

How do we improve predictions of drug concentration-time profiles?

5th FDA/PQRI Conference 'on Advancing Product Quality: Advancing Quality & Technology of Future Pharmaceuticals'



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December 1, 2021

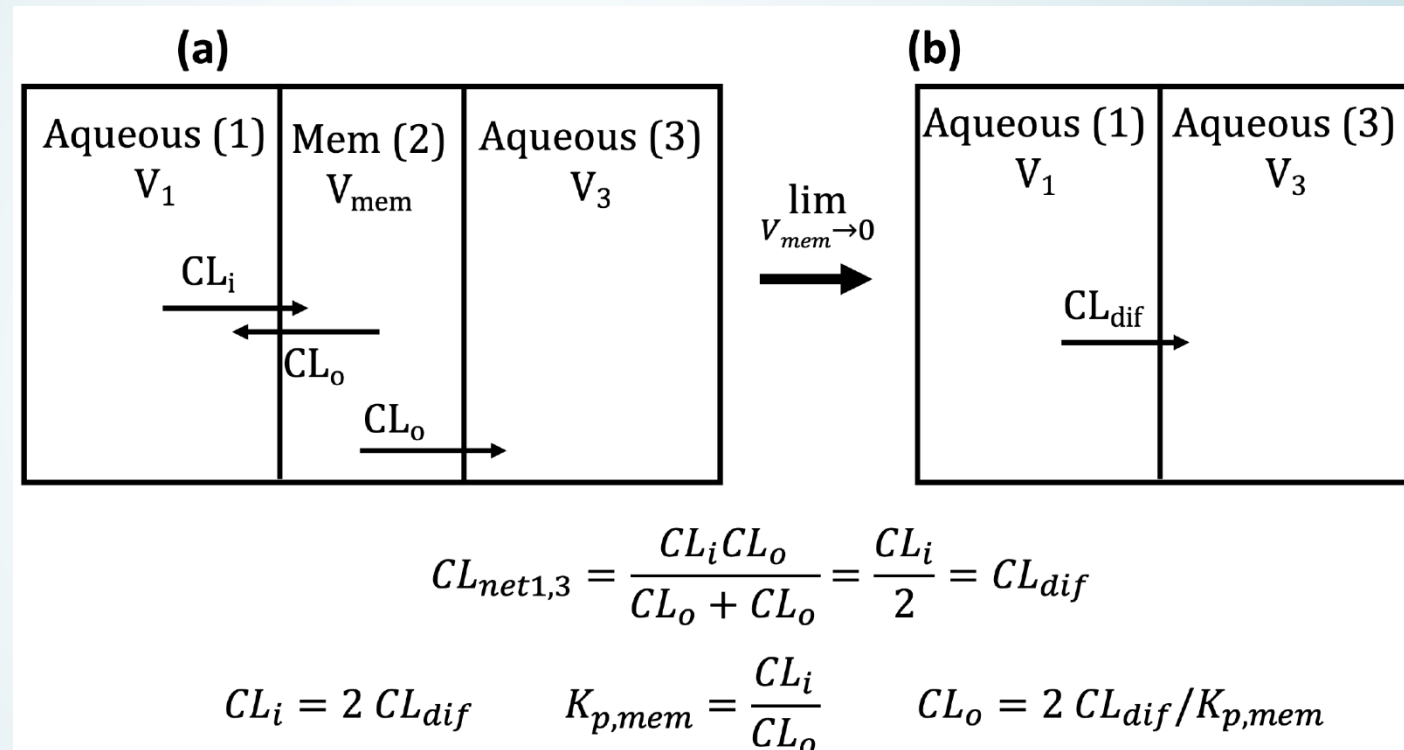
Department of Pharmaceutical Sciences

Temple University School of Pharmacy

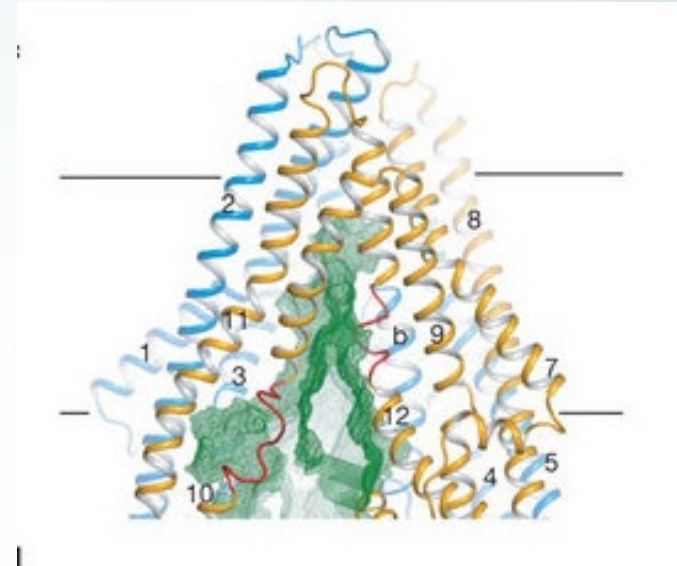
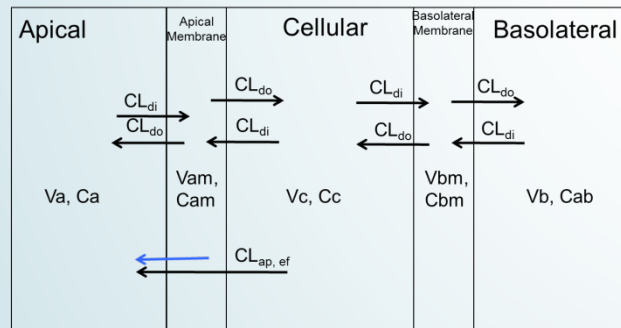
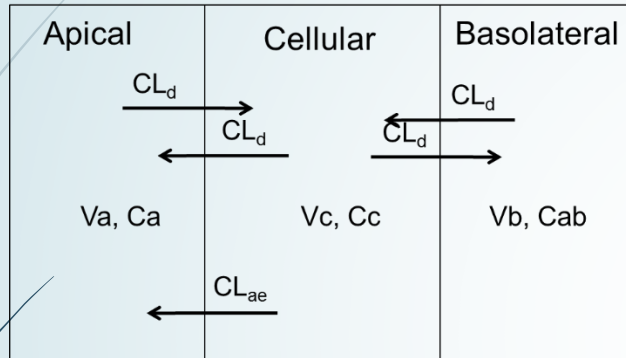
Outline

- ▶ Drug absorption and distribution – the membrane as a barrier
 - ▶ Membrane permeability, membrane partitioning, and membrane transporters
- ▶ Models to predict absorption
 - ▶ A continuous (PDE-based) absorption model
 - ▶ Modeling permeability-, dissolution-, and solubility-limited absorption
- ▶ The utility of pre-clinical absorption models as proof-of-concept
 - ▶ Modeling food effects, particle size, and uptake/efflux transporters
- ▶ Future directions

Membrane partitioning and permeability



Membrane partitioning, permeability, and transporters: e.g., P-gp

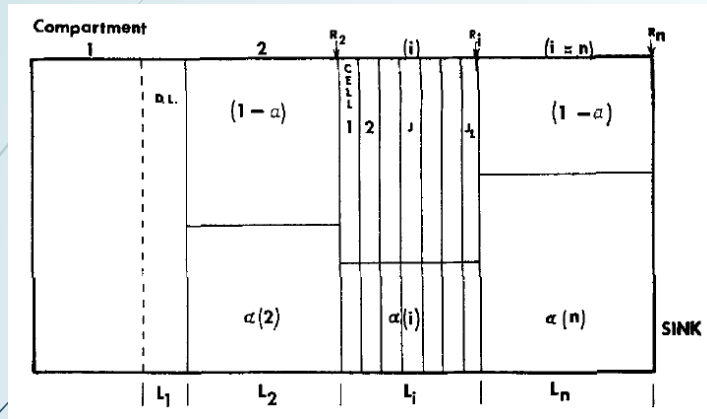


Jin 2012; Nature, 490:566-9.

