Challenges and opportunities in statistical neuroscience

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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

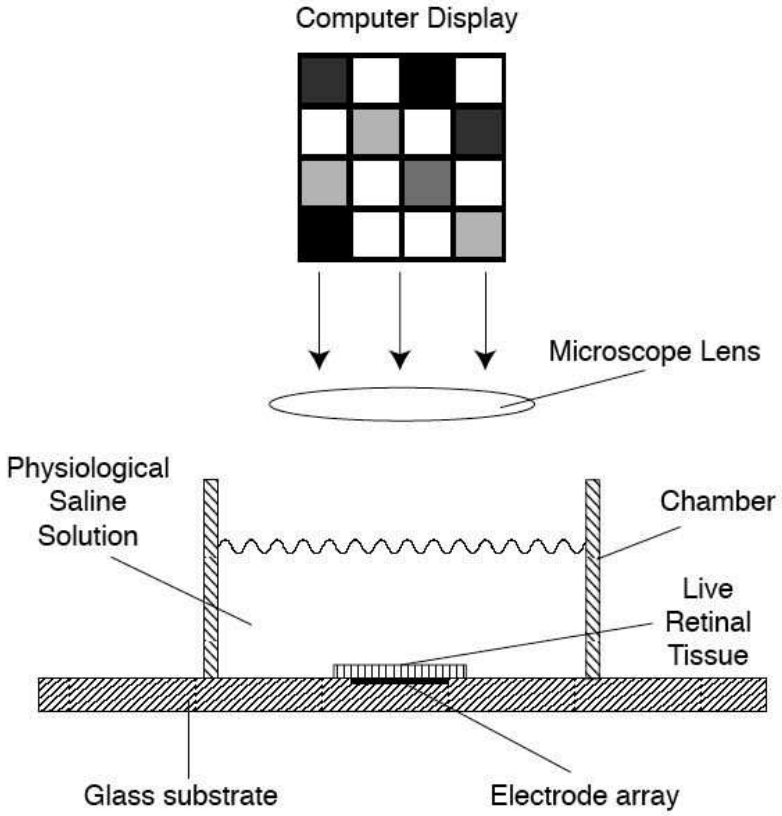
- inferring biophysical neuronal properties from noisy recordings
- reconstructing the full dendritic spatiotemporal voltage from noisy, subsampled observations
- estimating subthreshold voltage given superthreshold spike trains
- extracting spike timing from slow, noisy calcium imaging data
- reconstructing 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

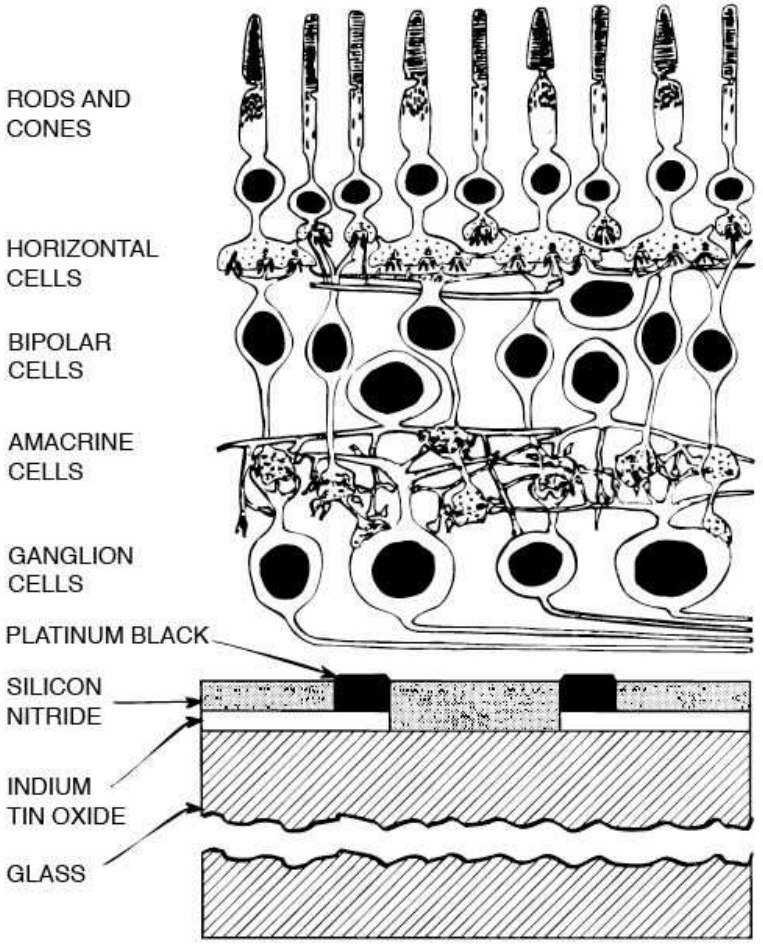
— to solve these, we need to combine the two classical branches of computational neuroscience: dynamical systems and neural coding

