Measuring and modeling the weight dynamics of many synapses onto diverse cell-types *in vivo*

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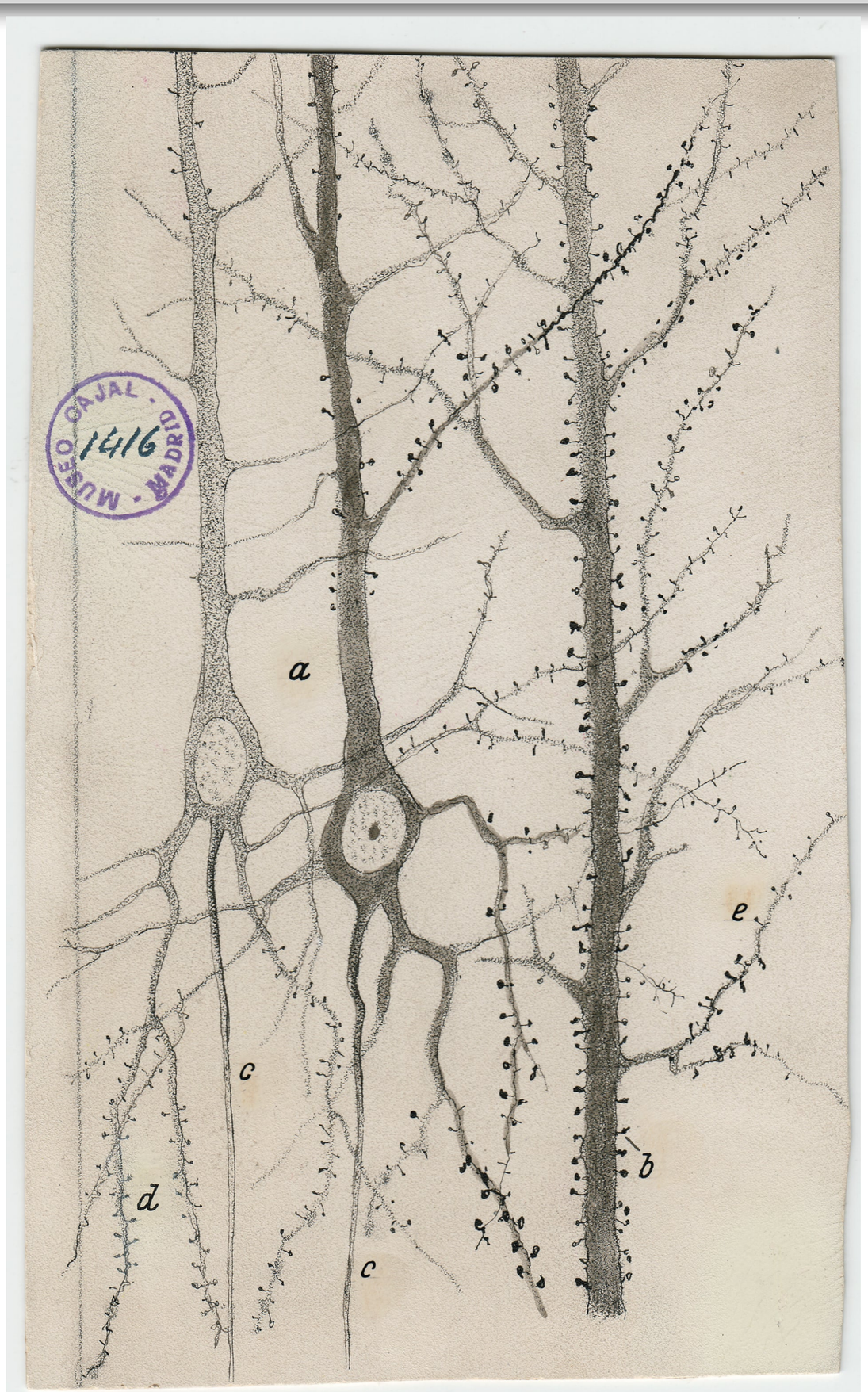
Tianyi Mao, Haining Zhong, and Surya Ganguli

Stanford University

Cosyne 2019
Lisbon, Portugal

Synaptic Dynamics as a Fundamental Basis for Learning



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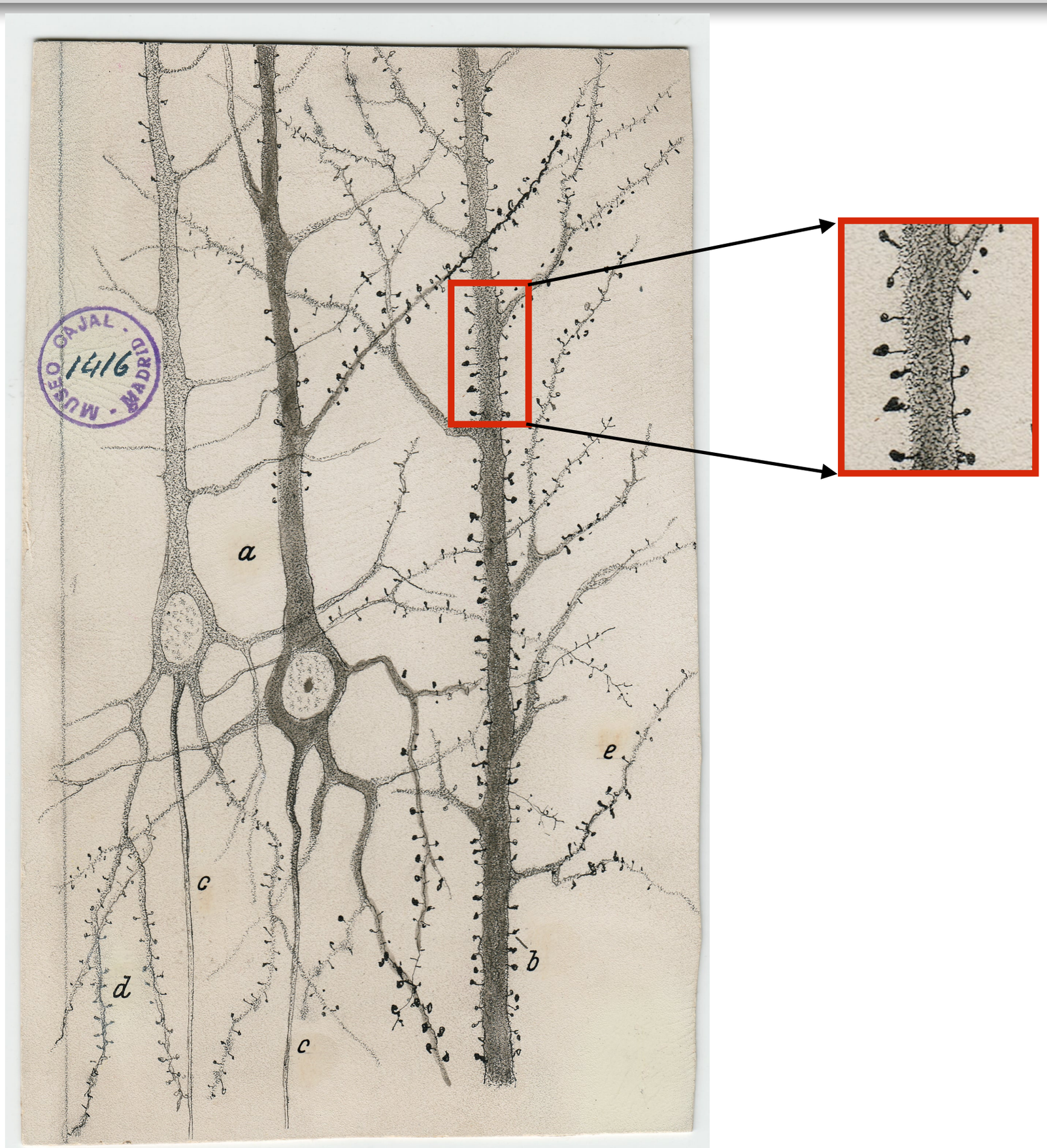


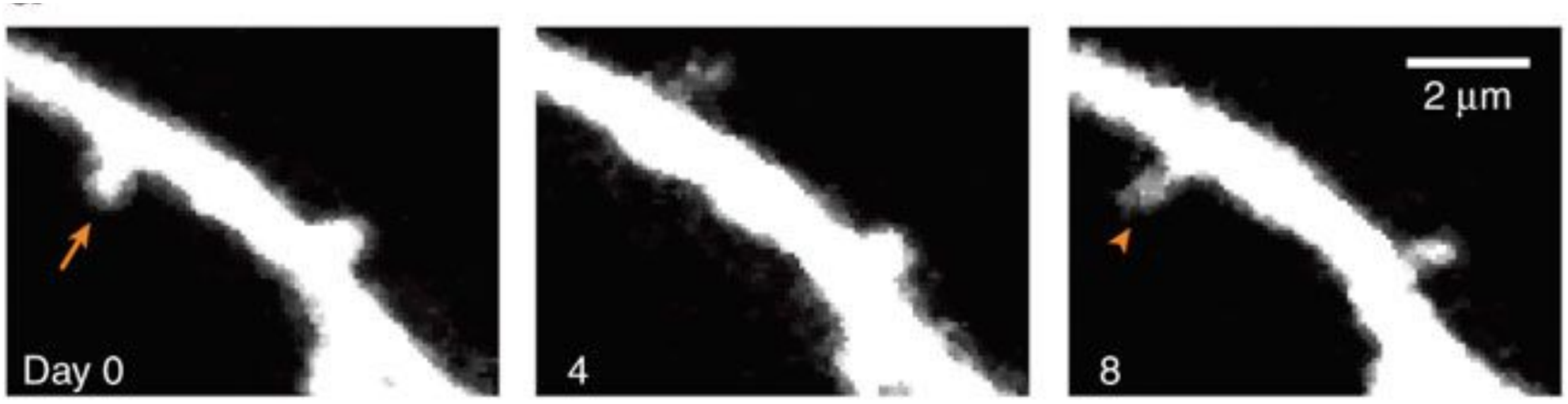
Prior work:
Spine Volume

Yasumatsu et al. 2008

Loewenstein et al. 2011

Imaging Can Miss Many Spines

Holtmaat et al. 2009



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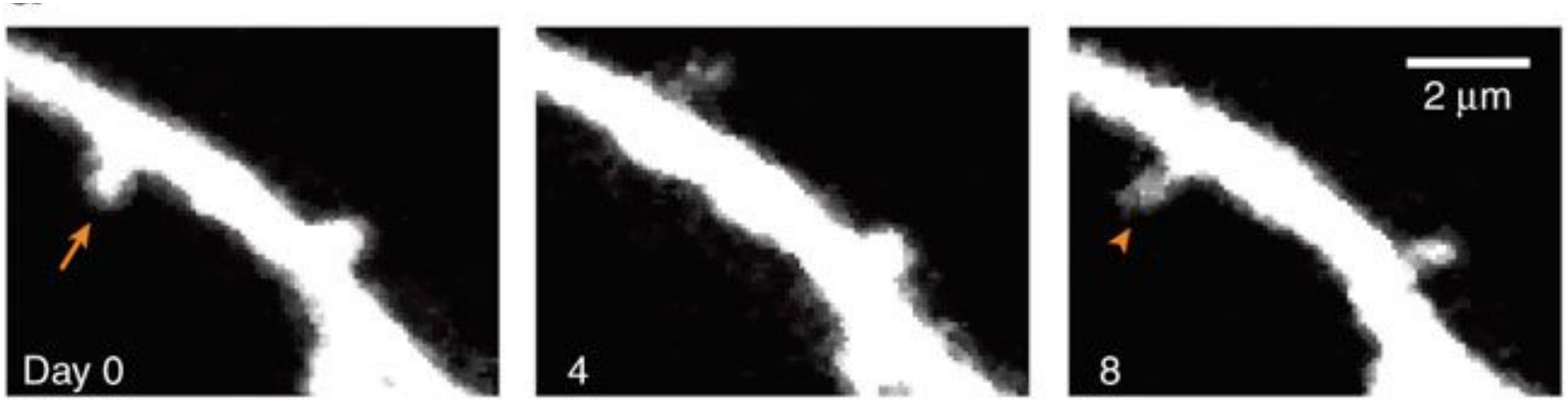
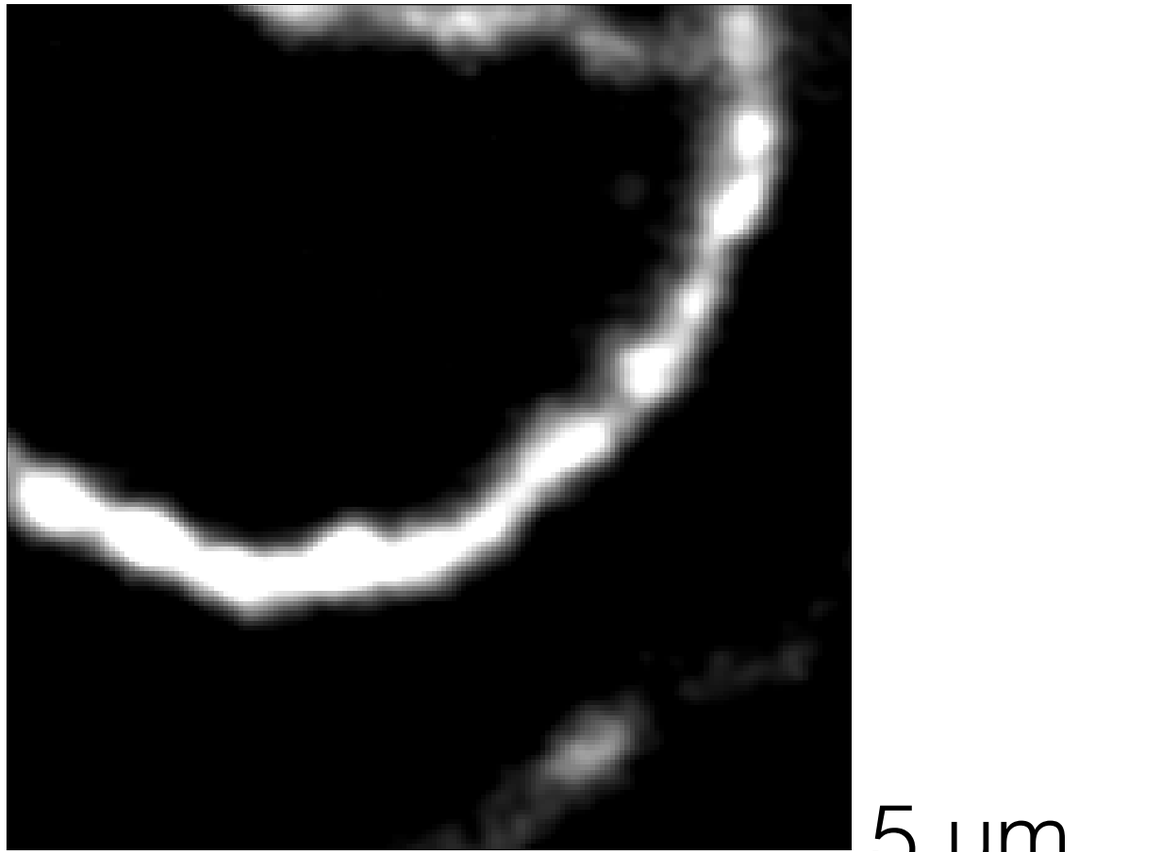


