Mechanistic Distribution

PSCI-599, Spring 2024

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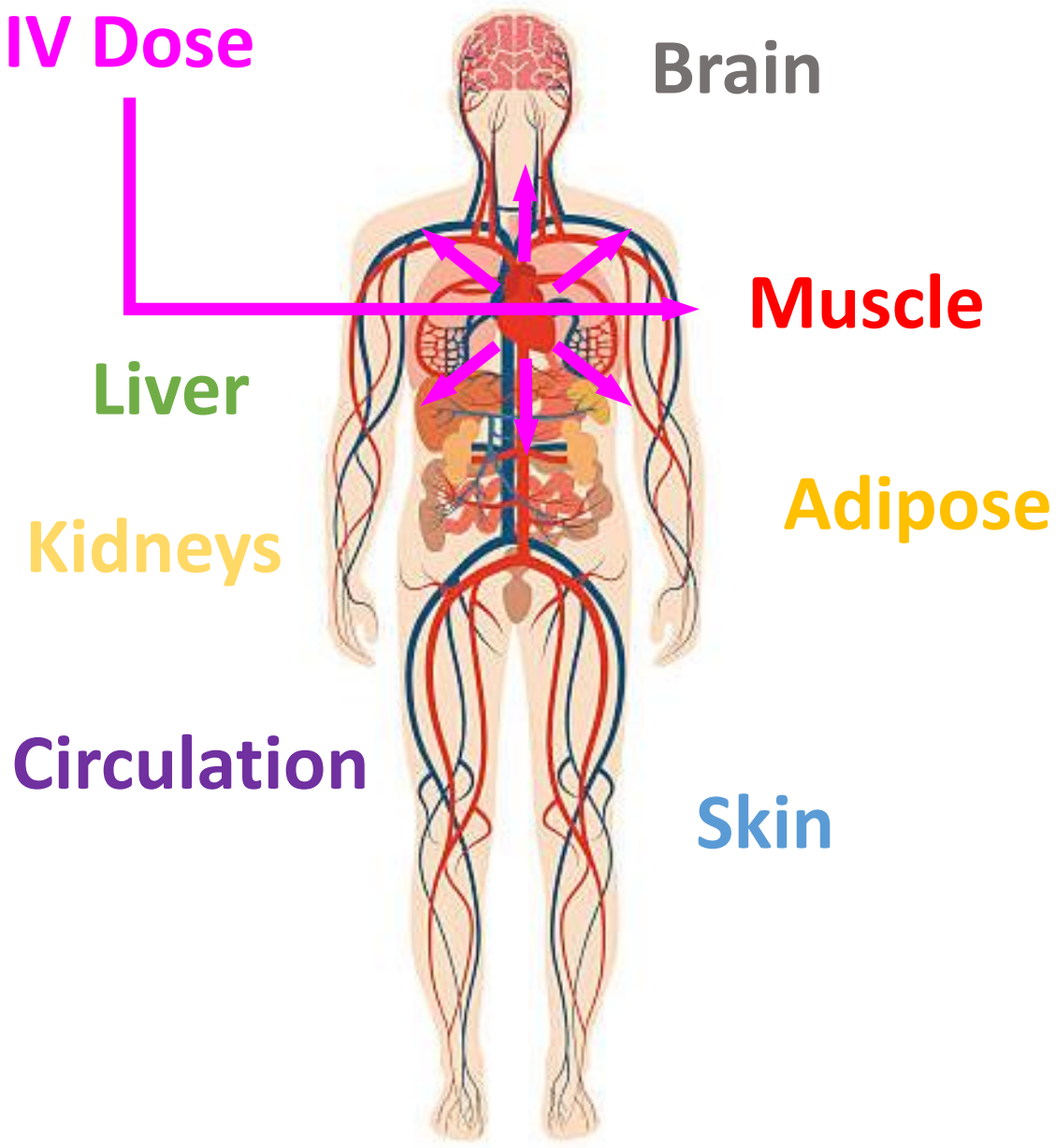
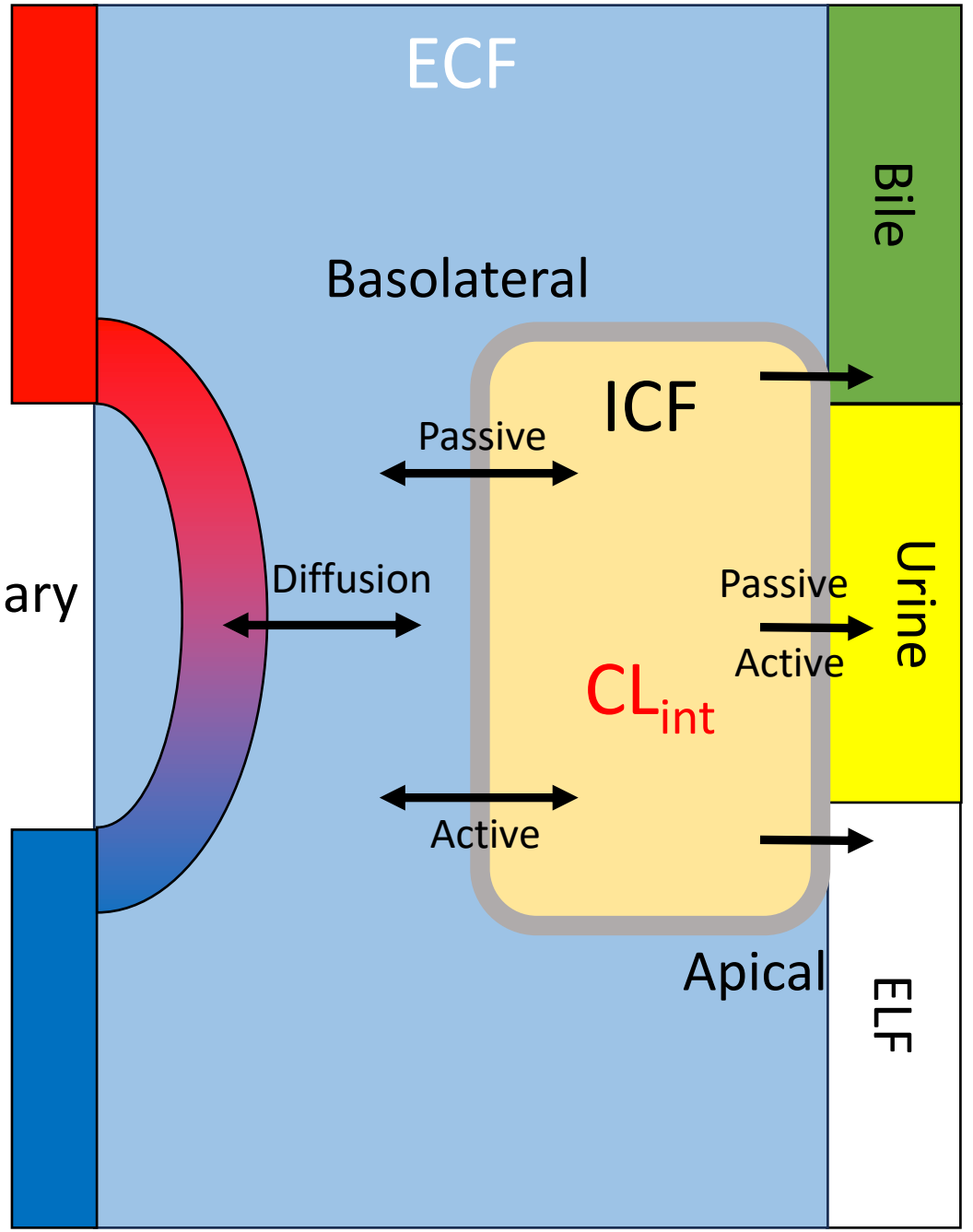

