Statistical challenges and opportunities in neural data analysis

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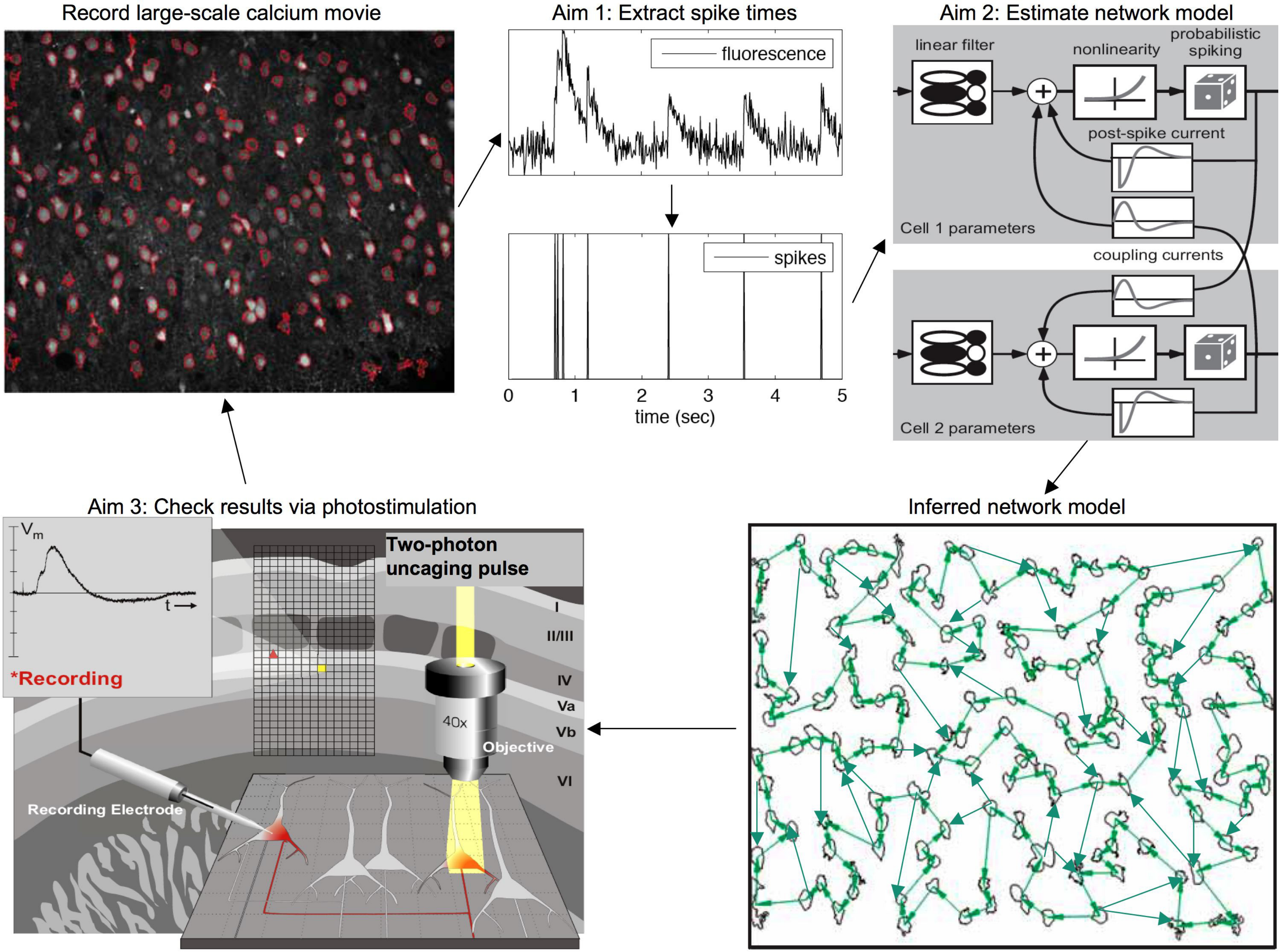
A golden age of statistical neuroscience

Some notable recent developments:

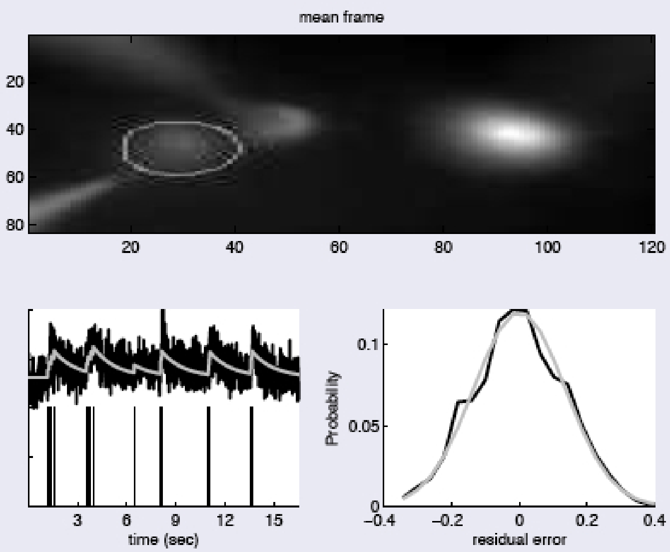
- machine learning / statistics / optimization methods for extracting information from high-dimensional data in a computationally-tractable, systematic fashion
- computing (Moore's law, massive parallel computing)
- optical and optogenetic methods for recording from and perturbing neuronal populations, at multiple scales
- large-scale, high-density multielectrode recordings
- growing acceptance that many fundamental neuroscience questions are in fact statistics questions in disguise

Circuit inference via optical methods

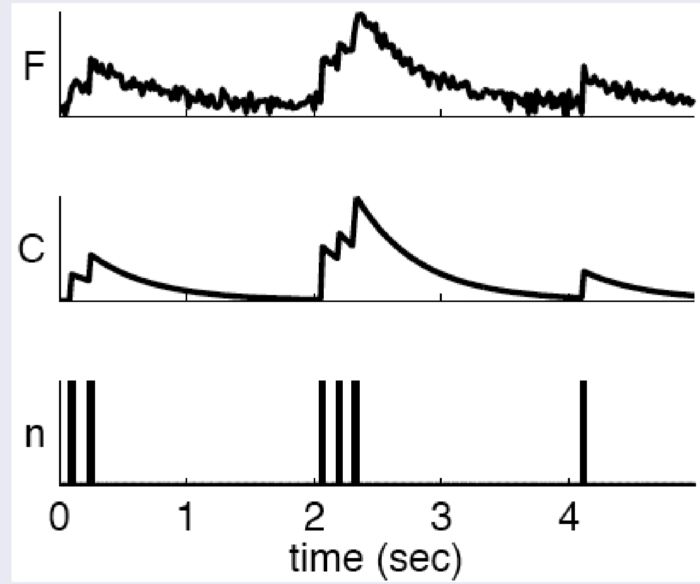


Aim 1: Model-based estimation of spike rates

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.

Fast maximum a posteriori (MAP) estimation

Start by writing out the posterior:

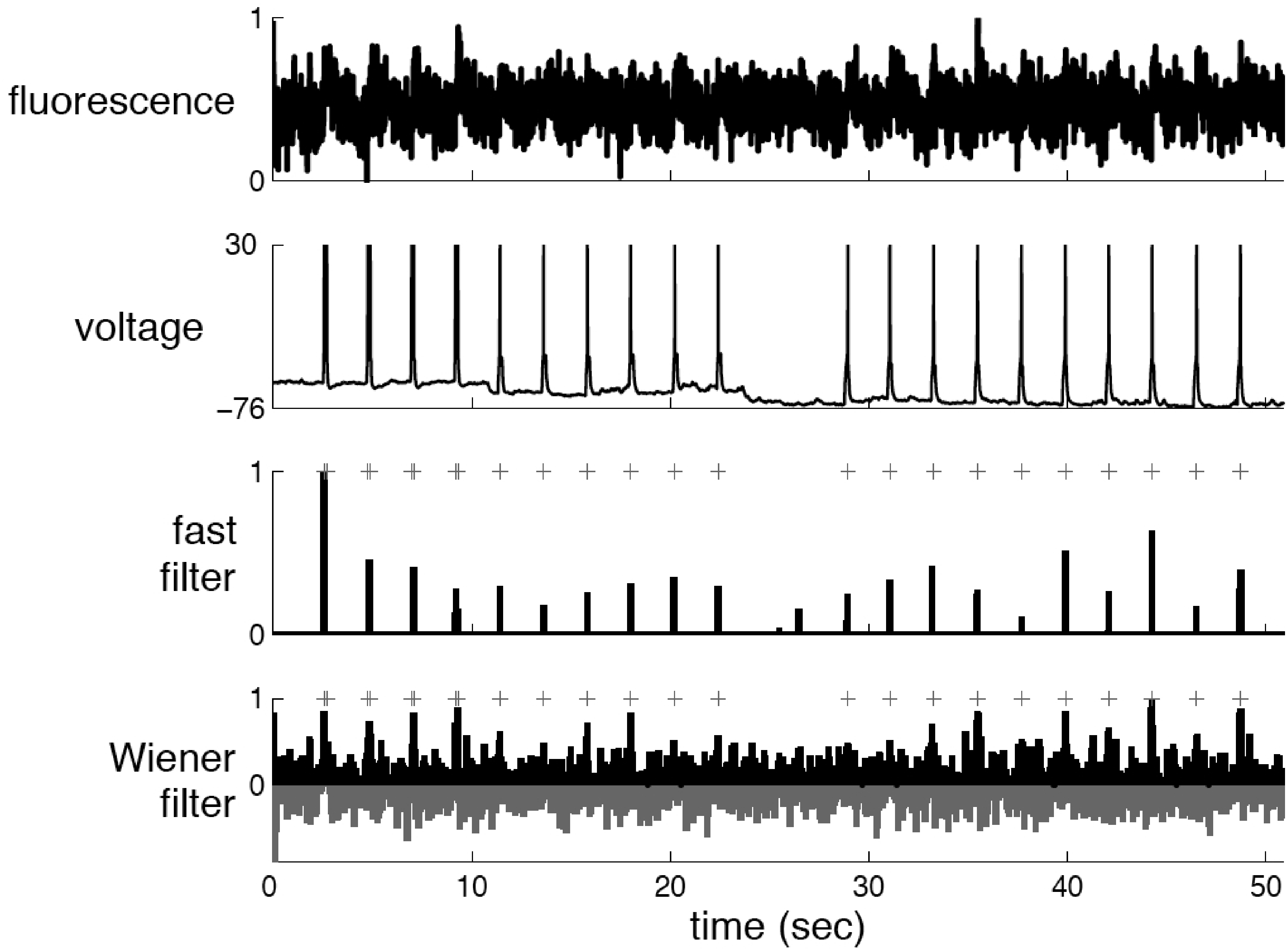
$$\begin{aligned}\log p(C|F) &= \log p(C) + \log p(F|C) + const. \\ &= \sum_t \log p(C_{t+1}|C_t) + \sum_t \log p(F_t|C_t) + const.\end{aligned}$$