Synapses onto inhibitory cells don't have spines



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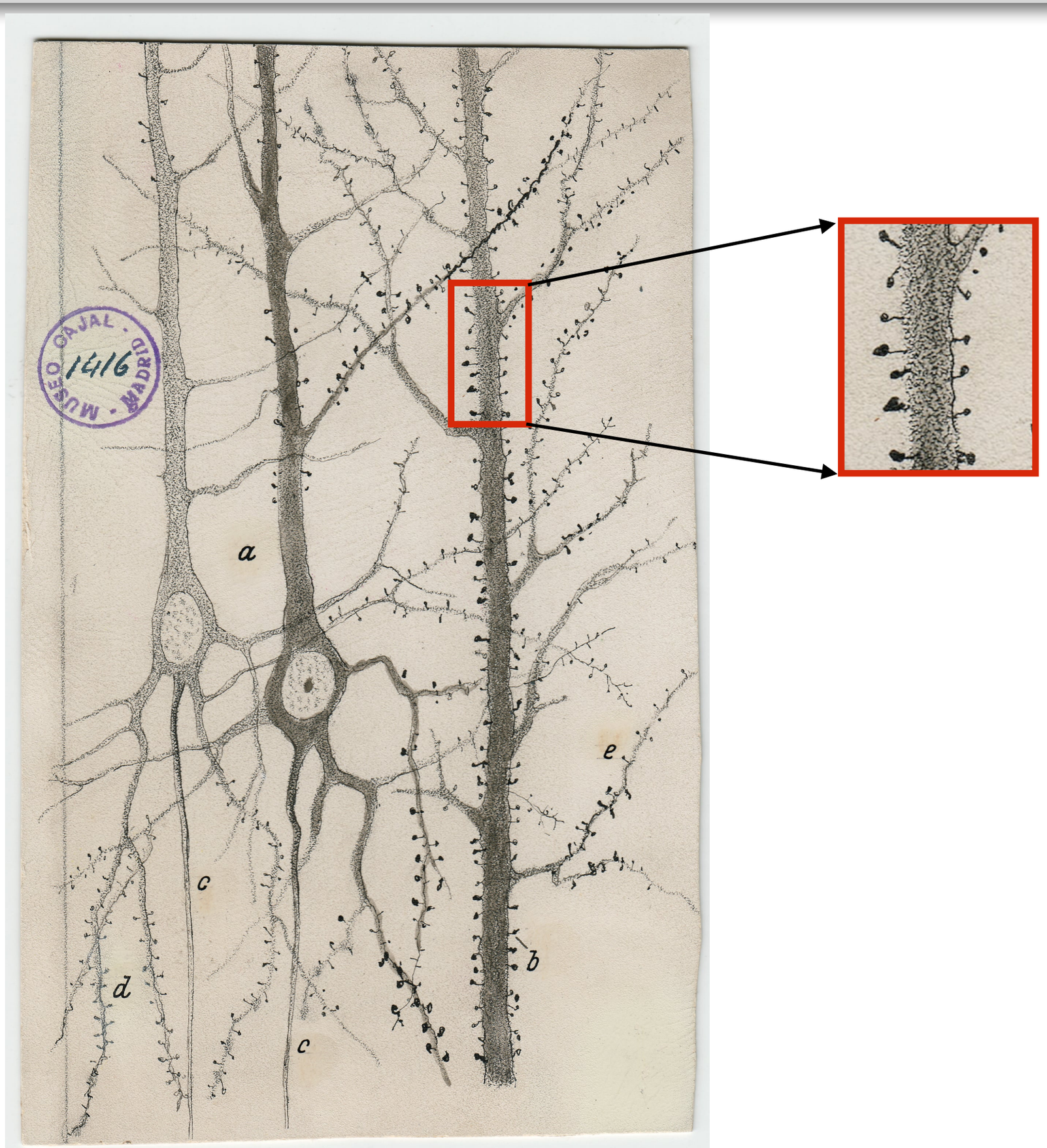

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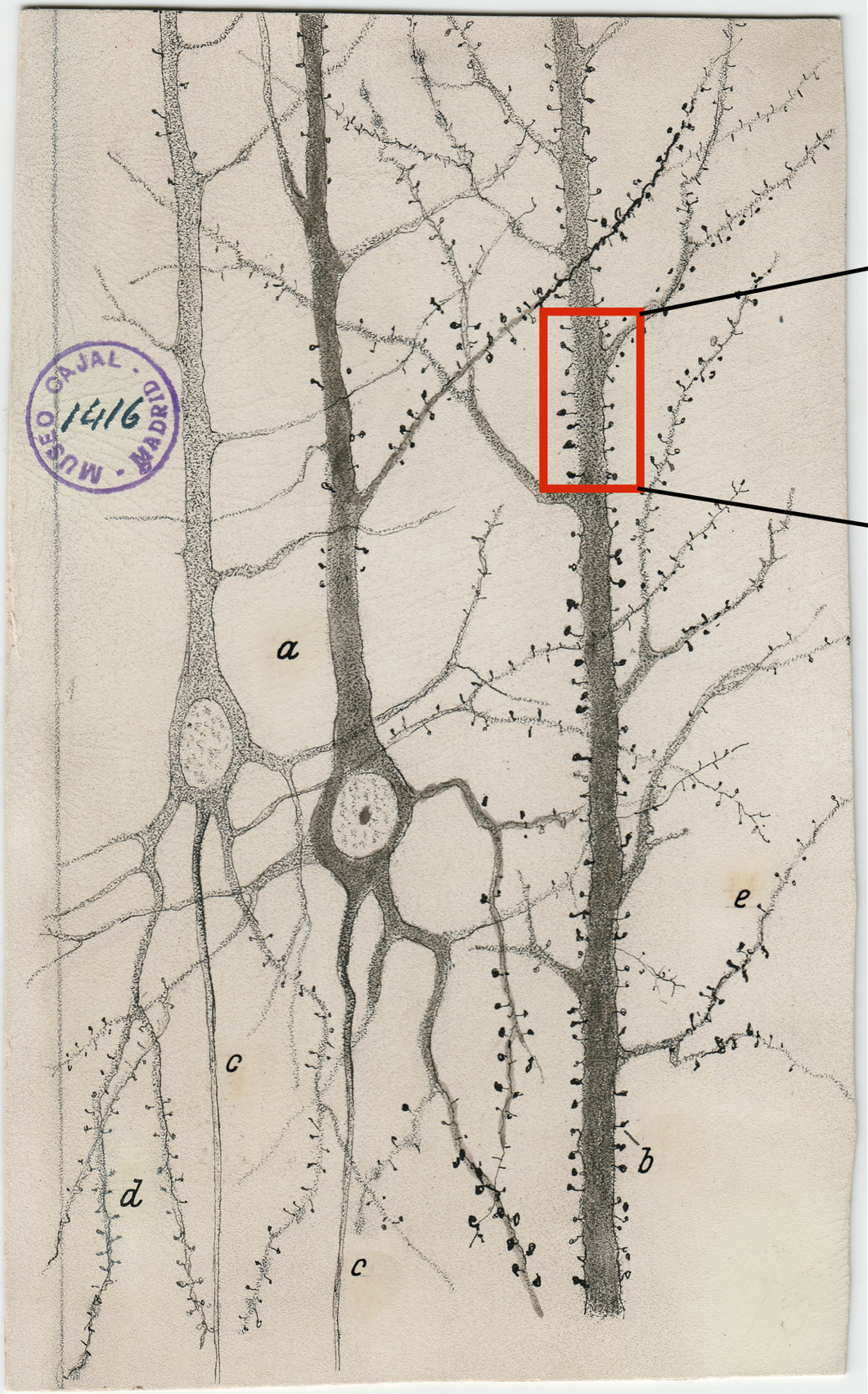

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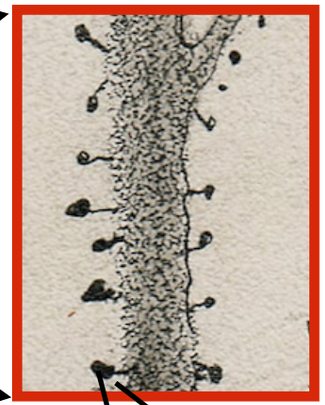
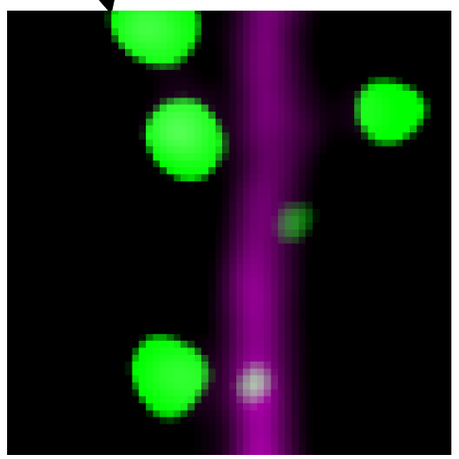
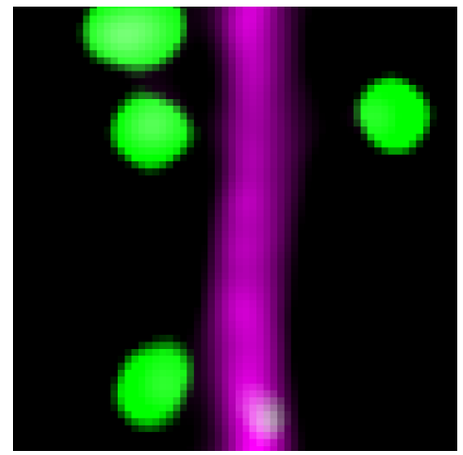
Our work:
Imaging Natural Expression Levels of PSD-95



Day *T*



Day *T + 4*

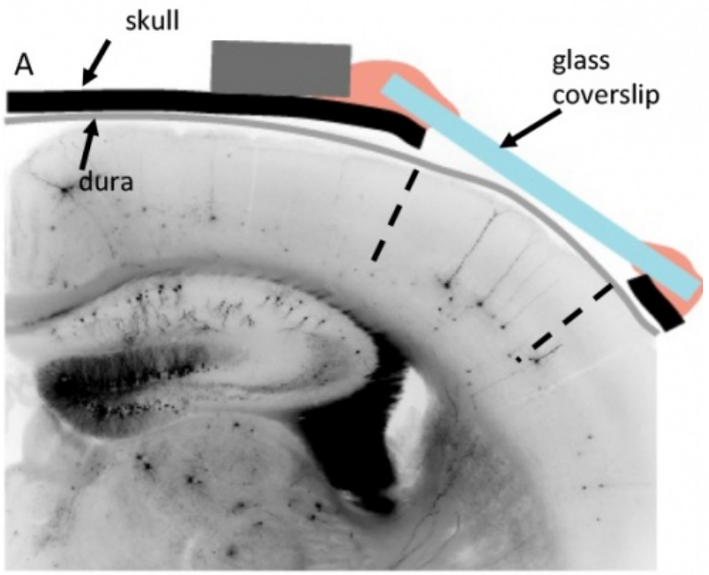


I. Experimental Strategy

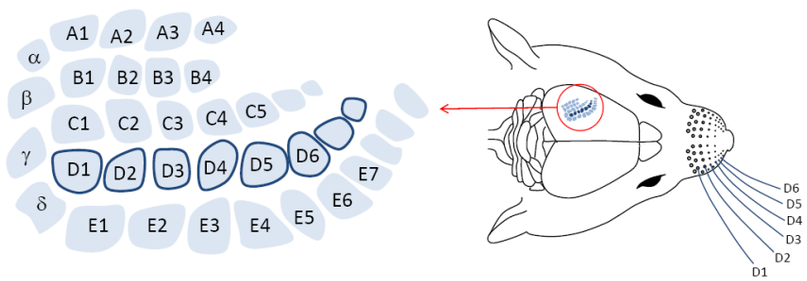
Is there a unified strategy to image populations of synapses onto both excitatory and inhibitory cell types?

Solution: PSD-95 ENABLED Strategy

Holtmaat et al. 2009

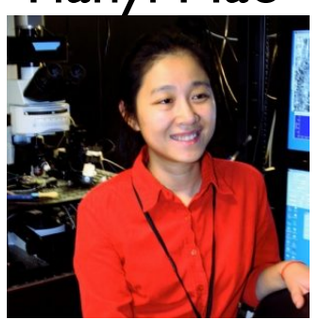


Valente et al. 2012



Barrel Cortex

Tianyi Mao



Haining Zhong

Fortin DA, ..., Mao T, & Zhong H (2014). J Neurosci. 34(50): 16698-712.

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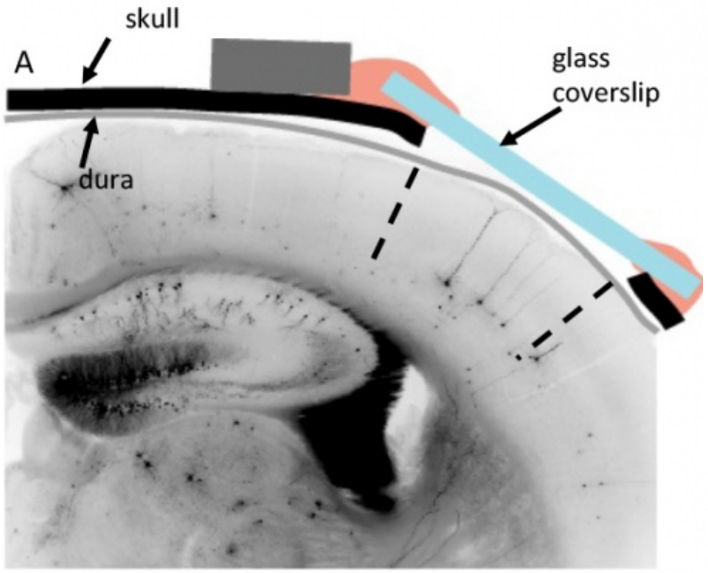

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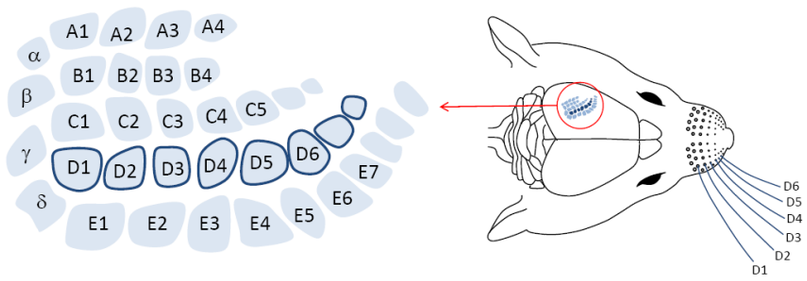
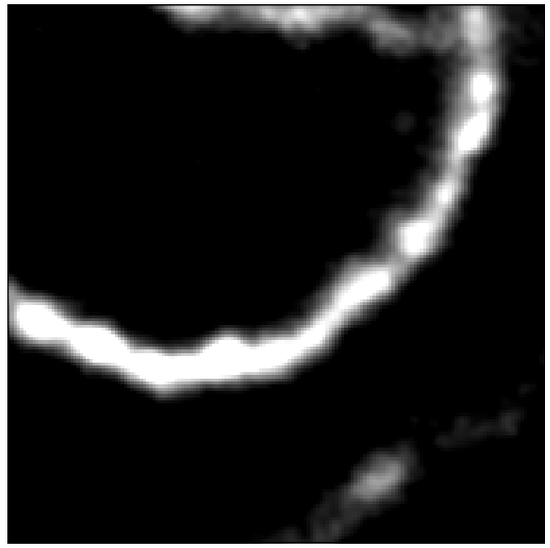


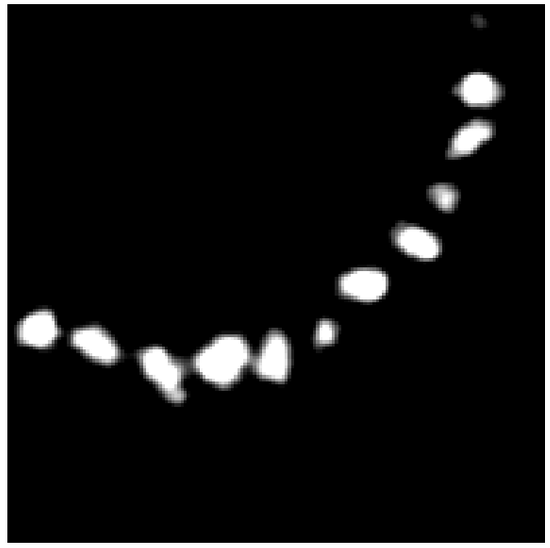
Barrel Cortex

PV

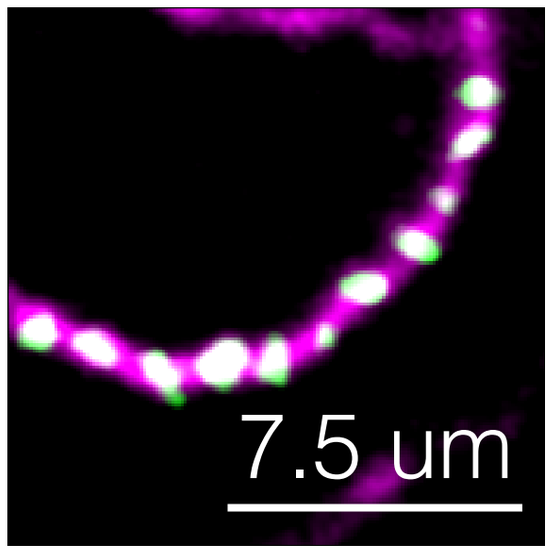
TdTomato



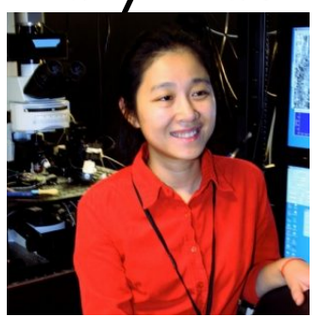
PSD-95-mVenus



Merge



Tianyi Mao



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Validation of ENABLED Strategy

