CERTARA®

Phoenix® Modeling Language Reference Guide

Applies to:

Phoenix WinNonlin® 8.1
Phoenix NLME™ 8.1

Phoenix Modeling Language Version 8.1

Destination Control Statement

United States Government Rights

Trademarks

Additional third party software acknowledgements

Certara, L.P.
100 Overlook Center, Suite 101, Princeton, NJ, 08540 USA
Telephone: +1.609.716.7900
www.certara.com

Contents

List of Tables . . . . **ix**

Chapter 1 **Introduction** **11**

Certara contact information 11

Chapter 2 **Language Structure and Syntax** **13**

Modeling project files 14
- Data files 14
- Model files 15
- Column mappings 16

General syntax conventions 20

Reserved and user-defined variable names 21

Modeling syntax 21
- Population PK model 21
- Closed-form models 23
- Transit Compartment models 25
- Action code 27
- Observations 29
- Math and special functions 37
- Dosing 38
- Covariates 38
- Modeling discontinuous events 39
- Discrete and distributed delays 40
- Sequence statements 44
- Group statements 46
- Sleep statements 47
- Time event switching in PML versus WinNonlin ASCII models 47
- Fixed effect parameter syntax 47
- Random effect parameter syntax 48

Chapter 3 **Running NLME Engines in Command Line Mode** **51**

Requirements and installation 52
- Software requirements 52
- Hardware requirements 52
- PML and multi-processor or multi-core computers 52
- Install the executables and examples 53

Licensing 53
Run the example models 53
Basic command line syntax 54
Input files 55
The lognlmeflags.asc control file 56
Running QRPEM in command line mode 58
QRPEM control flags 58

Chapter 4 **PML Examples 61**
Phenobarbital 61
Data 61
Column mappings 62
The model 62
NONMEM control file 63
Theophylline 63
Data 63
Column mappings 64
The model 64
NONMEM control file 65
User-defined logistic model 65
Data 65
Column mappings 65
The model 66
NONMEM control file 66
Structural parameters and QRPEM 67
Additional examples 71
Multinomial (ordered categorical) 72
Time to event model (exponential) 72
Time to event model (Weibull) 73
Emax (Hill) model with exponent 74
One-compartment IV bolus population PK 74
One-compartment IV bolus, two parallel models with common fixed effects75
One-compartment model with sequence 75
One-compartment model with sleep statement 76
One-compartment first-order absorption model, compartment initialized with sequence76
One-compartment first-order absorption, closed-form 77
One-compartment first-order absorption with lag time, closed-form . . . 77
One-compartment IV bolus with time-to-event outcome and PK observations78

Appendix A **Closed-Form and Matrix Exponent Computations 79**
Closed-form computations 79
Matrix exponent 80

Appendix B **Blocks, Statements, and Operators 83**
Blocks and statements 83
Expressions and operators 88

Appendix C **Reserved Words 89**

Appendix D **Supported Functions 91**

Special functions. 91

Math functions 92

Index 97

List of Tables

List of Tables ix

Chapter 1 **Introduction** 11

Chapter 2 **Language Structure and Syntax** 13
Dose cycle syntax 18

Chapter 3 **Running NLME Engines in Command Line Mode** 51
Engine numbering 54
Input files 55

Chapter 4 **PML Examples** 61
Observed values 73

Appendix A **Closed-Form and Matrix Exponent Computations** 79

Appendix B **Blocks, Statements, and Operators** 83
Supported statements 83
Supported operators 88

Appendix C **Reserved Words** 89
More common reserved variable names 89

Appendix D **Supported Functions** 91
Special functions 91
Trigonometric functions 92
Hyperbolic functions. 93
Exponential and logarithmic functions 93
Power functions 93
Error and gamma functions 93
Rounding and remainder functions 94
Floating-point manipulation functions 94
Minimum, maximum, difference functions 94
Other functions available in math.h 95
Classification macro/functions 95

Comparison macro/functions 95

Index 97

Chapter 1

Introduction

Phoenix Modeling Language capabilities and Certara contact information

Phoenix is a software platform that provides a single environment in which to perform individual and PK and PD modeling.

Phoenix is also designed to work efficiently with other Certara software, including Pharsight Knowledgebase Server™ (PKS).

Phoenix supports model building through a graphical model-building environment, model libraries, and a text-based modeling language with which users can describe, fit, and simulate models.

The language will support specification of input and/or output data, trial related settings such as dosing and treatment sequence, as well as flexible model definitions for PK/PD and general NLME modeling including survival analysis and modeling of categorical responses.

Phoenix will include the needed structures for seamless integration of modeling with trial simulation and related analyses. It will draw on established practices in S-PLUS and NONMEM to make it friendly for users familiar with those software packages.

Certara contact information

Technical Support

Consult the software documentation to address questions. If further assistance is needed, contact Certara Support through e-mail or our web site.

E-mail: support@certara.com

Web: support.certara.com/support

For the most efficient service, e-mail a complete description of the problem, including copies of the input data.

User Forum

Get tips and discuss Certara software with other users at:

https://support.certara.com/forums

Language Structure and Syntax

This chapter discusses the modeling language syntax and conventions in the following sections:

- “Modeling project files” on page 14
  - “Data files” on page 14
  - “Model files” on page 15
  - “Column mappings” on page 16
- “General syntax conventions” on page 20
- “Reserved and user-defined variable names” on page 21
- “Modeling syntax” on page 21
  - “Closed-form models” on page 23
  - “Action code” on page 27
  - “Observations” on page 29
  - “Math and special functions” on page 37
  - “Dosing” on page 38
  - “Covariates” on page 38
  - “Modeling discontinuous events” on page 39
  - “Discrete and distributed delays” on page 40
  - “Sequence statements” on page 44
  - “Group statements” on page 46
  - “Sleep statements” on page 47
  - “Time event switching in PML versus WinNonlin ASCII models” on page 47
  - “Fixed effect parameter syntax” on page 47
  - “Random effect parameter syntax” on page 48

This manual assumes that the reader is familiar with C++ and S-PLUS syntax, conventions, and concepts.

See Appendix B on page 83 for an alphabetized list of commands and functions.

Modeling project files

Most modeling projects will use three ASCII files: a data file in `*.dat`, `*.csv` or `*.txt` format, a `*.txt` file that maps the model data columns to Phoenix model columns, and a Phoenix model file in `*.mdl` or `*.txt` format. The `*.mdl` extension is used as a convention to identify PML model files.

– "Data files" on page 14
– "Model files" on page 15
– "Column mappings" on page 16

Data files

The ASCII model data files *`.dat`, *`.csv` or *`.txt` are used for model fitting and the data can be delimited by a space, a comma, or a tab. The first row should identify the column names, and must be preceded by ##. For example, the first row of the example Theophylline dataset listed below looks like this:

```
## id, wt, dose, time, conc.
```

Only the period "." character is an acceptable decimal separator.

Caution: The column header line in a PML dataset must be preceded by ## or Phoenix will not recognize the column headers.

Each subsequent row must contain data for each field. Use a period "." to represent a null value. The data for the first subject in the example Theophylline dataset `thbates.dat` are shown below.

```
thbates.dat
##    xid   wt    dose  time  yobs
      1     79.6  4.02  0     .74
      1     79.6  4.02  .25   2.84
      1     79.6  4.02  .57   6.57
      1     79.6  4.02  1.12  10.5
      1     79.6  4.02  2.02  9.66
      1     79.6  4.02  3.82  8.58
      1     79.6  4.02  5.1   8.36
      1     79.6  4.02  7.03  7.47
      1     79.6  4.02  9.05  6.89
      1     79.6  4.02  12.12 5.94
      1     79.6  4.02  24.37 3.28
```

Dataset row limitations:

The vast majority of memory is allocated and de-allocated dynamically as needed. In most cases, peak total memory demands for the Phoenix engines are easily accommodated within the memory available on modern computers (typically at least one gigabyte of memory per processor). However, there are still a number of static limits on model parameters as follows.

- **Maximum number of subjects** = 120,000 (This limit applies to all engines except the nonparametric engine, where the maximum number of subjects is 1000.)
- **Maximum number of observations per subject** = unlimited (See limit on total number of observations below.)
- **Maximum total number of observations** = 480,000

- **Maximum number of thetas (fixed effects)** = 1000 (This includes both fixed effects that are frozen to a user-specified value, as well as free fixed effects that are included in the likelihood optimization, which is given below as 401.)
- **Maximum number of etas (random effects)** = 101 (This is also the maximum dimension of the Omega matrix in the diagonal case. Although, if Omega has a full or partial block structure, the maximum dimension will be less (see remarks below for free parameters).)
- **Maximum number of free parameters to be optimized** = 401 (This includes both free fixed effect, residual error model, and Omega parameters. Only non-zero Omega parameters on and below the diagonal are counted against this limit. Thus a full block matrix with *Neta* random effects will consume *Neta*(Neta+1)/2* of these parameters, while a diagonal matrix will only consume *Neta* parameters. Omega matrices with a block diagonal structure will fall somewhere in between as determined by the particular block structure.
- **Maximum number of QRPEM samples** = no limit (Large values (e.g., > 100,000) may cause difficulties with total static + dynamic peak memory demands. Typical values of QRPEM sample size range between 300 and 10,000 and should cause no problems.
- **Maximum number of iterations** = 10,000.
- **Maximum number of covariate categories or occasions** = 40.

Depending on the available memory and actual combination of model and run parameters, it is possible for very large models technically within the above static limits to require more dynamically allocated memory than is available. However, this should be an extremely rare occurrence and the overwhelming majority of population NLME models should easily fit.

Model files

The Phoenix model file is an ASCII text file that contains the model definition statements. It must follow the general form:

```
mdl(variables){
   statements
}
```

where `mdl` is the assigned model name. All models are called test by default, but users can rename them. The `(variables)` parentheses are normally empty `()`, but they can contain a list of variables when the model is used in trial simulation. See “General syntax conventions” on page 20 and “Modeling syntax” on page 21 for details of the available statements.

The model file for the Theophylline example is shown below. See “Modeling syntax” on page 21 for an annotated example.

```
fm3theophx.mdl
fm1theo(){
# Theophylline model example coding
# One compartment model with first order absorption
# Single dose at time=0, explicit concentration prediction formula
      covariate(dose,time)
      fixef(
            tvlKa = c(, 0.5,)
            tvlKe = c(, -2.5,)
            tvlCl = c(, -3.0,)
            )
      ranef(
            diag(nlKa, nlCl) = c(1.0 1.0)
            )
      stparm(
            Ka = exp(tvlKa + nlKa)
            Ke = exp(tvlKe)

            )
      V = Cl/Ke
      cpred = dose
            * Ka
            / (V * (Ka - Ke))
            * (exp(-Ke * time) - exp(-Ka * time))
      error (eps1 = c(.5))
      observe(cObs = cpred + eps1)
}
```

This is an example model file of a well-known model, and it shows how to code an explicit closed-form single-dose solution. Note that any text string that is initiated by '#' is treated as a comment and does not affect model execution. Later examples show how to create models using differential equations, which are more adaptable to multiple dosing regimens and to trial simulation.

The example above shows a style in which indentation is used consistently throughout. This makes the model self-outlining for readability, and indicates a careful discipline, which makes errors less likely.

Including files in the generated C code

If one or more of the following statement appears in the PML ***outside of the model definition***:

```
include(“MyIncludeFile.h”)
test(){ # model definition
   …
}
```

where `MyIncludeFile.h` is the name of any C-style include file (enclosed in double quotes), it results in the following code being inserted near the top of the generated C file Model.c:

```
#include(“MyIncludeFile.h”)
```

This can be useful for purposes such as allowing access to additional functions that a user might include in the compile-and-link step for models.

Column mappings

The column mapping file is an ASCII text file (*`.txt`) that contains a series of statements that define the association between model concepts and columns in a dataset:

`id(subject_id_column_name)`

Example:

`id(SubjectID)`

says that “SubjectID” is the data column signifying the subject identifier. SubjectID is not used by Phoenix, but the column mapping is still required. It is acceptable to map to a nonexistent column, such as: `id(zzzDummyID)`.

`time(time_column_name)`

Example:

`time(T)`

says that T is the data column signifying time. The time values can be either simple decimal numbers, or they can be in hh:mm[:sec] format, with an optional “AM” or “PM”. Note that 12:06AM =

0:06 = 0.1, and 1:30PM = 13:30 = 13.5. This formate works for hours, but it does not imply any particular time units are being used. The AM and PM suffixes can be either lower or upper case.

Normally, time increases monotonically from one row to the next within each subject. If it does not, an error message is generated. However, if there is a reset column, time is allowed to be reset when that occurs. Also, if the `/sort` option is sent to the engine, data is automatically sorted by subject ID and time, so data does not have to be initially ordered.

`reset(reset_column_name = c(lowvalue, highvalue))`

Example:

```
reset(RESET = c(3, 4))
```

says that RESET is the data column signifying a resetting of subject time. If the value in the reset column is between three and four inclusive, time is allowed to be reset on that row. Also, all compartments in the model are reset to their initial values.

`date(date_column_name[, format string [, century base]])`

Examples:

```
date(DATE)
date(DATE, mdy)
date(DATE, mdy, 1980)
```

says that `DATE` is the data column signifying the date. The default format of the date is month-day-year with arbitrary separators. If two digit years are given, they are assumed to be between 1980-2079, which is the default.

`covr(covariate_name <- column_name)`

Example:

```
covr(W <- BW)
```

says that `BW` is the data column signifying the model covariate `W`. If the model contains covariate variables, then every covariate must be mapped in this way, or else an error message is generated.

`fcovr(covariate_name <- column_name)`

Example:

```
fcovr(W <- BW)
```

`fcovr` is identical to `covr`, except for the handling of covariate value changes. A covariate is set whenever it has any non-null value in a data record. Normally if a covariate such as bodyweight (`BW`) is set to value `BW1` at time `T1`, and another value `BW2` is set to a subsequent time point `T2`, the second value `BW2` holds during the interval `(T1,T2)`, so it is carried back in time. Similarly, `BW1` holds at time `T1` and during the period extending back from `T1` to `T0`, the closest previous time where the covariate is set.

If `fcovr` is used, the first value `BW1` holds during the forward interval `(T1,T2)`, and gets reset to `BW2` at time `T2`. However, if the covariate is interpolated, it doesn't matter if `covr` or `fcovr` are used, because the value is linearly interpolated.

`obs(observation_variable_name <- column_name)`

Example:

```
obs(cObs <- Conc)
```

says that `Conc` is the data column signifying the model covariate `W`. Use the `obs` mapping for all observation types such as `observe`, `multi`, `count`, `event`, and `LL`.

Example:

```
obs(cObs <- Conc, bql = BQL)
```

also says that the data column `BQL` contains the flag specifying that the observed value is less than or equal to the value in column `Conc`. To use this feature, it is also necessary that the `BQL` option is used in the `obs` statement in the model.

`mdv(mdv_column_name)`

Example:

```
mdv(MDV)
```

says that `MDV` is the data column signifying “missing data values” for any observation. If this column is present, then on any given row it specifies if there are any missing observations on that row. If the `MDV` value is 0 (zero) or “.”, then the observation on that row is present, otherwise it is missing.

`dose(dosepoint_name <- column_name)`

Example:

```
dose(A1 <- Dose)
```

says that `Dose` is the data column signifying the amount of drug administered to dosepoint `A1`.

Example:

```
dose(A1 <- Dose, Rate)
```

also says that data column `Rate` specifies the infusion rate associated with the dose. If the rate is zero or unspecified, then the dose is a bolus. The concepts “bolus” and “infusion” are not limited to the central compartment, but can apply to a dosepoint on any compartment, including an absorption compartment.

There are also the statements `dose1` and `dose2`, whose syntax is identical to `dose`. These match up with the `dosepoint1` and `dosepoint2` statements in the model. This is because there can be more than one dosepoint with the same name, so multiple dosepoints are referred to by sequential numbers, such as dosepoint 1 and dosepoint 2. `dose` can be used as a synonym for `dose1`, and `dosepoint` can be used as a synonym for `dosepoint1`.

ss(`ss column_name, dose_cycle_description`)

Examples:

```
ss(SS, 10 bolus(A1) 24 dt)
ss(SS, Dose bolus(A1) II dt)
ss(SS, 10 bolus(A1) 16 dt 10 bolus(A1) 8 dt)
```

says that SS is the data column that brings the model to steady-state. On a given row, if the value in the SS column is other than 0 (zero) or “.”, the model is brought to steady state by running the dose cycle description as many times as necessary.

```
ss(SS, 10 bolus(A1) 24 dt)
```

In the above example, the dose cycle is “administer 10 units of drug in a bolus to dosepoint A1, and then wait 24 time units.” The dose cycle description has a very simple syntax in reverse polish notation (RPN). the syntax is:

Table 2-1. Dose cycle syntax

Option	Definition
number	provide a number for an ensuing operation.
column-name	provide a column name for ensuing operation.
bolus (dosepoint)	give the previous number as a bolus to a dosepoint.

Table 2-1. Dose cycle syntax

Option	Definition
dt	sleep for the length of time of the preceding number
inf(dosepoint)	take the previous two numbers as an amount and a rate and give an infusion to a dosepoint.
bolus2, inf2	same as `bolus` and `inf`, but for dosepoint2.
value op value	simple arithmetic operators. `op` = +, -, *, /, ^.

When defining a dose cycle, there must be at least one `dt` statement. In general, a `dt` statement should come at the end of the cycle, so that any infusions or time lags in the cycle finish before the start of the next cycle. If a dose occurs on the same data row as an `ss` statement, then the model is first brought to steady state, and then the dose is administered.

```
addl(ss_column_name, dose_cycle_description)
```

Examples:

```
addl(ADDL, 24 dt 10 bolus(A1))
addl(ADDL, II dt Dose bolus(A1))
```

says that ADDL is the data column signifying additional doses. On a given row, if the value in the ADDL column is other than 0 (zero) or “.”, then additional dose cycles are given according to the dose cycle description.

The syntax of the dose cycle description is the same as for `ss`. The `dt` statement should come first in the dose cycle, since ADDL is usually specified on the same row as a dose, and it indicates follow-on doses.

```
table(
      [optional_file]
      [optional_dosepoints]
      [optional_covariates]
      [optional_observations]
      [optional_times]
      variable_list
      )
```

Example:

```
table(file="foo.csv"
      time(0,10,seq(2,8,0.1))
      dose(A1)
      covr(BW)
      obs(Conc)
      BW, C, cObs, V, Ke
      )
```

says a table is generated in file `foo.csv`, which consists of the variables BW, C, cObs, V, and Ke, whose values are generated at times 0, 2, 2.1,… 7.9, 8, and 10. (Note that the `seq` operator specifies a sequence of numbers, so `seq(60,80,5)` is shorthand for “60, 65, 70, 75, 80”). Values are also generated at the times of observations of Conc, when BW changes, and when a dose is given to A1. The times do not need to be specified in order, because they are automatically sorted. If multiple table statements are used, then multiple tables are generated.

The following are the contents of a column mapping file for the Theophylline model example:

```
colstheo.txt
id(xid)
covr(dose<-dose)
covr(time<-time)
obs(cObs<-yobs)
```

General syntax conventions

- Variable names are case sensitive and cannot contain special characters such as a period “.”. They can contain an underscore “_”, but if they do they are not compatible with S-PLUS syntax. The first character of a variable name cannot be an underscore “_”.
- Column names are case sensitive and can contain special characters. However, if a column name contains a blank space, the data must be given in CSV format, and a special argument, `/csv`, must be given to the engine.
- Line boundaries are not significant. Statements can span multiple lines, except for comments. Characters that denote comments include.

  # ***comment...*** end-of-line (S-PLUS convention)

  /* ***comment...*** */ (multi-line, non-nesting, C convention)

  // ***comment...*** end-of-line (C++ convention)
- Block delimiters: { …} (curly brackets, S-PLUS convention)
- Statement delimiter: An optional semicolon (S-PLUS convention)
- Sub-statement delimiter: An optional comma
- Assignment operators:

  “=” sign (S-PLUS convention)

  “<-” (S-PLUS convention)
- Declaration of variables: Variable types are double precision so scoping is not needed (S-PLUS convention). Variables are of two types:
  - **Declared** variables are introduced by a declaration, such as `deriv` or `real`. These can be changed at points in time, such as in `sequence` statements.
  - **Functional** variables are introduced by being assigned at the top level of a model, such as `C = A1/V1`. They are regarded as being computed “all of the time.”
- Model member reference: Models inherently act as structure. “$” is the model component reference operator (S-PLUS convention)
- Although the Phoenix Modeling Language uses the `real` variable for designating real numbers, `double` is also acceptable.

Reserved and user-defined variable names

All of the variable names in the Phoenix Modeling Language can be user-defined. However, some variable names are considered to be reserved for syntactical reasons. These words appear in the model code as blue text.

