

Modeling Capabilities Specification

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1 Introduction

This document describes the modeling capabilities for the three-tiered version of the System for Population Kinetics (SPK).

2 SPK Overview

The three tiers of this system are

- the NONMEM Model Design Agent (MDA),
- the Application Server for Population Kinetics (ASPK), and
- and the Computational Server for Population Kinetics (CSPK).

3 Major Modeling Capabilities

SPK will have the following major modeling capabilities:

- individual level estimation,
- individual level simulation,
- population level estimation,
- population level simulation, and
- population level likelihood evaluation.

4 Modeling Capability Extensions

SPK will have some capabilities that go beyond those of NONMEM.

In particular, the modeling capabilities associated with the evaluation of population level likelihoods and with the calculation of some types of residuals are unique to SPK. These capabilities are discussed in this section.

4.1 Population Level Likelihood Evaluation

SPK will allow for the evaluation of the population level likelihood using Monte Carlo integration techniques.

4.2 Residual Calculation

Some of the residuals that SPK will calculate are different than those that can be calculated using NONMEM. In particular, both NONMEM and SPK always output the three items PRED, RES and WRES. SPK also computes residuals in individual parameter space, and call those ETARES and WETARES. What these items contain in SPK depends on the method used. In general, for a given analysis, PRED, RES, ETARES, WRES and WETARES will contain the output of the last calculation performed to obtain predictions, residuals both in measurement and parameter space and weighted residuals both in measurement and parameter space.

4.2.1 Extended Least Squares Individual Level Residuals

Although the residuals discussed in this section are calculated in the same way by SPK and NONMEM, this discussion is included here for completeness.

When the extended least squares objective function is being used to perform individual level estimation, SPK's model for the j^{th} value of an individual's data is

$$y_{(j)} = f_{(j)}(b) + e_{(j)}, \quad (1)$$

where

$$e \sim N[0, R(b)], \quad (2)$$

b is the individual's vector of parameters, and e is a vector of random variables that describe the measurement noise. For a complete description of the models used at the individual level by SPK and NONMEM, see Appendix B.

Let the vector of residuals for the individual be defined as the differences between their data and the expected values for their data as predicted by the model,

$$\begin{aligned} r &= y - E_e[f(b) + e] \\ &= y - f(b). \end{aligned} \quad (3)$$

The covariance matrix for the individual's data is given by

$$\begin{aligned} \text{cov}[y] &= \text{cov}_e[f(b) + e] \\ &= R(b). \end{aligned} \quad (4)$$

The vector of weighted residuals for the individual is defined as

$$w = \{\text{cov}[y]\}^{-1/2} r, \quad (5)$$

where the term multiplying the residuals is the matrix square root of the inverse of the covariance.

The individual level residuals are calculated by evaluating the preceding quantities at the optimal values for the individuals' vectors of parameters that were determined during individual level estimation, i.e., by setting $b = \hat{b}$.

The following table lists the residual related quantities, their values as calculated by SPK, and their values as calculated by NONMEM. In this case, the NONMEM values are calculated using its standard individual estimation mode.

Quantity	SPK Value	Description	Name	NONMEM Value
$E[f]^{(\text{ELS})}$	$f(\hat{b})$	Predicted value for an individual's data.	IPRED = PRED	Same
$r^{(\text{ELS})}$	$y - f(\hat{b})$	Residuals for an individual.	IRES = RES	Same
$w^{(\text{ELS})}$	$\{R(\hat{b})\}^{-1/2} [y - f(\hat{b})]$	Weighted residuals for an individual.	IWRES = WRES	Same

4.2.2 Map Bayesian Individual Level Residuals

When the Map Bayesian objective function is being used to perform individual level estimation, SPK's model for the j^{th} value of an individual's data is

$$y_{(j)} = f_{(j)}(b) + e_{(j)}, \quad (6)$$

where

$$b \sim N[0, D], \quad (7)$$

$$e \sim N[0, R(b)], \quad (8)$$

b is the individual's vector of parameters, and e is a vector of random variables that describe the measurement noise. Note that b is also a random variable in this case. For a complete description of the models used at the individual level by SPK and NONMEM, see Appendix B.

For this objective function, there is an additional set of residuals that come from the terms that include the individual parameters b . Let the vector of residuals for the individual parameters be defined as the differences between zero and the expected values for the individual parameters,

$$\begin{aligned} \rho &= 0 - E_b[b] \\ &= -b. \end{aligned} \quad (9)$$

The covariance matrix for the individual parameters is

$$\begin{aligned} \text{cov}[b] &= \text{cov}_b[b] \\ &= D. \end{aligned} \quad (10)$$

The vector of weighted individual parameter residuals is defined as

$$z = \{\text{cov}[b]\}^{-1/2} \rho, \quad (11)$$

where the term multiplying the residuals is the matrix square root of the inverse of the covariance.

The individual level residuals are calculated by evaluating the preceding quantities at the optimal values for the individuals' vectors of parameters that were determined during individual level estimation, \hat{b} .

The following table lists the residual related quantities, their values as calculated by SPK, and their values as calculated by NONMEM. In this case, the NONMEM values are calculated for all of the individuals in the population using the POSTHOC option in the \$ESTIMATION command. SPK values are always calculated (whether POSTHOC was requested or not).

