

# Inferring spike trains given calcium-sensitive fluorescence observations

Joshua Vogelstein

Johns Hopkins University

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# The Most Important Slide of the Talk

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## Acknowledgments

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- Data: Brendon O. Watson and Rafael Yuste

# Outline

- 1 Introduction
- 2 Simplification
- 3 Sophistication
- 4 Generalization
- 5 Discussion

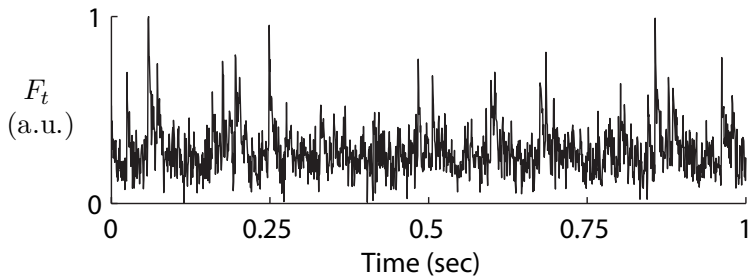
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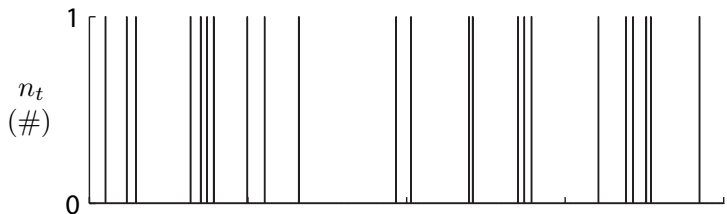
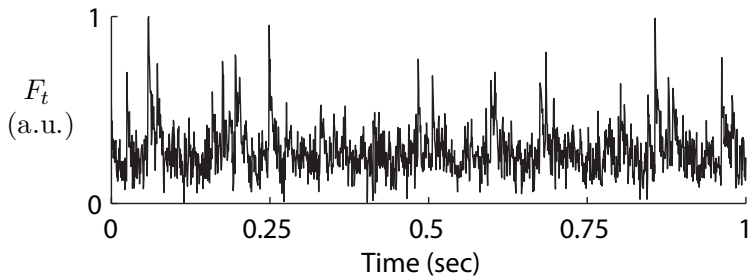
# Motivation

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

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## Why is this difficult

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## Approach

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

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# A simple setup

Model 1: Poisson spiking, linear calcium, iid noise

$$F_t = [\text{Ca}^{2+}]_t + \varepsilon_t, \quad \varepsilon_t \sim \mathcal{N}(0, 1)$$
$$\tau \frac{[\text{Ca}^{2+}]_t - [\text{Ca}^{2+}]_{t-1}}{\Delta} = -[\text{Ca}^{2+}]_{t-1} + [\text{Ca}^{2+}]_0 + An_t$$
$$n_t \sim \text{Poisson}(n_t; \lambda\Delta).$$

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

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

## A (relatively) simple method

## Method 1: a non-negative sparse solution

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

# A (relatively) simple method

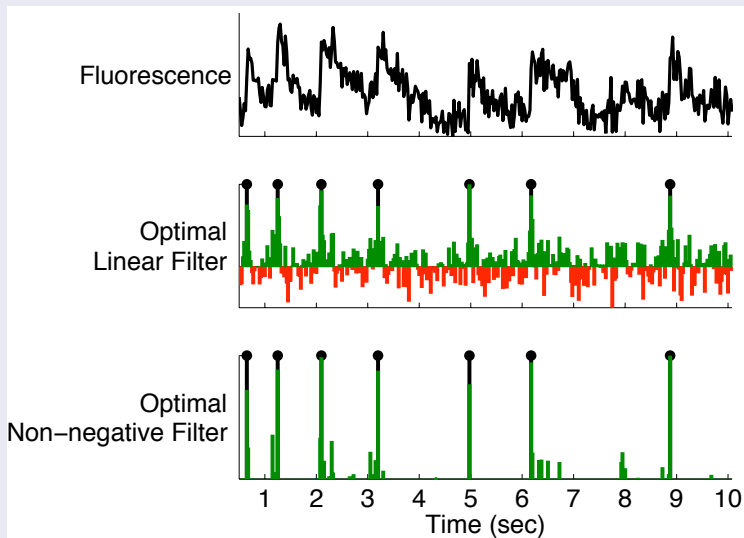
## Features of Method 1: Fast and Concave

