

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

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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
$[\text{Ca}^{2+}]_t$	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
$[\text{Ca}^{2+}]_b$	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

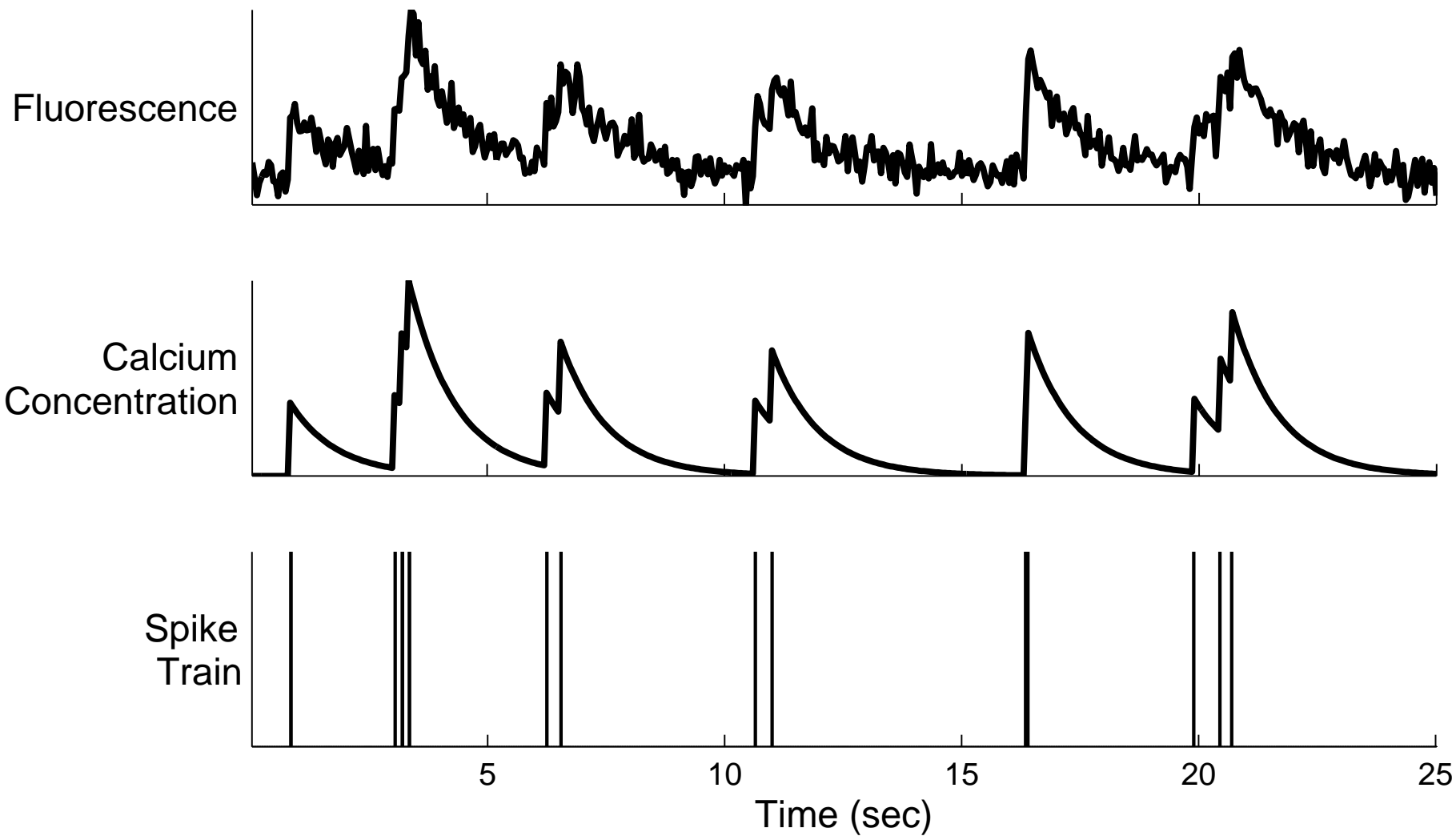
a simple model

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

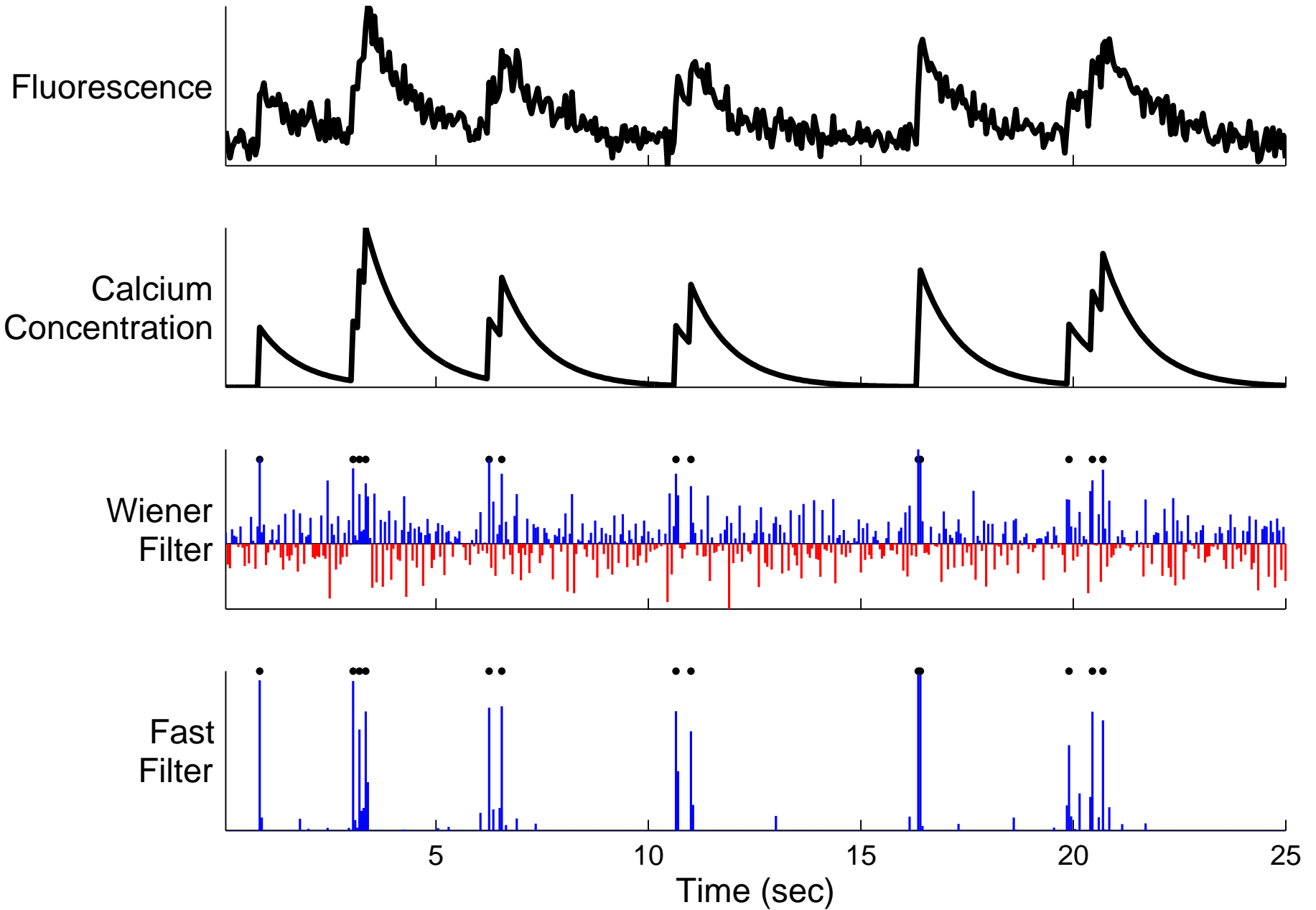
$$\tau \frac{[\text{Ca}^{2+}]_t - [\text{Ca}^{2+}]_{t-1}}{\Delta} = -[\text{Ca}^{2+}]_{t-1} + n_t$$

