

# Fast spike train inference from calcium imaging

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## Abstract

Experiments often yield measurements of variables that are naturally constrained to be nonnegative. In such scenarios, it may be desirable to filter (or deconvolve) the observations to find the most likely trajectory of the nonnegative variable, given the noisy observations. Here, we develop a computationally-efficient optimal filter for a certain subset of nonnegatively constrained deconvolutions. Specifically, for any nonnegative variable that is filtered by a matrix linear differential equation and observed with independent, log-concave noise, we can infer the optimal nonnegative trajectory via straightforward interior-point methods in  $O(T)$  (linear) time, as opposed to more standard approaches requiring  $O(T^3)$  time (where  $T$  is the total number of time steps). The key is to make use of the tridiagonal structure of the Hessian of the log-posterior here, which allows us to perform each Newton iteration in linear time. We apply this filter to an important problem in neuroscience: inferring a spike train from noisy calcium fluorescence observations. We demonstrate the filter's improved performance on simulated and real data. In conclusion, we propose that this filter is readily applicable for a number of real-time applications, including spike inference from simultaneously-observed large neural populations.

## 1 Introduction

## 2 Methods

### 2.1 Model

We assume a simple discrete-time state-space model relating spikes,  $n_t$ , baseline subtracted intracellular calcium concentration, denoted by  $C_t$ , and fluorescence measurements,  $F_t$ . First, we assume a linear relationship between  $F_t$  and  $C_t$ , with gaussian noise. Second, we assume that  $C_t$  jumps after each spike, and then decays according to some time constant. Finally, we assume that spikes are distributed according to a Poisson process. The above assumptions lead to the following model:

$$F_t = \alpha(C_t + \beta) + \varepsilon_t, \quad \varepsilon_t \sim \mathcal{N}(\mathbf{0}, \sigma^2 \mathbf{I}) \quad (1)$$

$$C_t = \gamma C_{t-1} + n_t, \quad n_t \sim \text{Poisson}(n_t; \lambda \Delta) \quad (2)$$

where  $\alpha$  and  $\beta$  set the fluorescence spatial filter and offset respectively,  $\sigma^2$  indicates the variance of the noise, and  $\gamma$  sets the decay rate.

### 2.2 Inference

Given such a model, our goal is to find the maximum *a posteriori* (MAP) spike train, i.e., the most likely spike train,  $\mathbf{n}$  (where we use the shorthand notation  $\mathbf{X} = [X_1, \dots, X_T]$ , and  $T$  is the final time step), given the fluorescence measurements,  $\mathbf{F}$ . Thus, the objective function that we'd like to solve may be written as:

$$\begin{aligned}
\hat{\mathbf{n}} &= \underset{n_t \in \mathbb{N}_0 \forall t}{\operatorname{argmin}} P[\mathbf{n}|\mathbf{F}] = \underset{n_t \in \mathbb{N}_0 \forall t}{\operatorname{argmin}} P[\mathbf{F}|\mathbf{n}]P[\mathbf{n}] \\
&= \underset{n_t \in \mathbb{N}_0 \forall t}{\operatorname{argmax}} \prod_{t=1}^T P[\mathbf{F}_t|C_t]P[n_t] = \underset{n_t \in \mathbb{N}_0 \forall t}{\operatorname{argmax}} \sum_{t=1}^T (\log P[\mathbf{F}_t|C_t] + \log P[n_t]) \\
&= \underset{n_t \in \mathbb{N}_0 \forall t}{\operatorname{argmin}} \sum_{t=1}^T \left( \frac{1}{2\sigma^2} \|\mathbf{F}_t - \boldsymbol{\alpha}(C_t + \beta)\|^2 - n_t \log \lambda \Delta + \log n_t! \right), \tag{3}
\end{aligned}$$

where  $\mathbb{N}_0 = \{0, 1, 2, \dots\}$ , and  $C_t$  is implicitly a function of  $n_t$ . Unfortunately, the computational complexity of solving Eq. (3) scales exponentially with  $T$ , i.e., is  $O(e^T)$ , making Eq. (3) an NP-hard problem. Thus, instead of an exact solution, we propose to make an approximation that reduces the complexity to be *polynomial* in  $T$ . In particular, we relax the assumption that we must have an integer number of spikes at any time step, by approximating the Poisson distribution with an exponential. Note that this is a common approximation technique in the machine learning literature [Hastie et al., 2001], as it is the closest convex relaxation to its non-convex counterpart. The constraint on  $n_t$  in Eq. (3) is therefore relaxed from  $n_t \in \mathbb{N}_0$  to  $n_t \geq 0$ :

$$\hat{\mathbf{n}} \approx \underset{n_t \geq 0 \forall t}{\operatorname{argmin}} \sum_{t=1}^T \left( \frac{1}{2\sigma^2} (\|\mathbf{F}_t - \boldsymbol{\alpha}(C_t + \beta)\|^2 + n_t \lambda \Delta) \right). \tag{4}$$

