Transparent, Open and Reproducible PBPK and QSP Modeling and Simulation Using an R-Based Framework

Ahmed Elmokadem, PhD

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Published in final edited form as:
Toxicol Sci. 2018 April 01; 162(2): 341–348. doi:10.1093/toxsci/kfy010.

Challenges Associated With Applying Physiologically Based Pharmacokinetic Modeling for Public Health Decision-Making.

YM Tan[1], **RR Worley**[2], **JA Leonard**[3], and **JW Fisher**[4]

[1]National Exposure Research Laboratory, United States Environmental Protection Agency, Research Triangle Park, North Carolina 27709.

[2]Agency for Toxic Substances and Disease Registry, Atlanta, Georgia 30341.

[3]Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee 37830.

[4]National Center for Toxicological Research, United States Food and Drug Administration, Jefferson, Arizona 72079.

"Ultimately, the submission documentation should contain sufficient information to allow reviewers and risk assessors to understand model assumptions, independently reproduce simulations, and evaluate the quality of the analysis and validity of the resulting conclusions (Loizou et al., 2008)"

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CPT: Pharmacometrics & Systems Pharmacology

TUTORIAL | Open Access

QSP and PBPK Modeling with mrgsolve: A Hands-on Tutorial

Ahmed Elmokadem, Matthew M Riggs, Kyle T Baron

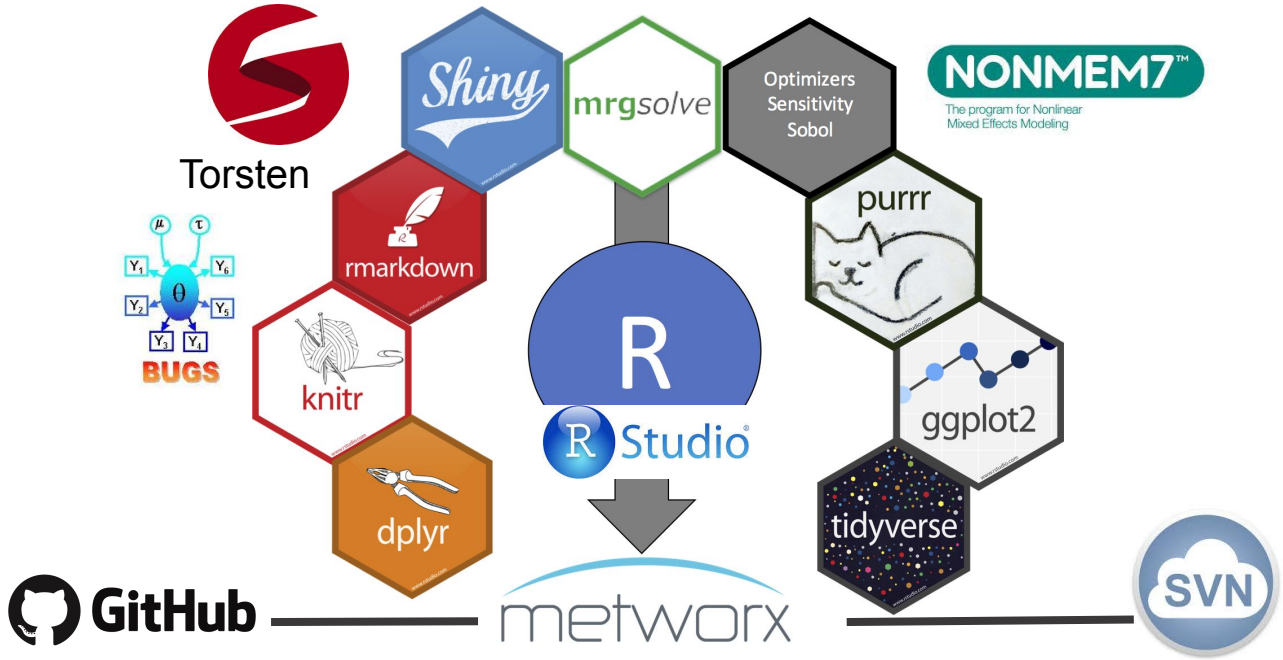
First published: 25 October 2019 | https://doi.org/10.1002/psp4.12467

https://github.com/metrumresearchgroup/cptpsp-tutorial-2019

Why R?

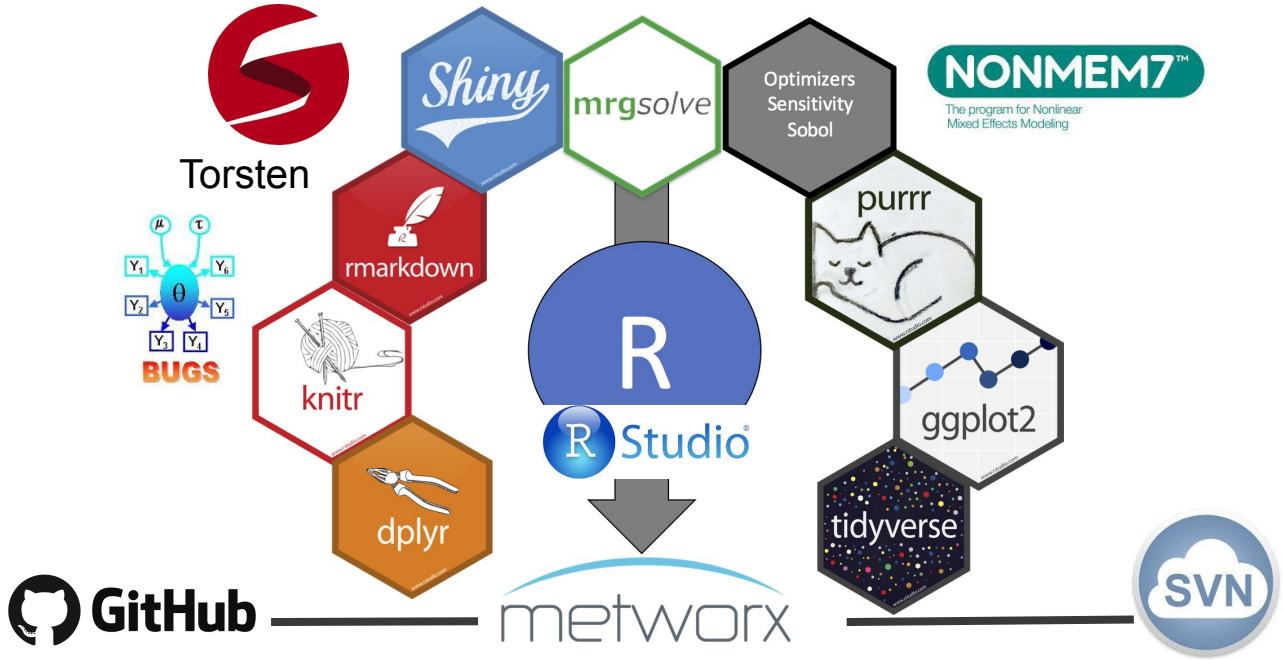
- Open-Source
  - transparency
  - reproducibility
  - active community
  - accessible and portable
  - … these can feed credibility

- Maximize utility of R ecosystem
  - data manipulation
  - graphics
  - estimation algorithms
  - sensitivity analysis
  - interactive visualization

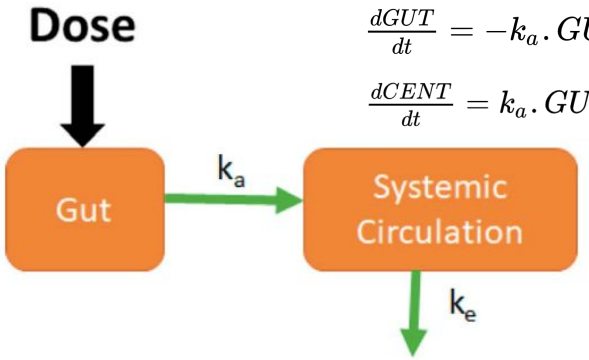


Why mrgsolve in R?