The C++ runtime and math libraries use several reserved variable names. These names are listed in Appendix C, “Reserved Words”. However, users are able to define the C++ runtime and math variable names in any way they need.

Modeling syntax

- “Population PK model” on page 21
- “Closed-form models” on page 23
- “Transit Compartment models” on page 25
- “Action code” on page 27
- “Observations” on page 29
- “Math and special functions” on page 37
- “Dosing” on page 38
- “Covariates” on page 38
- “Modeling discontinuous events” on page 39
- “Sequence statements” on page 44
- “Sleep statements” on page 47
- “Time event switching in PML versus WinNonlin ASCII models” on page 47
- “Fixed effect parameter syntax” on page 47
- “Random effect parameter syntax” on page 48

Population PK model

The following example demonstrates the syntax for defining a population PK model.

```
mymodel(){
      ## STRUCTURAL MODEL SECTION
      deriv(aa = - aa * ka)
      deriv(a1 = aa * ka - a1 * cl/v)
      dosepoint(aa)
      c = a1 / v
      ## PARAMETER MODEL SECTION
      stparm(
            ka = tvKa * exp(nKa)
            cl = tvCl * exp(nCl)
            v = tvV * exp(nV)
      )
      fixef(
            tvKa = c(, 10,)
            tvCl = c(, 5,)
            tvV = c(, 8,)
17          )
18          ranef(
19                diag(nKa, nCl, nV) = c(1.0, 0.5, 0.6)
20          )
21          ## ERROR MODEL SECTION
22          error(eps1 = 0.01)
23          observe(cObs = c + eps1)
24    }
```

Lines 1-24 define a model called “mymodel.” It is a one-compartment, first-order model parameterized by clearance and volume. The model statements can be roughly grouped into sections for structural, parameter, and error models. The model contains several user-defined and reserved names.

Line 3 gives the differential equation for the absorption compartment. It is read as “the derivative of `aa` is `-aa * ka`.” The variable `aa` represents the amount of the drug in the absorption compartment.

Line 4 gives the differential equation for amount in the central compartment, `a1`.

> ***Important Note:*** PML works best when the right-hand-side of each differential equation has no time-discontinuities. An example of a system which is time-discontinuous is:
>
> ```
> deriv (a1 = -a1*cl/v)
> cl = (t < t1 ? cl1:cl2)
> ```
>
> This is time-discontinuous because clearance jumps at time `t1` from `cl1` to `cl2` and it appears on the right-hand-side of the differential equation for `a1`. This has the effect of causing the ODE solver to step back and forth over time `t1`, in ever smaller steps, attempting to reduce its error. It is much better to use the `sequence` statement (explained below), which can run the ODE solver up to particular times (called change points), then perform some discontinuous modifications to the model and run the ODE solver forward again. In fact, if **Matrix Exponent** is requested, it will not run this code. It will switch to a different solver, because it requires that the system be not only continuous, but linear between change points.
>
> The use of `t`, representing time since the subject began processing, is discouraged, because it is most often used in the above manner.

Line 5, the dosepoint statement, says that `aa`, the absorption compartment, can receive doses. If the central compartment can also take doses, the model can include an additional dosepoint statement.

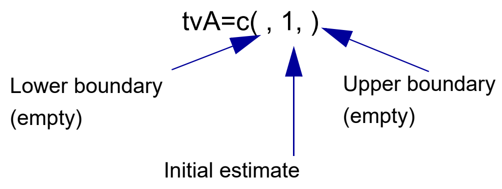
Line 6 is a simple `assignment` statement saying that concentration `c` in the central compartment is equal to the amount in the central compartment `a1` divided by volume `v`. This quantity is related to the observed quantity in line 23.

Lines 8-12 identify the structural parameters and their associations with the fixed and random effects. If a model is used for single-subject estimation, only the fixed effects are estimated. The model can include any number of stparm statements. Structural parameter statements should only include fixed effects, random effects, and covariates. They should not include variables that are evaluated as `assignment` statements. Structural parameter statements are executed before anything else and are only re-executed during a given iteration if a covariate changes, so any variables from `assignment` statements will be undefined on the initial execution of the stparm statements, possibly leading to model failure.

Lines 13-17 identify the population fixed effect parameters (thetas). It is recommended that a consistent naming convention is used to make the model more easily understood by others. In this example, variables representing typical values start with the letters “tv,” followed by a capitalized variable name, such as `tvCl` for clearance or `tvV` for volume. The model can include any number of fixed effect statements.

After each fixed effect is an optional `assignment`, providing either a single number representing the initial value of the parameter or a list of three numbers representing a lower bound, an initial value, and an upper bound, in that order.

If the `assignment` is used, then the initial estimate must be provided. The lower and upper bound values can be omitted, but the order must be maintained by using blank spaces and commas as delimiters. The correct syntax is:



If one value is provided it is assumed that the lower and upper boundaries are not being supplied, but the syntax must be correct. For example, `tvA=c(1)` does not work. However, users can omit the parenthesis and use `tvA=1`, and the PML assumes that one is the initial value assigned to the parameter.

Lines 18-20 identify the random effects (etas). In this model, there are three random effect variables grouped into a single block, which causes a diagonal omega matrix to be estimated. The initial value of the omega matrix is given as a list of numbers. Multiple blocks are supported. The model can include any number of `ranef` statements.

`Assignment` statements are performed in the order that they are displayed in the model. Otherwise, the statement order is flexible.

Line 22 identifies that there is an observational error variable (epsilon) called `eps1`, and its initial estimate of standard deviation is given. Supplying the initial estimate of standard deviation is optional. Models can include multiple error variables, but only one per observe statement.

Additional error variables are converted internally so that:

```
observe(Yobs = Y*(1+eps1)+eps2); error(eps1); error(eps2)
```

is equivalent to:

```
observe(Yobs = Y*(1+eps1)+eps2*eps1); error(eps1); fixef(eps2=c(0,1,))
```

Line 23 specifies the observed quantity `cObs` and says it is equal to the predicted concentration `c` plus the error variable. The expression must contain one and only one error variable. Various PK and PD error models can be expressed in this way.

Only a single error variable can be used in an `observe` statement such as the one on line 23. Compound residual error models for any given observation, such as mixed additive and proportional, must be built using a combination of fixed effects and a single error variable rather than multiple error variables.

For example, `observe(cObs=c*(1+eps1)+eps1*scale1)`is correct and `observe(cObs=c*(1+eps1)+eps2)` is not correct.

Closed-form models

The PML contains built-in support for closed-form models with up to three compartments, and with optional first order input, optional lag time, and optional bioavailability. The models are implemented recursively so they can handle any combination of dosing scenarios.

Closed-form example (micro-constant parameterization):

```
cfMicro(A1, Ke)
```

Specifies a 1-compartment model. `A1` is the amount in the central compartment, and `Ke` is the elimination rate parameter.

```
cfMicro(A1, Ke, K12, K21)
```

Specifies a 2-compartment model, same as the 1-compartment model, but with two additional parameters K12 and K21.

```
cfMicro(A1, Ke, K12, K21, K13, K31)
```

Specifies a 3-compartment model, same as the 2-compartment model, but with two additional parameters K13 and K31.

```
cfMicro(A1, Ke, first = (Aa = Ka))
```

Specifies first-order input to any of the models above. Aa is the amount in the absorption compartment, and Ka is the absorption rate.

Closed-form example (macro-constant parameterization, WinNonlin-compatible):

```
cfMacro(A1, C1, A1Dose, A, Alpha, strip=A1Strip)
cfMacro(A1, C1, A1Dose, A, Alpha, B, Beta, strip=A1Strip)
cfMacro(A1, C1, A1Dose, A, Alpha, B, Beta, C, Gamma, strip=A1Strip)
```

Specifies 1, 2, and 3-compartment models, in which observed concentration `C1` is modeled as the exponential sum `A*exp(-t*Alpha)+B*exp(-t*Beta)+C*exp(-t*Gamma)`. A1 is the dosing target, but is not a variable that can be referred to in the model. `A1Strip` is the name of a covariate specifying the “stripping dose” used to fit the model. The meaning, for example in the 2-compartment case, is that at the time of initial dose, `C1=(A+B)=A1Strip/V` where V is not a parameter in the model. V is implicitly equal to `A1Strip/(A+B)`. `A1Dose` is a variable that records the initial bolus amount. If the optional argument `strip=A1Strip` is not given, the initial bolus amount is used as the stripping dose. The model can be used with any dosing sequence, but it is an error if there is no specified stripping dose and no initial bolus.

```
cfMacro(Aa, C1, AaDose, A, Alpha, Ka, strip=A1Strip)
```

This model is the same as above except for the additional final parameter Ka, signifying first-order absorption. In this case, the model without first-order absorption is convolved with the one-term first-order absorption term, resulting in the final model. Everything else is the same as above.

Closed-form example (macro-constant parameterization, simple form):

```
cfMacro1(A, Alpha)
```

Specifies a 1-compartment model. A is the amount in the central compartment, and `Alpha` is the elimination rate parameter. It can be used with any dosing sequence, but its response to a bolus dose is `A = D*exp(-t*Alpha)`.

```
cfMacro1(A, Alpha, B, Beta)
```

Specifies a 2-compartment model. A is the amount in the central compartment. It can be used with any dosing sequence, but its response to a bolus dose is `D*[(1-B)*exp(-t*Alpha) + B*exp(-t*Beta)]`.

```
cfMacro1(A, Alpha, B, Beta, C, Gamma)
```

Specifies a 3-compartment model. A is the amount in the central compartment. It can be used with any dosing sequence, but its response to a bolus dose is `D*[(1-B-C)*exp(-t*Alpha) + B*exp(-t*Beta) + C*exp(-t*Gamma)]`.

```
cfMacro1(A, Alpha, first = (Aa = Ka))
```

Any of the above models can be converted to first-order absorption by putting the following after the other arguments.

```
, first = (Aa = Ka)
```

Aa is the amount in the absorption compartment, and Ka is the absorption rate. As above, A is the amount in the central compartment. It can be used with any dosing sequence, and it allows dosing to both Aa and A. (The model actually is two models superimposed, one is the base model, and the other is the base model convolved with a first-order model.)

Transit Compartment models

For modeling a time-delay as a sequence of transit compartments, there is the “transit” statement:

```
transit(<final compartment name>
   , <mean transit time expression>
   , <number of transit stages expression>
   [, max = nnn]
   [, in = <input rate expression>]
   [, out = <output rate expression>]
  )
```

For example, the following code models extravascular input with delay:

```
transit(Aa, mtt, ntr, max = 50, out = -Aa * Ka)
dosepoint(Aa)
deriv(A1 = Aa * Ka - A1 * Ke)
```

- Aa is the name of the final compartment in a hidden chain of 50 compartments.
- `mtt` is the structural parameter representing the mean transit lag time of drug compound in the chain.
- `ntr` (minimum 0) is the structural parameter representing one less than the number of transit stages. Fractional values as well as integer are accepted. Fractional values of `ntr` are modeled by logarithmic interpolation, corrected so as to closely approximate a closed-form solution.The role of the `ntr` parameter is to control the sigmoidicity of the rise of Aa in response to a single dose, where higher values of `ntr` indicate faster rise time.

The flow rate parameter between compartments is $k_{tr} = (ntr+1)/mtt$.

- `out` is additional flow rate out of (or into) the final compartment Aa.
- `in`, if provided, represents additional flow rate into the same upstream compartment that receives doses.
- Care should be taken in specifying “`max = nnn`”, because `nnn` determines the number of additional hidden differential equations. The default is 50, and the maximum is truncated at 200. `ntr` is truncated to range between zero and `nnn`.

The following images illustrate how this can be visualized.

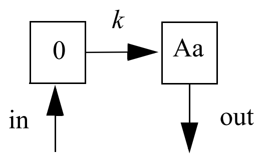


Figure 2-1. Model for ntr = 0 (the smallest possible value)

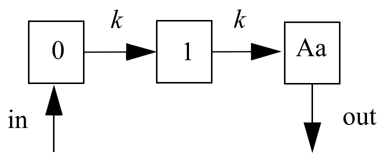


Figure 2-2. Model for ntr = 1

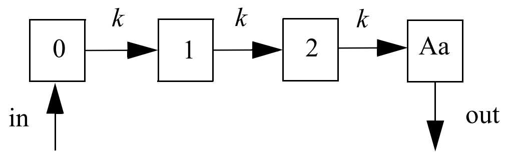


Figure 2-3. Model for ntr = 2

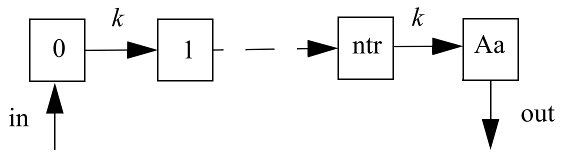


Figure 2-4. Model for ntr = more

The following model is implemented with extra upstream compartments, and `ntr` effectively chooses which upstream compartment will be considered compartment 0 and will receive doses:

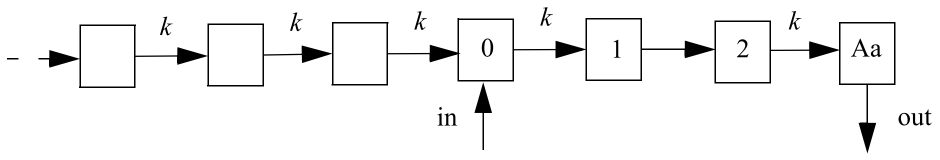


Figure 2-5. Model with extra upstream compartments

Doses go into compartment `0`, as well as any additional rate given by the *in* keyword. The value is read from the final compartment, which can have a supplemental output rate given by the `out` keyword. (If artificial dosing is done, such as by saving Aa `= Aa + d` in a sequence statement, it is understood as adding `d` to compartment `0`, not to compartment Aa.)

The following model shows how the interpolation is done, where `x` is an auxiliary compartment.

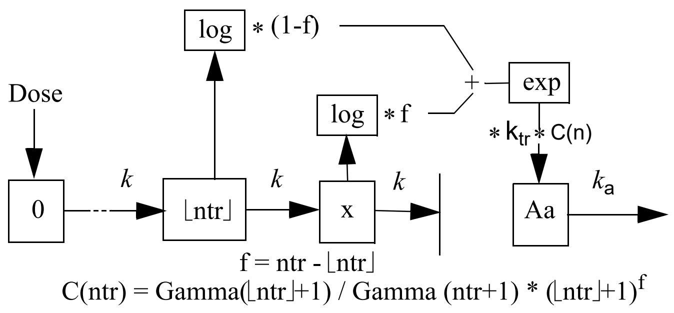


Figure 2-6. Interpolation process

Disclaimer: In the case where `ntr` is an integer, the `transit` statement is completely accurate for all inputs. If `ntr` is not an integer, but dosing consists of bolus doses sufficiently separated in time, it is also completely accurate. However, if `ntr` is a small non-integer, like 0.5, and multiple boluses occur close together or an infusion is given, the output in Aa is under-predicted by as much as 5%. The under-prediction becomes progressively smaller as `ntr` increases, but is always zero if `ntr` is an integer. This is an artifact of the interpolation formula used for fractional values of `ntr`.

Action code

This section discusses action code and what it does. Some basic action code statements include `dobefore`, `doafter`, `sequence`, and `sleep`.

First, the framework within which action code works must be explained.

A PML model either is or is not truly time-based. A model is truly time-based if:

- It contains a `deriv` or a `urinecpt` statement.
- It implicitly contains a `deriv` statement, such as an `event` or `count` statement, which causes the model to calculate a hidden differential equation that accumulates, or integrates, the hazard rate.
- It contains a `cfMicro` or a `cfMacro` statement.

If a model is truly time-based, then it automatically contains a variable called `t`, and time is assumed to be the independent variable. The model's input dataset must contain columns for time values and for any covariate values. Only truly time-based model can use multiple dose inputs.

If a model is not truly time-based, then covariates are its only inputs. Since the model does not automatically know what the independent variable is, it must be specified via syntax in the observe statement, such as:

```
observe(EObs(C) = …)
```

where the `(C)` tells the model that C is the independent variable.

In a non time-based model, there is no default variable for time (`t`) as there is for a time-based model. To include this variable, the user needs to do ***one*** of the following:

- Change the model into a time-based model by including a statement such as:
  `deriv(foo = 0)`

Or

- Make `t` a covariate (e.g., `covariate(t)`, be sure to map `t` and include the following statement to indicate the independent variable:
  `observe(Cobs(t) = C + CEps)`

Or

- Make `Time` a covariate (e.g., `covariate(Time)`), then replace `t` with `Time` in the model, and check the mapping.

Note: If C is not given on the same data row as EObs, that observation is ignored. If the user does not specify the independent variable in the observe statement, as for example `observe(EObs = E*exp(eps))`, observations of EObs are processed regardless, even though they are not associated with a corresponding independent variable.

If a model is truly time-based, it executes in a recursive fashion. That means model execution consists of a series of continuous simulation intervals, with stops between each interval.

In a continuous simulation interval, the state of the model evolves forward through time under control of an ODE solver such as Matrix Exponent, Runge-Kutta (non-stiff), Gear (stiff, analytic and finite difference Jacobian), Closed-Form (no ODE solver used), or a combination of these four.

Discontinuous actions can occur during a stop between continuous simulation intervals. Discontinuous actions include:

- delivering a dose into a compartment all at once as opposed to spreading the delivery over time
- start of an infusion
- end of an infusion

- taking of an observation
- setting a covariate value
- actions associated with an observation or dose, when they are specified with a `dobefore` or `doafter` action block
- actions specified with any `sequence` block.

Variables in a model fall into categories, depending on whether they can or cannot be modified when the model is stopped.

- Integrator variables (variables on the left side of `deriv` statements) such as compartment amounts, ***can*** be modified when the model is stopped. When the model is simulating, these variables are controlled by the ODE solver.
- Variables introduced with the `real` keyword, such as `real(G)`, ***can*** be modified when and only when the model stops running.
- Variables introduced with only an `assignment` statement, such as `C = A/V`, ***cannot*** be modified when the model is stopped. The variables are considered to only be functions of the continuous model state.

It is allowable to have multiple `assignment` statements assigned to the same variable, in which case the order between them matters. For example: `E = E0; E = E + E1; etc`. This statement is essentially a single `assignment` statement because all assignments could all be collapsed into one `assignment` statement. Note that variables on the right-side of `assignment` statements must be defined prior to their use.

A block refers to a pair of curly brackets `{...}` with zero or more statements in between them.

The `sequence` statement, of the form `sequence{...}`, specifies a sequence of actions to be performed when the model is stopped. This sequence acts like a typical programming language sequence in that order matters, because the sequence statements are performed one at a time, in order.

Caution: In PML models, `sequence` and `assignment` statements are the only statements in which order matters.

For all other statements in PML models, the order of the statements does not matter. This means that the statements inside a sequence block are very different from other statements in PML models. Sequence statements consist of:

- Assignments (only for variables that can be modified when the model is stopped)
- if(test-expression) statement-or-block [else statement-or-block]
- while(test-expression) statement-or-block
- sleep(duration-expression)
- function calls

These statements only run when the model is stopped. The model is considered to be “stopped” before it is executed. This means that sequence statements are executed before the model is “started”, and run until a `sleep` statement is encountered.

When a `sleep` statement is encountered, its argument, which is a delta-time, is calculated and then the sequence stops executing. The sequence is then put into a queue until it is used at a future time. At that time, the model stops, and the sequence block commences executing where it left off.

A model can contain multiple sequence blocks, and they are executed in a nearly parallel manner. If there are multiple sequence blocks, ***no assumptions should be made about which block is executed first***.

Because model execution stops for dose and observation events, actions can be performed at those times. For example:

```
observe(CObs = C + eps, doafter = {A = 0;})
```

In this example, immediately after `CObs` is observed, variable A is set to 0 (zero), where A could be the drug amount in a compartment. The action block consists of curly brackets {...} containing zero or more statements. The statements can be optionally separated by semicolons.

Note: The statements allowed in the `observe` statement as the same as those allowed in the `sequence` statement, except that `sleep` is not allowed in the `observe` statement.

Observations

Observations are the link between the model and the data. The model describes the relationships between covariates, parameters, and variables. The data represent a random sampling of the system that the model describes. The various types of observation statements that are available in the Phoenix Modeling Language serve to build a statistical structure around the likelihood of a given set of data.

Observation statements are used to build the likelihood function that is maximized during the modeling process. The observation statements indicate how to use the data in the context of the model.

