A Four-Compartment Model for Ca^{2+} Dynamics: An Interpretation of Ca^{2+} Decay after Repetitive Firing of Intact Nerve Terminals

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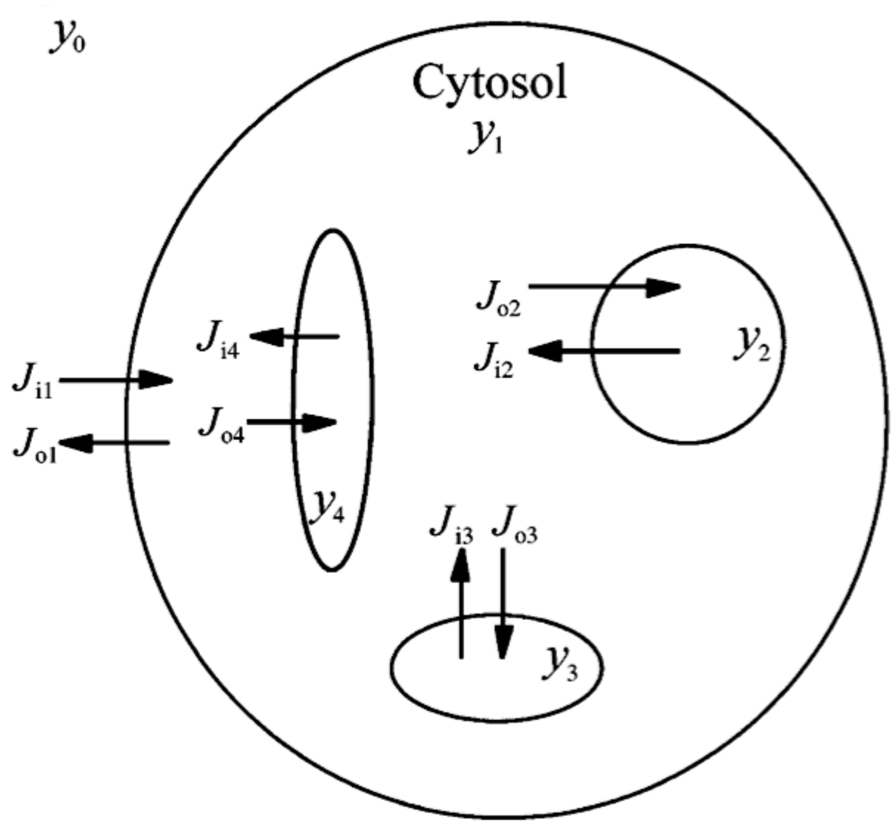
Overview

- System definition
- Model derivation
- Experimental manipulation
- Model predictions
- Applications
- Results

Ca^{2+} Ion Transfer

- Modeled after bullfrog sympathetic ganglia
- Cell behavior predicted in presynaptic nerve terminals
- Decay follows linear sum of multiple exponential functions due to various ion channels within the cytosol
- System equilibrium perturbed by stimulation of variable duration and frequency

Model Schematic



The system will resolve for up to four membrane-bound Ca^{2+} stores involved in monotonic decay

Assumptions

Expanded Friel compartment model, 1995

- Rapid inter-compartmental [Ca^{2+}] equilibration
- Uniform [Ca^{2+}] throughout individual compartment y_i
- Extracellular [Ca^{2+}], y_0, remains constant

Notation

- y_i = [Ca^{2+}] of i^{th} region, $i = \{0,1,\ldots 4\}$
- J_{ij} = influx into 1 from j, $j = \{2,3,4\}$
- J_{oj} = efflux out of 1 into j
- $J_{xj} = F(y_j, y_1; k_{xj})$, $x = \{i,o\}$

Differential Mass Balance

$$\begin{aligned} dy_1/dt &= (J_{i1} + J_{i2} + J_{i3} + J_{i4})/v_1 \\ &\quad - (J_{o1} + J_{o2} + J_{o3} + J_{o4})/v_1, \\ dy_2/dt &= -(J_{i2} - J_{o2})/v_2, \\ dy_3/dt &= -(J_{i3} - J_{o3})/v_3, \\ dy_4/dt &= -(J_{i4} - J_{o4})/v_4, \end{aligned}$$

y_1 is the only experimentally observable variable, typically done using fura-2 or bis-fura-2 fluorimetry

Internal Flux

$$J_{o1} = k_{o1} y_1,$$
$$J_{i1} = k_{i1}(y_0 - y_1),$$
$$J_{o2} = k_{o2} y_1,$$
$$J_{i2} = k_{i2}(y_2 - y_1),$$
$$J_{o3} = k_{o3} y_1,$$
$$J_{i3} = k_{i3}(y_3 - y_1),$$
$$J_{o4} = k_{o4} y_1,$$
$$J_{i4} = k_{i4}(y_4 - y_1),$$

$$K_{ij} = k_{ij}/v_j = (k_{ij}/v_1)/(v_j/v_1)$$
$$K_{oj} = k_{oj}/v_j = (k_{oj}/v_1)/(v_j/v_1)$$

$$\gamma K_{i2} = k_{i2}/v_1, \quad \beta K_{i3} = k_{i3}/v_1$$
$$\delta K_{i4} = k_{i4}/v_1$$

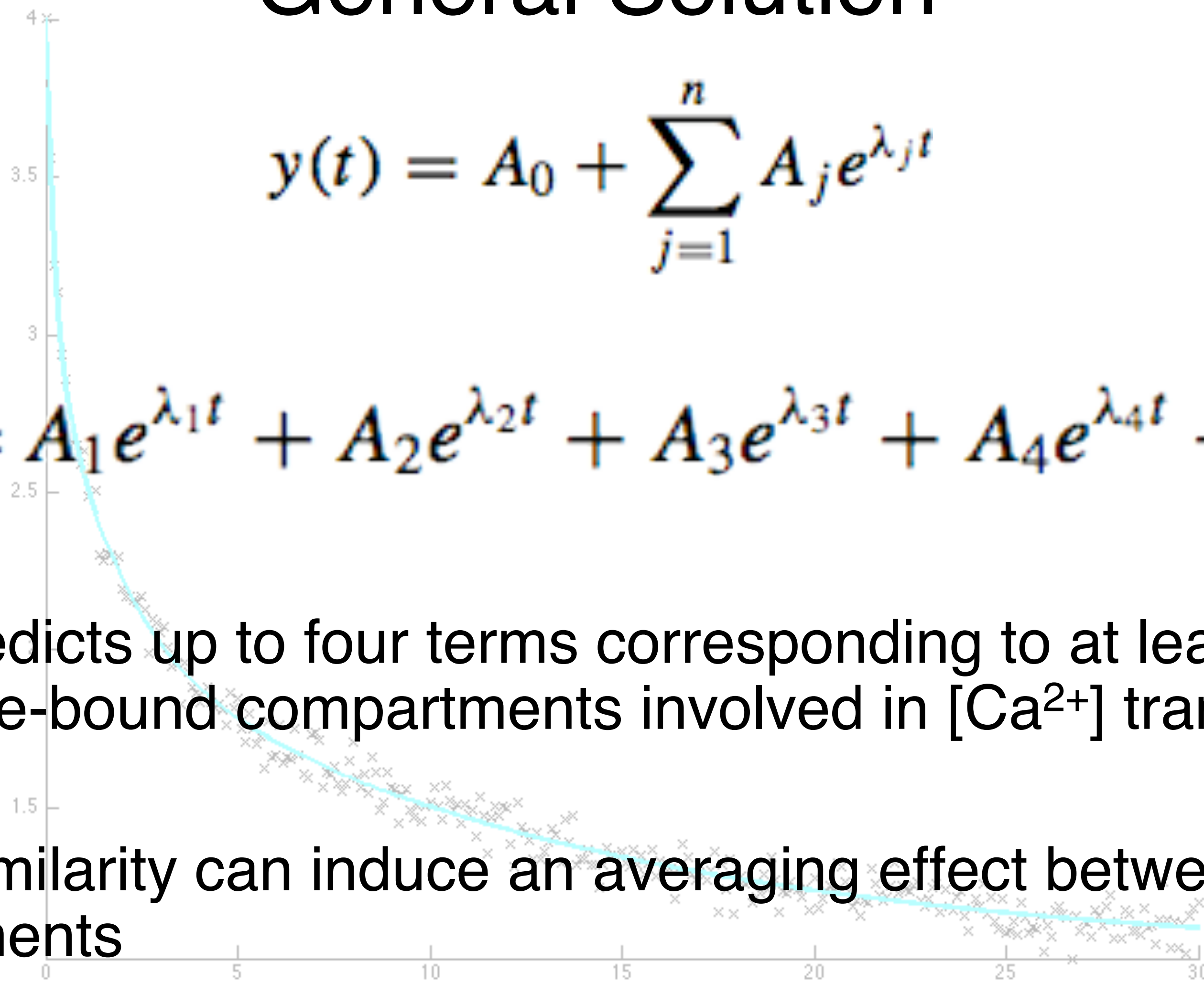
$$\gamma K_{o2} = k_{o2}/v_1, \quad \beta K_{o3} = k_{o3}/v_1$$
$$\delta K_{o4} = k_{o4}/v_1.$$