IV Dose
Brain
Muscle
Liver
Adipose
Kidneys
Circulation
Skin


ECF
Bile
Artery
Basolateral
ICF
Passive
Urine
Capillary
Diffusion
Passive
Active
CL_{int}
Active
Apical
ELF
Vein

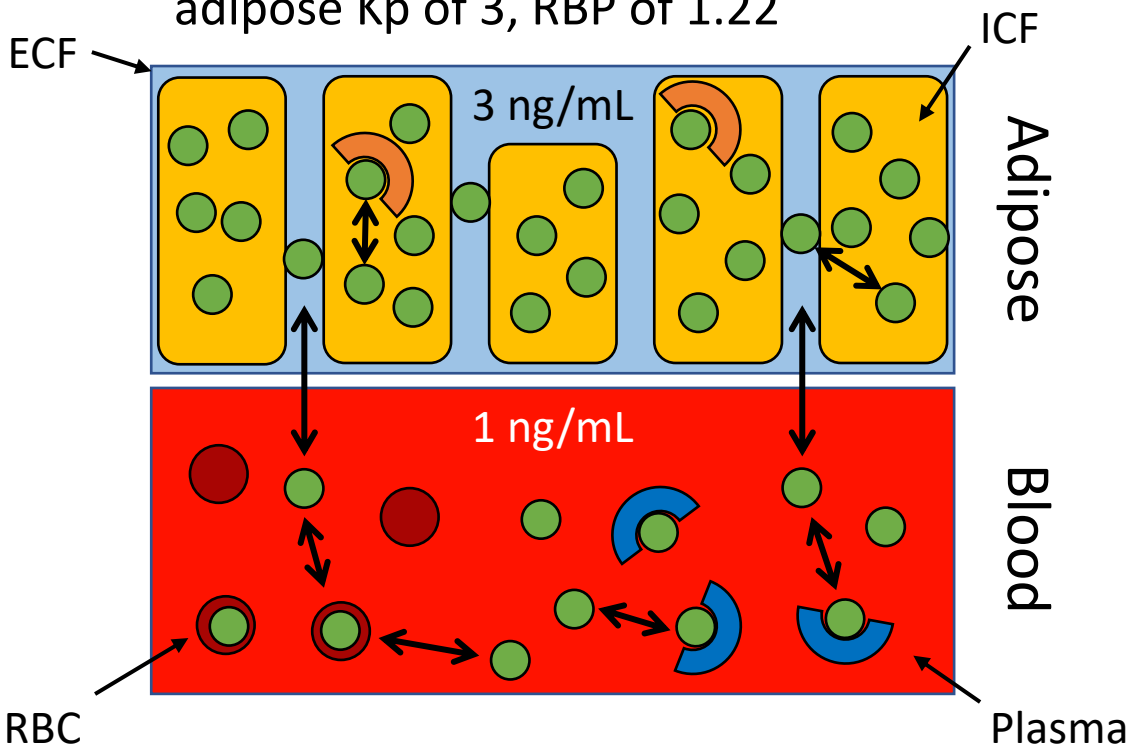
Distribution into Tissues

$$Kp = \frac{[Tissue]}{[Plasma]}$$

Kps define equilibrium concentrations between plasma and tissue, each tissue will have its own Kp for each drug.

Drug disposition, in terms of mass, will depend on both Kp and tissue size

Example: Lipophilic drug with adipose Kp of 3, RBP of 1.22



$$RBP = \frac{[Blood]}{[Plasma]} \neq \frac{[RBCs]}{[Plasma]}$$

Predicting Kps: Poulin-Theil Equations

$$Kp_{\text{homogenous}} = \frac{\left[K \cdot \left(V_{nlt} + 0.3V_{pht}\right)\right] + \left[1 \times \left(V_{wt} + 0.7V_{pht}\right)\right]}{\left[K \cdot \left(V_{nlp} + 0.3V_{php}\right)\right] + \left[1 \times \left(V_{wp} + 0.7V_{php}\right)\right]} \cdot \frac{fu_p}{fu_t}$$

