Inferring spike trains, learning tuning curves, and estimating connectivity, from calcium imaging

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Reference: Vogelstein JT, Watson BO, Packer AM, Yuste R, Jedynak B, Paninski L. Spike inference from calcium imaging using sequential Monte Carlo methods. Biophysical Journal. *in press*.

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background

- the neural signal of interest is a spike train, ie, the time of each action potential
- one could simultaneously observe an ensemble of neurons using calcium imaging technologies
- from the movie, we'd like to infer the precise spike train for each neuron
- we'd also like to estimate the tuning curve for each neuron
- finally, we want to know the effective connection strength between each pair of neurons
- this is a difficult computational problem, to which we humbly submit a potential step

definition of terms

States	
F_t	fluorescence
$[\mathrm{Ca}^{2+}]_t$	intracellular calcium concentration
n_t	spike
Parameters	
α	scale
β	offset
σ_F	measurement noise scale
τ	decay of calcium
A	jump size due to spike
$[\mathrm{Ca}^{2+}]_b$	baseline of calcium
σ_c	calcium noise scale
λ	probability of spiking
Other	
$S(\cdot)$	Hill Equation: $S(x) = x^m/(x^m + k_d)$
$\varepsilon_{\cdot,t}$	standard normal random variable
Δ	time step size
$\mathcal{B}(n_t; \lambda)$	Bernoulli random variable, $n_t = 1$ w.p. λ and 0 o.w.
T	total number of steps

