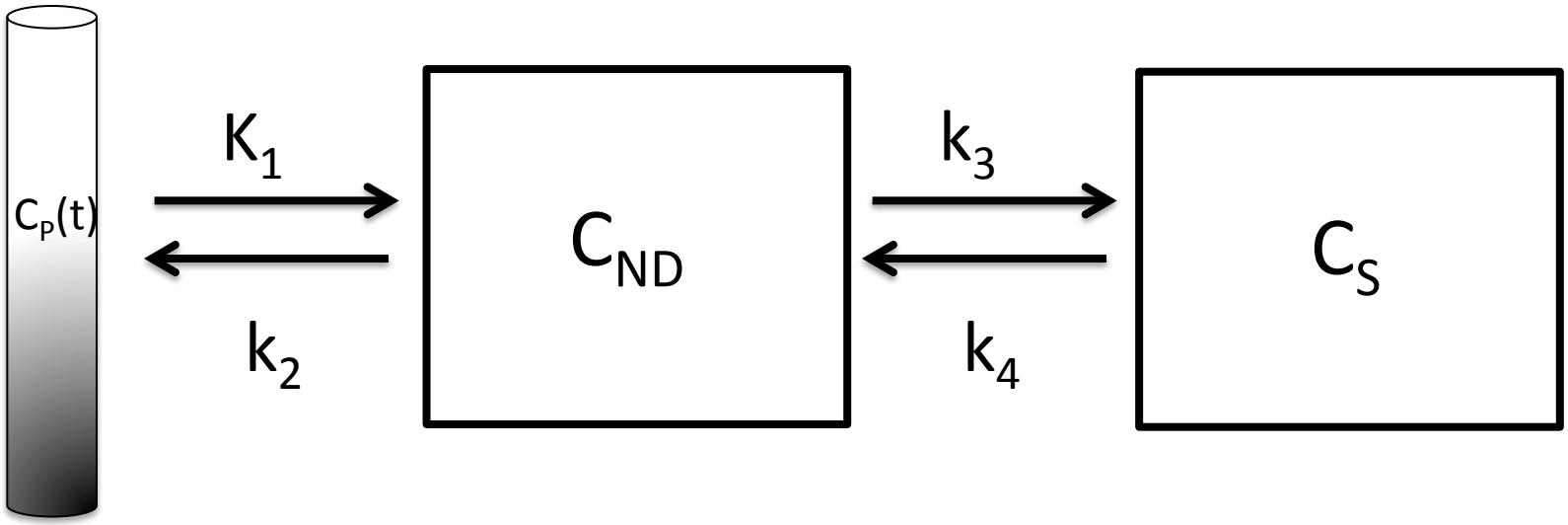
Introduction to PET Pharmacokinetics:

Stability/Reliability of Parameter Estimates
Convolutions, LTI Systems

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

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

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

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

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

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

Equlibria and Distribution Volumes

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

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

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

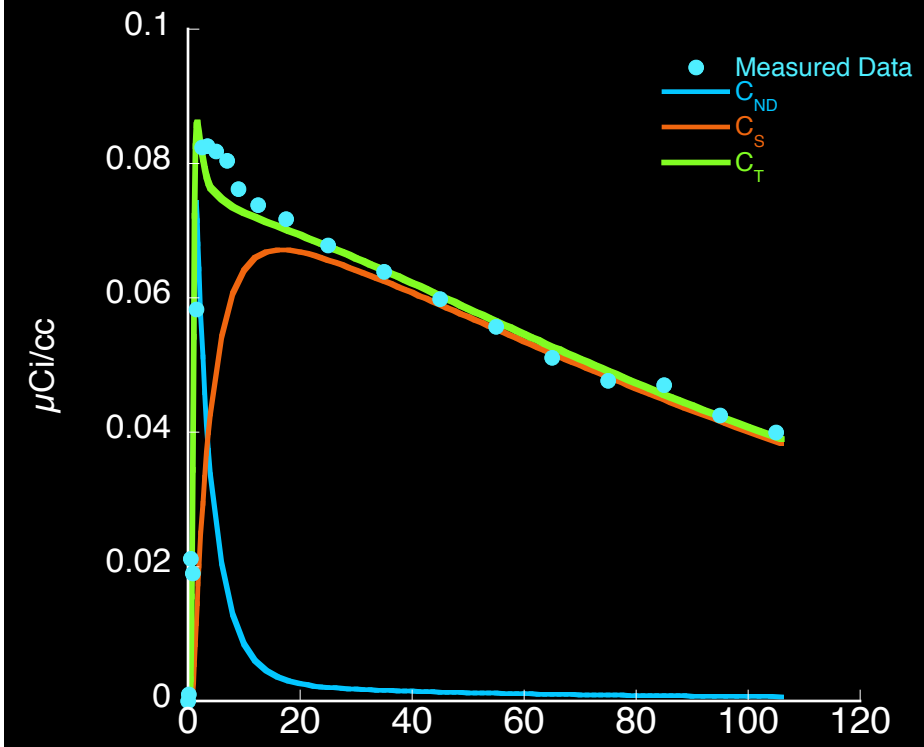
Binding Potentials

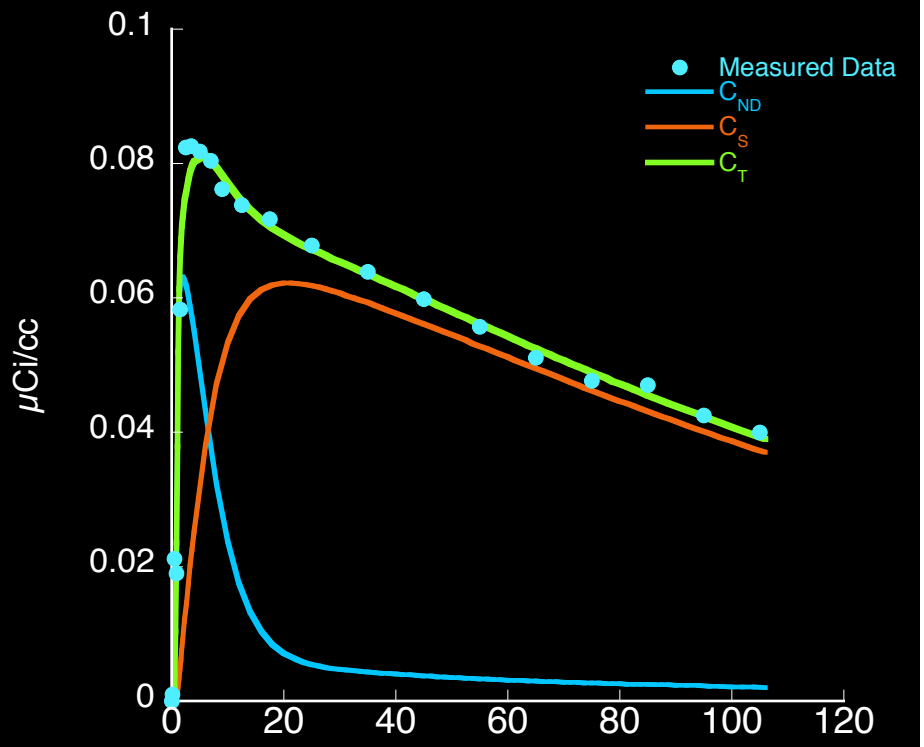
$$V_S = \frac{K_1 k_3}{k_2 k_4} = f_P \frac{B_{MAX}}{K_D} = BP_P$$

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

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

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



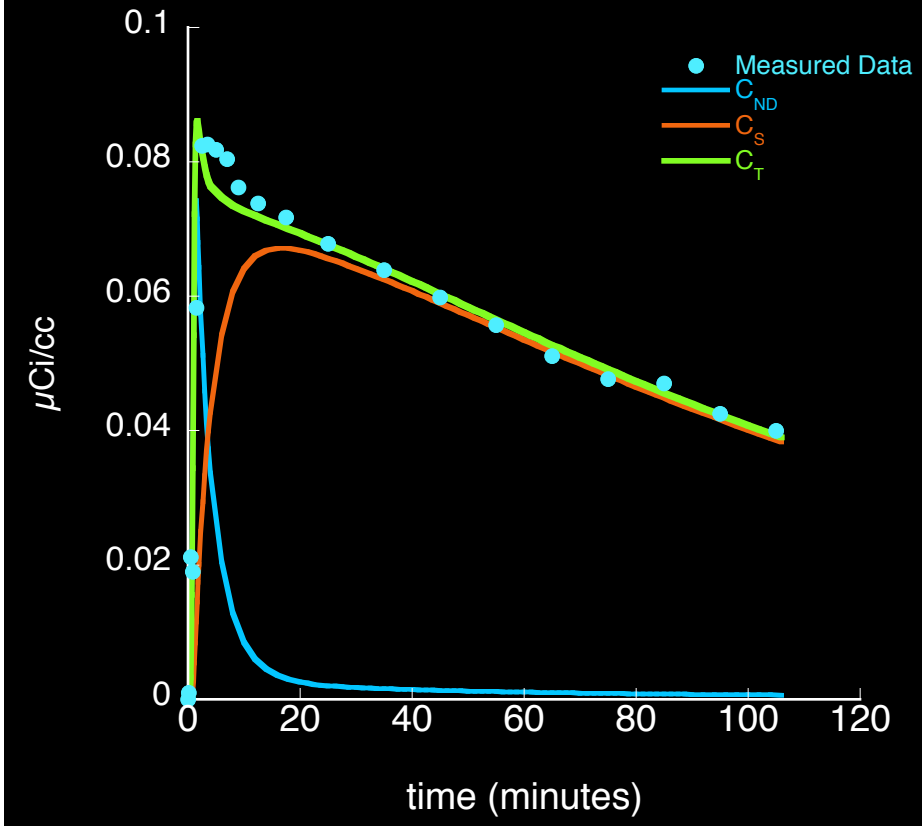


K1	0.0887
k2	0.5195
k3	0.2487
k4	0.0117
k3/k4	21.3228

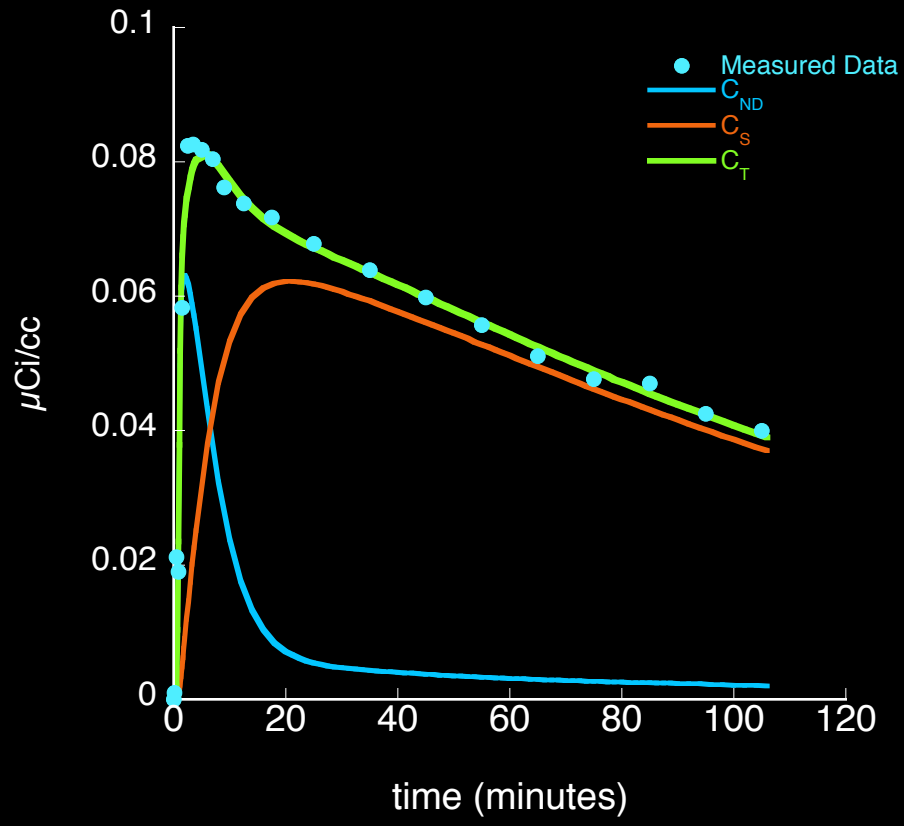
!!!!!!

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

Previous Example V_T within 1%

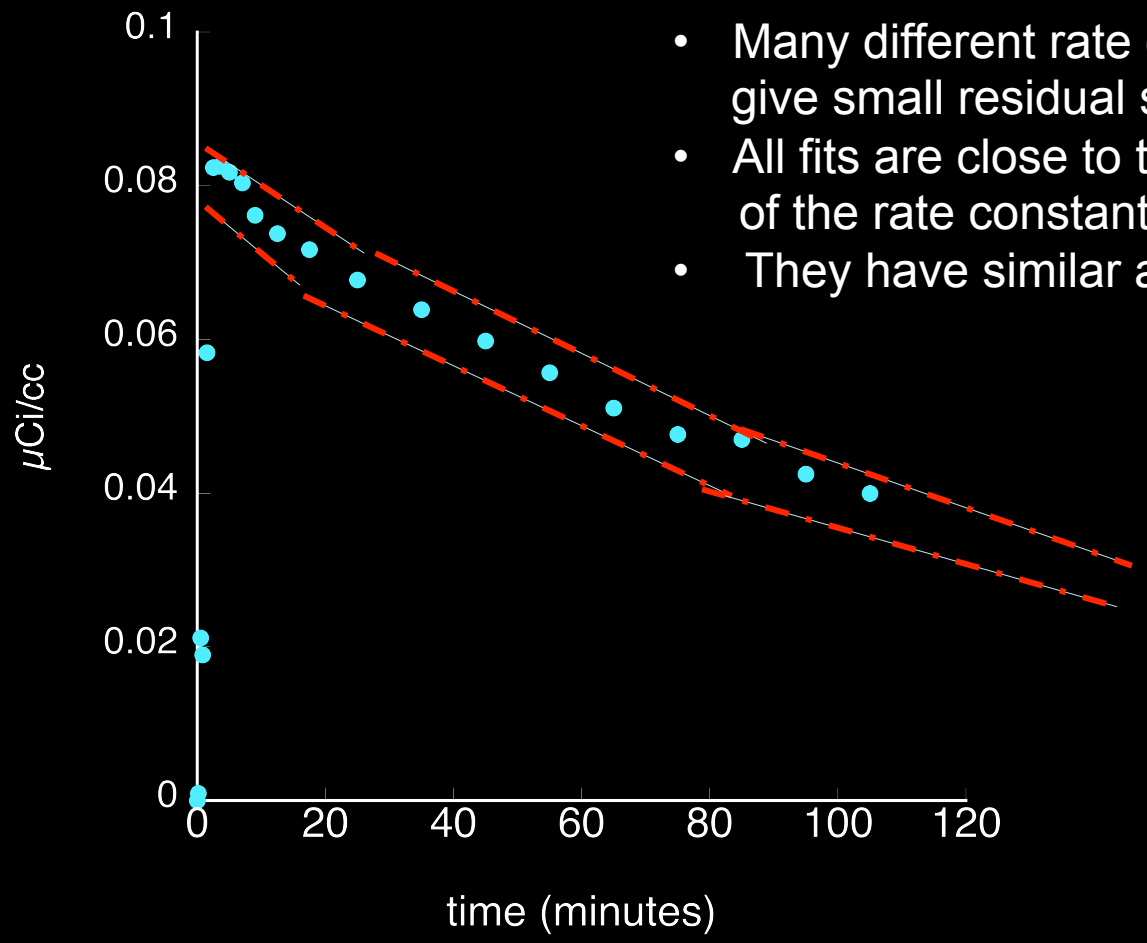


$V_T = 3.8122$



$V_T = 3.8575$

Intuitive Explanation:



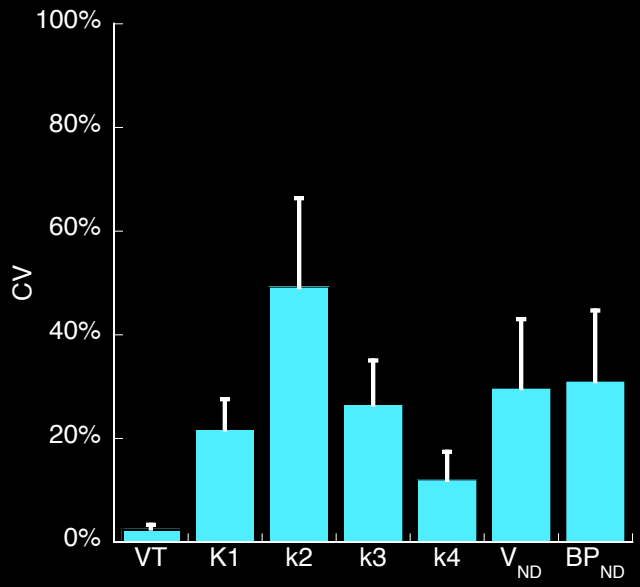
- Many different rate constant combinations will give small residual sum of squares.
- All fits are close to the data regardless of the rate constant values
- They have similar area under the curve (AUC)

$VT = AUC(C_T) / AUC(C_P)$

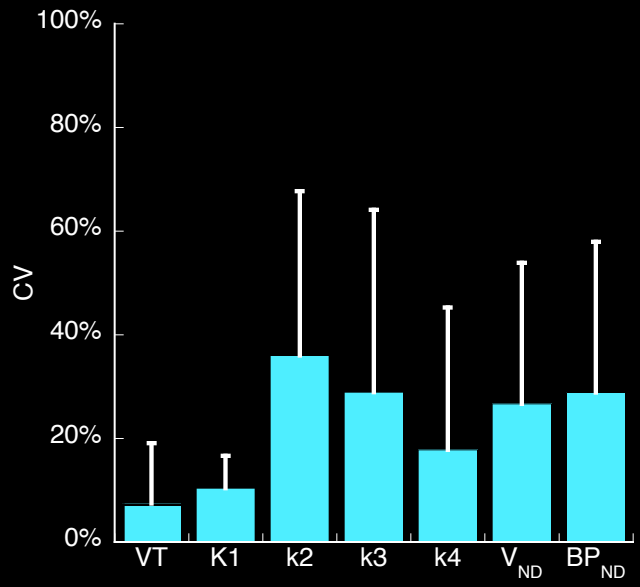
Statistical Evidence:

- Assess stability of fit using Fisher information **F**.
- For any fn of the parameters g(k), $\mathrm{Var}\left[g(\mathbf{k}) \right] \approx \nabla_k g^{\mathbf{T}} \mathbf{F}^{-1} \nabla_k g$
- Express as CV: SD(parameter)/parameter estimate
- V_T is consistently most stable

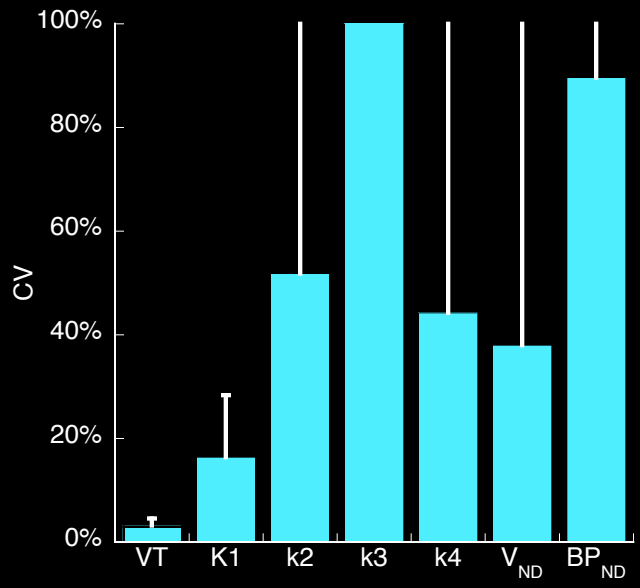
[^{18}F]fallypride high signal



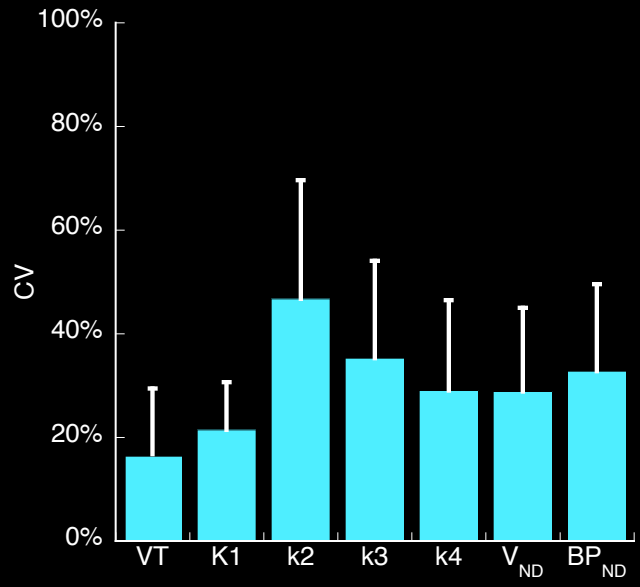
[^{11}C]WAY100635 high signal



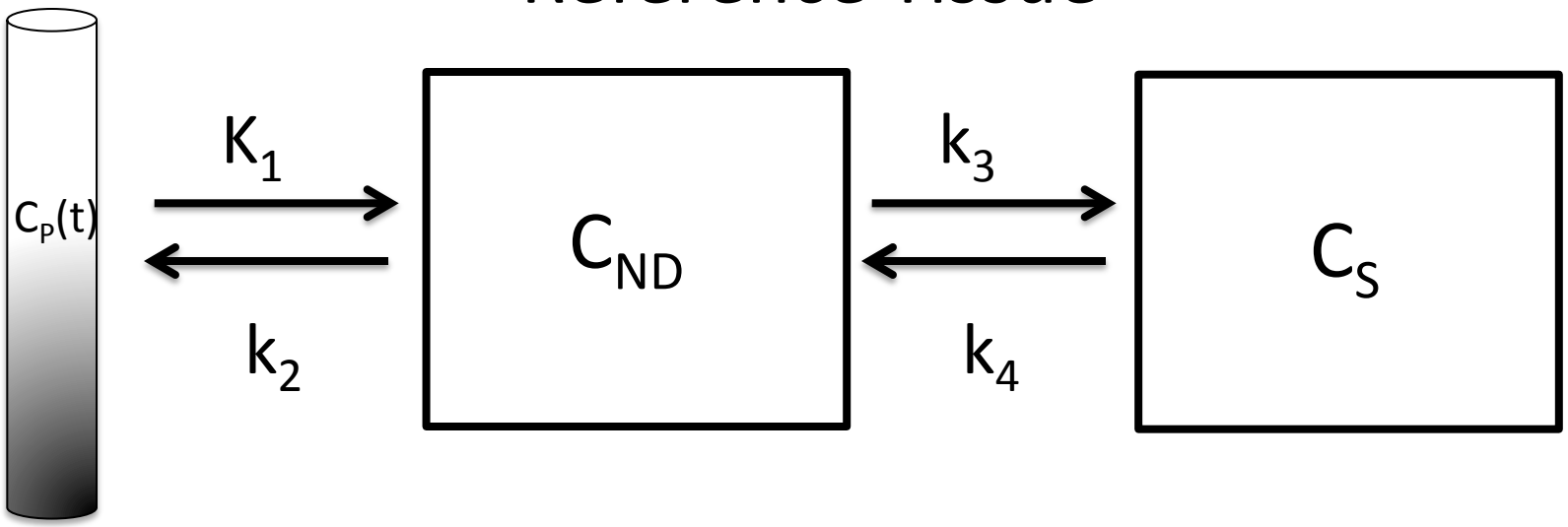
[^{18}F]fallypride low signal



[^{11}C]WAY100635 low signal



Reference Tissue



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

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

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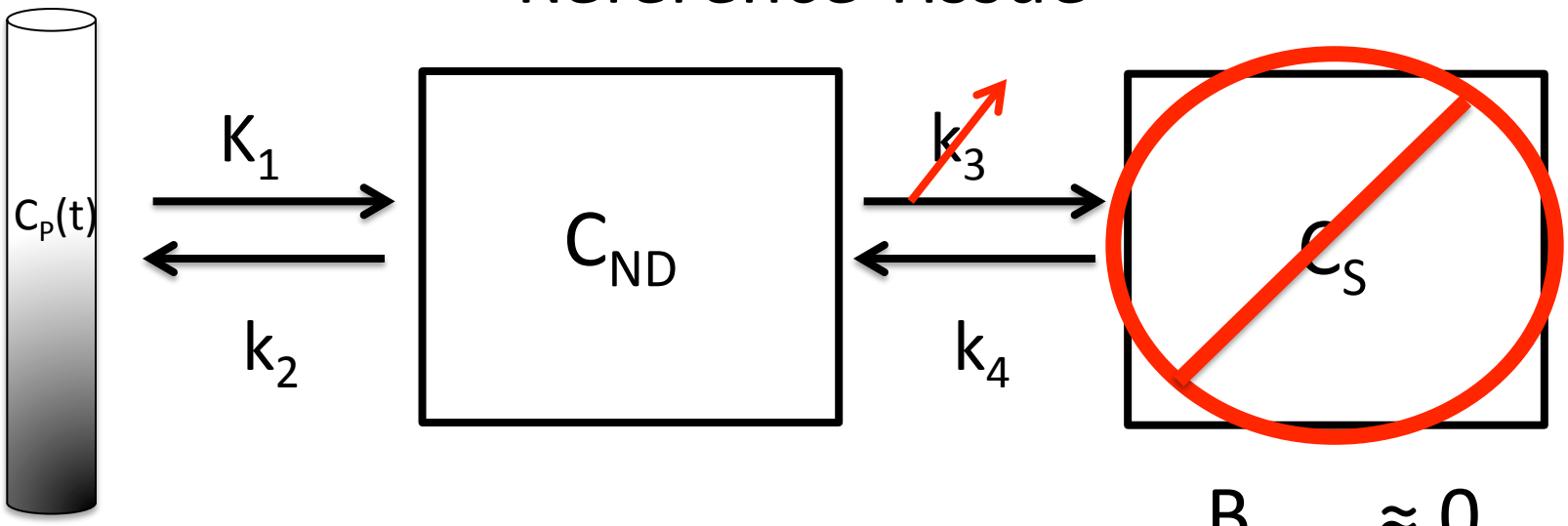

$B_{MAX} \approx 0$

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

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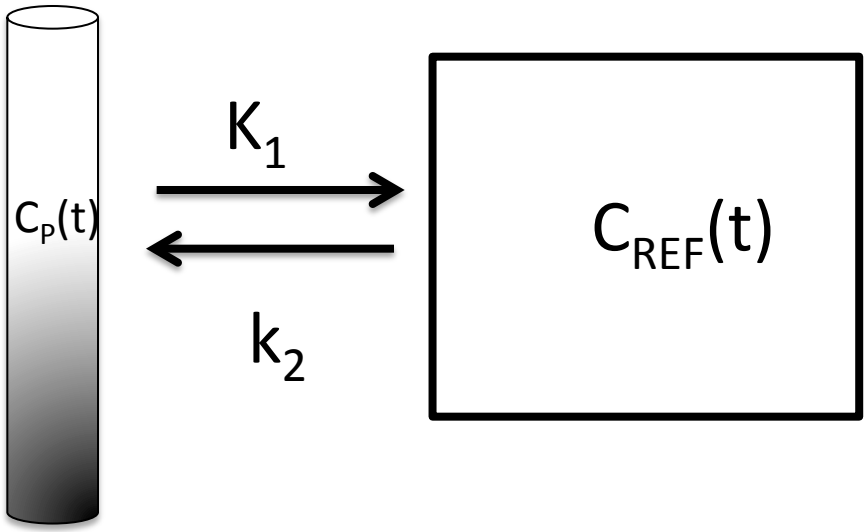
Reference Tissue



$$\frac{dC_{REF}(t)}{dt} = K_1 Cp(t) - k_2 C_{REF}(t)$$

$$V_T = V_{ND}$$

Indirect Estimation of BP

Region with $B_{MAX} > 0$: $$V_T = V_{ND} + BP_P$$

Reference Tissue: $$V_T = V_{ND}$$

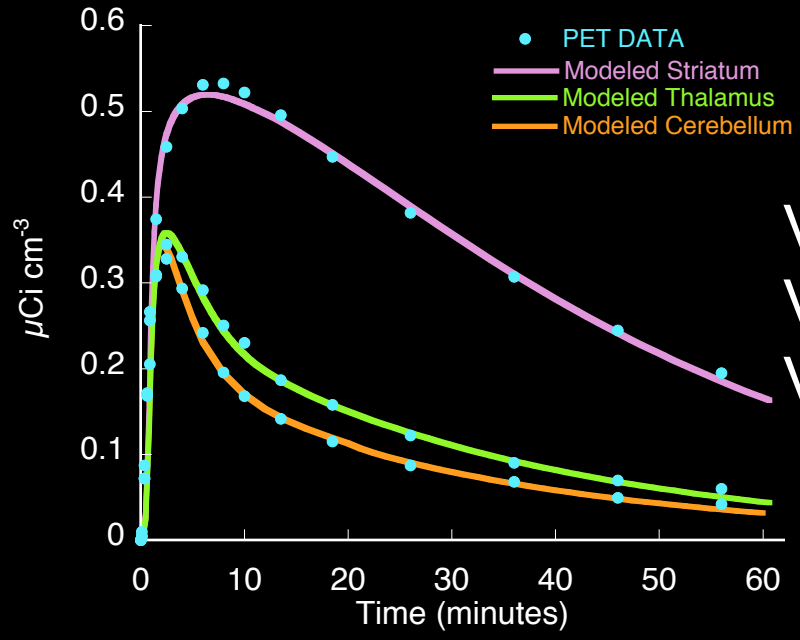
$$V_T(ROI) - V_T(REF) = BP_P$$

$$\frac{V_T(ROI) - V_T(REF)}{V_T(REF)} = BP_{ND}$$

$D_{2/3}$ Imaging

Antagonists: Kinetics

[^{11}C] raclopride
Baseline
(baboon)



V_T(striatum) = 3.89 BP_{ND} = 2.74
V_T (thalamus) = 1.37 BP_{ND} = 0.32
V_T(cerebellum) =1.04