K = lipid/water partition coefficient (e.g. LogP)

$$Kp_{extracellular} = V_e \cdot \frac{fu_p}{fu_t}$$

$$fu_t = 1/(1 + (((1 - fu_p)/fu_p) \cdot RA_t))$$

RA_t = ratio of albumin in tissue vs plasma

Predicting Kps: Lukacova Equation

$$Kpu = V_{ew} + \frac{1/X_{[D],iw}}{1/X_{[D],p}} V_{iw} + \left(\frac{P \cdot V_{nlt} + (0.3 \cdot P + 0.7) \cdot V_{pht} \cdot}{1/X_{[D],p}} \right) +$$

$$(Fn + Fa) \cdot \left[\frac{1}{fup} - 1 - \left(\frac{P \cdot V_{nlp} + (0.3 \cdot P + 0.7) \cdot V_{php} \cdot}{1/X_{[D],p}} \right) \right] \cdot RAtp +$$

$$(Fc) \cdot \left(\frac{Ka \cdot [AP]_T ((1/X_{[D],IW}) - 1)}{(1/X_{[D],P})} \right)$$

Ka = association constant between basic compounds and acidic phospholipids

Predicting Kp values: Lukacova Equation

$$Kpu = V_{ew} + \frac{1/X_{[D],iw}}{1/X_{[D],p}} V_{iw} + \left(\frac{P \cdot V_{nlt} + (0.3 \cdot P + 0.7) \cdot V_{pht} \cdot}{1/X_{[D],p}} \right) +$$

$$(Fn + Fa) \cdot \left[\frac{1}{fup} - 1 - \left(\frac{P \cdot V_{nlp} + (0.3 \cdot P + 0.7) \cdot V_{php} \cdot}{1/X_{[D],p}} \right) \right] \cdot RAtp +$$

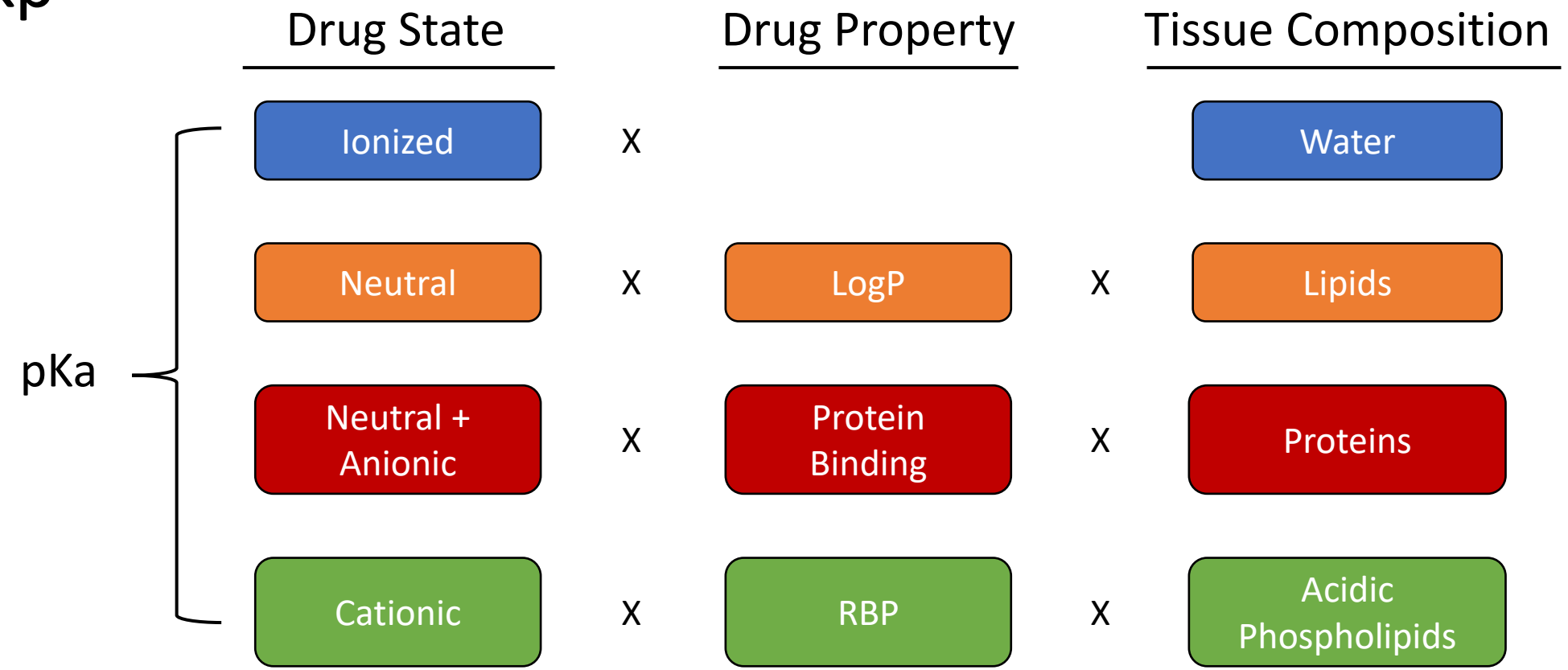
$$(Fc) \cdot \left(\frac{Ka \cdot [AP]_T ((1/X_{[D],IW}) - 1)}{(1/X_{[D],P})} \right)$$

Drug Properties

Tissue Properties

“Simplified” Lukacova relationships

Kp =



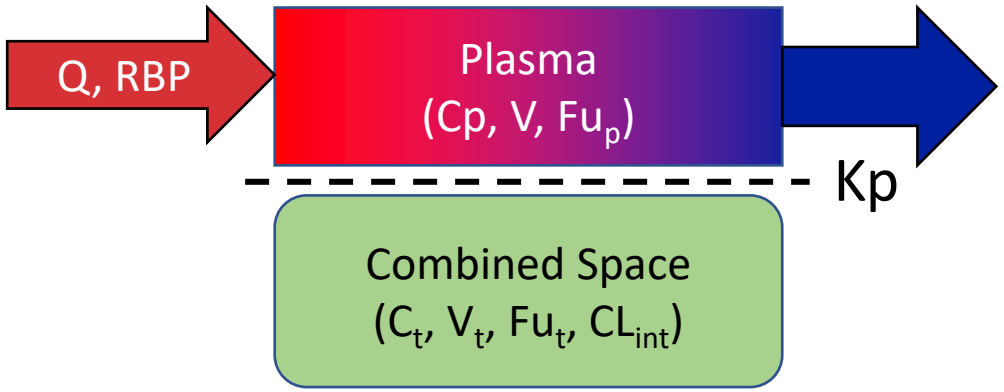
Kp (Lukacova method) is determined by **pKa**, **LogD**, **Fup**, and **RBP**

$$RBP = \frac{[Blood]}{[Plasma]} \neq \frac{[RBCs]}{[Plasma]}$$

Types of Tissue Models

Perfusion Limited (default):