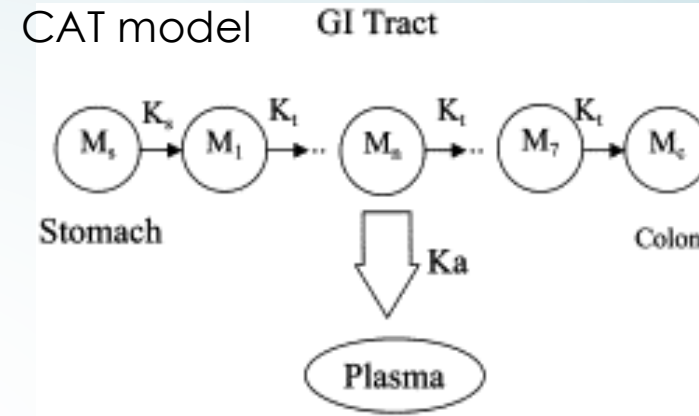
P-gp concerns in drug therapy:

- At the BBB (substrates)
- In the intestine (substrates and inhibitors)

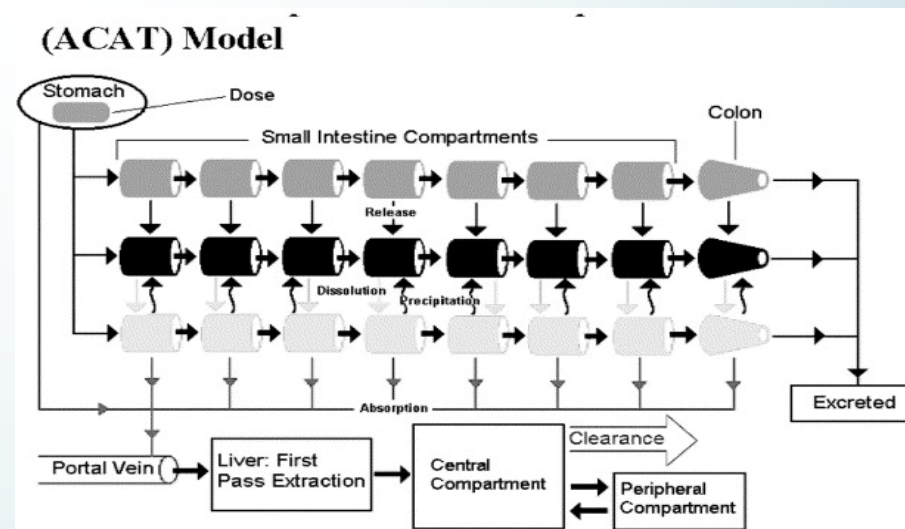
Compartmental models for oral absorption



Suzuki, Higuchi, and Ho, 1970, J Pharm Sci 59:651-659.



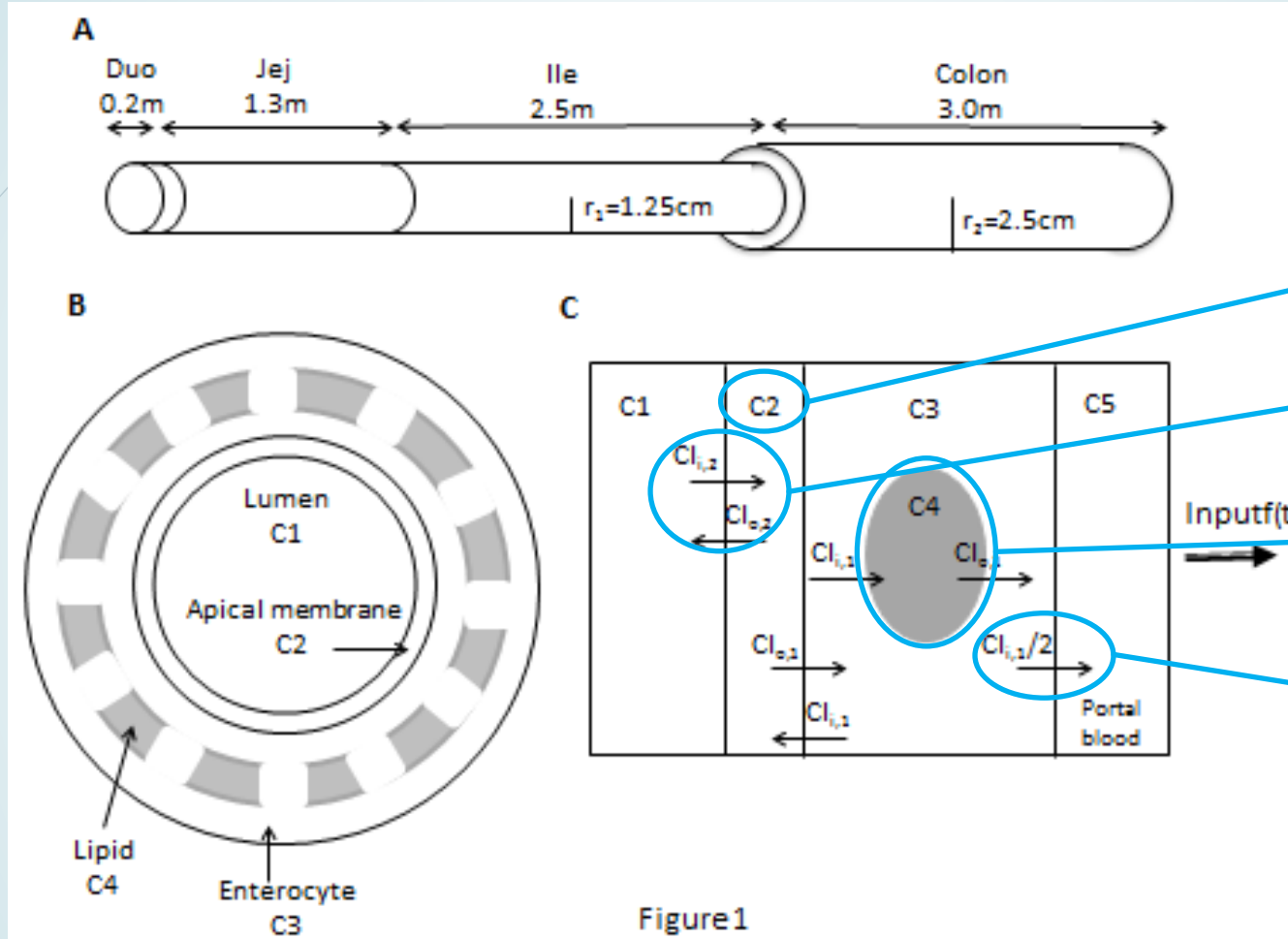
Yu and Amidon, 1999, Int J Pharm 186:119-125.



Agoram et al, 2001, Adv Drug Deliv Rev 50:S41-S67.

Prediction of drug absorption

6



Modeling an explicit apical membrane

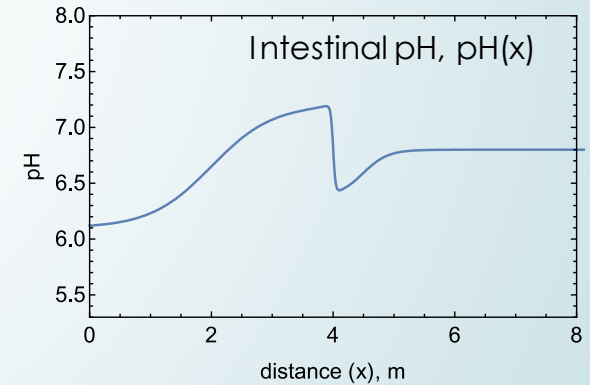
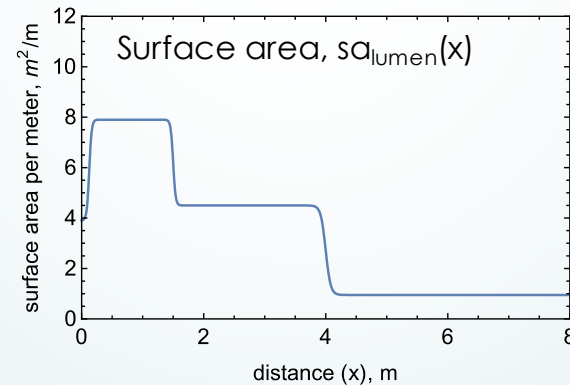
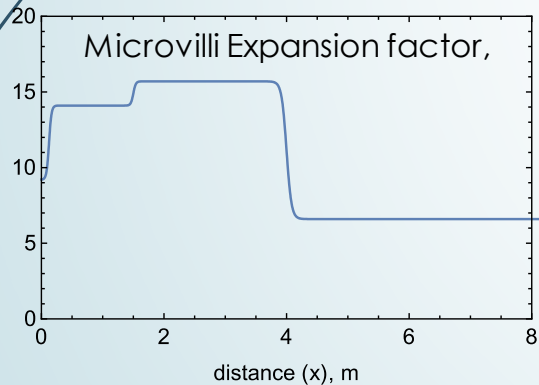
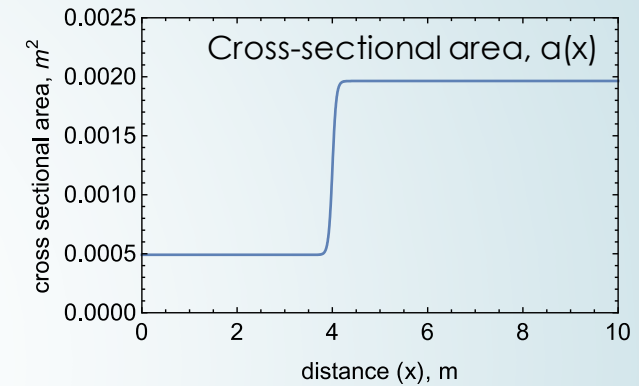
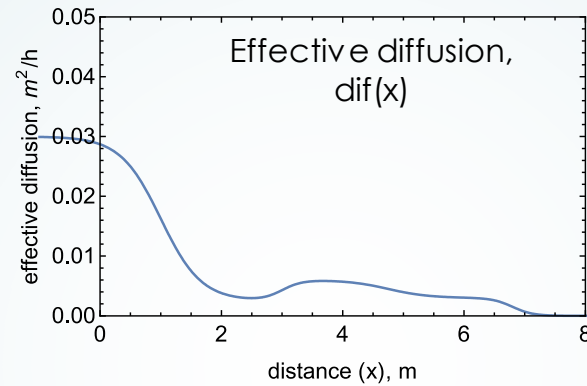
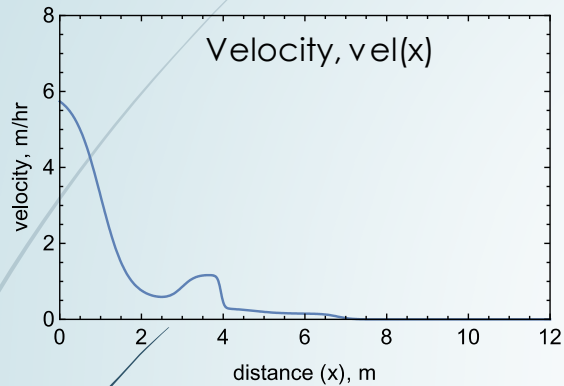
Modeling clearance in and out of membranes

