Inferring spike trains given calcium-sensitive fluorescence observations

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The Most Important Slide of the Talk

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Outline

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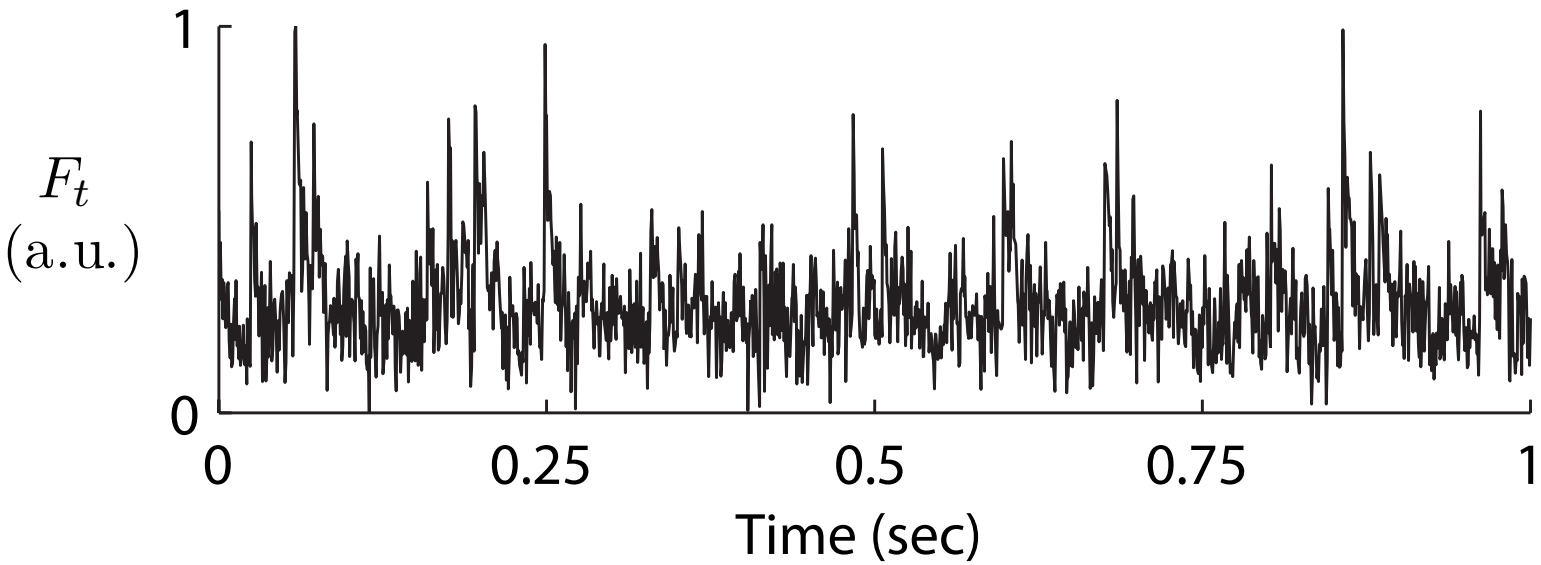
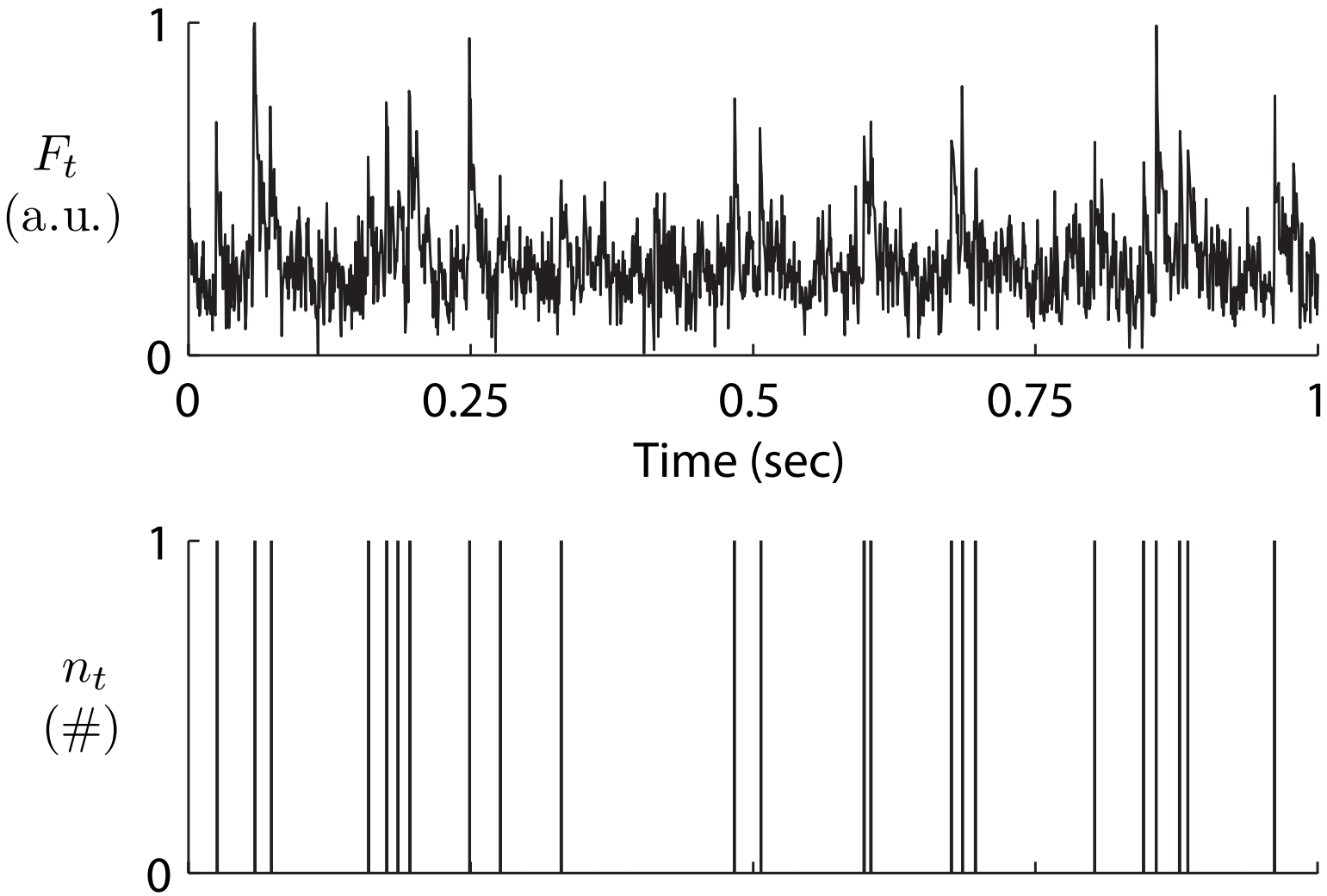
Motivation

