State-space methods for understanding neural computation

Liam Paninski

Department of Statistics and Center for Theoretical Neuroscience
Columbia University
http://www.stat.columbia.edu/∼liam
liam@stat.columbia.edu

April 1, 2010

— with S. Koyama (CMU), J. Vogelstein (JHU), W. Wu (FSU), M. Ahrens (UCL), Y. Ahmadian, Q. Huys, J. Kulkarni, T. Machado, Y. Mishchenko, A. Packer, K. Rahnama Rad, M. Vidne, R. Yuste (Columbia).

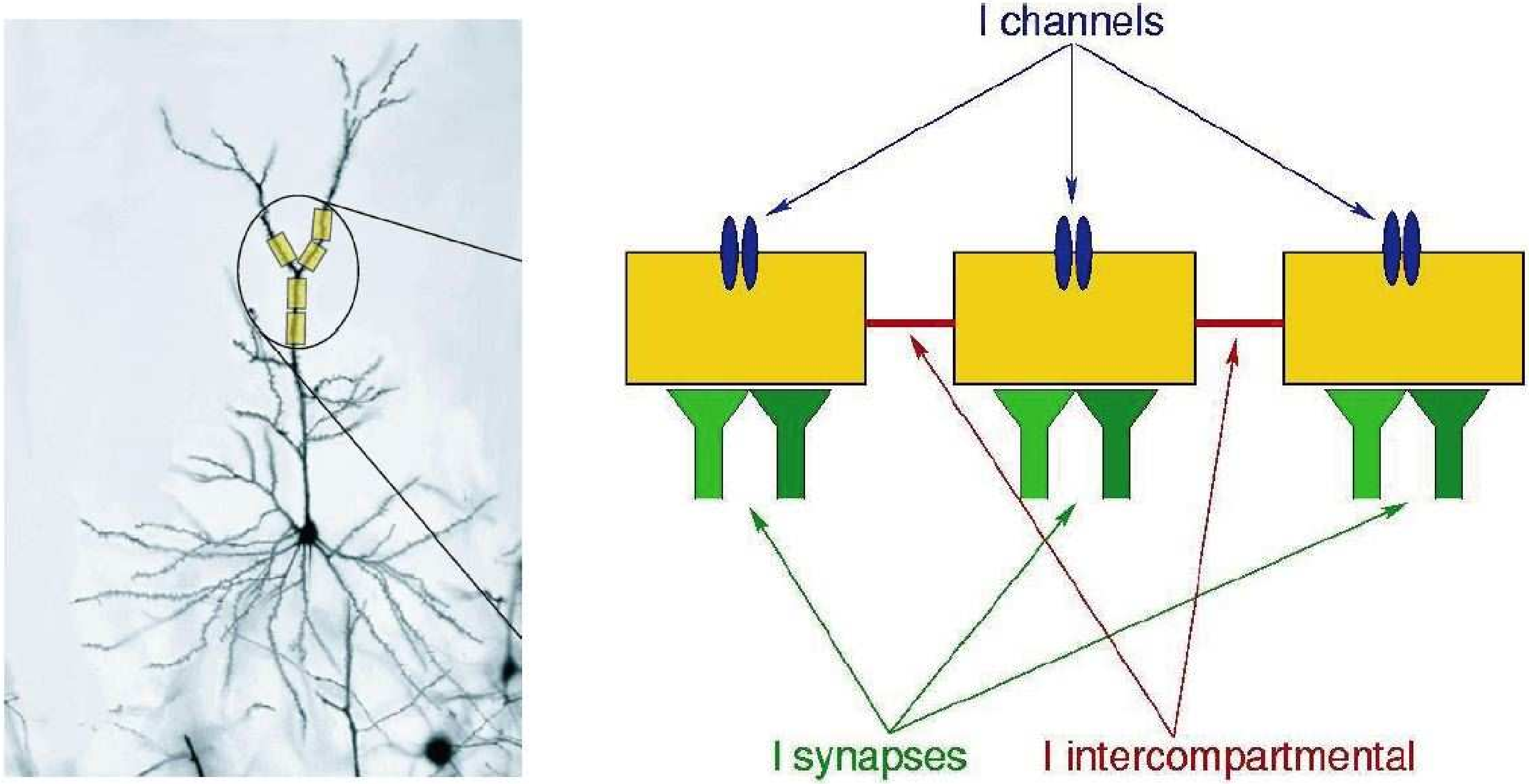
Support: NIH CRCNS, Sloan Fellowship, NSF CAREER, McKnight Scholar award.

Some exciting open challenges for statistical neuroscience

- 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

An inverse problem: inferring cable equation parameters



Can we recover detailed biophysical properties?

- Active: membrane channel densities
- Passive: axial resistances, “leakiness” of membranes
- Dynamic: spatiotemporal synaptic input

Estimating biophysical parameters from $V(x,t)$

$$C\frac{dV_i}{dt} = I_i^{\text{channels}} + I_i^{\text{synapses}} + I_i^{\text{intercompartmental}}$$

$$I_i^{\text{channels}} = \sum_c \bar{g}_c g_c(t)(E_c - V_i(t))$$

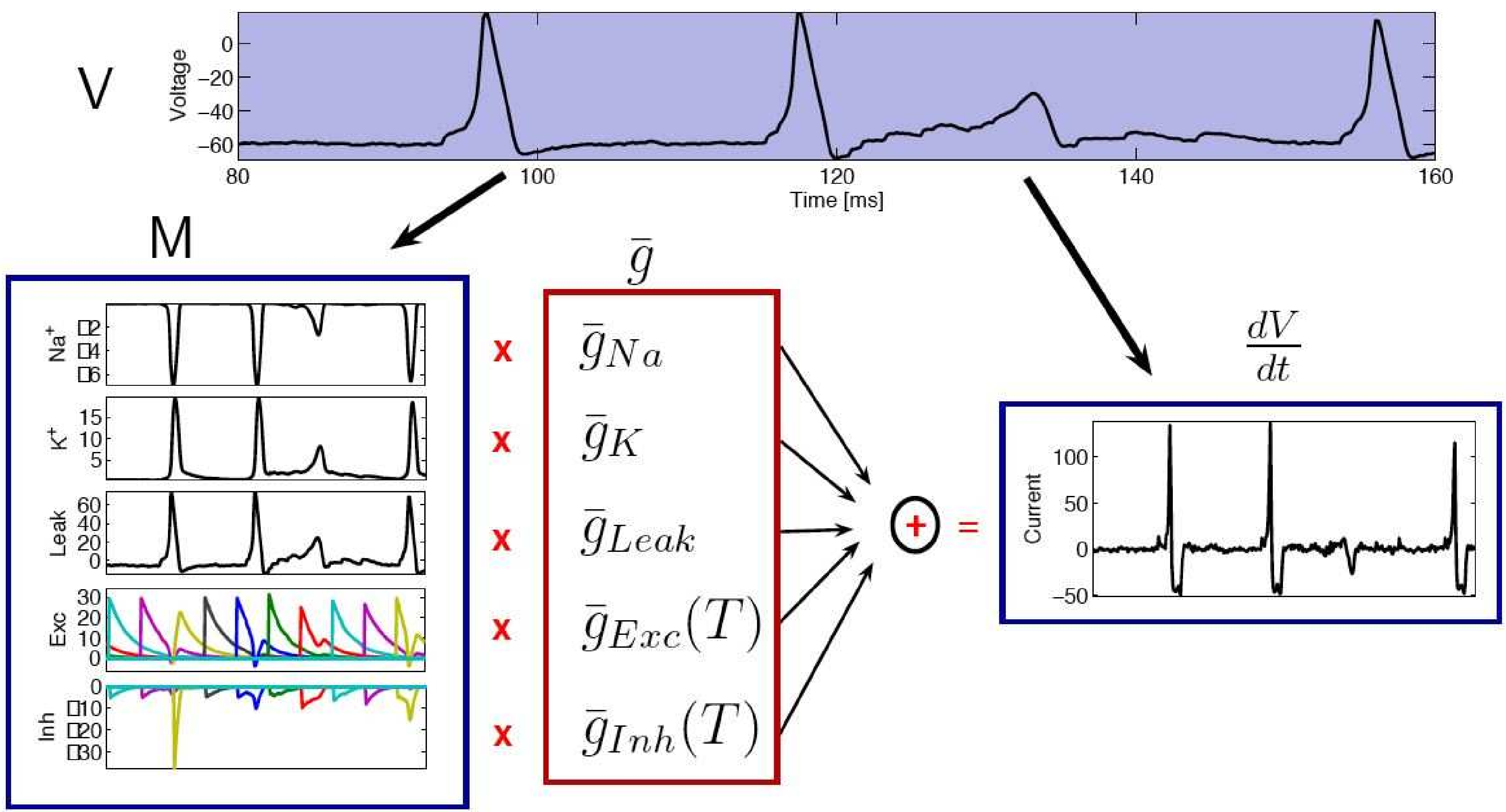
$$I_i^{\text{synapses}} = \sum_s (\xi_s * k_s)(t)(E_s - V_i(t))$$

$$I_i^{\text{intercompartmental}} = \sum_a g_a \Delta V_a(t)$$

Key point: **if** we observe full $V_i(t)$ + cell geometry, channel kinetics known + current noise is Gaussian,

