

# Efficient methods for sampling spike trains in networks of coupled neurons

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**INTRODUCTION:** We present a rigorous formalism for incorporating hidden neural circuit components into functional connectivity estimation. A central goal of neuroscience is to understand the connectivity of neural circuits. Functional approach to this problem consists in statistical analysis of neural activity observed, e.g., via multi-electrode recordings or calcium imaging. The biggest challenge for functional approach remains that of hidden neural components – that is the neurons whose activity could not be observed but that contributed inputs to observed neurons.

In order to properly account for the impact of such hidden components in the connectivity estimate, we model the observations using a neural network with observed and hidden neurons.  $P(\text{connectivity}|\text{observations})$  is then obtained by integrating out the activity of hidden neurons using Monte Carlo techniques. We develop a block-wise Gibbs approach and a set of specialized Metropolis-Hastings samplers to produce samples from the joint conditional distributions of the activity of observed and hidden neurons in the network, taking advantage of weak-coupling expansion of the conditional likelihoods and fast forward-backward algorithms from the theory of Hidden Markov Models. These allow us to perform Monte Carlo integration in  $P(\text{connectivity}|\text{observations})$  efficiently for very large neural populations in neurobiologically relevant settings.

## Sampling one neuron $P(n_i|\{n_j\}; w)$ for hidden component

Efficient Metropolis-Hastings (MH) sampling schemes -

Inspect  $P(n_i|\{n_j\}; w)$  in the limit of small  $w$  (weak coupling):

We find that in the weak coupling limit the conditioned spike train  $n_i \sim P(n_i|\{n_j\}; w)$  is a non-uniform Poisson spike train that can be described by an "effective" current,

$$J^a(t) = J_i(t) + \sum_{j \neq i, \tau > t} w_{ji}(\tau - t)[n_j(\tau) - f(b_j(\tau)\Delta)]$$

Note close connection with the work of (Pillow & Latham (2007) NIPS).

For stronger couplings, we incorporate strong short-delay interactions exactly via a *Hidden Markov Model dynamics* and weak long-delay interactions approximately via small- $w$  expansion (a *hybrid approach*):

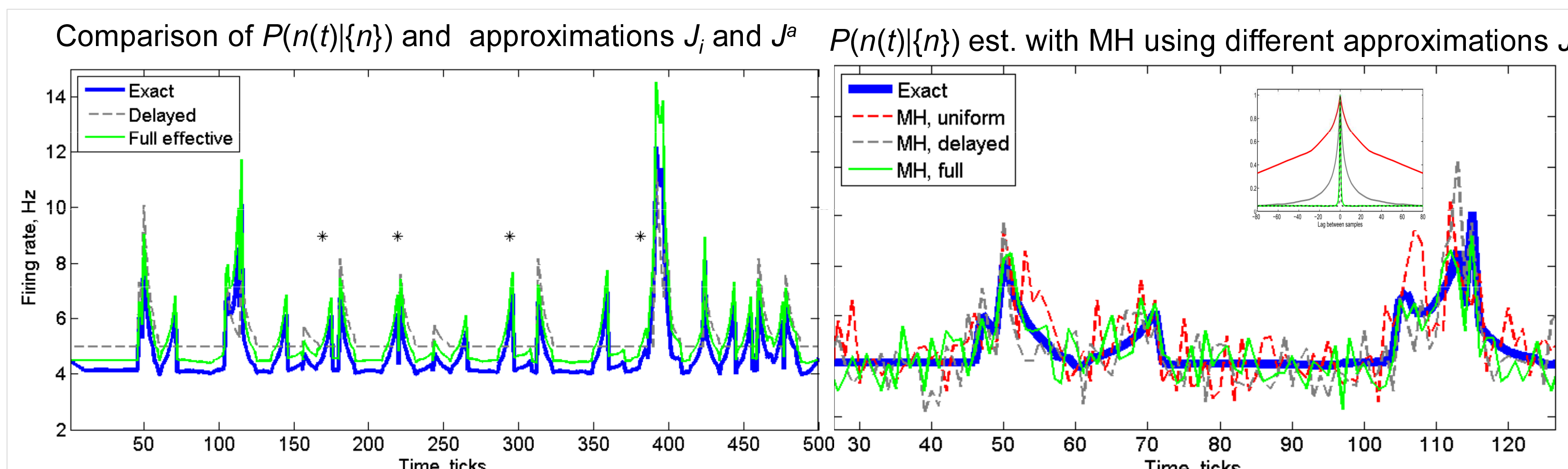
$$P(n_i|\{n_j\}) = \prod_i P_{HMM}(s_i(t)|s_i(t-\Delta)) \exp\left(n_i(t) \sum_{j \neq i, \tau > t+K\Delta} w_{ji}(\tau - t)[n_j(\tau) - f(b_j(\tau)\Delta)]\right)$$