- "Count statement for Count models" on page 29
- "Event statement for Survival models" on page 32
- "LL statement for Log Likelihood models" on page 34
- "Multi statement for Multinomial models" on page 34
- "Observe statement for Normal-inverse Gaussian Residual models" on page 37
- "Ordinal statement for Ordinal Responses" on page 37
- "Observation statement action codes:" on page 37

Count statement for Count models

```
count(observed variable, hazard expression[, options][, action code])
```

Similar to event, but instead of observing an occurrence variable, an occurrence count is observed. The log-likelihood is based on a Poisson or Negative Binomial distribution whose mean is the integrated hazard since the last observation. The options are:

```
, beta = <expression>
```

The presence of the *beta* option makes the distribution Negative Binomial, where the variance is `var = mean*[1+mean*alpha^power), and alpha=exp(beta)`

```
, power = <expression>
```

Power of alpha, default(1). Zero-inflation can be applied to either the Poisson or Negative-Binomial distributions, in one of two ways, by means of simply specifying the extra probability of zero, by giving the `zprob` argument, or by giving an inverse link function with `ilink` and its argument with `linkp`.

```
, zprob = <expression>
```

Zero-inflation probability, default(0) (incompatible with following two options)

```
, link = "ilogit", "iprobit"
```

Or other inverse link function. If not specified, it is blank.

```
, linkp = <expression>
```

Argument to inverse link function

`, noreset`

When present, this option will prevent the accumulated hazard from resetting after each observation.

For the default Poisson distribution, the mean and variance are equal. If that shows inadequate variance, use of the `beta` option, with optional *power*, may be indicated. Care should be taken, since if the value of `beta*power` becomes too negative, that means the distribution is very close to Poisson and the Negative Binomial distribution may incur a performance cost.

Note: The Negative-Binomial Distribution log likelihood expression can generate unreasonable results for reasonable cases. For example, if count data that is actually Poisson is used, the parameter r in the usual (r,p) parameterization can become very large (and p becomes very small). The large value of r can cause a problem in the log gamma function that is used in the evaluation. So such data, which is completely reasonable, may give an unreasonable fit if care is not taken in how the log likelihood is evaluated numerically.

All about Count models

Observing a *count*, such as the number of episodes of vertigo over a prior time interval of one week, is also a hazard-based measurement. The simplest model of the `count` is called a Poisson distribution and it is closely related to the coin-toss process in the time-to-event model (discussed in "All about Time-to-Event modeling" on page 32). In this model, the mean (average) count of events is simply the accumulated hazard. One can think of the hazard as simply the average number of events per time unit, so the longer the time, the more events. Also, in the Poisson distribution, the variance of the event count is equal to the mean.

In some cases, if one tries to fit a distribution to the event counts, it is found that the variance is greater than what a Poisson distribution would predict. In this case, it is usual to replace the Poisson distribution with a Negative Binomial distribution, which is very similar to the Poisson, except that it contains an additional parameter indicating how much to inflate the variance.

Another alternative is to notice that a `count` of 0 (zero) is more likely to occur than what would be predicted by either a Poisson or Negative Binomial distribution. If so, this is called "zero inflation." All of these alternatives can be modeled with the `count` statement.

The simplest case is a Poisson-distributed `count`:

```
count(n, h)
```

where `n` is the name of the observed variable, taking any non-negative integer value. `h` is the hazard expression, which can be time-varying.

To make it a Negative Binomial distribution, the `beta` keyword can be employed:

```
count(n, h, beta = b)
```

where `b` is the beta expression, taking any real value. The beta expression inflates the variance of the distribution by a factor `(1 + exp(b))`, so if `b` is strongly negative, `exp(b)` is very small, so the variance is inflated almost not at all. If `b` is zero or more, then `exp(b)` is one or more, so the variance is inflated by an appreciable factor. The reason for encoding the variance inflation this way is to make it difficult to have a variance inflation factor too close to unity, because 1) that makes it equivalent to Poisson, and 2) the computation of the log-likelihood can become very slow.

If the `beta` keyword is present, an additional optional keyword may be used, `power`:

```
count(n, h, beta = b, power = p)
```

in which case, the variance inflation factor is `(1 + exp(b)^p)`, which gives a little more control over the shape of the variance inflation function. If the `power` is not given, its default value is unity.

Whether the Poisson or Negative Binomial distribution is used, zero-inflation is an option, by using the `zprob` keyword:

```
count(n, h, zprob = z)
```

where `z` is the additional probability to be given to the response `n = 0`. Alternatively, the probability can be given through a link function, using keywords `ilink` and `linkp`:

```
count(n, h, ilink = ilogit, linkp = x)
```

where `x` is any real-numbered value, meaning that `ilogit(x)` yields the probability to be used for zero-inflation.

Count models can of course be written with the `LL` statement, but it can get complicated. In the simple Poisson case, it is:

```
deriv(cumhaz = h)
LL(n, lpois(cumhaz, n), doafter = {cumhaz = 0})
```

where `cumhaz` is the accumulated hazard over the time interval since the preceding observation, and `n` is the observed number of events in the interval. `lpois` is the built-in function giving the log-likelihood of a Poisson distribution having mean `cumhaz`. After the observation, the accumulated hazard must be reset to zero, in preparation for the following observation.

If the simple Poisson model is to be augmented with zero-inflation, it looks like this:

```
deriv(cumhaz = h)
LL(n, (n == 0 ? log(z + (1-z)*ppois(cumhaz, 0)):
      log(1-z) + lpois(cumhaz, n)
     )
   , doafter = {cumhaz = 0}
  )
```

where `z` is the excess probability of seeing zero. Think of it this way: before every observation, the subject flips a coin. If it comes up “heads” (with probability `z`), then a count of zero is reported. If it comes up “tails” (with probability `1-z`), then the reported count is drawn from a Poisson distribution, which might also report zero. So, if zero is seen, its probability is `z + (1-z)*pois(cumhaz, 0)`, where *pois* is the Poisson probability function. On the other hand, if a count `n > 0` is seen, the coin must have come up “tails,” so the probability of that happening is `(1-z)*pois(cumhaz, n)`. The log-likelihood given in the `LL` statement is just the log of all that.

If it is desired to use the link function instead of `z`, `z` can be replaced by `ilogit(x)`. (There are a variety of built-in link functions, including `iloglog`, `icloglog`, and `iprobit`.)

If the Negative Binomial model is to be used, because Poisson does not have sufficient variance, in place of:

```
lpois(cumhaz, n)
```

the expression:

```
lnegbin(cumhaz, beta, power, n)
```

is used instead, where the meaning of `beta` and `power` are as explained above. If `beta` is zero, that means the variance is inflated by a factor of two. Typically, `beta` would be something estimated. If it is not desired to use the `power` argument, the default power of one should be used.

Event statement for Survival models

```
event(observed variable, expression [, action code])
```

Specifies an occur `observed variable`, which has two values: `1`, which means the event occurred, or `0`, which means the event did not occur. The hazard is given by the `expression`.

The `event` statement creates a special hidden differential equation to accumulate, or integrate, the hazard rate, which is defined by the expression in the second argument. This integration is reset whenever the occur variable is observed, so the integral extends from the time `t0` of the previous occur observation to `t1`, the time of the current observation. Let `cum_hazard` = integral of the hazard during the period `[t0,t1]`:

$$\texttt{cum\_hazard} = \int_{t0}^{t1} h(t)dt\,.$$

Then the probability that an event will not occur in the period is: `S=exp(-cum_hazard)`. Therefore, if the period terminates with an observation `occur = 0` at `t1`, the likelihood is S. If the period terminates at `t1` because an event occurred at `time = t1 (occur = 1)`, then the likelihood is `S*hazard(t1)`, where `hazard(t1)` is the hazard rate at `t1`. These likelihood computations are performed automatically whenever an `occur` observation is made.

Note: The observations of `0` (no event) can occur at pre-defined sampling points, but observations of `1` (event occurred) are made at the time of the event.

Event models are inherently time based, and require a mapping for a time value.

All about Time-to-Event modeling

Consider a process modeled as a series of coin-tosses, where at each toss, if the coin comes up “heads,” that means an event occurred and the process stops. Otherwise, if it comes up “tails,” the coin is tossed again. The graph below shows that process if the probability of “heads” is 0.1, and the probability of “tails” is 0.9.

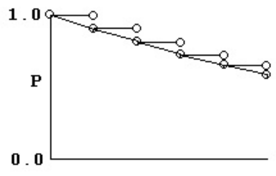


Figure 2-7. Coin toss probability graph

It is easy to see that the probability of getting to time 5 without getting a “heads” is 0.9 multiplied by itself 5 times. Similarly, the probability of getting a “heads” at time 5 is 0.1 multiplied by the probability of getting to time 4 without getting “heads” or 0.9^4 * 0.1.

To put it in symbols, if the probability of “heads” is p, then the probability of “heads” at time n is:

$$(1\text{-}p)(1\text{-}p)\ \ldots\ n\text{-}1 \text{ times}\ \ldots\ (1\text{-}p)\,p$$

Since in model fitting the log of the probability is desired, and since, if p is small, $log(1\text{-}p)$ is basically $\text{-}p$, it can be said that the log of the probability of “heads” at time n is:

$$\text{-}p\ \text{-}p\ \ldots\ n\text{-}1 \text{ times}\ \ldots\ \text{-}p + log(p)$$

Note that p does not have to be a constant. It can be different at one time versus another.

The concept of “hazard,” h, is simply probability per unit time. So if one cuts the time between tosses in half, and also cuts the probability of “heads” in half, the process has the same hazard. It also has much the same shape, except that the tossing times come twice as close together. In this way, the time between tosses can become infinitesimal and the curve becomes smooth.

If one looks at it that way, then the probability that “heads” occurs at time t is just:

$$\exp\left(-\int_0^t h(x)dx\right)h(t)$$

where the exponential part is the probability of no “heads” up to time t, and $h(t)$ is the instantaneous probability of “heads” occurring at time t. Again, note that hazard $h(t)$ need not be constant over time. If $h(t)$ is simply h, then the above simplifies to the possibly more familiar:

$$\exp(-ht)h$$

The log of the probability is:

$$\log\left[\exp\left(-\int_0^t h(x)dx\right)h(t)\right] = -\int_0^t h(x)dx + \log(h(t))$$

In other words, it consists of two parts. One part is the negative time integral of the hazard, and that represents the log of the probability that nothing happened in the interval up to time t. The second part is the log of the instantaneous hazard at time t, representing the probability that the event occurred at time t. (Actually, this last term is $\log(h(t) + 10^{-8})$ as a protection against the possibility that $h(t)$ is zero.)

The `event` statement models this process. It is very simple:

```
event(occur, h)
```

where `h` is an arbitrary hazard function, and `occur` is the name of an observed variable. `occur` is observed on one or more lines of the input data. If its value is `1` on a line having a particular time, that means the event occurred at that time, and it did not occur any time prior, since the beginning or since the time of the prior observation of `occur`.

If the observed value of `occur` is `0`, that means the event did not happen in the prior time interval, and it did ***not*** happen now. This is known as “right censoring” and is useful to represent if subjects, for example, withdraw from a study with no information about what happens to them afterward. It is easy to see how the log-likelihood of this is calculated. It is only necessary to omit the *log(h)* term.

Other kinds of censoring are possible. If `occur` equals 2, that means the event occurred one or more times in the prior interval, but it is not known when or how many times. If `occur` is a negative number like `-3`, that means the event occurred three times in the prior interval, but it is not known when. There is a special value of `occur`, `-999999`, meaning there is no information at all about the prior interval, as if the subject had amnesia. These are all variations on “interval censoring.” The log-likelihoods for all these possibilities are easily understood as variations on the formulas above.

This can be done with the log-likelihood (`LL`) statement instead, as follows:

```
deriv(cumhaz = h)
LL(occur, -cumhaz + occur*log(h), doafter = {cumhaz = 0})
```

The deriv statement is a differential equation that integrates the hazard. The `LL` statement says that variable `occur` is observed and it is either `1` (the event occurred) or `0` (it did not occur). It gives the log-likelihood in either case. Then, after performing the observation, the accumulated hazard is set to zero. This allows for the possibility of multiple occurrences.

LL statement for Log Likelihood models

```
LL(observed_variable, expression[, simulate = {simulation_code}]
  [, action code])
```

This statement specifies there is an observed variable, and when it is observed, its log-likelihood is the given expression. Optional action code is executed before or after the observation. If the “simulate” keyword is present, then during simulation or predictive check, the simulation code can assign a value to the observed variable.

The following is an example of a time to event model, illustrating how `simulate` can work on the `LL` statement.

```
covariate(DOSETOT,cycledays,uni01,timeforhistograms)
deriv(E = Kin *DOSETOT/cycledays - Kout * E)
sequence{E = E0}
real(u, i, prob)
LL(EObs
   ,-E + EObs*log(E) -lgamm(EObs+1)
   , simulate = {
      u = unif()
      prob = 0
      i = 0
      prob = prob + exp(-E + i*log(E) -lgamm(i+1))
      while(u >= prob){
         prob = prob + exp(-E + i*log(E) -lgamm(i+1))
         i = i + 1
         }
      EObs = i
   }
)
```

In the example above, `EObs` is the observed variable and `-E + EObs*log(E) -lgamm(EObs+1)` is the expression. The optional action follows the `simulate` keyword. It is separate from the last action code `[, action code]` (e.g. `[,doafter={E=0}]`).

Multi statement for Multinomial models

```
multi(observed variable, inverse link function(, expression)*
   [, action code])
```

This statement specifies an integer-valued categorical observed variable. The name of an `inverse link function` is given, such as `ilogit`. The next part of the statement is a series of offset expressions in ascending order, such as `C-X01` or `C-X12`, where `X01` is the value of `C` that evenly divides the response between zero and one, and `X12` divides the response between one and two.

This relationship between offset expressions is illustrated below, but without using a variable in the expression. The domain of the parameters `X01` and `X12` exists along the unbounded real line. The goal is to divide the range of the inverse function (0,1) into the probabilities of the categorical observations. This preserves the constraint that the sum of the probabilities equals one.

In the illustration below, the first breakpoint, proceeding from left to right, is `X01`. The value of the inverse function (ilogit, in this case) is taken at `X01` and `P0`, which is the probability of the first category, is `P0 = ilogit(X01)`. The next breakpoint is `X12`, and the probability of observing the second category is `P1 = ilogit(X12) - ilogit(X01)`, which is the cumulative probability between the first and second breakpoints. The third observation has probability `P2 = 1 - P0 - P1`, which is the remainder of the cumulative probability.

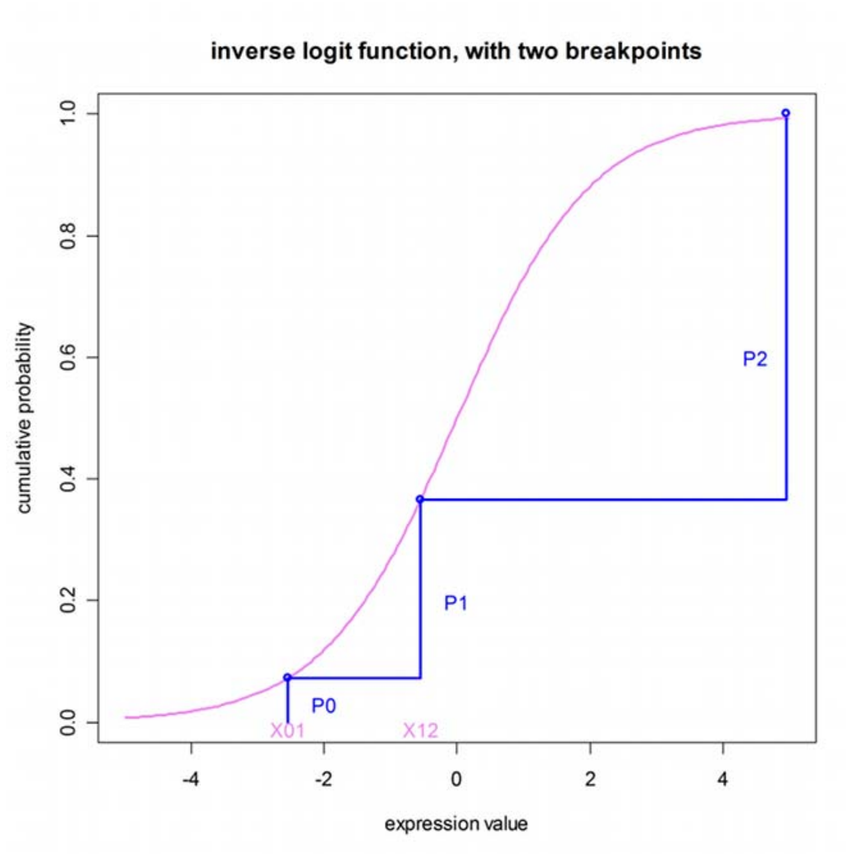


Figure 2-8. Relationship between offset expressions

It is simple to extend the example beyond simple values of `X01` and `X12`, to include a function of covariates. Given the relationship between the category probabilities and the probabilities, it is easy to why the initial estimates of the parameters should be given in such a way as to not cause the computed values of any of the probabilities to be negative. It is imperative that initial conditions be chosen carefully to ensure convergence.

All about Multinomial (ordered categorical) responses

Consider a model in which an observation can take values zero, one, and two. No matter what value concentration `C` is, any value of the observation is possible, but `C` affects the relative probabilities of the observed values. If `C` is low, the most likely observation is zero. If it is high, the most likely observation is two. In the middle, there is a value of `C` at which an observation of one is more likely than at other values of `C`.

The following figure illustrates the concept. At any value of `C`, there is a probability of observing zero, called `p0`. Similarly for one and two. The probability is given by the inverse of a link function, typically `logit`. In this picture, there are two curves. The left-hand curve is `ilogit(C - c1)` and it is the probability that the observation is ³1. The right-hand curve is `ilogit(C - c2)`, and it is the probability that the observation is ³2. The probability of observing one (`p1`) is the difference between the two curves. When doing model-fitting, the task is to find the optimum values *c1* and *c2*. Note that `c2` is the value of `C` at which the probability of observing two (`p2`) is exactly 1/2, and that `c1` is the value of `C` at which the probability of observing a value greater than or equal to one `(p1+p2)` is exactly 1/

2. Note also that `c1` and `c2` have to be in ascending order, resulting in the curves being in descending order.

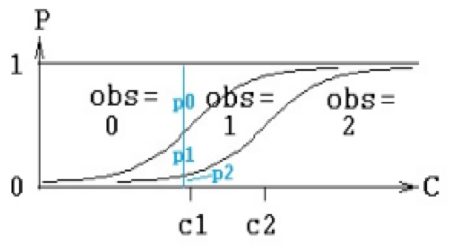


Figure 2-9. Multinomial responses

There are statements in PML for modeling such a response: `multi`, and `ordinal`, and it can also be done with the general log-likelihood statement, `LL`. The `multi` statement for the above picture is this:

```
multi(obs, ilogit, C - c1, C - c2)
```

`obs` is the name of the observed variable, `ilogit` is the inverse link function, and the remaining two arguments are the inputs to the inverse link function for each of the two curves. Since `c1` and `c2` are in ascending order, the inputs for the curves, `C - c1` and `C - c2`, are in descending order.

A more widely accepted way to express such a model is given by logistic regression, as in:

P(obs >= i) = ilogit(b*C + a_i)

where b is a slope (scale) parameter, and each a_i is an intercept parameter. The ordinal statement expresses it this way:

```
ordinal(obs, ilogit, C, b, a1, a2)
```

where the a_i are in ascending order. This is equivalent to the multi statement:

```
multi(obs, ilogit, -(b*C+a1), -(b*C+a2))
```

where, since the a_i are in ascending order, the arguments -(b*C+a_i) are in descending order, as they must be for the `multi` statement.

To do all this with the log-likelihood statement (`LL`) requires calculating the probabilities oneself, as shown below. Using the original parameterization with `c1` and `c2`:

```
pge1 = ilogit(C - c1)
pge2 = ilogit(C - c2)
LL(obs, obs == 0 ? log(1 - pge1):
        obs == 1 ? log(pge1 - pge2):
                   log(pge2 – 0)
)
```

The first statement computes the first curve, the probability that the observation is greater than or equal to one, `pge1`. The second statement computes the second curve, the probability that the observation is greater than or equal to two, `pge2`. Note that these are in descending order, because the probability of observing two has to be less than (or equal to) the probability of observing one or two.

The third statement says `obs` is the observed variable, and if its value is zero, then its log-likelihood is the log of the probability of zero, where the probability of zero is one minus the probability of greater than or equal to one, i.e., `log(1 - pge1)`. Similarly, if the observation is one, its probability is `pge2 - pge1`. Note that since `pg1e > pge2`, the probability of one is non-negative. Similarly, if the observation is two, its probability is `pge2 - pge3`, where `pge3` is zero because three is not a possible observation.

If, on the other hand, one were to use the typical slope-intercept parameterization from logistic regression, the first two lines of code would look like this:

```
pge1 = ilogit(-(b*C+a1))
pge2 = ilogit(-(b*C+a2))
```

and the `LL` statement would be the same.

