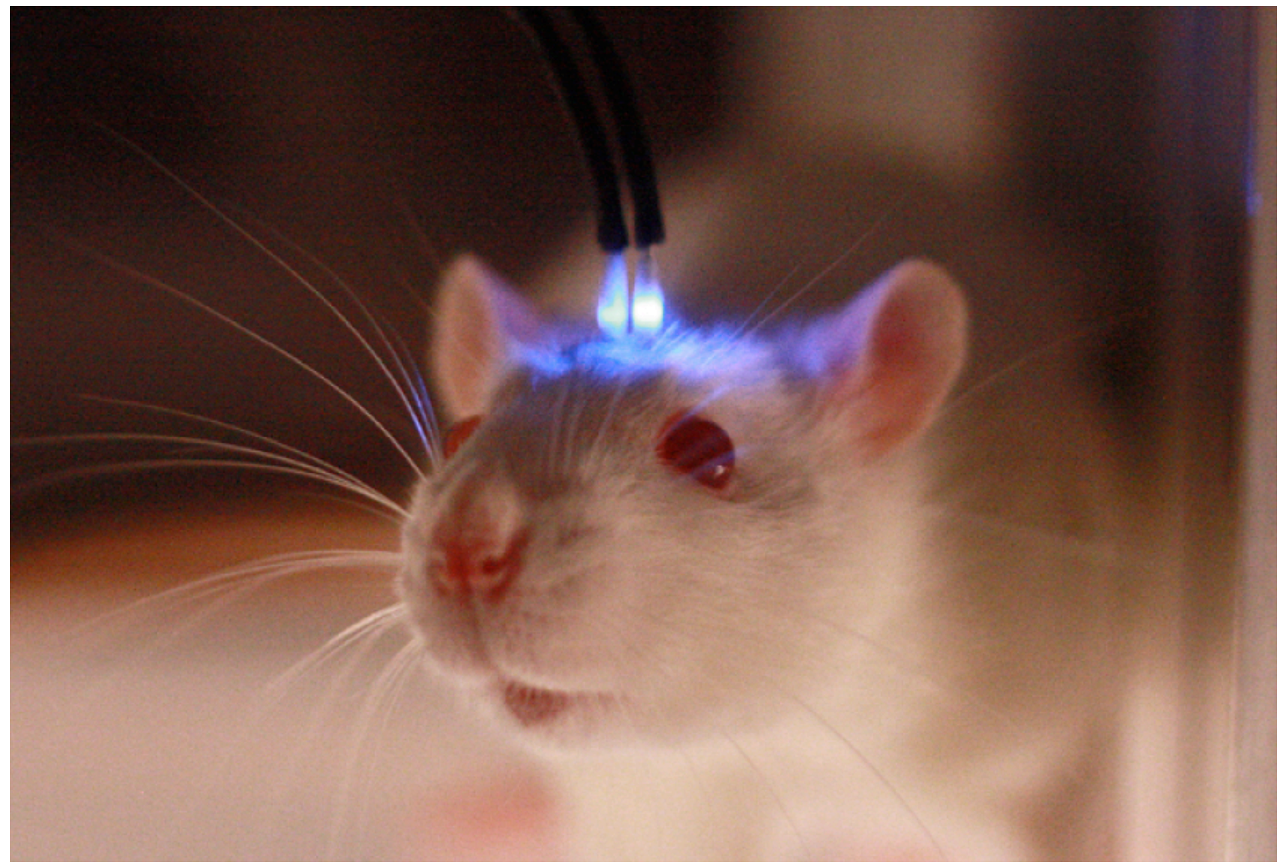
Bayesian target optimisation for high-precision holographic optogenetics

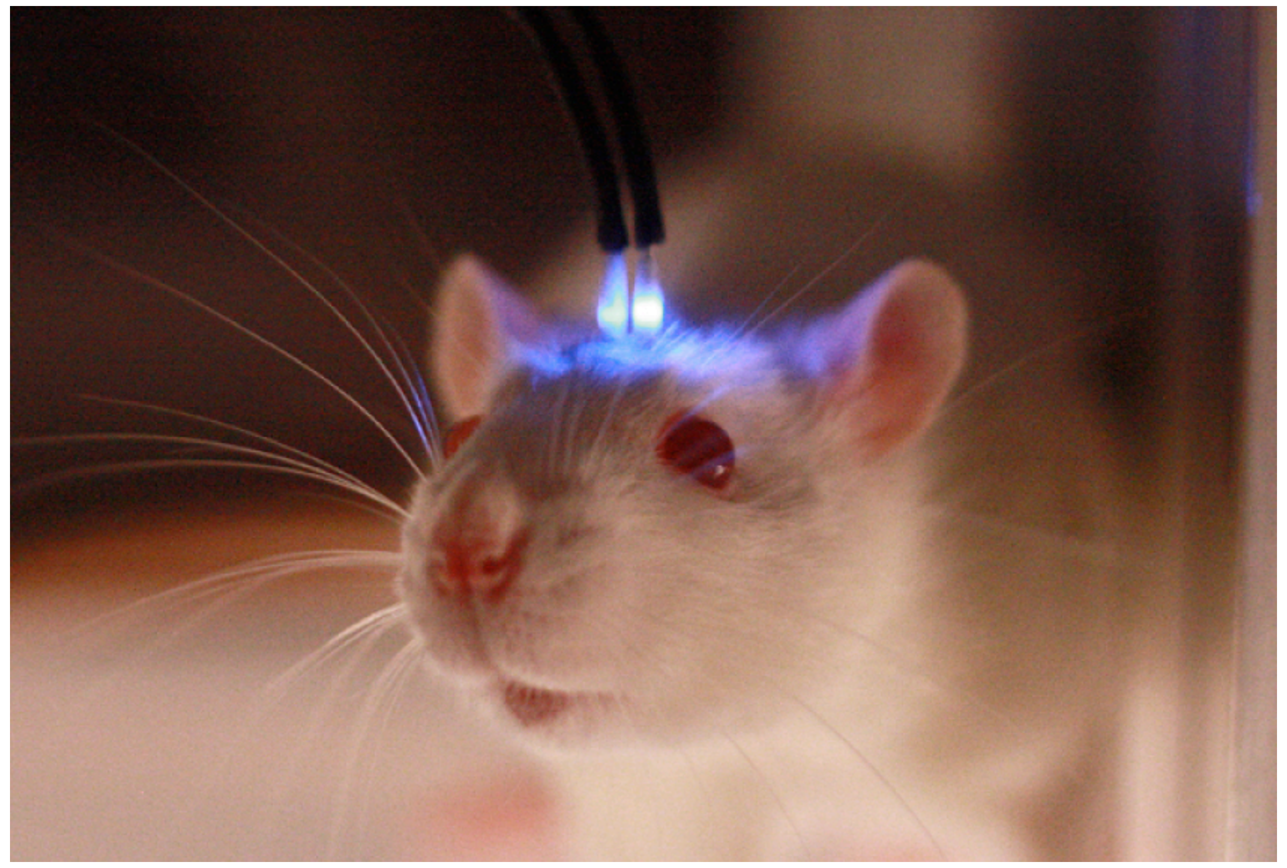
Marcus Triplett
Paninski Lab

“Classical” optogenetics

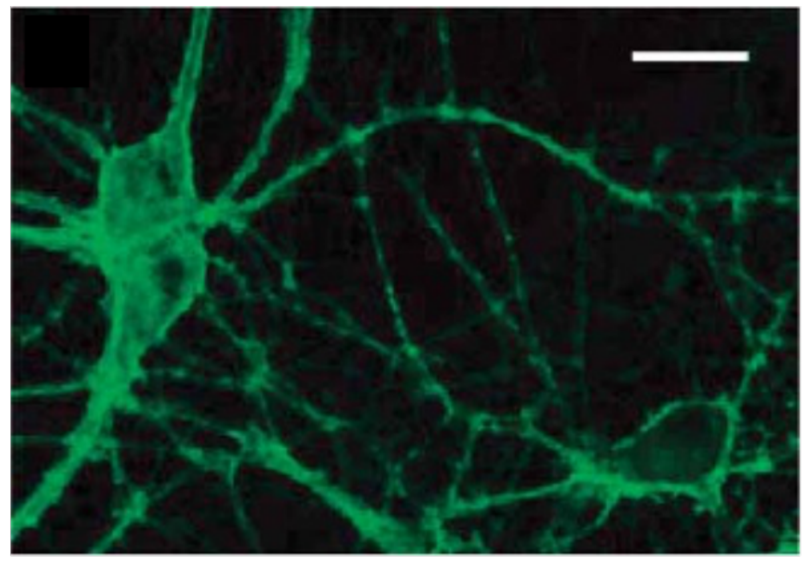


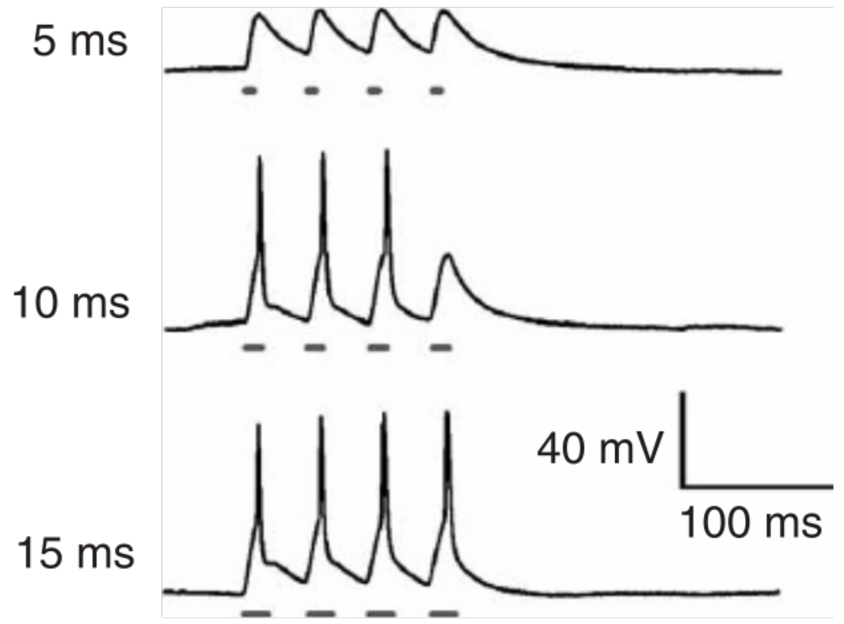
Boyden et al (2005)
Zhang et al (2007)

“Classical” optogenetics



“microbial opsin”





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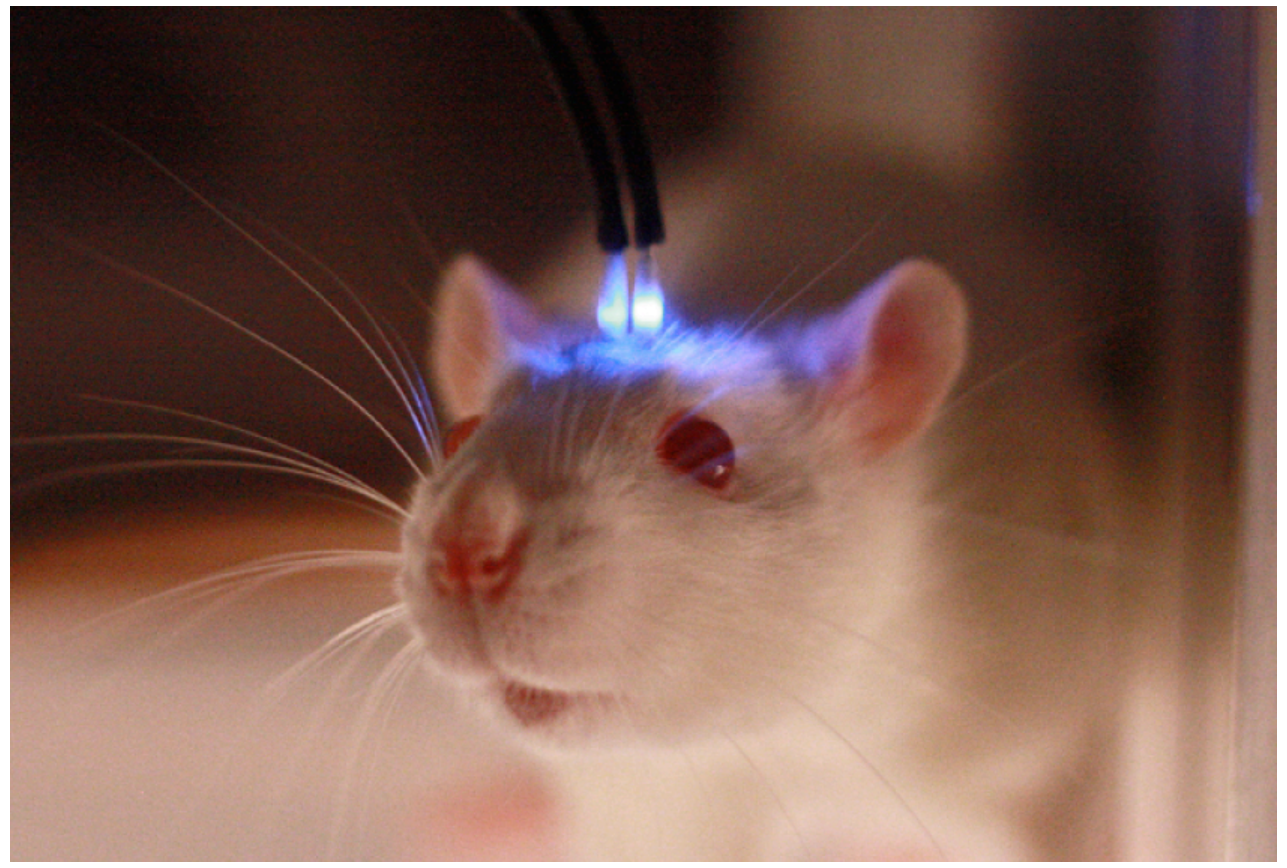

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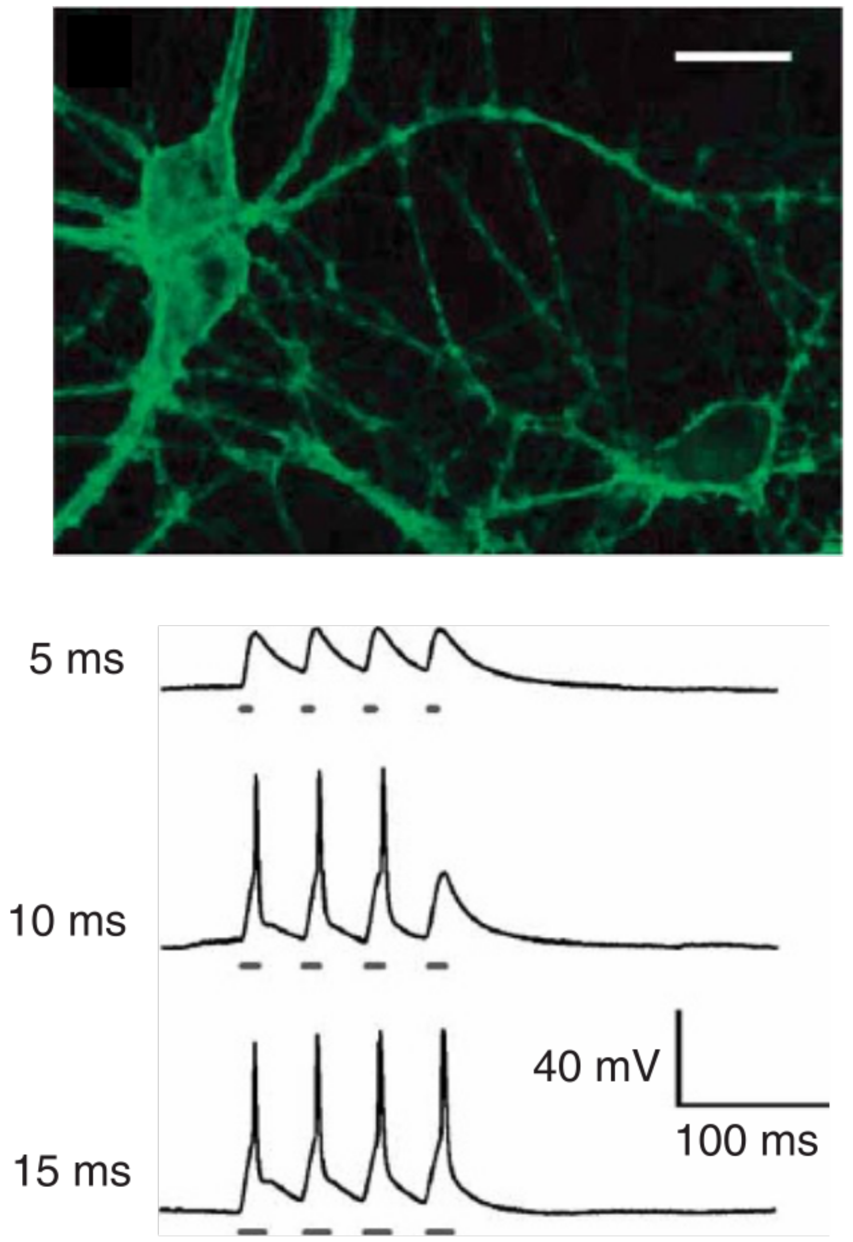
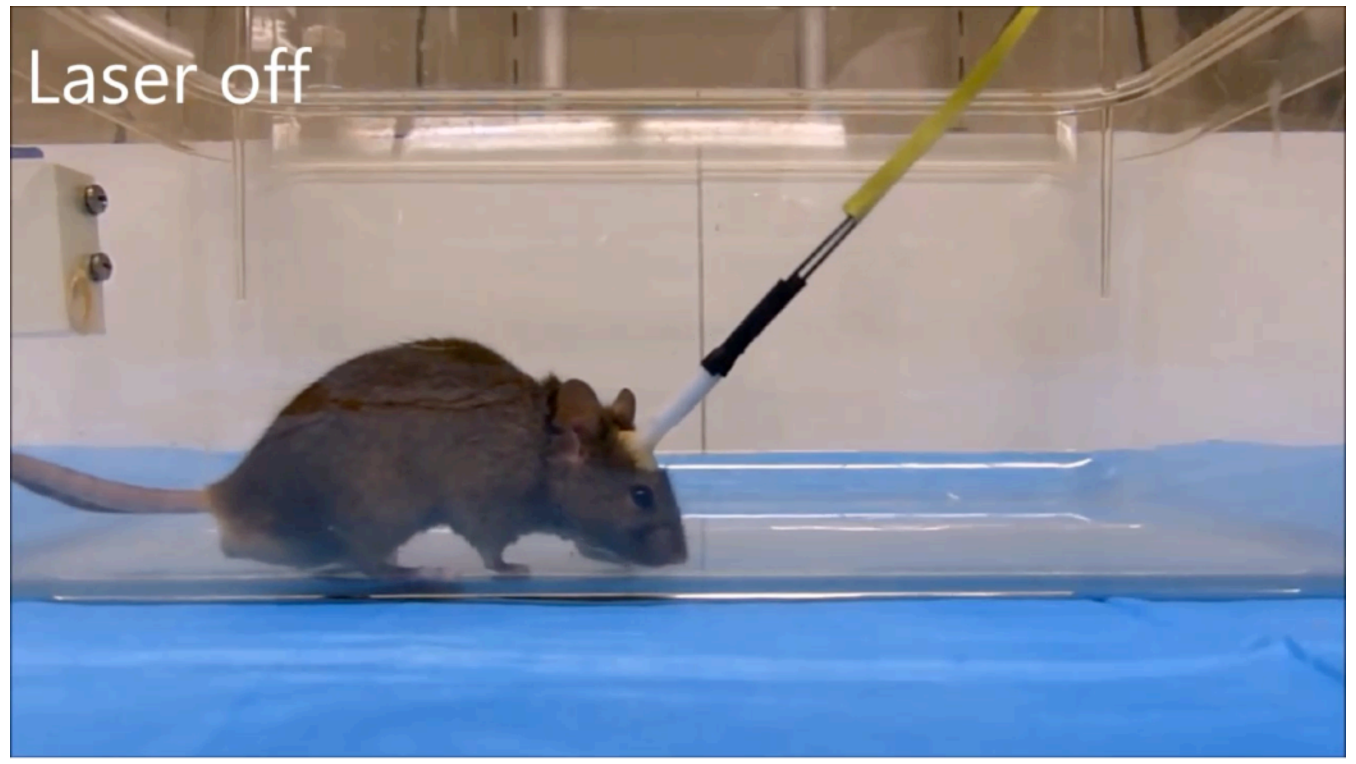
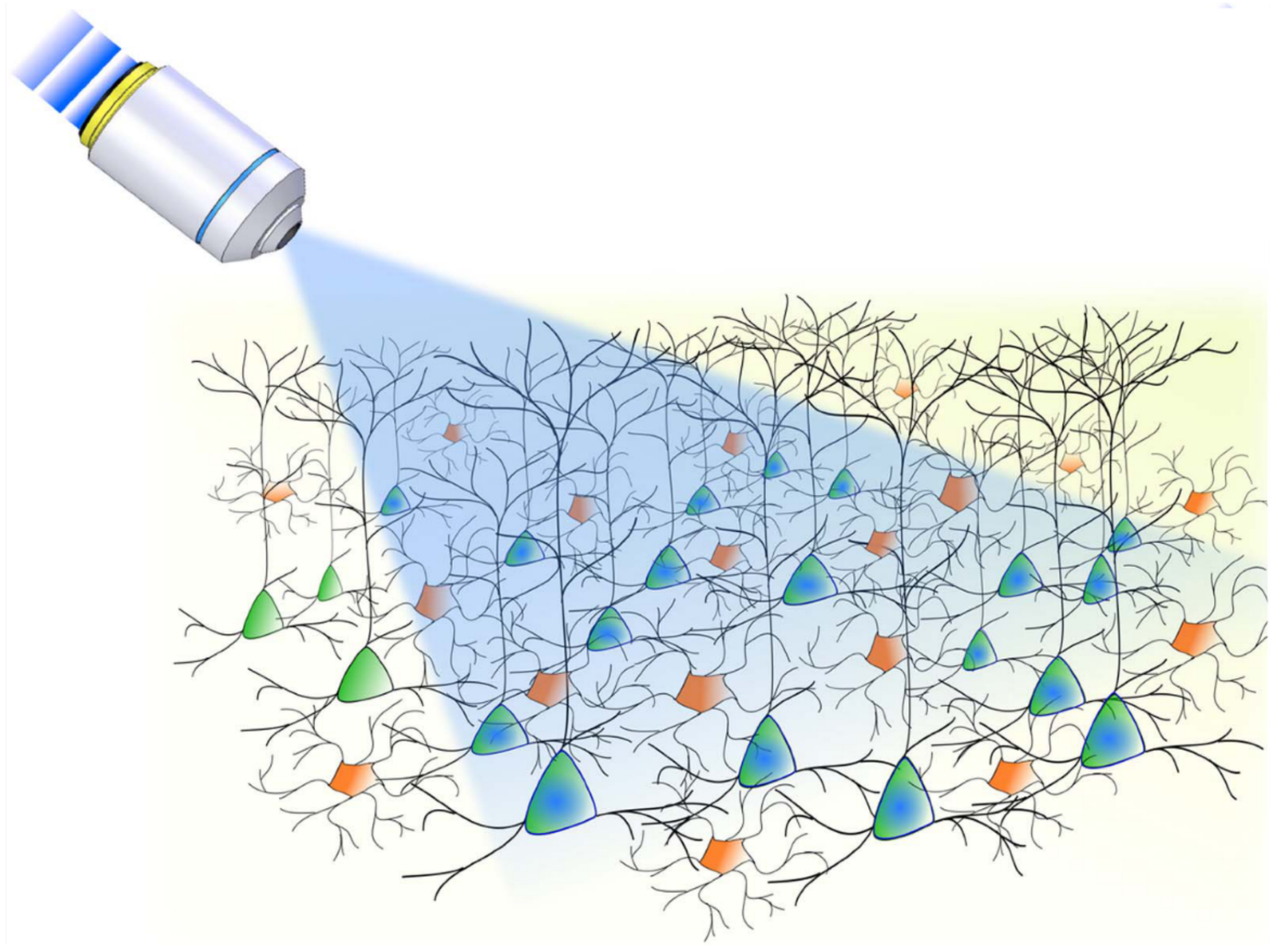




Han et al (2017)

“Classical” optogenetics



Ronzitti et al (2017)

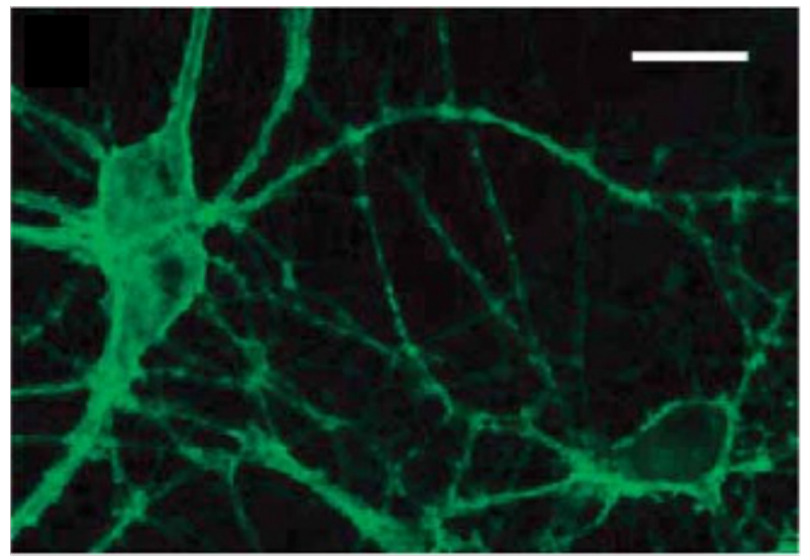
- Wide-spread activation of neural circuits can drive behavioural responses

- **But, no precision beyond genetically-defined cell types**

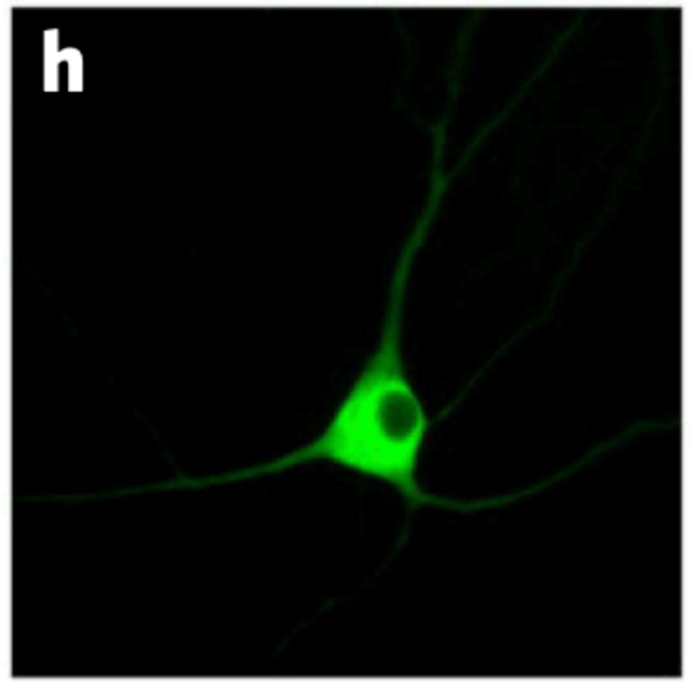
New technology for optogenetics

New technology for optogenetics

Untargeted opsin



Soma-targeted



Baker et al (2016), Shemesh et al (2017), Mardinly et al (2018)

New technology for optogenetics

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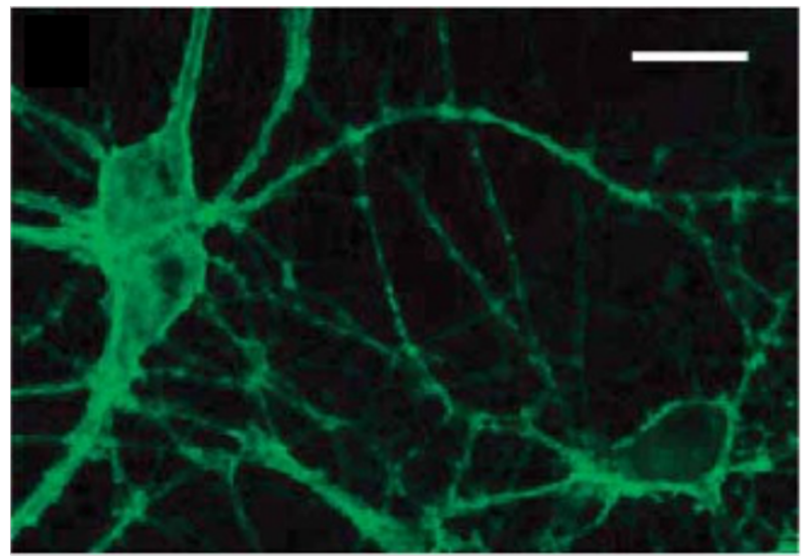

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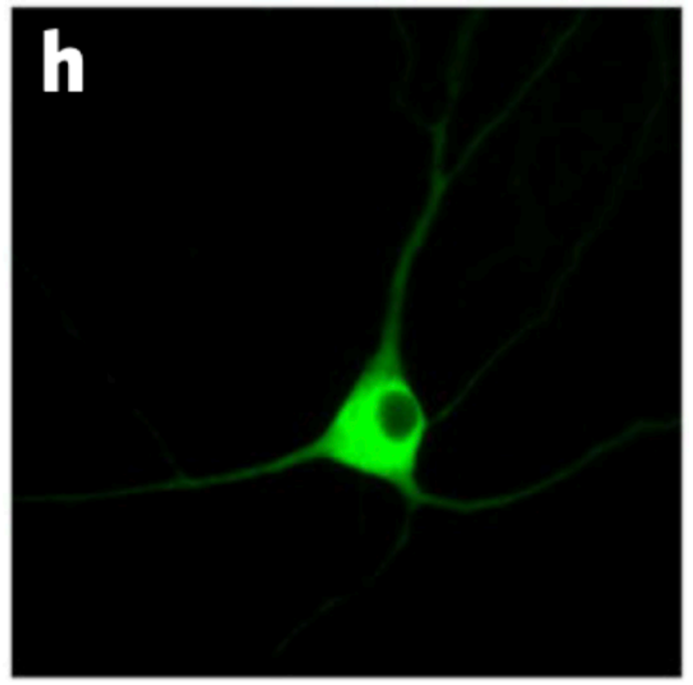
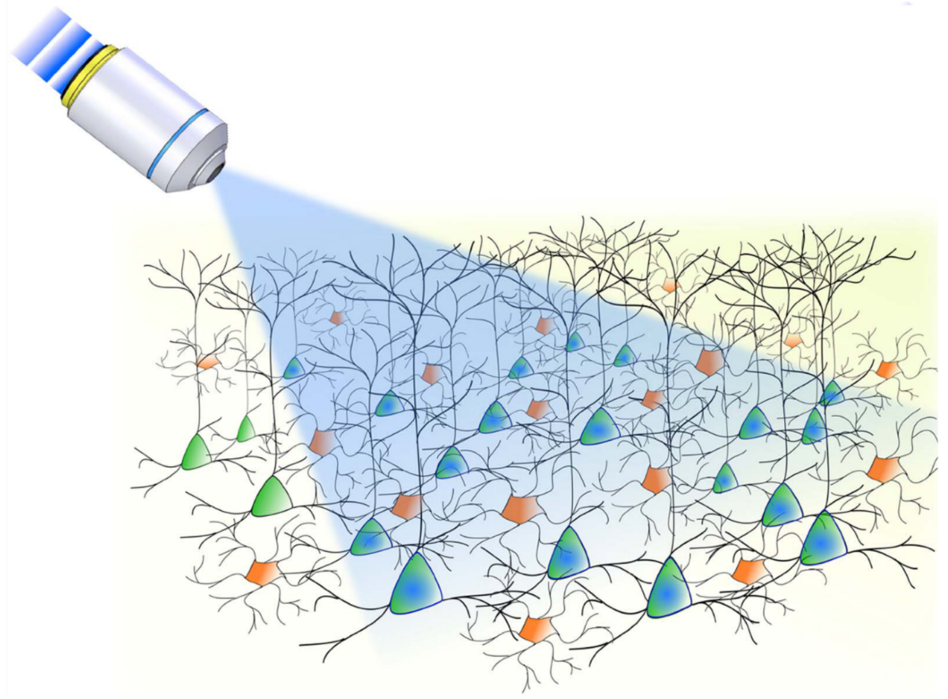


Baker et al (2016), Shemesh et al (2017), Mardinly et al (2018)

Widefield 1p illumination



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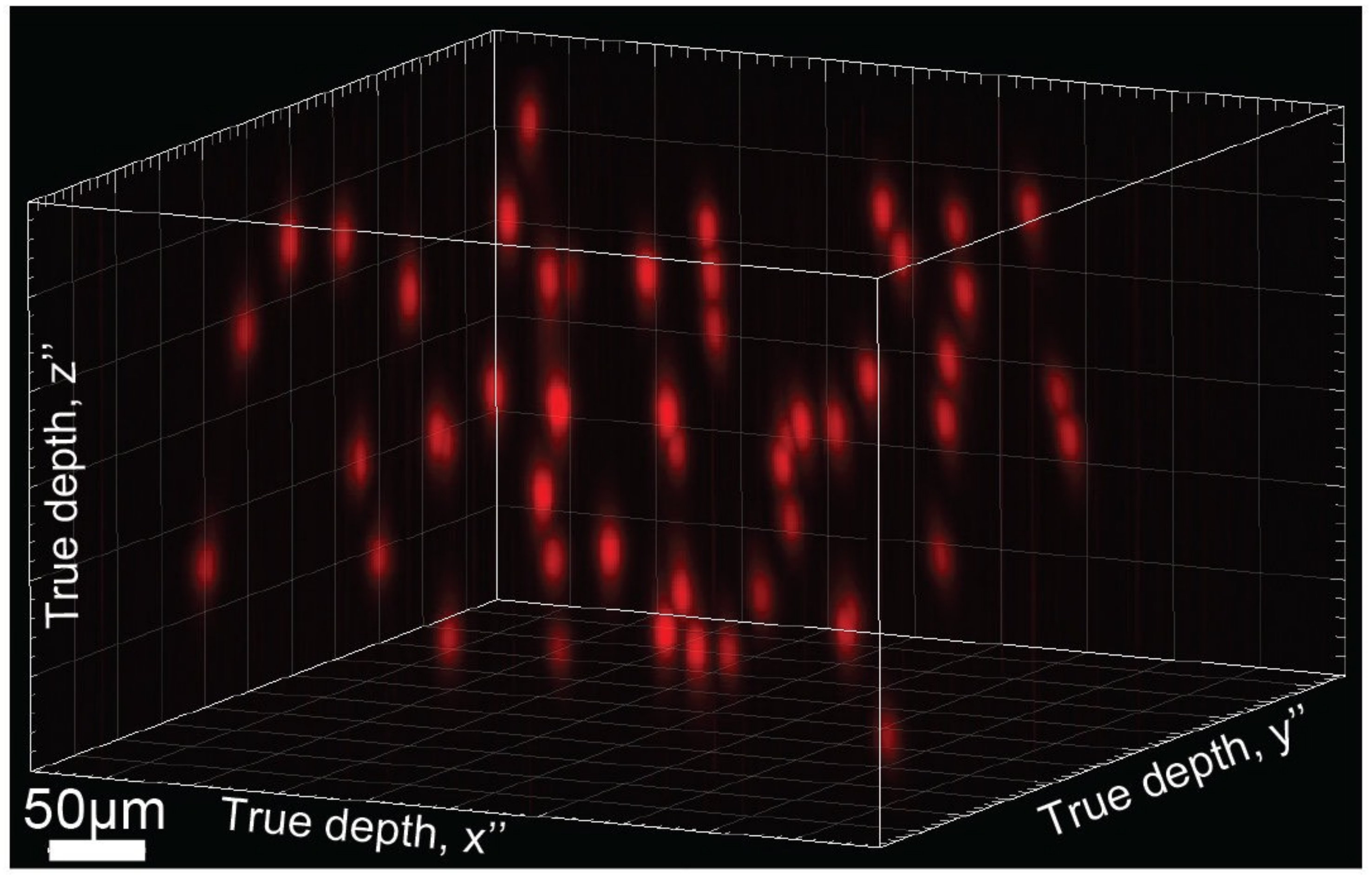
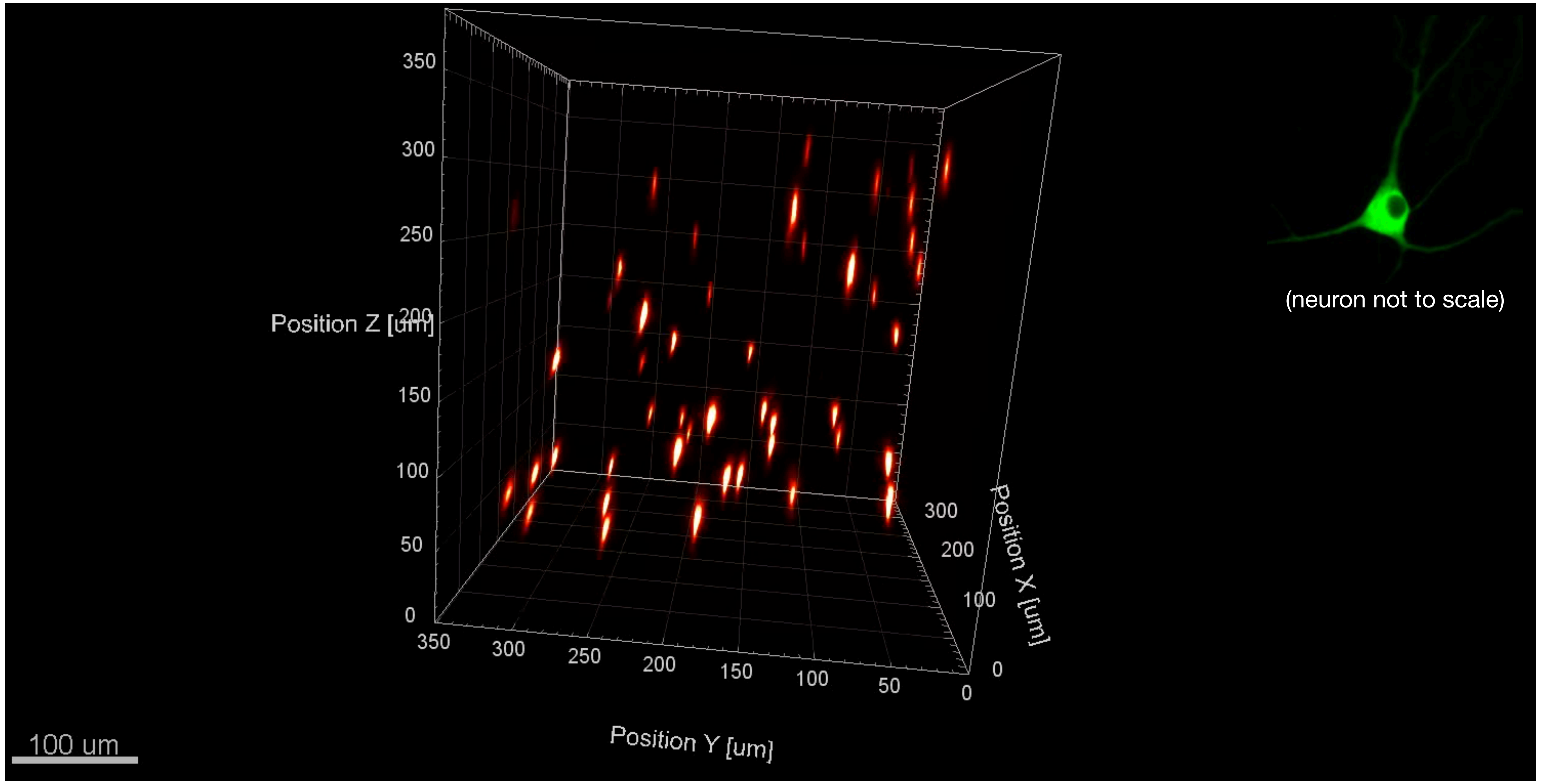
Holographic 2p

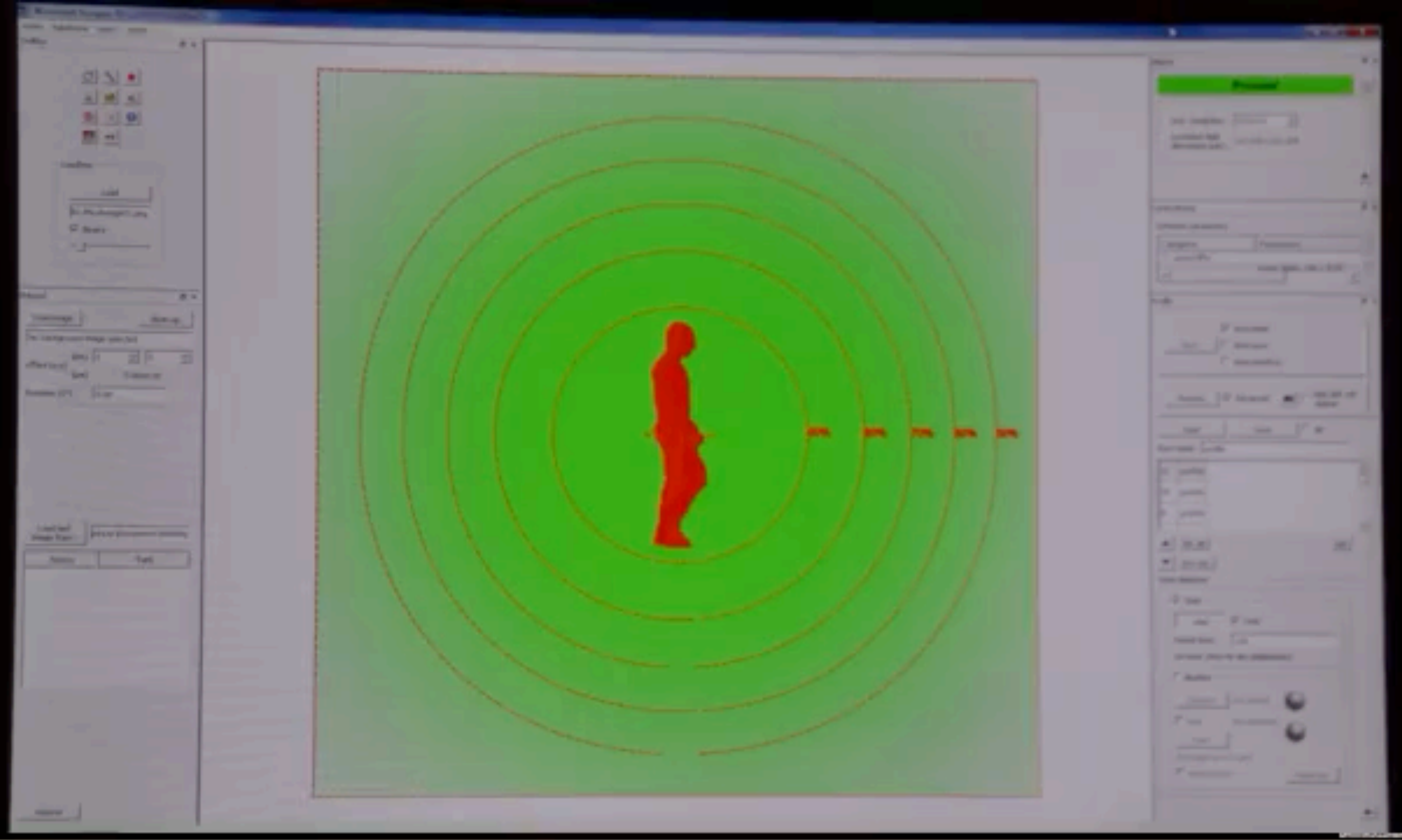


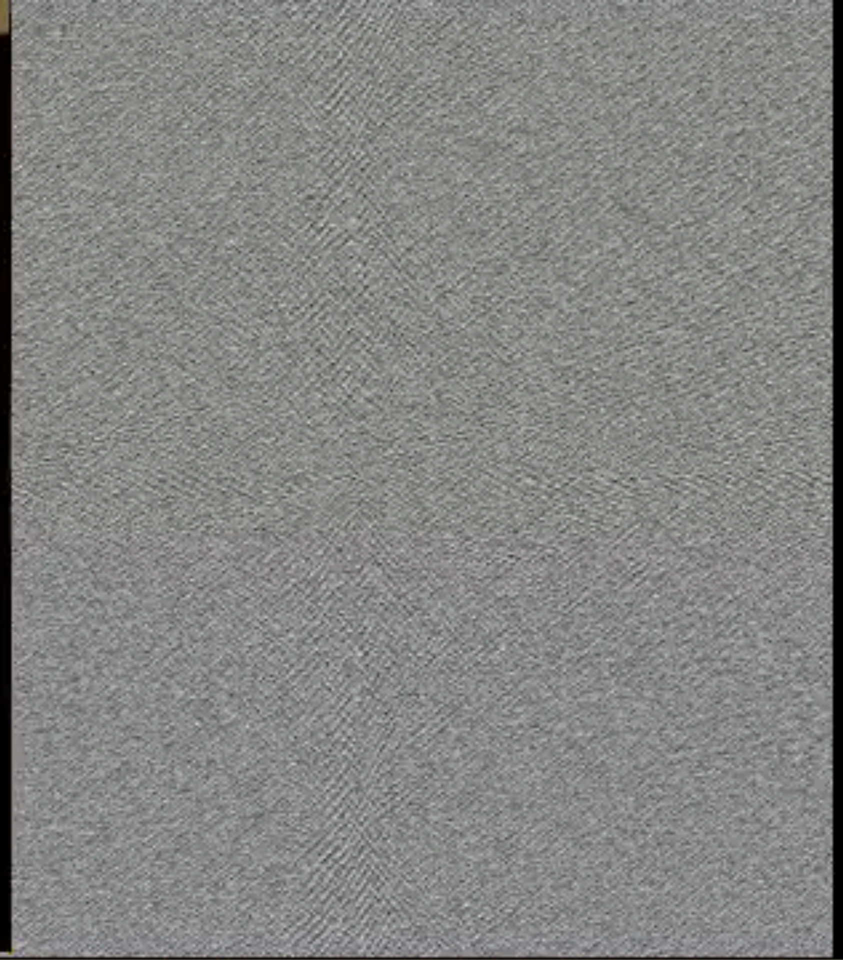
Papagiakoumou et al (2010), Pegard et al (2017)