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

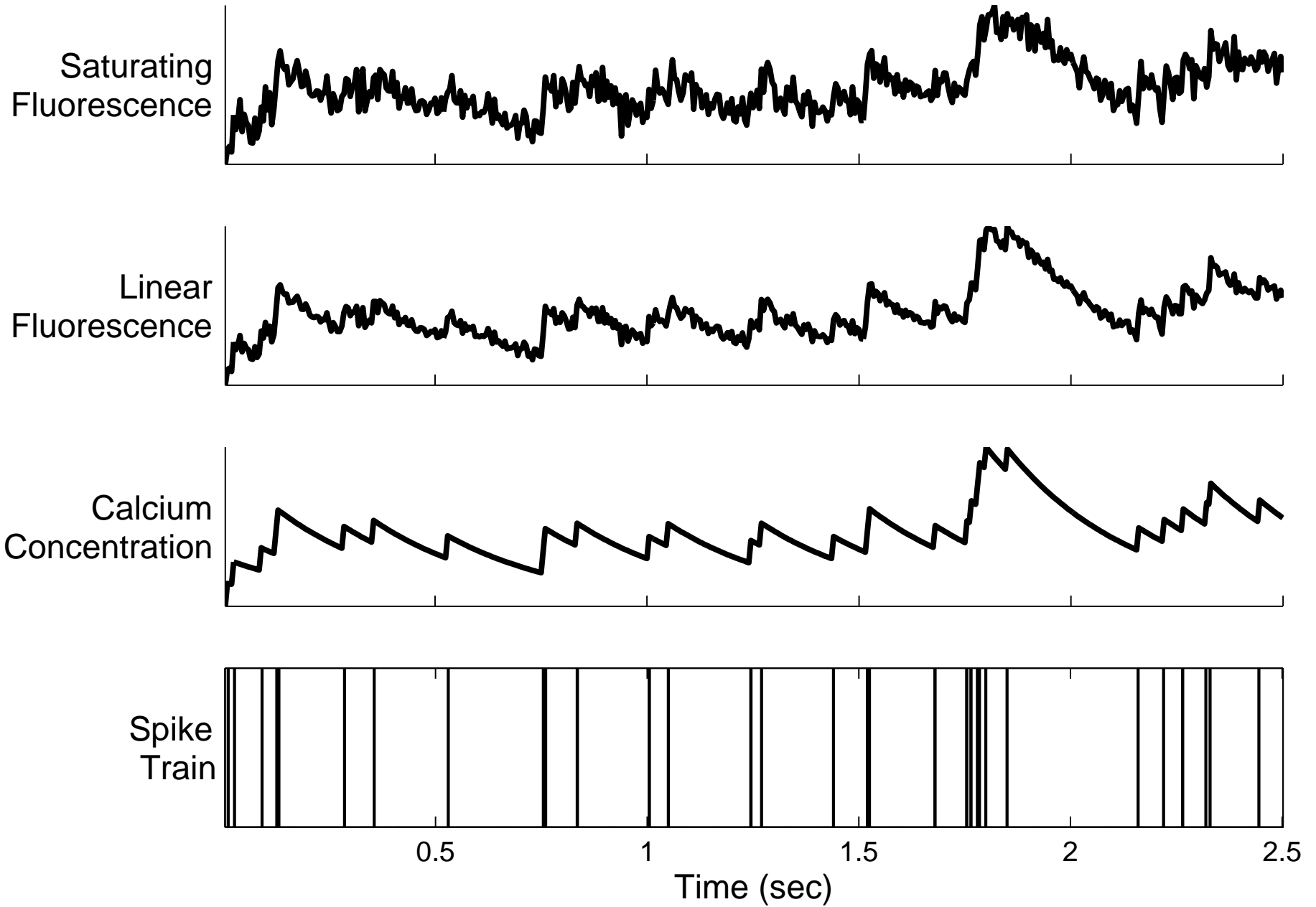
a simple schematic



a simple method



a less simple schematic: saturation



a less simple model: saturation

