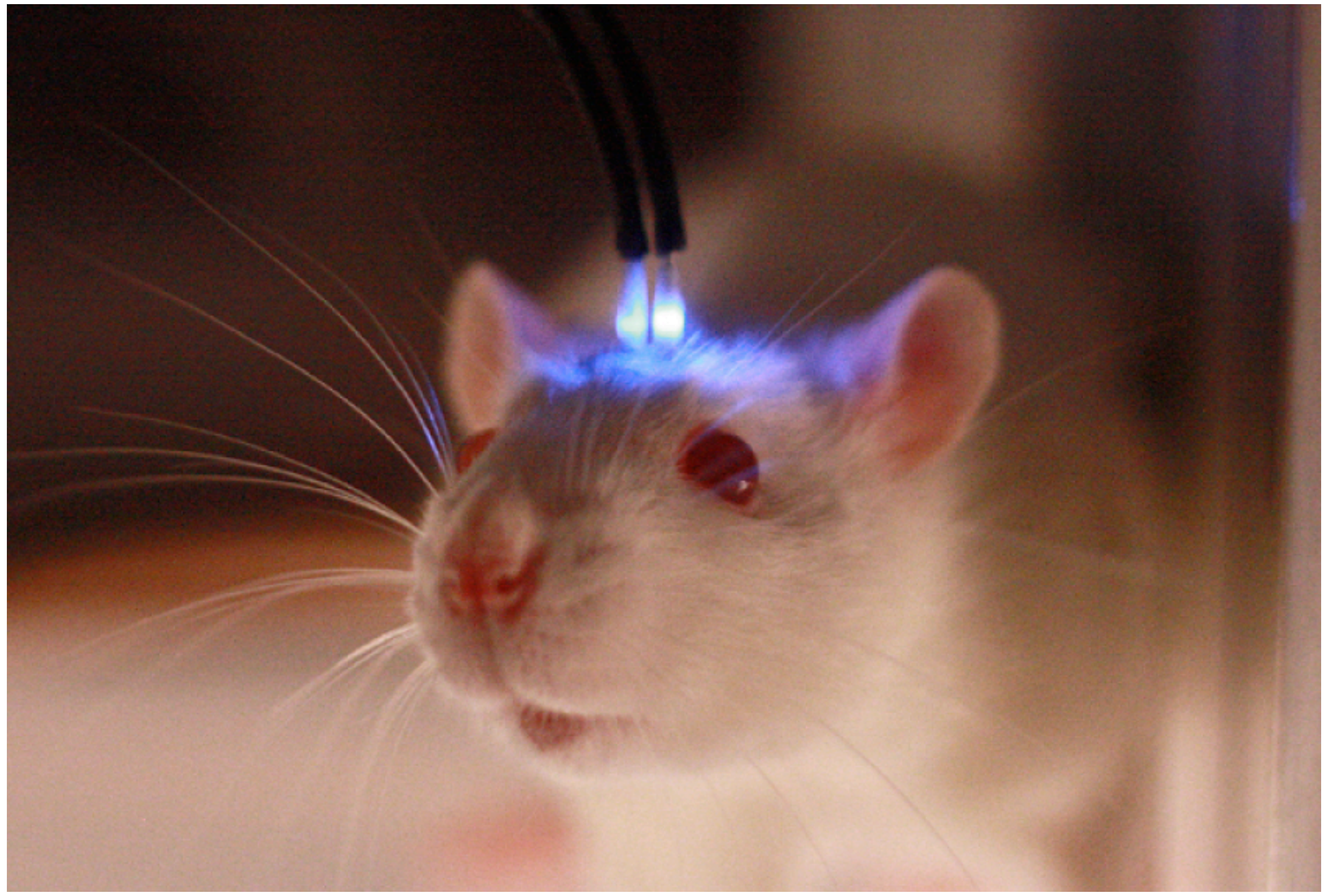
Computational methods for large-scale optical control and mapping of neural circuits

Statistical Analysis of Neural Data

Marcus Triplett

Probing brain function using **optogenetics**



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

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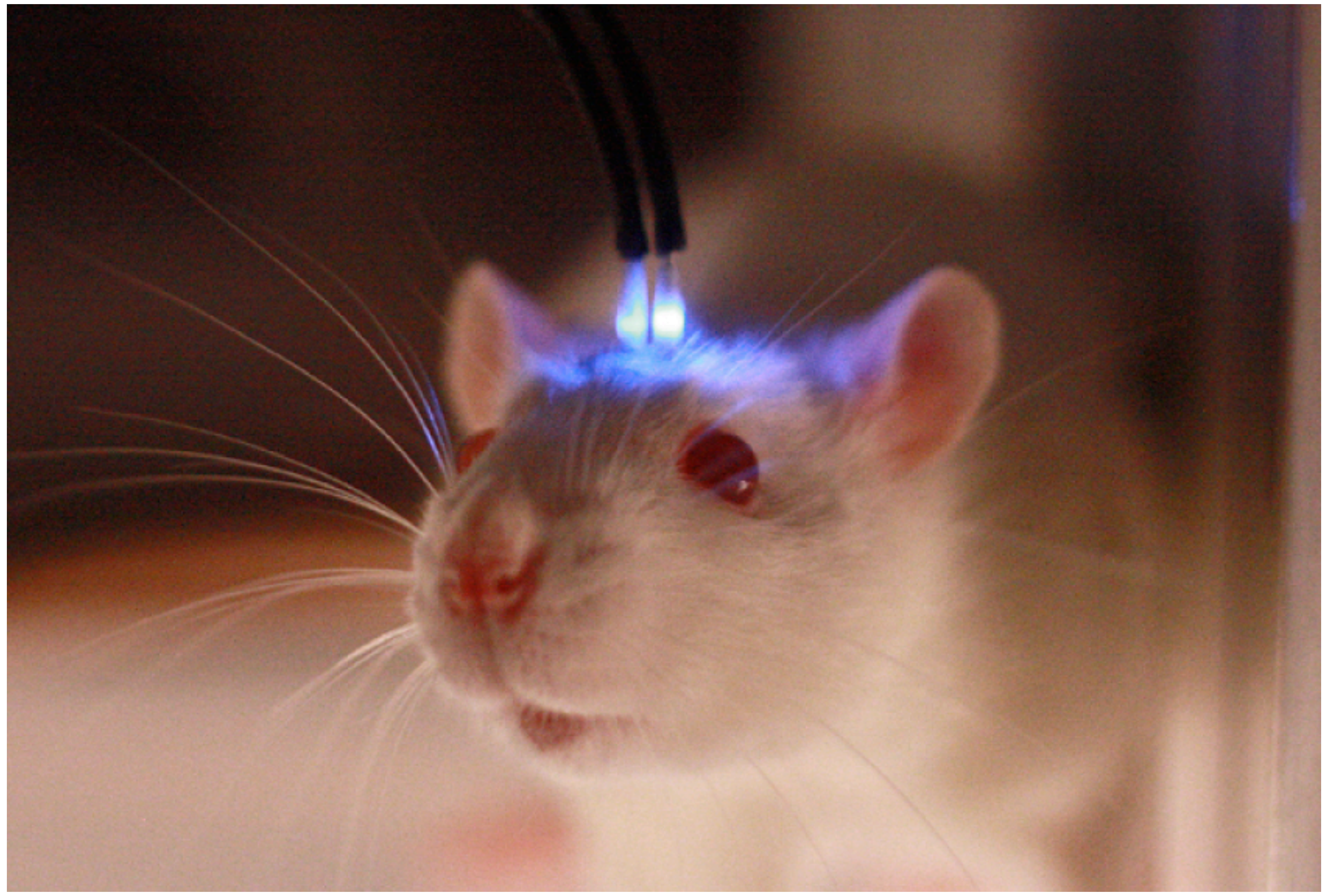

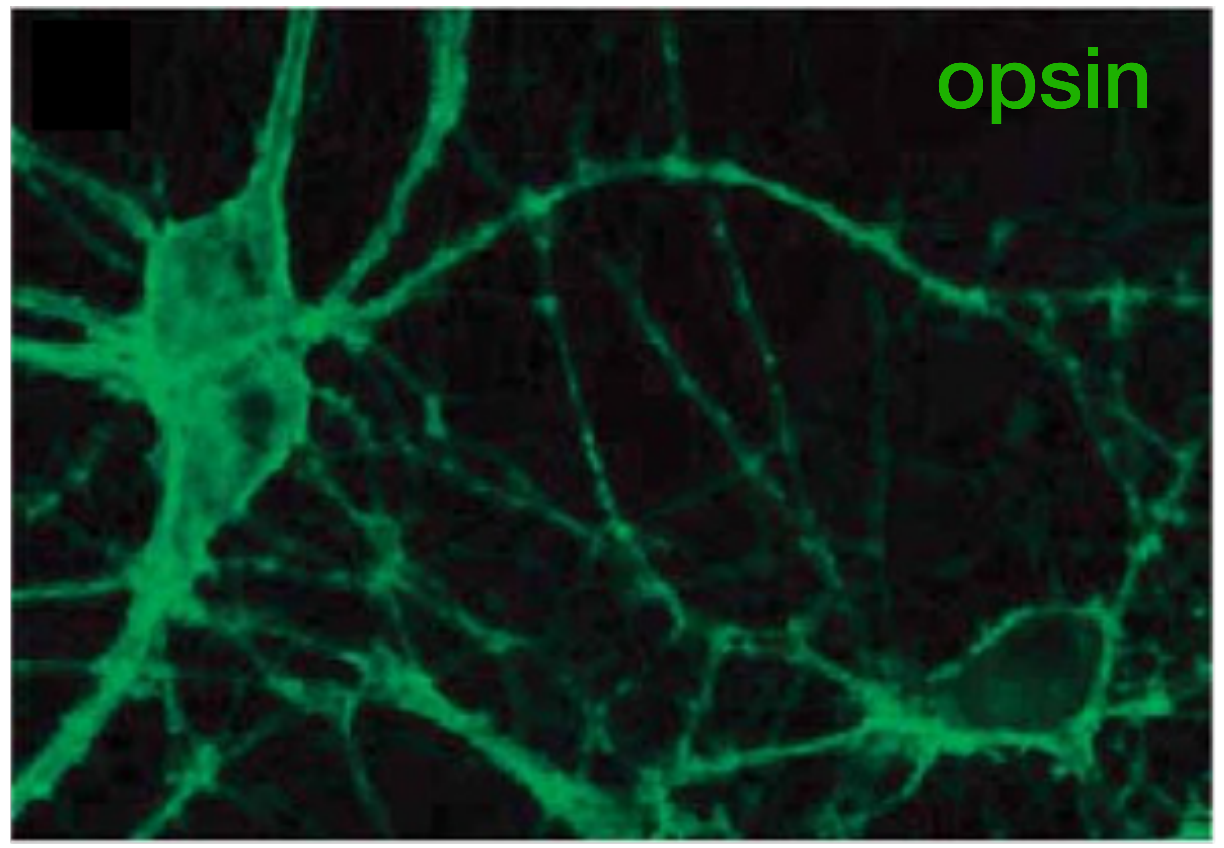

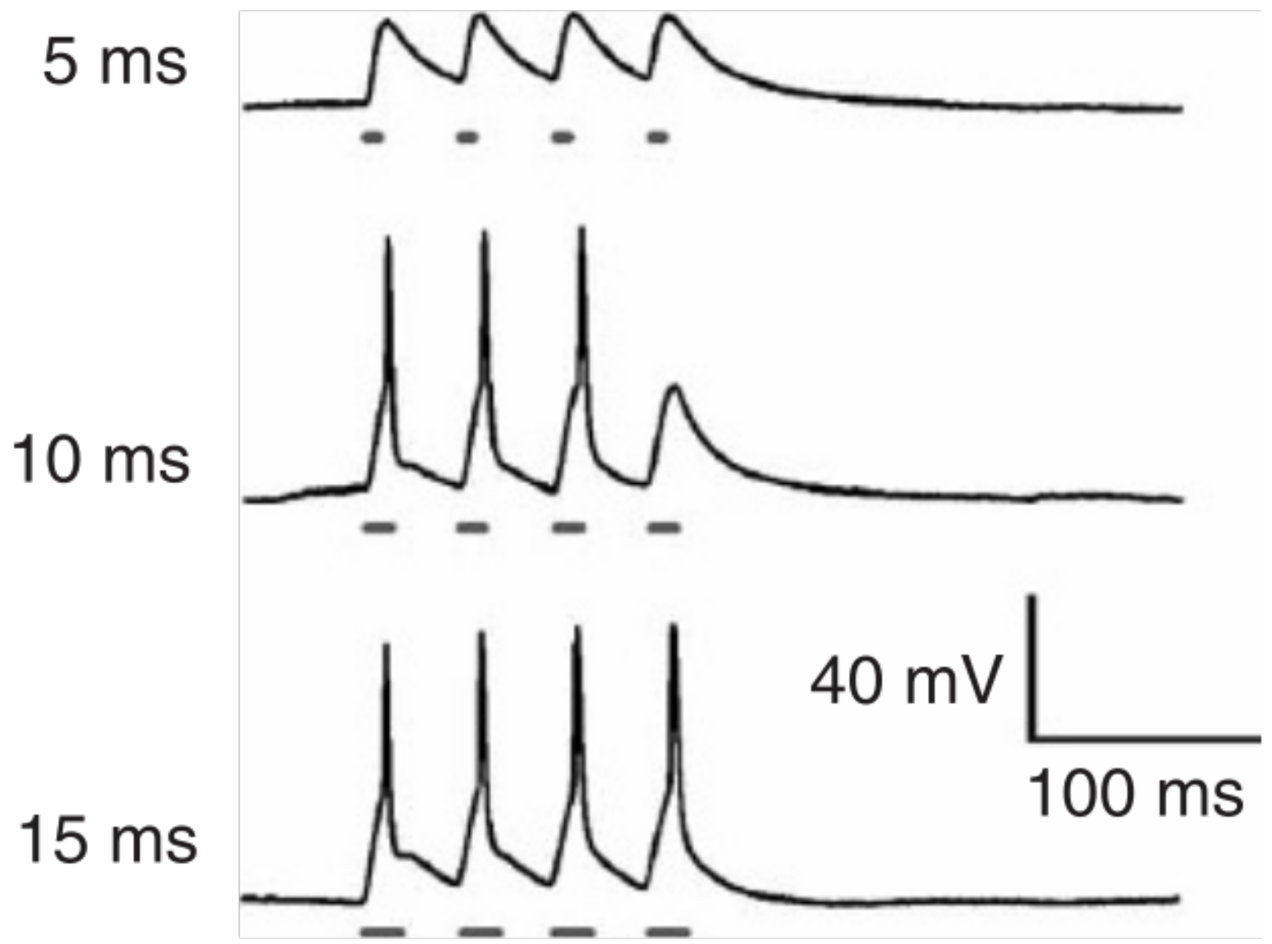

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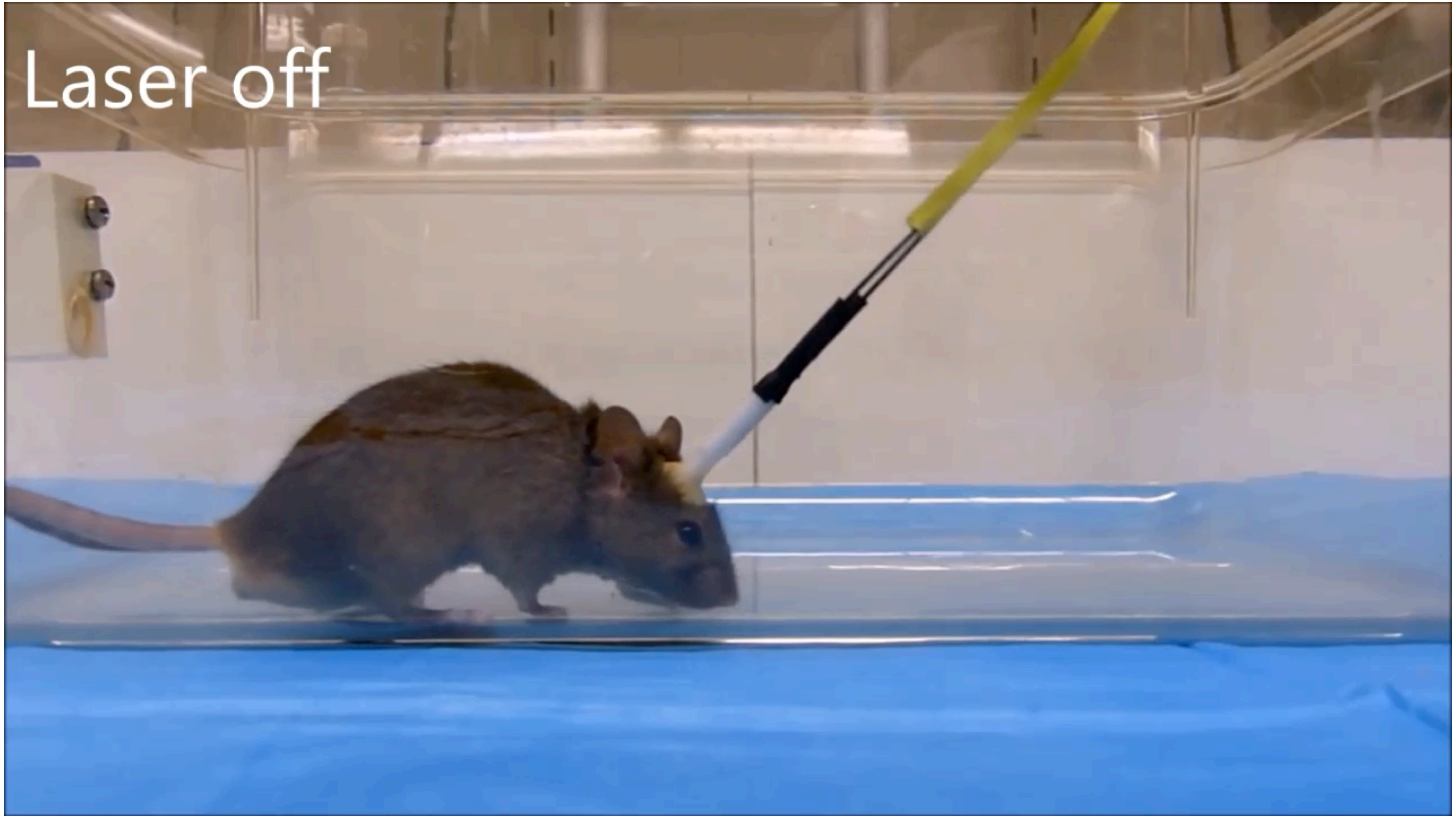
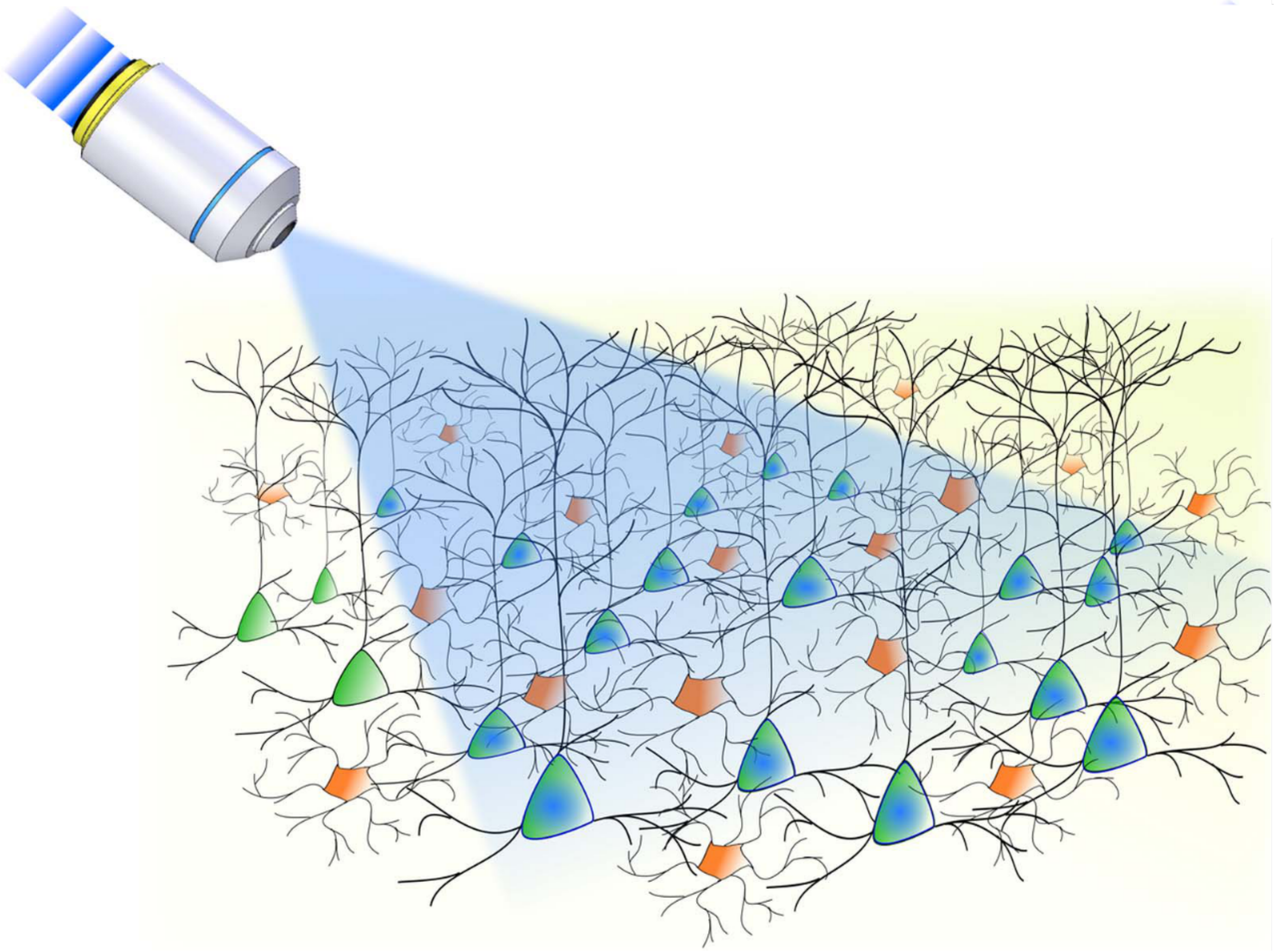


Han et al 2017, *Cell*

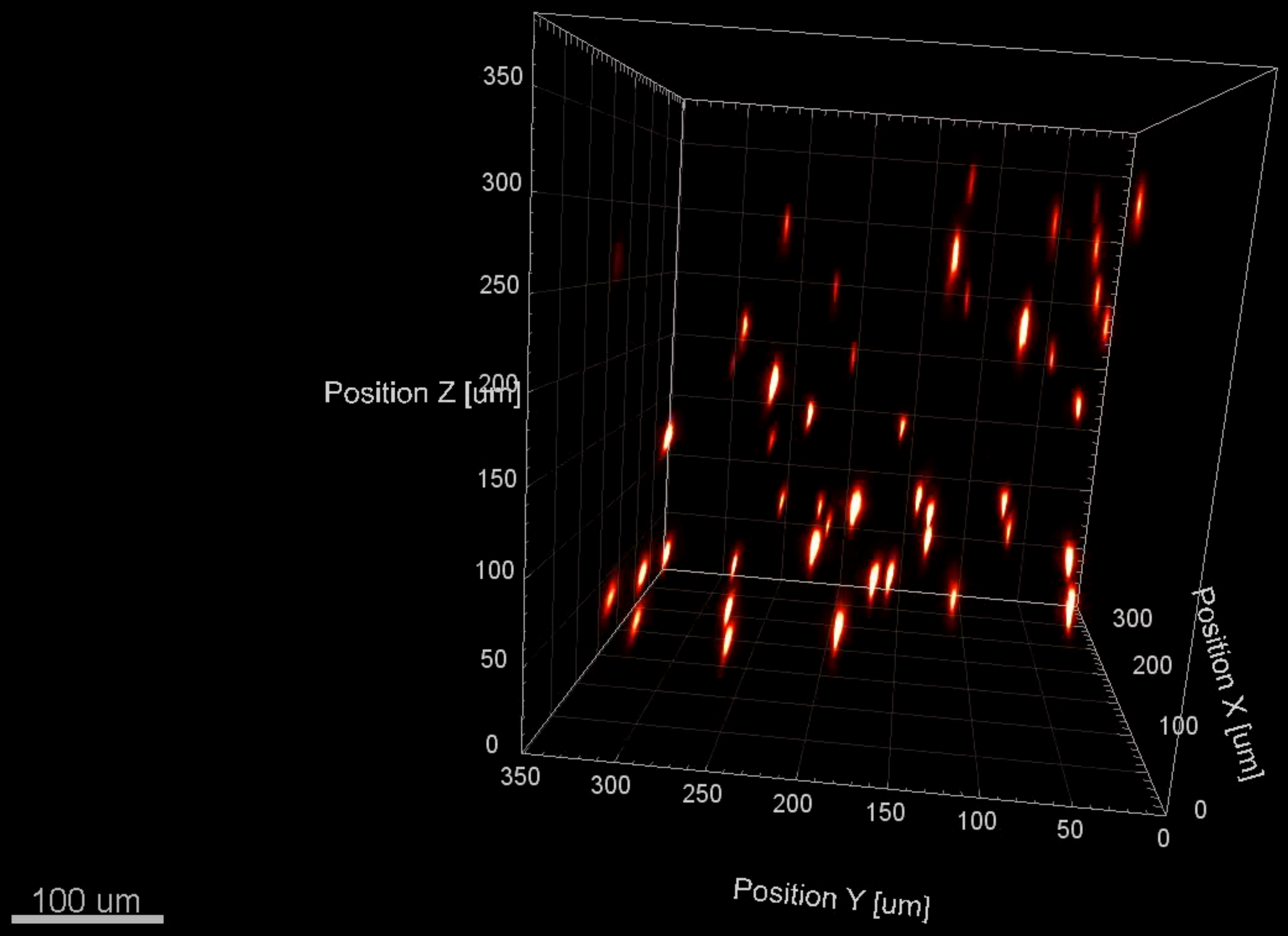
The limitation of classical optogenetics



No precision beyond cell-type specificity

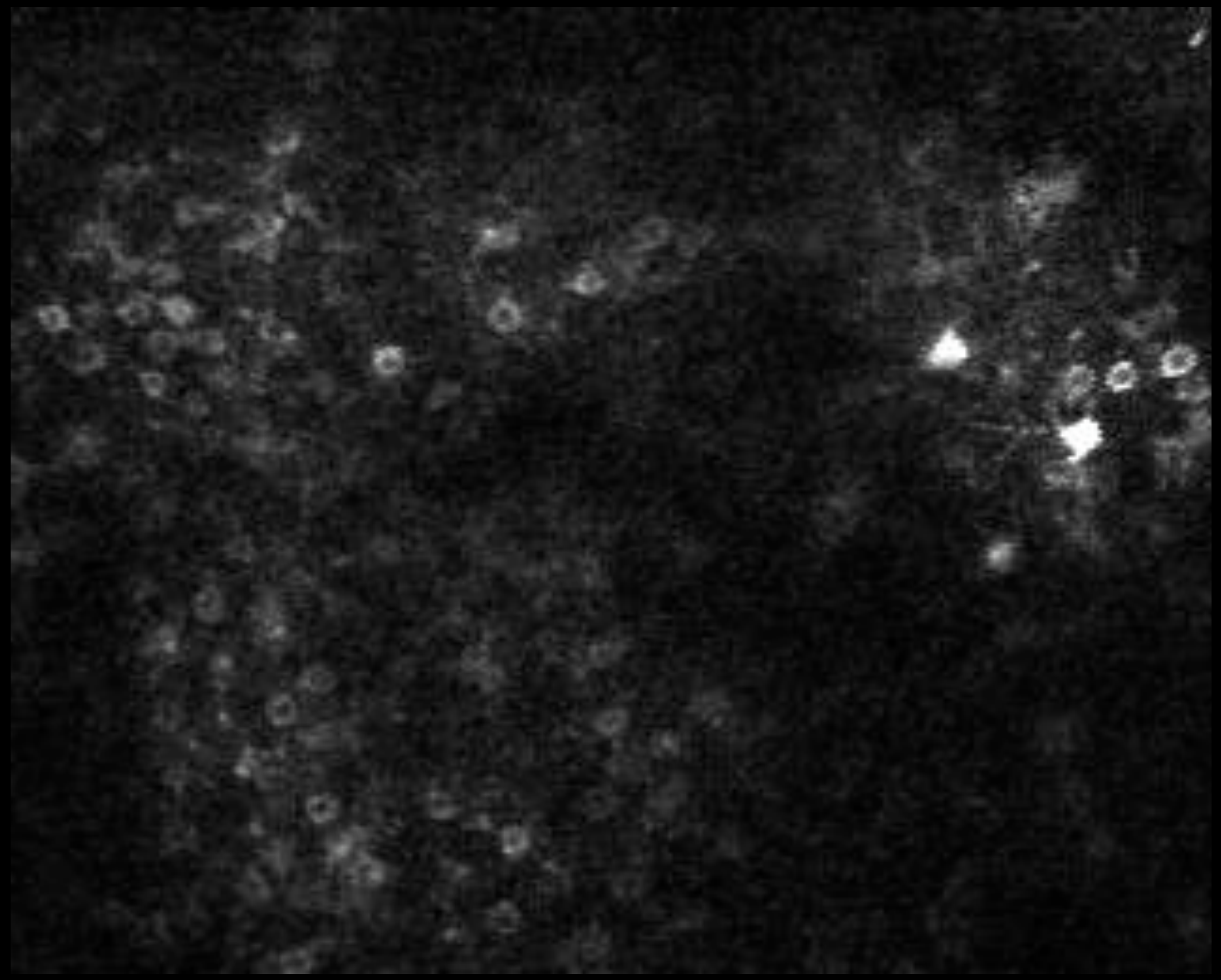
Image: Ronzitti et al (2017)

Two-photon holography as a potential solution



Adesnik lab

Two-photon holographic optogenetics



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

See also Emiliani, Yuste, Hausser, et al

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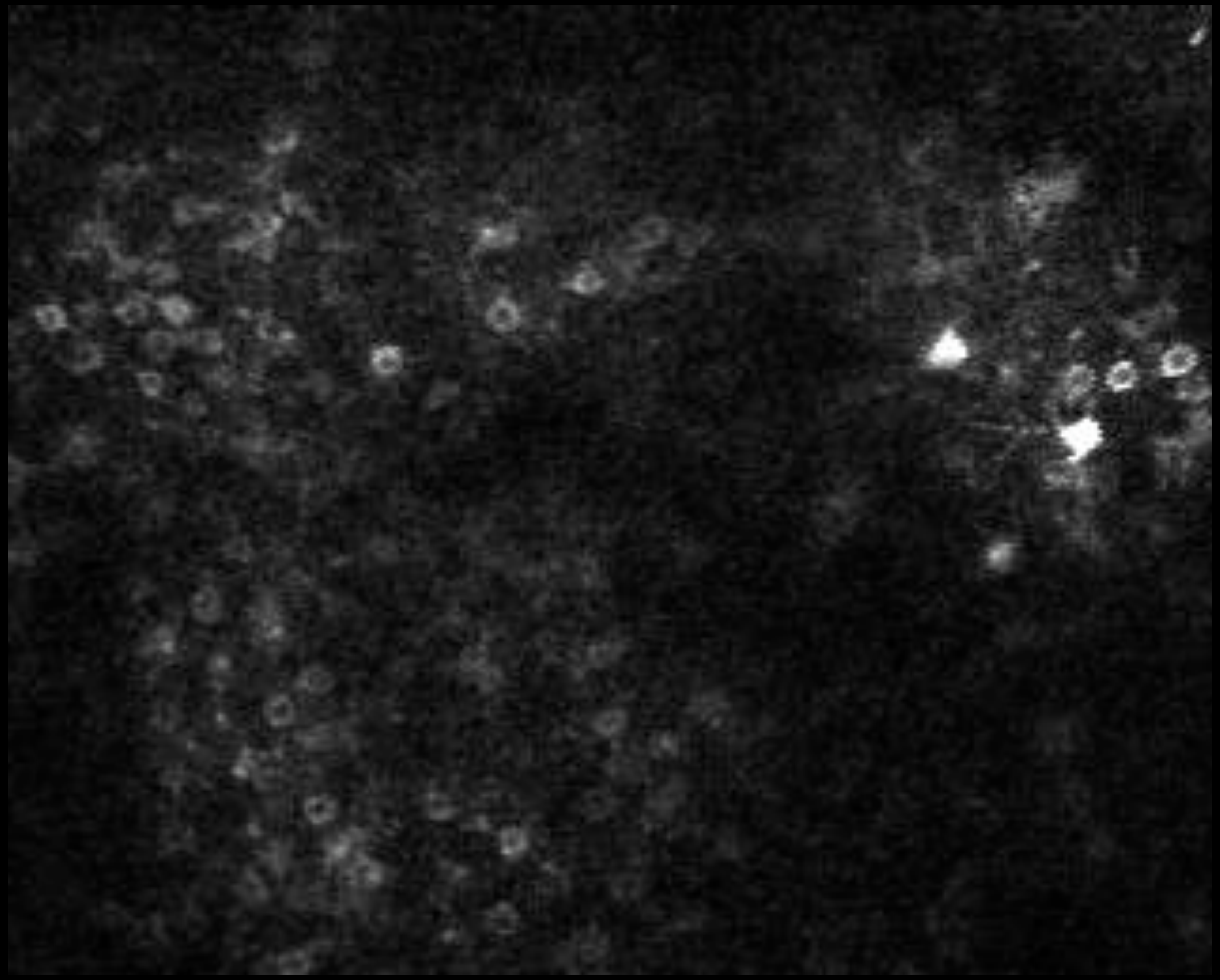

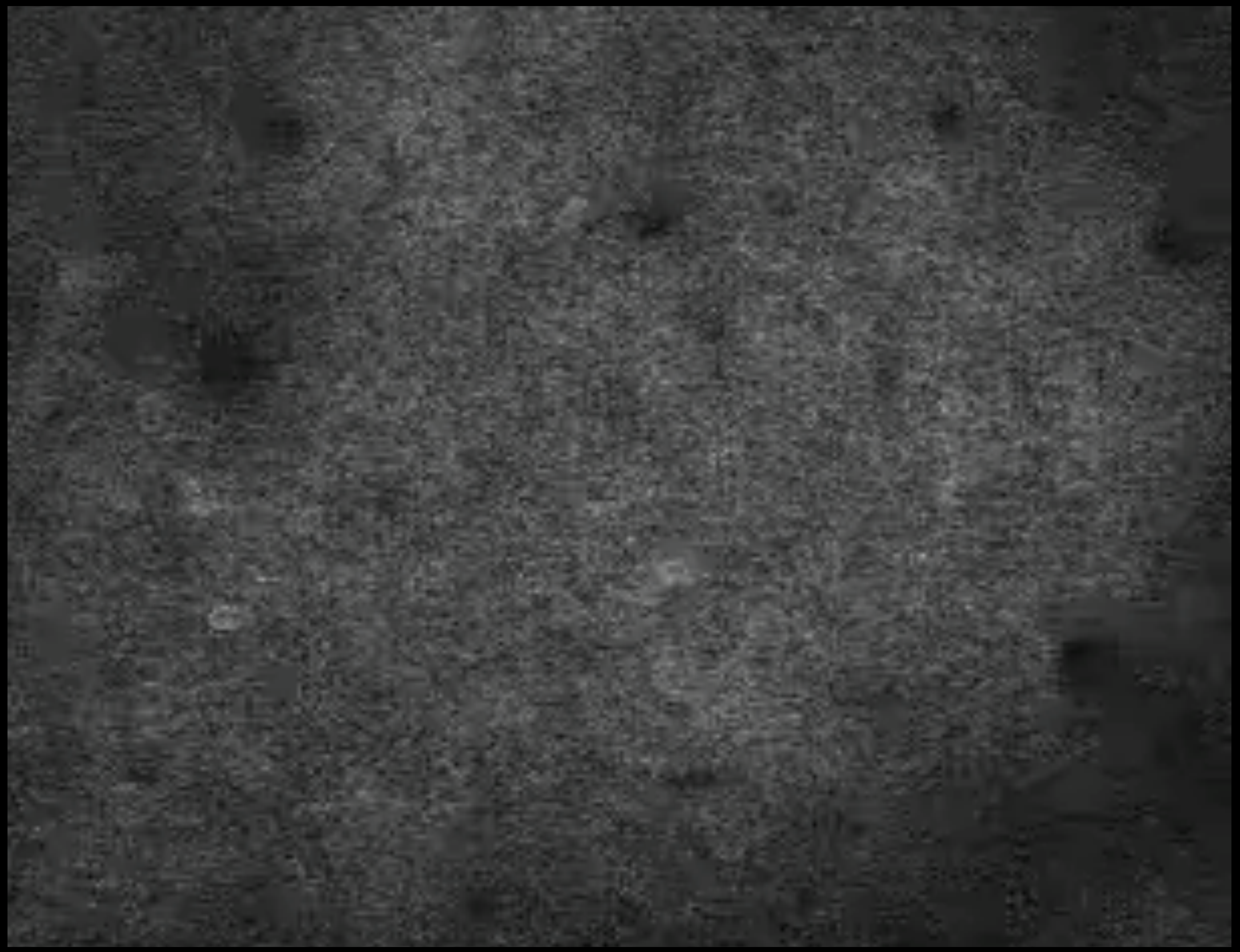

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Two challenges in neuroscience

1. Connectivity mapping

2. Ensemble control

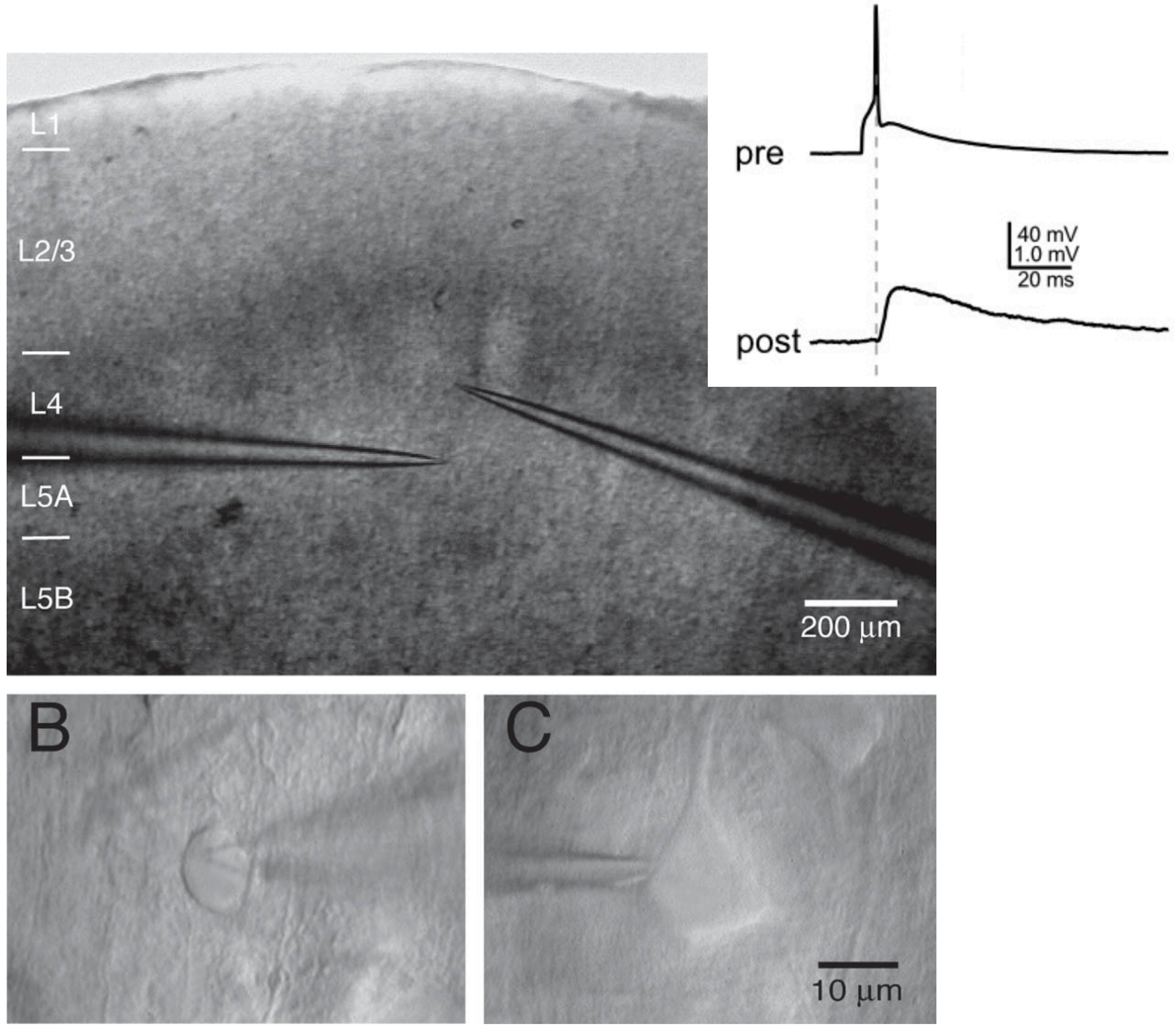
Two challenges in neuroscience

1. Connectivity mapping ◁

2. Ensemble control

Using stimulation to reveal connections

Electrical



Images: Feldmeyer et al (2005), Qi et al (2015)

Using stimulation to reveal connections

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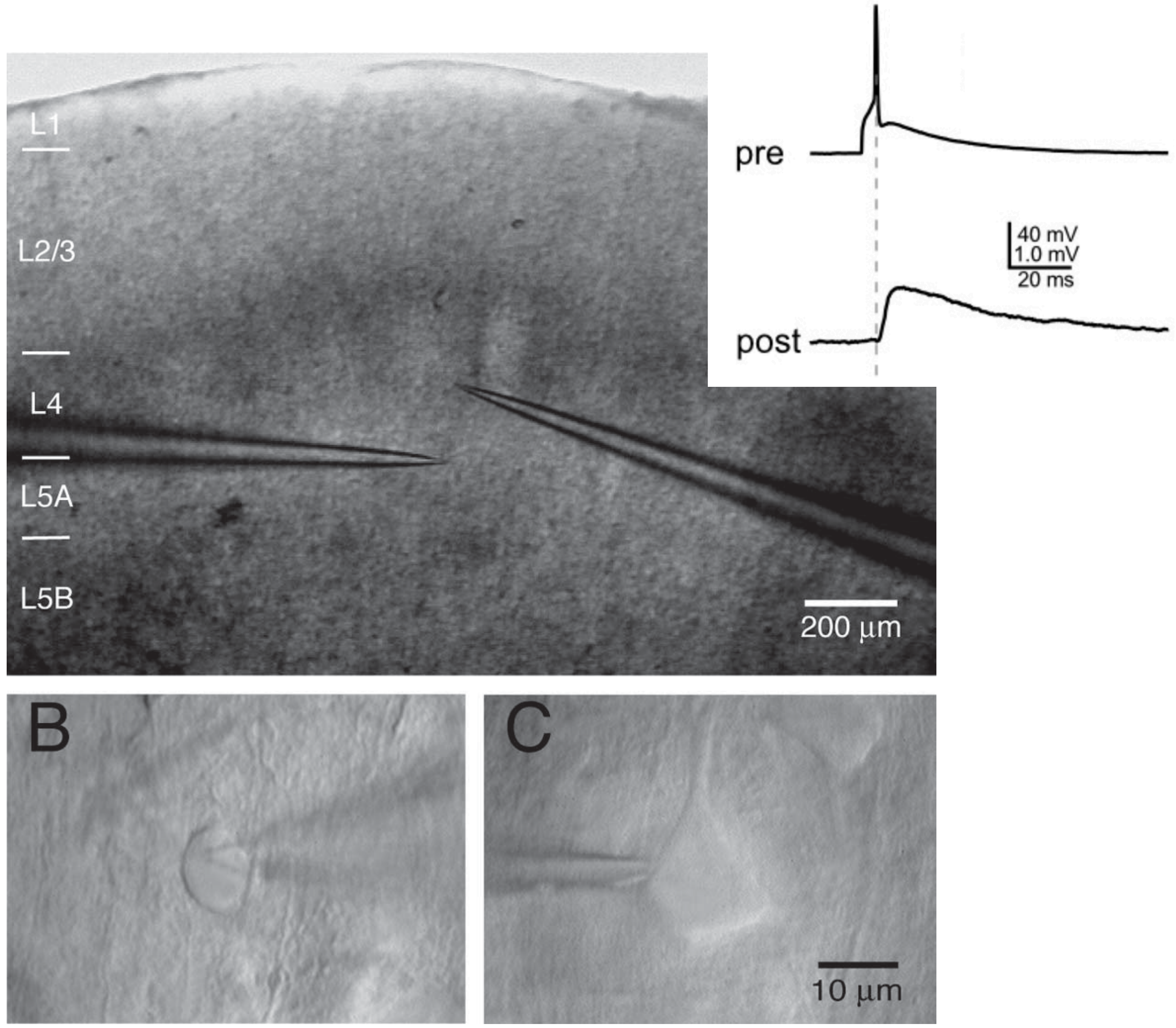

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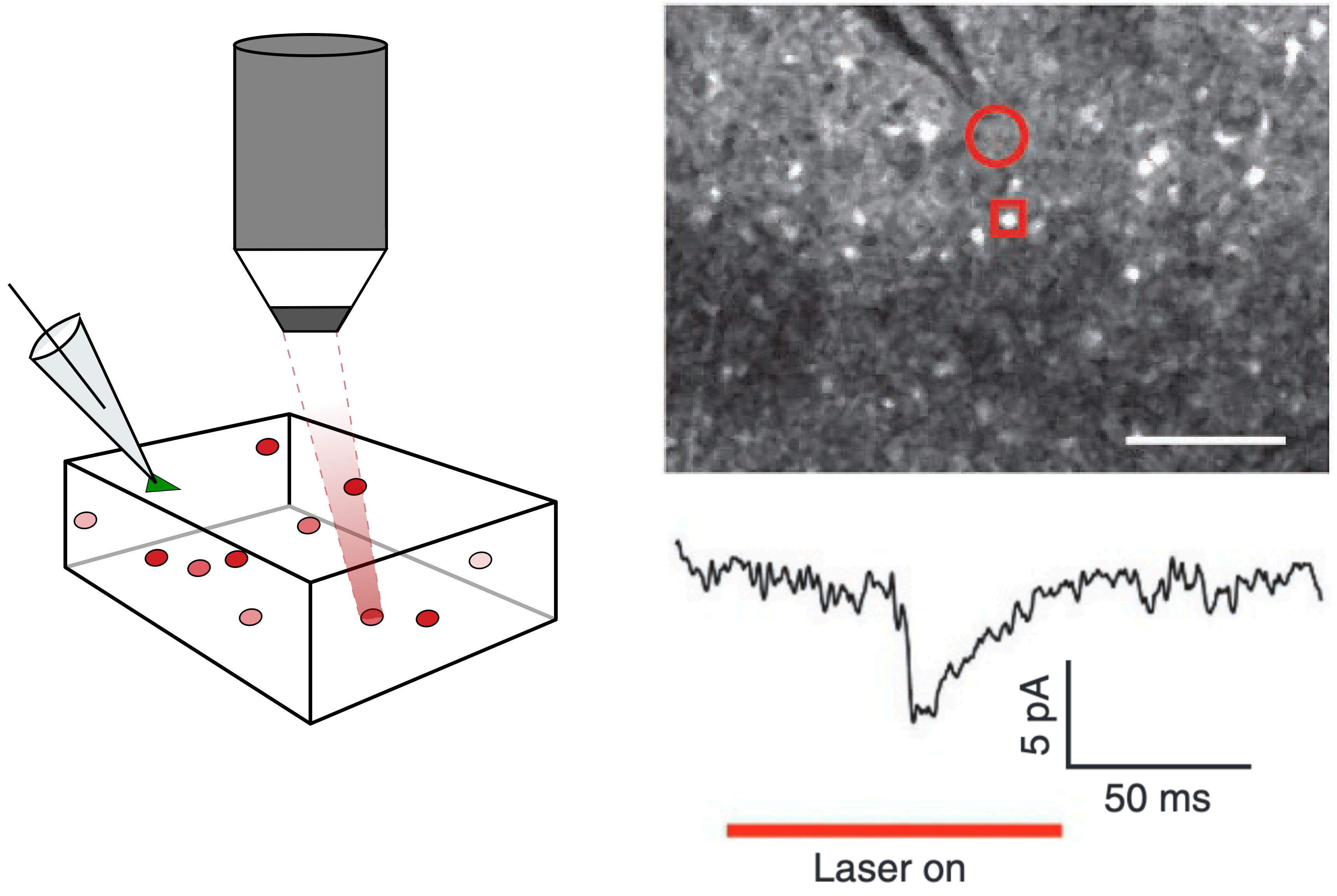
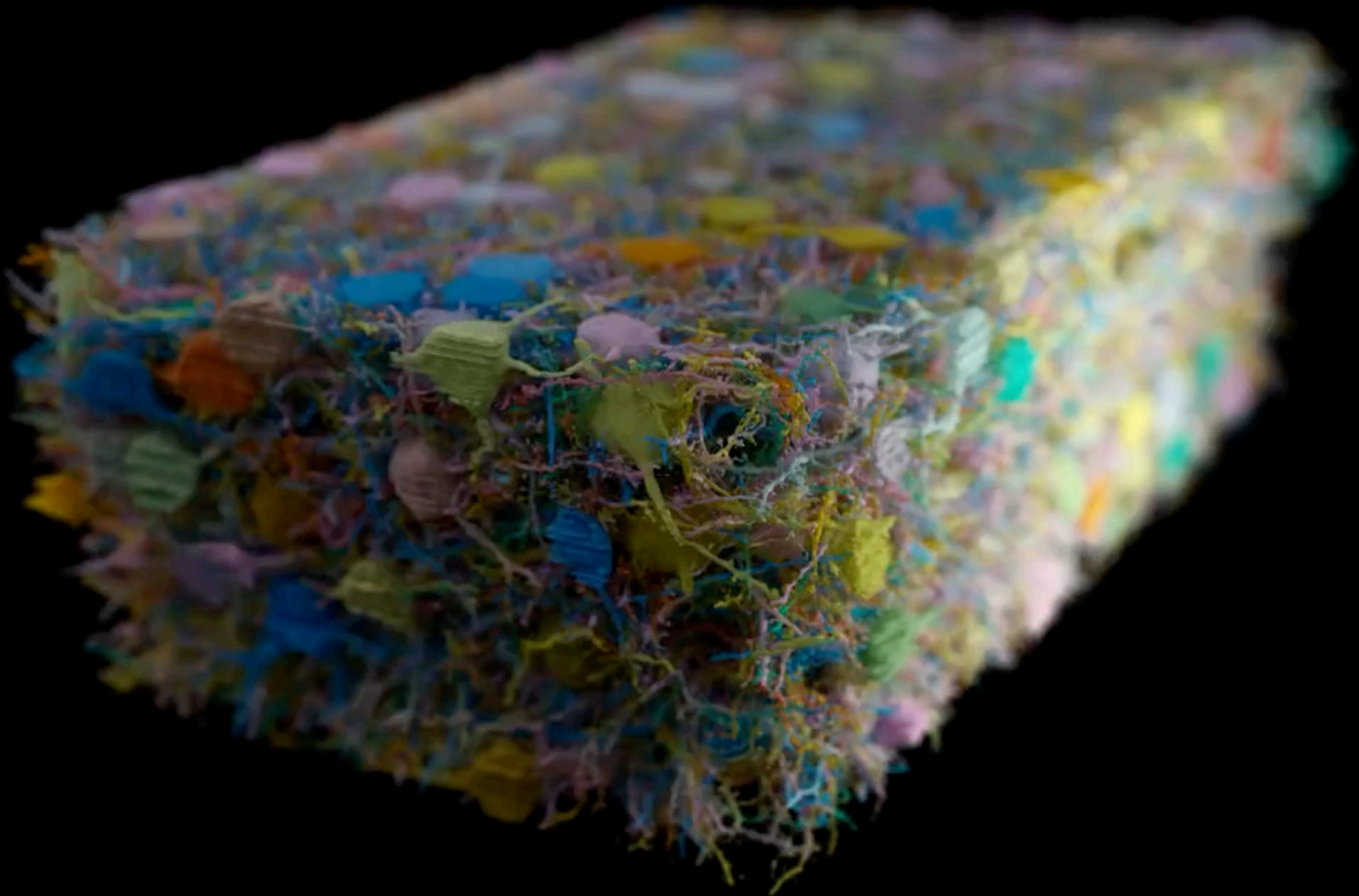
Optical

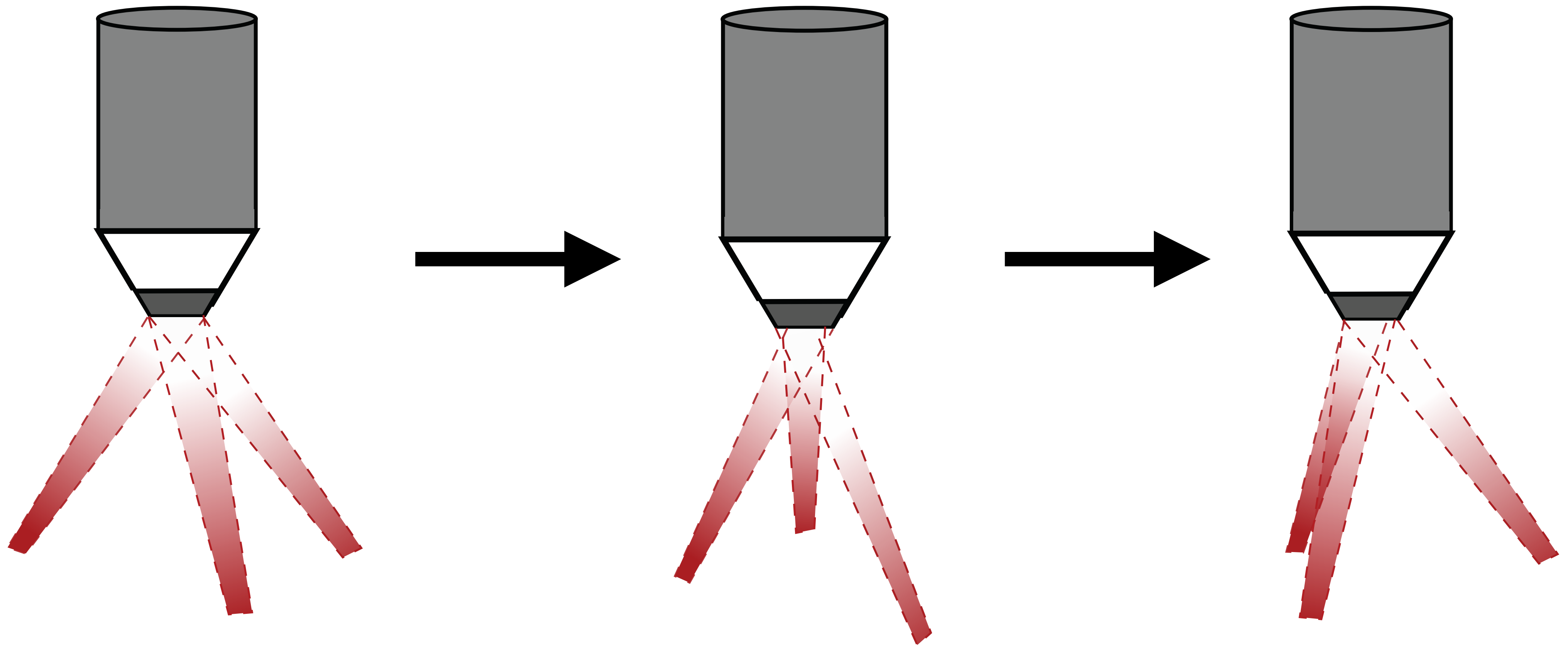


Packer, Peterka et al (2012), *Nat. Methods*



Allen Institute

Proposed approach



1. Speed up mapping by stimulating **quickly**

2. Use holographic optogenetics to stimulate **ensembles**

   Exploit sparsity by performing **compressed sensing**

Hu & Chklovskii (2009), *NeurIPS*
Fletcher et al (2011), *NeurIPS*
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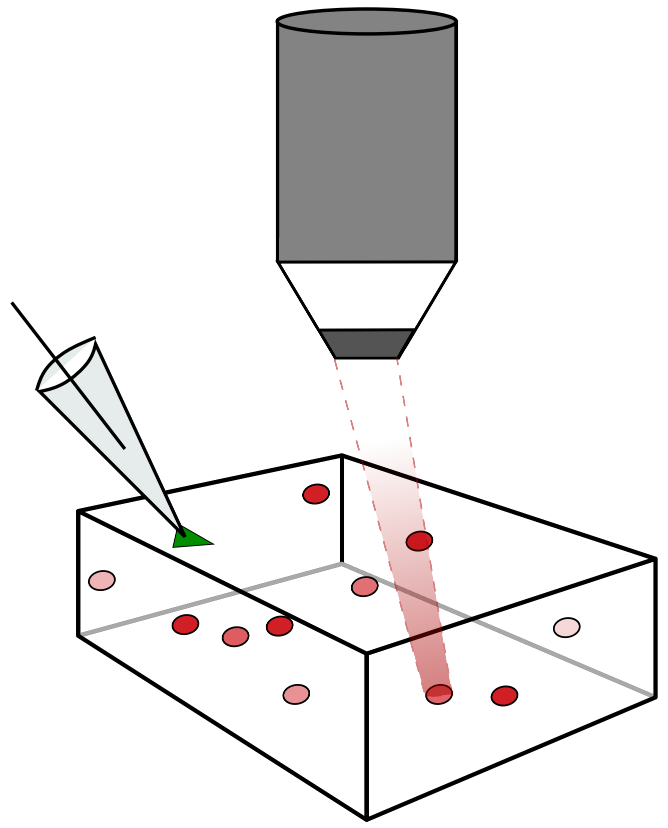
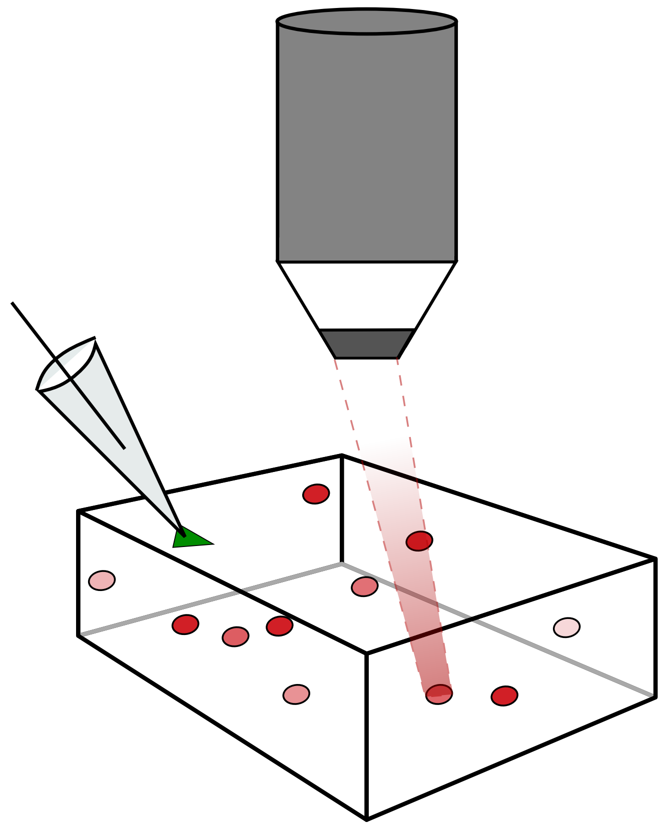
The trade-off with fast stimulation



Patch-clamp +
opto stim

The trade-off with fast stimulation



Patch-clamp +
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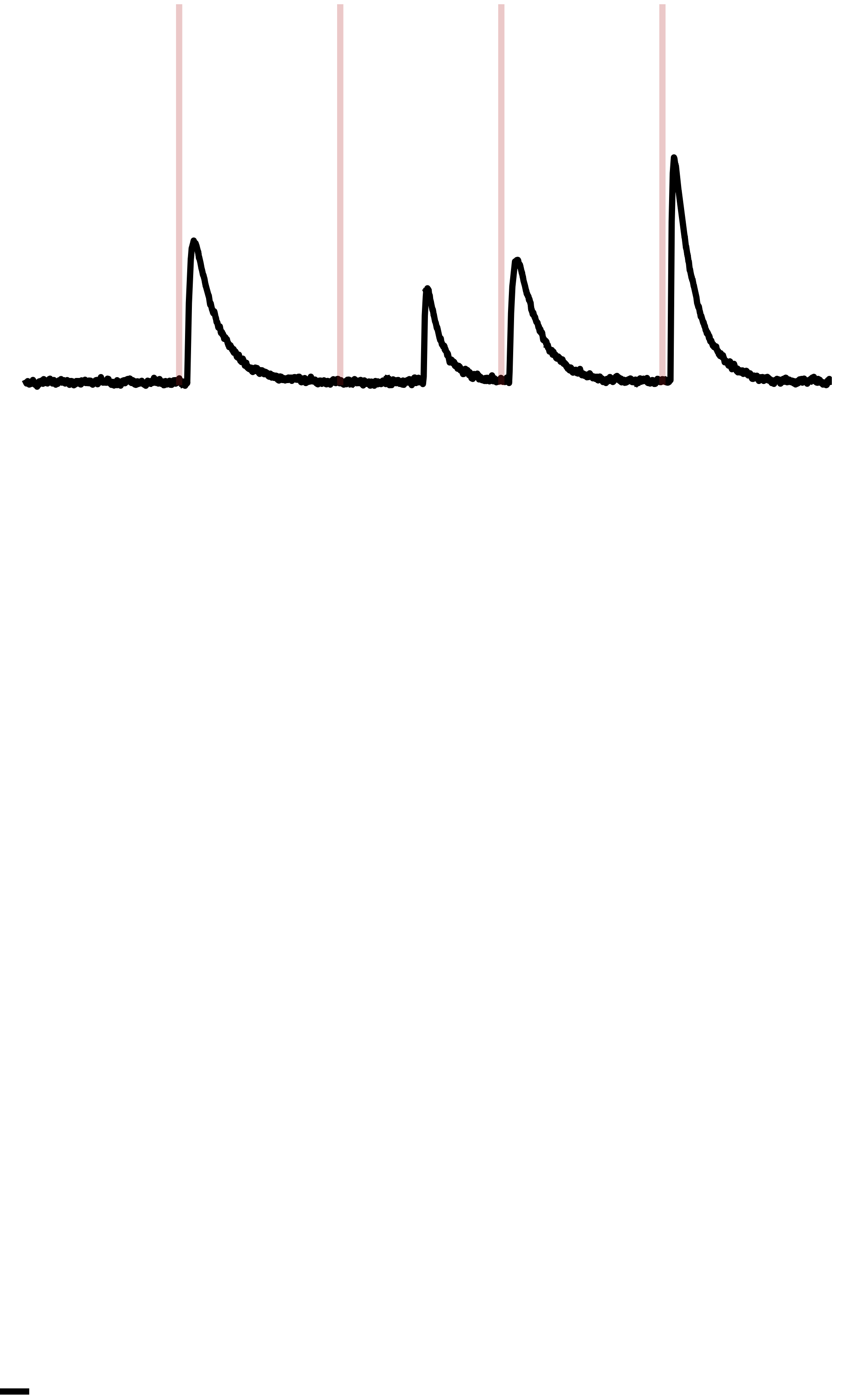
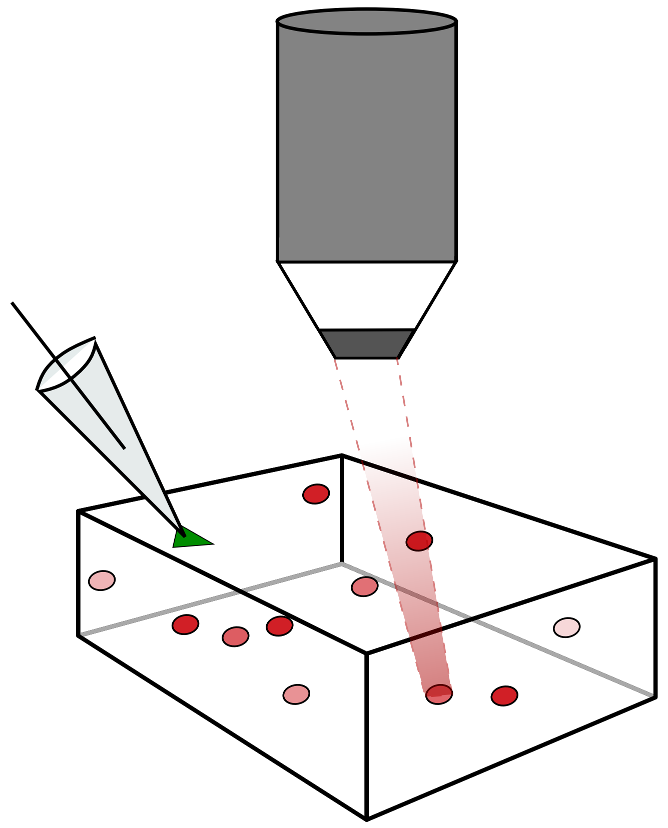
10 Hz



simulation

The trade-off with fast stimulation



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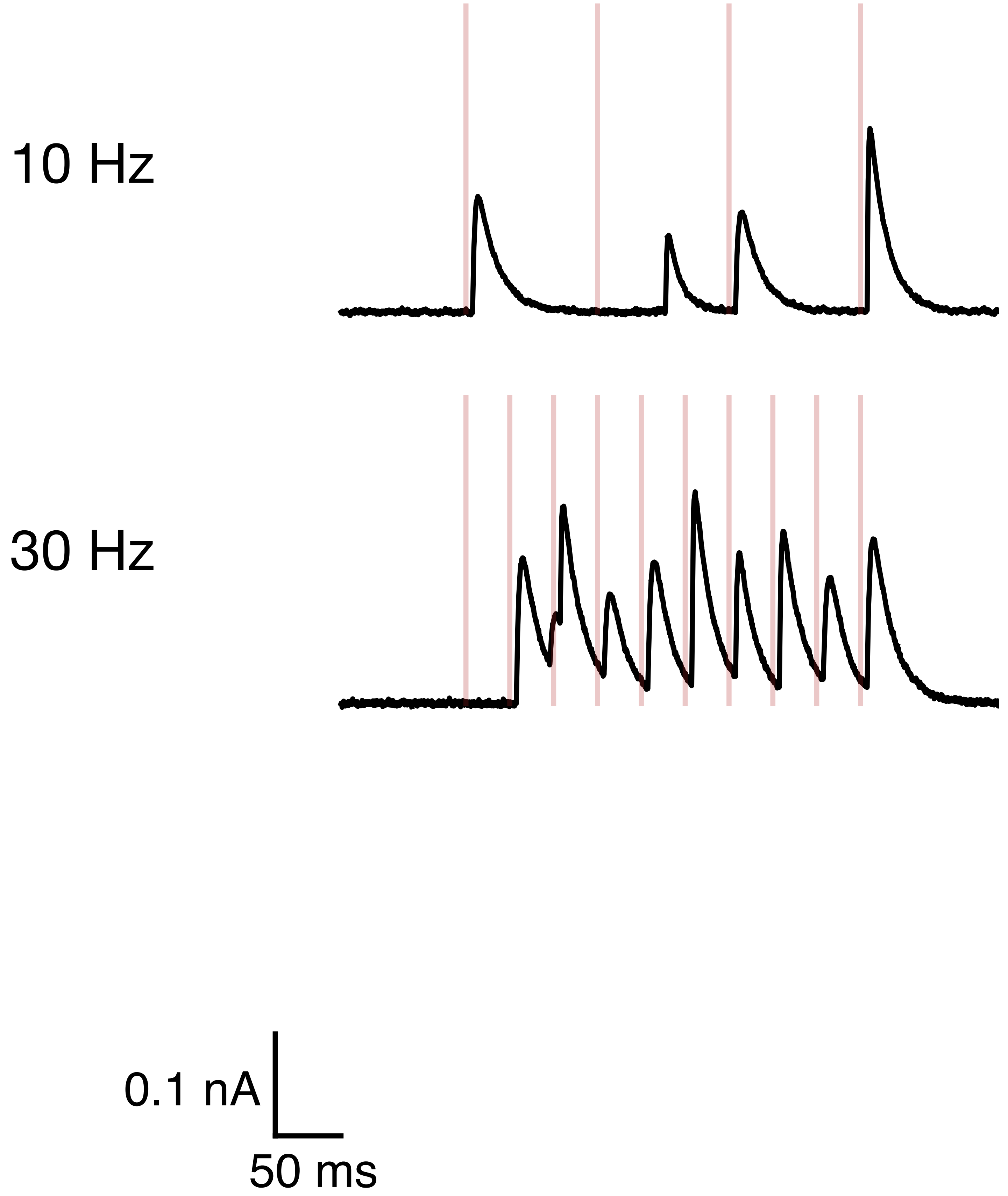

