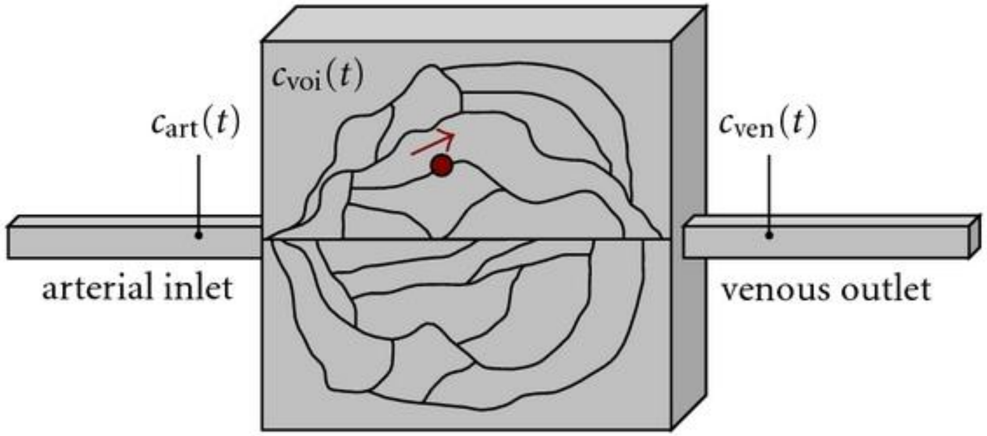
Basic physiology, blood, tissue and blood-brain barrier



volume of interest (V_{voi}) = volume of parenchyma and interstitial space (V^*_{voi}) + volume of capillary bed (V_{cap})

Tracers

- Present at tracer concentration only
- Steady-state with re. to tracee
- Well mixed with tracee
- Homogenous tissue
- Preservation of mass

Tracers

Radioisotopes
- β
- γ
- e^+

Stable isotopes
- $^2H = D$
- ^{13}C
- ^{15}N

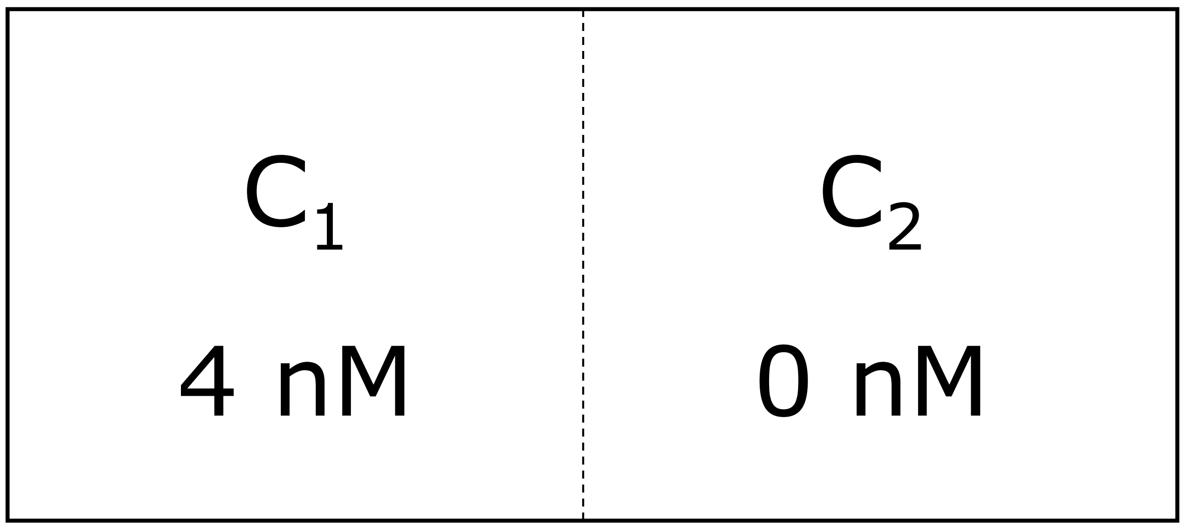
Dyes

Heat/cold

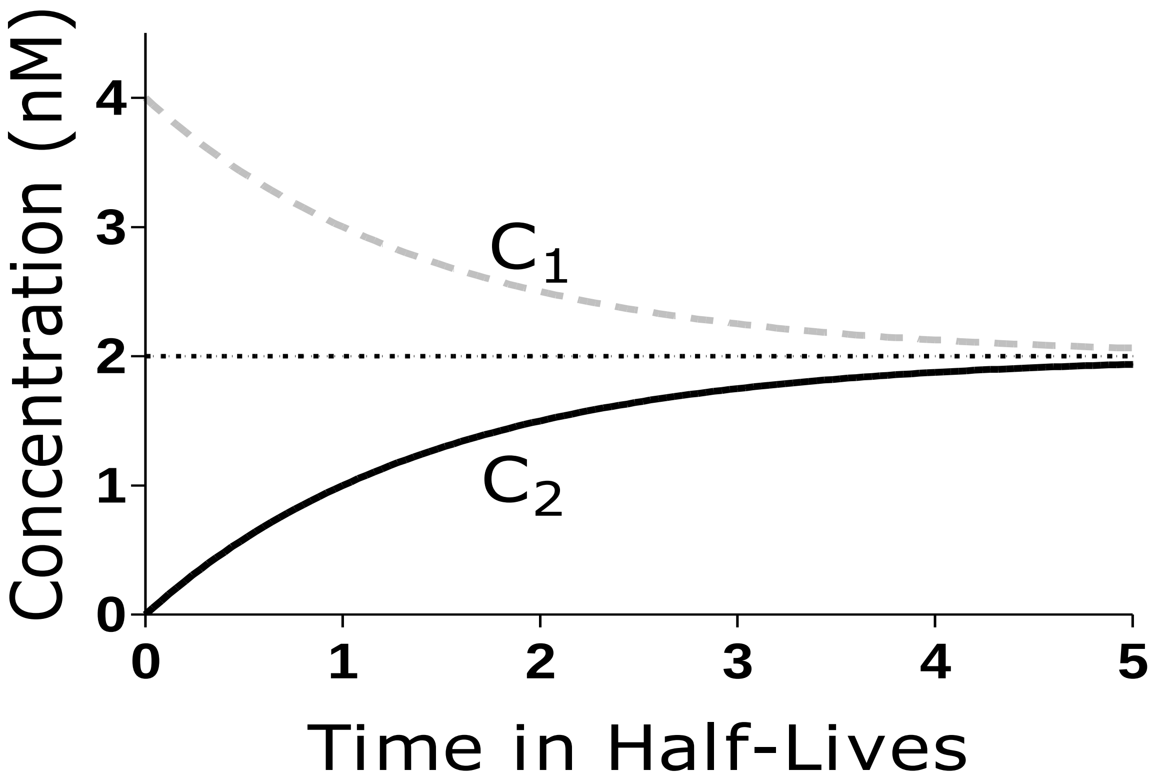
MR-based contrast (Gadolinium)

