

Towards confirming neural circuit inference from population calcium imaging

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485.1

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]

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**

generative model

$$\begin{aligned} F_i(t) &= \alpha_i \frac{C_i(t)}{C_i(t) + k_d} + \beta_i + \sigma_i^F \varepsilon_t \\ \tau_i^c \frac{dC_i(t)}{dt} &= -C_i(t) + C_i^b + A_i n_i(t) + \sigma_i^c \varepsilon_t \\ n_i(t) &\sim \text{Binomial}[f(b_i + \mathbf{k}_i \mathbf{s}(t) + \sum_j w_{ij} h_{ij}(t))] \\ \tau_i^h \frac{dh_{ij}(t)}{dt} &= -h_{ij}(t) + n_j(t) + \sigma_i^h \varepsilon_t \end{aligned}$$

$$\begin{aligned} \theta &= \{\theta_i\}_{i \leq N}, \theta_i = \{\alpha_i, \beta_i, \sigma_i^F, \tau_i^c, C_i^b, A_i, \sigma_i^c, \tau_i^h, \sigma_i^h\} \\ \mathbf{X} &= (\mathbf{X}_i)_{i \leq N}, \mathbf{X}_i = \{X_i(t)\}_{t \leq T}, X_i(t) = \{C_i(t), n_i(t), h_i(t)\} \end{aligned}$$

fast filter

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

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

$$\begin{aligned} \hat{n}_i(t) &= \underset{n_i(t) \in [0,1]}{\operatorname{argmax}} P[n_i(t) | \mathbf{F}; \theta] \\ P[\mathbf{X}_i, \mathbf{F}_i] &= P[\mathbf{X}_i(0)] \prod_t P[\mathbf{X}_i(t) | \mathbf{X}_i(t-1)] P[\mathbf{F}_i(t) | \mathbf{X}_i(t)] \end{aligned}$$

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, sme or particle filter). parameters are estimated (from the data) using a **expectation maximization** algorithm.

effective connectivity inference

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

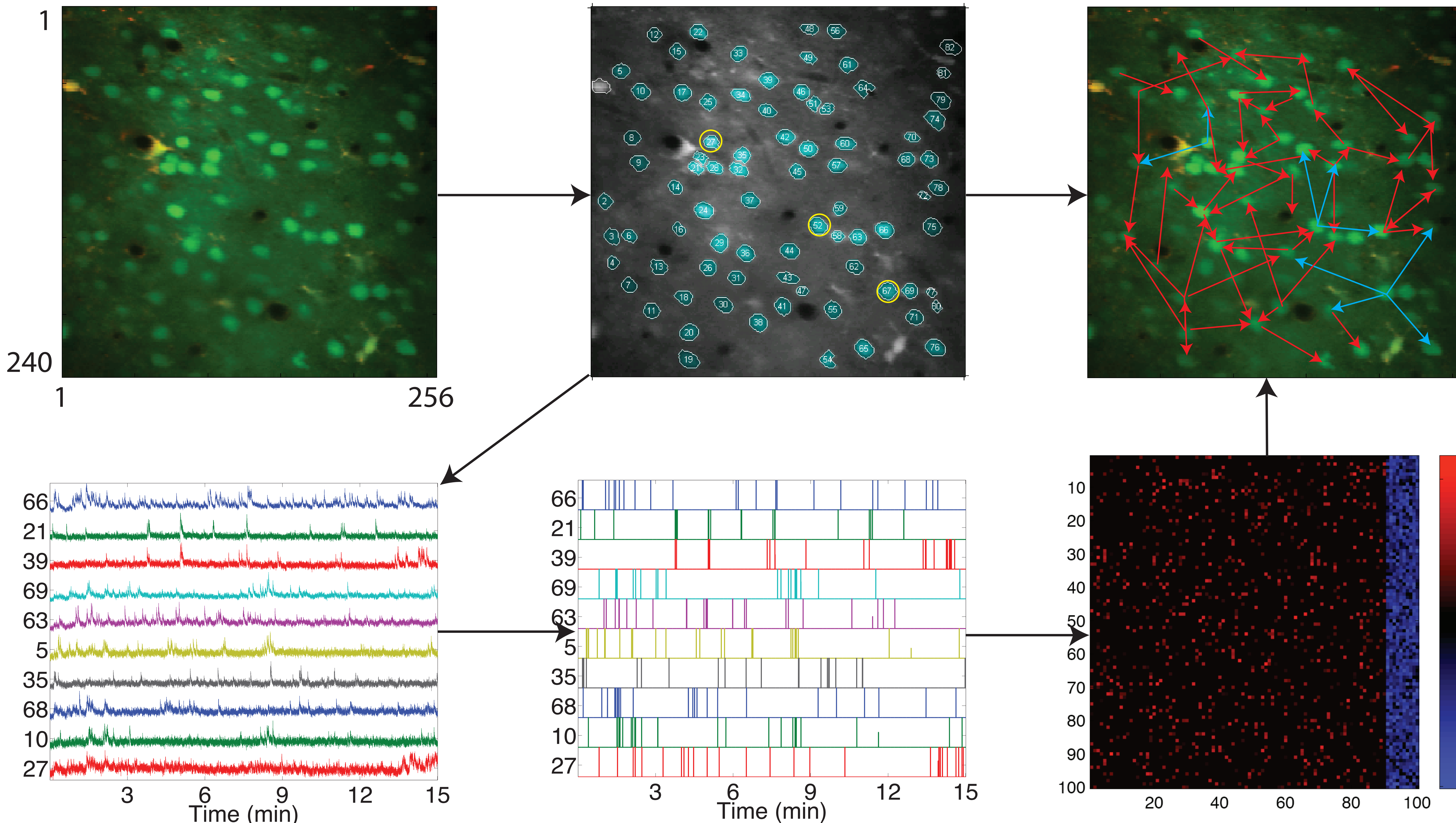
to obtain $P[\mathbf{X} | \mathbf{F}; \theta]$, we develop a specialized **blockwise Metropolis-within-Gibbs** sampler. for more efficient (but slightly less accurate) sampling, we approximate the joint posterior as the **product of marginals**. to estimate the connectivity, we impose a **sparse constraint**, via standard L₁ penalization methods.

