

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

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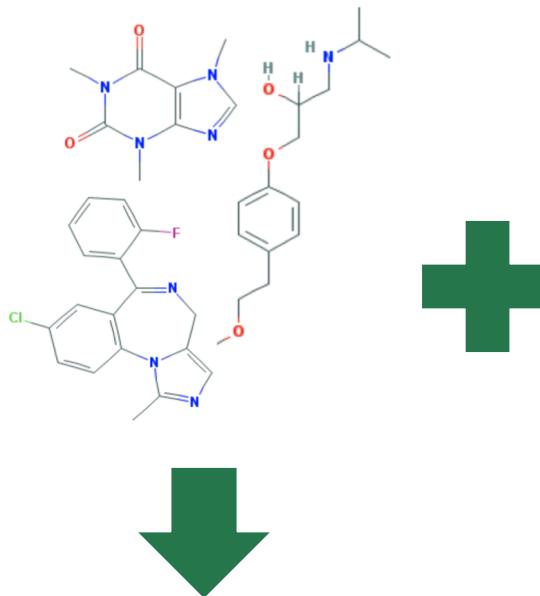
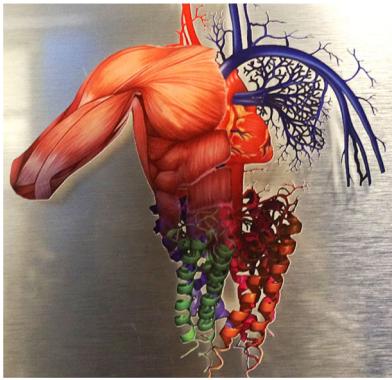
Clinical Pharmacology in Pregnancy

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



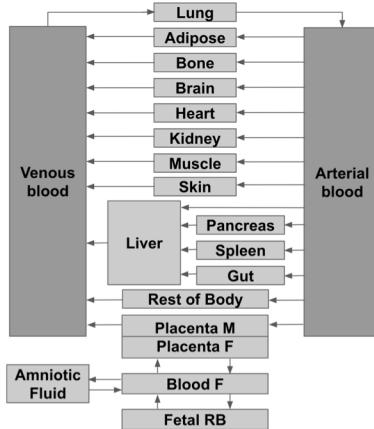
<https://www.medicalnewstoday.com/articles/317397.php>

Possible Solution



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

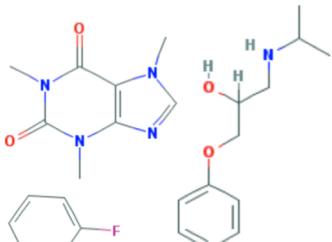
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Possible Solution



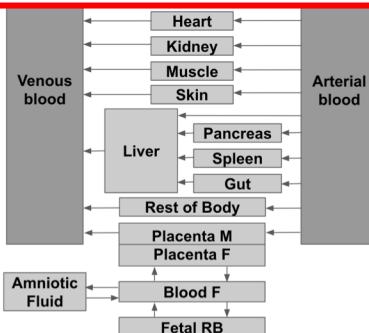
<http://ucdmc.ucdavis.edu/publish/news/giving/11772>