$D_{2/3}$ Imaging

Antagonists: Kinetics

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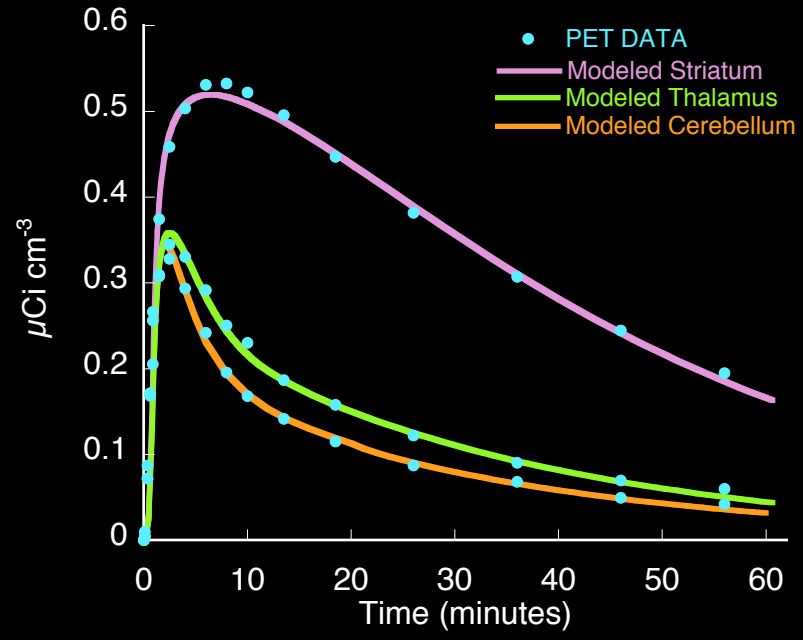
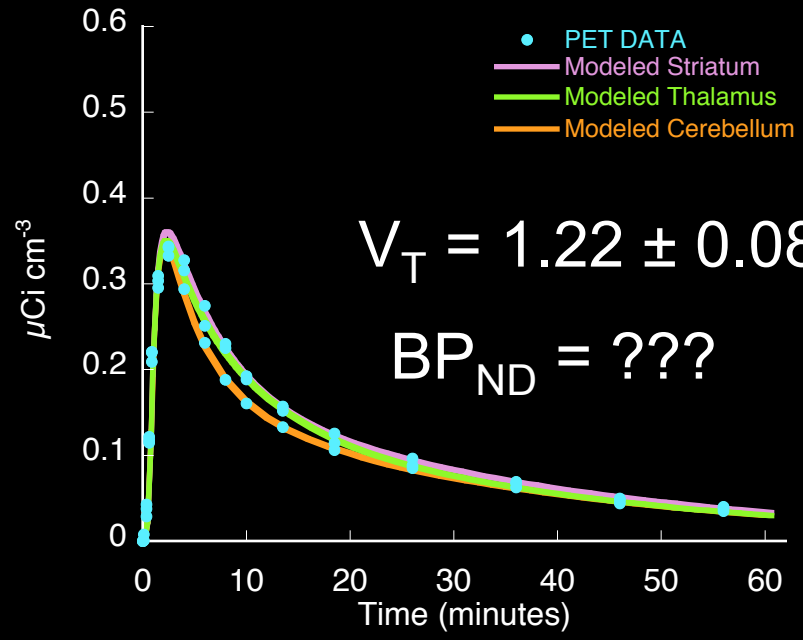


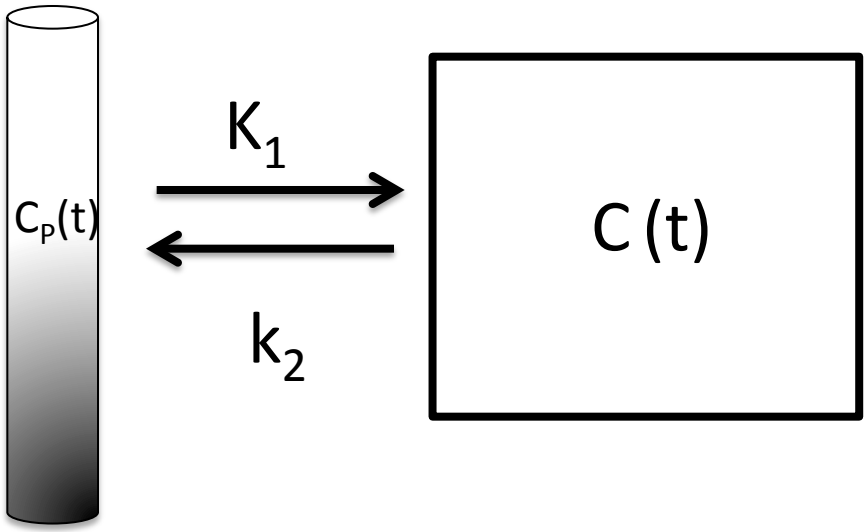
[^{11}C] raclopride
Haloperidol (1 mg/kg)
(baboon)



$V_T = 1.22 \pm 0.08$

$BP_{ND} = ???$

1TC Model



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

1TC Model

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

$$\frac{dC(t)}{dt} + k_2 C(t) = K_1 Cp(t)$$

$$e^{k_2 t}\left(\frac{dC(t)}{dt} + k_2 C(t)\right) = e^{k_2 t} K_1 Cp(t)$$

$$\frac{d}{dt}\left(e^{k_2 t} C(t)\right) = e^{k_2 t} K_1 Cp(t)$$

1TC Model

$$\frac{d}{dt}\left(e^{k_2 t}C(t)\right) = e^{k_2 t}K_1 Cp(t)$$

$$\int_0^t \frac{d}{dt'}\left(e^{k_2 t'}C(t')\right)dt = \int_0^t e^{k_2 t'}K_1 Cp(t')dt'$$

$$e^{k_2 t}C(t) = \int_0^t e^{k_2 t'}K_1 Cp(t')dt'$$

$$C(t) = \int_0^t K_1 e^{k_2 (t-t')}Cp(t')dt'$$

1TC Model

$$C(t) = \int_0^t K_1 e^{k_2(t-t')} Cp(t') dt'$$

"Convolution Integral of $K_1 e^{-k_2 t}$ with Cp"

$$K_1 e^{-k_2 t} \otimes C_P(t)$$

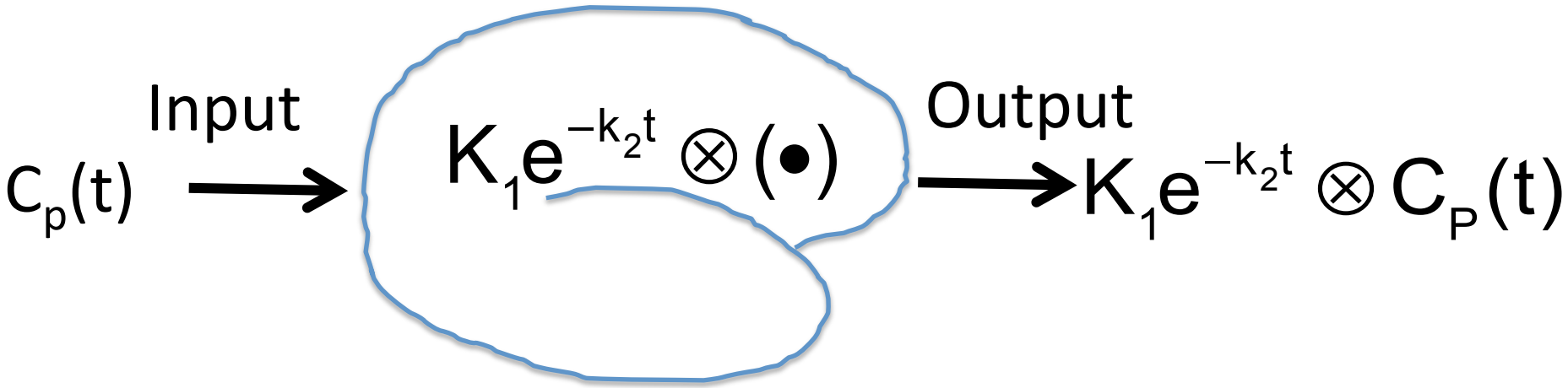
↑ Impulse Response

↑ Input

1TC Model

$$C(t) = \int_0^t K_1 e^{k_2(t-t')} Cp(t') dt'$$

Brain system: Convolution Operator

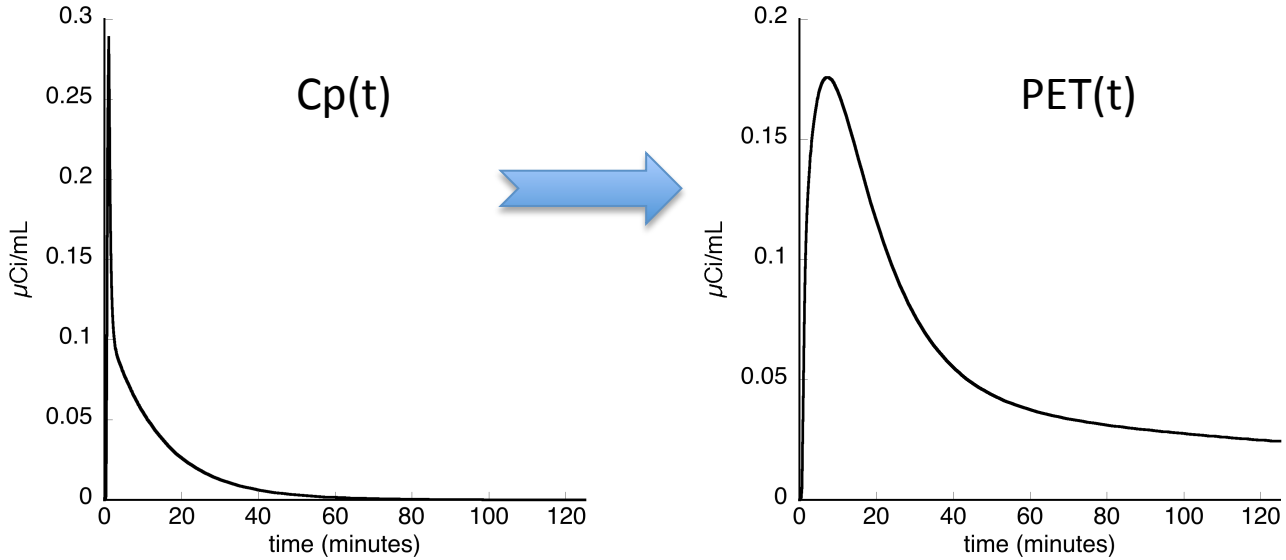


Application: Convolution

Background: We will be studying "input – output" systems:

INPUT: Concentration of tracer in plasma = Cp(t)

OUTPUT: Concentration of tracer in brain = PET(t)



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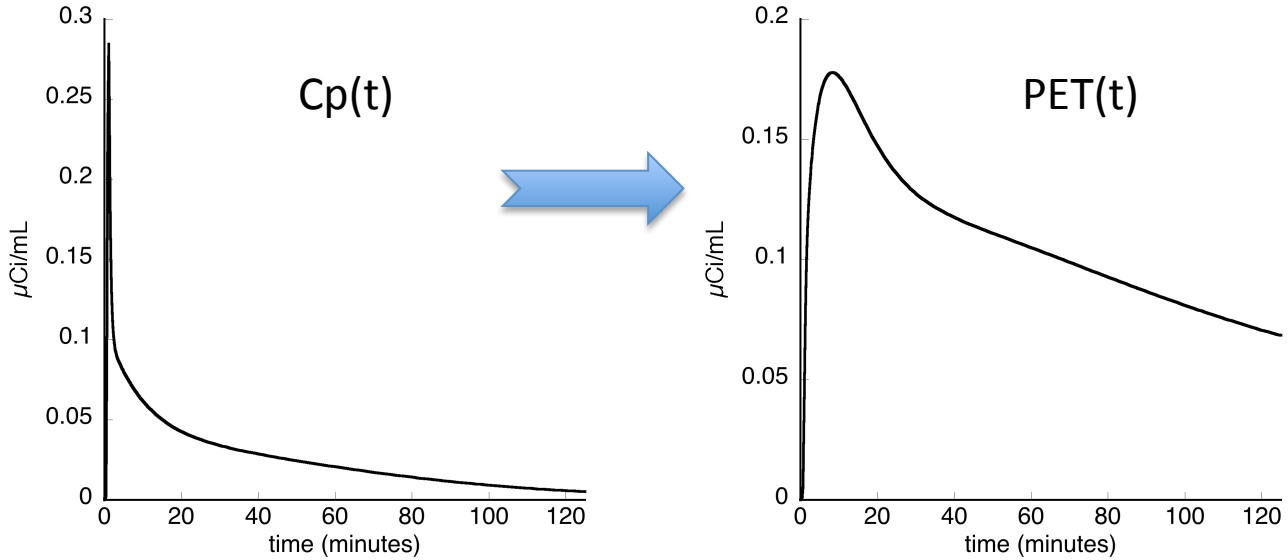


Application: Convolution

Background: The systems we will be studying are “linear”:

IF

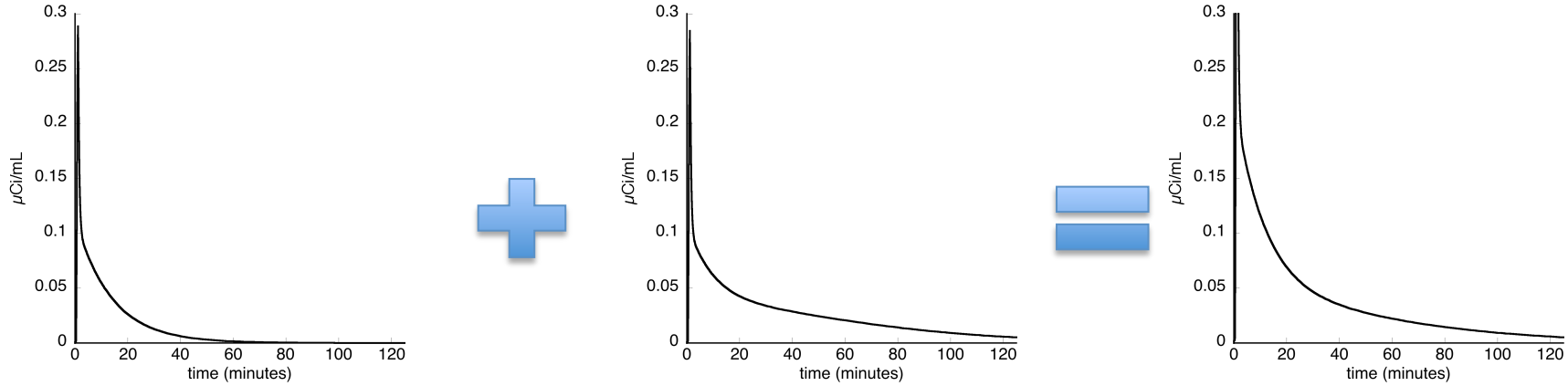
INPUT		OUTPUT
Cp1(t)	→	PET1(t)

AND

Cp2(t)	→	PET2(t)

