Towards Inferring Neural Circuits from Calcium Population Imaging

Joshua T Vogelstein[1], **Adam M Packer**[2], **Yuriy Mishchenko**[3], **Rafael Yuste**[2], **Liam Paninski**[3]

[1]Department of Neuroscience, Johns Hopkins School of Medicine, [2]Department of Biological Sciences, Columbia University, and Howard Hughes Medical Institute, [3]Department of Statistics and Center for Theoretical Neuroscience, Columbia University

joshuav@jhu.edu

1. Summary

Main Results

Calcium imaging is quickly becoming a prominent paradigm to collect data in neuroscience. We have developed a fully automatic method for processing data of this kind, ie, given a calcium movie, we provide the most likely spike trains for all the neurons in the movie, their stimulus filters, and a functional connectivity matrix. Code is available upon request.

References

[V09] Vogelstein JT, Watson BO, Packer AM, Yuste R, Jedynak B, and Paninski L. *Spike inference from calcium imaging using sequential Monte Carlo methods*. In Press at Biophysical Journal.

[N03] Neal RM, Beal MJ, Roweis, ST. *Inferring State Sequences for Non-linear Systems with Embedded Hidden Markov Mdels*. NIPS, 2003.

2. Models

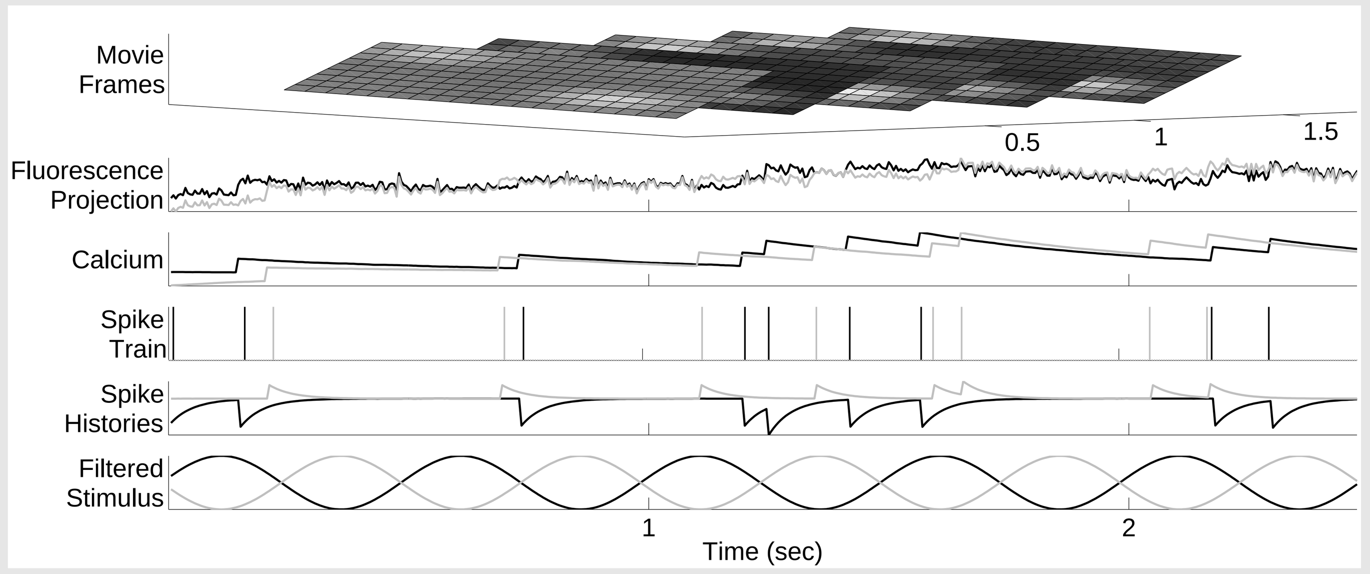
2.1 simple model

$$\boldsymbol{F}_t = \boldsymbol{\alpha}_i C_{i,t} + \boldsymbol{\beta}_i + \sigma_i \varepsilon_t, \qquad \varepsilon_t \sim \mathcal{N}(0, \mathbf{1})$$
$$C_{i,t} = \gamma_i C_{i,t-1} + n_{i,t}, \qquad n_{i,t} \sim \text{Poisson}(n_{i,t}; \lambda_i \Delta)$$

