

nonmem2mrgsolve: An R package for Automated NONMEM to mrgsolve Translation

Andrew Santulli¹, Donald E. Mager^{1,2}, Scott Van Wart¹

¹Enhanced Pharmacodynamics, LLC, Buffalo, NY, USA

²Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, The State University of New York, Buffalo, NY, USA

Purpose

Provide an R package that automates NONMEM to mrgsolve translation to reduce human errors and improve efficiency

Introduction

- Pharmacometricians often utilize multiple software, with NONMEM® (ICON plc, Dublin, Ireland) widely regarded as the current gold standard for PK and PK-PD modeling
- While NONMEM has the ability to simulate, it is often more convenient and practical to perform simulations using free open-source software such as R [1], which can also perform post-processing of the output
- Two popular pharmacometrics-orientated R packages for solving ODE systems are rxode2 [2] and mrgsolve [3]
- The translation of NONMEM models into rxode2 syntax has already been automated by others [4]
- Although mrgsolve has built-in functionality to streamline translation, to the best of our knowledge a previously-developed and publicly-available R package for automated NONMEM to mrgsolve translation does not exist

Methods

- Original nonmem2mrgsolve development used R Version 4.1.0, but testing has additionally been performed on R Version 4.4.0
- The package is open-source and is publicly available on GitHub
- NONMEM to mrgsolve model translation requires the NONMEM .ctl file, the NONMEM .ext (default) or .cnv file
- Translation is initiated via a single nonmem2mrgsolve function call, with the only required user input being the NONMEM run name
- During the translation:
 - The NONMEM .ctl and .ext (or .cnv) files are loaded into R
 - NONMEM code blocks within the .ctl that are applicable to mrgsolve simulations are identified
 - NONMEM syntax is converted to mrgsolve syntax
 - Final NONMEM-estimated fixed effect parameters and IIV magnitudes are imported from the .ext (or .cnv) into the newly-created mrgsolve code
 - By default, the nonmem2mrgsolve-translated mrgsolve code is written as an .R file, which can be loaded for use in simulation scripts

Results

- The nonmem2mrgsolve package has been successfully adopted internally and used to streamline the workflow of numerous population PK, population PK-PD, physiologically-based PK (PBPK), and quantitative systems pharmacology (QSP) projects
- The nonmem2mrgsolve translation adds necessary double precision floating point initializations (i.e., “double” before the first occurrence of each variable), statement terminators (i.e., a semicolon at the end of each line), performs common syntax conversions (ex. “EXP” to “exp”, “THEN ENDIF” to “{ }”, “base**pow” to “pow(base,pow)”, etc.), and imports the final NONMEM parameter estimates
- Key optional user inputs can control the number of significant digits reported in the mrgsolve code for final parameter estimates and can request that the .cnv file be used for obtaining final parameter estimates instead of the .ext (if stochastic expectation maximization estimation was used during modeling within NONMEM)
- Current limitations include not translating time variables (although comments within the mrgsolve code will identify lines requiring the user’s attention) and no option to import residual variability estimates

Conclusions

- The nonmem2mrgsolve R package automates NONMEM to mrgsolve translation and successfully handles most use cases and syntax nuances
- This improves time efficiency and removes a potential source for human error, especially for models with many equations
- Users remain responsible for validating the translation, for which there is an intuitive and established framework [5]
- Future work will expand upon the accommodated usage scenarios, build in automated validation, and will explore a potential release to CRAN

Workflow

NONMEM®

Step 1: Obtain the .ctl and .ext for the NONMEM model of interest



Step 2: Within R, run the nonmem2mrgsolve function

mrgsolve

Code

mcode()

mrgsolve

Model Object

Step 3: Check for successful model compilation and manually correct the code if necessary

User-Performed Model Validation

Sims

User-specified dosing, virtual subject demographics, simulation settings, etc.

Examples

Example 1: A 1-compartment Model with First-order Absorption

NONMEM

```
...  
  
$MODEL  
COMP=(DEPOT, DEFDOSE)  
COMP=(CENTRAL, DEFOBS)  
  
$PK  
TVKA = THETA(1)  
KA = TVKA  
TVCL = THETA(2)*(WTKG/71.0)**THETA(4)  
CL = TVCL*EXP(ETA(1))  
TVV = THETA(3)*(WTKG/71.0)**THETA(5)  
V = TVV*EXP(ETA(2))  
S2 = V  
  
$DES  
DADT(1) = -KA*A(1)  
DADT(2) = KA*A(1) - (CL/V)*A(2)  
  
...
```



nonmem2mrgsolve("mod1.ctl")

```
nonmem2mrgsolve::nonmem2mrgsolve(  
  filename = "nonmem-model.ctl",  
  dir = "./folder",  
  sigdig = NULL,  
  write = T,  
  return.orig = F,  
  out.filename = NULL,  
  use.cnv = F  
)
```

MRGSOLVE

```
$PARAM  
WTKG=NA_real_  
  
$THETA  
0.782 17.3 85.8 1.85 1.58  
  
$CMT  
DEPOT  
CENTRAL  
  
$MAIN  
double TVKA = THETA1;  
double KA = TVKA;  
double TVCL = THETA2*pow((WTKG/71.0),THETA4);  
double CL = TVCL*exp(ETA(1));  
double TVV = THETA3*pow((WTKG/71.0),THETA5);  
double V = TVV*exp(ETA(2));  
double S2 = V;  
  
$ODE  
dxdt_DEPOT=-KA*DEPOT;  
dxdt_CENTRAL=KA*DEPOT - (CL/V)*CENTRAL;  
  
$OMEGA @block  
0.0105  
0 0.00765  
  
$CAPTURE  
KA, CL, V, WTKG
```

Example 2: A QSS Target-Mediated Drug Disposition (TMDD) Model and Indirect Response PK-PD Model

Example 3: A Whole-body Physiologically-based Pharmacokinetic (PBPK) Model

Find on GitHub using the QR code below

References

- R Core Team (2024). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. <https://www.R-project.org/>.
- Matthew L. Fidler and Melissa Hallow and Justin Wilkins and Wenping Wang (2024). RxODE: Facilities for Simulating from ODE-Based Models. R package version 2.1.2. <https://CRAN.R-project.org/package=RxODE>
- Kyle T Baron (2024). mrgsolve: Simulate from ODE-Based Models. R package version 1.4.1. <https://CRAN.R-project.org/package=mrgsolve>
- Fidler and Philip Delff and Gabriel Staples (2023). nonmem2rx: ‘nonmem2rx’ Converts ‘NONMEM’ Models to ‘rxode2’. R package version 0.1.3. <https://CRAN.R-project.org/package=nonmem2rx>
- Kyle T Baron (2023, March 6). Update: Validate translation from NONMEM. [mrgsolve/blog](https://mrgsolve.org/blog/posts/2023-update-validation.html). <https://mrgsolve.org/blog/posts/2023-update-validation.html>

Citing nonmem2mrgsolve

- Andrew Santulli (2024). nonmem2mrgsolve: Automated NONMEM to mrgsolve Translation. R package version 1.2.0.



<https://www.epd-llc.com>

github.com/Andy0000000000/nonmem2mrgsolve