THEN

a*Cp1(t) + b*Cp2(t)	→	a*PET1(t)+b*PET2(2)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time (minutes)
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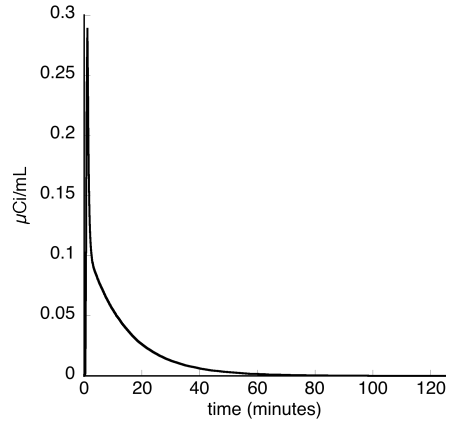
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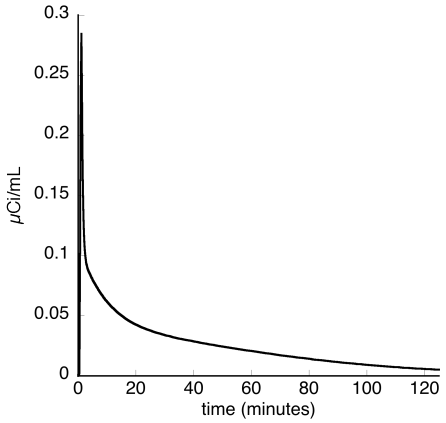
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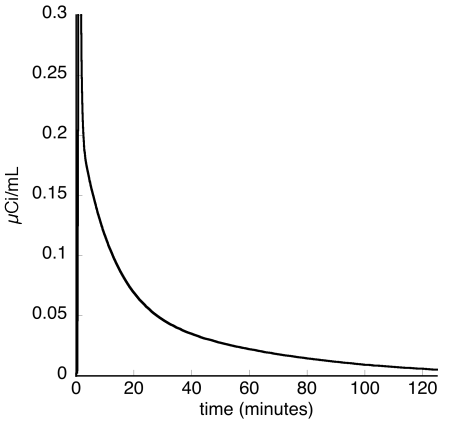
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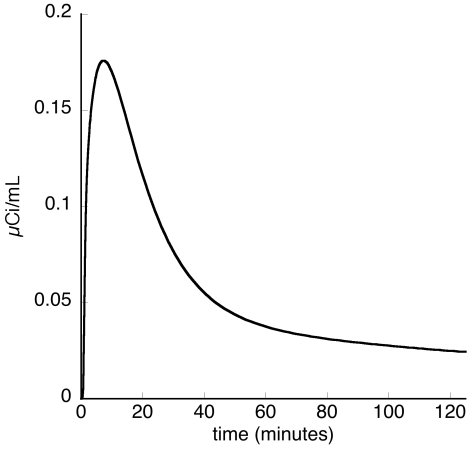
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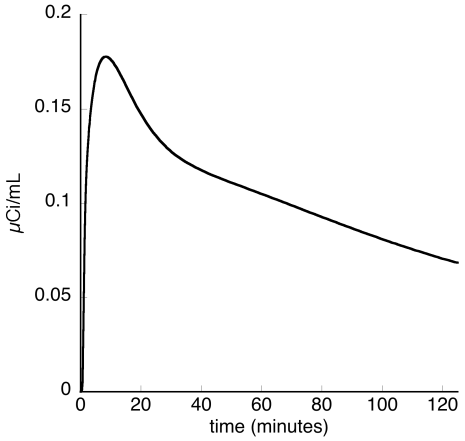
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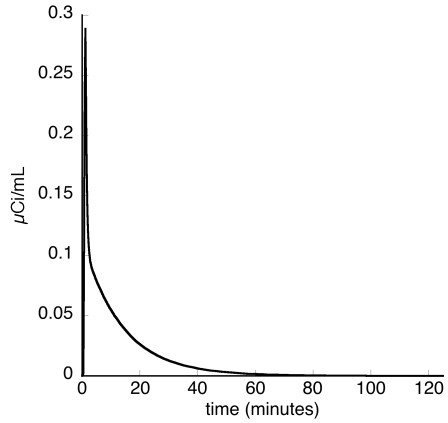
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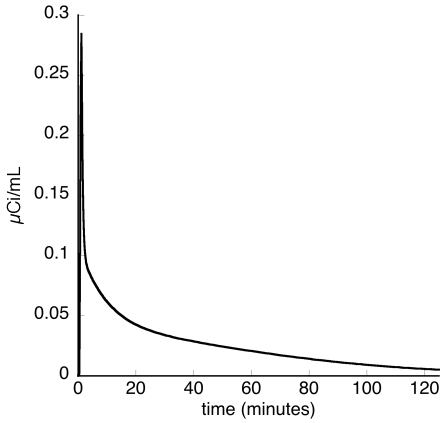
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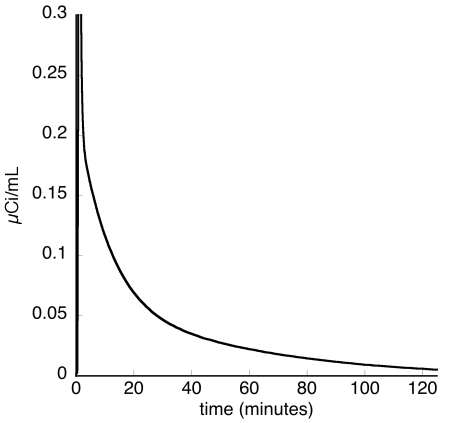
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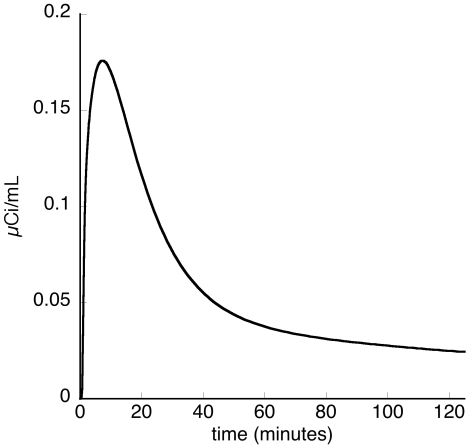
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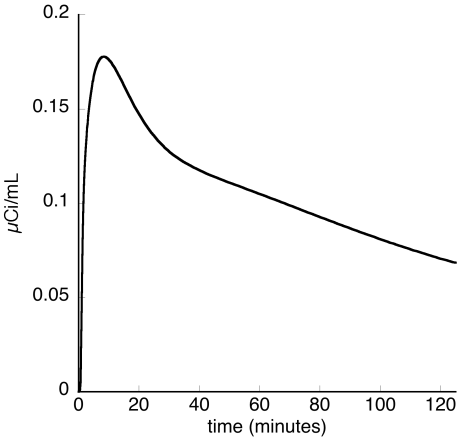
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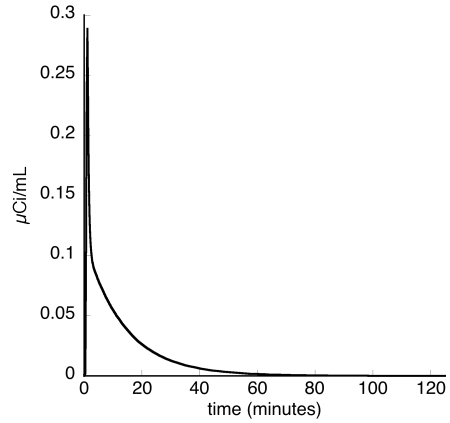
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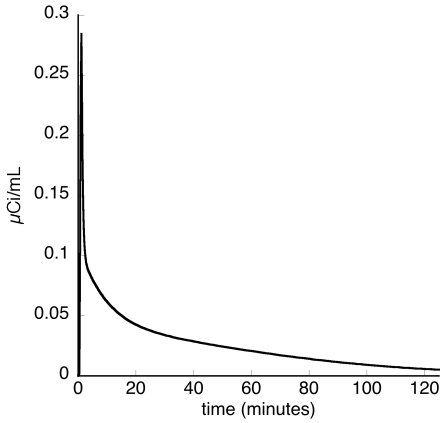
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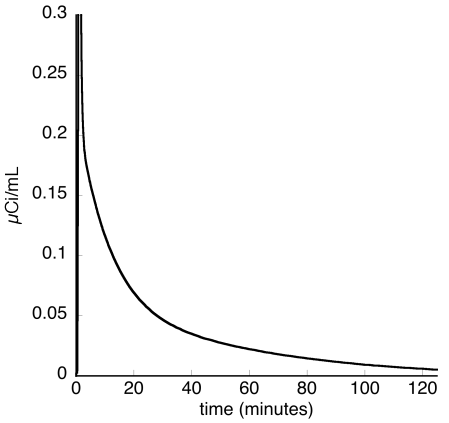
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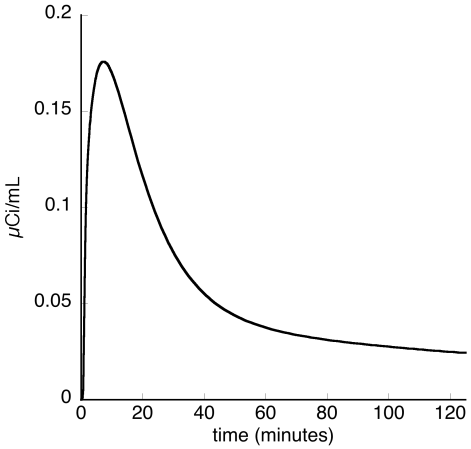
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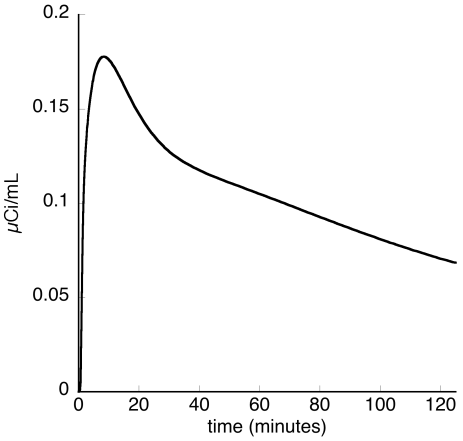
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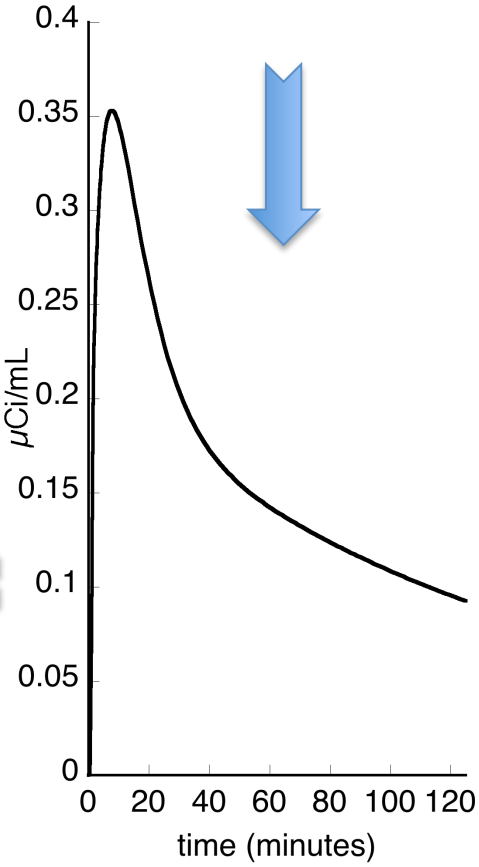
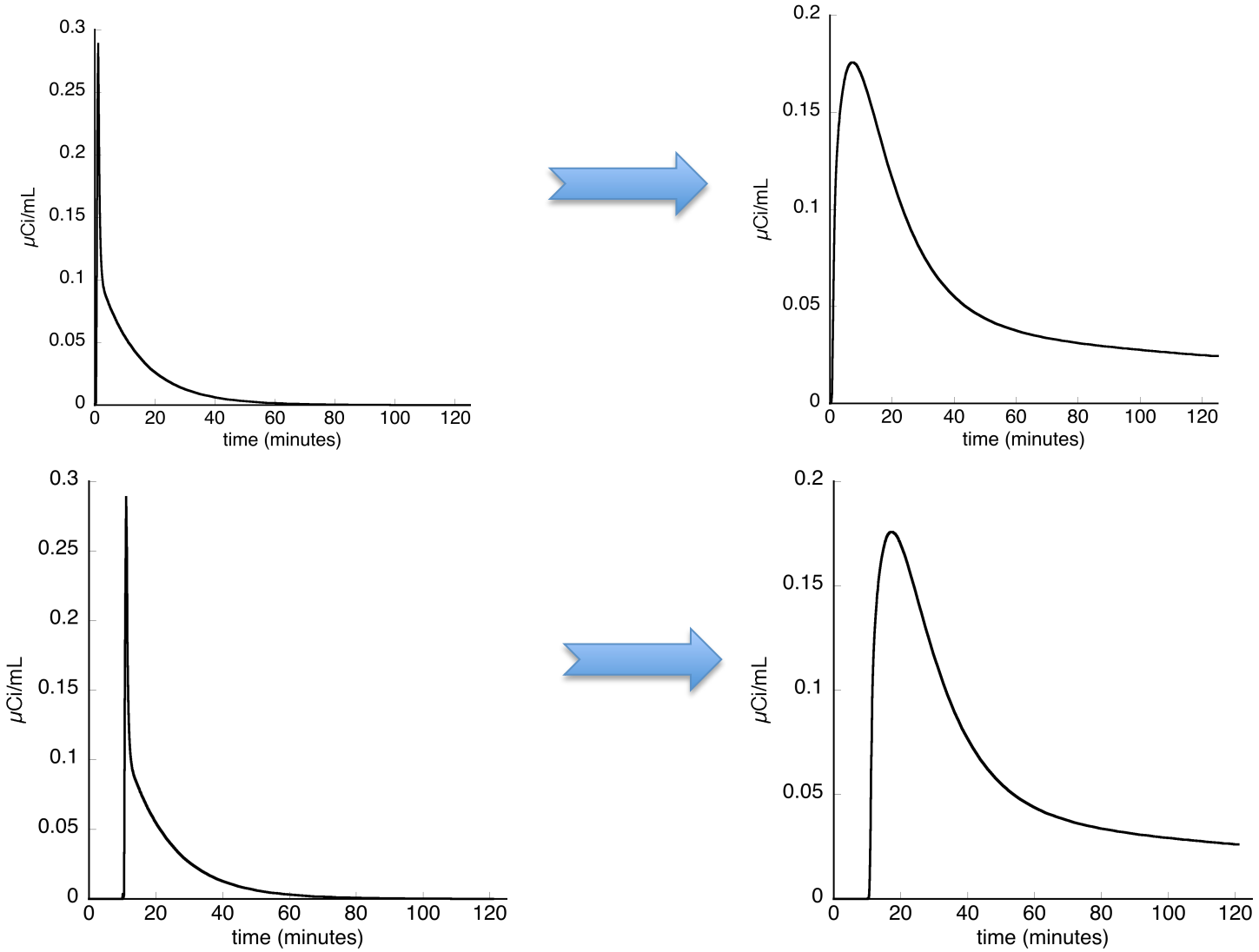
0 20 40 60 80 100 120
time (minutes)


0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
µCi/mL
0 20 40 60 80 100 120
time (minutes)