1. Does this method mark functional synapses?

2. Can we reliably extract synaptic strength from these images?

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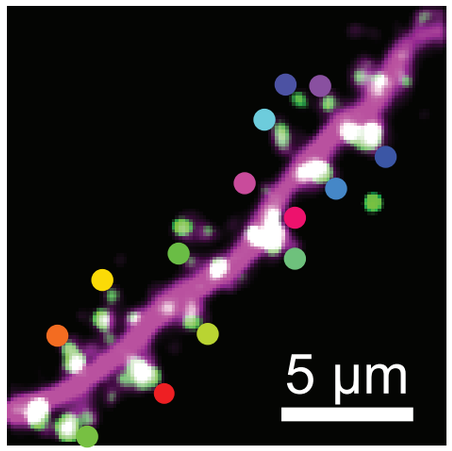
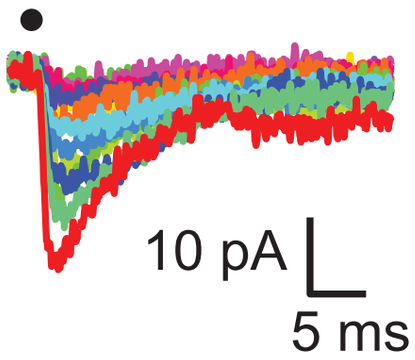
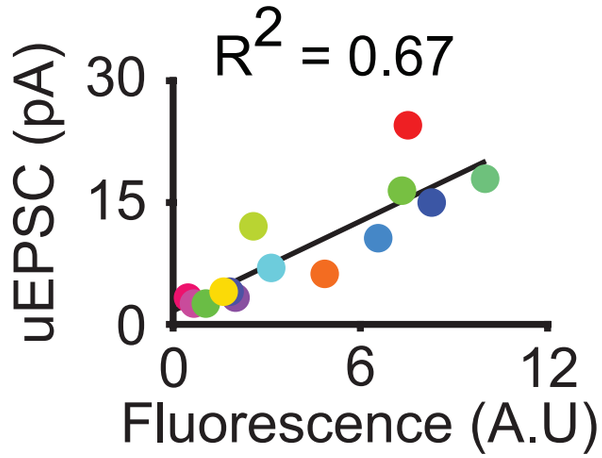
Functional Validation of PSD-95 ENABLED Strategy

Merge

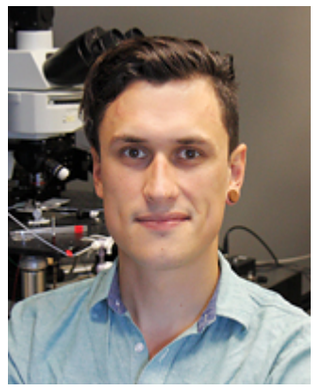
L2/3 Pyr





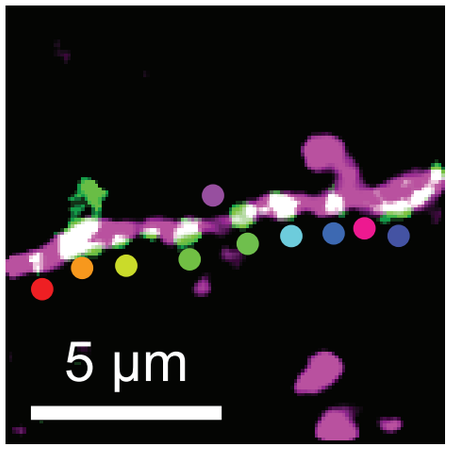


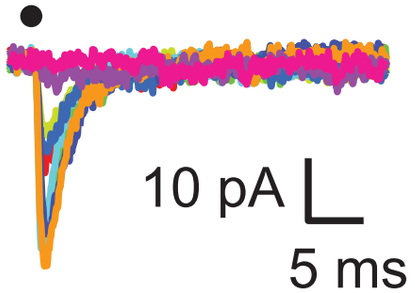
Bart Jongbloets

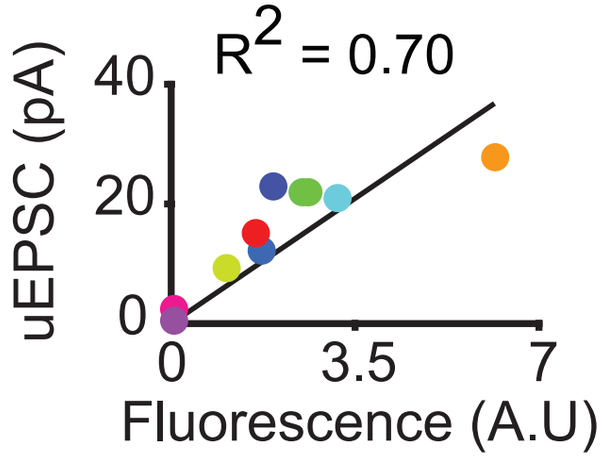


Merge

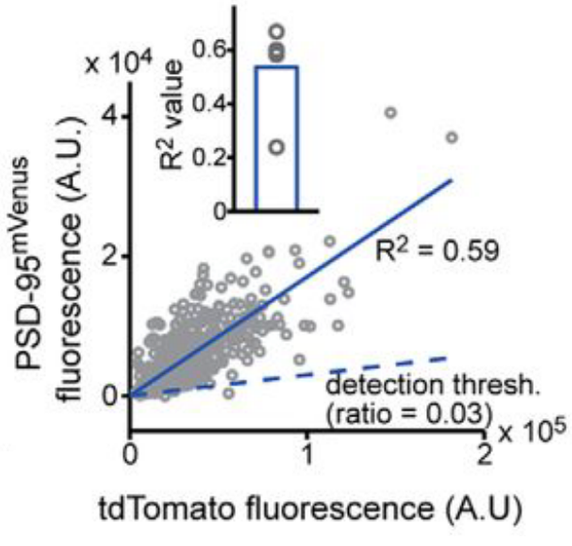
PV







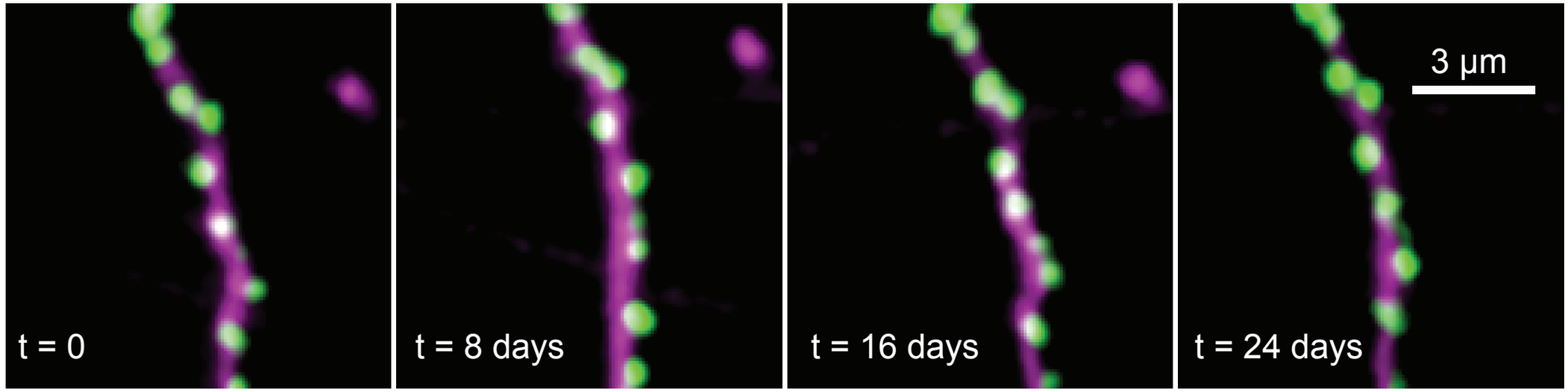
Joshua Melander



Fortin et al. 2014

In vivo Imaging of Synaptic Dynamics: Persistence, Addition, and Elimination

PV



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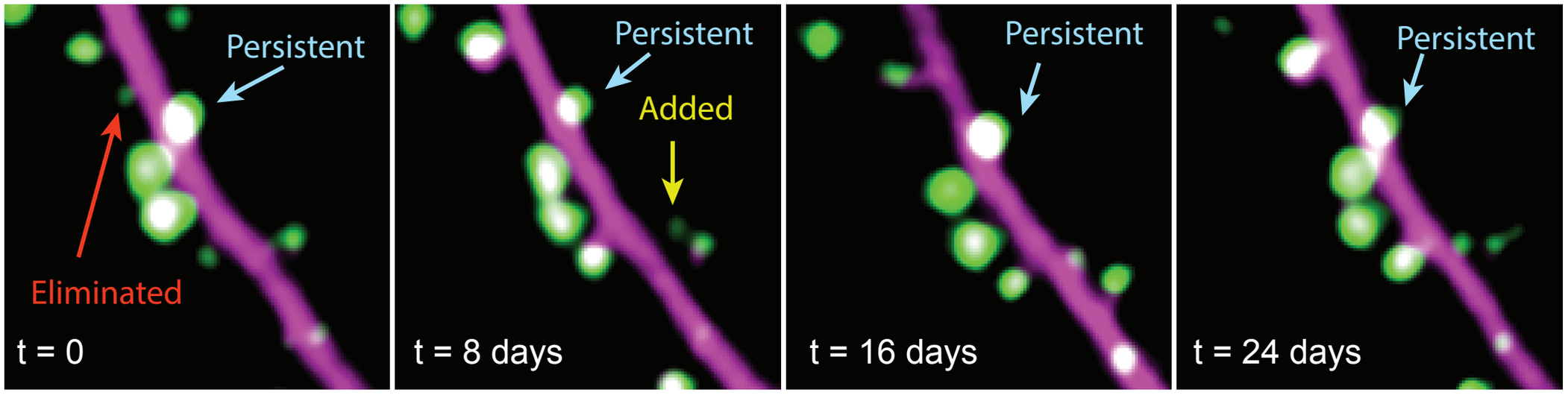
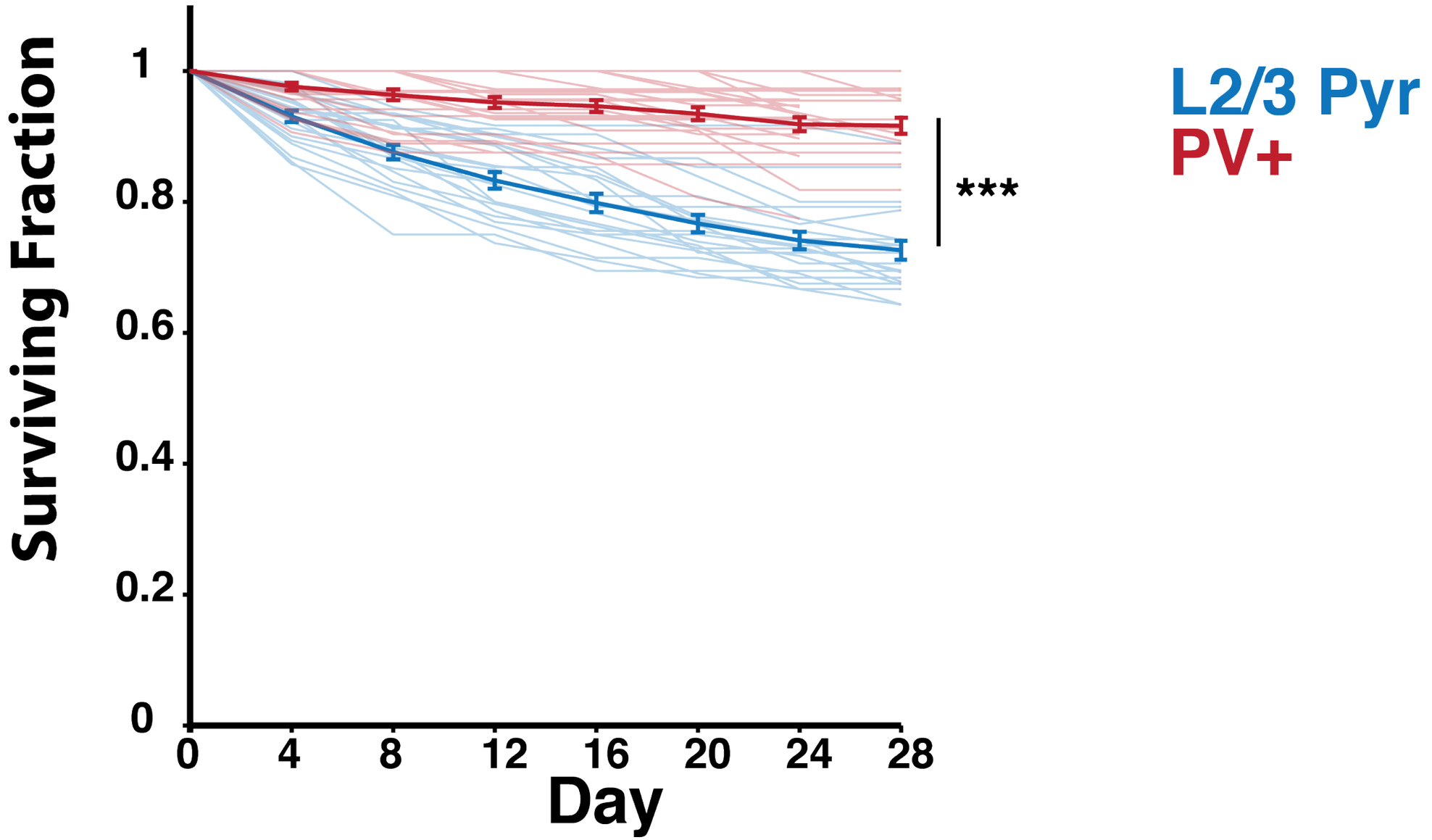
L2/3 Pyr



II. Gross Observations of Synaptic Stability

Are there any differences in excitatory synapse stability onto either excitatory or inhibitory cell types?

Excitatory Synapses onto PV Interneurons are More Stable than those onto Pyramidal Cells



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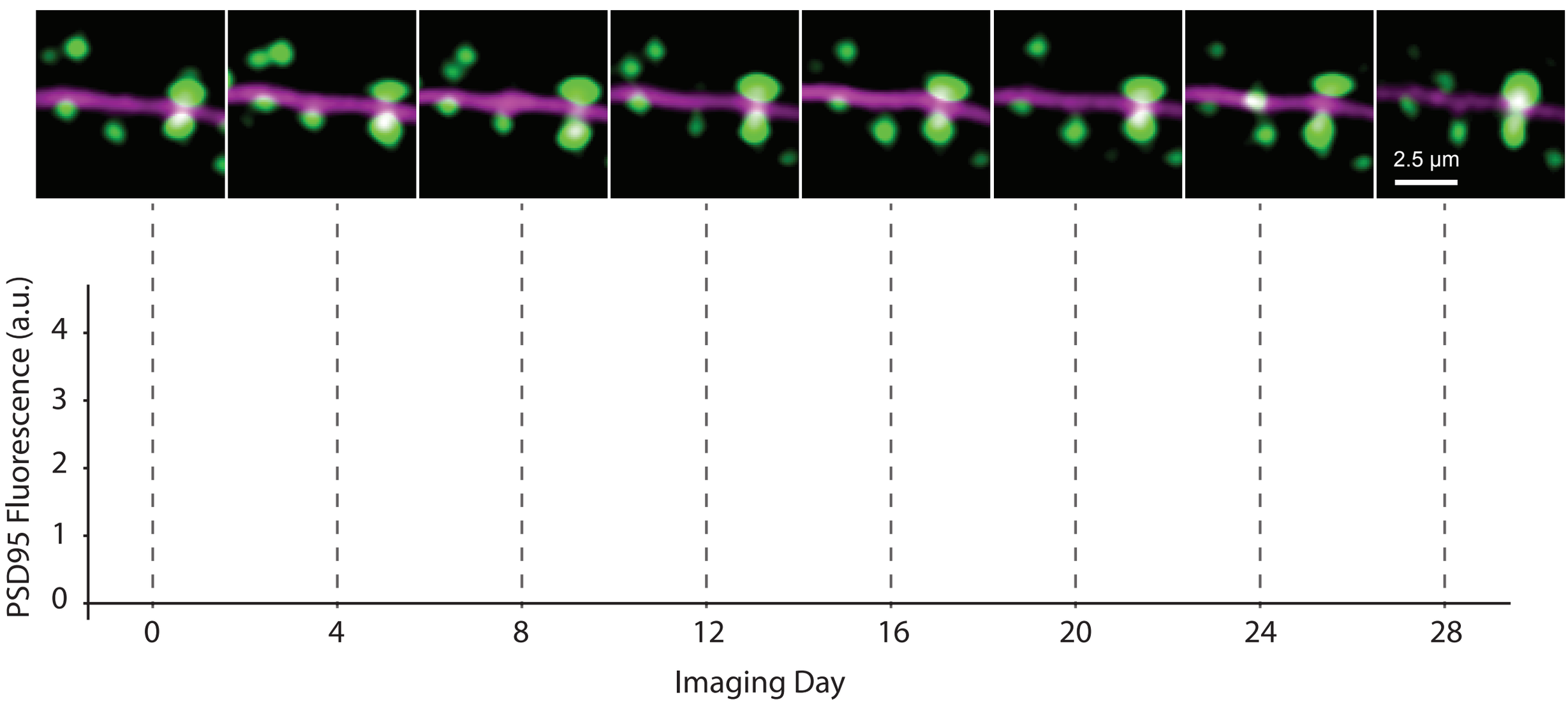
In vivo Observation of Synaptic Strength Dynamics

