Bayesian target optimisation for high-precision holographic optogenetics

Marcus Triplett
Paninski Lab
“Classical” optogenetics

Boyden et al (2005)
Zhang et al (2007)
“Classical” optogenetics

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“Classical” optogenetics

Boyden et al (2005)
Zhang et al (2007)
“Classical” optogenetics

- Wide-spread activation of neural circuits can drive behavioural responses
- But, no precision beyond genetically-defined cell types

*Ronzitti et al (2017)*
New technology for optogenetics
New technology for optogenetics

Untargeted opsin


Soma-targeted
New technology for optogenetics

Untargeted opsin

Widefield 1p illumination

Soma-targeted

Holographic 2p

Two-photon holography
Two-photon holographic optogenetics

Adesnik lab (UC Berkeley)
Sridharan et al (2022), Neuron
See also Emiliani, Yuste, Hausser, etc
Two-photon holographic optogenetics

Adesnik lab (UC Berkeley)
Sridharan et al (2022), Neuron

See also Emiliani, Yuste, Hauser, etc
A key limitation of two-photon optogenetics
A key limitation of two-photon optogenetics

Holographic ensemble stimulation

Target neuron
Naive holo

opsin concentration
low
high

Off-target stimulation

Triplett, …, Paninski (2023)
A key limitation of two-photon optogenetics

Holographic ensemble stimulation

Opstin concentration

low high

Target neuron

Naive holo

Off-target stimulation

Naive holo concentration

low high

Nuclear stimulation

Spike probability

Write-in error = 7.84

Target neurons

Triplett, …, Paninski (2023)
A key limitation of two-photon optogenetics

Probing neural codes with two-photon holographic optogenetics

Hillel Adesnik and Lamiae Abdeladim

Triplet, …, Paninski (2023)
A key limitation of two-photon optogenetics

Probing neural codes with two-photon holographic optogenetics

Harel Adesnik⁣ and Lamiae Abdeladim⁣

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
A key limitation of two-photon optogenetics

Optical resolution is not the limiting factor for spatial precision of two-photon optogenetic photostimulation

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

doi: https://doi.org/10.1101/2023.07.01.547318
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)
Target optimisation strategies

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Triplett et al (2023)
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Target optimisation strategies

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Triplett et al (2023)
Bayesian target optimisation
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**Goal:** Minimise off-target activation for any requested ensemble stimulus
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1. Mapping phase: learn optogenetic receptive fields
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
Optogenetic receptive field model

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

\[ \gamma_{nt} = \sum_{j=1}^{J} g_n(x^j_t) - \theta_n \]

Bernoulli observation model

summed 2p excitation from \( J \) holographic targets \( x^j_t \)
Optogenetic receptive field model

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

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Optogenetic receptive field model

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

\[ \gamma_{nt} = \sum_{j=1}^{J} g_{n}(x_{j}^{n}) - \theta_{n} \]

\[ g_{n} \sim \text{GP}(m_{n}(\cdot), k(\cdot, \cdot)) \]

Bernoulli observation model

summed 2p excitation from \( J \) holographic targets \( x_{j}^{n} \)

Gaussian process: nonparametric, smooth in space + power
Optogenetic receptive field model

\[ \gamma_{nt} \sim \text{Bernoulli}(\sigma(\gamma_{nt})) \]

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

summed 2p excitation from \( J \) holographic targets \( x^j_t \)

Gaussian process: nonparametric, smooth in space + power

\[ m_n(x) = \rho I \exp\left(-\|c - L_n\|^2/\sigma^2_m\right) \]

mean function (for stimulus \( x = (I, c) \))
Optogenetic receptive field model

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

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mean function (for stimulus \( x = (I, c) \))

\[ k(x, x') = \alpha^2 \exp(- (x - x')^T \Lambda (x - x')/2) \]

covariance kernel (RBF/radial basis function)
Optogenetic receptive field model

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

\[ \gamma_{nt} = \sum_{j=1}^{J} g_n(x_t^j) - \theta_n \]

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Mapping phase

Holographic ensemble stimulation + calcium imaging

- Map many ORFs simultaneously
- Model how neurons integrate 2p excitation from multiple holograms at once
Holographic ensemble stimulation + calcium imaging

Mapping phase
Holographic ensemble stimulation + calcium imaging

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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Holographic ensemble stimulation + calcium imaging

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Model

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a. Map many ORFs simultaneously

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

**Holographic ensemble stimulation + calcium imaging**

**Model**

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

\[ \gamma_{nt} = \sum_{j=1}^{J} g_n(x_j^t) - \theta_n \]

