Methods for neural circuit inference from population calcium imaging data

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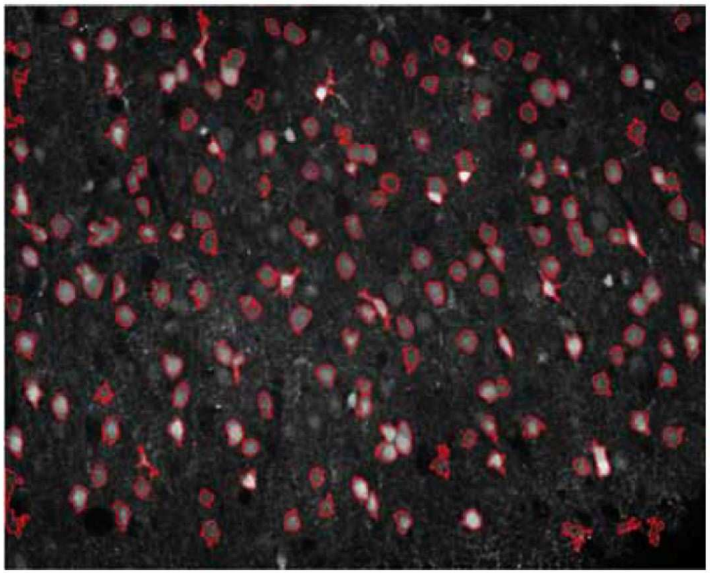
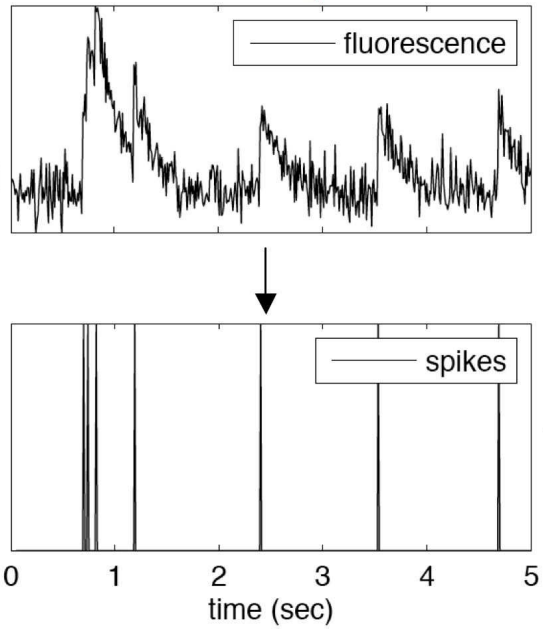
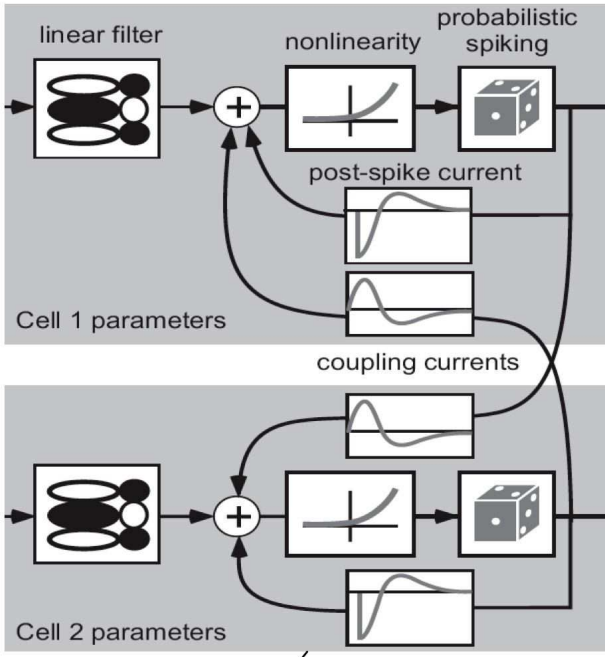
Record large-scale calcium movie