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

http://openclipart.org/image/240px/svg_to_png/102672/pregnant-woman-clip-art.png



Workflow

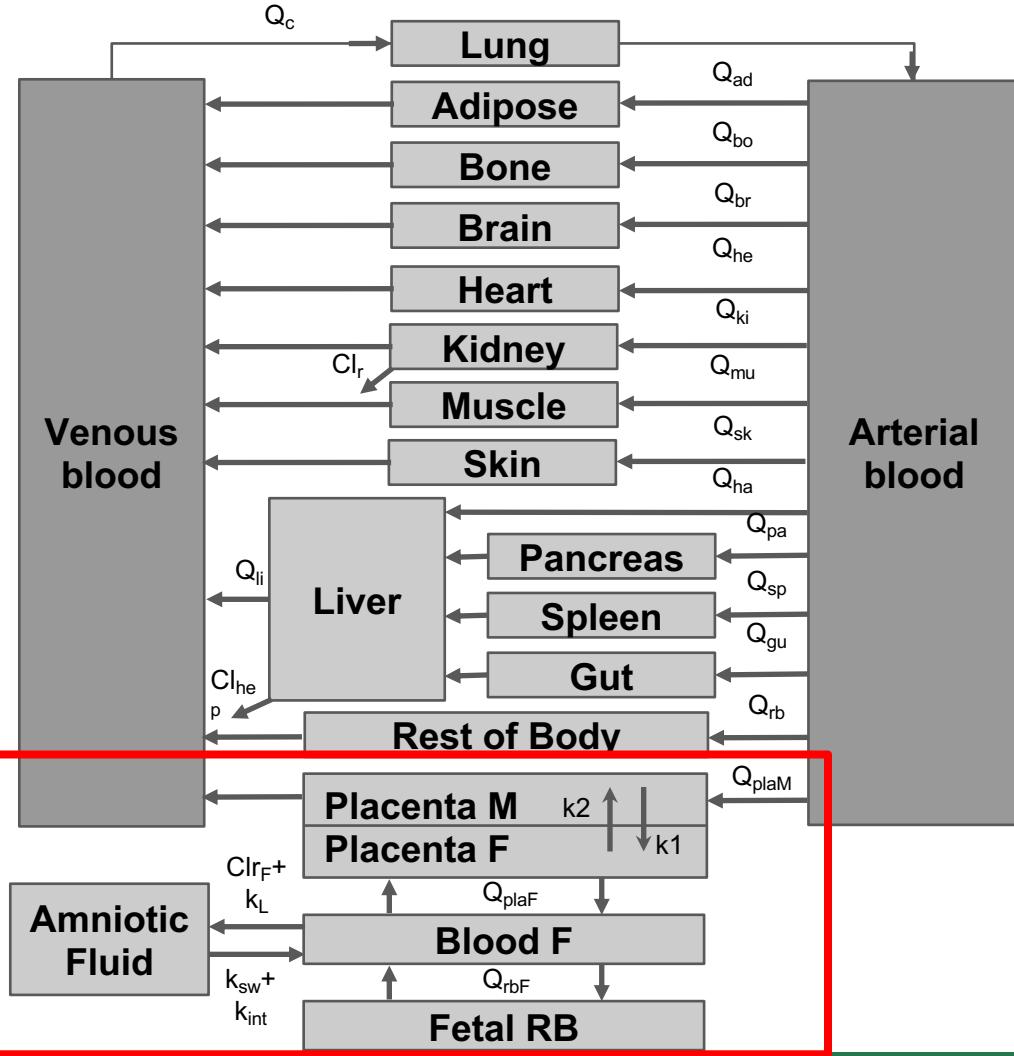
Model Structure

Female Physiology:

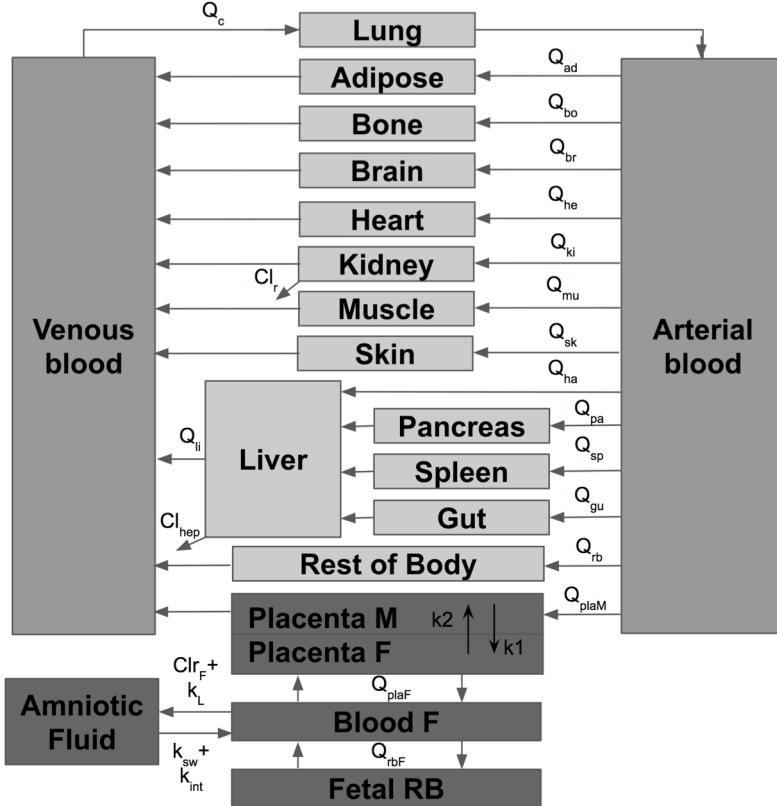
- 15 Compartments
- 17 Differential Equations

In Pregnancy:

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



System of Ordinary Differential Equations



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

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.

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

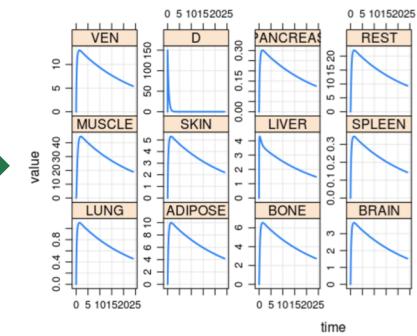
$$CYP1A2 = 1 + 0.0227 \cdot GA - 0.00035 \cdot GA^2$$

Implementation in R



PBPK Model Code *MFPBPKmodel.cpp*

```
//Differential Equations
dxdt_ADIPPOSE = 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;
```



