R/Pharma
August 21st-23rd, 2019

Prediction of maternal-fetal exposures of CYP450-metabolized drugs using physiologic pharmacokinetic modeling implemented in R and *mrgsolve*

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Clinical Pharmacology in Pregnancy

- Women use an average of 2-5 medications throughout pregnancy
- Several unaddressed questions
  - Drug development
  - Clinical therapeutics
- Orphan Population
  - Limited data available

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

Patil, Journal of Midwifery & Women's Health, 2017

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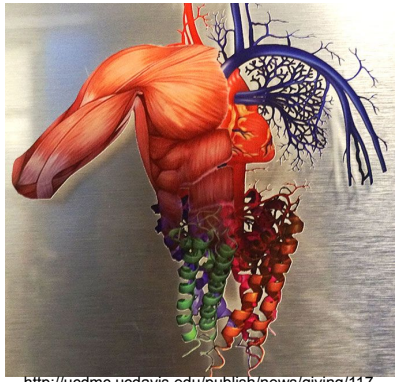
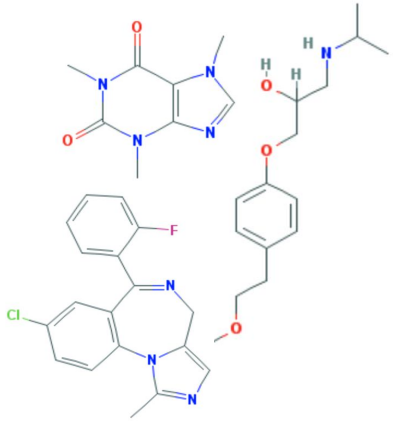
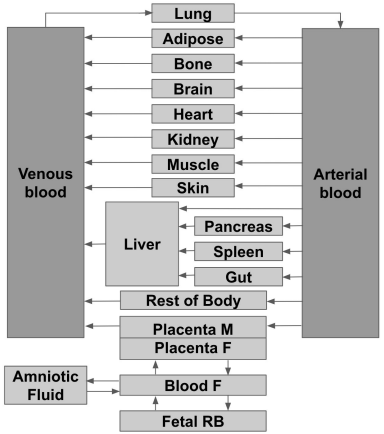
Possible Solution



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





https://www.pngkey.com/download/u2e6t4w7o0q8q8u2_cartoon-pregnant-woman-pregnant-clip-art/

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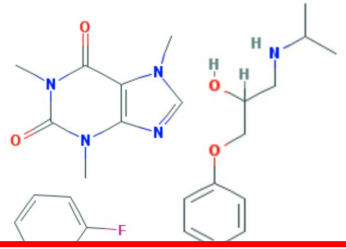

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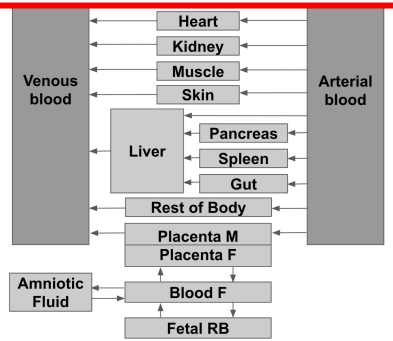
-woman-pregnant-clip-art/

