Physiologically-based pharmacokinetic pediatric skin model

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Mechanistic modeling of dermal absorption

- Mechanistic models try to represent a real physical entity:
  - Skin Structure: includes different skin layers (stratum corneum, epidermis, dermis)
  - Skin Parameterization: includes the depth of each of these layers
- Movement of a compound through the structure is defined by compound-specific properties (e.g. lipophilicity, molecular weight…)
- Can translate model predictions to risk assessments to address the following:
  - Exploratory studies for formulation development
  - Extrapolation to groups not included in clinical trials (e.g. children)

Degree of chemical absorption through skin is context-dependent

- Absorption depends on
  - **Physicochemical** properties of compound: log P, MW, pKa
  - **Skin-specific properties**: hydration, thickness
  - Formulation: volatility, pH, solubility w.r.t. API
  - Application protocol: leave-on, vs. wash-off, occlusion.

- Skin absorption is commonly assessed using in vitro skin penetration (IVPT) experimental set-ups under varying contexts

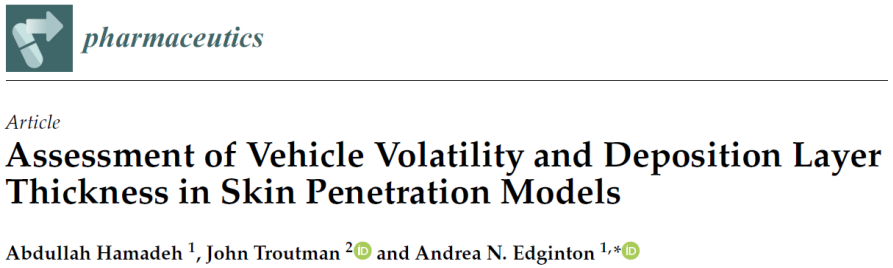
Today's workflow – the big picture

OBJECTIVE: Develop and evaluate a mechanistic skin model to predict absorption in children

1. Build a quantitative maturation model that quantifies evolution of skin-specific properties with age
2. Learn compound-specific parameters of the model using the adult model and experimental data
3. Use maturation model to adjust trained adult model to predict dermal absorption in children

Workflows for learning and extrapolation of dermal absorption models

- Learning formulation-specific properties to predict impact of excipients on absorption



- Learning compound-specific quantities from IVPT using Bayesian methods with extrapolation to the in vivo context where compound-specific parameters are assumed to not change

- **TODAY:** Develop maturation model to predict impact of age on dermal absorption

Open Systems Pharmacology Suite

PK-Sim

- Whole-body PBPK modeling and optimization software
- Simulates whole body responses at both the individual and population level

MoBi

- Software for building custom compartmental models that can be appended to PK-Sim whole-body models

OSPSuite-R

- R interface to PK-Sim and MoBi models

http://www.open-systems-pharmacology.org/

OPEN SYSTEMS PHARMACOLOGY

Model of skin penetration

Contents lists available at SciVerse ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Design and performance of a spreadsheet-based model for estimating bioavailability of chemicals from dermal exposure ☆