Observe statement for Normal-inverse Gaussian Residual models

```
observe(observedVariable([independentVariable]) =
   expression[, bql][, action code])
```

The above statement specifies that the `observedVariable` is a function of some prediction and some Gaussian error. The `bql` option specifies that a lower limit of quantification can be applied to this observation, allowing for occurrence observations to be included.

If action code is given, that indicates actions to be performed before or after each observation. If there are no differential equations, the `independentVariable` for the observations can be specified. This allows the Phoenix Model object to produce the appropriate output plots and worksheets.

For example, a **Michaelis-Menten model** of reaction kinetics can be written as:

```
observe(RxnRate (C) = Vmax*C/(C+Km) + eps)
```

Ordinal statement for Ordinal Responses

```
ordinal(observedVariable, inverseLinkFunction,
   explanatoryVariable, beta, alpha0, alpha1, …)
```

For example:

```
ordinal(Y, ilogit, C, slope, intercept0, intercept1, …)
```

where the intercepts are in numerically ascending order. It fits the model:

```
P(Y ? i | C) = ilogit(C*slope + intercepti)
```

And if there are `m` values of Y, they are 0, 1, … *m*-1, and there are `m`-1 intercepts.

This is equivalent to the multi statement:

```
multi(Y, ilogit, -(C*slope+intercept0), -(C*slope+intercept1), …)
```

Observation statement action codes:

Action codes may be given, within an observation statement, which specify computations to make either before or after an observation is made. For instance, if there is a urine compartment that is emptied at each observation, part of the model may resemble this:

```
deriv(urineVol = gfr)
deriv(urine_amt = gfr*Cp*fu)
observe(Uvol = urineVol + epsUv, doafter={urineVol=0})
```

Math and special functions

Phoenix PML supports a majority of the intrinsic math functions in the `Cmath.h` library (see “Math functions” on page 92 in Appendix D for a list of supported functions). In general, the function names are the same or very similar to the Fortran (and hence NONMEM) names of the same functions. There are some differences, however. For example, `fabs(x)`, which applies to floating-point values, computes the absolute value of `x`. ***Do not use ABS(x)***, the Fortran name for absolute value, as this will give incorrect results when called with real number arguments.

In addition to the `Cmath.h` library functions, Phoenix PML also supports a variety of special functions that are useful in PK/PD modeling, such as the cumulative normal distribution `phi(x)`, the inverse cumulative normal distribution `probit(x)`, the Lambert W-function `lambertw(x)` for closed-form solutions to one-compartment Michaelis-Menten nonlinear elimination models, as well as various link and inverse link functions, and some special functions useful for defining log likelihoods in certain count-type models. A complete list is provided in Appendix A.

Function names are typically written in lower case. For example, functions like `exp`, `sqrt`, `log`, are lower case, because PML uses the standard C library, in which lower case is the norm. This differs from other programs like NONMEM, which are not case sensitive. Spelling a function name incorrectly will result in a linker error message saying the function is undefined.

If numeric constants are needed in the code, and there is a concern about possible performance of calculating them, a simple way to include them is the following:

```
double(pi, e)
    sequence {
          pi = 3.1415926535897932384626433832795
          e = 2.7182818284590452353602874713527
    }
```

These are executed only once per subject, take essentially zero time to execute, and are far more precise than can possibly be required.

Do not be concerned about the performance of secondary parameter calculations, such as half-life, because those are only calculated once, after all model fitting is completed.

Dosing

Dosing can be specified in two places, the model file and the column definition file. For more, see "Modeling project files" on page 14.

In the model, the dosepoint statement described under "Modeling syntax" on page 21 can contain several options, including:

- `tlag = expr` dose delivery is delayed by expr
- `duration = expr` 0-order infusion spanning expr time units
- `rate = expr` 0-order infusion of expr units/time unit
- `bioavail = expr` expr is the fraction delivered

The dosepoint statement can also include statements to be executed before and/or after delivery of the dose, as follows.

```
dobefore = block
doafter = block
```

Covariates

Covariates can be simple or interpolated. See "Modeling project files" on page 14 for more information.

`covariate(covariate_name)`

This specifies that there is a covariate with the given name. For time-varying covariates, the `covariate` statement extrapolates backward. So, for example, if a covariate is given at time = 1, 2, and 3 to be 10, 20, and 30, respectively, then the covariate value in [0,1] is 10, in [1,2] is 20, and in [2,3] is 30.

`fcovariate(covariate_name)`

This is the same as covariate, except that it also specifies the covariate has forward direction. `fcovariate` extrapolates forward. So, for example, if a covariate is given at time = 1, 2, and 3 to be 10, 20, and 30, respectively, the fcovariate value for [1,2] is 10, for [2,3] is 20, and for times beyond 3 (if any) it is 30. If no covariate value is given at time = 0, the fcovariate value for [0,1] is also 10, as the first value propagates backward as well as forward.

There are actually two different ways to indicate forward direction, by using the `fcovariate` statement in the model text, or by using `fcovr` in the column definition text (or both).

`interpolate(covariate_name)`

This also specifies that there is a covariate with the given name, however, the value of the covariate varies linearly between time points at which it is set in time-based models. This feature should be used with caution, because in some cases it makes a linear model nonlinear so it cannot use the matrix exponent ODE solver.

This can happen in a simple PK model parameterized by Cl and V, if V is a function of bodyweight BW, and BW is interpolated. Alternatively if the model is parameterized by Ke and V, it is not affected because V does not enter the differential equations.

In a text model, if a covariate is categorical, its name must be followed by empty parentheses:

```
covariate(Form())
```

This informs the UI that the covariate is categorical, and thus available for stratification.

Modeling discontinuous events

There are many kinds of models involving discrete time-based events at which discontinuous changes can occur in a model. The following is a partial example of an entero-hepatic reflux model.

```
deriv(a = -a*k10 - a*k1b + g*kg1)
# central cpt
deriv(b = a*k1b - qbg)
# bile cpt
deriv(g = qbg - g*kg1)
# gut cpt
real(qbg)
#qbg is flow rate from bile to gut
stparm(tCycle=…, tReflux=…)
# times are parameters
      # introduce the time sequence:
real(i)
sequence{
     i = 0;
     while(i<10){
            i = i + 1;
            qbg = 0;
            sleep(tCycle - tReflux);
            qbg = (b/tReflux);
            sleep(tReflux);
            qbg = 0;
      }
 }
```

The model has three compartments: a for plasma, b for bile, and g for gut. Normally the compound flows from gut to plasma and from plasma to bile, as well as flowing through the normal elimination path. There is also a flow from bile to gut, which is the reflux path. This is modeled as a zero-order flow of rate `qbg`. The flow is turned on and off to model the reflux.

Lines 1-3 give the differential equations for the three compartments. The variable `qbg` is a variable representing the flow rate from bile to gut, and it is initially zero.

Line 4 declares a variable, `qbg`, which will be used in some of the equations and statements.

Line 5 designates that there are two structural parameters giving the cycle time between reflux events (`tCycle`) and the duration (`tReflux`) of each event.

Line 6 declares a variable, `i`, which will be used in some of the equations and statements.

Lines 7-17 are grouped with the `sequence` keyword. This introduces time-sequenced procedure into the model.

Line 8 sets the initial value for the variable `i` to zero.

Line 9 groups the next six statements into a loop that will repeat up to 10 times.

Line 10 adds one to the value of `i` (number of iterations).

Line 11 sets the initial value for the variable `qbg` to zero.

Line 12 allows `tCycle - tReflux` time units to pass.

Line 13 turns on the reflux by setting `qbg` to the rate necessary to empty the bile compartment within duration `tReflux`.

Lines 14-15 say to wait for `tReflux` time units, and then turn off the flow, after which the cycle repeats.

Discrete and distributed delays

Transit compartment models, described by systems of ordinary differential equations (ODEs), have been widely used to describe delayed outcomes in pharmacokinetics and pharmacodynamics studies. The obvious disadvantage for this type of model is it requires manually finding proper values for the number of compartments, and hence it is time-consuming. It is also difficult, if not impossible, to do population analysis using this model. In addition, it may require many differential equations to fit the data and may not adequately describe some complex features.

To alleviate these advantages, a distributed delay approach was proposed in "Hu, Dunlavey, Guzy, and Teuscher (2018)" to model delayed outcomes in pharmacokinetics and pharmacodynamics studies. It involves convolution of the signal to be delayed (S) and the probability density function (g) of the delay time,

$$\int_0^{+\infty} g(\tau)S(t-\tau)d\tau \tag{1}$$

Thus, for the distributed delay approach, the delay time may vary among signal mediators (e.g., drug molecules or cells), and hence it is a natural extension of the discrete delay approach that

$$S(t-\tau) \tag{2}$$

in which case, where the delay time is assumed to be the same (i.e., τ) for all signal mediators.

Differential equations involving discrete delays and/or distributed delays are called delay differential equations (DDEs). The difference between ODEs and DDEs is that the future state of the system governed by ODEs is totally determined by its present value while for DDEs it is determined not only by its present value, but also by its past. This means that, for DDEs, one has to specify the values of the system state prior to the system starts (assuming throughout that the system starts at time zero). For example, for the following differential equation with a distributed delay,

$$S(t) = f\left(t, S(t), \int_0^{+\infty} g(\tau)S(t-\tau)d\tau\right), t > 0 \tag{3}$$

$$S(t) = S_0(t), t \le 0$$

one has to specify the values of $S(t)$ over all negative t; that is, one has to specify S_0, which is often called the history function.

It was shown in "Hu, Dunlavey, Guzy, and Teuscher (2018)" that the distributed delay approach is general enough to incorporate a wide array of pharmacokinetic and pharmacodynamic models as special cases, including transit compartment models, effect compartment models, indirect response models with production either simulated or inhibited, typical absorption models (either zero-order or first-order absorption), and a number of atypical (or irregular) absorption models (e.g., parallel first-order, mixed first-order, and zero-order, inverse Gaussian, and Weibull absorption models). This was done through assuming a specific distribution form for the delay time.

Specifically, transit compartment models are based on the assumption that the delay time is Erlang distributed, with shape and rate parameters respectively determining the number of transit compartments and the transition rate between the compartments. Note that Erlang distribution is a special case of the gamma distribution, which allows for non-integer shape parameters. Hence, distributed delay models with delay time assumed to be gamma distributed (referred to as gamma distributed delay models) are natural extension of transit compartment models. Examples for extending transit compartment models to their corresponding gamma distributed delay models can be found in "Hu, Dunlavey, Guzy, and Teuscher (2018)" and "Krzyzanski, Hu, and Dunlavey (2018)".

The delay function

The delay function in PML can be used for both discrete and gamma distributed delays, and its syntax is given as follows:

```
delay(S, MeanDelayTime
      [, shape = ShapeParam]
      [, hist = HistExpression]
      )
```

If the shape option is not provided, then it returns the value of $S(t -$ MeanDelayTime). Otherwise, it returns the value of "1" with g assumed to be the probability density function of a gamma distribution with *shape* parameter being *ShapeParam* specified by the shape and *mean* being *MeanDelayTime.* The *hist* option is used to specify the value of S prior to time 0; that is, if $t < 0$, then $S(t)$ = *HistExpression*, which is required to be independent of time t, but can depend on variables that are defined at time 0 for the subject, such as covariates, fixed and random effects. If the *hist* option is not provided, then it is assumed that $S(t) = 0$ for $t < 0$.

It should be noted that the `delay` function relies on the fact that ODE solvers use shorter step sizes in the vicinity of rapid changes. Hence, it will not work in the presence of methods that have large step sizes, such as matrix exponent or closed-form. Even though there is no restriction on the number of delay functions put in a model, it should be used sparingly to avoid performance issue.

For the discrete `delay` function, the delay time can be estimated, and for the distributed delay case, both the mean and shape parameter for the gamma distribution can be estimated. In addition, the delay function can be put on the right-hand side of a differential equation, and hence can be used to numerically solve a differential equation with either discrete delays or gamma distributed delays, no matter whether the signal to be delayed, S, depends on model states or not. For example, the `delay` function can be used to numerically solve the well-known Hutchinson equation (a logistic growth model with a discrete delay):

$$\begin{aligned} \dot{S}(t) &= rS(t)\left(1 - \frac{S(t-\tau)}{K}\right) \\ S(t) &= S_0, -\tau \le t \le 0 \end{aligned} \tag{4}$$

where r denotes the intrinsic growth rate, K is the carrying capacity, and S_0 is a positive constant. The PML code for this model is given as follows:

```
deriv(S = r * S * (1 - delay(S, tau, hist = S0)/K))
sequence{S = S0}
```

The delay function can also be used to numerically solve the following logistic growth model with a distributed delay:

$$\begin{aligned} \dot{S}(t) &= rS(t)\left(1 - \frac{1}{K}\int_0^{+\infty} g(\tau)S(t-\tau)d\tau\right) \\ S(t) &= S_0, t \le 0 \end{aligned} \tag{5}$$

where g is the probability distribution function of a gamma distribution with $shape$ parameter being $ShapeParam$ and $mean$ being $MeanDelayTime$. The PML code for this model is given as follows:

```
delayedS = delay(S, MeanDelayTime,
                 shape = ShapeParam,
                 hist = S0
                )
deriv(S = r * S * (1 - delayedS/K))
sequence{S = S0}
```

A simple simulation of the logistic growth model with a gamma distributed delay, (5), is given in example project `LogisticGrowthModelWithGammaDistributedDelay.phxproj` (located in …`\Examples\NLME`). The project demonstrates that (5) can exhibit much richer dynamics than its corresponding ODE.

$$\begin{aligned} \dot{S}(t) &= rS(t)\left(1 - \frac{S(t)}{K}\right) \\ S(0) &= S_0 \end{aligned} \tag{6}$$

For example, it may produce an oscillation around the carrying capacity while the corresponding ODE cannot. In addition, adjusting the mean delay time can achieve the desired type of oscillations (either damped or sustained oscillations).

The delayInfCpt statement

Note that, the signal to be delayed, S, in the delay function cannot contain dosing information from the input data set. Hence, it cannot be used for the absorption delay case. To achieve this, a compartment modeling statement, `delayInfCpt`, was added to PML with its syntax given as follows:

```
delayInfCpt(A, MeanDelayTime,
            ShapeParamMinusOne
            [, in = inflow]
            [, out = outflow
           )
```

where A denotes a compartment that can receive doses (from the input data set) through the dosepoint statement. Mathematically, this statement means:

$$\dot{A}(t) = \int_0^{+\infty} g(\tau)S(t-\tau)d\tau + outflow(t) \qquad (7)$$

$$A(0) = 0$$

Here S denotes all the input to be delayed, including the dose and the *inflow* specified by the *in* option, with $S(t)$ = 0 if t < 0, and g is the probability distribution function of a gamma distribution with *mean* given by *MeanDelayTime* and shape parameter v given by:

$$v = ShapeParamMinusOne + 1 \qquad (8)$$

where *ShapeParamMinusOne* must be non-negative and is to prevent the shape parameter going from less than one (which cause singularity of g at time 0). The *outflow* defined by the *out* option is used to specify additional flow rates (either out of or into compartment A) that are not delayed.

There are two examples that demonstrate how to use `delayInfCpt` to model absorption delay. For the first one, the delay time between the administration time of the drug and the time when the drug molecules reach the central compartment is assumed to be gamma distributed with the *mean* given by `MeanDelayTime` and shape parameter v given by v = *ShapeParamMinusOne* + 1. In addition, the drug is assumed to be described by a one-compartment model with a first-order clearance rate. The PML code for the structure model of this example is then given by:

```
# central compartment
delayInfCpt(A1, MeanDelayTime,
            ShapeParamMinusOne,
            out = - Cl * C
           )
dosepoint(A1)
# drug concentration at the central compartment
C = A1 / V
```

The second example is about double sites of absorption, where the drug is assumed to be described by a two-compartment model with a first-order elimination from the central compartment. In addition, the delay time between the administration time of the drug and the time when the drug molecules reach the central compartment is assumed to be gamma distributed for each pathway. The PML code for the structure model of this example is then given by:

```
# 1st pathway contribution to the central compartment,
# where frac denotes the fraction of dose absorbed by
# the 1st pathway, and the remaining dose is
# absorbed by the 2nd pathway.
delayInfCpt(Ac1, MeanDelayTime1, ShapeParamMinusOne1,
            out = -Cl * C - Cl2 * (C - C2)
           )
dosepoint(Ac1, bioavail = frac)
# 2nd pathway contribution to the central compartment
delayInfCpt(Ac2, MeanDelayTime2, ShapeParamMinusOne2)
dosepoint(Ac2, bioavail = 1 - frac)
# Peripheral compartment
deriv(A2 = Cl2 * (C - C2))
# Drug concentration at the central compartment
C = (Ac1 + Ac2)/V
# Drug concentration at the peripheral compartment
C2 = A2/V2
```

The model fitting and visual predictive checks for the first example are demonstrated in the example project `ModelAbsorptionDelay_delayInfCpt.phxproj` (located in …`\Examples\NLME`). The project results show that the shape parameter can be reliably estimated along with the other parameters. In addition, standard diagnostic plots and visual predictive checks are good.

References

Hu, Dunlavey, Guzy, and Teuscher (2018). A distributed delay approach for modeling delayed outcomes in pharmacokinetics and pharmacodynamics studies. *J Pharmacokinet Pharmacodyn*. https://doi.org/10.1007/s10928-018-9570-4.

Krzyzanski, Hu, and Dunlavey (2018). Evaluation of performance of distributed delay model for chemotherapy-induced myelosuppression. *J Pharmacokinet Pharmacodyn*. https://doi.org/10.1007/s10928-018-9575-z.

Sequence statements

```
sequence(block)
```

Sequential execution is where there is a sequence of statements A, B, C, etc., where A executes first in time, and only after A completes does B get to start, and so on. If control is sequential, then one can have “if” statements and loops, and variables that act like counters. One can say “x = x + 1” and know what it means, because it takes place at a point in time.

By contrast, in a PML model, the statements are not sequential, they are descriptive of the problem. They do not take action at a point in time. Rather they apply “all the time”. So in PML code, outside of sequence blocks (and `assignment` statements), relative order of statements does not matter.

The `sequence` statement denotes a series of expressions to evaluate or statements to process at certain times in a time-based model. The incorporation of sequence blocks into PML allows handling of models like entero-hepatic reflux in a general way.

Processing a block of expressions and statements in a sequence statement is started at the initial time in the model, which is usually zero for differential equation models, and continues until the end of the sequence block, or until a `sleep` statement is encountered.

Initializing state:

In a `sequence` block, one can say:

```
sequence {
   Aa = some_expression
   A1 = some_other_expression
}
```

This sets the two state variables `Aa` and `A1` to initial values, because the sequence block starts executing immediately when the subject begins.

Take some action after some time has passed:

For example, to put in an extra dose at three time units after the subject has begun, and then yet another three time units later, one could say:

```
sequence {
   sleep(3)
   Aa = Aa + some_dose_amount
   sleep(3)
   Aa = Aa + some_dose_amount
}
```

The `sequence` block starts when the subject starts, but the first thing it does is hit the `sleep(3)` statement, which means “wake up again after three time units”.

When the three time units have passed, then it does the next thing, which is to add a dose to Aa. Notice that an integrator variable like Aa can only be modified at particular points in time, so it can only be modified inside a sequence block.

Then it sleeps for three more time units, gives another dose, and does nothing more.

If there is more than one sequence block, they run on parallel tracks and do not depend on the relative order in which the other sequence blocks do things. For example, if two sequence blocks both initialize things, one cannot depend on which one does the initialization first.

Do different things depending on different conditions:

The following `sequence` statement begins with sleeping for three time units, then checks if the amount in compartment Aa is less than two. If the amount is less than two, then add a dose to compartment Aa. Otherwise, do something else or do nothing, depending on code that would appear after the `else` line.

```
sequence {
    sleep(3)
    if (Aa < 2){
       Aa = Aa + some_dose_amount
    } else {
    }
}
```

Do things repeatedly:

The following `sequence` statement says that, as long as `t` is less than 10, sleep three time units and then add a dose.

```
sequence {
   while(t < 10){
      sleep(3)
      Aa = Aa + some_dose_amount
   }
   }
```

Alternatively, a variable can be declared that can be set to different values. Then a `sequence` statement can be used to repeat the sleep + dose cycle ten times, as shown below:

```
   real(i)
   sequence {
      i = 1
      while(i <= 10){
         sleep(3)
         Aa = Aa + some_dose_amount
         i = i + 1
      }
   }
```

Group statements

```
   group(block)
```

The `group` statement ensures that the `block` assignment statements get executed prior to the `stparm` statements.

There are two levels of a model:

- The structural level, which has compartments, doses, and observations, and parameters (called `structural` parameters)
- The population level, which has typical values of parameters (fixed effects), inter-individual variation (random effects), covariates, and covariate effects (which are also fixed effects)

The statement that ties the two levels together is called `stparm`. It defines each structural parameter as a function of fixed effects, covariates, and random effects for estimation and simulation.