Motivation

Problem Statement



Problem Statement



Problem Statement

Goal

Develop a framework to infer spike trains from calcium-sensitive fluorescence observations.

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Approach

Develop probabilistic "forward-models" of the experimental system, and invert them to find the spike trains.

Outline

A simple setup

Model 1: Poisson spiking, linear calcium, iid noise

$$F_t = [\mathrm{Ca}^{2+}]_t + \varepsilon_t, \qquad \varepsilon_t \sim \mathcal{N}(0,1)$$

$$\tau \frac{[\mathrm{Ca}^{2+}]_t - [\mathrm{Ca}^{2+}]_{t-1}}{\Delta} = -[\mathrm{Ca}^{2+}]_{t-1} + [\mathrm{Ca}^{2+}]_0 + An_t$$

$$n_t \sim Poisson(n_t; \lambda\Delta).$$

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Problem 1: Find most likely spike train, given the fluorescence

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

A (relatively) simple method

Method 1: a non-negative sparse solution

$$\begin{aligned}
\widehat{\mathbf{n}} &= \underset{n_t \geq 0 \forall t}{\operatorname{argmax}} P(\mathbf{n}|\mathbf{F}) \\
&= \underset{n_t \geq 0 \forall t}{\operatorname{argmax}} P(\mathbf{F}|\mathbf{n}) P(\mathbf{n}) \\
&= \underset{n_t \geq 0 \forall t}{\operatorname{argmax}} \mathcal{N}(\mathbf{F}; [\mathrm{Ca}^{2+}], 1) \mathit{Poisson}(\mathbf{n}; \lambda\Delta) \\
&\approx \underset{n_t \geq 0 \forall t}{\operatorname{argmax}} \mathcal{N}(\mathbf{F}; [\mathrm{Ca}^{2+}], 1) \mathit{Exp}(\mathbf{n}; \lambda\Delta).
\end{aligned}$$