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

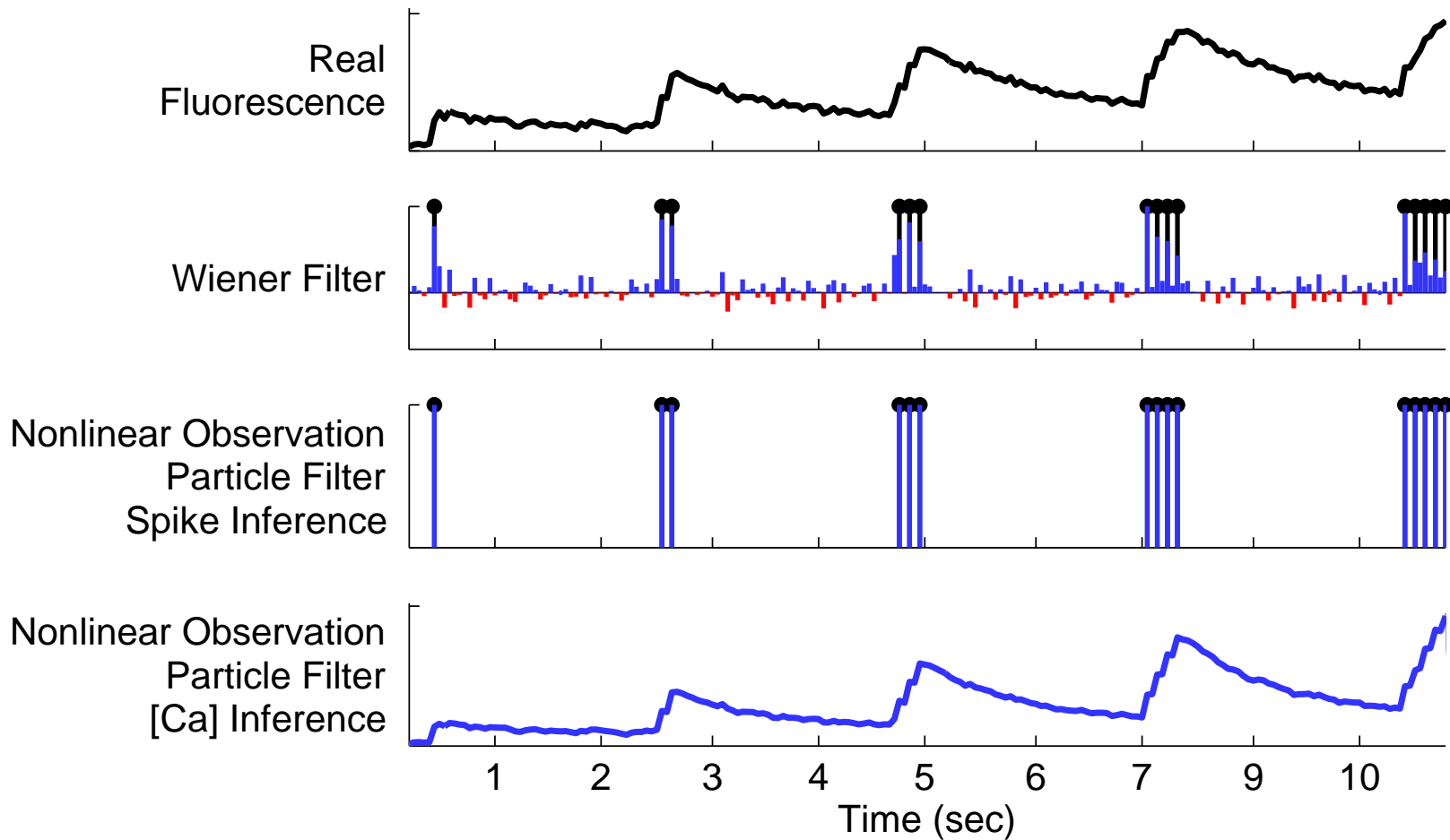
$$\tau \frac{[\text{Ca}^{2+}]_t - [\text{Ca}^{2+}]_{t-1}}{\Delta} = -[\text{Ca}^{2+}]_{t-1} + An_t + [\text{Ca}^{2+}]_b + \sigma_c \sqrt{\Delta} \varepsilon_{c,t}$$