L2/3 Pyr



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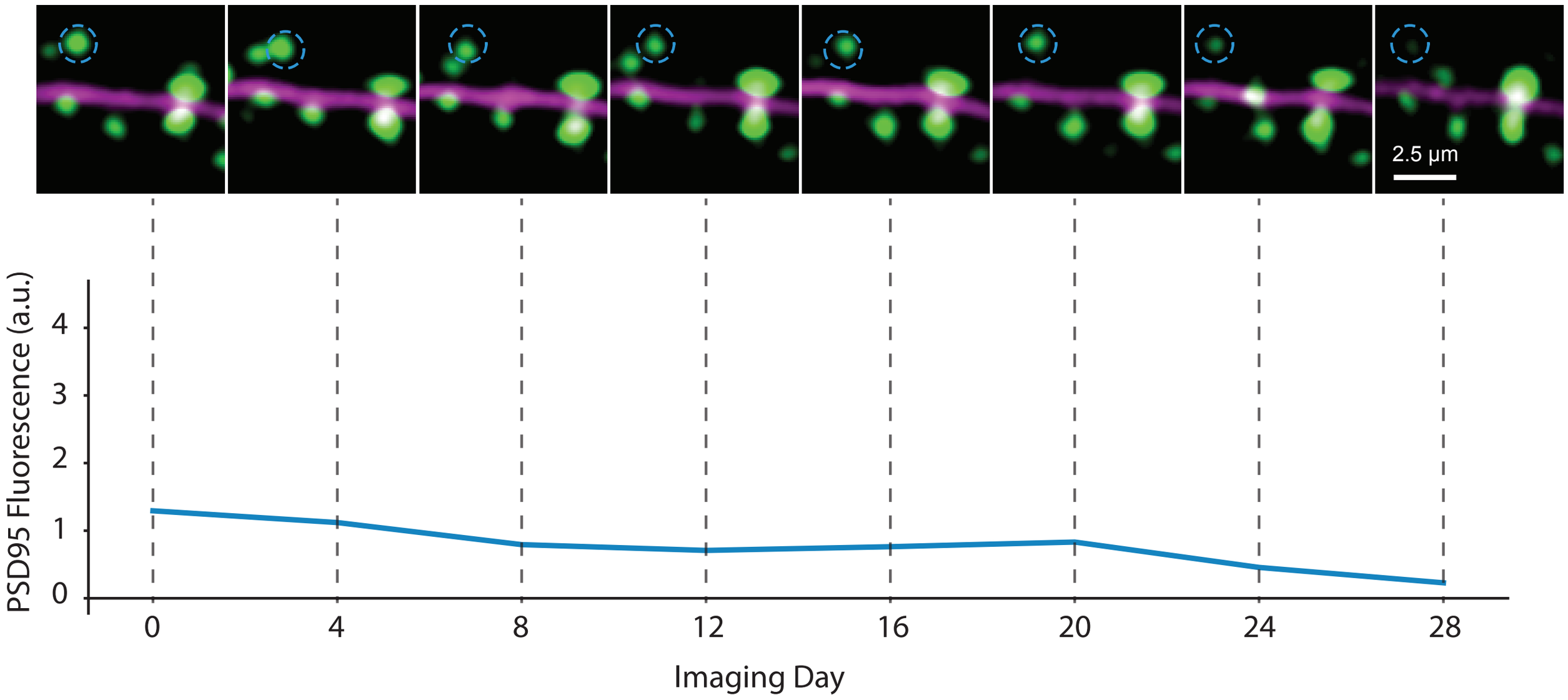

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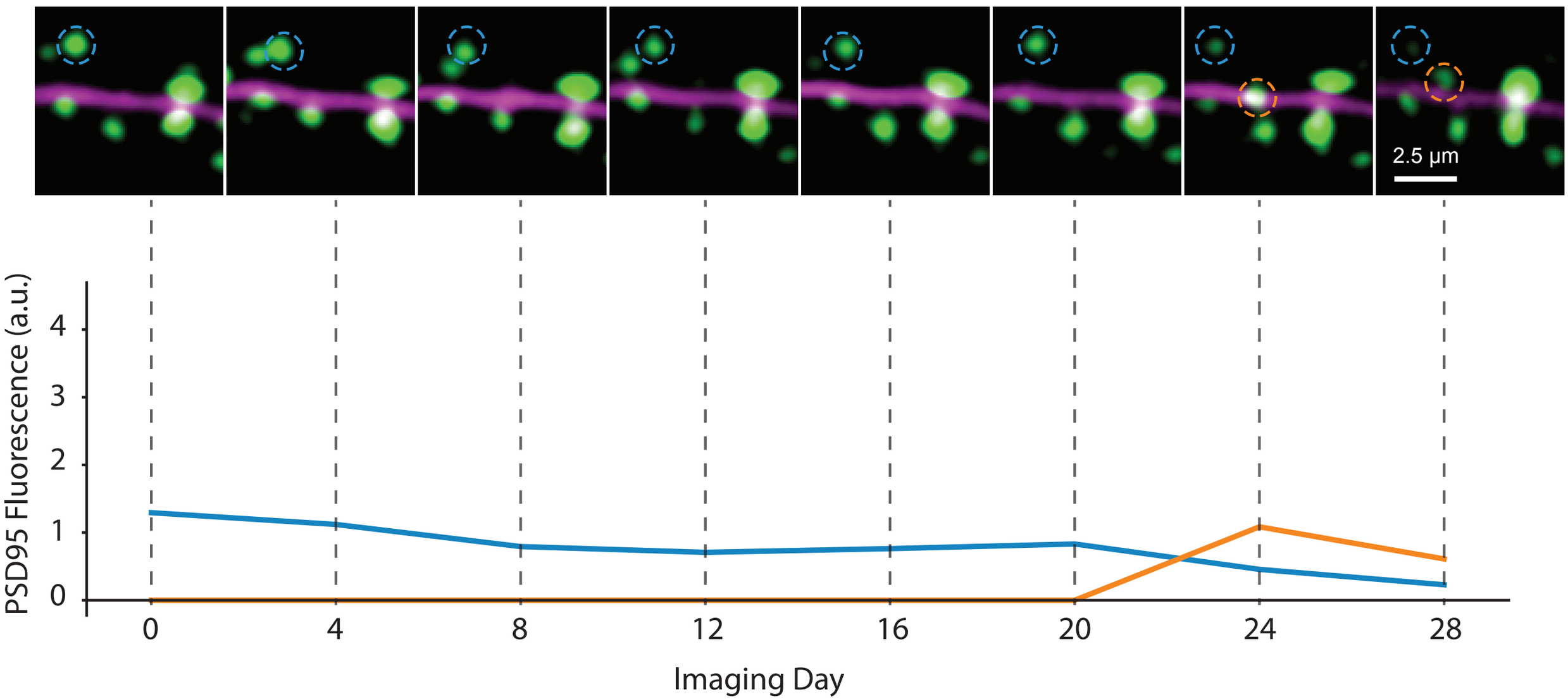
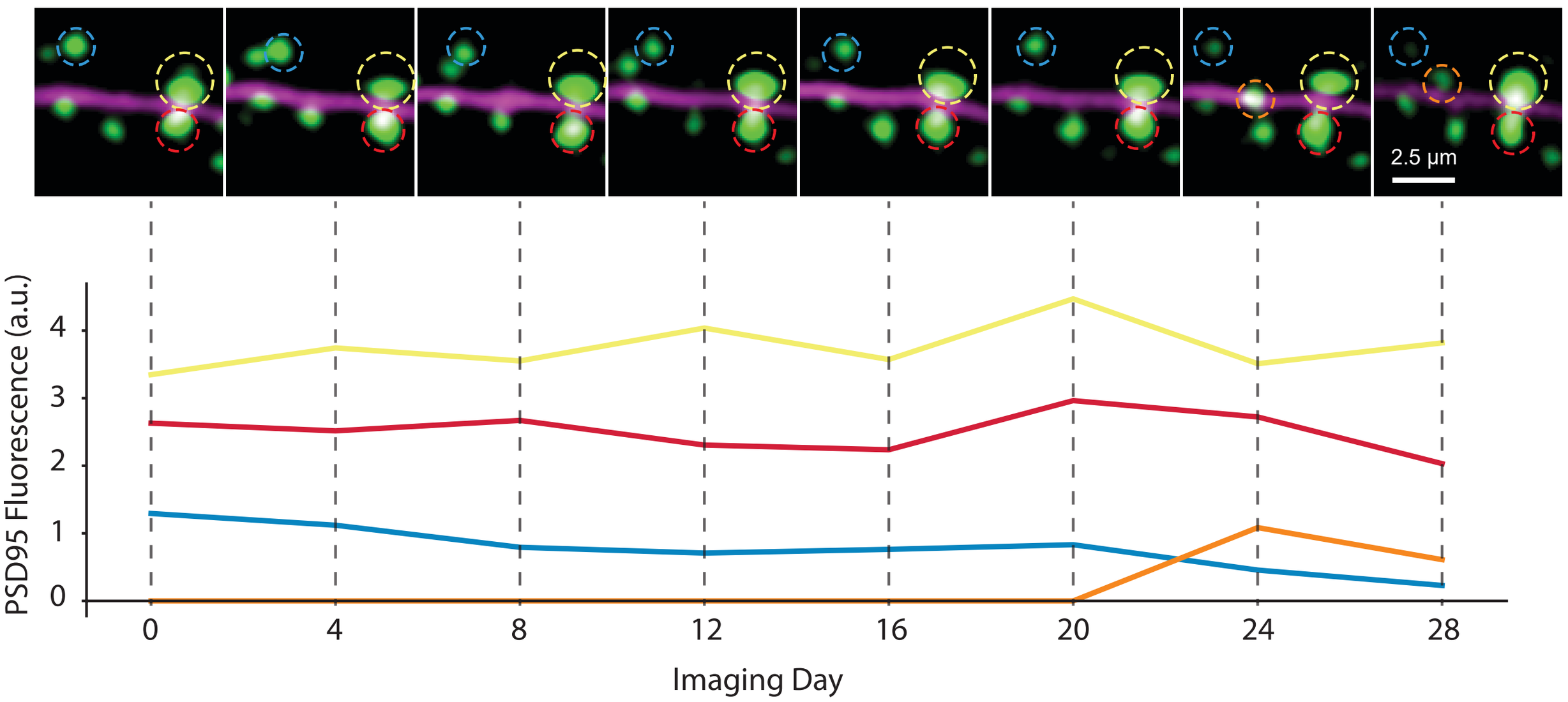


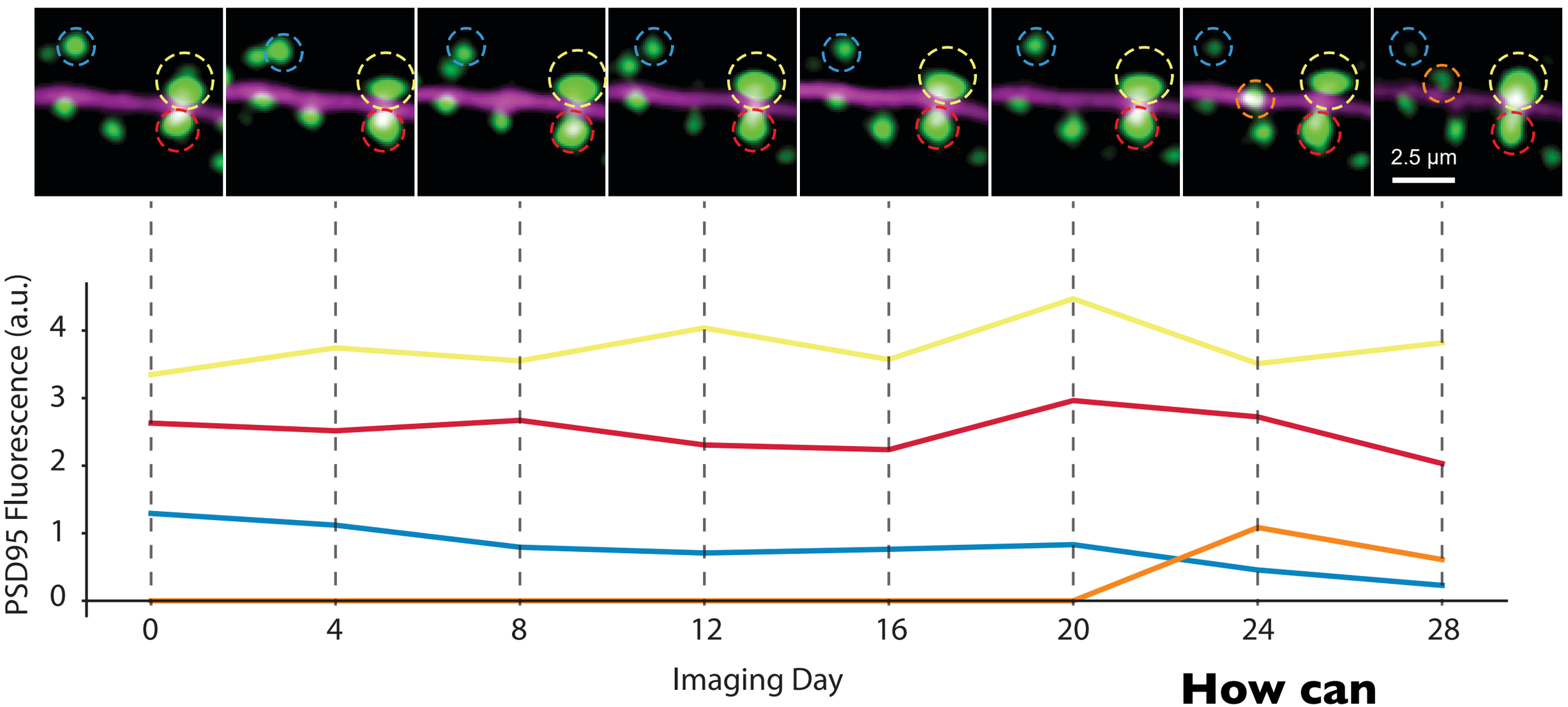
In vivo Observation of Synaptic Strength Dynamics

L2/3 Pyr



How can we quantify weight dynamics and extract biological principles?

L2/3 Pyr



How can we model the *in vivo* strength dynamics?

III. Modeling Framework for Synaptic Dynamics

Can we build a model to elucidate these dynamics across cell types?

Are the dynamics additive or multiplicative?

Are they time-reversible?