Three basic observations:

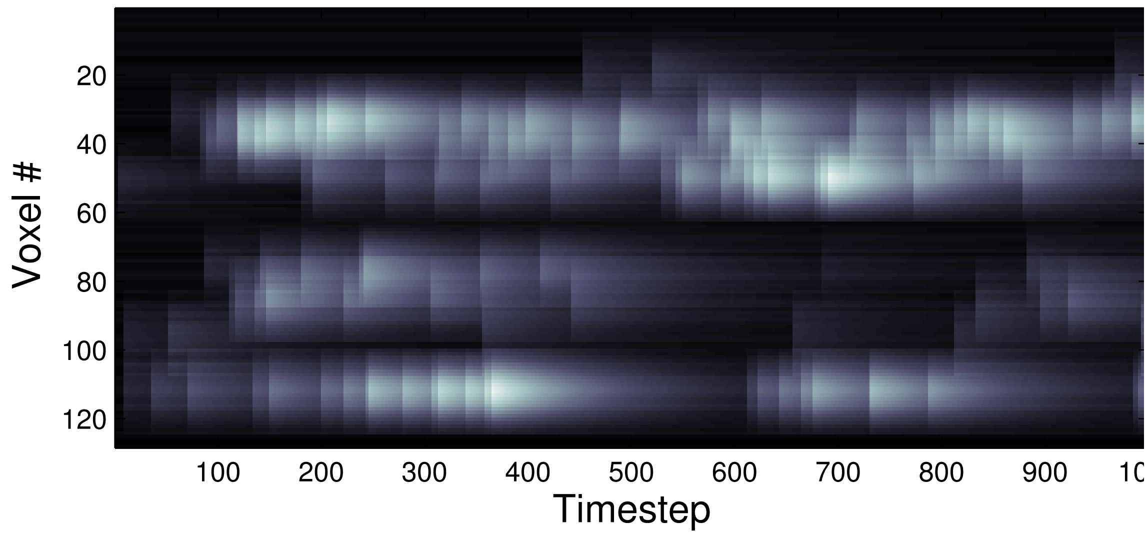
- If $\log p(C_{t+1}|C_t)$ and $\log p(F_t|C_t)$ are concave, then so is $\log p(C|F)$.
- Hessian H of $\log p(C|F)$ is tridiagonal: $\log p(F_t|C_t)$ contributes a diag term, and $\log p(C_{t+1}|C_t)$ contributes a tridiag term (Paninski et al., 2010).
- C is a linear function of n.

Newton's method: iteratively solve $HC_{dir} = \nabla$. Tridiagonal solver requires $O(T)$ time. Can include nonneg constraint $n_t \geq 0$ via log-barrier (Koyama and Paninski, 2010) — real-time deconvolution (Vogelstein et al., 2010).

Example: nonnegative MAP filtering



Multineuronal case: spatiotemporal demixing



Model:

$$
\begin{aligned}
Y &= C + \epsilon \\
C(x,t) &= \sum_{i=1}^{r} s_i(x) f_i(t) \\
f_i(t+dt) &= \left(1 - \frac{dt}{\tau_i}\right) f_i(t) + n_i(t)
\end{aligned}
$$

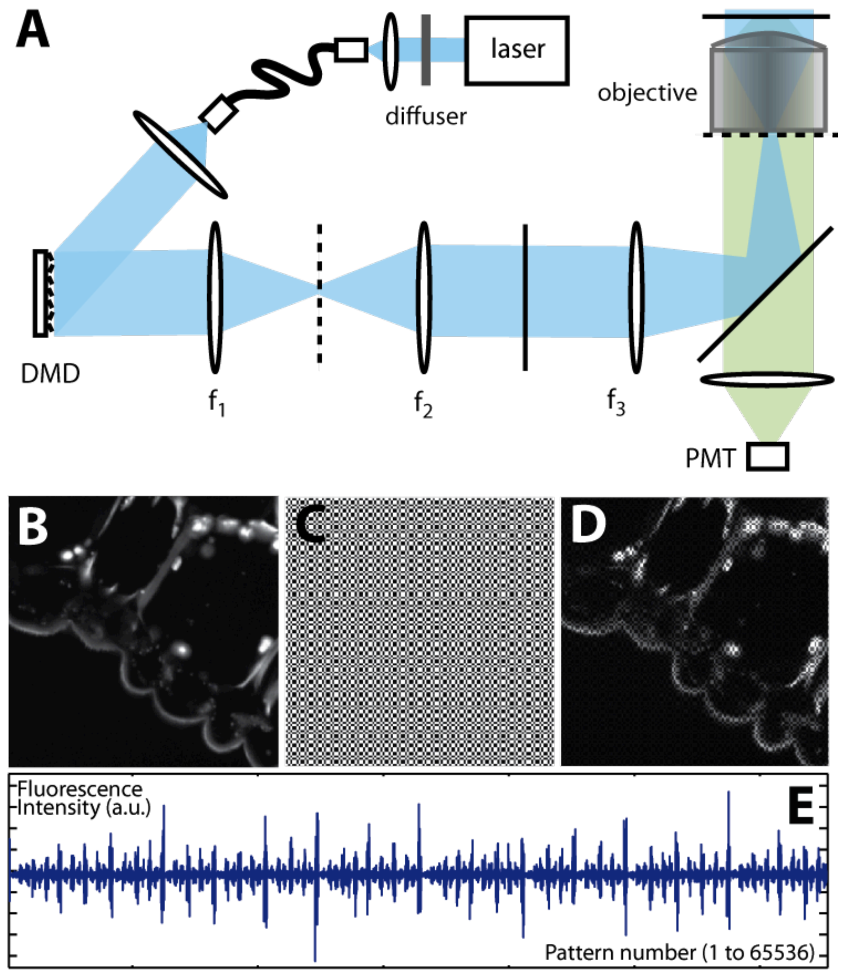
Goal: infer low-rank matrix C from noisy Y. Rank r = number of visible neurons

Additional structure: jumps in $f_i(t)$ are non-negative

Locally rank-penalized convex optimization with nonnegativity constraints to infer C, followed by iterative matrix factorization under nonnegativity constraints to infer $s_i(x), f_i(t)$ (Pnevmatikakis et al, 2013). Examples: Machado, Lacefield, Shababo

Compressed sensing imaging

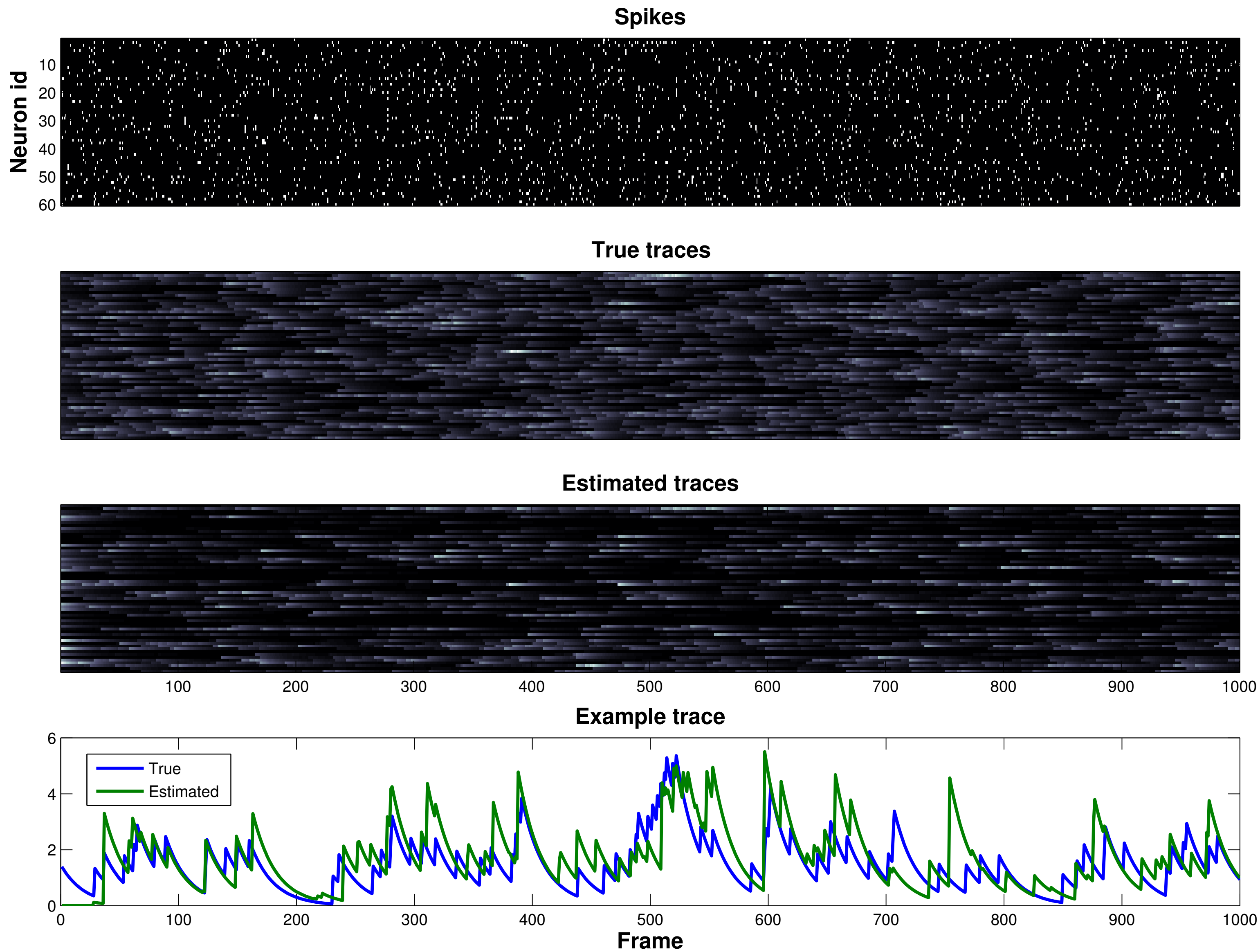
Idea: instead of raster scans, take randomized projections in each frame.