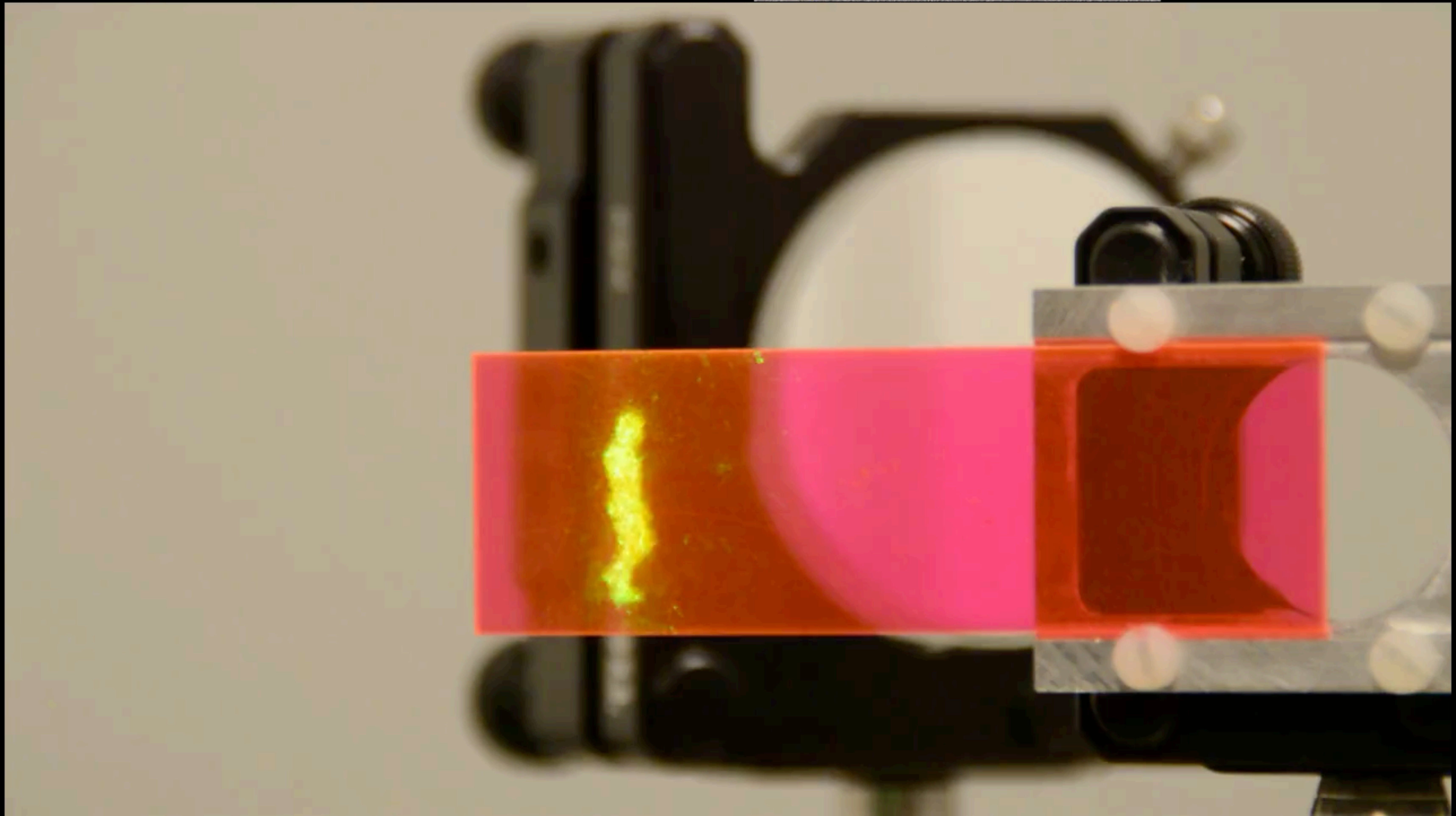
Two-photon holography



Adesnik lab

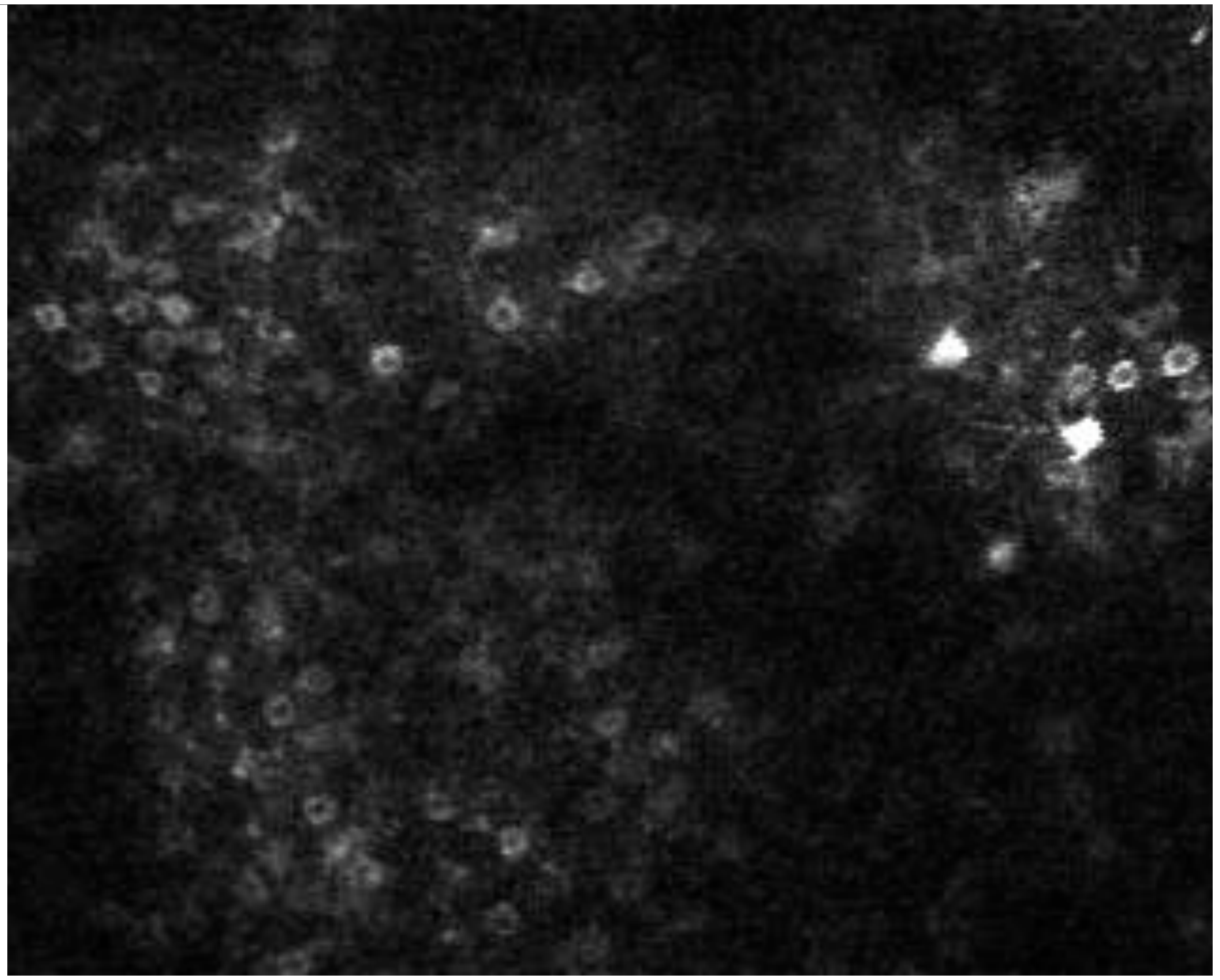






Niccolo Accanto

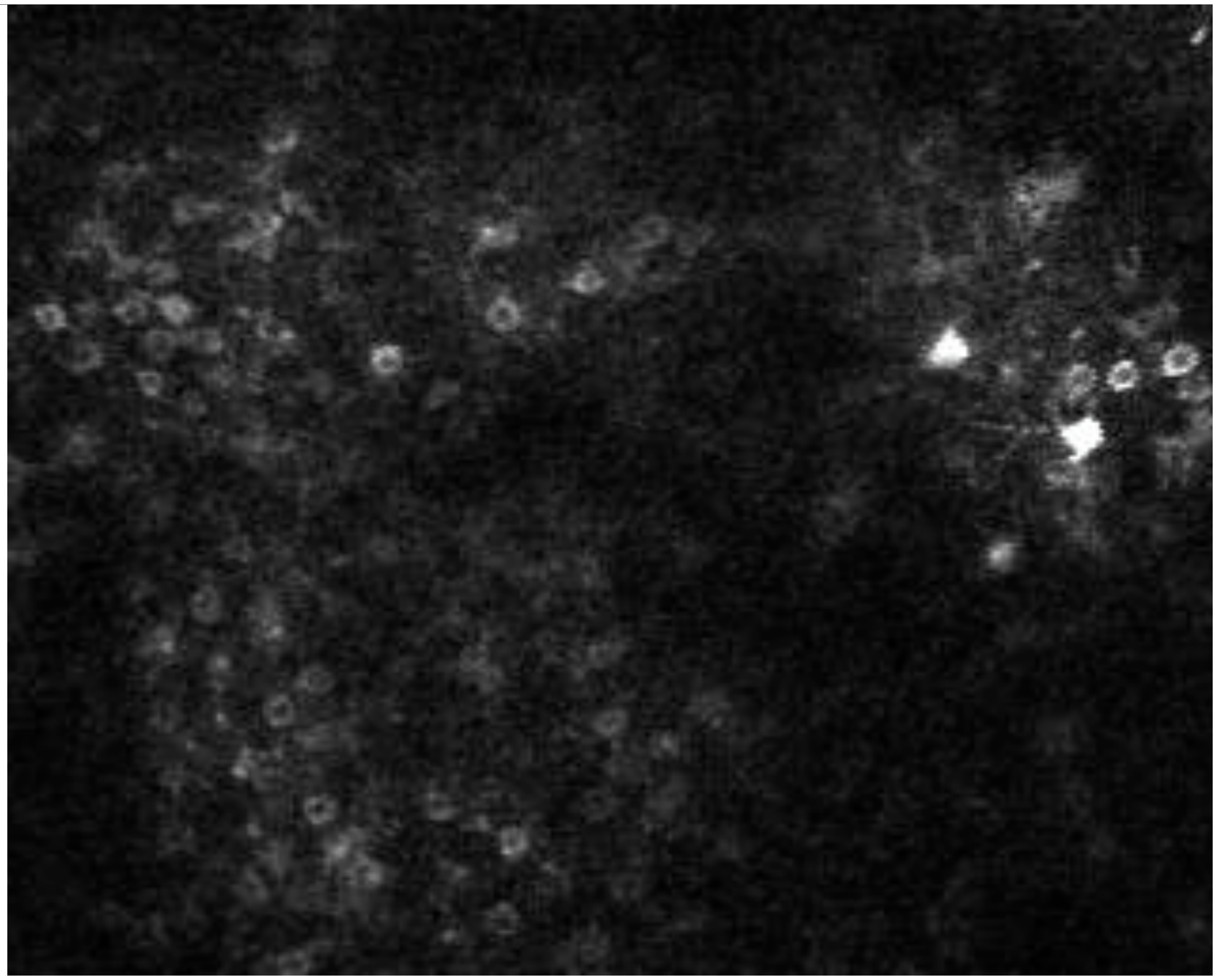
Two-photon holographic optogenetics

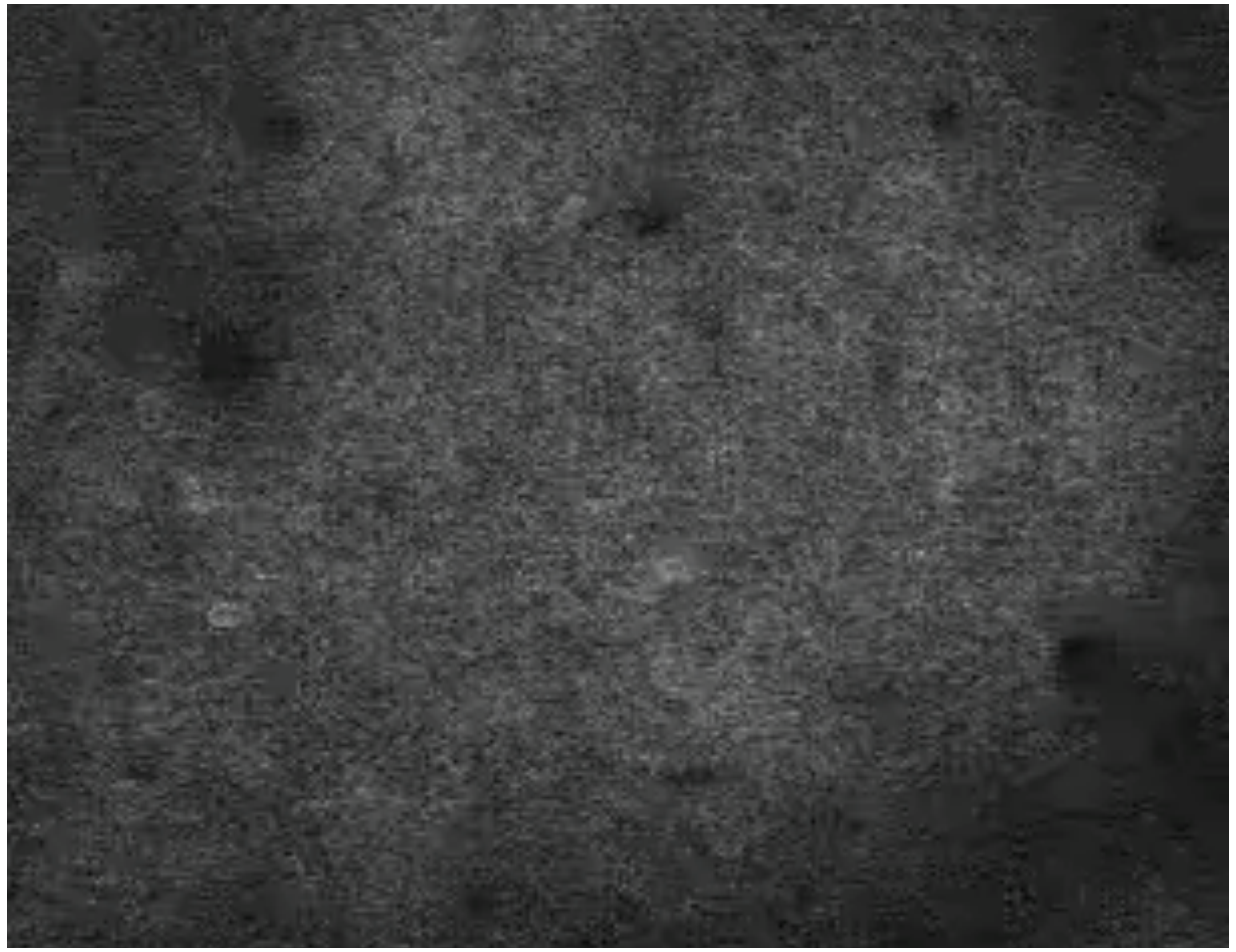


<u>Adesnik lab (UC Berkeley)</u>
Pegard et al (2017), *Nat. Comms.*
Mardinly et al (2018), *Nat. Neurosci.*
Sridharan et al (2022), *Neuron*

See also Emiliani, Yuste, Hausser, etc

Two-photon holographic optogenetics





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A key limitation of two-photon optogenetics

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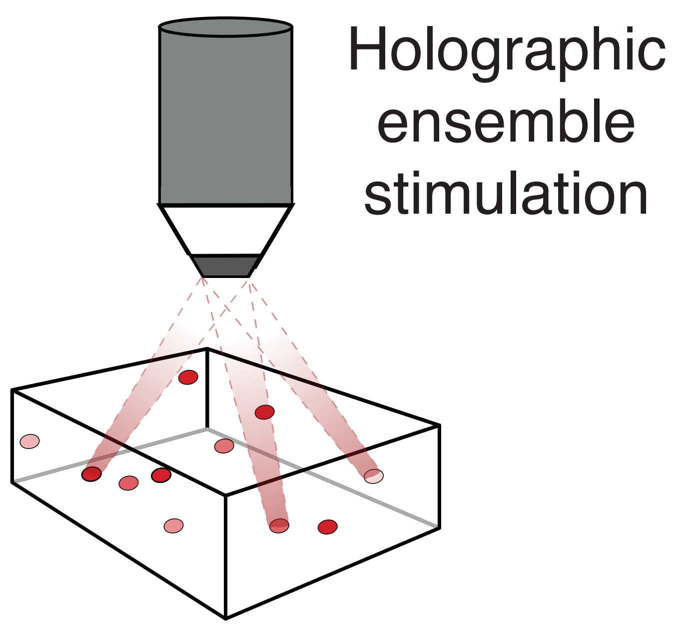

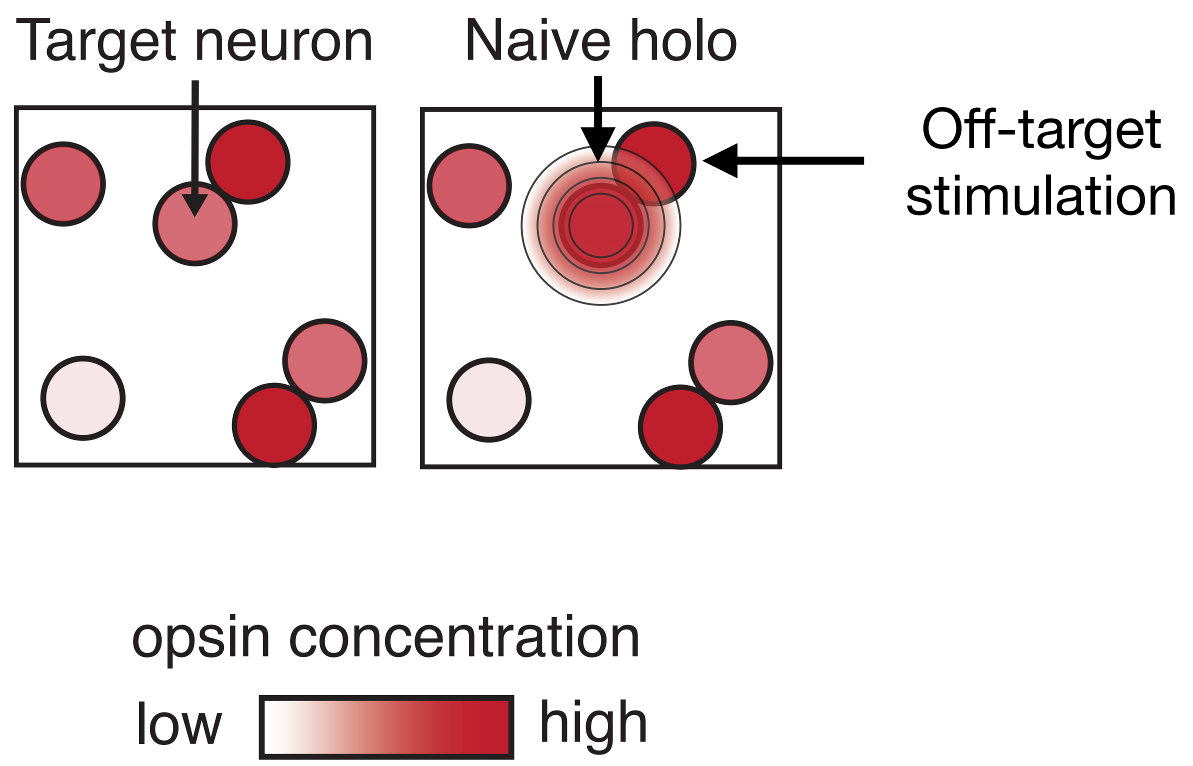

Triplett, …, Paninski (2023)

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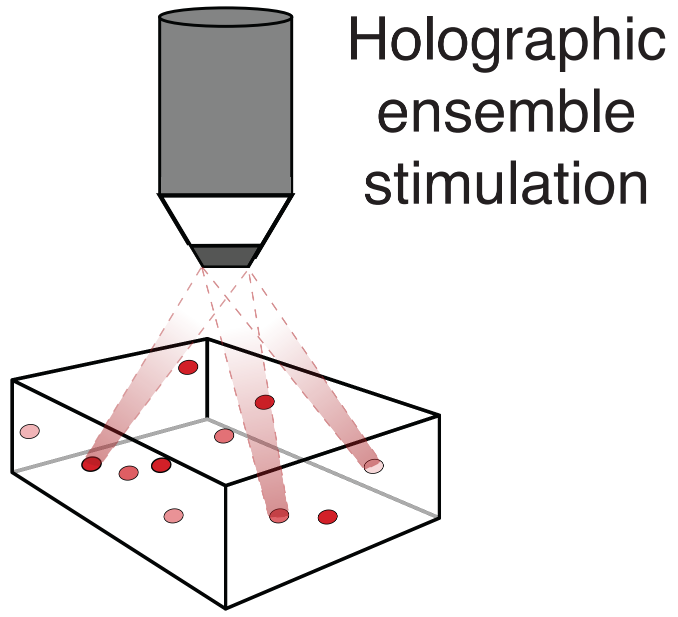

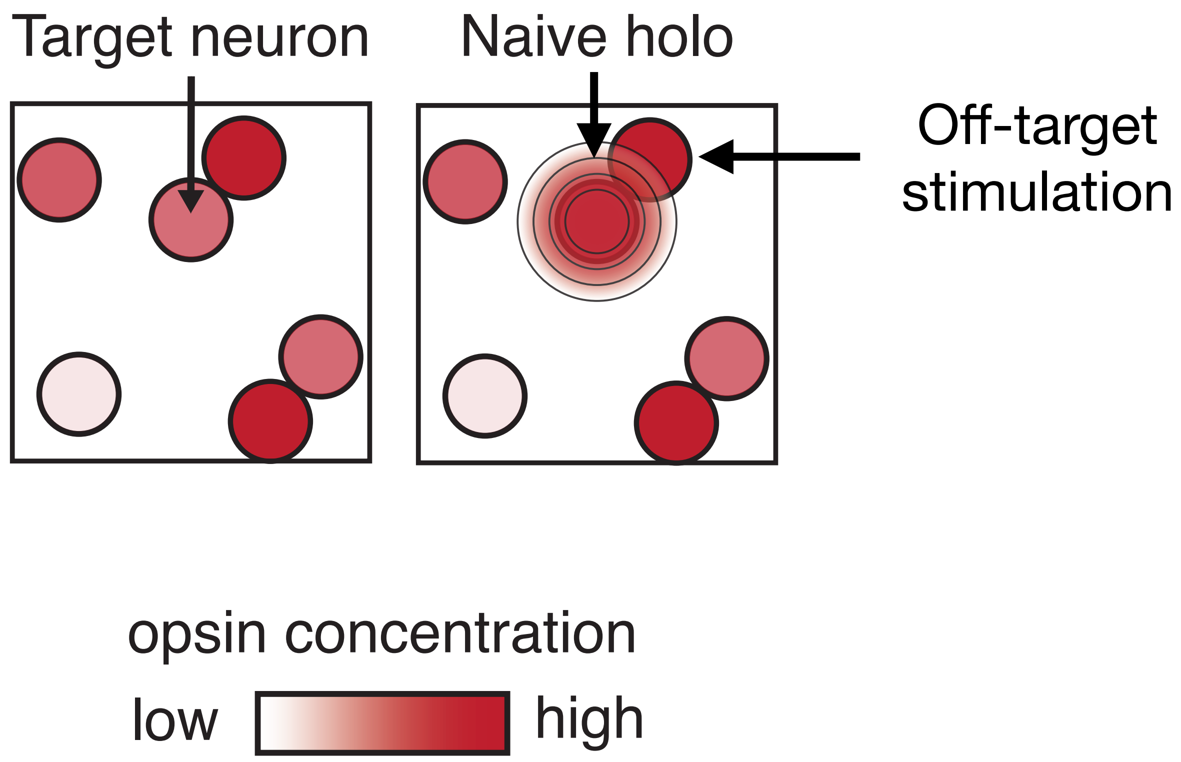

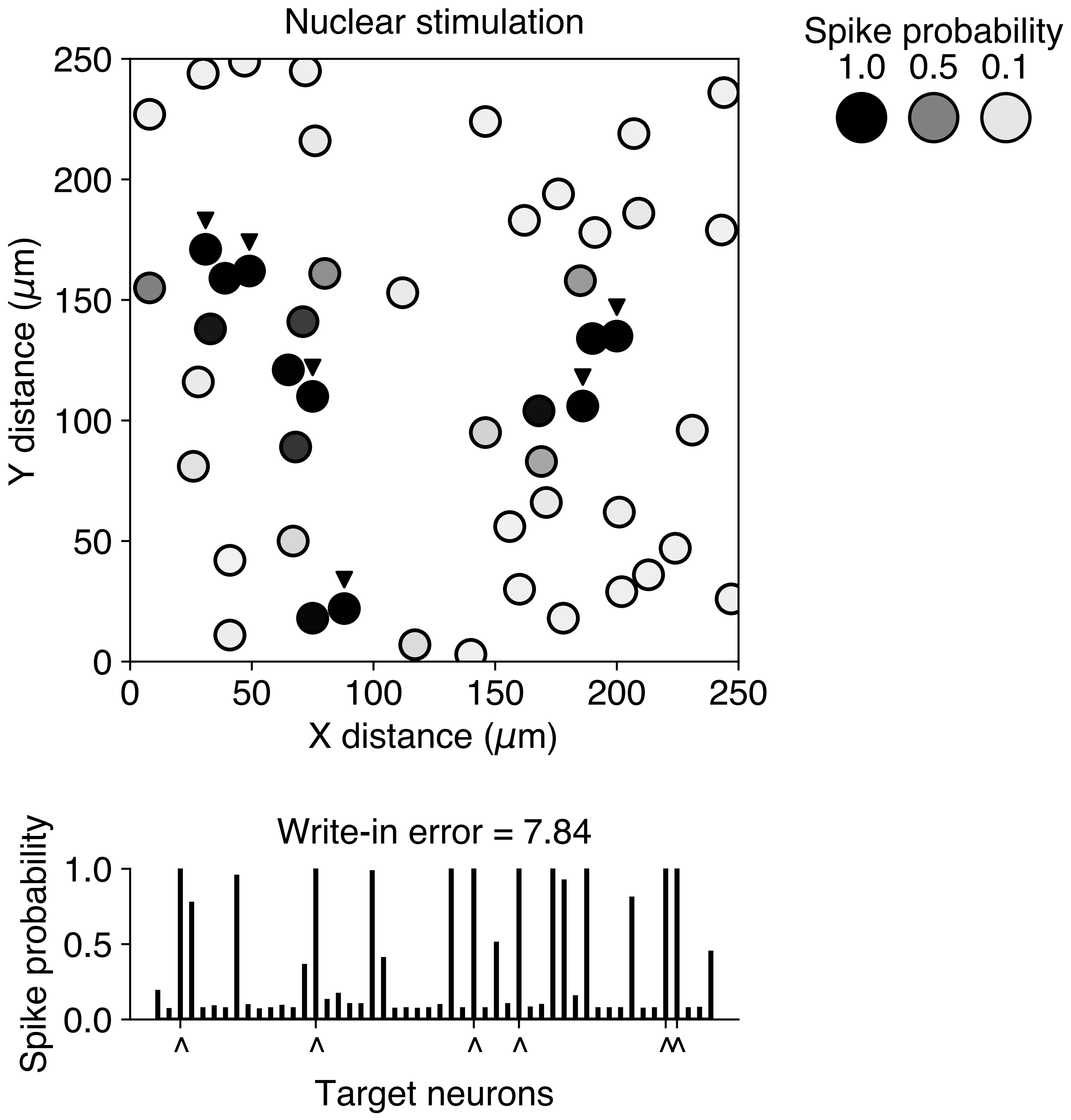

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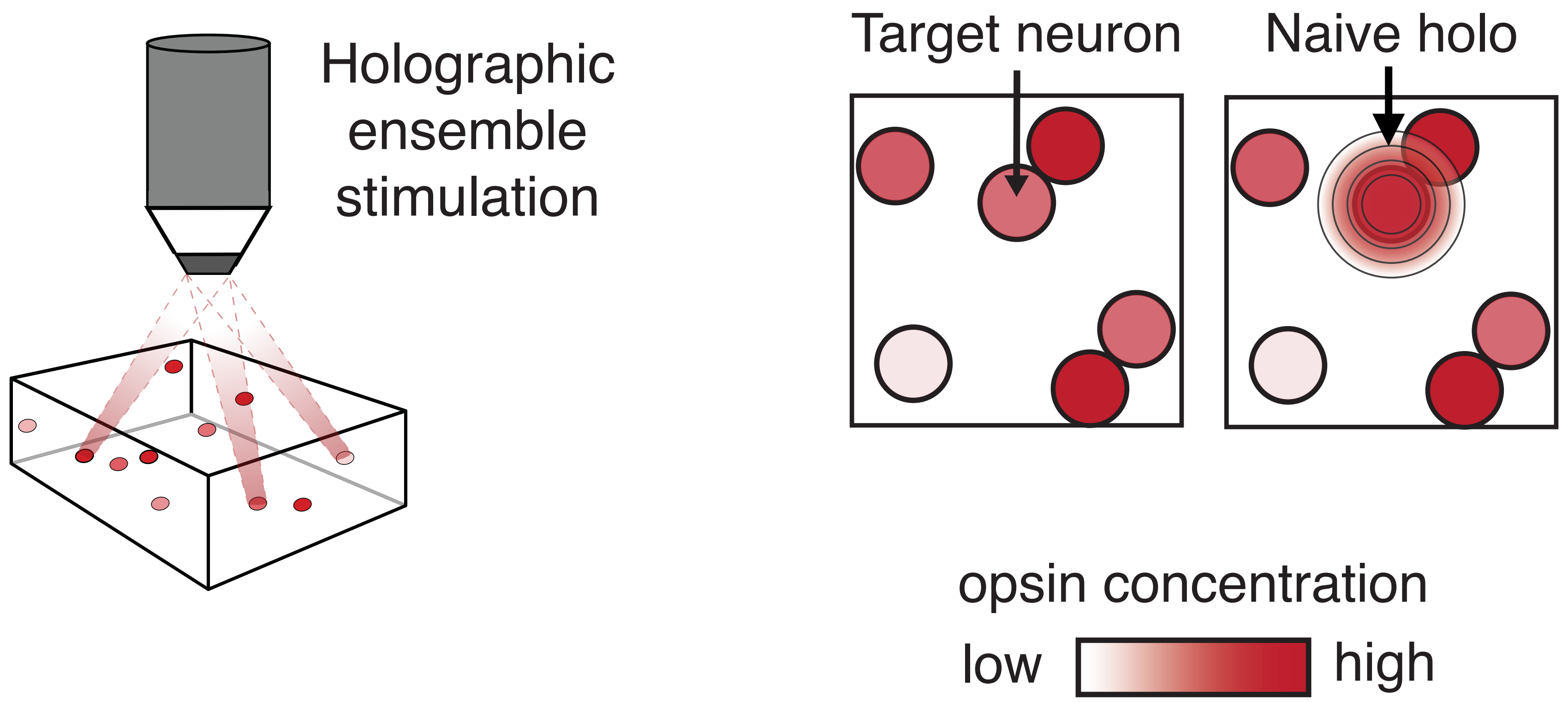

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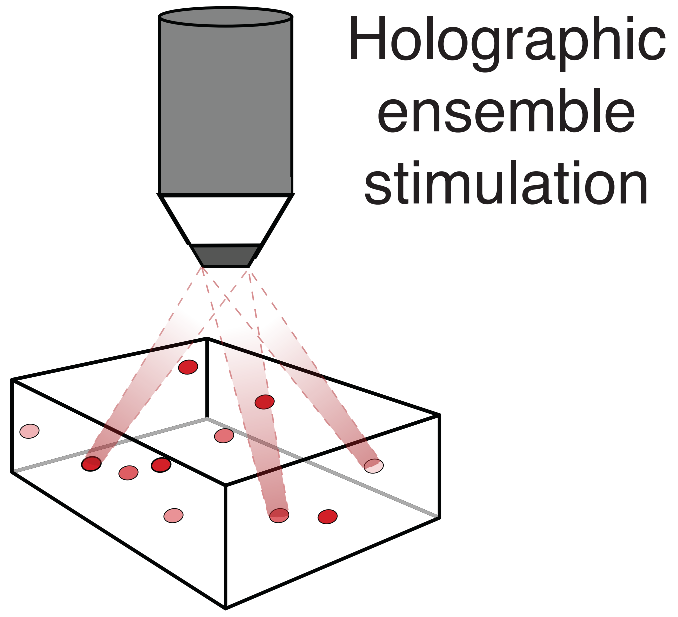
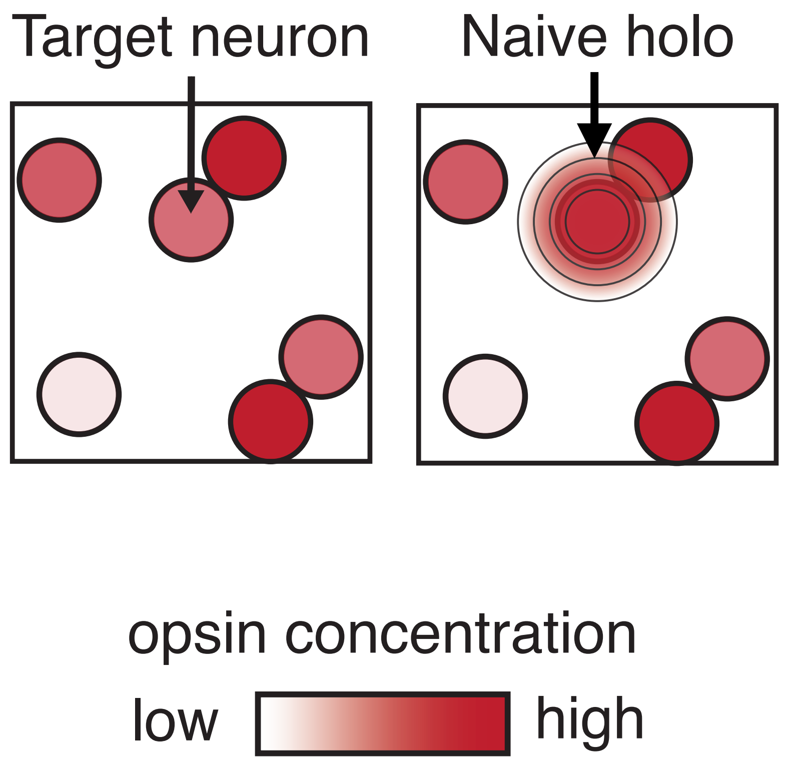
Probing neural codes with two-photon holographic optogenetics

Hillel Adesnik ✉ and Lamiae Abdeladim

Triplett, …, Paninski (2023)

A key limitation of two-photon optogenetics





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Outstanding challenges for multiphoton optogenetics

Although multiphoton optogenetics offers unparalleled opportunities for precisely perturbing neural activity (Box 1), there are several key challenges that must still be overcome to broaden its utility and increase its precision.

Achieving 'true' single-cell resolution. Although multiphoton excitation can achieve high optical resolution in the brain, empirical measurements from numerous technical studies indicate that

Triplett, …, Paninski (2023)

A key limitation of two-photon optogenetics

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Robert M. Lees, Bruno Pichler, Adam M. Packer

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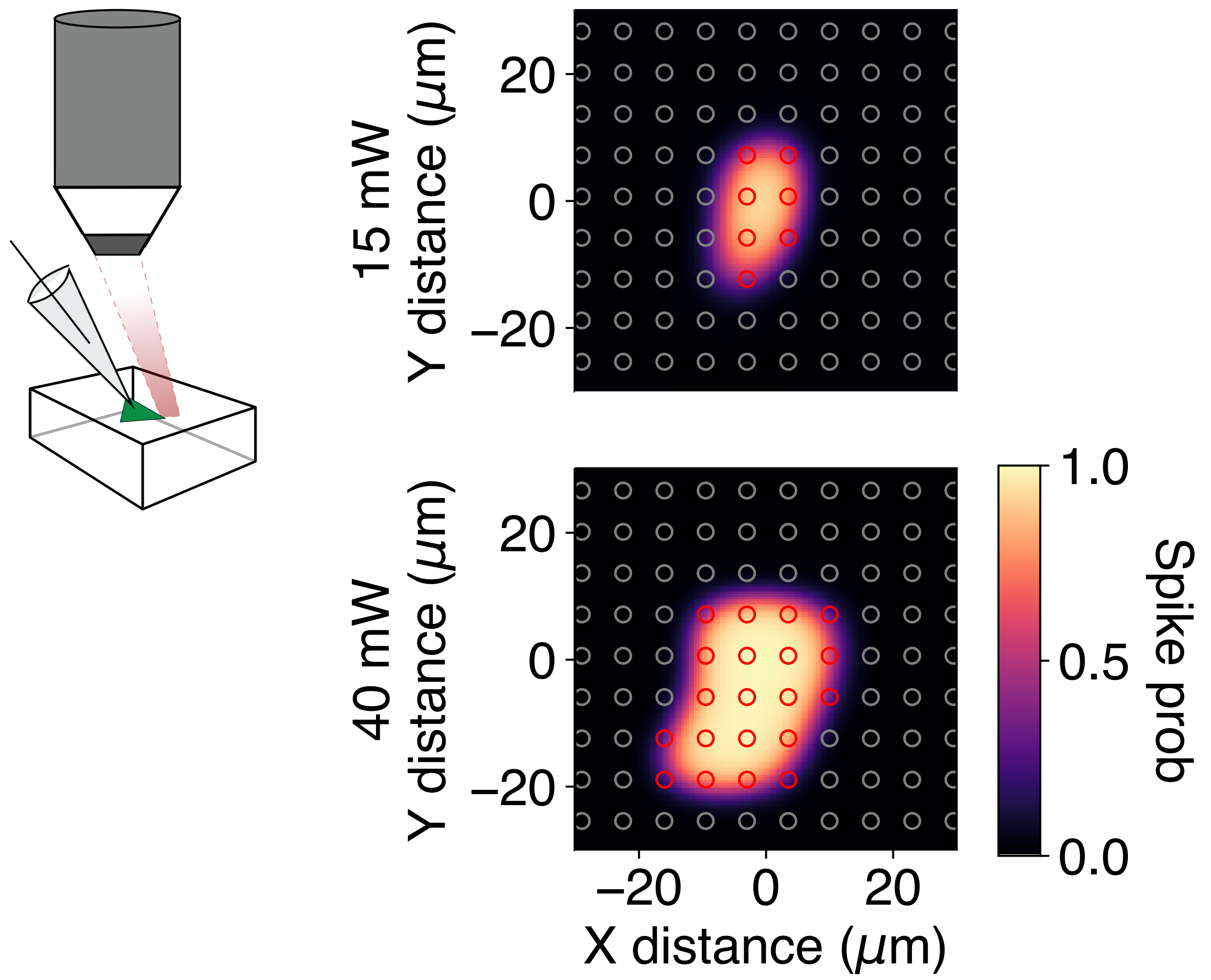
Computational holographic optogenetics

as a means to expand the experimental capabilities of this technology

Target optimisation strategies

"Optogenetic receptive field"



Data from Marta Gajowa (Adesnik lab)

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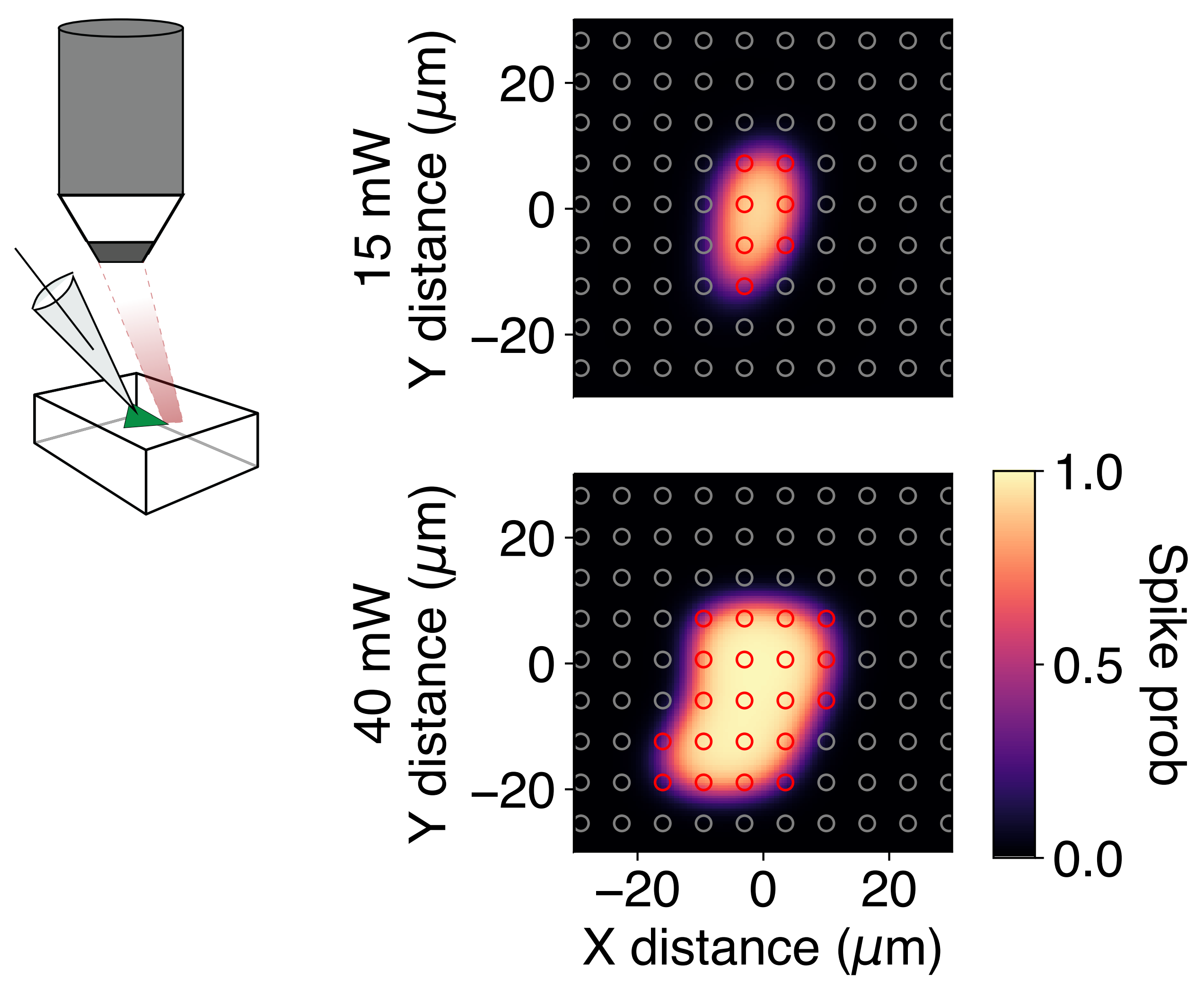

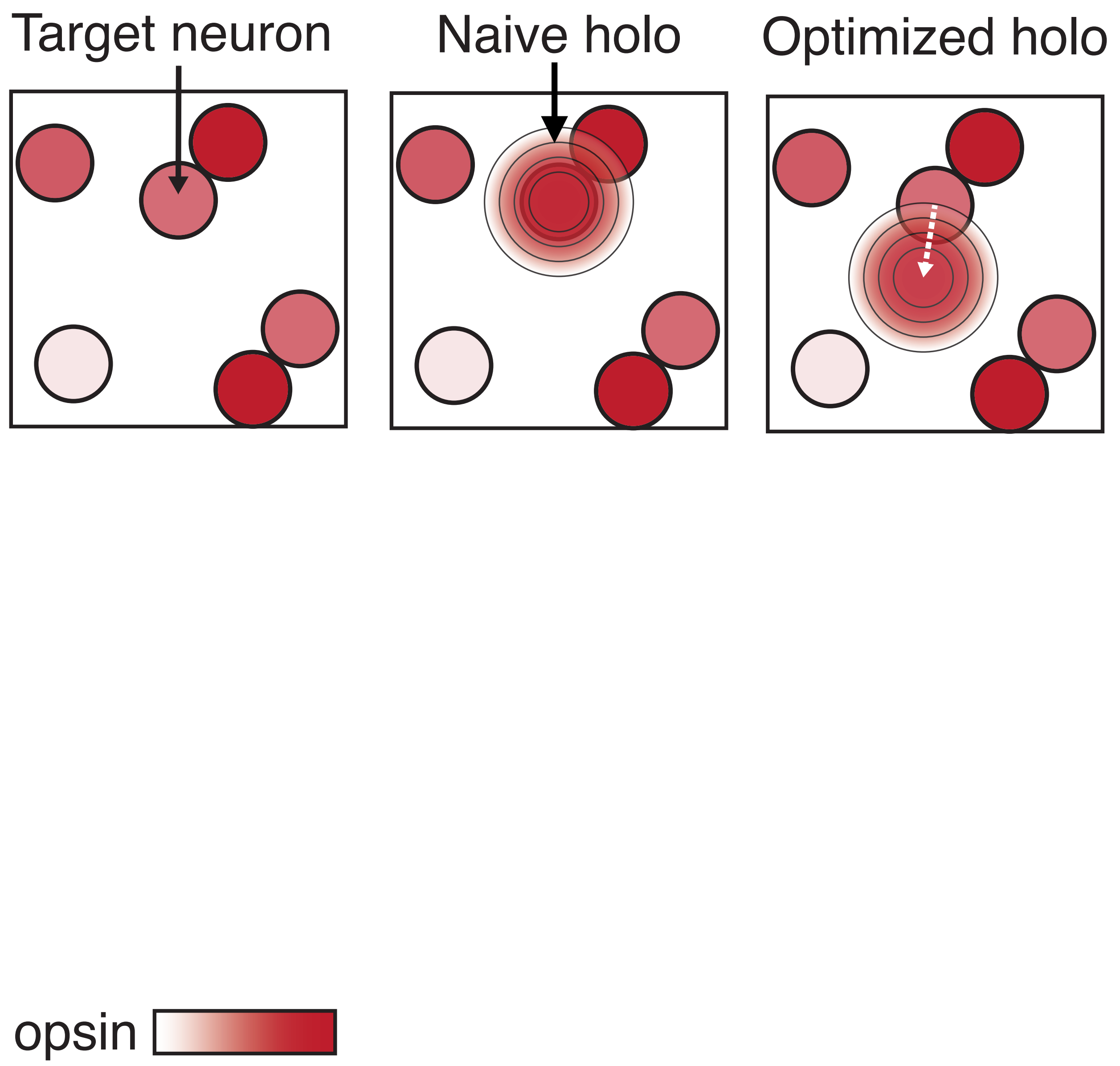

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Triplett et al (2023)