Retinal ganglion neuronal data

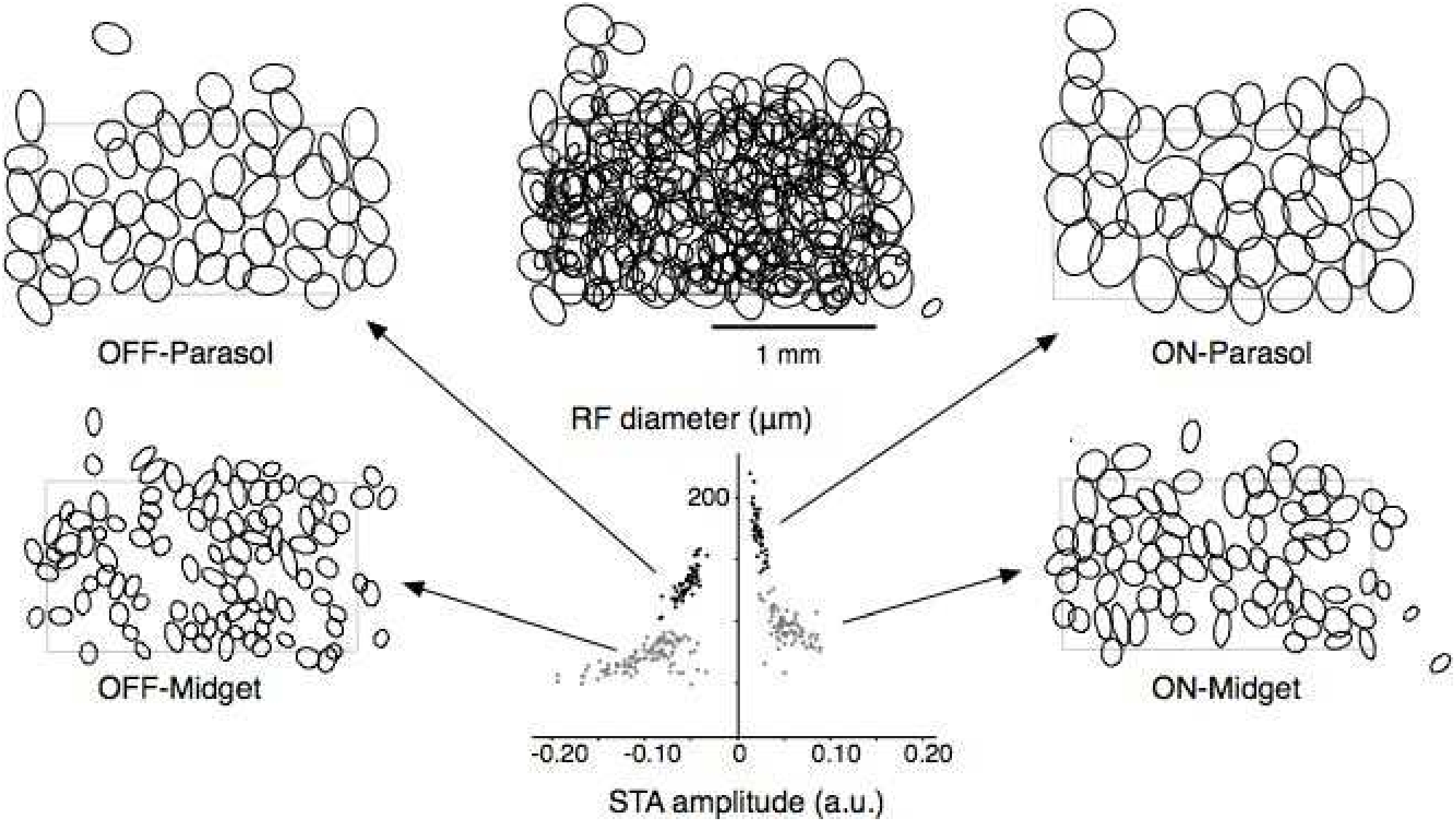
Preparation: dissociated macaque retina

— extracellularly-recorded responses of populations of RGCs



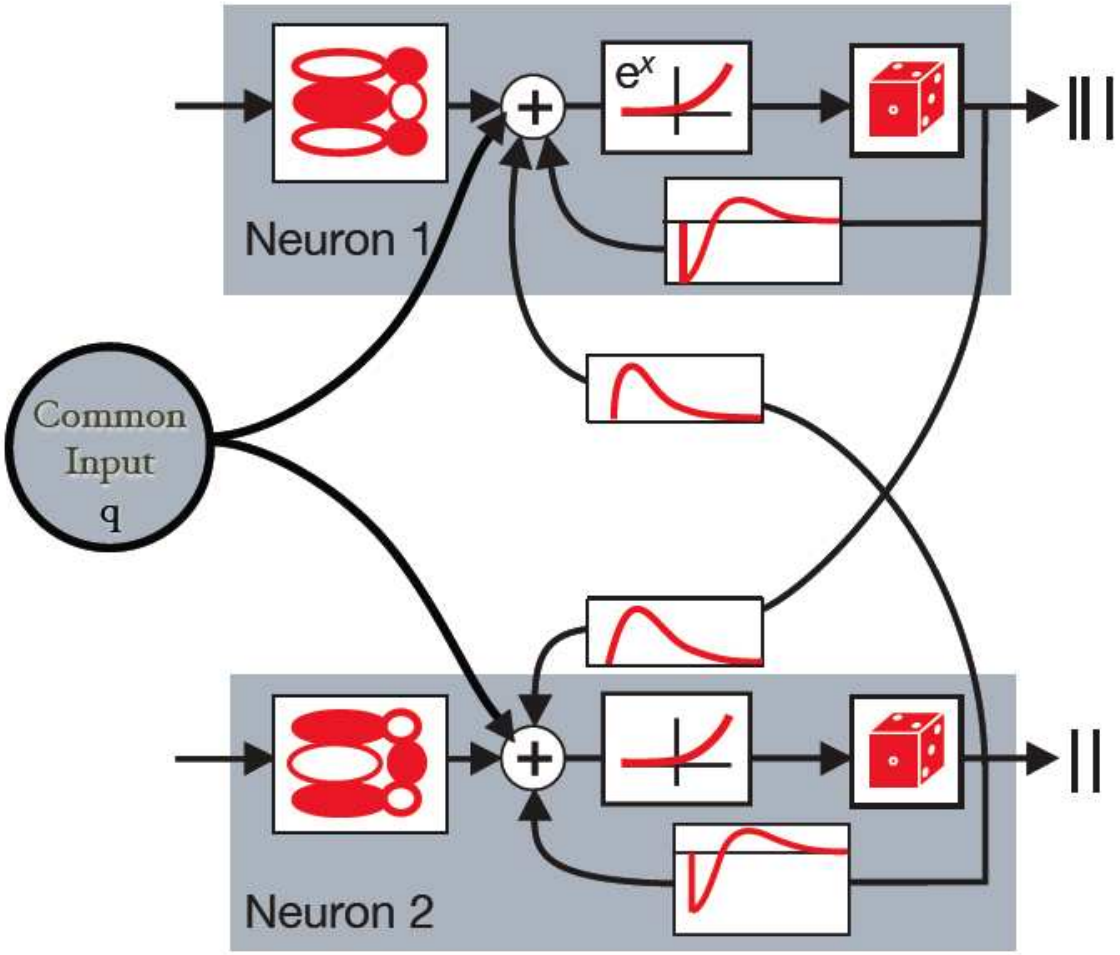


Receptive fields tile visual space



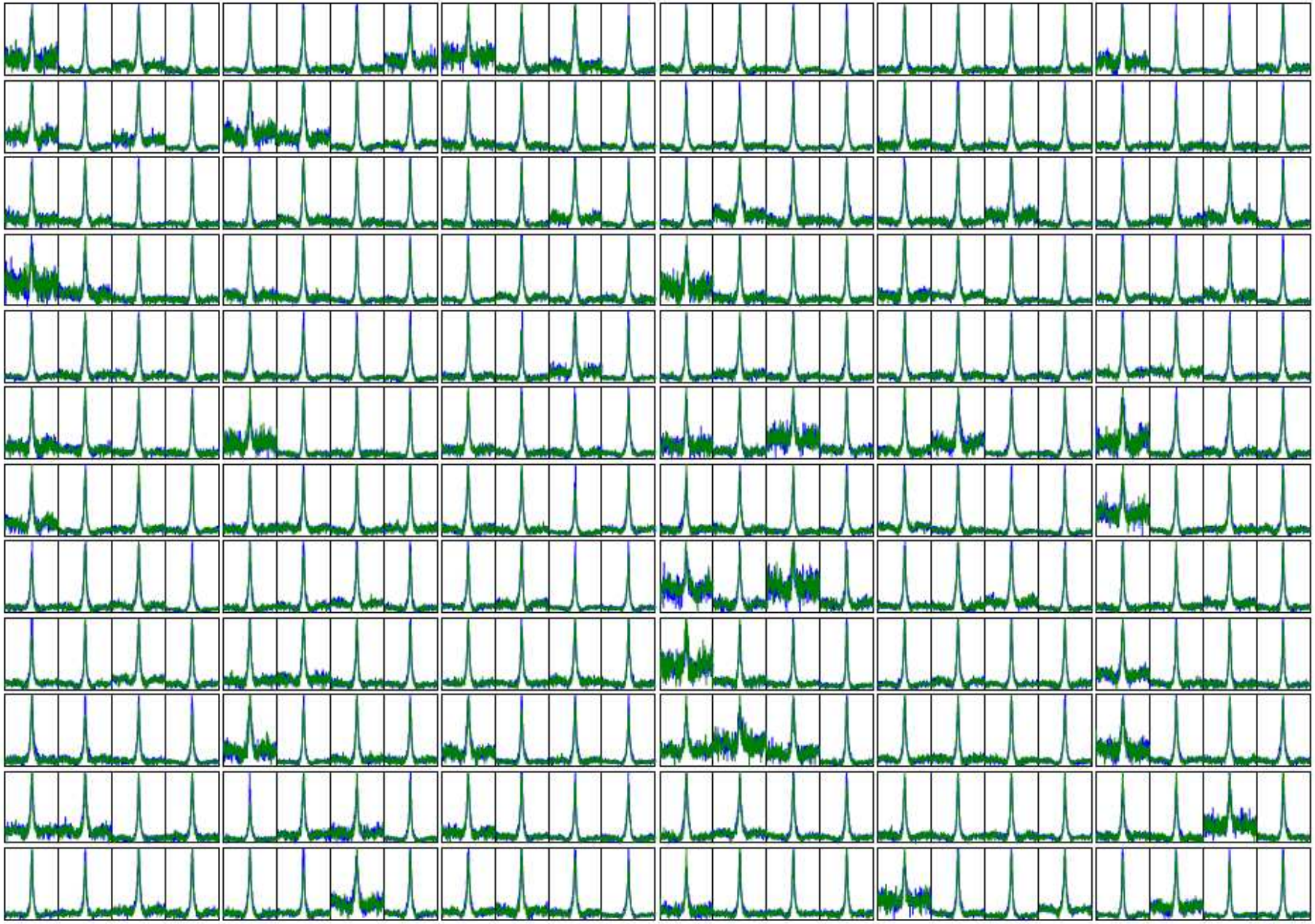
Multineuronal point-process model

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



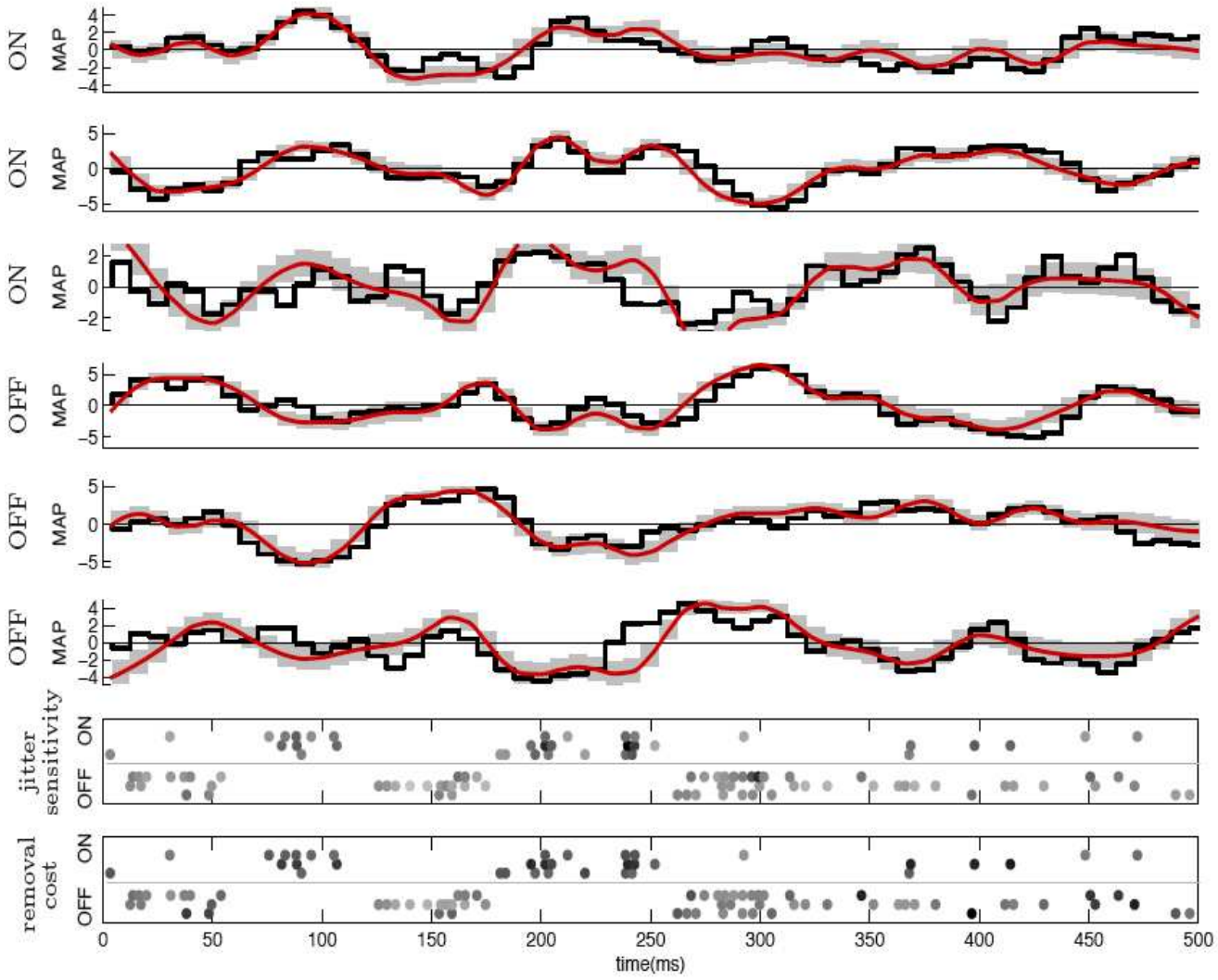