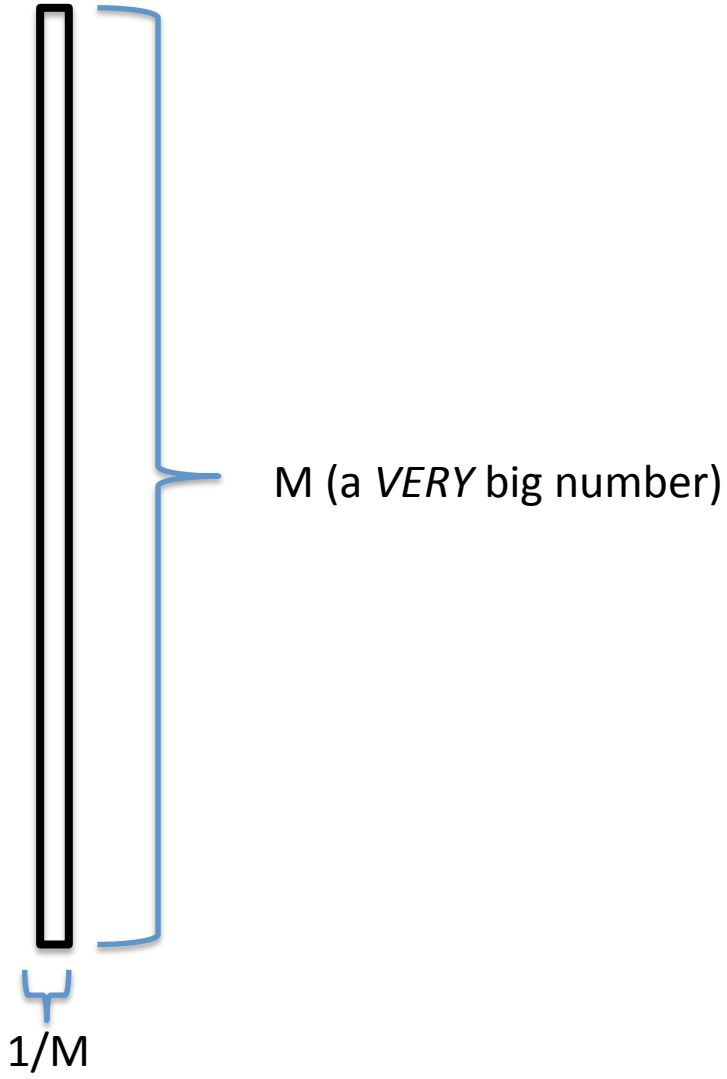
Application: Convolution

Background: The systems we will be studying are “time invariant”:



Application: Convolution

Background: CLAIM: such systems are characterized by response to a “unit impulse”



A <u>UNIT</u> impulse:

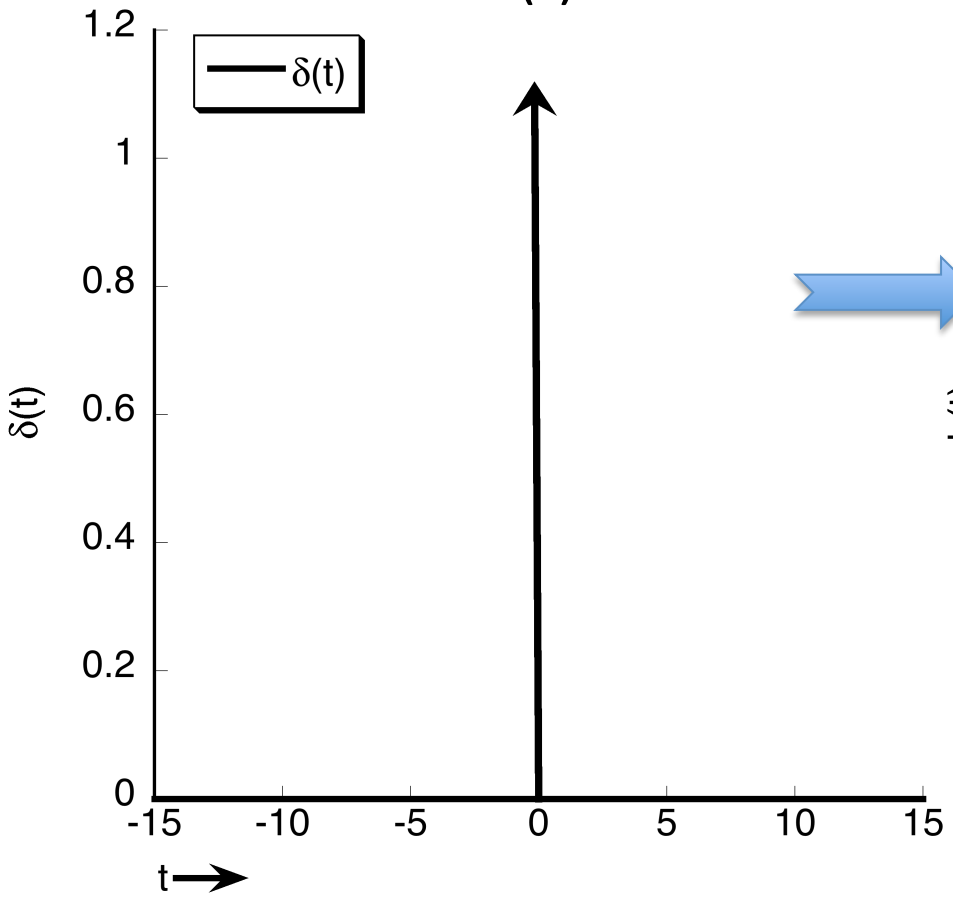
Area = M × 1/M = 1

Application: Convolution

Background: CLAIM: such systems are characterized by response to a “unit impulse”

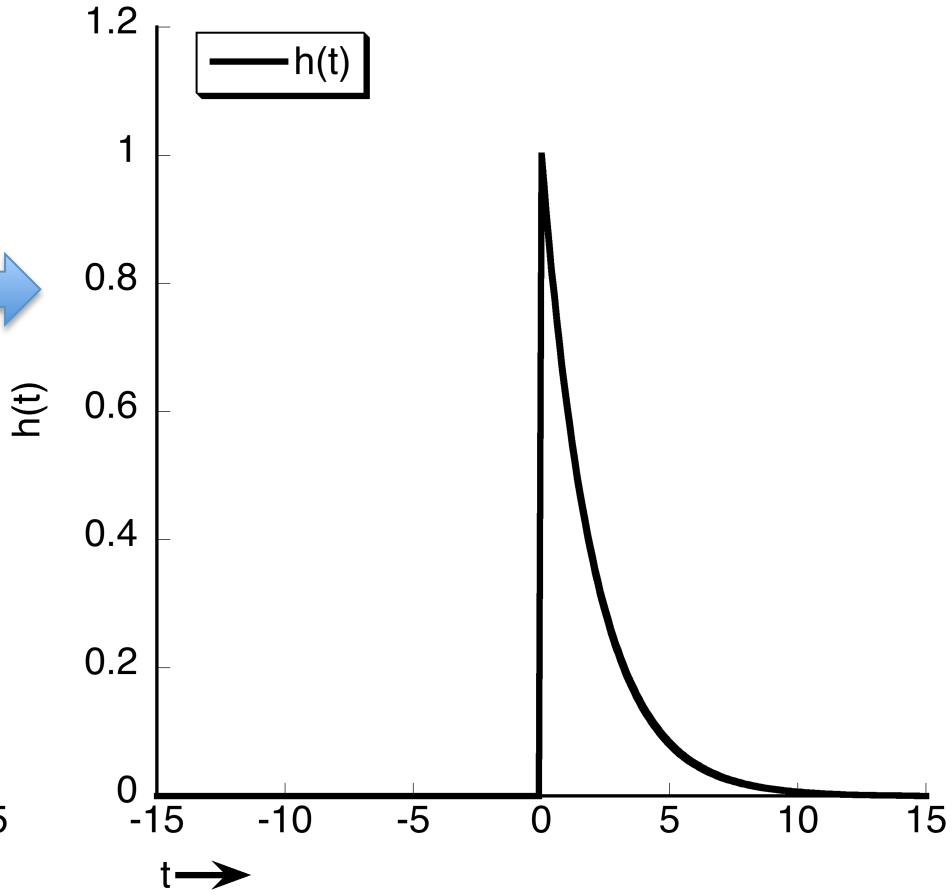
IDEALIZED UNIT impulse:

$\delta(t)$



Impulse response:

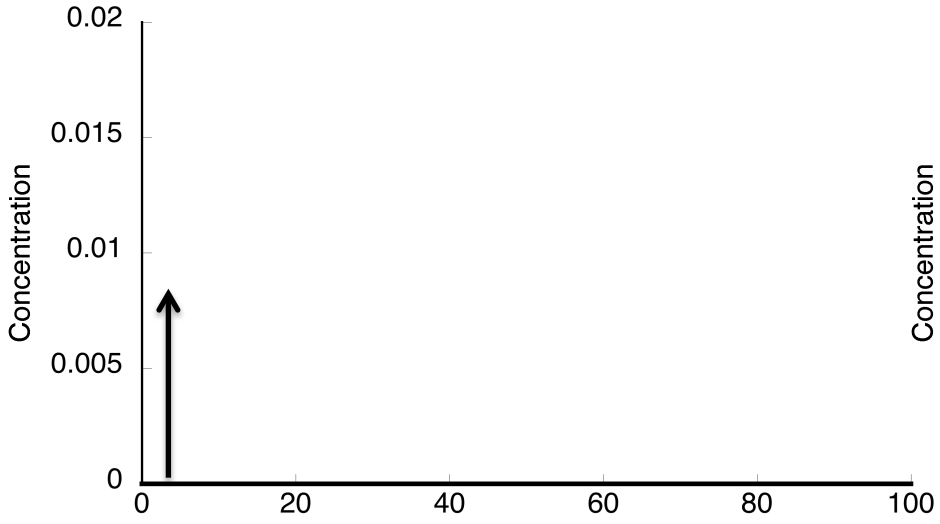
$h(t)$



Application: Convolution

Background: CLAIM: such systems are characterized by response to a “unit impulse”

Small impulse



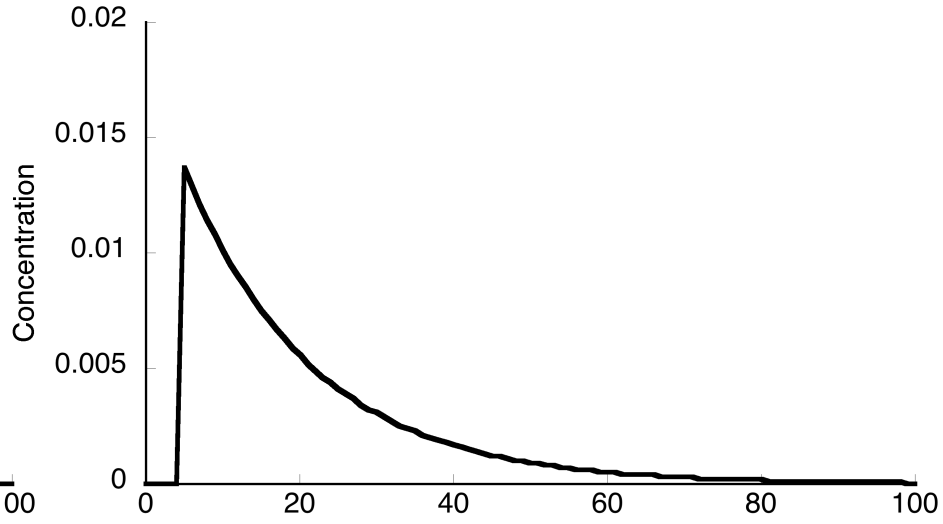
Height = $Cp(t_1)$

Base = Δt

AUC = $\Delta tCp(t_1)$

INPUT = $\Delta tCp(t_1)\delta(t-t_1)$

Response

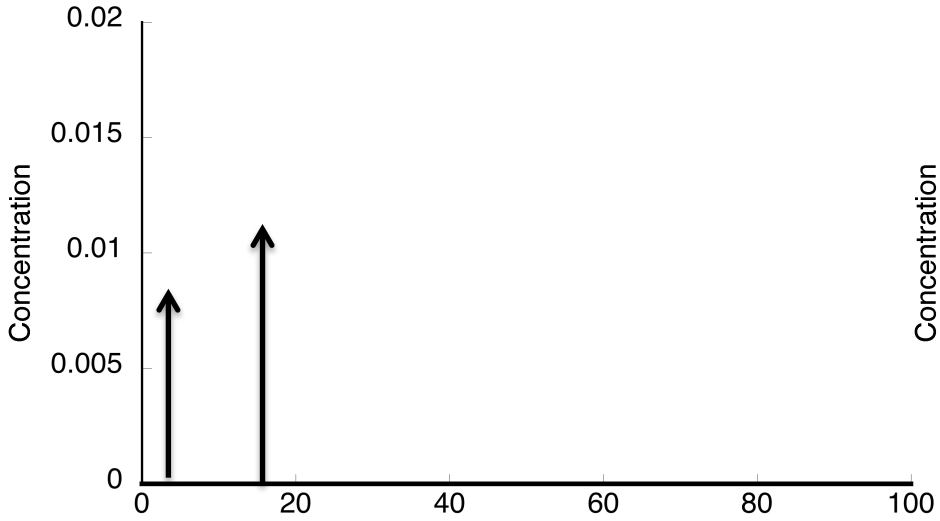


$\Delta tCp(t_1)*h(t-t_1)$

Application: Convolution

Background: CLAIM: such systems are characterized by response to a “unit impulse”

Several small impulses



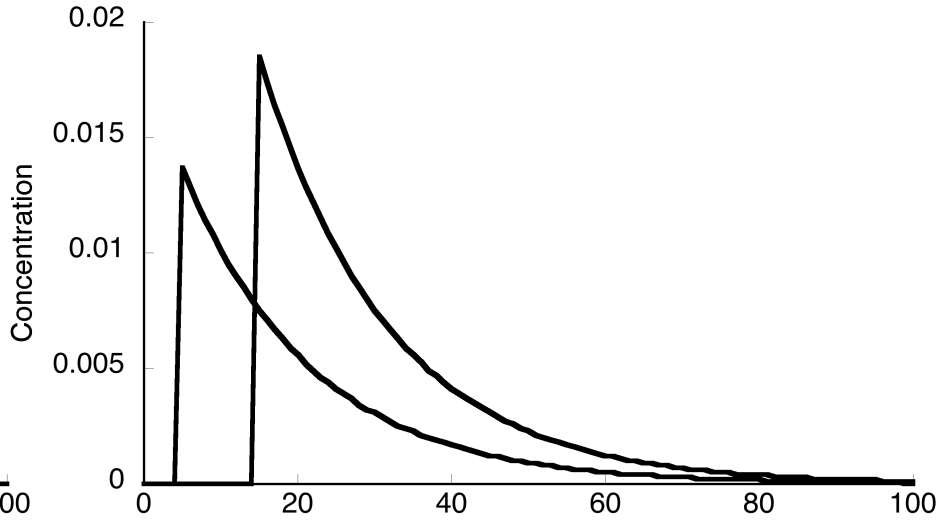
Height = $Cp(t_2)$

Base = Δt

AUC = $\Delta t Cp(t_2)$

INPUT = $\Delta t Cp(t_2)\delta(t-t_2)$

Responses

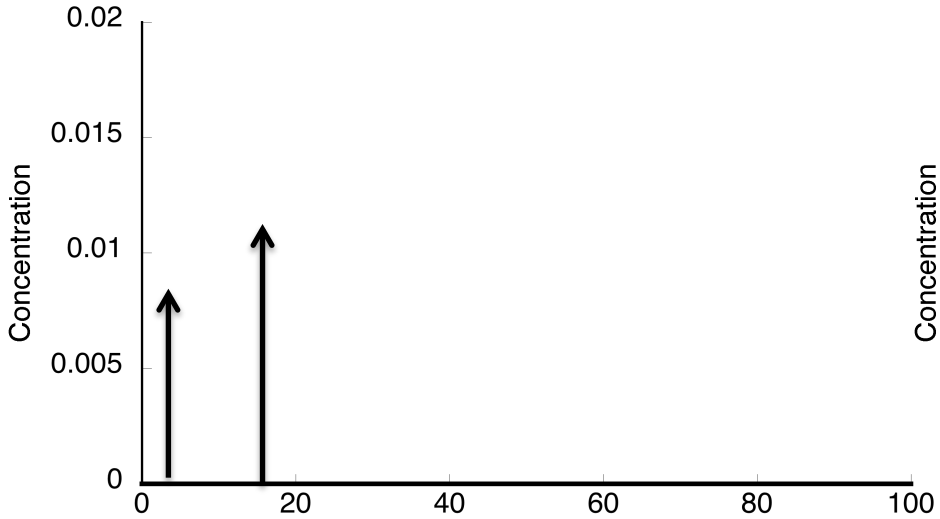


$\Delta t Cp(t_1)*h(t-t_1)$; $\Delta t Cp(t_2)*h(t-t_2)$

Application: Convolution

Background: CLAIM: such systems are characterized by response to a “unit impulse”