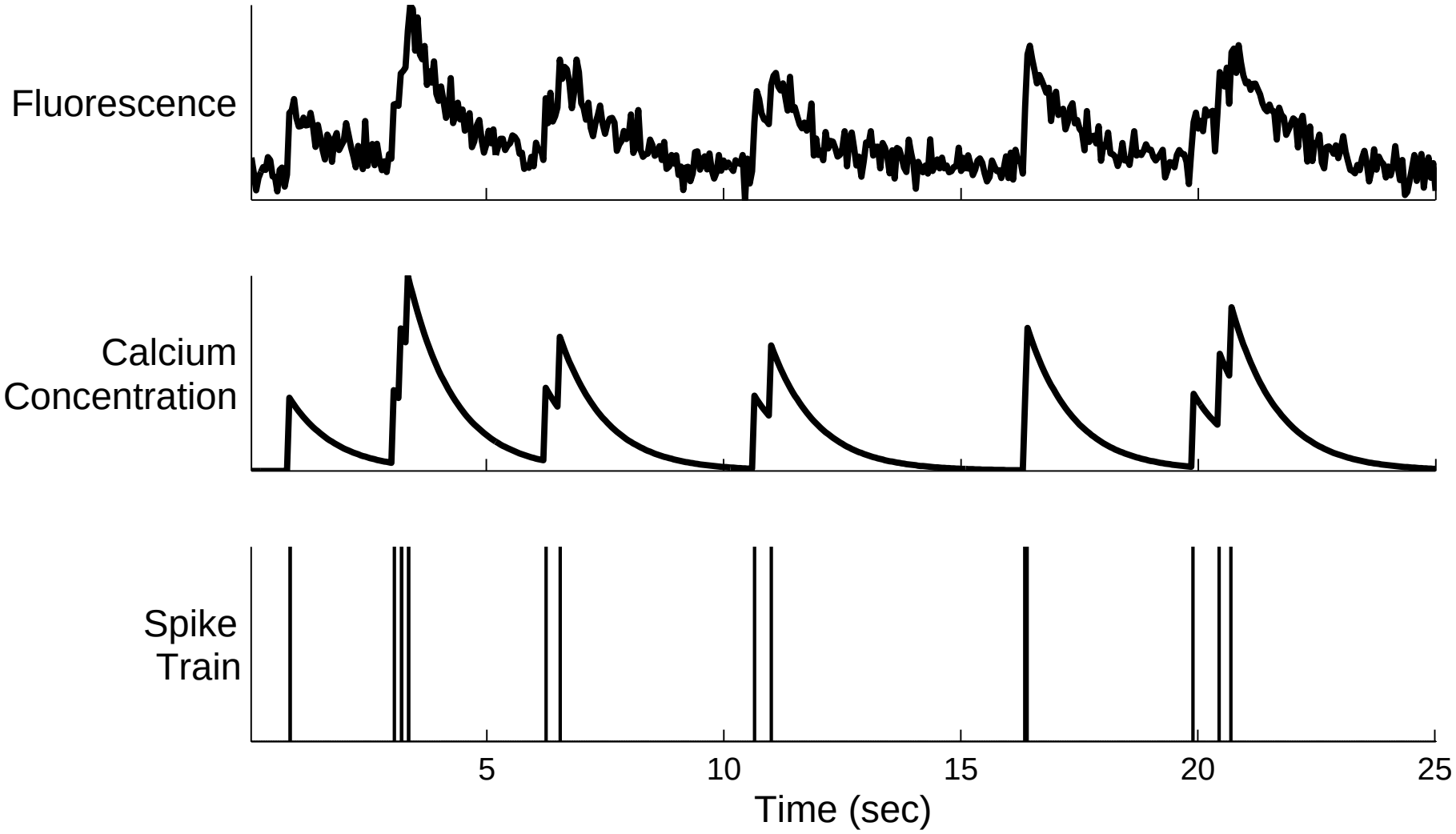
a simple model

$$F_t = \alpha[\mathrm{Ca}^{2+}]_t + \beta + \varepsilon_{F,t}$$

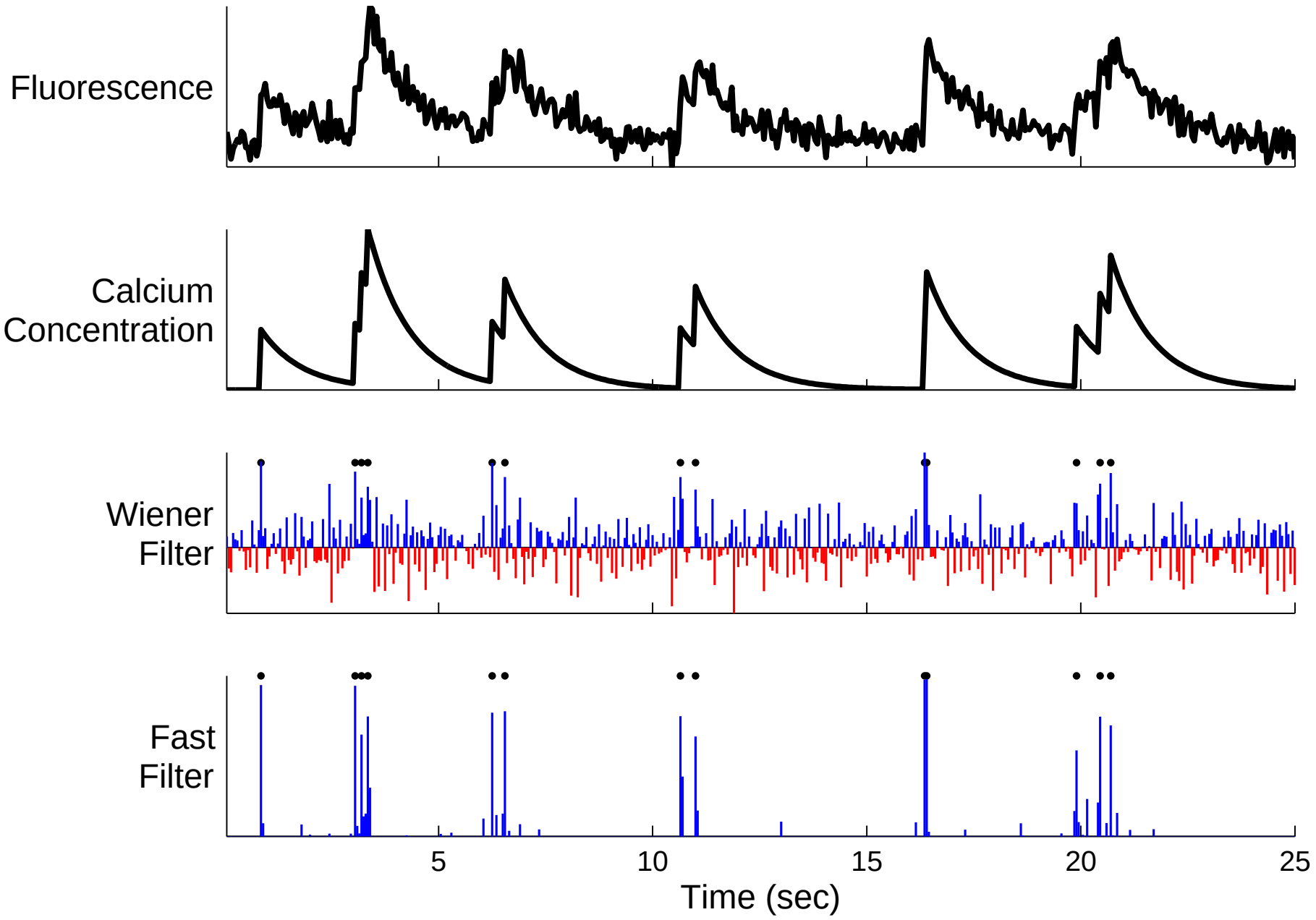
$$\tau \frac{[\mathrm{Ca}^{2+}]_t - [\mathrm{Ca}^{2+}]_{t-1}}{\Delta} = -[\mathrm{Ca}^{2+}]_{t-1} + n_t$$

