Developing Interactive Visualization Tools for Model-Supported R&D

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Outline

- Where we're heading: moxifloxacin PK dashboard app
- Some `mrgsolve`
- Some `Shiny`
- Create a simple app to explore the moxi model
- Review the moxi dashboard app
- Deploy the moxi app on Metworx Envision
- Look at other apps for clinical decision-making
- Metworx Envison hands-on

Moxifloxacin dashboard app

- `https://metrumrg.shinyapps.io/moxi`
- Moxifloxacin PK in diabetic foot infection
- Proposed dose: 400 mg IV Q24h

Decision questions

- Under the proposed dose, what is the highest MIC we can expect to cover?
- **M**inimum **I**nhibitory **C**oncentration
- Gram positive bacteria
- Gram negative bacteria
- What is the expected efficacy?
- AUC/MIC ratio
  - After first dose
  - After third dose
- How does patient body size affect expected efficacy?
- Weight / BMI

To answer these questions, we need . . .

- Moxifloxacin population PK model
  - Day 1 and day 3 AUC
  - Loading and maintenance doses
- Fraction unbound
- Simulate populations
  - Different body-size distribution
- Summaries by several factors
  - Bacteria type
  - MIC

A dashboard gives access to decision makers

- Real-time updates based on decision-maker input
- Let decision makers
  - interact with the model
  - explore the scenarios of their choosing
  - answer questions as the discussion develops
- Does not require any technical skill or modeling background

To build this dashboard, we need . . .

- Moxifloxacin PK model in agile format
  - Needs to be quick
  - Clean implementation
  - Accessible / portable
- User interface
  - Allow user input
  - Display simulation results
  - Easy to understand / navigate
- Other `R` code to turn user input into desired results

mrgsolve in brief

```
library(mrgsolve)
mod <- mread_cache("irm2", modlib())
```

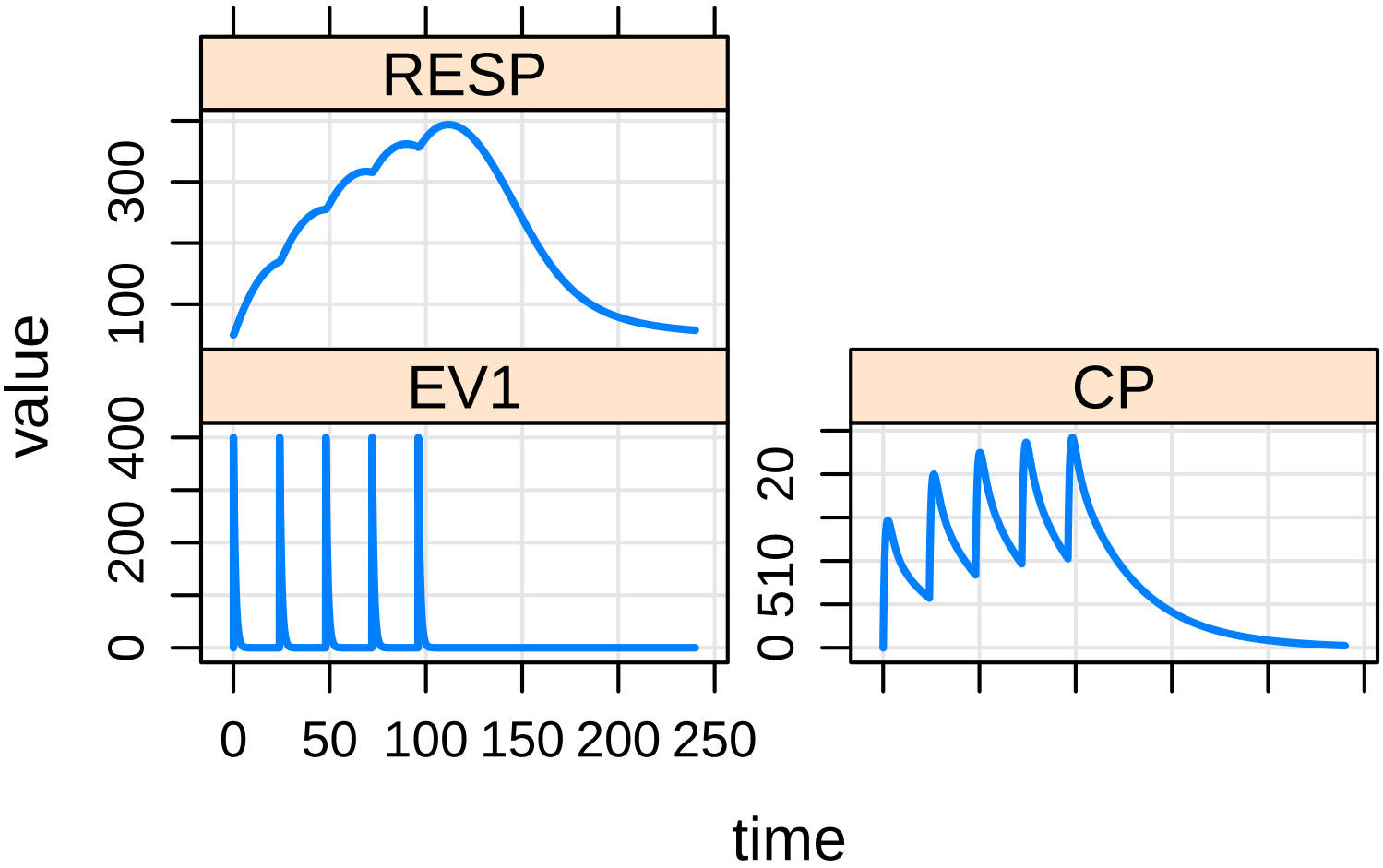
```
mod
```

```
.
.
. -------- mrgsolve model object (unix) --------
.   Project: /Users/kyleb/Rlibs/lib/mrgsolve/models
.   source:          irm2.cpp
.   shared object: irm2-so-d5db9707813
.
.   compile date:
.   Time:            start: 0 end: 24 delta: 1
.   >                add: <none>
.   >                tscale: 1
.
```

