

A background of a network graph with nodes and edges, rendered in a light gray color against a white background. The graph is composed of many interconnected points, forming a complex, web-like structure. The nodes are small black dots, and the edges are thin black lines. The overall appearance is that of a data network or a social graph.

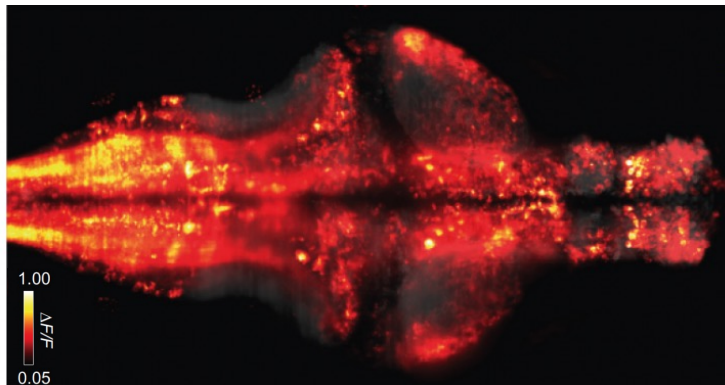
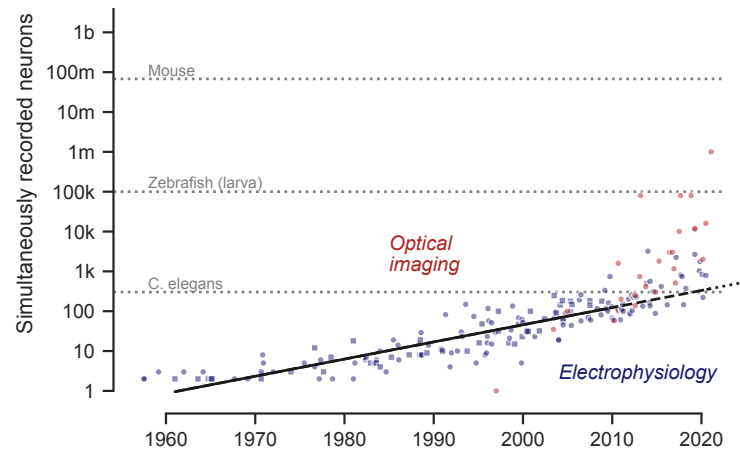
Real-time modeling with adaptive interventions

Anne Draelos, PhD

How do we design causal experiments that can tackle high-dimensional spaces?

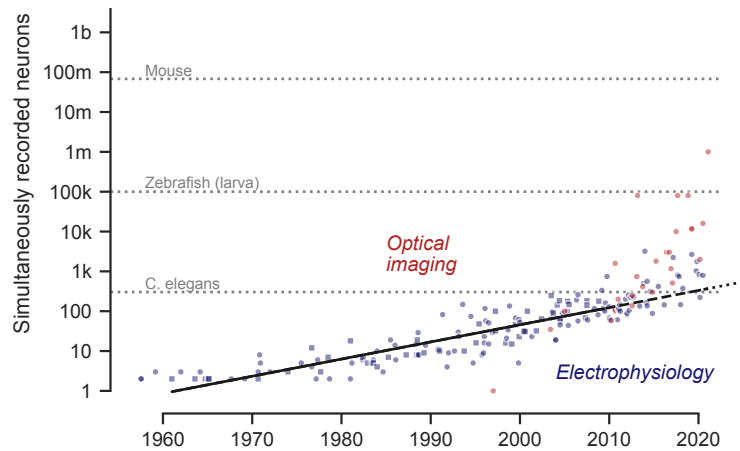
How do we design causal experiments that can tackle high-dimensional spaces?

Neural activity

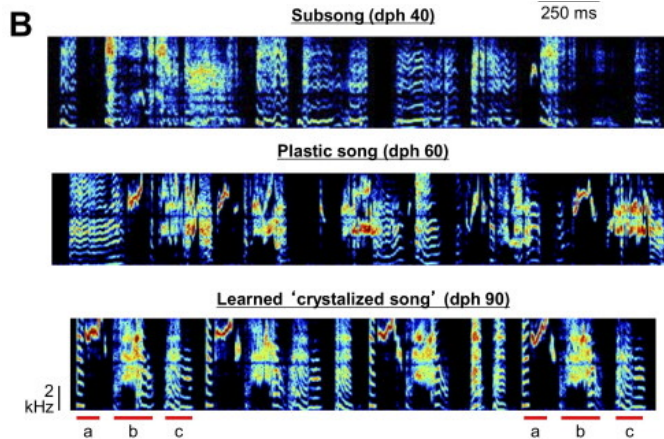
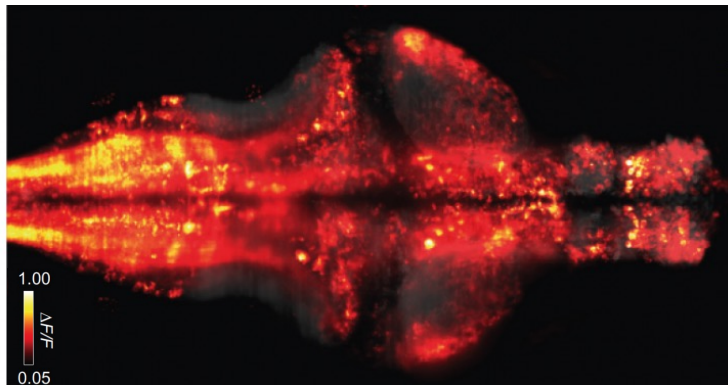
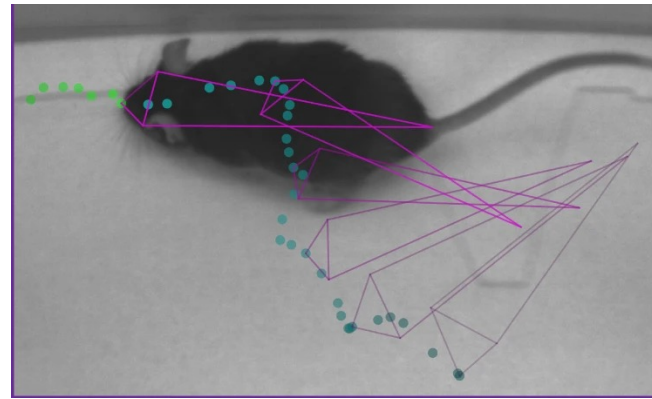


How do we design causal experiments that can tackle high-dimensional spaces?

Neural activity

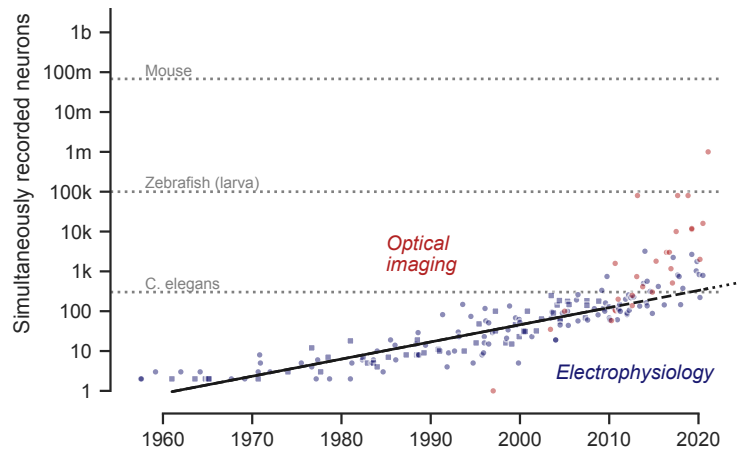


Behavior

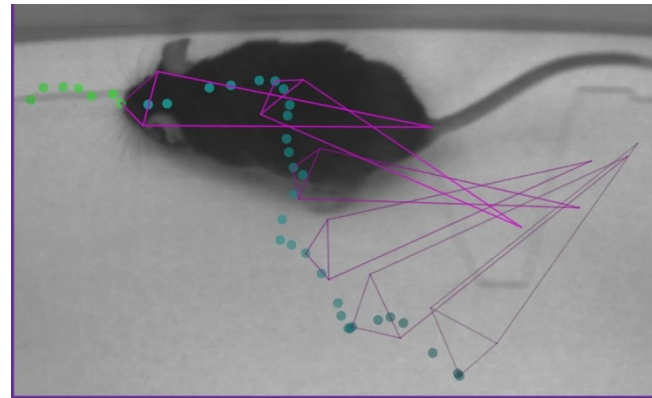


How do we design causal experiments that can tackle high-dimensional spaces?

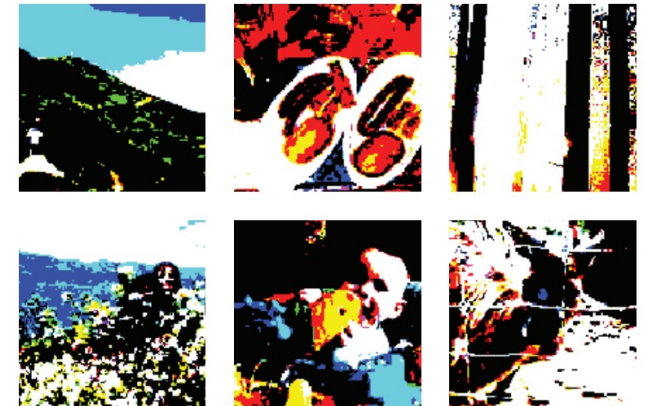
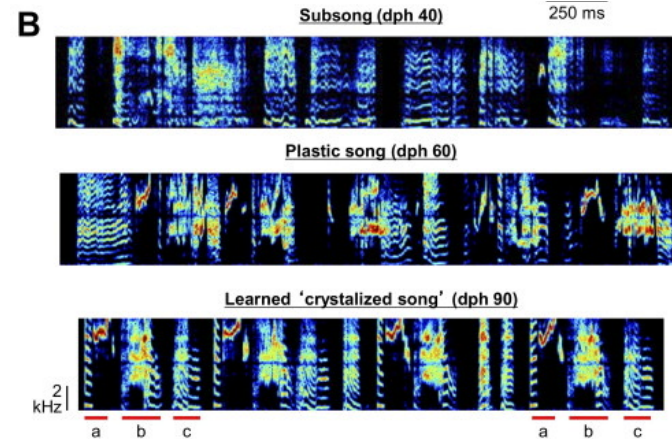
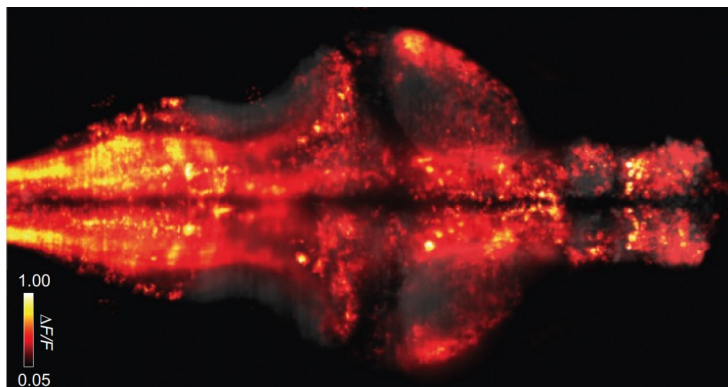
Neural activity



Behavior

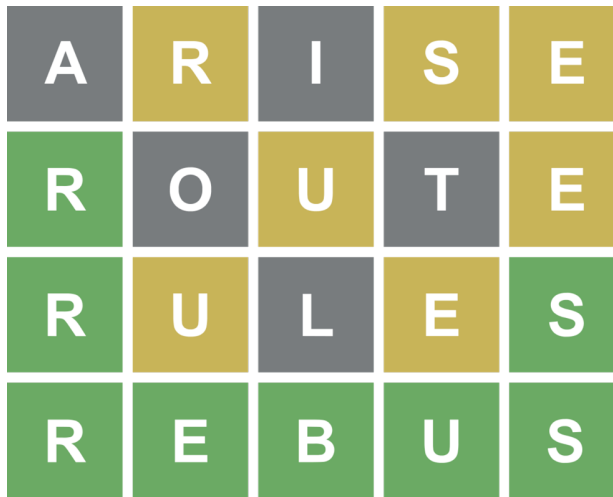


Stimuli / environment



Adaptive experimental designs

Adaptive experimental designs



Wordle

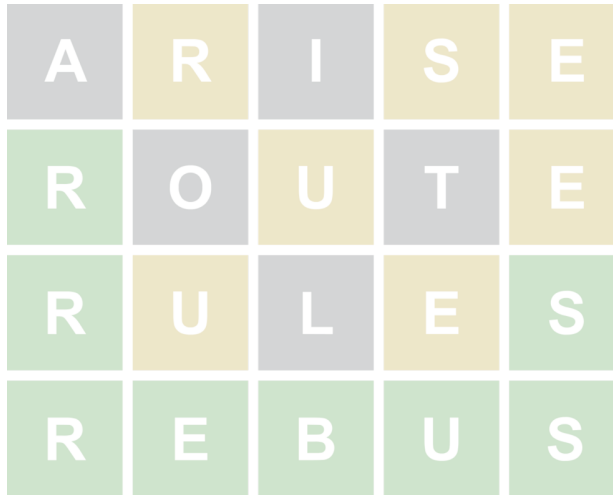


Battleship



20 Questions

Adaptive experimental designs



Wordle



Battleship



20 Questions

Adaptive experimental designs

- Simple example: 20 Questions



Adaptive experimental designs

- Simple example: 20 Questions
- Pick each next question sequentially
- Get an answer each time



Playing 20 Questions with the brain

- Pick each next question sequentially
- Get an answer each time



Playing 20 Questions with the brain

- ~~Pick each next question sequentially~~
- ~~Get an answer each time~~
- Ask all questions in advance



Playing 20 Questions with the brain

- Pick each next question sequentially
- Get an answer each time



Playing 20 Questions with the brain

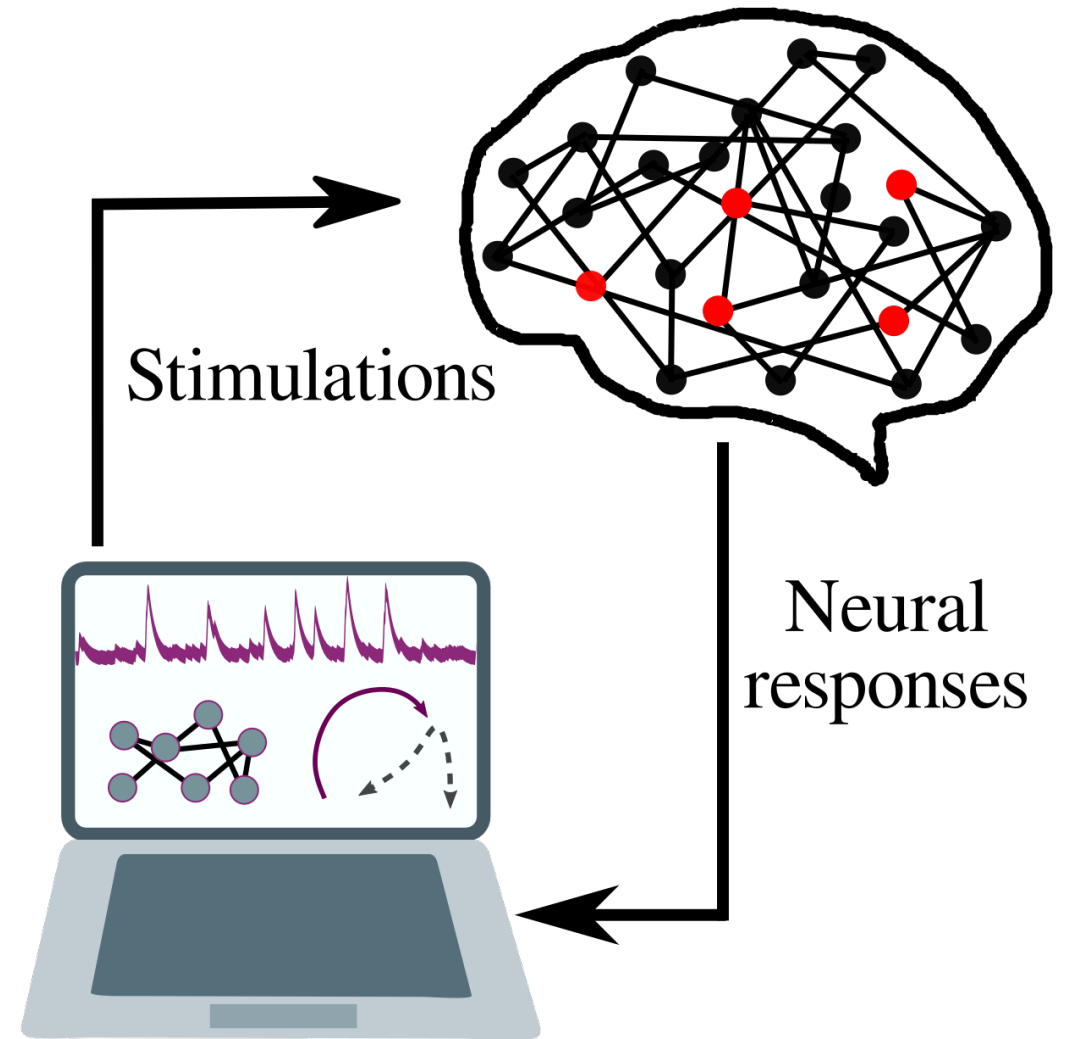
- Pick each next question sequentially
- Get an answer each time

→ Adaptive experimental designs



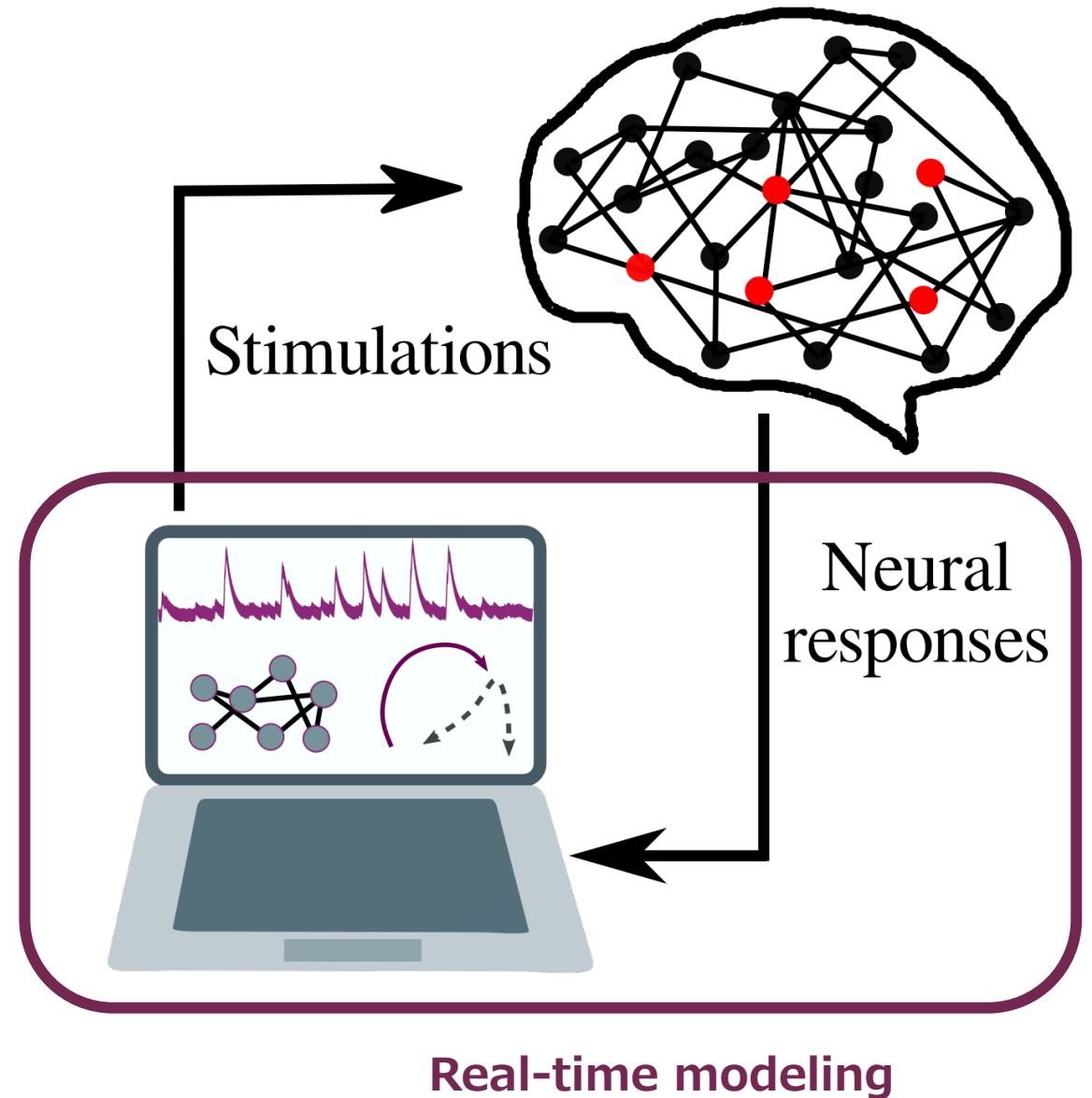
Outline:

- Build streaming models that adapt to current neural activity
- Optimize selection of interventions/stimulations



Outline:

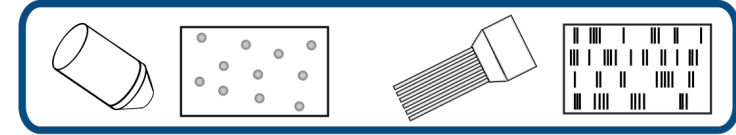
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Observe behavior



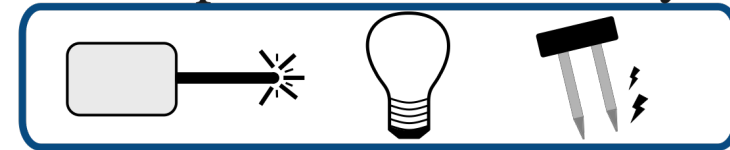
Record neural activity



Change stimuli



Manipulate neural activity

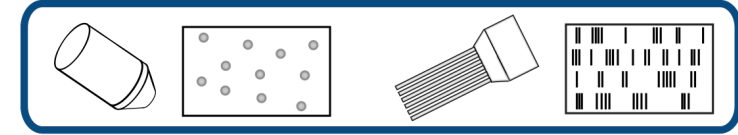


Handling diverse
data streams

Observe behavior



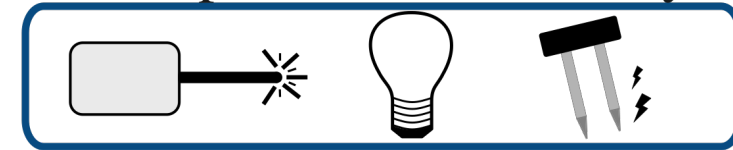
Record neural activity



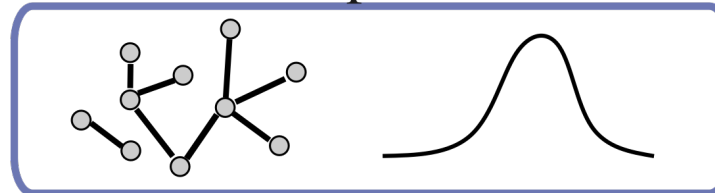
Change stimuli



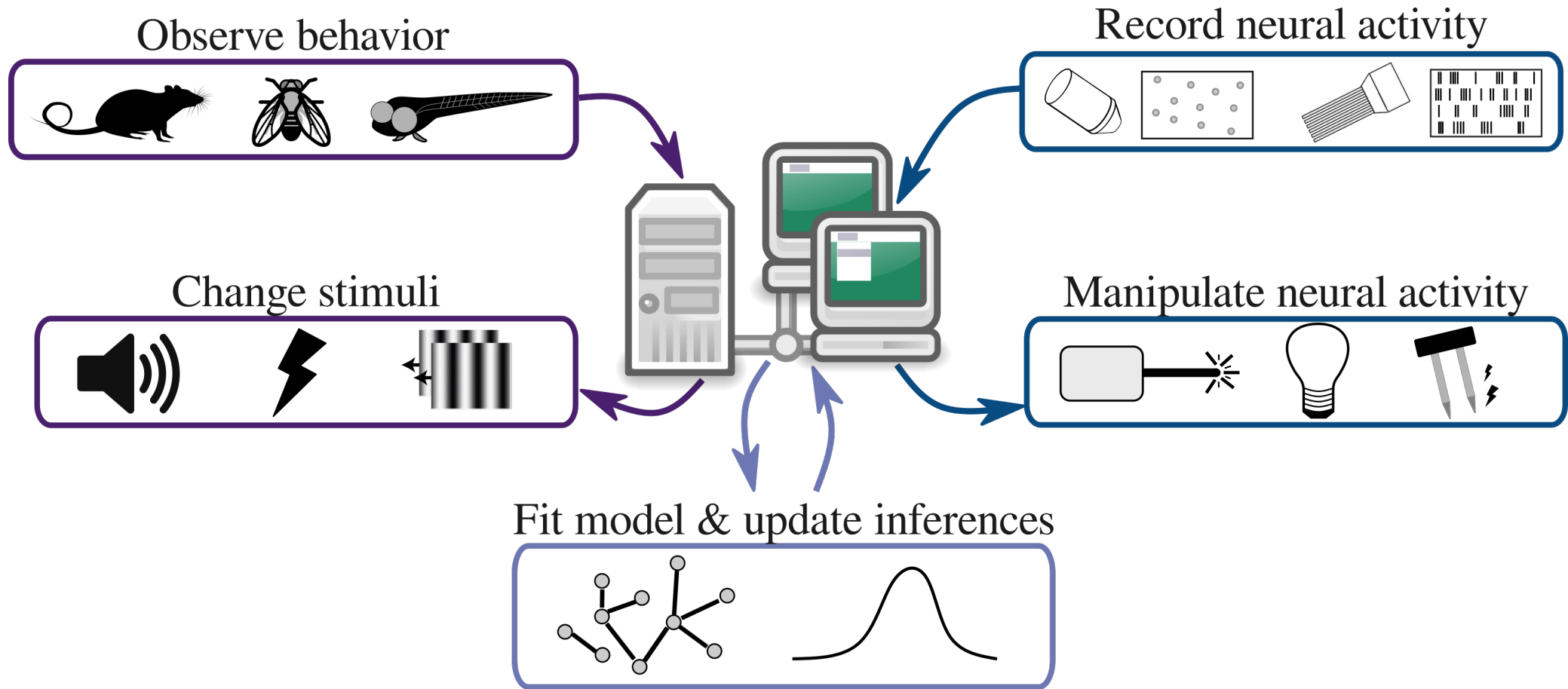
Manipulate neural activity



Fit model & update inferences

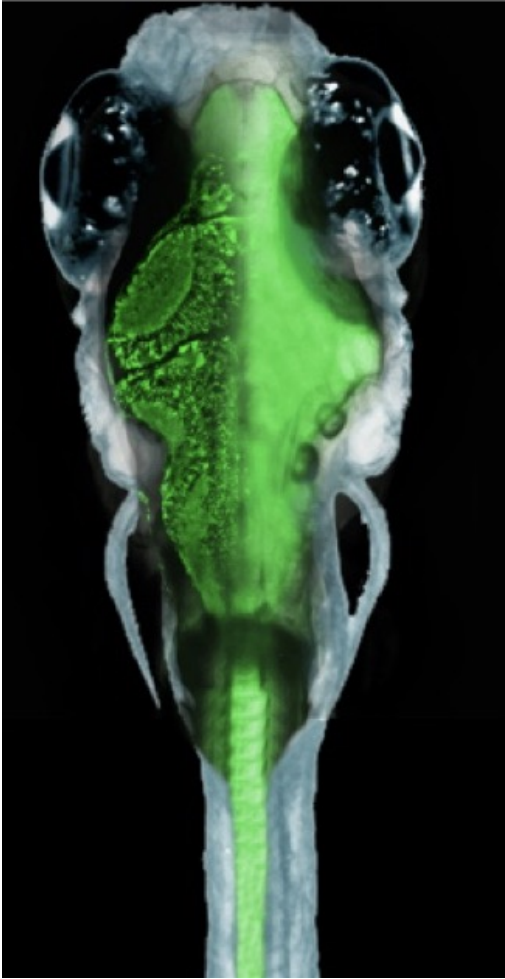


Incorporate real-time modeling



**improv: adaptive
experimental platform**

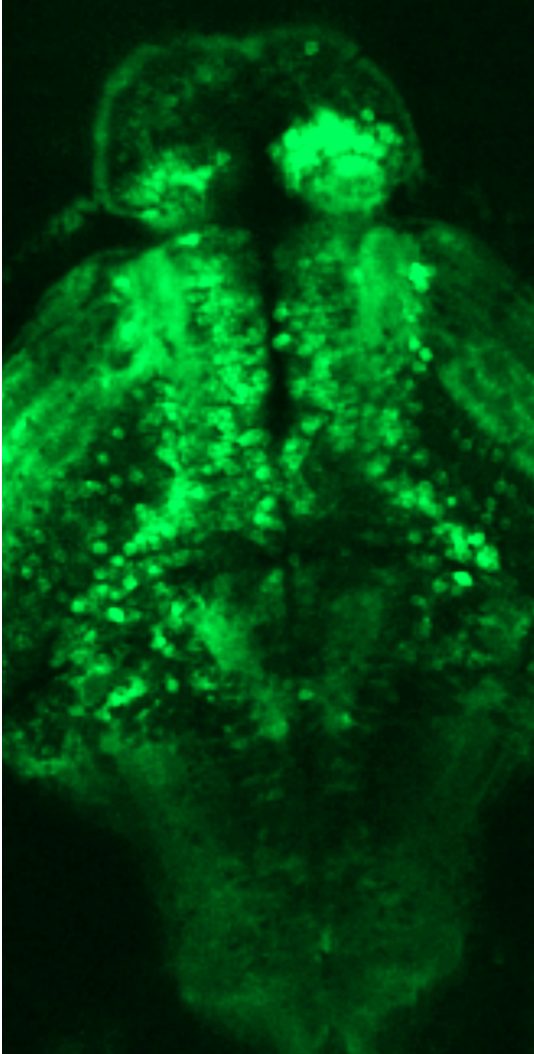
Case study: Zebrafish optomotor response



