Statistical methods for understanding neural coding and dynamics

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The coming statistical neuroscience decade

Some notable recent developments:

- machine learning / statistics methods for extracting information from high-dimensional data in a computationally-tractable, systematic fashion

- computing (Moore's law, massive parallel computing)

- optical methods (eg two-photon, FLIM) and optogenetics (channelrhodopsin, viral tracers, brainbow)

- high-density multielectrode recordings (Litke's 512-electrode retinal readout system; Shepard's 65,536-electrode active array)

Some exciting open challenges

- inferring biophysical neuronal properties from noisy recordings

- reconstructing the full dendritic spatiotemporal voltage from noisy, subsampled observations

- estimating subthreshold voltage given superthreshold spike trains

- extracting spike timing from slow, noisy calcium imaging data

- reconstructing presynaptic conductance from postsynaptic voltage recordings

- inferring connectivity from large populations of spike trains

- decoding behaviorally-relevant information from spike trains

- optimal control of neural spike timing

— to solve these, we need to combine the two classical branches of computational neuroscience: dynamical systems and neural coding
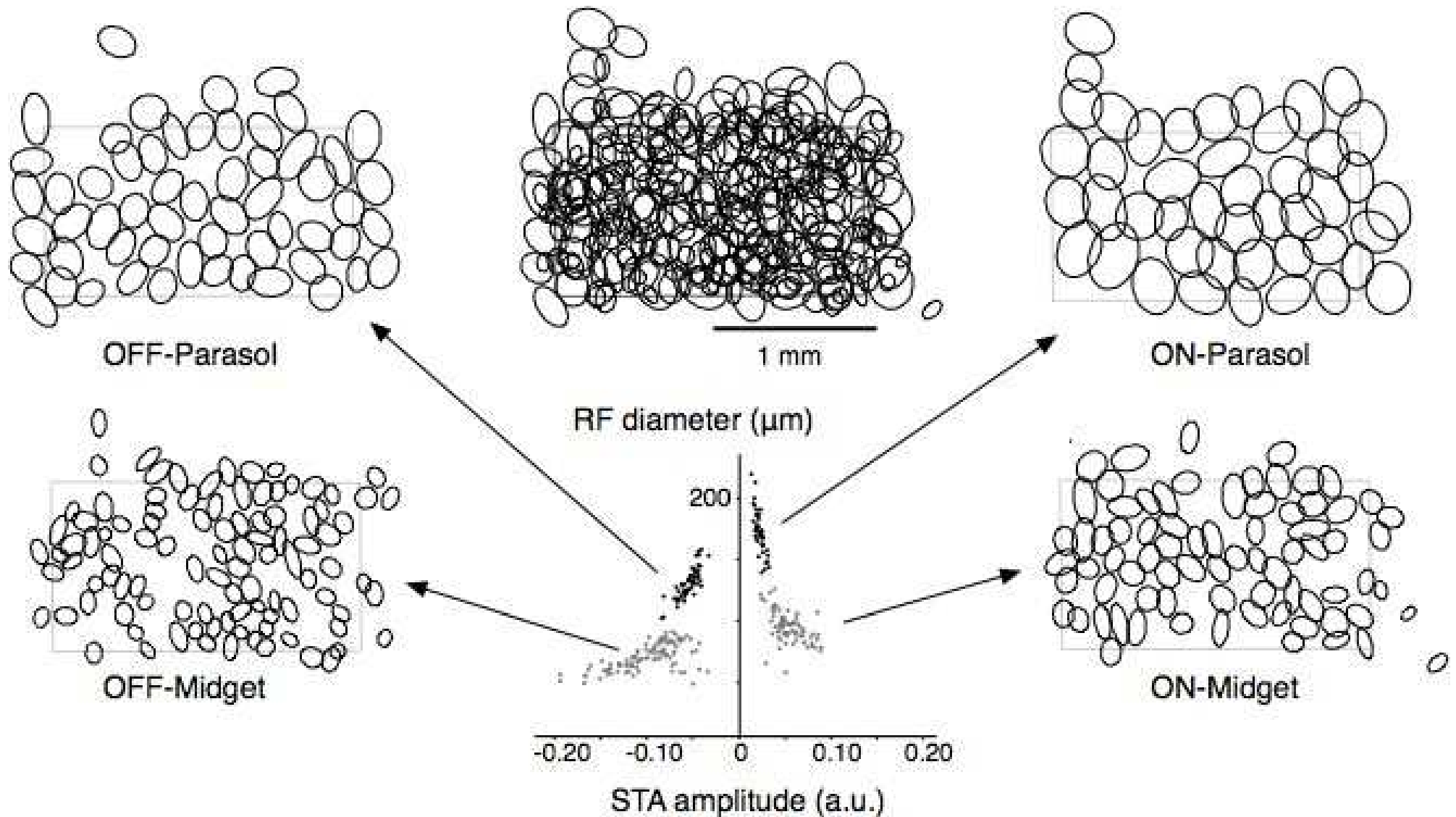
Part 1: modeling correlated spiking in retina

Preparation: dissociated macaque retina

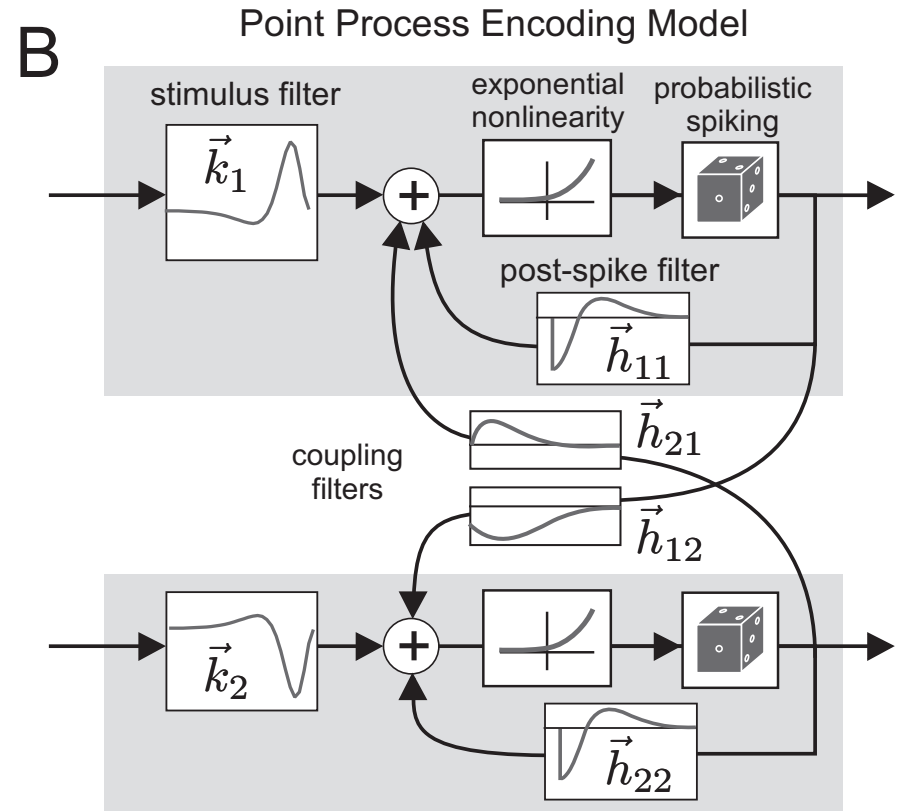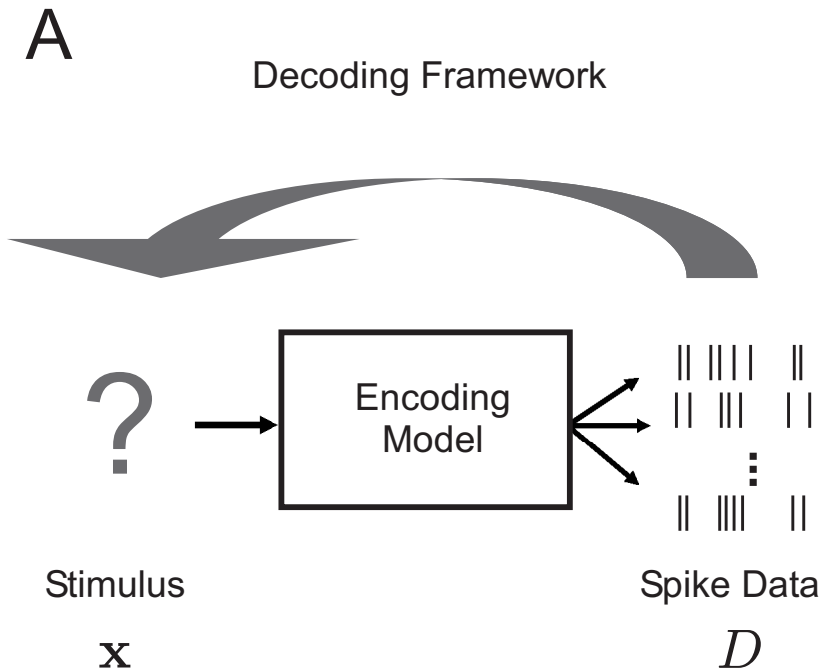— extracellularly-recorded responses of populations of RGCs
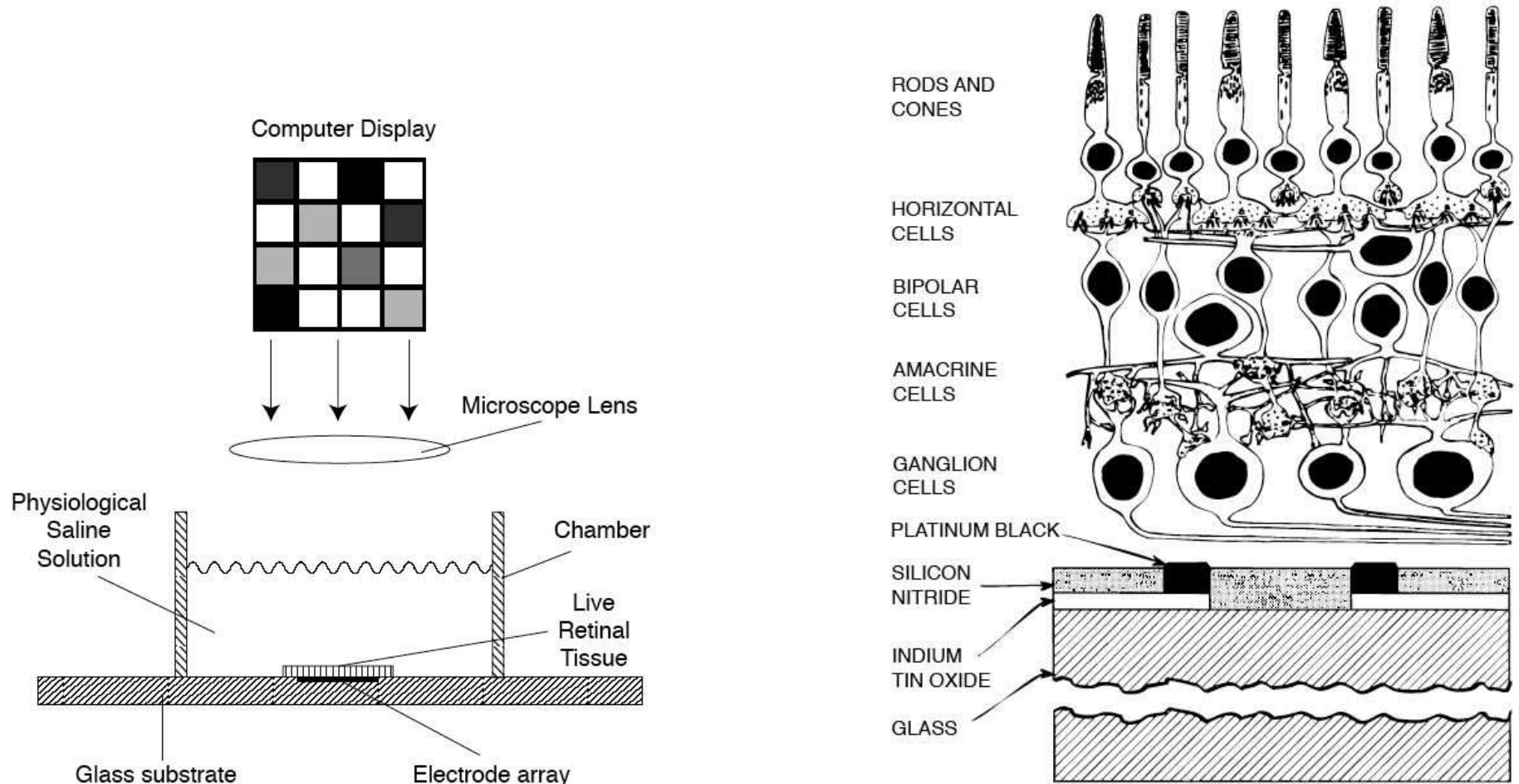
Stimulus: random spatiotemporal visual stimuli (Pillow et al., 2008)

