

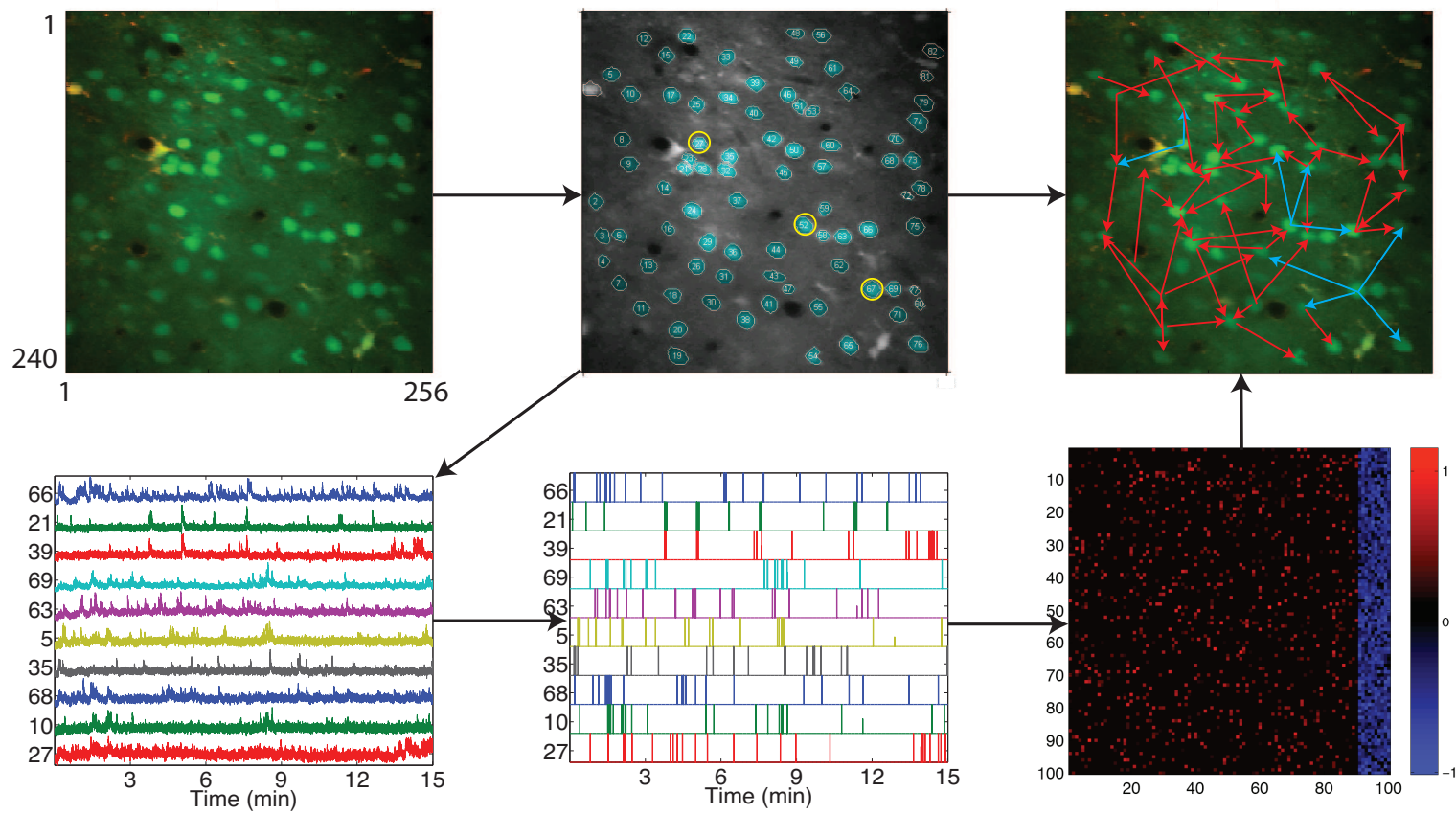
Towards confirming neural circuit inference from population calcium imaging