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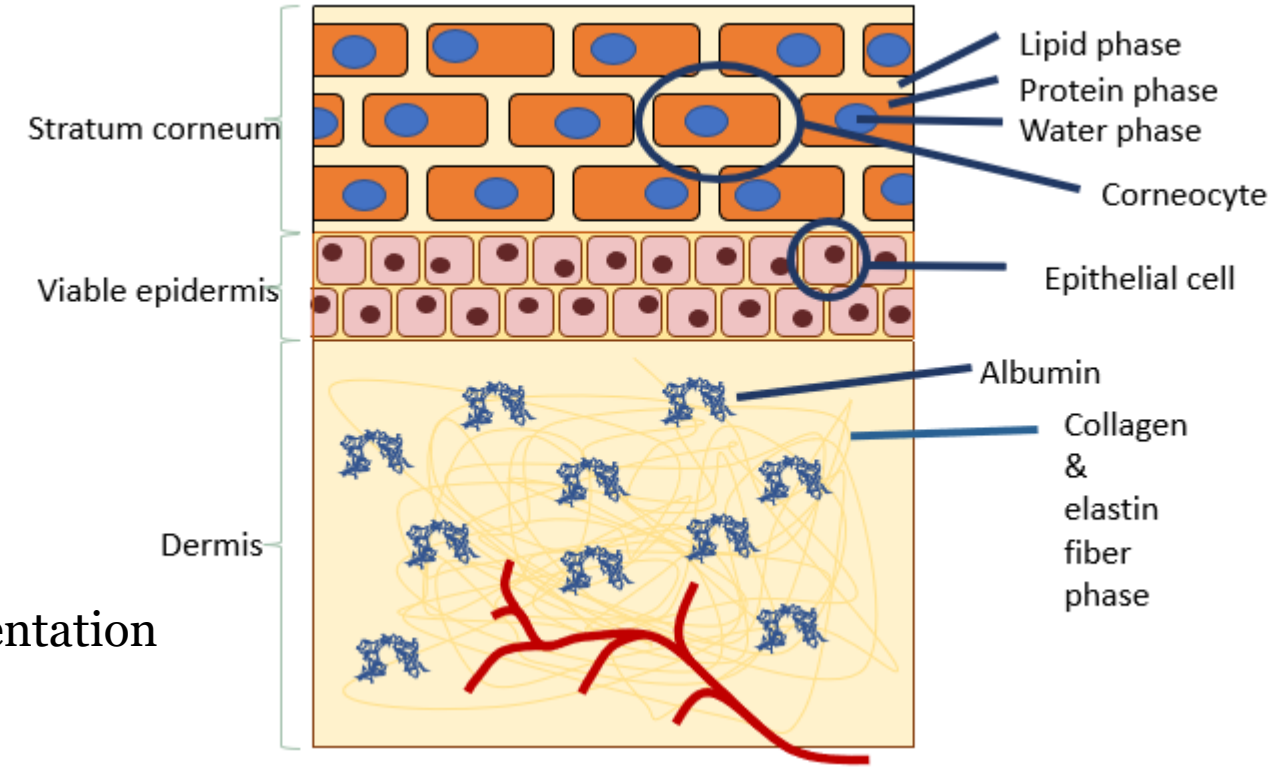
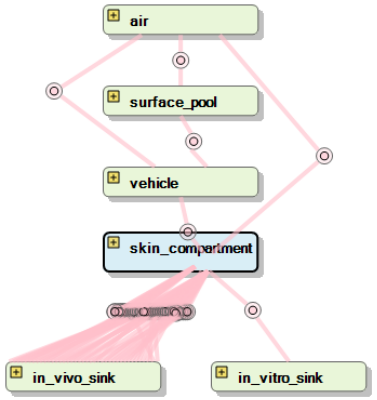
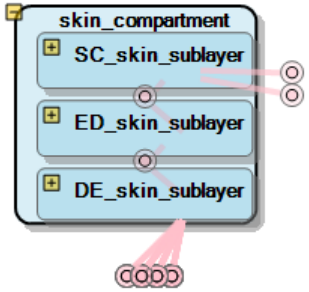


- One dimensional partial differential equation representation of skin permeation
- **Inputs include descriptors of:**
  - The applied permeant (physical/chemical properties)
  - Applied formulation
  - Skin condition
  - Experimental conditions
  - Application protocol
- **Outputs:**
  - Total accumulation in each skin layer and on skin surface
  - Flux and cumulative permeant amount that clears skin

https://github.com/Open-Systems-Pharmacology/Skin-permeation-model





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Mechanistic model: input descriptors of application context, output skin estimates

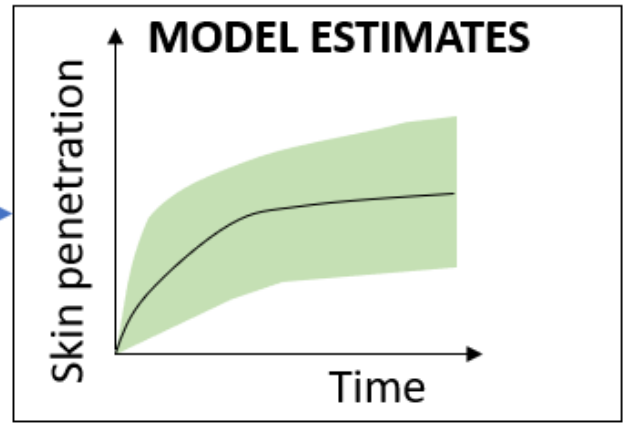
USER INPUTS
Phys/chem properties
Vehicle properties
Skin properties
Ambient conditions