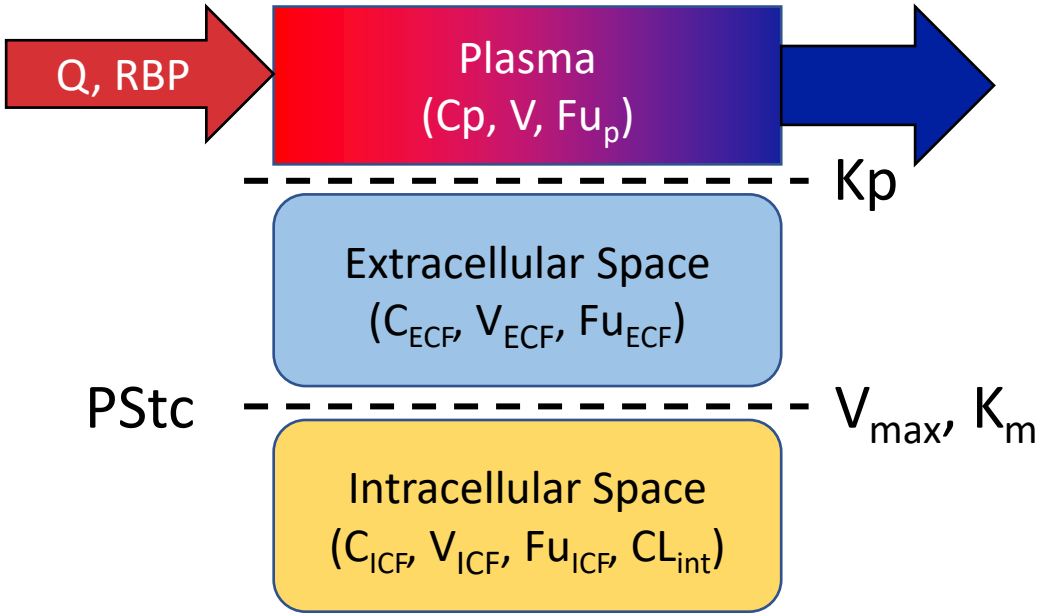
- Distribution is limited by unbound drug presentation via plasma
- Tissue is one "combined" compartment



Permeability Limited:

- Distribution is limited by drug transit across membrane
- Tissue has extracellular and intracellular compartments
- Kp dictates extracellular partitioning, Permeability-Surface Area Product (PStc) & transport control intracellular distribution

Permeability limited setting must be used for tissues with basolateral transporters