Quantity	SPK Value	Description	Name	NONMEM Value
$E[f]^{(I)}$	$f(\hat{b})$	Predicted value for an individual's data.	IPRED	Not available in NONMEM.
$r^{(I)}$	$y - f(\hat{b})$	Residuals for an individual.	IRES	Not available in NONMEM.
$w^{(I)}$	$\{R(\hat{b})\}^{-1/2} [y - f(\hat{b})]$	Weighted residuals for an individual.	IWRES	Not available in NONMEM.
$\rho^{(I)}$	$-\hat{b}$	Individual parameter residuals.	IETARES	Not available in NONMEM.
$z^{(I)}$	$\{D\}^{-1/2} (-\hat{b})$	Weighted individual parameter residuals.	IWETARES	Not available in NONMEM.

4.2.3 Population Level Residuals Background

SPK's mixed effects model for the i^{th} individual's data is

$$y_i = f_i(\alpha, b_i) + e_i, \quad (12)$$

where

$$b_i \sim N[0, D(\alpha)], \quad (13)$$

$$e_i \sim N[0, R_i(\alpha, b_i)], \quad (14)$$

α is a vector of fixed effects parameters, b_i is the individual's vector of random effects parameters, and e_i is a vector of random variables that describe the measurement noise. For a complete description of the models used at the population level by SPK and NONMEM, see Appendix C.

Different estimation methods arise from various approximations to the maximum likelihood objective function. Let $\tilde{f}_i(\alpha, b)$ be a particular Taylor series approximation for $f_i(\alpha, b)$. Let us now define classes of outputs to be calculated in the population case for individual i :

- NONMEM-compatible outputs (no prefix), which are always calculated at zero random effects and for the true model, or

$$f_i(\alpha, 0) \quad (15)$$

- population outputs (prefix P), or

$$\tilde{f}_i(\alpha, 0) \quad (16)$$

- linearized outputs (prefix L), or

$$\tilde{f}_i(\alpha, \tilde{b}_i) \quad (17)$$

- individual outputs (prefix I), or

$$f_i(\alpha, \hat{b}_i) \quad (18)$$

Let the vector of residuals for the i^{th} individual be defined as the differences between the individual's data and their respective approximation as predicted by the model,

$$r_i = y_i - \tilde{f}_i(\alpha, b) \quad (19)$$

The variance of the residuals is an approximation to the covariance of the measurements, $R_i(\alpha, b_i)$, which we will call $\tilde{R}_i(\alpha, b_i)$. Thus, $r_i \sim N(0, \tilde{R}_i(\alpha, b_i))$. The weighted residuals can then be defined as $w_i = \{\tilde{R}_i(\alpha, b_i)\}^{-1} r_i$ and it is easy to show that $\text{Var}[w_i] = I$. The covariance matrix for the i^{th} individual's data is given by

$$\begin{aligned} \text{cov}[y_i] &= \text{cov}_{b,e} [f_i(\alpha, b_i) + e_i] \\ &= \text{cov}_b [f_i(\alpha, b_i)] + R_i(\alpha, b_i). \end{aligned} \quad (20)$$

The vector of weighted residuals for the i^{th} individual is defined as

$$w_i = \{\text{cov}[y_i]\}^{-1/2} r_i, \quad (21)$$

where the term multiplying the residuals is the matrix square root of the inverse of the covariance.

In order to calculate the residuals and weighted residuals, SPK makes some approximations that are based on the derivations and discussion in Sections (6.2) and (6.3) of Davidian and Giltinan¹.

To be specific, SPK makes Taylor series approximations to (linearizes) the nonlinear function $f_i(\alpha, b)$ about the value b_i^* . Note that the value or b_i^* (either 0 or \hat{b}_i) will depend on the specific approximation method, see below for details,

$$\tilde{f}_i(\alpha, b_i) = f_i(\alpha, b_i^*) + \partial_b f_i(\alpha, b_i^*)(b_i - b_i^*), \quad (22)$$

$$R_i(\alpha, b_i) \approx R_i(\alpha, b_i^*). \quad (23)$$

The residuals are therefore in general approximated by

$$r_i \approx y_i - f_i(\alpha, b_i^*) + \partial_b f_i(\alpha, b_i^*) b_i^*. \quad (24)$$

¹Davidian M. and Giltinan D. M. (1998) *Nonlinear Models for Repeated Measurement Data*, Chapman & Hall/CRC, Boca Raton, Florida, pp. 152-66.

The covariance of the individual's data is approximated by

$$\text{cov}[y_i] \approx \partial_b f_i(\alpha, b_i^*) D(\alpha) \partial_b f_i(\alpha, b_i^*)^T + R_i(\alpha, b_i^*). \quad (25)$$

As a diagnostic, SPK will also provide the weighted individual parameter residuals at the population level. Let the vector of residuals for the i^{th} individual's parameters be defined as the differences between zero and the values for their individual parameters,

$$\rho_i = -b_i. \quad (26)$$

The covariance matrix for the individual parameters is

$$\begin{aligned} \text{cov}[b_i] &= \text{cov}_b [b_i] \\ &= D(\alpha). \end{aligned} \quad (27)$$

The vector of weighted individual parameter residuals is defined as

$$z_i = \{\text{cov}[b_i]\}^{-1/2} \rho_i, \quad (28)$$

where the term multiplying the residuals is the matrix square root of the inverse of the covariance.

