Bayesian Inference of Neural Activity and Connectivity from All-Optical Interrogation of a Neural Circuit

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Problem + Project Goals

All-optical techniques (simultaneous + *in vivo*)
1. 2-photon optogenetics → drive spikes in neurons
2. Calcium imaging → record fluorescence at cellular resolution

Goal: infer circuit mapping and neural connectivity from this data

Approach + Methodology

Global Bayesian inference strategy where we jointly infer distributions over the spikes and unknown connections

Why is this possible?
- GPU computing
- Automatic differentiation libraries
- Variational autoencoders

Conclusions

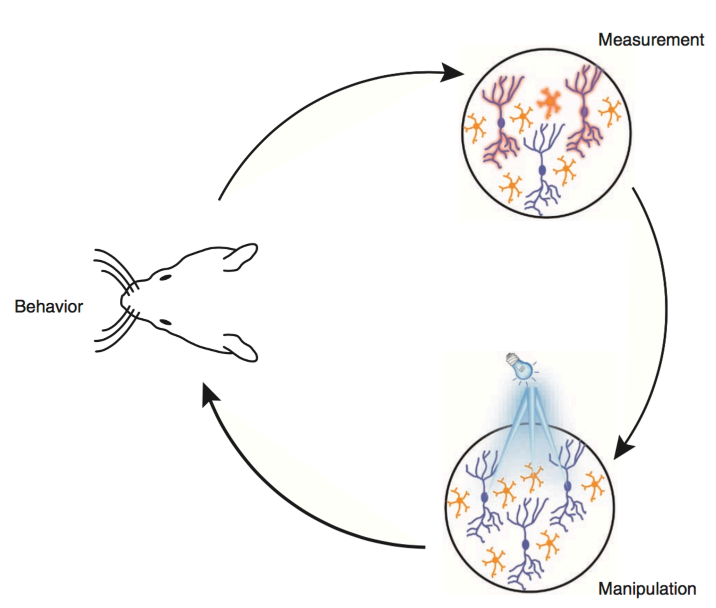
- Data shows evidence of sparse connectivity
- Inferred weights are consistent with known properties of neural circuits
- Joint inference is better than a pipeline

This is the first fully Bayesian model of calcium imaging designed for perturbation data that is able to extract posteriors over such a wide range of parameters with such efficiency

1 Data + Variational Inference

Optogenetic Experiment

- Mouse layer 2/3 of V1
- GCaMP6s calcium imaging, C1V1 opsin
- Stimulate five random cells twice per second, observe activity in rest of network
- Spontaneous data recording



Bayes' Rule

$$P(z|x) = \frac{P(x|z)P(z)}{P(x)}$$ posterior

latent variables — z — $P(z)$ — prior

generative model — $P(x|z)$ — likelihood

data — x — $P(x,z)$, $P(x|z)P(z)$, $P(x|z)P(z)$ — joint

Model Evidence

Log likelihood function where some parameters have been marginalized

$$P(x) = \int P(x|z)P(z)dz$$

- Computationally intractable
- Hinders application of Bayesian techniques to large-scale data

} VI solves this!

2 Model Framework

Recognition Model

VI + DNN, create posterior Q(z|x) intended to approximate P(z|x)

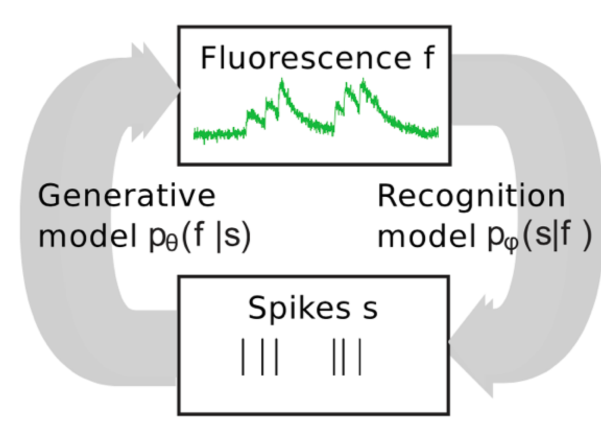
$$logP(x) \geq E_{Q(z|x)}[logP(x,z) - logQ(z|x)]$$

Factorize the approximate posterior over the spikes

$$Q(s(t)|v(t)) = Bernoulli(s(t); \sigma(v(t)))$$

$$v(t) = \underbrace{MLP(f(t-T:t+T)}_{} + D^e W^{se} e(t) + b^s$$

NN that takes a window of traces and linearly maps:
20 features → 2 standard layers → single value



