R/Medicine September 8th, 2018

Development of an Open and General Physiologically-Based Pharmacokinetic Model to Predict Maternal-Fetal Exposures for Drugs Metabolized by CYP Isoenzymes

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METRUM

RESEARCH GROUP

Clinical Pharmacology in Pregnancy

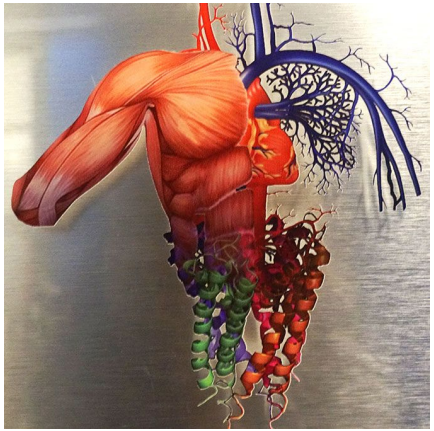
- Several unaddressed questions
  - Drug development
  - Clinical therapeutics

https://www.medicalnewstoday.com/articles/317397.php

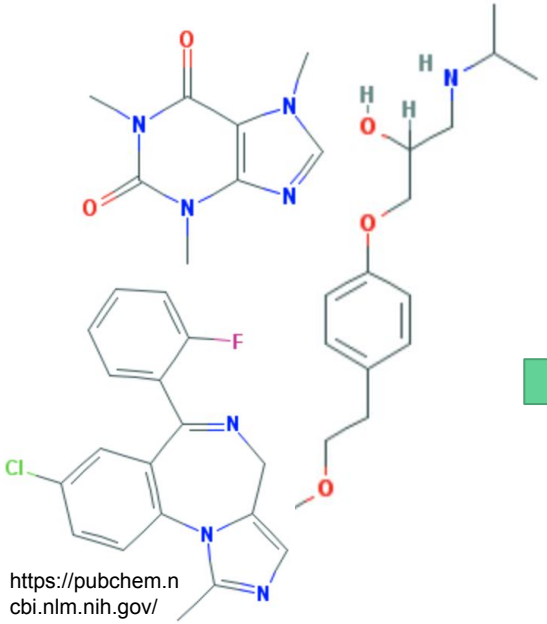
- Orphan population
- Limited data available
- Ethical issues
- Logistically difficult to study

Judgement Call in the Face of Large Uncertainty

Possible Solution



http://ucdmc.ucdavis.edu/publish/news/giving/11772

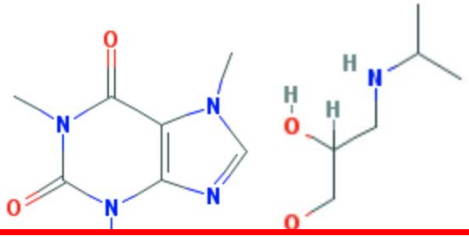


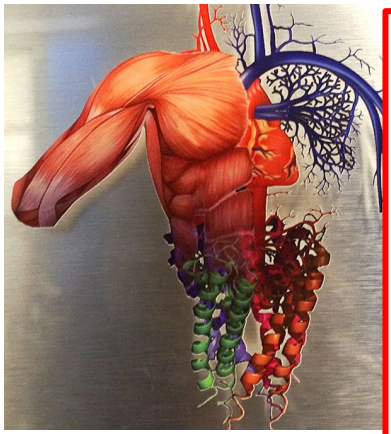
https://pubchem.ncbi.nlm.nih.gov/

https://www.kisspng.com/png-pregnancy-woman-mother-clip-art-1410225/

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

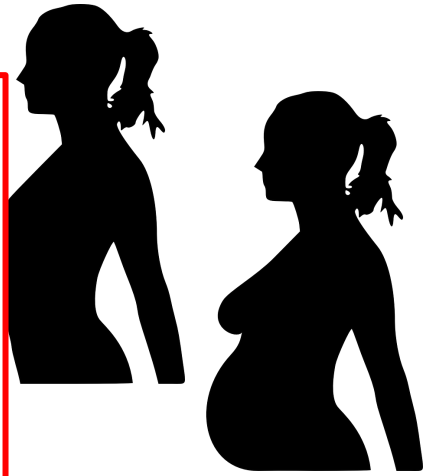
Possible Solution





This Approach Allows Us To:

- Integrate knowledge across multiple sources for decision-making in clinical therapeutics and drug development
- Explore answers to questions that are not directly addressed in clinical studies



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

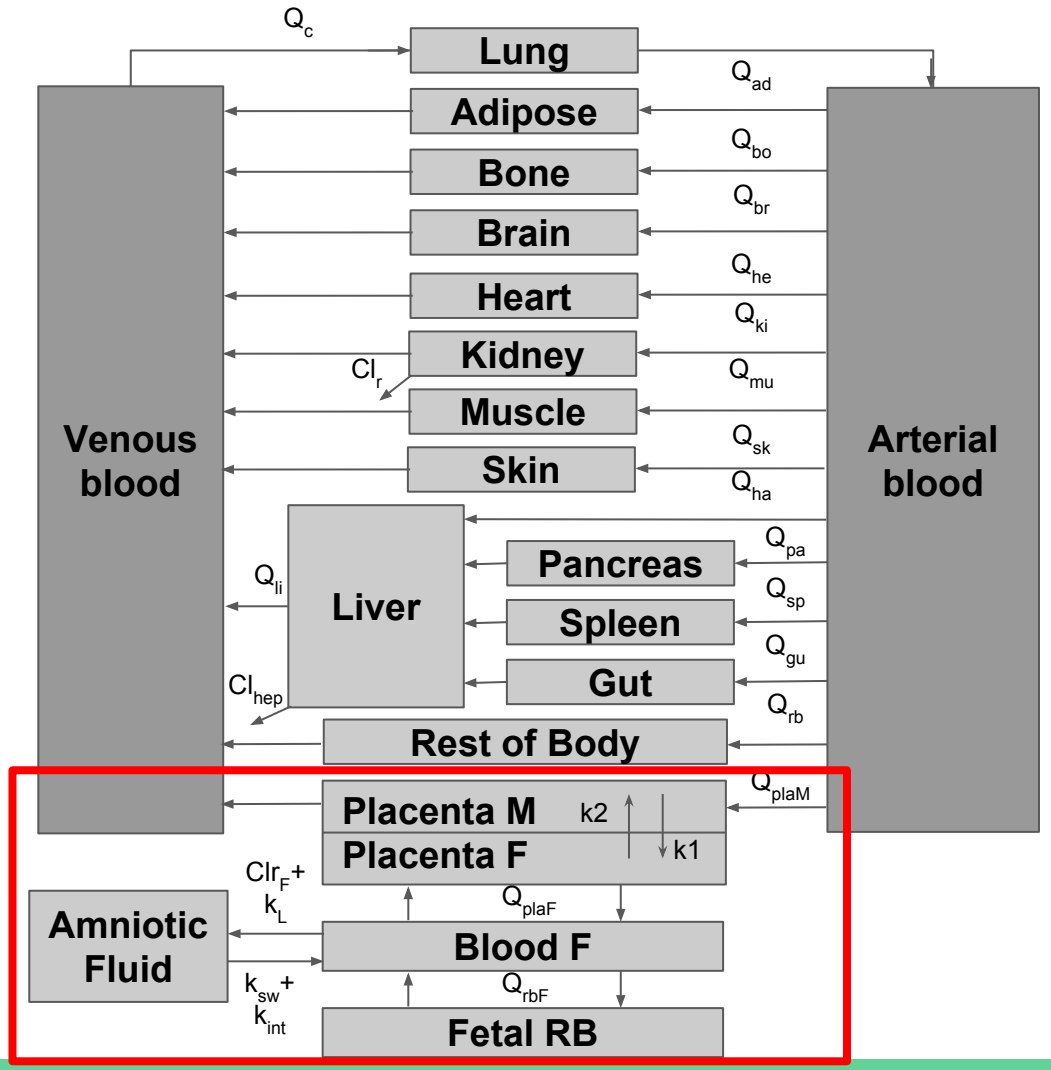
General Physiological Model Structure

Non-Pregnant:

- 15 Compartments
- 17 Differential Equations

Pregnant:

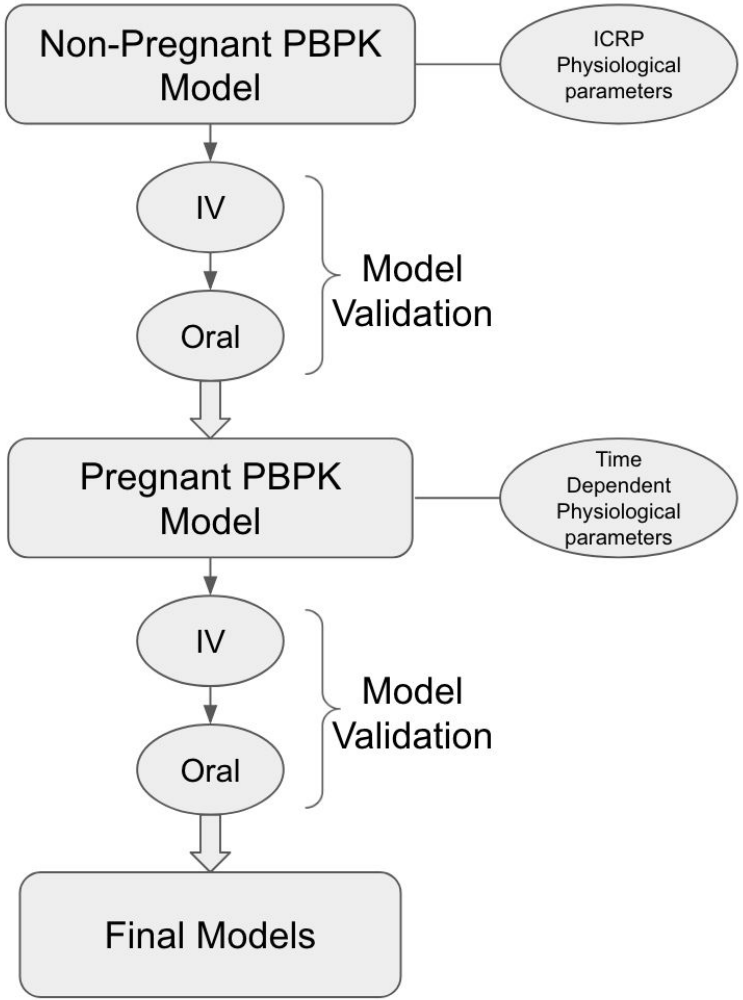
- 20 Compartments
- 22 Differential Equations
- 5 Compartments for Fetoplacental Unit



Modeling Workflow

Isoenzyme	Substrate	Validation Data
CYP3A4	Midazolam	Gaohua et al.
CYP2D6	Metoprolol	Gaohua et al.
CYP1A2	Caffeine	Gaohua et al.
CYP3A4, CYP2D6, CYP2B6	Nevirapine	Mendes et al.