- Larval zebrafish
- 100,000 neurons
- Whole-brain imaging

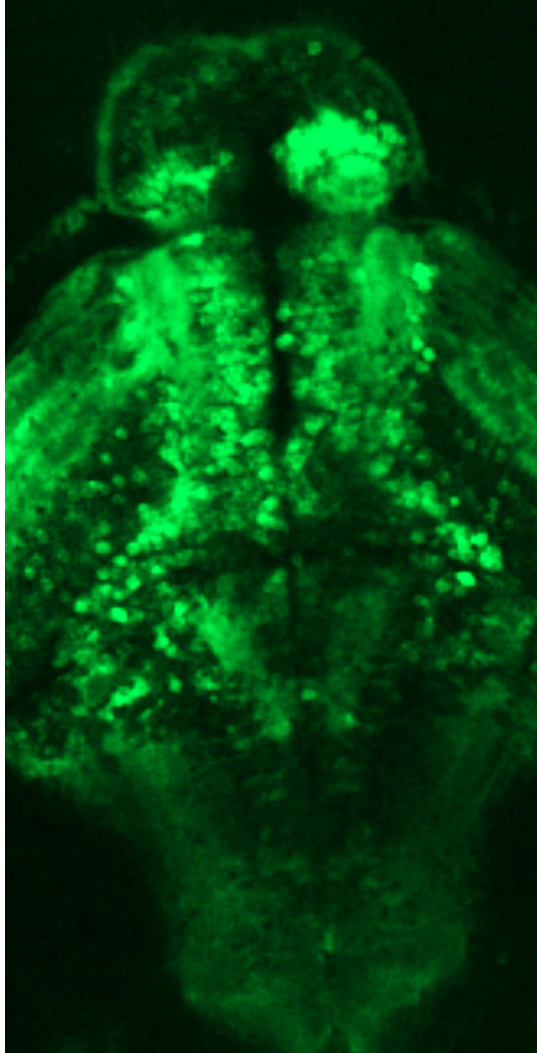
Image courtesy of Misha Ahrens

Case study: Zebrafish optomotor response



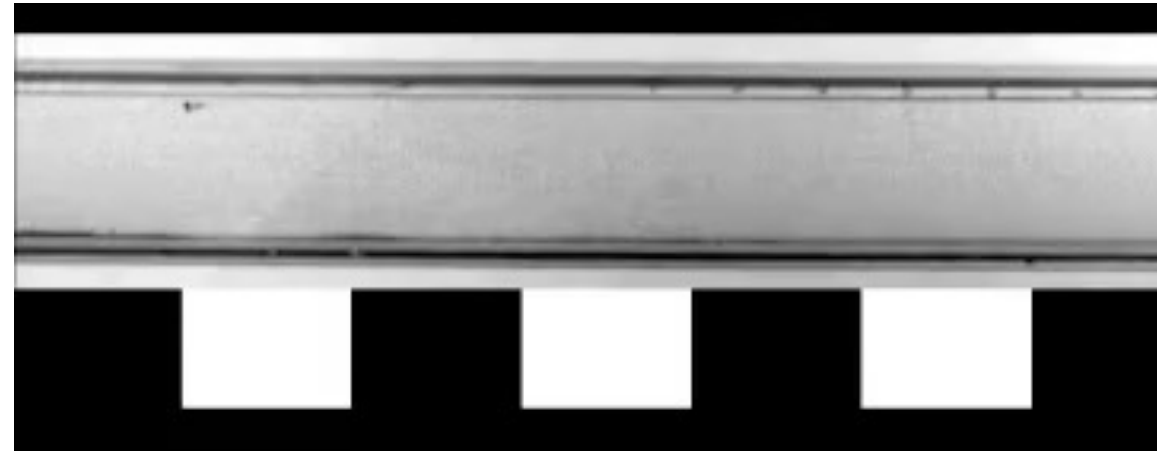
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Case study: Zebrafish optomotor response



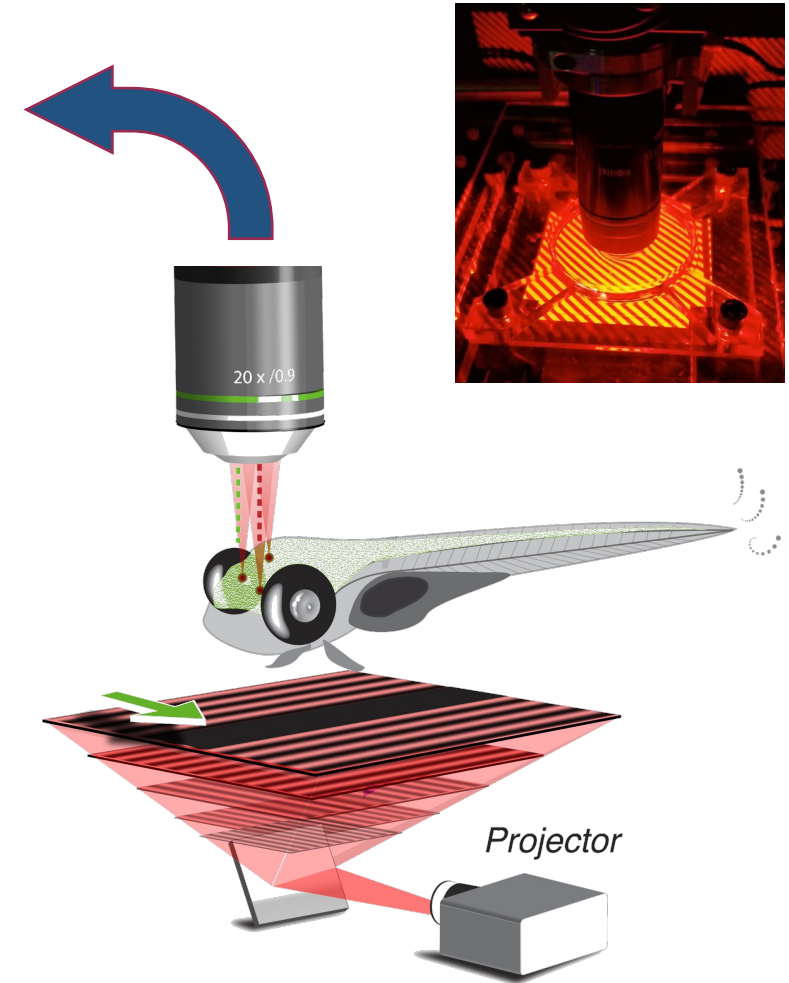
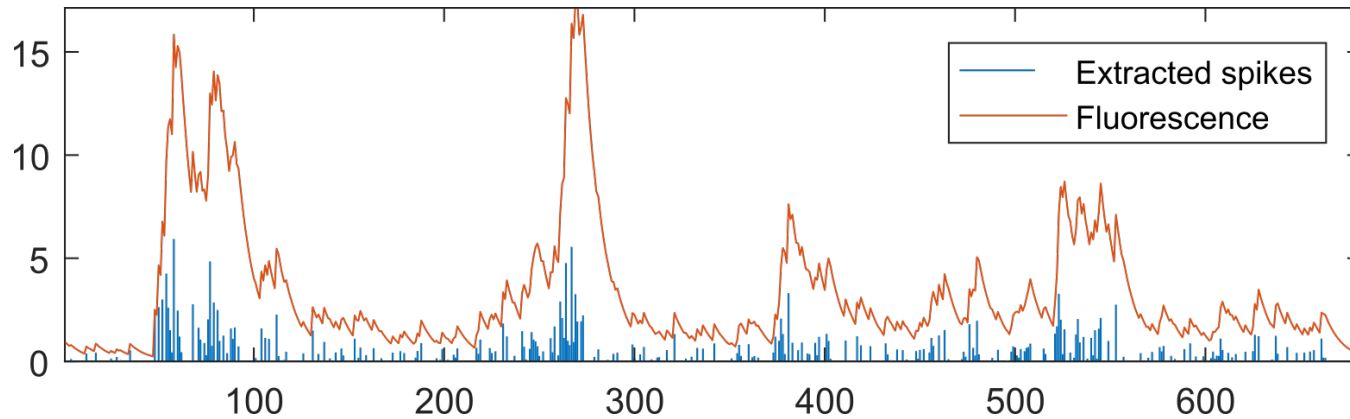
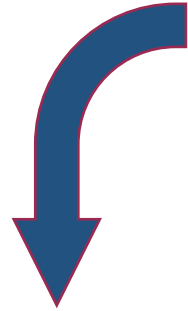
- Larval zebrafish
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Video courtesy of Ruben Portugues

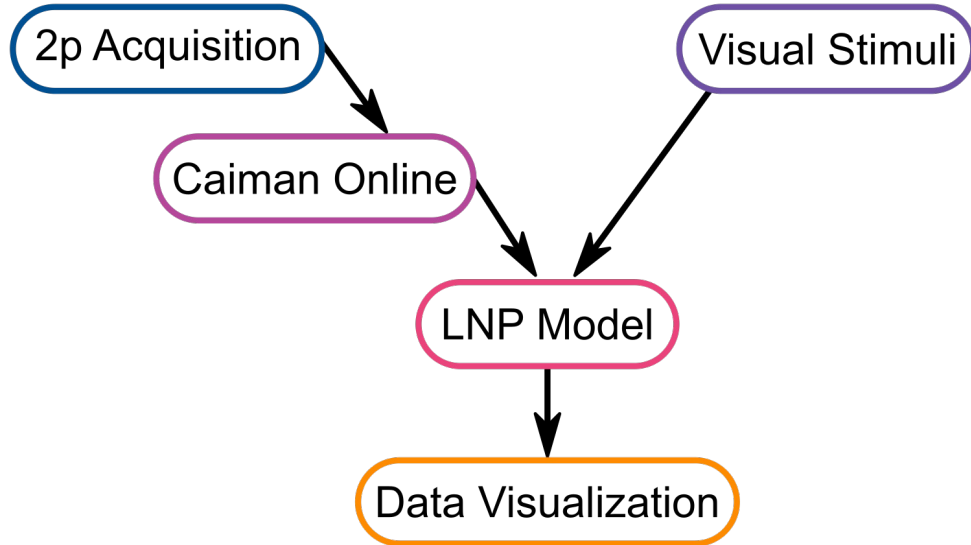
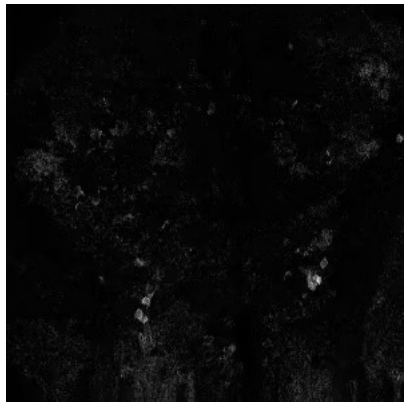


Zebrafish swim to align themselves to visual motion

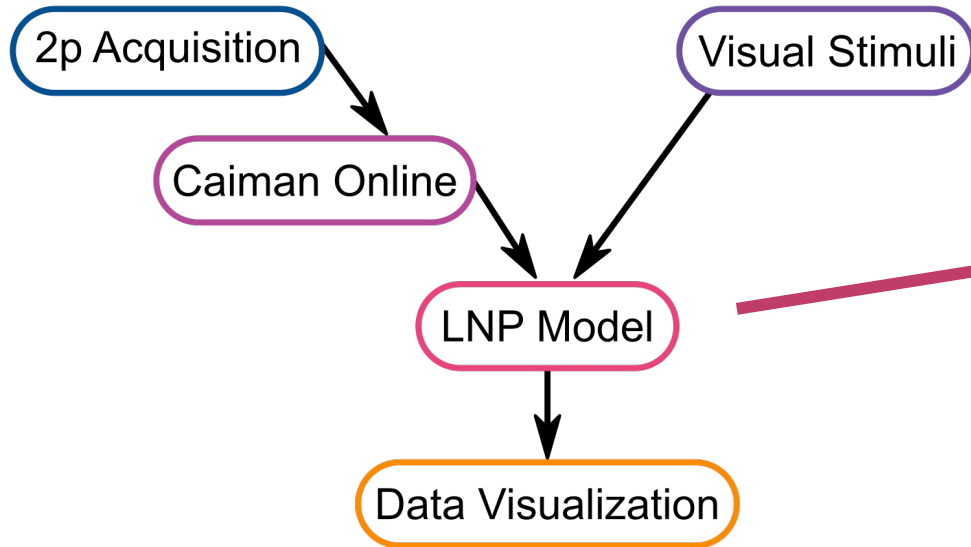
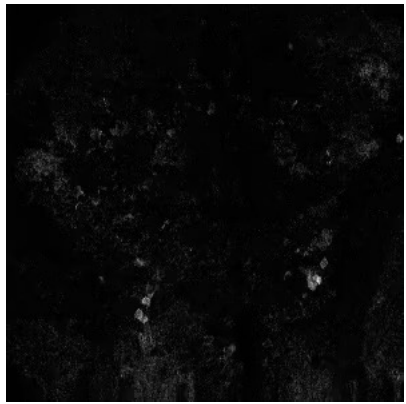
Identify single neurons
Estimate activity
Compute response
profiles
...



Real-time imaging & interventions *in vivo*

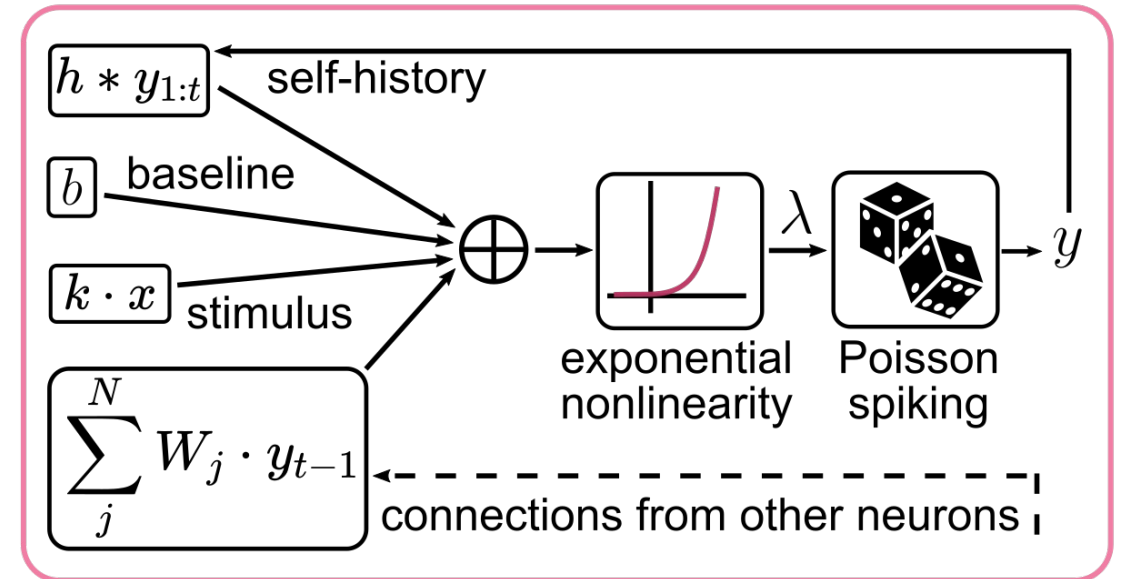


**improv: adaptive
experimental platform**



Linear-Nonlinear-Poisson model

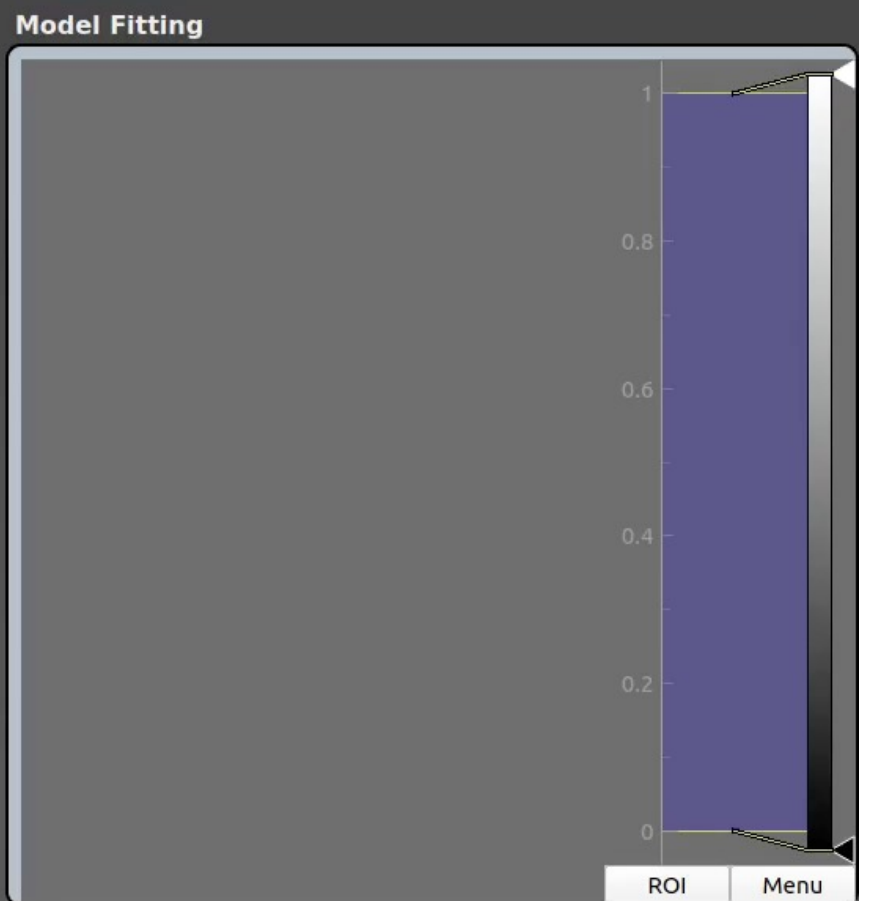
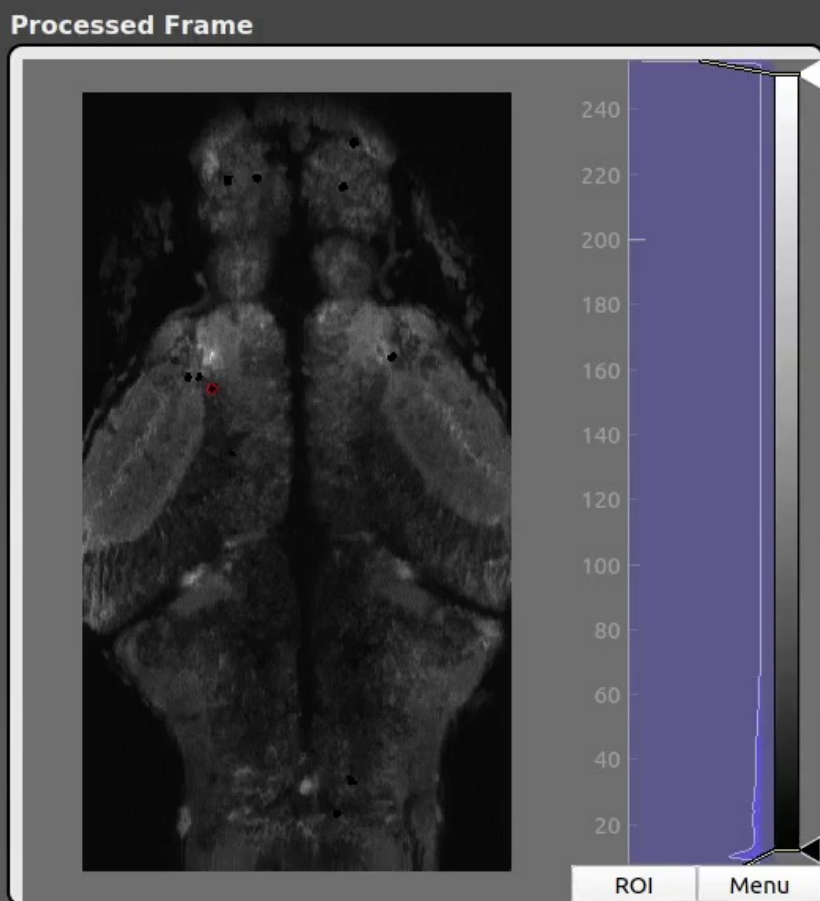
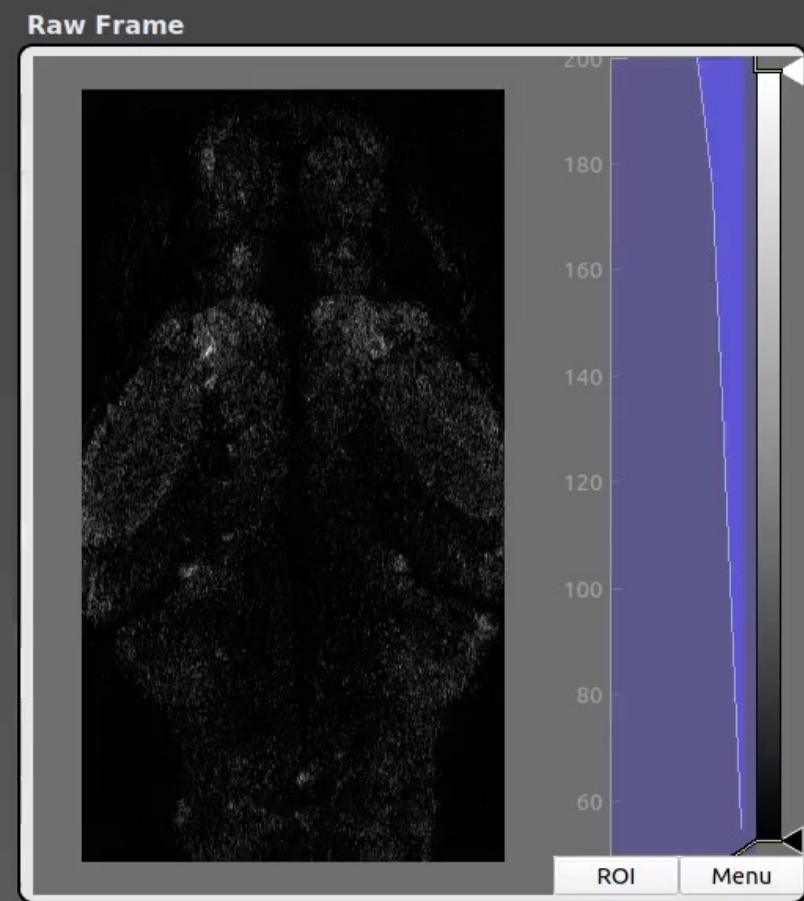
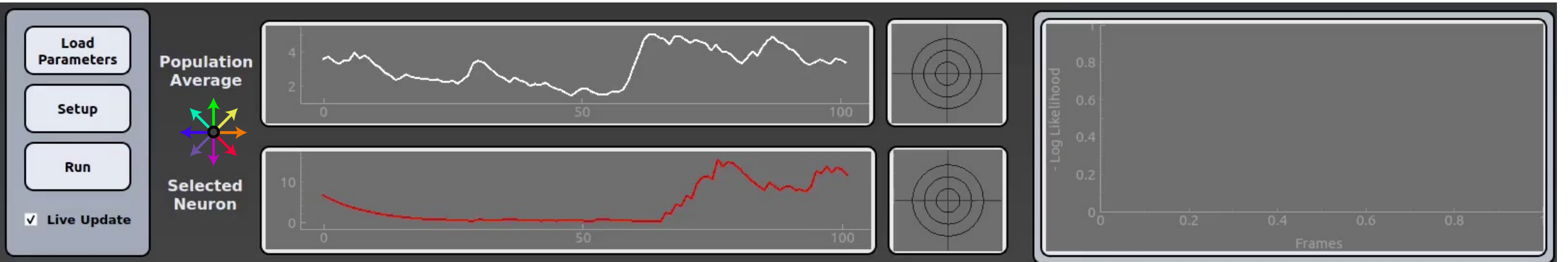
$$\log p(y|x) = \sum_i y_i \log \lambda_i - \Delta \sum_i \lambda_i$$