4.2.4 First Order Population Residuals

The first class of population residuals are calculated by evaluating the preceding approximations at the mean values for the individuals' vectors of random effects parameters, i.e., by setting $b_i^* = 0$ for all of the individuals. This corresponds to the approximations made for the First Order (FO) objective function, i.e.

$$\tilde{f}_i(\alpha, b) = f_i(\alpha, 0) + \partial_b f_i(\alpha, 0)b \quad (29)$$

The following table lists the residual related population outputs, their values as calculated by SPK, and their values as calculated by NONMEM. Eq. 16 applied to Eq. 29 provides the PPRED entry in the table below. The rest of the entries follow similarly.

Quantity	SPK Value	Description	Name	NONMEM Value
$E[f_i]^{(P)}$	$f_i(\alpha, 0)$	Approximate predicted value for an individual's data.	PPRED	PRED
$r_i^{(P)}$	$y_i - f_i(\alpha, 0)$	Approximate residuals for an individual.	PRES	RES
$w_i^{(P)}$	$\left\{ \partial_b f_i(\alpha, 0) D(\alpha) \partial_b f_i(\alpha, 0)^T + R_i(\alpha, 0) \right\}^{-1/2} * [y_i - f_i(\alpha, 0)]$	Approximate weighted residuals for an individual.	PWRES	WRES
$\rho_i^{(P)}$	0	Individual parameter residuals for an individual.	PETARES	Not available in NONMEM.
$z_i^{(P)}$	0	Weighted individual parameter residuals for an individual.	PWETARES	Not available in NONMEM.

The following table lists the residual related quantities, their values as calculated by SPK, and their values as calculated by NONMEM for the case variables without P, I or L prefix. These quantities are supposed to be compatible with NONMEM outputs. In this case, the NONMEM values are the same as above.

Quantity	SPK Value	Description	Name	NONMEM Value
$E[f_i]$	$f_i(\alpha, 0)$	Approximate predicted value for an individual's data.	PRED	PRED
r_i	$y_i - f_i(\alpha, 0)$	Approximate residuals for an individual.	RES	RES
w_i	$\left\{ \partial_b f_i(\alpha, 0) D(\alpha) \partial_b f_i(\alpha, 0)^T + R_i(\alpha, 0) \right\}^{-1/2} * [y_i - f_i(\alpha, 0)]$	Approximate weighted residuals for an individual.	WRES	WRES
ρ_i	0	Individual parameter residuals for an individual.	ETARES	Not available in NONMEM.
z_i	0	Weighted individual parameter residuals for an individual.	WETARES	Not available in NONMEM.

The following table lists the residual related linearized outputs, their values as calculated by SPK, and their values as calculated by NONMEM. In this case, the NONMEM values are not available. Eq. 17 applied to Eq. 29 provides the LPRED entry in the table below. The rest of the entries follow similarly. Note that the estimate of the individual random effects \check{b}_i is done for each individual and is the estimate that arises from the linearization of the model around zero (not from POSTHOC). In other words, it is the maximum likelihood estimate of the random effects conditional on the model $f(\alpha, b)$ being linear and conditional on α values. It can be obtained via the solution to a linear least squares problem. The formula for the linear least squares problem is:

$$\check{b}_i = \operatorname{argmin}_{b_i} \left[(y_i - f_i(\alpha, 0) - \partial_b f_i(\alpha, 0) b_i)^T R_i^{-1}(\alpha, 0) (y_i - f_i(\alpha, 0) - \partial_b f_i(\alpha, 0) b_i) + b_i^T D(\alpha) b_i \right] \quad (30)$$

The minimizer of this objective function is

$$\check{b}_i = \left[\partial_b f_i(\alpha, 0)^T R_i^{-1}(\alpha, 0) \partial_b f_i(\alpha, 0) + D \right]^{-1} \partial_b f_i(\alpha, 0)^T R_i^{-1}(\alpha, 0) (y_i - f_i(\alpha, 0)), \quad (31)$$

which can be determined by setting the derivative of the objective equal to zero.

The linear model is shown below as part of the definition of $r_i^{(\text{FO})}$.

Quantity	SPK Value	Description	Name	NONMEM Value
$E[f_i]^{(\text{L})}$	$f_i(\alpha, 0) + \partial_b f_i(\alpha, 0) \check{b}_i$	Approximate predicted value for an individual's data.	LPRED	Not available in NONMEM.
$r_i^{(\text{L})}$	$y_i - f_i(\alpha, 0) - \partial_b f_i(\alpha, 0) \check{b}_i$	Approximate residuals for an individual.	LRES	Not available in NONMEM.
$w_i^{(\text{L})}$	$\{R_i(\alpha, 0)\}^{-1/2} * [y_i - f_i(\alpha, 0) - \partial_b f_i(\alpha, 0) \check{b}_i]$	Approximate weighted residuals for an individual.	LWRES	Not available in NONMEM.
$\rho_i^{(\text{L})}$	$-\check{b}_i$	Individual parameter residuals for an individual.	LETARES	Not available in NONMEM.
$z_i^{(\text{L})}$	$\{D(\alpha)\}^{-1/2} (-\check{b}_i)$	Weighted individual parameter residuals for an individual.	LWETARES	Not available in NONMEM.

The following table lists the residual related individual outputs, their values as calculated by SPK, and their values as calculated by NONMEM. In this case, the NONMEM values would be calculated using the First Order (FO) Method in the \$ESTIMATION command with the POSTHOC option. Eq. 18 applied to Eq. 29 provides the IPRED entry in the table below. The rest of the entries follow similarly. Note that the estimate of the individual random effects \hat{b}_i is obtained for each individual and is the MAP Bayesian estimate.