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

**Inference**

\[ \hat{g}_n, \hat{\theta}_n = \arg\max_{g_n, \theta_n} \left\{ \sum_t \ln p(y_{nt} | x_t, g_n, \theta_n) + \ln p(g_n(X) | \phi) \right\} \]

such that \( g_n(x_t) \geq 0 \) for \( t = 1, \ldots, T \)
Holographic ensemble stimulation + calcium imaging

a. Map many ORFs simultaneously

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

Model

\[ y_{nt} \sim \text{Bernoulli}(\sigma(\gamma_{nt})) \]
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such that \( g_n(x_t) \geq 0 \) for \( t = 1, \ldots, T \)

Specifics:
- Newton’s method
- Backtracking linesearch for stepsize
- Log-barrier meets non-negativity constraints
- Implemented in JAX (GPU)
Mapping phase

Holographic ensemble stimulation + calcium imaging

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

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\[ y_{nt} \sim \text{Bernoulli}(\sigma(y_{nt})) \]
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Triplett et al (2023)
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- Newton’s method
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Triplett et al (2023)
Optimisation phase

Given inferred ORFs, how to optimally place holographic targets?
Optimisation phase

Given inferred ORFs, how to optimally place holographic targets?

**Predicted evoked response**

$$\hat{y}(x, \mathcal{G}) = (\sigma(\hat{\gamma}_1(x)), \ldots, \sigma(\hat{\gamma}_N(x))) \in \mathbb{R}^N$$

$$\hat{\gamma}_n(x) = \sum_{j=1}^{J} \hat{g}_n(x^j) - \hat{\theta}_n$$

$$\mathcal{G} = \{ \hat{g}_n, \hat{\theta}_n \}_{n=1}^{N}$$
Optimisation phase

Given inferred ORFs, how to optimally place holographic targets?

**Predicted evoked response**

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\hat{y}(x, \mathcal{G}) = (\sigma(\hat{\gamma}_1(x)), \ldots, \sigma(\hat{\gamma}_N(x))) \in \mathbb{R}^N
\]

\[
\hat{\gamma}_n(x) = \sum_{j=1}^{J} \hat{\gamma}_n(x^j) - \hat{\theta}_n
\]

\[
\mathcal{G} = \{\hat{\gamma}_n, \hat{\theta}_n\}_{n=1}^{N}
\]

**Target activity pattern**

\[
\Omega \in \{0,1\}^N
\]
Optimisation phase

Given inferred ORFs, how to optimally place holographic targets?

Predicted evoked response

\[ \hat{y}(x, G) = (\sigma(\hat{y}_1(x)), \ldots, \sigma(\hat{y}_N(x))) \in \mathbb{R}^N \]

\[ \hat{y}_n(x) = \sum_{j=1}^{J} \hat{g}_n(x^j) - \hat{\theta}_n \]

\[ G = \{\hat{g}_n, \hat{\theta}_n\}_{n=1}^{N} \]

Target activity pattern

\[ \Omega \in \{0,1\}^N \]

Optimisation problem

\[ x_{\text{optimal}} = \arg \min_x \|\Omega - \hat{y}(x, G)\|^2 \text{ such that } 0 \leq I \leq I_{\text{max}} \]
Optimisation phase

Given inferred ORFs, how to optimally place holographic targets?

Predicted evoked response

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\[ x_{\text{optimal}} = \arg \min_x \| \Omega - \hat{y}(x, \mathcal{G}) \|^2 \text{ such that } 0 \leq I \leq I_{\text{max}} \]

\[ x_{\text{optimal}} = \arg \min_x \mathbb{E}_{q(\mathcal{G})} \left[ \| \Omega - \hat{y}(x, \mathcal{G}) \|^2 \right] \text{ such that } 0 \leq I \leq I_{\text{max}} \] (single-target stim case)
Optimisation phase

Given inferred ORFs, how to optimally place holographic targets?

Predicted evoked response

\[
\hat{y}(\mathbf{x}, \mathcal{G}) = (\sigma(\hat{y}_1(\mathbf{x})), \ldots, \sigma(\hat{y}_N(\mathbf{x}))) \in \mathbb{R}^N
\]

\[
\hat{y}_n(\mathbf{x}) = \sum_{j=1}^{J} \hat{g}_n(x^j) - \hat{\theta}_n
\]

\[
\mathcal{G} = \{\hat{g}_n, \hat{\theta}_n\}^N_{n=1}
\]

Target activity pattern

\[
\Omega \in \{0,1\}^N
\]

Optimisation problem

\[
\mathbf{x}_{\text{optimal}} = \arg\min_x \|\Omega - \hat{y}(\mathbf{x}, \mathcal{G})\|^2 \text{ such that } 0 \leq I \leq I_{\text{max}}
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\]

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 $\frac{\partial}{\partial x_d} g_n(x)$ is also a GP.