Inter-enterocyte membrane partitioning

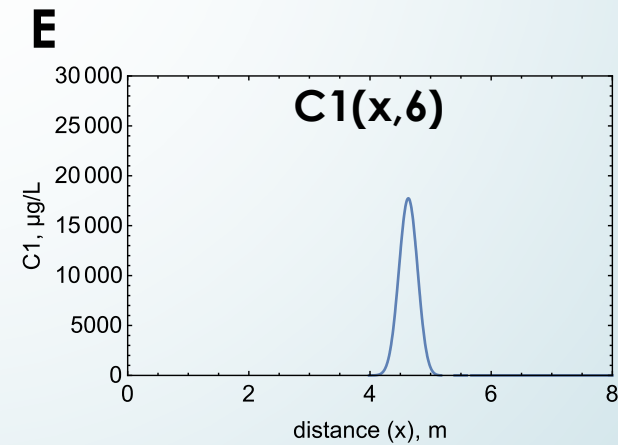
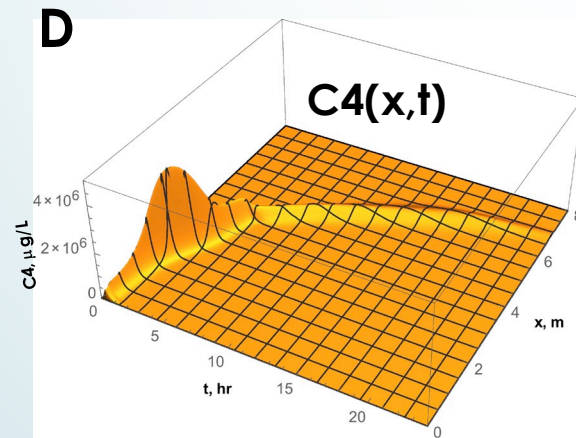
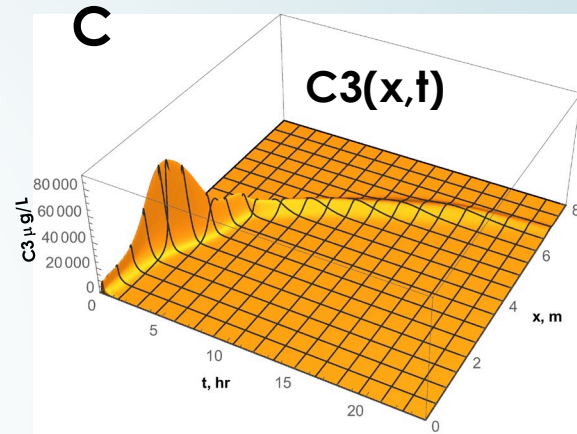
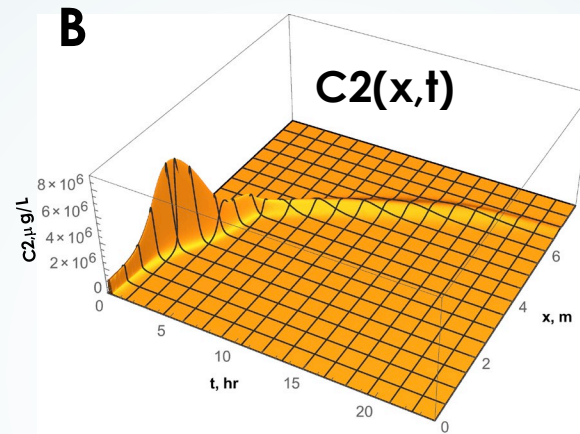
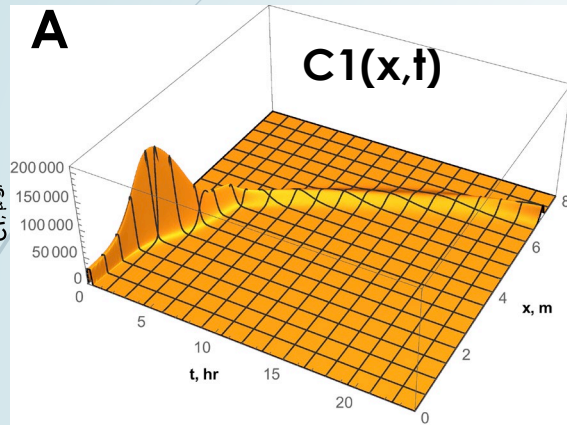
Output into the portal vein