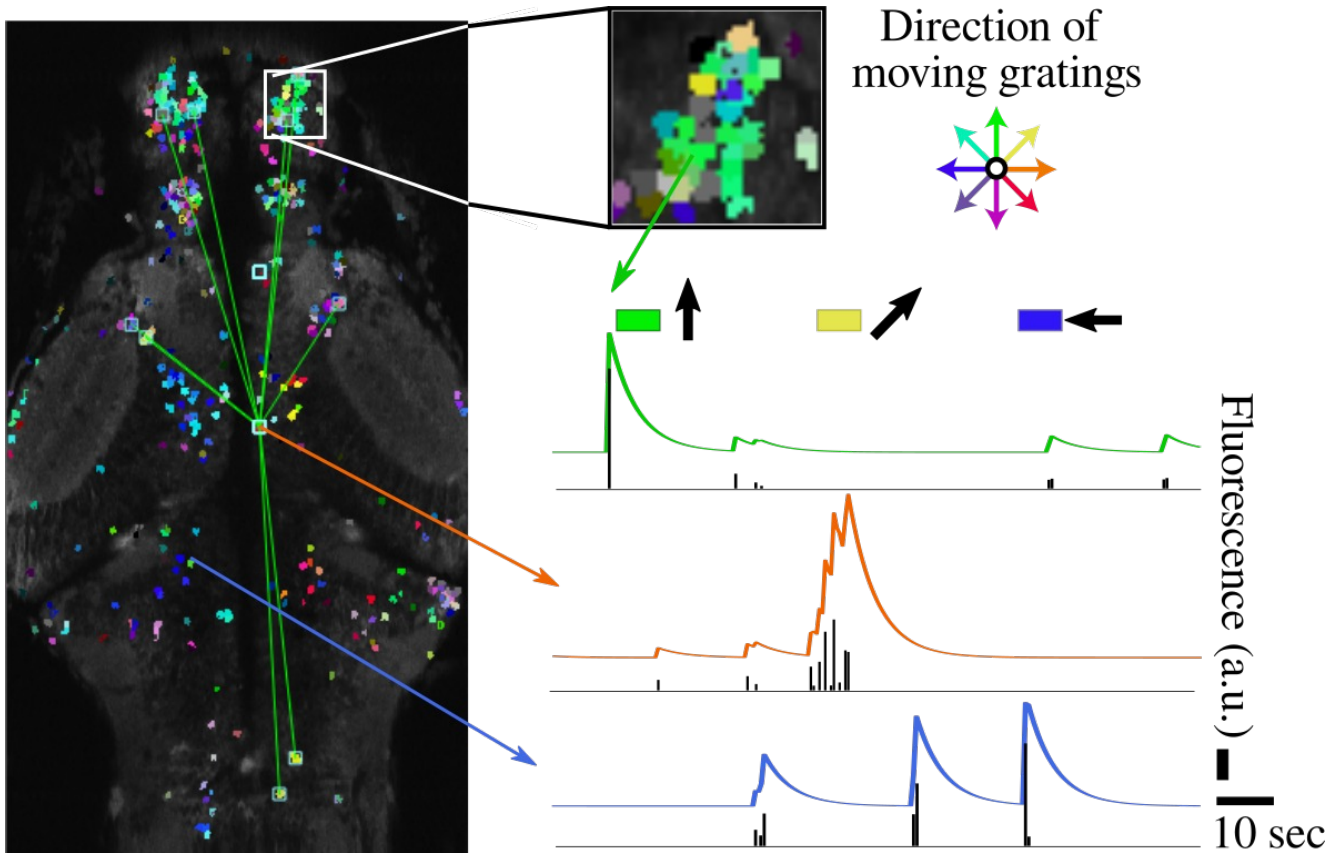


$$\log \lambda(t) = b + k \cdot x + h * y_{1:t} + \sum_j W_j \cdot y_{t-1}$$

improv: adaptive
experimental platform

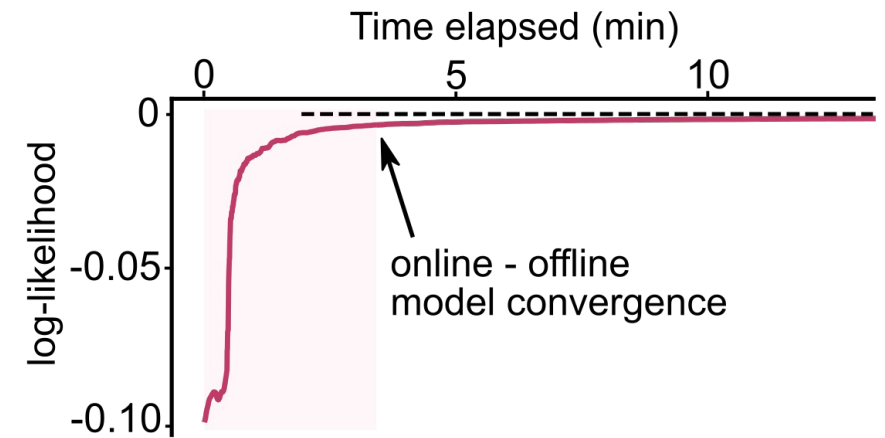
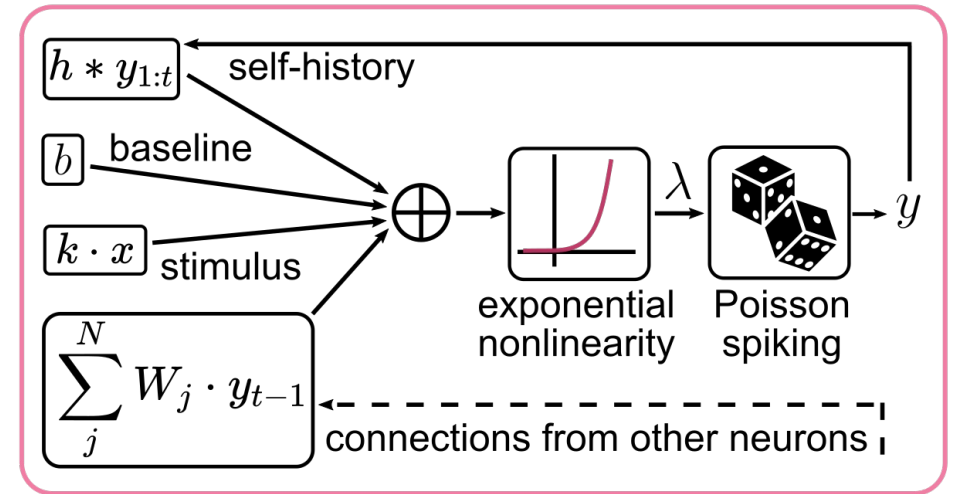
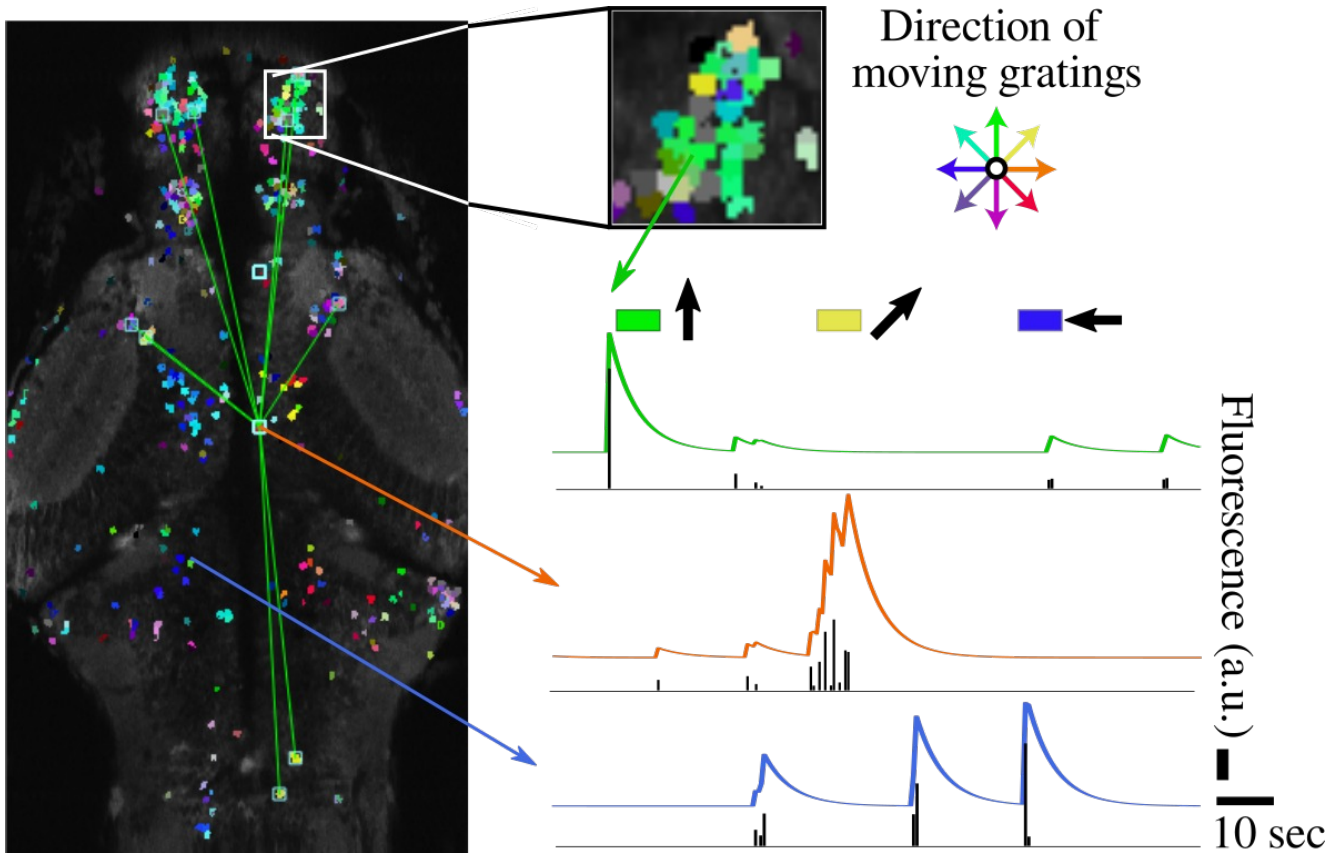
Real-time model fitting





Real-time analyses

Functional typing: directional tuning curves

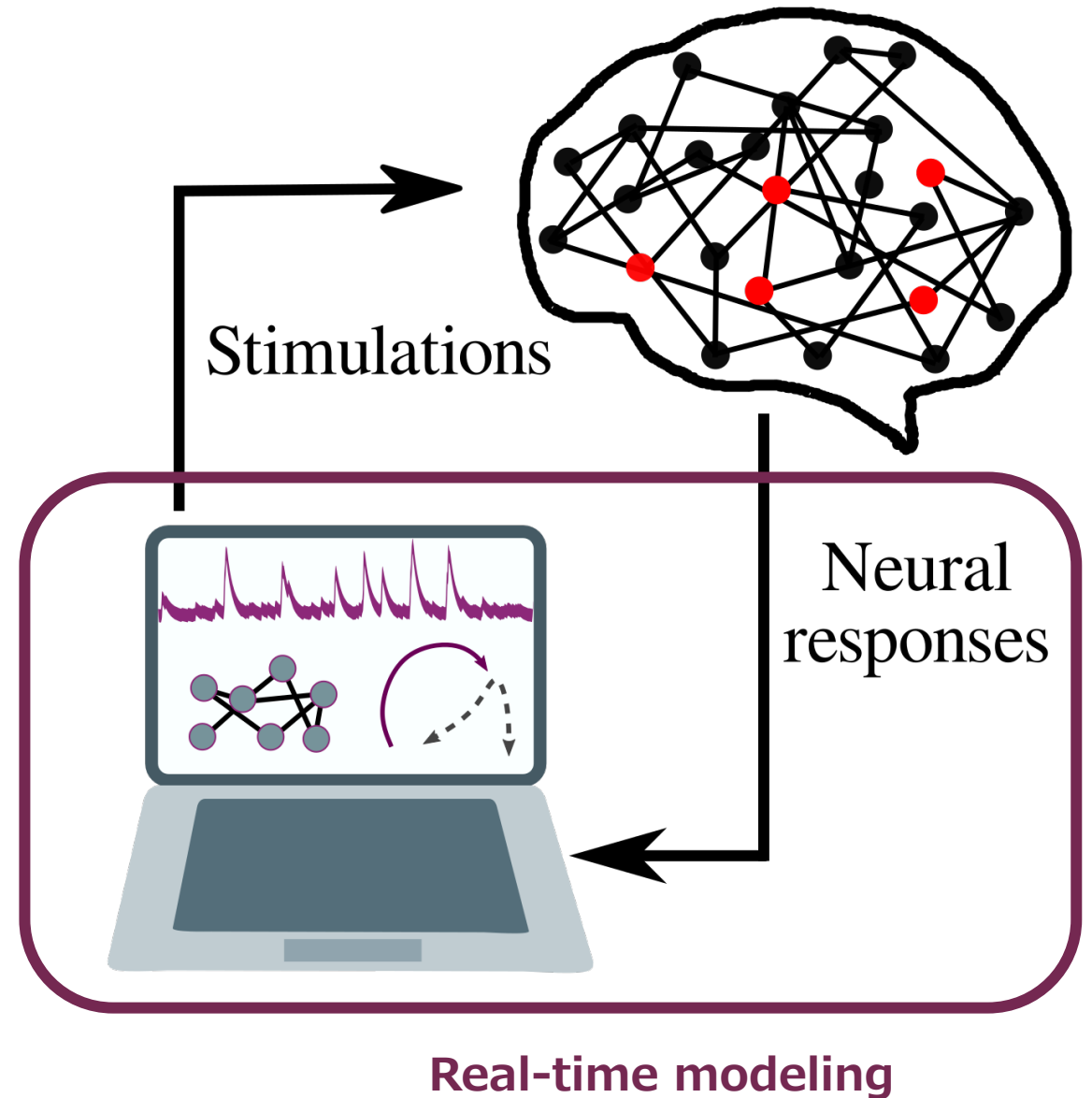


Real-time analyses +
streaming model fitting

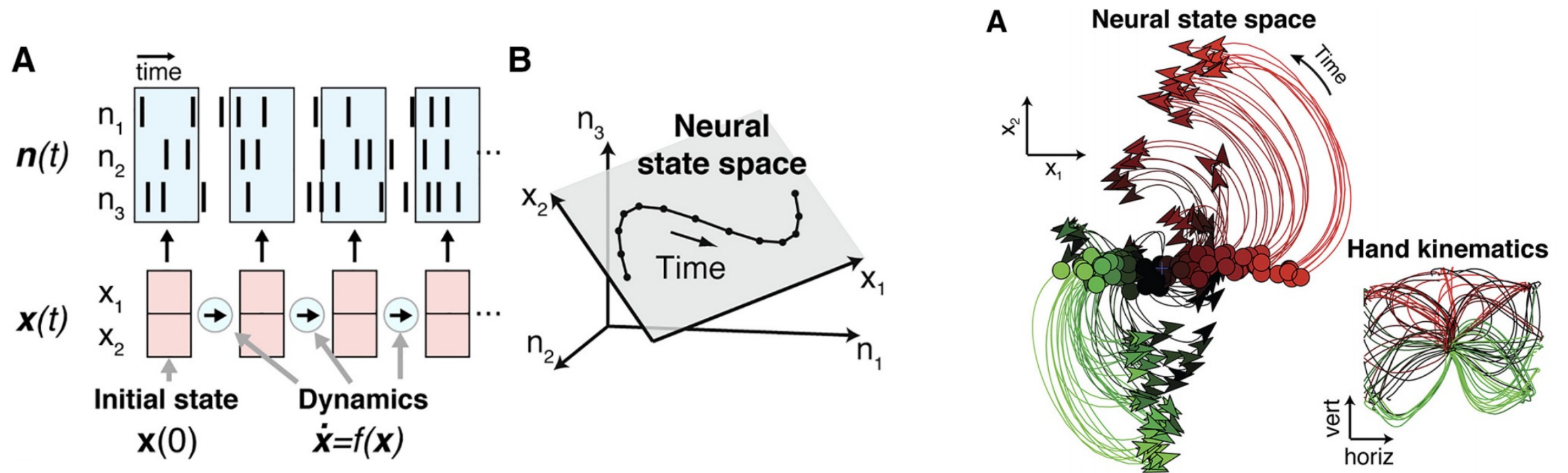
Functional types and functional
connectivity learned in real time

Outline:

- Build streaming models that adapt to current neural activity
- Optimize selection of interventions/stimulations

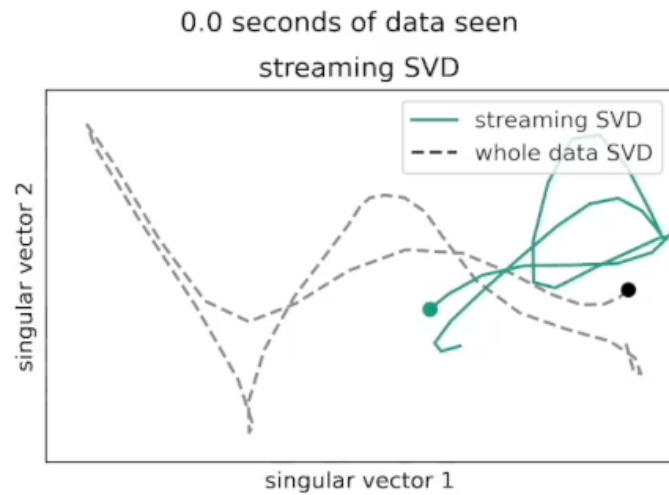


How do we learn and perturb neural trajectories?



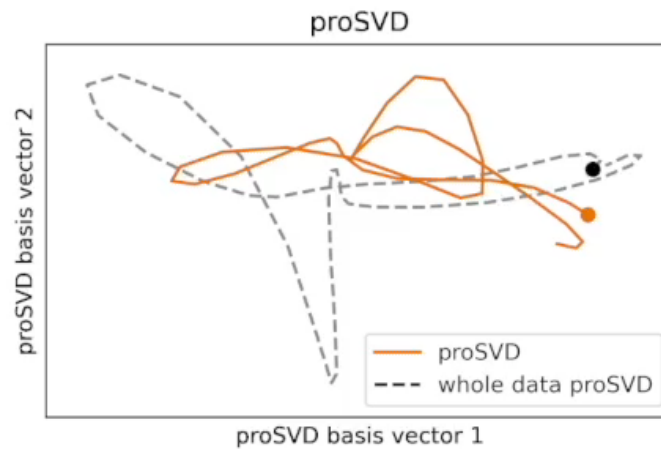
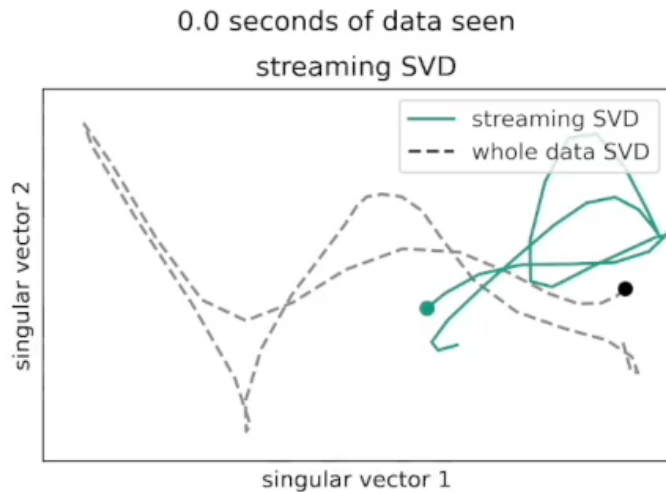
Streaming dimension reduction

Streaming dimension reduction



$$X \approx QRW^T$$

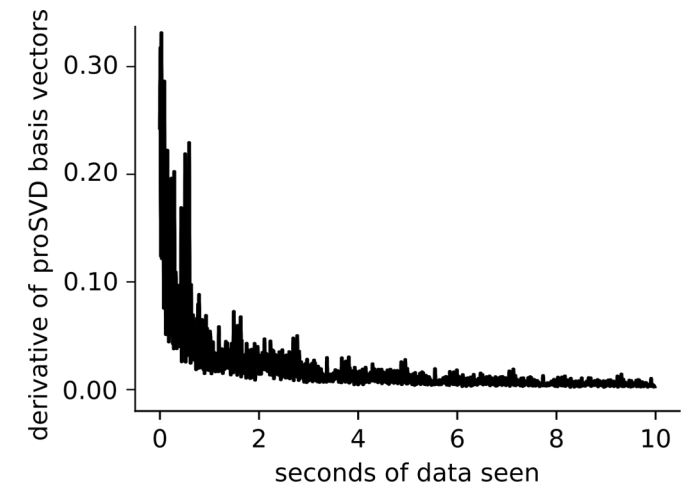
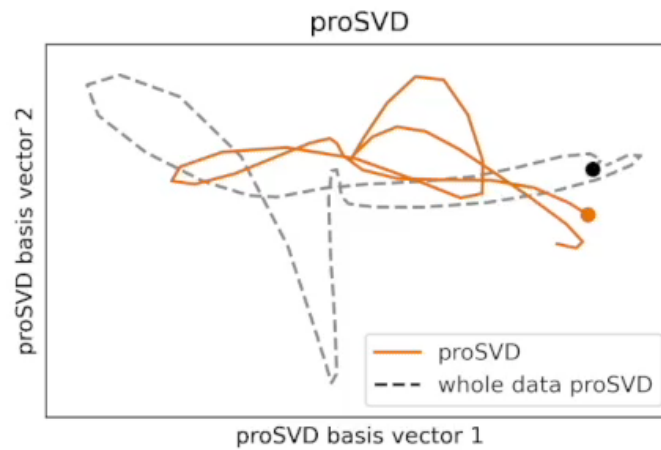
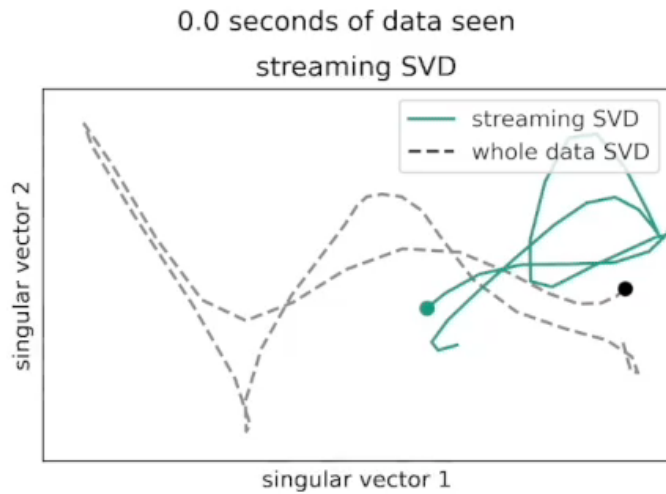
Streaming dimension reduction



$$X \approx QRW^T$$

$$\begin{aligned} & \min \|Q_t - Q_{t-1}\|_F \\ &= \min_{T_u} \|\hat{Q}U_1T_u^T - Q_{t-1}\|_F \end{aligned}$$

Streaming dimension reduction



$$X \approx QRW^T$$

$$\begin{aligned} & \min \|Q_t - Q_{t-1}\|_F \\ & = \min_{T_u} \|\hat{Q}U_1T_u^T - Q_{t-1}\|_F \end{aligned}$$

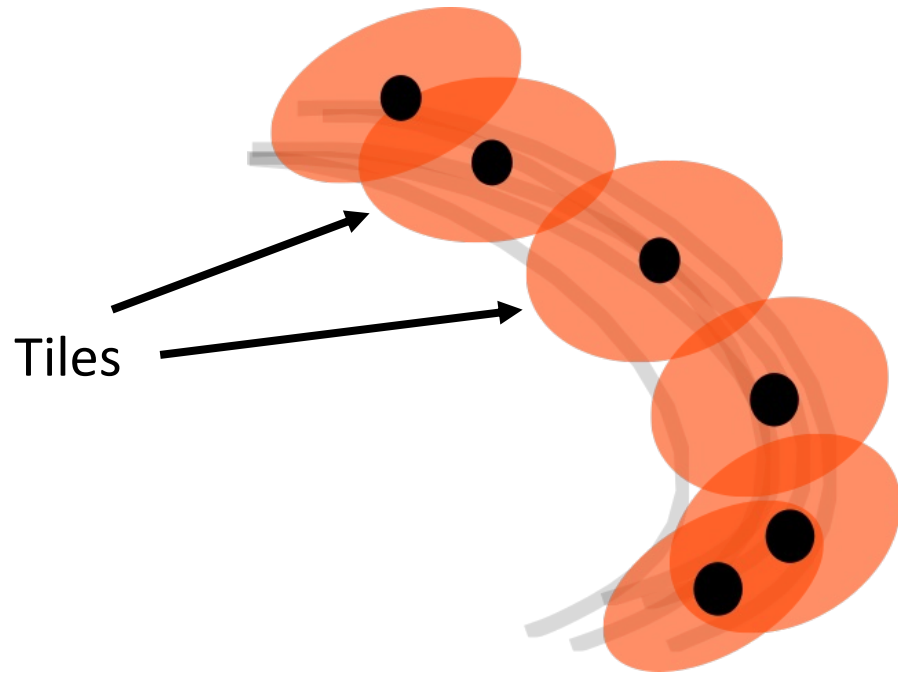
Streaming dimension reduction

→ streaming dynamical modeling: Bubblewrap



Streaming dimension reduction

→ streaming dynamical modeling: Bubblewrap

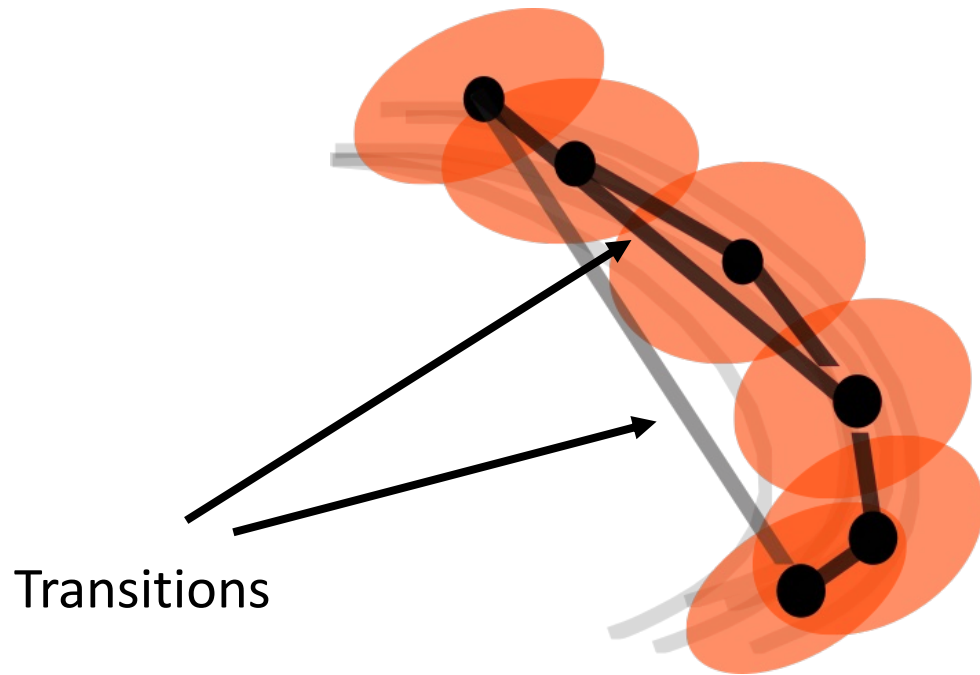


$$p(x_t | z_t) = \mathcal{N}(\mu_{z_t}, \Sigma_{z_t})$$

$$p(\mu_j, \Sigma_j) = \text{NIW}(\mu_{0j}, \lambda_j, \Psi_j, \nu_j)$$

Streaming dimension reduction

→ streaming dynamical modeling: Bubblewrap



$$p(x_t | z_t) = \mathcal{N}(\mu_{z_t}, \Sigma_{z_t})$$

$$p(\mu_j, \Sigma_j) = \text{NIW}(\mu_{0j}, \lambda_j, \Psi_j, \nu_j)$$

$$p(z_t = j | z_{t-1} = i) = A_{ij}$$

Streaming dimension reduction

→ streaming dynamical modeling: Bubblewrap

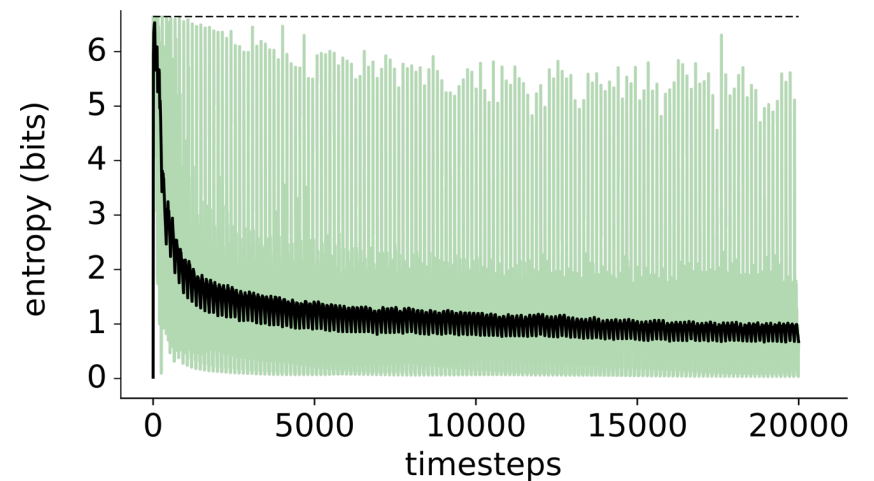
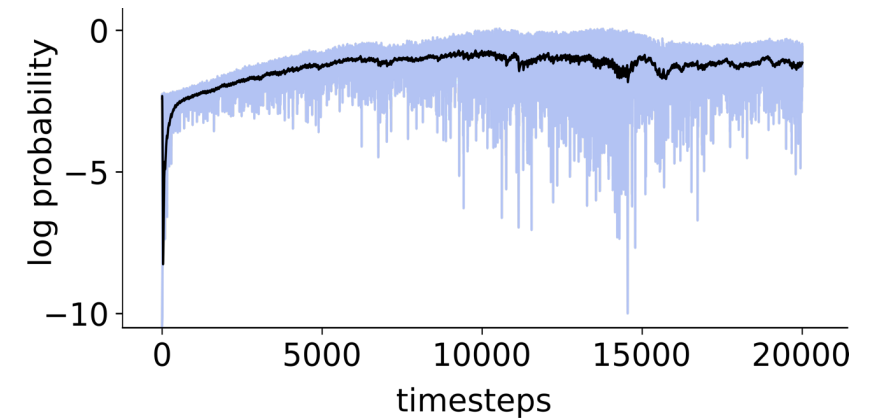