$$s_i(t) = \{n_i(\tau), t - K\Delta < \tau \leq t\}$$

e.g.  $s_i(t) = "100100001..."$

$s_i(t)$  encodes neuron's spiking during past  $K$  time steps, thus, all  $\tau < t - K\Delta$  terms in  $J_i$  are explicitly incorporated in  $P_{HMM}(s_i(t)|s_i(t-\Delta))$  (if  $J_i$  has exactly  $K$  time lags, then  $s_i(t)$  in fact suffices to fully describe the state of neuron)

The spike train  $n_i$  then can be sampled using standard fast forward-backward procedure from the theory of Hidden Markov Models.

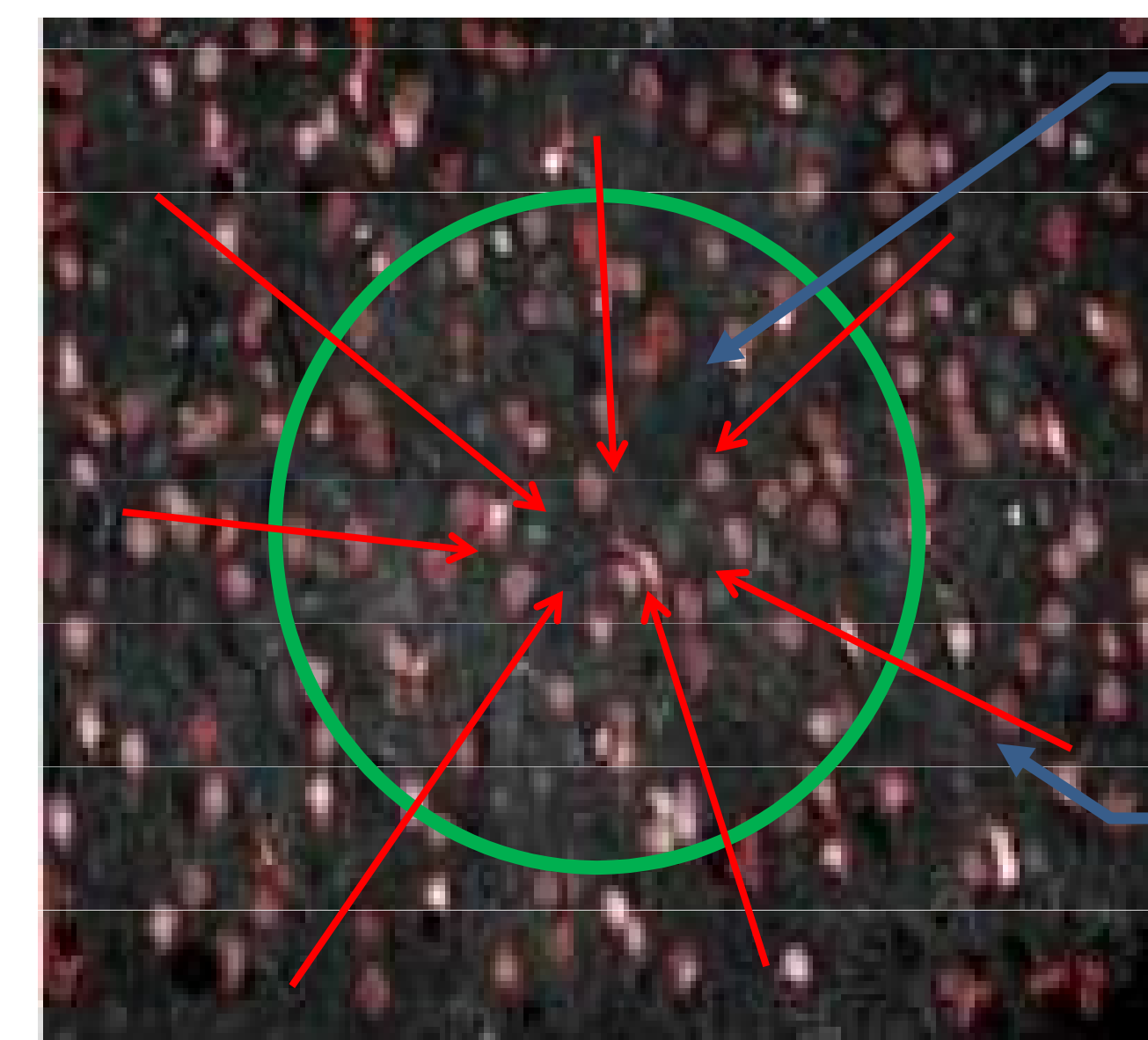


**FIG:** Comparison of delayed  $J_i(t)$  and full  $J^a(t)$  firing rates with the true posterior firing rate  $P(n_i(t)|\{n_j\})$  in simulated settings (left) and results of MH estimation of  $P(n_i(t)|\{n_j\})$  in the same settings using Poisson proposals using a uniform,  $J_i(t)$ , and  $J^a(t)$  currents (right). Actual spikes are indicated with stars. Inset shows the autocorrelation functions for such different MH samplers. Longer sample auto-correlation leads to longer mixing time and is bad. Advanced-time correction in  $J^a(t)$  (i.e.  $\tau > t$  terms in  $J^a$ ) allows us to both better approximate the true posterior spiking rate in the proposal samples and improve dramatically performance of the Metropolis-Hastings samplers.

## Hidden neural components in functional connectivity estimation

Mishchenko Y., Paninski L. (2010) Efficient methods for sampling spike trains in networks of coupled neurons. Submitted Annals of Applied Statistics.

(<http://www.stat.columbia.edu/~liam/research/pubs/yuri-network-samp.pdf>)



**Observed**  
(calcium imaging or multi-electrode rec.)

**Hidden**  
(not observed)

Observed neurons:

$$n_i(t) \sim P[f(J_i(t))]$$

$$J_i(t) = b_i(t) + k_i \cdot S(t) + \sum_j \sum_{\tau < t} w_{ij}(\tau) n_j(\tau)$$

(calcium imaging observations model, if needed:)