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



Workflow

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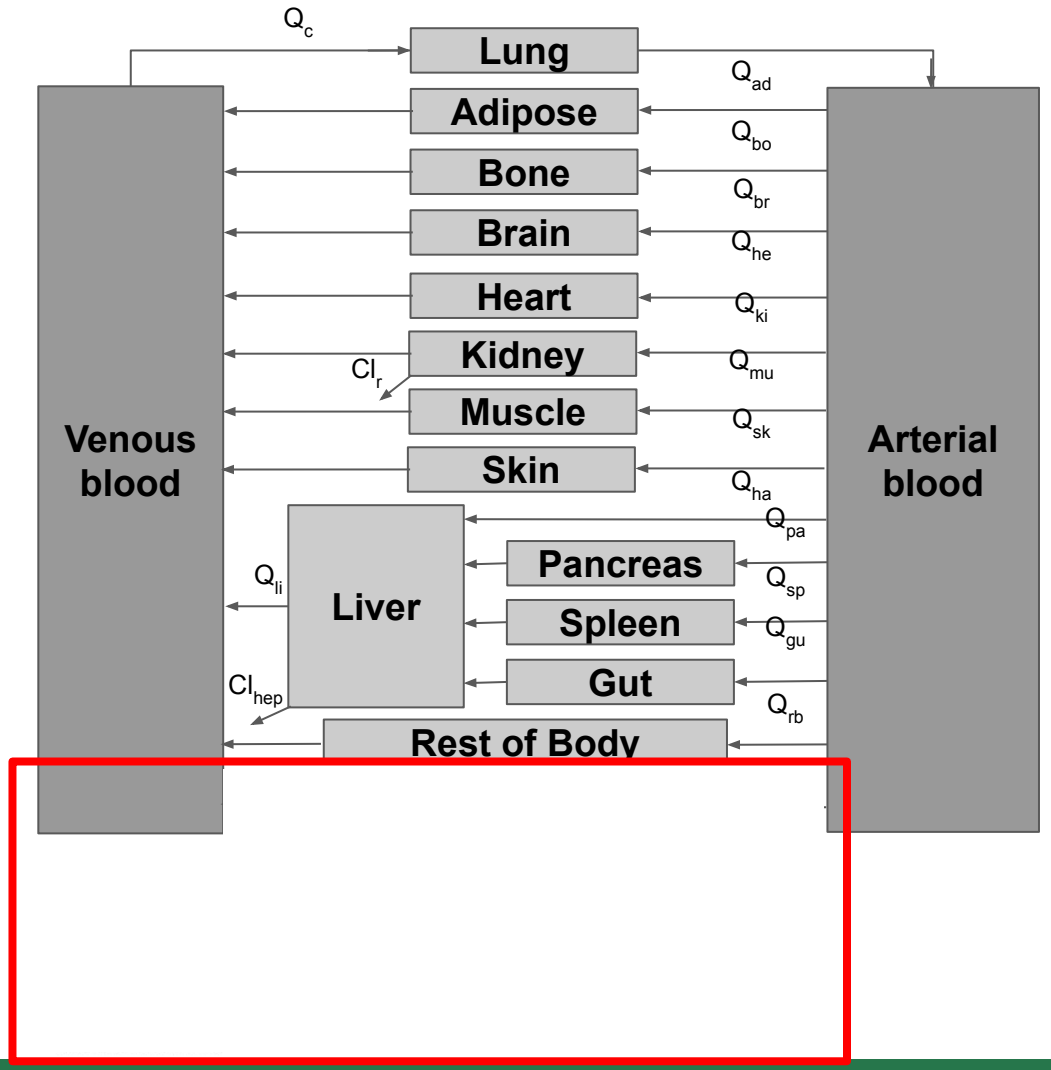
Model Structure

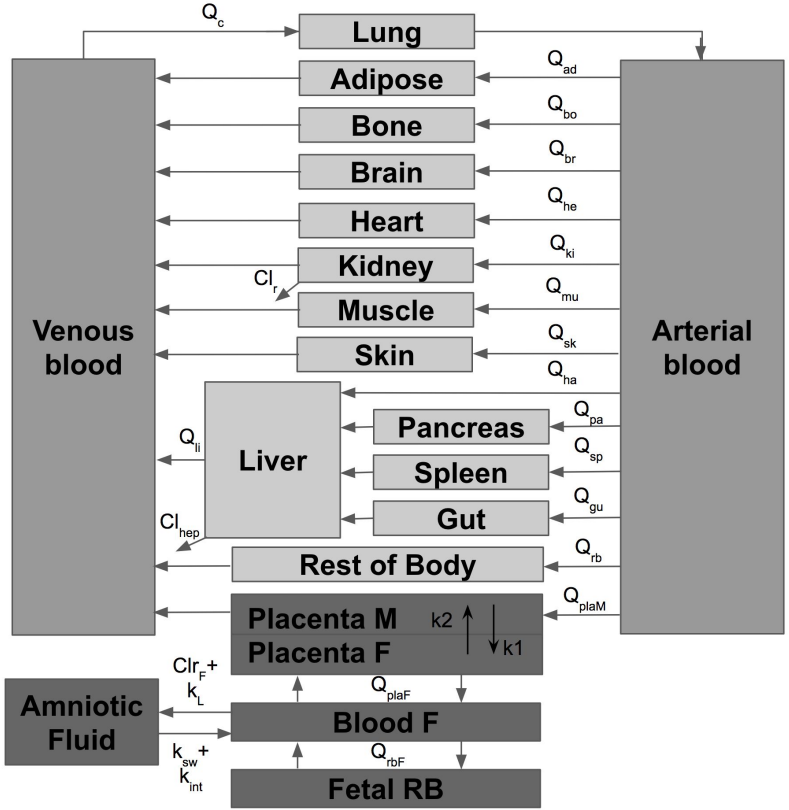
Female Physiology:

- 15 Compartments
- 17 Differential Equations



Mendes et al., Clinical Pharmacokinetics, 2016
Gaohua et al., British journal of Clinical Pharmacology, 2012

System of Ordinary Differential Equations



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

Where Q_T represents tissue blood flow in l/h, C_T is tissue concentration in mg, Kp_T is the partition coefficient of the tissue, and B:P is the blood to plasma partition coefficient.

$$Qc = 365.4 \cdot e^{-e^{-0.352 \cdot log(FA)+1.36}} + 354$$

$$CYP1A2 = 1 + 0.0227 \cdot GA - 0.00035 \cdot GA^2$$

Dallman et al., Clinical Pharmacokinetics, 2017
Gaohua et al., British journal of Clinical Pharmacology, 2012
Valentin J., Annals of the ICRP, 2002

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Implementation in R

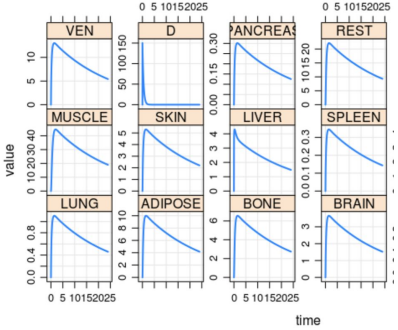
PBPK Model Code

MFPBPKmodel.cpp

```
//Differential Equations
dxdt_ADIPOSE = Qad*(Carterial - Cadipose/(Kpad/BPP));
dxdt_BRAIN = Qbr*(Carterial - Cbrain/(Kpbr/BPP));
dxdt_HEART = Qhe*(Carterial - Cheart/(Kphe/BPP));
dxdt_KIDNEY = Qki*(Carterial - Ckidney/(Kpki/BPP))- Ckidneyfree * Cl_r;
dxdt_GUT = Qgu*(Carterial - Cgut/(Kpgu/BPP)) + Ka*D*fg*fa;
```

R
Rcpp
C++
DLSODA (ODEPACK)

mrgsolve



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Simulate Using *mrgsolve*

```
mod <- mread("../model/MFPBPKmodel.cpp")

Pars_caf <- chooseDrug(drug = "caffeine", method = "PT", timeDep = TRUE)

mod %>%

  param(c(Pars_caf, GA = 36)) %>%

  ev(amt = 150, cmt = "D", ii = 12) %>%

  mrgsim(end = 24, delta = 0.001) %>%

  plot()
```

1. Load a model
2. Choose parameters
3. Select intervention
4. Simulate
5. Post-process (plot,summarize,...)

Kyle T Baron (2018). mrgsolve: Simulate from ODE-Based Population PK/PD and Systems Pharmacology Models. R package version 0.8.12. https://CRAN.R-project.org/package=mrgsolve

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https://mrgsolve.github.io/

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Shiny App

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 (l/h)
0

Y-axis Upper Bound | **Simulation End**
1 | 12

Partition Coefficient Method
Rodgers and Rowland

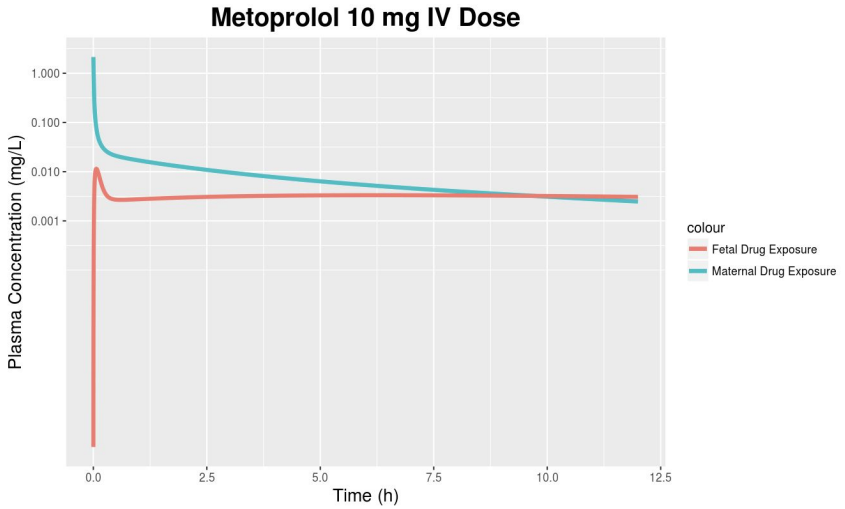
☑ Optimized Parameters?

