mrgsolve User Guide

Metrum Research Group, LLC

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Chapter 1

mrgsolve User Guide

For more information: https://mrgsolve.github.io

The following environment was used to generate this documentation:

```
##  setting  value
##  version  R version 3.4.2 (2017-09-28)
##  system   x86_64, darwin15.6.0
##  ui       RStudio (1.1.419)
##  language (EN)
##  collate  en_US.UTF-8
##  tz       America/Chicago
##  date     2018-02-16
##
##  package       * version    date       source
##  assertthat      0.2.0      2017-04-11 CRAN (R 3.4.0)
##  backports       1.1.2      2017-12-13 CRAN (R 3.4.2)
##  base          * 3.4.2      2017-10-04 local
##  bindr           0.1        2016-11-13 CRAN (R 3.4.0)
##  bindrcpp      * 0.2        2017-06-17 cran (@0.2)
##  bookdown      * 0.6        2018-01-25 CRAN (R 3.4.2)
##  cli             1.0.0      2017-11-05 cran (@1.0.0)
##  codetools       0.2-15     2016-10-05 CRAN (R 3.4.2)
##  colorspace      1.3-2      2016-12-14 CRAN (R 3.4.0)
##  compiler        3.4.2      2017-10-04 local
##  crayon          1.3.4      2017-09-16 CRAN (R 3.4.1)
##  datasets      * 3.4.2      2017-10-04 local
##  devtools        1.13.4     2017-11-09 CRAN (R 3.4.2)
##  digest          0.6.15     2018-01-28 CRAN (R 3.4.2)
##  dplyr         * 0.7.4      2017-09-28 CRAN (R 3.4.2)
##  evaluate        0.10.1     2017-06-24 CRAN (R 3.4.0)
##  ggplot2       * 2.2.1.9000 2018-01-29 Github (thomasp85/ggplot2@f53b99f)
```

```
##  glue            1.2.0.9000  2018-01-12 Github (tidyverse/glue@1592ee1)
##  graphics      * 3.4.2       2017-10-04 local
##  grDevices     * 3.4.2       2017-10-04 local
##  grid            3.4.2       2017-10-04 local
##  gtable          0.2.0       2016-02-26 CRAN (R 3.4.0)
##  htmltools       0.3.6       2017-04-28 CRAN (R 3.4.0)
##  knitr           1.19        2018-01-29 CRAN (R 3.4.2)
##  lattice         0.20-35     2017-03-25 CRAN (R 3.4.2)
##  lazyeval        0.2.1       2017-10-29 cran (@0.2.1)
##  magrittr      * 1.5         2014-11-22 CRAN (R 3.4.0)
##  memoise         1.1.0       2017-04-21 CRAN (R 3.4.0)
##  methods       * 3.4.2       2017-10-04 local
##  mrgsolve      * 0.8.10.9005 2018-02-17 local
##  munsell         0.4.3       2016-02-13 CRAN (R 3.4.0)
##  pillar          1.1.0       2018-01-14 cran (@1.1.0)
##  pkgconfig       2.0.1       2017-03-21 CRAN (R 3.4.0)
##  plyr            1.8.4       2016-06-08 CRAN (R 3.4.0)
##  R6              2.2.2       2017-06-17 CRAN (R 3.4.0)
##  Rcpp            0.12.15     2018-01-20 cran (@0.12.15)
##  RcppArmadillo   0.8.300.1.0 2017-12-06 CRAN (R 3.4.2)
##  rlang           0.1.6.9003  2018-01-29 Github (tidyverse/rlang@a8c15c6)
##  rmarkdown       1.8         2017-11-17 cran (@1.8)
##  rprojroot       1.3-2       2018-01-03 CRAN (R 3.4.2)
##  rstudioapi      0.7         2017-09-07 CRAN (R 3.4.1)
##  scales          0.5.0.9000  2018-01-29 Github (hadley/scales@d767915)
##  stats         * 3.4.2       2017-10-04 local
##  stringi         1.1.6       2017-11-17 CRAN (R 3.4.2)
##  stringr         1.2.0       2017-02-18 CRAN (R 3.4.2)
##  tibble          1.4.2       2018-01-22 cran (@1.4.2)
##  tools           3.4.2       2017-10-04 local
##  utf8            1.1.3       2018-01-03 cran (@1.1.3)
##  utils         * 3.4.2       2017-10-04 local
##  withr           2.1.1.9000  2018-01-29 Github (r-lib/withr@df18523)
##  xfun            0.1         2018-01-22 CRAN (R 3.4.2)
##  xml2            1.2.0       2018-01-24 CRAN (R 3.4.2)
##  yaml            2.1.16      2017-12-12 CRAN (R 3.4.2)

## [1] "Fri Feb 16 22:41:39 2018"
```

Chapter 2

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.

2.1 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 "paramter" 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: 3.2.2, `?param` in the R help system after loading `mrgsolve`.

2.1.1 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 manipulting 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 crutial 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 4.1 and in 6.3.

2.2   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 compartment 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. Nominal 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.

2.3   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 4.2 for discussion of the simulation time grid and input data sets and 2.3.1 and 6.4 for using time grid objects .

2.3.1   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.

2.4   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.

2.5   Functions

There are three C++ functions that mrgsolve creates and manages: 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. 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. $MAIN - **before** advancing the system
2. $ODE - the system **advances** to T2
3. $TABLE - **after** advancing the system

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

2.5.1 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 paramters (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 3.2.5 for details.

2.5.2 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 to calculate the differentation 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 3.2.6 for details.

2.5.3 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 3.2.7 for details.

2.6 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.

2.6.1 OMEGA

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

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

2.6.2 SIGMA

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

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

Chapter 3

Model specification

This chapter details the `mrgsolve` model specification format.

3.1   How / where to write a model

There are two ways to write your model:

3.1.1   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` curently 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.

3.1.2   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 3.1.1).

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.

3.2   Code blocks

3.2.1   About code blocks

Block identifier The mrgsolve model specification involves several different types of code that are written in different blocks. A block starts with an identifier that starts with $BLOCKID, where BLOCKID is a character designator. For example, parameters are written in $PARAM, differential equations are written in $ODE etc. 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.

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.

3.2.2 $PARAM

Define the parameter list in the current model.

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)
```

Notes:

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

See also: section 3.2.16 and 3.2.3.

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

3.2.3 $FIXED

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 3.2.2 and 3.2.16.

Notes:

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

3.2.4 $CMT and $INIT

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.

3.2.5 `$MAIN`

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 3.4 for details.

Examples:

```
$CMT CENT RESP

$PARAM KIN = 100, KOUT = 2, CL = 1, VC = 20

$MAIN

RESP_0 = KIN/KOUT;

double ke = CL/VC;
```

3.2.6 `$ODE`

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 3.4 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

3.2.7 `$TABLE`

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 3.2.9), 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.

3.2.8 `$PREAMBLE`

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 procees, 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: 3.2.15.

3.2.9 `$CAPTURE`

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 3.4 for details.

3.2.10 $OMEGA

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 preceeding 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

3.2.11 $SIGMA

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.

3.2.12 $SET

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 RESPonse compartment in the simulated output.

3.2.13 $GLOBAL

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 3.4)

Preprocessor directives Preprocessor `#define` directives are direct substibutions 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.

3.2.14 `$PKMODEL`

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`.

3.2.15 `$PLUGIN`

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: 3.2.8.

3.2.16 `$THETA`

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)
```

See also: 3.2.2 .