- Open-source
- Flexible (ODE-based)
- Combines efficiency (C++ core) and convenience (R interface)
- Built for pharmacometric applications (event handling, NM-TRAN like datasets, patient population (mixed effects), etc…)
- Compatible with R ecosystem



General mrgsolve workflow



$$\frac{dGUT}{dt} = -k_a . GUT$$

$$\frac{dCENT}{dt} = k_a . GUT - (\frac{CL}{V_c}) . CENT$$

Adapted from Lin and Wong. *Pharmaceutics* 2017, 9, 41

Model Specification

Model pk1.cpp

```
[PARAM] CL=0.02, VC=0.5, KA=0.9

[CMT] GUT CENT

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

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

R Script

Compile

```
mod <- mread("pk1")
```

Set intervention

```
evnt <- ev(amt = 100, ii = 24, addl = 9)
```

Simulate

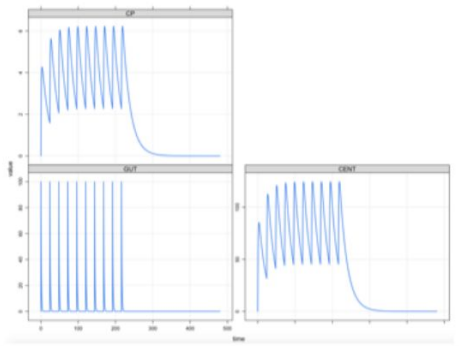
```
out <- mod %>%
       ev(evnt) %>%
       mrgsim(end = 480, delta = 0.1)
```

Output

```
out

   ID time       GUT      CENT        CP
1   1  0.0   0.00000  0.000000 0.0000000
2   1  0.0 100.00000  0.000000 0.0000000
3   1  0.1  90.48374  9.492112 0.4746056
4   1  0.2  81.87308 18.033587 0.9016794
5   1  0.3  74.08182 25.715128 1.2857564
6   1  0.4  67.03200 32.618803 1.6309401