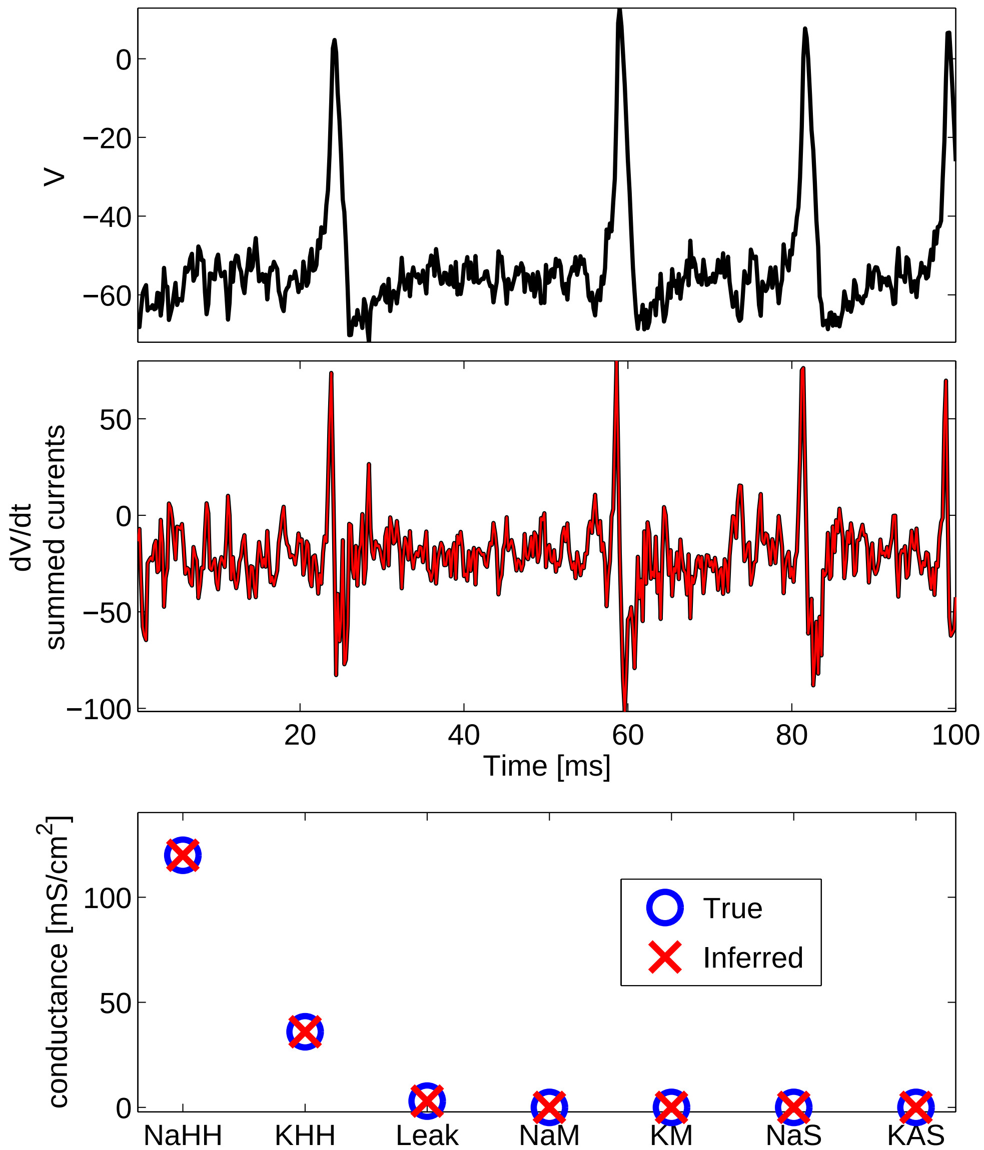
then estimating unknown parameters is standard convex nonnegative regression problem (albeit high-d): $\min_{\theta \geq 0} ||Y - X\theta||^2$.

Estimating channel densities from $V(t)$



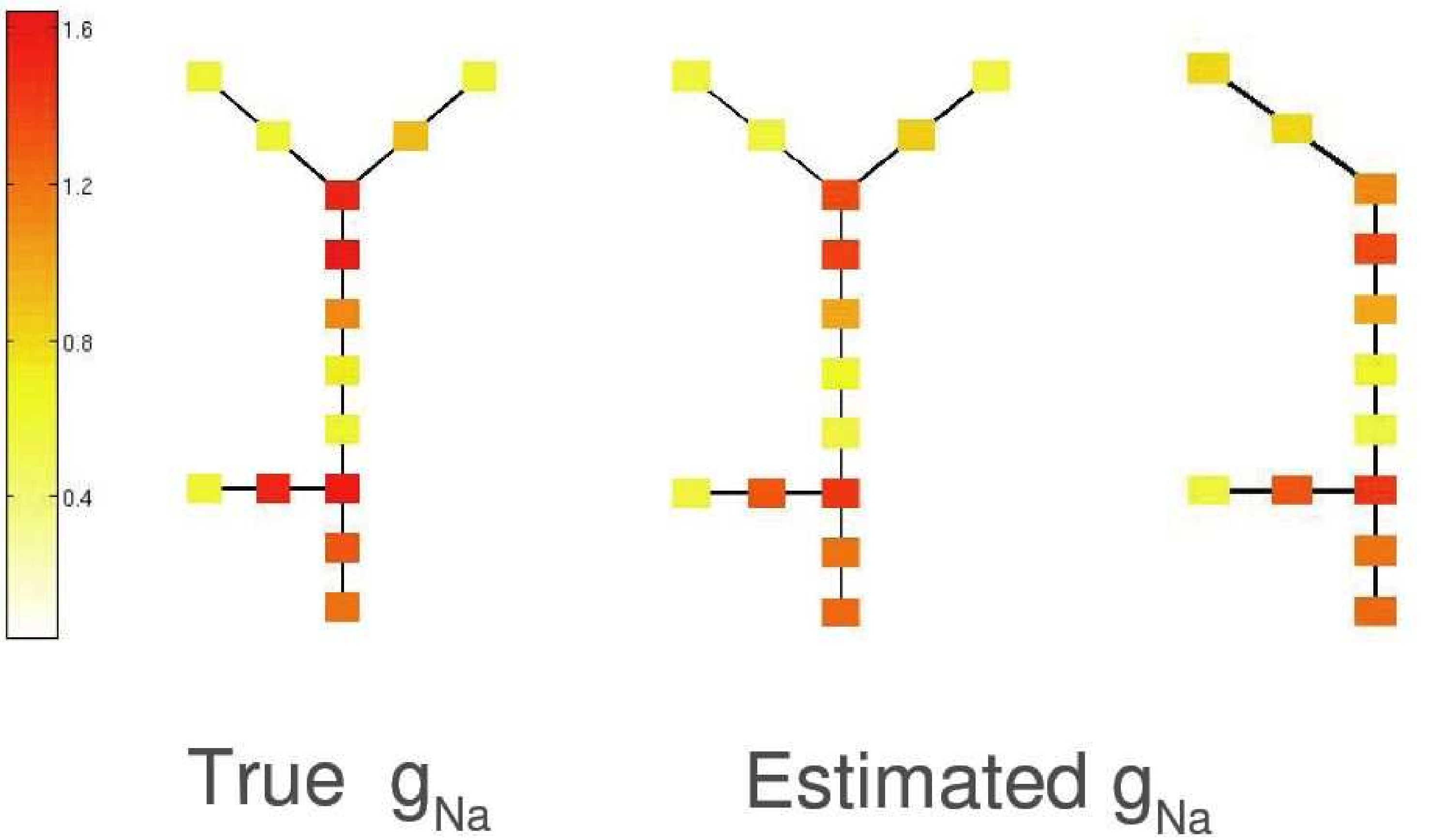
(Huys et al., 2006)

Estimating channel densities from $V(t)$



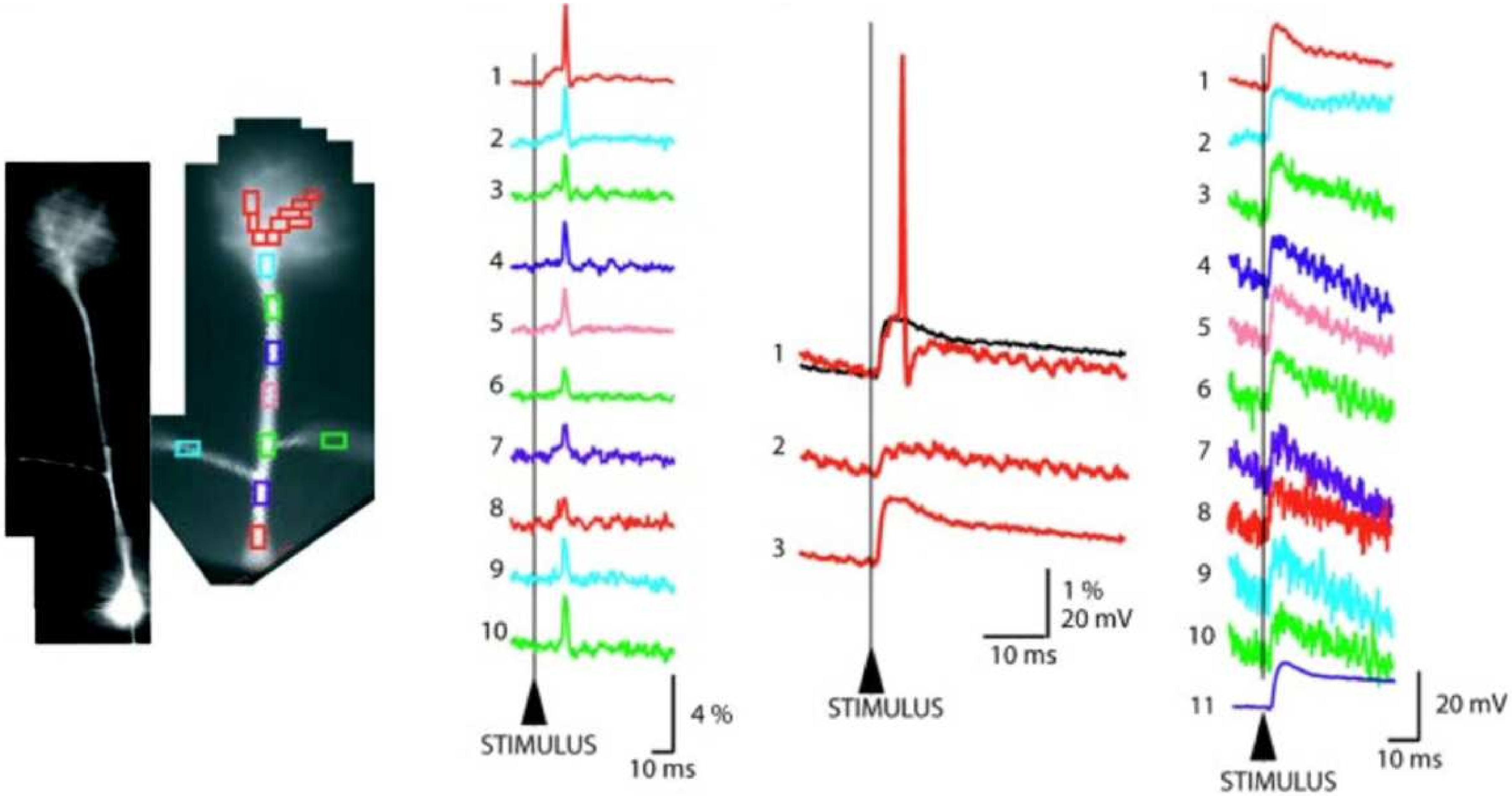
Estimating non-homogeneous channel densities

$$I_i^{\text{channels}} = \sum_c \bar{g}_c g_c(t)(E_c - V_i(t))$$



The filtering problem

Spatiotemporal imaging data is very exciting, 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. We also want errorbars: $Var(q_t|Y)$ quantifies how much we actually know about q_t.

If $f(.)$ and $g(.)$ are linear, and ϵ_t and η_t are Gaussian, then solution is classical: Kalman filter.