3.2.17 `$NMXML`

The `$NMXML` block lets you read and incorporate results from a NONMEM run into your `mrgsolve` model. From the NONMEM run, `THETA` will be imported into your parameter list (see 3.2.2 and 2.1), `OMEGA` will be captured as an `$OMEGA` block (3.2.10) and `SIGMA` will be captured as a `$SIGMA` block (3.2.11). 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"
.  [4] "1005/1005.cov"    "1005/1005.cpu"    "1005/1005.ctl"
.  [7] "1005/1005.ext"    "1005/1005.grd"    "1005/1005.lst"
. [10] "1005/1005.phi"    "1005/1005.shk"    "1005/1005.shm"
. [13] "1005/1005.tab"    "1005/1005.xml"    "1005/1005par.tab"
. [16] "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
theta = TRUE, omega = TRUE, sigma = TRUE
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 XML package.

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

```
mod
```

```
.
.
```

```
. -------- mrgsolve model object (unix) --------
.    Project: /private/var/fol.../T/RtmpFftcWI
.    source:          nmxml.cpp
.    shared object: nmxml-so-1405972bd5103
.
.    Time:            start: 0 end: 96 delta: 4
.    >                add: <none>
.    >                tscale: 1
.
.    Compartments:  GUT CENT PERIPH [3]
.    Parameters:    THETA1 THETA2 THETA3 THETA4 THETA5 THETA6
.    >              THETA7 [7]
.    Omega:         3x3
.    Sigma:         2x2
.
.    Solver:        atol: 1e-08 rtol: 1e-08
.    >              maxsteps: 2000 hmin: 0 hmax: 0
```

```r
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   | .      .
```

```r
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
```
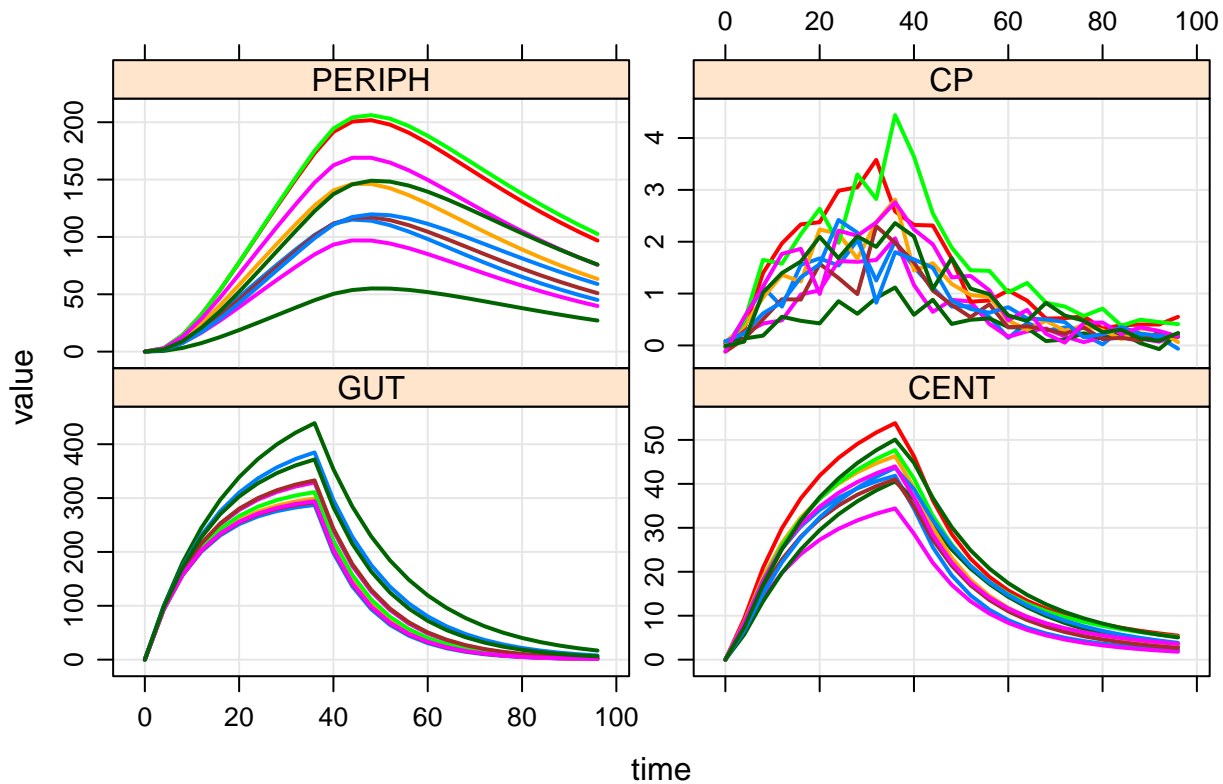
An infusion into GUT:

```r
set.seed(2922)
#+
mod %>%
  ev(amt=1000, rate=1000/36, cmt="GUT") %>%
  mrgsim(nid=10) %>%
  plot
```

3.2.18 `$INCLUDE`

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

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

or

```
$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` 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`.

3.2.19 $ENV

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 3.2.15) 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)
}
```

3.3 Variables and Macros

In the following section, we adopt the convention that `CMT` stands for a compartment in the model.

3.3.1 ID

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

3.3.2 TIME

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

3.3.3 SOLVERTIME

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

3.3.4 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
- 3 = system reset
- 4 = system reset and dose
- 8 = replace

EVID is an alias for `self.evid`.

3.3.5 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`.

3.3.6 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);
```

3.3.7 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`.

3.3.8 self.nid

The number of IDs in the data set.

3.3.9 `self.idn`

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

3.3.10 `self.nrow`

The number of rows in the output data set.

3.3.11 `self.rown`

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

3.3.12 `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.

3.3.13 `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=s(ADD,PROP)
25 0.0025

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

3.3.14 `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 3.2.7 and also 3.2.9

3.3.15 `F_CMT`

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

Example:

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

3.3.16 `ALAG_CMT`

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

Example:

```
$MAIN
ALAG_CENT = 0.25;
```

3.3.17 `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;
```

3.3.18 `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;
```

3.4 Derive new variables

New `C++` variables may be derived in `$GLOBAL`, `$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 derived a `boolean` variable, write

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

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

For example, the following code:

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

gets translated to:

```
$GLOBAL
double CLi;

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

This way, we can still read `CLi` 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));
```

3.5 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.

3.5.1   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 and $CAPTURE that value so that it appears in the simulated output

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

$CMT GUT CENT

$ODE

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

$TABLE
double CP = CENT/VC;

$CAPTURE CP
```

3.5.2   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 funciton 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
```

3.5.3 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
double CP = CENT/VCi;

$CAPTURE IOV ECL EVC CP
```

Chapter 4

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.

4.1 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 2.1, 3.2.2). `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.

4.2 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`: `mrgsolve` detects an new individual when the current value of `ID` is different from the immediate preceeding value of `ID`. However, we always recommend using unique `ID`.