McHutchon (2014, PhD Thesis)
Optimisation phase

Approach

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

$$\text{cov}(g_n(x_t), \frac{\partial}{\partial x_\star} g_n(x_\star)) = \frac{\partial k(x_t, x_\star)}{\partial x_\star}$$

for sampled point $x_t$ and test point $x_\star$.

McHutchon (2014, PhD Thesis)
Optimisation phase

Approach

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

$$\text{cov}(g_n(x_t), \frac{\partial}{\partial x_d} g_n(x^*)) = \frac{\partial k(x_t, x^*)}{\partial x_d^*}$$

for sampled point $x_t$ and test point $x^*$

> Can perform inference of derivatives from a few sampled points

McHutchon (2014, PhD Thesis)
Optimisation phase

**Approach**

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

\[
\text{cov}(g_n(x), \frac{\partial}{\partial x} g_n(x)) = \frac{\partial k(x, x^*)}{\partial x^*}
\]

for sampled point $x_i$ and test point $x^*$

> Can perform *inference* of derivatives from a few sampled points

\[
\frac{\partial \hat{g}_n(x^*)}{\partial x^*_d} = \frac{\partial m_n(x^*)}{\partial x^*_d} + \text{cov} \left( g_n(X), \frac{\partial g_n(x^*)}{\partial x^*_d} \right)^\top K^{-1}(\hat{g}_n(X) - m_n(X))
\]

McHutchon (2014, PhD Thesis)
Optimisation phase

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> Can perform inference of derivatives from a few sampled points
Optimisation phase

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

1. Initialise stimulus $x$
Optimisation phase

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

1. Initialise stimulus $x$

2. Infer gradient vectors $\nabla_x \hat{y}_n(x)$ for $n = 1, \ldots, N$

$$\hat{y}_n(x) = \sum_{j=1}^{J} \hat{g}_n(x^j) - \hat{\theta}_n$$
Optimisation phase

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

1. Initialise stimulus $x$

2. Infer gradient vectors $\nabla_x \hat{y}_n(x)$ for $n = 1, \ldots, N$

3. Set search direction $\delta_x = -2 \sum_{n=1}^{N} (\Omega_n - \sigma(\hat{y}_n(x) - \hat{\theta}_n))\sigma'(\hat{y}_n(x) - \hat{\theta}_n) \nabla_x \hat{y}_n(x)$

$\hat{y}_n(x) = \sum_{j=1}^{J} \hat{g}_n(x^j) - \hat{\theta}_n$
Optimisation phase

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

1. Initialise stimulus \( x \)

2. Infer gradient vectors \( \nabla_x \hat{y}_n(x) \) for \( n = 1, \ldots, N \)

3. Set search direction \( \delta_x = -2 \sum_{n=1}^{N} (\Omega_n - \sigma(\hat{y}_n(x) - \hat{\theta}_n)) \sigma'(\hat{y}_n(x) - \hat{\theta}_n) \nabla_x \hat{y}_n(x) \)

4. Update stimulus \( x \leftarrow x + \beta \delta_x \)

\[
\hat{y}_n(x) = \sum_{j=1}^{J} \hat{g}_n(x^j) - \hat{\theta}_n
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Optimisation phase

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

1. Initialise stimulus $x$

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4. Update stimulus $x \leftarrow x + \beta \delta_x$

5. Repeat 2-4 until convergence

$$\hat{y}_n(x) = \sum_{j=1}^{J} \hat{g}_n(x^j) - \hat{\theta}_n$$
Ensemble stimulus optimisation

Spike probability
1.0 0.5 0.1

Nuclear stimulation

Write-in error = 7.84

Target neurons
Ensemble stimulus optimisation

Spike probability
1.0  0.5  0.1

Nuclear stimulation

Optimised stimulation

Write-in error = 7.84

Write-in error = 1.61

Target neurons

Target neurons

Triplett et al (2023)
Ensemble stimulus optimisation

Spike probability
1.0 0.5 0.1

Nuclear stimulation

Optimised stimulation

Write-in error = 7.84
Write-in error = 1.61

random 6 target ensembles

Target neurons

Target neurons

Triplett et al (2023)
Ensemble stimulus optimisation

![Graph showing ensemble stimulus optimisation](image-url)
Ensemble stimulus optimisation

[Graph showing scatter plots for 50 and 150 neurons with their respective error values.]