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schematic



aim

given only a set of **fluorescence** traces collected simultaneously from a small (eg ≈ 100 neurons) population of neurons, obtain the **spike trains** for each of the neurons, and the **effective connectivity matrix** for the observed population.

steps

1. image a population of neurons using calcium
2. segment image into regions-of-interest (ROI)
3. extract fluorescence traces from each ROI
4. infer spike trains from neural populations using a **fast** non-negative deconvolution algorithm [1], and refine inference using **sequential monte carlo** methods [2]
5. infer **effective connectivity matrix** given the spike trains using a specialized **blockwise Metropolis-within-Gibbs** sampler [3]
6. confirm sign of neurons comparing with **genetically labeled** inhibitory neurons [4]

generative model

$$F_i(t) = \alpha_i \frac{C_i(t)}{C_i(t) + k_d} + \beta_i + \sigma_i^F \varepsilon_t$$

$$\tau_i^c \frac{dC_i(t)}{dt} = -C_i(t) + C_i^b + A_i n_i(t) + \sigma_i^c \varepsilon_t$$

$$n_i(t) \sim \text{Binomial}[f(b_i + \mathbf{k}_i \mathbf{s}(t) + \sum_i w_{ij} h_{ij}(t))]$$

$$\tau_i^h \frac{dh_j(t)}{dt} = -h_j(t) + n_j(t) + \sigma_i^h \varepsilon_t$$

$$\theta = \{\theta_i\}_{i \leq N}, \theta_i = \{\alpha_i, \beta_i, \sigma_i^F, \tau_i^c, C_i^b, A_i, \sigma_i^c, \tau_i^h, \sigma_i^h\}$$

$$\mathbf{X} = \{\mathbf{X}_i\}_{i \leq N}, \mathbf{X}_i = \{X_i(t)\}_{t \leq T}, X_i(t) = \{C_i(t), n_i(t), h_i(t)\}$$

fast filter

$$\hat{\mathbf{n}}_i = \operatorname{argmax}_{\mathbf{n}_i(t) \geq 0 \forall t} P[\mathbf{n}_i | \mathbf{F}_i; \theta_i] = \operatorname{argmax}_{\mathbf{n}_i(t) \geq 0 \forall t} P[\mathbf{F}_i | \mathbf{n}_i; \theta_i] P[\mathbf{n}_i | \theta_i]$$

we use an **interior point** method to impose the non-negativity constraint. since this is **concave**, we can use **gradient ascent** to find the **optimal solution**. we take advantage of the **tridiagonal Hessian** and use **gaussian elimination** to evaluate each newton step. parameters are estimated from the data using a pseudo **expectation maximization** algorithm.

smc filter

$$\hat{n}_i(t) = \operatorname{argmax}_{n_i(t) \in \{0,1\}} P[n_i(t)|\mathbf{F}; \theta]$$

$$P[\mathbf{X}_i, \mathbf{F}_i] = P[\mathbf{X}_i(0)] \prod_t P[\mathbf{X}_i(t)|\mathbf{X}_i(t-1)] P[\mathbf{F}_i(t)|\mathbf{X}_i(t)]$$