MoBi DERMAL MODEL

MODEL PARAMETERS
- Vehicle/SC partitioning
- SC diffusivity
- SC/epidermis partitioning
- Epidermis diffusivity
- Epidermis/dermis partitioning
- Dermis diffusivity
- Systemic update

DRUG TRANSPORT EQUATIONS

$$\frac{\partial c}{\partial t} = f\left(\frac{\partial^2 c}{\partial x^2}\right)$$



Stratum corneum diffusivity

Partitioning into lipid/corneocyte phases

Corneocyte phase diffusivity

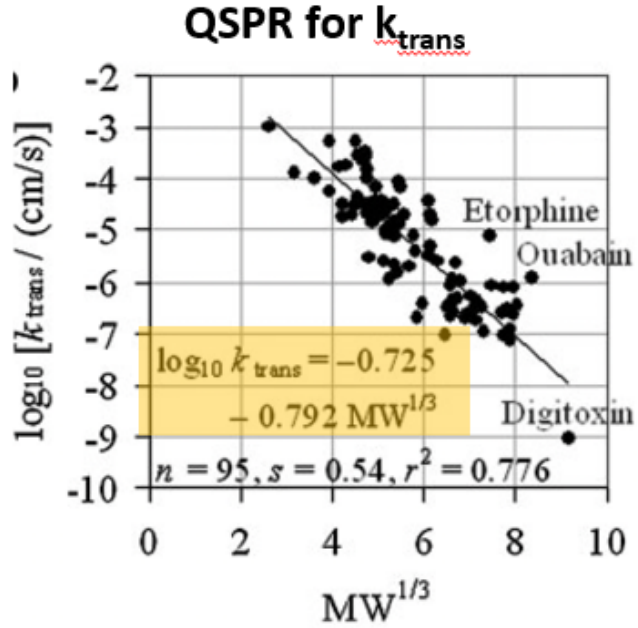
Lipid phase diffusivity

Trans-lipid bilayer permeability (k_{trans})

Lipophilicity

Molecular weight of permeant

Phys/chem user inputs



Development of an Age-Dependent Dermal Absorption Model 1: Model structure

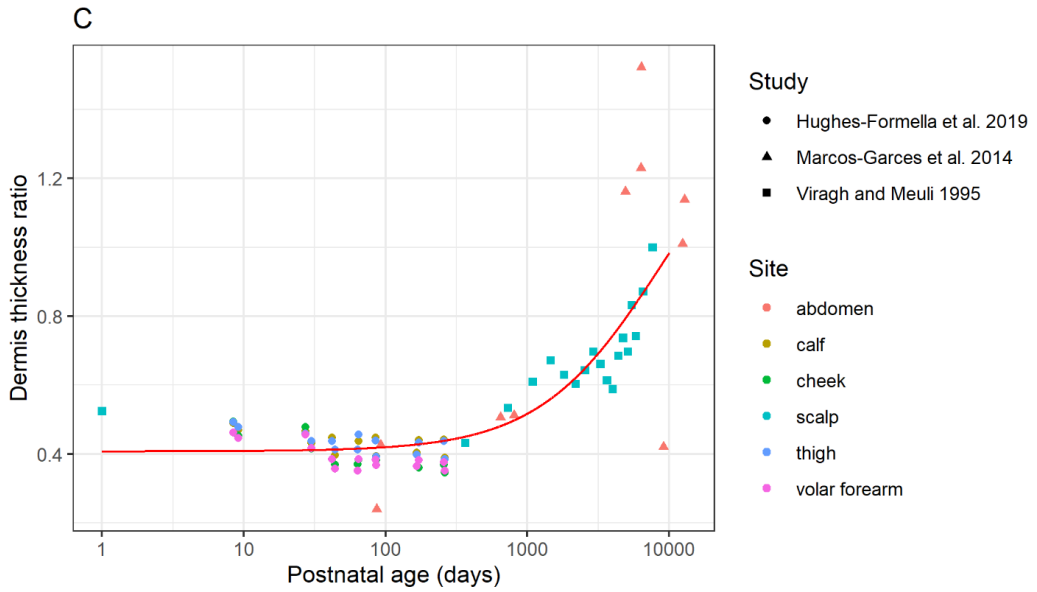
- Generalized the dermal absorption model to include an *Age* effect
- Model had identical structure to original adult model, with *Age* added where appropriate:
  - Some parameters (P) are assumed age-independent (e.g. trans-lipid bilayer permeability - k_{trans})
  - Other parameters (P_A) vary as a function of postnatal age (Age) (e.g. stratum corneum thickness)
- Basic structure:
  - Drug concentration $c(x,t)$ varies with skin depth (x) and over time (t)
  - Evolution of $c(x,t)$ over time depends on P and P_A, based on a partial differential equation model:

$$\frac{\partial c}{\partial t} = f\left(t, c, \frac{\partial c}{\partial x}, \frac{\partial^2 c}{\partial x^2}, P, P_A(Age)\right)$$

- Model outputs of interest are functions of time:
  - Flux of drug out of skin $y_J(t)$
  - Cumulative penetration by drug from skin $y_Q(t)$ (the AUC of $y_J(t)$)

Development of an Age-Dependent Dermal Absorption Model 2: Maturation models

- Age-dependent parameters P_A identified from literature:
  - Thickness of stratum corneum, epidermis, and dermis
  - Hydration of stratum corneum
- Candidate models of postnatal age-dependence for each parameter P_A developed as functions of postnatal Age (in days) from birth to adulthood
- Each expressed as a ratio compared to a reference adult value P_{adult} that depends on postnatal age (Age)

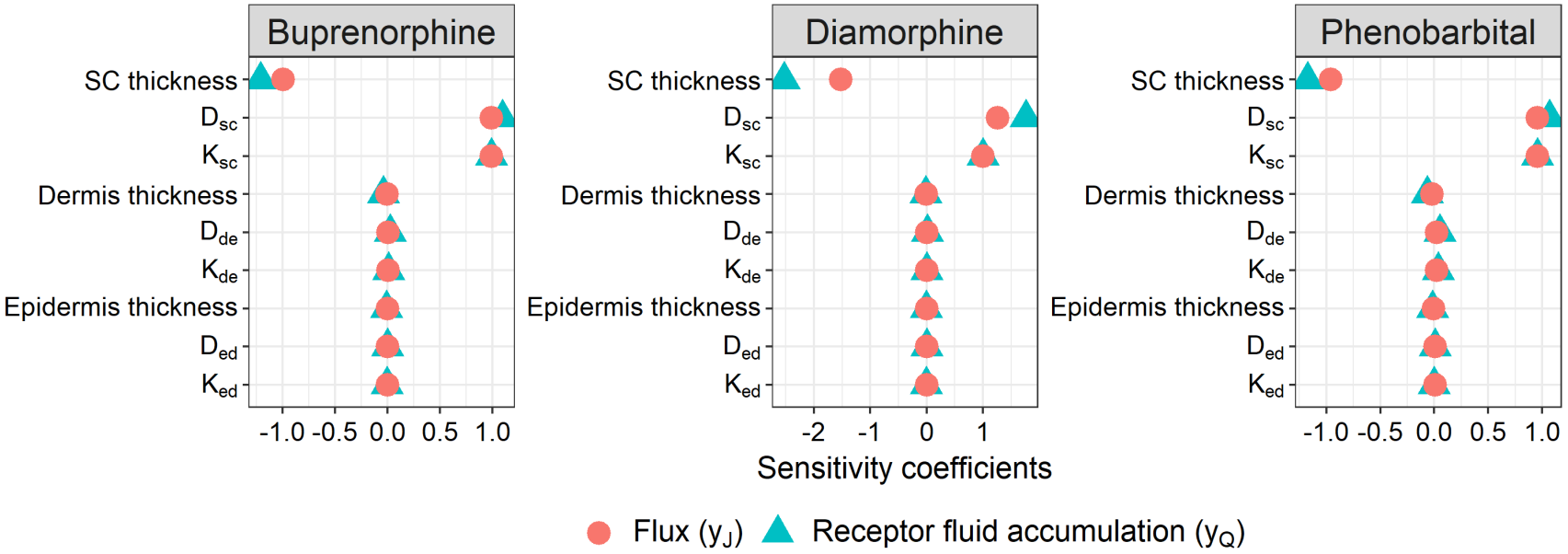


Model evaluation plan – the big picture