Receptive fields tile visual space

Multineuronal point-process model

A
Decoding Framework

? → Encoding Model →

‖ ‖‖‖ ‖
‖ ‖‖ ‖‖
⋮
‖ ‖‖‖ ‖

Stimulus

x

Spike Data

D

B
Point Process Encoding Model

stimulus filter $\vec{k}_1$ — exponential nonlinearity — probabilistic spiking

post-spike filter $\vec{h}_{11}$

$\vec{h}_{21}$

coupling filters

$\vec{h}_{12}$

$\vec{k}_2$

$\vec{h}_{22}$

$$\lambda_i(t) = f\left(b_i + \vec{k}_i \cdot \vec{x}(t) + \sum_{i',j} h_{i',j} n_{i'}(t-j)\right),$$

— likelihood is easy to compute and to maximize (concave optimization)
(Paninski, 2004; Paninski et al., 2007; Pillow et al., 2008)

— close connections to noisy integrate-and-fire model

— captures spike timing precision and details of spatiotemporal correlations in retinal ganglion cell network

Reconsidering the model

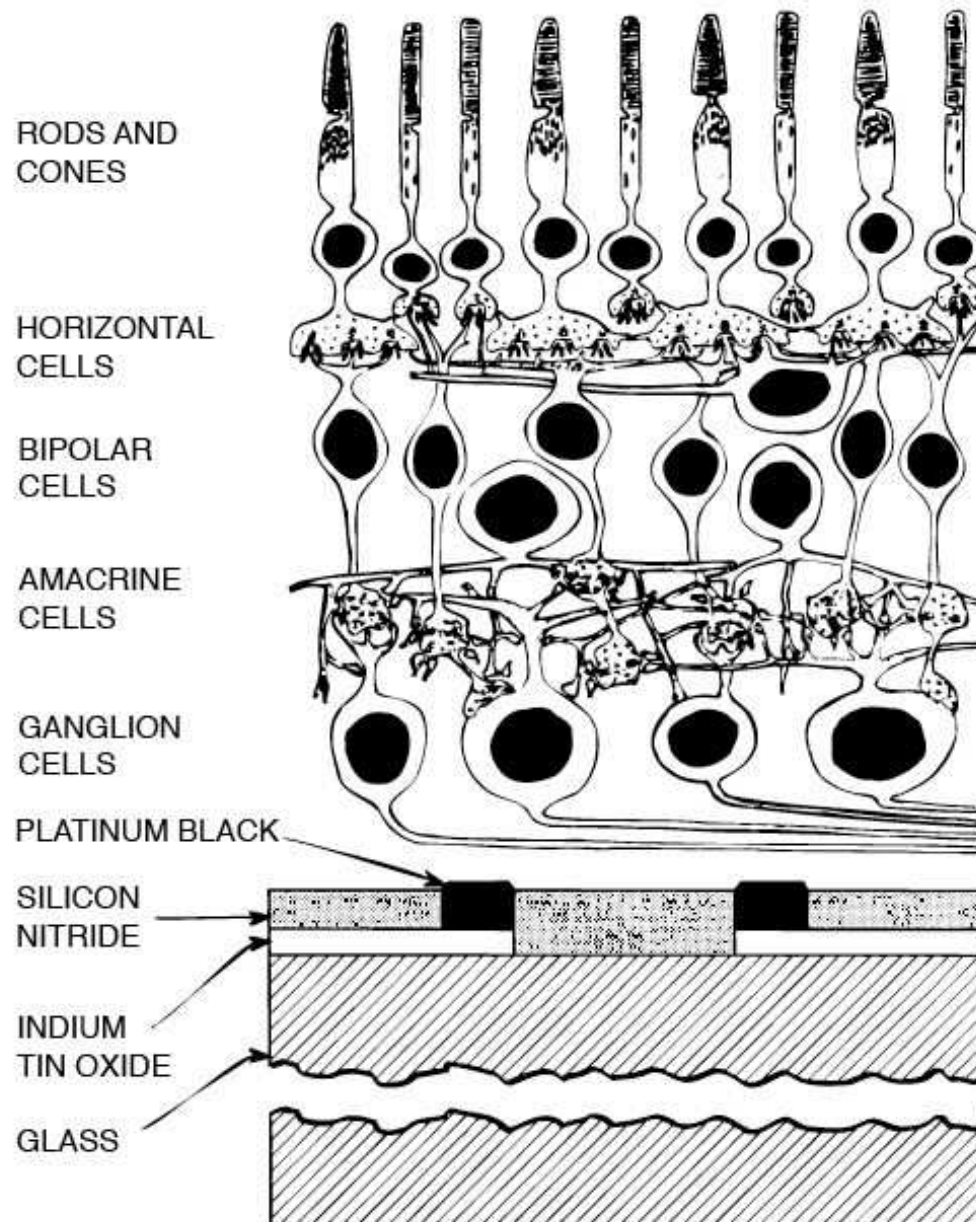$$\lambda_i(t) = \exp\left(k_i \cdot x(t) + h_i \cdot y_i(t) + \sum_{i \neq j} l_{i,j} \cdot y_j(t)\right)$$
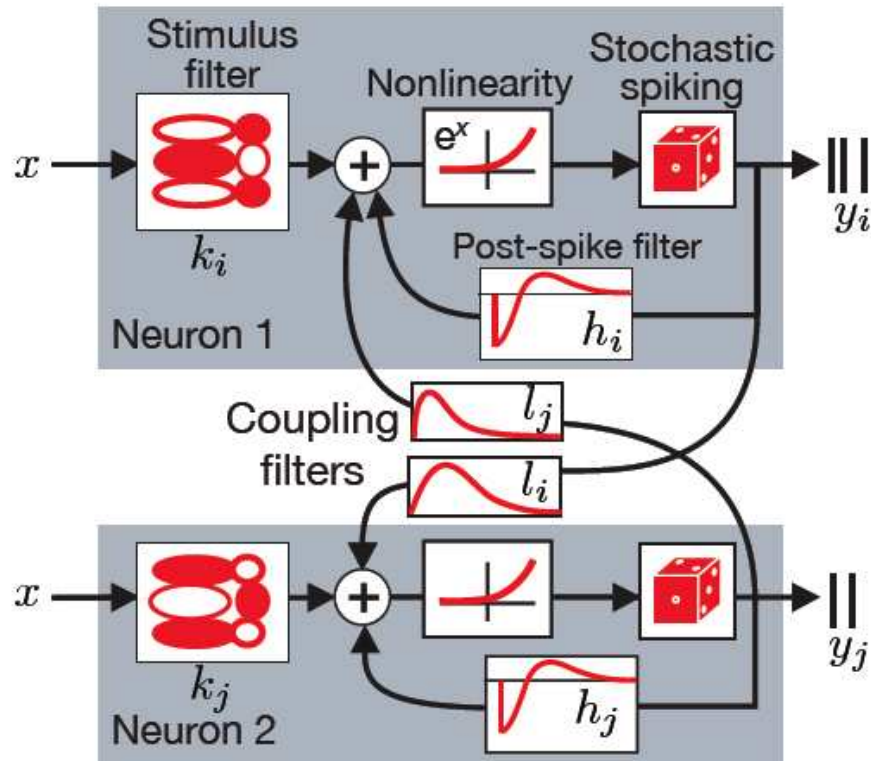
Pros:

- Tractable model-fitting and optimal decoding

- Captures response statistics

Cons:

- Instantaneous coupling filters

- No explicit Common Input

Considering common input effects

RODS AND CONES

HORIZONTAL CELLS

BIPOLAR CELLS

AMACRINE CELLS

GANGLION CELLS

PLATINUM BLACK

SILICON NITRIDE

INDIUM TIN OXIDE

GLASS
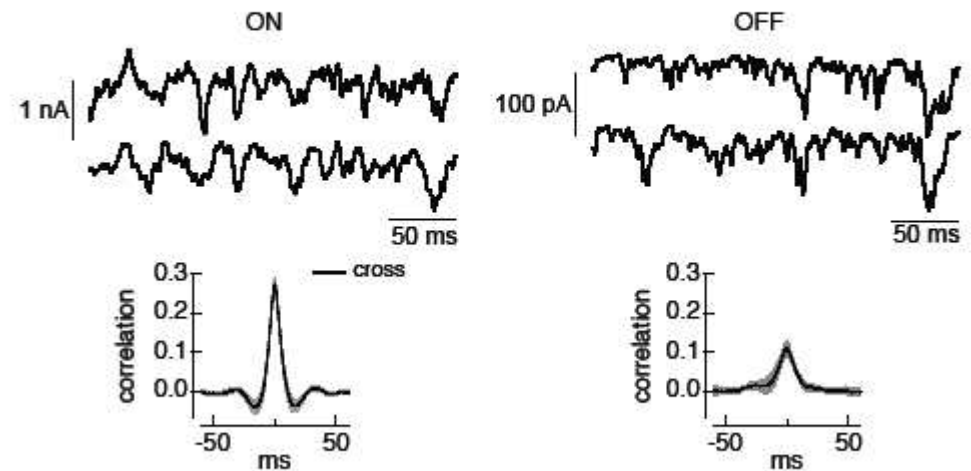
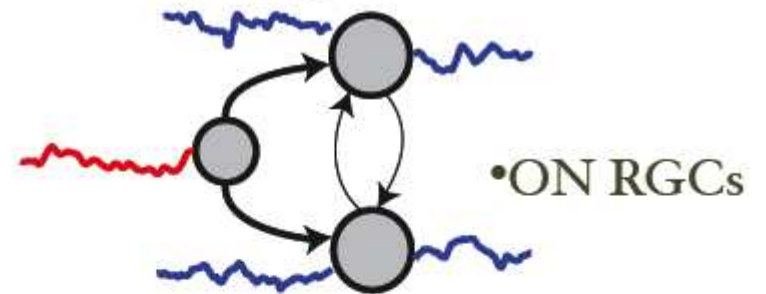— universal problem in network analysis: can't observe all neurons!