The forward recursion

We want $p(q_t|Y_{1:t}) \propto p(q_t, Y_{1:t})$. We know that

$$p(Q,Y) = p(Q)p(Y|Q) = p(q_1)\left(\prod_{t=2}^{T} p(q_t|q_{t-1})\right)\left(\prod_{t=1}^{T} p(y_t|q_t)\right)$$

To compute $p(q_t, Y_{1:t})$ recursively, just write out marginal and pull out constants from the integrals:

$$\begin{aligned} p(q_t, Y_{1:t}) &= \int_{q_1}\int_{q_2}\ldots\int_{q_{t-1}} p(Q_{1:t}, Y_{1:t}) = \int_{q_1}\int_{q_2}\ldots\int_{q_{t-1}} p(q_1)\left(\prod_{i=2}^{t} p(q_i|q_{i-1})\right)\left(\prod_{i=1}^{t} p(y_i|q_i)\right) \\ &= p(y_t|q_t)\int_{q_{t-1}} p(q_t|q_{t-1})p(y_{t-1}|q_{t-1})\int_{q_{t-2}}\ldots\int_{q_2} p(q_3|q_2)p(y_2|q_2)\int_{q_1} p(q_2|q_1)p(y_1|q_1)p(q_1). \end{aligned}$$

So, just recurse

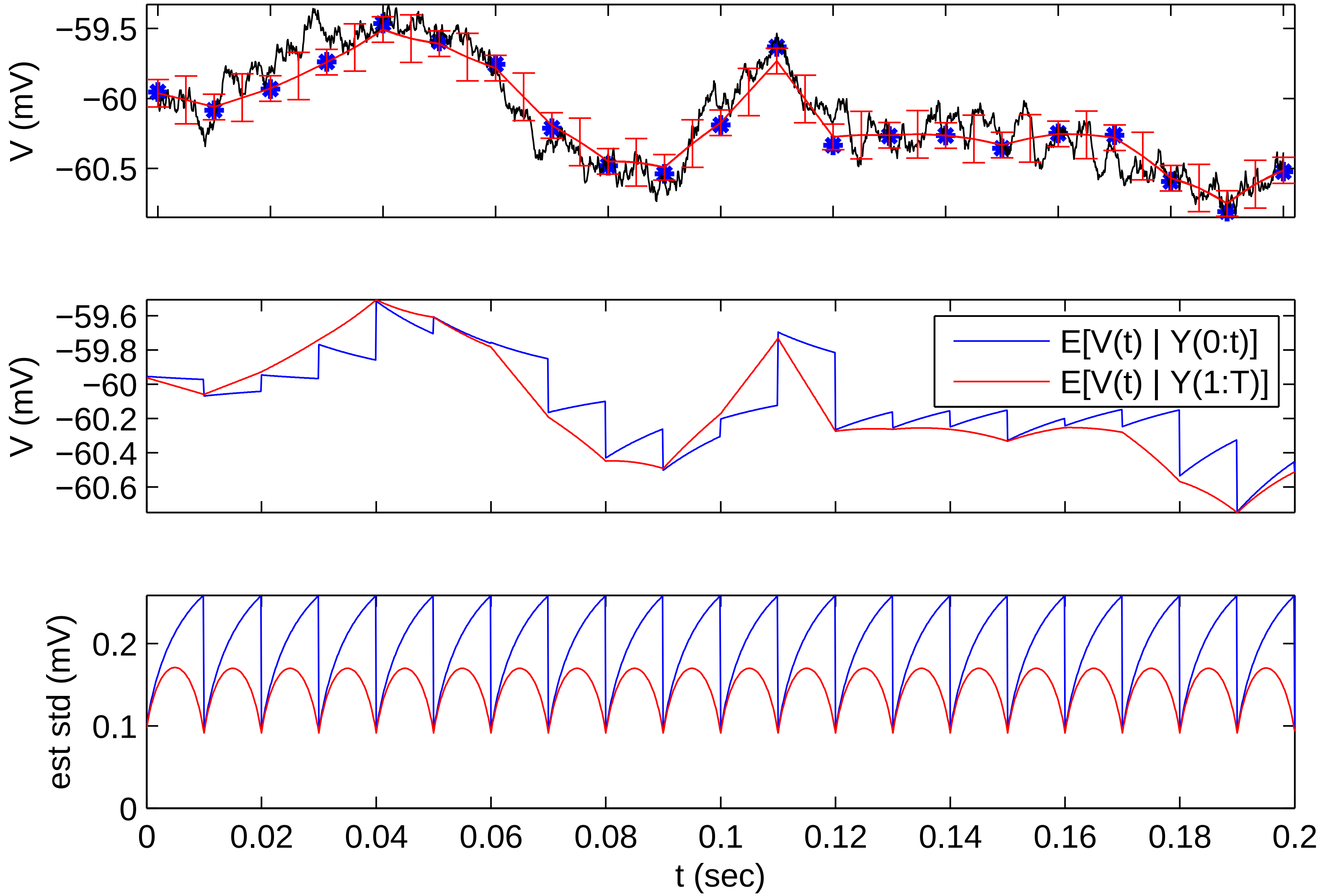
$$p(q_t, Y_{1:t}) = p(y_t|q_t)\int_{q_{t-1}} p(q_t|q_{t-1})p(q_{t-1}, Y_{1:t-1}).$$

Linear-Gaussian case: requires $O(\dim(q)^3 T)$ time; just matrix algebra.
Approximate solutions in more general case, e.g., Gaussian approximations (Brown et al., 1998), or Monte Carlo ("particle filtering").

Key point: efficient recursive computations $\implies O(T)$ time.

Application: incomplete observations of $V(t)$

— Leaky integrator model: $dV/dt = g_l[V_l - V(t)] + \epsilon_t$



Multicompartmental case

Easy extension of Kalman method:

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

$$\vec{y}(t) = B\vec{V}(t) + \vec{\eta}_t$$

Example:

$V_i(t) =$ voltage at compartment i

$A =$ dynamics matrix (cable equation): includes leak ($A_{ii} = -g_l$) and inter-compartmental terms ($A_{ij} = 0$ for non-adjacent compartments)

$B =$ observation matrix

Low-rank approximations

Key fact: current experimental methods provide just a few low-SNR observations per time step.

Basic idea: if dynamics are approximately linear and time-invariant, we can approximate Kalman covariance $C_t = cov(q_t|Y_{1:t})$ as a perturbation of the marginal covariance $C_0 + U_t D_t U_t^T$, with $C_0 = \lim_{t\to\infty} cov(q_t)$.

C_0 is the solution to a Lyapunov equation. It turns out that we can solve linear equations involving C_0 in $O(\dim(q))$ time via Gaussian belief propagation, using the fact that the dendrite is a tree.

The necessary recursions — i.e., updating U_t, D_t and the Kalman mean $E(q_t|Y_{1:t})$ — involve linear manipulations of C_0, using

$$
\begin{aligned}
C_t &= [(AC_{t-1}A^T + Q)^{-1} + B_t]^{-1} \\
C_0 + U_t D_t U_t^T &= \left([A(C_0 + U_{t-1}D_{t-1}U_{t-1}^T)A^T + Q]^{-1} + B_t\right)^{-1},
\end{aligned}
$$

and can be done in $O(\dim(q))$ time (Paninski, 2009a).

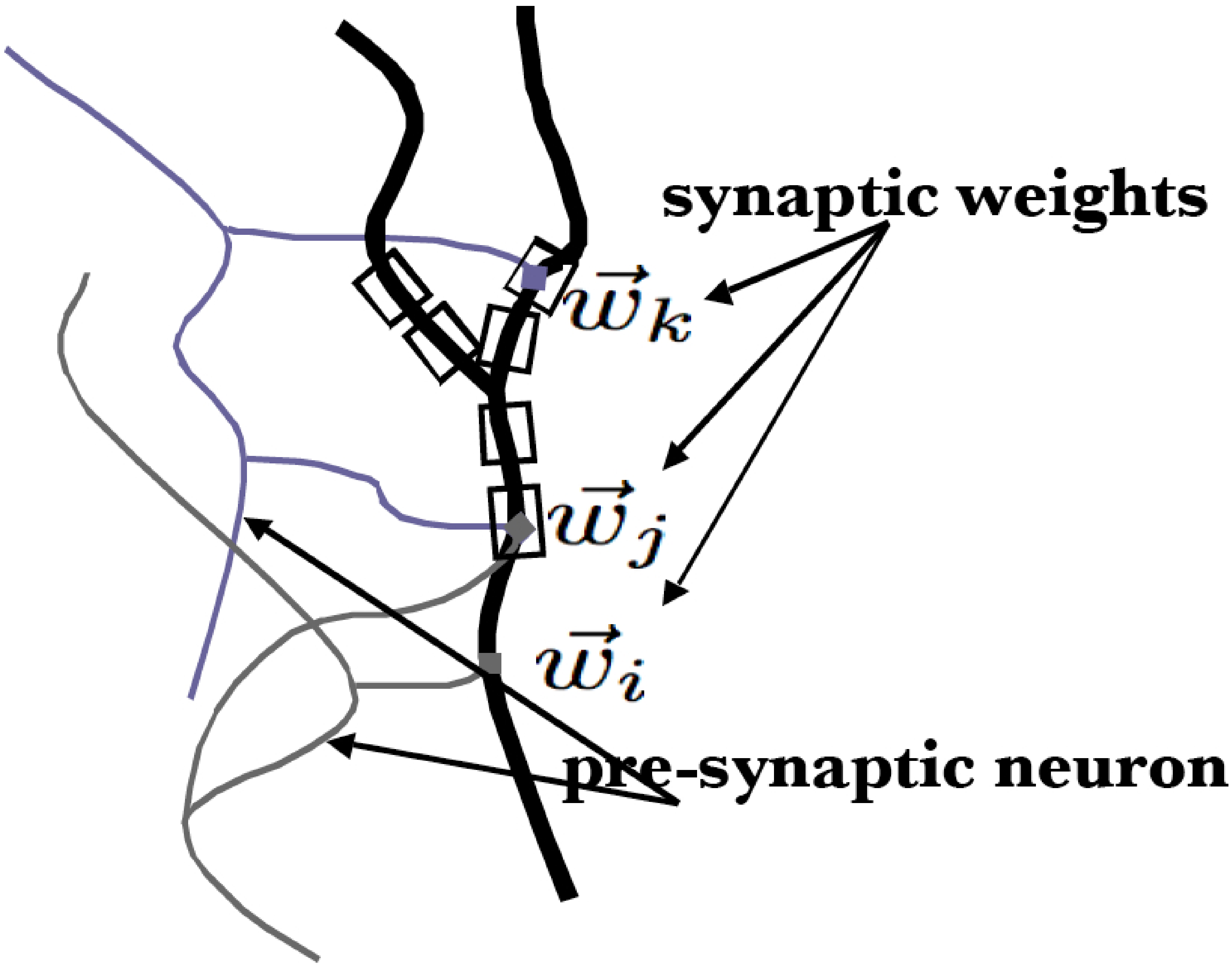
Example: inferring voltage from subsampled observations

