# mrgsolve User Guide

Metrum Research Group

2019-12-14

# Contents

# Introduction

Welcome to the mrgsolve user guide. The user guide is the main documentation source for how mrgsolve works and how to best use mrgsolve in your modeling and simulation project. As with most of the mrgsolve documentation, this is a work in progress. I am currently working to transition this to more of a reference resource, rather than demonstration. So key content in the user guide includes chapter 2 on model specification, chapter 1 on model components and chapter 5 on the simulation sequence. Installation is a big topic but we defer to the wiki page for installation help since requirements tend to change frequently with new R releases. The other content is hopefully helpful as well. I'm leaving it all in place for now, but will gradually transition the "how-to" and demo type content over to the vignettes repository or the gallery repository (see below).

Please feel free to ask questions about anything mrgsolve-related on the issue tracker on the main github repo: https://github.com/metrumresearchgroup/mrgsolve/issues.

Other Resources

- Main resource page: mrgsolve.github.io
- Vignettes: mrgsolve.github.io/vignettes
- R documentation: mrgsolve.github.io/docs
- Gallery: github.com/mrgsolve/gallery

This book was assembled on Sat Dec 14 22:53:05 2019 with mrgsolve version 0.10.0.9000.

# Chapter 1

# Model components

This chapter details the different components of a model in `mrgsolve`. Each component listed here is maintained within a "model object". This is an updatable S4 object in `R` that contains all of the basic information required to properly configure and simulate from the model.

## 1.1 Parameter list

The parameter list is an updatable set of name-value pairs. Referencing the name of an item in the parameter list will substitute the current value associated with that name. While the name "parameter" may have a certain connotation in the modeling world, in `mrgsolve` a "parameter" could be any category of numeric data: covariates (e.g. `WT`, `AGE`, `SEX`), flags, other numeric data that we commonly call "parameter" (e.g. `CL` or `VC`).

The parameter list is declared in the code block `$PARAM`. While there may be multiple `$PARAM` blocks in a model, these are condensed to a single parameter list stored in the model object. The names and numbers of all parameters in the model must be declared at the time that the model is compiled. Also, a default value for each parameter must be declared at model compile time, but the value of each parameter may be updated in one of several ways.

The parameters in a model object can be queried or updated with the `param()` function.

See also: 2.2.3, `?param` in the `R` help system after loading `mrgsolve`.

### 1.1.1   Central role of parameters in planning simulations

The data items in the parameter list are more than just values associated with a
name. When an name is added to the parameter list, that name becomes a key word
that `mrgsolve` will start to recognize in input data sets or when manipulating the
model object.

For example, when you want to include a covariate in the model, say weight (`WT`),
you'll include a column in the data set called `WT` that will indicate the weight of
this or that patient. It is crucial that you also list `WT` in `$PARAM` with some default
value. It helps if that value is sensible too. When `mrgsolve` receives the data set
prior to simulating, the `WT` column is matched up with the `WT` parameter name. As
`mrgsolve` works its way through the input data set (from person to person or from
time to time), the value of `WT` is updated so that the symbol `WT` in `$MAIN` or `$ODE` or
`$TABLE` always points to the value of `WT`. If the `WT` name is not in the parameter list,
it won't matter if it is in the data set or not. Only listing a name in `$PARAM` gets it
"into the game".

Understanding the parameter update mechanism is very important for planning
complicated simulations with `mrgsolve`. Please see the information in 3.1 and in
6.3.

## 1.2   Compartment list

Like the parameter list, the compartment list is a series of name-value pairs. The
compartment list defines the number, names, and initial values of each compart-
ment in the model. The names, numbers, and order of the compartment in a model
is established at the time of model compile and changes to the compartment list
require re-compilation of the model.

Compartments are declared in one of two code blocks: `$INIT` and `$CMT`. Nomi-
nal initial values must be supplied for each compartment. The main difference
between `$INIT` and `$CMT` is that `$CMT` assumes a default initial value of `0` for each
compartment; thus only compartment names are entered. When using `$INIT`, both
names and values must be explicitly stated for each compartment.

The initial values for each compartment can be queried with the `init()` function.
There are several different ways to set the initial conditions in a model; section 6.2
illustrates several of these.

See also: section 6.2 and `?init` in the R help system after loading `mrgsolve`.

## 1.3 Simulation time grid

The `mrgsolve` model object stores the parameters for the series of time points to be output for a a simulation. This is the default output time grid that will be used if not over-ridden by another mechanism.

The elements of the simulation time grid are: `start`, `end`, `delta` and `add`. `start`, `end`, `delta` are passed to `seq()` as `from`, `to`, and `by`, respectively. `add` is any arbitrary vector of additional times to simulate.

The simulation time grid in a model object may be queried with the `stime()` function or by printing the model object to the `R` console.

See also section 3.2 for discussion of the simulation time grid and input data sets and 1.3.1 and 6.4 for using time grid objects .

### 1.3.1 `tgrid` objects

A `tgrid` object has `start`, `end`, `delta` and `add` attributes. This object is independent of the model object. `tgrid` objects may be created and combined to create complex sampling designs.

See section 6.4 for examples and usage.

## 1.4 Solver settings

`mrgsolve` uses the `DLSODA` solver from `ODEPACK`. Several of the settings for that solver are stored in the model object and passed to the solver when the problem is started. Settings include: `atol`, `rtol`, `maxsteps`, `hmax`, `hmin`, `ixpr`, `mxhnil`.

### 1.4.1 `atol`

Absolute tolerance parameter. Adjust this value lower when you see state variables (compartments) that are becoming very small and possibly turning negative. For example:

```
mod <- modlib("viral1", end = 144)

. Loading model from cache.
out <- mrgsim_e(mod, ev(amt = 1000)) %>% filter(V < 0)

out
```

```
. # A tibble: 6 x 8
.       ID  time expos        T          I          V  logV logChange
.    <dbl> <dbl> <dbl>    <dbl>      <dbl>      <dbl> <dbl>     <dbl>
. 1     1   95    1000 5187630. -2.74e-10 -1.79e-12   NaN       NaN
. 2     1   97.5  1000 5298189. -3.18e-10 -2.09e-12   NaN       NaN
. 3     1  120    1000 6252828. -1.55e-10 -1.01e-12   NaN       NaN
. 4     1  122.   1000 6354547. -2.90e-10 -1.90e-12   NaN       NaN
. 5     1  125    1000 6455422. -1.97e-10 -1.30e-12   NaN       NaN
. 6     1  128.   1000 6555459. -7.81e-11 -5.21e-13   NaN       NaN
```

Adjusting `atol` to 1E-20 or 1E-30 will prevent this.

```r
mrgsim_e(mod, ev(amt = 1000), atol = 1E-20) %>% filter(time %in% out$time)
```

```
. # A tibble: 6 x 8
.       ID  time expos        T         I         V  logV logChange
.    <dbl> <dbl> <dbl>    <dbl>     <dbl>     <dbl> <dbl>     <dbl>
. 1     1   95    1000 5187630. 1.33e-11 8.72e-14 -13.1     -18.7
. 2     1   97.5  1000 5298189. 5.13e-12 3.36e-14 -13.5     -19.2
. 3     1  120    1000 6252828. 1.01e-15 6.62e-18 -17.2     -22.9
. 4     1  122.   1000 6354547. 3.94e-16 2.58e-18 -17.6     -23.3
. 5     1  125    1000 6455422. 1.54e-16 1.01e-18 -18.0     -23.7
. 6     1  128.   1000 6555459. 5.99e-17 3.92e-19 -18.4     -24.1
```

### 1.4.2  `rtol`

Relative tolerance parameter. Adjust this value lower when you want more precision around the calculation of state variables as the system advances.

### 1.4.3  `maxsteps`

This is the maximum number of steps the solver will take when advancing from one time to the next. If the solver can't make it in `maxsteps` it will stop and give an error message like this:

```
DLSODA-  At current T (=R1), MXSTEP (=I1) steps
      taken on this call before reaching TOUT
In above message, I =
[1] 2000
In above message, R =
[1] 0.0004049985
DLSODA-  ISTATE (=I1) illegal.
In above message, I =
[1] -1
DLSODA-  Run aborted.. apparent infinite loop.
```

```
Error in (function (x, data, idata = null_idata, carry.out = character(0),  :
  error from XERRWD
```

You might see this when you have to integrate along time between records in a data set. There isn't necessarily a problem, but the solver might have to advance over many doses to get to the next record and it only has a limited number of steps it can take between those records before it stops with this error.

When you see this, increase `maxsteps` to 50000 or larger.

But keep in mind that sometimes the solver can't make it to the next record because there are issues with the model. It might take thousands of steps to make it 24 hours down the road. In that case, go back to the model code and look for problems in how it is coded.

### 1.4.4  `hmax`

The **maximum** step size. By default, the solver will take steps of different sizes based on what is happening in the simulation. Setting `hmax` tells the solver not to take a step larger than that value. So in a model where `time` is in hours, reducing `hmax` to `0.1` will prevent the solver from taking a step larger than `0.1` hours as it tries to advance to the next time. The will slow down the simulation a bit. But sometimes helpful when the solver starts taking large steps. We don't recommend using this routinely; for most applications, it should be reserved for troubleshooting situations. If your model doesn't give the results that you want without setting `hmax`, we'd recommend a new setup where this isn't needed.

### 1.4.5  `hmin`

The **minimum** step size. Only set this if you know what you're doing.

### 1.4.6  `ixpr`

A flag to enable printing messages to the R console when the solver switches between non-stiff and stiff solving modes. Rarely used.

### 1.4.7  `mxhnil`

The maximum number of messages printed when the model is solving. If you have a lot of messages, keep working on your model code.

## 1.5   Functions

There are four `C++` functions that `mrgsolve` creates and manages: `PREAMBLE`, `MAIN`, `ODE`, `TABLE`. Each function is created from an entire code block in the model specification file.  The user is responsible for writing correct `C++` code in each of these blocks. mrgsolve will parse these blocks and augment this code with the necessary elements to create the `C++` function.

These functions may be specified in any order in the model specification file, but there is a **specific calling order** for these functions.  Recognizing and understanding this calling order will help understand how the different pieces of the model specification fit together.

Just prior to starting the problem, mrgsolve calls `$PREAMBLE`. Then, during advance from time `T1` to `T2`, first `$MAIN` is called, then `$ODE` is called repeatedly as the solver finds the values of state variables at `T2`, and, once the solution is found, `$TABLE` is called to calculate derived quantities at `T2` and to specify variables that should be included in the model output. So, it is helpful to write model specification files in the order:

1. `$PREAMBLE` - called **only once** just prior to processing the first record of the data set
2. `$MAIN` - **before** advancing the system
3. `$ODE` - the system **advances** to `T2`
4. `$TABLE` - **after** advancing the system

But the order in which they are coded will not affect model compilation or the simulation result.

### 1.5.1   The `$PREAMBLE` function

The `PREAMBLE` function gets called only once, just prior to processing the first record of the data set.  This function is composed of `C++` code and is used to initialize variables and get them set up prior to starting on the problem.

See 2.2.9 for details.

### 1.5.2   The `$MAIN` function

The `MAIN` function gets called at least once before the the solver advances from the current time (`T1`) to the next time (`T2`). In the `MAIN` function, the user may:

- Set initial conditions for any compartment
- Derive new variables to be used in the model
- Write covariate models

- Add between-subject variability to quantities to structural model parameters (e.g. `CL` or `VC`).

In addition to getting called once per record, the `MAIN` function may be called several times prior to starting the simulation run. The `MAIN` function is also called whenever the user queries the compartment list.

See 2.2.6 for details.

### 1.5.3   The `$ODE` function

The `ODE` function is where the user writes the model differential equations.
Any derived quantity that depends on a state variable and is used to advanced the system must be calculated inside `$ODE`. But, this function is called repeatedly during the simulation run, so any calculation that **can** be moved out of `$ODE` (for example: to `$MAIN`) should be.

See 2.2.7 for details.

### 1.5.4   The `$TABLE` function

The `TABLE` function is called **after** the solver advances in time. The purpose of `TABLE` is to allow the user to interact with the values of the state variables after advancing, potentially derive new variables, and to insert different outputs into the table of simulated results.

See 2.2.8 for details.

## 1.6   Random effect variances

The `mrgsolve` model object keeps track of a arbitrary number of block matrices that are used to simulate variates from multivariate normal distributions. Users can specify `OMEGA` matrices for simulating between-subject random effects (one draw per individual) or `SIGMA` matrices for simulating within-subject random effects (one draw per observation).

The user may use the `revar()` function to query both `OMEGA` and `SIGMA`.

### 1.6.1   `OMEGA`

The matrices are specified in `$OMEGA` blocks in the model specification file.

`OMEGA` may be queried or updated with the `omat()` function.

### 1.6.2  SIGMA

The matrices are specified in $SIGMA blocks in the model specification file.

SIGMA may be queried or updated by the smat() function.

# Chapter 2

# Model specification

This chapter details the `mrgsolve` model specification format.

## 2.1 How / where to write a model

There are two ways to write your model:

### 2.1.1 Separate file

Open a text editor and type the model into a file with name that has the format `<model-name>.cpp`. This filename format identifies a "name" for your model (`<model-name>`, the "stem" of the file name). The extension **MUST** be `.cpp` (`mrgsolve` currently assumes the extension). Note: this whole file will be read and parsed, so everything in it must be valid `mrgsolve` model specification elements.

Use the `mread()` function to read and parse this file. For the model called `mymodel` saved in `mymodel.cpp` (in the current working directory), issue the command:

```
mod <- mread("mymodel")
```

`mread()` returns a model object from which you can simulate.

### 2.1.2 Inline / `code`

Often it is more convenient to write a model right in your R script. The model might look something like this:

```
code <- '
$PARAM CL = 1, VC = 20
$PKMODEL ncmt=1
'
```

Here, we created a character vector of length 1 and saved it to the R object called `code`. The name of this object is irrelevant. But `code` will be passed into `mrgsolve` as the model definition. When `mrgsolve` gets a model like this along with a "name" for the model, mrgsolve will write the code to a file called `<model-name>.cpp` and read it right back in as if you had typed the code into this file (section 2.1.1).

To parse and load this model, use the `mcode()` command:

```
mod <- mcode("mymodel", code)
```

`mcode()` is a convenience wrapper for `mread()`. `mcode` writes the code to `mymodel.cpp` in `tempdir()`, reads it back in, compiles and loads.

The `mcode` call is equivalent to:

```
mod <- mread("mymodel", tempdir(), code)
```

For help, see `?mread` , `?mcode` in the R help system after loading `mrgsolve`.

## 2.2   Code blocks

### 2.2.1   About code blocks

**Block identifier**

Different types of code are organized in the model specification file and separated by block identifiers. There are two ways to formulate block identifiers that can be used in mrgsolve. In the first type, a dollar-sign is placed at the start of the block name

```
$BLOCKNAME
<block-code>
```

For example, a block of parameters would be

```
$PARAM
CL = 1
```

The second way to write this is with brackets

```
[ BLOCKNAME ]
<block-code>
```

There is no functional difference between the dollar-sign notation and the brackets. When model specification code is saved into a file with a `.cpp` extension, the code editor may make certain assumptions about formatting or styling the code. Using brackets will most-likely work better with the editor in that case.

Users are free to include block code on the same line as the block identifier, but must include a space after the identifier. For example, the parser will recognize `$PARAM CL = 1` but not `$PARAMCL=1` as parameters.

**Block syntax** Different blocks may require different syntax. For example, code written in `$PARAM` will be parsed by the R parser and will generally need to adhere to R syntax requirements. On the other hand, code in `$MAIN`, `$ODE`, and `$TABLE` will be used to make functions in `C++` and therefore will need to be valid C++ code, including terminal `;` on each line.

**Block options** Options may be specified on some code blocks that signal how the code is to be parsed or used in the simulation.

### 2.2.2 `$PROB`

**Syntax**: text
**Multiple allowed**: yes
**Options**: `@annotated`, `@covariates`

Use this block to make notes about the model. There are no restrictions on the text that gets entered here. mrgsolve does not routinely process the text in any way, except when rendering the model as a document. Frequently, we write the text here in markdown format so that it will render nicely in the model document. But this is completely optional.

See the annotated model in section 6.1 for an example.

### 2.2.3 `$PARAM`

**Syntax**: R
**Multiple allowed**: yes
**Options**: `@annotated`, `@covariates`

Define the parameter list in the current model. Parameters are names associated with values that can be used throughout the model. A value must be given for every parameter name. Names (and numbers) of parameters must be set at the time the model is compiled, but parameter values may be updated without re-compiling the model.

The `@covariates` option allows you to tag a collection of parameters as "covariates". It does not change the functionality of the model or simulation workflow in any way, but allows you to get that list of covariate names out of the model object.