Two-Chamber Model: Equal Volumes
Semi-permeable membrane

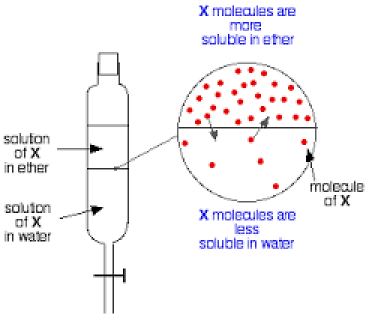
Experiment #1: Initial Conditions



Concentrations exponentially approach 2 nM



Partition coefficient



$$\lambda = C_{tissue}/C_{blood}$$

- at equilibrium

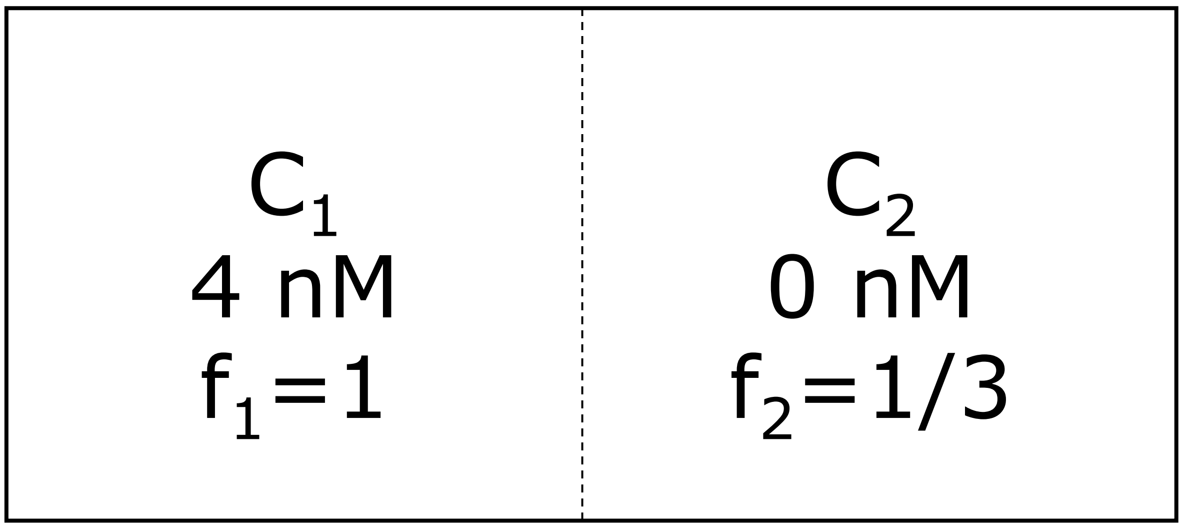
- usually λ is measured *in vitro*

- whereas the *in vivo* measured distribution volume is noted V_T

Two-Chamber Model: Equal Volumes
Semi-permeable membrane

Experiment #2: Initial Conditions

Add protein to chamber 2 to bind 2/3rd of drug



Free Concentration: F
Free fraction: f

C_1	C_2
4 nM	0 nM
$f_1=1$	$f_2=1/3$

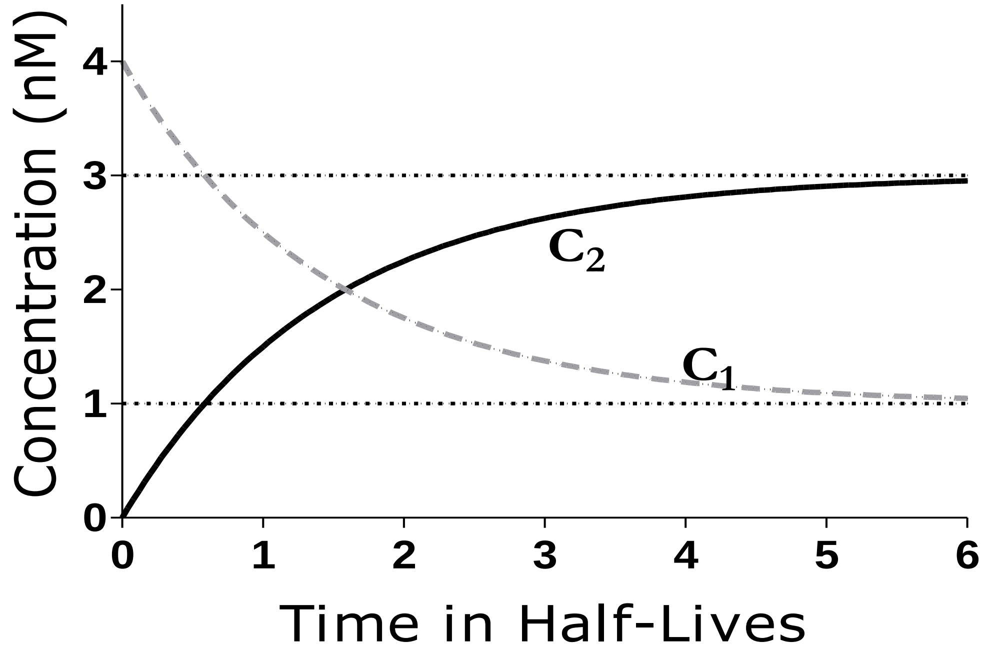
$$F_1 = f_1 * C_1$$

$$F_2 = f_2 * C_2$$

Equilibrium:

$$F_1 = F_2$$

Equilibrium concentrations



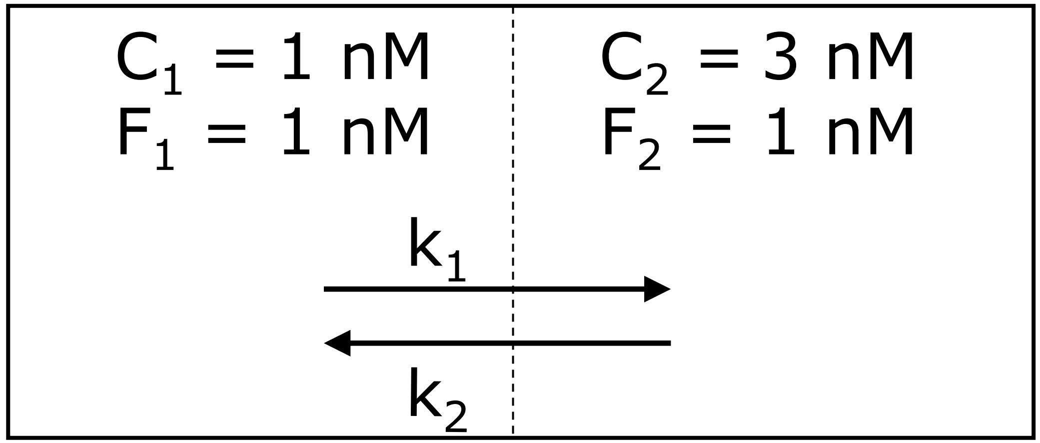
Equilibrium: C_1 = 1 nM C_2 = 3 nM

$F_1 = f_1 * C_1 = 1 * 1$ nM = 1 nM

$F_2 = f_2 * C_2 = 1/3 * 3$ nM = 1 nM

$F_1 = F_2$

Dynamic Equilibrium Conditions



Equilibrium: Forward rate = reverse rate

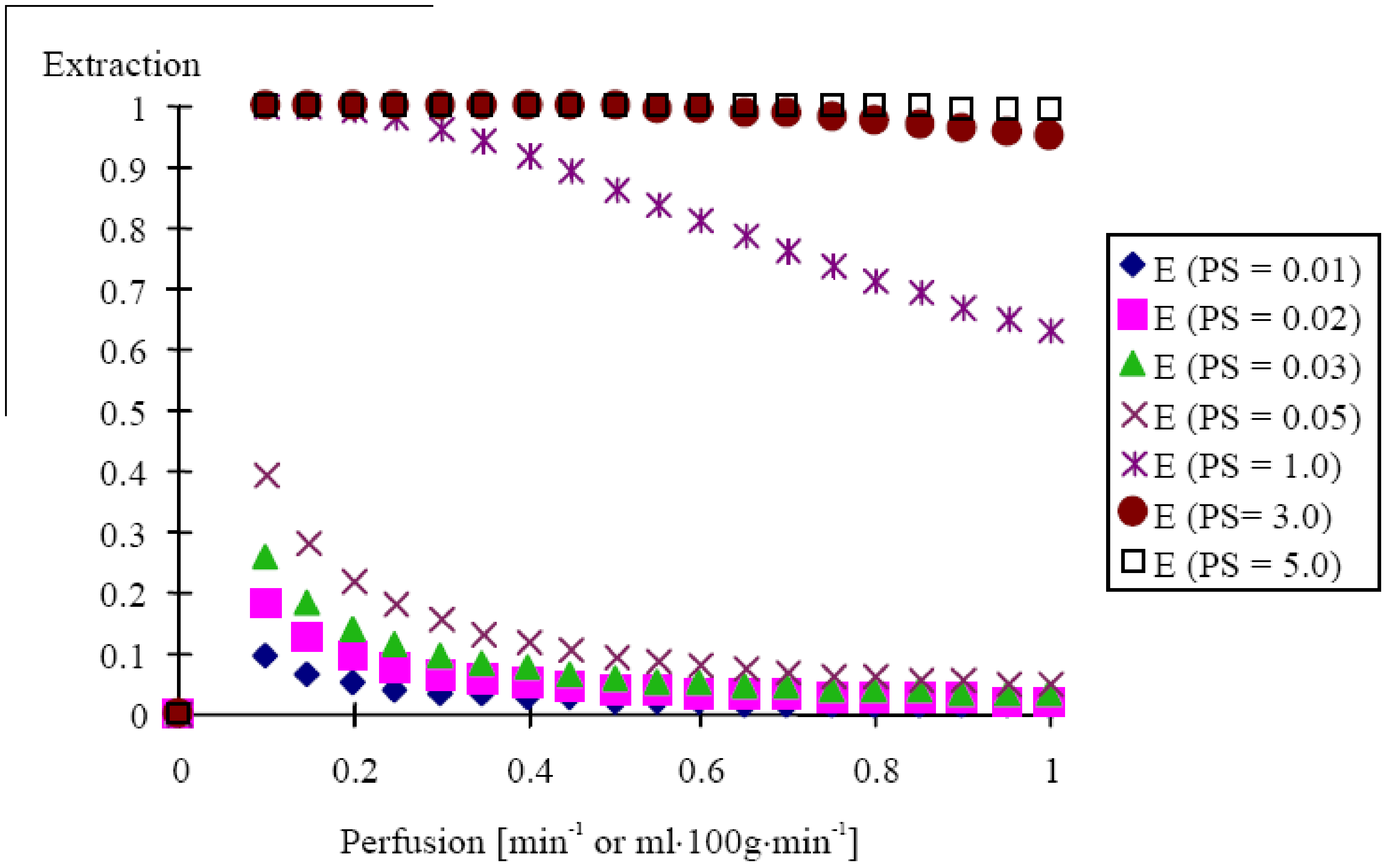
$$k_1 C_1 = k_2 C_2$$

$$\frac{k_1}{k_2} = \frac{C_2}{C_1} = \frac{3}{1}$$

Kinetics vs. Equilibrium

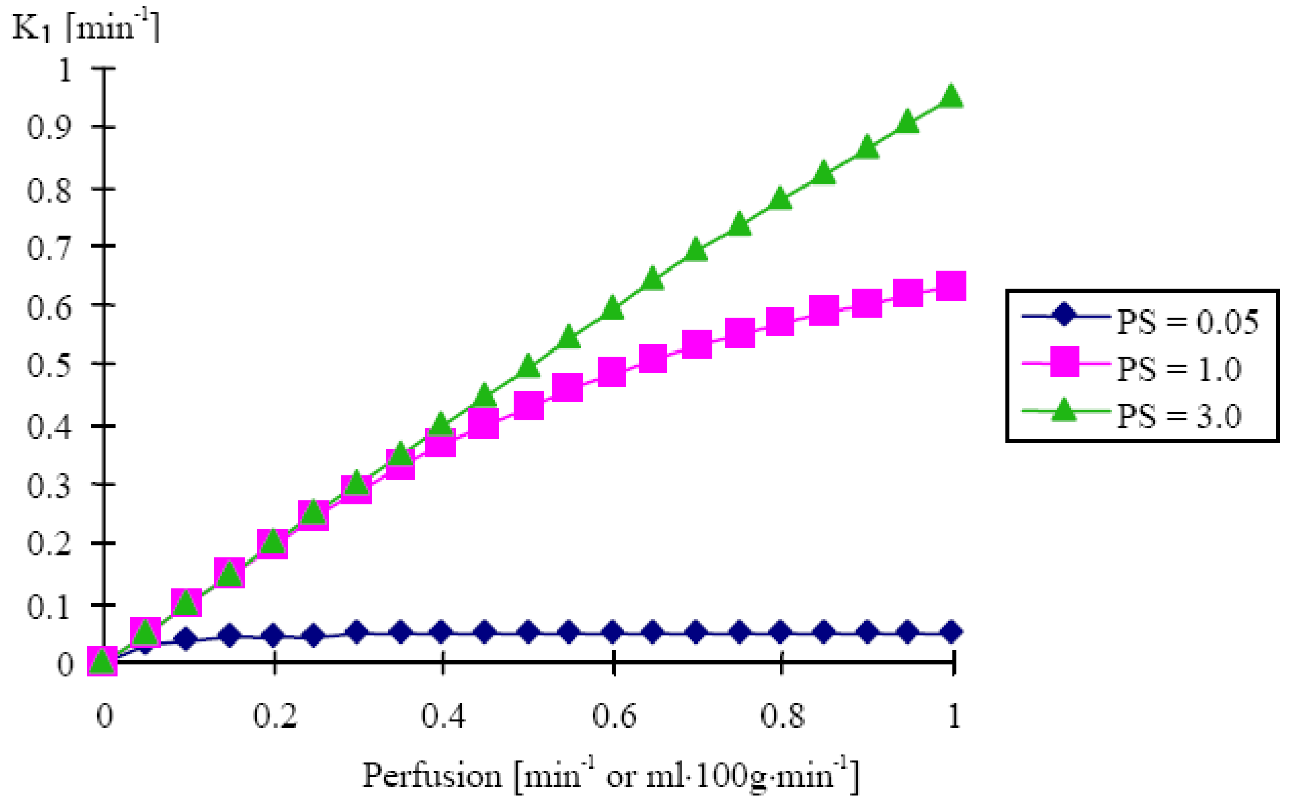