bibliography

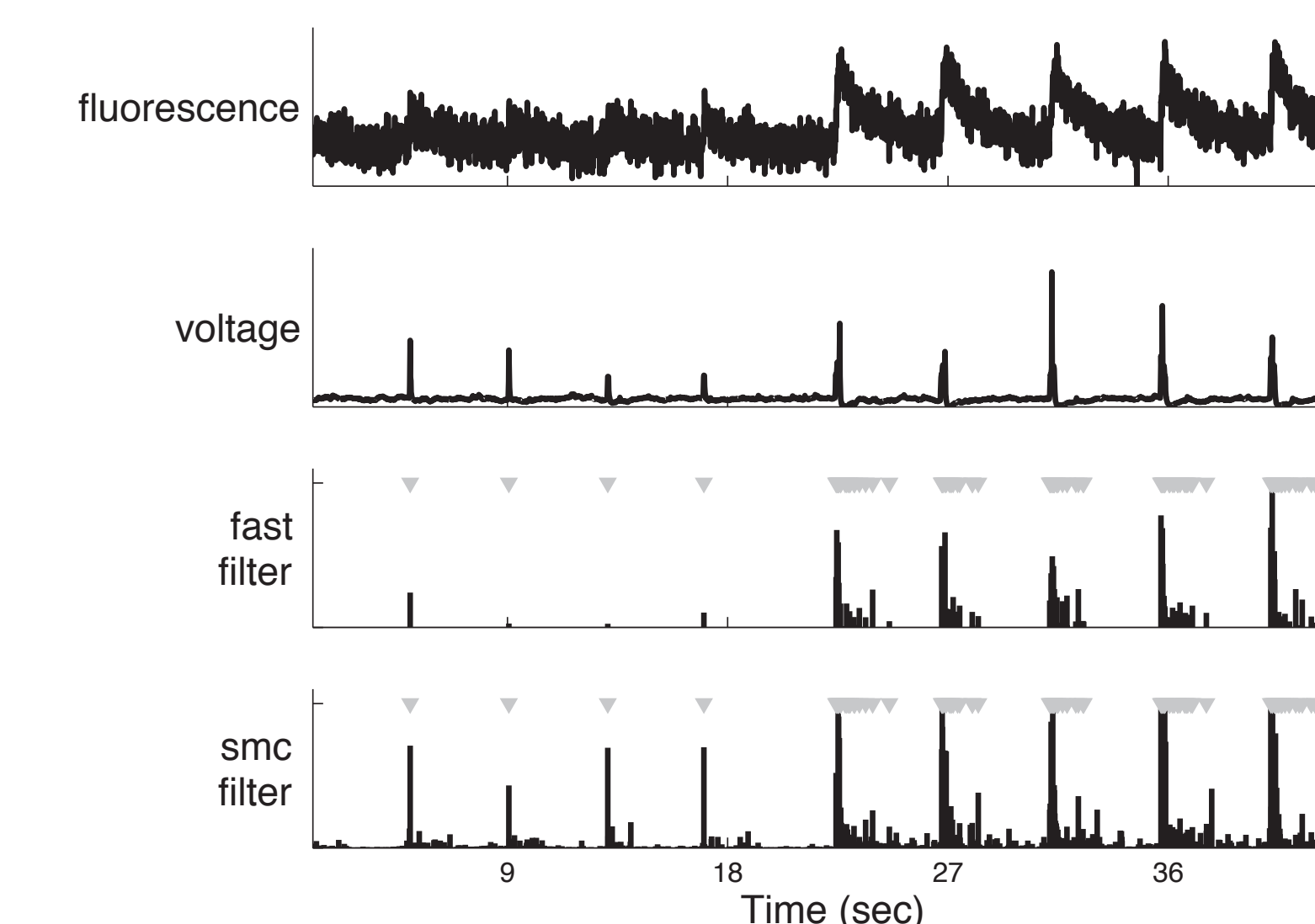
- [1] JT Vogelstein, B Babadi, AM Packer, T Machado, R Yuste, L Paninski. In preparation. Fast spike train inference from calcium imaging. <http://jovo.github.com/fast-oopsi/>
- [2] JT Vogelstein, BO Watson, AM Packer, R Yuste, L Paninski. 2009. Spike inference from calcium imaging using sequential monte carlo methods. Biophysical Journal, 97: 636-655. <http://jovo.github.com/smc-oopsi/>
- [3] Y Mishchenko, JT Vogelstein, L Paninski. In press. A Bayesian approach for inferring neuronal connectivity from calcium fluorescent imaging data. Annals of Applied Statistics. <http://jovo.github.com/pop-oopsi/>
- [4] AA Oliva Jr, M Jiang, T Lam, KL Smith, JW Swann. 200. Novel hippocampal interneuronal subtypes identified using transgenic mice that express green fluorescent protein in GABAergic interneurons, J Neurosci, 20:3354:3368.