Linear relation between [Ca^{2+}] and transfer rate fit with permeability coefficient k_{xj}

General Solution

$$y(t) = A_0 + \sum_{j=1}^{n} A_j e^{\lambda_j t}$$

$$y_1 = A_1 e^{\lambda_1 t} + A_2 e^{\lambda_2 t} + A_3 e^{\lambda_3 t} + A_4 e^{\lambda_4 t} + A_0$$



Model predicts up to four terms corresponding to at least four membrane-bound compartments involved in [Ca^{2+}] transfer

Spatial similarity can induce an averaging effect between two compartments

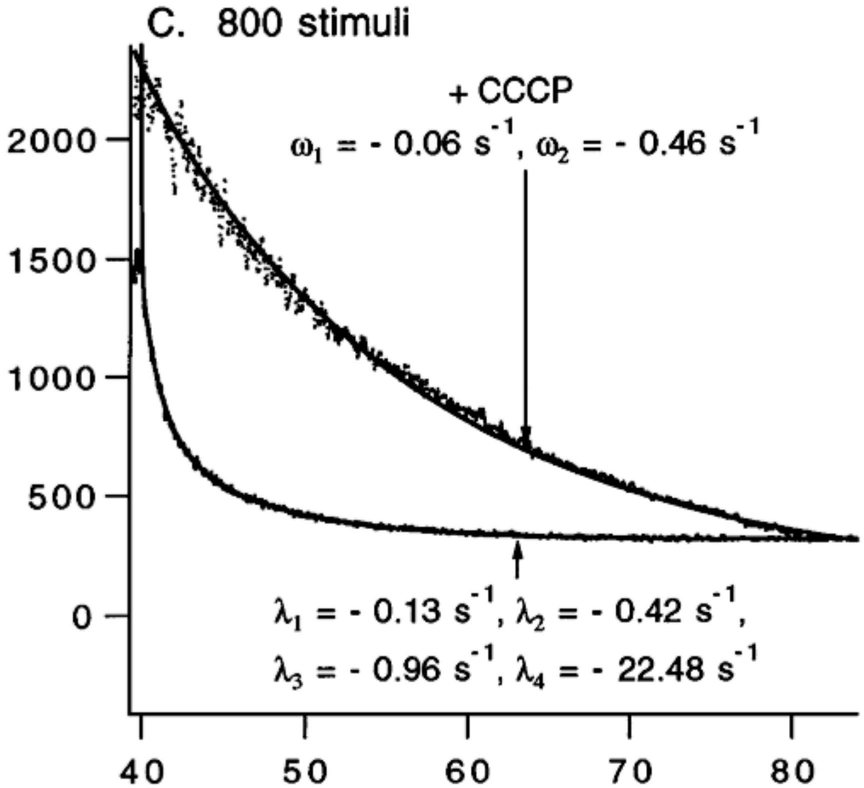
Four Compartment System

$$D_t \begin{bmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \end{bmatrix} = M_4 \begin{bmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \end{bmatrix} + \begin{bmatrix} K_{i1} y_0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

$$M_4 = \begin{bmatrix} -[K_{o1} + K_{i1} + \gamma(K_{o2} + K_{i2}) + \beta(K_{o3} + K_{i3}) + \delta(K_{o4} + K_{i4})] & \gamma K_{i2} & \beta K_{i3} & \delta K_{i4} \\ (K_{o2} + K_{i2}) & -K_{i2} & 0 & 0 \\ (K_{o3} + K_{i3}) & 0 & -K_{i3} & 0 \\ (K_{o4} + K_{i4}) & 0 & 0 & -K_{i4} \end{bmatrix}$$

$$y_1 = A_1 e^{\lambda_1 t} + A_2 e^{\lambda_2 t} + A_3 e^{\lambda_3 t} + A_4 e^{\lambda_4 t} + A_0$$

Balance Variable Reduction



$$D_t \begin{bmatrix} y_1 \\ y_2 \\ y_3 \end{bmatrix} = M_3 \begin{bmatrix} y_1 \\ y_2 \\ y_3 \end{bmatrix} + \begin{bmatrix} K_{i1} y_0 \\ 0 \\ 0 \end{bmatrix}$$

$$D_t \begin{bmatrix} y_1 \\ y_2 \end{bmatrix} = M_2 \begin{bmatrix} y_1 \\ y_2 \end{bmatrix} + \begin{bmatrix} K_{i1} y_0 \\ 0 \end{bmatrix}$$

If the influx permeability coefficient $k_{ij} \rightarrow 0$, then the j^{th} term is removed from overall differential balance

Overall Rate

$$M_4 = \begin{bmatrix} -[K_{o1} + K_{i1} + \gamma(K_{o2} + K_{i2}) + \beta(K_{o3} + K_{i3}) + \delta(K_{o4} + K_{i4})] & \gamma K_{i2} & \beta K_{i3} & \delta K_{i4} \\ (K_{o2} + K_{i2}) & -K_{i2} & 0 & 0 \\ (K_{o3} + K_{i3}) & 0 & -K_{i3} & 0 \\ (K_{o4} + K_{i4}) & 0 & 0 & -K_{i4} \end{bmatrix}$$

