Neural Structure Reconstruction from Fluorescence Imaging

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Objectives

The task is to predict the **connectivity** in **neural structures** monitored through calcium-based **fluorescence imaging**. We investigate various algorithmic techniques used for inferring statistical causality.

In the process, we come across some interesting features exhibited by biological neural networks. We also successfully mitigate a few challenges particular to the problem.

Introduction

Understanding the topology underlying the neurons promises to be a step forward to unravelling the working of the brain and shed some light on its learning capabilities. The study of how the network structure is modified by diseases could catalyse the research on neuro-pathologies, eg. epilepsy, Alzheimer's disease. However, the traditional methods of axonal tracing do not scale enough of be practical value; and electron microscopy is very cost-intensive and lacks the benefit of in vivo operation.

A promising approach is to observe neural activity sampled at different time points through fluorescence imaging. We tackle the task of detecting the presence of excitatory connections among neurons given the imaging data.

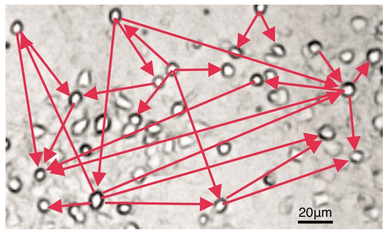

Figure 1: Network reconstruction of neural cultures imaged with fluorescent calcium imaging.[Credits:connectomics.chalearn.org]

Data

The data set contains synthetic time series activity of 100 neurons sampled at 1,70,000 points with a resolution of 20 ms, along with the ground topology and position of neurons.

Algorithmic Techniques

To infer the directed connections between a pair of neurons X and Y, we use the following techniques.

- **Cross Correlation**: Reconstruction is based on the standard Pearson cross-correlation.

$$XC_{Y\to X} = max_{\Delta t=0\ldots t_{max}} corr(X_S, Y_{S-\Delta t})$$

- **Mutual Information**: It is a measure of how much excess information does the joint distribution of 2 variables contain over the product of marginals.

$$MI_{Y\to X} = max_{\Delta t=0\ldots t_{max}} \sum_{\vec{n}} (P(X_n, Y_{n-\Delta t}) \log \frac{P(X_n, Y_{n-\Delta t})}{P(X_n)P(Y_{n-\Delta t})})$$

- **Granger Causality**: The idea is to see if the current value of X gives a better fit with a linear model, if the past of Y is taken as a covariate.

$$x_t = \sum_{l=1}^{k} a_l^0 x_{t-l} + \eta_t^0 \ \textit{and}\ x_t = \sum_{l=1}^{k} a_l^1 x_{t-l} + \sum_{m=1}^{k} b_m^1 y_{t-m} + \eta_t^1$$

$$GC_{Y\to X} = \log \frac{\Gamma_{0,0}^0 + \Gamma_{1,1}^0}{\Gamma_{0,0}^1 + \Gamma_{1,1}^1}$$

- **Generalized Transfer Entropy**: It is a measure of distance between the conditional distribution of X given its past and the conditional distribution of X given both its own past, as well as past of Y.

$$TE_{Y\to X} = \sum_{\vec{n}} (P(X_{n+1}, X_n^{(k)}, Y_n^{(k)}) \log \frac{P(X_{n+1}|X_n^{(k)}, Y_n^{(k)})}{P(X_{n+1}|X_n^{(k)})})$$

- **Information Gain**: This is a general causality inference framework, parameterized to support any function on the distribution of X and Y. In particular, we use Entropy and Gini Index.

$$IG_{Y\to X} = I(X) - I(X|Y)$$

$$G(X) = 1 - \sum_{i=1}^{n} P(X_i)^2 \ \textit{and}\ I(X) = \sum_{i=1}^{n} P(X_i) \log \frac{1}{P(X_i)}$$

- **Combined Linear Model**: We use the probability output by other methods to learn a linear model which outputs probability of existence of a directed edge, given the above measures as covariates.

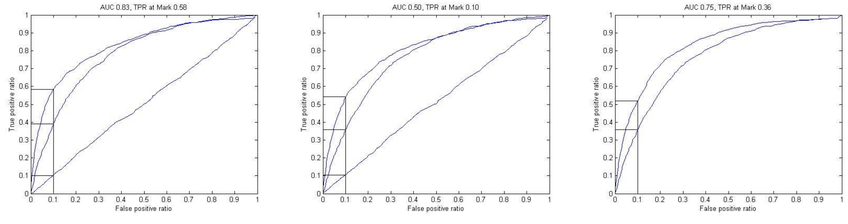

Figure 2: ROC curves for {GTE, Gini Index, Granger Causality}, {Cross Correlation, Information Gain (Entropy), Random Guess}, and {Combined Linear Model, Mutual Information}

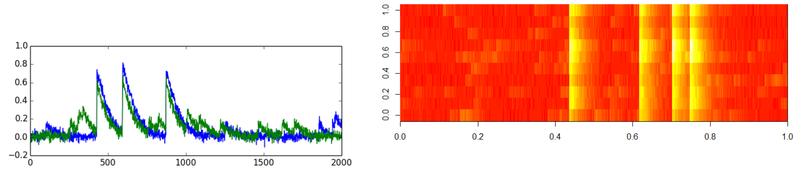

Figure 3: (1) Neural Activity vs. Time (2) Heat Map of Neural Activity

Challenges and Solutions

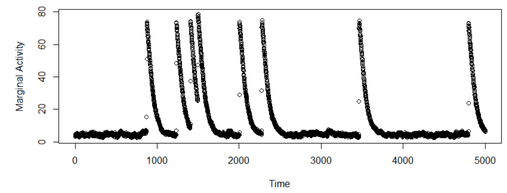

Figure 4: Spikes in neural activity indicate collective synchrony.

- **Low Signal-to-noise Ratio**: We observe small random spikes in the data, which do not map with activation of neurons. For this, we discretize the input, after setting a proper threshold.
- **Collective Synchrony**: There are identifiably prominent region where the net global activity suddenly increases. In these time regions of collective synchrony, mono-synaptic connections are difficult to infer. We discard such regions of high neural activation.
- **Low Resolution**: Since the time series is heavily under-sampled, for each algorithmic technique, we include "same bin" interactions.

Results

Algorithm	AUC
Generalized Transfer Entropy	0.83
Combined Linear Model	0.83
Cross Correlation	0.81
Information Gain (Gini)	0.78
Information Gain (Entropy)	0.76
Mutual Information	0.75
Granger Causality	0.49
Random Guess	0.50

References

[1] Olav Stetter, Demian Battaglia, Jordi Soriano
Model-Free Reconstruction of Excitatory Neuronal Connectivity from Calcium Imaging Signals
PLOS Computational Biology 2012