acknowledgements

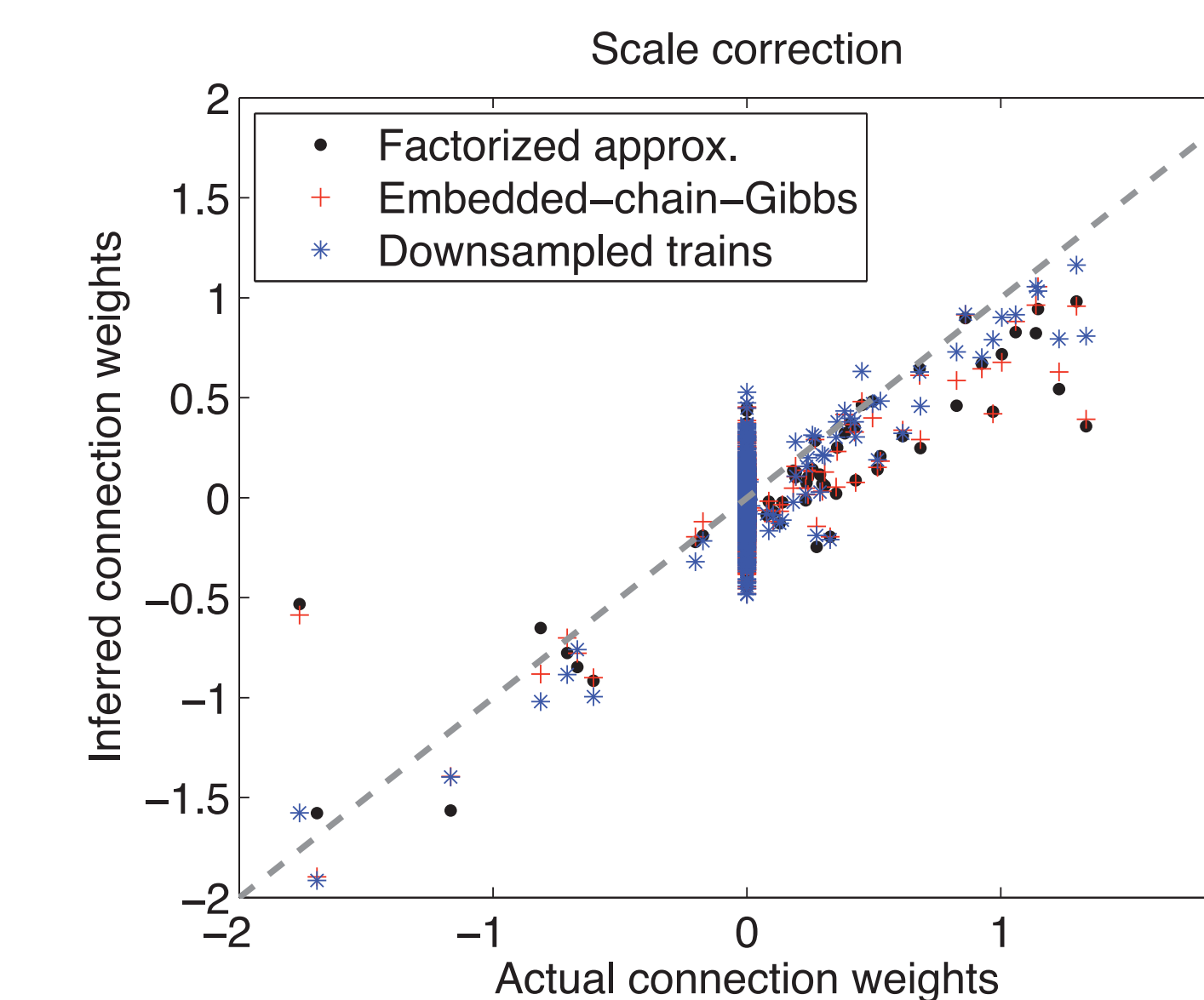
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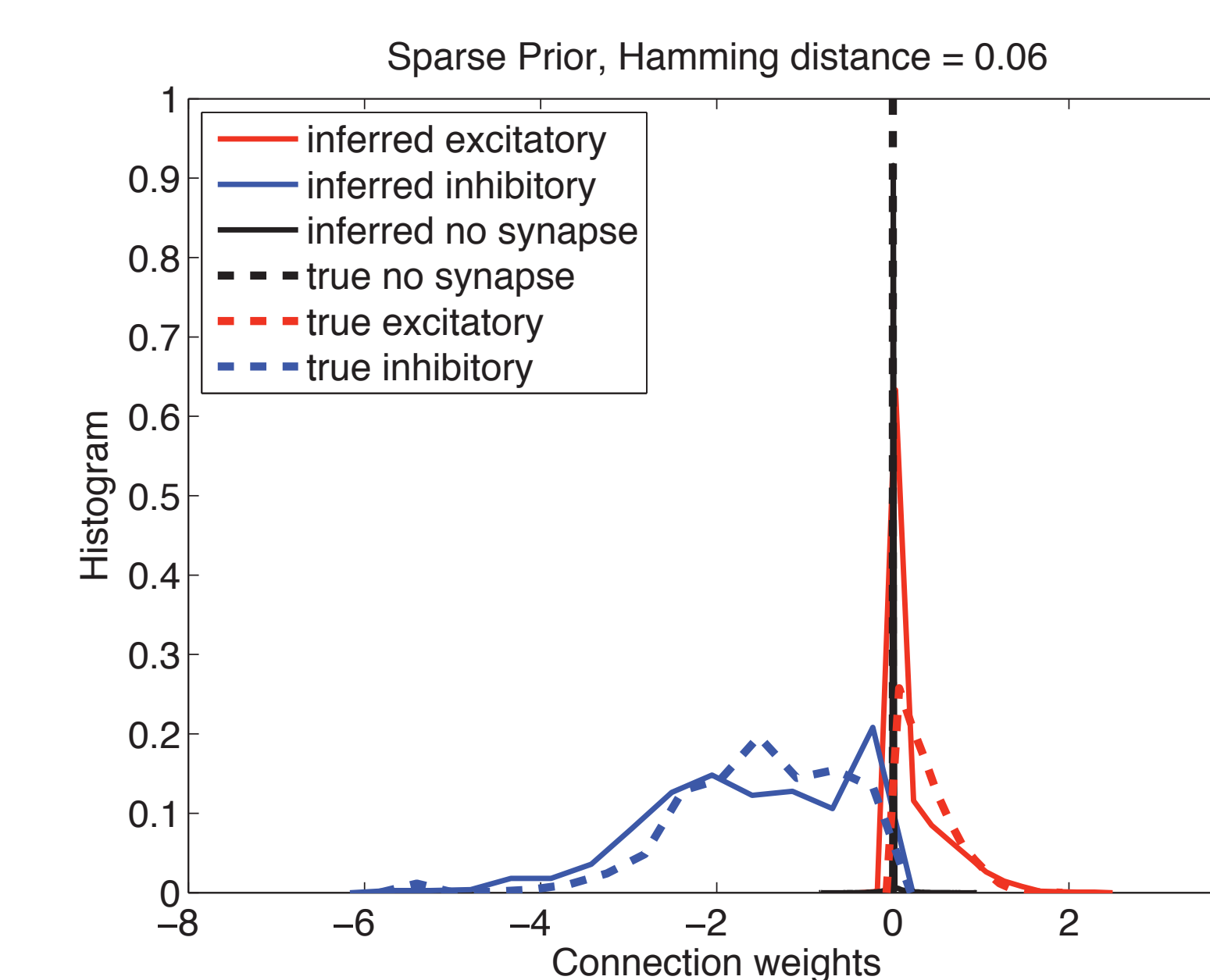
in vitro spike inference



in silico connectivity inference



in silico connectivity inference



in silico connectivity inference