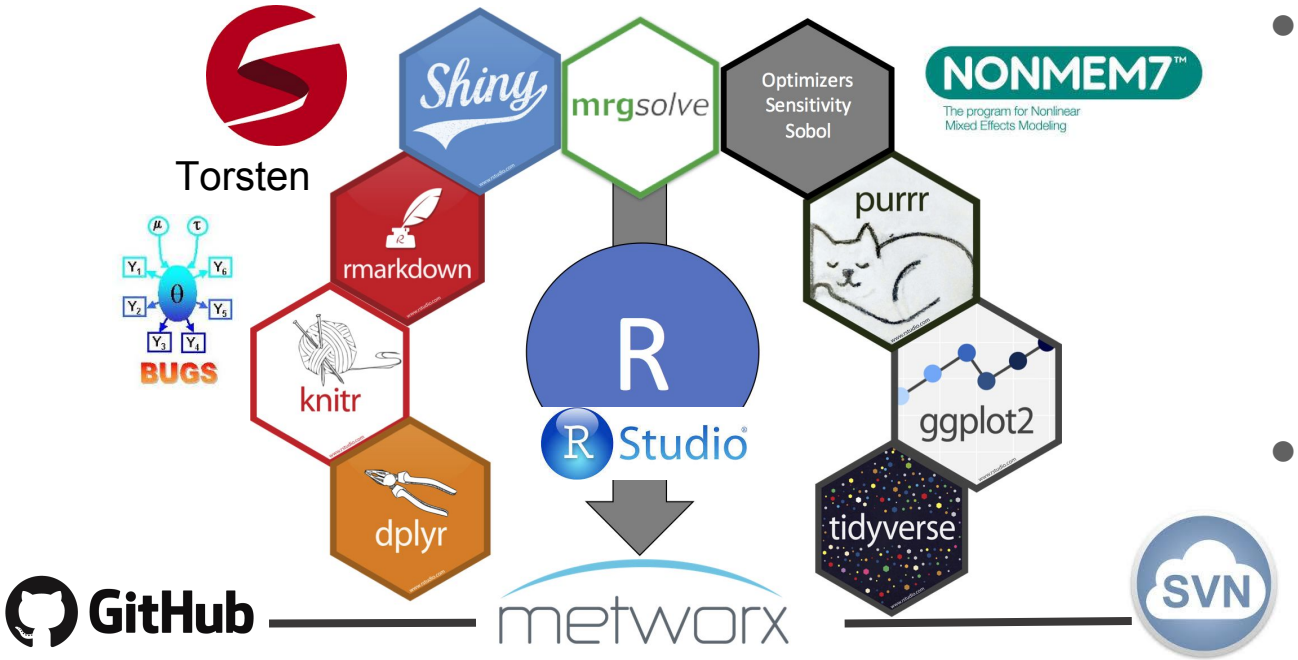
- Other drugs tested: Nifedipine, Artemether, Indinavir, Buprenorphine, Codeine, Methadone



Gaohua L, Abduljalil K, Jamei M, Johnson TN, Rostami-Hodjegan A. A pregnancy physiologically based pharmacokinetic (p-PBPK) model for disposition of drugs metabolized by CYP1A2, CYP2D6 and CYP3A4. Br J Clin Pharmacol. 2012;74: 873–885.

De Sousa Mendes M, Lui G, Zheng Y, Pressiat C, Hirt D, Valade E, et al. A Physiologically-Based Pharmacokinetic Model to Predict Human Fetal Exposure for a Drug Metabolized by Several CYP450 Pathways. Clin Pharmacokinet. 2017;56: 537–550.

Computation Platform



- ODE model in R using *mrgsolve*
  - Rcpp and BH packages
  - Boost [c++ library]
  - https://mrgsolve.github.io/
  - https://cran.r-project.org/web/packages/mrgsolve/index.html
- Maximize utility of the R ecosystem for data manipulation, graphics, interactive visualization

Choose Drug

Metoprolol

Choose Model

Pregnant

☑ Graph Fetal Plasma Concentration

Dose Type

IV

Dose Amount (mg)