- *In vitro skin penetration data* for buprenorphine, diamorphine, and phenobarbital data sourced from literature for **adults** and **children**.
- **Step 1**: *Sensitivity analysis* conducted on **adult** model to identify all skin-specific parameters that impact outputs y_J and y_Q
- **Step 2**: Literature searched to build *probability distributions* of any **uncertain**, **age-dependent** parameters for **adults**
- **Step 3**: *Optimization* of **uncertain**, **age-independent** sensitive parameters for adult model using the in vitro data for the three compounds
- **Step 4**: *Validation via stochastic simulation* of optimized model based on estimates of y_J and y_Q for **children** using samples of **age-dependent parameters** from distributions in **Step 2**, scaled to appropriate age using **maturation models**

Sensitivity analysis

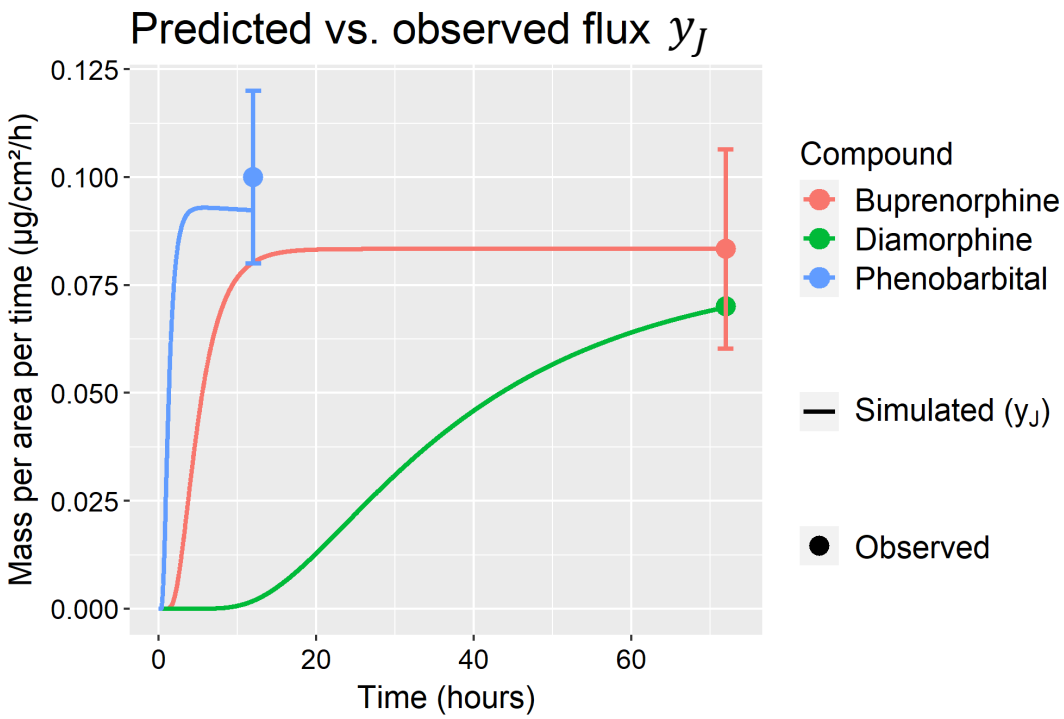
- Local **sensitivity** analysis conducted on the adult (Age = 30) model for each compound