Sometimes, to simplify the `stparm` statements, it is desirable to calculate parts of them outside in separate statements. This cannot be done with ordinary assignment statements like A=B+C, but it can be done inside a `group` statement, like `group(A=B+C)`, where B and C can only be functions of covariates and fixed effects. Then A is called a `group` parameter and it can be used in the right-hand-side of an `stparm` statement. In situations with complex covariate effects, this can lead to substantial performance improvement, by avoiding frequent calls to math functions.

Example 1:

A covariate model can be defined in using standard PML, as follows:

```
   stparm(V = ((Gender==0) ? tvV:  tvV *dVdGender) * exp(nV))
```

If the user prefers separate lines, each group can be defined separately (by combining covariate values):

```
   group(
     tvVMale = tvV
     tvVFemale = tvV *dVdGender
     stparm(V = ((Gender==0) ? tvMale : tvFemale) * exp(nV))
   )
```

Example 2:

The following calculates body surface area (BSA) in a `group` statement using covariates weight (WT) and height (HT), and is only done when covariates change, not on every ODE evaluation. This `group` statement avoids the calculation of BSA at each iteration of ODE solver steps.

```
covariate(WT) # WT: body weight
covariate(HT) # HT: height
# BSA: body surface area
group(BSA = (WT^0.5378) * (HT^0.3964) * 0.024265)
```

Sleep statements

```
sleep(number)
```

This statement instructs the processing of the statements and expressions in the current sequence block to stop for the amount of time specified by the number argument. The number argument is a ***relative*** time, not an absolute time.

The block inside a `sequence` statement can consist of multiple blocks controlled by logical switches. For instance, in the example above, the expressions and statements inside the sequence statement are contained within a `while` block which instructs the sequence to repeat itself through the entire time period that observations are made.

It is important to use the sleep statement rather than tests against the time variable to ensure the stability of the algorithms. For example, write `{sleep(10); A0=0}` and not `{if(t=10);A0=0}`. The latter does not function as is intended. For a model to work, the `sequence` statement must be used any time a user would otherwise intend to write something like: `if(t>=Tmax){do stuff}`.

There can be multiple sequence statements in a model, and they are executed as if they were running in parallel. No assumption should be made about which sequence statement is processed first. When a reset is encountered in the data, due to mapping a reset column, the `sequence` statement(s) are restarted.

Time event switching in PML versus WinNonlin ASCII models

The `while` or `if` statements that were required to switch between time events in the WinNonlin ASCII model do not work as effectively as the `sleep` statement in the PML. Using the `sequence` statement in conjunction with the `sleep` statement is the best way to switch between time events in Phoenix text models.

If a user uses `if` statements to perform these tasks in the PML, the integrator can jump over the time point of interest. The Jacobian matrix it computes will be very inaccurate because the derivatives are different on each side of the discontinuity. The integrator goes back and forth trying to reduce the compounding errors that it sees, which can cause the integrator to miss the time point of interest.

The stability that the `sequence` statement offers allows models to be solved more quickly and accurately.

What the `sequence` statement with `sleep` statements does is stop the integrator at the appropriate times to make state changes, like RESET or DOSING, or set time discontinuous variables.

Fixed effect parameter syntax

The `fixef` statement declares zero or more fixed effect parameters. There can be more than one such statement in a model.

```
fixef(a
      b = 6.02
      c(freeze) = 3.14
      d = c(0.01, 0.1, 5)
      e = c(0.01, 0.1, 5)
      f(enable=c(1)) = c(0.01, 0.1, 5)
7                 )
```

In this example `a`, `b`, `c`, `d`, `e`, and `f` are fixed effect parameters.

Line 1 says that `a` is a fixed effect parameter.

Line 2 gives `b` an initial value of 6.02.

Line 3 gives `c` a fixed, non-estimated initial value.

Line 4 gives `d` an initial value of 0.1, and provides a lower bound of 0.01 and an upper bound of five.

Line 5 is like line 4.

Note: Any of the lower bounds or upper bounds can be omitted in the above statements.

Line 6 is like line 4, but the fixed effect `f` is enabled within an estimation run. This is used in covariate effect modeling procedures. Enabling the fixed effect means that it is estimated. If a fixed effect is disabled, that means its value is frozen to 0.0 and it is not estimated. There is a command-line argument, `/xe`, that determines which variables are chosen to be disabled. If there is no such argument, all fixed effects having an enable clause are disabled.

Rules for using boundaries and initial estimates:

If bounds are used, a log-transformation is used to find the values closest to the boundaries. Boundaries cannot be solved.

Note: It is best practice to try to solve the model without first using boundaries.

If a one-sided lower bound is used, then the log-transformation is:

$$thetaY = \log(theta - a)$$

If a one-sided upper bound is used, then the log-transformation is:

$$thetaY = \log(a - theta)$$

In the above equations, $thetaY$ is the unconstrained transformed variable, and $a < theta$.

However, if $a < theta < b$, then:

$$thetaY = \log\left(\frac{(b - theta)}{theta - a}\right)$$

Fixed effect initial values must be a numerical value. Functions, such as log or exponent, cannot be used as initial estimates. The PML wants a numerical value, not a function. This is similar to how NONMEM works.

Correct: `Fixef tvV = C(, 0.7,)`

Incorrect: `Fixef = tvV = C(, log(C),)`

Random effect parameter syntax

The `ranef` statement specifies zero or more random effect parameters and their covariance structure.

```
1  ranef(eta1
2        eta2 = 6
3        diag(eta3, eta4)
4        diag(eta5, eta6) = c(2, 3,)
5        same(eta7, eta8)
6        block(eta9, eta10)
7        block(eta11, eta12) = c(1, 2, 3)
8        block(eta13, eta14)(freeze) = c(1, 2, 3)
9        )
```

Line 1 says `eta1` is a random effect parameter that has its own variance independent of the others parameters. No upper or lower bounds are used, and the initial estimate of variance is one, the default.

Line 2 says `eta2` is independent and that the initial estimate of its variance is six. When no initial estimate of variance value is given, the PML uses a default value of one.

Line 3 says `eta3` and `eta4` have a diagonal variance-covariance matrix. The initial estimate of variance is one, the default.

Line 4 is like line 3, and the function `c` of the diagonal variance-covariance matrix is given.

Line 5 says that `eta7` and `eta8` have the same diagonal variance-covariance matrix initial estimate as line 4. Also, the covariance matrix is constrained to be the same as in the previous block. The random effects are different, but drawn from the same distribution as those specified on line 4.

Line 6 says that `eta9` and `eta10` have a full variance-covariance matrix. The initial estimate of variance for both parameters is one, the default.

Line 7 is like line 6 and gives an initial estimate of the lower triangle of the matrix in row-wise order.

Line 8 is like line 7 and says that the matrix is fixed and is not estimated.

Chapter 3

Running NLME Engines in Command Line Mode

Using NLME and PML from the command line

The Phoenix Modeling Language (PML) supports model building through a text-based modeling language that allows users to describe, fit, and simulate models.

The PML language supports specification of input and/or output data, trial related settings such as dosing and treatment sequence, as well as flexible model definitions for PK/PD and general Nonlinear Mixed Effects (NLME) modeling including survival analysis and modeling of categorical responses.

PML includes the necessary structures for seamless integration of modeling with trial simulation and related analyses. PML draws on established practices in S-PLUS and NONMEM to make PML user-friendly for people familiar with those software packages.

> ***Users do not need to have Phoenix running in order to run PML models from the command line.*** When Phoenix is installed, the files necessary to run PML models from the command line are also installed.

This chapter describes how to operate the NLME engine in Windows command line mode using batch scripts named `RunNLME.bat` and `RunNLMEMPI.bat`.

This chapter covers the following topics:

- "Requirements and installation" on page 52
  - "Software requirements" on page 52
  - "Hardware requirements" on page 52
  - "PML and multi-processor or multi-core computers" on page 52
  - "Install the executables and examples" on page 53
  - "Licensing" on page 53
  - "Run the example models" on page 53
- "Basic command line syntax" on page 54
- "Input files" on page 55
  - "The lognlmeflags.asc control file" on page 56
  - "QRPEM control flags" on page 58
- "Running QRPEM in command line mode" on page 58

Requirements and installation

- "Software requirements" on page 52
- "Hardware requirements" on page 52
- "PML and multi-processor or multi-core computers" on page 52
- "Install the executables and examples" on page 53
- "Licensing" on page 53
- "Run the example models" on page 53

Software requirements

Phoenix Platform/WinNonlin 8.1

MinGW (Minimalist GNU for Windows) C++ compiler

For more on MinGW, see the MinGW Web site. MinGW is installed during the Phoenix installation process. Only use the version of MinGW that comes with the Phoenix installation package.

Caution: Certara makes no guarantee that a different version of MinGW other than the one included in the installer is compatible with Certara software.

Hardware requirements

- two Ghz. Intel-compatible CPU
- four gigabyte RAM minimum, but eight gigabytes is recommended
- 300 megabytes free harddrive space

PML and multi-processor or multi-core computers

PML supports parallel processing through the use of the Message Passing Interface (MPI).

- Use the `RunNLMEMPI.bat` batch file to run models using multiple processors or processor cores.
- Users with multiple processor or multiple-core computers can install MPICH2, a free and portable implementation of the Message Passing Interface.
- MPICH2 is installed as part of the Phoenix installation process during Complete Installation or can be selected during Custom Installation.
- Or users can install MPICH2 themselves using the `mpich2-1.4.1p1-win-x86-64.msi` installer, which is included with the Phoenix installation package.
- For more on MPICH2, visit the MPICH2 Web site.
- Installing MPICH2 is optional, and is not necessary for computers with one processor or one processor core.

Install the executables and examples

Run the `setup.exe` installation program that comes with the Phoenix installation package. For more on installing Phoenix, *see the Phoenix Getting Started Guid*e.

This installs the executables, DLLs, and C++ files needed to run the NLME engines in command line mode into `<Phoenix_install_dir>\application\lib\NLME\Executables`.

A group of seven modeling examples are installed in separate subfolders in `<Phoenix_install_dir>\application\Examples\NLME\Command Line`. You can save a copy of the `Examples` directory (installed with Phoenix) to your Phoenix project directory via the Project Settings in the *Phoenix Preferences* dialog.

In addition to the model, column definition, and data files, each example folder includes three batch files: `Cmd.bat`, `RunNLME.bat`, and `RunNLMEMPI.bat`.

Licensing

Caution: Command line users will need an NLME license and a PML license in order to run models from the command line.

Users should follow the instructions that came with their licenses to use the Phoenix Licensing Wizard for installing the PML license.

Run the example models

Note: The Command window used to execute the command line scripts ***must*** be **Run as Administrator**. If running on a server, the user must be logged in as an administrator.

1. Navigate to ...`\Examples\NLME\Command Line\Model 1`.
2. Double-click the file `Cmd.bat`, or right-click to **Run as Administrator**.

   A Windows command line window is opened.
3. In the command window, navigate to the `Model 1` subdirectory.
4. Run 500 iterations using engine 3 (-LB) on model `lyon04.mdl` with the column mapping file `COLS04.txt` and the data file `EMAX02.csv` with this command:

   ```
   RunNLME 3 500 lyon04.mdl COLS04.txt EMAX02.csv
   ```

The output is created in the `Model 1` subdirectory.

Run example models 2 - 7:

1. Select the `Model 2` subdirectory.
2. Double-click the file `Cmd.bat`, or right-click to **Run as Administrator**.
3. In the command window, navigate to the `Model 2` subdirectory.
4. Run 500 iterations using engine 3 on model `lyon05.mdl` with the column mapping file `COLS05.txt` and the data file `EM01.csv` with the command:

   ```
   RunNLME 3 500 lyon05.mdl cols05.txt em01.csv
   ```
5. To run the models 3 - 7, open each model subdirectory and double-click `Cmd.bat`, or right-click to **Run as Administrator**.

6. Use the following statements to run each model from the command line:

Model 3:

```
RunNLME 5 200 fm1theo.mdl colstheo.txt ThBates.csv
```

Model 4:

```
RunNLME 5 200 fm3theo.mdl colstheo.txt ThBates.csv
```

Model 5:

```
RunNLME 5 200 pheno2.mdl colspheno2.txt pheno2.csv
RunNLME 5 200 pheno2.mdl colspheno2.txt phobs.csv
```

Model 6:

```
RunNLME 5 200 apolipo.mdl colsapolipo.txt apo2.csv
```

Model 7:

```
RunNLME 5 200 apolipo2.mdl colsapolipo.txt apo2.csv
```

Basic command line syntax

Note: The Command window used to execute the command line scripts ***must*** be **Run as Administrator**.

The NLME command line statement has a basic syntax that is composed of six command line arguments.

```
runNLME engine_number maxiterations model colmap data
```

where:

– `runNLME`: The name of the batch file used to call the compiler to compile the model, in this case, the file is called `runNLME`.

– `engine_number`: The number corresponding to the specific engine to use with the model.

Table 3-1. Engine numbering

Number	Engine
1	QRPEM (Quasi-Random Parametric expectation-maximization)
2	IT2S-EM (Iterated 2-stage expectation-maximization)
3	FOCE L-B (First-Order Conditional Estimation, Lindstrom-Bates)
4	FO (First Order)
5	General likelihood engine, which includes FOCE ELS (Extended Least Squares), Laplacian, and adaptive Gaussian quadrature methods. The default method is FOCE ELS. Method selection is controlled by flags and parameters in file `nlmeflags.asc`.
6	Naive pooled

– `maxiterations`: An integer between zero and 10000 that specifies the maximum number of iterations to run the main optimization routine in each engine. If `maxiterations` is zero, no optimization is run but the model is evaluated at the initial solution defined in the model file or restart file. In this case, the standard output files are written using the initial solution as the fitted solution. Any post optimization computations such as a nonparametric analysis or a standard error computation specified in `nlmeflags*.asc` are also run.

– `model`: Name of the model file.
– `colmap`: Name of a column mapping file that associates variable names in the model file with column names in the data file. Use of quotes in this file is optional to allow otherwise non-permitted column names to be resolved.
– `data`: Name of the data file.

For example,

```
runNLME 3 200 lyon04.mdl COLS04.txt EMAX02.csv
```

runs the FOCE L-B engine (engine number 3) on model file `lyon04.mdl` with the column mapping file `COLS04.txt` and the data file `EMAX02.csv` for a maximum of 200 iterations.

Input files

Table 3-2. Input files

File	Purpose
model file	mandatory command line argument 4
colmap file	mandatory command line argument 5
data file	mandatory command line argument 6
nlmeflags.asc	optional control file
logrestart.asc	optional restart file

The three mandatory input files are always designated in the command line.

An optional fourth control input file called `nlmeflags.asc` is used to set certain environmental flags and tolerances to values other than the default values. If this file is not present in the command line arguments, then the environmental flags and tolerances are set to their default values. The file is created with every modeling run.

The format and default values of the `nlmeflags.asc` file are listed below. Every successful run of the NLME engine creates a `lognlmeflags.asc` file which contains flags and values that can be copied to the `nlmeflags.asc` file.

Copy the text from `lognlmeflags.asc` to `nlmeflags.asc` and change the applicable values in order to create and use `nlmeflags.asc` file in a modeling run.

The optional fifth command line argument input file is called `logrestart.asc`. It is used to designate an initial starting solution other than that specified in the model file. Every successful run of the NLME engine creates a `logrestart.asc` file which can then be used to initialize later runs.

The flag for controlling whether or not to use `logrestart.asc` is in the `!iflagrestart` line in `nlmeflags.asc`.

Example usage for the command line arguments:

```
RunNLME 5 500 lyon04.mdl COLS04.txt EMAX02.csv nlmeflags.asc logrestart.asc
```

The lognlmeflags.asc control file

The standard `lognlmeflags.asc` control file consists of 11 lines with standard default values specified as entries. The following lines are typical contents of a `lognlmeflags.asc` file:

```
0  !iflagnp (0 = do not run, otherwise # of nonparametric generations)
   0   !iflagrestart (0 = no, 1 = start from solution in logrestart.asc)
   1   !norderAGQ
   1   !iflagfocehess (1 = foce, 0 = Laplacian numerical Hessian)
   1   !iflagverbose (verbose mode is always used)
   0   !iflagstderr (0 = none, 1 = central diff, 2 = forward diff)
   1 -1   !METHODblup, NDIGITblup (expert usage, do not change)
   1  7   !METHODlagl, NDIGITlagl (expert usage, do not change)
0.100D-02 !tolmodlinz (step size for model linearization by numerical
derivatives)
   1     !iflagIEXP (1 = secant, 0 = hessian)
0.100D-01 !tolstderr (step size for numerical derivatives in standard error
computation)
   0   !nrep_pcwres (0=do not run, otherwise # of replicates for pcwres
statistic)
      0   !npresample (not currently used)
      0   !niter_mapnp (0=do not run, otherwise # of MAP_NP iterations)
```

Note: If the `nlmeflags.asc` control file is not used then the default values are used. The file `lognlmeflags.asc` logs which values were used in a modeling run.

The control flags include:

- **!iflagnp** – Controls whether and how intensively to run a nonparametric analysis after the initial parametric analysis is run.
  - If `iflagnp`=0, no nonparametric analysis is run.
  - If `iflagnp`>0, `iflagnp` designates the number of generations to run in the evolutionary nonparametric algorithm.
  - If `iflagnp`=1, optimal probabilities on support points placed at the parametric post hoc estimates are computed.
  - If `iflagnp`>1, support point positions are also optimized, but this can be computationally intensive. The output of probabilities and support points is sent to the file `nparsupport.asc`.
- **!iflagrestart** – Specifies the source of the initial solution.
  - If `iflagrestart=`0, the initial solution consists of the starting values in the model file.
  - If `iflagrestart=`1, the initial solution is read from the `logrestart.asc` file, which is created during a previous run of the same model.
- **!norderAGQ** – Only applicable to engine five, and is ignored for other engines. This flag designates the number of adaptive Gaussian quadrature (AGQ) points along each random effects dimension. The maximum value=40, but note that the total number of quadrature points is `norderAGQ^(number of random effects)`, so it is best practice to use a small integer, unless the number of random effects is one.
  - If `norderAGQ`=1, this corresponds to the Laplacian approximation.
  - If `norderAGQ`<1, then adaptive Gaussian quadrature is used.

Exceptions:

- If `norderAGQ=1` and `iflaghess=1`, then the FOCE ELS (Extended Least Squares) objective function is used, which is similar to NONMEM FOCE.
- If `norderAGQ=1` and `iflaghess=0`, then the Laplacian objective function is used, which is similar to NONMEM Laplacian objective function.
- `norderAGQ>1` and `iflaghess=1` creates an adaptive Gaussian quadrature with a Gaussian kernel defined by the FOCE approximation.
- `norderAGQ>1` and `iflaghess=0` creates an adaptive Gaussian quadrature with a Gaussian kernel defined by a numerical differentiation Hessian approximation.

- **!iflagfocehess** – Controls how the Hessian matrix is approximated.
  - If `iflagfocehess=1`, the FOCE L-B approximation to compute the approximation to the Hessian matrix of the joint log likelihood function for each individual.
  - If `iflagfocehess=0`, the Hessian matrix is approximated by numerical differentiation.
- **!iflagverbose** – This value is always set to 1, so verbose mode always used.
- !**iflagstderr** – Controls the standard error computation.
  - If `iflagstderr=0`, then no standard error computation is attempted.
  - If `iflagstderr=1`, a standard error computation with central differences for the required second derivatives of the log likelihood is attempted. This is much more computationally intensive but more accurate than forward differences.
  - If `iflagstderr=2`, forward differences are used.
  - If `iflagstderr>0`, then the relative step size to be used is specified in **!tolstderr**.
- **!METHODblup** – Expert usage only. This flag specifies the optimization method (1=line search, 2=dogleg, 3= Levenberg-like trust region) to be used in the OPTIF9 routine for optimization of the “blups,” which are post hoc estimates or modes of the joint likelihood function for each individual. ***It is best practice to not deviate from the default***.
- **NDIGITblup** – Expert usage only. This is an input of the estimate of the available accuracy of the OPTIF9 blup objective function in terms of decimal places. ***It is best practice to not deviate from the default***.
- **!METHODlagl** – Similar to `!METHODblup`, but applicable to the OPTIF9 optimization of overall likelihood function in engine five. It is not suggested to deviate from the default.
- **NDIGITlagl** – Similar to `NDIGITblup`, but applicable to the OPTIF9 optimization of overall likelihood function in engine five. ***It is best practice to not deviate from the default***.
- **!tolmodlinz** – Relative step size to use in numerical differentiation of the model function for FOCE L-B linearization.
- **!iflagIEXP** – Specifies whether calculation of the likelihood function is too expensive or not to calculate.
  - If `iflagIEXP=0`, then the overall quasi-Newton optimization step assumes that the likelihood function is not too “expensive” to evaluate and a numerical Hessian matrix is used for the Newton step.
  - If `iflagIEXP=1`, the overall likelihood function is assumed to be too “expensive” to evaluate, which is almost always true for NLME estimation problems, and a secant approximation is used. It is suggested that you always use iflagIEXP=1.
- **!tolstderr** – Relative step size to use in differentiation of log likelihood function for computation of standard errors.