$$C_i(t) = (1 - \Delta/\tau_c) C_i(t - \Delta) + A_c n_i(t)$$

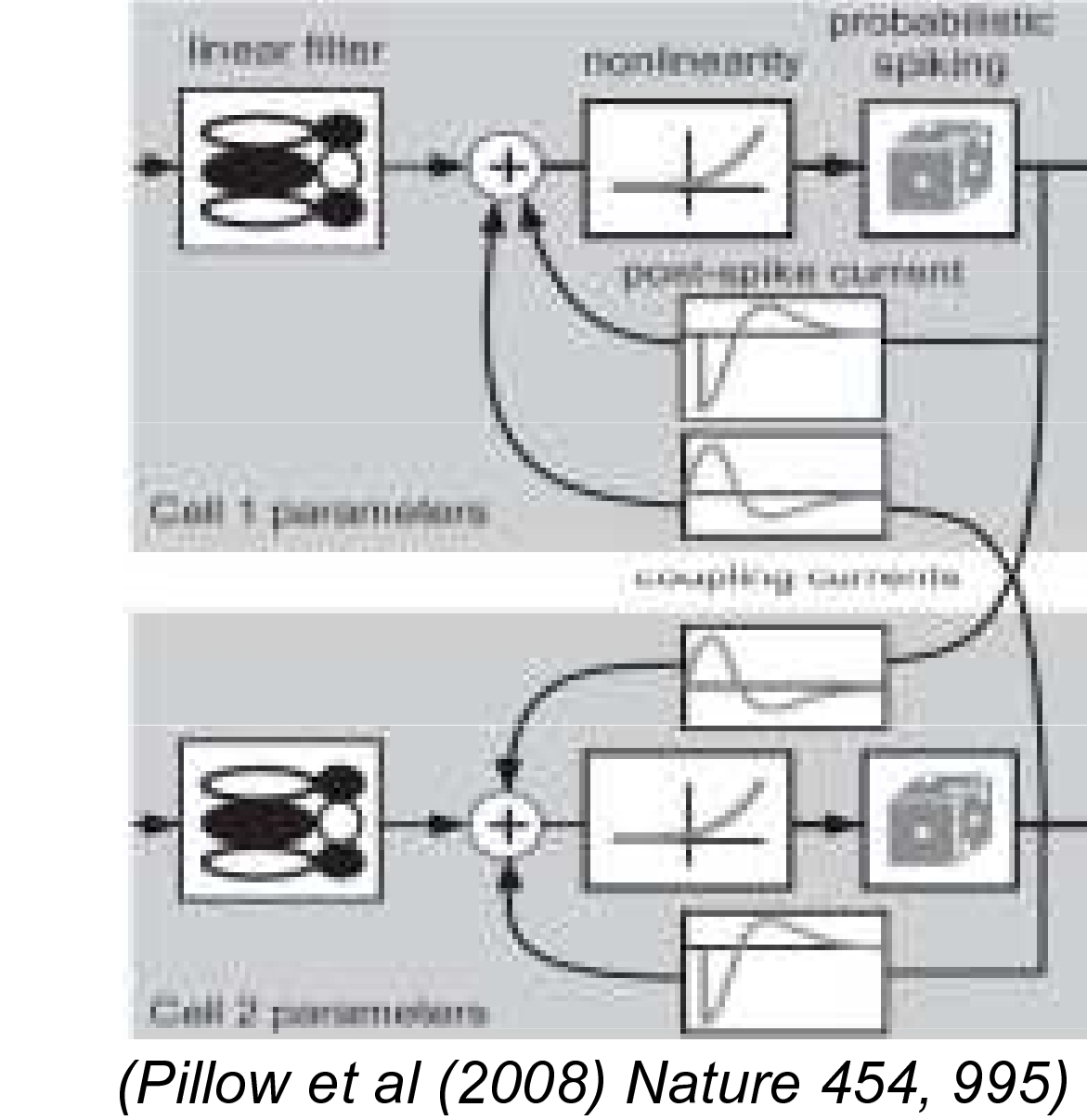
$$F_i(t) = \text{Hill}(C_i(t), \alpha_c)$$

Hidden neurons:

$$n_i(t) \sim P[f(J_i(t))]$$

$$J_i(t) = b_i(t) + k_i \cdot S(t) + \sum_j \sum_{\tau < t} w_{ij}(\tau) n_j(\tau)$$

Neurons are modeled as a network of coupled GLMs:



Notation legend:

$n_i(t)$  – spike variable of neuron  $i$  at time  $t$  ( $n_i(t) = 0$  or  $1$ )