plot(out)
```



Adapted from Elmokadem, A. *et al.*, *CPT:PSP* (2019)

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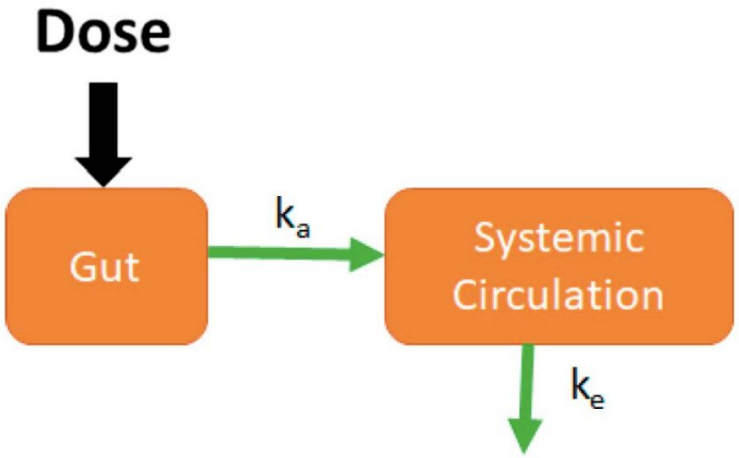
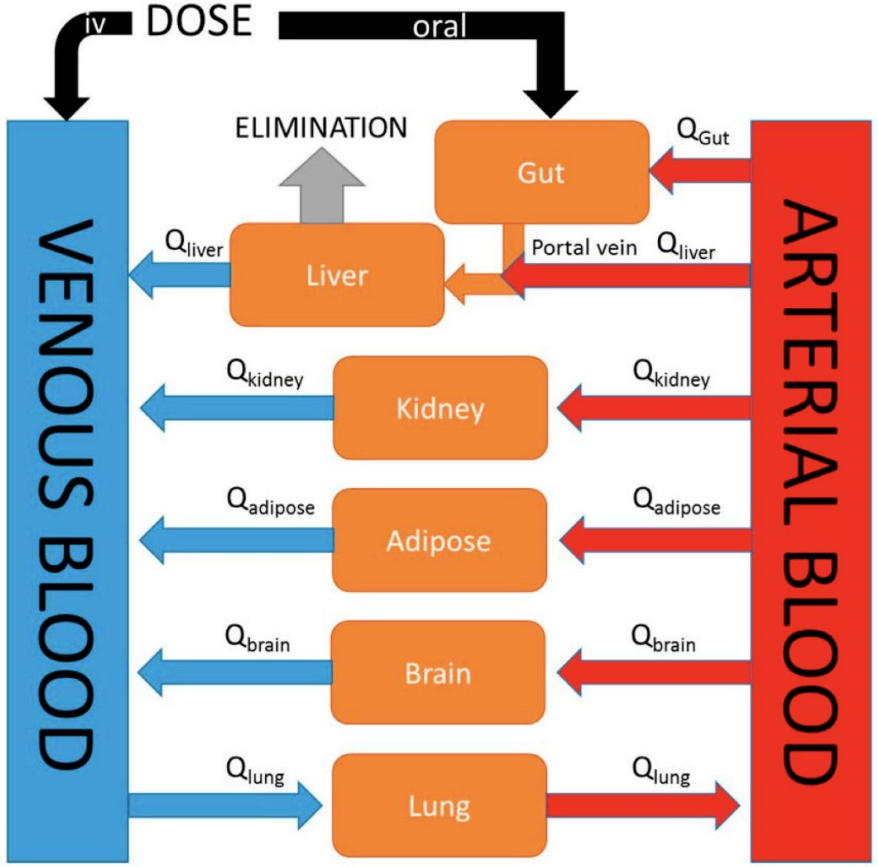
What Differentiates PK and PBPK?





$$\frac{dCENT}{dt} = ka.GUT - (\frac{CL}{V_c}).CENT$$

$$\frac{dA_T}{dt} = Q_T \cdot (C_{art} - \frac{C_T}{\frac{Kp_T}{B:P}})$$

Lin and Wong. *Pharmaceutics* 2017, 9, 41

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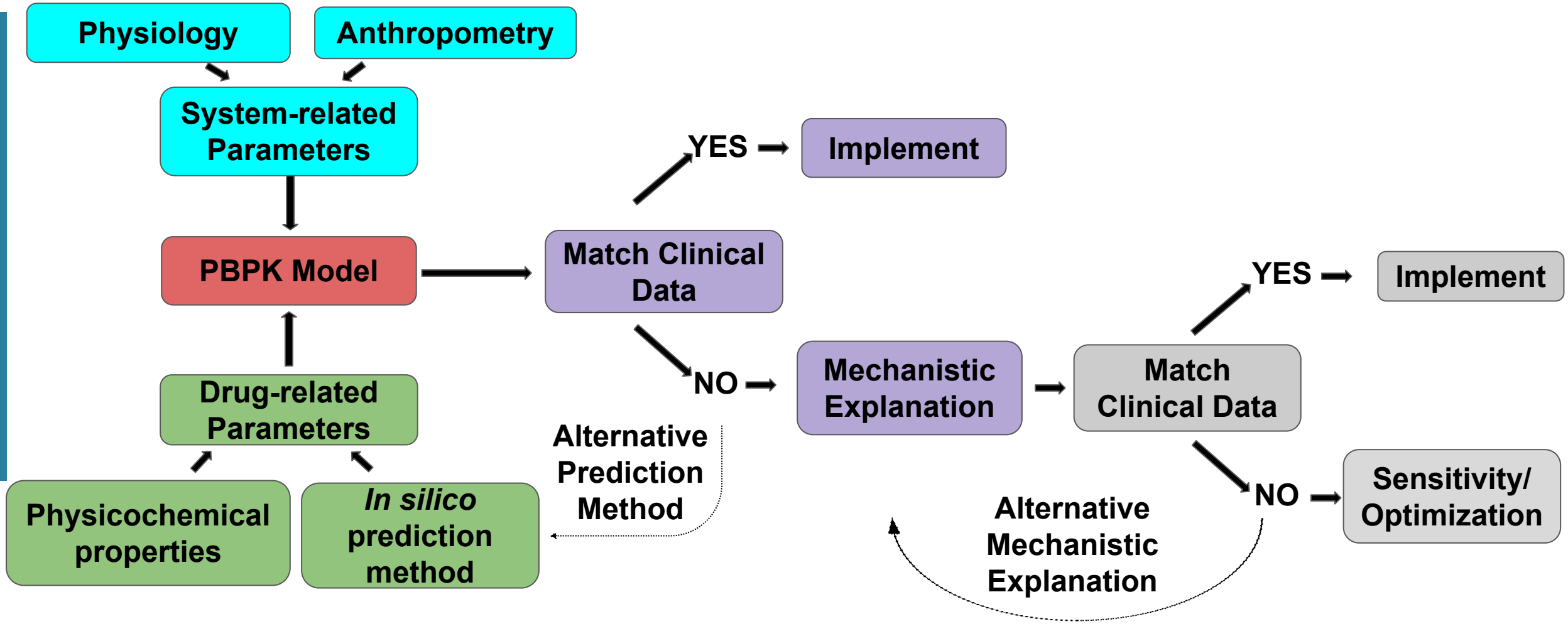
Why Develop a PBPK Model?

- Mechanistic approach to explaining PK
  - Integrating *in-vitro* data (metabolism, permeability)
  - *a priori* predictions
  - Confirm/refine with experimental data
  - Exposure predictions in different tissues or organs (skin, eyes, lungs, brain, etc..)
- First principles -> Bottom-up approach -> Scalability:
  - Inter-species
  - Within-species differences: Age (maturational), Disease, Genotype/Phenotype, etc

When to Develop a PBPK Model?

- Special populations
  - pregnant woman/fetus
  - pediatrics
  - rare diseases
- Environmental toxicology
- Translational studies
- Drug-drug interactions
- Drug absorption characterization