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

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

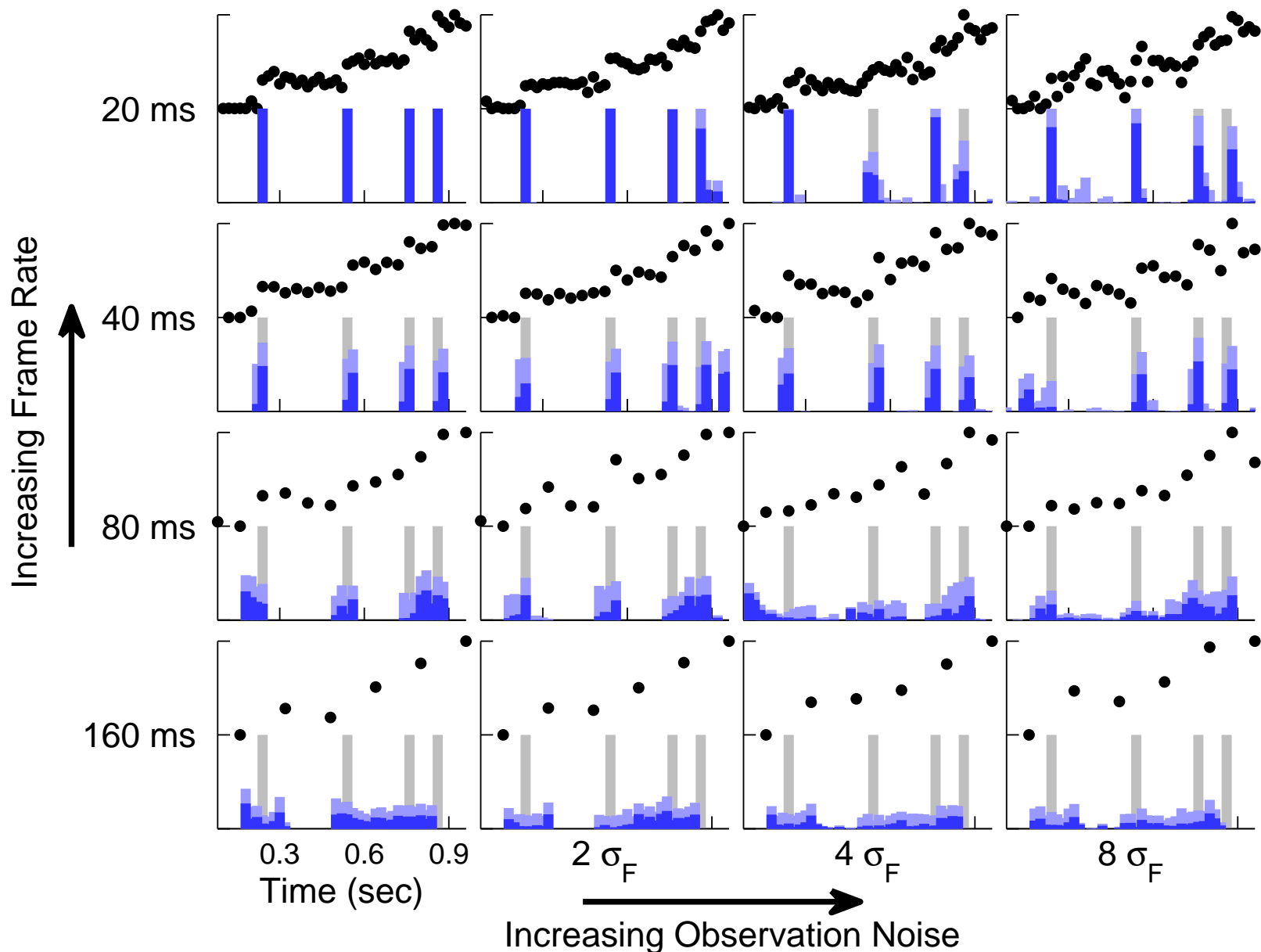
$$F_t = \alpha S([\text{Ca}^{2+}]_t) + \beta + (S([\text{Ca}^{2+}]_t) + \sigma_F)\varepsilon_{F,t}$$