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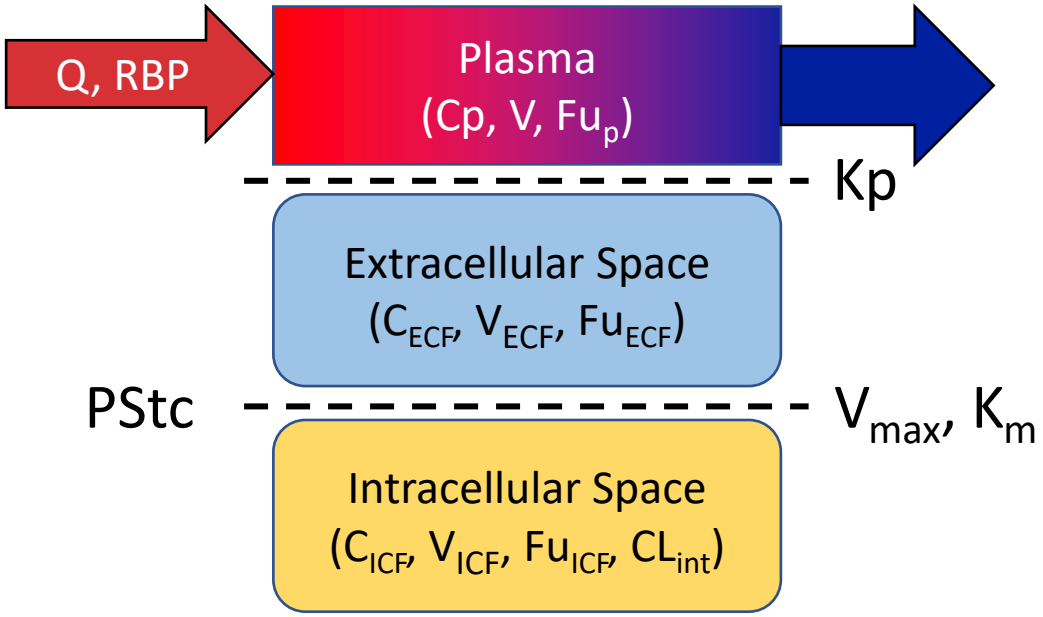
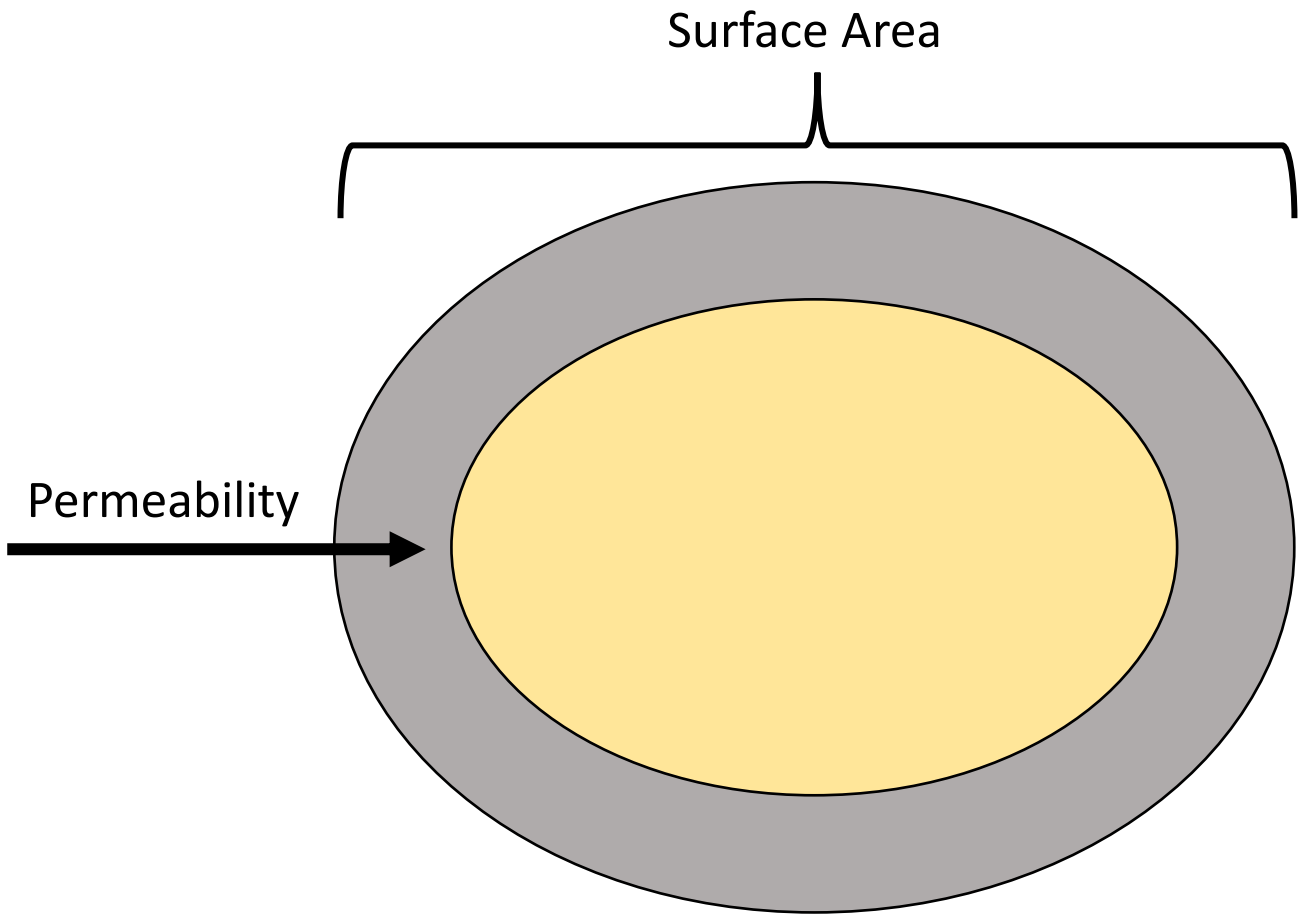