(from Studer et al, 2011)

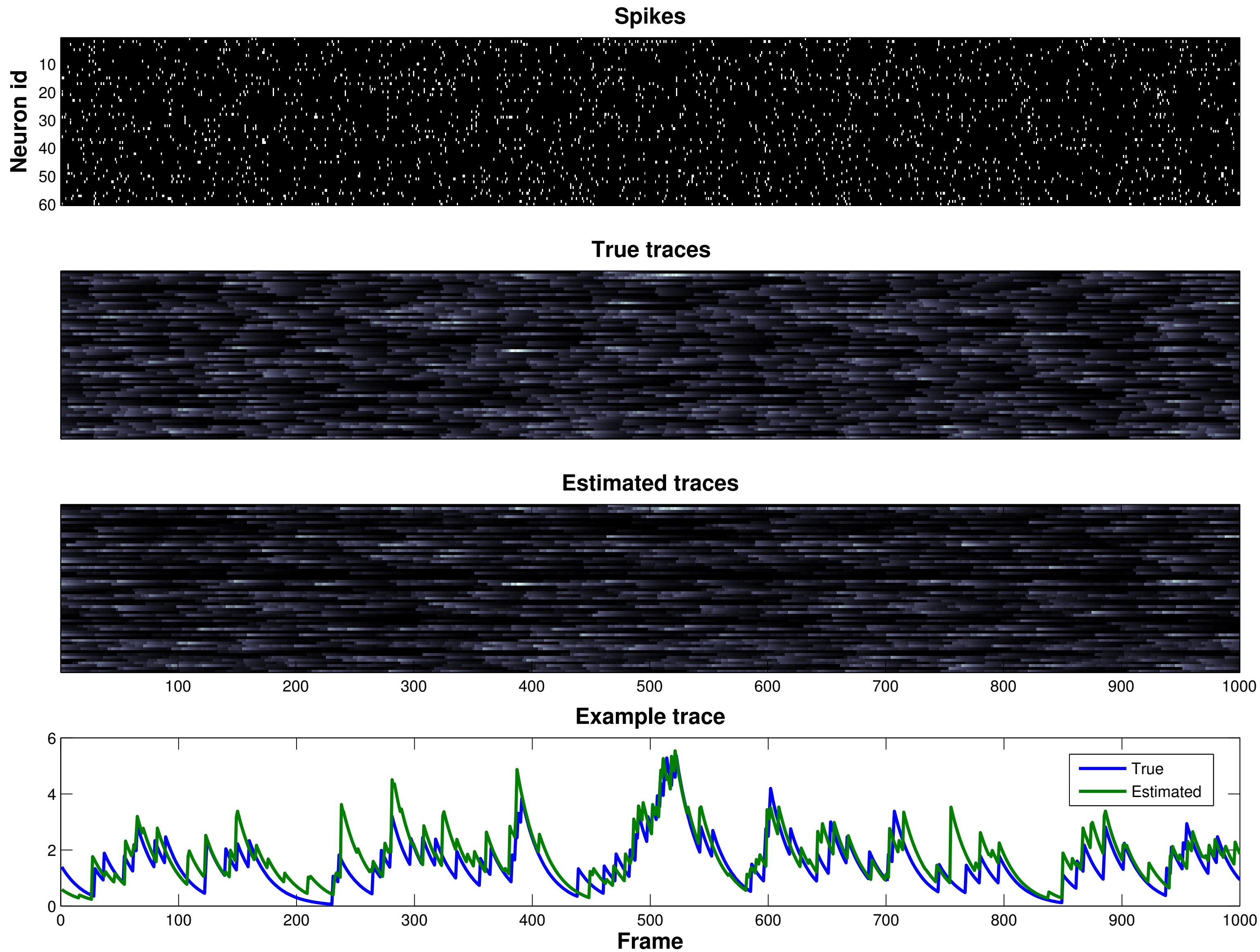
Estimating C given randomized projections Y can be cast as a similar convex optimization.

Compressed sensing imaging



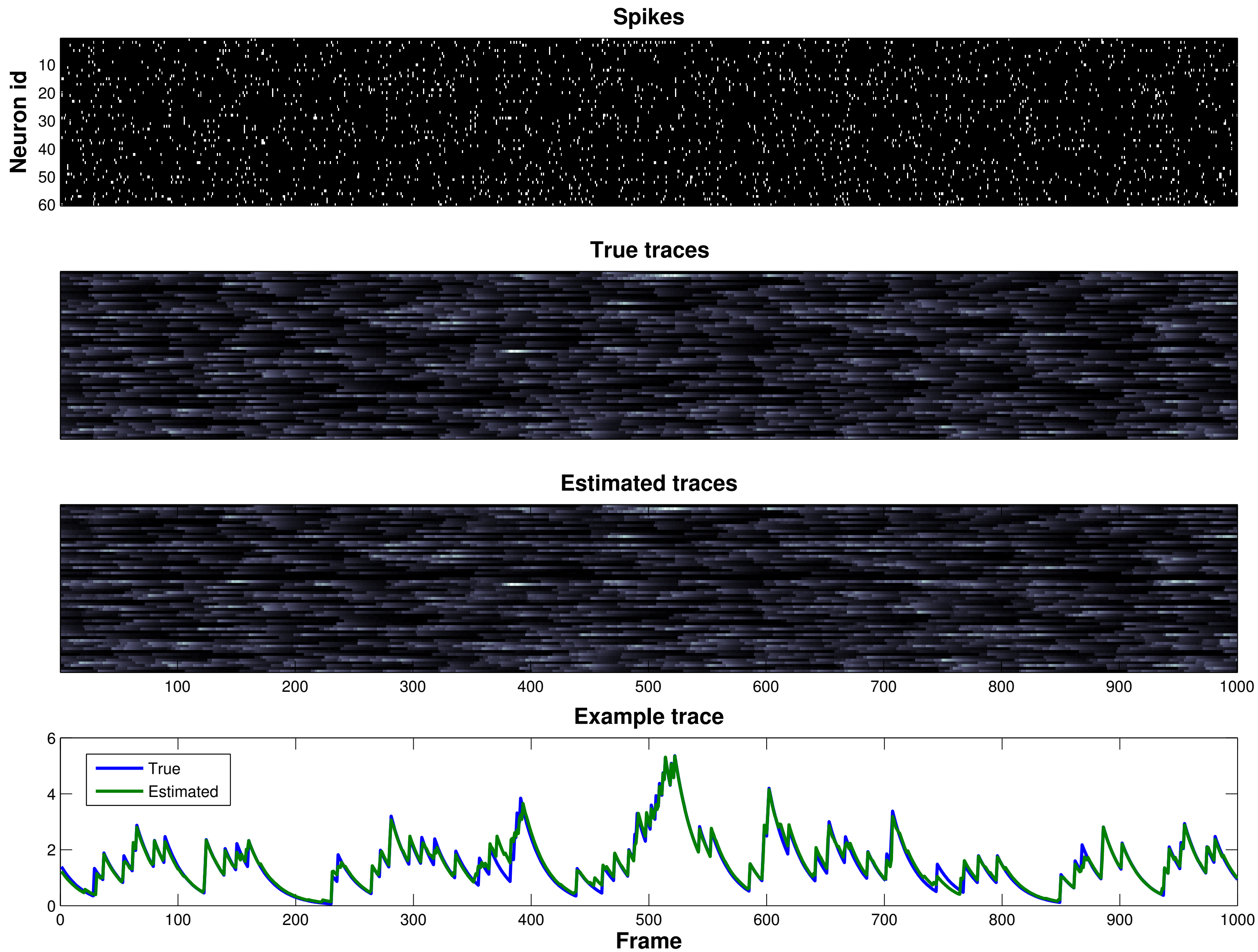
2 measurements per timestep (30x undersampling); Pnevmatikakis et al (2013)