— likelihood is tractable to compute and to maximize (concave optimization)
(Paninski, 2004; Paninski et al., 2007; Pillow et al., 2008; Paninski et al., 2010)

Network model predicts correlations correctly



— single and triple-cell activities captured as well (Vidne et al., 2009)

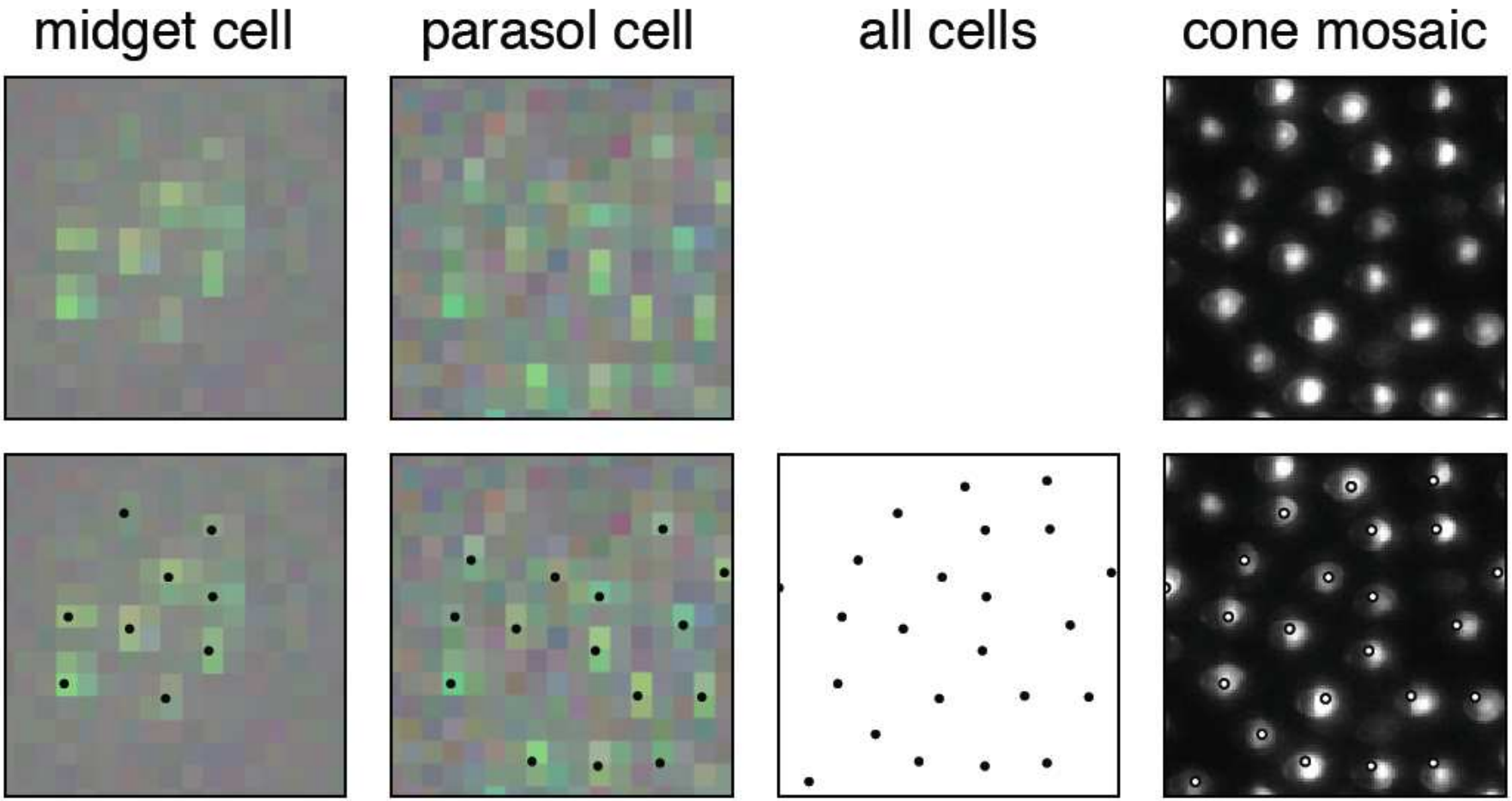
Optimal Bayesian decoding



— further applications: decoding velocity signals (Lalor et al., 2009), tracking images perturbed by eye jitter (Pfau et al., 2009)