While this convex relaxation makes the problem tractable, the “sharp” threshold imposed by the nonnegativity constraint prohibits the use of standard gradient ascent techniques [Boyd and Vandenberghe, 2004]. We therefore take an “interior-point” (or “barrier”) approach, in which we drop the sharp threshold, and add a barrier term, which must approach  $-\infty$  as  $n_t$  approaches zero (e.g.,  $-\log n_t$ ) [Boyd and Vandenberghe, 2004]. By iteratively reducing the weight of the barrier term,  $z > 0$ , we are guaranteed to converge to the correct solution [Boyd and Vandenberghe, 2004],  $\hat{\mathbf{n}}$ . Thus, our goal is to efficiently solve:

$$\hat{\mathbf{n}}_z = \underset{n_t \geq 0 \forall t}{\operatorname{argmin}} \sum_{t=1}^T \left( \frac{1}{2\sigma^2} \|\mathbf{F}_t - \boldsymbol{\alpha}(C_t + \beta)\|^2 + n_t \lambda \Delta - z \log(n_t) \right), \tag{5}$$

which is concave and may therefore be solved exactly and efficiently using a gradient ascent technique. To see how, we first note that spikes and calcium are related to one another via a simple linear transformation, namely,  $n_t = f(C_t, C_{t-1}) = C_t - \gamma C_{t-1}$ , or, in matrix notation:

$$\mathbf{M}\mathbf{C} = \begin{bmatrix} 1 & 0 & 0 & \dots & \dots \\ 1 & -\gamma & 0 & \dots & \dots \\ 0 & 1 & -\gamma & 0 & \dots \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & 1 & -\gamma \end{bmatrix} \begin{bmatrix} C_1 \\ C_2 \\ \vdots \\ \vdots \\ C_T \end{bmatrix} = \begin{bmatrix} n_1 \\ n_2 \\ \vdots \\ \vdots \\ n_T \end{bmatrix} = \mathbf{n} \tag{6}$$

where  $\mathbf{M} \in \mathbb{R}^{T \times T}$  is a bidiagonal matrix, and  $\mathbf{C} = (C_1, \dots, C_T)^\top$  and  $\mathbf{n}$  are  $T$  dimensional column vectors ( $^\top$  indicates matrix transpose). Given Eq. (6), we may rewrite Eq. (5) in terms of  $\mathbf{C}$ :

$$\begin{aligned}
\hat{\mathbf{C}}_z &= \underset{C_t - \gamma C_{t-1} \geq 0 \forall t}{\operatorname{argmin}} \sum_{t=1}^T \left( \frac{1}{2\sigma^2} \|\mathbf{F}_t - \boldsymbol{\alpha}(C_t + \beta)\|^2 + (C_t - \gamma C_{t-1}) \lambda \Delta - z \log(C_t - \gamma C_{t-1} - \nu) \right) \\
&= \underset{\mathbf{M}\mathbf{C} \geq \mathbf{0}}{\operatorname{argmin}} \frac{1}{2\sigma^2} \left\| \mathbf{F} - \boldsymbol{\alpha}(\mathbf{C}^\top + \beta + \mathbf{1}^\top) \right\|^2 + \lambda \Delta (\mathbf{M}\mathbf{C})^\top \mathbf{1} - z \log(\mathbf{M}\mathbf{C})^\top \mathbf{1}, \tag{7}
\end{aligned}$$

where  $\mathbf{MC} \geq \mathbf{0}$  indicates that every element of  $\mathbf{MC}$  is greater than or equal to zero,  $'$  indicates transpose, and  $\mathbf{1}$  is a  $T$  dimensional column vector, and  $\log(\cdot)$  indicates an element-wise logarithm. As (7) is concave (it is identical to Eq. (5) with different notation), we may use any descent technique to find  $\hat{\mathbf{C}}_z$ . We elect to use the Newton-Raphson approach:

$$\hat{\mathbf{C}}_z \leftarrow \hat{\mathbf{C}}_z + s\mathbf{d} \quad (8a)$$

$$\mathbf{H}\mathbf{d} = \mathbf{g} \quad (8b)$$

$$\mathbf{g} = -\frac{\alpha}{\sigma^2}(\mathbf{F} - \alpha(\hat{\mathbf{C}}_z^\top + \beta)) + \lambda\Delta\mathbf{M}^\top\mathbf{1} - z\mathbf{M}^\top(\mathbf{M}\hat{\mathbf{C}}_z)^{-1} \quad (8c)$$

$$\mathbf{H} = \frac{\alpha^\top\alpha}{\sigma^2}\mathbf{I} + z\mathbf{M}^\top(\mathbf{M}\hat{\mathbf{C}}_z)^{-2}\mathbf{M} \quad (8d)$$

where  $s$  is the step size,  $\mathbf{d}$  is the step direction, and  $\mathbf{g}$  and  $\mathbf{H}$  are the gradient (first derivative) and Hessian (second derivative) of the likelihood, respectively (the likelihood is the argument to be minimized in Eq. (7)), and the exponents indicate element-wise operations. Note that we use “backtracking linesearches”, meaning that for each iteration, we find the maximal  $s$  that is between 0 and 1 and decreases the likelihood.

Typically, implementing Newton-Raphson requires inverting the Hessian, i.e.,  $\mathbf{d} = \mathbf{H}^{-1}\mathbf{g}$ , a computation consuming  $O(T^3)$  time. Instead, because  $\mathbf{M}$  is bidiagonal, the Hessian is tridiagonal, so the solution may be found in  $O(T)$  time via standard banded Gaussian elimination techniques (which can be implemented efficiently in Matlab using  $\mathbf{H} \setminus \mathbf{g}$ ). The resulting fast algorithm for solving the optimization problem in (4) is the main result of this paper, i.e. we may approximately infer the optimal solution for models characterized by equations such as (1) and (2) in linear time, whereas an exact solution would require exponential time, and a naïve approximate solution would require polynomial time.

