds to the **ALPHA=** option in the PROC NLMIXED statement.

**DF=***d*

specifies the degrees of freedom to be used in computing  $p$ -values and confidence limits. The default value corresponds to the **DF=** option in the PROC NLMIXED statement.

---

## ID Statement

**ID** *names* ;

The ID statement identifies additional quantities to be included in the **OUT=** data set of the **PREDICT** statement. These can be any symbols you have defined with SAS programming statements.

---

## MODEL Statement

**MODEL** *dependent-variable*  $\sim$  *distribution* ;

The MODEL statement is the mechanism for specifying the conditional distribution of the data given the random effects. You must specify a single dependent variable from the input data set, a tilde  $\sim$ , and then a distribution with its parameters. Valid distributions are as follows.

- *normal*(*m*,*v*) specifies a normal (Gaussian) distribution with mean *m* and variance *v*.
- *binary*(*p*) specifies a binary (Bernoulli) distribution with probability *p*.
- *binomial*(*n*,*p*) specifies a binomial distribution with count *n* and probability *p*.
- *gamma*(*a*,*b*) specifies a gamma distribution with shape *a* and scale *b*.
- *negbin*(*n*,*p*) specifies a negative binomial distribution with count *n* and probability *p*.
- *poisson*(*m*) specifies a Poisson distribution with mean *m*.
- *general*(*ll*) specifies a general log likelihood function that you construct using SAS programming statements.

The MODEL statement must follow any SAS programming statements you specify for computing parameters of the preceding distributions. See the section “[Built-in Log-Likelihood Functions](#)” on page 5386 for expressions of the built-in conditional log-likelihood functions.

---

## PARMS Statement

**PARMS** *< name-list <=numbers> > <, name-list <=numbers> ... >*  
*</ options>* ;

The PARMS statement lists names of parameters and specifies initial values, possibly over a grid. You can specify the parameters and values directly in a list, or you can provide the name of a SAS data set that contains them by using the **DATA=** option.

While the PARMS statement is not required, you are encouraged to use it to provide PROC NLMIXED with accurate starting values. Parameters not listed in the PARMS statement are assigned an initial value of 1.

PROC NLMIXED considers all symbols not assigned values to be parameters, so you should specify your modeling statements carefully and check the output from the “Parameters” table to make sure the proper parameters are identified.

A list of parameter names in the PARMS statement is not separated by commas and is followed by an equal sign and a list of numbers. If the number list consists of only one number, this number defines the initial value for all the parameters listed to the left of the equal sign.

If the number list consists of more than one number, these numbers specify the grid locations for each of the parameters listed to the left of the equal sign. You can use the TO and BY keywords to specify a number list for a grid search. If you specify a grid of points in a PARMS statement, PROC NLMIXED computes the objective function value at each grid point and chooses the best (feasible) grid point as an initial point for the optimization process. You can use the BEST= option to save memory for the storing and sorting of all grid point information.

The following options are available in the PARMS statement after a slash (/):

**BEST=*i* > 0**

specifies the maximum number of points displayed in the “Parameters” table, selected as the points with the maximum likelihood values. By default, all grid values are displayed.

**BYDATA**

enables you to assign different starting values for each BY group by using the DATA=SAS-*data-set* option during BY processing. By default, BY groups are ignored in the PARMS data set. For the BYDATA option to be effective, the DATA= data set must contain the BY variables and the same BY groups as the primary input data set. When you supply a grid of starting values with the DATA= data set and the BYDATA option is in effect, the size of the grid is determined by the first BY group.

**DATA=SAS-*data-set***

specifies a SAS data set containing parameter names and starting values. The data set should be in one of two forms: narrow or wide. The narrow-form data set contains the variables Parameter and Estimate, with parameters and values listed as distinct observations. The wide-form data set has the parameters themselves as variables, and each observation provides a different set of starting values. By default, BY groups are ignored in this data set, so the same starting grid is evaluated for each BY group. You can vary the starting values for BY groups by using the BYDATA option.

---

## PREDICT Statement

**PREDICT** *expression* **OUT=SAS-*data-set*** < *options* > ;

The PREDICT statement enables you to construct predictions of an expression across all of the observations in the input data set. Any valid SAS programming expression involving the input data set variables, parameters, and random effects is valid. Predicted values are computed using the parameter estimates and empirical Bayes estimates of the random effects. Standard errors of prediction are computed using the delta method (Billingsley 1986; Cox 1998). Results are placed in an output data set that you specify with the OUT= option. Besides all variables from the input data set, the OUT= data set contains the following variables: Pred, StdErrPred, DF, tValue, Probt, Alpha, Lower, Upper. You can also add other computed quantities to this data set with the ID statement.

The following options are available in the PREDICT statement:

**ALPHA=** $\alpha$

specifies the alpha level to be used in computing  $t$  statistics and intervals. The default value corresponds to the **ALPHA=** option in the **PROC NLMIXED** statement.

**DER**

requests that derivatives of the predicted expression with respect to all parameters be included in the OUT= data set. The variable names for the derivatives are the same as the parameter names with the prefix “Der\_” appended. All of the derivatives are evaluated at the final estimates of the parameters and the empirical Bayes estimates of the random effects.

**DF=** $d$

specifies the degrees of freedom to be used in computing  $t$  statistics and intervals in the OUT= data set. The default value corresponds to the **DF=** option in the **PROC NLMIXED** statement.

---

## RANDOM Statement

**RANDOM** *random-effects* ~ *distribution* **SUBJECT=***variable* < *options* > ;

The RANDOM statement defines the random effects and their distribution. The random effects must be represented by symbols that appear in your SAS programming statements. They typically influence the mean value of the distribution specified in the **MODEL** statement. The RANDOM statement consists of a list of the random effects (usually just one or two symbols), a tilde ~, the distribution for the random effects, and then a **SUBJECT=** variable.

**NOTE:** The input data set must be clustered according to the **SUBJECT=** variable. One easy way to accomplish this is to sort your data by the **SUBJECT=** variable prior to calling PROC NLMIXED. PROC NLMIXED does not sort the input data set for you; rather, it processes the data sequentially and considers an observation to be from a new subject whenever the value of its **SUBJECT=** variable changes from the previous observation.

The only distribution available for the random effects is normal( $m,v$ ) with mean  $m$  and variance  $v$ .

This syntax is illustrated as follows for one effect:

```
random u ~ normal(0,s2u) subject=clinic;
```

For multiple effects, you should specify bracketed vectors for  $m$  and  $v$ , the latter consisting of the lower triangle of the random-effects variance matrix listed in row order. This is illustrated for two and three random effects as follows:

```
random b1 b2 ~ normal([0,0],[g11,g21,g22]) subject=person;
random b1 b2 b3 ~ normal([0,0,0],[g11,g21,g22,g31,g32,g33])
    subject=person;
```

The **SUBJECT=** variable determines when new realizations of the random effects are assumed to occur. PROC NLMIXED assumes that a new realization occurs whenever the value of the **SUBJECT=** variable changes from the previous observation, so your input data set should be clustered according to this variable. One easy way to accomplish this is to run PROC SORT prior to calling PROC NLMIXED by using the **SUBJECT=** variable as the BY variable.



Only one RANDOM statement is permitted, so multilevel nonlinear mixed models are not accommodated. However, you can specify certain nested random effects structure with a single RANDOM statement (see Chapter 15 of Littell et al. (2006) for an example).

The following options are available in the RANDOM statement:

**ALPHA=** $\alpha$

specifies the alpha level to be used in computing  $t$  statistics and intervals. The default value corresponds to the ALPHA= option in the PROC NLMIXED statement.

**DF=** $d$

specifies the degrees of freedom to be used in computing  $t$  statistics and intervals in the OUT= data set. The default value corresponds to the DF= option in the PROC NLMIXED statement.

**OUT=***SAS-data-set*

requests an output data set containing empirical Bayes estimates of the random effects and their approximate standard errors of prediction.

---

## REPLICATE Statement

**REPLICATE** *variable* ;

The REPLICATE statement provides a way to accommodate models in which different subjects have identical data. This occurs most commonly when the dependent variable is binary. When you specify a REPLICATE variable, PROC NLMIXED treats its value as the number of subjects that have data identical to the data for the current value of the SUBJECT= variable (specified in the RANDOM statement). Only the last observation of the REPLICATE variable for each subject is used, and the replicate variable must have only positive values.

The function of a REPLICATE statement is related to but not quite the same as the function of either a FREQ or a WEIGHT statement in other statistical modeling procedures, such as the GLM, GENMOD, GLIMMIX, and LOGISTIC procedures. A FREQ or a WEIGHT value essentially multiplies the log likelihood or sum of squares contribution for each observation. On the other hand, a REPLICATE value multiplies the log likelihood contribution of each subject, which consists of one or more observations. When no SUBJECT= variable is specified, the REPLICATE value behaves like a weight, multiplying each observation's log likelihood contribution.

---

## Programming Statements

This section lists the programming statements used to code the log-likelihood function in PROC NLMIXED. It also documents the differences between programming statements in PROC NLMIXED and programming statements in the SAS DATA step. The syntax of programming statements used in PROC NLMIXED is identical to that used in the CALIS and GENMOD procedures (see Chapter 27 and Chapter 40, respectively), and the MODEL procedure (see the *SAS/ETS User's Guide*). Most of the programming statements that can be used in the SAS DATA step can also be used in the NLMIXED procedure. See *SAS Language Reference: Dictionary* for a description of SAS programming statements. The following are valid statements:

```

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;

```

For the most part, the SAS programming statements work the same as they do in the SAS DATA step, as documented in *SAS Language Reference: Concepts*; however, there are the following differences:

- The ABORT statement does not allow any arguments.
- The DO statement does not allow a character index variable. Thus

```
do i = 1,2,3;
```

is supported, but the following statement is not supported:

```
do i = 'A', 'B', 'C';
```

- The LAG function does work appropriately with PROC NLMIXED, but you can use the ZLAG function instead.
- The PUT statement, used mostly for program debugging in PROC NLMIXED, supports only some of the features of the DATA step PUT statement, and it has some new features that the DATA step PUT statement does not.
  - The PROC NLMIXED PUT statement does not support line pointers, factored lists, iteration factors, overprinting, \_INFILE\_, the colon (:) format modifier, or “\$”.
  - The PROC NLMIXED PUT statement does support expressions, but the expression must be enclosed in parentheses. For example, the following statement displays the square root of x:
 

```
put (sqrt(x));
```

- The PROC NLMIXED PUT statement supports the item `_PDV_` to display a formatted listing of all variables in the program. For example, the following statement displays a much more readable listing of the variables than the `_ALL_` print item:

```
put _pdv_;
```

- The WHEN and OTHERWISE statements enable you to specify more than one target statement. That is, DO/END groups are not necessary for multiple statement WHENs. For example, the following syntax is valid:

```
select;
  when (exp1) stmt1;
               stmt2;
  when (exp2) stmt3;
               stmt4;
end;
```

When coding your programming statements, you should avoid defining variables that begin with an underscore (`_`), because they might conflict with internal variables created by PROC NLMIXED. The **MODEL** statement must come after any SAS programming statements that define or modify terms used in the construction of the log-likelihood.

---

## Details: NLMIXED Procedure

This section contains details about the underlying theory and computations of PROC NLMIXED.

---

### Modeling Assumptions and Notation

PROC NLMIXED operates under the following general framework for nonlinear mixed models. Assume that you have an observed data vector  $\mathbf{y}_i$  for each of  $i$  subjects,  $i = 1, \dots, s$ . The  $\mathbf{y}_i$  are assumed to be independent across  $i$ , but within-subject covariance is likely to exist because each of the elements of  $\mathbf{y}_i$  is measured on the same subject. As a statistical mechanism for modeling this within-subject covariance, assume that there exist latent random-effect vectors  $\mathbf{u}_i$  of small dimension (typically one or two) that are also independent across  $i$ . Assume also that an appropriate model linking  $\mathbf{y}_i$  and  $\mathbf{u}_i$  exists, leading to the joint probability density function

$$p(\mathbf{y}_i | \mathbf{X}_i, \boldsymbol{\phi}, \mathbf{u}_i) q(\mathbf{u}_i | \boldsymbol{\xi})$$

where  $\mathbf{X}_i$  is a matrix of observed explanatory variables and  $\boldsymbol{\phi}$  and  $\boldsymbol{\xi}$  are vectors of unknown parameters.

Let  $\boldsymbol{\theta} = [\boldsymbol{\phi}, \boldsymbol{\xi}]$  and assume that it is of dimension  $n$ . Then inferences about  $\boldsymbol{\theta}$  are based on the marginal likelihood function

$$m(\boldsymbol{\theta}) = \prod_{i=1}^s \int p(\mathbf{y}_i | \mathbf{X}_i, \boldsymbol{\phi}, \mathbf{u}_i) q(\mathbf{u}_i | \boldsymbol{\xi}) d\mathbf{u}_i$$

In particular, the function

$$f(\boldsymbol{\theta}) = -\log m(\boldsymbol{\theta})$$

is minimized over  $\boldsymbol{\theta}$  numerically in order to estimate  $\boldsymbol{\theta}$ , and the inverse Hessian (second derivative) matrix at the estimates provides an approximate variance-covariance matrix for the estimate of  $\boldsymbol{\theta}$ . The function  $f(\boldsymbol{\theta})$  is referred to both as the negative log likelihood function and as the objective function for optimization.

As an example of the preceding general framework, consider the nonlinear growth curve example in the section “Getting Started: NLMIXED Procedure” on page 5350. Here, the conditional distribution  $p(y_i | \mathbf{X}_i, \boldsymbol{\phi}, u_i)$  is normal with mean

$$\frac{b_1 + u_{i1}}{1 + \exp[-(d_{ij} - b_2)/b_3]}$$

and variance  $\sigma_e^2$ ; thus  $\boldsymbol{\phi} = [b_1, b_2, b_3, \sigma_e^2]$ . Also,  $u_i$  is a scalar and  $q(u_i | \xi)$  is normal with mean 0 and variance  $\sigma_u^2$ ; thus  $\xi = \sigma_u^2$ .

The following additional notation is also found in this chapter. The quantity  $\boldsymbol{\theta}^{(k)}$  refers to the parameter vector at the  $k$ th iteration, the vector  $\mathbf{g}(\boldsymbol{\theta})$  refers to the gradient vector  $\nabla f(\boldsymbol{\theta})$ , and the matrix  $\mathbf{H}(\boldsymbol{\theta})$  refers to the Hessian  $\nabla^2 f(\boldsymbol{\theta})$ . Other symbols are used to denote various constants or option values.

## Integral Approximations

An important part of the marginal maximum likelihood method described previously is the computation of the integral over the random effects. The default method in PROC NLMIXED for computing this integral is adaptive Gaussian quadrature as described in Pinheiro and Bates (1995). Another approximation method is the first-order method of Beal and Sheiner (1982, 1988). A description of these two methods follows.

### Adaptive Gaussian Quadrature

A quadrature method approximates a given integral by a weighted sum over predefined abscissas for the random effects. A good approximation can usually be obtained with an adequate number of quadrature points as well as appropriate centering and scaling of the abscissas. Adaptive Gaussian quadrature for the integral over  $\mathbf{u}_i$  centers the integral at the empirical Bayes estimate of  $\mathbf{u}_i$ , defined as the vector  $\hat{\mathbf{u}}_i$  that minimizes

$$-\log [p(y_i | \mathbf{X}_i, \boldsymbol{\phi}, \mathbf{u}_i)q(\mathbf{u}_i | \xi)]$$

with  $\boldsymbol{\phi}$  and  $\xi$  set equal to their current estimates. The final Hessian matrix from this optimization can be used to scale the quadrature abscissas.

Suppose  $(z_j, w_j; j = 1, \dots, p)$  denote the standard Gauss-Hermite abscissas and weights (Golub and Welsch 1969, or Table 25.10 of Abramowitz and Stegun 1972). The adaptive Gaussian quadrature integral approximation is as follows:

$$\int p(y_i | \mathbf{X}_i, \boldsymbol{\phi}, \mathbf{u}_i)q(\mathbf{u}_i | \xi) d\mathbf{u}_i \approx 2^{r/2} |\boldsymbol{\Gamma}(\mathbf{X}_i, \boldsymbol{\theta})|^{-1/2} \sum_{j_1=1}^p \cdots \sum_{j_r=1}^p \left[ p(y_i | \mathbf{X}_i, \boldsymbol{\phi}, \mathbf{a}_{j_1, \dots, j_r})q(\mathbf{a}_{j_1, \dots, j_r} | \xi) \prod_{k=1}^r w_{j_k} \exp z_{j_k}^2 \right]$$

where  $r$  is the dimension of  $u_i$ ,  $\Gamma(\mathbf{X}_i, \boldsymbol{\theta})$  is the Hessian matrix from the empirical Bayes minimization,  $\mathbf{z}_{j_1, \dots, j_r}$  is a vector with elements  $(z_{j_1}, \dots, z_{j_r})$ , and

$$\mathbf{a}_{j_1, \dots, j_r} = \hat{\mathbf{u}}_i + 2^{1/2} \Gamma(\mathbf{X}_i, \boldsymbol{\theta})^{-1/2} \mathbf{z}_{j_1, \dots, j_r}$$

PROC NLMIXED selects the number of quadrature points adaptively by evaluating the log-likelihood function at the starting values of the parameters until two successive evaluations have a relative difference less than the value of the **QTOL=** option. The specific search sequence is described under the **QFAC=** option. Using the **QPOINTS=** option, you can adjust the number of quadrature points  $p$  to obtain different levels of accuracy. Setting  $p = 1$  results in the Laplacian approximation as described in: Beal and Sheiner (1992); Wolfinger (1993); Vonesh (1992, 1996); Vonesh and Chinchilli (1997); Wolfinger and Lin (1997).