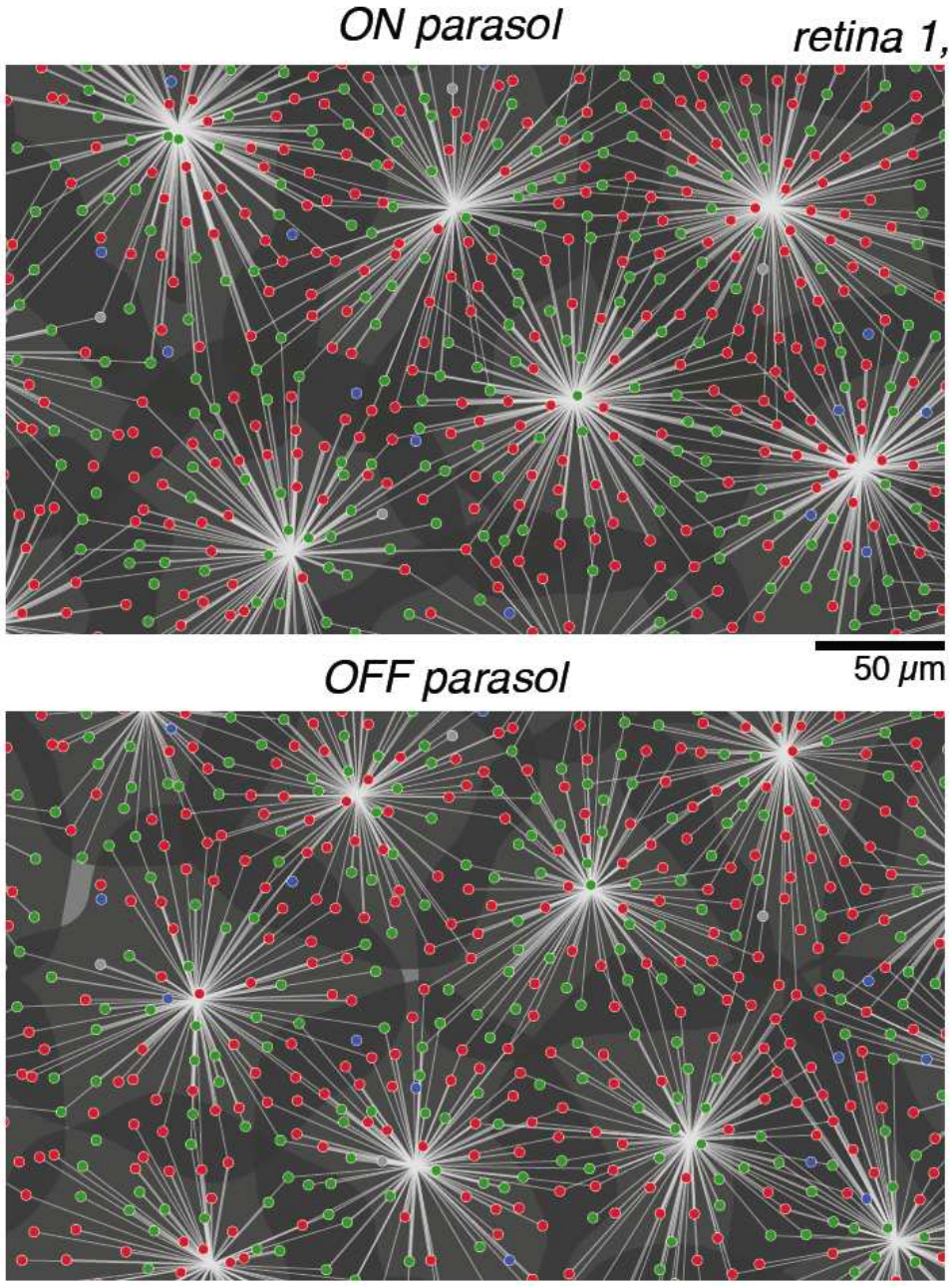
— paying attention to correlations improves decoding accuracy (Pillow et al., 2008).

