Dynamical principles of synaptic receptor sharing across spines in a dendritic branch

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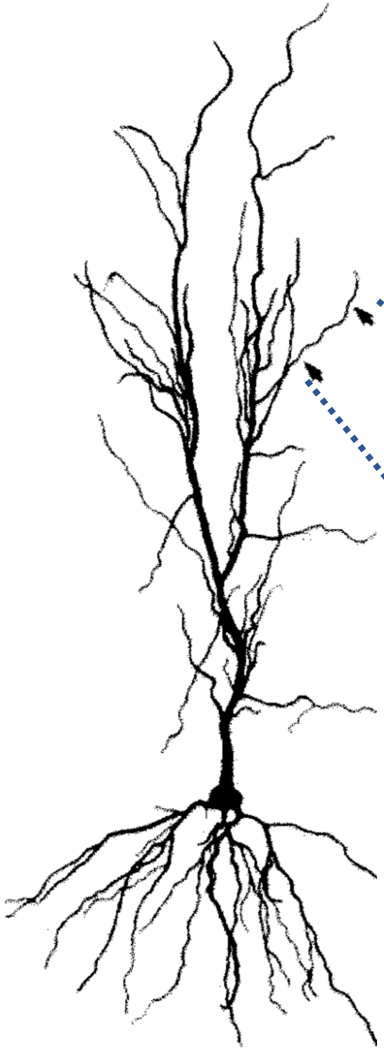
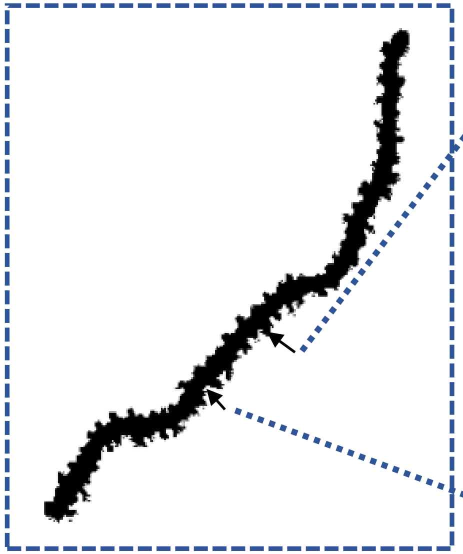
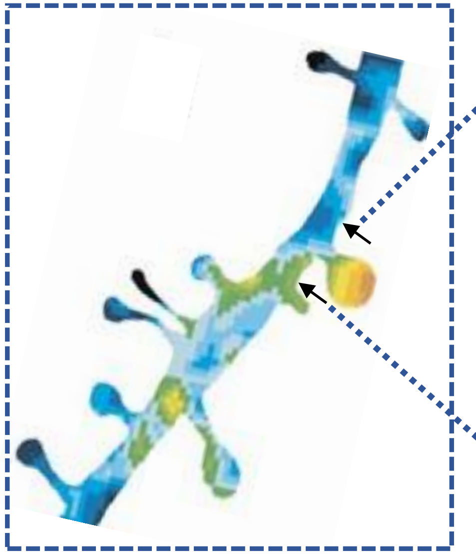
Dendritic spines and Synaptic AMPA receptors

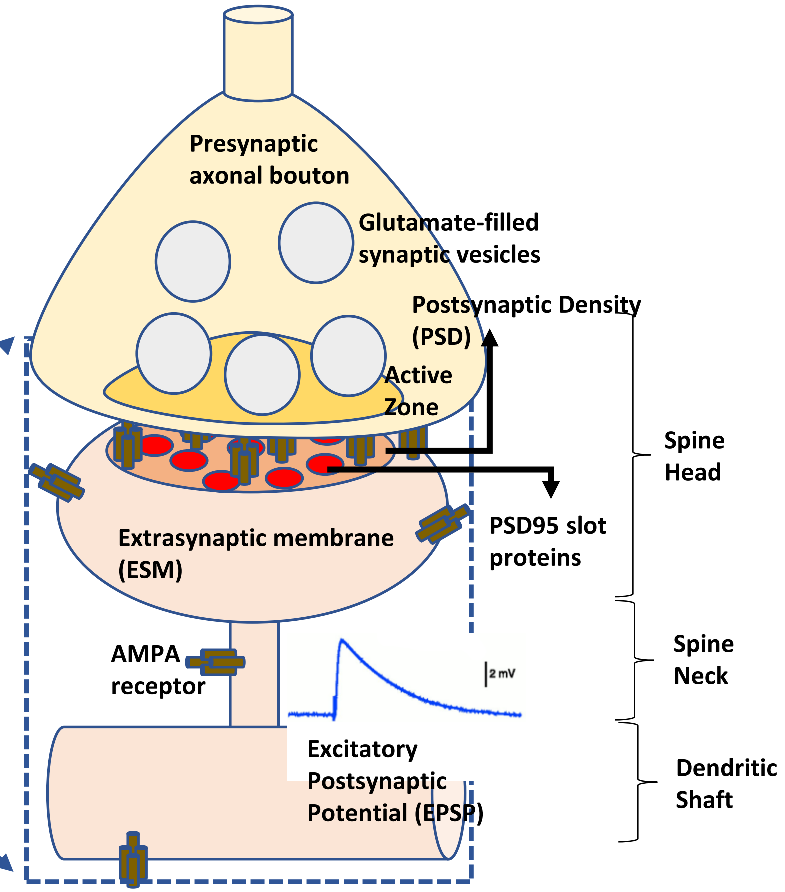




50μm dendritic stretch



10μm dendritic stretch



A single spine

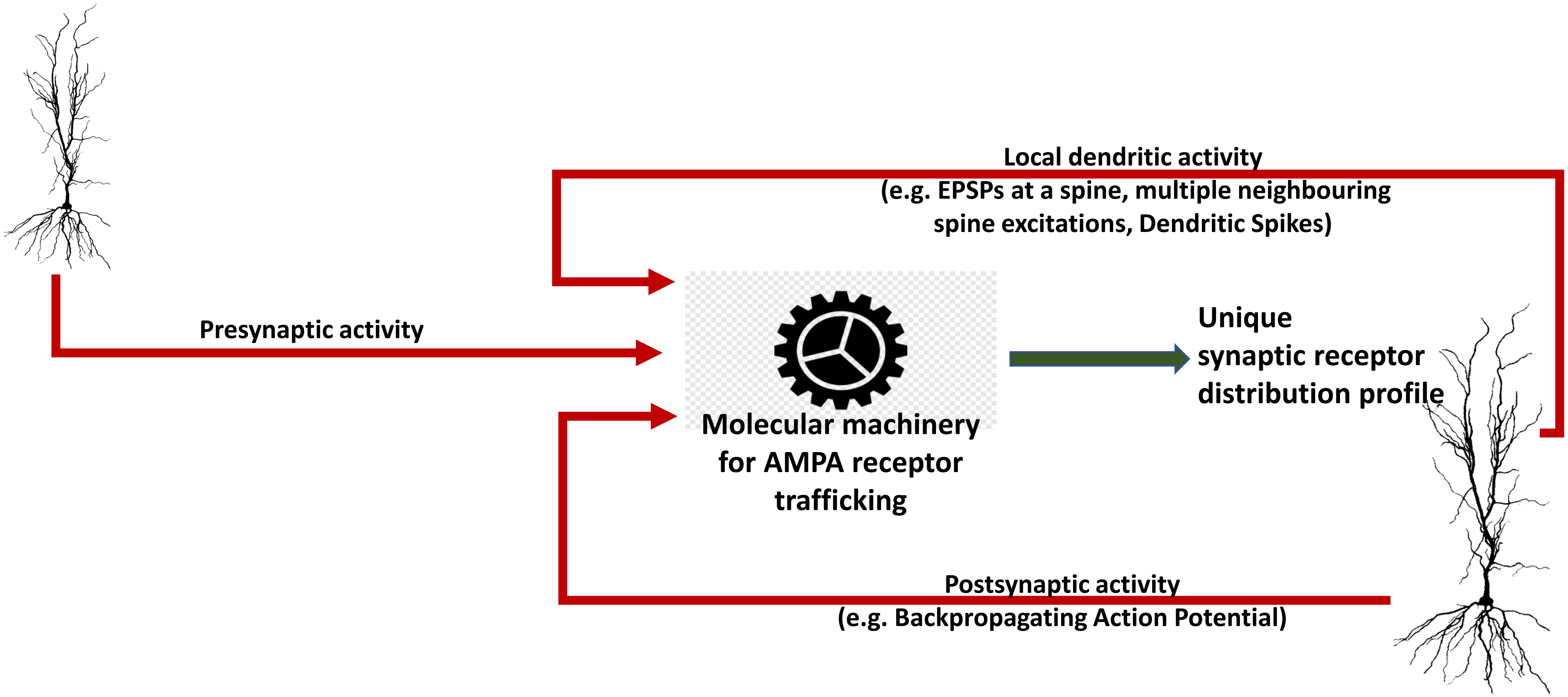
Synaptic AMPA receptors:

Freely-diffusing and PSD95-bound receptors in PSD

How is it controlled at a single spine and distributed amongst spines?