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

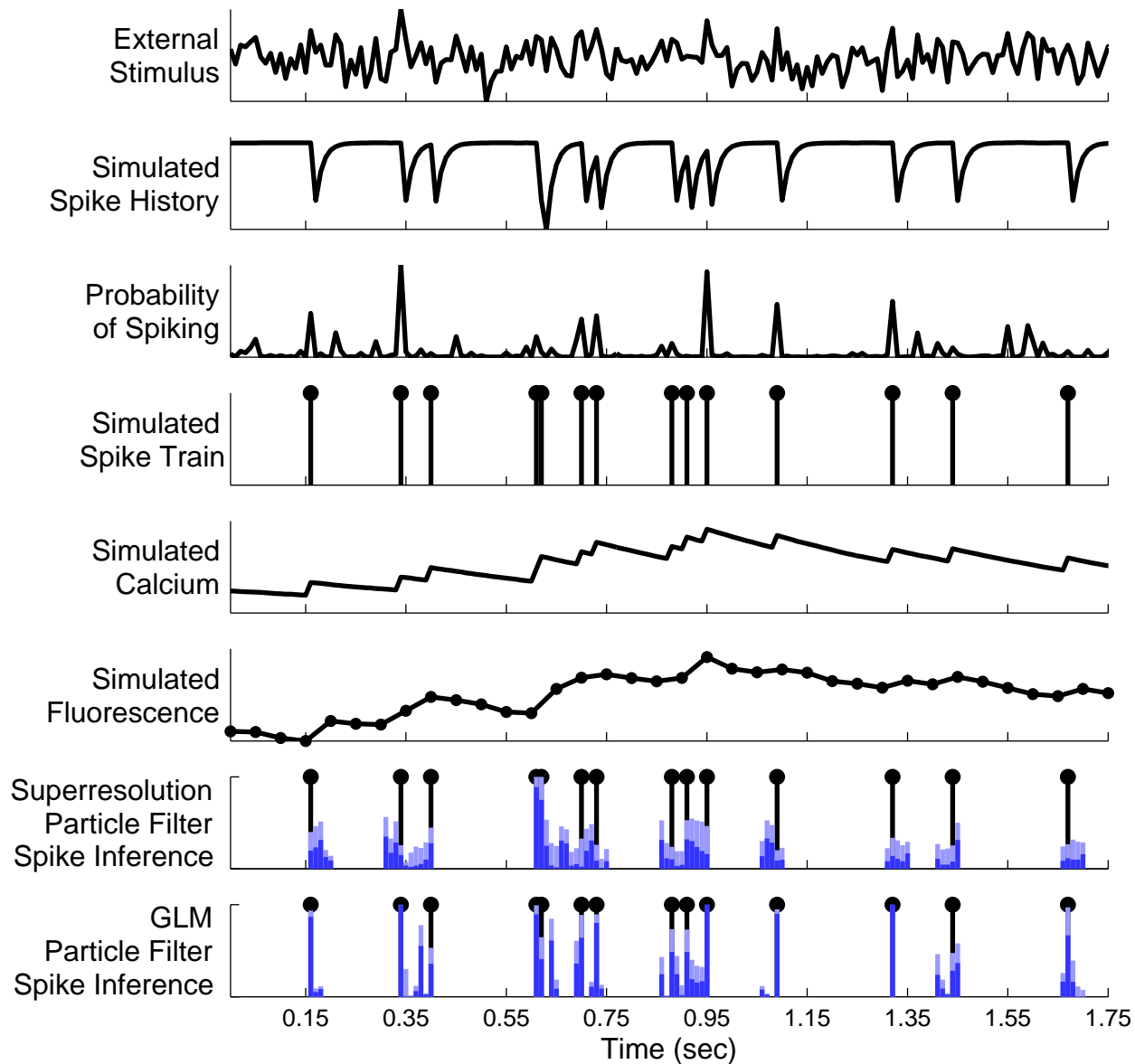
$$n_t \sim \mathcal{B}(n_t; \lambda\Delta)$$