The **NOAD** option in the **PROC NLMIXED** statement requests nonadaptive Gaussian quadrature. Here all  $\hat{\mathbf{u}}_i$  are set equal to zero, and the Cholesky root of the estimated variance matrix of the random effects is substituted for  $\Gamma(\mathbf{X}_i, \boldsymbol{\theta})^{-1/2}$  in the preceding expression for  $\mathbf{a}_{j_1, \dots, j_r}$ . In this case derivatives are computed using the algorithm of Smith (1995). The **NOADSCALE** option requests the same scaling substitution but with the empirical Bayes  $\hat{\mathbf{u}}_i$ .

PROC NLMIXED computes the derivatives of the adaptive Gaussian quadrature approximation when carrying out the default dual quasi-Newton optimization.

## First-Order Method

Another integral approximation available in PROC NLMIXED is the first-order method of Beal and Sheiner (1982, 1988) and Sheiner and Beal (1985). This approximation is used only in the case where  $p(\mathbf{y}_i | \mathbf{X}_i, \boldsymbol{\phi}, \mathbf{u}_i)$  is normal—that is,

$$p(\mathbf{y}_i | \mathbf{X}_i, \boldsymbol{\phi}, \mathbf{u}_i) = (2\pi)^{-n_i/2} |\mathbf{R}_i(\mathbf{X}_i, \boldsymbol{\phi})|^{-1/2} \exp \left\{ -(1/2) [\mathbf{y}_i - \mathbf{m}_i(\mathbf{X}_i, \boldsymbol{\phi}, \mathbf{u}_i)]' \mathbf{R}_i(\mathbf{X}_i, \boldsymbol{\phi})^{-1} [\mathbf{y}_i - \mathbf{m}_i(\mathbf{X}_i, \boldsymbol{\phi}, \mathbf{u}_i)] \right\}$$

where  $n_i$  is the dimension of  $\mathbf{y}_i$ ,  $\mathbf{R}_i$  is a diagonal variance matrix, and  $\mathbf{m}_i$  is the conditional mean vector of  $\mathbf{y}_i$ .

The first-order approximation is obtained by expanding  $\mathbf{m}_i(\mathbf{X}_i, \boldsymbol{\phi}, \mathbf{u}_i)$  with a one-term Taylor series expansion about  $\mathbf{u}_i = \mathbf{0}$ , resulting in the approximation

$$p(\mathbf{y}_i | \mathbf{X}_i, \boldsymbol{\phi}, \mathbf{u}_i) \approx (2\pi)^{-n_i/2} |\mathbf{R}_i(\mathbf{X}_i, \boldsymbol{\phi})|^{-1/2} \exp \left\{ -(1/2) [\mathbf{y}_i - \mathbf{m}_i(\mathbf{X}_i, \boldsymbol{\phi}, \mathbf{0}) - \mathbf{Z}_i(\mathbf{X}_i, \boldsymbol{\phi}) \mathbf{u}_i]' \mathbf{R}_i(\mathbf{X}_i, \boldsymbol{\phi})^{-1} [\mathbf{y}_i - \mathbf{m}_i(\mathbf{X}_i, \boldsymbol{\phi}, \mathbf{0}) - \mathbf{Z}_i(\mathbf{X}_i, \boldsymbol{\phi}) \mathbf{u}_i] \right\}$$

where  $\mathbf{Z}_i(\mathbf{X}_i, \boldsymbol{\phi})$  is the Jacobian matrix  $\partial \mathbf{m}_i(\mathbf{X}_i, \boldsymbol{\phi}, \mathbf{u}_i) / \partial \mathbf{u}_i$  evaluated at  $\mathbf{u}_i = \mathbf{0}$ .

Assuming that  $q(\mathbf{u}_i | \boldsymbol{\xi})$  is normal with mean  $\mathbf{0}$  and variance matrix  $\mathbf{G}(\boldsymbol{\xi})$ , the first-order integral approximation is computable in closed form after completing the square:

$$\int p(\mathbf{y}_i | \mathbf{X}_i, \boldsymbol{\phi}, \mathbf{u}_i) q(\mathbf{u}_i | \boldsymbol{\xi}) d\mathbf{u}_i \approx (2\pi)^{-n_i/2} |\mathbf{V}_i(\mathbf{X}_i, \boldsymbol{\theta})|^{-1/2} \exp \left\{ -(1/2) [\mathbf{y}_i - \mathbf{m}_i(\mathbf{X}_i, \boldsymbol{\phi}, \mathbf{0})]' \mathbf{V}_i(\mathbf{X}_i, \boldsymbol{\theta})^{-1} [\mathbf{y}_i - \mathbf{m}_i(\mathbf{X}_i, \boldsymbol{\phi}, \mathbf{0})] \right\}$$

where  $\mathbf{V}_i(\mathbf{X}_i, \boldsymbol{\theta}) = \mathbf{Z}_i(\mathbf{X}_i, \boldsymbol{\phi}) \mathbf{G}(\boldsymbol{\xi}) \mathbf{Z}_i(\mathbf{X}_i, \boldsymbol{\phi})' + \mathbf{R}_i(\mathbf{X}_i, \boldsymbol{\phi})$ . The resulting approximation for  $f(\boldsymbol{\theta})$  is then minimized over  $\boldsymbol{\theta} = [\boldsymbol{\phi}, \boldsymbol{\xi}]$  to obtain the first-order estimates. PROC NLMIXED uses finite-difference derivatives of the first-order integral approximation when carrying out the default dual quasi-Newton optimization.

## Built-in Log-Likelihood Functions

This section displays the basic formulas used by the NLMIXED procedure to compute the conditional log-likelihood functions of the data given the random effects. Note, however, that in addition to these basic equations, the NLMIXED procedure employs a number of checks for missing values and floating-point arithmetic. You can see the entire program used by the NLMIXED procedure to compute the conditional log-likelihood functions  $l(\phi; y)$  by adding the **LIST** debugging option to the **PROC NLMIXED** statement.

$Y \sim \text{normal}(m, v)$

$$l(m, v; y) = -\frac{1}{2} \left( \log\{2\pi\} + \frac{(y - m)^2}{v} + \log\{v\} \right)$$

$$E[Y] = m$$

$$\text{Var}[Y] = v$$

$$v > 0$$

$Y \sim \text{binary}(p)$

$$l_1(p; y) = \begin{cases} y \log\{p\} & y > 0 \\ 0 & \text{otherwise} \end{cases}$$

$$l_2(p; y) = \begin{cases} (1 - y) \log\{1 - p\} & y < 1 \\ 0 & \text{otherwise} \end{cases}$$

$$l(p; y) = l_1(p; y) + l_2(p; y)$$

$$E[Y] = p$$

$$\text{Var}[Y] = p(1 - p)$$

$$0 < p < 1$$

$Y \sim \text{binomial}(n, p)$

$$l_c = \log\{\Gamma(n + 1)\} - \log\{\Gamma(y + 1)\} - \log\{\Gamma(n - y + 1)\}$$

$$l_1(n, p; y) = \begin{cases} y \log\{p\} & y > 0 \\ 0 & \text{otherwise} \end{cases}$$

$$l_2(n, p; y) = \begin{cases} (n - y) \log\{1 - p\} & n - y > 0 \\ 0 & \text{otherwise} \end{cases}$$

$$l(n, p; y) = l_c + l_1(n, p; y) + l_2(n, p; y)$$

$$E[Y] = n p$$

$$\text{Var}[Y] = n p (1 - p)$$

$$0 < p < 1$$

$Y \sim \text{gamma}(a, b)$

$$l(a, b; y) = -a \log\{b\} - \log\{\Gamma(a)\} + (a - 1) \log\{y\} - y/b$$

$$E[Y] = ab$$

$$\text{Var}[Y] = ab^2$$

$$a > 0$$

$$b > 0$$

This parameterization of the gamma distribution differs from the parameterization used in the GLIMMIX and GENMOD procedures. The following statements show the equivalent reparameterization in the NLMIXED procedure that fits a generalized linear model for gamma-distributed data in the parameterization of the GLIMMIX procedure:

```
proc glimmix;
  model y = x / dist=gamma s;
run;

proc nlmixed;
  parms b0=1 b1=0 scale=14;
  linp = b0 + b1*x;
  mu   = exp(linp);
  b    = mu/scale;
  model y ~ gamma(scale,b);
run;
```

$$Y \sim \text{negbin}(n, p)$$

$$\begin{aligned} l(n, p; y) &= \log\{\Gamma(n + y)\} - \log\{\Gamma(n)\} - \log\{\Gamma(y + 1)\} \\ &\quad + n \log\{p\} + y \log\{1 - p\} \\ E[Y] &= nP = n \left( \frac{1 - p}{p} \right) \\ \text{Var}[Y] &= nP(1 - P) = n \left( \frac{1 - p}{p} \right) \frac{1}{p} \\ n &\geq 0 \\ 0 &< p < 1 \end{aligned}$$

This form of the negative binomial distribution is one of the many parameterizations in which the mass function or log-likelihood function appears. Another common parameterization uses

$$\begin{aligned} l(n, p; y) &= \log\{\Gamma(n + y)\} - \log\{\Gamma(n)\} - \log\{\Gamma(y + 1)\} \\ &\quad + n \log\{1 - P/(1 + P)\} + y \log\{P/(1 + P)\} \end{aligned}$$

with  $P = (1 - p)/p$ ,  $P > 0$ .

Note that the parameter  $n$  can be real-numbered; it does not have to be integer-valued. The parameterization of the negative binomial distribution in the NLMIXED procedure differs from that in the GLIMMIX and GENMOD procedures. The following statements show the equivalent formulations for maximum likelihood estimation in the GLIMMIX and NLMIXED procedures in a negative binomial regression model:

```
proc glimmix;
  model y = x / dist=negbin s;
run;
```

```

proc nlmixed;
  parms b0=3, b1=1, k=0.8;
  linp = b0 + b1*x;
  mu = exp(linp);
  p = 1/(1+mu*k);
  model y ~ negbin(1/k,p);
run;

```

$Y \sim \text{Poisson}(m)$

$$l(m; y) = y \log\{m\} - m - \log\{\Gamma(y + 1)\}$$

$$E[Y] = m$$

$$\text{Var}[Y] = m$$

$$m > 0$$

## Optimization Algorithms

There are several optimization techniques available in PROC NLMIXED. You can choose a particular optimizer with the **TECH=** option in the **PROC NLMIXED** statement.

Algorithm	TECH=
trust region method	TRUREG
Newton-Raphson method with line search	NEWRAP
Newton-Raphson method with ridging	NRRIDG
quasi-Newton methods (DBFGS, DDFP, BFGS, DFP)	QUANNEW
double-dogleg method (DBFGS, DDFP)	DBLDOG
conjugate gradient methods (PB, FR, PR, CD)	CONGRA
Nelder-Mead simplex method	NMSIMP

No algorithm for optimizing general nonlinear functions exists that always finds the global optimum for a general nonlinear minimization problem in a reasonable amount of time. Since no single optimization technique is invariably superior to others, PROC NLMIXED provides a variety of optimization techniques that work well in various circumstances. However, you can devise problems for which none of the techniques in PROC NLMIXED can find the correct solution. Moreover, nonlinear optimization can be computationally expensive in terms of time and memory, so you must be careful when matching an algorithm to a problem.

All optimization techniques in PROC NLMIXED use  $O(n^2)$  memory except the conjugate gradient methods, which use only  $O(n)$  of memory and are designed to optimize problems with many parameters. Since the techniques are iterative, they require the repeated computation of the following:

- the function value (optimization criterion)
- the gradient vector (first-order partial derivatives)
- for some techniques, the (approximate) Hessian matrix (second-order partial derivatives)



However, since each of the optimizers requires different derivatives, some computational efficiencies can be gained. The following table shows, for each optimization technique, which derivatives are required (FOD: first-order derivatives; SOD: second-order derivatives).

Algorithm	FOD	SOD
TRUREG	x	x
NEWRAP	x	x
NRRIDG	x	x
QUANEW	x	-
DBLDOG	x	-
CONGRA	x	-
NMSIMP	-	-

Each optimization method employs one or more convergence criteria that determine when it has converged. The various termination criteria are listed and described in the “**PROC NLMIXED Statement**” section. An algorithm is considered to have converged when any one of the convergence criteria is satisfied. For example, under the default settings, the QUANEW algorithm will converge if `ABSGCONV` < 1E-5, `FCONV` <  $10^{-\text{FDIGITS}}$ , or `GCONV` < 1E-8.

## Choosing an Optimization Algorithm

The factors that go into choosing a particular optimization technique for a particular problem are complex and can involve trial and error.

For many optimization problems, computing the gradient takes more computer time than computing the function value, and computing the Hessian sometimes takes *much* more computer time and memory than computing the gradient, especially when there are many decision variables. Unfortunately, optimization techniques that do not use some kind of Hessian approximation usually require many more iterations than techniques that do use a Hessian matrix, and as a result the total run time of these techniques is often longer. Techniques that do not use the Hessian also tend to be less reliable. For example, they can more easily terminate at stationary points rather than at global optima.

A few general remarks about the various optimization techniques follow:

- The second-derivative methods TRUREG, NEWRAP, and NRRIDG are best for small problems where the Hessian matrix is not expensive to compute. Sometimes the NRRIDG algorithm can be faster than the TRUREG algorithm, but TRUREG can be more stable. The NRRIDG algorithm requires only one matrix with  $n(n + 1)/2$  double words; TRUREG and NEWRAP require two such matrices.
- The first-derivative methods QUANEW and DBLDOG are best for medium-sized problems where the objective function and the gradient are much faster to evaluate than the Hessian. The QUANEW and DBLDOG algorithms, in general, require more iterations than TRUREG, NRRIDG, and NEWRAP, but each iteration can be much faster. The QUANEW and DBLDOG algorithms require only the gradient to update an approximate Hessian, and they require slightly less memory than TRUREG or NEWRAP (essentially one matrix with  $n(n + 1)/2$  double words). QUANEW is the default optimization method.

- The first-derivative method CONGRA is best for large problems where the objective function and the gradient can be computed much faster than the Hessian and where too much memory is required to store the (approximate) Hessian. The CONGRA algorithm, in general, requires more iterations than QUANEW or DBLDOG, but each iteration can be much faster. Since CONGRA requires only a factor of  $n$  double-word memory, many large applications of PROC NLMIXED can be solved only by CONGRA.
- The no-derivative method NMSIMP is best for small problems where derivatives are not continuous or are very difficult to compute.

## Algorithm Descriptions

Some details about the optimization techniques follow.

### **Trust Region Optimization (TRUREG)**

The trust region method uses the gradient  $\mathbf{g}(\boldsymbol{\theta}^{(k)})$  and the Hessian matrix  $\mathbf{H}(\boldsymbol{\theta}^{(k)})$ ; thus, it requires that the objective function  $f(\boldsymbol{\theta})$  have continuous first- and second-order derivatives inside the feasible region.

The trust region method iteratively optimizes a quadratic approximation to the nonlinear objective function within a hyperelliptic trust region with radius  $\Delta$  that constrains the step size corresponding to the quality of the quadratic approximation. The trust region method is implemented using: Dennis, Gay, and Welsch (1981); Gay (1983); Moré and Sorensen (1983).

The trust region method performs well for small- to medium-sized problems, and it does not need many function, gradient, and Hessian calls. However, if the computation of the Hessian matrix is computationally expensive, one of the (dual) quasi-Newton or conjugate gradient algorithms might be more efficient.

### **Newton-Raphson Optimization with Line Search (NEWRAP)**

The NEWRAP technique uses the gradient  $\mathbf{g}(\boldsymbol{\theta}^{(k)})$  and the Hessian matrix  $\mathbf{H}(\boldsymbol{\theta}^{(k)})$ ; thus, it requires that the objective function have continuous first- and second-order derivatives inside the feasible region. If second-order derivatives are computed efficiently and precisely, the NEWRAP method can perform well for medium-sized to large problems, and it does not need many function, gradient, and Hessian calls.

This algorithm uses a pure Newton step when the Hessian is positive definite and when the Newton step reduces the value of the objective function successfully. Otherwise, a combination of ridging and line search is performed to compute successful steps. If the Hessian is not positive definite, a multiple of the identity matrix is added to the Hessian matrix to make it positive definite (Eskow and Schnabel 1991).

