METRUM
RESEARCH GROUP

mrgsolve: Overview

mrgsolve Workshop
March 12, 2016
San Diego, CA

What is mrgsolve?

- Simulation from PK/PD and systems pharamcology models in R
- Useful for models that you may have previously been required to go to:
  - NONMEM - ODEs, drug dosing mechanism, awareness of populations
  - MATLAB, Stella, Berkeley Madonna - ODEs or flexible exploration of models

mrgsolve is a package for R

- Open source
- Active development
- R, C++, and fortran
- Models are written in C++
- Solver written in fortran
  - ODE solver is DLSODA from **ODEPACK**
  - https://computation.llnl.gov/casc/odepack/odepack_home.html
  - Same as **ADVAN 13** in NONMEM

mrgsolve key features

- Code models based in systems of ODEs
  - But also $ADVAN2 and $ADVAN4
- Implement complex dosing regimens
- Run population simulation
- **Runs completely in R**
  - Models are compiled and dynamically loaded into the current R session
  - Input data are passed into the probelm as R objects; no need to write data sets to file
  - Simulated data are returned as R objects; no need to read simulated data from file
  - Seamless hand-off of simulated data to plotting (ggplot2) and data summary (dplyr) infrastructure that R does best
- We try to use names rather than positions
  - CENT ... rather than ... A(2)
  - dxdt_CENT ... rather than ... DADT(2)
- Virtually unlimited utilization of C++ capabilities

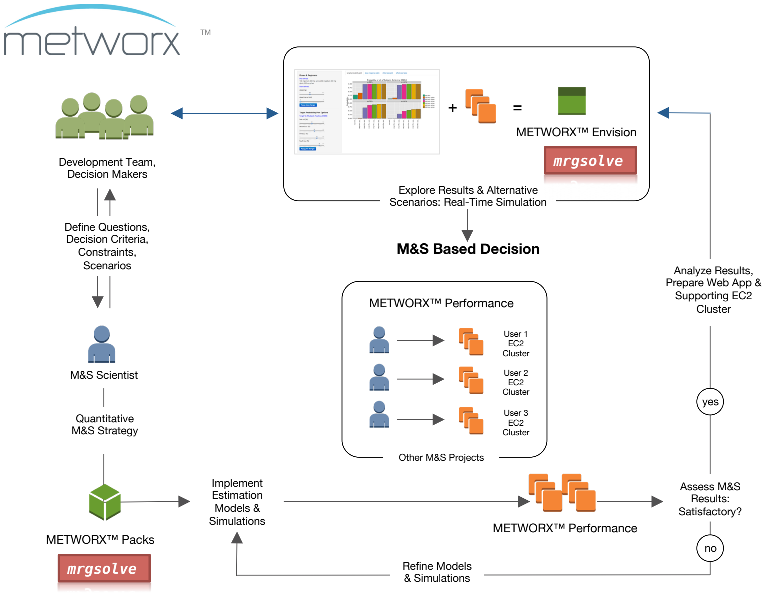
What are we using mrgsolve for?

Types of models

- Population PK
- Population PK/PD
- Large QSP
  - Including Ca/Bone model
  - 50+ species
  - 350+ parameters
  - Translation from SBML
- Viral dynamics
- Malarial parasite dynamics
- Time-to-event

Types of applications

- Routine project work
  - Simulation deliverables
  - Simulation-based diagnostics
- Shiny app
- Parameter estimation
  - MAP Bayes for TDM
  - NLME
- Optimal design
  - PopED, PFIM



Development Team, Decision Makers

Define Questions, Decision Criteria, Constraints, Scenarios

M&S Scientist

Quantitative M&S Strategy

METWORX™ Packs

mrgsolve

Implement Estimation Models & Simulations

METWORX™ Performance

Assess M&S Results: Satisfactory?

no

Refine Models & Simulations

yes

Analyze Results, Prepare Web App & Supporting EC2 Cluster

+ =

METWORX™ Envision

mrgsolve

Explore Results & Alternative Scenarios: Real-Time Simulation

M&S Based Decision

METWORX™ Performance

User 1 EC2 Cluster

User 2 EC2 Cluster

User 3 EC2 Cluster

Other M&S Projects

Write a model

```
// intro_model.cpp

$PARAM CL=1, VC=10, WT=80

$CMT CENT

$MAIN
double CLi = exp(log(CL) + 0.75*log(WT/70) + ETA(1));

$OMEGA 0.04

$ODE dxdt_CENT = -(CLi/VC)*CENT;

$TABLE table(DAY) = floor(TIME/24);
```