- $[\text{Ca}^{2+}]$  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:  

$$[\text{Ca}^{2+}] \leftarrow [\text{Ca}^{2+}] + s\mathbf{H}^{-1}\mathbf{g}$$
- 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	✓

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# A sophisticated model

## Model 2: Incorporating saturation and signal-dependent noise

$$F_t = S([\text{Ca}^{2+}]_t) + \text{"noise}_t\text{"}$$
$$\text{"noise}_t\text{"} = S([\text{Ca}^{2+}]_t) + \sigma_F \varepsilon_t, \quad \varepsilon_t \sim \mathcal{N}(0, 1)$$
$$S(x) = \alpha \frac{x^n}{x^n + k_d} + \beta.$$

# A sophisticated method

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

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

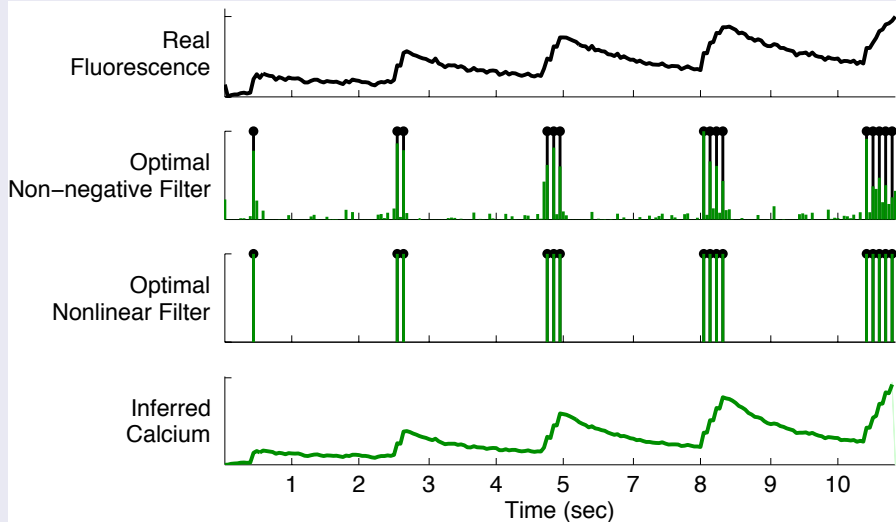
$$E[n_t = 1 | \mathbf{F}].$$

## 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	✓	✓✓

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# Generalizations

## Generalization 1: Stimulus and spike history dependence

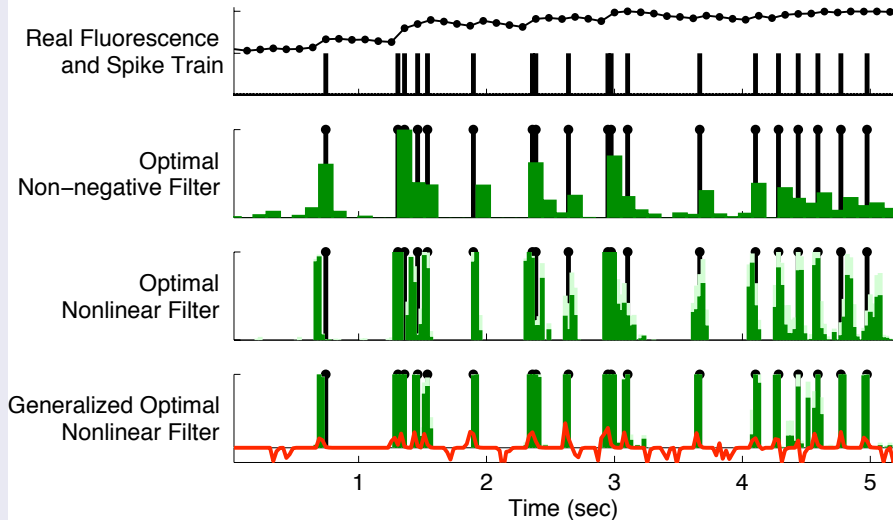
Replace Poisson spiking with a Generalized Linear Model (GLM)

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

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# 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.