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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Clinical Pharmacology in Pregnancy

- Several unaddressed questions
  - Drug development
  - Clinical therapeutics

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

Judgement Call in the Face of Large Uncertainty

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

\[
\frac{dA_T}{dt} = Q_T \cdot (C_{art} - \frac{C_T}{K_{PT \cdot B:P}})
\]
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

\[
\frac{dA_T}{dt} = QT \cdot \left( C_{art} - \frac{C_T}{K_{PT}} \right)
\]
General Physiological Model Structure

Non-Pregnant:

- 15 Compartments
- 17 Differential Equations

Pregnant:

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

<table>
<thead>
<tr>
<th>Isoenzyme</th>
<th>Substrate</th>
<th>Validation Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4</td>
<td>Midazolam</td>
<td>Gaohua et al.</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Metoprolol</td>
<td>Gaohua et al.</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>Caffeine</td>
<td>Gaohua et al.</td>
</tr>
<tr>
<td>CYP3A4, CYP2D6, CYP2B6</td>
<td>Nevirapine</td>
<td>Mendes et al.</td>
</tr>
</tbody>
</table>

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


Computation Platform

- ODE model in R using `mrgsolve`
  - Rcpp and BH packages
  - Boost [c++ library]
  - [https://mrgsolve.github.io/](https://mrgsolve.github.io/)
  - [https://cran.r-project.org/web/packages/mrgsolve/index.html](https://cran.r-project.org/web/packages/mrgsolve/index.html)

- Maximize utility of the R ecosystem for data manipulation, graphics, interactive visualization
- 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

GitHub

RStudio

Shiny

mrgsolve

Optimizers Sensitivity Sobol

purrr

rmarkdown

knitr

dplyr

tidyverse

ggplot2

metworx
Interoperability of Open Models

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