Intracellular findings:

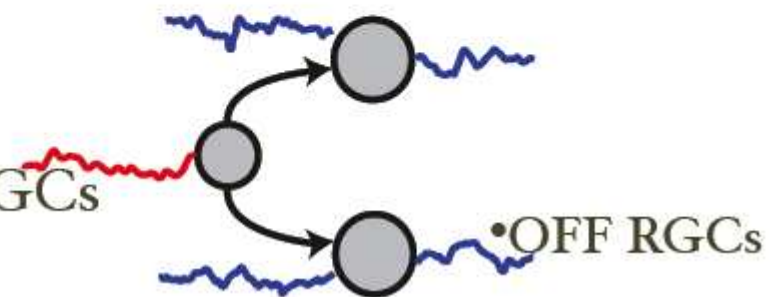- RGCs receive strongly correlated synaptic input in the absence of modulated light stimuli

Khuc Trong & Rieke Nature Neuro 2008

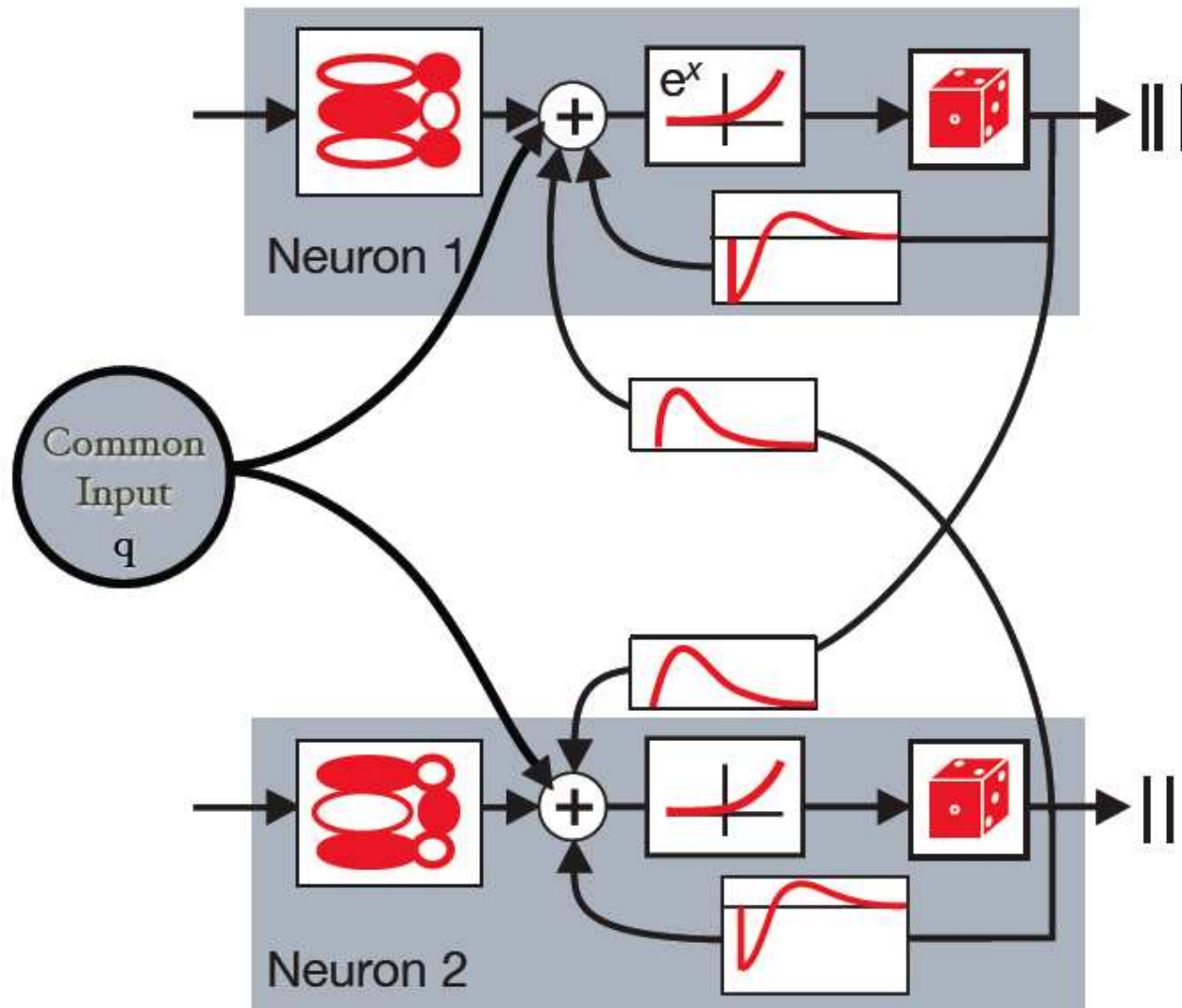- ON RGCs are weakly electrically coupled

•ON RGCs

- No electrical coupling seen between OFF RGCs

•OFF RGCs

Extension: including common input effects

$$\lambda_i(t) = \exp\left(k_i \cdot x(t) + h_i \cdot y_i(t) + \sum_{i \neq j} l_{i,j} \cdot y_j(t) + Lq(t)\right)$$

Direct state-space optimization methods

To fit parameters, optimize approximate marginal likelihood:

$$
\begin{aligned}
\log p(spikes|\theta) &= \log \int p(Q|\theta)p(spikes|\theta, Q)dQ \\
&\approx \log p(\hat{Q}_\theta|\theta) + \log p(spikes|\hat{Q}_\theta) - \frac{1}{2}\log|J_{\hat{Q}_\theta}| \\
\hat{Q}_\theta &= \arg\max_Q \{\log p(Q|\theta) + \log p(spikes|Q)\}
\end{aligned}
$$

— Q is a very high-dimensional latent (unobserved) "common input" term. Taken to be a Gaussian process here with autocorrelation time ≈ 5 ms (Khuc-Trong and Rieke, 2008).

— correlation strength specified by one parameter per cell pair.

— all terms can be computed in $O(T)$ via banded matrix methods (Paninski et al., 2010).

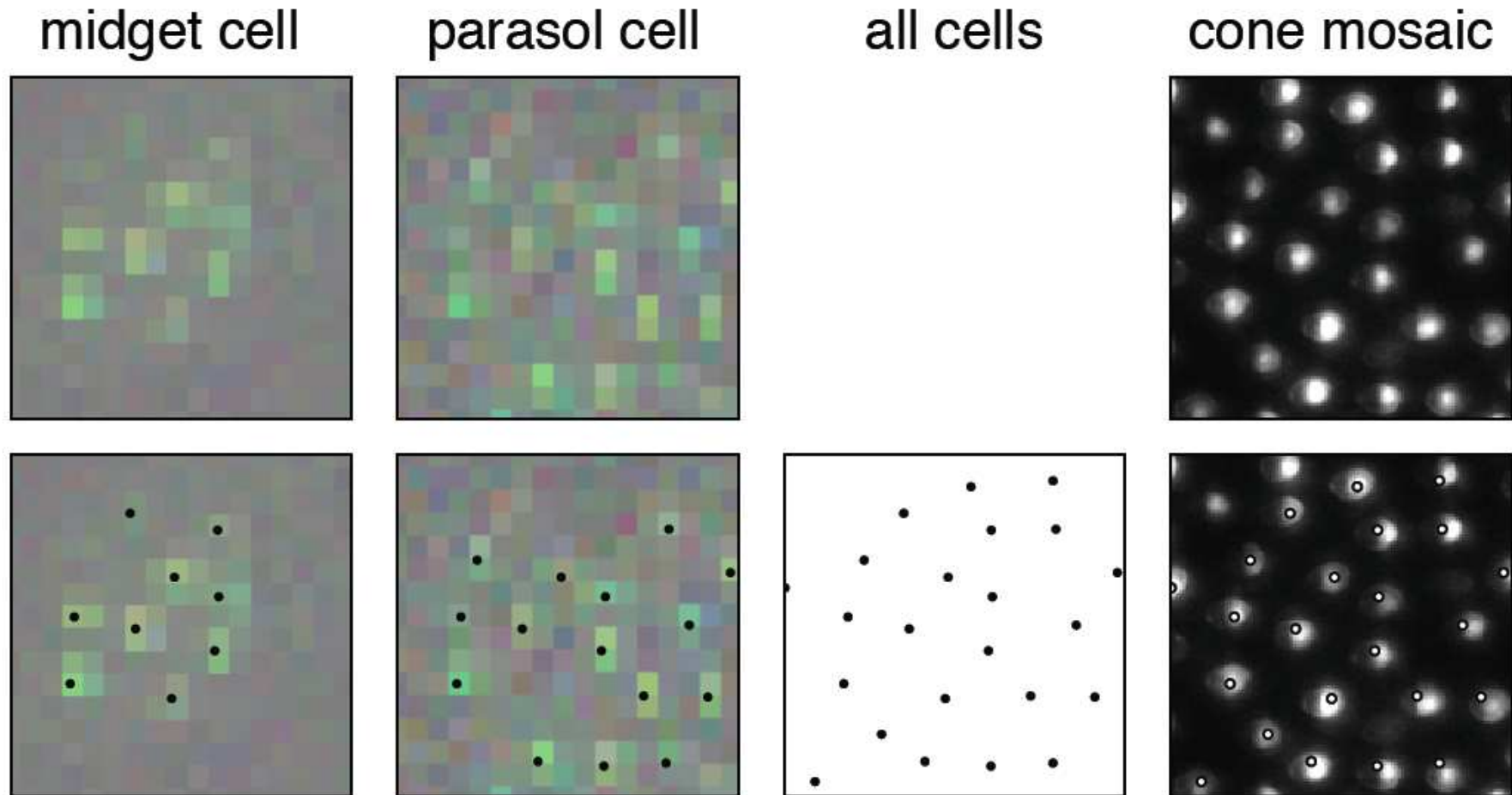# Inferred common input effects are strong
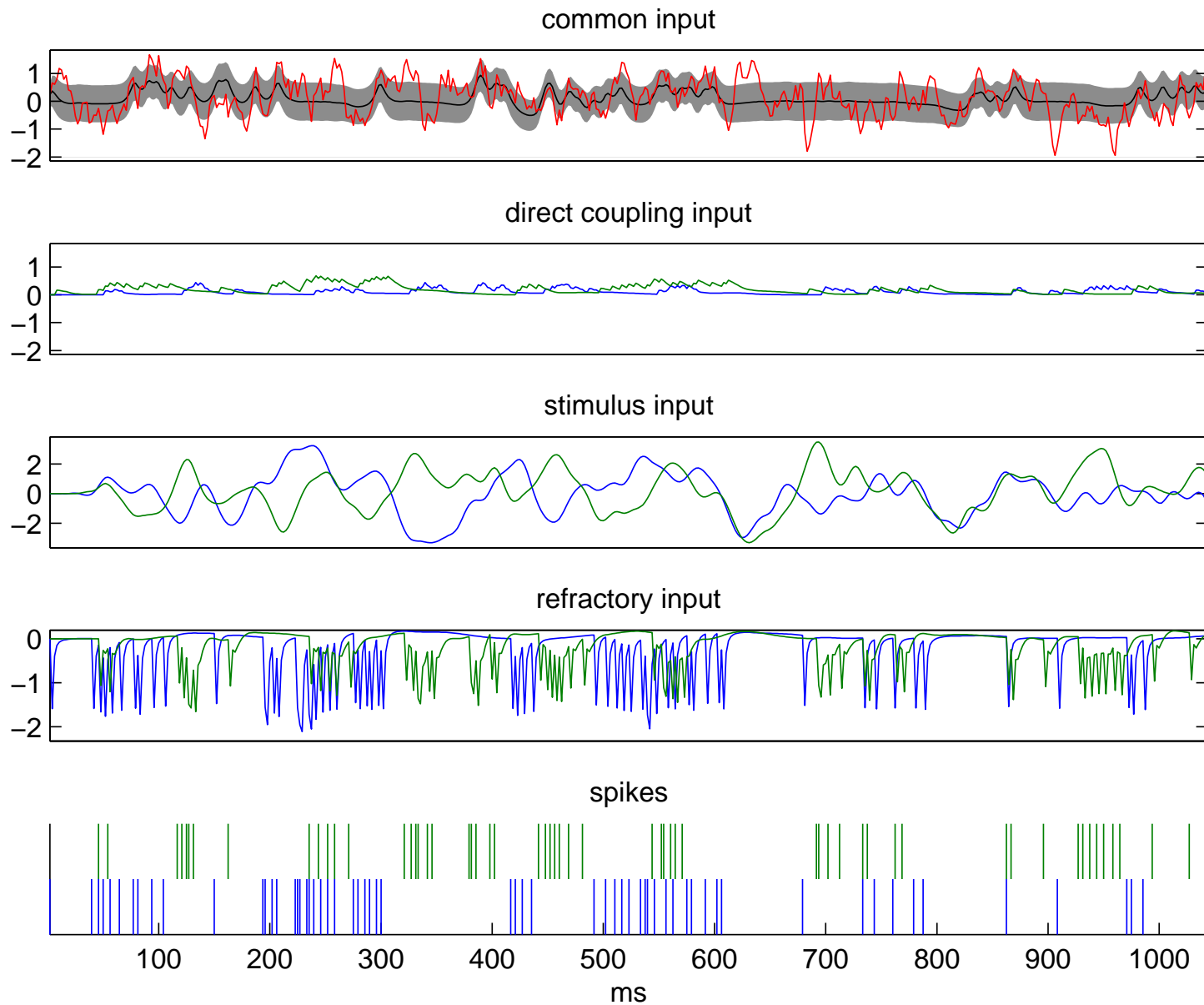
— note that inferred direct coupling effects are now relatively small.

