Modeling Absorption in GastroPlus

PSCI-518, Spring 2024

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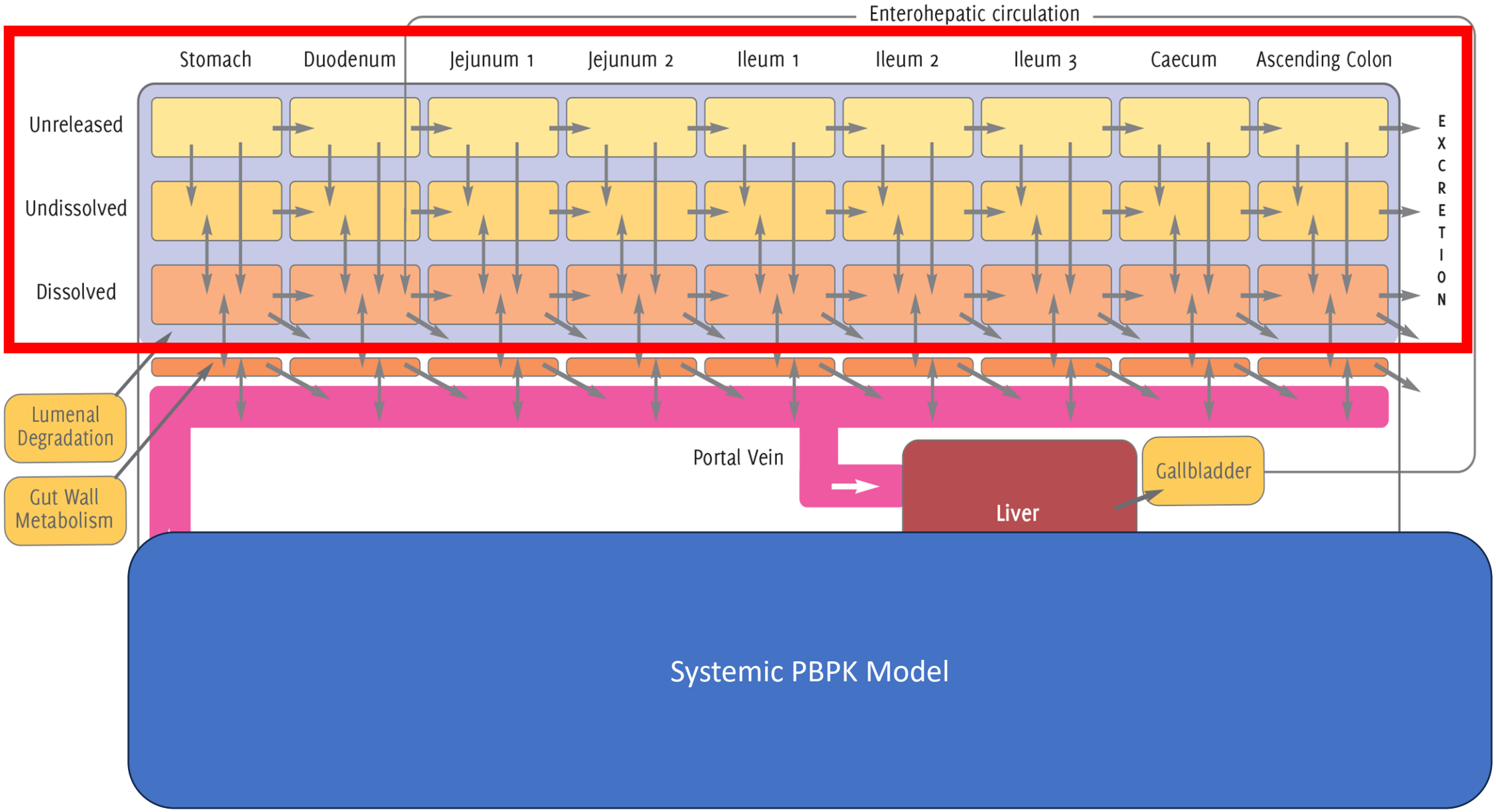