Example:

```
[ PARAM ] CL = 1, VC = 20, KA = 1.2
KM = 25, VMAX = 400, FLAG = 1, WT = 80
SEX = 0, N = sqrt(25)
```

Annotated example:

```
[ PARAM ] @annotated
CL :    1 : Clearance (L/hr)
VC :   20 : Volume of distribution (L)
KA:   1.2 : Absorption rate constant (1/hr)
```

See the popex model for an example of using @covariates

```
$PROB
# Example population PK model

$PARAM TVKA = 0.5, TVCL = 1, TVV = 24

$PARAM @covariates
WT = 70

$PKMODEL cmt="GUT CENT", depot=TRUE

$SET end=240, delta=0.5

$MAIN
double CL = exp(log(TVCL) + 0.75*log(WT/70) + ECL);
double V  = exp(log(TVV)  +      log(WT/70) + EV );
double KA = exp(log(TVKA)                   + EKA);

$OMEGA @labels ECL EV EKA
0.3 0.1 0.5

$SIGMA 0

$TABLE
capture IPRED = CENT/V;
capture DV = IPRED*exp(EPS(1));

$CAPTURE CL V ECL
```

then

```
mod <- modlib("popex")
```

```
as.list(mod)$covariates
```

```
. character(0)
```

Notes:

- Multiple blocks are allowed
- Values are evaluated by the R interpreter

See also: section 2.2.18 and 2.2.4.

See ?param in the R help system after loading mrgsolve.

### 2.2.4  $FIXED

**Syntax**: R
**Multiple allowed**: yes
**Options**: @annotated

Like $PARAM, $FIXED is used to specify name=value pairs. Unlike $PARAM, however, the values associated with names in $FIXED are not able to be updated.

By default, names in $FIXED are associated with their value through a C++ preprocessor #define statement.

Usually, $FIXED is only used when there are a very large number of parameters (> 100 or 200). When some of these parameters never need to be updated, you can move them to a $FIXED block to get a modest gain in efficiency of the simulation.

Items in $FIXED will not be shown when parameters are queried.

Example:

```
[ PARAM ] CL = 2, VC = 20

[ FIXED ]
g = 9.8
```

Annotated example:

```
$FIXED @annotated
g : 9.8 : Acceleration due to gravity (m/s^2)
```

See also: section 2.2.3 and 2.2.18.

Notes:

- Multiple blocks are allowed
- Values are evaluated by the R interpreter

### 2.2.5  `$CMT` and `$INIT`

**Syntax**: text
**Multiple allowed**: yes
**Options**: `@annotated`

Declare the names of all compartments in the model.

- For `$CMT` give the names of compartments; initial values are assumed to be 0
- For `$INIT` give the name and initial value for all compartments

Examples:

```
[ CMT ] GUT CENT RESPONSE
```

```
[ INIT ] GUT  = 0, CENT = 0, RESPONSE = 25
```

Annotated examples:

```
[ CMT ] @annotated
GUT      : Dosing compartment (mg)
CENT     : Central PK compartment (mg)
RESPONSE : Response
```

```
$INIT @annotated
GUT      :   0 : Dosing compartment (mg)
CENT     :   0 : Central PK compartment (mg)
RESPONSE :  25 : Response
```

See `?init` in the R help system after loading `mrgsolve`.

### 2.2.6  `$MAIN`

**Syntax**: C++
**Multiple allowed**: no

This code block has two main purposes:

- Derive new algebraic relationships between parameters, random, effects and other derived variables
- Set the initial conditions for model compartments

For users who are familiar with NONMEM, `$MAIN` is similar to `$PK`.

`$MAIN` is wrapped into a C++ function and compiled / loaded by `mrgsolve`.
The `MAIN` function gets called just prior to advancing the system from the current time to the next time for each record in the data set. `$MAIN` also gets called several times before starting the problem (`NEWIND == 0`) and just prior to simulating each individual (`NEWIND == 1`). Finally, `$MAIN` gets called every time the model initial conditions are queried with `init()`.

New variables may be declared in $MAIN. See section 2.4 for details.

Examples:

```
[ CMT ] CENT RESP

[ PARAM ] KIN = 100, KOUT = 2, CL = 1, VC = 20

[ MAIN ]

RESP_0 = KIN/KOUT;

double ke = CL/VC;
```

### 2.2.7 $ODE

**Syntax**: C++
**Multiple allowed**: no
**Options**: @param

Use $ODE to define model differential equations. For all compartments assign the value of the differential equation to dxdt_CMT where CMT is the name of the compartment. The dxdt_ equation may be a function of model parameters (via $PARAM), the current value of any compartment (CMT) or any user-derived variable.

For example:

```
[ CMT ] GUT CENT

[ ODE ]
dxdt_GUT = -KA*GUT;
dxdt_CENT = KA*GUT - KE*CENT;
```

It is important to make sure that there is a dxdt_ expression defined for every compartment listed in $CMT or $INIT, even if it is dxdt_CMT = 0;

The $ODE function is called repeatedly during a simulation run. So it is wise to do as many calculations as possible outside of $ODE, usually in $MAIN. But remember that any calculation that depends on an amount in a compartment and helps determine the dxdt_ expression in a model must be written in $ODE.

New variables may be declared in $ODE. See section 2.4 for details.

For example:

```
$CMT CENT RESP
$PARAM VC = 100, KE = 0.2, KOUT = 2, KIN = 100
$ODE
double CP = CENT/VC;
```

```
double INH = CP/(IMAX+CP)

dxdt_CENT = -KE*CENT;
dxdt_RESP =  KIN*(1 - INH) - RESP*KOUT;
```

If the model needs to refer to the current time, use the `SOLVERTIME` variable.

Notes:

- `$ODE` is written in C++ syntax; every line must end in ;
- There may be only one `$ODE` block in a model

### 2.2.8  `$TABLE`

**Syntax**: C++
**Multiple allowed**: no

Use `$TABLE` to interact with parameters, compartment values, and other user-defined variables **after** the system advances to the next time.

For example:

```
[ TABLE ]
double CP = CENT/VC;
```

**NOTE** `mrgsolve` formerly had a `table()` macro for inserting derived values into simulated output. This macro has been deprecated. The only way to insert derived values into the simulated output is via `$CAPTURE`.

**NOTE** When variables are marked for capture (see 2.2.11), the values of those variables are saved at the **end** of the `$TABLE` function.  This process is carried out automatically by `mrgsolve` and therefore requires no user intervention.

### 2.2.9  `$PREAMBLE`

**Syntax**: C++
**Multiple allowed**: no

This is the fourth C++ code block. It is called once in two different settings:

1. Immediately prior to starting the simulation run
2. Immediately prior to calling `$MAIN` when calculating initial conditions

`$PREAMBLE` is a function that allows you to set up your C++ environment. It is only called one time during the simulation run (right at the start). The code in this block is typically used to configure or initialize C++ variables or data structures that were declared in `$GLOBAL`.

For example:

```
[ PLUGIN ] Rcpp

[ GLOBAL ]
namespace{
  Rcpp::NumericVector x;
}

[ PREAMBLE ]
x.push_back(1);
x.push_back(2);
x.push_back(3);

[ MAIN ]
<some code that uses x vector>
```

In this example, we want to use a numeric vector x and declare it in `$GLOBAL` so that we can use it anywhere else in the code (the declaration is also made in an unnamed namespace to ensure that the variable is local to the model file). Then, in `$PREAMBLE`, we put 3 numbers into the vector and we use x in `$MAIN`. Since `$MAIN`, `$TABLE` and (especially) `$ODE` are called repeatedly as the simulation run progresses, we put the initialization of x in `$PREAMBLE` to make sure the initialization of x only happens once.

Notes:

- `$PREAMBLE` is written in `C++` syntax; every line must end in `;`
- There may be only one `$PREAMBLE` block in a model
- Like `$MAIN`, `$ODE` and `$TABLE`, `double`, `int` and `bool` variables initialized in `$PREAMBLE` are actually initialized for global (within the model file)

See also: 2.2.17.

## 2.2.10  `$PRED`

**Syntax**: C++
**Multiple allowed**: no

Use $PRED to write a model without differential equations. In this block, write all algebraic expressions for derived parameters, the response, and any other derived output quantities.

For example:

```
[ PARAM ] TVE0 = 100, AUC50 = 100, IMAX = 40, AUC = 0

[ PRED ]
double E0 = EVE0*exp(ETA(1));
```

```
double RESP = E0 - IMAX*AUC/(AUC50+AUC);
```

In this example, the entire model is written in the $PRED block. It is an error to include the following blocks when $PRED is being used: $MAIN, $TABLE, $PKMODEL, $ODE, $CMT, $INIT.

See the section 3.6 for additional information regarding data sets in use with $PRED block.

### 2.2.11  $CAPTURE

**Syntax**: text
**Multiple allowed**: yes
**Options**: @annotated

This is a block to identify variables that should be captured in the simulated output.

For example:

```
[ PARAM ] A = 1, B = 2

[ MAIN ]
double C = 3;
bool yes = true;

[ CAPTURE ] A B C yes
```

This construct will result in 4 additional columns in the simulated output with names A, B, C, and yes.

Users can also rename captured variables by providing a newname = oldname specification.

```
$PARAM WT = 70, THETA1 = 2.2

$MAIN
double CL = THETA1*pow(WT/70,0.75)*exp(ETA(1));

$OMEGA 1

$CAPTURE WEIGHT = WT TVCL = THETA2 CL  ETA(1)
```

In this example, the names of the captured data items will be WEIGHT,TVCL,CL,ETA_1.

Users can use the capture type to declare variables in $MAIN and $TABLE. capture types are really doubles, but using that type will signal mrgsolve to automatically capture that value. For example:

```
$PARAM VC = 300

$CMT CENT

$TABLE
capture DV = (CENT/VC);
```

Since we used type `capture` for DV, DV will show up as a column in the simulated data.

Annotated example:

```
$MAIN
double CLi = TVCL*exp(ECL);

$TABLE
double DV = (CENT/VC)*exp(PROP);

$CAPTURE @annotated
CLi : Individual clearance (L/hr)
DV  : Plasma concentration (mcg/ml)
```

New variables may be declared in `$TABLE`. See section 2.4 for details.

### 2.2.12  $OMEGA

**Syntax**: text
**Multiple allowed**: yes
**Options**: @annotated, @block, @correlation, @labels, @name

See ?modMATRIX for more details about options for this block.

Use this block to enter variance/covariance matrices for subject-level random effects drawn from multivariate normal distribution. All random effects are assumed to have mean of 0. Off diagonal elements for block matrices are assumed to be correlation coefficients if the `@correlation` option is used (see below).

By default, a **diagonal** matrix is assumed. So:

```
$OMEGA
1 2 3
```

will generate a 3x3 omega matrix.

A **block** matrix may be entered by using `block=TRUE`. So:

```
$OMEGA @block
0.1 0.02 0.3
```

will generate a 2x2 matrix with covariance 0.02.

A 2x2 matrix where the off-diagonal element is a correlation, not a covariance can be specified like this:

```
$OMEGA @correlation
0.1 0.67 0.3
```

Here, the correlation is 0.67. `mrgsolve` will calculate the covariances and substitute these values. The matrix will be stored and used with these covariances, not the correlation.

A name can be assigned to each matrix:

```
$OMEGA @name PK @block
0.2 0.02 0.3

$OMEGA @name PD
0.1 0.2 0.3 0.5
```

to distinguish between multiple `$OMEGA` blocks and to facilitate updating later. The model in the preceding example will have two `$OMEGA` matrices: 2x2 and 4x4.

Annotated example (diagonal matrix):

```
$OMEGA @annotated
ECL: 0.09 : ETA on clearance
EVC: 0.19 : ETA on volume
EKA: 0.45 : ETA on absorption rate constant
```

Annotated example (block matrix):

```
$OMEGA @annotated @block
ECL: 0.09 : ETA on clearance
EVC: 0.001 0.19 : ETA on volume
EKA: 0.001 0.001 0.45 : ETA on absorption rate constant
```

Notes:

- Multiple `$OMEGA` blocks are allowed

### 2.2.13   `$SIGMA`

**Syntax**: text
**Multiple allowed**: yes
**Options**: `@annotated`, `@block`, `@correlation`, `@labels`, `@name`

See `?modMATRIX` for more details about options for this block.

Use this block to enter variance/covariance matrices for within-subject random effects drawn from multivariate normal distribution. All random effects are assumed

to have mean of 0. Off diagonal elements for block matrices are assumed to be correlation coefficients if the `@correlation` option is used (see below).

The `$SIGMA` block functions like the `$OMEGA` block. See `$OMEGA` for details.

### 2.2.14 `$SET`

**Syntax**: R
**Multiple allowed**: no

Use this code block to set different options for the simulation. Use a `name=value` format, where `value` is evaluated by the R interpreter.

Most of the options that can be entered in `$SET` are passed to `update`.

For example:

```
[ SET ] end = 240, delta=0.5, req=s(RESP)
```

Here, we set the simulation `end` time to 240, set the time difference between two adjacent time points to 0.25 time units, and request only the `RESP` compartment in the simulated output.

### 2.2.15 `$GLOBAL`

**Syntax**: C++
**Multiple allowed**: no

The `$GLOBAL` block is for writing `C++` code that is outside of `$MAIN`, `$ODE`, and `$TABLE`.

There are no artificial limit on what sort of `C++` code can go in `$GLOBAL`.
However there are two more-common uses:

1. Write `#define` preprocessor statements
2. Define global variables, usually variables other than `double`, `bool`, `int` (see 2.4)

**Preprocessor directives** Preprocessor `#define` directives are direct substitutions that the `C++` preprocessor makes prior to compiling your code.

For example:

```
[ GLOBAL ]
#define CP (CENT/VC)
```

When this preprocessor directive is included, everywhere the preprocessor finds a `CP` token it will substitute `(CENT/VC)`. Both `CENT` and `VC` must be defined and the ratio of `CENT` to `VC` will be calculated depending on whatever the current values are.

Notice that we included parentheses around (`CENT/VC`).
This makes sure the ratio between the two is taken first, before any other operations
involving `CP`.

**Declaring global variables** Sometimes, you may wish to use global variables and
have more control over how they get declared.

```
$GLOBAL
bool cure = false;
```

With this construct, the boolean variable `cure` is declared and defined right as the
model is compiled.

### 2.2.16  `$PKMODEL`

**Syntax**: R
**Multiple allowed**: no

This code block implements a one- or two-compartment PK model where the system
is calculated by algebraic equations, not ODEs. `mrgsolve` handles the calculations
and an error is generated if both `$PKMODEL` and `$ODE` blocks are included in the
same model specification file.

This is an options-only block. The user must specify the number of compartments
(1 or 2) to use in the model as well as whether or not to include a depot dosing
compartment. See `?PKMODEL` for more details about this block, including specific
requirements for symbols that must be defined in the model specification file.

The `$CMT` or `$INIT` block must also be included with an appropriate number of
compartments. Compartment names, however, may be determined by the user.

Example:

```
[ CMT ] GUT CENT PERIPH

[ PKMODEL ] ncmt=2, depot=TRUE
```

As of version `0.8.2`, we can alternatively specify the compartments right in the
`$PKMODEL` block:

```
$PKMODEL cmt="GUT CENT PERIPH", depot = TRUE
```

Specifying three compartments with `depot=TRUE` implies `ncmt=2`. Notice that a
separate `$CMT` block is not appropriate when `cmt` is specified in `$PKMODEL`.

### 2.2.17 `$PLUGIN`

**Syntax**: text
**Multiple allowed**: no

Plugins are a way to add extensions to your `mrgsolve` model. When a plugin is recruited into the model, `mrgsolve` may do one or more of the following:

- Link to another `R` package during compilation, including
  - `Rcpp` to allow you to write `Rcpp` code in your specification
  - `mrgx` to provide some extra C++ functions (see below)
  - `RcppArmadillo` to both `Rcpp` and `Armadillo` in your specification
  - `BH` to use `boost` headers
- Include appropriate header files during compilation
  - For example, when the `Rcpp` plugin is called, `mrgsolve` will `#include <Rcpp.h>` at the top of your model file

You recruit a plugin in the `$PLUGIN` block

```
[ PLUGIN ] Rcpp
```

The example above will bring `Rcpp` headers into the model code.

Plugins that you can use: - `Rcpp` to write any `Rcpp` code - `mrgx` additional functions provided by `mrgsolve` that help use `Rcpp` in your model - `RcppArmadillo` to write any `Rcpp` or `RcppArmadillo` code - `BH` to link to `boost` headers

Note that `Rcpp`, `RcppArmadillo` and `BH` only allow you to link to those headers. To take advantage of that, you will need to know how to use `Rcpp`, `boost` etc. For the `BH` plugin, no headers are included for you; you must include the proper headers you want to use in `$GLOBAL`.