CA3 Pyramidal Neuron

Factors controlling synaptic receptor distribution amongst spines



Approach:

1st : Study the **Machinery**

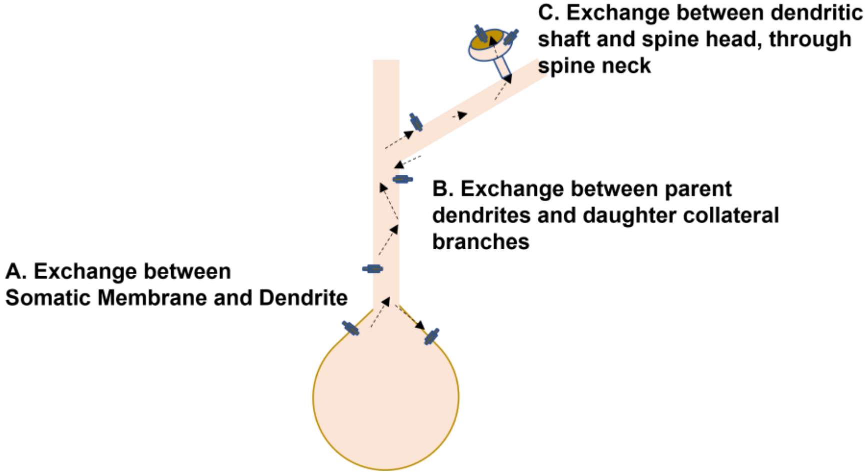
2nd : Study the response of the machinery to **Inputs**

Molecular Machinery for AMPA receptor trafficking: Three Principle Mechanisms

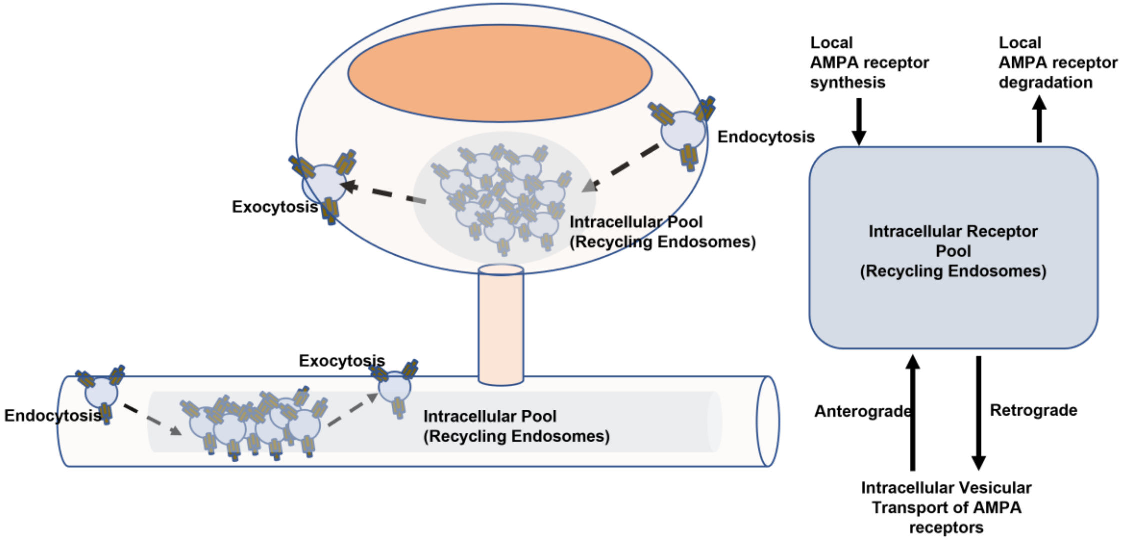
1. Membrane Receptor Diffusion: Lateral 2-D Brownian diffusion

$D_{AMPA} \approx 0.1\mu m^2.s^{-1}$

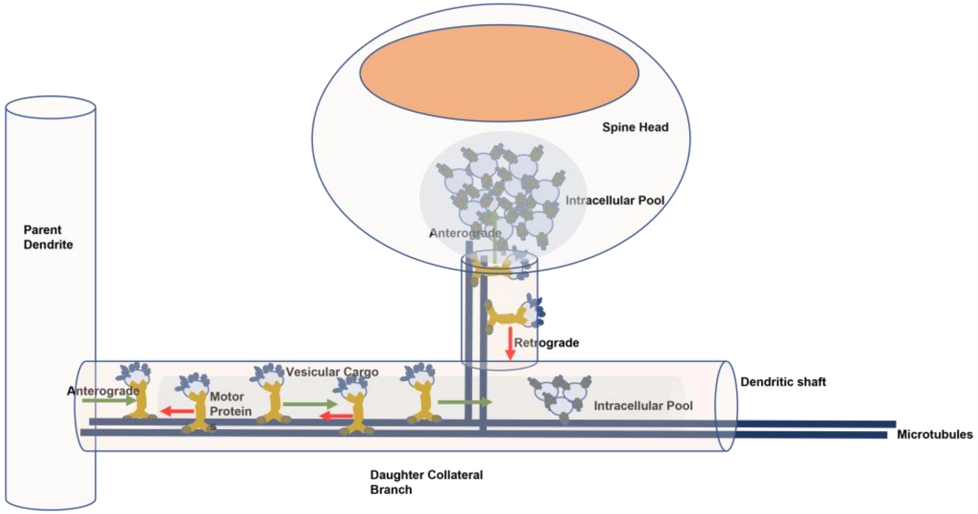
$D_{AMPA} \approx 0.01\mu m^2.s^{-1}$ (PSD)



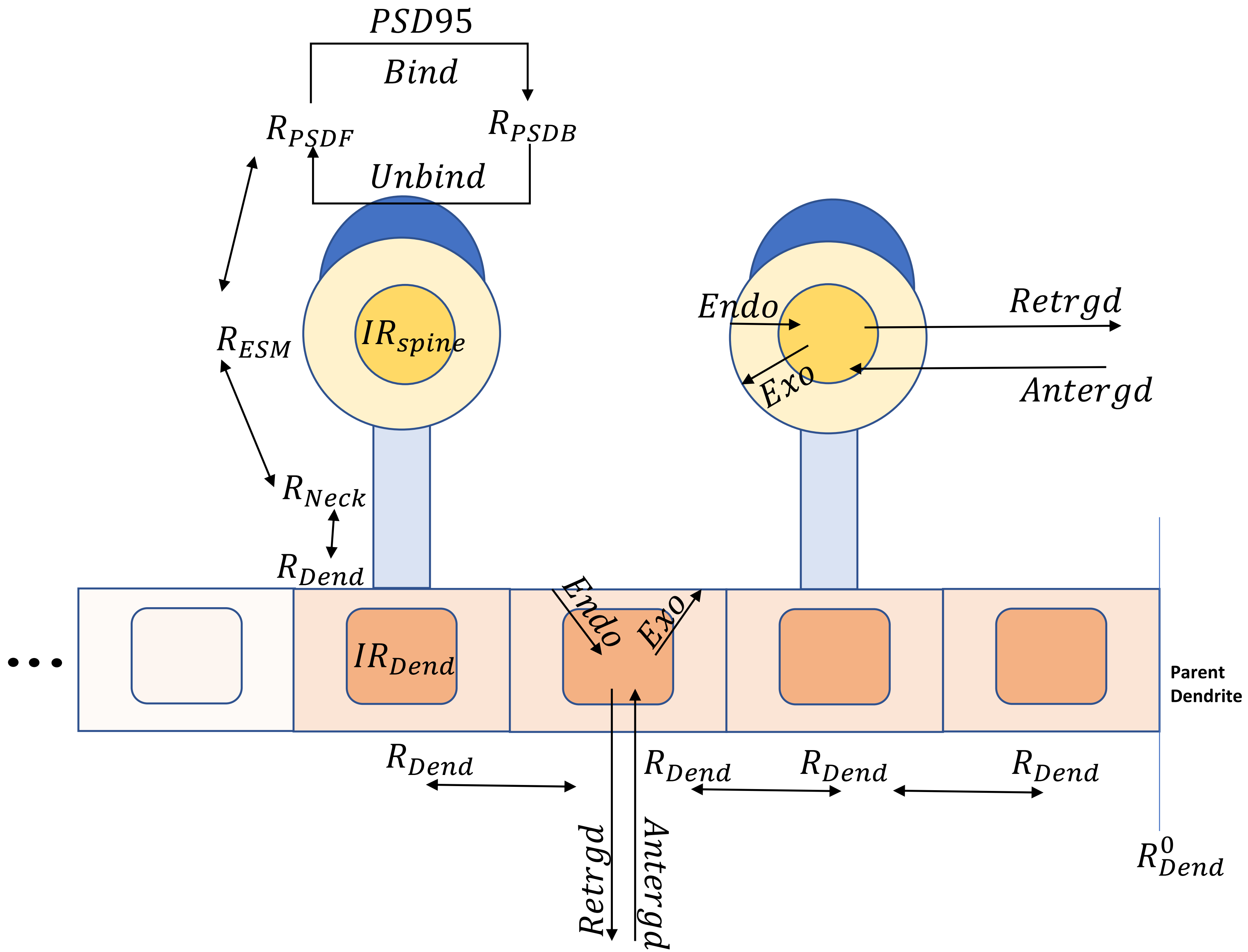
2. Membrane Receptor Trafficking: Exocytosis and Endocytosis