### 3 Results

### 3.1 Main Result

To evaluate the efficacy of our fast filter, we compare it with the optimal linear (i.e., Wiener) filter [Wiener, 1949]. The top three panels of Fig. 1 depict a typical dataset simulated according to our model, Eqs. (1) and (2). Beneath the simulation, we show both the Wiener filter output (fourth panel) and our fast filter output (bottom panel). For both filters, we provided only the fluorescence observations depicted in the top panel, and  $\eta$ . From this data, we estimate the remaining parameters, and infer the hidden spike train. Several differences between these two approaches should be apparent. First, the effective signal-to-noise ratio (SNR) of our fast filter improves upon the optimal linear filter. Second, while the Wiener filter induces a “ringing” effect (where the inferred signal oscillates above and below zero), our fast filter completely eliminates this effect. These two improvements are common observations upon imposing a non-negative constraint when appropriate [Shumway and Stoffer, 2006]. Importantly, both our implementation of the Wiener filter and our fast filter require only  $O(T)$  time, whereas the naïve implementation of the Wiener filter requires  $O(T \log(T))$ , and the naïve implementation of a non-negative filter requires  $O(T^3)$ . Thus, when our approximation in Eq (4) is good, our filter outperforms the Wiener filter, and imposes approximately the same computational burden.

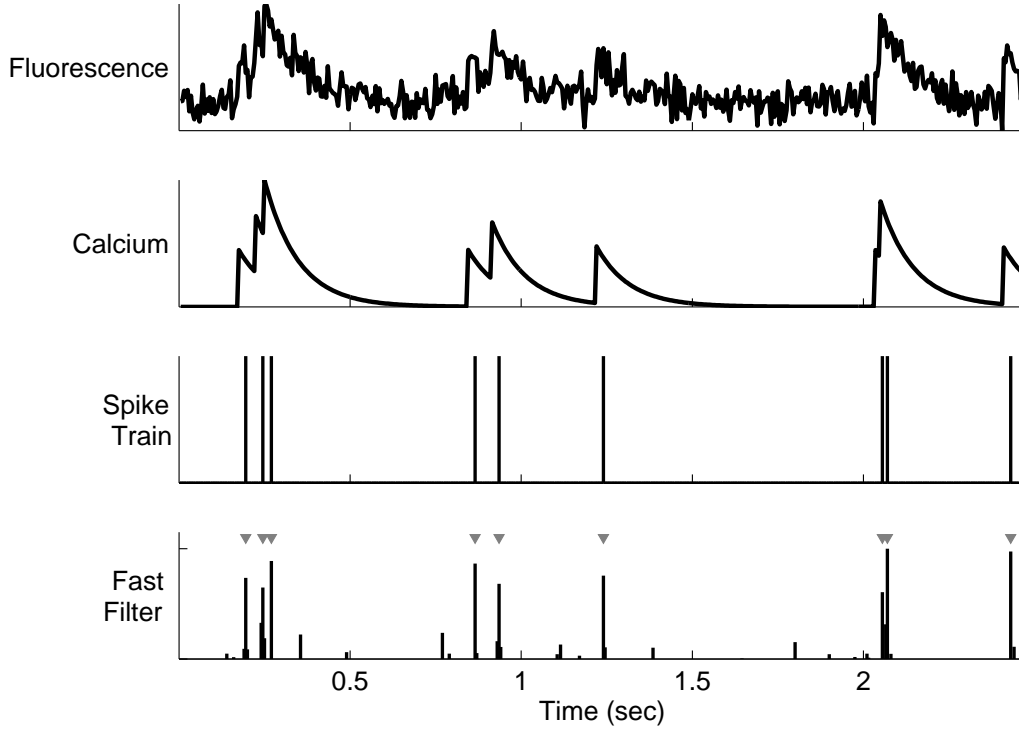


Figure 1: A simulation demonstrating that given a fluorescence time series, and the parameters of our model, we can accurately infer a close approximation to the most likely spike train. Top panel: simulated fluorescence time series. Second panel: simulated intracellular calcium concentration. Third panel: simulated spike train. Fourth panel: the fast filter’s inferred spike train (gray triangles indicate true spike times here, and elsewhere, unless indicated otherwise). Parameters:  $\Delta = 5$  msec,  $\alpha = 1$  photons/ $\mu\text{M}$ ,  $\beta = 0$  unitless,  $\sigma = 0.25$  photons,  $\tau = 100$  msec,  $\lambda = 5$  Hz.

### 3.2 Comparison with Wiener filter

When the observed neuron is spiking quickly, the Poisson distribution may be well approximated by a Gaussian distribution, suggesting that the Wiener filter may be optimal in this regime. But the exponential approximation of a Poisson is also very accurate in the fast spiking regime. To compare these two strategies, we simulated a fast spiking neuron, where the expected number of spikes per bin exceeds 10 (Fig. ??). In this scenario, both the Wiener filter and our fast filter perform approximately equally well. Both filters infer peaks in the firing rate that are obscured by the low-pass filter properties of the calcium dynamics. Thus, it seems from this analysis that regardless of the firing rate of the observable neuron, (1) filtering the signal may provide valuable information, and (2) our fast filter performs at least as well as the Wiener filter, without requiring more computational time.