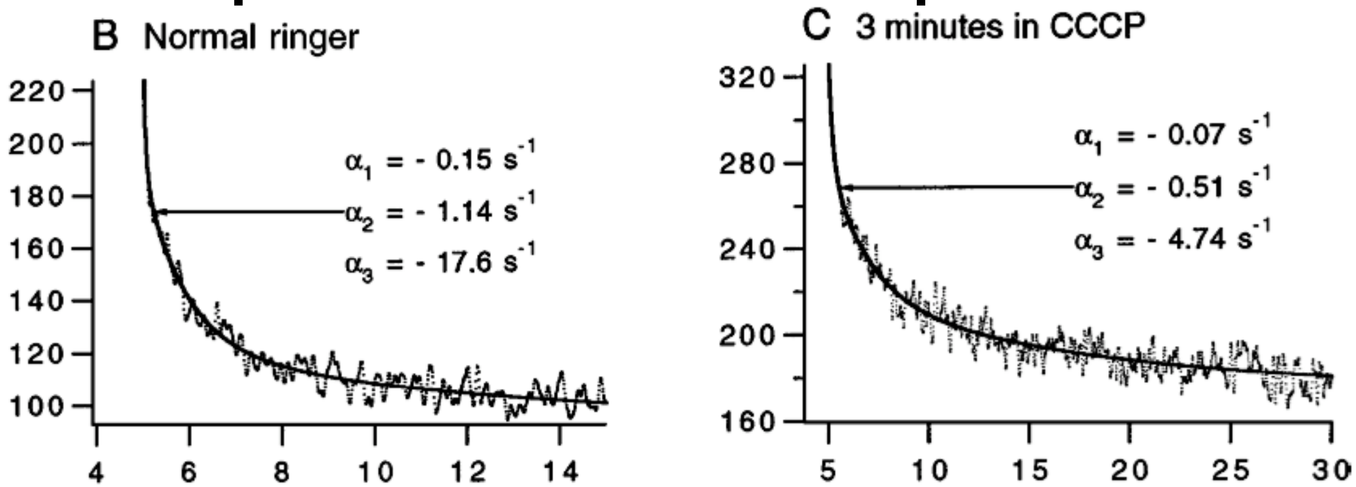
$$OR(M_4) = \mathrm{tr}(M_4) = \lambda_1 + \lambda_2 + \lambda_3 + \lambda_4$$

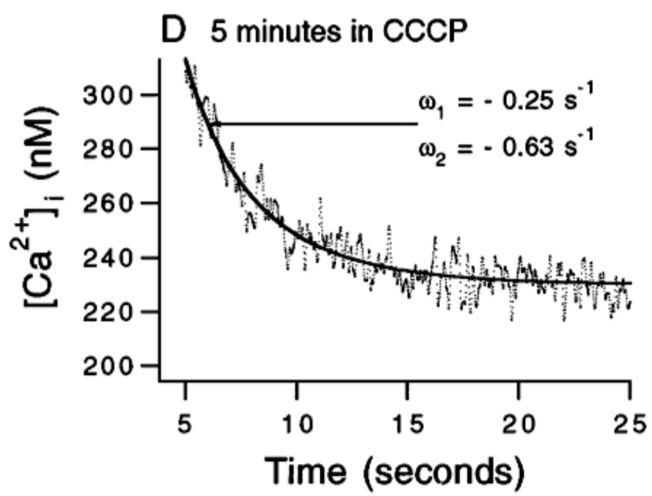
$$\Delta OR = OR(M_{\mathrm{exp}}) - OR(M_{\mathrm{cntrl}})$$

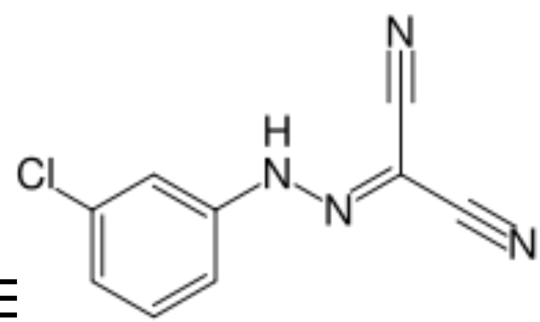
Summation of differential system Eigenvalues is used to quantify the overall decay rate, OR