2.2 generalized model

$$\boldsymbol{F}_{i,t} = \boldsymbol{\alpha}_i S(C_{i,t}) + \boldsymbol{\beta}_i + (\xi_i S(C_{i,t}) + \sigma_{F_i,t})\varepsilon_{F_i,t}, \qquad S(x) = x^n/(x^n + k_d)$$
$$C_{i,t} = \gamma_i C_{i,t-1} + \eta_i + \rho_i n_{i,t} + \sigma_{c_i,t}\sqrt{\Delta}\varepsilon_{c_i}, \qquad \varepsilon_{\cdot,t} \sim \mathcal{N}(0,1)$$
$$h_{i_l,t} = \gamma_{i_l} h_{i_l,t-1} + n_{i,t-1} + \sigma_{h_i}\sqrt{\Delta}\varepsilon_{h_{i_l},t}, \qquad n_{i,t} \sim \text{Bern}\Big(n_{i,t}; f\big(b_i + \boldsymbol{k}_i'\boldsymbol{x}_t + \sum_{j=1}^{N} \boldsymbol{\omega}_{ij}'\boldsymbol{h}_{j,t}\big)\Big)$$

2.3 schematic



Schematic demonstrating our model. Top panel: slices from a simulated movie of calcium dynamics in spiking neurons. Second panel: 1D fluorescence projection for the two neurons. Third panel: calcium dynamics of the neurons. Fourth panel: spike train of the neurons. Fifth panel: spike history terms from the neurons. Bottom panel: filtered stimulus for the two neurons.

3. theory

3.1 fast filter

We would like to solve the following optimization problem:

$$\widehat{\boldsymbol{n}} = \underset{n_t \geq 0 \forall t}{\operatorname{argmax}} P(\boldsymbol{n}|\boldsymbol{F}) = \underset{n_t \geq 0 \forall t}{\operatorname{argmax}} P(\boldsymbol{F}|\boldsymbol{n})P(\boldsymbol{n})$$

where $\boldsymbol{n}$ is the spike train and $\boldsymbol{F}$ is the fluorescence observations. To impose the non-negative constraint, we use an interior point method, making this a concave constrained optimization approach. To solve it effeciently, we make use of the tridiagonal structure of the Hessian, and use Gaussian elimination to take Newton-Raphson steps in $O(T)$ time. A naïve approach would require $O(T^3)$. To learn the parameters, we make the following approximation:

$$\begin{aligned}\widehat{\boldsymbol{\theta}} &= \underset{\boldsymbol{\theta}\in\boldsymbol{\Theta}}{\operatorname{argmax}} \iint_{\boldsymbol{\theta}\in\boldsymbol{\Theta}} P(\boldsymbol{F}|\boldsymbol{C},\boldsymbol{n},\boldsymbol{\theta})P(\boldsymbol{C}|\boldsymbol{n},\boldsymbol{\theta})d\boldsymbol{C}d\boldsymbol{n} \\ &\approx \underset{\boldsymbol{\theta}\in\boldsymbol{\Theta}}{\operatorname{argmax}} P(\boldsymbol{F}|\boldsymbol{C},\widehat{\boldsymbol{n}},\boldsymbol{\theta})P(\boldsymbol{C}|\widehat{\boldsymbol{n}},\boldsymbol{\theta})\end{aligned}$$

3.2 particle filter

Instead of finding $\boldsymbol{n}_{MAP}$, we can find the probability that there was a spike in any time bin, conditioned on the entire fluorescence time series: $P_{\boldsymbol{\theta}}(n_t|\boldsymbol{F})$.We then use a forward-backward approach to compute the desired distributions, approximating the forward recursion by using a sequential Monte Carlo algorithm (aka, a particle filter). Computing these distibutions suffices for the expectation step of an expectation maximization algorithm. The maximization step is concave in all the parameters, so we can quickly estimate all the parameters. For details, consult [V09].