**Rcpp** example

```
[ PLUGIN ] Rcpp

[ MAIN ]

if(NEWIND <=1) {
  double wt = R::rnorm(70,20);
  double sex = R::rbinom(1,0.51);
}
```

**mrgx**

For example

```
$PLUGIN Rcpp mrgx
```

Functions provided by `mrgx`:

- `T get<T>(std::string <pkgname>, std::string <objectname>)`
  - This gets an object of any Rcpp-representable type (T) from any package
- `T get<T>(std::string <objectname)`
  - This gets an object of any Rcpp-representable type (T) from `.GlobalEnv`
- `T get<T>(std::string <objectname>, databox& self)`
  - This gets an object of any Rcpp-representable type (T) from `$ENV`
- `double rnorm(double mean, double sd, double min, double max)`
  - Simulate one variate from a normal distribution that is between `min` and `max`
- `double rlognorm(double mean, double sd, double min, double max)`
  - Same as `mrgx::rnorm`, but the simulated value is passed to `exp` after simulating
- `Rcpp::Function mt_fun()`
  - Returns `mrgsolve::mt_fun`; this is usually used when declaring a R function in `$GLOBAL`
  - Example: `Rcpp::Function print = mrgx::mt_fun();`

**IMPORTANT** All of these functions are in the `mrgx` namespace. So, in order to call these functions you must include `mrgx::` namespace identifier to the front of the function name. For example, don't use `rnorm(50,20,40,140)`; use `mrgx::rnorm(50,20,40,140)`.

**Get a numeric vector from `$ENV`**

```
[ PLUGIN ] Rcpp mrgx

[ ENV ]
x <- c(1,2,3,4,5)

[ GLOBAL ]
Rcpp::NumericVector x;

[ PREAMBLE ]
x = mrgx::get<Rcpp::NumericVector>("x", self);
```

**Get the `print` function from `package:base`**

```
$PLUGIN Rcpp mrgx

$GLOBAL
Rcpp::Function print = mrgx::mt_fun();

$PREAMBLE
print = mrgx::get<Rcpp::Function>("base", "print");

$MAIN
```

```
print(self.rown);
```

Note that we declare the `print` in `$GLOBAL` and use the `mt_fun()` place holder.

**Simulate truncated normal variables** This simulates a weight that has mean 80, standard deviation 20 and is greater than 40 and less than 140.

```
$PLUGIN Rcpp mrgx

$MAIN
if(NEWIND <=1) {
  double WT = mrgx::rnorm(80,20,40,140);
}
```

See also: 2.2.9.

### 2.2.18  `$THETA`

**Syntax**: text
**Multiple allowed**: yes
**Options**: `@annotated`, `@name`

Use this code block as an efficient way to add to the parameter list where names are determined by a prefix and a number. By default, the prefix is `THETA` and the number sequentially numbers the input values.

For example:

```
[ THETA ]
0.1 0.2 0.3
```

is equivalent to

```
$PARAM THETA1 = 0.1, THETA2 = 0.2, THETA3 = 0.3
```

Annotated example:

```
$THETA @annotated
0.1 : Typical value of clearance (L/hr)
0.2 : Typical value of volume (L)
0.3 : Typical value of ka (1/hr)
```

To change the prefix, use `@name` option

```
$THETA @name theta
0.1 0.2 0.3
```

would be equivalent to

```
[ PARAM ] theta1 = 0.1, theta2 = 0.2, theta3 = 0.3
```

See also: 2.2.3 .


### 2.2.19  `$NMXML`

**Syntax**: R
**Multiple allowed**: yes

The `$NMXML` block lets you read and incorporate results from a NONMEM run into your `mrgsolve` model. From the NONMEM run, `THETA` will be imported into your parameter list (see 2.2.3 and 1.1), `OMEGA` will be captured as an `$OMEGA` block (2.2.12) and `SIGMA` will be captured as a `$SIGMA` block (2.2.13). Users may optionally omit any one of these from being imported.

`$NMXML` contains a `project` argument and a `run` argument. By default, the estimates are read from from the file `project/run/run.xml`. That is, it is assumed that there is a directory named `run` that is inside the `project` directory where `$NMXML` will find `run.xml`. Your NONMEM run directories may not be organized in a way that is compatible with this default. In that case, you will need to provide the `file` argument, which should be the path to the `run.xml` file, either as a full path or as a path relative to the current working directory.

For help on the arguments / options for `$NMXML`, please see the `?nmxml` help topic in your R session after loading the `mrgsolve` package.

**An example**

There is a NONMEM run embedded in the `mrgsolve` package

```
path <- file.path(path.package("mrgsolve"),"nonmem")
list.files(path, recursive=TRUE)
```

```
.  [1] "1005/1005.cat"   "1005/1005.coi"   "1005/1005.cor"   "1005/1005.cov"
.  [5] "1005/1005.cpu"   "1005/1005.ctl"   "1005/1005.ext"   "1005/1005.grd"
.  [9] "1005/1005.lst"   "1005/1005.phi"   "1005/1005.shk"   "1005/1005.shm"
. [13] "1005/1005.tab"   "1005/1005.xml"   "1005/1005par.tab" "1005/INTER"
```

We can create a `mrgsolve` control stream that will import `THETA`, `OMEGA` and `SIGMA` from that run using the `$NMXML` code block.

```
code <- '
$NMXML
run = 1005
project = path
olabels = s_(ECL, EVC, EKA)
slabels = s_(PROP, ADD)
```

```
$MAIN
double CL = THETA1*exp(ECL);
double V2 = THETA2*exp(EVC);
double KA = THETA3*exp(EKA);
double Q = THETA4;
double V3 = THETA5;

$PKMODEL ncmt=2, depot=TRUE

$CMT GUT CENT PERIPH

$TABLE
double CP = (CENT/V2)*(1+PROP) + ADD/5;

$CAPTURE CP

$SET delta=4, end=96
'
```

**NOTE**: in order to use this code, we need to install the xml2 package.

```
mod <- mcode("nmxml", code, quiet=TRUE)
```

```
. Loading required namespace: xml2
```

```
param(mod)
```

```
.
.  Model parameters (N=7):
.  name    value  . name    value
.  THETA1 9.51   | THETA5 113
.  THETA2 22.8   | THETA6 1.02
.  THETA3 0.0714 | THETA7 1.19
.  THETA4 3.47   | .      .
```

```
revar(mod)
```

```
. $omega
. $...
.               [,1]        [,2]         [,3]
. ECL:    0.21387884  0.12077020 -0.01162777
. EVC:    0.12077020  0.09451047 -0.03720637
. EKA:   -0.01162777 -0.03720637  0.04656315
.
.
. $sigma
. $...
```

```
.                  [,1]        [,2]
. PROP:  0.04917071 0.0000000
. ADD:   0.00000000 0.2017688
```

### 2.2.20  `$INCLUDE`

**Syntax**: text
**Multiple allowed**: no

To include your own header file(s) in a model use `$INCLUDE`

```
$INCLUDE
mystuff.h
otherstuff.h
```

or

```
$INCLUDE
mystuff.h,  otherstuff.h
```

`mrgsolve` will insert proper `#include` preprocessor directives into the `C++` code that gets compiled.

**Requirements**

- All header files listed in `$INCLUDE` are assumed (expected) to be under the `project` directory; don't use `$INCLUDE` for header files that are in any other location
- An error is generated if the header file does not exist
- An error is generated if any quotation marks are found in the file name (don't use quotes around the file name; `mrgsolve` will take care of that)
- A warning is issued if the header file does not end in `.h`
- When the header file is changed (MD5 checksum changes), the model will be forced to be rebuilt (recompiled) when `mread` or `mcode` (but not `mread_cache` or `mcode_cache`) is called; this feature is only available for header files listed in `$INCLUDE` (see below)
- Do not use `$INCLUDE` to include `Rcpp`, `boost`, `RcppArmadillo` or `RcppEigen` headers; use the appropriate `$PLUGIN` instead

For applications that don't fit into the requirements listed above, users can always include header files in the model in `$GLOBAL` like this:

```
$GLOBAL
#include "/Users/me/libs/mystuff.h"
```

But be careful when doing this: if there are changes to `mystuff.h` but not to any other part of the model specification, the model may not be fully compiled when calling `mread`. In this case, always use `preclean=TRUE` argument to `mread` to force the model to be built when calling `mread`.

### 2.2.21 `$ENV`

**Syntax**: R
**Multiple allowed**: no

This block is all R code (just as you would code in a stand-alone R script. The code is parsed and evaluated into a new environment when the model is compiled. Objects inside $ENV can be utilized in different C++ functions (see 2.2.17) or other parts of the simulation process.

For example:

```
$ENV

Sigma <- cmat(1,0.6,2)

mu <- c(2,4)

cama <- function(mod) {
  mod %>%
    ev(amt=100, ii=12, addl=10) %>%
    mrgsim(obsonly=TRUE,end=120)
}
```

## 2.3 Variables and Macros

This section describes some macros and internal variables that can be used in model specification files. In the following section, we adopt the convention that CMT stands for a compartment in the model.

**IMPORTANT NOTE**:

It should be clear from the usage examples which variables can be set by the user and which are to be read or checked. **All internal variables are pre-defined and pre-initialized by mrgsolve.** *The user should never try to declare an internal variable; this will always result in an compile-time error*.

### 2.3.1 `ID`

The current subject identifier. `ID` is an alias for `self.id`.

### 2.3.2  TIME

Gives the time in the current data set record.  This is usually only used in `$MAIN` or `$TABLE`. TIME is an alias for `self.time`. Contrast with SOLVERTIME.

### 2.3.3  SOLVERTIME

Gives the time of the current timestep taken by the solver.  *This is can only be used in $ODE*. Contrast with TIME.

### 2.3.4  EVID

EVID is an event id indicator. `mrgsolve` recognized the following event IDs:

- 0 = an observation record
- 1 = a bolus or infusion dose
- 2 = other type event, with solver reset
- 3 = system reset
- 4 = system reset and dose
- 8 = replace

EVID is an alias for `self.evid`.

### 2.3.5  CMT

CMT is the current compartment number.  In this case, `CMT` is used literally (not a stand-in for the name of a compartment).  For example:

```
$CMT GUT CENT PERIPH

$MAIN

if(CMT==2) {
  // ....
}
```

In the example, `GUT`, `CENT` and `PERIPH` are the amounts in the respective compartments and `CMT` refers to the value of `CMT` in the data record / data set.

CMT is an alias for `self.cmt`.

### 2.3.6  AMT

AMT is the current value of dose amount.

AMT is an alias for `self.amt`.

### 2.3.7 `NEWIND`

NEWIND is a new individual indicator, taking the following values:

- 0 for the first event record of the data set
- 1 for the first event record of a subsequent individual
- 2 for subsequent event record for an individual

For example:

```
[ GLOBAL ]
int counter = 0;

[ MAIN ]
if(NEWIND <=1) {
  counter  = 0;
}
```

NEWIND is an alias for `self.newind`.

### 2.3.8 `self.cmt`

The current compartment number regardless of whether it was given as `cmt` or `CMT` in the data set. There is no alias for `self.cmt`.

For example:

```
$TABLE

double DV = CENT/VC + EPS(1);

if(self.cmt==3) DV = RESPOSE + EPS(2);
```

### 2.3.9 `self.amt`

The current `amt` value regardless of whether it was given as `amt` or `AMT` in the data set. There is no alias for `self.amt`.

```
[ PREAMBLE ]
double last_dose = 0;

[ MAIN ]
```

```
if(EVID==1) {
  last_dose = self.amt;
}
```

### 2.3.10  `self.nid`

The number of IDs in the data set.

### 2.3.11  `self.idn`

The current id number. Numbers start at 0 and increase by one to `self.nid-1`.

### 2.3.12  `self.nrow`

The number of rows in the output data set.

### 2.3.13  `self.rown`

The current row number. Numbers start at 0 and increase by one to `self.rown-1`.

### 2.3.14  `self.tad()`

This is a function that calculates and returns the time after the most recent dose. This function should be called in $MAIN every time $MAIN is called.

For example:

```
$MAIN

double TAD = self.tad();
```

Do not make this calculation depend on any test or condition; it must be called every time $MAIN is called in order to see every dose.

### 2.3.15  `self.mtime(<time>)`

This is a function that creates a modeled even time. The only argument is a numeric time in the future for the current individual that indicates when a discontinuity should be included in the simulation.

When when `self.mtime()` is called, a new record is added to the current individual's record set with `EVID` set to 2. This means that when the system advances to this record (this time), the differential equation solver will reset and restart, creating the discontinuity. The function returns the time of this event so the user can work with it in subsequent code.

For example,

```
$PARAM change_point = 5.13;

$MAIN

double KA = 1.1;

double mt1 = self.mtime(change_point);

if(TIME >= mt1) KA = 2.1;
```

### 2.3.16 `self.stop()`

This `self` function is available to be called from `$PREAMBLE`, `$MAIN`, and `$TABLE`. When this function is called, the entire problem is stopped upon processing the next simulation record.

This might be called when something really bad happened and you just want to stop the simulation with an error.

### 2.3.17 `self.stop_id()`

This `self` function is available to be called from `$PREAMBLE`, `$MAIN`, and `$TABLE`. When this function is called, processing of the current individual is stopped and missing values (`NA_real`) are filled in for remaining compartment' and capture outputs.

This might be called when some condition is reached in the current individual that indicates either that the rest of the outputs are inconsequential or there was a problem with this particular individual.

See also `self.stop_id()` and `self.stop()`.

### 2.3.18 `self.stop_id_cf()`

This `self` function is available to be called from `$PREAMBLE`, `$MAIN`, and `$TABLE`. When this function is called, processing of the current individual is stopped and

current values are carried forward (`cf`) for the remaining output records for that individual.

This might be called when some condition is reached in the current individual that indicates either that the rest of the outputs are inconsequential or there was a problem with this particular individual.

See also `self.stop_id_cf()` and `self.stop()`.

### 2.3.19   ETA(n)

`ETA(n)` is the value of the subject-level variate drawn from the model `OMEGA` matrix. `ETA(1)` through `ETA(25)` have default values of zero so they may be used in a model even if appropriate `OMEGA` matrices have not been provided.

For example:

```
$OMEGA
1 2 3

$MAIN
double CL = TVCL*exp(ETA(1));
double VC = TVVC*exp(ETA(2));
double KA = TVKA*exp(ETA(3));
```

Here, we have a 3x3 `OMEGA` matrix. `ETA(1)`, `ETA(2)`, and `ETA(3)` will be populated with variates drawn from this matrix. `ETA(4)` through `ETA(25)` will be populated with zero.

### 2.3.20   EPS(n)

`EPS(n)` holds the current value of the observation-level random variates drawn from `SIGMA`. The basic setup is the same as detailed in `ETA(n)`.

Example:

```
[ CMT ] CENT

[ PARAM ] CL=1, VC=20

[ SIGMA ] @labels ADD PROP
25 0.0025

[ TABLE ]
double DV = (CENT/VC)*(1+PROP) + ADD;
```

### 2.3.21 `table(<name>)`

This macro has been deprecated. Users should **not** use code like this:

```
[ TABLE ]
table(CP) = CENT/VC;
```

But rather this:

```
$TABLE
double CP = CENT/VC;

$CAPTURE CP
```

See: section 2.2.8 and also 2.2.11

### 2.3.22 `F_CMT`

For the `CMT` compartment, sets the bioavailability fraction for that compartment.

Example:

```
$MAIN
F_CENT = 0.7;
```

### 2.3.23 `ALAG_CMT`

For the `CMT` compartment, sets the lag time for doses into that compartment.

Example:

```
$MAIN
ALAG_GUT = 0.25;
```

### 2.3.24 `R_CMT`

For the `CMT` compartment, sets the infusion rate for that compartment. The infusion rate is only set via `R_CMT` when `rate` in the data set or event object is set to `-1`.

Example:

```
$MAIN
R_CENT = 100;
```

### 2.3.25  `D_CMT`

For the `CMT` compartment, sets the infusion duration for that compartment.
The infusion duration is only set via `D_CMT` when `rate` in the data set or event object
is set to `-2`.

Example:

```
$MAIN
D_CENT = 2;
```

## 2.4   Derive new variables

New C++ variables may be derived in `$GLOBAL`, `$PREAMBLE` `$MAIN`, `$ODE` and `$TABLE`.
Because these are C++ variables, the type of variable being used must be declared.
For the vast majority of applications, the `double` type is used (double-precision
numeric value).

```
$MAIN

double CLi = TVCL*exp(ETA(1));
```

We want `CLi` to be a numeric value, so we use `double`.  To initialize a `boolean`
variable (true / false), write

```
$MAIN
bool cure = false;
```

### 2.4.1   Special handling for `double, int, bool`

When variables of the type `double`, `int`, and `bool` are declared and initialized
in `$PREAMBLE`, `$MAIN`, `$ODE`, `$TABLE`, mrgsolve will detect those declarations, and
modify the code so that the variables are actually declared once in `$GLOBAL` not in
`$MAIN`, `$ODE`, or `$TABLE`. This is done so that variables declared in one code block
(e.g. `$MAIN`) can be read and modified in another code block (e.g. `$TABLE`).