- `time` states the time of the data record

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

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

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

- cmt the dosing compartment number. This may also be a character value naming the compartment name

- rate if non-zero and evid=1, implements a zero-order infusion of duration F*amt/rate, where F 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 3.2.5, 3.3.15,3.3.17, 3.3.18).

- ii inter-dose interval; ii=24 means daily dosing

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

- ss steady state indicator; use 1 to implement steady-state dosing; 0 otherwise. mrgsolve also recoginzes 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).

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 3.2.2 and 2.1). 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 **??**(topic-parameter-update)).

4.2.1   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 2.3 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 2.3 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 customised 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)

```
data(extran1)
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(extran1)

```
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
```

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

Augmenting observations in a clinical data set Occassionally, 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
. [12]  5.00  5.10  6.00  7.00  7.03  8.00  9.00  9.05 10.00 11.00 12.00
. [23] 12.12 13.00 14.00 15.00 16.00 17.00 18.00 19.00 20.00 21.00 22.00
. [34] 23.00 24.00 24.37
```

`obsaug` requests that the data set be augmented with observations from the simulation 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.

4.2.2   Sorting requirements

The `ID`s 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`.

4.2.3   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.

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

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

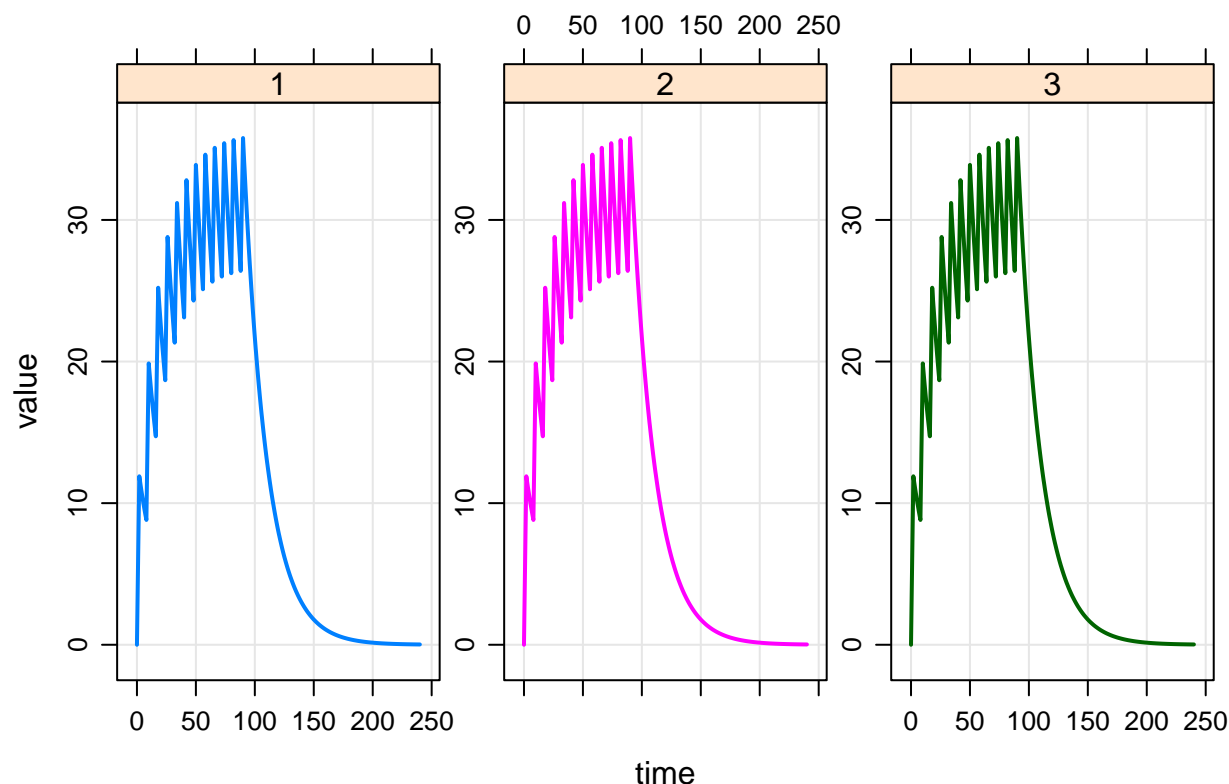Use `data_set` to pass the data into the problem.

For example:

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

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

4.3 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 4.2).

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.

4.3.1   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 population 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
```
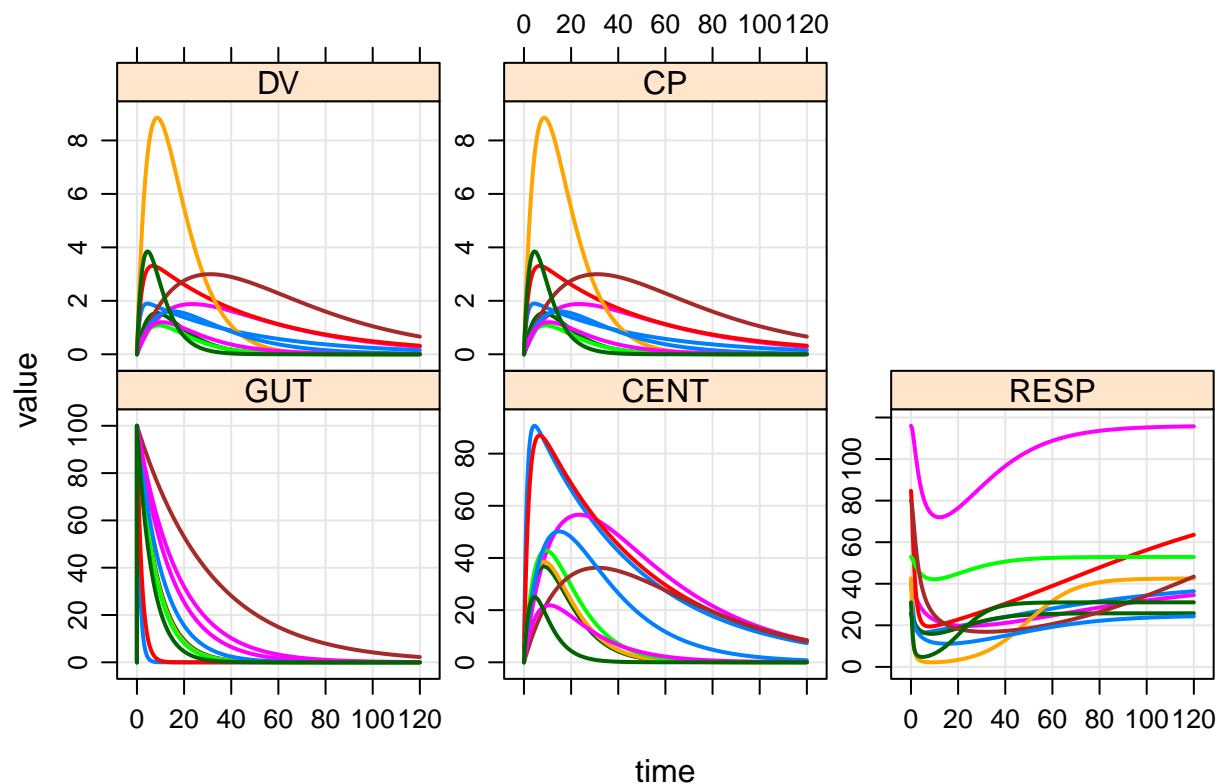
Because there were 10 subjects in the `idata_set`, we get 10 profiles in the output. Each "individual" or "unit" received the same 100 mg dose. We would use a `data_set` to assign different doses to different individuals.

4.4 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.

Chapter 5

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.

5.1   Coersion 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

5.2   Query methods

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

5.3   Methods for `dplyr` verbs

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

For example