  - oral
  - topical
  - nasal/inhalation
  - alternative routes

PBPK Workflow



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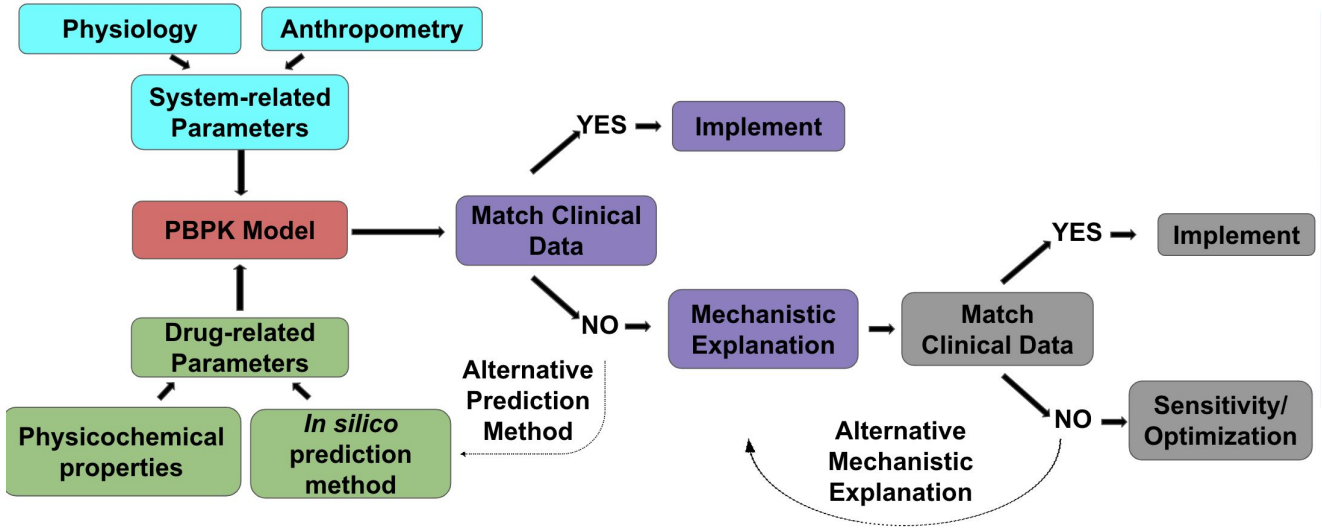
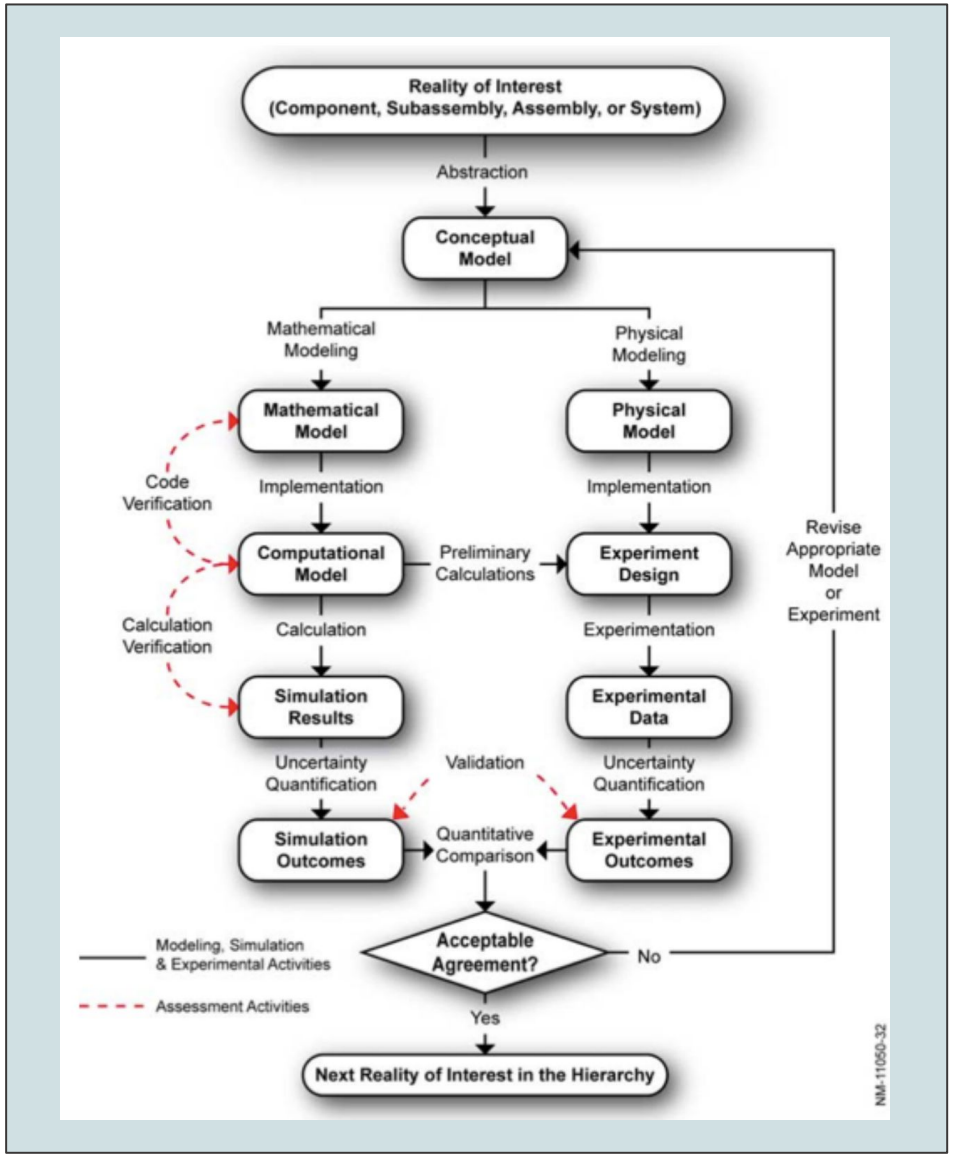
PBPK Workflow

Aligns well with ASME V&V credibility workflow —>





https://nanohub.org/courses/UQ/ss2015/asset/9466

ASME V&V 10 2006 (Guide Figure)

PBPK Application - Voriconazole

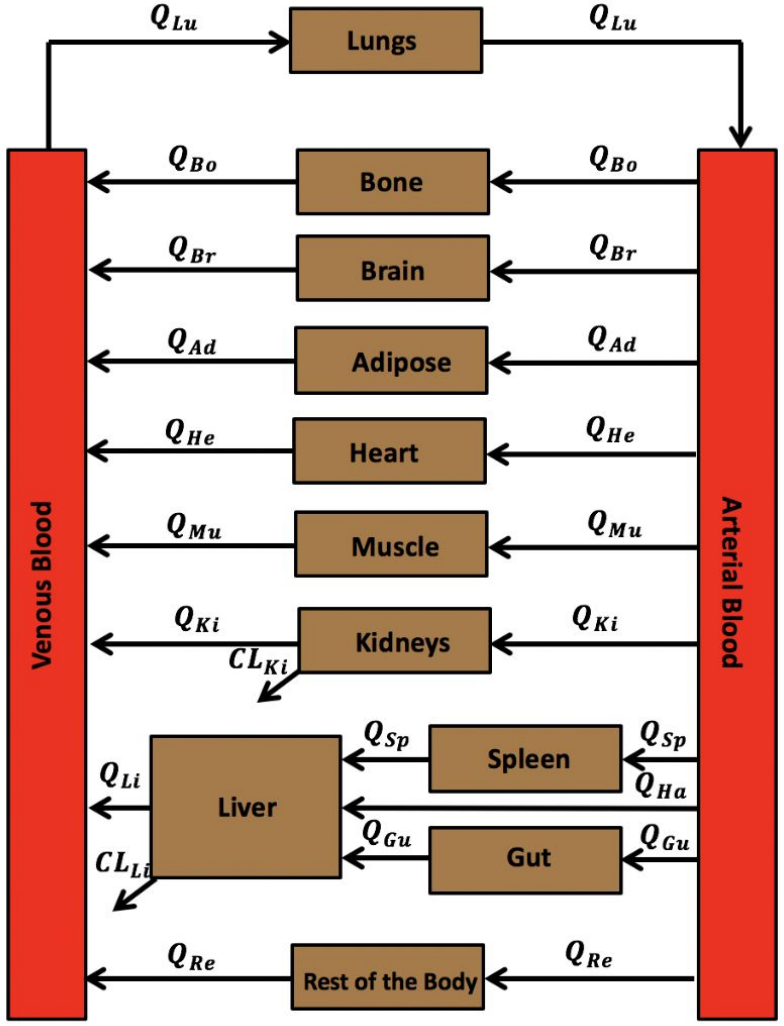
Clin Pharmacokinet (2014) 53:1171–1182
DOI 10.1007/s40262-014-0181-y

ORIGINAL RESEARCH ARTICLE

A Physiologically Based Pharmacokinetic Model for Voriconazole Disposition Predicts Intestinal First-pass Metabolism in Children

Nicole R. Zane · Dhiren R. Thakker

PBPK Application - Voriconazole



Adapted from Elmokadem, A. *et al.*, *CPT:PSP* (2019)

$$\frac{dA_T}{dt} = Q_T(C_A - \frac{C_T}{\frac{Kp_T}{BP}})$$

$$\frac{dA_T}{dt} = Q_T(C_A - \frac{C_T}{\frac{Kp_T}{BP}}) - fu.CL_T.\frac{C_T}{\frac{Kp_T}{BP}}$$

$$\frac{dA_A}{dt} = Q_{Lu}(\frac{C_{Lu}}{\frac{Kp_{Lu}}{BP}} - C_A)$$

$$\frac{dA_V}{dt} = \sum_{T \neq Lu}(Q_T.\frac{C_T}{\frac{Kp_T}{BP}}) - Q_{Lu}.C_V$$

$$\frac{dA_{Lu}}{dt} = Q_{Lu}(C_V - \frac{C_{Lu}}{\frac{Kp_{Lu}}{BP}})$$

