

mrgsolve User Guide

Metrum Research Group

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Introduction

Welcome to the mrgsolve user guide. The user guide is the main documentation source for how mrgsolve works and how to best use mrgsolve in your modeling and simulation project. As with most of the mrgsolve documentation, this is a work in progress. I am currently working to transition this to more of a reference resource, rather than demonstration. So key content in the user guide includes chapter 2 on model specification, chapter 1 on model components and chapter 7 on the simulation sequence. Installation is a big topic but we defer to the wiki page for installation help since requirements tend to change frequently with new R releases. The other content is hopefully helpful as well. I'm leaving it all in place for now, but will gradually transition the “how-to” and demo type content over to the vignettes repository or the gallery repository (see below).

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

Overview

If you are accessing the user guide via html, you should be able to see a table of contents on the left. That has a lot of detail in there so I'm going to give you high-level overview of what is here (the high-level should be pretty clear in the pdfbook).

- Chapter 1 tells you about what is in the mrgsolve model object (like parameters, compartments, C++ functions and the like)
- Chapter 2 tells you about model specification. There are two main sections to this chapter: Section 2.2 lists the different model code blocks and Section 2.3 lists the different variables that you can get (or set) in the different code blocks
- Chapter 3 shows you how to format input data sets
- Chapter 4 shows you how to create and work with simple data set objects called event objects
- Chapter ?? shows how to work with model matrices
- Chapter 6 tells you about the simulated output object and how you can work with it

- Chapter 7 dives into the simulation sequence, showing you the steps that mrgsolve takes to work through a problem
- Chapter 8 gives the details on how mrgsolve advances the system to a pharmacokinetic steady state
- Chapter 9 talks about different plugins you can use for more advanced modeling
- Chapter 10 talks about modeled events (discontinuities in the simulation that are triggered from within the model rather than from the data set)
- Chapter 11 is a collection of applied examples on different topics
- Chapter 12 are brief questions and answers providing some bits of information that don't obviously fit into another chapter
- Chapter 13 provides links to some Wiki pages that can help with installation

Other Resources

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

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Chapter 1

Model components

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

1.1 Parameter list

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

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

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

See also: 2.2.4, `?param` in the R help system after loading `mrgsolve`.

1.1.1 Central role of parameters in planning simulations

The data items in the parameter list are more than just values associated with a name. When an name is added to the parameter list, that name becomes a key word

that `mrgsolve` will start to recognize in input data sets or when manipulating the model object.

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

Understanding the parameter update mechanism is very important for planning complicated simulations with `mrgsolve`. Please see the information in 3.1 and in 11.3.

1.2 Compartment list

Like the parameter list, the compartment list is a series of name-value pairs. The compartment list defines the number, names, and initial values of each 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 11.2 illustrates several of these.

See also: section 11.2 and `?init` in the R help system after loading `mrgsolve`.

1.3 Simulation time grid

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

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

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

See also section 3.2 for discussion of the simulation time grid and input data sets and 1.3.1 and 11.4 for using time grid objects.

1.3.1 tgrid objects

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

See section 11.4 for examples and usage.

1.4 Solver settings

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

1.4.1 atol

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

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

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

```
out <- mrgsim_e(mod, ev(amt = 1000)) %>% filter(V < 0)
```

```
out
```

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

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

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

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

1.4.2 rtol

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

1.4.3 maxsteps

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

```
DLSODA- At current T (=R1), MXSTEP (=I1) steps
        taken on this call before reaching TOUT
In above message, I =
[1] 2000
In above message, R =
[1] 0.0004049985
DLSODA- ISTATE (=I1) illegal.
In above message, I =
[1] -1
DLSODA- Run aborted.. apparent infinite loop.
Error in (function (x, data, idata = null_idata, carry.out = character(0), :
  error from XERRWD
```

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

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

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

1.4.4 hmax

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

1.4.5 hmin

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

1.4.6 ixpr

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

1.4.7 mxhnil

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

1.5 Functions

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

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

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

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

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

1.5.1 The \$PREAMBLE function

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

See 2.2.13 for details.

1.5.2 The \$MAIN function

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

- Set initial conditions for any compartment
- Derive new variables to be used in the model
- Write covariate models
- Add between-subject variability to quantities to structural model parameters (e.g. CL or VC).

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

See 2.2.7 for details.

1.5.3 The \$ODE function

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

See 2.2.9 for details.

1.5.4 The \$TABLE function

The TABLE function is called **after** the solver advances in time. The purpose of TABLE is to allow the user to interact with the values of the state variables after advancing,

potentially derive new variables, and to insert different outputs into the table of simulated results.

See 2.2.11 for details.

1.6 Random effect variances

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

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

1.6.1 OMEGA

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

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

1.6.2 SIGMA

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

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

Chapter 2

Model specification

This chapter details the `mrgsolve` model specification format.

2.1 How / where to write a model

There are two ways to write your model:

1. Code in a **separate file** and source into your R script
2. Code **inline** as a character string already in your R script

We recommend method 1 (separate file) for any non-trivial modeling work. Method 2 is handy for quickly coding a model and you'll also see us using that approach frequently when demonstrating how to use `mrgsolve`.

2.1.1 Separate file

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

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

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

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

2.1.2 Inline / code

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

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

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

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

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

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

The `mcode` call is equivalent to:

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

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

2.2 Code blocks

2.2.1 About code blocks

Block identifier

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

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

For example, a block of parameters would be

```
$PARAM
CL = 1
```

The second way to write this is with brackets

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

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

Block identifiers are case-insensitive so all of these also work

```
$param
CL = 1
```

```
[ param ]
CL = 1
```

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

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

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

Block options can be boolean in which case you indicate the option name with nothing following. For example, to indicate block = TRUE for an OMEGA matrix, write

```
$OMEGA @block
1 2 3
```

Here @block indicates block = TRUE. Starting with mrgsolve 1.0.0, block options can be negated by writing ! between @ and the option name. To request a non-block (diagonal) OMEGA matrix

```
$OMEGA @!block
1 2 3
```

But note well that diagonal is the default configuration for OMEGA, so it is never necessary to write this.

Other non-boolean block options state the name and then a value to be assigned to that name. For example, if we wanted to assign labels to the ETAs from an OMEGA block, we'd write

```
$OMEGA @labels ECL EVC
1 2
```

This essentially sets labels equal to the vector `c("ECL", "EVC")`.

We note two specific boolean options (`@object` and `@as_object`) that have similar function across multiple blocks.

2.2.2 Programmatic or bulk initialization

The following describes syntax for initializing blocks as R objects using R code. This can be helpful, say, when you need to initialize a 50x50 OMEGA matrix or a series of systematically named parameters. We will describe the `@object` and `@as_object` options that are available on select blocks.

The `@object` option lets you name an object defined in `$ENV` to use to instantiate the block data. For example, to specify a series of parameters using the `@object` option, you'd write

```
$ENV
params <- list(CL = 1, V = 20, KA = 1.2)

$PARAM @object params
```

This tells `mrgsolve` that there is an object called `params` that it is in the `$ENV` environment and `mrgsolve` will use that to define the names and values. This is a trivial example to show how a simple series of parameters could be defined. However, the intended use for this functionality is to allow efficient creation of a large, systematically-named series of parameters in a large model.

The `@as_object` option is a boolean option that tells `mrgsolve` that the block code will actually return the object (rather than asking `mrgsolve` to look in `$ENV` for the object). The equivalent specification for the block above would be:

```
$PARAM @as_object
list(CL = 1, V = 20, KA = 1.2)
```

The following blocks contain both the `@object` and `@as_object` options:

- `$PARAM`
- `$THETA`
- `$CMT`
- `$INT`
- `$OMEGA`
- `$SIGMA`

Please see the specific block documentation for more details on the specific type of object that should be returned when this syntax is invoked.

2.2.3 \$PROB

Syntax: text

Multiple allowed: yes

Options: @annotated, @covariates

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

See the annotated model in section 11.1 for an example.

2.2.4 \$PARAM

Syntax: R

Multiple allowed: yes

Options: @annotated, @covariates, @object, @as_object

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

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

Example:

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

Annotated example:

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

See the popex model for an example of using @covariates

```
.
. Model file: popex.cpp
.
. $PARAM
. TVKA = 0.5, TVCL = 1, TVV = 24
```

```

.
. $PARAM
. @covariates
. WT = 70

then
mod <- modlib("popex")

as.list(mod)$covariates

. [1] "WT"

```

Notes:

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

The `@object` and `@as_object` options should name or return a named list of parameters.

See also: section 2.2.22 and 2.2.5.

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

2.2.5 \$FIXED

Syntax: R

Multiple allowed: yes

Options: `@annotated`, `@object`, `@as_object`

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

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

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

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

Example:

```

[ PARAM ] CL = 2, VC = 20

[ FIXED ]
g = 9.8

```

Annotated example:

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

See also: section 2.2.4 and 2.2.22.

Notes:

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

2.2.6 \$CMT and \$INIT

Syntax: text

Multiple allowed: yes

Options: @annotated, @object, @as_object

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
```

The @object and @as_object options should name or return a named list of compartments and initial values when used in \$INIT and a character vector of compartment names when used in \$CMT.

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

2.2.7 \$MAIN

Syntax: C++

Multiple allowed: no

This code block has two main purposes:

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

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

\$MAIN is wrapped into a C++ function and compiled / loaded by `mrgsolve`.

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

New variables may be declared in \$MAIN. See section 2.5 for details.

Examples:

```
[ CMT ] CENT RESP

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

[ MAIN ]

RESP_0 = KIN/KOUT;

double ke = CL/VC;
```

2.2.8 \$PK

This is an alias for \$MAIN.

2.2.9 \$ODE

Syntax: C++

Multiple allowed: no

Options: @param

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

For example:

```
[ CMT ] GUT CENT

[ ODE ]

dxdt_GUT = -KA*GUT;
dxdt_CENT = KA*GUT - KE*CENT;
```


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

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

New variables may be declared in `$ODE`. See section 2.5 for details.

For example:

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

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

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

Notes:

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

2.2.10 \$DES

This is an alias for `$ODE`.

2.2.11 \$TABLE

Syntax: C++

Multiple allowed: no

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

For example:

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

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

NOTE When variables are marked for capture (see 2.2.15), the values of those variables are saved at the **end** of the `$TABLE` function. This process is carried out

automatically by `mrgsolve` and therefore requires no user intervention.

2.2.12 \$ERROR

This is an alias for `$TABLE`.

2.2.13 \$PREAMBLE

Syntax: C++

Multiple allowed: no

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

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

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

For example:

```
[ PLUGIN ] Rcpp

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

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

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

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

Notes:

- `$PREAMBLE` is written in C++ syntax; every line must end in `;`

- There may be only one \$PREAMBLE block in a model
- Like \$MAIN, \$ODE and \$TABLE, double, int and bool variables initialized in \$PREAMBLE are actually initialized for global (within the model file)

See also: 2.2.21.

2.2.14 \$PRED

Syntax: C++

Multiple allowed: no

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

For example:

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

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

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

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

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

2.2.15 \$CAPTURE

Syntax: text

Multiple allowed: yes

Options: @annotated

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

For example:

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

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

[ CAPTURE ] A B C yes
```

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

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

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

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

$OMEGA 1

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

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

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

```
$PARAM VC = 300

$CMT CENT

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

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

Annotated example:

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

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

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

New variables may be declared in \$TABLE. See section 2.5 for details.

2.2.16 \$OMEGA

Syntax: text

Multiple allowed: yes

Options: @annotated, @block, @correlation, @labels, @name, @object, @as_object

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

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

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

```
$OMEGA
1 2 3
```

will generate a 3x3 omega matrix.

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

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

will generate a 2x2 matrix with covariance 0.02.

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

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

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

A name can be assigned to each matrix:

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

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

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

Annotated example (diagonal matrix):

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

Annotated example (block matrix):

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

The @object and @as_object options should name or return a square numeric matrix. If rownames are included in the matrix, then they will be used to form labels for the realized ETAs.

Notes:

- Multiple \$OMEGA blocks are allowed

2.2.17 \$SIGMA

Syntax: text

Multiple allowed: yes

Options: @annotated, @block, @correlation, @labels, @name, @object, @as_object

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 @object and @as_object options should name or return a square numeric matrix. If rownames are included in the matrix, then they will be used to form labels for the realized EPS values.

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

2.2.18 \$SET

Syntax: R

Multiple allowed: no

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

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

For example:

```
[ SET ] end = 240, delta = 0.5, req = "RESP"
```

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

2.2.19 \$GLOBAL

Syntax: C++

Multiple allowed: no

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

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

1. Write `#define` preprocessor statements
2. Define global variables, usually variables other than `double`, `bool`, `int` (see 2.5)

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

For example:

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

When this preprocessor directive is included, everywhere the preprocessor finds a CP token it will substitute (CENT/VC). Both CENT and VC must be defined and the ratio of CENT to VC will be calculated depending on whatever the current values are. Notice that we included parentheses around (CENT/VC). This makes sure the ratio between the two is taken first, before any other operations involving CP.

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

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

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

Declare in bulk

If you have a large number of variables to declare, you can do that in bulk in \$GLOBAL. For example, we know we will need a long list of `double` precision variable for covariate modeling, we can declare them all at once like this:

```
[ global ]
double TVCL, TVV2, TVQ = 0, TVV3 = 0;

[ main ]

TVCL = THETA1 * pow(WT / 70.0, 0.75);
TVV2 = THETA2 * WT / 70.0;
```

```
TVQ  = THETA3 * pow(WT / 70.0, 0.75);
TVV3 = THETA4 * WT / 70.0;
```

This isn't a terribly long list, but let's pretend it is to illustrate how to do this. You can also declare `int`, `bool` and other types like this. I've initialized the last two (TVVQ and TVV3) to illustrate how to do this. It's good practice to do that but not necessary as long as everything gets initialized to **something** before they are used.

2.2.20 \$PKMODEL

Syntax: R

Multiple allowed: no

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

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

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

Example:

```
[ CMT ] GUT CENT PERIPH

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

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

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

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

2.2.21 \$PLUGIN

Syntax: text

Multiple allowed: no

Plugins are a way to add extensions to your `mrqsolve` model. Plugins can either link your model to external libraries (like `boost` or `Rcpp`) or they can open up access to additional functionality provided by `mrqsolve` itself.

Plugins are listed and discussed in more detail in Chapter 9.

Usage

To invoke a plugin, list the plugin name in the code block. For requesting Rcpp headers in your model, call

```
$PLUGIN Rcpp
```

Available plugins

The following plugins make additional mrgsolve-specific functionality available

- **mrgx**: extra C++ functions (see below)
- **tad**: track time after dose in your model
- **N_CMT**: get the number of a compartment

The following plugins give you a different model specification experience

- **autodec**: mrgsolve will find assignments in your model and automatically declare them as doubles
- **nm-vars**: a NONMEM look and feel for compartmental models; use F1, A(1) and DADT(1) rather than F_GUT, GUT and dxd_t_GUT

The following plugin lets you customize how your model is compiled

- **CXX11**: compile your model with C++11 standard; this adds the compiler flag `-std=c++11`

The following plugins will let you link to external libraries

- **Rcpp**: include Rcpp headers in your model
- **BH**: include boost headers in your model
- **RcppArmadillo**: include Armadillo headers in your model

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`.

mrgx This is a general collection of functions that we made available.

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 `mrgr::rnorm`, but the simulated value is passed to `exp` after simulating
- `Rcpp::Function mt_fun()`
 - Returns `mrgrsolve::mt_fun`; this is usually used when declaring a R function in `$GLOBAL`
 - Example: `Rcpp::Function print = mrgr::mt_fun();`

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

2.2.21.1 Some examples

Get a numeric vector from `$ENV`

```
[ PLUGIN ] Rcpp mrgr

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

[ GLOBAL ]
Rcpp::NumericVector x;

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

Get the print function from `package:base`

```
$PLUGIN Rcpp mrgr

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

$PREAMBLE
print = mrgr::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 mrgr

$MAIN
```

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

See also: 2.2.13.