Compressed sensing imaging



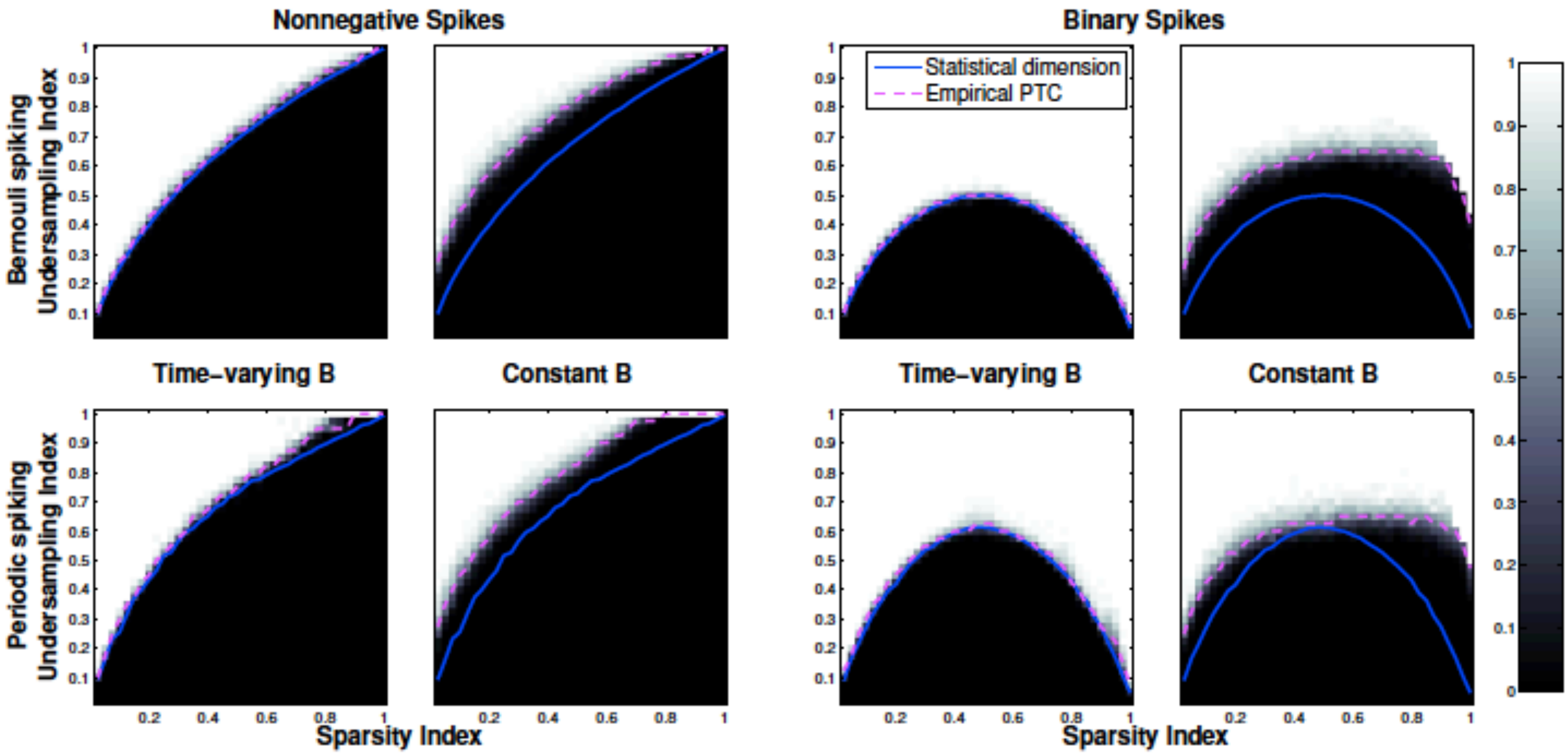
4 measurements per timestep (15x undersampling); Pnevmatikakis et al (2013)

Compressed sensing imaging



8 measurements per timestep (7.5x undersampling); Pnevmatikakis et al (2013)

Phase transitions in decoding accuracy



New tool: "statistical dimension" (Amelunxen, Lotz, McCoy, Tropp '13).

Interesting feature of this problem: phase transition depends on pattern of spikes, not just sparsity (as in standard LASSO problem).

Fully Bayesian approaches

Can we sample over $\{n_i(t)\}$ instead? In general, challenging: high-dimensional binary vector; not much structure to exploit.

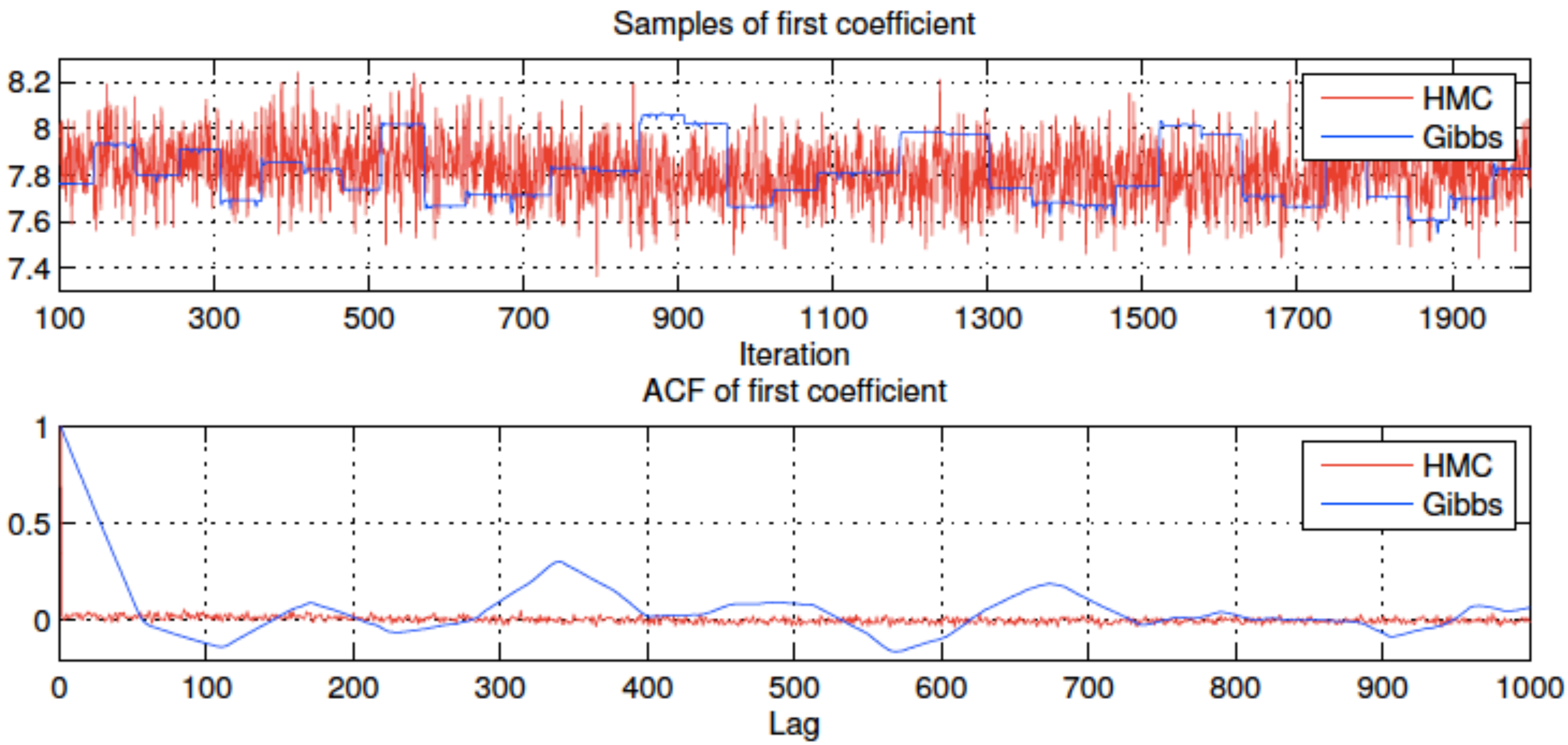
Currently exploring Hamiltonian Monte Carlo (HMC) methods.

Two tricks:

- Piecewise log-quadratic (PLQ) densities (e.g., truncated multivariate normals) are easy to sample from using exact integration of Hamiltonian dynamics - no step-size parameter needed (Pakman and Paninski, '13a). Can use similar $O(T)$ tricks as before.