understand model assumptions, independently reproduce simulations, and evaluate the quality

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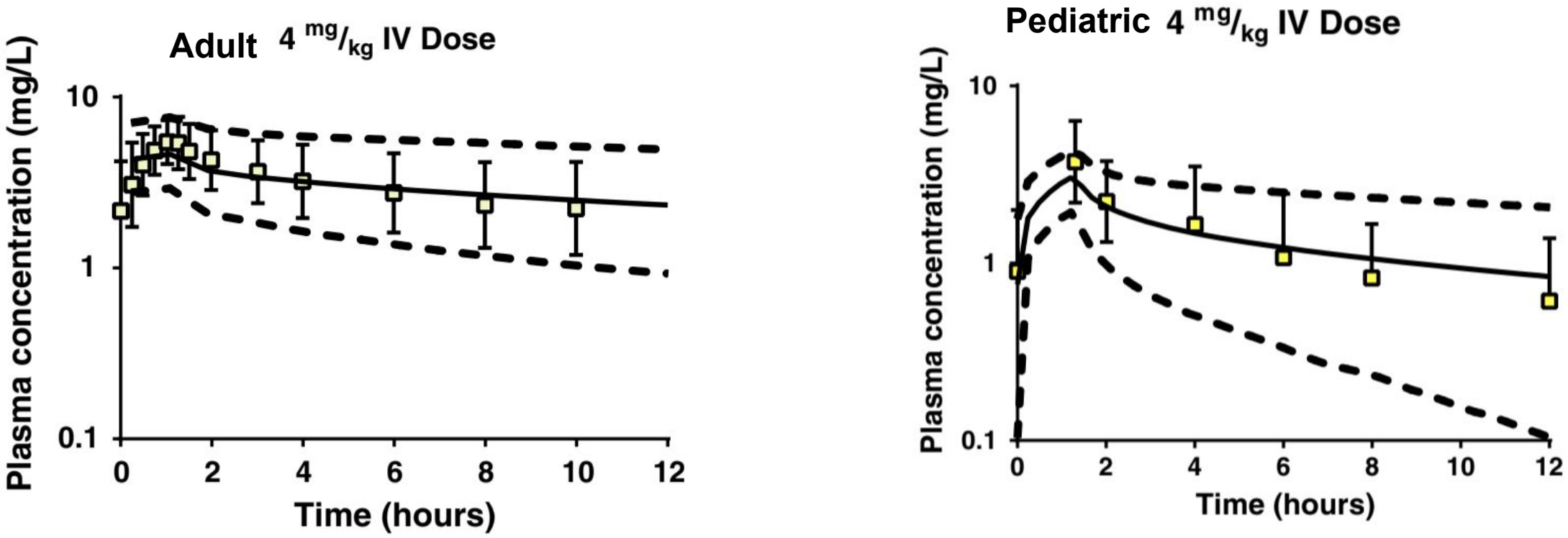
PBPK Application - Voriconazole



Adapted from Zane and Thakker, *Clin Pharmacokinet* (2014) 53:1171–1182

(a) Can we reproduce this research?
(b) Can we do better?

understand model assumptions, independently reproduce simulations, and evaluate the quality

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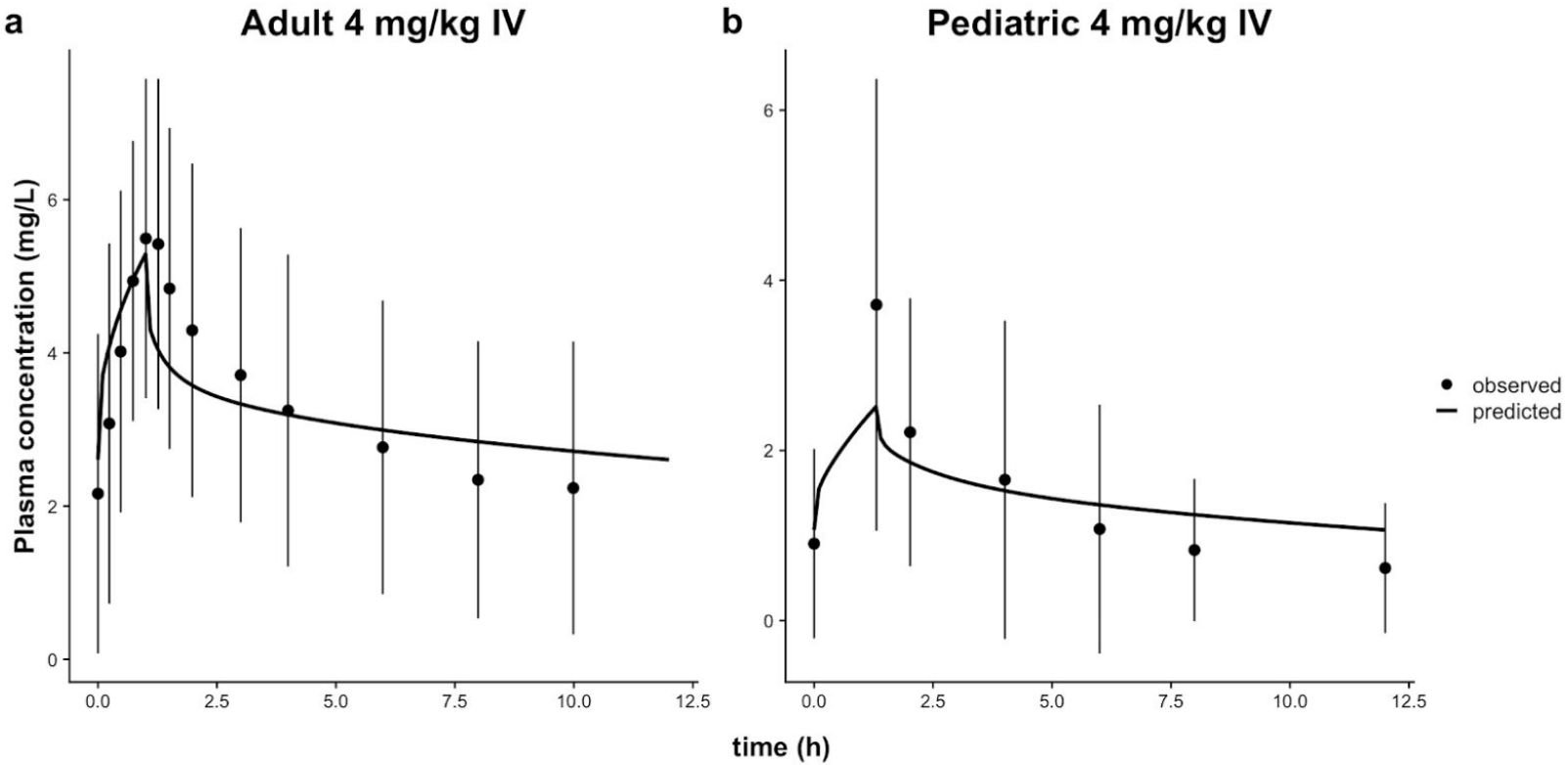
PBPK Application - Voriconazole

Reproduce simulation results



Adapted from Elmokadem, A. *et al.*, *CPT:PSP* (2019)

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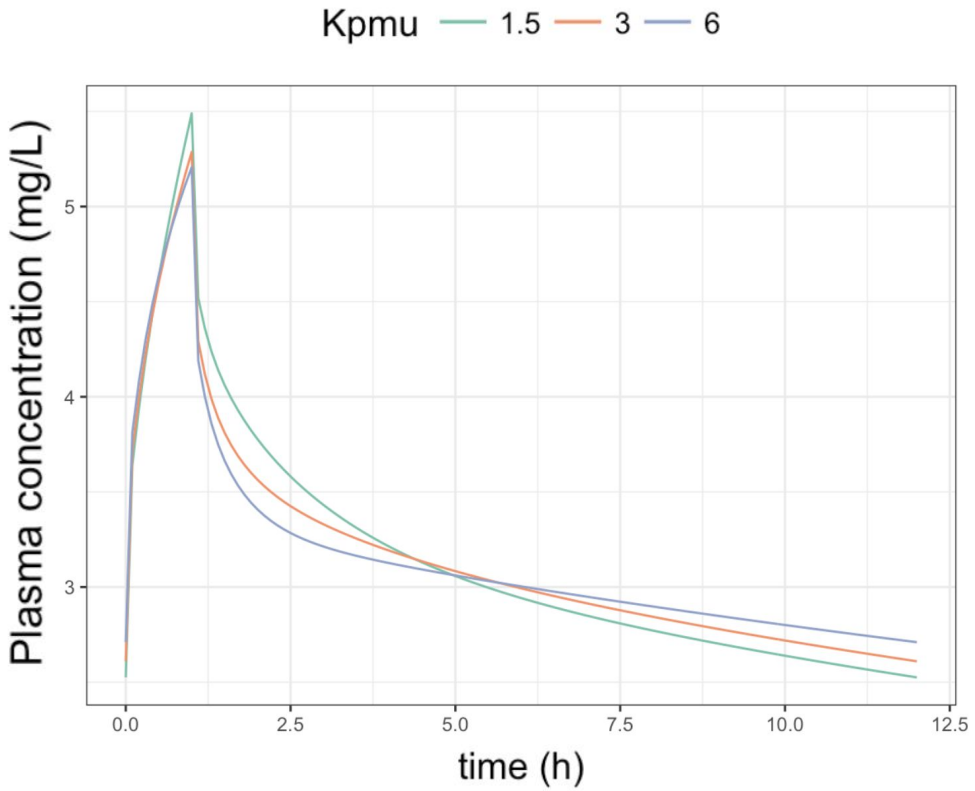
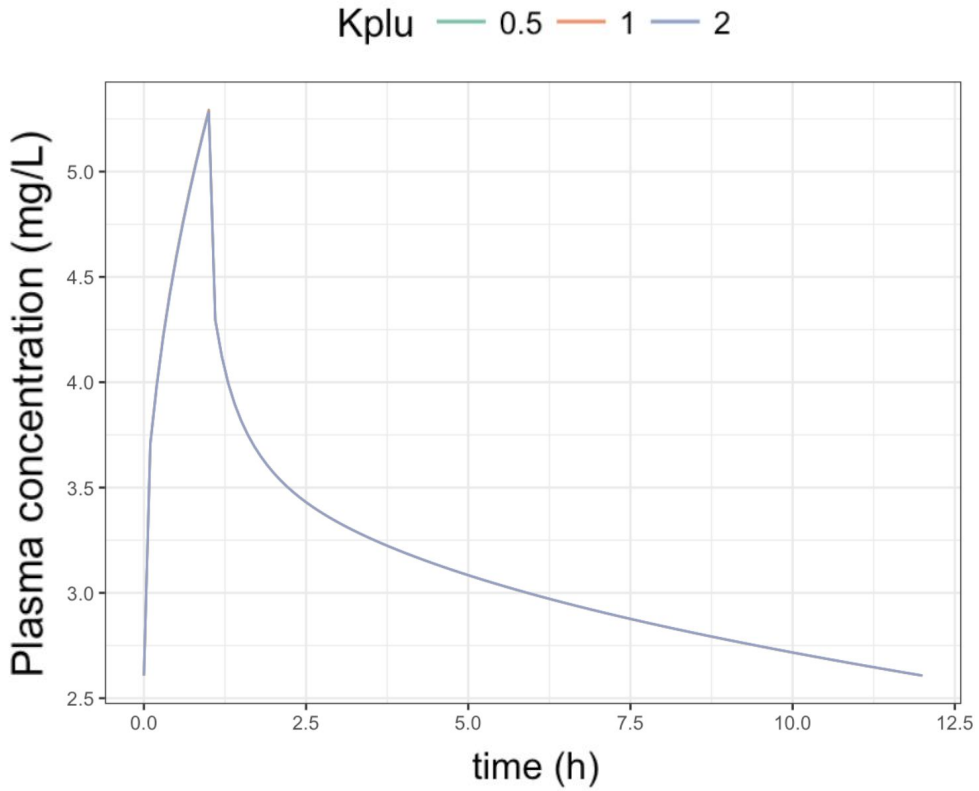
PBPK Application - Voriconazole

Run sensitivity analysis to find most influential parameters:

- **Graphical. Vignette:** https://mrgsolve.github.io/docs/reference/knobs.html





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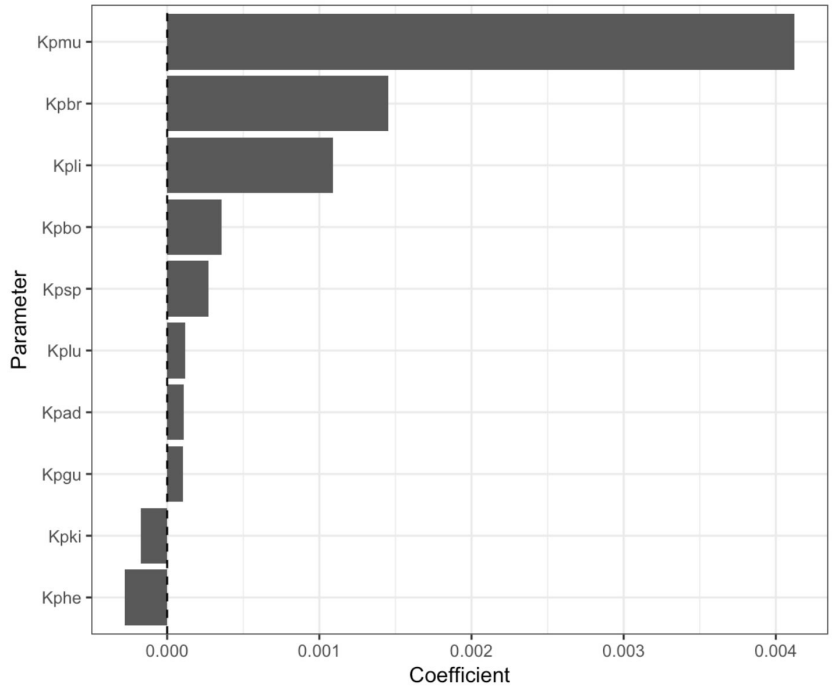