```
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  1.00  10.0 0.000614   63.3  37.7  3.16  3.16
.  2  1.00  10.2 0.000455   62.5  37.9  3.13  3.13
.  3  1.00  10.5 0.000337   61.7  38.0  3.09  3.09
.  4  1.00  10.8 0.000250   61.0  38.1  3.05  3.05
.  5  1.00  11.0 0.000185   60.2  38.2  3.01  3.01
.  6  1.00  11.2 0.000137   59.5  38.3  2.97  2.97
.  7  1.00  11.5 0.000102   58.7  38.4  2.94  2.94
.  8  1.00  11.8 0.0000752  58.0  38.5  2.90  2.90
.  9  1.00  12.0 0.0000557  57.3  38.7  2.86  2.86
. 10  1.00  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 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)
```

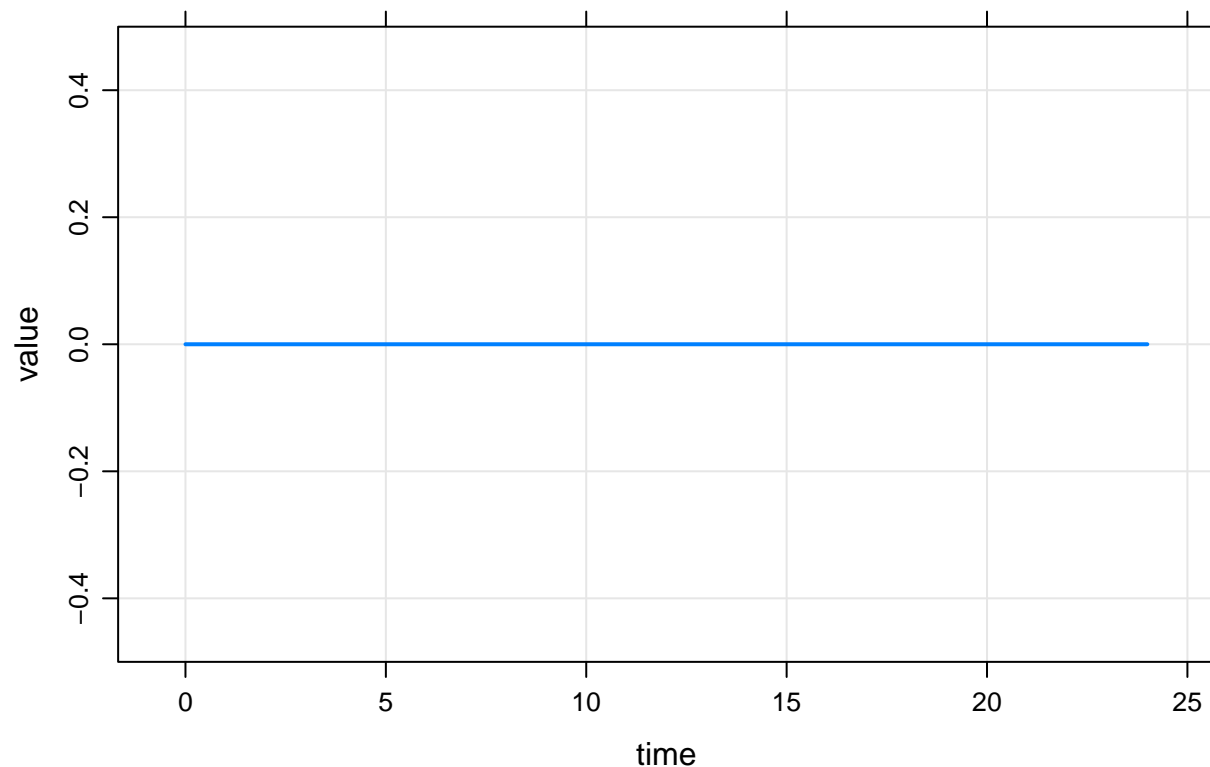**Check the initial condition**

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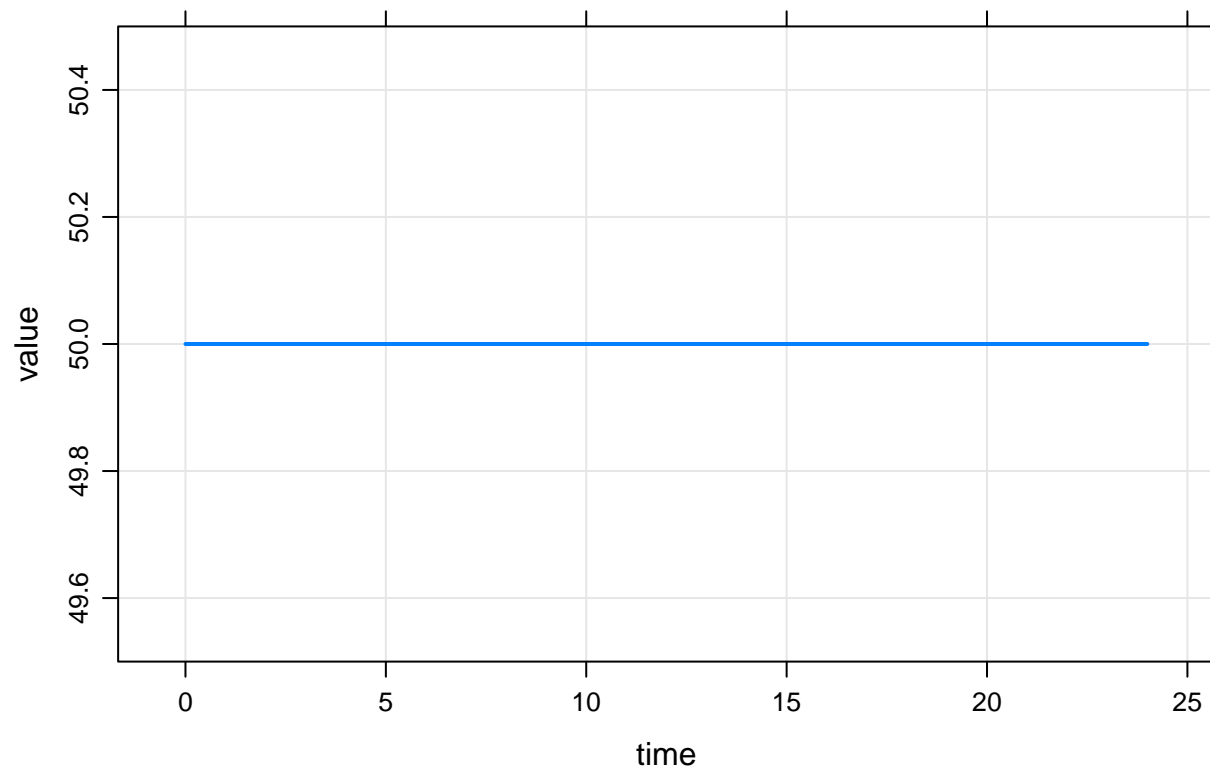
```
mod %>% mrgsim %>% plot
```

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
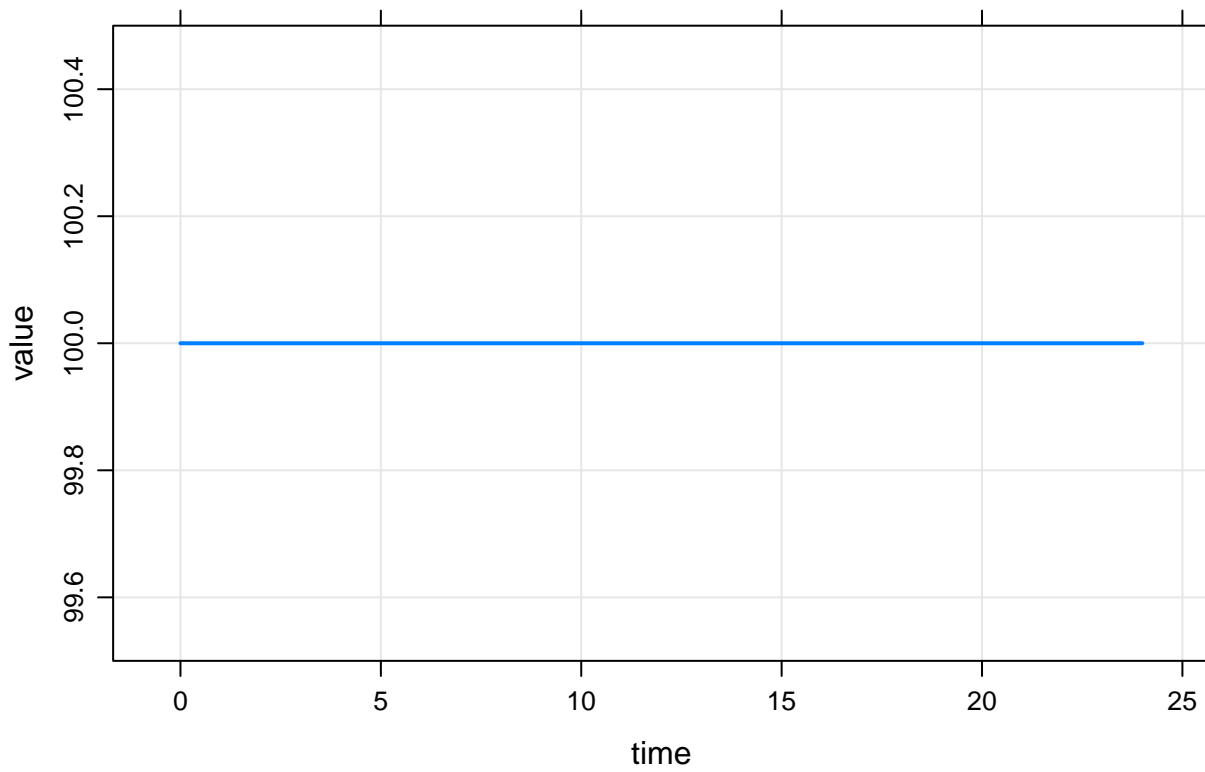
```
mod %>% init(A = 50) %>% mrgsim %>% plot
```
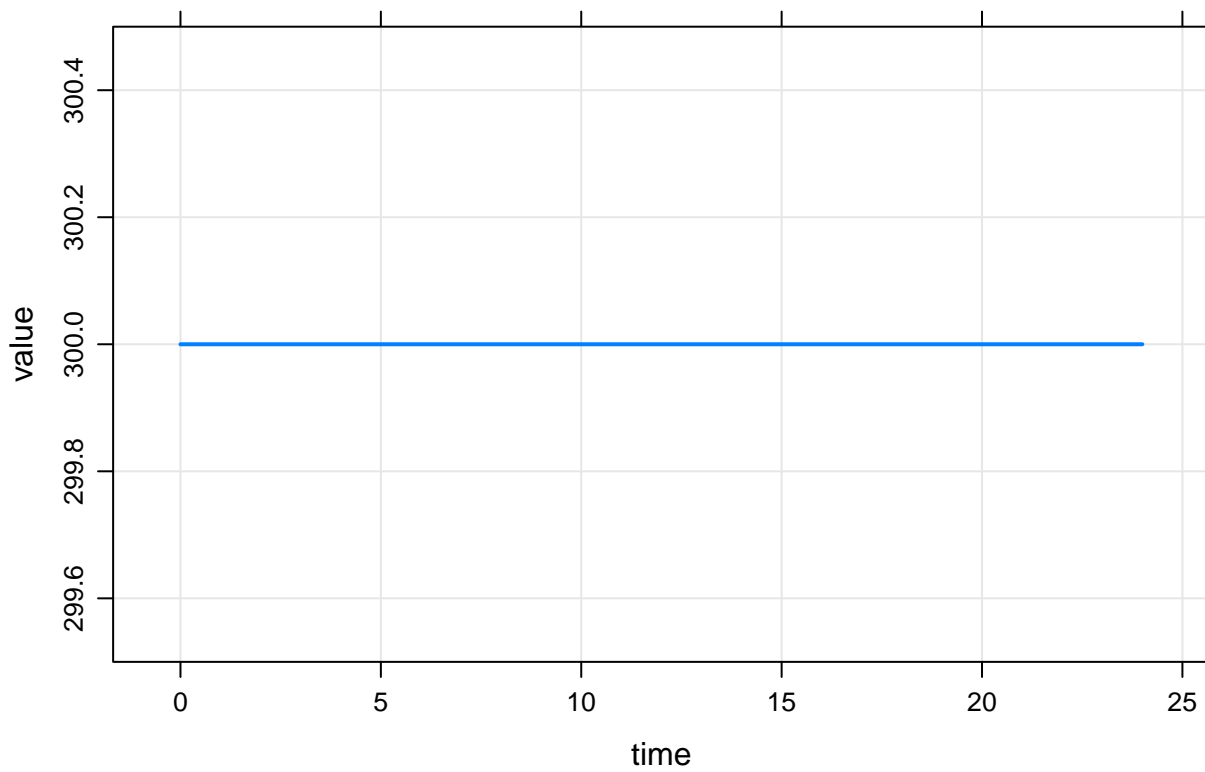

Now, turn on `IFLAG`

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.

