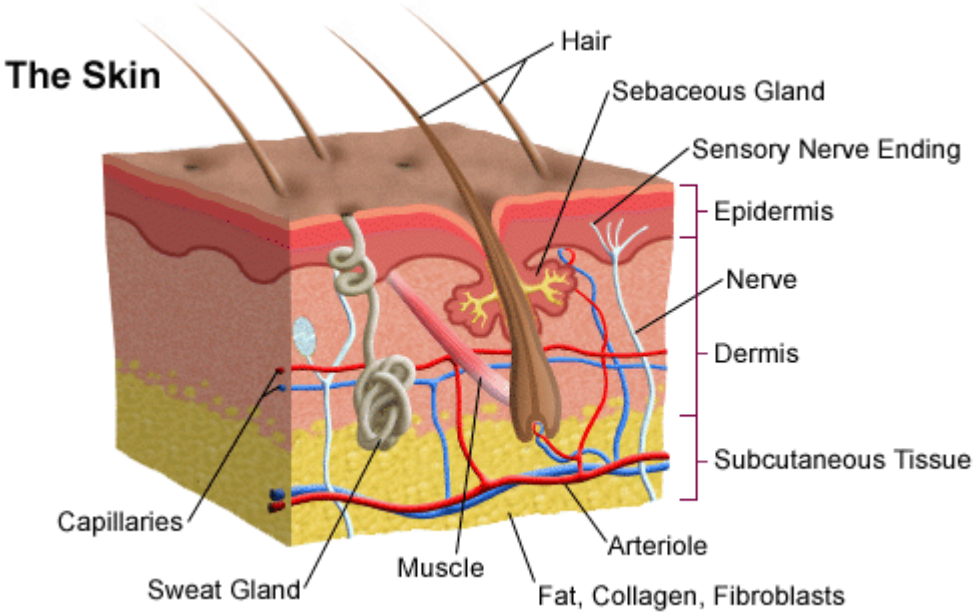
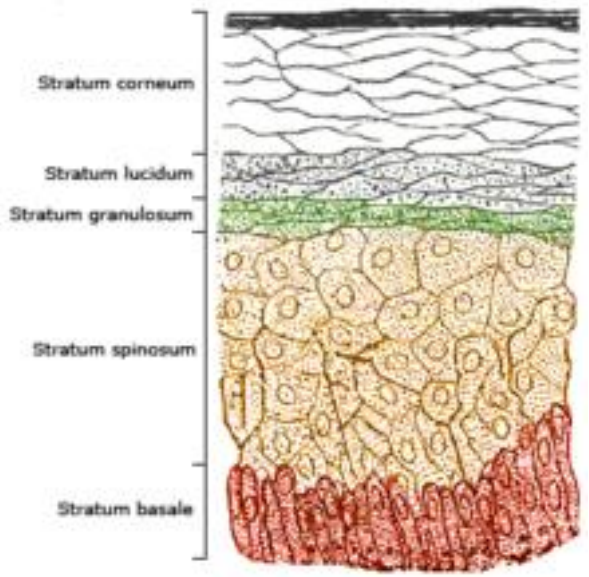
Mathematical models for dermal absorption