- 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

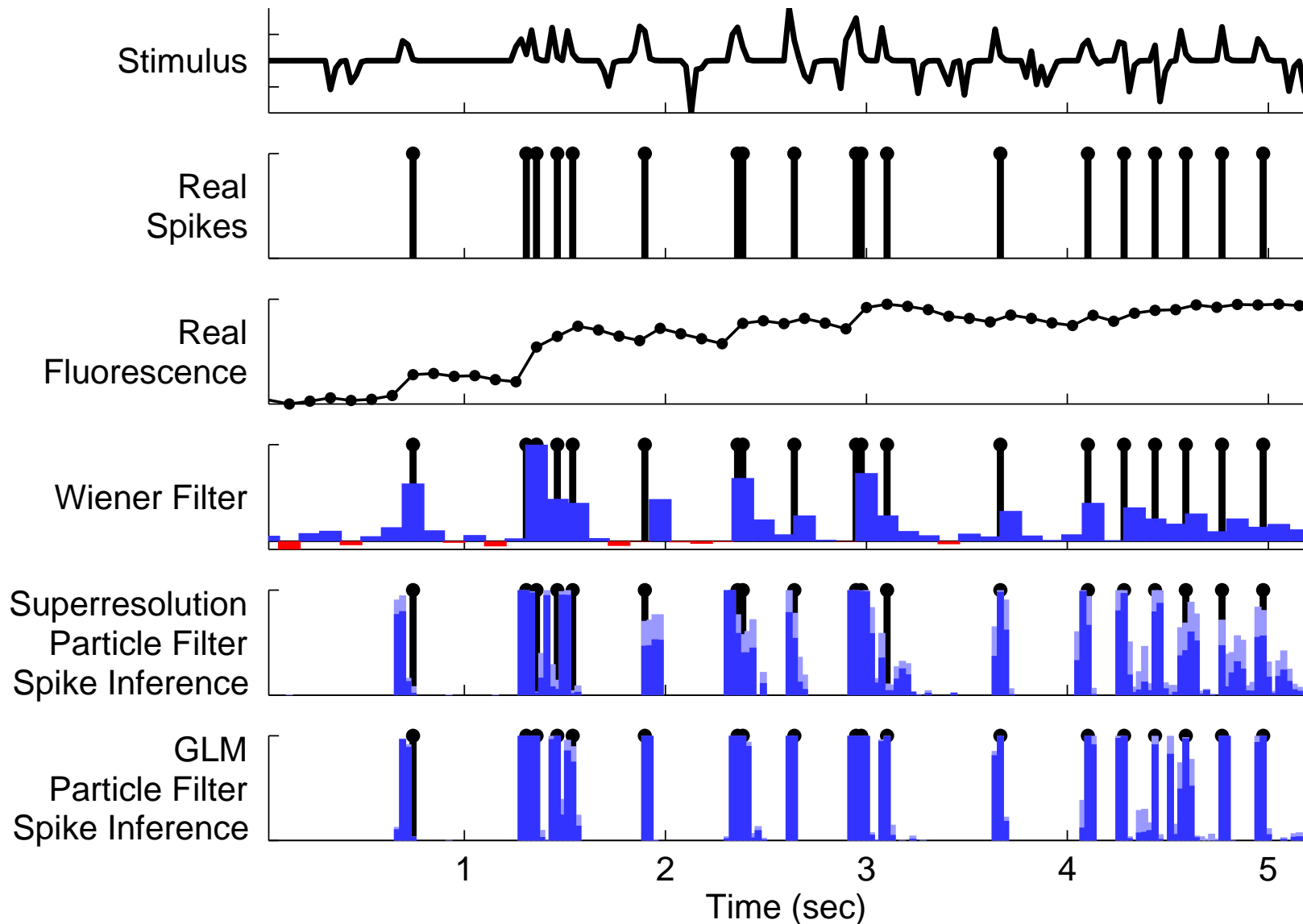
$$F_t = \alpha S([\text{Ca}^{2+}]_t) + \beta + (S([\text{Ca}^{2+}]_t) + \sigma_F)\varepsilon_{F,t}$$