Several small impulses



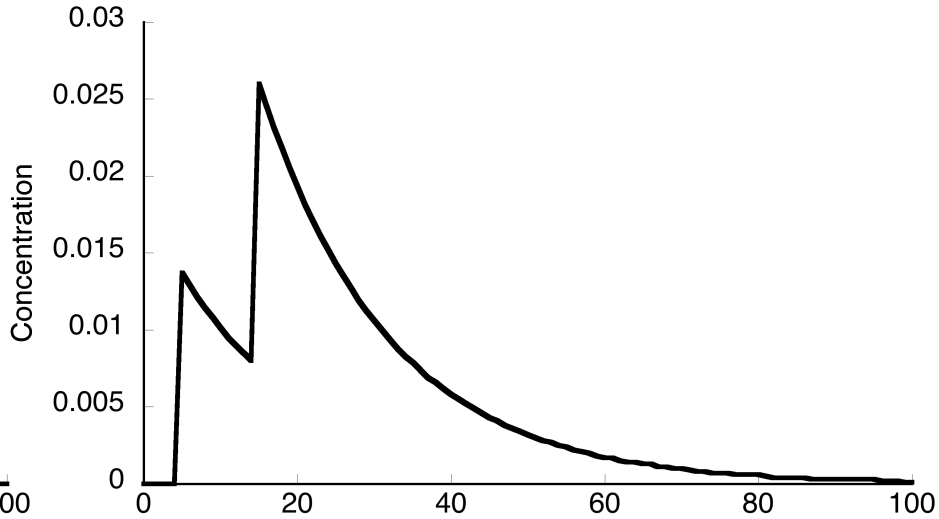
Height = $Cp(t_2)$

Base = Δt

AUC = $\Delta t Cp(t_2)$

INPUT = $\Delta t Cp(t_2)\delta(t-t_2)$

Sum of Responses

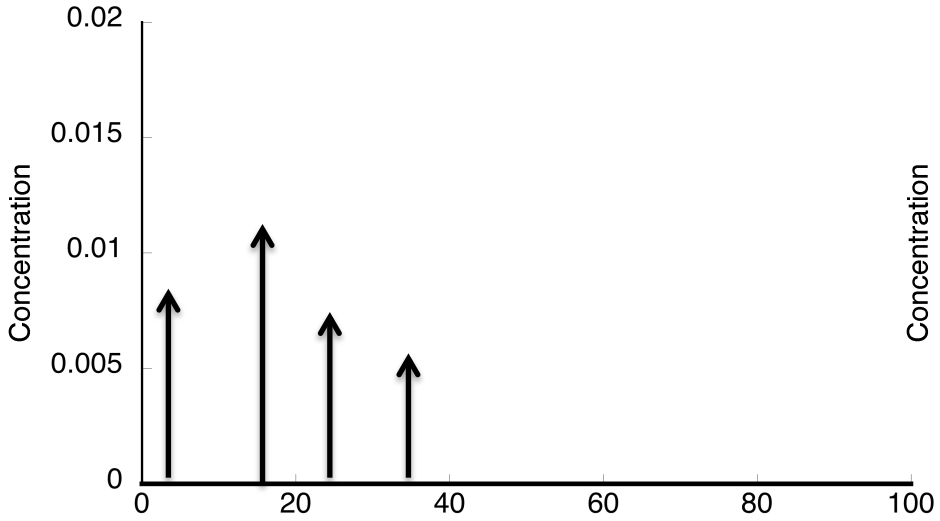


$\Delta t Cp(t_1)*h(t-t_1) + \Delta t Cp(t_2)*h(t-t_2)$

Application: Convolution

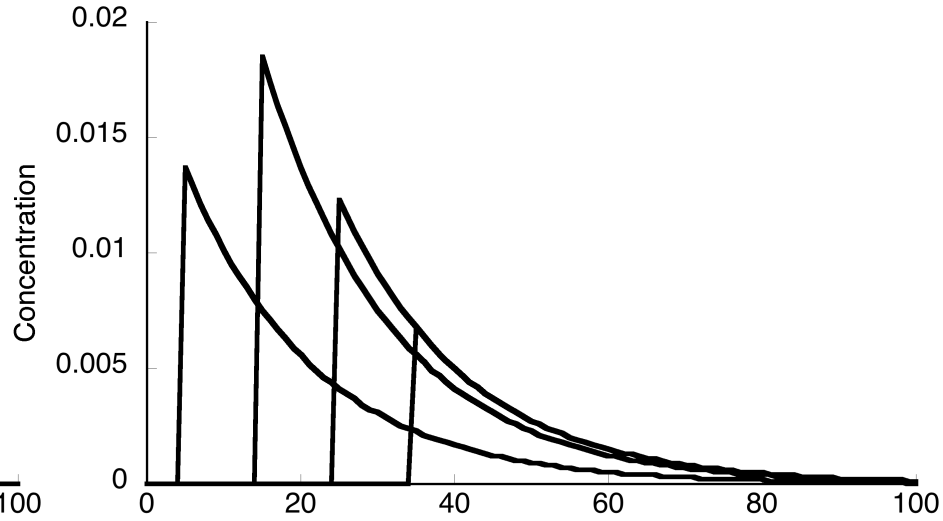
Background: CLAIM: such systems are characterized by response to a “unit impulse”

Several small impulses



$$\sum_{j=1}^{4} \Delta t Cp(t_j)\delta(t - t_j)$$

Responses

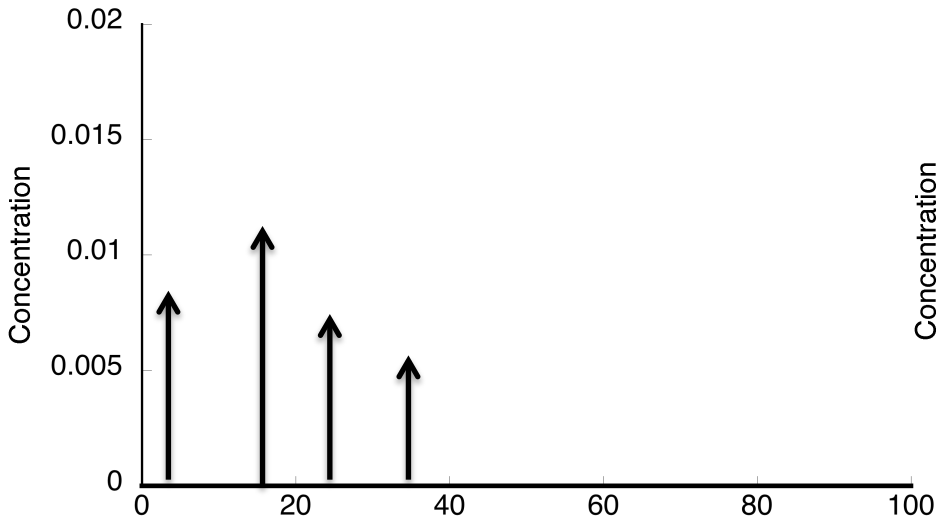


$$\left\{\Delta t \times Cp(t_j) \times h(t - t_j)\right\}_{j=1}^{4}$$

Application: Convolution

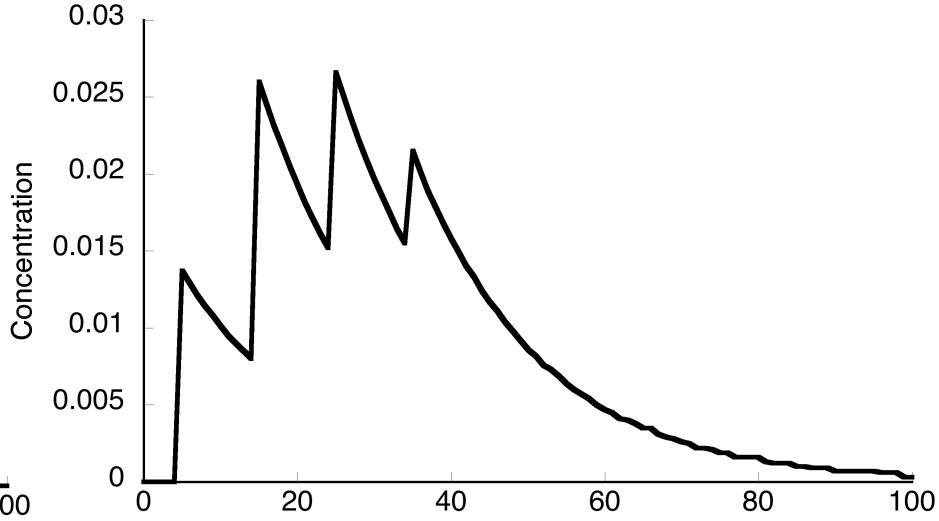
Background: CLAIM: such systems are characterized by response to a “unit impulse”

Several small impulses



$$\sum_{j=1}^{4} \Delta t \, Cp(t_j)\delta(t - t_j)$$

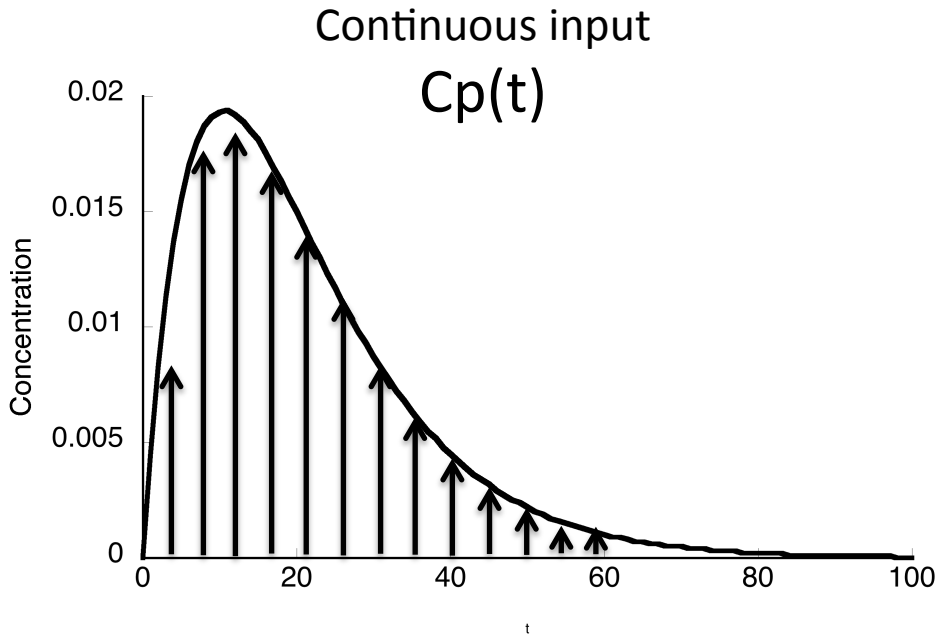
Sum of Responses

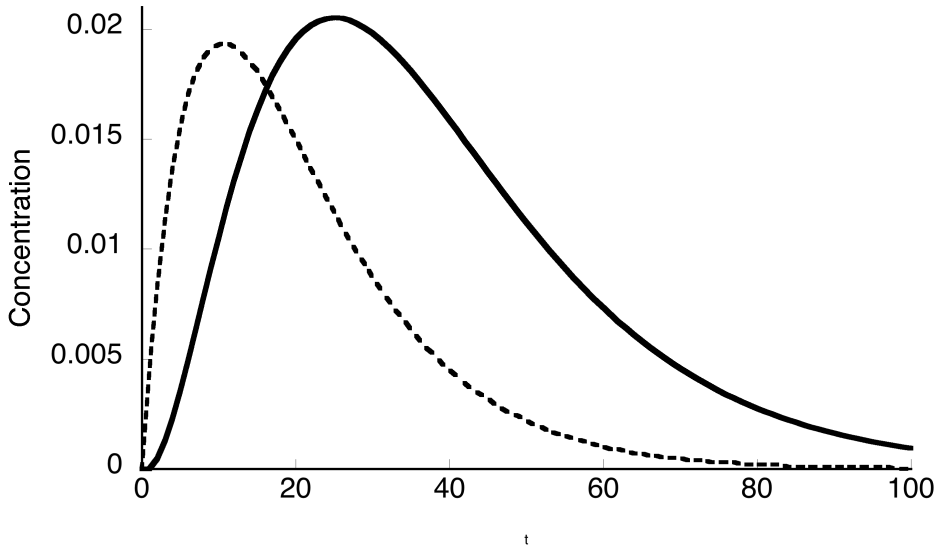


$$\sum_{j=1}^{4} \Delta t \times Cp(t_j) \times h(t - t_j)$$

Application: Convolution

Background: CLAIM: such systems are characterized by response to a “unit impulse”





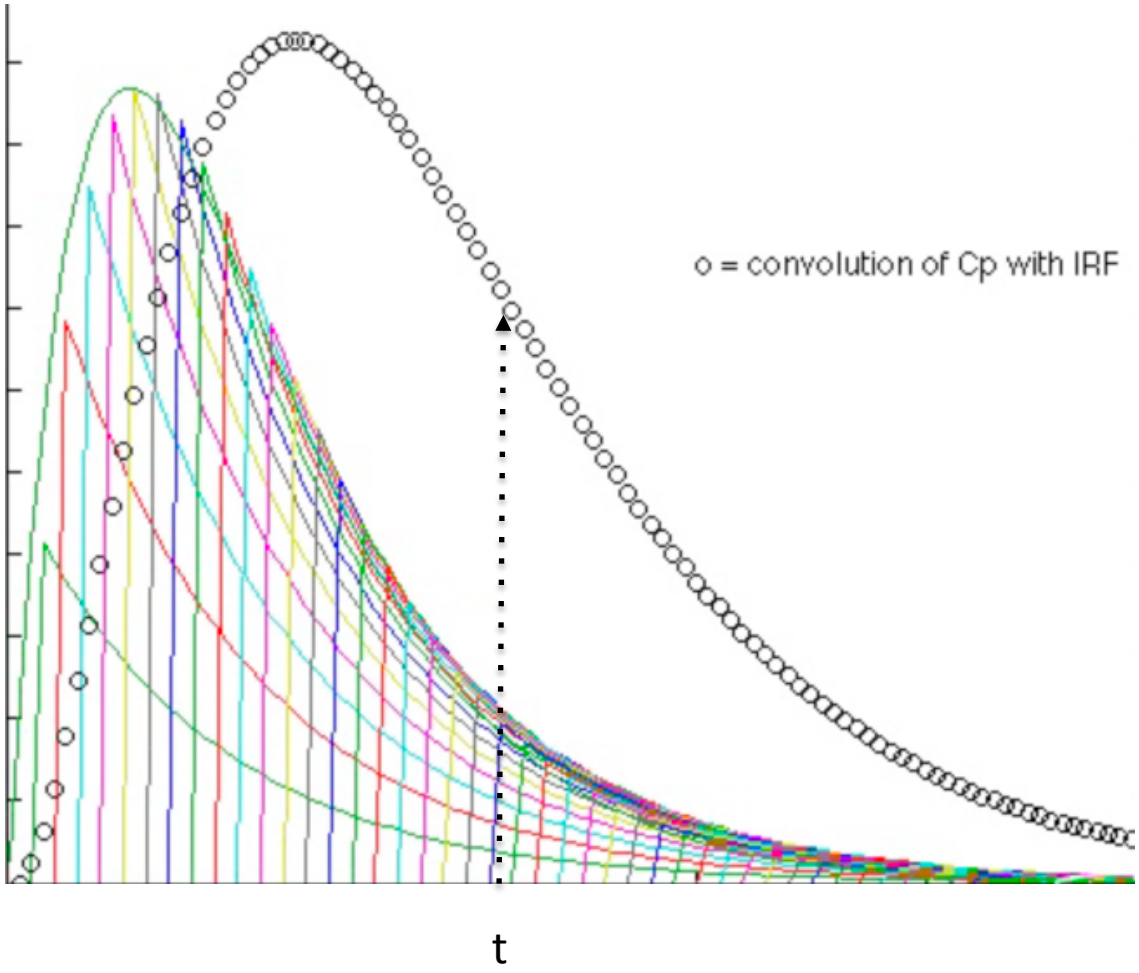
Think of it as a sequence of small impulses

Application: Convolution

√ Background: CLAIM: such systems are characterized by response to a “unit impulse”

Application: Convolution

How do we represent this as a mathematical function of time?