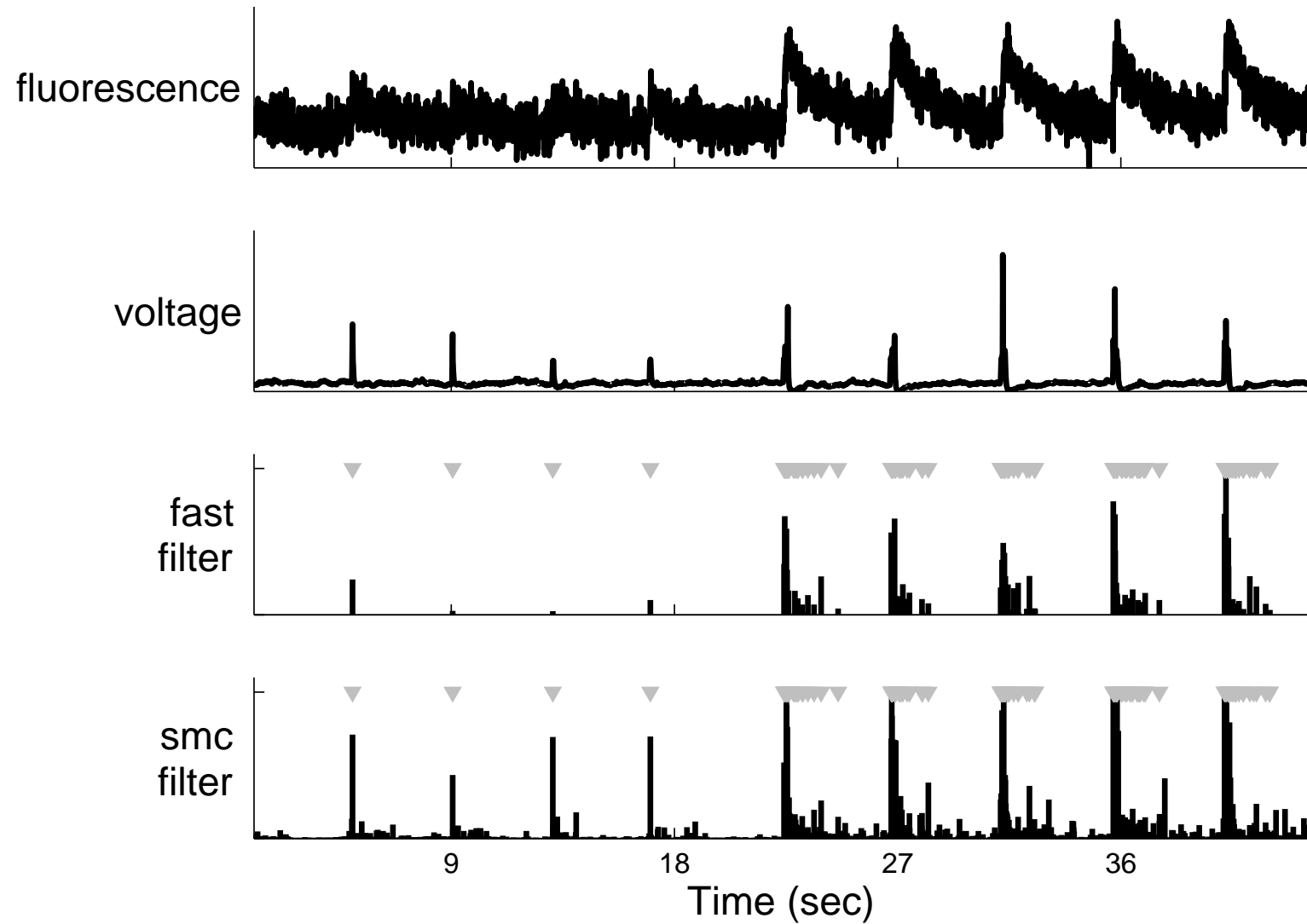
because we have a **hidden markov model** we use a **forward-backward algorithm** to infer the desired posterior probabilities. because we don't know how to solve the integrals, we approximate them using **sequential monte carlo** (aka, smc or particle filter). parameters are estimated (from the data) using a **expectation maximization** algorithm.