(Loading low-rank-speckle.mp4)

Example: summed observations

(Loading low-rank-horiz.mp4)

Application: synaptic locations/weights



Application: synaptic locations/weights

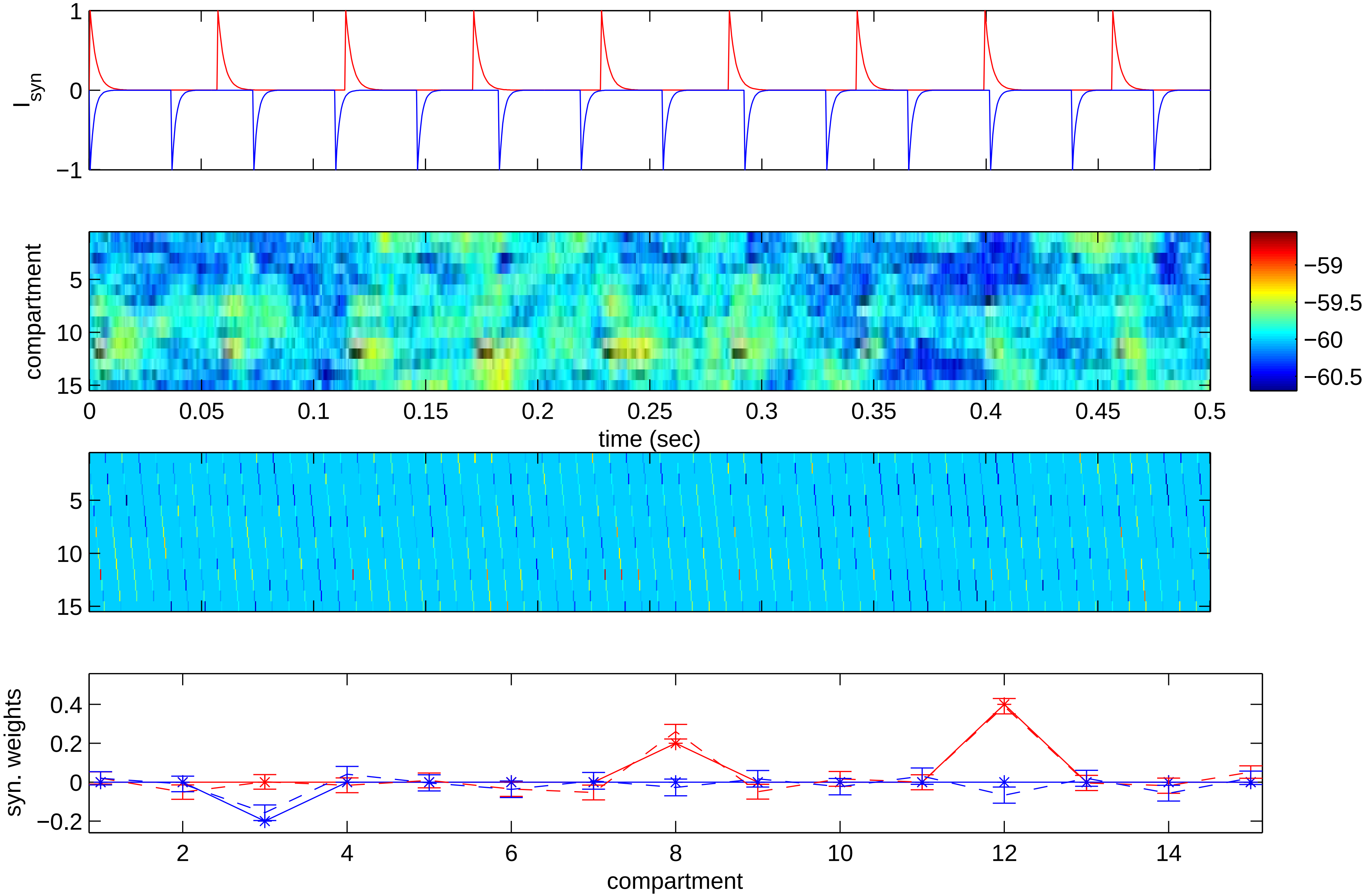
Including known terms:

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

$U_j(t)$ = 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 and Ferreira, 2008; Paninski et al., 2009)

Another application: neural prosthetics

q_t: hand position (red square); $E(q_t|Y_{1:t})$: green circle

y_t: vector of observed spike counts at time t from multiple simultaneously recorded motor cortical neurons

(Loading Kalman-neural-decoding.mp4)

(Wu et al., 2006; Wu et al., 2009)

Another look: computing the MAP path

We often want to compute the MAP estimate

$$\hat{Q} = \arg\max_{Q} p(Q|Y).$$

In standard Kalman setting, forward-backward recursions also compute MAP (because $E(Q|Y)$ and $\hat{Q}$ coincide if $p(Q|Y)$ is Gaussian).

More generally, write out the posterior:

$$\begin{aligned} \log p(Q|Y) &= \log p(Q) + \log p(Y|Q) + const. \\ &= \sum_t \log p(q_{t+1}|q_t) + \sum_t \log p(y_t|q_t) + const. \end{aligned}$$

Two basic observations:

- If $\log p(q_{t+1}|q_t)$ and $\log p(y_t|q_t)$ are concave, then so is $\log p(Q|Y)$.
- Hessian H of $\log p(Q|Y)$ is block-tridiagonal: $p(y_t|q_t)$ contributes a block-diag term, and $\log p(q_{t+1}|q_t)$ contributes a block-tridiag term.

Now recall Newton's method: iteratively solve $HQ_{dir} = \nabla$. Solving tridiagonal systems requires $O(T)$ time.

— computing MAP by Newton's method requires $O(T)$ time, even in highly non-Gaussian cases.

Constrained optimization

In many cases we need to impose constraints on q_t (e.g., nonnegativity). Easy to incorporate here, via interior-point (barrier) methods:

$$
\begin{aligned}
\arg\max_{Q \in C} \log p(Q|Y) &= \lim_{\epsilon \searrow 0} \arg\max_{Q} \left\{ \log p(Q|Y) + \epsilon \sum_t f(q_t) \right\} \\
&= \lim_{\epsilon \searrow 0} \arg\max_{Q} \left\{ \sum_t \log p(q_{t+1}|q_t) + \log p(y_t|q_t) + \epsilon f(q_t) \right\};
\end{aligned}
$$

$f(.)$ is concave and approaching $-\infty$ near boundary of constraint set C. The Hessian remains block-tridiagonal and negative semidefinite for all $\epsilon > 0$, so optimization still requires just $O(T)$ time.

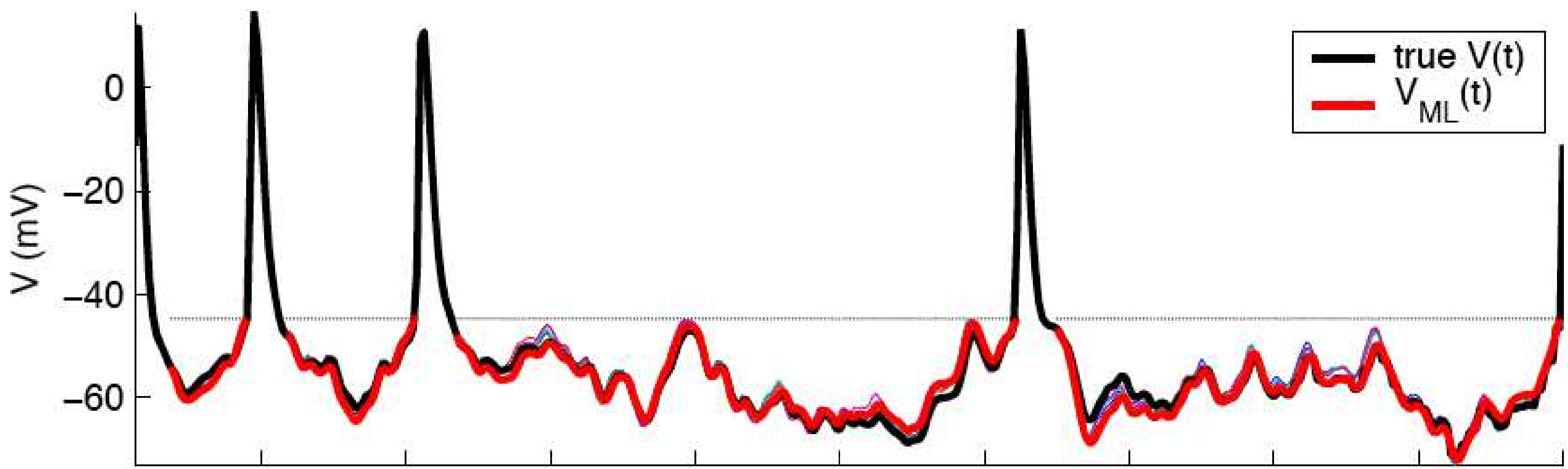
Example: computing the MAP subthreshold voltage given superthreshold spikes

Leaky, noisy integrate-and-fire model:

$$V_{t+dt} = V_t + \left(-\frac{V_t}{\tau} + I_t\right) dt + \sigma\sqrt{dt}\epsilon_t, \;\; \epsilon_t \sim \mathcal{N}(0,1)$$

Observations: $y_t = 0$ (no spike) if $V_t < V_{th}$; $y_t = 1$ if $V_t = V_{th}$

Hard threshold $\implies$ $p(V|Y)$ is very non-Gaussian: "corners" at $V_t = V_{th}$.