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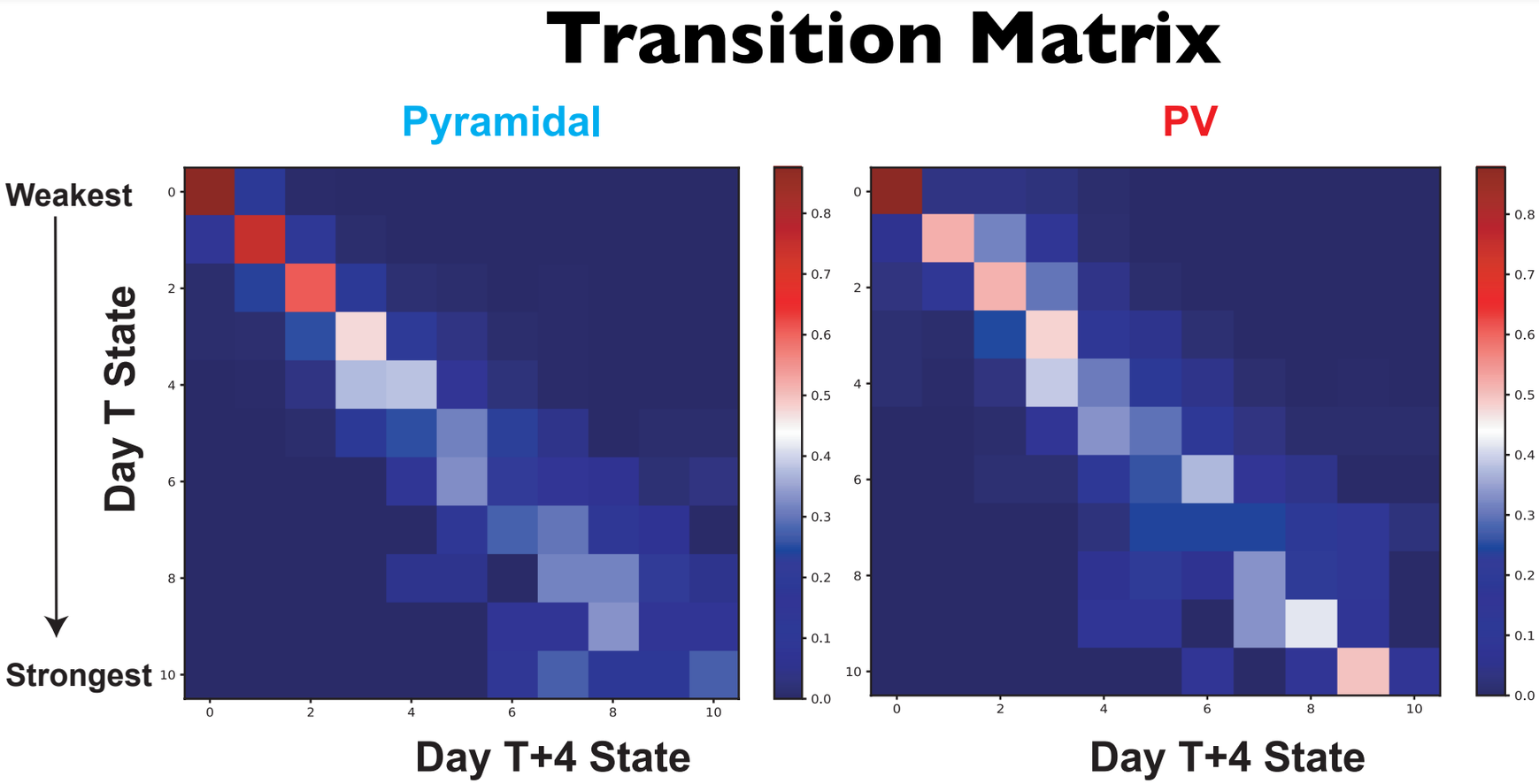
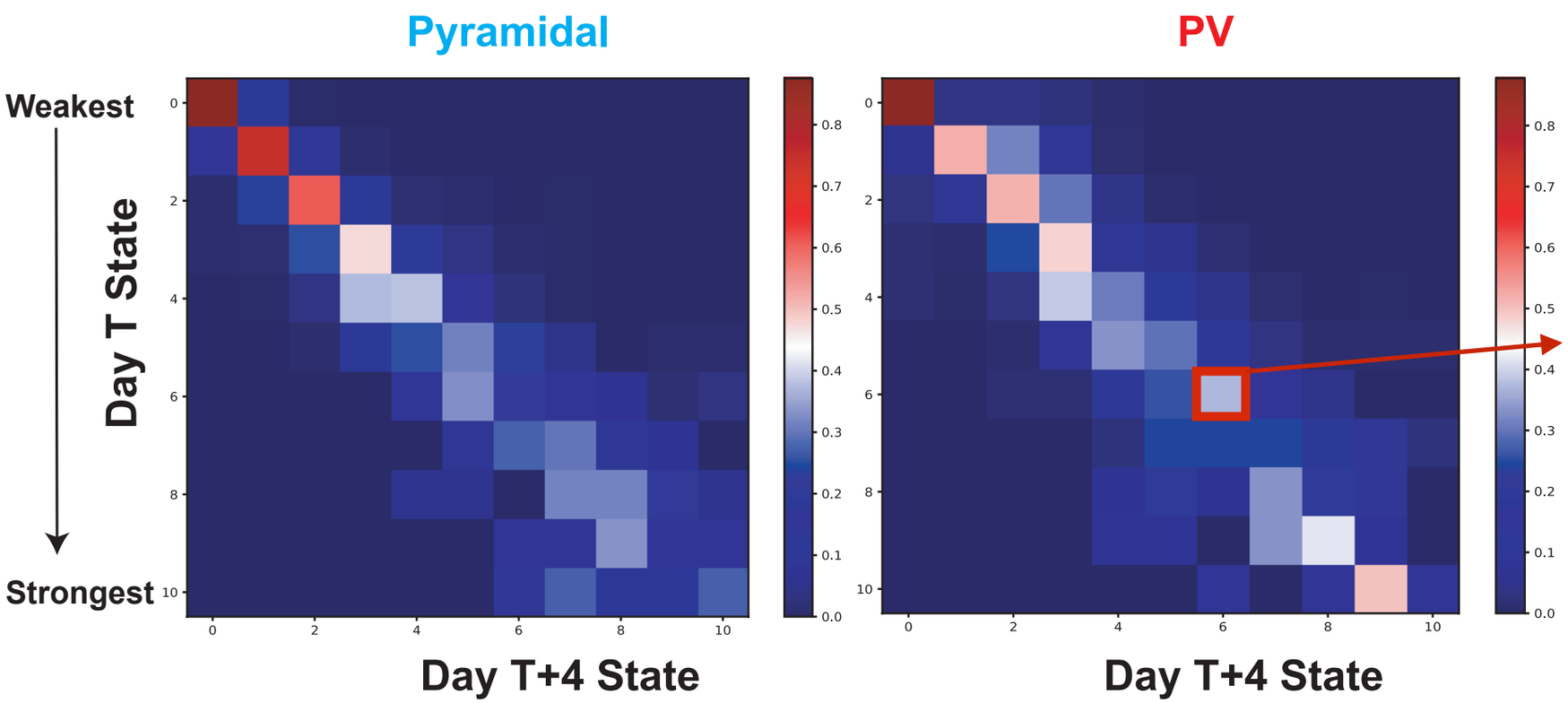
Markov Chain Model of Single Synapse Dynamics



Markov Chain Model of Single Synapse Dynamics

Transition Matrix

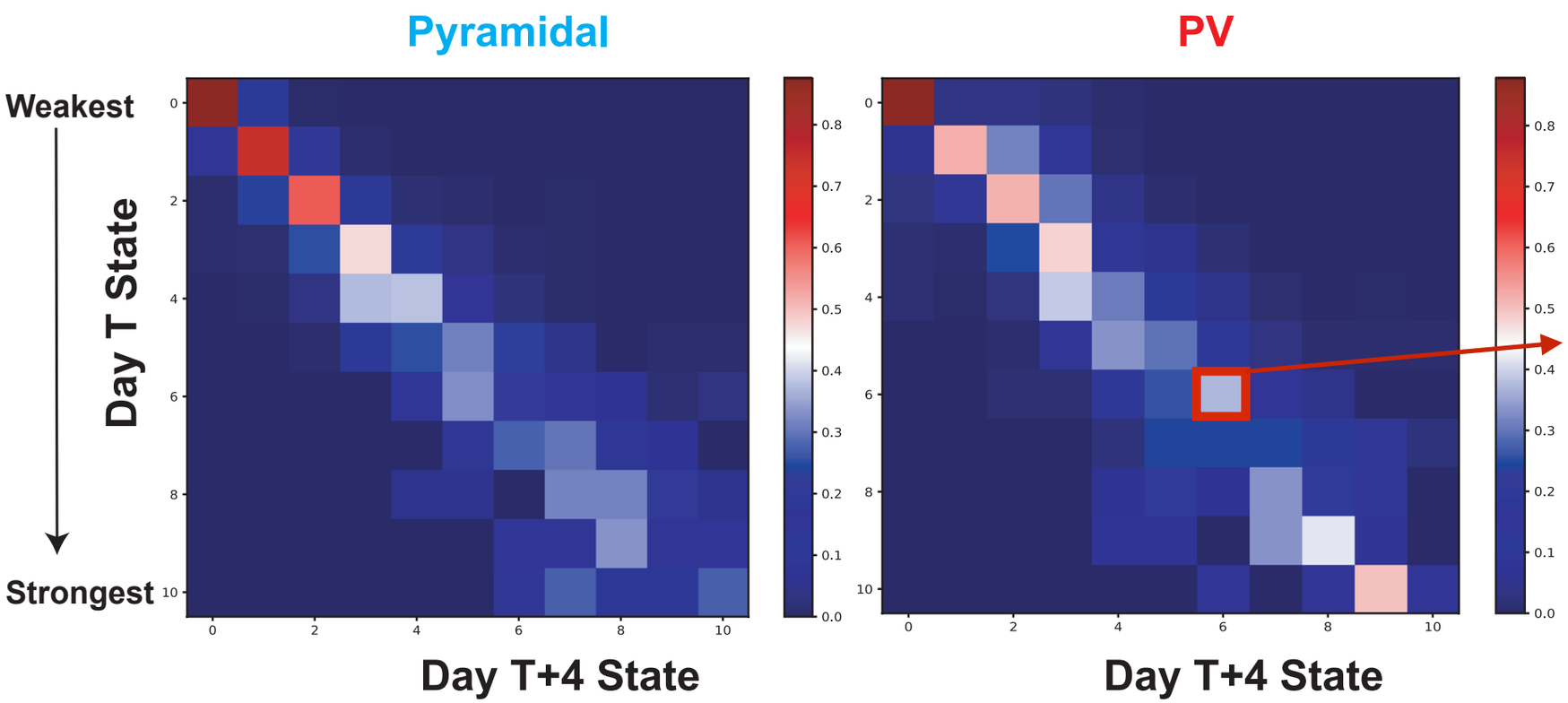


$$M_{i,j} = \mathbb{P}(w(T+4) = j \mid w(T) = i)$$

$$M\vec{s}_T = \vec{s}_{T+4}$$

Markov Chain Model of Single Synapse Dynamics

Transition Matrix

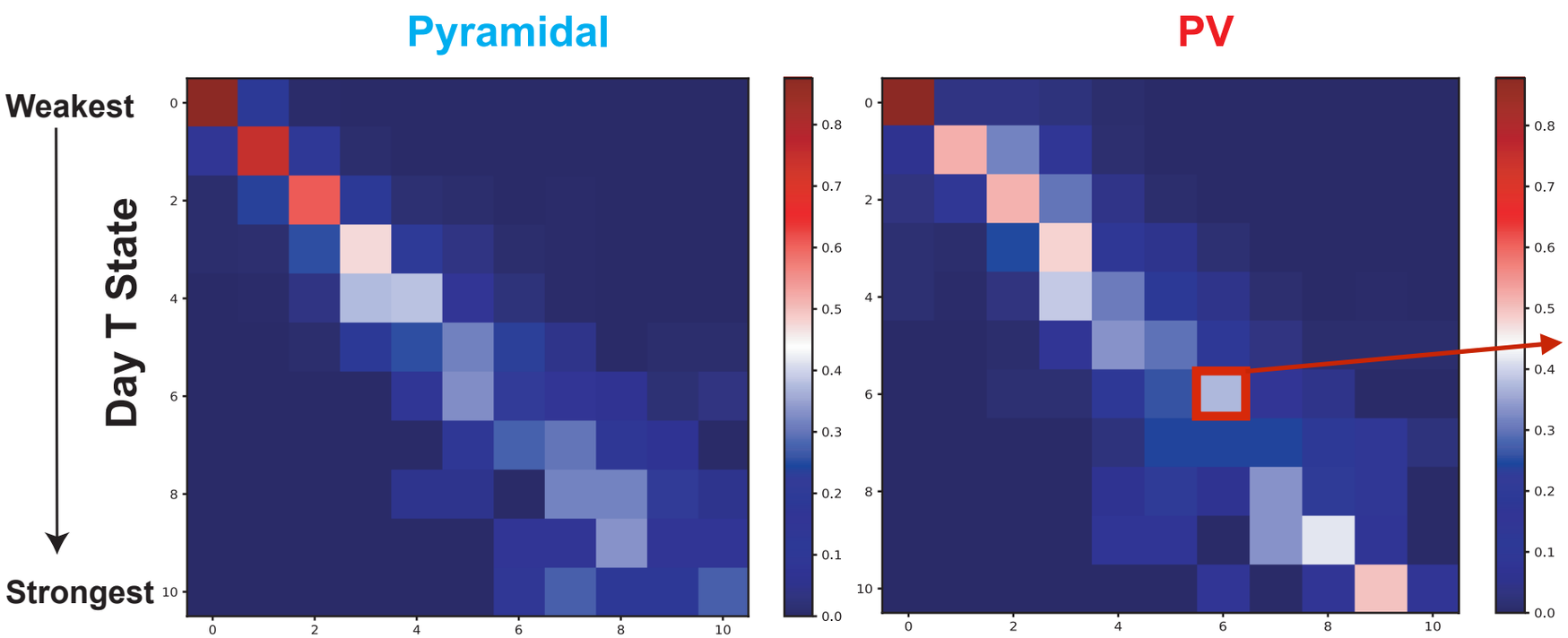


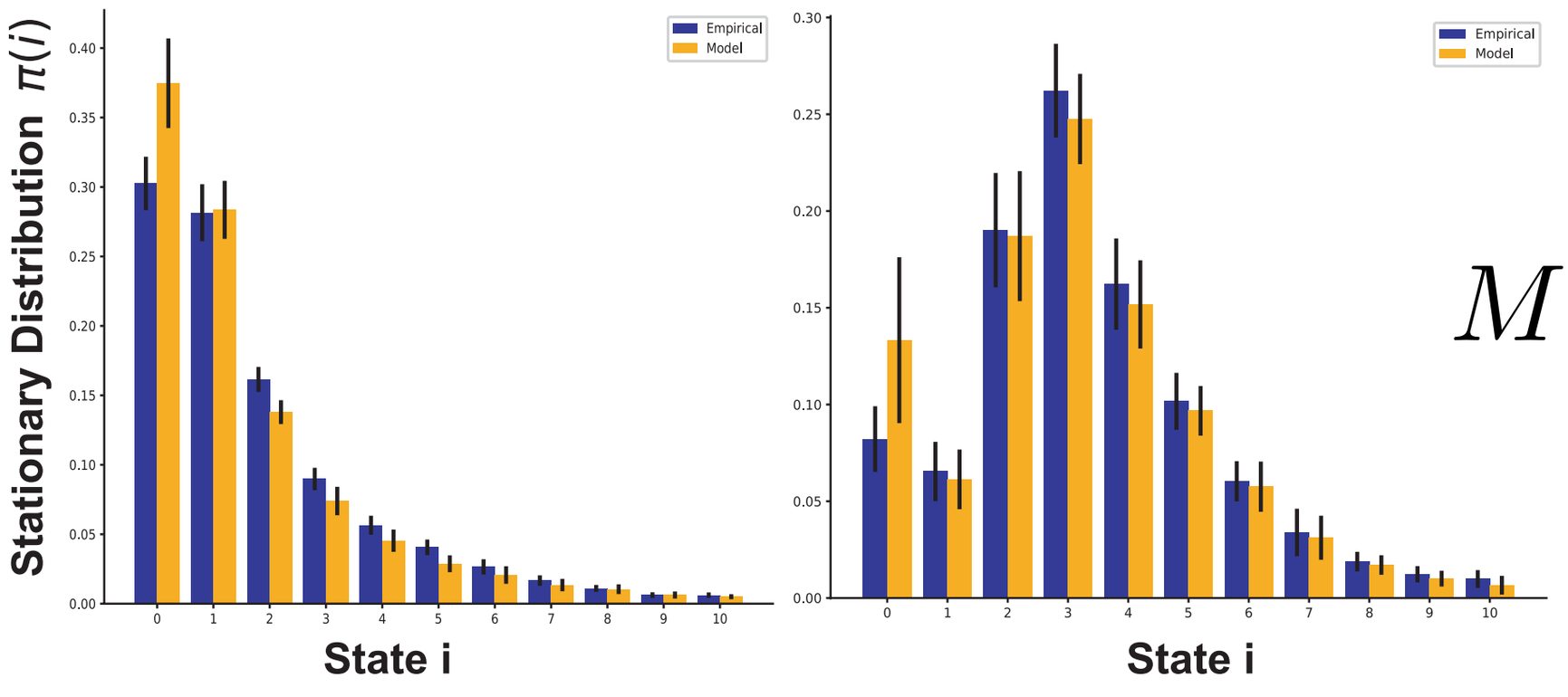
$$M\vec{s}_T = \vec{s}_{T+4}$$

How well can these Markov chains predict synaptic distributions over very long time scales?

