Model-based optimal inference of spike times and calcium dynamics given noisy and intermittent calcium-fluorescence imaging

Joshua T Vogelstein[1], **Baktash Babadi**[2], **Liam Paninski**[2,3]

[1]Department of Neuroscience, Johns Hopkins School of Medicine, [2]Department of Neuroscience, Columbia University, [3]Department of Statistics, Columbia University

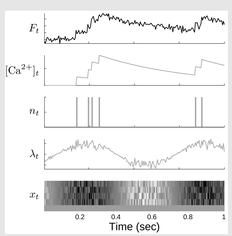
joshuav@jhu.edu, bb2280@columbia.edu, liam@stat.columbia.edu

Abstract

The goal of this work is to infer spike trains, having only the fluorescence time-series available to us. To do so, we propose a parametric model of the experimental system. Then, we develop a number of algorithms, each iteratively estimating the parameters and then using those parameters to infer the hidden spike trains. Our algorithms make significant advances over previous approaches, in that they naturally facilitate: (i) intermittent observations, (ii) stimulus information, (iii) saturation effects, (iv) error bars, and (v) refractoriness.

1. a simple model

$$
\begin{aligned}
F_t &= [\mathrm{Ca}^{2+}]_t + \varepsilon_t, \qquad \varepsilon_t \sim \mathcal{N}(0, 1/2c) \\
[\mathrm{Ca}^{2+}]_t &= a[\mathrm{Ca}^{2+}]_{t-1} + An_t + d \\
n_t &\sim \lambda_t \\
\lambda_t &= f(b + \vec{k}'\vec{x})\Delta
\end{aligned}
$$



References

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3) Sato T, Gray NW, Mainen ZF, Svoboda K. *The Functional Microarchitecture of the Mouse Barrel Cortex.* PLOS Biol 2007 Jul 10; 5(7):e189.

4) Vogelstein JT and Paninski L *Model-based optimal inference of spike times and calcium dynamics given noisy and intermittent calcium-fluorescence imaging* . Under review at Biophysical Journal.

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2. non-negative spike train: log barrier method

We would like to solve the following optimization problem:

$$\vec{n}_{nng} = \underset{\vec{n}:n_t \geq 0}{\operatorname{argmin}} \sum_{t=0}^{T} \left(c(F_t - [\mathrm{Ca}^{2+}]_t)^2 + \lambda_t n_t \right)$$

where $\lambda_t n_t$ is a prior. To do so efficiently, we iteratively solve the following concave problem, reducing η with each iteration:

$$\vec{n}_\eta = \underset{\vec{n}}{\operatorname{argmin}} \sum_{t=0}^{T} \left(c(F_t - [\mathrm{Ca}^{2+}]_t)^2 + \lambda_t n_t - \eta \log(n_t) \right)$$

The key is that we can write $\vec{n}$ as a linear function of $\vec{C}$:

$$\begin{bmatrix} n_1 \\ \vdots \\ n_T \end{bmatrix} = \begin{bmatrix} 1/A & 0 & 0\,0 & \dots & 0 \\ -a/A & 1/A & 0\,0 & \dots & 0 \\ 0 & \dots & 0\,0 & -a/A & 1/A \end{bmatrix} \begin{bmatrix} [\mathrm{Ca}^{2+}]_1 \\ \vdots \\ [\mathrm{Ca}^{2+}]_T \end{bmatrix}$$

We compute the gradient and Hessian of $\vec{n}_\eta$, and plug the solution into:

$$
\begin{aligned}
\vec{C} &\leftarrow \vec{C} + s\boldsymbol{H}^{-1}\vec{g} \\
\vec{g} &= -2c(\vec{F} - \vec{C}) + \lambda \boldsymbol{M} - \eta \boldsymbol{M}'(\boldsymbol{M}\vec{C})^{-1} \\
\boldsymbol{H} &= 2c\boldsymbol{I} + 2\eta \boldsymbol{M}'(\boldsymbol{M}\vec{C})^{-2}\boldsymbol{M}
\end{aligned}
$$

Each iteration may be solved in $O(T)$ time because $\boldsymbol{H}$ is tridiagonal. Note that s is chosen such that $\vec{n} = \boldsymbol{M}(\vec{C} + s\boldsymbol{H}^{-1}\vec{g}) > 0$ and the likelihood decreases.

3. integer spike train: projection pursuit regression

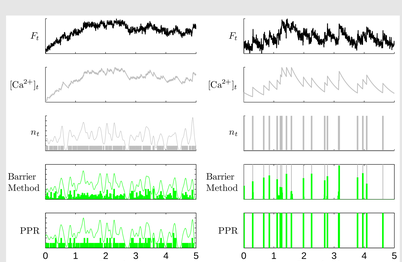
$$\vec{n}_{ppr} = \underset{\vec{n}:n_t \in 0,1,2,\dots}{\operatorname{argmin}} \sum_{t=0}^{T} \left(c(F_t - [\mathrm{Ca}^{2+}]_t)^2 + \lambda_t n_t \right).$$