Simulate a dosing regimen

```
out <-
  mod %>%
  param(KOUT=0.2,IC50=2) %>%
  ev(amt=400,ii=24, addl=4) %>%
  mrgsim(end=240, delta=0.1)
```

```
plot(out,EV1+CP+RESP~.)
```



Population simulation

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

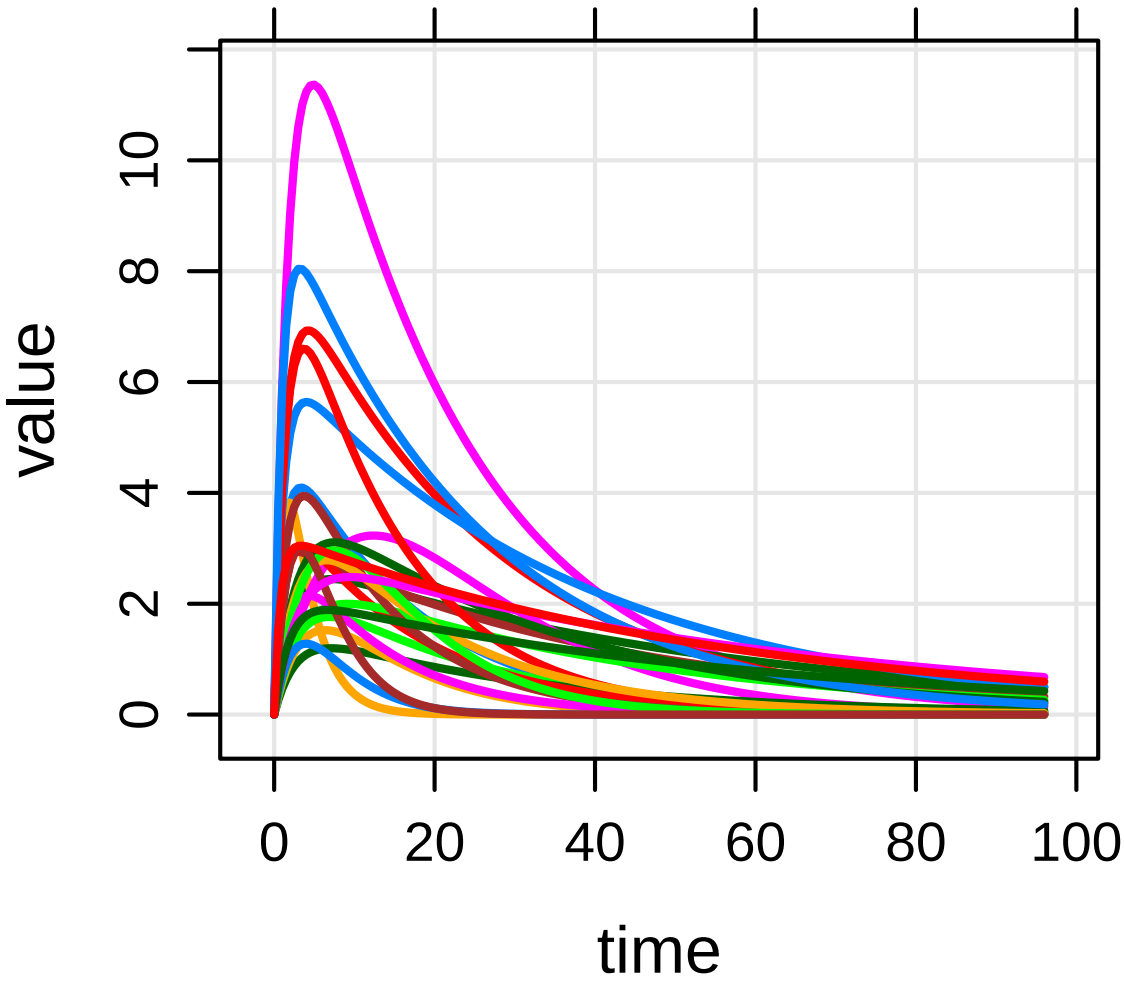
```
cov1 <- covset(WT~rnorm(80,30),SEX~rbinomial(0.4))
idata <- data_frame(ID=1:25) %>% mutate_random(cov1)

head(idata,n=3)
```

```
. # A tibble: 3 × 3
.      ID        WT   SEX
.   <int>     <dbl> <dbl>
. 1     1  59.49823     0
. 2     2  24.70408     0
. 3     3 106.04048     1
```

```
out <- mod %>% ev(amt=100) %>% mrgsim(end=96,idata=idata)
```