```
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;

'
```
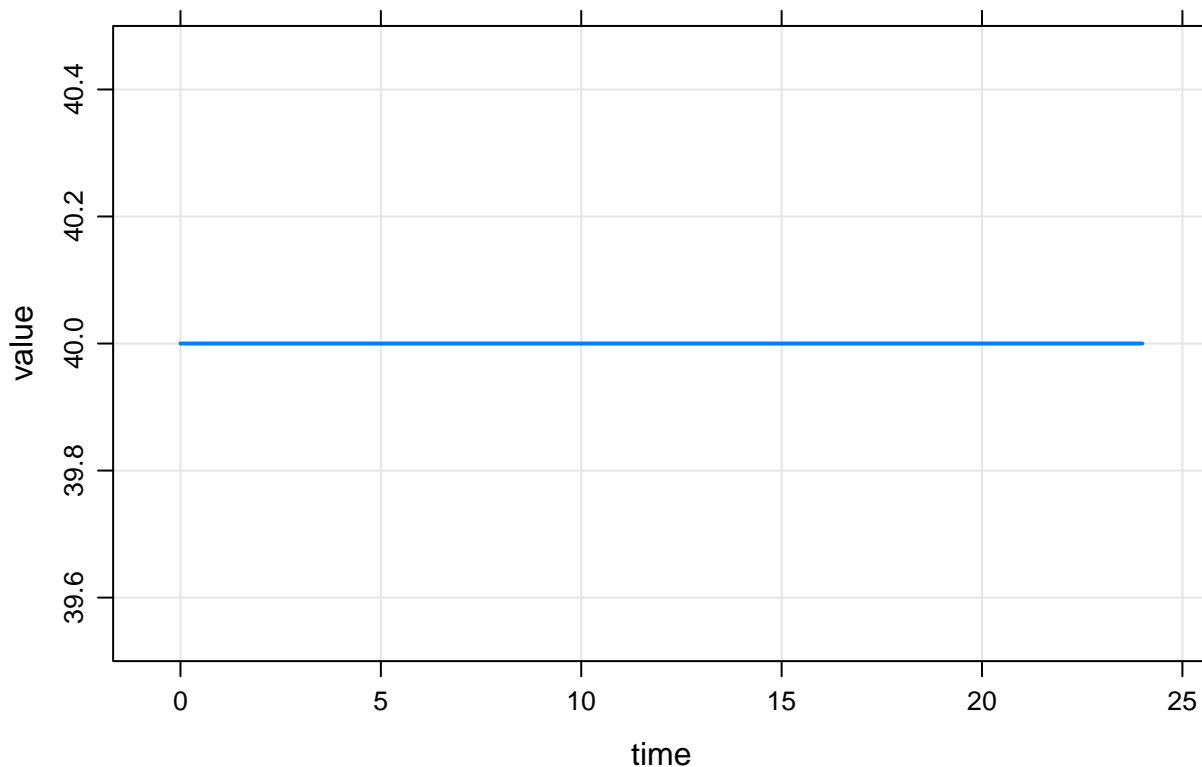
```
mod <- mcode("init2", code)
```

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)     40      | . ...    .
```

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

```
.
.  Model initial conditions (N=1):
.  name         value . name     value
.  RESP (1)     20      | . ...    .
```

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
```
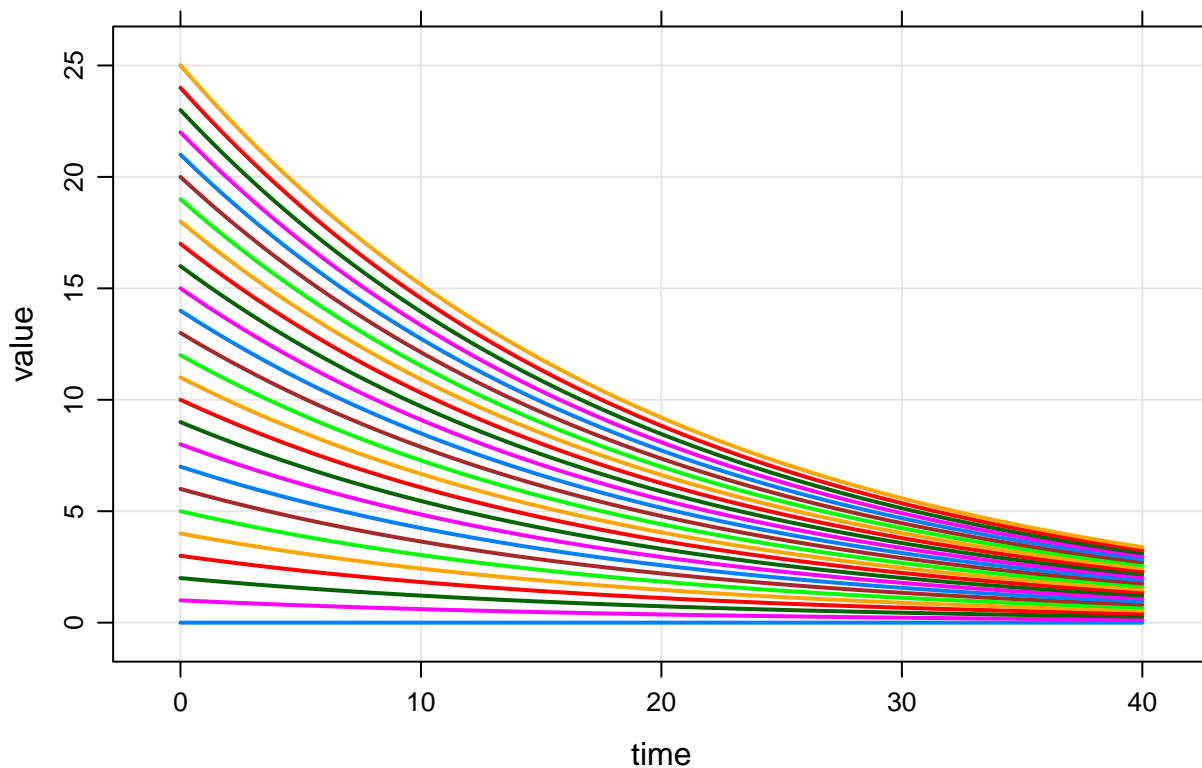
```
. 2   2       1
. 3   3       2
. 4   4       3
. 5   5       4
. 6   6       5
```

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

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


6.3   Updating parameters

The parameter list was introduced in section 2.1 and the $PARAM code block was shown in 3.2.2.

As an overview: 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

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)
```

```
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 7.

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

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`
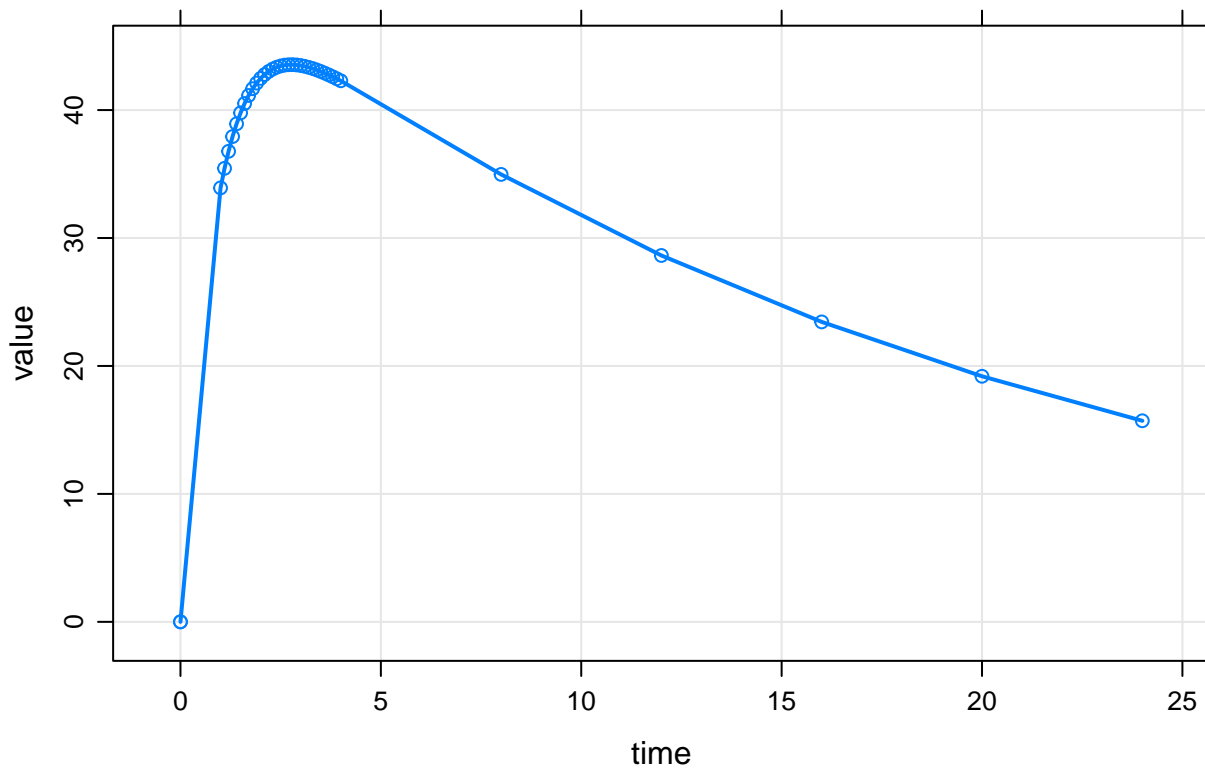
```
stime(day1)
```