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

$$n_t \sim \mathcal{B}(n_t; f(b + \mathbf{k}'\mathbf{x}_t + \omega h_t))$$

$$\tau_h \frac{h_t - h_{t-1}}{\Delta} = -h_t + n_{t-1} + \sigma_h \sqrt{\Delta} \varepsilon_{h,t}$$

inferring precise spike trains from noisy saturated in vitro data



learning the tuning curve

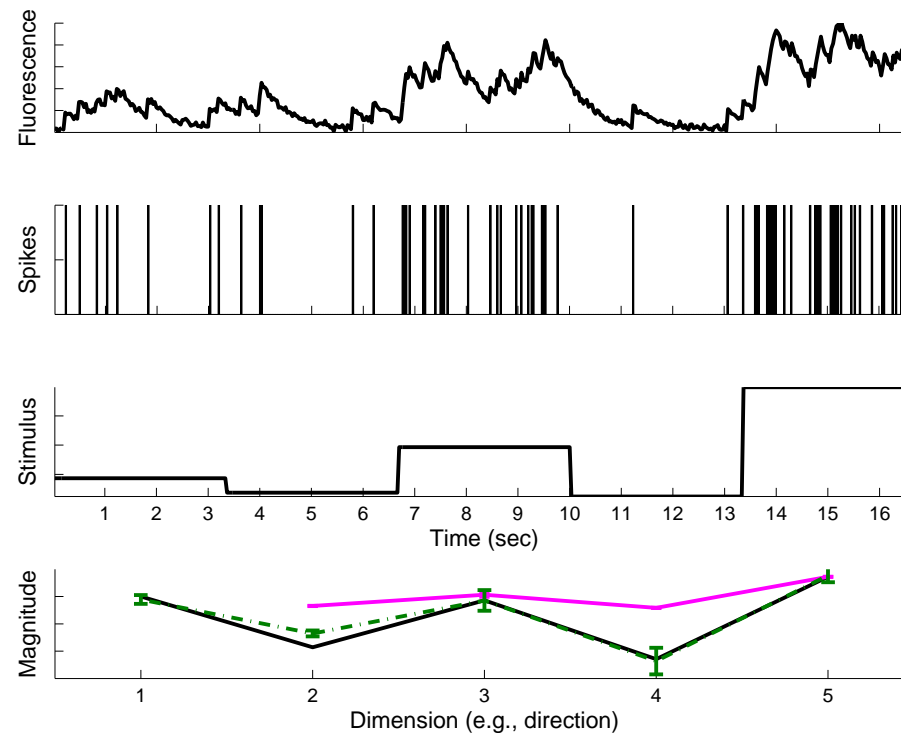


Figure 1: Estimating tuning curves using particle filtering vs. raw fluorescence data. Top panel: simulated fluorescence trial. Second panel: simulated spike train. Third panel: time-varying stimulus. Fourth panel: true tuning curve (black), estimate from raw fluorescence (purple), estimate from particle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

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

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

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

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

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