- **Local (FME package https://cran.r-project.org/web/packages/FME/index.html). Vignette: https://github.com/metrumresearchgroup/ub-cdse-2019/blob/master/content/tools_sensitivity_local.md**

$$\frac{\partial y_i}{\partial \Theta_j} \cdot \frac{w_{\Theta_j}}{w_{y_i}}$$



- **Global (sensitivity package https://cran.r-project.org/web/packages/sensitivity/index.html). Vignette: https://github.com/metrumresearchgroup/pbpk-qsp-mrgsolve/blob/master/docs/global_sensitivity_analysis.md**

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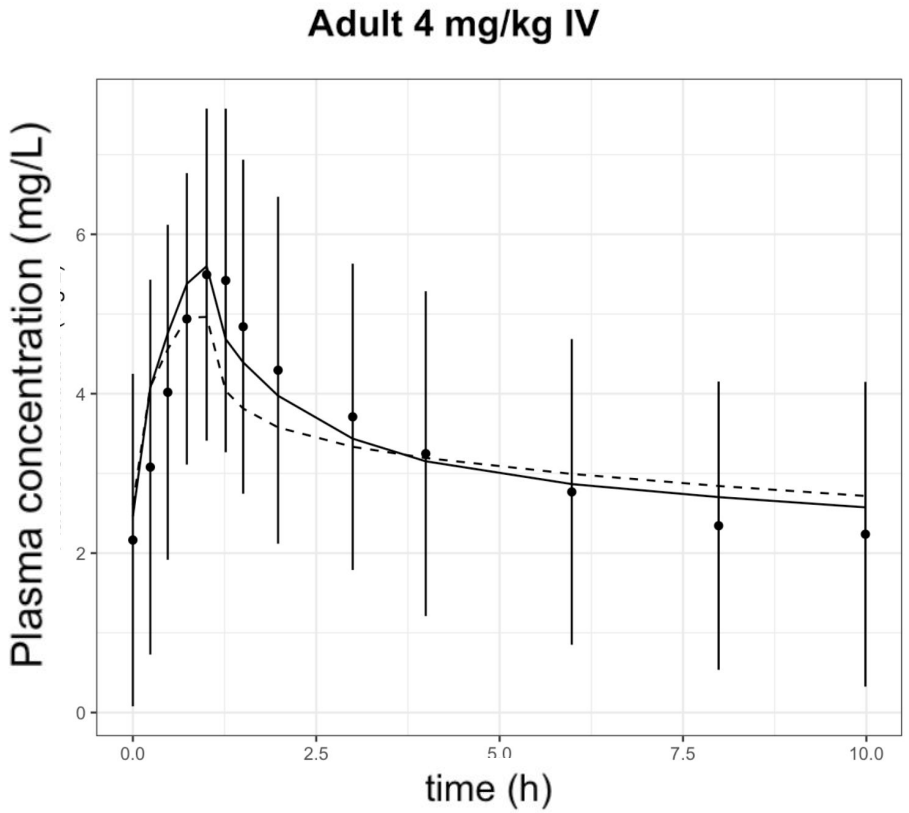
PBPK Application - Voriconazole

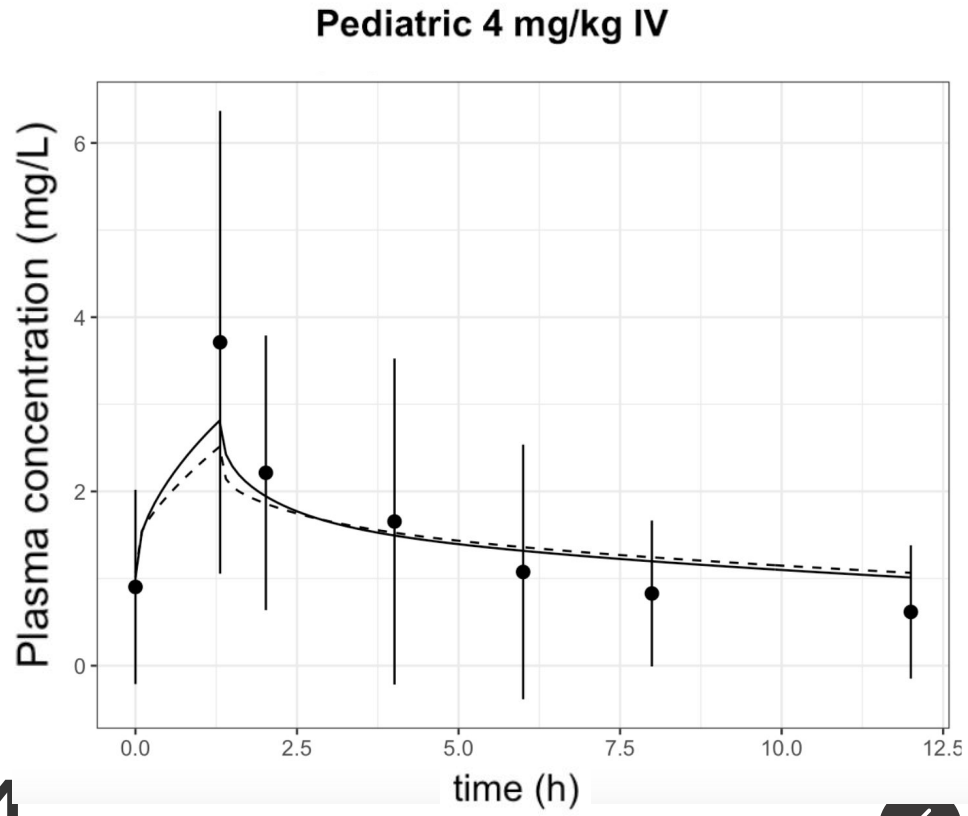
Optimize for most influential parameters

- **minqa** https://cran.r-project.org/web/packages/minqa/index.html
- **nloptr** https://cran.r-project.org/web/packages/nloptr/index.html

Vignette:

https://github.com/metrumresearchgroup/pbpk-qsp-mrgsolve/blob/master/docs/oatp_ddi_optimization.md





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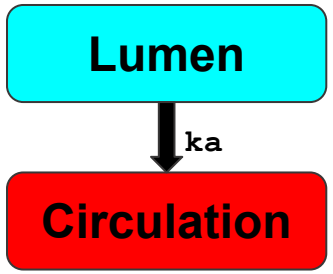
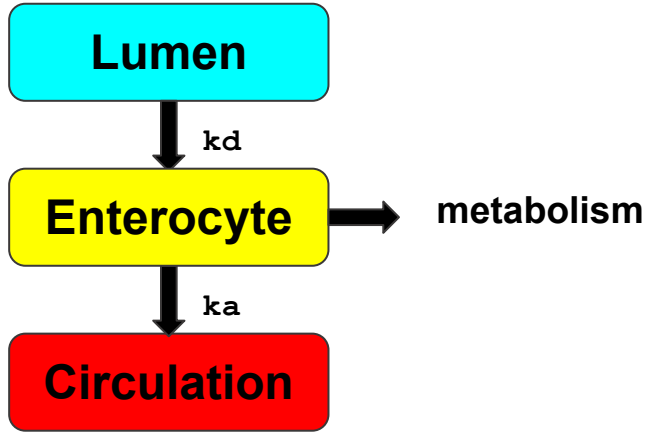
PBPK Application - Voriconazole

Explore alternative mechanisms:

- Intestinal metabolism



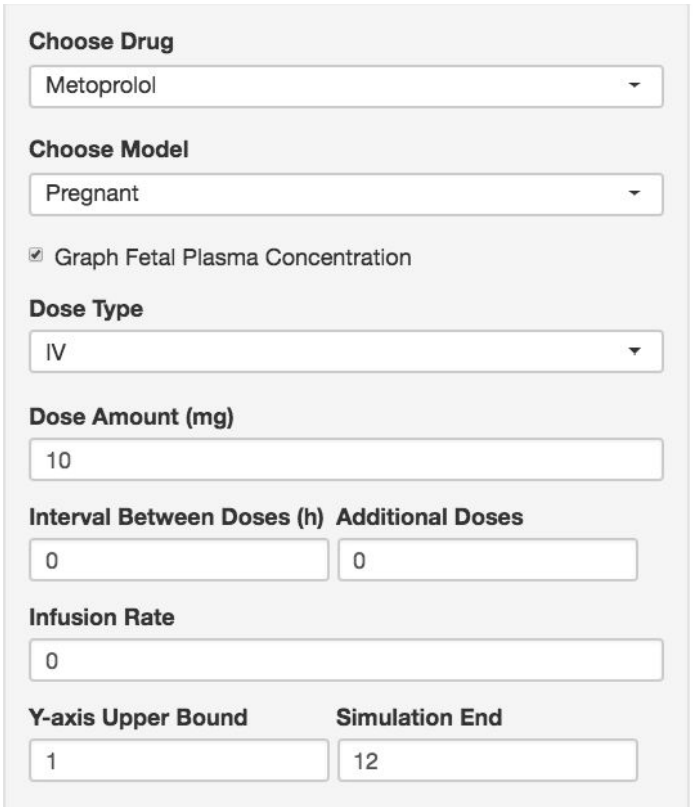


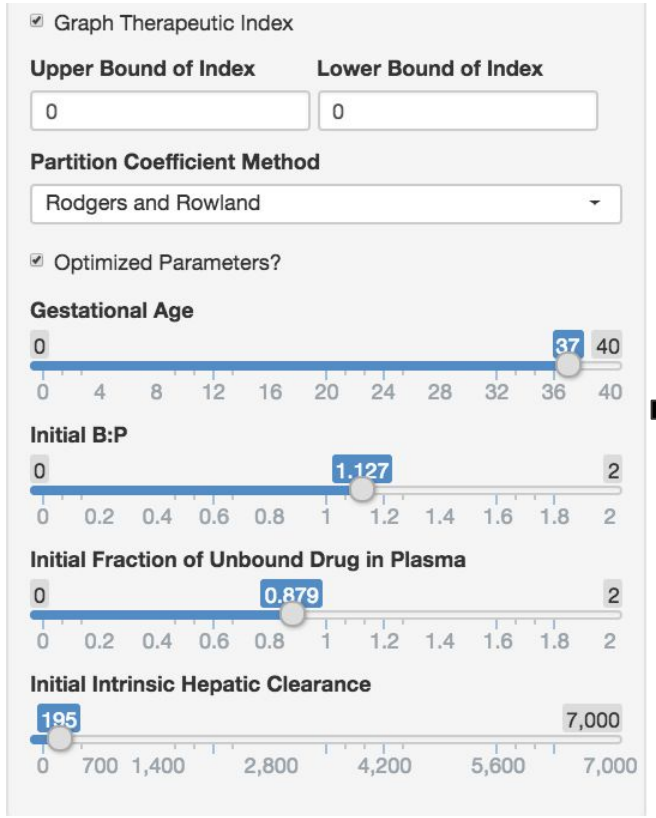

