Introduction to PET Pharmacokinetics:

One and Two Tissue Compartment Models

Review

	FULL	LINEARIZED
MASS ACTION LAW:	$\frac{dB}{dt} = k_{ON}(B_{MAX} - B)F - k_{OFF}B$	$\frac{dB}{dt} = k_{ON}B_{MAX}F - k_{OFF}B$
EQUILIBRIUM:	$B = B_{MAX} \times \frac{F}{K_D + F}$	$\frac{B}{F} = \frac{B_{MAX}}{K_D}$
NONSPECIFIC BINDING:	$\frac{dNS}{dt} = k_{ON}(M_{MAX} - NS)F - k_{OFF}NS$	$NS \propto F$

TRANSPORT:

$$\frac{dC_2}{dt} = f_1C_1 - f_2C_2$$

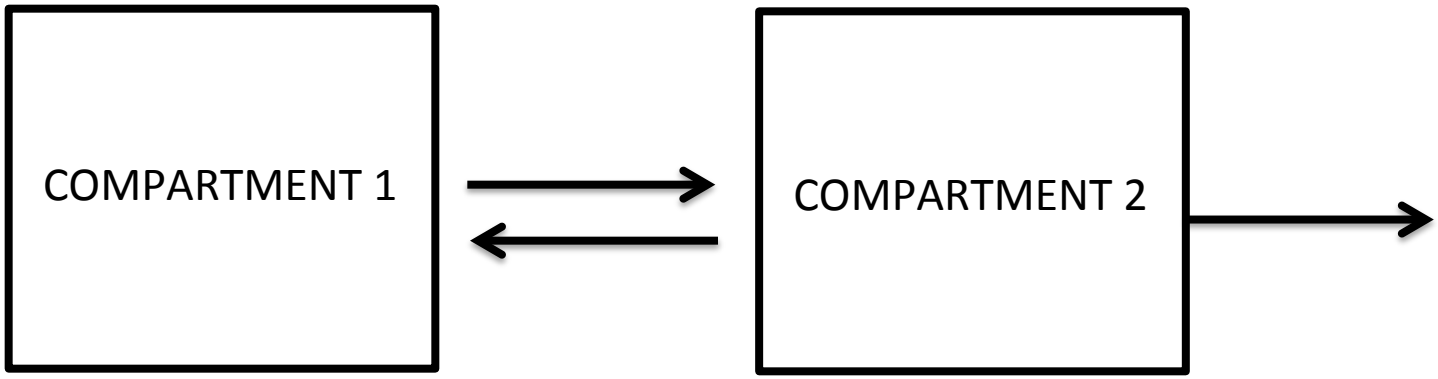
Compartment Model Concept

- Simplified way to trace a quantity through different states
- The states of the quantity may or may not occupy the same physical space (in our case they will)
- Will only be concerned with *LINEAR* compartment models

Compartment Model Concept

RULES: 1. EACH COMPARMENT IS DEPICTED BY A BOX
2. THE QUANTITY (RADIOACTIVITY, TRACER CONCENTRATION) MOVES BETWEEN STATES (COMPARTMENTS) IN DIRECTIONS DESIGNATED BY ARROWS

Goes from C1 to C2 and from C2 to C1 and effluxes from C2



Compartment Model Concept

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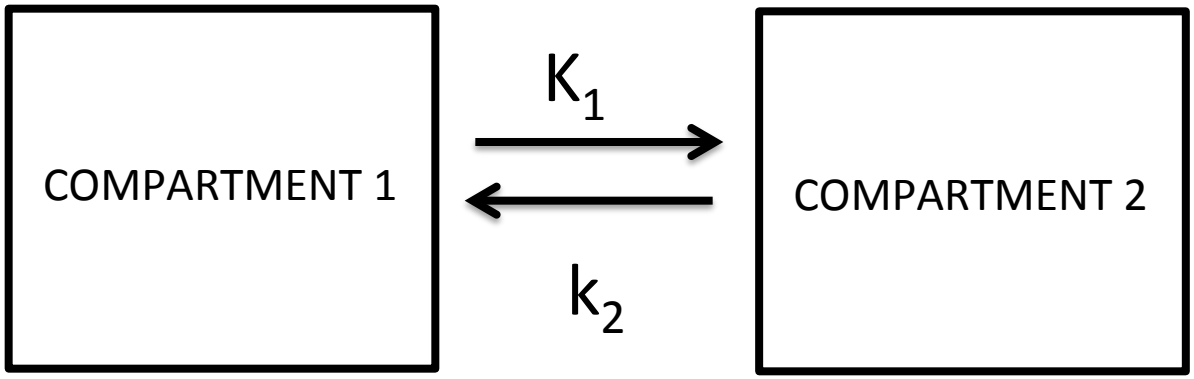
2. THE QUANTITY (RADIOACTIVITY, TRACER CONCENTRATION) MOVES BETWEEN STATES (COMPARTMENTS) IN DIRECTIONS DESIGNATED BY ARROWS

3. RATE IS PROPORTIONAL TO CONCENTRATION IN COMPARTMENT OF ORIGIN; CONSTANTS OF PROPORTIONALITY ARE RATE CONSTANTS K.



Forward Rate = K_1C1

Backward Rate = k_2C2

Compartment Model Concept

RULES: 1. EACH COMPARMENT IS DEPICTED BY A BOX

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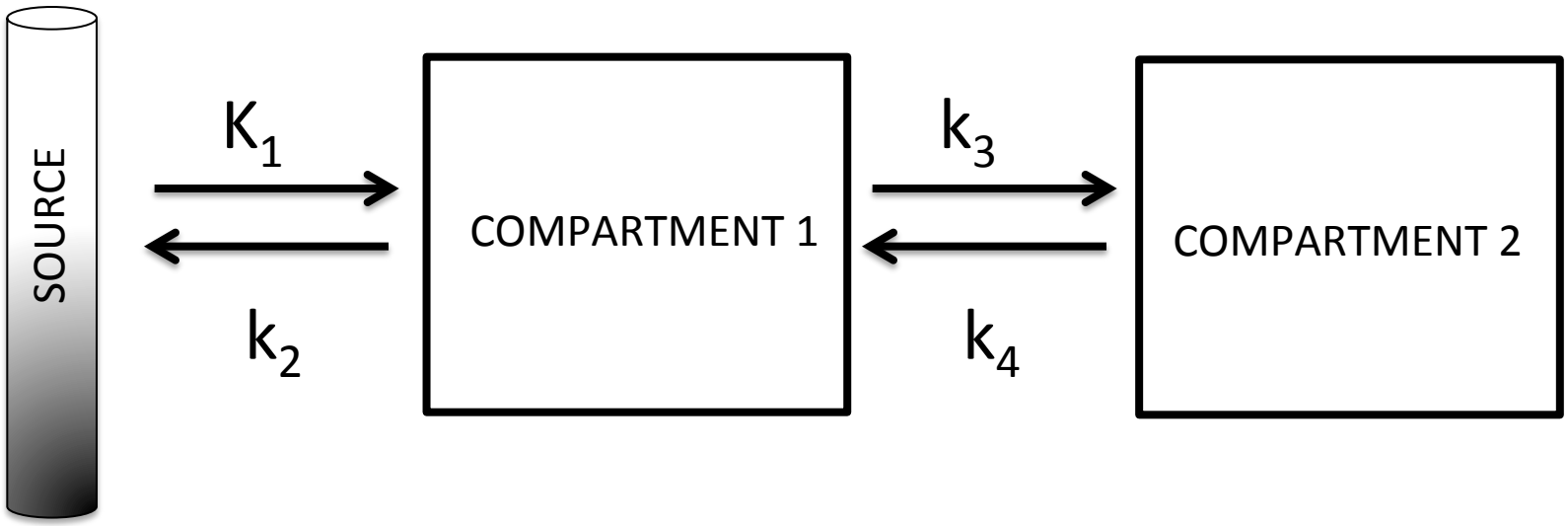
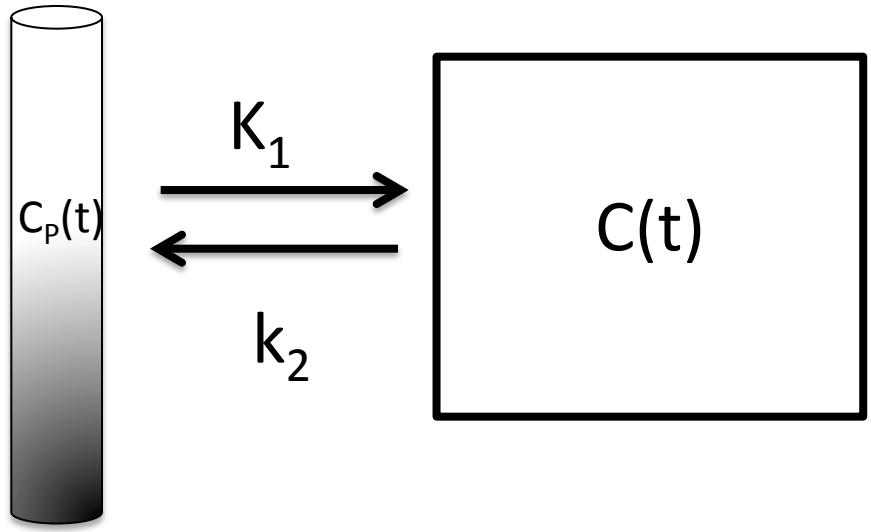


Compartment Model Concept

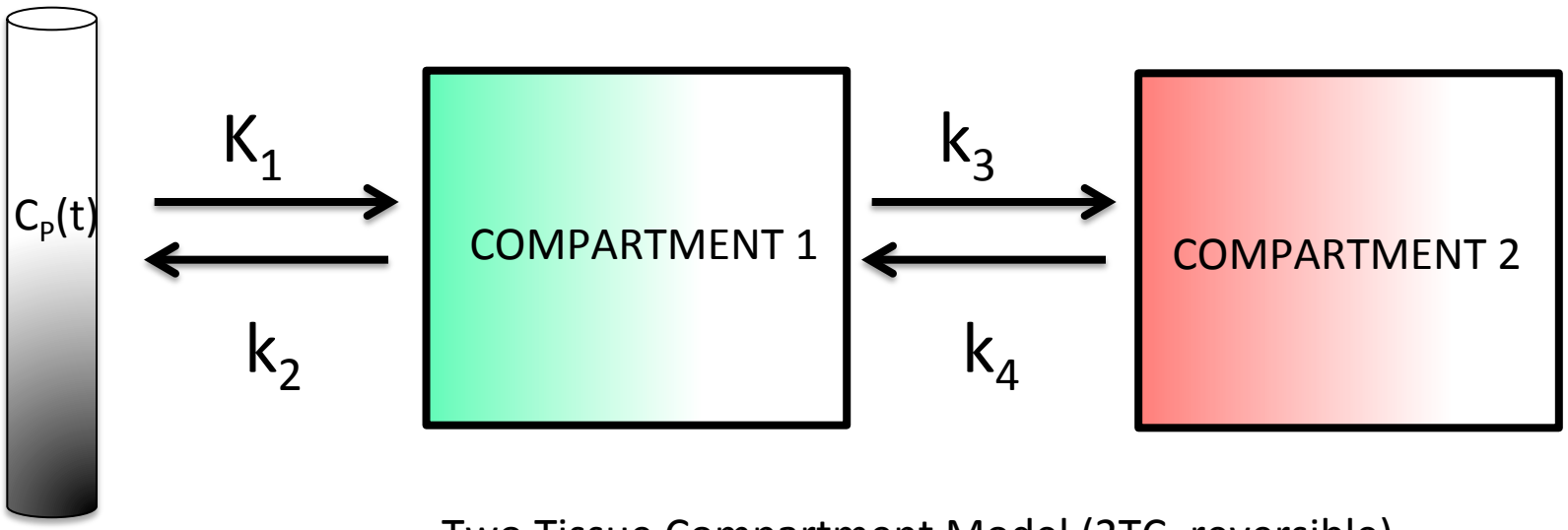


One Tissue Compartment Model (1TC, reversible)

C(t) *increases* at the rate $K_1Cp(t)$
C(t) *decreases* at the rate $k_2C(t)$

$$\frac{dC(t)}{dt} = K_1Cp(t) - k_2C(t)$$

Compartment Model Concept

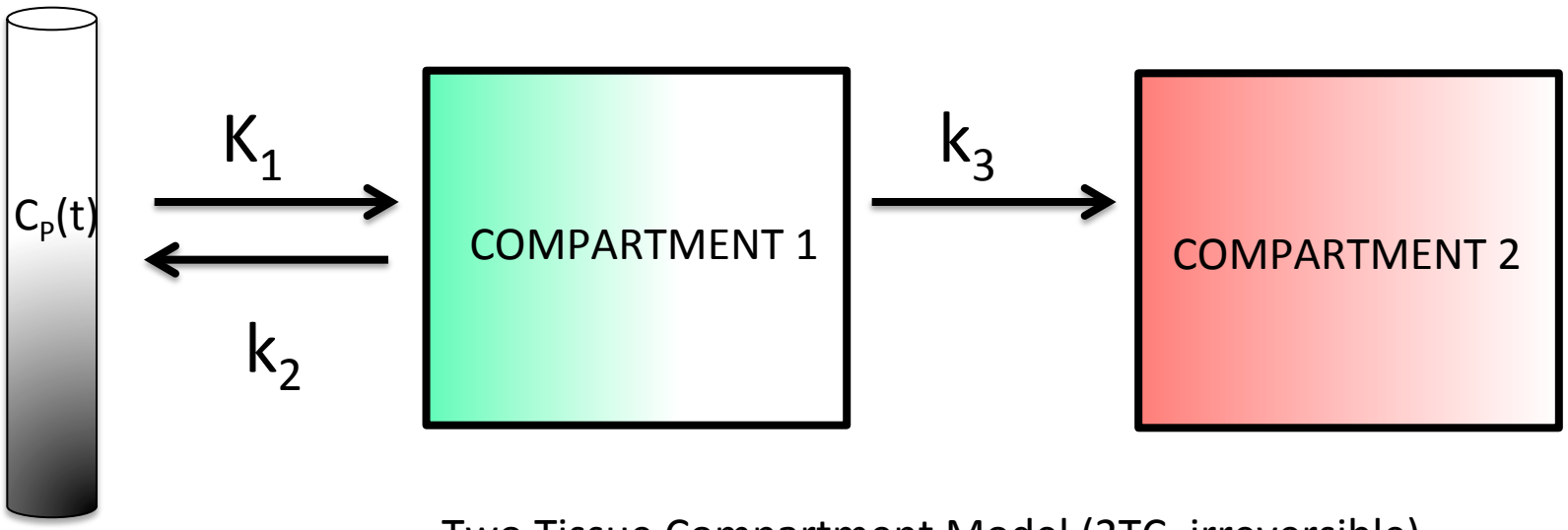


Two Tissue Compartment Model (2TC, reversible)

