RxODE user manual

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Chapter 1

Introduction

Welcome to the RxODE user guide; **RxODE** is an R package for solving and simulating from ode-based models. These models are convert the RxODE mini-language to C and create a compiled dll for fast solving. ODE solving using RxODE has a few key parts:

- `RxODE()` which creates the C code for fast ODE solving based on a simple syntax (Chapter **??**) related to Leibnitz notation.
- The event data, which can be:
  - a `NONMEM` or `deSolve` compatible data frame (Chapter **??**), or
  - created with `et()` or `EventTable()` for easy simulation of events(Chapter **??**)
  - The data frame can be augmented by adding time varying or adding individual covariates (`iCov=` as needed)
- `rxSolve()` which solves the system of equations using initial conditions and parameters to make predictions
  - With multiple subject data, this may be parallelized.
  - With single subject the output data frame is adaptive
  - Covariances and other metrics of uncertanty can be used to simulate while solving.

While this is the user guide, there are other places that you can visit for help:

This book was assembled on Fri Dec 11 15:14:00 2020 with RxODE version 1.0.0.0 automatically by github actions.

Chapter 2

Related R packages

2.1 ODE solving

This is a brief comparison of pharmacometric ODE solving R packages to `RxODE`.

There are several R packages for differential equations. The most popular is deSolve.

However for pharmacometrics-specific ODE solving, there are only 2 packages other than RxODE released on CRAN. Each uses compiled code to have faster ODE solving.

- mrgsolve, which uses C++ lsoda solver to solve ODE systems. The user is required to write hybrid R/C++ code to create a mrgsolve model which is translated to C++ for solving.

  In contrast, `RxODE` has a R-like mini-language that is parsed into C code that solves the ODE system.

  Unlike `RxODE`, `mrgsolve` does not currently support symbolic manipulation of ODE systems, like automatic Jacobian calculation or forward sensitivity calculation (`RxODE` currently supports this and this is the basis of nlmixr's FOCEi algorithm)

- dMod, which uses a unique syntax to create "reactions". These reactions create the underlying ODEs and then created c code for a compiled deSolve model.

  In contrast `RxODE` defines ODE systems at a lower level. `RxODE`'s parsing of the mini-language comes from C, whereas `dMod`'s parsing comes from R.

  Like `RxODE`, `dMod` supports symbolic manipulation of ODE systems and calculates forward sensitivities and adjoint sensitivities of systems.

Unlike `RxODE`, `dMod` is not thread-safe since `deSolve` is not yet thread-safe.

And there is one package that is not released on CRAN:

- PKPDsim which defines models in an R-like syntax and converts the system to compiled code.

  Like `mrgsolve`, `PKPDsim` does not currently support symbolic manipulation of ODE systems.

  `PKPDsim` is not thread-safe.

The open pharmacometrics open source community is fairly friendly, and the RxODE maintainers has had positive interactions with all of the ODE-solving pharmacometric projects listed.

2.2 PK Solved systems

RxODE supports 1-3 compartment models with gradients (using stan math's auto-differentiation). This currently uses the same equations as PKADVAN to allow time-varying covariates.

RxODE can mix ODEs and solved systems.

2.2.1 The following packages for solved PK systems are on CRAN

- mrgsolve currently has 1-2 compartment (poly-exponential models) models built-in. The solved systems and ODEs cannot currently be mixed.
- pmxTools currently have 1-3 compartment (super-positioning) models built-in. This is a R-only implementation.
- PKPDmodels has a one-compartment model with gradients.

2.2.2 Non-CRAN libraries:

- PKADVAN Provides 1-3 compartment models using non-superpositioning. This allows time-varying covariates.

Chapter 3

Installation

You can install the released version of RxODE from CRAN with:

```r
install.packages("RxODE")
```

To build models with RxODE, you need a working c compiler. To use parallel threaded solving in RxODE, this c compiler needs to support open-mp.