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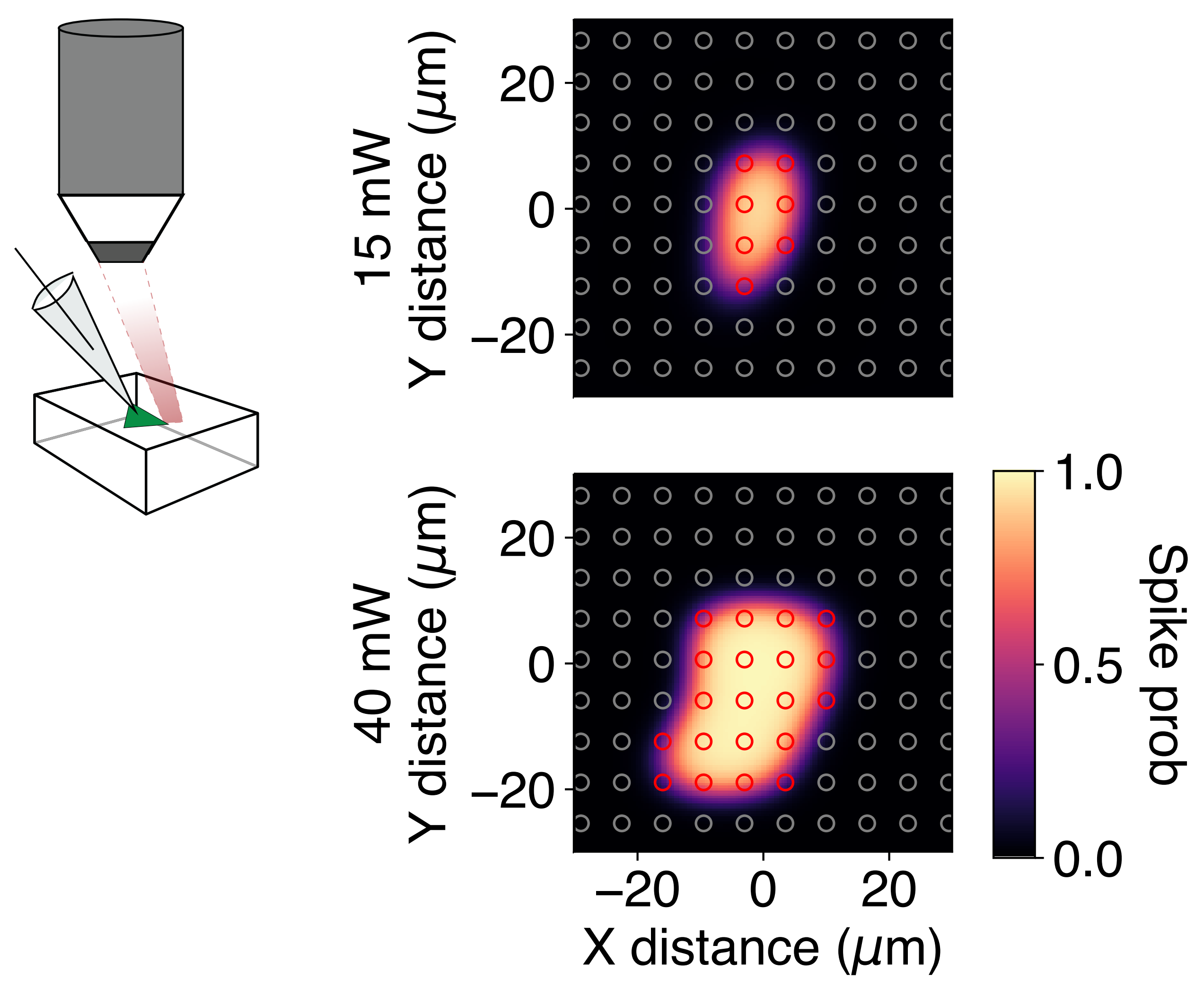

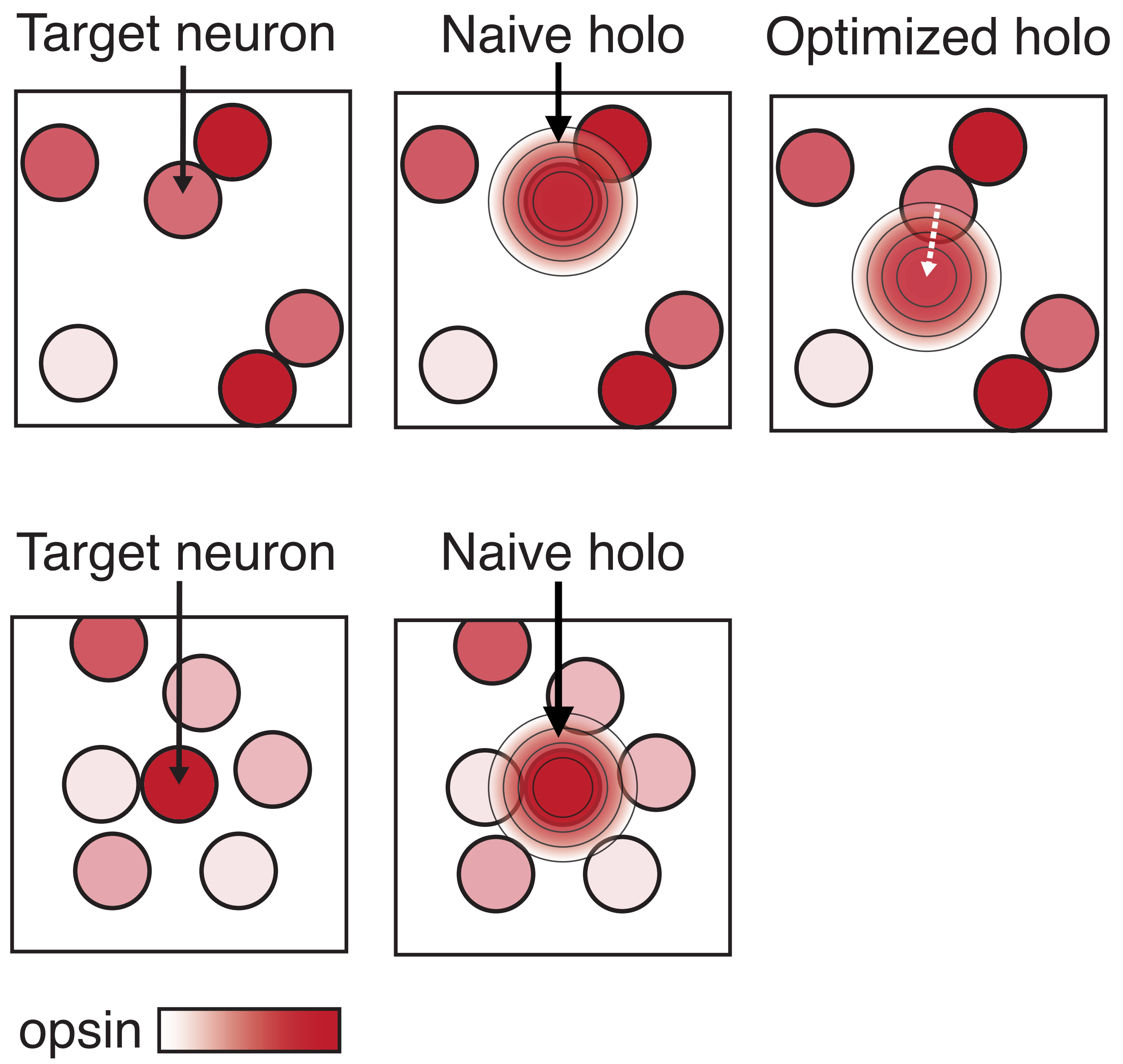

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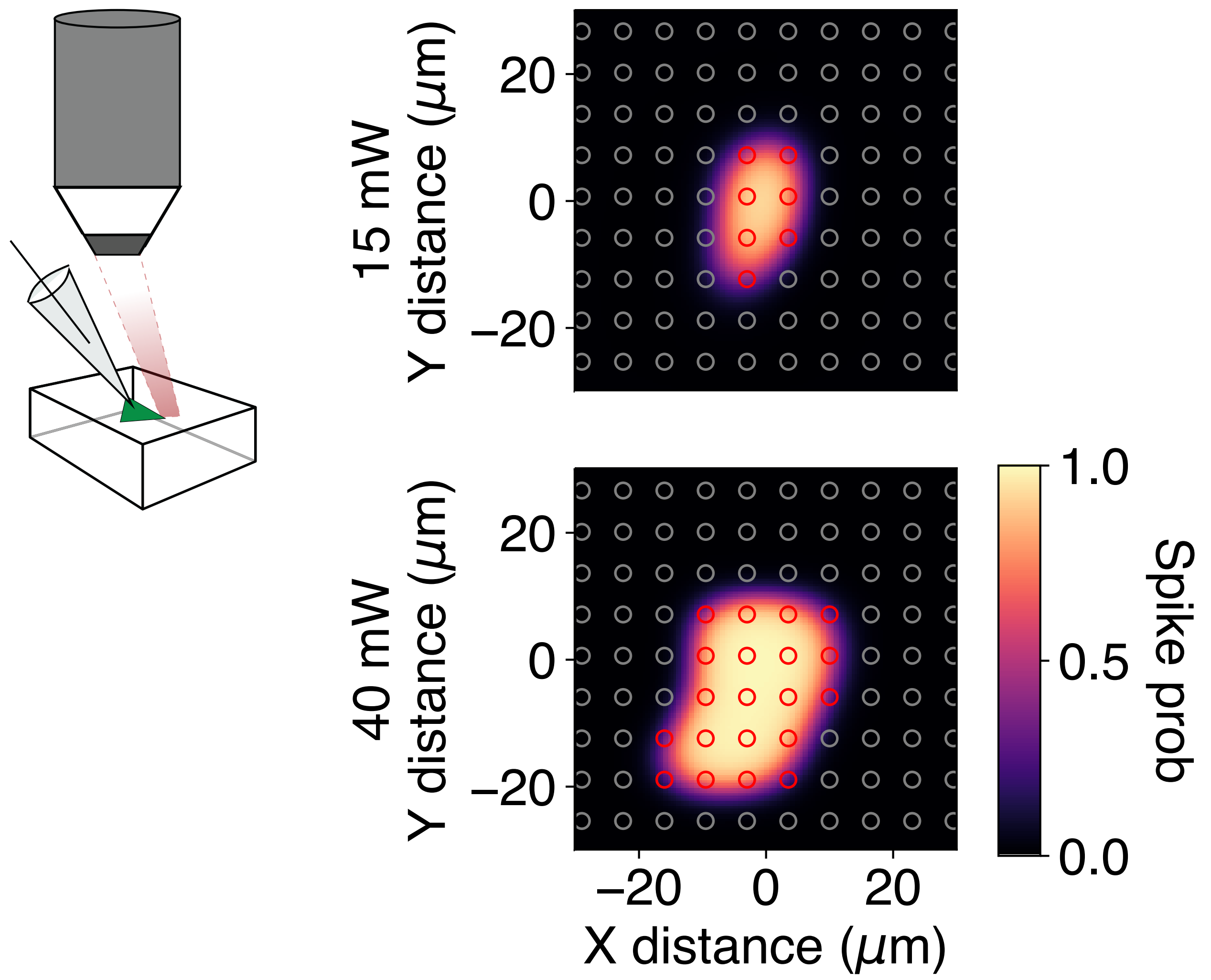

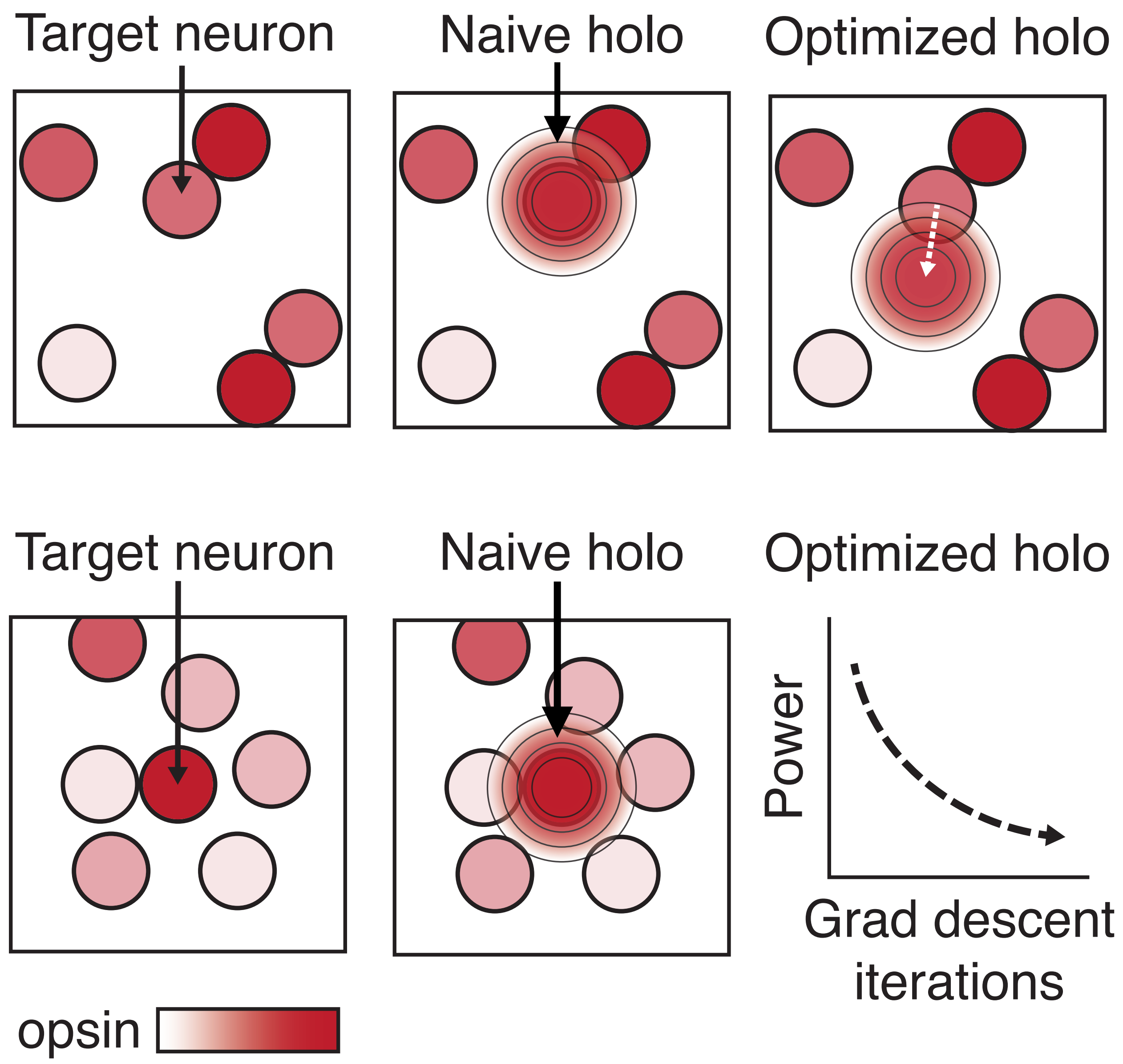

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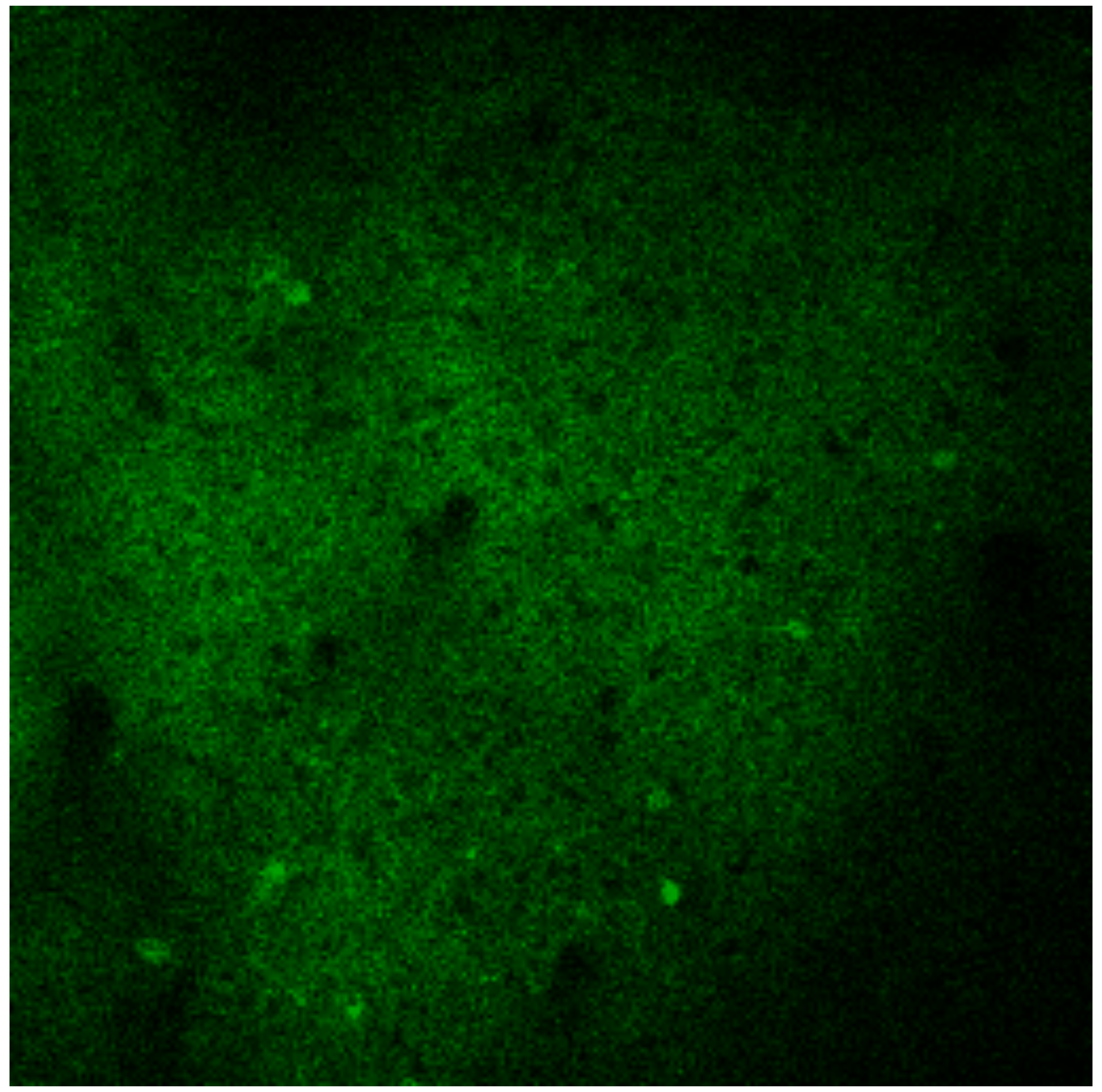
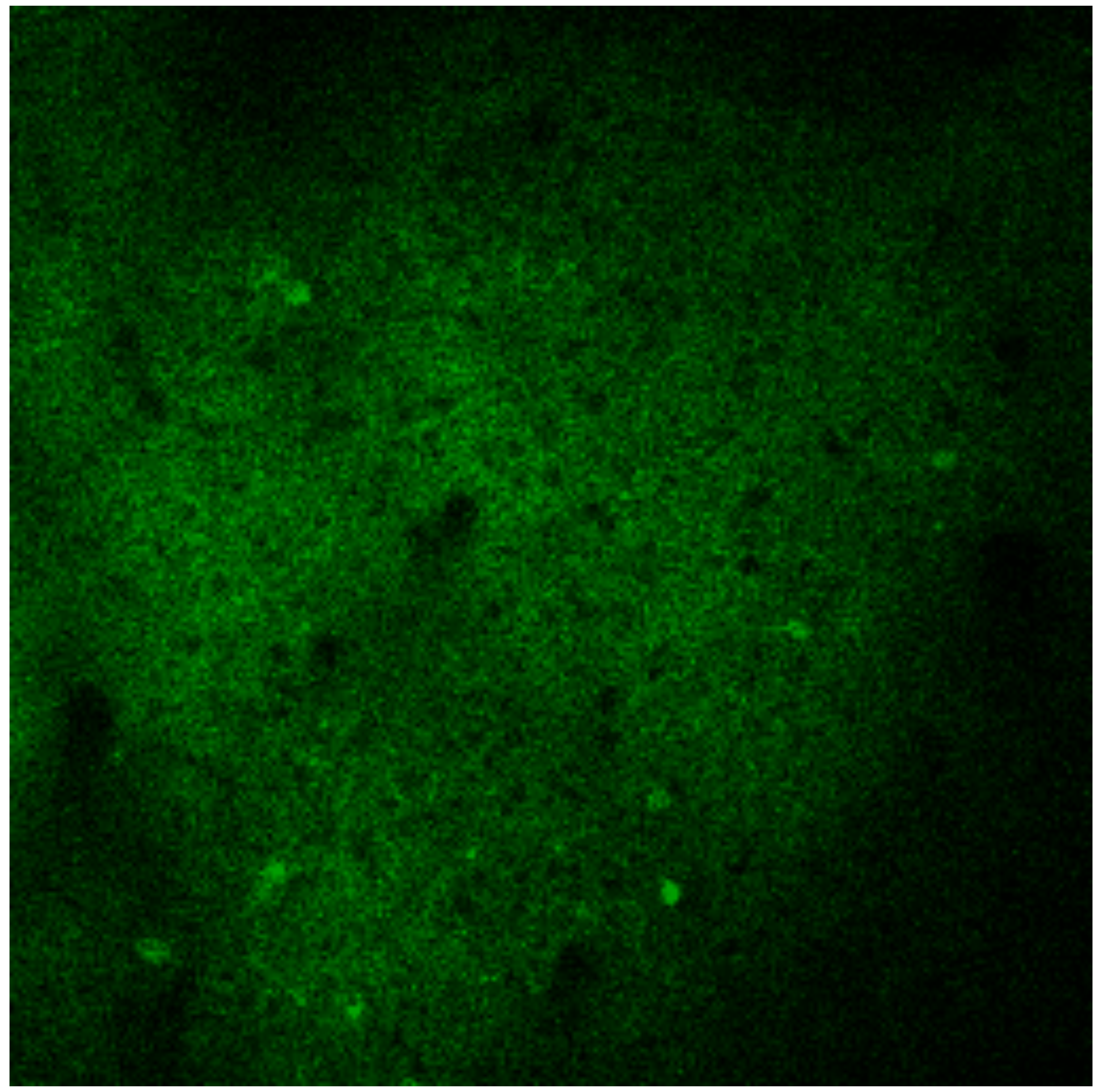


Triplett et al (2023)

Bayesian target optimisation

Goal: Minimise off-target activation for any requested ensemble stimulus



Triplett et al (2023)

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1. Mapping phase: learn optogenetic receptive fields

Triplett et al (2023)

Bayesian target optimisation

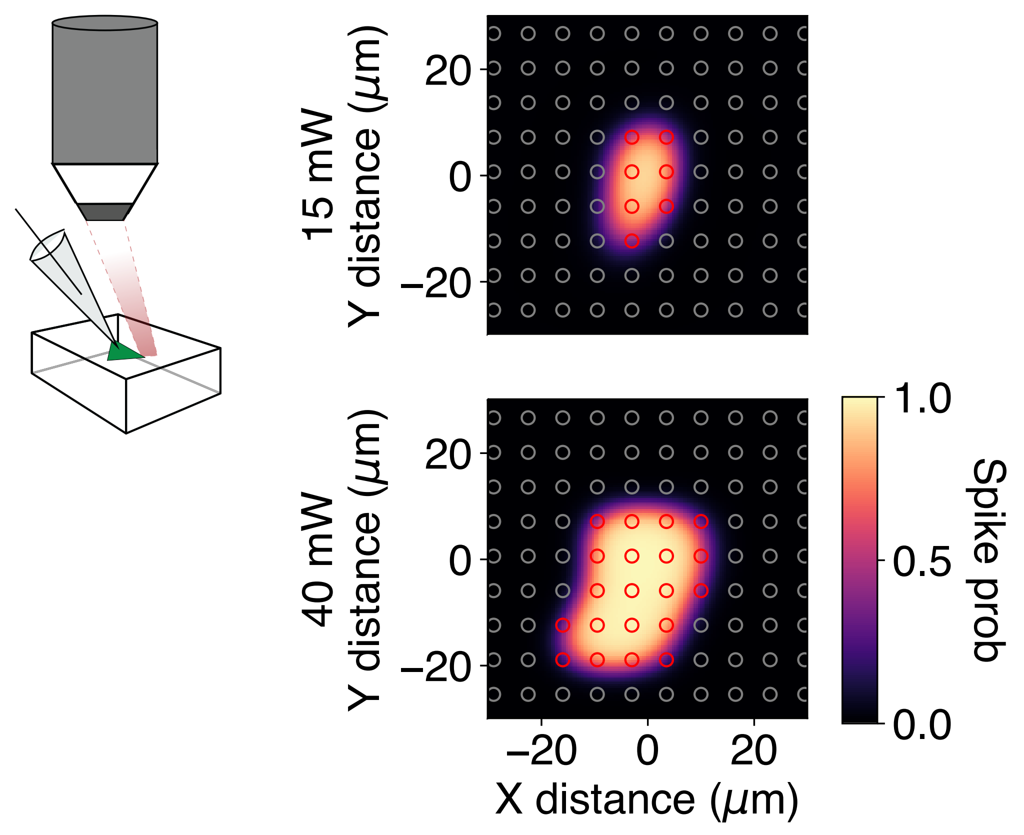
Goal: Minimise off-target activation for any requested ensemble stimulus

1. Mapping phase: learn optogenetic receptive fields

2. Optimisation phase: computationally identify optimal holographic targets

Triplett et al (2023)

Optogenetic receptive field model



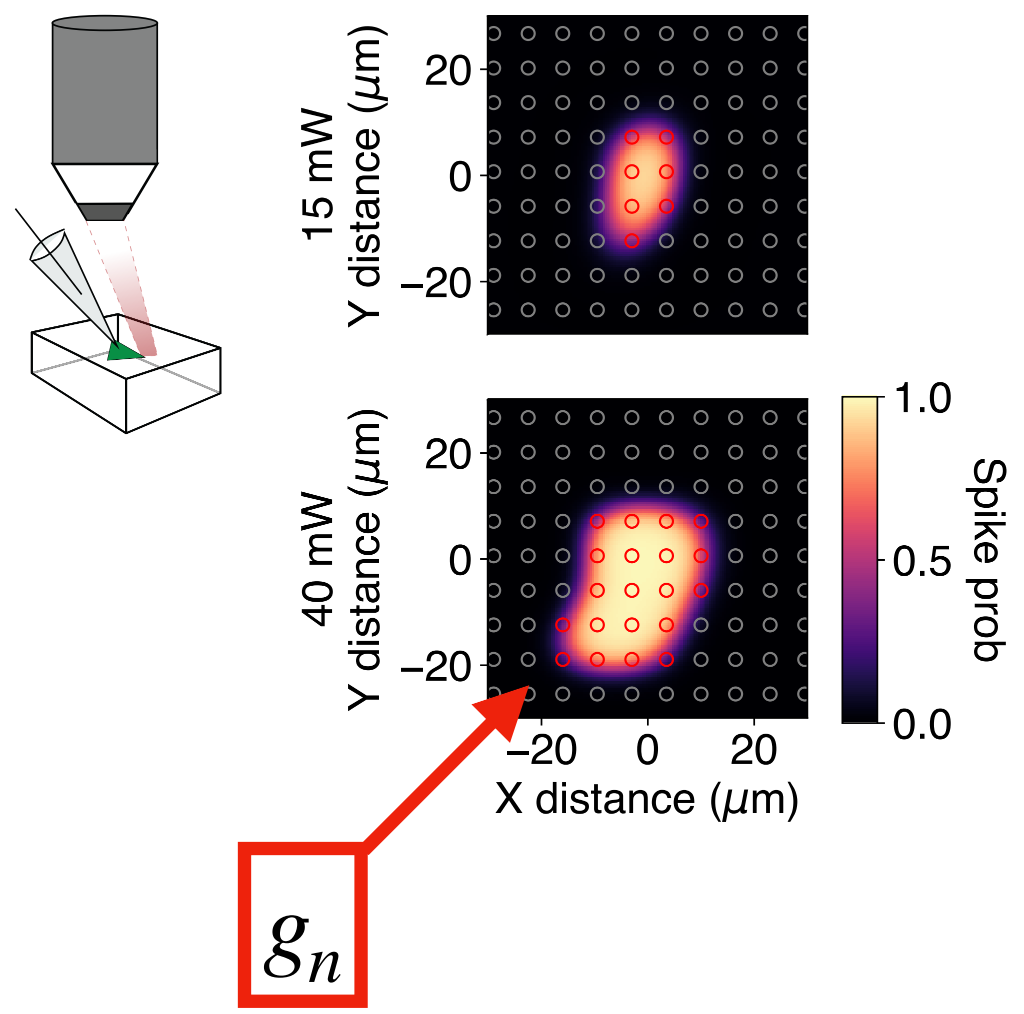
$$y_{nt} \sim \text{Bernoulli}(\sigma(\gamma_{nt}))$$

Bernoulli observation model

$$\gamma_{nt} = \sum_{j=1}^{J} g_n(\mathbf{x}_t^j) - \theta_n$$

summed 2p excitation from J holographic targets $\mathbf{x}_t^j$

Optogenetic receptive field model



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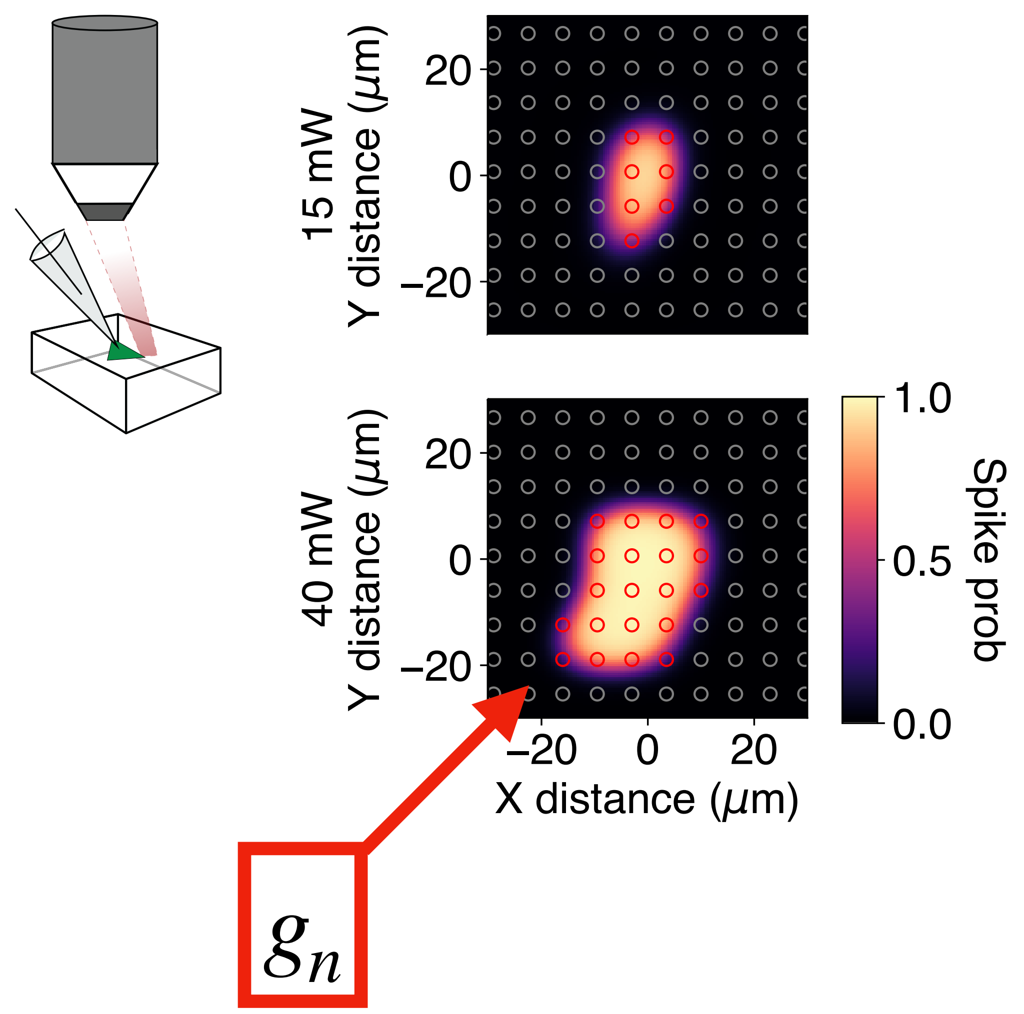

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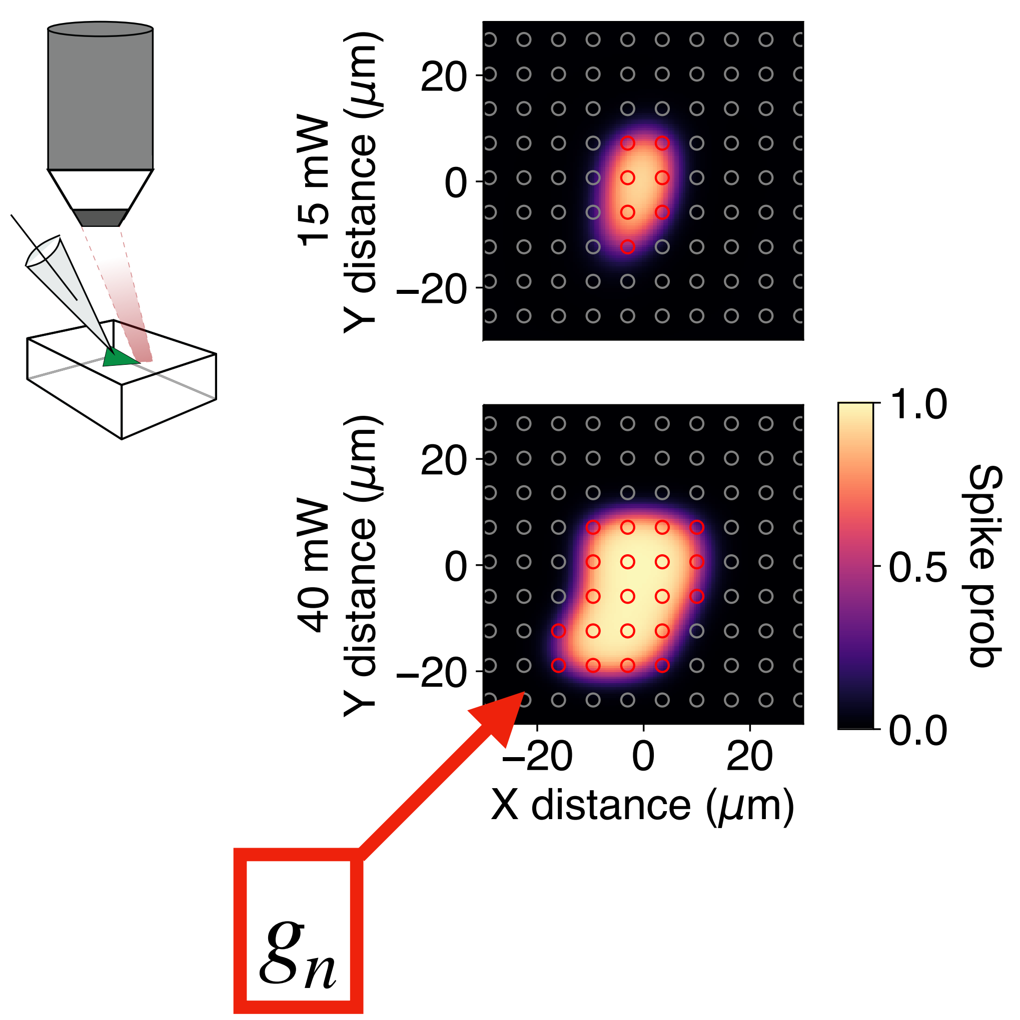
$$g_n \sim \text{GP}(m_n(\cdot), k(\cdot, \cdot))$$

Gaussian process: nonparametric, smooth in space + power

Optogenetic receptive field model



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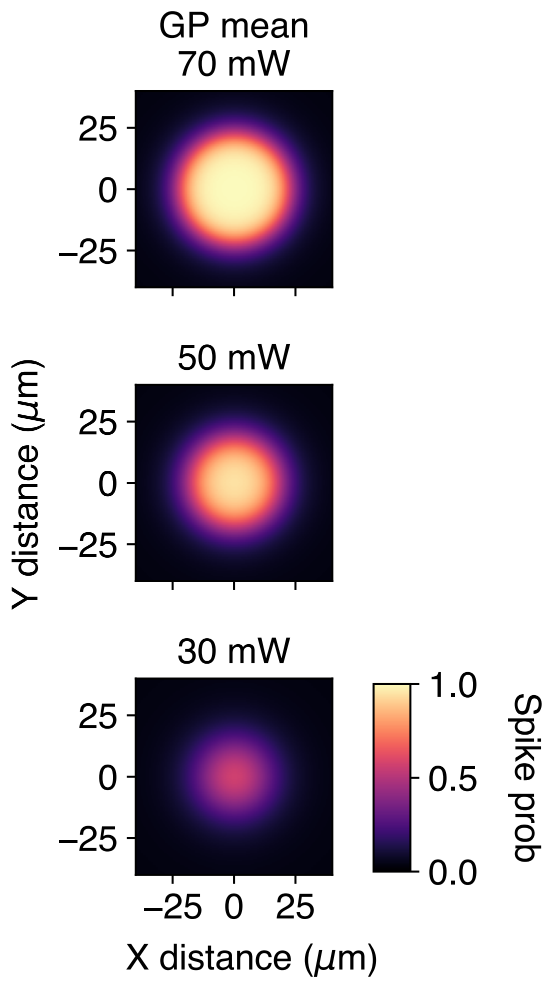
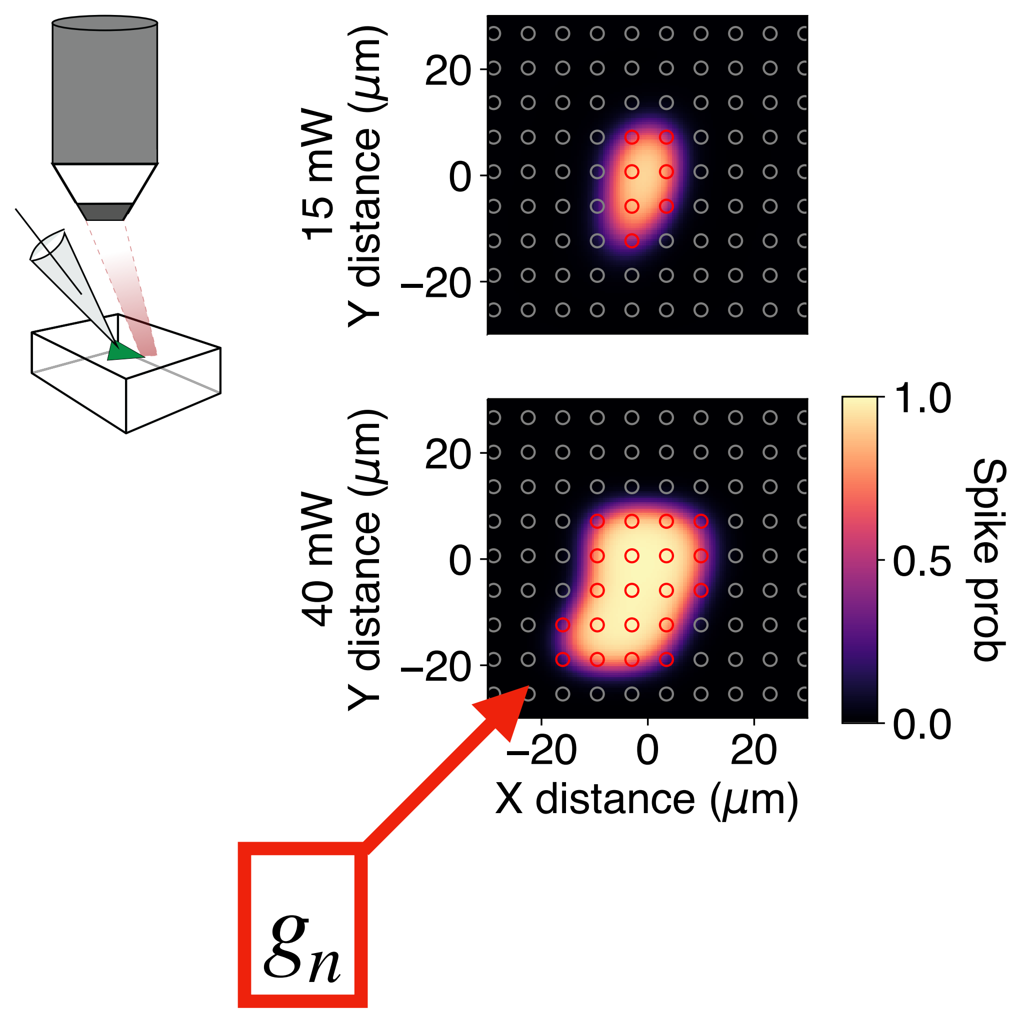


$$m_n(\mathbf{x}) = \rho I \exp(-\|\mathbf{c} - \mathbf{L}_n\|^2/\sigma_m^2)$$

mean function (for stimulus $\mathbf{x} = (I, \mathbf{c})$)

Optogenetic receptive field model



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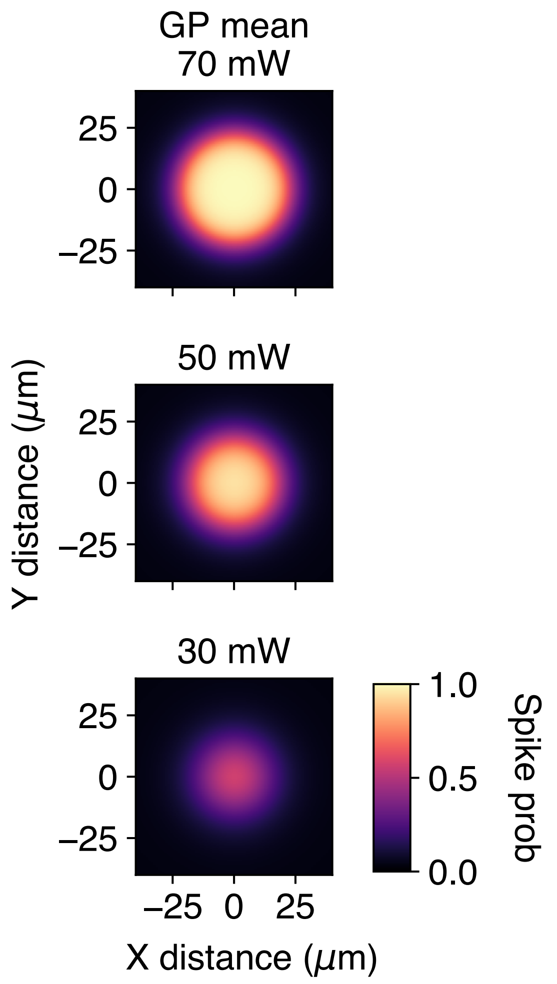

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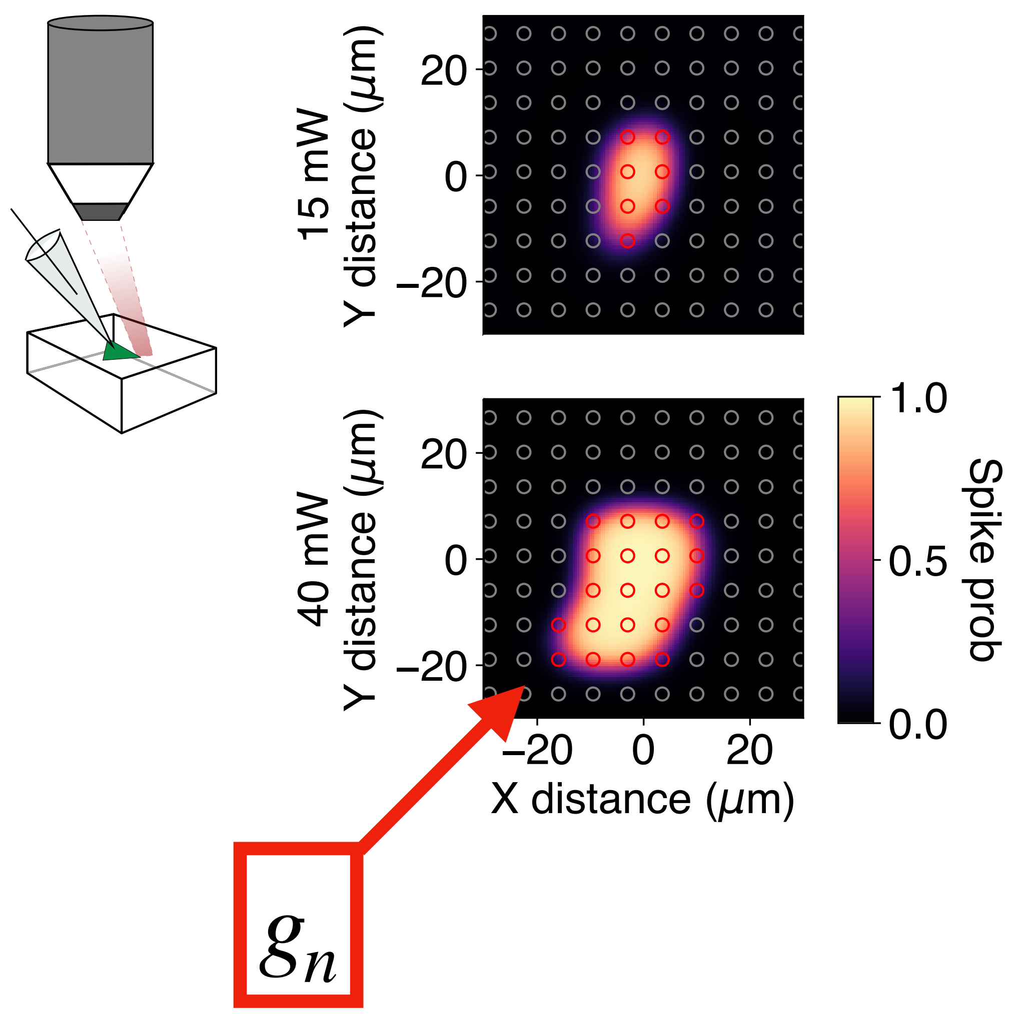
covariance kernel (RBF/radial basis function)