In each iteration, a line search is performed along the search direction to find an approximate optimum of the objective function. The default line-search method uses quadratic interpolation and cubic extrapolation (LINESEARCH=2).

### **Newton-Raphson Ridge Optimization (NRRIDG)**

The NRRIDG technique uses the gradient  $\mathbf{g}(\boldsymbol{\theta}^{(k)})$  and the Hessian matrix  $\mathbf{H}(\boldsymbol{\theta}^{(k)})$ ; thus, it requires that the objective function have continuous first- and second-order derivatives inside the feasible region.

This algorithm uses a pure Newton step when the Hessian is positive definite and when the Newton step reduces the value of the objective function successfully. If at least one of these two conditions is not satisfied, a multiple of the identity matrix is added to the Hessian matrix.

The NRRIDG method performs well for small- to medium-sized problems, and it does not require many function, gradient, and Hessian calls. However, if the computation of the Hessian matrix is computationally expensive, one of the (dual) quasi-Newton or conjugate gradient algorithms might be more efficient.

Since the NRRIDG technique uses an orthogonal decomposition of the approximate Hessian, each iteration of NRRIDG can be slower than that of the NEWRAP technique, which works with Cholesky decomposition. Usually, however, NRRIDG requires fewer iterations than NEWRAP.

### Quasi-Newton Optimization (QUANEW)

The (dual) quasi-Newton method uses the gradient  $g(\theta^{(k)})$ , and it does not need to compute second-order derivatives since they are approximated. It works well for medium to moderately large optimization problems where the objective function and the gradient are much faster to compute than the Hessian; but, in general, it requires more iterations than the TRUREG, NEWRAP, and NRRIDG techniques, which compute second-order derivatives. QUANEW is the default optimization algorithm because it provides an appropriate balance between the speed and stability required for most nonlinear mixed model applications.

The QUANEW technique is one of the following, depending on the value of the `UPDATE=` option.

- the original quasi-Newton algorithm, which updates an approximation of the inverse Hessian
- the dual quasi-Newton algorithm, which updates the Cholesky factor of an approximate Hessian (default)

You can specify four update formulas with the `UPDATE=` option:

- DBFGS performs the dual Broyden, Fletcher, Goldfarb, and Shanno (BFGS) update of the Cholesky factor of the Hessian matrix. This is the default.
- DDFP performs the dual Davidon, Fletcher, and Powell (DFP) update of the Cholesky factor of the Hessian matrix.
- BFGS performs the original BFGS update of the inverse Hessian matrix.
- DFP performs the original DFP update of the inverse Hessian matrix.

In each iteration, a line search is performed along the search direction to find an approximate optimum. The default line-search method uses quadratic interpolation and cubic extrapolation to obtain a step size  $\alpha$  satisfying the Goldstein conditions. One of the Goldstein conditions can be violated if the feasible region defines an upper limit of the step size. Violating the left-side Goldstein condition can affect the positive definiteness of the quasi-Newton update. In that case, either the update is skipped or the iterations are restarted with an identity matrix, resulting in the steepest descent or ascent search direction. You can specify line-search algorithms other than the default with the `LINESEARCH=` option.

The QUANEW algorithm uses its own line-search technique. No options and parameters (except the `INSTEP=` option) controlling the line search in the other algorithms apply here. In several applications, large steps in the first iterations are troublesome. You can use the `INSTEP=` option to impose an upper bound for the step size  $\alpha$  during the first five iterations. You can also use the `INHESIAN= $r$`  option to specify a different starting approximation for the Hessian. If you specify only the `INHESIAN` option, the Cholesky factor of a (possibly ridged) finite difference approximation of the Hessian is used to initialize the quasi-Newton update process. The values of the `LCSINGULAR=`, `LCEPSILON=`, and `LCDEACT=`

options, which control the processing of linear and boundary constraints, are valid only for the quadratic programming subroutine used in each iteration of the QUANEW algorithm.

### **Double-Dogleg Optimization (DBLDOG)**

The double-dogleg optimization method combines the ideas of the quasi-Newton and trust region methods. In each iteration, the double-dogleg algorithm computes the step  $s^{(k)}$  as the linear combination of the steepest descent or ascent search direction  $s_1^{(k)}$  and a quasi-Newton search direction  $s_2^{(k)}$ :

$$s^{(k)} = \alpha_1 s_1^{(k)} + \alpha_2 s_2^{(k)}$$

The step is requested to remain within a prespecified trust region radius; see Fletcher (1987, p. 107). Thus, the DBLDOG subroutine uses the dual quasi-Newton update but does not perform a line search. You can specify two update formulas with the **UPDATE=** option:

- DBFGS performs the dual Broyden, Fletcher, Goldfarb, and Shanno update of the Cholesky factor of the Hessian matrix. This is the default.
- DDFP performs the dual Davidon, Fletcher, and Powell update of the Cholesky factor of the Hessian matrix.

The double-dogleg optimization technique works well for medium to moderately large optimization problems where the objective function and the gradient are much faster to compute than the Hessian. The implementation is based on Dennis and Mei (1979) and Gay (1983), but it is extended for dealing with boundary and linear constraints. The DBLDOG technique generally requires more iterations than the TRUREG, NEWRAP, and NRRIDG techniques, which require second-order derivatives; however, each of the DBLDOG iterations is computationally cheap. Furthermore, the DBLDOG technique requires only gradient calls for the update of the Cholesky factor of an approximate Hessian.

### **Conjugate Gradient Optimization (CONGRA)**

Second-order derivatives are not required by the CONGRA algorithm and are not even approximated. The CONGRA algorithm can be expensive in function and gradient calls, but it requires only  $O(n)$  memory for unconstrained optimization. In general, many iterations are required to obtain a precise solution, but each of the CONGRA iterations is computationally cheap. You can specify four different update formulas for generating the conjugate directions by using the **UPDATE=** option:

- PB performs the automatic restart update method of Powell (1977) and Beale (1972). This is the default.
- FR performs the Fletcher-Reeves update (Fletcher 1987).
- PR performs the Polak-Ribiere update (Fletcher 1987).
- CD performs a conjugate-descent update of Fletcher (1987).

The default, **UPDATE=PB**, behaved best in most test examples. You are advised to avoid the option **UPDATE=CD**, which behaved worst in most test examples.

The CONGRA subroutine should be used for optimization problems with large  $n$ . For the unconstrained or boundary constrained case, CONGRA requires only  $O(n)$  bytes of working memory, whereas all other

optimization methods require order  $O(n^2)$  bytes of working memory. During  $n$  successive iterations, uninterrupted by restarts or changes in the working set, the conjugate gradient algorithm computes a cycle of  $n$  conjugate search directions. In each iteration, a line search is performed along the search direction to find an approximate optimum of the objective function. The default line-search method uses quadratic interpolation and cubic extrapolation to obtain a step size  $\alpha$  satisfying the Goldstein conditions. One of the Goldstein conditions can be violated if the feasible region defines an upper limit for the step size. Other line-search algorithms can be specified with the `LINESEARCH=` option.

### **Nelder-Mead Simplex Optimization (NMSIMP)**

The Nelder-Mead simplex method does not use any derivatives and does not assume that the objective function has continuous derivatives. The objective function itself needs to be continuous. This technique is quite expensive in the number of function calls, and it might be unable to generate precise results for  $n \gg 40$ .

The original Nelder-Mead simplex algorithm is implemented and extended to boundary constraints. This algorithm does not compute the objective for infeasible points, but it changes the shape of the simplex adapting to the nonlinearities of the objective function, which contributes to an increased speed of convergence. It uses a special termination criterion.

---

## **Finite-Difference Approximations of Derivatives**

The `FD=` and `FDHESSIAN=` options specify the use of finite-difference approximations of the derivatives. The `FD=` option specifies that all derivatives are approximated using function evaluations, and the `FDHESSIAN=` option specifies that second-order derivatives are approximated using gradient evaluations.

Computing derivatives by finite-difference approximations can be very time-consuming, especially for second-order derivatives based only on values of the objective function (`FD=` option). If analytical derivatives are difficult to obtain (for example, if a function is computed by an iterative process), you might consider one of the optimization techniques that use first-order derivatives only (`QUANEW`, `DBLDOG`, or `CONGRA`). In the expressions that follow,  $\theta$  denotes the parameter vector,  $h_i$  denotes the step size for the  $i$ th parameter, and  $e_i$  is a vector of zeros with a 1 in the  $i$ th position.

### **Forward-Difference Approximations**

The forward-difference derivative approximations consume less computer time, but they are usually not as precise as approximations that use central-difference formulas.

- For first-order derivatives,  $n$  additional function calls are required:

$$g_i = \frac{\partial f}{\partial \theta_i} \approx \frac{f(\theta + h_i e_i) - f(\theta)}{h_i}$$

- For second-order derivatives based on function calls only (Dennis and Schnabel 1983, p. 80),  $n + n^2/2$  additional function calls are required for dense Hessian:

$$\frac{\partial^2 f}{\partial \theta_i \partial \theta_j} \approx \frac{f(\theta + h_i e_i + h_j e_j) - f(\theta + h_i e_i) - f(\theta + h_j e_j) + f(\theta)}{h_i h_j}$$

- For second-order derivatives based on gradient calls (Dennis and Schnabel 1983, p. 103),  $n$  additional gradient calls are required:

$$\frac{\partial^2 f}{\partial \theta_i \partial \theta_j} \approx \frac{g_i(\boldsymbol{\theta} + h_j \mathbf{e}_j) - g_i(\boldsymbol{\theta})}{2h_j} + \frac{g_j(\boldsymbol{\theta} + h_i \mathbf{e}_i) - g_j(\boldsymbol{\theta})}{2h_i}$$

### Central-Difference Approximations

Central-difference approximations are usually more precise, but they consume more computer time than approximations that use forward-difference derivative formulas.

- For first-order derivatives,  $2n$  additional function calls are required:

$$g_i = \frac{\partial f}{\partial \theta_i} \approx \frac{f(\boldsymbol{\theta} + h_i \mathbf{e}_i) - f(\boldsymbol{\theta} - h_i \mathbf{e}_i)}{2h_i}$$

- For second-order derivatives based on function calls only (Abramowitz and Stegun 1972, p. 884),  $2n + 4n^2/2$  additional function calls are required.

$$\frac{\partial^2 f}{\partial \theta_i^2} \approx \frac{-f(\boldsymbol{\theta} + 2h_i \mathbf{e}_i) + 16f(\boldsymbol{\theta} + h_i \mathbf{e}_i) - 30f(\boldsymbol{\theta}) + 16f(\boldsymbol{\theta} - h_i \mathbf{e}_i) - f(\boldsymbol{\theta} - 2h_i \mathbf{e}_i)}{12h_i^2}$$

$$\frac{\partial^2 f}{\partial \theta_i \partial \theta_j} \approx \frac{f(\boldsymbol{\theta} + h_i \mathbf{e}_i + h_j \mathbf{e}_j) - f(\boldsymbol{\theta} + h_i \mathbf{e}_i - h_j \mathbf{e}_j) - f(\boldsymbol{\theta} - h_i \mathbf{e}_i + h_j \mathbf{e}_j) + f(\boldsymbol{\theta} - h_i \mathbf{e}_i - h_j \mathbf{e}_j)}{4h_i h_j}$$

- For second-order derivatives based on gradient calls,  $2n$  additional gradient calls are required:

$$\frac{\partial^2 f}{\partial \theta_i \partial \theta_j} \approx \frac{g_i(\boldsymbol{\theta} + h_j \mathbf{e}_j) - g_i(\boldsymbol{\theta} - h_j \mathbf{e}_j)}{4h_j} + \frac{g_j(\boldsymbol{\theta} + h_i \mathbf{e}_i) - g_j(\boldsymbol{\theta} - h_i \mathbf{e}_i)}{4h_i}$$

You can use the **FDIGITS=** option to specify the number of accurate digits in the evaluation of the objective function. This specification is helpful in determining an appropriate interval size  $h$  to be used in the finite-difference formulas.

The step sizes  $h_j$ ,  $j = 1, \dots, n$  are defined as follows:

- For the forward-difference approximation of first-order derivatives that use function calls and second-order derivatives that use gradient calls,  $h_j = \sqrt[3]{\eta}(1 + |\theta_j|)$ .
- For the forward-difference approximation of second-order derivatives that use only function calls and all central-difference formulas,  $h_j = \sqrt[3]{\eta}(1 + |\theta_j|)$ .

The value of  $\eta$  is defined by the **FDIGITS=** option:

- If you specify the number of accurate digits by using **FDIGITS= $r$** ,  $\eta$  is set to  $10^{-r}$ .
- If you do not specify the **FDIGITS=** option,  $\eta$  is set to the machine precision  $\epsilon$ .

## Hessian Scaling

The rows and columns of the Hessian matrix can be scaled when you use the trust region, Newton-Raphson, and double-dogleg optimization techniques. Each element  $H_{i,j}$ ,  $i, j = 1, \dots, n$  is divided by the scaling factor  $d_i d_j$ , where the scaling vector  $d = (d_1, \dots, d_n)$  is iteratively updated in a way specified by the **HESCAL=i** option, as follows:

$i = 0$  : No scaling is done (equivalent to  $d_i = 1$ ).

$i \neq 0$  : First iteration and each restart iteration sets:

$$d_i^{(0)} = \sqrt{\max(|H_{i,i}^{(0)}|, \epsilon)}$$

$i = 1$  : See Moré (1978):

$$d_i^{(k+1)} = \max \left[ d_i^{(k)}, \sqrt{\max(|H_{i,i}^{(k)}|, \epsilon)} \right]$$

$i = 2$  : See Dennis, Gay, and Welsch (1981):

$$d_i^{(k+1)} = \max \left[ 0.6d_i^{(k)}, \sqrt{\max(|H_{i,i}^{(k)}|, \epsilon)} \right]$$

$i = 3$  :  $d_i$  is reset in each iteration:

$$d_i^{(k+1)} = \sqrt{\max(|H_{i,i}^{(k)}|, \epsilon)}$$

In the preceding equations,  $\epsilon$  is the relative machine precision or, equivalently, the largest double-precision value that, when added to 1, results in 1.

## Active Set Methods

The parameter vector  $\theta \in \mathcal{R}^n$  can be subject to a set of  $m$  linear equality and inequality constraints:

$$\begin{aligned} \sum_{j=1}^n a_{ij} \theta_j &= b_i & i &= 1, \dots, m_e \\ \sum_{j=1}^n a_{ij} \theta_j &\geq b_i & i &= m_e + 1, \dots, m \end{aligned}$$

The coefficients  $a_{ij}$  and right-hand sides  $b_i$  of the equality and inequality constraints are collected in the  $m \times n$  matrix **A** and the  $m$  vector **b**.

The  $m$  linear constraints define a feasible region  $\mathcal{G}$  in  $\mathcal{R}^n$  that must contain the point  $\theta_*$  that minimizes the problem. If the feasible region  $\mathcal{G}$  is empty, no solution to the optimization problem exists.

In PROC NLMIXED, all optimization techniques use *active set methods*. The iteration starts with a feasible point  $\theta^{(0)}$ , which you can provide or which can be computed by the Schittkowski and Stoer (1979) algorithm



implemented in PROC NLMIXED. The algorithm then moves from one feasible point  $\theta^{(k-1)}$  to a better feasible point  $\theta^{(k)}$  along a feasible search direction  $s^{(k)}$ ,

$$\theta^{(k)} = \theta^{(k-1)} + \alpha^{(k)} s^{(k)}, \quad \alpha^{(k)} > 0$$

Theoretically, the path of points  $\theta^{(k)}$  never leaves the feasible region  $\mathcal{G}$  of the optimization problem, but it can reach its boundaries. The active set  $\mathcal{A}^{(k)}$  of point  $\theta^{(k)}$  is defined as the index set of all linear equality constraints and those inequality constraints that are satisfied at  $\theta^{(k)}$ . If no constraint is active at  $\theta^{(k)}$ , the point is located in the interior of  $\mathcal{G}$ , and the active set  $\mathcal{A}^{(k)} = \emptyset$  is empty. If the point  $\theta^{(k)}$  in iteration  $k$  hits the boundary of inequality constraint  $i$ , this constraint  $i$  becomes active and is added to  $\mathcal{A}^{(k)}$ . Each equality constraint and each active inequality constraint reduce the dimension (degrees of freedom) of the optimization problem.

In practice, the active constraints can be satisfied only with finite precision. The `LCEPSILON= $r$`  option specifies the range for active and violated linear constraints. If the point  $\theta^{(k)}$  satisfies the condition

$$\left| \sum_{j=1}^n a_{ij} \theta_j^{(k)} - b_i \right| \leq t$$

where  $t = r(|b_i| + 1)$ , the constraint  $i$  is recognized as an active constraint. Otherwise, the constraint  $i$  is either an inactive inequality or a violated inequality or equality constraint. Due to rounding errors in computing the projected search direction, error can be accumulated so that an iterate  $\theta^{(k)}$  steps out of the feasible region.

In those cases, PROC NLMIXED might try to pull the iterate  $\theta^{(k)}$  back into the feasible region. However, in some cases the algorithm needs to increase the feasible region by increasing the `LCEPSILON= $r$`  value. If this happens, a message is displayed in the log output.