The change in OR, ΔOR, is independent of initial experimental conditions

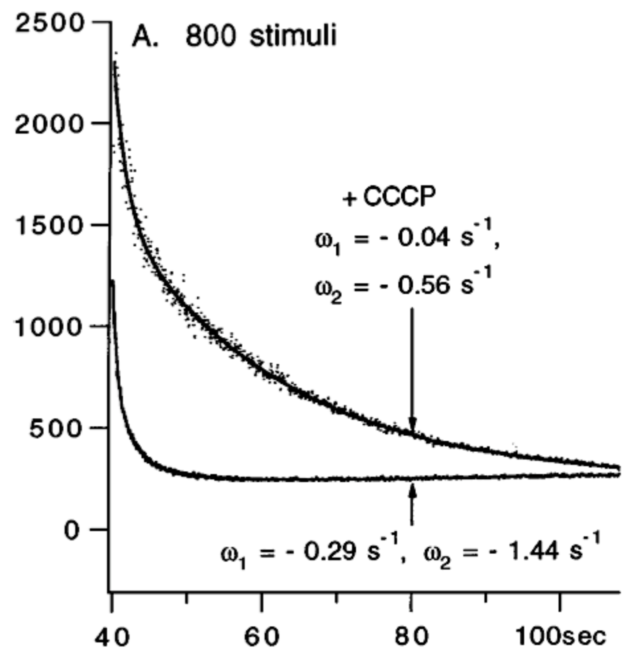
Experimental Manipulation

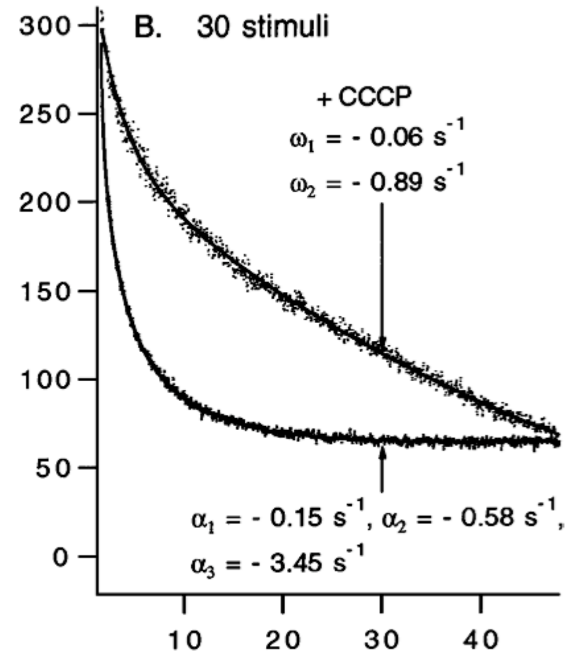




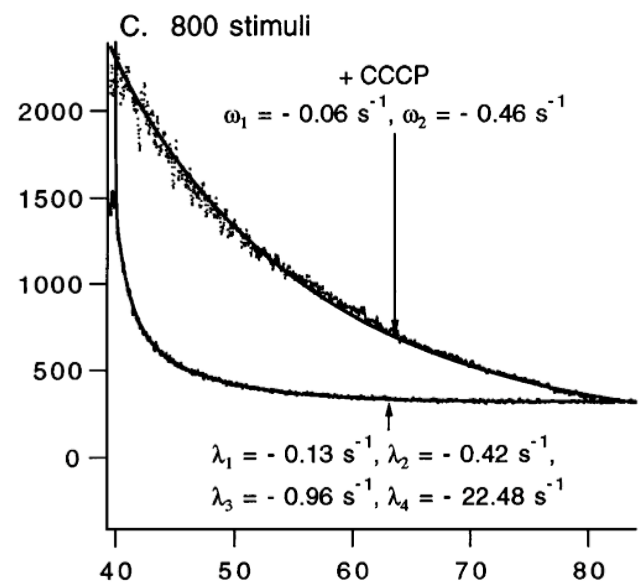
CCCP ≡ 

Carbonyl cyanide m-chlorophenylhydrazone

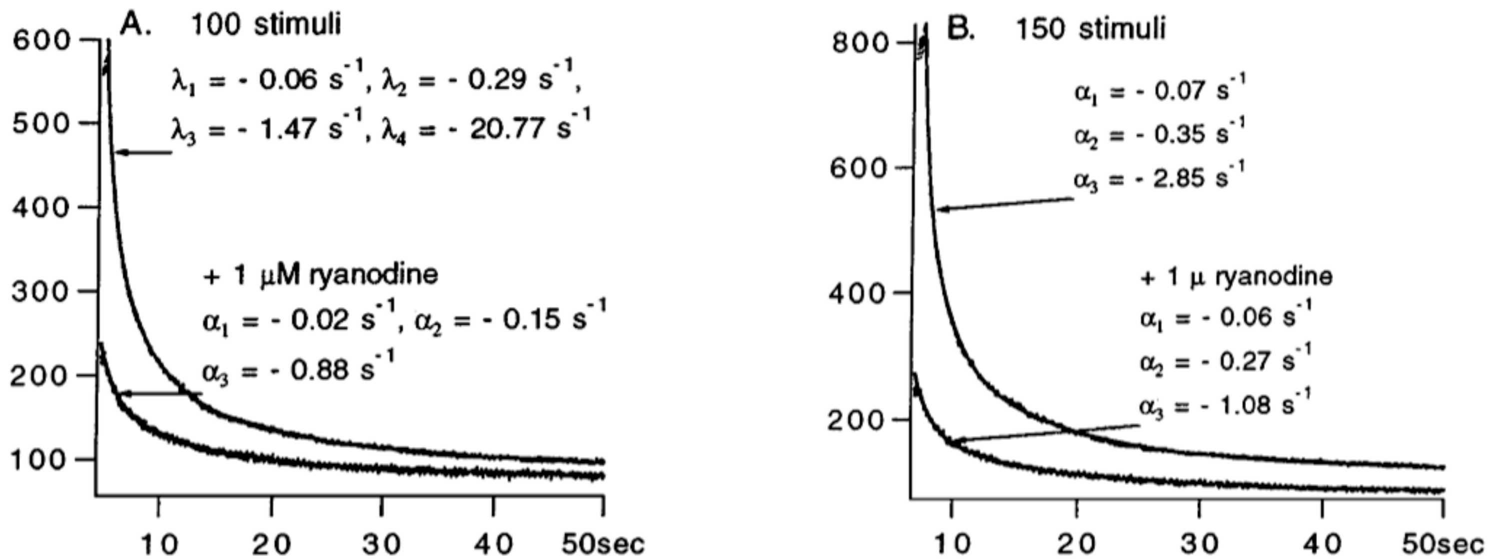


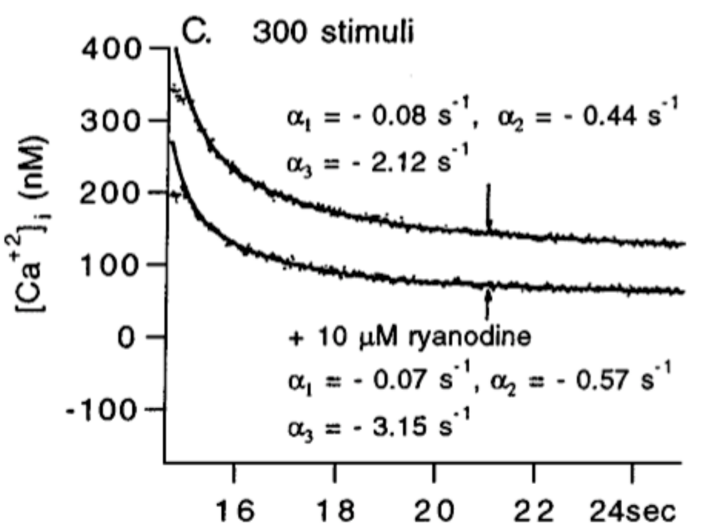


- A. $k_{i2} \neq 0$
- B. $k_{i3} \rightarrow 0$
- C. k_{i3}, $k_{i4} \rightarrow 0$



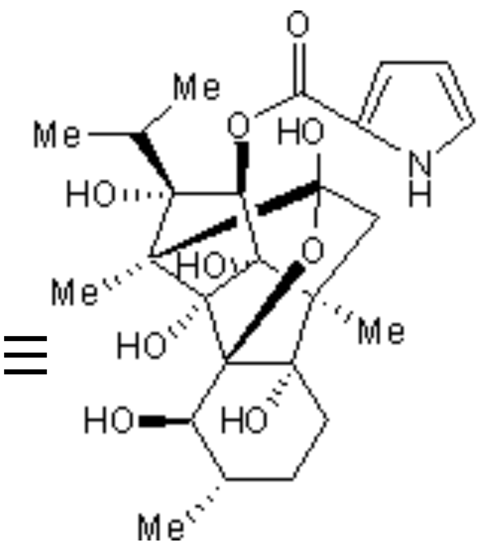
Assumed mitochondrial activity affects membrane permeability





$k_{i3} \neq 0$

Ryanodine ≡



Various inhibitory compounds affect Ca^{2+} uptake and release via different mechanisms and targets

Model Predictions

- The minimal amount of compartments involved in Ca^{2+} decay correspond to the number of linear terms of the overall balance solution, N
- N-1 of these compartments must be membrane-bound and intercellular
- $N = F(k_{ij})$; $N \neq F(k_{oj})$
- $OR = G(k_{ij}, k_{oj})$
- $\tau = \lambda^{-1}$ does not affect compartment buffer time
- j^{th} term, where $j = \{2,3,4\}$, most likely accounts for the average of several compartments

CCCP Effect

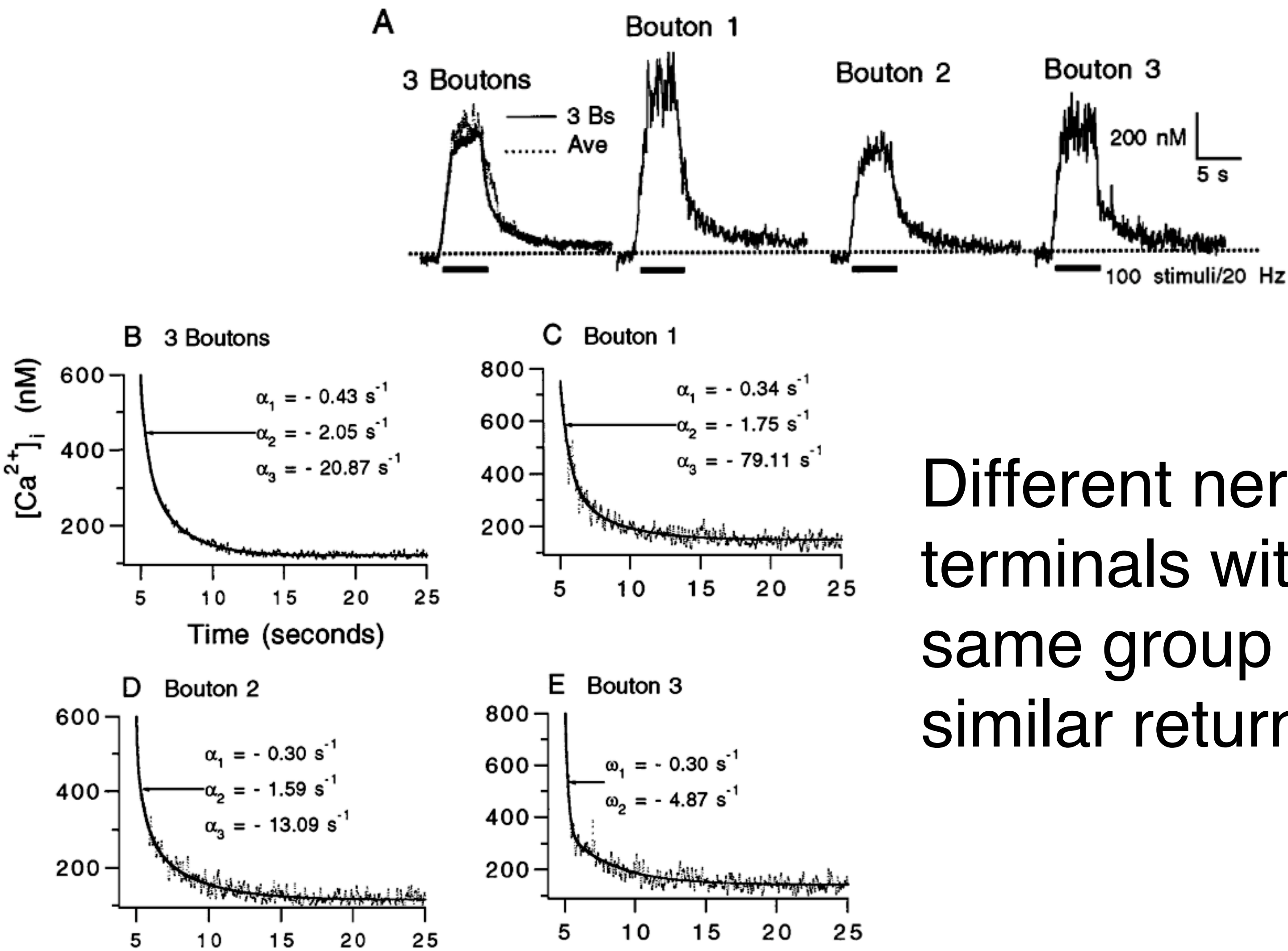
- Loss of linear term from fitting solution observed in most cases, $k_{i3} \rightarrow 0$
- At least one Ca^{2+} compartment is inhibited by drug exposure
- CCCP blockade of mitochondrial Ca^{2+} uptake by altering membrane potential could abolish Ca^{2+} release