$$\frac{k_1}{k_2} = \frac{C_2}{C_1} = \frac{3}{1}$$

The rate constants determine equilibrium values. Where you are on a given time point depends on how fast the compounds are moving.



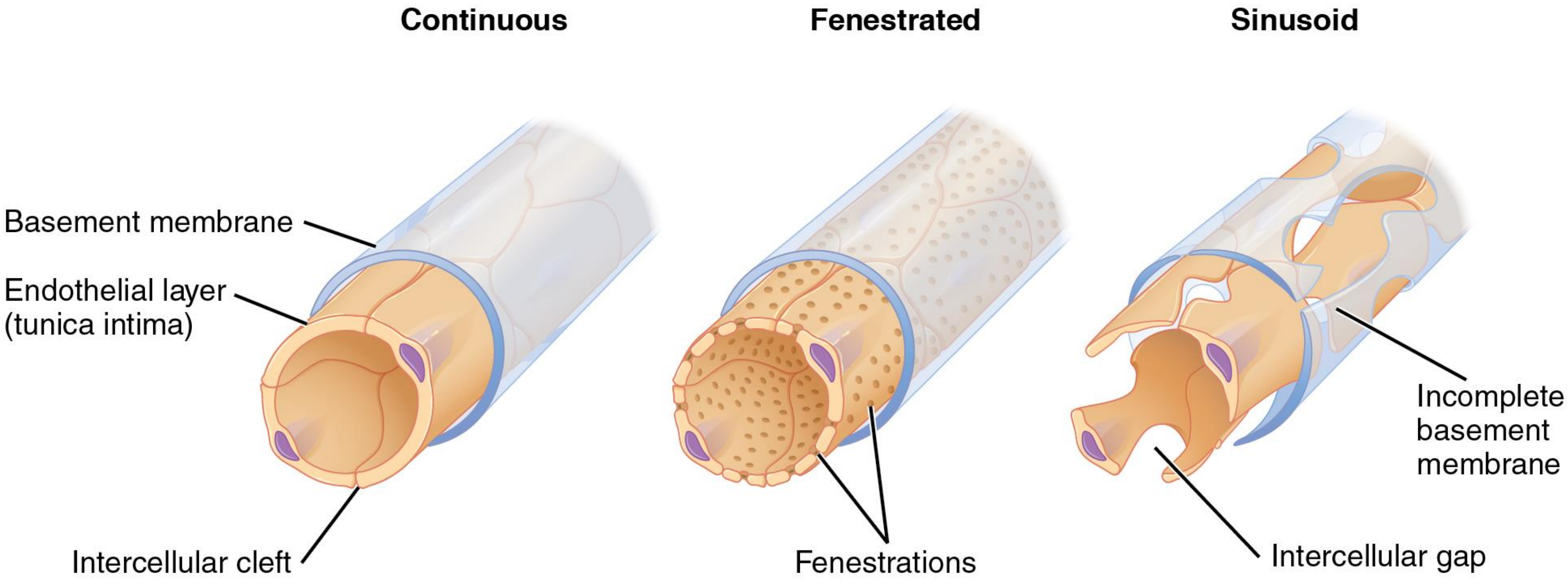
Extraction
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.2
0.4
0.6
0.8
1
Perfusion [min-1 or ml·100g·min-1]
E (PS = 0.01)
E (PS = 0.02)
E (PS = 0.03)
E (PS = 0.05)
E (PS = 1.0)
E (PS= 3.0)
E (PS = 5.0)