Quantity	SPK Value	Description	Name	NONMEM Value
$E[f_i]^{(I)}$	$f_i(\alpha, \hat{b})$	Predicted value for an individual's data.	IPRED	Not available in NONMEM.
$r_i^{(I)}$	$y_i - f_i(\alpha, \hat{b})$	Residuals for an individual.	IRES	Not available in NONMEM.
$w_i^{(I)}$	$\{R_i(\alpha, \hat{b})\}^{-1/2} [y_i - f_i(\alpha, \hat{b})]$	Weighted residuals for an individual.	IWRES	Not available in NONMEM.
$\rho_i^{(I)}$	$-\hat{b}_i$	Individual parameter residuals.	IETARES	Not available in NONMEM.
$z_i^{(I)}$	$\{D(\alpha)\}^{-1/2} (-\hat{b}_i)$	Weighted individual parameter residuals.	IWETARES	Not available in NONMEM.

4.2.5 Conditional Methods Population Residuals

The conditional estimation methods in SPK use either the Expected Hessian objective function, which is equivalent to NONMEM'S First Order Conditional Estimation (FOCE) method, or the Laplace objective, which is equivalent to NONMEM's Laplace method. Both conditional estimation methods perform Taylor series approximation of the model function $f(\alpha, b)$ by setting $b_i^* = \hat{b}_i$ for all of the individuals.

$$\tilde{f}_i(\alpha, b) = f_i(\alpha, \hat{b}) + \partial_b f_i(\alpha, \hat{b})(b - \hat{b}) \quad (32)$$

The following table lists the residual related quantities, their values as calculated by SPK, and their values as calculated by NONMEM. Eq. 16 applied to Eq. 32 provides the PPRED entry in the table below. The rest of the entries follow similarly. In this case, the NONMEM values are calculated using one of NONMEM's conditional estimation that are available in the \$ESTIMATION command.

Quantity	SPK Value	Description	Name	NONMEM Value
$E[f_i]^{(P)}$	$f_i(\alpha, \hat{b}_i) - \partial_b f_i(\alpha, \hat{b}_i) \hat{b}_i$	Approximate predicted value for an individual's data.	PPRED	Not available in NONMEM.
$r_i^{(P)}$	$y_i - f_i(\alpha, \hat{b}_i) + \partial_b f_i(\alpha, \hat{b}_i) \hat{b}_i$	Approximate residuals for an individual.	PRES	Not available in NONMEM.
$w_i^{(P)}$	$\left\{ \partial_b f_i(\alpha, \hat{b}_i) D(\alpha) \partial_b f_i(\alpha, \hat{b}_i)^T + R_i(\alpha, \hat{b}_i) \right\}^{-1/2} * [y_i - f_i(\alpha, \hat{b}_i) + \partial_b f_i(\alpha, \hat{b}_i) \hat{b}_i]$	Approximate weighted residuals for an individual.	PWRES	Not available in NONMEM.
$\rho_i^{(P)}$	$-\hat{b}_i$	Individual parameter residuals for an individual.	PETARES	Not available in NONMEM.
$z_i^{(P)}$	$\{D(\alpha)\}^{-1/2} (-\hat{b}_i)$	Weighted individual parameter residuals for an individual.	PWETARES	Not available in NONMEM.

The following table lists the residual related quantities, their values as calculated by SPK, and their values as calculated by NONMEM for the case variables without P, I or L prefix. These quantities are supposed to be compatible with NONMEM outputs. In this case, the NONMEM values are the same. Note that in the case of the First Order method in SPK, PPRED and PRED coincide, but this is not true for the Expected Hessian.

Quantity	SPK Value	Description	Name	NONMEM Value
$E[f_i]$	$f_i(\alpha, 0)$	Approximate predicted value for an individual's data.	PRED	Same.
r_i	$y_i - f_i(\alpha, 0)$	Approximate residuals for an individual.	RES	Same.
w_i	$\left\{ \partial_b f_i(\alpha, 0) D(\alpha) \partial_b f_i(\alpha, 0)^T + R_i(\alpha, 0) \right\}^{-1/2} * [y_i - f_i(\alpha, 0)]$	Approximate weighted residuals for an individual.	WRES	Same.
ρ_i	0	Individual parameter residuals for an individual.	ETARES	Not available in NONMEM.
z_i	0	Weighted individual parameter residuals for an individual.	WETARES	Not available in NONMEM.

When Eq. 17 applied to Eq. 32, the optimal value for \check{b}_i actually coincides with \hat{b}_i due to the properties of Gauss-Newton optimization. Thus, in the Expected Hessian, $\check{b}_i = \hat{b}_i$ and so the linerarized quantities are equal to the individual quantities.

Quantity	SPK Value	Description	Name	NONMEM Value
$E[f_i]^{(L)}$	$f_i(\alpha, \hat{b}_i)$	Approximate predicted value for an individual's data.	LPRED	Not available in NONMEM.
$r_i^{(L)}$	$y_i - f_i(\alpha, \hat{b}_i)$	Approximate residuals for an individual.	LRES	Not available in NONMEM.
$w_i^{(L)}$	$\{R_i(\alpha, \hat{b}_i)\}^{-1/2} [y_i - f_i(\alpha, \hat{b}_i)]$	Approximate weighted residuals for an individual.	LWRES	Not available in NONMEM.
$\rho_i^{(L)}$	$-\hat{b}_i$	Individual parameter residuals for an individual.	LETARES	Not available in NONMEM.
$z_i^{(L)}$	$\{D(\alpha)\}^{-1/2} (-\hat{b}_i)$	Weighted individual parameter residuals for an individual.	LWETARES	Not available in NONMEM.