Streaming dimension reduction

→ streaming dynamical modeling: Bubblewrap

$$\begin{aligned} & \log p(x_{t+T} | x_{1:t}) \\ &= \log \sum_{i,j} \mathcal{N}(x_{t+1}; \mu_j, \Sigma_j) (A^T)_{ij} \alpha_i(t) \end{aligned}$$

$$\begin{aligned} & H(t, T) \\ &= - \sum_{ij} (A^T)_{ij} \alpha_i(t) \log \sum_k (A^T)_{kj} \alpha_k(t) \end{aligned}$$



jpc1

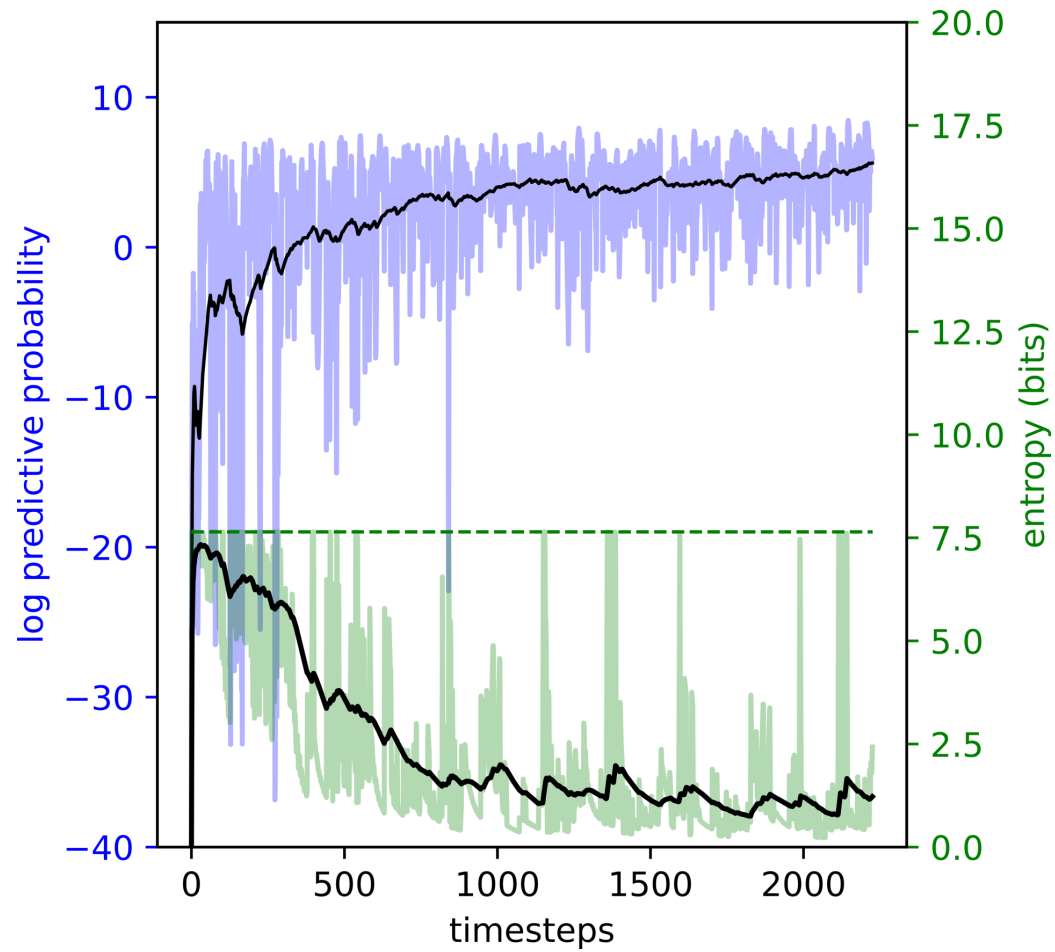
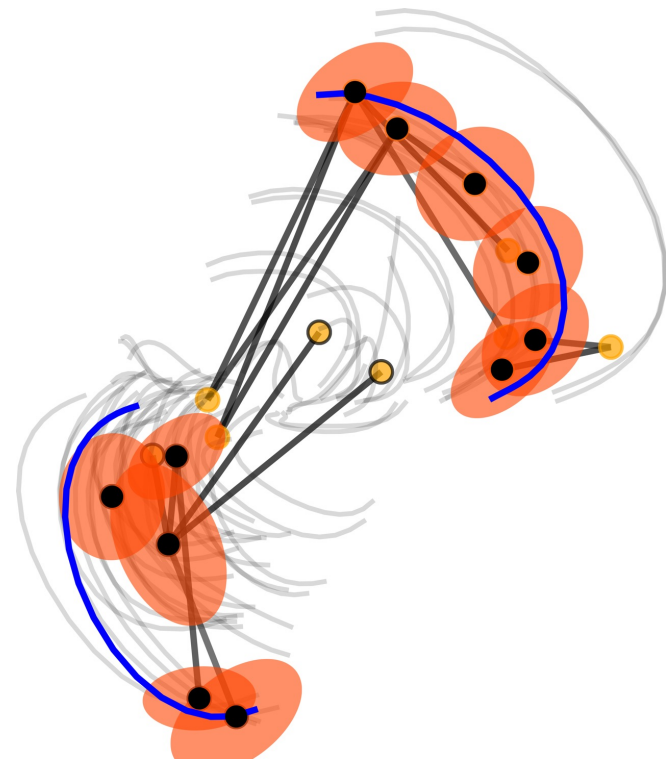
Bubblewrap on real data

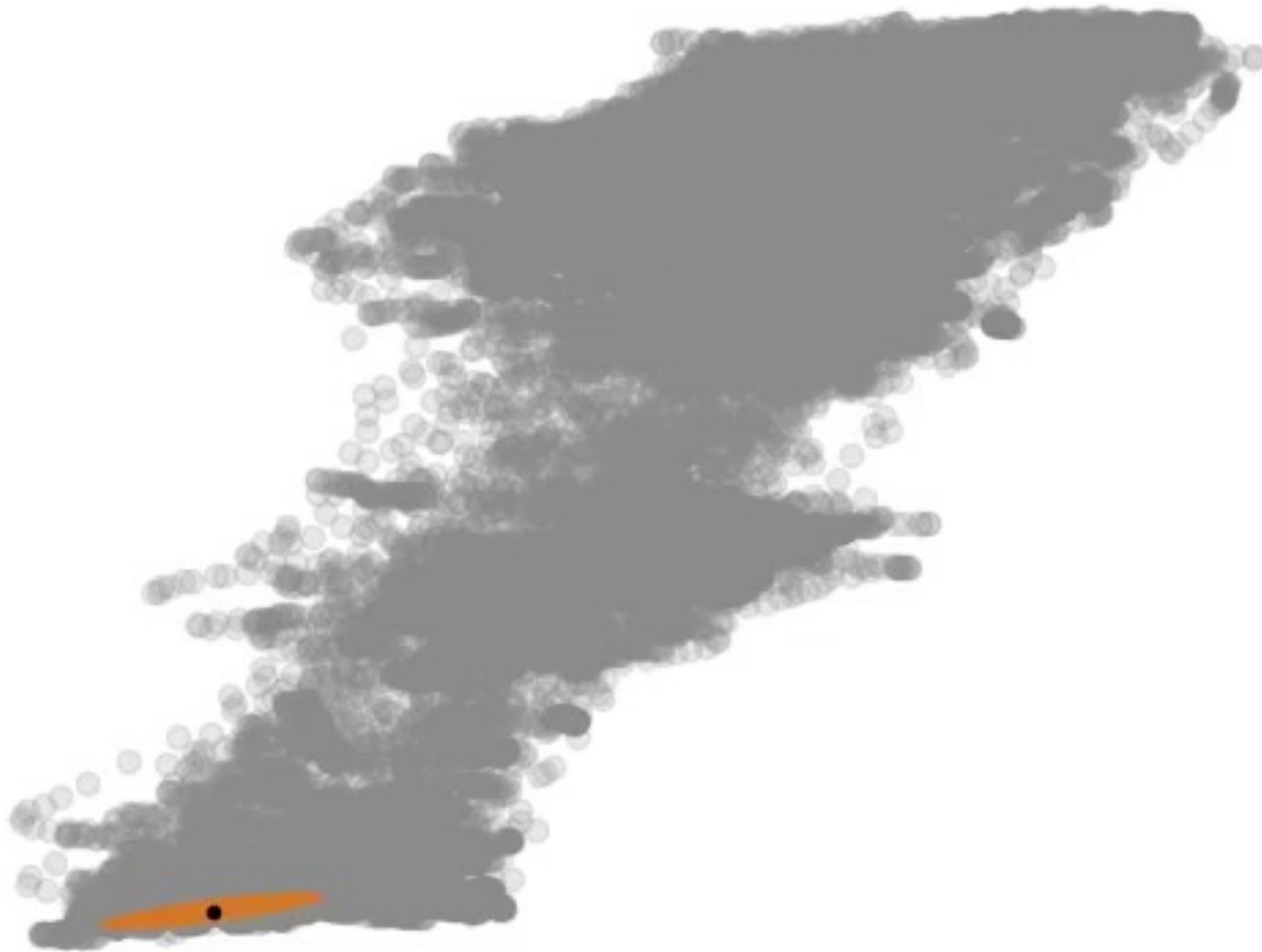
- Spiking data

jpc2

Bubblewrap on real data

- Spiking data



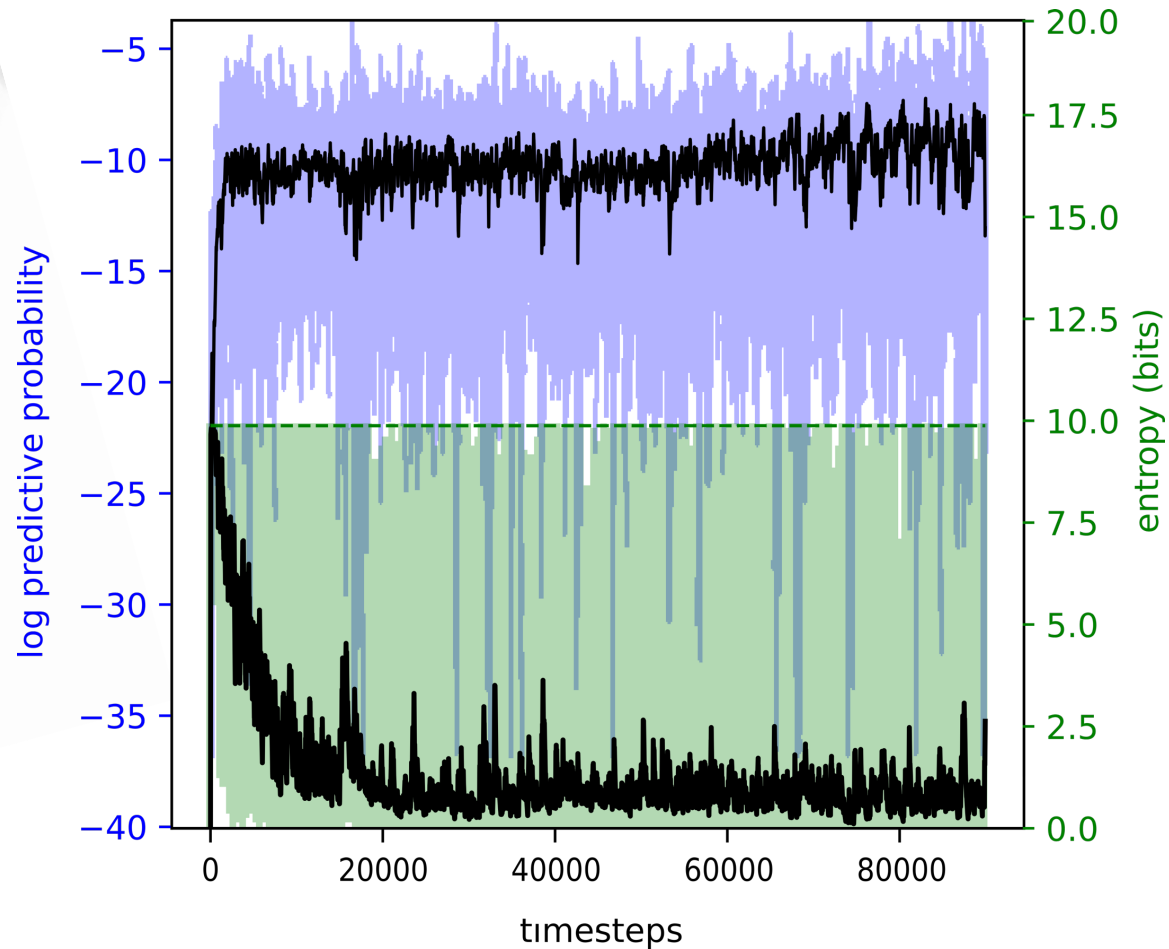


Bubblewrap on real data

- Spiking data
- Continuous video data (behavior)

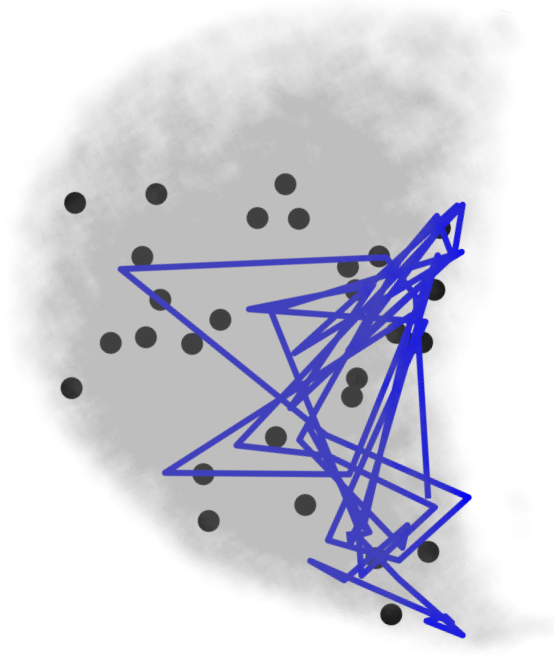
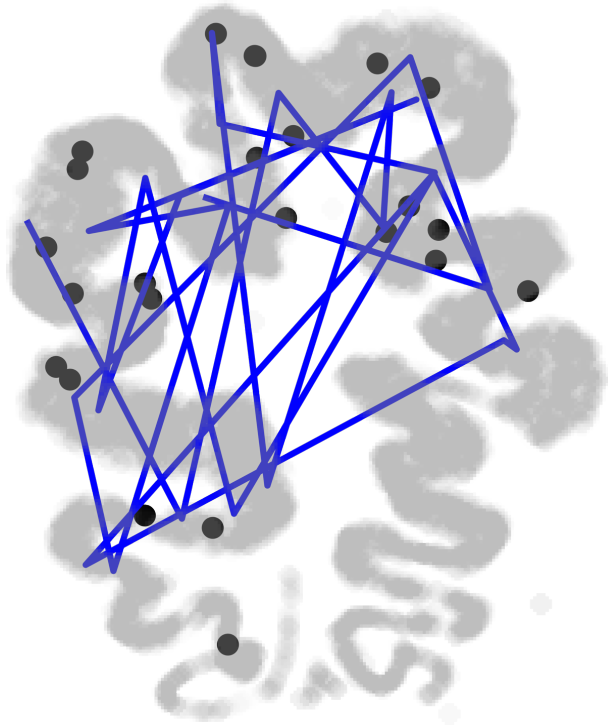
Bubblewrap on real data

- Spiking data
- Continuous video data (behavior)



Bubblewrap on real data

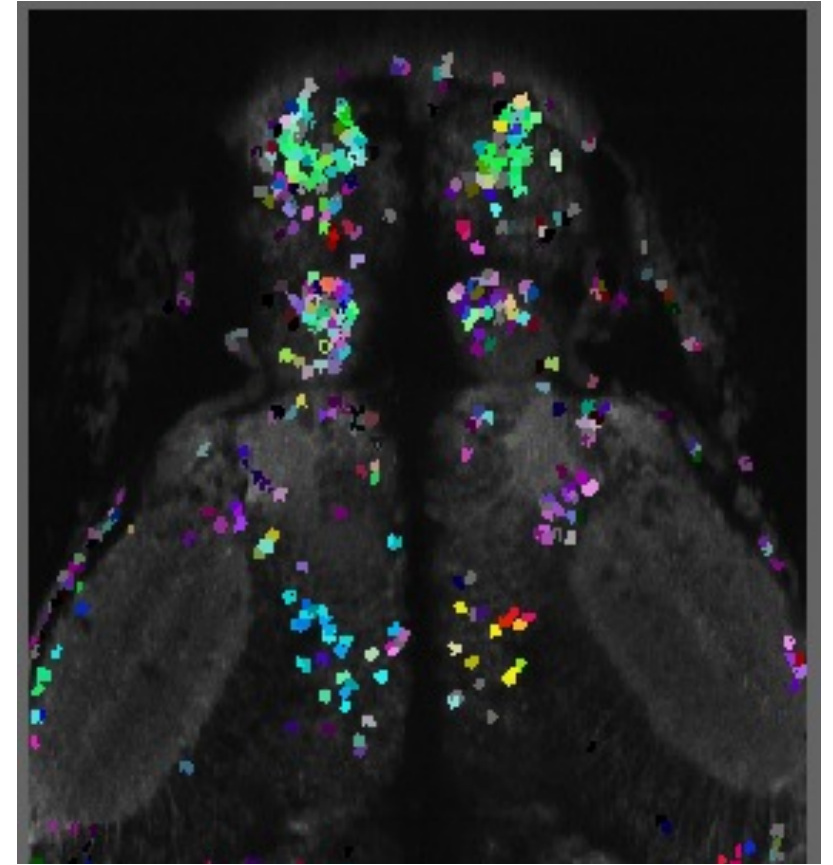
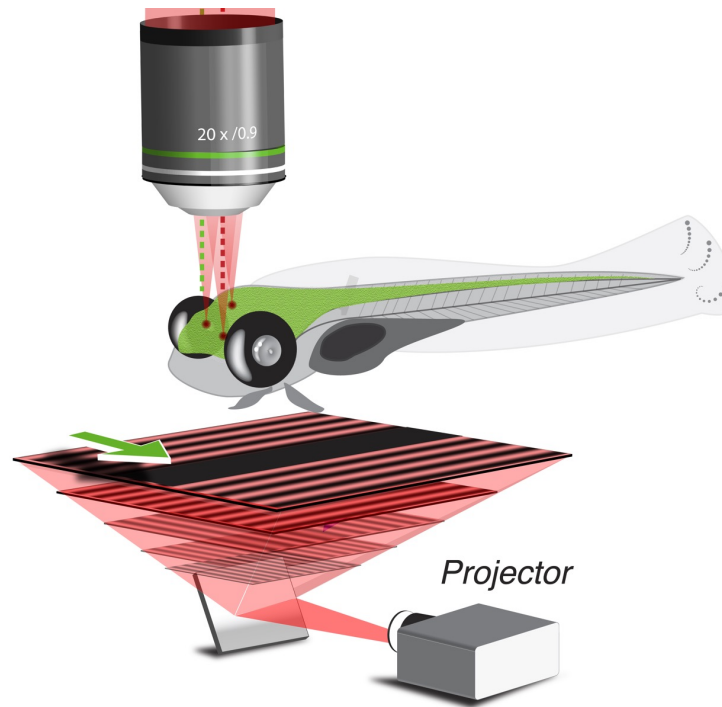
- Spiking data
- Continuous video data (behavior)
- Wide-field calcium imaging
- High-throughput Neuropixels data



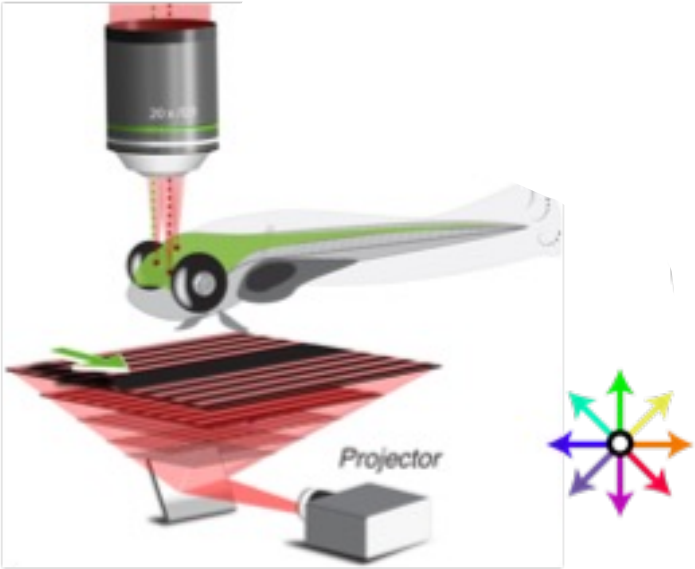
Bubblewrap in the lab: zebrafish optomotor response

Show 8 different directions of moving gratings

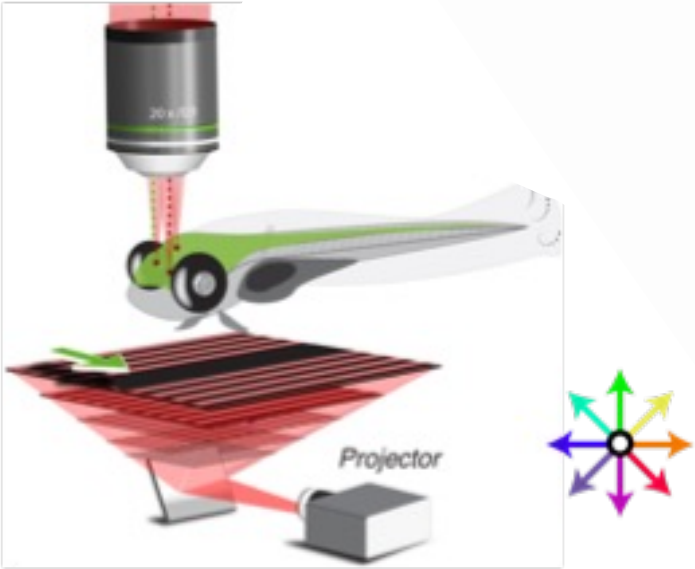
Analyze neural responses to stimuli in real-time



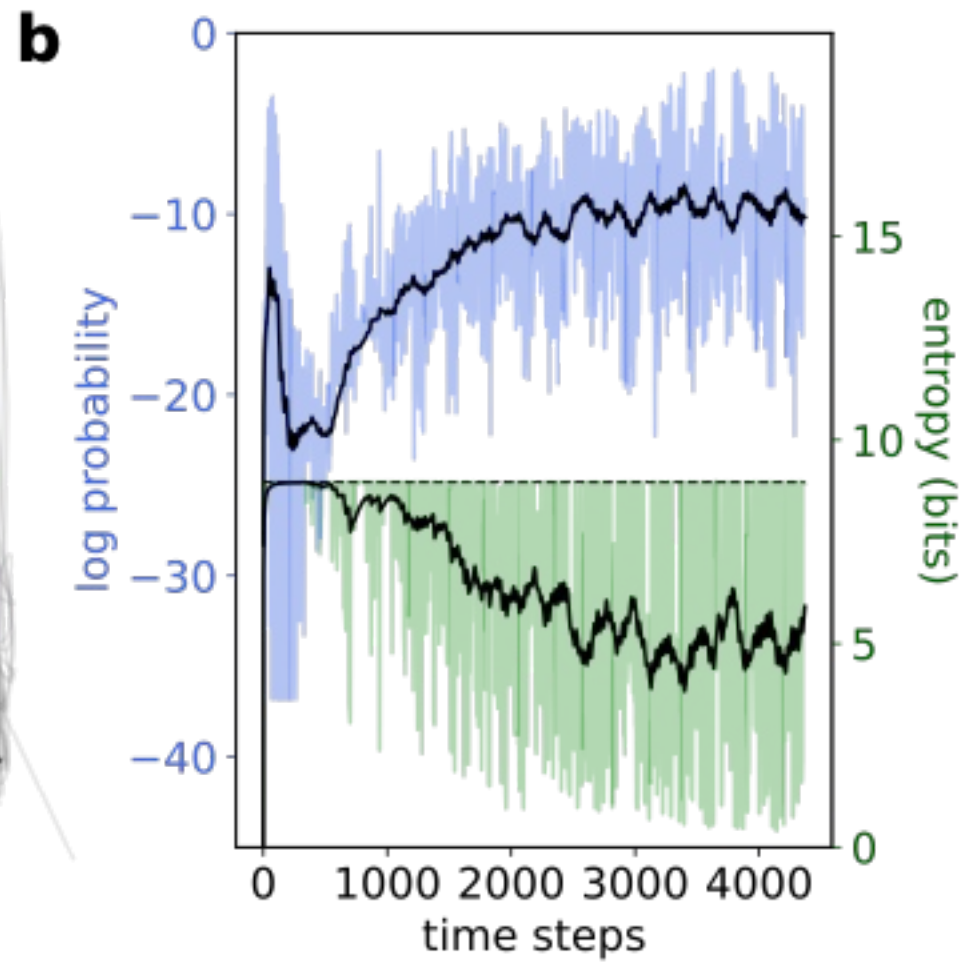
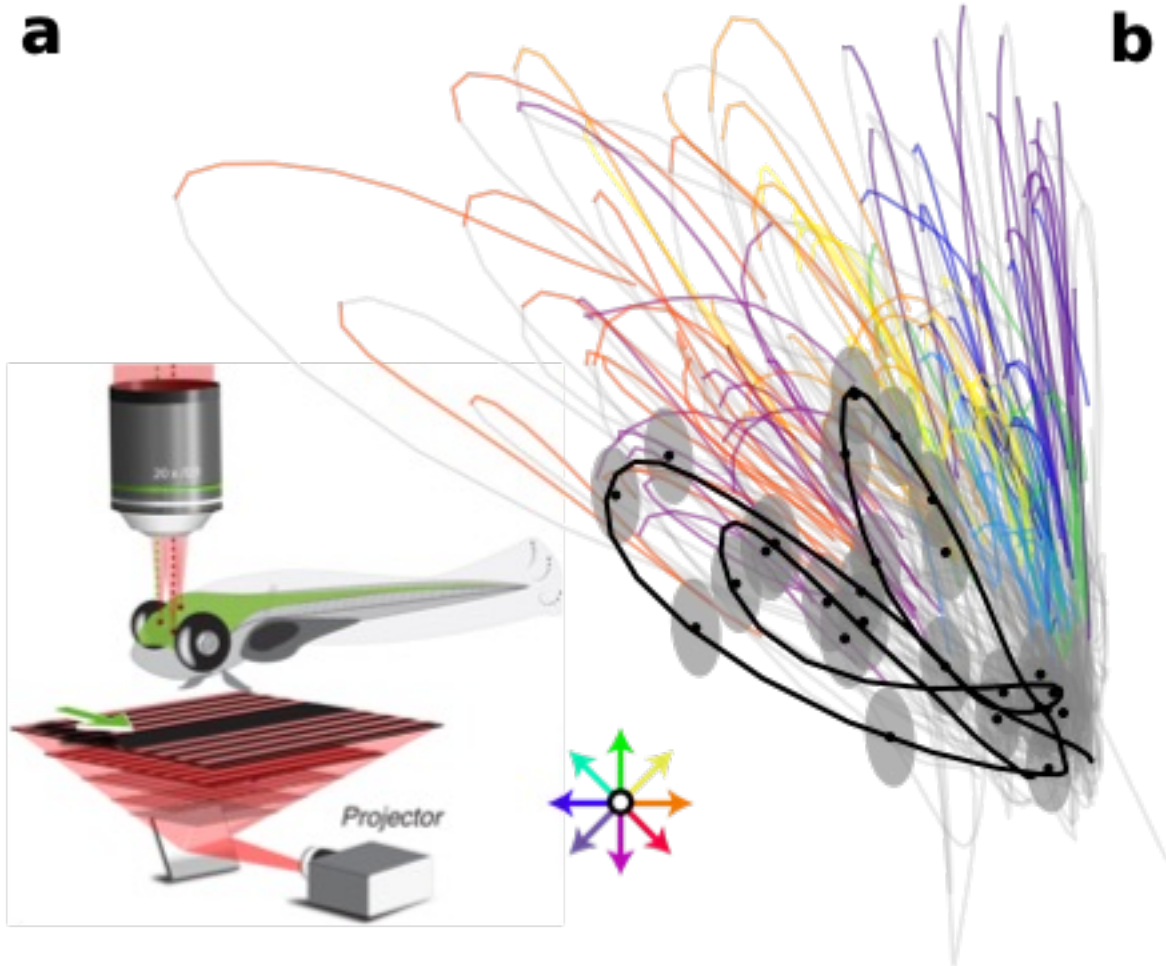
Bubblewrap in the lab