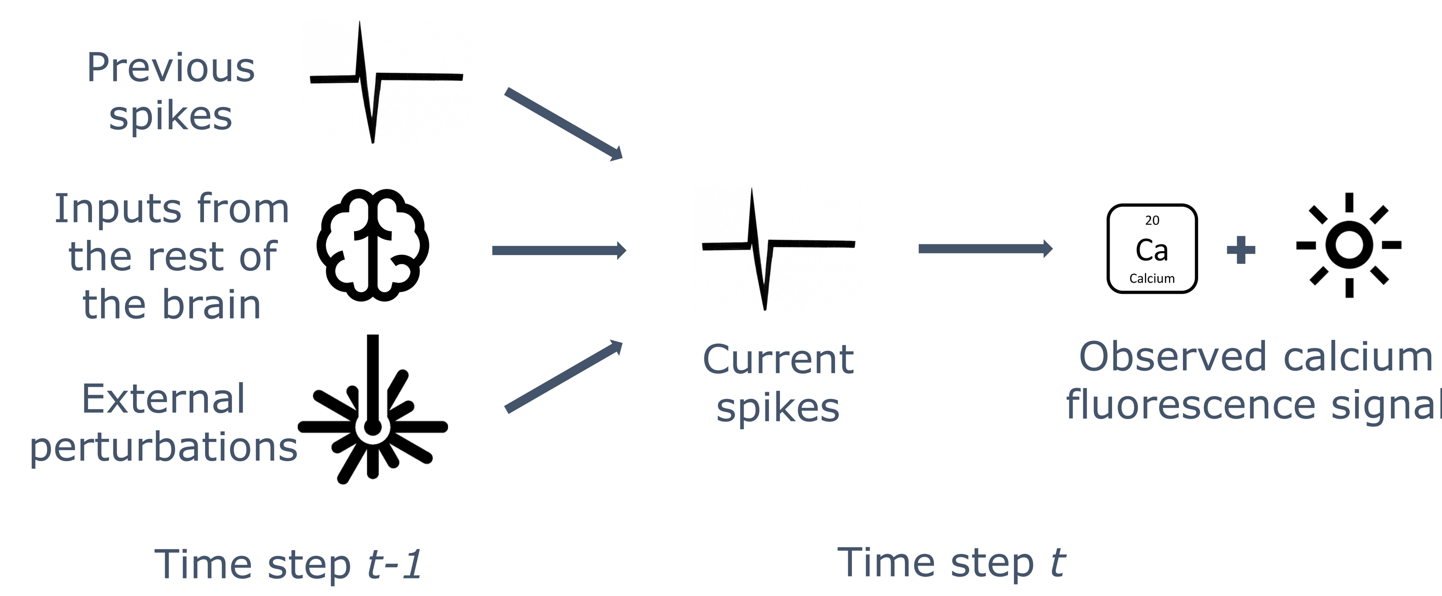
Generative Model

$$P(f(t)) = \mathrm{N}(f(t); r(t), \Sigma^f)$$

Fluorescence signals at time *t* | Reconstruction with Gaussian noise | Learned, diagonal covariance matrix

