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 $\approx$ 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

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

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

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

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

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

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

fast filter

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

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

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

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

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

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

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 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

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