$$n_t \sim \mathcal{B}(n_t; \lambda\Delta)$$

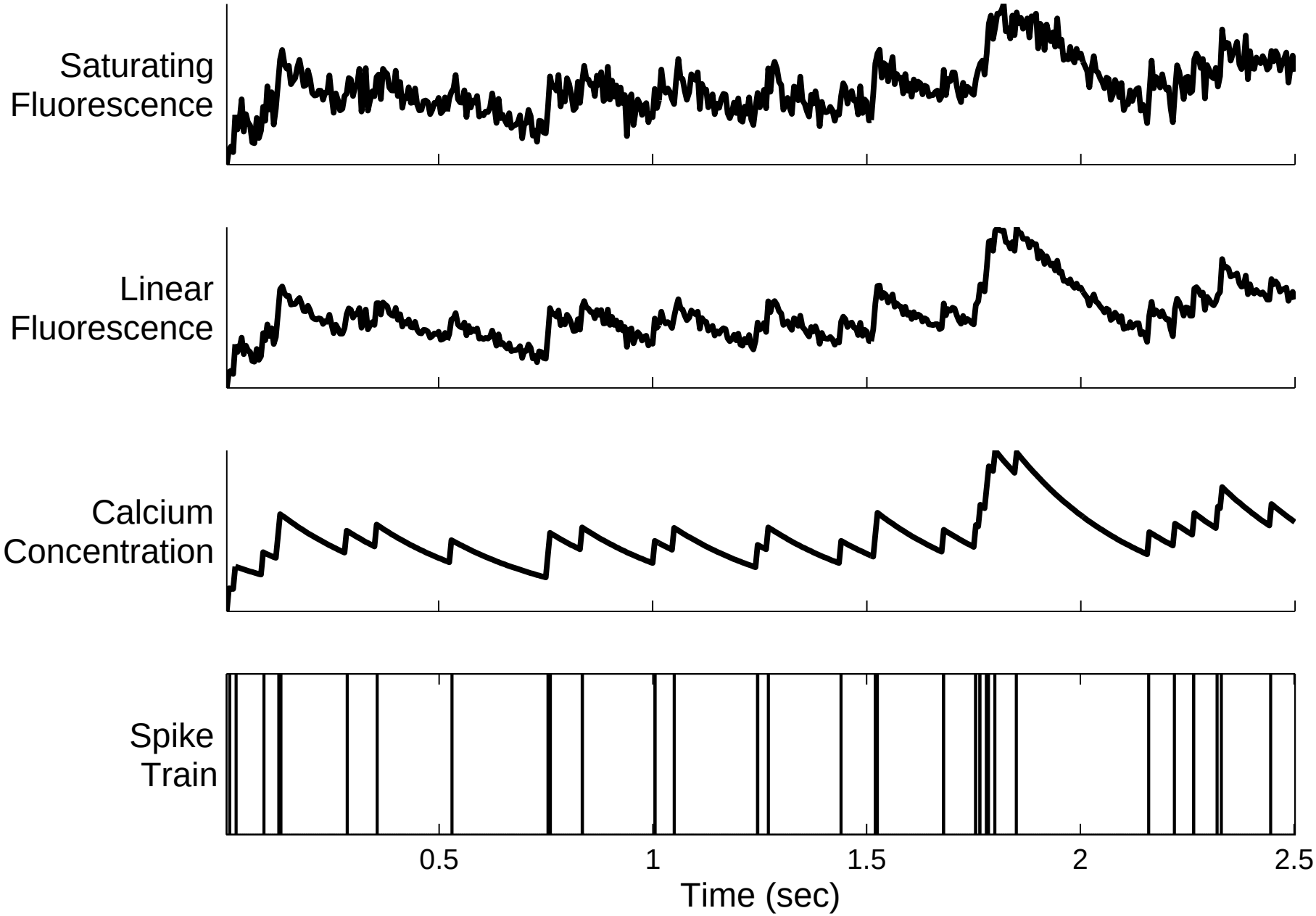
a simple schematic



a simple method



a less simple schematic: saturation



a less simple model: saturation

$$F_t = \alpha S([\mathrm{Ca}^{2+}]_t) + \beta + (S([\mathrm{Ca}^{2+}]_t) + \sigma_F)\varepsilon_{F,t}$$