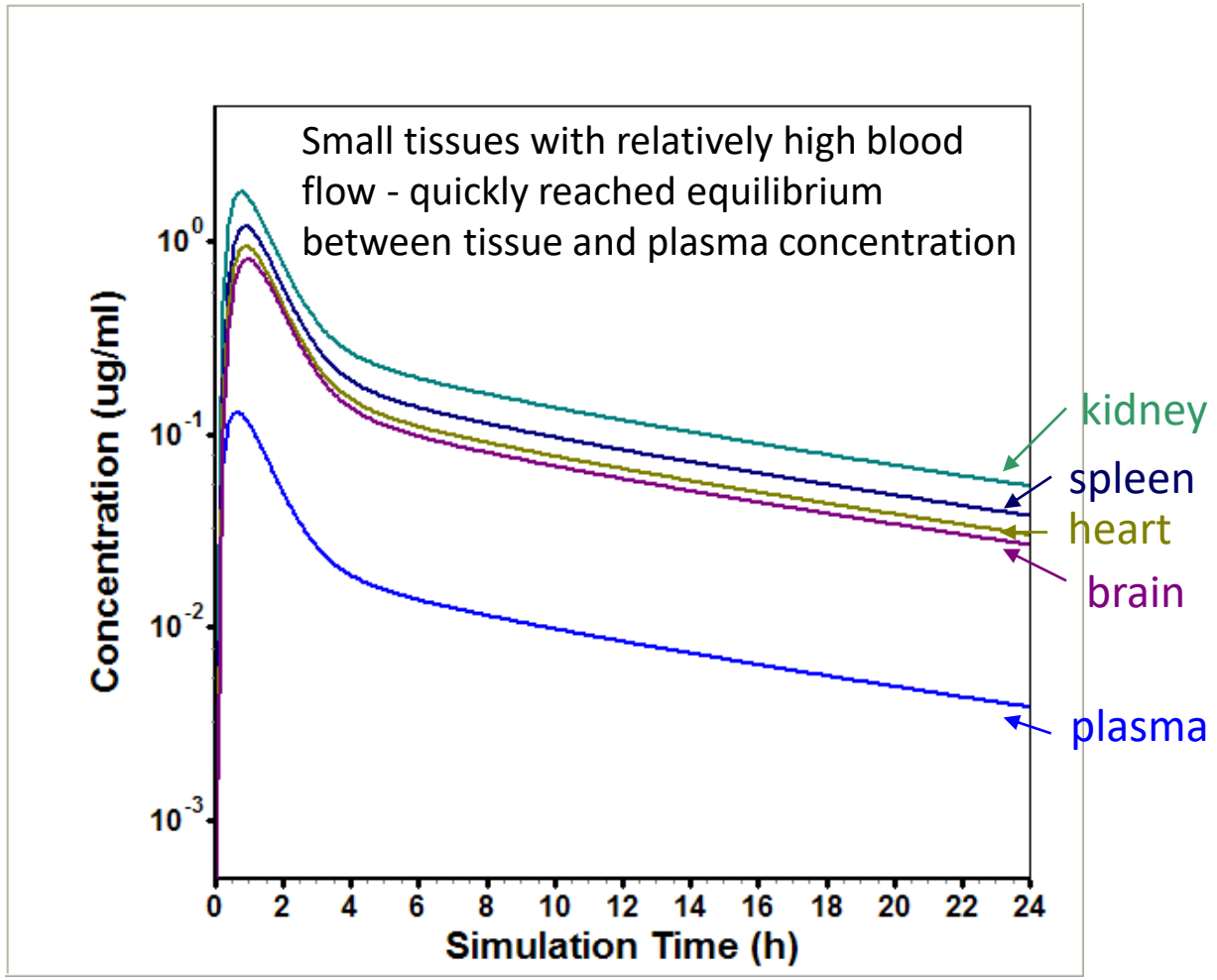


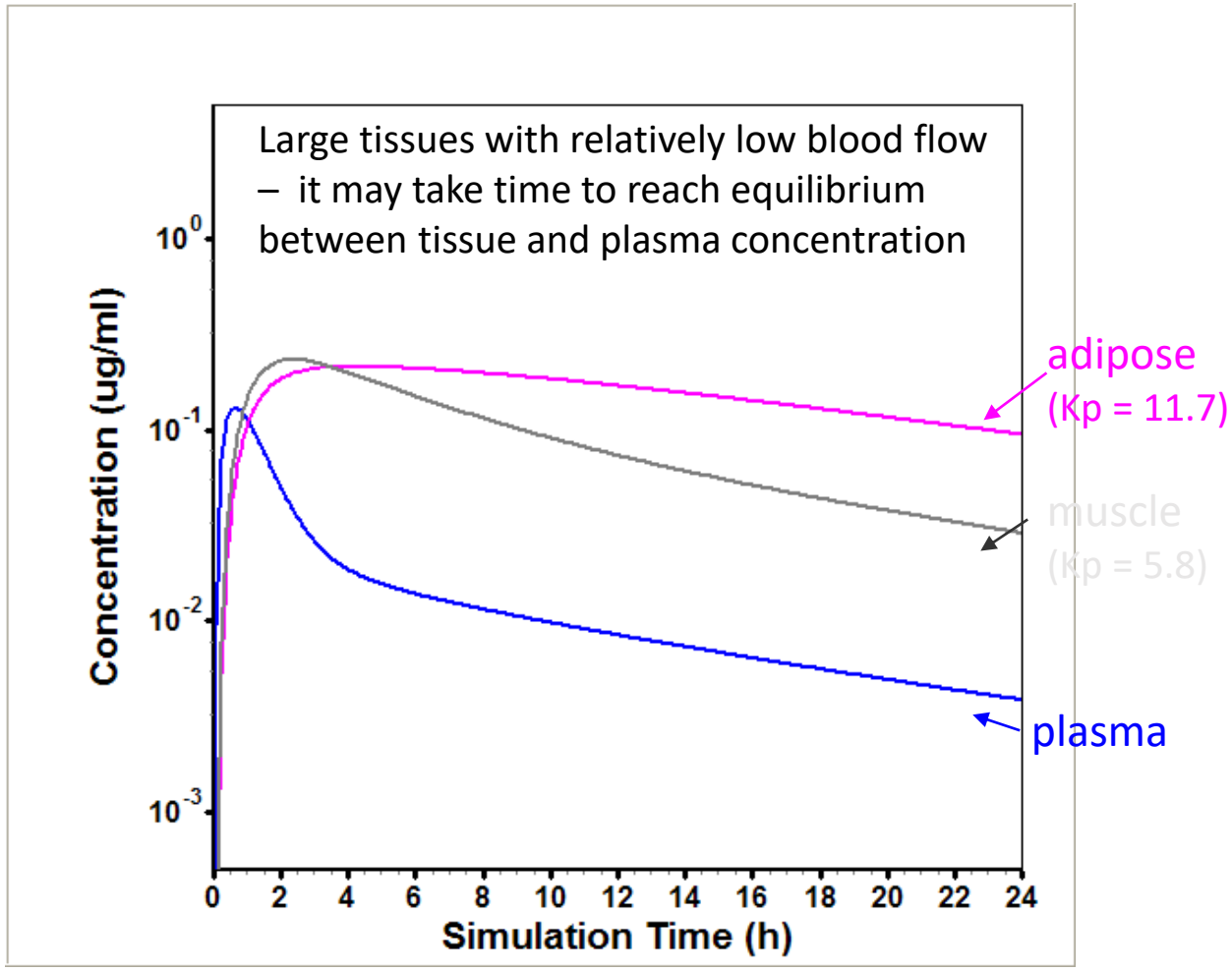
PStc has units of mL/s; multiply by mg/mL, and we get **mg/s**

Tissue PStc = **Specific PStc** x Tissue Volume x Cellular Fraction x Basolateral Fraction

Spec-PStc allows calculation of PStc for all tissues based on relative volumes (estimates surface area to volume ratio)