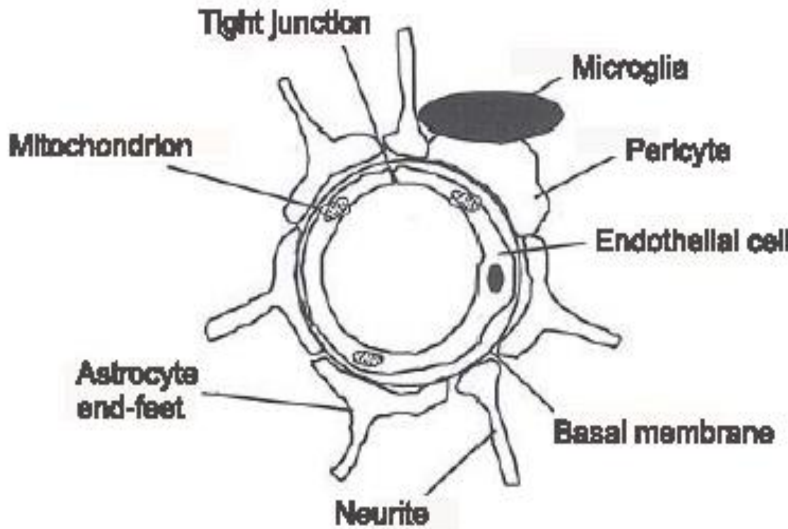
$$E = 1 - \exp(-PS/F)$$

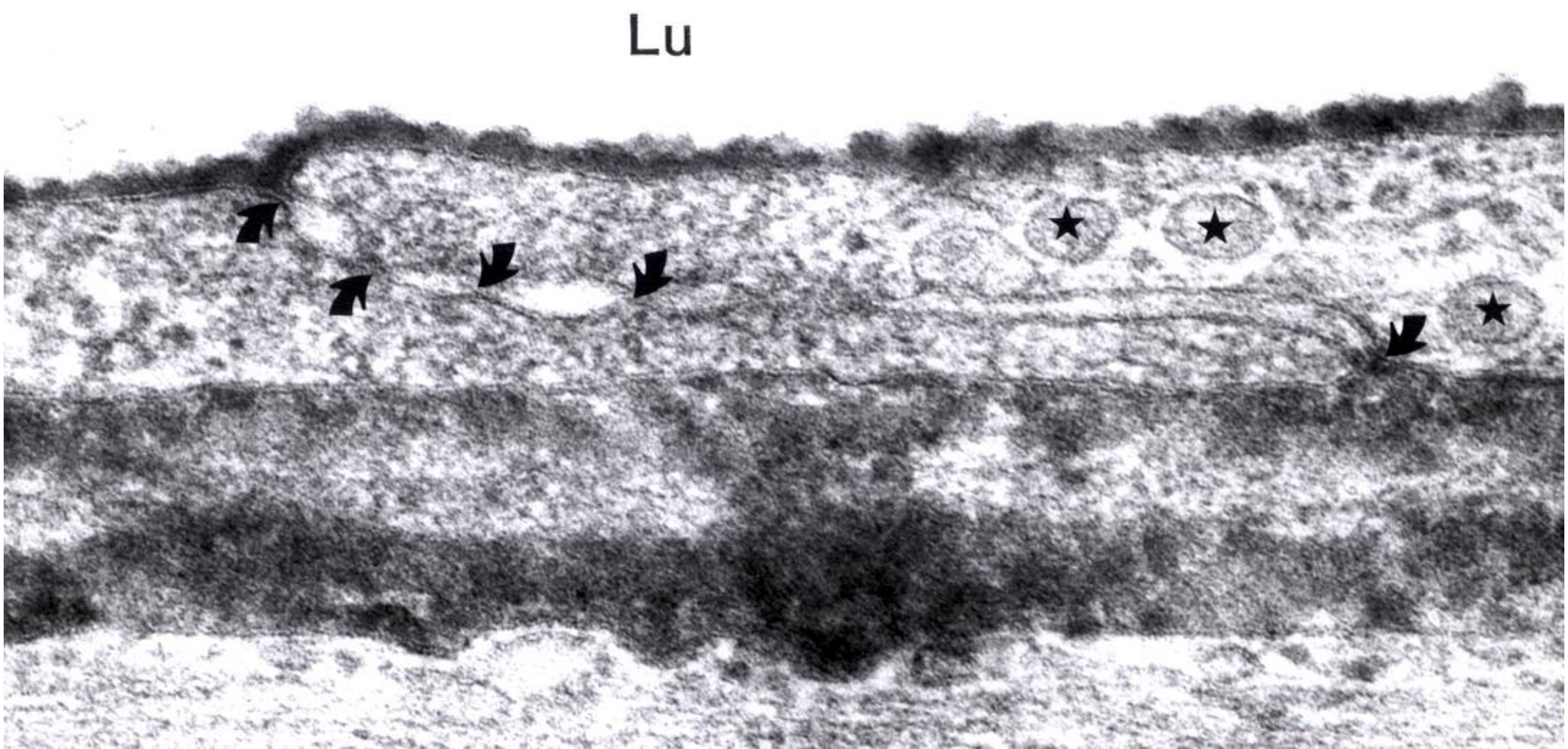


K_1 [min^{-1}]
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.2
0.4
0.6
0.8
1
Perfusion [min^{-1} or ml·100g·min^{-1}]
PS = 0.05
PS = 1.0
PS = 3.0