```
.  [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
. [15]  2.3  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
. [29]  3.7  3.8  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')
```
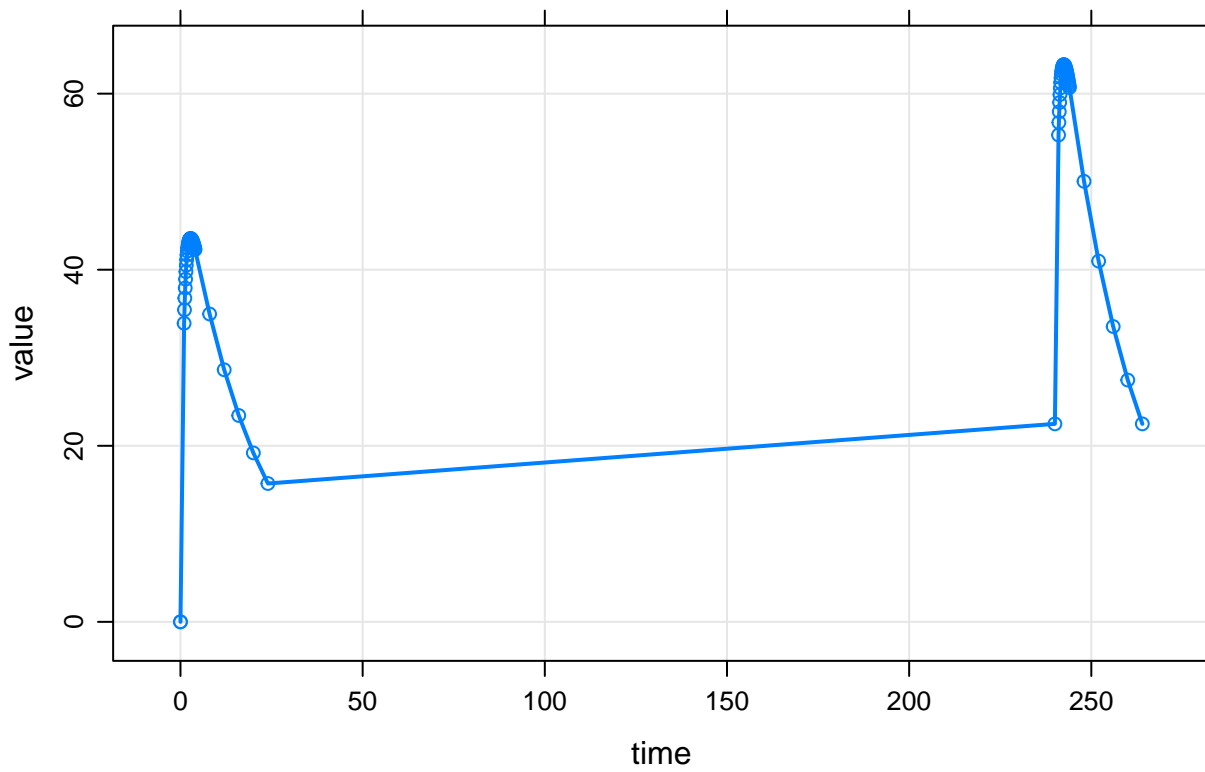
Now, look at both day 1 and day 10:

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')
```
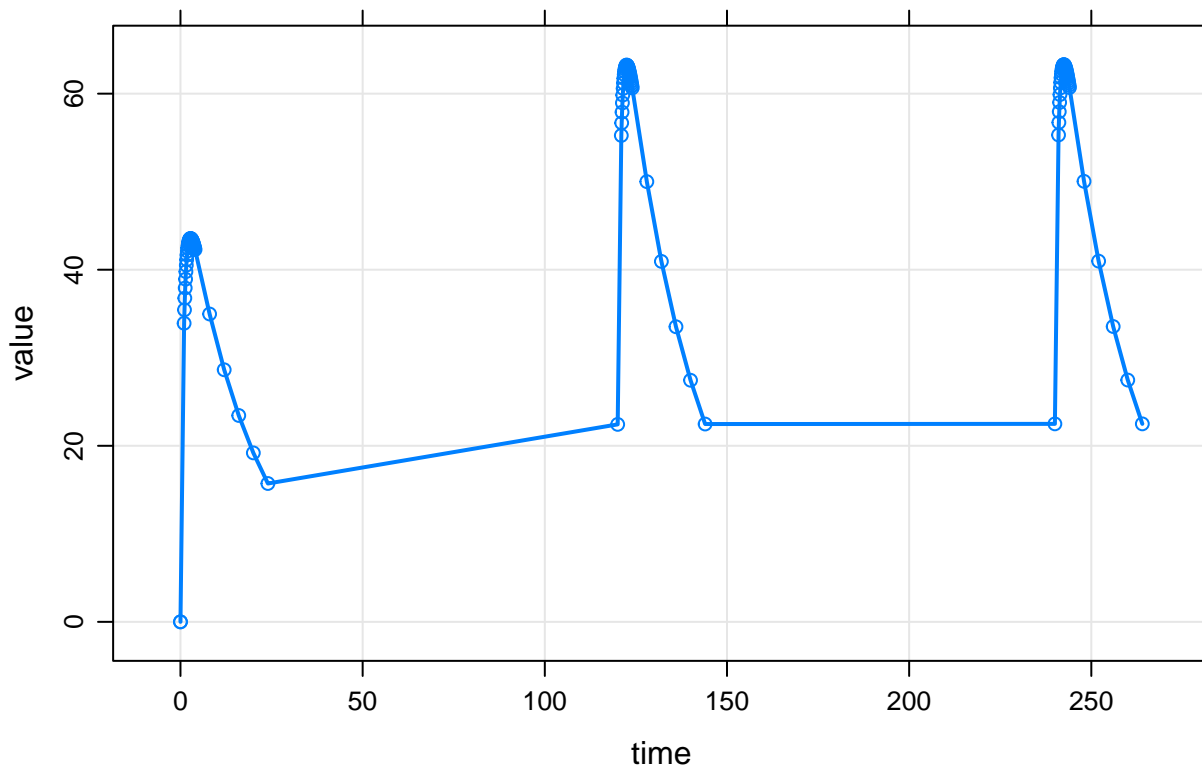
Pick up day 5 as well