2.2.22 \$THETA

Syntax: text

Multiple allowed: yes

Options: @annotated, @name, @object, @as_object

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

For example:

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

is equivalent to

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

Annotated example:

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

To change the prefix, use @name option

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

would be equivalent to

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

The @object and @as_object options should name or return an unnamed vector of parameter values (names are ignored).

See also: 2.2.4.

2.2.23 \$NMXML

Syntax: R

Multiple allowed: yes

The `$NMXML` block lets you read and incorporate results from a NONMEM run into your `mrgsolve` model. From the NONMEM run, `THETA` will be imported into your parameter list (see 2.2.4 and 1.1), `OMEGA` will be captured as an `$OMEGA` block (2.2.16) and `SIGMA` will be captured as a `$SIGMA` block (2.2.17). Users may optionally omit any one of these from being imported.

`$NMXML` contains a `project` argument and a `run` argument. By default, the estimates are read from the file `project/run/run.xml`. That is, it is assumed that there is a directory named `run` that is inside the `project` directory where `$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.

Once the model object is obtained, the path to the `xml` file that formed the source for imported parameters can be retrieved by coercing the model object to list and looking for `nm_import`:

```
mod <- modlib("1005", compile = FALSE)

as.list(mod)$nm_import
```

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

An example

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

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

```
. [1] "1005/1005.cat"      "1005/1005.coi"      "1005/1005.cor"      "1005/1005.cov"
. [5] "1005/1005.cpu"      "1005/1005.ctl"      "1005/1005.ext"      "1005/1005.grd"
. [9] "1005/1005.lst"      "1005/1005.phi"      "1005/1005.shk"      "1005/1005.shm"
. [13] "1005/1005.tab"      "1005/1005.xml"      "1005/1005par.tab"   "1005/INTER"
. [17] "2005/2005.ext"
```

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
root = "cppfile"

olabels = c("ECL", "EVC", "EKA")
slabels = c("PROP", "ADD")
```

```

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

$PKMODEL ncmt=2, depot=TRUE

$CMT GUT CENT PERIPH

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

$CAPTURE CP

$SET delta=4, end=96
'

```

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

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

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

```
mod
```

```

.
.
. ----- source: nmxml.cpp -----
.
. project: /private/var/fo.../T/RtmpBA9bPH
. shared object: nmxml-so-97d5ca5e509
.
. time:          start: 0 end: 96 delta: 4
.               add: <none>
.
. compartments: GUT CENT PERIPH [3]
. parameters:   THETA1 THETA2 THETA3 THETA4 THETA5
.               THETA6 THETA7 [7]
. captures:     CP [1]
. omega:        3x3
. sigma:        2x2
.
. solver:       atol: 1e-08 rtol: 1e-08 maxsteps: 20k
. -----

```

```

param(mod)

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

revar(mod)

. $omega
. $...
.           [,1]      [,2]      [,3]
. ECL:    0.21387884  0.12077020 -0.01162777
. EVC:    0.12077020  0.09451047 -0.03720637
. EKA:   -0.01162777 -0.03720637  0.04656315
.
.
. $sigma
. $...
.           [,1]      [,2]
. PROP:   0.04917071  0.00000000
. ADD:    0.00000000  0.2017688

```

root argument: please use the `root = "cppfile"` argument going forward.

As of mrgsolve 0.11.0, we added an argument called `root` to `$NMXML` that tells mrgsolve the location where it should read the `xml` file from. The default behavior is the "working" directory. When this is the case, mrgsolve assumes that the `xml` file can be found relative to the "working" directory. The only other value that `root` can take is "cppfile". When `root = "cppfile"`, then mrgsolve will look for the `xml` file in a directory that is relative to **where the model source code file is located**. Please take a look at section 2.2.24 for more discussion and examples.

Please see the `?nmxml` help topic for more information on arguments that can be passed to `$NMXML`.

See also: 2.2.24.

2.2.24 \$NMEXT

Syntax: R

Multiple allowed: yes

Like `$NMXML`, `$NMEXT` allows the import of `$THETA`, `$OMEGA`, and `$SIGMA` from your NONMEM run into your mrgsolve model, but the estimates are read from the `.ext`

file output. \$NMEXT is able to import the NONMEM estimates much faster than \$NMXML when loading from sampling based methods (mainly METHOD=BAYES).

We can load the same model as the \$NMXML example above with the following code:

```
path <- file.path(path.package("mrgsolve"), "nonmem")
```

```
code <- '
$NMEXT
run = 1005
project = path
root = "cppfile"

olabels = c("ECL", "EVC", "EKA")
slabels = c("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
'
```

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

```
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  | .      .
```

Once the model object is obtained, the path to the `ext` file that formed the source for imported parameters can be retrieved by coercing the model object to list and looking for `nm_import`. See the `$NMXML` topic in section 2.2.23 for an example of equivalent functionality.

IMPORTANT: while `$NMEXT` works very similarly to `$NMXML`, there is one key difference between the two: when using `$NMEXT`, you will always get one `$OMEGA` matrix and one `$SIGMA` matrix, regardless of the block structure used in the NONMEM control stream. When using `$NMXML`, you get the same block structure in the `mrgsolve` model as the NONMEM model. For example: in the NONMEM control stream, `$OMEGA` is one 2x2 matrix and one 3x3 matrix. Importing those estimates with `$NMEXT` will give you one 5x5 matrix, while importing the estimates with `$NMXML` will give you a list of one 2x2 and one 3x3 matrix.

root argument: please use the `root = "cppfile"` argument going forward.

As of `mrgsolve 0.11.0`, we added an argument called `root` to `$NMEXT` that tells `mrgsolve` the location where it should read the `ext` file from. The default behavior is the "working" directory. When this is the case, `mrgsolve` assumes that the `ext` file can be found relative to the "working" directory. The only other value that `root` can take is "cppfile". When `root = "cppfile"`, then `mrgsolve` will look for the `ext` file in a directory that is relative to **where the model source code file is located**.

We recommend that users start using the `root` argument and set it to "cppfile". This will eventually become the default. For example:

```
$NMEXT
run = 1005
project = "../..model/pk"
root = "cppfile"
```

This tells `mrgsolve` to find the nonmem run back two directories (`../..`) and then into `model --> pk --> 1005` relative to where the `mrgsolve` model file is located. This is in contrast to the previous expected behavior that the path should be relative to the current working directory.

We also note here that when users pass an absolute path, the relative path doesn't matter at all. Users are free to use pathing tools to generate the absolute path to the project. For example, the `here::here()` function can be used like this

```
$NMEXT
run = 1005
project = here::here("model/pk")
```

When used in the proper context, `here()` will generate an absolute path from your projects root directory to the nonmem project directory. Please refer to the `here::here()` documentation for proper use of this function.

See the `?nmext` R help topic for arguments that can be passed to `$NMEXT` block.

Notably, the user can select the function to read in the ext file. By default, `mrgsolve` will try to load `data.table` and use the `fread` function. If `data.table` can't be loaded, then `mrgsolve` will use `utils::read.table`.

See also: 2.2.23.

2.2.25 \$INCLUDE

Syntax: text

Multiple allowed: no

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

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

or

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

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

Requirements

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

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

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

But be careful when doing this: if there are changes to `mystuff.h` but not to any other part of the model specification, the model may not be fully compiled when

calling `mread`. In this case, always use `preclean=TRUE` argument to `mread` to force the model to be built when calling `mread`.

2.2.26 \$ENV

Syntax: R

Multiple allowed: no

This block is all R code (just as you would code in a stand-alone R script. The code is parsed and evaluated into a new environment when the model is compiled. Objects inside `$ENV` can be utilized in different C++ functions (see 2.2.21) or other parts of the simulation process.

For example:

```
$ENV

Sigma <- cmat(1,0.6,2)

mu <- c(2,4)

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

2.3 Variables and Macros

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

IMPORTANT NOTE:

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

2.3.1 ID

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

2.3.2 TIME

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

2.3.3 SOLVERTIME

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

Starting with `mrgsolve` version 1.0.0, the variable `T` is provided as a synonym to `SOLVERTIME` inside `$ODE` when you invoke the `nm-vars` plugin (Section 9.2).

2.3.4 T

Only provided when the `nm-vars` plugin is invoked; see `SOLVERTIME`.

2.3.5 EVID

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

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

`EVID` is an alias for `self.evid`.

2.3.6 CMT

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

```
$CMT GUT CENT PERIPH
```

```
$MAIN
```

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

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

`CMT` is an alias for `self.cmt`.

2.3.7 AMT

AMT is the current value of dose amount.

AMT is an alias for `self.amt`.

2.3.8 NEWIND

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

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

For example:

```
[ GLOBAL ]
int counter = 0;

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

NEWIND is an alias for `self.newind`.

2.3.9 SS_ADVANCE

This is a `bool` data item (either `true` or `false`) which is always `false` unless `mrsgsolve` is currently advancing the system to steady state (Chapter 8); then it will be `true`. This variable is only available in the `$ODE` (or `$DES`) block.

Use this variable to modify the calculation of your model differential equations while the system is advancing to steady state. One use case is when you have an accumulation compartment to calculate AUC but you want to halt accumulation while the system is working toward steady state

```
$ODE
dxdt_CENT = -(CL/V) * CENT;
dxdt_AUC = CENT/V;
if(SS_ADVANCE) dxdt_AUC = 0;
```

2.3.10 simeta()

The `simeta()` function can be used to re-simulate ETA values. For example,

```
$MAIN
simeta();
```

will re-simulate all `ETA(n)`.

2.3.11 `simeps()`

`simeps()` works like `simeta()`, but all `EPS(n)` values are re-simulated rather than the ETA values.

2.3.12 `self`

`self` is an object that gets passed to your model function that contains data items and functions that can be called. It is a `struct` (see the source code [here](#)). A partial list of members are documented in the following sections.

`self` functions include

- `self.tad()`
- `self.mtime()`
- `self.mevent()`
- `self.stop()`
- `self.stop_id()`
- `self.stop_id_cf()`

`self` data members include

- `self.id` (ID)
- `self.amt` (AMT)
- `self.cmt` (CMT)
- `self.evid` (EVID)
- `self.newind` (NEWIND)
- `self.nid`
- `self.idn`
- `self.rown`
- `self.nrow`
- `self.envir` (see note below)

This information is provided for transparency and is not exhaustive. We provide an interface to these data items through pre-processor directives with simpler names (e.g. EVID will translate to `self.evid`) and users are encouraged to use the simpler, API name.

2.3.13 `self.cmt`

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

For example:

```
$TABLE
```

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

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

2.3.14 self.amt

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

```
[ PREAMBLE ]
double last_dose = 0;

[ MAIN ]

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

2.3.15 self.nid

The number of IDs in the data set.

2.3.16 self.idn

The current ID number. Numbers start at 0 and increase by one to self.nid-1. So if you want to test for the last ID in the output data set, you would write:

```
[ table ]

if(self.idn == (self.nid-1)) {
    // do something ....
}
```

2.3.17 self.nrow

The total number of rows in the output data set.

2.3.18 self.rown

The current row number. Numbers start at 0 and increase by one to self.rown-1. So if you want to test for the last row in the output data set, you would write:

```
[ table ]

if(self.rown == (self.nrow-1)) {
    // do something ....
}
```

2.3.19 self.envir

This item is a null pointer that can be cast to an `Rcpp::Environment` only when the Rcpp plugin is invoked (see Section 9.5).

For example

```
[ plugin ] Rcpp mrgx

[ preamble ]
Rcpp::Environment env = mrgx::get_envir(self);
```

2.3.20 self.tad()

This is a function that calculates and returns the time after the most recent dose event record (any record with EVID equal to 1 or 4). `self.tad()` will return -1 when it is called before the first dose record within an individual (`NEWIND <= 1`).

This function should be called in `$MAIN` every time `$MAIN` is called.

For example:

```
$MAIN

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

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

2.3.21 self.mtime(<time>)

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

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

For example,

```
$PARAM change_point = 5.13;

$MAIN

double KA = 1.1;

double mt1 = self.mtime(change_point);
```

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

2.3.22 self.mevent(<time>, <evid>)

Related to `self.mtime()` (Section @ref(self.mtime)), except you can set a specific EVID for this intervention and you track the change time via EVID rather than the time. You'd use this if you want to anchor several events in the future and be sure you can distinguish between them. For example

```
[ main ]
self.mevent(change_point1, 33);
self.mevent(change_point2, 34);
```

Now, you can look for `EVID==33` to know you have hit `change_point1` or `EVID==34` to indicate that you have hit `change_point2`. Notice that `self.mevent()` doesn't return any value. You will know that you've hit the change time by checking EVID.

2.3.23 self.stop()

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

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

2.3.24 self.stop_id()

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

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

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

2.3.25 self.stop_id_cf()

This `self` function is available to be called from `$PREAMBLE`, `$MAIN`, and `$TABLE`. When this function is called, processing of the current individual is stopped and current values are carried forward (`cf`) for the remaining output records for that individual.

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

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

2.3.26 THETA(n)

THETA(n) is ubiquitous in NONMEM control streams, representing estimated fixed effect parameters. `mrgsolve` does not attach any special meaning to THETA(n) but starting with version 1.0.0 it will translate THETA(n) to THETA_n. This is useful when importing NONMEM estimates using \$NMXML or \$NMEXT, where THETAs are imported as parameters with names THETA1, THETA2, THETA3 and so on (see Sections 2.2.23 and 2.2.24). THETA(n) is simply a NONMEM-oriented style for referring to THETA_n.

2.3.27 ETA(n)

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

For example:

```
$OMEGA
1 2 3

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

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

2.3.28 EPS(n)

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

Example:

```
[ CMT ] CENT

[ PARAM ] CL=1, VC=20

[ SIGMA ] @labels ADD PROP
```

```
25 0.0025

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

2.3.29 table(<name>)

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

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

But rather this:

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

$CAPTURE CP
```

See: section 2.2.11 and also 2.2.15

2.3.30 F_CMT

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

Example:

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

2.3.31 ALAG_CMT

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

Example:

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

2.3.32 R_CMT

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

Example:

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

2.3.33 Rn

Only available when the `nm-vars` plugin is invoked; see `R_CMT`.

2.3.34 D_CMT

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

Example:

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

2.3.35 NONMEM-like syntax

There is a NONMEM-like syntax that lets you write `F1` rather than `F_GUT`, `D2` rather than `D_CENT` as well as other variables that are commonly used in a NONMEM control stream. To make this syntax available, the `nm-vars` plugin must be invoked.

See Section 9.2 on the `nm-vars` plugin for details.