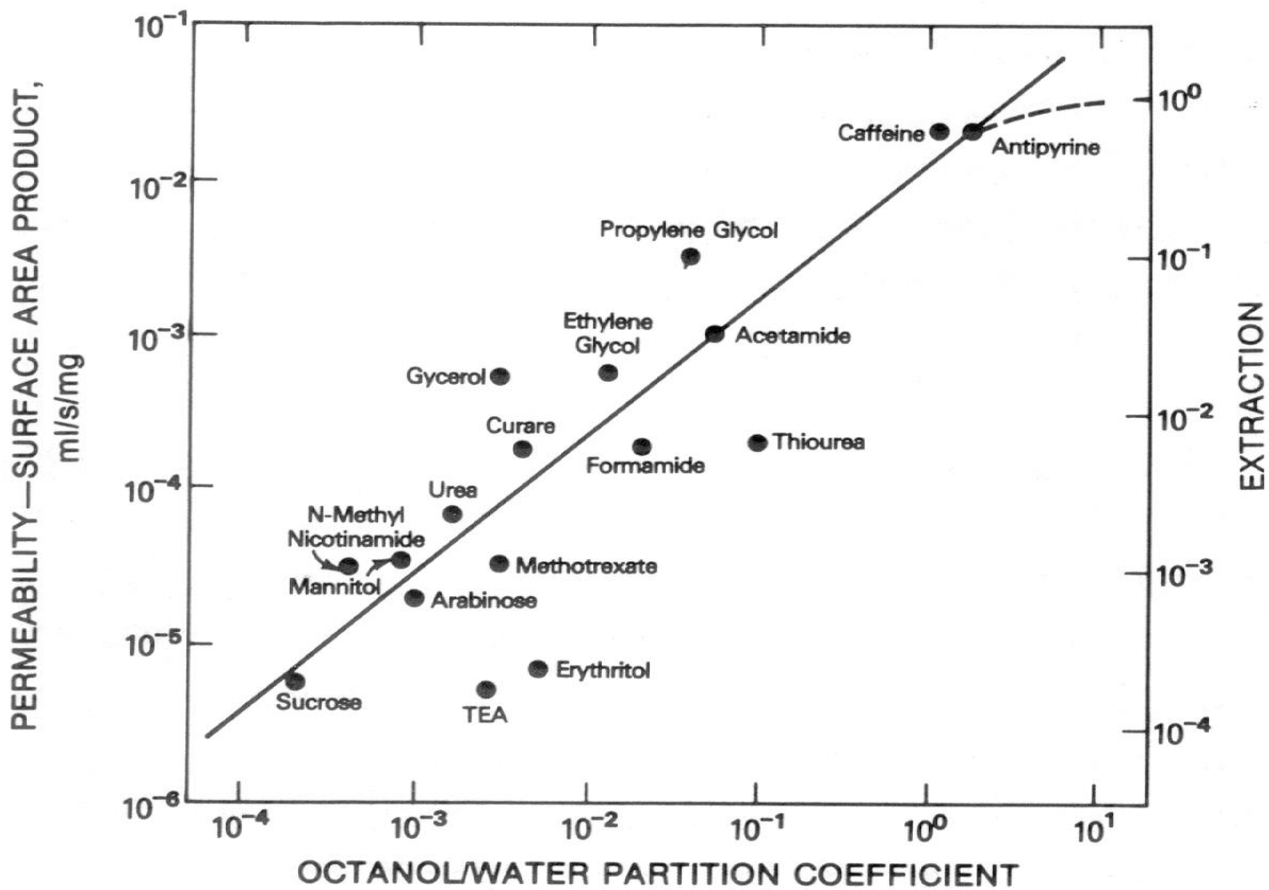
Different types of capillaries



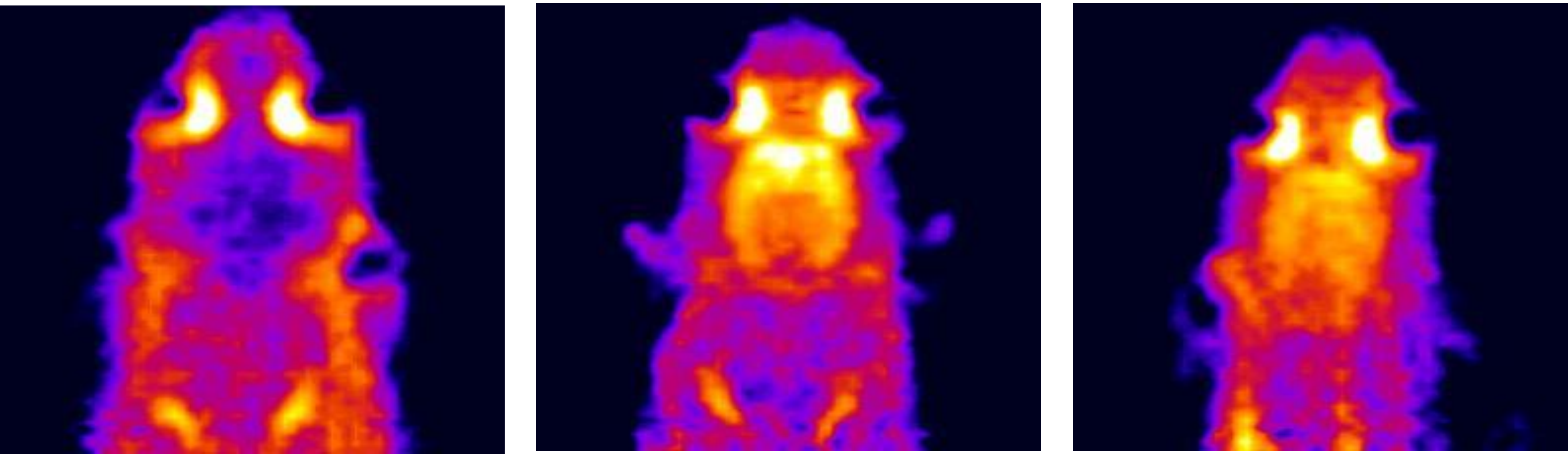

Tight junction
Microglia
Mitochondrion
Pericyte
Endothelial cell
Astrocyte
end-feet
Basal membrane
Neurite