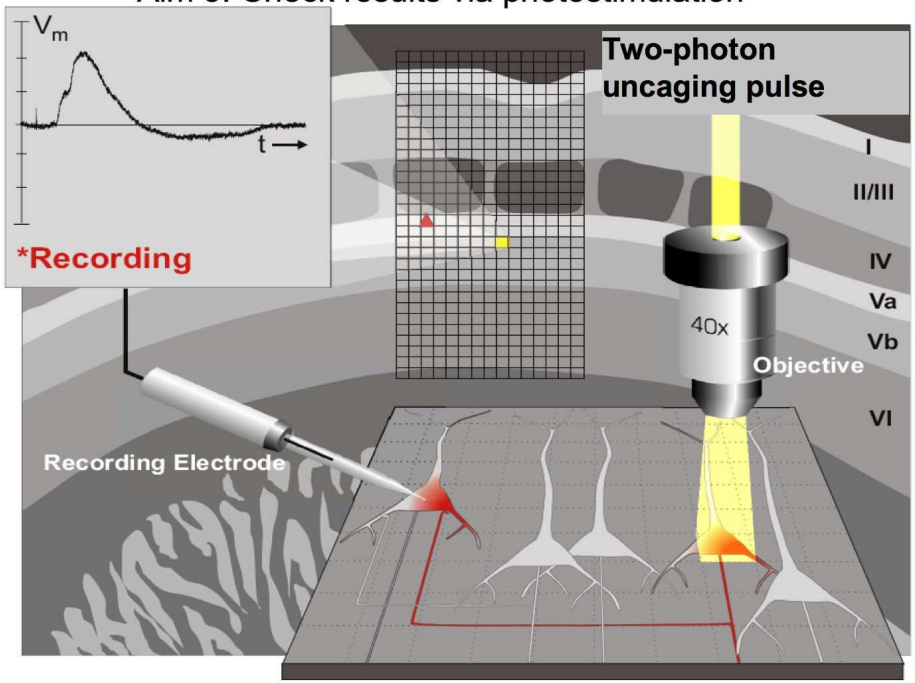
Aim 1: Extract spike times



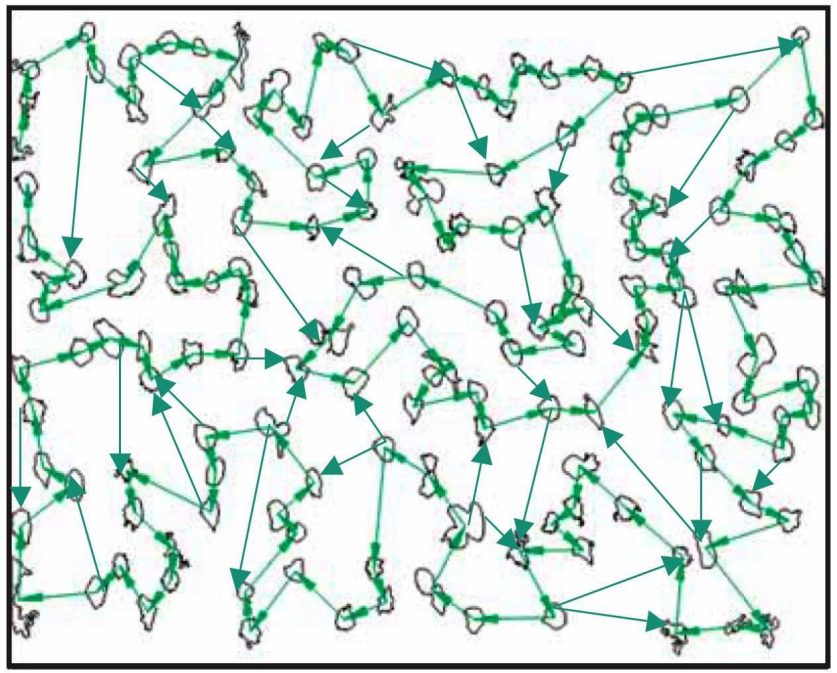
Aim 2: Estimate network model



Aim 3: Check results via photostimulation

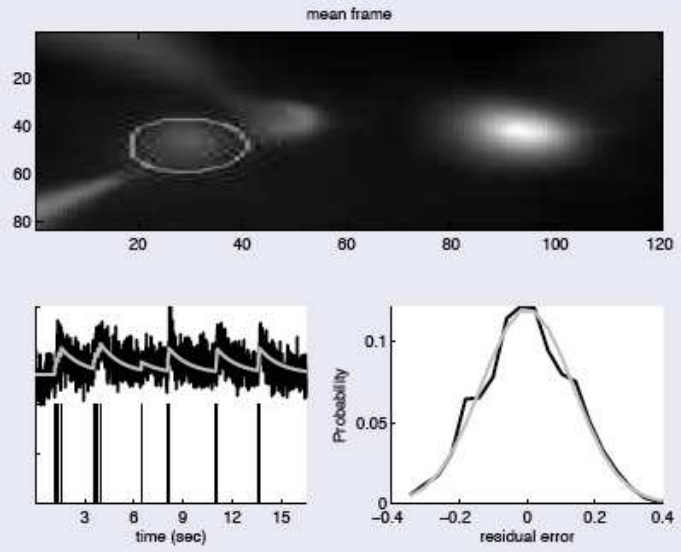


Inferred network model

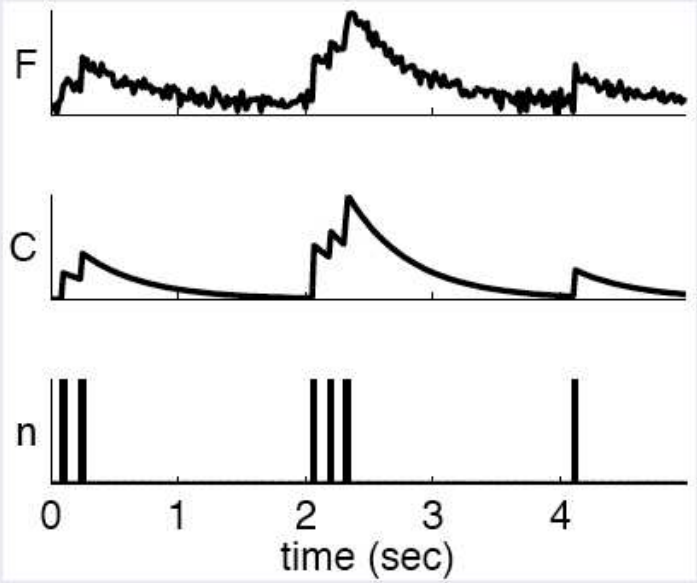


Aim 1: Model-based estimation of spike rates

data



schematic