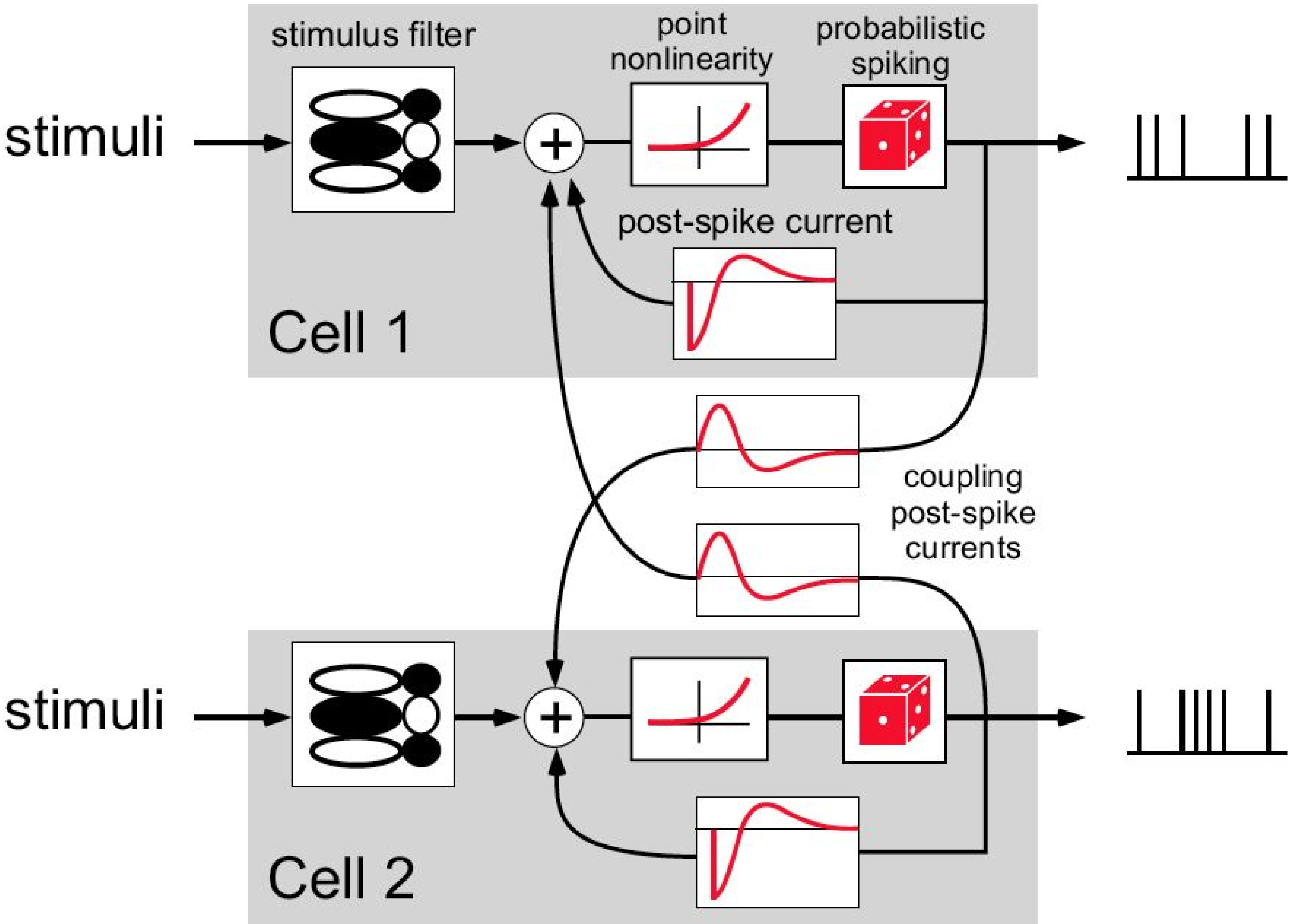
- Arbitrary binary vectors or spike-and-slab posteriors can be embedded in a PLQ density via simple augmented-variable approach (Pakman and Paninski, '13b)

Exact HMC truncated spike-and-slab sampling



(Pakman and Paninski '13b)

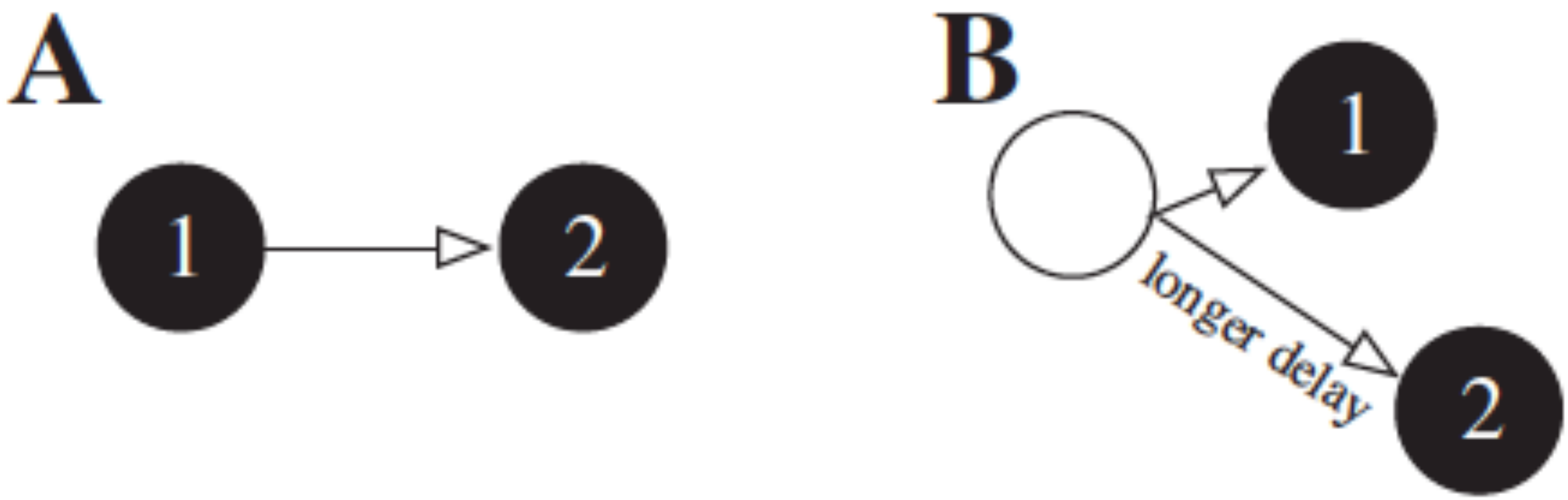
Aim 2: estimating network connectivity



Coupled GLM structure; concave loglikelihoods, optimization is straightforward (Paninski, 2004; Pillow et al., 2008).

The dreaded common input problem

How to distinguish direct connectivity from common input?



(from Nykamp '07)

Previous work (e.g., Vidne et al, 2012) modeled common input terms explicitly as latent variables; works well given enough a priori information, but not a general solution.

A "shotgun sampling" approach

We can only observe K cells at a time.

Idea: don't observe the same subset of K cells throughout the experiment.

Instead, observe as many different K-subsets as possible.

Hard with multi-electrode arrays; easy with imaging approaches.

Statistics problem: how to patch together all of the estimated subnetworks?

Want to integrate over $\{n_i(t)\}$, but scaling to large networks is a big challenge.

Approximate sufficient statistics in large Poisson regressions

Model:

$$n_{i,t} \sim Poiss(\lambda_{i,t}), \quad \lambda_{i,t} = \exp(b_i + W_i n_{t-1})$$

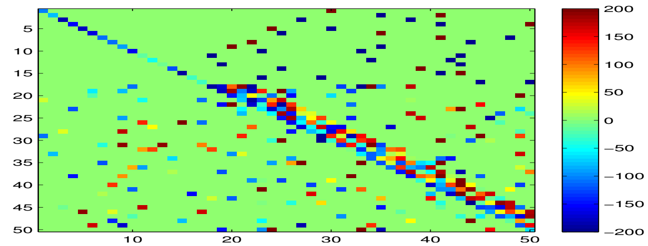
$$LL_i = \sum_t n_{i,t}(b_i + W_i n_{t-1}) - \sum_t \exp(b_i + W_i n_{t-1})$$

Idea: CLT approximation for second term. ($W_i n_{t-1}$ is a big sum; appeal to Diaconis-Freedman.)

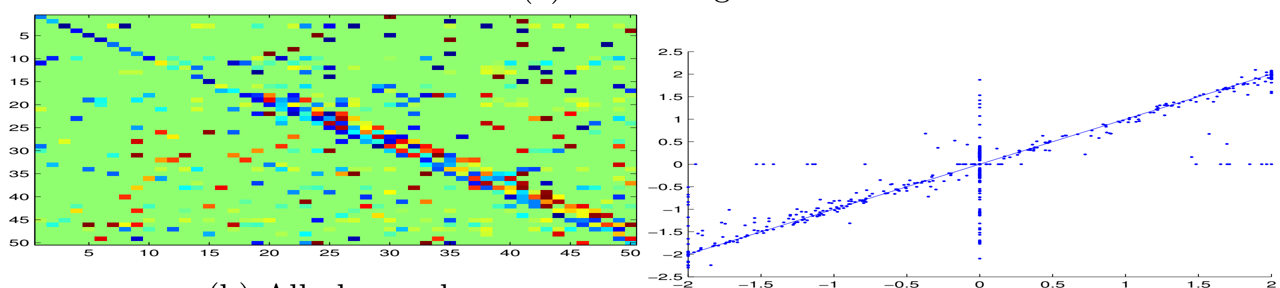
Dramatic simplification: profile approx log-likelihood is quadratic! (Ramirez and Paninski '13)

Approximate sufficient statistics: $E(n_t), E(n_t n_{t-1}^T)$. Can be estimated from just the observed data - no need to impute unobserved $\{n_{i,t}\}$.