Common-input-only model captures x-corrs
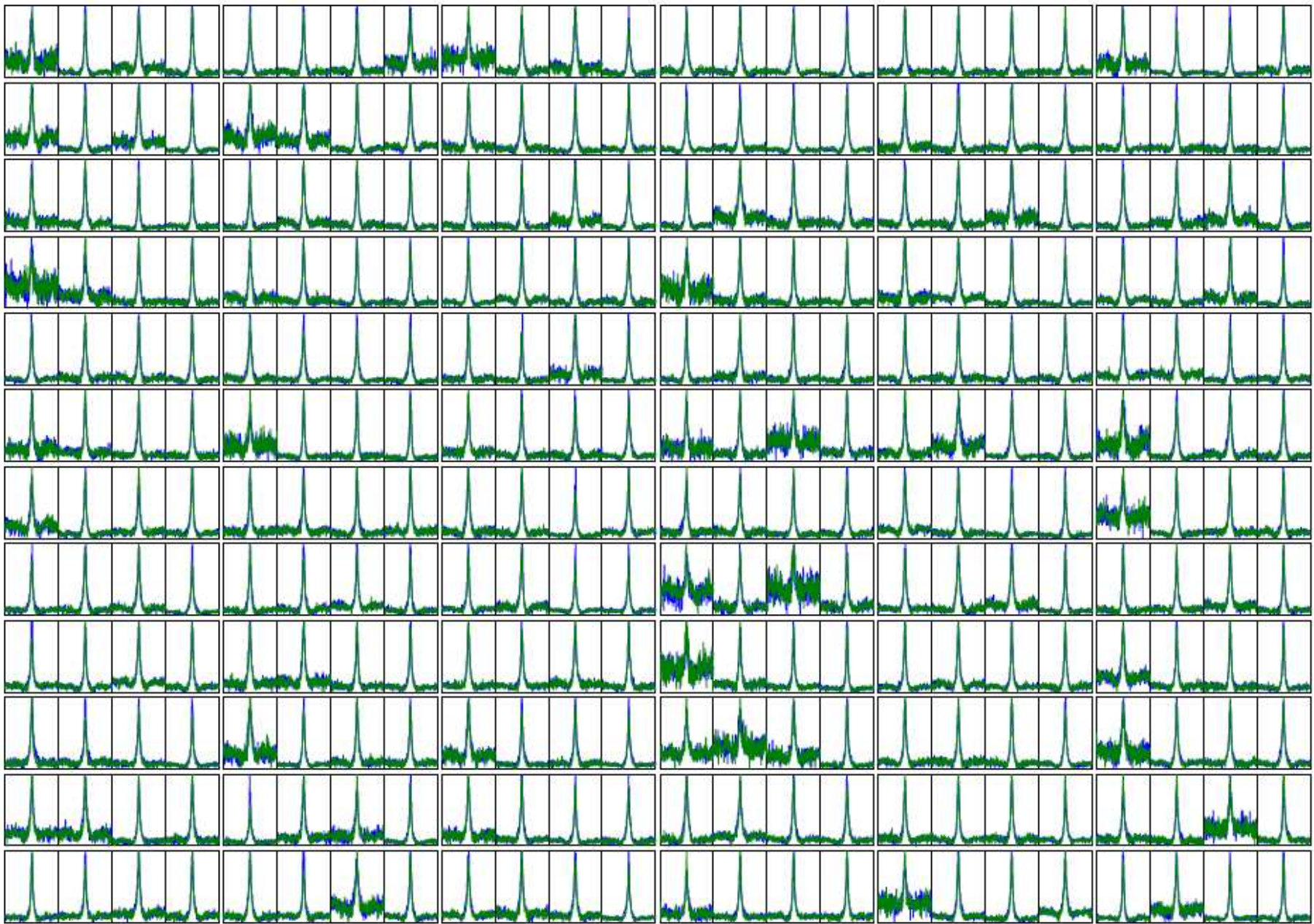
— single and triple-cell activities captured well, too (Vidne et al., 2009)

Inferring cone locations

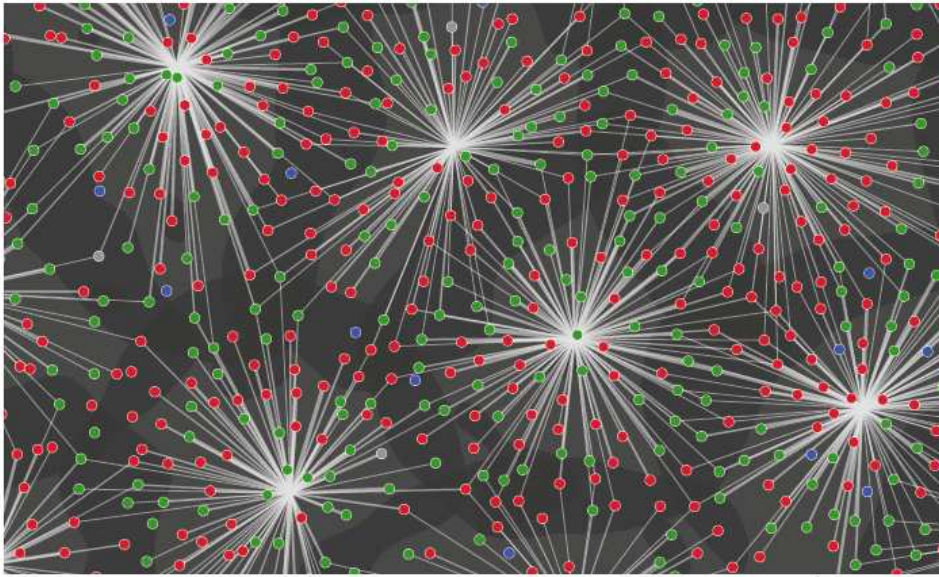midget cell   parasol cell   all cells   cone mosaic

— cone locations and color identity can be inferred accurately with high spatial-resolution stimuli via maximum a posteriori estimates (Field et al., 2010).

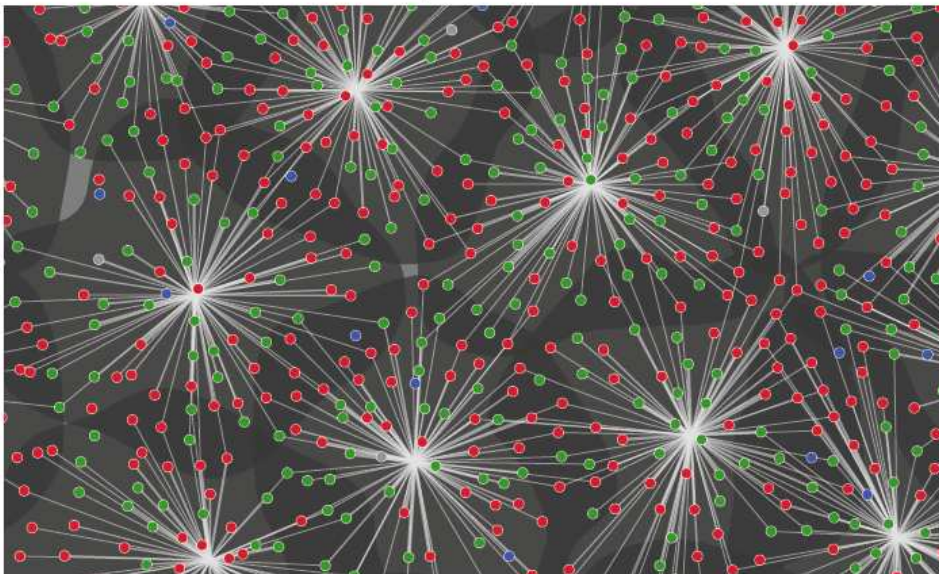# Inferring cone-to-RGC effective connectivity