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

Compartment Model Concept

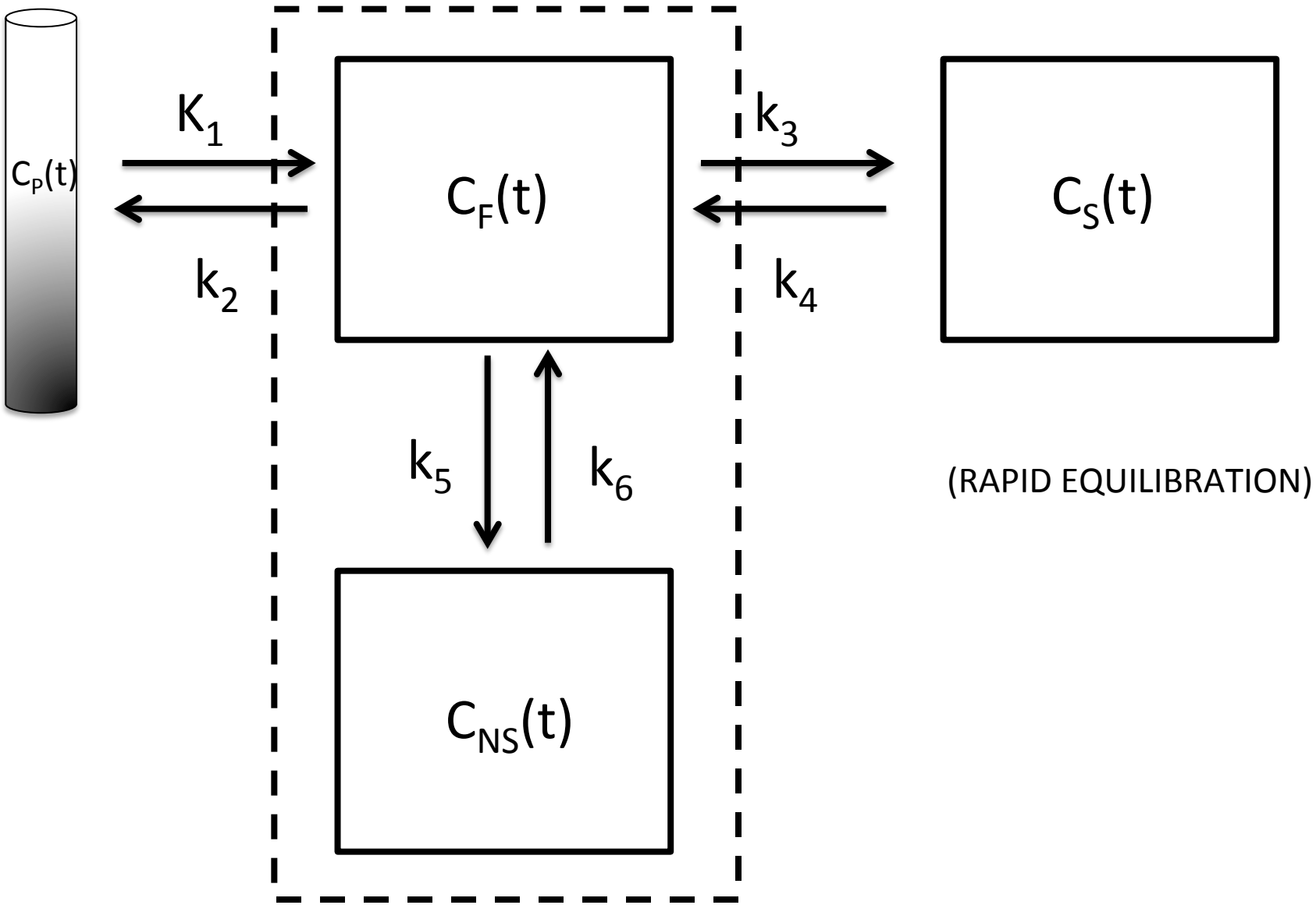


Two Tissue Compartment Model (2TC, irreversible)

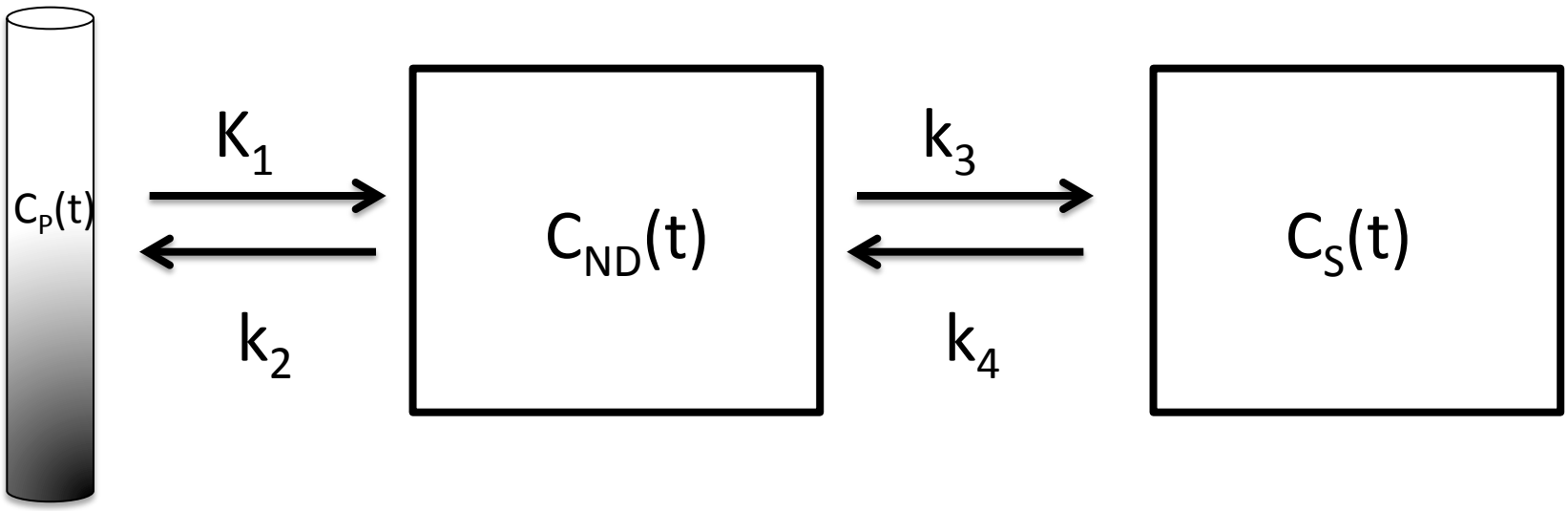
$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t)$$

Compartment Model Application



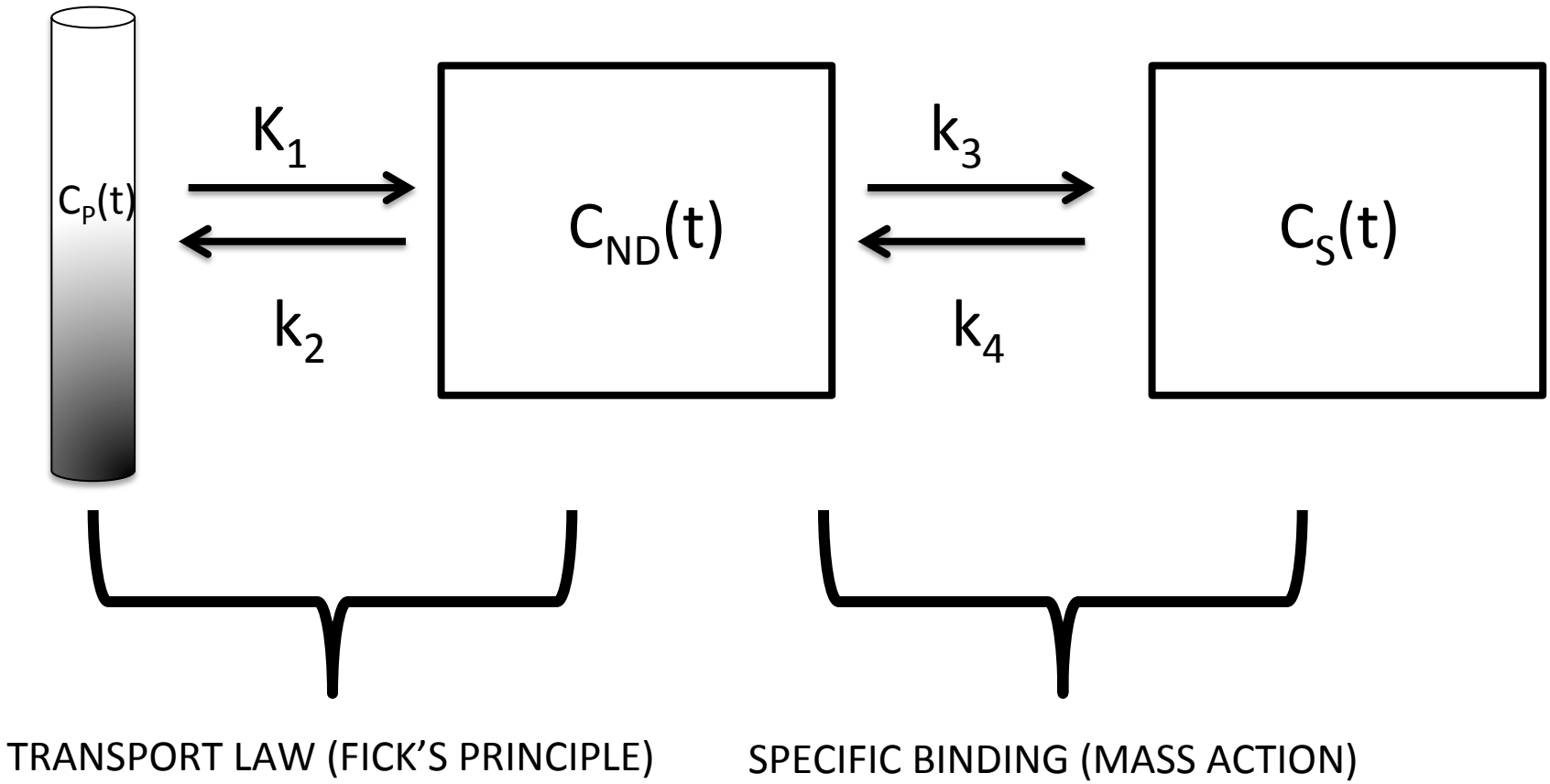
Compartment Model Application



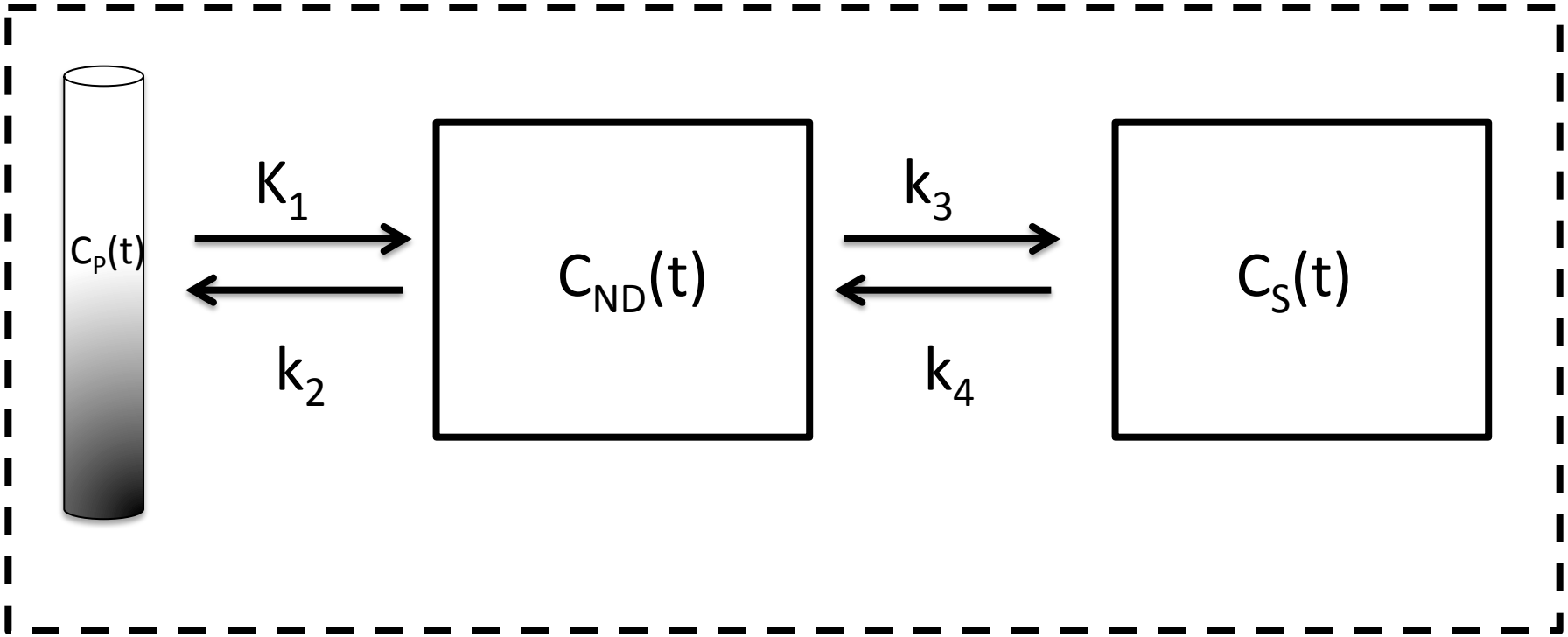
$$C_{ND} = C_F + C_{NS}$$

(RAPID EQUILIBRATION)