3.3 mcmc filter

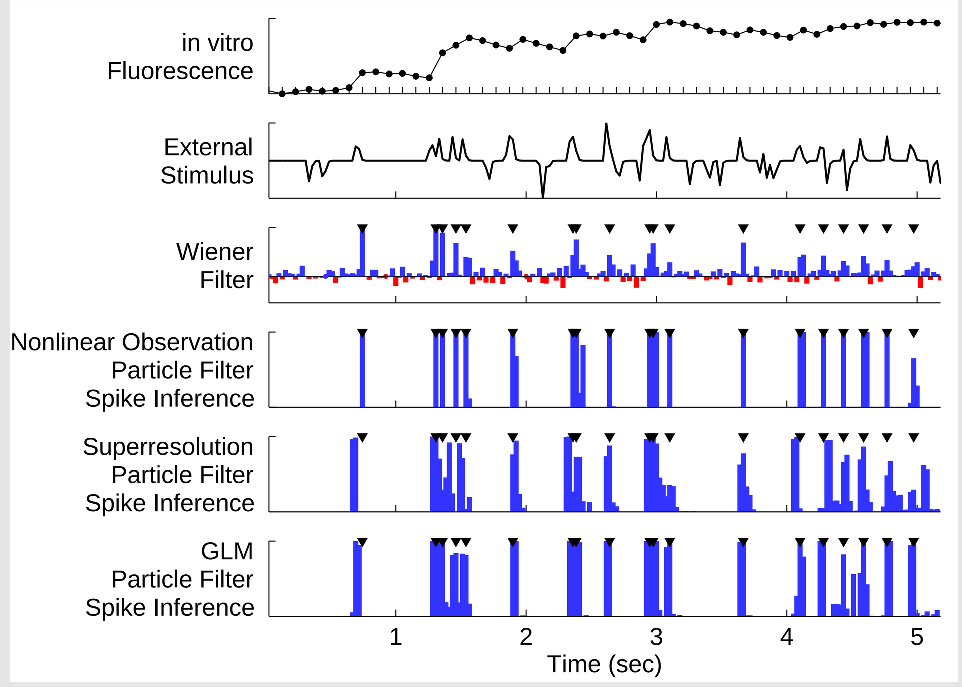
The particle filter provides an estimate of the marginal distribution $P_{\boldsymbol{\theta}}(n_t|\boldsymbol{F})$, but we would like an estimate of the full joint posterior, $P_{\boldsymbol{\theta}}(\boldsymbol{n}|\boldsymbol{F})$. Given neuron model $\boldsymbol{\theta}$ obtained in Section 3.2, a sample of spike train can be drawn from $P_{\boldsymbol{\theta}}(\boldsymbol{n}|\boldsymbol{F})$, using a markov chain monte carlo approach. Naïvely making a grid (from which we'd sample) introduces discretization bias. Instead, to obtain an unbiased spike train sample, we define a stochastic grid of MxT points $\{n, C\}_t^{(i)}$ drawn independently using the estimated $P_{\boldsymbol{\theta}}(n_t, C_t|\boldsymbol{F})$ from Section 3.2. Sample train $\{\boldsymbol{n}, \boldsymbol{C}\}$ then may be drawn over this grid in $O(MT)$ time. This process is iterated, adding the previous sample $\{\boldsymbol{n}, \boldsymbol{C}\}$ to subsequent grid, thus defining a markov chain of samples $\{\boldsymbol{n}, \boldsymbol{C}\}$ with equilibrium distribution $P_{\boldsymbol{\theta}}(\boldsymbol{n}, \boldsymbol{C}|\boldsymbol{F})$ [N03].