Markov Models Accurately Predict Stationary Strength Distributions

Transition Matrix





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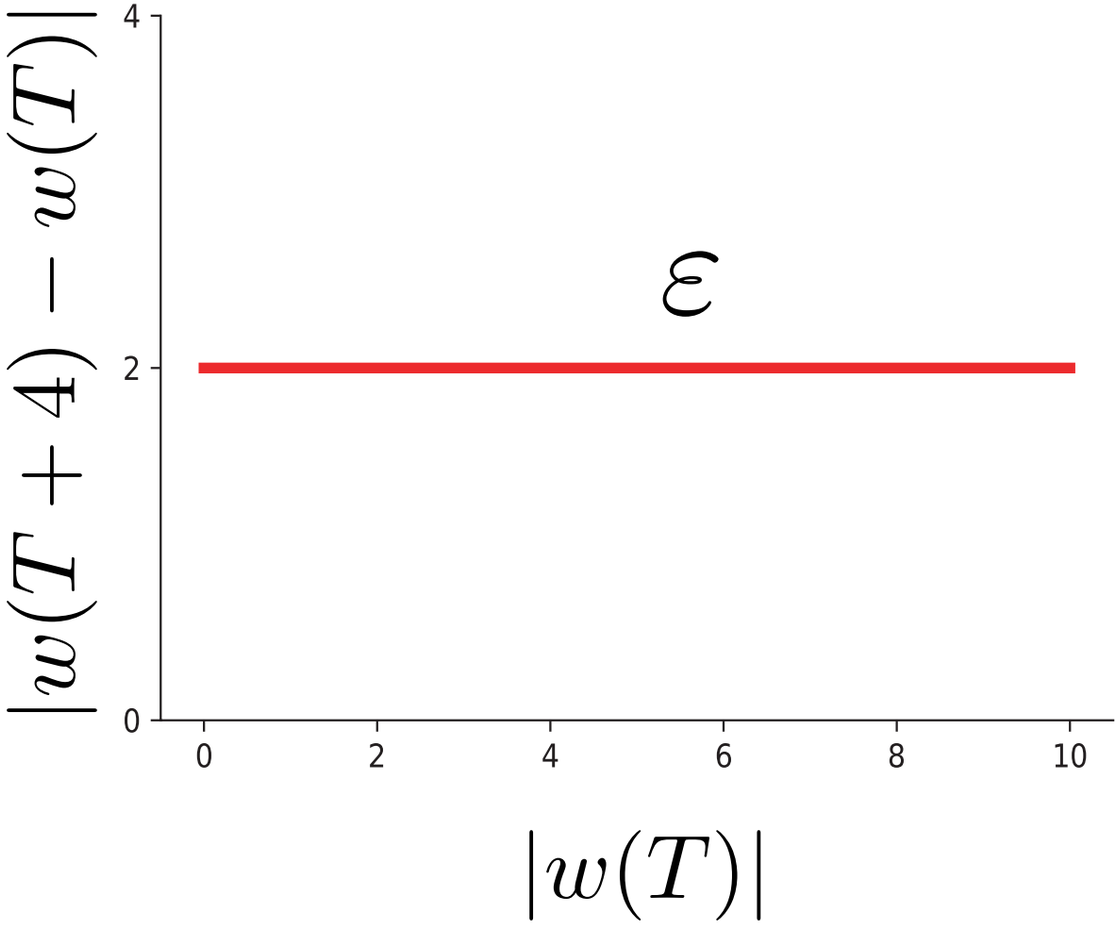
Additive versus Multiplicative Strength Dynamics?

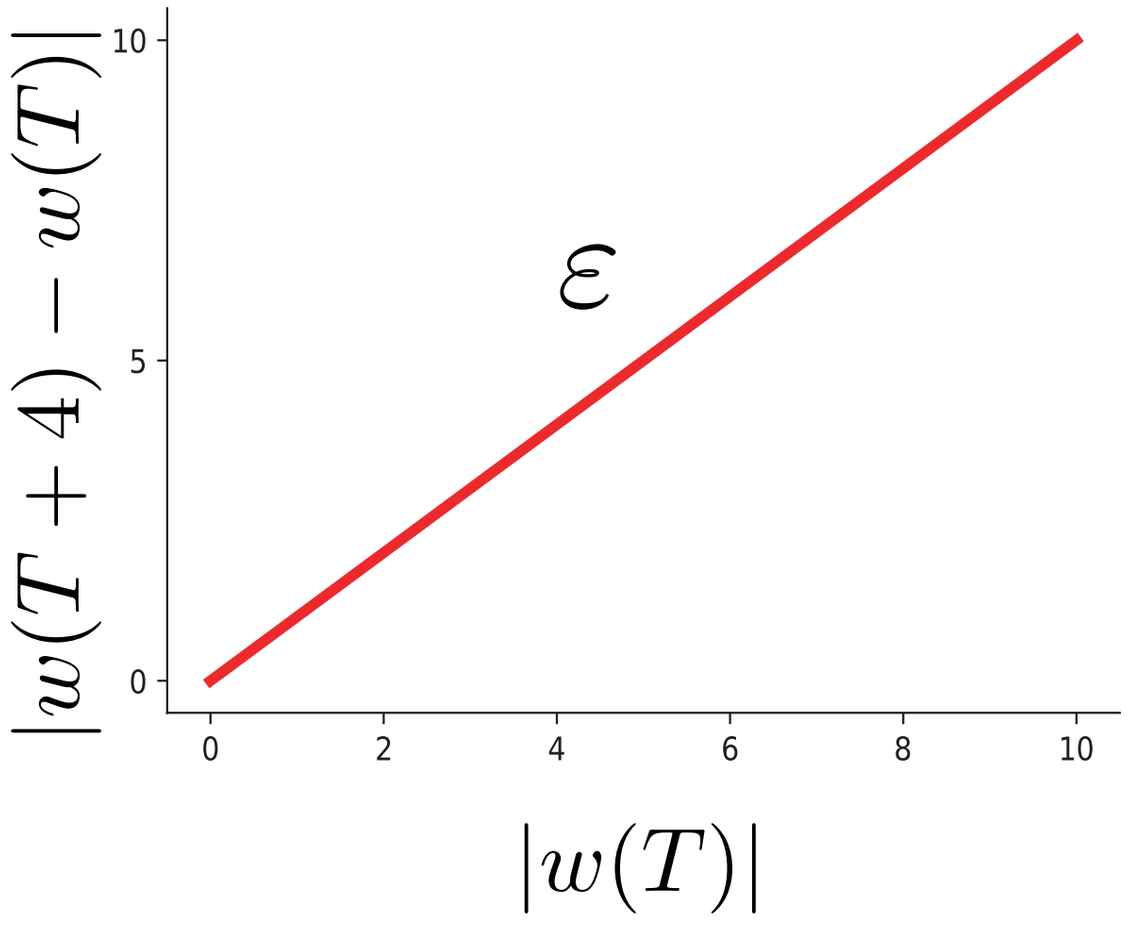
Weight Changes Under Additive Dynamics

$$w(T+4) = w(T) + \varepsilon$$



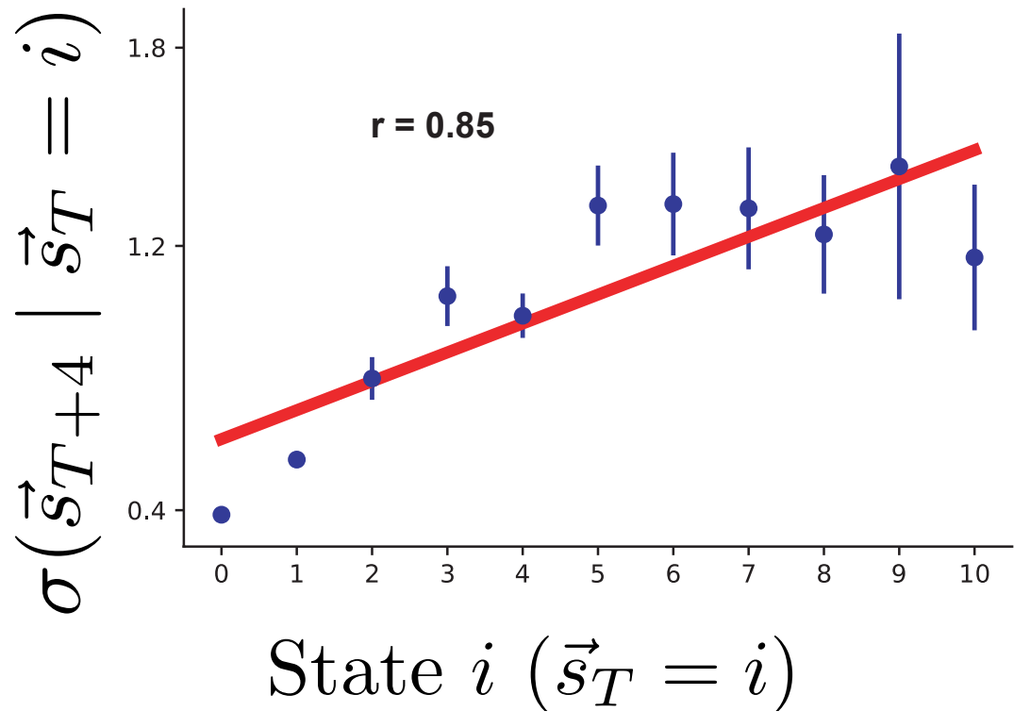
Weight Changes Under Multiplicative Dynamics

$$w(T+4) = w(T) \cdot (1+\varepsilon)$$

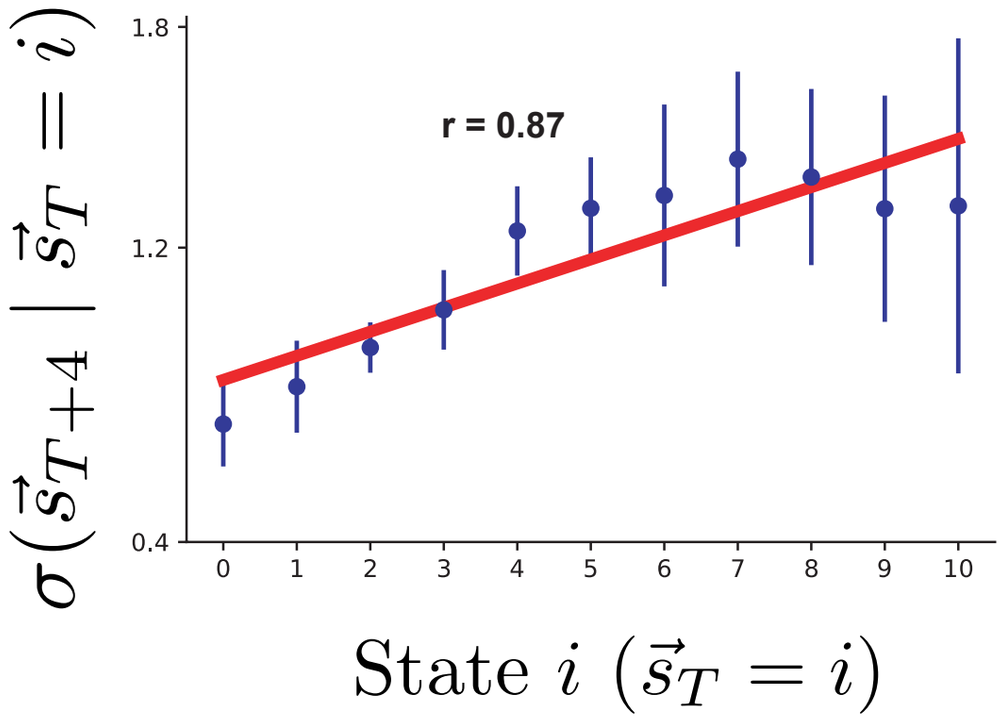


Evidence of Multiplicative Dynamics Across Cell Types

Pyramidal $w(T+4) = w(T) \cdot (1+\varepsilon)$ **PV**



Markov Chain Conditional Standard Deviation



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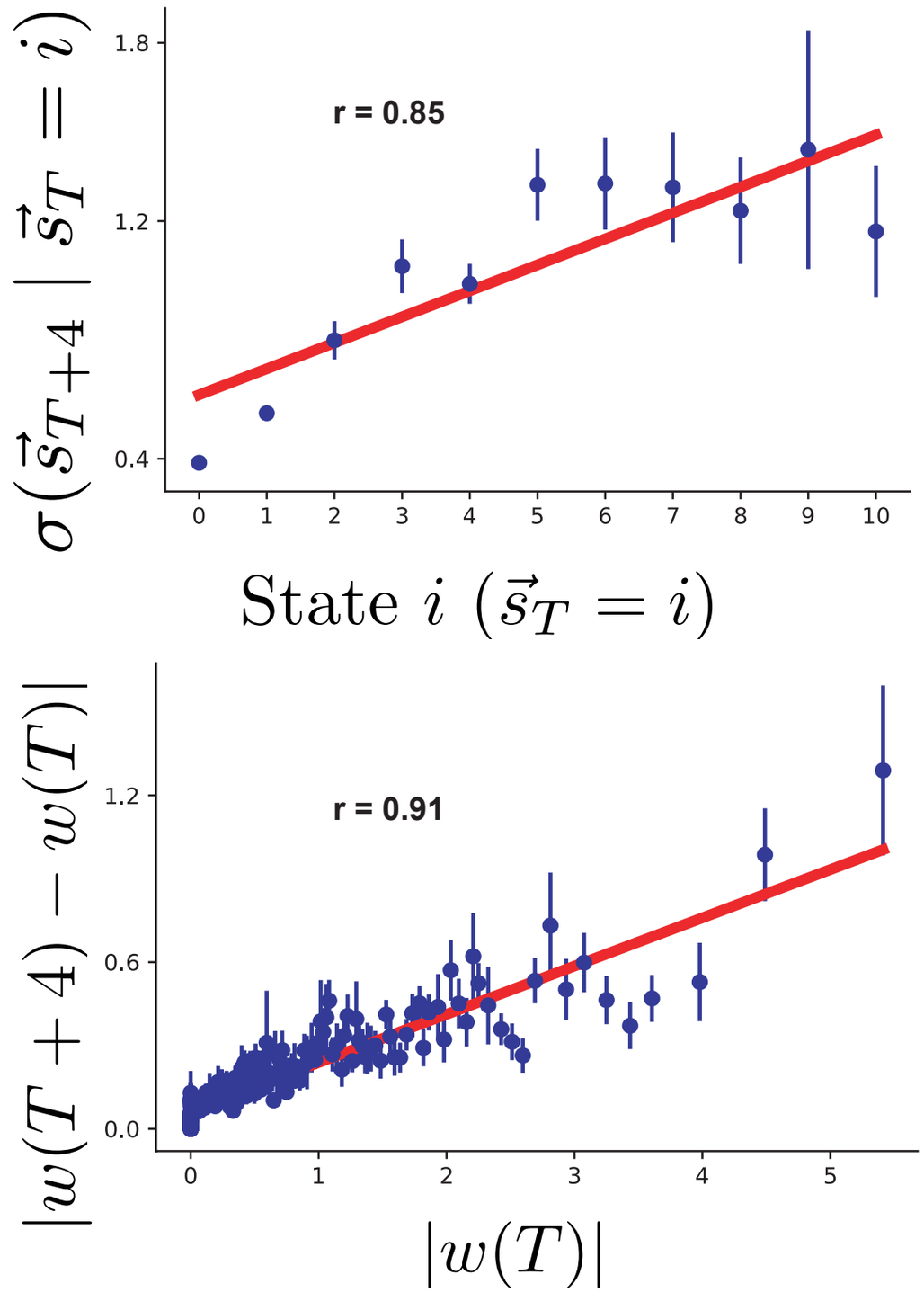
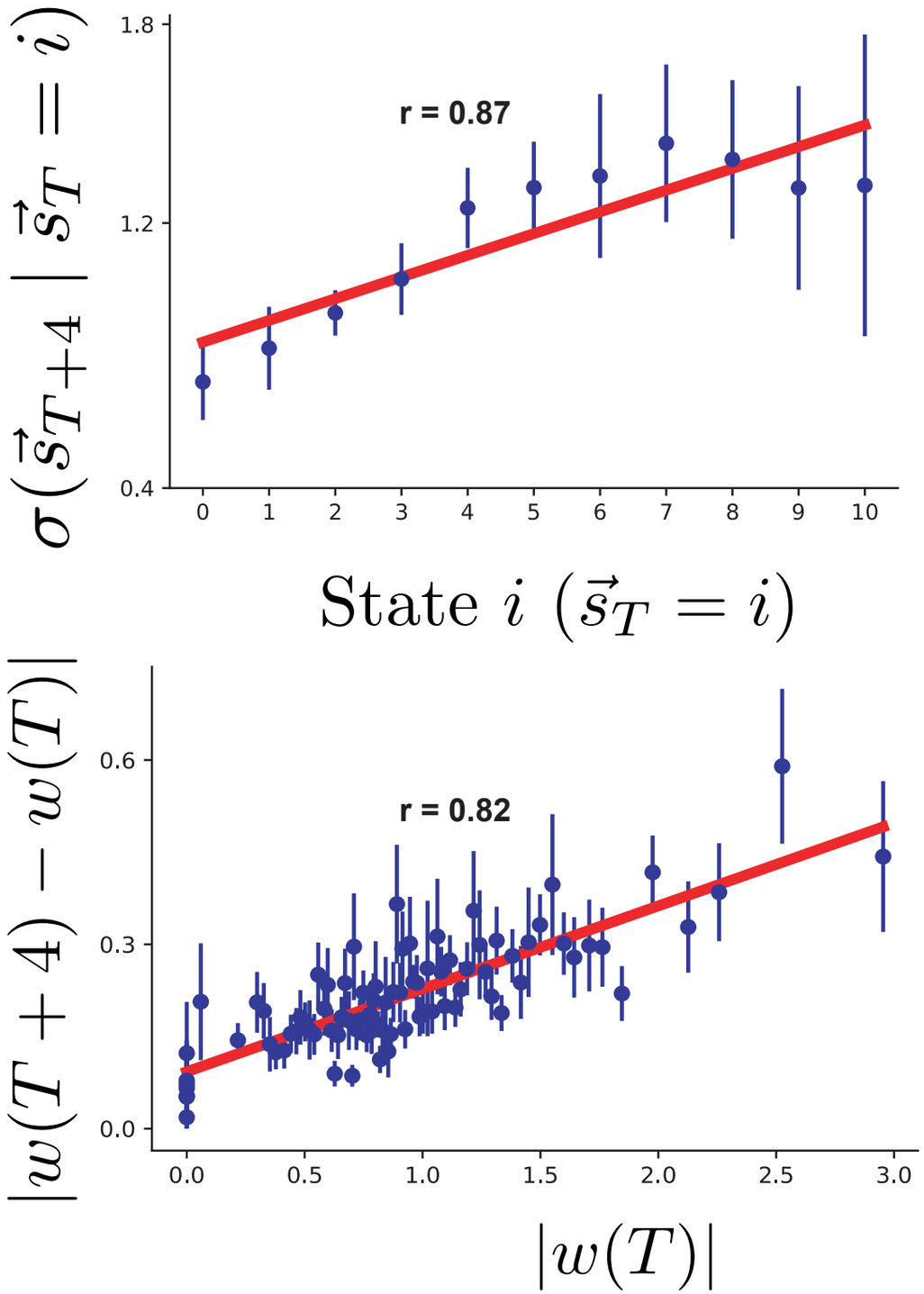