- **!nrep_pcwres** – Controls whether or not the simulation based PCWRES statistic is computed in the residuals table. If `nrep_pcwres`=0, the statistic is not computed. Otherwise, it is computed using `nrep_pcwres` simulation replicates (maximum of 1000).
- **!npresample** – Not currently used.
- **!niter_mapnp** – Controls whether or not the MAP_NP procedure for improving initial fixed effect guesses is used. If `niter_mapnp`=0, this option is not used. Otherwise, it is used for `niter_mapnp` iterations (a reasonable value to use is `niter_mapnp`=3).

Running QRPEM in command line mode

The numerical engine code for the QRPEM engine is 1, so a typical command line invocation of QRPEM with model file `test.mdl`, column mapping file `cols1.txt`, data file `data1.txt`, and a maximum iteration limit of 200 takes the form:

```
runnlme.bat 1 200 test.mdl cols1.txt data1.txt
```

The output files for QRPEM are the same as for the other engines.

QRPEM control flags

In addition to the standard engine controls that can be provided in the file `nlmeflags.asc` discussed previously (see "The lognlmeflags.asc control file" on page 56) and which generally apply to all engines, there are some QRPEM-specific controls that apply only to the QRPEM engine and that are passed in a simple text file `qrpemflags.asc`.

Note: In UI mode, these controls are set in the Run Options tab.

As with `nlmeflags.asc`, if the `qrpemflags.asc` file is omitted, the default values of the various QRPEM controls will be used. However, if the user wants to override any of the QRPEM default control values, the `qrpemflags.asc` file must be provided in the current active directory (typically the directory containing the model, mapping, and data files). A sample `qrpemflags.asc` file containing default values of the controls is shown below and is also provided in …`\Examples\NLME\Command Line`.

```
300   ! Nsamp          number of eta samples per subject
0     ! impsamptype    type of importance sampling
0     ! impmapflag     0=no MAP assist after first iteration, 1=MAP step
                       on every iteration
0     ! iflagmcpem     0=QRPEM sampling, 1=MCPEM sampling
1     ! iflagscramble  0=none, 1=Owen, 2=Faure-Tezuka
10    ! NSIR sample size for estimating fixed effects not
           associated with random effects
0.1d0 ! acceptance ratio
0     ! irunall - if irunall=1, all iterations will be run,
           regardless of convergence behavior
0     ! Nburn - number of burn in iterations
0     ! ifreezeOmega - freeze Omega during burn-ins flag (0=no, 1=yes)
0     ! ipostrestart - posterior restart flag: 0=no, 1=use
           posteriors from previous run if available
! end qrpemflags.asc
```

The QRPEM control flags include:

- **Nsamp** – The number of samples used to evaluate the posterior mean and covariance integrals for each subject. Increasing this value will improve the accuracy of the integrals and the likelihood evaluation, and generally will result in better (closer to the true maximum likelihood values) parameter estimates, but will also increase execution time. The maximum permissible value is 30000.
- **impsamptype** – Specifies the importance sampling type:
  - impsamptype = -2 – Use a defensive Gaussian mixture with 2 components.
  - impsamptype = -3 – Use a defensive Gaussian mixture with 3 components.
  - impsamptype = -0 – Use a standard Gaussian distribution (no mixture), also referred to as multivariate normal (MVN).
  - impsamptype = 1 – Use a multivariate Laplace distribution (MVL). The MVL distribution has fatter tails than the corresponding normal distribution with the same mean and covariance matrix.
  - impsamptype = 2 – Use a direct sampling, which means to sample directly from the N(0,Omega) population distribution, and not use any importance sampling at all.
  - impsamptype > 2 – Use a multivariate T (MVT) with impsamptype degrees of freedom. A value within the general range of four to 10 is recommended if an MVT distribution is desired. Any values larger than this are not significantly different than the MVN distribution and will be inefficient relative to simply using MVN. The T distribution has fatter tails that decay more slowly than the corresponding MVN distribution. The MVT decay rate is governed by the degrees of freedom – lower values correspond to slower decay and fatter tails.

  The rationale for using MVL or MVT is to increase the sampling frequency from the target posterior distribution tails in case that distribution has more slowly decaying tails than that of a multivariate normal distribution. An alternative to using MVL or MVT to accomplish this is to use a lower value of acceptance ratio, as discussed below.
- **iflagmcpem** – A binary 0/1 flag.
  - Default = 0 or off.
  - If set to 1, QR sampling is turned off and replaced by Monte Carlo random sampling. This may be of interest for pedagogical purposes or if the most direct comparison possible is desired with other MCPEM algorithms such as those found in NONMEM 7 or S-ADAPT. However for production runs, using the default setting MCPEM = 0 is strongly recommended to get the speed and accuracy advantages of QR sampling.
- **iflagscramble** – A numeric selector that determines whether and what type of ‘scrambling’ is used. The possible values are 0 (no scrambling), 1 (Owen scrambling, the default), and 2 (Faure-Tezuka scrambling). Scrambling is a technique that de-correlates the components of the quasi-random sequence, making it look more random, without affecting the basic low discrepancy property that improves the accuracy of QR relative to random sampling for numeric integration. In some cases, use of scrambling can further improve the numerical accuracy of the integrals relative to a basic non-scrambled QR sequence.
- **NSIR** – Samples is an integer value (default=10) that determines the number of Sampling-Importance-Resampling points/per subject to include in the nonlinear log likelihood optimization that is used to estimated fixed effects that appear in nonlinear covariate models, residual error models, and any instance of a fixed effect that is not paired with a random effect in a structural parameter definition. Increasing # SIR samples will improve the accuracy of these estimates but at higher computational cost. The total number of samples is the product of # SIR samples and the number of subjects. Thus with 100 subjects and the default value of # SIR samples = 10, a total of 1000 samples is used, which is usually more than adequate. Normally # SIR samples should only be

increased if the number of subjects is small. The maximum value of # SIR samples is ISAMPLE, the total number of sample points per subject.

- **acceptance ratio** – A real valued (default = 0.1) parameter that controls the ratio g of the covariance matrix of the importance sampling distribution to the estimated covariance matrix of the underlying posterior distribution through the formula:

  $$\text{acceptance ratio} = \gamma^{-2/d}$$

  where d is the number of random effects. To insure an adequate sampling in the tails of the target posterior distribution, a $\gamma > 1$, corresponding to acceptance ratio < 1, is desired. Decreasing the acceptance ratio increases γ and widens the tails of the importance sampling distribution. However, if this is taken too far, the sampling becomes very inefficient since most sample points will lie in the tails far from the highest likelihood region and hence will be uninformative. Note that as an alternative to decreasing acceptance ratio, one of the fatter tail distributions MVL or MVT can be used.
- **irunall** – A binary (0 or 1) flag that, if set to 1, will cause all iterations that are requested on the command line to be run. If **irunall** is set to its default value of 0, then iterations will be run until either a) convergence is achieved, or b) the maximum number of iterations is hit. Thus setting **irunall** in effect turns off application of the convergence criterion.
- **Nburn** – An integer that specifies how many ***burn in*** or preconditioning iterations are performed before actual optimization steps are attempted. During these burn in iterations, only internal parameter values related to the estimated means and covariances of the posteriors are changed, but no changes are made to fixed or random effect parameter estimates. Generally, burn in iterations are only necessary when evaluating the log likelihood at the initial estimate (this is done by specifying zero iterations in the command line iteration limit), in which case about 15 burn in iterations are usually adequate. During the burn in process, the reported log likelihood value at the starting point will converge to an accurate estimate of the actual log likelihood at that point. The default setting is zero burn in iterations.
- **ifreezeomega** – Modifies the meaning of Nburn. If `ifreezeomega` = 1, then Omega is frozen during the burn in iterations.
- **ipostrestart** – The posterior restart flag.
  - If `ipostrestart`=0, restart is not used.
  - If `ipostrestart`=1, the final posterior means and covariance matrices from the immediately preceding run are used to initiate the current run.

PML Examples

Example models and comparable scripts in NONMEM

This chapter provides the following examples, modeled in both Phoenix and NONMEM.

– "Phenobarbital" on page 61: simple kinetics
– "Theophylline" on page 63: population modeling
– "User-defined logistic model" on page 65
– "Structural parameters and QRPEM" on page 67

The following section includes examples covering a range of functions.

– "Additional examples" on page 71

Phenobarbital

This example illustrates simple PK modeling for a one-compartment model with Cl (clearance) and V (volume) parameterization, and multiple doses per subject.

Data

The subject data are contained in an ASCII file (*.dat). The headers and the first subject data read as follows:

```
pheno.dat
## xid      time  dose  wt    apgr  yobs
1           0.0   25.0  1.4   7     .
1           2.0   .     1.4   7     17.3
1           12.5  3.5   1.4   7     .
1           24.5  3.5   1.4   7     .
1           37.0  3.5   1.4   7     .
1           48.0  3.5   1.4   7     .
1           60.5  3.5   1.4   7     .
1           72.5  3.5   1.4   7     .
1           85.3  3.5   1.4   7     .
1           96.5  3.5   1.4   7     .
1           108.5 3.5   1.4   7     .
1           112.5 .     1.4   7     31.0
```

Column mappings

The ASCII file containing column mappings reads as follows.

```
colspheno.txt
id(xid)
time(time)
dose(a < -dose)
covr(wt < -wt)
obs(cObs < -yobs)
```

The model

The Phoenix model file reads as follows.

```
phenophxexam.mdl
# One compartment model with IV bolus dosing
# Cl, V parameterization with differential equation
# formulation
Pheno(){
      dosepoint(a)
      covariate(wt)     #wt is a covariate for Cl and V
      deriv(a = -a*Cl/V)
      c = a/V
      fixef(
            tvCl = c(0, 0.0001,)
            wtCl = c(0, 0.005,)
            tvV = c(0, 0.1,)
            wtV = c(0, 1,)
            )
      ranef(
            diag(nCl, nV) = c(0.1, 0.1,)
            )
      stparm(
            Cl = (tvCl+wtCl*wt)*exp(nCl)
            V = (tvV+wtV*wt)*exp(nV)
            )
#NONMEM initial estimate for sigma variance is 10
#Phoenix initial estimate represents a standard deviation
#rather than a variance, so the equivalent initial estimate #is
#eps1 = sqrt(10) = 3.16
#     error(eps1 = 3.16)
#     observe(cObs = c + eps1)
}
```

NONMEM control file

The equivalent model, written as a NONMEM control file (*.ctl), would read as follows.

```
$PROBLEM PHENOBARB SIMPLE MODEL
$INPUT ID TIME AMT WGT APGR DV
$DATA pheno.dat
$SUBR ADVAN6
$MODEL COMP=(CENTRAL,DEFOBS,NOOFF)
$PK
      TVCL = THETA(1) + WGT*THETA(2)
      TVV = THETA(3) + WGT*THETA(4)
      CL = TVCL*EXP(ETA(1))
      V = TVV*EXP(ETA(2))
      S1 = V
$THETA(0, 0.0001,)(0, 0.005,)(0, .1,)(0, 1,)
$OMEGA .1 .1
$DES
      DADT(1) = -CL/V*A(1)
$ERROR
      Y = F+EPS(1)
$SIGMA 10
$ESTIMATION METHOD=1 PRINT=5 POSTHOC
```

Theophylline

This example performs population PK modeling based on a one-compartment, first-order input PK model.

Data

The subject data are contained in an ASCII file (*`.dat`). The headers and the first subject data read as follows:

`thbates.dat`

```
## xid wt   dose  time  yobs
1     79.6  4.02  0     0.74
1     79.6  4.02  0.25  2.84
1     79.6  4.02  0.57  6.57
1     79.6  4.02  1.12  10.5
1     79.6  4.02  2.02  9.66
1     79.6  4.02  3.82  8.58
1     79.6  4.02  5.1   8.36
1     79.6  4.02  7.03  7.47
1     79.6  4.02  9.05  6.89
1     79.6  4.02  12.12 5.94
1     79.6  4.02  24.37 3.28
```

Column mappings

The ASCII file containing column mappings reads as follows.

```
colstheo.txt
id(xid)
covr(dose < -dose)
covr(time < -time)
obs(cObs < -yobs)
```

The model

The Phoenix model file reads as follows.

```
fm3theophx.mdl
#One compartment model with first order absorption with a
#single dose at time=0
#The use of an explicit prediction formula in the model text
#requires that dose and time are entered as covariates, that
#is, there is no defined compartment name in which to dose,
#and there is no implicit continuous time structure as in an
#ODE model.
theo(){
      covariate(dose,time)
      fixef(
                  tvlKe = c(, -2.5,)
                  tvlKa = c(, 0.1,)
                  tvlCl = c(, -3.0,)
                  )
      ranef(
                  diag(nlKa, nlCl) = c(1.0, 1.0,)
                  )
      stparm(
                  Ke = exp(tvlKe)
                  Ka = exp(tvlKa + nlKa)
                  Cl = exp(tvlCl + nlCl)
                  )
      V = Cl/Ke
      cpred = dose*Ka/(V*(Ka-Ke))*(exp(-Ke*time) - exp(
      -Ka*time))
      error(eps1 = 0.5)
      observe(cObs = cpred + eps1)
}
```

NONMEM control file

The equivalent model, written as a NONMEM control file (*.`ctl`), would read as follows.

```
$PROB THEOPHYLLINE POPULATION DATA
$INPUT ID WT DOSE TIME CP=DV
$DATA ThBates.dat
$PRED
      KE=EXP(THETA(1))
      KA=EXP(THETA(2) + ETA(1))
      CL=EXP(THETA(3) + ETA(2))
F = DOSE*KA*KE/(CL*(KA - KE))*(EXP(-KE*TIME)-EXP(-KA*TIME))
Y = F + EPS(1)
$THETA -2.5 0.1 -3.0
$OMEGA 1 1
$SIGMA .5
$EST METHOD=1 MAXEVAL=450 PRINT=5
$COV
```

User-defined logistic model

This example illustrates a repeated measures logistic response. It is adapted from a logistic example in the NONMEM archives. The data consist of the number of successes in 1000 simulated trials at a given dose.

Data

The subject data are contained in an ASCII file (*.`dat`). The headers and the first subject data read as follows:

`logistic1000a.dat`

```
## id dose        frac        ntrial
1     0.200000    0.269010    1000
1     0.600000    0.499010    1000
1     1.000000    0.625010    1000
1     1.400000    0.690010    1000
1     1.800000    0.735010    1000
```

Column mappings

The ASCII file containing column mappings reads as follows.

`colslogistic.txt`

```
id(id)
covr(dose < -dose)
covr(ntrial < -ntrial)
obs(cObs < -frac)
```

The model

The Phoenix model file reads as follows.

`logistic.mdl`

```
logist2(){
      covariate(dose,ntrial)
      fixef(
            gamma = c(0, 1,)
            tvd50 = c(0, 1,)
            )
      ranef(
            diag(neta1) = c(0.1)
            )
      stparm(
            d50 = tvd50*exp(neta1)
            )
      a=gamma*log(dose/d50)
      prob=exp(a)/(1+exp(a))
#note cObs is the fraction of successes observed in ntrial
#trials - corresponding count is ntrial*cObs
      LL(cObs, ntrial*cObs*log(prob) + ntrial*(1 - cObs)*
      log(1 - prob))
}
```

NONMEM control file

The equivalent model, written as a NONMEM control file (*`.ctl`), would read as follows.

```
$PROB Repeated measures logistic response
$DATA logistic1000a.dat
$INPUT ID DOSE DV NT
$PRED
      GAMMA=THETA(1)
      D50 = THETA(2)*EXP(ETA(1))
      LDOS= LOG(DOSE)
      A = GAMMA*LDOS - GAMMA*LOG(D50)
      B = EXP(A)
      P = B/(1 + B)
      Y = -2*NT*(DV*LOG(P) + (1 - DV)*LOG(1 - P))
$THETA (0,1.) (0,1.)
$OMEGA .1
$EST NOABORT METH=1 LAPLACE -2LL PRINT=1
$COV
```

Structural parameters and QRPEM

QRPEM (Quasi-Random Parametric Expectation) is an importance sampling-based EM engine in Phoenix NLME that is based on the general EM paradigm of sampling the empirical Bayesian posterior of each subject given the current estimate of the fixed and random effect parameters, and then updating these parameters based on simple statistics computed from the samples. In particular, the fixed effect updates are based on posterior sample means of the random effect samples. In the most ideal case, each random effect is associated with a unique set of one or more fixed effects, and the updates to the fixed effects can be made from simple means or a simple linear regression model on the means of the corresponding sampled random effects.

Due the specific fixed effect update algorithm used by QRPEM, the correspondences between fixed and random effects in the PML `stparm` statements that define structural parameters in the model must be clear and restricted to a few acceptable types that are compatible with the fixed effect update methodology. Thus some `stparm` statements in models that are acceptable for other engines cannot be used directly with QRPEM. For example, non-linear covariate models within a PML `stparm` statement are perfectly acceptable for other engines, but will not work with QRPEM. Attempting to execute such a model with QRPEM will result in the error message (in the Core Status file in the Results tab)

```
FATAL ERROR IN QRPEM/IMPEM!
 Model not suitable for QRPEM analysis
 Possibly non linear covariate model or
 some other unimplemented feature
```

Similarly, time varying covariates inside a `stparm` statement can be used freely with other engines but not QRPEM. Attempting to run such a model will result in an error message that the selected engine cannot work with covariate effects where the covariate(s) have multiple values within a given subject, and will identify the variable covariate.

However, in such cases there is almost always an easy workaround that is based on splitting the `stparm` statement or block into two parts, a conforming part that remains inside the `stparm` and is acceptable to QRPEM, and a second nonconforming part, which is inserted into the body of the model outside the `stparm` and contains the offending features.

This section describes the splitting technique and gives some examples. It also points to two 'ready-to-go' working example projects (`Remifen.phxproj` and `QRPEM_with_time_varying_covariate.phxproj`) that illustrate the method. All such example NLME projects are in the directory `<Phoenix_install_dir>\application\Examples\NLME`. You can save a copy of the `Examples` directory (installed with Phoenix) to your Phoenix project directory via the Project Settings in the *Phoenix Preferences* dialog.

The QRPEM method works most naturally and efficiently when all structural parameters in a model can be expressed simply in terms of fixed effects and random effects in such a way that either the structural parameter or its log is a normal random variable, and the mean of the normal random variable is a linear function of fixed effects and random effects. This is essentially the same concept as "mu-modeling" in NONMEM. When all the structural parameters are expressed this way, a very simple and efficient EM update formula allows the fixed effects to be updated in by estimating the means of the empirical Bayesian posterior distribution of each subject's random effects by random or quasi-random importance sampling. A simple linear regression of the estimated means with the fixed effects (including any linear covariate models) as predictors provides the update.

For example, consider a simple volume of distribution structural parameter V. The most common way to model this in an `stparm` statement (because V is inherently nonnegative) is one of the two alternative, but mathematically equivalent, lognormal forms.

a) `stparm(V = tvV*exp(etaV))`

Or

b) `stparm(V = exp(tvlogV + etaV))`

But also the simple additive parameterization:

c) `stparm(V = tvV + etaV)`

fits the 'mu-modeled' framework of acceptable QRPEM structural parameters, although technically this additive parameterization might be more suitable for a structural parameter that can be positive or negative.

In both a) and b), log(V) is the normally distributed structural parameter, where in c) V is normally distributed. Clearly b) is mathematically equivalent to a) with `tvV = exp(tvlogV)`. In the log normal cases, either formulation a) or b) is can be used with QRPEM, which does the log transforms automatically when it encounters case a). This contrasts with NONMEM, where only b) can be used in the mu-modeled case.

A simple extension allows the mean of the structural parameter to include a linear function of covariates. For example, suppose V includes a covariate on weight (here we assume a mean of 75 on weight, and use wt-75 as the centered covariate):

d) `stparm(V = exp(tvlogv + coefwt*(weight - 75) + etaV))`

Or

e) `stparm(V = tvV*exp(coefwt*(weight - 75) + etaV))`

Then clearly `log(V)~N(tvlogv + coefwt*(weight - 75), OmegaV)`, and the mean is a linear function of the fixed effects tvlogV and coefwt, so the conditions for simple EM updates apply.

But there are a number of cases where this simple update formula breaks down.