2.4 Reserved words

Reserved words cannot be used as names for parameters, compartments or other derived variables in the model. **Note** that some of these words are “reserved” for you to use in your data set.

```
ID  
amt  
cmt  
ii  
ss  
evid  
addl  
rate  
time  
SOLVERTIME  
table  
ETA  
EPS  
AMT  
CMT  
ID  
TIME  
EVID
```

```
simeps
self
simeta
NEWIND
DONE
CFONSTOP
DXDTZERO
CFONSTOP
INITSOLV
_F
_R
_ALAG
SETINIT
report
_VARS_
VARS
SS_ADVANCE
AMT
CMT
II
SS
ADDL
RATE
THETA
pred_CL
pred_VC
pred_V
pred_V2
pred_KA
pred_Q
pred_VP
pred_V3
double
int
bool
capture
```

Other reserved words depend on the compartment names in your model. For example, if you have a compartment called CENT in the model, then the the following will be reserved

```
F_CENT
R_CENT
D_CENT
ALAG_CENT
N_CENT
```

2.5 Derive new variables

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

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

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

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

2.5.1 Special handling for double, int, bool

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

For example, in the following code:

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

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

```
$GLOBAL
namespace {
  double CLi;
}

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

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

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

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

```
$TABLE
double KEi = CLi/VCi;

$CAPTURE KEi
```

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

```
$MAIN

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

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

2.5.2 Using other types globally

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

For example:

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

or

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

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

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

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

2.6 Random number generation

Users can simulate random numbers inside a model file using functions that are similar to the functions you'd normally use in R (e.g. `rnorm()` and `runif()`). This functionality is provided by Rcpp and therefore requires using the Rcpp plugin (see Chapter 9 and Section 9.5).

Rcpp provides these functions inside the R namespace so you will have to prefix the function call with `R::`.

As an example, to make a draw from Uniform (0,1)

```
[ plugin ] Rcpp  
  
[ error ]  
double draw = R::runif(0,1);
```

Note that the 0 gets used as min and the 1 gets used as max; we didn't pass `n` here and `draw` is a single number (not a vector like you'd get from `runif(100, 0, 1)` on your R console). So in general, these functions work like their R counterparts, but without the `n` argument.

Another example showing how to draw from binomial distribution with probability 0.5

```
[ plugin ] Rcpp  
  
[ error ]  
double draw = R::rbinom(1, 0.5);
```

Here, the 1 is used as `size` (not `n`) and 0.5 is used as `prob`.

Other helpful functions could be `R::rnorm()` or `R::rlnorm()` but you can call any of the `r` functions as well as the corresponding `dpq` functions through this R namespace.

Documentation, including functions to call and arguments can be found in the Rcpp API docs

<http://dirk.eddelbuettel.com/code/rcpp/html/namespaceR.html>

2.7 Examples

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

2.7.1 Simple PK model

Notes:

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

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

$CMT GUT CENT

$ODE

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

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

This model can also be written without differential equations

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

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

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

2.7.2 PK/PD model

Notes:

- We use a preprocessor `#define` directive in \$GLOBAL; everywhere in the model where a CP token is found, the expression (CENT/VC) ... with parentheses ... is inserted
- We write the initial value for the RESP compartment in \$MAIN as a function of two parameters KIN/KOUT
- A new variable - INH- is declared and used in \$ODE
- Since CP is defined as CENT/VC, we can “capture” that name/value in \$CAPTURE

- Both \$MAIN and \$ODE are C++ code blocks; don't forget to add the ; at the end of each statement

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

$GLOBAL
#define CP (CENT/VC)

$CMT GUT CENT RESP

$MAIN
RESP_0 = KIN/KOUT;

$ODE

double INH = CP/(IC50+CP);

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

$CAPTURE CP
```

2.7.3 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 ??)

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

$SET delta=0.1, end=240

$CMT GUT CENT

$MAIN

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

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

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

$SIGMA 0

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

$TABLE
capture CP = CENT/VCi;

$CAPTURE IOV ECL EVC
```

Chapter 3

Input data sets

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

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

3.1 Overview

Data sets are the primary mechanism for establishing the scope of your simulations in `mrgsolve`, including individuals, interventions, observation times, and parameter values. For both `data_set` and `idata_set` (see below), you may include columns in the data sets that have the same names as the parameters in your model (section 1.1, 2.2.4). `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 11.3.

3.2 Event data sets (data)

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

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

- `ID` the subject id. This id does not need to be unique in the `data_set`: `mrgsolve` detects a new individual when the current value of `ID` is different from

the immediate preceding value of ID. However, we always recommend using unique ID.

- `time` or `TIME`: states the time of the data record
- `evid` or `EVID`: the event id indicator. `evid` can take the values:
 - `0` = observation record
 - `1` = dosing event (bolus or infusion)
 - `2` = other type event, with solver stop and restart
 - `3` = system reset
 - `4` = reset and dose
 - `8` = replace the amount in the compartment with `amt`
- `amt` or `AMT`: the dose amount (if `evid==1`)
- `cmt` or `CMT`: the dosing compartment number. This may also be a character value naming the compartment name. The compartment number must be consistent with the number of compartments in the model for dosing records (`evid==1`).
For observation records, a `cmt` value of 0 is acceptable. Use a negative compartment number with `evid 2` to turn a compartment off.
- `rate` or `RATE`: if non-zero and `evid=1` or `evid=4`, implements a zero-order infusion of duration $F_CMT \cdot amt / rate$, where F_CMT is the bioavailability fraction for the dosing compartment. Use `rate = -1` to model the infusion rate and `rate = -2` to model the infusion duration, both in \$MAIN (see sections 2.2.7, 2.3.30, 2.3.32, 2.3.34).
- `ii` or `II`: inter-dose interval; `ii=24` means daily dosing when the model time unit is hours
- `add1` or `ADDL`: additional doses; a non-zero value in `add1` requires non-zero `ii` on the same record
- `ss` or `SS` steady state indicator; use 1 to implement steady-state dosing; 0 otherwise. `mrsgsolve` also recognizes dosing records where `ss=2`. This allows combination of different steady state dosing regimens under linear kinetics (e.g. 10 mg QAM and 20 mg QPM daily to steady state).

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

In addition to these special column names, `mrsgsolve` will recognize columns in `data_set` that have the same name as items in the parameter list (see 2.2.4 and 1.1). When `mrsgsolve` 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 11.3).

3.2.1 Two types of data_set

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

- **Full data sets** have a mix of observations and dosing events (likely, but not required). When mrgsolve finds one record with evid=0, it assumes that **ALL** output observation times are to come from the data set. In this case the simulation output time grid discussed in 1.3 is ignored and only observations found in the data set appear in the simulated output. Use full data sets when you want a highly customized sampling schedule or you are working with a clinical data set.
- **Condensed data sets** have no records with evid=0. In this case, mrgsolve will fill the simulated output with observations at times specified by the output time grid (section 1.3 and see section 11.5). These are very convenient to use because there is less data assembly burden and output data sets can easily be created with very dense sampling scheme or highly customized sampling schemes with very little work. Use a condensed data set when you want a uniform set of sampling times for all subjects in the data set.

Example of condensed data set

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

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

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

Example of full data set

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

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

```
. 5  1 79.6 4.02 2.02  9.66  0 0.00  0
. 6  1 79.6 4.02 3.82  8.58  0 0.00  0
```

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

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

For example:

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

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

```
out
```

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

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

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

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

3.2.2 Sorting requirements

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

3.2.3 Creating data sets

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

3.2.4 Example

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

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

```
data
```

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

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

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

```
data
```

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

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

For example:

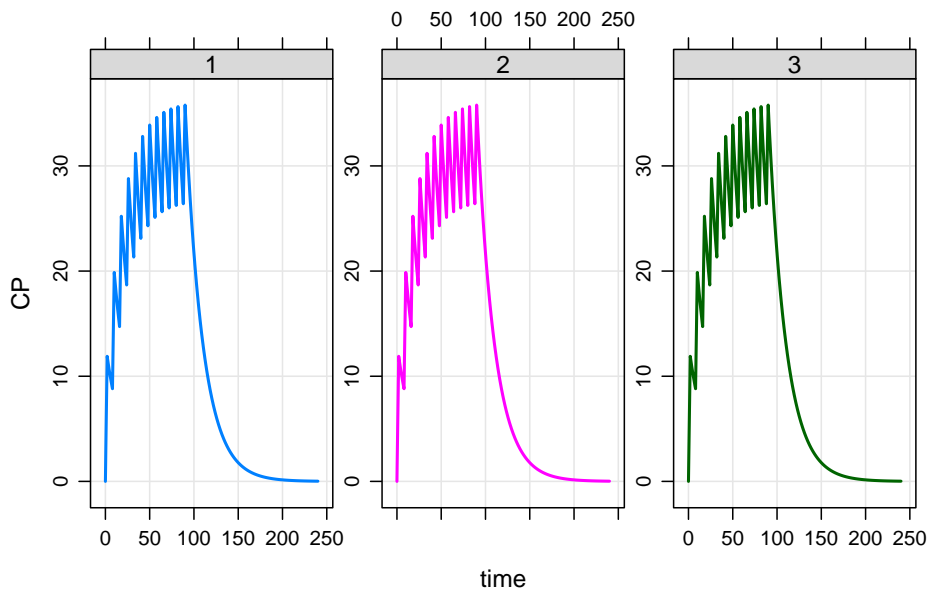
```
mod <- mrgsolve:::house()
```

```
mod %>%
```

```
  data_set(data) %>%
```

```
  mrgsim(end=240) %>%
```

```
  plot(CP~time|factor(ID))
```



3.3 Individual data sets (idata)

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

- **Individual-level parameters:** Just prior to simulating any individual, mrgsolve checks the appropriate row in `idata` (if supplied) for any columns with parameter names. If parameter names are found, the parameter list is updated and that update remains in effect for the duration of that individual's data records.
- **Individual- or group-level designs:** Each individual or group of individual may be assigned a different sampling design. For example, individuals in arm 1 may need to be simulated for 4 weeks whereas individuals in arm 2 may need to be simulated for 8 weeks. `idata` may be used to identify one of several sampling designs for each individual or group of individuals.
- **Individual-level compartment initialization:** if a model has a compartment called CMT and mrgsolve finds a column in `idata` called `CMT_0`, the value of `CMT_0` will be used to initialize that compartment with, potentially a different value for each individual. Note that there are several other ways to initialize compartments detailed in 11.2.

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

An `idata_set` looks like this:


```
data(exidata)
```

```
exidata
```

```
.   ID   CL   VC   KA  KOUT  IC50 F00
.  1    1 1.050 47.80 0.8390 2.450 1.280   4
.  2    2 0.730 30.10 0.0684 2.510 1.840   6
.  3    3 2.820 23.80 0.1180 3.880 2.480   5
.  4    4 0.552 26.30 0.4950 1.180 0.977   2
.  5    5 0.483  4.36 0.1220 2.350 0.483  10
.  6    6 3.620 39.80 0.1260 1.890 4.240   1
.  7    7 0.395 12.10 0.0317 1.250 0.802   8
.  8    8 1.440 31.20 0.0931 4.030 1.310   7
.  9    9 2.570 18.20 0.0570 0.862 1.950   3
. 10   10 2.000  6.51 0.1540 3.220 0.699   9
```

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

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

3.3.1 Use case

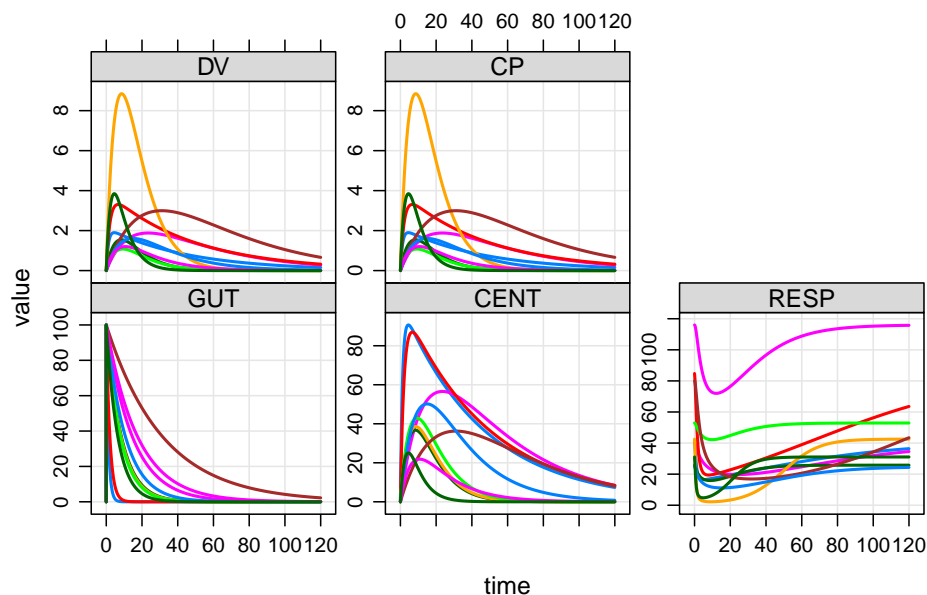
`idata_set` is usually helpful for implementing a batch of simulations when a `data_set` is not used. The batch may be as a sensitivity analysis or for population simulation. Usually, an events object is used with `idata`, but it is not required.

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.

3.4 Numeric data only

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

3.5 Data set validation

At the time of simulation, `mrqsolve` will validate the input data set, removing non-numeric columns, checking for missing values in parameter columns, checking compartment numbers, etc.

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

```
data(exTheoph)
```

```
head(exTheoph)
```

```
.   ID   WT Dose time  conc cmt  amt evid
.  1   1 79.6 4.02 0.00  0.00   1 4.02    1
.  2   1 79.6 4.02 0.25  2.84   0 0.00    0
```

```

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

mod <- modlib("pk1")

. Loading model from cache.
valid <- valid_data_set(exTheoph,mod)

str(valid)

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

```

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

3.6 Data sets for use with \$PRED

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

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

Chapter 4

Event objects

Event objects are similar to the data sets described in 3, but are simpler and easier to create. This is the fastest way to implement a basic intervention (like dosing) for a single “individual” into your model.

Event objects also offer an elegant way to compose complicated dosing regimens. Typically, the different parts of a regimen are composed as individual event objects and then combined to create a multi-faceted dose regiment.

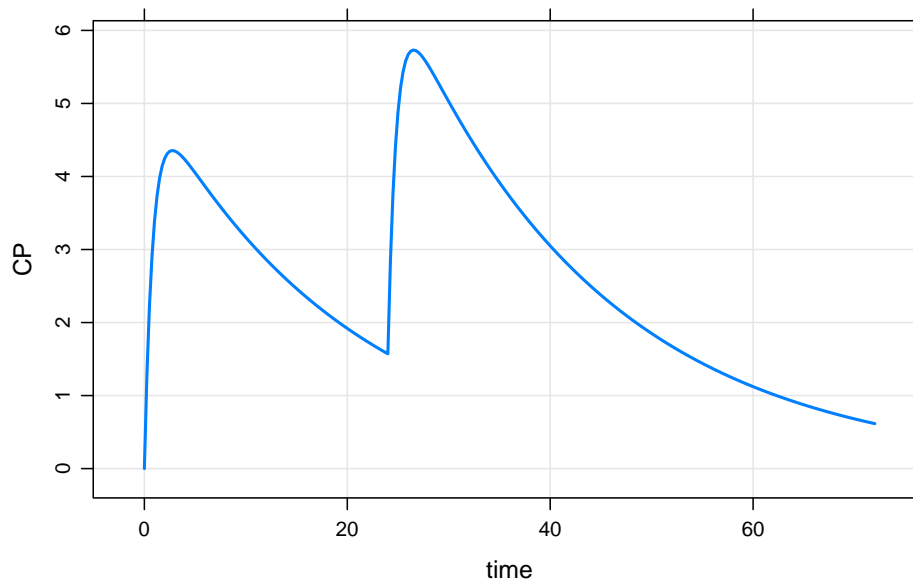
Finally, once an event object is created (either simple or complex), this object can be “expanded” into multiple individuals to create a population data set for simulation.

See details in the subsequent sections.