```
dxdt_GUTLUMEN = -ka*GUTLUMEN;

dxdt_GUT = ka*GUTLUMEN + Qgu*(Carterial - Cgut/(Kpgu/BP));
```

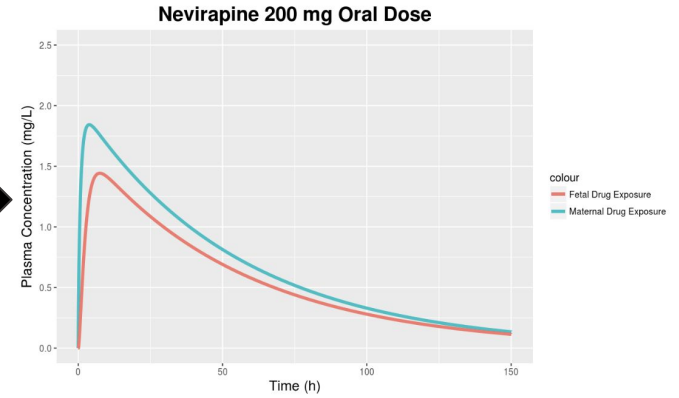
```
dxdt_GUTLUMEN = -kd*GUTLUMEN;

dxdt_GUTWALL = kd*GUTLUMEN - ka*GUTWALL - CL_GUT*GUTWALL;