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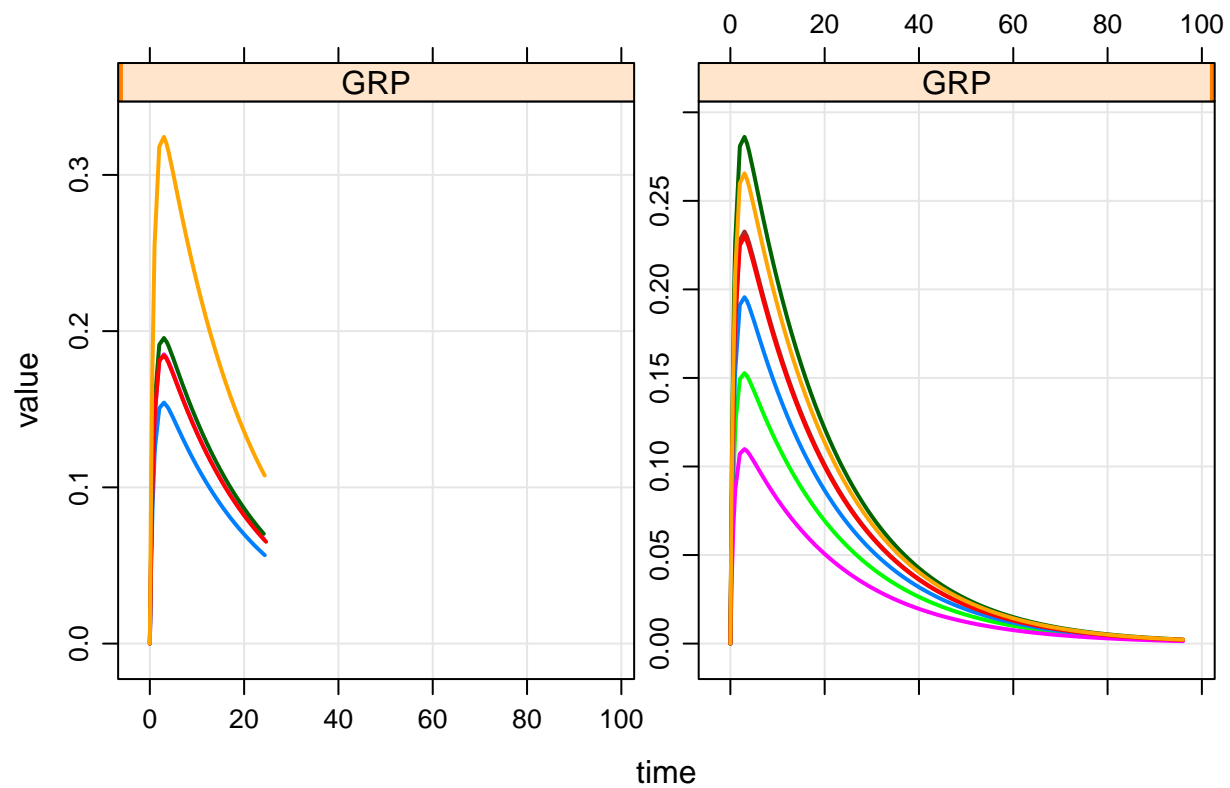
```
  carry.out(a.u.g,GRP) %>%
  idata_set(id) %>%
  data_set(df) %>%
  design(descol="GRP", deslist=list(des1,des2)) %>%
  obsaug %>%
  mrgsim

plot(out, CP~time|GRP)
```


6.6   Some helpful C++

```cpp
// If
if(a == 2) b = 2;

// If else
if(b <= 2) {
c=3;
} else {
c=4;
}

// x <- ifelse(c == 4, 8, 10)
double x = c == 4 ? 8 : 10;

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

```
double e = exp(3);
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);
```

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.    :-0.147157   Min.    :60.42
.  1st Qu.: 25.75   1st Qu.:0   1st Qu.:-0.067350   1st Qu.:65.44
.  Median : 50.50   Median :0   Median : 0.002623   Median :70.18
.  Mean    : 50.50   Mean    :0   Mean    :-0.006769   Mean    :69.73
.  3rd Qu.: 75.25   3rd Qu.:0   3rd Qu.: 0.053306   3rd Qu.:73.83
.  Max.    :100.00   Max.    :0   Max.    : 0.126415   Max.    :79.43
```

Call `simeps()` to resimulate `EPS`

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

For example, we can resimulate untill 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.    : 0.4829
. 1st Qu.:1    1st Qu.:11.25    1st Qu.: 15.93    1st Qu.: 3.4087
. Median :1    Median :23.50    Median : 29.38    Median : 6.4026
. Mean   :1    Mean    :23.52   Mean    : 37.47   Mean    : 6.9016
. 3rd Qu.:1    3rd Qu.:35.75    3rd Qu.: 54.21    3rd Qu.: 9.1498
. Max.   :1    Max.    :48.00   Max.    :100.00   Max.    :19.5884
```

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 3.2.10). 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

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

```
.       [,1] [,2] [,3]
. [1,]    1    0    0
. [2,]    0    2    0
. [3,]    0    0    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
. 1    1 -0.7634  2.280  0.8472 0.12860  0.046130  0.2874 0.13820 -0.02164
. 2    2 -0.4816  2.076  0.5355 0.12000  0.051000  0.2409 0.06754 -0.07759
```

```
. 3   3 -0.5865  2.334 -0.4597 0.11460  0.097150  0.2130 0.16650  0.18100
. 4   4 -0.6881  1.824  0.7736 0.14990  0.000003  0.2738 0.24700 -0.05466
. 5   5  0.2909  1.519 -1.2440 0.07308  0.003842  0.2989 0.06475  0.05078
. 6   6  0.1135  2.144 -1.0040 0.13390 -0.019270  0.1640 0.10740 -0.01170
.    OMEGA33  SIGMA11 SIGMA21 SIGMA22
. 1  0.3933 0.002579      0  1.0300
. 2  0.3342 0.002228      0  1.0050
. 3  0.4699 0.002418      0  1.0890
. 4  0.5536 0.002177      0  0.8684
. 5  0.2500 0.001606      0  0.8996
. 6  0.3412 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 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)))
```

```
ans
```

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

6.8.3   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)))
ans
```

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

6.8.4 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,

```r
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 7.

Chapter 7

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.

7.1 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`

7.2 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.

7.3 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

7.4   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).
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 8

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

Bibliography