3. Intracellular Receptor Trafficking: Motor protein-assisted vesicular transport



Coarse-Grain Rate Mass Model: Compartment-based Reaction-Diffusion Approach



Simpler mechanical perspective: bare essentials of the trafficking and binding processes

A system of Linear ODEs: With nonlinear reaction terms for Receptor-PSD95 Binding and Unbinding

$$\frac{dR_{PSDB}}{dt} = Bind.(PSD95 - R_{PSDB}).R_{PSDF} - Unbind.R_{PSDB}$$

$$\frac{dR_{PSDF}}{dt} = -\frac{h_{PSD\to ESM}}{A_{PSD}}R_{PSDF} + \frac{h_{ESM\to PSD}}{A_{PSD}}R_{ESM} - Bind.(PSD95 - R_{PSDB}).R_{PSDF} + Unbind.R_{PSDB}$$

$$\frac{dIR_{spine}}{dt} = A_{ESM}.Endo_{spine}.R_{ESM} - Exo_{spine}.IR_{spine} - Retrgd_{spine}.IR_{spine} + Antrgd_{spine}$$

$$\frac{dR_{ESM}}{dt} = -\frac{h_{ESM\to PSD}}{A_{ESM}}R_{ESM} - \frac{h_{ESM\to Neck}}{A_{ESM}}R_{ESM} + \frac{h_{PSD\to ESM}}{A_{ESM}}R_{PSDF} + \frac{h_{Neck\to ESM}}{A_{ESM}}R_{Neck}$$
$$-Endo_{spine}.R_{ESM} + \frac{Exo_{spine}.IR_{spine}}{A_{ESM}}$$

$$\frac{dR_{Neck}}{dt} = -\frac{h_{Neck\to ESM}}{A_{Neck}}R_{Neck} - \frac{h_{Neck\to Dend}}{A_{Neck}}R_{Neck} + \frac{h_{ESM\to Neck}}{A_{Neck}}R_{ESM} + \frac{h_{Dend\to Neck}}{A_{Neck}}R_{Dend}$$

$$\frac{dIR_{dend}}{dt} = A_{dend}.Endo_{dend}.R_{Dend} - Exo_{dend}.IR_{dend} - Retrgd_{dend}.IR_{dend} + Antrgd_{dend}$$

$$\frac{dR^{i}_{Dend}}{dt} = -\frac{h_{Dend\to Neck}}{A_{Dend}}R^{i}_{Dend} - \frac{h_{Dend\to Dend}}{A_{Dend}}R^{i}_{Dend} + \frac{h_{Neck\to Dend}}{A_{Dend}}R_{Neck} + \frac{h_{Dend\to Dend}}{A_{Dend}}R^{i-1}_{Dend}$$
$$-Endo_{Dend}.R^{i}_{Dend} + \frac{Exo_{Dend}.IR^{i}_{Dend}}{A_{Dend}}$$

A recurrent structure for steady-state solutions

$$R_{PSDB}^{1,*} = f\left(R_{PSDF}^{1,*}\right)$$

$$R_{PSDF}^{1,*} = \nu^{1}.R_{ESM}^{1,*}$$

$$R_{ESM}^{1,*} = \eta_1^1.R_{Neck}^{1,*} + \eta_2^1$$

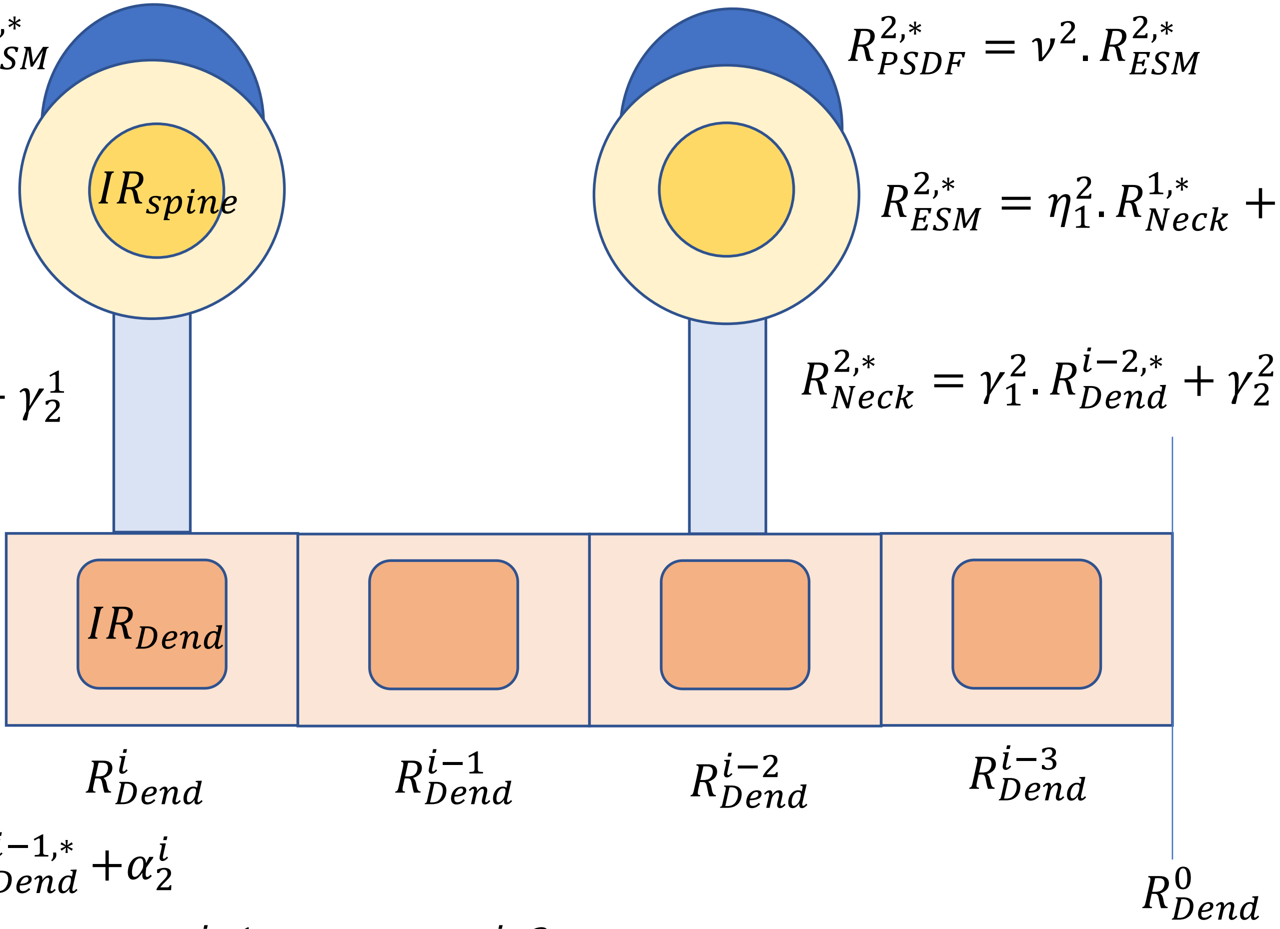
$$R_{Neck}^{1,*} = \gamma_1^1.R_{Dend}^{i,*} + \gamma_2^1$$

$$R_{PSDB}^{2,*} = f\left(R_{PSDF}^{2,*}\right)$$

$$R_{PSDF}^{2,*} = \nu^{2}.R_{ESM}^{2,*}$$

$$R_{ESM}^{2,*} = \eta_1^2.R_{Neck}^{1,*} + \eta_2^2$$

$$R_{Neck}^{2,*} = \gamma_1^2.R_{Dend}^{i-2,*} + \gamma_2^2$$



BAM!!!!
Reduces hours of numerical simulation for steady-state to seconds and minutes, for large to larger dendritic arbours.