Optogenetic receptive field model



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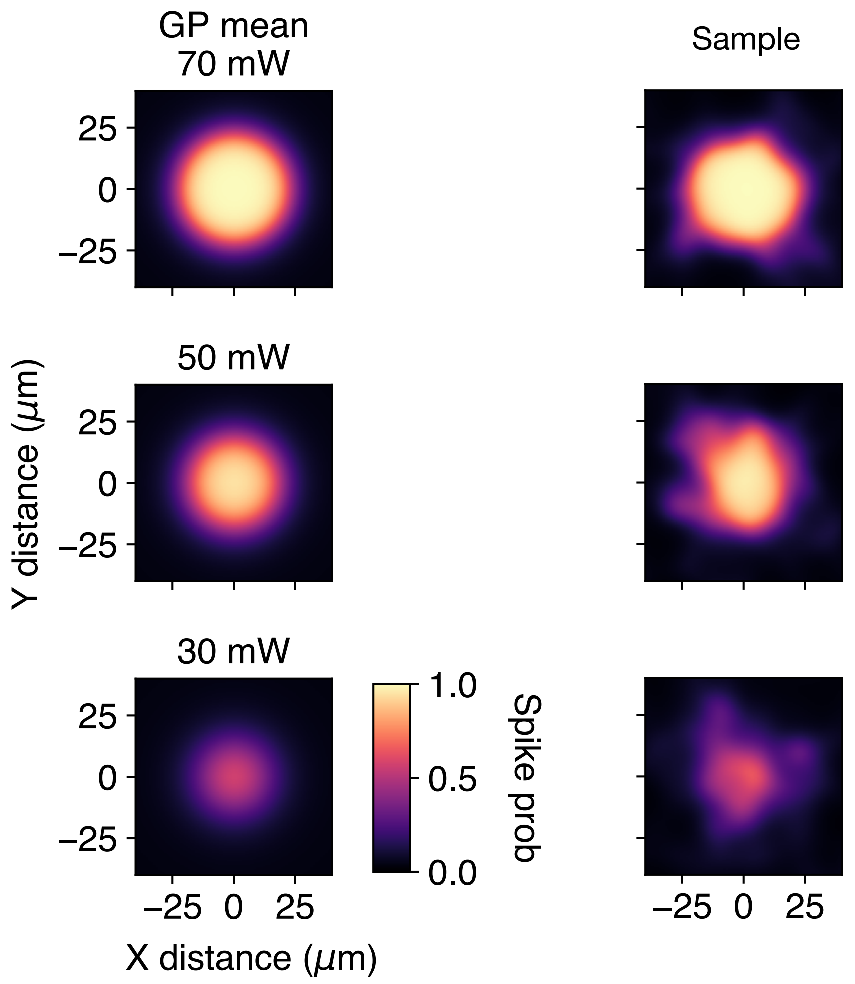

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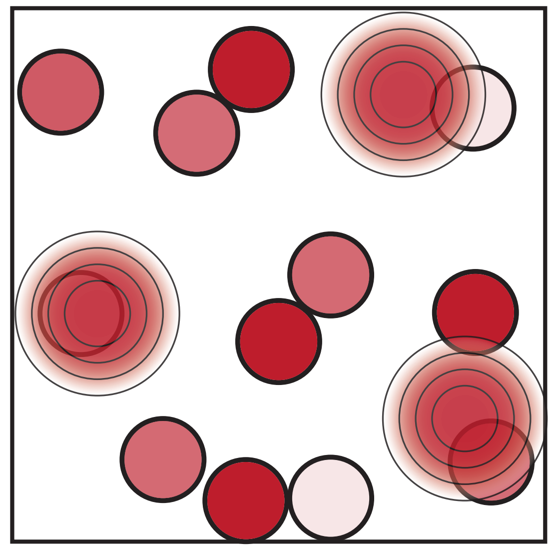
Mapping phase

Holographic ensemble stimulation + calcium imaging



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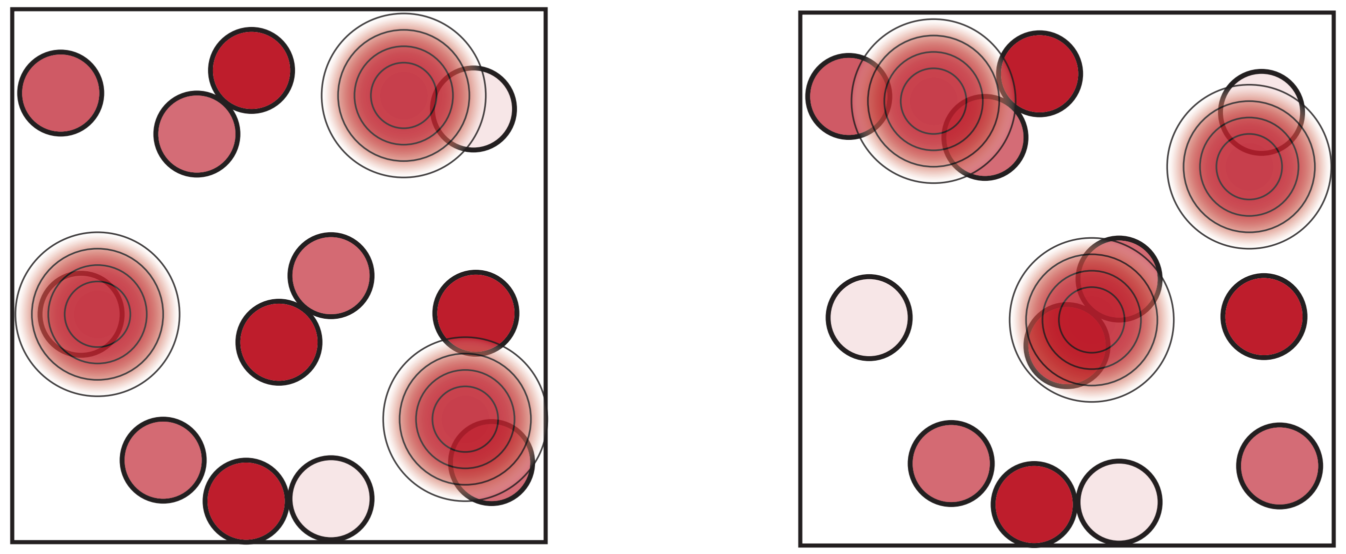

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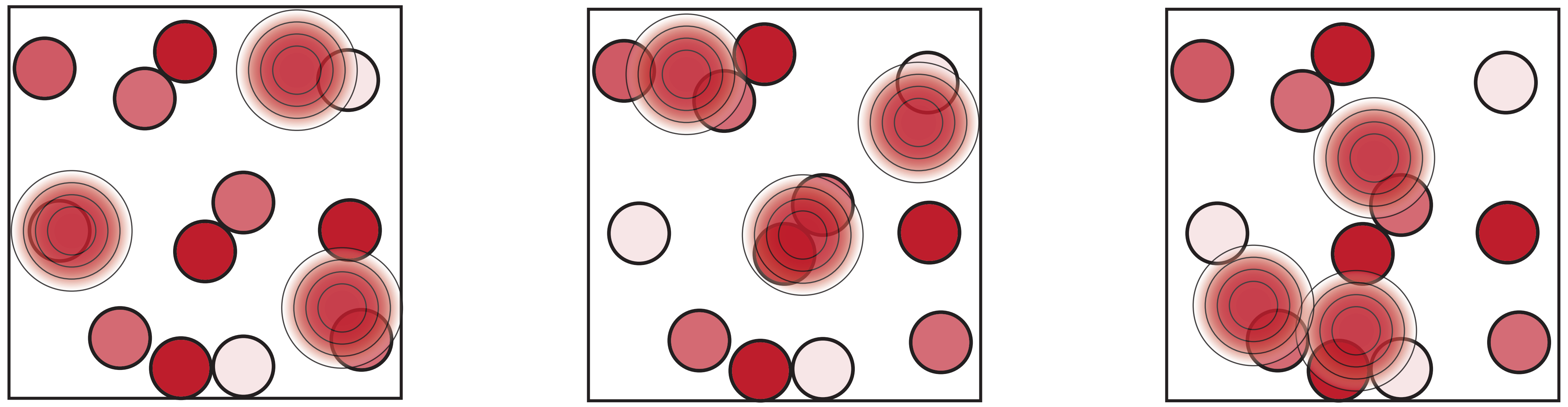
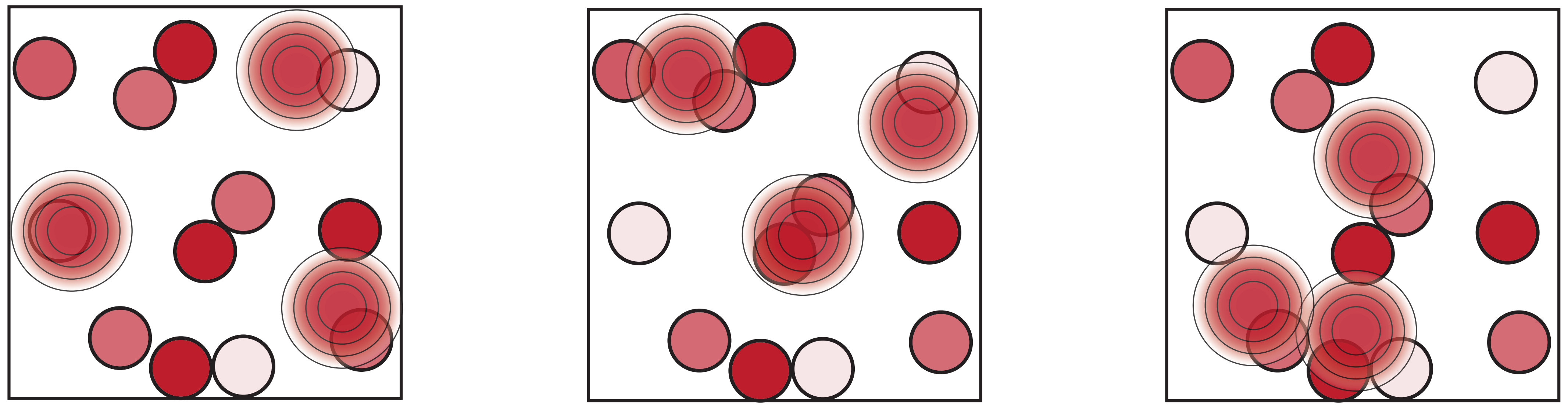


Mapping phase

Holographic ensemble stimulation + calcium imaging

a. Map many ORFs simultaneously

b. Model how neurons integrate 2p excitation from multiple holograms at once



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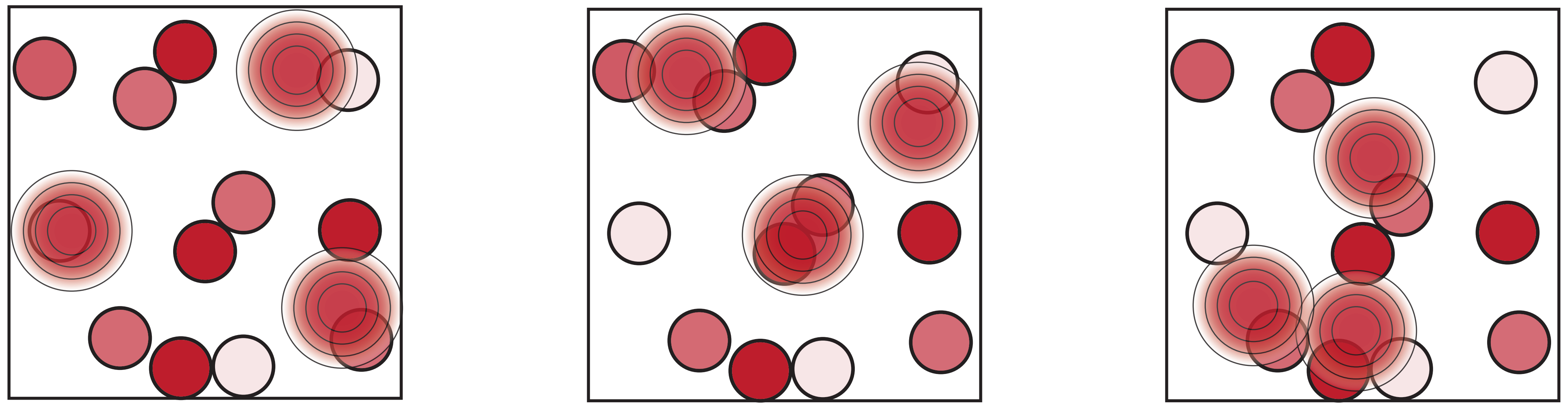

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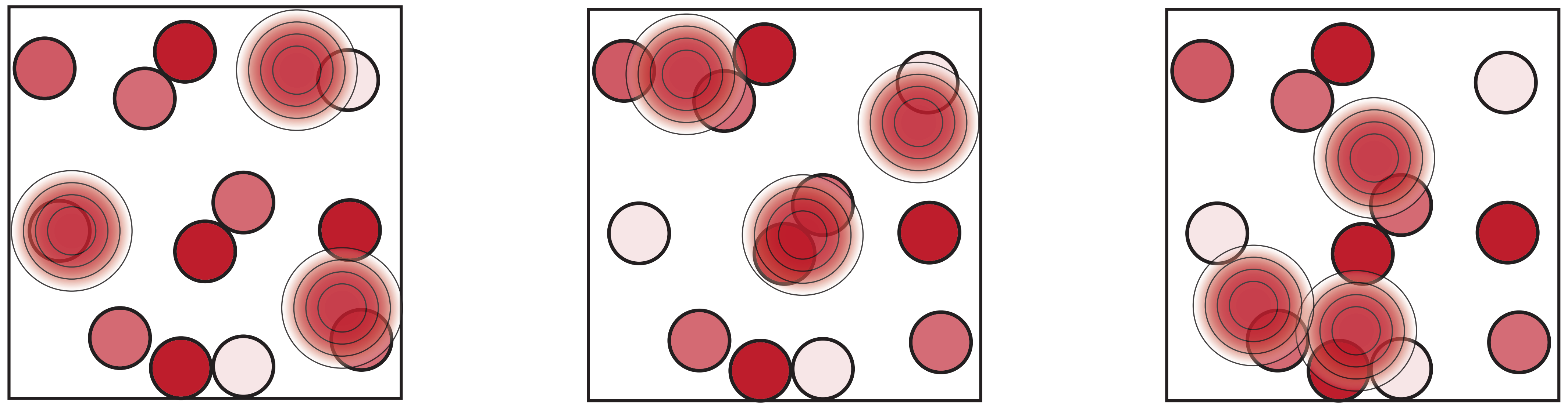


Model

$y_{nt} \sim \text{Bernoulli}(\sigma(\gamma_{nt}))$

$$\gamma_{nt} = \sum_{j=1}^{J} g_n(\mathbf{x}_t^j) - \theta_n$$

$g_n \sim \text{GP}(m_n(\cdot), k(\cdot, \cdot))$

Inference

$$\hat{g}_n, \hat{\theta}_n = \arg\max_{g_n, \theta_n} \left\{ \sum_t \ln p(y_{nt} \mid \mathbf{x}_t, g_n, \theta_n) + \ln p(g_n(\mathbf{X}) \mid \phi) \right\}$$

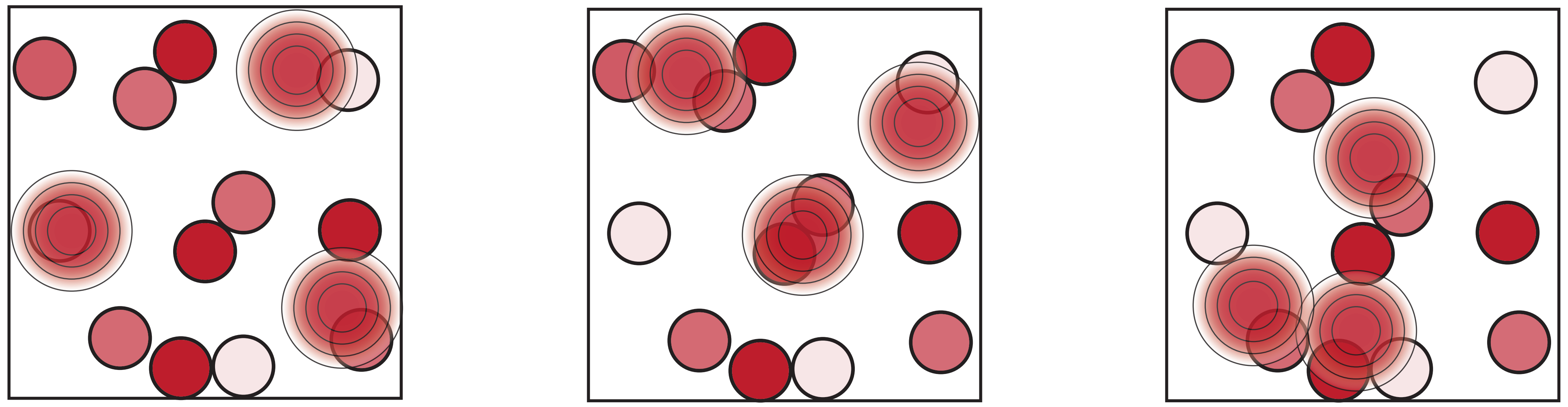
such that $g_n(\mathbf{x}_t) \geq 0$ for $t = 1, \ldots, T$

Mapping phase

Holographic ensemble stimulation + calcium imaging

a. Map many ORFs simultaneously

b. Model how neurons integrate 2p excitation from multiple holograms at once



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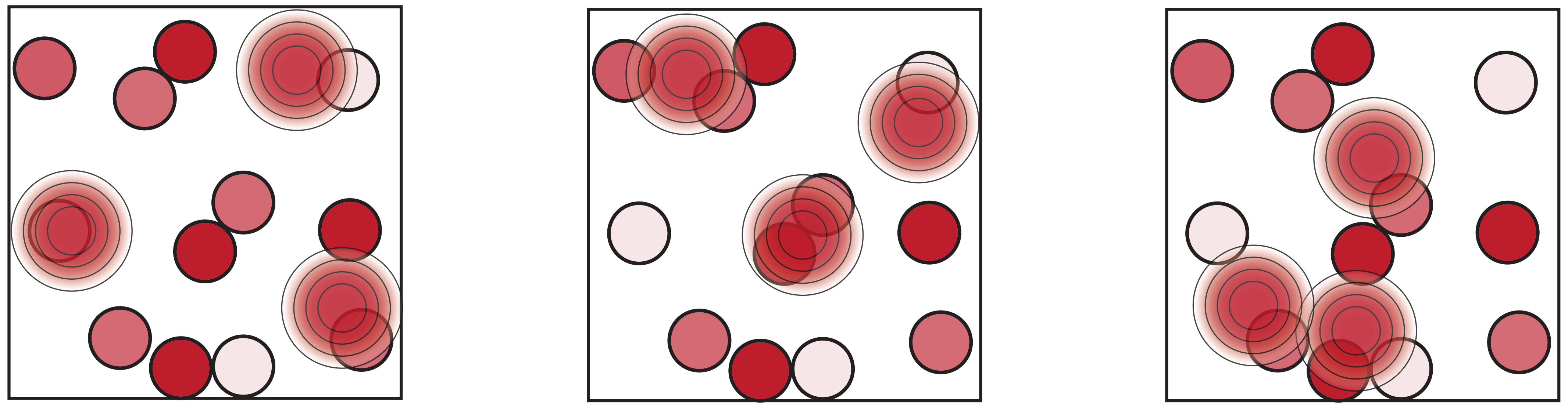

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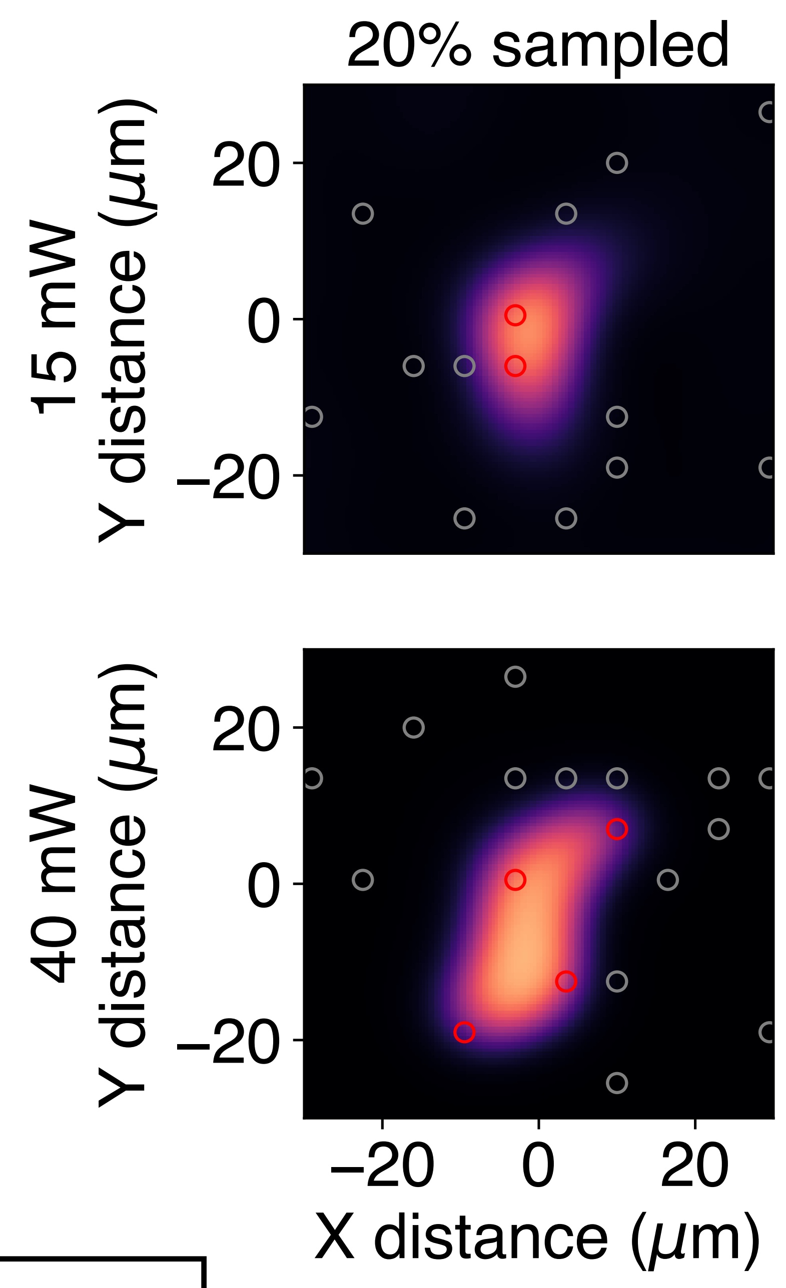

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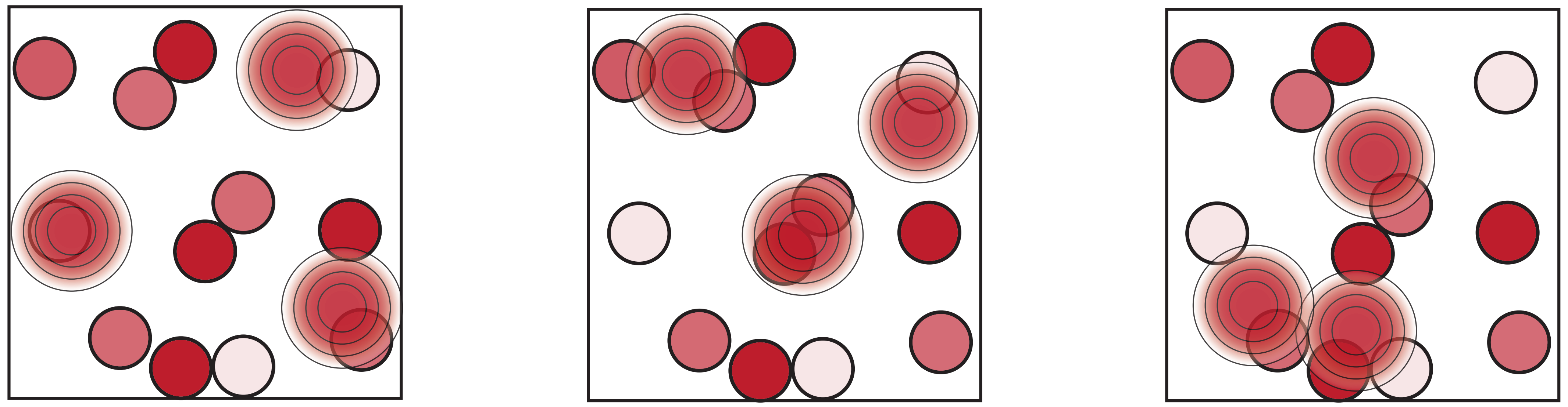

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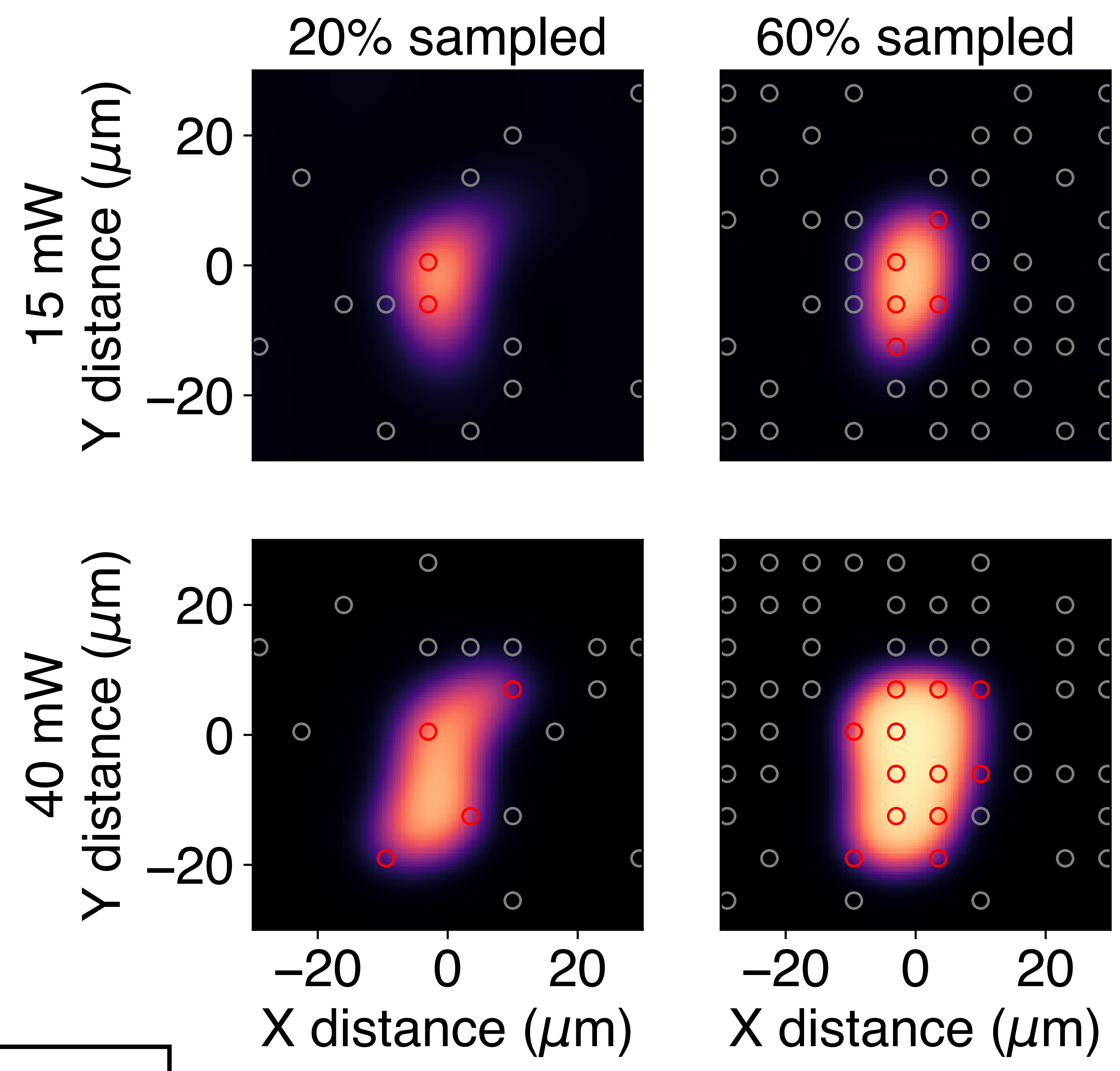

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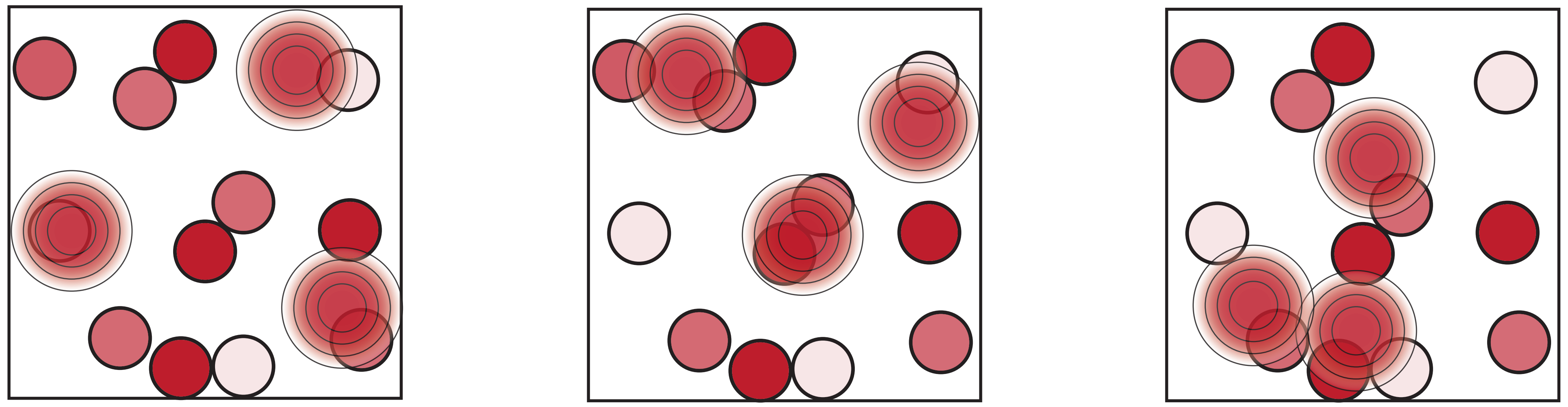

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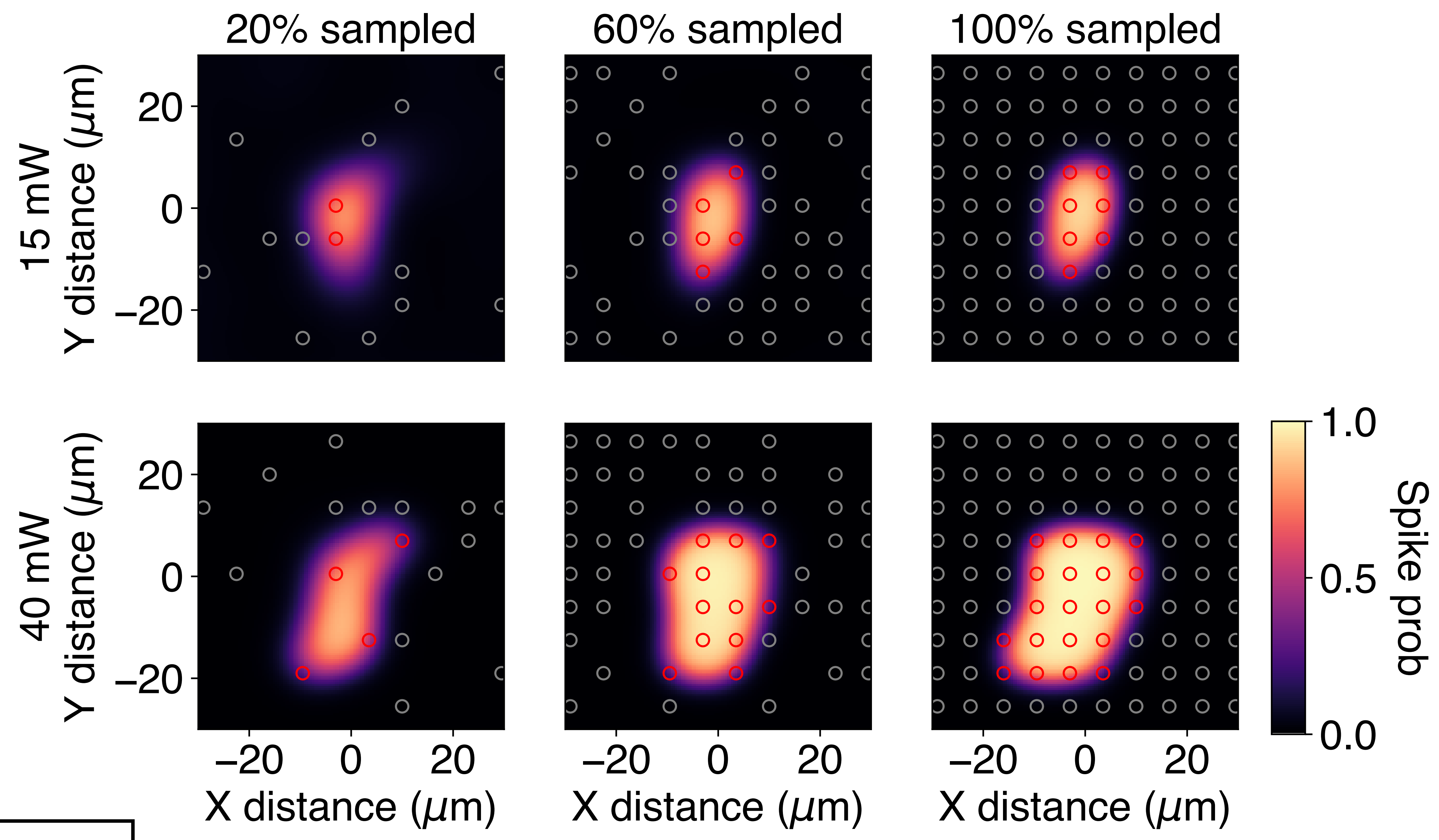

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(single-target stim case)

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Approach

Run gradient descent on objective function

But: requires differentiating through nonparametric surface g_n

Optimisation phase

Approach

Use fact that for a GP g_n, its derivative $\frac{\partial}{\partial x_d} g_n(\mathbf{x})$ is also a GP

McHutchon (2014, PhD Thesis)

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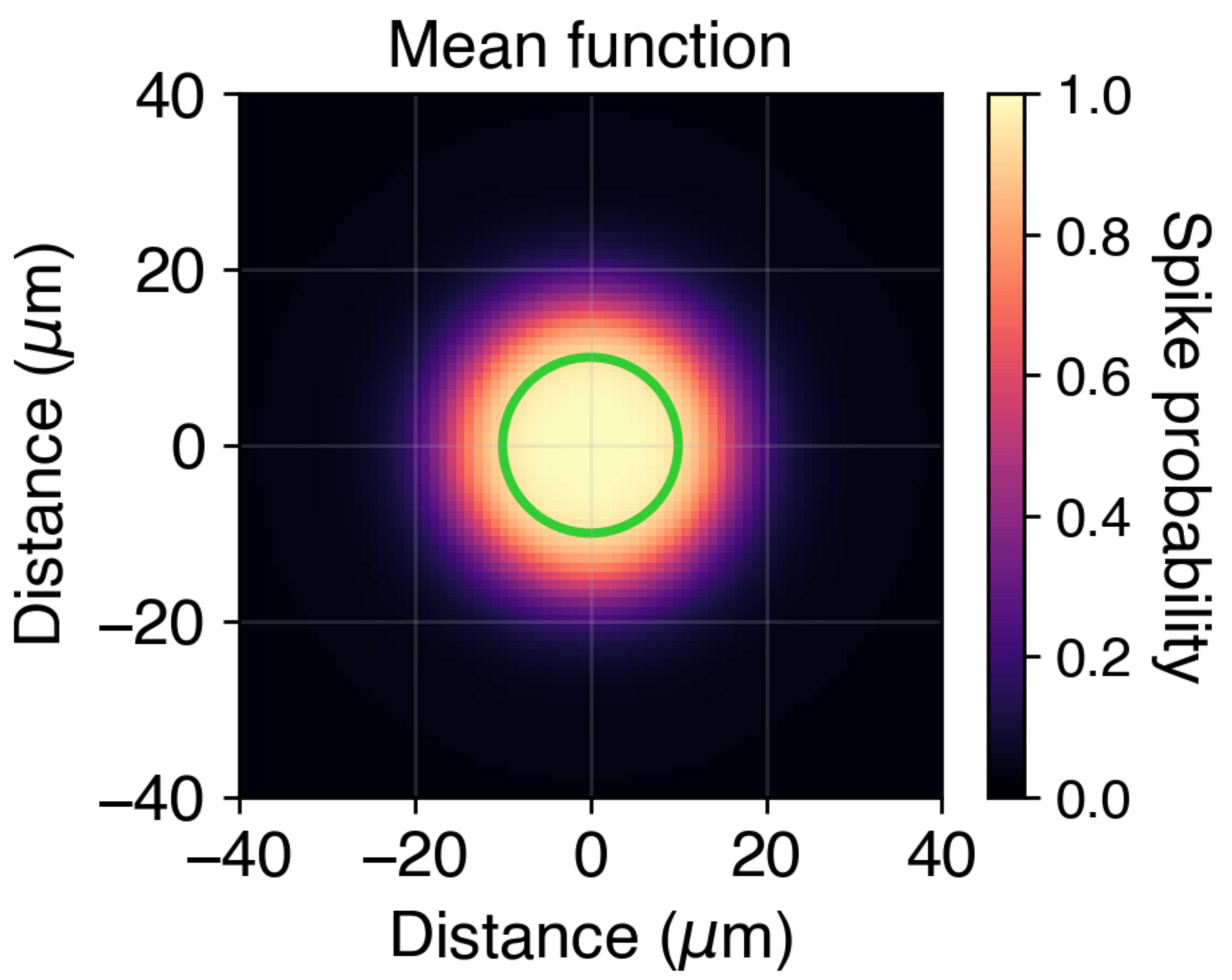

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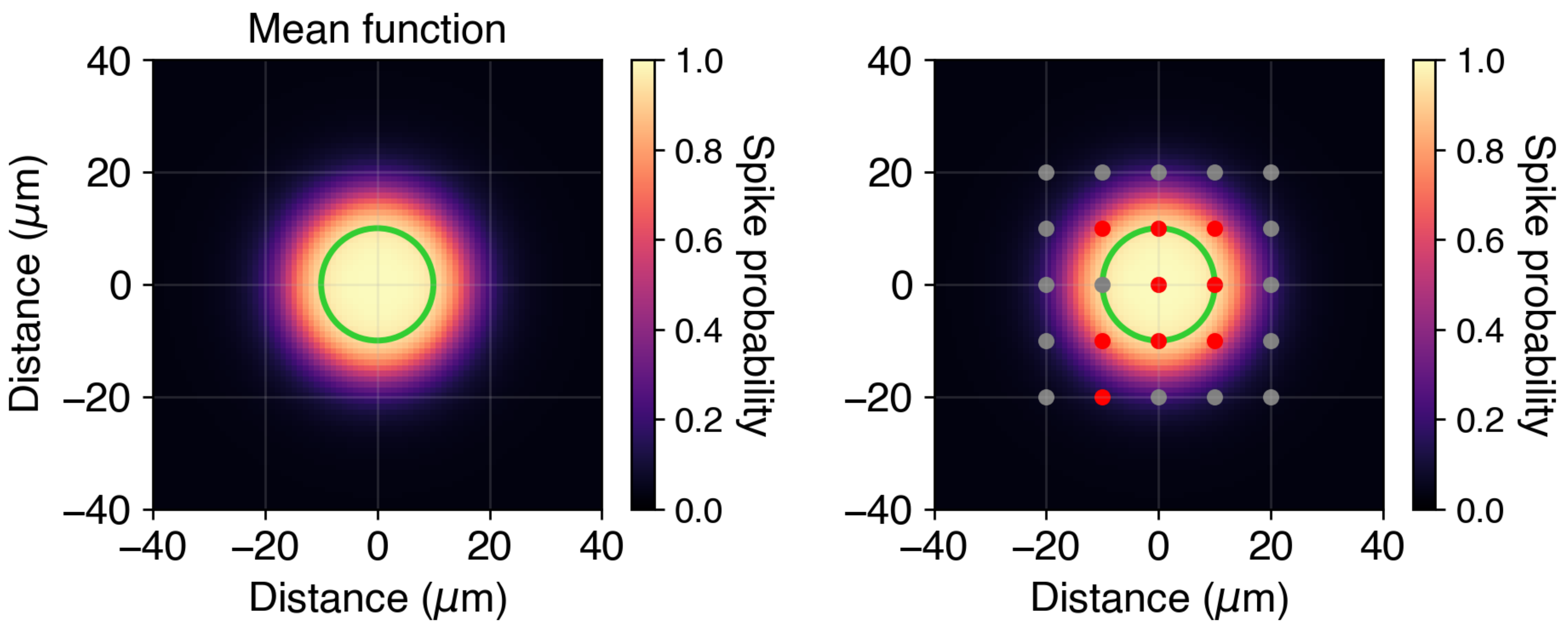

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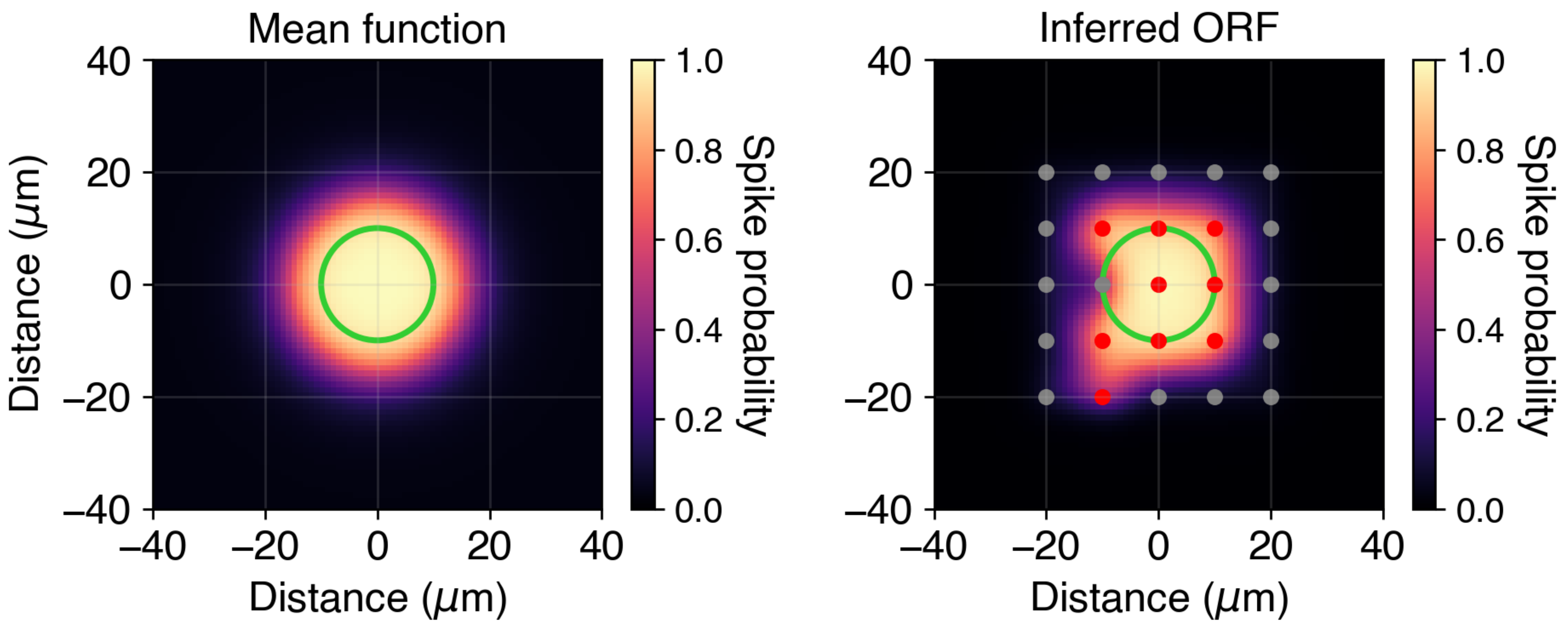

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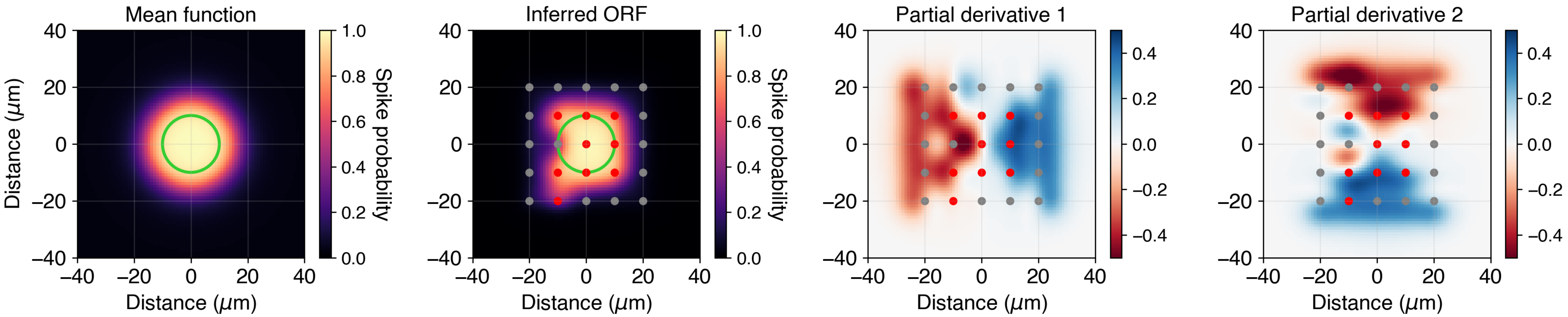

Optimisation phase

Approach: Gradient descent on $||\mathbf{\Omega} - \hat{y}(\mathbf{x}, \mathcal{G})||^2$

1. Initialise stimulus $\mathbf{x}$

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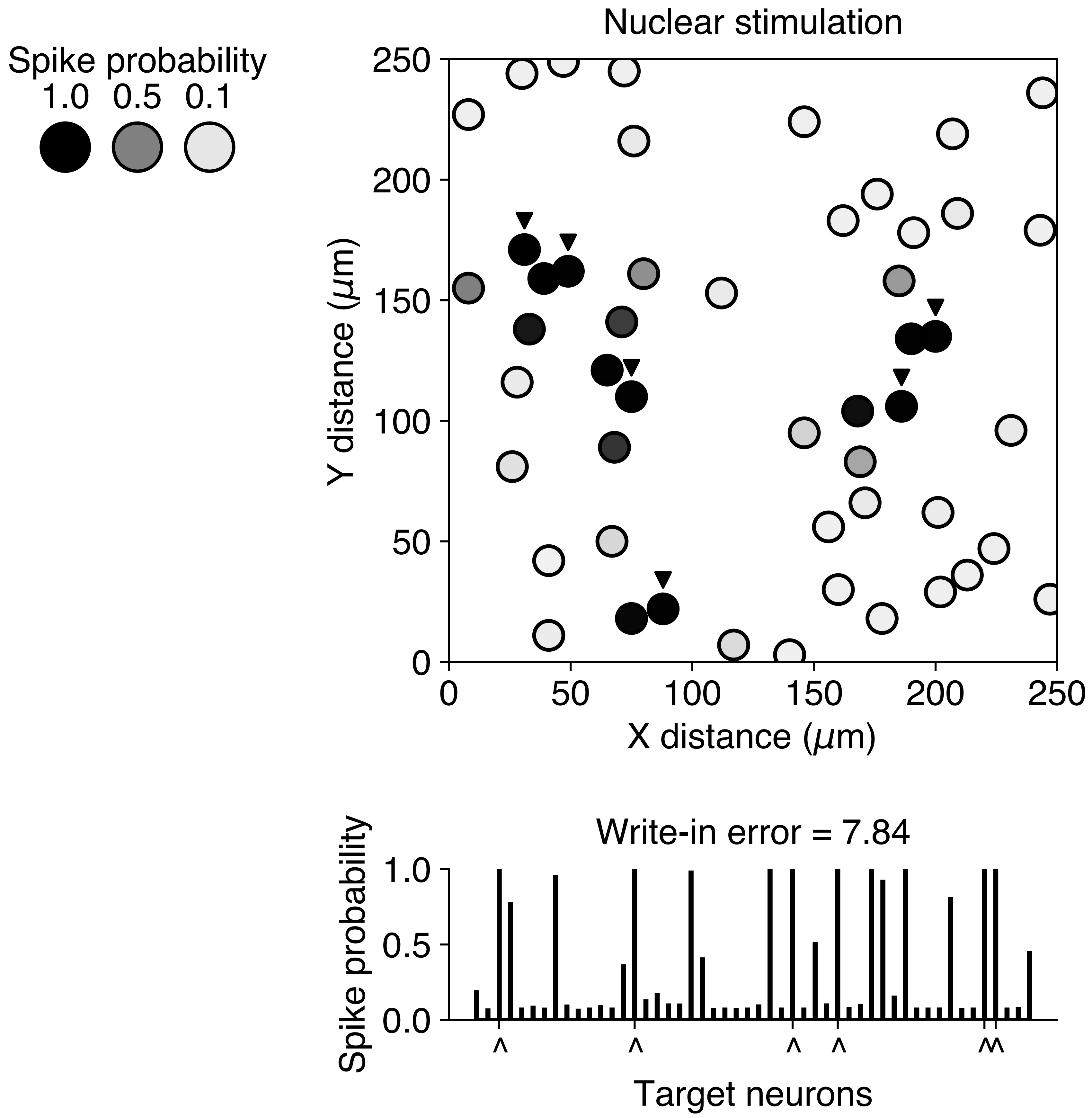