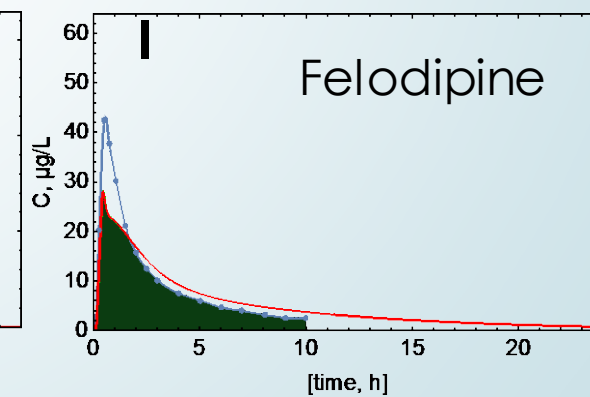
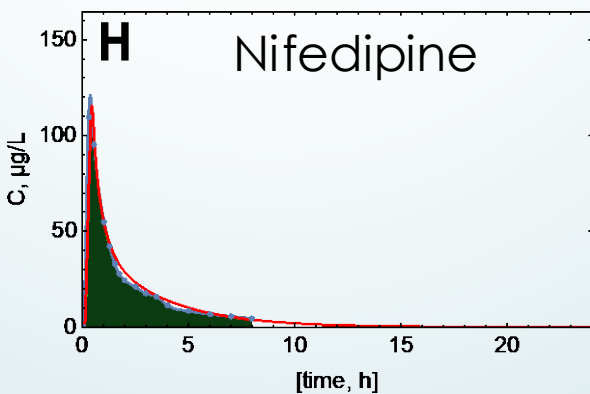
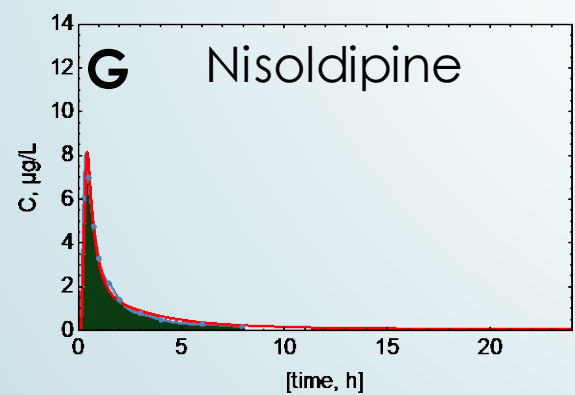
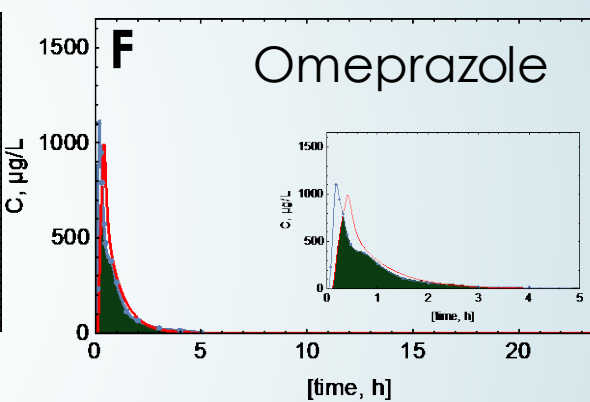
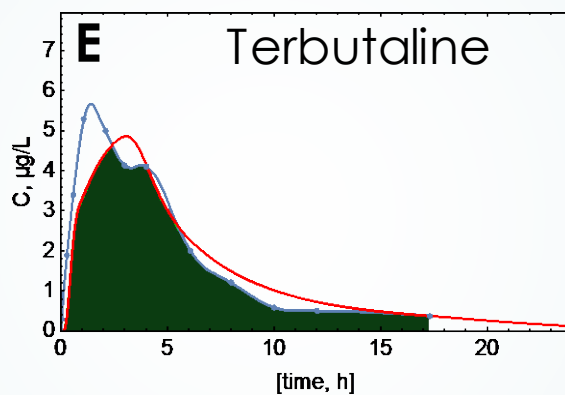
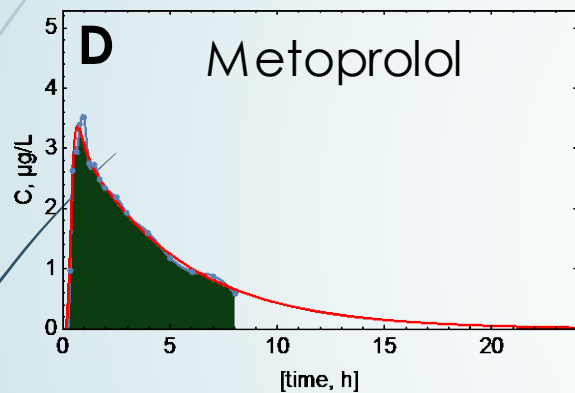
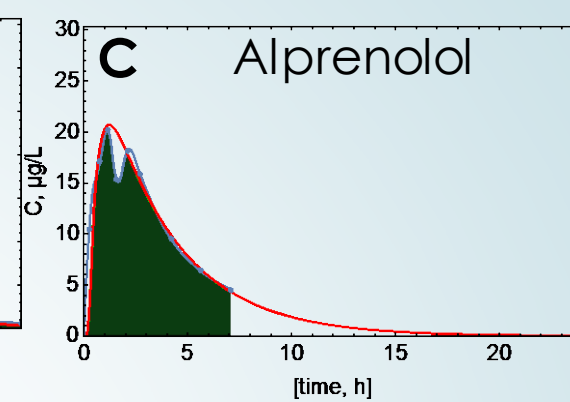
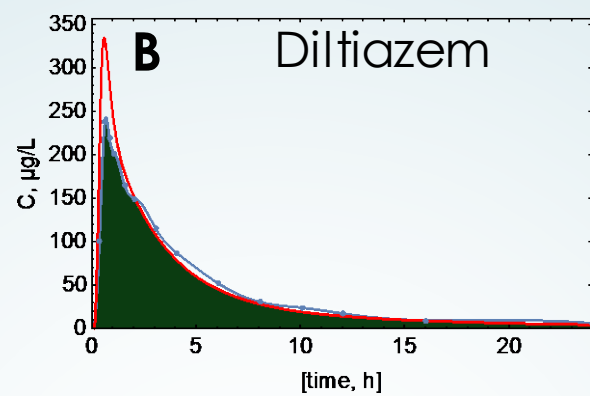
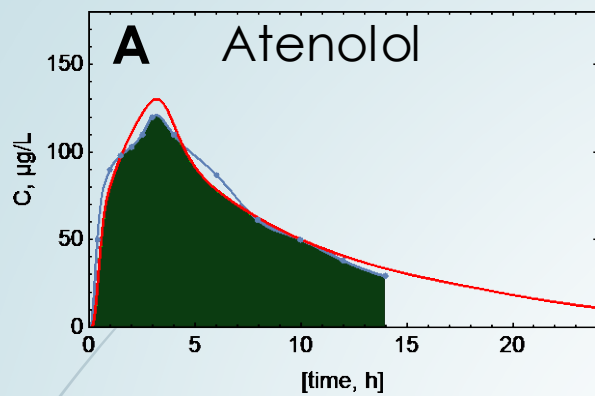
$$\frac{\partial}{\partial t} C(x, t) = D \frac{\partial^2}{\partial x^2} C(x, t) - \frac{Q}{\pi r^2} \frac{\partial}{\partial x} C(x, t) - \sum_{i=1}^n k_i C(x, t)$$

Modeling intestinal physiology



Atenolol solution dose





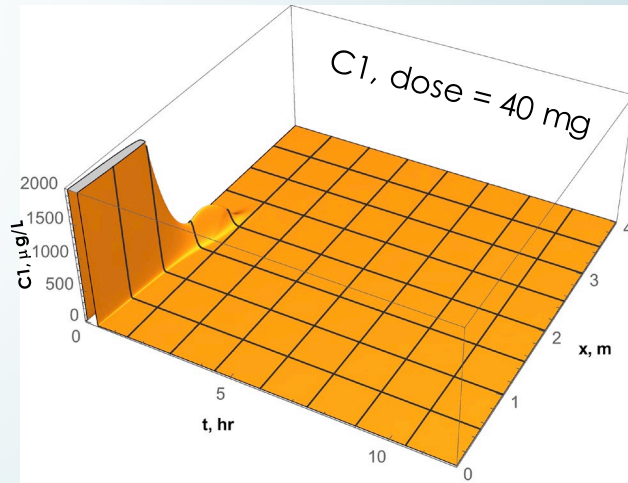
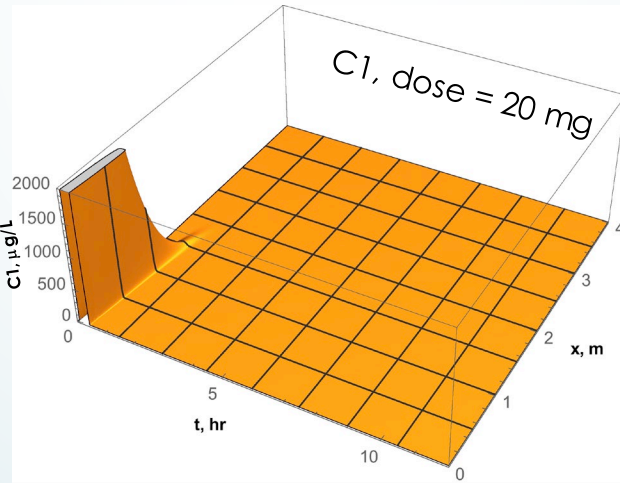
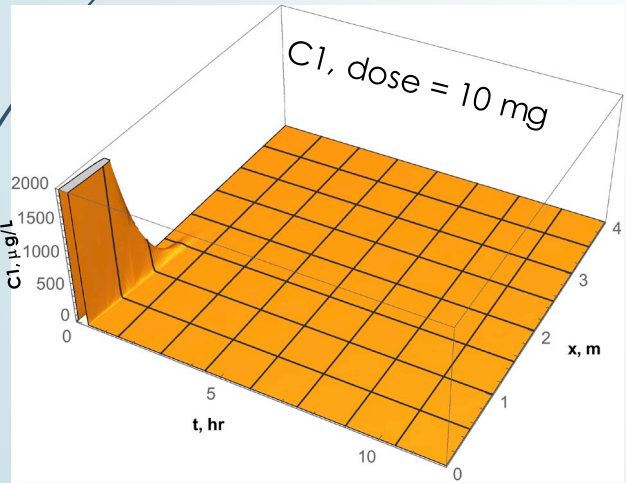
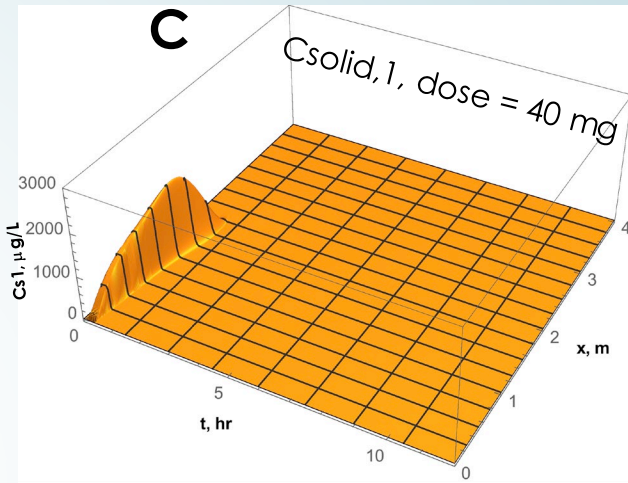
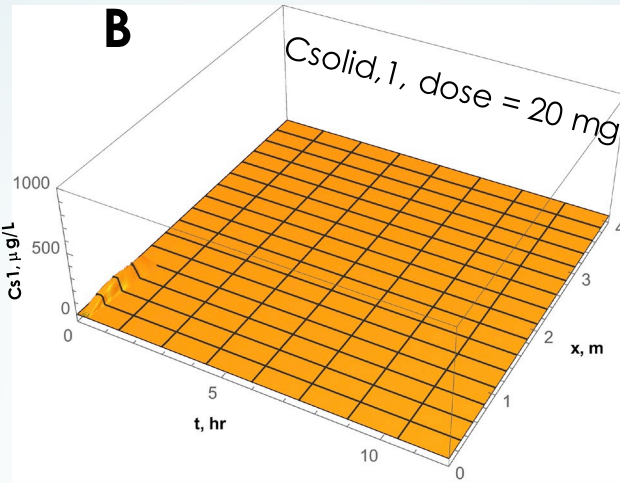
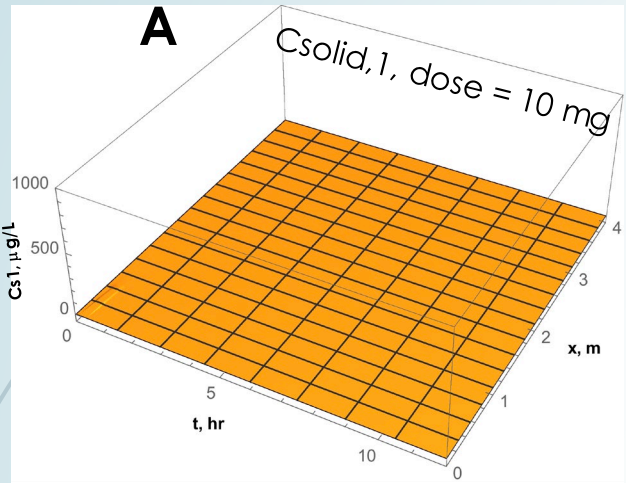
Drug Dissolution and Precipitation