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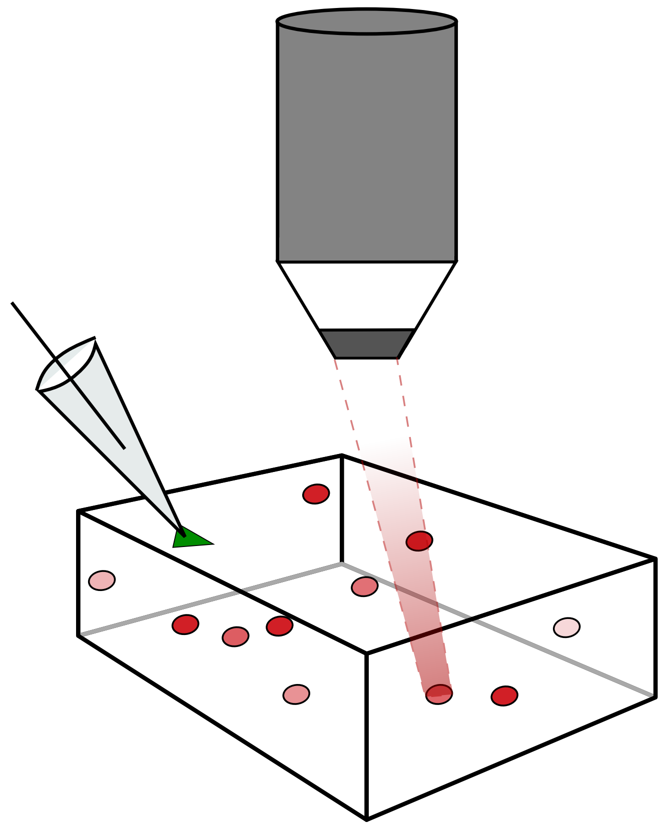

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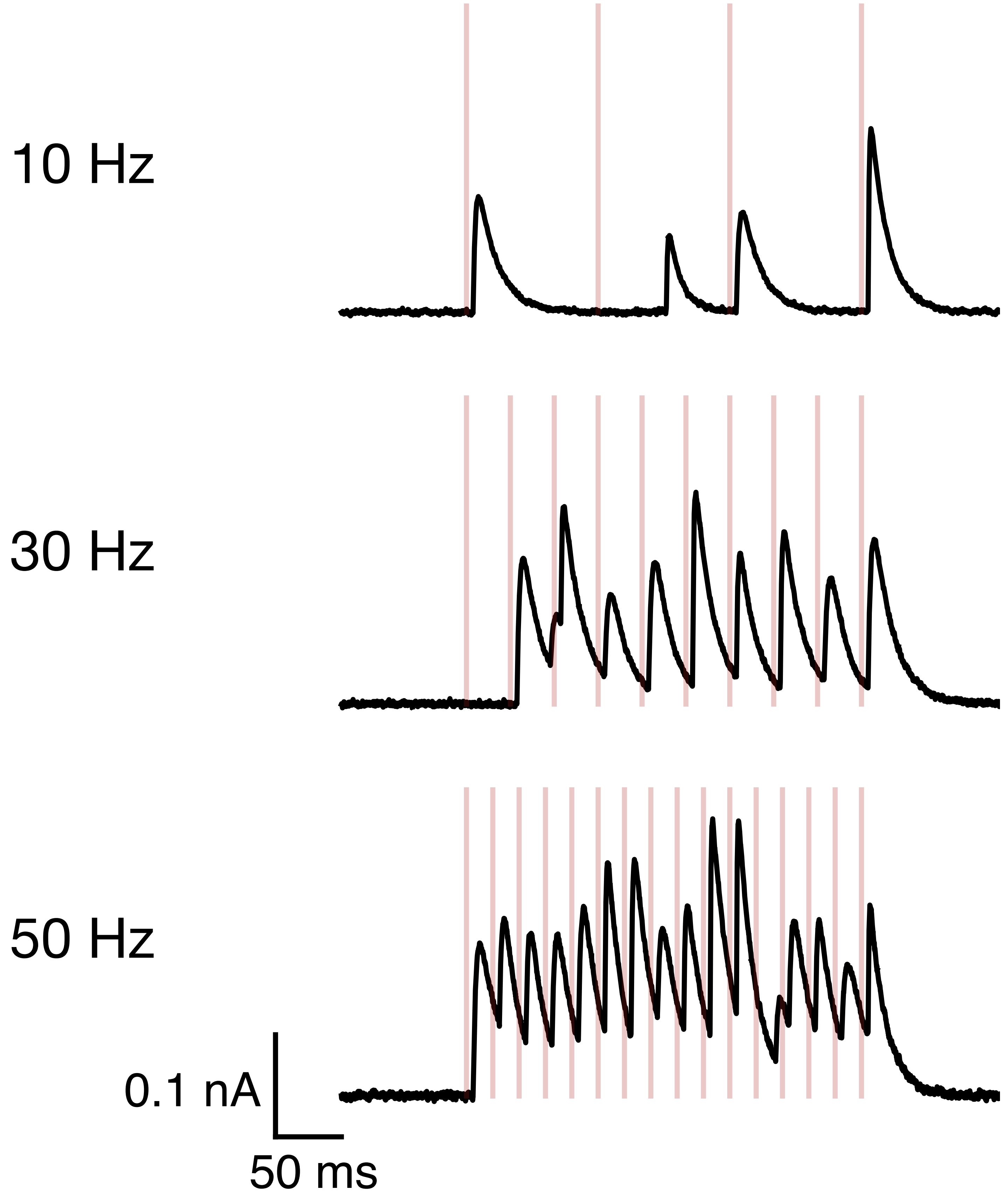

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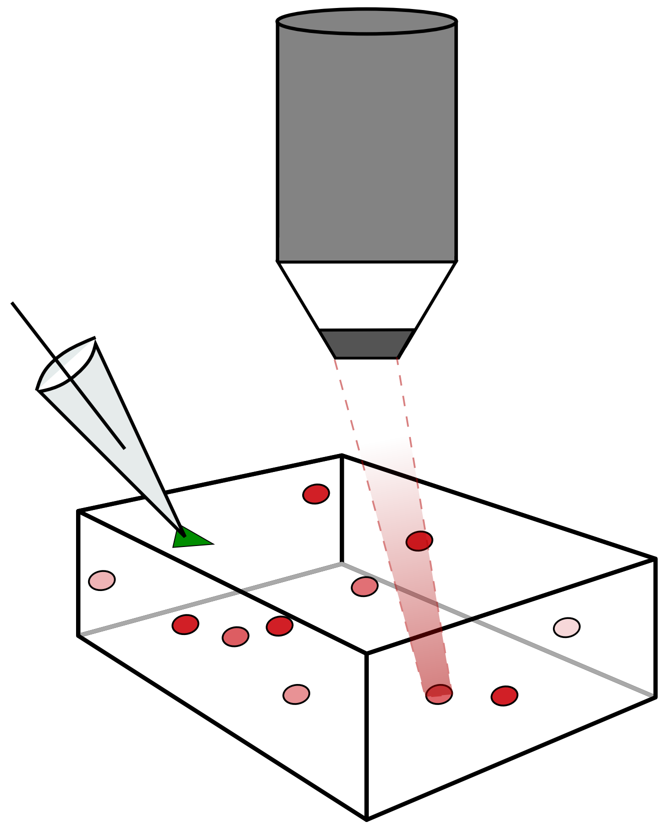

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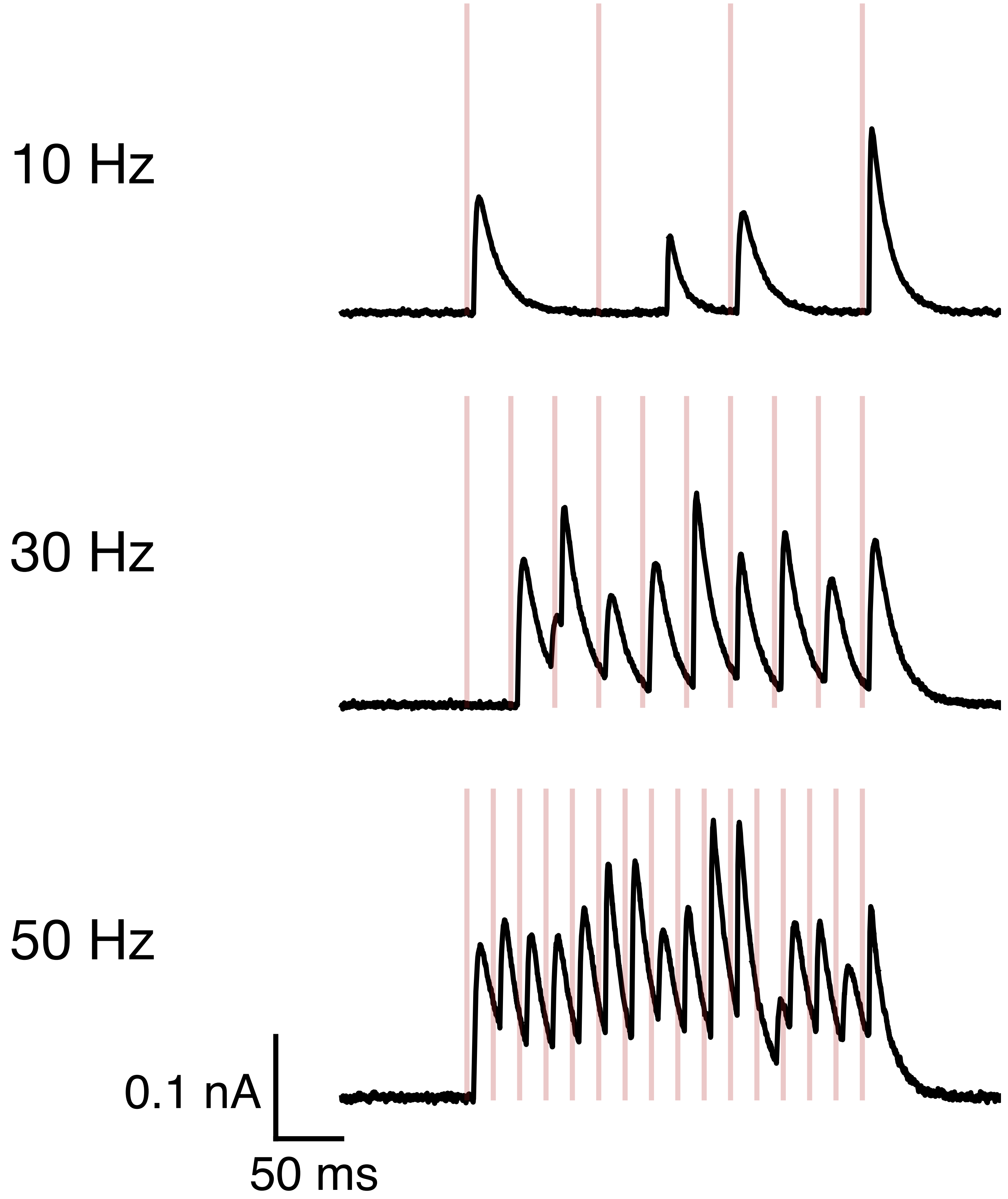

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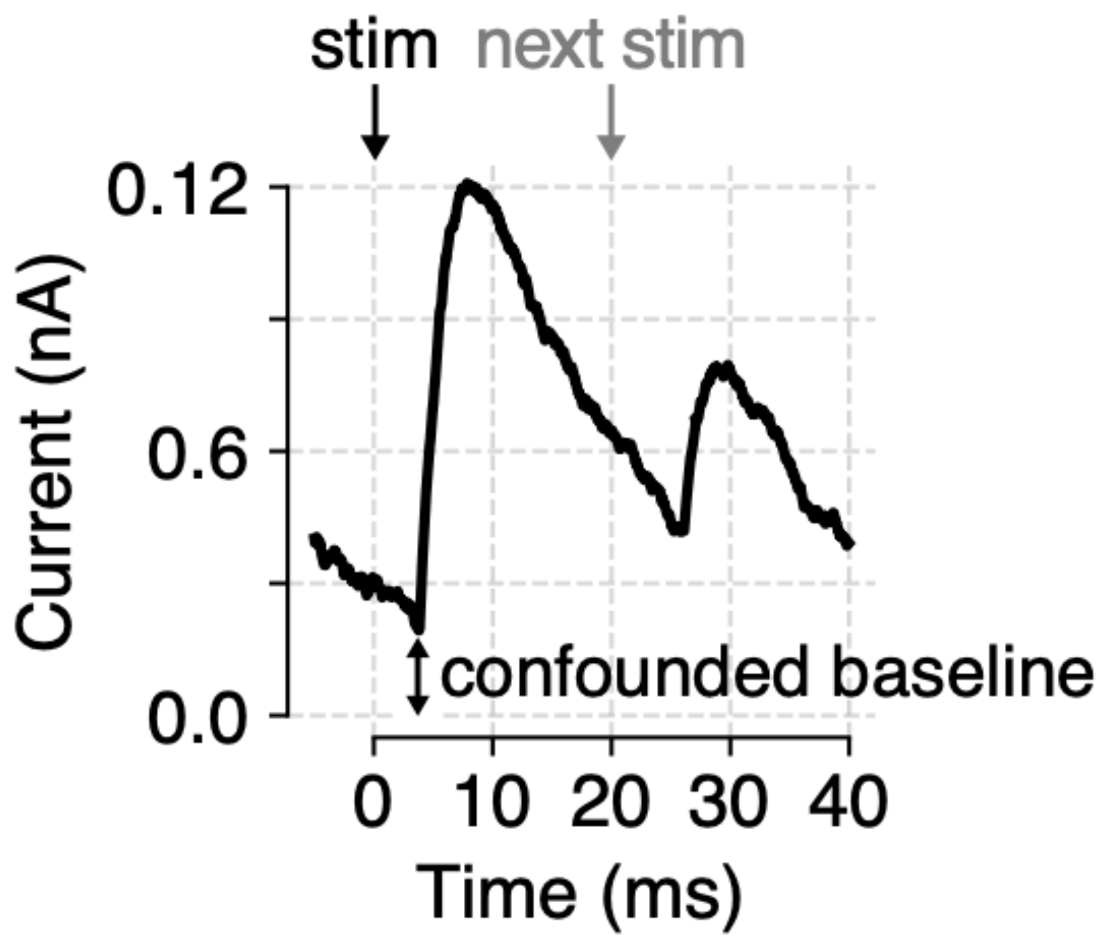

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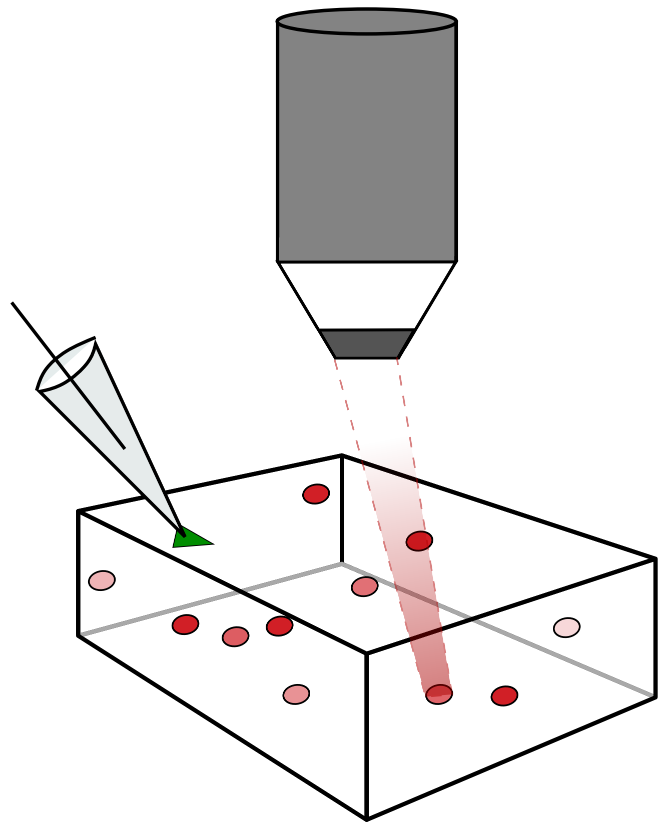

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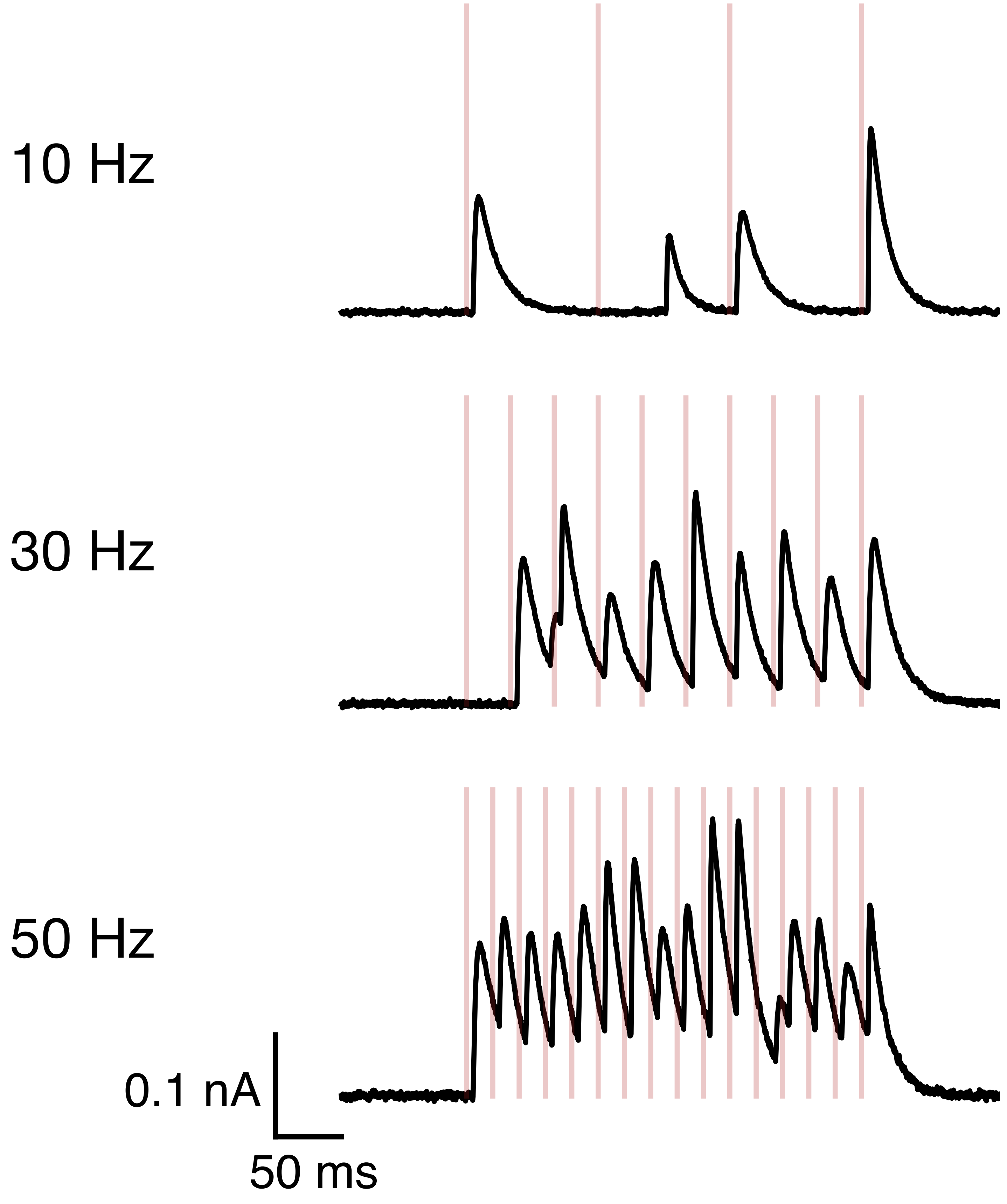

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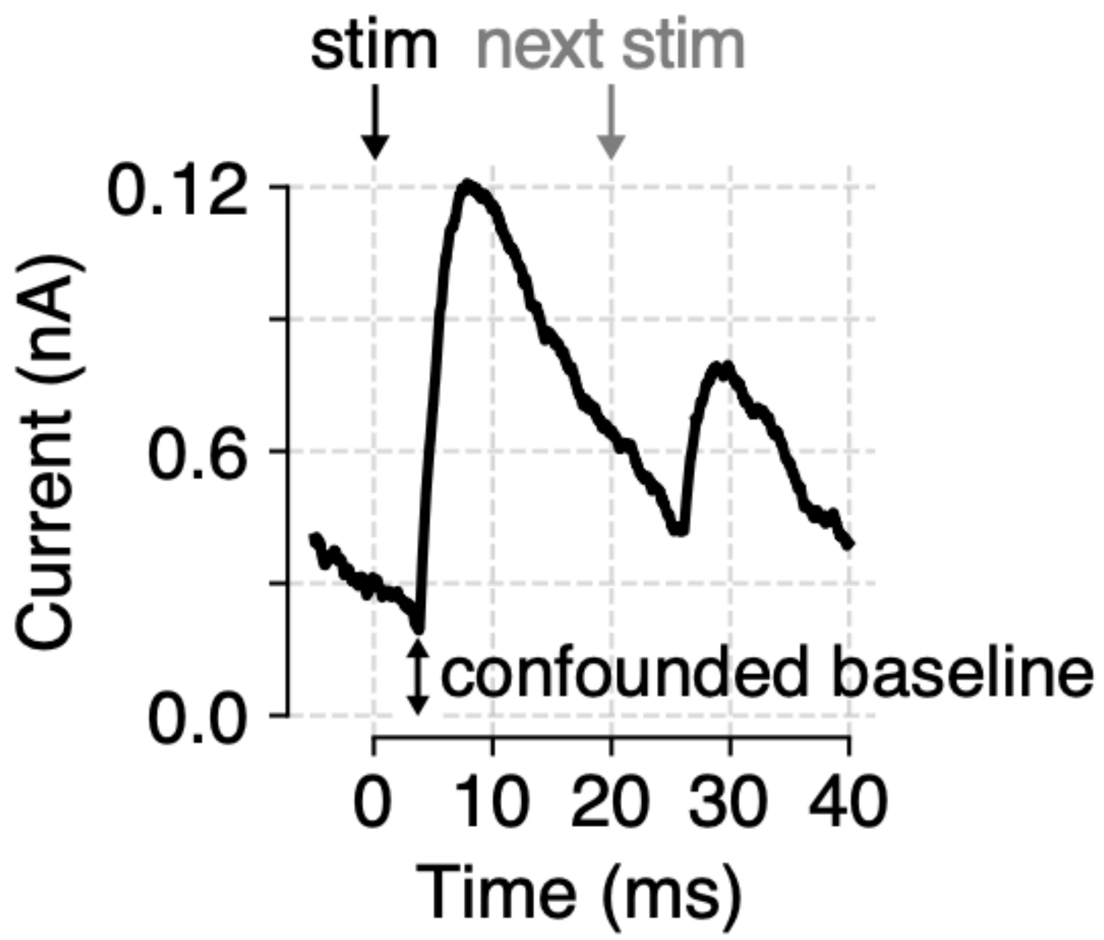
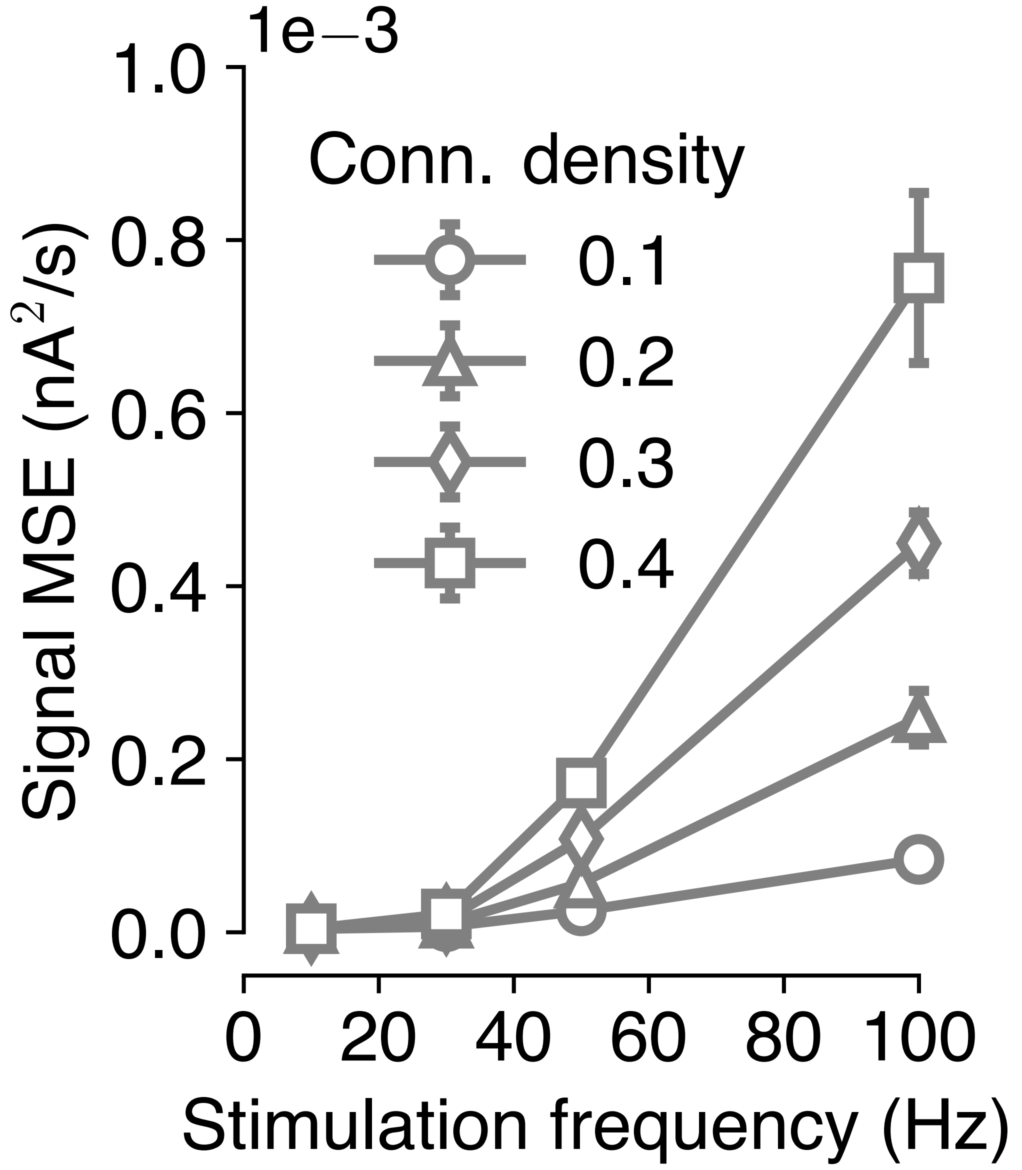
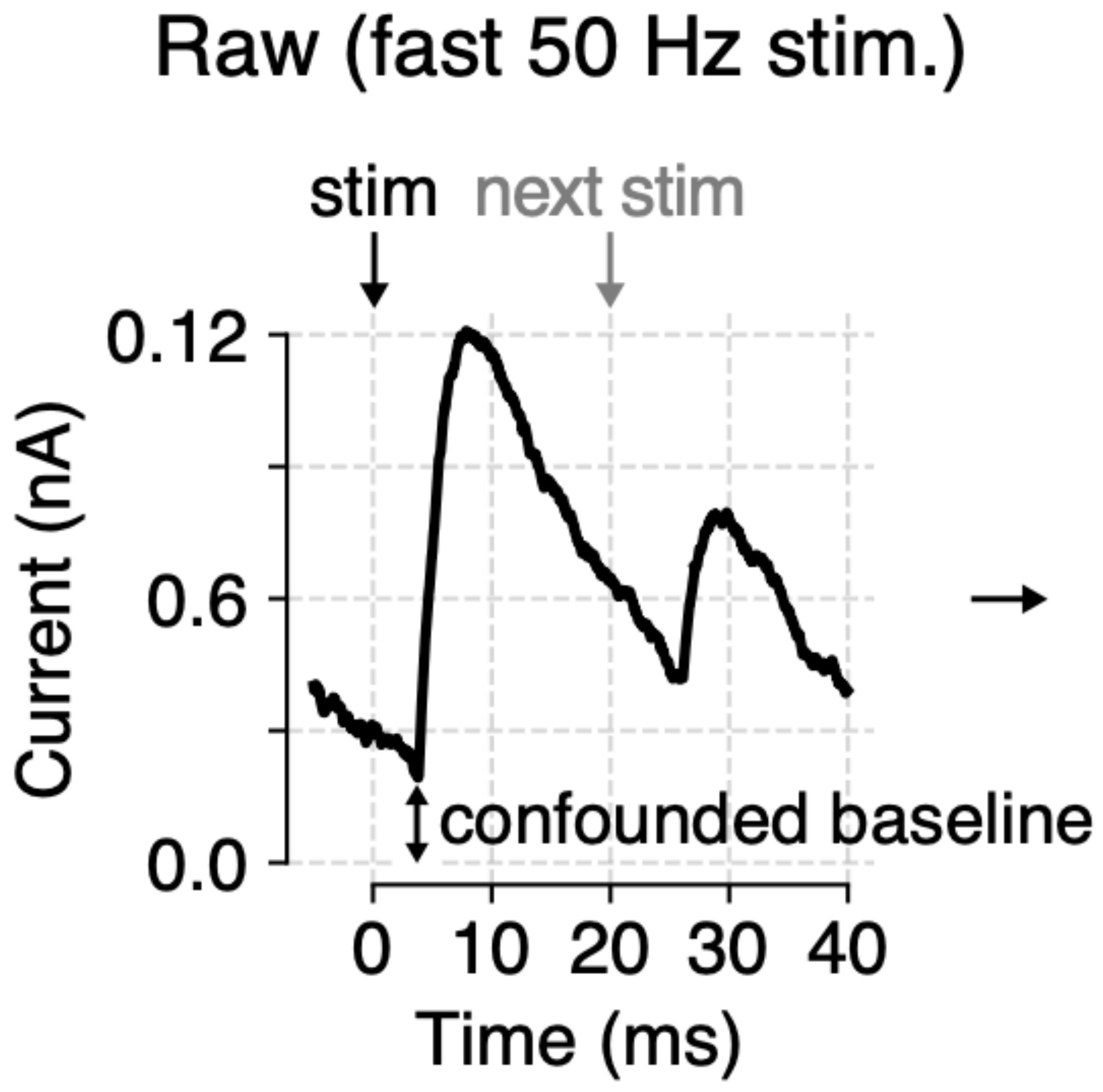




Neural waveform demixing



Triplett*, Gajowa* et. al. (2023), *bioRxiv*

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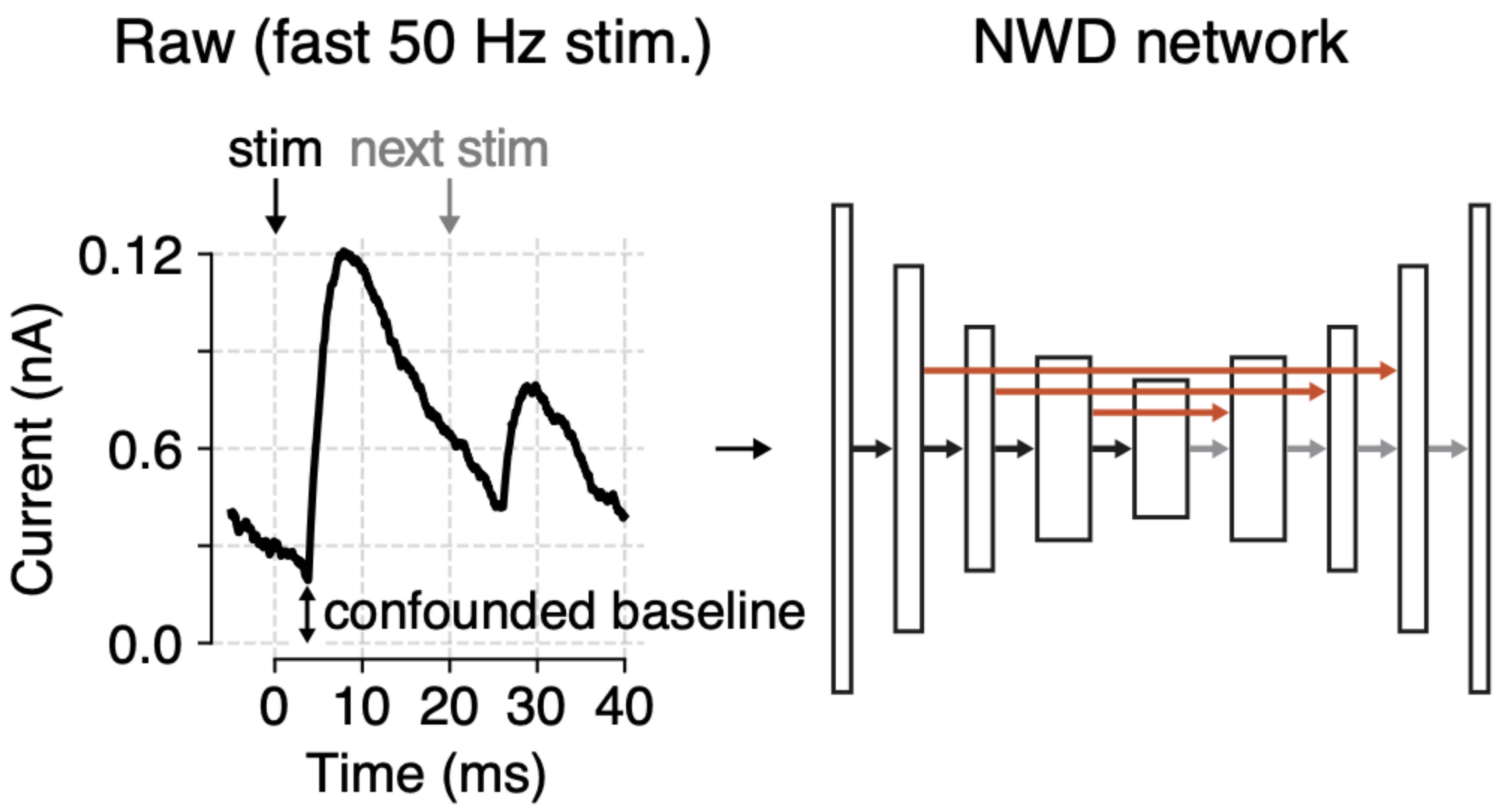
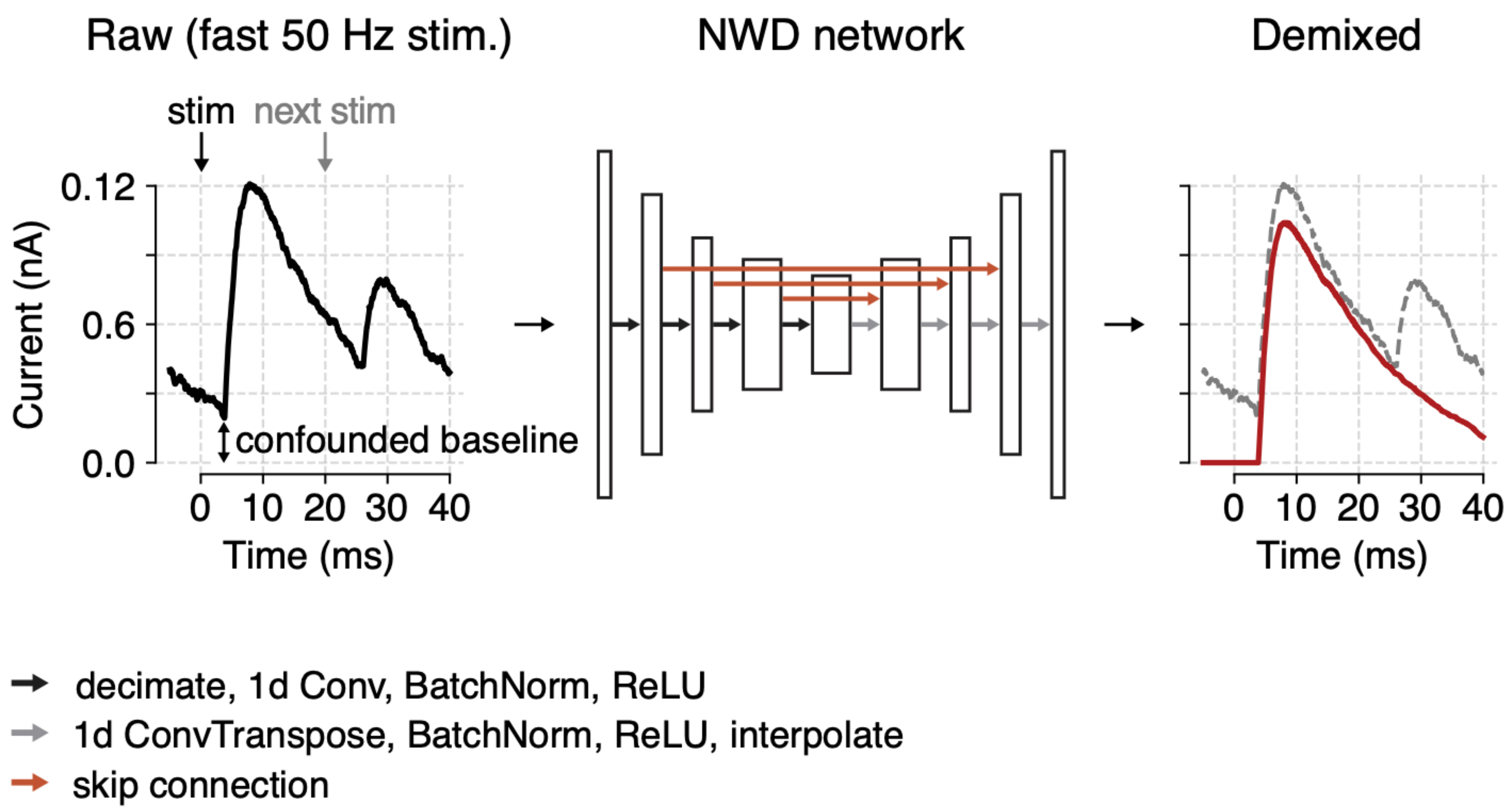


→ decimate, 1d Conv, BatchNorm, ReLU
→ 1d ConvTranspose, BatchNorm, ReLU, interpolate
→ skip connection

Triplett*, Gajowa* et. al. (2023), *bioRxiv*

Neural waveform demixing



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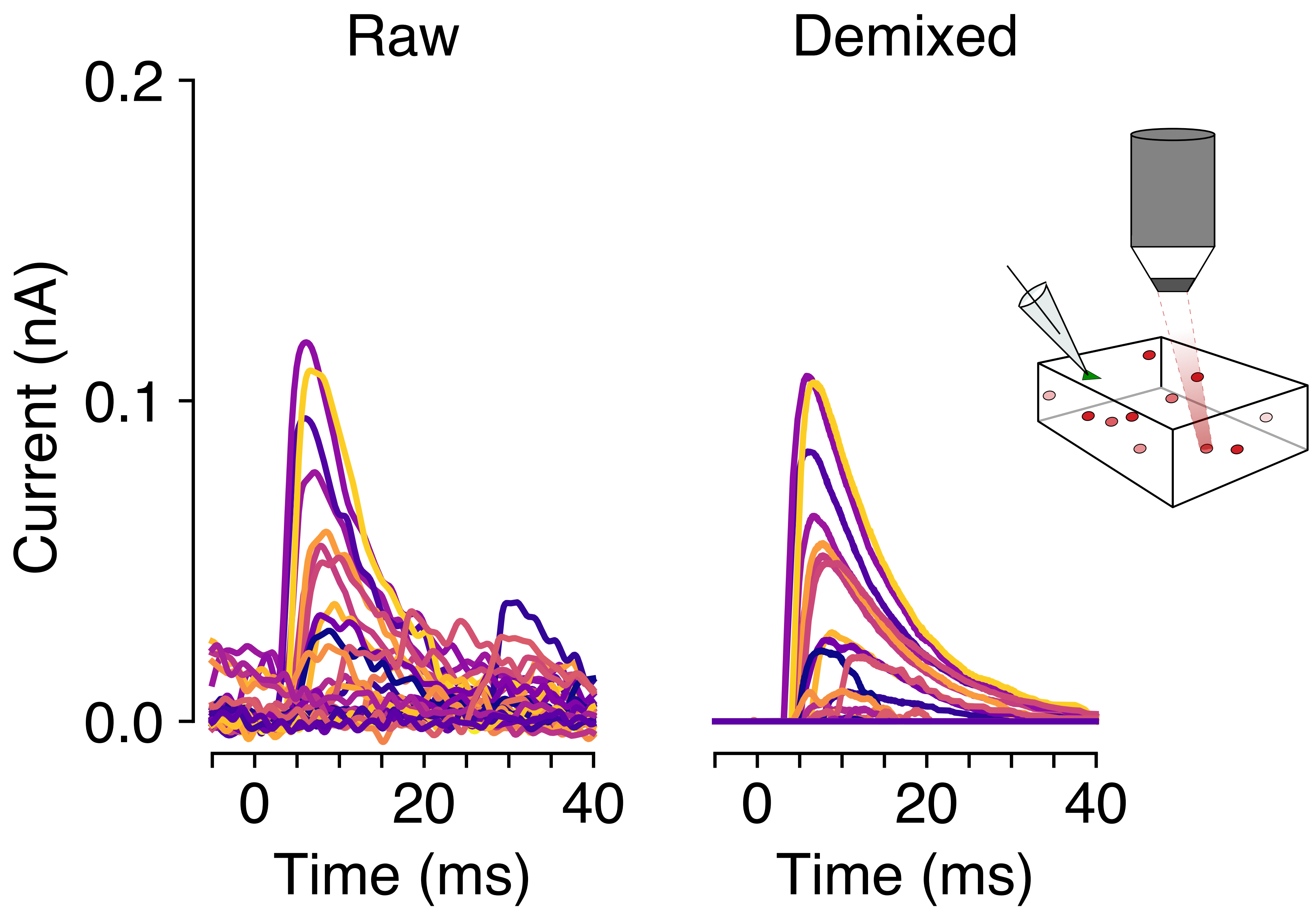
Application to cortical mapping data

Single-target stimulation



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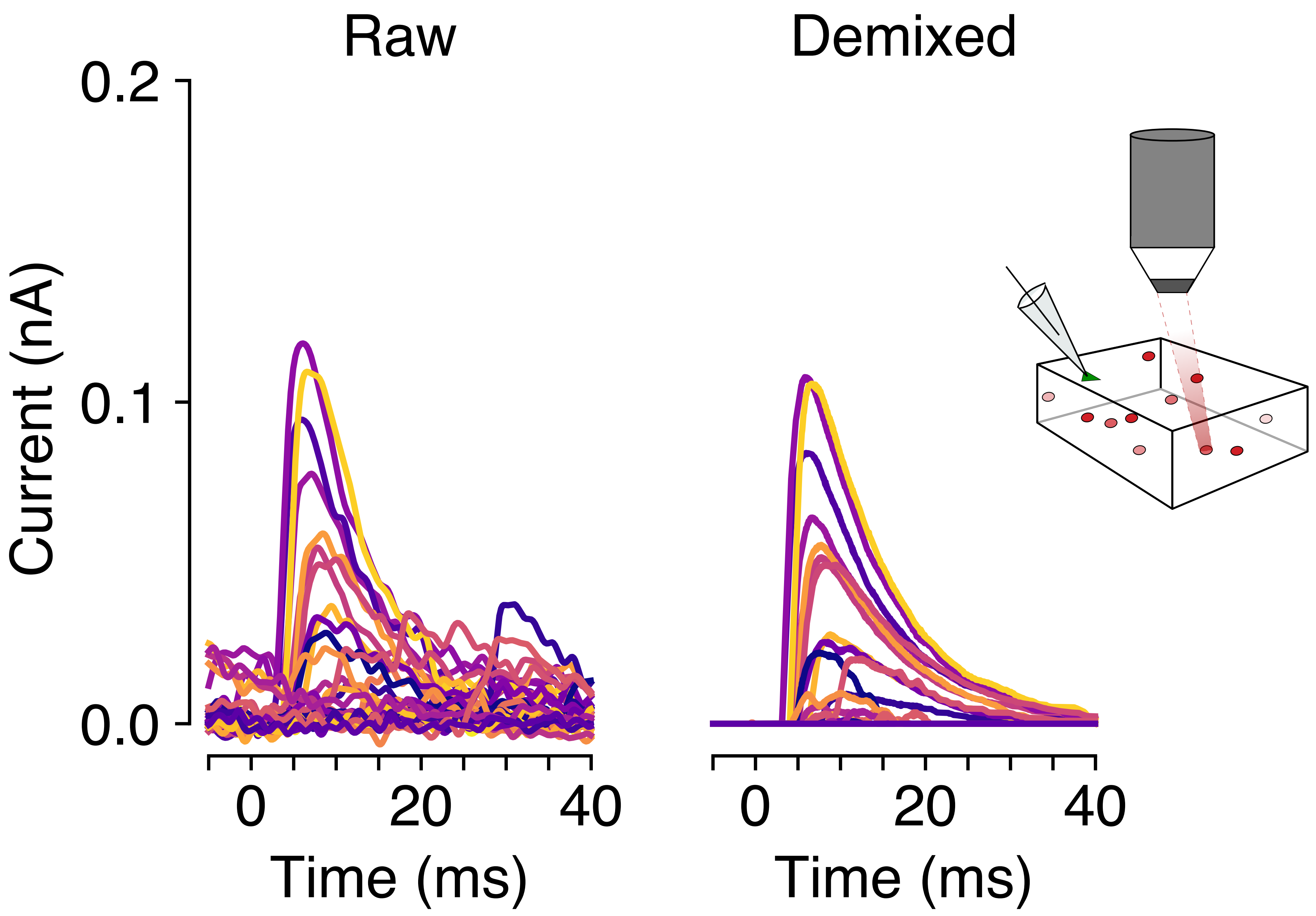
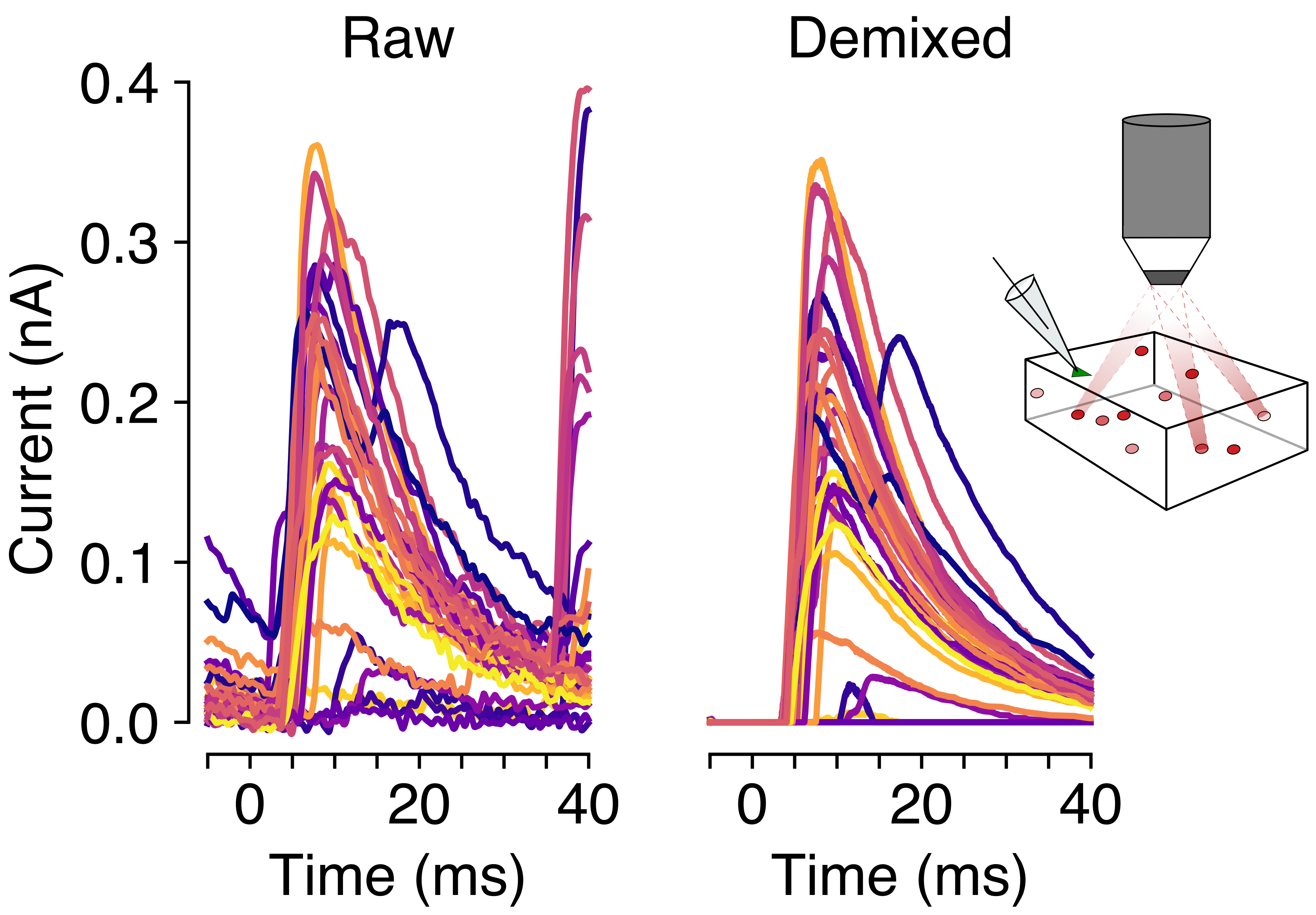
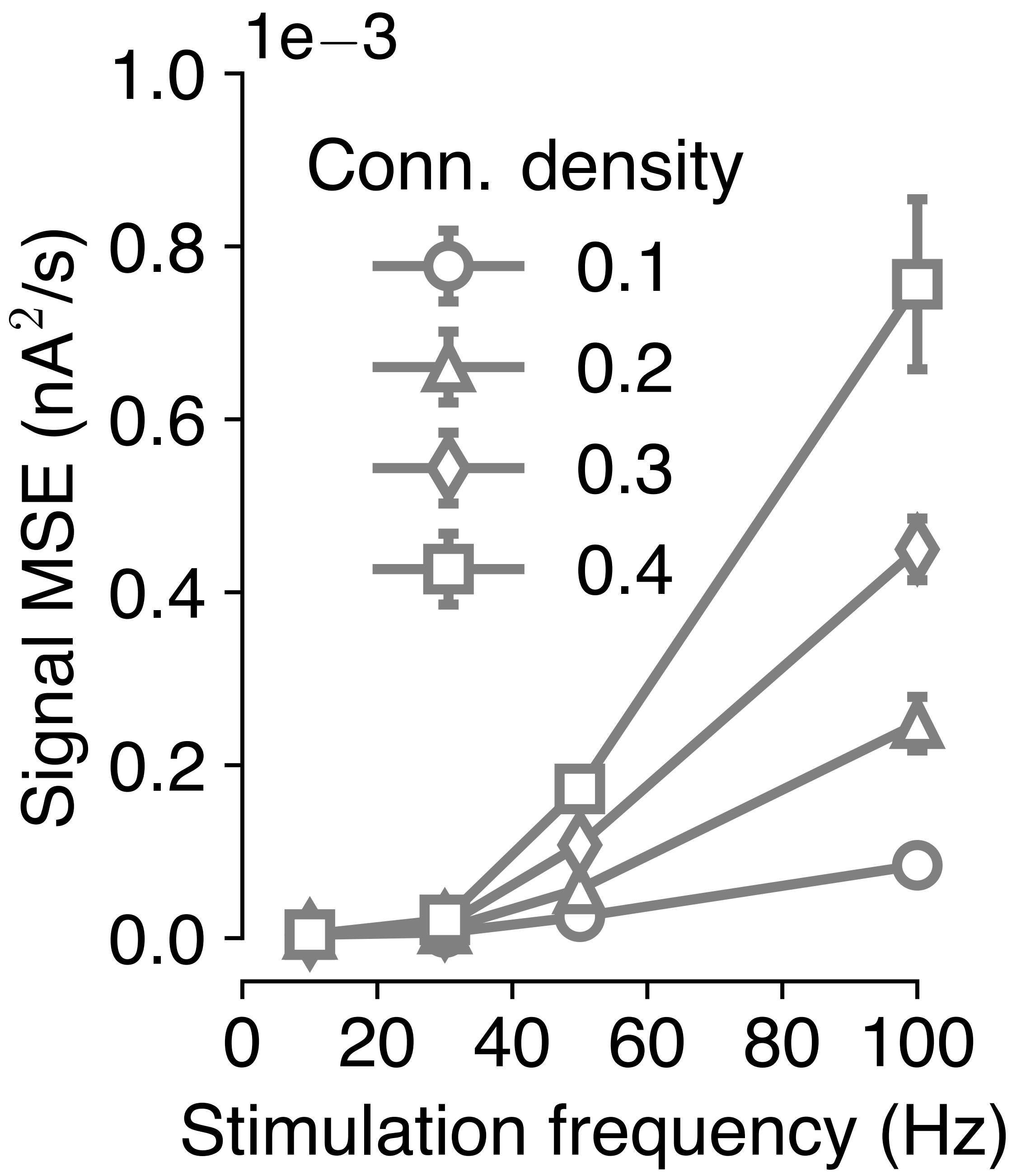


10-target ensemble stimulation



Triplett*, Gajowa* et. al. (2023), *bioRxiv*

Implications for connectivity mapping



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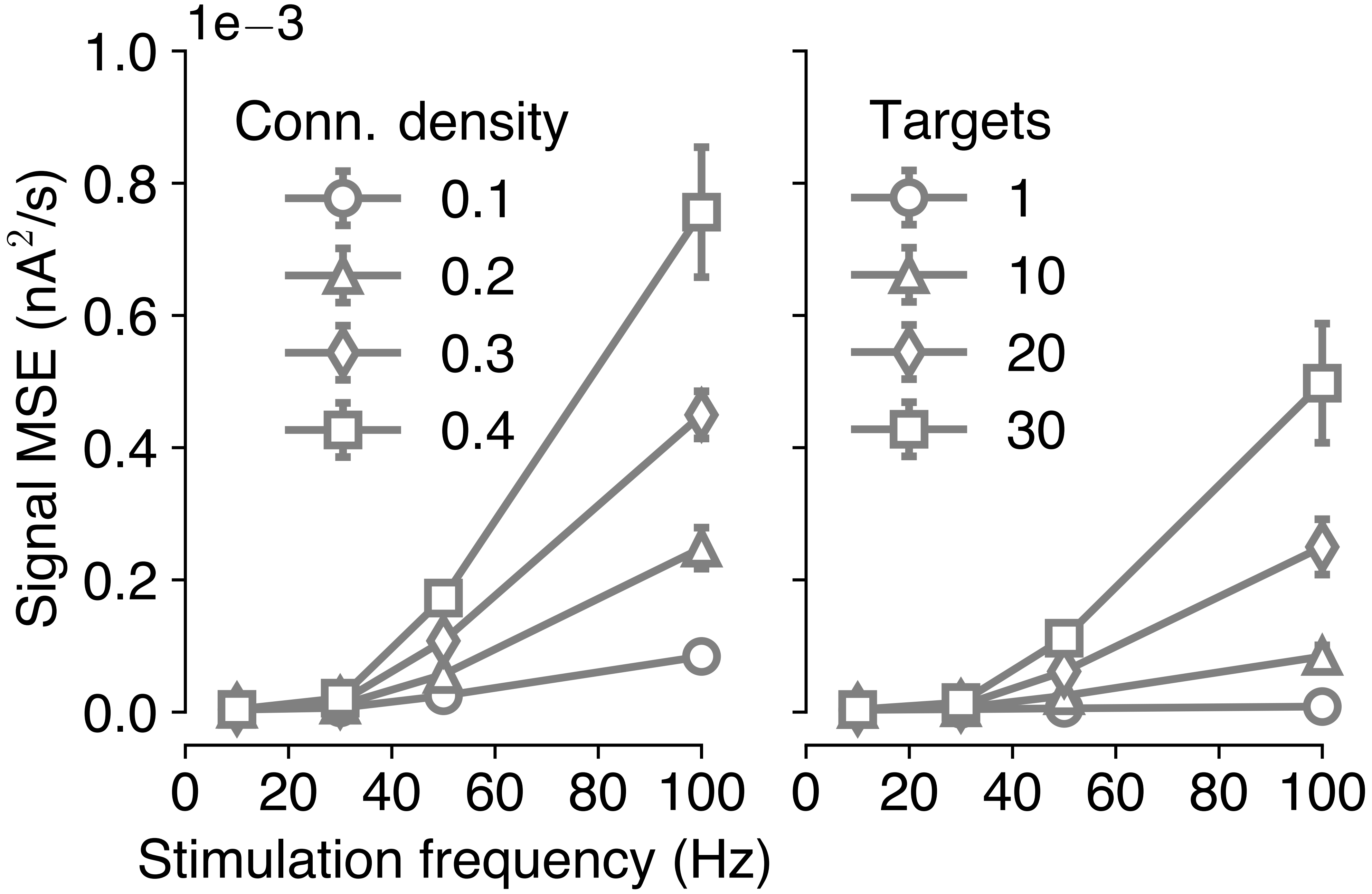

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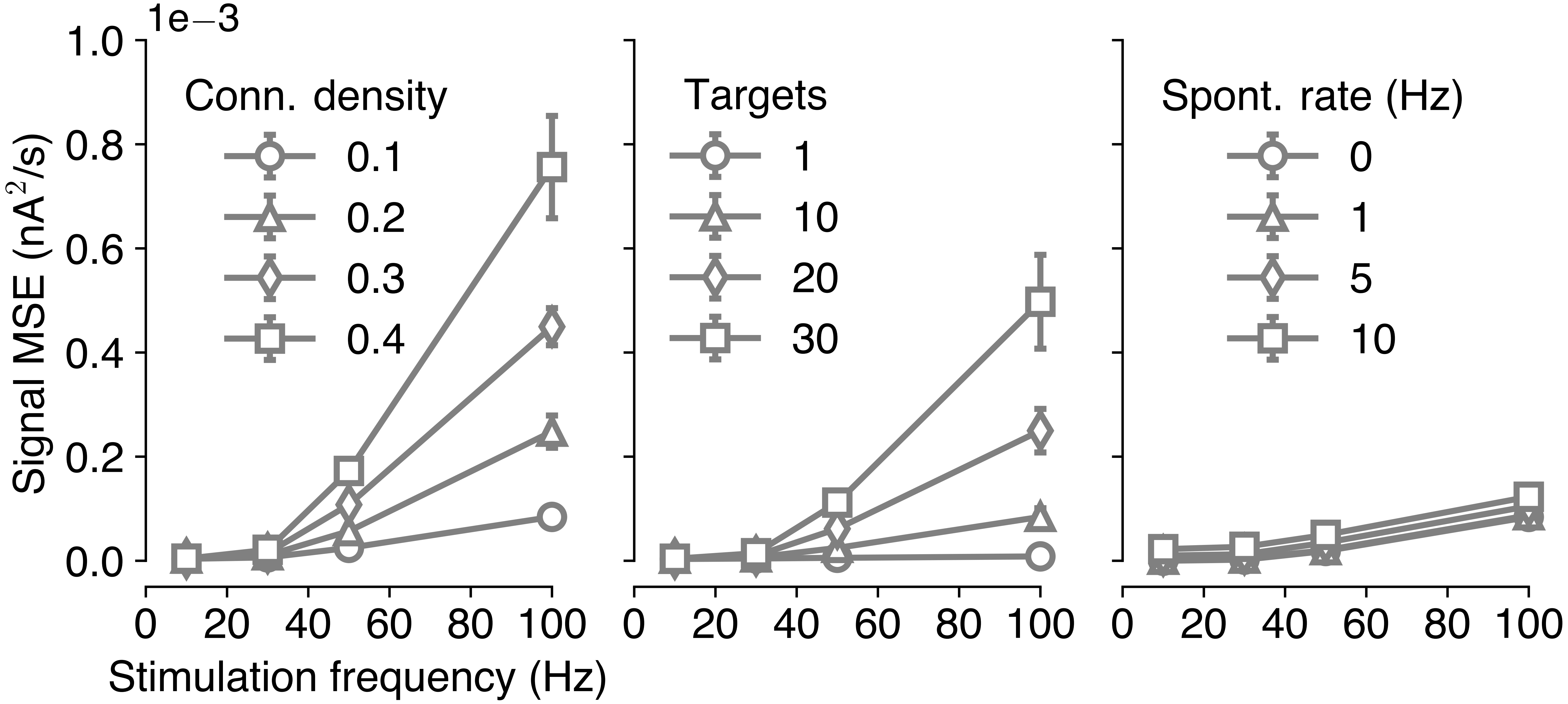

Triplett*, Gajowa* et. al. (2023), *bioRxiv*

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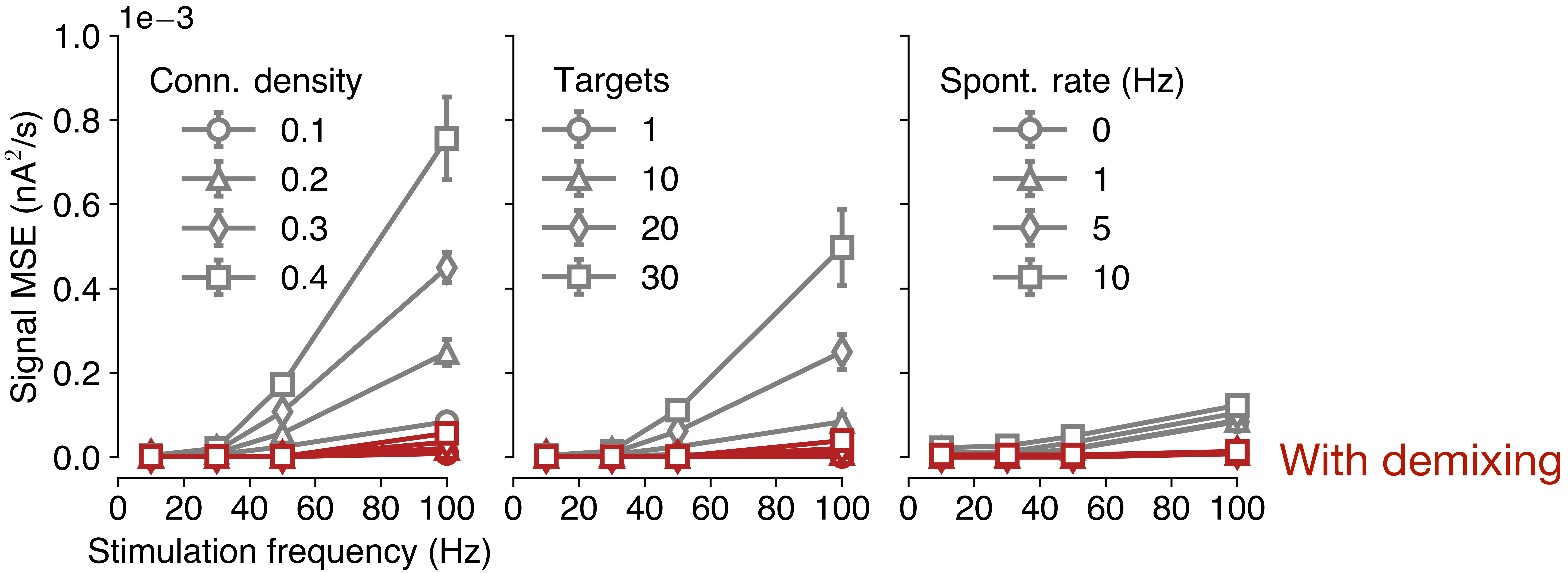
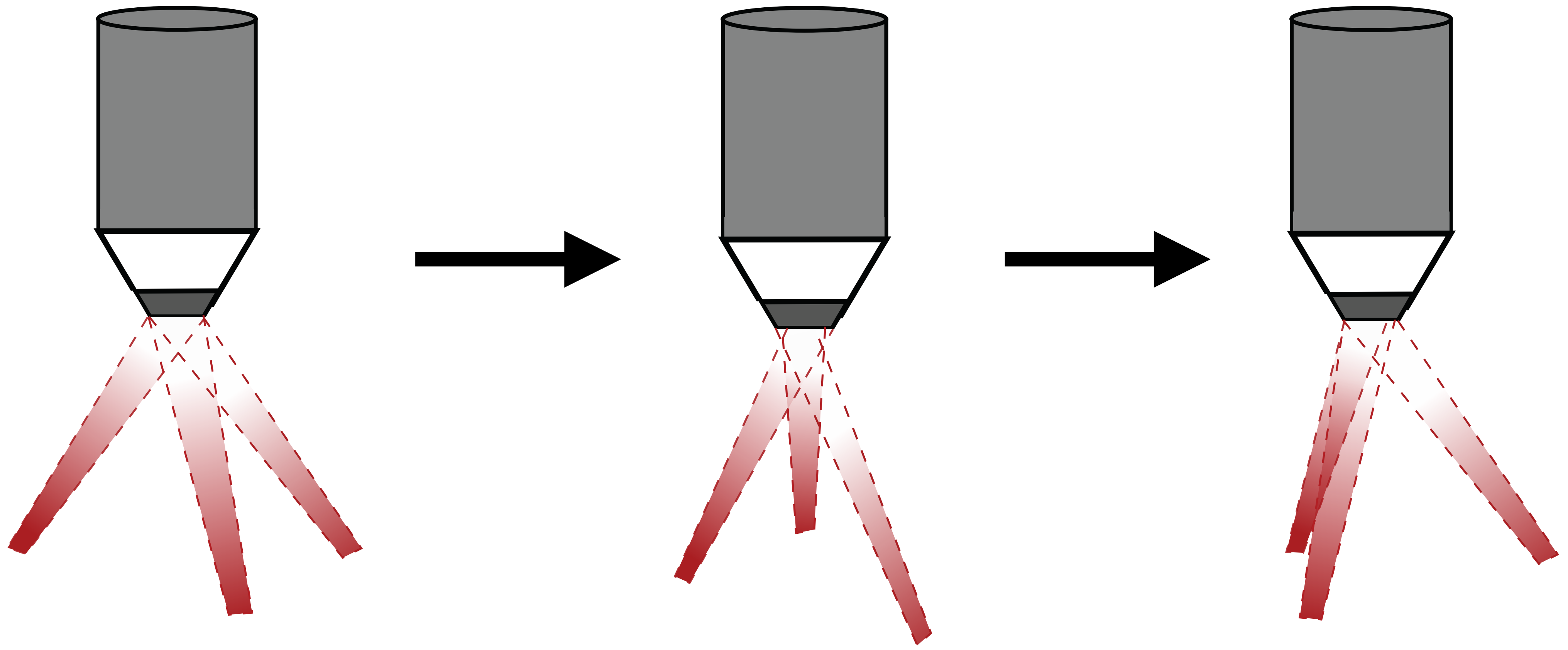