Eq. 18 applied to Eq. 32 provides the IPRED entry in the table below. The rest of the entries follow similarly.

Quantity	SPK Value	Description	Name	NONMEM Value
$E[f_i]^{(I)}$	$f_i(\alpha, \hat{b}_i)$	Approximate predicted value for an individual's data.	IPRED	Not available in NONMEM.
$r_i^{(I)}$	$y_i - f_i(\alpha, \hat{b}_i)$	Approximate residuals for an individual.	IRES	Not available in NONMEM.
$w_i^{(I)}$	$\{R_i(\alpha, \hat{b}_i)\}^{-1/2} * [y_i - f_i(\alpha, \hat{b}_i)]$	Approximate weighted residuals for an individual.	IWRES	Not available in NONMEM.
$\rho_i^{(I)}$	$-\hat{b}_i$	Individual parameter residuals for an individual.	IETARES	Not available in NONMEM.
$z_i^{(I)}$	$\{D(\alpha)\}^{-1/2} (-\hat{b}_i)$	Weighted individual parameter residuals for an individual.	IWETARES	Not available in NONMEM.

5 Modeling Capability Restrictions

SPK will not support all of NONMEM's modeling capabilities.

In particular, the modeling capabilities associated with some of the NM-TRAN records and keywords will be restricted. These restriction are discussed in this section.

5.1 Data Item Types (\$INPUT)

The only reserved labels for the \$INPUT record that SPK will recognize as having special meanings are the DV, EVID, and ID labels.

5.1.1 Reserved Labels not Recognized by SPK

The other reserved labels (L1, L2, MDV, RAW_, MRG_, TIME, DATE, DAT1, DAT2, DAT3, DROP, SKIP, AMT, RATE, SS, II, ADDL, CMT, PCMT, CALL, CONT) can still be used as valid data item

types in the \$INPUT record. If one of these reserved labels appears in the \$INPUT record, then it may be referenced within the \$PRED block in the usual way.

However, SPK will not recognize it as having special meaning and will not consider it to be different than any other user defined label. It will be the responsibility of the expressions in the \$PRED block to perform the tasks corresponding to these reserved data item labels. These tasks are usually performed by NM-TRAN, NONMEM, and the ADVAN library.

5.1.2 Dependent Variable Data Item (DV)

The dependent variable (DV) data item indicates which column in the data file contains the observed values.

5.1.3 Event Identification Data Item (EVID)

The event identification (EVID) data item is used to indicate which column in the data file contains the EVID values. These values describe the kind of event: observation, dose, other-type, reset, or reset-and-dose. The only value in the EVID column that will have any special meaning within SPK is $EVID = 0$, which corresponds to observation events.

Note that if every event is an observation event, then the EVID column can be left out of the data file and the EVID label does not need to be included in the \$INPUT record.

5.1.4 Identification Data Item (ID)

The identification (ID) data item indicates which column in the data file contains the ID values. A change in the ID value indicates the start of a new individual record.

5.2 Data Sets (\$DATA)

The NONMEM format data files that are supported will have some restrictions.

5.2.1 Event Identification Data Items (EVID)

The expressions from the \$PRED block will be evaluated for all of the data values in the file. But, only observation events ($EVID = 0$) will be associated with dependent variable (DV) values, i.e., with $y_{i(j)}$. If the data set does not contain an EVID column, then every event will be assumed to be an observation event.

5.2.2 Steady State Data Items (SS)

No steady state (SS) data items will be allowed.

5.3 Model Specification via the PRED Block (\$PRED)

The specification of general models using the \$PRED block will be allowed. See Appendix A for an example C++ implementation of the expressions in this block.

5.3.1 Variable Naming Restrictions

Variable names beginning with the characters “spk_” are restricted for use within SPK.

5.3.2 Special NONMEM-PREDPP Arguments (NEWIND and ICALL)

SPK will not support the NEWIND or ICALL arguments.

5.3.3 Variables from NONMEM-PREDPP Common Blocks

SPK will not allow variables from NONMEM-PREDPP common blocks to be accessed in the \$PK block.

5.3.4 Controlling the Calling Frequency (CALLFL)

SPK will not allow the calling frequency to be set via NM-TRAN pseudo assignment statements or via the CALLFL parameter.

5.3.5 First-order Approximation for the Intraindividual Error Model during Population Level Estimation

Because NM-TRAN makes a first-order approximation for the intraindividual error model during population level estimation², the corresponding SPK models generated by ASPK will do the same.

To be specific, let the model for the j^{th} value of the i^{th} individual's data be expressed as the following functional:

$$y_{i(j)} = y_{i(j)} \left(f(x_{ij}, \theta, \eta_i), x_{ij}, \theta, \eta_i, \epsilon_i \right). \quad (33)$$

where $f(x_{ij}, \theta, \eta_i)$ is the mean or expected value for the data, x_{ij} is a vector of known quantities for the individual such as times and covariates, θ is a vector of fixed effects parameters, η_i is the individual's vector of random effects parameters, and ϵ_i is a vector of random variables that appears in NONMEM'S intraindividual error model. For a complete description of the models used at the population level by SPK and NONMEM, see Appendix C.