If the algorithm cannot improve the value of the objective function by moving from an active constraint back into the interior of the feasible region, it makes this inequality constraint an equality constraint in the next iteration. This means that the active set  $\mathcal{A}^{(k+1)}$  still contains the constraint  $i$ . Otherwise, it releases the active inequality constraint and increases the dimension of the optimization problem in the next iteration.

A serious numerical problem can arise when some of the active constraints become (nearly) linearly dependent. PROC NLMIXED removes linearly dependent equality constraints before starting optimization. You can use the `LCSINGULAR= $r$`  option to specify a criterion  $r$  used in the update of the QR decomposition that determines whether an active constraint is linearly dependent relative to a set of other active constraints.

If the solution  $\theta^*$  is subjected to  $n_{act}$  linear equality or active inequality constraints, the QR decomposition of the  $n \times n_{act}$  matrix  $\hat{\mathbf{A}}'$  of the linear constraints is computed by  $\hat{\mathbf{A}}' = \mathbf{Q}\mathbf{R}$ , where  $\mathbf{Q}$  is an  $n \times n$  orthogonal matrix and  $\mathbf{R}$  is an  $n \times n_{act}$  upper triangular matrix. The  $n$  columns of matrix  $\mathbf{Q}$  can be separated into two matrices,  $\mathbf{Q} = [\mathbf{Y}, \mathbf{Z}]$ , where  $\mathbf{Y}$  contains the first  $n_{act}$  orthogonal columns of  $\mathbf{Q}$  and  $\mathbf{Z}$  contains the last  $n - n_{act}$  orthogonal columns of  $\mathbf{Q}$ . The  $n \times (n - n_{act})$  column-orthogonal matrix  $\mathbf{Z}$  is also called the *null-space matrix* of the active linear constraints  $\hat{\mathbf{A}}'$ . The  $n - n_{act}$  columns of the  $n \times (n - n_{act})$  matrix  $\mathbf{Z}$  form a basis orthogonal to the rows of the  $n_{act} \times n$  matrix  $\hat{\mathbf{A}}$ .

At the end of the iterating, PROC NLMIXED computes the *projected gradient*  $\mathbf{g}_Z$ ,

$$\mathbf{g}_Z = \mathbf{Z}'\mathbf{g}$$

In the case of boundary-constrained optimization, the elements of the projected gradient correspond to the gradient elements of the free parameters. A necessary condition for  $\theta^*$  to be a local minimum of the optimization problem is

$$\mathbf{g}_Z(\theta^*) = \mathbf{Z}'\mathbf{g}(\theta^*) = \mathbf{0}$$



The symmetric  $n_{act} \times n_{act}$  matrix  $\mathbf{G}_Z$ ,

$$\mathbf{G}_Z = \mathbf{Z}'\mathbf{G}\mathbf{Z}$$

is called a *projected Hessian matrix*. A second-order necessary condition for  $\boldsymbol{\theta}^*$  to be a local minimizer requires that the projected Hessian matrix is positive semidefinite.

Those elements of the  $n_{act}$  vector of first-order estimates of *Lagrange multipliers*,

$$\lambda = (\hat{\mathbf{A}}\hat{\mathbf{A}}')^{-1}\hat{\mathbf{A}}\mathbf{Z}\mathbf{Z}'\mathbf{g}$$

that correspond to active inequality constraints indicate whether an improvement of the objective function can be obtained by releasing this active constraint. For minimization, a significant negative Lagrange multiplier indicates that a possible reduction of the objective function can be achieved by releasing this active linear constraint. The `LCDEACT=r` option specifies a threshold  $r$  for the Lagrange multiplier that determines whether an active inequality constraint remains active or can be deactivated. (In the case of boundary-constrained optimization, the Lagrange multipliers for active lower (upper) constraints are the negative (positive) gradient elements corresponding to the active parameters.)

---

## Line-Search Methods

In each iteration  $k$ , the (dual) quasi-Newton, conjugate gradient, and Newton-Raphson minimization techniques use iterative line-search algorithms that try to optimize a linear, quadratic, or cubic approximation of  $f$  along a feasible descent search direction  $\mathbf{s}^{(k)}$ ,

$$\boldsymbol{\theta}^{(k+1)} = \boldsymbol{\theta}^{(k)} + \alpha^{(k)}\mathbf{s}^{(k)}, \quad \alpha^{(k)} > 0$$

by computing an approximately optimal scalar  $\alpha^{(k)}$ .

Therefore, a line-search algorithm is an iterative process that optimizes a nonlinear function  $f(\alpha)$  of one parameter ( $\alpha$ ) within each iteration  $k$  of the optimization technique. Since the outside iteration process is based only on the approximation of the objective function, the inside iteration of the line-search algorithm does not have to be perfect. Usually, it is satisfactory that the choice of  $\alpha$  significantly reduces (in a minimization) the objective function. Criteria often used for termination of line-search algorithms are the Goldstein conditions (see Fletcher 1987).

You can select various line-search algorithms by specifying the `LINESEARCH=` option. The line-search method `LINESEARCH=2` seems to be superior when function evaluation consumes significantly less computation time than gradient evaluation. Therefore, `LINESEARCH=2` is the default method for Newton-Raphson, (dual) quasi-Newton, and conjugate gradient optimizations.

You can modify the line-search methods `LINESEARCH=2` and `LINESEARCH=3` to be exact line searches by using the `LSPRECISION=` option and specifying the  $\sigma$  parameter described in Fletcher (1987). The line-search methods `LINESEARCH=1`, `LINESEARCH=2`, and `LINESEARCH=3` satisfy the left-side and right-side Goldstein conditions (see Fletcher 1987). When derivatives are available, the line-search methods `LINESEARCH=6`, `LINESEARCH=7`, and `LINESEARCH=8` try to satisfy the right-side Goldstein condition; if derivatives are not available, these line-search algorithms use only function calls.

## Restricting the Step Length

Almost all line-search algorithms use iterative extrapolation techniques that can easily lead them to (feasible) points where the objective function  $f$  is no longer defined or is difficult to compute. Therefore, PROC NLMIXED provides options restricting the step length  $\alpha$  or trust region radius  $\Delta$ , especially during the first main iterations.

The inner product  $\mathbf{g}'\mathbf{s}$  of the gradient  $\mathbf{g}$  and the search direction  $\mathbf{s}$  is the slope of  $f(\alpha) = f(\boldsymbol{\theta} + \alpha\mathbf{s})$  along the search direction  $\mathbf{s}$ . The default starting value  $\alpha^{(0)} = \alpha^{(k,0)}$  in each line-search algorithm ( $\min_{\alpha>0} f(\boldsymbol{\theta} + \alpha\mathbf{s})$ ) during the main iteration  $k$  is computed in three steps:

1. The first step uses either the difference  $|\Delta f| = |f^{(k)} - f^{(k-1)}|$  of the function values during the last two consecutive iterations or the final step-size value  $\alpha^-$  of the last iteration  $k - 1$  to compute a first value of  $\alpha_1^{(0)}$ .

- If the **DAMPSTEP** option is not used,

$$\alpha_1^{(0)} = \begin{cases} \text{step} & \text{if } 0.1 \leq \text{step} \leq 10 \\ 10 & \text{if } \text{step} > 10 \\ 0.1 & \text{if } \text{step} < 0.1 \end{cases}$$

with

$$\text{step} = \begin{cases} |\Delta f|/|\mathbf{g}'\mathbf{s}| & \text{if } |\mathbf{g}'\mathbf{s}| \geq \epsilon \max(100 \times |\Delta f|, 1) \\ 1 & \text{otherwise} \end{cases}$$

This value of  $\alpha_1^{(0)}$  can be too large and can lead to a difficult or impossible function evaluation, especially for highly nonlinear functions such as the EXP function.

- If the **DAMPSTEP=r** option is used,

$$\alpha_1^{(0)} = \min(1, r\alpha^-)$$

The initial value for the new step length can be no larger than  $r$  times the final step length  $\alpha^-$  of the former iteration. The default value is  $r = 2$ .

2. During the first five iterations, the second step enables you to reduce  $\alpha_1^{(0)}$  to a smaller starting value  $\alpha_2^{(0)}$  by using the **INSTEP=r** option:

$$\alpha_2^{(0)} = \min(\alpha_1^{(0)}, r)$$

After more than five iterations,  $\alpha_2^{(0)}$  is set to  $\alpha_1^{(0)}$ .

3. The third step can further reduce the step length by

$$\alpha_3^{(0)} = \min(\alpha_2^{(0)}, \min(10, u))$$

where  $u$  is the maximum length of a step inside the feasible region.

The `INSTEP=r` option enables you to specify a smaller or larger radius  $\Delta$  of the trust region used in the first iteration of the trust region and double-dogleg algorithms. The default initial trust region radius  $\Delta^{(0)}$  is the length of the scaled gradient (Moré 1978). This step corresponds to the default radius factor of  $r = 1$ . In most practical applications of the TRUREG and DBLDOG algorithms, this choice is successful. However, for bad initial values and highly nonlinear objective functions (such as the EXP function), the default start radius can result in arithmetic overflows. If this happens, you can try decreasing values of `INSTEP=r`,  $0 < r < 1$ , until the iteration starts successfully. A small factor  $r$  also affects the trust region radius  $\Delta^{(k+1)}$  of the next steps because the radius is changed in each iteration by a factor  $0 < c \leq 4$ , depending on the ratio  $\rho$  expressing the goodness of quadratic function approximation. Reducing the radius  $\Delta$  corresponds to increasing the ridge parameter  $\lambda$ , producing smaller steps aimed more closely toward the (negative) gradient direction.

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## Computational Problems

### Floating-Point Errors and Overflows

Numerical optimization of a numerically integrated function is a difficult task, and the computation of the objective function and its derivatives can lead to arithmetic exceptions and overflows. A typical cause of these problems is parameters with widely varying scales. If the scaling of your parameters varies by more than a few orders of magnitude, the numerical stability of the optimization problem can be seriously reduced and can result in computational difficulties. A simple remedy is to rescale each parameter so that its final estimated value has a magnitude near 1.

If parameter rescaling does not help, consider the following actions:

- Specify the `ITDETAILS` option in the `PROC NLMIXED` statement to obtain more detailed information about when and where the problem is occurring.
- Provide different initial values or try a grid search of values.
- Use boundary constraints to avoid the region where overflows can happen.
- Delete outlying observations or subjects from the input data, if this is reasonable.
- Change the algorithm (specified in programming statements) that computes the objective function.

The line-search algorithms that work with cubic extrapolation are especially sensitive to arithmetic overflows. If an overflow occurs during a line search, you can use the `INSTEP=` option to reduce the length of the first trial step during the first five iterations, or you can use the `DAMPSTEP` or `MAXSTEP` option to restrict the step length of the initial  $\alpha$  in subsequent iterations. If an arithmetic overflow occurs in the first iteration of the trust region or double-dogleg algorithm, you can use the `INSTEP=` option to reduce the default trust region radius of the first iteration. You can also change the optimization technique or the line-search method.

### Long Run Times

`PROC NLMIXED` can take a long time to run for problems involving complex models, many parameters, or large input data sets. Although the optimization techniques used by `PROC NLMIXED` are some of the best ones available, they are not guaranteed to converge quickly for all problems. Ill-posed or misspecified

models can cause the algorithms to use more extensive calculations designed to achieve convergence, and this can result in longer run times. So first make sure that your model is specified correctly, that your parameters are scaled to be of the same order of magnitude, and that your data reasonably match the model you are contemplating.

If you are using the default adaptive Gaussian quadrature algorithm and no iteration history is printing at all, then PROC NLMIXED might be bogged down trying to determine the number of quadrature points at the first set of starting values. Specifying the `QPOINTS=` option will bypass this stage and proceed directly to iterations; however, be aware that the likelihood approximation might not be accurate if there are too few quadrature points.

PROC NLMIXED can also have difficulty determining the number of quadrature points if the initial starting values are far from the optimum values. To obtain more accurate starting values for the model parameters, one easy method is to fit a model with no `RANDOM` statement. You can then use these estimates as starting values, although you will still need to specify values for the random-effects distribution. For normal-normal models, another strategy is to use `METHOD=FIRO`. If you can obtain estimates by using this approximate method, then they can be used as starting values for more accurate likelihood approximations.

If you are running PROC NLMIXED multiple times, you will probably want to include a statement like the following in your program:

```
ods output ParameterEstimates=pe;
```

This statement creates a SAS data set named PE upon completion of the run. In your next invocation of PROC NLMIXED, you can then specify

```
parms / data=pe;
```

to read in the previous estimates as starting values.

To speed general computations, you should double-check your programming statements to minimize the number of floating-point operations. Using auxiliary variables and factoring amenable expressions can be useful changes in this regard.

## Problems Evaluating Code for Objective Function

The starting point  $\theta^{(0)}$  must be a point for which the programming statements can be evaluated. However, during optimization, the optimizer might iterate to a point  $\theta^{(k)}$  where the objective function or its derivatives cannot be evaluated. In some cases, the specification of boundary for parameters can avoid such situations. In many other cases, you can indicate that the point  $\theta^{(0)}$  is a bad point simply by returning an extremely large value for the objective function. In these cases, the optimization algorithm reduces the step length and stays closer to the point that has been evaluated successfully in the former iteration.

## No Convergence

There are a number of things to try if the optimizer fails to converge.

- Change the initial values by using a grid search specification to obtain a set of good feasible starting values.
- Change or modify the update technique or the line-search algorithm.

This method applies only to **TECH=QUANEW** and **TECH=CONGRA**. For example, if you use the default update formula and the default line-search algorithm, you can do the following:

- change the update formula with the **UPDATE=** option
  - change the line-search algorithm with the **LINESEARCH=** option
  - specify a more precise line search with the **LSPRECISION=** option, if you use **LINESEARCH=2** or **LINESEARCH=3**
- Change the optimization technique.  
For example, if you use the default option, **TECH=QUANEW**, you can try one of the second-derivative methods if your problem is small or the conjugate gradient method if it is large.
  - Adjust finite-difference derivatives.  
The forward-difference derivatives specified with the **FD=** or **FDHESSIAN=** option might not be precise enough to satisfy strong gradient termination criteria. You might need to specify the more expensive central-difference formulas. The finite-difference intervals might be too small or too big, and the finite-difference derivatives might be erroneous.
  - Double-check the data entry and program specification.

## Convergence to Stationary Point

The gradient at a stationary point is the null vector, which always leads to a zero search direction. This point satisfies the first-order termination criterion. Search directions that are based on the gradient are zero, so the algorithm terminates. There are two ways to avoid this situation:

- Use the **PARMS** statement to specify a grid of feasible initial points.
- Use the **OPTCHECK=r** option to avoid terminating at the stationary point.

The signs of the eigenvalues of the (reduced) Hessian matrix contain the following information regarding a stationary point:

- If all of the eigenvalues are positive, the Hessian matrix is positive definite, and the point is a minimum point.
- If some of the eigenvalues are positive and all remaining eigenvalues are zero, the Hessian matrix is positive semidefinite, and the point is a minimum or saddle point.
- If all of the eigenvalues are negative, the Hessian matrix is negative definite, and the point is a maximum point.
- If some of the eigenvalues are negative and all remaining eigenvalues are zero, the Hessian matrix is negative semidefinite, and the point is a maximum or saddle point.
- If all of the eigenvalues are zero, the point can be a minimum, maximum, or saddle point.

## Precision of Solution

In some applications, PROC NLMIXED can result in parameter values that are not precise enough. Usually, this means that the procedure terminated at a point too far from the optimal point. The termination criteria define the size of the termination region around the optimal point. Any point inside this region can be accepted for terminating the optimization process. The default values of the termination criteria are set to satisfy a reasonable compromise between the computational effort (computer time) and the precision of the computed estimates for the most common applications. However, there are a number of circumstances in which the default values of the termination criteria specify a region that is either too large or too small.

If the termination region is too large, then it can contain points with low precision. In such cases, you should determine which termination criterion stopped the optimization process. In many applications, you can obtain a solution with higher precision simply by using the old parameter estimates as starting values in a subsequent run in which you specify a smaller value for the termination criterion that was satisfied at the former run.

If the termination region is too small, the optimization process might take longer to find a point inside such a region, or it might not even find such a point due to rounding errors in function values and derivatives. This can easily happen in applications in which finite-difference approximations of derivatives are used and the **GCONV** and **ABSGCONV** termination criteria are too small to respect rounding errors in the gradient values.

---

## Covariance Matrix

The estimated covariance matrix of the parameter estimates is computed as the inverse Hessian matrix, and for unconstrained problems it should be positive definite. If the final parameter estimates are subjected to  $n_{act} > 0$  active linear inequality constraints, the formulas of the covariance matrices are modified similar to Gallant (1987) and Cramer (1986, p. 38) and additionally generalized for applications with singular matrices.

There are several steps available that enable you to tune the rank calculations of the covariance matrix.