Triplett*, Gajowa* et. al. (2023), *bioRxiv*

Proposed approach



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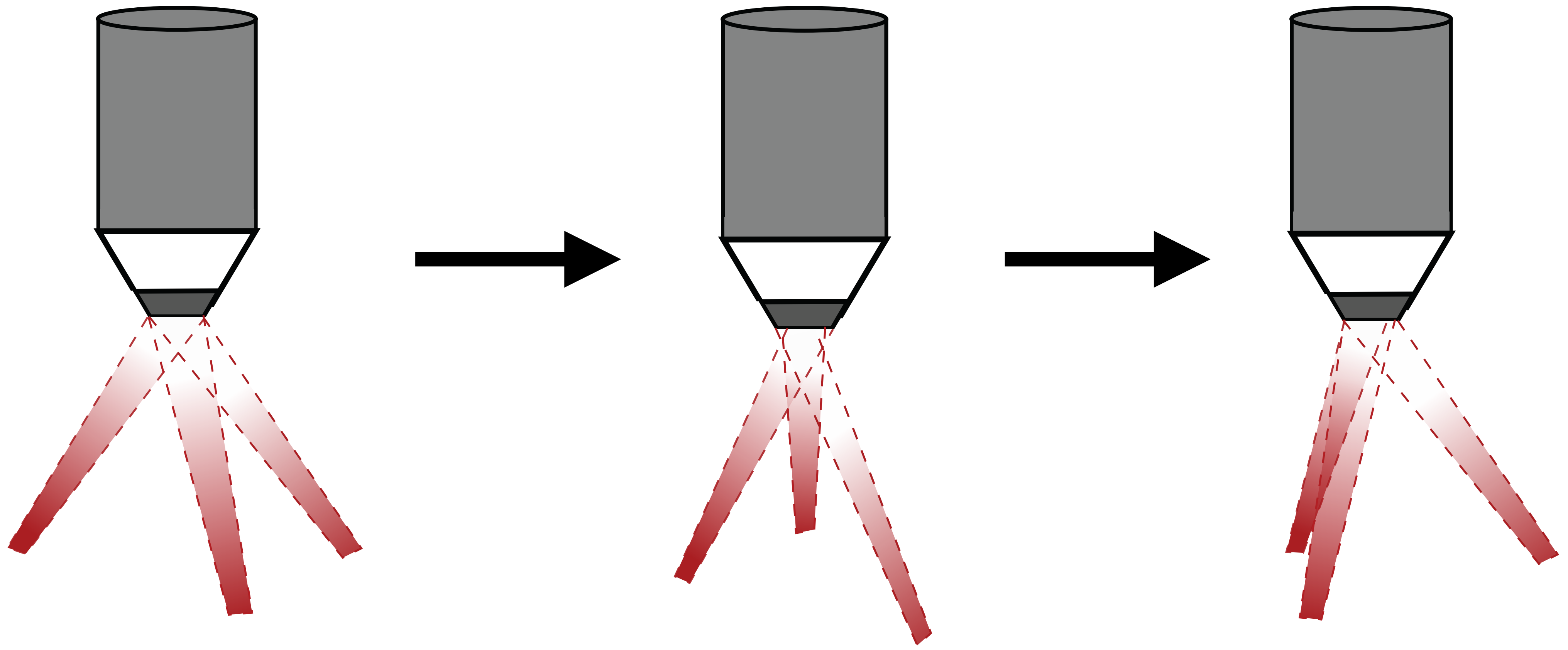

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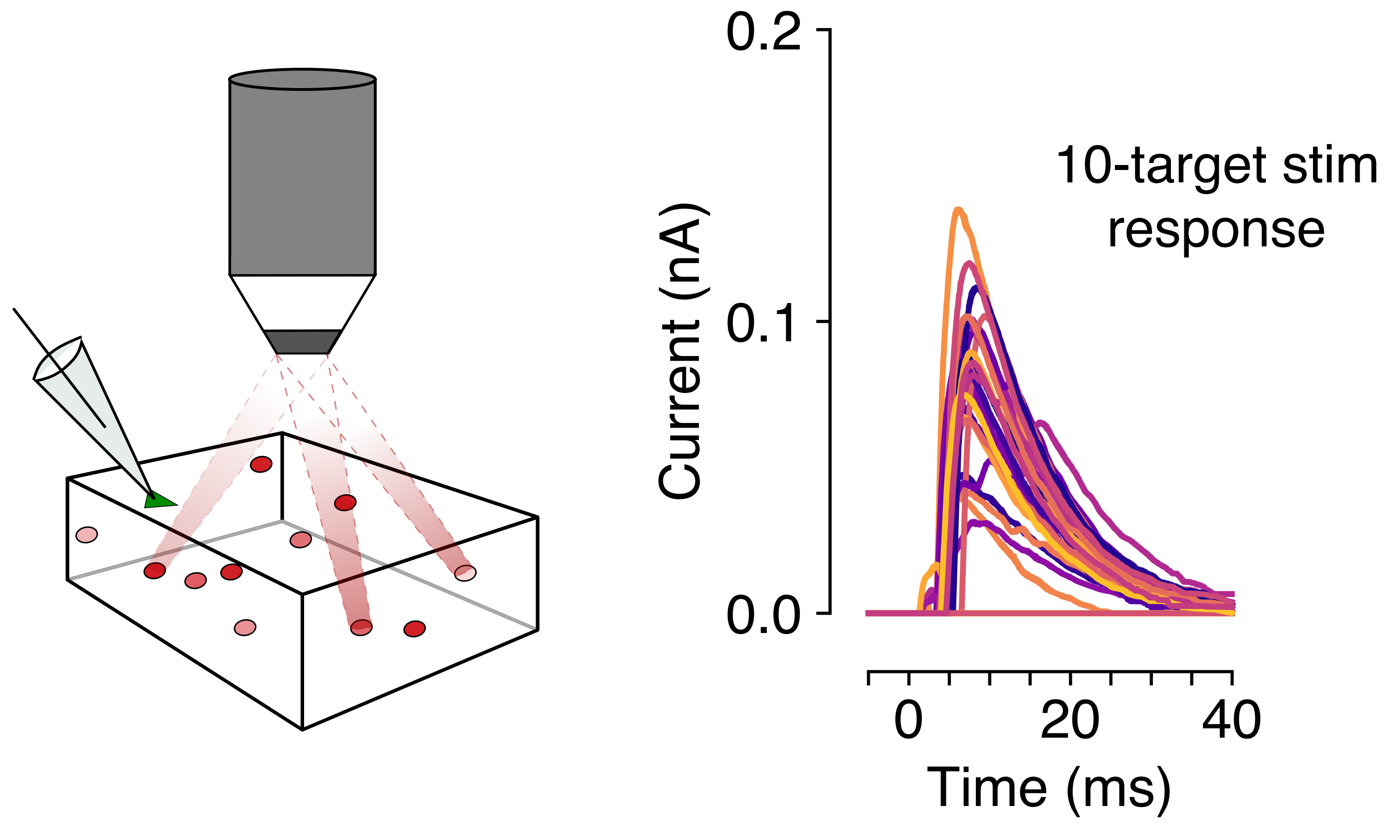
Application of ordinary compressed sensing

Randomized ensemble stimulation



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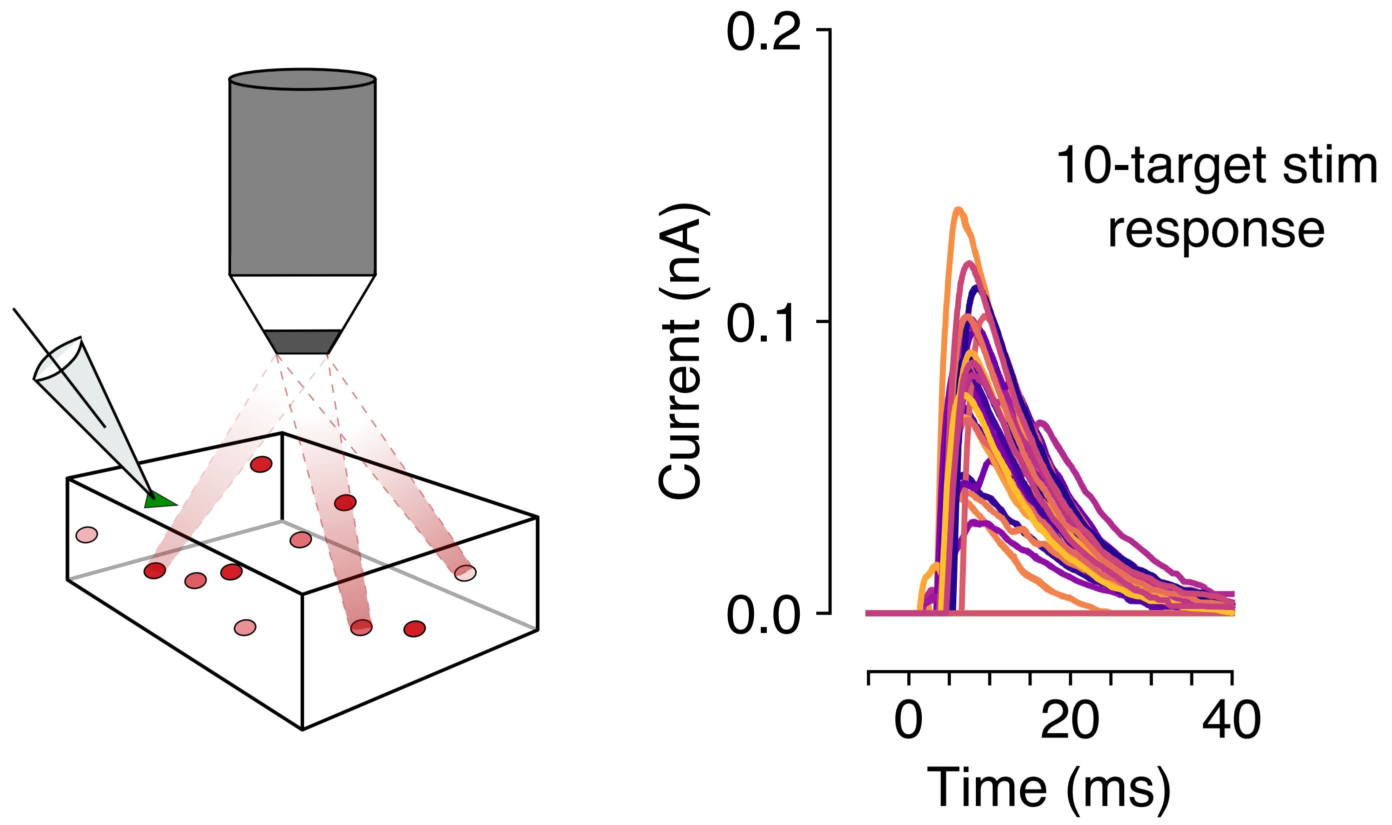

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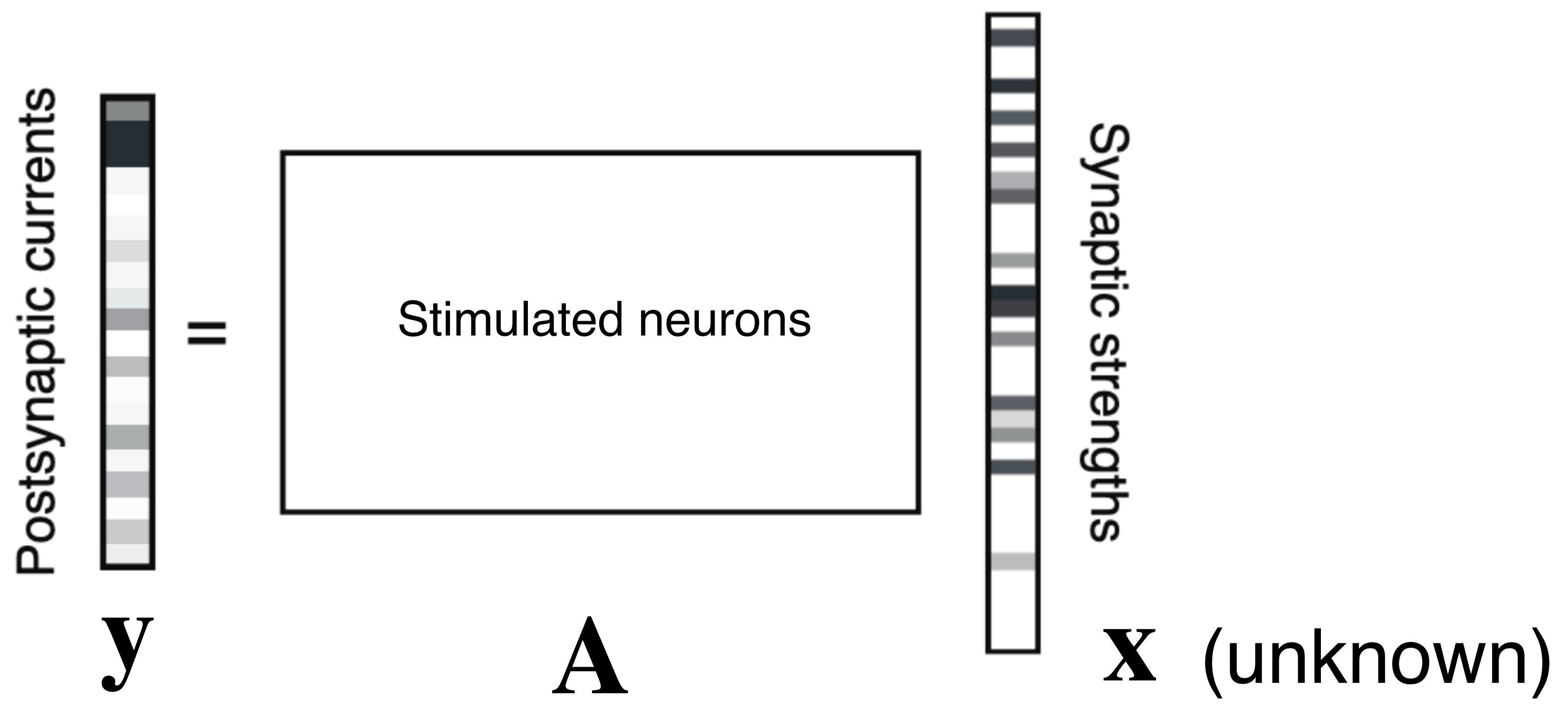

Solve $\mathbf{y} = \mathbf{A}\mathbf{x}$ such that $\mathbf{x}$ is sparse

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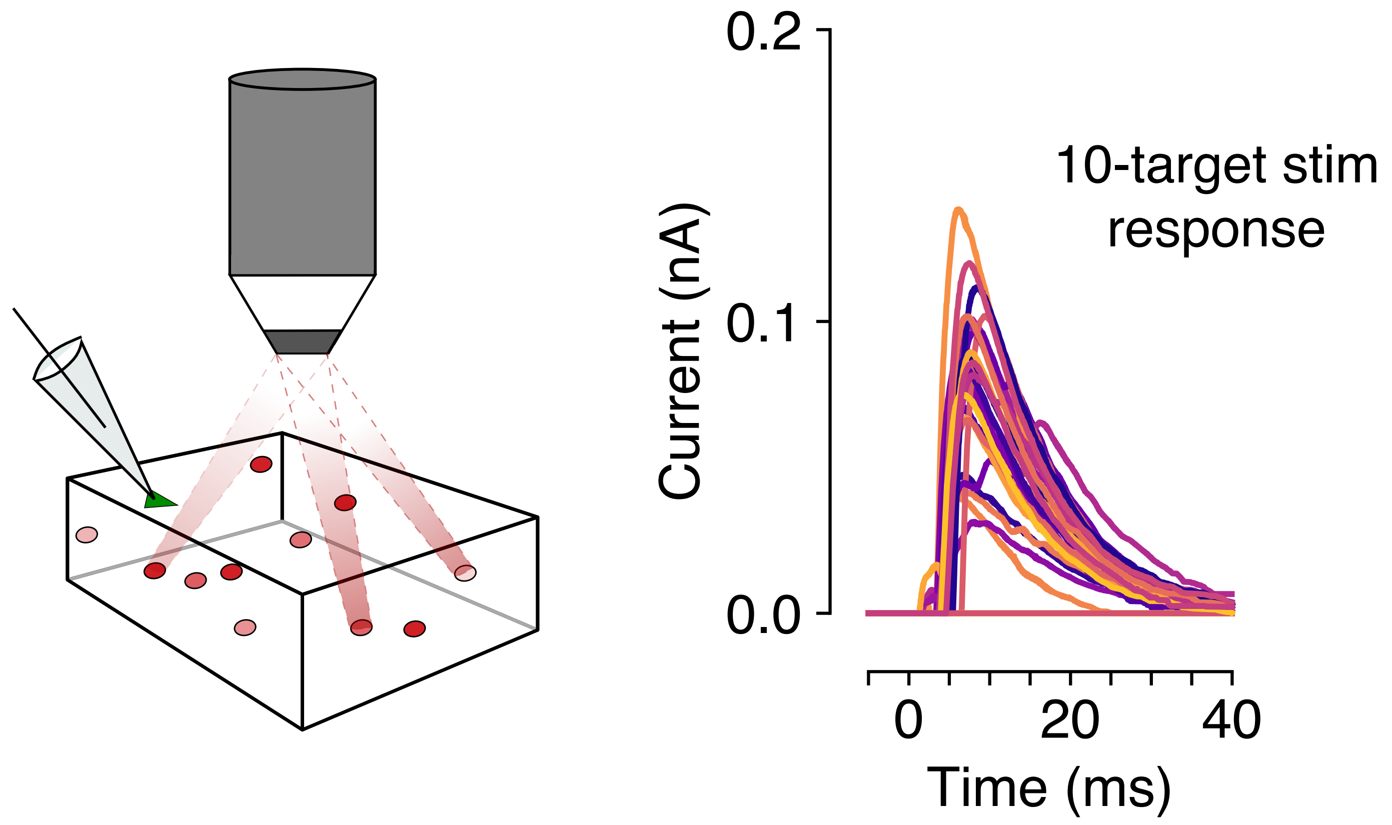

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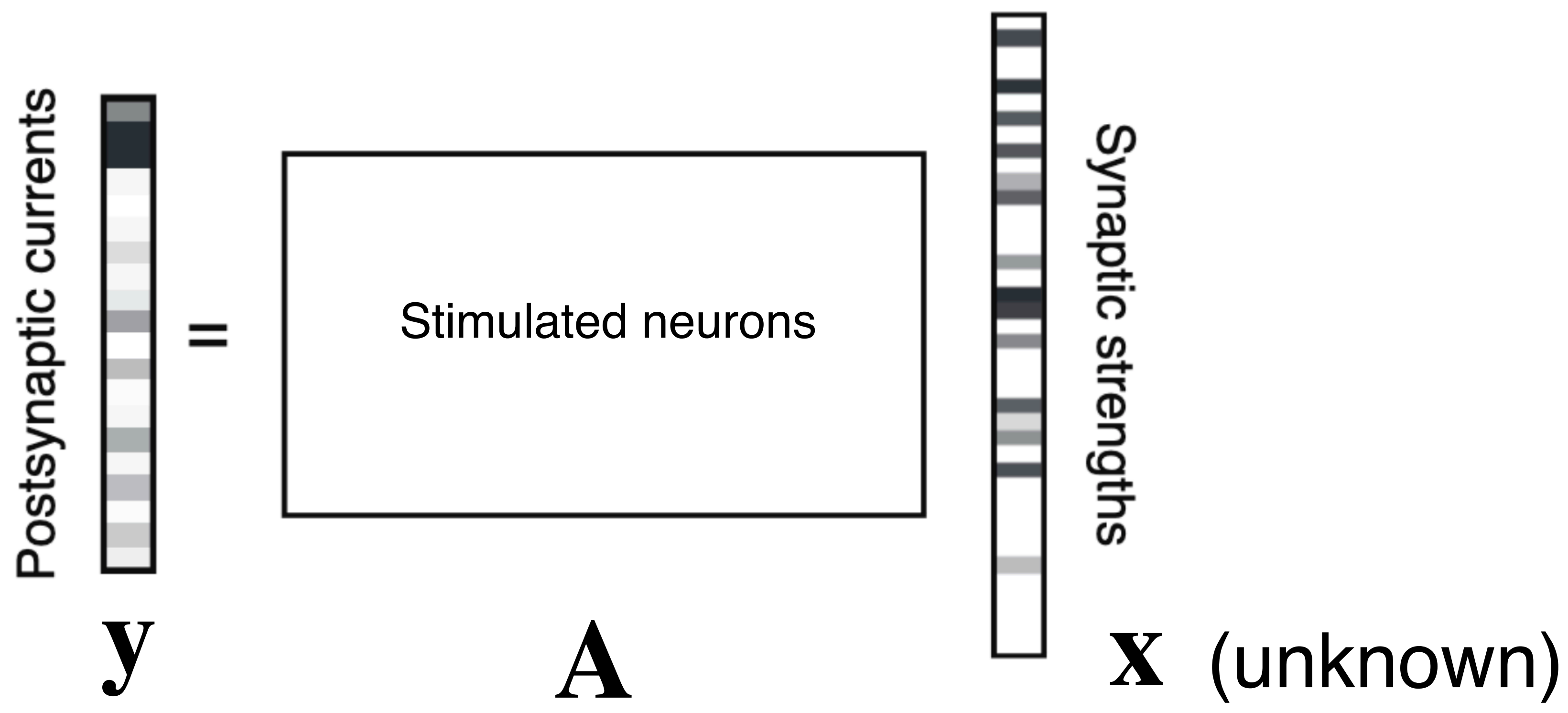


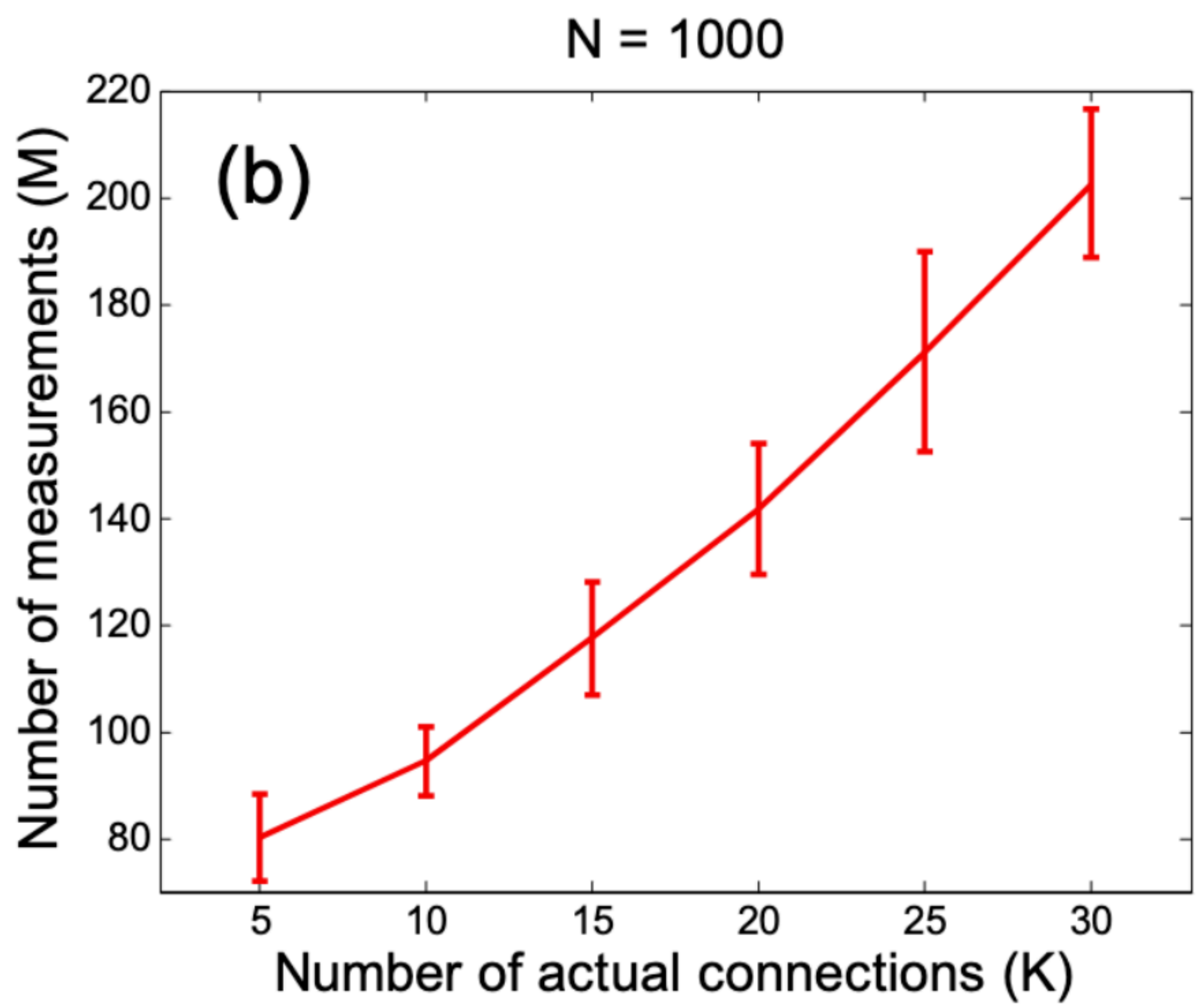
Solve $\mathbf{y} = \mathbf{A}\mathbf{x}$ such that $\mathbf{x}$ is sparse

Minimize $\|\mathbf{y} - \mathbf{A}\mathbf{x}\|_2 + \gamma\|\mathbf{x}\|_1$
subject to conditions on $\mathbf{A}$ and $\mathbf{x}$

Tao, Candes, Donoho, 2005-2008

Compressed sensing can be extremely efficient

Hu & Chklovskii 2009, *NeurIPS*



(100 neurons stimulated at once)

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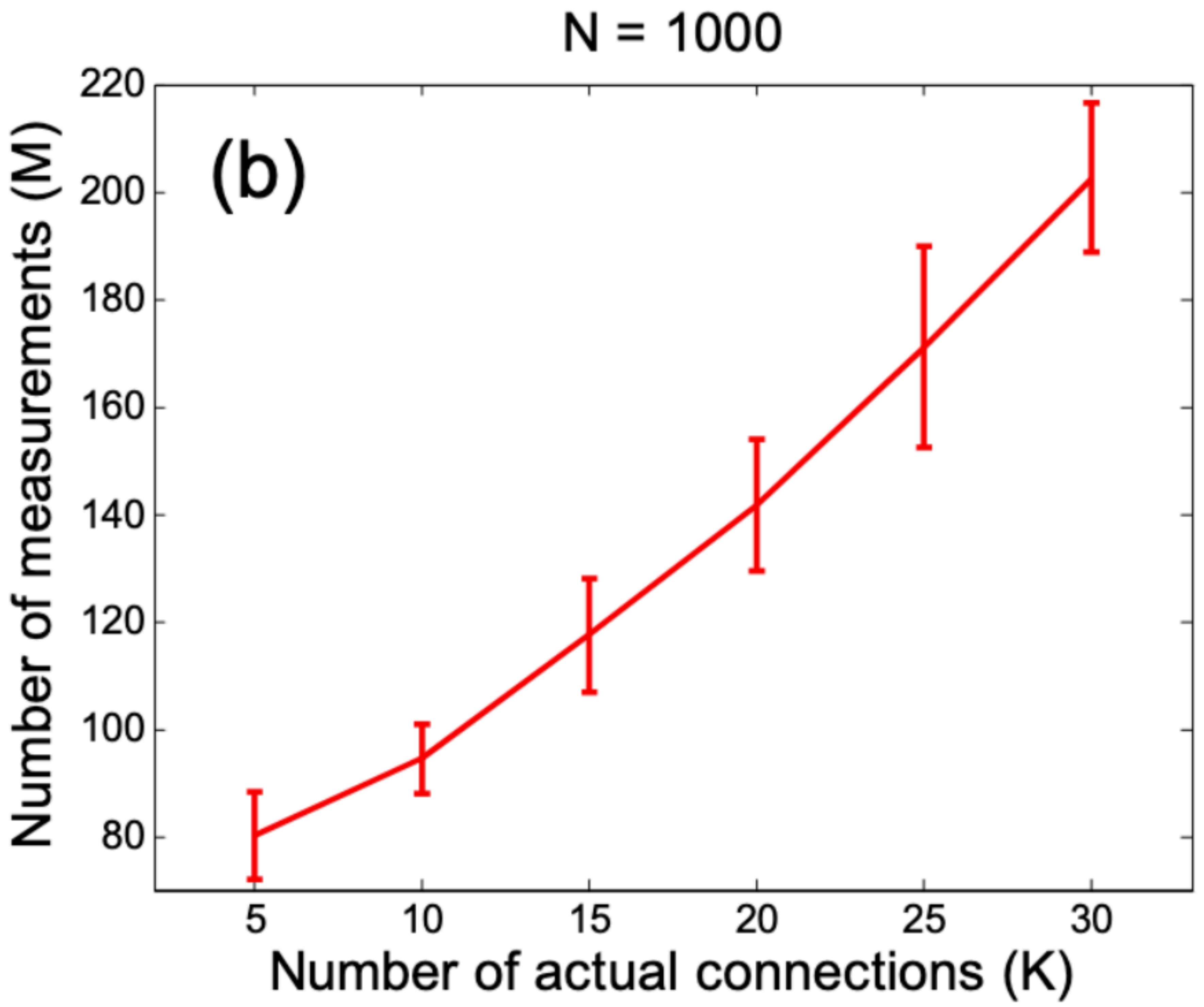
Hu & Chklovskii 2009, *NeurIPS*

Naive single-target stimulation
requires ~10,000 stims



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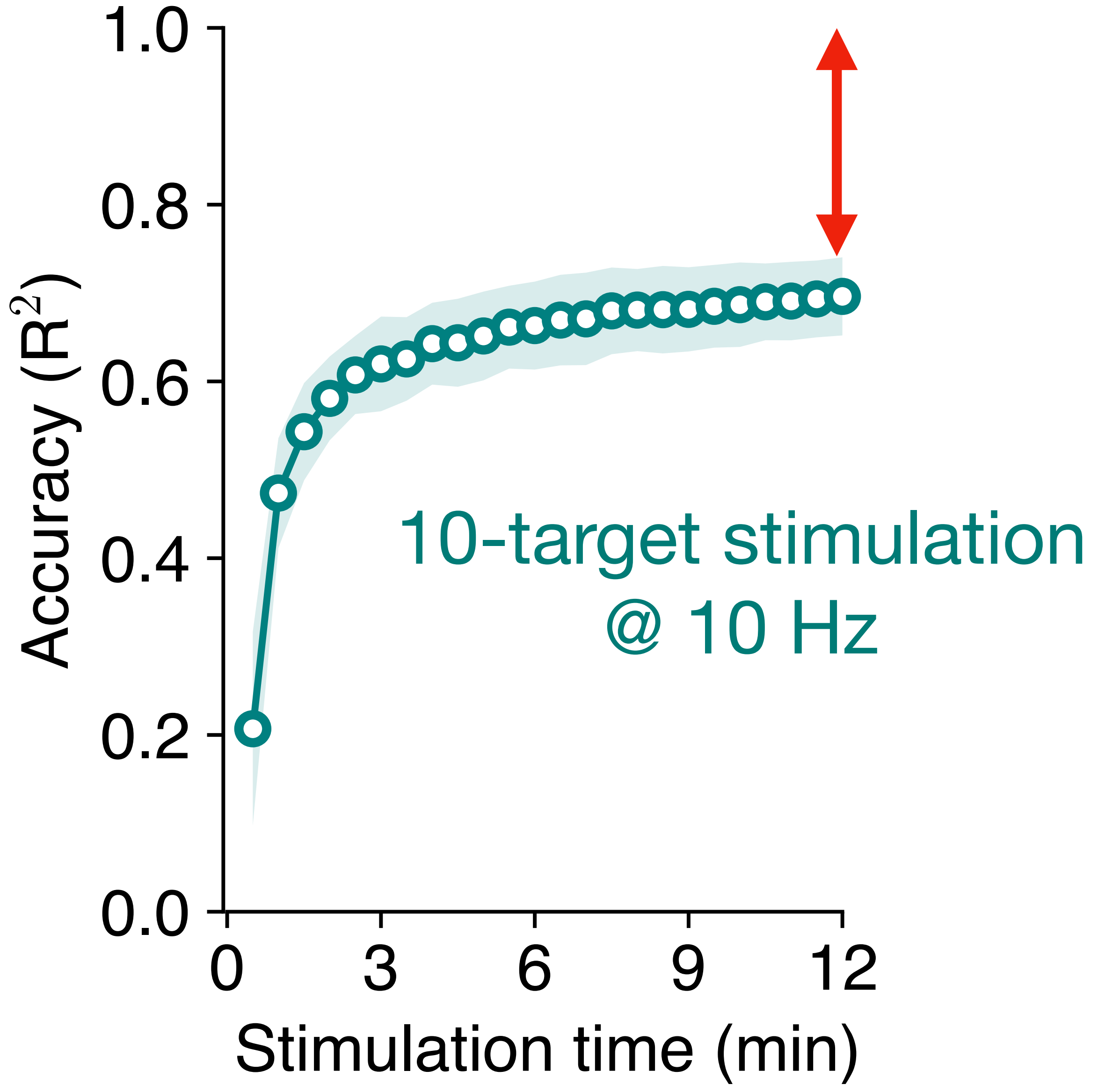
Ordinary CS is limited in realistic simulations

Performance
in simulation



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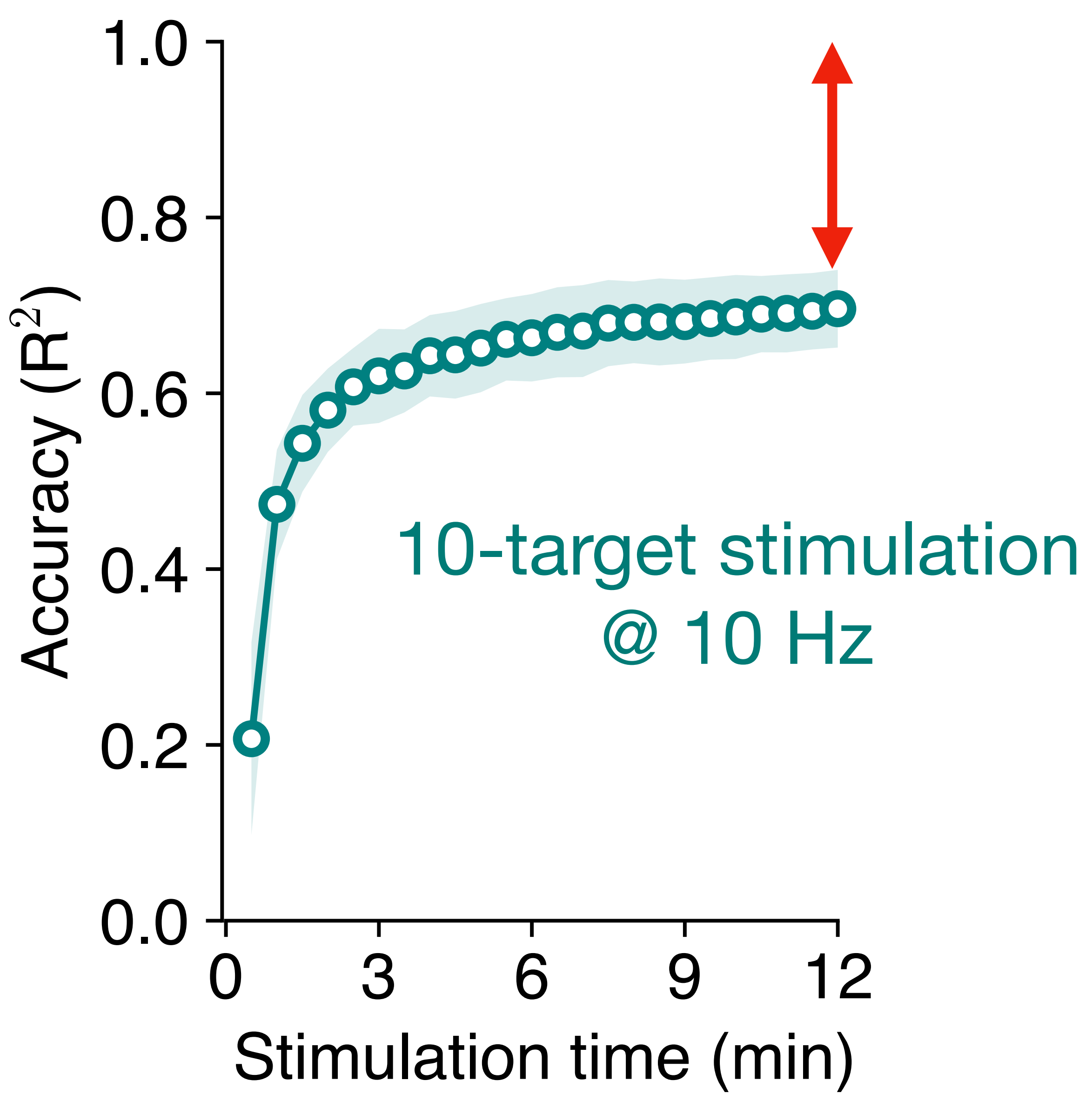

Missing variables

Stochastic spikes

Opsin expression

Synaptic failures

Spontaneous activity

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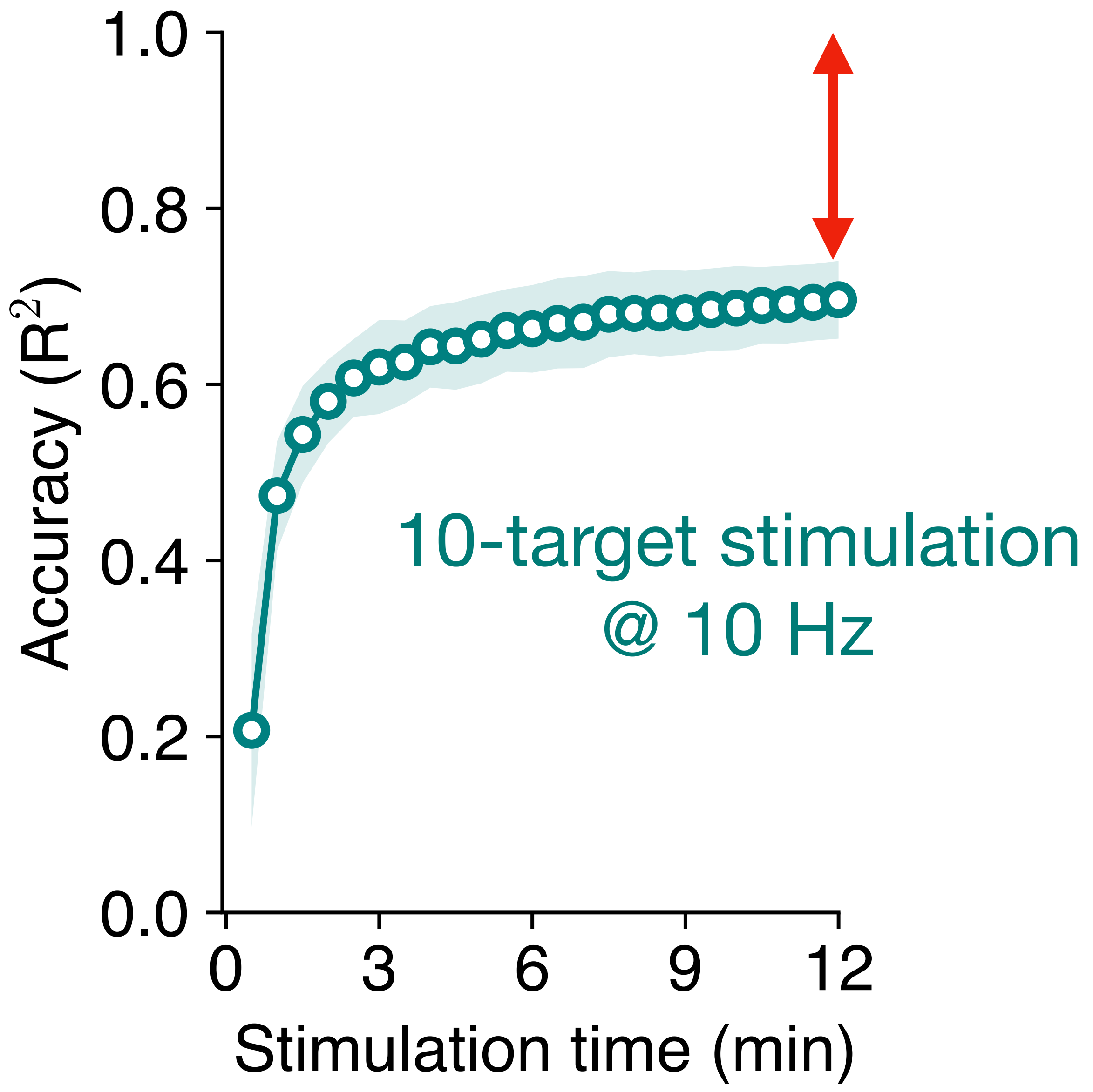

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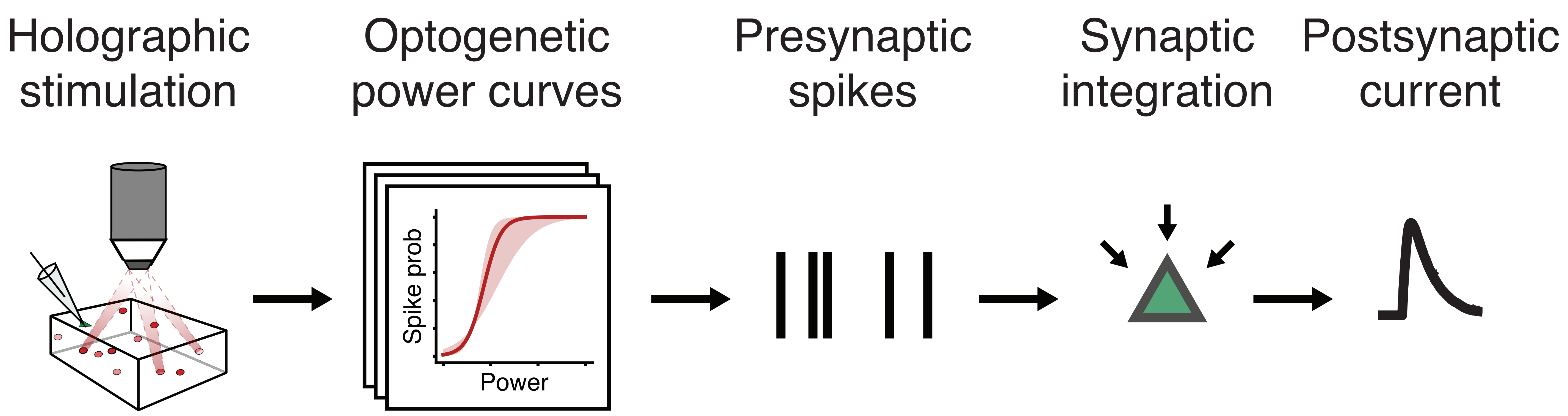
Instead, **leverage prior knowledge** of relevant biophysics

Model-based compressed sensing

Statistical model



Triplett*, Gajowa* et. al. (2023), *bioRxiv*

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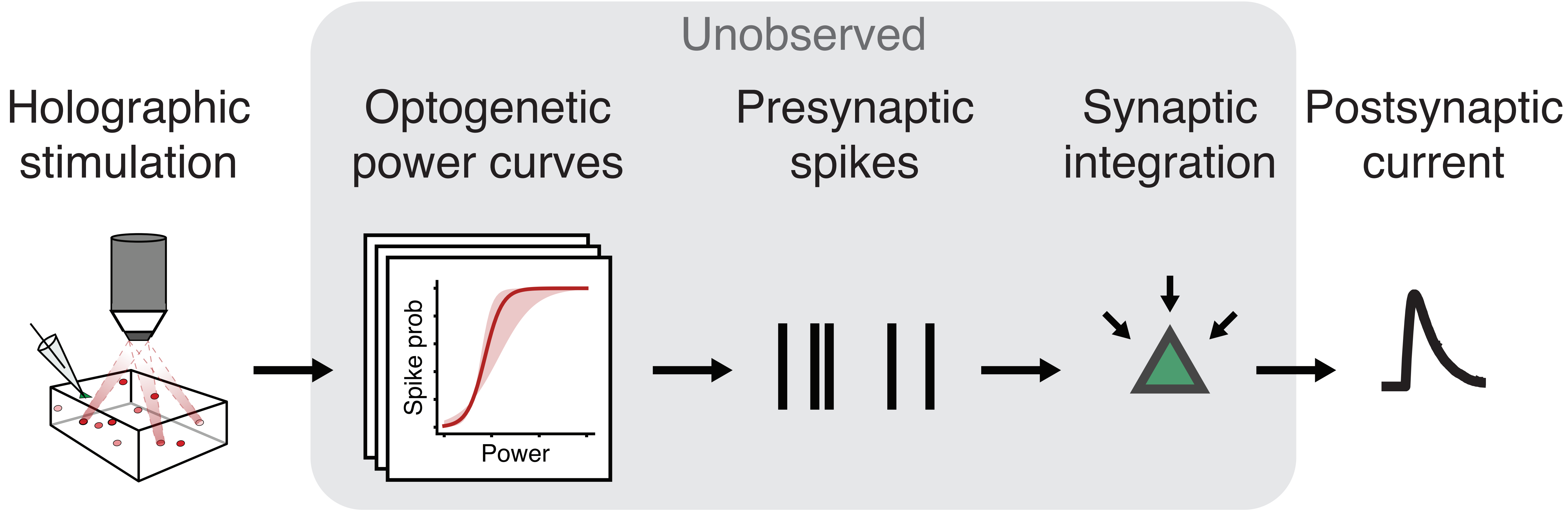

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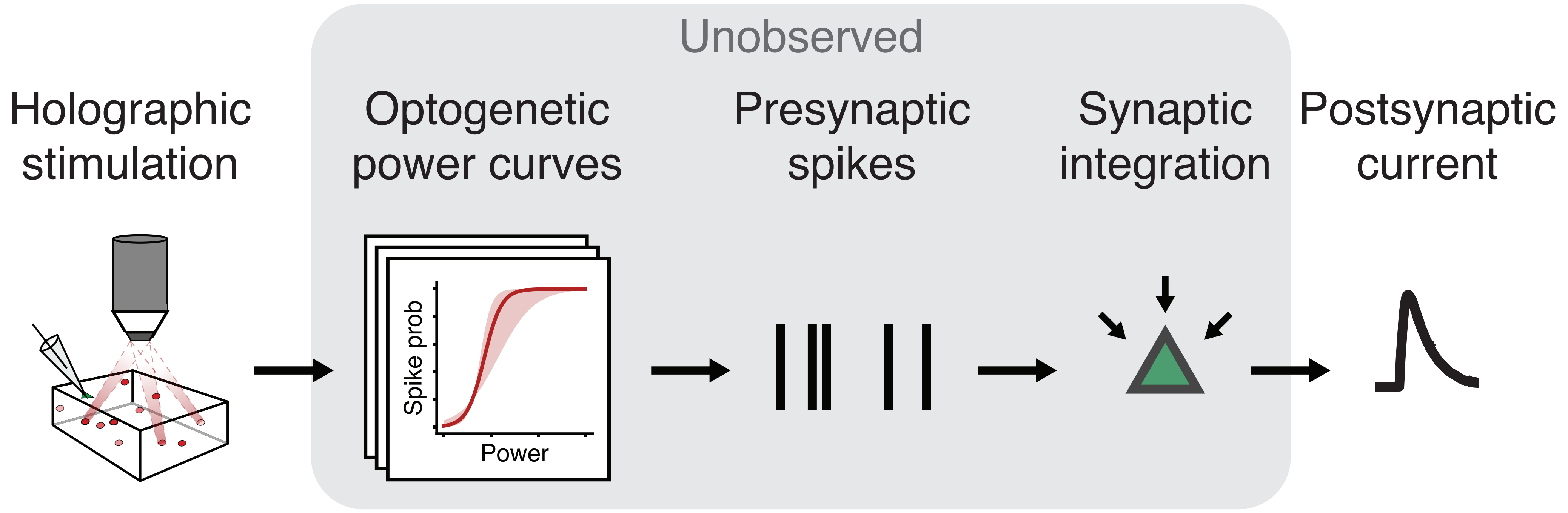
A variational inference approach



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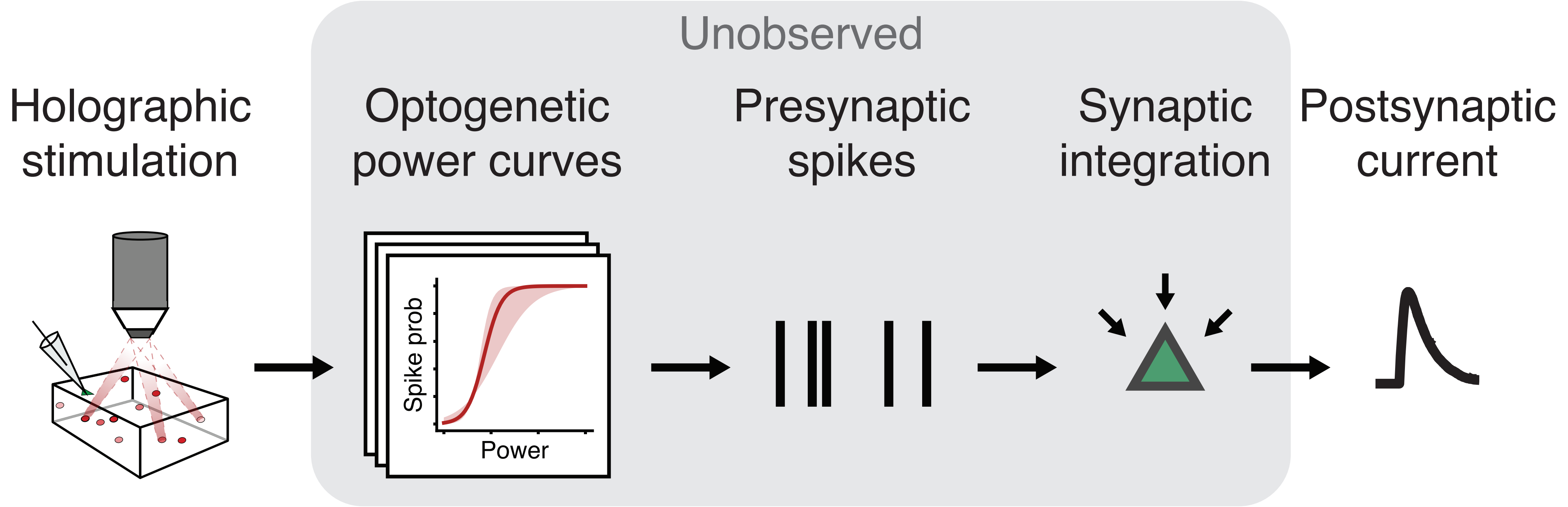
A variational inference approach

Probabilistic model:

$y_k \sim \text{Normal}\left(\mathbf{w}^\top \mathbf{s}_{:,k}, \sigma^2\right)$ PSCs



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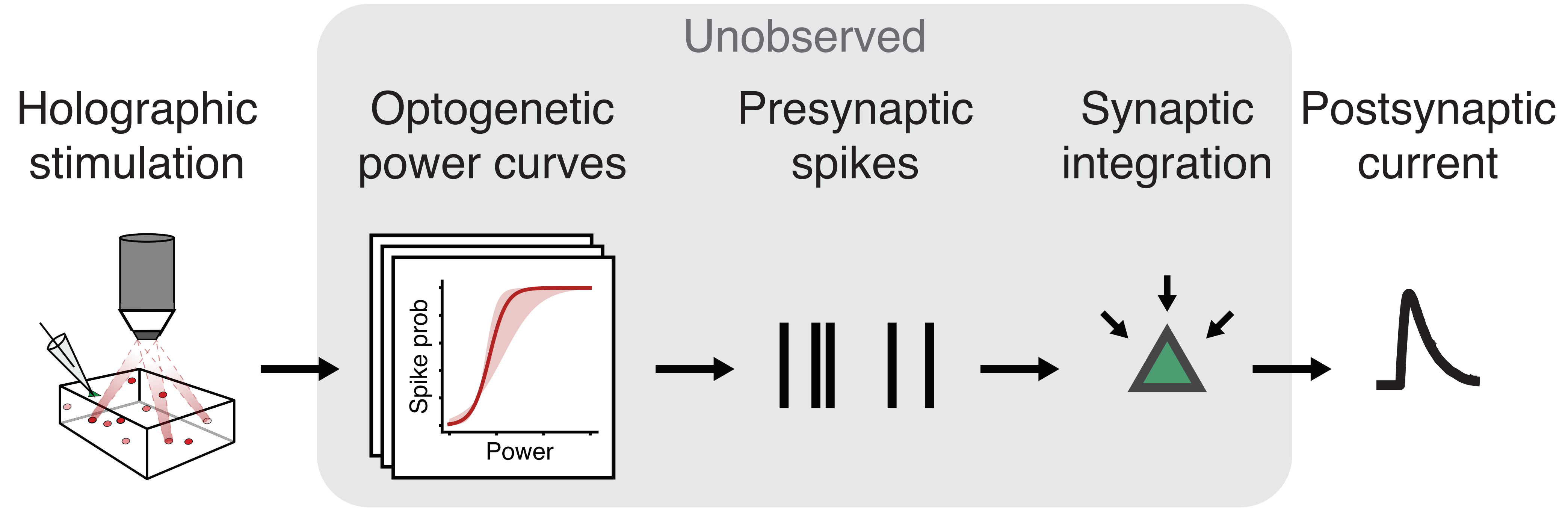

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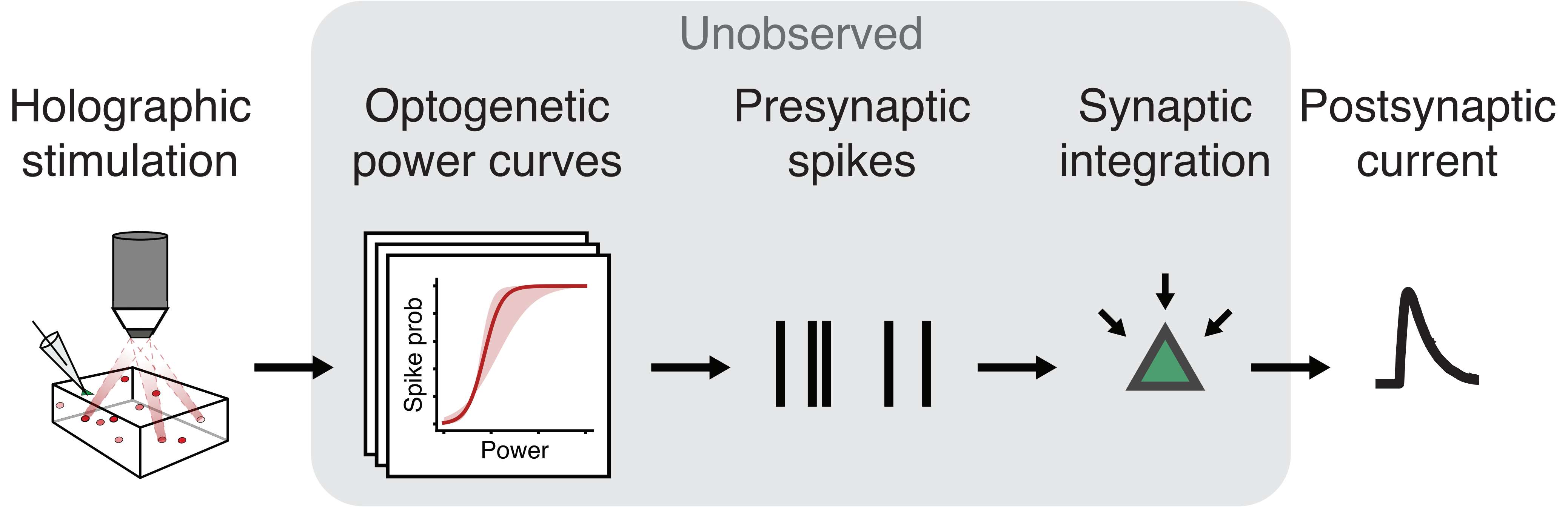

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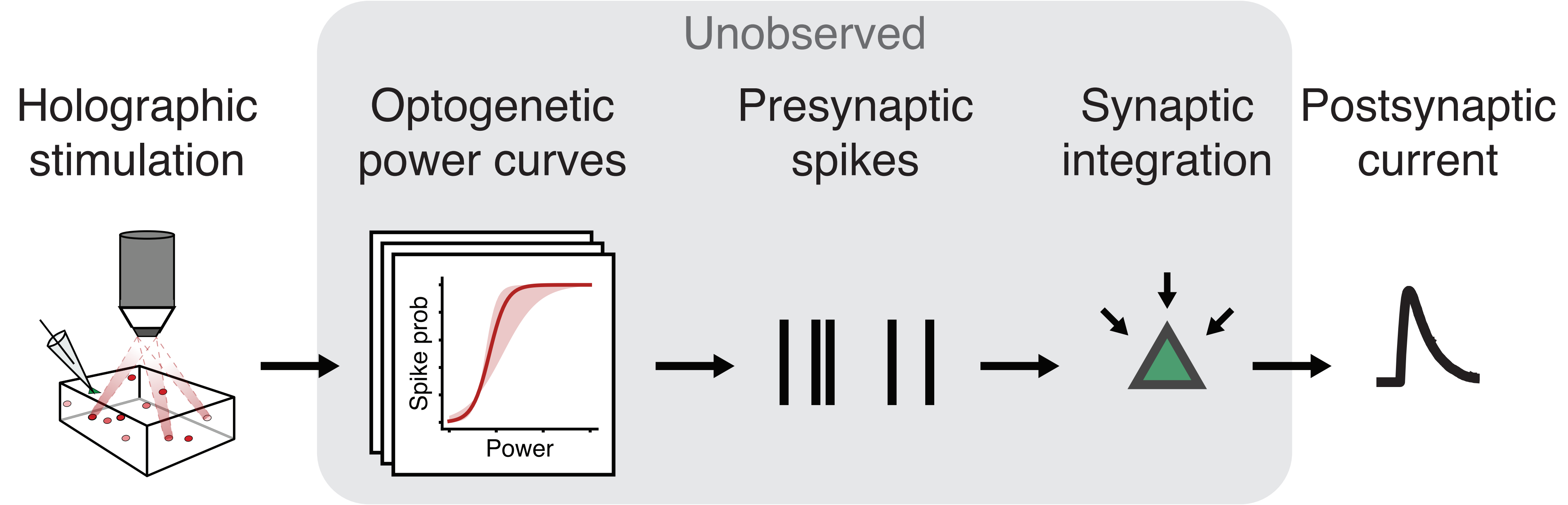
$s_{nk} \mid \boldsymbol{\phi}_n \sim \text{Bernoulli}\left(f\left(\phi_n^0 I_{nk} - \phi_n^1\right)\right)$	spikes



Triplett*, Gajowa* et. al. (2023), *bioRxiv*

A variational inference approach

Probabilistic model:

$y_k \sim \text{Normal}\left(\mathbf{w}^\top \mathbf{s}_{:,k}, \sigma^2\right)$	PSCs
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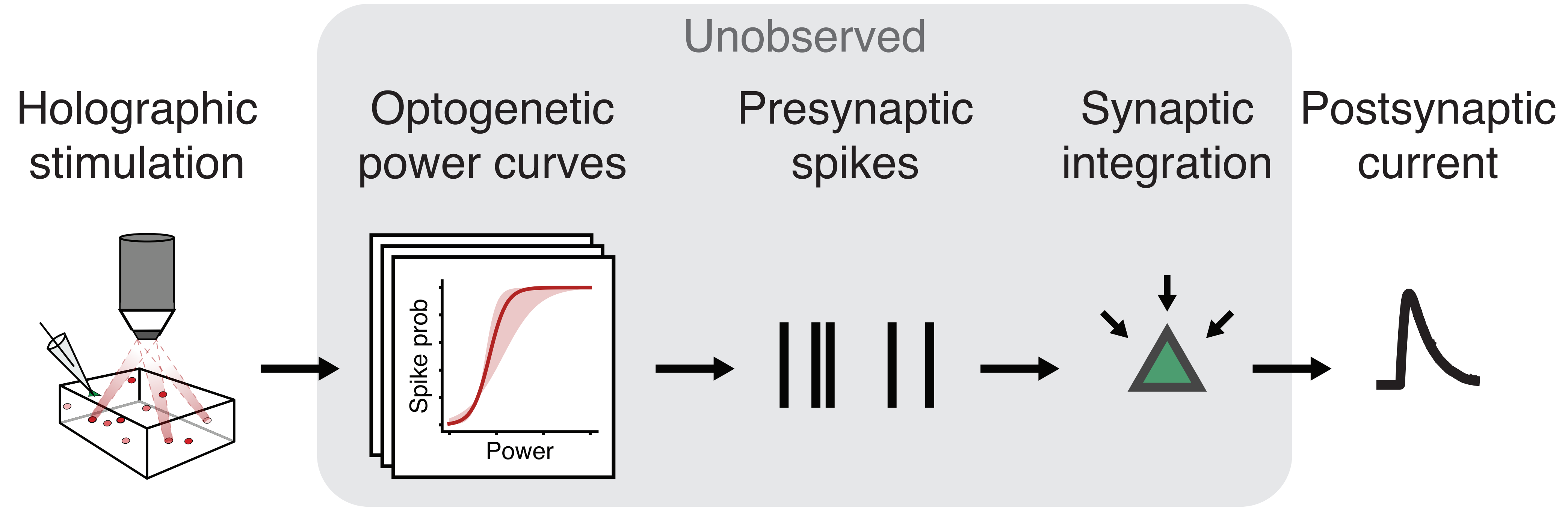
$\boldsymbol{\phi}_n \sim \text{Normal}(\mathbf{v}_n, \mathbf{L}_n)$	power curves



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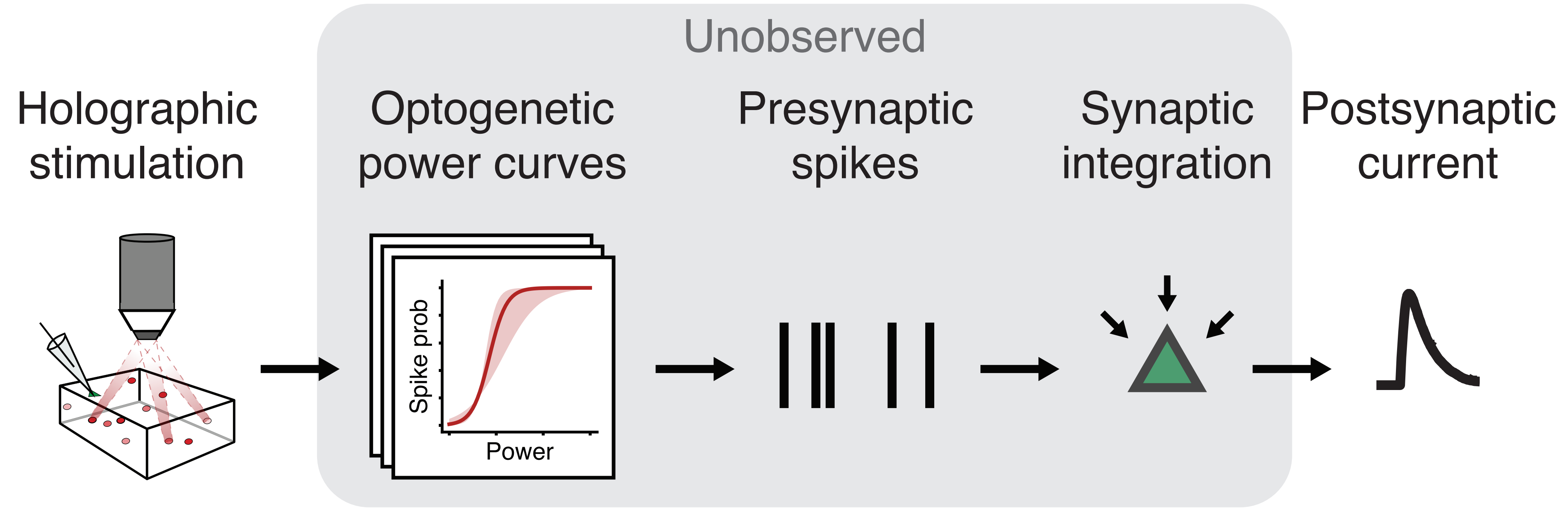

Posterior distribution:

$$p(\mathbf{w}, \mathbf{s}, \boldsymbol{\phi}, \sigma^2 \mid \mathbf{y}, \mathcal{I}) \propto p(\sigma^2) \prod_{n=1}^{N} p(w_n) p(\boldsymbol{\phi}_n) \prod_{k=1}^{K} p(s_{nk} \mid I_{nk}, \boldsymbol{\phi}_n) p(y_k \mid \mathbf{w}, \mathbf{s}_{:,k}, \sigma^2)$$

prior x likelihood

Triplett*, Gajowa* et. al. (2023), *bioRxiv*

A variational inference approach

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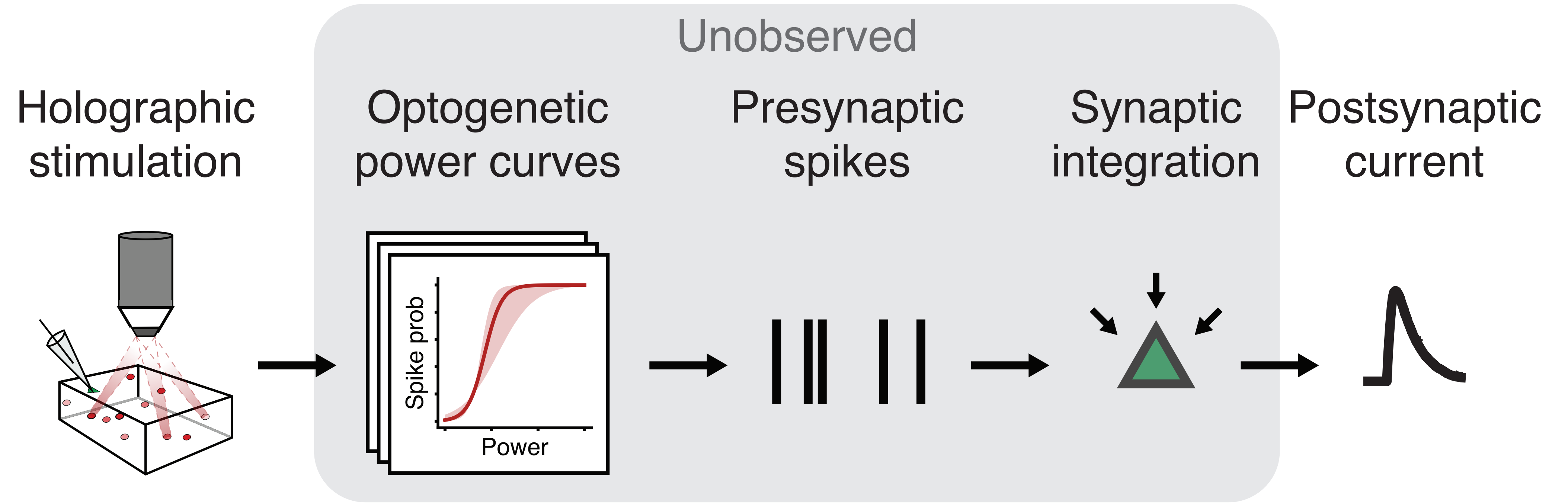