ON parasol

retina 1,

OFF parasol

50 μm

RODS AND CONES

HORIZONTAL CELLS

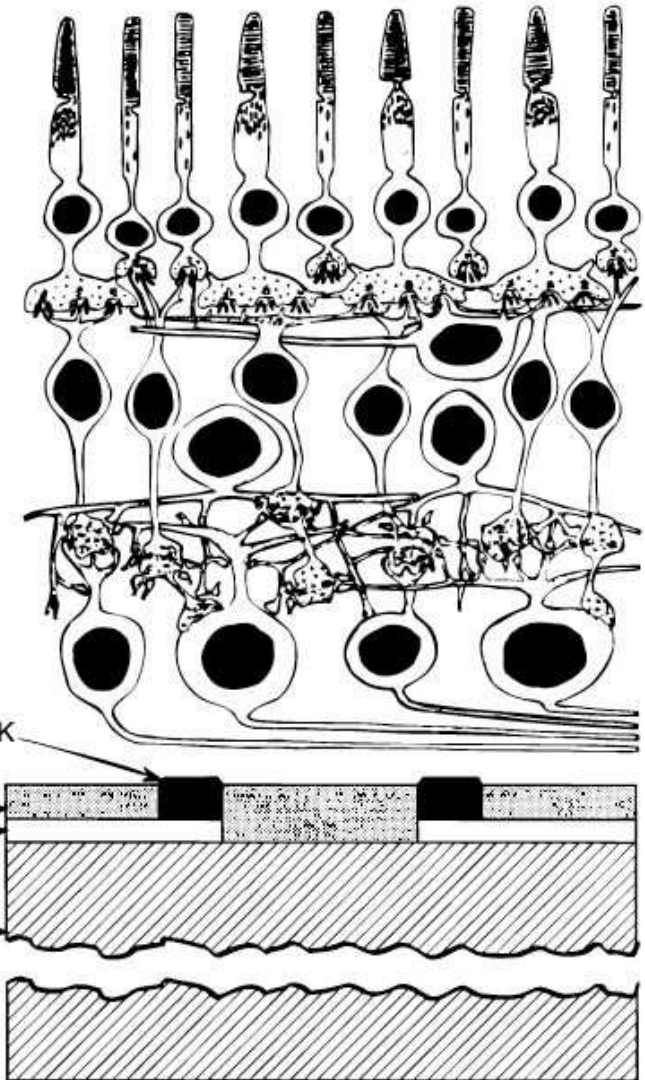BIPOLAR CELLS

AMACRINE CELLS

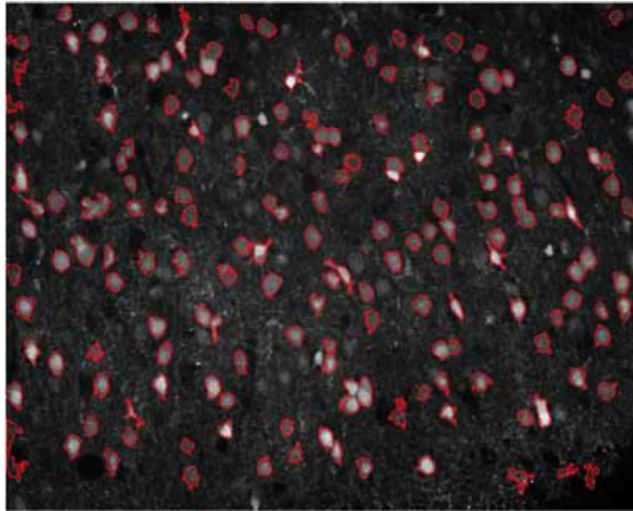GANGLION CELLS

PLATINUM BLACK

SILICON NITRIDE

INDIUM TIN OXIDE

GLASS

Part 2: applications to cortex

Record large-scale calcium movie

Aim 1: Extract spike times

fluorescence

spikes

0   1   2   3   4   5
time (sec)
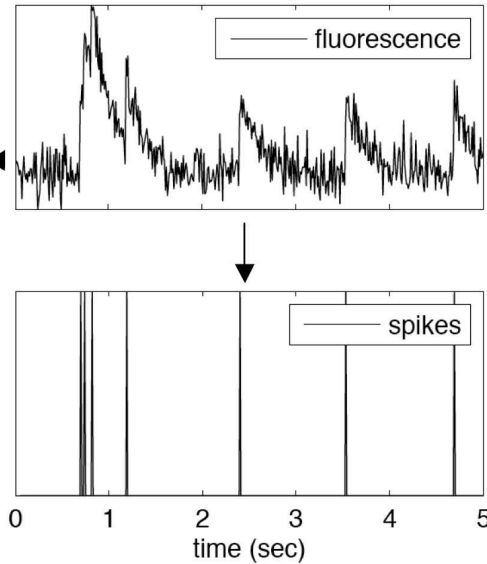
Aim 2: Estimate network model

linear filter   nonlinearity   probabilistic spiking

post-spike current

Cell 1 parameters

coupling currents

Cell 2 parameters
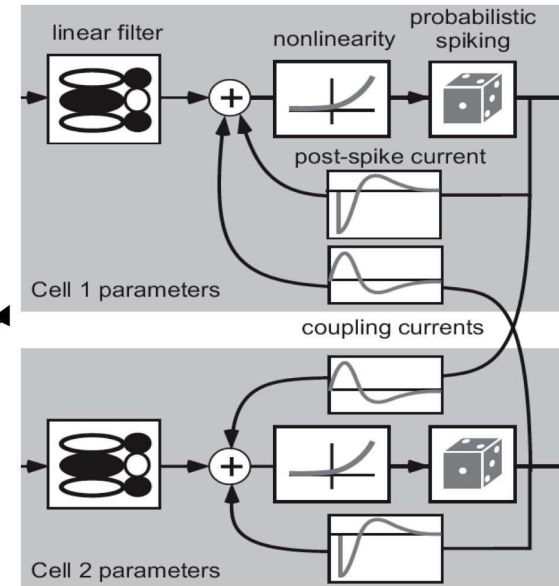
Aim 3: Check results via photostimulation

V_m

t →

*Recording

Two-photon uncaging pulse

I
II/III
IV
Va
Vb
VI

40x

Objective

Recording Electrode
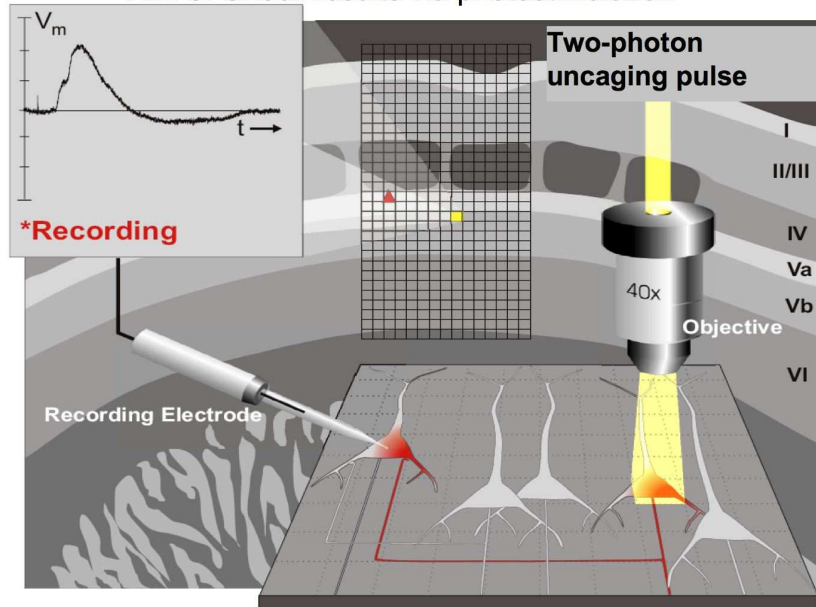
Inferred network model
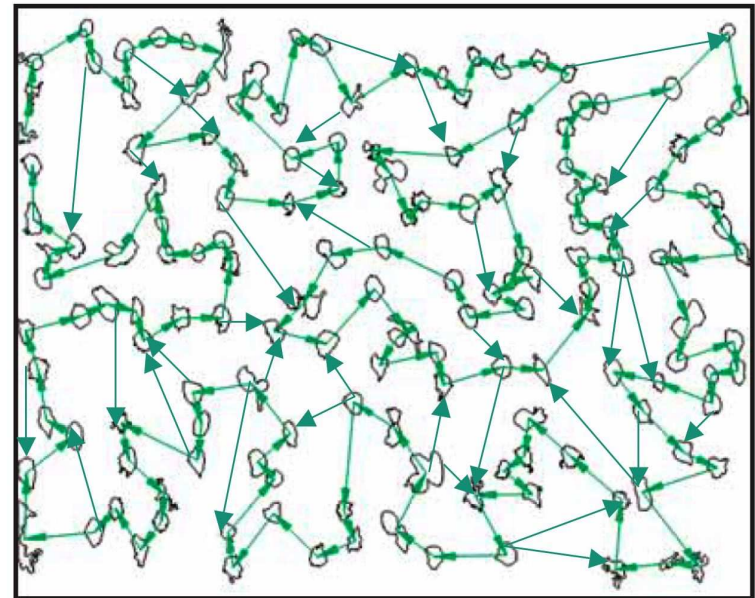
Model-based estimation of spike rates

data

schematic

equations

$$F_t = \alpha C_t + \beta + \sigma \varepsilon_t, \qquad \varepsilon_t \overset{iid}{\sim} \mathcal{N}(0,1)$$

$$C_t = -(1 - \Delta/\tau)C_{t-1} + n_t$$

$$n_t \sim \text{poisson}(\lambda \Delta)$$

Note: each component here can be generalized easily (Vogelstein et al., 2009).

Fast maximum a posteriori (MAP) filter

Start by writing out the posterior:

$$
\begin{aligned}
\log p(C|F) &= \log p(C) + \log p(F|C) + const. \\
&= \sum_t \log p(C_{t+1}|C_t) + \sum_t \log p(F_t|C_t) + const.
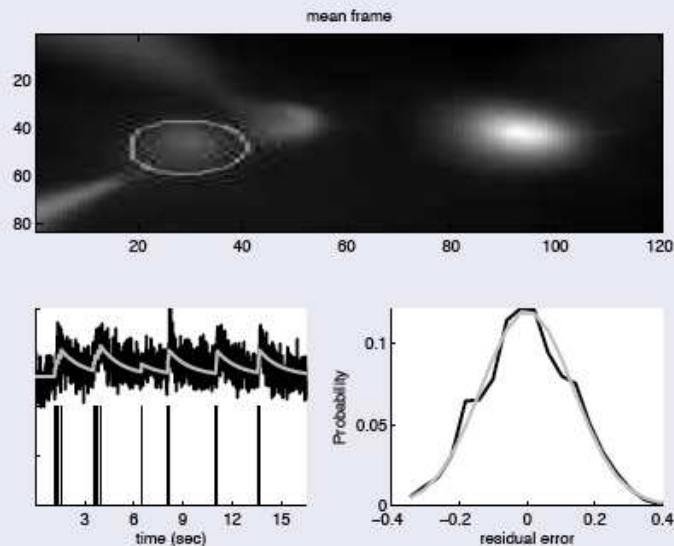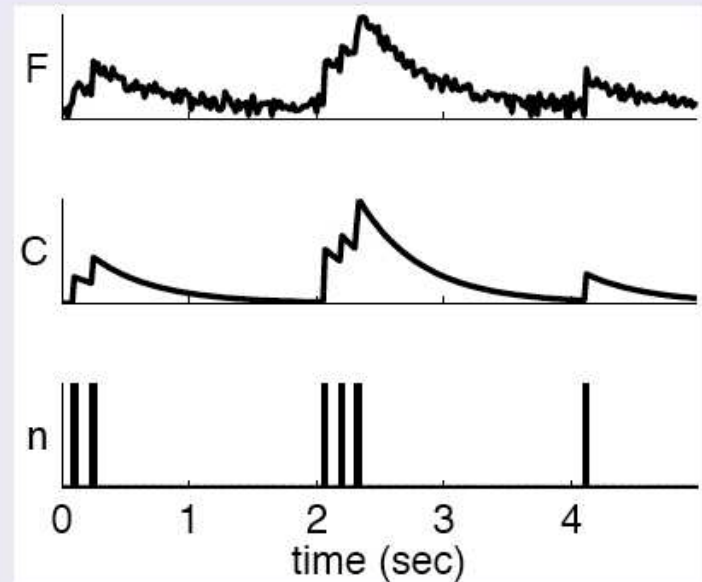\end{aligned}
$$

Three basic observations:

- If $\log p(C_{t+1}|C_t)$ and $\log p(F_t|C_t)$ are concave, then so is $\log p(C|F)$.

- Hessian H of $\log p(C|F)$ is tridiagonal: $\log p(F_t|C_t)$ contributes a diag term, and $\log p(C_{t+1}|C_t)$ contributes a tridiag term (Paninski et al., 2010).

- C is a linear function of n.