① Generate spikes at times step t

② Generate calcium fluorescence signals from the spikes

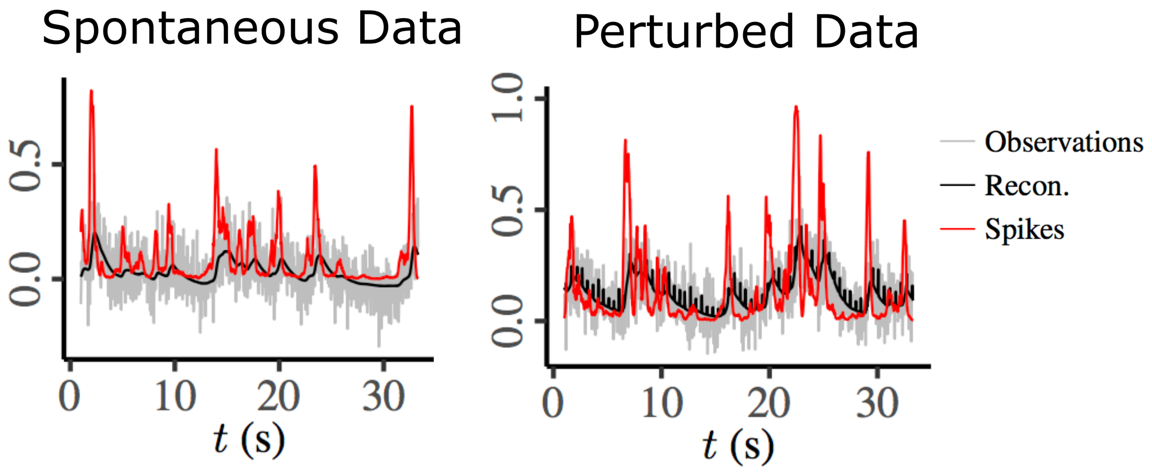


3 Results

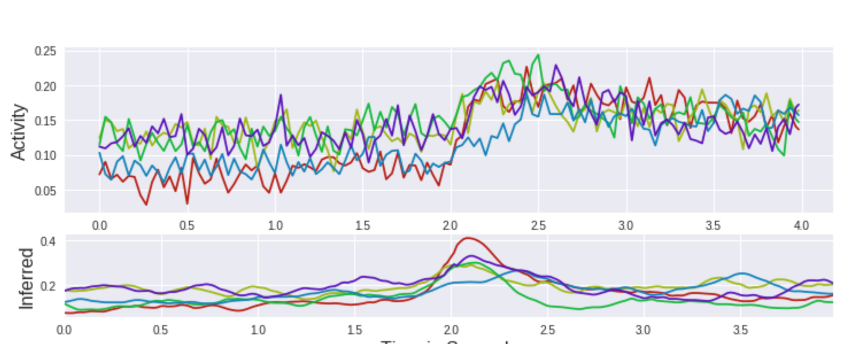
Spike Inference

Spontaneous Data

Perturbed Data

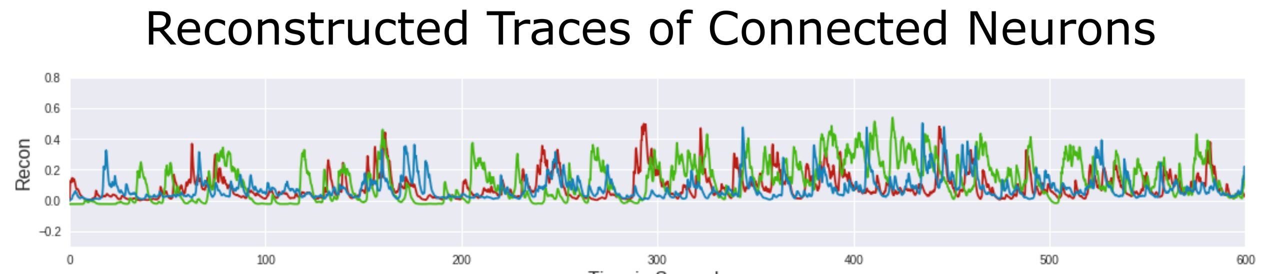


Stim-Triggered Averages

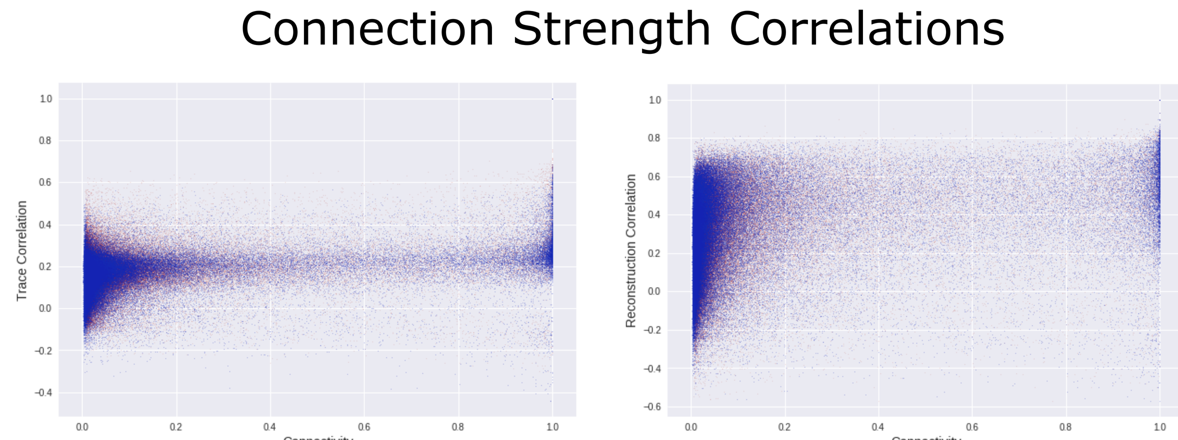


Confirming Synapse Predictions + Need for Sparser Inferences

Reconstructed Traces of Connected Neurons

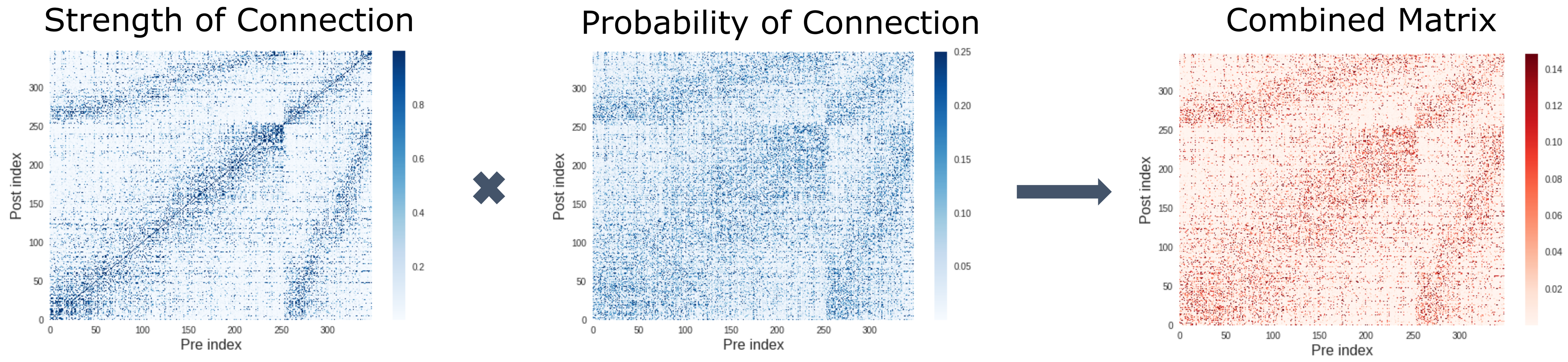


Connection Strength Correlations



Synaptic Connectivity Matrices

Strength of Connection | Probability of Connection | Combined Matrix



4 Next Steps

Improving the Model

① Upsampling to increase the resolution of the data

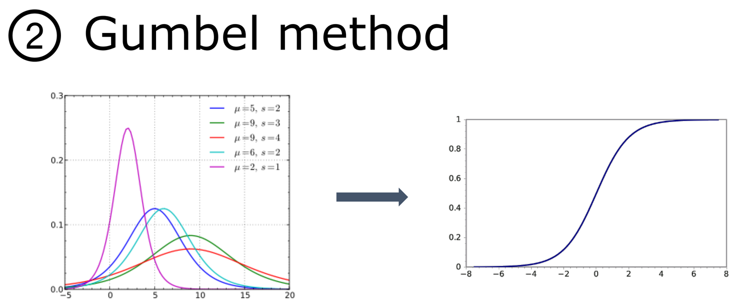
Calcium Traces

$$\begin{bmatrix} 0.32 & 0.22 \\ 0.57 & 0.09 \end{bmatrix} \xrightarrow{\text{linear interpolation}} \begin{bmatrix} 0.32 & 0.22 \\ 0.445 & 0.155 \\ 0.57 & 0.09 \end{bmatrix}$$

Perturbations