During population level estimation this functional is approximated by

$$\begin{aligned} & \tilde{y}_{i(j)} \left(f(x_{ij}, \theta, \eta_i), x_{ij}, \theta, \eta_i, \epsilon_i \right) \\ &= y_{i(j)} \left(f(x_{ij}, \theta, \eta_i), x_{ij}, \theta, \eta_i, \epsilon_i \right) \Big|_{\epsilon_i=0} + \sum_{m=1}^{n_{\Sigma}} \left[\partial_{\epsilon}^{(m)} y_{i(j)} \left(f(x_{ij}, \theta, \eta_i), x_{ij}, \theta, \eta_i, \epsilon_i \right) \Big|_{\epsilon_i=0} \right] \epsilon_{i(m)}. \end{aligned} \quad (34)$$

Define the derivative of the functional evaluated at $\epsilon_i = 0$ as

$$h_{(m)} \left(f(x_{ij}, \theta, \eta_i), x_{ij}, \theta, \eta_i \right) = \partial_{\epsilon}^{(m)} y_{i(j)} \left(f(x_{ij}, \theta, \eta_i), x_{ij}, \theta, \eta_i, \epsilon_i \right) \Big|_{\epsilon_i=0}. \quad (35)$$

²NONMEM User's Guide - Part V, NONMEM Project Group, p. 81, 1994.

Then, the covariance of the j^{th} and k^{th} values of the i^{th} individual's data is given by

$$\text{cov}[\tilde{y}_{i(j)}, \tilde{y}_{i(k)}] = \text{cov} \left[\sum_{m=1}^{n_{\Sigma}} h_{(m)} \left(f(x_{ij}, \theta, \eta_i), x_{ij}, \theta, \eta_i \right) \epsilon_{i(m)}, \sum_{n=1}^{n_{\Sigma}} h_{(n)} \left(f(x_{ik}, \theta, \eta_i), x_{ik}, \theta, \eta_i \right) \epsilon_{i(n)} \right] \quad (36)$$

$$= \sum_{m=1}^{n_{\Sigma}} \sum_{n=1}^{n_{\Sigma}} \left[h_{(m)} \left(f(x_{ij}, \theta, \eta_i), x_{ij}, \theta, \eta_i \right) \right] \text{cov}[\epsilon_{i(m)}, \epsilon_{i(n)}] \left[h_{(n)} \left(f(x_{ik}, \theta, \eta_i), x_{ik}, \theta, \eta_i \right) \right] \quad (37)$$

$$= \sum_{m=1}^{n_{\Sigma}} \sum_{n=1}^{n_{\Sigma}} \left[h_{(m)} \left(f(x_{ij}, \theta, \eta_i), x_{ij}, \theta, \eta_i \right) \right] \Sigma_{(m,n)} \left[h_{(n)} \left(f(x_{ik}, \theta, \eta_i), x_{ik}, \theta, \eta_i \right) \right] \quad (38)$$

This corresponds to $R_{i(j,k)}$ in SPK notation.

If the intraindividual error model can be expressed in traditional NONMEM form,

$$y_{i(j)} = f(x_{ij}, \theta, \eta_i) + \sum_{m=1}^{n_{\Sigma}} h_{(m)} \left(f(x_{ij}, \theta, \eta_i), x_{ik}, \theta, \eta_i \right) \epsilon_{i(m)}, \quad (39)$$

then

$$\tilde{y}_{i(j)} = y_{i(j)}, \quad (40)$$

and there is no difference between the approximate and exact intraindividual error models.

If the intraindividual error model is not linear in ϵ , however, the two forms are not equal. For example, in the case of an exponential error model with a single ϵ component,

$$y_{i(j)} = f(x_{ij}, \theta, \eta_i) \exp[\epsilon_{i(1)}], \quad (41)$$

which implies that

$$\tilde{y}_{i(j)} = f(x_{ij}, \theta, \eta_i) + f(x_{ij}, \theta, \eta_i) \epsilon_{i(1)} \quad (42)$$

$$\neq y_{i(j)}, \quad (43)$$

and the intraindividual error models are therefore different.

Note that as a result of this first-order approximation an exponential model is equivalent to a constant coefficient of variation (CCV) model during population level estimation.

5.4 Pharmacokinetic Model Specification (\$SUBROUTINE)

The specification of models using the \$SUBROUTINE block will not be allowed.

5.4.1 Pharmacokinetic Library Subroutines (ADVAN)

SPK will not support any of the models from the ADVAN pharmacokinetic library.

5.4.2 Translator Routines (TRANS)

SPK will not support any of the parameterizations from the TRANS parameter translation library.

5.5 Pharmacokinetic Parameter Models (\$PK)

The methods for specification of pharmacokinetic parameter models will be restricted.

5.5.1 No Support for \$PK Block

SPK will not support the specification of pharmacokinetic parameter models using the \$PK block.

5.5.2 Specifying Pharmacokinetic Parameter Models using \$PRED

The pharmacokinetic parameter model must be specified within the \$PRED block.

5.6 Initial Estimates and Bounds for Theta (\$THETA)

The capabilities of the Theta vectors that are supported will have some restrictions.