Markov Chain Conditional Standard Deviation

Binned Strength Changes



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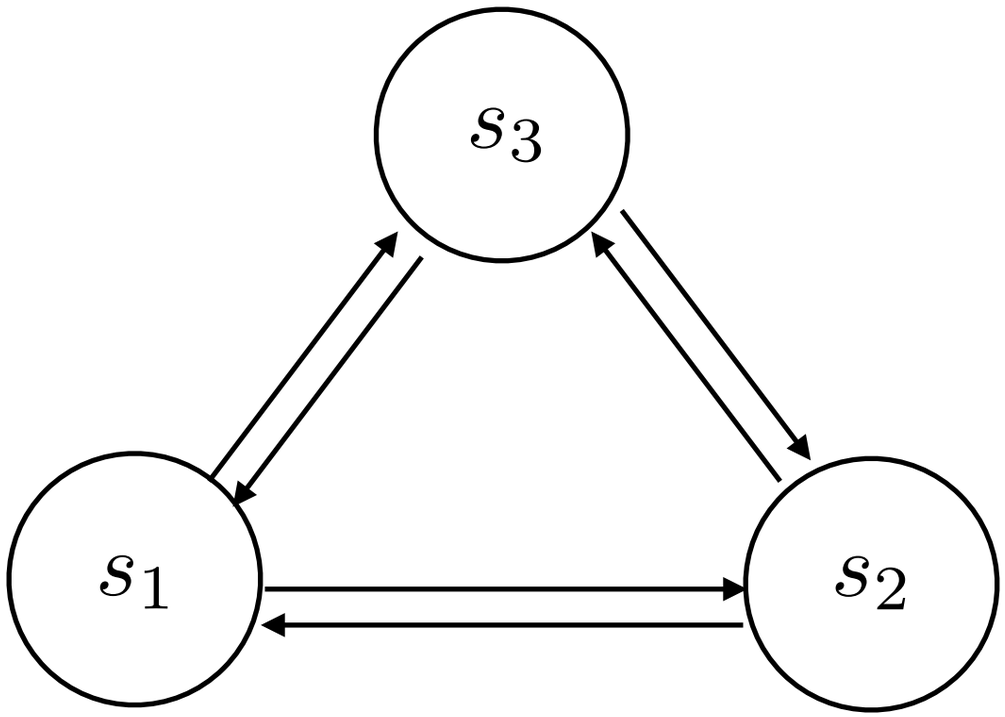
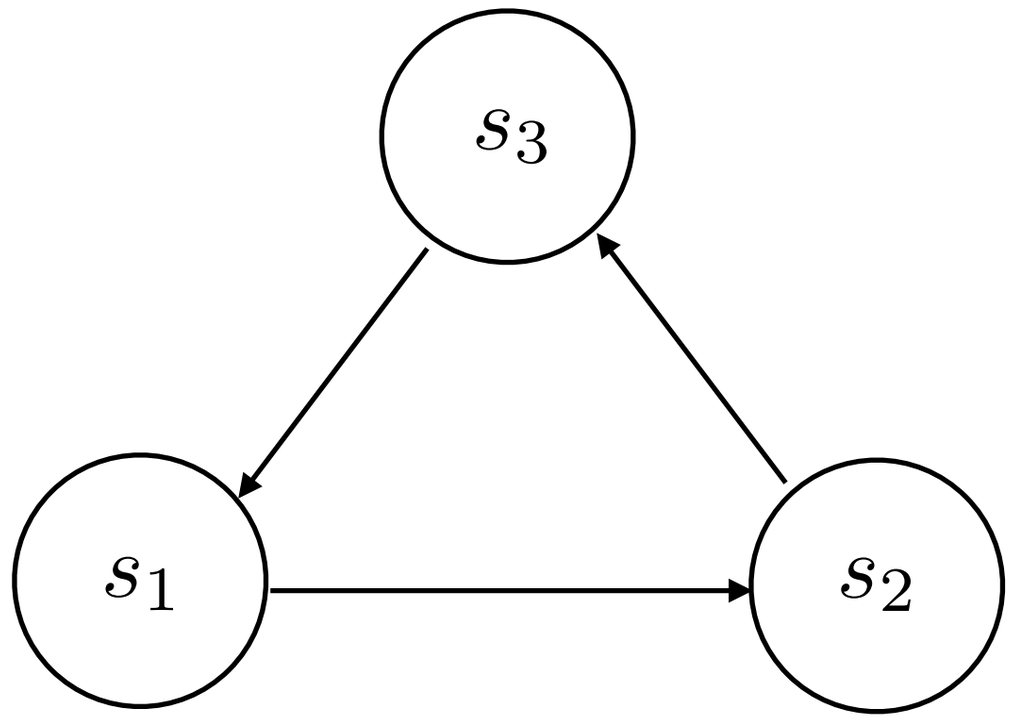
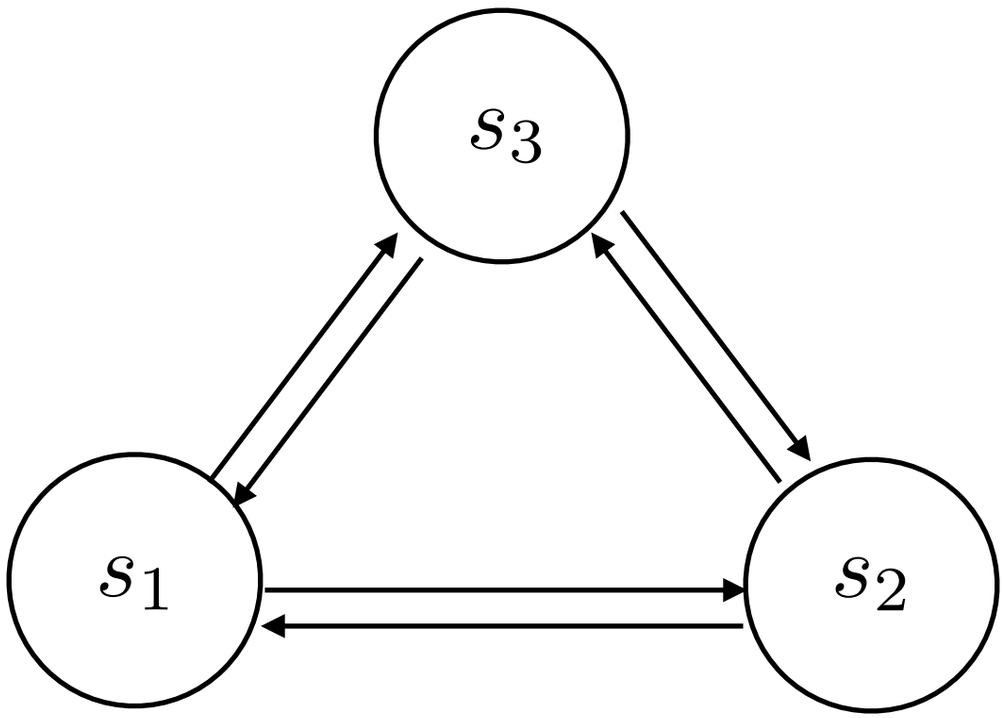
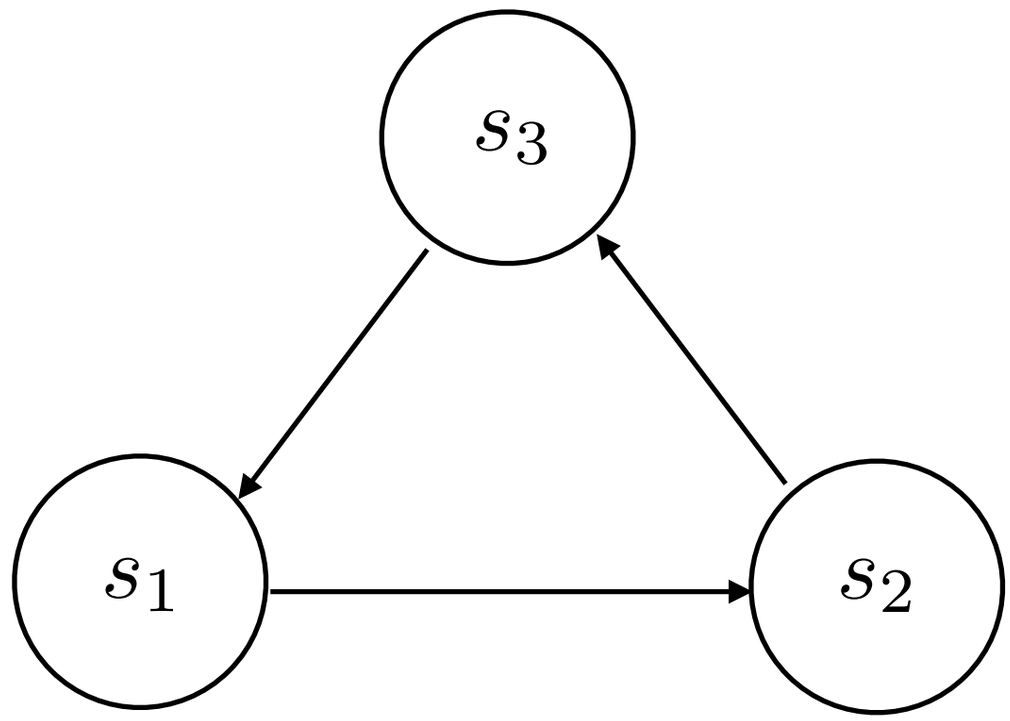
Are Synaptic Dynamics Time-Reversible?





Are Synaptic Dynamics Time-Reversible?

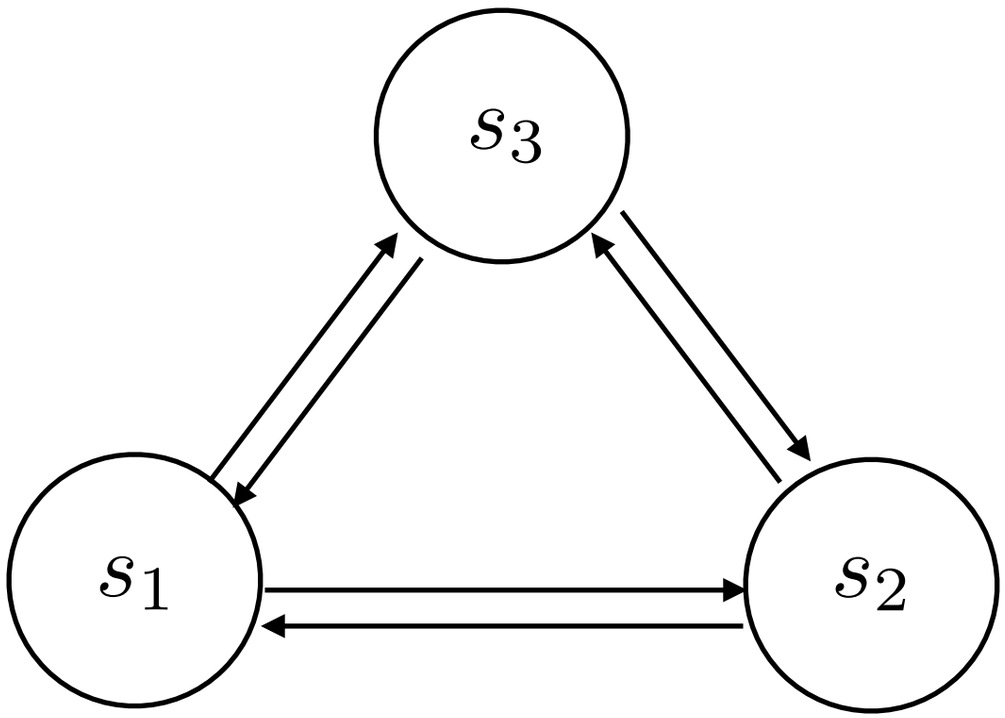




Detailed Balance:
Zero Net Flow

$$p(j \mid i)\pi(i) = p(i \mid j)\pi(j)$$

Are Synaptic Dynamics Time-Reversible?