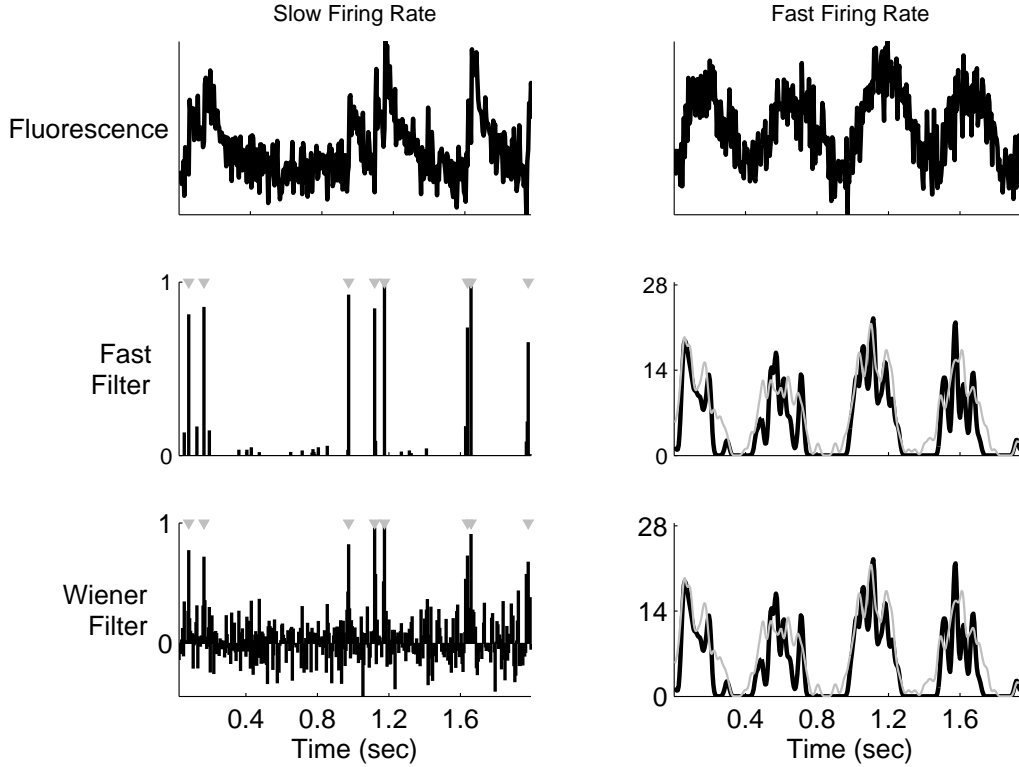


Figure 2: A simulation demonstrating that the fast filter performs at least as well as the optimal linear filter. The left panels show that in the slow firing regime, the fast filter — which approximates the Poisson distribution governing spiking with an exponential distribution — outperforms the Wiener filter — which approximates the Poisson distribution with a Gaussian. The right panels show that both approximations are sufficient in the fast firing regime. Top left panel: fluorescence time series for a neuron with a slow firing rate. Middle left panel: the fast filter’s inferred spike train. Bottom left panel: Wiener filter’s inferred spike train. Note that (i) the Wiener filter does not impose a non-negativity constraint, and (ii) the effective SNR of this filter in this example is higher than the fast filter’s. Top right panel: same as top left panel, for a neuron with a high firing rate. Middle right panel: the fast filter’s inferred spike train smoothed with a Gaussian kernel for visualization purposes (black line), and the true spike train smoothed with the same Gaussian kernel (gray line). Bottom right panel: same as middle right panel, but with the Wiener filter. Parameters for left panels: same as above. Parameters for right panels: same as above, except:  $\sigma = 8$  photons,  $\lambda = 500$  Hz.

### 3.3 Spatial Filtering

Model

$$\mathbf{F}_t = \boldsymbol{\alpha}(C_t + \beta) + \boldsymbol{\varepsilon}_t, \quad \boldsymbol{\varepsilon}_t \sim \mathcal{N}(\mathbf{0}, \sigma^2 \mathbf{I}) \quad (9)$$

Inference

initialize: use approximate pca algorithm

recursion: solve for  $\boldsymbol{\alpha}$  first, then  $\beta$

stopping criteria: likelihood stops improving significantly

Note that we can expand

$$P_{\boldsymbol{\theta}}[\mathbf{F}|\mathbf{C}] = \prod_{t=1}^T P_{\boldsymbol{\theta}}[\mathbf{F}_t|C_t] = \prod_{t=1}^T \prod_{x=1}^N P_{\boldsymbol{\theta}}[F_{t,x}|C_t] \quad (10)$$

Therefore, maximizing  $P_{\boldsymbol{\theta}}[\mathbf{F}|\mathbf{C}]$

$$\hat{\boldsymbol{\alpha}} = \underset{\boldsymbol{\alpha}}{\operatorname{argmax}} \prod_{t,x=1}^{T,N} P_{\boldsymbol{\theta}}[F_{t,x}|C_t] = \underset{\boldsymbol{\alpha}}{\operatorname{argmax}} \prod_{t,x=1}^{T,N} \mathcal{N}(F_{t,x}; \alpha_x(C_t + \beta), \sigma^2) \quad (11)$$

$$= \underset{\boldsymbol{\alpha}}{\operatorname{argmax}} \sum_{t,x=1}^{T,N} \log \mathcal{N}(F_{t,x}; \alpha_x(C_t + \beta), \sigma^2) \quad (12)$$

$$= \underset{\boldsymbol{\alpha}}{\operatorname{argmax}} -\frac{NT}{2} \log(2\pi\sigma^2) - \frac{1}{2\sigma^2} \sum_{t,x=1}^{T,N} (F_{t,x} - \alpha_x(C_t + \beta))^2 \quad (13)$$

$$= \underset{\boldsymbol{\alpha}}{\operatorname{argmin}} \sum_{t,x=1}^{T,N} (F_{t,x} - \alpha_x(C_t + \beta))^2. \quad (14)$$