Compartment Model Application

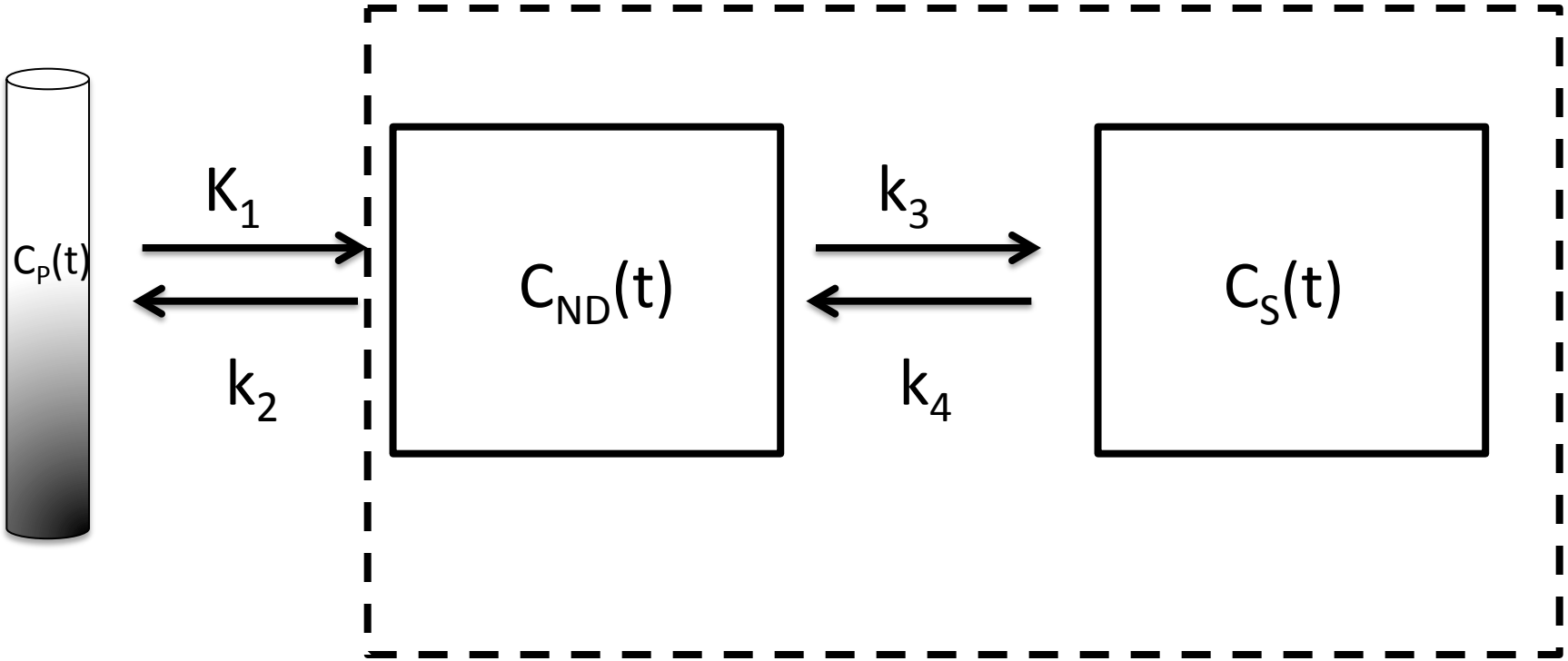


Compartment Model Application



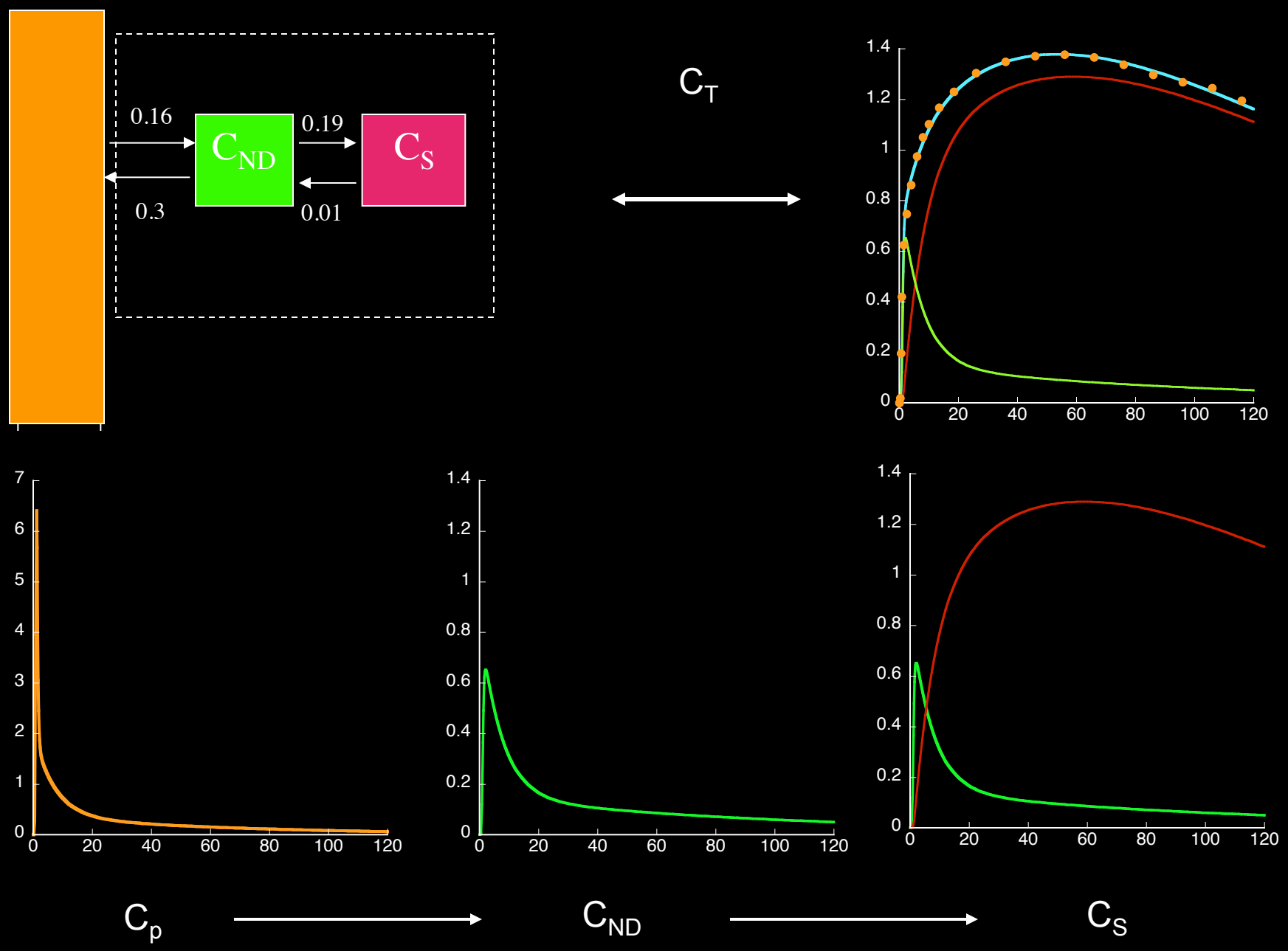
WHAT WE SEE: $C_T + \%BV*C_B$

Compartment Model Application

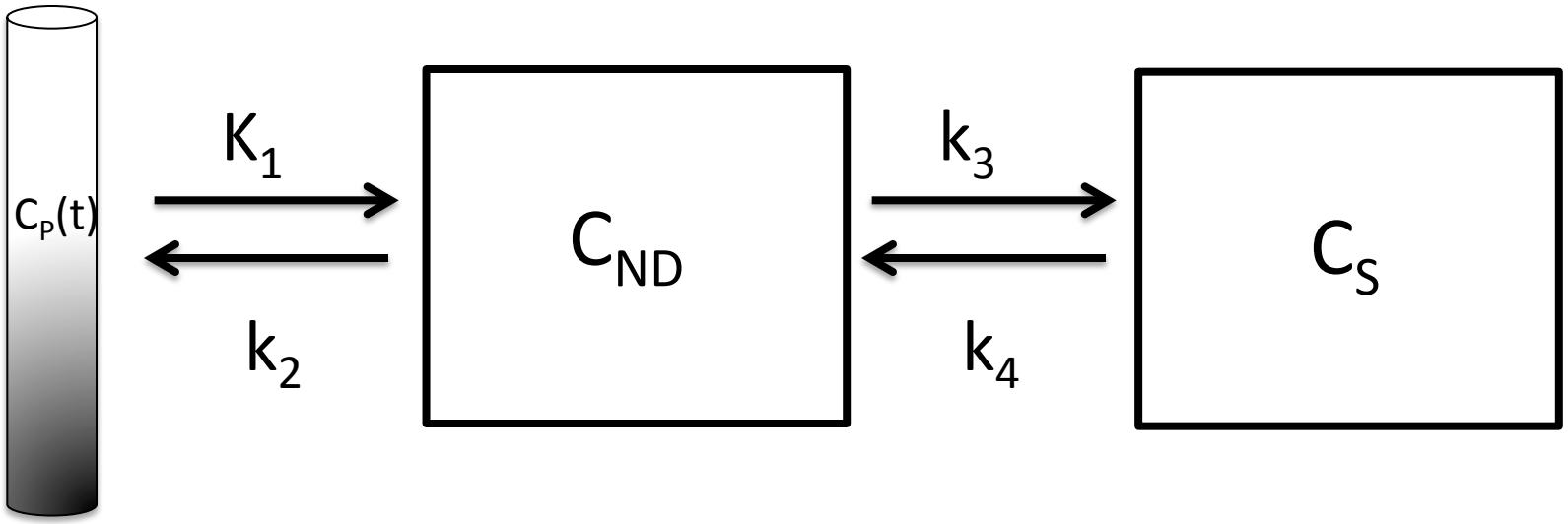


WHAT WE SEE: C_T

CANNOT DISAMBIGUATE C_{ND} FROM C_S; ONLY THEIR SUM C_T


0.16
0.19
0.3
0.01
C_{ND}
C_S
C_T
C_p
C_{ND}
C_S

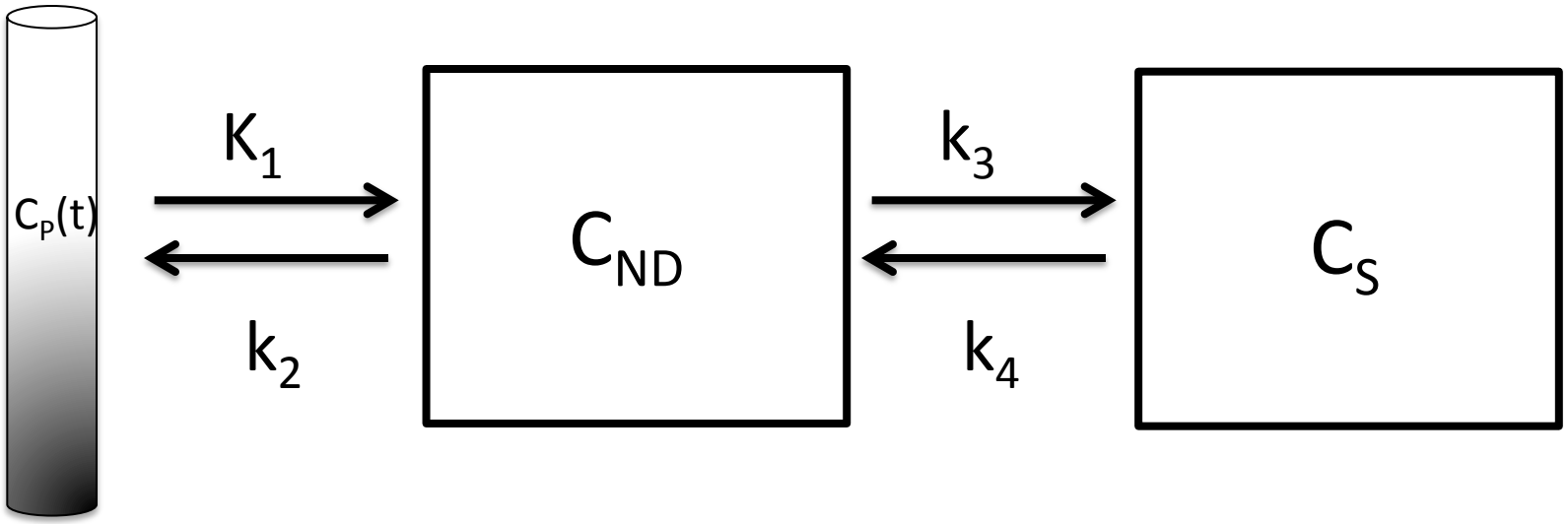
Equlibria and Distribution Volumes



$$\frac{dC_{ND}(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_{ND}(t) + k_4 C_S(t)$$

$$\frac{dC_S(t)}{dt} = k_3 C_{ND}(t) - k_4 C_S(t)$$

Equlibria and Distribution Volumes



$$0 = K_1 C_P(t) - (k_2 + k_3) C_{ND}(t) + k_4 C_S(t)$$

$$0 = k_3 C_{ND}(t) - k_4 C_S(t)$$

Equlibria and Distribution Volumes

$$\frac{C_{ND}}{C_P} = V_{ND} = \frac{K_1}{k_2}$$

$$\frac{C_S}{C_P} = V_S = \frac{K_1 k_3}{k_2 k_4}$$

$$\frac{C_T}{C_P} = V_T = \frac{K_1}{k_2}\left(1 + \frac{k_3}{k_4}\right)$$

$$0 = K_1 C_P(t) - (k_2 + k_3) C_{ND}(t) + k_4 C_S(t)$$

$$0 = k_3 C_{ND}(t) - k_4 C_S(t)$$

Equlibria and Distribution Volumes

$$\frac{dC_{ND}(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_{ND}(t) + k_4 C_S(t)$$

$$\frac{dC_S(t)}{dt} = k_3 C_{ND}(t) - k_4 C_S(t)$$

$$\int_0^\infty \frac{dC(t)}{dt} dt = \lim_{T \to \infty} \left(C(T) - C(0) \right) = 0$$