Newton's method: iteratively solve $HC_{dir} = \nabla$. Tridiagonal solver requires $O(T)$ time. Can include nonneg constraint $n_t \geq 0$ (Koyama and Paninski, 2009).

— Two orders of magnitude faster than particle filter: can process data from ≈ 100 neurons in real time on a laptop (Vogelstein et al., 2010).

Example: nonnegative MAP filtering
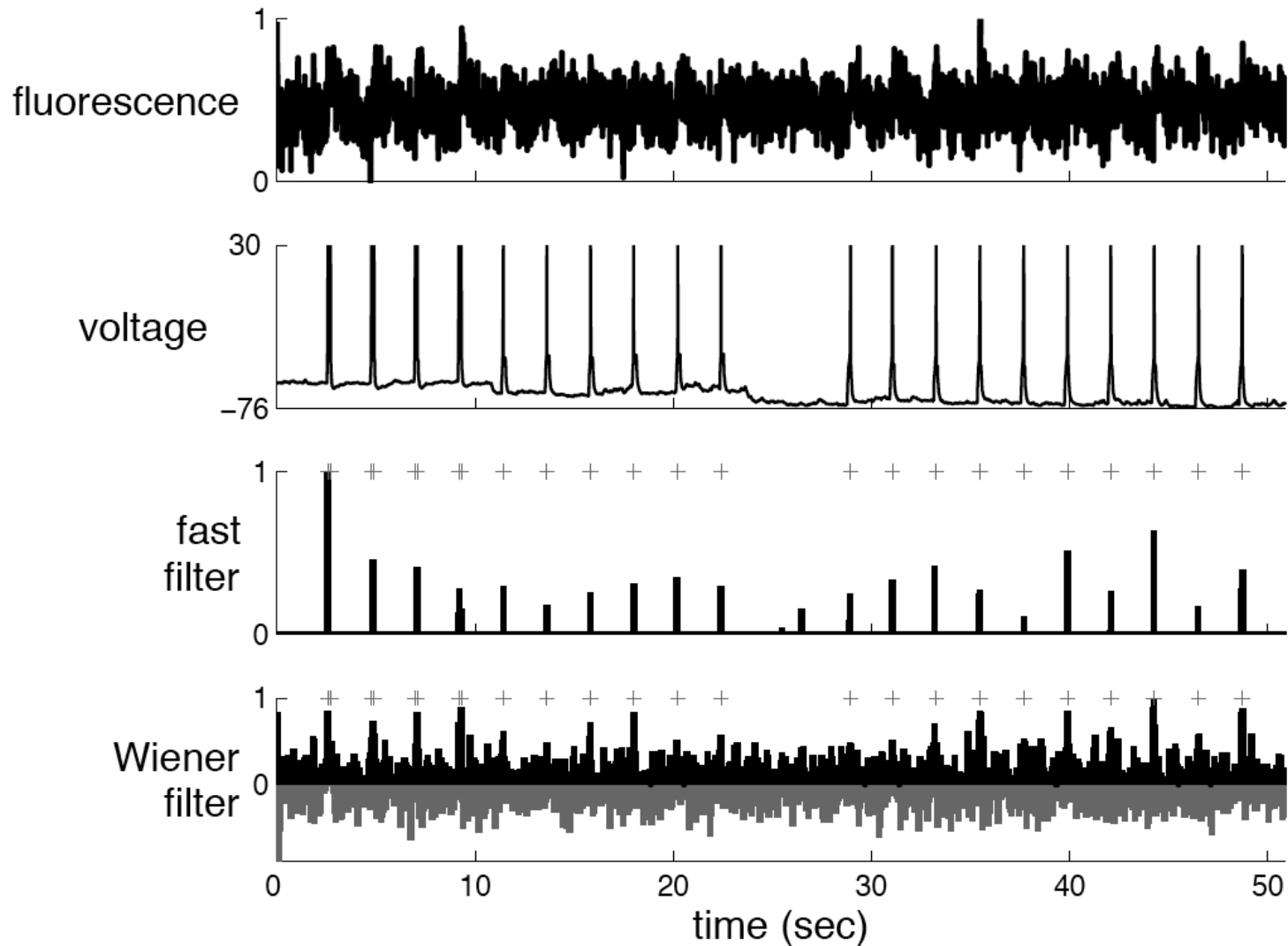
— nonnegative deconvolution is a recurring problem (Vogelstein et al., 2010)
(e.g., deconvolution of PSPs in intracellular recordings (Paninski et al., 2010))

Simulated circuit inference
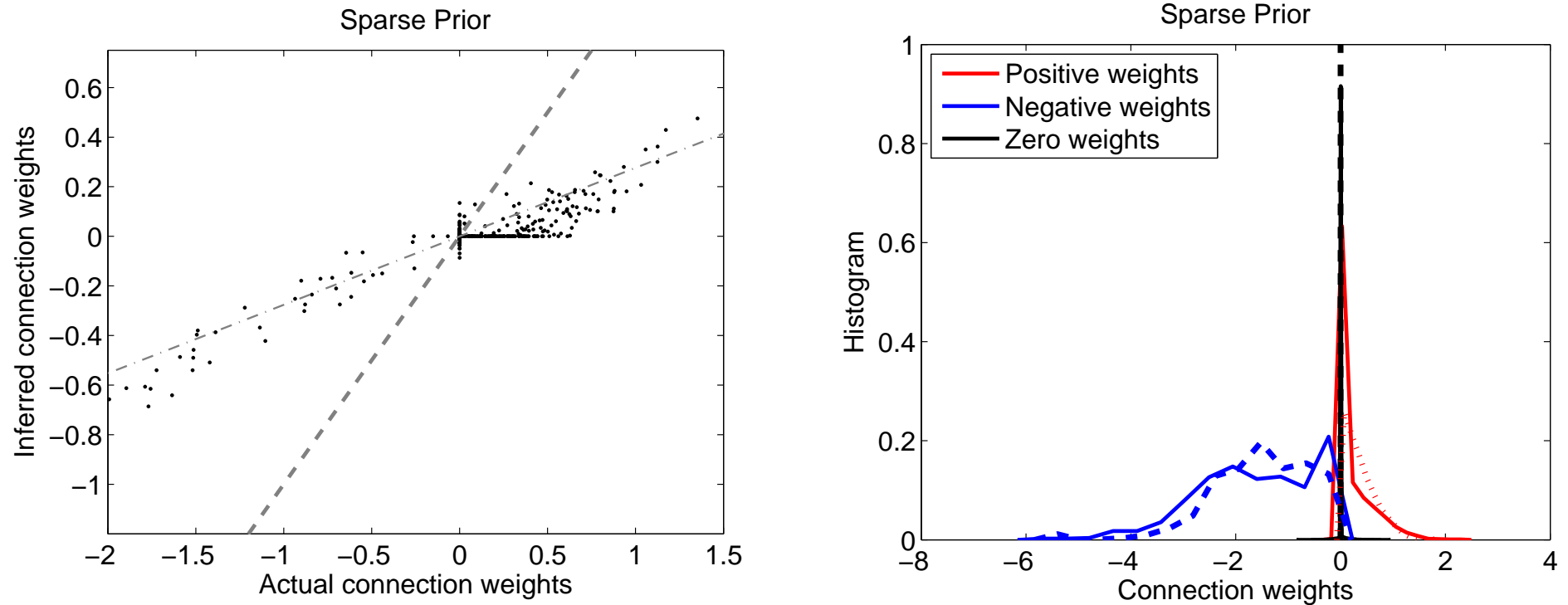
— conductance-based integrate-and-fire networks with biologically plausible connectivity matrices, imaging speed, SNR (Mishchencko et al., 2009).

Good news: MAP connections are inferred with the correct sign, in just a couple minutes of compute time, if network is fully observed. Current work focusing on improved Monte Carlo sampling methods, to better quantify uncertainty in unobserved neurons (Mishchenko and Paninski, 2010).

Optimal control of spike timing

To test our results, we want to perturb the network at will. How can we make a neuron fire exactly when we want it to?

Assume bounded inputs; otherwise problem is trivial.

Start with a simple model:

$$
\begin{aligned}
\lambda_t &= f(V_t + h_t) \\
V_{t+dt} &= V_t + dt\,(-gV_t + aI_t) + \sqrt{dt}\,\sigma\epsilon_t, \quad \epsilon_t \sim \mathcal{N}(0, 1).
\end{aligned}
$$

Now we can just optimize the likelihood of the desired spike train, as a function of the input I_t, with I_t bounded.

Concave objective function over convex set of possible inputs I_t + Hessian is tridiagonal $\implies O(T)$ optimization.

— again, can be done in real time (Ahmadian et al., 2010).