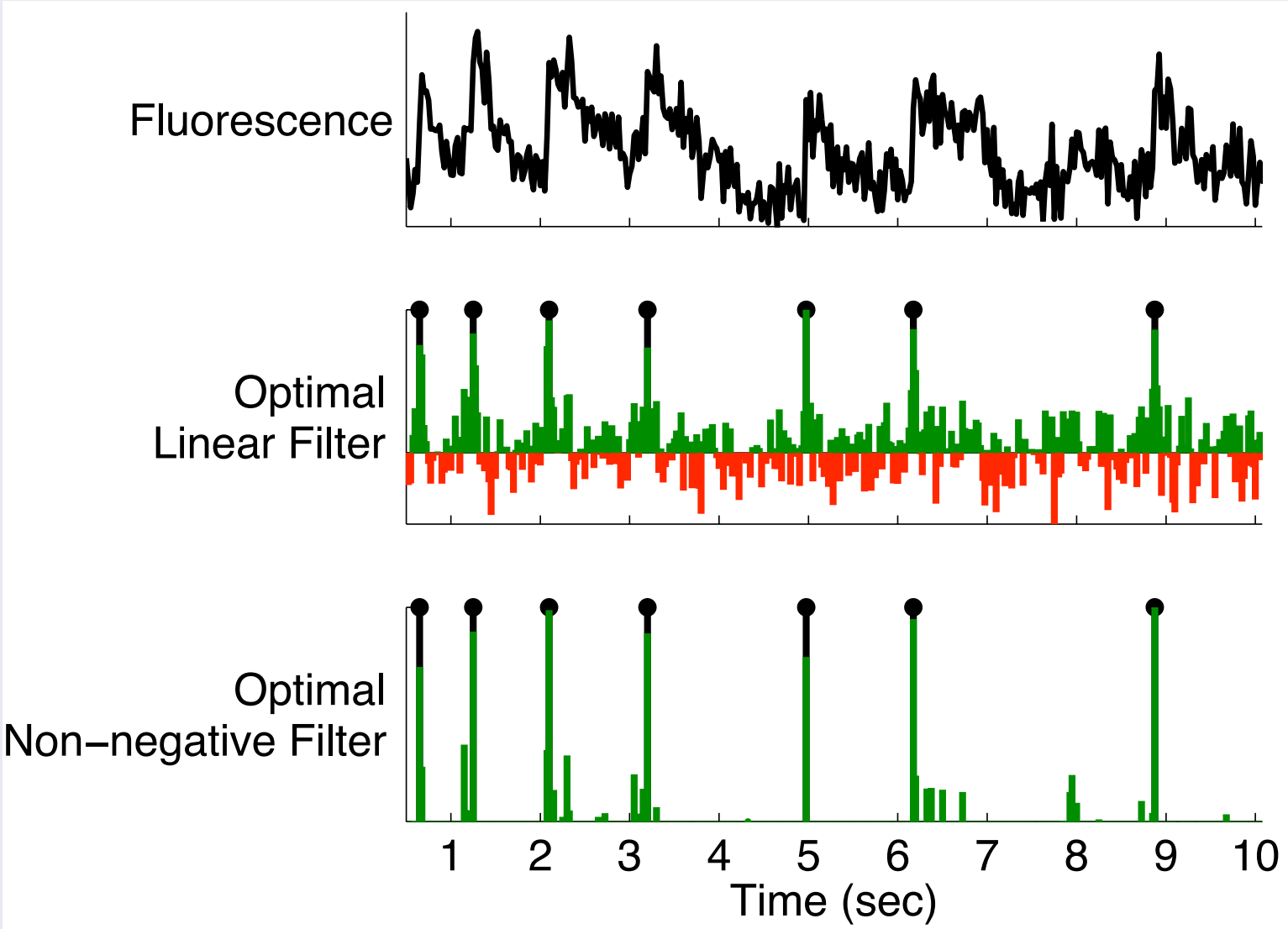
A (relatively) simple method

Features of Method 1: Fast and Concave

- $[Ca^{2+}]$ is a linear function of n
- Replace sharp threshold $n_t \geq 0$ with log-concave threshold $\eta f(n_t)$, and slowly "sharpen" until converging
- The soft threshold makes the argument log-concave
- We use Newton-Raphson to maximize argument: $[Ca^{2+}] \leftarrow [Ca^{2+}] + s\mathbf{H}^{-1}\mathbf{g}$
- Because calcium filter is exponential, $\mathbf{H}$ is tridiagonal
- Therefore $\mathbf{H}^{-1}$ may be computed in $O(T)$ instead of $O(T^3)$
- Wiener filter (optimal for $n \sim$ Gaussian) requires $O(T \log T)$

A simple demo

Simulated demo 1: Fluorescence, optimal linear and non-negative filter



A simple comparison

Comparison 1: Optimal linear vs. Optimal non-negative

	Optimal linear	Optimal non-negative
Parameters	$\{A, \tau, \sigma, \lambda\}$	$\{A, \tau, \sigma, \lambda\}$
Speed	$O(T \log T)$	$O(T)$
Performance	good	better
Overall	X	✓

Outline

A sophisticated model

Model 2: Incorporating saturation and signal-dependent noise

$$F_t = S([\mathrm{Ca}^{2+}]_t) + \text{"noise}_t\text{"}$$

$$\text{"noise}_t\text{"} = S([\mathrm{Ca}^{2+}]_t) + \sigma_F \varepsilon_t, \qquad \varepsilon_t \sim \mathcal{N}(0,1)$$

$$S(x) = \alpha \frac{x^n}{x^n + k_d} + \beta.$$

A sophisticated method

Method 2: A sequential Monte Carlo (a.k.a., particle filtering) expectation maximization (SMC-EM) solution

The goal is the find the probability of a spike occurring in any image frame, given the entire sequence of fluorescence observations:

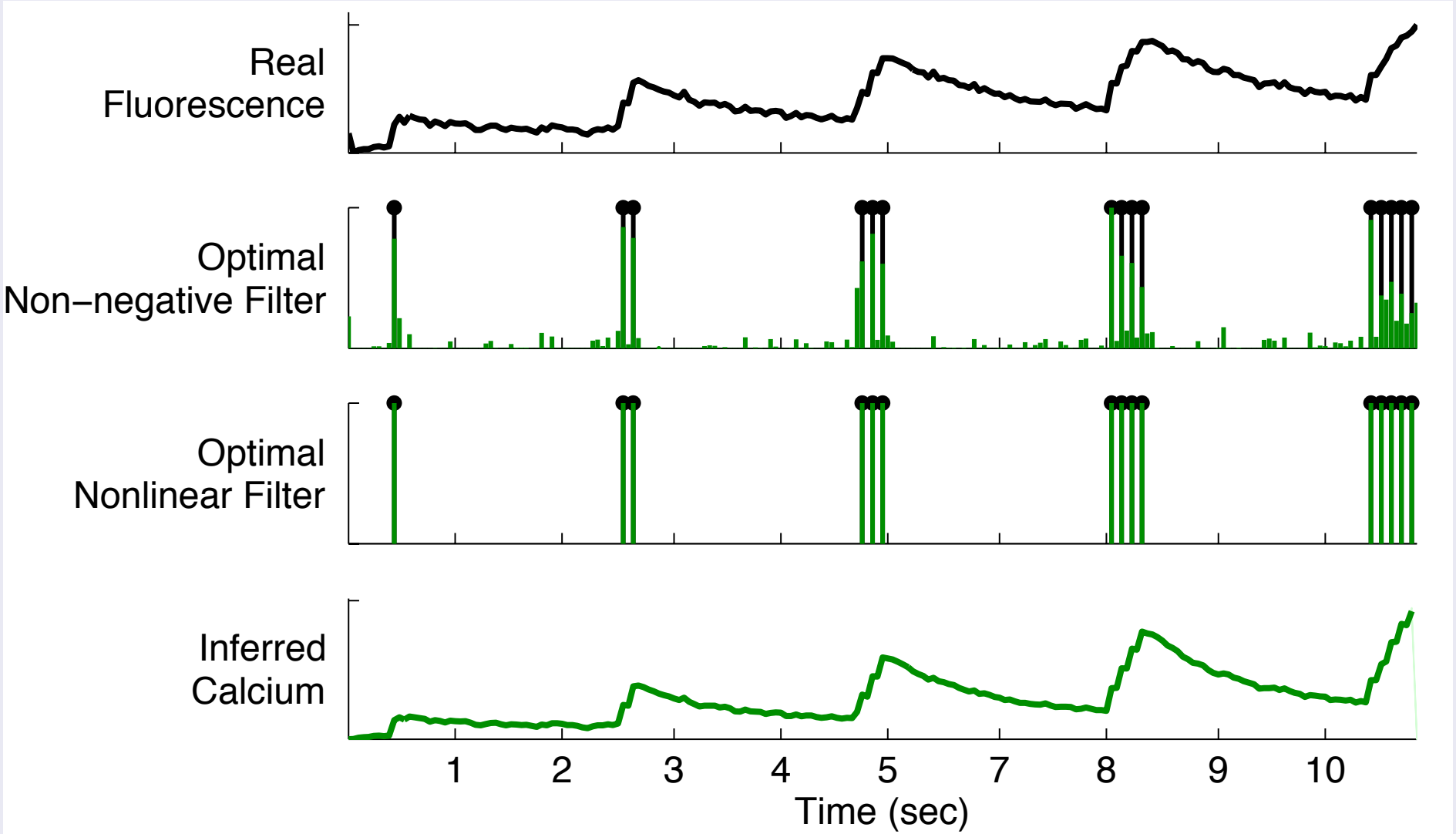
$$E[n_t = 1|\mathbf{F}].$$

Technical note

We use a Forward-Backward approach to estimate the E step (where the Forward recursion is approximated using SMC), and gradient ascent to solve the M step, which is concave.

A sophisticated demo

In vitro demo 1: Inferring spike times given saturating observations



A sophisticated comparison

Comparison 2: Optimal linear vs. non-negative vs. nonlinear

	Linear	Non-negative	Nonlinear
Parameters	$\{A, \tau, \sigma, \lambda\}$	$\{A, \tau, \sigma, \lambda\}$	$+\{n, k_d, \alpha, \beta, \sigma_F\}$
Speed	$O(T \log T)$	$O(T)$	$O(N^2 T)$
Performance	good	better	best
Errorbars	X	X	✓
Overall	X	✓	✓✓