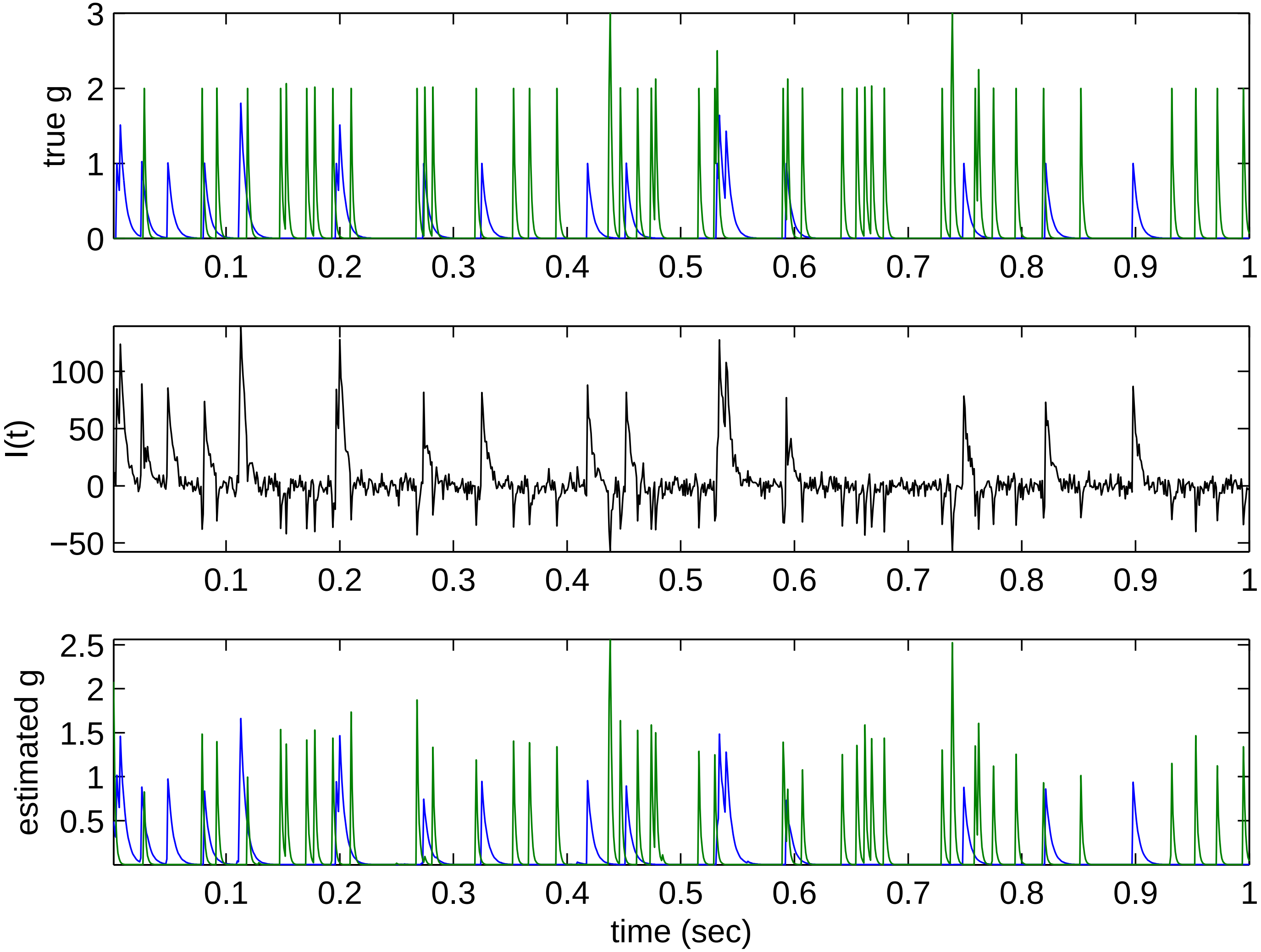


(Paninski, 2006)

Example: inferring presynaptic input

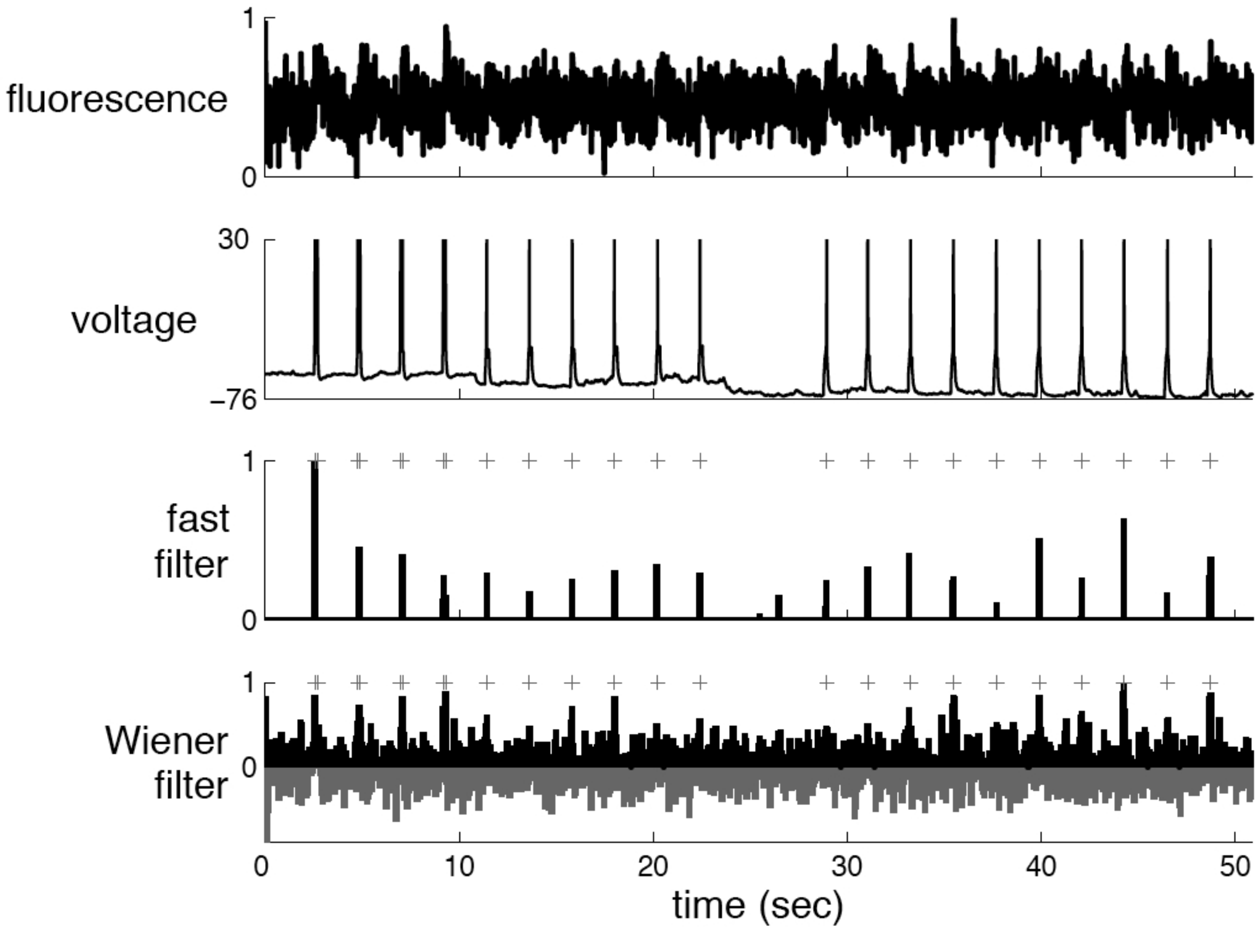
$$\begin{aligned} g_j(t+dt) &= g_j(t) - dt g_j(t)/\tau_j + N_j(t), \;\; N_j(t) \geq 0 \\ y_t &= I_t = \sum_j g_j(t)(V_j - V_t) + \epsilon_t \end{aligned}$$

Hidden state q_t: vector of conductances g_t (Paninski, 2009b)



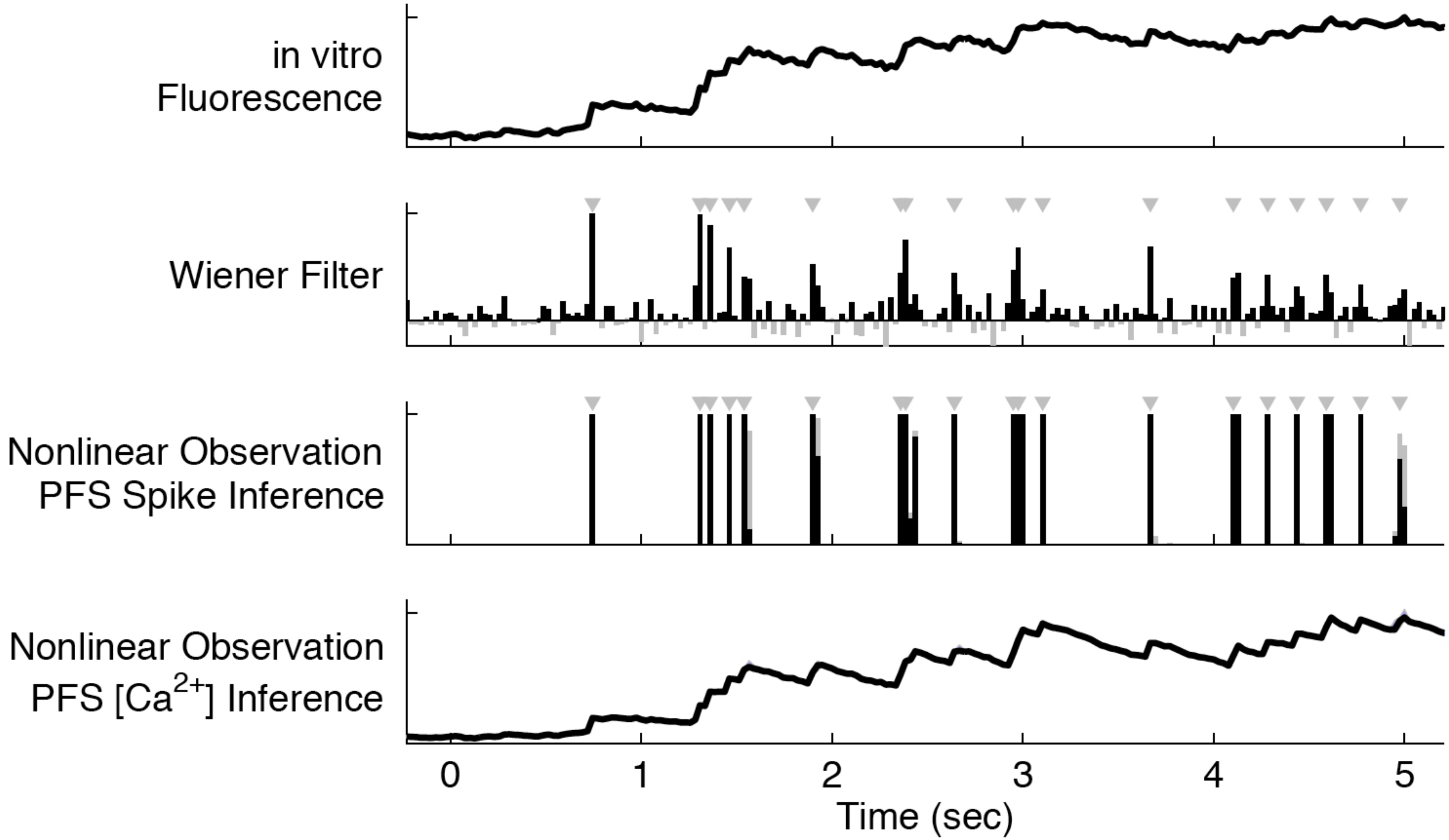
Example: inferring spike times from slow, noisy calcium data