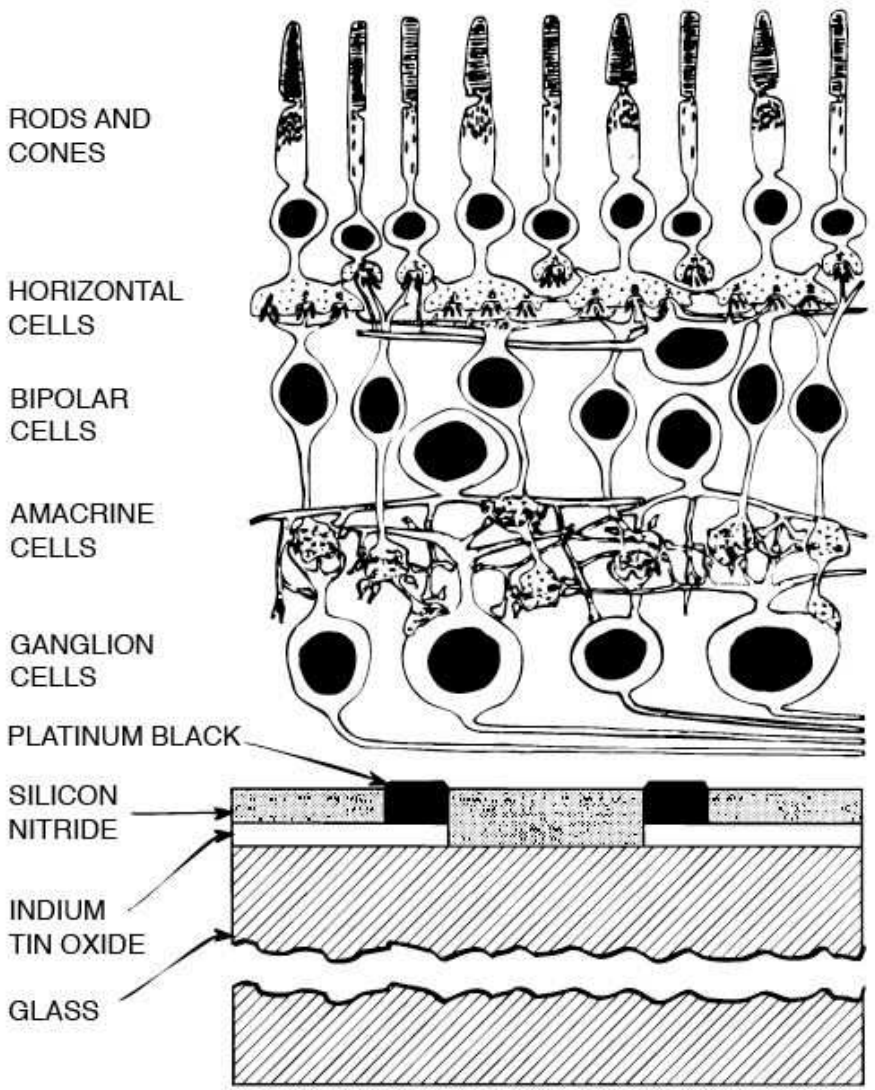
Inferring cones



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

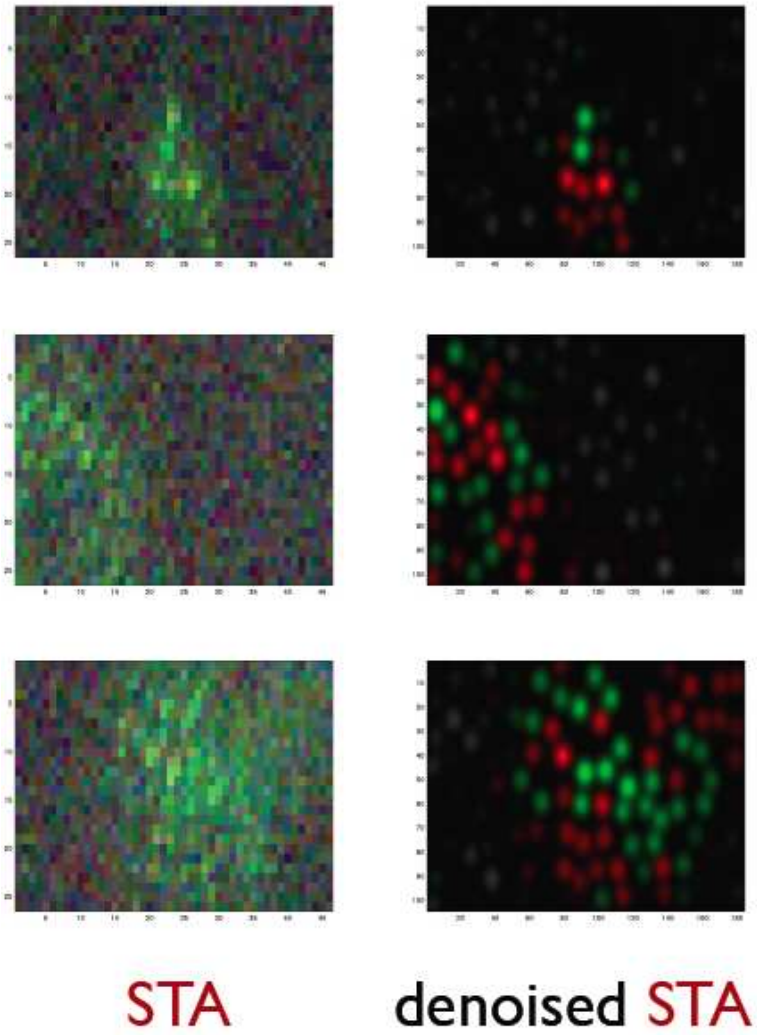
Next step: inferring nonlinear subunits





Opportunity: hierarchical models

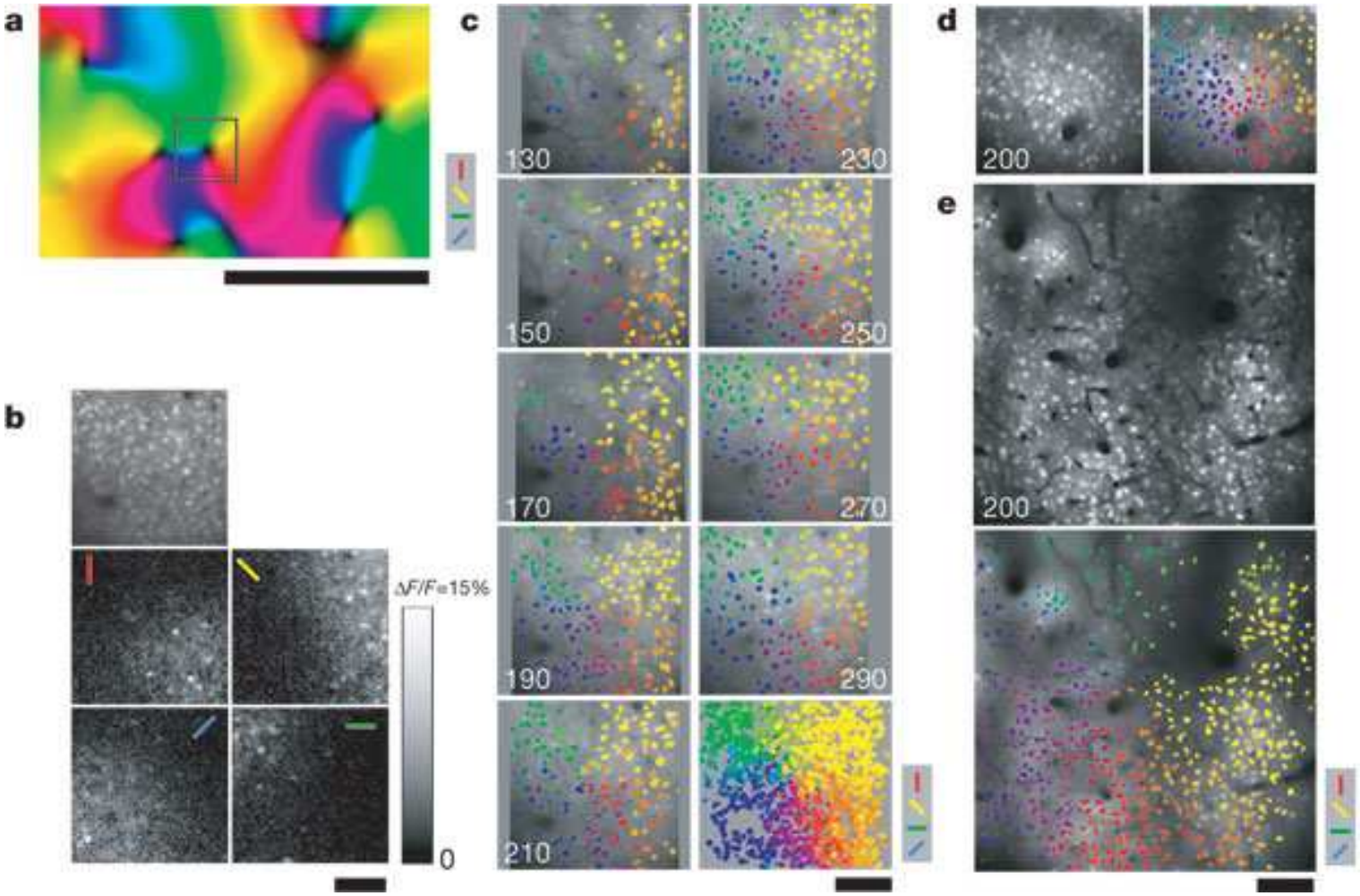
More general idea: sharing information across multiple simultaneously-recorded cells can be very useful.



(Field et al, Nature '10; Sadeghi et al, in preparation)

Opportunity: hierarchical models

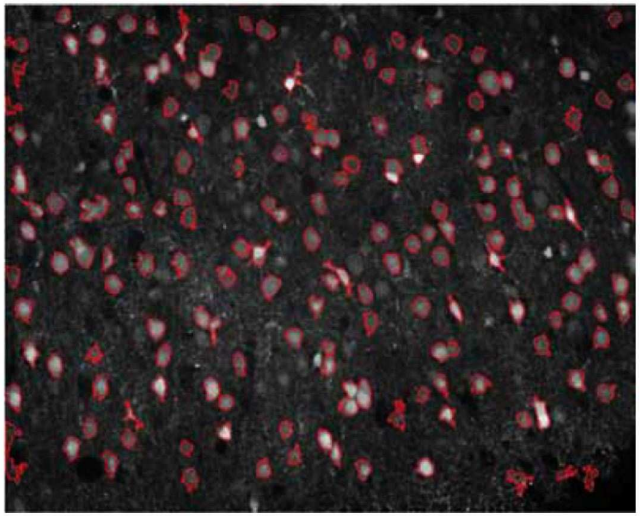
More general idea: sharing information across multiple simultaneously-recorded cells can be very useful. Exploit location, markers, other information to extract more information from noisy data.