An algorithm for solving the above constrained optimization problem in $O(T)$ time:

while residual error continues to decrease **do**
- Find the max of the xcorr of the residual and the calcium kernel
- Subtract the effect of a spike having occurred there from the residual
- Update the residual error

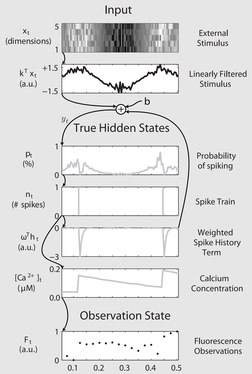
end while

4. fast methods comparison



5. a less simple model

$$
\begin{aligned}
F_t &= \alpha S([\mathrm{Ca}^{2+}]_t) + \beta + \sigma_F \varepsilon_t, && t \in \mathcal{T}_o \\
\sigma^2_{F_t} &= \gamma S([\mathrm{Ca}^{2+}]_t) + \delta, && t \in \mathcal{T}_o \\
[\mathrm{Ca}^{2+}]_t &= a[\mathrm{Ca}^{2+}]_{t-1} + An_t + d + \sqrt{\Delta}\varepsilon_t / 2c \\
n_t &\sim 1 - \exp\{-f(b + \vec{k}'\vec{x} + w'\vec{h}_t)\Delta\} \\
h_{i,t} &= a_i h_{i,t-1} + n_{t-1} + \sigma_h \varepsilon_t
\end{aligned}
$$



6. sequential Monte Carlo

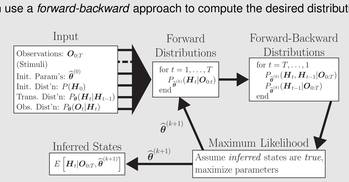
Instead of finding the $\vec{n}$ that minimizes the error, we can estimate the entire distribution of each n_t, conditioned on the entire fluorescence time series, $\vec{F}$:

$$P_\theta(n_t|\vec{F})$$

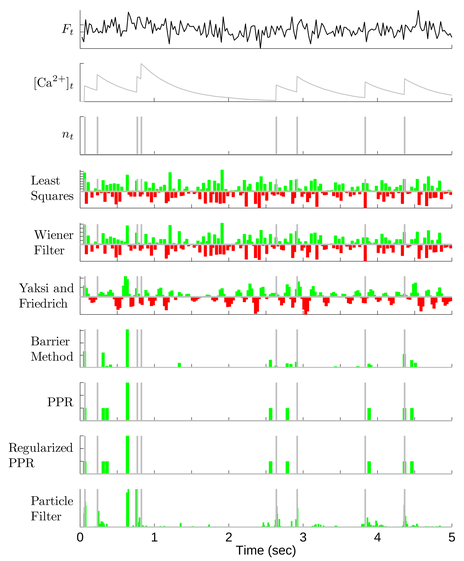
This requires that we describe the transition distribution, $P_\theta(\vec{H}_t|\vec{H}_{t-1})$ and observation distribution, $P_\theta(\vec{O}_t|\vec{H}_t)$ of our model:

$$
\begin{aligned}
P_\theta(\vec{H}_t|\vec{H}_{t-1}) &= P_\theta([\mathrm{Ca}^{2+}]_t|[\mathrm{Ca}^{2+}]_t, n_t) P_\theta(n_t|\vec{h}_t) P_\theta(\vec{h}_t|\vec{h}_{t-1}) \\
P_\theta(\vec{O}_t|\vec{H}_t) &= P_\theta(F_t|[\mathrm{Ca}^{2+}]_t)
\end{aligned}
$$

We then use a *forward-backward* approach to compute the desired distributions

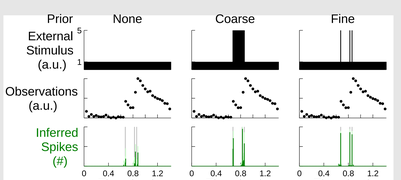


7. main result

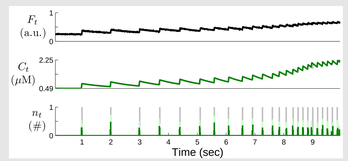


8. features

8.1 including stimuli



8.2 saturation



9. comparison

	other	barrier	PPR	SMC
parameters	variable	$\{a, b, c, d, k, A\}$	$\{a, b, c, d, k, A\}$	$+\{\alpha, \beta, \gamma, \delta, \omega, \sigma_h, \vec{a}_h\}$
speed	$O(T)$	$O(T)$	$O(T)$	$O(N^2T)$
intermittency	X	✓	X	✓
stimulus	X	✓	✓	✓
saturation	X	X	X	✓
errorbars	X	X	X	✓
refractoriness	X	X	X	✓
noise assumptions	?	gaussian	gaussian	arbitrary

10. assumptions that may easily be relaxed

	barrier	PPR	SMC
static noise distributions	X	X	✓
instantaneous fluorescence	X	✓	✓
fast $[\mathrm{Ca}^{2+}]$ rise time	X	✓	✓
constant A	X	X	✓
exponential decay	X	✓	✓
no movement artifacts	X	X	✓
no image blur	X	X	✓
spiking model	✓	✓	✓