5.6.1 Unbounded Upper or Lower Limits

SPK will not allow unbounded lower or upper limits, which are represented in the \$THETA record as -1000000 or 1000000.

5.7 Initial Estimates for Omega (\$OMEGA)

The capabilities of the Omega matrices that are supported will have some restrictions.

5.7.1 Diagonal or Full Matrices Only

SPK will only support diagonal or full Omega matrices.

5.7.2 Only One Block for Nondiagonal Matrices (BLOCK)

SPK will only support nondiagonal Omega matrices that have a single block.

5.8 Intraindividual Error Models (\$ERROR)

The methods for specification of intraindividual error models will be restricted.

5.8.1 No Support for \$ERROR Block

SPK will not support the specification of intraindividual error models using the \$ERROR block.

5.8.2 Specifying Intraindividual Error Models using \$PRED

The intraindividual error model must be specified within the \$PRED block.

5.9 Initial Estimates for Sigma (\$SIGMA)

The capabilities of the Sigma matrices that are supported will have some restrictions.

5.9.1 Diagonal or Full Matrices Only

SPK will only support diagonal or full Sigma matrices.

5.9.2 Only One Block for Nondiagonal Matrices (BLOCK)

SPK will only support nondiagonal Sigma matrices that have a single block.

5.10 Instructions for the Estimation Step (\$ESTIMATION)

The support SPK will give to some of NONMEM's more complex parameter estimation capabilities will be limited.

5.10.1 Continue Estimation when Theta is Nonphysiological (NOABORT)

SPK will not support this.

5.10.2 Conditional Likelihood for Noncontinuous Observed Responses (LIKELIHOOD)

SPK will not support this.

5.10.3 Constrain Average Eta Estimates to be Close to Zero (CENTERING)

SPK will not support this.

5.10.4 Request Second Eta Derivatives to not be Numerical (NONNUMERICAL)

SPK will not support this.

5.10.5 Fix Selected Etas to be Zero (ZERO)

SPK will not support this.

A Appendix: The C++ Equivalent of the \$PRED Block

The following C++ function is an example implementation of the expressions in the NM-TRAN \$PRED block for the CONTROL4 Example ³

This function will be generated by the Application Server for Population Kinetics (ASPK) from the expressions in the \$PRED block. Note that this function interface and example implementation will serve as preliminary specifications for the function.

```
#include <libspkcompiler/nonmem.h>
#include "IndData.h"
namespace {
IndDataSet spk_all;
double cl;
double cp;
double d;
double dose;
double dv;
double e;
double evid;
double ka;
double ke;
double mdv;
double spk_time;
double wt;
};
template< class Type >
bool evalPred( const Type* const theta,
               int          spk_nTheta,
               const Type* const eta,
               int          spk_nEta,
               const Type* const eps,
               int          spk_nEps,
               int          spk_i,
               int          spk_j,
               double       &f,
               double       &y )
{
```

³NONMEM User's Guide - Part VIII, NONMEM Project Group, pp. 306, 1998.

```

cp = spk_all[spk_i].cp[spk_j];
dv = spk_all[spk_i].dv[spk_j];
dose = spk_all[spk_i].dose[spk_j];
evid = spk_all[spk_i].evid[spk_j];
mdv = spk_all[spk_i].mdv[spk_j];
spk_time = spk_all[spk_i].time[spk_j];
wt = spk_all[spk_i].wt[spk_j];
//=====
//  User's Code Begin
//-----
if( dose != 0 ){
    ds = dose * wt;
    w = wt;
}
ka = theta[0] + eta[0];
ke = theta[1] + eta[1];
cl = theta[2] * w + eta[2];
d = exp(-ke * spk_time) - exp(-ka * spk_time);
e = cl * (ka - ke);
f = ds * ke * ka / e * d;
y = f + eps[0];
y = f + eps[0];
//-----
//  End of User's Code
//=====
if( spk_all[spk_i].evid[spk_j] == nonmem::EVID_OBSERVATION )
    return true;
return false;
}

```

B Appendix: Individual Level Models

This appendix describes the models used at the individual level by SPK and NONMEM.

B.1 SPK Model for an Individual's Data

SPK's model for the j^{th} value of an individual's data is

$$y_{(j)} = f_{(j)}(b) + e_{(j)}, \quad (44)$$

where

$$R_{(j,k)}(b) = \text{cov}[e_{(j)}, e_{(k)}], \quad (45)$$

and b is the individual's vector of parameters. If the MAP Bayesian objective function is used, then

$$D_{(p,q)} = \text{cov}[b_{(p)}, b_{(q)}], \quad (46)$$

is the covariance of the individual's parameters.

The output of SPK's individual level estimation is

$$b^{\text{Out}}, \quad (47)$$

which is an estimate for the optimal value for the individual's parameters.

B.2 NONMEM Model for an Individual's Data

NONMEM's model ⁴ for the j^{th} value of an individual's data is

$$y_{(j)} = f(x_j, \theta) + \sum_{m=1}^{n_\Omega} h_{(m)}(x_j, \theta) \eta_{(m)}. \quad (48)$$

where

$$\Omega_{(m,n)} = \text{cov}[\eta_{(m)}, \eta_{(n)}], \quad (49)$$

θ and Ω are a vector and diagonal matrix of the individual's parameters, x_j is a vector of known quantities for the individual such as times and covariates, and n_Ω is the number of elements along the diagonal of Ω . NONMEM does not support the MAP Bayesian objective function at the individual level.