$w_{ij}(\tau)$  – effective conn. matrix

$k_i$  – stimulus filter of neuron  $i$

$S(t)$  – external stimulus

$f(J)$  – spiking nonlinearity (here,  $f(J) = \exp(J)$ ;  $\Delta$  is time discretization step)

$C_i(t)$  – calcium concentration variable of neuron  $i$  at time  $t$

$F_i(t)$  – fluorescence variable of neuron  $i$  at time  $t$

$\tau_c, A_c, \alpha_c$  – fluor. calcium imaging model parameters

(Pillow et al (2008) Nature 454, 995)

Maximum a Posteriori connectivity matrix can be estimated using the Expectation Maximization (EM) algorithm (\*). A key problem is how to produce samples from high dimensional ( $\dim \sim NT$ ) distribution over the joint activity of observed and hidden neurons for E-step (optimization in M-step reduces to a simple GLM fitting and is relatively straightforward),

$$\{C^k, n_o^k, n_h^k\} \sim P[C, n_o, n_h | F, w]$$

Constructing efficient solutions for this problem is the main goal of this work.

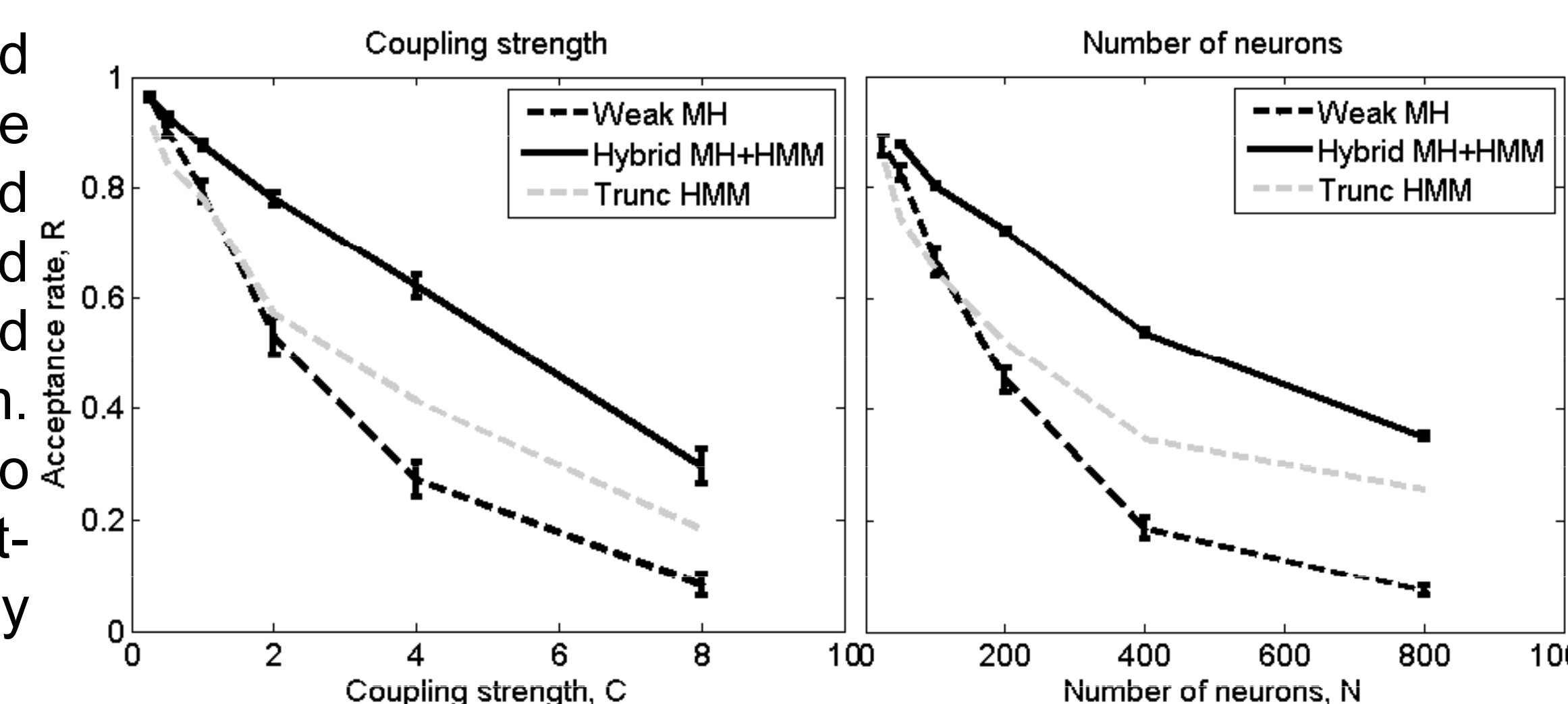
*Block-wise Gibbs approach:* sample spike trains one neuron at a time,