1. You can use the **ASINGULAR=**, **MSINGULAR=**, and **VSINGULAR=** options to set three singularity criteria for the inversion of the Hessian matrix **H**. The singularity criterion used for the inversion is

$$|d_{j,j}| \leq \max(\text{ASING}, \text{VSING} * |H_{j,j}|, \text{MSING} * \max(|H_{1,1}|, \dots, |H_{n,n}|))$$

where  $d_{j,j}$  is the diagonal pivot of the matrix **H**, and **ASING**, **VSING**, and **MSING** are the specified values of the **ASINGULAR=**, **VSINGULAR=**, and **MSINGULAR=** options, respectively. The default values are as follows:

- **ASING**: the square root of the smallest positive double-precision value
- **MSING**: 1E-12 if you do not specify the **SINGHESS=** option and  $\max(10\epsilon, 1\text{E} - 4 \times \text{SINGHESS})$  otherwise, where  $\epsilon$  is the machine precision
- **VSING**: 1E-8 if you do not specify the **SINGHESS=** option and the value of **SINGHESS** otherwise

Note that, in many cases, a normalized matrix  $\mathbf{D}^{-1}\mathbf{AD}^{-1}$  is decomposed, and the singularity criteria are modified correspondingly.

2. If the matrix  $\mathbf{H}$  is found to be singular in the first step, a generalized inverse is computed. Depending on the `G4=` option, either a generalized inverse satisfying all four Moore-Penrose conditions is computed (a  $g_4$ -inverse) or a generalized inverse satisfying only two Moore-Penrose conditions is computed (a  $g_2$ -inverse, Pringle and Rayner 1971). If the number of parameters  $n$  of the application is less than or equal to `G4=i`, a  $g_4$ -inverse is computed; otherwise, only a  $g_2$ -inverse is computed. The  $g_4$ -inverse is computed by the (computationally very expensive but numerically stable) eigenvalue decomposition, and the  $g_2$ -inverse is computed by Gauss transformation. The  $g_4$ -inverse is computed using the eigenvalue decomposition  $\mathbf{A} = \mathbf{Z}\mathbf{\Lambda}\mathbf{Z}'$ , where  $\mathbf{Z}$  is the orthogonal matrix of eigenvectors and  $\mathbf{\Lambda}$  is the diagonal matrix of eigenvalues,  $\mathbf{\Lambda} = \text{diag}(\lambda_1, \dots, \lambda_n)$ . The  $g_4$ -inverse of  $\mathbf{H}$  is set to

$$\mathbf{A}^- = \mathbf{Z}\mathbf{\Lambda}^-\mathbf{Z}'$$

where the diagonal matrix  $\mathbf{\Lambda}^- = \text{diag}(\lambda_1^-, \dots, \lambda_n^-)$  is defined using the `COVSING=` option:

$$\lambda_i^- = \begin{cases} 1/\lambda_i & \text{if } |\lambda_i| > \text{COVSING} \\ 0 & \text{if } |\lambda_i| \leq \text{COVSING} \end{cases}$$

If you do not specify the `COVSING=` option, the  $nr$  smallest eigenvalues are set to zero, where  $nr$  is the number of rank deficiencies found in the first step.

For optimization techniques that do not use second-order derivatives, the covariance matrix is computed using finite-difference approximations of the derivatives.

## Prediction

The nonlinear mixed model is a useful tool for statistical prediction. Assuming a prediction is to be made regarding the  $i$ th subject, suppose that  $f(\boldsymbol{\theta}, \mathbf{u}_i)$  is a differentiable function predicting some quantity of interest. Recall that  $\boldsymbol{\theta}$  denotes the vector of unknown parameters and  $\mathbf{u}_i$  denotes the vector of random effects for the  $i$ th subject. A natural point prediction is  $f(\hat{\boldsymbol{\theta}}, \hat{\mathbf{u}}_i)$ , where  $\hat{\boldsymbol{\theta}}$  is the maximum likelihood estimate of  $\boldsymbol{\theta}$  and  $\hat{\mathbf{u}}_i$  is the empirical Bayes estimate of  $\mathbf{u}_i$  described previously in the section “Integral Approximations” on page 5384.

An approximate prediction variance matrix for  $(\hat{\boldsymbol{\theta}}, \hat{\mathbf{u}}_i)$  is

$$\mathbf{P} = \begin{bmatrix} \hat{\mathbf{H}}^{-1} & \hat{\mathbf{H}}^{-1} \left( \frac{\partial \hat{\mathbf{u}}_i}{\partial \boldsymbol{\theta}} \right)' \\ \left( \frac{\partial \hat{\mathbf{u}}_i}{\partial \boldsymbol{\theta}} \right) \hat{\mathbf{H}}^{-1} & \hat{\mathbf{\Gamma}}^{-1} + \left( \frac{\partial \hat{\mathbf{u}}_i}{\partial \boldsymbol{\theta}} \right) \hat{\mathbf{H}}^{-1} \left( \frac{\partial \hat{\mathbf{u}}_i}{\partial \boldsymbol{\theta}} \right)' \end{bmatrix}$$

where  $\hat{\mathbf{H}}$  is the approximate Hessian matrix from the optimization for  $\hat{\boldsymbol{\theta}}$ ,  $\hat{\mathbf{\Gamma}}$  is the approximate Hessian matrix from the optimization for  $\hat{\mathbf{u}}_i$ , and  $(\partial \hat{\mathbf{u}}_i / \partial \boldsymbol{\theta})$  is the derivative of  $\hat{\mathbf{u}}_i$  with respect to  $\boldsymbol{\theta}$ , evaluated at  $(\hat{\boldsymbol{\theta}}, \hat{\mathbf{u}}_i)$ . The approximate variance matrix for  $\hat{\boldsymbol{\theta}}$  is the standard one discussed in the previous section, and that for  $\hat{\mathbf{u}}_i$  is an approximation to the conditional mean squared error of prediction described by Booth and Hobert (1998).

The prediction variance for a general scalar function  $f(\boldsymbol{\theta}, \mathbf{u}_i)$  is defined as the expected squared difference  $E[f(\hat{\boldsymbol{\theta}}, \hat{\mathbf{u}}_i) - f(\boldsymbol{\theta}, \mathbf{u}_i)]^2$ . PROC NLMIXED computes an approximation to it as follows. The derivative of  $f(\boldsymbol{\theta}, \mathbf{u}_i)$  is computed with respect to each element of  $(\boldsymbol{\theta}, \mathbf{u}_i)$  and evaluated at  $(\hat{\boldsymbol{\theta}}, \hat{\mathbf{u}}_i)$ . If  $\mathbf{a}_i$  is the resulting vector, then the approximate prediction variance is  $\mathbf{a}_i' \mathbf{P} \mathbf{a}_i$ . This approximation is known as the delta method (Billingsley 1986; Cox 1998).

## Computational Resources

Since nonlinear optimization is an iterative process that depends on many factors, it is difficult to estimate how much computer time is necessary to find an optimal solution satisfying one of the termination criteria. You can use the **MAXTIME=**, **MAXITER=**, and **MAXFUNC=** options to restrict the amount of CPU time, the number of iterations, and the number of function calls in a single run of PROC NLMIXED.

In each iteration  $k$ , the NRRIDG technique uses a symmetric Householder transformation to decompose the  $n \times n$  Hessian matrix  $\mathbf{H}$ ,

$$\mathbf{H} = \mathbf{V}'\mathbf{T}\mathbf{V}, \quad \mathbf{V}: \text{orthogonal}, \quad \mathbf{T}: \text{tridiagonal}$$

to compute the (Newton) search direction  $\mathbf{s}$ ,

$$\mathbf{s}^{(k)} = -[\mathbf{H}^{(k)}]^{-1}\mathbf{g}^{(k)} \quad k = 1, 2, 3, \dots$$

The TRUREG and NEWRAP techniques use the Cholesky decomposition to solve the same linear system while computing the search direction. The QUANEW, DBLDOG, CONGRA, and NMSIMP techniques do not need to invert or decompose a Hessian matrix; thus, they require less computational resources than the other techniques.

The larger the problem, the more time is needed to compute function values and derivatives. Therefore, you might want to compare optimization techniques by counting and comparing the respective numbers of function, gradient, and Hessian evaluations.

Finite-difference approximations of the derivatives are expensive because they require additional function or gradient calls:

- forward-difference formulas
  - For first-order derivatives,  $n$  additional function calls are required.
  - For second-order derivatives based on function calls only, for a dense Hessian,  $n + n^2/2$  additional function calls are required.
  - For second-order derivatives based on gradient calls,  $n$  additional gradient calls are required.
- central-difference formulas
  - For first-order derivatives,  $2n$  additional function calls are required.
  - For second-order derivatives based on function calls only, for a dense Hessian,  $2n + 2n^2$  additional function calls are required.
  - For second-order derivatives based on gradient calls,  $2n$  additional gradient calls are required.

Many applications need considerably more time for computing second-order derivatives (Hessian matrix) than for computing first-order derivatives (gradient). In such cases, a dual quasi-Newton technique is recommended, which does not require second-order derivatives.



---

## Displayed Output

This section describes the displayed output from PROC NLMIXED. See the section “ODS Table Names” on page 5407 for details about how this output interfaces with the Output Delivery System.

### **Specifications**

The NLMIXED procedure first displays the “Specifications” table, listing basic information about the non-linear mixed model that you have specified. It includes the principal variables and estimation methods.

### **Dimensions**

The “Dimensions” table lists counts of important quantities in your nonlinear mixed model, including the number of observations, subjects, parameters, and quadrature points.

### **Parameters**

The “Parameters” table displays the information you provided with the **PARMS** statement and the value of the negative log-likelihood function evaluated at the starting values.

### **Starting Gradient and Hessian**

The **START** option in the **PROC NLMIXED** statement displays the gradient of the negative log-likelihood function at the starting values of the parameters. If you also specify the **HESS** option, then the starting Hessian is displayed as well.

### **Iterations**

The iteration history consists of one line of output for each iteration in the optimization process. The iteration history is displayed by default because it is important that you check for possible convergence problems. The default iteration history includes the following variables:

- Iter, the iteration number
- Calls, the number of function calls
- NegLogLike, the value of the objective function
- Diff, the difference between adjacent function values
- MaxGrad, the maximum of the absolute (projected) gradient components (except NMSIMP)
- Slope, the slope  $g'$ s of the search direction  $s$  at the current parameter iterate  $\theta^{(k)}$  (QUANEW only)
- Rho, the ratio between the achieved and predicted values of Diff (NRRIDG only)
- Radius, the radius of the trust region (TRUREG only)
- StdDev, the standard deviation of the simplex values (NMSIMP only)
- Delta, the vertex length of the simplex (NMSIMP only)
- Size, the size of the simplex (NMSIMP only)

For the QUANEW method, the value of Slope should be significantly negative. Otherwise, the line-search algorithm has difficulty reducing the function value sufficiently. If this difficulty is encountered, an asterisk (\*) appears after the iteration number. If there is a tilde ~ after the iteration number, the BFGS update is skipped, and very high values of the Lagrange function are produced. A backslash (\ ) after the iteration number indicates that Powell's correction for the BFGS update is used.

For methods using second derivatives, an asterisk (\*) after the iteration number means that the computed Hessian approximation was singular and had to be ridged with a positive value.

For the NMSIMP method, only one line is displayed for several internal iterations. This technique skips the output for some iterations because some of the termination tests (StdDev and Size) are rather time-consuming compared to the simplex operations, and they are performed only every five simplex operations.

The **ITDETAILS** option in the **PROC NLMIXED** statement provides a more detailed iteration history. Besides listing the current values of the parameters and their gradients, the **ITDETAILS** option provides the following values in addition to the default output:

- Restart, the number of iteration restarts
- Active, the number of active constraints
- Lambda, the value of the Lagrange multiplier (TRUREG and DBLDOG only)
- Ridge, the ridge value (NRRIDG only)
- Alpha, the line-search step size (QUANEW only)

An apostrophe (') trailing the number of active constraints indicates that at least one of the active constraints was released from the active set due to a significant Lagrange multiplier.

### Convergence Status

The "Convergence Status" table contains a status message describing the reason for termination of the optimization. The ODS name of this table is **ConvergenceStatus**, and you can query the nonprinting numeric variable **Status** to check for a successful optimization. This is useful in batch processing, or when processing BY groups, for example, in simulations. Successful convergence is indicated by **Status=0**.

### Fitting Information

The "Fitting Information" table lists the final minimized value of  $-2$  times the log likelihood as well as the information criteria of Akaike (AIC) and Schwarz (BIC), as well as a finite-sample corrected version of AIC (AICC). The criteria are computed as follows:

$$\text{AIC} = 2f(\hat{\theta}) + 2p$$

$$\text{AICC} = 2f(\hat{\theta}) + 2pn/(n - p - 1)$$

$$\text{BIC} = 2f(\hat{\theta}) + p \log(s)$$

where  $f()$  is the negative of the marginal log-likelihood function,  $\hat{\theta}$  is the vector of parameter estimates,  $p$  is the number of parameters,  $n$  is the number of observations, and  $s$  is the number of subjects. See Hurvich and Tsai (1989) and Burnham and Anderson (1998) for additional details.

### Parameter Estimates

The “Parameter Estimates” table lists the estimates of the parameter values after successful convergence of the optimization problem or the final values of the parameters under nonconvergence. If the problem did converge, standard errors are computed from the final Hessian matrix. The ratio of the estimate with its standard error produces a  $t$  value, with approximate degrees of freedom computed as the number of subjects minus the number of random effects. A  $p$ -value and confidence limits based on this  $t$  distribution are also provided. Finally, the gradient of the negative log-likelihood function is displayed for each parameter, and you should verify that they each are sufficiently small for unconstrained parameters.

### Covariance and Correlation Matrices

Following standard maximum likelihood theory (for example, Serfling 1980), the asymptotic variance-covariance matrix of the parameter estimates equals the inverse of the Hessian matrix. You can display this matrix with the **COV** option in the **PROC NLMIXED** statement. The corresponding correlation form is available with the **CORR** option.

### Additional Estimates

The “Additional Estimates” table displays the results of all **ESTIMATE** statements that you specify, with the same columns as the “Parameter Estimates” table. The **ECOV** and **ECORR** options in the **PROC NLMIXED** statement produce tables displaying the approximate covariance and correlation matrices of the additional estimates. They are computed using the delta method (Billingsley 1986; Cox 1998). The **EDER** option in the **PROC NLMIXED** statement produces a table that displays the derivatives of the additional estimates with respect to the model parameters evaluated at their final estimated values.

## ODS Table Names

**PROC NLMIXED** 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 in Table 64.2. For more information about ODS, see Chapter 20, “Using the Output Delivery System.”

**Table 64.2** ODS Tables Produced by **PROC NLMIXED**

ODS Table Name	Description	Statement or Option
AdditionalEstimates	Results from <b>ESTIMATE</b> statements	<b>ESTIMATE</b>
Contrasts	Results from <b>CONTRAST</b> statements	<b>CONTRAST</b>
ConvergenceStatus	Convergence status	default
CorrMatAddEst	Correlation matrix of additional estimates	<b>ECORR</b>
CorrMatParmEst	Correlation matrix of parameter estimates	<b>CORR</b>
CovMatAddEst	Covariance matrix of additional estimates	<b>ECOV</b>
CovMatParmEst	Covariance matrix of parameter estimates	<b>COV</b>
DerAddEst	Derivatives of additional estimates	<b>EDER</b>
Dimensions	Dimensions of the problem	default
FitStatistics	Fit statistics	default
Hessian	Second derivative matrix	<b>HESS</b>
IterHistory	Iteration history	default
Parameters	Parameters	default
ParameterEstimates	Parameter estimates	default

Table 64.2 continued

ODS Table Name	Description	Statement or Option
Specifications	Model specifications	default
StartingHessian	Starting Hessian matrix	START HESS
StartingValues	Starting values and gradient	START

## Examples: NLMIXED Procedure

### Example 64.1: One-Compartment Model with Pharmacokinetic Data

A popular application of nonlinear mixed models is in the field of pharmacokinetics, which studies how a drug disperses through a living individual. This example considers the theophylline data from Pinheiro and Bates (1995). Serum concentrations of the drug theophylline are measured in 12 subjects over a 25-hour period after oral administration. The data are as follows.

```
data theoph;
  input subject time conc dose wt;
  datalines;
1  0.00  0.74  4.02  79.6
1  0.25  2.84  4.02  79.6
1  0.57  6.57  4.02  79.6
1  1.12 10.50  4.02  79.6
1  2.02  9.66  4.02  79.6
1  3.82  8.58  4.02  79.6
1  5.10  8.36  4.02  79.6
1  7.03  7.47  4.02  79.6

... more lines ...

12 24.15  1.17  5.30  60.5
;
```

Pinheiro and Bates (1995) consider the following first-order compartment model for these data:

$$C_{it} = \frac{Dk_{e_i}k_{a_i}}{Cl_i(k_{a_i} - k_{e_i})}[\exp(-k_{e_i}t) - \exp(-k_{a_i}t)] + e_{it}$$

where  $C_{it}$  is the observed concentration of the  $i$ th subject at time  $t$ ,  $D$  is the dose of theophylline,  $k_{e_i}$  is the elimination rate constant for subject  $i$ ,  $k_{a_i}$  is the absorption rate constant for subject  $i$ ,  $Cl_i$  is the clearance for subject  $i$ , and  $e_{it}$  are normal errors. To allow for random variability between subjects, they assume

$$Cl_i = \exp(\beta_1 + b_{i1})$$

$$k_{a_i} = \exp(\beta_2 + b_{i2})$$

$$k_{e_i} = \exp(\beta_3)$$

where the  $\beta$ s denote fixed-effects parameters and the  $b_i$ s denote random-effects parameters with an unknown covariance matrix.