For example, in the following code:

```
$MAIN
double CLi = TVCL*exp(ETA(1));
```

a double-precision numeric variable is created (`CLi`) in the `$MAIN` block.  When
mrgsolve parses the model file, this code gets translated to

```
$GLOBAL
namespace {
```

```
   double CLi;
}

$MAIN
CLi = TVCL*exp(ETA(1));
```

That is, `CLi` is declared in `$GLOBAL` in an unnamed namespace so that variables like this are global variables within the model file only.

This way, we can still read the `CLi` variable in `$TABLE`:

```
$MAIN
double CLi = TVCL*exp(ETA(1));
double VCi = TVVC*exp(ETA(2));

$TABLE
double KEi = CLi/VCi;

$CAPTURE KEi
```

To declare a variable that is local to a particular code block:

```
$MAIN

localdouble CLi = TVCL*exp(ETA(1));
```

The `localdouble` type is still just a double-precision variable. The difference is that it is protected from this re-declaration process and the variable will be local to (in this case) the `$MAIN` block.

## 2.4.2 Using other types globally

As we noted in the previous section, `double`, `int`, and `bool` are processed in a special way so that they are by default global to the file. Many times we want to work with other variable types in a global manner. Whenever you want a data structure to be accessible across functions (e.g. `$MAIN`, `$TABLE`, etc.) they should be declared in `$GLOBAL`, optionally in an unnamed namespace.

For example:

```
[ GLOBAL ]
std::vector<double> myvec;
```

or

```
[ GLOBAL ]
namespace {
```

```
  std::vector<double> myvec;
}
```

In case that object needs some configuration prior to starting the problem, use $PREAMBLE to do that work

```
[ GLOBAL ]
std::vector<double> myvec;

[ PREAMBLE ]
myvec.assign(3,1);
```

## 2.5   Examples

The following sections show example model specification. The intention is to show how the different blocks, macros and variables can work together to make a functional model. Some models are given purely for illustrative purpose and may not be particularly useful in application.

### 2.5.1   Simple PK model

Notes:

- Basic PK parameters are declared in $PARAM; every parameter needs to be assigned a value
- Two compartments GUT and CENT are declared in $CMT; using $CMT assumes that both compartments start with 0 mass
- Because we declared GUT and CENT as compartments, we write dxdt_ equations for both in $ODE
- In $ODE, we refer to parameters (CL/VC/KA) and the amounts in each compartment at any particular time (GUT and CENT)
- $ODE should be C++ code; each line ends in ;
- We derive a variable called CP in $TABLE that has type capture; mrgsolve will enter the CP name into the $CAPTURE block list

```
$PARAM CL = 1, VC = 30, KA = 1.3

$CMT GUT CENT

$ODE

dxdt_GUT = -KA*GUT;
dxdt_CENT = KA*GUT - (CL/VC)*CENT;
```

```
$TABLE
capture CP = CENT/VC;
```

This model can also be written without differential equations

```
[ PARAM ] CL = 1, VC = 30, KA = 1.3

[ PKMODEL ] cmt = "CMT GUT CENT", depot = TRUE

$TABLE
capture CP = CENT/VC;
```

## 2.5.2 PK/PD model

Notes:

- We use a preprocessor #define directive in $GLOBAL; everywhere in the model where a CP token is found, the expression (CENT/VC) ... with parentheses ... is inserted
- We write the initial value for the RESP compartment in $MAIN as a function of two parameters KIN/KOUT
- A new variable - INH- is declared and used in $ODE
- Since CP is defined as CENT/VC, we can "capture" that name/value in $CAPTURE
- Both $MAIN and $ODE are C++ code blocks; don't forget to add the ; at the end of each statement

```
$PARAM CL = 1, VC = 30, KA = 1.3
KIN = 100, KOUT = 2, IC50 = 2

$GLOBAL
#define CP (CENT/VC)

$CMT GUT CENT RESP

$MAIN
RESP_0 = KIN/KOUT;

$ODE

double INH = CP/(IC50+CP);

dxdt_GUT = -KA*GUT;
dxdt_CENT = KA*GUT - (CL/VC)*CENT;
dxdt_RESP = KIN*(1-INH) - KOUT*CENT;
```

```
$CAPTURE CP
```

### 2.5.3   Population PK model with covariates and IOV

Notes:

- Use $SET to set the simulation time grid from 0 to 240 by 0.1
- There are two $OMEGA matrices; we name them IIV and IOV
- The IIV "etas" are labeled as ECL/EVC/EKA; these are aliases to ETA(1)/ETA(2)/ETA(3). The IOV matrix is unlabeled; we must refer to ETA(4)/ETA(5) for this
- Because ETA(1) and ETA(2) are labeled, we can "capture" them as ECL and EVC
- We added zeros for both $OMEGA matrices; all the etas will be zero until we populate those matrices (section 6.8)

```
$PARAM TVCL = 1.3, TVVC=28, TVKA=0.6, WT=70, OCC=1

$SET delta=0.1, end=240

$CMT GUT CENT

$MAIN

double IOV = IOV1
if(OCC==2) IOV = IOV2;

double CLi = exp(log(TVCL) + 0.75*log(WT/70) + ECL + IOV);
double VCi = exp(log(TVVC) + EVC);
double KAi = exp(log(TVKA) + EKA);

$OMEGA @name IIV @labels ECL EVC EKA
0 0 0
$OMEGA @name IOV @labels IOV1 IOV2
0 0

$SIGMA 0

$ODE
dxdt_GUT = -KAi*GUT;
dxdt_CENT = KAi*GUT - (CLi/VCi)*CENT;

$TABLE
capture CP = CENT/VCi;

$CAPTURE IOV ECL EVC
```

# Chapter 3

# Input data sets

Input data sets are used in mrgsolve to allow the user to specify interventions and input data items.

Please see the mrgsolve help topic `?exdatasets` for examples of all of the data sets discussed in this chapter. The example data sets are embedded in the mrgsolve package and may be used at any time.

## 3.1   Overview

Data sets are the primary mechanism for establishing the scope of your simulations in `mrsolve`, including individuals, interventions, observation times, and parameter values. For both `data_set` and `idata_set` (see below), you may include columns in the data sets that have the same names as the parameters in your model (section 1.1, 2.2.3). mrgsolve can recognize these columns and update the parameter list as the simulation proceeds. This process is of key importance when planning and executing complex simulations and is further discussed in section 6.3.

## 3.2   Event data sets (`data`)

Event data sets are entered as `data.frame`, with one event per row. Events may be observations, doses, or other type events. In mrgsolve documentation, we refer to these data sets as `data` or `data_set` (after the function that is used to associate the data set with the model object prior to simulation).

Event data sets have several special column names that mrgsolve is always aware of:

- `ID` the subject id. This id does not need to be unique in the `data_set`: mrg-solve detects an new individual when the current value of `ID` is different from the immediate preceding value of `ID`. However, we always recommend using unique `ID`.

- `time` or `TIME`: states the time of the data record

- `evid` or `EVID`: the event id indicator. `evid` can take the values:

  - **0** = observation record
  - **1** = dosing event (bolus or infusion)
  - **2** = other type event, with solver stop and restart
  - **3** = system reset
  - **4** = reset and dose
  - **8** = replace the amount in the compartment with `amt`

- `amt` or `AMT`: the dose amount (if `evid==1`)

- `cmt` or `CMT`: the dosing compartment number. This may also be a character value naming the compartment name. The compartment number must be consistent with the number of compartments in the model for dosing records (`evid==1`).
  For observation records, a `cmt` value of 0 is acceptable.  Use a negative compartment number with `evid` 2 to turn a compartment off.

- `rate` or `RATE`: if non-zero and `evid=1` or `evid=4`, implements a zero-order infusion of duration `F_CMT*amt/rate`, where `F_CMT` is the bioavailability fraction for the dosing compartment. Use `rate = -1` to model the infusion rate and `rate = -2` to model the infusion duration, both in `$MAIN` (see sections 2.2.6, 2.3.22,2.3.24, 2.3.25).

- `ii` or `II`: inter-dose interval; `ii=24` means daily dosing when the model time unit is hours

- `addl` or `ADDL`: additional doses; a non-zero value in `addl` requires non-zero `ii` on the same record

- `ss` or `SS` steady state indicator; use 1 to implement steady-state dosing; 0 otherwise. mrgsolve also recognizes dosing records where `ss=2`. This allows combination of different steady state dosing regimens under linear kinetics (e.g. 10 mg QAM and 20 mg QPM daily to steady state).

The column names in the preceding list were written either as lower case form (e.g. `amt`) or upper case form (e.g. `AMT`). Either may be used, however the data set will be checked for consistency of usage. An error will be issued in case a mixture of lower and upper case names are found.

In addition to these special column names, mrgsolve will recognize columns in `data_set` that have the same name as items in the parameter list (see 2.2.3 and 1.1). When mrgsolve sees that the names match up, it will update the values of those

matching names based on what it finds as it moves through the data set (see section 6.3).

### 3.2.1 Two types of `data_set`

mrgsolve distinguishes between two types of data sets: data sets that have *at least one observation record* (`evid=0`) and data sets that have *no records with `evid=0`*.

- **Full data sets** have a mix of observations and dosing events (likely, but not required). When mrgsolve finds one record with `evid=0`, it assumes that **ALL** output observation times are to come from the data set. In this case the simulation output time grid discussed in 1.3 is ignored and only observations found in the data set appear in the simulated output. Use full data sets when you want a highly customized sampling schedule or you are working with a clinical data set.
- **Condensed data sets** have no records with `evid=0`. In this case, mrgsolve will fill the simulated output with observations at times specified by the output time grid ( section 1.3 and see section 6.5). These are very convenient to use because there is less data assembly burden and output data sets can easily be created with very dense sampling scheme or highly customized sampling schemes with very little work. Use a condensed data set when you want a uniform set of sampling times for all subjects in the data set.

**Example of condensed data set**

```
data(extran1, package = "mrgsolve")
extran1
```

```
.    ID  amt cmt time addl ii rate evid
. 1   1 1000   1    0    3 24    0    1
. 2   2 1000   2    0    0  0   20    1
. 3   3 1000   1    0    0  0    0    1
. 4   3  500   1   24    0  0    0    1
. 5   3  500   1   48    0  0    0    1
. 6   3 1000   1   72    0  0    0    1
. 7   4 2000   2    0    2 48  100    1
. 8   5 1000   1    0    0  0    0    1
. 9   5 5000   1   24    0  0   60    1
```

See `?exdatasets` in the R help system after loading mrgsolve.

**Example of full data set**

```
data(exTheoph, package = "mrgsolve")

head(exTheoph)
```

```
.    ID   WT Dose time  conc cmt   amt evid
```

```
. 1  1 79.6 4.02 0.00   0.00   1 4.02    1
. 2  1 79.6 4.02 0.25   2.84   0 0.00    0
. 3  1 79.6 4.02 0.57   6.57   0 0.00    0
. 4  1 79.6 4.02 1.12  10.50   0 0.00    0
. 5  1 79.6 4.02 2.02   9.66   0 0.00    0
. 6  1 79.6 4.02 3.82   8.58   0 0.00    0
```

See ?exdatasets in the R help system after loading mrgsolve.

**Augmenting observations in a clinical data set** Occasionally, we want to simulate from a clinical data set (with observation records as actually observed in a population of patients) but we also want to augment those observations with a regular sequence of times (for example, to make a smooth profile on a plot). In that case, you can set obsaug  = TRUE when calling mrgsim.

For example:

```
mod <- mrgsolve:::house()

out <-
  mod %>%
    data_set(exTheoph, ID==1) %>%
    carry.out(a.u.g) %>%
    obsaug %>%
    mrgsim(end=24, delta=1)

out
```

```
. Model:  housemodel
. Dim:    36 x 8
. Time:   0 to 24.37
. ID:     1
.      ID time a.u.g   GUT   CENT  RESP      DV        CP
. 1:   1 0.00     1 0.0000 0.000 50.00 0.00000 0.00000
. 2:   1 0.00     0 4.0200 0.000 50.00 0.00000 0.00000
. 3:   1 0.25     0 2.9781 1.035 49.95 0.04552 0.04552
. 4:   1 0.57     0 2.0285 1.961 49.81 0.08624 0.08624
. 5:   1 1.00     1 1.2108 2.729 49.61 0.12001 0.12001
. 6:   1 1.12     0 1.0484 2.875 49.57 0.12643 0.12643
. 7:   1 2.00     1 0.3647 3.422 49.34 0.15048 0.15048
. 8:   1 2.02     0 0.3560 3.428 49.33 0.15072 0.15072
```

```
out %>% select(time) %>% unlist %>% unname
```

```
.  [1]  0.00  0.00  0.25  0.57  1.00  1.12  2.00  2.02  3.00  3.82  4.00  5.00
. [13]  5.10  6.00  7.00  7.03  8.00  9.00  9.05 10.00 11.00 12.00 12.12 13.00
. [25] 14.00 15.00 16.00 17.00 18.00 19.00 20.00 21.00 22.00 23.00 24.00 24.37
```

obsaug requests that the data set be augmented with observations from the simu-

lation time grid. We can optionally request an indicator called `a.u.g` to appear in the output that takes value of 1 for augmented observations and 0 for observations from the data set.

### 3.2.2 Sorting requirements

The IDs in the data set can appear in any order. However, an error will be generated if `time` on any record is less that `time` on the previous record within any ID.

### 3.2.3 Creating data sets

The `expand.ev` function is provided by mrgsolve to help in creating data sets of a certain style. But any R code that produces a valid data set is fine to use.

### 3.2.4 Example

To create a data set of 3 people each receiving **250 mg every 8 hours for 12 total doses**:

```
data <- expand.ev(ID=1:3, amt=250, ii=8, addl=11)

data
```

```
.    ID time amt ii addl cmt evid
. 1  1     0 250  8   11   1    1
. 2  2     0 250  8   11   1    1
. 3  3     0 250  8   11   1    1
```

Notice that `expand.ev` assumes that `time` is 0 and `cmt` is 1. To dose as a 2-hour infusion into the second compartment use:

```
data <- expand.ev(ID=1:3, amt=250, rate=125, ii=8, addl=11, cmt=2)

data
```
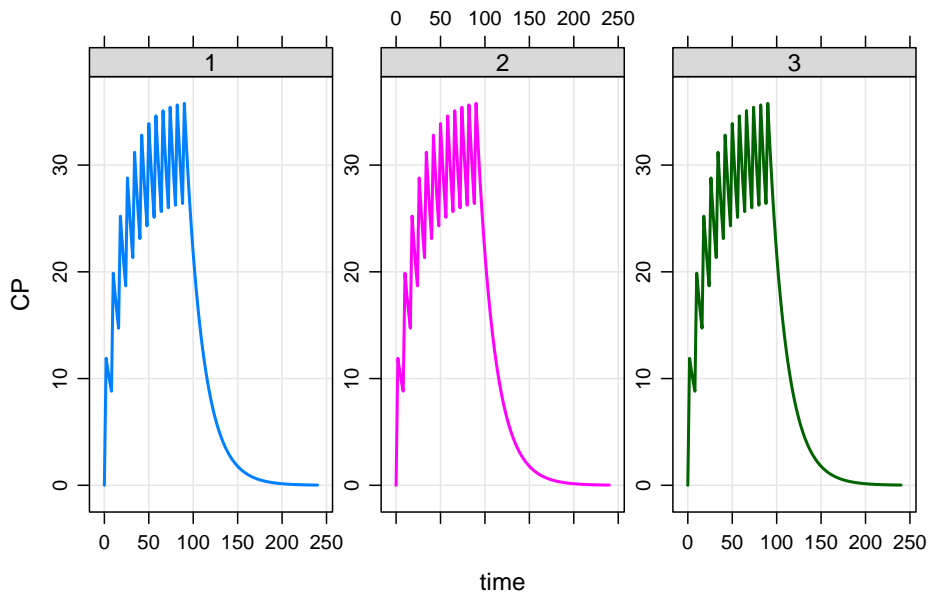
```
.    ID time amt rate ii addl cmt evid
. 1  1     0 250  125  8   11   2    1
. 2  2     0 250  125  8   11   2    1
. 3  3     0 250  125  8   11   2    1
```

Use `data_set` to pass the data into the problem.

For example:

```
mod <- mrgsolve:::house()

mod %>%
  data_set(data) %>%
  mrgsim(end=240) %>%
  plot(CP~time|factor(ID))
```



## 3.3   Individual data sets (`idata`)

Individual data sets carry individual-level data.  This individual data is used in several different ways:

- **Individual-level parameters**: Just prior to simulating any individual, mrgsolve checks the appropriate row in `idata` (if supplied) for any columns with parameter names.  If parameter names are found, the parameter list is updated and that update remains in effect for the duration of that individual's data records.
- **Individual- or group-level designs**: Each individual or group of individual may be assigned a different sampling design.  For example, individuals in arm 1 may need to be simulated for 4 weeks whereas individuals in arm 2 may need to be simulated for 8 weeks.  `idata` may be used to identify one of several sampling designs for each individual or group of individuals.
- **Individual-level compartment initialization**: if a model has a compartment called `CMT` and mrgsolve finds a column in `idata` called `CMT_0`, the value of `CMT_0` will be used to initialize that compartment with, potentially a different

value for each individual. Note that there are several other ways to initialize
compartments detailed in 6.2.

idata_set are entered as data.frame with one unique ID per row. In mrgsolve
documentation, we refer to individual data sets idata or idata_set to distinguish
them from event data sets (see section 3.2).