Outline

Generalizations

Generalization 1: Stimulus and spike history dependence

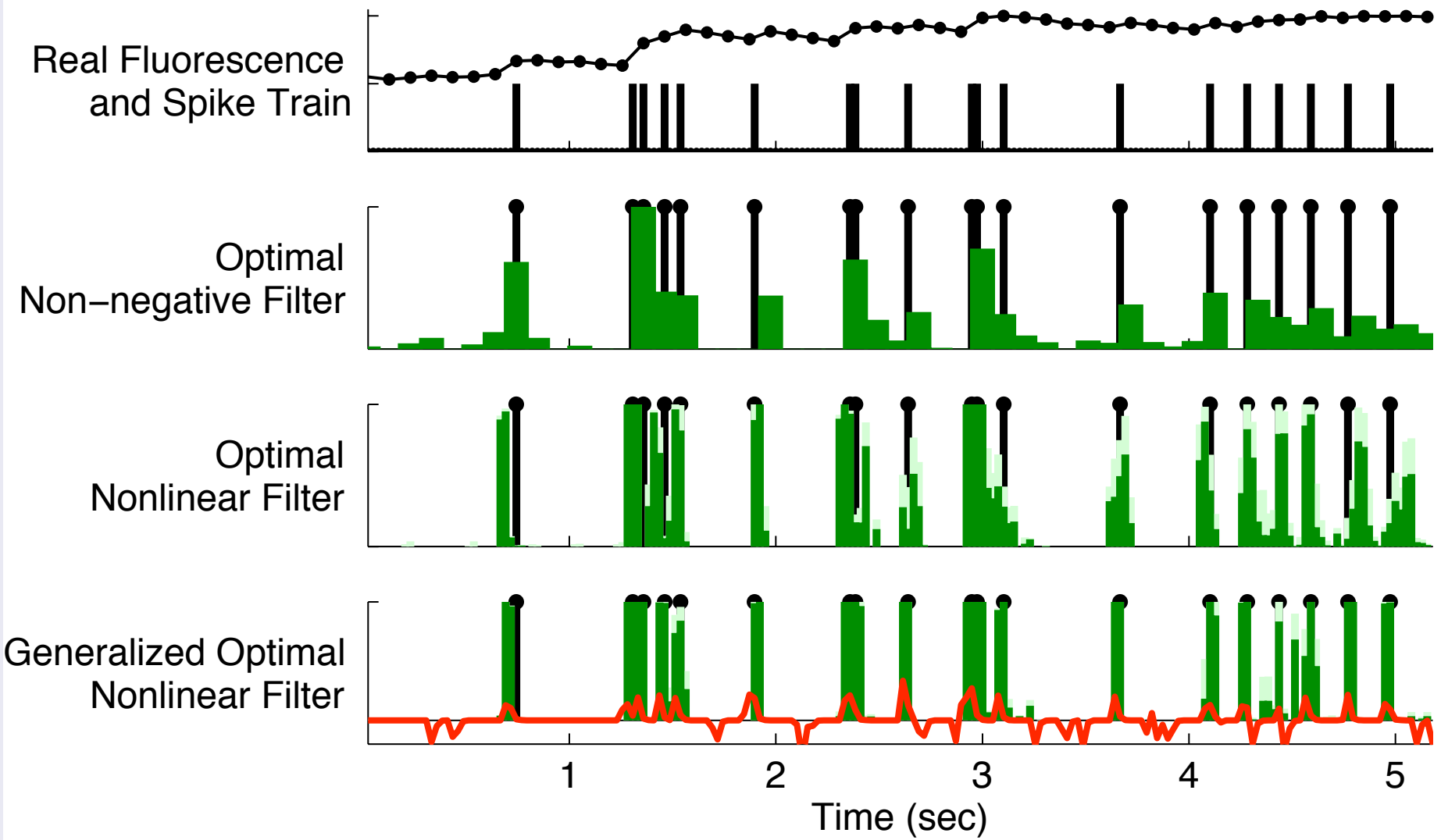
Replace Poisson spiking with a Generalized Linear Model (GLM)

Generalization 2: Superresolution

Sampling spikes with finer temporal resolution than image frames, to determine when within a frame a spike occurs

A generalized demo

In vitro demo 2: incorporating input and superresolution



A generalized comparison

Comparison 3: Optimal non-negative vs. Generalized optimal nonlinear

	Non-negative	Generalized nonlinear
Parameters	$\{A, \tau, \sigma, \lambda\}$	$+\{n, k_d, \alpha, \beta, \sigma_F, \mathbf{k}, \boldsymbol{\omega}, \tau_h, \sigma_h\}$
Speed	$O(T)$	$O(N^2 T)$
Performance	good	better
Errorbars	X	✓
Spike histories	X	✓
Stimulus	ish	✓
Superresolution	ish	✓
Overall	✓	✓✓

Outline

Further generalizations

Relaxing the assumptions

- Slower rise time for fluorescence
- Multiple time constants for calcium

Other

- Movement artifacts
- Spatial filtering of image
- Populations of neurons

References

Coming soon...

- Vogelstein JT et al. *Fast algorithms for inferring spike trains from calcium sensitive fluorescence observations*. In preparation.
- Vogelstein, JT, et al. *Model-based optimal inference of spike times given noisy calcium sensitive fluorescence observations*. Under review at Biophysical Journal.