Equlibria and Distribution Volumes

$$\frac{dC_{ND}(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_{ND}(t) + k_4 C_S(t)$$

$$\frac{dC_S(t)}{dt} = k_3 C_{ND}(t) - k_4 C_S(t)$$

$$\underset{\lim T \to \infty}{C_{ND}(T)} = K_1 \int_0^T C_P dt - (k_2 + k_3) \int_0^T C_{ND} dt + k_4 \int_0^T C_S \, dt$$

$$\underset{\lim T \to \infty}{C_S(T)} = k_3 \int_0^T C_{ND} \, dt - k_4 \int_0^T C_S \, dt$$

Equlibria and Distribution Volumes

$$\frac{dC_{ND}(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_{ND}(t) + k_4 C_S(t)$$

$$\frac{dC_S(t)}{dt} = k_3 C_{ND}(t) - k_4 C_S(t)$$

$$0 = K_1 \int_0^\infty C_P dt - (k_2 + k_3) \int_0^\infty C_{ND} dt + k_4 \int_0^\infty C_S \, dt$$

$$0 = k_3 \int_0^\infty C_{ND} \, dt - k_4 \int_0^\infty C_S \, dt$$

Equlibria and Distribution Volumes

$$V_{ND} = \frac{\int_0^\infty C_{ND}\,dt}{\int_0^\infty C_P\,dt} \qquad V_S = \frac{\int_0^\infty C_S\,dt}{\int_0^\infty C_P\,dt} \qquad V_T = \frac{\int_0^\infty C_T\,dt}{\int_0^\infty C_P\,dt}$$

$$0 = K_1\int_0^\infty C_P dt - (k_2 + k_3)\int_0^\infty C_{ND} dt + k_4\int_0^\infty C_S\,dt$$

$$0 = k_3\int_0^\infty C_{ND}\,dt - k_4\int_0^\infty C_S\,dt$$

Equlibria and Distribution Volumes

$$C_T = C_{ND} + C_S$$

$$\frac{C_T}{C_P} = \frac{C_{ND}}{C_P} + \frac{C_S}{C_P}$$

$$\boxed{V_T = V_{ND} + V_S}$$

Interpretation of Rate Constants

K_1 and the Renkin-Crone Model

F_L (perfusion; we call it flow) $\quad \text{Units} = \dfrac{\text{mL(blood)}}{\text{g(tissue)} \times \text{minute}}$

E (First pass extraction fraction, unitless) $\quad \dfrac{c_a - c_v}{c_a}$

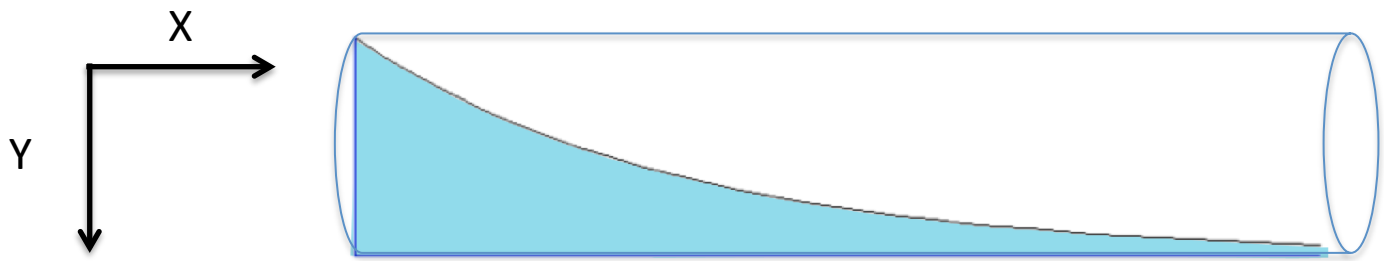
Kety: Rate of Delivery = $F_L E C_P(t)$

$$\text{Units} = \frac{\text{mL(blood)}}{\text{g(tissue)} \times \text{minute}} \times \frac{\text{mass}}{\text{mL(blood)}} = \frac{\text{mass}}{\text{gram} \times \text{minute}}$$

Interpretation of Rate Constants

K_1 and the Renkin-Crone Model

Extraction Fraction ~ exponential



Fick's Priniciple: $dC_a(y)/dt \propto C_T(y) - C_a(y) \sim -kC_a(x)$

Interpretation of Rate Constants

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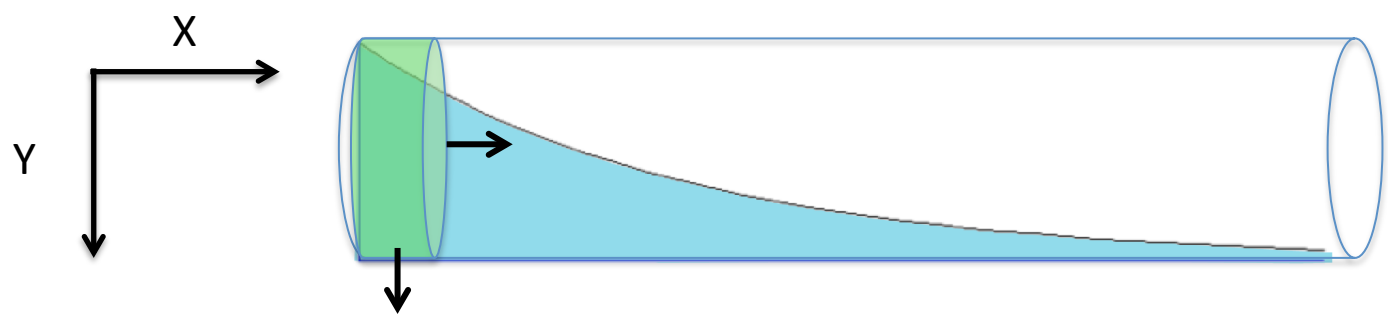

Time 0

Distance 0

Concentration C_a

Interpretation of Rate Constants

K_1 and the Renkin-Crone Model

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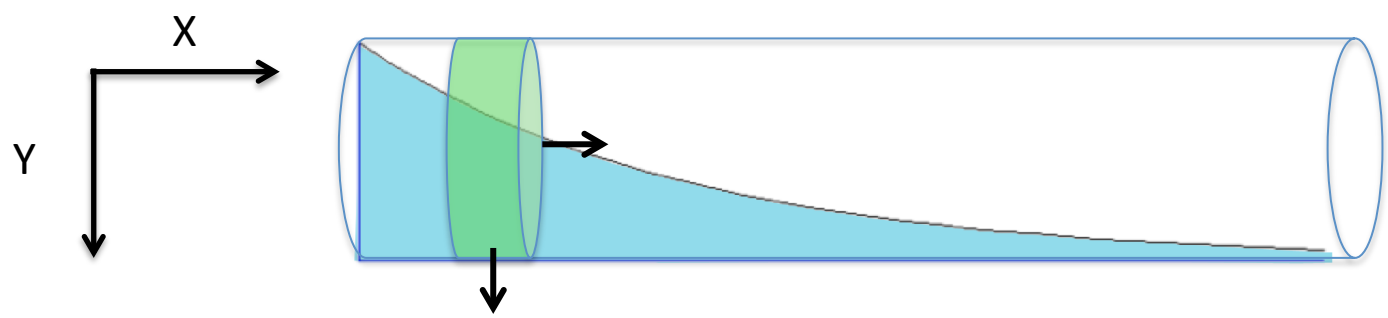

Time	Δt
Distance	Δx
Concentration	$C_a(1-k\Delta t)$

Interpretation of Rate Constants

K_1 and the Renkin-Crone Model

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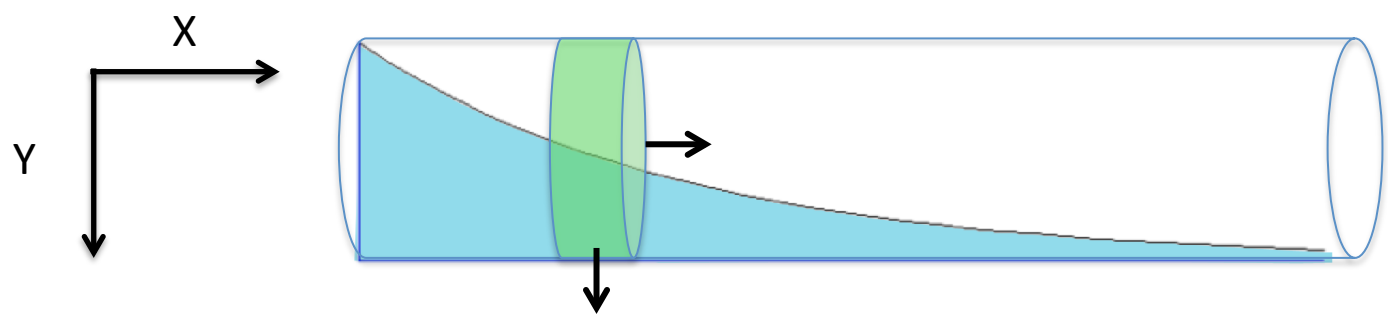
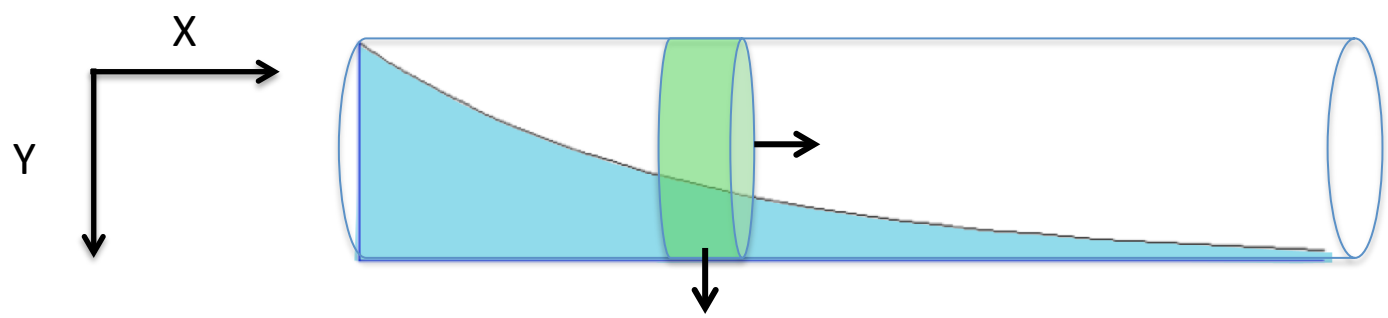