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prior x likelihood

Variational approximation:

$$q(\mathbf{w}, \mathbf{s}, \boldsymbol{\phi}, \sigma^2) = q(\sigma^2 \mid \theta_{\text{sh}}, \theta_{\text{ra}}) q(\mathbf{w} \mid \boldsymbol{\mu}, \boldsymbol{\Omega}) \prod_{n=1}^{N} q(\boldsymbol{\phi}_n \mid \boldsymbol{\nu}_n, \boldsymbol{\Sigma}_n) \prod_{k=1}^{K} q(s_{nk} \mid \lambda_{nk})$$

Triplett*, Gajowa* et. al. (2023), *bioRxiv*

A variational inference approach

Probabilistic model:

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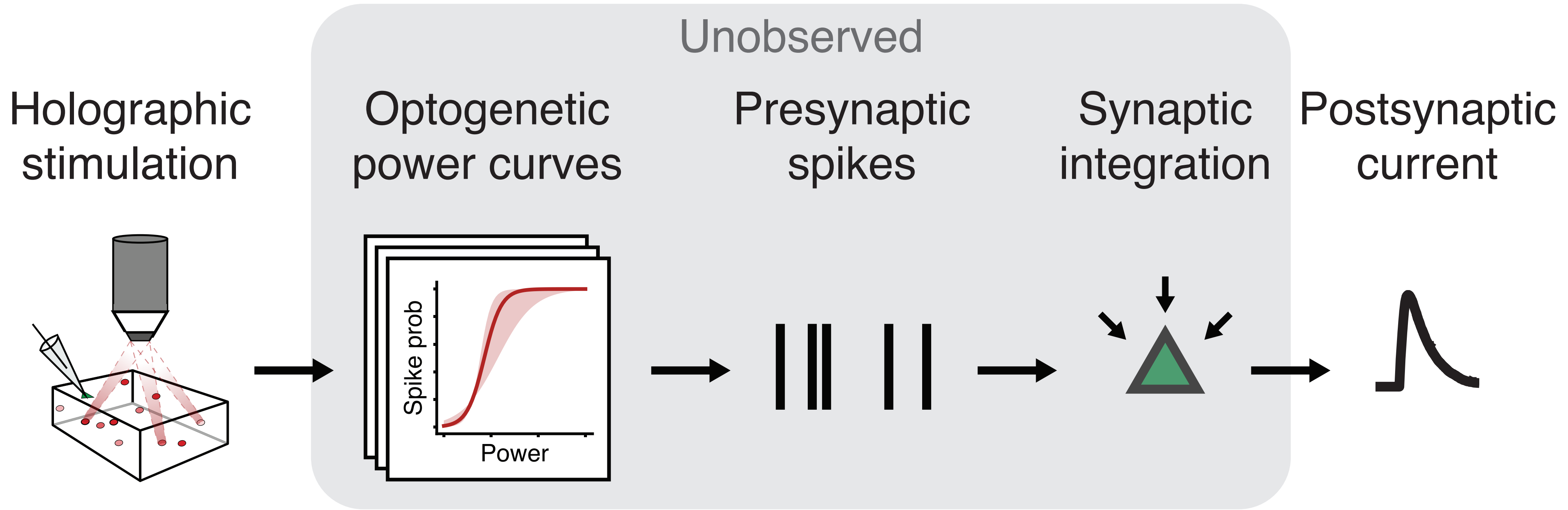

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> Minimize KL-divergence from *q* to *p* via block-coordinate descent

Triplett*, Gajowa* et. al. (2023), *bioRxiv*

Engineering a solution

Algorithm 1: Coordinate-ascent variational inference and isotonic regularization (CAVIaR)

input: PSC traces $\mathbf{c}$, stimulus information $\mathcal{I}$, PAVA threshold θ_{PAVA}, spontaneous penalty backtracking scalar α, soft orthogonality threshold θ_{orthog}, minimal test statistic τ_{min}, number of iterations *iters*

initialise $\lambda_{nk} \leftarrow 1$ for all n, k such that $I_{nk} > 0$ and $\tau_{\text{test}}(\mathbf{c}_k) \geq \tau_{\text{min}}$
$\lambda_{\text{spont}} \leftarrow 0$ // initialize spontaneous rate to 0
$i \leftarrow 1$
while $i \leq iters$ **do**
  update $q(\mathbf{w} \mid \boldsymbol{\mu}, \boldsymbol{\Omega}) \propto \exp \mathbb{E}_{q(\mathcal{Z} \setminus \mathbf{w})} [\ln p(\mathbf{y}, \mathcal{Z} \mid \mathcal{I})]$ // variational solution for synaptic weights
  for $n = 1, \ldots, N$ **do** // infer spikes via Monte Carlo ELBO solution
    sample $\boldsymbol{\phi}_n[m] \sim q(\boldsymbol{\phi}_n \mid \boldsymbol{\nu}, \boldsymbol{\Sigma})$ for $m = 1, \ldots, M$
    for $k = 1, \ldots, K$ **do**
      $\lambda_{nk} \leftarrow \text{argmax}_{\lambda_{nk}}$ ELBO$(\lambda_{nk} \mid \{\boldsymbol{\phi}_n[m]\}_{m=1}^{M})$
    end
    $\hat{F}_n \leftarrow$ PAVA$(\mathcal{I}, \boldsymbol{\lambda}_n)$ // estimate optogenetic power curve
    if $\hat{F}_n(\max_k I_{nk}) < \theta_{PAVA} + \lambda_{spont}$ **then** // check plausibility criterion
      $\mu_n \leftarrow 0, \boldsymbol{\lambda}_n \leftarrow \mathbf{0}$
    end
  end
  for $n = 1, \ldots, N$ **do** // Laplace approx of receptive field posterior
    $\boldsymbol{\nu}_n, \boldsymbol{\Sigma}_n \leftarrow$ RECEPTIVEFIELDLAPLACE$(\mathbf{s}_n, \boldsymbol{\phi}_n, \mathbf{v}, \mathbf{L})$
  end
  update $q(\sigma^{-2} \mid \theta_{\text{sh}}, \theta_{\text{ra}}) \propto \exp \mathbb{E}_{q(\mathcal{Z} \setminus \sigma^{-2})} [\ln p(\mathbf{y}, \mathcal{Z} \mid \mathcal{I})]$ // variational solution for noise precision
  while $\|\mathbf{y} - \boldsymbol{\mu}^\top \boldsymbol{\Lambda} - \mathbf{z}\|_2^2 / \|\mathbf{y}\|_2^2 \geq \epsilon$ **do** // begin spontaneous PSC inference
    for $k = 1, \ldots, K$ **do**
      if $\sum_{n=1}^{N} \lambda_{nk} \leq \theta_{orthog}$ *and* $\tau_{test}(\mathbf{c}_k) \geq \tau_{min}$ **then**
        $z_k \leftarrow S([y_k - \boldsymbol{\mu}^\top \boldsymbol{\lambda}_{:,k}]_+, \gamma)$ // soft-threshold residual with penalty γ
      end
    end
    $\gamma \leftarrow \alpha\gamma$ // shrink penalty
  end
  $\lambda_{\text{spont}} \leftarrow \frac{1}{K} \sum_{k=1}^{K} \mathbb{1}_{[z_k \neq 0]}$ // update spontaneous rate
  $i \leftarrow i + 1$
end
$\boldsymbol{\mu}, \boldsymbol{\Omega}, \boldsymbol{\Lambda}, \boldsymbol{\phi}, \mathbf{z} \leftarrow$ FNSCAN$(\boldsymbol{\mu}, \mathbf{z})$ // scan resulting spontaneous PSCs for potential false negatives

Algorithm 2: RECEPTIVEFIELDLAPLACE

for $n = 1, \ldots, N$ **do**
  for $t = 1, \ldots, T_{max}$ **do**
    $\kappa \leftarrow 1$ // Newton stepsize
    $\Psi_n(\boldsymbol{\phi}_n) = -\mathbb{E}_{q(s_n \mid \boldsymbol{\lambda}_n)} \left[\sum_{k=1}^{K} \ln p(\mathbf{s}_{nk} \mid \boldsymbol{\phi}_n, I_{nk}) + \ln p(\boldsymbol{\phi}_n \mid \mathbf{v}, \mathbf{L}) \right] - \frac{1}{\alpha_{\text{barrier}}} \sum_{i=0}^{1} \ln(\phi_n^i)$
    $\mathbf{J} = \nabla_{\boldsymbol{\phi}_n} \Psi_n$, $\mathbf{H} = \nabla\nabla_{\boldsymbol{\phi}_n} \Psi_n$
    $\mathbf{d} = \mathbf{H}_n^{-1} \mathbf{J}_n$ // search direction
    while $\Psi_n(\boldsymbol{\phi}_n + \kappa \mathbf{d}) > \Psi_n(\boldsymbol{\phi}_n) + \alpha_{backtrack}\, \kappa\, \mathbf{J}_n^\top \mathbf{d}$ **do** // backtrack
      $\kappa \leftarrow \beta_{\text{backtrack}}\, \kappa$
    end
    $\boldsymbol{\phi}_n \leftarrow \boldsymbol{\phi}_n - \kappa \mathbf{d}$ // make step
  end
  $\boldsymbol{\nu}_n \leftarrow \boldsymbol{\phi}_n$
  $\boldsymbol{\Sigma}_n \leftarrow \mathbf{H}_n^{-1}$
end
$q(\boldsymbol{\phi} \mid \boldsymbol{\nu}_n, \boldsymbol{\Sigma}_n) =$ TruncNormal$(\boldsymbol{\nu}_n, \boldsymbol{\Sigma}, 0, \infty)$ // truncate support to $(0, \infty)$

Algorithm 3: FNSCAN

input: Synaptic weights $\boldsymbol{\mu}$, spontaneous synaptic currents $\mathbf{z}$, stimulus information $\mathcal{I}$, PAVA threshold θ_{PAVA}

$S_{\text{disc}} \leftarrow \{n \in \{1, \ldots, N\} : \mu_n = 0\}$ // initialize pool of candidate neurons
while $|S_{disc}| > 0$ **do**
  for $n = 1, \ldots, N$ **do** // collect spontaneous PSC indices aligning with neuron stim times
    $\text{spont}_n \leftarrow \{k \in \{1, \ldots, K\} : z_k \neq 0$ and $I_{nk} > 0\}$
  end
  $n^* \leftarrow \text{argmax}_n |\text{spont}_n|$ // select neuron with most coincidental spontaneous PSCs
  $\hat{F}_{n^*}^{\text{spont}} \leftarrow$ PAVA $\left((I_{n^*k})_{k \in \text{spont}_n}, (z_k)_{k \in \text{spont}_n}\right)$ // estimate putative power curve
  if $\hat{F}_{n^*}^{spont}(\max_k I_{n^*k}) \geq \theta_{PAVA}$ **then**
    $\mu_{n^*} \leftarrow$ mean$(\{z_k : k \in \text{spont}_{n^*}\})$ // neuron passes PAVA criterion, declare connected
    $\beta_{n^*} \leftarrow$ s.e.m.$(\{z_k : k \in \text{spont}_{n^*}\})$
    for $k \in spont_{n^*}$ **do**
      $\lambda_{n^*k} \leftarrow 1$ // declare spontaneous PSC to be spike from neuron n^*
      $z_k \leftarrow 0$ // remove spontaneous PSC from vector $\mathbf{z}$
    end
  end
  $S_{\text{disc}} \leftarrow S_{\text{disc}} \setminus \{n^*\}$ // remove n^* from pool of disconnected neurons
end

CAVIaR: Open-source software

"Coordinate-ascent variational inference and isotonic regularization"

github.com/marcustriplett/circuitmap

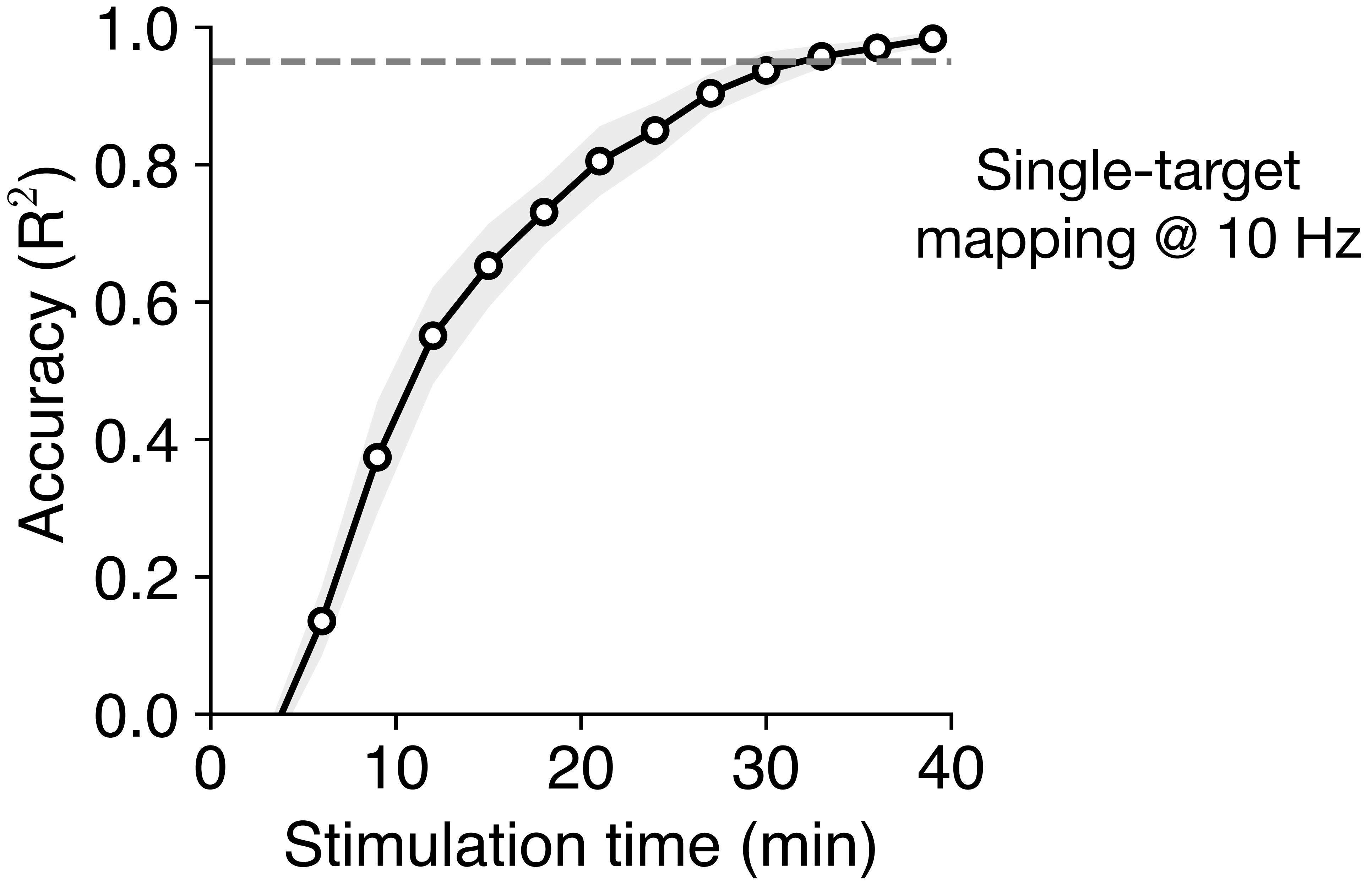
CAVIaR: Open-source software

"Coordinate-ascent variational inference and isotonic regularization"

```python
import circuitmap as cm

# Choose your NWD network
demix = cm.NeuralDemixer(path='demixers/nwd_ie_ChroME2f.ckpt', device=device)

# Demix PSCs
psc_dem = demix(psc)

# Setup model
model = cm.Model(population_size, priors=priors)

# Fit model to demixed PSCs
model.fit(psc_dem, stimulus_matrix, method='caviar', fit_options=fit_options)
```

github.com/marcustriplett/circuitmap

Ensemble stimulation yields order-of-magnitude speedup



Simulation: 1000 neurons, 10% connectivity

Triplett*, Gajowa* et. al. (2023), *bioRxiv*

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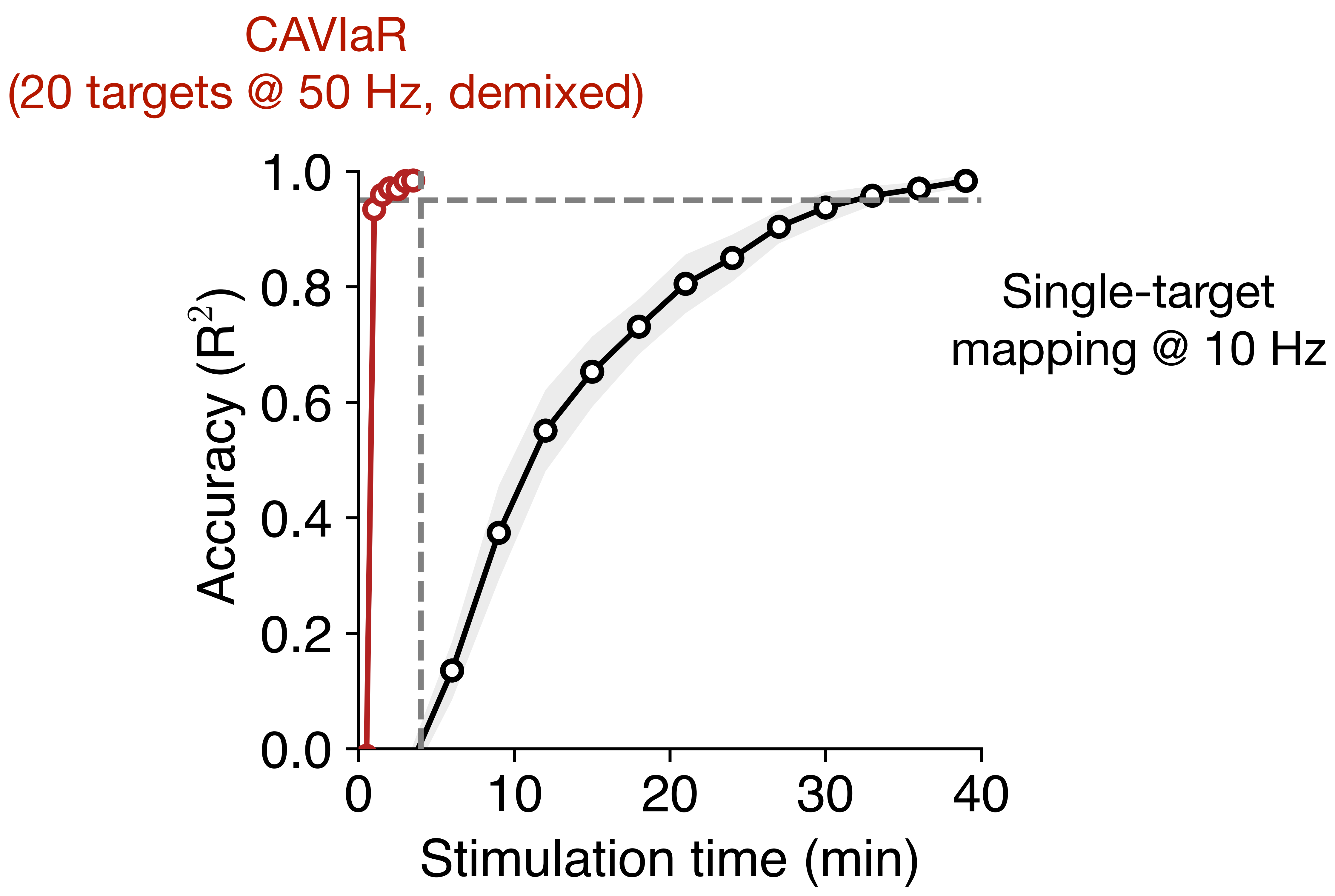

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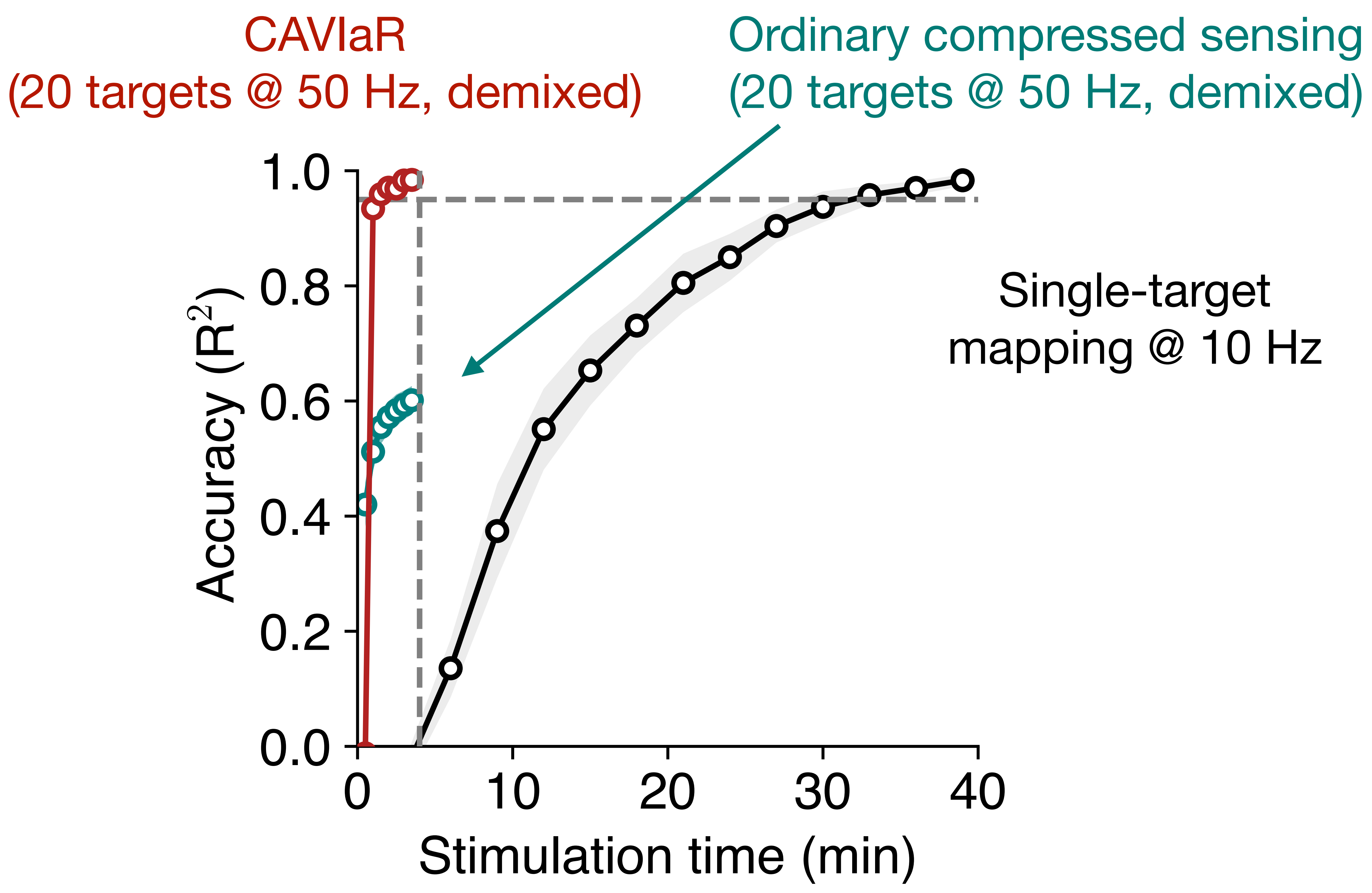

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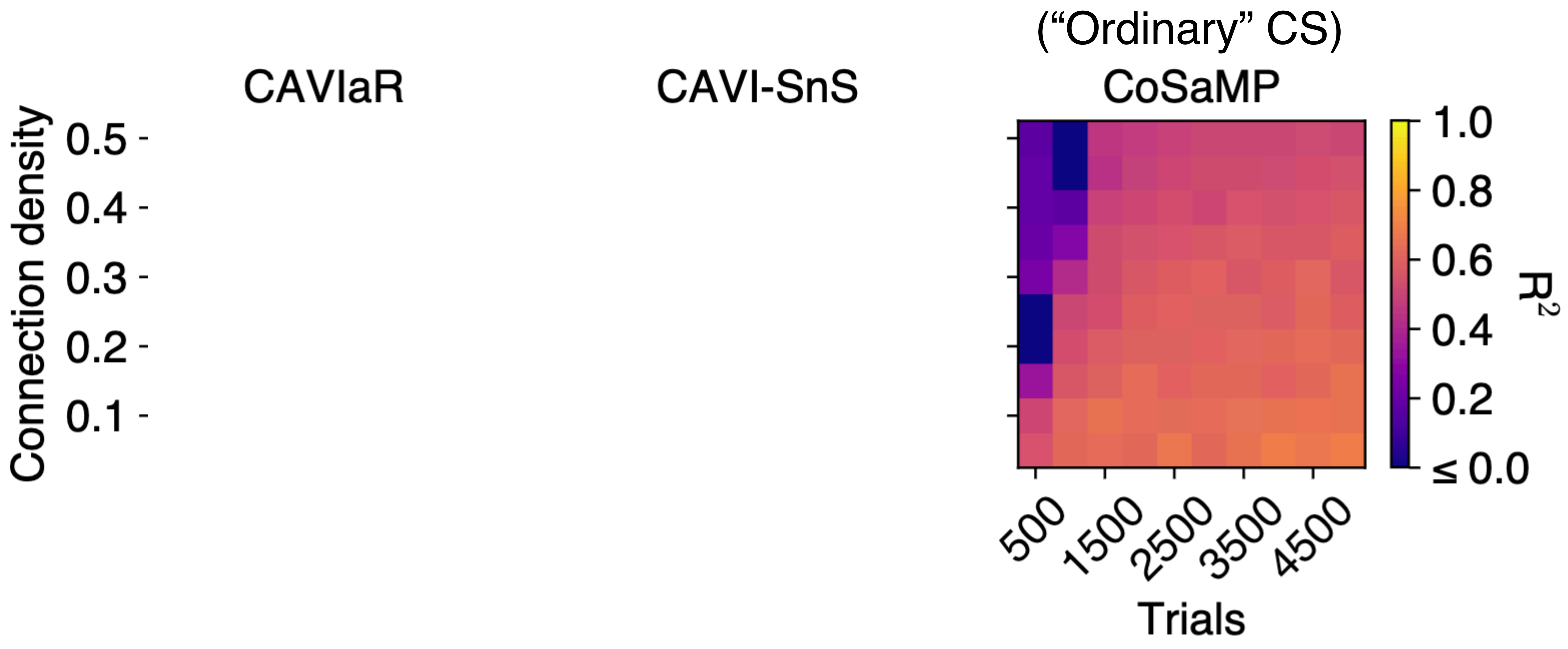
Dependence on connection probability



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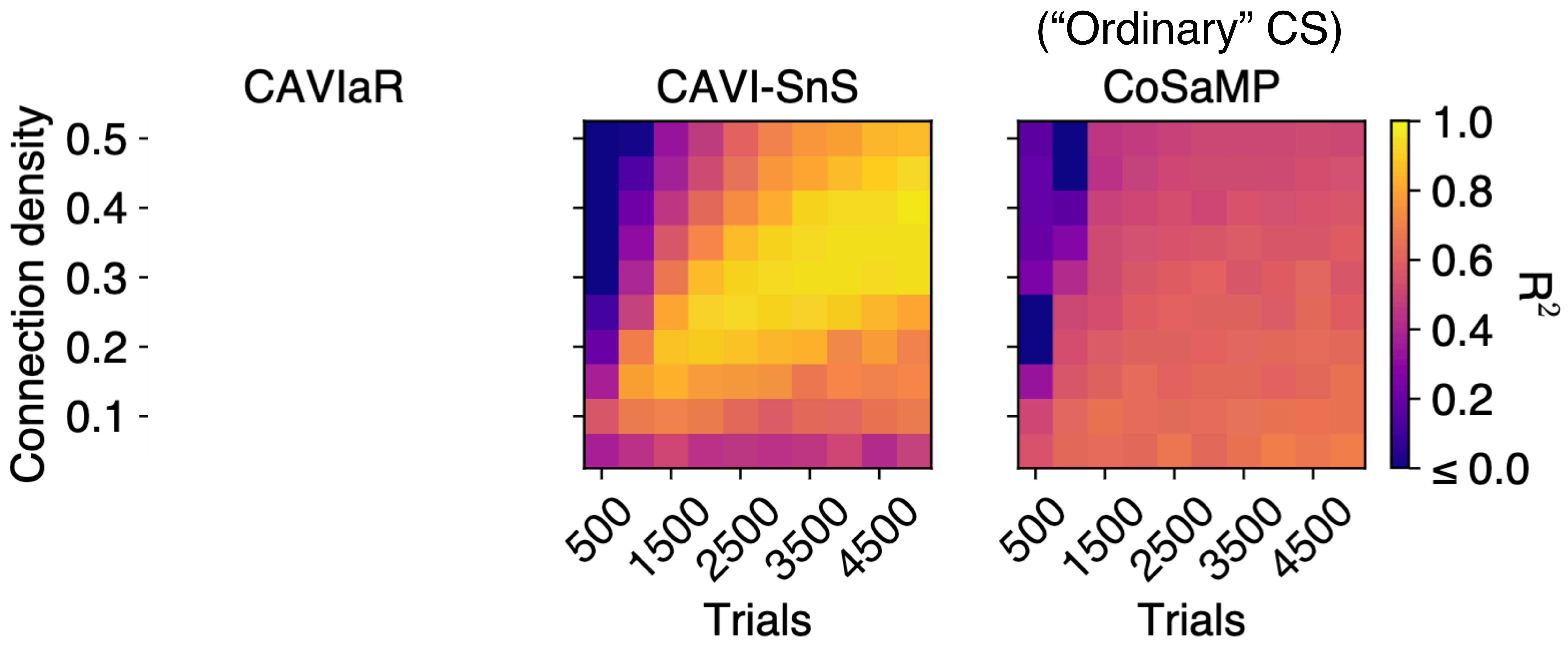

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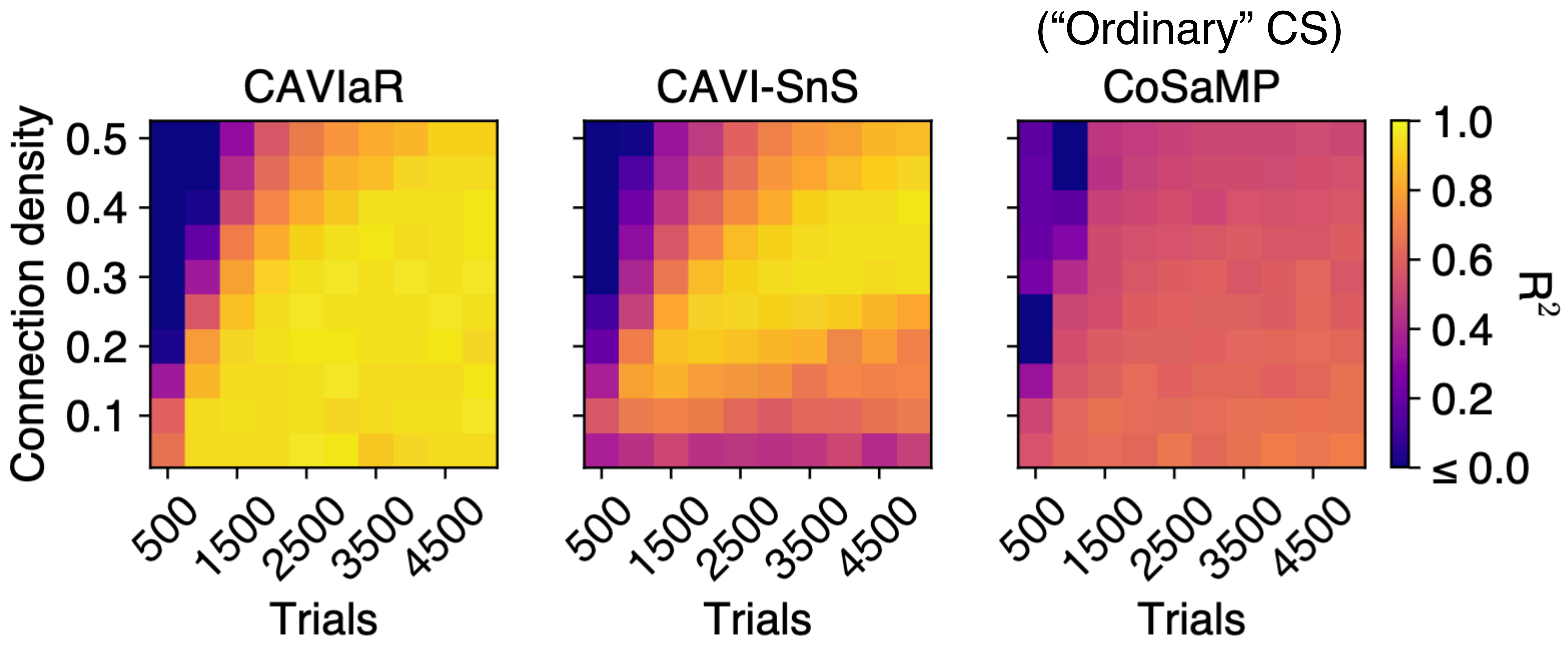

Making the leap to real mapping experiments

Marta Gajowa (Berkeley)

Hillel Adesnik (Berkeley)

Making the leap to real mapping experiments

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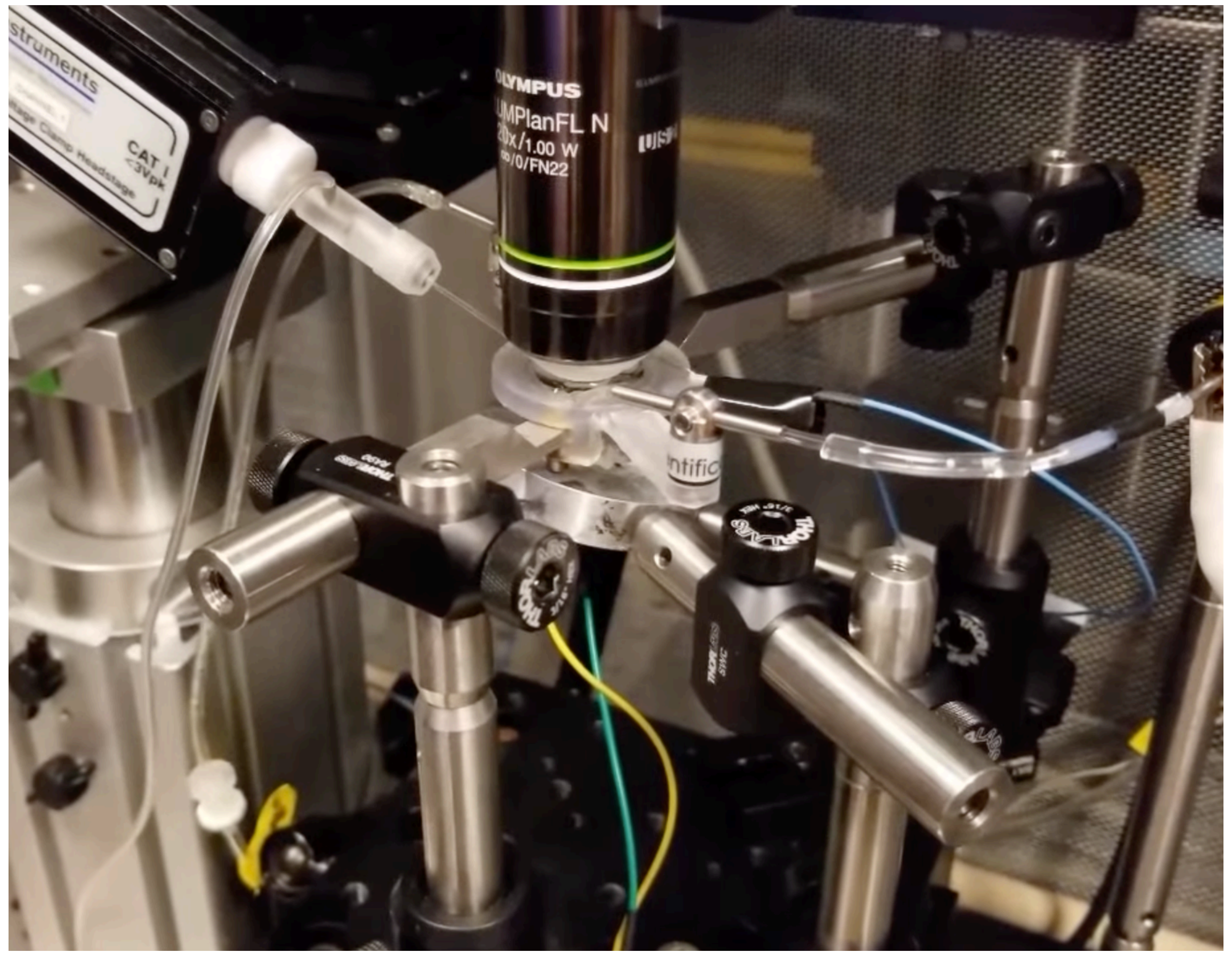

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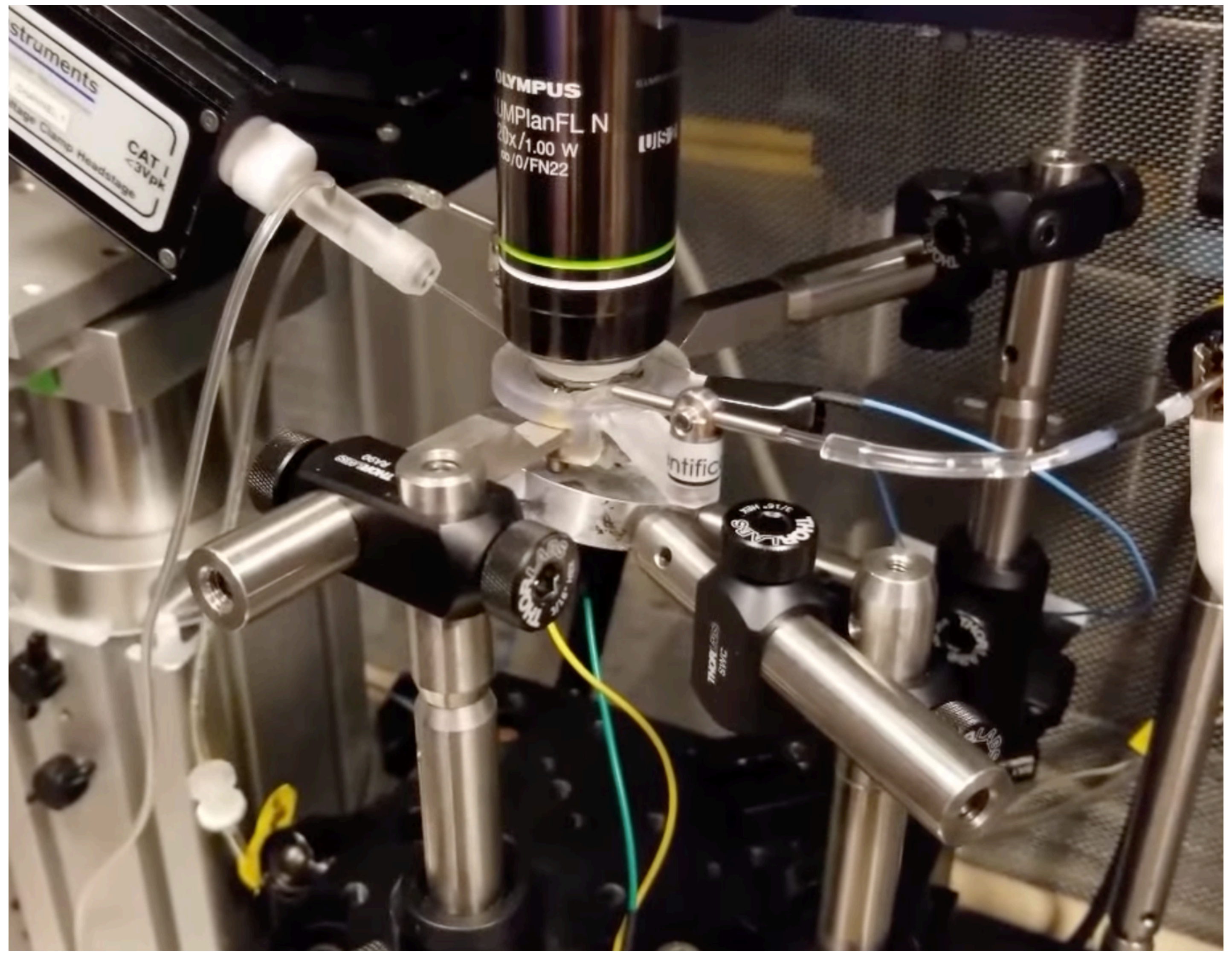
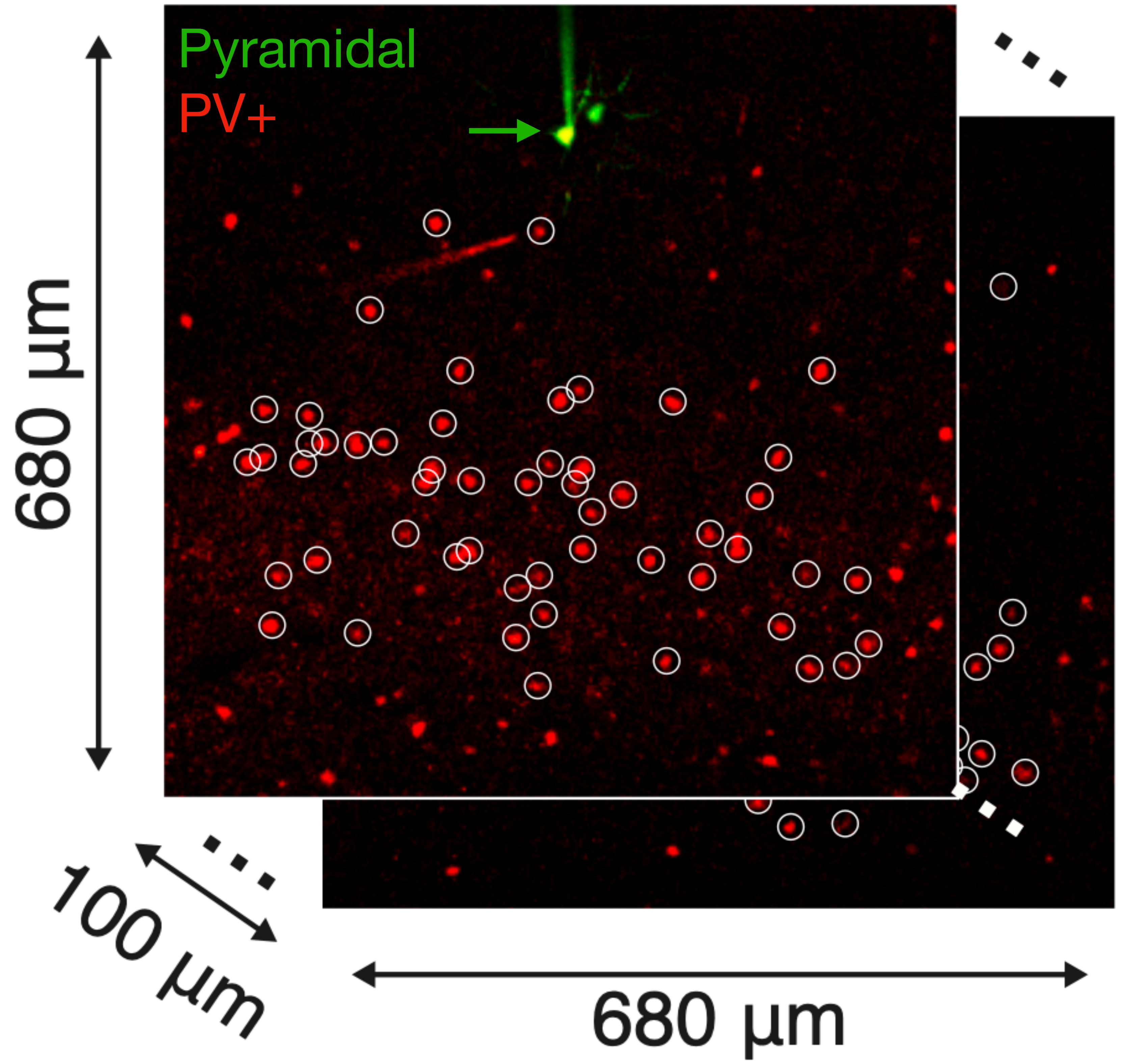
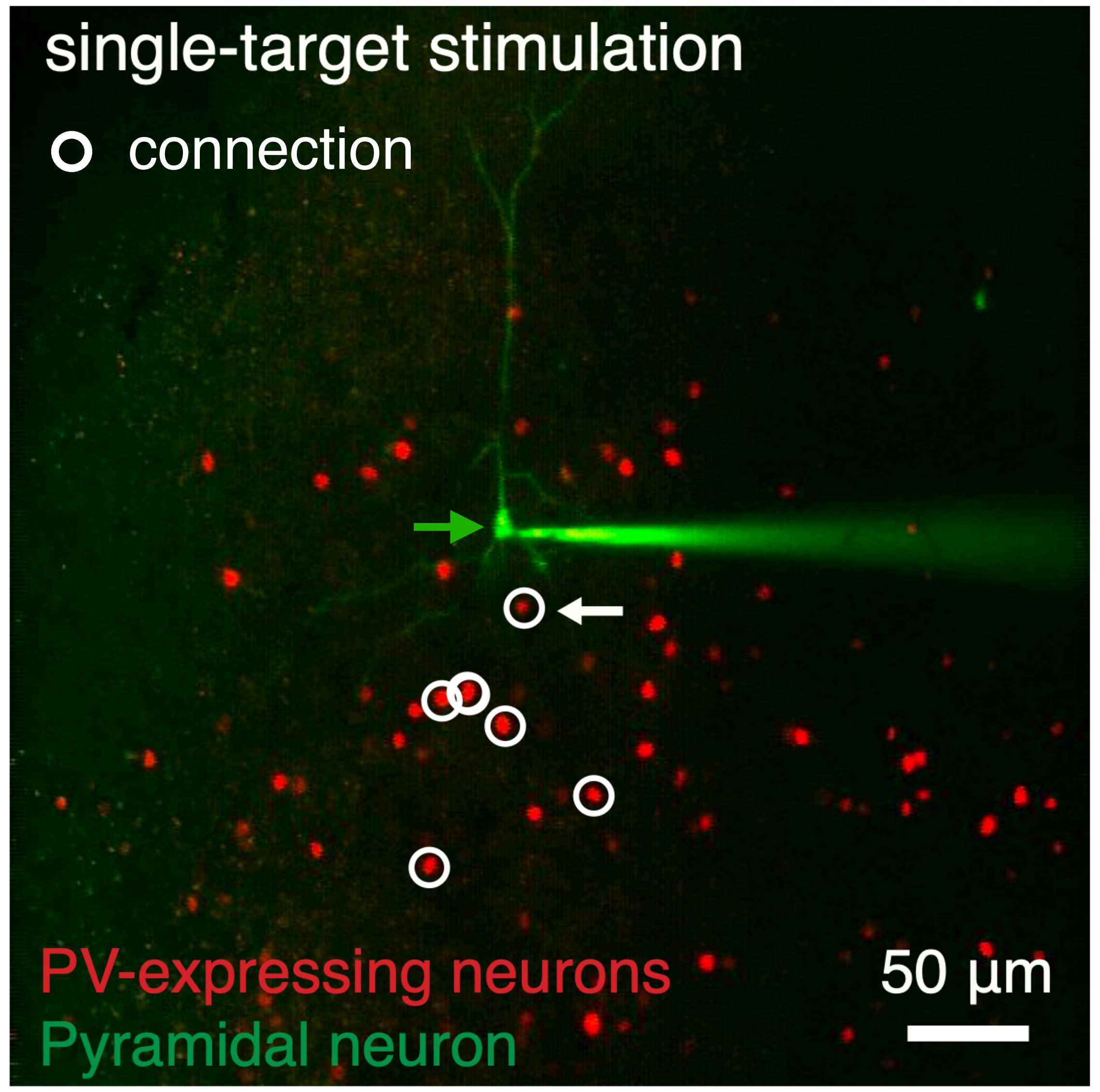




Performance testing in primary visual cortex



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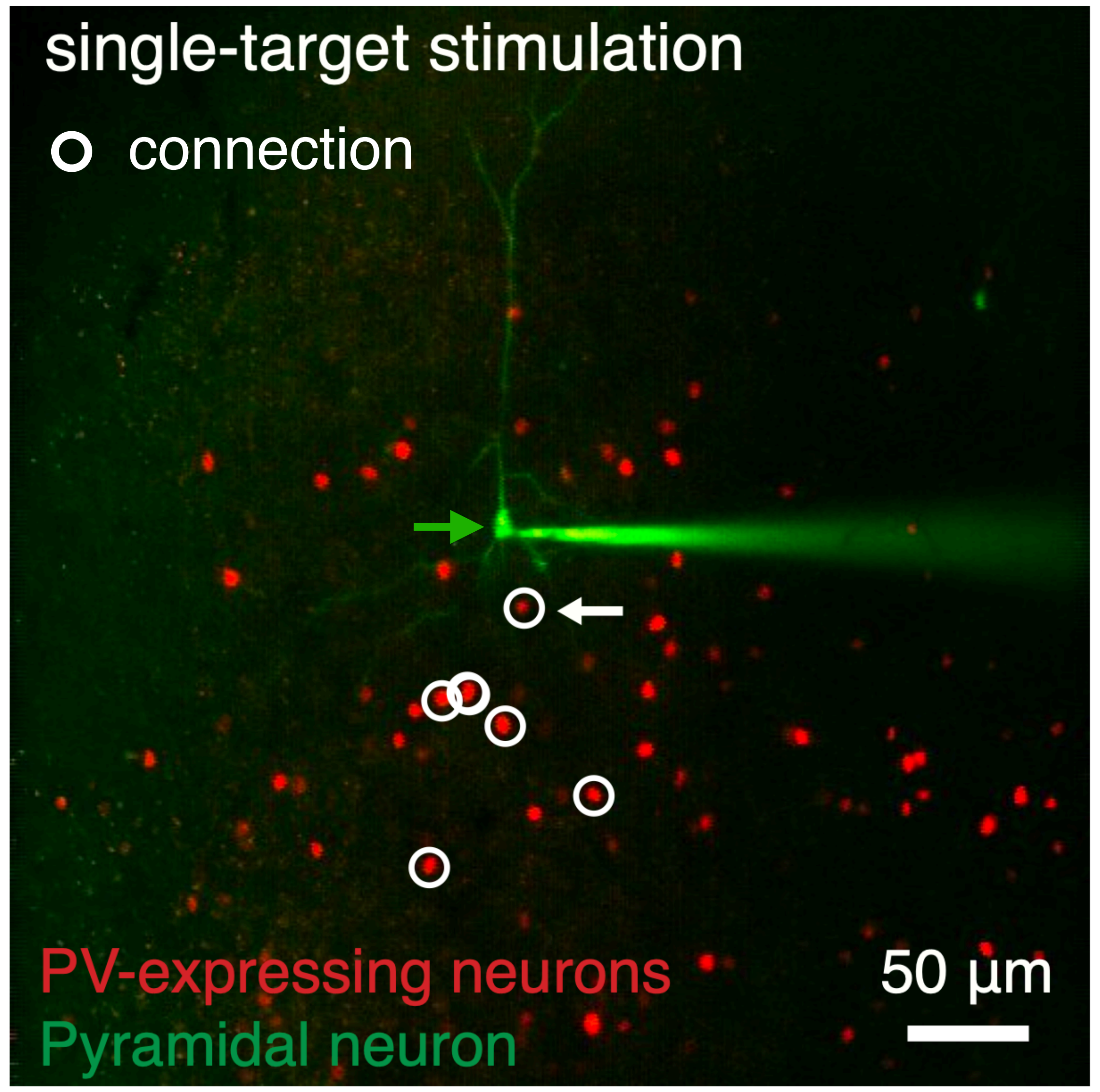

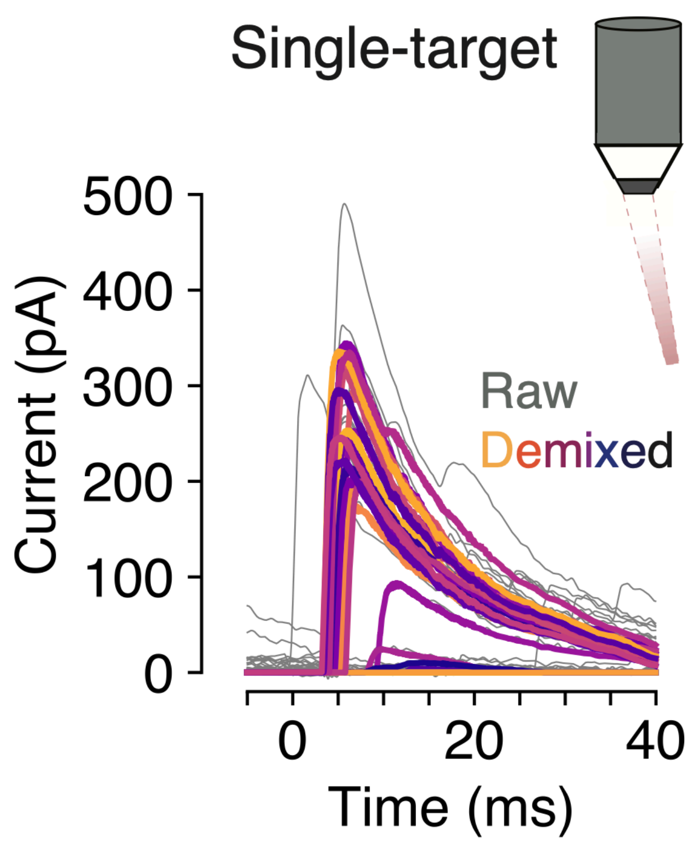

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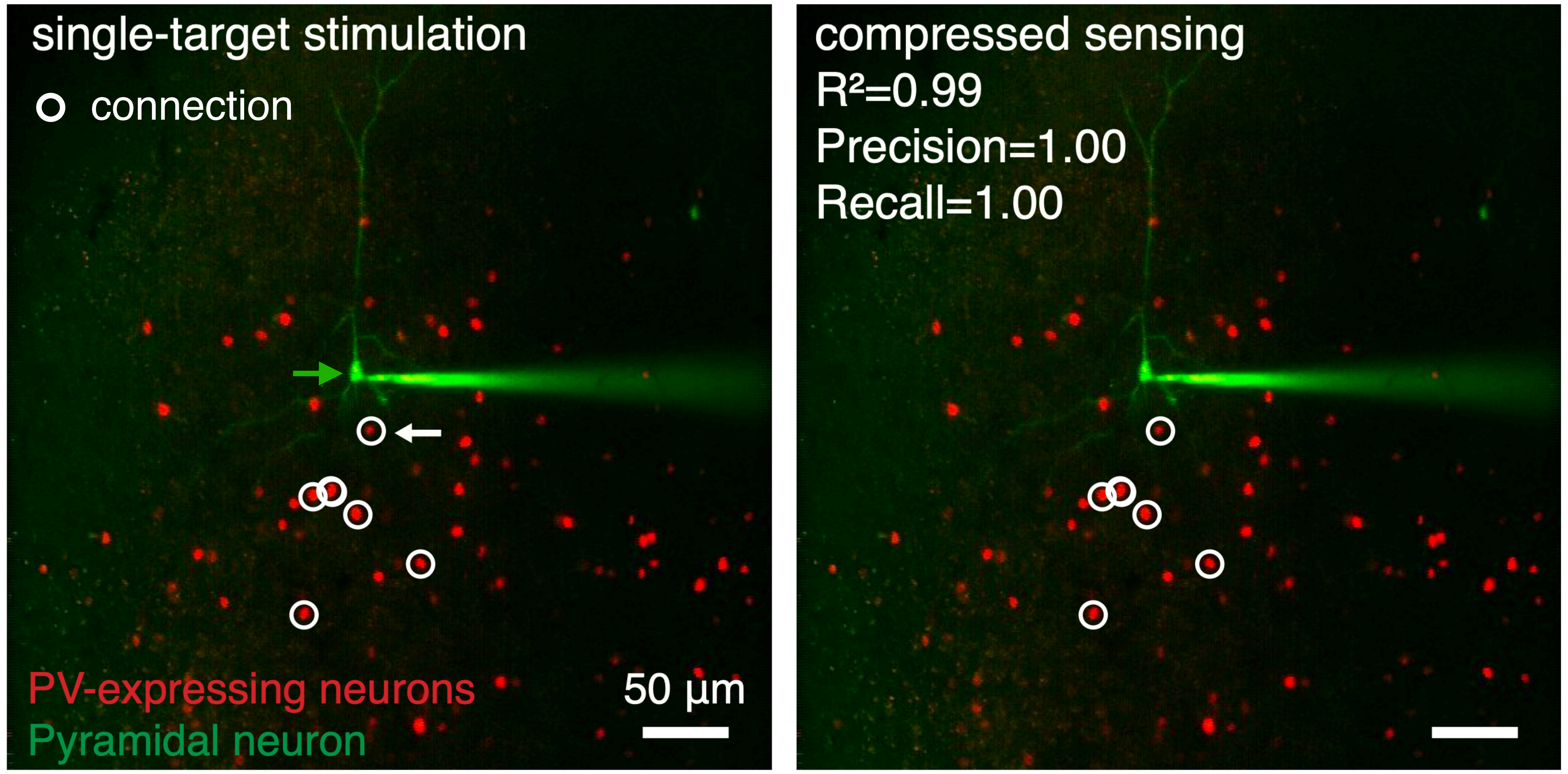

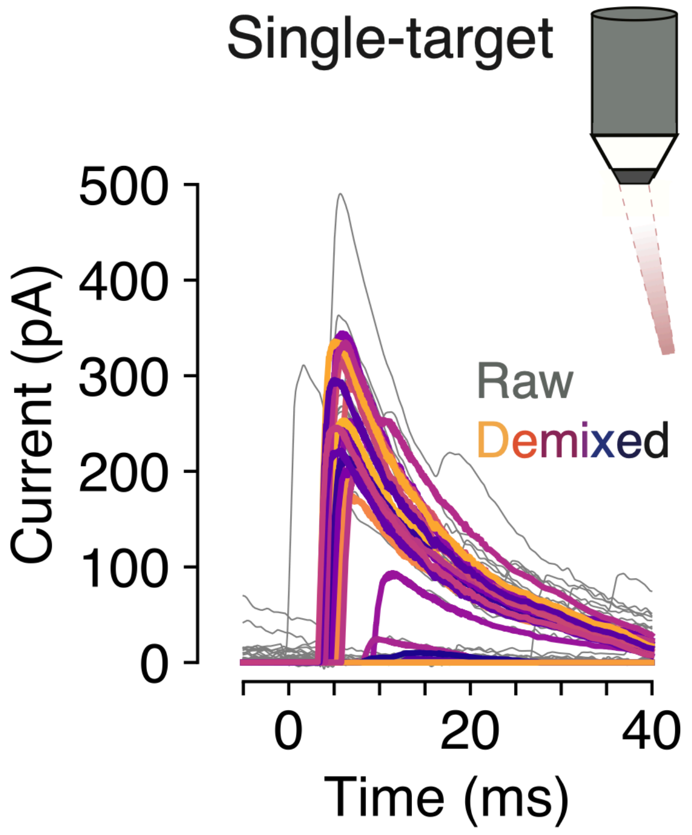

Precision: % found connections that are true

Recall: % true connections found

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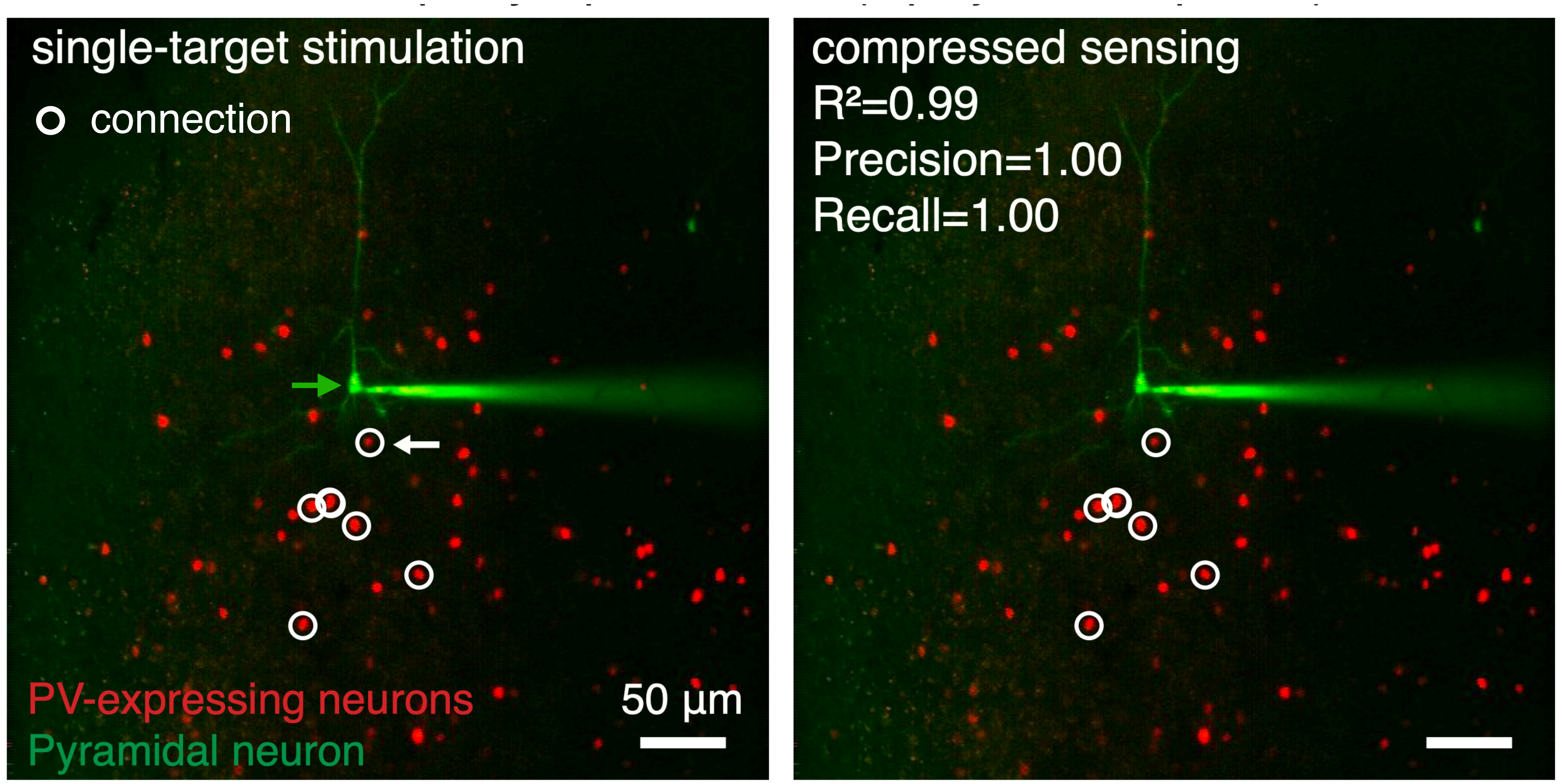