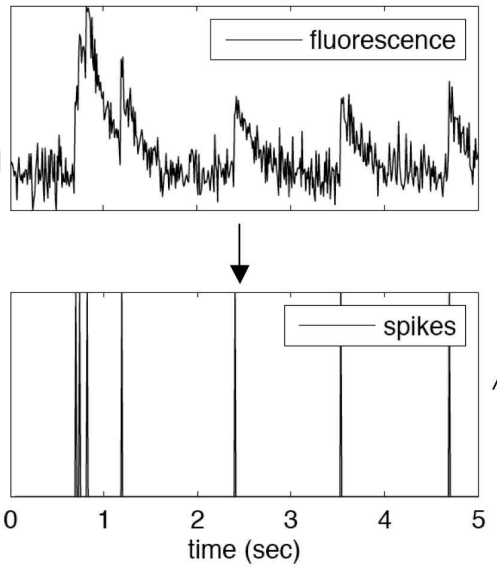
- w/ M. Gabitto (Zuker lab)

Another major challenge: circuit inference

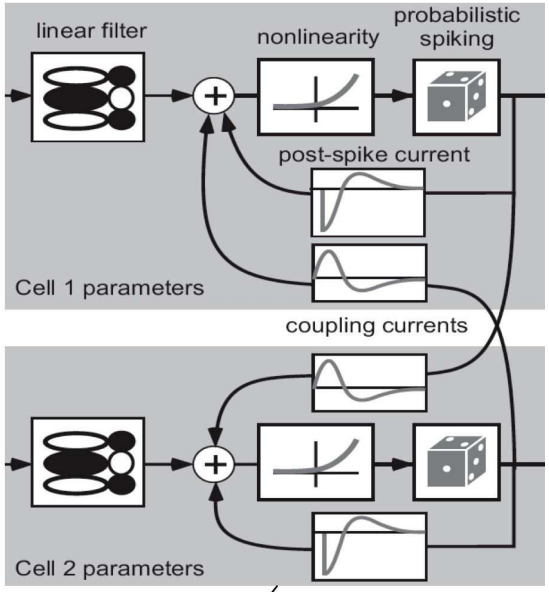
Record large-scale calcium movie



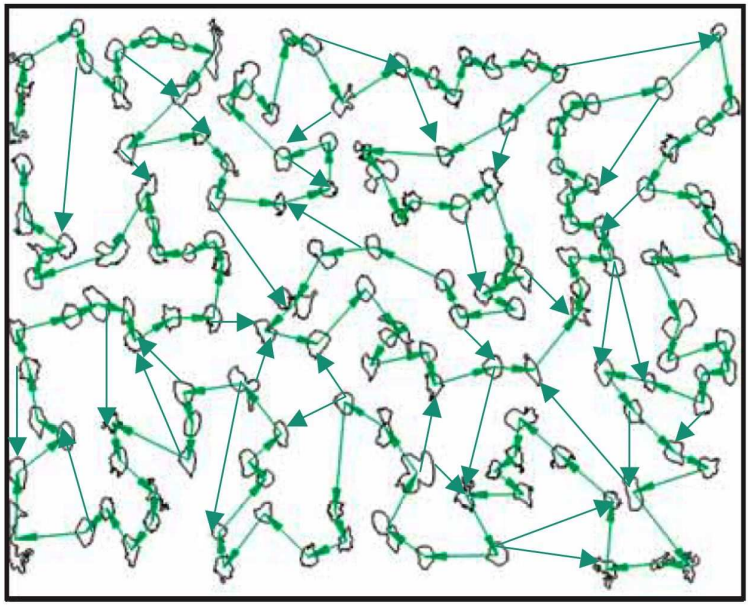
Aim 1: Extract spike times



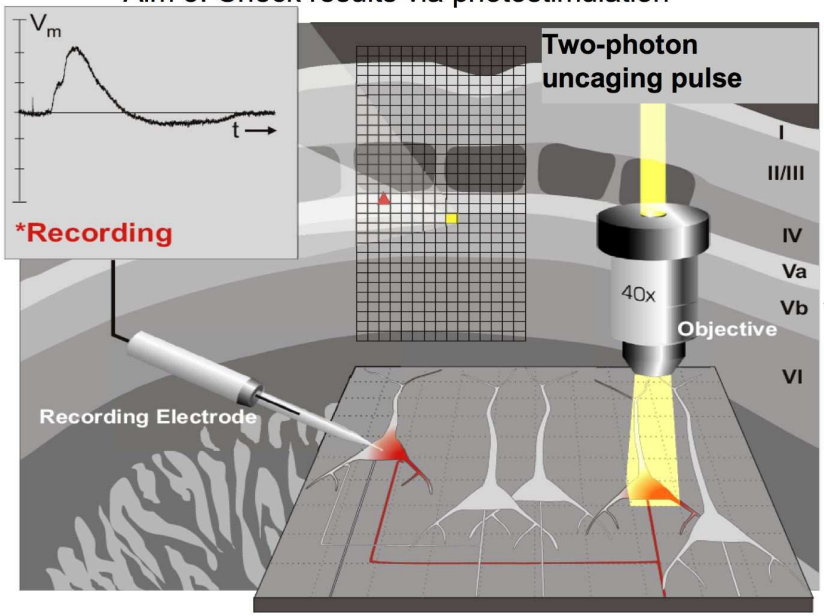
Aim 2: Estimate network model



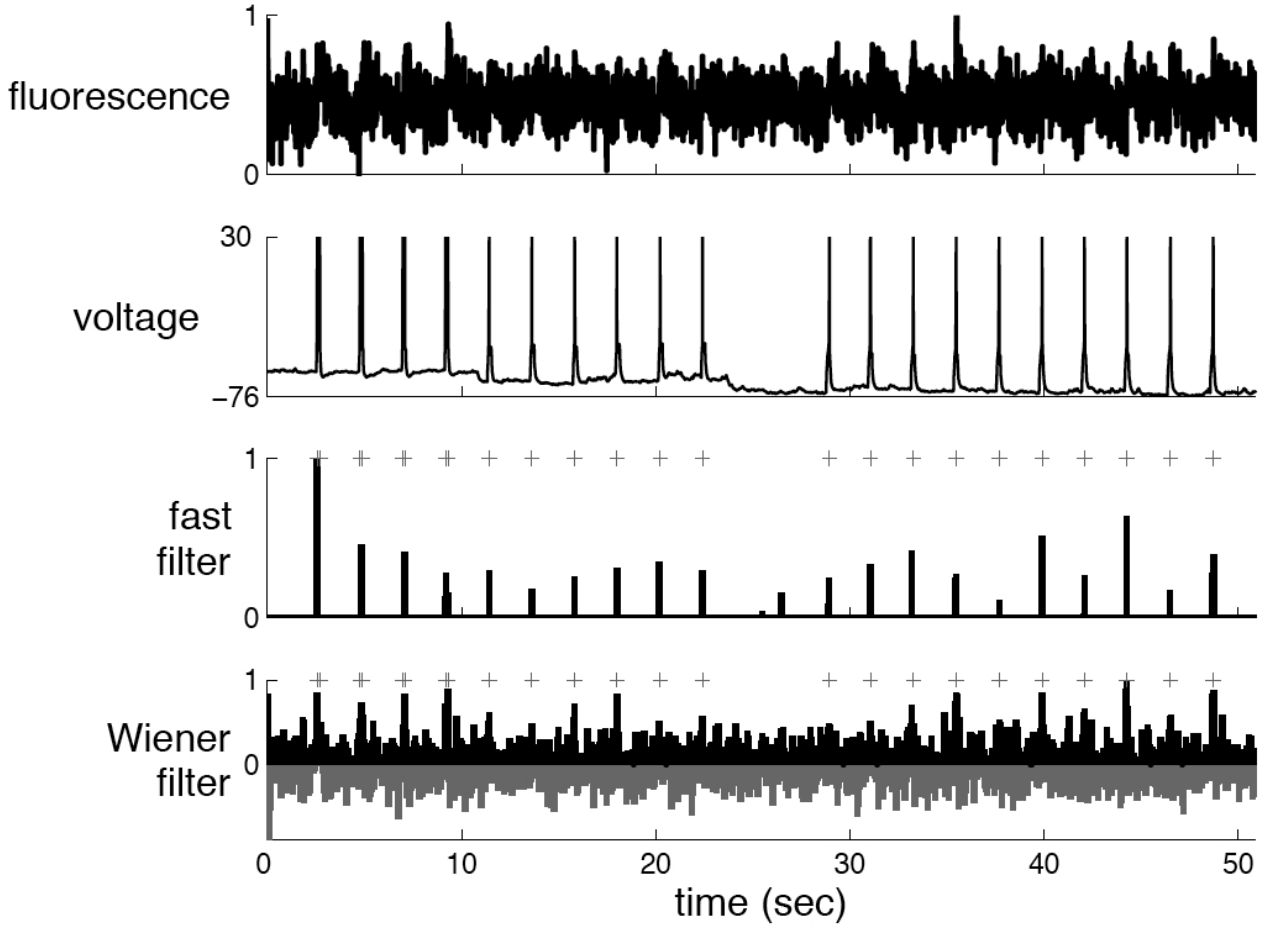
Inferred network model



Aim 3: Check results via photostimulation



Challenge: slow, noisy calcium data

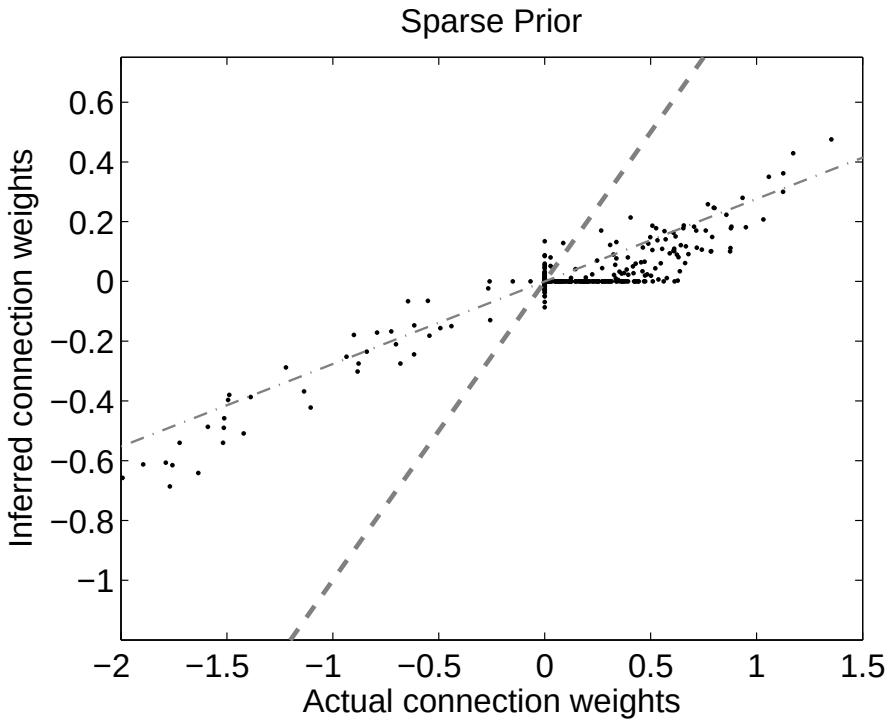