An idata_set looks like this:

```
data(exidata)

exidata
```

```
.     ID   CL    VC     KA   KOUT   IC50 FOO
. 1    1 1.050 47.80 0.8390 2.450 1.280    4
. 2    2 0.730 30.10 0.0684 2.510 1.840    6
. 3    3 2.820 23.80 0.1180 3.880 2.480    5
. 4    4 0.552 26.30 0.4950 1.180 0.977    2
. 5    5 0.483  4.36 0.1220 2.350 0.483   10
. 6    6 3.620 39.80 0.1260 1.890 4.240    1
. 7    7 0.395 12.10 0.0317 1.250 0.802    8
. 8    8 1.440 31.20 0.0931 4.030 1.310    7
. 9    9 2.570 18.20 0.0570 0.862 1.950    3
. 10  10 2.000  6.51 0.1540 3.220 0.699    9
```

Here we have an idata_set with 10 subjects, one subject per row. The ID column
connects the data in each row to the data in a data_set, which also requires an ID
column.

The ID column is the only required column name in idata_set and ID should
always be a unique identifier for that row.

### 3.3.1 Use case

idata_set is usually helpful for implementing a batch of simulations when a
data_set is not used. The batch may be as a sensitivity analysis or for popula-
tion simulation. Usually, an events object is used with idata, but it is not required.

Use the idata_set function to pass the data set into the problem.

For example:

```
mod <- mrgsolve:::house()

mod %>%
  idata_set(exidata) %>%
  ev(amt=100) %>%
  mrgsim %>% plot
```
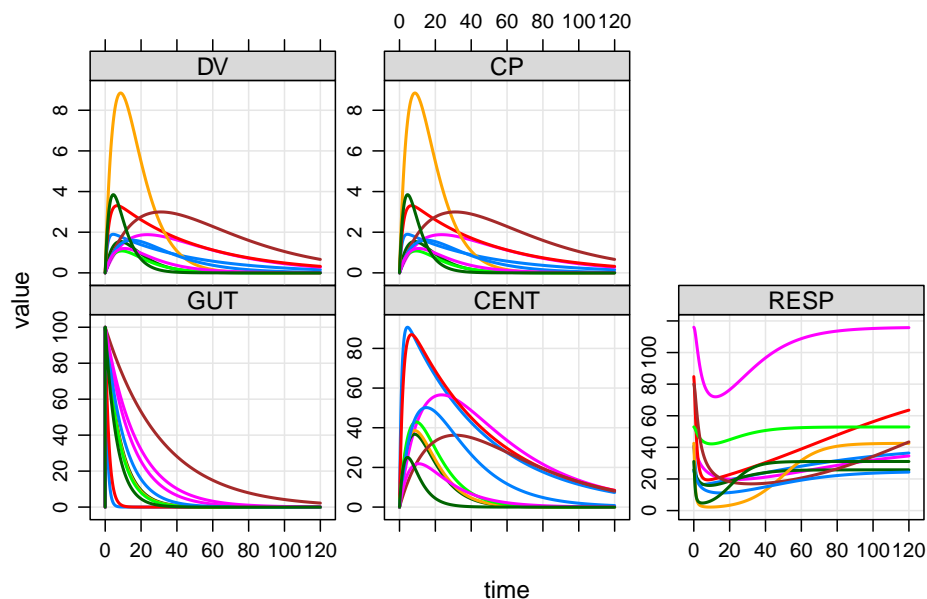
Because there were 10 subjects in the `idata_set`, we get 10 profiles in the output. Each "individual" or "unit" received the same 100 mg dose. We would use a `data_set` to assign different doses to different individuals.

## 3.4   Numeric data only

The `data.frame` holding the `data_set` or `idata_set` may have any type of data in its columns. However, only numeric data can actually get passed into the simulation engine. mrgsolve will automatically look for non-numeric columns and drop them from the `data_set` or `idata_set` with a warning.

## 3.5   Data set validation

A the time of simulation, mrgsolve will validate the input data set, removing character column, checking for missing values in parameter columns, checking compartment numbers etc.

Users can pre-validate the data set so that this does not need to happen at run time.

```
data(exTheoph)

head(exTheoph)

.    ID   WT Dose time   conc cmt   amt evid
```

```
. 1  1 79.6 4.02 0.00  0.00   1 4.02   1
. 2  1 79.6 4.02 0.25  2.84   0 0.00   0
. 3  1 79.6 4.02 0.57  6.57   0 0.00   0
. 4  1 79.6 4.02 1.12 10.50   0 0.00   0
. 5  1 79.6 4.02 2.02  9.66   0 0.00   0
. 6  1 79.6 4.02 3.82  8.58   0 0.00   0
```

```
mod <- modlib("pk1")
```

```
. Loading model from cache.
```

```
valid <- valid_data_set(exTheoph,mod)
```

```
str(valid)
```

```
.   'valid_data_set' num [1:132, 1:9] 1 1 1 1 1 1 1 1 1 1 ...
.   - attr(*, "dimnames")=List of 2
.    ..$ : chr [1:132] "1" "2" "3" "4" ...
.    ..$ : chr [1:9] "ID" "WT" "Dose" "time" ...
```

This can improve efficiency when performing a very large number of replicate simulations on the same data set, but is unlikely to provide a meaningful speed-up for a single simulation or a small number of simulations.

## 3.6 Data sets for use with `$PRED`

Because there are no compartments involved, there are relaxed data set requirements for models that utilize `$PRED`.

- `time` or `TIME` is not required as input; when this is not supplied, a `time` column will be included in output with value 0
- When `time` or `TIME` is supplied, it may be negative; but records must still be sorted by `time` or `TIME`
- If supplied, `cmt` or `CMT` must be zero
- An error is generated if `rate` or `RATE` is supplied
- An error is generated if `ss` or `SS` is supplied

# Chapter 4

# Simulated output

When `mrgsim` is used to simulate from a model, it returns an object with class `mrgsims`. It is an S4 object containing a matrix of simulated output and a handful of other pieces of data related to the simulation run.

`mrgsolve` provides several methods for working with `mrgsims` objects or coercing the simulation matrix into other R objects.

## 4.1   Coercion methods

- `as.data.frame` convert to `data.frame`
- `as.matrix` convert to `matrix`
- `as.tbl` convert to `tbl`
- `as_data_frame` convert to `tbl` via `tibble` package

## 4.2   Query methods

- `head`
- `tail`
- `names`
- `dim`
- `summary`
- `show`
- `$`

## 4.3   Methods for `dplyr` verbs

`mrgsolve` provides several S3 methods to make it possible to include `dplyr` verbs in your simulation pipeline.

For example

```r
library(dplyr)

mod <- mrgsolve:::house()

mod %>%
  ev(amt=100) %>%
  mrgsim %>%
  filter(time >=10)
```

```
. # A tibble: 441 x 7
.        ID  time        GUT  CENT  RESP    DV    CP
.     <dbl> <dbl>      <dbl> <dbl> <dbl> <dbl> <dbl>
. 1      1  10    0.000614   63.3  37.7  3.16  3.16
. 2      1  10.2 0.000455    62.5  37.9  3.13  3.13
. 3      1  10.5 0.000337    61.7  38.0  3.09  3.09
. 4      1  10.8 0.000250    61.0  38.1  3.05  3.05
. 5      1  11   0.000185    60.2  38.2  3.01  3.01
. 6      1  11.2 0.000137    59.5  38.3  2.97  2.97
. 7      1  11.5 0.000102    58.7  38.4  2.94  2.94
. 8      1  11.8 0.0000752   58.0  38.5  2.90  2.90
. 9      1  12   0.0000557   57.3  38.7  2.86  2.86
. 10     1  12.2 0.0000413   56.6  38.8  2.83  2.83
. # ... with 431 more rows
```

Here, `mrgsim` returns an `mrgsims` object.  When `dplyr` is also loaded, this object can be piped directly to `dplyr::summarise`.

Other `dplyr` functions that can be used with `mrgsims` objects

- `group_by`
- `mutate`
- `filter`
- `summarise`
- `select`
- `slice`
- `summarise.each` (use a `<dot>` not an `<underscore>`)

# Chapter 5

# Simulation sequence

This section is intended to help the user understand the steps `mrgsolve` takes when working through a simulation problem. The focus is on the order in which `mrgsolve` calls different user-defined functions as well as when parameter updates and output writing happens during the simulation sequence.

## 5.1   Functions to call

The model specification results in the definition of four functions that `mrgsolve` calls during the simulation sequence. Naming them by their code block identifiers, the functions are

1. `$PREAMBLE`
2. `$MAIN`
3. `$ODE`
4. `$TABLE`

## 5.2   Problem initiation

Just prior to starting the problem (when `NEWIND` is equal to 0), `mrgsolve` calls `$PREAMBLE`. This function is only called once during the simulation sequence. The goal of `$PREAMBLE` is to allow the user to work with different `C++` data structures to get them ready for the simulation run.

## 5.3   Subject initiation

After the `$PREAMBLE` call, `mrgsolve` simulates each `ID` in the data set, one after another. `mrgsolve` runs this sequence just prior to simulating a given `ID`

1. Copy any parameters that are found in the `idata_set` to the working parameter list
2. Copy any parameters that are found in the `data_set` to the working parameter list, with the copy being taken from the first actual data set row for that individual. If the first actual data set record in the data set is not the first record for the individual, `mrgsolve` still copies from the first data set record as long as the `fillbak` argument to `mrgsim` is `TRUE`.
3. Set initial estimates from the base initial estimate list
4. Copy initial estimates from `idata_set` if they are found there.
5. Call `$MAIN`
6. Start simulating the records for that individual

## 5.4   Sequence for a single record

`mrgsolve` executes this sequence while working from record to record for a given `ID`

1. If `nocb` (next observation carried backward) is `TRUE`, then parameters are copied from the current record if that is an actual data set record. Note that if `nocb` is `FALSE` then `locf` (first observation carried forward) is assumed to be `TRUE` (see below). This is the last parameters will be copied from any input data set prior to advancing the system (when `locf` is being used). Therefore, when parameter columns are found in both an `idata_set` and a `data_set`, it will be the value found in the `data_set` that will overwrite both the base list and any parameter value that was copied from an `idata_set`. It is not an error to have different parameter values in an `idata_set` and a `data-set`, but the value found in the `data_set` will be used when this happens. More on parameters and the parameter update sequence can be found in sections 6.3 and 1.1.
2. `$MAIN` is called
3. The system is advanced via `$ODE` or `$PKMODEL`, whichever one is invoked in the model specification file.
4. If the current record is a dosing record, the dose is implemented (e.g. bolus made or infusion started).
5. If the system is advancing according to `locf`, then parameters are copied from the current record if that is an actual data set record. This is in contrast to `nocb` advance (see above).
6. The `$TABLE` function is called

7. If the current record is marked for inclusion in the simulated output, results are written to the output matrix.
8. Continue to the next record in the individual.
9. Once the last record is processed in an individual, a new individual is started.

# Chapter 6

# Topics

## 6.1 Annotated model specification

Here is a complete annotated `mrgsolve` model. The goal was to get in several of the most common blocks that you might want to annotate. The different code blocks are rendered here separately for clarity in presentation; but users should include all relevant blocks in a single file (or R string).

```
$PROB

# Final PK model

- Author: Pmetrics Scientist
- Client: Pharmaco, Inc.
- Date: `r Sys.Date()`
- NONMEM Run: 12345
- Structure: one compartment, first order absorption
- Implementation: closed form solutions
- Error model: Additive + proportional
- Covariates:
  - WT on clearance
- SEX on volume
- Random effects on: `CL`, `V`, `KA`
```

```
[PARAM] @annotated
TVCL : 1.1   : Clearance (L/hr)
TVV  : 35.6  : Volume of distribution (L)
TVKA : 1.35  : Absorption rate constant (1/hr)
WT   : 70    : Weight (kg)
SEX  : 1     : Male = 0, Female 1
```

```
WTCL : 0.75  : Exponent weight on CL
SEXV : 0.878 : Volume female/Volume male
```

```
[MAIN]
double CL = TVCL*pow(WT/70,WTCL)*exp(ECL);
double V  = TVV *pow(SEXVC,SEX)*exp(EV);
double KA = TVKA*exp(EKA);
```

```
[OMEGA] @name OMGA @correlation @block
ECL : 1.23 : Random effect on CL
EV  : 0.67 0.4 : Random effect on V
EKA : 0.25 0.87 0.2 : Random effect on KA
```

```
[SIGMA] @name SGMA
PROP: 0.25 : Proportional residual error
ADD : 25   : Additive residual error
```

```
[CMT]
GUT  : Dosing compartment  (mg)
CENT : Central compartment (mg)
```

```
[PKMODEL] ncmt = 1, depot=TRUE
```

```
[TABLE]
capture IPRED = CENT/V;
double DV = IPRED*(1+PROP) + ADD;
```

```
[CAPTURE]
DV  : Concentration (mg/L)
ECL : Random effect on CL
CL  : Individual clearance (L/hr)
```

## 6.2   Set initial conditions

```
library(mrgsolve)
library(dplyr)
```

### 6.2.1   Summary

- mrgsolve keeps a base list of compartments and initial conditions that you can update **either** from R or from inside the model specification
- When you use $CMT, the value in that base list is assumed to be 0 for every compartment

- `mrgsolve` will by default use the values in that base list when starting the problem
- When only the base list is available, every individual will get the same initial condition
- You can **override** this base list by including code in $MAIN to set the initial condition
- Most often, you do this so that the initial is calculated as a function of a parameter
- For example, `$MAIN RESP_0 = KIN/KOUT;` when `KIN` and `KOUT` have some value in `$PARAM`
- This code in $MAIN overwrites the value in the base list for the current `ID`
- For typical PK/PD type models, we most frequently initialize in $MAIN
- This is equivalent to what you might do in your NONMEM model
- For larger systems models, we often just set the initial value via the base list

### 6.2.2 Make a model only to examine `init` behavior

Note: `IFLAG` is my invention only for this demo. The demo is always responsible for setting and interpreting the value (it is not reserved in any way and `mrgsolve` does not control the value).

For this demo

- Compartment `A` initial condition defaults to 0
- Compartment `A` initial condition will get set to BASE **only** if `IFLAG > 0`
- Compartment `A` always stays at the initial condition

```
code <- '
$PARAM BASE=100, IFLAG = 0

$CMT A

$MAIN

if(IFLAG > 0) A_0 = BASE;

$ODE dxdt_A = 0;
'
```

```
mod <- mcode("init",code)
```
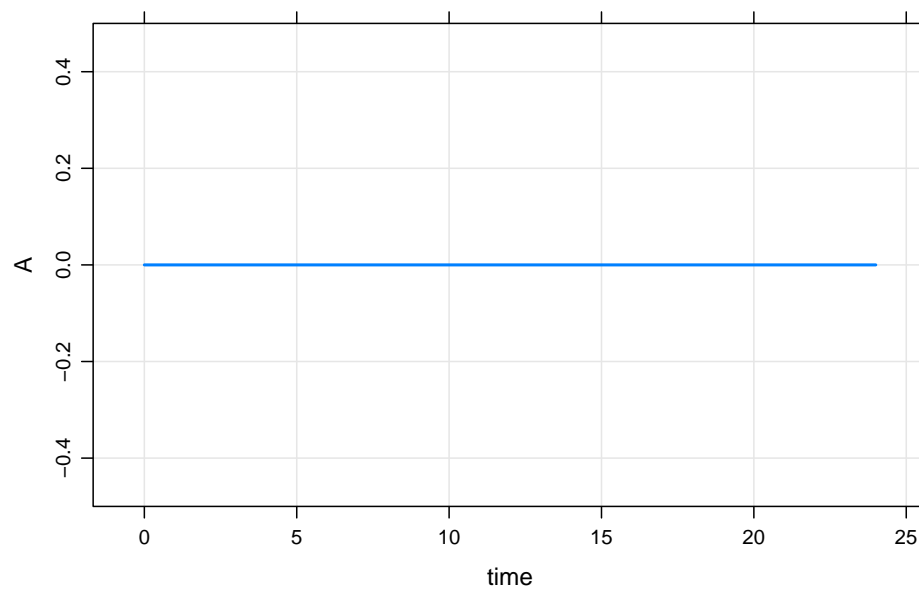
**Check the initial condition**

```
init(mod)
```

```
.
.  Model initial conditions (N=1):
```

```
.  name     value . name      value
.  A (1)    0      | . ...     .
```

Note:

- We used `$CMT` in the model spec; that implies that the base initial condition for `A` is set to 0
- In this chunk, the code in `$MAIN` doesn't get run because `IFLAG` is 0
- So, if we don't update something in `$MAIN` the initial condition is as we set it in the base list
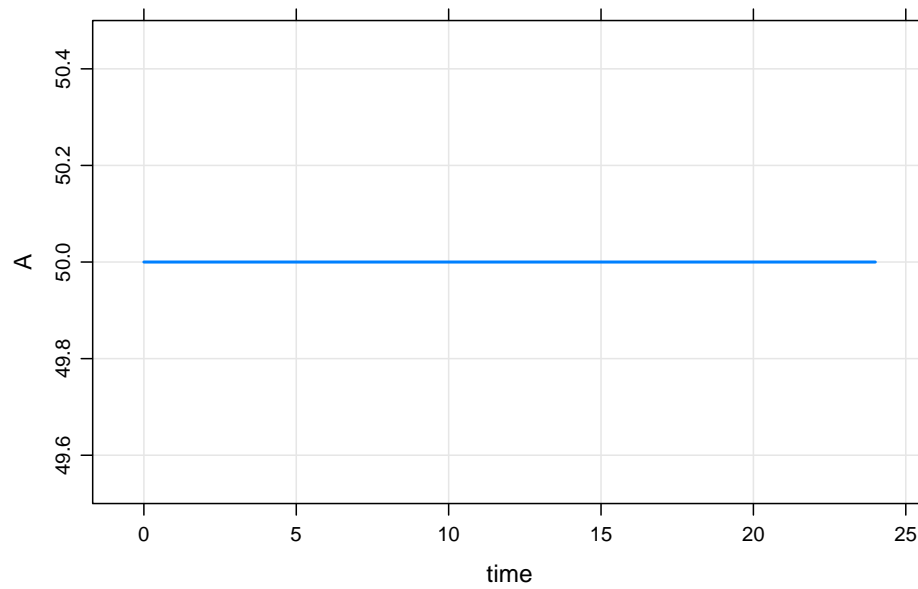
```
mod %>% mrgsim %>% plot
```



**Next, we update the base initial condition for `A` to 50**

Note:

- The code in `$MAIN` still doesn't get run because `IFLAG` is 0
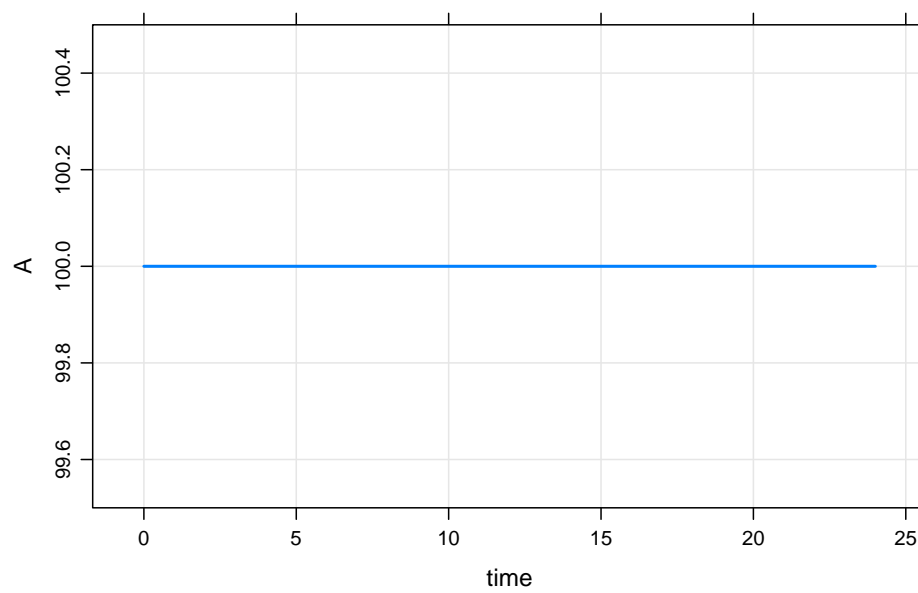
```
mod %>% init(A = 50) %>% mrgsim %>% plot
```
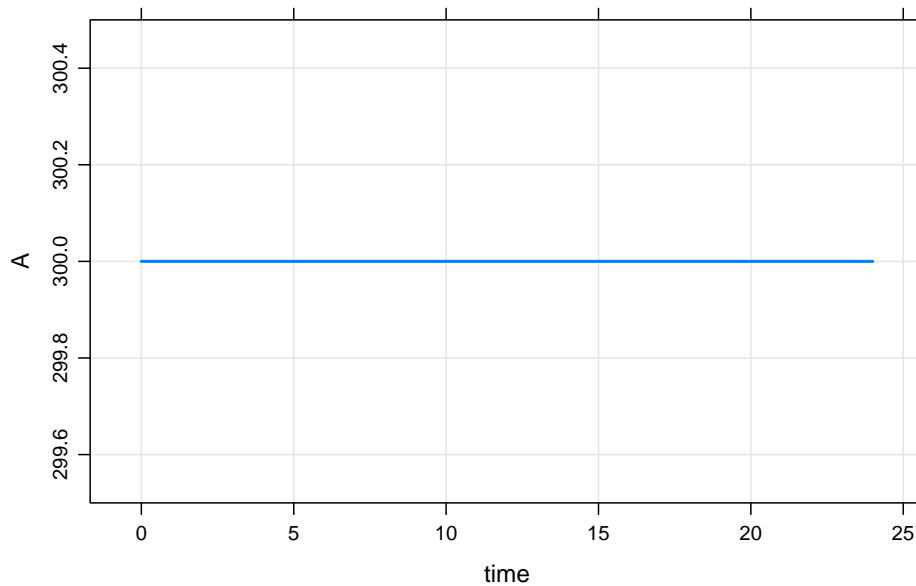
**Now, turn on `IFLAG`**

Note:

- Now, that code in $MAIN gets run
- A_0 is set to the value of BASE

```
mod %>% param(IFLAG=1) %>% mrgsim %>% plot
```

```
mod %>% param(IFLAG=1, BASE=300) %>% mrgsim %>% plot
```



### 6.2.3   Example PK/PD model with initial condition

Just to be clear, there is no need to set any sort of flag to set the initial condition as seen here:

```
code <- '
$PARAM AUC=0, AUC50 = 75, KIN=200, KOUT=5

$CMT RESP

$MAIN
RESP_0 = KIN/KOUT;

$ODE

dxdt_RESP = KIN*(1-AUC/(AUC50+AUC)) - KOUT*RESP;

'

mod <- mcode("init2", code)
```
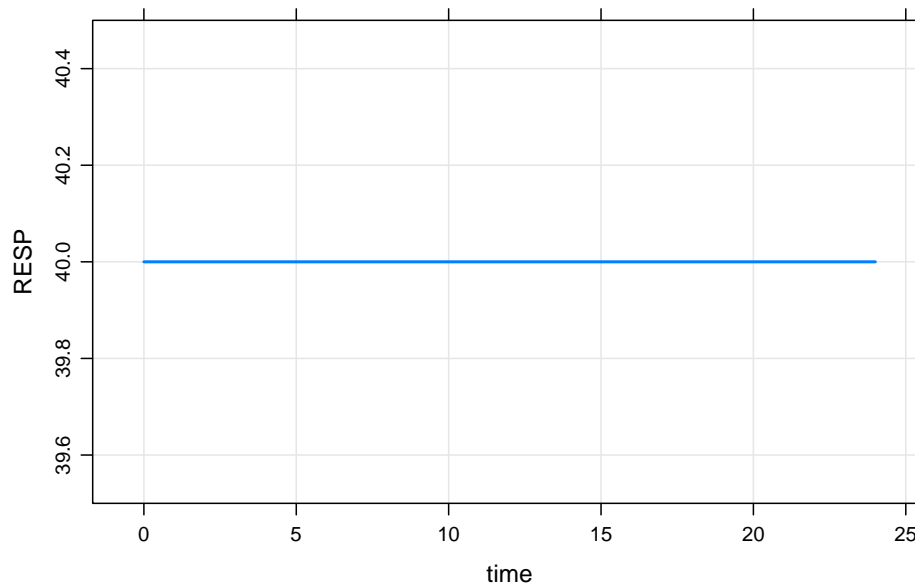
The initial condition is set to 40 per the values of KIN and KOUT

```
mod %>% mrgsim %>% plot
```



Even when we change `RESP_0` in `R`, the calculation in `$MAIN` gets the final say

```
mod %>% init(RESP=1E9) %>% mrgsim
```

```
. Model:   init2
. Dim:     25 x 3
. Time:    0 to 24
. ID:      1
.      ID time RESP
. 1:    1    0   40
. 2:    1    1   40
. 3:    1    2   40
. 4:    1    3   40
. 5:    1    4   40
. 6:    1    5   40
. 7:    1    6   40
. 8:    1    7   40
```

### 6.2.4  Remember: calling `init` will let you check to see what is going on

- It's a good idea to get in the habit of doing this when things aren't clear
- `init` first takes the base initial condition list, then calls `$MAIN` and does any calculation you have in there; so the result is the calculated initials

```
init(mod)
```

```
.
.  Model initial conditions (N=1):
.  name        value . name     value
.  RESP (1)   0      | . ...     .
```

```
mod %>% param(KIN=100) %>% init
```

```
.
.  Model initial conditions (N=1):
.  name        value . name     value
.  RESP (1)   0      | . ...     .
```

### 6.2.5   Set initial conditions via `idata`

Go back to house model

```
mod <- mrgsolve:::house()
```

```
init(mod)
```

```
.
.  Model initial conditions (N=3):
.  name        value . name        value
.  CENT (2)   0      | RESP (3)   50
.  GUT (1)    0      | . ...       .
```

Notes

- In `idata` (only), include a column with `CMT_0` (like you'd do in $MAIN).
- When each ID is simulated, the `idata` value will override the base initial list for that subject.
- But note that if `CMT_0` is set in $MAIN, that will override the `idata` update.

```
idata <- expand.idata(CENT_0 = seq(0,25,1))
```
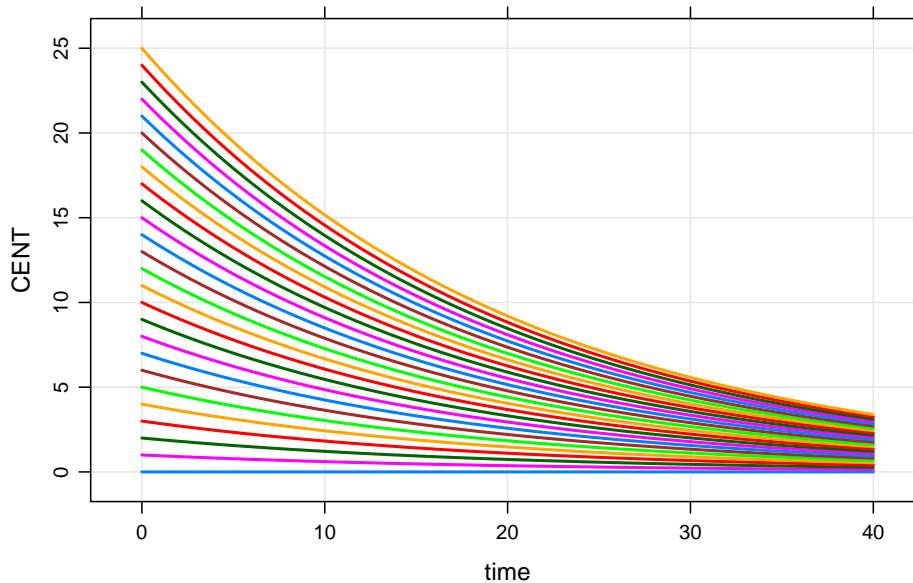
```
idata %>% head
```

```
.    ID CENT_0
. 1  1       0
. 2  2       1
. 3  3       2
. 4  4       3
. 5  5       4
. 6  6       5
```

```
out <-
  mod %>%
  idata_set(idata) %>%
  mrgsim(end=40)
```

```
plot(out, CENT~.)
```



## 6.3 Updating parameters

The parameter list was introduced in section 1.1 and the `$PARAM` code block was shown in 2.2.3. Once a model is compiled, the names and number of parameters in a model is fixed. However, the values of parameters can be changed: parameters may be updated either by the user (in R) or by `mrgsolve` (in the C++ simulation engine, as the simulation proceeds).

- To update in R, use the `param()` function (see examples below)
- To have `mrgsolve` update the parameters, attach columns to your data set (either `data_set` or `idata_set`) with the same name as items in the parameter list

Both of these methods are discussed and illustrated in the following sections.

### 6.3.1 Parameter update hierarchy

As we noted above, new parameter values can come from three potential sources:

1. Modification of the (base) parameter list
2. A column in an `idata_set` that has the same name as a model parameter
3. A column in a `data_set` that has the same name as a model parameter

These sources for new parameter values are discussed below. We note here that the sources listed above are listed in the order of the parameter update *hierarchy*. So, the base parameter list provides the value by default. A parameter value coming from an `idata_set` will override the value in the base list. And a parameter value coming from a `data_set` will override the value coming from the base list or an `idata_set` (in case a parameter is listed in both the `idata_set` and the `data_set`). In other words, the hierarchy is:

1. base parameter list is the default
2. the `idata_set` overrides the base list
3. the `data_set` overrides the `idata_set` and the base list

The parameter update hierarchy is discussed in the following sections.

**Base parameter set**

- Every model has a base set of "parameters"
- These are named and set in `$PARAM`
- Parameters can only get into the parameter list in `$PARAM` (or `$THETA`)
- No changing the names or numbers of parameters once the model is compiled
- But, several ways to change the values

```
code <- '
$VCMT KYLE
$PARAM CL = 1.1, VC=23.1, KA=1.7, KM=10
$CAPTURE CL VC KA KM
'
mod <- mcode("tmp", code, warn=FALSE)
```

```
param(mod)
```

```
.
.  Model parameters (N=4):
.  name value . name value
.  CL   1.1   | KM   10
.  KA   1.7   | VC   23.1
```

**The base parameter set is the default**

The base parameter set allows you to run the model without entering any other data; there are some default values in place.

**The parameters in the base list can be changed or updated in `R`**

Use the `param()` function to both set and get:

```
mod %<>% param(CL=2.1)
```

```
param(mod)
```

```
.
.  Model parameters (N=4):
.  name value . name value
.  CL    2.1   | KM    10
.  KA    1.7   | VC    23.1
```

But whatever you've done in R, there is a base set (with values) to use. See section 6.3.2 for a more detailed discussion of using `param()` to updated the base list.

**Parameters can also be updated during the simulation run**

Parameters can be updated by putting columns in `idata` set or `data_set` that have the same name as one of the parameters in the parameter list. But there is no changing values in the base parameter set once the simulation starts.
That is, the following model specification will not compile:

```
$PARAM CL = 2

$MAIN CL = 3; // ERROR
```

You cannot over-write the value of a parameter in the model specification.
Let `mrgsolve` do the updating.

`mrgsolve` always reverts to the base parameter set when starting work on a new individual.

**Parameters updated from `idata_set`**

When `mrgsolve` finds parameters in `idata`, it will update the base parameter list with those parameters prior to starting that individual.

```
data(exidata)
head(exidata)
```

```
.    ID     CL     VC      KA KOUT   IC50 FOO
. 1   1 1.050 47.80 0.8390 2.45 1.280    4
. 2   2 0.730 30.10 0.0684 2.51 1.840    6
. 3   3 2.820 23.80 0.1180 3.88 2.480    5
. 4   4 0.552 26.30 0.4950 1.18 0.977    2
. 5   5 0.483  4.36 0.1220 2.35 0.483   10
. 6   6 3.620 39.80 0.1260 1.89 4.240    1
```

Notice that there are several columns in `exidata` that match up with the names in the parameter list

```
names(exidata)
```

```
. [1] "ID"    "CL"    "VC"    "KA"    "KOUT" "IC50" "FOO"
```

```
names(param(mod))
```

```
. [1] "CL" "VC" "KA" "KM"
```

The matching names tell `mrgsolve` to update, assigning each individual their individual parameter.

```
out <-
  mod %>%
  idata_set(exidata) %>%
  mrgsim(end=-1 , add=c(0,2))
```

```
out
```

```
. Model:   tmp
. Dim:     20 x 7
. Time:    0 to 2
. ID:      10
.      ID time KYLE    CL    VC      KA KM
. 1:   1    0    0 1.050 47.8 0.8390 10
. 2:   1    2    0 1.050 47.8 0.8390 10
. 3:   2    0    0 0.730 30.1 0.0684 10
. 4:   2    2    0 0.730 30.1 0.0684 10
. 5:   3    0    0 2.820 23.8 0.1180 10
. 6:   3    2    0 2.820 23.8 0.1180 10
. 7:   4    0    0 0.552 26.3 0.4950 10
. 8:   4    2    0 0.552 26.3 0.4950 10
```

**Parameters updated from `data_set`**

Like an `idata` set, we can put parameters on a `data` set

```
data <- expand.ev(amt=0, CL=c(1,2,3), VC=30)
```

```
out <-
  mod %>%
  data_set(data) %>%
  obsonly %>%
  mrgsim(end=-1, add=c(0,2))
```

```
out
```

```
. Model:   tmp
. Dim:     6 x 7
. Time:    0 to 2
. ID:      3
.      ID time KYLE CL VC   KA KM
. 1:   1    0    0  1 30 1.7 10
```

```
.  2:    1     2     0  1 30 1.7 10
.  3:    2     0     0  2 30 1.7 10
.  4:    2     2     0  2 30 1.7 10
.  5:    3     0     0  3 30 1.7 10
.  6:    3     2     0  3 30 1.7 10
```

This is how we do time-varying parameters:

```
data <-
  data_frame(CL=seq(1,5)) %>%
  mutate(evid=0,ID=1,cmt=1,time=CL-1,amt=0)
```

```
. Warning: `data_frame()` is deprecated, use `tibble()`.
. This warning is displayed once per session.
```

```
mod %>%
  data_set(data) %>%
  mrgsim(end=-1)
```

```
. Model:  tmp
. Dim:    5 x 7
. Time:   0 to 4
. ID:     1
.      ID time KYLE CL   VC   KA KM
. 1:    1    0    0  1 23.1 1.7 10
. 2:    1    1    0  2 23.1 1.7 10
. 3:    1    2    0  3 23.1 1.7 10
. 4:    1    3    0  4 23.1 1.7 10
. 5:    1    4    0  5 23.1 1.7 10
```

For more information on time-varying covariates (parameters), see sections 6.9 and 5.