Ryanodine Effect

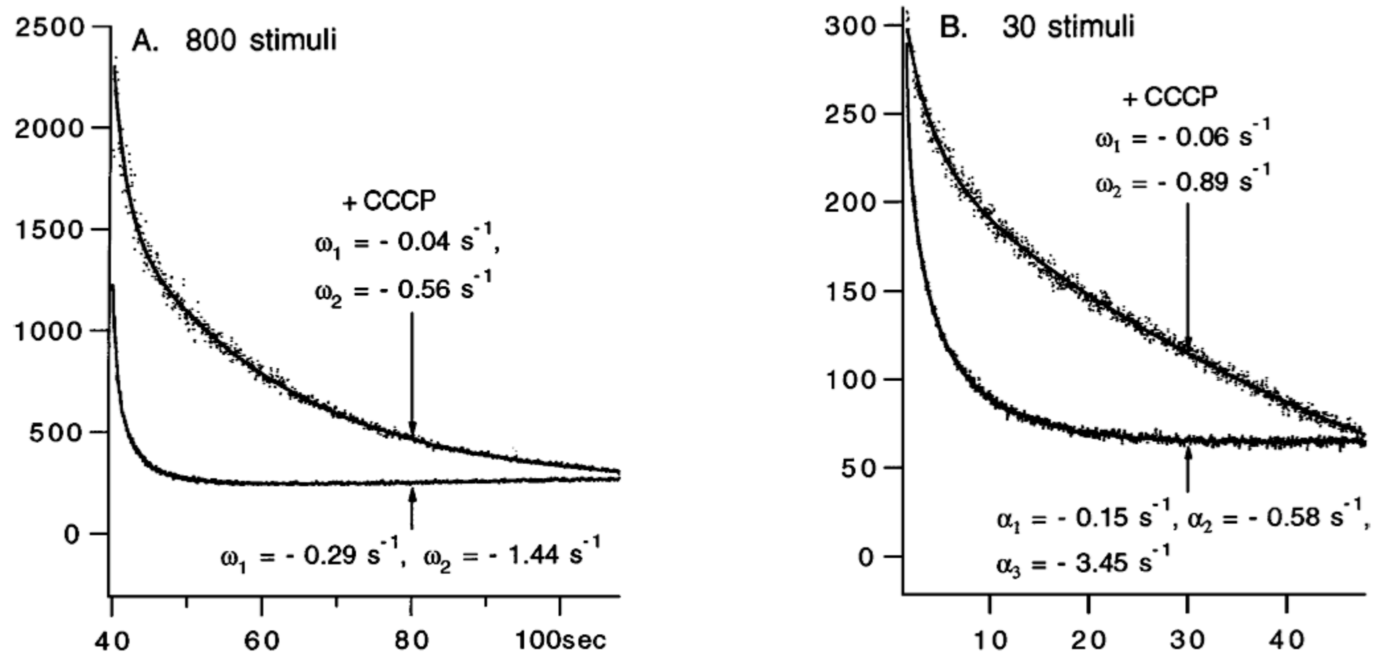
- No loss of linear term from fitting solution observed, $k_{i3} \neq 0$
- $|OR^{EXP}| < |OR^{IC}|$ suggests that $k_{oj}^{EXP} < k_{oj}^{IC}$

- Model predicts third Ca^{2+} store (insensitive to both CCCP and Ryanodine) due to remaining solution terms