http://www.stanfordchildrens.org/



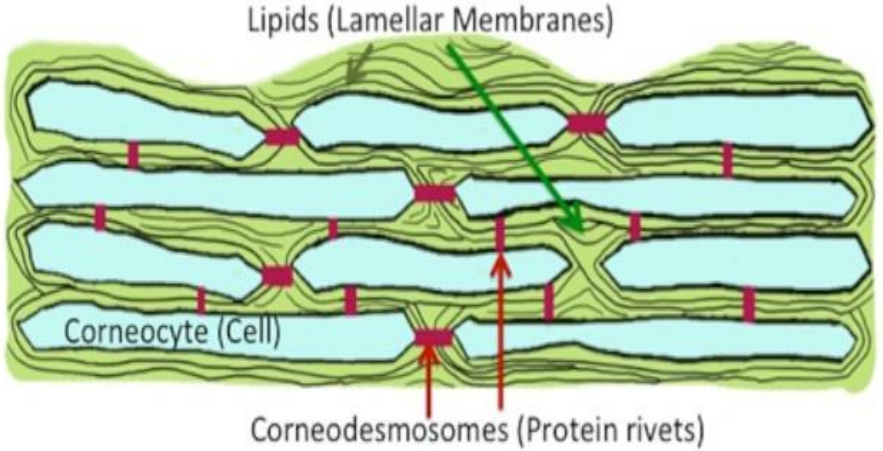
https://en.wikipedia.org/wiki/Epidermis

Key Considerations

Spatially heterogeneous domain

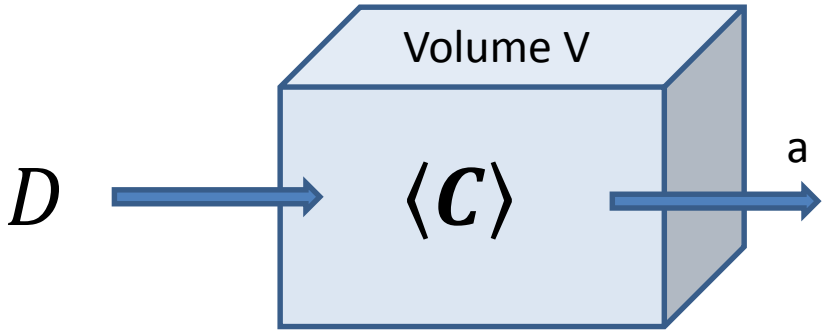
Boundary conditions

Dynamic processes



http://eliasandwilliams.com/skin-barrier/

PK (Pharmacokinetic) modelling



Conservation equation

$$V\frac{d\langle C\rangle}{dt} = \alpha D - a\langle C\rangle$$

McCarley & Bunge (2001) J. Pharm. Sci. **9:** 1699-1719

Key Considerations

What information is lost by assuming average concentration?

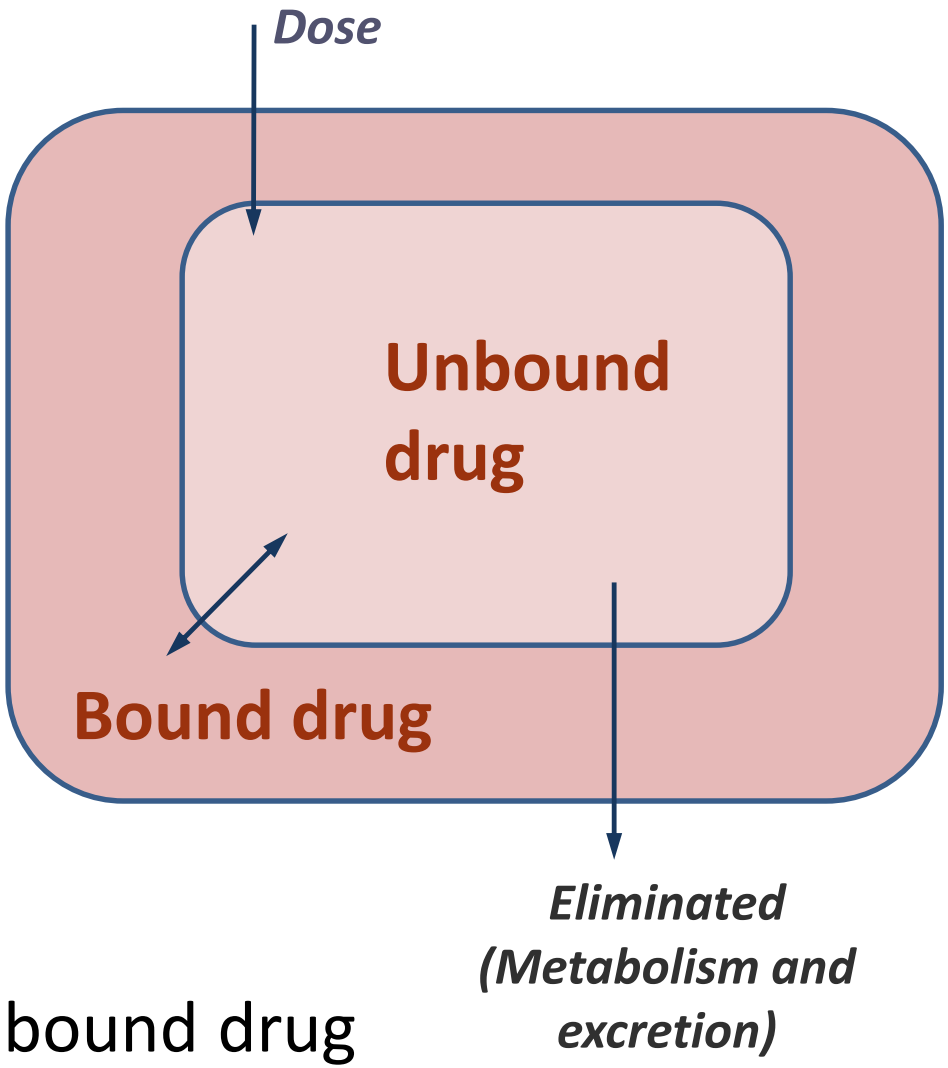
Should the model have multiple compartments?