dxdt_GUT = ka*GUTWALL + Qgu*(Carterial - Cgut/(Kpgu/BP));
```

Build an interactive interface:

https://www.metrumrg.com/publication/prediction-of-maternal-fetal-exposures-of-cyp450-metabolized-drugs-using-physiologic-pharmacokinetic-modeling-implemented-in-r-and-mrgsolve/







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QSP Application - MAPK

Article | Open Access | Published: 02 June 2017

Clinical responses to ERK inhibition in BRAF ^{V600E}–mutant colorectal cancer predicted using a computational model

Daniel C. Kirouac, Gabriele Schaefer, Jocelyn Chan, Mark Merchant, Christine Orr, Shih-Min A. Huang, John Moffat, Lichuan Liu, Kapil Gadkar & Saroja Ramanujan

npj Systems Biology and Applications **3**, Article number: 14 (2017) | Cite this article

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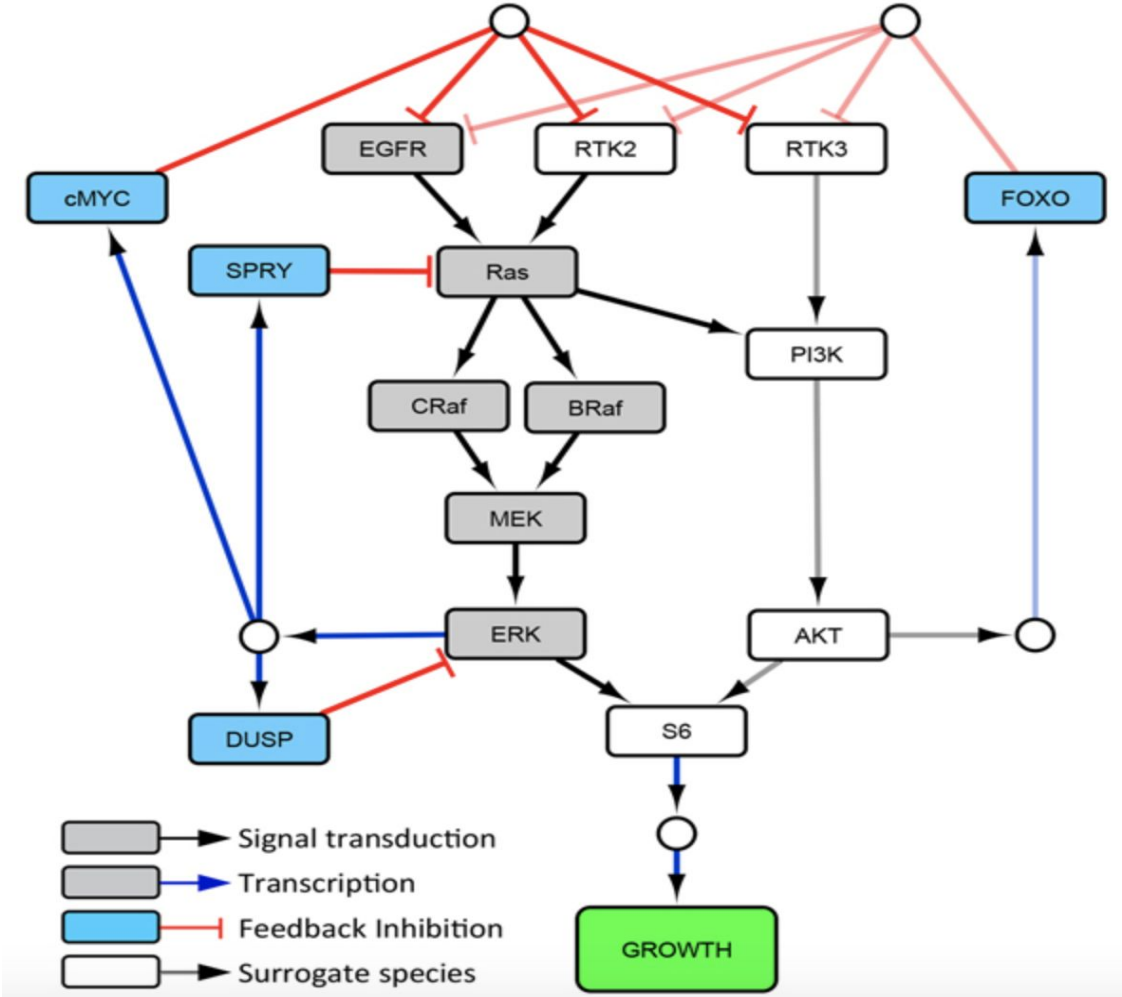
QSP Application - MAPK



Adapted from Kirouac, Daniel C. *et al.*, *npj Systems Biology and Applications* (2017) 14

understand model assumptions, independently reproduce simulations, and evaluate the quality

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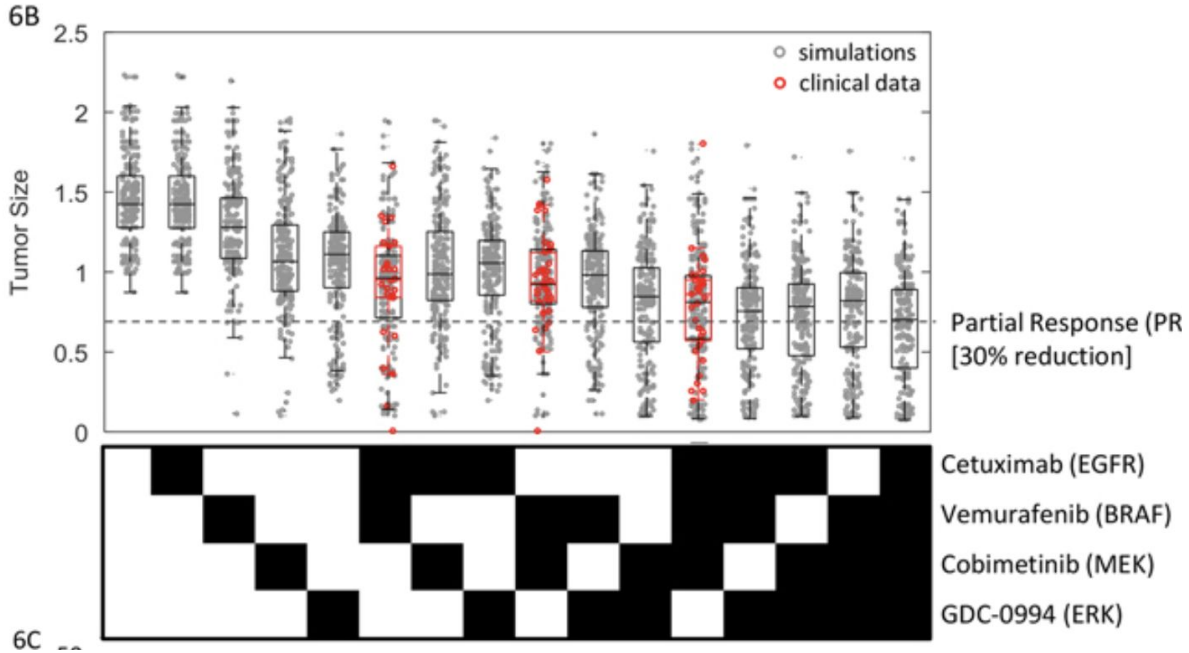
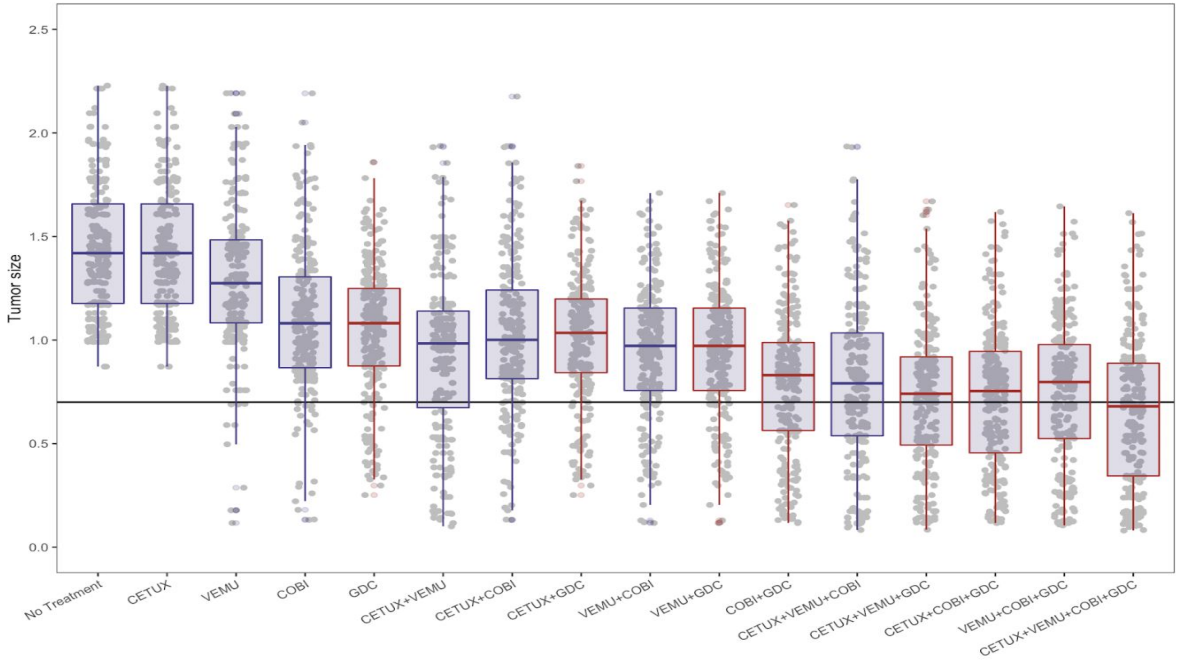
QSP Application - MAPK

- vemurafenib: BRAF inhibitor (selective for V600E mutant)
- cobimetinib: MEK inhibitor
- cetuximab: EGFR antibody
- GDC-0994: ERK inhibitor

```
sims <- mutate(sims, out =
parallel::mclapply(object,sim, Vp = vp, Mod =
mod))
```



Adapted from Kirouac, Daniel C. *et al.*, *npj Systems Biology and Applications* (2017) 14



Adapted from Elmokadem, A. *et al.*, *CPT:PSP* (2019)

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Resources

- NHANES https://www.cdc.gov/nchs/nhanes/index.htm
- ICRP http://www.icrp.org/publication.asp?id=ICRP%20Publication%2089
- Enzyme expression https://www.jstage.jst.go.jp/article/dmpk/21/5/21_5_357/_article
- mrgsolve vignettes https://mrgsolve.github.io/vignettes/
- Open Systems Pharmacology (PK-Sim®/MoBi®) http://www.systems-biology.com/products/pk-sim.html
- mrgsolve tutorial https://github.com/metrumresearchgroup/cptpsp-tutorial-2019

Acknowledgements

- Kyle T Baron
- Eric Jordie
- Mike Heathman
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  - Marc Gastonguay
  - Bill Knebel
  - Matthew Riggs
  - Michelle Johnson
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Thank You

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