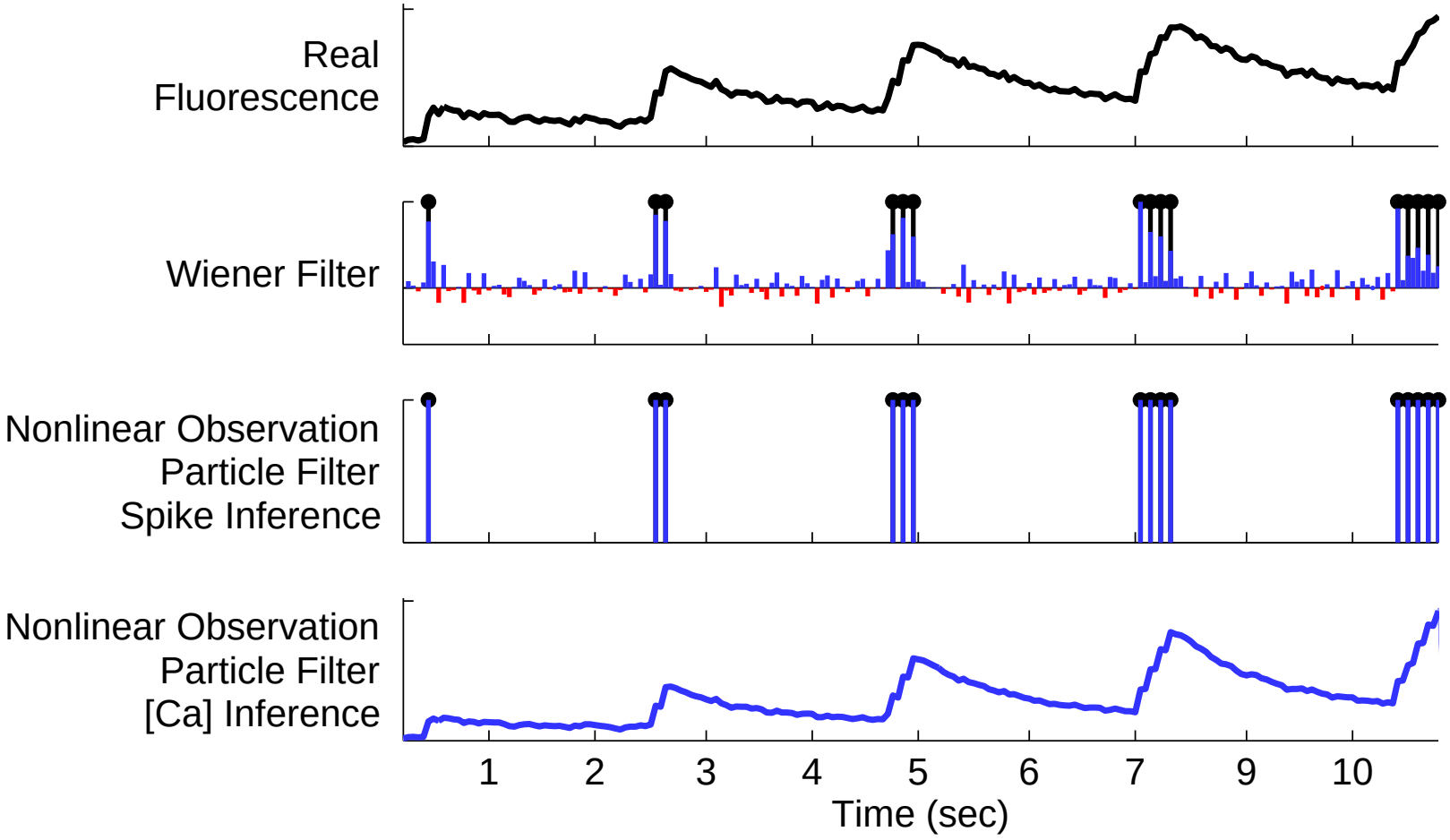
$$\tau \frac{[\mathrm{Ca}^{2+}]_t - [\mathrm{Ca}^{2+}]_{t-1}}{\Delta} = -[\mathrm{Ca}^{2+}]_{t-1} + An_t + [\mathrm{Ca}^{2+}]_b + \sigma_c\sqrt{\Delta}\varepsilon_{c,t}$$

$$n_t \sim \mathcal{B}(n_t; \lambda\Delta)$$

a less simple simple method: sequential monte carlo (aka, particle filter)