Gestational Age (weeks)
0 — 37 — 40
0 4 8 12 16 20 24 28 32 36 40

Initial B:P
0 — 1.127 — 2
0 0.2 0.4 0.6 0.8 1 1.2 1.4 1.6 1.8 2

Initial Fraction of Unbound Drug in Plasma
0 — 0.879 — 2
0 0.2 0.4 0.6 0.8 1 1.2 1.4 1.6 1.8 2

Initial Intrinsic Hepatic Clearance (l/h)
195 — 7,000
0 700 1,400 2,100 2,800 3,500 4,200 4,900 5,600 6,300 7,000



Winston Chang, Joe Cheng, JJ Allaire, Yihui Xie and Jonathan McPherson (2017). shiny: Web Application Framework for R. R package version 1.0.0. https://CRAN.R-project.org/package=shiny

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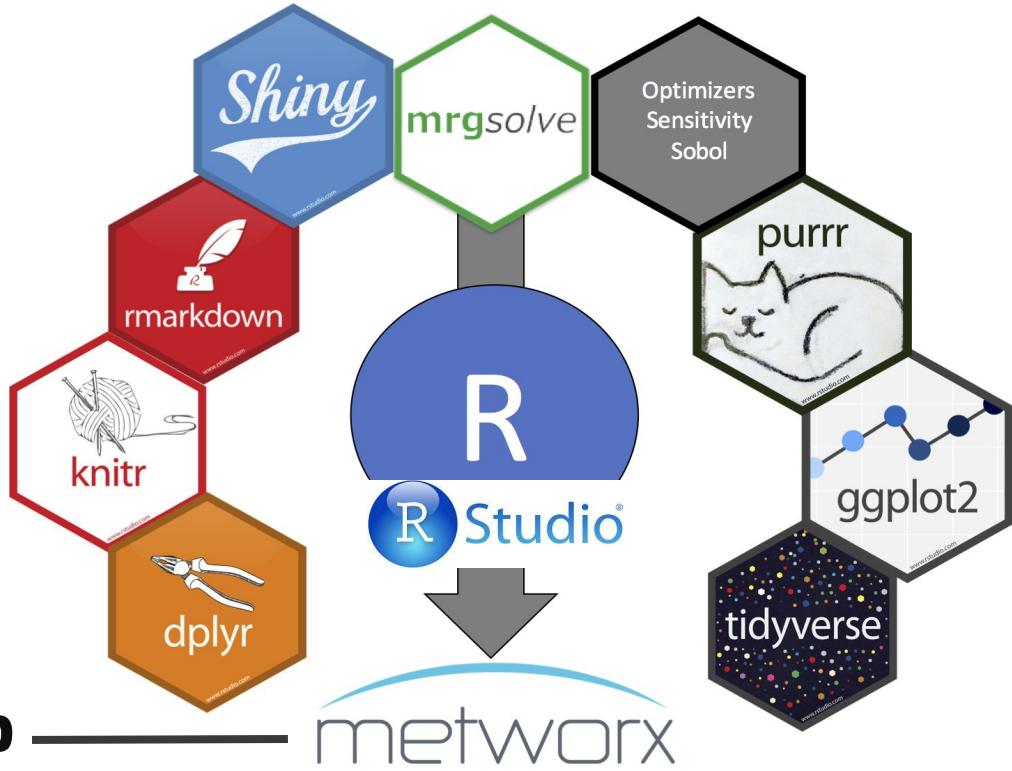
Why R instead of Commercial PBPK Software?

- Customizable physiologic model
- Access to R ecosystem
- Optimized for performance - cloud computing and parallelization
- Full transparency facilitates open science
- Interoperability with other open science projects



GitHub

metworx

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