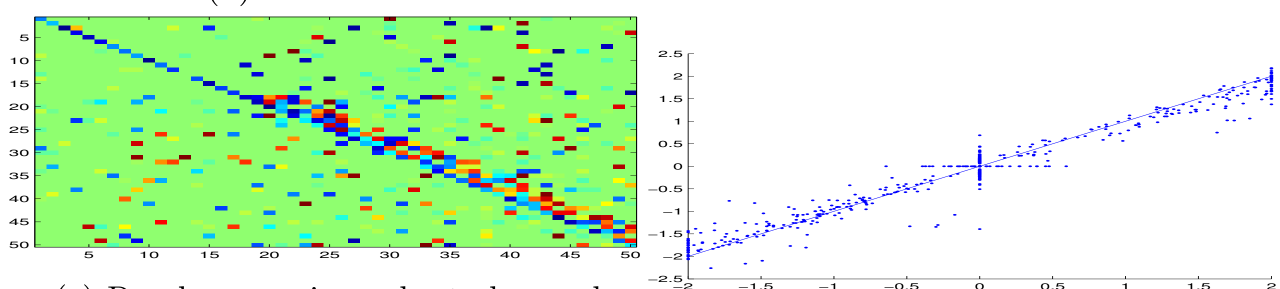
Simulated "shotgun" results



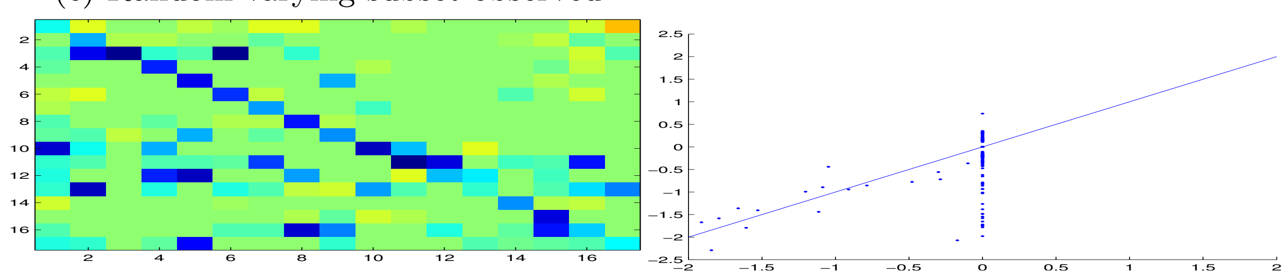
(a) True Weights



(b) All observed



(c) Random varying subset observed



(d) Fixed subset observed

$K = 20\%$ of network size; spike-and-slab priors (Keshri et al, 2013)

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.

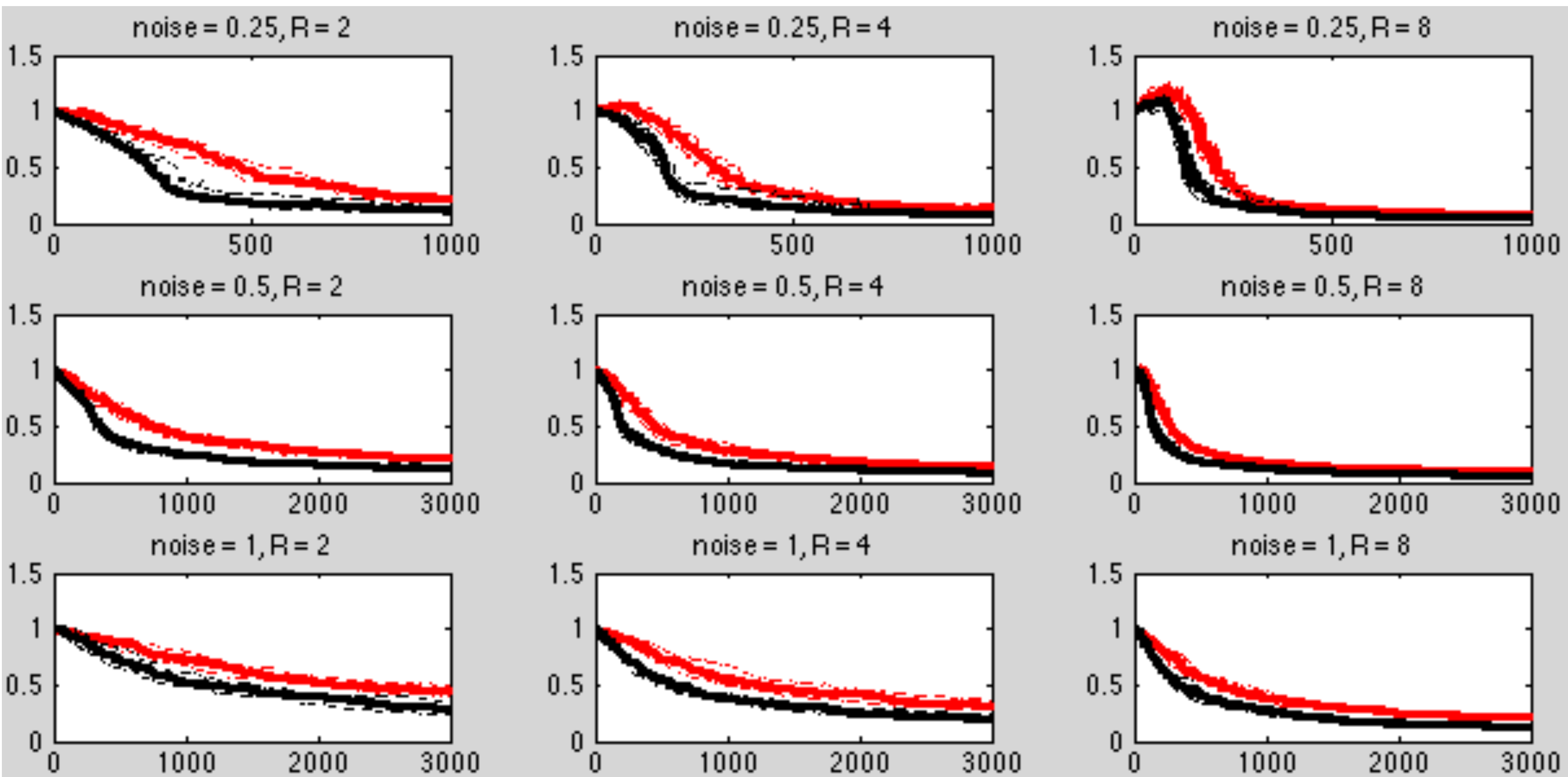
Concave objective function over convex set of possible inputs I_t + Hessian is tridiagonal $\implies$ $O(T)$ optimization.

— again, can be done in real time (Ahmadian et al., 2011)... though some open challenges when I_t is high-d, spatiotemporal

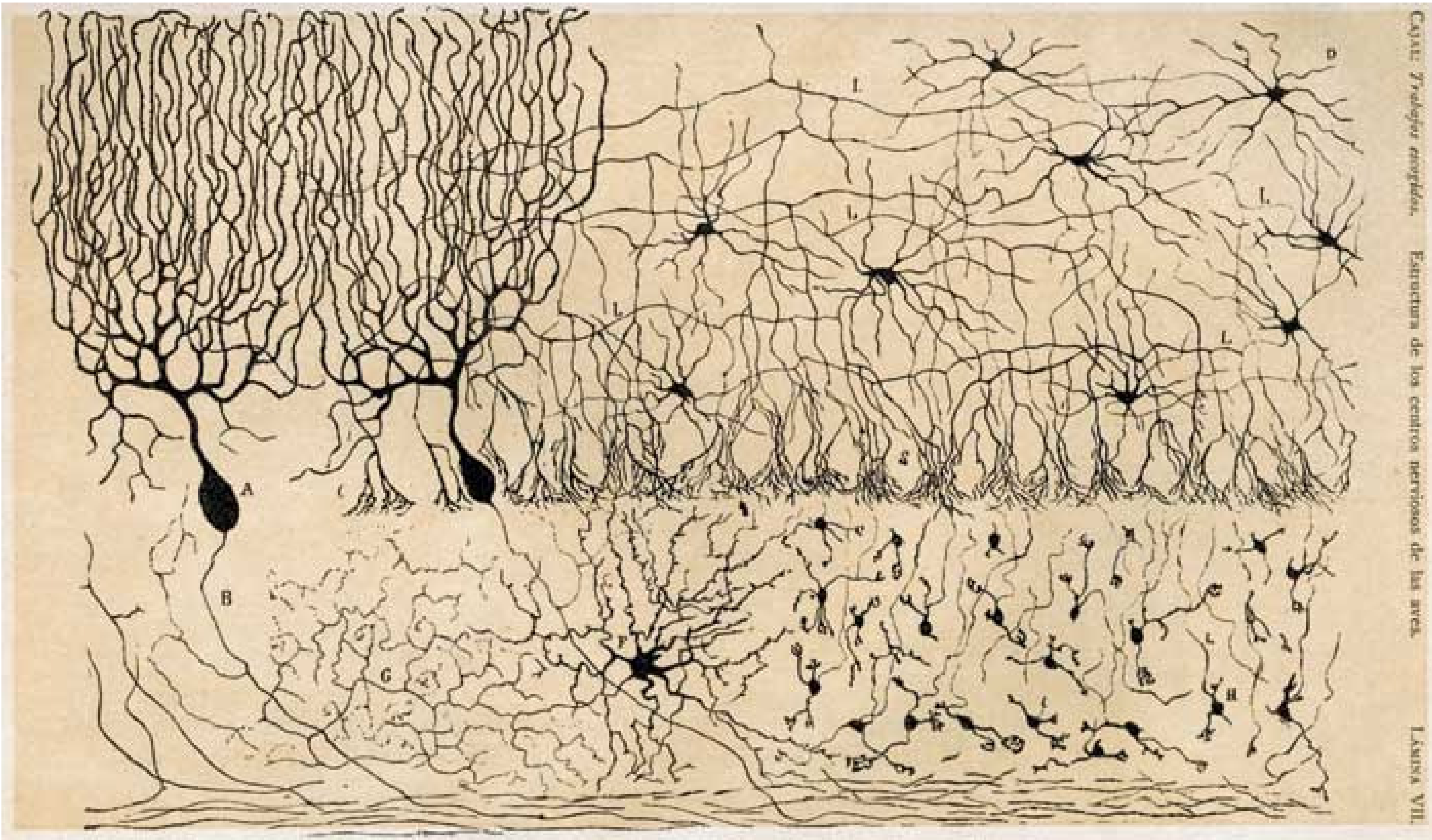
Applications

- sensory prosthetics, e.g. retinal prosthetics

- online adaptive experimental design: choose stimuli which provide as much information about network as possible. Major problem here: updating sparse posteriors. Factorized approximations to spike-and-slab posteriors are effective in this problem (Shababo, Paige et al, '13)