BAM BAM!!!!
Greatly helpful in reducing 8-dimensional parameter space into 5-dimensional parameter space, for quick model optimization, under homogeneous spine condition.

$$R_{Dend}^{i,*} = \alpha_1^i.R_{Dend}^{i-1,*} + \alpha_2^i$$

$$R_{Dend}^{i-1,*} = \alpha_1^{i-1}.R_{Dend}^{i-2,*} + \alpha_2^{i-1}$$

$$R_{Dend}^{i-2,*} = \alpha_1^{i-2}.R_{Dend}^{i-3,*} + \alpha_2^{i-2}$$

$$R_{Dend}^{i-3,*} = \alpha_1^{i-3}.R_{Dend}^{0} + \alpha_2^{i-3}$$

Explicit expressions of Recurrence Solution

$$R^*_{PSDB} = \frac{Bind.\,PSD95.\,R^*_{PSDF}}{Bind.\,R^*_{PSDF} + Unbind}$$

$$R^*_{PSDF} = \nu.\,R^*_{ESM}, \nu = \frac{h_{ESM\to PSD}}{h_{PSD\to ESM}}$$

$$IR^*_{spine} = \lambda_1^{spine}.\,R^*_{ESM} + \lambda_2^{spine}, \quad \lambda_1^{spine} = \frac{A_{ESM}.\,Endo_{spine}}{Exo_{spine} + Retrgd_{spine}}$$ and $$\lambda_2^{spine} = \frac{Antrgd_{spine}}{Exo_{spine} + Retrgd_{spine}}$$

$$R^*_{ESM} = \eta_1\, R^*_{Neck} + \eta_2$$

$$\eta_1 = \frac{h_{Neck\to ESM}}{\left(h_{ESM\to PSD} + h_{ESM\to Neck} - \nu.\,h_{PSD\to ESM} + A_{ESM}.\,Endo_{spine} - \lambda_1^{spine}.\,Exo_{spine}\right)}$$

$$\eta_2 = \frac{\lambda_2^{spine}.\,Exo_{spine}}{\left(h_{ESM\to PSD} + h_{ESM\to Neck} - \nu.\,h_{PSD\to ESM} + A_{ESM}.\,Endo_{spine} - \lambda_1^{spine}.\,Exo_{spine}\right)}$$

Explicit expressions of Recurrence Solution

$$R^*_{Neck} = \gamma_1 \, R^*_{Dend} + \gamma_2$$

$$\gamma_1 = \frac{h_{Dend\to Neck}}{(h_{Neck\to ESM} + h_{Neck\to Dend} - \eta_1 . h_{ESM\to Neck})}$$

$$\gamma_2 = \frac{\eta_2 . h_{ESM\to Neck}}{(h_{Neck\to ESM} + h_{Neck\to Dend} - \eta_1 . h_{ESM\to Neck})}$$

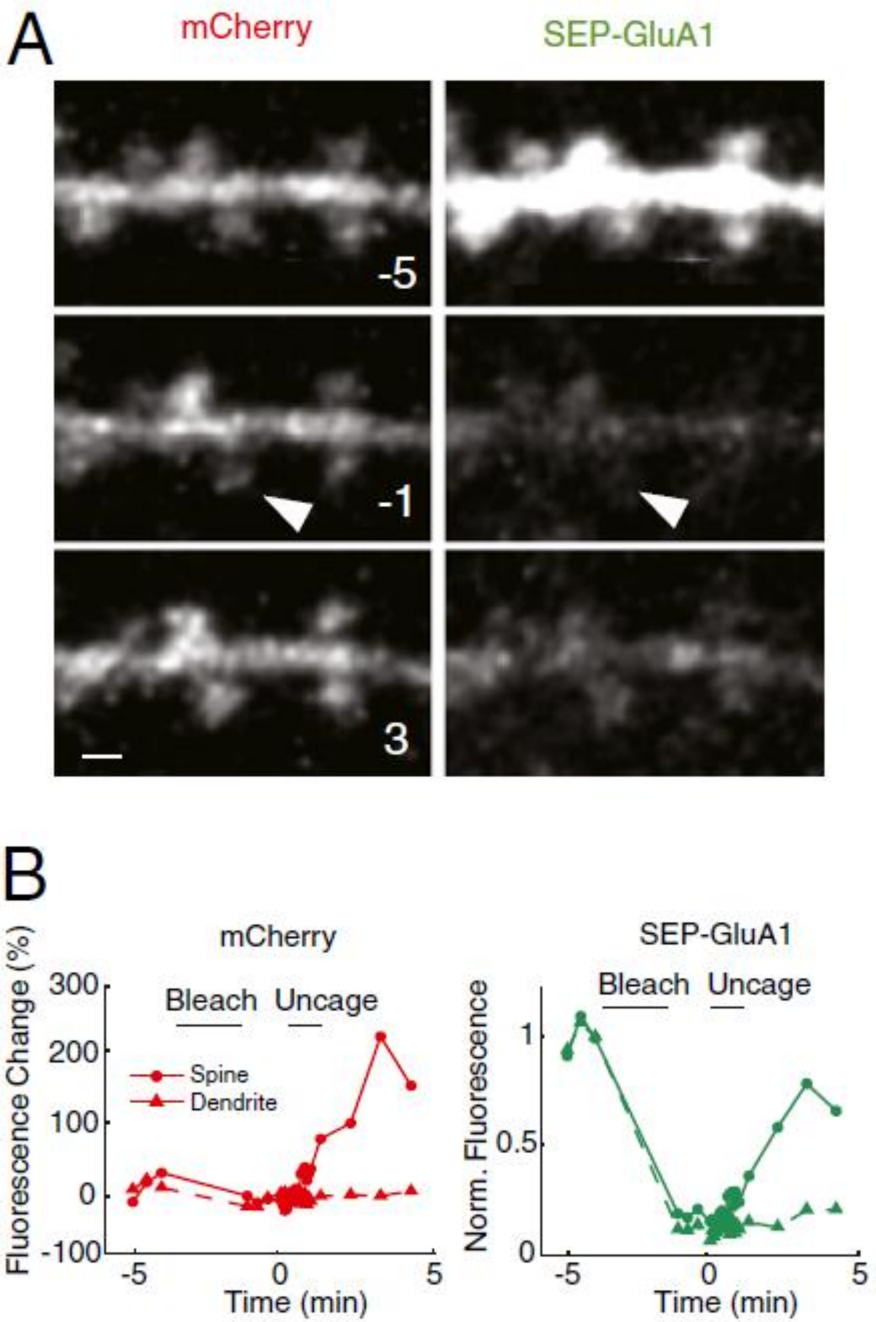
$$IR^*_{dend} = \lambda_1^{dend} . R^*_{dend} + \lambda_2^{dend}, \quad \lambda_1^{dend} = \frac{A_{dend} . Endo_{dend}}{Exo_{dend} + Retrgd_{dend}} \quad \text{and} \quad \lambda_2^{dend} = \frac{Antrgd_{dend}}{Exo_{dend} + Retrgd_{dend}}$$

$$R^{i,*}_{Dend} = \alpha_1^i . R^{i-1,*}_{Dend} + \alpha_2^i$$

$$\alpha_1^i = \frac{h_{Dend\to Dend}}{(h_{Dend\to Neck} + h_{Dend\to Dend} - \gamma_1 . h_{Neck\to Dend} + A_{Dend} . Endo_{Dend} - \lambda_1^{dend} . Exo_{Dend})}$$

$$\alpha_2^i = \frac{\gamma_2 . h_{Neck\to Dend} + \lambda_2^{dend} . Exo_{Dend}}{(h_{Dend\to Neck} + h_{Dend\to Dend} - \gamma_1 . h_{Neck\to Dend} + A_{Dend} . Endo_{Dend} - \lambda_1^{dend} . Exo_{Dend})}$$

DATA 1: Fluorescence Recovery After Photobleaching (FRAP)



AMPA receptors are exocytosed in stimulated spines and adjacent dendrites in a Ras-ERK–dependent manner during long-term potentiation

Michael A. Patterson[a], Erzsebet M. Szatmari[a], and Ryohei Yasuda[a,b,1]