equations

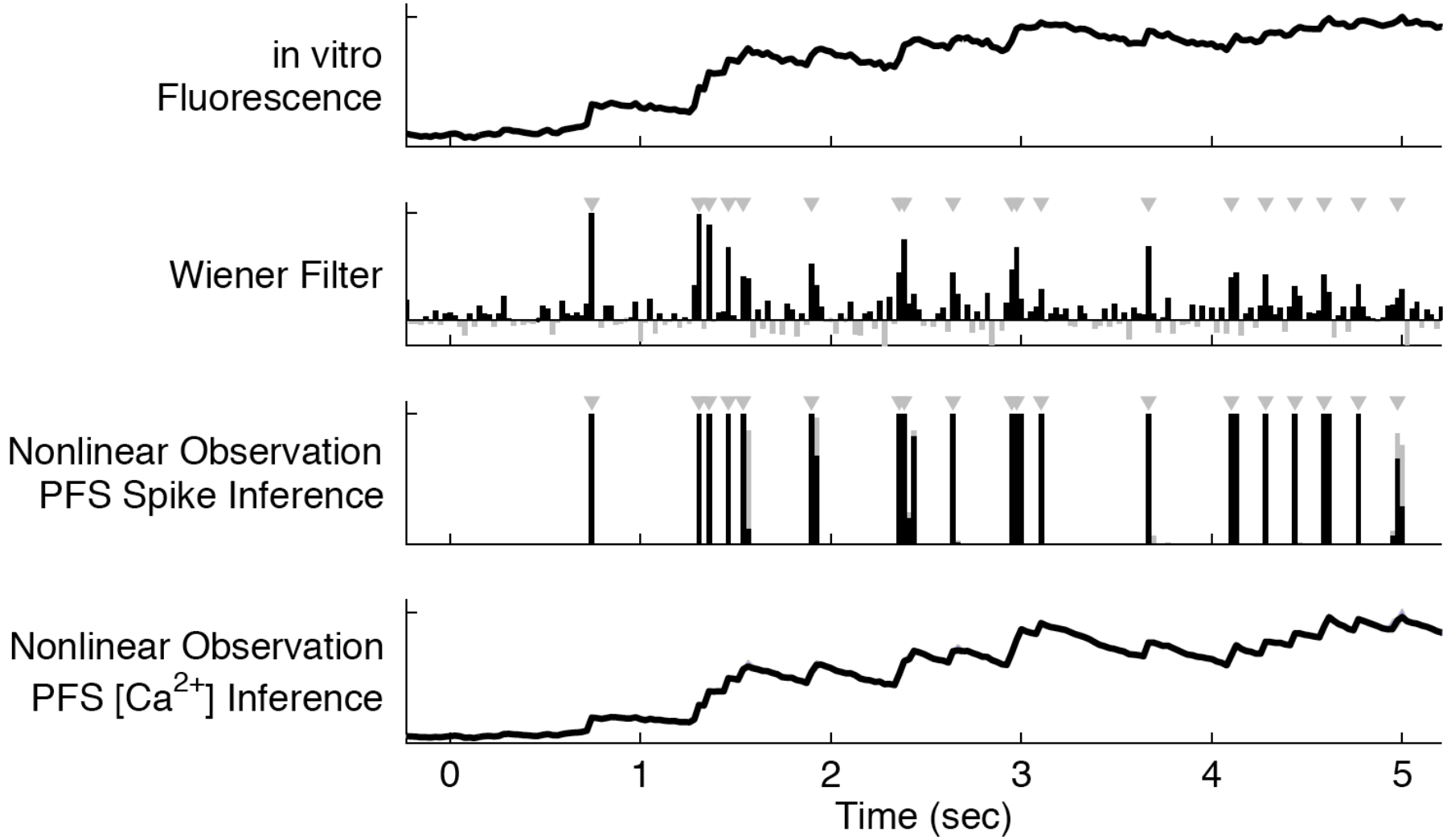
$$F_t = \alpha C_t + \beta + \sigma\varepsilon_t, \qquad \varepsilon_t \overset{iid}{\sim} \mathcal{N}(0,1)$$

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

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

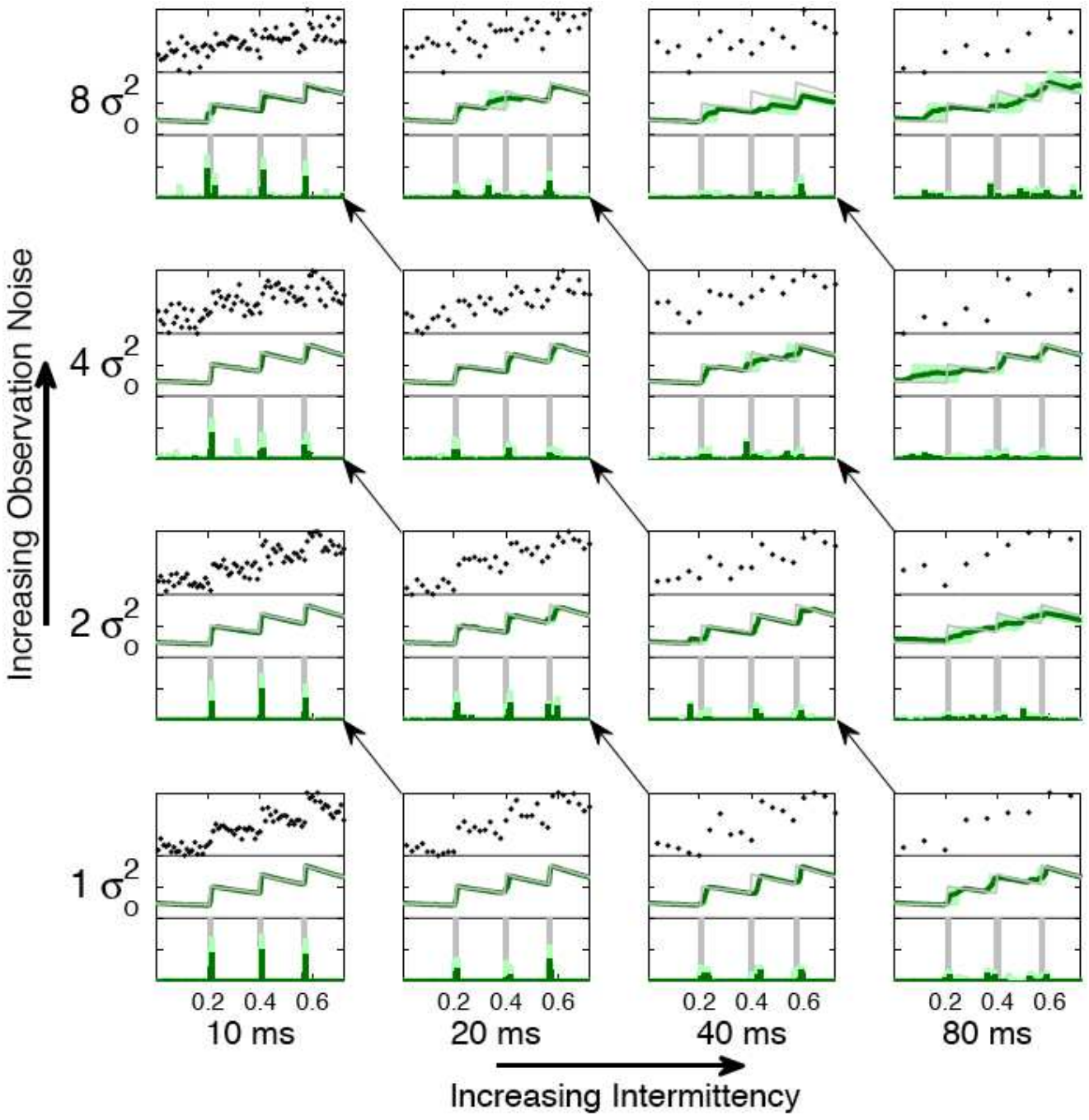
Note: each component here can be generalized easily.