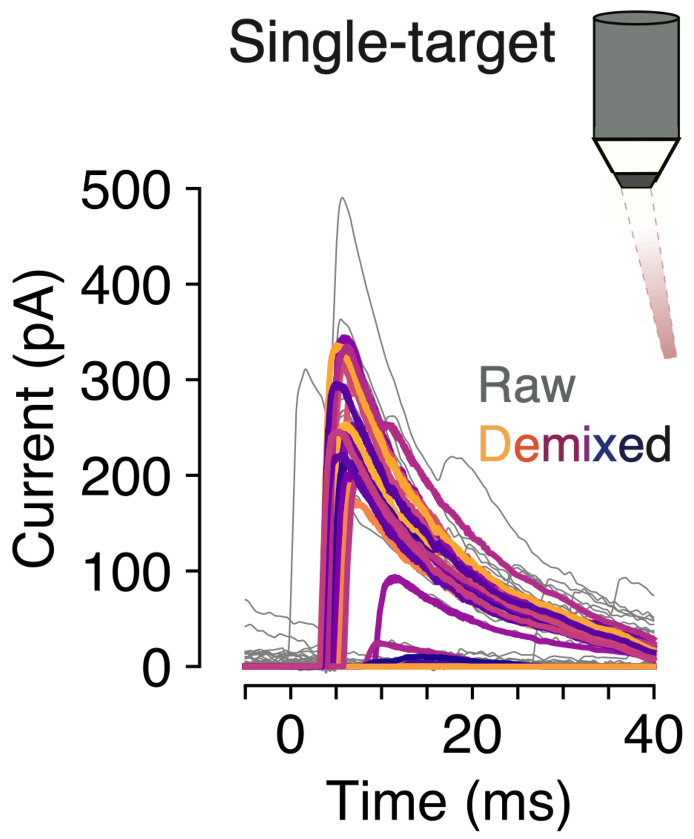

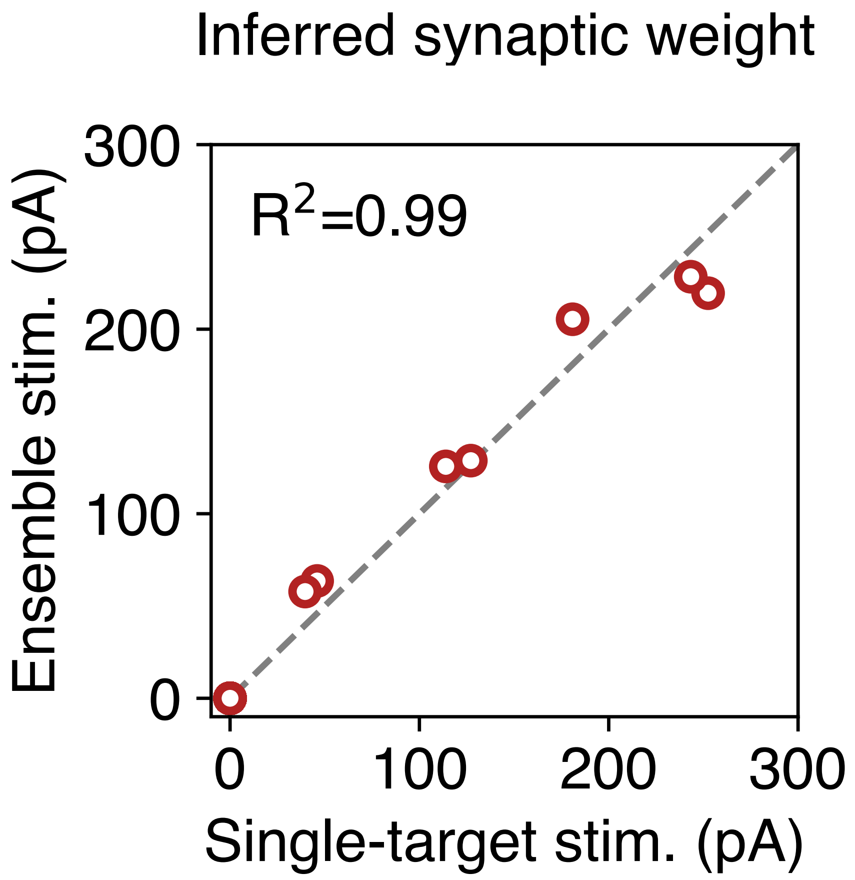

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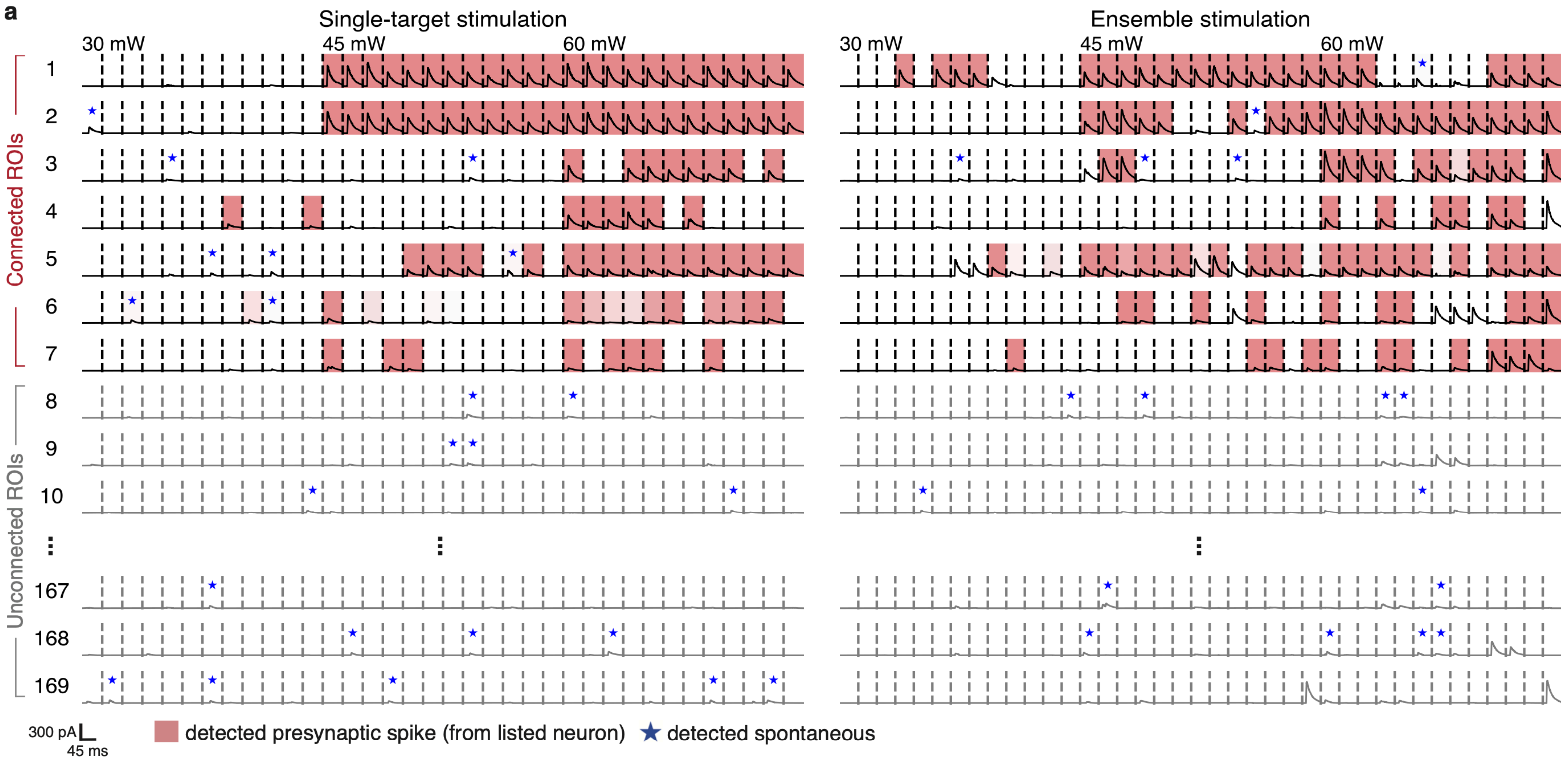
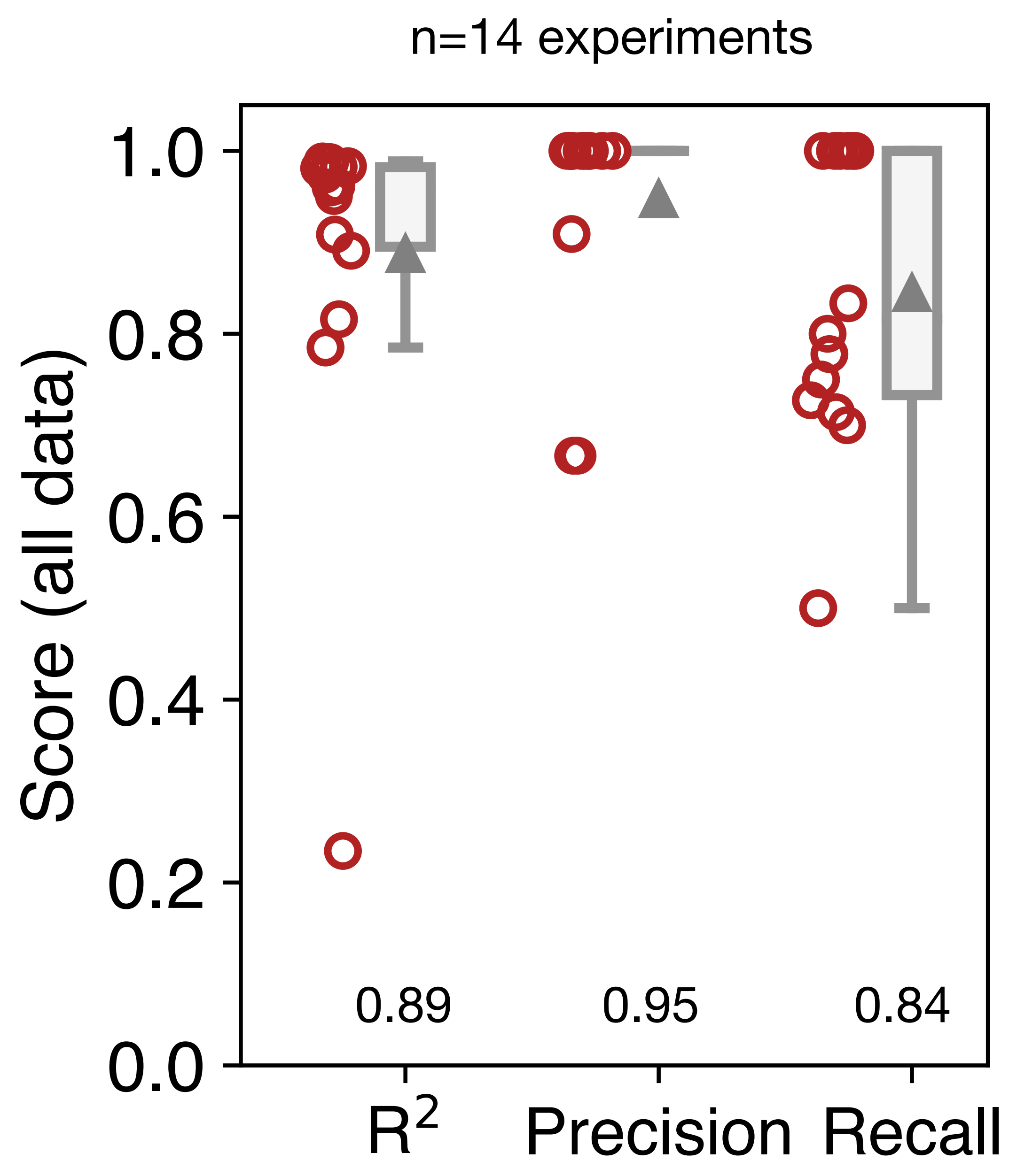
“Checkerboard” visualization



CAVIaR achieves high accuracy across experiments



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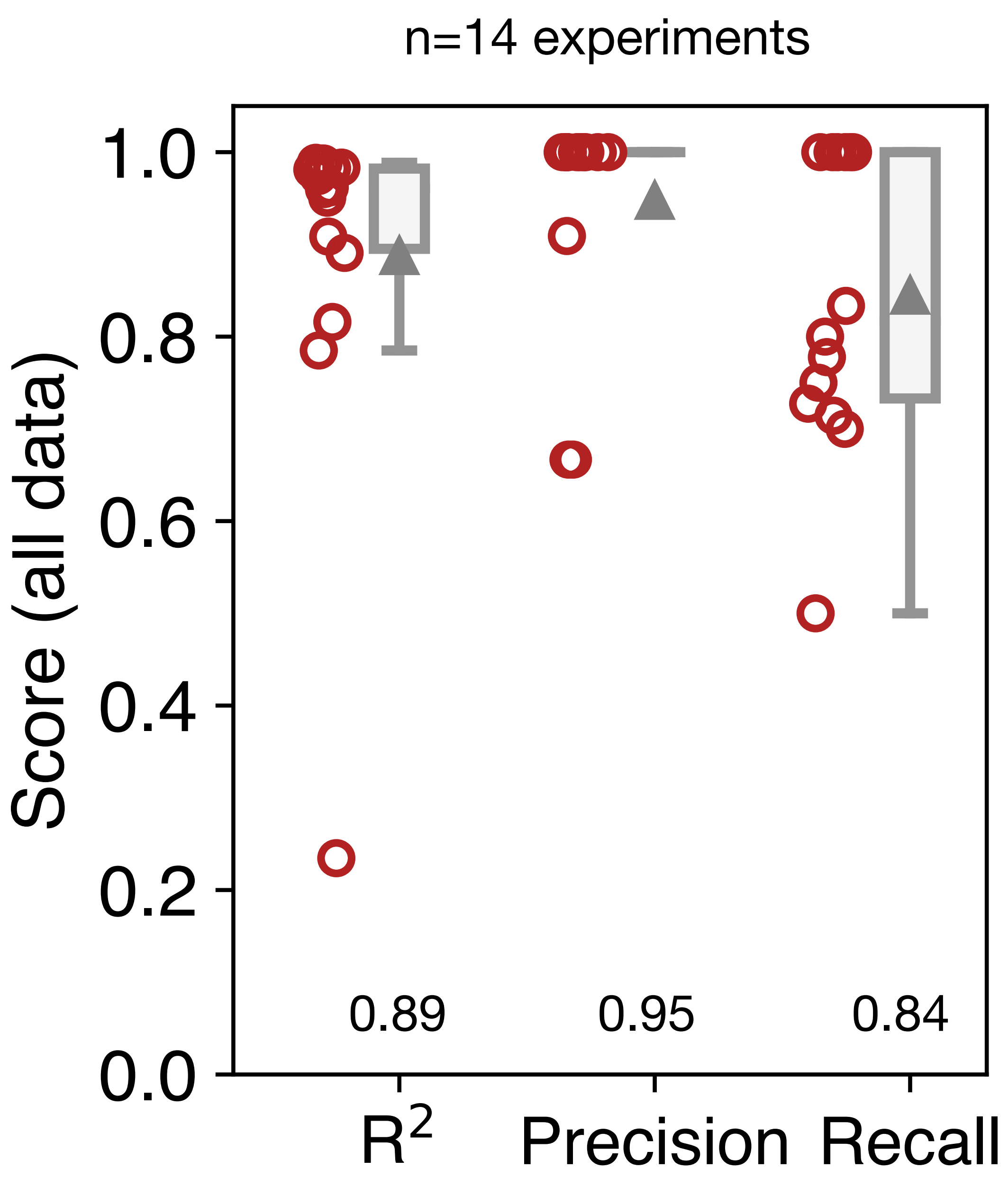

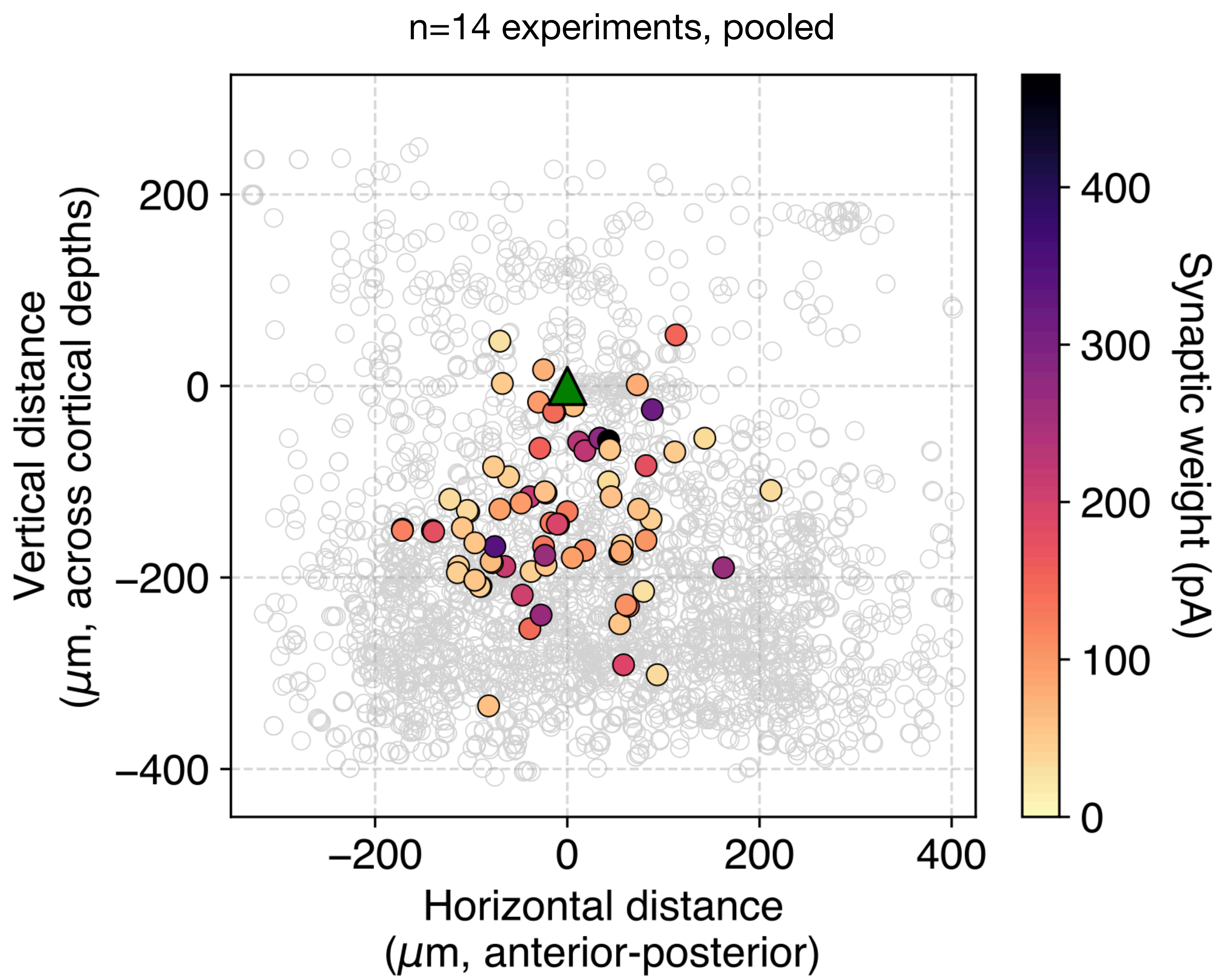

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Triplett*, Gajowa* et. al. (2023), *bioRxiv*

A critical test

Predicting responses to novel holograms

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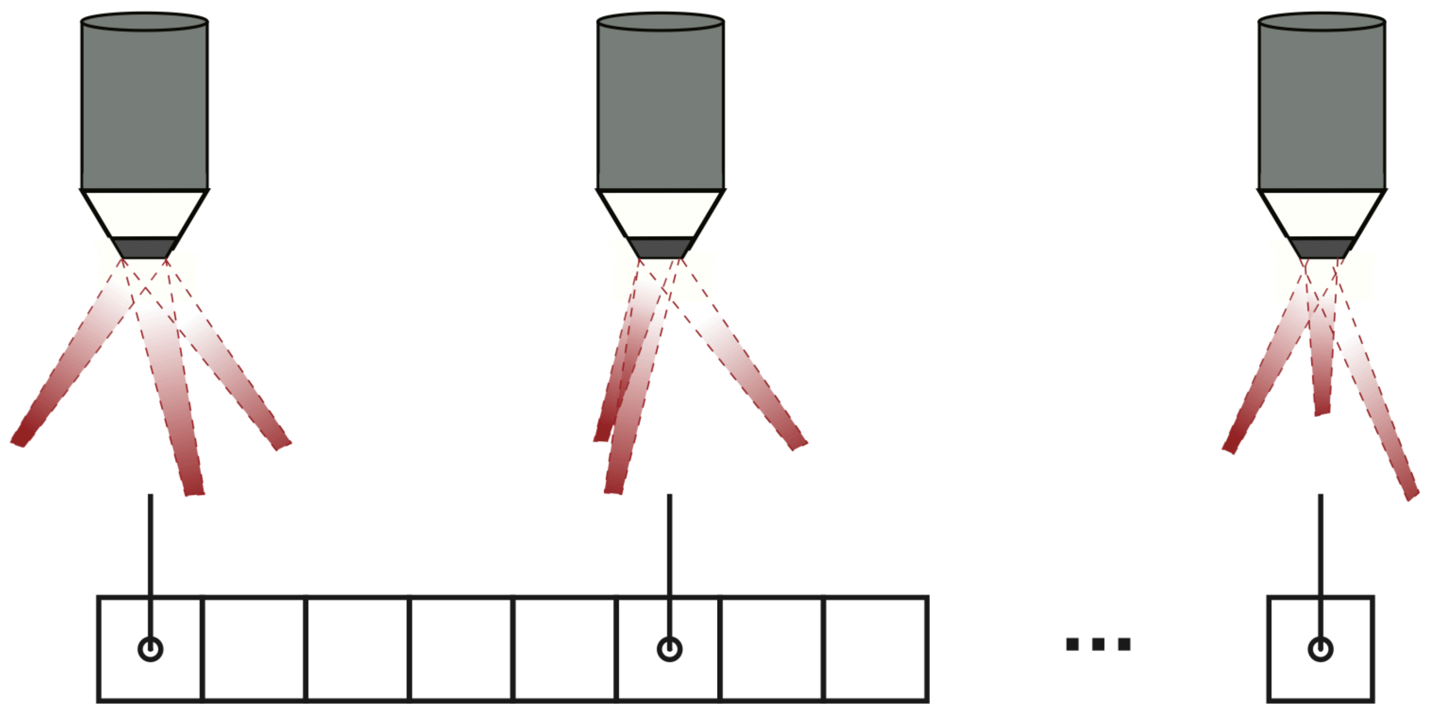
A critical test

Predicting responses to novel holograms

“Leave-one-hologram-out” cross-validation
(LOHO-CV)



H–1 holograms

Infer synaptic connectivity

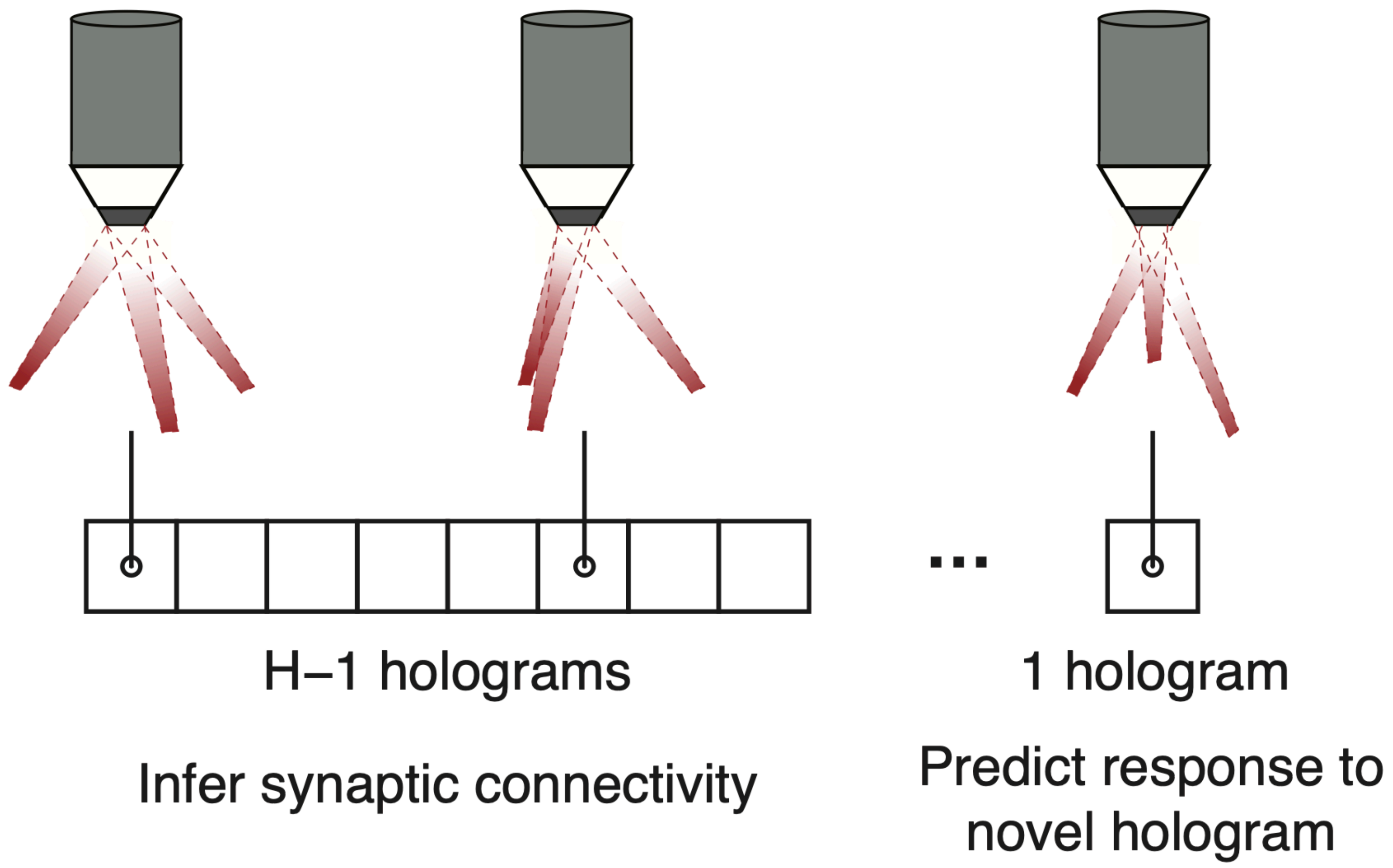
1 hologram

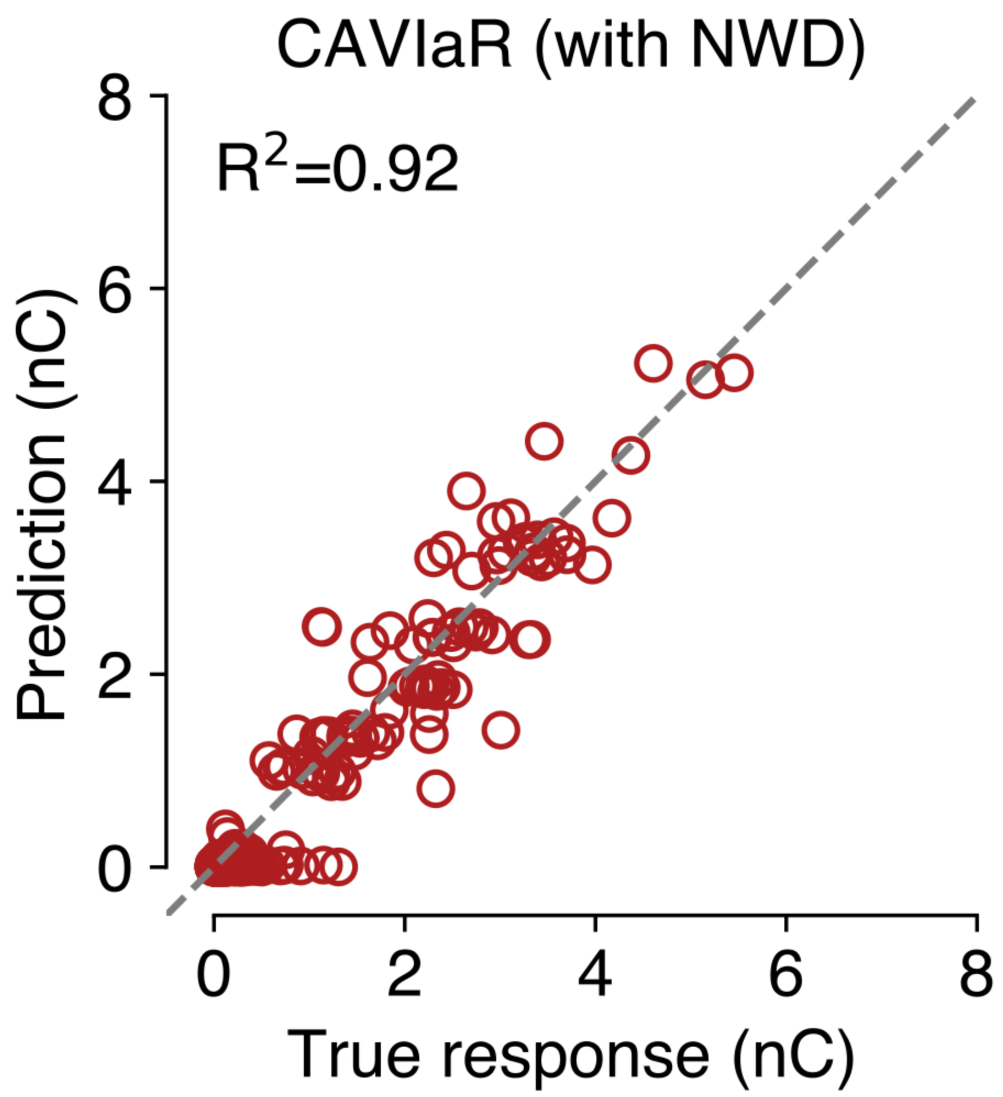
Predict response to
novel hologram

A critical test

Predicting responses to novel holograms

“Leave-one-hologram-out” cross-validation (LOHO-CV)





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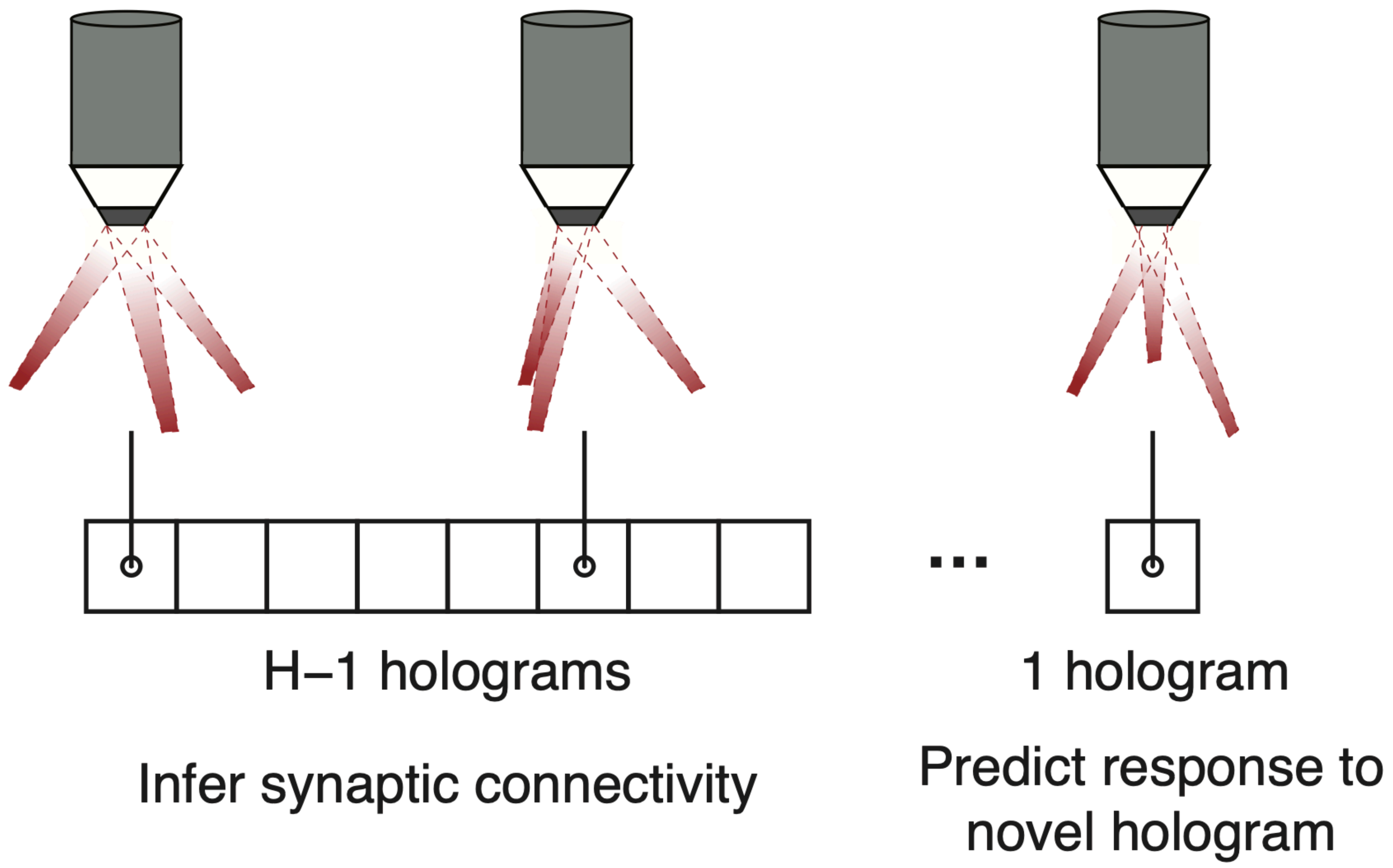
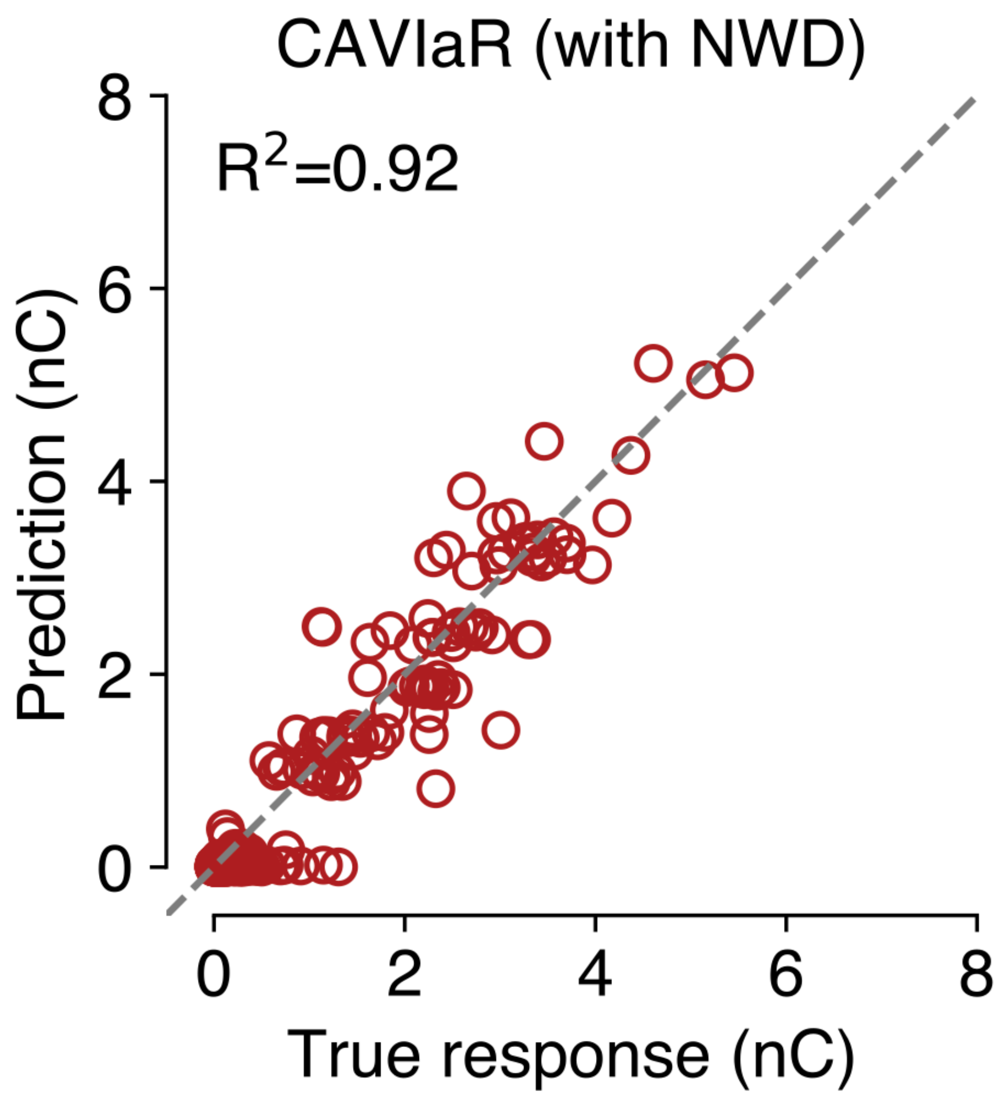
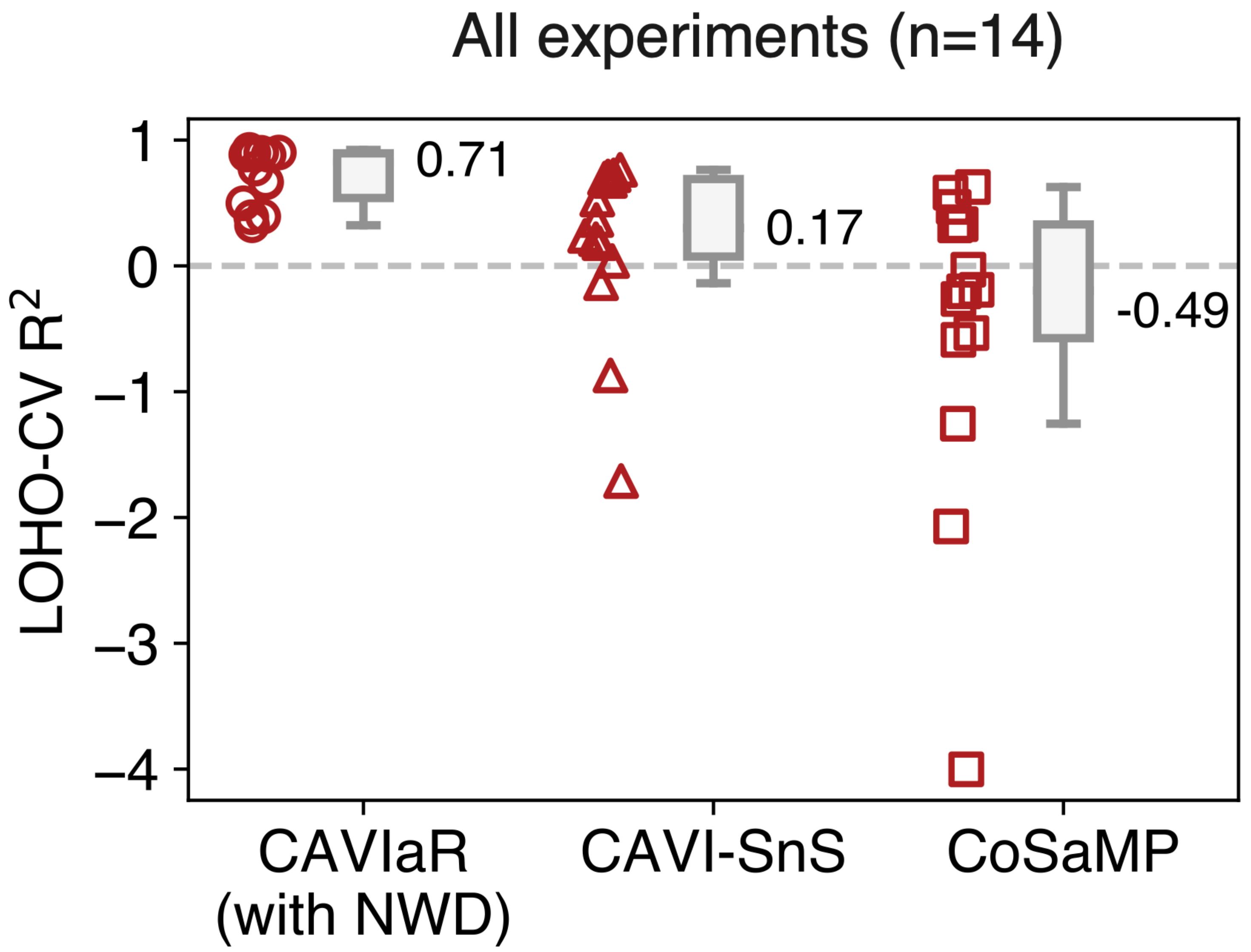
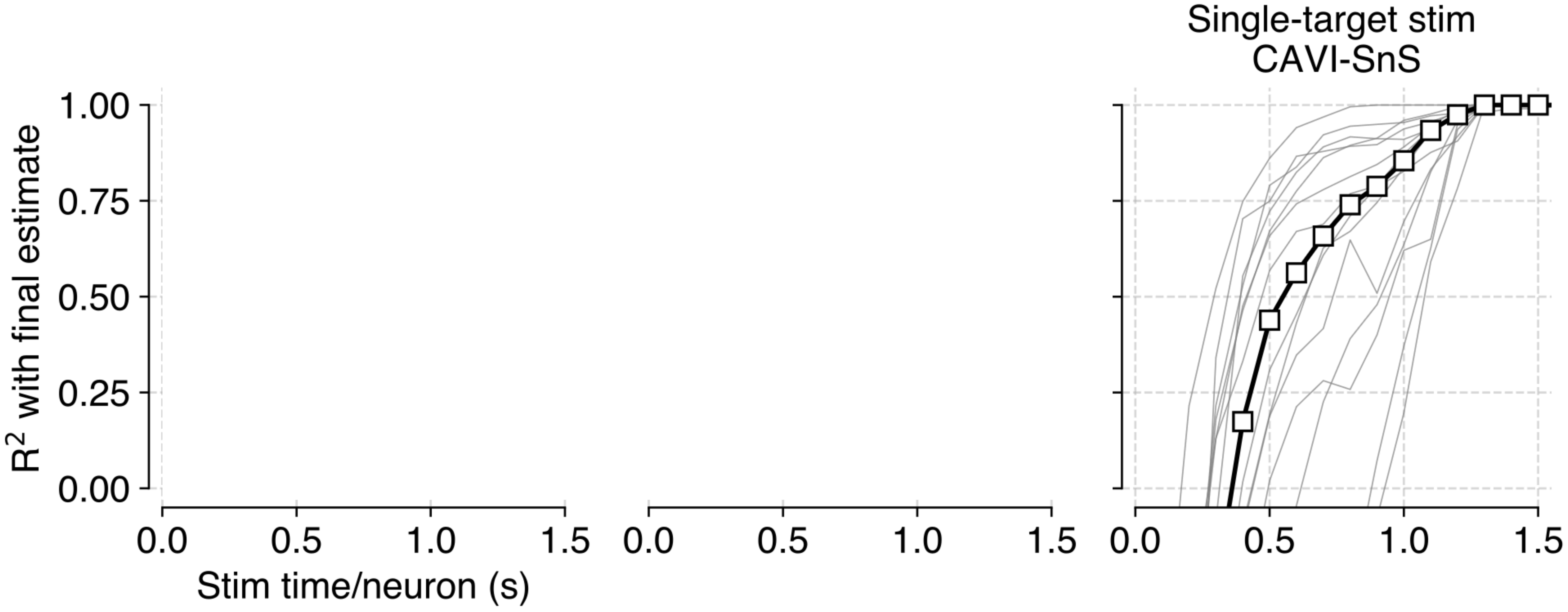




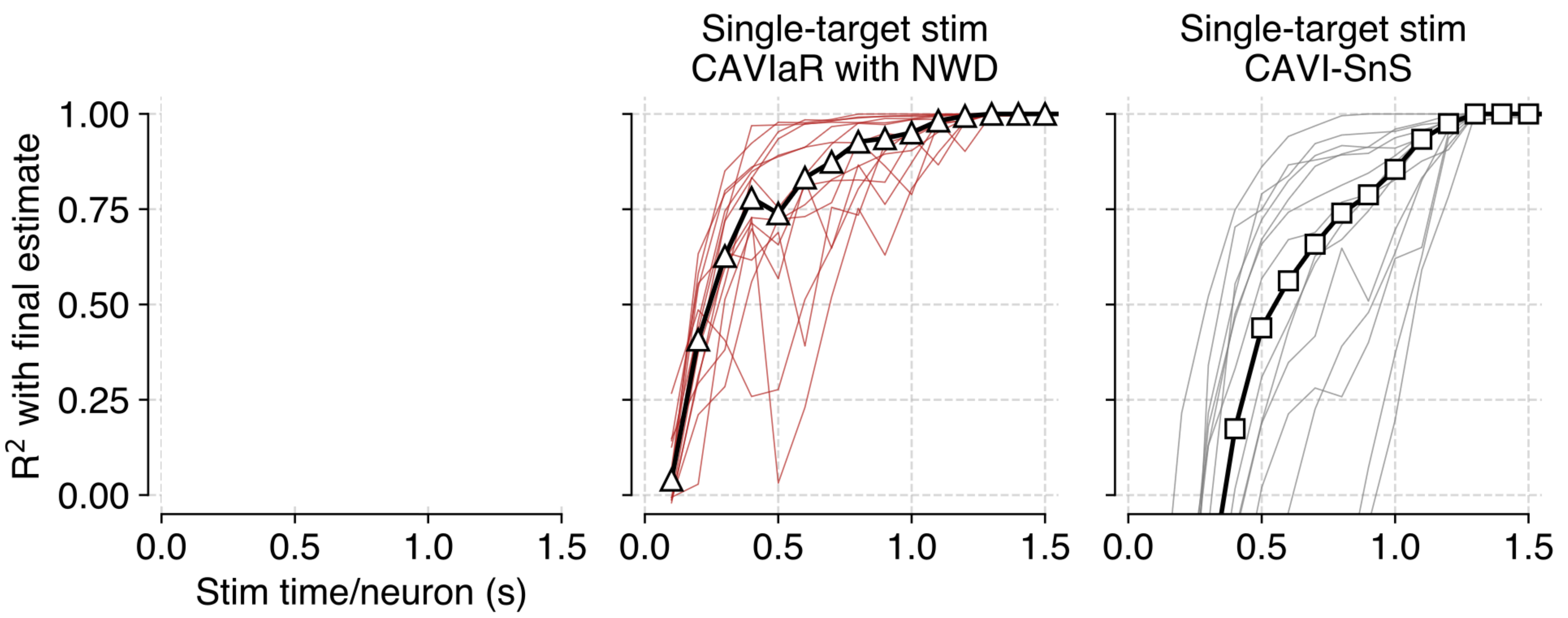


CAVIaR converges rapidly in real experiments



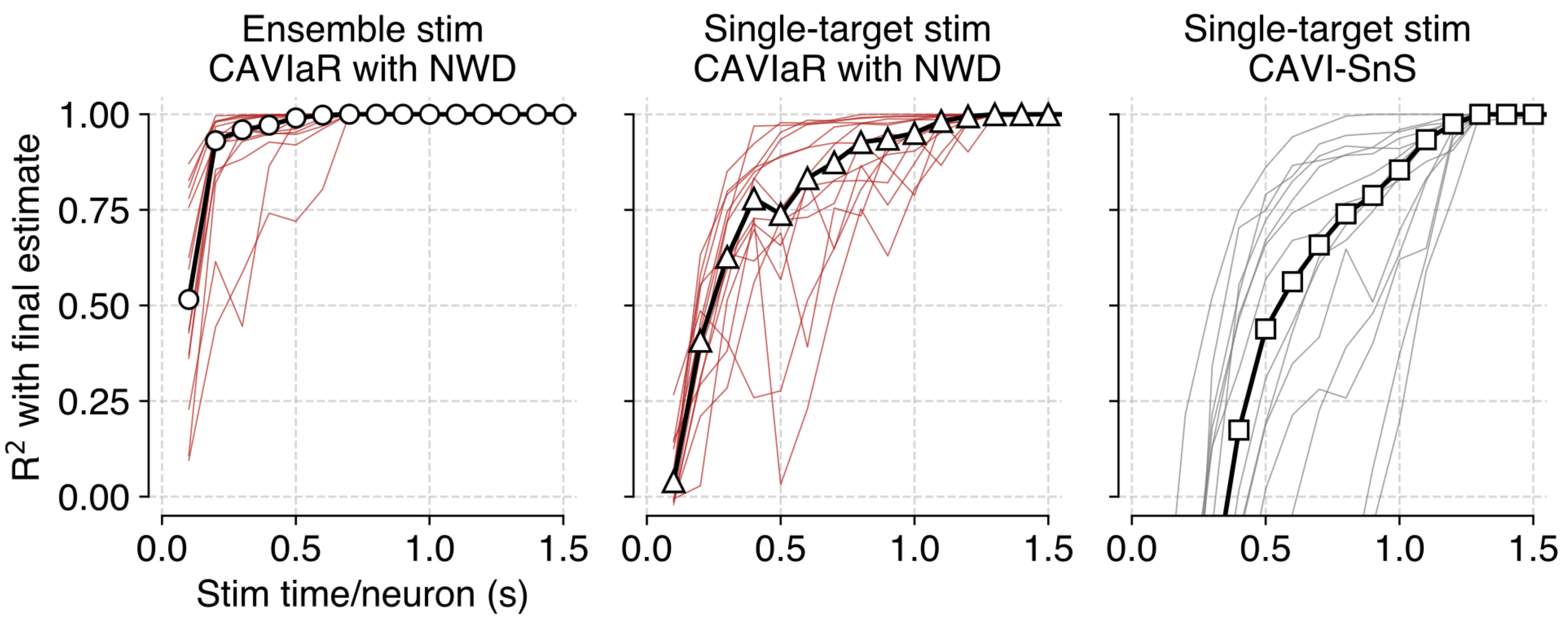
Convergence time: 1100 ms / neuron

CAVIaR converges rapidly in real experiments



Convergence time: 800 ms / neuron 1100 ms / neuron

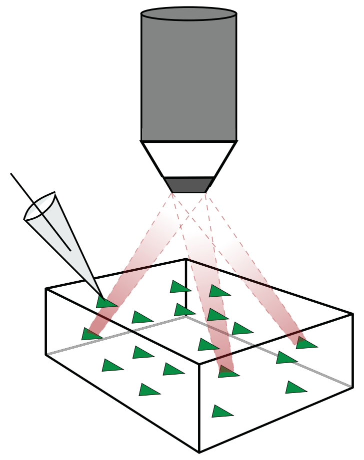
CAVIaR converges rapidly in real experiments

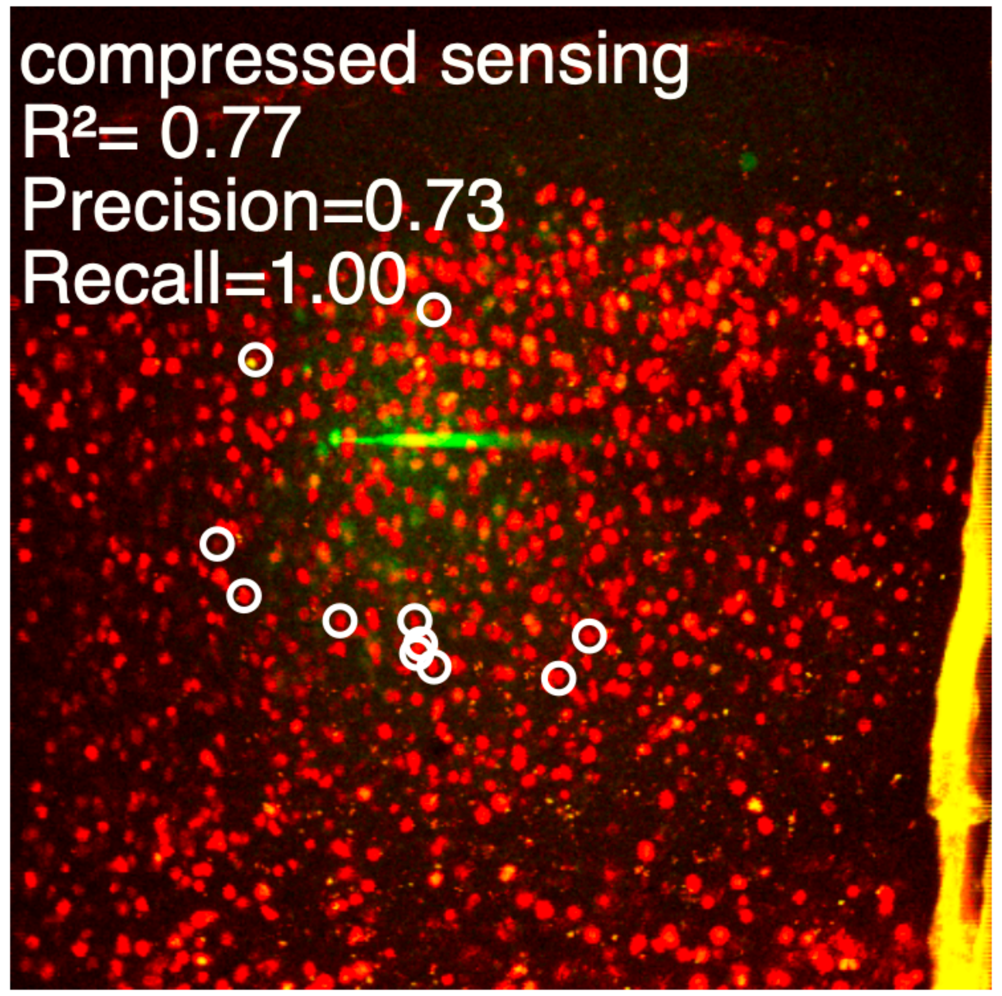


Convergence time: 200 ms / neuron 800 ms / neuron 1100 ms / neuron

An important application: mapping multiple cell types

Presynaptic: **pyramidal**
Postsynaptic: **pyramidal**





Triplett*, Gajowa* et. al. (2023), *bioRxiv*

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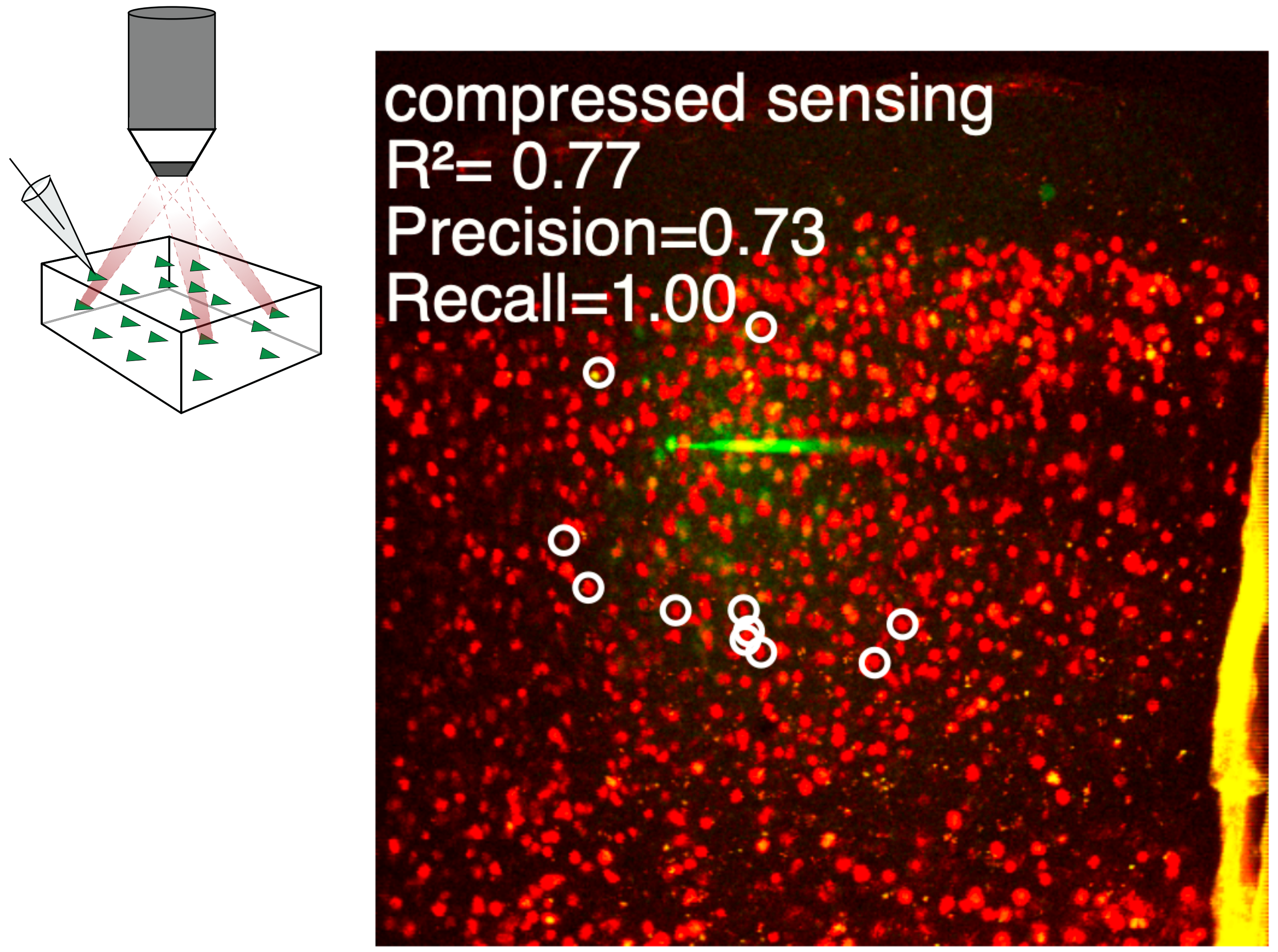

Presynaptic: **pyramidal**
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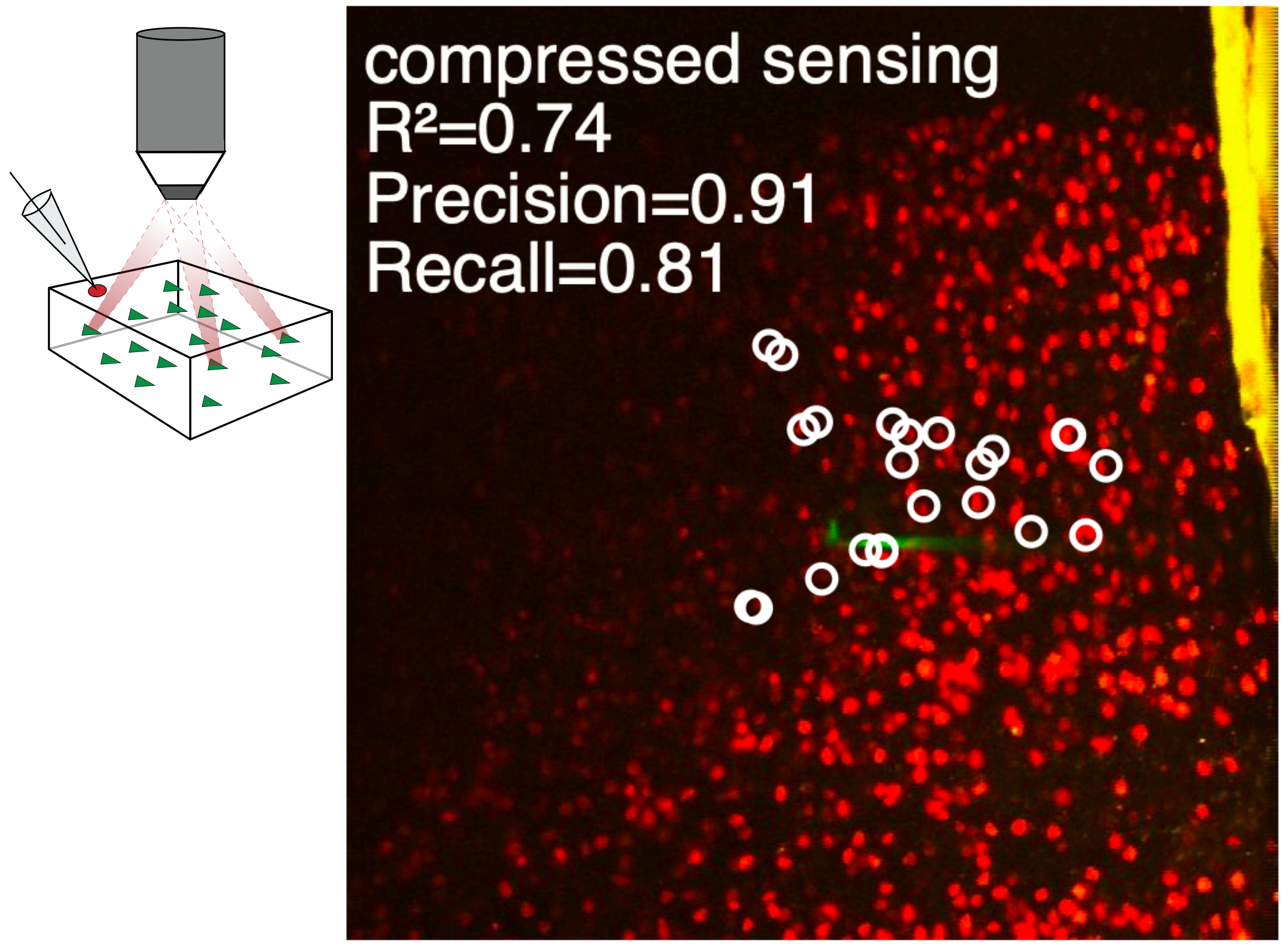

Triplett*, Gajowa* et. al. (2023), *bioRxiv*

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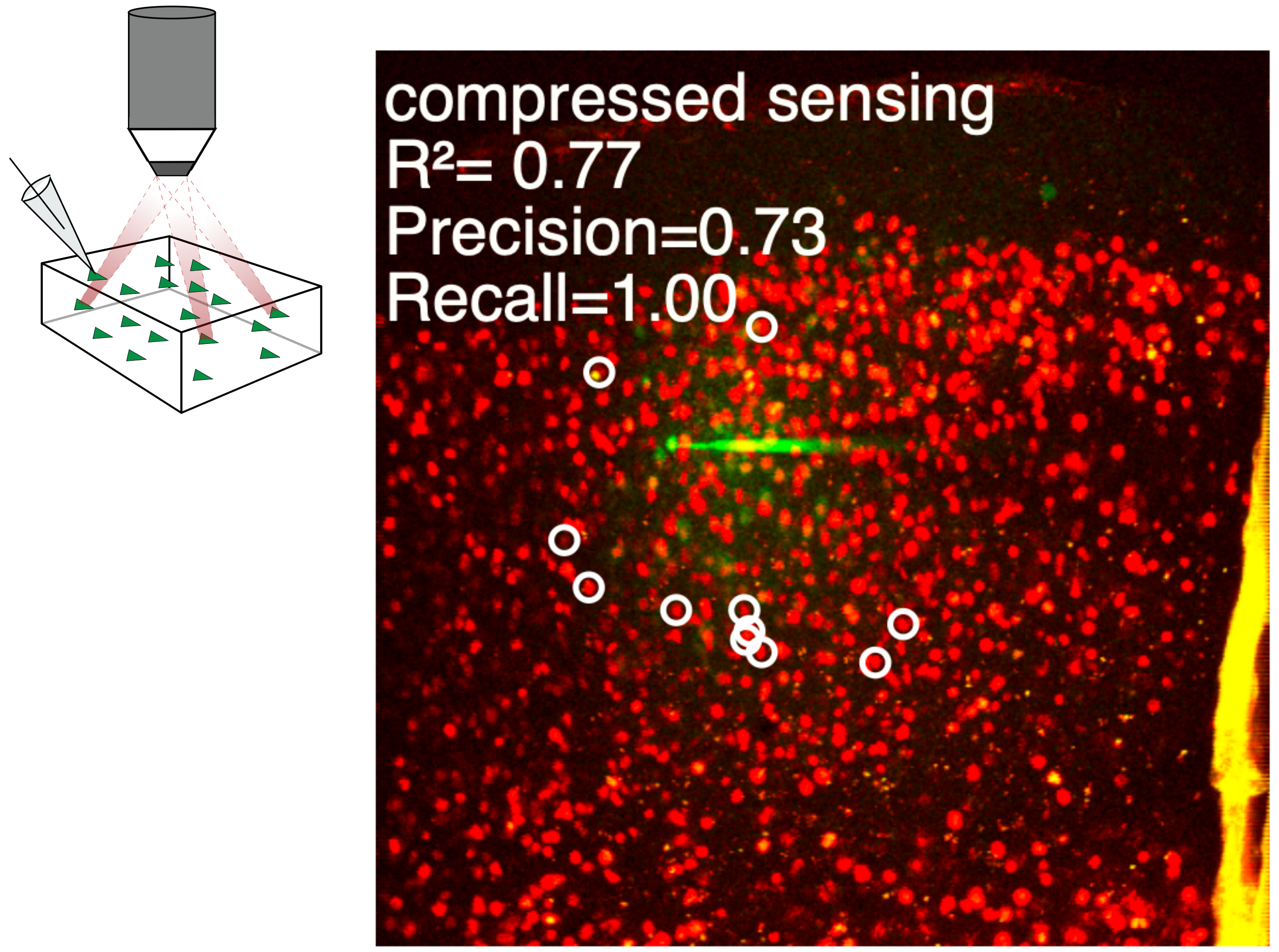

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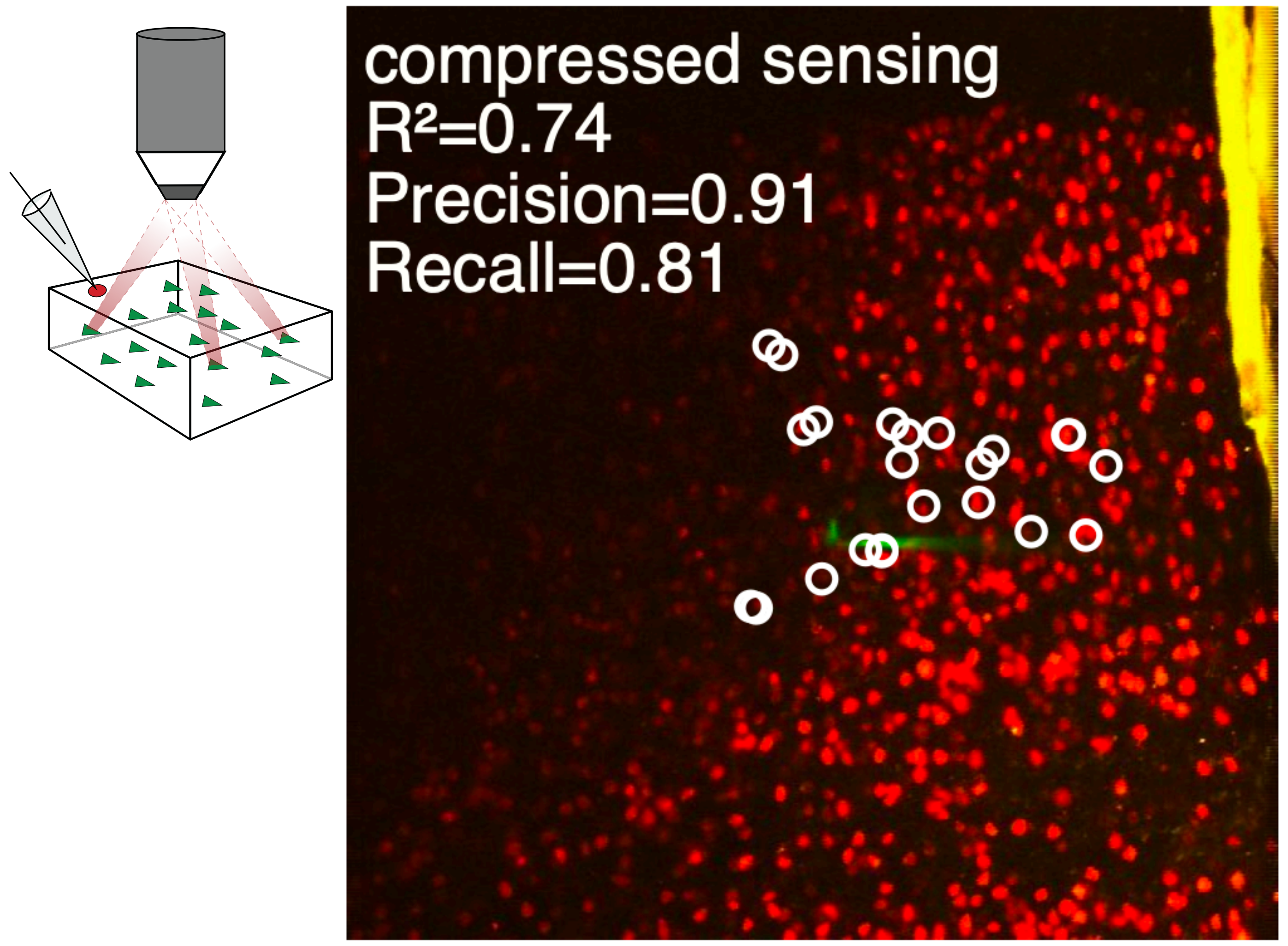
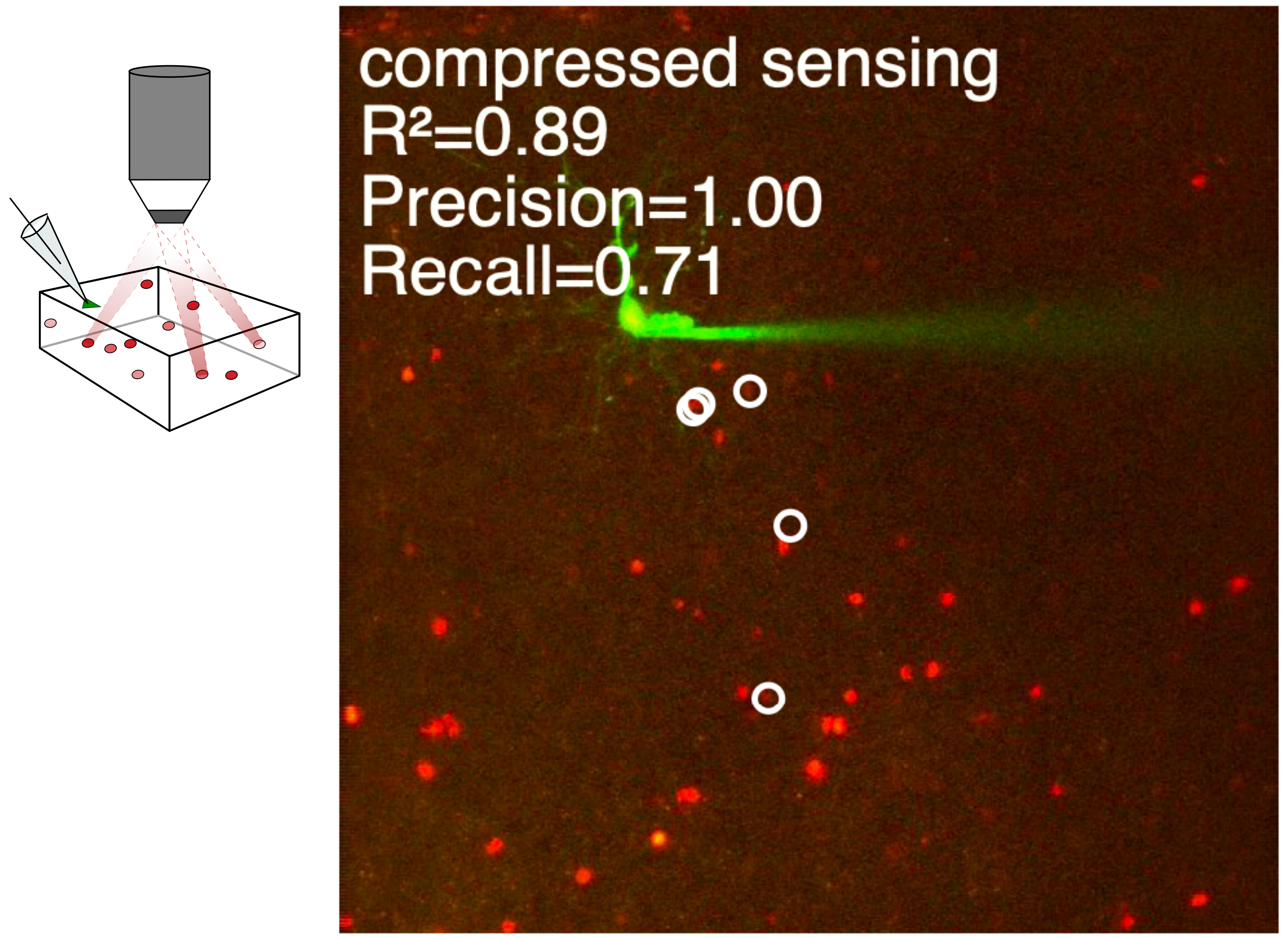
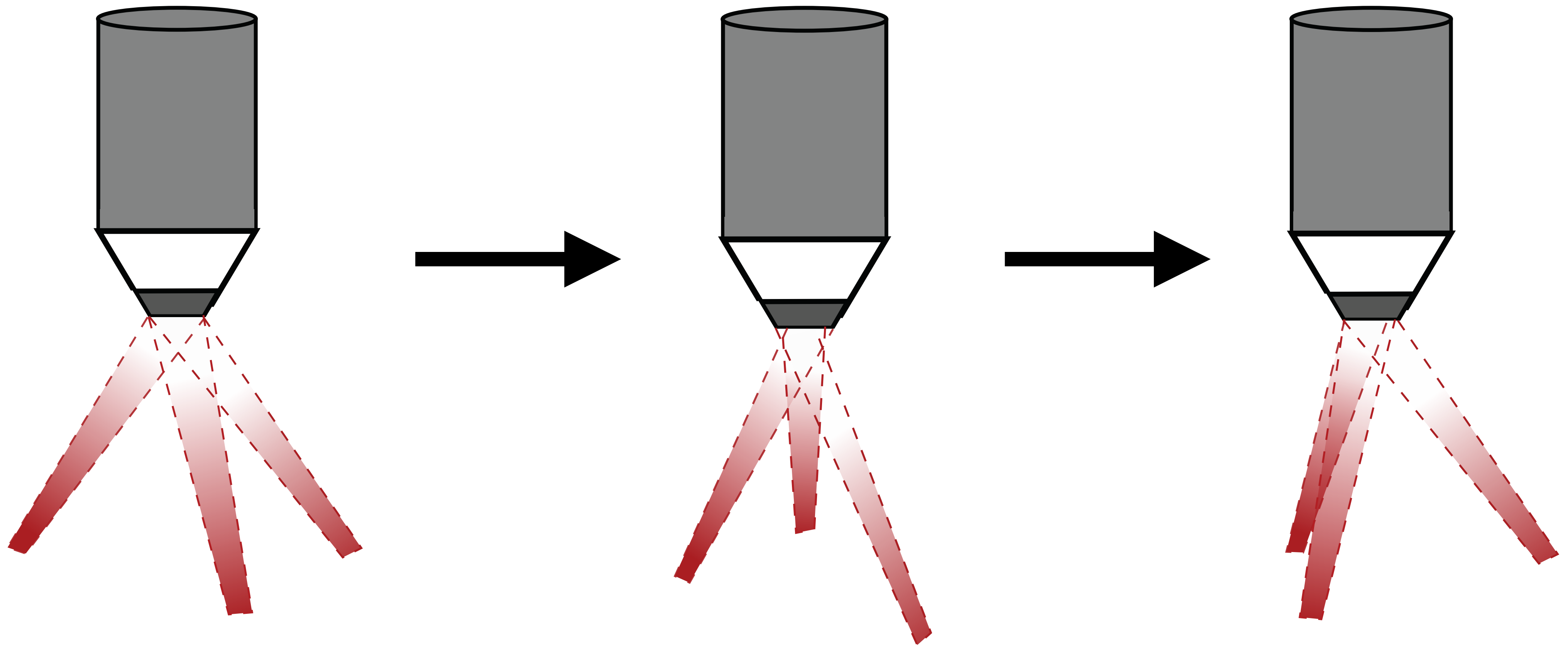