Simulated electrical control of spike timing
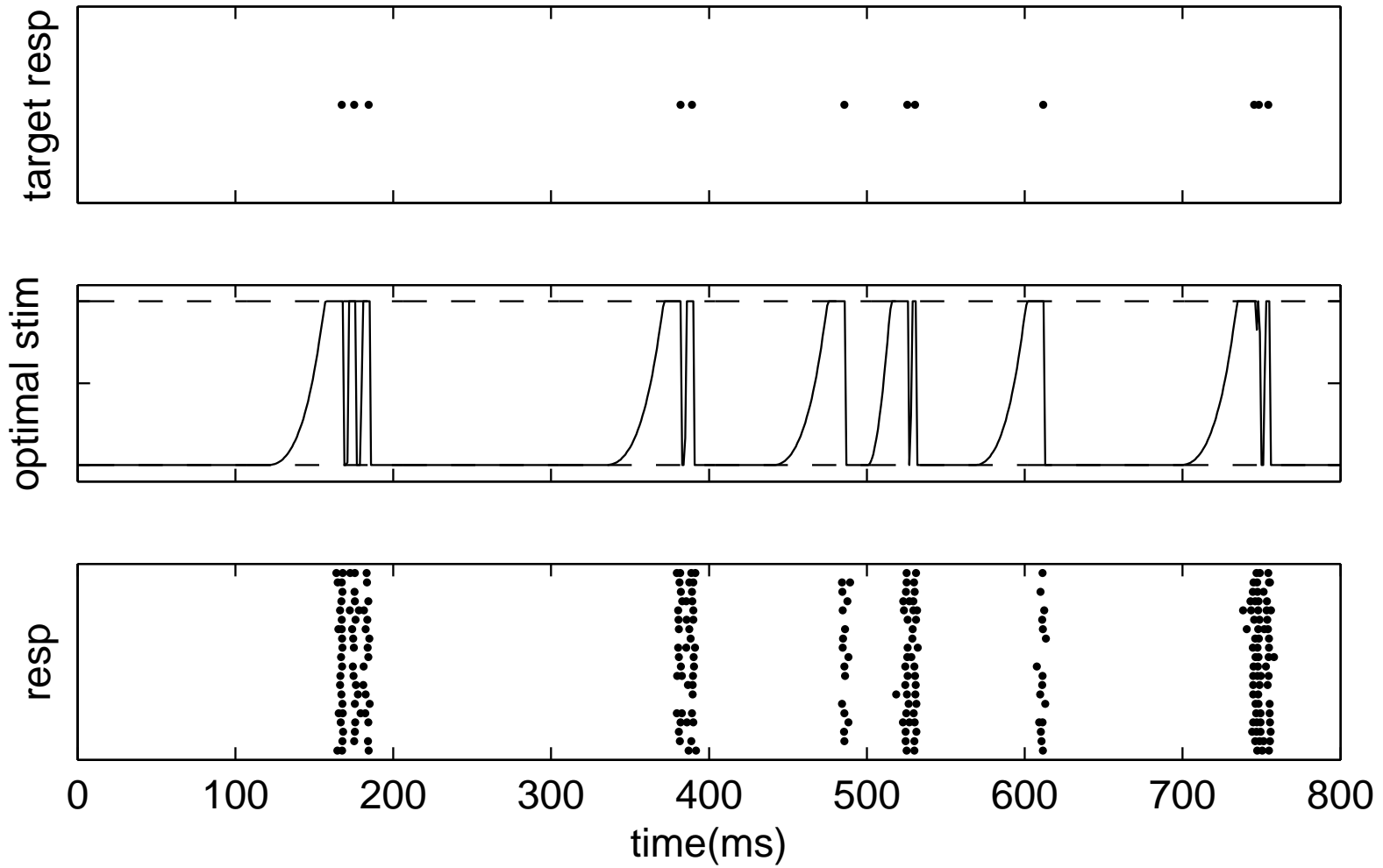
Example: intracellular control of spike timing
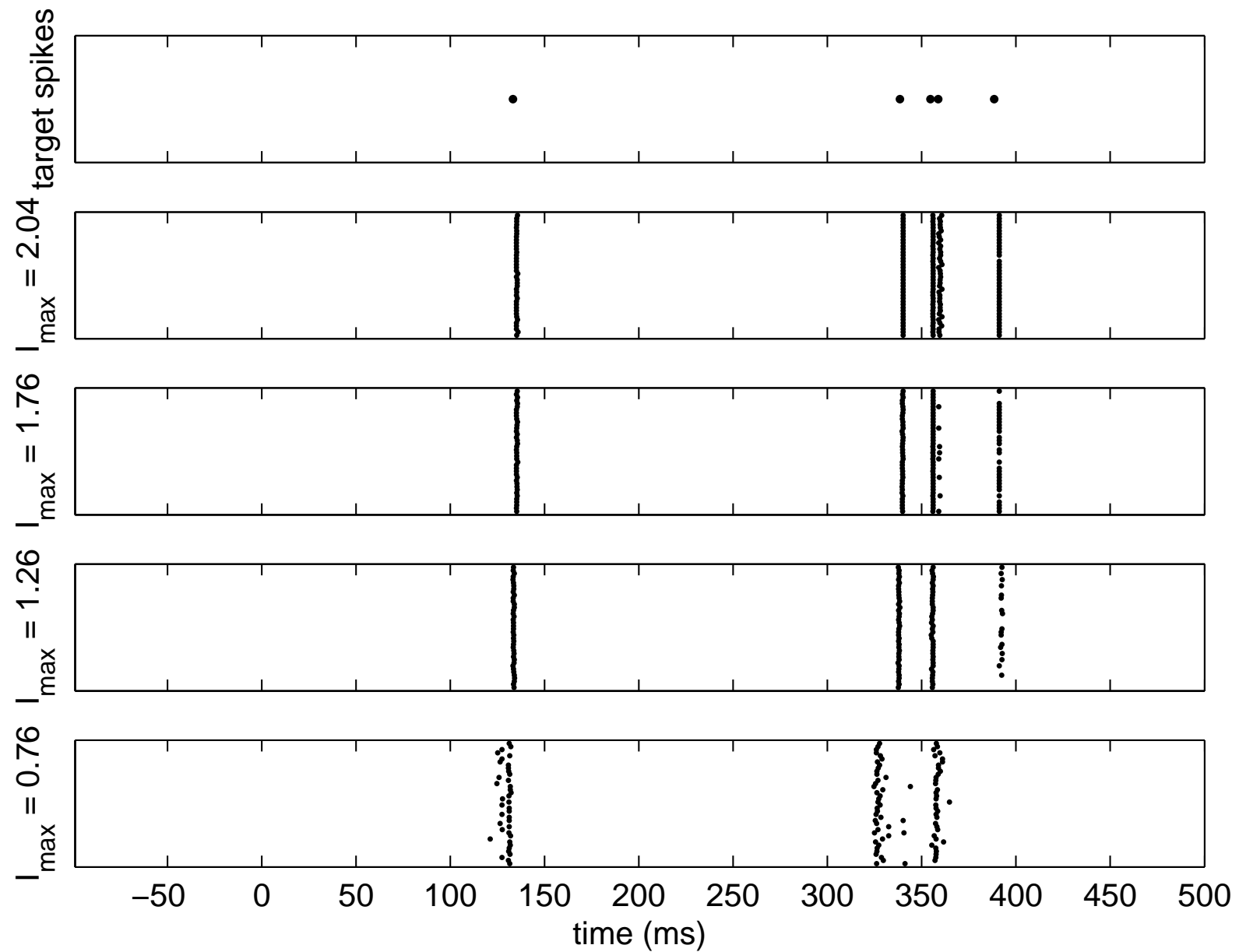
(Ahmadian et al., 2010)

Optical conductance-based control of spiking

$$V_{t+dt} \quad = \quad V_t + dt\left(-gV_t + g_t^i(V^i - V_t) + g_t^e(V^e - V_t)\right) + \sqrt{dt}\sigma\epsilon_t, \quad \epsilon_t \sim \mathcal{N}(0,1)$$

$$g_{t+dt}^i \quad = \quad g_t^i + dt\left(-\frac{g_t^i}{\tau_i} + a_{ii}L_t^i + a_{ie}L_t^e\right); \; g_{t+dt}^e = g_t^e + dt\left(-\frac{g_t^e}{\tau_i} + a_{ee}L_t^e + a_{ei}L_t^i\right)$$
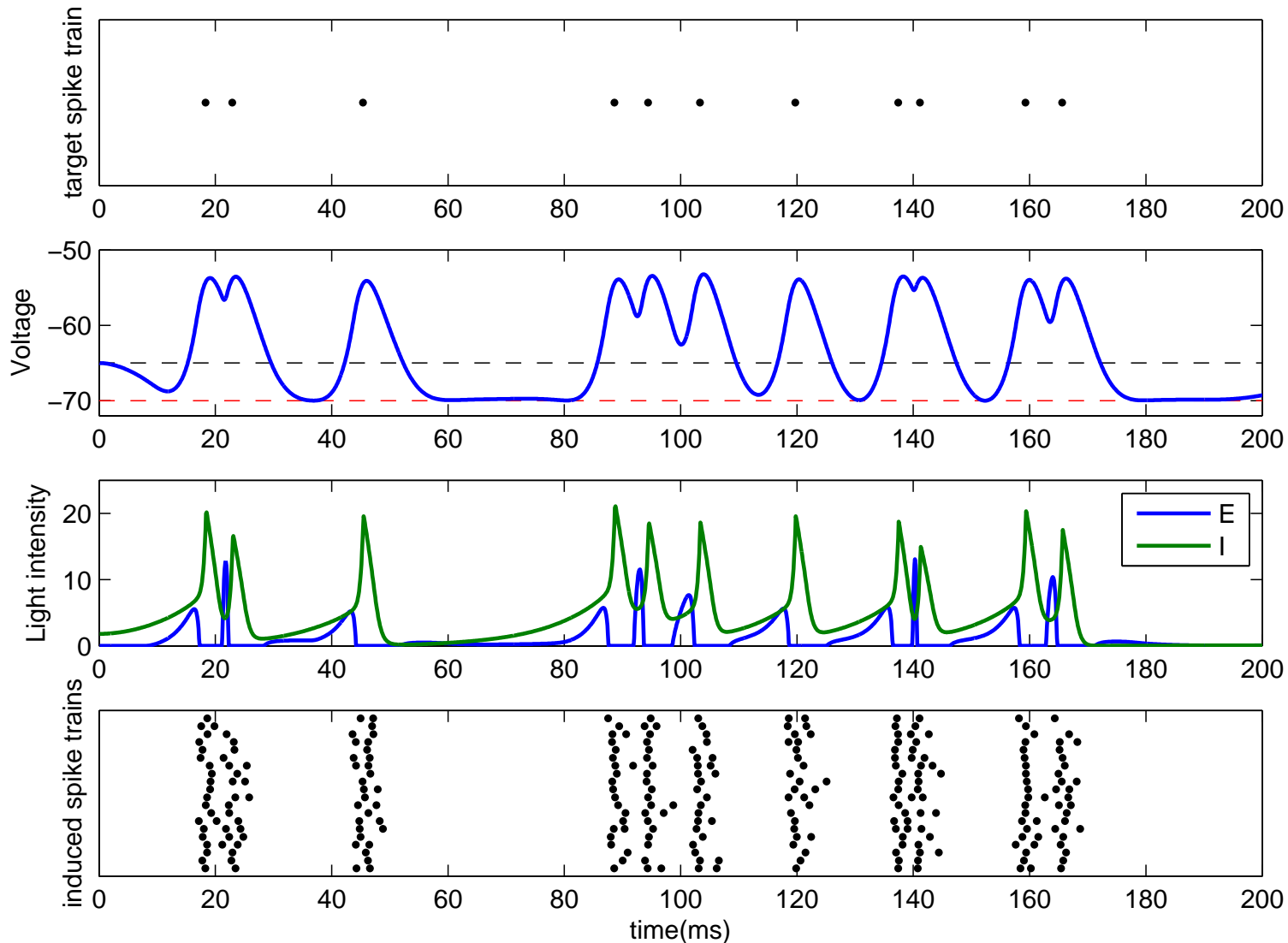
Part 3: spatiotemporal filtering on dendrites

Spatiotemporal imaging data opens an exciting window on the computations performed by single neurons, but we have to deal with noise and intermittent observations.
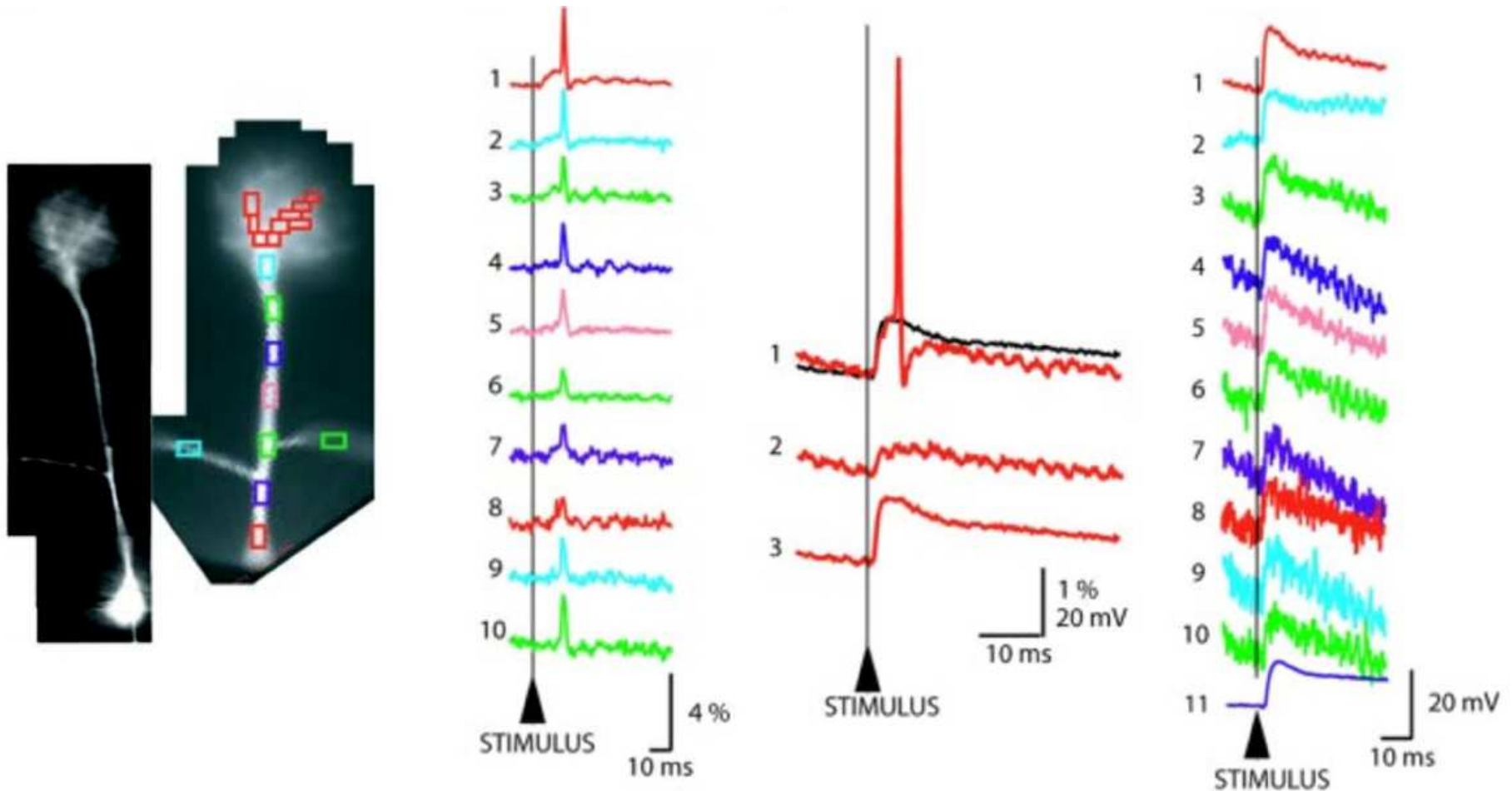
(Djurisic et al., 2004; Knopfel et al., 2006)