**Parameters are carried back when first record isn't at `time == 0`**

What about this?

```
data <- expand.ev(amt=100,time=24,CL=5,VC=32)
data
```

```
.   ID time amt cmt evid CL VC
. 1  1   24 100   1    1  5 32
```

The first `data` record happens at `time==24`

```
mod %>%
  data_set(data) %>%
  mrgsim(end=-1, add=c(0,2))
```

```
. Model:  tmp
. Dim:    3 x 7
```

```
. Time:   0 to 24
. ID:     1
.     ID time KYLE CL VC  KA KM
. 1:   1    0    0 5 32 1.7 10
. 2:   1    2    0 5 32 1.7 10
. 3:   1   24  100 5 32 1.7 10
```

Since the data set doesn't start until `time==5`, we might think that `CL` doesn't change from the base parameter set until then.

But by default, `mrgsolve` carries those parameter values back to the start of the simulation. This is by design ... by far the more useful configuration.

If you wanted the base parameter set in play until that first data set record, do this:

```
mod %>%
  data_set(data) %>%
  mrgsim(end=-1,add=c(0,2), filbak=FALSE)
```

```
. Model:  tmp
. Dim:    3 x 7
. Time:   0 to 24
. ID:     1
.     ID time KYLE  CL   VC  KA KM
. 1:   1    0    0 2.1 23.1 1.7 10
. 2:   1    2    0 2.1 23.1 1.7 10
. 3:   1   24  100 5.0 32.0 1.7 10
```

Will this work?

```
idata <- do.call("expand.idata", as.list(param(mod)))

idata
```

```
.   ID  CL   VC  KA KM
. 1  1 2.1 23.1 1.7 10
```

Here, we'll pass in **both** `data_set` and `idata_set` and they have conflicting values for the parameters.

```
mod %>%
  data_set(data) %>%
  idata_set(idata) %>%
  mrgsim(end=-1,add=c(0,2))
```

```
. Model:  tmp
. Dim:    3 x 7
. Time:   0 to 24
. ID:     1
.     ID time KYLE CL VC  KA KM
```

```
. 1:   1    0     0  5 32 1.7 10
. 2:   1    2     0  5 32 1.7 10
. 3:   1   24   100  5 32 1.7 10
```

The data set always gets the last word.

## 6.3.2   Updating the base parameter list

From the previous section

```
param(mod)
```

```
.
.  Model parameters (N=4):
.  name value . name value
.  CL   2.1  | KM   10
.  KA   1.7  | VC   23.1
```

**Update with `name-value` pairs**

We can call `param()` to update the model object, directly naming the parameter to update and the new value to take

```
mod %>% param(CL = 777, KM = 999) %>% param
```

```
.
.  Model parameters (N=4):
.  name value . name value
.  CL   777  | KM   999
.  KA   1.7  | VC   23.1
```

The parameter list can also be updated by scanning the names in a list

```
what <- list(CL = 555, VC = 888, KYLE = 123, MN = 100)
```

```
mod %>% param(what) %>% param
```

```
.
.  Model parameters (N=4):
.  name value . name value
.  CL   555  | KM   10
.  KA   1.7  | VC   888
```

`mrgsolve` looks at the names to drive the update. `KYLE` (a compartment name) and `MN` (not in the model anywhere) are ignored.

Alternatively, we can pick a row from a data frame to provide the input for the update

```
d <- data_frame(CL=c(9,10), VC=c(11,12), KTB=c(13,14))

mod %>% param(d[2,]) %>% param
```

```
.
.  Model parameters (N=4):
.  name value . name value
.  CL    10    | KM    10
.  KA    1.7   | VC    12
```

Here the second row in the data frame drives the update. Other names are ignored.

A warning will be issued if an update is attempted, but no matching names are found

```
mod %>% param(ZIP = 1, CODE = 2) %>% param
```

```
Warning message:
Found nothing to update: param
```

## 6.4   Time grid objects

**Simulation times in `mrgsolve`**

```
mod <- mrgsolve:::house() %>% Req(CP) %>% ev(amt=1000,ii=24, addl=1000)
```

mrgsolve keeps track of a simulation `start` and `end` time and a fixed size step between `start` and `end` (called `delta`). mrgsolve also keeps an arbitrary vector of simulation times called `add`.

```
mod %>%
  mrgsim(end=4,delta=2,add=c(7,9,50)) %>%
  as.data.frame
```

```
.    ID time        CP
. 1  1     0  0.00000
. 2  1     0  0.00000
. 3  1     2 42.47580
. 4  1     4 42.28701
. 5  1     7 36.75460
. 6  1     9 33.26649
. 7  1    50 60.97754
```

**`tgrid` objects**

The `tgrid` object abstracts this setup and allows us to make complicated sampling designs from elementary building blocks.

**Make a day 1 sampling with intensive sampling around the peak and sparser otherwise**

```
peak1 <- tgrid(1,4,0.1)
sparse1 <- tgrid(0,24,4)
```

**Use the c operator to combine simpler designs into more complicated designs**

```
day1 <- c(peak1,sparse1)
```
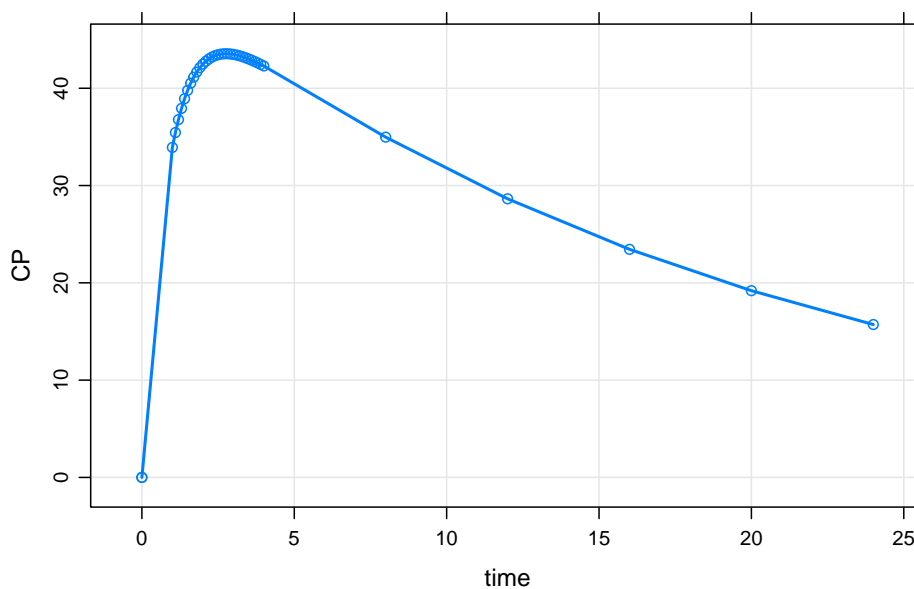
Check this by calling stime

```
stime(day1)
```

```
.  [1]  0.0  1.0  1.1  1.2  1.3  1.4  1.5  1.6  1.7  1.8  1.9  2.0  2.1  2.2  2.3
. [16]  2.4  2.5  2.6  2.7  2.8  2.9  3.0  3.1  3.2  3.3  3.4  3.5  3.6  3.7  3.8
. [31]  3.9  4.0  8.0 12.0 16.0 20.0 24.0
```

Pass this object in to mrgsim as tgrid. It will override the default start/end/delta/add sequence.

```
mod %>%
  mrgsim(tgrid=day1) %>%
  plot(type='b')
```
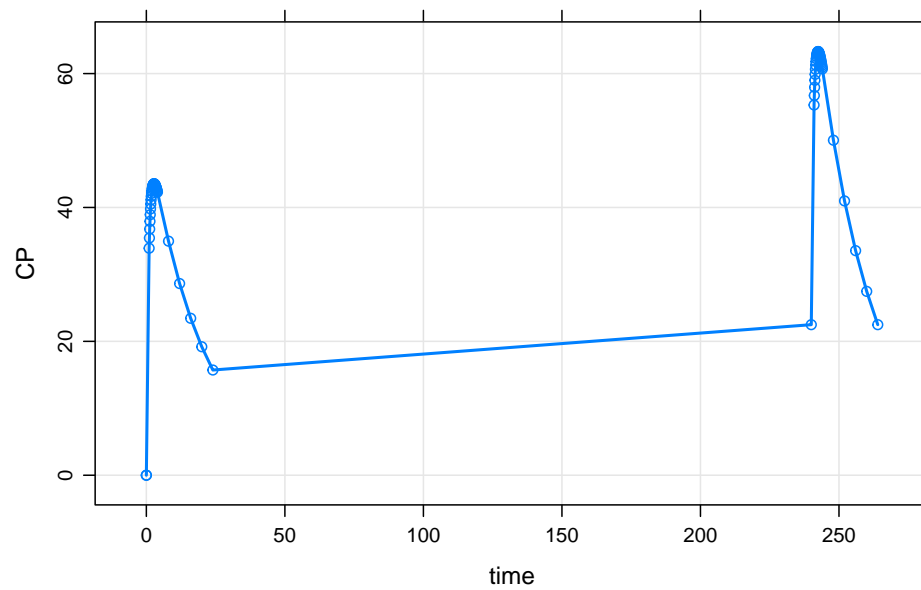


**Now, look at both day 1 and day 10**:

Adding a number to a tgrid object will offset those times by that amount.

```
des <- c(day1, day1+10*24)
```
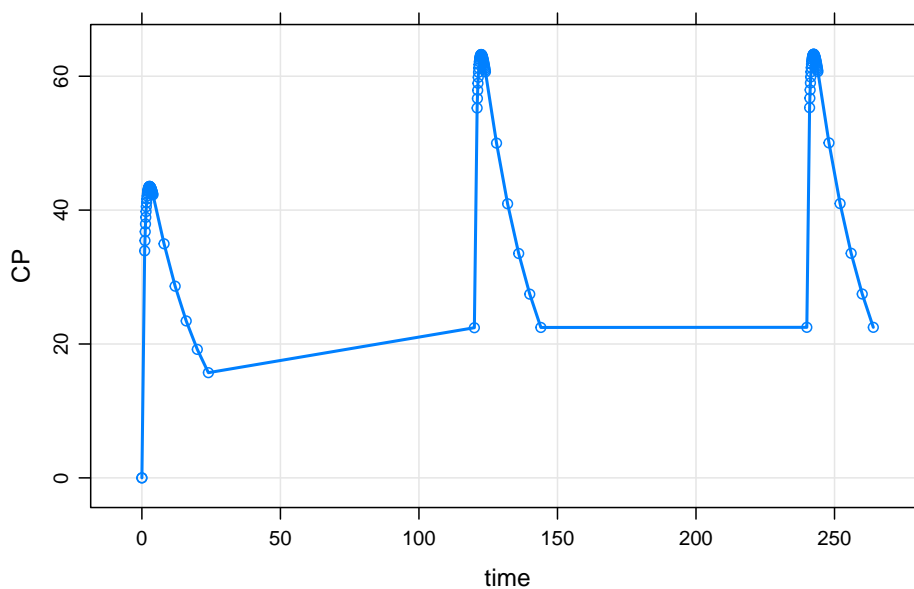
```
mod %>%
  mrgsim(tgrid=des) %>%
  plot(type='b')
```



Pick up day 5 as well

```
des <- c(des, day1+5*24)

mod %>%
  mrgsim(tgrid=des) %>%
  plot(type='b')
```

## 6.5   Individualized sampling designs

Here is a PopPK model and a full `data_set`.

```
mod <- mrgsolve:::house()

data(exTheoph)

df <- exTheoph

head(df)
```

```
.    ID   WT Dose time  conc cmt  amt evid
. 1   1 79.6 4.02 0.00  0.00   1 4.02    1
. 2   1 79.6 4.02 0.25  2.84   0 0.00    0
. 3   1 79.6 4.02 0.57  6.57   0 0.00    0
. 4   1 79.6 4.02 1.12 10.50   0 0.00    0
. 5   1 79.6 4.02 2.02  9.66   0 0.00    0
. 6   1 79.6 4.02 3.82  8.58   0 0.00    0
```

```
mod %>%
  Req(CP) %>%
  carry.out(a.u.g) %>%
  data_set(df) %>%
  obsaug %>%
  mrgsim
```

```
. Model:   housemodel
. Dim:      5904 x 4
. Time:    0 to 120
. ID:       12
.      ID time a.u.g       CP
. 1:    1 0.00      1 0.00000
. 2:    1 0.00      0 0.00000
. 3:    1 0.25      1 0.04552
. 4:    1 0.25      0 0.04552
. 5:    1 0.50      1 0.07870
. 6:    1 0.57      0 0.08624
. 7:    1 0.75      1 0.10274
. 8:    1 1.00      1 0.12001
```

Now, define two time grid objects: des1 runs from 0 to 24 and des2 runs from 0 to 96, both every hour.

```
des1 <- tgrid(0,24,1)
des2 <- tgrid(0,96,1)

range(stime(des1))
```

```
. [1]   0 24
```

```
range(stime(des2))
```

```
. [1]   0 96
```

Now, derive an idata_set after adding a grouping column (GRP) that splits the data set into two groups

```
df %<>% mutate(GRP = as.integer(ID > 5))

id <- df %>% distinct(ID,GRP)

id
```

```
.     ID GRP
. 1   1   0
. 2   2   0
. 3   3   0
. 4   4   0
. 5   5   0
. 6   6   1
. 7   7   1
. 8   8   1
. 9   9   1
```

```
. 10 10    1
. 11 11    1
. 12 12    1
```

Now, we have two groups in GRP in idata_set and we have two tgrid objects.

- Pass in both the idata_set and the data_set
- Call design
- Identify GRP as descol; the column **must** be in idata_set
- Pass in a list of designs; it **must** be at least two because there are two levels in GRP

When we simulate, the individuals in GRP 1 will get des1 and those in GRP 2 will get des2

```
out <-
  mod %>%
  Req(CP) %>%
  carry.out(a.u.g,GRP) %>%
  idata_set(id) %>%
  data_set(df) %>%
  design(descol="GRP", deslist=list(des1,des2)) %>%
  obsaug %>%
  mrgsim

plot(out, CP~time|GRP)
```
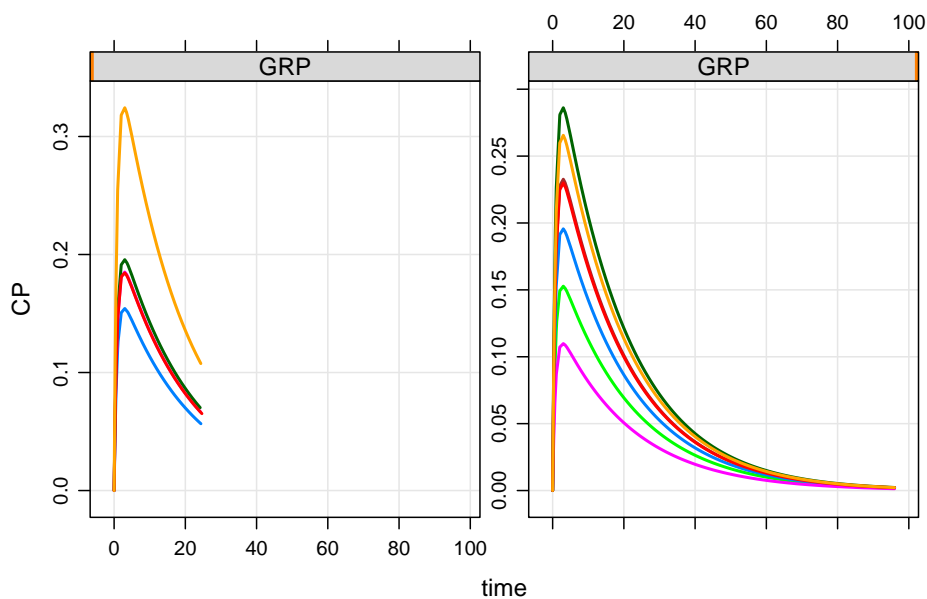
## 6.6   Some helpful `C++`

Recall that the following blocks require valid `C++` code:

1. `$PREAMBLE`
2. `$MAIN`
3. `$ODE`
4. `$TABLE`
5. `$GLOBAL`
6. `$PRED`

We don't want users to have to be proficient in `C++` to be able to use mrgsolve. and we've created several macros to help simplify things as much as possible.
However, it is required to become familiar with some of the basics and certainly additional knowledge of how to do more than just the basics will help you code more and more complicated models in mrgsolve.