- given the above model, we would like to find the probability of a neuron spiking at any time given the entire sequence of fluorescence measurements
- this requires estimating all the parameters in the model
- we embed a forward-backward particle filter-smoother into and expectation-maximization algorithm to infer the spike trains and learn the parameters
- our code runs in approximately real time (ie, 10 sec of data requires 10 sec of analysis)

a less simple simple result: in vitro data



an even less simple model: intermittent observations

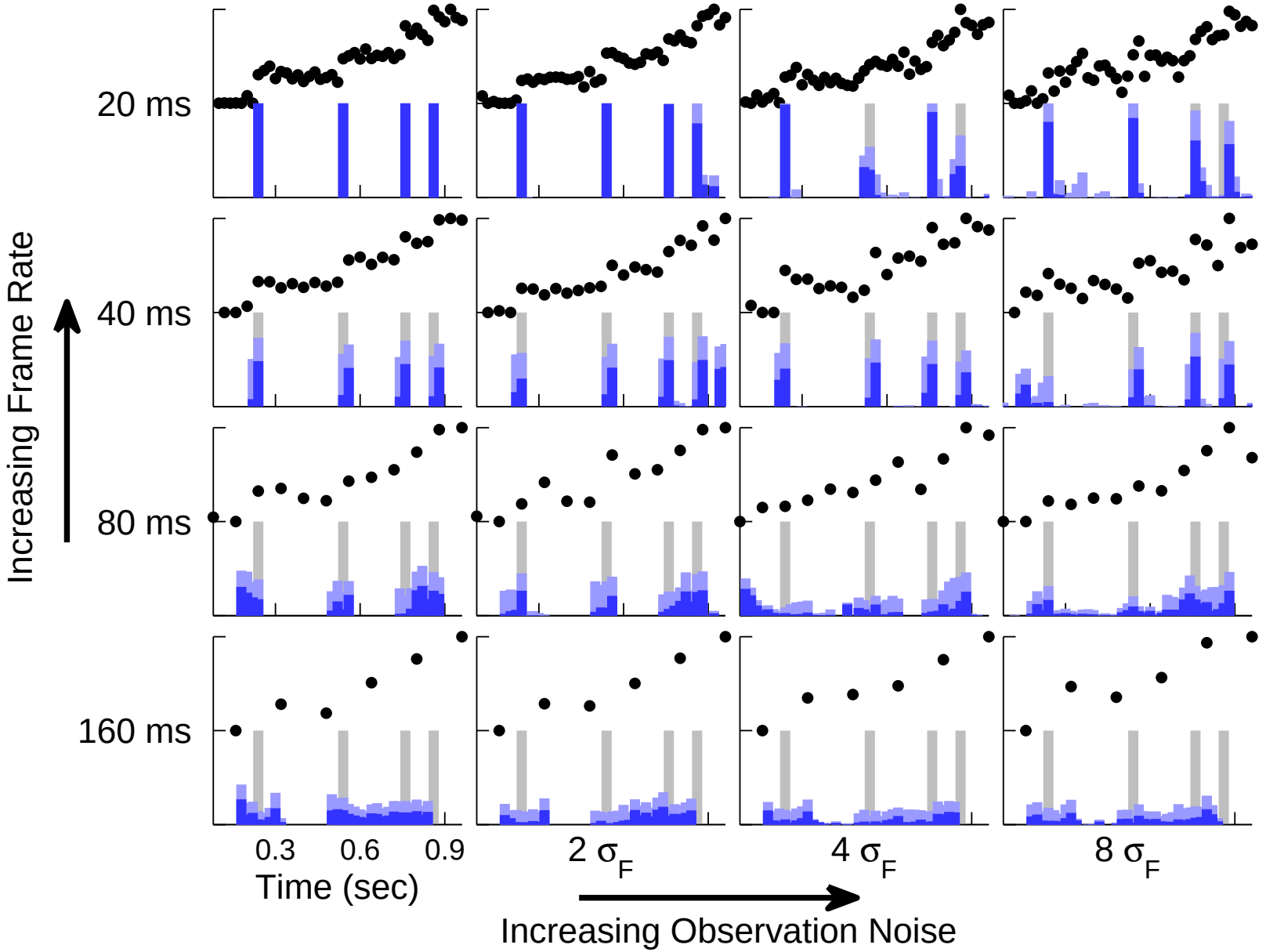
$$F_t = \alpha S([\mathrm{Ca}^{2+}]_t) + \beta + (S([\mathrm{Ca}^{2+}]_t) + \sigma_F)\varepsilon_{F,t}$$

$$\tau \frac{[\mathrm{Ca}^{2+}]_t - [\mathrm{Ca}^{2+}]_{t-1}}{\Delta} = -[\mathrm{Ca}^{2+}]_{t-1} + An_t + [\mathrm{Ca}^{2+}]_b + \sigma_c\sqrt{\Delta}\varepsilon_{c,t}$$