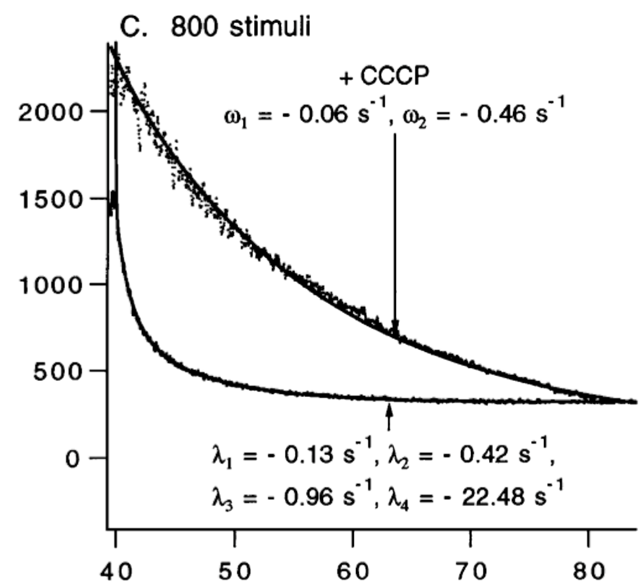
Applications

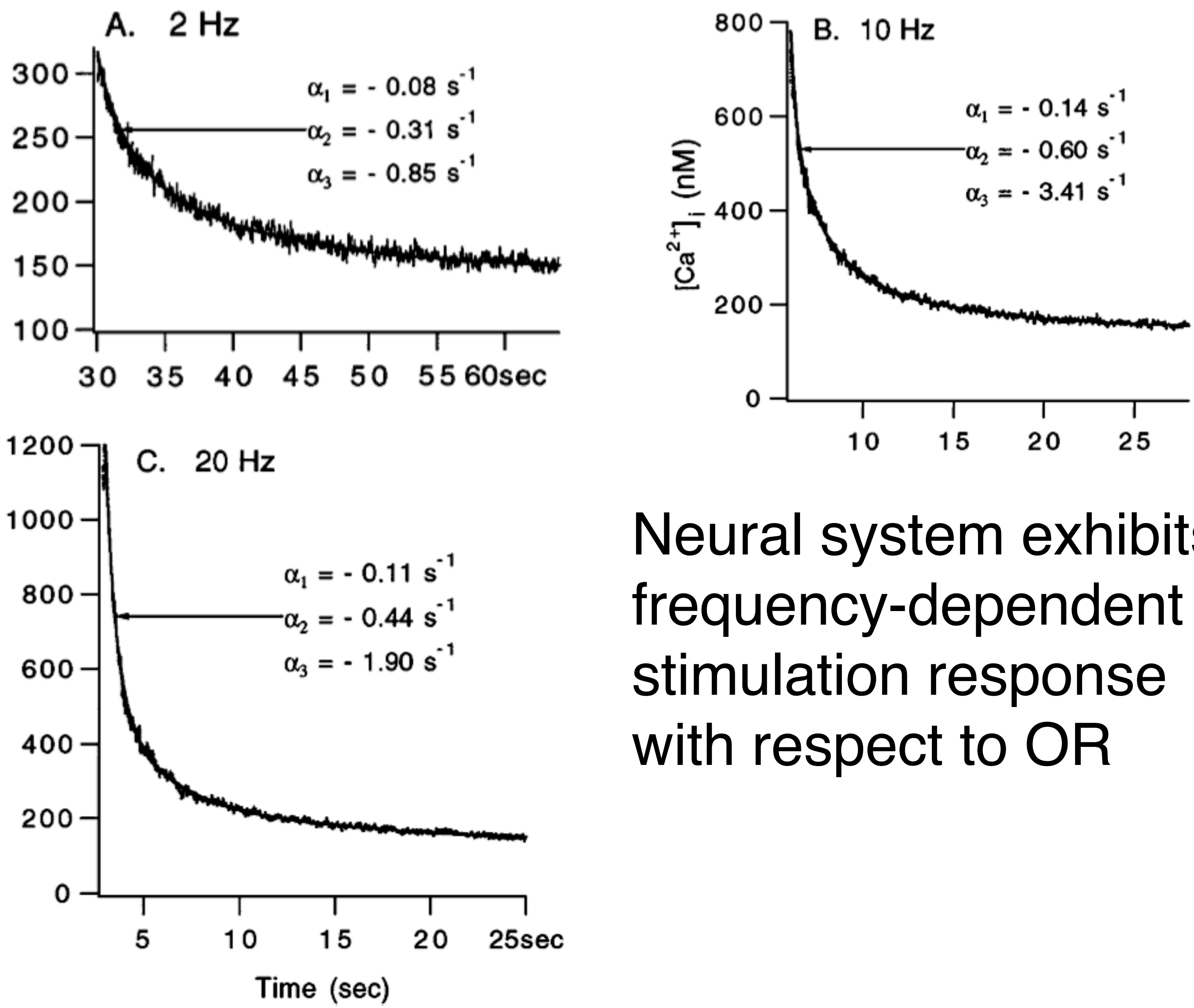


Different nerve terminals within the same group exhibit similar return behavior



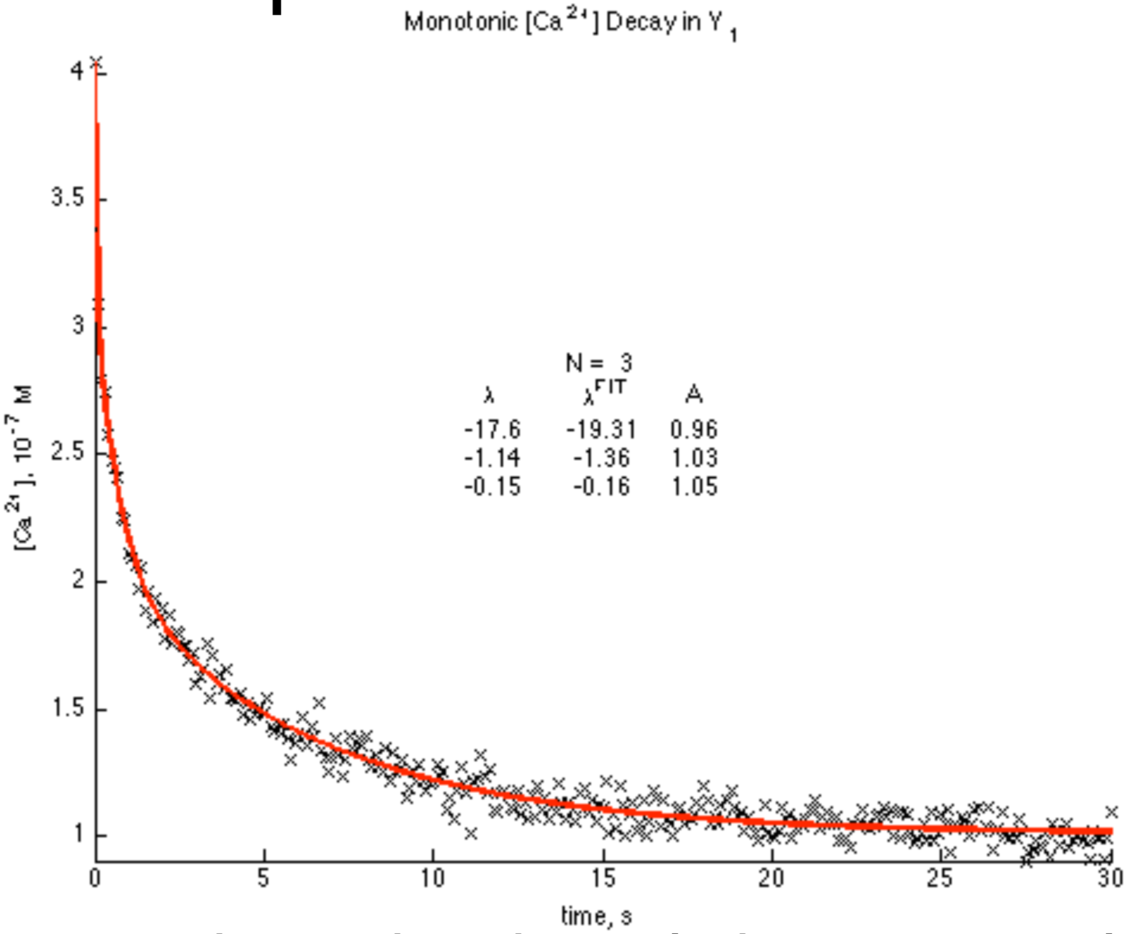
Mitochondrial obstruction by CCCP evokes predicted reduction of at least one balance term