Presynaptic: **SST+**
Postsynaptic: **pyramidal**



Triplett*, Gajowa* et. al. (2023), *bioRxiv*

Proposed approach



1. ~~Speed up mapping by stimulating **quickly**~~

2. Use holographic optogenetics to stimulate **ensembles**

   Exploit sparsity by performing **compressed sensing**

Hu & Chklovskii (2009), *NeurIPS*
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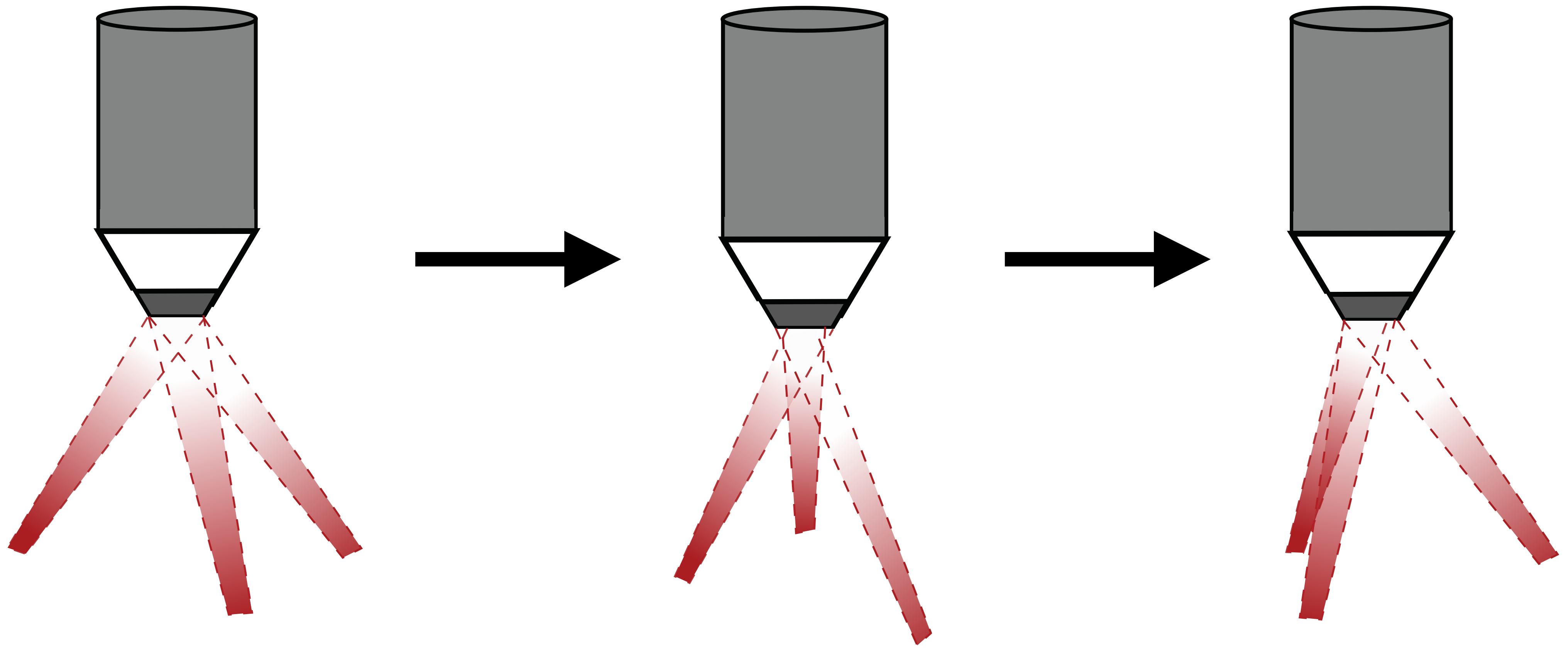

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Some future directions

A. Inference of physiological parameters (synaptic time constants, short-term plasticity, facilitating synapses)

B. Inference with variable presynaptic spike-counts

C. Connectivity mapping with calcium or voltage imaging

Acknowledgements

Columbia:

- **Liam Paninski (PI)**
- Darcy Peterka
- Benjamin Antin
- Kenneth Kay

UC Berkeley:

- **Hillel Adesnik (PI)**
- **Marta Gajowa**
- Masato Sadahiro

UCL:

- Michael Hausser (PI)
- **Edgar Baumler**

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MORTIMER B. ZUCKERMAN MIND BRAIN BEHAVIOR INSTITUTE

NIH

Funding:
NIH BRAIN K99/R00

Two challenges in neuroscience

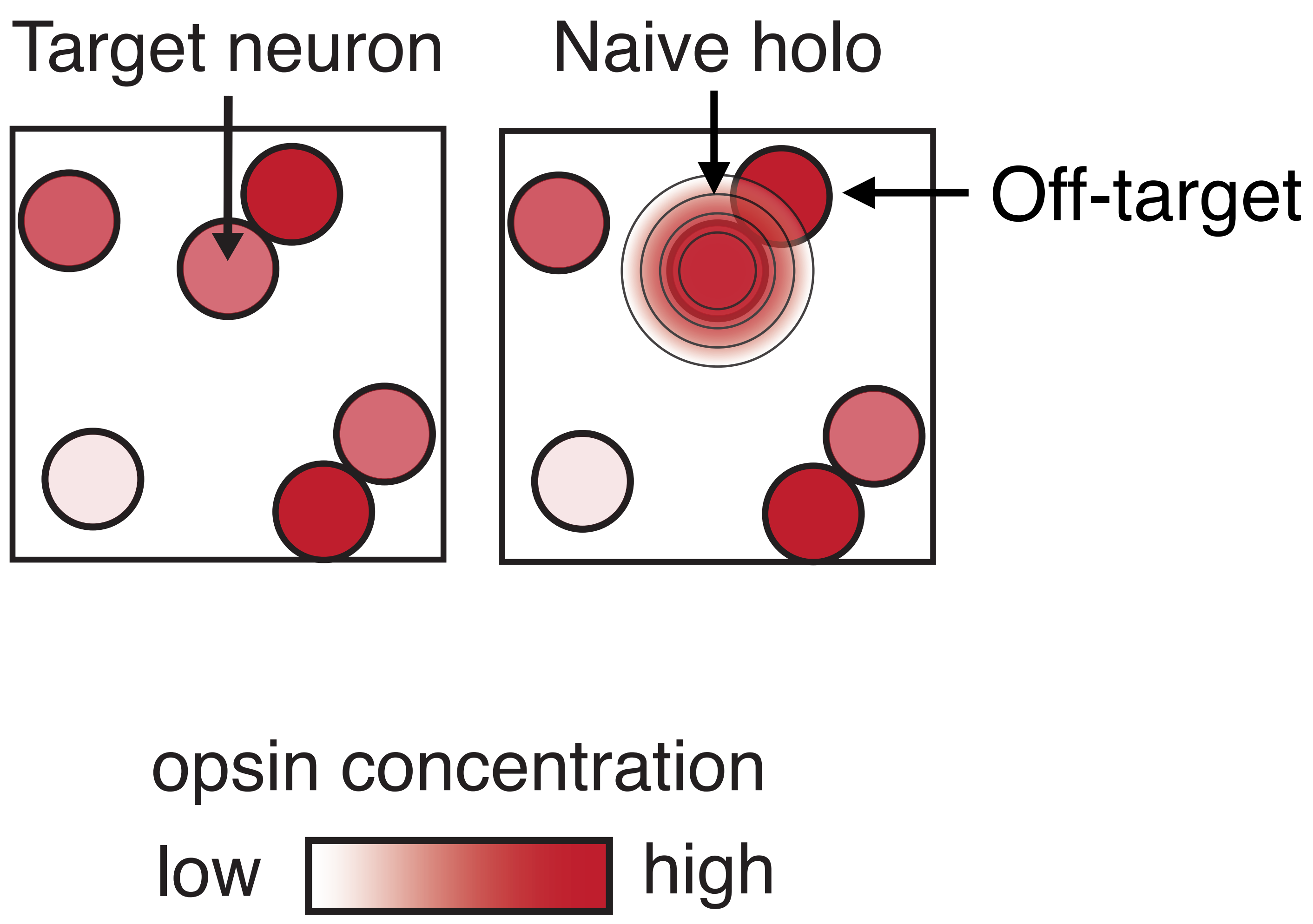
1. Connectivity mapping ◁
2. Ensemble control

Two challenges in neuroscience

1. Connectivity mapping

2. Ensemble control ◁

The problem of off-target stimulation



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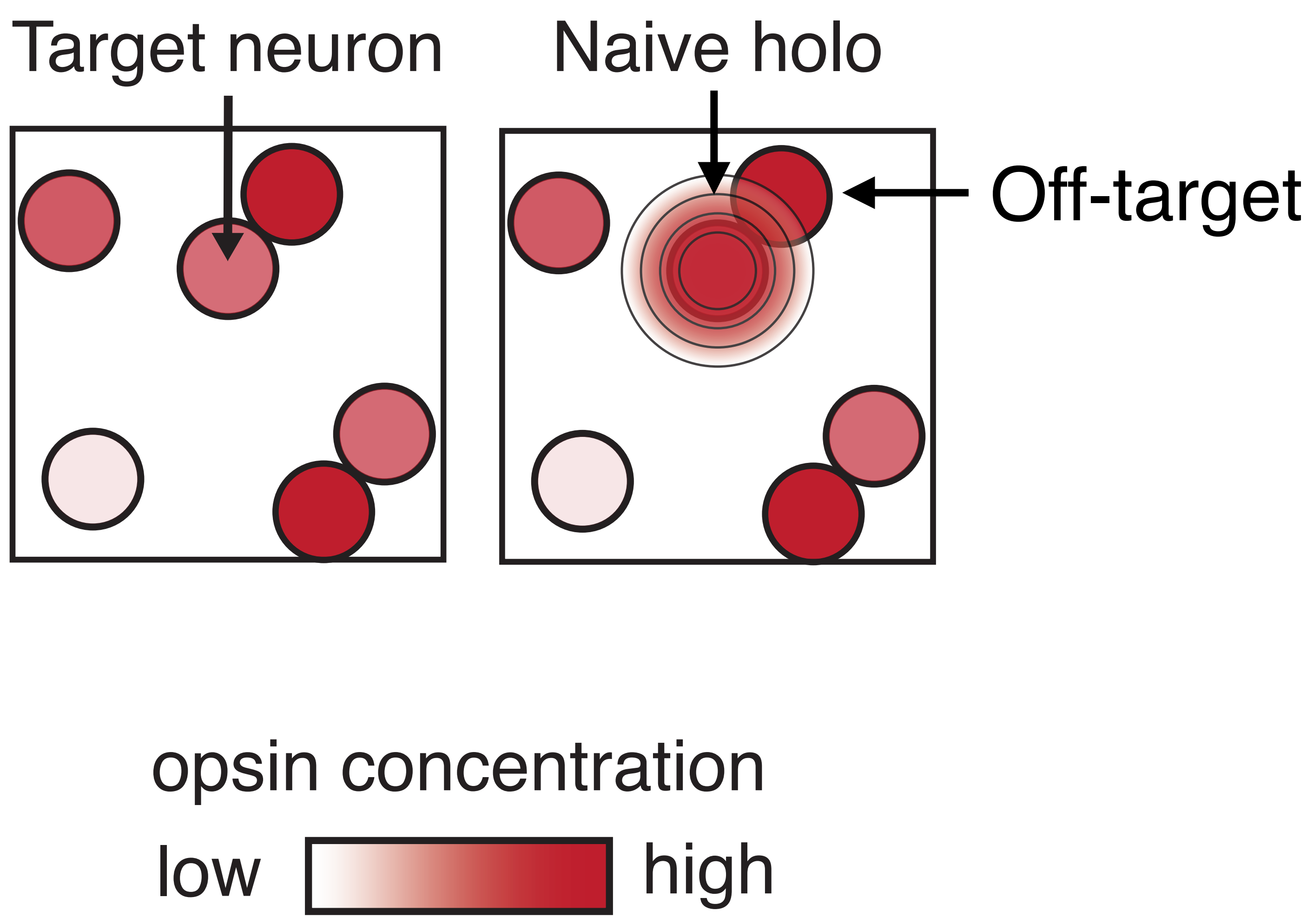

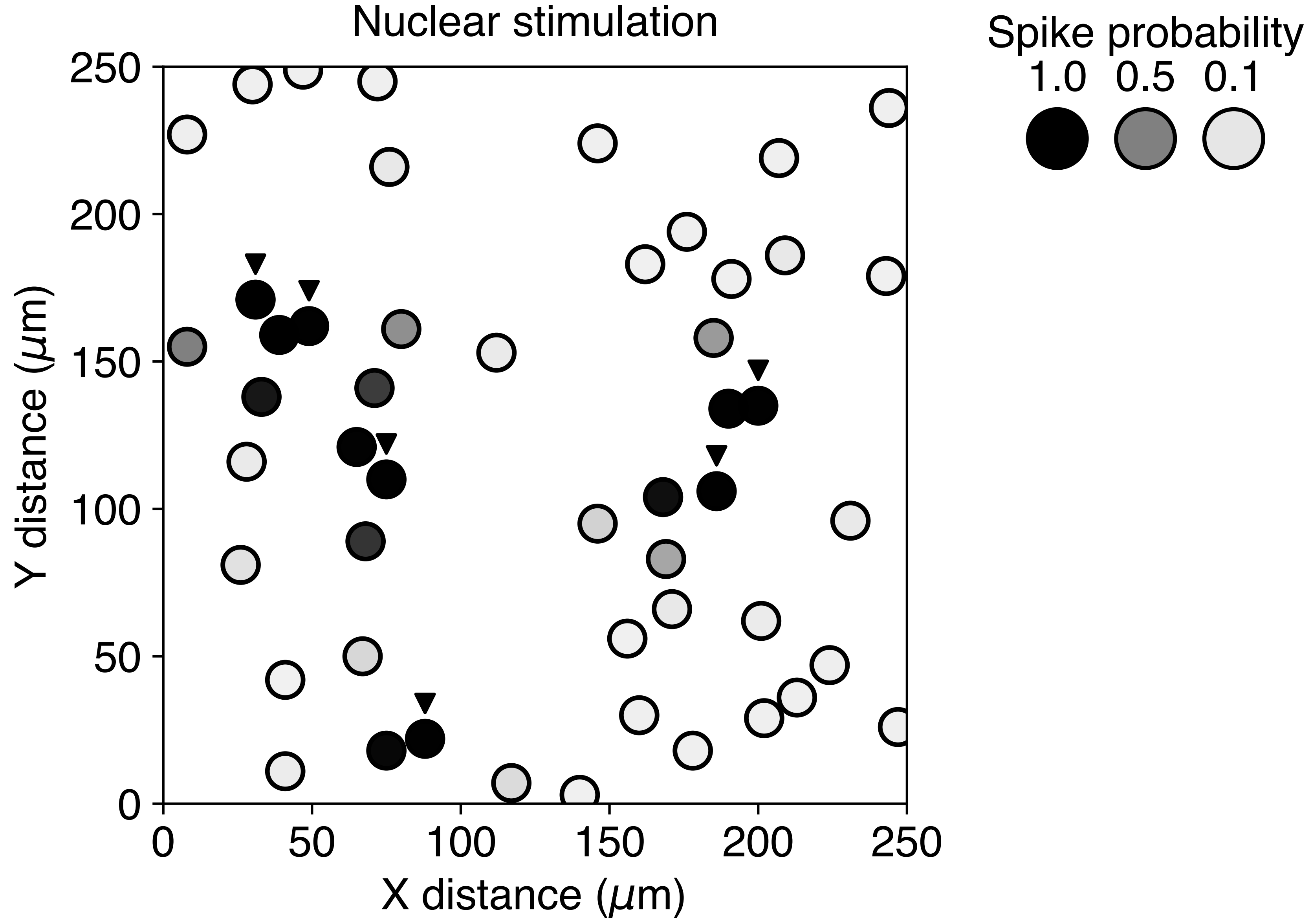

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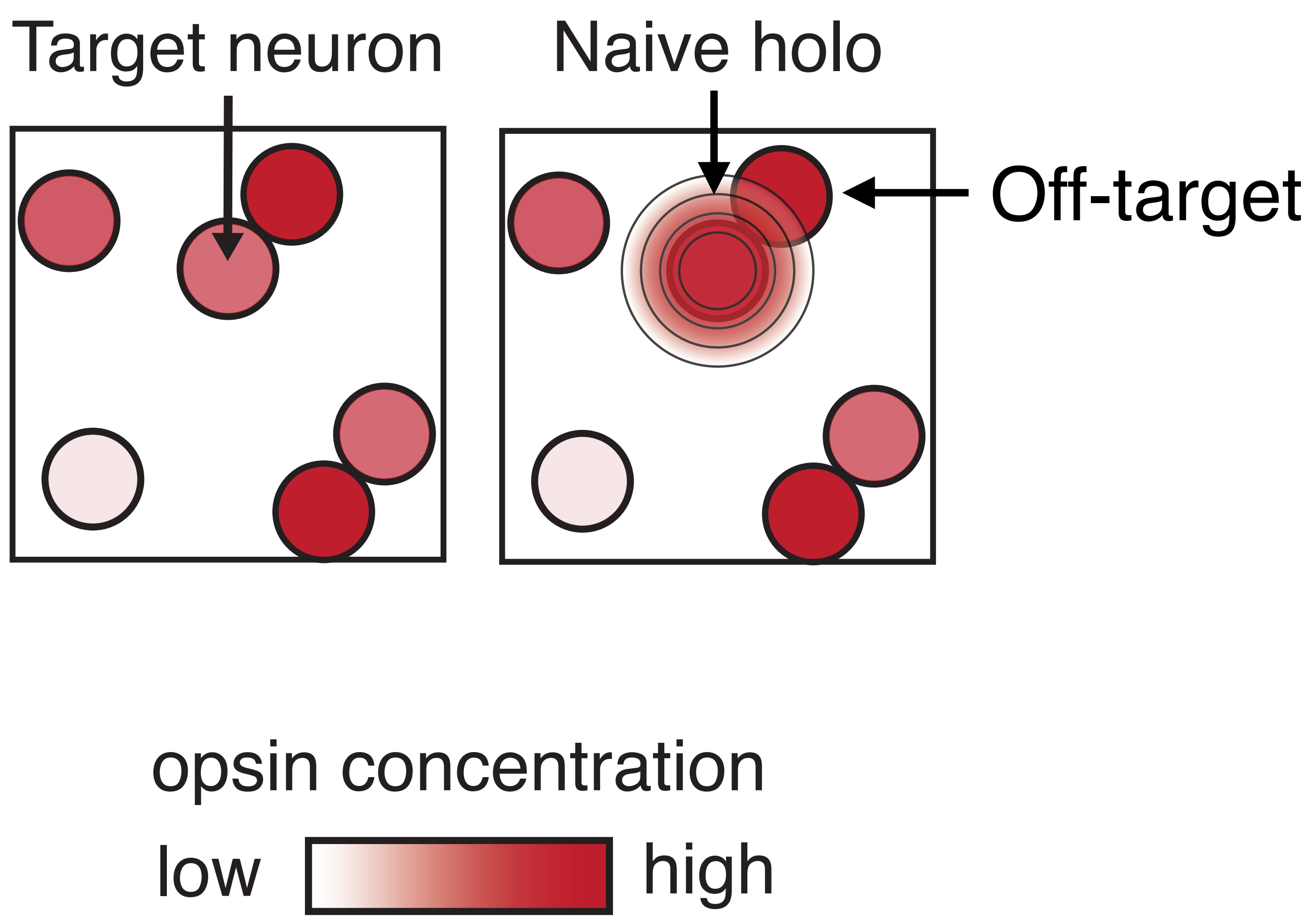
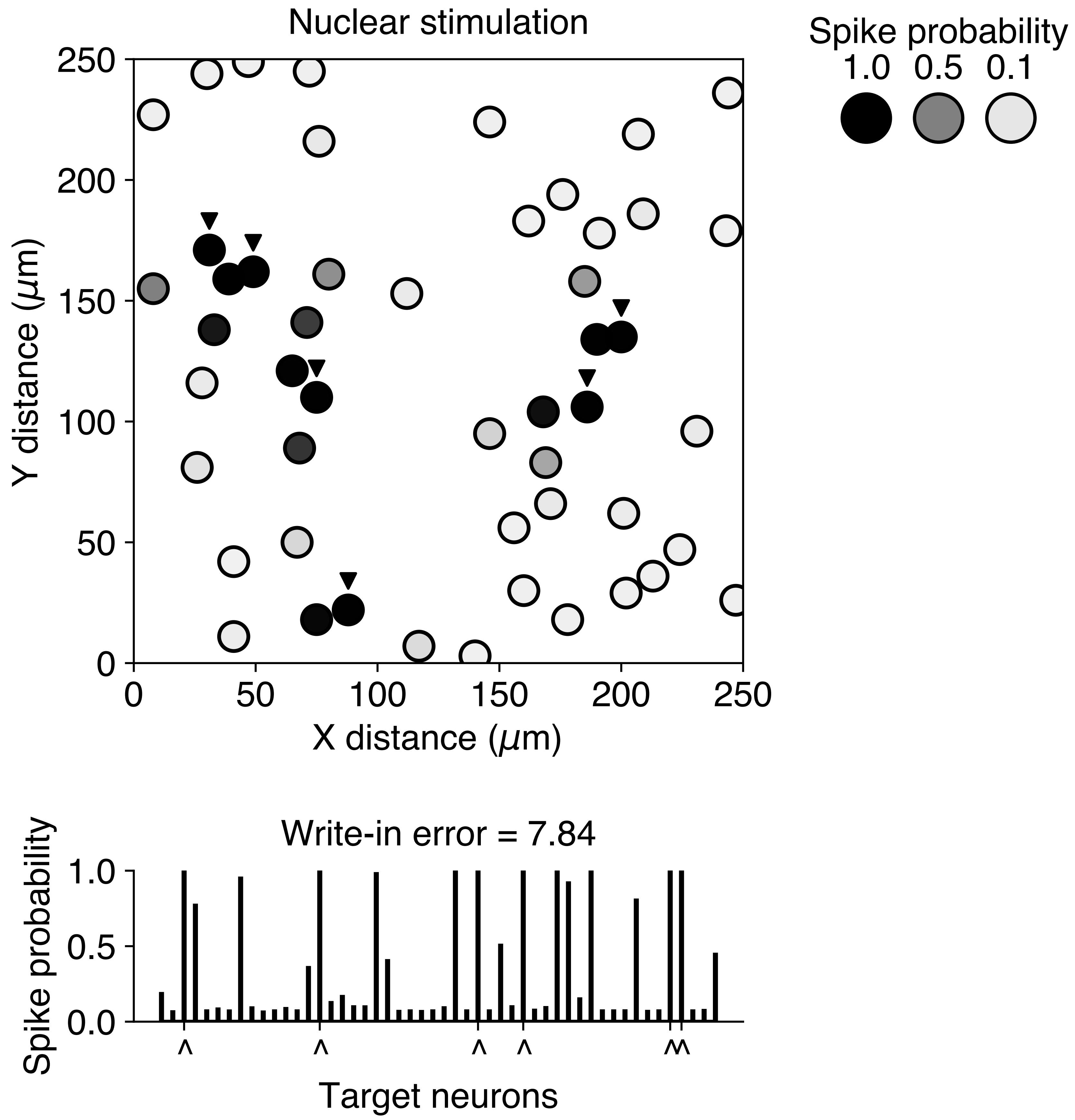
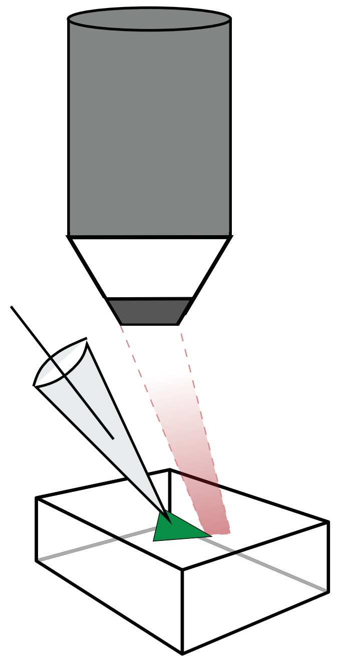
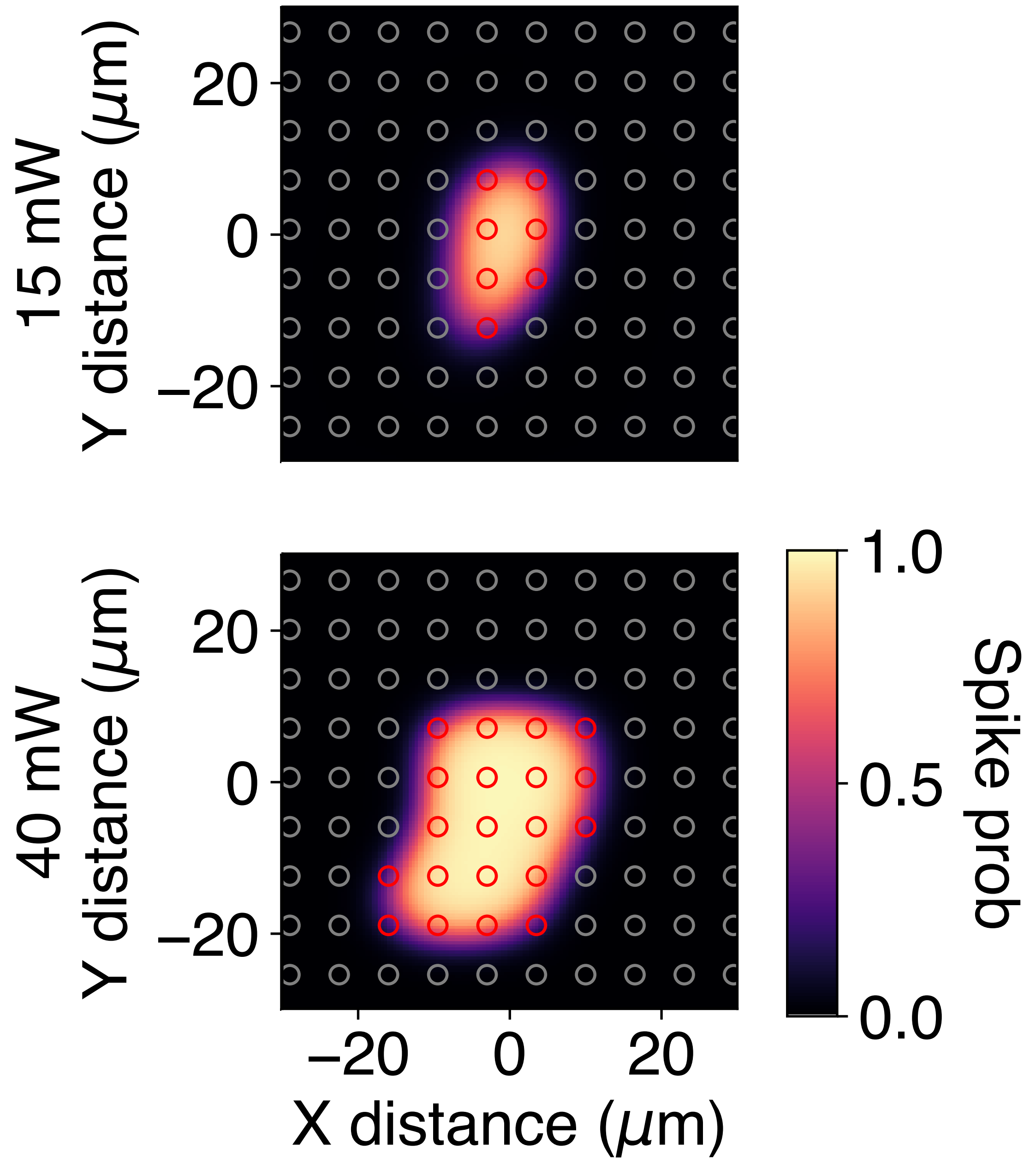




Target optimization strategies

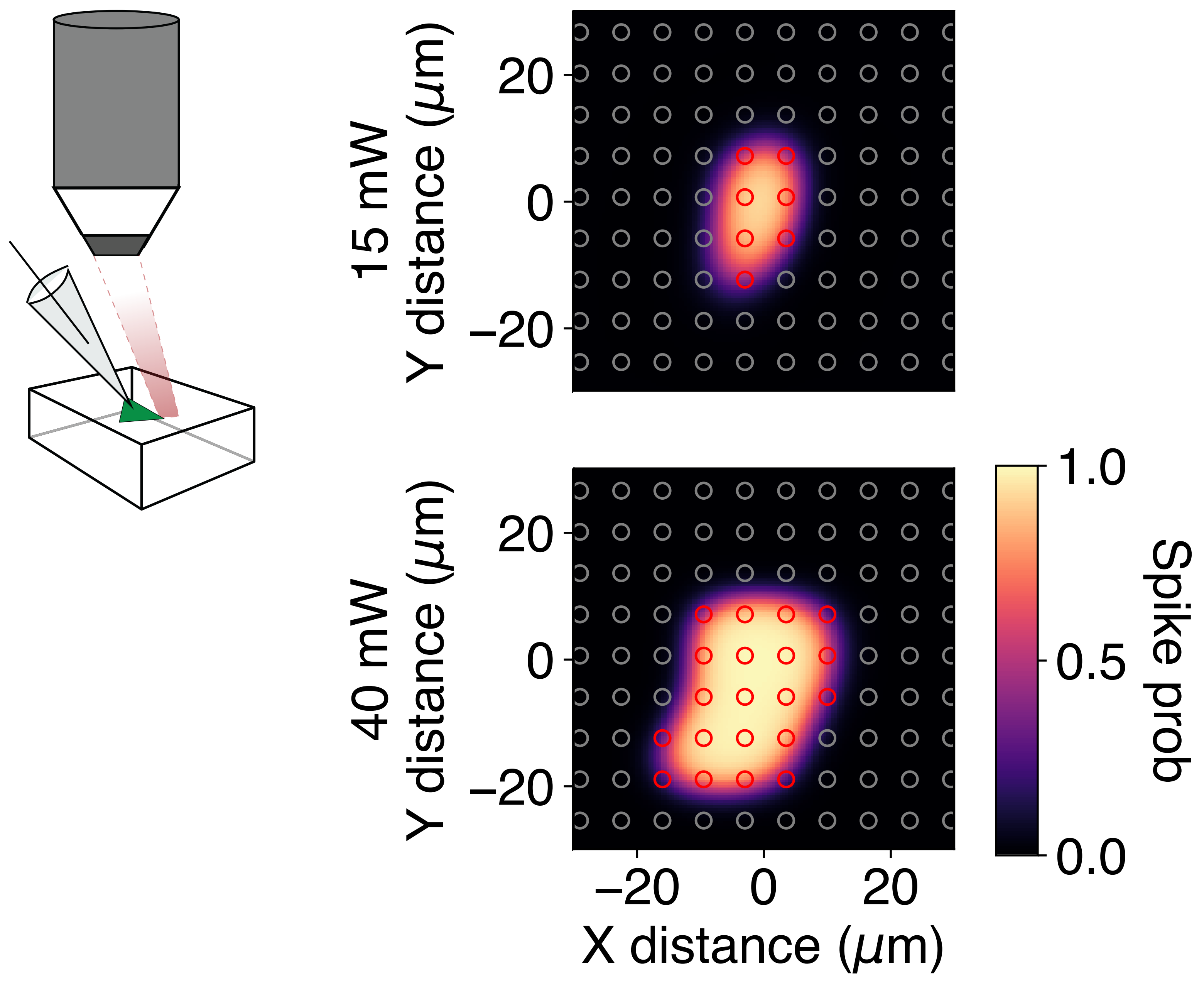


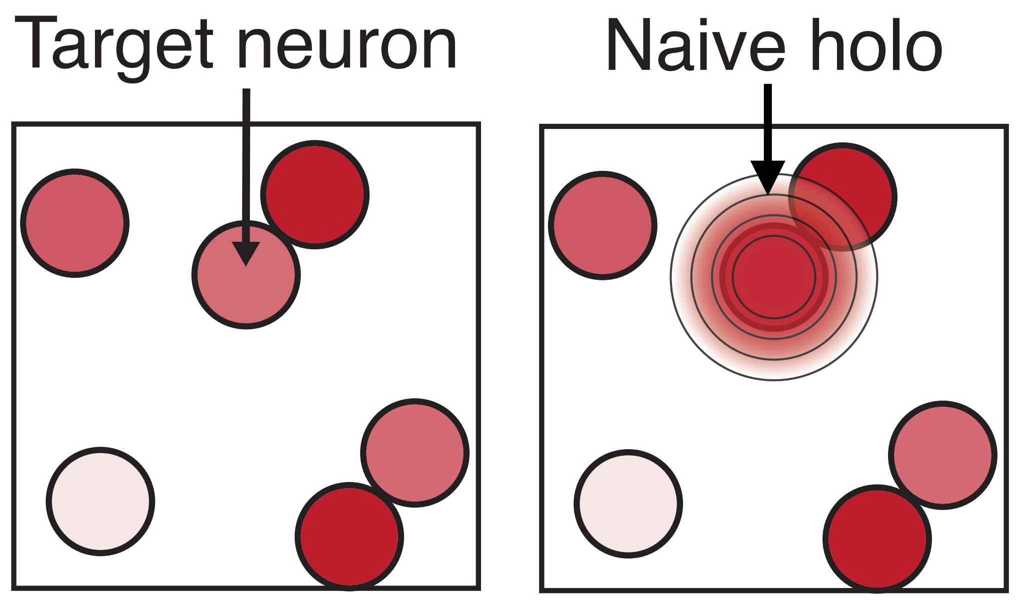


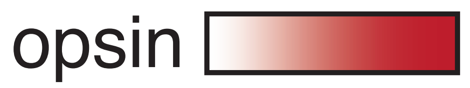
“Optogenetic receptive field”

Data from Marta Gajowa (Adesnik lab)

Target optimization strategies







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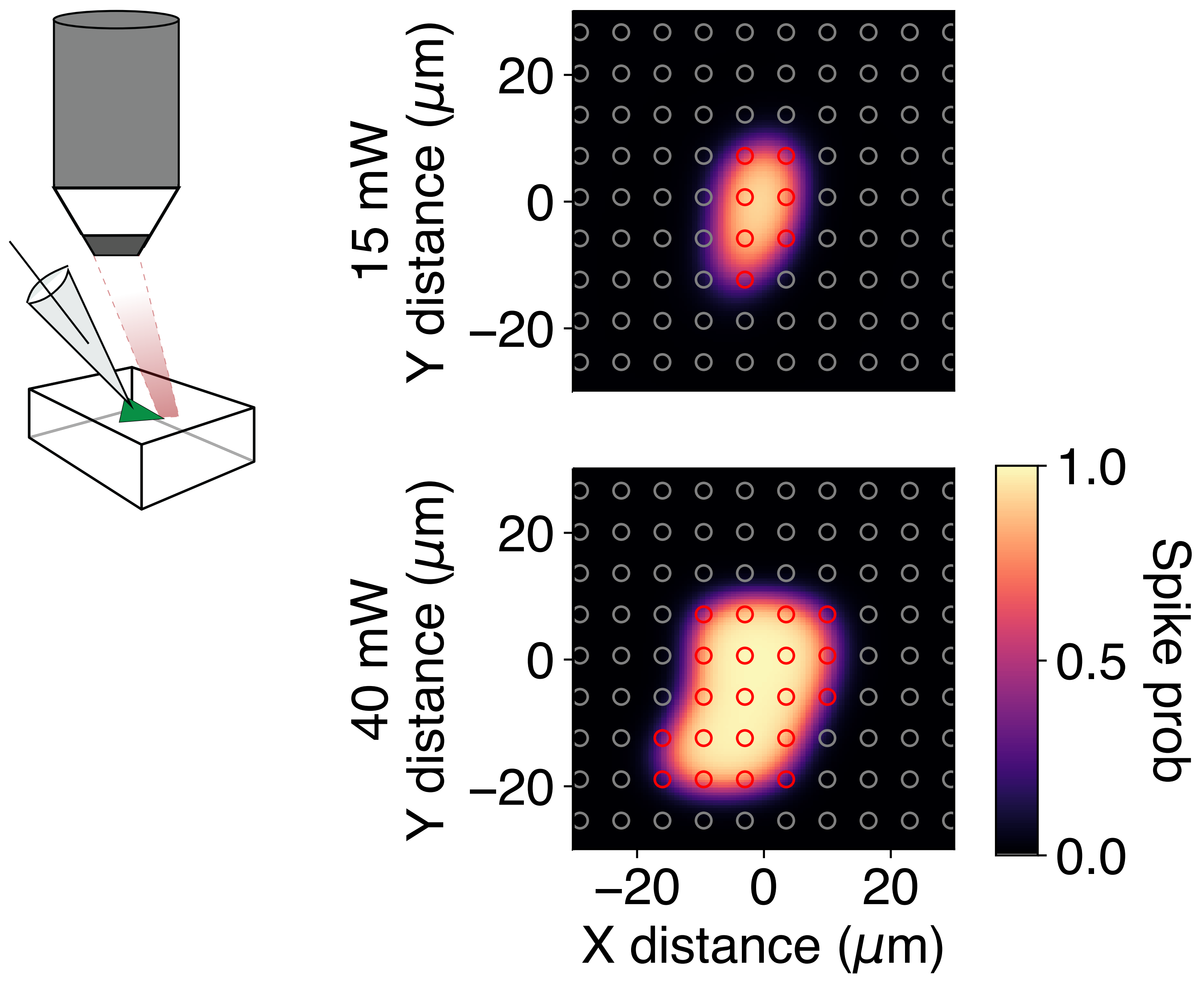

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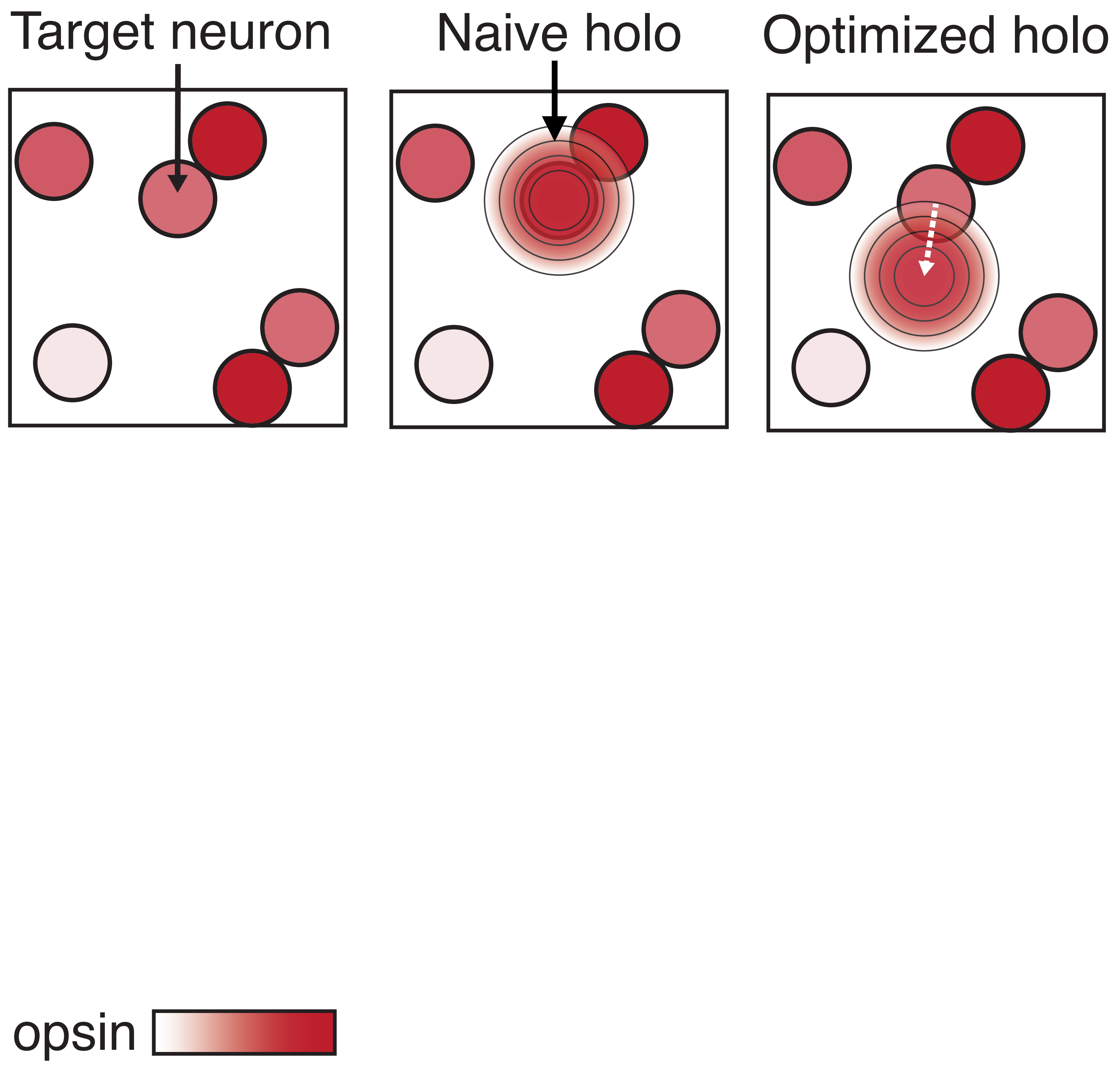

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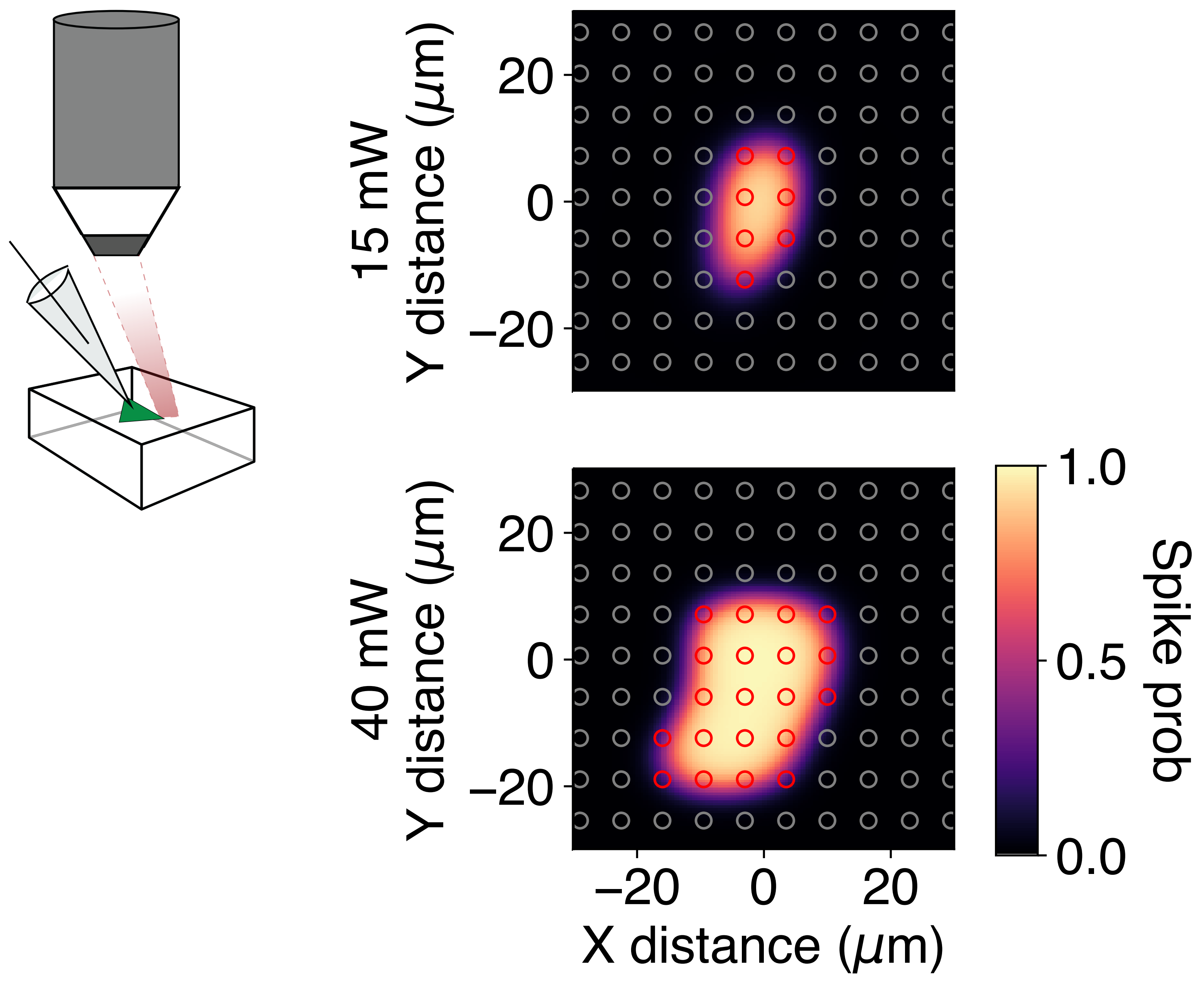

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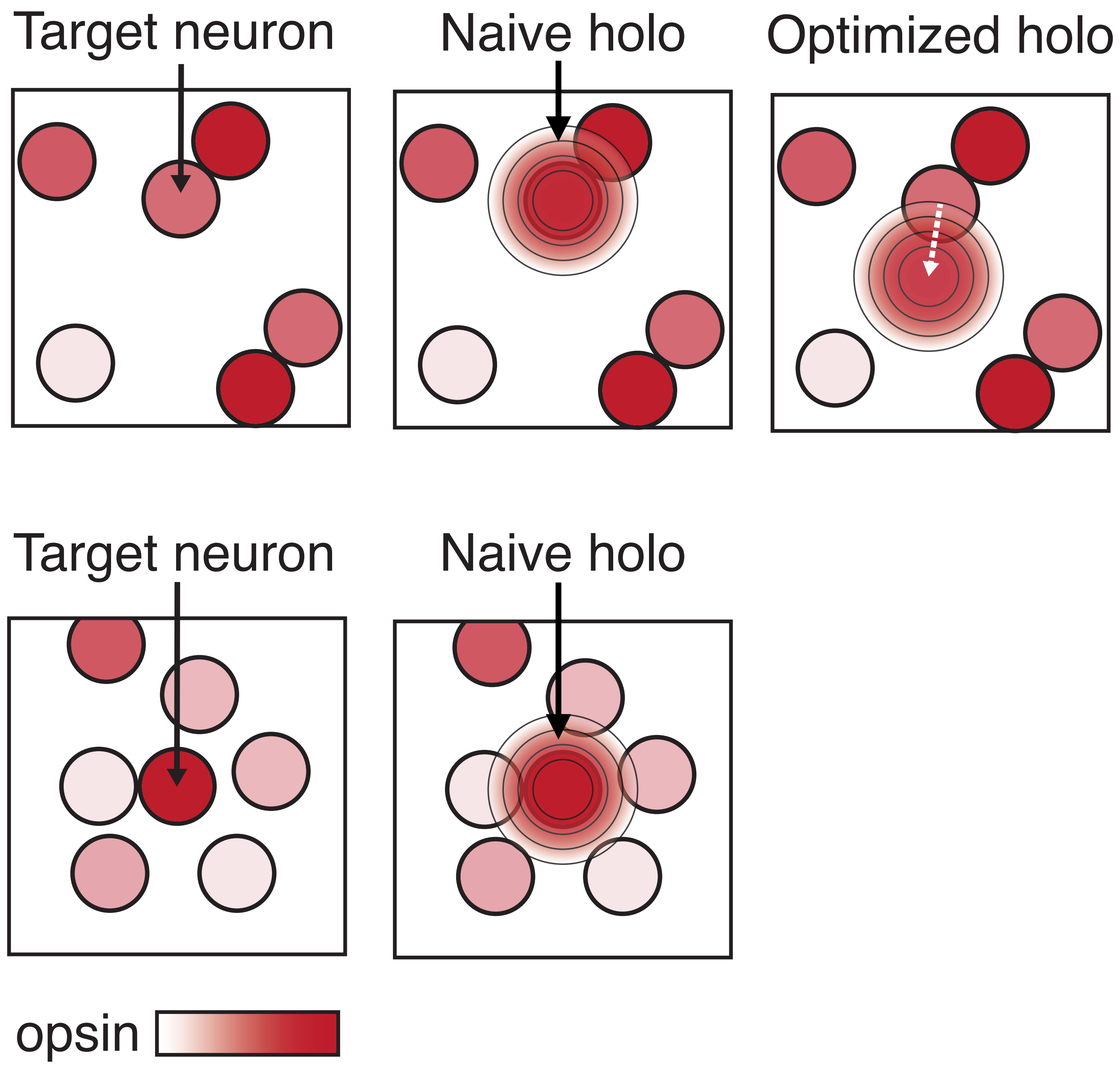

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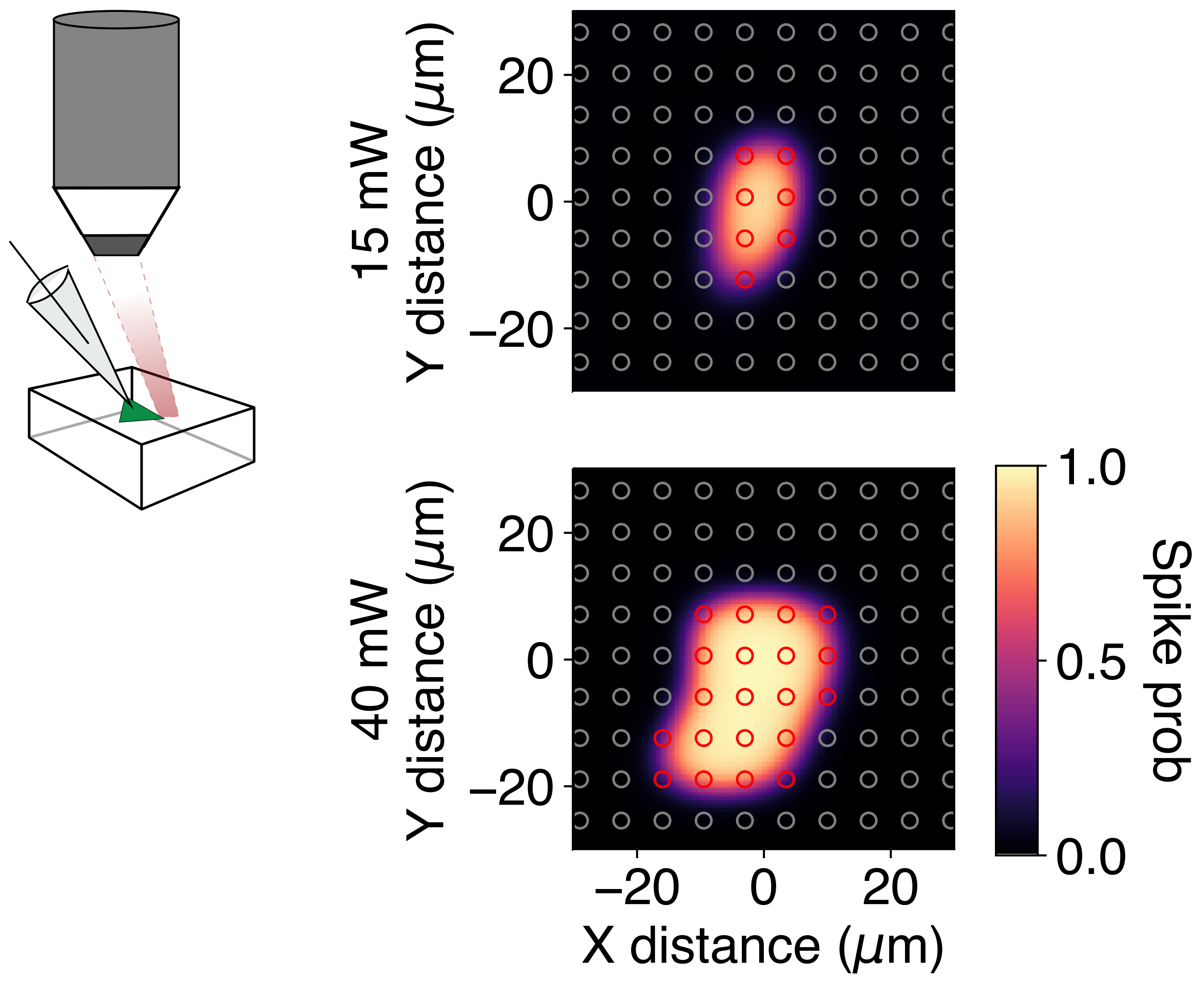

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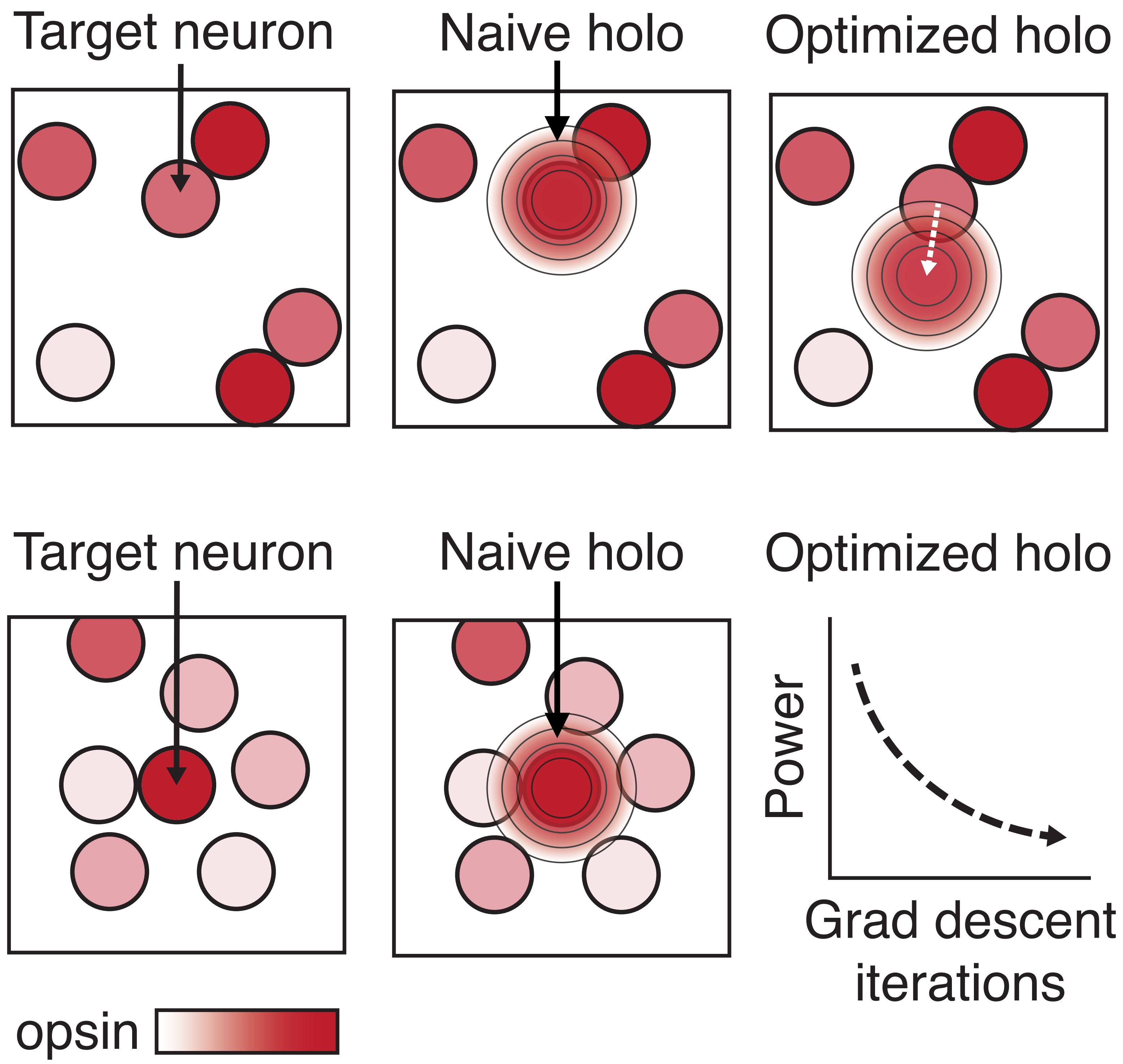

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Triplett et al (2024), *NeurIPS*

Bayesian target optimization

Mapping phase

Optimization phase

Triplett et al (2024), *NeurIPS*

Bayesian target optimization

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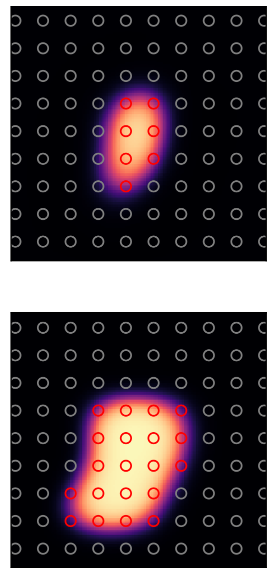
Model optogenetic receptive fields
using **Gaussian processes**



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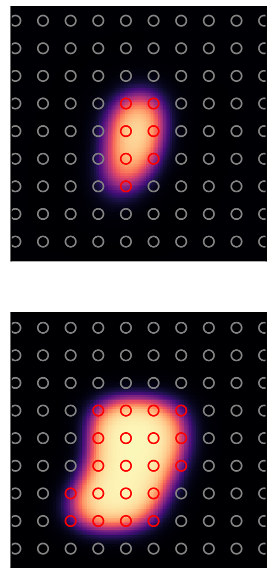

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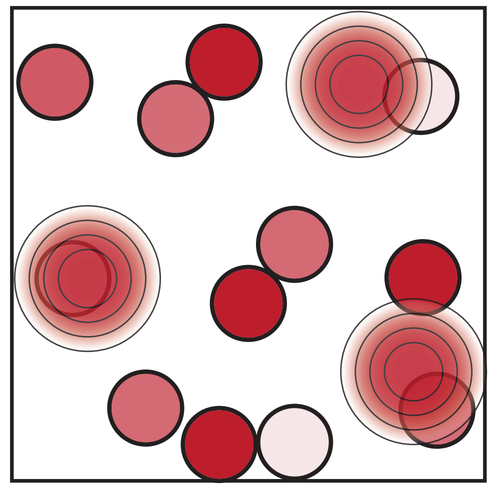

trial 1

Optimization phase

Triplett et al (2024), *NeurIPS*

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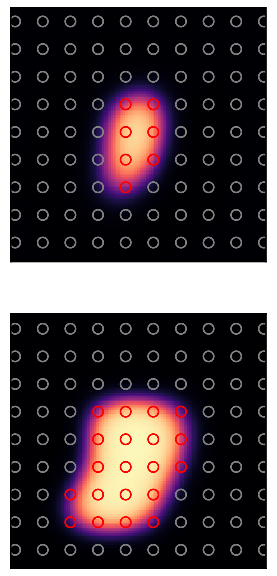

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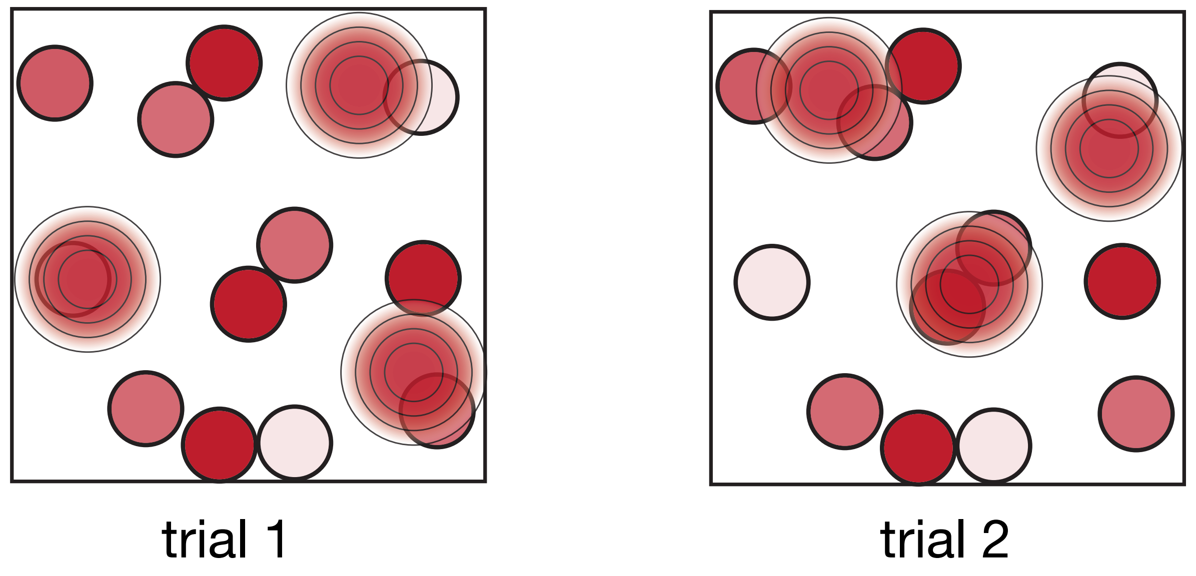

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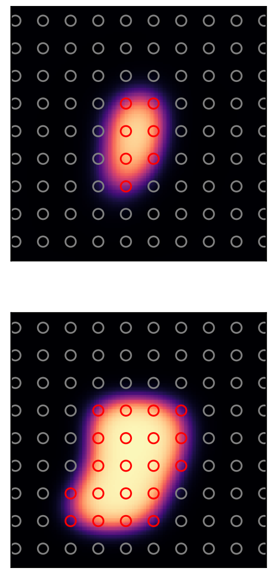

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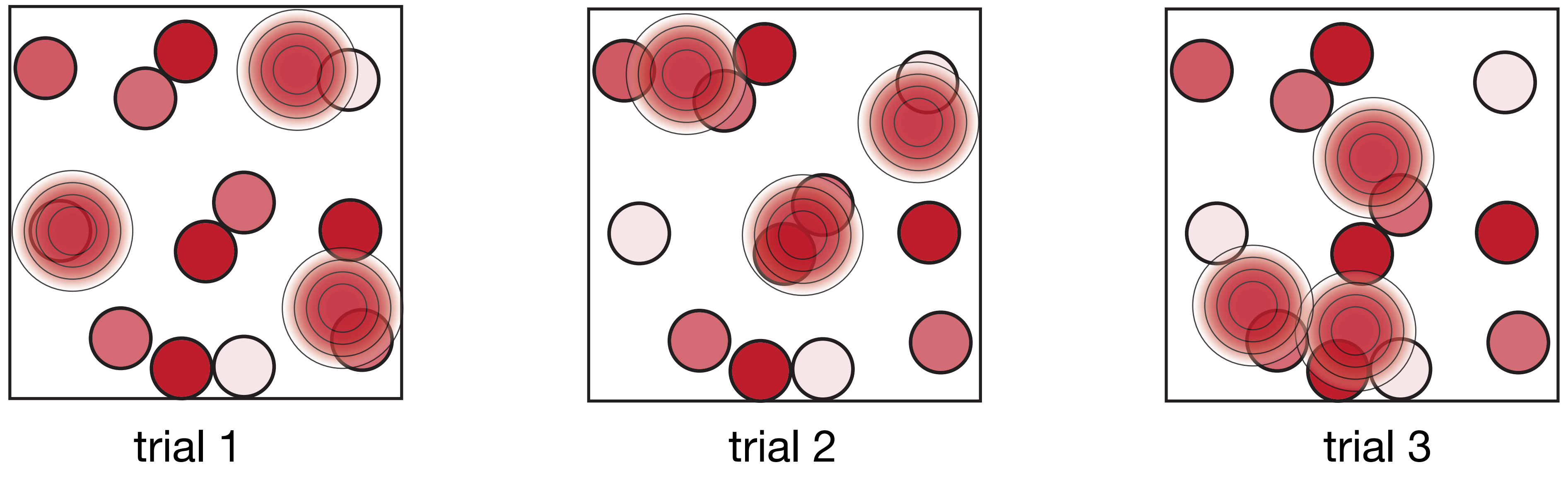