Therefore, we can solve for each of the  $N$   $\hat{\alpha}_x$ 's separately and efficiently using Matlab's `mldivide`,

$$\hat{\alpha}_x = (\mathbf{C} + \beta \mathbf{1}) \setminus \mathbf{F}_x, \quad (15)$$

where  $\mathbf{F}_x = [F_{1,x}, \dots, F_{T,x}]^\top$ . Given  $\hat{\boldsymbol{\alpha}}$ , we can estimate  $\beta$ :

$$\hat{\beta} = \underset{\beta}{\operatorname{argmax}} \sum_{t,x=1}^{T,N} (F_{t,x} - \hat{\alpha}_x(C_t + \beta))^2 = \underset{\beta}{\operatorname{argmax}} \sum_{t,x=1}^{T,N} (F_{t,x} - \hat{\alpha}_x C_t + \beta \hat{\alpha}_x)^2 \quad (16)$$

$$\hat{\beta} = \hat{\alpha}_x \setminus \left( \sum_{t=1}^T F_{t,x} - \hat{\alpha}_x C_t \right) \quad (17)$$

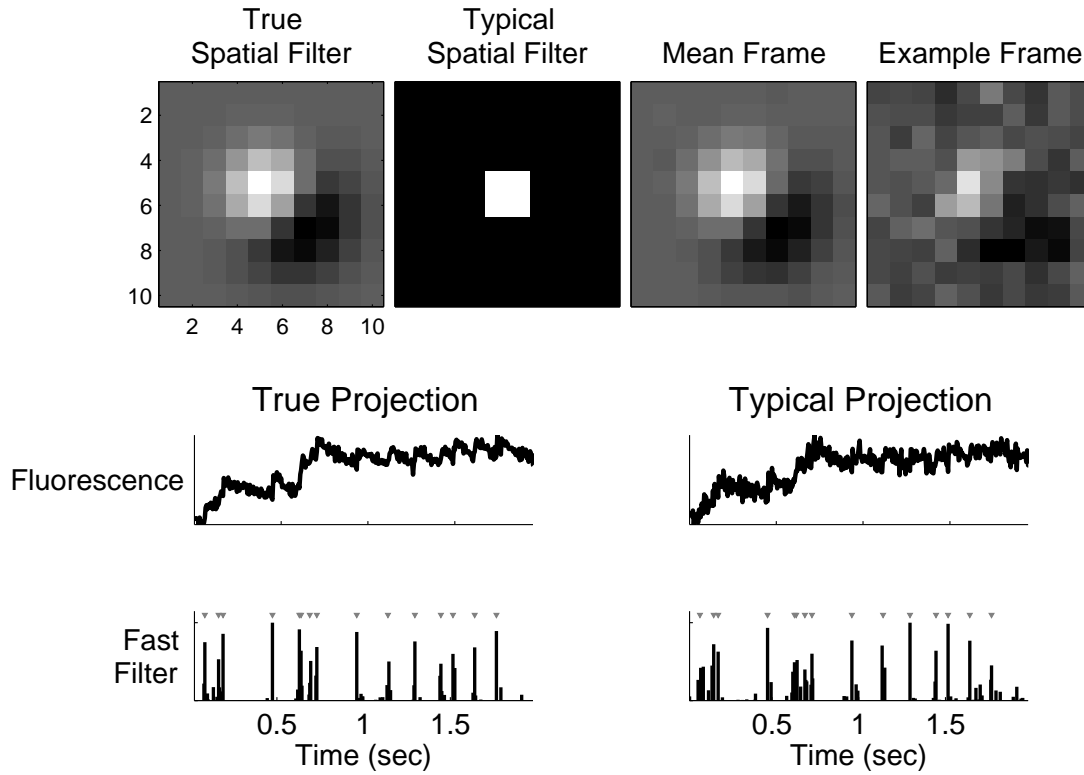


Figure 3: A simulation demonstrating that using a better spatial filter can significantly enhance the effective SNR (see Supplementary Movie 1 for the full movie associated with this simulation). Top: four movie frames. Middle left: projection of the entire movie onto the optimal spatial filter, yielding a 1D fluorescence time series, with a large SNR. Bottom left: fast filter’s inferred spike train using the optimal spatial filter. Middle right: projection of the entire movie onto the “mean” spatial filter, yielding a 1D fluorescence time series with a small SNR. Bottom right: fast filter’s inferred spike train using the mean spatial filter. Parameters different from Fig 1:  $\alpha$  is a mixture of two 2D-Gaussians, with mean  $\mu_1 = \mu_2 = [0, 0]$  and covariance matrices,  $\Sigma_i = \sigma_i^2 \mathbf{I}$ , with  $\sigma_1 = 2$  and  $\sigma_2 = 4$  and  $\mathbf{I}$  is the identity matrix.  $\beta = 1$ .