Triplett et al (2023)

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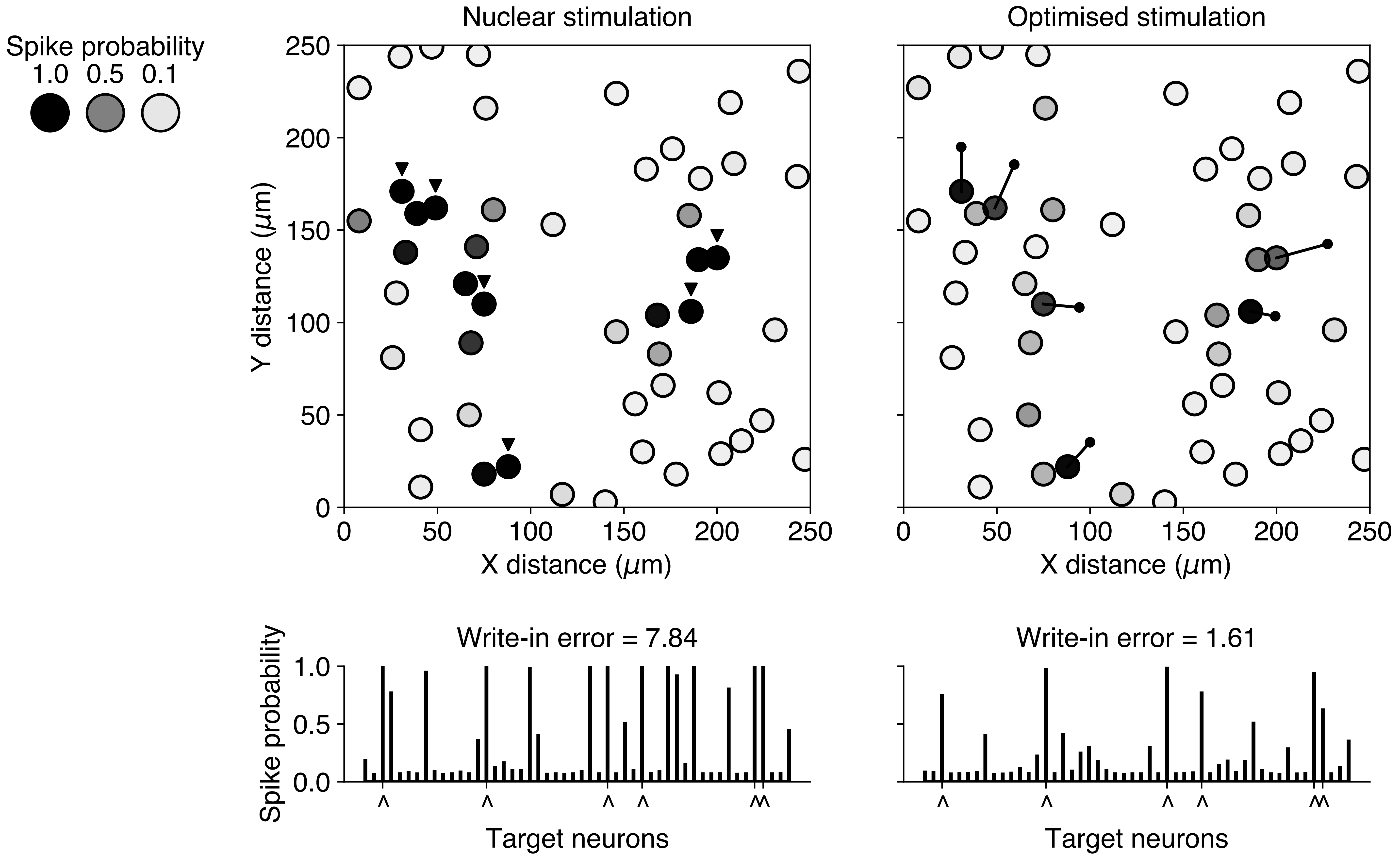

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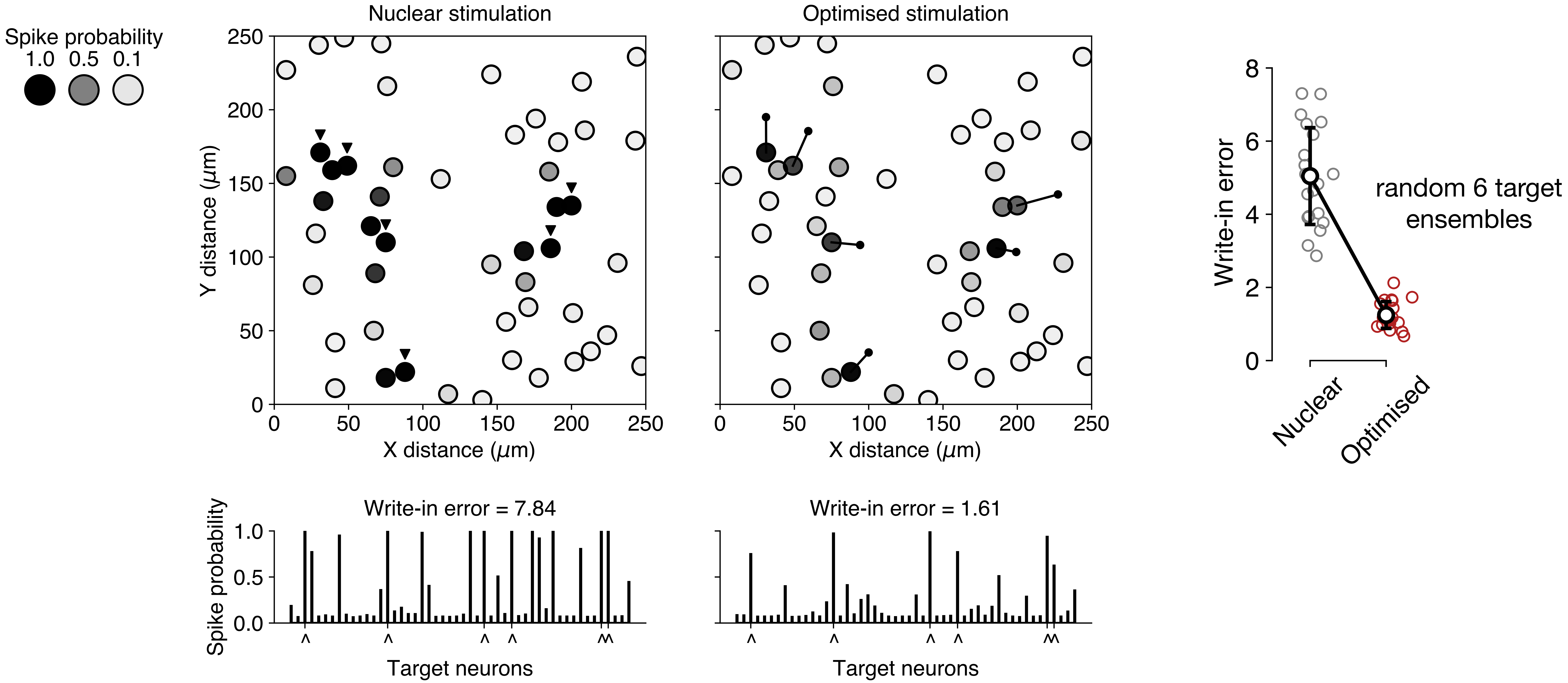

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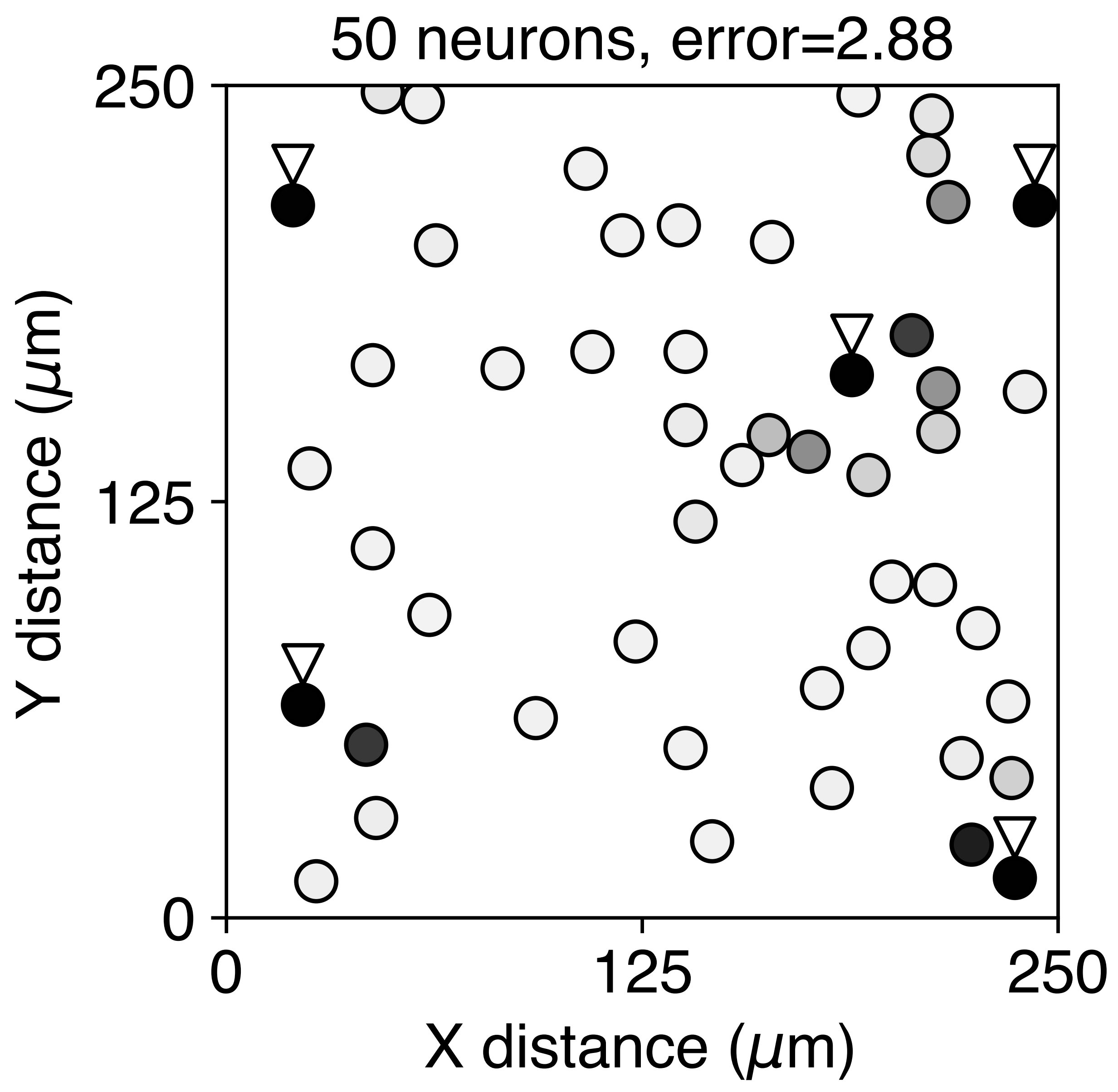

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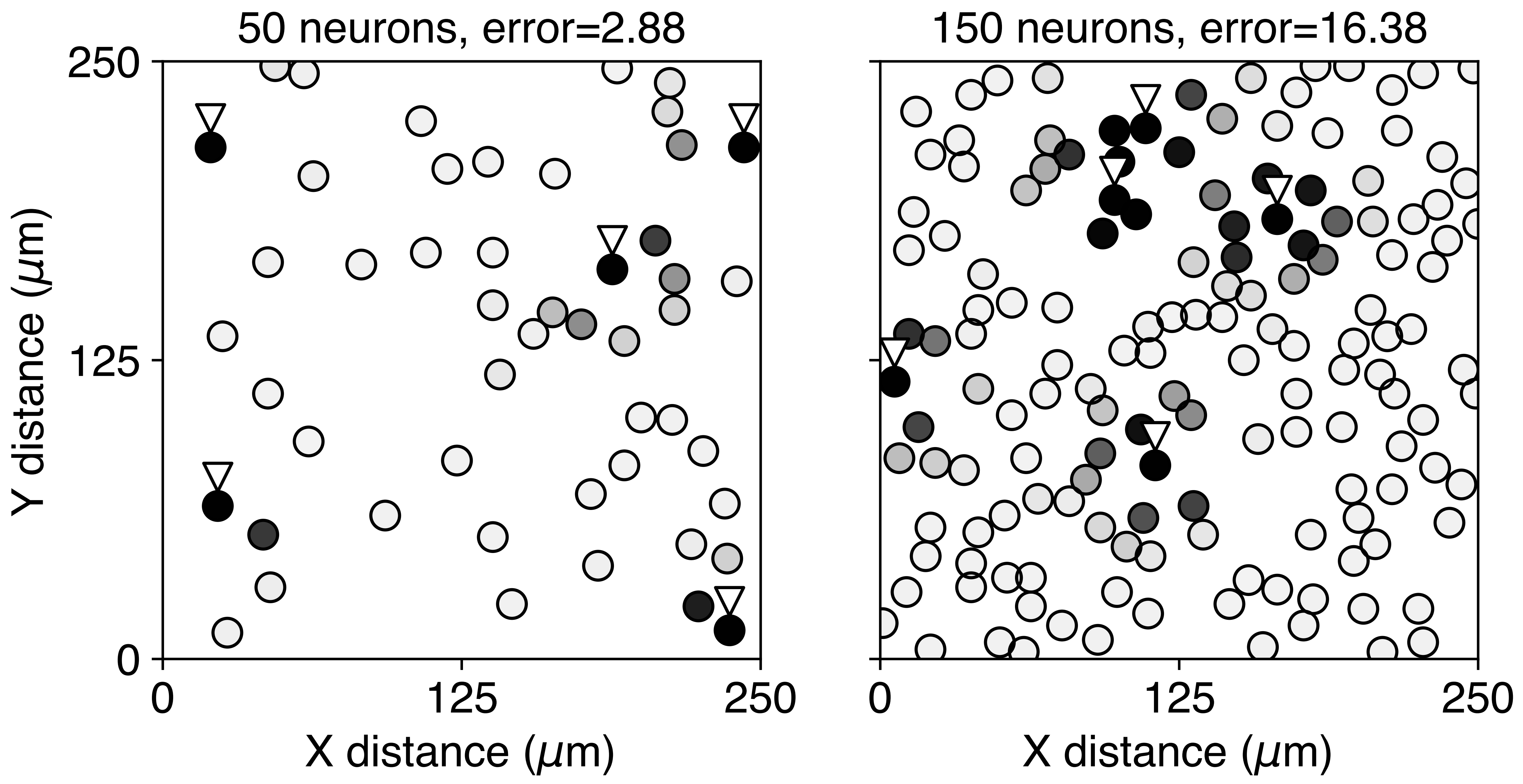

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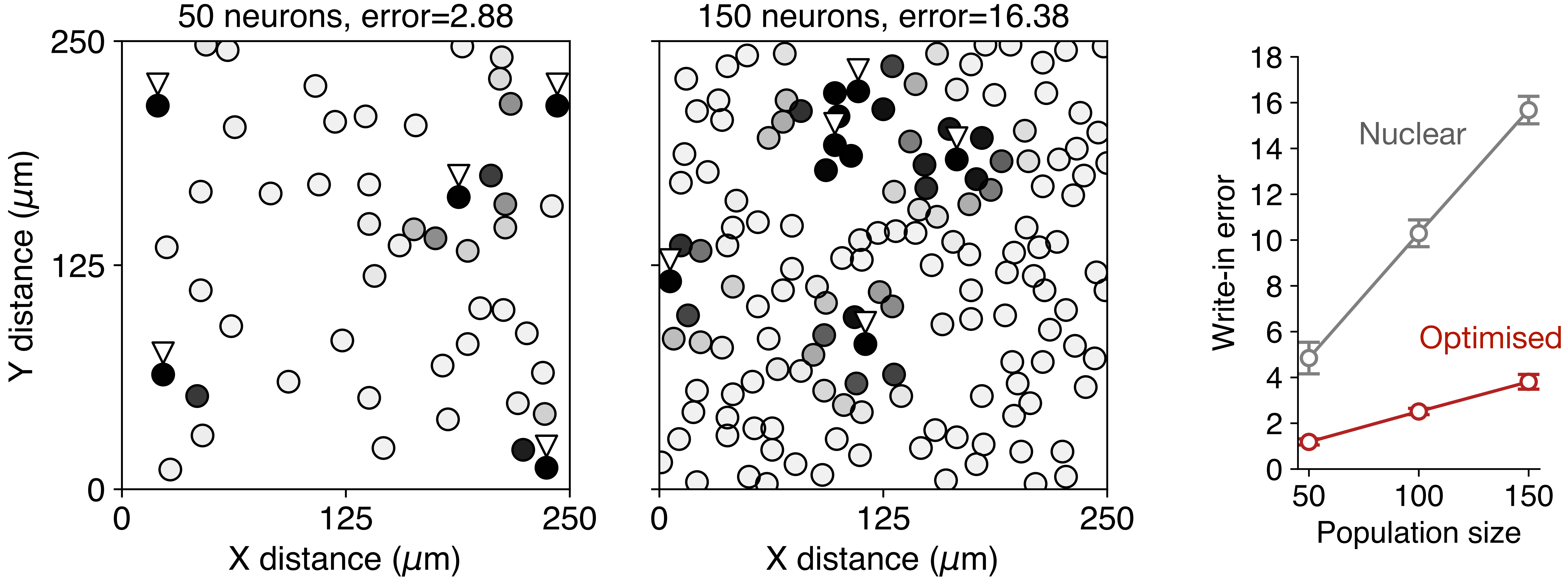

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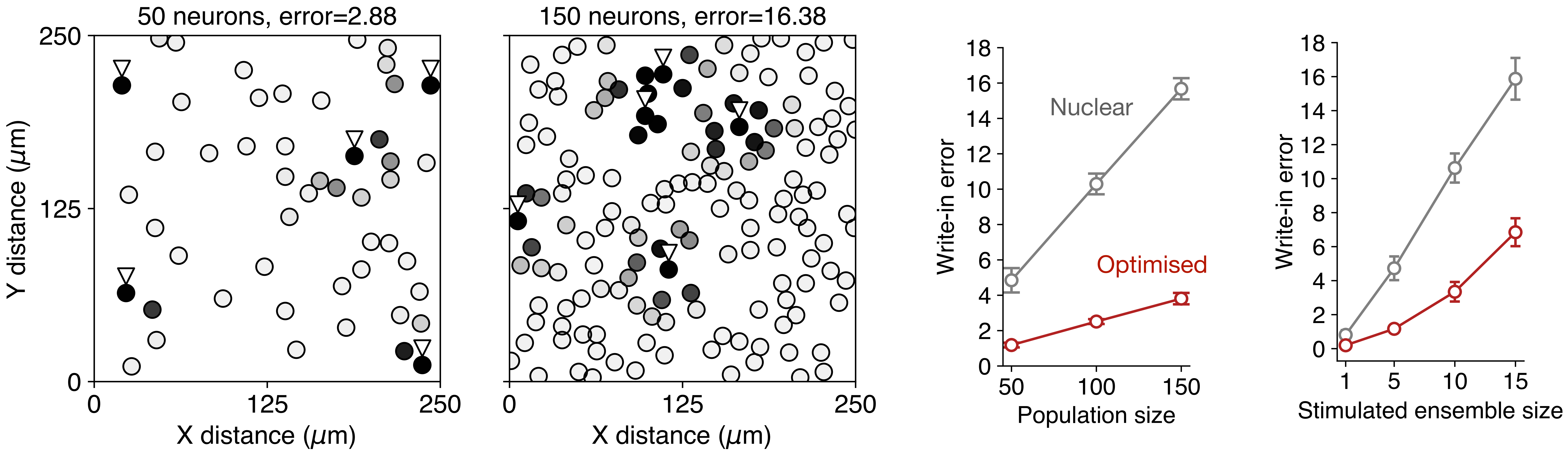

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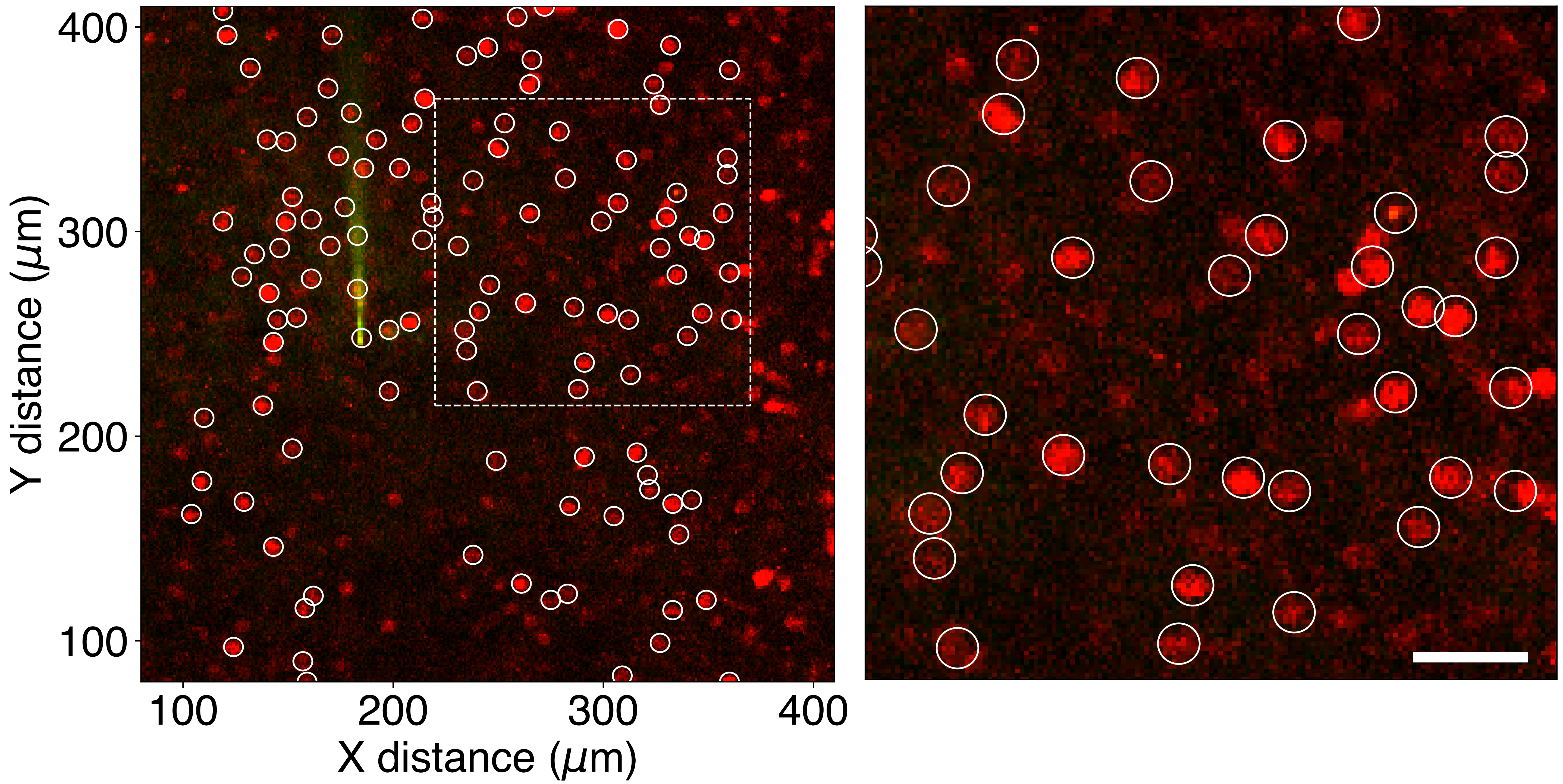
Validated in “hybrid” experimental data



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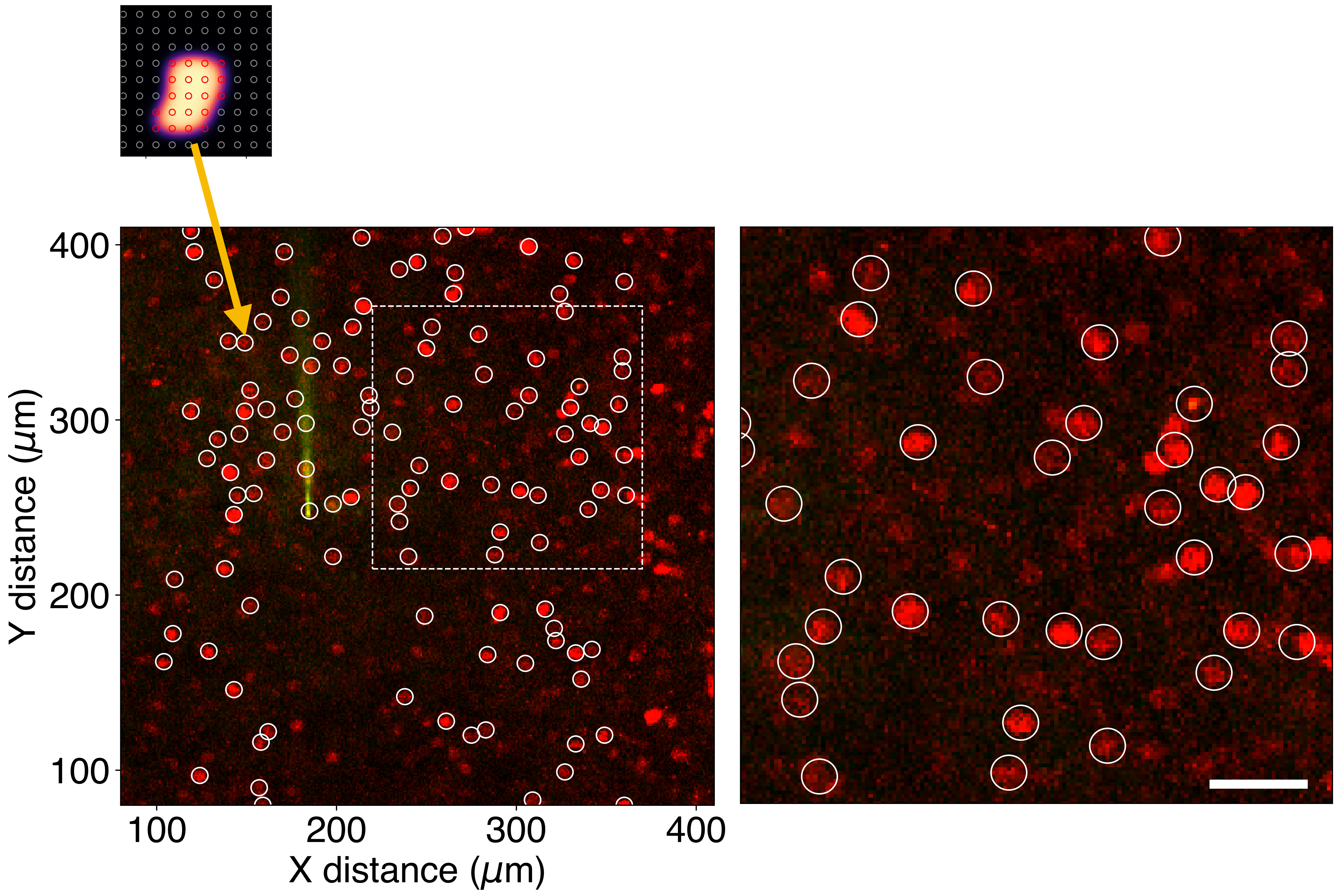

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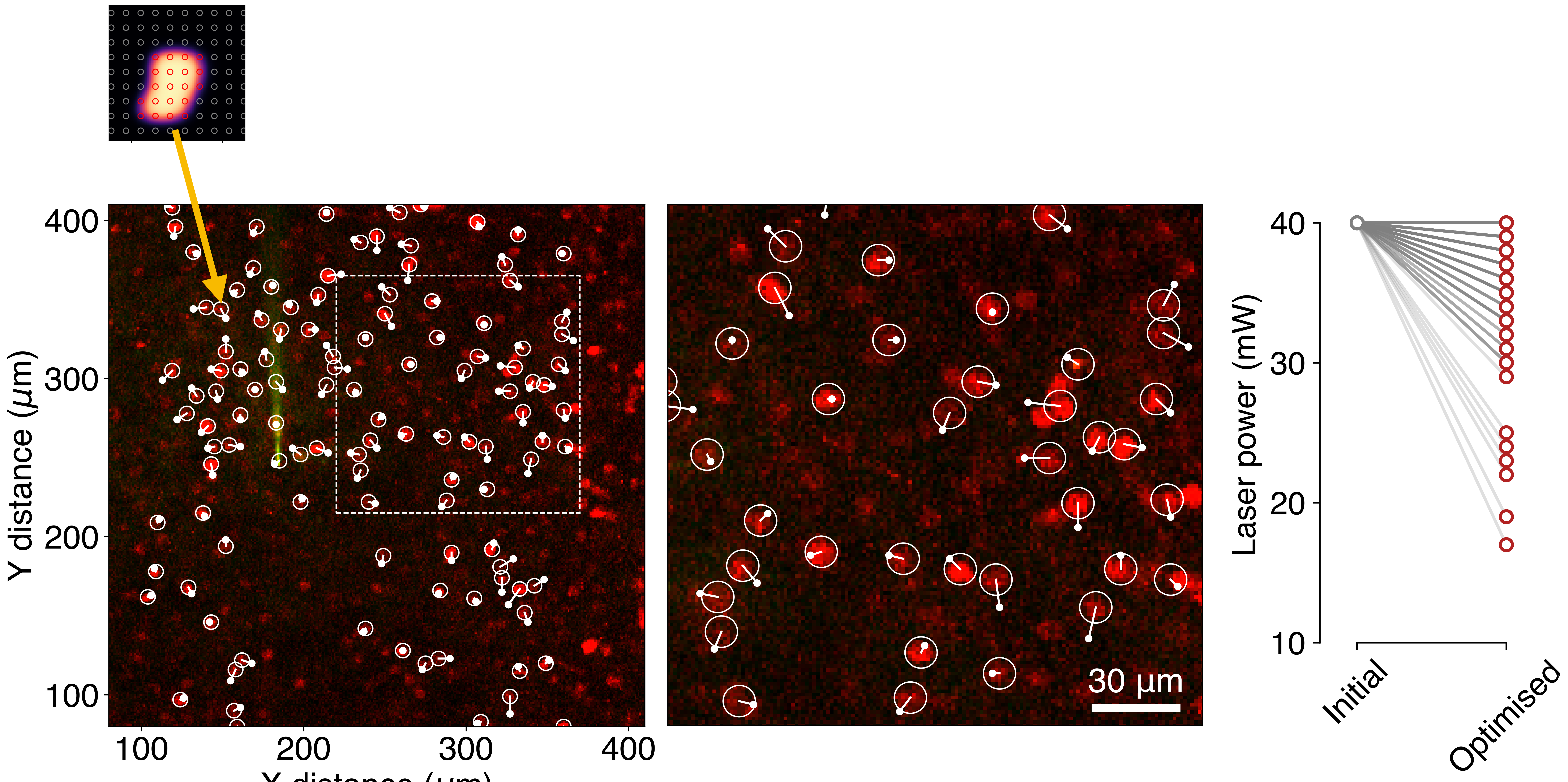

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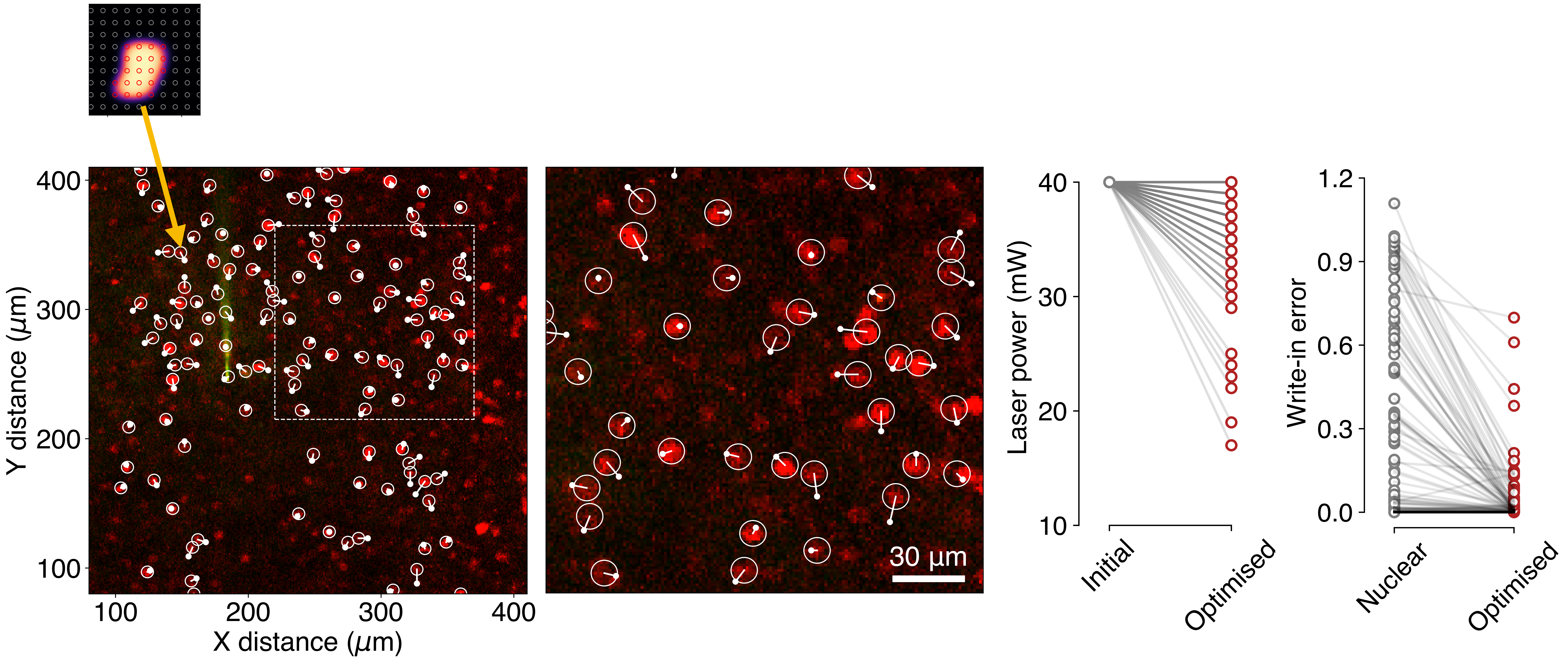

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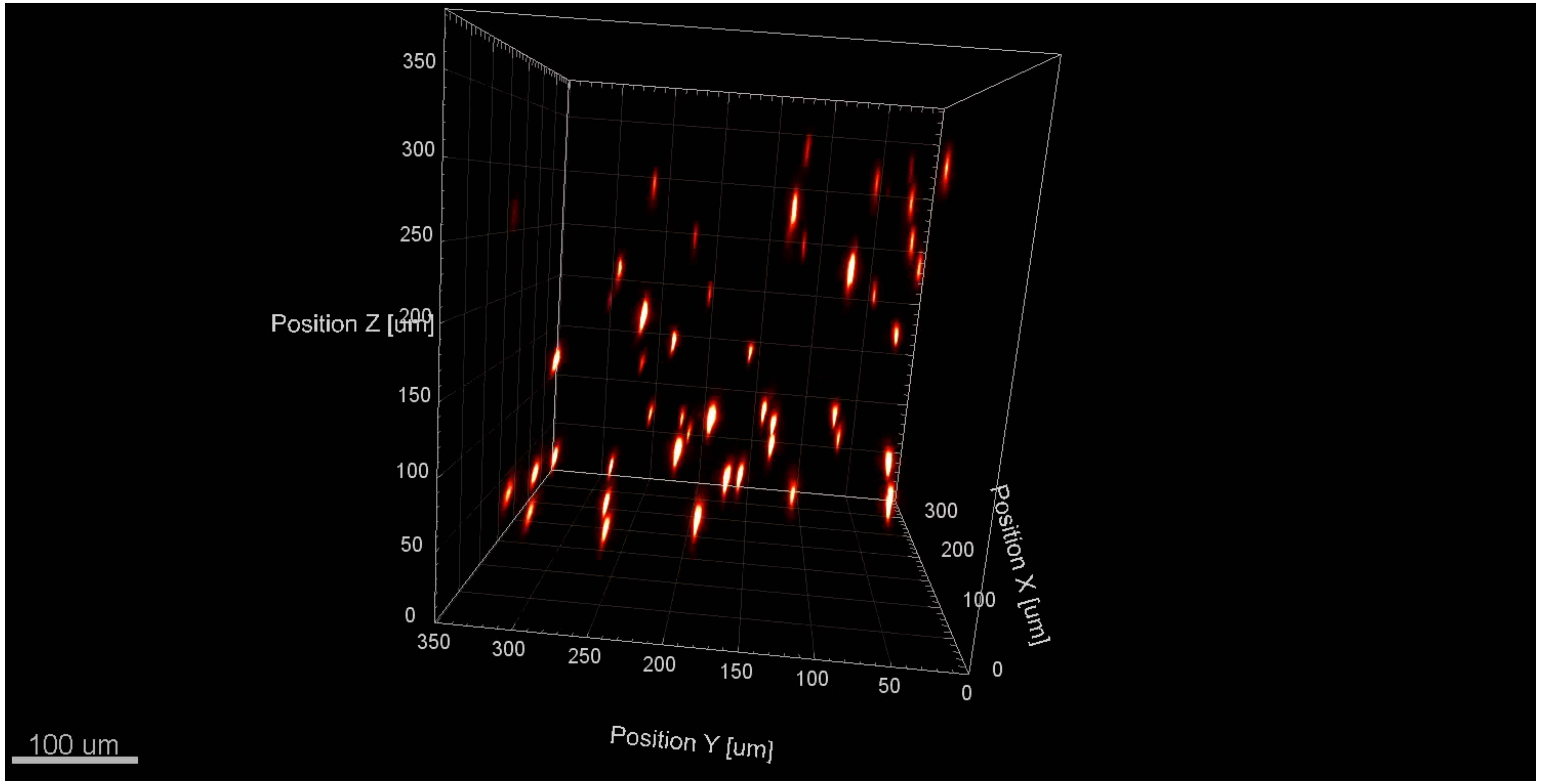
Three-dimensional target optimisation



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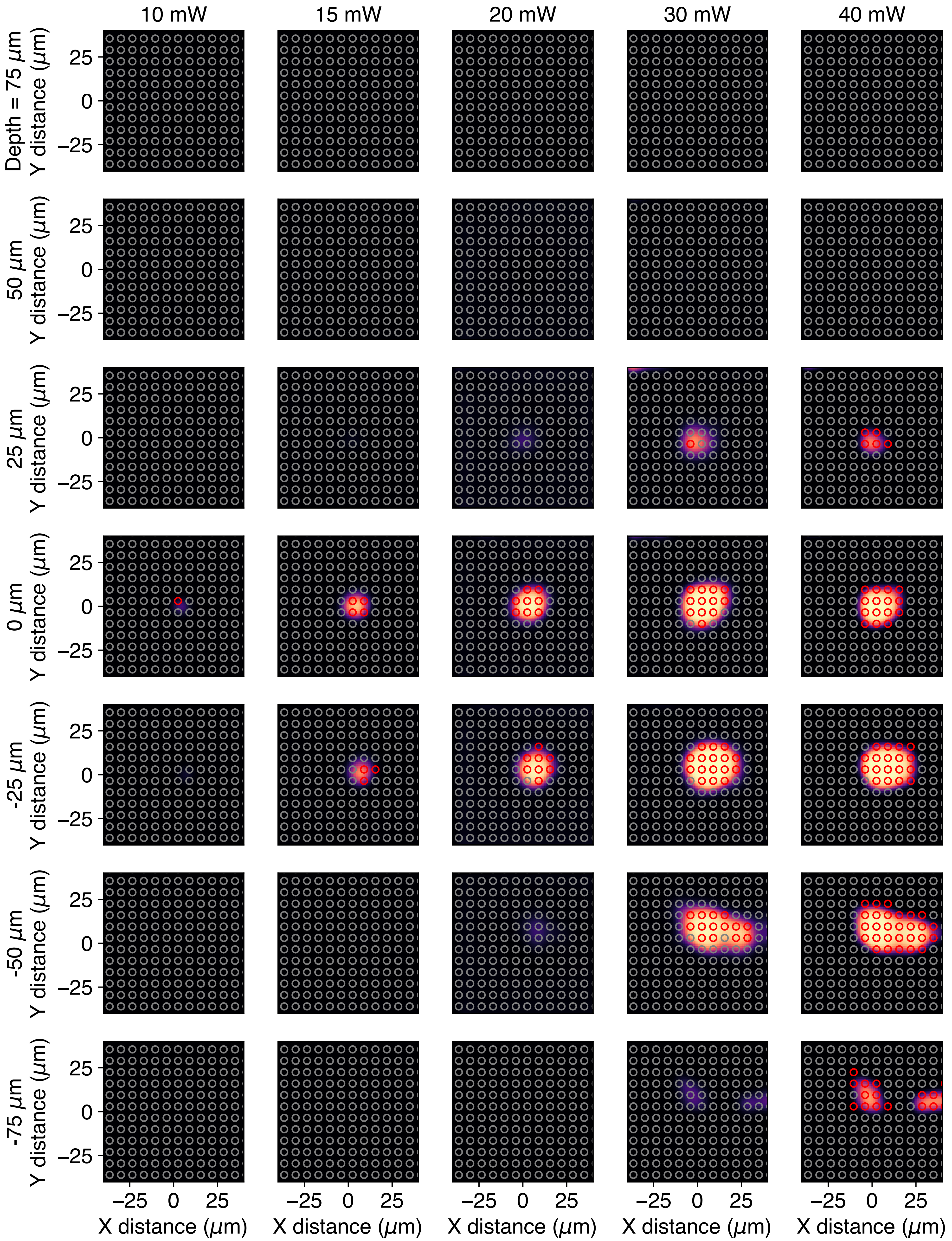

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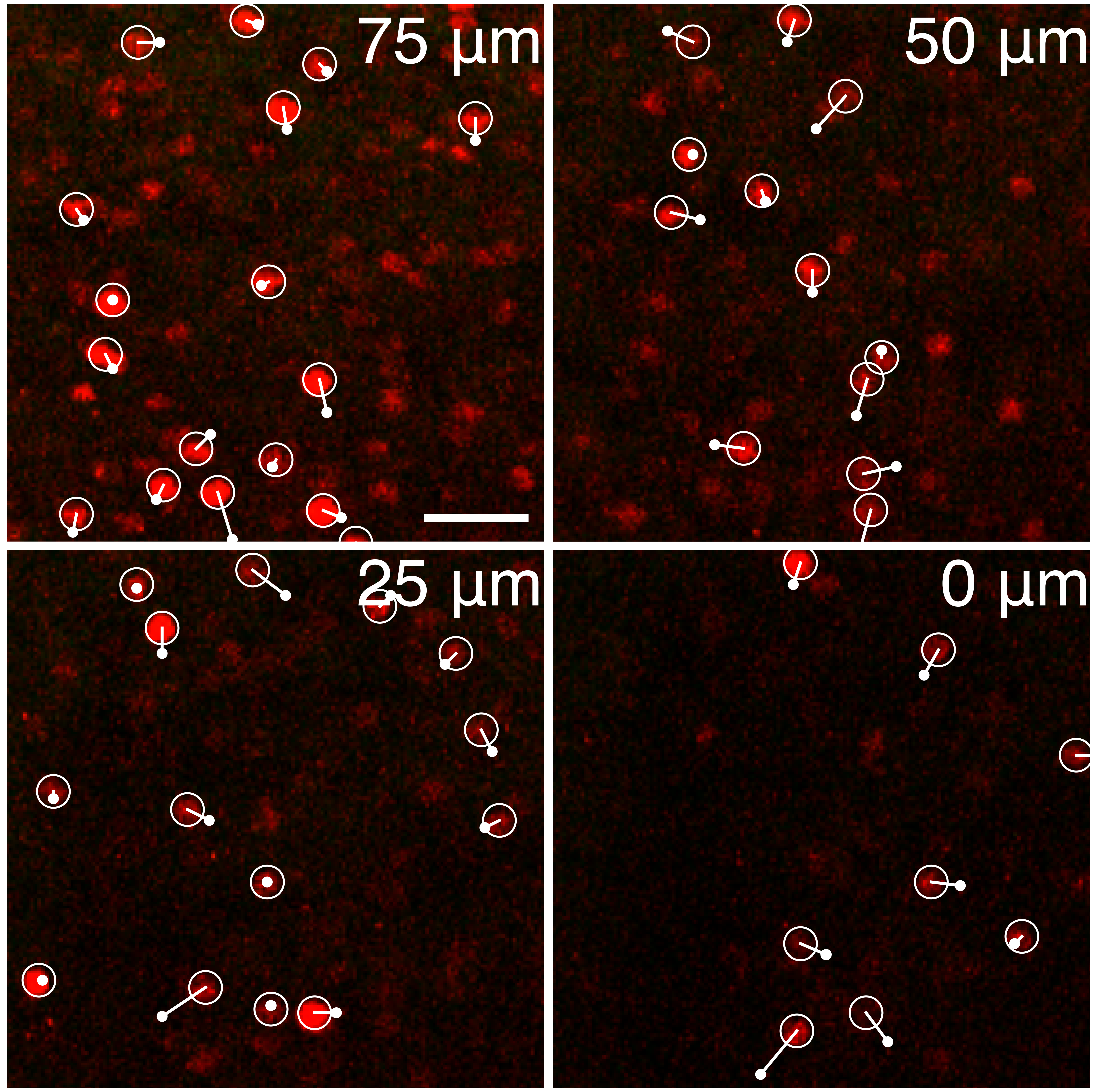