4.1 Usage

Event objects are frequently used in a pipeline to simulate a dosing regimen. For example

```
mod <- house(end = 72)
mod %>% ev(amt = 100, ii = 24, addl = 1) %>% mrgsim() %>% plot("CP")
```



This used the `ev()` constructor to make an event object for two 100 mg doses and this is passed into `mrksim()` to implement this regimen.

Alternatively, we can create a standalone object and feed that into the pipeline

```
regimen <- ev(amt = 100, ii = 24, addl = 1)
mod %>% ev(regimen) %>% mrksim() %>% plot("CP")
```

If you are not using the pipe syntax, the following would be equivalent calls

```
mrksim(mod, events = regimen) %>% plot("CP")
```

And there are `mrksim()` variants that explicitly accept an event object

```
mrksim_e(mod, regimen) %>% plot("CP")
```

More will be said about how to create and manipulate event objects in the following sections.

4.2 Construction

A new event object can be created with the `ev()` constructor. For a single, 100 mg dose it would be

```
e <- ev(amt = 100)
```

When you print the object to the R console we see the 100 mg dose along with the following defaults

- time set to 0
- cmt set to 1 (the first compartment)
- evid set to 1 (a bolus dose)

```
e
```

```
. Events:
.   time amt cmt evid
. 1    0 100   1    1
```

Of course, we can override any of these defaults or add additional items as needed. For a single 100 mg dose infused over 2 hours in compartment 2 one hour after the simulation starts

```
e <- ev(amt = 100, rate = 50, cmt = 2, time = 1)
```

To use this event object, we can pass it into `mrghsim()` under the `events` argument

```
mod <- house(delta = 1, end = 24)
```

```
mrghsim(mod, events = e)
```

```
. Model:  housemodel
. Dim:    26 x 7
. Time:   0 to 24
. ID:     1
.   ID time GUT  CENT  RESP    DV    CP
. 1:   1    0   0  0.00 50.00 0.000 0.000
. 2:   1    1   0  0.00 50.00 0.000 0.000
. 3:   1    1   0  0.00 50.00 0.000 0.000
. 4:   1    2   0 48.77 44.12 2.439 2.439
. 5:   1    3   0 95.16 36.98 4.758 4.758
. 6:   1    4   0 90.52 34.61 4.526 4.526
. 7:   1    5   0 86.11 34.75 4.305 4.305
. 8:   1    6   0 81.91 35.22 4.095 4.095
```

Event object inputs can be functions of previously defined inputs. For example

```
ev(amt = 100, rate = amt / 2)
```

```
. Events:
.   time amt rate cmt evid
. 1    0 100   50   1    1
```

See the `?ev()` help topic for more information on additional arguments when constructing event objects. Here, I'd like to specifically highlight a handful of options that can be helpful when constructing event objects.

Infusion duration

Above, we created some infusion event objects by adding an infusion rate to the

input. We can also indicate an infusion by adding an infusion time through the `tinf` argument

```
ev(amt = 100, tinf = 2)
```

```
. Events:
.   time amt rate cmt evid tinf
. 1    0 100   50   1    1    2
```

ID

While the primary use case for event objects are for *single individuals*, we can code a series of IDs into the object too

```
ev(amt = 100, ID = 1:3)
```

```
. Events:
.   ID time amt cmt evid
. 1  1    0 100   1    1
. 2  2    0 100   1    1
. 3  3    0 100   1    1
```

Here, we asked for 3 IDs in the object. Once this is turned into a simulation data set (see below), we'll have a population data set from which to simulate.

Additional data items

We can also pass through arbitrary data columns through the event object. For example, we can pass through `WT`

```
ev(amt = 100, WT = 80)
```

```
. Events:
.   time amt cmt evid WT
. 1    0 100   1    1 80
```

4.3 Coerce to data set

As we noted, event objects are very similar to data sets and they are nothing but data sets under the hood. We can take the event objects we created above and coerce them to other objects.

Using `as_data_set`

```
as_data_set(e)
```

```
.   time amt rate cmt evid ID
. 1    1 100   50   2    1  1
```

This will ensure that there is an `ID` column in the output and it will be suitable to use for simulation.

Using as.data.frame

```
as.data.frame(e) %>% mutate(ID = 5)
```

```
.   time amt rate cmt evid ID
. 1     1 100   50   2    1  5
```

4.4 Extract information

There is a \$ operator for event objects

```
e$amt
```

```
. [1] 100
```

4.5 Combining event objects**4.5.1 Concatenate**

Two or more event objects can be concatenated using the c operator

```
e1 <- ev(amt = 100)
e2 <- ev(amt = 200, time = 24)
```

```
c(e1, e2)
```

```
. Events:
.   time amt cmt evid
. 1     0 100   1    1
. 2    24 200   1    1
```

This essentially “rbinds” the rows of the individual event objects and sorts the rows by time.

NOTE: the result of this manipulation is another event object.

4.5.2 Sequence

Event objects can also be combined to happen in a sequence. In the previous example, we wanted the 200 mg to happen at 24 hours and we had to code that fact into time accordingly.

By specifying a dosing interval (ii) we can ask mrgsolve to do that automatically by calling the seq() method.

```
e1 <- ev(amt = 100, ii = 24)
e2 <- ev(amt = 200, ii = 24)
```

```
seq(e1, e2)
```

```
. Events:
.   time amt ii addl cmt evid
. 1    0 100 24    0  1    1
. 2   24 200 24    0  1    1
```

This was a trivial example to get a simple result. We can try something more complicated to make the point

```
e3 <- ev(amt = 100, ii = 6, addl = 28)
e4 <- ev(amt = 200, ii = 12, addl = 124)
e5 <- ev(amt = 400, ii = 24, addl = 3)

seq(e3, e4, e5)
```

```
. Events:
.   time amt ii addl cmt evid
. 1    0 100  6   28   1    1
. 2  174 200 12  124   1    1
. 3 1674 400 24    3   1    1
```

NOTE: when `mrgsolve` puts event objects into a sequence, it starts the next segment of the regimen one dosing interval after the previous regimen finished. Going back to the simple example

```
seq(e1, e2)
```

```
. Events:
.   time amt ii addl cmt evid
. 1    0 100 24    0  1    1
. 2   24 200 24    0  1    1
```

`e1` was just a single dose at time 0. `mrgsolve` will have `e2` start one dosing interval (24 hours) after the last (only) dose in `e1`. We can alter the amount of time between segments of the regimen by using the `wait` argument. For example, to push `e2` out by an additional 24 hours we'd use

```
seq(e1, wait = 24, e2)
```

```
. Events:
.   time amt ii addl cmt evid
. 1    0 100 24    0  1    1
. 2   48 200 24    0  1    1
```

We can also use a negative value for `wait` to make the next dose happen sooner

```
seq(e1, wait = -12, e2)
```

```
. Events:
.   time amt ii addl cmt evid
```

```
. 1    0 100 24    0  1  1
. 2   12 200 24    0  1  1
```

Finally, we should note that event objects can be used multiple times in a sequence

```
seq(e1, e2, wait = 7*24, e2, e1)
```

```
. Events:
.   time amt ii addl cmt evid
. 1    0 100 24    0  1  1
. 2   24 200 24    0  1  1
. 3  216 200 24    0  1  1
. 4  240 100 24    0  1  1
```

4.5.3 repeat

Like the `seq()` method for event objects, `ev_repeat` will put an event object into a sequence `n` times

```
ev_repeat(e1, n = 3)
```

```
.   ID time amt ii cmt evid addl
. 1  1    0 100 24  1  1  0
. 2  1   24 100 24  1  1  0
. 3  1   48 100 24  1  1  0
```

By default, this function returns a regular data frame. To return an event object instead call

```
ev_repeat(e1, n = 3, as.ev = TRUE)
```

You can put a waiting period too. To illustrate this, let's compose a more complicated regimen and repeat that

```
e1 <- ev(amt = 500, ii = 24)
e2 <- ev(amt = 250, ii = 24, addl = 5)
e3 <- ev_seq(e1, e2)
```

```
e3 %>% realize_addl()
```

```
. Events:
.   time amt ii addl cmt evid
. 1    0 500  0    0  1  1
. 2   24 250  0    0  1  1
. 3   48 250  0    0  1  1
. 4   72 250  0    0  1  1
. 5   96 250  0    0  1  1
. 6  120 250  0    0  1  1
. 7  144 250  0    0  1  1
```

In this regimen, we have daily dosing for 7 doses. The last dose is given at 144 hours. When putting this into a sequence, we'll wait one dosing interval and then the wait period and then start again

```
ev_repeat(e3, n = 3, wait = 7*24)
```

```
.   ID time amt ii addl cmt evid
.  1  1    0 500 24    0   1    1
.  2  1   24 250 24    5   1    1
.  3  1  336 500 24    0   1    1
.  4  1  360 250 24    5   1    1
.  5  1  672 500 24    0   1    1
.  6  1  696 250 24    5   1    1
```

4.5.4 Create a “data_set”

Use the `as_data_set()` function to combine multiple event objects into a single data set.

```
as_data_set(e1, e2)
```

```
.   ID time cmt evid amt ii addl
.  1  1    0   1    1 500 24    0
.  2  2    0   1    1 250 24    5
```

It's important to note that

1. The result is a regular old `data.frame()`; once you call `as_data_set()`, you exit the event object world
2. Each event object is given a different ID

Recall that we can create event objects with multiple IDs; `as_data_set()` is handy to use with this feature

```
as_data_set(
  ev(amt = 100, ID = 1:3),
  ev(amt = 200, ID = 1:3),
  ev(amt = 300, ID = 1:2)
)
```

```
.   ID time cmt evid amt
.  1  1    0   1    1 100
.  2  2    0   1    1 100
.  3  3    0   1    1 100
.  4  4    0   1    1 200
.  5  5    0   1    1 200
.  6  6    0   1    1 200
.  7  7    0   1    1 300
.  8  8    0   1    1 300
```

Notice that `as_data_set` has created unique IDs for the 3 subjects in the 100 mg group, the 3 subjects in the 200 mg group, and the 2 subjects in the 300 mg group.

We'll cover a function called `ev_rep()` below to “expand” an event object to multiple individuals

```
as_data_set(
  e1 %>% ev_rep(1:300),
  e2 %>% ev_rep(1:300)
)
```

4.6 Modifying an event object

4.6.1 Tidy-like manipulation

Event objects can be mutated

```
mutate(e, amt = 200)
```

```
. Events:
.   time amt rate cmt evid
. 1     1 200   50   2    1
```

Columns can be removed from event objects

```
ev(amt = 100, WT = 50, AGE = 12) %>% select(-WT)
```

```
. Events:
.   time amt cmt evid AGE
. 1     0 100   1    1  12
```

Rows can be removed from event objects

```
e <- c(ev(amt = 100), ev(amt = 200, time = 12), ev(amt = 300, time = 24))
filter(e, time <= 12)
```

```
. Events:
.   time amt cmt evid
. 1     0 100   1    1
. 2    12 200   1    1
```

4.6.2 realize_addl

“Additional” doses can be made explicit in an event object

```
ev(amt = 100, ii = 6, addl = 3) %>% realize_addl()
```

```
. Events:
.   time amt ii addl cmt evid
```

```
. 1    0 100 0    0 1    1
. 2    6 100 0    0 1    1
. 3   12 100 0    0 1    1
. 4   18 100 0    0 1    1
```

4.6.3 ev_rep

Event objects can be “expanded” into multiple IDs to create a population; use the `ev_rep()` function for this.

```
ev(amt = 100) %>% ev_rep(1:5)
```

```
.   ID time amt cmt evid
. 1  1    0 100  1    1
. 2  2    0 100  1    1
. 3  3    0 100  1    1
. 4  4    0 100  1    1
. 5  5    0 100  1    1
```

By default, `ev_rep()` returns a regular data frame. You can request that an event object is returned

```
ev(amt = 100) %>% ev_rep(1:5, as.ev = TRUE)
```

`ev_rep()` can work on an event object with any complexity.

4.7 Creative composition

`mrqsolve` has a couple of more creative ways to construct event objects.

4.7.1 ev_days

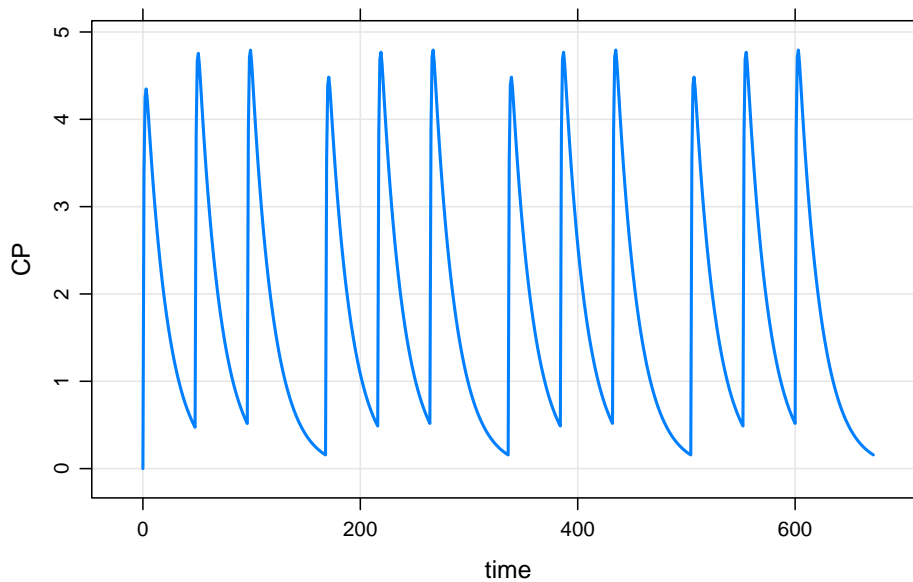
`ev_days()` will create dosing sequences when dosing are on certain days (of the week). For example, to dose only on Monday, Wednesday, and Friday for on month

```
e <- ev_days(ev(amt = 100), ii = 168, addl = 3, days = 'm,w,f')
e
```

```
.   time amt cmt evid  ii addl
. 1    0 100  1    1 168    3
. 2   48 100  1    1 168    3
. 3   96 100  1    1 168    3
```

We can see how this works by simulating the regimen

```
mrqsim_e(mod, e, end = 168*4) %>% plot("CP")
```



4.7.2 ev_rx

`ev_rx()` is a way to write a regimen out with notation similar to what you might see on a prescription. For example, 100 mg twice daily for 3 doses into compartment 2 would be

```
ev_rx("100 mg q12h x3 in 2")
```

```
. Events:
.   time amt ii addl cmt evid
. 1    0 100 12    2    2    1
```

To code an infusion

```
ev_rx("500 mg over 2 hours q 24 h x3 in 1")
```

```
. Events:
.   time amt rate ii addl cmt evid
. 1    0 500  250 24    2    1    1
```

See the `ev_rx()` documentation for more details and limitations.

Chapter 5

Model Matrices

Model matrices include `$OMEGA` (for subject-level variability) and `$SIGMA` (for residual unexplained variability). These matrices are coded into the model file (see Sections 2.2.16 and 2.2.17) and can be manipulated in different ways via the model object. Because, `$OMEGA` and `$SIGMA` matrices are handled using identical approach (only the names of the functions change), we will focus on working with `$OMEGA` in the following examples with references to the equivalent functions that can be used to work on `$SIGMA`. Also note that, for simplicity, we will not compile the examples presented in this chapter.

5.1 Simple matrix lists

We can look at the `popex` model in the internal library for a starting example to show how model matrices can be seen from the model object.