Perfusion-Limited Distribution





Perfusion Limited Example

Plasma Vol = 5,000 mL Muscle Vol = 25,000 mL Muscle Perfusion = 13 mL/s

Muscle Kp = 2

Dose = 100mg

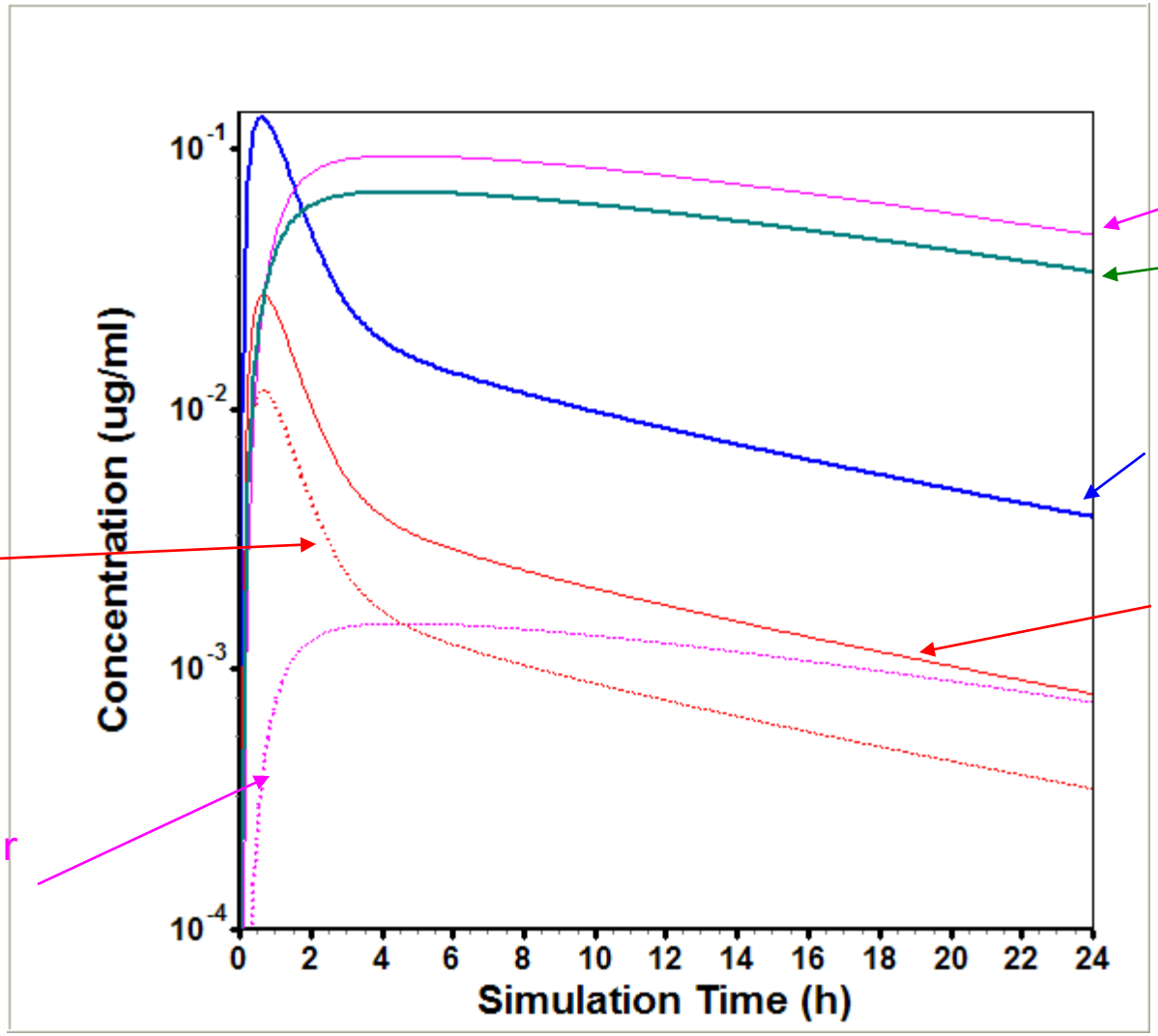
Initial Cp = 100 mg / 5000 mL = 0.02 mg/mL Muscle Conc. = 0 Obs Kp = 0

Drug mass delivered to muscle after 10s = 0.02 mg/mL * 13 mL/s * 10 s = 2.6 mg

Max muscle conc after 10s = 2.6 mg / 25000 mL = 0.000104 mg/mL
vs “expected” muscle conc of 0.04 mg/mL (Kp of 2 * 0.02 mg/mL)

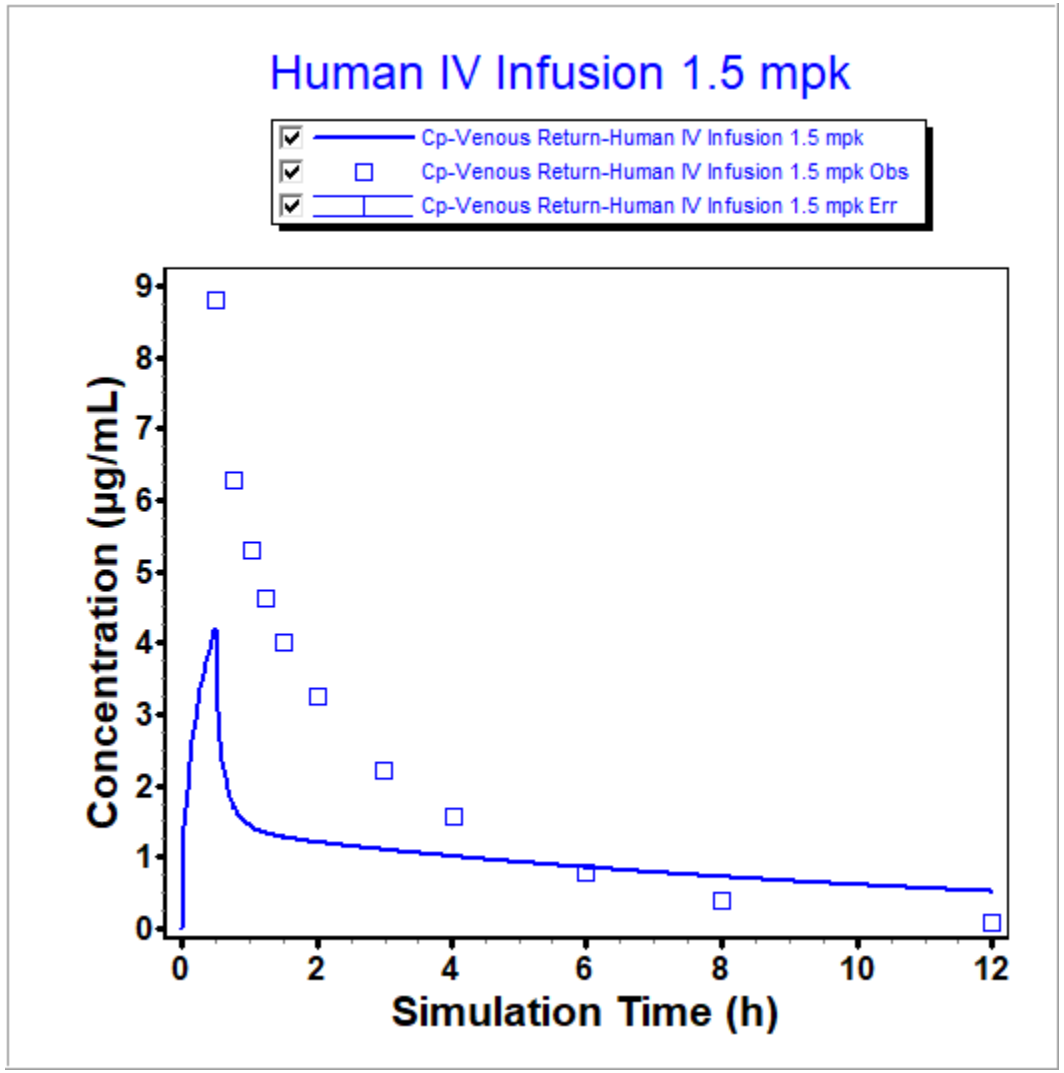
Resulting plasma mass = 100 mg – 2.6 mg = 97.4 mg
New plasma conc = 97.4 mg / 5000 mL = 0.01948
Obs Kp = 0.000104 / 0.01948 = 0.0053