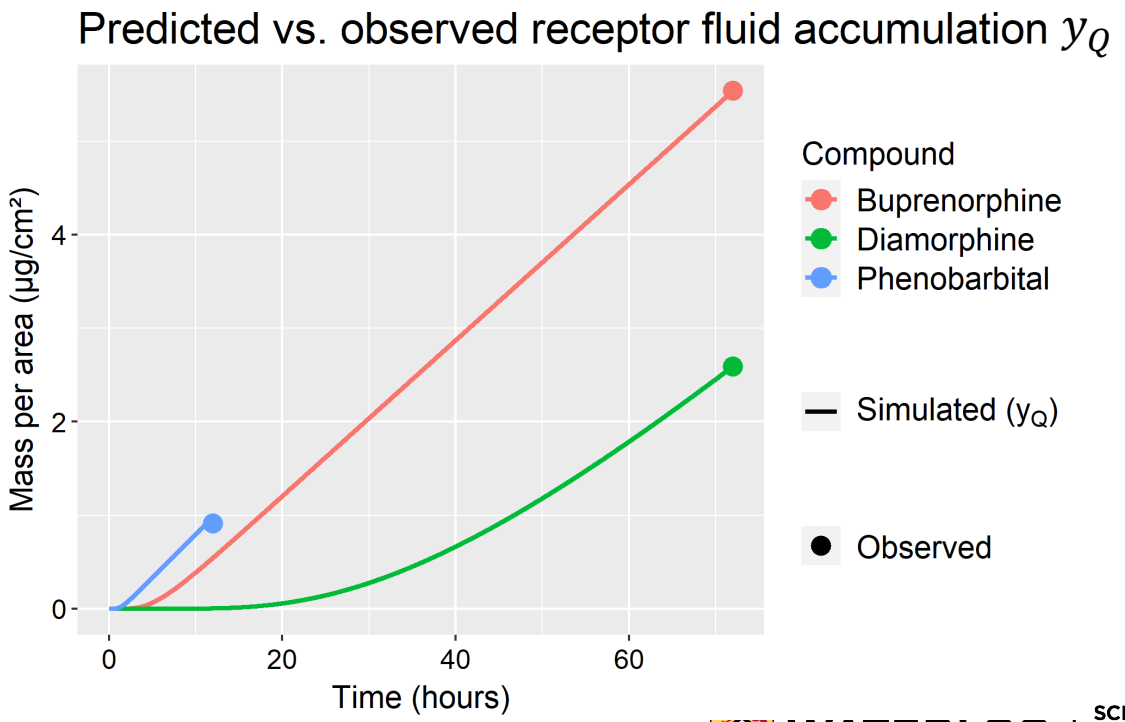


- Sensitivity highest for stratum corneum (SC) parameters:
  - **Age-independent:** Drug diffusivity in SC (D_{sc}), drug partitioning into SC (K_{sc})
  - **Age-dependent:** Thickness of SC (h_{sc}).

Model optimization

- Sensitive **age-independent** parameters of the model were optimized for each parameter via the MoBi Monte Carlo algorithm