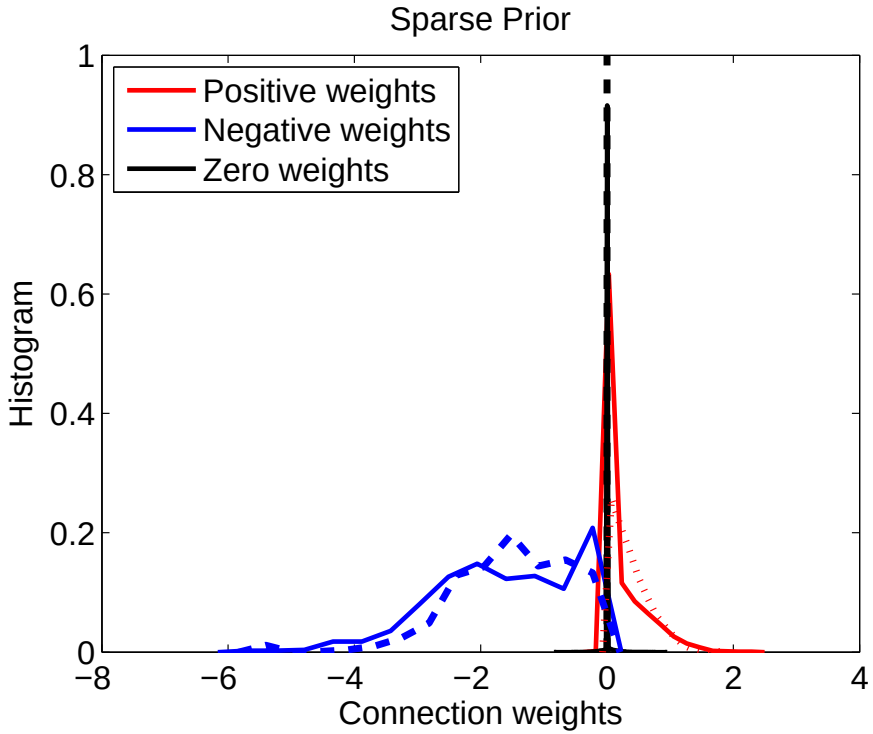
First-order model:

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

— $\tau \approx 100$ ms; nonnegative deconvolution problem. Can be solved by new $O(T)$ methods (Vogelstein et al., 2010).

Simulated circuit inference

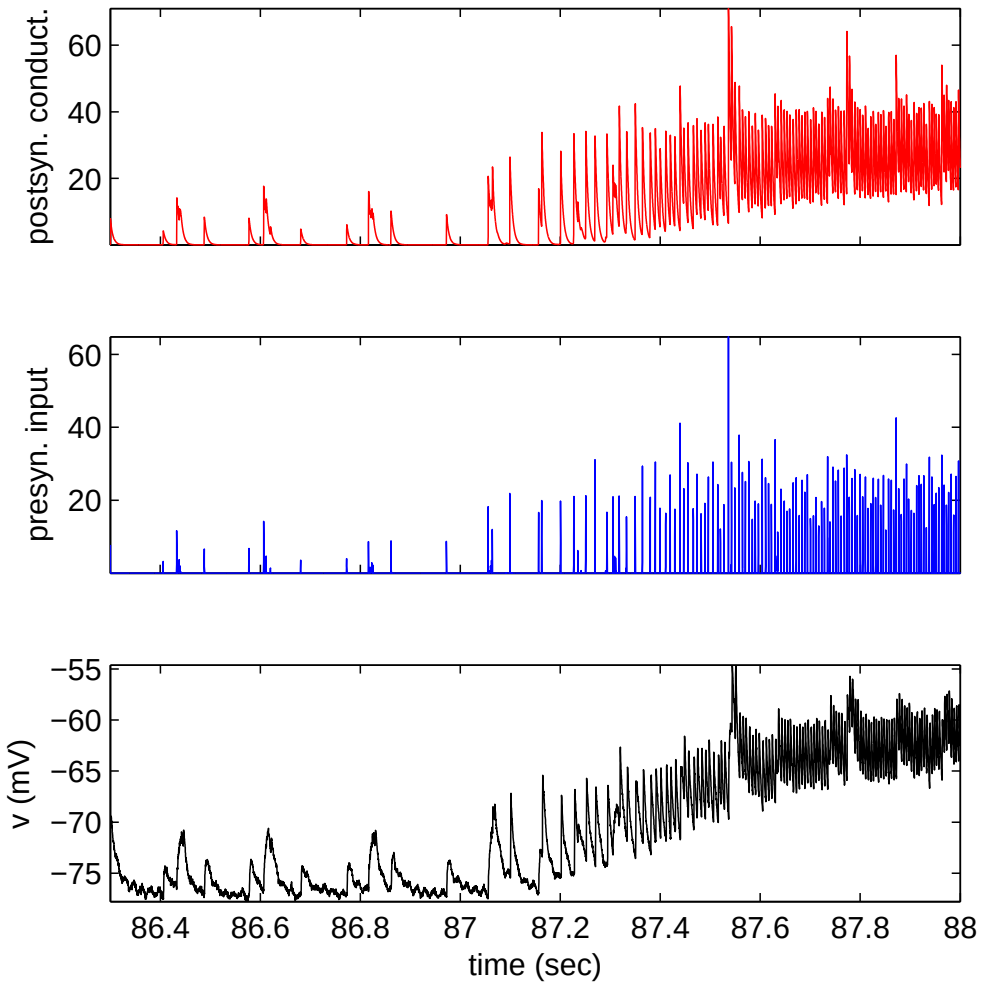




— Connections are inferred with the correct sign in conductance-based integrate-and-fire networks with biologically plausible connectivity matrices (Mishchencko et al., 2009).