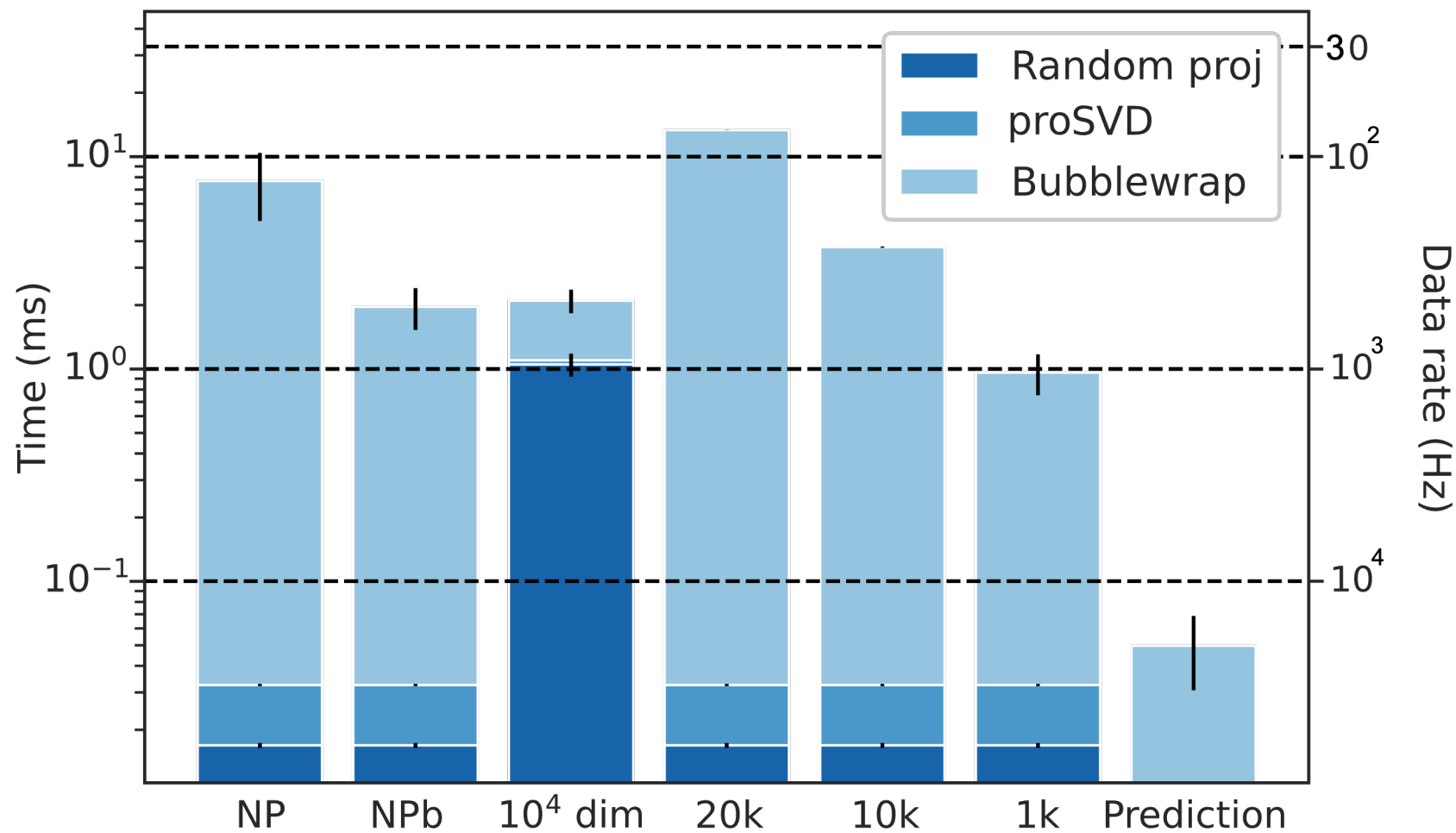
Bubblewrap in the lab



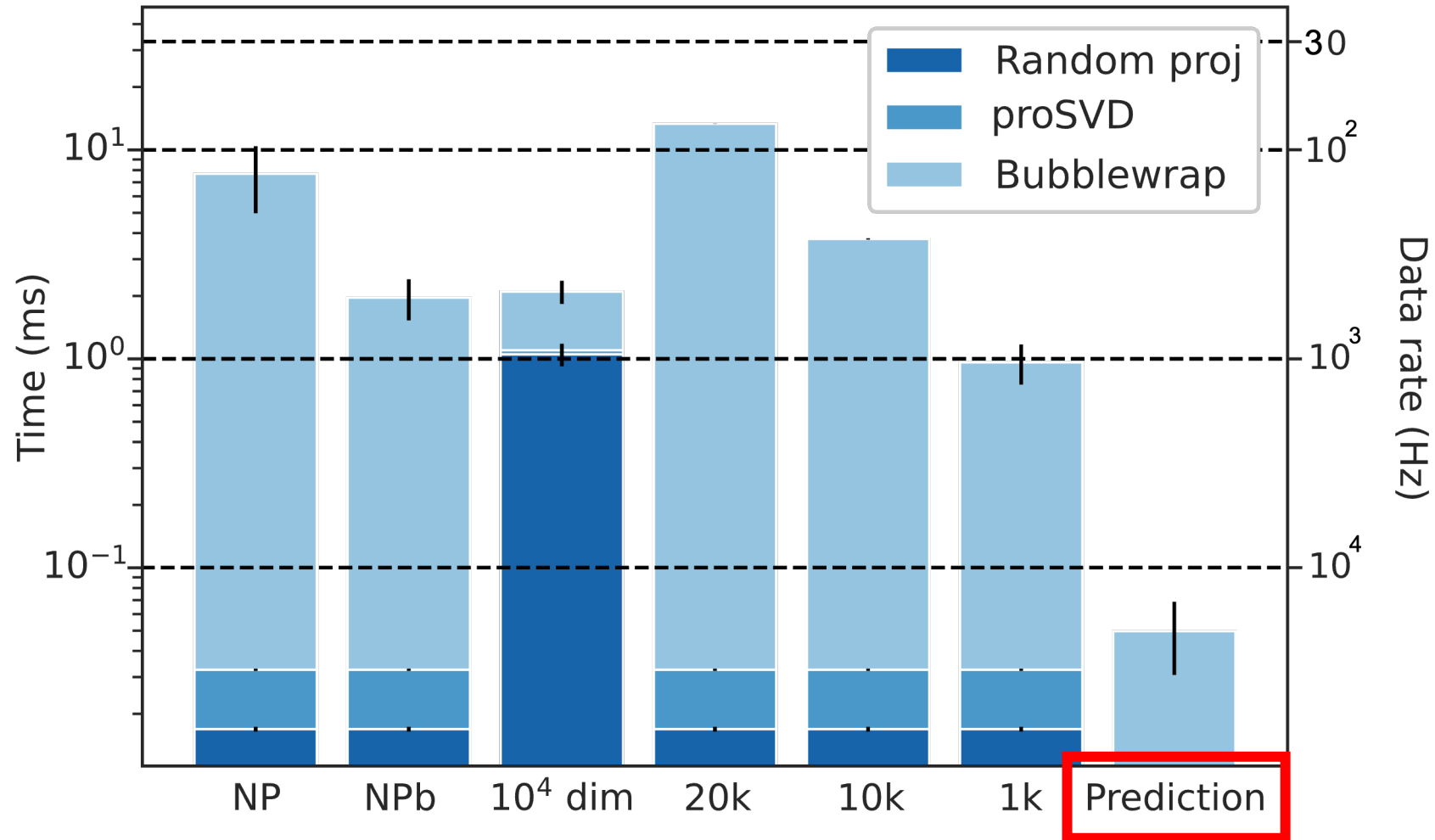
Bubblewrap in the lab



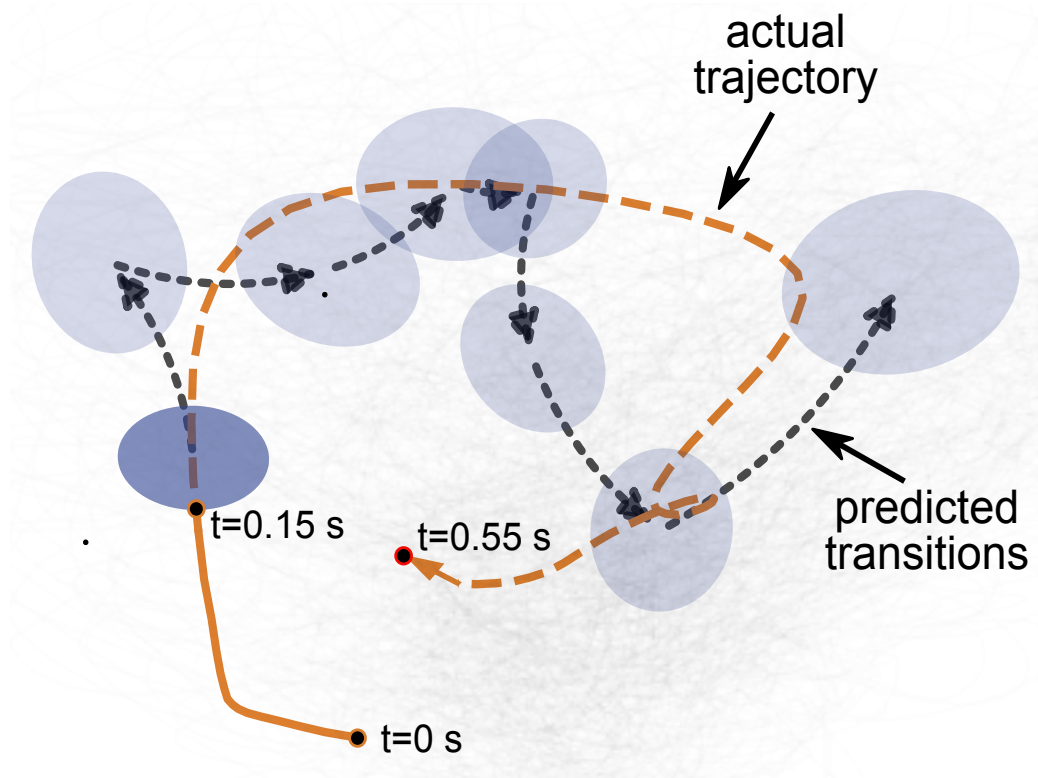
Fast dimension reduction, learning, & prediction



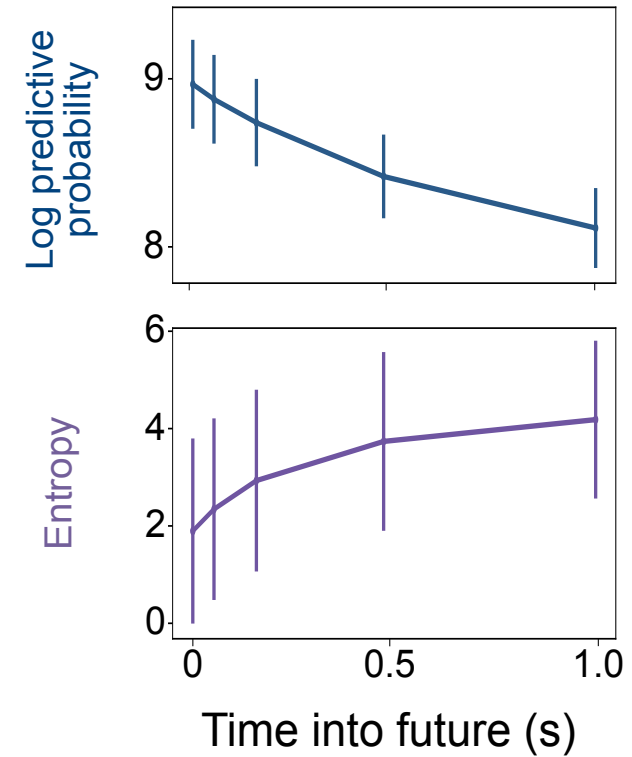
Fast dimension reduction, learning, & prediction



Robust multi-step ahead predictions



Future predictions maintain accuracy

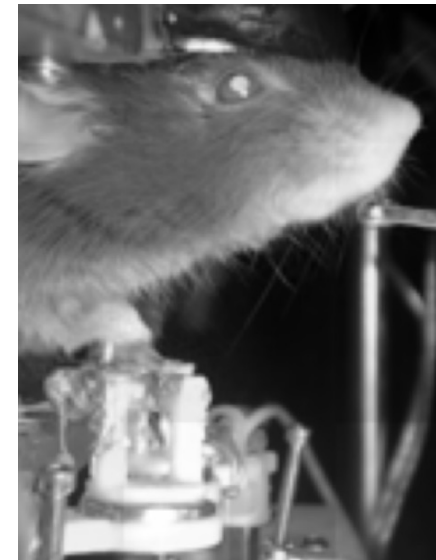
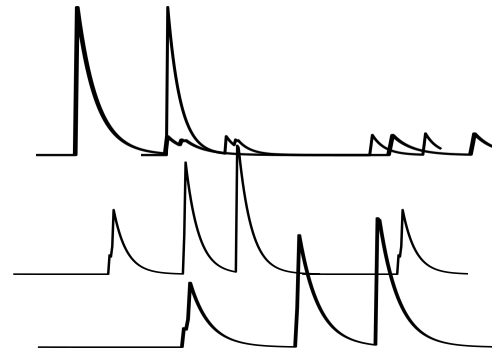


Streaming dimension reduction
→ streaming regression

Streaming dimension reduction → streaming regression

$$Y = X\beta$$

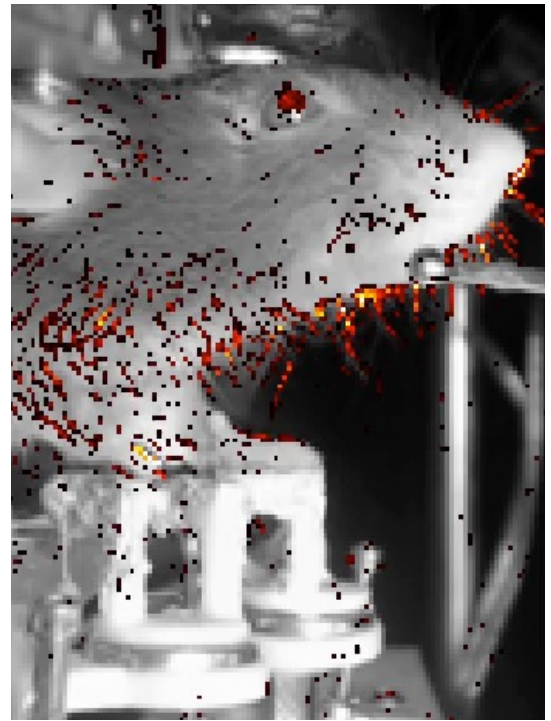
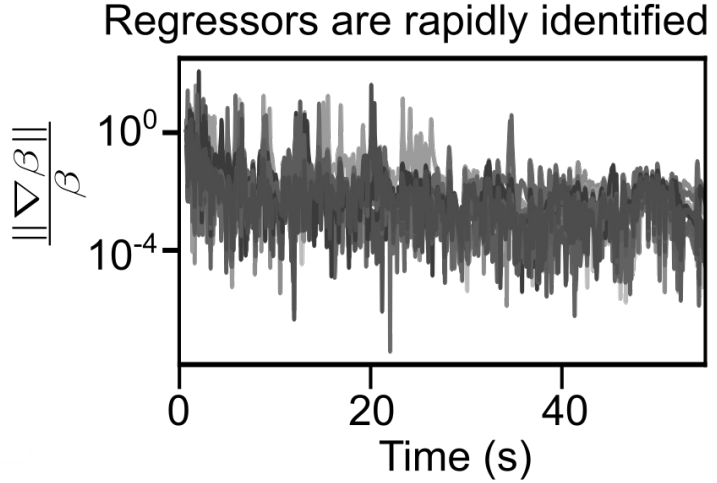
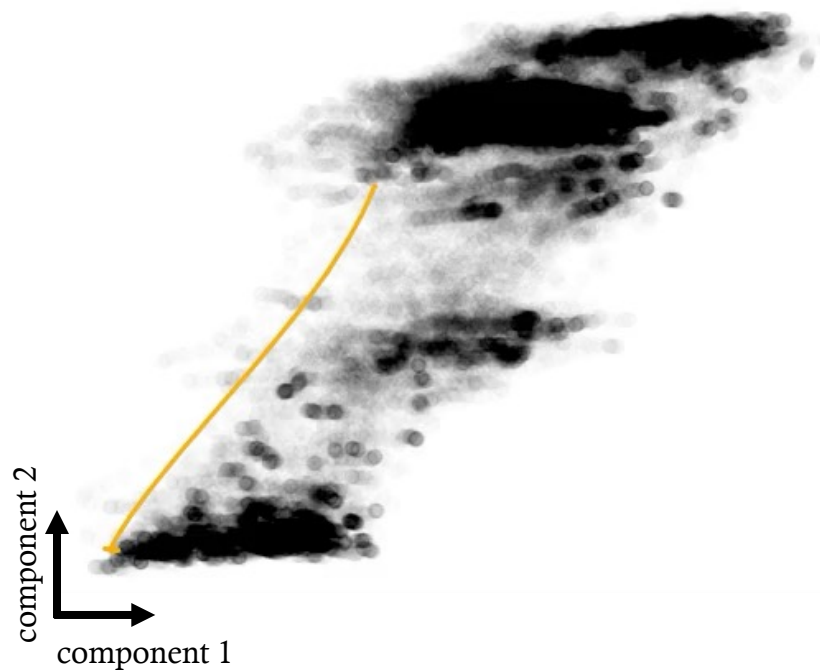
neural activity = behavior features * regression coefficients



Streaming dimension reduction → streaming regression

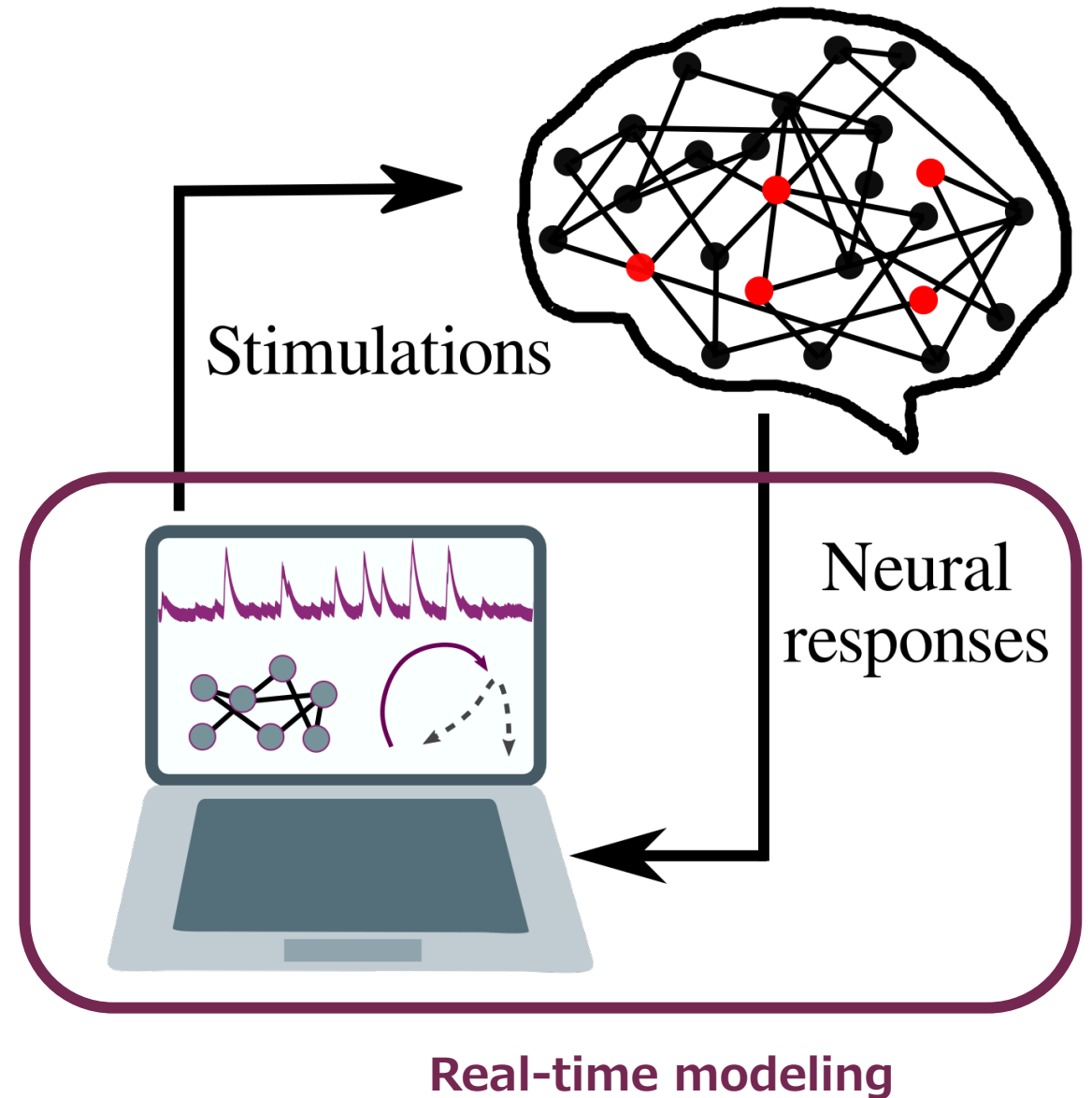
$$Y = X\beta$$

neural activity = behavior features * regression coefficients



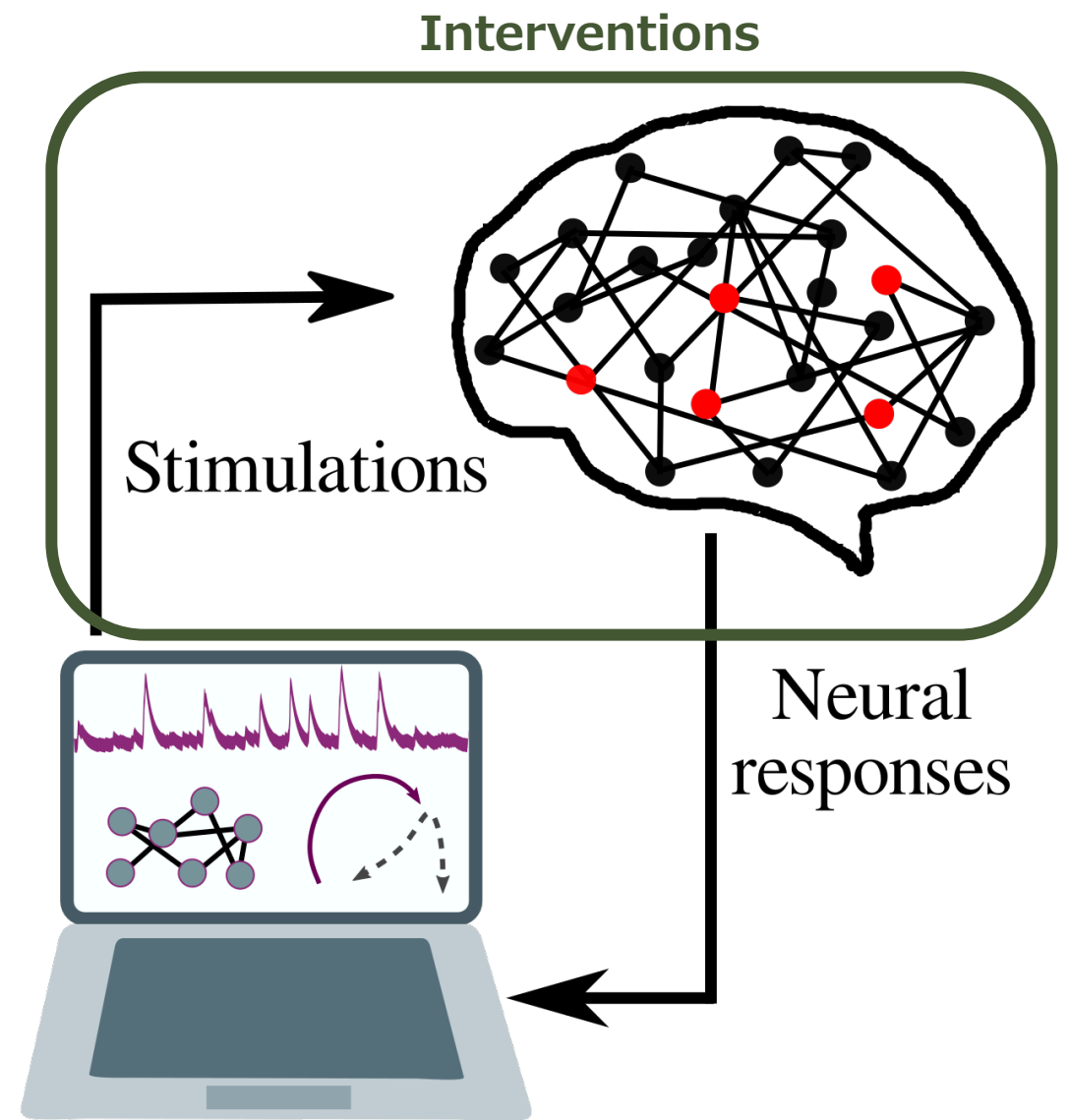
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- Optimize selection of interventions/stimulations



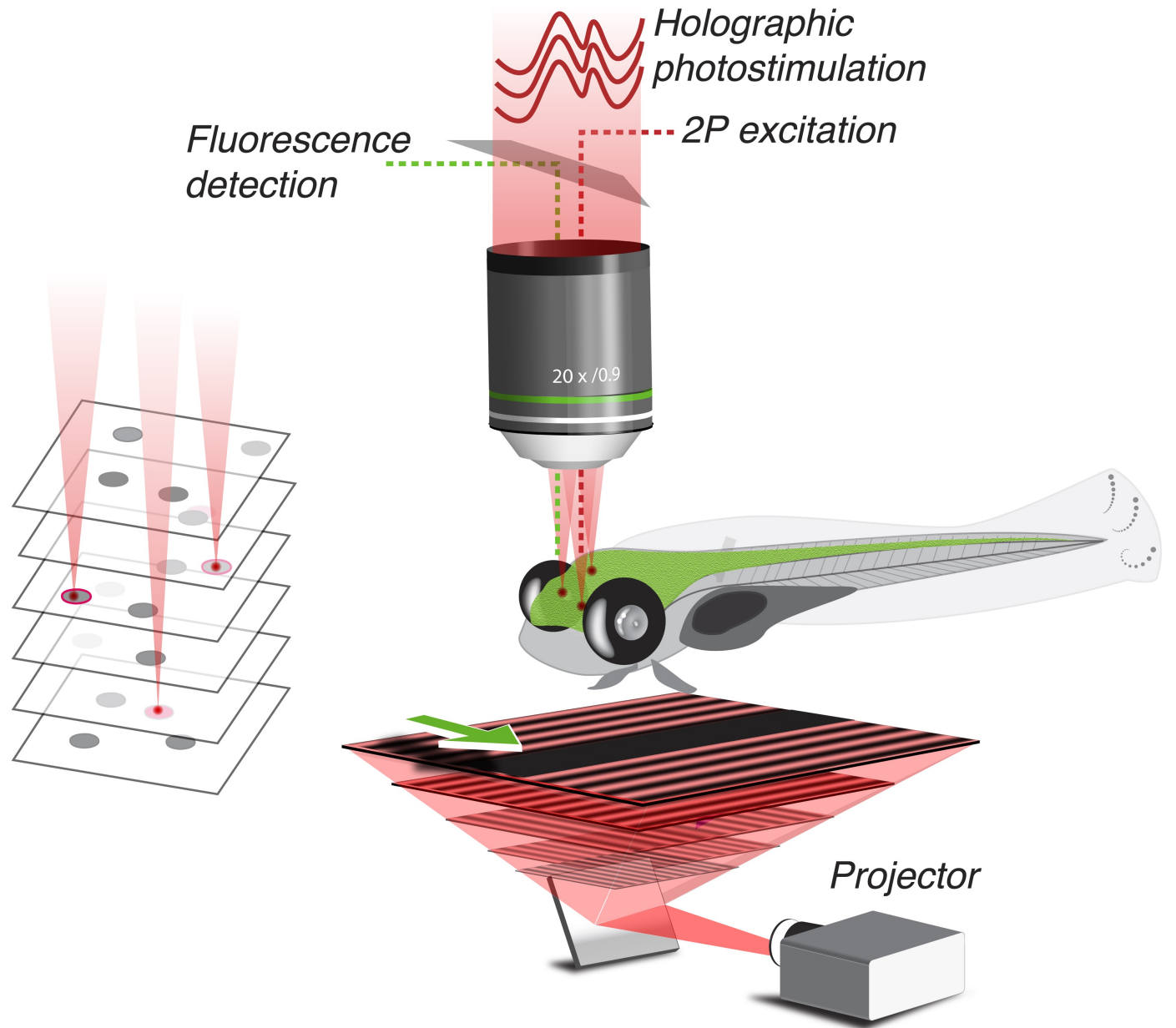
Outline:

- Build streaming models that adapt to current neural activity
- Optimize selection of interventions/stimulations

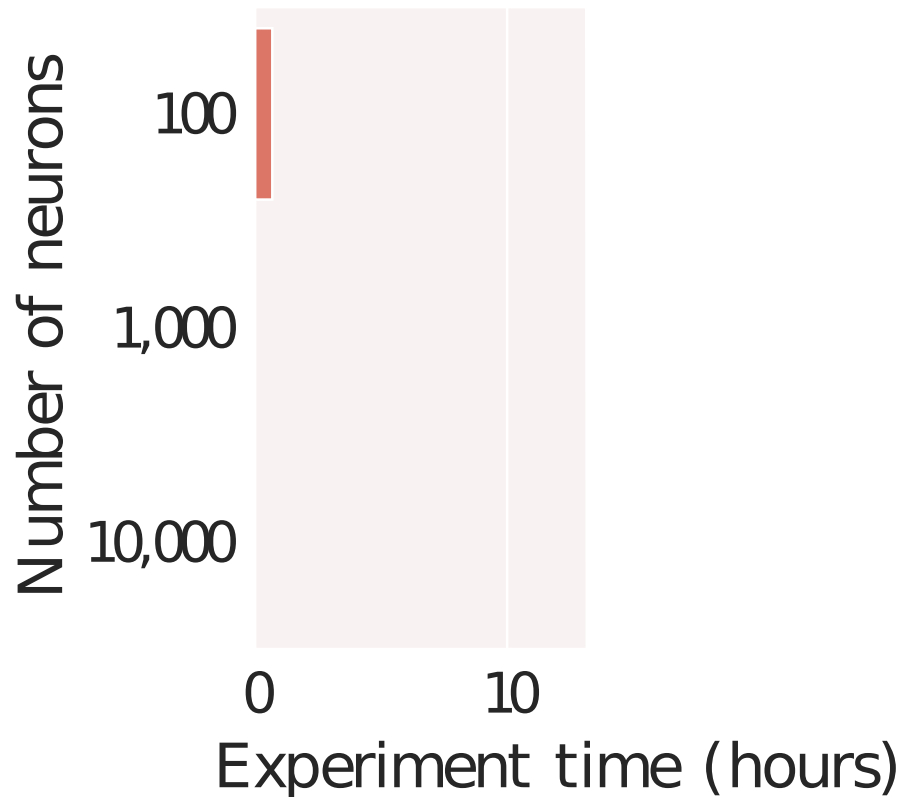


Adaptive 'questions'

Neural stimulations for mapping connections

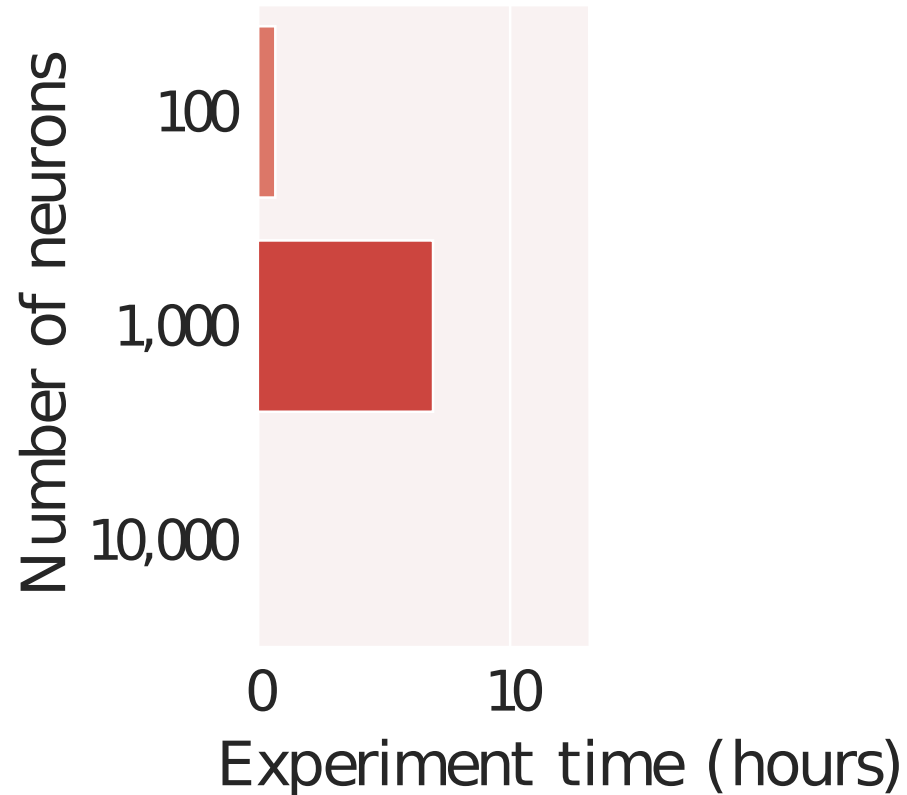


Naïve method: one neuron at a time



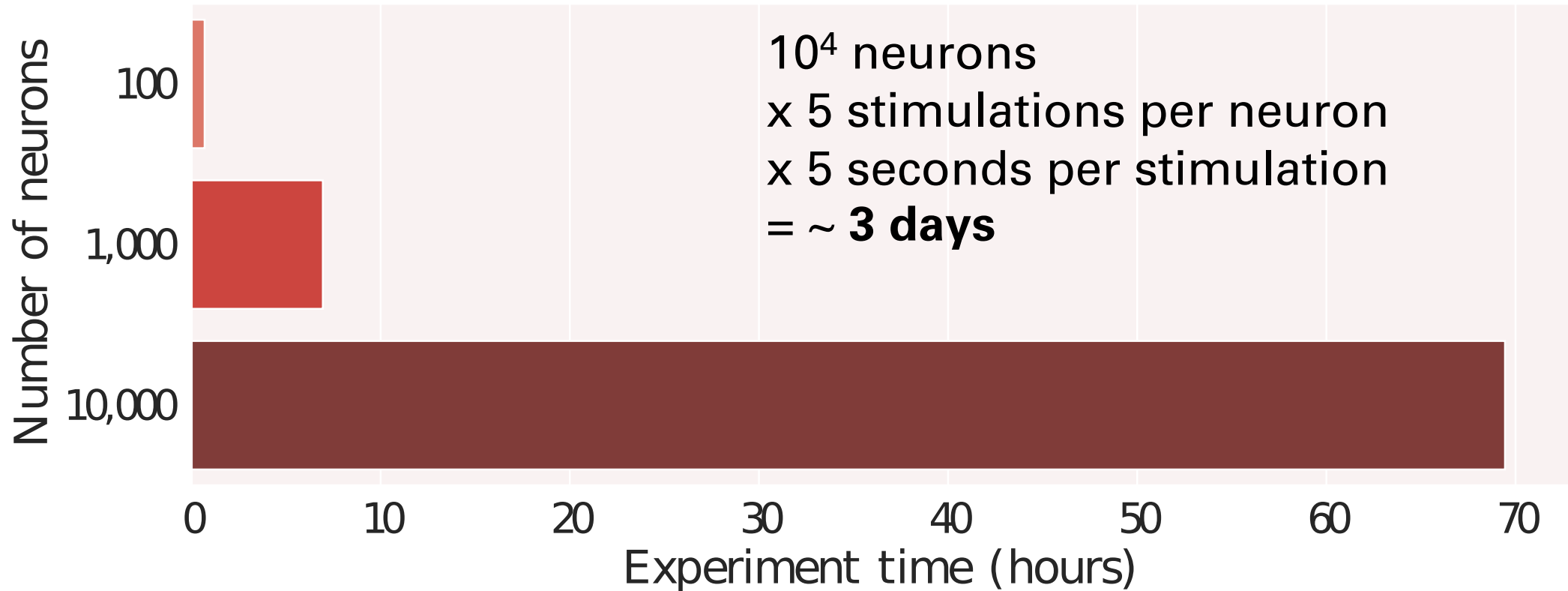
10^2 neurons
x 5 stimulations per neuron
x 5 seconds per stimulation
= ~ **42 minutes**

What about 1,000 neurons?



10^3 neurons
x 5 stimulations per neuron
x 5 seconds per stimulation
= ~ **7 hours**

What about 10,000 neurons?





Nasal or throat swabs from several people can be combined in a single test.

THE MATHEMATICAL STRATEGY THAT COULD TRANSFORM CORONAVIRUS TESTING

To save time and money, several countries are using a technique called group testing, which pools samples from many people.

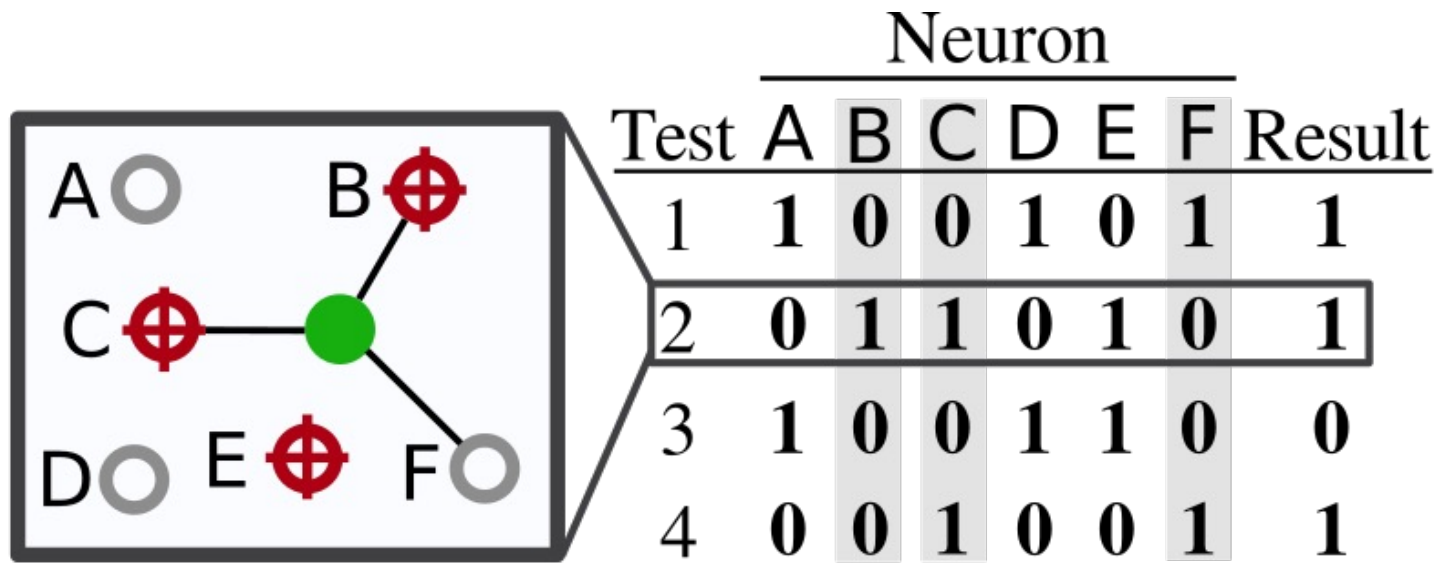
By Smriti Mallapaty

are already using group testing.

mixed together and tested o

Alternative: stimulate groups of neurons

- Pool samples into single tests (groups)
- Developed for testing soldiers for syphilis
- Recently used for COVID-19 testing



- Observed neuron
- ⊕ Stimulated neurons
- Other neurons

■ Connections

If connected neurons are stimulated, the result is 1.

Neural stimulation as group testing

Neural responses

We can predict if a neuron i is activated by a trial stimulation t as

$$a_{ti} = \bigvee_{j=1}^N w_{ij} x_{tj} = \max(w_i \odot x_t)$$

Our measurements are noisy, with false positives and false negatives

$$y_{ti} \mid (a_{ti} = 0) \sim \text{Bern}(\alpha) \qquad y_{ti} \mid (a_{ti} = 1) \sim \text{Bern}(1 - \beta)$$

Relaxation to linear program

$$\log p(\{y_t\} | \{w_i, x_t\}) =$$

$$\sum_t \left[\log \frac{(1-\alpha)(1-\beta)}{\alpha\beta} y_t - \log \frac{1-\alpha}{\beta} \right] a_t(w) + \text{const}$$

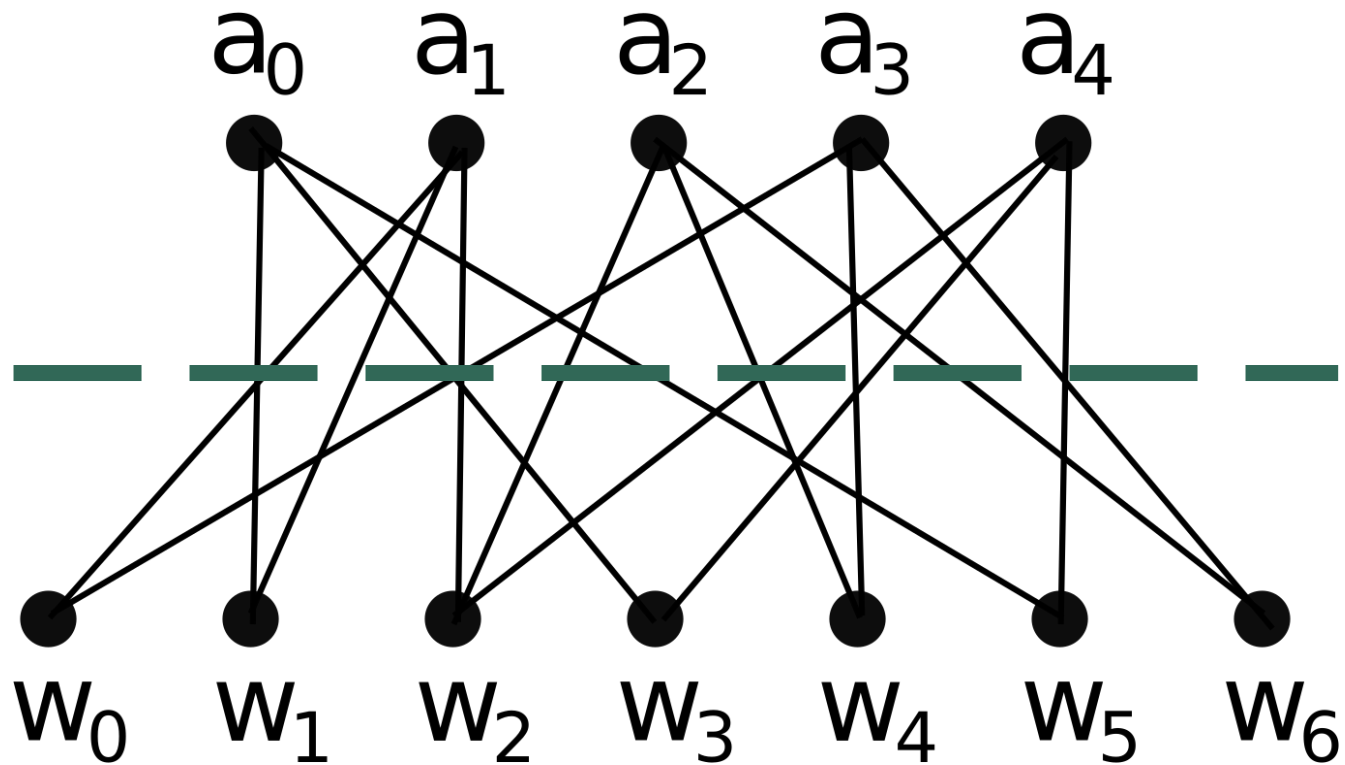
Relaxation to linear program

$$\log p(\{y_t\}|\{w_i, x_t\}) =$$

$$\sum_t \left[\log \frac{(1-\alpha)(1-\beta)}{\alpha\beta} y_t - \log \frac{1-\alpha}{\beta} \right] a_t(w) + \text{const}$$

$$\longrightarrow \max_{\{w_i, a_t\}} \sum_t c_t a_t$$

$$\text{subject to } x_{ti} w_i \leq a_t \leq \sum_i x_{ti} w_i, \quad w_i, a_t \in [0, 1]$$



$$\max_{\{w_i, a_t\}} \sum_t c_t a_t$$

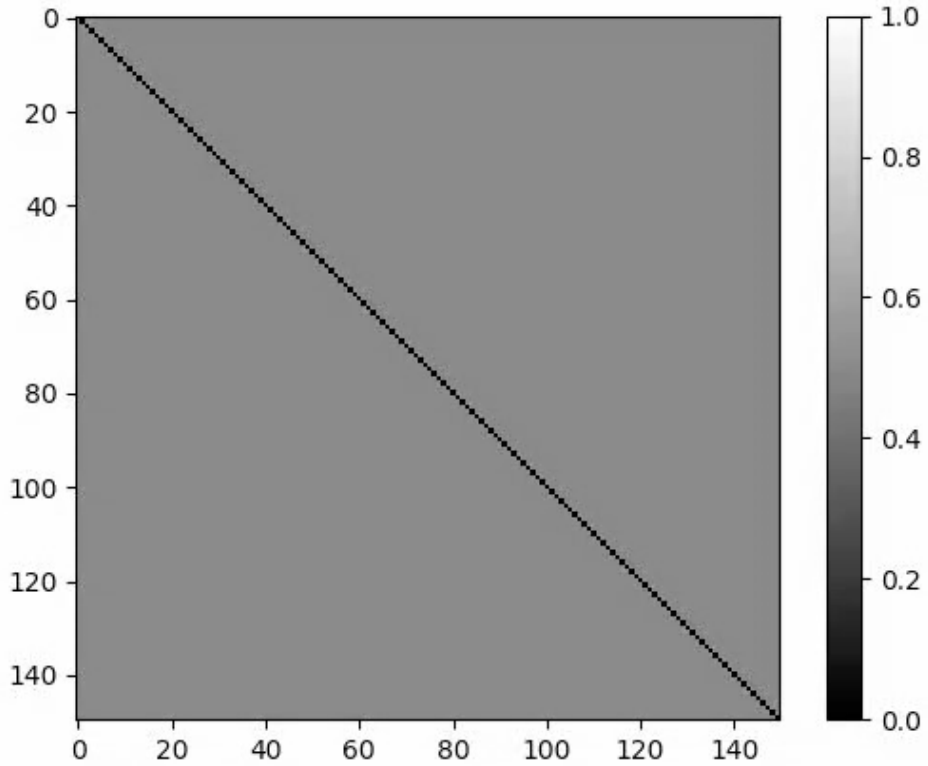
subject to:

$$x_{ti} w_i \leq a_t \leq \sum_i x_{ti} w_i,$$

$$w_i, a_t \in [0, 1]$$

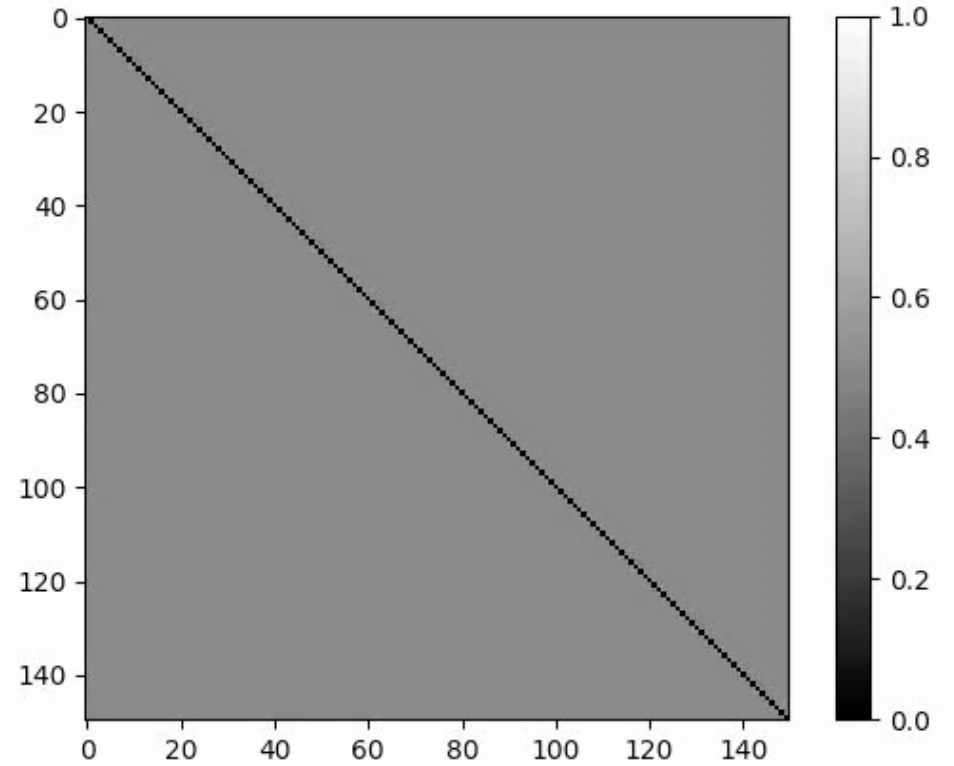
Dual decomposition

Number of tests: 0



Naïve Method

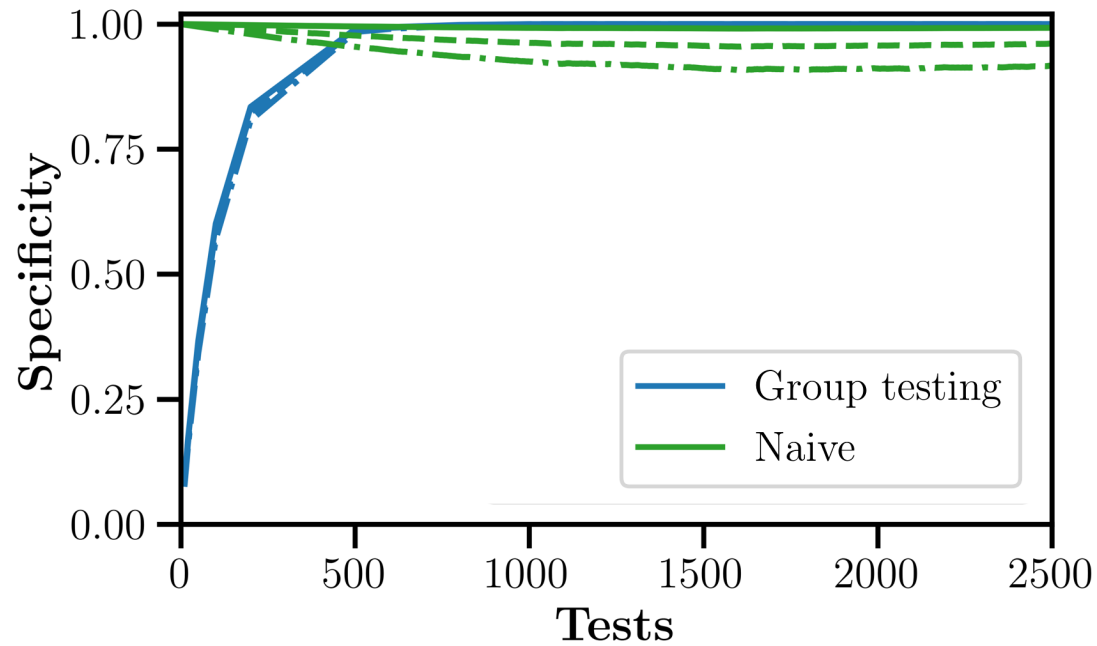
Number of tests: 0



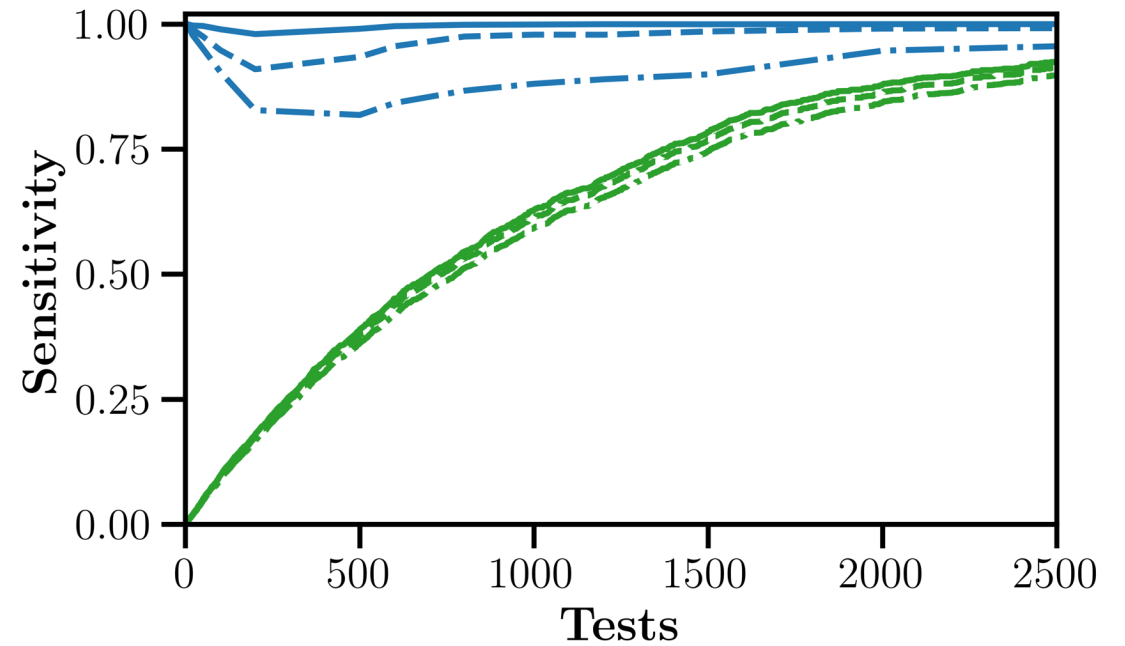
Group Testing

Efficient questioning
with adaptive group testing

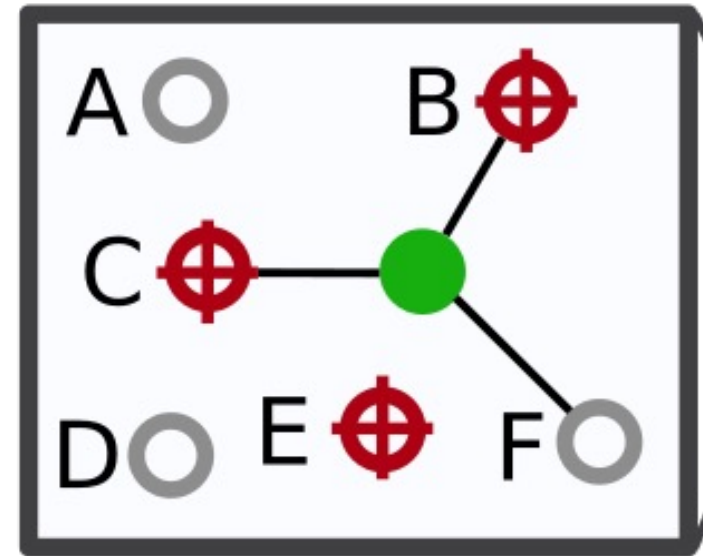
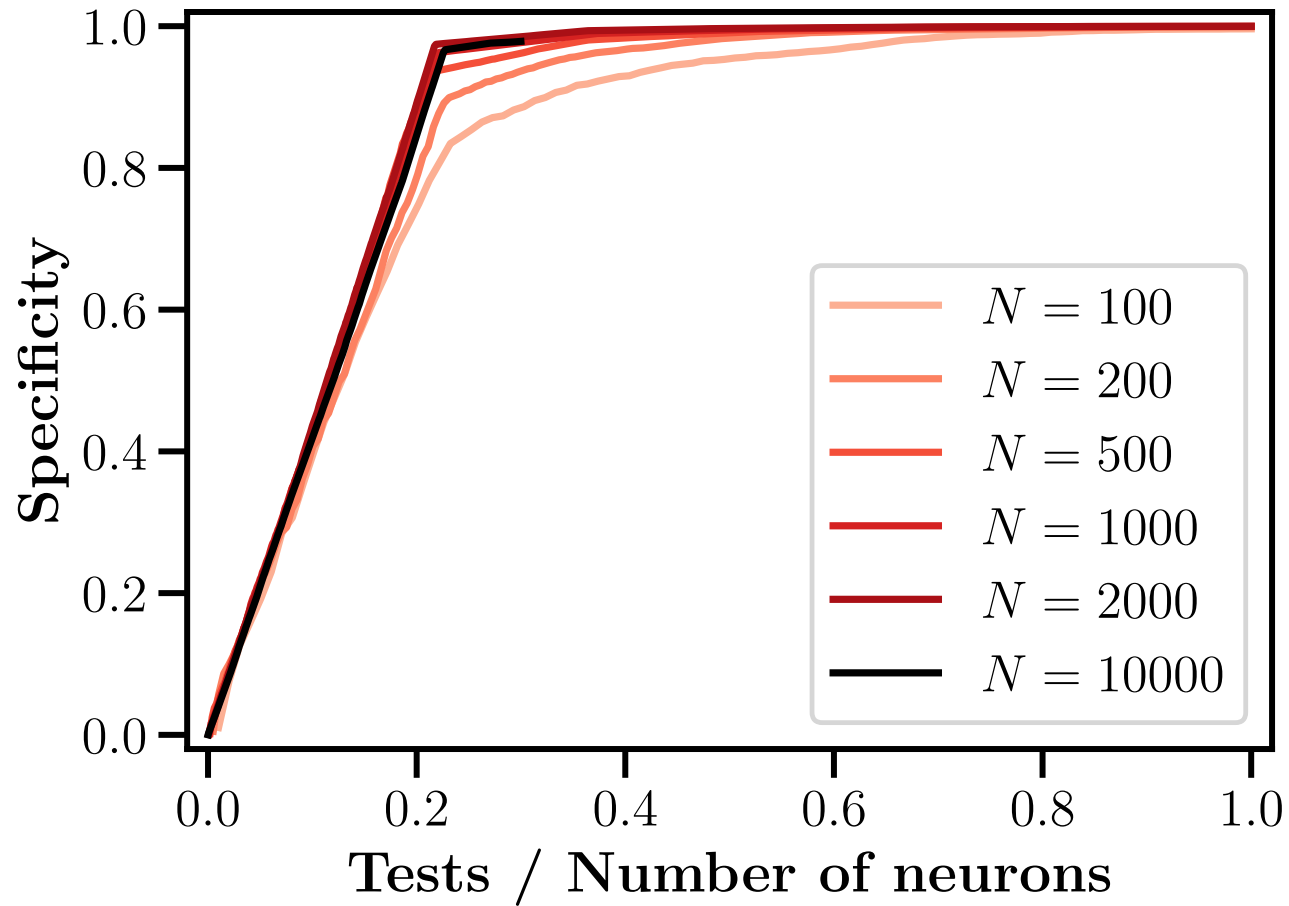
Accurate recovery with many fewer tests



$$\textit{Specificity} = \frac{TN}{TN + FP} \sim \text{Finding correct zeros}$$



$$\textit{Sensitivity} = \frac{TP}{TP + FN} \sim \text{Finding correct ones (connections)}$$

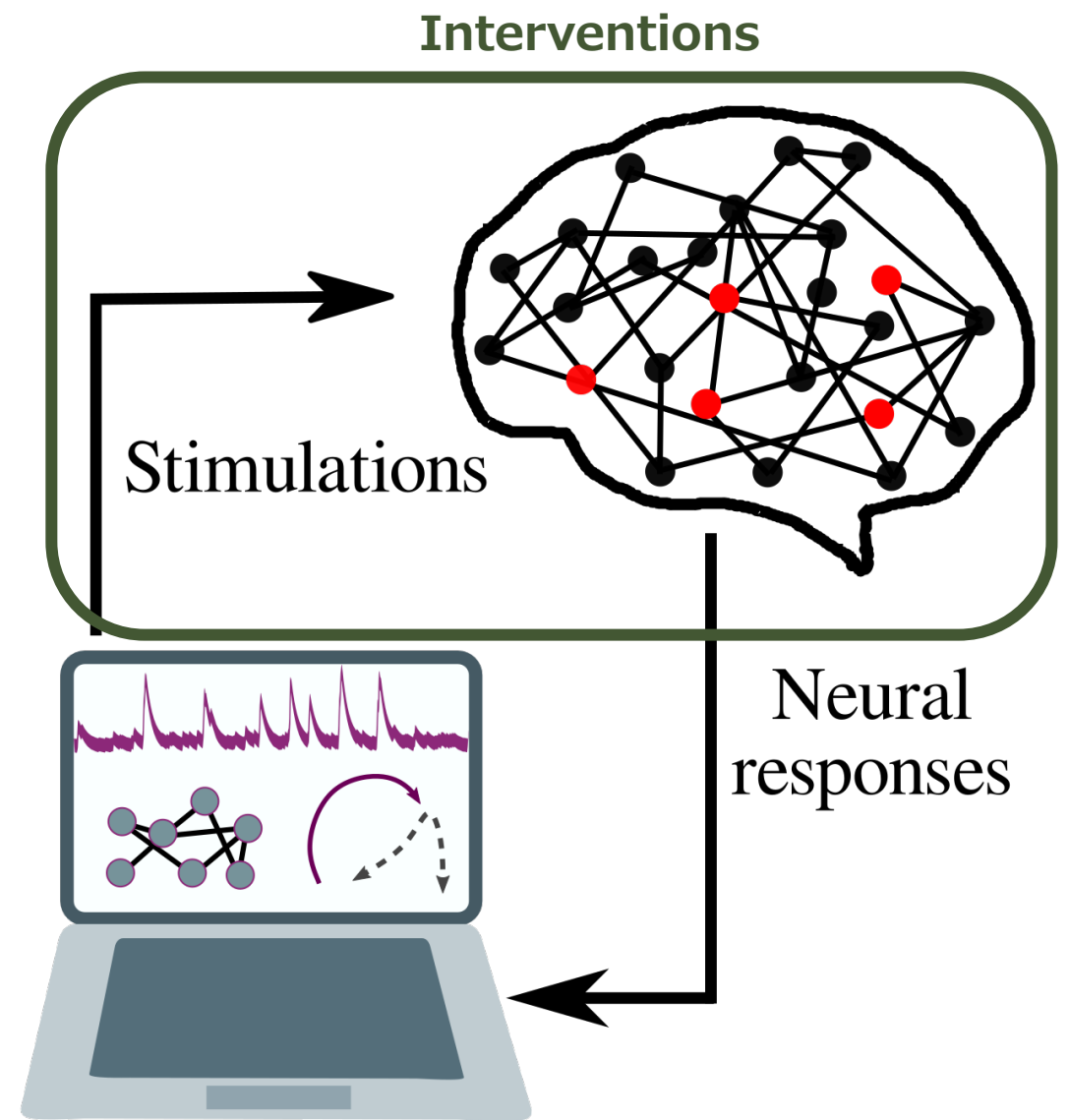


What about 1,000 neurons?
10,000?

Efficient questioning
with adaptive group testing

Outline:

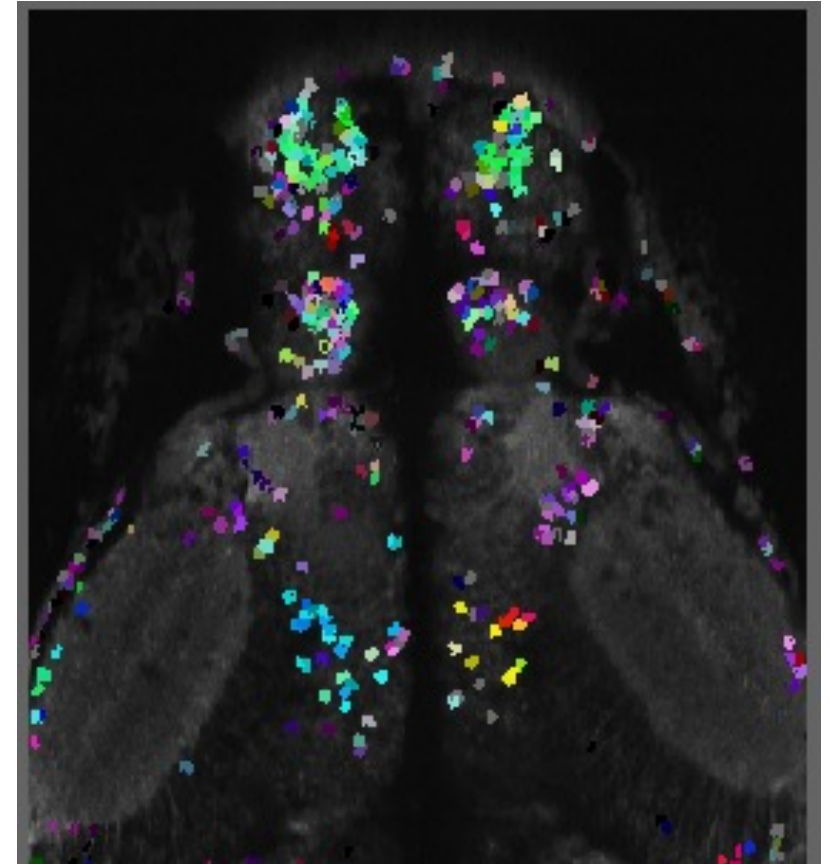
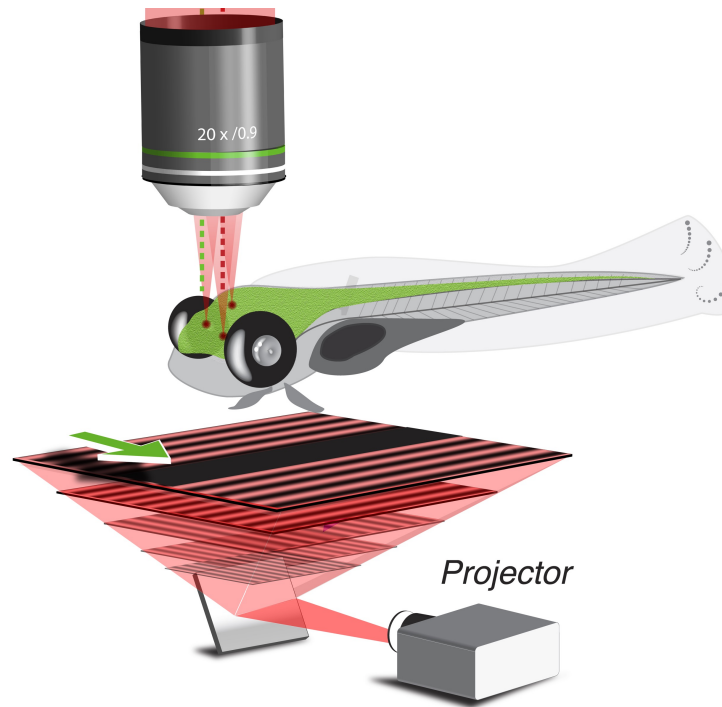
- Build streaming models that adapt to current neural activity
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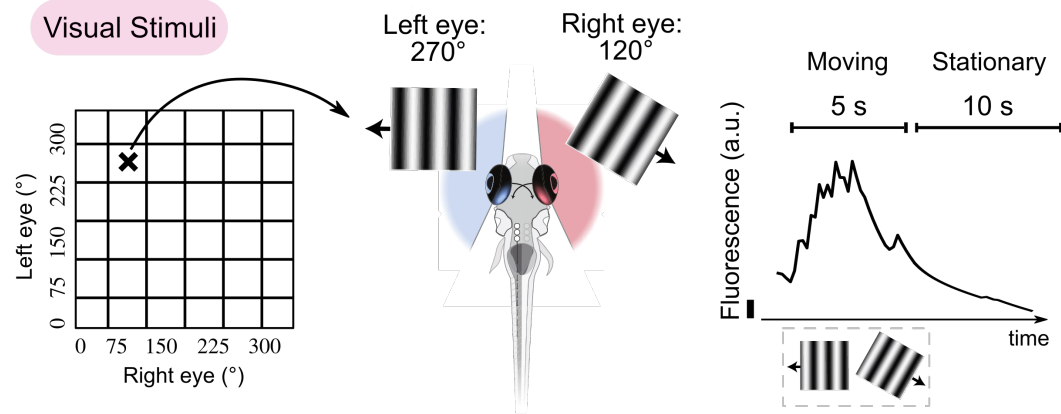
Optimize neural responses: choose next visual stimulus to display

Show 8 different directions of moving gratings

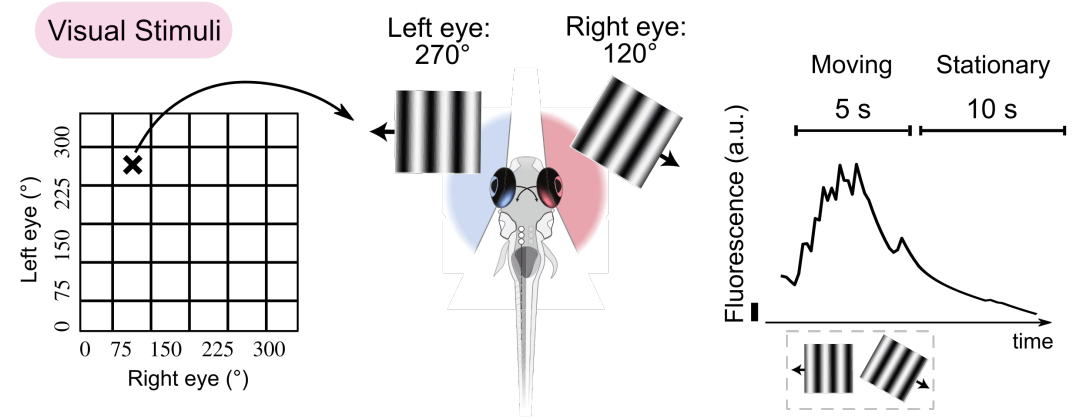
Analyze neural responses to stimuli in real-time



Online Bayesian Optimization

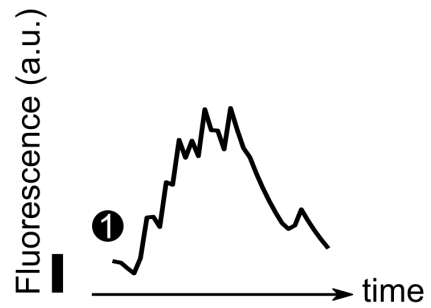


Online Bayesian Optimization

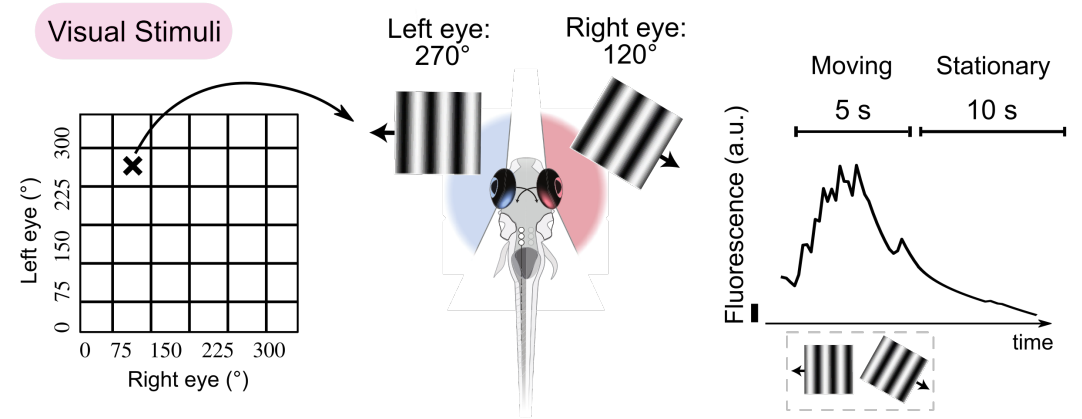


Observe a data point

$$x = (210^\circ, 345^\circ)$$



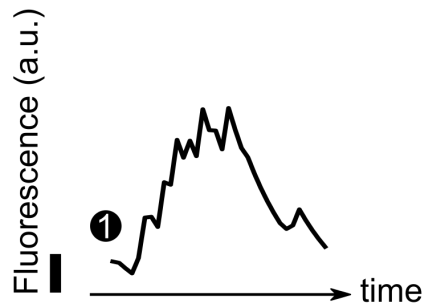
Online Bayesian Optimization



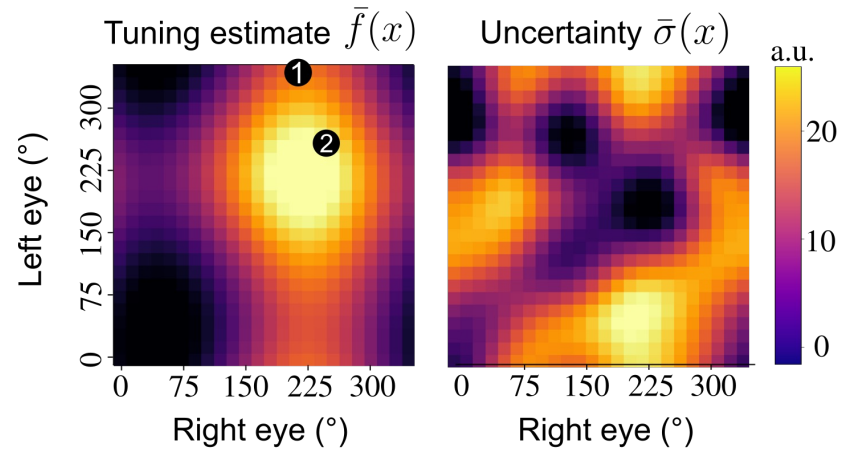
$$f(\mathbf{x}) \sim \mathcal{GP}(m(\mathbf{x}), k(\mathbf{x}, \mathbf{x}'))$$

Observe a data point

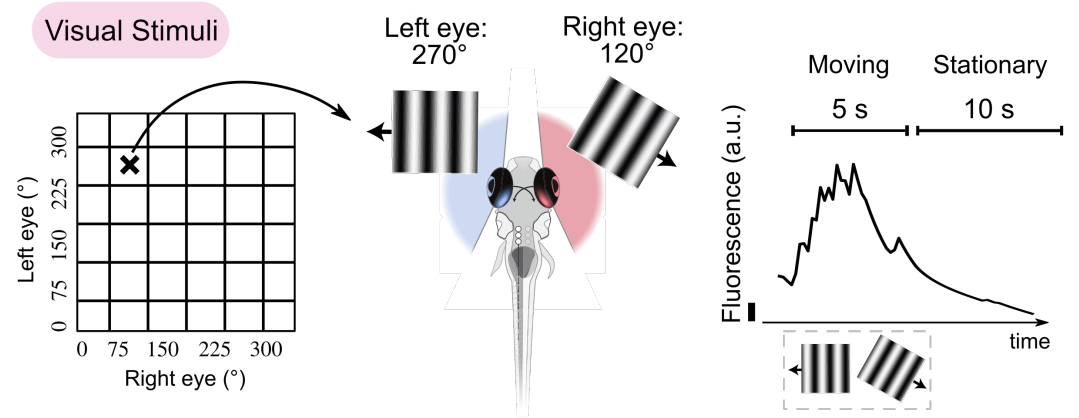
$$x = (210^\circ, 345^\circ)$$



▼ Update estimate of tuning curve

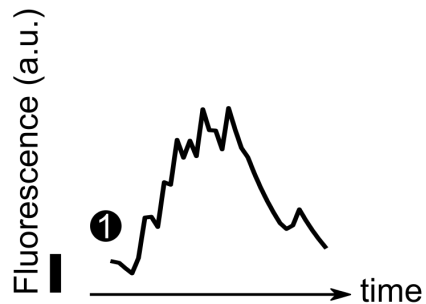


Online Bayesian Optimization

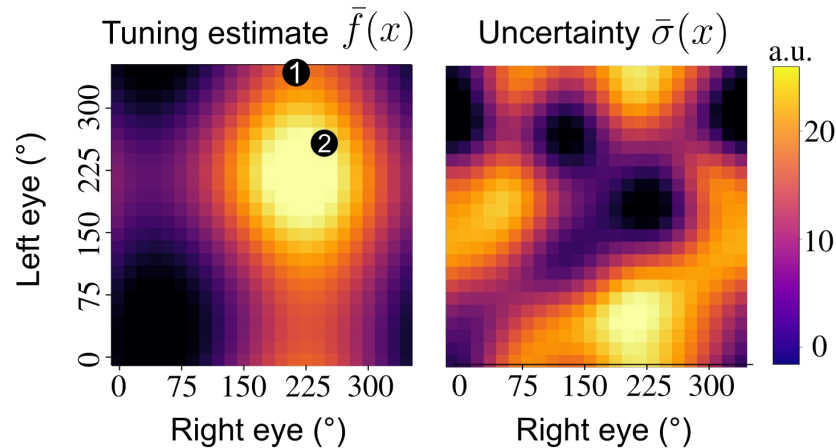


Observe a data point

$$x = (210^\circ, 345^\circ)$$



Update estimate of tuning curve



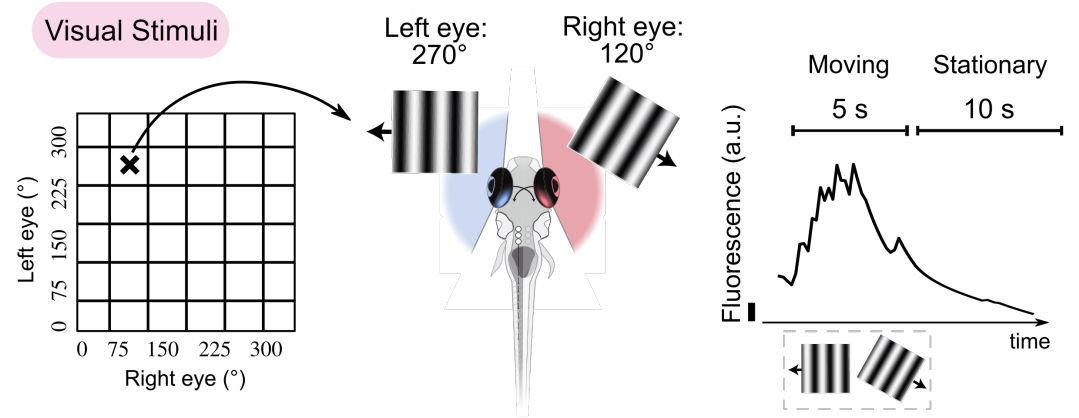
Select next stimulus to sample

$$f|x, y \sim \mathcal{N}(\bar{f}, \bar{\sigma}^2)$$

Next stimulus chosen by maximizing priority score

$$\arg \max_x \bar{f}(x) + \alpha \bar{\sigma}(x)$$

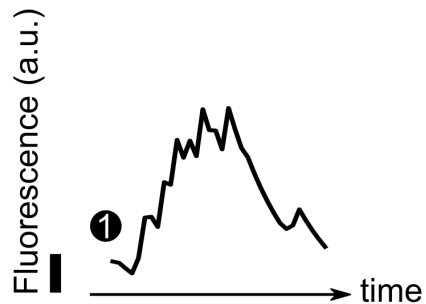
Online Bayesian Optimization



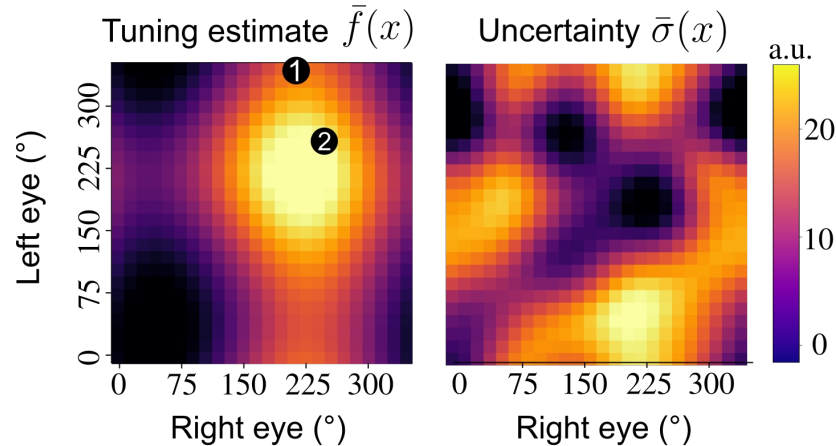
Bayesian Optimization

Observe a data point

$$x = (210^\circ, 345^\circ)$$



Update estimate of tuning curve



Select next stimulus to sample

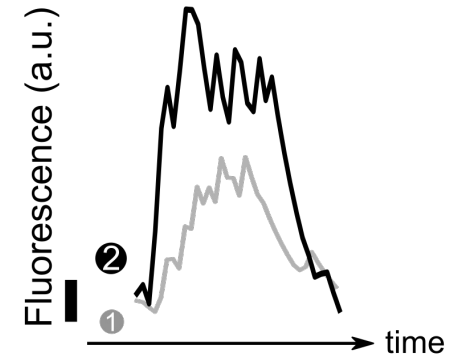
$$f|x, y \sim \mathcal{N}(\bar{f}, \bar{\sigma}^2)$$

Next stimulus chosen by maximizing priority score

$$\arg \max_x \bar{f}(x) + \alpha \bar{\sigma}(x)$$

Observe a new data point

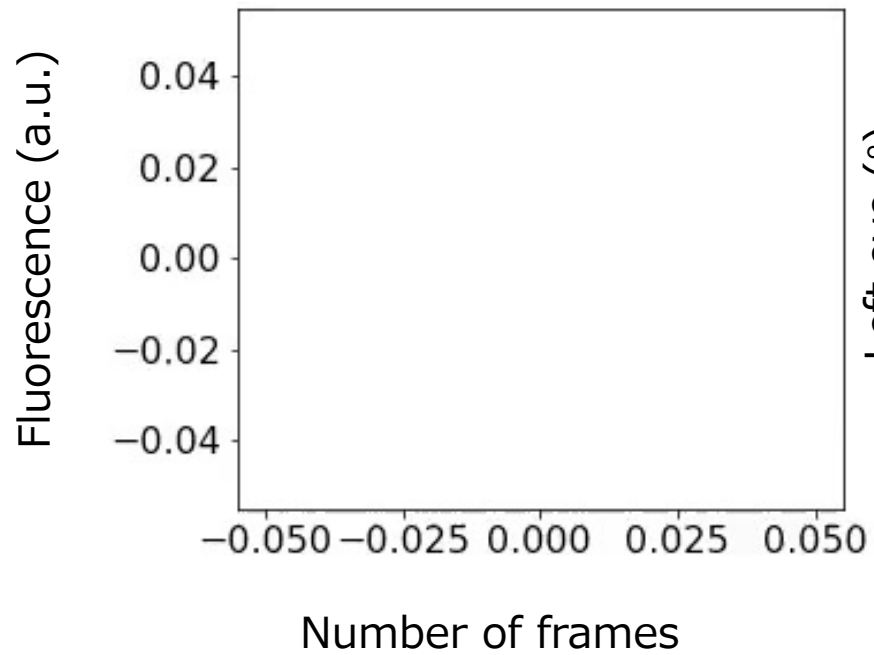
$$x^* = (240^\circ, 240^\circ)$$



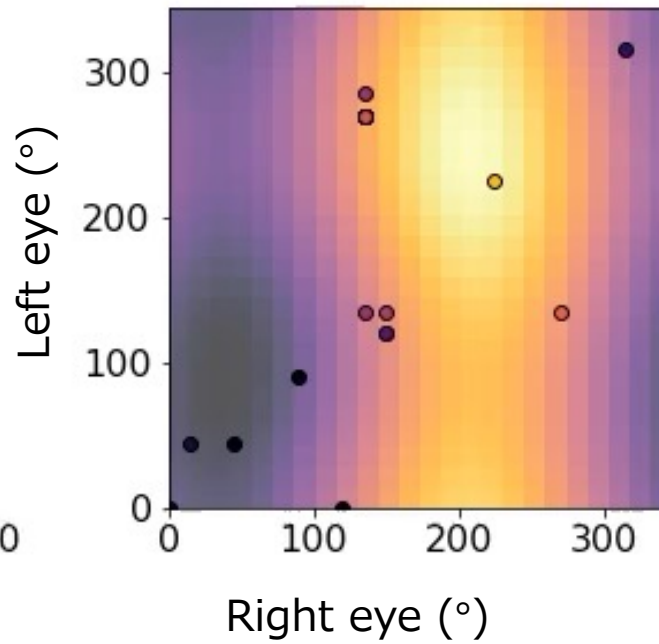
Repeat until chosen confidence level reached