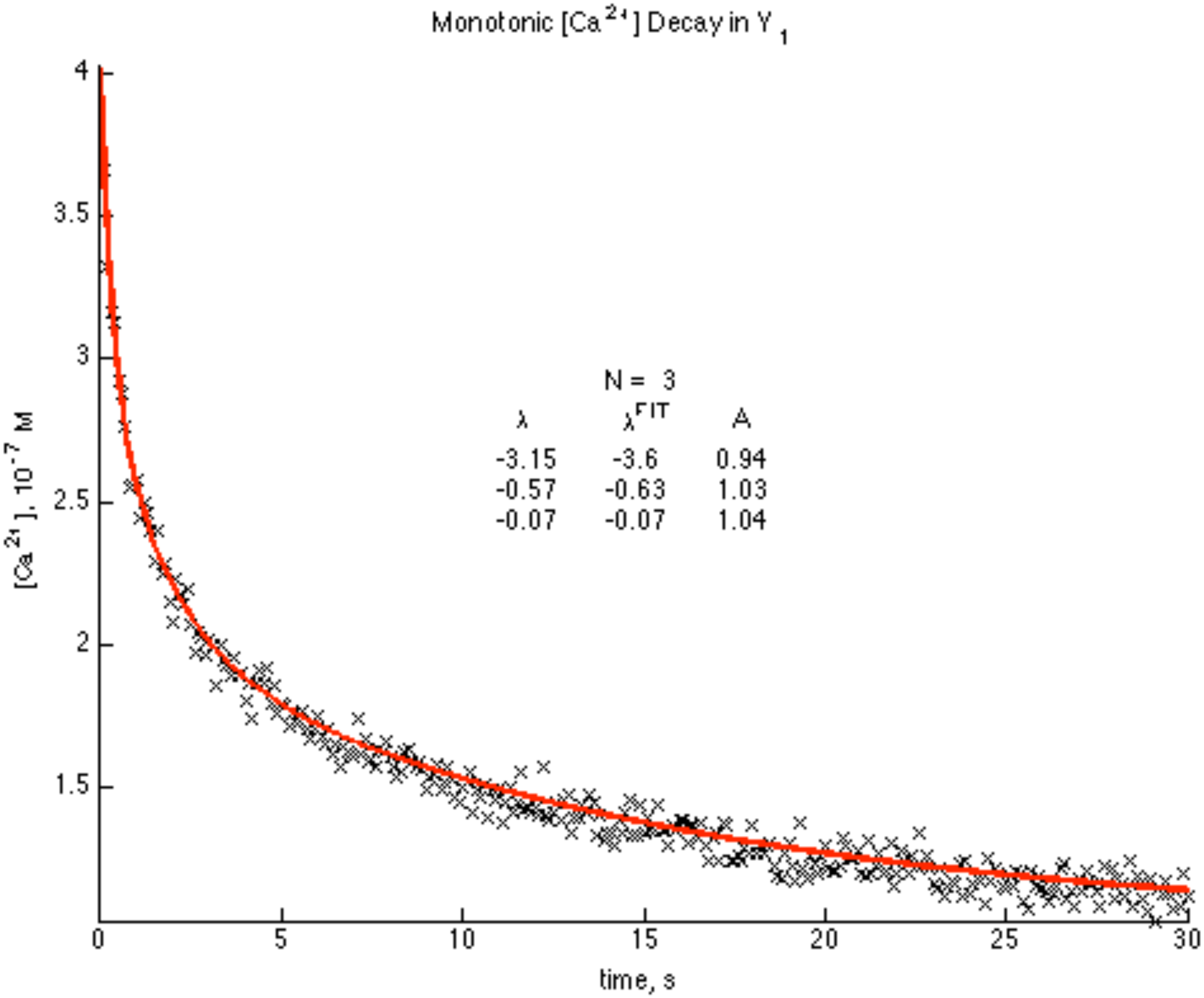


Neural system exhibits a frequency-dependent stimulation response with respect to OR