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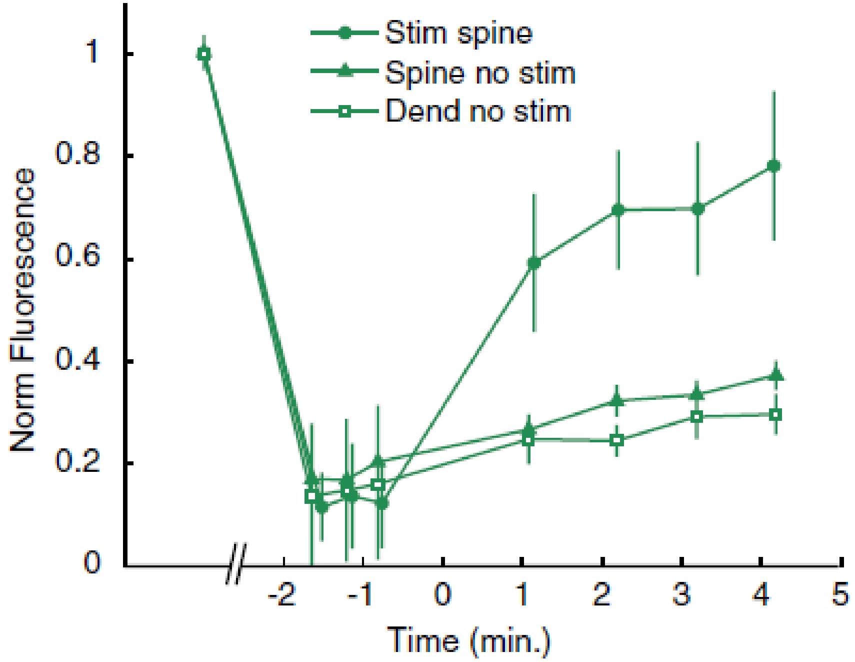
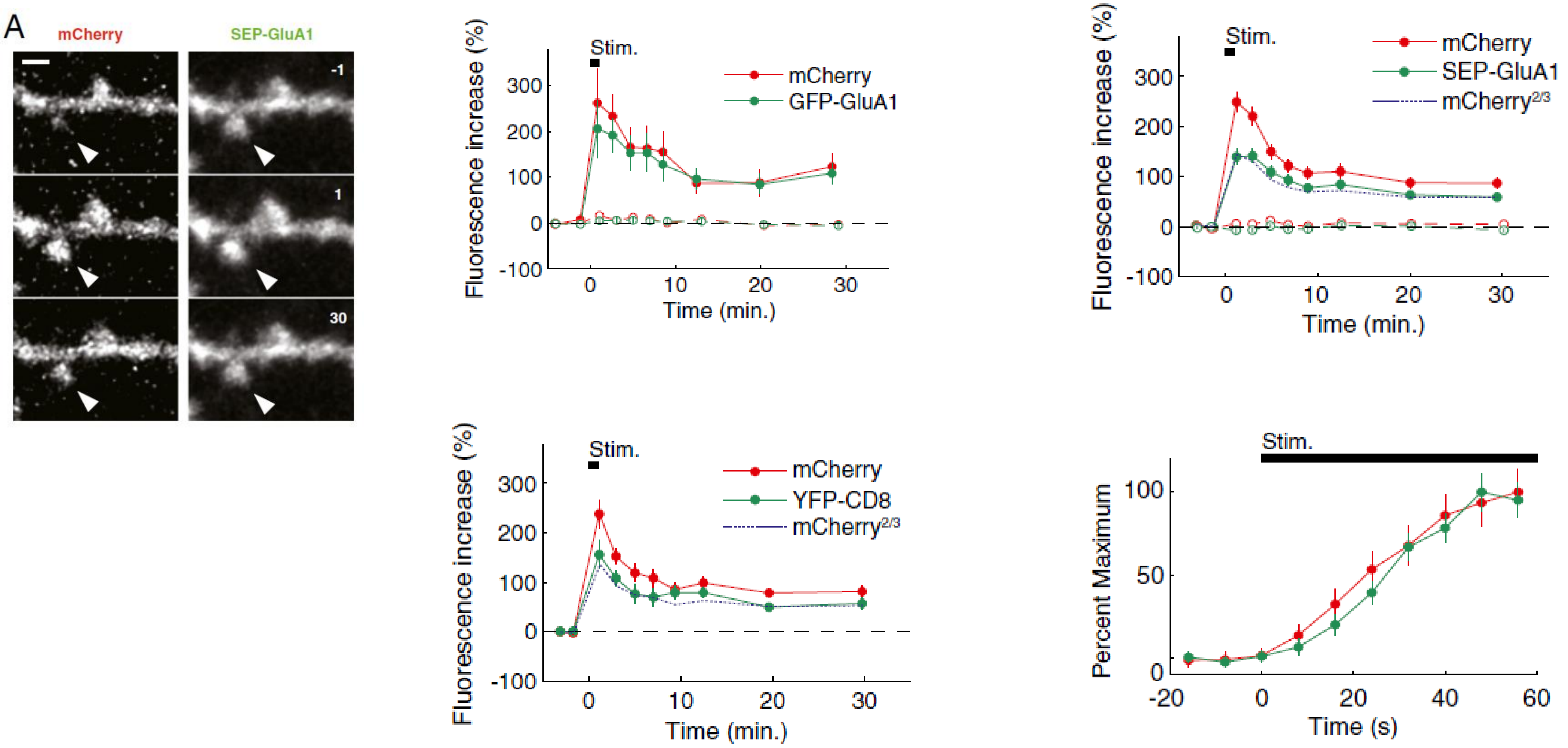
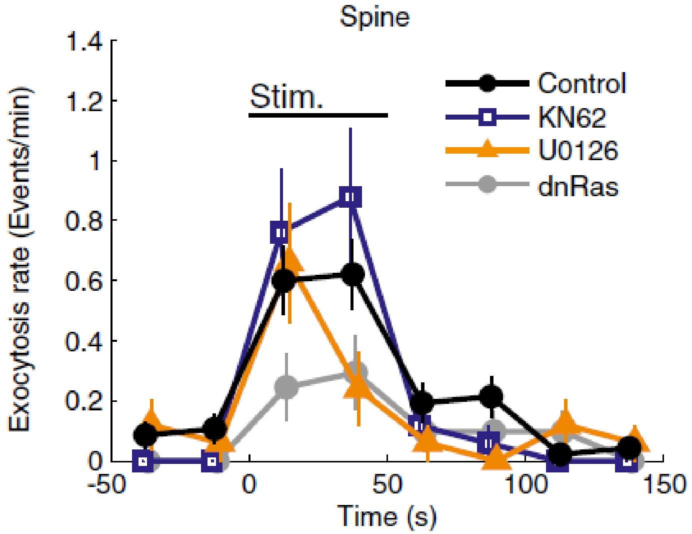
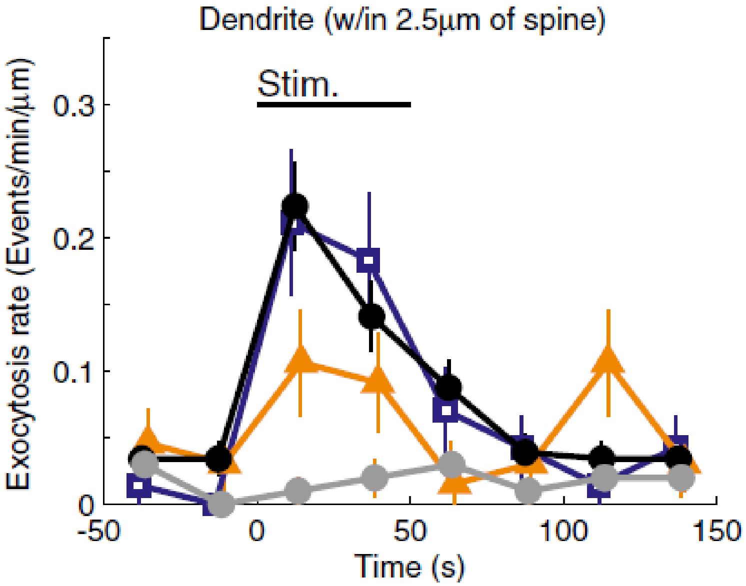


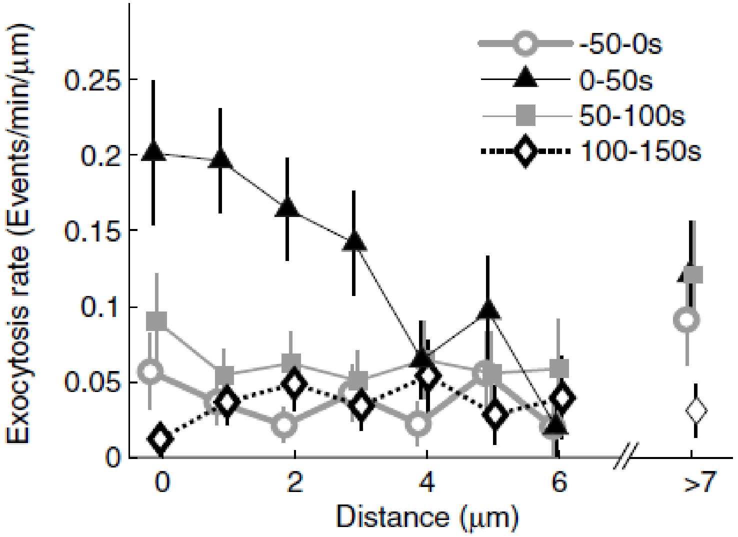
DATA 2: Total Fluorescence Change under stimulation through Glutamate Uncaging



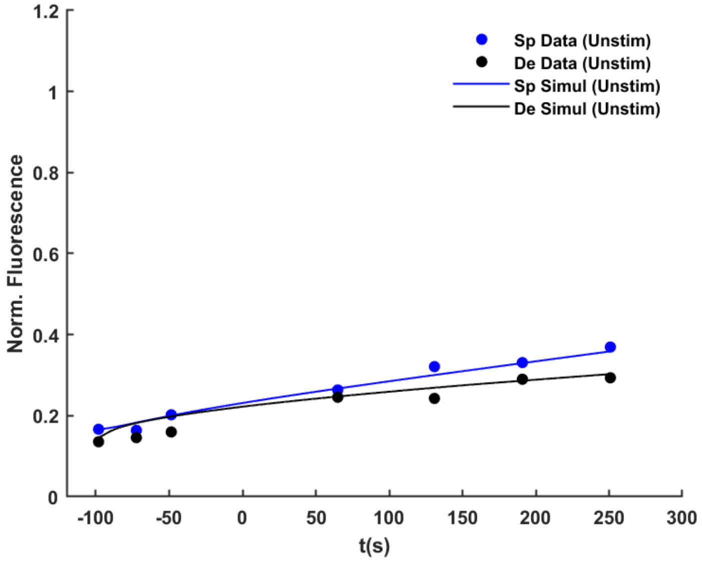
DATA 3: Fluorescence Recovery under Constant Photobleaching