Basic paradigm: the Kalman filter

Variable of interest, q_t, evolves according to a noisy differential equation (Markov process):

$$dq/dt = f(q_t) + \epsilon_t.$$

Make noisy observations:

$$y_t = g(q_t) + \eta_t.$$

We want to infer $E(q_t|Y)$: optimal estimate given observations.

Problem: Kalman filter requires $O(d^3 T)$ time ($d = dim(q)$).

Reduction to $O(dT)$: exploit tree structure of dendrite (Paninski, 2010). Can be applied to voltage- or calcium-sensitive imaging data (Pnevmatikakis et al, 2010).

Example: inferring voltage from subsampled observations

(Loading low-rank-speckle.mp4)

Example: summed observations

(Loading low-rank-horiz.mp4)

Applications

- Optimal experimental design: which parts of the neuron should we image? (Huggins and Paninski, 2010)

- Estimation of biophysical parameters (e.g., membrane channel densities, axial resistance, etc.): reduces to a simple nonnegative regression problem once $V(x, t)$ is known (Huys et al., 2006)

- Detecting location and weights of synaptic input (Huggins and Paninski, 2011)

Application: synaptic locations/weights

synaptic weights

$\vec{w}_k$

$\vec{w}_j$

$\vec{w}_i$

pre-synaptic neuron
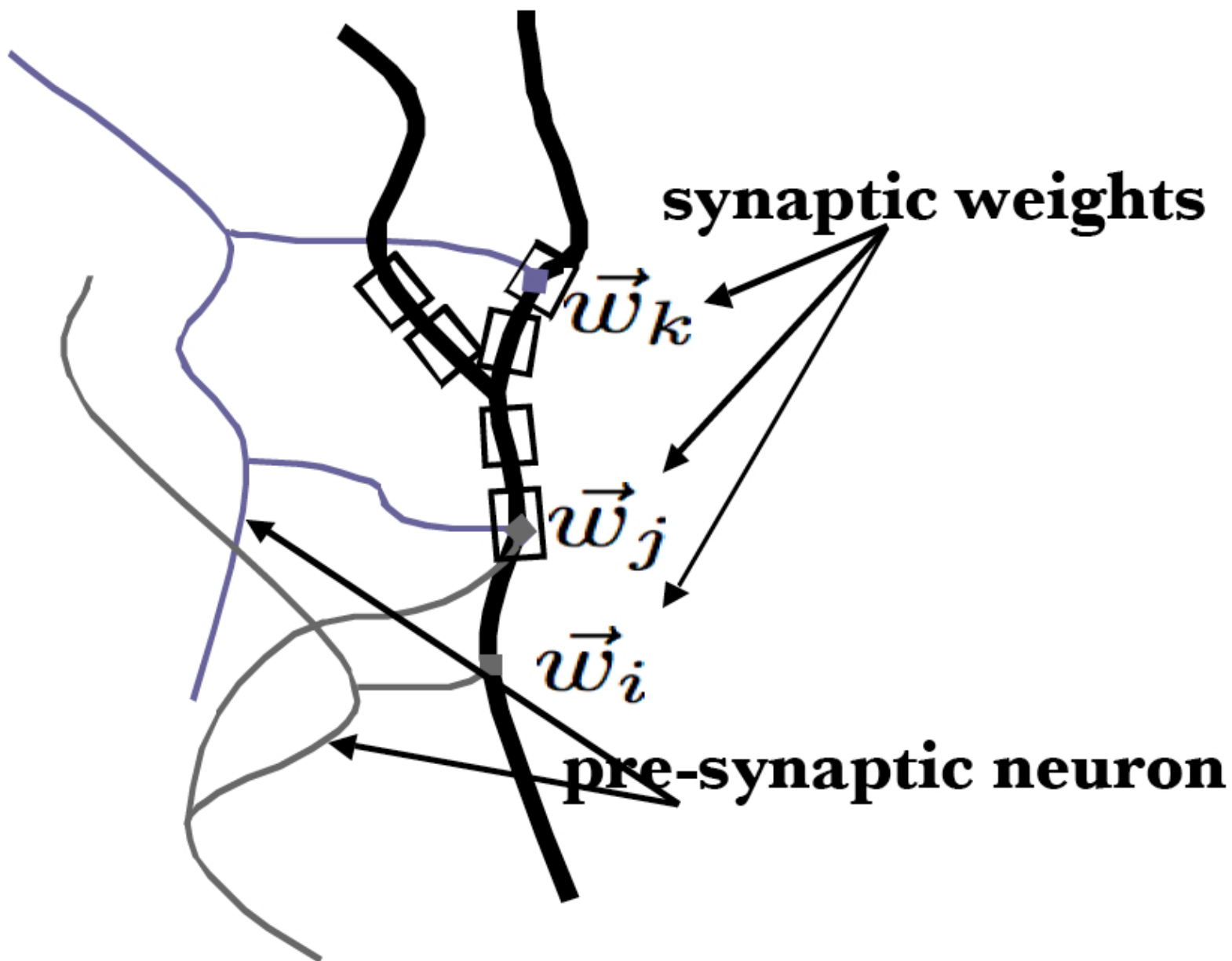
Application: synaptic locations/weights

Including known terms:

$$d\vec{V}/dt = A\vec{V}(t) + W\vec{U}(t) + \vec{\epsilon}(t);$$

$U_j(t) =$ known input terms.

Example: $U(t)$ are known presynaptic spike times, and we want to detect which compartments are connected (i.e., infer the weight matrix W).

Detecting synapses
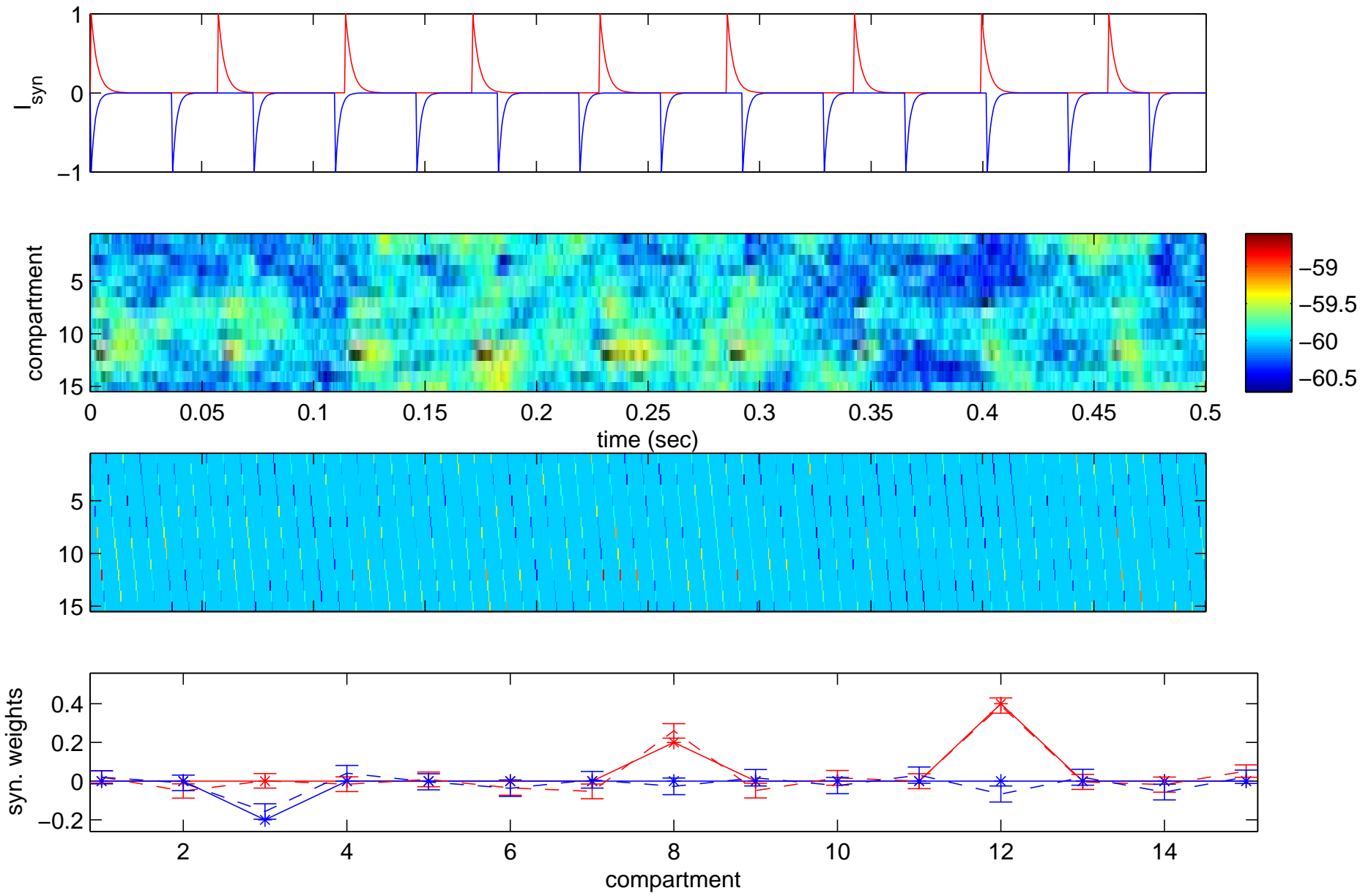
(Paninski et al., 2010; Huggins and Paninski, 2011)

Conclusions

- GLM and state-space approaches provide flexible, powerful methods for answering key questions in neuroscience

- Concave optimizations, banded matrix methods make computations very tractable — real-time, in many cases

- Co-development of experiment and analysis: exciting time for statistical neuroscience

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