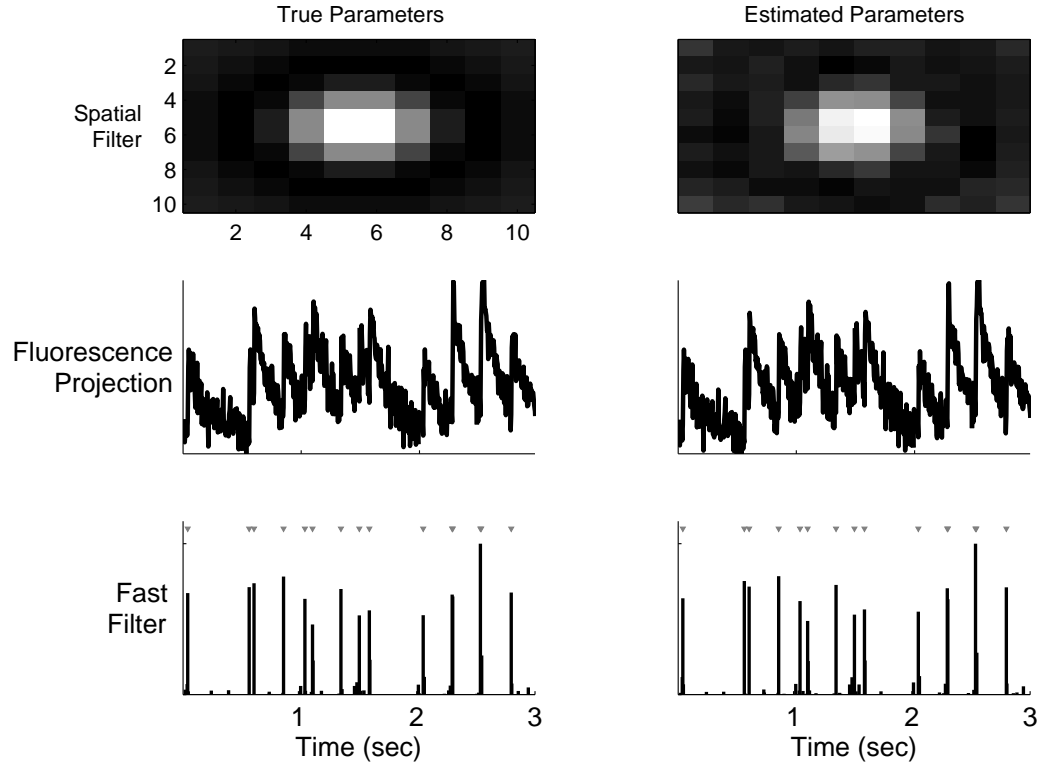


Figure 4: A simulation demonstrating that given only the fluorescence movie, the parameters may be estimated, and the spike train inferred (c.f. Supplementary Movie 2). Top left panel: true spatial filter. Middle left panel: projection of movie onto true spatial filter. Bottom left panel: inferred spike train using true parameters. Right panels: same as left except estimating parameters.  $\alpha$  initialized with the first singular value of  $F$ .  $\beta$  initialized with  $\mathbf{0}$ .  $\lambda$  and  $\sigma$  were initialized at double their true value.  $\tau$  was assumed known. Parameters same as above.