Once the model is loaded

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

We can print the model object to the console and see the matrix structure

```
mod

.
.
. ----- source: popex.cpp -----
.
.   project: /Users/kyleb/Rli...gsolve/models
.   shared object: popex-so-97d6bf33b36 <not loaded>
.
.   time:          start: 0 end: 240 delta: 0.5
.                  add: <none>
```

```
.
. compartments: GUT CENT [2]
. parameters:   TVKA TVCL TVV WT [4]
. captures:     CL V ECL IPRED DV [5]
. omega:        3x3
. sigma:        1x1
.
. solver:       atol: 1e-08 rtol: 1e-08 maxsteps: 20k
. -----
```

In this output, we see that `omega` is a 3 by 3 matrix and `sigma` is 1 by 1. We can view both matrices by calling `revar()` on the model object

```
revar(mod)
```

```
. $omega
. $...
.      [,1] [,2] [,3]
. ECL:  0.3  0.0  0.0
. EV:   0.0  0.1  0.0
. EKA:  0.0  0.0  0.5
.
.
. $sigma
. $...
.      [,1]
. 1:      0
```

This shows the 3x3 `$OMEGA` matrix with all off-diagonals set to zero and the 1x1 `$SIGMA` which is currently fixed to 0.

The `$OMEGA` matrix can be extracted with the `omat()` function

```
omat(mod)
```

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

Use the `smat()` function to extract the `$SIGMA` matrix. The result of these calls are `matlist` objects; for `$OMEGA` the class is `omegalist` (which inherits from `matlist`)

```
omat(mod) %>% class()
```

```
. [1] "omegalist"
. attr(,"package")
. [1] "mrgsolve"
```

and for `$SIGMA` it is `sigmalist`. These are lists of matrices. In this example, there is just one `$OMEGA` block in the code

```
blocks(mod, OMEGA)
```

```
.
. Model file: popex.cpp
.
. $OMEGA
. @labels ECL EV EKA
. 0.3 0.1 0.5
```

so the length of the `omegalist` object is also 1

```
om <- omat(mod)
length(om)
```

```
. [1] 1
```

Functions are provided to check the names

```
names(om)
```

```
. [1] "..."
```

and the labels

```
labels(om)
```

```
. [[1]]
. [1] "ECL" "EV" "EKA"
```

The `omegalist` (`sigmalist`) object can be converted to a standard R list

```
as.list(om) %>% str()
```

```
. List of 1
. $ ...: num [1:3, 1:3] 0.3 0 0 0 0.1 0 0 0 0.5
.   ..- attr(*, "dimnames")=List of 2
.     .. ..$ : chr [1:3] "ECL" "EV" "EKA"
.     .. ..$ : chr [1:3] "ECL" "EV" "EKA"
```

or it can be rendered as a matrix

```
as.matrix(om)
```

```
.      [,1] [,2] [,3]
. [1,] 0.3  0.0  0.0
. [2,] 0.0  0.1  0.0
. [3,] 0.0  0.0  0.5
```

5.2 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.

5.2.1 Matrix helper functions

`mr.solve` keeps \$OMEGA and \$SIGMA in block matrices (regardless of whether the off-diagonal elements are zeros or not). Recall that in the model specification file we can enter data for \$OMEGA and \$SIGMA as the lower triangle of the matrix (see section 2.2.16). In R, we need to provide a matrix (as an R object). `mr.solve` provides some convenience functions to help ... allowing the user to enter lower diagonals instead of the full matrix.

`dmat()` for diagonal matrix

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

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

`bmat()` for block matrix

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

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

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

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

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

`mr.solve` will convert the correlations to covariances.

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

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

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

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

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

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

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

Frequently, we have estimates in a data frame like this

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

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

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

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

```
. [1] 100
```

```
dim(exBoot)
```

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

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

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

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

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

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

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

Note in this example, we could have called

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

to grab the `$SIGMA` matrices.

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

5.2.2 Fill a matrix with zeros

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

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

For example we have this population PK model

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

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

We can turn that matrix to all zeros with

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

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

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

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

5.2.3 Example: unnamed matrix

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

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

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

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

```
mod %>% omat

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

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

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

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

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

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

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

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

```
. <simpleError: improper signature: omat>
```

5.2.4 Example: named matrices

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

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

```
. $omega
. $IIV
.      [,1] [,2] [,3]
. 1:      1    0    0
. 2:      0    2    0
. 3:      0    0    3
.
. $IOV
.      [,1] [,2]
. 4:      4    0
. 5:      0    5
.
.
. $sigma
. No matrices found
```

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

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

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



```
. 4:    11    0
. 5:     0   12
```

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

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

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

```
ans
```

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

5.2.5 Example: unnamed matrices

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

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

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

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

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

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


Chapter 6

Simulated output

6.1 Output types

When `mrgsim()` is used to simulate from a model, it by default returns an object with class `mrgsims`. This is an S4 object containing a `data.frame` of simulated output and a handful of other pieces of data related to the simulation run that can be coerced to other types (like `data.frame` or `tibble`).

For simulations with large outputs or extremely brief simulations where efficiency is important, users can request the output be returned as a data frame. This is most efficient when the features provided by the `mrgsims` object are not needed. To do this, pass the `output` argument to `mrgsim()`

```
out <- mrgsim(mod, ..., output = "df")
```

or use `mrgsim_df()`

```
out <- mrgsim_df(mod, ....)
```

6.2 Methods for `mrgsim` output

`mrgsolve` provides several methods for working with `mrgsims` objects or coercing the simulation matrix into other R objects. Note the discussion in the following subsections all refer to working with `mrgsims` objects, not `data.frame` output.

6.2.1 Coercion methods

- `as_tibble()`: convert to `tibble`
- `as.data.frame()`: convert to `data.frame`
- `as.matrix()`: convert to `matrix`

6.2.2 Query methods

- `head()`: shows the first `n = 5` rows
- `tail()`: shows the last `n = 5` rows
- `names()`: shows the column names
- `dim()`: shows the number of rows and columns
- `summary()`: shows a numeric summary of all columns
- `$`: extracts a column

6.2.3 Graphical methods

There is a `plot()` methods for simulated output that is aware of independent and dependent variables from the simulation. If `out` is the simulated output (an `mrgsims` object)

```
plot(out)
```

Plot with a formula; the following example selects only the CP and RESPONSE outputs and plots them versus time

```
plot(out, CP + RESPONSE ~ time)
```

To select a large number of responses to plot, pass a character vector or comma-separated character data containing output columns to plot

```
plot(out, "CP, RESPONSE, WT, DOSE")
```

6.2.4 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)
library(mrgsolve)

mod <- mrgsolve::house()

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

Here, `mrgsim()` returns an `mrgsims` object. When `dplyr` is also loaded, this object can be piped directly to `dplyr::filter()` or `dplyr::mutate()` etc.

It is important to note that when `mrgsims` output is piped to `dplyr` functionality, it is coerced to `tibble` (`data.frame`) and there is no way to get the data back to

`mrgsims` object. Most of the time, this is desirable and there is no need to explicitly coerce to `tibble()` when calling `dplyr` verbs on simulated output.

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

- `group_by()`
- `mutate()`
- `filter()`
- `summarise()`
- `select()`
- `slice()`
- `pull()`
- `distinct()`
- `slice()`

6.2.5 Modify methods

You can modify the underlying data in the `mrgsims` object and keep it as an `mrgsims` object.

- `filter_sims()`: calls `dplyr::filter()` to pick rows to keep or discard
- `select_sims()`: calls `dplyr::select()`; note that `ID` and `time` columns are always retained
- `mutate_sims()`: calls `dplyr::mutate()` to add or modify columns

6.3 Controlling output scope

6.3.1 Background

Limiting the volume of simulated data can have a major impact on simulation efficiency, memory footprint, and ease (or lack of ease) in reviewing and dealing with the output. For any large simulation or any simulation from a large model, the user should consider selecting what gets returned when the simulation is performed.

By default, `mrgsim()` returns a `data.frame` with the following

1. `ID`: regardless of whether you simulated a population or not
2. `time` / `TIME`: the independent variable
3. Simulated values for all model compartments
4. Simulated values for derived outputs listed in `$CAPTURE`

You will always get `ID` and `time` and the compartments and any captured items must be written into the model file. This defines the list of data items that **could** (possibly) get returned under items 3 and 4 above. Again: this must be written into the model file and is locked at the time the model is compiled.

However, `mrgsolve` allows the user to pick what is actually returned at run time. Because this is done at run time, different runs can return different data items. And (importantly) `mrgsim()` only allocates space in the output for data items that are

requested. So, opting **out** of unneeded outputs will decrease memory consumption and increase efficiency.

6.3.2 Implementation

The `mrghsolve` model object tracks compartments and captures that are currently being requested. This can be queried using `outvars()`

```
mod <- house()

outvars(mod)

. $cmt
. [1] "GUT" "CENT" "RESP"
.
. $capture
. [1] "DV" "CP"
```

Items are listed under `cmt` and `capture`. The user can update the model object with the names of columns that are being requested by passing `outvars` to `update()`

```
mod <- update(mod, outvars = "CP, RESP")

outvars(mod)
```

```
. $cmt
. [1] "RESP"
.
. $capture
. [1] "CP"
```

This will exclude anything that isn't named in the update. The `outvars` list can be reset by passing `(all)`

```
mod <- update(mod, outvars = "(all)")
```

Remember that ... passed to `mrghsim()` are also passed to `update()` so it is possible to select outputs right in your `mrghsim()` call

```
out <- mrghsim(mod, outvars = "CP, RESP")
```

6.3.3 Copy items from data to simulated output

Users can also use `carry_out` and `recover` to copy items from the input data into the output. This is covered in a different chapter.

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). This is the last parameters will be copied from any input data set prior to advancing the system (when `locf` is being used). Therefore, when parameter columns are found in both an `idata_set` and a `data_set`, it will be the value found in the `data_set` that will overwrite both the base list and any parameter value that was copied from an `idata_set`. It is not an error to have different parameter values in an `idata_set` and a `data_set`, but the value found in the `data_set` will be used when this happens. More on parameters and the parameter update sequence can be found in sections 11.3 and 1.1.
2. `$MAIN` is called
3. The system is advanced via `$ODE` or `$PKMODEL`, whichever one is invoked in the model specification file.
4. If the current record is a dosing record, the dose is implemented (e.g. bolus made or infusion started).
5. If the system is advancing according to `locf`, then parameters are copied from the current record if that is an actual data set record. This is in contrast to `nocb` advance (see above).
6. The `$TABLE` function is called
7. If the current record is marked for inclusion in the simulated output, results are written to the output matrix.
8. Continue to the next record in the individual.
9. Once the last record is processed in an individual, a new individual is started.

Chapter 8

Steady state

8.1 Key information

Keep reading for all the details; I'm including this brief list of key items up front for your convenience.

- Use `ss_rtol` and `ss_atol` arguments to `mrghsim()` to control the local error estimate when `mrghsolve` is finding steady state
- Use `ss_n` to limit the number of doses that will be administered when advancing to steady state; if the number of doses exceeds `ss_n` then a warning is issued and `mrghsolve` moves on
- Use `ss_fixed = TRUE` to silence the warning when `ss_n` is exceeded; you are essentially saying dose up to `ss_n` and then give up and move on without warning
- Use `SS_ADVANCE` in `$ODE` to check if the system is currently being advanced
- Use `ss_cmt` in `[set]` (inside your model) to select the compartments to be considered when finding steady state; you might have better success / efficiency if you focus on key compartments (or exclude unhelpful compartments like a depot compartment)

8.2 Introduction

Within `mrghsolve`, the term “steady state” (SS) applies specifically to the pharmacokinetic dosing system and indicates that the rate of drug administration is equal to the rate of drug elimination. Steady state dosing can take the form of repeated intermittent doses (bolus or infusion, administered intermittently at a given dosing interval) or a continuous infusion administered to steady state.

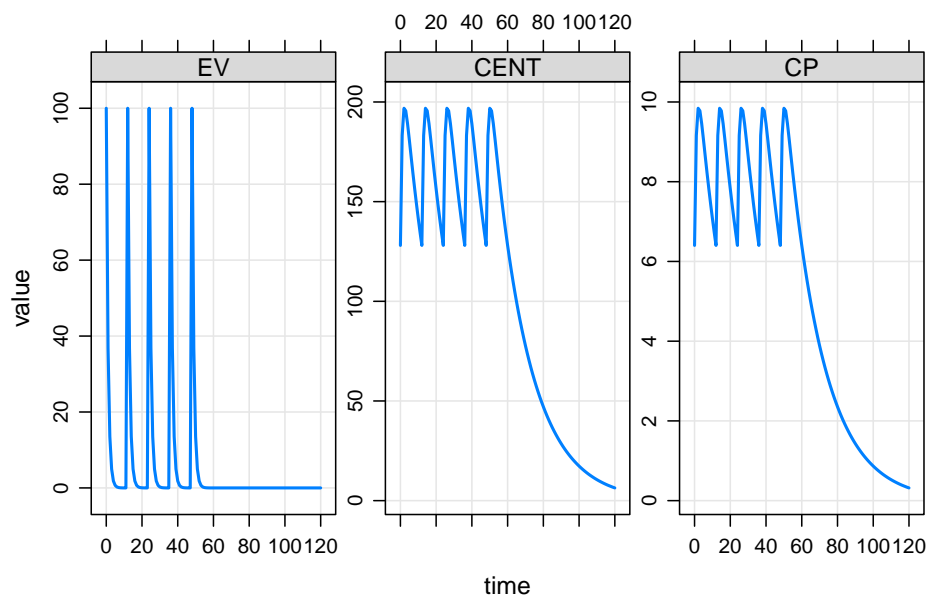
8.2.1 Intermittent doses

The user can direct mrgsolve to advance the system to steady state for intermittent dosing by including `ss=1` in an event object or input data set. For example:

```
mod <- modlib("pk1", end = 120)

. Loading model from cache.
dose <- ev(amt = 100, ii = 12, addl = 4, ss = 1)

mrgsim(mod, dose, recsort = 3) %>% plot()
```



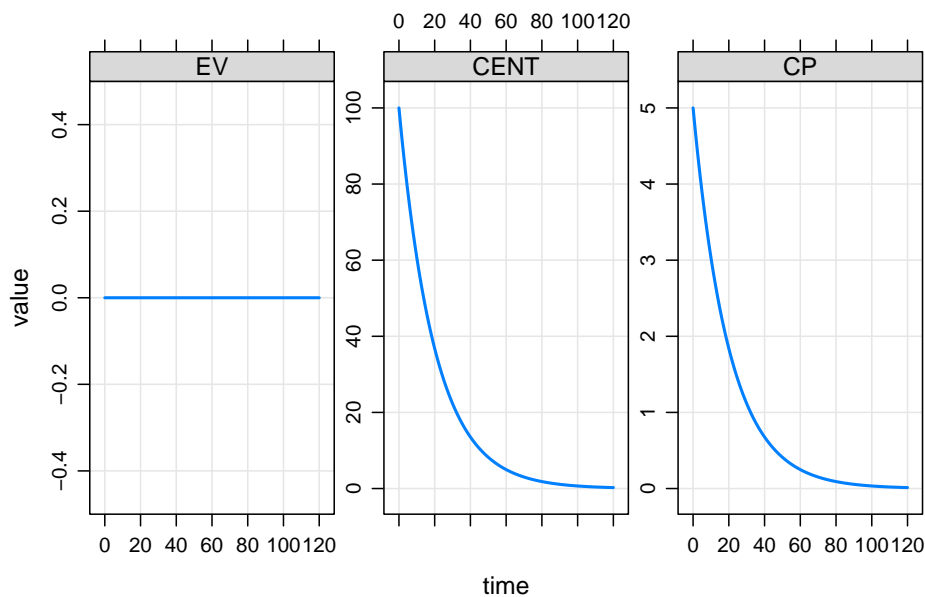
In this example, the `ss=1` flag tells mrgsolve to advance the system to steady state under a dosing regimen of 100 mg every 12 hours (and then give a total of 5 doses). When using the `ss=1` flag, the user is required to indicate the dosing interval (here every 12 hours) and additional doses are optional. Similar behavior can be achieved for intermittent infusions by setting the infusion rate.

8.2.2 Continuous infusion

A continuous infusion can be dosed to steady state by including the `ss=1` flag, a value for rate (any positive rate or -1 if the rate is being modeled), and setting the dose amount (`amt/AMT`) to zero:

```
infus <- ev(amt = 0, rate = 5, ss = 1, cmt = "CENT")

mrgsim(mod, infus, recsort = 3) %>% plot()
```



Because CL is equal to 1 in this model, we see that the continuous (never-ending) infusion was started at steady state with a value of 5.

8.3 Advance to SS

It's important to recognize that SS is related to the PK dosing system; it is finding the state of the system after an infinite number of doses have been administered under a certain regimen. And this is essentially how mrgsolve goes about finding steady state: when the `ss=1` flag is encountered, mrgsolve starts repeatedly administering doses and advancing the system to the next dose according to the inter-dose interval (ii). Once mrgsolve determines that the amounts in the system at any dose are the same as they were at the preceding dose, mrgsolve declares that SS has been achieved.

8.4 Control advance to SS

8.4.1 Tolerances for SS

mrgsolve uses a local error estimate to determine the degree to which concentrations are changing or not changing between doses on the way to SS. This is determined by a relative tolerance parameter (`ss_rtol`) and an absolute tolerance parameter (`ss_atol`). As of mrgsolve version 0.10.3, these tolerances are distinct from the tolerances used for solving the differential equations (`rtol` and `atol`, respectively). Note that when advancing to SS in an ODE model, `ss_rtol` (the relative tolerance for determining SS) must be larger (less precise) than `rtol` (the relative tolerance

used by the ODE solver). Once the difference between two trough concentrations is less than $A_{trough} * ss_rtol + ss_atol$, then the system is said to be at steady state. By default, this calculation is done for every single compartment in the model and all compartments have to meet this criteria before the system is said to be at steady state. So, increasing ss_rtol (say from $1e-8$ to $1e-3$) will also allow us to call it “good” with respect to steady state sooner.

Both tolerances for steady state are stored in the model object and can be set with the update method. For example,

```
mod <- house()
mod <- update(mod, ss_rtol = 1e-5, ss_atol = 1e-8)
```

8.4.2 Max dose number

It was noted above that `mrsgsolve` advances the system to steady state with a brute force approach: doses are repeatedly administered at a regular interval (for intermittent SS) until pre-dose concentrations are the same dose to dose. `mrsgsolve` sets an upper limit (equal to 500) to the number of doses that will be administered before giving up on trying to find steady state. Once this maximum number of doses is exceeded, `mrsgsolve` will issue a warning that steady state was not achieved and continue on with the problem. For example:

```
dose <- ev(amt = 100, ii = 12, ss = 1, VC = 800)
out <- mrgsim(house(), dose)
```

```
. Warning in (function (x, data, idata = no_idata_set(), carry_out = carry.out, : [stea
.   ss_n: 500, ss_rtol: 1e-08, ss_atol: 1e-08
```

Here, `mrsgsolve` administered 500 doses and the pre-dose concentrations were still not similar enough to declare the system to be at steady state.

The maximum dose number can be set with the `ss_n` argument to `mrgsim` (or one of the variants; see `?do_mrgsim` help topic). This number can be increased to prevent the warning:

```
out <- mrgsim(house(), dose, ss_n = 1000)
```

Alternatively, the `ss_fixed` argument to `mrgsim` (see `?do_mrgsim`) can be set to `TRUE` to silence the warning. In this case, **up to** `ss_n` doses will be administered and if SS is not achieved with that many doses, the problem will continue with no warning.

8.4.3 Include / exclude compartments for SS

Sometimes it might be sufficient to only consider one compartment when determining SS (e.g. the central compartment in a PK model). Other times, it might

be helpful to exclude a compartment when determining SS (e.g. a depot dosing compartment when concentrations can get very small toward the end of the dosing interval).

mrgsolve allows the user to identify compartments to include or exclude in determining SS. This is done through the `ss_cmt` option in `$SET`. To only consider the CENT compartment, write the following in the model file:

```
[ set ] ss_cmt = "CENT"
```

This says to **only** look at the CENT compartment when determining SS.

Alternatively, you can exclude certain compartments like this:

```
[ set ] ss_cmt = "-GUT,DEPOT"
```

This says to ignore the GUT and DEPOT compartments when determining SS.

As another example, you might want to exclude an accumulator compartment when calculating SS

```
[ set ] ss_cmt = "-AUC"
```

```
[ ode ]
dxdt_CENT = -kel * CENT;

dxdt_AUC = CENT/VC;
```

This is just a partial model snippet, but it shows how you might exclude the AUC compartment when determining SS.

8.4.4 SS_ADVANCE flag

mrgsolve also provides an `SS_ADVANCE` indicator that is passed into `$ODE` and evaluates to `true` when the system is being advanced to steady state. So a better way to exclude the accumulator compartment from being considered for SS calculation would be this:

```
[ ode ]

dxdt_AUC = CENT/VC;

if(SS_ADVANCE) dxdt_AUC = 0;
```

This code prevents the AUC compartment from changing during the advance to SS and the dose to dose difference in AUC will always be zero, effectively excluding this compartment from factoring into the SS determination. This should be the preferred approach to dealing with an AUC compartment.

Chapter 9

Plugins

9.1 autodec

Available as of mrgsolve version 1.0.0.

When this plugin is invoked, mrgsolve will search your model code for assignments and automatically declare them as double precision numbers. The following blocks are searched

- \$PREAMBLE
- \$MAIN (or \$PK)
- \$ODE (or \$DES)
- \$TABLE (or \$ERROR)
- \$PRED

For example, the following code requires that CL gets assigned a type

```
$PARAM WT = 70, TVCL = 1.2

$PK
double CL = TVCL * pow(WT/70, 0.75);
```

This is the default mrgsolve behavior and has been since the beginning.

The autodec plugin lets you write the following

```
$PLUGIN autodec

$PARAM WT = 70, TVCL = 1.2

$PK
CL = TVCL * pow(WT/70, 0.75);
```

mrgsolve will find `CL = . . .` and understand that this is a user initiated variable and will declare it as `double` for you. Don't worry about `WT = 70` in `$PARAM`; mrgsolve should already know about that won't try to declare it.

When you are using the `autodec` plugin, you can still declare variables as `double` or `int` or `bool`. mrgsolve already finds those variables and will understand to leave those declarations alone. Note that it may still very convenient to declare using the `capture` type those variables that you want captured into the output

```
$PLUGIN autodec

$ERROR
capture Y = IPRED * exp(EPS(1));
```

The `capture` typedef makes `Y` a `double`; we didn't need to declare it with `autodec` in play, but decided to declare with `capture` so that it is copied into the simulated output.

The `autodec` plugin is intended for more straightforward models where most / all variables are real valued. Because mrgsolve can handle any valid C++ code in these blocks, there is a possibility that the code could get much more complicated, including custom classes and methods. In this case, we recommend to bypass this feature and take control of declaring variables as you would in the default mode.

In case mrgsolve does try to declare (as `double`) a variable that shouldn't be handled that way, you can note this name in an environment variable inside your model called `MRGSOLVE_AUTODEC_SKIP`

```
$ENV MRGSOLVE_AUTODEC_SKIP = c("my_variable_1")
```

This can be a vector of variable names to NOT declare when `autodec` is invoked.

9.2 nm-vars

Available as of mrgsolve version 1.0.0.

The `nm-vars` plugin provides a more NONMEM-like set of macros to use when coding your compartmental model. Only a small subset of the NONMEM model syntax is replicated here.

F, R, D, ALAG

- To set bioavailability for the `n`th compartment, use `Fn`
- To set the infusion rate for the `n`th compartment, use `Rn`
- To set the infusion duration for the `n`th compartment, use `Dn`
- To set the lag time for the `n`th compartment, use `ALAGn`

For example


```
$CMT GUT CENT GUT2

$PK
F1 = 0.87;    // equivalent to F_GUT = 0.87;
R2 = 2.25;    // equivalent to R_CENT = 2.25;
ALAG3 = 0.25; // equivalent to ALAG_GUT2 = 0.25;
```

A, A_0, DADT

- To refer to the amount in the nth compartment, use A(n)
- To refer to the initial amount in the nth compartment, use A_0(n)
- To refer to the differential equation for the nth compartment, use DADT(n)

For example

```
$CMT CMT1 CMT2

$PK
A_0(2) = 50;

$DES
DADT(1) = -KA * A(1);
DADT(2) = KA * A(1) - KE * A(2);
```

Other syntax

- Using THETA(n) in model code will resolve to THETA_n; this feature is always available, even when nm-vars hasn't been invoked; we mention it here since it is a fundamental piece of the NONMEM syntax that mrgsolve has internalized
- Use T in \$DES to refer to the current time in the odesolver rather than SOLVERTIME

Reserved words with nm-vars is invoked

There are some additional reserved words when the nm-vars plugin is invoked

- A
- A_0
- DADT
- T

It is an error to use one of these symbols as the name of a parameter or compartment or to try to declare them as variables.

mrgsolve syntax that is still required

There are a lot of differences remaining between mrgsolve and NONMEM syntax. We mention a few here to make the point

- mrgsolve continues to require pow(base, exponent) rather than base**exponent

- mrgsolve continues to use `exp()`, `log()` and `sqrt()`, rather than `EXP()`, `LOG()`, and `SQRT()`
- mrgsolve continues to require a semi-colon at the end of each statement (this is a C++ requirement)
- mrgsolve continues to require that user-defined variables are declared with a type, except when the autodec plugin (Section 9.1) is invoked

An example

There is an example of this syntax (along with autodec features) in the internal model library

```
mod <- modlib("nm-like")
see(mod)
```

```
.
. Model file:  nm-like.cpp
. $PROB Model written with some nonmem-like syntax features
.
. $PLUGIN nm-vars autodec
.
. $PARAM
. THETA1 = 1, THETA2 = 21, THETA3 = 1.3, WT = 70, F1I = 0.5, D2I = 2
. KIN = 100, KOUT = 0.1, IC50 = 10, IMAX = 0.9
.
. $CMT @number 3
.
. $PK
. CL = THETA(1) * pow(WT/70, 0.75);
. V  = THETA(2);
. KA = THETA(3);
.
. F1 = F1I;
. D2 = D2I;
. A_0(3) = KIN / KOUT;
.
. $DES
. CP = A(2)/V;
. INH = IMAX*CP/(IC50 + CP);
.
. DADT(1) = -KA*A(1);
. DADT(2) =  KA*A(1) - (CL/V)*A(2);
. DADT(3) =  KIN * (1-INH) - KOUT * A(3);
.
. $ERROR
. CP = A(2)/V;
```

9.3 tad

Purpose Advanced calculation time after dose within your model. We call this “advanced” because it lets you track doses in multiple compartments. See the note below about a simpler way to calculate time after dose that should work fine if doses are only in a single compartment. This functionality is provided by mrgsolve.

Usage

First, tell mrgsolve that you want to use the tad plugin

```
$PLUGIN tad
```

The create tadose objects, one for each compartment where you want to track time after dose. One approach is to do this in [global]

```
[plugin] tad

[ global ]
mrg::tadose tad_cmt_1(1);
mrg::tadose tad_cmt_2(2);
```

Notice that we pass the compartment number that we want to track in each case and also that we refer to the `mrg::` namespace for the `tadose` class.

The `tadose` objects contain the following (public) members

- `cmt` the compartment to track
- `told` the time of last dose; defaults to `-1e9`
- `had_dose` indicates if a dose has already been given for the current individual
- `tad(self)` the function to call to calculate time after dose
 - the `self` object (Section 2.3.12) must be passed as the only argument
 - when the member function is called prior to the first administered dose, a value of `-1.0` is returned
- `reset()` resets the state of the object; be sure to reset prior to simulating a new individual

As an example, you can call the `reset()` method on one of the `tadose` objects

```
tad_cmt_1.reset();
```

You can find the source code for this object [here](#).

A working example model that tracks doses in compartments 1 and 2 is provided [here](#)

```
[plugin] tad

[ global ]
mrg::tadose tad_cmt_1(1);
mrg::tadose tad_cmt_2(2);
```

```
[ pkmodel ] cmt = "GUT,CENT", depot = TRUE

[ param ] CL = 1, V = 20, KA = 1

[ main ]
capture tad1 = tad_cmt_1.tad(self);
capture tad2 = tad_cmt_2.tad(self);
```

Static approach

Another approach would be to make these static in [main] but this approach would only work if you only use these in [main]; the [global] approach is preferable since then you can access the object in any block (function).

9.3.1 Note

Note there is a simpler way to calculate time after dose when only dosing into a single compartment

```
[ main ]
double tad = self.tad();
```

The `self` object (Section 2.3.20) contains a `tad()` member which will track time after dose. Note that this needs to be called every record.

9.4 CXX11

Purpose

Compile your model file with C++11 standard.

Usage

```
$PLUGIN CXX11
```

9.5 Rcpp

Purpose

Link to Rcpp headers into your model.

Usage

```
$PLUGIN Rcpp
```

Note that once your model is linked to Rcpp, you can start using that functionality immediately (without including `Rcpp.h`).

A very useful feature provided by Rcpp is that it exposes all of the `dpqr` functions that you normally use in R (e.g. `rnorm()` or `runif()`). So, if you want to simulate a number from Uniform (0,1) you can write

```
$PLUGIN Rcpp

$TABLE
double uni = R::runif(0,1);
```

Note that the arguments are the same as the R version (`?runif`) **except** there is no `n` argument; you always only get one draw.

Information about Rcpp can be found here: <https://github.com/RcppCore/Rcpp>

9.6 mrgx

Compile in extra C++ / Rcpp functions that can be helpful to you for more advanced model coding. The `mrgx` plugin is dependent on the Rcpp plugin.

The functions provided by `mrgx` are in a namespace of the same name, so to invoke these functions, you always prepend `mrgx::`.

9.6.1 Get the model environment

Note that your model object (`mod`) contains an R environment. For example

```
mrgsolve::house()@envir

. <environment: 0x7feb3deec228>
```

The objects in this environment are created by a block called `$ENV` in your model code (see Section 2.2.26);

To access this environment in your model, call

```
Rcpp::Environment env = mrgx::get_envir(self);
```

9.7 Extract an object from the model environment

When you have an object created in `$ENV`

```
[ env ]
rand <- rnorm(100)
```

You can extract this object with

```
[ preamble ]
Rcpp::NumericVector draw = mrgx::get("rand", self);
```

9.8 RcppArmadillo

Purpose

Link to RcppArmadillo headers into your model.

Usage

```
$PLUGIN RcppArmadillo
```

Information about `armadillo` can be found here: <http://arma.sourceforge.net/>
Information about RcppArmadillo can be found here: <https://github.com/RcppCore/RcppArmadillo>

9.9 BH

Purpose

Link to boost headers into your model.

Usage

```
$PLUGIN BH
```

Note that once your model is linked to BH (boost), you will be able to include the boost header file that you need. You have to include the header file that contains the boost function you want to use.

Information about boost can be found here: <https://boost.org>. Information about BH can be found here: <https://github.com/eddelbuettel/bh>

Chapter 10

Modeled events

Modeled events are interventions that you can introduce into your simulation from within your model. These aren't any different in substance to the dosing records (EVID=1) or other intervention type records (EVID=2) that you might include in your input data set when you know what they are before you run the simulation. Modeled events do the same thing (stop the simulation and execute some event at some time) but you don't need to know about them prior to running the simulation. These are similar to the MTIME functionality that you get in NONMEM but they have a very different syntax and there is more functionality provided.

Note that there is no way to get additional records in your simulated output. Regardless of the approach or level of complexity, you will not see modeled events in your simulated output. These are always executed under the hood and the number of rows in the simulated output and their times will be the same regardless of what modeled events you set up as discussed here.

10.1 Simple MTIME

Use this when you just want to introduce a non-dose discontinuity in your simulation at a specific time. For example, you want a parameter to change value at a specific time and you don't know about the values or times prior to simulating.

To schedule a discontinuity, call the `mtime()` member (Section [@ref\(self.time\)](#)) of the `self` object (Section 2.3.12). This is typically done in the `$MAIN` block.