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



Get started with mrgsolve

- mrgsolve.github.io

Moxifloxacin model

- Let's do side-by-side conversion from NONMEM control stream
- Model downloaded from DDMoRe model repository
  - `http://repository.ddmore.eu/model/DDMODEL00000034`
- First, do a one-to-one conversion
  - Model amounts computed in closed form (like ADVAN2/ADVAN4)
- Then, code an ODE-based version
  - This let's us get the day 1 and 3 `AUC` values we need for the dashboard

$PROBLEM

NONMEM

```
;; 1. Based on: run021
;; 2. Description: PK of moxifloxacin in patients with diab
;; x1. Author: Sebastian G. Wicha, Freie Universitaet Berli
;; 3. Label:
$PROBLEM PK
```

mrgsolve

```
$PROB
# Wicha et al. 2015
- Moxifloxacin PK in diabetic foot infection
- Author: Sebastian G. Wicha, Freie Universitaet Berlin, Ge
- https://www.ncbi.nlm.nih.gov/pubmed/25600294
```

$INPUT

NONMEM

```
$INPUT ID TIME DV AMT RATE MDV EVID CMT WGT IBW
```

mrgsolve

```
$PARAM WGT = 70, IBW = 70, fu = 0.6
```

- We tell `mrgsolve` what columns to look for
- Every data item has a "default" value

$DATA

NONMEM

```
$DATA MOX02_sim.csv ; IGNORE=#
```

mrgsolve

```
## Not required
```

- `mrgsolve` will work with your NONMEM data set
- Pass in as `R` data frame

$SUBROUTINES

NONMEM

```
$SUBROUTINES ADVAN3 TRANS4
```

mrgsolve

```
$PKMODEL cmt="CENT PERIPH"
```

- `mrgsolve` is ADVAN13 by default
- Also have 1- and 2- compartment in closed form
- General compartment models on the horizon

NONMEM

```
$PK
TVCL  = THETA(1)
ASCCL = TVCL * (IBW/70)**0.75
CL    = ASCCL * EXP(ETA(1))
TVV1  = THETA(2)
ASCV1 = TVV1 * (WGT/70)**1
V1    = ASCV1 * EXP(ETA(2))
Q  = THETA(3)
TVV2 = THETA(4)
ASCV2 = TVV2 * (WGT/70)**1
V2    = ASCV2
S1 = V1
```

mrgsolve

```
$MAIN
double TVCL  = THETA1;
double ASCCL = TVCL*pow(IBW/70,0.75);
double CL    = ASCCL*exp(ETA(1));

double TVV1  = THETA2;
double ASCV1 = TVV1*WGT/70.0;
double V1    = ASCV1*exp(ETA(2));

double Q = THETA3;

double TVV2  = THETA4;
double ASCV2 = TVV2*WGT/70.0;
double V2    = ASCV2;
```

$ERROR

NONMEM

```
IPRED = F
DEL   = 0
IF (IPRED.EQ.0) DEL=0.0001
W     = F
Y     = F+F*EPS(1)+EPS(2)
IRES  = DV-IPRED
IWRES = IRES/(W+DEL)
```

mrgsolve

```
$TABLE
capture IPRED = CENT/V1;
double  DV = IPRED*(1+EPS(1)) + EPS(2);

capture fIPRED = fu*IPRED;
capture fDV = fu*DV;

$CAPTURE DV
```