Case 1 – Bare fixed effects

If a structural parameter enters the model as a 'bare' fixed effect that is not paired or associated with a random effect, for example stparm(V = tvV), with no associated random effect, then that bare fixed effect tvV cannot be estimated from the mean of a sampled empirical Bayesian posterior distribution, since there is no posterior associated with V. Such bare fixed effects must be estimated from a direct numerical optimization of a log likelihood function involving those parameters. Details are not presented here, but it is simply noted that such bare fixed effects are allowed within QRPEM 'stparm' statements, which automatically sets up the necessary log likelihood optimizations.

However, there are other cases that also cannot be handled, even if all the fixed effects are paired with random effects. These require some restructuring to make them work in QRPEM. The two most important are a) nonlinear covariate models, and b) covariate models with time-varying covariates, whether linear or not in the fixed effects in the covariate model.

Case 2 – Nonlinear covariate models

Suppose a covariate model of the form:

f) `stparm(V = tvV*(1 + coefwt*(weight - 75)) *exp(etaV))`

is desired rather than one of the forms given in d) or e) above. Now the mean of log(V) is `log(tvV + coefwt*(weight - 75))`, which cannot be expressed as a linear function of fixed effects. This is a common choice of covariate model, but cannot be accommodated within the simple "mu-modeled" EM update framework.

All engines, other than QRPEM, allow such non-linear covariate models to be included within a 'stparm' statement. However, if QRPEM encounters such a 'stparm' statement, it will exit with an error message as described above. But the above nonlinear covariate model can be run in QRPEM after a simple restructuring. The non-linear covariate model must be broken into two parts, a standard log normal 'mu-modeled' part:

```
stparm(Vbase = tvV*exp(etaV))
```

and a non-linear part in the body of the model outside the `stparm` statement:

```
    V = Vbase*(1 + coefwt*(weight - 75))
```

Note this reformulated 'split' covariate model is obviously mathematically equivalent to the original model. Also, the common similar alternative version:

g) `stparm(V = (tvV + coefwt*(weight - 75))*exp(etaV))`

can be rewritten as:

```
    stparm(V = tvV*(1 + coefwt/tvV)*(weight - 75)*exp(etaV))
```

and the 'split version' looks like:

```
    stparm(Vbase = tvV*exp(etaV))
    V = Vbase*(1 + coefwt2*(weight - 75))
```

where now, `coefwt2 = coefwt/tvV`.

An example of this splitting technique is included in the 'ready-to-go' project `Remifen.phxproj` in the examples directory. The `stparm` block of the original model in 'ELS_ FOCE_ Formulation' in this project has the form:

```
stparm(
   V1TV = theta1 - theta7*(AGE - 40) + theta12*(LBM - 55)
   V2TV = theta2 - theta8*(AGE - 40) + theta13*(LBM - 55)
   V3TV = theta3
   CL1TV = theta4 - theta9*(AGE - 40) + theta14*(LBM - 55)
   CL2TV = theta5 - theta10*(AGE - 40)
   CL3TV = theta6 - theta11*(AGE - 40)
   V1 = V1TV*exp(eta1)
   V2 = V2TV*exp(eta2)
   V3 = V3TV*exp(eta3)
   CL1 = CL1TV*exp(eta4)
   CL2 = CL2TV*exp(eta5)
   CL3 = CL3TV*exp(eta6)
   K10 = CL1/V1
   K12 = CL2/V1
   K13 = CL3/V1
   K21 = CL2/V2
   K31 = CL3/V3
)
```

This will run correctly with the FOCE ELS engine, but not QRPEM since clearly this has multiple instances of type of nonlinear covariate model of the type discussed in g) above. Another difficulty is the inclusion of the `assignment` statements defining the rate constants K10, K12, K13, K21, and K31, which are prohibited in `stparm` statements in correctly formulated QRPEM models.

The equivalent QRPEM-compatible 'split version' is:

```
stparm(
   V1qr =  theta1*exp(eta1)
   V2qr =  theta2*exp(eta2)
   V3 =    theta3*exp(eta3)
   CL1qr = theta4*exp(eta4)
   CL2qr = theta5*exp(eta5)
   CL3qr = theta6*exp(eta6)
)
   V1 = V1qr*(1 - theta7*(AGE - 40) + theta12*(LBM - 55))
   V2 = V2qr*(1 - theta8*(AGE - 40) + theta13*(LBM - 55))
   CL1 = CL1qr*(1 - theta9*(AGE - 40) + theta14*(LBM - 55))
   CL2 = CL2qr*(1 - theta10*(AGE - 40))
   CL3 = CL3qr*(1 - theta11*(AGE - 40))
   K10 = CL1/V1
   K12 = CL2/V1
   K13 = CL3/V1
   K21 = CL2/V2
   K31 = CL3/V3
```

The second main type of example where splitting is useful is time varying covariates where not all instances of a covariate within a given individual have the same value. This violates some of the basic assumptions that allow simple linear regression based updates even if the covariate model is linear. Consider for example the linear covariate model in d) above:

```
    stparm(V = exp(tvlogv + coefwt*(weight - 75) + etaV)
```

If the covariate weight has several different values within a single individual, then attempting to run this otherwise acceptable model with QRPEM will fail with an error message describing the specific offending time varying covariate.

However, the same simple basic splitting technique where the time-varying covariate is placed outside the `stparm` statement allows it to run in QRPEM:

```
    stparm(Vbase = exp(tvlogv + etaV)
    V = Vbase*exp(coefwt*(weight - 75))
```

An example of this is given in the example project `QRPEM_with_time_varying_covariate.phxproj`. Here the basic model is a Cl/V parameterization of a simple one-compartment IV-bolus case, where log(Cl) has a linear dependency on a covariate ‘scr’:

```
test(){
      cfMicro(A1, Cl / V)
      dosepoint(A1)
      C = A1 / V
      error(CEps = 1)
      observe(CObs = C*(1 + CEps))
      stparm(V = tvV*exp(nV))
      stparm(Cl = tvCl*exp(scr*dCldscr + nCl))
      fcovariate(scr)
      fixef(tvV = c(, 2,))
      fixef(tvCl = c(, 0.5,))
      fixef(dCldscr(enable = c(0)) = c(, 1,))
      ranef(diag(nV, nCl) = c(1, 1))
}
```

The model as written is acceptable for QRPEM if `scr` is not time-varying but rather has a fixed value for each individual. The QRPEM_with_fixed_cov and ELSFOCE_with_fixed_cov models in this project are set up to run QRPEM and FOCE ELS, respectively, on exactly this model for such a dataset with fixed `scr` covariate. A second data set with a time-varying `scr` is also provided. Here exactly the same model as above will run FOCE ELS correctly (model ELSFOCE_with_var_cov), but the `stparm` for Cl must be split for QRPEM to work in this case (workflow (QRPEM_with_var_cov):

```
test(){
   cfMicro(A1, Cl / V)
   dosepoint(A1)
   C = A1 / V
   error(CEps = 1)
   observe(CObs = C*(1 + CEps))
   stparm(V = tvV*exp(nV))
   stparm(Clbase = tvCl*exp(nCl))
   #following moves time-varying covariate out of stparm statement
   #and now model is acceptable for QRPEM
   Cl = Clbase*exp(scr*dCldscr)
   fcovariate(scr)
   fixef(tvV = c(, 1,))
   fixef(tvCl = c(, 0.5,))
   fixef(dCldscr(c(, 1,))
   ranef(diag(nV, nCl) = c(1, 1))
}
```

Finally, note that the split version can be run with the fixed covariate dataset, but it is more efficient to use the un-split version when feasible. The splitting in effect forces the use of the less efficient log likelihood optimization method to update the fixed effect `dCldscr` in the Cl covariate model, whereas this can be updated with the more efficient linear regression technique in the un-split case.

Additional examples

This section provides example modeling code for the following cases.

- “Multinomial (ordered categorical)” on page 72
- “Time to event model (exponential)” on page 72
- “Time to event model (Weibull)” on page 73
- “Emax (Hill) model with exponent” on page 74
- “One-compartment IV bolus population PK” on page 74
- “One-compartment IV bolus, two parallel models with common fixed effects” on page 75
- “One-compartment model with sequence” on page 75
- “One-compartment model with sleep statement” on page 76
- “One-compartment first-order absorption model, compartment initialized with sequence” on page 76
- “One-compartment first-order absorption, closed-form” on page 77
- “One-compartment first-order absorption with lag time, closed-form” on page 77
- “One-compartment IV bolus with time-to-event outcome and PK observations” on page 78

Multinomial (ordered categorical)

```
category3(){
#observed values are one of three categories 0, 1, or 2
#probability of observing a higher category number increases #with
covariate x
      covariate(x)
      fixef(
            x1 = c(0, 1.5,)
            x12 = c(0, 1,)
            )
      ranef(nx1 = 0.25)
      stparm(xx1 = x1 + nx1, xx2 = xx1 + x12)
#xx2 > xx1 since x12 > 0
      y1 = x - xx1
      y2 = x - xx2
#xx2 > xx1, so y1 > y2
#ilogit(y) = exp(y)/(1+exp(y)), built in function
      p01 = ilogit(y1)
      p12 = ilogit(y2)
#by construction, y2<y1, so 0<p12<p01<1
#p12 = prob(category2)
#p01 = prob(category 2) + prob(category 1)
#1 - p01 = prob(category 0)
      LL(y, log(y == 0 ? 1 - p01:y == 1 ? p01 - p12:p12 - 0))
}
```

Time to event model (exponential)

Hazard model data for subject 1. Events occurred at time=1.72 and 2.43, then from 2.43 to 4.00 no event occurred (right censored). The first record with an empty observation establishes the time of the start of the first period.

```
## id       time        dose        occur
1           0           10          .
1           1.72        10          1
1           2.43        10          1
1           4.00        10          0
#The above data says the event occurred at times 1.72 and
#2.43, then between times 2.43 and 4.00 it did not occur,
#so it is right-censored.
```

Model file:

```
hazard(){
      covariate(dose)
      fixef(
            tvlHaz = c(, -2,)
            dlHazdDose = c(-0.8, 1.2, 1.2)
            )
      stparm(haz = exp((tvlHaz+nlHaz)+dlHazdDose*dose))
      ranef(nlHaz = 0.01)
#The hazard function haz (which here is a constant) is
#integrated over the current period by a hidden differential
#equation dcumhazard/dt = haz, which yields a survival
#probability of S = exp(-cumhazard). That integral is reset
#to zero after every observation.
#
#The likelihood (if the event occurred) is S*haz and S (if
#an event did not occur). This likelihood computation and
#the differential equation computation are automatically
#invoked by event(occur,haz).
      event(occur, haz)
}
```

Interval censoring capabilities of the event statement are signified by observed values.

Table 4-1. Observed values

Observed value	Meaning
2	Indicates the end of an interval in which the event occurred one or more times, but at unknown times. In this case $P = 1 - S$.
-1, -2, -…	Indicates the end of an interval in which the event occurred exactly n=1, or 2, or … times, where the time is unknown. In this case, $P = (cumhaz^n S)/n!$ (a Poisson distribution). Note: this is equivalent to a simple Poisson count model.
-999999	Indicates the end of an interval in which the event occurred an unknown number of times, i.e., the subject was simply out of contact with no information, so $P = 1$.

Time to event model (Weibull)

To model Weibull-distributed events, whether censored or not, if there is more than one event per subject, a decision must be made as to what time value to use for each observation. There are usually two possibilities:

– Delta-time since prior observation (or start of subject)
– Delta-time since start of subject

This section shows how to do both possibilities.

First, Weibull has two structural parameters, which will be called $lambda$ and k in this example. $lambda$ is the scale parameter. The larger the $lambda$, the larger the expected time to observation. k is the shape parameter. The larger the k, the more sigmoidal the survival function. The hazard rate is a function of these two parameters:

```
hazard = k/lambda * (T/lambda)^(k- 1)
```

where T is one of the two Delta-time values mentioned above.

To follow option 1, one could say:

```
hazard = k/lambda*(T/ lambda)^(k - 1)
deriv(T = 1) # take explicit control of time
deriv(cumhaz = hazard)
LL(flag, log(flag ? hazard*exp(-cumhaz):
   exp(-cumhaz)), doafter = {cumhaz = 0; T = 0;})
```

or use the built-in `event` statement:

```
hazard = k/lambda*(T/ lambda)^(k - 1)
deriv(T = 1)
event(occur, hazard, doafter = {T = 0;})
```

To follow option 2, one could say:

```
hazard = k/lambda*(T/lambda)^(k - 1)
deriv(T = 1)
deriv(cumhaz = hazard)
LL(occur, log(occur ? hazard*exp(-cumhaz):
   exp(-cumhaz)))
# Notice that t could be used in place of T, and
# deriv(T = 1) could be removed.
```

Notice that the `event` statement can only be used in option 1 because it automatically resets the accumulated hazard, where in option 2, that is not desired.

Emax (Hill) model with exponent

```
emaxhill(){
      e = e0 + (emax - e0)*c^Power/(c^Power+ec50^Power)
      fixef(
                  tvE0 = c(0, 2,)
                  tvEMax = c(0, 5,)
                  tvlEC50 = c(0, 1.1,)
                  tvPower = c(0, 1,)
                  )
      covariate(c)
      stparm(
                  e0 = tvE0 + nE0
                  emax = tvEMax + nEMax
                  ec50 = exp(tvlEC50 + nlEC50)
                  Power = tvPower         #no random effect
                  )
      ranef(nE0 = 1, nEMax = 2, nlEC50 = 1)
      error(eps1 = 2)
      observe(eObs = e + eps1)
}
```

One-compartment IV bolus population PK

```
ivbolus(){
      dosepoint(a)
      deriv(a = -a*ke)
#replace above line with “cfMicro(a, ke)” for closed form
#formulation
      c = a/v
      fixef(
                  tvlKe = c(, -4.6,)
                  tvlV = c(, 2.3,)
                  )
      stparm(ke = exp(tvlKe + nlKe), v = exp(tvlV + nlV))
      ranef(nlKe = 0.25, nlV = 0.25)
      error(eps1 = 0.5)       #initial estimate res err cv
                              #= 50%
      observe(cObs = c*(1 + eps1))        #proportional
                                          #residual error
}
```

One-compartment IV bolus, two parallel models with common fixed effects

```
ivboluspar(){
      dosepoint(a1)
      deriv(a1 = -a1*ke1)
      c1 = a1/v1
      dosepoint(a2)
      deriv(a2 = -a2*ke2)
      c2 = a2/v2
      fixef(
                  tvlKe = c(, -4.6,)
                  tvlV = c(, 2.3,)
                  )
      ranef(block(nlKe1, nlV1) = c(0.25, 0.01, 0.25)
                  same(nlKe2,nlV2))
      stparm(ke1=exp(tvlKe + nlKe1), v1=exp(tvlV + nlV1))
      stparm(ke2=exp(tvlKe + nlKe2), v2=exp(tvlV+nlV2))
      error(eps1 = 1)
      observe(cObs1 = c1 + eps1)
      observe(cObs2 = c2 + eps1)
}
```

One-compartment model with sequence

```
onecompfoseq(){
      deriv(a = -a*ke)
      c = a/v
      fixef(
                  tvlKe = c(, -4.6,)
                  tvlV = c(, 2.3,)
                  )
      stparm(ke = exp(tvlKe + nlKe), v = exp(tvlV + nlV))
      ranef(nlKe = 0.5, nlV = 0.5)
      error(eps1 = 1)
      observe(cObs = c + c*eps1)    #proportional residual
                                    #error
      sequence {
            a = 10      #sets initial value of compartment
                        #a to 10
#useful if all subjects have a single bolus dose of 10 at
#time=0
      }
}
```

One-compartment model with sleep statement

```
testmodel(){
      deriv(a = -a*ke)
      c = a/v
      fixef(
                  tvlKe = c(, -4.6,)
                  tvlV = c(, 2.3,)
                  )
      stparm(ke = exp(tvlKe + nlKe), v = exp(tvlV + nlV))
      ranef(nlKe = 0.5, nlV = 0.5)
      error(eps1 = 1)
      observe(cObs = c + c*eps1)
      sequence {
                  sleep(1)    #sleep for time duration = 1
                  a = 10      #set compartment a to 10
                              #after sleep i.e., at time = 1
                  }
}
```

One-compartment first-order absorption model, compartment initialized with sequence

```
onecmtfo(){
      deriv(aa = -aa*ka)
      deriv(a1 = aa*ka - a1*ke)
      #replace above two lines with "cfMicro(aa, ke, first =
      #(depot = ka))" to obtain faster closed form version
      dosepoint(aa)
      sequence {a1 = 4.8}     #initializes compartment a1
                              #to 4.8
      c = a1/v
      stparm(
            ka = exp(tvlKa + nlKa)
            ke = exp(tvlKe + nlKe)
            v = exp(tvlV + nlV)
            )
      ranef(nlKa = 0.25, nlKe = 0.25, nlV = 0.25)
      fixef(
            tvlKa = c(, -0.7,)
            tvlKe = c(, -3,)
            tvlV = c(, 2.3,)
            )
      error(eps1 = 1)
      observe(cObs = c + eps1)
}
```

One-compartment first-order absorption, closed-form

```
onecmptfocf(){
      cfMicro(a1, ke, first = (aa = ka))
#aa is an arbitrary name of the depot (dosing) compartment -
#not used elsewhere in the model.
      dosepoint(aa)
      c = a1/v
      stparm(
            ka = exp(tvlKa + nlKa)
            ke = exp(tvlKe + nlKe)
            v = exp(tvlV + nlV)
            )
      ranef(nlKa = 0.25, nlKe = 0.25, nlV = 0.25)
      fixef(
            tvlKa = c(, -0.7,)
            tvlKe = c(, -3,)
            tvlV = c(, 2.3,)
            )
      error(eps1 = 1)
      observe(cObs = c + c*eps1)
}
```

One-compartment first-order absorption with lag time, closed-form

```
onecmptfolag(){
      dosepoint(aa, tlag = tlag)
      cfMicro(aa,ke,first = (depot = ka))
#faster evaluation than equivalent ODE system
#deriv(aa = -aa*ka)
#deriv(a1 = aa*ka - a1*ke)
      c = a1/v
      stparm(
            ka = exp(tvlKa + nlKa)
            tlag = exp(tvlTLag + nlTLag)
            ke = exp(tvlKe + nlKe)
            v = exp(tvlV + nlV)
            )
      ranef(nlKa = 0.25, nlTLag = 0.25, nlKe=0.25, nlV=0.25)
      fixef(
            tvlKa = c(, 1,)
            tvlTLag = c(, 0.1,)
            tvlKe = c(, -3,)
            tvlV = c(, 2.3,)
            )
      error(eps1 = 1)
      observe(cObs = c + c*eps1)
}
```

One-compartment IV bolus with time-to-event outcome and PK observations

```
timetoeventconc(){
      dosepoint(a)
      deriv(a = -a*ke)
      c = a/v
      fixef(
            tvlKe = c(, -4.6,)
            tvlV = c(, 2.3,)
            dHdC = c(0, 0.01,)
            )
      stparm(ke = exp(tvlKe + nlKe), v = exp(tvlV + nlV))
      ranef(nlKe = 0.5, nlV = 0.5)
      error(eps1 = 1)
      observe(cObs = c + c*eps1)
#instantaneous hazard rate is assumed proportional to
#concentration c
#proportionality constant dHdC is a fixed effect to be
#estimated
      event(occur, c*dHdC)
}
```

Closed-Form and Matrix Exponent Computations

- “Closed-form computations” on page 79
- “Matrix exponent” on page 80

Closed-form computations

Closed form computations for 1, 2, and 3-compartment first-order library models with simple single compartment dosing are handled recursively, where the model solution is defined by n residue parameters A_i which sum to one and exponential decay rates a_i. These parameters are derived from micro constants in the usual way via Laplace transforms assuming unit dose (including convolution with an extra exponential for first-order input).

There is a “state vector” $[s_1(t),\ldots,s_n(t)]$ representing the model at any point in time, where each state component is a term in the overall solution corresponding to a particular decay rate a_i. Each separate state evolves over time in the following way, where r is the infusion rate into a single predefined compartment:

$$s_i(t) = s_i(0)e^{-\alpha_i t} + r\frac{A_i}{\alpha_i}(1-e^{-\alpha_i t})$$

The output value of the model, which is usually an amount in a specified compartment, at a point in time is the sum of the state vector components:

$$y(t) = \sum_i s_i(t)$$

When a bolus dose D is administered, the state is modified in the following way:

$$s_i(t^{\dagger}) = s_i(t) + DA_i$$

Regarding `cfMicro` models, the above description models the central compartment amount as a function of input to the depot compartment, whether central or absorption. However, the actual implementation must take into account the following complicating factor.