```
[ main ]
double mt = self.mtime(14.12);

if(TIME >= mt) {
    // do something
}
```

Here, we have told `mrgsolve` to stop at 14.12 hours so we can do something. Notice that `self.mtime()` returns the value of the modeled even time so you can check it later.

We can also schedule an event to happen some amount of time in the future

```
[ main ]
if(NEWIND <= 1) {
  double mt = 1e9;
}

if(EVID==1) {
  mt = self.mtime(TIME + 8.2);
}

if(TIME >= mt) {
  // do something
}
```

10.2 MTIME with specific EVID

You can call `self.mevent()` and pass both time and evid and then check for when that EVID comes around again. For example

```
self.mevent(TIME + 8.2, 33);

if(EVID==33) {
  // do something
}
```

This is similar in functionality to `self.mevent()`.

10.3 Modeled doses

The previous examples showed you how to get the simulation to stop so you can do something in `$MAIN`. In this section, we show you how to schedule doses in a similar way. This will take some extra coding and will also serve to uncover how `self.mtime()` and `self.mevent()` work.

You can set up the following code in either `$MAIN` or `$TABLE`.

Create an evdata object

Once you know when you want the dose, create an `evdata` object.

```
mrg::evdata ev(14.2, 1);
```


This will create (construct) an object called `ev` with class `evdata`. The constructor takes two arguments:

1. the TIME the event should happen
2. the EVID for the event

This is the only available constructor for `evdata` objects. You can browse the source code for the `evdata` object [here](#).

Modify the `evdata` object Once the object is created, you can modify the following public members

- `time`: the event time (double)
- `evid`: the event ID (int)
- `amt`: the dose amount (double)
- `cmt`: the compartment number (int)
- `rate`: the rate to infuse `amt` (double)
- `now`: should the dose be given immediately? (bool)

If you are using this (lower-level) interface, chances are you will want to set at least `amt` and `cmt`. As an example, we will dose 100 mg into compartment 2 immediately (now)

```
ev.amt = 100;  
ev.cmt = 2;  
ev.now = true;
```

The other members are set in a similar way.

Push the `evdata` object into the `self` object

After the object has been created and modified, you have to attach this object to the `self` object in order to make it available to `mrqsolve`. Do this by calling `push_back()` on `self.mevector`

```
self.mevector.push_back(ev);
```

Again, this sequence should get called in either `$MAIN` or `$TABLE`. When that code block finishes running (for the current record), `mrqsolve` will find the event record and add that event to the simulation sequence.

Chapter 11

Topics

11.1 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)
```

11.2 Set initial conditions

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

11.2.1 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

11.2.2 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

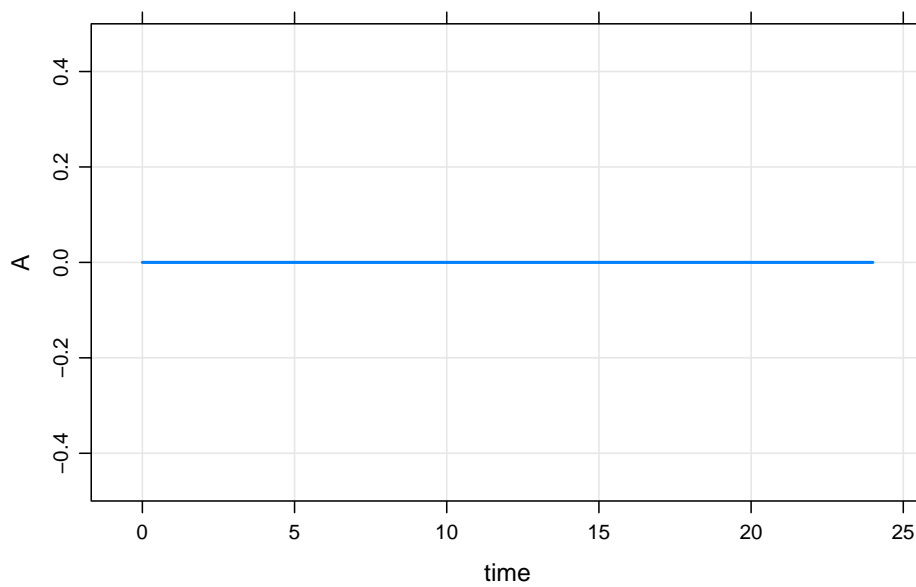
```
init(mod)
```

```
.
. 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
```

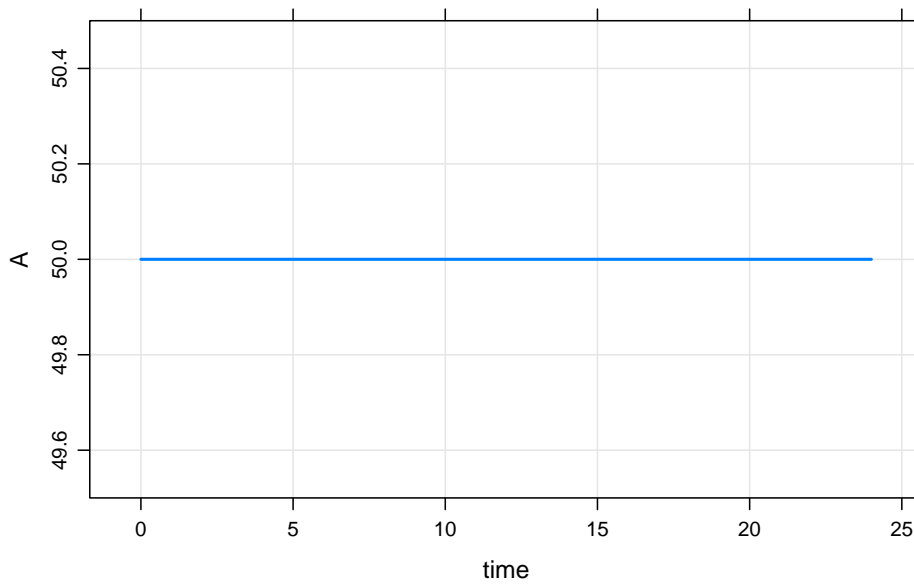


Next, we update the base initial condition for A to 50

Note:

- The code in \$MAIN still doesn't get run because IFLAG is 0

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

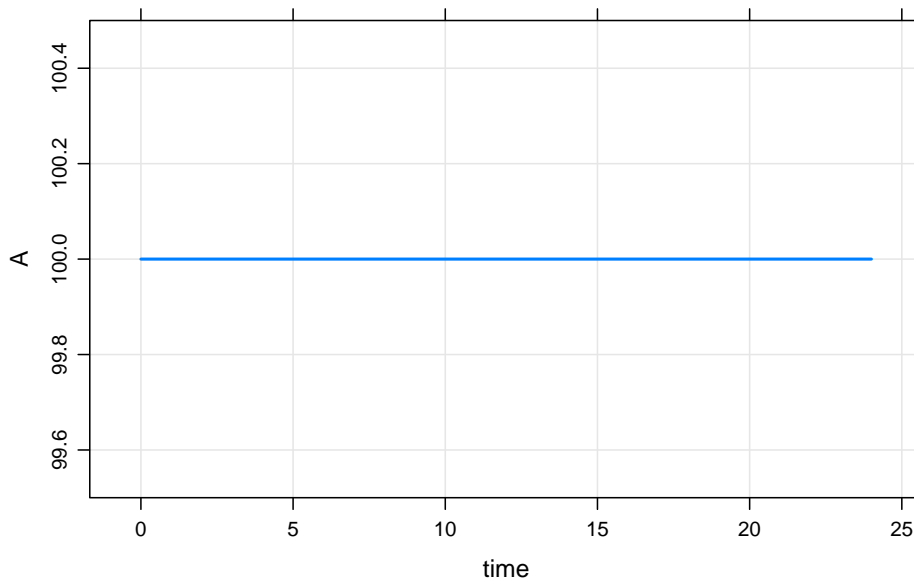


Now, turn on IFLAG

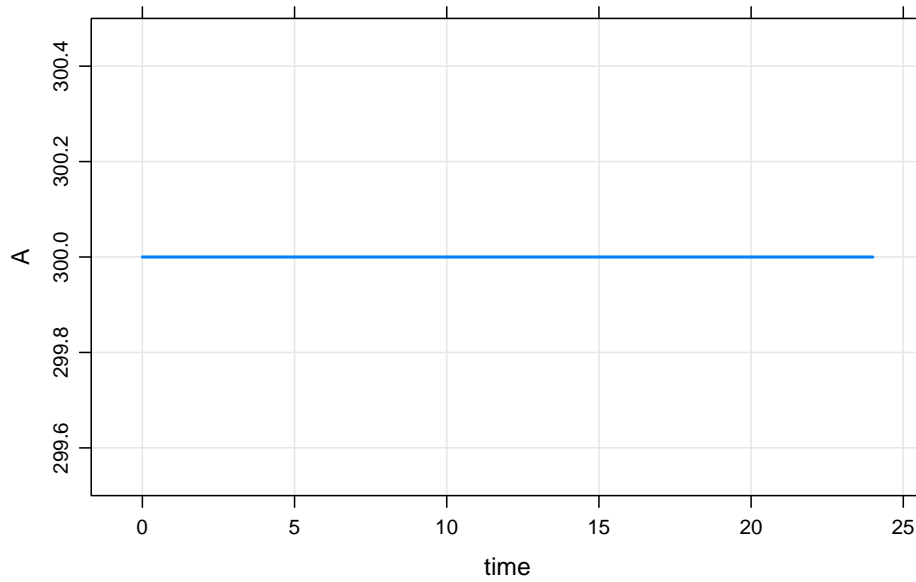
Note:

- 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
```



11.2.3 Example PK/PD model with initial condition

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

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

$CMT RESP

$MAIN
RESP_0 = KIN/KOUT;

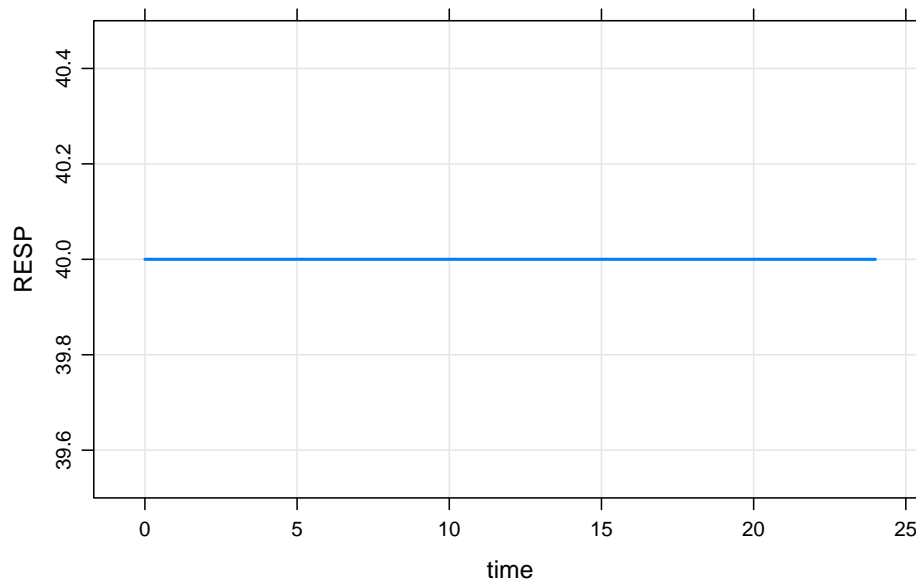
$ODE

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

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

The initial condition is set to 40 per the values of KIN and KOUT

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

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

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

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

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

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

```
init(mod)
```

```
.
```

```
. Model initial conditions (N=1):
. name      value . name      value
. RESP (1)   0    | . ...     .
mod %>% param(KIN=100) %>% init
```

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

11.2.5 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.

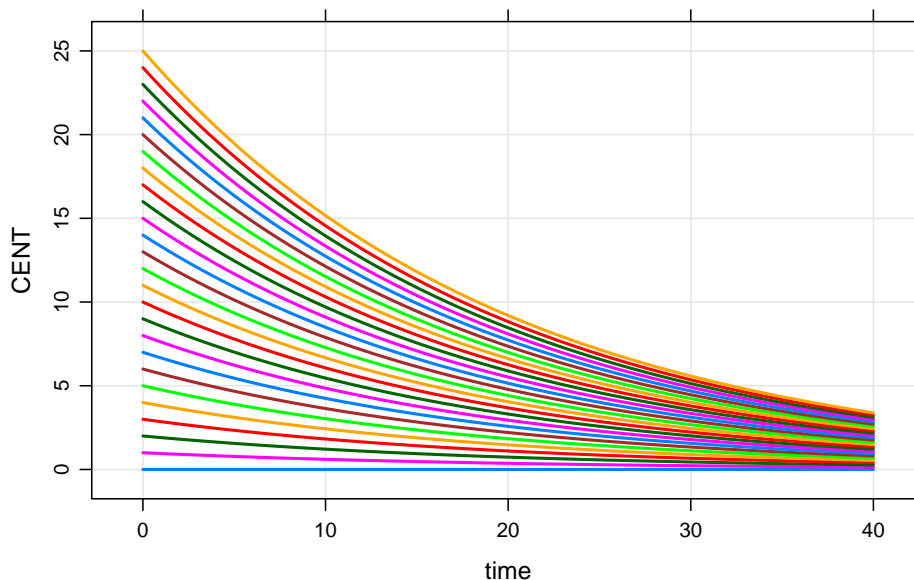
```
idata <- expand.idata(CENT_0 = seq(0,25,1))
```

```
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~.)
```



11.3 Updating parameters

The parameter list was introduced in section 1.1 and the `$PARAM` code block was shown in 2.2.4. Once a model is compiled, the names and number of parameters in a model is fixed. However, the values of parameters can be changed: parameters may be updated either by the user (in R) or by `mrgsolve` (in the C++ simulation engine, as the simulation proceeds).

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

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

11.3.1 Parameter update hierarchy

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

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

These sources for new parameter values are discussed below. We note here that the sources listed above are listed in the order of the parameter update *hierarchy*. So,

the base parameter list provides the value by default. A parameter value coming from an `idata_set` will override the value in the base list. And a parameter value coming from a `data_set` will override the value coming from the base list or an `idata_set` (in case a parameter is listed in both the `idata_set` and the `data_set`). In other words, the hierarchy is:

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

The parameter update hierarchy is discussed in the following sections.

Base parameter set

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

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

```
param(mod)
```

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

The base parameter set is the default

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

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

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

```
mod <- param(mod, 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 11.3.2 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 F00
. 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" "F00"
names(param(mod))

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

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

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

```
out
```

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

Parameters updated from data_set

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

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

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

```
out
```

```
. Model:  tmp
. Dim:    6 x 7
. Time:   0 to 2
. ID:     3
.      ID time KYLE CL VC  KA KM
. 1:    1    0    0  1 30 1.7 10
. 2:    1    2    0  1 30 1.7 10
. 3:    2    0    0  2 30 1.7 10
. 4:    2    2    0  2 30 1.7 10
. 5:    3    0    0  3 30 1.7 10
. 6:    3    2    0  3 30 1.7 10
```

This is how we do time-varying parameters:

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

. Warning: `data_frame()` was deprecated in tibble 1.1.0.
 . Please use `tibble()` instead.
 . This warning is displayed once every 8 hours.
 . Call `lifecycle::last_lifecycle_warnings()` to see where this warning was generated.