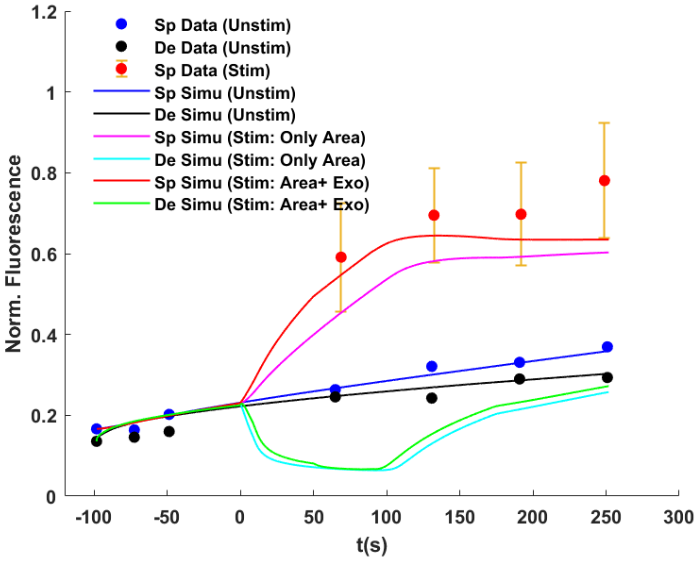




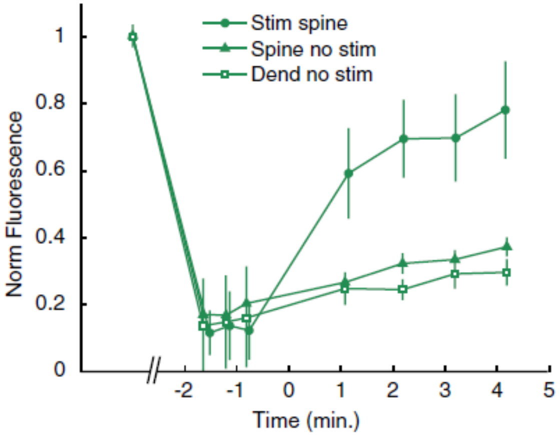


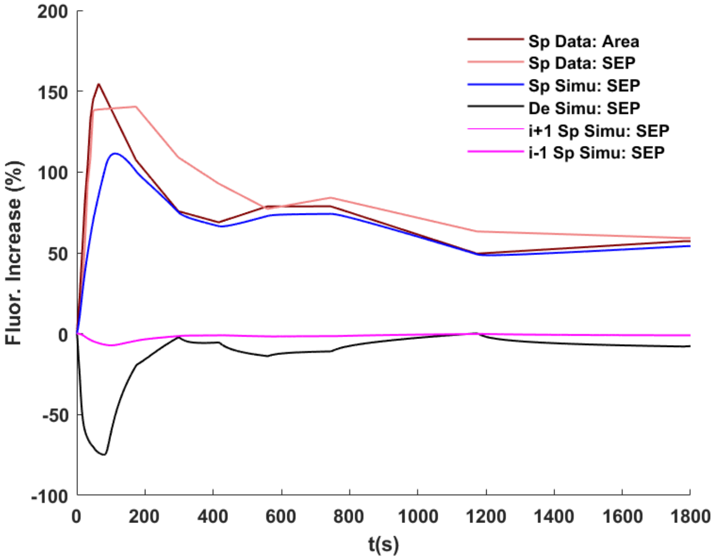
Nonlinear Convex Optimization of Model Parameters

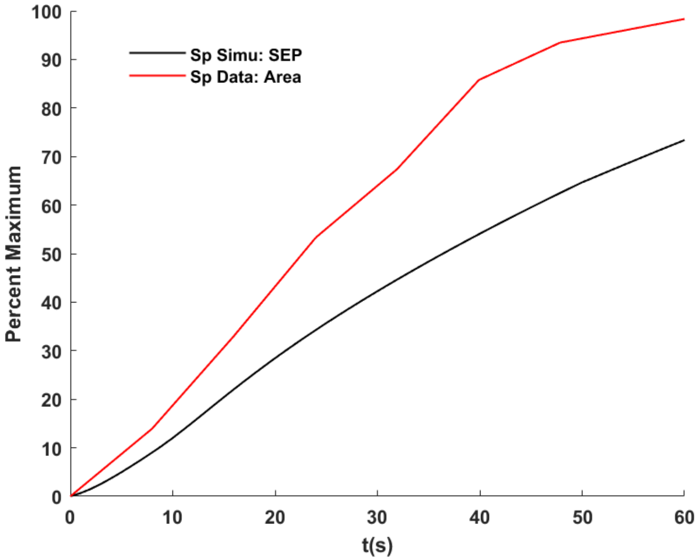


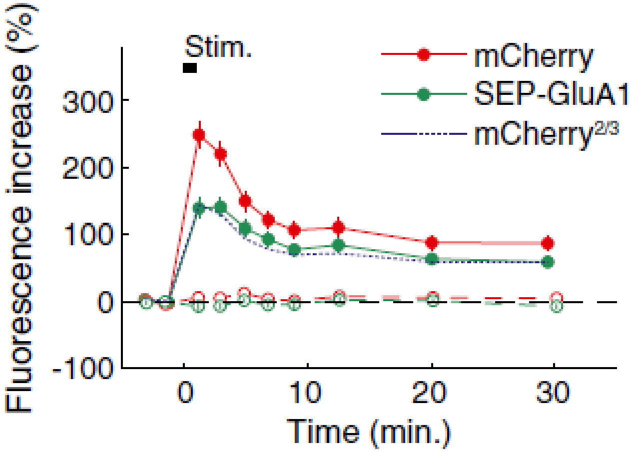


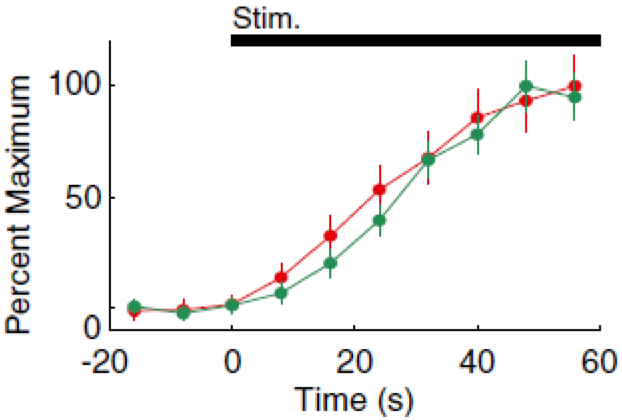
Parameters	Optim Val
Exo Spine	0.0072
Retrgd Spine	0.0087
Exo Dend	5.4599e-5
Retrgd Dend	0.6160
Bind PSD	2.3220