### 3.4 in vivo data

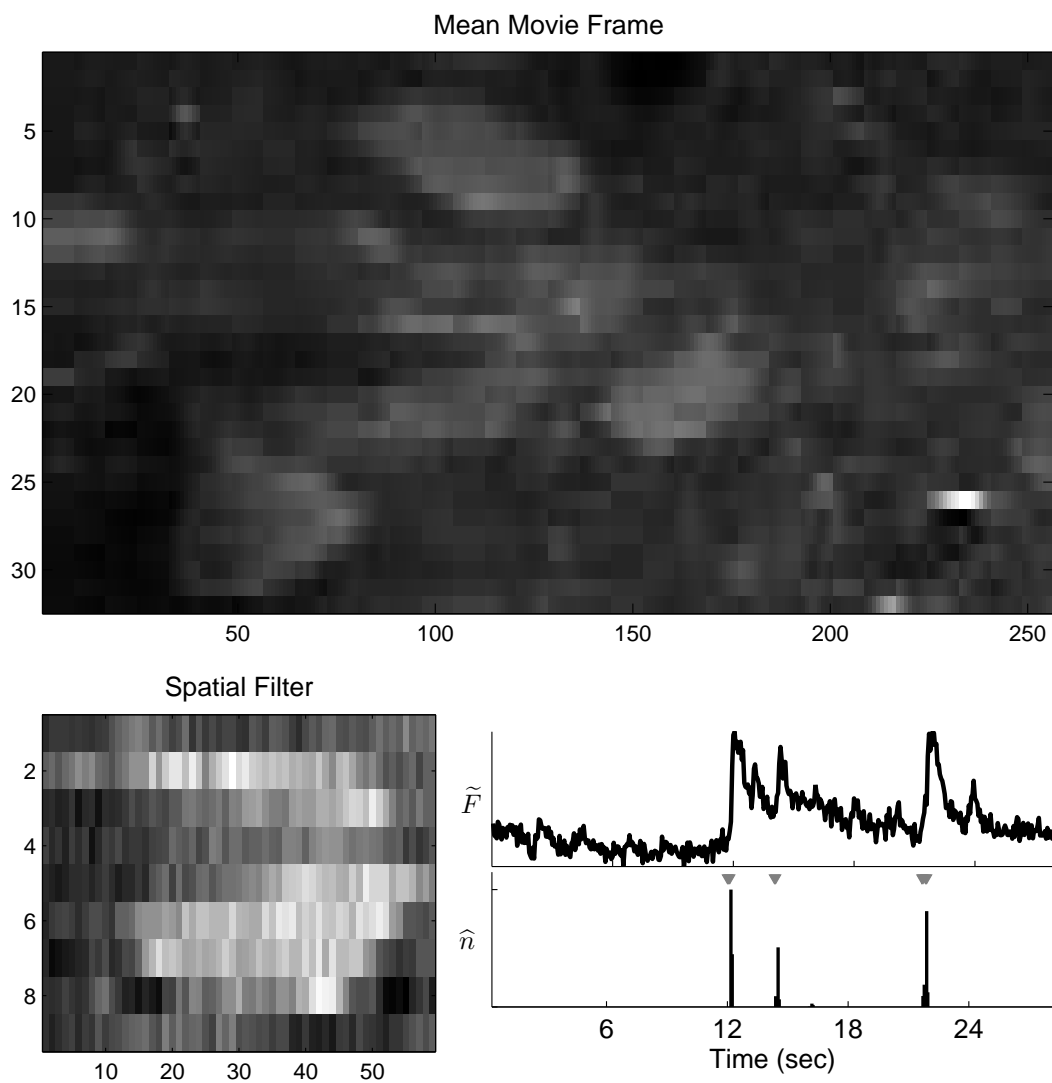


Figure 5: Given only a fluorescence movie, recorded in vivo, we can learn the parameters necessary to correctly infer the spike trains. Left: mean frame. Left: projection of movie onto mean frame. Left: the fast filter's inference.

Figure 6: distribution of errors in spike inference from real data



### 3.5 Overlapping spatial filters

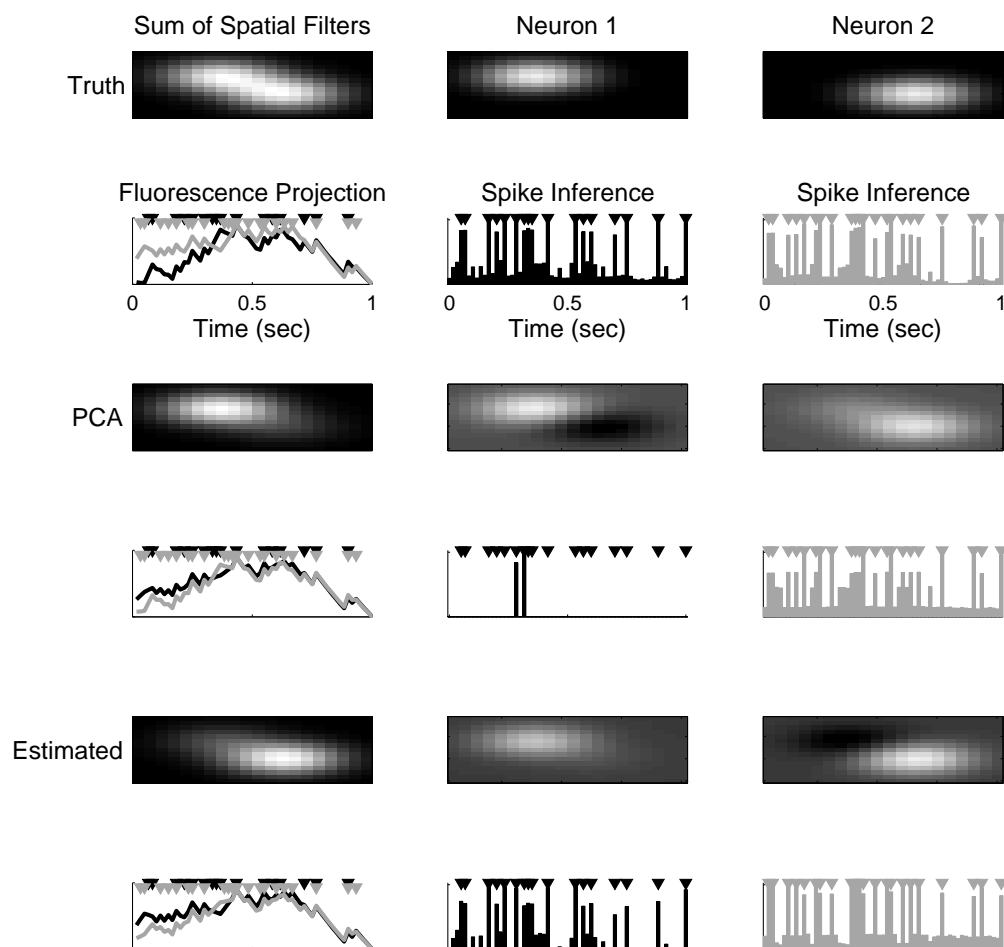


Figure 7: Simulation showing that even when two neuron's spatial filters are largely overlapping, our inference is as good as spatial EM, but with 2 cells in ROI