Simulate Using *mrgsolve*



```
mod <- mread("../model/MFPBPModel.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`, ...)

Shiny App



Choose Drug

Choose Model

Graph Fetal Plasma Concentration

Dose Type

Dose Amount (mg)

Interval Between Doses (h) Additional Doses

Infusion Rate (l/h)

Y-axis Upper Bound Simulation End

Partition Coefficient Method

Optimized Parameters?

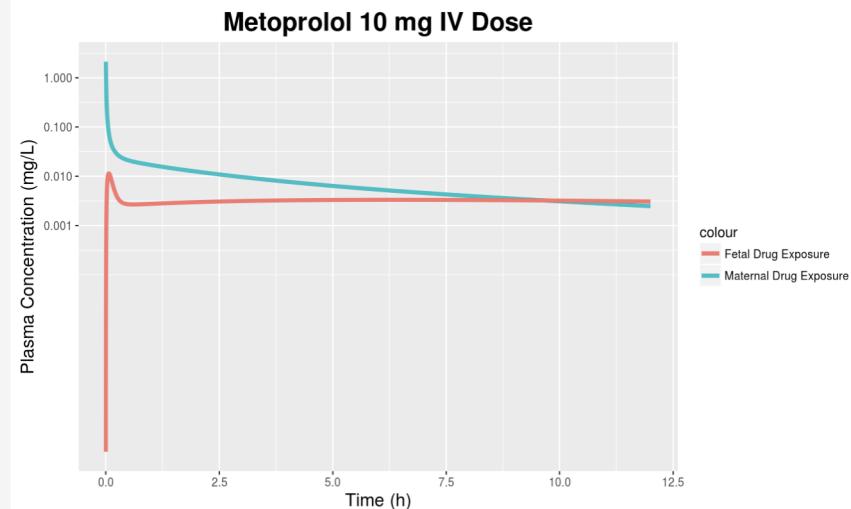
Gestational Age (weeks)

Initial B:P

Initial Fraction of Unbound Drug in Plasma

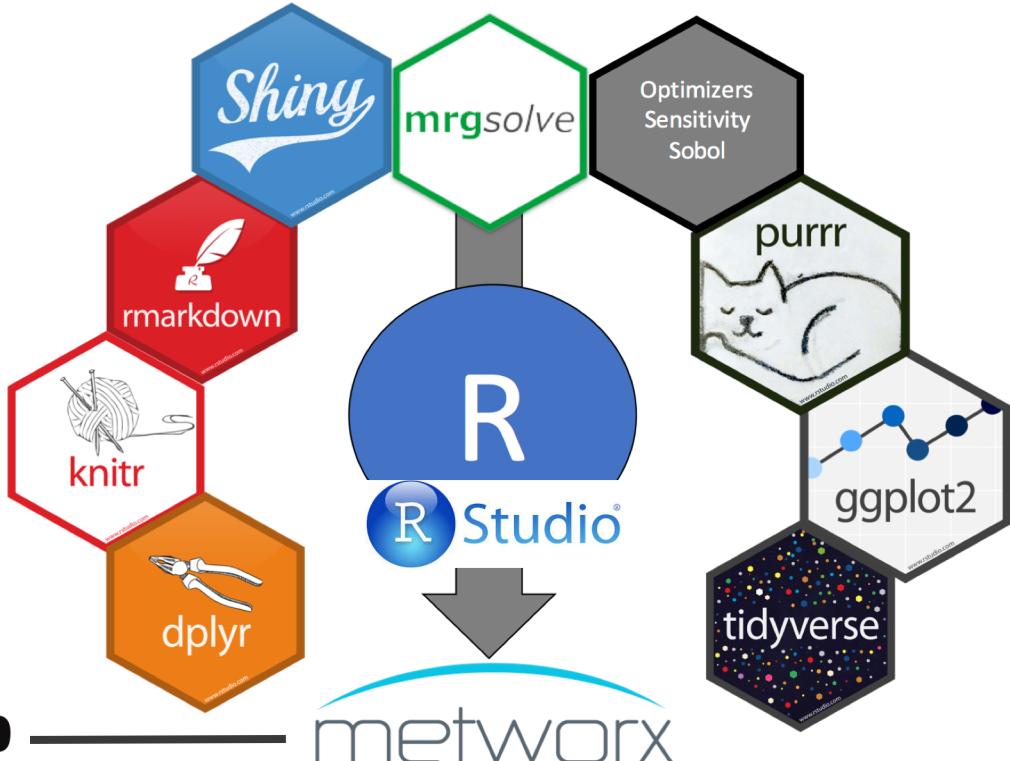
Initial Intrinsic Hepatic Clearance (l/h)

This section contains five sliders for input parameters: Gestational Age (weeks), Initial B:P, Initial Fraction of Unbound Drug in Plasma, and Initial Intrinsic Hepatic Clearance (l/h). Each slider has a numerical value displayed in a blue box above it.



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**

Acknowledgements

- Ahmed Elmokadem, PhD
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Coming Soon ...