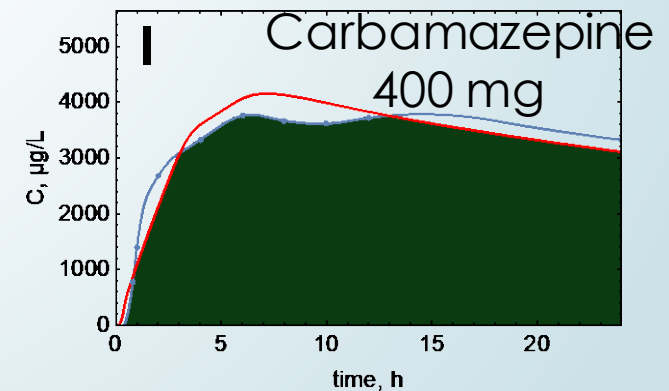
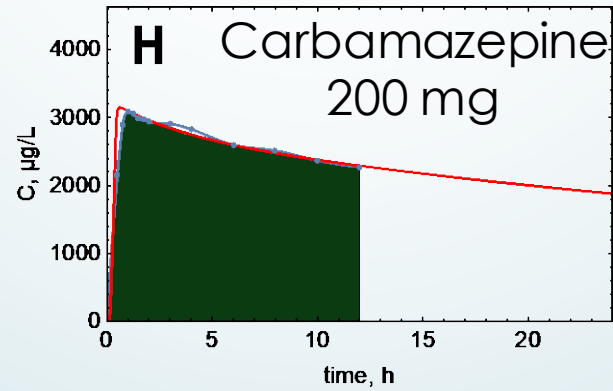
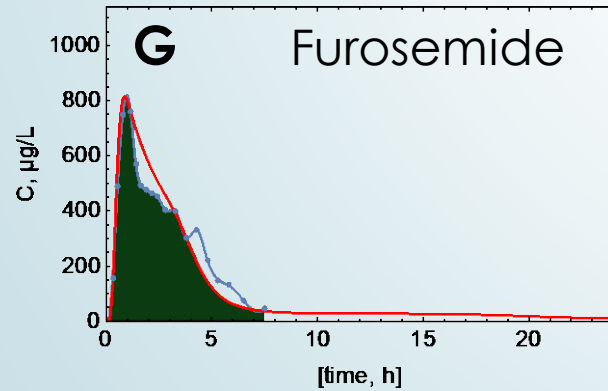
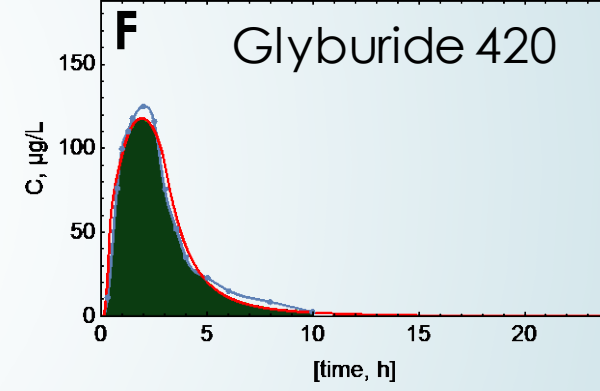
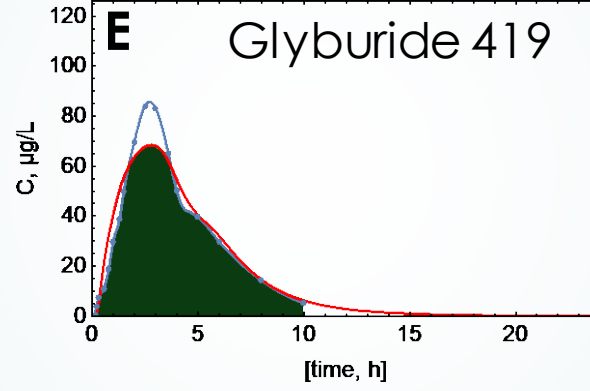
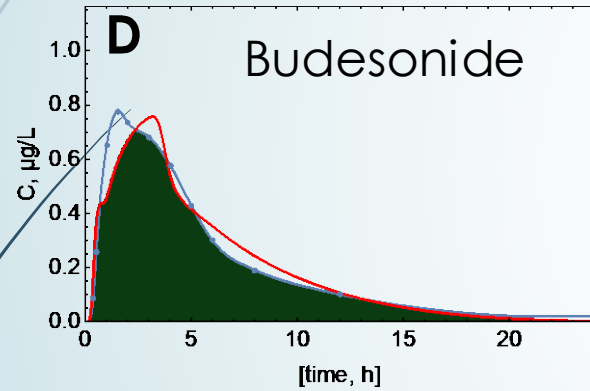
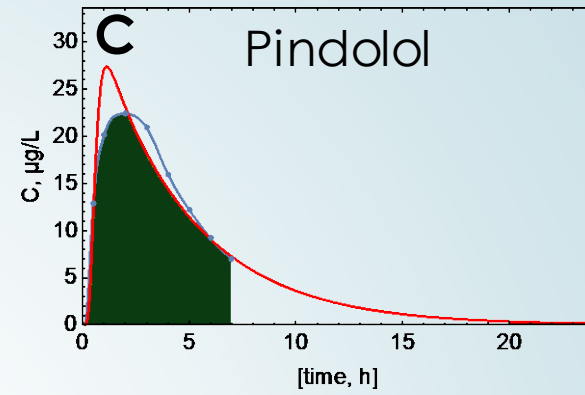
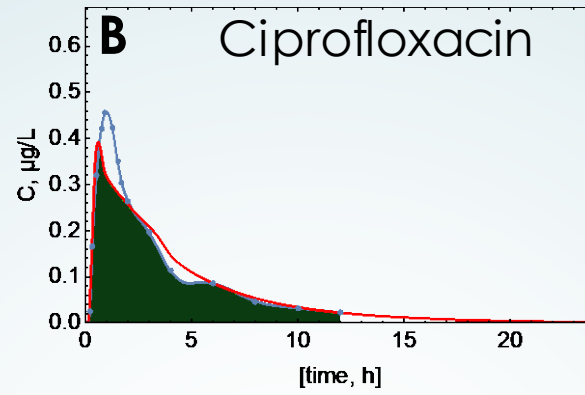
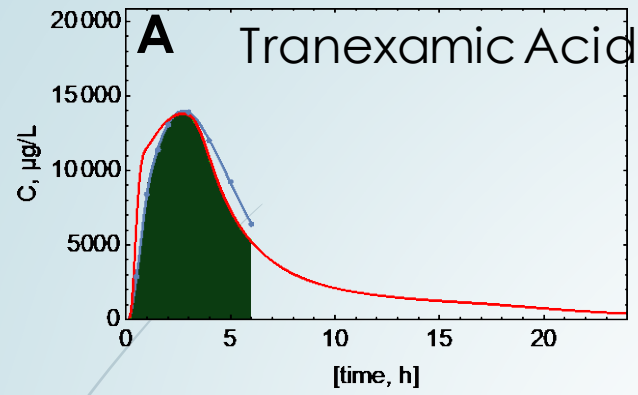
- For dissolution of drug particles, the equation proposed by Wang and Flanagan was modified as follows:

$$f_{\text{diss}}(x, t) = \left(8C_{\text{part}}(x, t)\pi D_3 \sqrt[3]{\frac{3C_{\text{solid}}(x, t)}{4\pi\rho C_{\text{part}}(x, t)}} \right) (S - C_1(x, t))$$

- Basing drug amount on the particle size and number allows us to retain the number of particles in the system.
- These particles with minimal mass continue to move along the intestine.
- These particles can then be used for precipitation.