You can check to see if R has working c compiler you can check with:

```r
## install.packages("pkgbuild")
pkgbuild::has_build_tools(debug = TRUE)
```

If you do not have the toolchain, you can set it up as described by the platform information below:

3.0.1 Windows

In windows you may simply use installr to install rtools:

```r
install.packages("installr")
library(installr)
install.rtools()
```

Alternatively you can download and install rtools directly.

3.0.2 Mac OSX

To get the most speed you need OpenMP enabled and compile RxODE against that binary. Here is some discussion about this:

https://mac.r-project.org/openmp/

3.0.3 Linux

To install on linux make sure you install `gcc` (with openmp support) and `gfortran` using your distribution's package manager.

3.1 Development Version

Since the development version of RxODE uses StanHeaders, you will need to make sure your compiler is setup to support C++14, as described in the rstan setup page

Once the C++ toolchain is setup appropriately, you can install the development version from GitHub with:

```r
# install.packages("devtools")
devtools::install_github("nlmixrdevelopment/RxODE")
```

Chapter 4

Getting Started

The model equations can be specified through a text string, a model file or an R expression. Both differential and algebraic equations are permitted. Differential equations are specified by `d/dt(var_name) =`. Each equation can be separated by a semicolon.

To load `RxODE` package and compile the model:

```r
library(RxODE)
```

```
## RxODE 1.0.0.0 using 4 threads (see ?getRxThreads)
```

```r
library(units)
```

```
## udunits system database from /usr/share/xml/udunits
```

```r
mod1 <-RxODE({
    C2 = centr/V2;
    C3 = peri/V3;
    d/dt(depot) =-KA*depot;
    d/dt(centr) = KA*depot - CL*C2 - Q*C2 + Q*C3;
    d/dt(peri)  =                    Q*C2 - Q*C3;
    d/dt(eff)  = Kin - Kout*(1-C2/(EC50+C2))*eff;
})
```

```
## qs v0.23.4.
```

4.1 Specify ODE parameters and initial conditions

Model parameters can be defined as named vectors. Names of parameters in the vector must be a superset of parameters in the ODE model, and the order of parameters within the vector is not important.

```
theta <-
   c(KA=2.94E-01, CL=1.86E+01, V2=4.02E+01, # central
     Q=1.05E+01,  V3=2.97E+02,              # peripheral
     Kin=1, Kout=1, EC50=200)               # effects
```

Initial conditions (ICs) can be defined through a vector as well. If the elements are not specified, the initial condition for the compartment is assumed to be zero.

```
inits <- c(eff=1);
```

If you want to specify the initial conditions in the model you can add:

```
eff(0) = 1
```

4.2 Specify Dosing and sampling in RxODE

`RxODE` provides a simple and very flexible way to specify dosing and sampling through functions that generate an event table. First, an empty event table is generated through the "eventTable()" function:

```
ev <- eventTable(amount.units='mg', time.units='hours')
```

Next, use the `add.dosing()` and `add.sampling()` functions of the `EventTable` object to specify the dosing (amounts, frequency and/or times, etc.) and observation times at which to sample the state of the system. These functions can be called multiple times to specify more complex dosing or sampling regiments. Here, these functions are used to specify 10mg BID dosing for 5 days, followed by 20mg QD dosing for 5 days:

```
ev$add.dosing(dose=10000, nbr.doses=10, dosing.interval=12)
ev$add.dosing(dose=20000, nbr.doses=5, start.time=120, dosing.interval=24)
ev$add.sampling(0:240)
```

If you wish you can also do this with the `mattigr` pipe operator `%>%`

```
ev <- eventTable(amount.units="mg", time.units="hours") %>%
    add.dosing(dose=10000, nbr.doses=10, dosing.interval=12) %>%
    add.dosing(dose=20000, nbr.doses=5, start.time=120,dosing.interval=24) %>%
    add.sampling(0:240);
```