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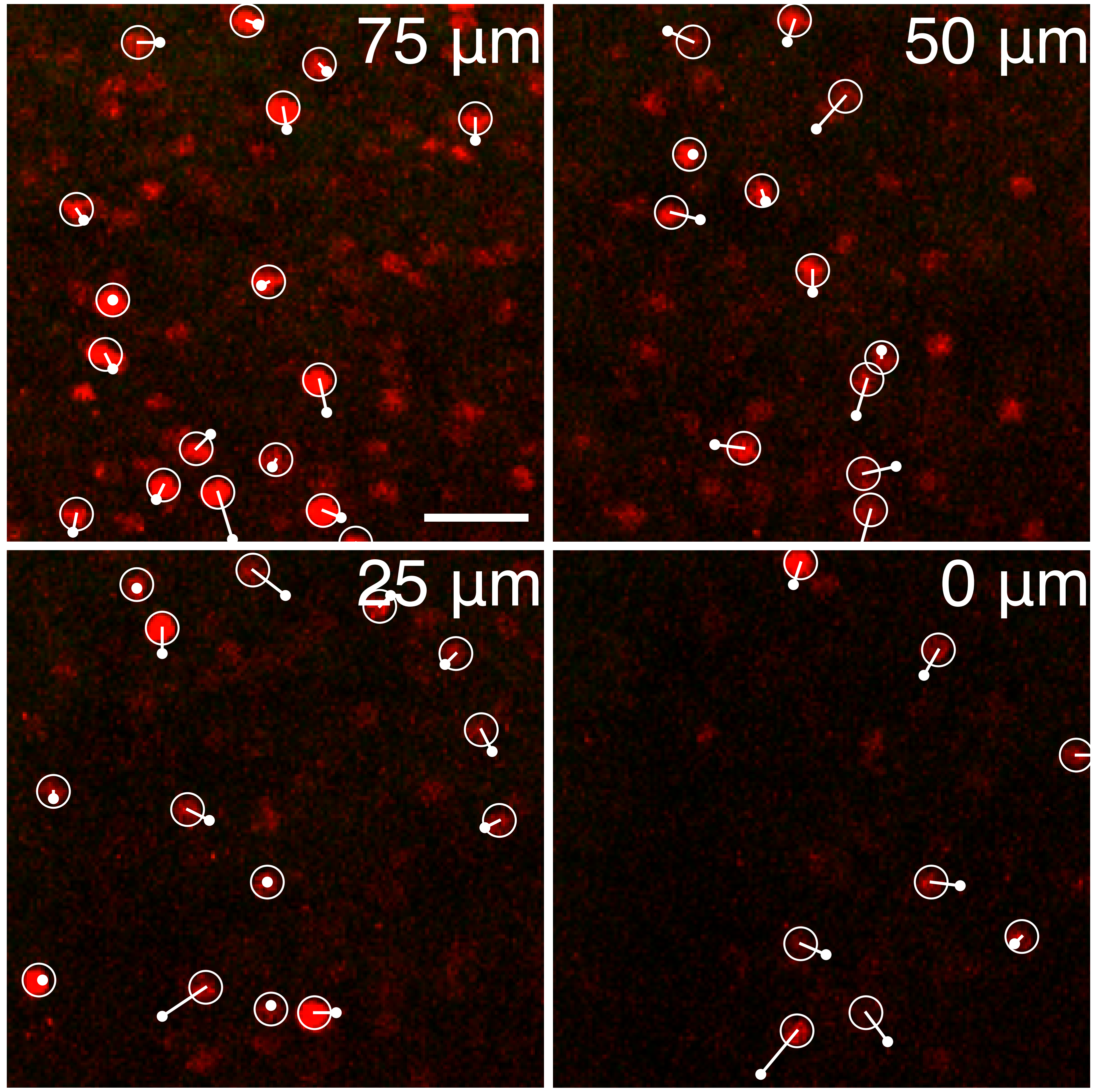

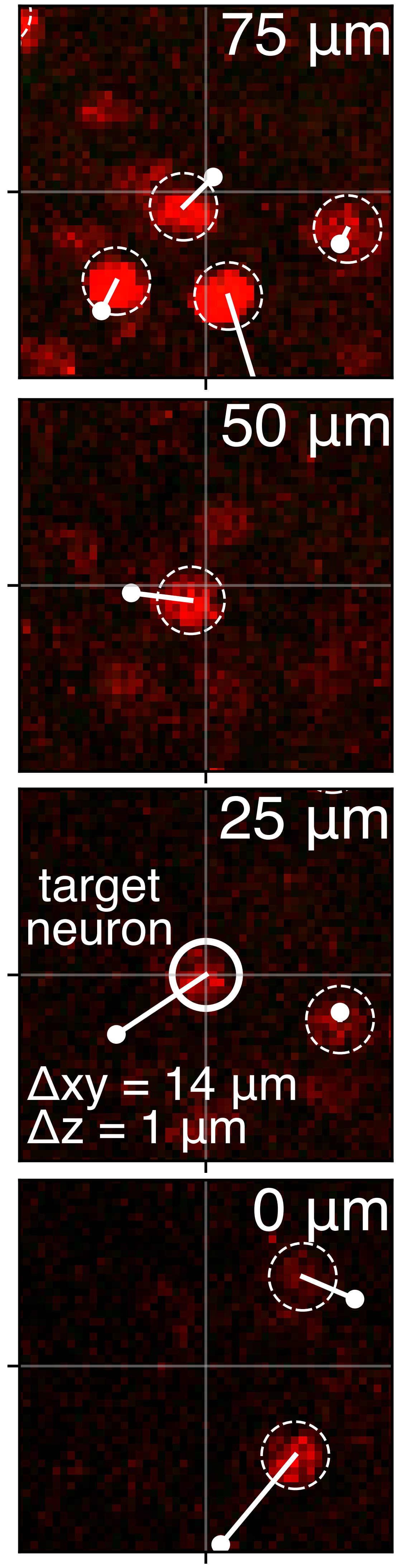

Triplett et al (2023)

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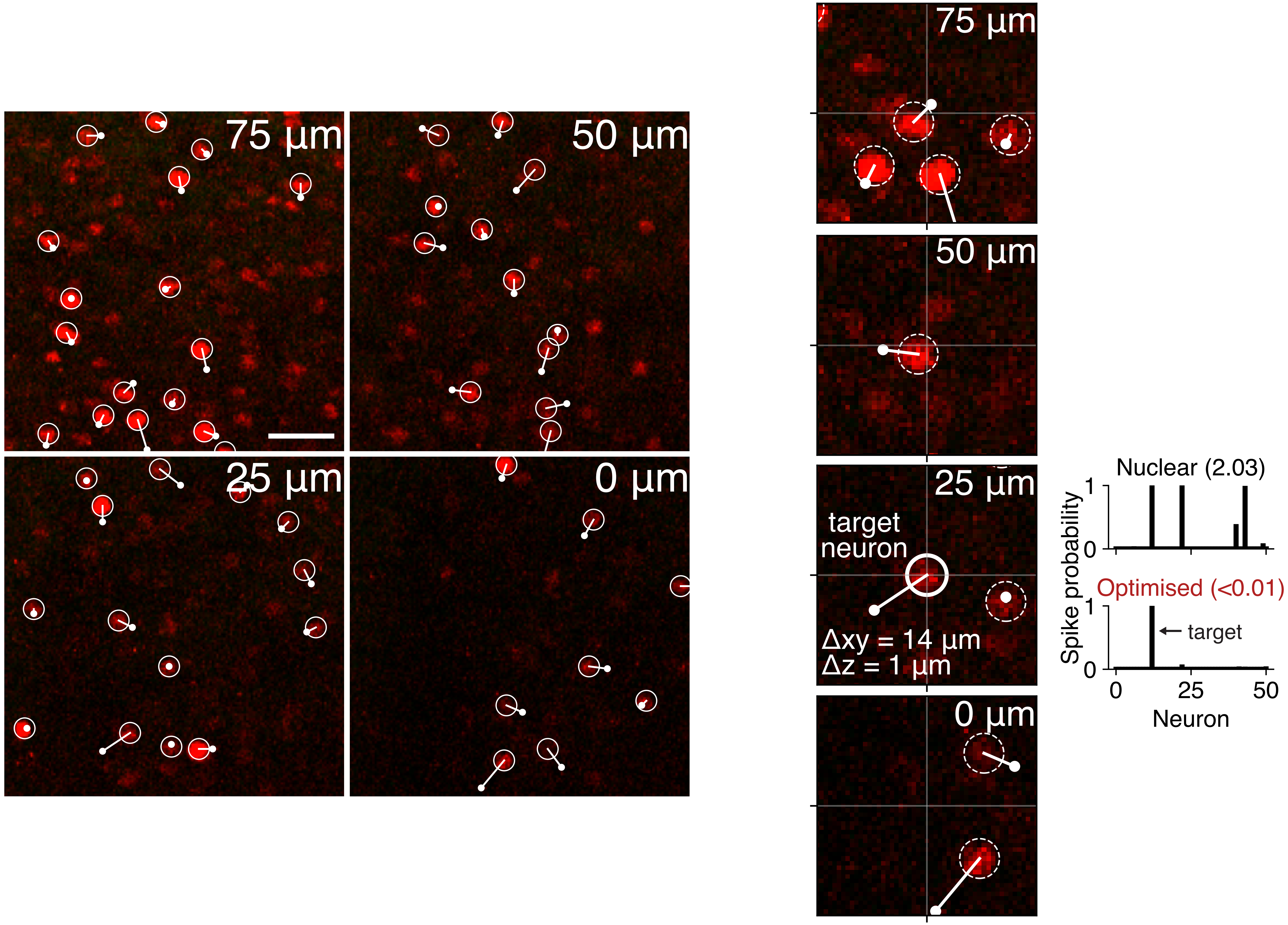

Triplett et al (2023)

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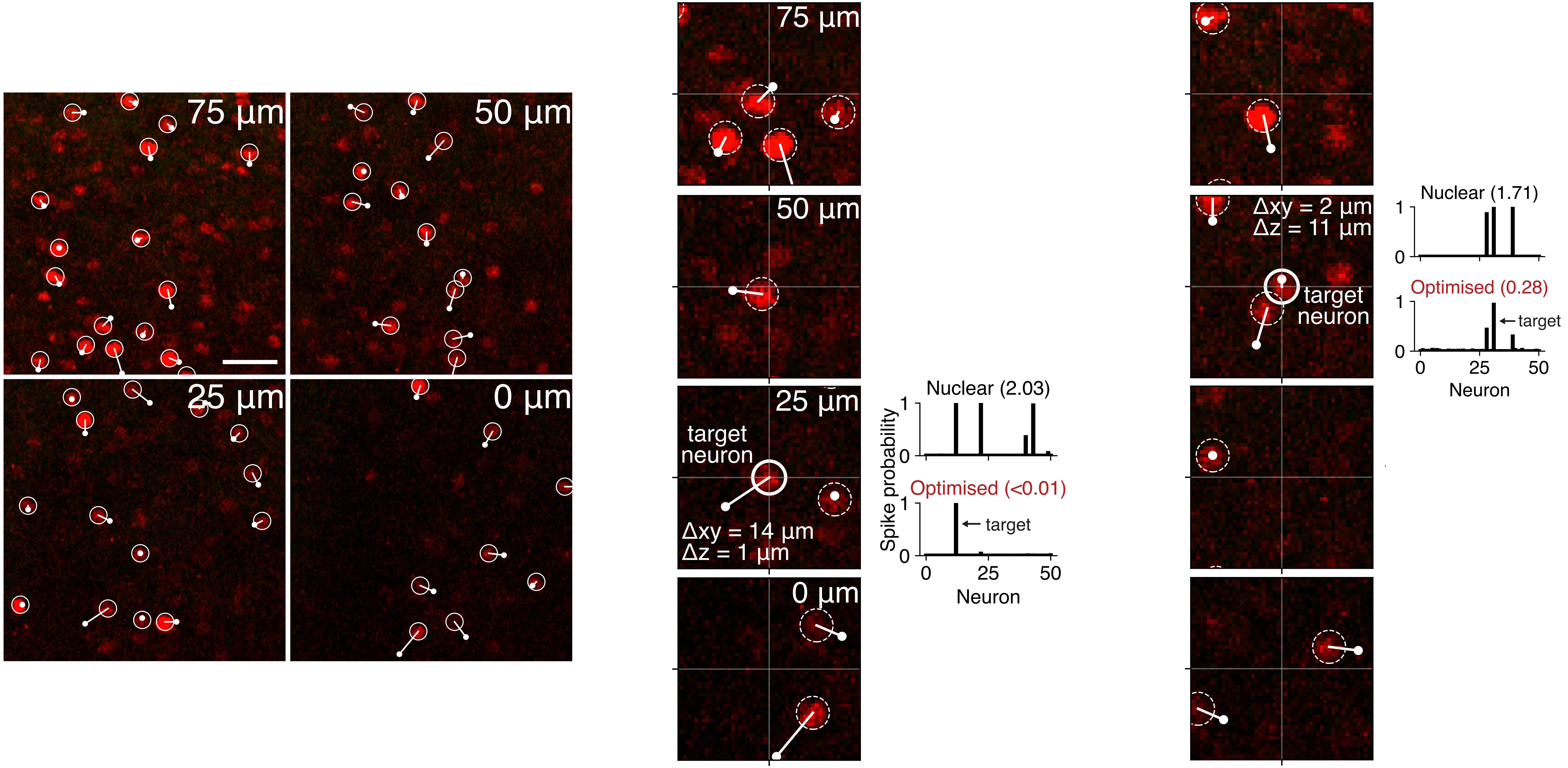


Triplett et al (2023)

Conclusion & next steps

- A computational solution to off-target stimulation
- *In vivo* validation coming soon via collaboration

Acknowledgements

Columbia:

Liam Paninski

Benny Antin

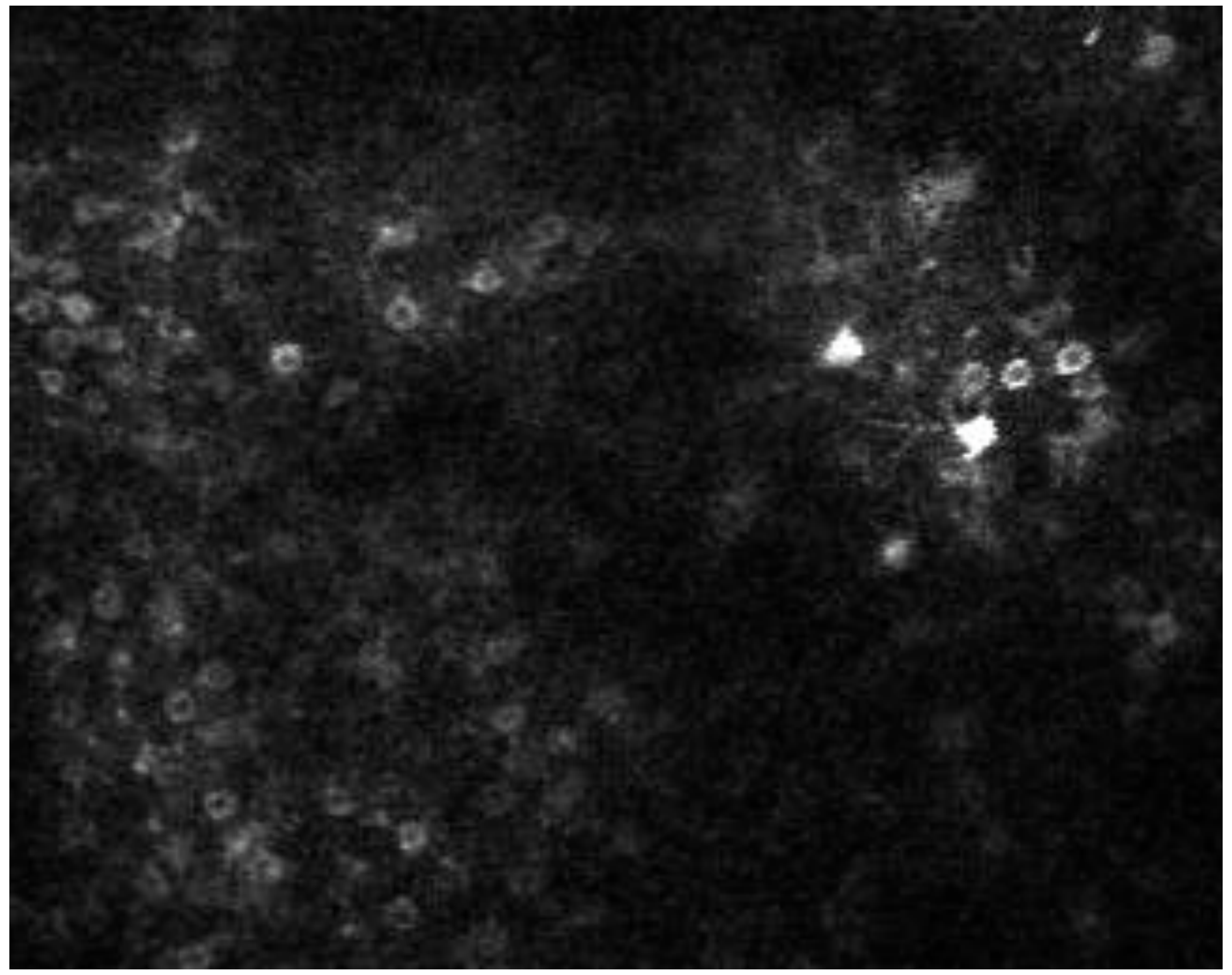
Darcy Peterka

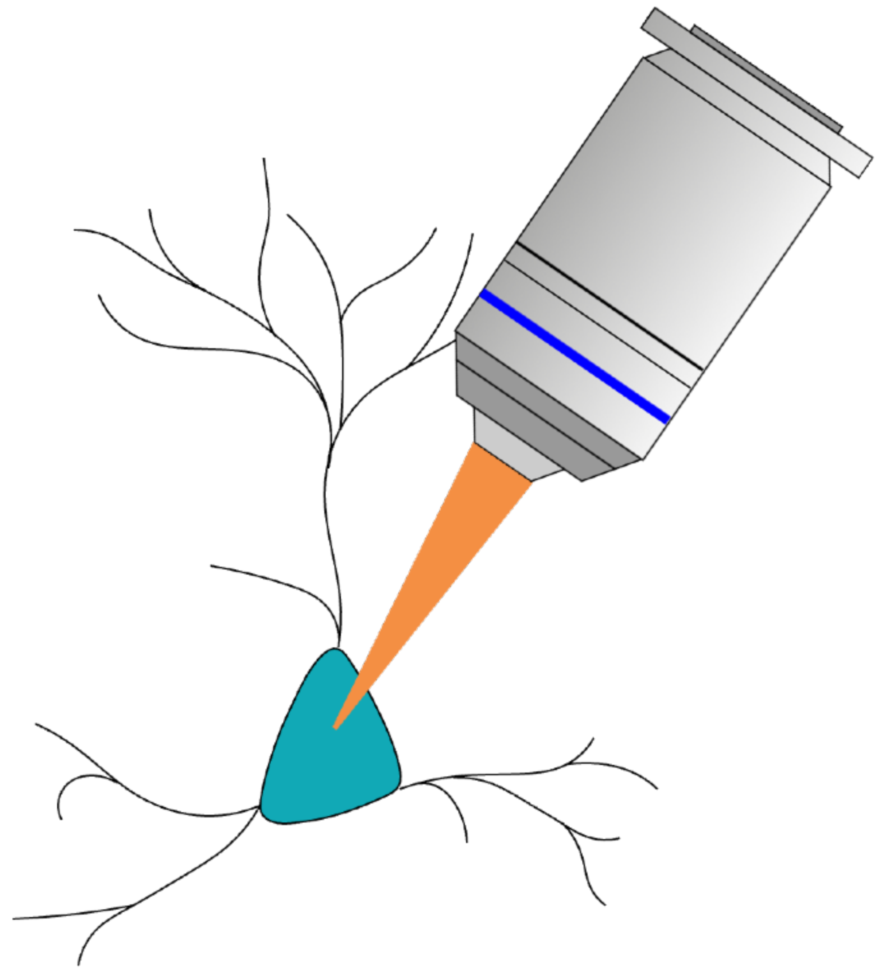
Kenny Kay

Berkeley:

Marta Gajowa

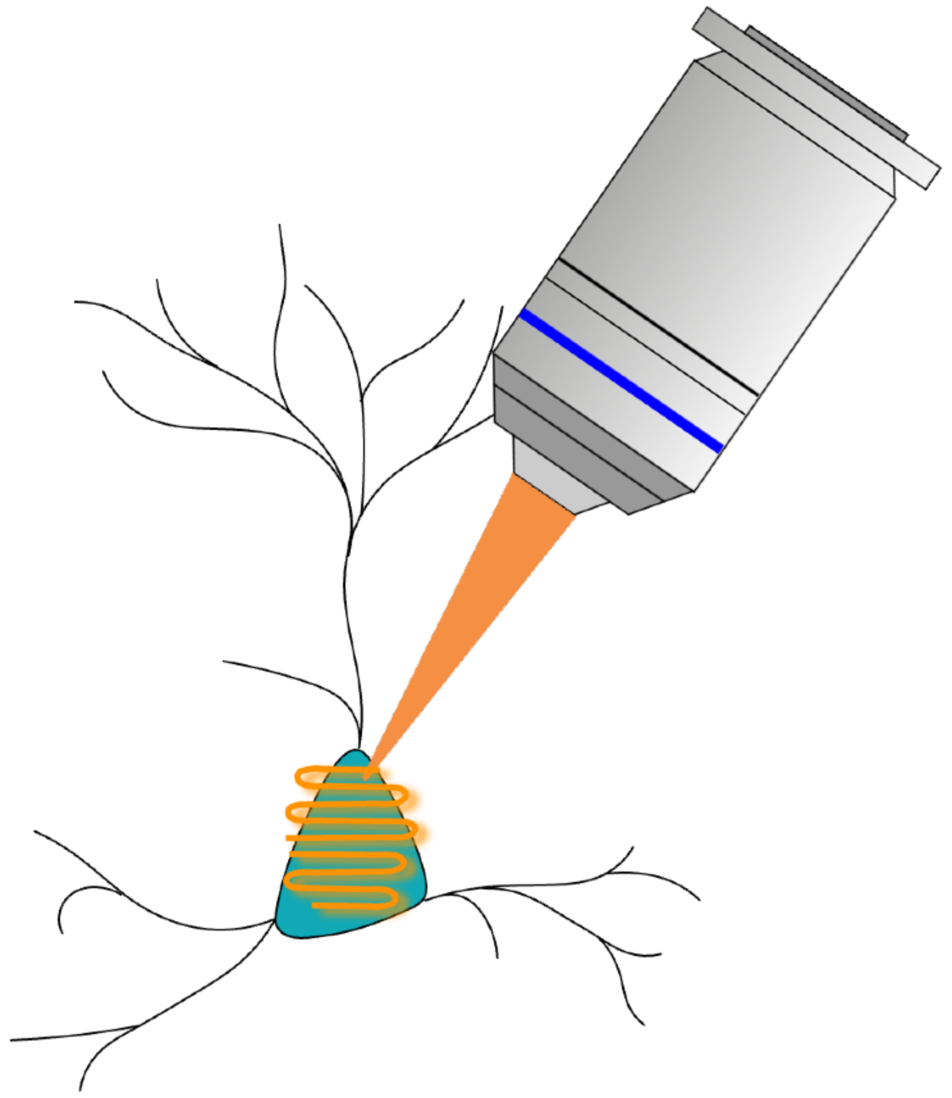
Hillel Adesnik



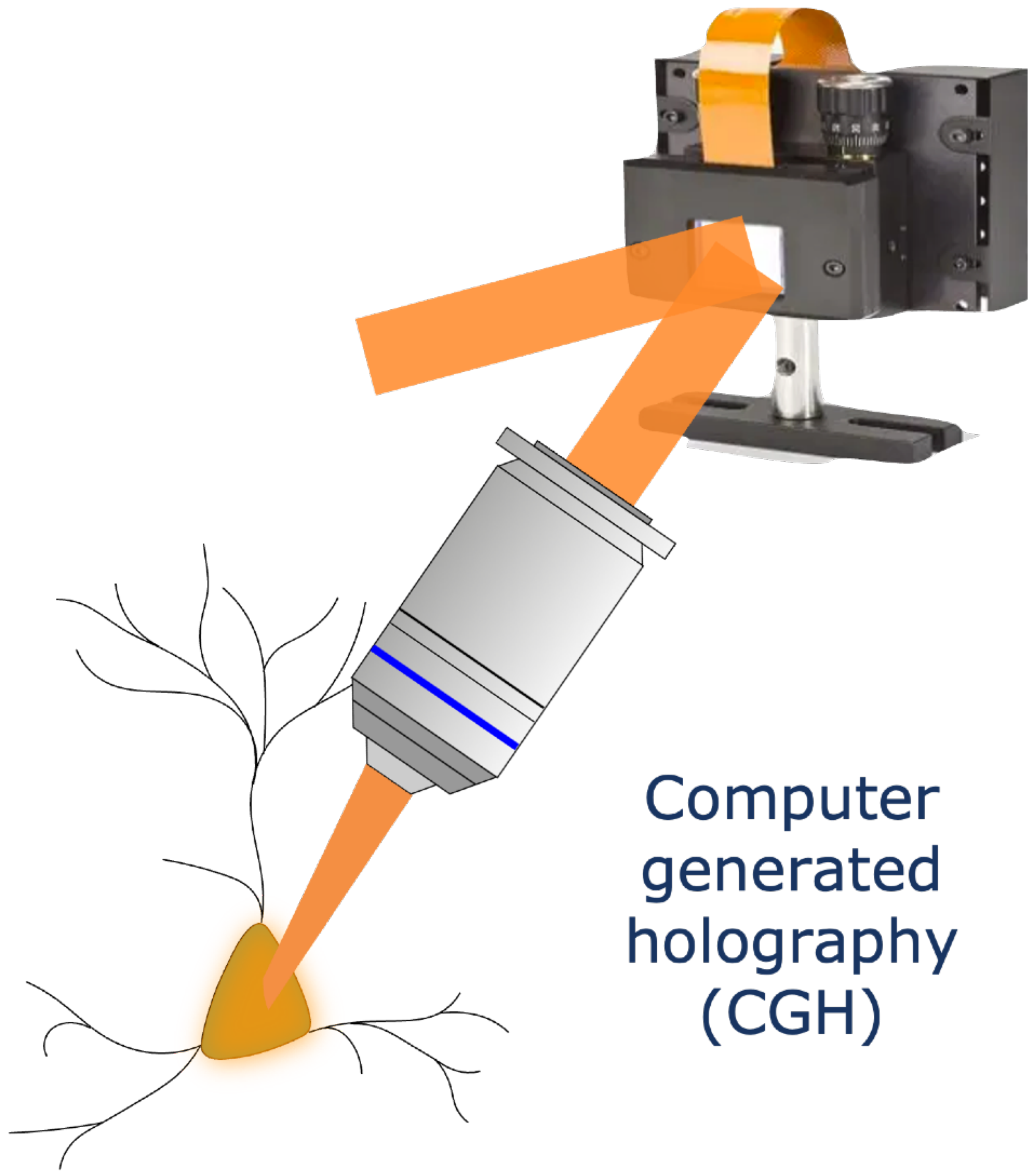


Small focal volume
Small number opsin
Not enough current for AP

Scanning spot



Rickgauger, Tank, PNAS, 2009



Computer generated holography (CGH)

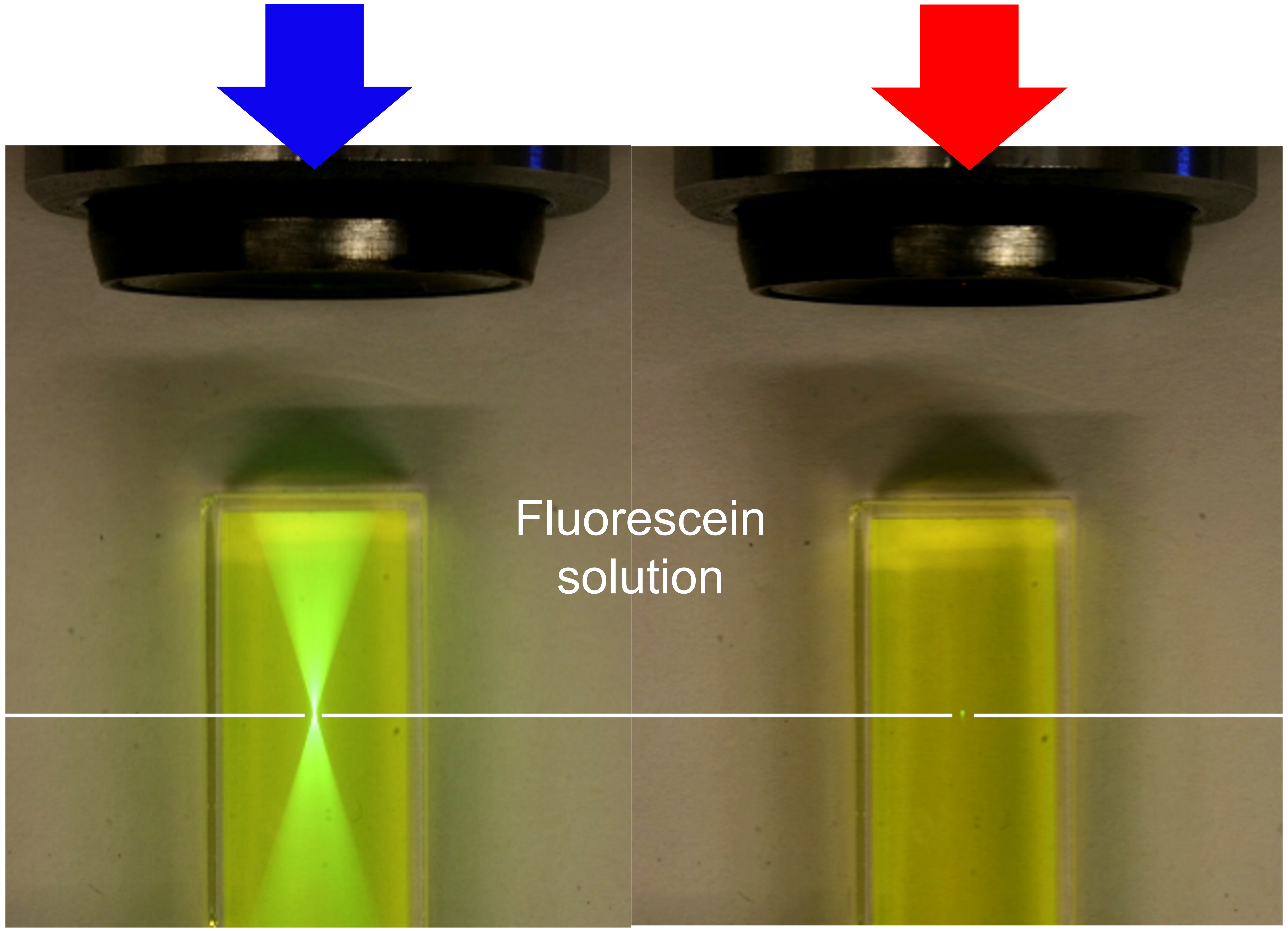
Niccolo Accanto

One Photon

$Signal \propto I$

Two Photon

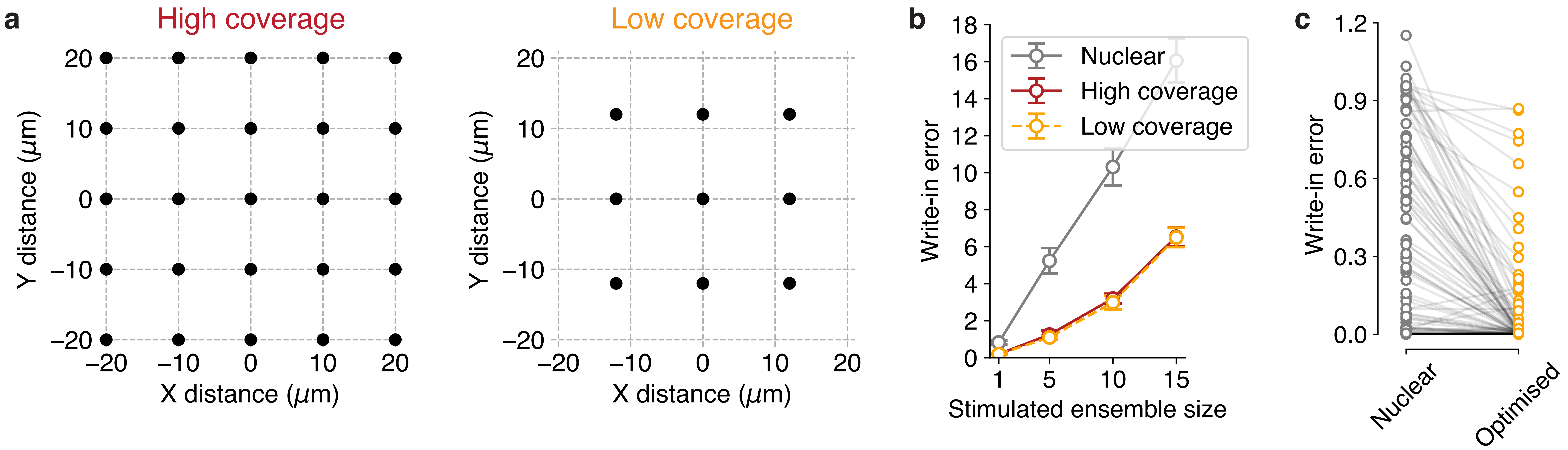
$Signal \propto I^2$

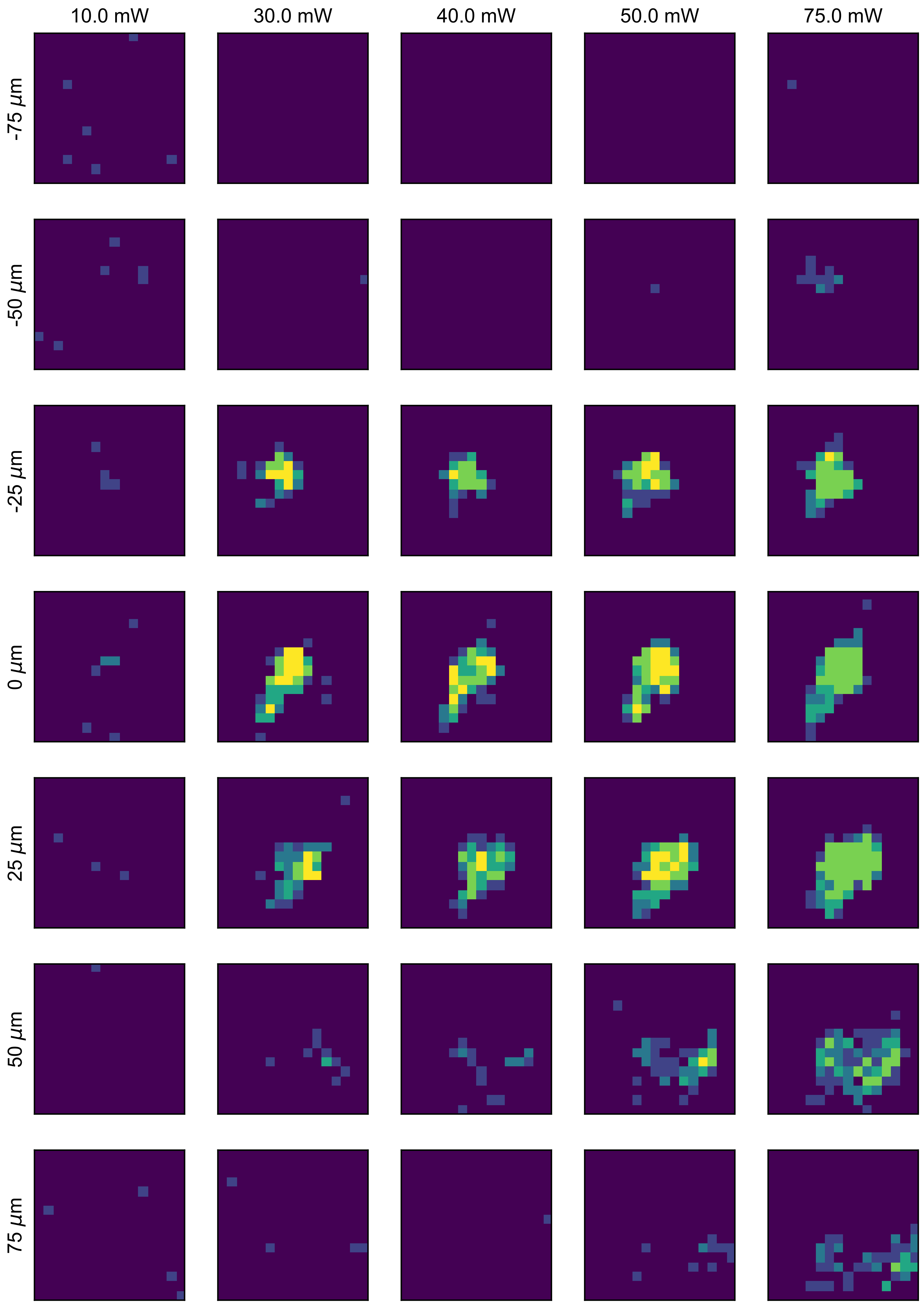


3D scanning of the focal spot to form a 3D image.

Chris Xu

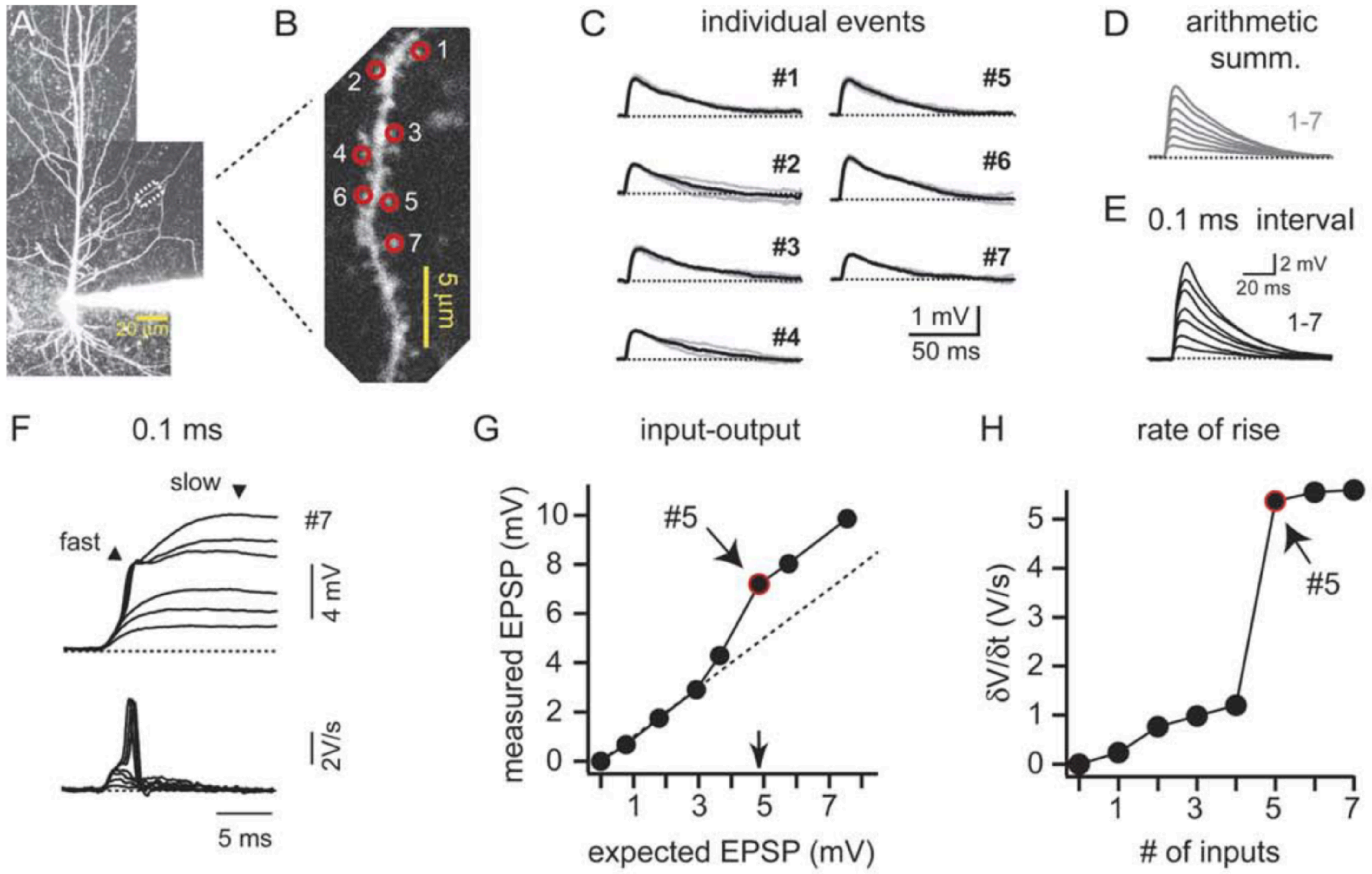
ORF coverage





Marta Gajowa (Bekerley)

2p glutamate uncaging of dendritic spines

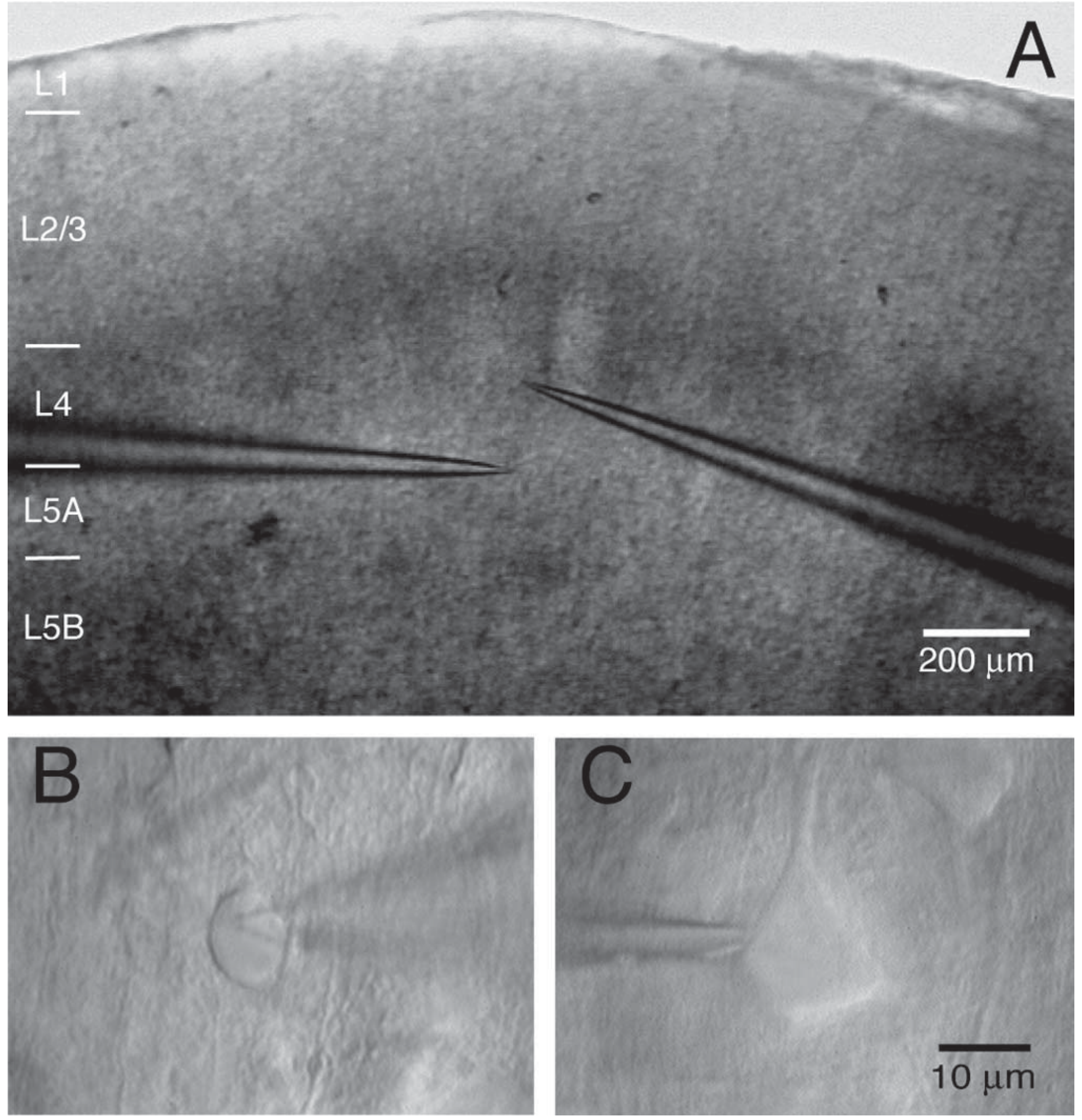


Losonczy & Magee (2006)