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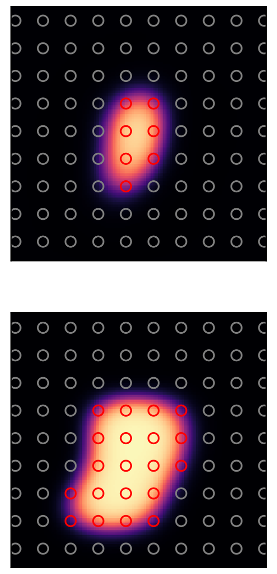

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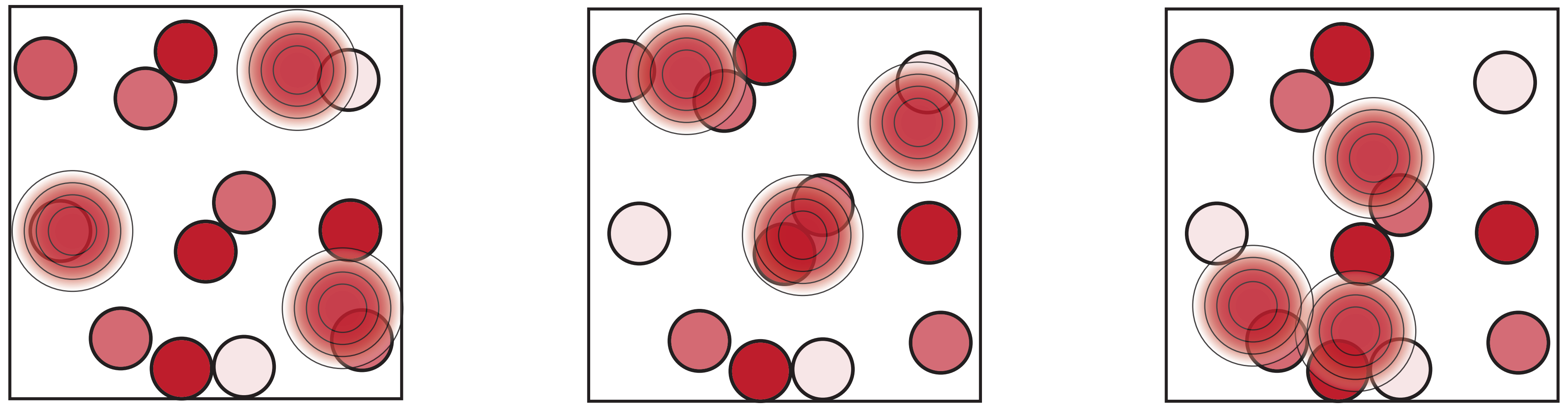

trial 1 trial 2 trial 3

Estimate receptive fields via **MAP inference**

using non-negative log-barrier method

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Triplett et al (2024), *NeurIPS*

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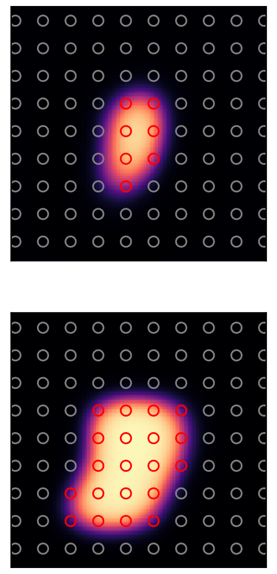

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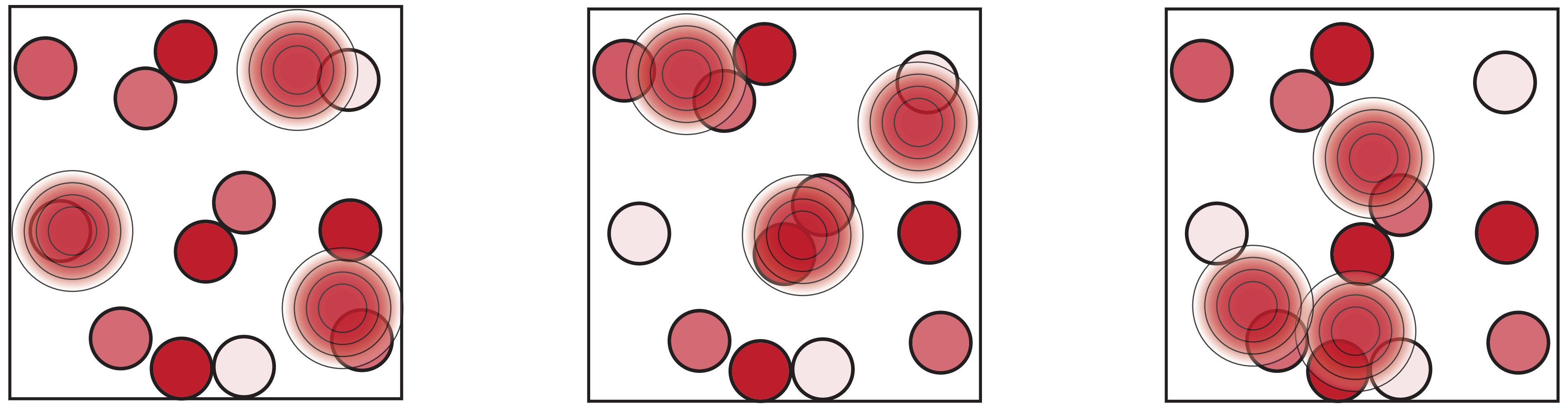

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Bayesian target optimization

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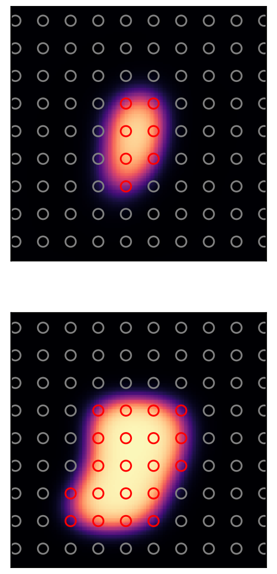

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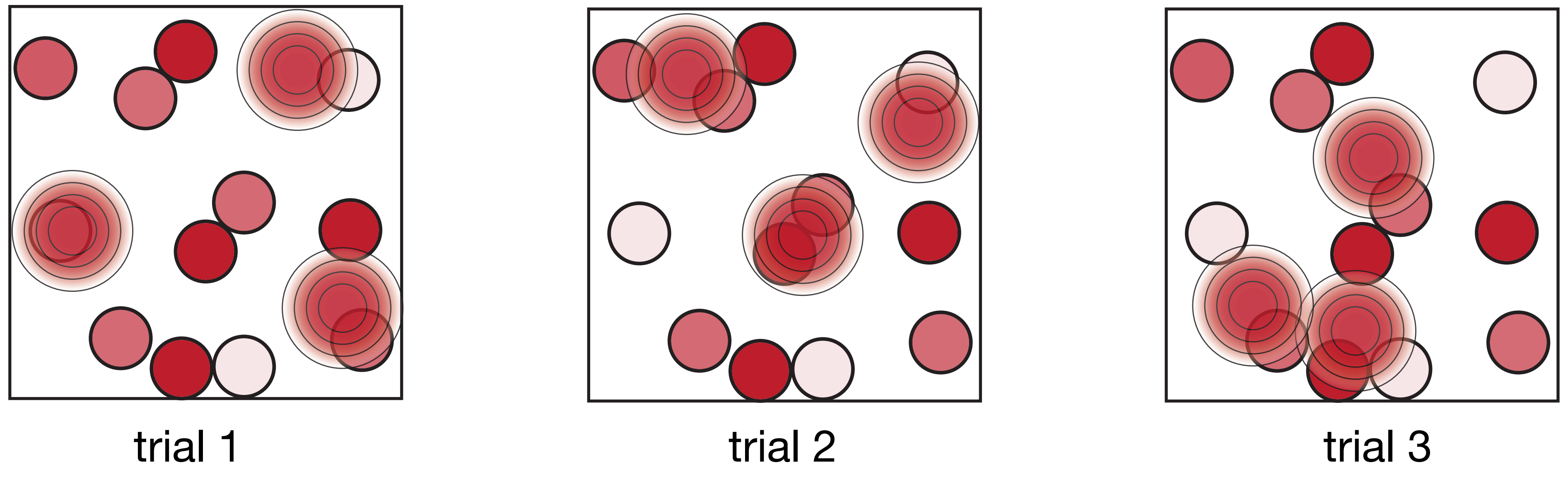

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Minimize $\|\mathbf{\Omega} - \hat{y}(\mathbf{x}, \mathcal{G})\|^2$ with laser power constraints

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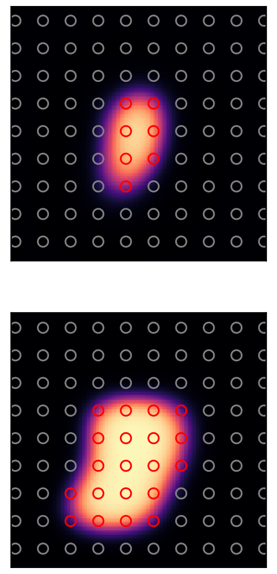

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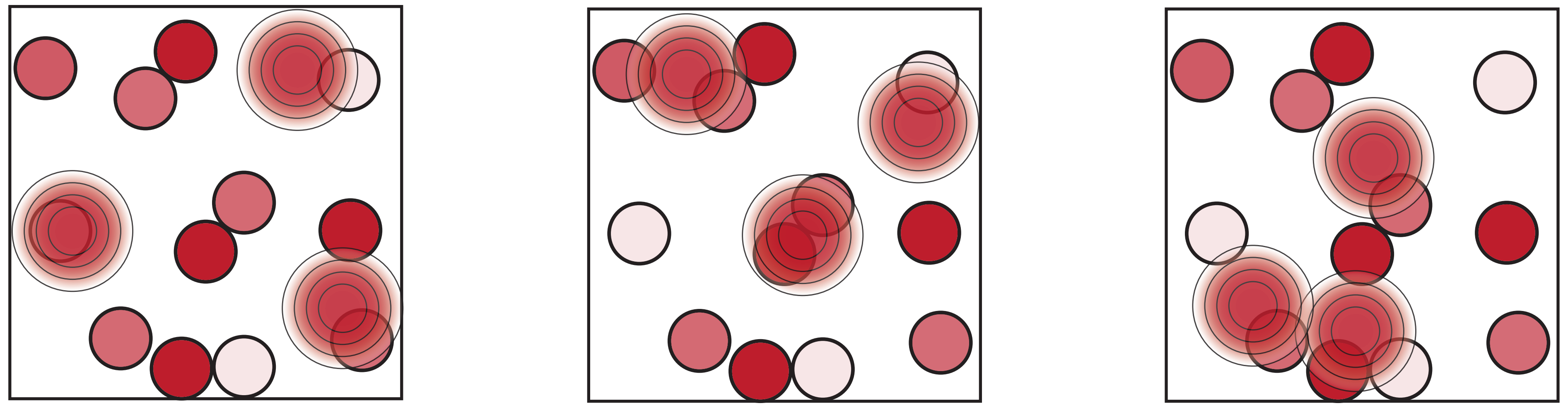

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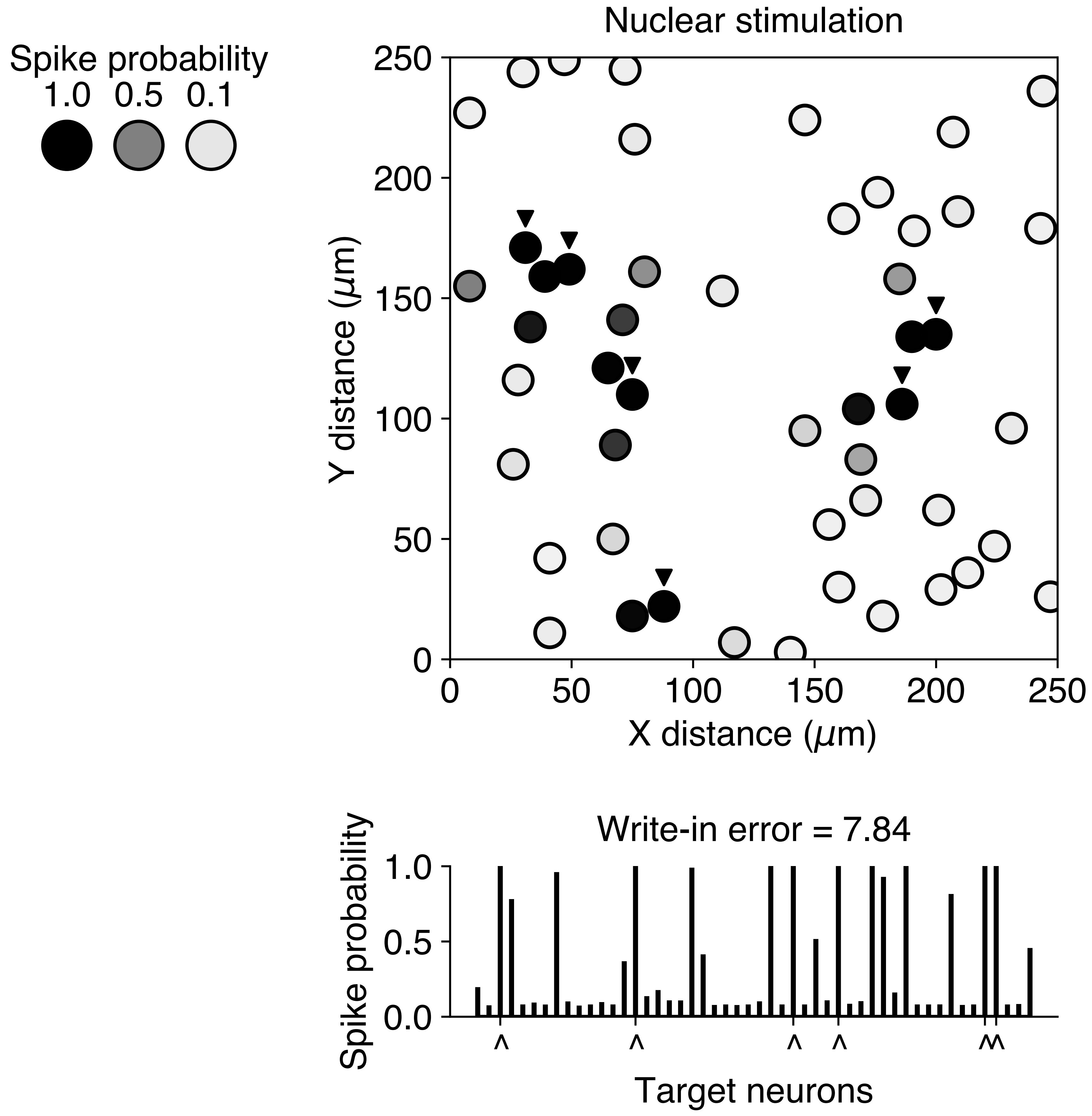
Algorithm 1: Bayesian target optimisation (Bataro).

Compute MAP estimates of ORFs $\{\hat{g}_n, \hat{\theta}_n\}_{n=1}^N$ from calibration data $\{\mathbf{y}_n\}_{n=1}^N, \{\mathbf{x}_t\}_{t=1}^T$ using Newton's method with log-barrier.
Initialise targets $\mathbf{x} \in \mathbb{R}^{J \times 3}$ to random locations near the somas of the J target neurons and with random laser powers.
while *target not converged* **do**
  Construct gradient vectors $\nabla_{\mathbf{x}} \hat{\gamma}_n(\mathbf{x})$ for $n = 1, \ldots, N$ using inference of ORF derivatives (Equation 8).
  Set $\boldsymbol{\delta}_{\mathbf{x}} = -2 \sum_{n=1}^N (\Omega_n - \sigma(\hat{\gamma}_n(\mathbf{x}) - \hat{\theta}_n))\sigma'(\hat{\gamma}_n(\mathbf{x}) - \hat{\theta}_n)\nabla_{\mathbf{x}} \hat{\gamma}_n(\mathbf{x})$.
  Perform gradient descent update $\mathbf{x} \leftarrow \mathbf{x} + \beta \boldsymbol{\delta}_{\mathbf{x}}$ with step-size β.
  Project laser power onto feasible domain, $I_j \leftarrow \min(I_j, I_{\max})$ for $j = 1, \ldots, J$.
end

Triplett et al (2024), *NeurIPS*

Optimizing holographic ensemble stimuli



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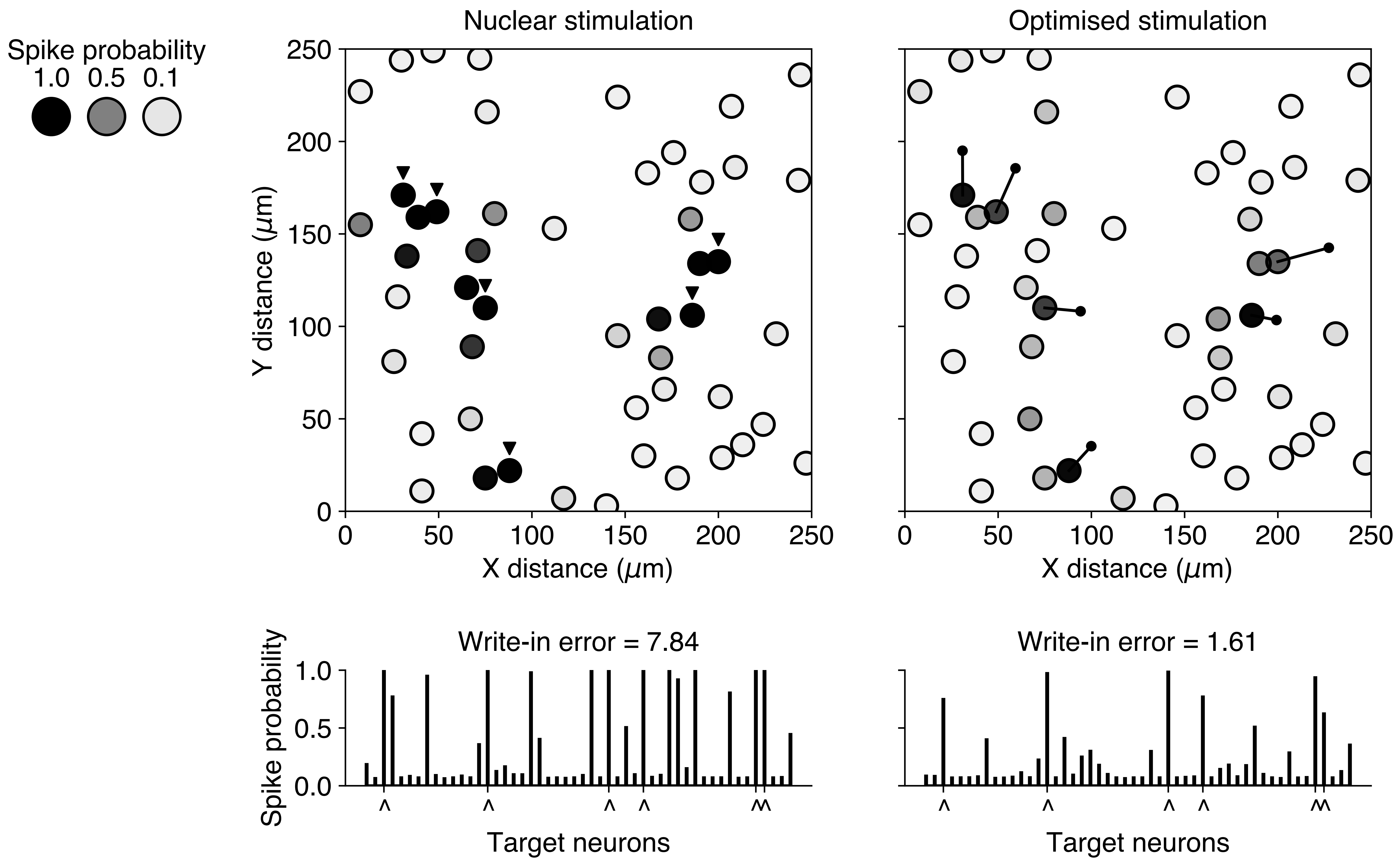

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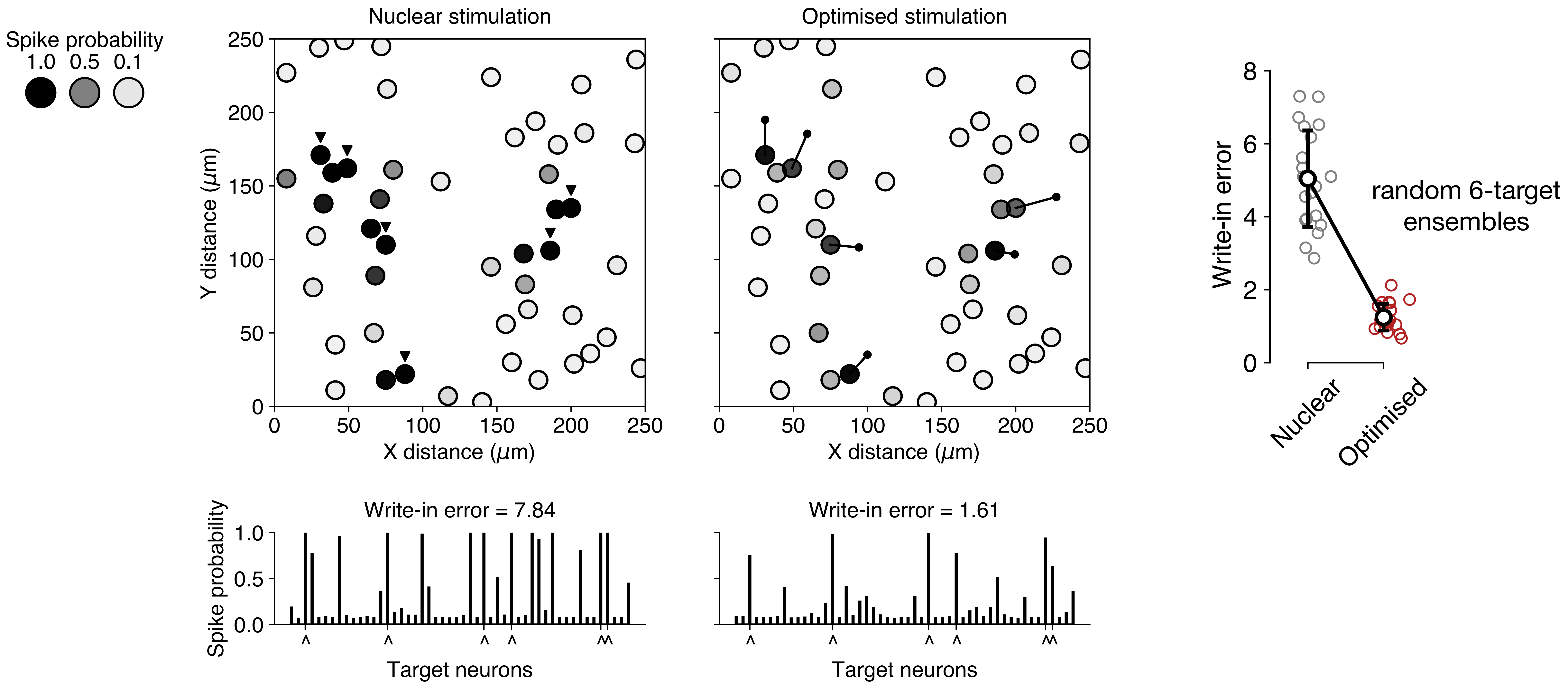
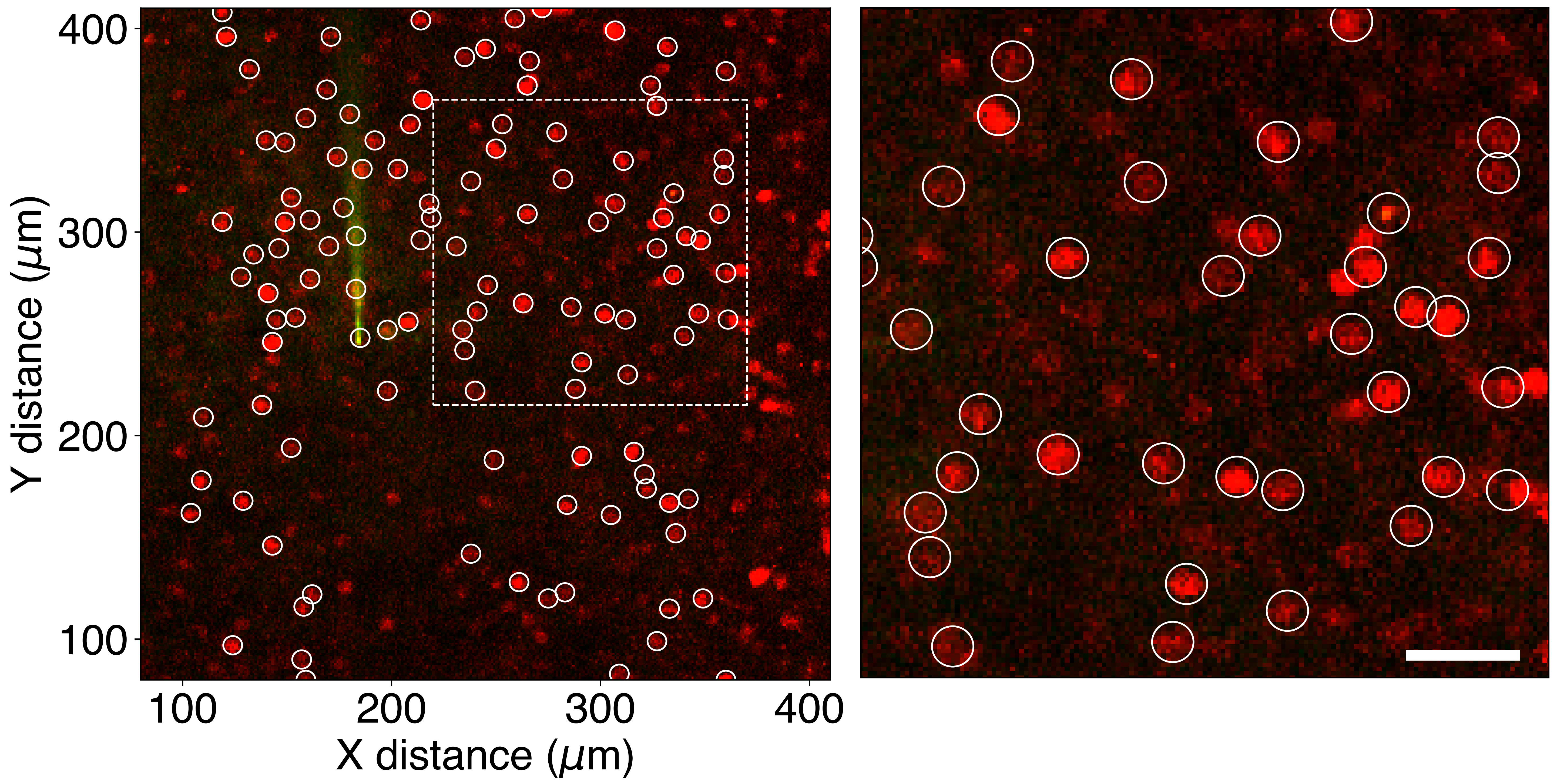


Triplett et al (2024), *NeurIPS*

Validated in realistic conditions



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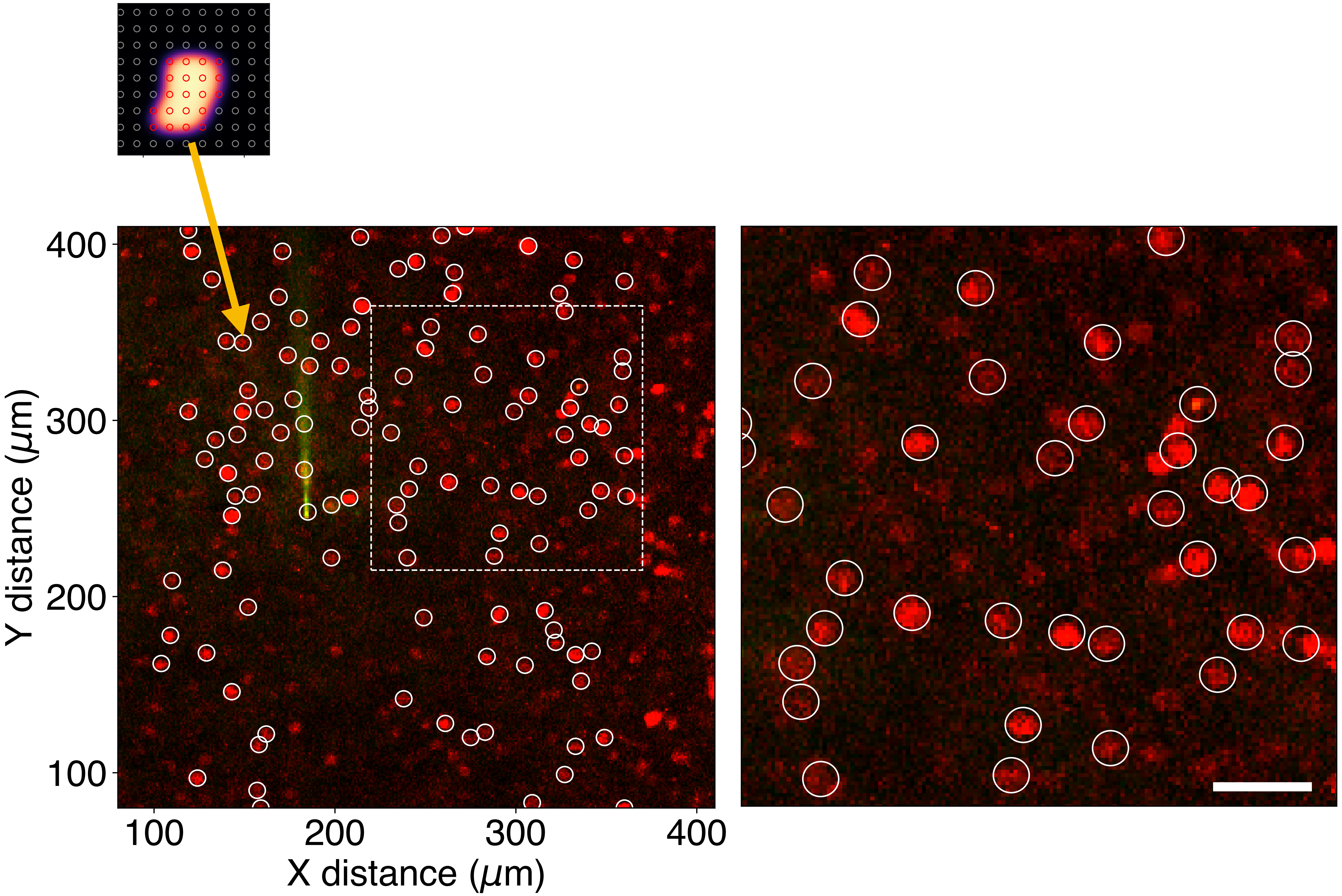

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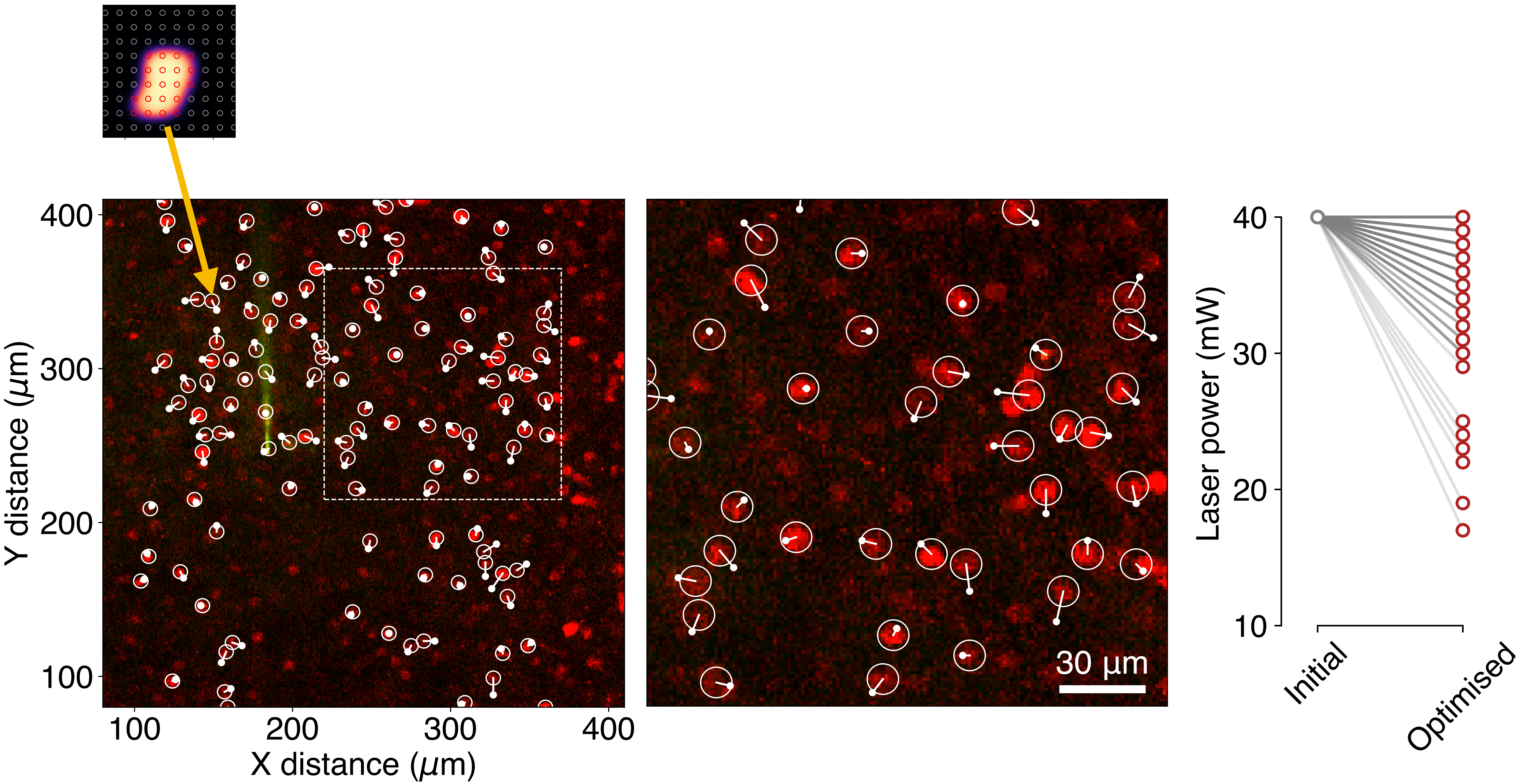

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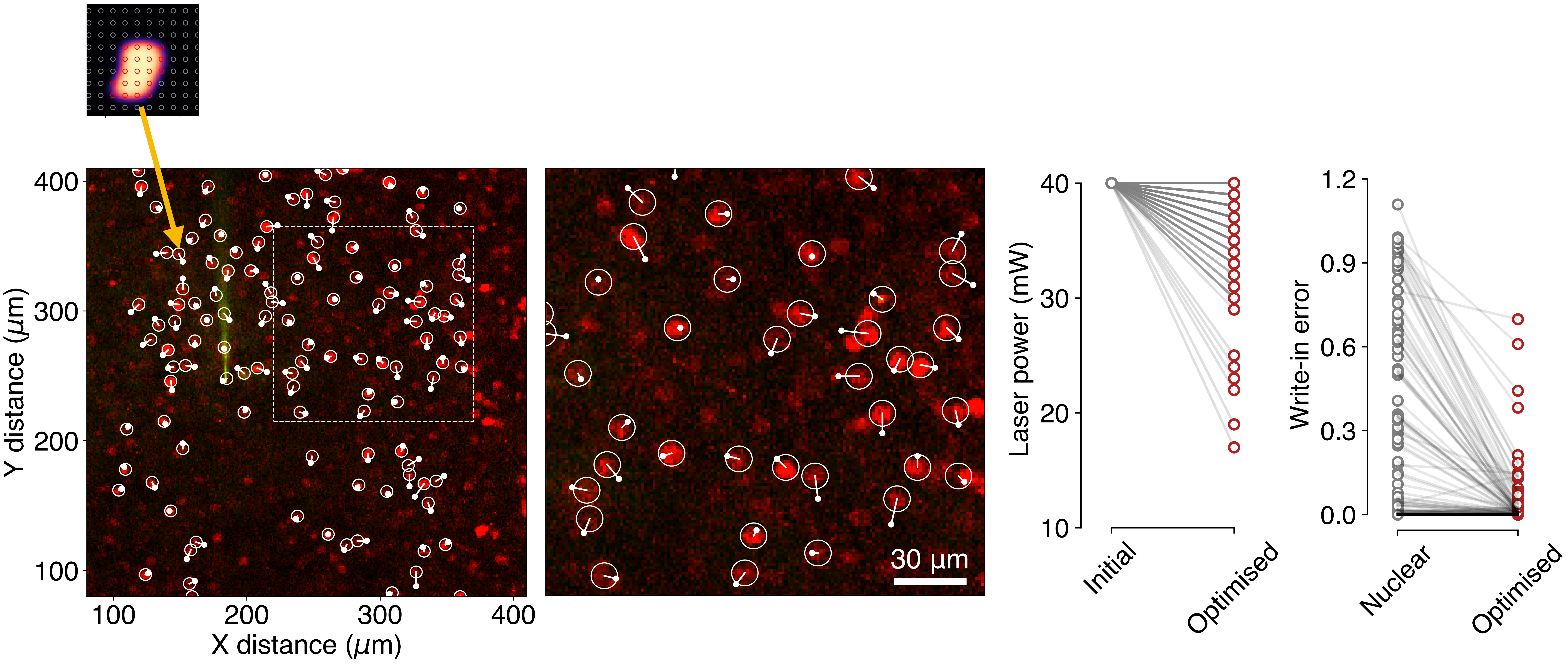
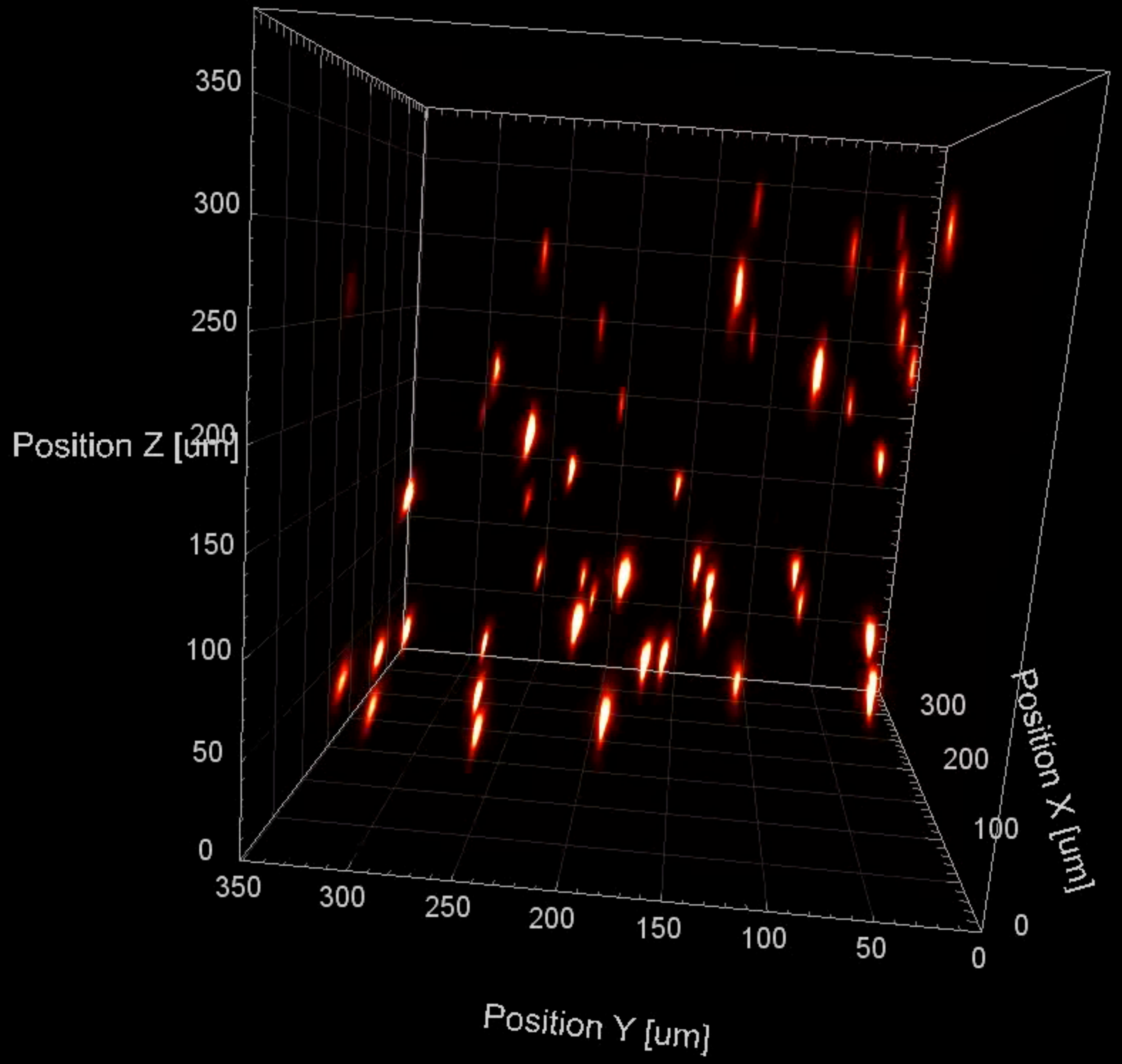
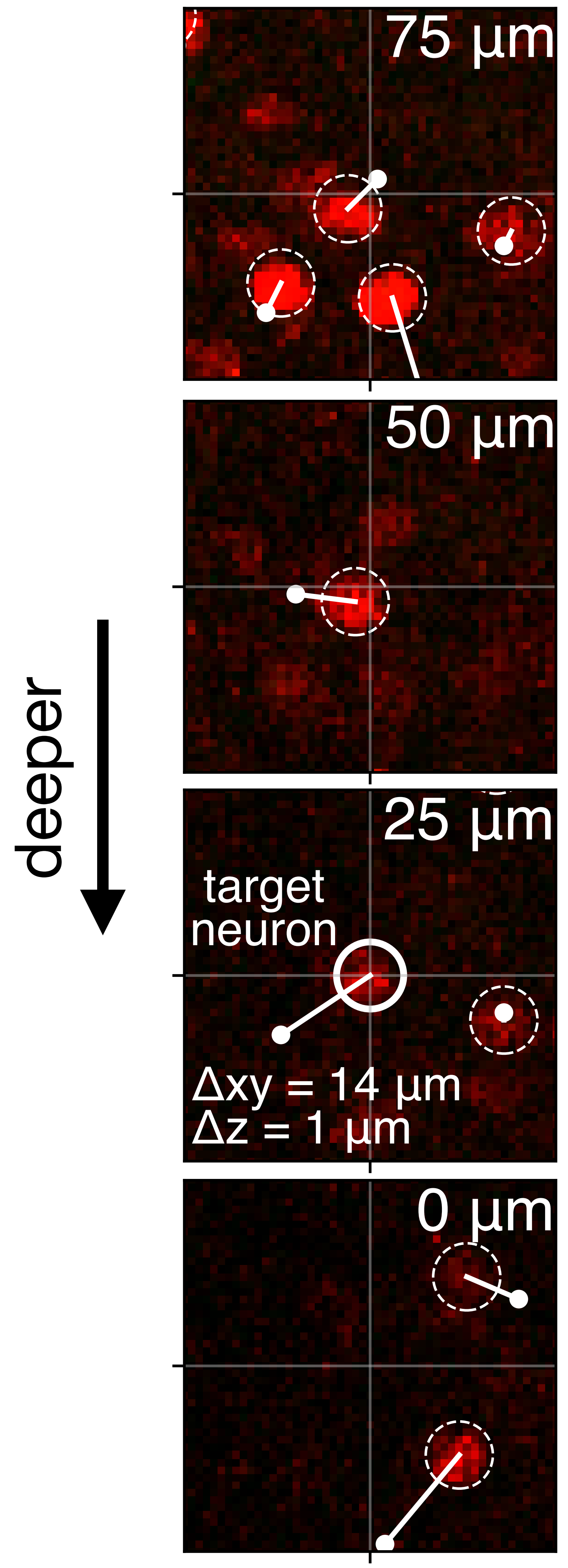


Triplett et al (2024), *NeurIPS*

Can Bayesian target optimization help in 3D?

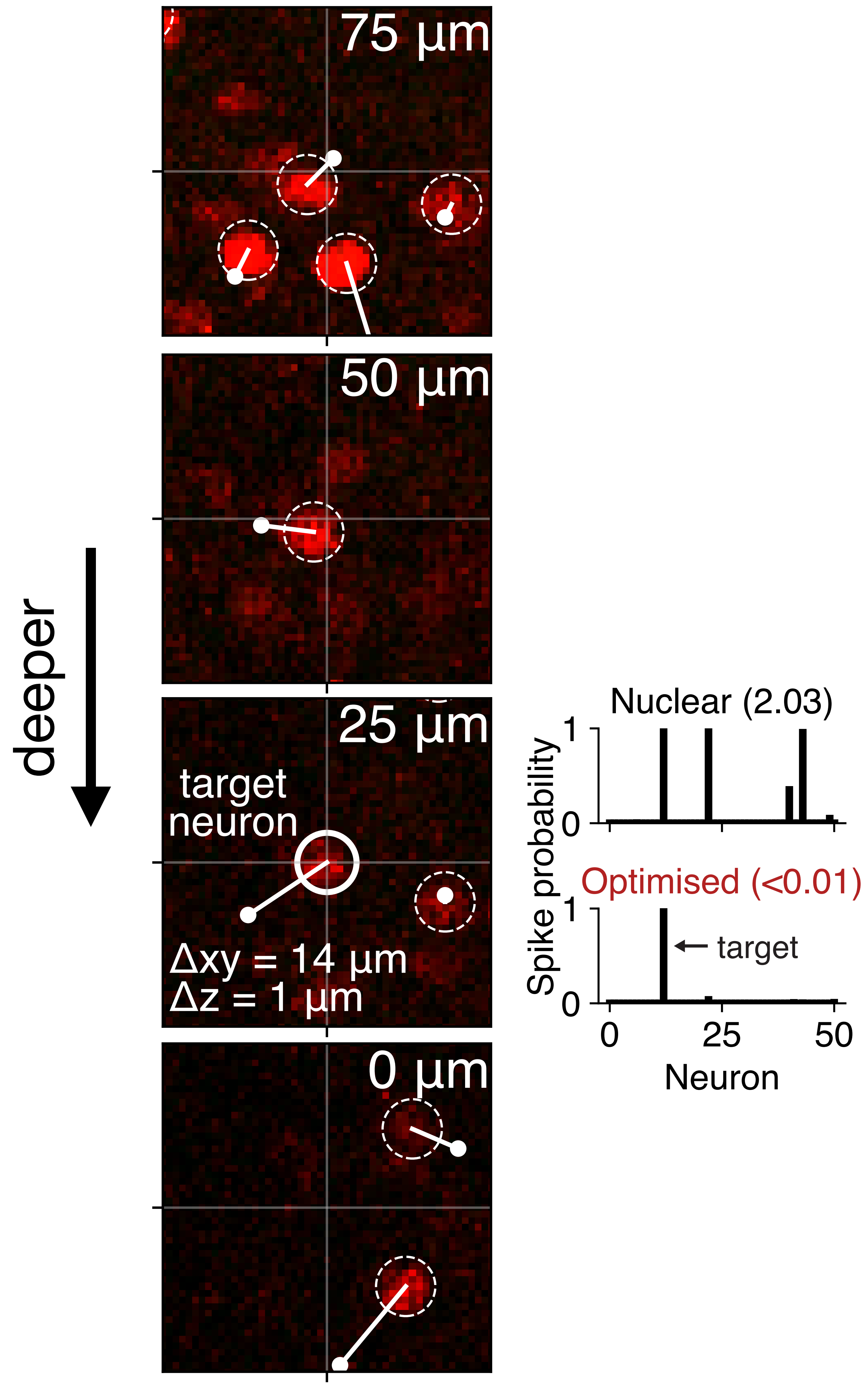


3D target optimization resolves off-target stimulation



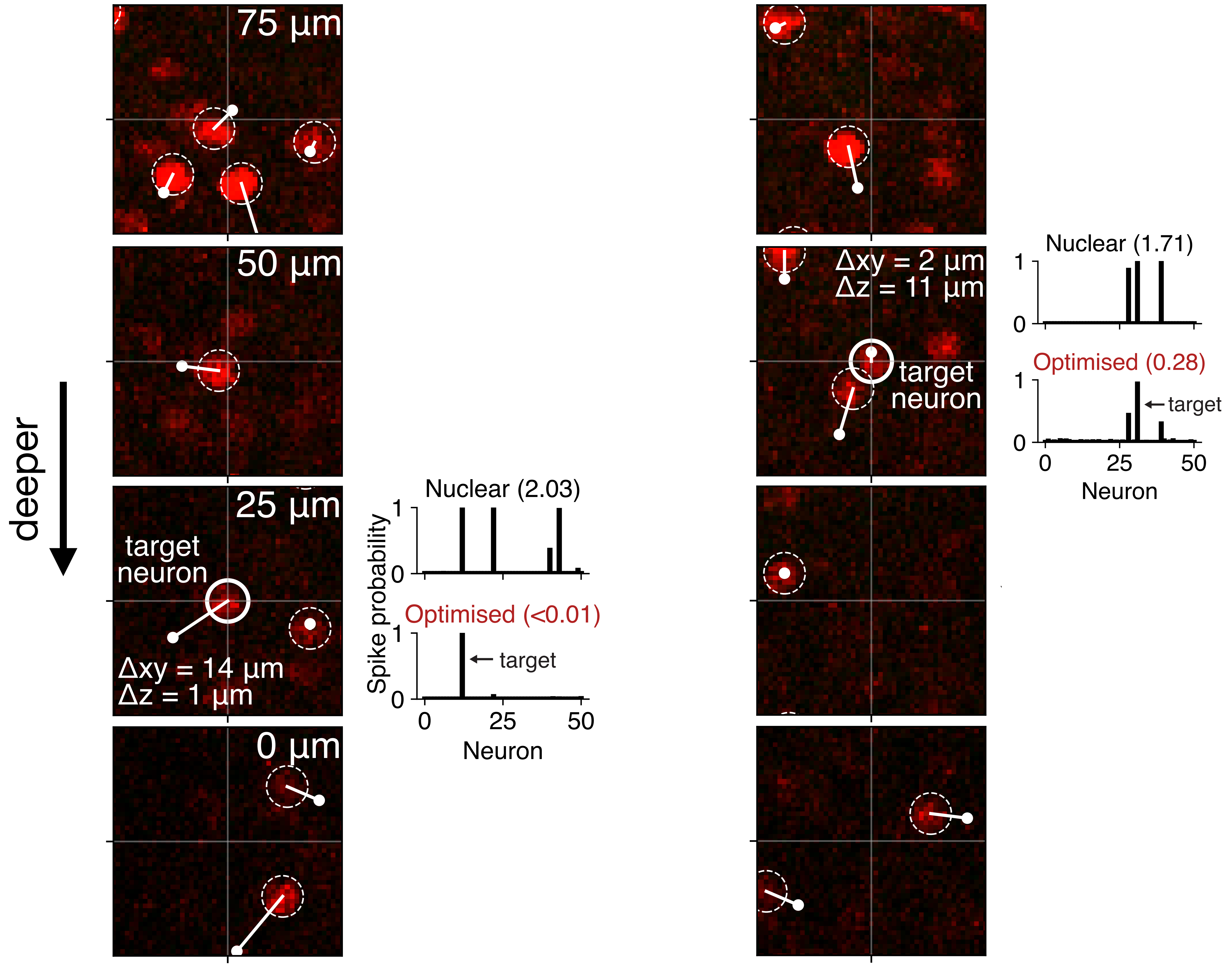
Triplett et al (2024), *NeurIPS*

3D target optimization resolves off-target stimulation



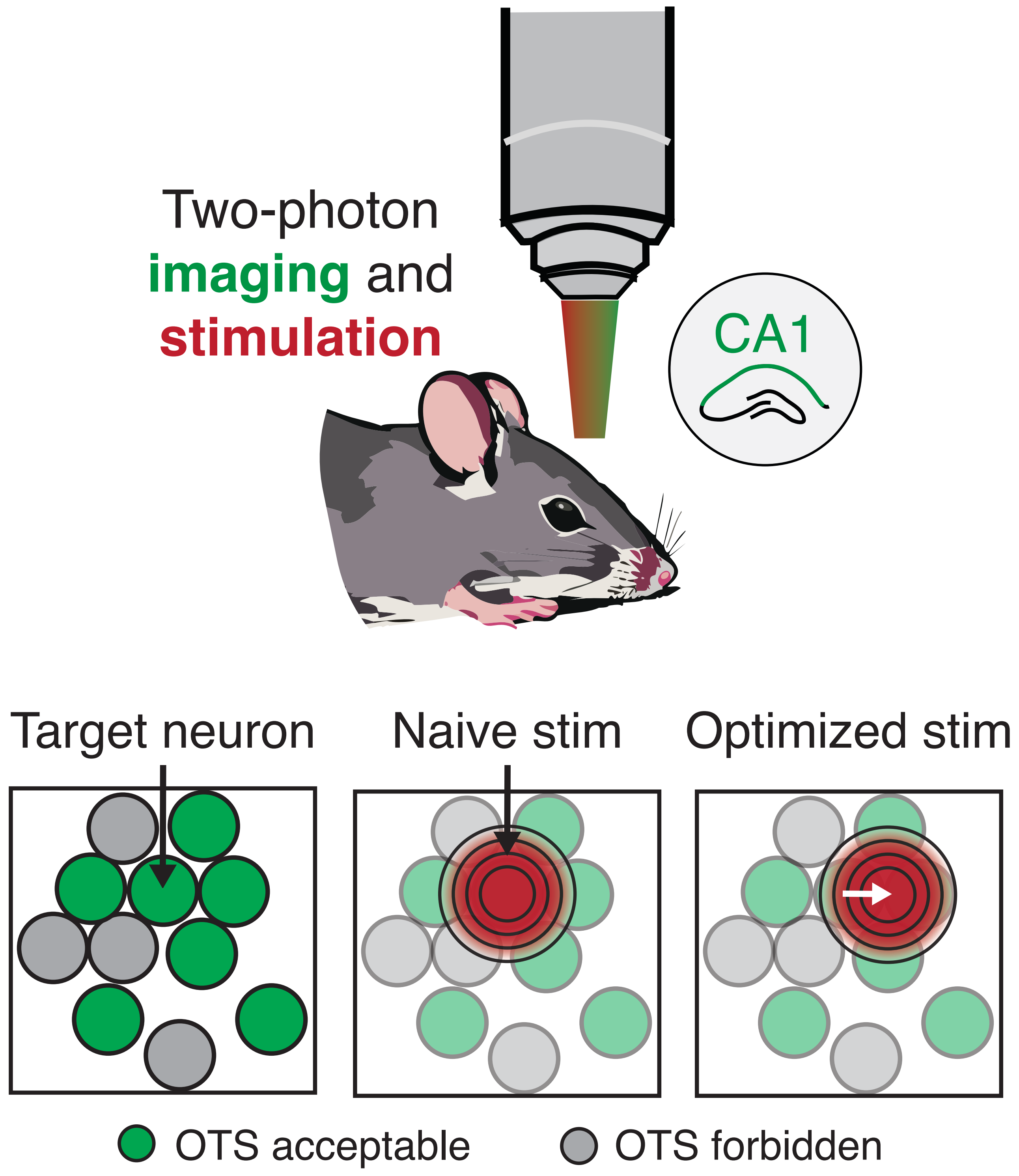
Triplett et al (2024), *NeurIPS*

3D target optimization resolves off-target stimulation

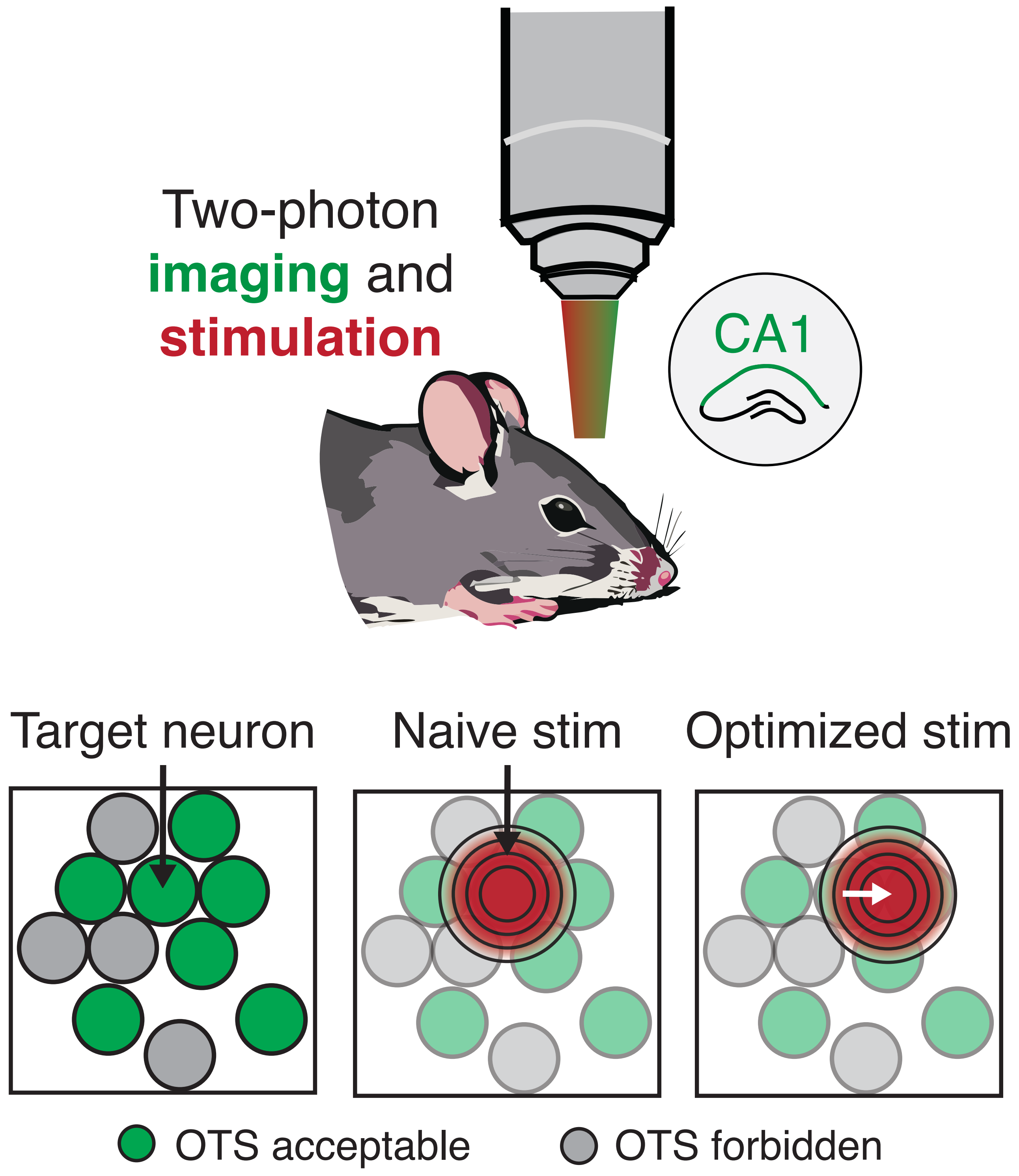


Triplett et al (2024), *NeurIPS*

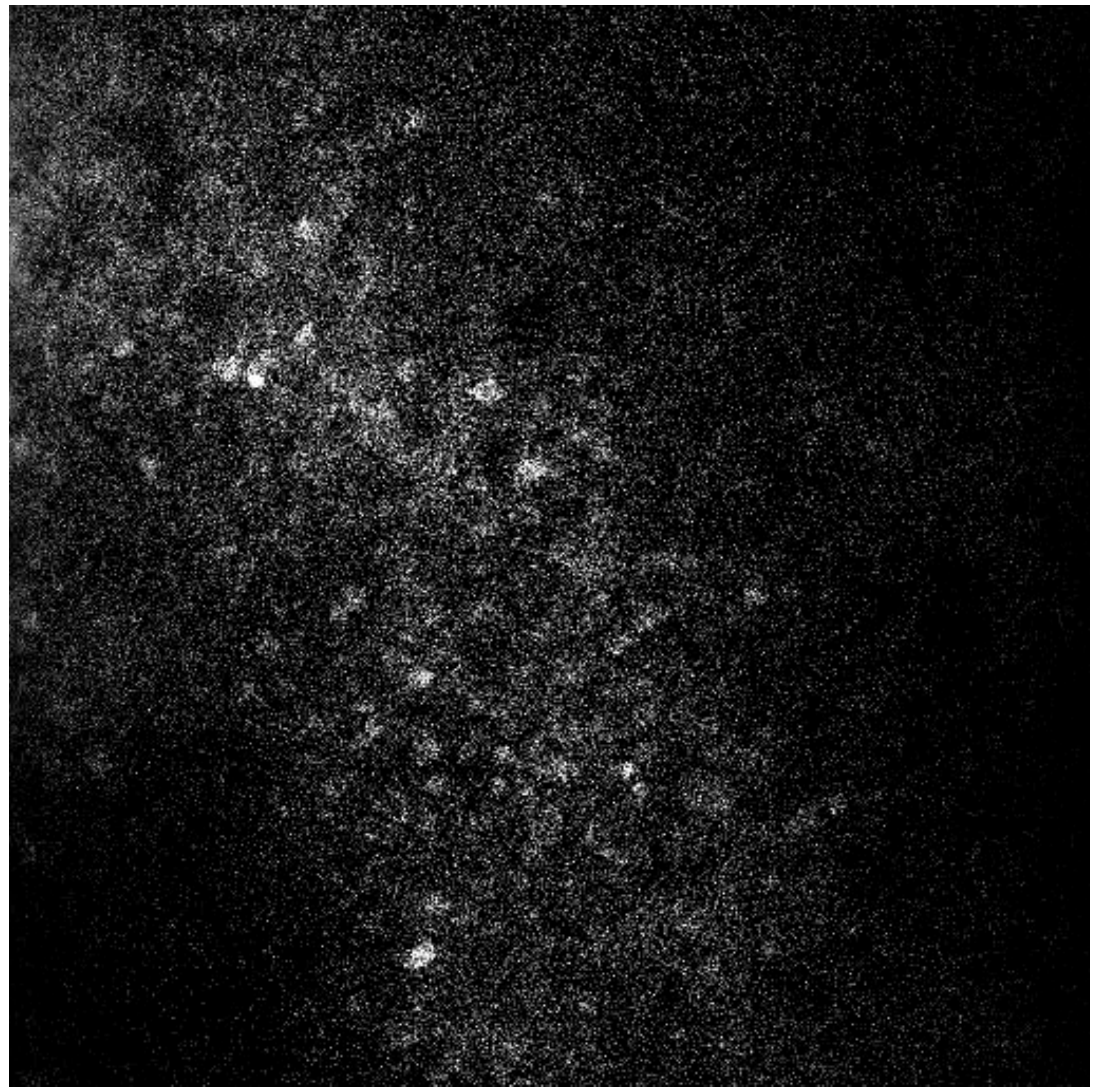
Application to the hippocampus (ongoing)



Application to the hippocampus (ongoing)