The PROC NLMIXED statements to fit this model are as follows:

```
proc nlmixed data=theoph;
  parms beta1=-3.22 beta2=0.47 beta3=-2.45
        s2b1=0.03  cb12=0    s2b2=0.4 s2=0.5;
  cl  = exp(beta1 + b1);
  ka  = exp(beta2 + b2);
  ke  = exp(beta3);
  pred = dose*ke*ka*(exp(-ke*time)-exp(-ka*time))/cl/(ka-ke);
  model conc ~ normal(pred,s2);
  random b1 b2 ~ normal([0,0],[s2b1,cb12,s2b2]) subject=subject;
run;
```

The **PARMS** statement specifies starting values for the three  $\beta$ s and four variance-covariance parameters. The clearance and rate constants are defined using SAS programming statements, and the conditional model for the data is defined to be normal with mean *pred* and variance *s2*. The two random effects are *b1* and *b2*, and their joint distribution is defined in the **RANDOM** statement. Brackets are used in defining their mean vector (two zeros) and the lower triangle of their variance-covariance matrix (a general  $2 \times 2$  matrix). The **SUBJECT=** variable is *subject*.

The results from this analysis are as follows.

#### Output 64.1.1 Model Specification for One-Compartment Model

The NLMIXED Procedure	
Specifications	
Data Set	WORK.THEOPH
Dependent Variable	conc
Distribution for Dependent Variable	Normal
Random Effects	b1 b2
Distribution for Random Effects	Normal
Subject Variable	subject
Optimization Technique	Dual Quasi-Newton
Integration Method	Adaptive Gaussian Quadrature

The “Specifications” table lists the setup of the model (Output 64.1.1). The “Dimensions” table indicates that there are 132 observations, 12 subjects, and 7 parameters. PROC NLMIXED selects 5 quadrature points for each random effect, producing a total grid of 25 points over which quadrature is performed (Output 64.1.2).

**Output 64.1.2** Dimensions Table for One-Compartment Model

Dimensions	
Observations Used	132
Observations Not Used	0
Total Observations	132
Subjects	12
Max Obs Per Subject	11
Parameters	7
Quadrature Points	5

The “Parameters” table lists the 7 parameters, their starting values, and the initial evaluation of the negative log likelihood using adaptive Gaussian quadrature (Output 64.1.3). The “Iteration History” table indicates that 10 steps are required for the dual quasi-Newton algorithm to achieve convergence.

**Output 64.1.3** Starting Values and Iteration History

Parameters						
beta1	beta2	beta3	s2b1	cb12	s2b2	s2 NegLogLike
-3.22	0.47	-2.45	0.03	0	0.4	0.5 177.789945

Iteration History					
Iter	Calls	NegLogLike	Diff	MaxGrad	Slope
1	5	177.776248	0.013697	2.873367	-63.0744
2	8	177.7643	0.011948	1.698144	-4.75239
3	10	177.757264	0.007036	1.297439	-1.97311
4	12	177.755688	0.001576	1.441408	-0.49772
5	14	177.7467	0.008988	1.132279	-0.8223
6	17	177.746401	0.000299	0.831293	-0.00244
7	19	177.746318	0.000083	0.724198	-0.00789
8	21	177.74574	0.000578	0.180018	-0.00583
9	23	177.745736	3.88E-6	0.017958	-8.25E-6
10	25	177.745736	3.222E-8	0.000143	-6.51E-8

NOTE: GCONV convergence criterion satisfied.

**Output 64.1.4** Fit Statistics for One-Compartment Model

Fit Statistics	
-2 Log Likelihood	355.5
AIC (smaller is better)	369.5
AICC (smaller is better)	370.4
BIC (smaller is better)	372.9

The “Fit Statistics” table lists the final optimized values of the log-likelihood function and information criteria in the “smaller is better” form ([Output 64.1.4](#)).

**Output 64.1.5** Parameter Estimates for One-Compartment Model

Parameter Estimates							
Parameter	Estimate	Standard Error	DF	t Value	Pr >  t	Alpha	Lower
beta1	-3.2268	0.05950	10	-54.23	<.0001	0.05	-3.3594
beta2	0.4806	0.1989	10	2.42	0.0363	0.05	0.03745
beta3	-2.4592	0.05126	10	-47.97	<.0001	0.05	-2.5734
s2b1	0.02803	0.01221	10	2.30	0.0445	0.05	0.000833
cb12	-0.00127	0.03404	10	-0.04	0.9710	0.05	-0.07712
s2b2	0.4331	0.2005	10	2.16	0.0560	0.05	-0.01353
s2	0.5016	0.06837	10	7.34	<.0001	0.05	0.3493

Parameter Estimates		
Parameter	Upper	Gradient
beta1	-3.0942	-0.00009
beta2	0.9238	3.645E-7
beta3	-2.3449	0.000039
s2b1	0.05523	-0.00014
cb12	0.07458	-0.00007
s2b2	0.8798	-6.98E-6
s2	0.6540	6.133E-6

The “Parameter Estimates” table contains the maximum likelihood estimates of the parameters ([Output 64.1.5](#)). Both s2b1 and s2b2 are marginally significant, indicating between-subject variability in the clearances and absorption rate constants, respectively. There does not appear to be a significant covariance between them, as seen by the estimate of cb12.

The estimates of  $\beta_1$ ,  $\beta_2$ , and  $\beta_3$  are close to the adaptive quadrature estimates listed in Table 3 of Pinheiro and Bates (1995). However, Pinheiro and Bates use a Cholesky-root parameterization for the random-effects variance matrix and a logarithmic parameterization for the residual variance. The PROC NL MIXED statements using their parameterization are as follows, and results are similar.

```

proc nlmixed data=theoph;
  parms l11=-1.5 l2=0 l13=-0.1 beta1=-3 beta2=0.5 beta3=-2.5 ls2=-0.7;
  s2    = exp(ls2);
  l1    = exp(l11);
  l3    = exp(l13);
  s2b1  = l1*l1*s2;
  cb12  = l2*l1*s2;
  s2b2  = (l2*l2 + l3*l3)*s2;
  c1    = exp(beta1 + b1);
  ka    = exp(beta2 + b2);
  ke    = exp(beta3);
  pred  = dose*ke*ka*(exp(-ke*time)-exp(-ka*time))/c1/(ka-ke);
  model conc ~ normal(pred,s2);
  random b1 b2 ~ normal([0,0],[s2b1,cb12,s2b2]) subject=subject;
run;

```

## Example 64.2: Probit-Normal Model with Binomial Data

For this example, consider the data from Weil (1970), also studied by: Williams (1975); Ochi and Prentice (1984); McCulloch (1994). In this experiment 16 pregnant rats receive a control diet and 16 receive a chemically treated diet, and the litter size for each rat is recorded after 4 and 21 days. The SAS data set follows:

```

data rats;
  input trt $ m x @@;
  if (trt='c') then do;
    x1 = 1;
    x2 = 0;
  end;
  else do;
    x1 = 0;
    x2 = 1;
  end;
  litter = _n_;
  datalines;
c 13 13   c 12 12   c 9 9   c 9 9   c 8 8   c 8 8   c 13 12   c 12 11
c 10 9    c 10 9    c 9 8    c 13 11   c 5 4    c 7 5    c 10 7    c 10 7
t 12 12   t 11 11   t 10 10   t 9 9    t 11 10   t 10 9    t 10 9    t 9 8
t 9 8     t 5 4     t 9 7    t 7 4    t 10 5    t 6 3    t 10 3    t 7 0
;

```

Here, *m* represents the size of the litter after 4 days, and *x* represents the size of the litter after 21 days. Also, indicator variables *x*<sub>1</sub> and *x*<sub>2</sub> are constructed for the two treatment levels.

Following McCulloch (1994), assume a latent survival model of the form

$$y_{ijk} = t_i + \alpha_{ij} + e_{ijk}$$

where *i* indexes treatment, *j* indexes litter, and *k* indexes newborn rats within a litter. The *t<sub>i</sub>* represent treatment means, the  $\alpha_{ij}$  represent random litter effects assumed to be iid  $N(0, s_i^2)$ , and the *e<sub>ijk</sub>* represent iid residual errors, all on the latent scale.

Instead of observing the survival times *y<sub>ijk</sub>*, assume that only the binary variable indicating whether *y<sub>ijk</sub>* exceeds 0 is observed. If *x<sub>ij</sub>* denotes the sum of these binary variables for the *i*th treatment and the *j*th litter,



then the preceding assumptions lead to the following generalized linear mixed model:

$$x_{ij}|\alpha_{ij} \sim \text{Binomial}(m_{ij}, p_{ij})$$

where  $m_{ij}$  is the size of each litter after 4 days and

$$p_{ij} = \Phi(t_i + \alpha_{ij})$$

The PROC NLMIXED statements to fit this model are as follows:

```
proc nlmixed data=rats;
  parms t1=1 t2=1 s1=.05 s2=1;
  eta = x1*t1 + x2*t2 + alpha;
  p   = probnorm(eta);
  model x ~ binomial(m,p);
  random alpha ~ normal(0,x1*s1*s1+x2*s2*s2) subject=litter;
  estimate 'gamma2' t2/sqrt(1+s2*s2);
  predict p out=p;
run;
```

As in [Example 64.1](#), the PROC NLMIXED statement invokes the procedure and the PARMS statement defines the parameters. The parameters for this example are the two treatment means,  $t_1$  and  $t_2$ , and the two random-effect standard deviations,  $s_1$  and  $s_2$ .

The indicator variables  $x_1$  and  $x_2$  are used in the program to assign the proper mean to each observation in the input data set as well as the proper variance to the random effects. Note that programming expressions are permitted inside the distributional specifications, as illustrated by the random-effects variance specified here.

The **ESTIMATE** statement requests an estimate of  $\gamma_2 = t_2/\sqrt{1+s_2^2}$ , which is a location-scale parameter from Ochi and Prentice (1984).

The **PREDICT** statement constructs predictions for each observation in the input data set. For this example, predictions of  $p$  and approximate standard errors of prediction are output to a SAS data set named P. These predictions are functions of the parameter estimates and the empirical Bayes estimates of the random effects  $\alpha_i$ .

The output for this model is as follows.

#### Output 64.2.1 Specifications, Dimensions, and Starting Values

The NLMIXED Procedure	
Specifications	
Data Set	WORK.RATS
Dependent Variable	x
Distribution for Dependent Variable	Binomial
Random Effects	alpha
Distribution for Random Effects	Normal
Subject Variable	litter
Optimization Technique	Dual Quasi-Newton
Integration Method	Adaptive Gaussian Quadrature

**Output 64.2.1** *continued*

Dimensions				
Observations Used				32
Observations Not Used				0
Total Observations				32
Subjects				32
Max Obs Per Subject				1
Parameters				4
Quadrature Points				7
Parameters				
t1	t2	s1	s2	NegLogLike
1	1	0.05	1	54.9362323

The “Specifications” table provides basic information about this nonlinear mixed model ([Output 64.2.1](#)). The “Dimensions” table provides counts of various variables. Note that each observation in the data comprises a separate subject. Using the starting values in the “Parameters” table, PROC NLMIXED determines that the log-likelihood function can be approximated with sufficient accuracy with a seven-point quadrature rule.

**Output 64.2.2** Iteration History for Probit-Normal Model

Iteration History					
Iter	Calls	NegLogLike	Diff	MaxGrad	Slope
1	2	53.9933934	0.942839	11.03261	-81.9428
2	3	52.875353	1.11804	2.148952	-2.86277
3	5	52.6350386	0.240314	0.329957	-1.05049
4	6	52.6319939	0.003045	0.122926	-0.00672
5	8	52.6313583	0.000636	0.028246	-0.00352
6	11	52.6313174	0.000041	0.013551	-0.00023
7	13	52.6313115	5.839E-6	0.000603	-0.00001
8	15	52.6313115	9.45E-9	0.000022	-1.68E-8
NOTE: GCONV convergence criterion satisfied.					

The “Iteration History” table indicates successful convergence in 8 iterations ([Output 64.2.2](#)).

**Output 64.2.3** Fit Statistics for Probit-Normal Model

Fit Statistics	
-2 Log Likelihood	105.3
AIC (smaller is better)	113.3
AICC (smaller is better)	114.7
BIC (smaller is better)	119.1

The “Fit Statistics” table lists useful statistics based on the maximized value of the log likelihood (Output 64.2.3).

**Output 64.2.4** Parameter Estimates for Probit-Normal Model

Parameter Estimates							
Parameter	Estimate	Standard Error	DF	t Value	Pr >  t	Alpha	Lower
t1	1.3063	0.1685	31	7.75	<.0001	0.05	0.9626
t2	0.9475	0.3055	31	3.10	0.0041	0.05	0.3244
s1	0.2403	0.3015	31	0.80	0.4315	0.05	-0.3746
s2	1.0292	0.2988	31	3.44	0.0017	0.05	0.4198

Parameter Estimates		
Parameter	Upper	Gradient
t1	1.6499	-0.00002
t2	1.5705	9.283E-6
s1	0.8552	0.000014
s2	1.6385	-3.16E-6

The “Parameter Estimates” table indicates significance of all the parameters except S1 (Output 64.2.4).

**Output 64.2.5** Additional Estimates

Additional Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr >  t	Alpha	Lower	Upper
gamma2	0.6603	0.2165	31	3.05	0.0047	0.05	0.2186	1.1019

The “Additional Estimates” table displays results from the **ESTIMATE** statement (Output 64.2.5). The estimate of  $\gamma_2$  equals 0.66, agreeing with that obtained by McCulloch (1994). The standard error 0.22 is computed using the delta method (Billingsley 1986; Cox 1998).

Not shown is the P data set, which contains the original 32 observations and predictions of the  $p_{ij}$ .

### Example 64.3: Probit-Normal Model with Ordinal Data

The data for this example are from Ezzet and Whitehead (1991), who describe a crossover experiment on two groups of patients using two different inhaler devices (A and B). Patients from group 1 used device A for one week and then device B for another week. Patients from group 2 used the devices in reverse order. The data entered as a SAS data set are as follows:

```
data inhaler;
  input clarity group time freq @@;
  gt = group*time;
  sub = floor((_n_+1)/2);
  datalines;
1 0 0 59 1 0 1 59 1 0 0 35 2 0 1 35 1 0 0 3 3 0 1 3 1 0 0 2
4 0 1 2 2 0 0 11 1 0 1 11 2 0 0 27 2 0 1 27 2 0 0 2 3 0 1 2
2 0 0 1 4 0 1 1 4 0 0 1 1 0 1 1 4 0 0 1 2 0 1 1 1 1 0 63
1 1 1 63 1 1 0 13 2 1 1 13 2 1 0 40 1 1 1 40 2 1 0 15 2 1 1 15
3 1 0 7 1 1 1 7 3 1 0 2 2 1 1 2 3 1 0 1 3 1 1 1 4 1 0 2
1 1 1 2 4 1 0 1 3 1 1 1
;
```

The response measurement, clarity, is the patients' assessment on the clarity of the leaflet instructions for the devices. The clarity variable is on an ordinal scale, with 1=easy, 2=only clear after rereading, 3=not very clear, and 4=confusing. The group variable indicates the treatment group, and the time variable indicates the time of measurement. The freq variable indicates the number of patients with exactly the same responses. A variable gt is created to indicate a group-by-time interaction, and a variable sub is created to indicate patients.

As in the previous example and in Hedeker and Gibbons (1994), assume an underlying latent continuous variable, here with the form

$$y_{ij} = \beta_0 + \beta_1 g_i + \beta_2 t_j + \beta_3 g_i t_j + u_i + e_{ij}$$

where  $i$  indexes patient and  $j$  indexes the time period,  $g_i$  indicates groups,  $t_j$  indicates time,  $u_i$  is a patient-level normal random effect, and  $e_{ij}$  are iid normal errors. The  $\beta$ s are unknown coefficients to be estimated.

Instead of observing  $y_{ij}$ , however, you observe only whether it falls in one of the four intervals:  $(-\infty, 0)$ ,  $(0, I1)$ ,  $(I1, I1 + I2)$ , or  $(I1 + I2, \infty)$ , where  $I1$  and  $I2$  are both positive. The resulting category is the value assigned to the clarity variable.