Future applications to connectivity mapping

Existing mapping methods are low-throughput

Electrical



Feldmeyer et al (2005), *J. Neurosci*

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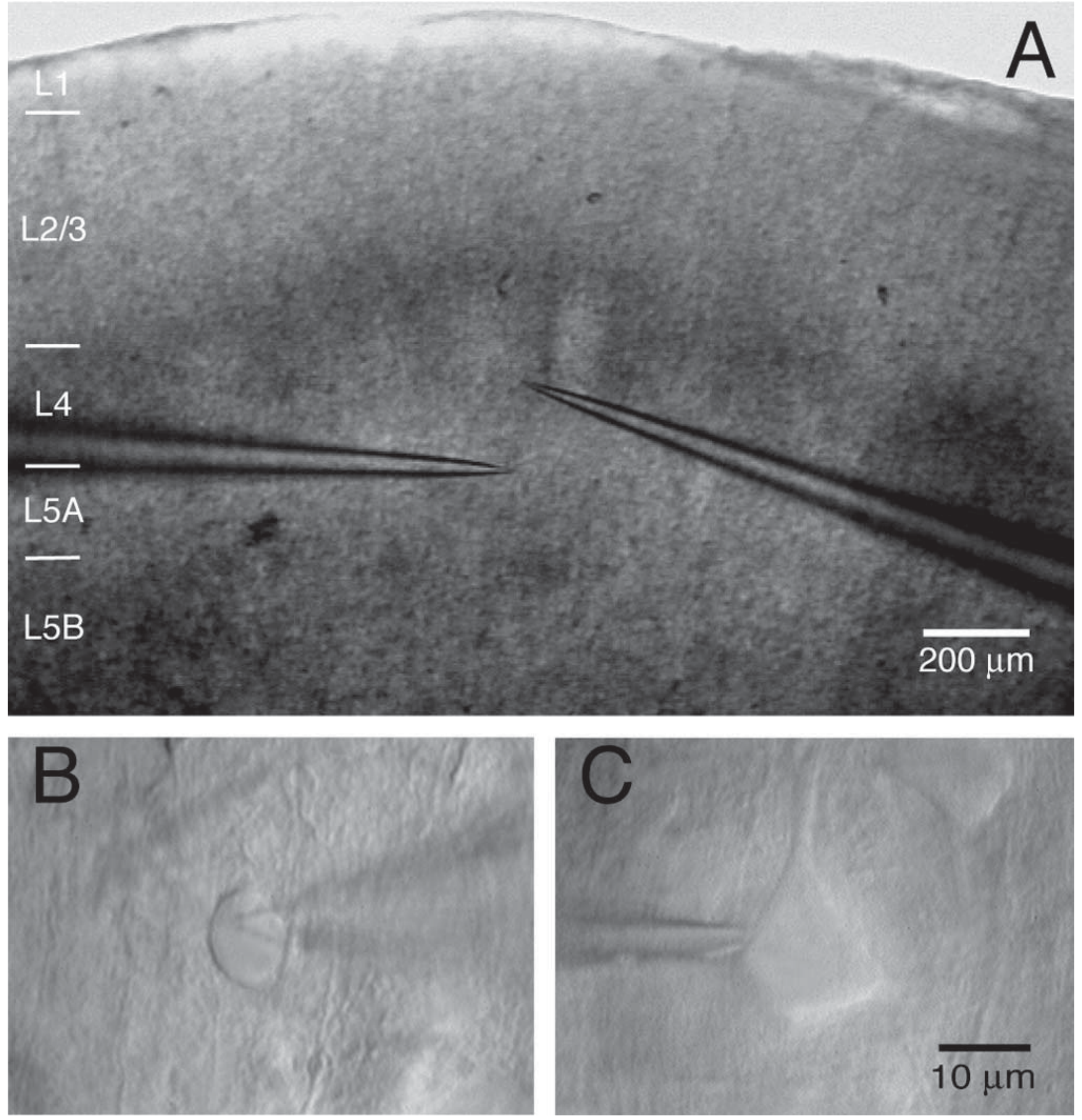
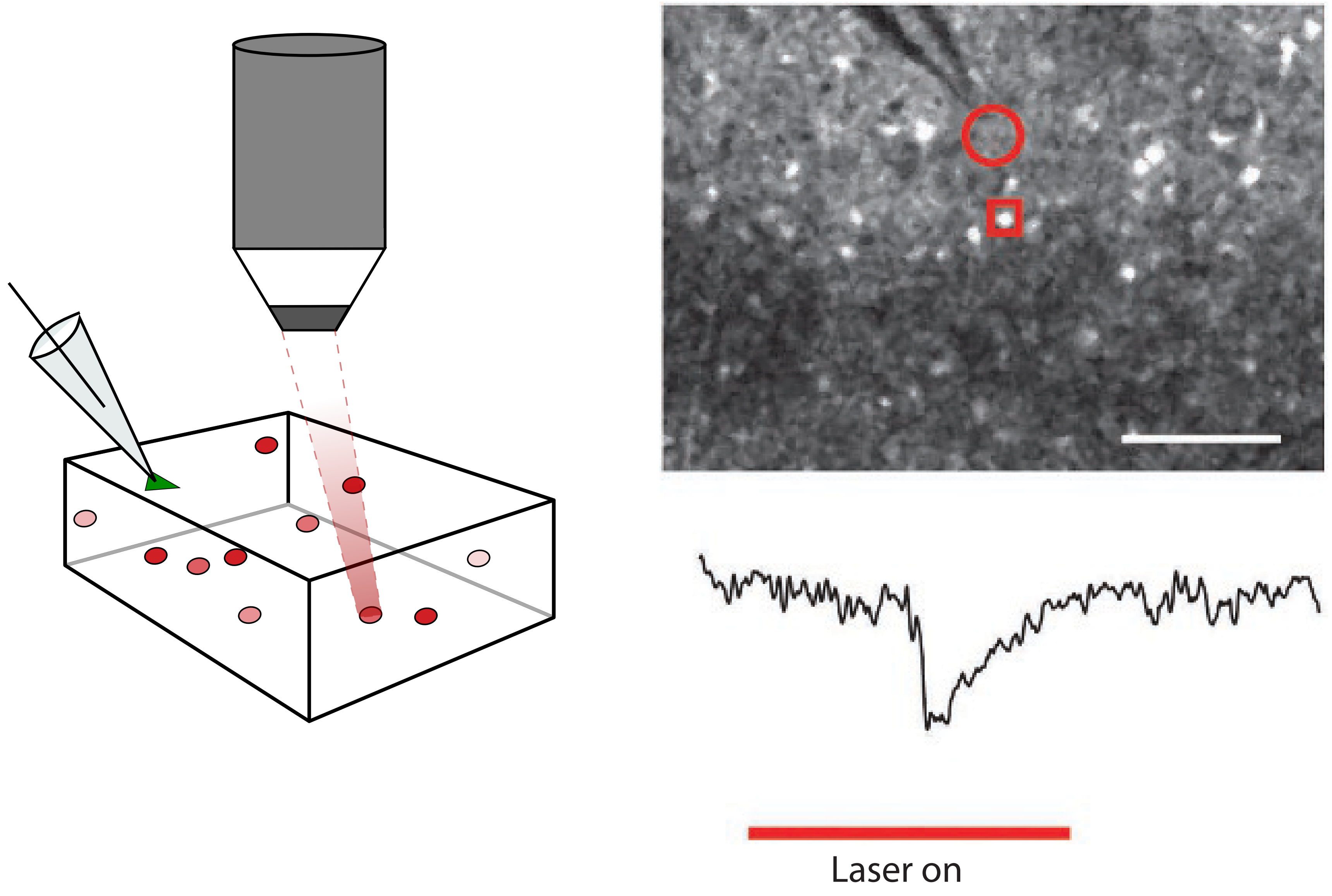


Feldmeyer et al (2005), *J. Neurosci*

Optical



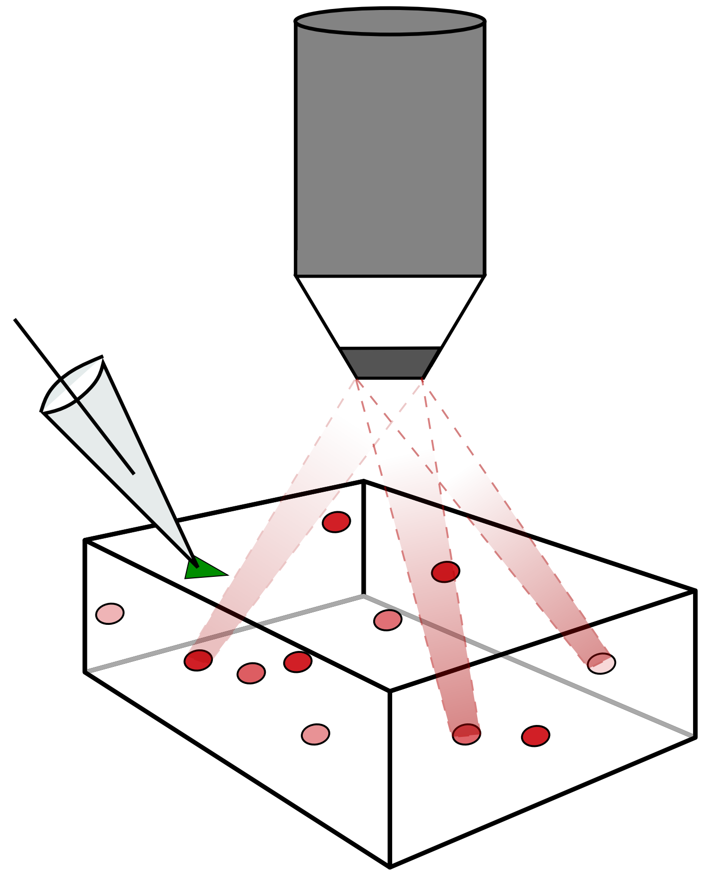
Packer, Peterka et al (2012), *Nat. Methods*

How to enable high-throughput connectivity mapping?

Possible strategy:

use holographic optogenetics to stimulate many (specific) neurons at once

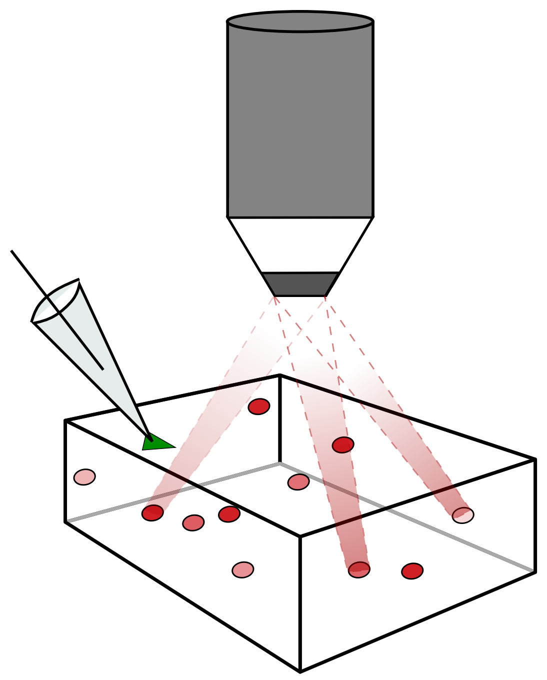
combine with compressed sensing

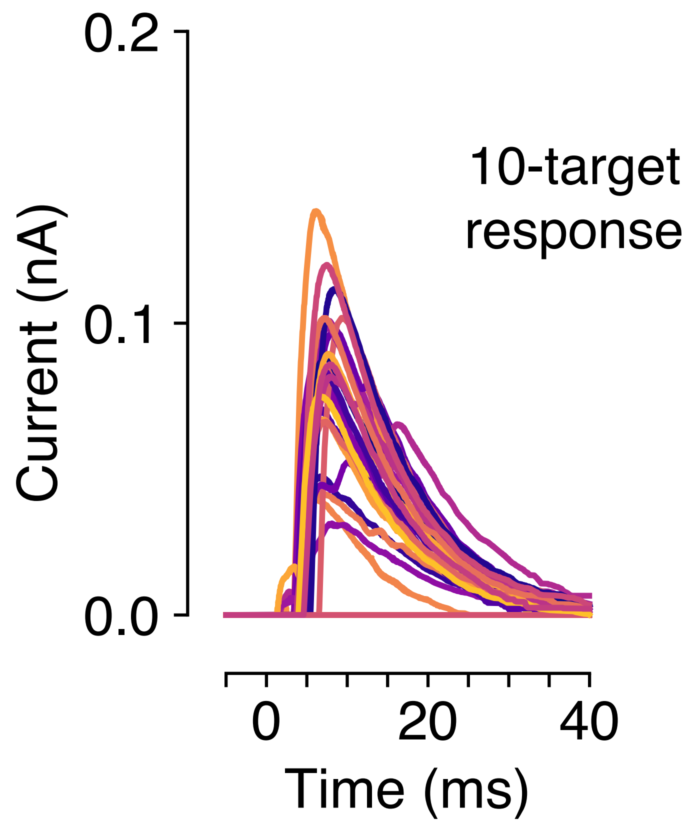


Triplett*, Gajowa* et al. (2022), *bioRxiv*

Limitations of ordinary compressed sensing

Stimulate random ensembles



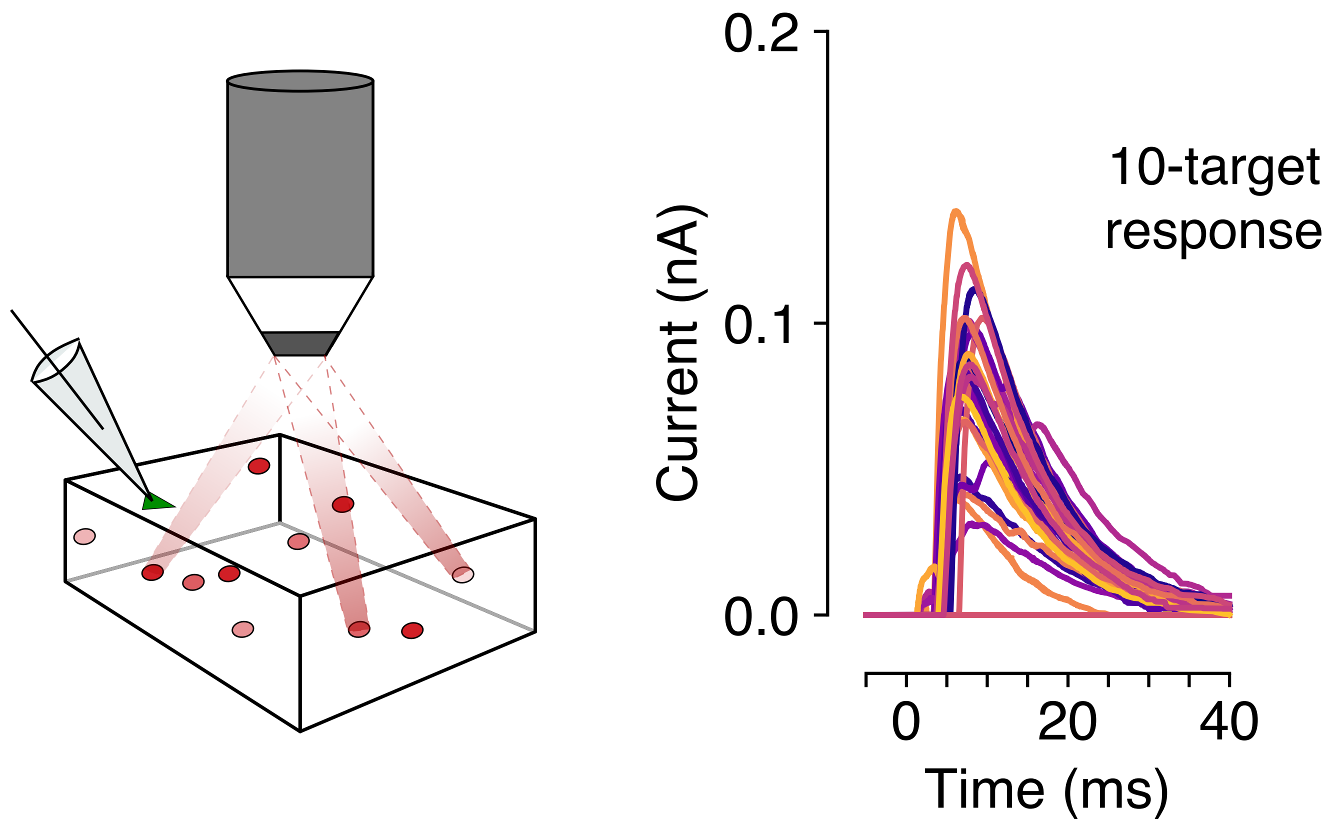


Critical variables

- Power dependence
- Opsin expression
- Synaptic failures
- Spontaneous activity

Limitations of ordinary compressed sensing

Stimulate random ensembles



Critical variables

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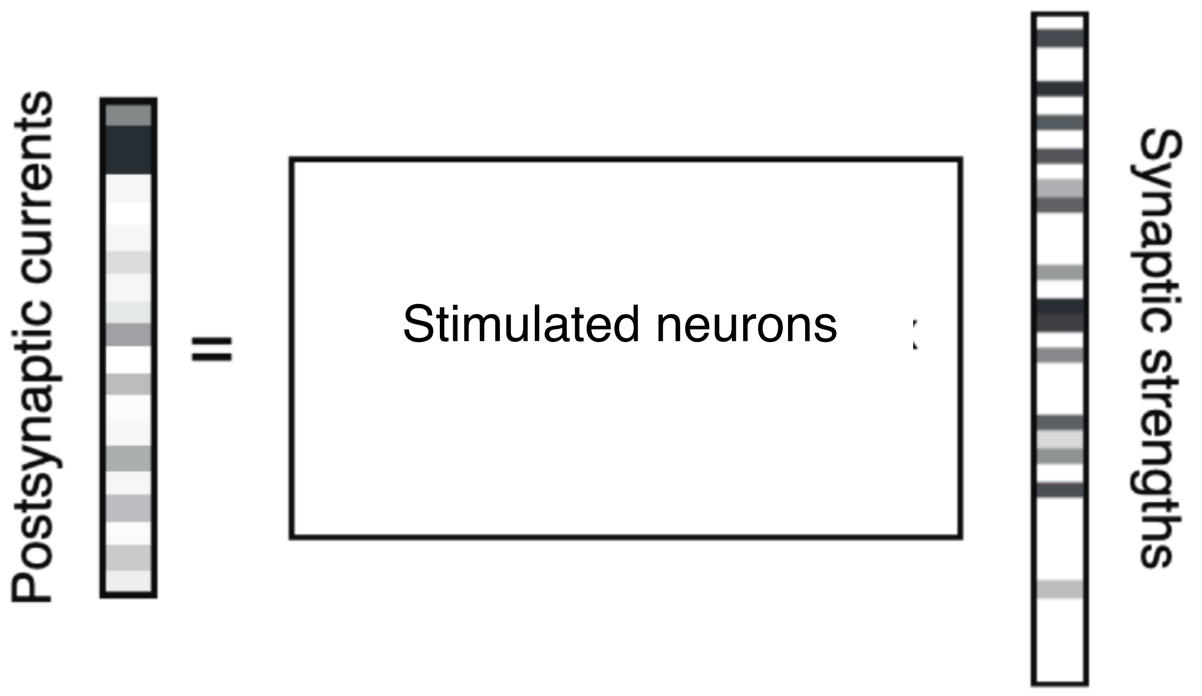
- Spontaneous activity

Apply ordinary compressed sensing



Solve $\mathbf{y} = \mathbf{A}\mathbf{x}$ such that $\mathbf{x}$ is sparse

(Candes, Tao, Donoho, 2004+)

Limitations of ordinary compressed sensing

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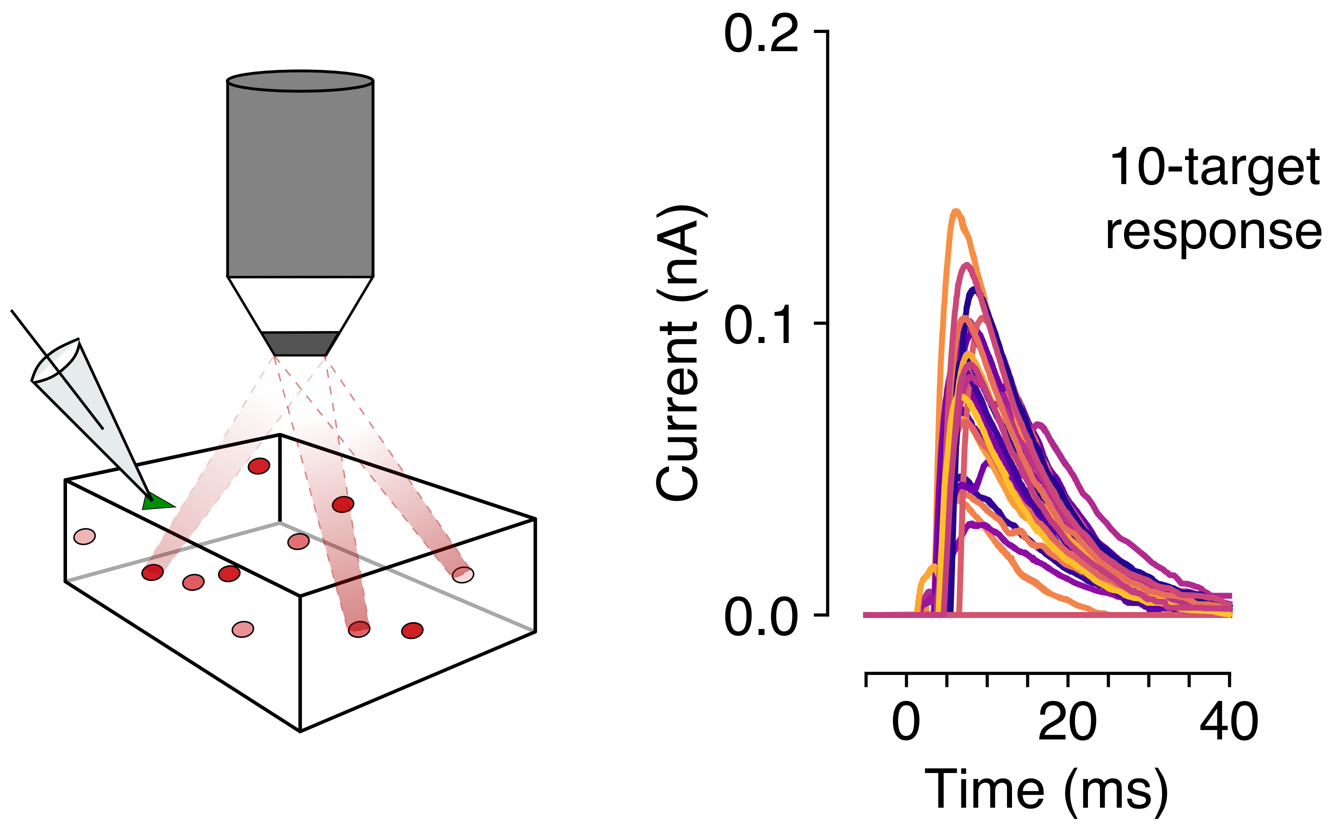

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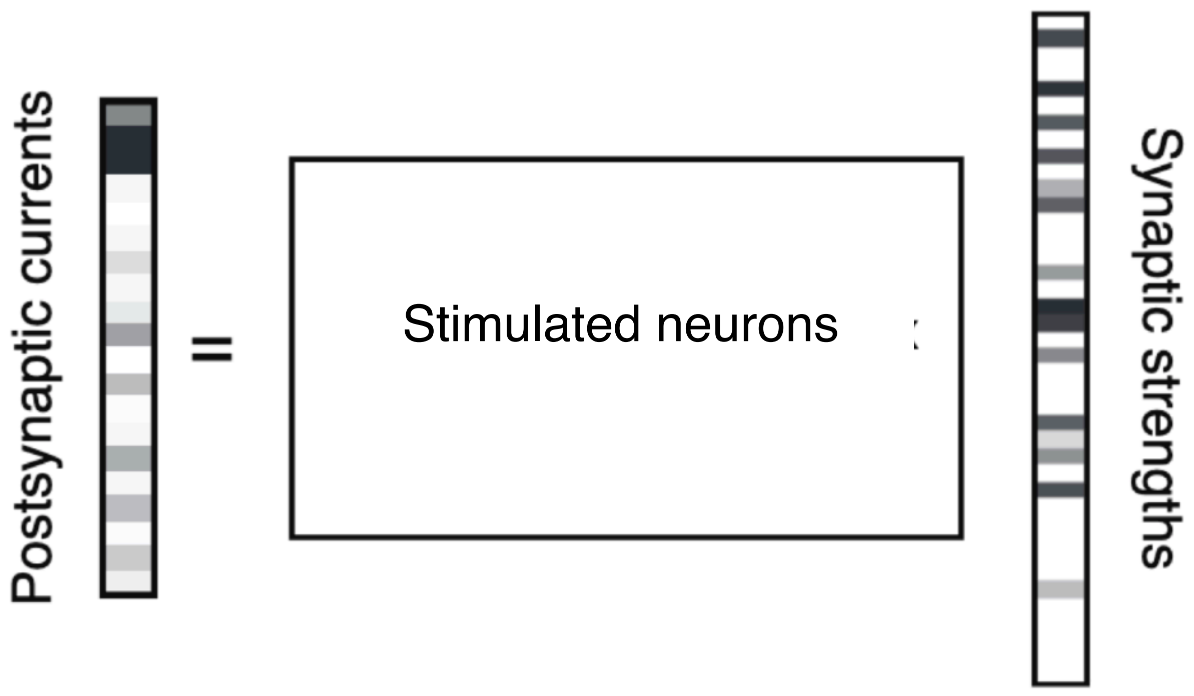

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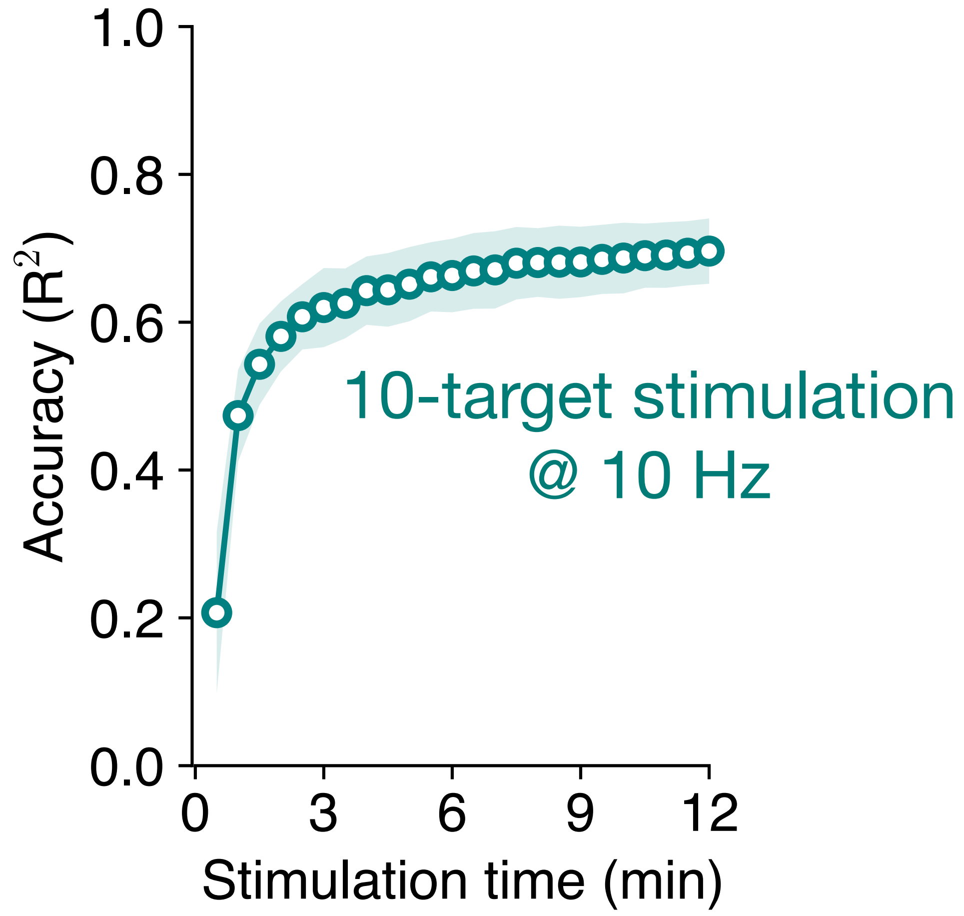
Performance

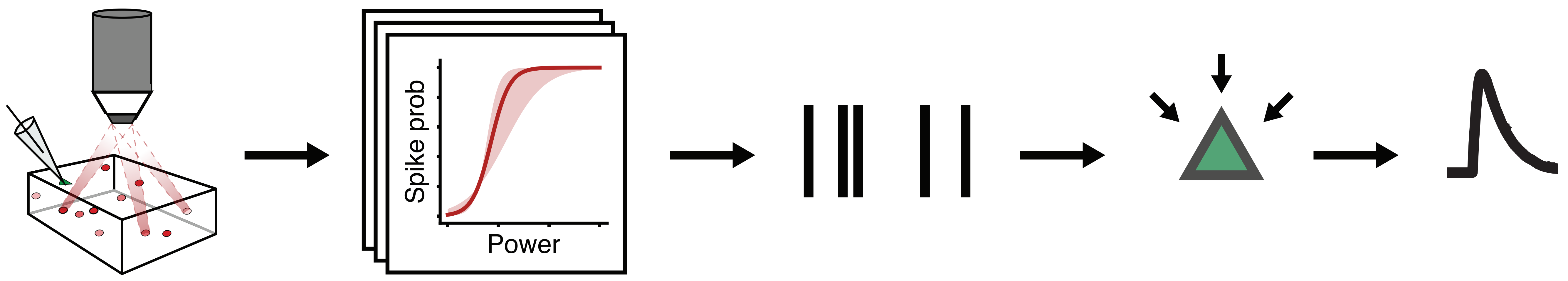


(simulation)

Model-based compressed sensing

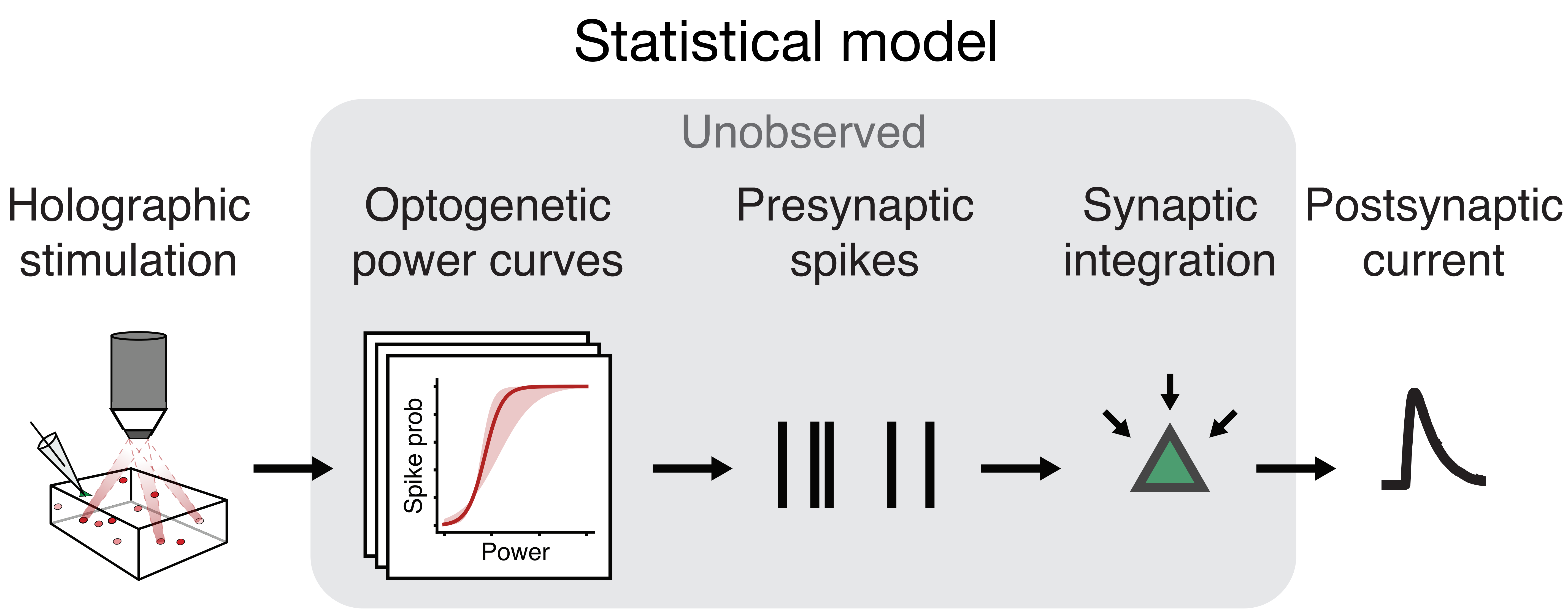
Statistical model

Holographic stimulation | Optogenetic power curves | Presynaptic spikes | Synaptic integration | Postsynaptic current



Triplett*, Gajowa* et al. (2022), *bioRxiv*

Model-based compressed sensing



Triplett*, Gajowa* et al. (2022), *bioRxiv*

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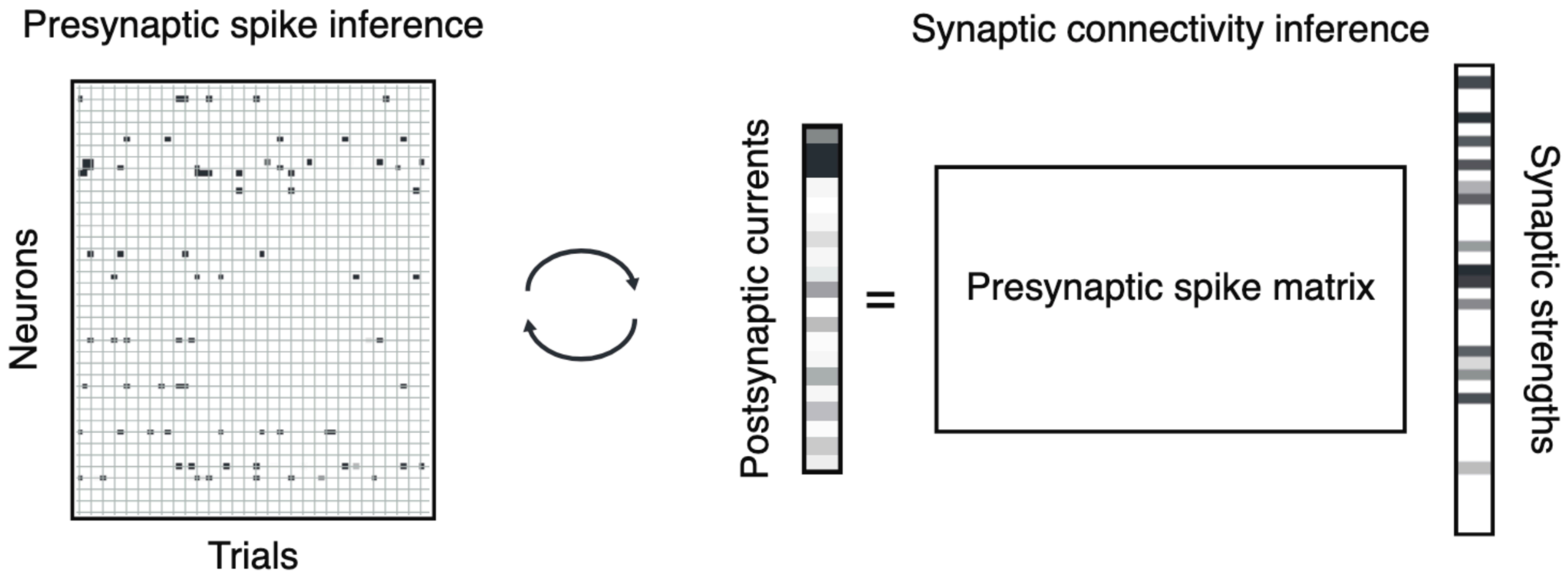
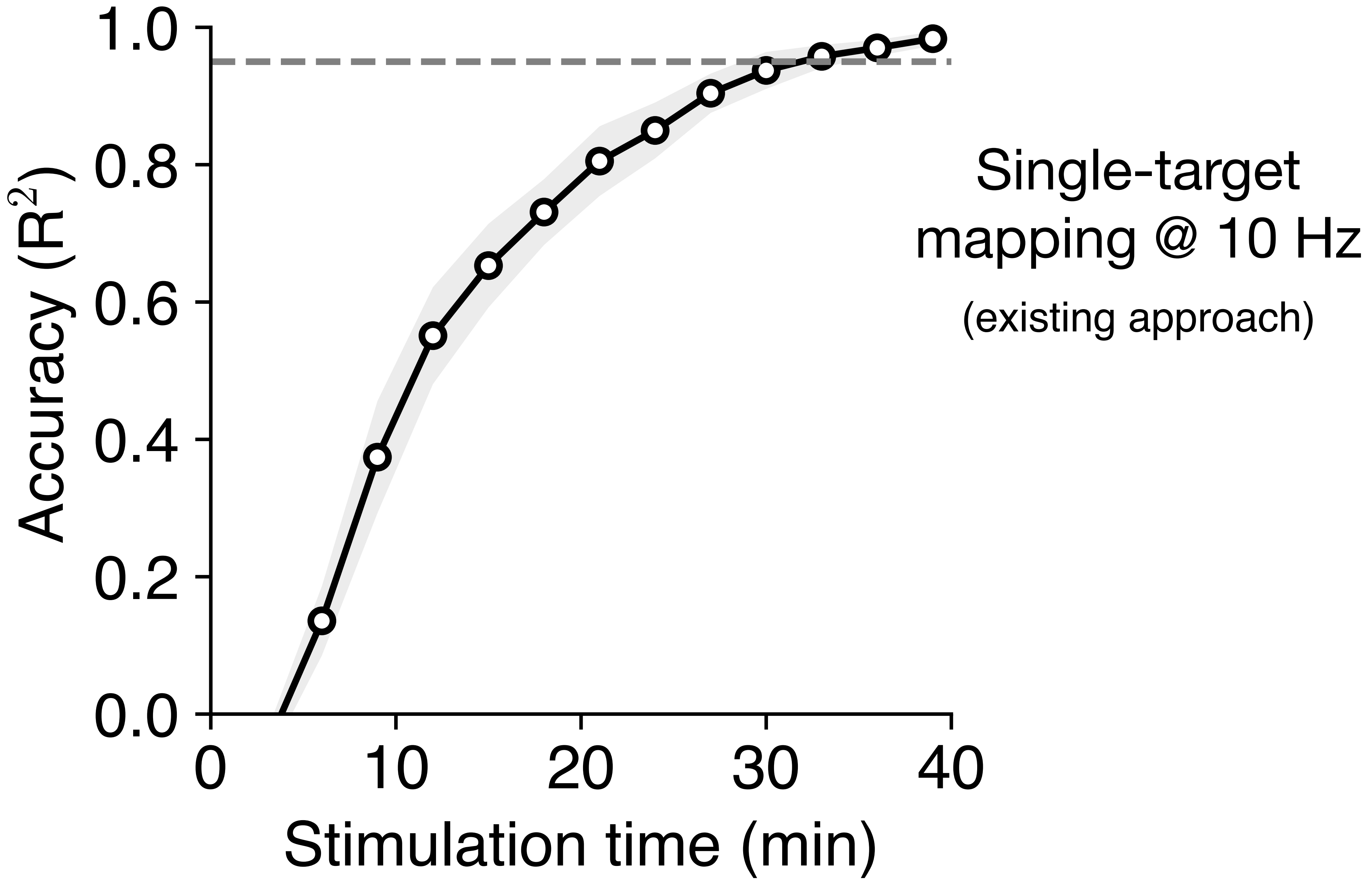


Triplett*, Gajowa* et al. (2022), *bioRxiv*

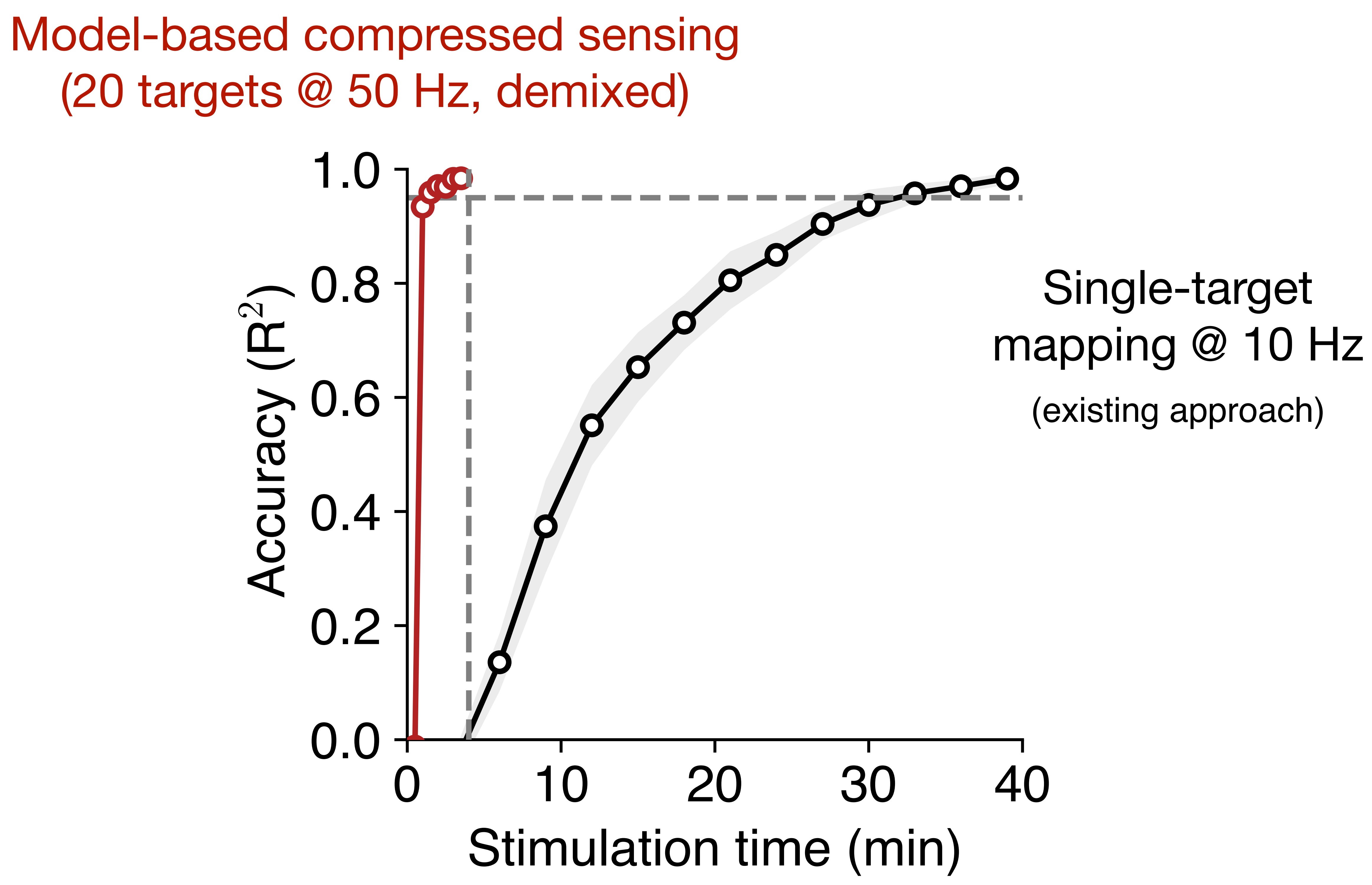
Order-of-magnitude mapping speedup



Simulation: 1000 neurons, 10% connectivity

Triplett*, Gajowa* et al. (2022), *bioRxiv*

Order-of-magnitude mapping speedup



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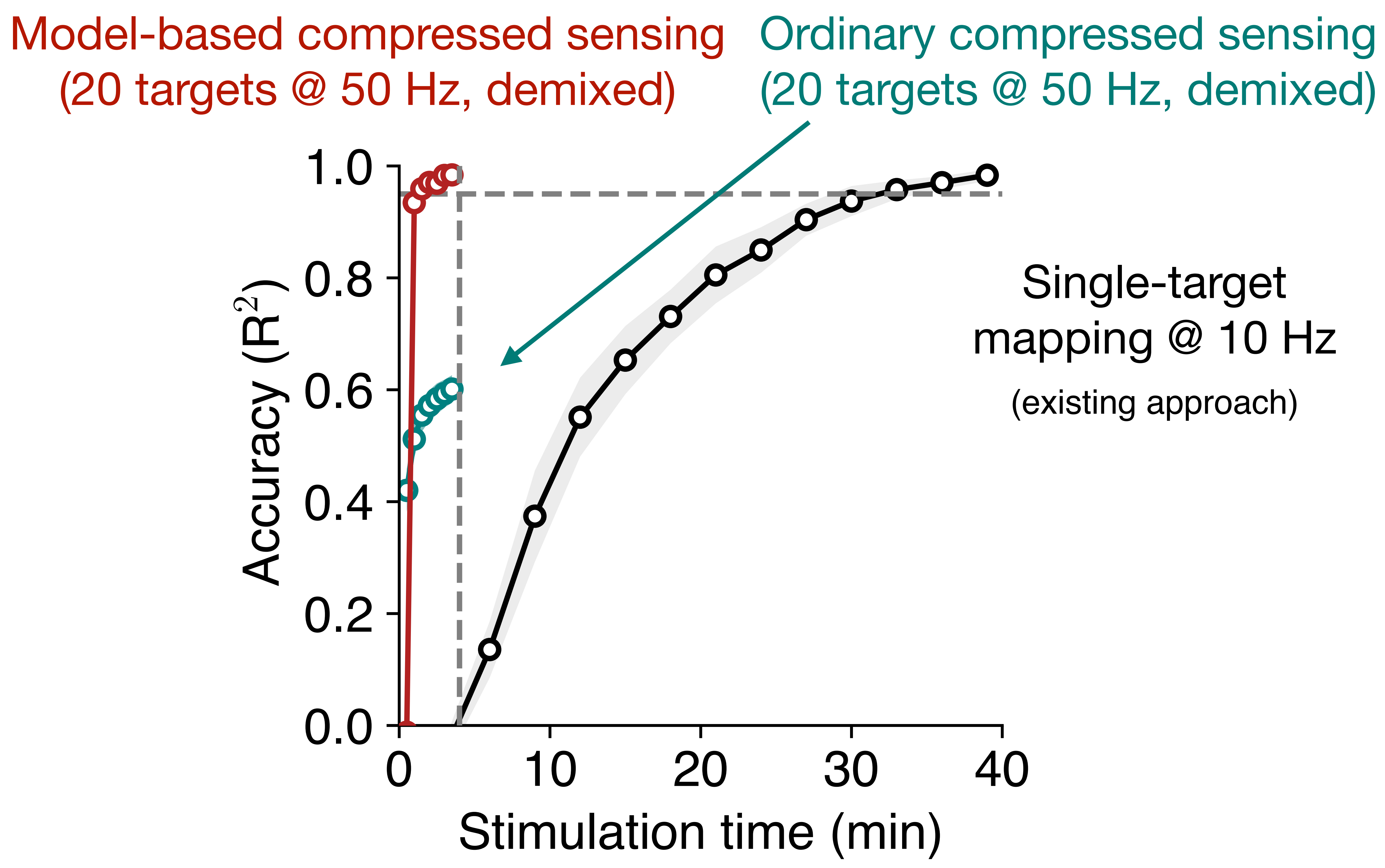