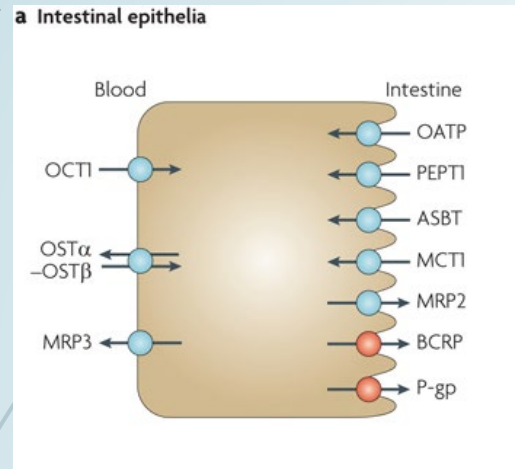
Nifedipine Precipitation



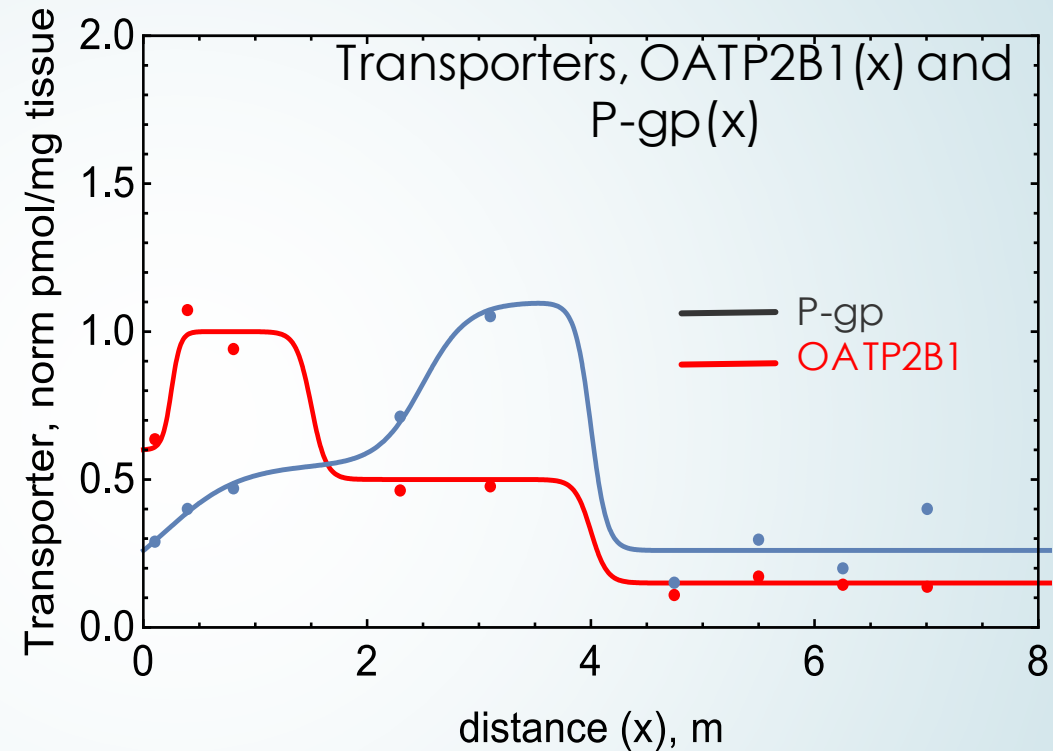


Modeling OATP and P-gp Content

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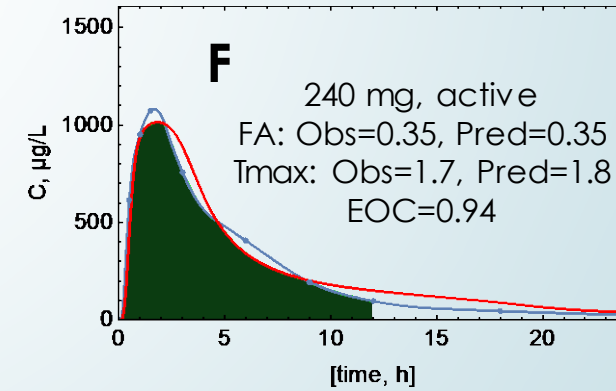
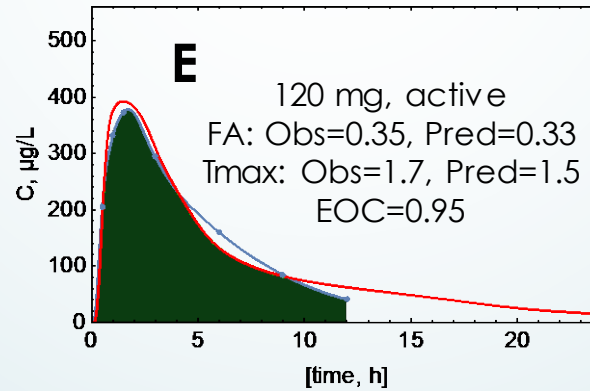
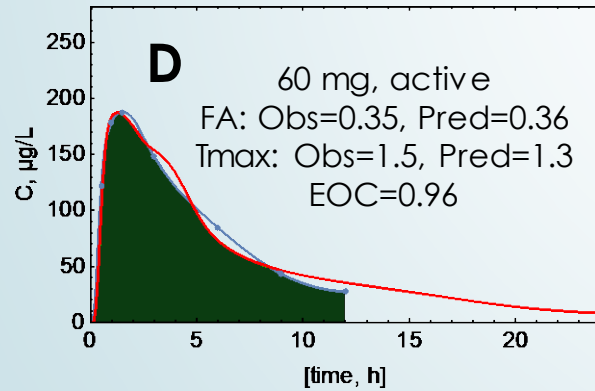
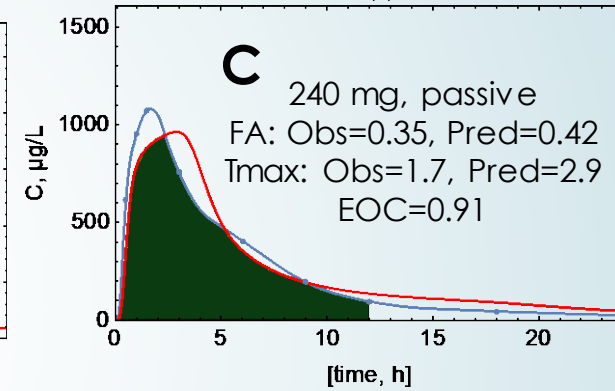
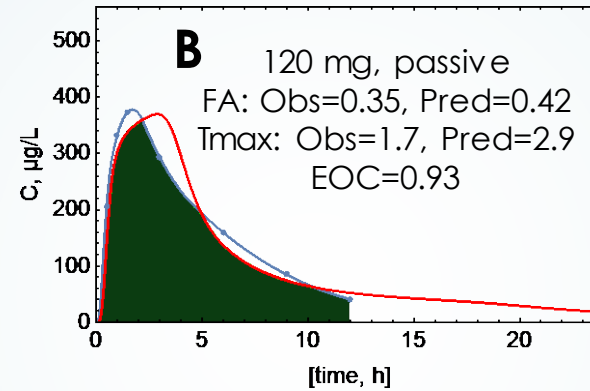
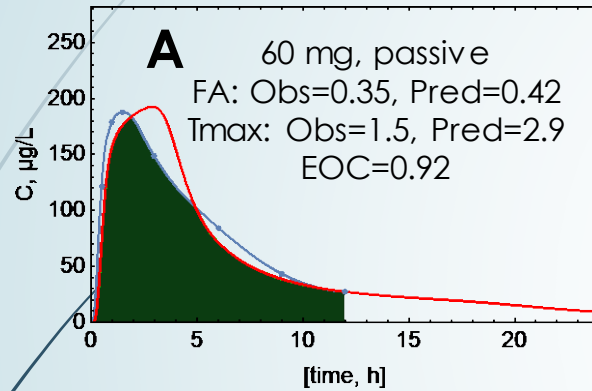
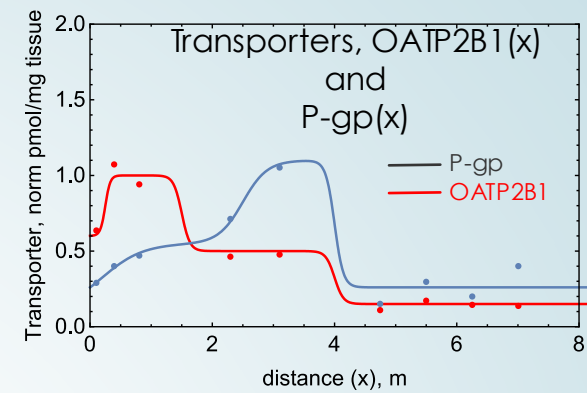
Giacomini et al, Nature Reviews Drug Discovery 2010, 9:215-236.