Detailed Balance: Zero Net Flow

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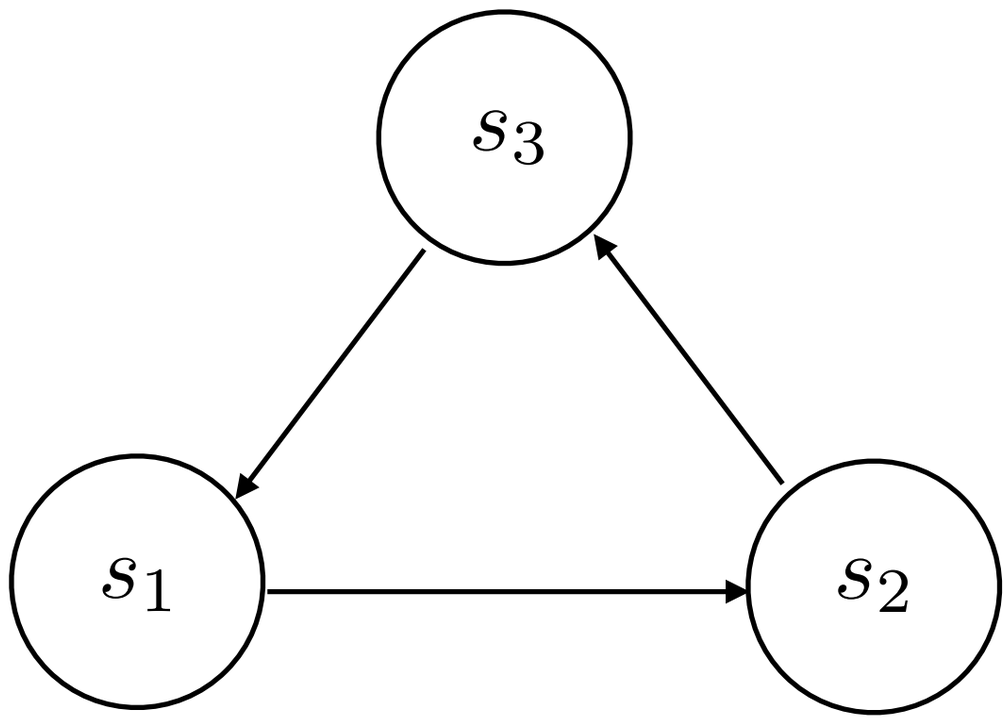
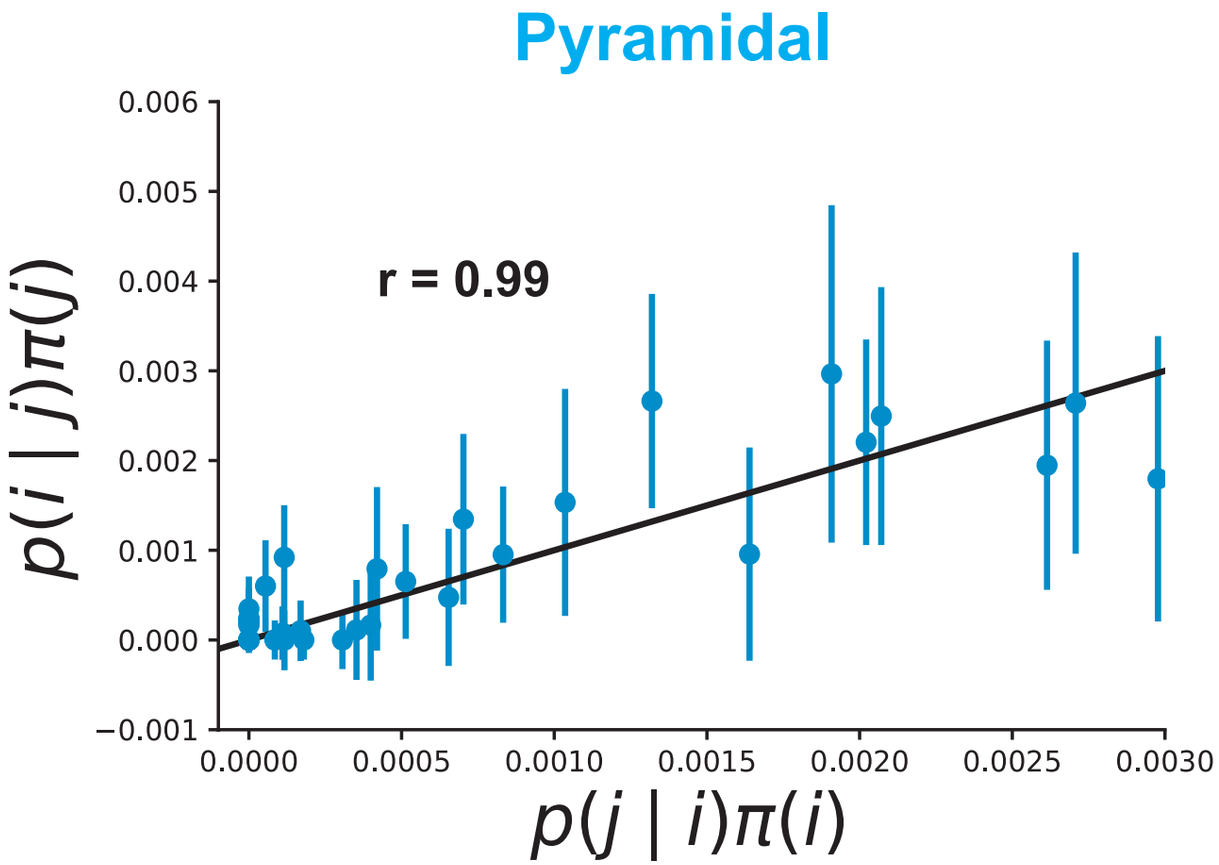
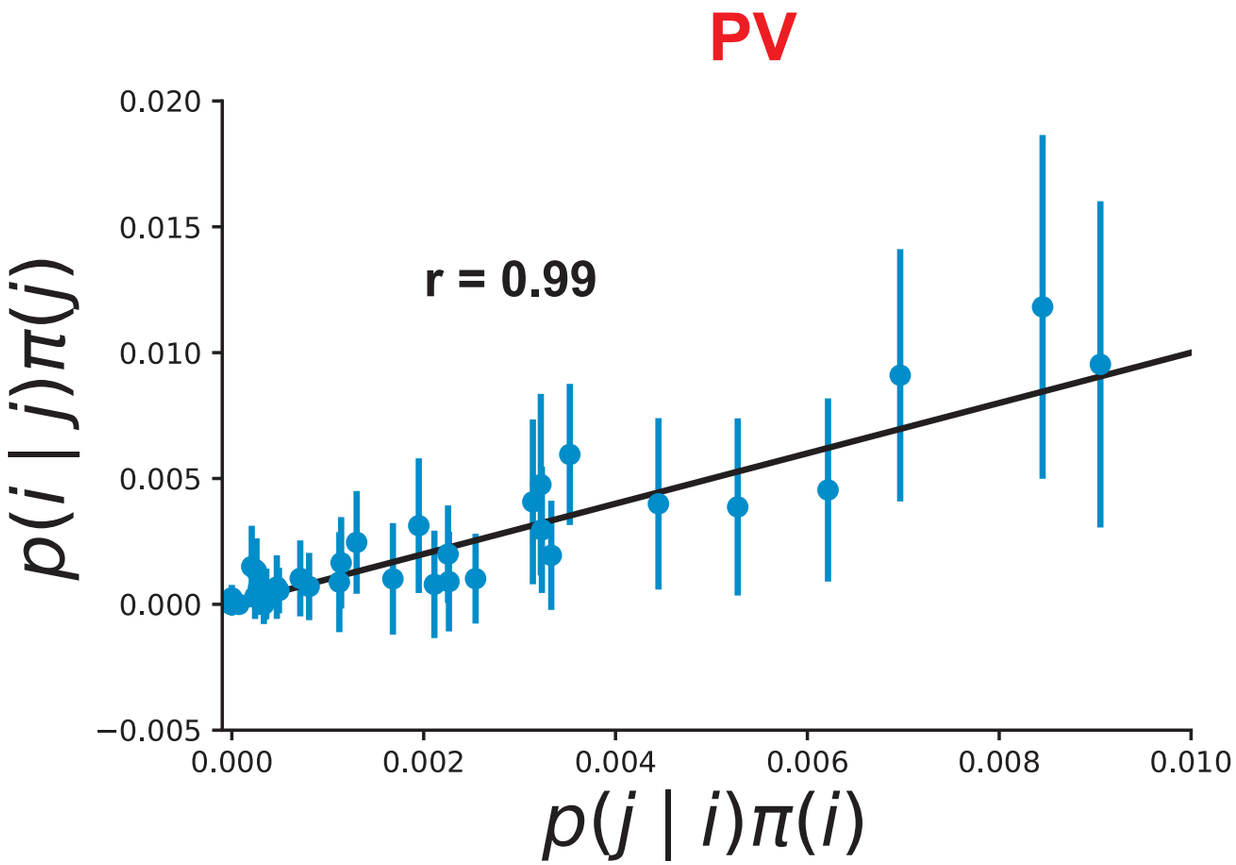


Nonzero Net Flow

$$p(j \mid i)\pi(i) \neq p(i \mid j)\pi(j)$$

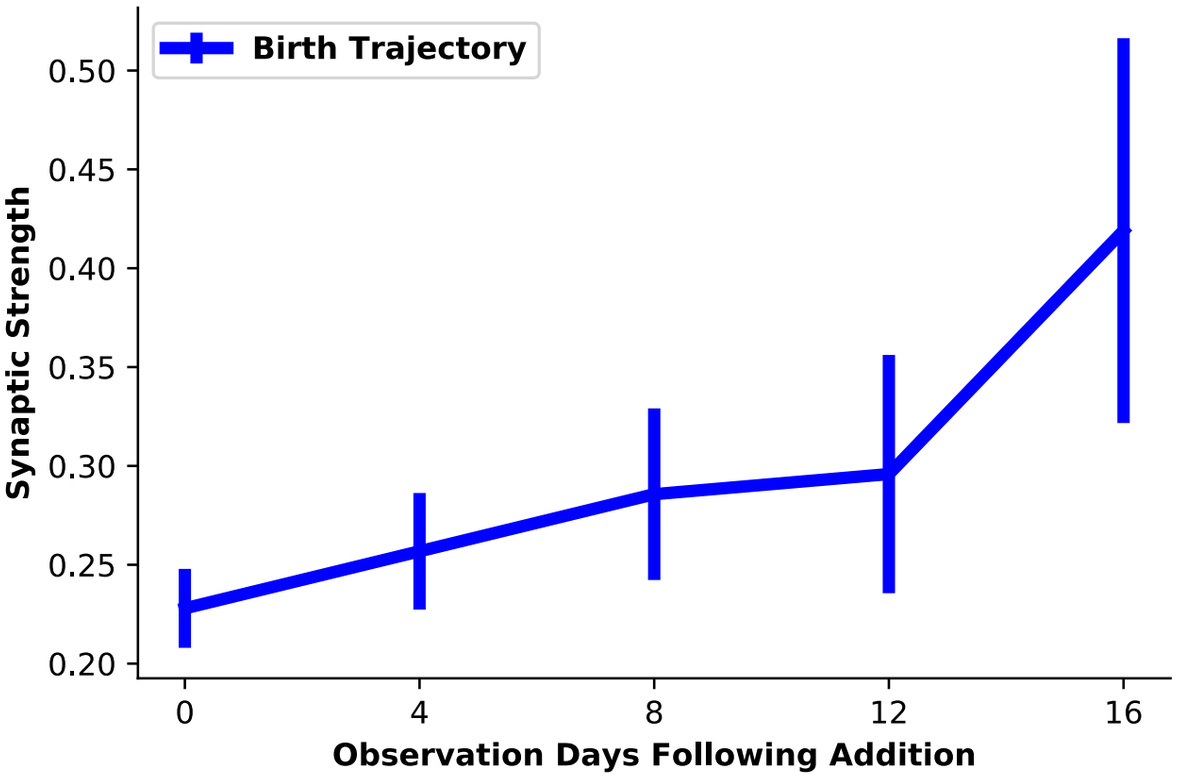
Synaptic Dynamics is Time-Reversible



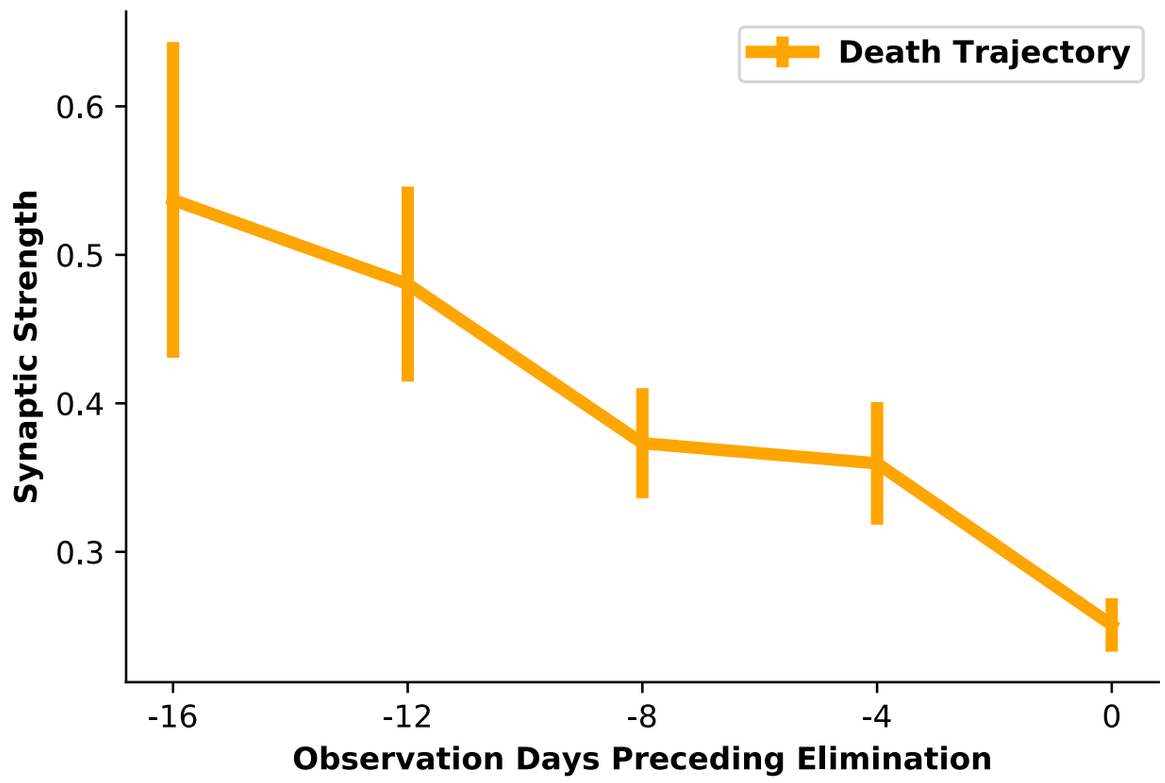


"The Path to Death is the Reverse of the Path from Birth"

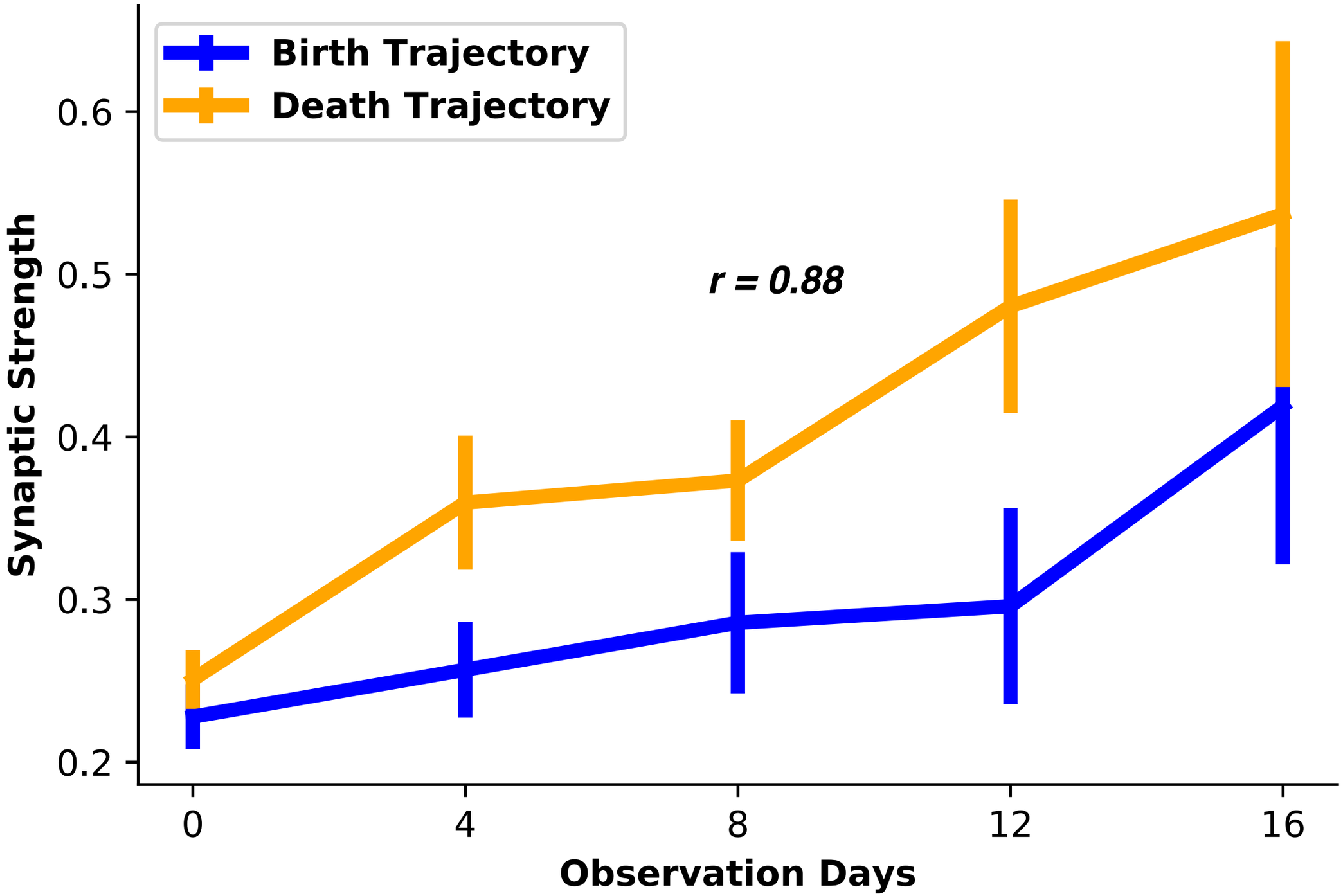
Synaptic weight following addition



Synaptic weight preceding elimination



Birth and Death Weight Symmetry



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4. The future: comparing this baseline synaptic dynamics to the process of synaptic change during task learning

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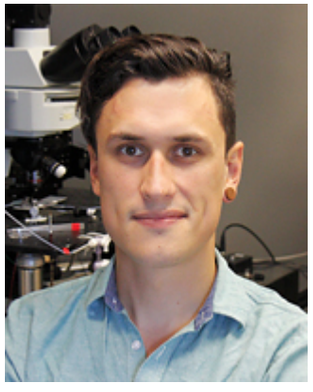
OHSU



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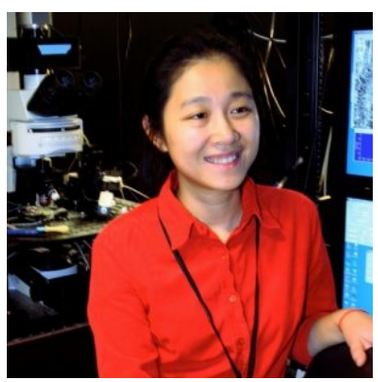

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