RESPONSE IS APPROXIMATELY

$$\sum_{j=1}^{N} \Delta t \times Cp(t_j) \times h(t - t_j)$$

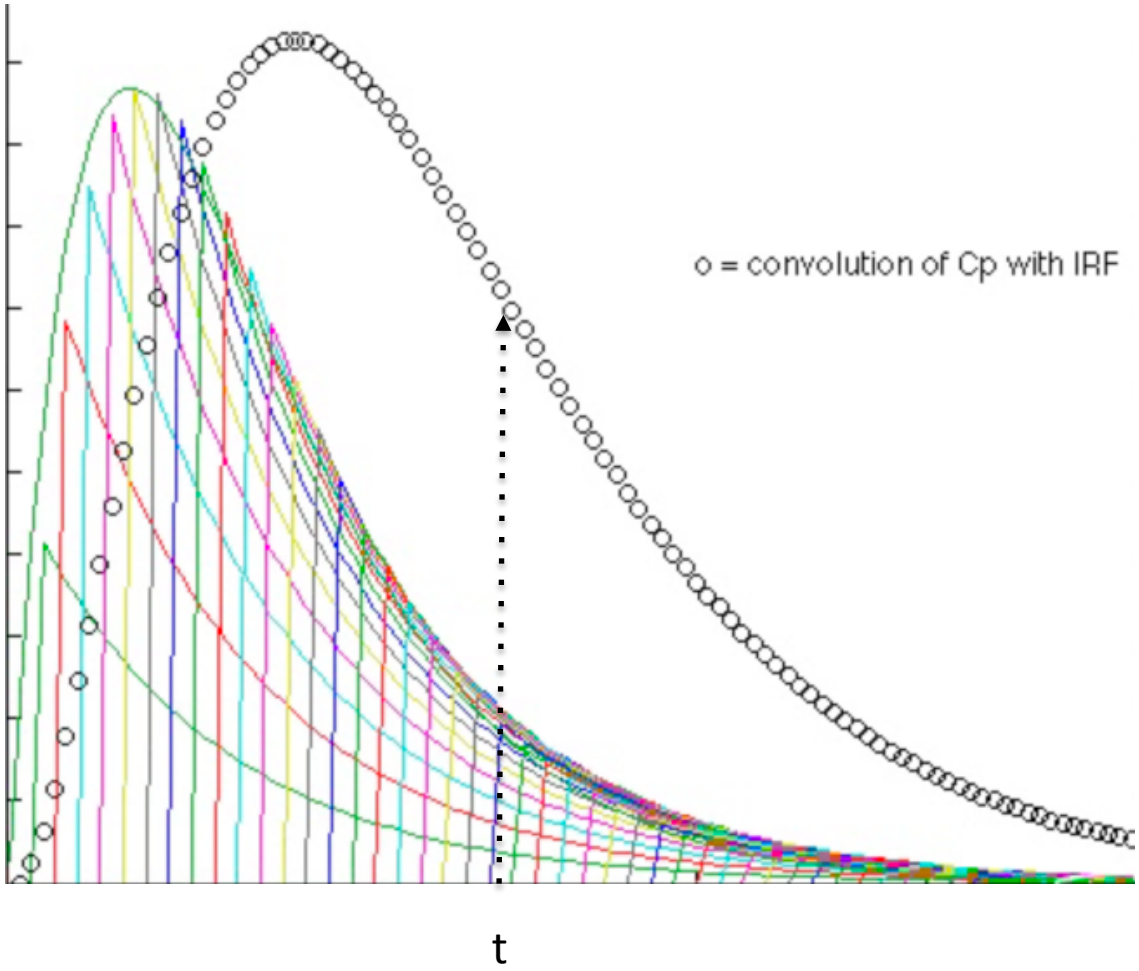
where

$t_N = t$

$t_1 = 0$

Application: Convolution

How do we represent this as a mathematical function of time?



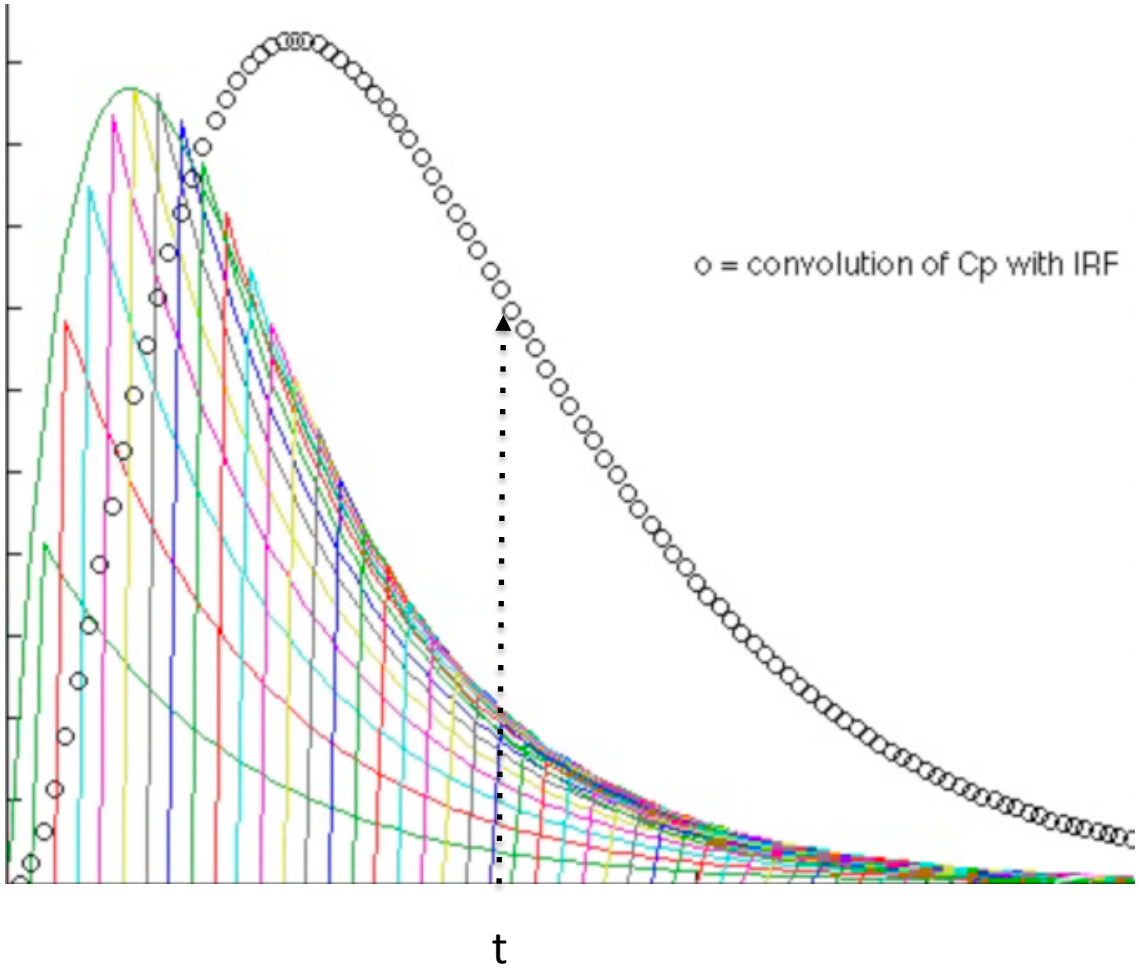
RESPONSE IS APPROXIMATELY

$$\sum_{j=1}^{N} \Delta t \times Cp(t_j) \times h(t - t_j)$$

DELAY

Application: Convolution

How do we represent this as a mathematical function of time?



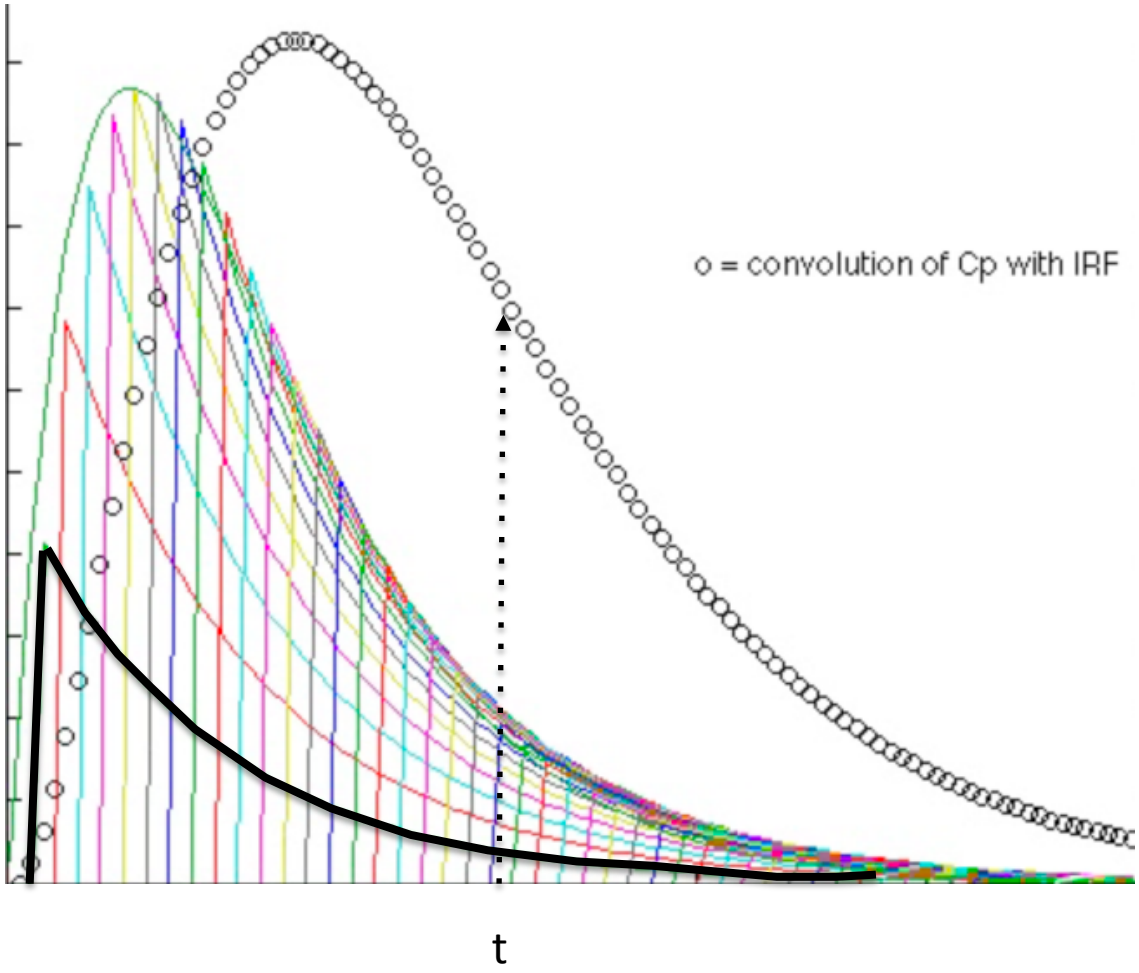
RESPONSE IS APPROXIMATELY

$$\sum_{j=1}^{N} \Delta t \times Cp(t_j) \times h(t - t_j)$$

SCALING OF AREA

Application: Convolution

How do we represent this as a mathematical function of time?



EXAMPLE

$$j = 1$$

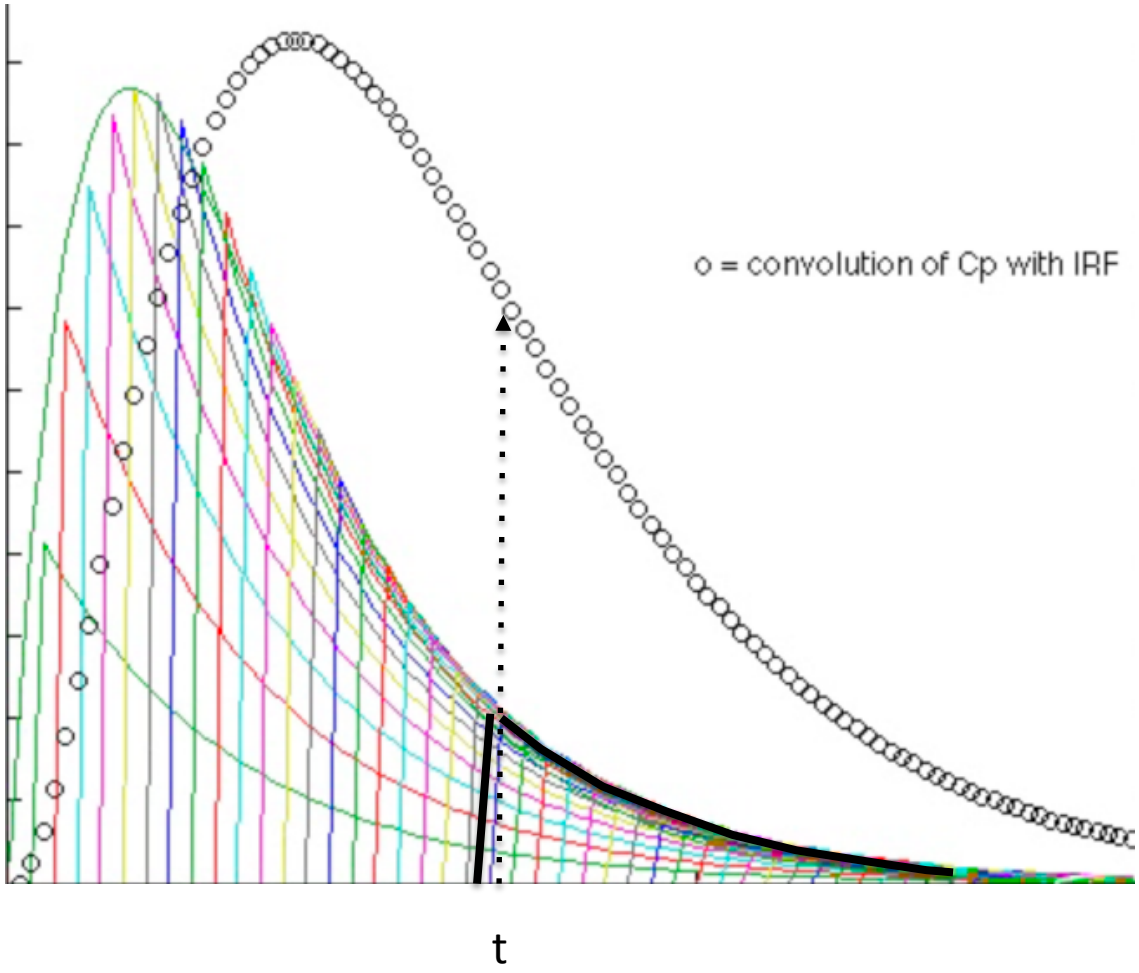
$$t_1 = 0$$

$$\Delta t \times Cp(0) \times h(t - 0)$$

$$= \Delta t \times Cp(0) \times h(t)$$

Application: Convolution

How do we represent this as a mathematical function of time?