The functions `get.dosing()` and `get.sampling()` can be used to retrieve information from the event table.

```
head(ev$get.dosing())
```

```
##   id low time high       cmt   amt rate ii addl evid ss dur
## 1  1  NA    0   NA (default) 10000    0 12    9    1  0   0
## 2  1  NA  120   NA (default) 20000    0 24    4    1  0   0
```

```
head(ev$get.sampling())
```

```
##   id low time high   cmt amt rate ii addl evid ss dur
## 1  1  NA    0   NA (obs)  NA   NA NA   NA    0 NA  NA
## 2  1  NA    1   NA (obs)  NA   NA NA   NA    0 NA  NA
## 3  1  NA    2   NA (obs)  NA   NA NA   NA    0 NA  NA
## 4  1  NA    3   NA (obs)  NA   NA NA   NA    0 NA  NA
## 5  1  NA    4   NA (obs)  NA   NA NA   NA    0 NA  NA
## 6  1  NA    5   NA (obs)  NA   NA NA   NA    0 NA  NA
```

You may notice that these are similar to NONMEM event tables; If you are more familiar with NONMEM data and events you could use them directly with the event table function `et`

```
ev  <- et(amountUnits="mg", timeUnits="hours") %>%
    et(amt=10000, addl=9,ii=12,cmt="depot") %>%
    et(time=120, amt=2000, addl=4, ii=14, cmt="depot") %>%
    et(0:240) # Assumes sampling when there is no dosing information
```

You can see from the above code, you can dose to the compartment named in the RxODE model. This slight deviation from NONMEM can reduce the need for compartment renumbering.

These events can also be combined and expanded (to multi-subject events and complex regimens) with `rbind`, `c`, `seq`, and `rep`. For more information about creating complex dosing regimens using RxODE see the RxODE events vignette.

4.3 Solving ODEs

The ODE can now be solved by calling the model object's `run` or `solve` function. Simulation results for all variables in the model are stored in the output matrix x.

```
x <- mod1$solve(theta, ev, inits);
knitr::kable(head(x))
```

time	C2	C3	depot	centr	peri	eff
0	0.00000	0.0000000	10000.000	0.000	0.0000	1.000000
1	44.37555	0.9198298	7452.765	1783.897	273.1895	1.084664
2	54.88296	2.6729825	5554.370	2206.295	793.8758	1.180825
3	51.90343	4.4564927	4139.542	2086.518	1323.5783	1.228914
4	44.49738	5.9807076	3085.103	1788.795	1776.2702	1.234610
5	36.48434	7.1774981	2299.255	1466.670	2131.7169	1.214742