Rapid optimization of peak neural responses

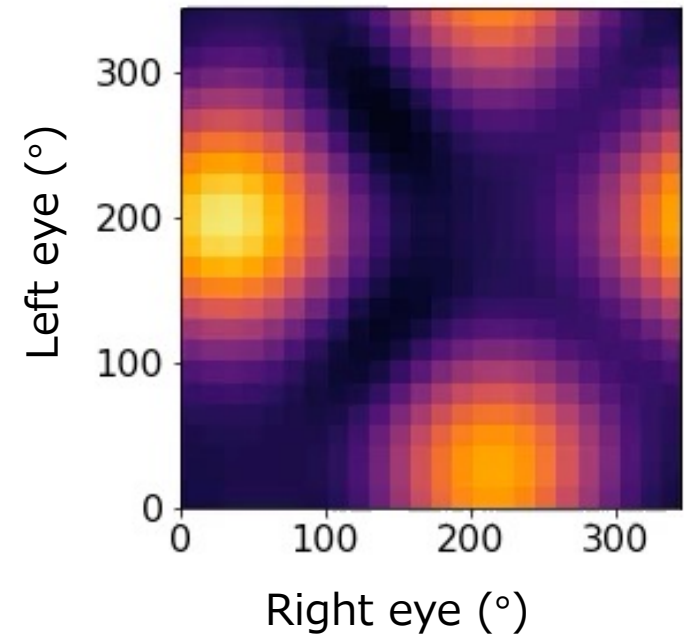
Neural response



Current tuning estimate

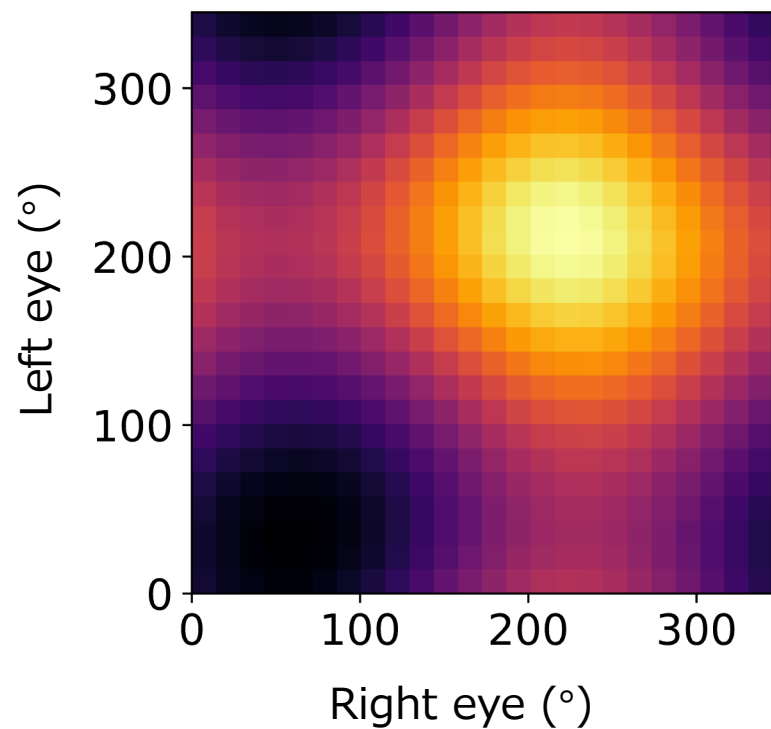


Current uncertainty

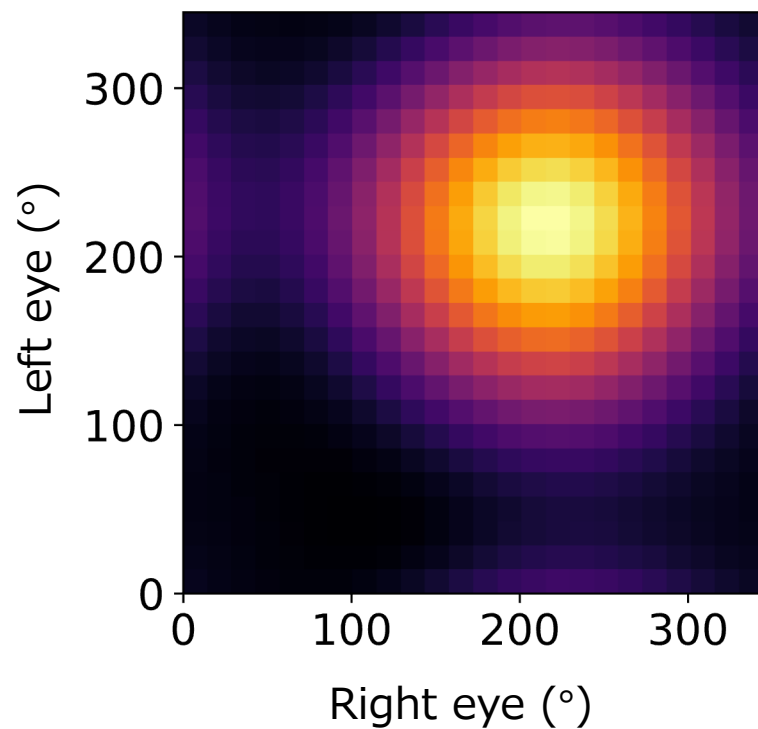


Neural tuning curve estimates

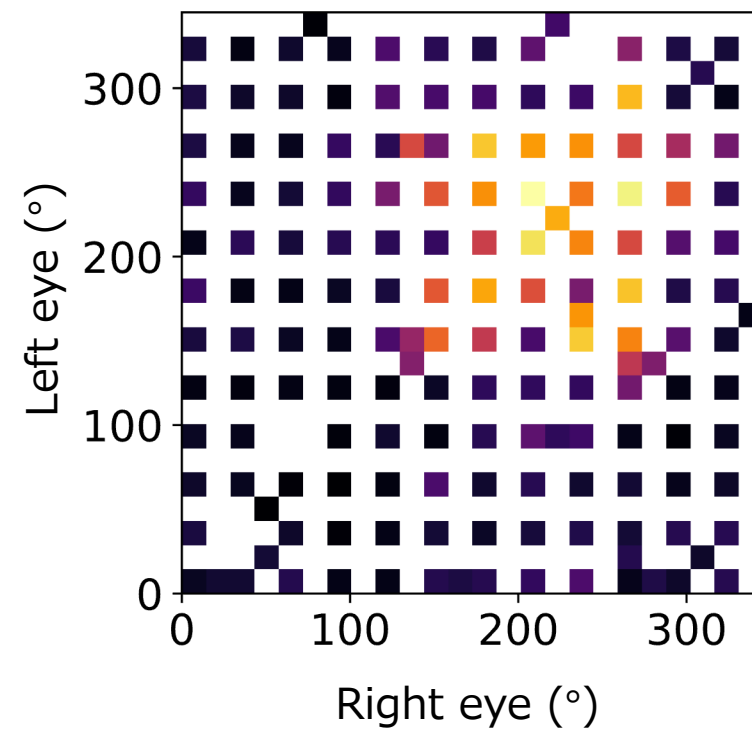
Real-time GP: 8 stimuli



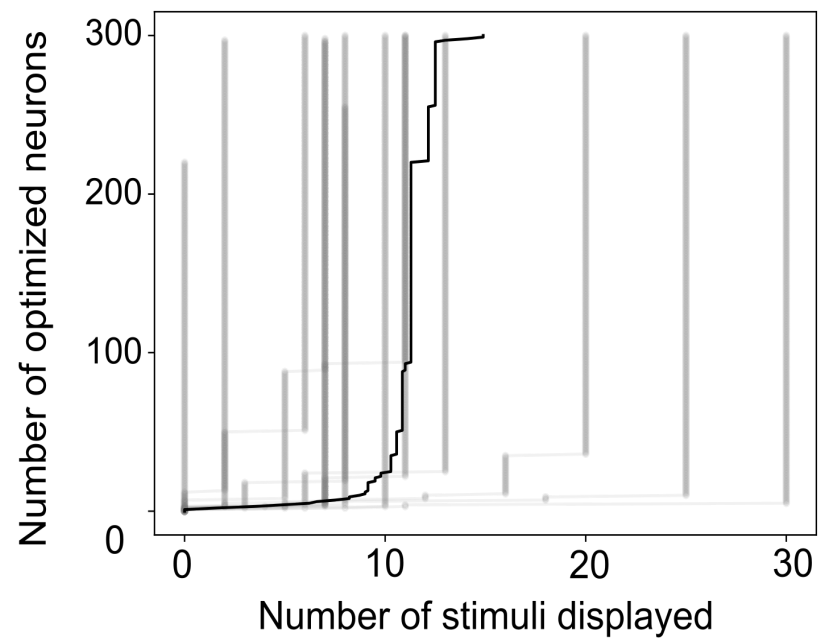
Offline GP: 144 stimuli



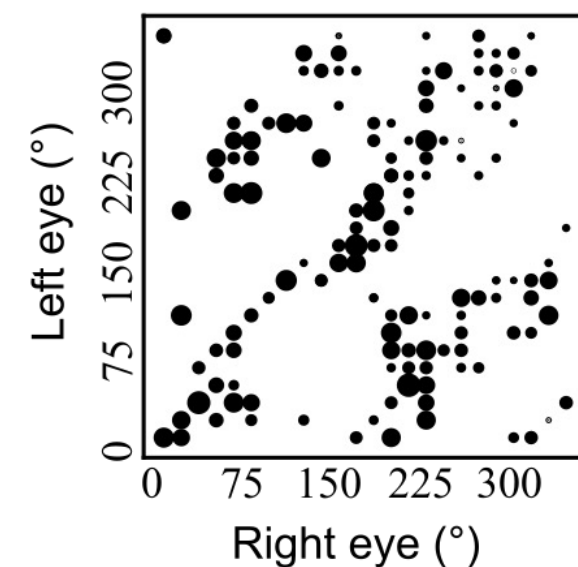
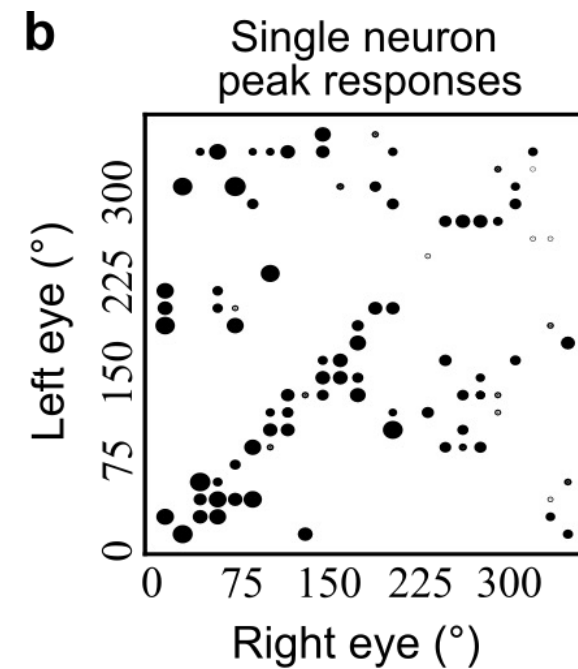
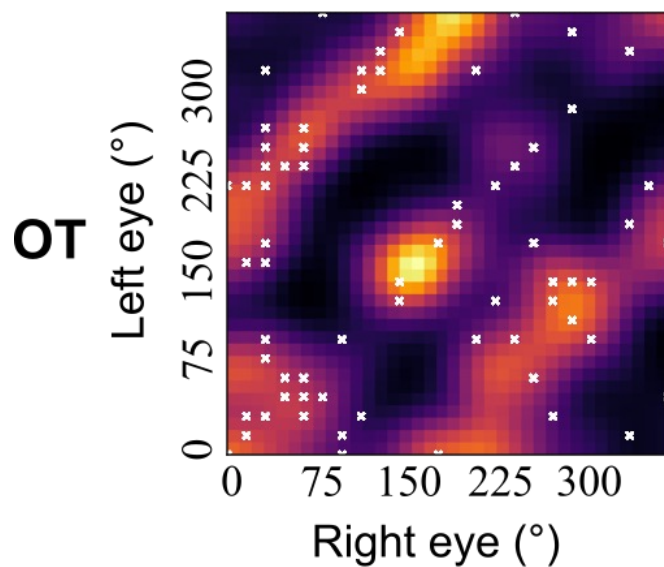
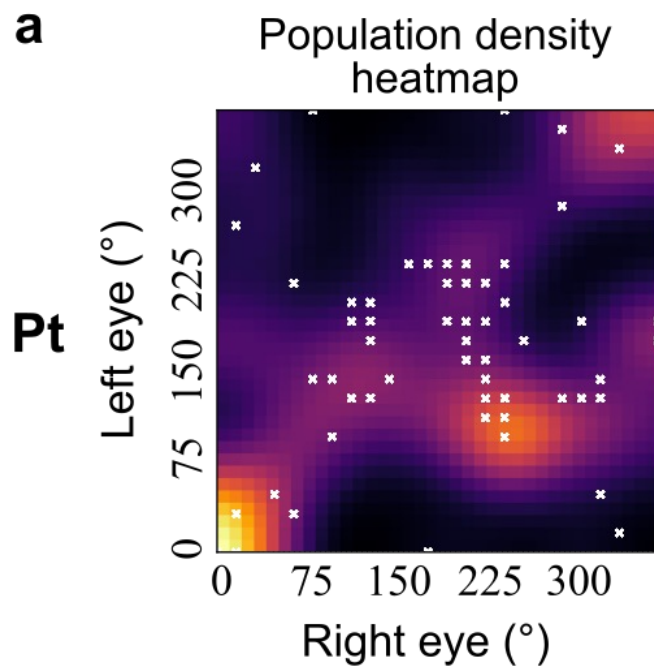
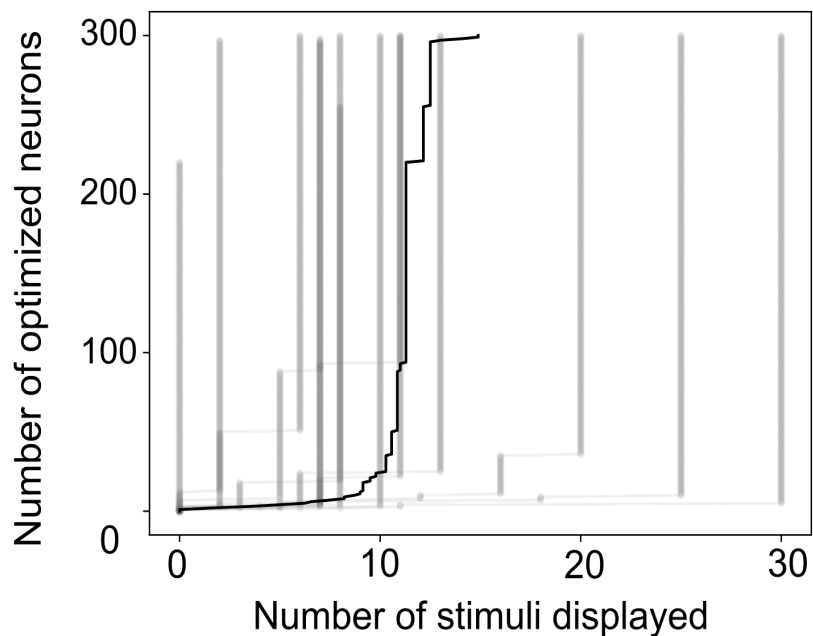
Grid search: 144 stimuli



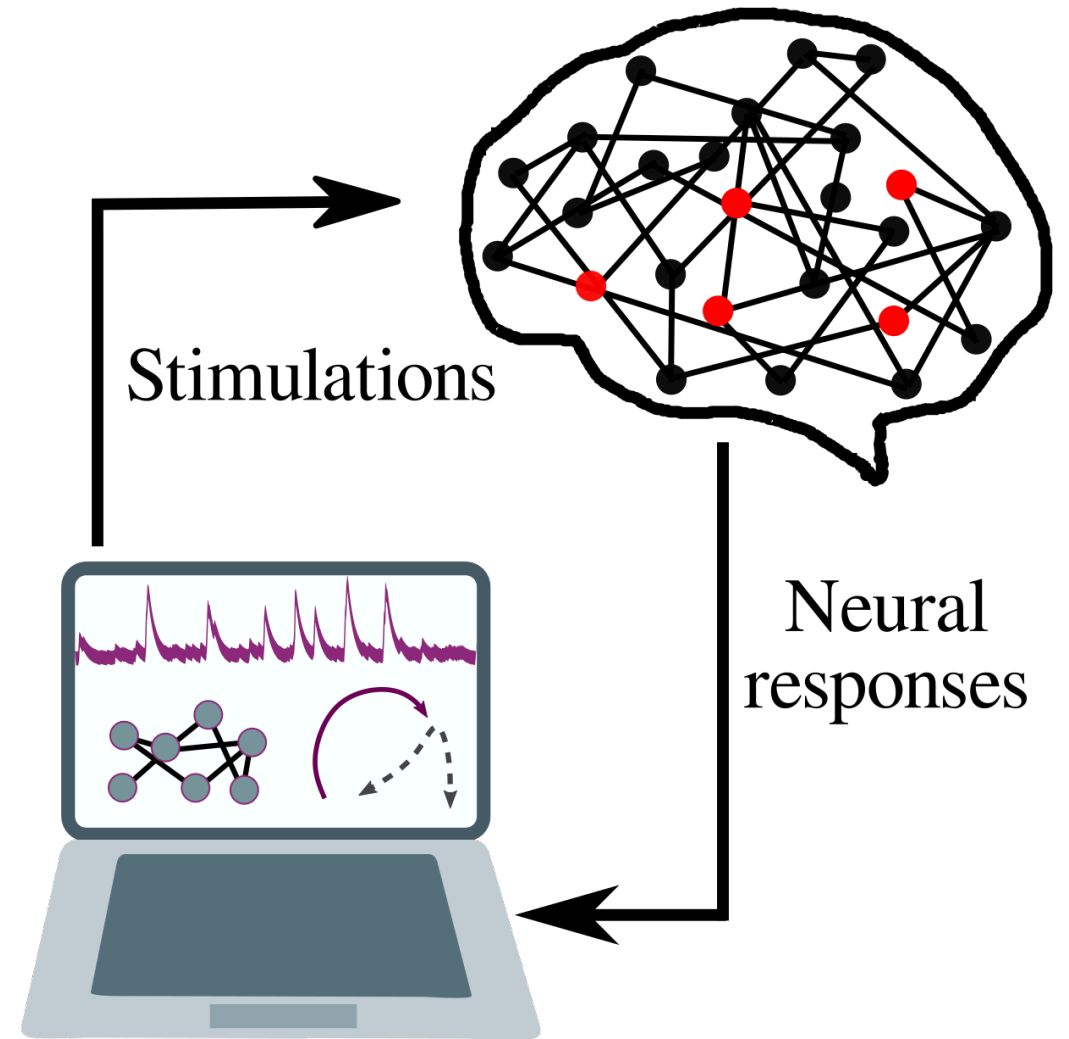
Rapid optimization



Adapts to different neural populations

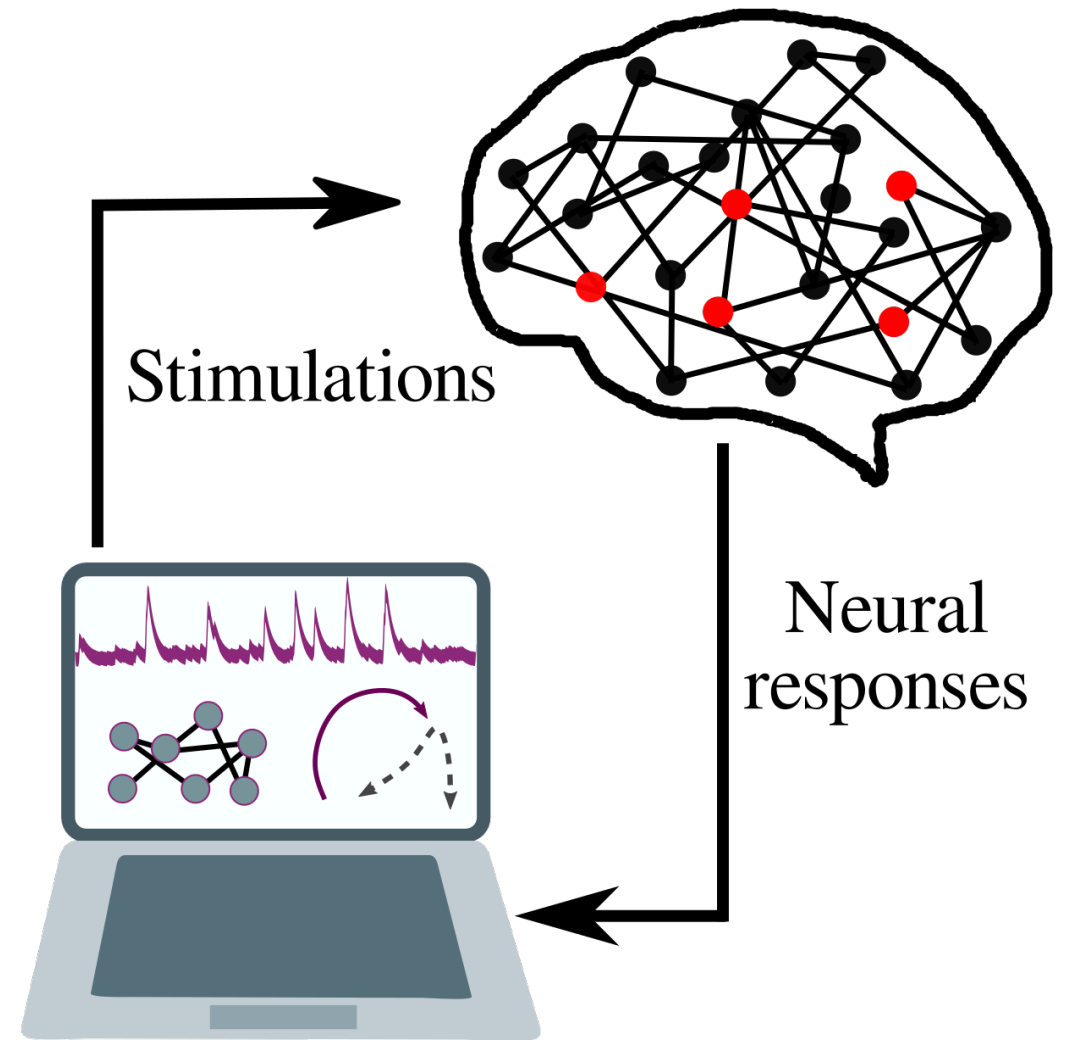


How do we design causal experiments that can scale to large or whole-brain populations of neurons?



How do we design causal experiments that can scale to large or whole-brain populations of neurons?

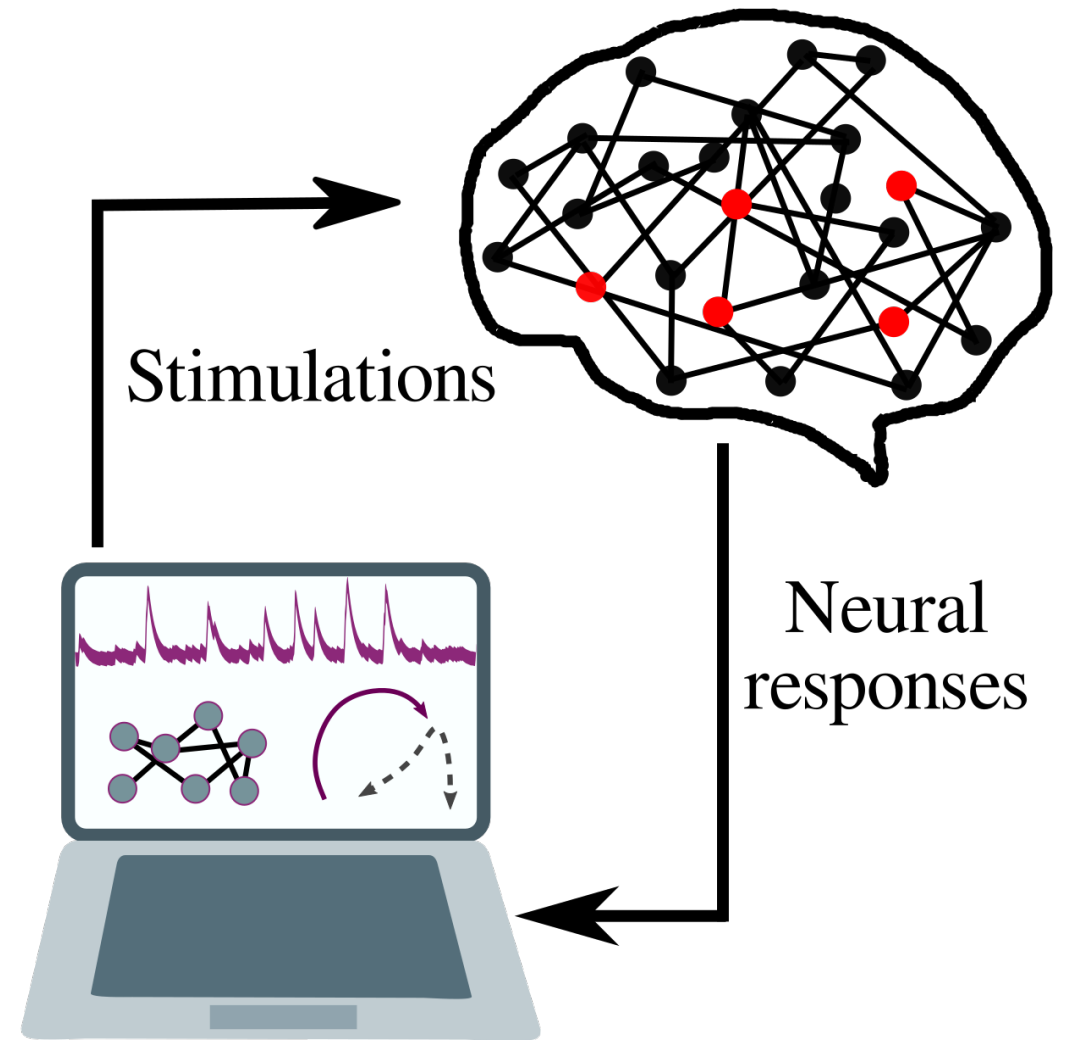
Adaptive experimental designs



How do we design causal experiments that can scale to large or whole-brain populations of neurons?

Adaptive experimental designs

- Real-time data analysis
- Streaming neural models
- Algorithms to tailor interventions



Thank you!

John Pearson

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Andrea

Giovannucci

Eftychios

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