$$\begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} \xrightarrow{\text{interpolate with zeros}} \begin{bmatrix} 1 & 0 \\ 0 & 0 \\ 0 & 1 \end{bmatrix}$$

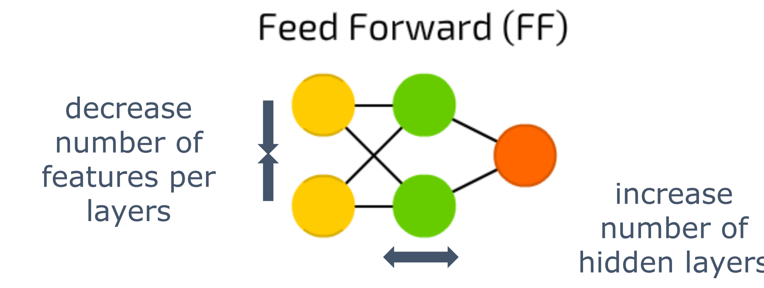
② Gumbel method



Sample from a Logistic distribution instead of a Normal/Gaussian → Propagate through a sigmoid

③ Expand convolutional neural network in recognition model

Feed Forward (FF)



④ Nonlinear generative model

- Linear: instant rise, exponential decay
- Nonlinear: incorporate intracellular dynamics of calcium in neurons
- Possible with Gumbel

Adaptation

Refactor model to **plug-and-play** spike-inference and fitting methods

Optogenetic + observational datasets

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References

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[3] Packer, A.M., Russell, L.E., Dalgleish, H.W., & Häusser, M. Simultaneous all-optical manipulation and recording of neural circuit activity with cellular resolution in vivo. *Nature Methods*. vol. 12, no. 2, pp. 140–146, (2015).

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