The following code sets up and fits this ordinal probit model:

```
proc nlmixed data=inhaler corr ecorr;
  parms b0=0 b1=0 b2=0 b3=0 sd=1 i1=1 i2=1;
  bounds i1 > 0, i2 > 0;
  eta = b0 + b1*group + b2*time + b3*gt + u;
  if (clarity=1) then p = probnorm(-eta);
  else if (clarity=2) then
    p = probnorm(i1-eta) - probnorm(-eta);
  else if (clarity=3) then
    p = probnorm(i1+i2-eta) - probnorm(i1-eta);
  else p = 1 - probnorm(i1+i2-eta);
  if (p > 1e-8) then ll = log(p);
  else ll = -1e20;
```

```

model clarity ~ general(11);
random u ~ normal(0,sd*sd) subject=sub;
replicate freq;
estimate 'thresh2' i1;
estimate 'thresh3' i1 + i2;
estimate 'icc' sd*sd/(1+sd*sd);
run;

```

The **PROC NLMIXED** statement specifies the input data set and requests correlations both for the parameter estimates (**CORR** option) and for the additional estimates specified with **ESTIMATE** statements (**ECORR** option).

The parameters as defined in the **PARMS** statement are as follows: **b0** (overall intercept), **b1** (group main effect), **B2** (time main effect), **b3** (group-by-time interaction), **sd** (standard deviation of the random effect), **i1** (increment between first and second thresholds), and **i2** (increment between second and third thresholds). The **BOUND**s statement restricts **i1** and **i2** to be positive.

The SAS programming statements begin by defining the linear predictor **eta**, which is a linear combination of the **b** parameters and a single random effect **u**. The next statements define the ordinal likelihood according to the **clarity** variable, **eta**, and the increment variables. An error trap is included in case the likelihood becomes too small.

A general log-likelihood specification is used in the **MODEL** statement, and the **RANDOM** statement defines the random effect **u** to have standard deviation **sd** and subject variable **sub**. The **REPLICATE** statement indicates that data for each subject should be replicated according to the **freq** variable.

The **ESTIMATE** statements specify the second and third thresholds in terms of the increment variables (the first threshold is assumed to equal zero for model identifiability). Also computed is the intraclass correlation.

The output is as follows.

**Output 64.3.1** Specifications for Ordinal Data Model

The NLMIXED Procedure	
Specifications	
Data Set	WORK.INHALER
Dependent Variable	clarity
Distribution for Dependent Variable	General
Random Effects	u
Distribution for Random Effects	Normal
Subject Variable	sub
Replicate Variable	freq
Optimization Technique	Dual Quasi-Newton
Integration Method	Adaptive Gaussian Quadrature

The “Specifications” table echoes some primary information specified for this nonlinear mixed model (Output 64.3.1). Because the log-likelihood function was expressed with SAS programming statements, the distribution is displayed as *General* in the “Specifications” table.

The “Dimensions” table reveals a total of 286 subjects, which is the sum of the values of the FREQ variable for the second time point. Five quadrature points are selected for log-likelihood evaluation ([Output 64.3.2](#)).

**Output 64.3.2** Dimensions Table for Ordinal Data Model

Dimensions	
Observations Used	38
Observations Not Used	0
Total Observations	38
Subjects	286
Max Obs Per Subject	2
Parameters	7
Quadrature Points	5

**Output 64.3.3** Parameter Starting Values and Negative Log Likelihood

Parameters							
b0	b1	b2	b3	sd	i1	i2	NegLogLike
0	0	0	0	1	1	1	538.484276

The “Parameters” table lists the simple starting values for this problem ([Output 64.3.3](#)). The “Iteration History” table indicates successful convergence in 13 iterations ([Output 64.3.4](#)).

**Output 64.3.4** Iteration History

Iteration History					
Iter	Calls	NegLogLike	Diff	MaxGrad	Slope
1	2	476.382511	62.10176	43.75062	-1431.4
2	4	463.228197	13.15431	14.24648	-106.753
3	5	458.528118	4.70008	48.31316	-33.0389
4	6	450.975735	7.552383	22.60098	-40.9954
5	8	448.012701	2.963033	14.86877	-16.7453
6	10	447.245153	0.767549	7.774189	-2.26743
7	11	446.72767	0.517483	3.793533	-1.59278
8	13	446.518273	0.209396	0.868638	-0.37801
9	16	446.514528	0.003745	0.328568	-0.02356
10	18	446.513341	0.001187	0.056778	-0.00183
11	20	446.513314	0.000027	0.010785	-0.00004
12	22	446.51331	3.956E-6	0.004922	-5.41E-6
13	24	446.51331	1.989E-7	0.00047	-4E-7

NOTE: GCONV convergence criterion satisfied.

**Output 64.3.5** Fit Statistics for Ordinal Data Model

Fit Statistics	
-2 Log Likelihood	893.0
AIC (smaller is better)	907.0
AICC (smaller is better)	910.8
BIC (smaller is better)	932.6

The “Fit Statistics” table lists the log likelihood and information criteria for model comparisons ([Output 64.3.5](#)).

**Output 64.3.6** Parameter Estimates at Convergence

Parameter Estimates							
Parameter	Estimate	Standard Error	DF	t Value	Pr >  t	Alpha	Lower
b0	-0.6364	0.1342	285	-4.74	<.0001	0.05	-0.9006
b1	0.6007	0.1770	285	3.39	0.0008	0.05	0.2523
b2	0.6015	0.1582	285	3.80	0.0002	0.05	0.2900
b3	-1.4817	0.2385	285	-6.21	<.0001	0.05	-1.9512
sd	0.6599	0.1312	285	5.03	<.0001	0.05	0.4017
i1	1.7450	0.1474	285	11.84	<.0001	0.05	1.4548
i2	0.5985	0.1427	285	4.19	<.0001	0.05	0.3177

Parameter Estimates		
Parameter	Upper	Gradient
b0	-0.3722	0.00047
b1	0.9491	0.000265
b2	0.9129	0.00008
b3	-1.0122	0.000102
sd	0.9181	-0.00009
i1	2.0352	0.000202
i2	0.8794	0.000087

The “Parameter Estimates” table indicates significance of all the parameters ([Output 64.3.6](#)).

**Output 64.3.7** Threshold and Intraclass Correlation Estimates

Additional Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr >  t	Alpha	Lower	Upper
thresh2	1.7450	0.1474	285	11.84	<.0001	0.05	1.4548	2.0352
thresh3	2.3435	0.2073	285	11.31	<.0001	0.05	1.9355	2.7515
icc	0.3034	0.08402	285	3.61	0.0004	0.05	0.1380	0.4687

The “Additional Estimates” table displays results from the ESTIMATE statements ([Output 64.3.7](#)).

### Example 64.4: Poisson-Normal Model with Count Data

This example uses the pump failure data of Gaver and O’Muircheartaigh (1987). The number of failures and the time of operation are recorded for 10 pumps. Each of the pumps is classified into one of two groups corresponding to either continuous or intermittent operation. The data are as follows:

```
data pump;
  input y t group;
  pump = _n_;
  logtstd = log(t) - 2.4564900;
  datalines;
5  94.320 1
1  15.720 2
5  62.880 1
14 125.760 1
3   5.240 2
19 31.440 1
1   1.048 2
1   1.048 2
4   2.096 2
22 10.480 2
;
```

Each row denotes data for a single pump, and the variable logtstd contains the centered operation times.

Letting  $y_{ij}$  denote the number of failures for the  $j$ th pump in the  $i$ th group, Draper (1996) considers the following hierarchical model for these data:

$$\begin{aligned}
 y_{ij} | \lambda_{ij} &\sim \text{Poisson}(\lambda_{ij}) \\
 \log \lambda_{ij} &= \alpha_i + \beta_i (\log t_{ij} - \overline{\log t}) + e_{ij} \\
 e_{ij} | \sigma^2 &\sim \text{Normal}(0, \sigma^2)
 \end{aligned}$$

The model specifies different intercepts and slopes for each group, and the random effect is a mechanism for accounting for overdispersion.



The corresponding PROC NLMIXED statements are as follows:

```
proc nlmixed data=pump;
  parms logsig 0 beta1 1 beta2 1 alpha1 1 alpha2 1;
  if (group = 1) then eta = alpha1 + beta1*logtstd + e;
  else eta = alpha2 + beta2*logtstd + e;
  lambda = exp(eta);
  model y ~ poisson(lambda);
  random e ~ normal(0,exp(2*logsig)) subject=pump;
  estimate 'alpha1-alpha2' alpha1-alpha2;
  estimate 'beta1-beta2' beta1-beta2;
run;
```

The selected output is as follows.

**Output 64.4.1** Dimensions Table for Poisson-Normal Model

The NLMIXED Procedure	
Dimensions	
Observations Used	10
Observations Not Used	0
Total Observations	10
Subjects	10
Max Obs Per Subject	1
Parameters	5
Quadrature Points	5

The “Dimensions” table indicates that data for 10 pumps are used with one observation for each (Output 64.4.1).

**Output 64.4.2** Iteration History for Poisson-Normal Model

Iteration History					
Iter	Calls	NegLogLike	Diff	MaxGrad	Slope
1	2	30.6986932	2.162768	5.107253	-91.602
2	5	30.0255468	0.673146	2.761738	-11.0489
3	7	29.726325	0.299222	2.990401	-2.36048
4	9	28.7390263	0.987299	2.074431	-3.93678
5	10	28.3161933	0.422833	0.612531	-0.63084
6	12	28.09564	0.220553	0.462162	-0.52684
7	14	28.0438024	0.051838	0.405047	-0.10018
8	16	28.0357134	0.008089	0.135059	-0.01875
9	18	28.033925	0.001788	0.026279	-0.00514
10	20	28.0338744	0.000051	0.00402	-0.00012
11	22	28.0338727	1.681E-6	0.002864	-5.09E-6
12	24	28.0338724	3.199E-7	0.000147	-6.87E-7
13	26	28.0338724	2.532E-9	0.000017	-5.75E-9

NOTE: GCONV convergence criterion satisfied.

The “Iteration History” table indicates successful convergence in 13 iterations ([Output 64.4.2](#)).

### Output 64.4.3 Fit Statistics for Poisson-Normal Model

Fit Statistics	
-2 Log Likelihood	56.1
AIC (smaller is better)	66.1
AICC (smaller is better)	81.1
BIC (smaller is better)	67.6

The “Fit Statistics” table lists the final log likelihood and associated information criteria ([Output 64.4.3](#)).

#### Output 64.4.4 Parameter Estimates and Additional Estimates

Parameter Estimates							
Parameter	Estimate	Standard Error	DF	t Value	Pr >  t	Alpha	Lower
logsig	-0.3161	0.3213	9	-0.98	0.3508	0.05	-1.0429
beta1	-0.4256	0.7473	9	-0.57	0.5829	0.05	-2.1162
beta2	0.6097	0.3814	9	1.60	0.1443	0.05	-0.2530
alpha1	2.9644	1.3826	9	2.14	0.0606	0.05	-0.1632
alpha2	1.7992	0.5492	9	3.28	0.0096	0.05	0.5568
Parameter Estimates							
Parameter	Upper	Gradient					
logsig	0.4107	-0.00002					
beta1	1.2649	-0.00002					
beta2	1.4724	-1.61E-6					
alpha1	6.0921	-5.25E-6					
alpha2	3.0415	-5.73E-6					
Additional Estimates							
Label	Estimate	Standard Error	DF	t Value	Pr >  t	Alpha	Lower
alpha1-alpha2	1.1653	1.4855	9	0.78	0.4529	0.05	-2.1952
beta1-beta2	-1.0354	0.8389	9	-1.23	0.2484	0.05	-2.9331
Additional Estimates							
Label	Upper						
alpha1-alpha2	4.5257						
beta1-beta2	0.8623						

The “Parameter Estimates” and “Additional Estimates” tables list the maximum likelihood estimates for each of the parameters and two differences (Output 64.4.4). The point estimates for the mean parameters agree fairly closely with the Bayesian posterior means reported by Draper (1996); however, the likelihood-based standard errors are roughly half the Bayesian posterior standard deviations. This is most likely due to the fact that the Bayesian standard deviations account for the uncertainty in estimating  $\sigma^2$ , whereas the likelihood values plug in its estimated value. This downward bias can be corrected somewhat by using the  $t_9$  distribution shown here.

## Example 64.5: Failure Time and Frailty Model

In this example an accelerated failure time model with proportional hazard is fitted with and without random effects. The data are from the “Getting Started” example of PROC LIFEREG; see Chapter 51, “The LIFEREG Procedure.” Thirty-eight patients are divided into two groups of equal size, and different pain relievers are assigned to each group. The outcome reported is the time in minutes until headache relief. The variable *sensor* indicates whether relief was observed during the course of the observation period (*sensor* = 0) or whether the observation is censored (*sensor* = 1). The SAS DATA step for these data is as follows:

```
data headache;
  input minutes group sensor @@;
  patient = _n_;
  datalines;
11 1 0    12 1 0    19 1 0    19 1 0
19 1 0    19 1 0    21 1 0    20 1 0
21 1 0    21 1 0    20 1 0    21 1 0
20 1 0    21 1 0    25 1 0    27 1 0
30 1 0    21 1 1    24 1 1    14 2 0
16 2 0    16 2 0    21 2 0    21 2 0
23 2 0    23 2 0    23 2 0    23 2 0
25 2 1    23 2 0    24 2 0    24 2 0
26 2 1    32 2 1    30 2 1    30 2 0
32 2 1    20 2 1
;
```

In modeling survival data, censoring of observations must be taken into account carefully. In this example, only right censoring occurs. If  $g(t, \boldsymbol{\beta})$ ,  $h(t, \boldsymbol{\beta})$ , and  $G(t, \boldsymbol{\beta})$  denote the density of failure, the hazard function, and the survival distribution function at time  $t$ , respectively, then the log likelihood can be written as

$$\begin{aligned} l(\boldsymbol{\beta}; \mathbf{t}) &= \sum_{i \in U_u} \log g(t_i, \boldsymbol{\beta}) + \sum_{i \in U_c} \log G(t_i, \boldsymbol{\beta}) \\ &= \sum_{i \in U_u} \log h(t_i, \boldsymbol{\beta}) + \sum_{i=1}^n \log G(t_i, \boldsymbol{\beta}) \end{aligned}$$

(See Cox and Oakes 1984, Ch. 3.) In these expressions  $U_u$  is the set of uncensored observations,  $U_c$  is the set of censored observations, and  $n$  denotes the total sample size.

The proportional hazards specification expresses the hazard in terms of a baseline hazard, multiplied by a constant. In this example the hazard is that of a Weibull model and is parameterized as  $h(t, \boldsymbol{\beta}) = \gamma \alpha (\alpha t)^{\gamma-1}$  and  $\alpha = \exp\{-\mathbf{x}'\boldsymbol{\beta}\}$ .

The linear predictor is set equal to the intercept in the reference group (group = 2); this defines the baseline hazard. The corresponding distribution of survival past time  $t$  is  $G(t, \beta) = \exp\{-(\alpha t)^\gamma\}$ . See Cox and Oakes (1984, Table 2.1) and the section “Supported Distributions” in Chapter 51, “The LIFEREG Procedure,” for this and other survival distribution models and various parameterizations.

The following NLMIXED statements fit this accelerated failure time model and estimate the cumulative distribution function of time to headache relief:

```
proc nlmixed data=headache;
  bounds gamma > 0;
  lnp = b0 - b1*(group-2);
  alpha = exp(-lnp);
  G_t = exp(-(alpha*minutes)**gamma);
  g = gamma*alpha*((alpha*minutes)**(gamma-1))*G_t;
  ll = (censor=0)*log(g) + (censor=1)*log(G_t);
  model minutes ~ general(ll);
  predict 1-G_t out=cdf;
run;
```

**Output 64.5.1** Specifications Table for Fixed-Effects Failure Time Model

The NLMIXED Procedure	
Specifications	
Data Set	WORK.HEADACHE
Dependent Variable	minutes
Distribution for Dependent Variable	General
Optimization Technique	Dual Quasi-Newton
Integration Method	None

The “Specifications” table shows that no integration is required, since the model does not contain random effects (Output 64.5.1).

**Output 64.5.2** Negative Log Likelihood with Default Starting Values

Parameters			
gamma	b0	b1	NegLogLike
1	1	1	263.990327

No starting values were given for the three parameters. The NLMIXED procedure assigns the default value of 1.0 in this case. The negative log likelihood based on these starting values is shown in Output 64.5.2.

**Output 64.5.3** Iteration History for Fixed-Effects Failure Time Model

Iteration History					
Iter	Calls	NegLogLike	Diff	MaxGrad	Slope
1	2	169.244311	94.74602	22.5599	-2230.83
2	4	142.873508	26.3708	14.88631	-3.64643
3	6	140.633695	2.239814	11.25234	-9.49454
4	8	122.890659	17.74304	19.44959	-2.50807
5	9	121.396959	1.493699	13.85584	-4.55427
6	11	120.623843	0.773116	13.67062	-1.38064
7	12	119.278196	1.345647	15.78014	-1.69072
8	14	116.271325	3.006871	26.94029	-3.2529
9	16	109.427401	6.843925	19.88382	-6.9289
10	19	103.298102	6.129298	12.15647	-4.96054
11	22	101.686239	1.611863	14.24868	-4.34059
12	23	100.027875	1.658364	11.69853	-13.2049
13	26	99.9189048	0.108971	3.602552	-0.55176
14	28	99.8738836	0.045021	0.170712	-0.16645
15	30	99.8736392	0.000244	0.050822	-0.00041
16	32	99.8736351	4.071E-6	0.000705	-6.9E-6
17	34	99.8736351	6.1E-10	4.768E-6	-1.23E-9

NOTE: GCONV convergence criterion satisfied.