Time	$2\Delta t$
Distance	$2\Delta x$
Concentration	$C_a(1-k\Delta t)^2$

Interpretation of Rate Constants

K_1 and the Renkin-Crone Model

Extraction Fraction ~ exponential



Time	$3\Delta t$
Distance	$3\Delta x$
Concentration	$C_a(1-k\Delta t)^3$

Interpretation of Rate Constants

K_1 and the Renkin-Crone Model

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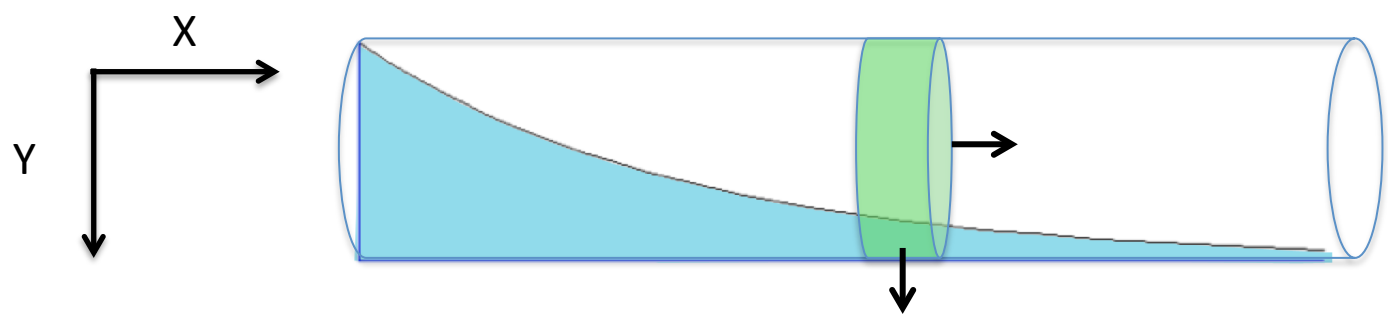
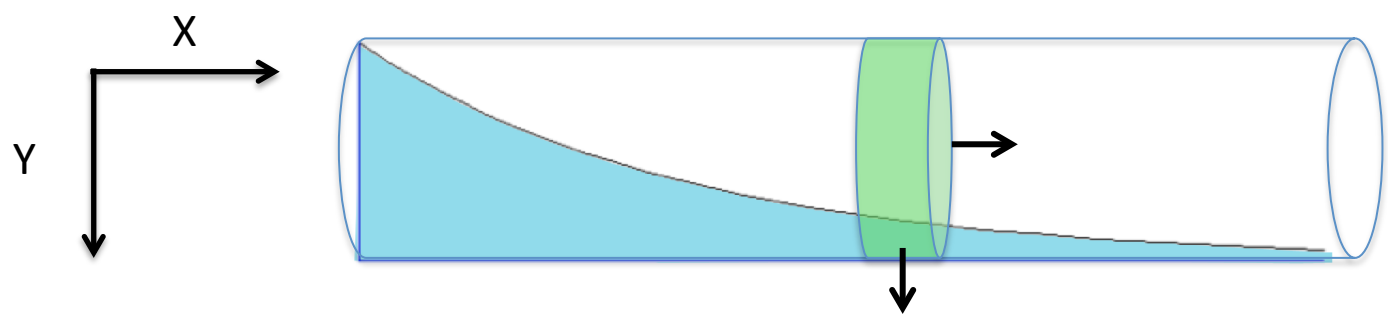


Time	▪ ▪ ▪ ▪ ▪	$n\Delta t$
Distance	▪ ▪ ▪ ▪ ▪	$n\Delta x$
Concentration	▪ ▪ ▪ ▪ ▪	$C_a(1-k\Delta t)^n$

Interpretation of Rate Constants

K_1 and the Renkin-Crone Model

Extraction Fraction ~ exponential



Time	· · · · ·	$n\Delta t$
Distance	· · · · ·	$n\Delta x$
Concentration	· · · · ·	$C_a(1-k'\Delta x)^n$

$$v \approx \frac{\Delta x}{\Delta t}$$

$$\Delta t \approx \Delta x / v$$

Interpretation of Rate Constants

K_1 and the Renkin-Crone Model

Extraction Fraction ~ exponential

Have established: $C_{CAP}(n\Delta x) \approx C_a \times \left(1 - k\Delta x\right)^n$

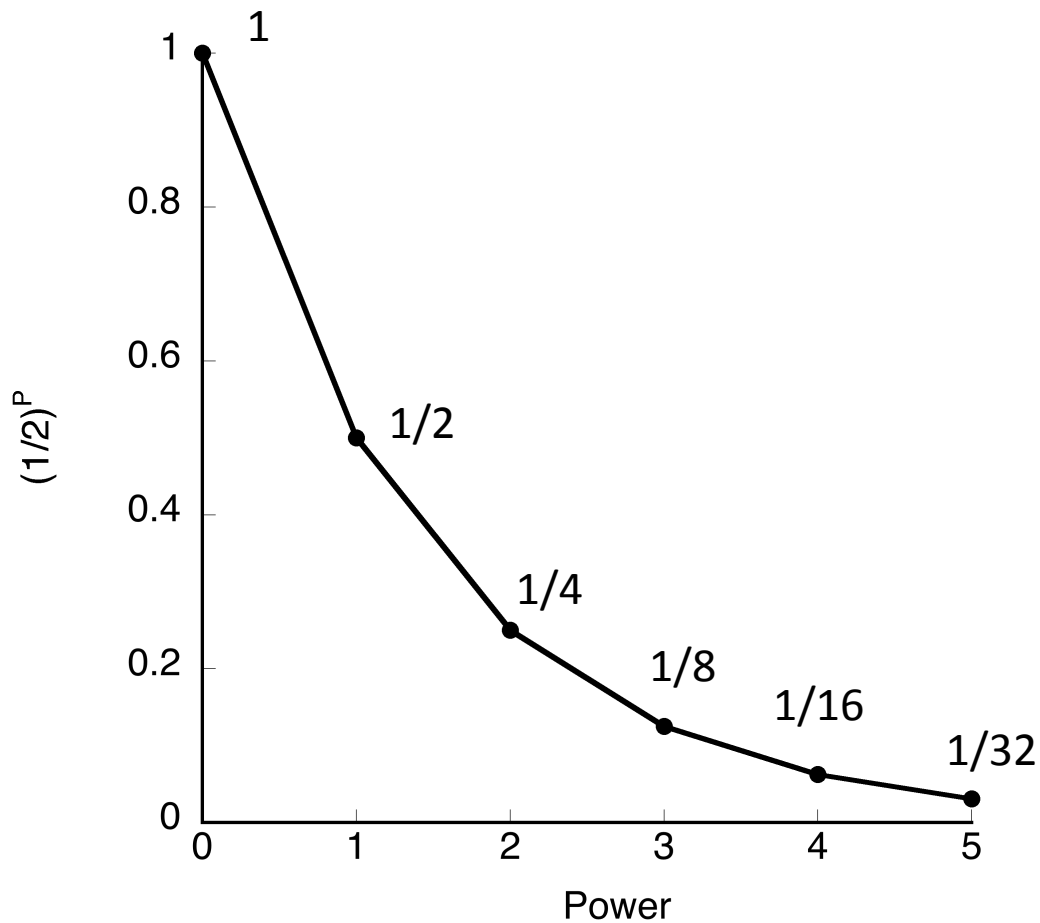
Taylor's Theorem (or mean value theorem):

$$\text{for } 0 < k\Delta x << 1, \quad e^{-k\Delta x} \approx 1 - k\Delta x$$

$$\left(1 - k\Delta x\right)^n \approx \left(e^{-k\Delta x}\right)^n = e^{-k\left(n\Delta x\right)}$$

Mathematical Aside: Exponential Decay

- Powers of a fixed number
- Start with a "base" number, say ½
- Compute successive values $(½)^0$, $(½)^1$, $(½)^2$, $(½)^3$, etc



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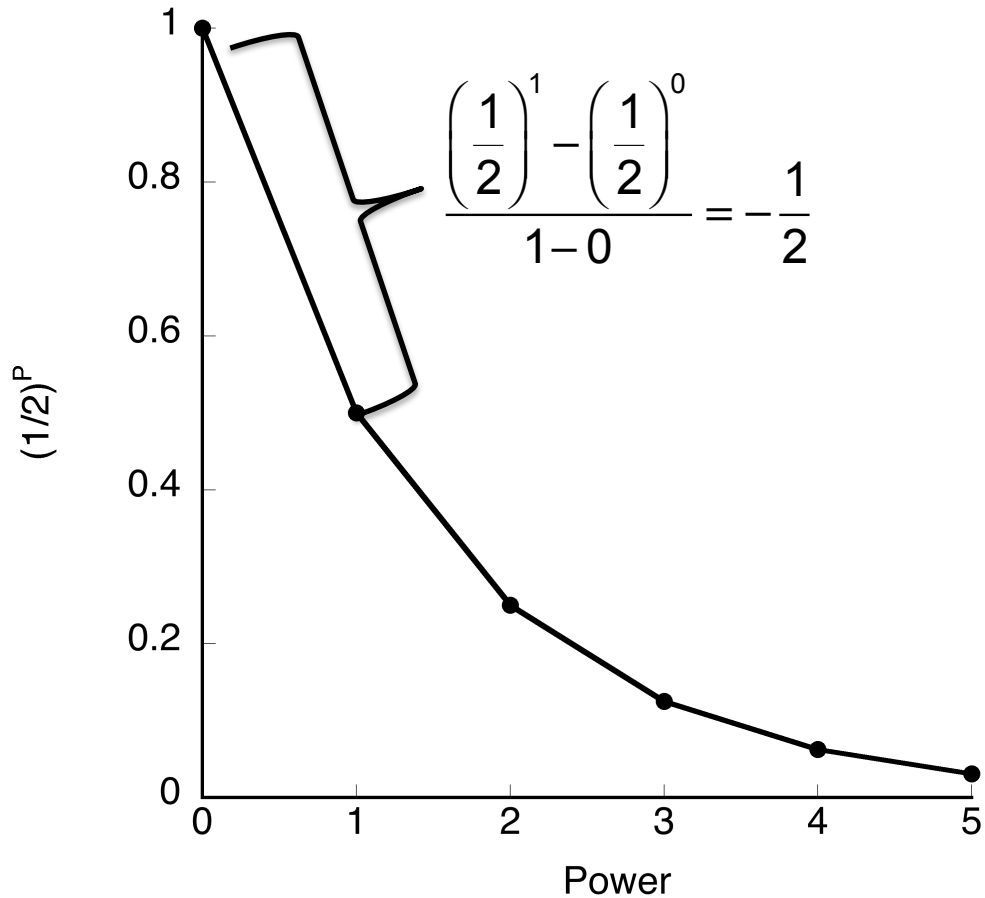

$$\frac{\left(\frac{1}{2}\right)^1 - \left(\frac{1}{2}\right)^0}{1-0} = -\frac{1}{2}$$

Mathematical Aside: Exponential Decay

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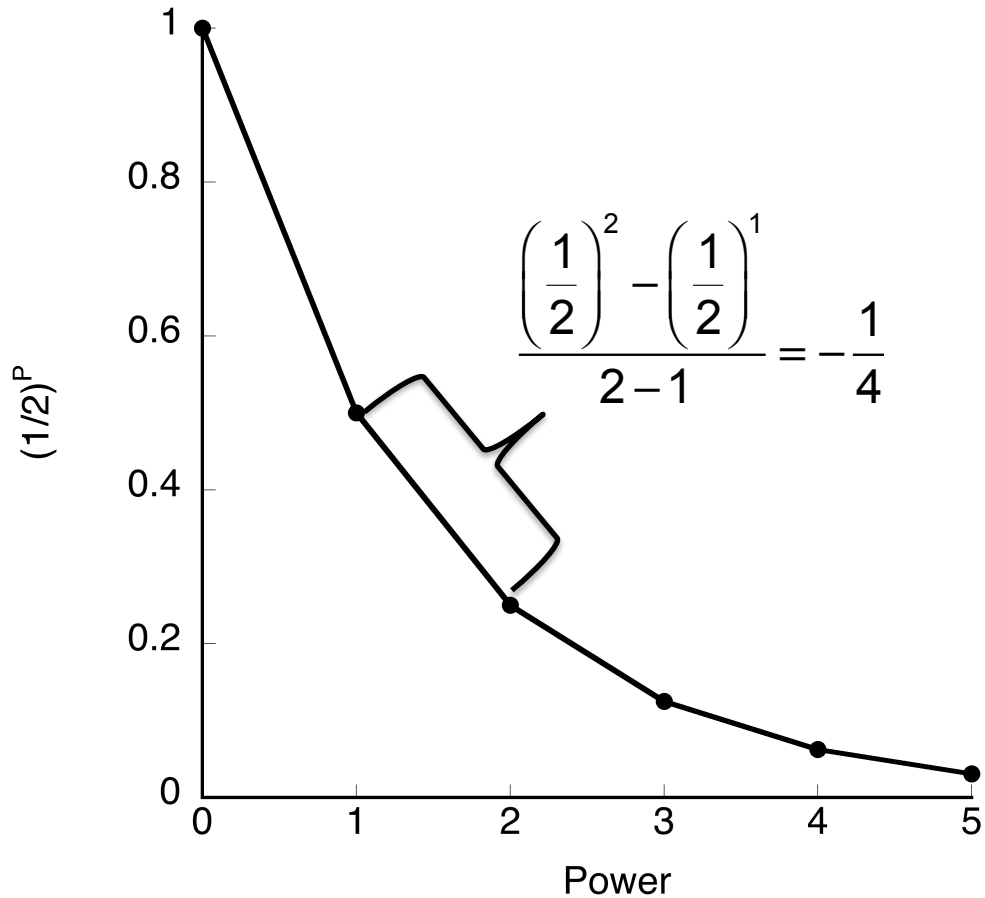
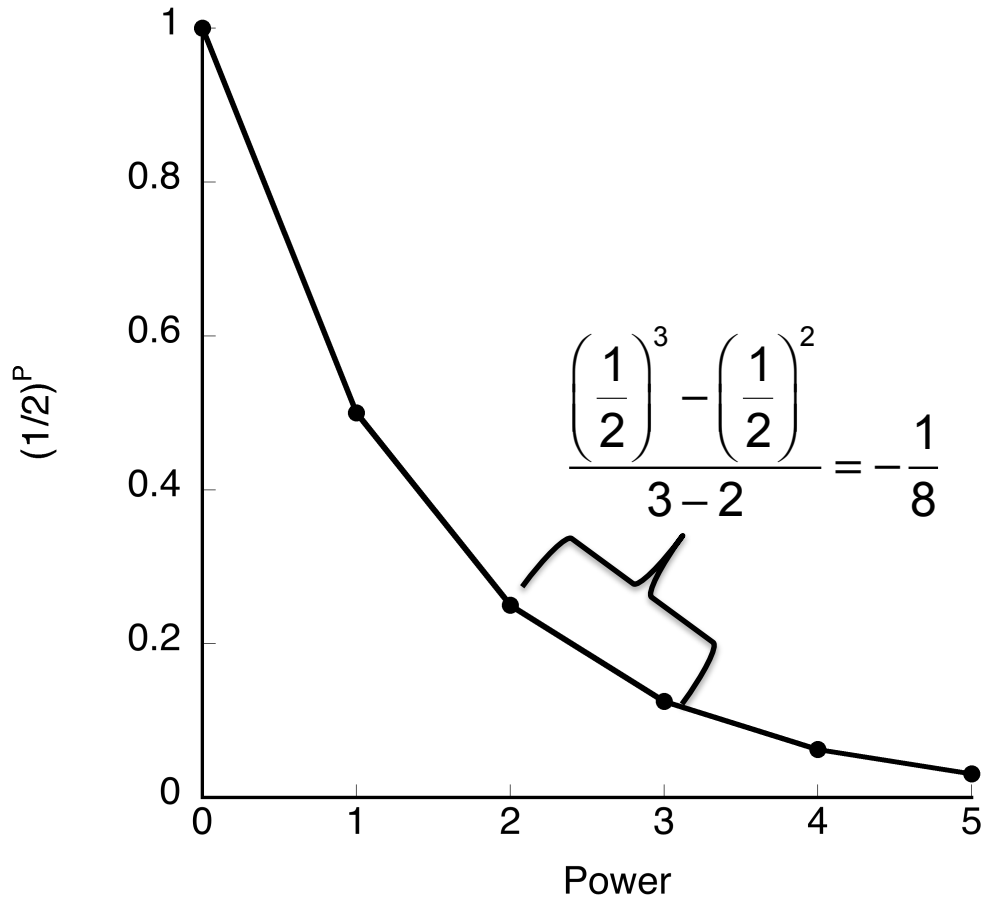
- Compute successive values $(½)^0$, $(½)^1$, $(½)^2$, $(½)^3$, etc