effective connectivity inference

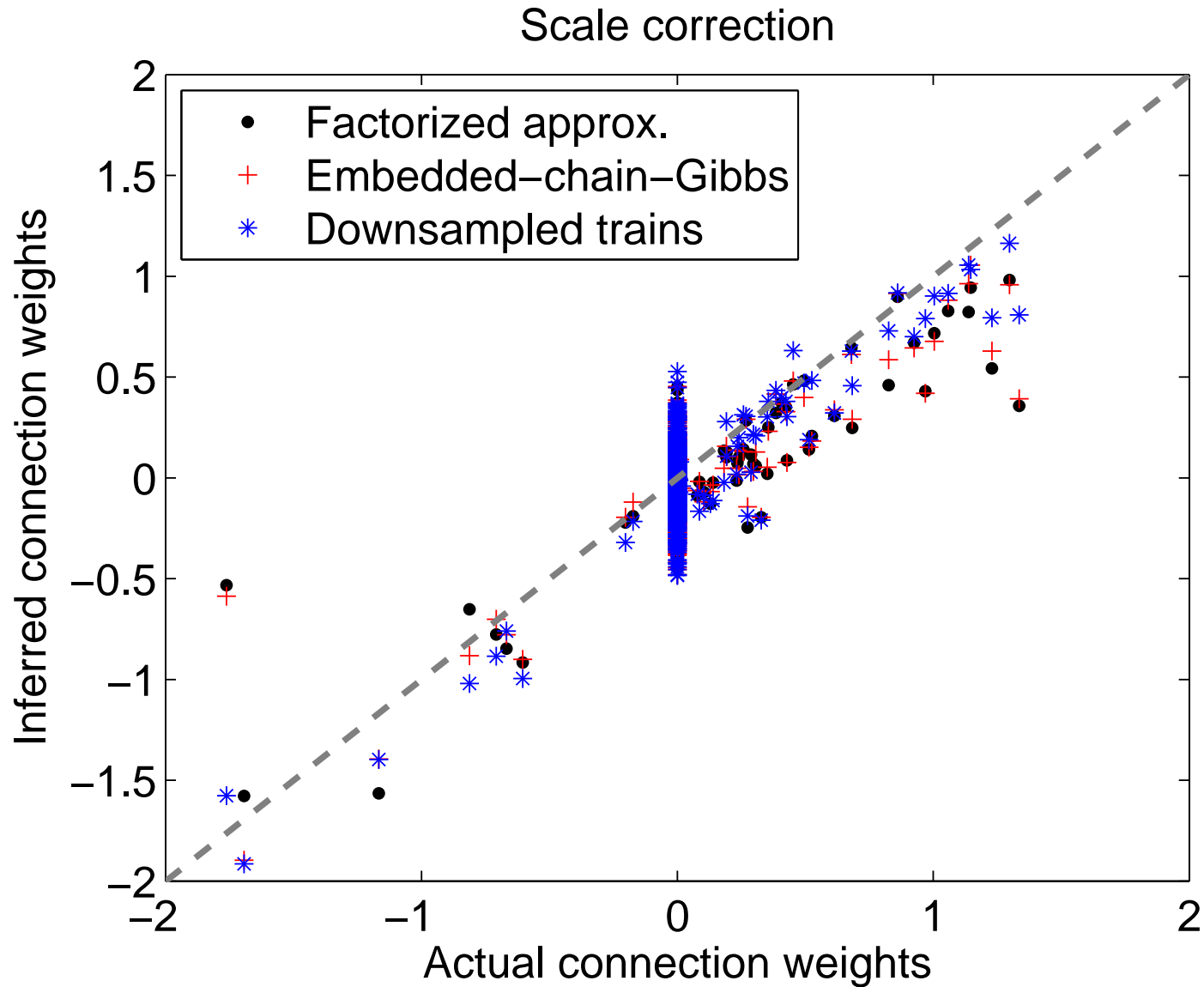
$$\hat{\mathbf{w}} = \operatorname{argmax}_{\mathbf{w} \in \{0,1\}} P[\mathbf{X}|\mathbf{F}; \theta] \approx \prod_i P[\mathbf{X}_i|\mathbf{F}_i; \theta_i]$$

to obtain $P[\mathbf{X}|\mathbf{F}; \theta]$, we develop a specialized **blockwise Metropolis-within-Gibbs** sampler. for more efficient (but slightly less accurate) sampling, we approximate the joint posterior as the **product of marginals**. to estimate the connectivity, we impose a **sparse constraint**, via standard L_1 penalization methods.