The “Iteration History” table shows that the procedure converges after 17 iterations and 34 evaluations of the objective function (Output 64.5.3).

**Output 64.5.4** Fit Statistics and Parameter Estimates

Fit Statistics							
-2 Log Likelihood				199.7			
AIC (smaller is better)				205.7			
AICC (smaller is better)				206.5			
BIC (smaller is better)				210.7			

Parameter Estimates							
Parameter	Estimate	Standard Error	DF	t Value	Pr >  t	Alpha	Lower
gamma	4.7128	0.6742	38	6.99	<.0001	0.05	3.3479
b0	3.3091	0.05885	38	56.23	<.0001	0.05	3.1900
b1	-0.1933	0.07856	38	-2.46	0.0185	0.05	-0.3523

Parameter Estimates		
Parameter	Upper	Gradient
gamma	6.0777	5.327E-8
b0	3.4283	-4.77E-6
b1	-0.03426	-1.22E-6

The parameter estimates and their standard errors shown in [Output 64.5.4](#) are identical to those obtained with the LIFEREG procedure and the following statements:

```
proc lifereg data=headache;
  class group;
  model minutes*censor(1) = group / dist=weibull;
  output out=new cdf=prob;
run;
```

The  $t$  statistic and confidence limits are based on 38 degrees of freedom. The LIFEREG procedure computes  $z$  intervals for the parameter estimates.

For the two groups you obtain

$$\begin{aligned}\hat{\alpha}(\text{group} = 1) &= \exp\{-3.3091 + 0.1933\} = 0.04434 \\ \hat{\alpha}(\text{group} = 2) &= \exp\{-3.3091\} = 0.03655\end{aligned}$$

The probabilities of headache relief by  $t$  minutes are estimated as

$$\begin{aligned}1 - G(t, \text{group} = 1) &= 1 - \exp\{-(0.04434 * t)^{4.7128}\} \\ 1 - G(t, \text{group} = 2) &= 1 - \exp\{-(0.03655 * t)^{4.7128}\}\end{aligned}$$

These probabilities, calculated at the observed times, are shown for the two groups in [Output 64.5.5](#) and printed with the following statements:

```
proc print data=cdf;
  var group censor patient minutes pred;
run;
```

Since the slope estimate is negative with  $p$ -value of 0.0185, you can infer that pain reliever 1 leads to overall significantly faster relief, but the estimated probabilities give no information about patient-to-patient variation within and between groups. For example, while pain reliever 1 provides faster relief overall, some patients in group 2 might respond more quickly than some patients in group 1. A frailty model enables you to accommodate and estimate patient-to-patient variation in health status by introducing random effects into a subject's hazard function.

**Output 64.5.5** Estimated Cumulative Distribution Function

Obs	group	censor	patient	minutes	Pred
1	1	0	1	11	0.03336
2	1	0	2	12	0.04985
3	1	0	3	19	0.35975
4	1	0	4	19	0.35975
5	1	0	5	19	0.35975
6	1	0	6	19	0.35975
7	1	0	7	21	0.51063
8	1	0	8	20	0.43325
9	1	0	9	21	0.51063
10	1	0	10	21	0.51063
11	1	0	11	20	0.43325
12	1	0	12	21	0.51063
13	1	0	13	20	0.43325
14	1	0	14	21	0.51063
15	1	0	15	25	0.80315
16	1	0	16	27	0.90328
17	1	0	17	30	0.97846
18	1	1	18	21	0.51063
19	1	1	19	24	0.73838
20	2	0	20	14	0.04163
21	2	0	21	16	0.07667
22	2	0	22	16	0.07667
23	2	0	23	21	0.24976
24	2	0	24	21	0.24976
25	2	0	25	23	0.35674
26	2	0	26	23	0.35674
27	2	0	27	23	0.35674
28	2	0	28	23	0.35674
29	2	1	29	25	0.47982
30	2	0	30	23	0.35674
31	2	0	31	24	0.41678
32	2	0	32	24	0.41678
33	2	1	33	26	0.54446
34	2	1	34	32	0.87656
35	2	1	35	30	0.78633
36	2	0	36	30	0.78633
37	2	1	37	32	0.87656
38	2	1	38	20	0.20414

The following statements model the hazard for patient  $i$  in terms of  $\alpha_i = \exp\{-\mathbf{x}_i'\boldsymbol{\beta} - z_i\}$ , where  $z_i$  is a (normal) random patient effect. Notice that the only difference from the previous NLMIXED statements are the **RANDOM** statement and the addition of  $z$  in the linear predictor. The empirical Bayes estimates of the random effect (**RANDOM** statement), the parameter estimates (ODS OUTPUT statement), and the estimated cumulative distribution function (**PREDICT** statement) are saved to subsequently graph the patient-specific distribution functions.

```

ods output ParameterEstimates=est;
proc nlmixed data=headache;
  bounds gamma > 0;
  linp = b0 - b1*(group-2) + z;
  alpha = exp(-linp);
  G_t = exp(-(alpha*minutes)**gamma);
  g = gamma*alpha*((alpha*minutes)**(gamma-1))*G_t;
  ll = (censor=0)*log(g) + (censor=1)*log(G_t);
  model minutes ~ general(ll);
  random z ~ normal(0,exp(2*logsig)) subject=patient out=EB;
  predict 1-G_t out=cdf;
run;

```

**Output 64.5.6** Specifications for Random Frailty Model

The NLMIXED Procedure	
Specifications	
Data Set	WORK.HEADACHE
Dependent Variable	minutes
Distribution for Dependent Variable	General
Random Effects	z
Distribution for Random Effects	Normal
Subject Variable	patient
Optimization Technique	Dual Quasi-Newton
Integration Method	Adaptive Gaussian Quadrature

The “Specifications” table shows that the objective function is computed by adaptive Gaussian quadrature because of the presence of random effects (compare [Output 64.5.6](#) and [Output 64.5.1](#)). The “Dimensions” table reports that nine quadrature points are being used to integrate over the random effects ([Output 64.5.7](#)).

**Output 64.5.7** Dimensions Table for Random Frailty Model

Dimensions	
Observations Used	38
Observations Not Used	0
Total Observations	38
Subjects	38
Max Obs Per Subject	1
Parameters	4
Quadrature Points	9



**Output 64.5.8** Iteration History for Random Frailty Model

Iteration History					
Iter	Calls	NegLogLike	Diff	MaxGrad	Slope
1	5	142.121411	28.82225	12.14484	-88.8664
2	7	136.440369	5.681042	25.93096	-65.7217
3	9	122.972041	13.46833	46.56546	-146.887
4	11	120.904825	2.067216	23.77936	-94.2862
5	13	109.224144	11.68068	57.65493	-92.4075
6	15	105.064733	4.159411	4.824649	-19.5879
7	16	101.902207	3.162526	14.1287	-6.33767
8	18	99.6907395	2.211468	7.676822	-3.42364
9	20	99.3654033	0.325336	5.689204	-0.93978
10	22	99.2602178	0.105185	0.317643	-0.23408
11	24	99.254434	0.005784	1.17351	-0.00556
12	25	99.2456973	0.008737	0.247412	-0.00871
13	27	99.2445445	0.001153	0.104942	-0.00218
14	29	99.2444958	0.000049	0.005646	-0.0001
15	31	99.2444957	9.147E-8	0.000271	-1.84E-7
NOTE: GCONV convergence criterion satisfied.					

The procedure converges after 15 iterations ([Output 64.5.8](#)). The achieved  $-2$  log likelihood is only 1.2 less than that in the model without random effects (compare [Output 64.5.9](#) and [Output 64.5.4](#)). Compared to a chi-square distribution with one degree of freedom, the addition of the random effect appears not to improve the model significantly. You must exercise care, however, in interpreting likelihood ratio tests when the value under the null hypothesis falls on the boundary of the parameter space (see, for example, Self and Liang 1987).

**Output 64.5.9** Fit Statistics for Random Frailty Model

Fit Statistics	
-2 Log Likelihood	198.5
AIC (smaller is better)	206.5
AICC (smaller is better)	207.7
BIC (smaller is better)	213.0

**Output 64.5.10** Parameter Estimates

Parameter Estimates							
Parameter	Estimate	Standard Error	DF	t Value	Pr >  t	Alpha	Lower
gamma	6.2867	2.1334	37	2.95	0.0055	0.05	1.9641
b0	3.2786	0.06576	37	49.86	<.0001	0.05	3.1453
b1	-0.1761	0.08264	37	-2.13	0.0398	0.05	-0.3436
logsig	-1.9027	0.5273	37	-3.61	0.0009	0.05	-2.9711

Parameter Estimates		
Parameter	Upper	Gradient
gamma	10.6093	-1.89E-7
b0	3.4118	0.000271
b1	-0.00868	0.000111
logsig	-0.8343	0.000027

The estimate of the Weibull parameter has changed drastically from the model without random effects (compare [Output 64.5.10](#) and [Output 64.5.4](#)). The variance of the patient random effect is  $\exp\{-2 \times 1.9027\} = 0.02225$ . The listing in [Output 64.5.11](#) shows the empirical Bayes estimates of the random effects. These are the adjustments made to the linear predictor in order to obtain a patient's survival distribution. The listing is produced with the following statements:

```
proc print data=eb;
  var Patient Effect Estimate StdErrPred;
run;
```

**Output 64.5.11** Empirical Bayes Estimates of Random Effects

Obs	patient	Effect	Estimate	StdErr Pred
1	1	z	-0.13597	0.23249
2	2	z	-0.13323	0.22793
3	3	z	-0.06294	0.13813
4	4	z	-0.06294	0.13813
5	5	z	-0.06294	0.13813
6	6	z	-0.06294	0.13813
7	7	z	-0.02568	0.11759
8	8	z	-0.04499	0.12618
9	9	z	-0.02568	0.11759
10	10	z	-0.02568	0.11759
11	11	z	-0.04499	0.12618
12	12	z	-0.02568	0.11759
13	13	z	-0.04499	0.12618
14	14	z	-0.02568	0.11759
15	15	z	0.05980	0.11618
16	16	z	0.10458	0.12684
17	17	z	0.17147	0.14550
18	18	z	0.06471	0.13807
19	19	z	0.11157	0.14604
20	20	z	-0.13406	0.22899
21	21	z	-0.12698	0.21667
22	22	z	-0.12698	0.21667
23	23	z	-0.08506	0.15701
24	24	z	-0.08506	0.15701
25	25	z	-0.05797	0.13294
26	26	z	-0.05797	0.13294
27	27	z	-0.05797	0.13294
28	28	z	-0.05797	0.13294
29	29	z	0.06420	0.13956
30	30	z	-0.05797	0.13294
31	31	z	-0.04266	0.12390
32	32	z	-0.04266	0.12390
33	33	z	0.07618	0.14132
34	34	z	0.16292	0.16460
35	35	z	0.13193	0.15528
36	36	z	0.06327	0.12124
37	37	z	0.16292	0.16460
38	38	z	0.02074	0.14160

The predicted values and patient-specific survival distributions can be plotted with the SAS code that follows:

```
proc transpose data=est (keep=estimate)
    out=trest(rename=(col1=gamma col2=b0 col3=b1));
run;

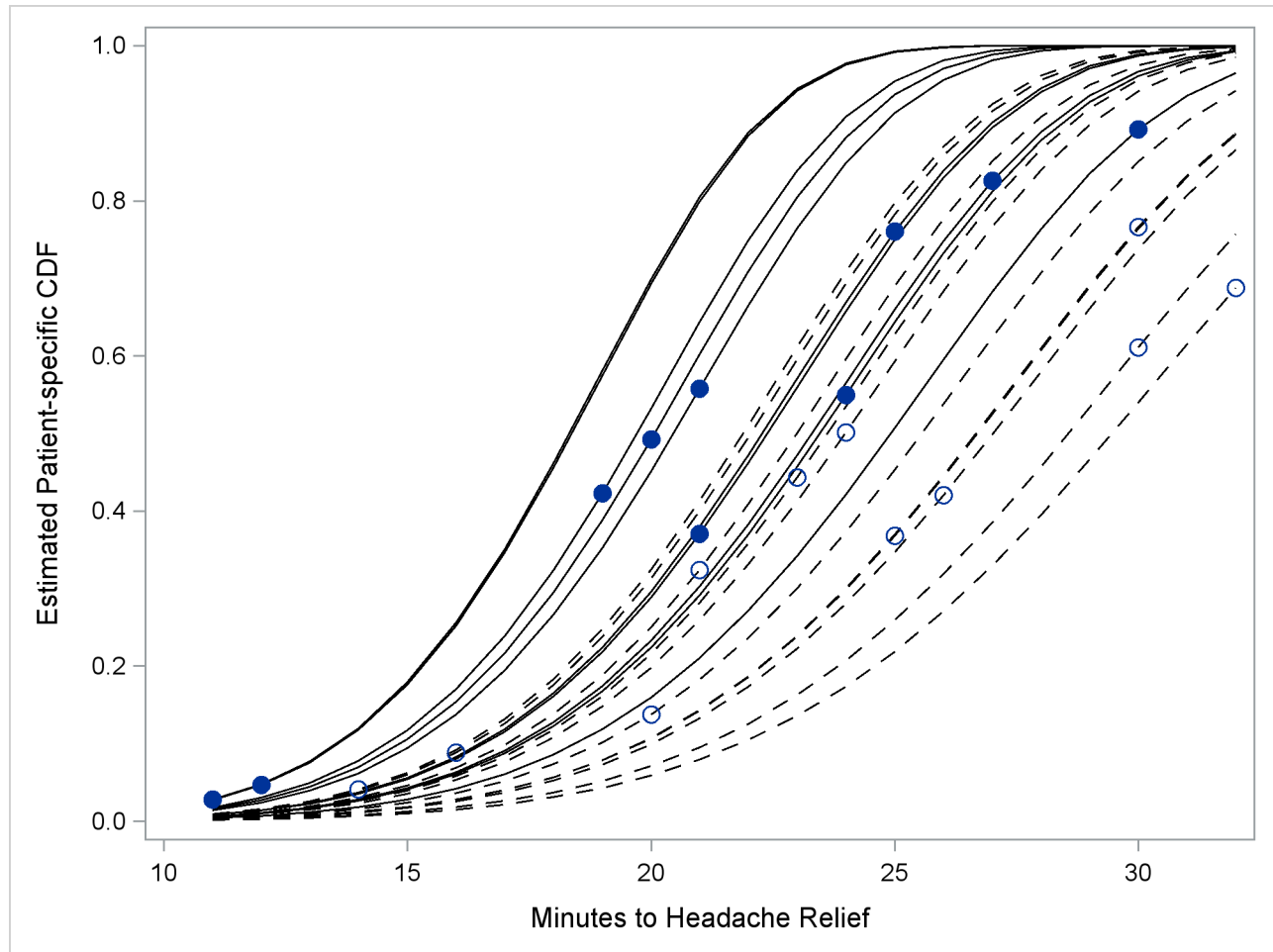
data pred;
    merge eb(keep=estimate) headache(keep=patient group);
    array pp{2} pred1-pred2;
    if _n_ = 1 then set trest(keep=gamma b0 b1);
    do time=11 to 32;
        linp      = b0 - b1*(group-2) + estimate;
        pp{group} = 1-exp(- (exp(-linp)*time)**gamma);
        symbolid  = patient+1;
        output;
    end;
    keep pred1 pred2 time patient;
run;

data pred;
    merge pred
        cdf(where = (group=1)
            rename = (pred=pcdf1 minutes=minutes1)
            keep   = pred minutes group)
        cdf(where = (group=2)
            rename = (pred=pcdf2 minutes=minutes2)
            keep   = pred minutes group);
    drop group;
run;

proc sgplot data=pred noautolegend;
    label minutes1='Minutes to Headache Relief'
          pcdf1    ='Estimated Patient-specific CDF';
    series x=time    y=pred1 /
          group=patient
          lineattrs=(pattern=solid color=black);
    series x=time    y=pred2 /
          group=patient
          lineattrs=(pattern=dash color=black);
    scatter x=minutes1 y=pcdf1 /
          markerattrs=(symbol=CircleFilled size=9);
    scatter x=minutes2 y=pcdf2 /
          markerattrs=(symbol=Circle      size=9);
run;
```

The separation of the distribution functions by groups is evident in [Output 64.5.12](#). Most of the distributions of patients in the first group are to the left of the distributions in the second group. The separation is not complete, however. Several patients who are assigned the second pain reliever experience headache relief more quickly than patients assigned to the first group.

**Output 64.5.12** Patient-Specific CDFs and Predicted Values. Pain Reliever 1: Solid Lines, Closed Circles; Pain Reliever 2: Dashed Lines, Open Circles.



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