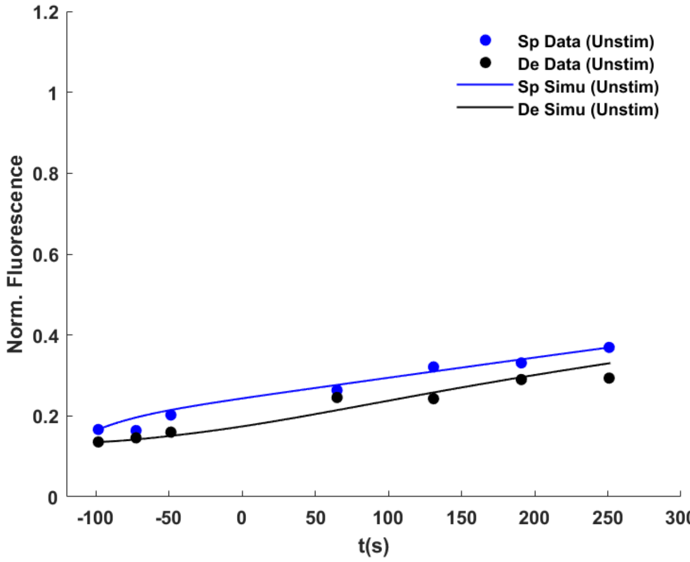


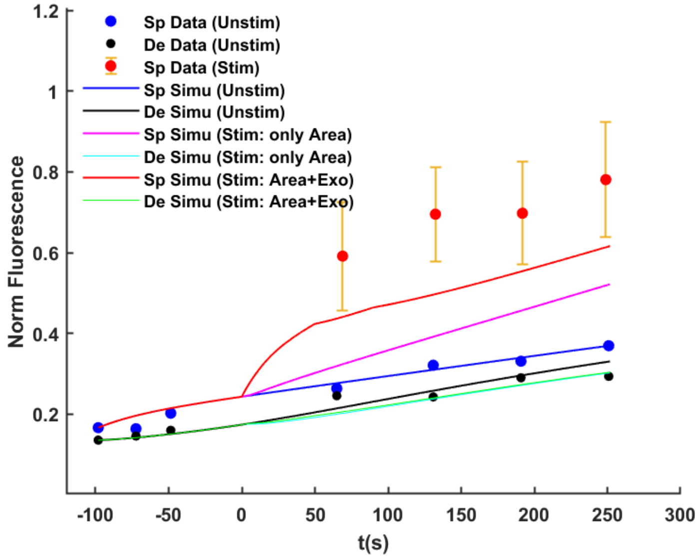




Model Parameter Optimization for Restricted Neck

$$p_{dend\ vs\ neck} = 0.0045$$





Parameters	Optim Val
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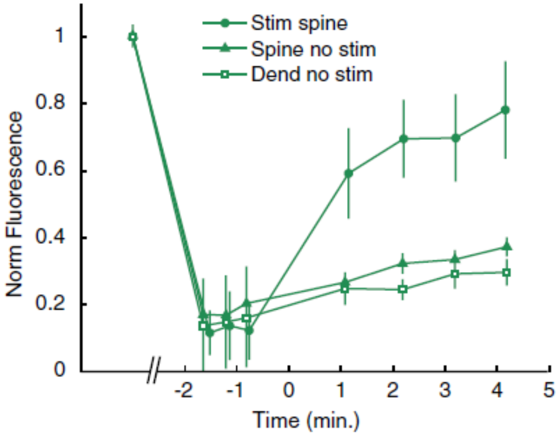
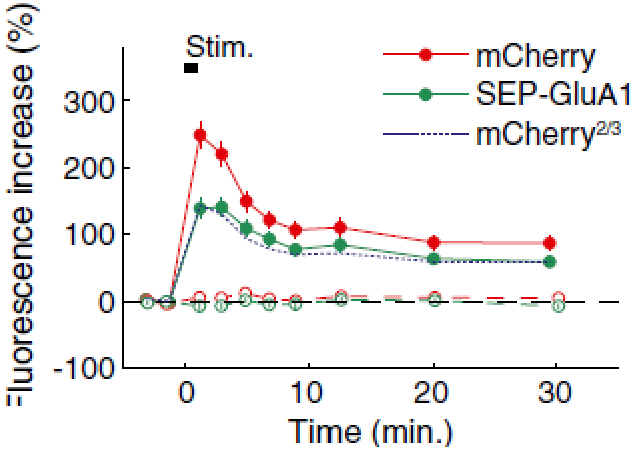
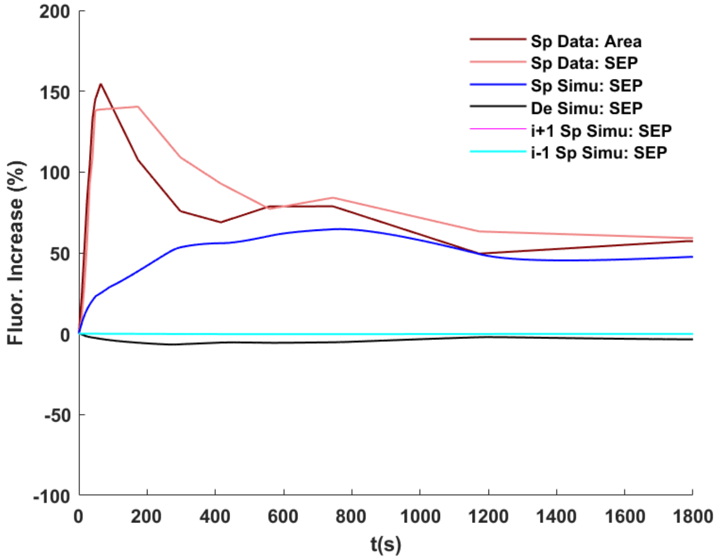
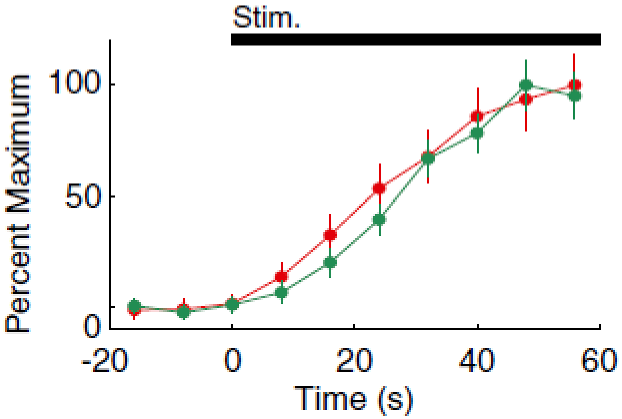
Retrgd Spine	0.0108
Exo Dend	8.8392e-5
Retrgd Dend	0.5027
Bind PSD	0.0267

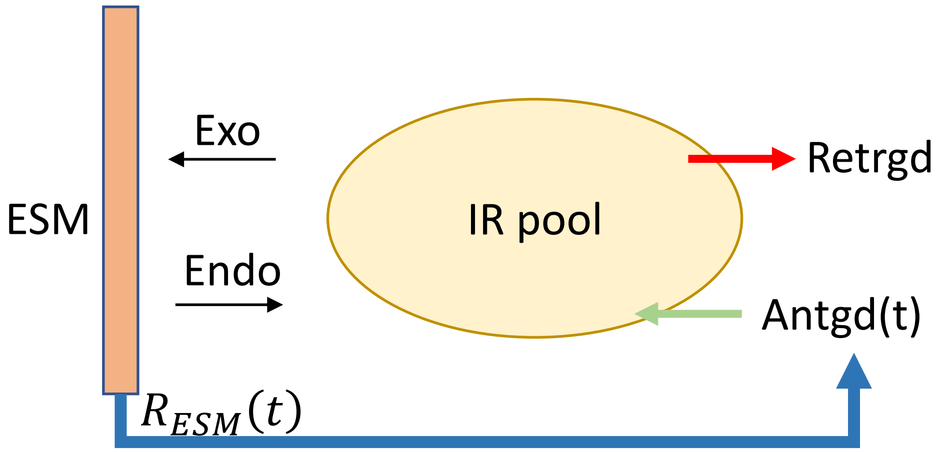








Control-Theoretic Approach for Time-dependent $Antrgd_{spine}$



$$\frac{d\ Antrgd_{spine}}{dt} = \vartheta\left(R_{ESM}^{setpoint} - R_{ESM}(t)\right)$$

$$R_{ESM}^{setpoint} = 10.\,\mu m^{-2}$$

If $Antrgd_{spine}(t) < 0:\ Antrgd_{spine} \equiv 0$

$Antrgd_{spine} \epsilon \mathbb{R}^{+}$

If $Antrgd_{spine}(t) > \Psi:\ Antrgd_{spine} \equiv \Psi$

Ψ is the Resource-constrained upper-limit

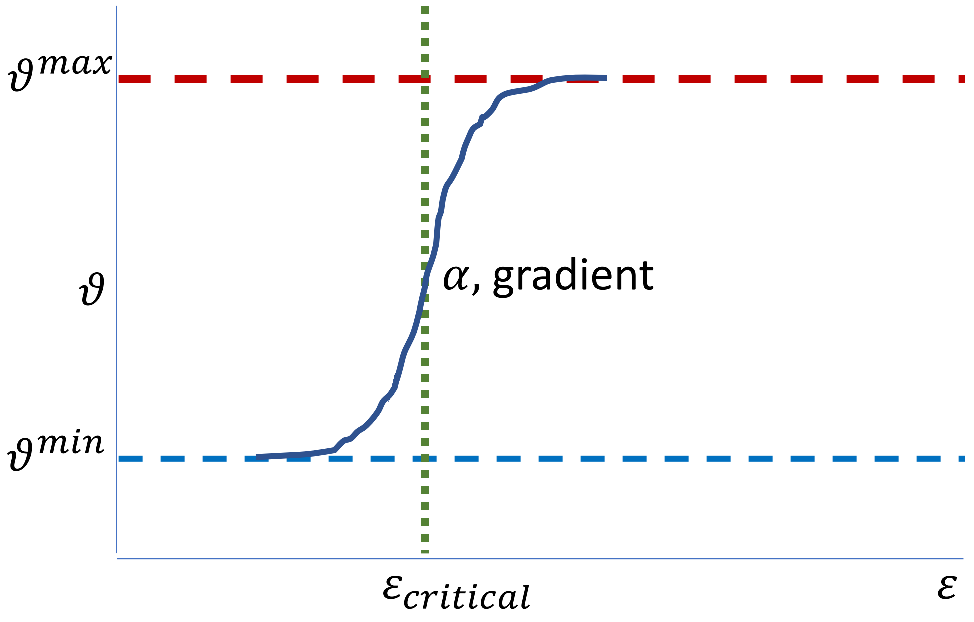
Hard Bounds

Learning Rate

Option 1: $\vartheta \epsilon \mathbb{R}^{+}$

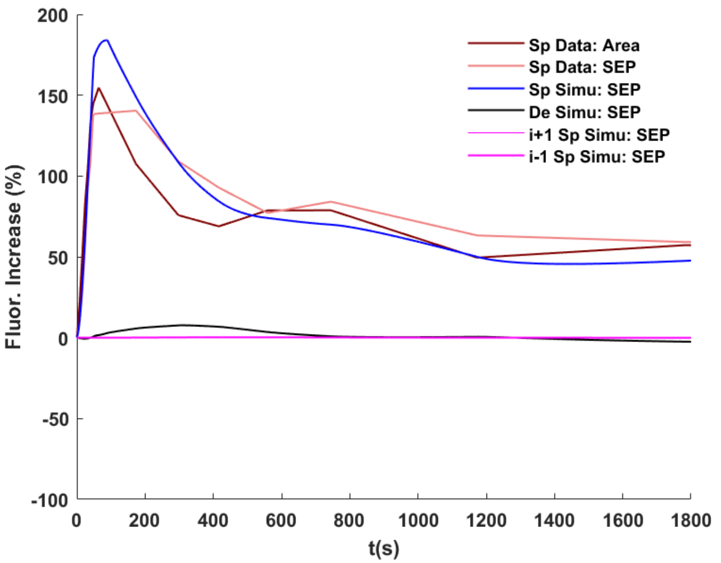
Option 2: $\vartheta = \dfrac{\vartheta^{max} - \vartheta^{min}}{1 + exp(-\alpha.\varepsilon)} + \vartheta^{min}$