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

The first data record happens at time==24

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

```
. Model: tmp
. Dim: 3 x 7
. Time: 0 to 24
. ID: 1
.      ID time KYLE CL VC KA KM
. 1: 1 0 0 5 32 1.7 10
```

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

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

But by default, `mrksolve` 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) %>%
  mrksim(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 5 32 1.7 10
. 2: 1 2 0 5 32 1.7 10
. 3: 1 24 100 5 32 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) %>%
  mrksim(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.

11.3.2 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

11.4 Time grid objects

Simulation times in `mrgsolve`

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

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

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

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

`tgrid` objects

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

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

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

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

```
day1 <- c(peak1, sparse1)
```

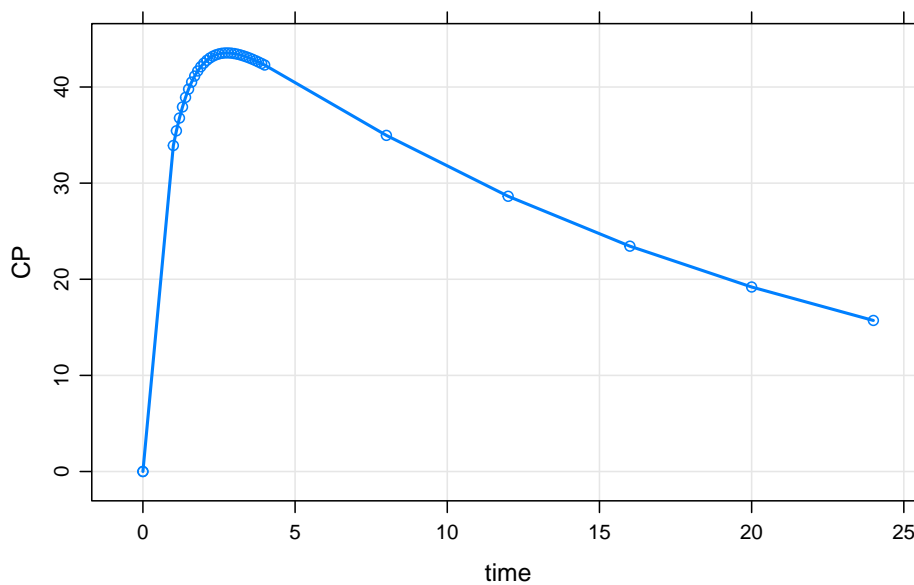
Check this by calling `stime`

```
stime(day1)
```

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

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

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

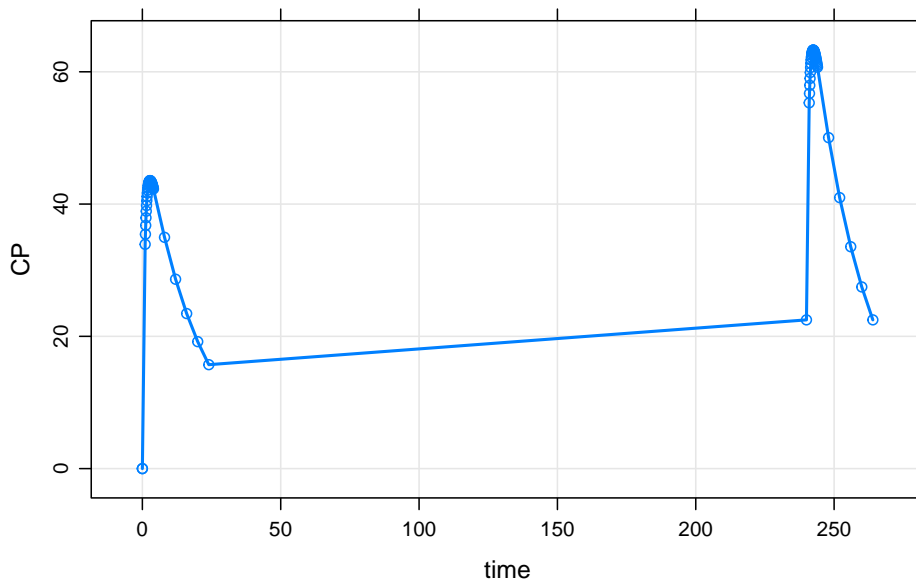


Now, look at both day 1 and day 10:

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

```
des <- c(day1, day1+10*24)

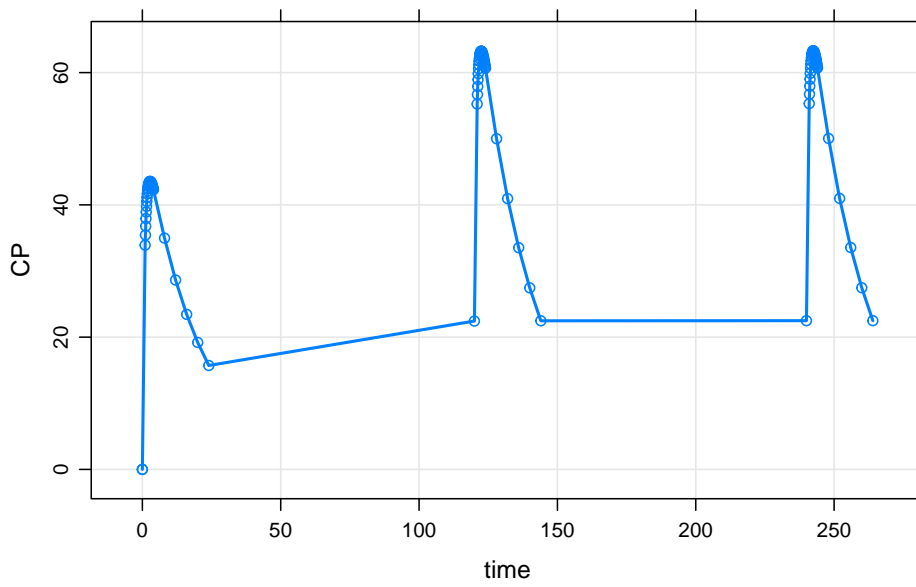
mod %>%
  mrgsim(tgrid=des) %>%
  plot(type='b')
```



Pick up day 5 as well

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

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



11.5 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(df, 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
```

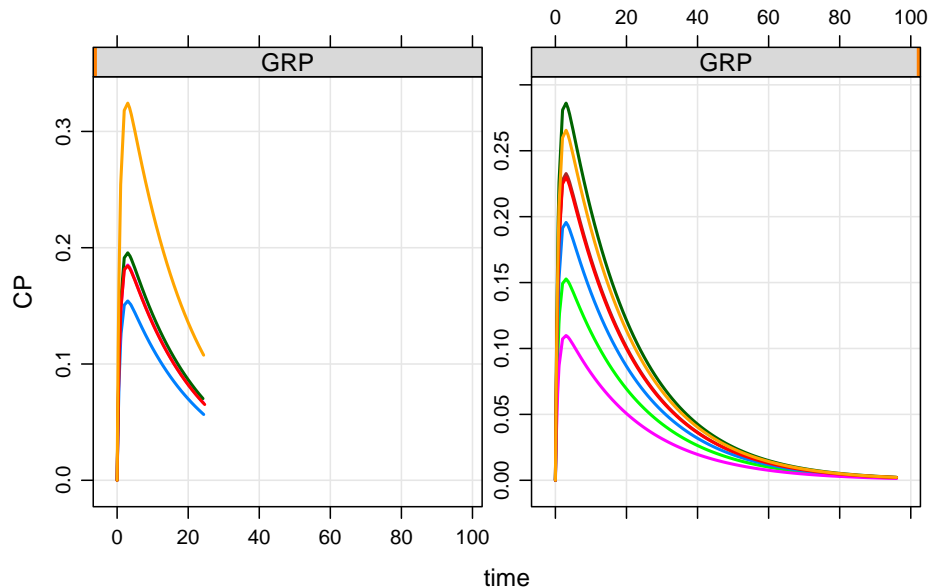
Now, we have two groups in GRP in `idata_set` and we have two `tgrid` objects.

- 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)
```



11.6 Some helpful C++

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

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

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

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

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

11.6.1 Semi-colons

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

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

or

```
[ ODE ]  
  
dxdt_DEPOT = -KA * DEPOT;
```

11.6.2 if-else

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

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

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

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

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

11.6.3 Functions

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

```
# base^exponent  
double d = pow(base,exponent);  
  
double e = exp(3);  
  
# absolute value  
double f = fabs(-4);  
  
double g = sqrt(5);  
  
double h = log(6);
```



```
double i = log10(7);

double j = floor(4.2);

double k = ceil(4.2);

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

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

11.6.4 Integer division

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

```
3/4
```

```
. [1] 0.75
```

But in C++ it evaluates to 0:

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

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

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

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

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

```
[ PARAM ] a = 3

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

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

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

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

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

here.

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

```
library(mrgsolve)

code <- '
[ param ] a = 3

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

mrgsim(mod)
```

```
. Model:  foo
. Dim:    25 x 5
. Time:   0 to 24
. ID:     1
.      ID time x    y    z
. 1:    1    0 0 0.75 0.75
. 2:    1    1 0 0.75 0.75
. 3:    1    2 0 0.75 0.75
. 4:    1    3 0 0.75 0.75
. 5:    1    4 0 0.75 0.75
. 6:    1    5 0 0.75 0.75
. 7:    1    6 0 0.75 0.75
. 8:    1    7 0 0.75 0.75
```

11.6.5 Pre-processor directives

Pre-processor directives are global substitutions that are made in your model code at the time the model is compiled. For example

```
$GLOBAL

#define CP (CENT/VC)
```

When you write this into your model, the pre-processor will find every instance of CP and **replace** it with (CENT/VC). This substitution happens right as the model is compiled; you won't see this substitution happen anywhere, but think of it as literal replacement of CP with (CENT/VC).

Note:

- Put all pre-processor directives in \$GLOBAL.
- It is usually a good idea to enclose the substituted coded in parentheses; this ensures that, for example, CENT/VC is evaluated as is, regardless of the surrounding code where it is evaluated.
- Under the hood, mrgsolve uses lots of pre-processor directives to define parameter names, compartment names and other variables; you will see a compiler error if you try to re-define an existing pre-processor directive. If so, just choose another name for your directive.

11.7 Resimulate ETA and EPS

Call `simeps(n)` to resimulate ETA

- No \$PLUGIN is required
- `simeta(n)` takes a single argument (n), the ETA number to resimulate

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(1);
  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.	:-0.15238	Min.	:60.11
. 1st Qu.:	25.75	1st Qu.:	0	1st Qu.:	-0.09696	1st Qu.:	63.53
. Median :	50.50	Median :	0	Median :	-0.02681	Median :	68.15
. Mean :	50.50	Mean :	0	Mean :	-0.02220	Mean :	68.73
. 3rd Qu.:	75.25	3rd Qu.:	0	3rd Qu.:	0.05875	3rd Qu.:	74.24
. Max.	:100.00	Max.	:0	Max.	: 0.13253	Max.	:79.92

Call `simeps(n)` to resimulate EPS

- No `$PLUGIN` is required
- `simeps()` takes a single argument (`n`), the EPS number to resimulate

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

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

$CMT CENT

$SIGMA 50

$PKMODEL ncmt=1

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

int i = 0;

while(CP < 0 && i < 100) {
  simeps(1);
  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. : 0.044
. 1st Qu.:	1	1st Qu.:11.25	1st Qu.: 15.93	1st Qu.: 3.060
. Median :	1	Median :23.50	Median : 29.38	Median : 6.148
. Mean :	1	Mean :23.52	Mean : 37.47	Mean : 6.729

```
. 3rd Qu.:1    3rd Qu.:35.75    3rd Qu.: 54.21    3rd Qu.: 9.338
. Max.    :1    Max.    :48.00    Max.    :100.00    Max.    :17.488
```

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.

11.8 Time varying covariates

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

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

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

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

There is additional information about the sequence of events that takes place during system advance in section 7.

Chapter 12

Questions and Answers

I'm using this chapter as a place to provide miscellaneous information that might not have an obvious place to live. I'd call this a FAQ, but not all of the questions are asked frequently or at all.

12.1 Can I interrupt a simulation?

Starting with `mrgsolve` version 0.11.1, you can interrupt a long simulation by pressing `Control-C` or `Esc`, the standard way to pass an interrupt signal through R. `mrgsolve` will stop every so often to look for the interrupt signal.

You can control the frequency with which `mrgsolve` looks for the interrupt signal through an argument to `mrgsim` (default: 256 simulation records). Increase to check less frequently, increase to check more frequently (this might be needed for a model where a large amount of work is required to advance one step) or set to negative number to never check.

12.2 Can I pass compiler flags to my model?

Compiler flags can be passed to your model by setting `PKG_CXXFLAGS` in `$ENV`. For example

```
$ENV  
PKG_CXXFLAGS = "-std=c++11"
```

will compile your model according to C++11 standard (but note that there is a special plugin that will do this automatically for you; see Section 9.4).

12.3 Can I compile my model with C++11?

Yes, you can do this by invoking the CXX11 plugin (Section 9.4).

12.4 How can I calculate time after dose?

There are three approaches

tad argument to mrgsim()

To get time after dose into your output you can call

```
mrgsim(mod, tad = TRUE)
```

and the output will have a tad column. Note this does not let you interact with the tad value inside your model.

Simple calculation in the model

Most applications will call `self.tad()` (Section @ref(self.tad)). For example

```
[ main ]  
double tad = self.tad();
```

More complicated calculation in the model

You can get more control and track tad in a specific compartment by using the tad plugin. See Section 9.3 for details.

12.5 My model failed to compile; what now?

The model can fail to compile for a variety of reasons, including an error in the C++ code or inability of R to find the compiler and other pieces of the tool chain.

If your model is not compiling, try the `recover` argument to `mread()` (or `mcode()`)

```
mod <- mread(..., recover = TRUE)
```

You will see a warning on the console and `mread()` will return a list of build information. You can look into that information or share it in the mrgsolve issue tracker on GitHub.

If your model has C++ syntax problems, the errors should be printed on the console. If you possibly have problems with the compiler or the rest of the toolchain, take a look at the `pkgbuild` package, which provides some helpful tools, especially if you are working on a Windows platform

```
pkgbuild::check_build_tools()  
pkgbuild::has_build_tools()  
pkgbuild::has_rtools()
```


12.6 Can I run mrgsolve on a network drive?

No; do not run mrgsolve on a network drive. Your R installation, mrgsolve installation, and R working directory should be on a local hard disk.

12.7 Can I run mrgsolve on a cloud-synced folder?

No; do not run mrgsolve in a synced folder for cloud services like OneDrive, GoogleDrive, DropBox etc. Your R installation, mrgsolve installation, and R working directory should be on a local hard disk.

12.8 Can I run mrgsolve in a path that includes spaces?

No; do not run mrgsolve in a path that includes spaces. Your R installation, mrgsolve installation, and R working directory should all be in locations whose paths do not include spaces.

Chapter 13

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>