Lu

Permeability vs. lipophilicity

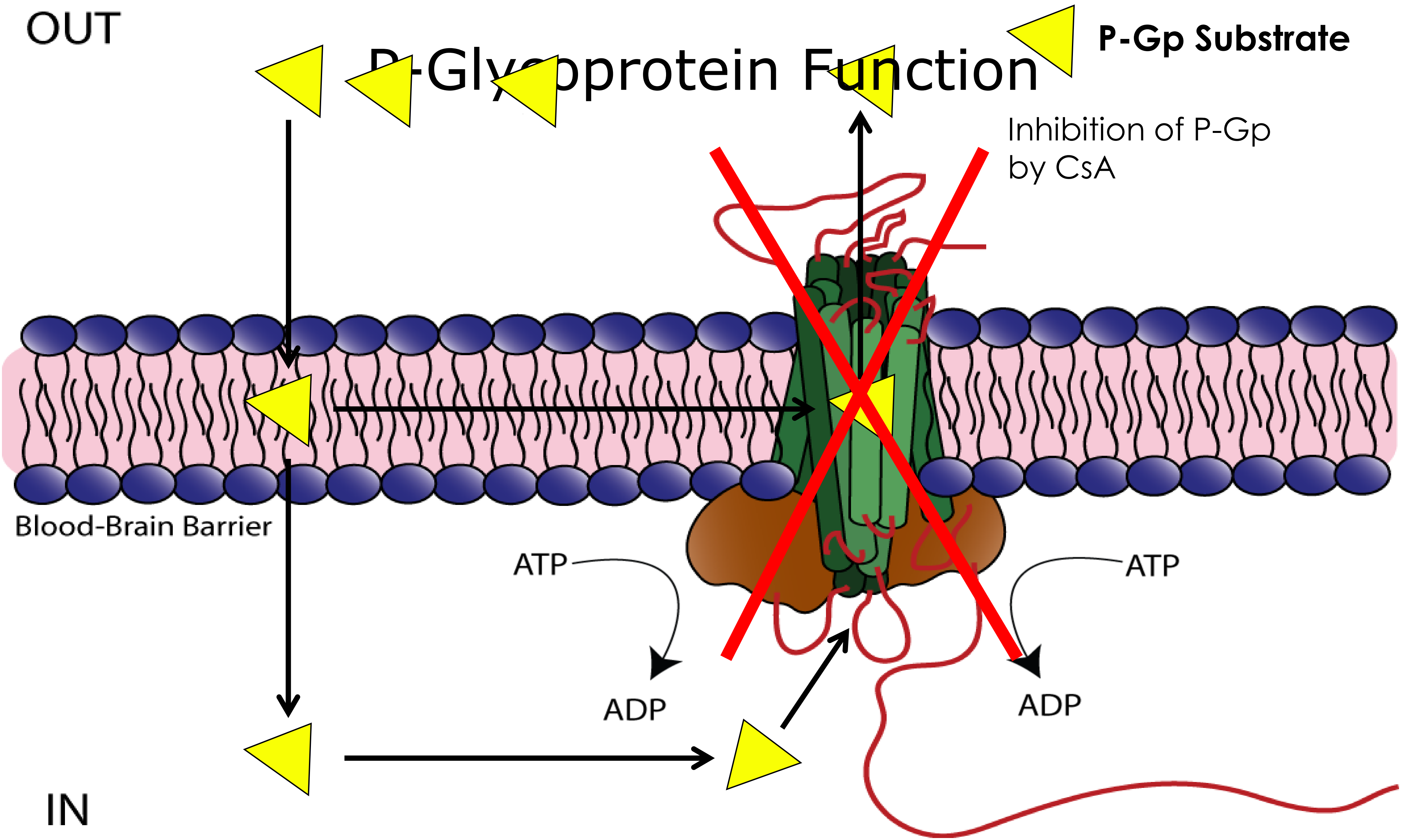


P-glycoprotein

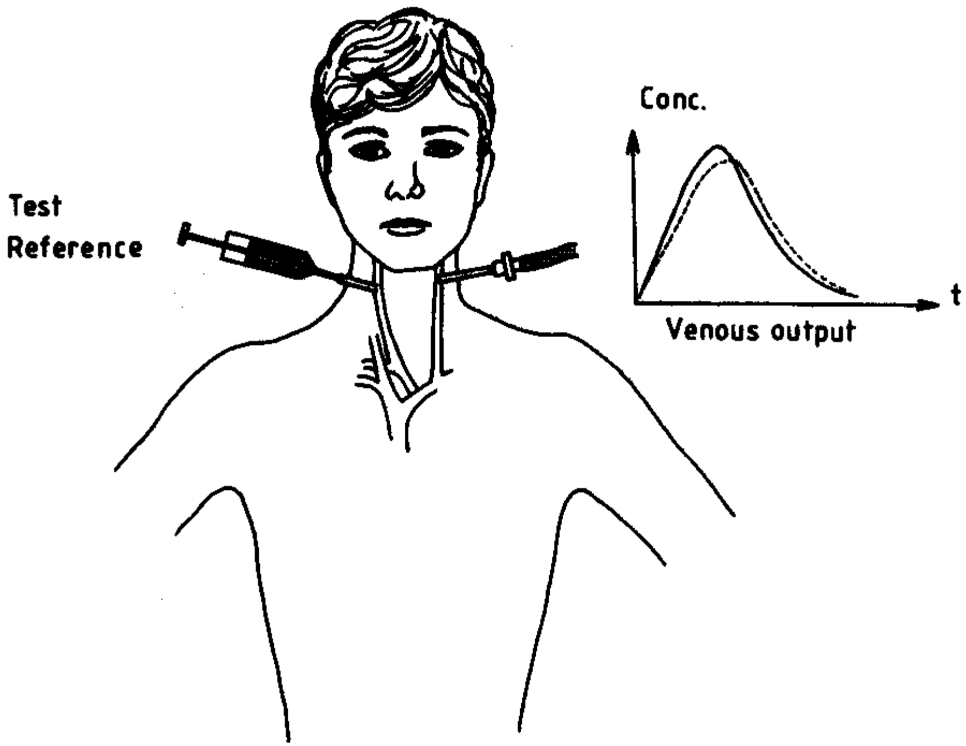


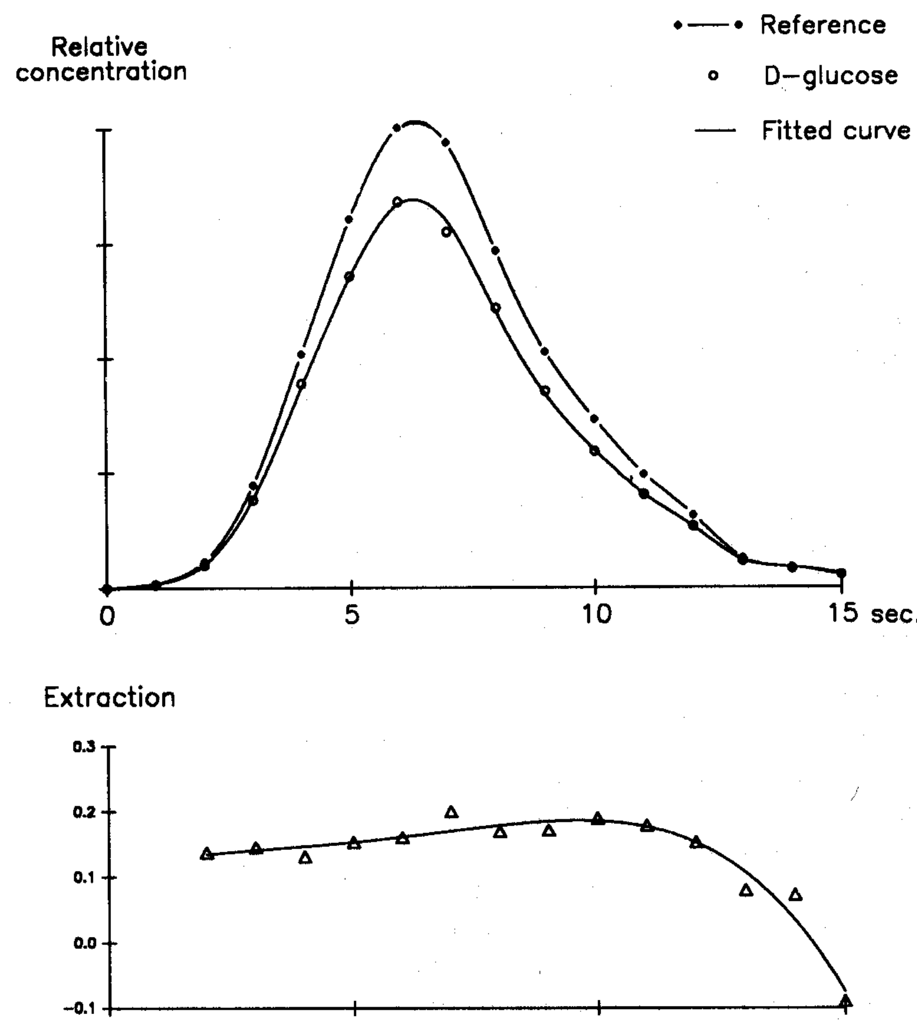
Baseline Cyclosporine Cyclosporine+ketanserin