3.4 comparison table

	Wiener	Fast	Particle	MCMC
parameters	$\boldsymbol{\theta} = \{\boldsymbol{\alpha}, \boldsymbol{\beta}, \sigma, \gamma, \lambda\}_{i=1}^K$	$\boldsymbol{\theta}$	$\phi = \boldsymbol{\theta} \cup \{\xi, \eta, \rho, \sigma_c, \sigma_h, b, \boldsymbol{k}, \boldsymbol{\omega}\}_{i=1}^K$	ϕ
speed	$O(T)$	$O(T)$	$O(T \times N^2)$	$O(T \times M)$
superresolution	X	✓	✓✓	✓✓
stimuli	X	✓	✓✓	✓✓
refractoriness	X	X	✓	✓
connectivity	X	X	✓	✓
accuracy	X	✓	✓✓	✓✓✓

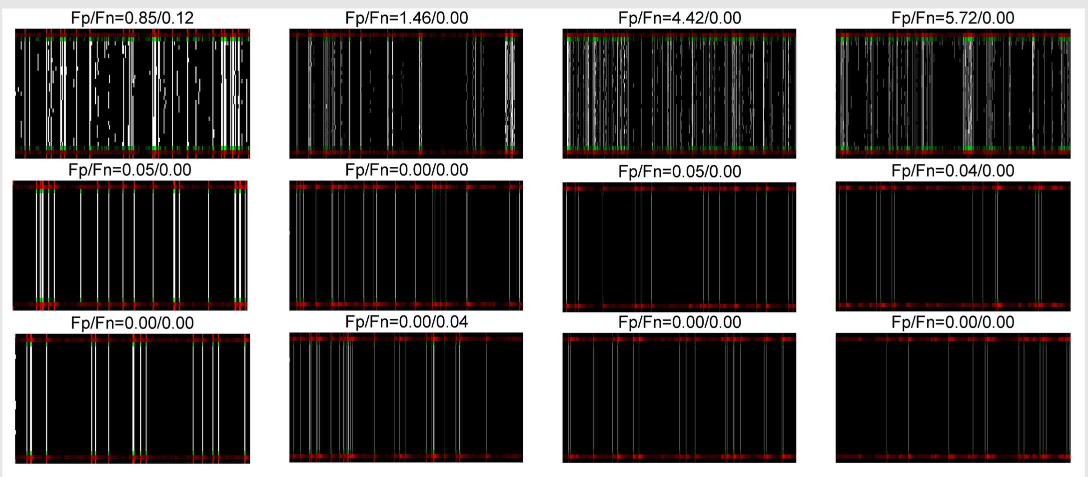
4. inference results

4.1 does this work in a real cell?



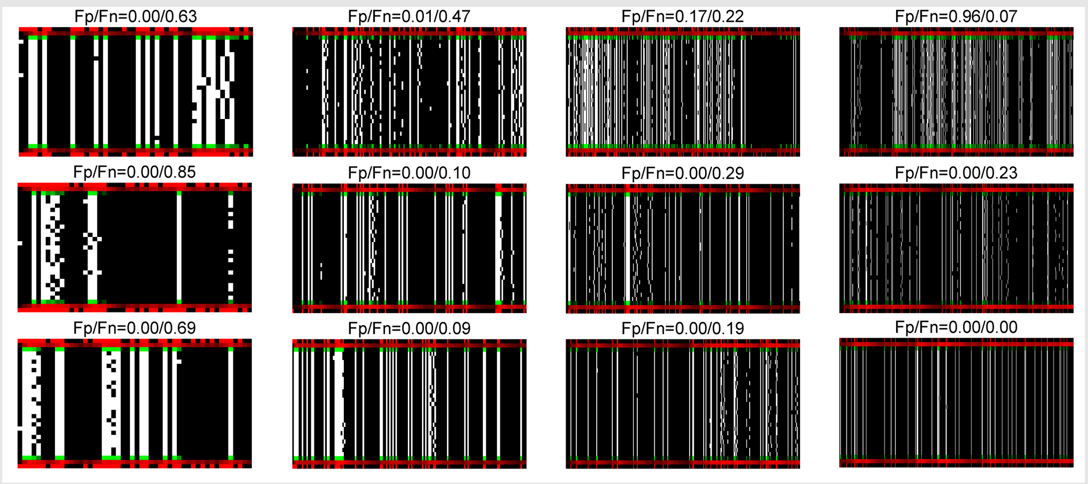
Improving inference with more sophisticated algorithms using simultaneously recorded imaging and electrophysiology (to obtain ground truth; indicated by triangles). Top panel: in vitro fluorescence signal. Second panel: injected external stimulus. Third panel: Wiener filter inference (note negative spikes). Fourth panel: fast filter inference. Fifth panel: particle filter inference. Sixth panel: mcmc particle filter.