$$C_{t+dt} = C_t - dtC_t/\tau + N_t; \;\; N_t > 0; \;\; y_t = C_t + \epsilon_t$$



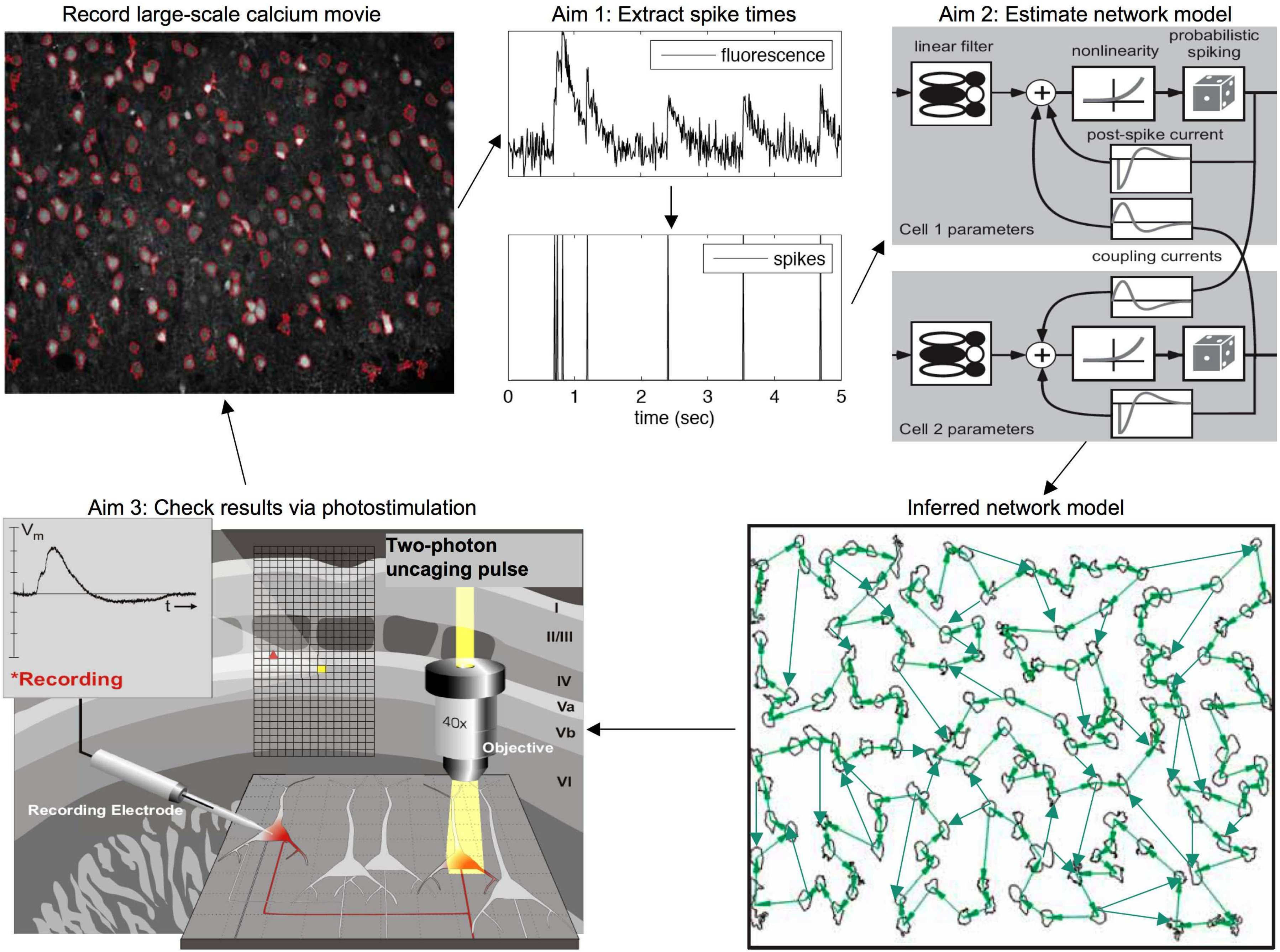
— nonnegative deconvolution is a recurring problem in signal processing (Vogelstein et al., 2008).

Particle filter can extract spikes from saturated recordings



(Vogelstein et al., 2009)

Next challenge: circuit inference



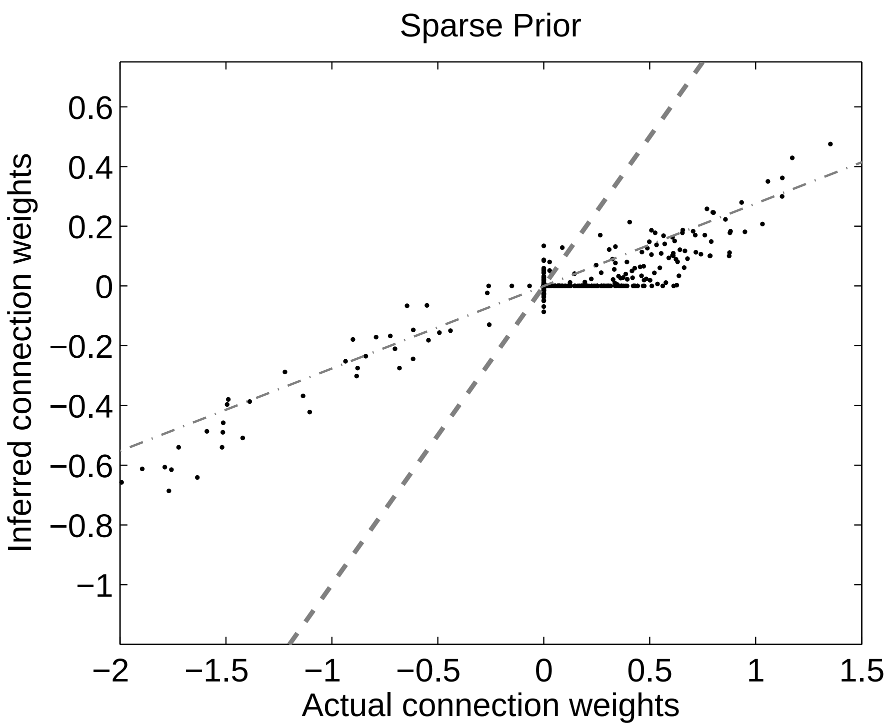
Monte Carlo EM approach

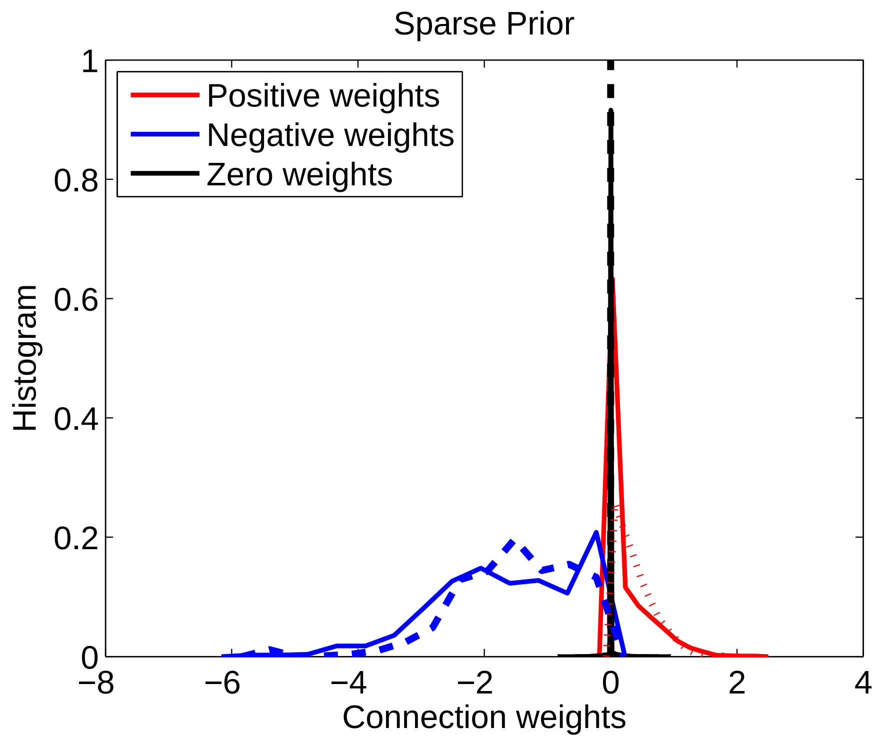
Given the spike times in the network, L_1-penalized likelihood optimization is easy. But we only have noisy calcium observations Y; true spike times are hidden variables. Thus an EM approach is natural.

- E step: sample spike train responses R from $p(R|Y, \theta)$
- 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 (Neal et al., 2003).

Simulated circuit inference





— Connections are inferred with the correct sign in conductance-based integrate-and-fire networks with biologically plausible connectivity matrices (Mishchencko et al., 2009).

Good news: connections are inferred with the correct sign. But process is slow; current work focusing on improved sampling methods (exploiting hybrid forward-backward blockwise-Gibbs approach).

Optimal control of spike timing

Optimal experimental design and neural prosthetics applications require us to perturb the network at will. How can we make a neuron exactly fire when we want it to?

Assume bounded inputs; otherwise problem is trivial.