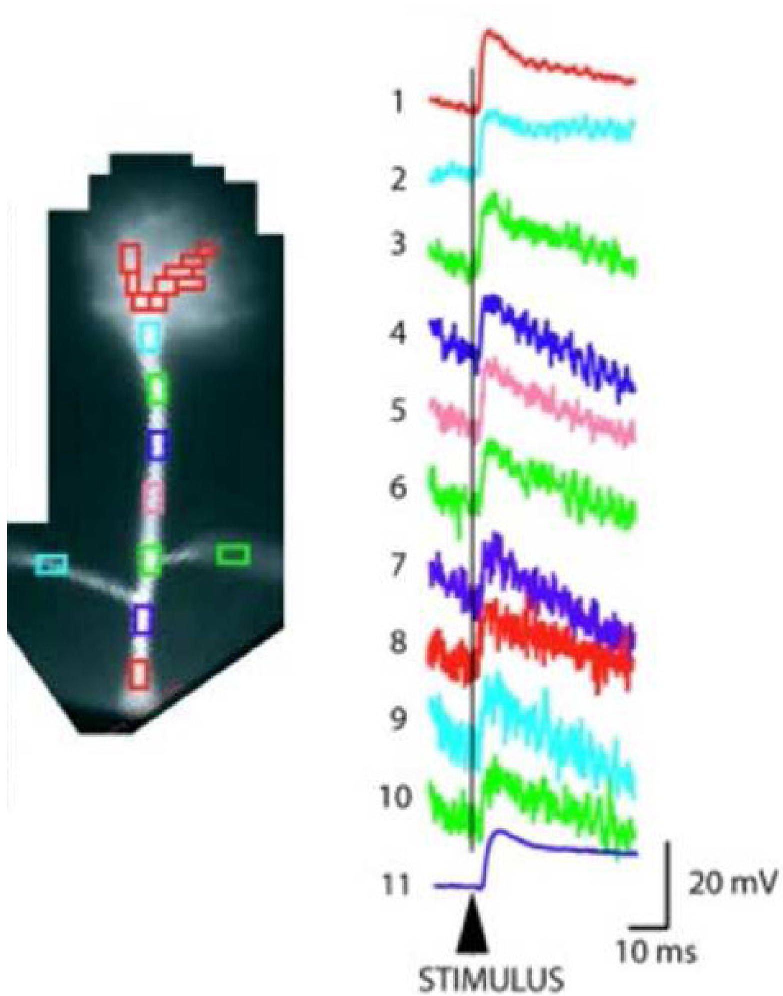
Extension: Connectivity at the dendritic scale



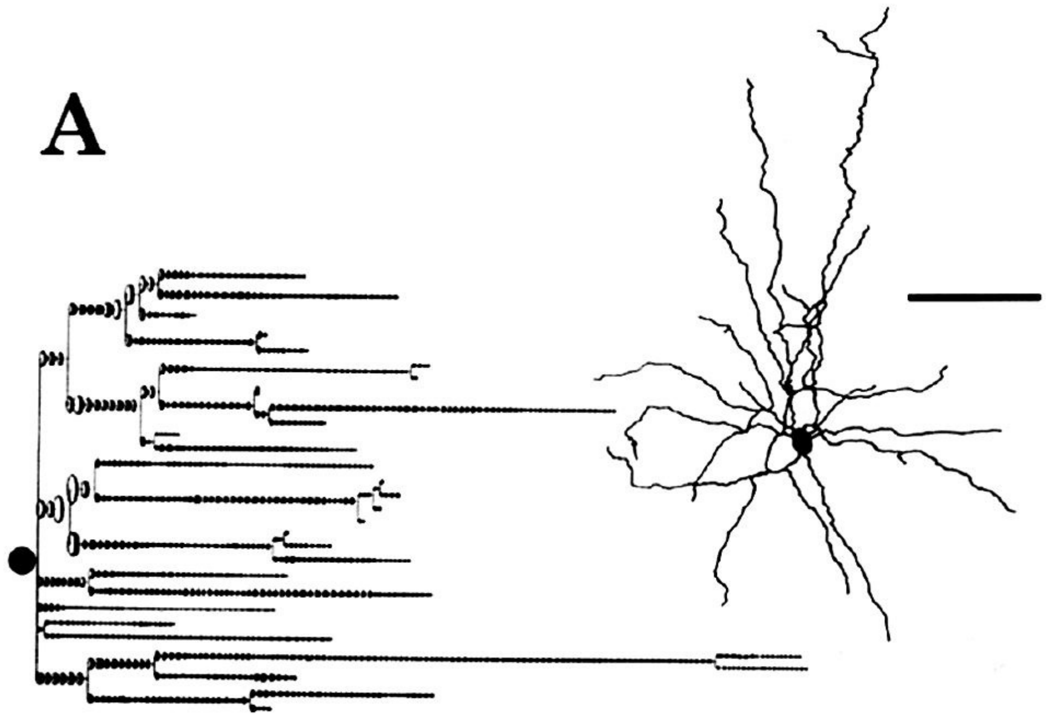
Ramon y Cajal, 1888.

The filtering problem

Spatiotemporal imaging data opens an exciting window on the computations performed by single neurons, but we have to deal with noise and intermittent observations.



Basic paradigm: compartmental models



- write neuronal dynamics in terms of equivalent nonlinear, time-varying RC circuits
- leads to a coupled system of stochastic differential equations

Simplest case: Kalman filter

Dynamics and observation equations:

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

$$\vec{y}_t = B_t\vec{V} + \vec{\eta}_t$$

$V_i(t)$ = voltage at compartment i

A = cable dynamics matrix: includes leak terms ($A_{ii} = -g_l$) and intercompartmental terms ($A_{ij} = 0$ unless compartments are adjacent)

B_t = observation matrix: point-spread function of microscope

Even this case is challenging, since $d = \dim(\vec{V})$ is very large

Standard Kalman filter: $O(d^3)$ computation per timestep (matrix inversion)

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.

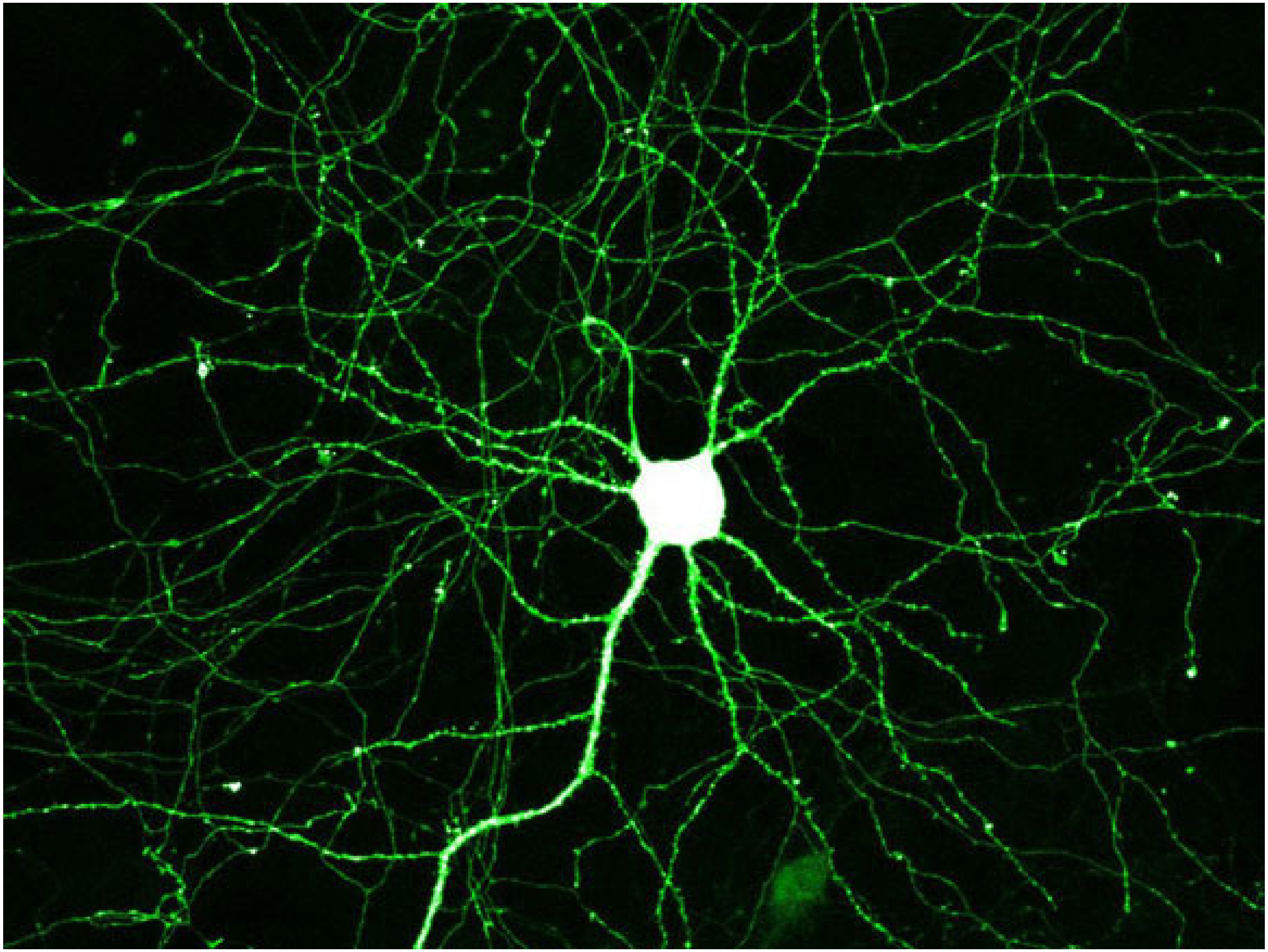
The necessary recursions — i.e., updating U_t, D_t and the Kalman mean $E(q_t|Y_{1:t})$ — involve linear manipulations of C_0, using