10

Interval Between Doses (h) **Additional Doses**

0 0

Infusion Rate

0

Y-axis Upper Bound **Simulation End**

1 12

☑ Graph Therapeutic Index

Upper Bound of Index **Lower Bound of Index**

0 0

Partition Coefficient Method

Rodgers and Rowland

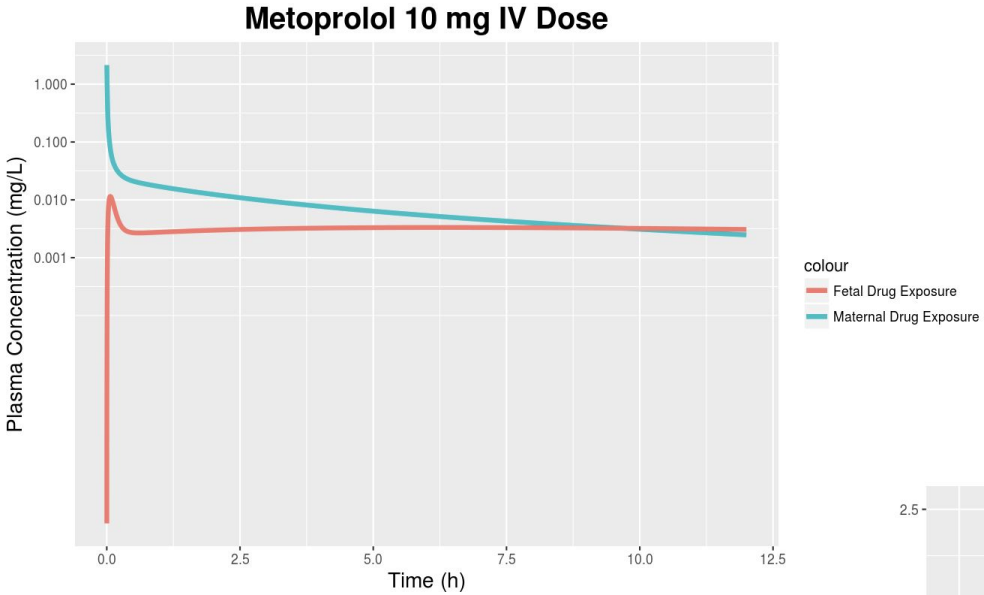
☑ Optimized Parameters?

Gestational Age

Initial B:P

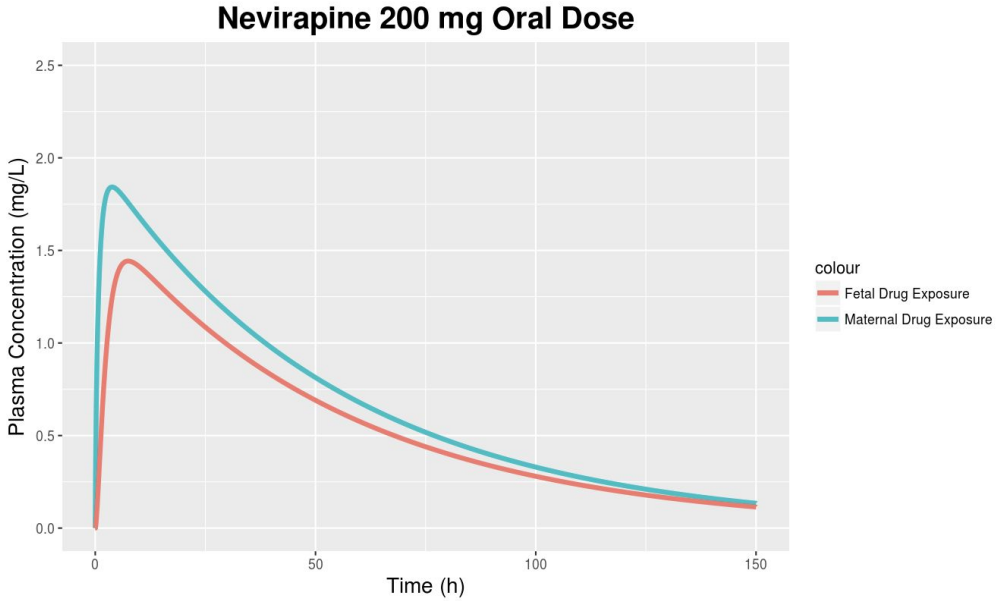
Initial Fraction of Unbound Drug in Plasma

Initial Intrinsic Hepatic Clearance



Useful in healthcare setting and drug development

- Easy for non-technical users
- Interactive plots
- Real time simulations with Shiny and cloud computing



Why R?

- Easy integration with cloud computing and parallelization
  - Model is computationally intensive
  - Interactive simulation with Shiny
- Facilitates open science
  - Accessible tools and code
  - Easily extensible
  - Traceability/reproducible
- Interoperability with other open science projects

Interoperability of Open Models

- R/Pharma Presentation
- Lightning Talk - 3.32 The Use of R in the Development of Physiological Model for Healthy Growth