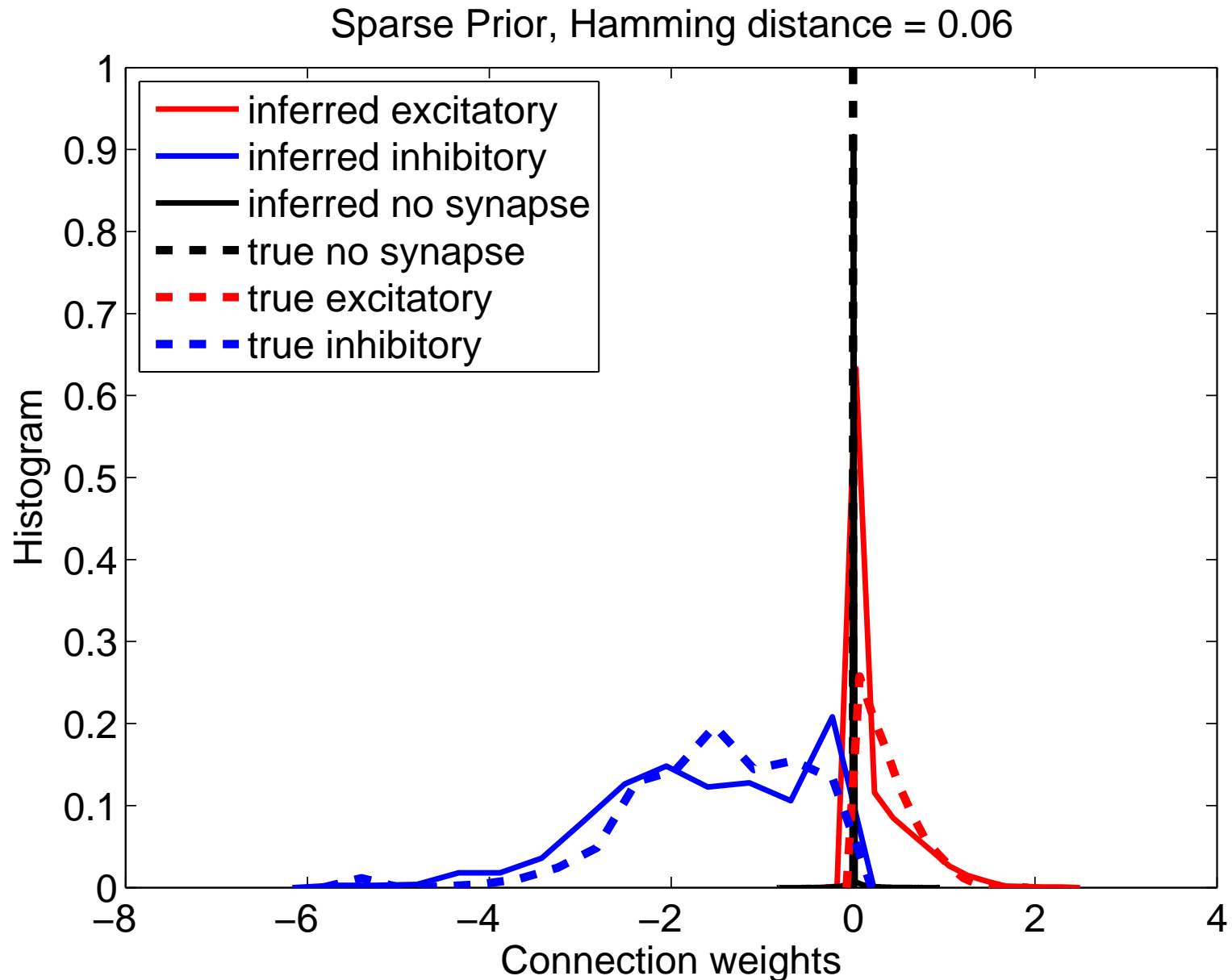
in vitro spike inference



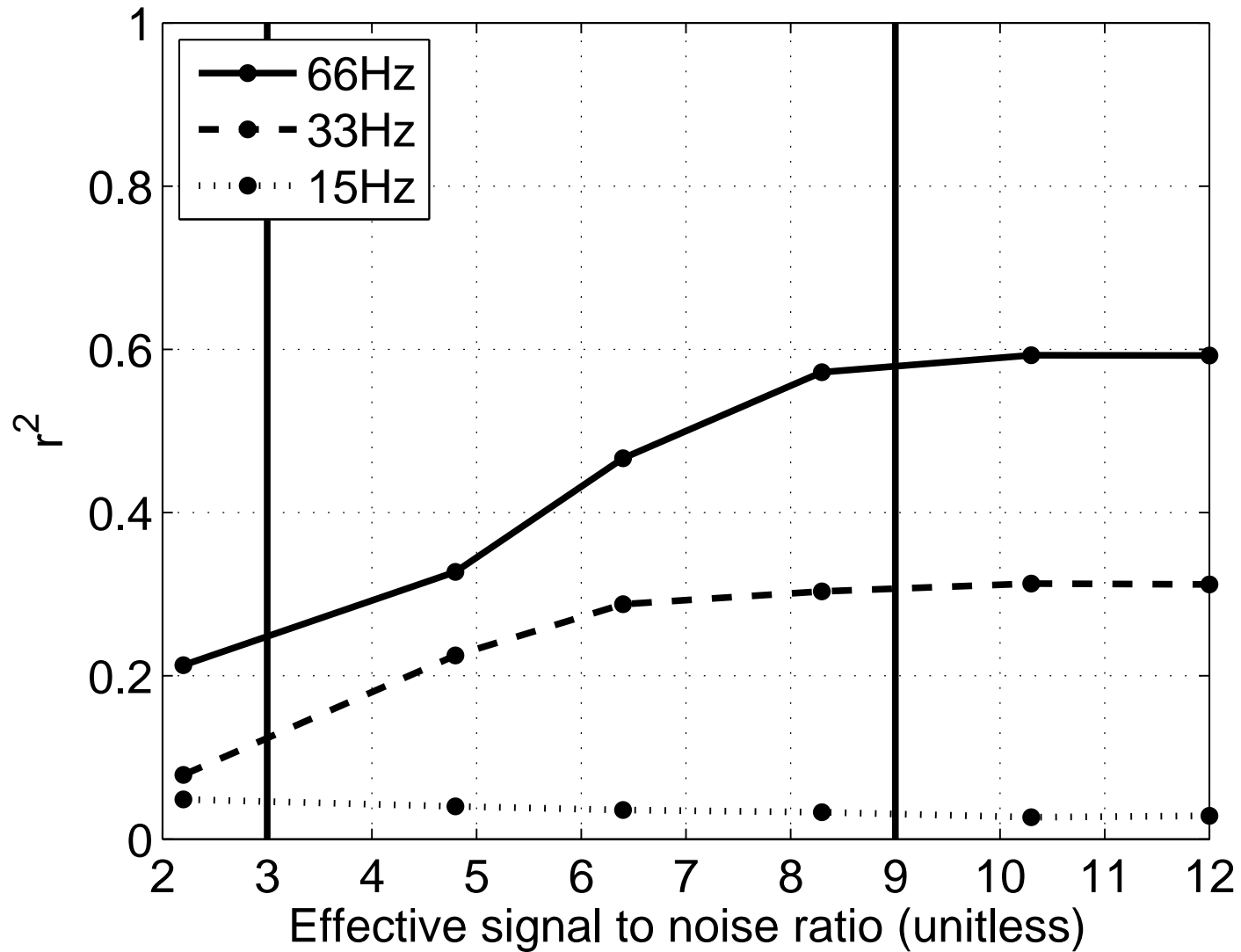
in silico connectivity inference



in silico connectivity inference



in silico connectivity inference



next steps

- applying the connectivity inference to **real data**
- while already computational time is only **a few minutes per cell** per node on a cluster, we'd like to be able to run this **online**
- incorporating **external stimulus** and **unobserved neurons**

bibliography

[1] JT Vogelstein, B Babadi, AM Packer, T Machado, R Yuste, L Paninski. In preparation. Fast spike train inference from calcium imaging.

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[4] AA Oliva Jr, M Jiang, T Lam, KL Smith, JW Swann. 200. Novel hippocampal interneuronal subtypes indentified using transgenic mice that express green fluorescent protein in GABAergic interneurons, J Neurosci, 20:3354:3368.

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