There are an unending stream of tutorials, references and help pages on `C++` to be found on the interweb. As a general source, I like to use https://en.cppreference.com/. But, again, there many other good resources out there that can suit your needs.

The rest of this section provides a very general reference of the types of `C++` code and functions that you might be using in your model.

### 6.6.1   Semi-colons

Every statement in `C++` must end with a semi-colon. For example;

```
[ MAIN ]
double CL = exp(log_TVCL + ETA(1));
```

or

```
[ ODE ]

dxdt_DEPOT = -KA * DEPOT;
```

### 6.6.2   if-else

```
if(a == 2) b = 2;
```

```
if(a==2) {
  b = 2;
}
```

```
if(a == 2) {
  b=2;
} else {
  b=3;
}
```

This is the equivalent of x <- ifelse(c == 4, 8, 10) in R

```
double x = c == 4 ? 8 : 10;
```

### 6.6.3 Functions

The following functions are hopefully understandable based on the function name. Consult https://cppreference.com for further details.

```
# base^exponent
double d = pow(base,exponent);

double e = exp(3);

# absolute value
double f = fabs(-4);

double g = sqrt(5);

double h = log(6);

double i = log10(7);

double j = floor(4.2);

double k = ceil(4.2);

double l = std::max(0.0, -3.0);

double m = std::min(0.0, -3.0);
```

### 6.6.4 Integer division

The user is warned about division with two integers. In R, the following statement evaluates to 0.75:

```
3/4
```

```
. [1] 0.75
```

But in `C++` it evaluates to 0:

```cpp
double x = 3/4;
```

This is because both the 3 and the 4 are taken as integer literals. This produces the same result as

```cpp
int a = 3;
int b = 4;
double x = a/b;
```

When one integer is divided by another integer, the remainder is discarded (the result is rounded down). This is the way `C++` works. The user is warned.

Note that parameters in mrgsolve are `doubles` so this will evaluate to `0.75`

```
[ PARAM ] a = 3

[ MAIN ]
double x = a/4;
```

Since `a` is a parameter the operation of `a/4` is not integer division and the result is `0.75`.

Unless you are already very comfortable with this concept, users are encouraged to add `.0` suffix to any literal number **written as C++ code**. For example:

```cpp
double x = 3.0 / 4.0;
```

I think it's fair to say that the vast majority of time you want this to evaluate to `0.75` and writing `3.0/4.0` rather than `3/4` will ensure you will not discard any remainder here.

If you would like to experiment with these concepts, try running this code

```r
library(mrgsolve)

code <- '
[ param ] a = 3

[ main ]
capture x = 3/4;
capture y = 3.0/4.0;
capture z = a/4;
'
mod <- mcode("foo", code)

mrgsim(mod)

. Model:  foo
. Dim:    25 x 5
```

```
. Time:   0 to 24
. ID:     1
.      ID time x    y    z
. 1:   1    0 0 0.75 0.75
. 2:   1    1 0 0.75 0.75
. 3:   1    2 0 0.75 0.75
. 4:   1    3 0 0.75 0.75
. 5:   1    4 0 0.75 0.75
. 6:   1    5 0 0.75 0.75
. 7:   1    6 0 0.75 0.75
. 8:   1    7 0 0.75 0.75
```

## 6.7   Resimulate ETA and EPS

**Call `simeps()` to resimulate ETA**

- No $PLUGIN is required
- `simeta()` takes no arguments

For example, we can simulate individual-level covariates within a certain range:

```
code <- '
$PARAM TVCL = 1, TVWT = 70

$MAIN
capture WT = TVWT*exp(EWT);

int i = 0;

while((WT < 60) || (WT > 80)) {
  if(++i > 100) break;
  simeta();
  WT = TVWT*exp(EWT);
}

$OMEGA @labels EWT
4

$CAPTURE EWT WT
'

mod <- mcode("simeta", code)

out <- mod %>% mrgsim(nid=100, end=-1)
```

```
sum <- summary(out)
```

```
sum
```

```
.         ID               time          EWT                    WT
.  Min.   :  1.00   Min.   :0   Min.   :-0.84207   Min.   :30.16
.  1st Qu.: 25.75   1st Qu.:0   1st Qu.:-0.10677   1st Qu.:62.91
.  Median : 50.50   Median :0   Median :-0.03276   Median :67.74
.  Mean   : 50.50   Mean   :0   Mean   :-0.03078   Mean   :68.29
.  3rd Qu.: 75.25   3rd Qu.:0   3rd Qu.: 0.04745   3rd Qu.:73.40
.  Max.   :100.00   Max.   :0   Max.   : 0.13351   Max.   :80.00
```

**Call `simeps()` to resimulate EPS**

- No $PLUGIN is required
- simeps() takes no arguments

For example, we can resimulate until all concentrations are greater than zero:

```
code <- '
$PARAM CL = 1, V = 20,

$CMT CENT

$SIGMA 50

$PKMODEL ncmt=1

$TABLE
capture CP = CENT/V + EPS(1);

int i = 0;

while(CP < 0 && i < 100) {
  simeps();
  CP = CENT/V + EPS(1);
  ++i;
}

'

mod <- mcode("simeps", code)

out <- mod %>% ev(amt=100) %>% mrgsim(end=48)
sum <- summary(out)

sum
```

```
.         ID          time            CENT             CP
.  Min.   :1   Min.   : 0.00   Min.   :  0.00   Min.   : 0.00845
.  1st Qu.:1   1st Qu.:11.25   1st Qu.: 15.93   1st Qu.: 2.38279
.  Median :1   Median :23.50   Median : 29.38   Median : 5.40452
.  Mean   :1   Mean   :23.52   Mean   : 37.47   Mean   : 6.78749
.  3rd Qu.:1   3rd Qu.:35.75   3rd Qu.: 54.21   3rd Qu.:10.03886
.  Max.   :1   Max.   :48.00   Max.   :100.00   Max.   :27.75195
```

**A safety check is recommended** Note that in both examples, we implement a safety check: an integer counter is incremented every time we resimulated. The resimulation process stops if we don't reach the desired condition within 100 replicates. You might also consider issuing a message or a flag in the simulated data if you are not able to reach the desired condition.

## 6.8   Updating `$OMEGA` and `$SIGMA`

Like the values of parameters in the parameter list, we may want to update the values in $OMEGA and $SIGMA matrices. We can do so without re-compiling the model.

### 6.8.1   Matrix helper functions

mrgsolve keeps $OMEGA and $SIGMA in block matrices (regardless of whether the off-diagonal elements are zeros or not). Recall that in the model specification file we can enter data for $OMEGA and $SIGMA as the lower triangle of the matrix (see section 2.2.12). In R, we need to provide a matrix (as an R object). mrgsolve provides some convenience functions to help … allowing the user to enter lower diagonals instead of the full matrix.

dmat() for diagonal matrix

```
dmat(1,2,3)
```

```
.      [,1] [,2] [,3]
. [1,]    1    0    0
. [2,]    0    2    0
. [3,]    0    0    3
```

bmat() for block matrix

```
bmat(1,2,3)
```

```
.      [,1] [,2]
. [1,]    1    2
. [2,]    2    3
```

`cmat()` for a block matrix where the diagonal elements are variances and the off-diagonals are taken to be correlations, not covariances

```
cmat(0.1, 0.87,0.3)
```

```
.               [,1]      [,2]
. [1,] 0.1000000 0.1506884
. [2,] 0.1506884 0.3000000
```

`mrgsolve` will convert the correlations to covariances.

`mrgsolve` also provides `as_bmat()` and `as_dmat()` for converting other R objects to matrices or lists of matrices.

Consider this list with named elements holding the data for a matrix:

```
m <- list(OMEGA1.1 = 0.9, OMEGA2.1 = 0.3, OMEGA2.2 = 0.4)
```

These data could form either a 3x3 diagonal matrix or a 2x2 block matrix. But the names suggest a 2x2 form. `as_bmat()` can make the matrix like this

```
as_bmat(m, "OMEGA")
```

```
.      [,1] [,2]
. [1,]  0.9  0.3
. [2,]  0.3  0.4
```

The second argument is a regular expression that `mrgsolve` uses to find elements in the list to use for building the matrix.

Frequently, we have estimates in a data frame like this

```
data(exBoot)
head(exBoot)
```

```
.   run   THETA1 THETA2  THETA3 OMEGA11    OMEGA21 OMEGA22 OMEGA31   OMEGA32 OMEGA33
. 1   1 -0.7634  2.280  0.8472 0.12860   0.046130  0.2874 0.13820 -0.02164  0.3933
. 2   2 -0.4816  2.076  0.5355 0.12000   0.051000  0.2409 0.06754 -0.07759  0.3342
. 3   3 -0.5865  2.334 -0.4597 0.11460   0.097150  0.2130 0.16650  0.18100  0.4699
. 4   4 -0.6881  1.824  0.7736 0.14990   0.000003  0.2738 0.24700 -0.05466  0.5536
. 5   5  0.2909  1.519 -1.2440 0.07308   0.003842  0.2989 0.06475  0.05078  0.2500
. 6   6  0.1135  2.144 -1.0040 0.13390  -0.019270  0.1640 0.10740 -0.01170  0.3412
.    SIGMA11 SIGMA21 SIGMA22
. 1 0.002579       0  1.0300
. 2 0.002228       0  1.0050
. 3 0.002418       0  1.0890
. 4 0.002177       0  0.8684
. 5 0.001606       0  0.8996
. 6 0.002134       0  0.9744
```

We can use `as_bmat()` with this data frame to extract the $OMEGA matrices

```
omegas <- as_bmat(exBoot, "OMEGA")
length(omegas)
```

```
. [1] 100
```

```
dim(exBoot)
```

```
. [1] 100  13
```

```
omegas[[6]]
```

```
.          [,1]     [,2]     [,3]
. [1,]   0.13390 -0.01927  0.1074
. [2,] -0.01927  0.16400 -0.0117
. [3,]   0.10740 -0.01170  0.3412
```

```
omegas[[16]]
```

```
.          [,1]    [,2]    [,3]
. [1,] 0.08126 0.01252 0.1050
. [2,] 0.01252 0.16860 0.0149
. [3,] 0.10500 0.01490 0.4062
```

The result of calling `as_bmat` or `as_dmat` is a list of matrices, one for each row in the data frame.

Note in this example, we could have called

```
sigmas <- as_bmat(exBoot,"SIGMA")
```

to grab the $SIGMA matrices.

For help on these helper functions, see `?dmat`, `?bmat`, `?cmat`, `?as_bmat`, `?as_dmat` in the R help system after loading `mrgsolve`.

### 6.8.2 Fill a matrix with zeros

Sometimes we write a population model that includes random effects, but we would like to simulate from that same model without the random effects implemented. For example, we want to simulate some typical PK profiles from a population PK model that includes IIV on some parameters and / or RUV on the simulated outputs.

To do this, pass the model through the `zero_re()` function. By default, this will convert all $OMEGA and $SIGMA matrix elements to zeros. See the R help file (`?zero_re`) to see some options for selectively zeroing out only one or the other.

For example we have this population PK model

```
mod <- modlib("popex", compile = FALSE)

omat(mod)
```

```
. $...
.         [,1] [,2] [,3]
. ECL:   0.3  0.0  0.0
. EV:    0.0  0.1  0.0
. EKA:   0.0  0.0  0.5
```

We can turn that matrix to all zeros with

```
mod %>% zero_re() %>% omat
```

```
. $...
.         [,1] [,2] [,3]
. ECL:     0    0    0
. EV:      0    0    0
. EKA:     0    0    0
```

And when we simulate right after that, all ETA(n) will be zero as well and you'll get your fixed-effects simulation (the following is for example only and is not evaluated)

```
mod %>%
  zero_re() %>%
  ev(amt = 100) %>%
  mrgsim() %>%
  plot()
```

### 6.8.3   Example: unnamed matrix

Here is a model with only a 3x3 $OMEGA matrix

```
code <- '
$OMEGA
1 2 3
'

mod <- mcode("matrix", code, compile=FALSE)
```

Let's check the values in the matrix using omat()

```
mod %>% omat
```

```
. $...
.      [,1] [,2] [,3]
. 1:     1    0    0
. 2:     0    2    0
```

```
. 3:     0    0    3
```

We also use `omat()` to update the values in the matrix

```
mod %>% omat(dmat(4,5,6)) %>% omat
```

```
. $...
.      [,1] [,2] [,3]
. 1:     4    0    0
. 2:     0    5    0
. 3:     0    0    6
```

To update $OMEGA, we must provide a matrix of the same dimension, in this case 3x3. An error is generated if we provide a matrix with the wrong dimension.

```
ans <- try(mod %>% omat(dmat(11,23)))
```

```
. Error : improper signature: omat
```

```
ans
```

```
. [1] "Error : improper signature: omat\n"
. attr(,"class")
. [1] "try-error"
. attr(,"condition")
. <simpleError: improper signature: omat>
```

### 6.8.4   Example: named matrices

When there are multiple $OMEGA matrices, it can be helpful to assign them names. Here, there are two matrices: one for interindividual variability (IIV) and one for interoccasion variability (IOV).

```
code <- '
$OMEGA @name IIV
1 2 3
$OMEGA @name IOV
4 5
'
mod <- mcode("iov", code, compile=FALSE)

revar(mod)
```

```
. $omega
. $IIV
.      [,1] [,2] [,3]
. 1:     1    0    0
. 2:     0    2    0
. 3:     0    0    3
```

```
.
. $IOV
.       [,1] [,2]
. 4:      4    0
. 5:      0    5
.
.
. $sigma
. No matrices found
```

Now, we can update either `IIV` or `IOV` (or both) by name

```
mod %>%
  omat(IOV = dmat(11,12), IIV = dmat(13,14,15)) %>%
  omat
```

```
. $IIV
.       [,1] [,2] [,3]
. 1:     13    0    0
. 2:      0   14    0
. 3:      0    0   15
.
. $IOV
.       [,1] [,2]
. 4:     11    0
. 5:      0   12
```

Again, an error is generated if we try to assign a 3x3 matrix to the `IOV` position

```
ans <- try(mod %>% omat(IIV=dmat(1,2)))
```

```
. Error : improper dimension: omat
```

```
ans
```

```
. [1] "Error : improper dimension: omat\n"
. attr(,"class")
. [1] "try-error"
. attr(,"condition")
. <simpleError: improper dimension: omat>
```

### 6.8.5   Example: unnamed matrices

If we do write the model with unnamed matrices, we can still update them

```
code <- '
$OMEGA
1 2 3
```

```
$OMEGA
4 5
'
mod <- mcode("multi", code, compile=FALSE)
```

In this case, the only way to update is to pass in a **list** of matrices, where (in this example) the first matrix is 3x3 and the second is 2x2

```
mod %>% omat(list(dmat(5,6,7),dmat(8,9))) %>% omat
```

```
. $...
.      [,1] [,2] [,3]
. 1:     5    0    0
. 2:     0    6    0
. 3:     0    0    7
.
. $...
.      [,1] [,2]
. 4:     8    0
. 5:     0    9
```

## 6.9  Time varying covariates

A note in a previous section showed how to implement time-varying covariates or other time-varying parameters by including those parameters as column in the data set.

By default, `mrgsolve` performs next observation carried backward (`nocb`) when processing time-varying covariates. That is, when the system advances from TIME1 to TIME2, and the advance is a function of a covariate found in the data set, the system advances using the covariate value COV2 rather than the covariate COV1.

The user can change the behavior to last observation carried forward (`locf`), so that the system uses the value of COV1 to advance from TIME1 to TIME2. To use `locf` advance, set `nocb` to FALSE when calling `mrgsim`. For example,

```
mod %>% mrgsim(nocb = FALSE)
```

Note that time-varying covariates are not possible when using `qsim` simulation.

There is additional information about the sequence of events that takes place during system advance in section 5.

# Chapter 7

# Installation

The most up to date installation instructions can be found on our `github` site:

https://github.com/metrumresearchgroup/mrgsolve/     https://github.com/metrumresearchgroup/mrgsolve/wiki/mrgsolve-Installation