$THETA, $OMEGA, $SIGMA

NONMEM

```
$THETA
1.21E+01 ; CL
6.81E+01 ; V1
2.03E+01 ; Q
4.46E+01 ; V2

$OMEGA
6.33E-02          ; CL
7.25E-02          ; V1

$SIGMA
3.40E-02 ; Prop
4.65E-03 ; Add
```

mrgsolve

```
$THETA
1.21E+01
6.81E+01
2.03E+01
4.46E+01

$OMEGA
6.33E-02
7.25E-02

$SIGMA
3.40E-02
4.65E-03
```

No equivalent

NONMEM

```
$EST METHOD=1 INTER MAXEVAL=0
NOABORT SIG=3 PRINT=1 POSTHOC
;$COV
```

mrgsolve

```
$SET delta=0.1, end=24*3
```

- Easy to simulate at the times you want observations
- `mrgsolve` itself doesn't not generate estimates; but it may be used as a part of optimization process in `R`

Let's expand the mrgsolve model

- Differential equations
- Calculate AUC0-24 and AUC48-72

Develop R code for moxi sims

- Need cohort with 1000 patients
- Covariates
  - Weight, height,SEX (IBW,BMI)
- Dosing
  - 400 mg IV Q24h
  - Option for loading dose (hypothetical)
- Simulate out to day 3

Introduce dmutate package

- `https://cran.r-project.org/package=dmutate`
- Quickly simulate variates
  - any distribution at any level
  - bounds
- Specified as formula
- Collect in sets

dmutate example

```
library(dmutate)
muwt <- 90
sdwt <- 90
pfe <- 0.65
```

```
cov1 <- covset(WT[40,140] ~ rnorm(muwt,sdwt)|ID,
               SEX ~ rbinomial(pfe)|ID)
```

```
cov1
```

```
.  Formulae
.    WT[40, 140] ~ rnorm(muwt, sdwt) | ID
.    SEX ~ rbinomial(pfe) | ID
```

```
set.seed(1133)
data_frame(ID=1:25) %>% mutate_random(cov1)
```

```
. # A tibble: 25 × 3
.       ID        WT   SEX
.    <int>     <dbl> <dbl>
.  1     1  72.70968     0
.  2     2 113.04180     0
.  3     3  48.01491     0
.  4     4 136.14602     1
.  5     5  45.96462     0
.  6     6  49.44370     0
.  7     7  53.01213     0
.  8     8  58.69607     1
.  9     9  90.22743     1
. 10    10  42.13365     0
. # ... with 15 more rows
```

```
data(exTheoph)

exTheoph %<>% mutate_random(cov1)

head(exTheoph)
```

```
.    ID Dose time   conc cmt  amt evid       WT SEX
. 1   1 4.02 0.00   0.00   1 4.02    1 104.4561   1
. 2   1 4.02 0.25   2.84   0 0.00    0 104.4561   1
. 3   1 4.02 0.57   6.57   0 0.00    0 104.4561   1
. 4   1 4.02 1.12 10.50   0 0.00    0 104.4561   1
. 5   1 4.02 2.02   9.66   0 0.00    0 104.4561   1
. 6   1 4.02 3.82   8.58   0 0.00    0 104.4561   1
```

Shiny

- A huge topic; we will just scratch the surface
- Developed by Rstudio + lots of contributors
- The place to start: `http://shiny.rstudio.com/`
  - Tutorials, galleries, articles, example code

Elements of Shiny

- Two main elements to shiny app
  - User interface (UI, `ui.R`)
  - Server (`server.R`)
- User interface
  - Data input (widgets: text, numeric, select, checkbox)
  - Return data (plots, tables, text)
  - Layout (fluidPage, tabSet)
- Server
  - All computations
  - Generate outputs to be displayed in UI
  - Largely plain old `R` code written in server environment
- Reactivity

Get started example app

`https://metrumrg.shinyapps.io/getstarted`

Explore Shiny with a flexdashboard

- Interactive Rmarkdown document
  - Define some inputs
  - Return some outputs
- flexdashboard puts it all together for you
  - Widgets (input)
  - Render (output)
  - Reactivity
  - Control reactivity with action button

Recommend shinydashboard as environment for your app

- `https://rstudio.github.io/shinydashboard/`
- Similar concept to flexdashboard
- Menu bar on the left
  - Add submenus
- Main app space on the right
  - Arrange with boxes
  - Add tabsets

Let's take a look at the Moxifloxacin code

- `./moxi2/ui.R` and `./moxi2/server.R`

Here's what I'd do

1. Work out your model in a separate file
   - Make sure it is doing what you think it is doing
2. Work out the `R` code that will run your model
   - Use functions that do one thing very well
   - Hard code UI inputs and replace later with `input$name`
3. Code UI and layout
   - Tabsets, boxes, rows
4. Fill in server code

At each step, make incremental changes and re-run the code/app