Particle filter can extract spikes from saturated recordings



Optimal nonlinear filter given model; runs in linear time (like optimal linear filter). Parameters inferred via expectation-maximization: no need for intracellular calibration experiments (Vogelstein et al., 2009).

Experimental design: speed vs. SNR tradeoff



Another look: fast maximum a posteriori (MAP) optimization

In standard linear filtering setting, forward-backward recursions also compute MAP (because $E(n|F)$ and $\hat{n} = \arg\max_n p(n|F)$ coincide if $p(n|F)$ is Gaussian).

More generally, write out the posterior:

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

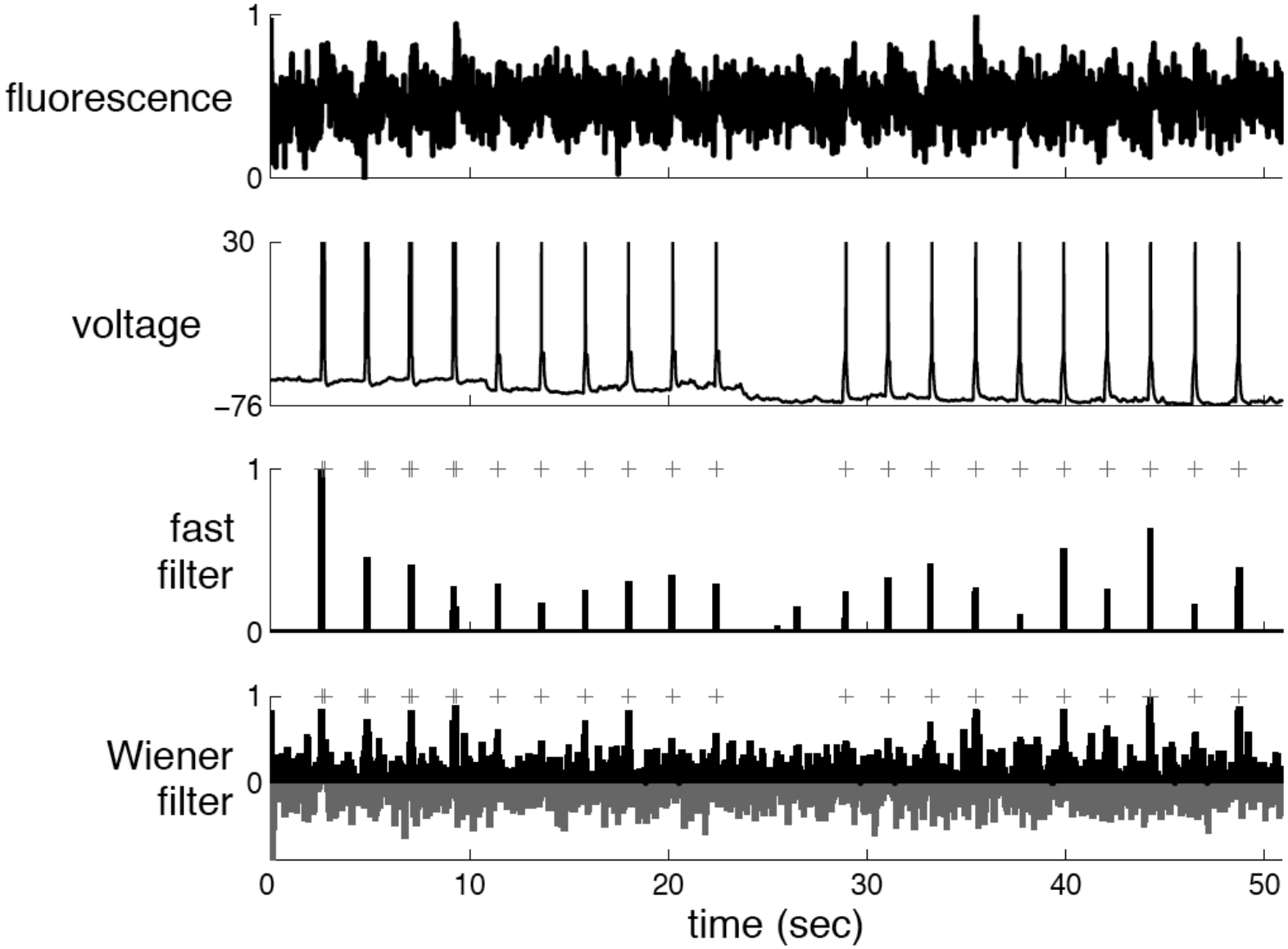
Three basic observations:

- 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).