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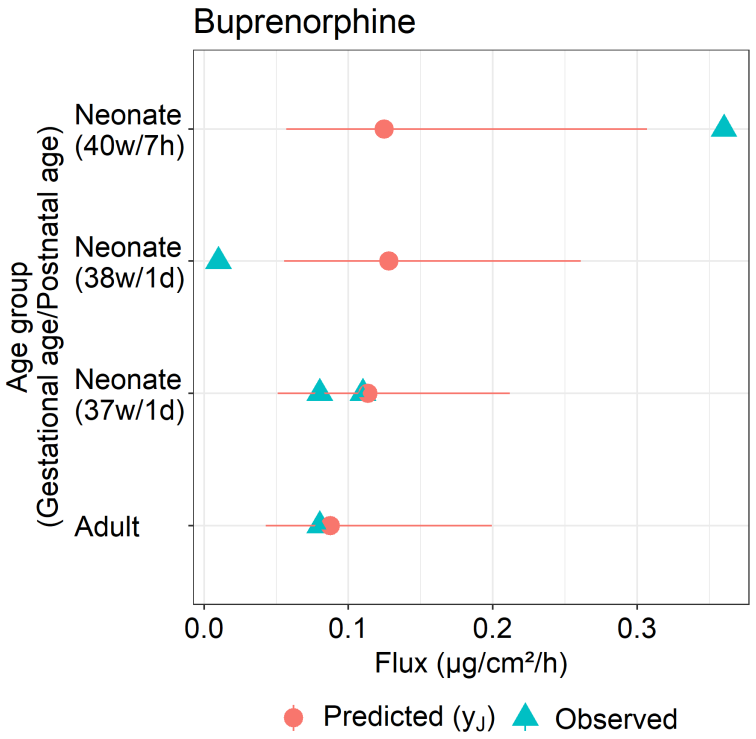
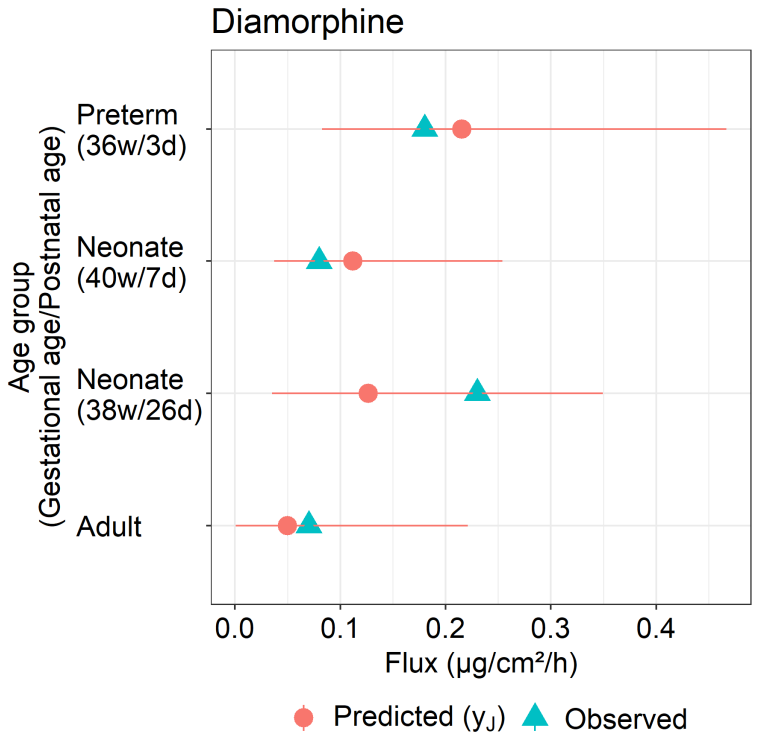
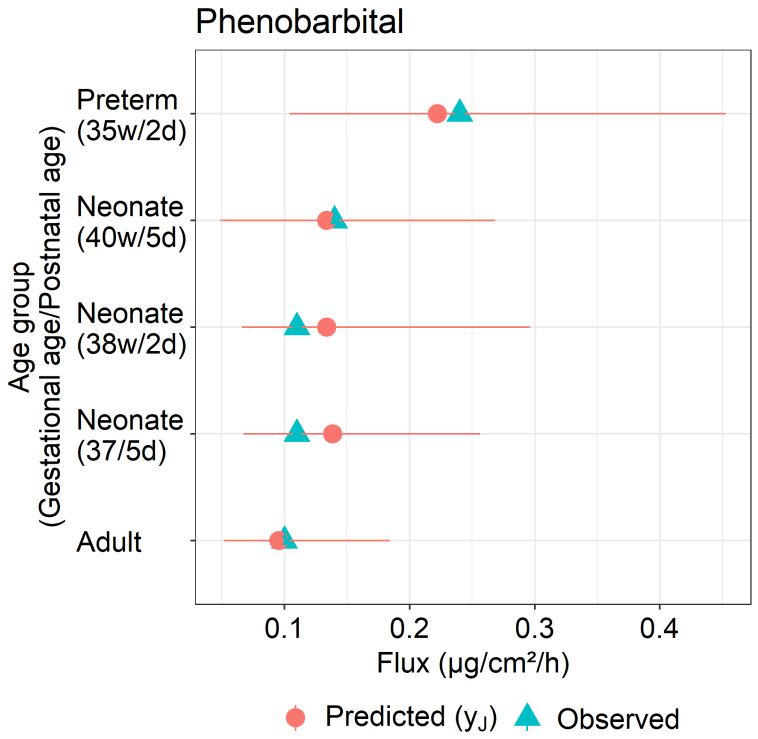
Optimized model evaluation

- Model simulated using samples from distribution of uncertain and sensitive age-dependent parameters, adjusted for age using maturation model







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Summary

- Lehman et al (2011) – the closer the IVPT context is to the in vivo scenario, the more predictive the IVPT
- However, in human health risk assessment/formulation development, extrapolation to a novel context is often needed
- Take advantage of the mechanistic model to learn with IVPT, modify context parameters and simulate in vivo in a new scenario
- Pediatric skin model + adult IVPT data will allow for in vivo exposure (risk) assessment in children
- More pediatric model evaluation is advisable but is limited by a lack of IVPT data from neonatal skin

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