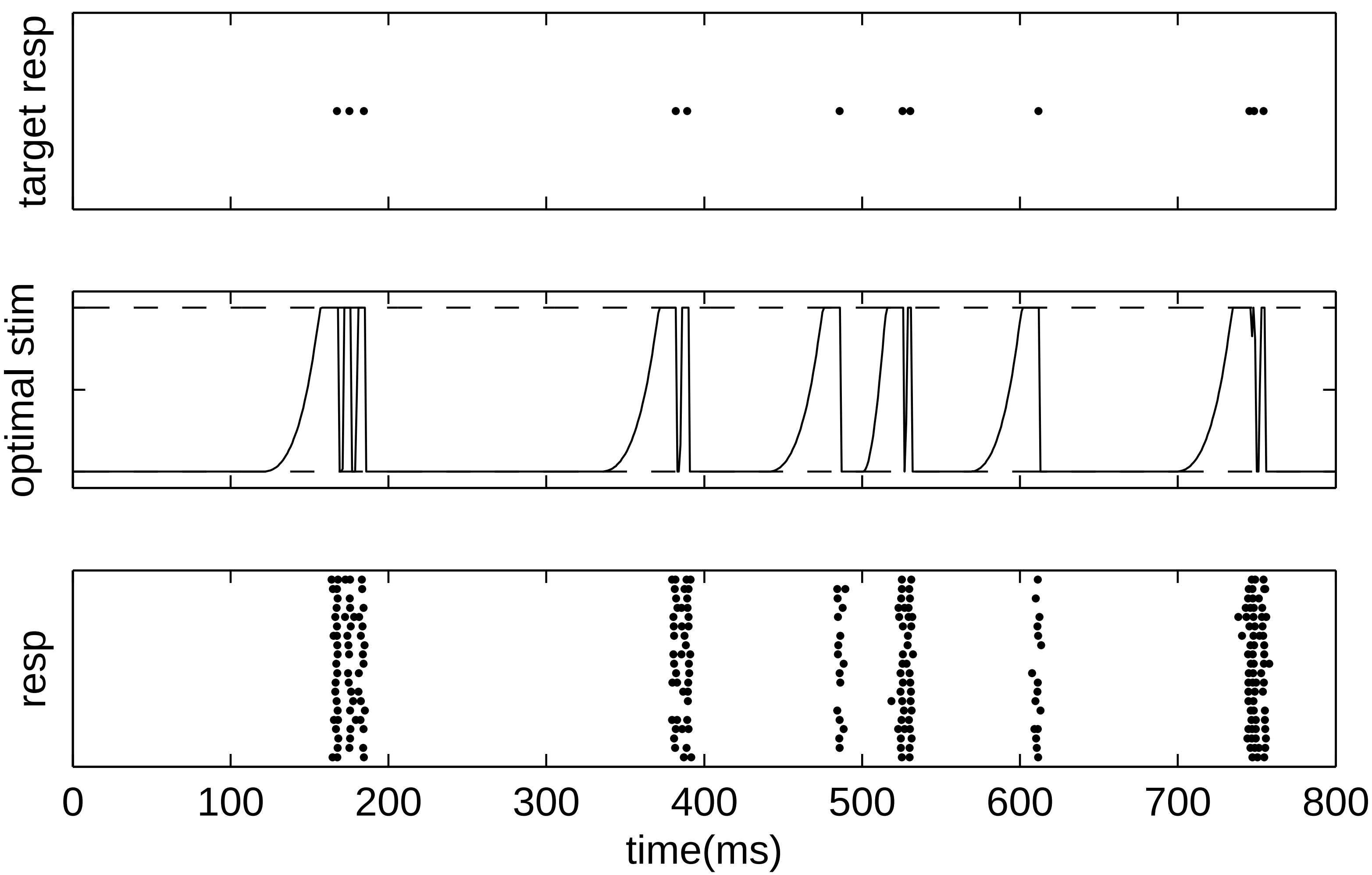
Start with a simple model:

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

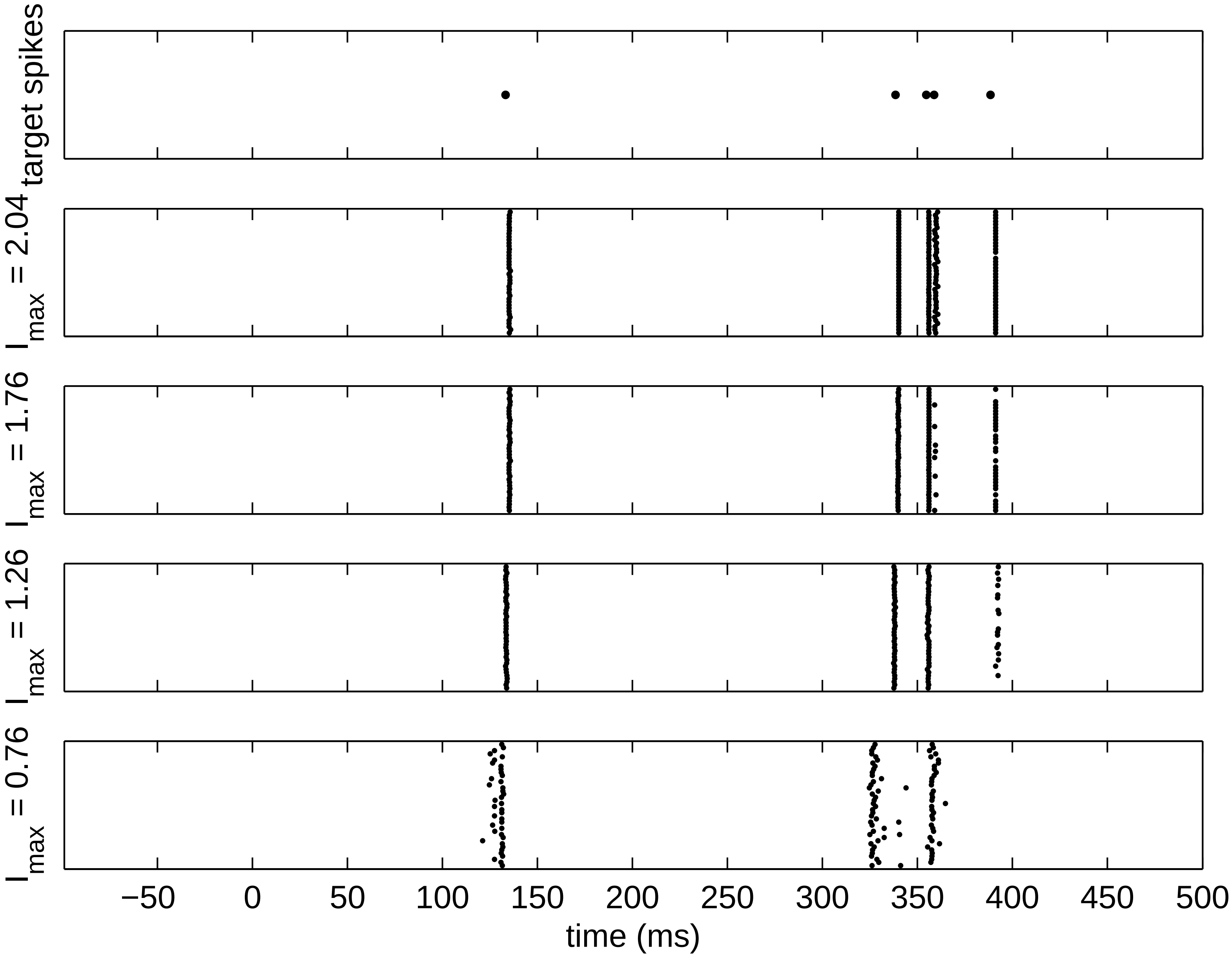
Now we can just optimize the likelihood of the desired spike train, as a function of the input I_t, with I_t bounded.

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

Simulated electrical control of spike timing



Example: intracellular control of spike timing

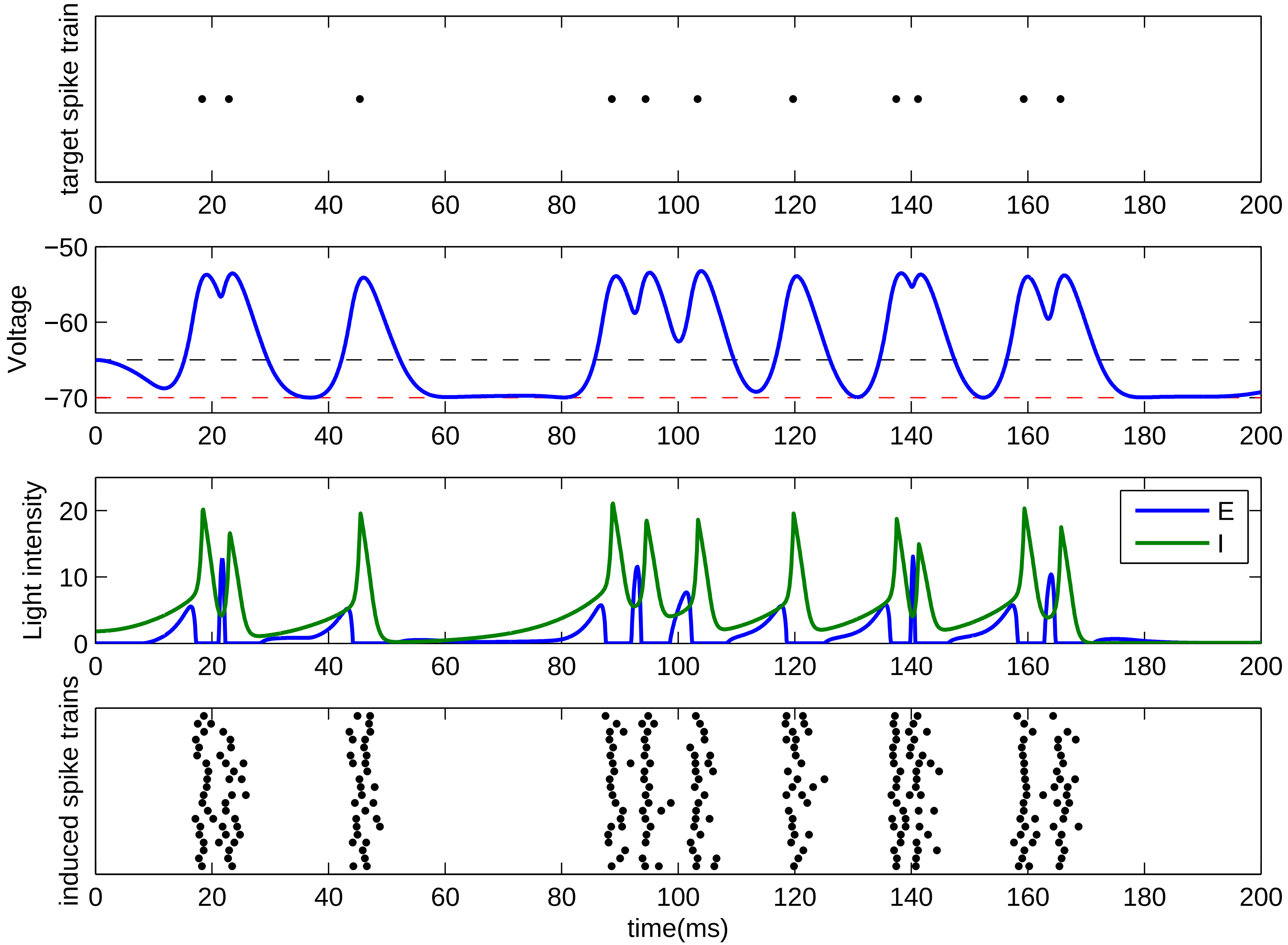


(Ahmadian et al 2010)

Optical conductance-based control of spiking

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

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



One last extension: two-d smoothing

Estimation of two-d firing rate surfaces comes up in a number of examples:

- place fields / grid cells
- post-fitting in spike-triggered covariance analysis
- tracking of non-stationary (time-varying) tuning curves
- "inhomogeneous Markov interval" models for spike-history dependence