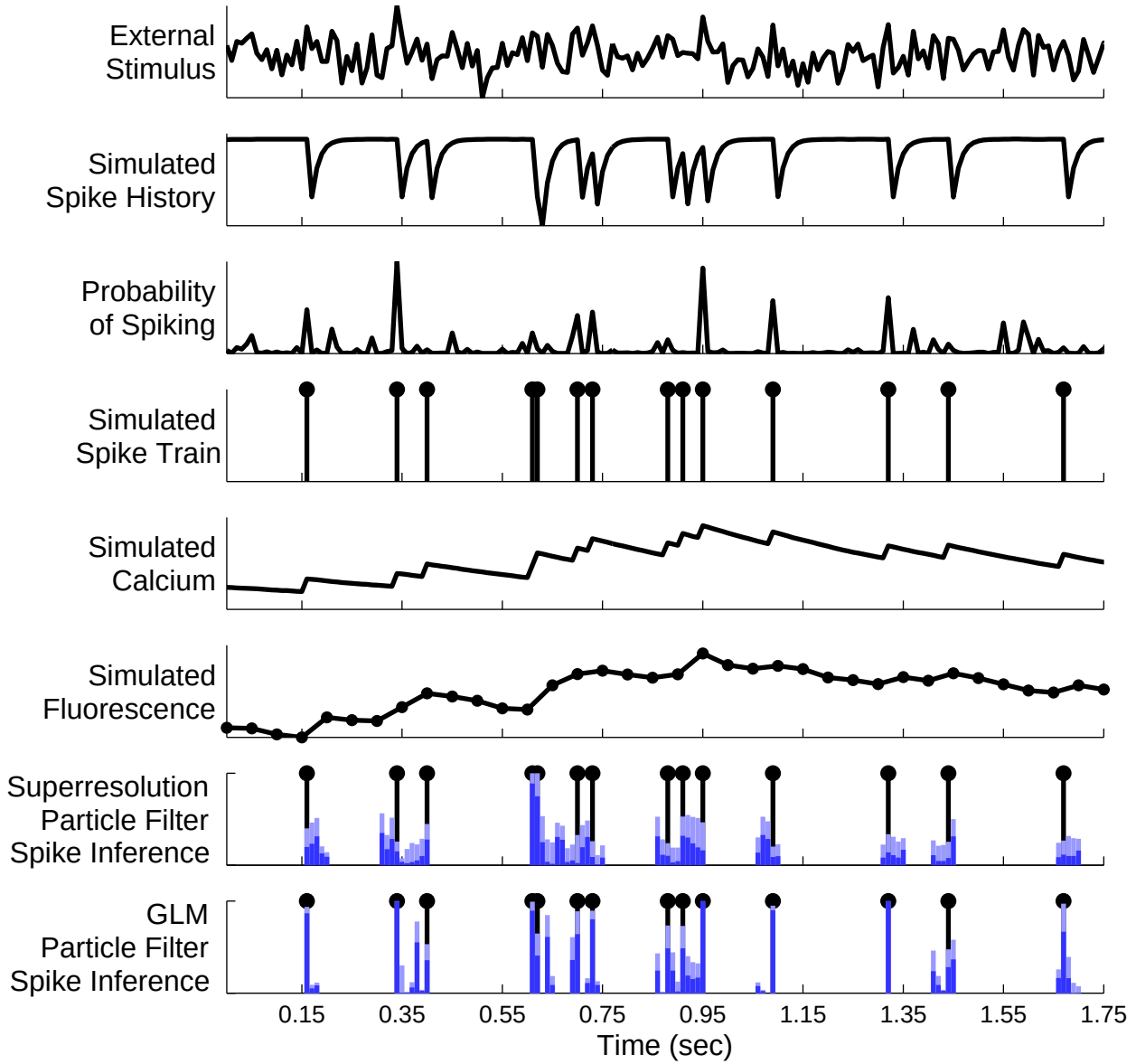
$$n_t \sim \mathcal{B}(n_t; \lambda\Delta)$$