Should other dynamic behaviours be included in model?

Potential to estimate parameters from literature.

Drug Kinetics: ADME processes

- **A**bsorption
- **D**istribution
- **M**etabolism
- **E**xcretion



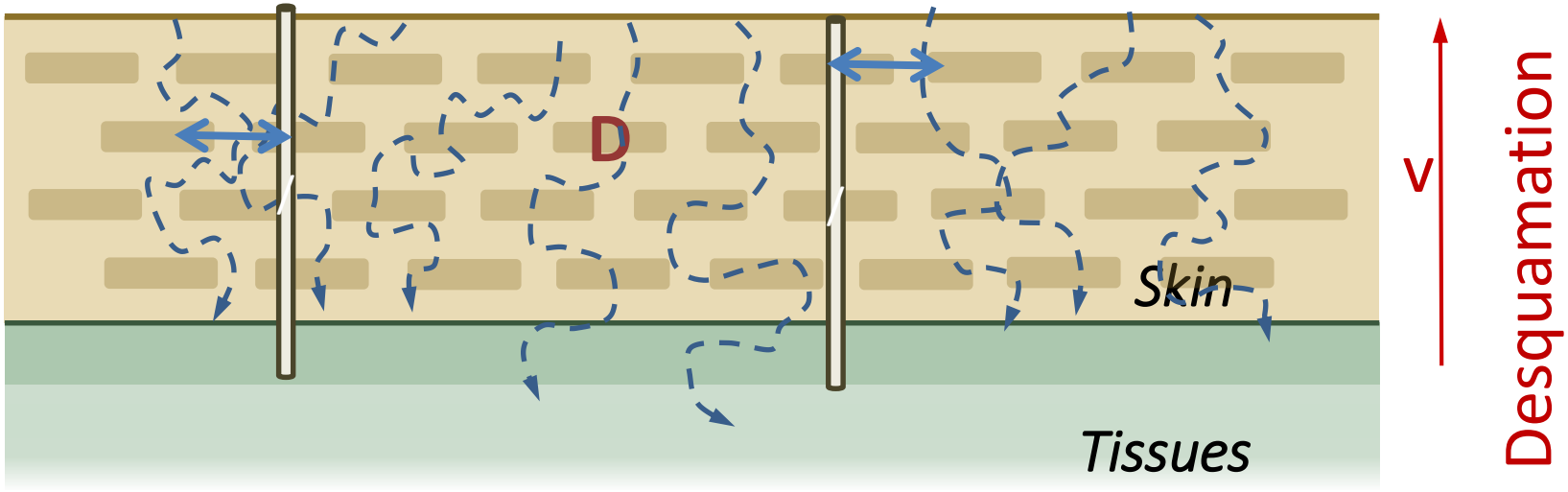
Key Considerations

Mechanisms for binding

Reversible process?

Differences bound vs. unbound drug

Movement in skin



Key Considerations

Components of movement

Routes through skin – aqueous vs lipid

Spatial domain

Path length

Boundary conditions

Conservation equation

$$\frac{\partial \boldsymbol{c}}{\partial t} + \nabla \cdot J = \boldsymbol{f}(\boldsymbol{c})$$

Boundary conditions specified on J and/or $\boldsymbol{c}$

Example $\boldsymbol{c} = (C_u(\boldsymbol{x}, t), C_b(\boldsymbol{x}, t))$

$C_u(\boldsymbol{x}, t) =$ Concentration unbound drug at $\boldsymbol{x}$ at time t