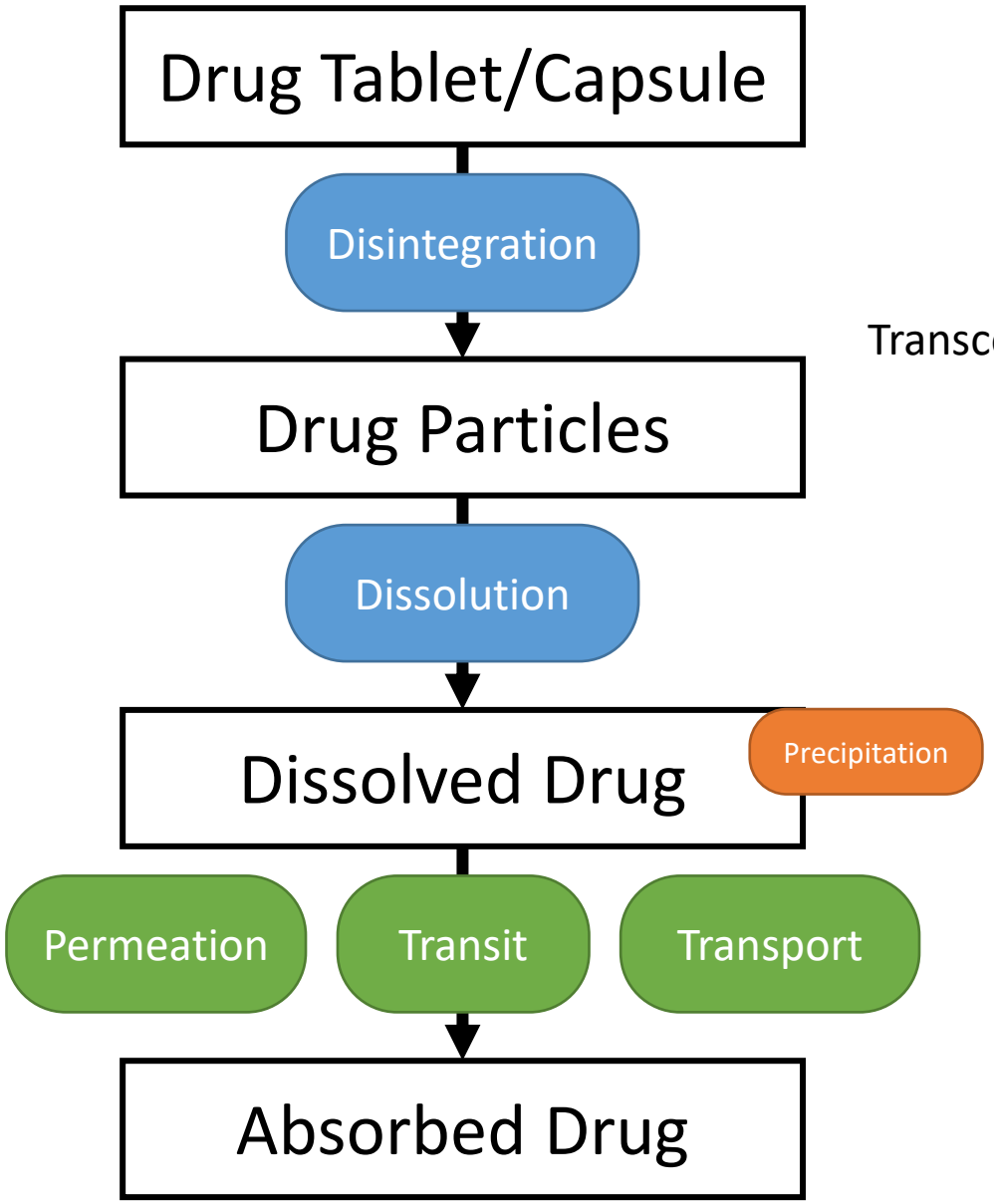
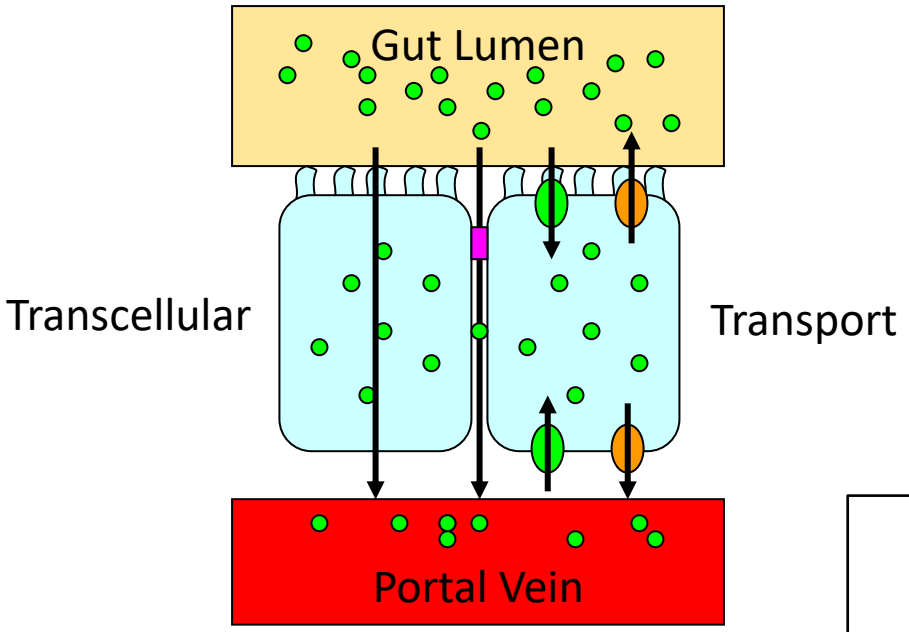
Advanced Compartmental Absorption and Transit Model (ACAT™)