$$\{n_i\} \sim P[n_i | F, \{n_o, n_h\}_{\setminus i}; w] \text{ for all } i \text{ in a cycle}$$

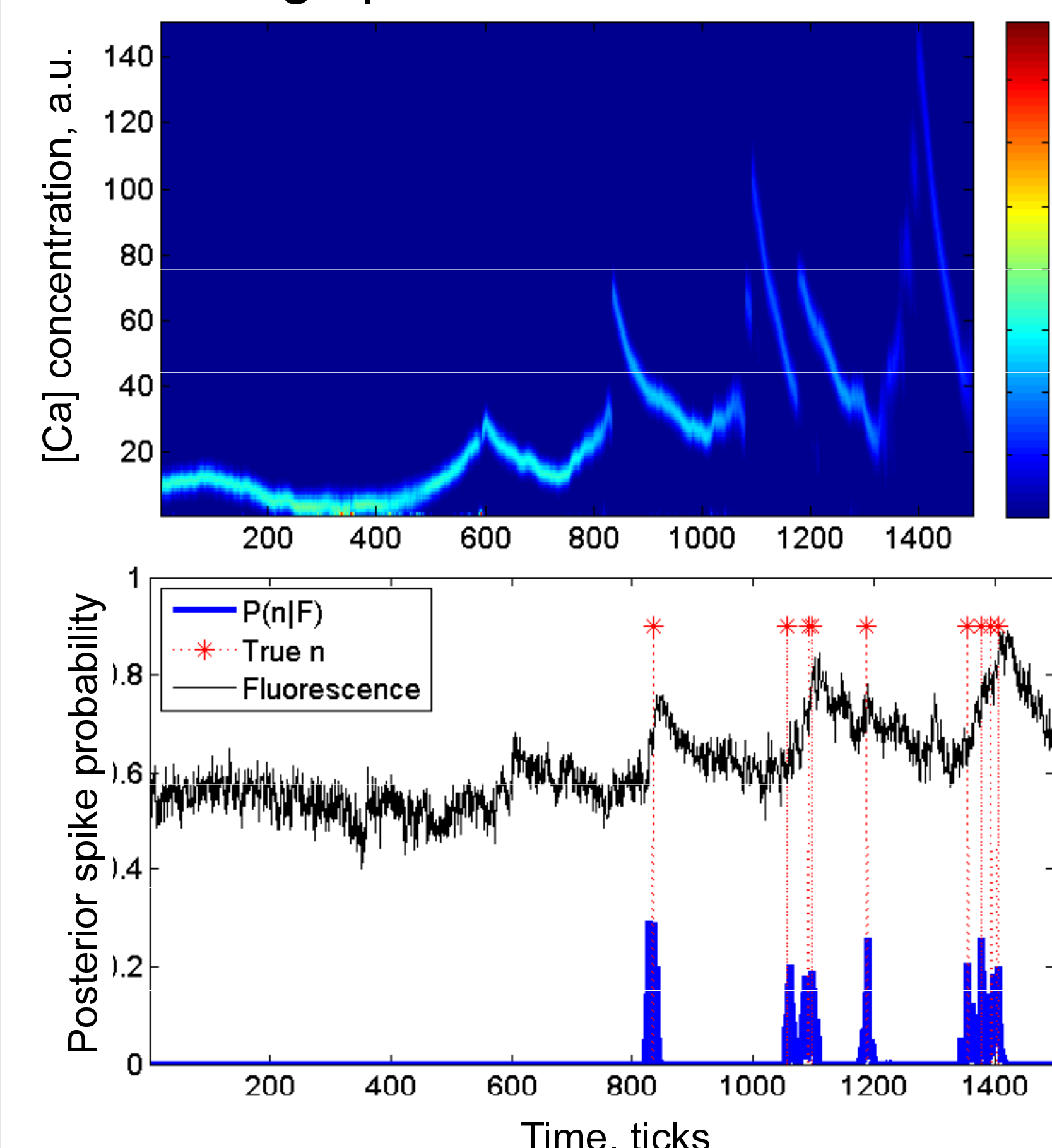
Thus, we want to develop a method to efficiently sample one spike train given all the other neurons in the network,  $P(n_i|\{n_j\}; w)$  (sufficient for the above objective).