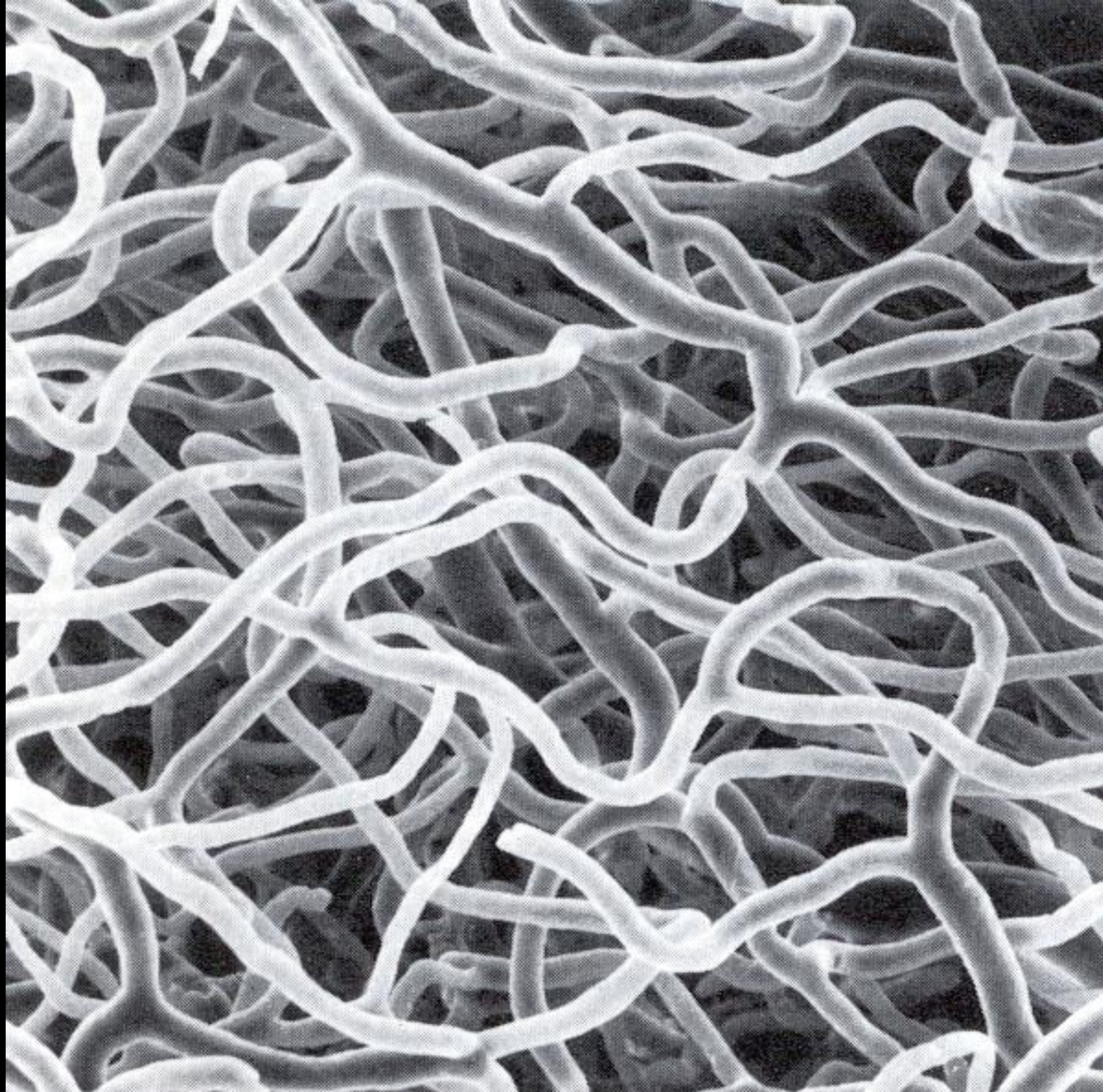
P-Glycoprotein Function

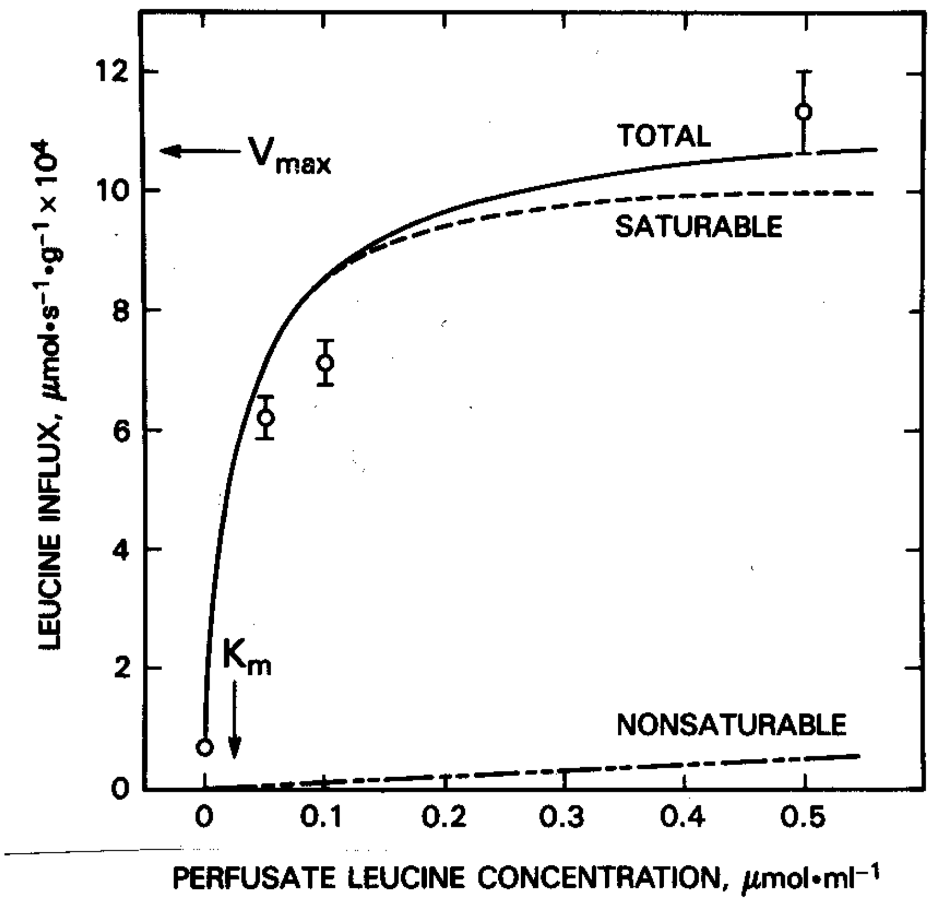


Intracarotid bolus injection




Relative concentration
Reference
D–glucose
Fitted curve
0
5
10
15 sec.
Extraction
0.3
0.2
0.1
0.0
–0.1





$$PS_1 = \frac{V_m}{C_p + K_m} \qquad Km(app) = Km\,(1 + \Sigma[AA_i]/Km_i)$$

Michaelis-Menten behaviour