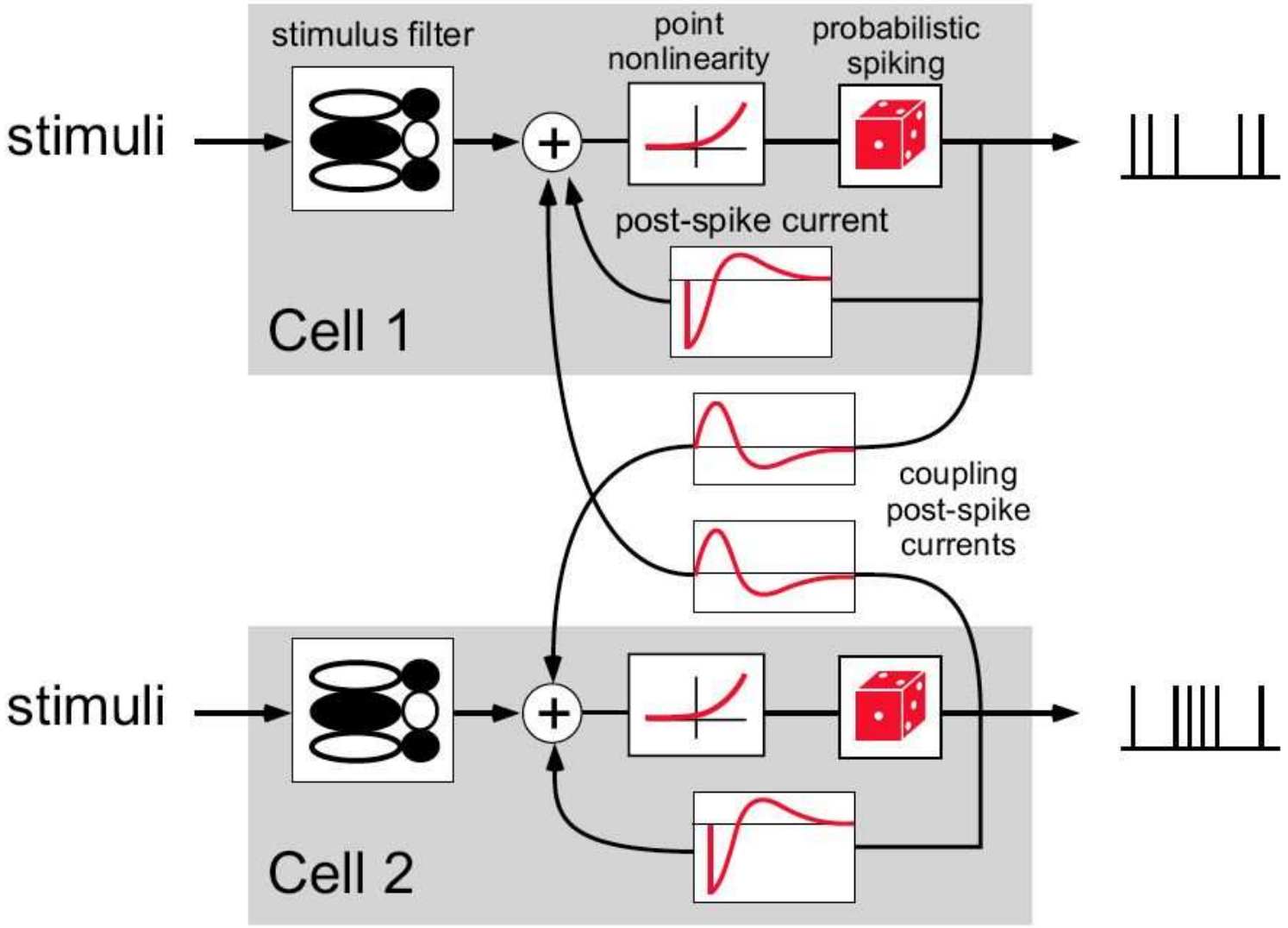
— **Two orders of magnitude faster** than particle filter: can process data from ≈ 100 neurons in real time on a laptop (Vogelstein et al., 2010).

Example: nonnegative MAP filtering



— nonnegative deconvolution is a recurring problem in signal processing (Vogelstein et al., 2010).

Aim 2: estimating network connectivity



Given the spike times in the network, L_1-penalized concave loglikelihood optimization is easy (Paninski, 2004; Pillow et al., 2008). Fast, efficient methods from generalized linear model, compressed sensing literature.