- observations occur at a subset of time steps
- this is natural due to scanning of laser in two-photon imaging experiments

superresolution: array of results upon subsampling in temporal domain



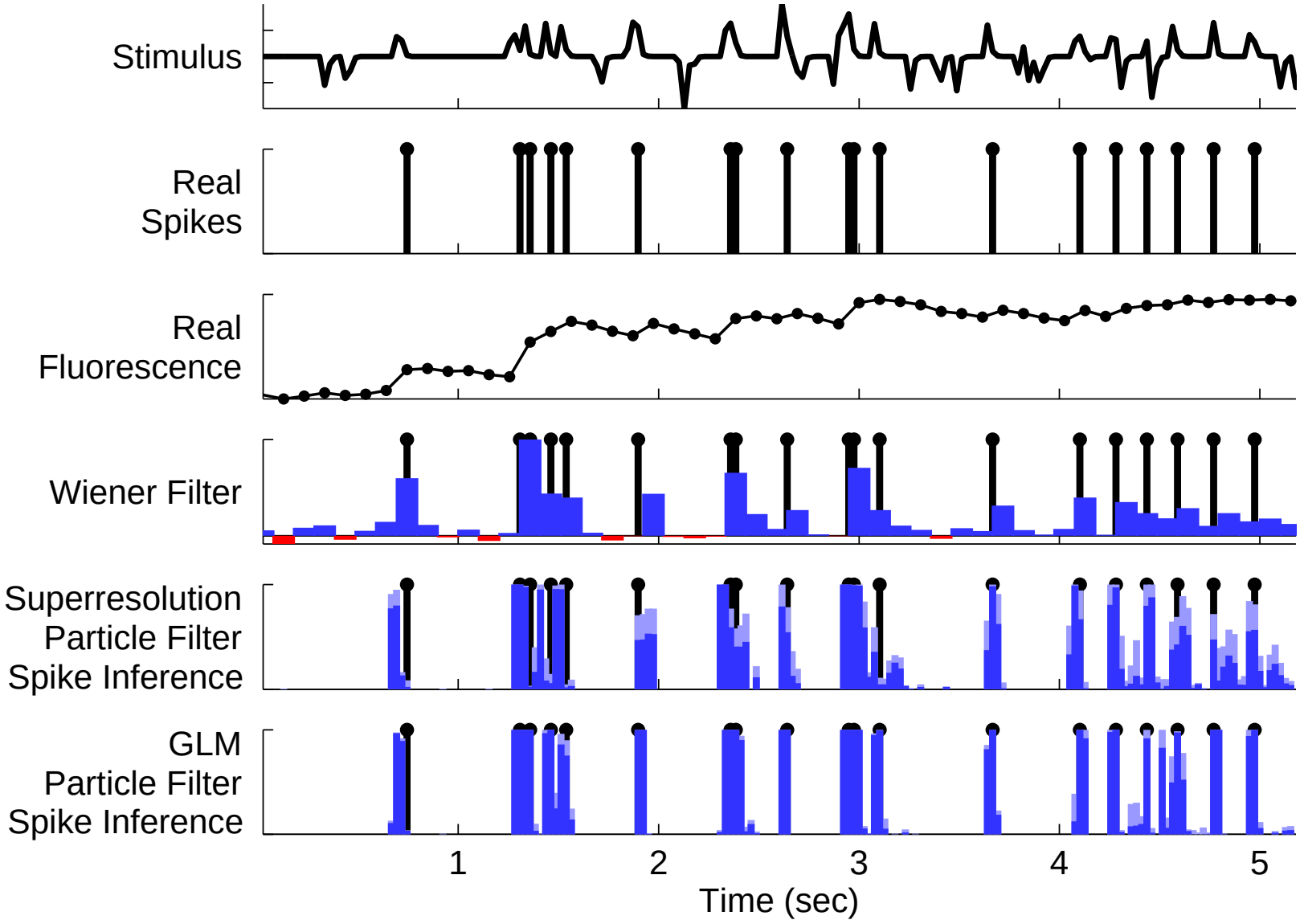
a complicated schematic: stimulus and spike history dependence



a complicated model: stimulus and spike history dependence

$$
\begin{aligned}
F_t &= \alpha S([\mathrm{Ca}^{2+}]_t) + \beta + (S([\mathrm{Ca}^{2+}]_t) + \sigma_F)\varepsilon_{F,t} \\
\tau \frac{[\mathrm{Ca}^{2+}]_t - [\mathrm{Ca}^{2+}]_{t-1}}{\Delta} &= -[\mathrm{Ca}^{2+}]_{t-1} + An_t + [\mathrm{Ca}^{2+}]_b + \sigma_c \sqrt{\Delta}\varepsilon_{c,t} \\
n_t &\sim \mathcal{B}\big(n_t; f\big(b + \boldsymbol{k}'\boldsymbol{x}_t + \omega h_t\big)\big) \\
\tau_h \frac{h_t - h_{t-1}}{\Delta} &= -h_t + n_{t-1} + \sigma_h \sqrt{\Delta}\varepsilon_{h,t}
\end{aligned}
$$