EXAMPLE

$$j = N$$

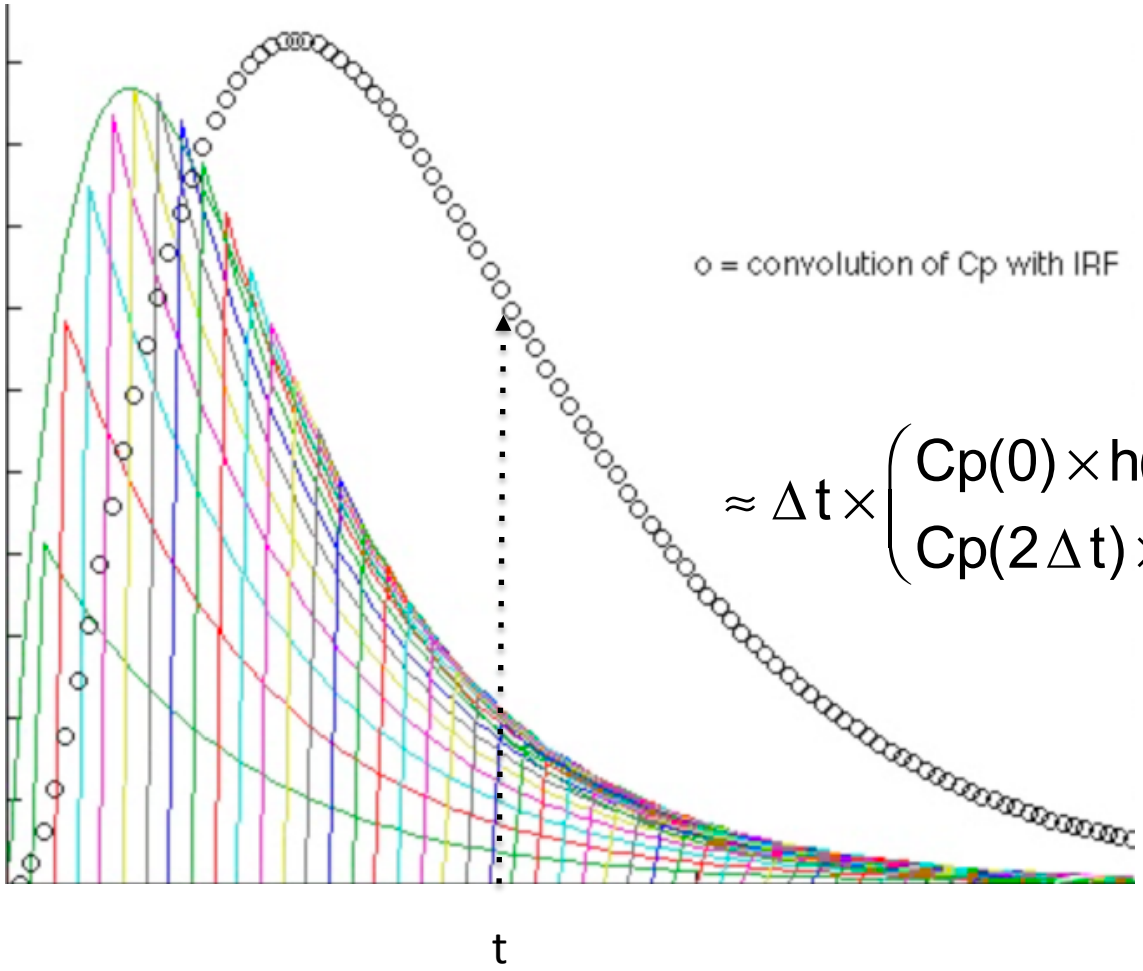
$$t_N = t$$

$$\Delta t \times Cp(t) \times h(t - t)$$

$$= \Delta t \times Cp(t) \times h(0)$$

Application: Convolution

How do we represent this as a mathematical function of time?



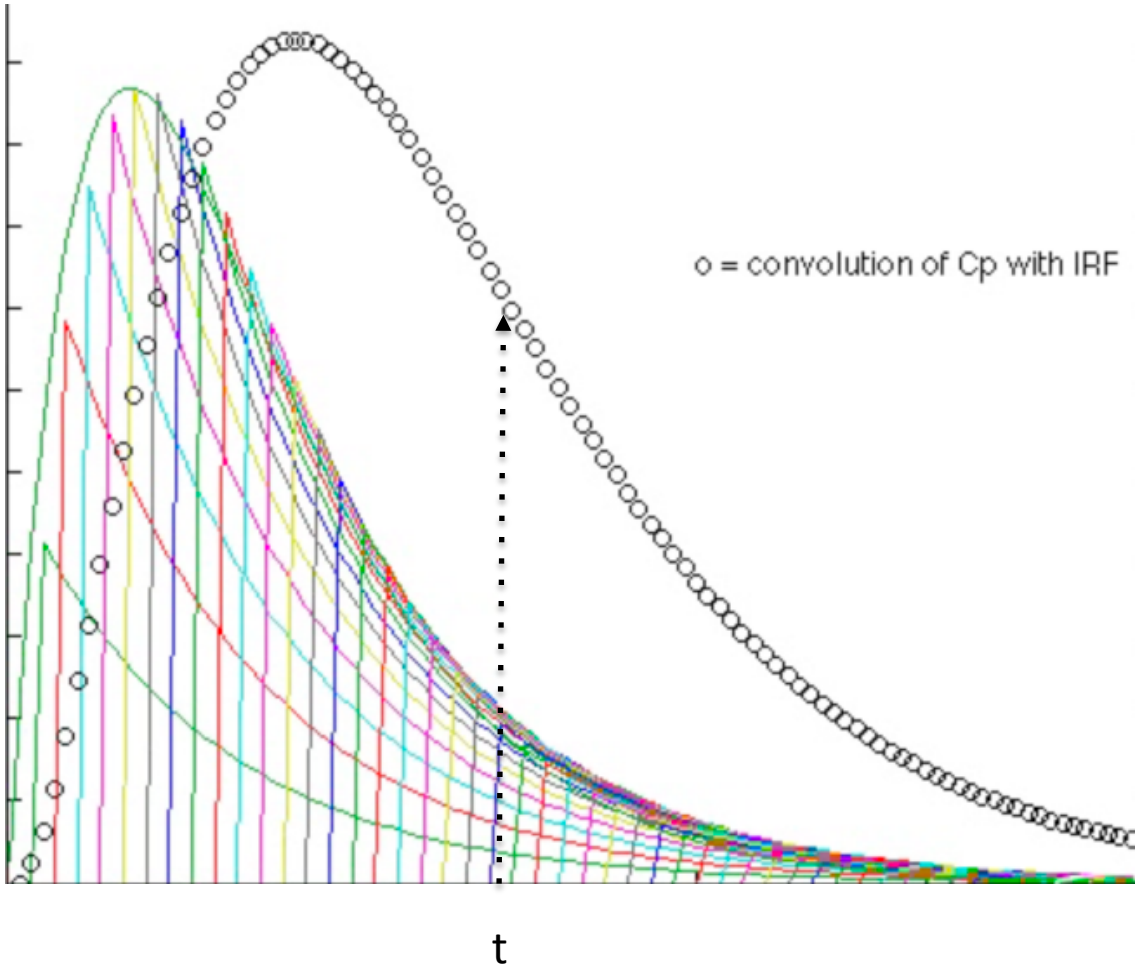
RESPONSE IS APPROXIMATELY

$$\sum_{j=1}^{N} \Delta t \times Cp(t_j) \times h(t - t_j)$$

$$\approx \Delta t \times \left(\begin{array}{l} Cp(0) \times h(t) + Cp(\Delta t) \times h(t - \Delta t) + \cdots \\ Cp(2\Delta t) \times h(t - 2\Delta t) + \cdots + Cp(t) \times h(0) \end{array} \right)$$

Application: Convolution

How do we represent this as a mathematical function of time?



Limit as $\Delta t \downarrow 0$

$$\sum_{j=1}^{N} \Delta t \times Cp(t_j) \times h(t - t_j)$$

$$\approx \int_0^t Cp(\tau) h(t - \tau) d\tau$$

"Convolution Integral"

Sometimes written as:

$$Cp(t) \otimes h(t)$$

More Compartments

- In general, if there are n compartments, IRF = linear combination of n exponentials:

$$h(t) = A_1 e^{\alpha_1 t} + \cdots + A_n e^{\alpha_n t}$$

- The α's are called the "eigenvalues" of the system
- The α's and A's are functions of the rate constants
- For n = 1, reversible model, $\alpha = -k_2$

More Compartments

- In general, if there are n compartments, IRF = linear combination of n exponentials:

$$h(t) = A_1 e^{\alpha_1 t} + \cdots + A_n e^{\alpha_n t}$$

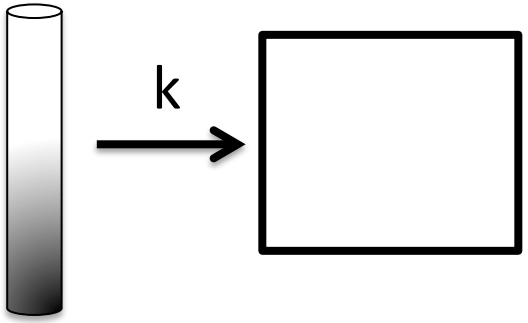
- The α's are called the "eigenvalues" of the system

- For n = 2, reversible: $h(t) = A_1 e^{\alpha_1 t} + A_2 e^{\alpha_2 t}$

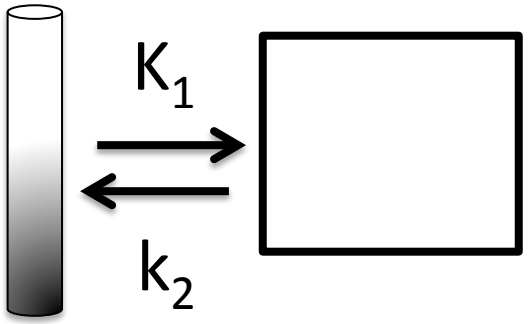
$$C_T(t) = C_p(t) \otimes h(t)$$

$$\alpha_{\pm} = -\frac{1}{2}\left\{k_2 + k_3 + k_4 \pm \sqrt{\left(k_2 + k_3 + k_4\right)^2 - 4k_2k_4}\right\}$$

Impulse Response Functions:

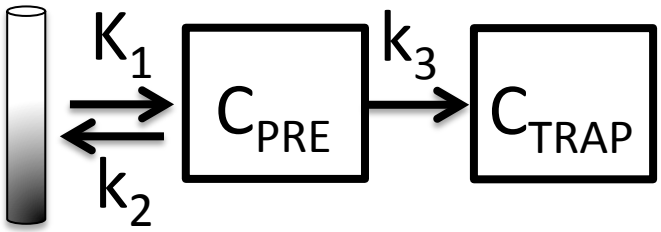
Irreversible 1 TC	Equation	IRF
	$\frac{dC}{dt} = kC_P(t)$	k

Reversible 1 TC

	$\frac{dC}{dt} = K_1C_P(t) - k_2C(t)$	$K_1e^{-k_2t}$

Impulse Response Functions:

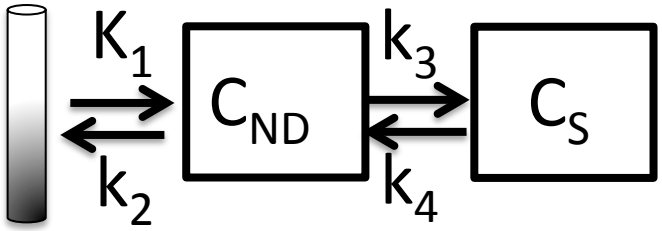
Irreversible 2 TC



IRF

$$\frac{K_1}{k_2+k_3}\left[k_3+k_2\exp\left\{-\left(k_2+k_3\right)\right\}t\right]$$

Reversible 2 TC



$$A_1e^{\alpha_1 t}+A_2e^{\alpha_2 t}$$

$$\alpha_{\pm}=-\frac{1}{2}\left\{k_2+k_3+k_4\pm\sqrt{\left(k_2+k_3+k_4\right)^2-4k_2k_4}\right\}$$

$$A_{\pm}=\pm K_1\frac{k_3+k_4-\alpha_{\pm}}{\alpha_{-}-\alpha_{+}}$$

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!

METHOD 2:

- DO SOME MATH, MODEL DATA AS CONVOLUTION INTEGRAL, LET THE COMPUTER DO THE REST.

APPENDIX: N COMPARTMENT IRF

$$\frac{d}{dt}\mathbf{C}(t) = \mathbf{M}\mathbf{C}(t) + \mathbf{b}(t)$$

$$= \mathbf{P}\Lambda\mathbf{P}^{-1}\mathbf{C}(t) + C_P(t)\mathbf{b}$$

$$\mathbf{Y} = \mathbf{P}^{-1}\mathbf{C}$$

$$\frac{d}{dt}\mathbf{Y} = \Lambda\mathbf{Y}(t) + C_P(t)\mathbf{P}^{-1}\mathbf{b}$$

$$\mathbf{Y}(t) = \exp(\Lambda t) \otimes C_P(t)\mathbf{P}^{-1}\mathbf{b}$$

$$\mathbf{C}(t) = \mathbf{P}\exp(\Lambda t) \otimes C_P(t)\mathbf{P}^{-1}\mathbf{b}$$

$$C_T(t) = \mathbf{1}_N^T\mathbf{C}(t)$$

C is a vector of compartments
M is a matrix of rate constants
b is a vector of rate constants from the input to the system

P diagonalizes **M**
Λ is a diagonal matrix of eigenvalues

Y is a tranformation of variables

The **Y** equations are uncoupled; Each Y_j is a convolution of an exponential of the jth eigenvalue with the jth row of $\mathbf{P}^{-1}\mathbf{b}$

$\exp(\mathbf{\Lambda t})\otimes C_P(t)$ is a diagonal matrix with the convolutions on the main diagonal

$\mathbf{1}_N$ is a vector of ones, representing summation. The observed scalar time activity curve $C_T(t)$ is the sum of the compartments in vector **C**(t).