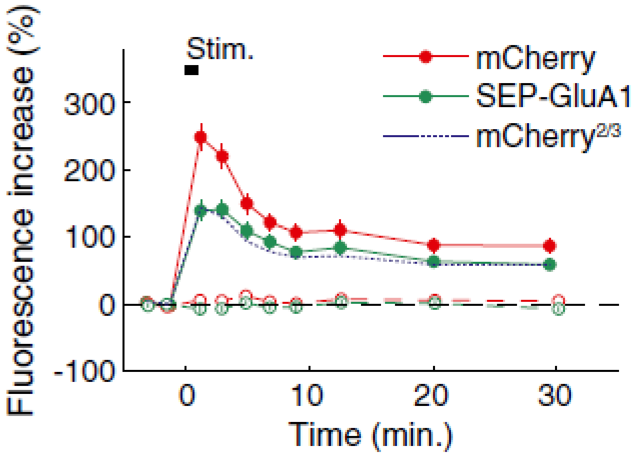
$$\varepsilon = \left\| R_{ESM}^{setpoint} - R_{ESM}(t) \right\|_1 - \varepsilon_{critical}$$

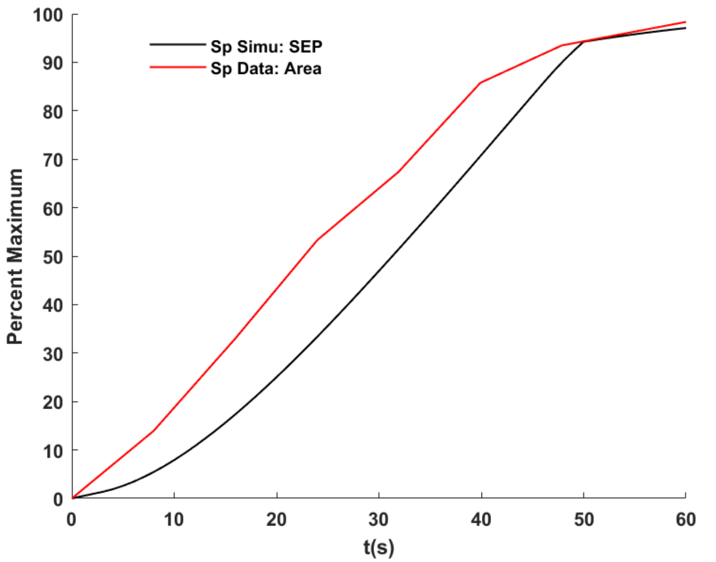


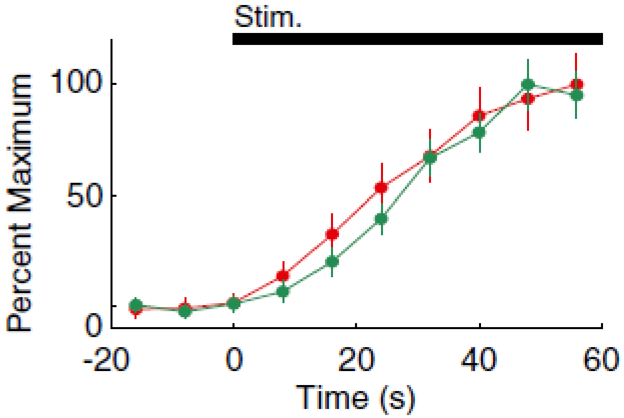
$$\vartheta^{max} = 10, \vartheta^{min} = 10^{-4}, \varepsilon_{critical} = 2, \alpha = 1000$$

$p_{dend\ vs\ neck} = 0.0045$ captures the data better when combined with $Antrgd_{spine}(t)$

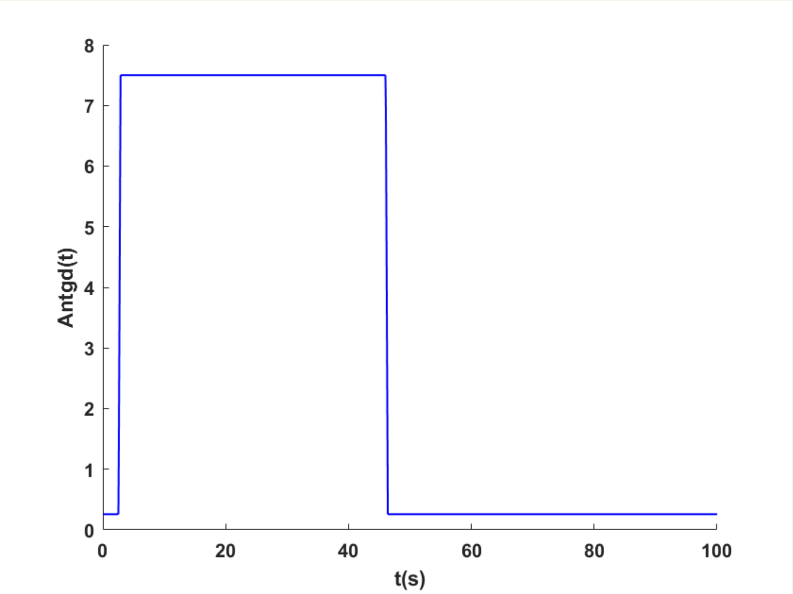


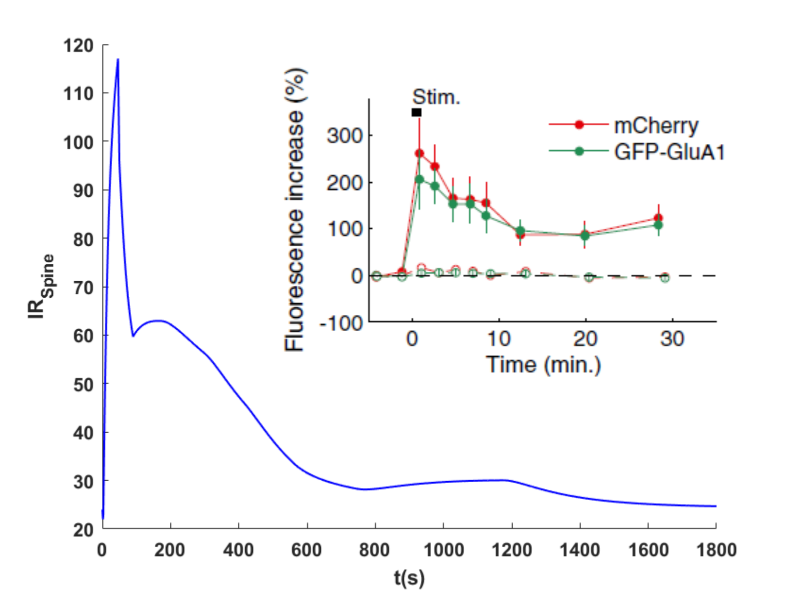






Additional dynamics predicted:





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Colleagues:

Members, O'Donnell Lab
Members, Computational Neuroscience Unit

Past Works: Synaptic Plasticity, Cortical Dynamics and Dopaminergic Neuromodulation

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RESEARCH ARTICLE

Self-crowding of AMPA receptors in the excitatory postsynaptic density can effectuate anomalous receptor sub-diffusion

Rahul Gupta *

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RESEARCH ARTICLE

Stochastic Mesocortical Dynamics and Robustness of Working Memory during Delay-Period

Melissa Reneaux[1], Rahul Gupta[1], Karmeshu[1,2]*

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RESEARCH ARTICLE

Role of Heterogeneous Macromolecular Crowding and Geometrical Irregularity at Central Excitatory Synapses in Shaping Synaptic Transmission

Rahul Gupta[1], Melissa Reneaux[1], Karmeshu[1,2]*

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RESEARCH ARTICLE

Prefronto-cortical dopamine D1 receptor sensitivity can critically influence working memory maintenance during delayed response tasks

Melissa Reneaux *, Rahul Gupta *


THANKS
ISRC-CN³ AUTUMN SCHOOL