inferring precise spike trains from noisy saturated in vitro data



learning the tuning curve

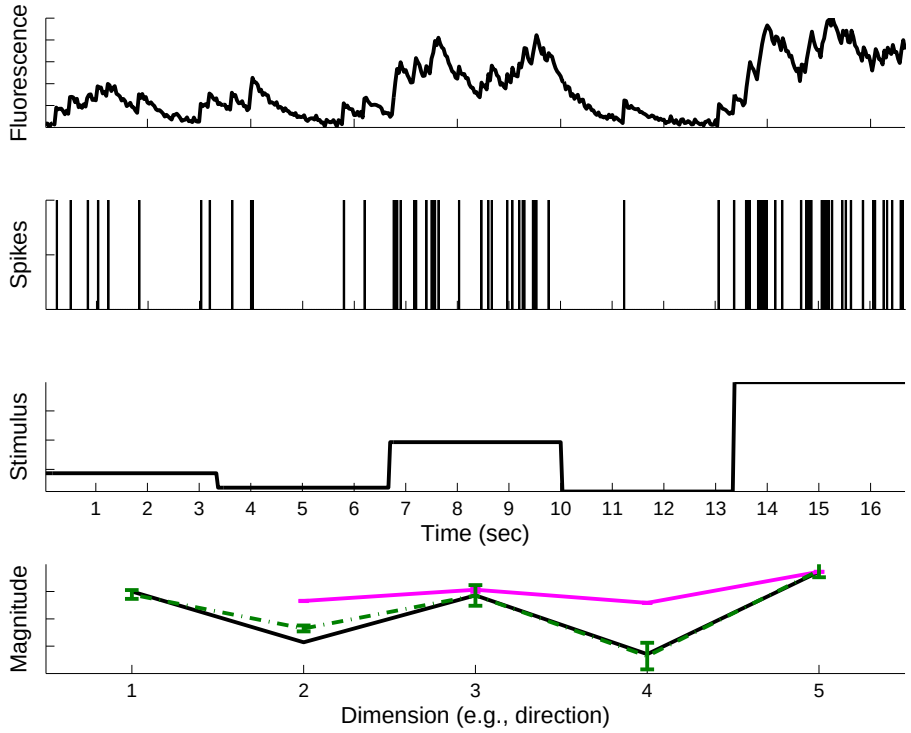


Figure 1: Estimating tuning curves using particle filtering vs. raw fluorescence data. Top panel: simulated fluorescence trial. Second panel: simulated spike train. Third panel: time-varying stimulus. Fourth panel: true tuning curve (black), estimate from raw fluorescence (purple), estimate from particle filter (green)

errors in estimating the tuning curve when using raw fluorescence

- particle filtering approach (green line, bottom panel) provides an unbiased estimate of tuning curve
- particle filtering also obtains an estimate of baseline firing rate (Dimension 1)
- raw fluorescence (purple line, bottom panel) provides a biased estimate
- selectivity of neurons is vastly underestimated upon using raw fluorescence

a population model:
an ensemble of N neurons

$$F_{i,t} = \alpha_i S([\mathrm{Ca}^{2+}]_{i,t}) + \beta_i + (S([\mathrm{Ca}^{2+}]_{i,t}) + \sigma_{i,F})\varepsilon_{F_i,t}$$

$$[\mathrm{Ca}^{2+}]_{i,t} = a_i[\mathrm{Ca}^{2+}]_{i,t-1} + A_i n_{i,t} + d_i + \sigma_{c_i}\sqrt{\Delta}\varepsilon_{c_i,t}$$

$$n_{i,t} \sim \mathcal{B}(n_{i,t}; f(b_i + \boldsymbol{k}_i'\boldsymbol{x}_t + \sum_{j=1}^{N} \omega_{ij} h_{i,t}))$$

$$\tau_{h_i}\frac{h_{i,t} - h_{i,t-1}}{\Delta} = -h_{i,t} + n_{i,t-1} + \sigma_{h_i}\sqrt{\Delta}\varepsilon_{h,t}$$

summary

- we use novel algorithms to infer spike trains from calcium activity
- a simple fast method can operate on hundreds of neurons in real time
- a less simple particle filter can operate on a single neuron in real time
- using this approach, we can obtain superresolution
- all the parameters (e.g., a tuning curve) may be estimated using a very short sequence of observations (and does not ever require obtaining ground truth)
- this method can be used to estimate the connection matrix between populations of neurons