$$\frac{\left(\frac{1}{2}\right)^2 - \left(\frac{1}{2}\right)^1}{2-1} = -\frac{1}{4}$$

Mathematical Aside: Exponential Decay

- Powers of a fixed number
- Start with a "base" number, say ½
- Compute successive values $(½)^0$, $(½)^1$, $(½)^2$, $(½)^3$, etc



Mathematical Aside: Exponential Decay

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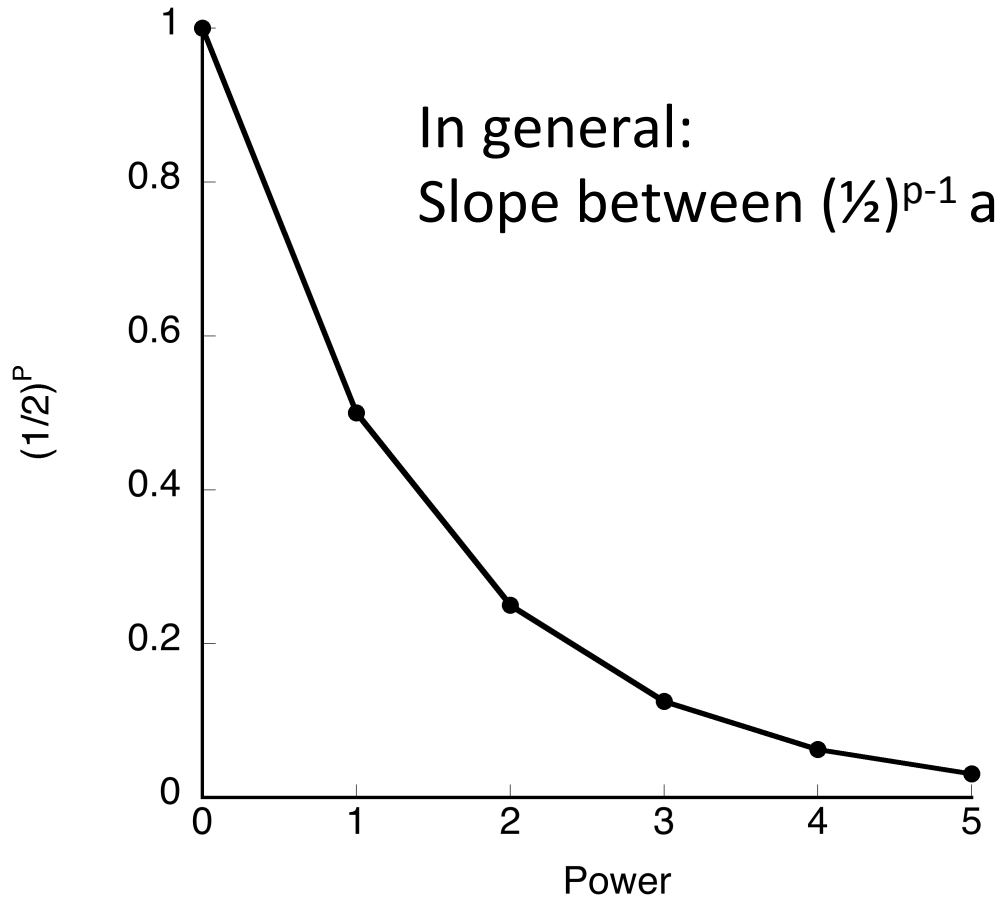


In general:
Slope between $(½)^{p-1}$ and $(½)^p$ is - $(½)^p$

Mathematical Aside: Exponential Decay

- Exponentials: Need all real number powers, not just whole number powers

Reminder about powers:

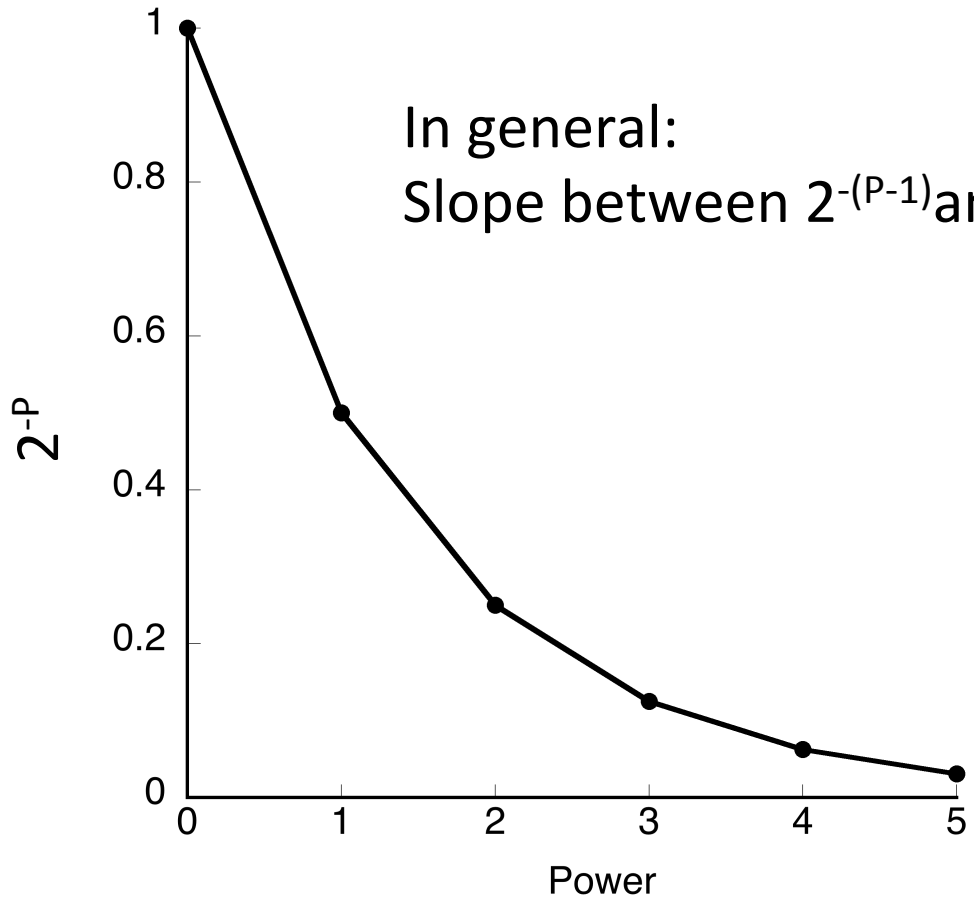
$$\left(\frac{1}{2}\right)^{P} = 2^{-P}$$

This allows us to write:

$$\begin{aligned}\left(\frac{1}{2}\right)^{P} \times 2^{P} &= \left(\frac{1}{2^{P}}\right) \times 2^{P} = \frac{2^{P}}{2^{P}} = 2^{-P} \times 2^{P} \\ &= 2^{(-P+P)} \\ &= 2^{0} \\ &= 1\end{aligned}$$

Mathematical Aside: Exponential Decay

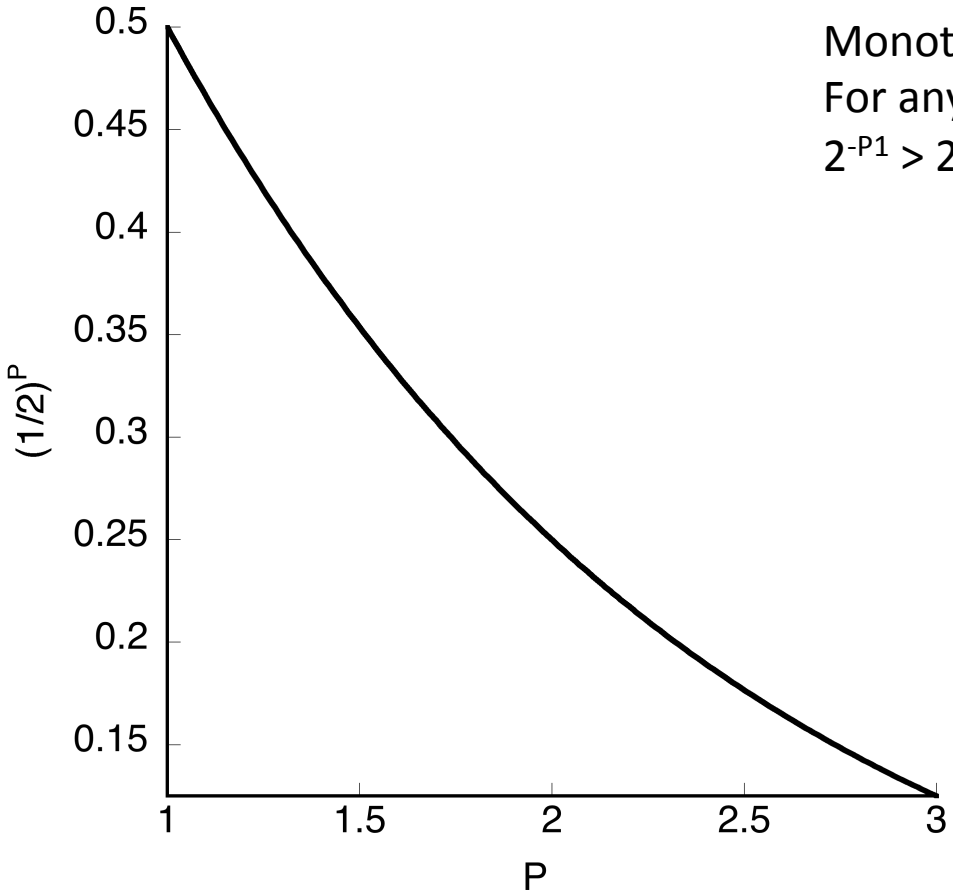
- Powers of a fixed number
- Start with a "base" number, say ½
- Compute successive values 2^0 , 2^{-1}, 2^{-2}, 2^{-3}, etc



In general:
Slope between $2^{-(P-1)}$ and 2^{-P} is -2^{-P}

Mathematical Aside: Exponential Decay

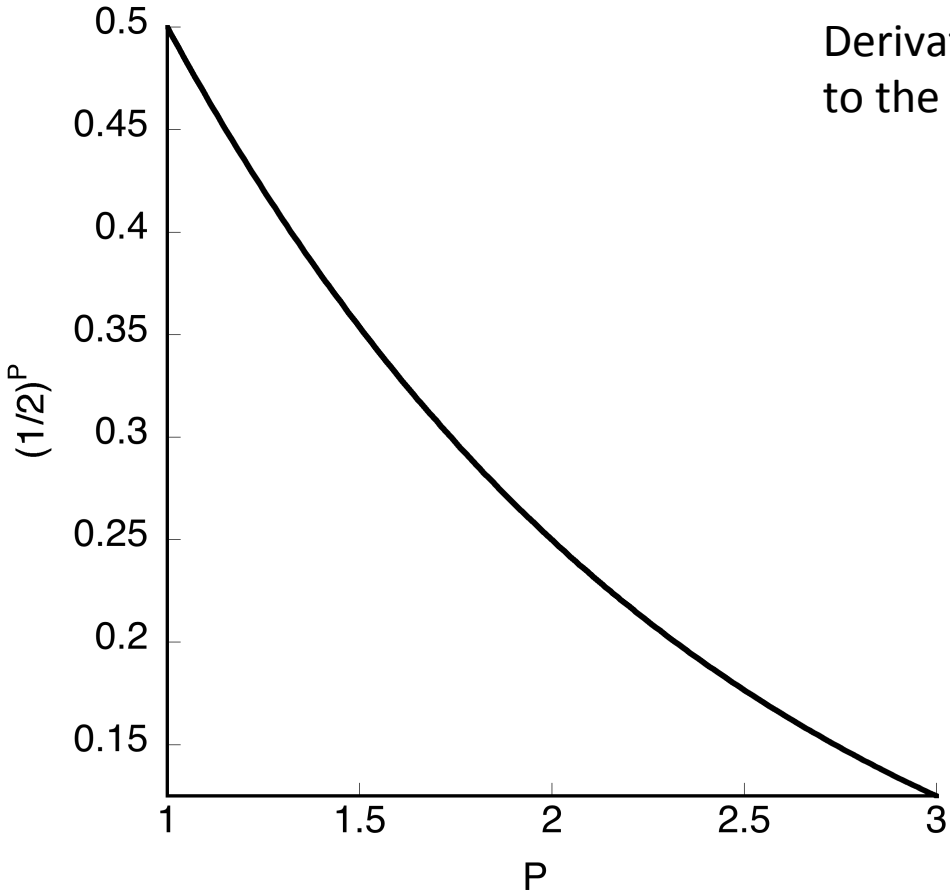
- Exponentials: Need all real number powers, not just whole number powers