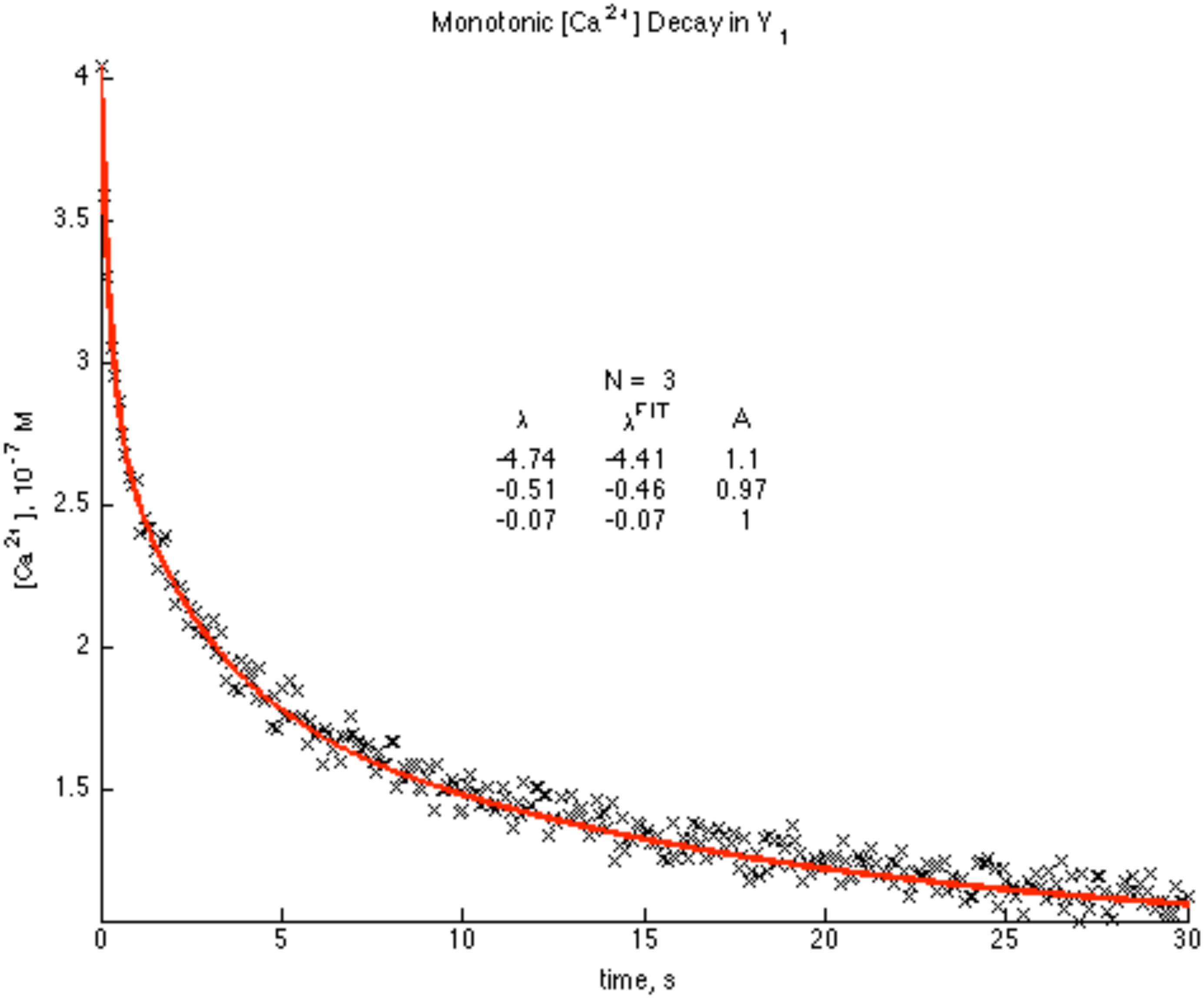
Reproduced Results

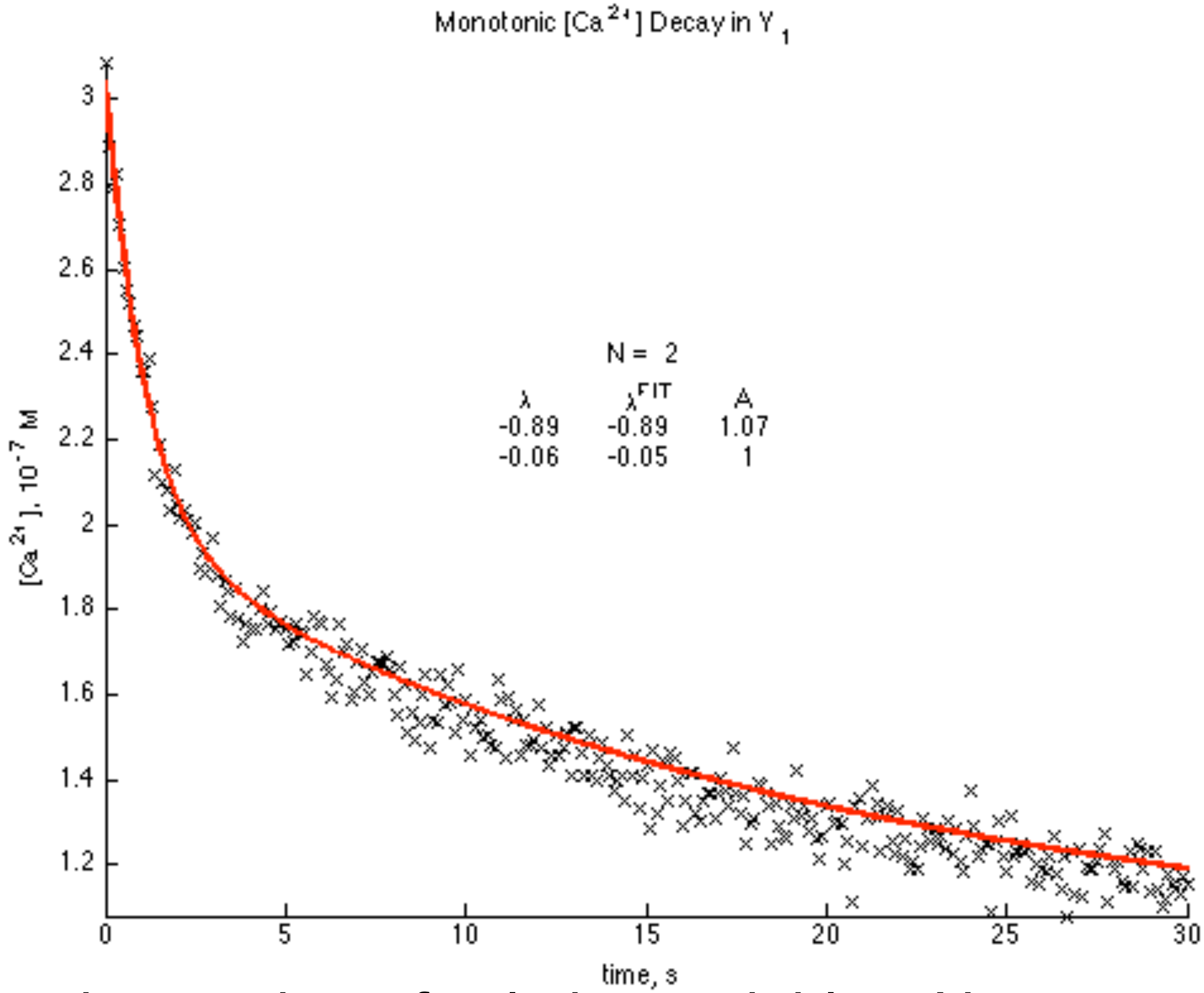


Algorithm can determine the solution to a novel data set, including the number of linear terms involved and all constituent parameters

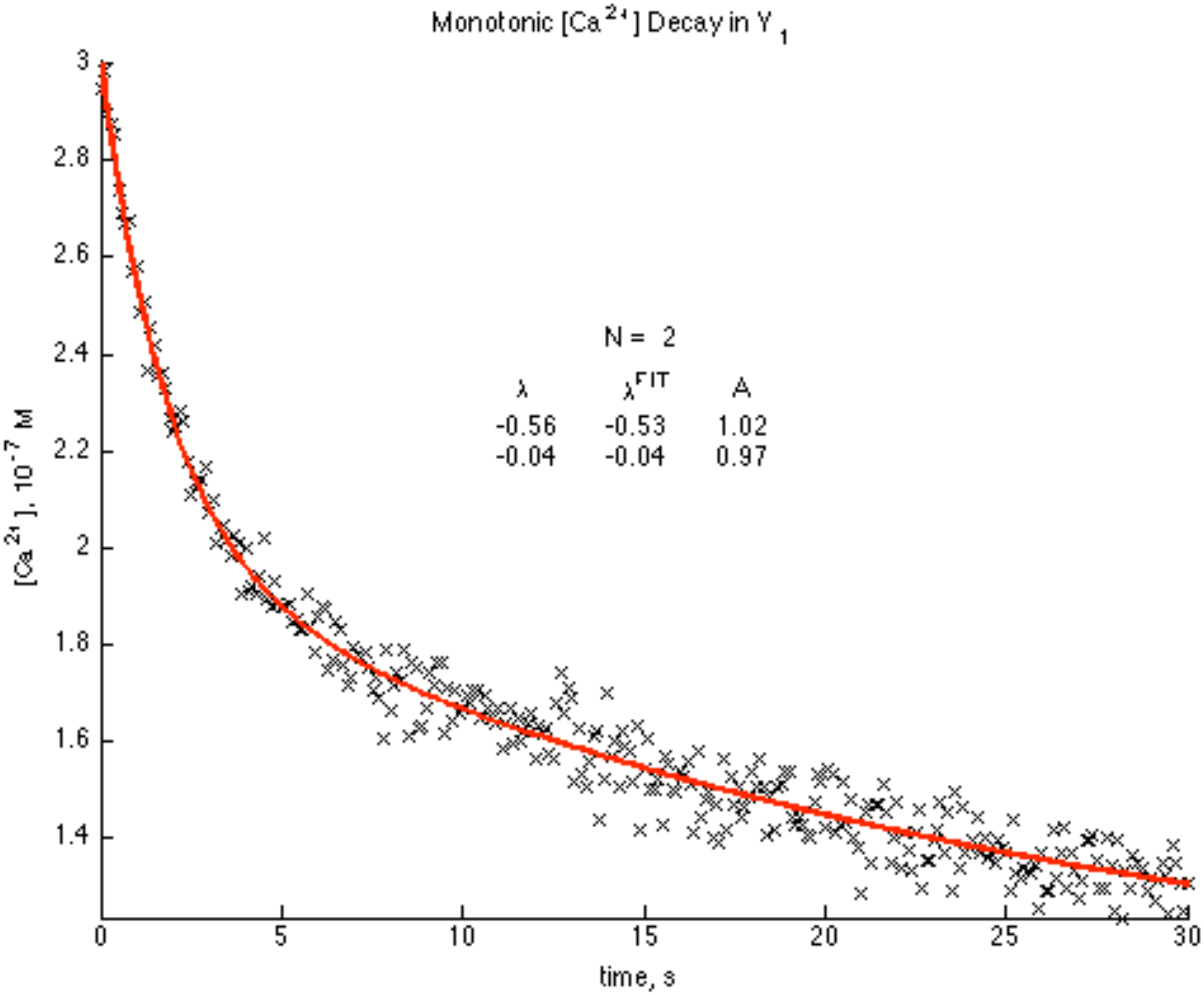


Monotonic [Ca 2+] Decay in Y 1
N = 3
λ
λ^FIT
A
-3.15
-3.6
0.94
-0.57
-0.63
1.03
-0.07
-0.07
1.04
[Ca 2+], 10 -7 M
time, s
4
3.5
3
2.5
2
1.5
0
5
10
15
20
25
30


Monotonic [Ca2+] Decay in Y1
N = 3
λ λFIT A
-4.74 -4.41 1.1
-0.51 -0.46 0.97
-0.07 -0.07 1
[Ca2+], 10-7 M
time, s
0 5 10 15 20 25 30
1.5 2 2.5 3 3.5 4



Reducing the number of solution variables, N, was performed through a least squares fit for N = 4 followed by consolidation of redundant liner terms



Monotonic [Ca2+] Decay in Y1
N = 2
λ λFIT A
-0.56 -0.53 1.02
-0.04 -0.04 0.97
[Ca2+], 10-7 M
time, s
0 5 10 15 20 25 30
3 2.8 2.6 2.4 2.2 2 1.8 1.6 1.4