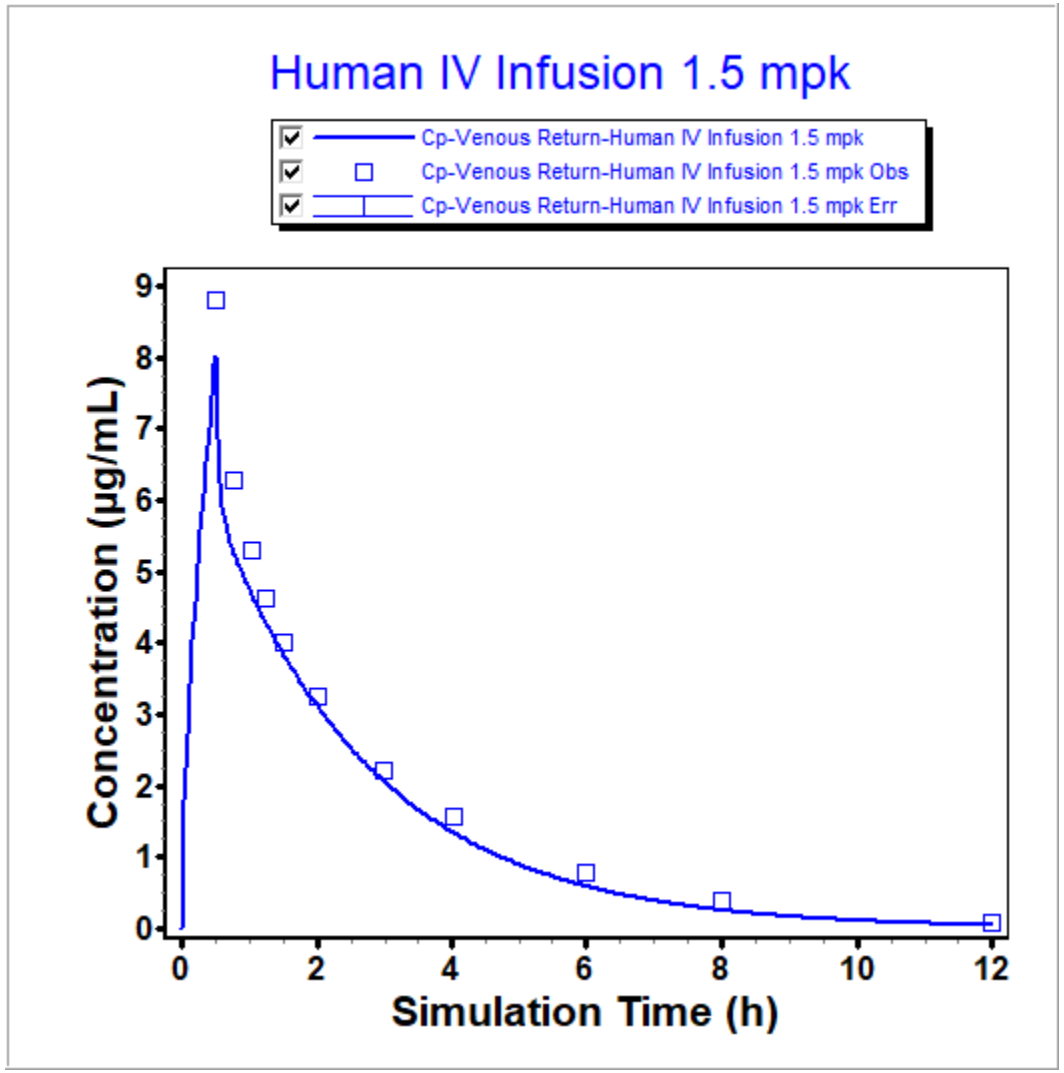
Permeability-Limited Distribution



Equilibration between plasma and ECF is still limited by tissue perfusion

Comparing Rate Limiting Steps





Perfusion Limited Tissues → Permeability Limited Tissues

Tips for GastroPlus

- Start with all tissues being perfusion-limited
  - Change to permeability-limited as needed
    - Transporters
    - Time-dependent distribution

- Perfusion limited = Lukacova Kp method
- Permeability limited = Poulin-Thiel Extracellular Kp method

GastroPlus Activities

Part 1 (Demo then Group Work)

- Enter Fup & RBP
- Recalculate Kps
- Run simulation, look at results, assess distribution
- Refine distribution