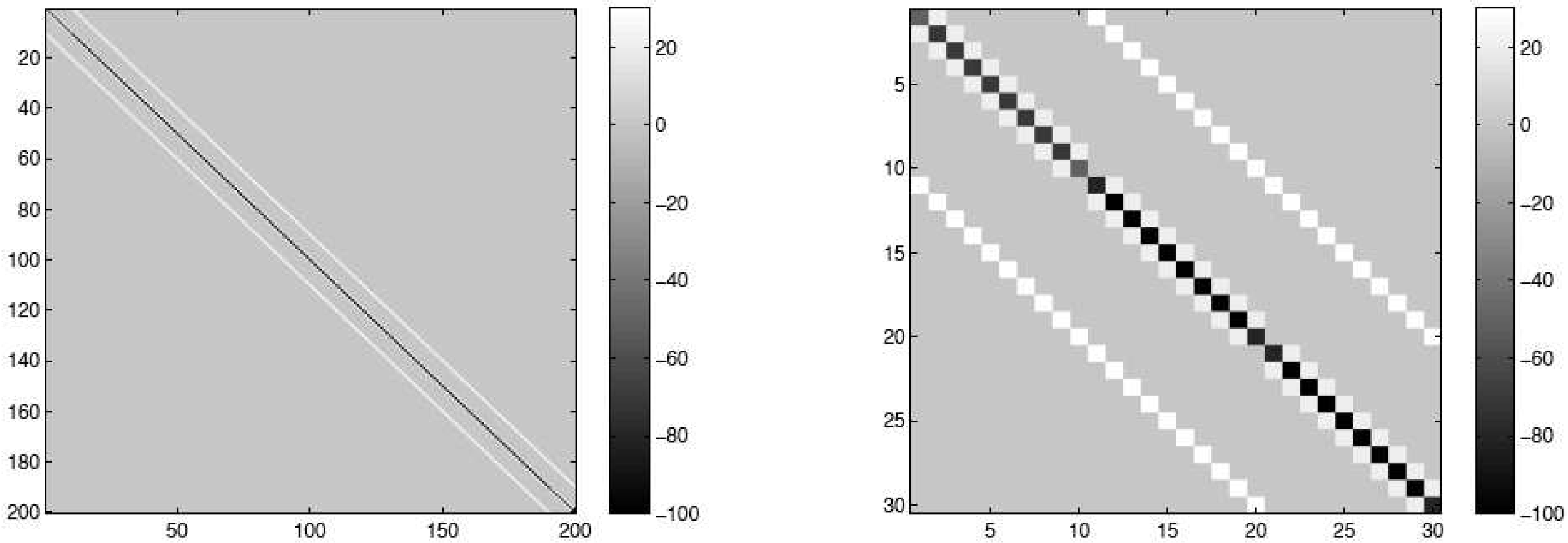
How to generalize fast 1-d state-space methods to 2-d case? Idea: use Gaussian process priors which are carefully selected to give banded Hessians.

Model: hidden variable Q is a random surface with a Gaussian prior:
$Q \sim \mathcal{N}(\mu, C)$;

Spikes are generated by a point process whose rate is a function of Q:
$\lambda(\vec{x}) = f[Q(\vec{x})]$ (easy to incorporate additional effects here, e.g. spike history)

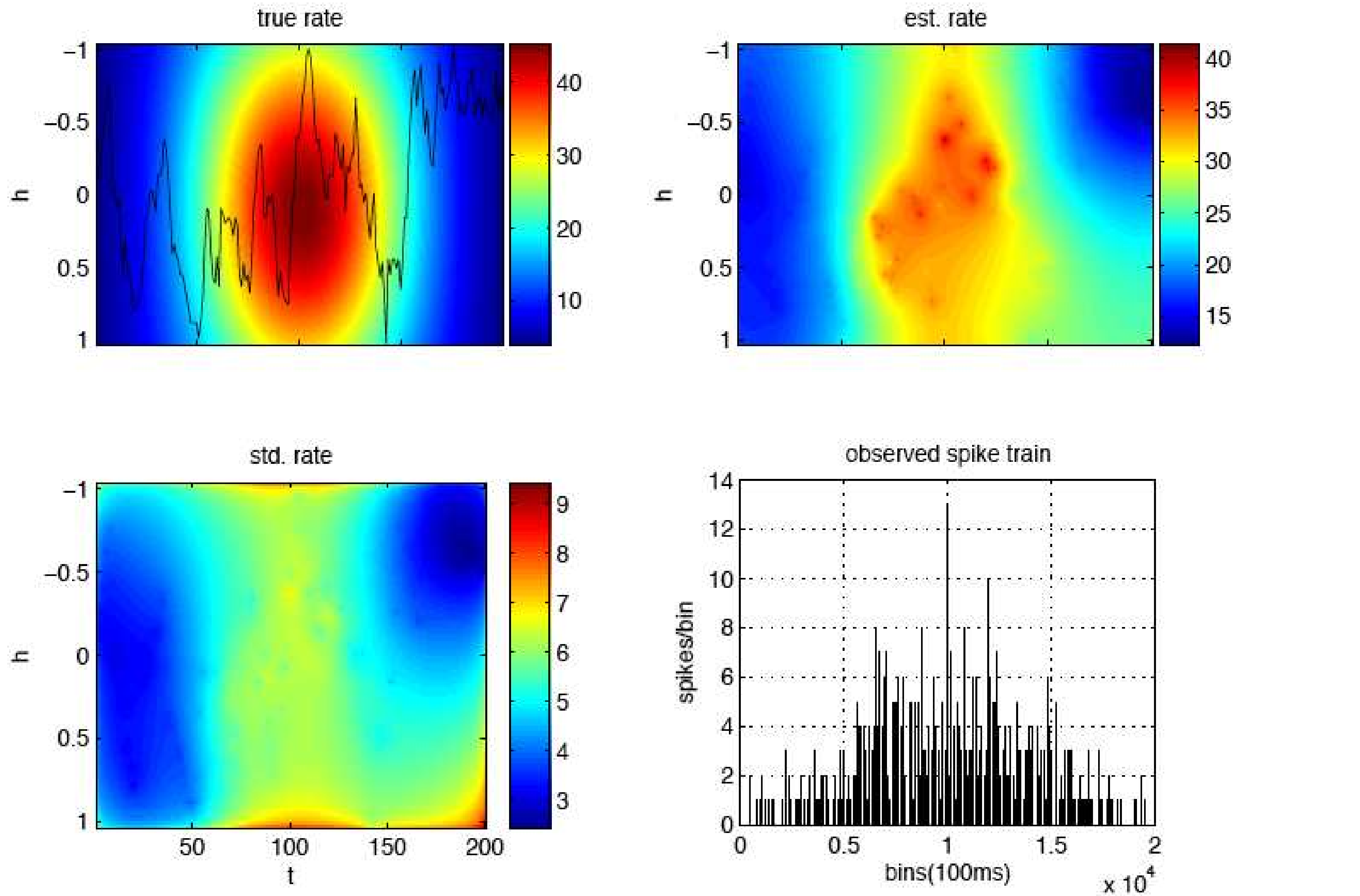
Now the Hessian of the log-posterior of Q is $C^{-1} + D$, where D is diagonal (Cunningham et al., 2007). For Newton, we need to solve $(C^{-1} + D)Q_{dir} = \nabla$.

Example: nearest-neighbor smoothing prior



For prior covariance C such that C^{-1} contains only neighbor potentials, we can solve $(C^{-1} + D)Q_{dir} = \nabla$ in $O(\dim(Q)^{1.5})$ time using direct methods ("approximate minimum degree" algorithm — built-in to Matlab sparse $A\backslash b$ code) and potentially in $O(\dim(Q))$ time using multigrid (iterative) methods (Rahnama Rad and Paninski, 2009).

Estimating a time-varying tuning curve given a limited sample path



Conclusions

- GLM and state-space approaches provide flexible, powerful methods for answering key questions in neuroscience
- Close relationships between forward-backward methods familiar from state-space theory and banded matrices familiar from spline theory
- Log-concavity, banded matrix methods make computations very tractable

References

Brown, E., Frank, L., Tang, D., Quirk, M., and Wilson, M. (1998). A statistical paradigm for neural spike train decoding applied to position prediction from ensemble firing patterns of rat hippocampal place cells. *Journal of Neuroscience*, 18:7411–7425.

Cunningham, J., Yu, B., Shenoy, K., and Sahani, M. (2007). Inferring neural firing rates from spike trains using Gaussian processes. *NIPS*.

Djurisic, M., Antic, S., Chen, W. R., and Zecevic, D. (2004). Voltage imaging from dendrites of mitral cells: EPSP attenuation and spike trigger zones. *J. Neurosci.*, 24(30):6703–6714.

Huys, Q., Ahrens, M., and Paninski, L. (2006). Efficient estimation of detailed single-neuron models. *Journal of Neurophysiology*, 96:872–890.

Knopfel, T., Diez-Garcia, J., and Akemann, W. (2006). Optical probing of neuronal circuit dynamics: genetically encoded versus classical fluorescent sensors. *Trends in Neurosciences*, 29:160–166.

Neal, R., Beal, M., and Roweis, S. (2003). Inferring state sequences for non-linear systems with embedded hidden Markov models. *NIPS*, 16.

Paninski, L. (2006). The most likely voltage path and large deviations approximations for integrate-and-fire neurons. *Journal of Computational Neuroscience*, 21:71–87.

Paninski, L. (2009a). Fast Kalman filtering on dendritic trees. *In progress*.

Paninski, L. (2009b). Inferring synaptic inputs given a noisy voltage trace via sequential Monte Carlo methods. *Journal of Computational Neuroscience*, Under review.

Paninski, L., Ahmadian, Y., Ferreira, D., Koyama, S., Rahnama, K., Vidne, M., Vogelstein, J., and Wu, W. (2009). A new look at state-space models for neural data. *Journal of Computational Neuroscience*, In press.

Paninski, L. and Ferreira, D. (2008). State-space methods for inferring synaptic inputs and weights. *COSYNE*.

Rahnama Rad, K. and Paninski, L. (2009). Efficient estimation of two-dimensional firing rate surfaces via Gaussian process methods. *Under review*.

Vogelstein, J., Babadi, B., Watson, B., Yuste, R., and Paninski, L. (2008). Fast nonnegative deconvolution via tridiagonal interior-point methods, applied to calcium fluorescence data. *Statistical analysis of neural data (SAND) conference*.

Vogelstein, J., Watson, B., Packer, A., Jedynak, B., Yuste, R., and Paninski, L. (2009). Model-based optimal inference of spike times and calcium dynamics given noisy and intermittent calcium-fluorescence imaging. *Biophysical Journal*, In press; http://www.stat.columbia.edu/~liam/research/abstracts/vogelstein-bj08-abs.html.