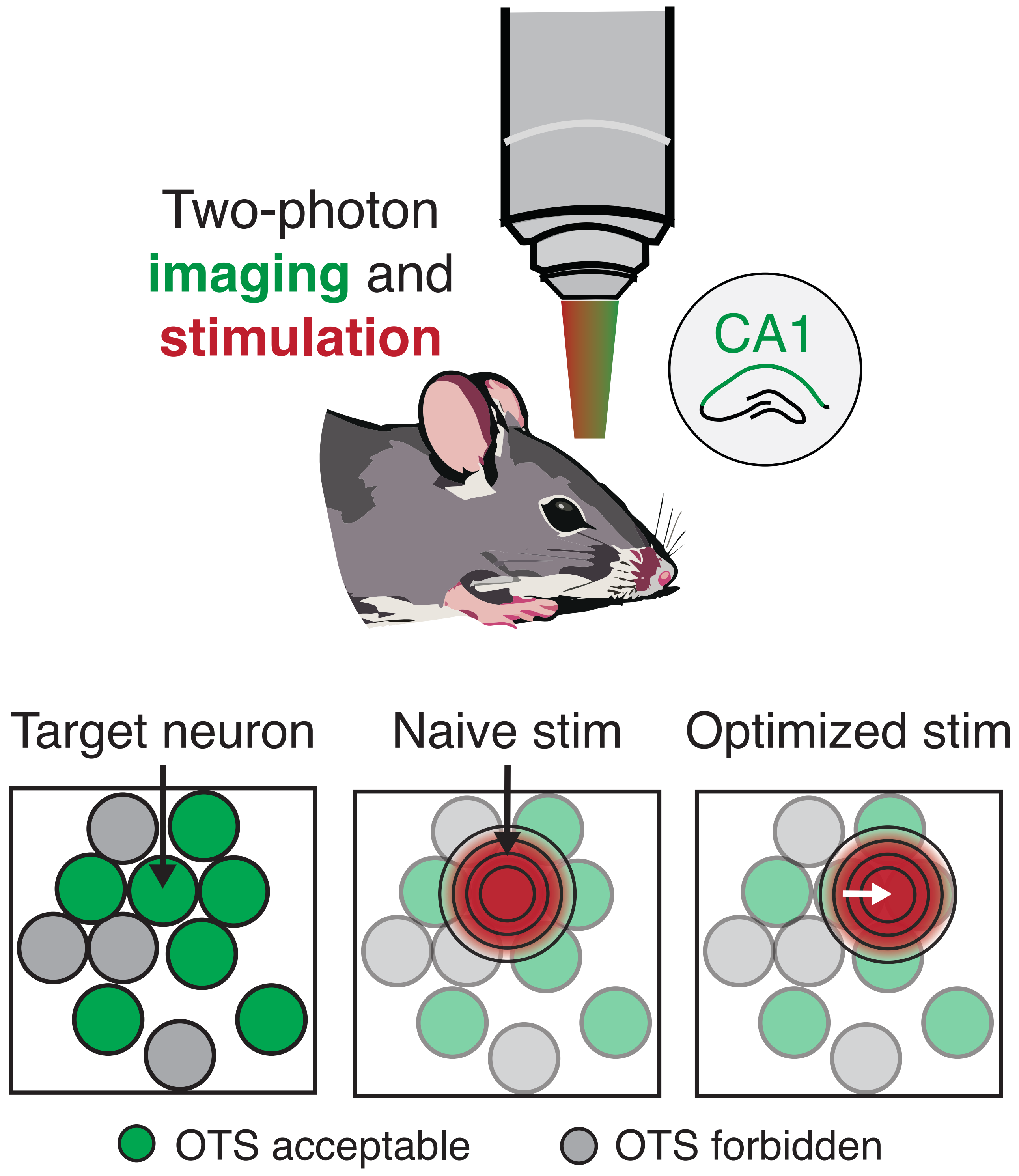


optogenetic receptive field mapping in CA1

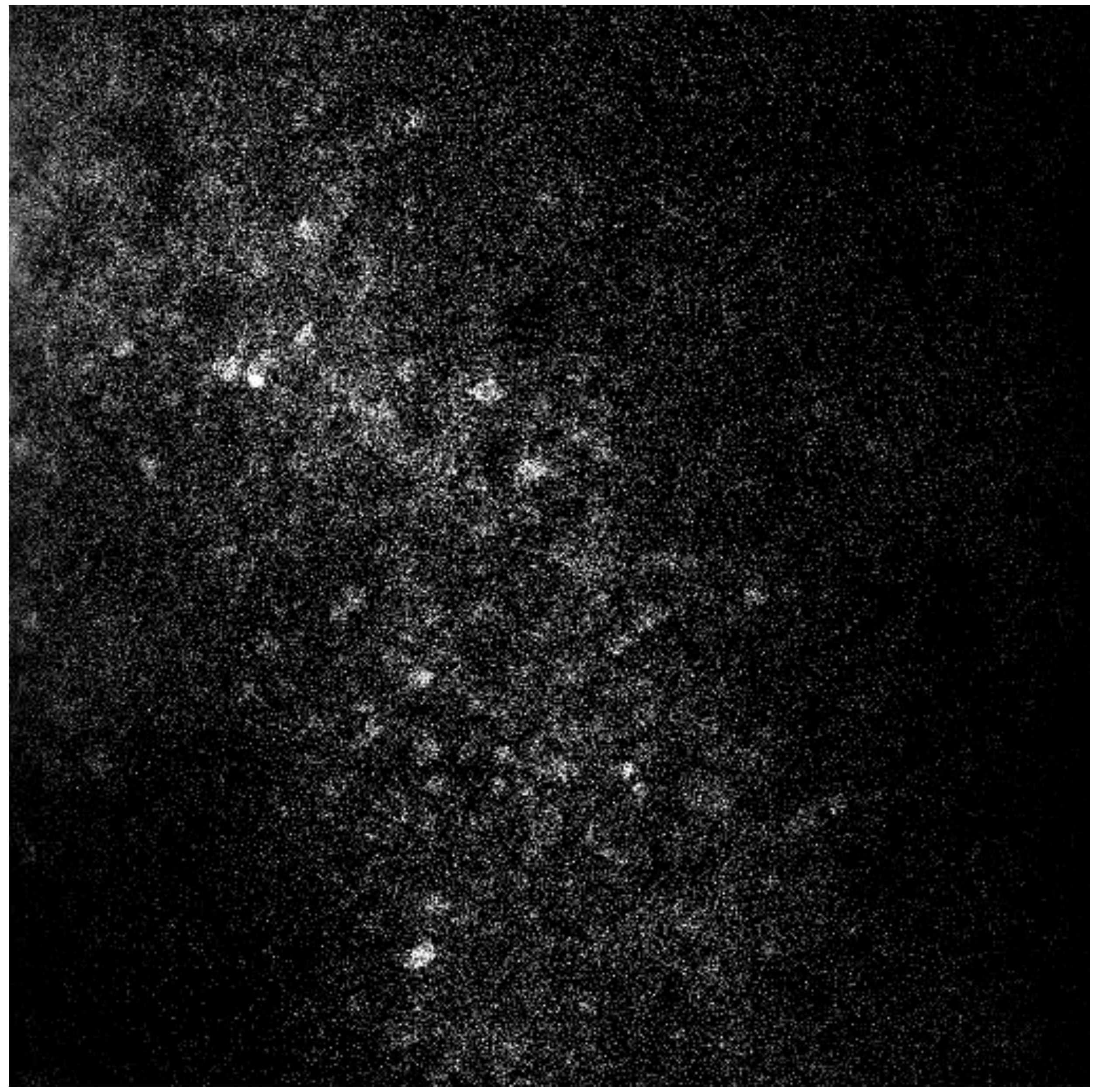


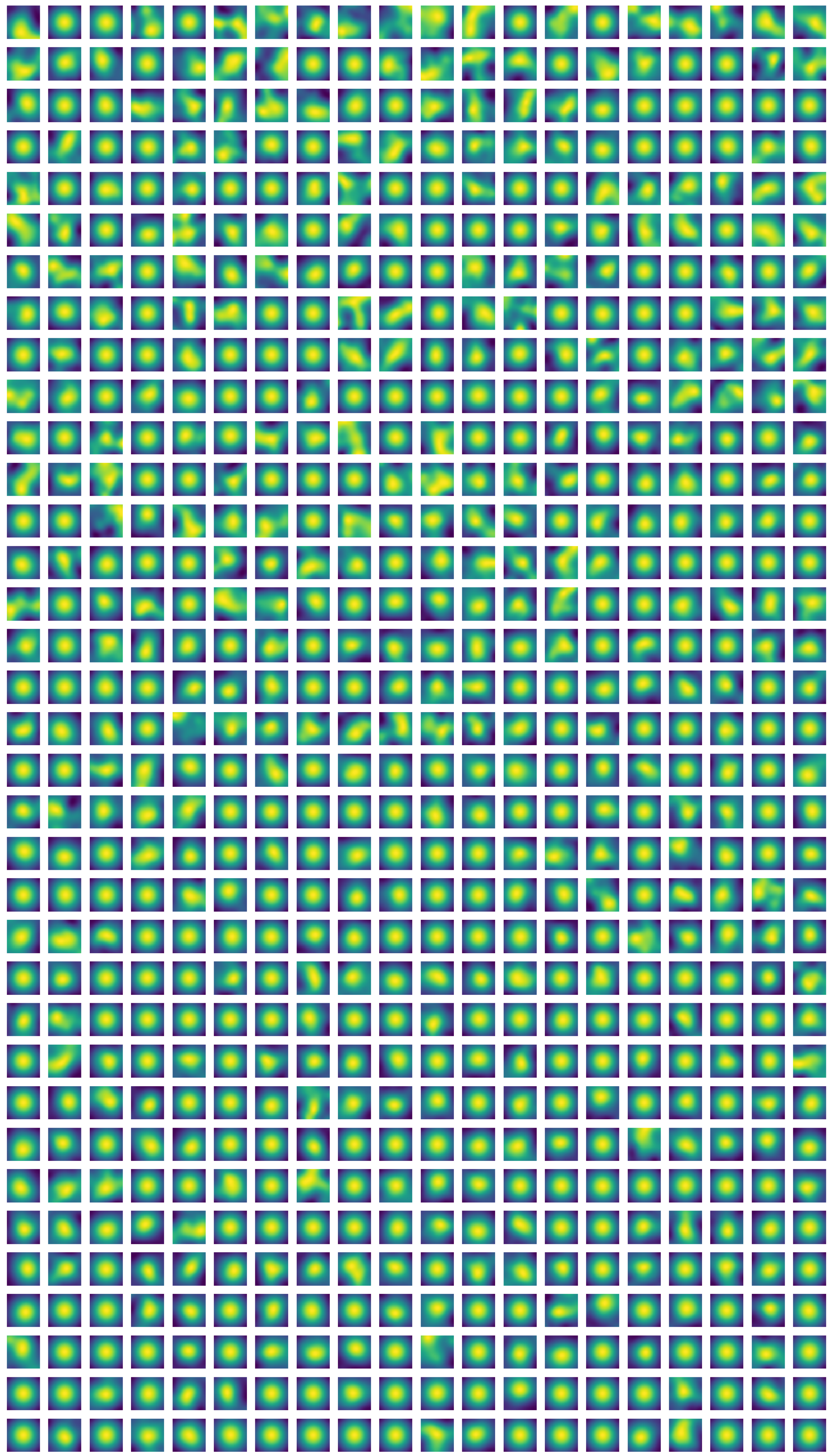
Edgar Baumler (Hausser lab, UCL)

Application to the hippocampus (ongoing)



optogenetic receptive field mapping in CA1





Edgar Baumler (Hausser lab, UCL)

Possible future directions

A. Uncertainty-aware stimulus optimization

B. Adaptive closed-loop approaches to mapping ORFs

C. Hologram shape optimization

Acknowledgements

Columbia:
- **Liam Paninski (PI)**
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- **Marta Gajowa**
- Masato Sadahiro

UCL:
- Michael Hausser (PI)
- **Edgar Baumler**

COLUMBIA | Zuckerman Institute
MORTIMER B. ZUCKERMAN MIND BRAIN BEHAVIOR INSTITUTE

NIH

Funding:
NIH BRAIN K99/R00

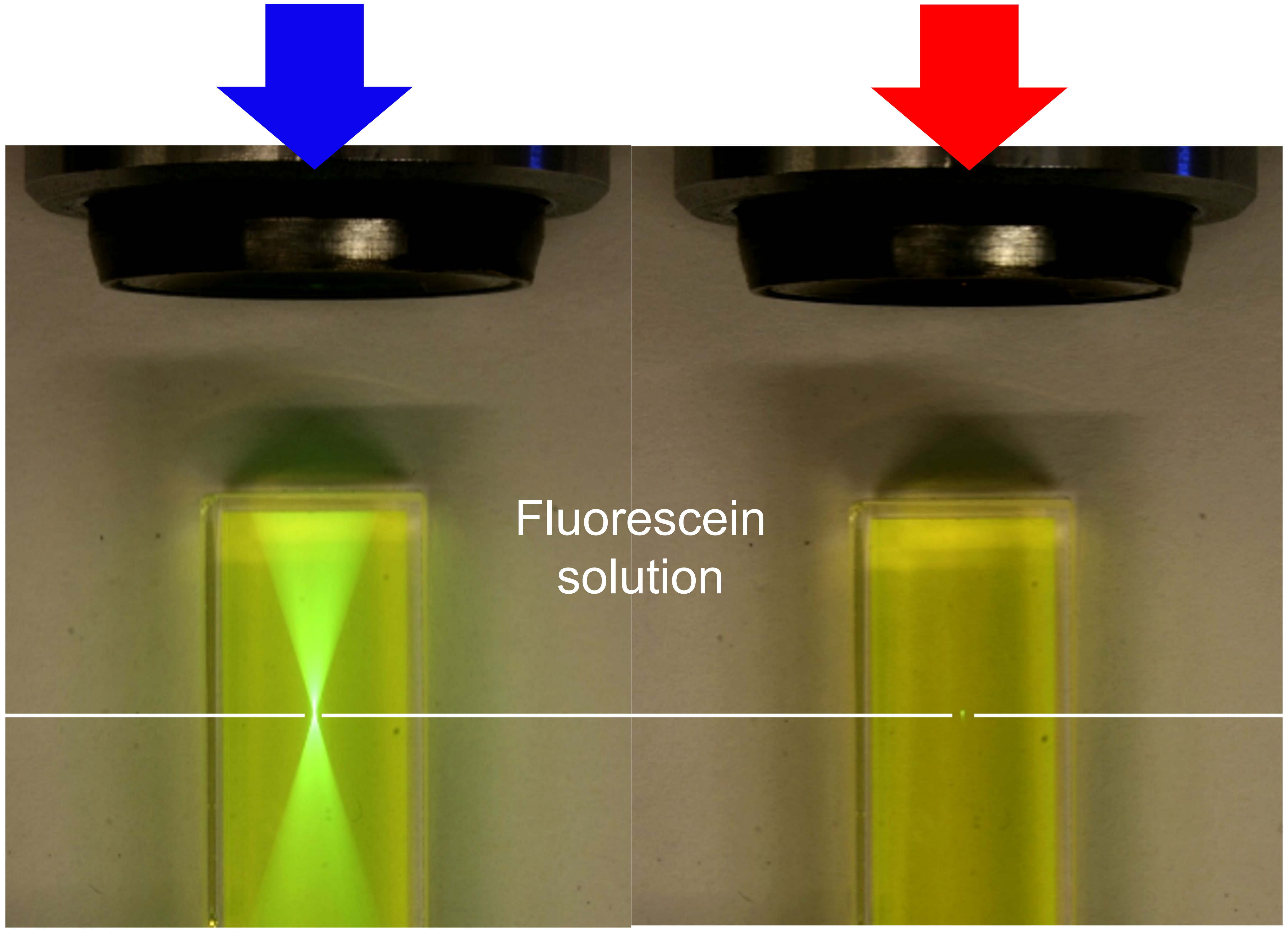
Two-photon microscopy

One Photon

$Signal \propto I$

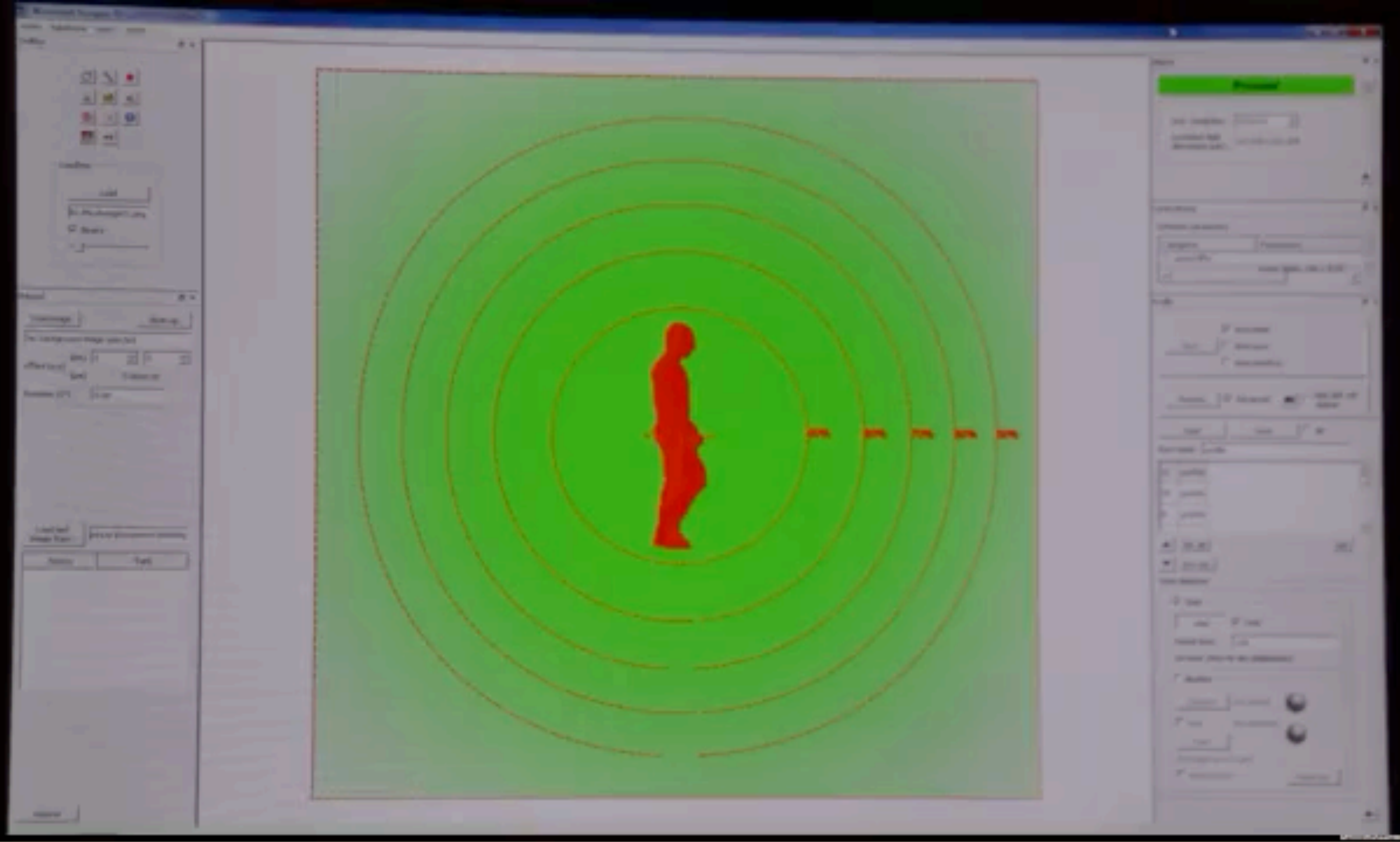
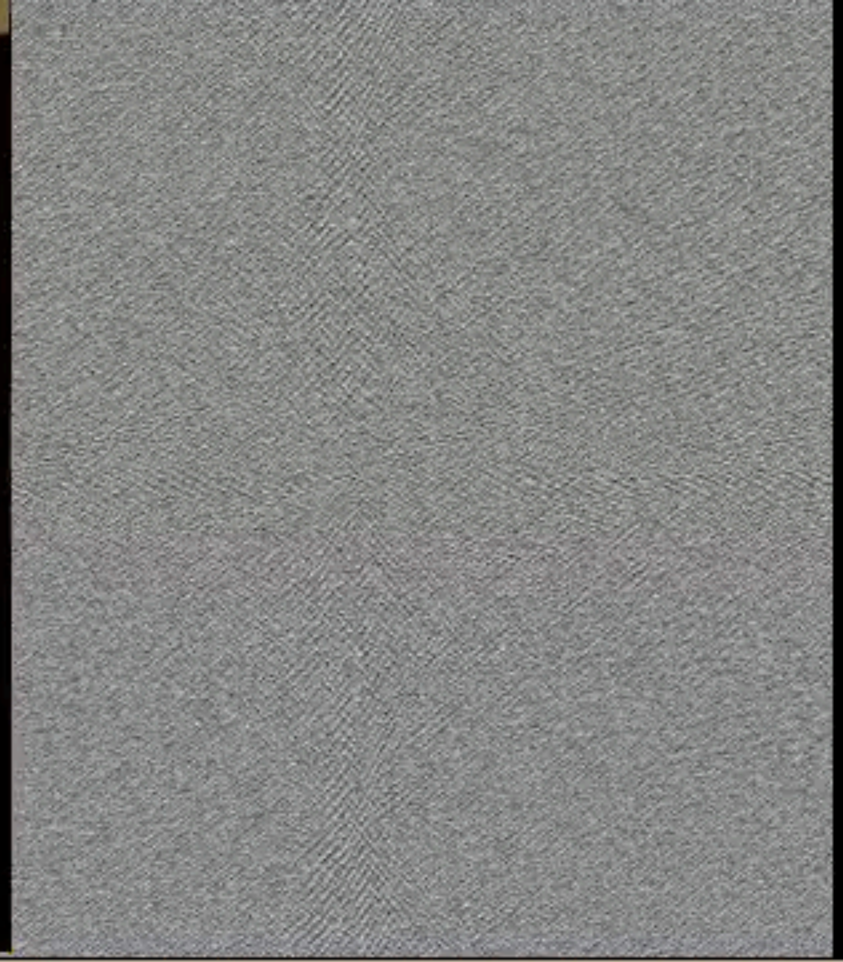
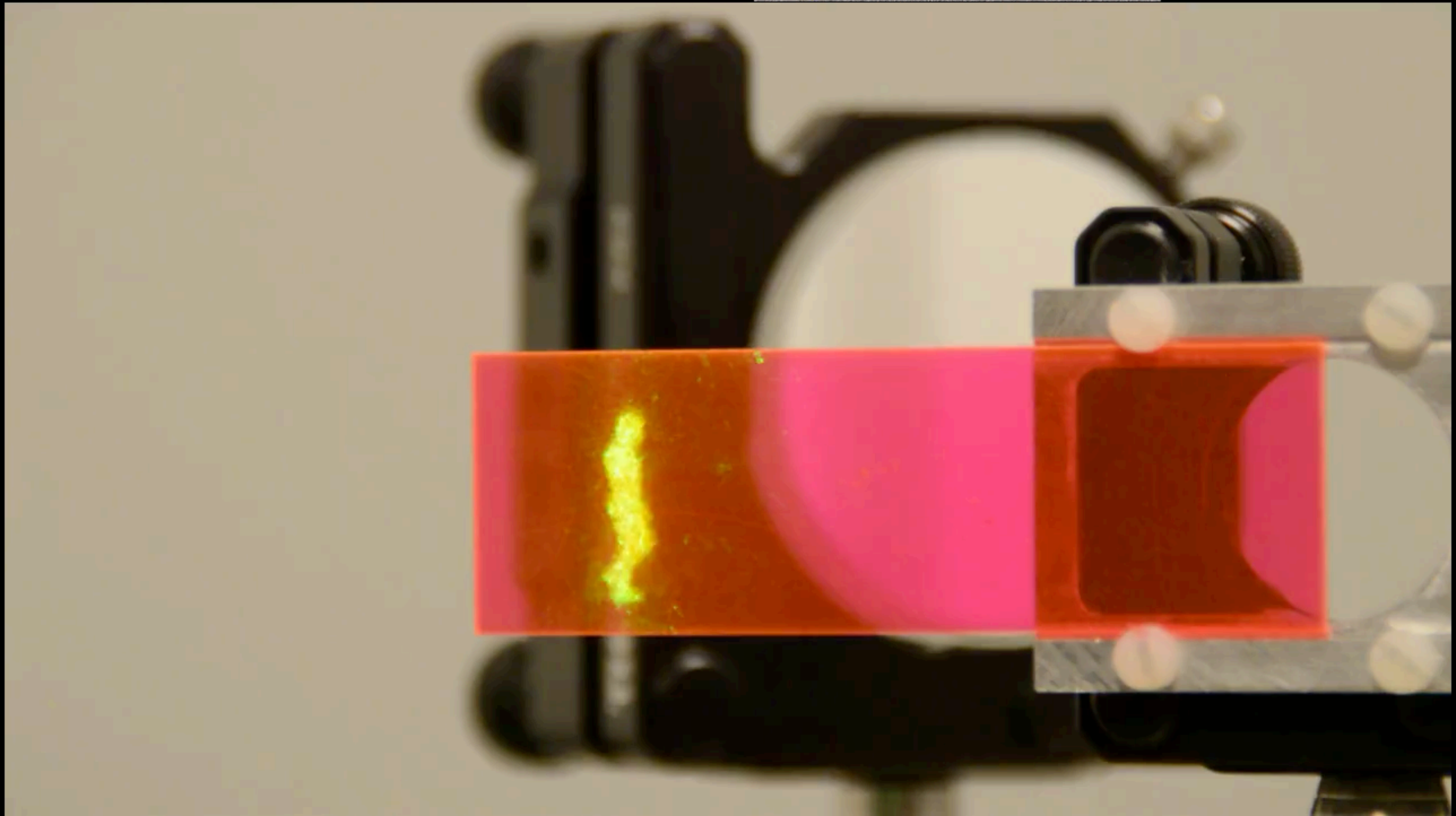
Two Photon

$Signal \propto I^2$

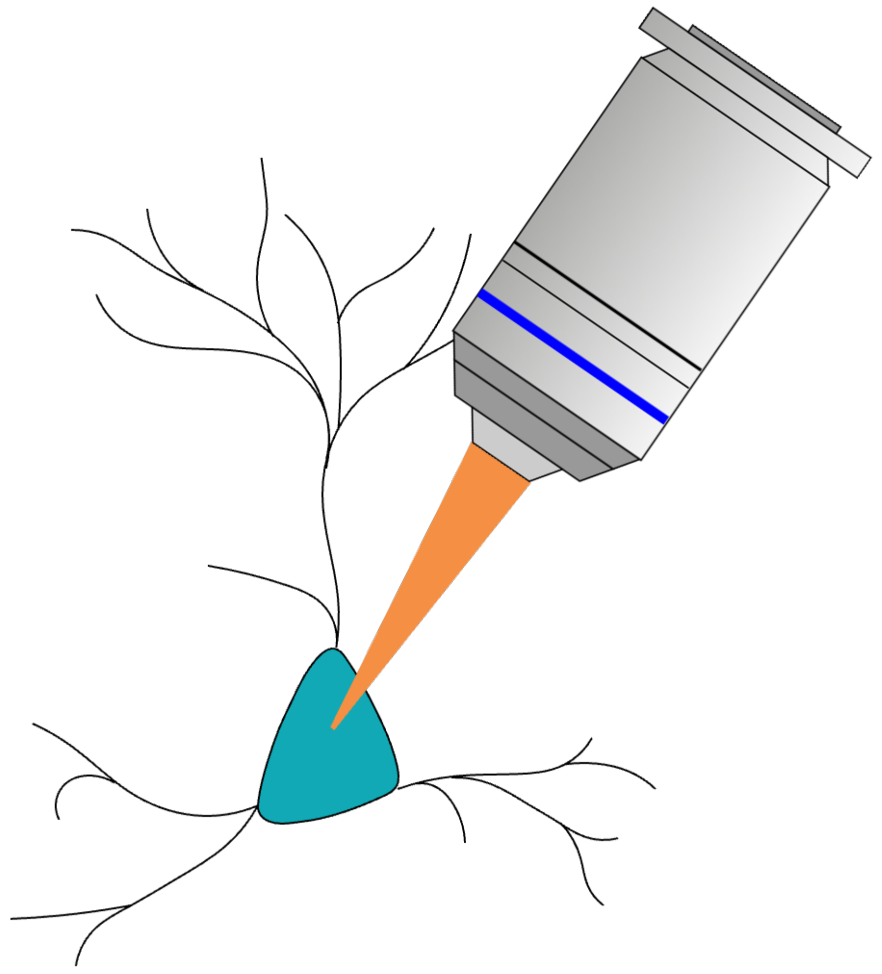


3D scanning of the focal spot to form a 3D image.

Chris Xu

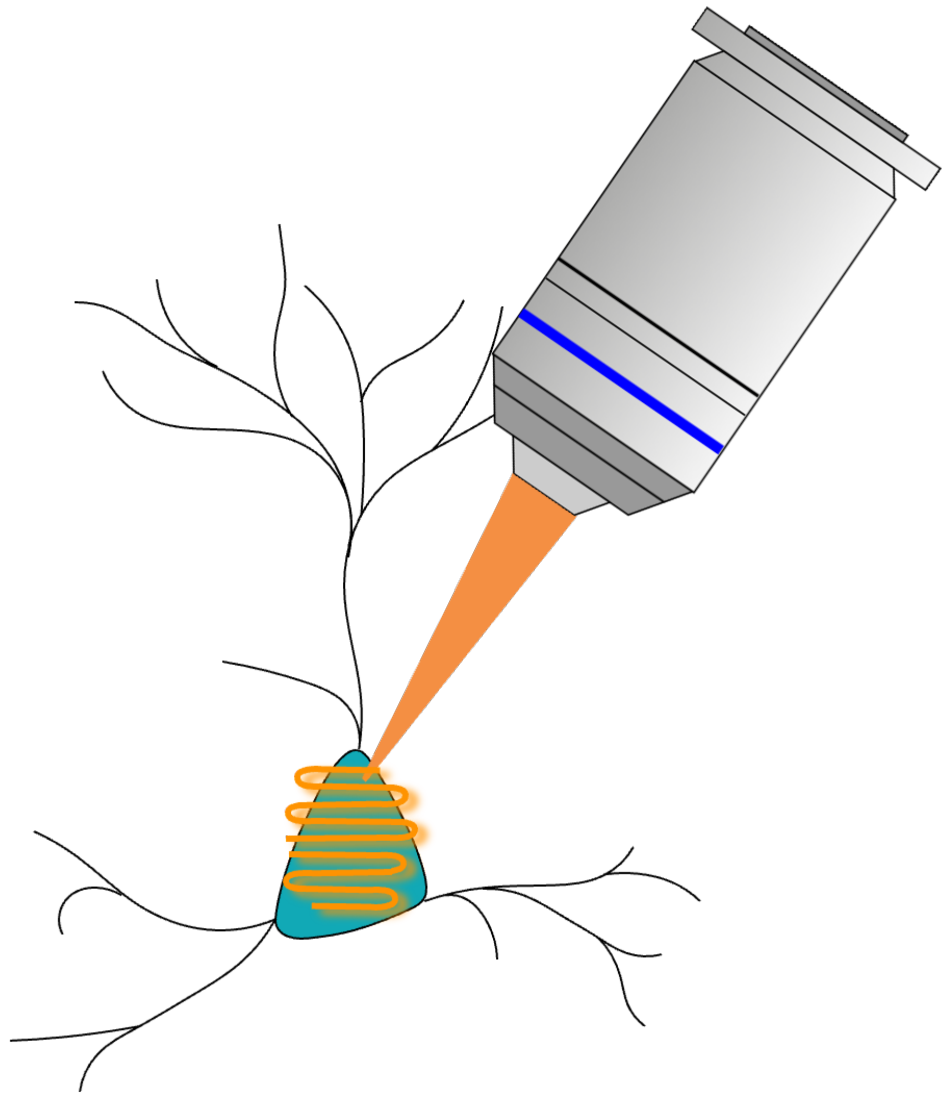




Niccolo Accanto

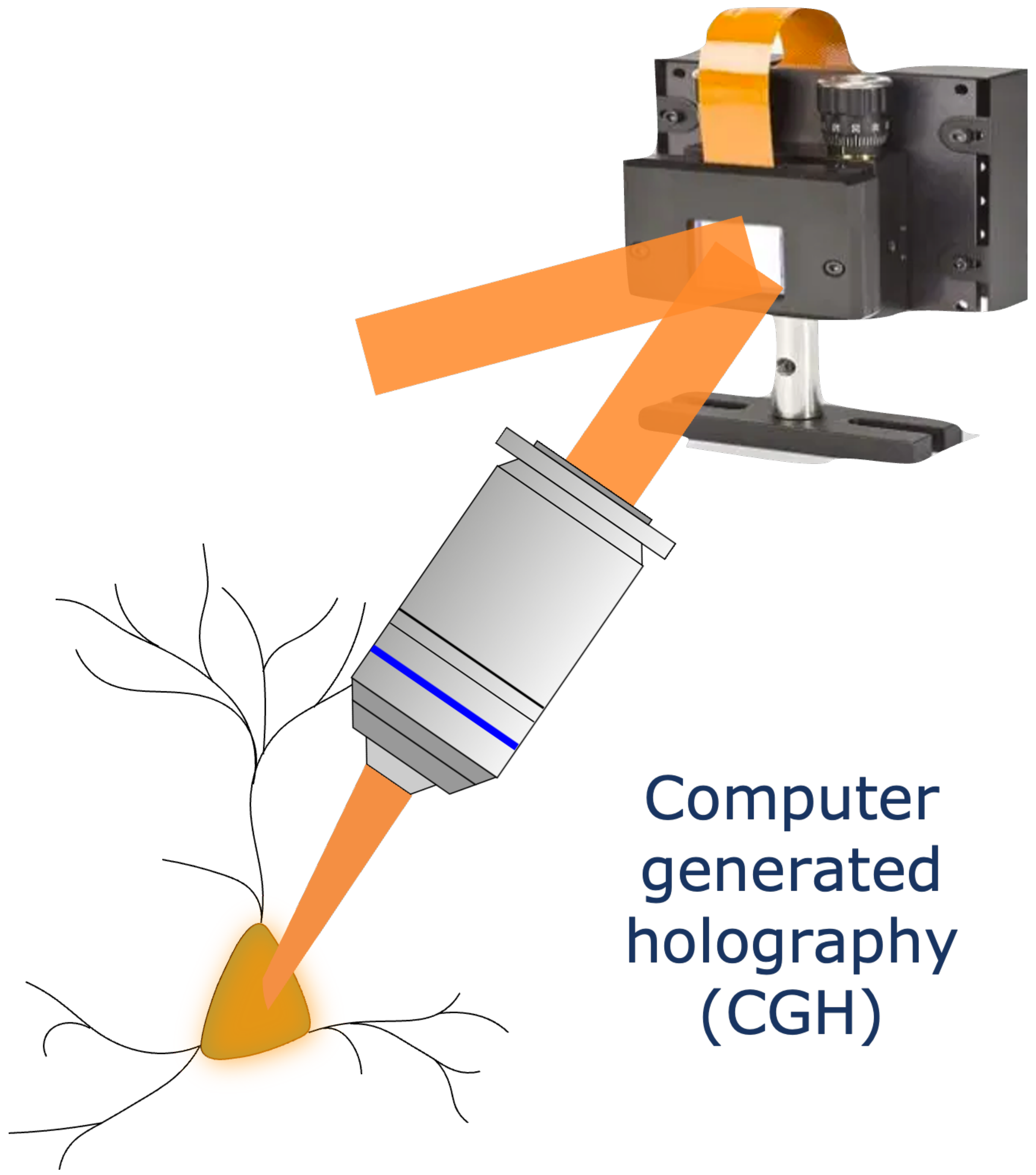


Small focal volume
Small number opsin
Not enough current for AP

Scanning spot



Rickgauger, Tank, PNAS, 2009

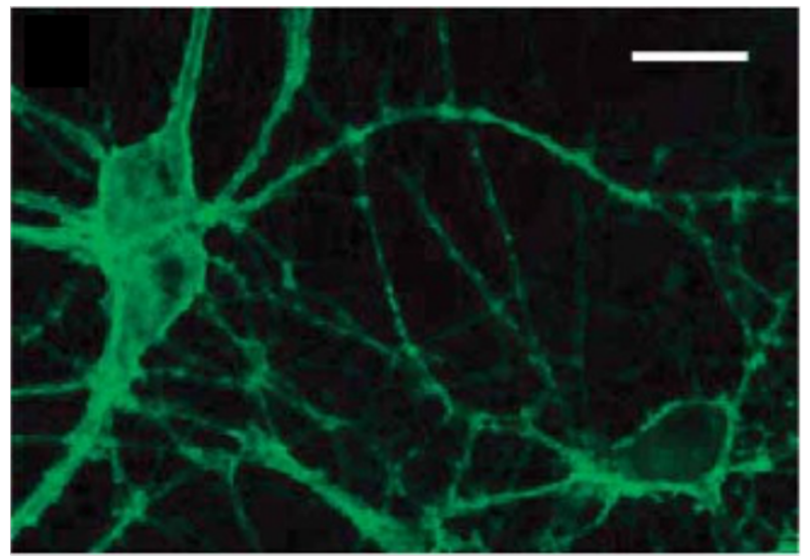


Computer generated holography (CGH)

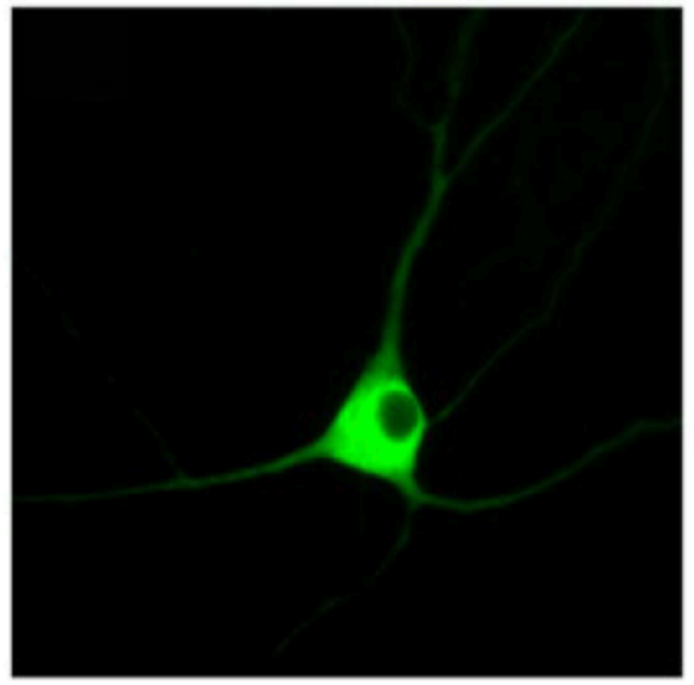
New technology for optogenetics

New technology for optogenetics

Untargeted opsin



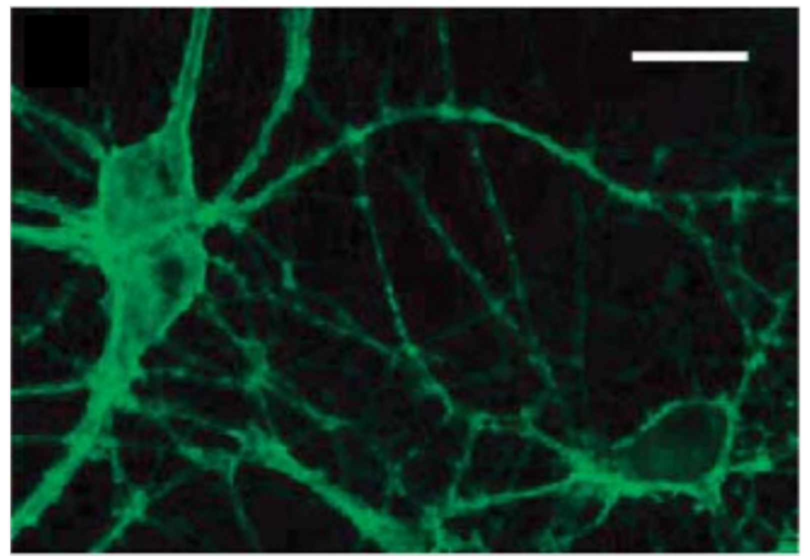
Soma-targeted



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

New technology for optogenetics

Untargeted opsin



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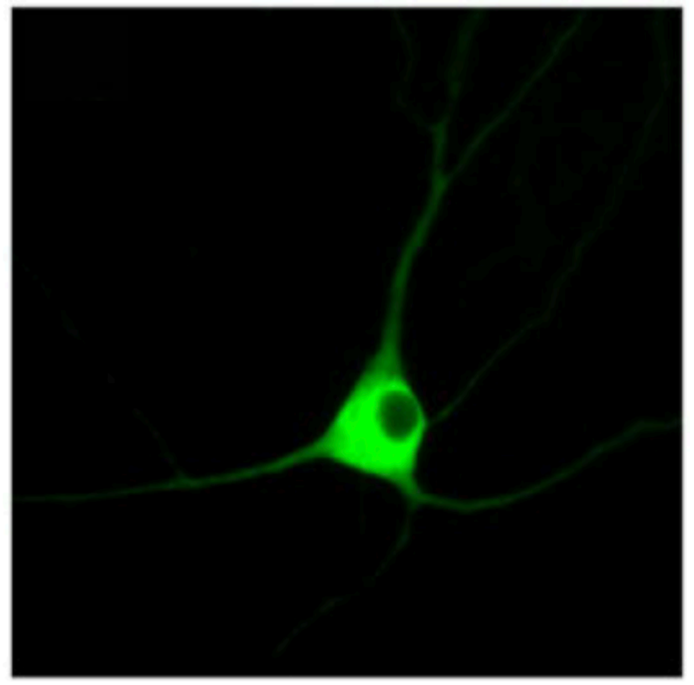
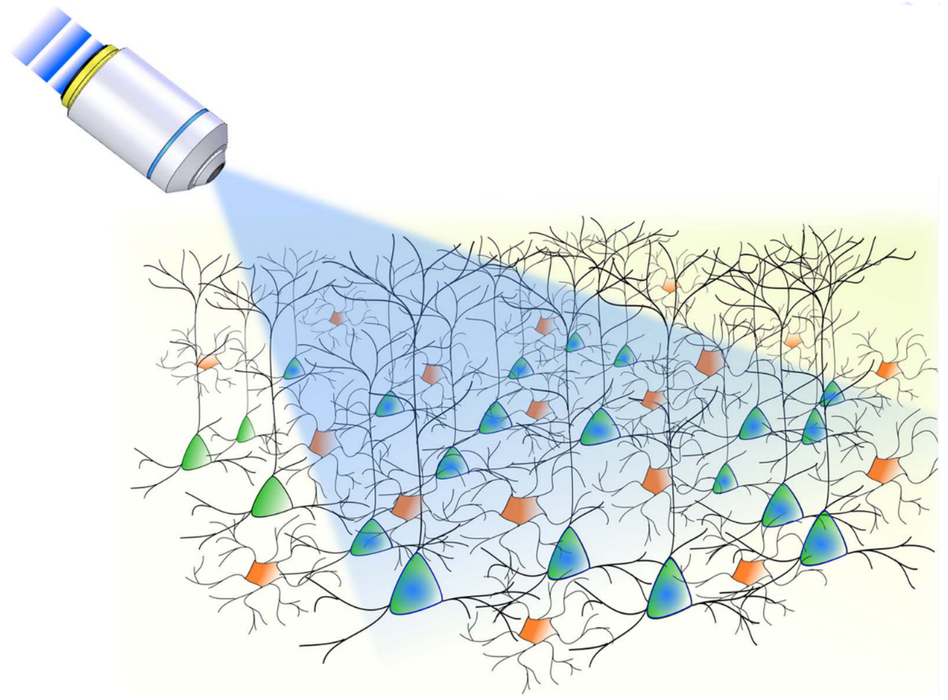
Soma-targeted



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

Widefield 1p illumination



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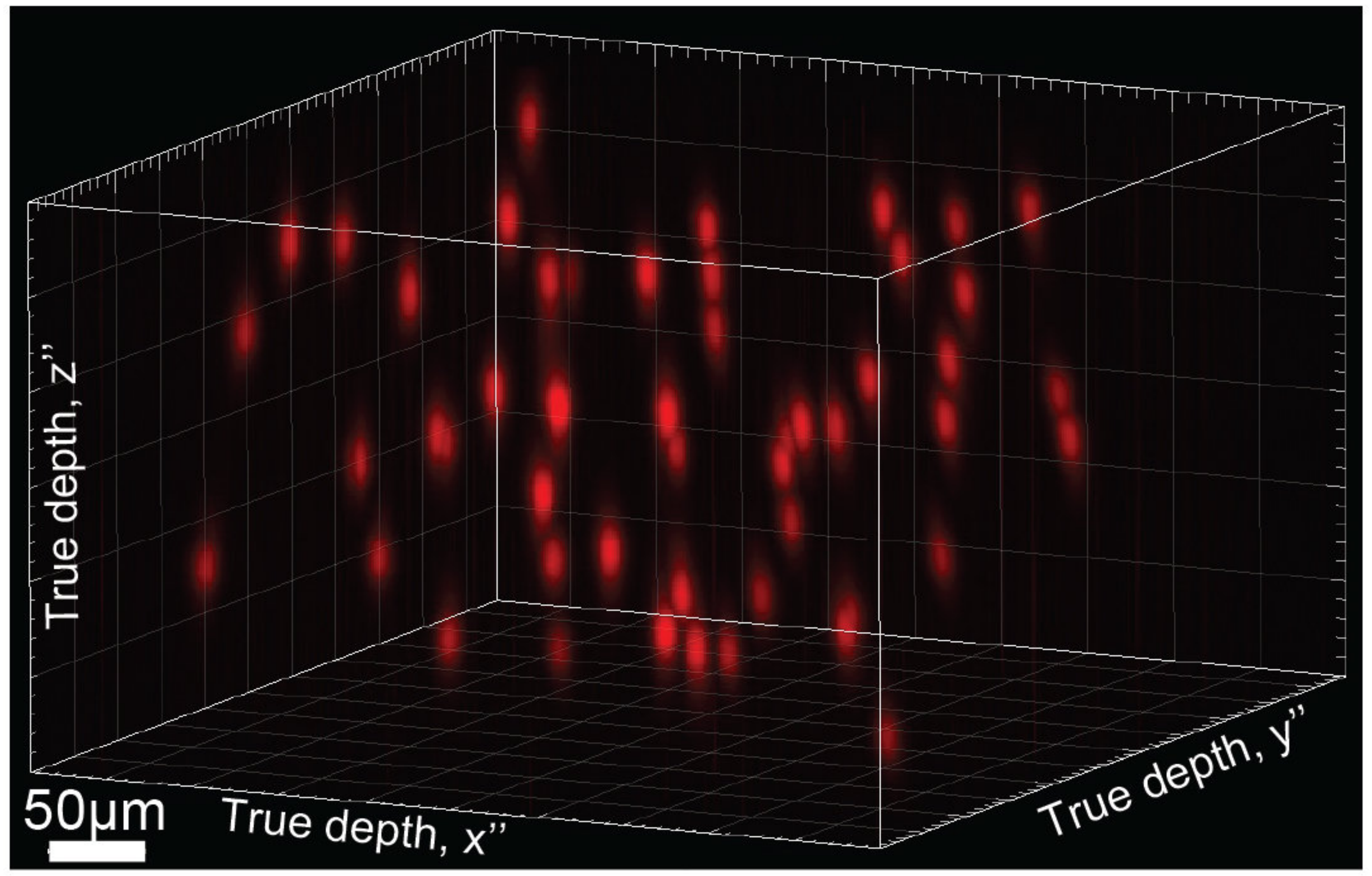
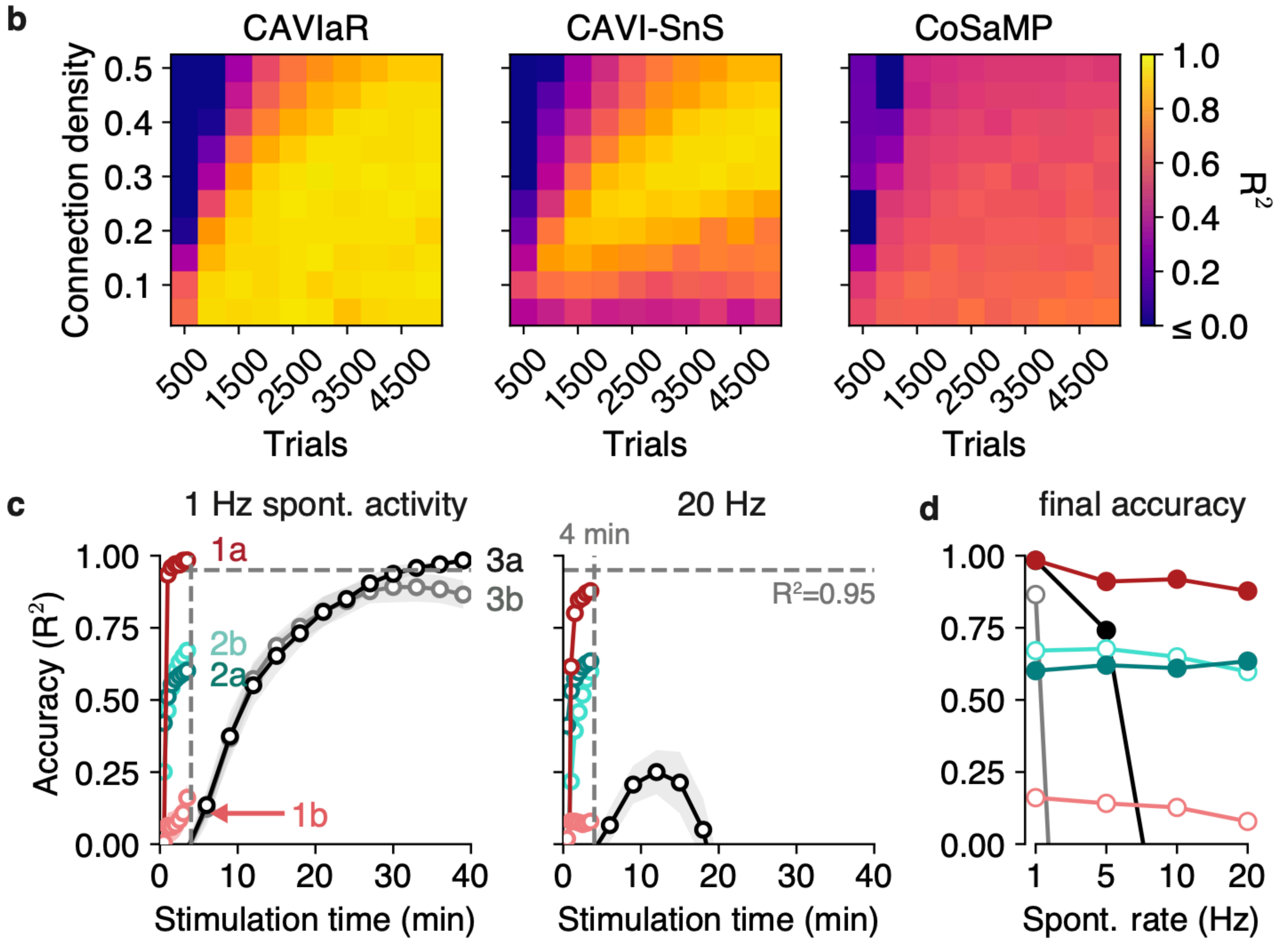
Holographic 2p



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

Performance testing in simulation



1a. 20-cell ensemble mapping (50 Hz, CAVIaR with NWD)

1b. 20-cell ensemble mapping (50 Hz, CAVIaR without NWD)

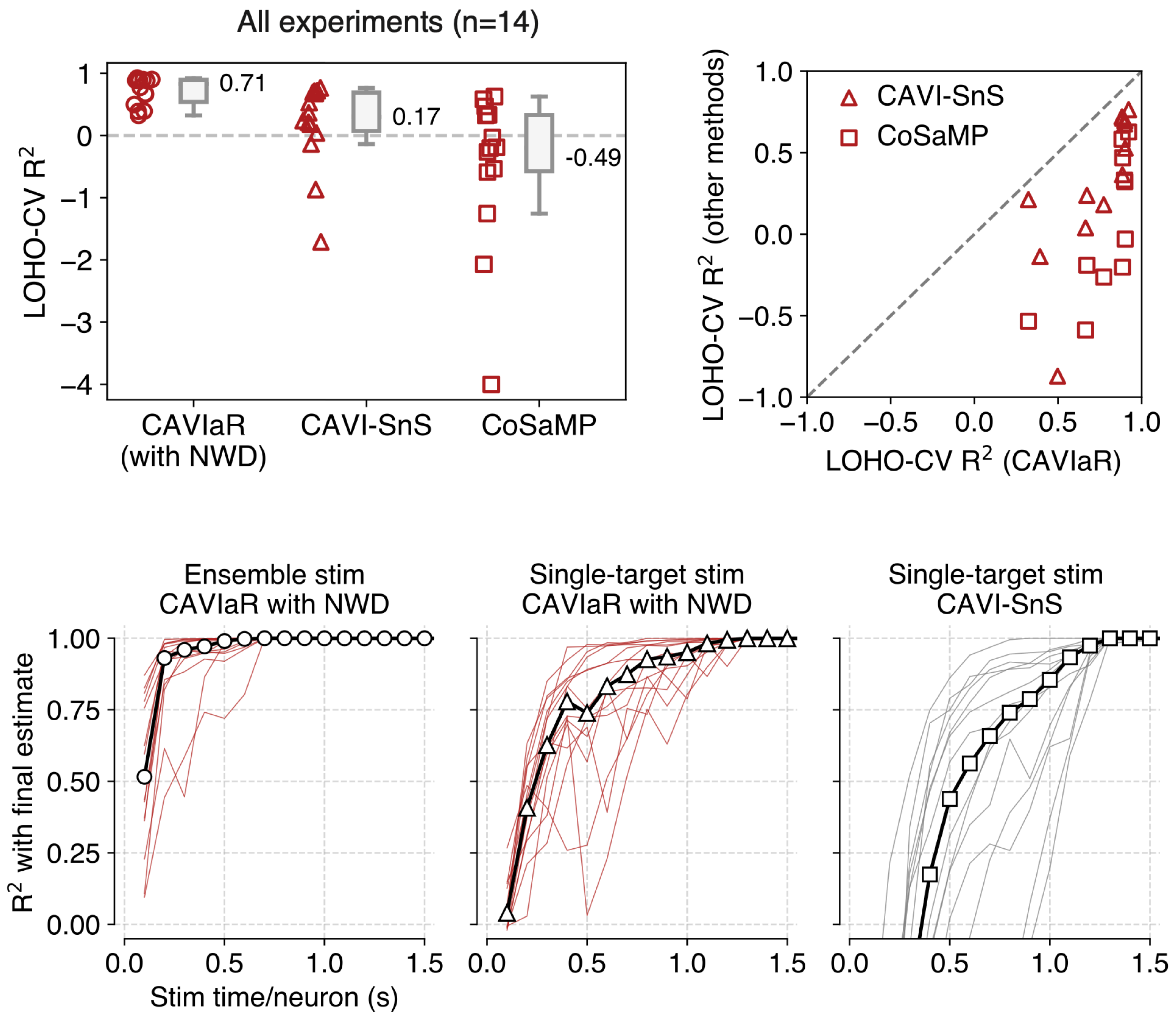
2a. 20-cell ensemble mapping (50 Hz, CoSaMP with NWD)

2b. 20-cell ensemble mapping (50 Hz, CoSaMP without NWD)

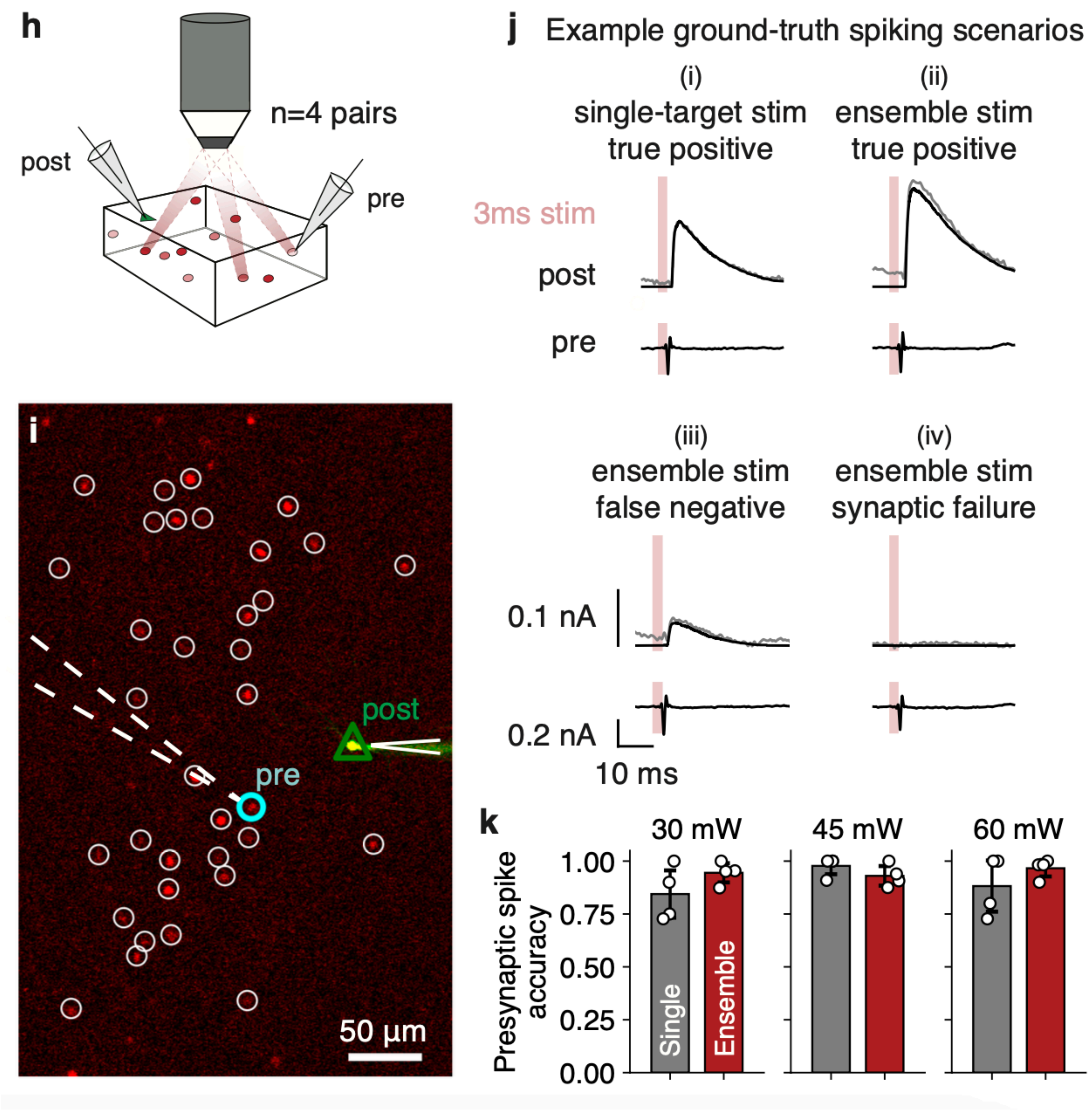
3a. Single-cell mapping (10 Hz, CAVI-SnS with NWD)

3b. Single-cell mapping (10 Hz, CAVI-SnS without NWD)

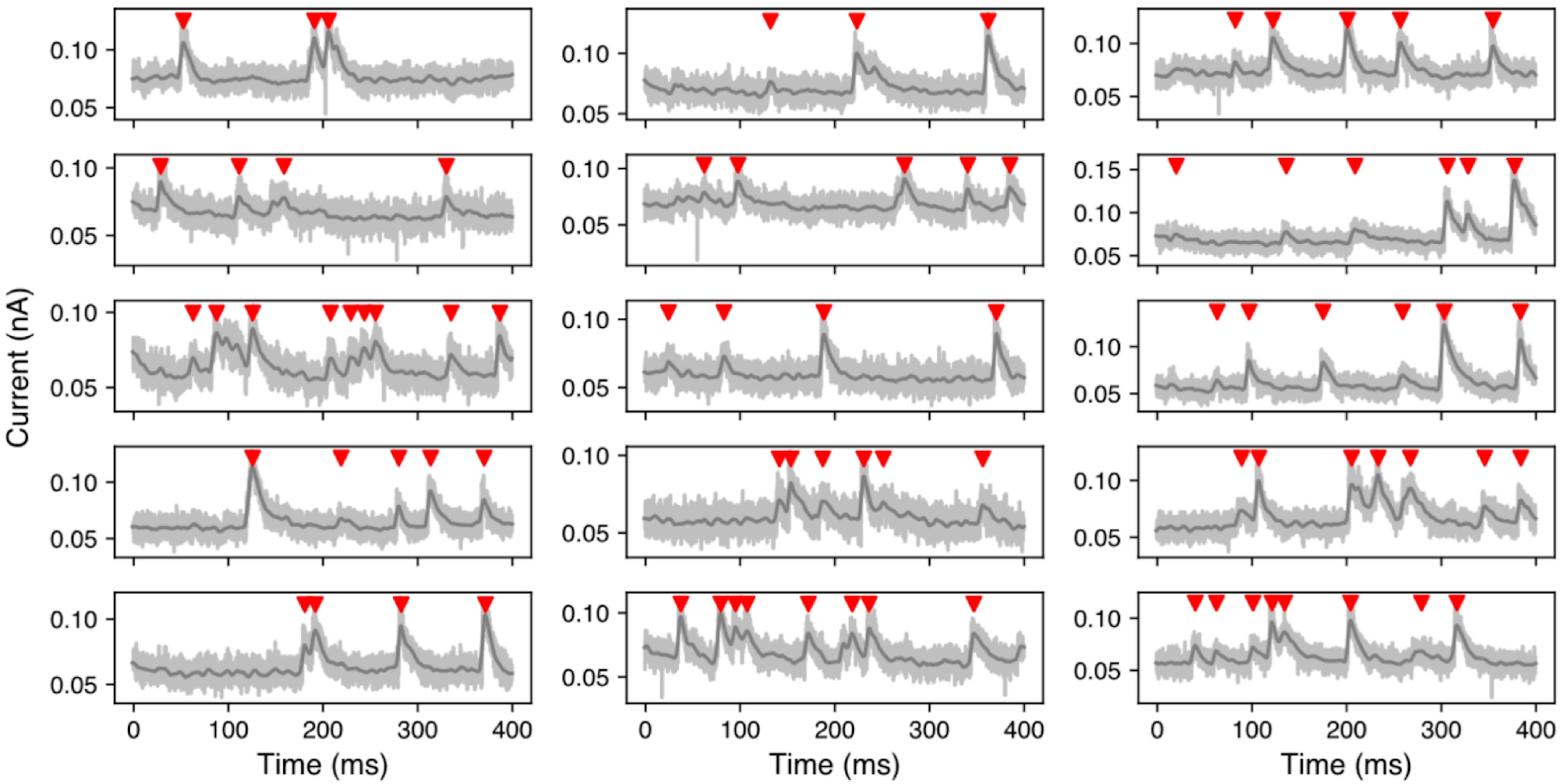
Predictive performance and convergence rates

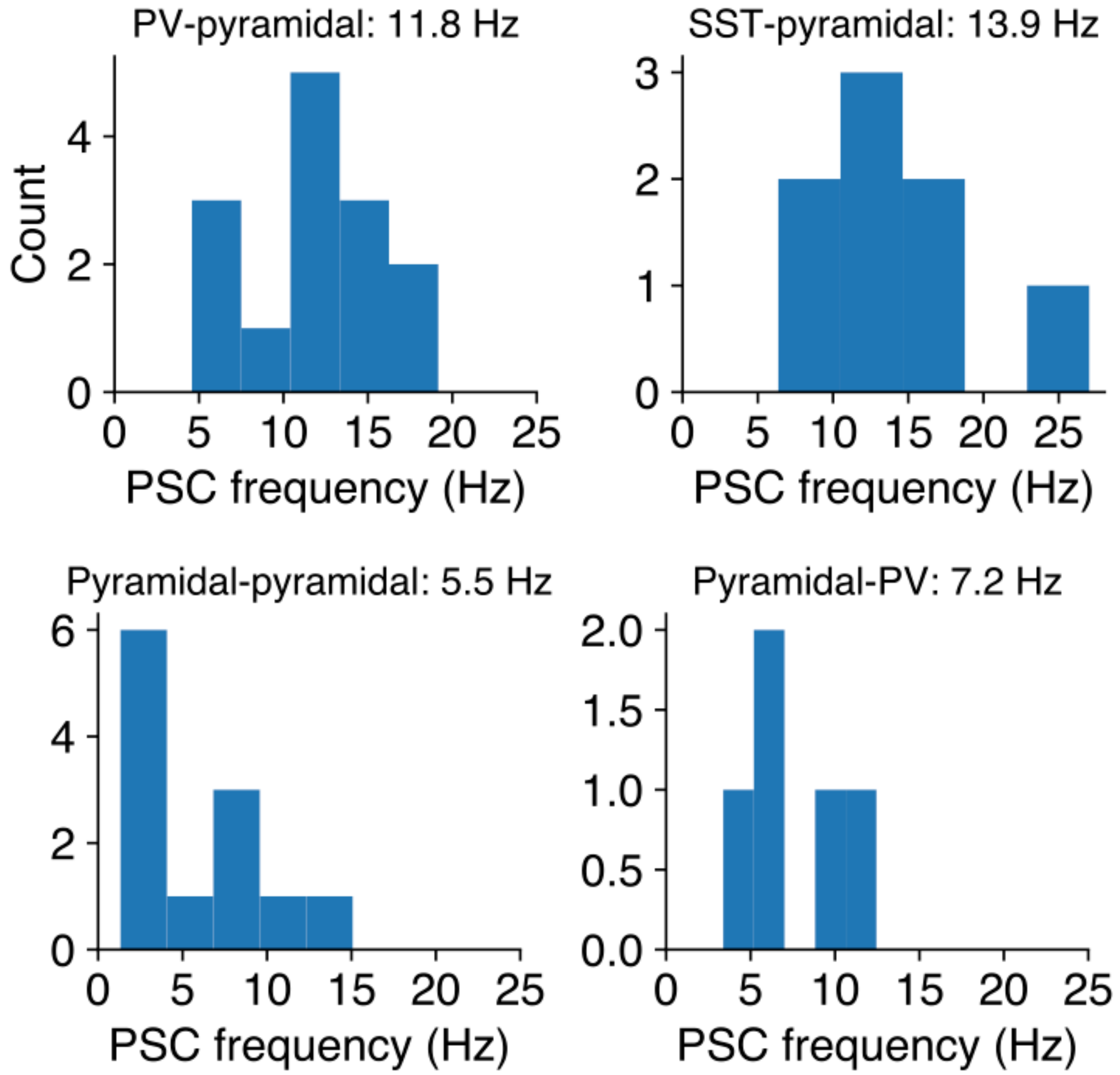


Paired-patch experiments

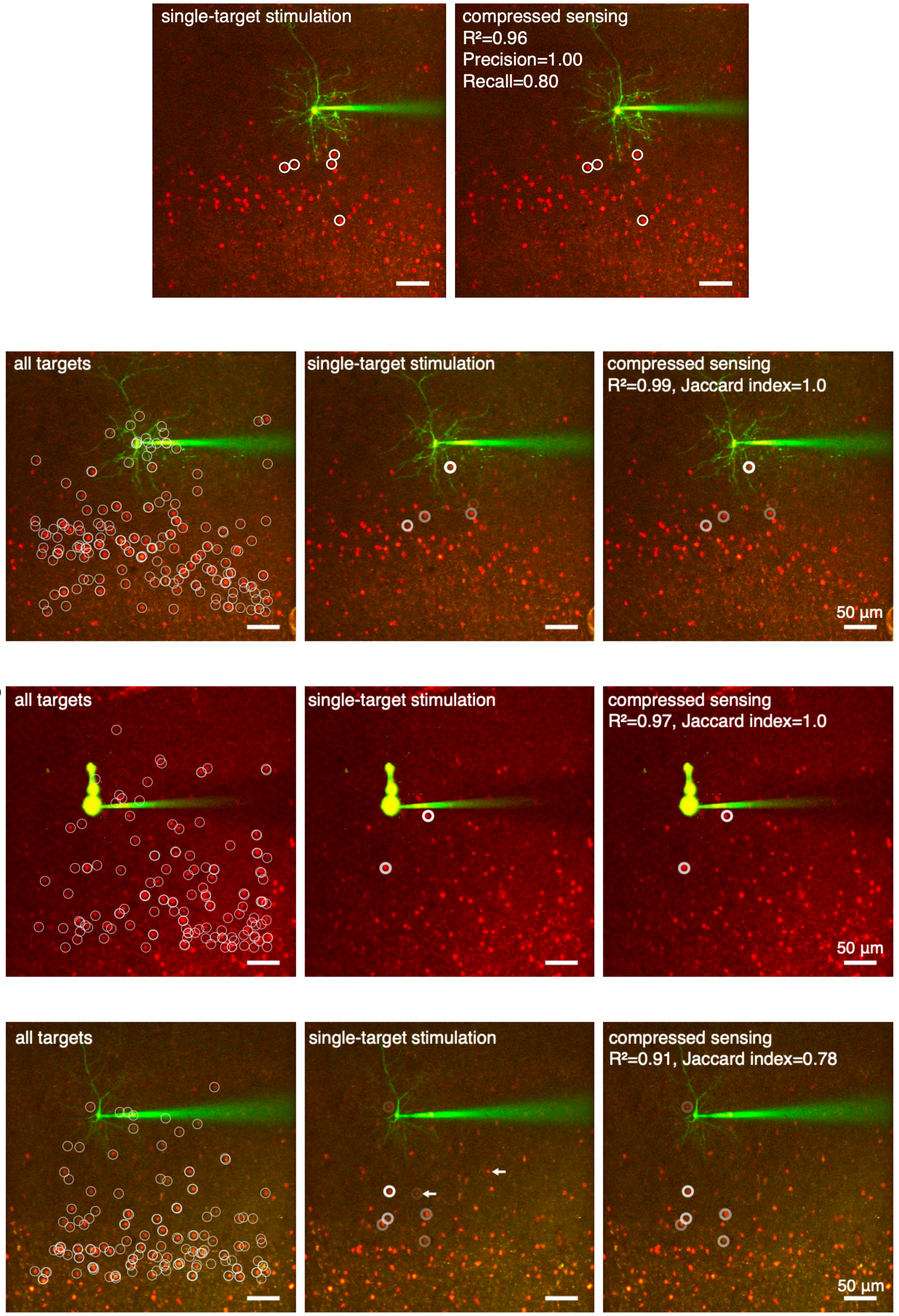


In vitro spontaneous activity rates





Additional examples



Photocurrent removal using NWD