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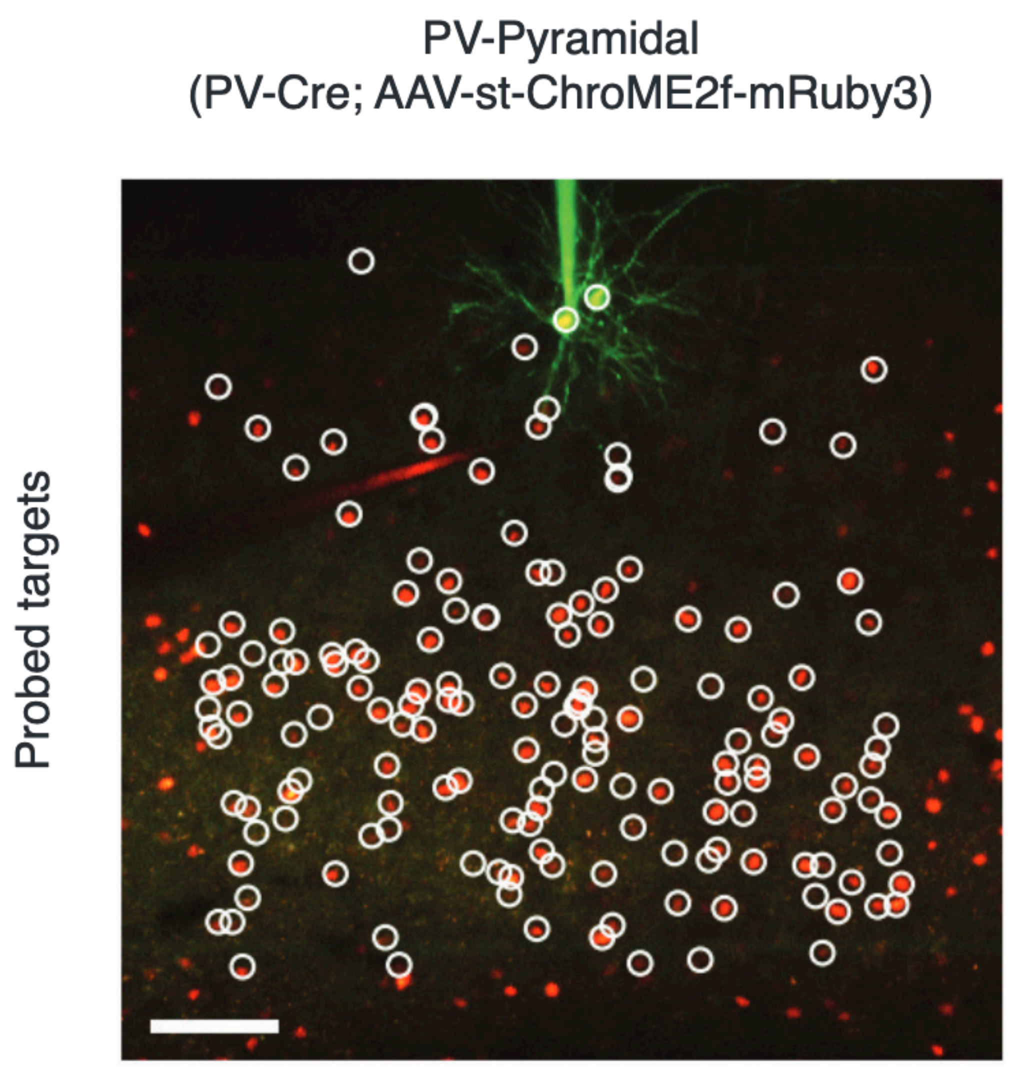
Triplett*, Gajowa* et al. (2022), *bioRxiv*

10x faster experiments without loss of accuracy

Marta Gajowa (Berkeley)

Hillel Adesnik (Berkeley)



(z-projection)

Triplett*, Gajowa* et al. (2022), *bioRxiv*

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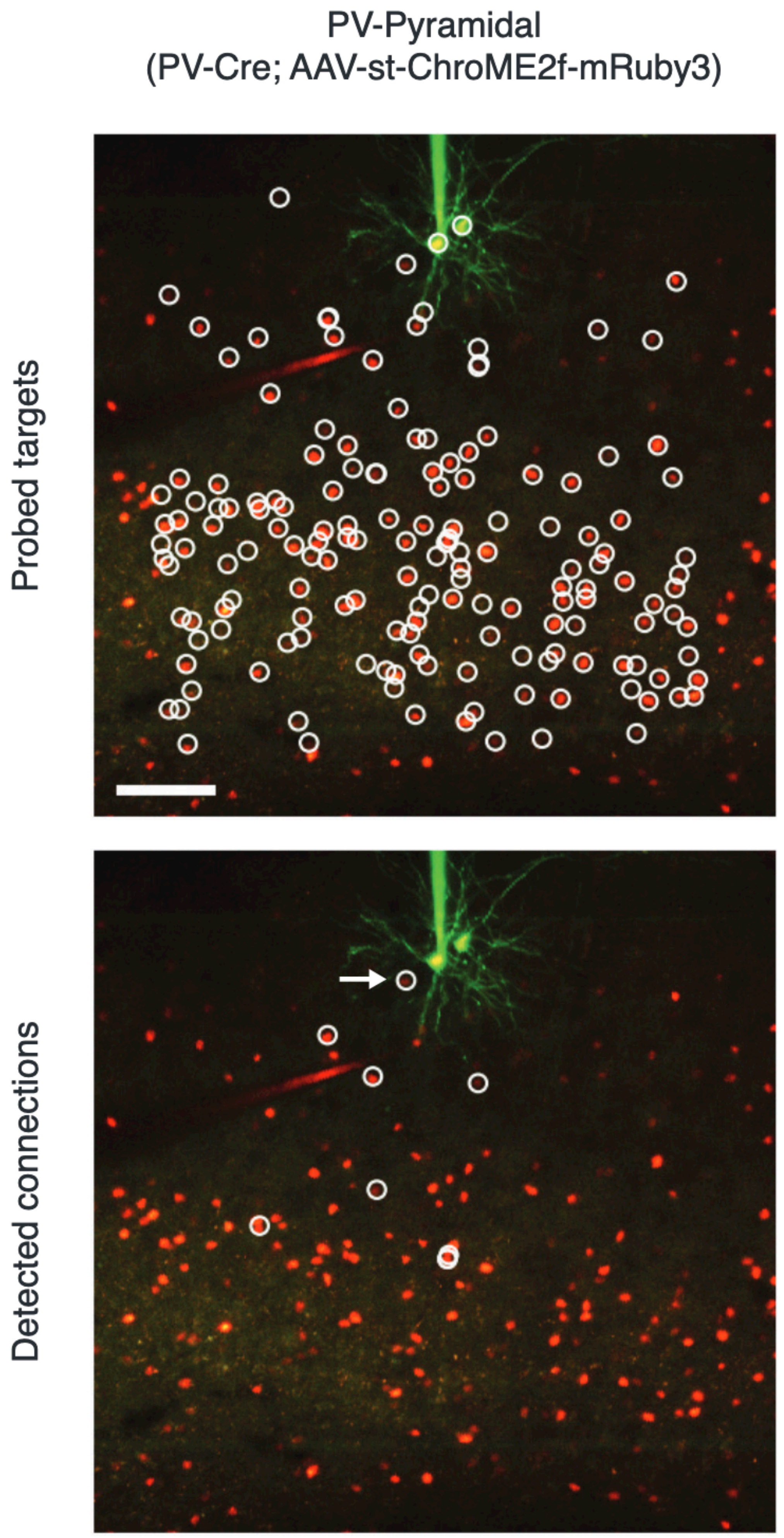

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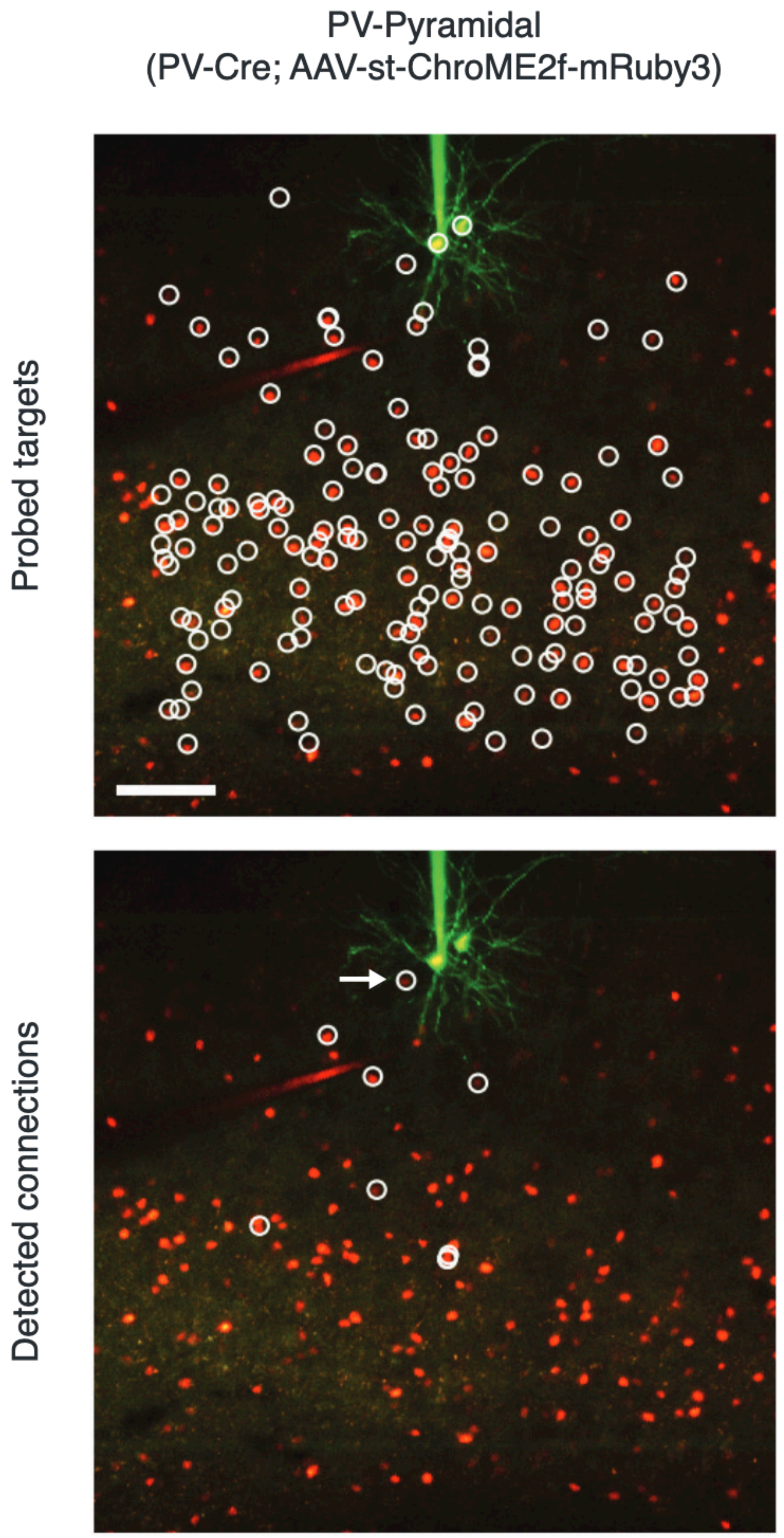

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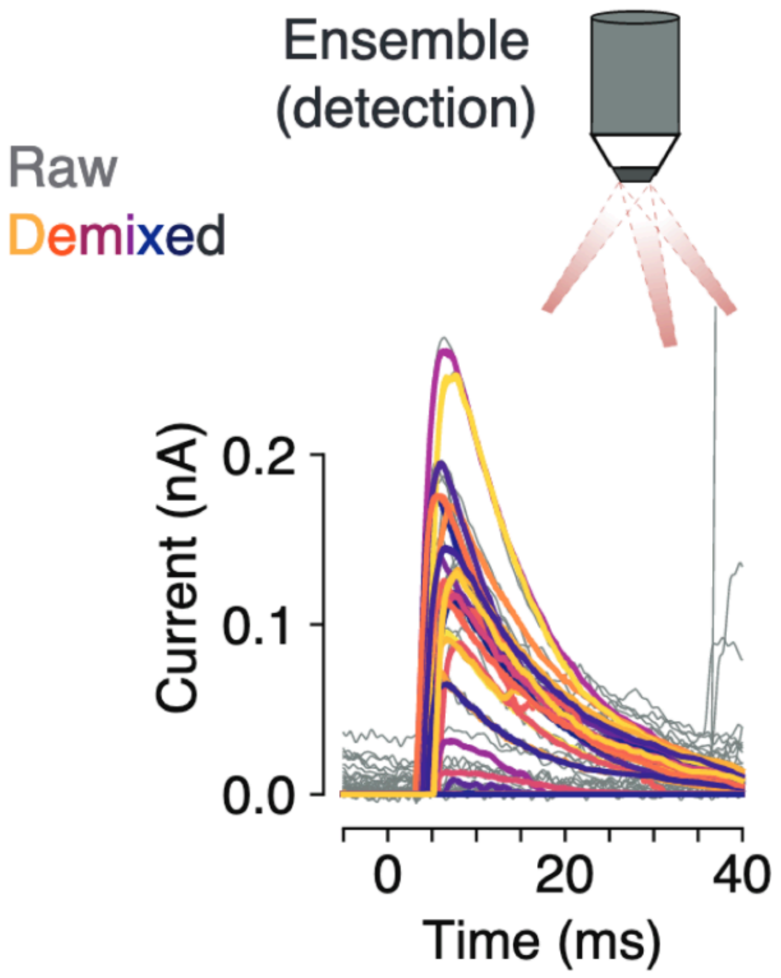

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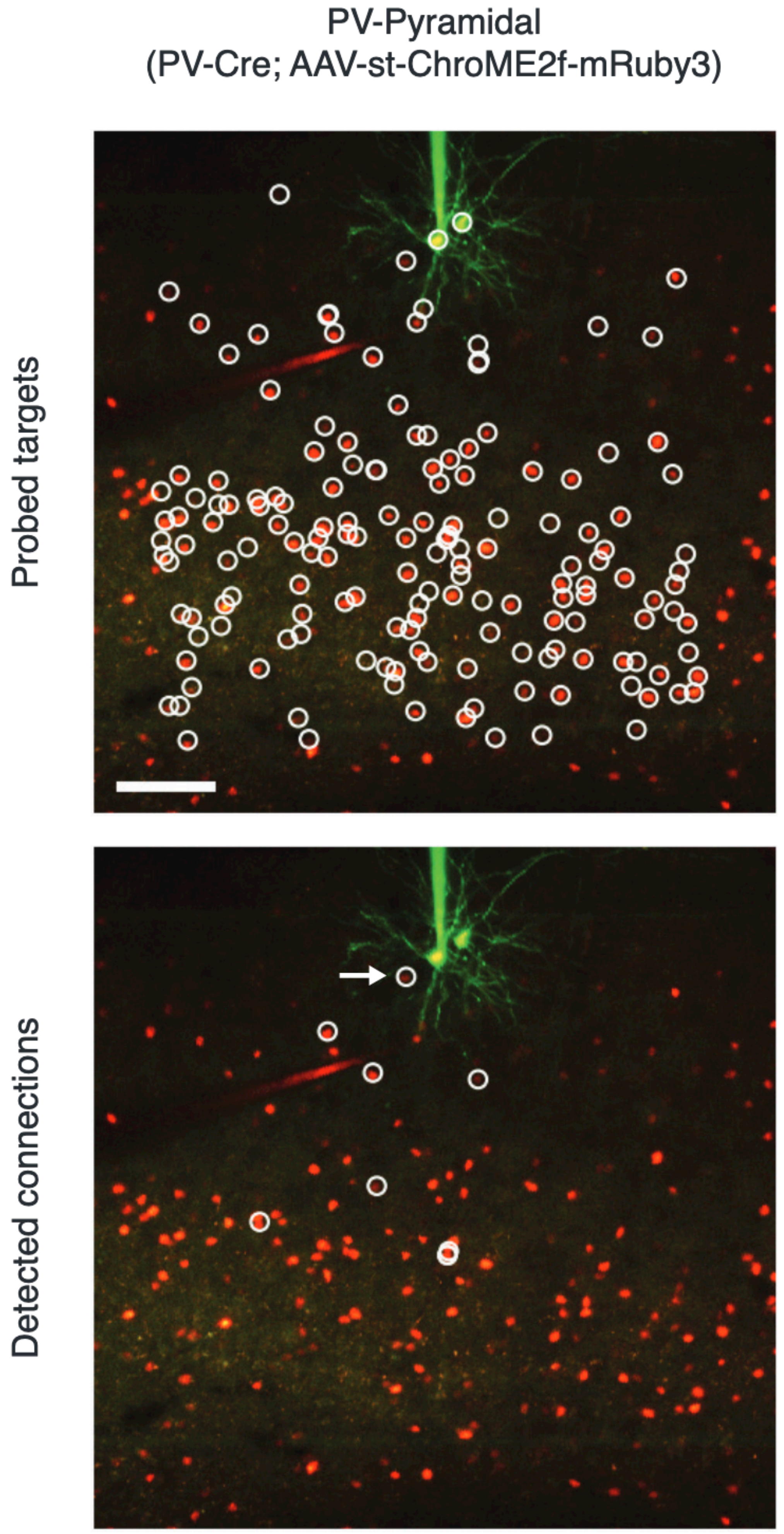

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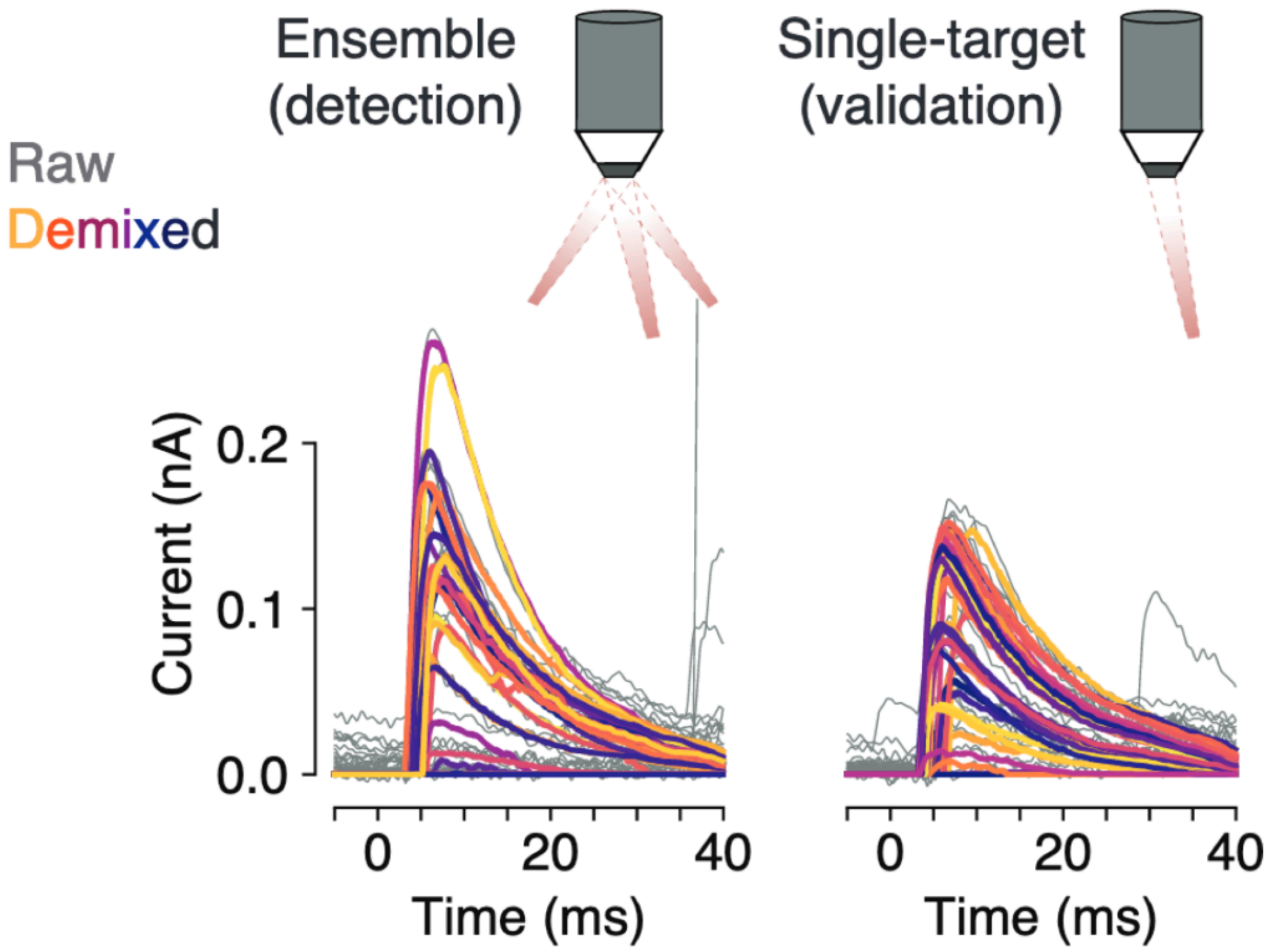

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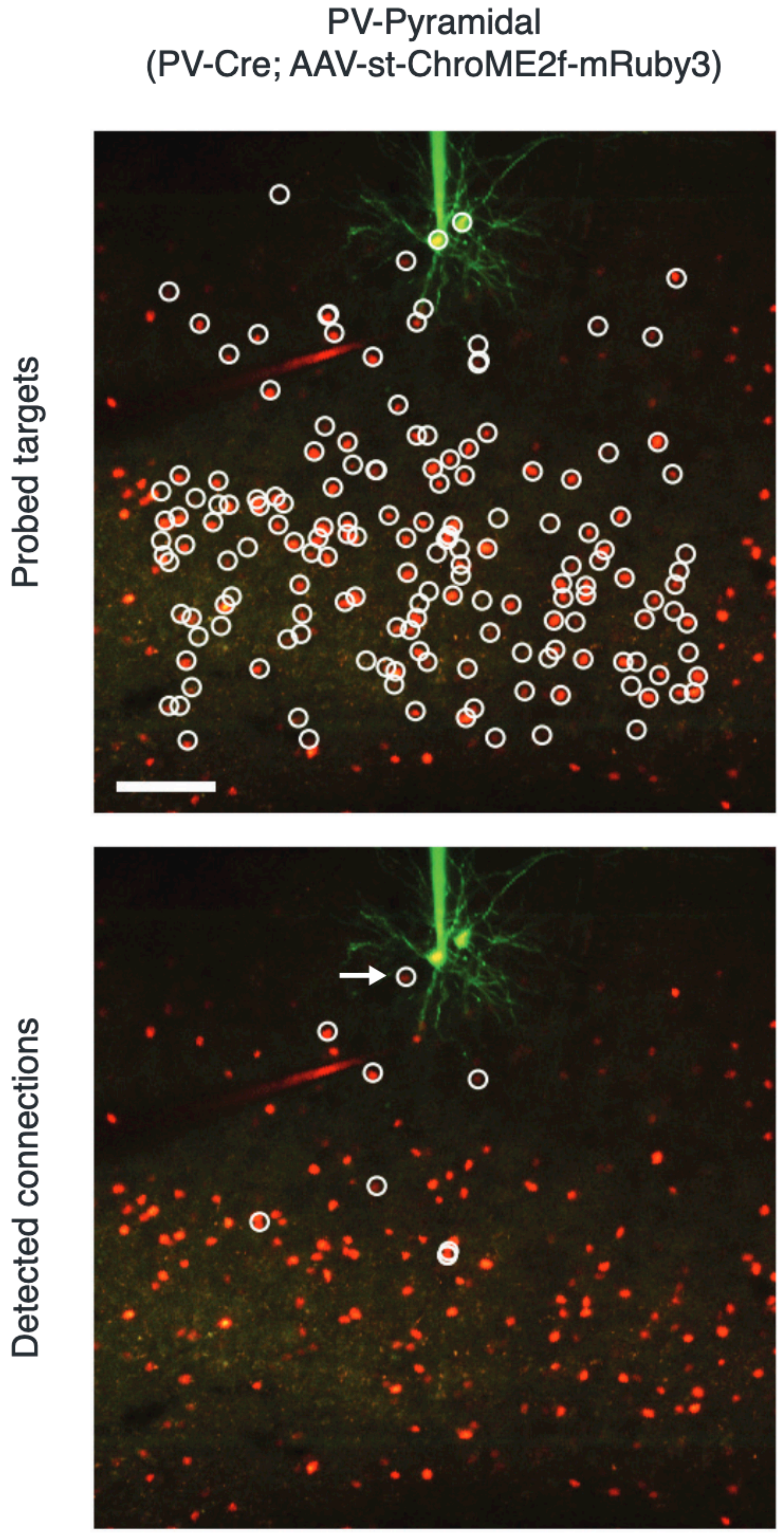

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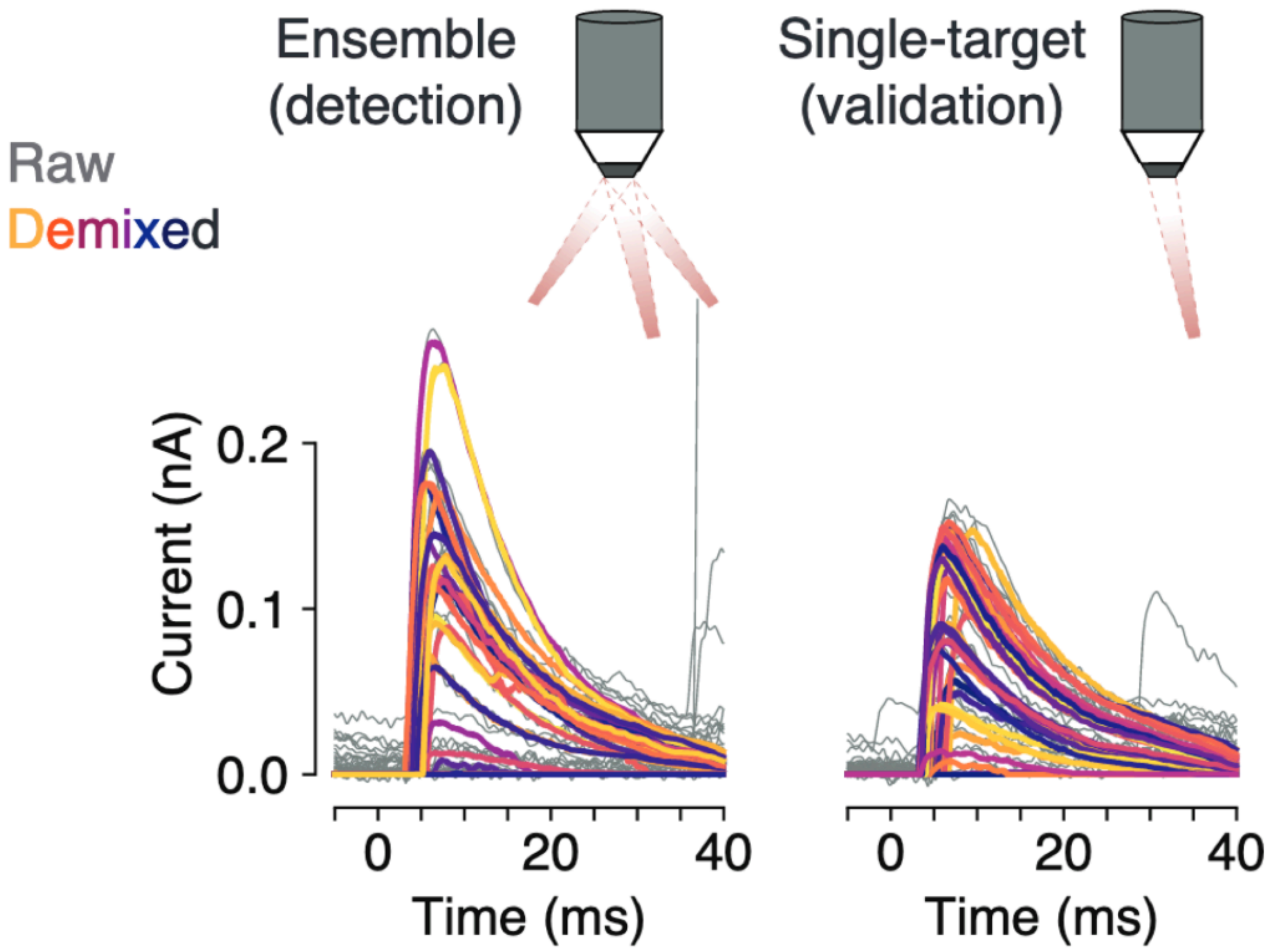
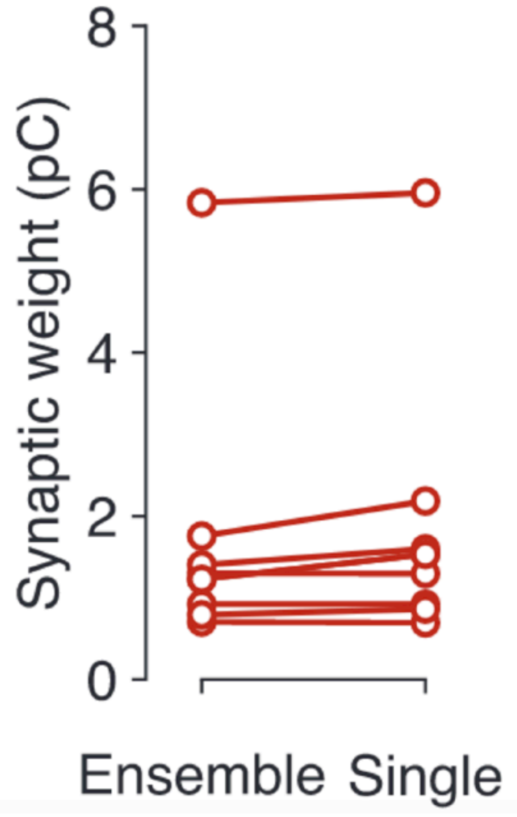


<10% synaptic weight difference
(this expt)



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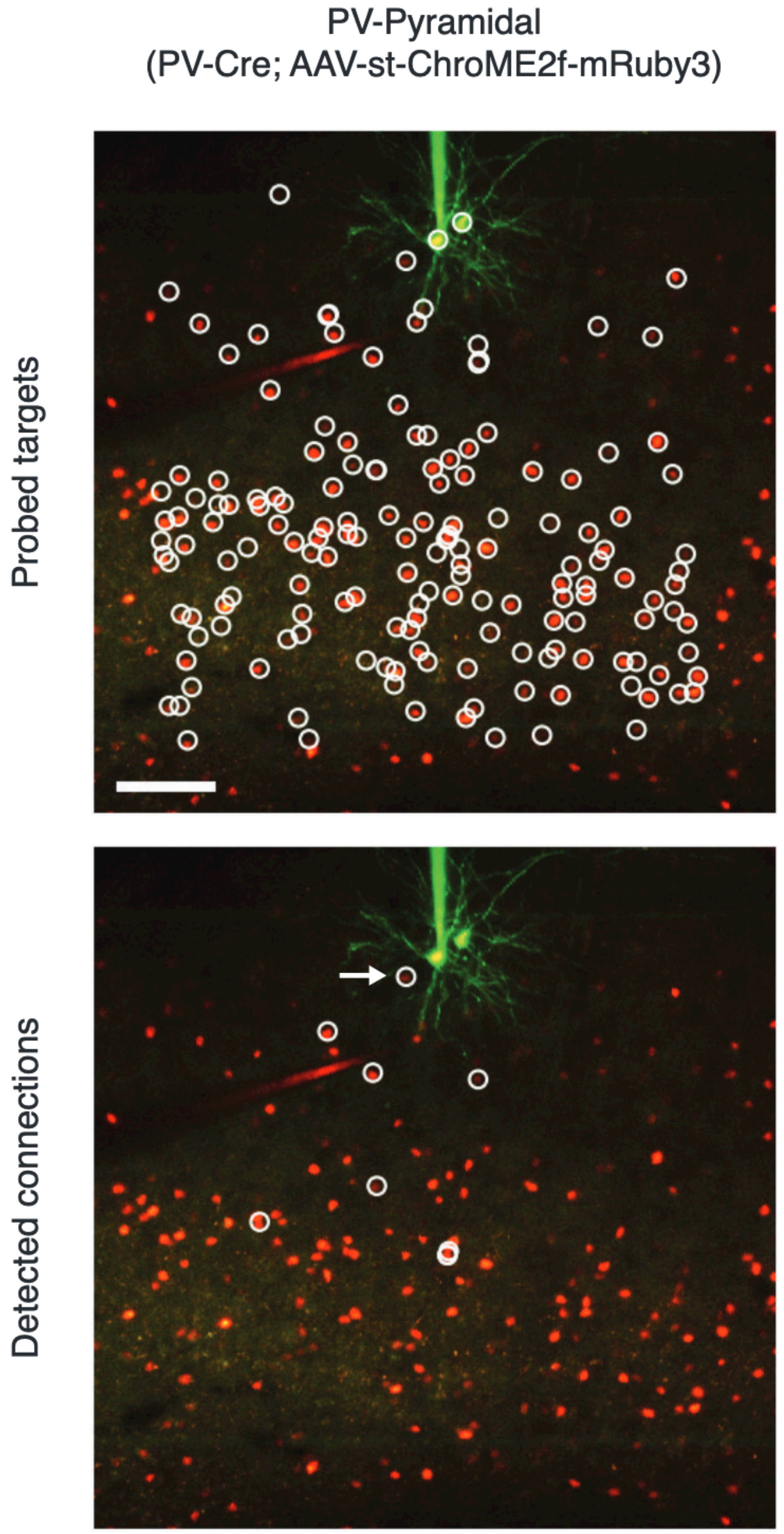

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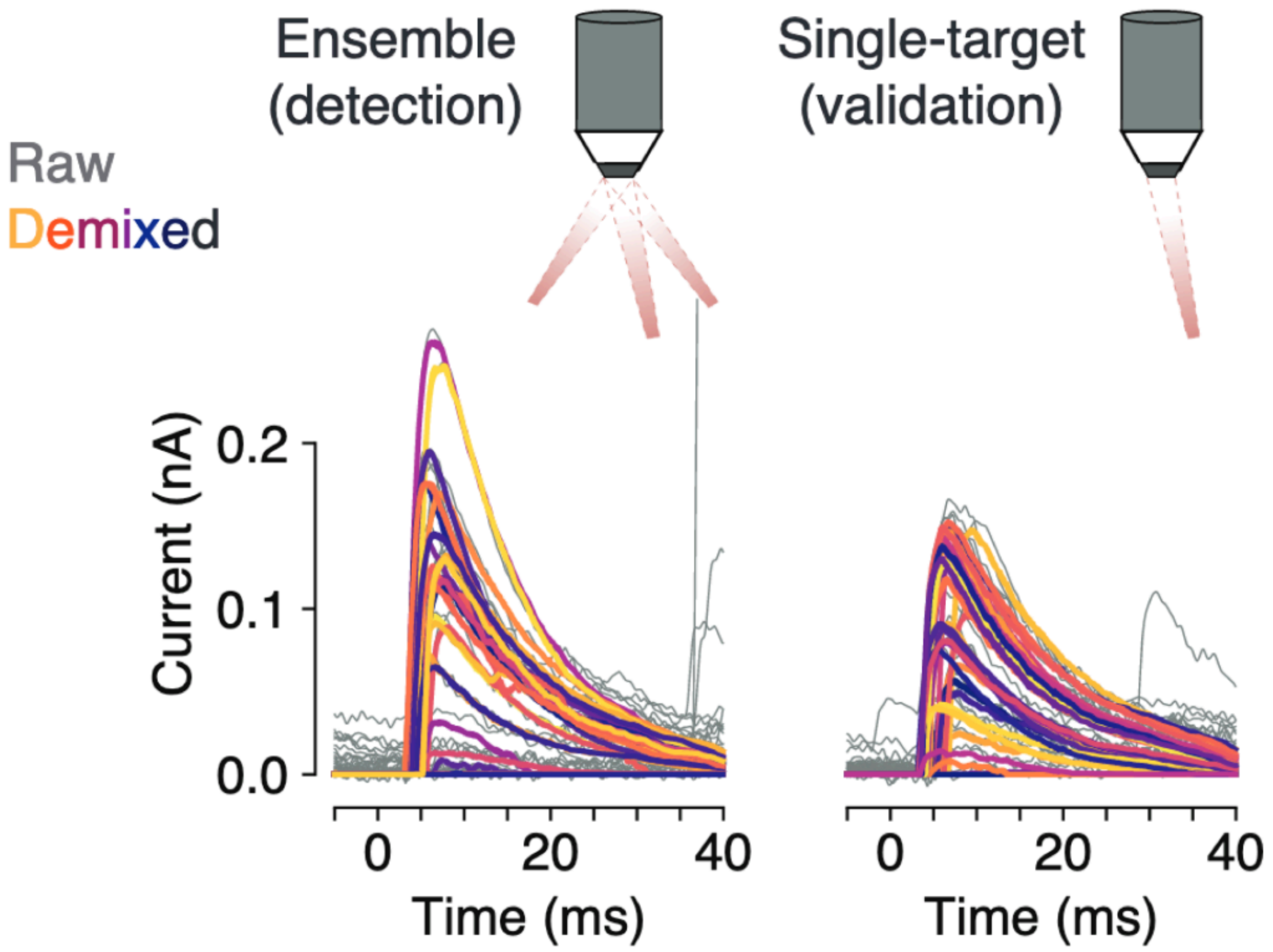

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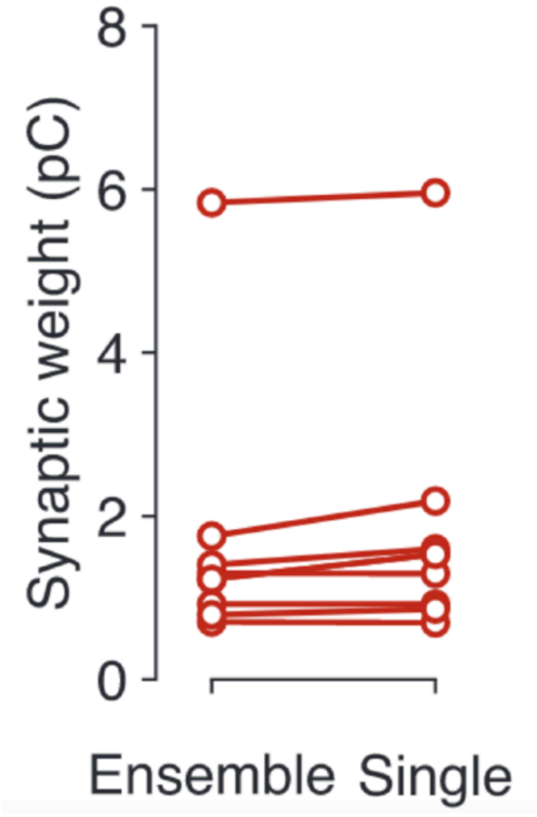
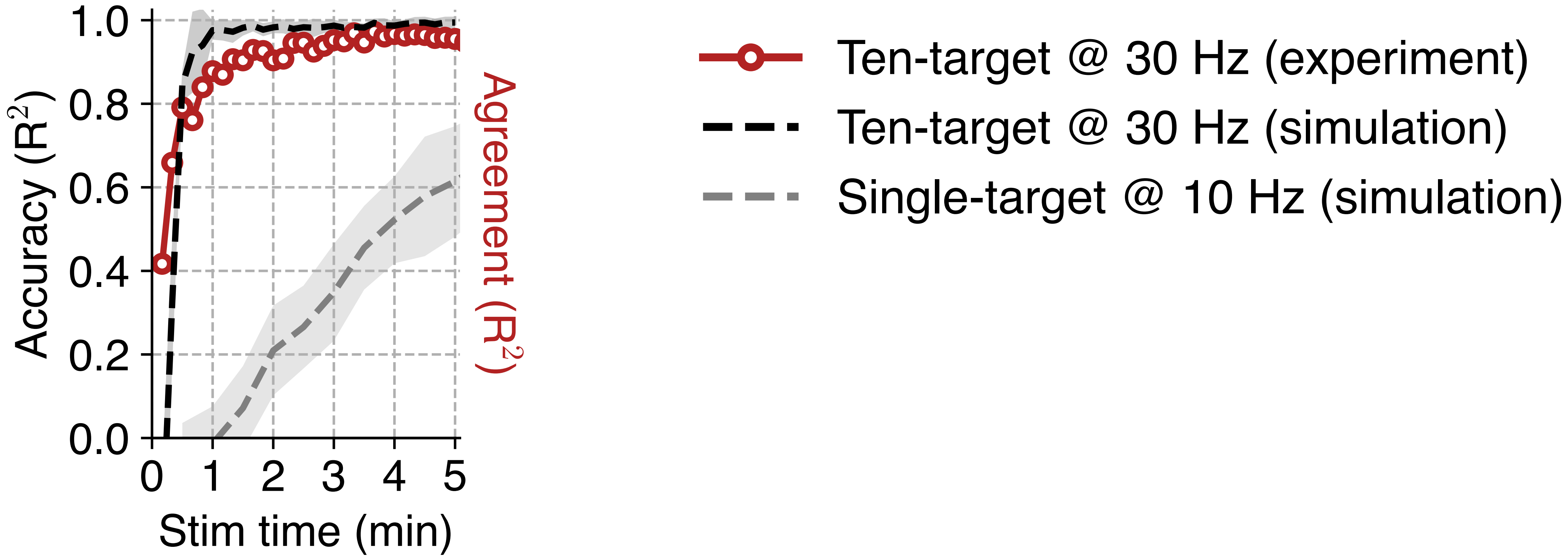
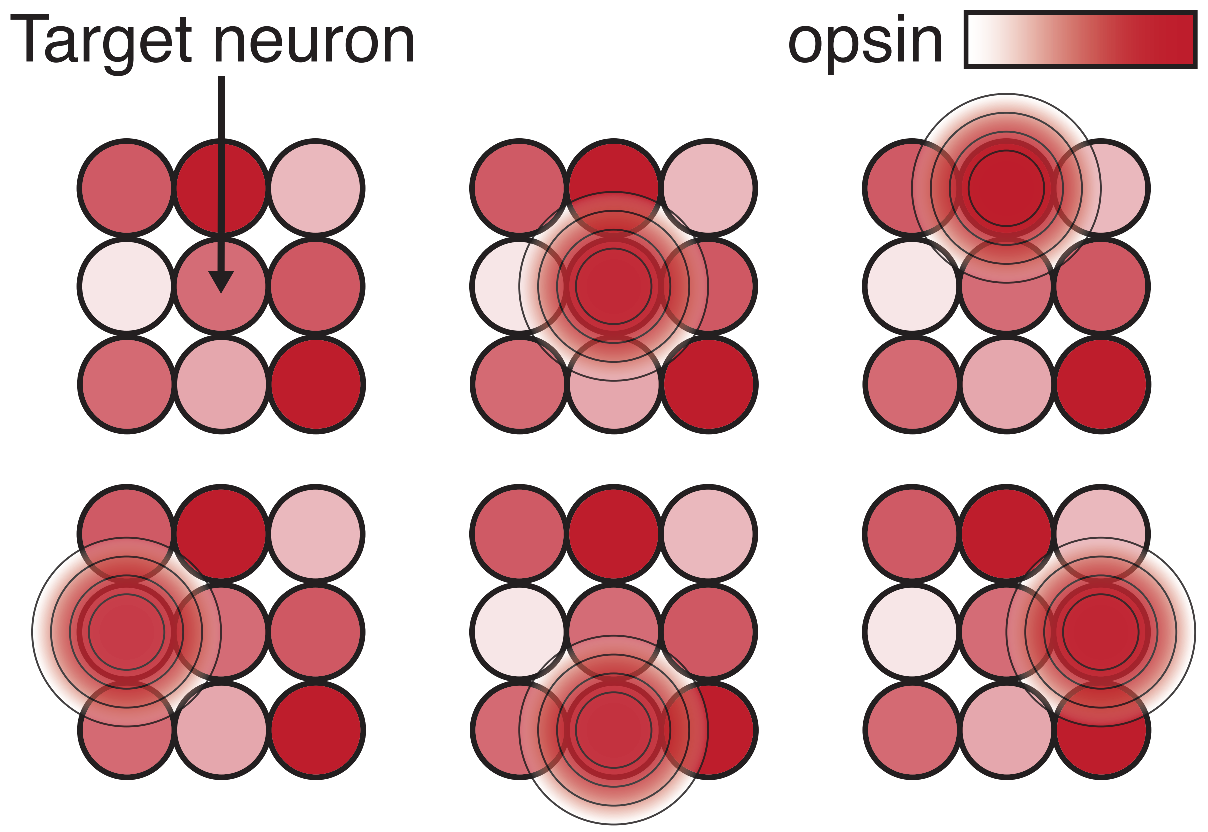




Triplett*, Gajowa* et al. (2022), *bioRxiv*

Strategies for connectivity mapping with dense expression

Decorrelate local activity



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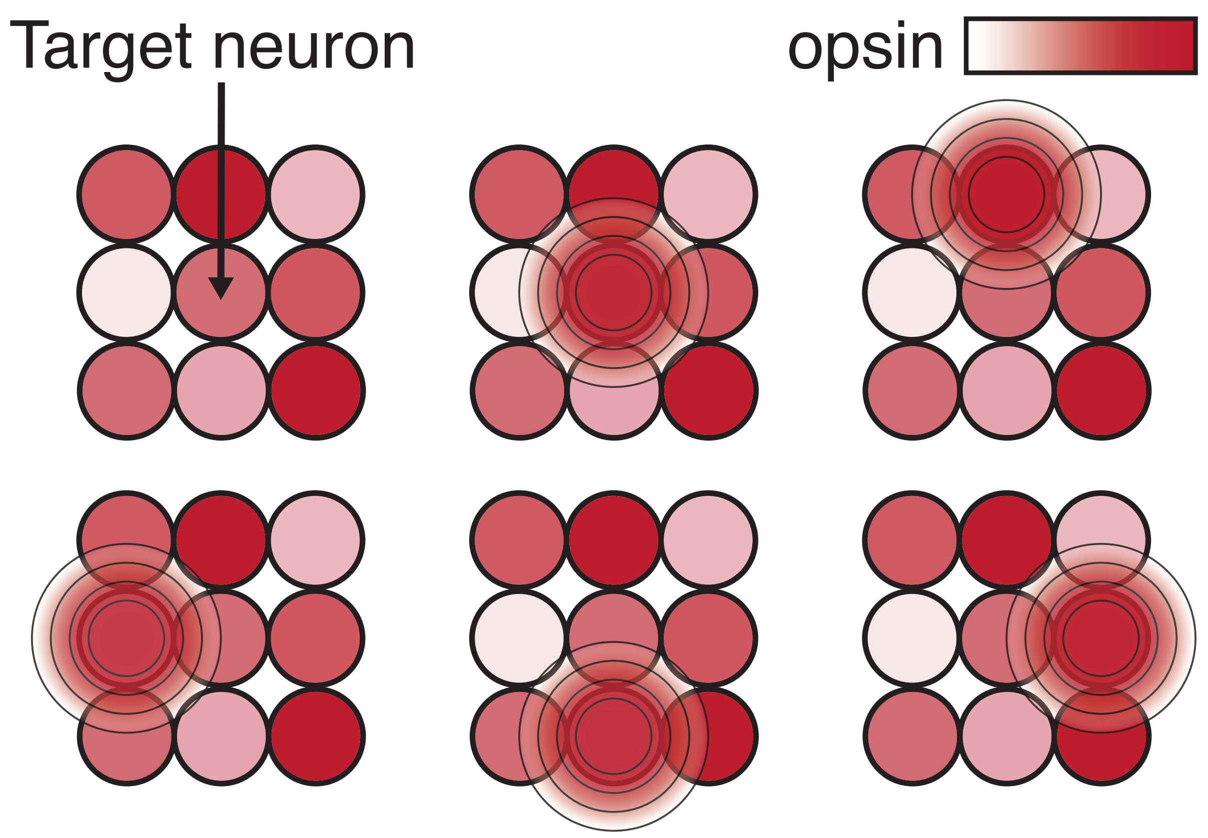

Optimise targets