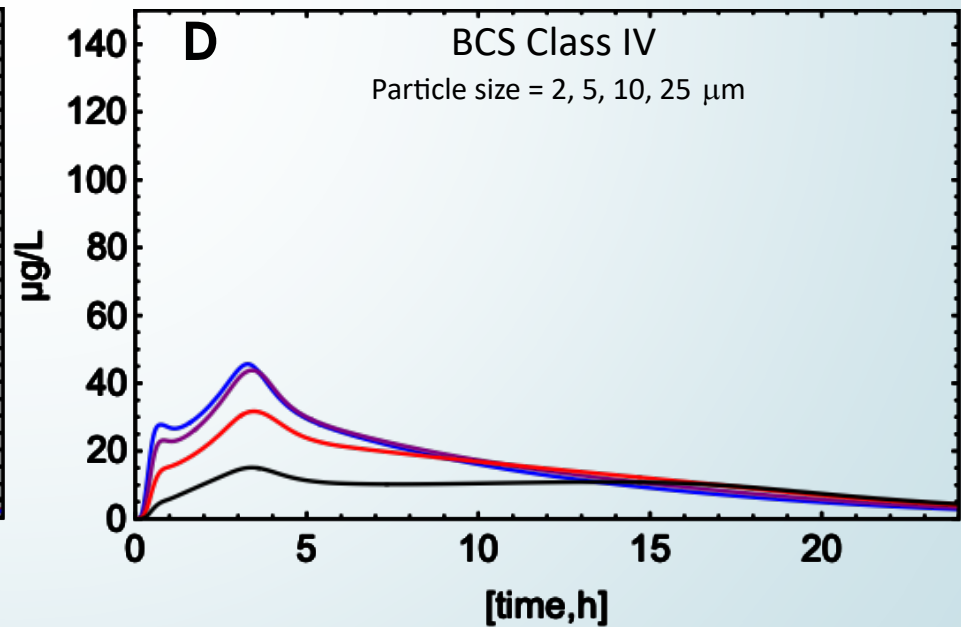
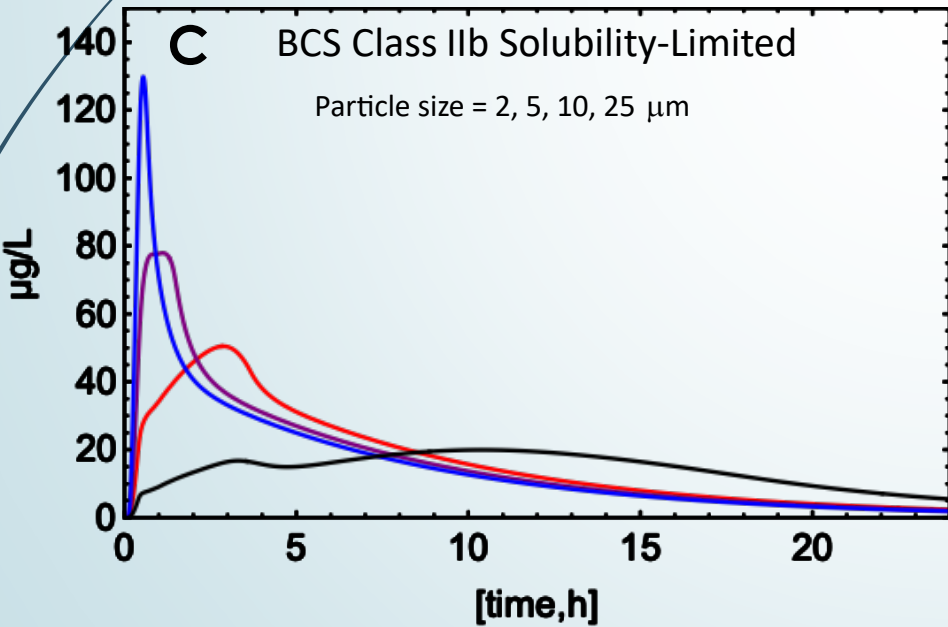
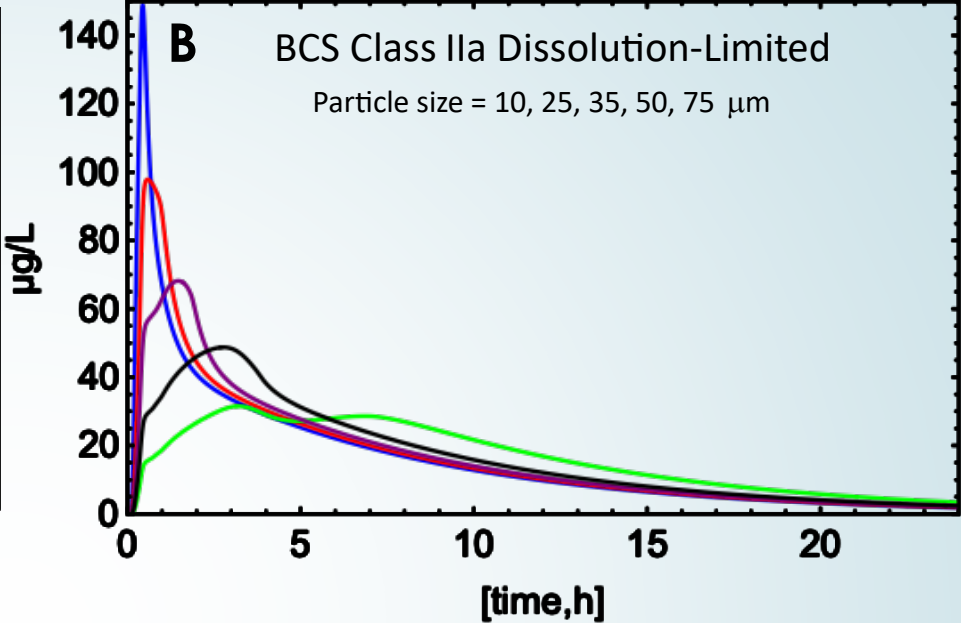
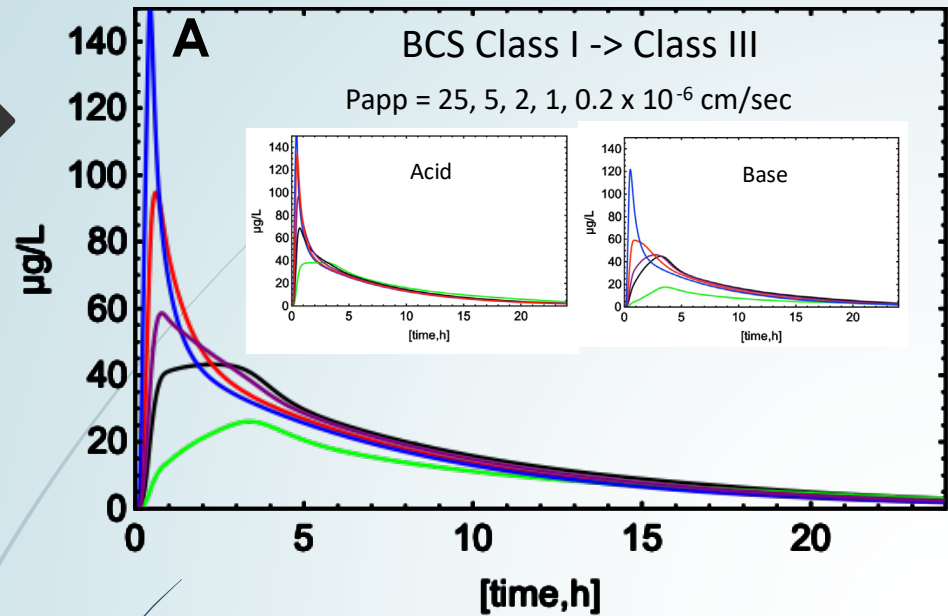


Protein abundance from Drozdzik, M., et al. *Mol Pharmaceutics* **11**, 3547-3555 (2014).