Monotonic:
For any $P_1 < P_2$,
$2^{-P1} > 2^{-P2}$

Mathematical Aside: Exponential Decay

- Exponentials: Need all real number powers, not just whole number powers



Derivative is always proportional to the value of the function

Mathematical Aside: Exponential Decay

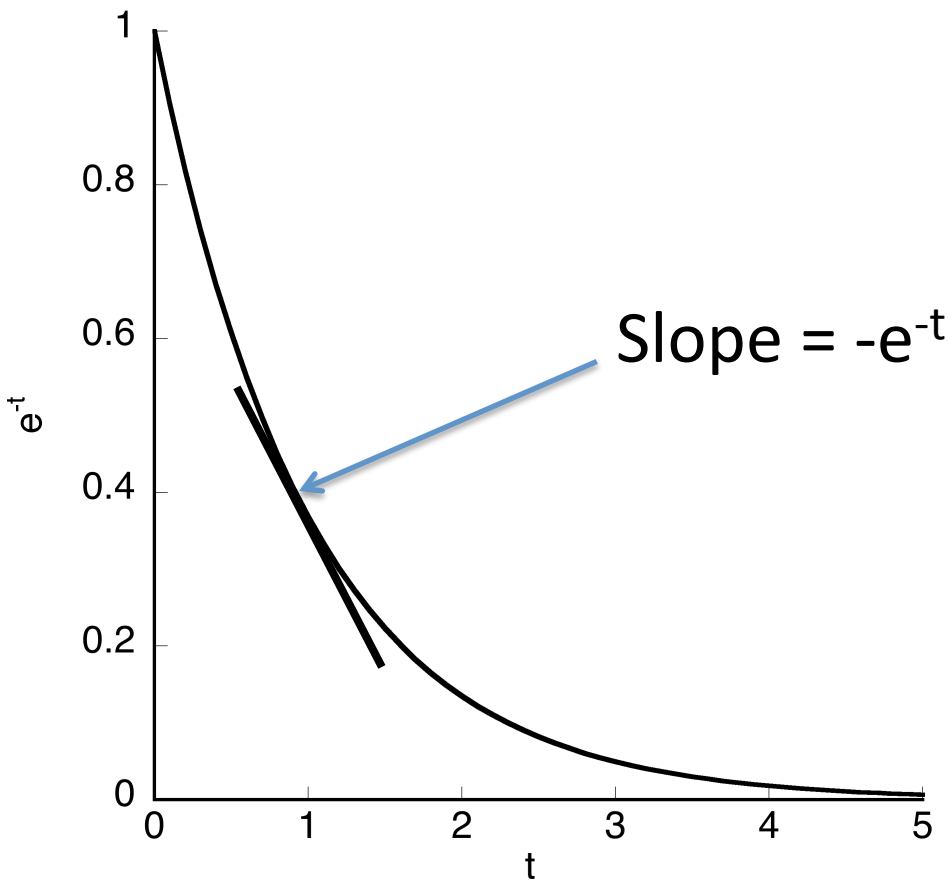
There is a special base number called the “natural” base

$$e \approx 2.72$$

$$1/e \approx 1/2.72$$

Mathematical Aside: Exponential Decay

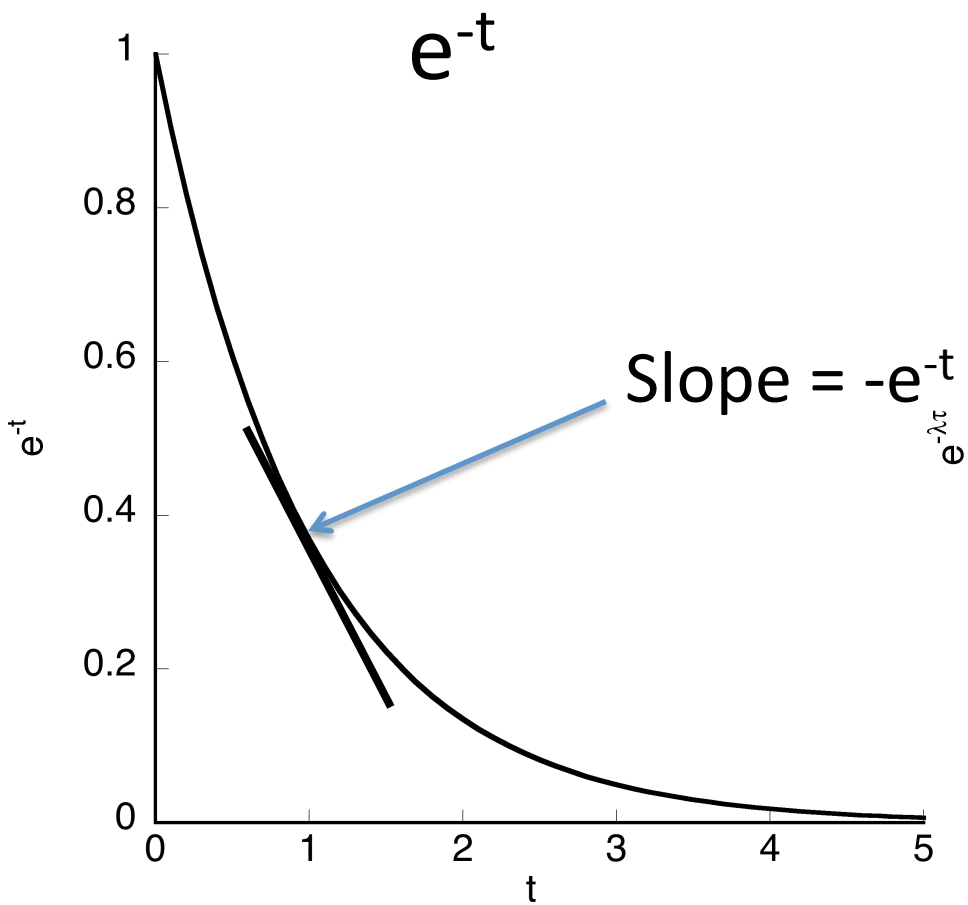
At each point, the derivative of e^{-t} is $-e^{-t}$

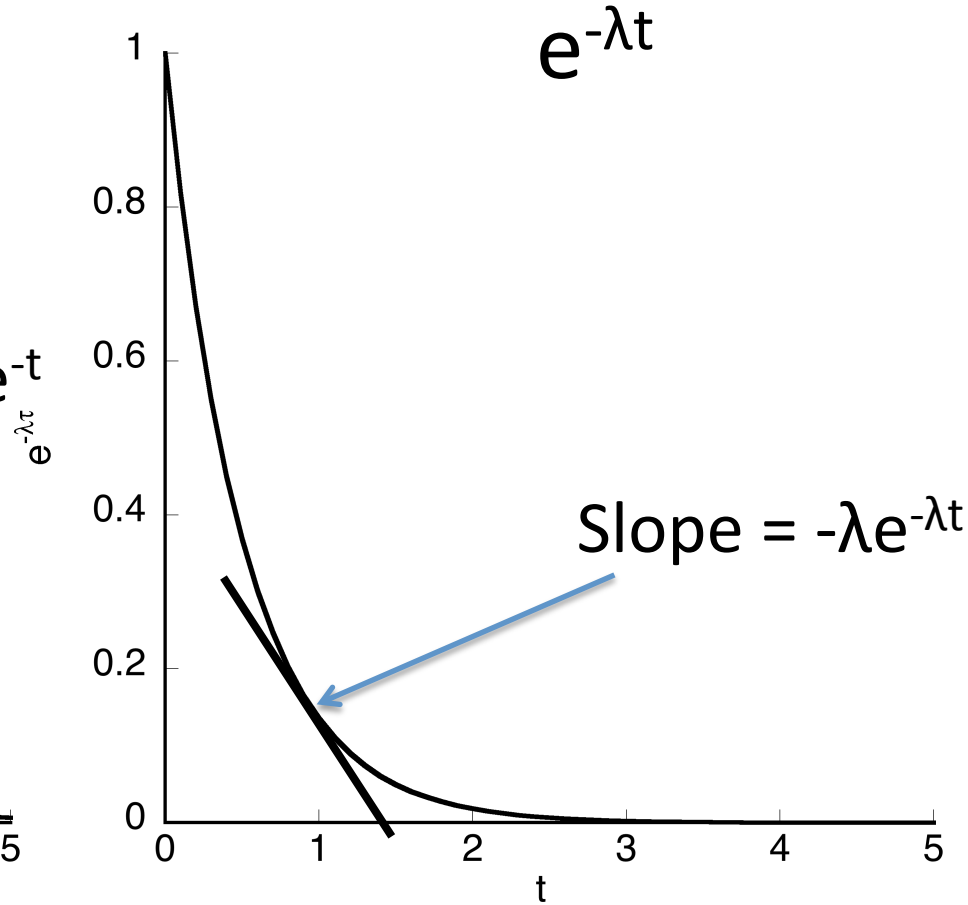


Mathematical Aside: Exponential Decay

Make the powers go faster:
Let $\lambda > 1$

Consider $e^{-\lambda t}$





Mathematical Aside: Exponential Decay

DIFFERENTIAL EQUATION:

$$\frac{dC(t)}{dt} = -\lambda C(t)$$

$$C(t) = C(0)e^{-\lambda t}$$

Interpretation of Rate Constants

K_1 and the Renkin-Crone Model

$$\Delta C_a(x) \sim \text{exponential}$$

P (Permeability) $$\text{Units} = \frac{\text{mL(blood)} \times c_a}{\text{cm}^2\text{(capillary surface)}(c_{cap} - c_T)\text{min}}$$

Interpretation of Rate Constants

K_1 and the Renkin-Crone Model

P (Permeability) $$\text{Units} = \frac{\text{mL(blood)} \times c_a}{\text{cm}^2\text{(capillary surface)}(c_{cap} - c_T)\text{min}}$$

PS (perm* surface/g) $$\frac{\text{mL(blood)} \times c_a \times (\text{cm}^2 / \text{g})}{\text{cm}^2\text{(capillary surface)}(c_a - c_T)\text{min}}$$

$$\left(= \frac{\text{mL}}{\text{g} \times \text{min}} \right)$$

Interpretation of Rate Constants

K_1 and the Renkin-Crone Model

- Approximate c_{CAP} as its mean value
- Get the mean value from exponential model
- Obtain expression for E in terms of PS and F_L
- Use Kety model to equate K_1 to $F_L E$

$$E = 1 - \exp\left(-\frac{PS}{F_L}\right)$$

$$K_1 = F_L\left(1 - \exp\left(-\frac{PS}{F_L}\right)\right)$$

Interpretation of Rate Constants

K_1 and the Renkin-Crone Model

$$K_1 = F_L\left(1 - \exp(-\frac{PS}{F_L})\right)$$

Two Extremes:

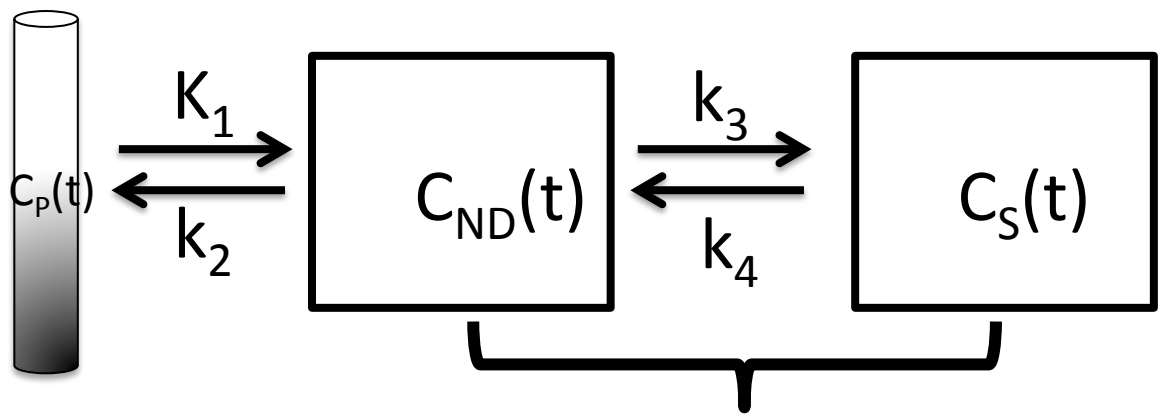
CASE 1: $F_L << PS$ $\quad \exp(\frac{-PS}{F_L}) \approx 0\,; \quad K_1 \approx F_L$ "FLOW LIMITED DELIVERY"