*Note: We assume that the size of the hidden component  $N$  is known; in practice, a model selection method such as BIC, AIC, or cross-validation should be used to select  $N$ .*

**FIG:** Acceptance rate  $R$  of the hybrid sampling strategy (the higher is the better) in strong coupling (left) and large network (right) simulated settings vs. MH-only algorithm and short-delay HMM-only algorithm. Use of hybrid strategy allows us to significantly and uniformly outperform such MH- or MHH-only samplers.



Extracting spike trains from calcium imaging data:



**FIG:** Deduced posterior calcium concentration (top) and posterior spike probability (bottom) for a real calcium imaging data sample, courtesy of T. Sippy, R. Yuste, J. Vogelstein. Positions of the true spikes, identified via simultaneous patch-clamp recording, are indicated with red stars. Spike positions and respective jumps in calcium concentration are all accurately inferred from the calcium imaging data.

Note that our approach allows drawing full samples from the posterior  $P(n|F)$  as opposed, e.g., to only computing marginals  $p(n_i(t)|F_i)$  such as in (Vogelstein et al. (2009) Biophys J).

(\*) EM algorithm is an iterative method for locally Maximum a Posteriori estimation in complex setting with hidden variables. Each iteration consists of two steps:

- E-step: Calculate average log-probability over hidden variables given current  $w^{(l)}$ :

$$Q(w; w^{(l)}) = E_{P[C, n_o, n_h | F, w^{(l)}}} \ln P[F, C, n_o, n_h | w^{(l)}]$$

- M-step: Obtain new approximation  $w^{(l+1)}$  by maximizing expected log-probability:

$$w^{(l+1)} = \arg \max_w Q(w; w^{(l)}) + \ln P(w)$$

## Sampling one neuron $P(n_i|\{n_j\}; F_i, w)$ for observed component

Efficient Metropolis-Hastings (MH) sampling schemes -

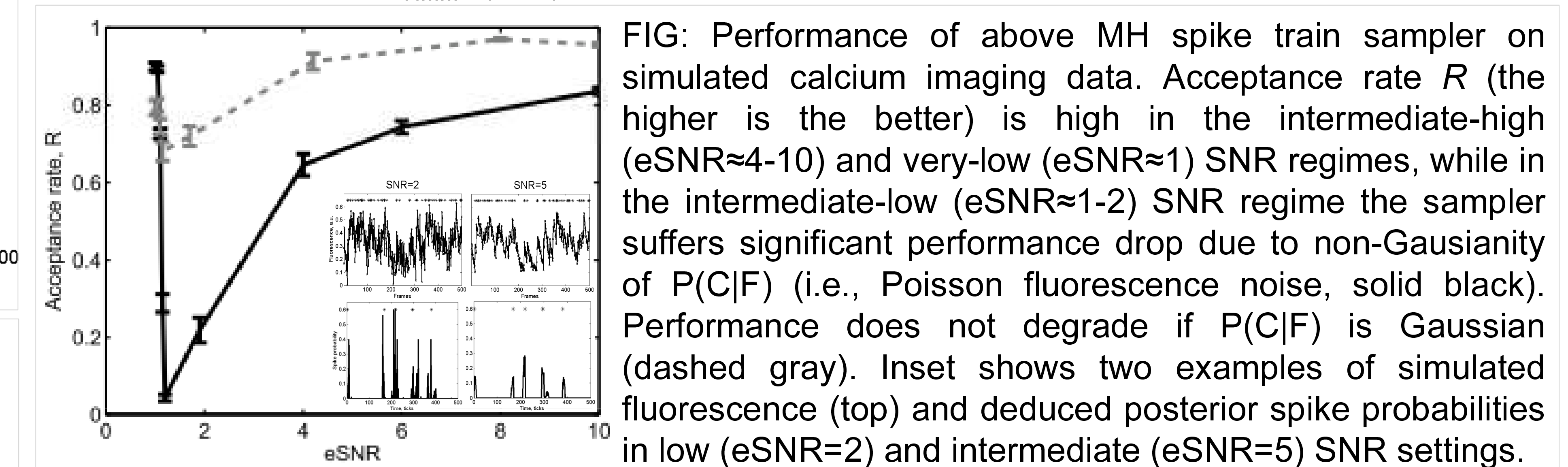
To generate proposals for the spike train  $n_i$  we adapt filter-backward sample-forward algorithm from the theory of Hidden Markov Models. We first pre-compute approximately, backward in  $t$ ,  $P(F(t:T)|s_i(t), C_i(t))$  as a mixture of Gaussians, and then sample  $n_i$  forward in  $t$  using:

$$s_i(t) \sim P(F_i(t:T) | s_i(t), C_i(t)) \times P_{HMM}(s_i(t) | s_i(t-\Delta); \{n_j\}_{\setminus i})$$

$$s_i(t) = \{n_i(\tau), t - K\Delta < \tau \leq t\}$$

e.g.  $s_i(t) = "100100001..."$

$s_i(t)$  encodes neuron's spiking during past  $K$  time steps, so that all refractory self-interactions are incorporated in  $P_{HMM}(s_i(t)|s_i(t-\Delta))$



**FIG:** Performance of above MH spike train sampler on simulated calcium imaging data. Acceptance rate  $R$  (the higher is the better) is high in the intermediate-high (eSNR=4-10) and very-low (eSNR=1) SNR regimes, while in the intermediate-low (eSNR=1-2) SNR regime the sampler suffers significant performance drop due to non-Gaussianity of  $P(C|F)$  (i.e., Poisson fluorescence noise, solid black). Performance does not degrade if  $P(C|F)$  is Gaussian (dashed gray). Inset shows two examples of simulated fluorescence (top) and deduced posterior spike probabilities in low (eSNR=2) and intermediate (eSNR=5) SNR settings.

## SUMMARY

- We develop efficient methods for sampling from the spike train of a single neuron given the spikes of all of the other neurons putatively connected to it.
- By the theory of Gibbs sampling, this enables us to sample also from the full distribution of a hidden population spike trains given the observations of the spike trains from a set of neurons, collected with multi-electrodes or calcium imaging recordings.
- These methods are based on two ideas: a weak-coupling approximation of the spike train log-likelihood and the forward-backward algorithms from the theory of Hidden Markov Models.
- These methods can be used for practical estimation of neural connectivity in an Expectation-Maximization approach; for more details see (Mishchenko, Vogelstein, and Paninski, AOAS: <http://www.stat.columbia.edu/~liam/research/pubs/yuri-ca-network.pdf>).

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