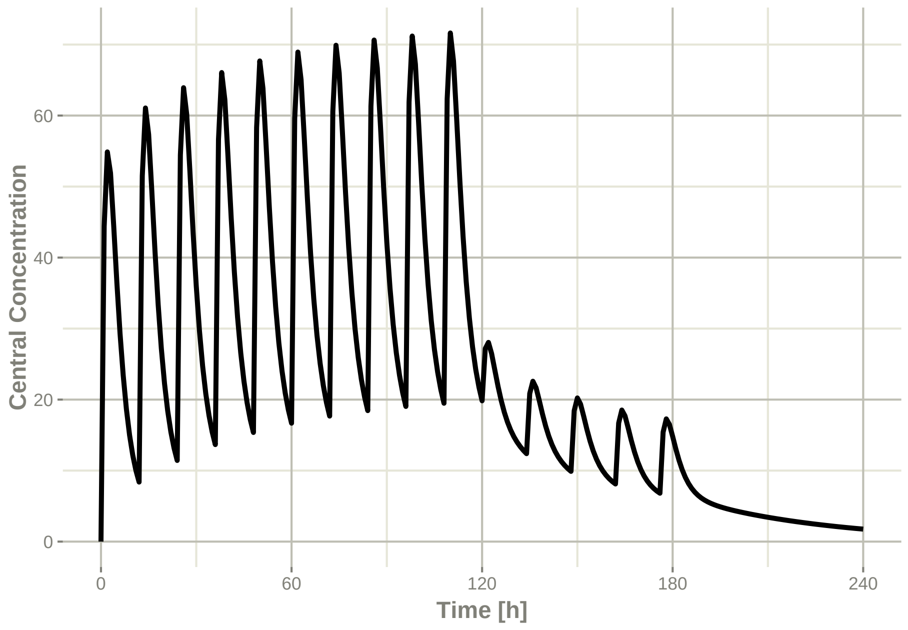
You can also solve this and create a RxODE data frame:

```
x <- mod1 %>% rxSolve(theta, ev, inits);
x
```

```
## ____________________________________________________________________________ Solved 
## -- Parameters (x$params): ----------------------------------------------------------
##      V2      V3      KA      CL       Q     Kin    Kout    EC50
##  40.200 297.000   0.294  18.600  10.500   1.000   1.000 200.000
## -- Initial Conditions (x$inits): ---------------------------------------------------
## depot centr  peri   eff
##     0     0     0     1
## -- First part of data (object): ----------------------------------------------------
## # A tibble: 241 x 7
##    time    C2    C3  depot centr  peri   eff
##     [h] <dbl> <dbl>  <dbl> <dbl> <dbl> <dbl>
## 1     0     0    0     10000     0     0    1
## 2     1  44.4 0.920  7453. 1784.  273.  1.08
## 3     2  54.9 2.67   5554. 2206.  794.  1.18
## 4     3  51.9 4.46   4140. 2087. 1324.  1.23
## 5     4  44.5 5.98   3085. 1789. 1776.  1.23
## 6     5  36.5 7.18   2299. 1467. 2132.  1.21
## # ... with 235 more rows
## ___________________________________________________________________________________
```

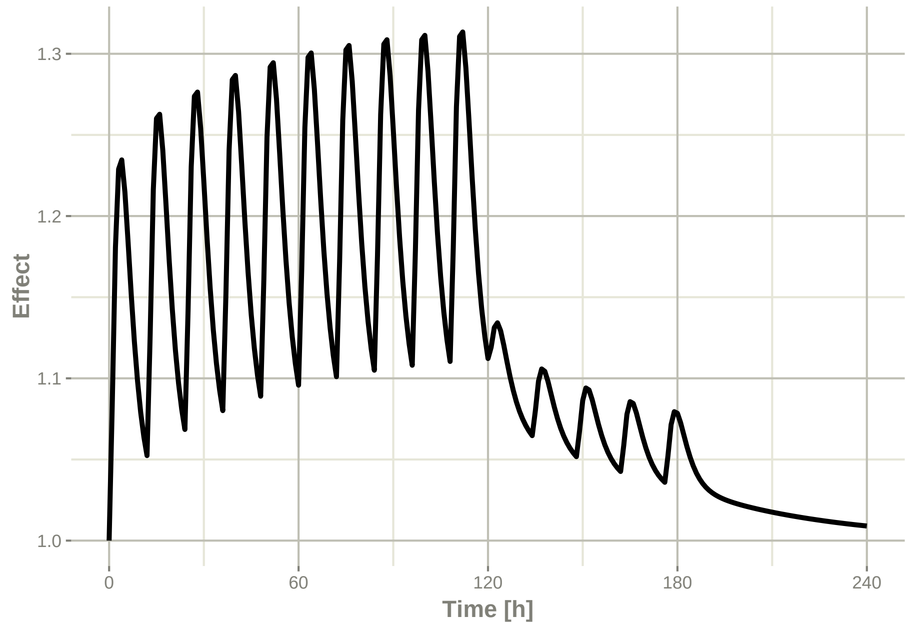
This returns a modified data frame. You can see the compartment values in the plot below:

```
library(ggplot2)
plot(x,C2) + ylab("Central Concentration")
```



Or,

```
plot(x,eff)  + ylab("Effect")
```



Note that the labels are automatically labeled with the units from the initial event table. RxODE extracts `units` to label the plot (if they are present).