### **3.6 Analyzing a whole movie**

Figure 8: full movie, fully automated

Figure 9: full movie, fully automated, real data

### **3.7 Poisson observation model**

### **3.8 Time varying prior**

### **3.9 Slow dynamics**

### **3.10 Incorporating a nonlinear observation model**

### **3.11 Optimal thresholding**

## 4 Discussion

We show here that for certain nonnegative deconvolution problems, we can derive an algorithm that is both optimal and efficient. More specifically, our algorithm may be applied to any model with a nonnegative signal that is linearly filtered by a matrix linear ordinary differential equation. We apply this approach to the problem of inferring the most likely spike train given noisy calcium sensitive fluorescence observations (c.f. Fig. ??), and demonstrate, in simulations, that the optimal nonnegative filter outperforms the optimal linear (i.e., Wiener) filter in both slow and fast firing rate regimes (c.f. Fig. ??). Furthermore, when applied to data from a live cell, the optimal nonnegative filter outperforms a fast projection pursuit regression filter, which constrains the inferred spike train to be nonnegative integers (c.f. Fig. ??). On the other hand, the nonnegative filter is based on a linear observation model, and therefore suffers a loss of precision in the presence of strong saturation effects, in contrast to the optimal nonlinear particle filter (c.f. Fig. ??).

The implications of these results are severalfold. First, it seems as if there is no reason to use the Wiener filter for scenarios in which our algorithm may apply. Second, as our filter is so efficient, it may be used for many real-time processing applications. Specifically, upon simultaneously imaging a population of neurons [Ikegaya et al., 2004, Niell and Smith, 2005, Ohki et al., 2005, Yaksi and Friedrich, 2006, Sato et al., 2007], our filter may be applied essentially online. This could greatly expedite the tuning of important experimental parameters — such as laser intensity — to optimize signal-to-noise ratio for inferring spikes. Third, the parameters estimated from this filter may be used to initialize the parameters of the optimal nonlinear particle filter, which may then be used offline, to further refine the spike train inference.

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## A Wiener Filter

Sections 2.2 and ?? outline one approach to solving Eq. (3), by approximating the Poisson distribution with an exponential distribution, and imposing a non-negative constraint on the inferred  $\hat{\mathbf{n}}$ . Perhaps a more straightforward approach would be to approximate the Poisson distribution with a Gaussian distribution. In fact, as rate increases above about 10 spikes/sec, a Poisson distribution with rate  $\lambda\Delta$  is well approximated by a Gaussian with mean and variance  $\lambda\Delta$ . Given such an approximation, instead of Eq. (4), we would obtain:

$$\hat{\mathbf{n}}_w \approx \underset{\mathbf{n}_t \in \mathbb{R}, \forall t}{\operatorname{argmin}} \sum_{t=1}^T \left( \frac{1}{2\sigma^2} (F_t - C_t)^2 + \frac{1}{2\lambda\Delta} (n_t - \lambda\Delta)^2 \right) \quad (18)$$

As above, we can rewrite Eq. (18) in matrix notation in terms of  $\mathbf{C}$ :

$$\hat{\mathbf{C}}_w = \underset{\mathbf{C}_t \in \mathbb{R}, \forall t}{\operatorname{argmin}} \frac{1}{2\sigma^2} \|\mathbf{F} - \mathbf{C}\|^2 + \frac{1}{2\lambda\Delta} \|\mathbf{M}\mathbf{C} - \lambda\Delta\mathbf{1}\|^2 \quad (19)$$

which is quadratic in  $\mathbf{C}$ , and may therefore be solved analytically using quadratic programming,  $\hat{\mathbf{C}}_w = \hat{\mathbf{C}}_0 + \mathbf{d}_w$ , where  $\hat{\mathbf{C}}_0$  is the initial guess and  $\mathbf{d}_w = \mathbf{H}_w \setminus \mathbf{g}_w$ , where

$$\mathbf{g}_w = \frac{1}{\sigma^2} (\mathbf{C}'_0 - \mathbf{F}) + \frac{1}{\lambda\Delta} ((\mathbf{M}\hat{\mathbf{C}}_0)' \mathbf{M} - \lambda\Delta \mathbf{M}' \mathbf{1}) \quad (20)$$

$$\mathbf{H}_w = \frac{1}{\sigma^2} \mathbf{I} + \frac{1}{\lambda\Delta} \mathbf{M}' \mathbf{M} \quad (21)$$

Note that this solution is the optimal linear solution, under the assumption that spikes follow a Gaussian distribution, and is often referred to as the Wiener filter, regression with a smoothing prior, or ridge regression. To estimate the parameters for the Wiener filter, we take the same approach as above:

$$\hat{\boldsymbol{\theta}}_w \approx \underset{\boldsymbol{\theta}_w}{\operatorname{argmax}} P[\mathbf{F} | \hat{\mathbf{n}}_w, \boldsymbol{\theta}_w] P[\hat{\mathbf{n}}_w | \boldsymbol{\theta}_w] \quad (22a)$$

$$= \underset{\boldsymbol{\theta}_w}{\operatorname{argmax}} -\frac{T}{2} \log(4\pi^2 \sigma^2 \lambda\Delta) - \frac{1}{2\sigma^2} \|\mathbf{Y}_w + \boldsymbol{\eta}_w \mathbf{X}_w\|^2 - \frac{1}{2\lambda\Delta} \|\hat{\mathbf{n}}_w - \lambda\Delta\mathbf{1}\|^2 \quad (22b)$$

where  $\mathbf{Y}_w$ ,  $\boldsymbol{\eta}_w$ , and  $\mathbf{X}_w$  are defined as their subscriptless counterparts in Eq. (??).