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

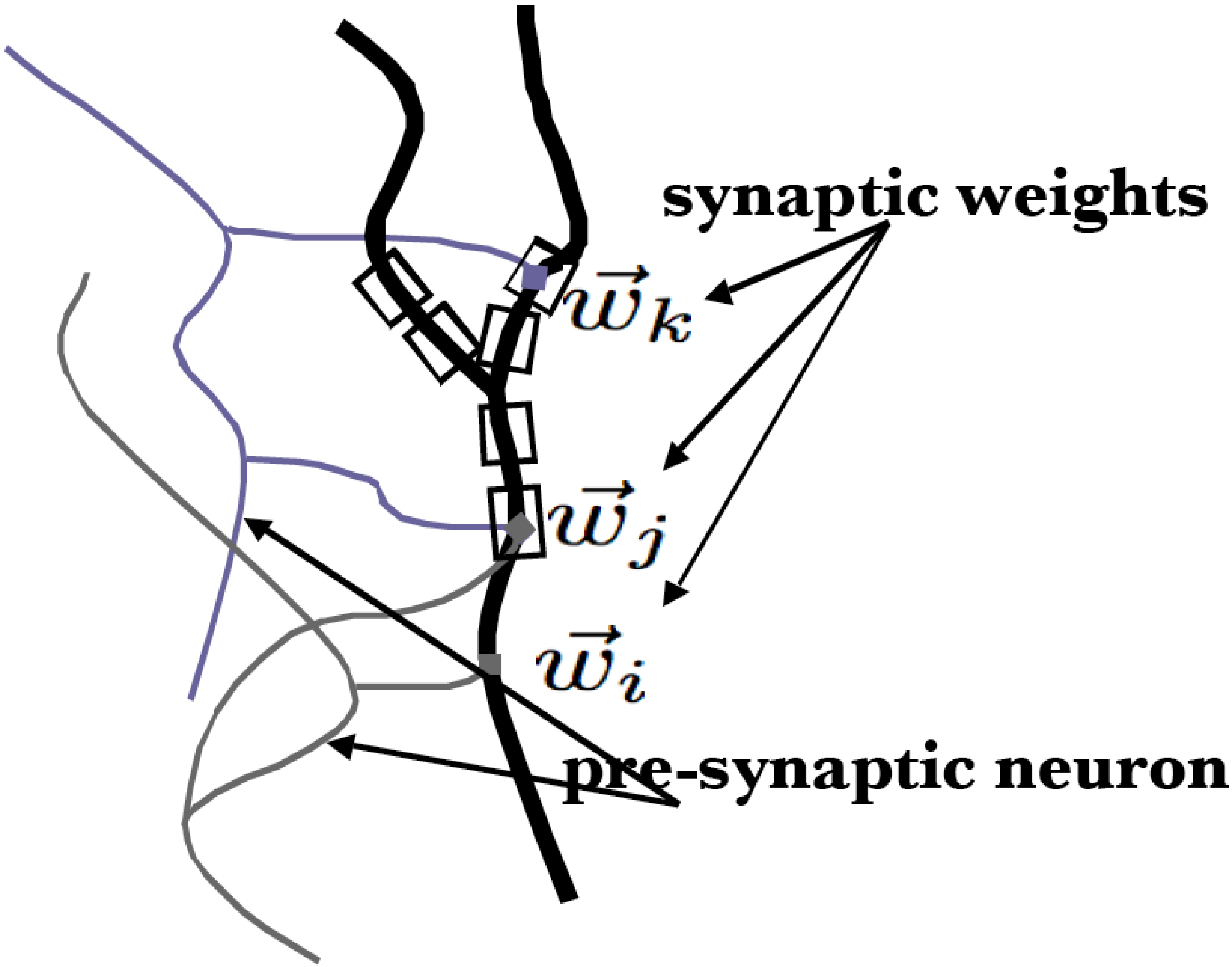
and can be done in $O(\dim(q))$ time (Paninski, 2010). Generalizable to many other state-space models (Pnevmatikakis and Paninski, 2011).

Examples: speckle, vertical

Application: synaptic locations/weights



Application: synaptic locations/weights



Application: synaptic locations/weights

Including known terms:

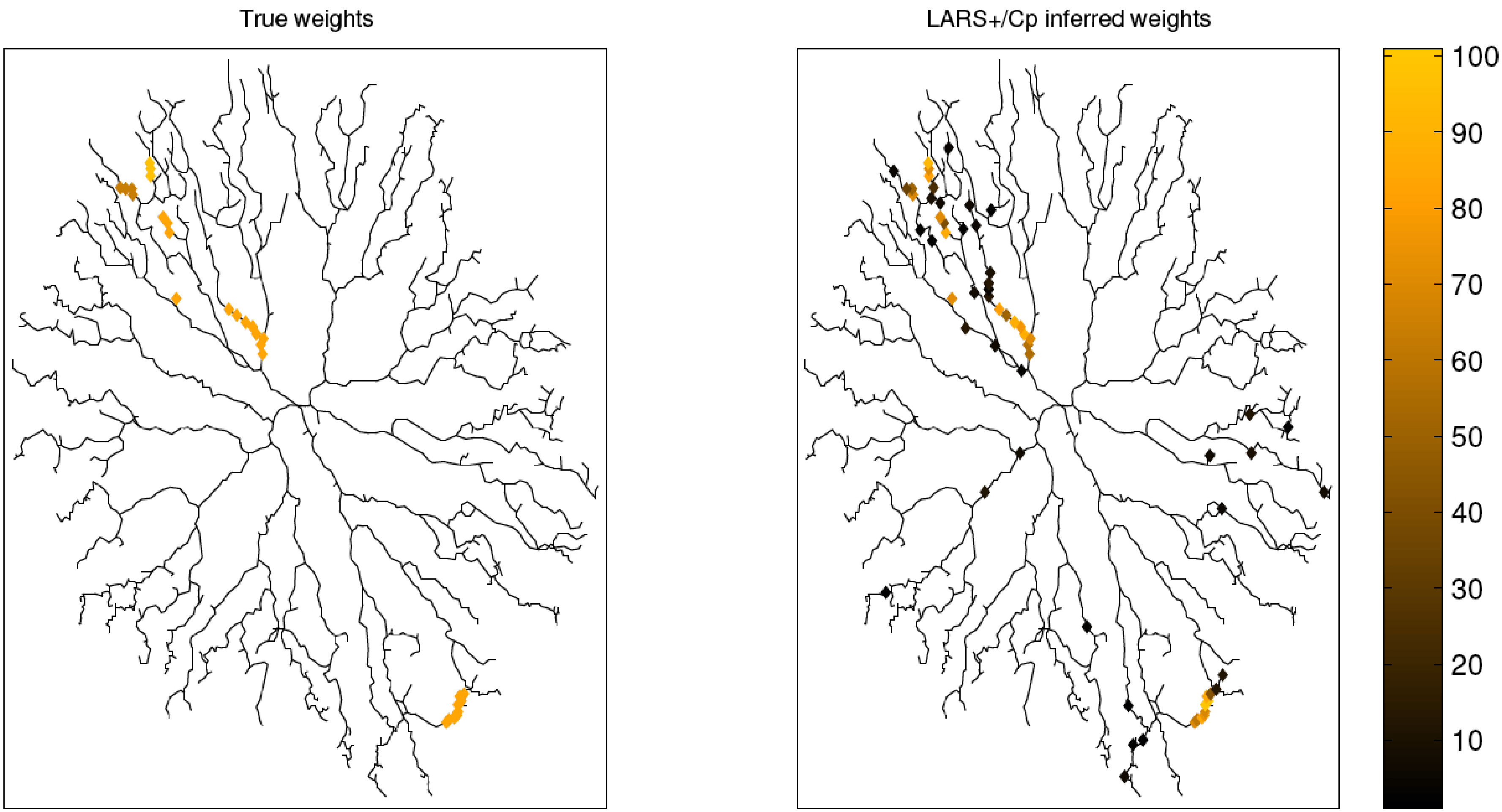
$$d\vec{V}/dt = A\vec{V}(t) + W\vec{U}(t) + \vec{\epsilon}(t);$$

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

Loglikelihood is quadratic; W is a sparse vector. L_1-penalized loglikelihood can be optimized efficiently with homotopy (LARS) approach.

Total computation time: $O(dTk)$; $d = \#$ compartments, $T = \#$ timesteps, $k = \#$ nonzero weights.

Example: real neural geometry



700 timesteps observed; 40 random compartments (of > 2000) observed per timestep

Compressed sensing measurements improve accuracy further (Pakman et al 2013).

Conclusions

- Modern statistical approaches provide flexible, powerful methods for answering key questions in neuroscience — many of these problems are statistics problems in disguise
- Close relationships between biophysics, statistical modeling, and experimental design
- Modern optimization methods make computations very tractable; suitable for closed-loop experiments
- Dimensionality reduction is a key area for further research: new methods, new ideas
- Experimental methods progressing rapidly; many new challenges and opportunities for breakthroughs based on statistical ideas

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