$C_b(\boldsymbol{x}, t) =$ Concentration bound drug at $\boldsymbol{x}$ at time t

$$\boldsymbol{J}_u = -\mathrm{D}\nabla C_u - \boldsymbol{v}C_u,$$

$$\boldsymbol{J}_b = -\boldsymbol{v}C_b$$

$$\boldsymbol{f} = (\mu C_b - \varphi C_u, \varphi C_u - \mu C_b)$$

Relationship between movement and physico-chemical properties of drugs

Partition between skin and formulation

Diffusion coefficient

$$k_p = \frac{KD}{h}$$

Permeability coefficient

Path length

$$\log\left[k_p(cmh^{-1})\right] = -2.7 + 0.71 \log K_{oct} - 0.0061MW$$

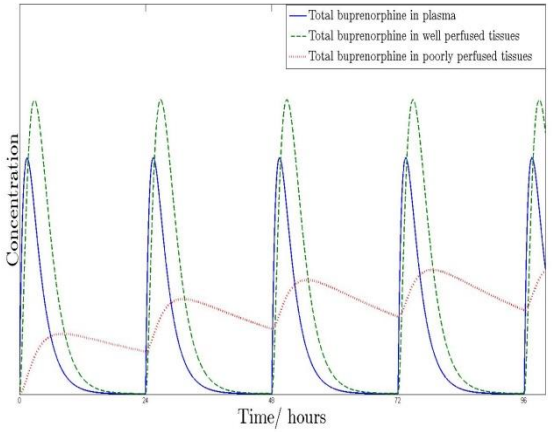
Octanol-water partition coefficient

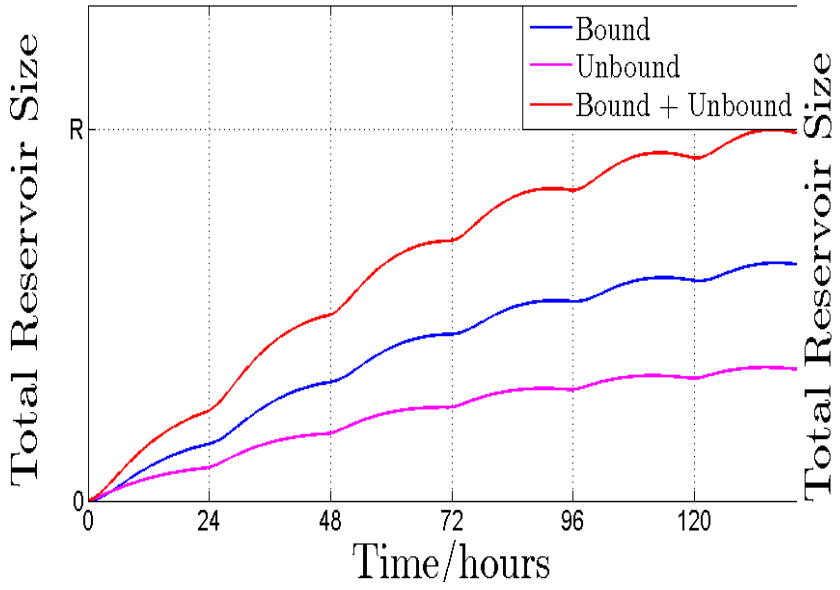
Molecular weight

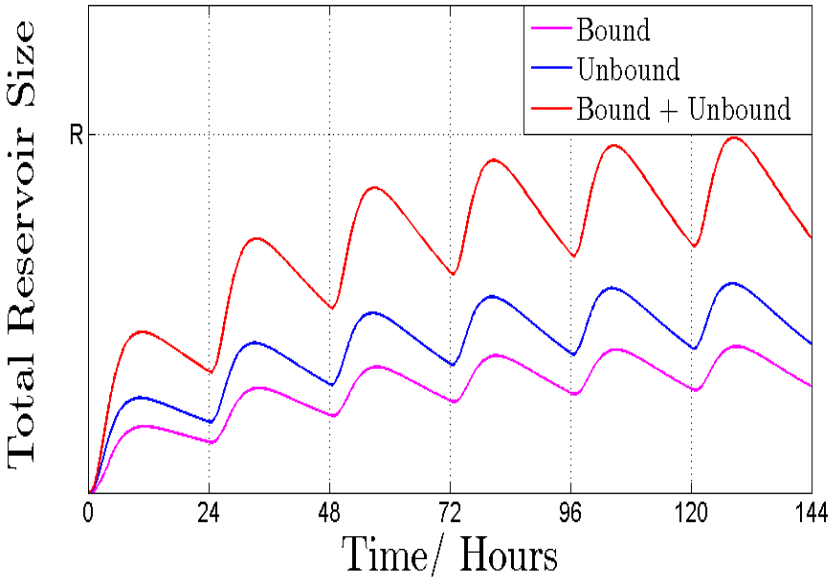
Potts & Guy (1992) Pharm. Res. **9:** 663-669
Hadgraft(2004) Eur. J. Pharm. & Biopharm. **58**: 291-299

Impact of diffusion rate on skin drug reservoir

Systemic drug concentration







D

Drug extraction from skin reservoir