CASE 2: $F_L >> PS$ $\quad 1 - \exp(\frac{-PS}{F_L}) \approx \frac{PS}{F_L}\,; \quad K_1 \approx PS$ "PERMEABILITY LIMITED DELIVERY"

Interpretation of Rate Constants

$$K_1 = F_L E = F_L(1 - \exp(PS/F_L))$$
$$k_2 = K_1/V_{ND}$$
$$k_3 = k_{ON} B_{MAX} f_{ND}$$
$$k_4 = k_{OFF}$$

$$\frac{dC_S}{dt} = k_{ON} B_{MAX} f_{ND} C_{ND} - k_{OFF} C_S$$



LINEARIZED MASS ACTION LAW

Binding Potentials

First, recall V_{ND} derived from Fick's Principle:

AT EQUILIBRIUM

Free in Arterial Plasma = Free in Brain

$$f_P C_P = f_{ND} C_{ND}$$

$$\frac{C_{ND}}{C_P} = \frac{f_P}{f_{ND}}$$

Binding Potentials

Recall $$V_S = \frac{K_1 k_3}{k_2 k_4}$$

Binding Potentials

$$V_S = \frac{K_1 k_3}{k_2 k_4} = \frac{f_P}{f_{ND}} \frac{k_{ON} B_{MAX} f_{ND}}{k_{OFF}}$$

Binding Potentials

$$V_S = \frac{K_1 k_3}{k_2 k_4} = f_P \frac{B_{MAX}}{K_D} = BP_P$$

Binding Potentials

$$V_S = \frac{K_1 k_3}{k_2 k_4} = f_P \frac{B_{MAX}}{K_D} = BP_P$$

$$\frac{V_S}{f_P} = \frac{K_1 k_3}{f_P k_2 k_4} = \frac{B_{MAX}}{K_D} = BP_F$$

$$\frac{V_S}{V_{ND}} = \frac{k_3}{k_4} = \frac{f_{ND}}{f_P} BP_P = f_{ND} \frac{B_{MAX}}{K_D} = BP_{ND}$$

Introduction to Data Fitting and Parameter Estimation

- We have shown that ***DISTRIBUTION VOLUMES*** and ***BINDING POTENTIALS*** are functions of the ***RATE CONSTANTS***

- How do we extract the ***RATE CONSTANTS***from the ***DATA***?

Introduction to Data Fitting and Parameter Estimation

METHOD 1:

- LET THE COMPUTER DO ALL THE WORK!
- **USE A NUMERICAL DIFF. EQ. SOLVER**
- USE AN OPTIMIZER (LEAST SQUARES MINIMIZER)

$$\frac{dC(t)}{dt} = K_1 C_P(t) - k_2 C(t)$$

$$\frac{C(t+\Delta t) - C(t)}{\Delta t} \approx K_1 C_P(t) - k_2 C(t)$$

$$C(t+\Delta t) \approx C(t) + \left(K_1 C_P(t) - k_2 C(t)\right)\Delta t$$

Introduction to Data Fitting and Parameter Estimation

METHOD 1:

- LET THE COMPUTER DO ALL THE WORK!
- USE A NUMERICAL DIFF. EQ. SOLVER
- **USE AN OPTIMIZER (LEAST SQUARES MINIMIZER)**

$$\min_{K_1, k_2 > 0} \sum_{j=1}^{N} \left(\mathrm{PET}(t_j) - \mathrm{MODEL}(t_j) \right)^2$$

Are Rate Constants Estimated Robustly Enough to Estimate Binding Potentials from their formulae?

Are the parameters unique in a *deterministic* sense? Yes;

$$\frac{L(C_T)}{L(C_p)} = K_1 \frac{s + k_3 + k_4}{(s + \alpha_1)(s + \alpha_2)} \qquad \text{(transfer function)}$$

s is the Laplace Transform variable

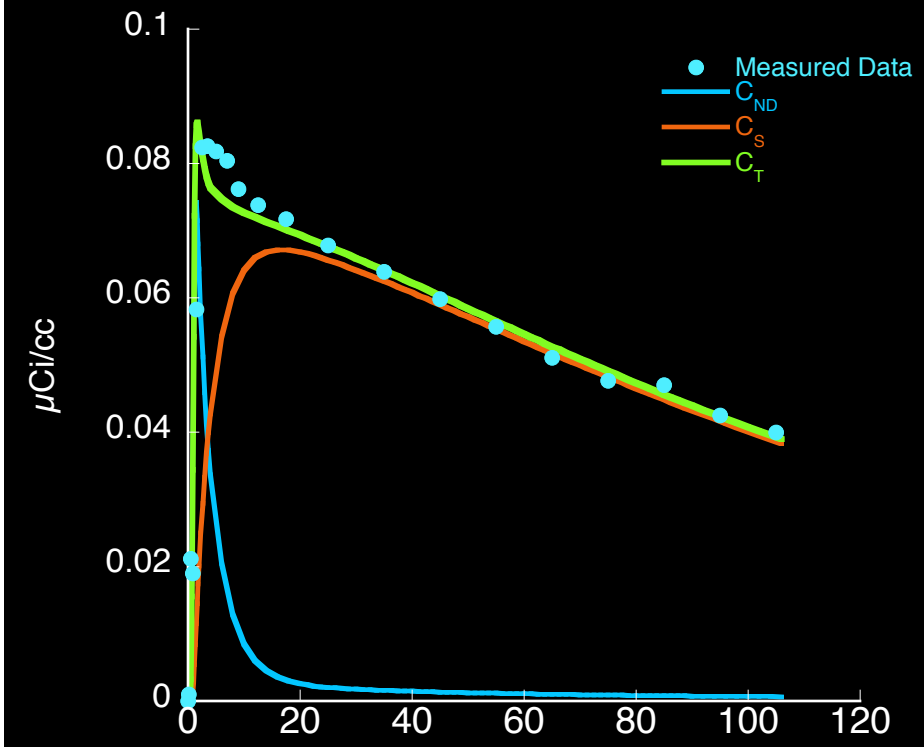
the α's are the eigenvalues of the system (functions of the k's)

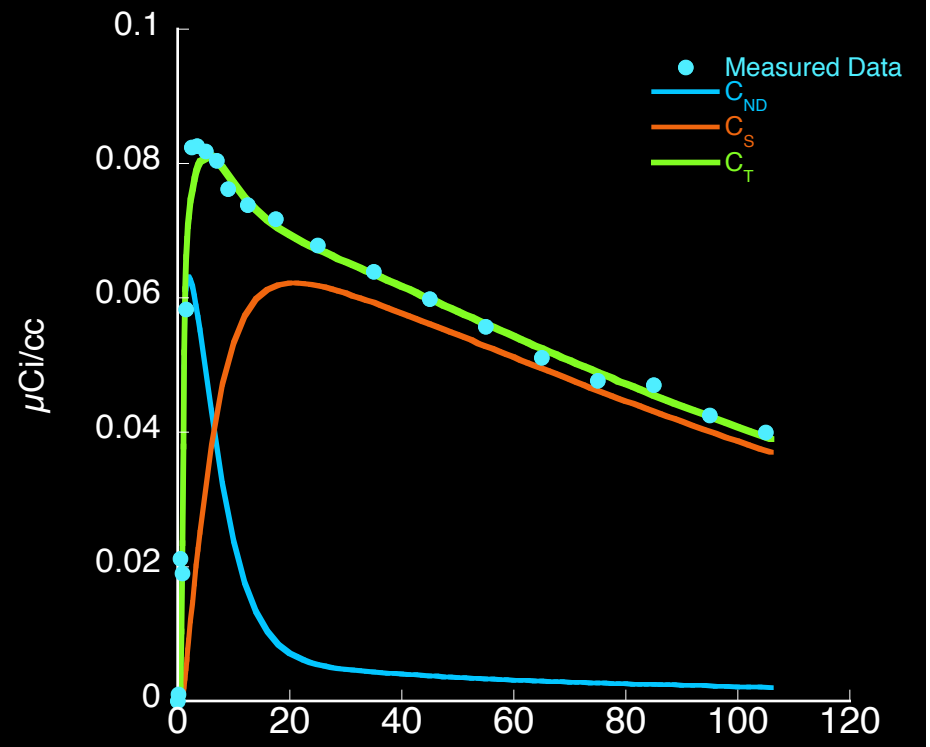
It can be shown that for a given C_T and C_p pair,

These are all unique.

(Bellman, 1960)

Are the parameters unique in *practical* terms? NO!



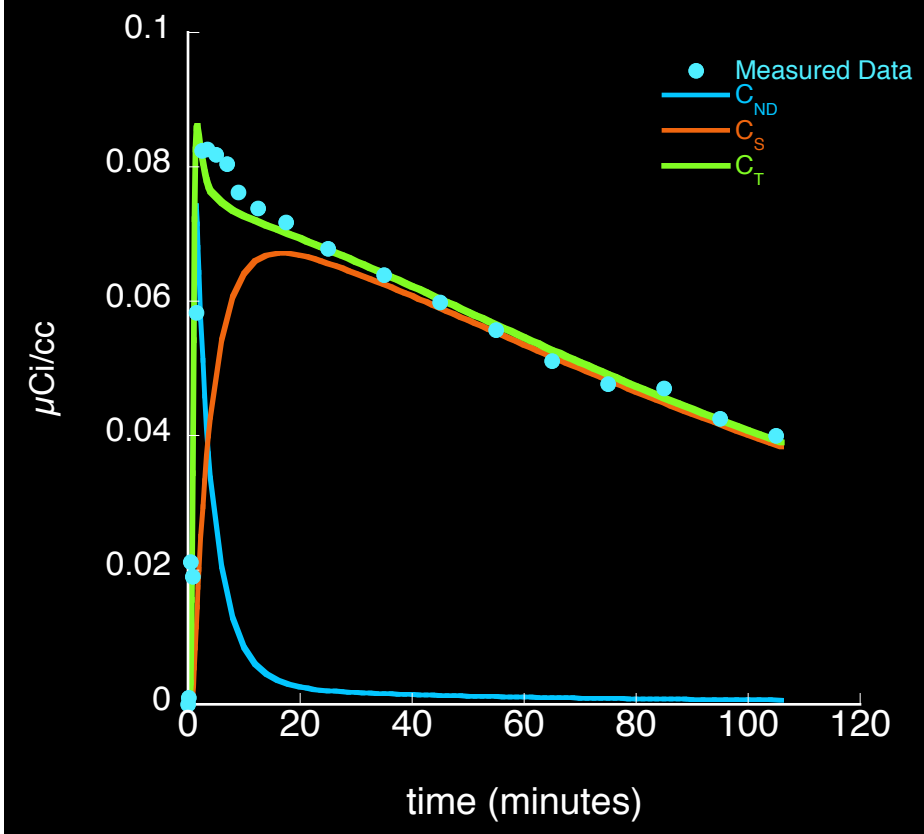


K1	0.0887
k2	0.5195
k3	0.2487
k4	0.0117
k3/k4	21.3228

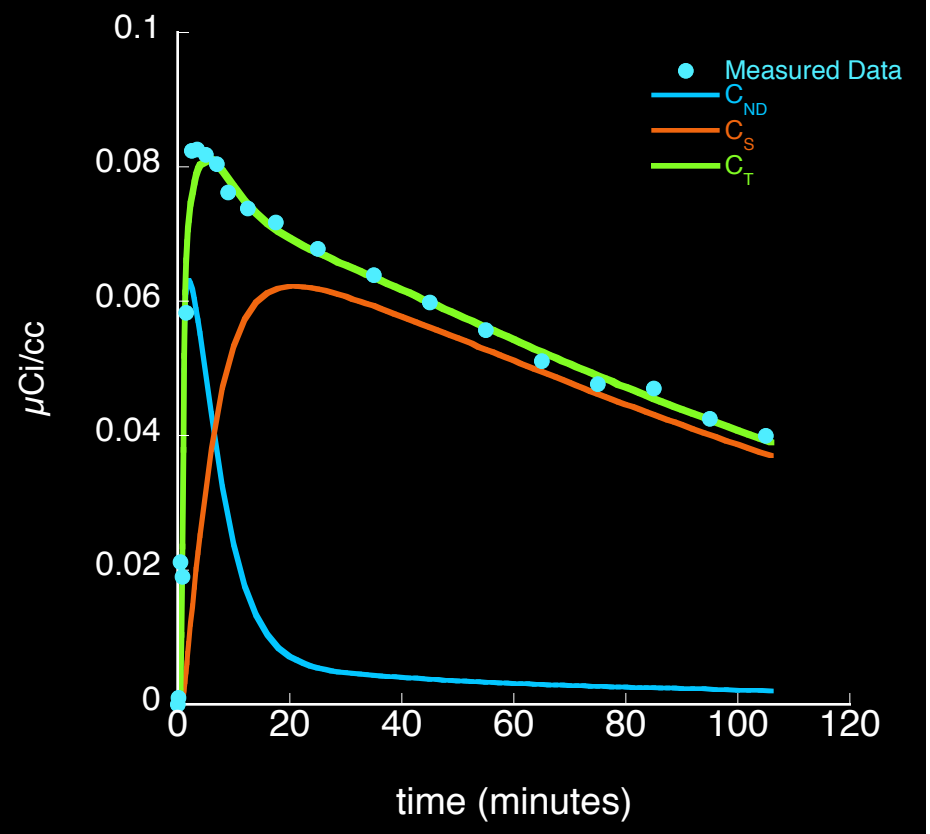
!!!!!

K1	0.0576
k2	0.1526
k3	0.1379
k4	0.015
k3/k4	9.2151

Previous Example V_T within 1%



$V_T = 3.8122$



$V_T = 3.8575$