The output of NONMEM's individual level estimation is

$$\left\{ \theta^{\text{Out}}, \Omega^{\text{Out}} \right\}, \quad (50)$$

which are estimates for the optimal values for the individual's parameters.

⁴NONMEM User's Guide - Part V, NONMEM Project Group, pp. 23-31, 1994.

B.3 Comparison of the Models for an Individual's Data

In these two formulations, b and η are not equivalent, and there is no relationship between the covariance matrices D and Ω .

Although e and η are also not equivalent, the covariance matrices $R(b)$ and Ω are related as follows,

$$\begin{aligned}
 R_{(j,k)}(b) &= \text{cov} \left[\sum_{m=1}^{n_\Omega} h_{(m)}(x_j, \theta) \eta_{(m)}, \sum_{n=1}^{n_\Omega} h_{(n)}(x_k, \theta) \eta_{(n)} \right] \\
 &= \sum_{m=1}^{n_\Omega} \sum_{n=1}^{n_\Omega} h_{(m)}(x_j, \theta) \text{cov}[\eta_{(m)}, \eta_{(n)}] h_{(n)}(x_k, \theta) \\
 &= \sum_{m=1}^{n_\Omega} \sum_{n=1}^{n_\Omega} h_{(m)}(x_j, \theta) \Omega_{(m,n)} h_{(n)}(x_k, \theta) \\
 &= \sum_{m=1}^{n_\Omega} h_{(m)}(x_j, \theta) \Omega_{(m,m)} h_{(m)}(x_k, \theta).
 \end{aligned}$$

C Appendix: Population Level Models

This appendix describes the mixed effects models used at the population level by SPK and NONMEM.

C.1 SPK Mixed Effects Model

SPK's mixed effects model for the j^{th} value of the i^{th} individual's data is

$$y_{i(j)} = f_{i(j)}(\alpha, b_i) + e_{i(j)}, \quad (51)$$

where

$$R_{i(j,k)}(\alpha, b_i) = \text{cov}[e_{i(j)}, e_{i(k)}], \quad (52)$$

$$D_{(p,q)}(\alpha) = \text{cov}[b_{i(p)}, b_{i(q)}], \quad (53)$$

α is a vector of fixed effects parameters, and b_i is the individual's vector of random effects parameters.

The output of SPK's population level estimation is

$$\left\{ \alpha^{\text{Out}}, \{b_i^{\text{Out}}(\alpha^{\text{Out}})\} \right\}, \quad (54)$$

which are estimates for the optimal values for the fixed effects parameters along with estimate for the optimal values for each individual's random effects parameters.

C.2 NONMEM Mixed Effects Model

NONMEM's mixed effects model ⁵ for the j^{th} value of the i^{th} individual's data is

$$y_{i(j)} = f(x_{ij}, \theta, \eta_i) + \sum_{m=1}^{n_{\Sigma}} h_{(m)}(x_{ij}, \theta, \eta_i) \epsilon_{i(m)}. \quad (55)$$

where

$$\Sigma_{(m,n)} = \text{cov}[\epsilon_{i(m)}, \epsilon_{i(n)}], \quad (56)$$

$$\Omega_{(p,q)} = \text{cov}[\eta_{i(p)}, \eta_{i(q)}], \quad (57)$$

θ , Σ , and Ω are vectors and matrices of fixed effects parameters, η_i is the individual's vector of random effects parameters, x_{ij} is a vector of known quantities for the individual such as times and covariates, and n_{Σ} is the number of nonzero elements in the lower triangle of Σ .

The output of NONMEM's population level estimation is

$$\left\{ \theta^{\text{Out}}, \Omega^{\text{Out}}, \Sigma^{\text{Out}} \right\}, \quad (58)$$

which are estimates for the optimal values for the fixed effects parameters.

⁵ *NONMEM User's Guide - Part V*, NONMEM Project Group, pp. 32-9, 1994.

C.3 Comparison of the Mixed Effects Models

In these two formulations, b_i and η_i are equivalent. Thus, the covariance matrices $D(\alpha)$ and Ω are equal to one another, and

$$D_{(p,q)}(\alpha) = \Omega_{(p,q)}. \quad (59)$$

Although e_i and ϵ_i are not equivalent, the covariance matrices $R_i(\alpha, b_i)$ and Σ are related as follows,

$$\begin{aligned} R_{i(j,k)}(\alpha, b_i) &= \text{cov} \left[\sum_{m=1}^{n_\Sigma} h_{(m)}(x_{ij}, \theta, \eta_i) \epsilon_{i(m)}, \sum_{n=1}^{n_\Sigma} h_{(n)}(x_{ik}, \theta, \eta_i) \epsilon_{i(n)} \right] \\ &= \sum_{m=1}^{n_\Sigma} \sum_{n=1}^{n_\Sigma} h_{(m)}(x_{ij}, \theta, \eta_i) \text{cov}[\epsilon_{i(m)}, \epsilon_{i(n)}] h_{(n)}(x_{ik}, \theta, \eta_i) \\ &= \sum_{m=1}^{n_\Sigma} \sum_{n=1}^{n_\Sigma} h_{(m)}(x_{ij}, \theta, \eta_i) \Sigma_{(m,n)} h_{(n)}(x_{ik}, \theta, \eta_i) \end{aligned}$$

Note that Σ is the same for all of the individuals in the population.