Good news: connections are inferred with the correct sign. Fast enough to estimate connectivity in real time (T. Machado). Next step: close the loop.

Opportunities: in vivo whole-cell recordings



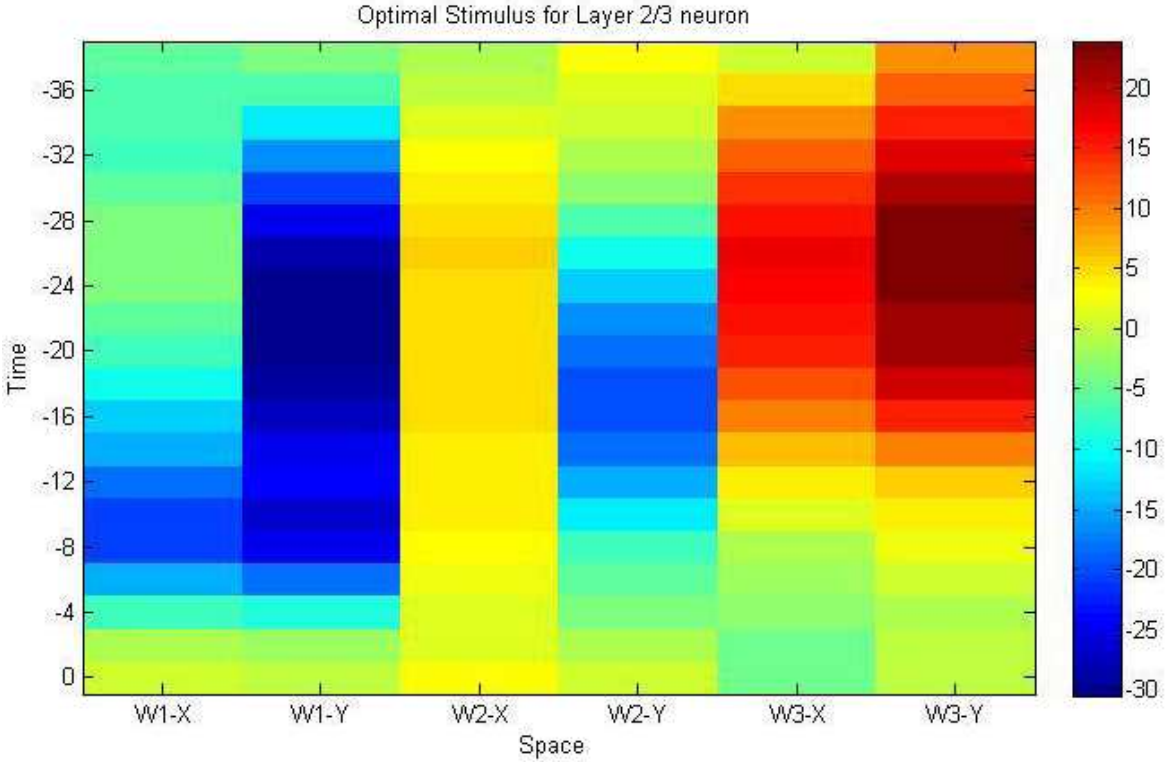
- data from Sawtell lab. Same fast nonnegative deconvolution methods as in calcium setting.

Optimal stimuli for layer 2/3 barrel neurons

Problem: spiking in layer 2/3 appears very sparse.

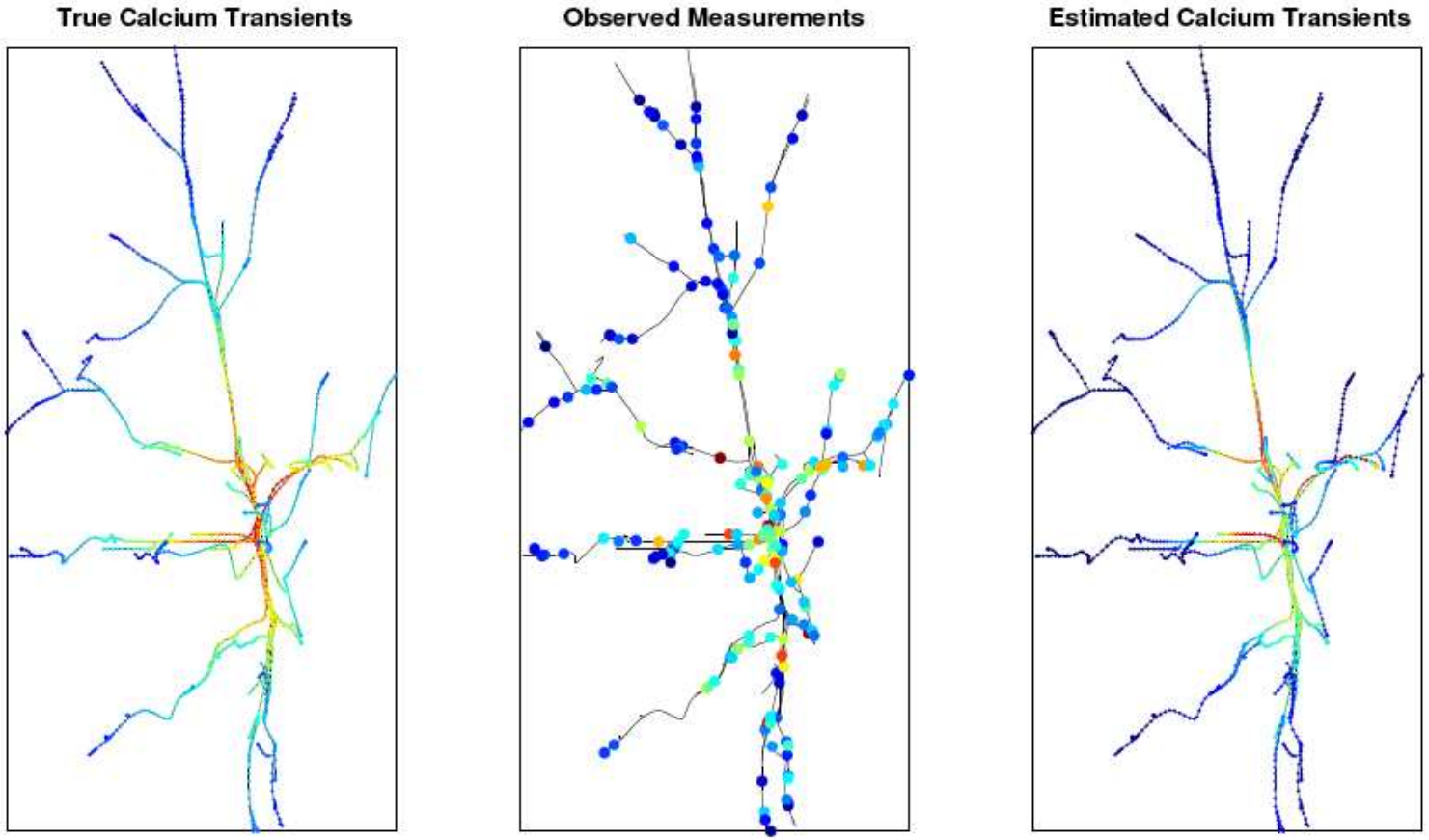
Hypothesis: driven by complex, multi-whisker stimuli?

Approach: estimate a model $dV/dt = f(stim)$, then compute stimulus which leads to the most reliable input, then apply this stim and observe response. (All done while holding the cell...)



- New nonlinear models provide much more predictive power; experiments in progress (w/ A. Ramirez; Bruno lab)

A final example: spatiotemporal dendritic imaging data



- fast methods for optimal inference of spatiotemporal Ca, V on trees.

Applications: synaptic localization, improved modeling of dendritic dynamics (e.g., backpropagating APs), many more

Conclusions

- Modern statistical approaches provide flexible, powerful methods for answering key questions in neuroscience
- Close relationships between biophysics and statistical modeling
- Modern optimization methods make computations very tractable; suitable for closed-loop experiments
- Experimental methods progressing rapidly; many new challenges and opportunities for breakthroughs based on statistical ideas

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