4.2 will this work in other cells?



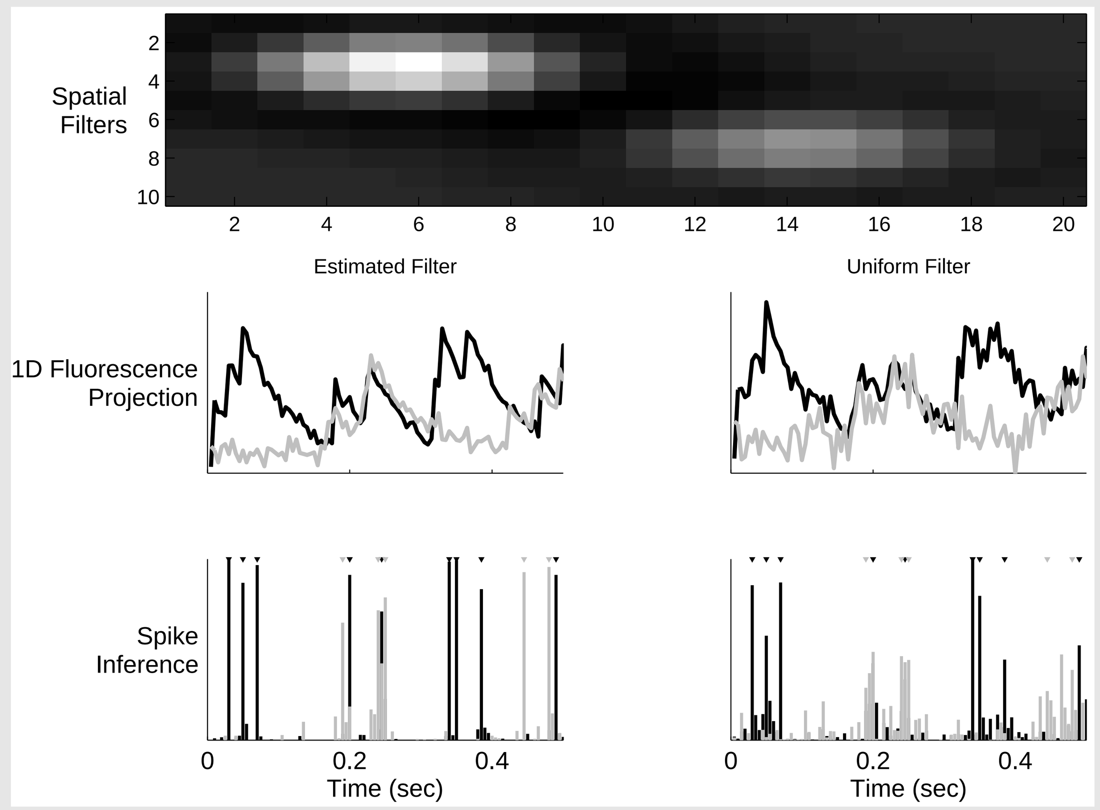
An array of results for simulations with different physiologically realistic scenarios. Top figure: slow spiking neuron. Bottom figure: fast spiking neurons. Columns left-to-right increase sampling rates. Rows bottom-to-top increase photon noise.

4.3 slow spiking simulations



5. learning results

5.1 learning spatial filters



5.2 learning connection matrices