Absorptive Processes





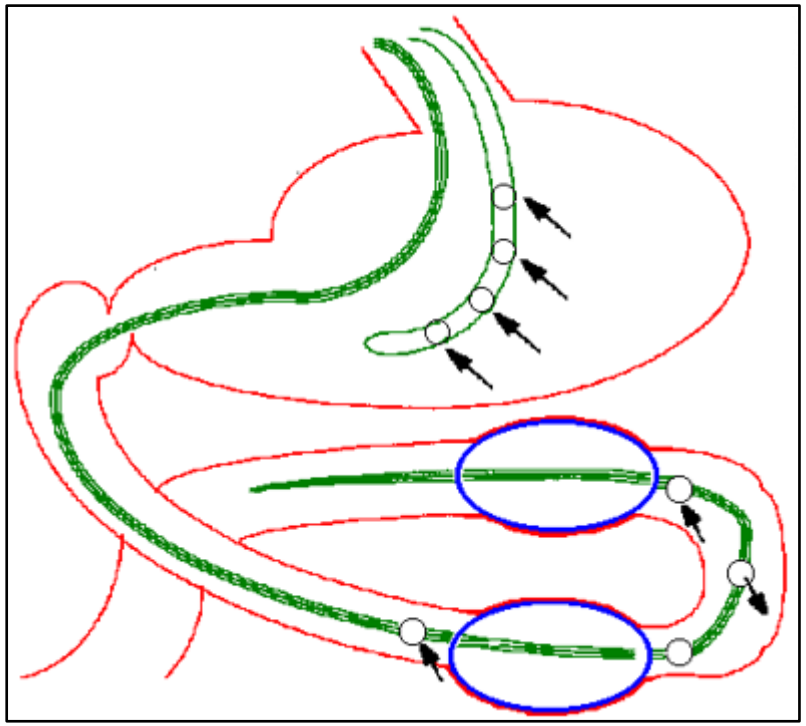
Paracellular Transit

Passive Routes:

- Transcellular Diffusion
- Paracellular Transit
- Passive transport

Active Routes:

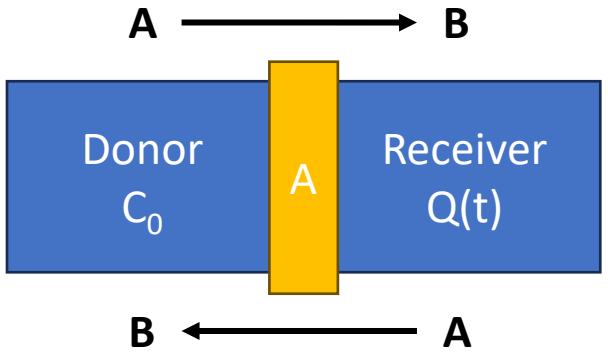
- Active transport



Device for the measurement of effective jejunal permeability (Peff)

Permeability

- Effective Jejunal Permeability (Peff) is rate of penetration into membrane (10^{-4} cm/s)
  - Units derived from typical convention of experiments measuring Papp/Peff



$$Papp = \frac{dQ}{dt} \times \frac{1}{A \times C_0}$$

- Does not account for ionization, concentration, or surface area of intestine → GP uses Absorption Scale Factors (ASFs) to account for this
- Must convert *in vitro* Papp to *in vivo* Peff

Absorption Scale Factors

- ASFs take into account ionization and intestinal geometry
- Default model is Optimized LogD SA/V
  - LogD accounts for ionization, change with pH of gut section
    - Only neutral form can absorb passively, still dependent on lipophilicity
  - Surface area and volume account for exposed absorption surface, including Surface Enhancement Factor (SEF) to account for species-specific anatomy
- ASFs have units of 1/cm, multiplied by Peff, yields **Ka in 1/s**
- Each gut section will thus have a unique Ka, which is applied to the concentration gradient of drug to calculate absorption over time

Permeability Conversions

- Built in correlations:
  - Caco-2 (ABS, SOLVO, COV)
  - PAMPA
  - Interspecies (dog, rat)

- Scaling to Controls method

$$\frac{Papp\ Control}{Peff\ Control} = Ratio = \frac{Papp\ Drug}{Peff\ Drug}$$

$$Peff\ Drug = Papp\ Drug \times \frac{Peff\ Control}{Papp\ Control}$$

Table 2. Permeability of Standard Compounds*

Drug	Direction	Concentration (mg/mL)	P_{app}	n
Metoprolol	AP→BL	0.4	29.88 ± 3.17	18
Atenolol	AP→BL	0.4	1.86 ± 0.47	4

Direction	Concentration (mg/mL)	P_{app}
AP→BL	3.0	2.49 ± 0.43
AP→BL	0.3	0.42 ± 0.06
AP→BL	0.03	1.82 ± 0.41

Avg Drug Papp = 1.58 e-6 cm/s

Closest to atenolol in experiment, so use atenolol as reference

Reference: Papp = 1.86 e-6 cm/s, Peff = 0.2 e-4 cm/s

$$Peff\ Drug = 1.58 \times \frac{0.2}{1.86} = \mathbf{0.17}$$

GastroPlus Activities

- Find experimental permeability, convert and put into GastroPlus
- Look at ASFs in ACAT table, relate to LogD vs pH profile
- Examine simulation results
  - Where does drug absorb?
  - How does it absorb?
  - Is absorption limited by dissolution or permeation?
  - Does this make sense based on the structure?
  - What about transporters…?