Simulated fexofenadine C-t profiles

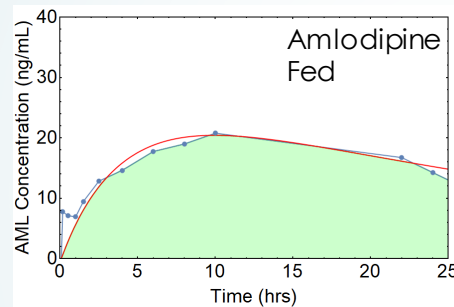
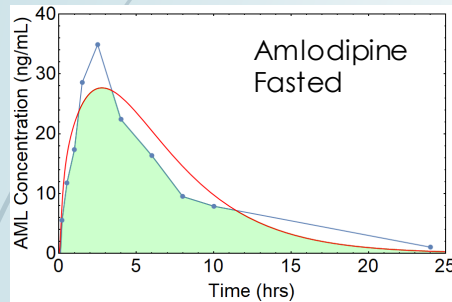
Addition of OATP2B1 and P-gp





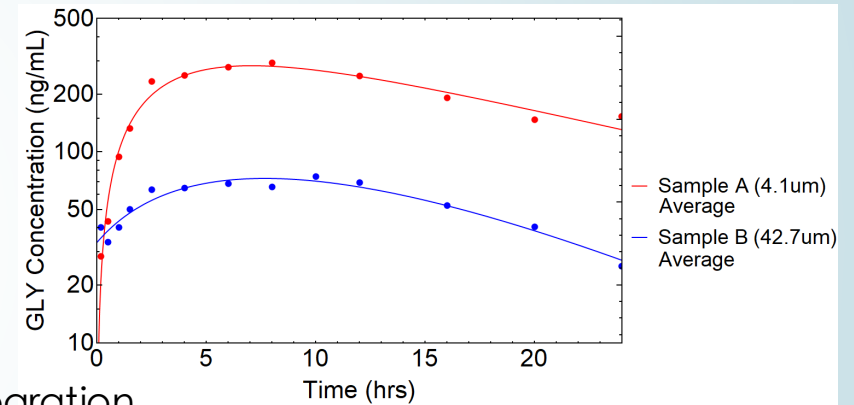
Rat absorption model to incorporate food effects, particle size effects, and intestinal CYP inhibition

Food effect

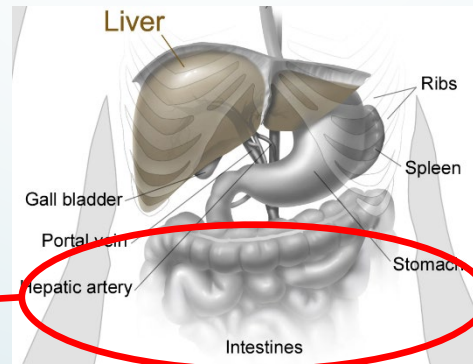


Casey et al, manuscript in preparation

Particle size effect



Intestinal CYP inhibition and impact on F

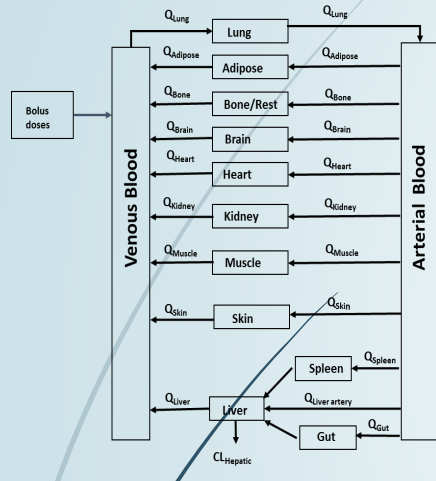


$$F = F_a * F_g * F_h$$

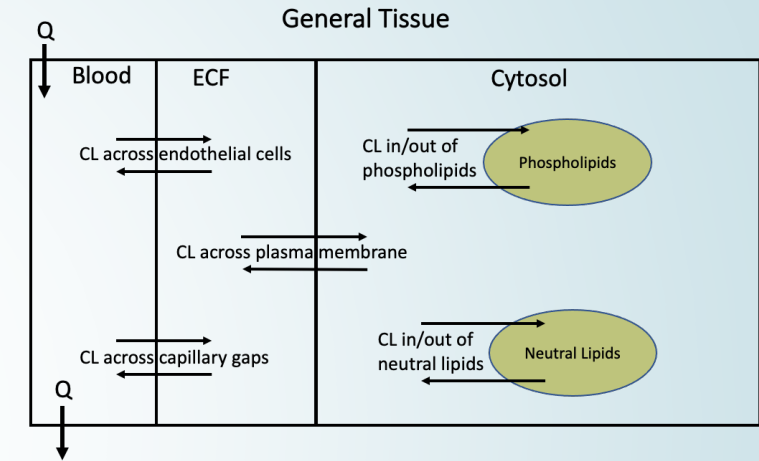
Metabolism
CYP3A4
UGTs

Predicting Concentration-time profiles...are we there yet? (Absorption, distribution, elimination)

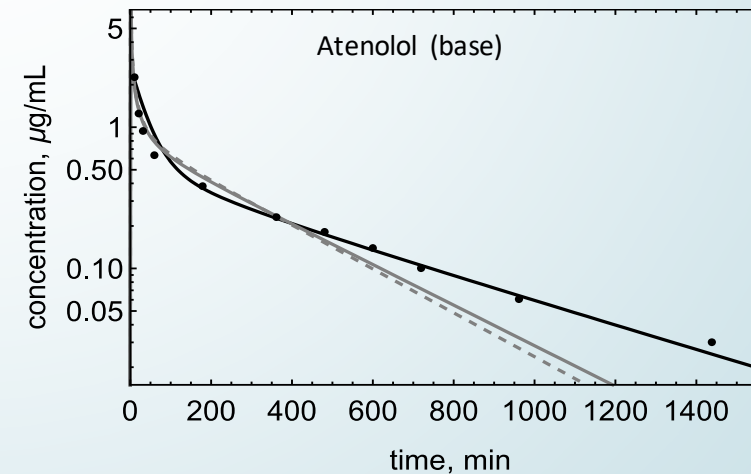
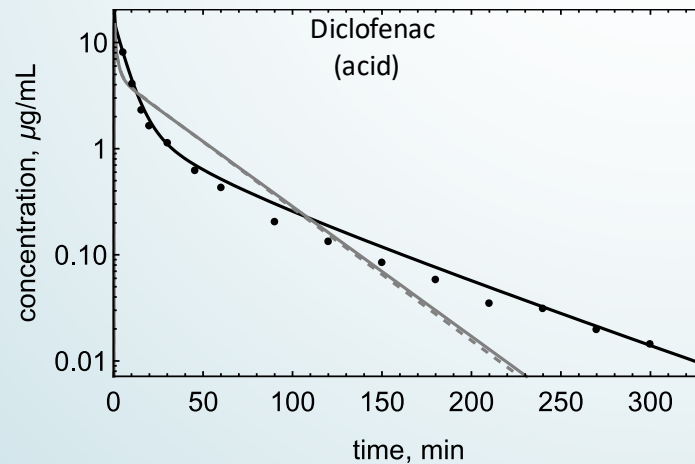
Perfusion-limited distribution in traditional PBPK



Ye, Biopharm Drug Dispos 2016;37:123-141



Permeability-limited distribution in a new PBPK framework



Summary and Future Directions

- Modeling membranes as explicit compartments can greatly improve absorption and distribution predictions
- We have developed a continuous absorption model that is completely flexible. Drug permeability, partitioning, and active transport can be incorporated into this model
- Complexities such as food and formulation effects, transporters, enzyme activity, and inhibition can be modeled to evaluate their impact of drug absorption and bioavailability
- Future Directions
 - Develop rat and mouse absorption models to incorporate experimental and physiological complexities into mathematical models for absorption
 - Characterize the impact of pH on permeability
 - Develop a more efficient method to incorporate enterohepatic recycling

Acknowledgments

- ▶ Nagar Lab
 - ▶ Casey Radice, PhD
 - ▶ Tirtha Nandi
- ▶ Korzekwa Lab
 - ▶ Kim Holt, PhD
 - ▶ Min Ye
- ▶ Richard Korzekwa, PhD

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