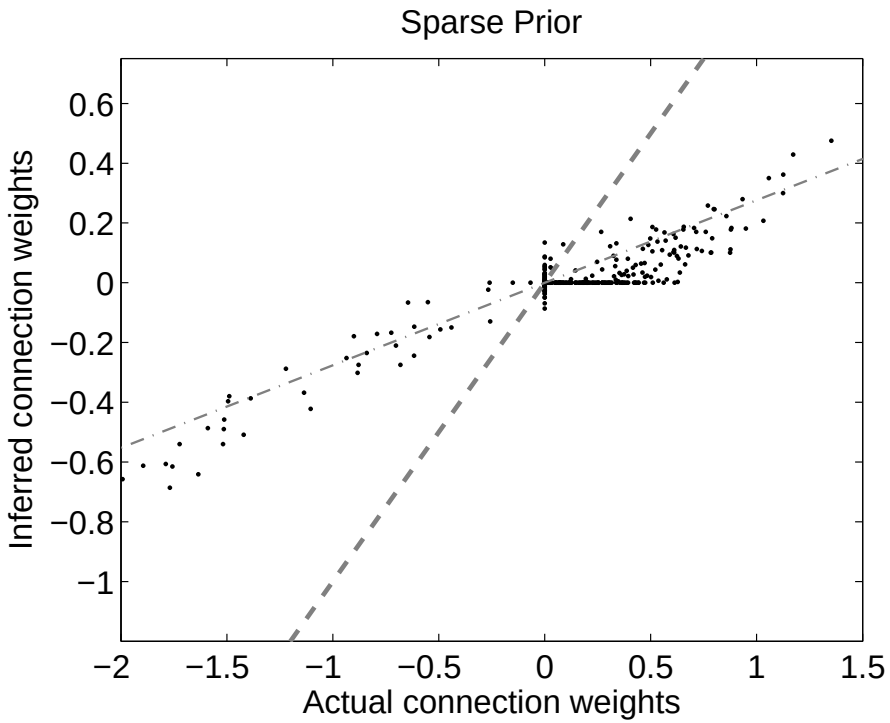
Monte Carlo EM approach

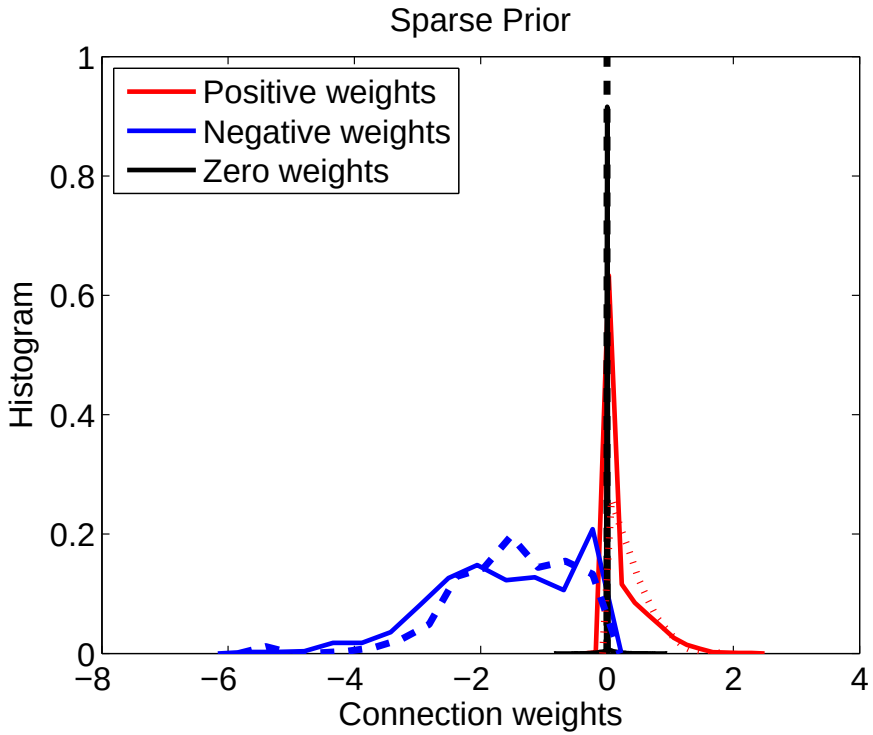
...But we only have noisy calcium observations F; true spike times are hidden variables. Thus an EM approach is once again natural.

- E step: sample spike train responses n from $p(n|F, \theta)$
- M step: given sampled spike trains, perform L_1-penalized likelihood optimization to update parameters θ.

E step is hard part here. Use the fact that neurons interact fairly weakly; thus we need to sample from a collection of weakly-interacting Markov chains, via Metropolis-within-blockwise-Gibbs forward-backward methods (Mishchenko 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. Current work focusing on improved sampling methods, to better quantify uncertainty (exploiting hybrid forward-backward blockwise-Gibbs approach) (Mishchenko and Paninski, 2010).

Aim 3: 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:

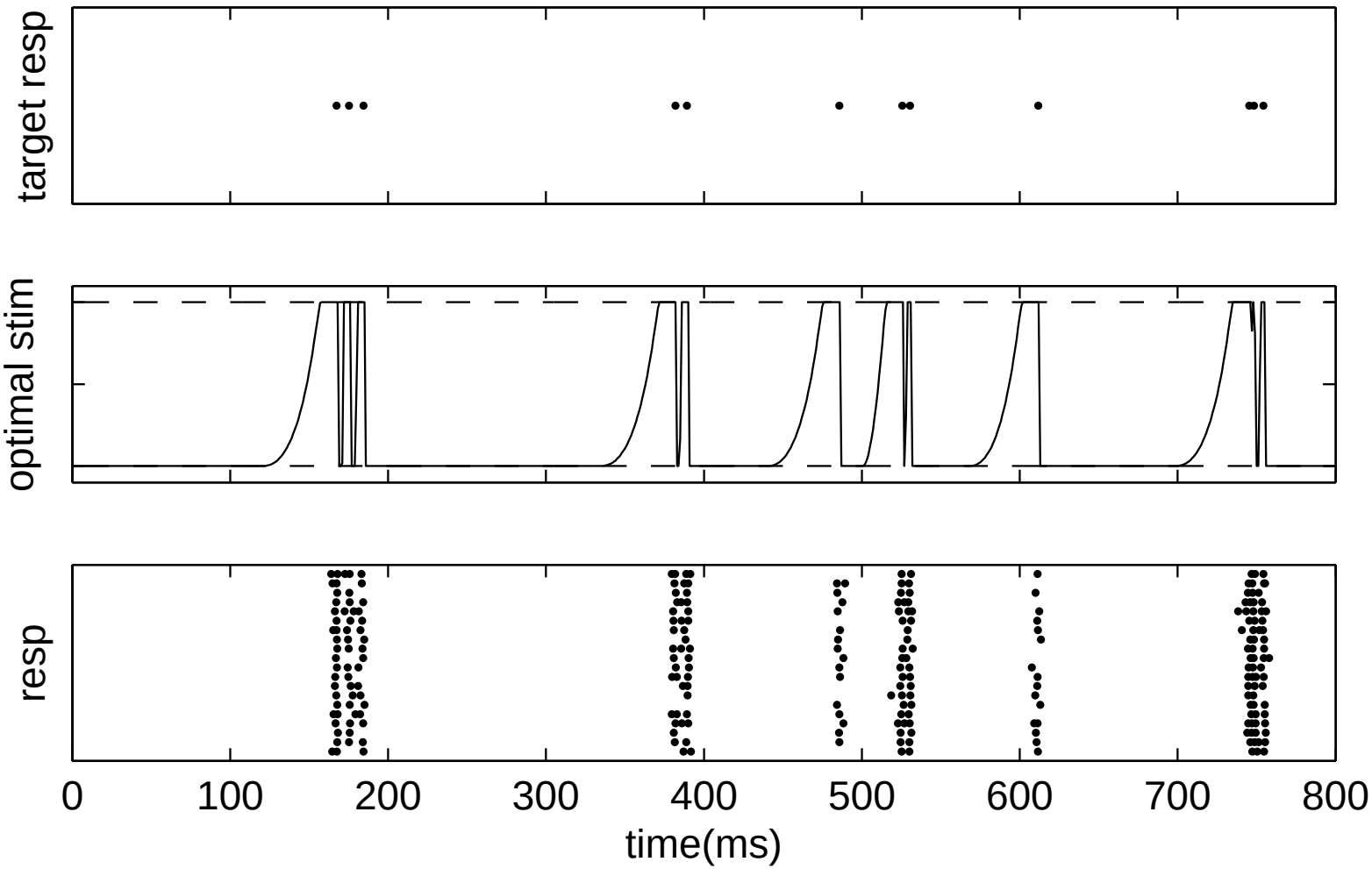
$$\begin{aligned} \lambda_t &= f(V_t + h_t) \\ V_{t+dt} &= V_t + dt\,(-gV_t + aI_t) + \sqrt{dt}\sigma\epsilon_t, \quad \epsilon_t \sim \mathcal{N}(0,1). \end{aligned}$$

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

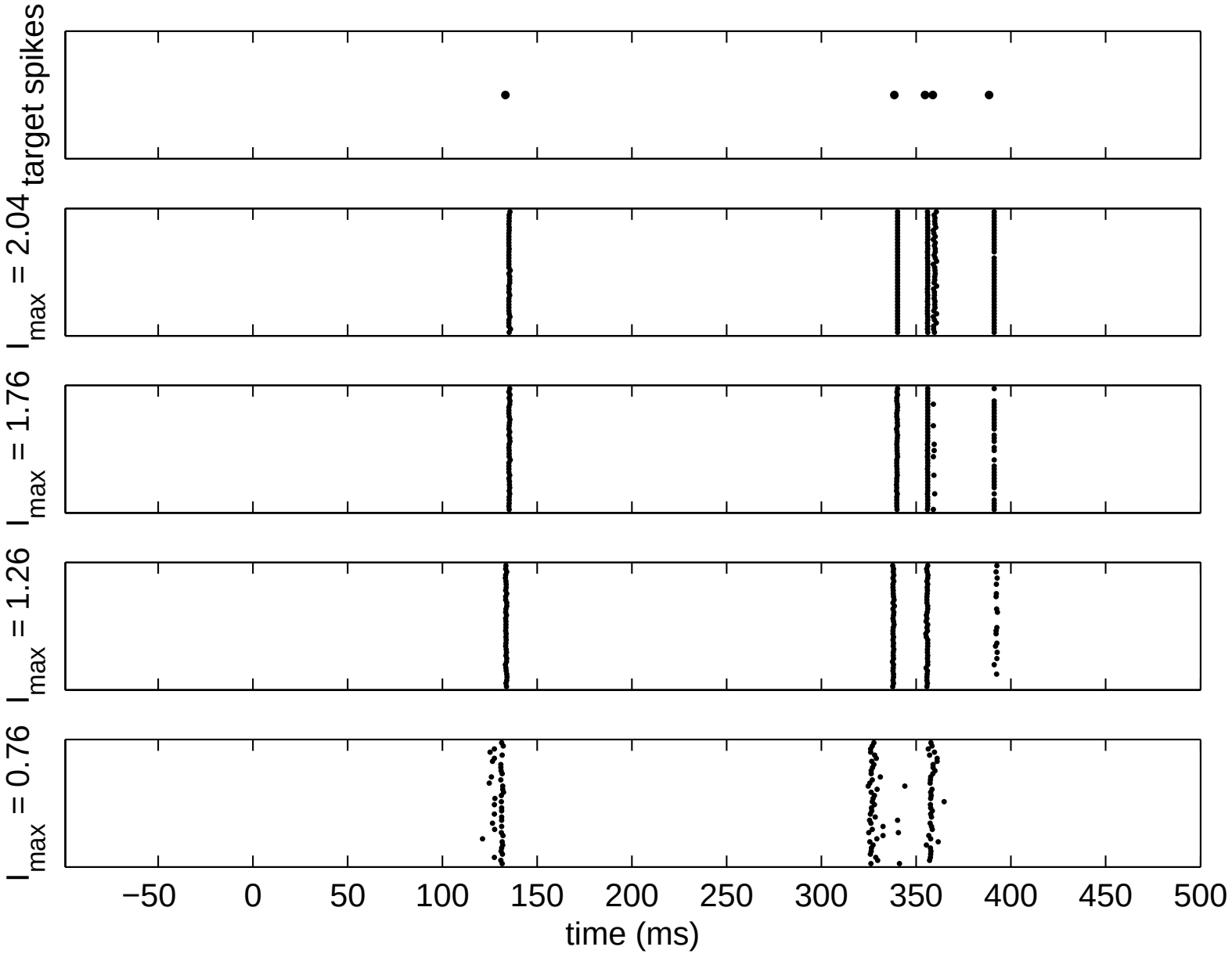
Concave objective function over convex set of possible inputs I_t + Hessian is tridiagonal $\implies$ $O(T)$ optimization.