Compile and load

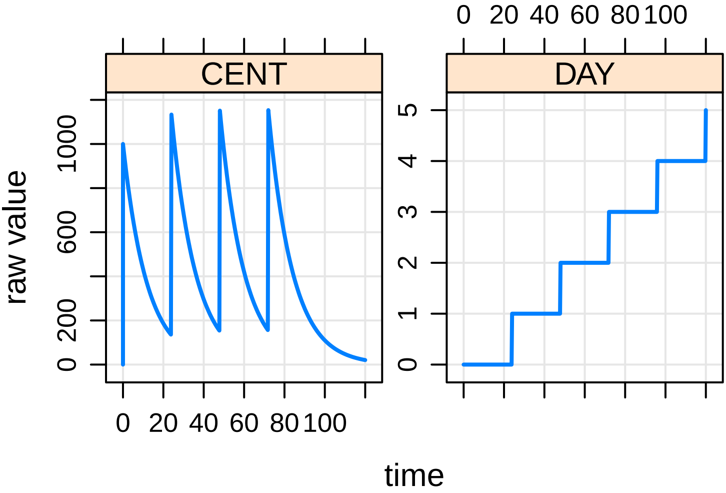
```
mod <-
  mread("intro_model",proj) %>%
  update(delta=0.25,end=120)
```

Simulate

```
set.seed(2192)

out <-
  mod %>%
  ev(amt=1000,ii=24,addl=3) %>%
  mrgsim
```

```
plot(out)
```



Summarize

```r
out %>%
  group_by(DAY) %>%
  summarise(Amax=max(CENT))
```

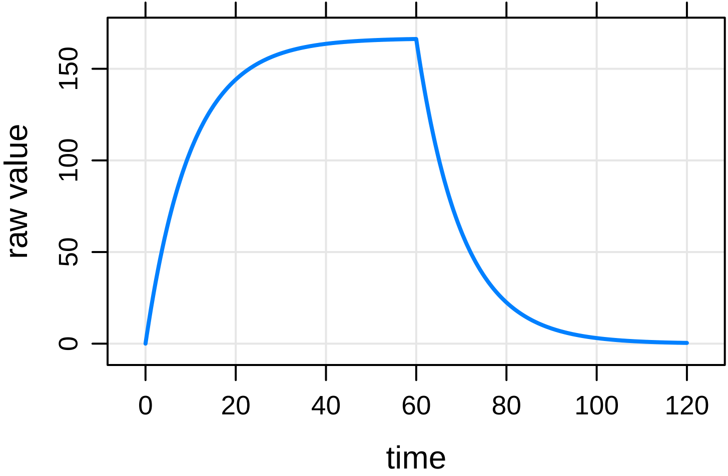
```
. Source: local data frame [6 x 2]
.
.     DAY       Amax
.   (dbl)      (dbl)
. 1     0 1000.00000
. 2     1 1133.25386
. 3     2 1151.01045
. 4     3 1153.37659
. 5     4  153.69188
. 6     5   20.48004
```

Simulate something else

- Change VC to 10
- Take the random effects out of the simulation
- Simulate an infusion rather than repeated bolus
- We don't want DAY in the output

```
out <-
  mod %>%
  param(VC=10) %>%
  drop.re %>%
  Req(CENT) %>%
  ev(amt=1000,rate=1000/60) %>%
  mrgsim
```

```r
plot(out)
```



Installing mrgsolve

- Detailed help is available at **www.metrumrg.com**
- mrgsolve is distributed as a **source** R package
  - www.github.com/metrumresearchgroup/mrgsolve
  - No special requirements other than than which R requires to build R or install packages from source
- mrgsolve and dependencies **MUST** be installed from source
- Install compilers that R binary distributions require

Depencencies

- Required packages
  - `dplyr`, `Rcpp`, `BH`
  - `RcppArmadillo`
- It is **critical** that you install `Rcpp` and `RcppArmadillo` from source
  - `install.pacakges(c("Rcpp", "RcppArmadillo"), type="source")`
- It is **critical** that you re-compile, re-install `Rcpp`, `RcppArmadillo` and `BH` every time you re-install `mrgsolve` **OR** when you change / upgrade your compiler

Compilers

- Windows
  - Install `Rtools.exe` `https://cran.r-project.org/bin/windows/Rtools/`
  - Read and follow **every** instruction, execute every check / test
  - Compile all dependencies from source with `Rtools` toolchain
- Mac OSX
  - Install `Xcode`
  - You will need to install a specific `gfortran` compiler (`R` requirement)
  - Follow the install directions carefully
  - Compile all dependencies from source with this toolchain
- UNIX
  - Tends to work out of the box
  - Extensive use on Ubuntu system

Where to get help?

- Use the R help system
  - ?mrgsolve
  - ?mrgsim
  - ?modspec
  - ?exdatasets
- mrgsolve discussion and questions
  - https://groups.google.com/a/metrumrg.com/forum/#!forum/mrgsolve
- GitHub
  - https://github.com/metrumresearchgroup/mrgsolve
- MetrumRG website
  - www.metrumrg.com/opensourcetools.html
  - www.metrumrg.com/mrgsolve-gallery.html

Goals for today

- Introduction to the mrgsolve workflow in R
  - Compile and load a model object
  - Update a model object
  - Simulation
  - Sensitivity analysis
- Introduction to the mrgsolve model specification format
  - Code blocks
  - Variables and macros
  - All the C++ you need to know to work with mrgsolve
- Some applications and examples