Since, in general, models can depend on covariates that change discontinuously with time, the closed-form models must not only model the central compartment as a function of dosing to the depot, they must model ***every*** compartment as a function of ***every other*** compartment. The reason is that, if a covariate is changed, three steps must be performed:

1. Record the amount in every compartment.
2. Empty the system and calculate the new parameters of the model.

3. Put back the prior amounts into the compartments as if they were bolus doses, thus restoring all compartments to their prior amounts.

If the model allows dosing to both central and absorption compartments, this is done using the above scheme, since doses can go into both compartments.

In the steady-state case with bolus dose D given at intervals t, the solution takes the form:

$$s_i(t) = (DA_i e^{-\alpha_i t})/(1 - e^{-\alpha_i \tau})$$

Matrix exponent

The general N-compartment model governed by ordinary differential equations takes the form:

$$\dot{y} = f(y) + r$$

where $y(t) = (y_1(t), \ldots, y_N(t))^T$ is an N-dimensional column vector of amounts in each compartment as a function of time, $f(y)$ is a column vector-valued function which gives the structural dependence of the time derivatives of y on the compartment amounts, and r is an n-dimensional column vector of infusion rates into the compartments. Note that as opposed to the closed form solution first-order models, dosing can be made into any combination of compartments, and all of the compartments are modeled.

To account for infusion rates, define the augmented system $Y = [y, 1]$, and $R = [r, 0]$. In the special first-order case, the equations are represented as:

$$\dot{Y} = JY$$

where J is the Jacobian matrix:

$$J = \begin{bmatrix} \frac{\partial f(y)_i}{\partial y_j} & r_i \\ 0 & 0 \end{bmatrix}$$

The partial derivatives are obtained by symbolic differentiation of $f(Y)$. If any of them are not constant over the given time interval, then matrix exponent cannot be used, and a numerical ODE solver is used. The case where J is constant requires that the overall differential equation system is linear with no explicit time dependencies - that is the system can be described by a series of fixed inter-compartmental rate constants which are the entries in the matrix J.

Note that any model (such as Michaelis-Menten) with at least one nonlinear flow does not satisfy the constant J condition and must be solved with a numerical ODE solver.

Assuming J is a constant, the state vector Y evolves according to:

$$Y(t) = e^{Jt} Y(0)$$

where e^{Jt} is defined by the Taylor series expansion I + Jt + (Jt)2/2! +… of the standard exponential function. Standard math library routines are available for the computation of the matrix exponential. These are faster and more accurate than the equivalent computation with a numerical ODE solver and do not suffer from stiffness.

For steady state computations, regardless of whether a matrix exponential or numerical ODE solution is used for the single dose case, repeated dosing cycles are made to allow the system to approach steady state within a specified tolerance. An extrapolation technique known as Aitken acceleration is used to accelerate the convergence of steady state computations so that usually only a few such cycles are needed to achieve high accuracy steady state results.

Blocks, Statements, and Operators

Alphabetical listings of supported elements

This section is a quick reference to supported elements in the modeling language.

– “Blocks and statements” on page 83
– “Expressions and operators” on page 88

Blocks and statements

Blocks are sets of statements grouped together inside curly brackets. Statements include assignment of values and variables. Statements within the model (and within blocks) can span multiple lines of code, and can be separated with (optional) semicolons.

In the following table:

`var` = a variable name

`varlist` = a list of variables, optionally separated by commas

`numlist` = a list of numbers, optionally separated by commas

`assign` = an assignment operator

`expr` = any numerical expression, including variable names, numbers and arithmetic operators

[…] = indicates the content of the brackets is optional

| = represents “or” and separates options

* = means zero or more of an item can be displayed

+ = means one or more of an item can be displayed

`statement` = a statement of the form: `variable = expression`

Table B-1. Supported statements

Statement	Purpose
cfMacro(id,parameters, [strip=stripping_dose_covari-ate])	Macro-parameter model of concentration, using optional stripping dose.
cfMacro(id,parameters, [first=abs_cpt_name])	Macro-parameter model of amount in central compart-ment (cpt).
cfMicro(id,parameters, [first=abs_cpt_name])	Micro-parameter model. See “One-compartment first-order absorption, closed-form” on page 77.
count(var,expr[,action])	Defines an occurrence count.

Table B-1. Supported statements

Statement	Purpose
covariate(var(var)*)	Defines one or more variables as covariates. Include an empty pair of parentheses after the covariate name to indicate that it is categorical. `covariate(dose,time,Gender())`
delay(expression, MeanDelayTime [, shape = ShapeExpression] [, hist = HistExpression])	Models delayed outcomes using convolution of the signal to be delayed (S) and the probability density function (g) of the delay time. • MeanDelayTime: The value (positive) associated with the mean delay time. • ShapeExpression: The value (positive) representing the shape parameter that defines the distribution of the delay time. • HistExpression: The value of the expression prior to time 0. Any number of delay functions can be included in a model. The MeanDelayTime and shape parameters can be estimated. See also “Discrete and distributed delays” on page 40.
delayInfCpt(A, MeanDelayTime, ShapeParamMinusOne [, in = inflow][, out = outflow])	A statement related to a compartment (that can receive a dose through a dosepoint statement) with all of its input delayed (where the delay time is assumed to be gamma distribution), including the rate of administered dose (if provided) and the inflow specified by the “in” option (if provided). • A: Name of the compartment. • MeanDelayTime: The value (positive) associated with the mean delay time. • ShapeParamMinusOne: The value (non-negative) representing one less than the shape parameter that defines the distribution of the delay time. • out = outflow: (Optional) Represents the flow out of compartment A. • in = inflow: (Optional) Represents the additional inflow that is delayed. See also “Discrete and distributed delays” on page 40.
deriv(var assign expr)	Defines a differential equation. `deriv(a = -a*Cl/V)`

dosepoint| dosepoint2(id
[tlag = expr]
[duration = expr]
[rate = expr])
	Defines dosing. Example:
	`dosepoint(a1)`
	`deriv(a1 = -a1*ke1)`
	`c1 = a1/v1`
	`dosepoint(a2)`
	`deriv(a2 = -a2*ke2)`
	`c2 = a2/v2`

error(var(var)(*))	

Table B-1. Supported statements

Statement	Purpose
event(var,expr)	Defines an unscheduled (e.g., adverse) event, where var is an occur variable, expr is its hazard. `event(occur,haz)` The occur variable can be: • 0 = did not occur • 1 = occurred at the given time • 2 = occurred at least once in the prior interval • -n = occurred n times in the prior interval • -999999 = no information about the prior interval

fixef(var
[()]
[(enable = int)]
[= ([lower bound],[initial estimate],[upper bound])]
	Defines variable(s) as fixed effects parameters, optionally with a fixed value (), with optional initial estimate and bounds.
	`fixef`
	`tvE0 = c(1,2,3)`
	`tvEMax = c(4,5,6)`
	`tvlEC50 = c(0.09,1.1,2.0)`
	`tvLambda = c(1,2,3)`
	See also “Fixed effect parameter syntax” on page 47.

interpolate(id(id) (*))	For more on the interpolate statement, see “Covariates” on page 38.
LL(obsvar,expr)	Defines log-likelihood where obsvar is the observation variable, expr is its log-likelihood.

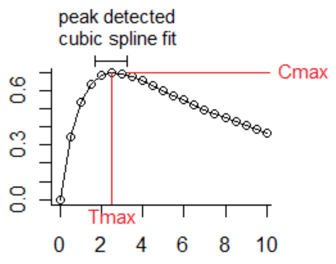
multi(var,invlink(,expr)*[,action])	Defines an integer-valued categorical observation, where invlink is an inverse link function and the rest is a series of ascending offset expressions.
	`multi(Y,ilogit,-C*slope+intercept0,`
	`-C*slope + intercept1), …)`

observe(id1 [(i d2)] [= expr] [,bql] [,dobefore = { …}] [,doafter = { …}])	Defines predicted observations, where id1 is the Gaussian prediction variable, id2 is the independent variable, and expr is the value assigned to id1. `observe(cObs = cpred + eps1)`

ordinal(var,invlink,input,slope,(,intercept)*)	Variation on the multi statement.
	`ordinal(Y,ilogit,C,slope,intercept0,interc`
	`ept1)`

Table B-1. Supported statements

Statement	Purpose

Tmax = peak(Cmax = C)
or
Tmax = peak(Cmax = C, max)
or
Tmax = peak(Cmax = C, max = (t < 6))
Or
Tmin = peak(Cmin = C, min)
or
Tmin = peak(Cmin = C, min = (t >= 6))
 	
where Cmax and Cmin are the internal variables and do not need defining.
	Use in model code (not in a sequence block, doafter, or dobefore).
	Where Cmax, Tmax, Cmin, Tmin are variable names of user choice, and C is any user-written expression.
	Variables Tmax and Cmax are initially 0, and hold their value until after a peak is detected.
	After a peak is detected, variables Tmax and Cmax are set to the peak of a cubic spline fitted to the points around the peak, where the points are what is seen on the trajectory of the differential equations.
	
	If a subsequent peak is found, the process will only be repeated if the peak is higher than the first.
	If the keyword max is not included, it is assumed.
	If the keyword min is included, it will look for a trough rather than a peak.
	Either keyword, max or min may be followed by a logical expression, such as max=test. In that case, it test is true, it looks for a peak. If test is false, it looks for the opposite.

peakreset(Cmax)	Use in a sequence block, doafter, or dobefore. This statement takes place at a point in time and will reset the peak-finder, after which it can detect another peak.
proc{ statement*}	

ranef((block(varlist) = numlist)*)	Defines variable(s) as random effects parameters, optionally defining the covariance matrix.
	`ranef(nlKe = 0.01,nlV = 0.01)`
	`ranef(eta1,eta2 = 6`
	` diag(eta5,eta6) = c(1,3)`
	` same(eta7,eta8)`
	` block(eta11,eta12) = c(1,2,3)`
	`)`
	See also "Random effect parameter syntax" on page 48.

section(<int>,section-stmt)	

Table B-1. Supported statements

Statement	Purpose

sequence{ statement*}	Defines a block of statements to be executed together and can contain conditional statements. It can contain special statements:
	• `if` statements set statements to be executed conditional on expr being true
	`if(expr){statement*}`
	`[ else if(expr){statement*}]*`
	`[ else {statement*}]`
	• `while` statements set zero or more statements to be executed while expr is true
	`while (expr){statement*}`
	• `sleep` statements pause computations for expr time units. (The expr value for the `sleep` statement is a relative time, not an absolute time.)
	`sleep (expr)`
	See “Modeling discontinuous events” on page 39, “One-compartment model with sequence” on page 75, and “One-compartment model with sleep statement” on page 76.

stparm((var | var = expr) +)	Defines one or more structural model parameters, var, with optional values, expr.
	`stparm(`
	`  ka = exp(tvlKa + nlKa)`
	`  ke = exp(tvlKe + nlKe)`
	`  v = exp(tvlV + nlV)`
	`)`

urinecpt(var assign expr)	Defines an elimination compartment. The urinecpt is like deriv, except in a steady state dosing situation, urinecpt is ignored.

Expressions and operators

Expressions and other sub-statement entities can span multiple lines and can be separated by optional commas. The following operators are supported. (The Phoenix Modeling Language follows the C++/C syntax for function names.)

Table B-2. Supported operators

Operator	Function
+	Addition `ka = exp(tvlKa + nlKa)`
-	Subtraction `deriv(a = -a*ke)`
*	Multiplication `deriv(a = -a*Cl/V)`
/	Division `deriv(a = -a*Cl/V)`
^ or **	Power `V = tvV*(W/70)^dVdW*exp(nV)`
= or <-	Assignment
>=	Comparison: greater than or equal to `if(t> = Tmax)`
<=	Comparison: less than or equal to
==	Comparison: equal to `LL(y, log(y == 0 ? 1 - p01:y == 1 ? p01 - p12:p12 - 0))`
!=	Comparison: not equal to
>	Comparison: greater than
<	Comparison: less than
<>	Comparison: not equal
&&	Logical: and
||	Logical: or
ln, log	Natural log (log base e) `ln(x), log(x)`
log10	Log base 10 `log10(x)`
fabs	Absolute value `fabs(x)`
?	Switch `(cond) ? actionA:actionB`

Reserved Words

Listing of reserved variable names

When building a model, the following should not be used as variable names:

- Words that already part of the Phoenix modeling language
- Words that are in the C runtime or C math libraries
- Words that are GNU library calls or GNU reserved words

If a reserved word is used, it will cause a compilation error when the model is being built and will appear in the model code as blue text.

The table below lists some of the more common reserved words to avoid.

Table C-1. More common reserved variable names

block	error	ranef3
bioavail	event	rate
bolus	first	real
bql	fixef	repl
break	for	return
call	gamma (Linux systems only)	same
cfMacro	goto	secondary
cfMicro	if	section
char	in	sequence
continue	include	short
covariate	infuse	signed
count	int	sleep
default	interpolate	start
deriv	interval	stparm
diag	join	struct
do	LL	switch
doafter	long	tlag
dobefore	mean	uncertainty
dosepoint	model	unit
dosepoint1	multi	units
dosepoint2	observe	unsigned
dropout	override	urine

Table C-1. More common reserved variable names

duration	proc	urinecpt
else	ranef	wait
enable	ranef1	while
enum	ranef2	

Supported Functions

- "Special functions" on page 91
- "Math functions" on page 92

Special functions

The following special functions (with some duplicates of the intrinsic versions, but with different names) are defined within the Phoenix PML language. The detailed C language code implementing each can be found in `<Phoenix_install_dir>\application\lib\NLME\Executables\mutil.c`.

Table D-1. Special functions

Name	Usage	Definition
lnorm	lnorm(x, std);	log of probability density function of normal distribution with mean (μ)=0. Since probability density of the normal distribution is f(x) = 1/(v(2π)s)e^-((x-μ)^2/(2s^2)), then assuming that μ = 0, log f(x) = -0.5 * (log2π + log(s^2) + (x/s)^2).

lnegbin_rp
rnegnin_rp
	lnegbin_rp(r, p, y);
	rnegbin_rp(r, p);
		neg. binomial, parameterized by r, p (LL)
		(sample)

lnegbin
pnegbin
rnegbin
	lnegbin(mean, beta, power, y);
	pnegbin(mean, beta, power, y);
	rnegbin(mean, beta, power);
		neg. binom., param. by mean, beta (= log(alpha)), power (LL)
		(exp(LL))
		(sample)

lpois
ppois
rpois
	lpois(mean, int _x);
	ppois(mean, int _x);
	int rpois(lambda);
		log(mean^n * exp(-mean)/n!) (LL)
		(exp(LL))
		(sample)

lgamm
factorial
	lgamm(x);
	factorial(x);
		gamma function
		x! = x*(x-1)*…*1

lphi
phi
probit
erfunc
	lphi(x, v);
	phi(x);
	probit(p);
	erfunc(x);
		log(phi(x/stdev))
		normal(0,1) cum. dist. function
		inverse N(0,1) cum.dist. function
		error function

lambertw	lambertw(const z);	inverse of x(y)=y*exp(y)

Table D-1. Special functions

Name	Usage	Definition

ilogit
iloglog
icloglog
iprobit
	ilogit(x);
	iloglog(x);
	icloglog(x);
	iprobit(x);
		exp(x)/(exp(x)+1)
		inverse log-log link function
		inverse complementary log-log link function
		inverse probit (same as phi(x))

unifToPois-son	unifToPoisson(mean, r);	convert uniform distribution to poisson

min
max
log10
abs
ln
	min(x, y);
	max(x, y);
	log10(x);
	abs(x);
	ln(x);
		minimum
		maximum
		log base10
		absolute
		natural log

CalcTMax	CalcTMax(A, a, B, b, C, c);	obtain Tmax for a macro-parameter model
vfwt	vfwt(f, p);	make an observation variance function

Math functions

Phoenix PML supports a majority of the intrinsic math functions in the `Cmath.h` library. See the following tables for a list of supported functions. (Refer to http://www.cplusplus.com/reference/cmath/ for more information on the Cmath.h library.)

- “Trigonometric functions” on page 92
- “Hyperbolic functions” on page 93
- “Exponential and logarithmic functions” on page 93
- “Power functions” on page 93
- “Error and gamma functions” on page 93
- “Rounding and remainder functions” on page 94
- “Floating-point manipulation functions” on page 94
- “Minimum, maximum, difference functions” on page 94
- “Other functions available in math.h” on page 95
- “Classification macro/functions” on page 95
- “Comparison macro/functions” on page 95

Table D-2. Trigonometric functions

Function	Description
cos	Compute cosine
sin	Compute sine
tan	Compute tangent
acos	Compute arc cosine
asin	Compute arc sine
atan	Compute arc tangent
atan2	Compute arc tangent with two parameters

Table D-3. Hyperbolic functions

Function	Description
cosh	Compute hyperbolic cosine
sinh	Compute hyperbolic sine
tanh	Compute hyperbolic tangent
acosh	Compute arc hyperbolic cosine
asinh	Compute arc hyperbolic sine
atanh	Compute arc hyperbolic tangent

Table D-4. Exponential and logarithmic functions

Function	Description
exp	Compute exponential function
ldexp	Generate value from significand and exponent
log	Compute natural logarithm
log10	Compute common logarithm
exp2	Compute binary exponential function
expm1	Compute exponential minus one
ilogb	Integer binary logarithm
log1p	Compute logarithm plus one
log2	Compute binary logarithm
logb	Compute floating-point base logarithm
scalbn	Scale significand using floating-point base exponent
scalbln	Scale significand using floating-point base exponent (long)

Table D-5. Power functions

Function	Description
pow	Raise to power
sqrt	Compute square root
cbrt	Compute cubic root
hypot	Compute hypotenuse

Table D-6. Error and gamma functions

Function	Description
erf	Compute error function

Table D-6. Error and gamma functions

Function	Description
erfc	Compute complementary error function
tgamma	Compute gamma function
lgamma	Compute log-gamma function

Table D-7. Rounding and remainder functions

Function	Description
ceil	Round up value
floor	Round down value
fmod	Compute remainder of division
trunc	Truncate value
round	Round to nearest
lround	Round to nearest and cast to long integer
llround	Round to nearest and cast to long long integer
rint	Round to integral value
lrint	Round and cast to long integer
llrint	Round and cast to long long integer
nearbyint	Round to nearby integral value
remain-der	Compute remainder

Table D-8. Floating-point manipulation functions

Function	Description
copysign	Copy sign
nextafter	Next representable value
nextfor-ward	Next representable value toward precise value

Table D-9. Minimum, maximum, difference functions

Function	Description
fdim	Positive difference
fmax	Maximum value
fmin	Minimum value

Table D-10. Other functions available in math.h

Function	Description
fabs	Compute absolute value
abs	Compute absolute value
fma	Multiply-add

Table D-11. Classification macro/functions

Function	Description
isfinite	Is a finite value
isinf	Is infinity
isnormal	Is normal
signbit	Sign bit (whether the sign of x is negative)

Table D-12. Comparison macro/functions

Function	Description
isgreater	Is greater
isgreatereq-ual	Is greater or equal
isless	Is less
islessequal	Is less or equal
islessgreater	Is less or greater
isunordered	Is unordered

Index

C

Closed-form
- computations, 79
- example, 77
- syntax, 23

Column mappings, 16
Comments syntax, 20
Count statement, 29
Customer support, 11

D

Data input data, 14
delay function, 41
delayInfCpt statement, 43
Delays, 40
Discontinuous events, 39
Dosing syntax, 27

E

Emax, 74
Event statement, 32
Examples
- closed-form, 77
- Emax model, 74
- first-order, 76
- lag time, 77
- logistic, 65
- multinomial, 72
- parallel, 75
- phenobarbital, 61
- population PK, 63, 74
- sequence, 75
- simple PK, 61
- sleep, 76
- theophylline, 63
- time to event model (exponential), 72
- time to event model (Weibull), 73
- time-to-event, 78

Exponential time to event model, 72

F

Fixed effects
- enabled or disabled, 47
- syntax, 47

I

Including files in code, 16

L

Lag time example, 77
Limits for dataset rows, 14
LL statement, 34
Logistic model, 65

M

Macroconstants closed-form, 23
Matrix exponent, 80
Microconstants closed-form, 23
Model file, 15
Modeling syntax, 21
Multi statement, 34
Multinomial
- example, 72
- responses, 35

O

Observe statement, 37
Operators, 88
Ordinal statement, 37

P

Parallel, 75
Phenobarbital example, 61
PK
    example, 61
    model syntax, 21
    population example, 63, 74
PML examples, 61

R

Random effects syntax, 48
Responses, time-to-event, 78

S

Sequence, 75
Sleep statement, 76
Syntax
    closed-form, 23
    comments, 20
    discrete events, 39
    dosing, 27
    fixed effects, 47
    general, 20
    modeling, 21
    random effects, 48

T

Technical support, 11
Theophylline example, 63
Time to event model, 32
    exponential, 72
    Weibull, 73

U

User-defined model, 65

W

Weibull time to event model, 73