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

Simulated electrical control of spike timing



Example: intracellular control of spike timing

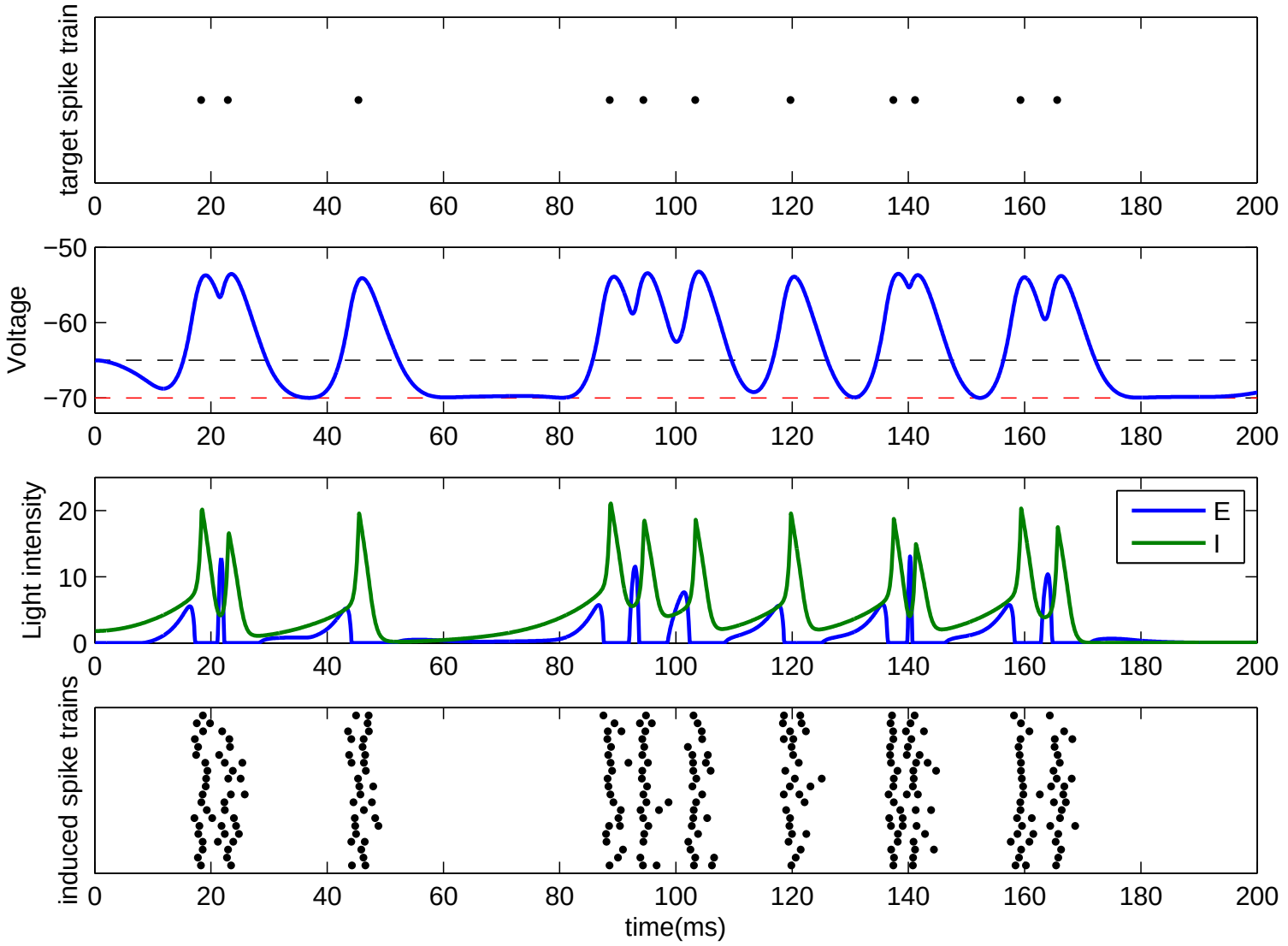


(Ahmadian et al., 2010)

Optical conductance-based control of spiking

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

$$g_{t+dt}^i = g_t^i + dt\left(-\frac{g_t^i}{\tau_i} + a_{ii}L_t^i + a_{ie}L_t^e\right);\ g_{t+dt}^e = g_t^e + dt\left(-\frac{g_t^e}{\tau_i} + a_{ee}L_t^e + a_{ei}L_t^i\right)$$



Next steps

- Optimize experimental parameters: imaging speed, number of neurons, scanning in 3D. Spatial light modulation microscopy a key tool (Nikolenko et al., 2008).
- Stimulate network electrically and optically to increase number of observed distinct spiking patterns: Shepard 256×256 electrode array, channelrhodopsin, new uncaging compounds (Rial Verde et al., 2008)
- Incorporate hidden neuron effects in analysis (Vidne et al., 2009)
- Check results with genetically-labeled inhibitory cells, dual patching, optical stimulation of putative presynaptic neurons (Nikolenko et al., 2007)

— Postdocs wanted!

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