Triplett et al (2023)
Ensemble stimulus optimisation

![Graphs showing the relationship between population size and write-in error, with optimised and nuclear conditions compared.](image-url)

50 neurons, error=2.88

150 neurons, error=16.38

Write-in error
Ensemble stimulus optimisation

- 50 neurons, error=2.88
- 150 neurons, error=16.38

- Y distance (µm)
- X distance (µm)

- Optimised
- Nuclear

- Write-in error vs Population size
- Write-in error vs Stimulated ensemble size

Triplett et al (2023)
Validated in “hybrid” experimental data

Triplett et al (2023)
Validated in “hybrid” experimental data
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Triplet et al (2023)
Validated in “hybrid” experimental data
Three-dimensional target optimisation
Three-dimensional target optimisation
Three-dimensional target optimisation

Δxy = 2 μm
Δz = 11 μm

Δxy = 14 μm
Δz = 1 μm

Triplett et al (2023)
Three-dimensional target optimisation

Δxy = 2 μm
Δz = 11 μm

Δxy = 14 μm
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Target neuron

Triplett et al (2023)
Three-dimensional target optimisation

Δxy = 2 μm
Δz = 11 μm

Δxy = 14 μm
Δz = 1 μm

Target neuron

Spike probability

Nuclear (2.03)

Optimised (<0.01)

Neuron

Triplett et al (2023)
Three-dimensional target optimisation

Target neuron

Δxy = 2 μm
Δz = 11 μm

Δxy = 14 μm
Δz = 1 μm

Target neuron

Spike probability

Triplet 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 opsins
Not enough current for AP

Scanning spot

Rickgauger, Tank, PNAS, 2009

Computer generated holography (CGH)
One Photon

\[ \text{Signal } \propto I \]

Two Photon

\[ \text{Signal } \propto I^2 \]

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

(a) High coverage

(b) Low coverage

(c) Write-in error
2p glutamate uncaging of dendritic spines

Marta Gajowa (Bekerley)

Losonczy & Magee (2006)
Future applications to connectivity mapping
Existing mapping methods are low-throughput

Electrical

Feldmeyer et al (2005), J. Neurosci
Existing mapping methods are low-throughput

Electrical

Optical

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

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

Apply ordinary compressed sensing

Solve $y = Ax$ such that $x$ is sparse

(Candes, Tao, Donoho, 2004+)
Limitations of ordinary compressed sensing

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

Apply ordinary compressed sensing

Solve $y = Ax$ such that $x$ is sparse

Performance

(Candes, Tao, Donoho, 2004+)

(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

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

Statistical model

Triplett*, Gajowa* et al. (2022), bioRxiv
Model-based compressed sensing

Presynaptic spike inference

Neurons

Trials

Synaptic connectivity inference

Postsynaptic currents

= Presynaptic spike matrix

Synaptic strengths

Triplett*, Gajowa* et al. (2022), bioRxiv
Order-of-magnitude mapping speedup

Simulation: 1000 neurons, 10% connectivity

Single-target mapping @ 10 Hz
(existing approach)

Simulated data points:
- Accuracy ($R^2$) vs. Stimulation time (min)
- Data shows an improvement in accuracy over time.
Order-of-magnitude mapping speedup

Model-based compressed sensing
(20 targets @ 50 Hz, demixed)

Single-target mapping @ 10 Hz
(existing approach)

Simulation: 1000 neurons, 10% connectivity

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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)
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PV-Pyramidal (PV-Cre; AAV-st-ChroME2f-mRuby3)

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<10% synaptic weight difference (this expt)

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PV-Pyramidal (PV-Cre; AAV-st-ChroME2f-mRuby3)

Ensemble (detection) Single-target (validation)

Stim time (min)

0.0 0.2 0.4 0.6 0.8 1.0

Accuracy ($R^2$)

Ten-target @ 30 Hz (experiment)

Ten-target @ 30 Hz (simulation)

Single-target @ 10 Hz (simulation)

$<10\%$ synaptic weight difference (this expt)

<10% synaptic weight difference (this expt)

Triplett*, Gajowa* et al. (2022), bioRxiv
Strategies for connectivity mapping with dense expression

Decorrelate local activity
Strategies for connectivity mapping with dense expression

Decorrelate local activity

Optimise targets

Target neuron

opsin

Optimized holo

Naive holo

Power

Grad descent iterations