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14. ABSTRACT
A two-photon imaging technique is able to capture a large number of in-vivo multi-region neuronal activities simultaneously. We carry out a causal interaction study on neuronal activities of mice's visual cortex. We applied a proposed data-driven causal interaction measure (earlier developed in our Laboratory) to the florescent calcium data. By estimating the fractal dimension of the delay-embedding point cloud, we give a nonlinear causality measure and a signal delay estimation between activities of an ordered pair of neurons. This leads to a weighted directed network of neurons or a binary network by thresholding. Despite high variability of single neuron activities

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Report Title

Final Report: Neuron-based Measurements for Brain Functionality Understanding

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A two-photon imaging technique is able to capture a large number of in-vivo multi-region neuronal activities simultaneously. We carry out a causal interaction study on neuronal activities of mice's visual cortex. We applied a proposed data-driven causal interaction measure (earlier developed in our Laboratory) to the florescent calcium data. By estimating the fractal dimension of the delay-embedding point cloud, we give a nonlinear causality measure and a signal delay estimation between activities of an ordered pair of neurons. This leads to a weighted directed network of neurons or a binary network by thresholding. Despite high variability of single neuron activities over trials, for the same stimulus, we observed consistent patterns of the networks, such as hub neurons, population activities and topological characteristics. We defined and computed dissimilarity measure between networks to show our method is robust against trial-to-trial variability.

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Neuron-based Measurements for Brain Functionality Understanding

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Abstract

A two-photon imaging technique is able to capture a large number of in-vivo multi-region neuronal activities simultaneously. We carry out a causal interaction study on neuronal activities of mice's visual cortex. We applied an earlier proposed data-driven causal interaction measure to the florescent calcium data. By estimating the fractal dimension of the delay-embedding point cloud, we give a nonlinear causality measure and a signal delay estimation between activities of an ordered pair of neurons. This leads to a weighted directed network of neurons or a binary network by thresholding. Despite high variability of single neuron activities over trials, for the same stimulus, we observed consistent patterns of the networks, such as hub neurons, population activities and topological characteristics. We defined and computed dissimilarity measure between networks to show our method is robust against trial-to-trial variability.

Statement of the problem

Given times series data of activities of *N* neurons in mice's visual cortex,

$$X = \{x_{1,1}, \dots, x_{1,T}, x_{2,1}, \dots, x_{2,T}, \dots, x_{N,1}, \dots, x_{N,T}\}$$

we aim to find neuron firing patterns associated to certain visual stimuli, and to infer the causal/interaction networks of these neurons. The construction of the networks is based on our causal interaction measure. Then we are to analyze the networks to discover sensible patterns and to validate our approach.

Data description

The dataset is provided by Dr. Smith's SLAB in UNC at Chapel Hill, who developed a unique experimental platform for large scale neuronal activity imaging using two-photon excitation microscopy [1]. This technique uses longer wavelength laser as exciting light, to achieve deeper tissue penetration and lower background noise than traditional fluorescence microscopy. The neuron data contains the Ca2+ fluorescence time series for which the time resolution is about 70 milliseconds per frame. The number of observed neurons is 590 in the V1 (primary visual cortex) and 301 in the AL (anterolateral area) of the mouse brain, respectively. All of those neurons are distributed in a single layer of certain depth shown in **Fig.1**.

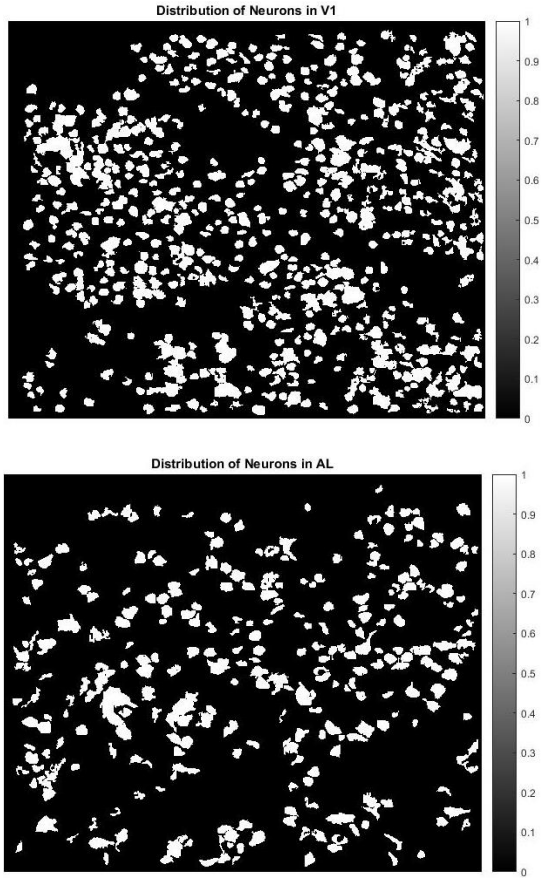

Figure 1 Distribution of neurons. The top and the bottom images correspond to the observed

neurons at the site of V1 and AL of the mouse brain, respectively. The white spots are segmented regions of interest (ROI) corresponding to neurons. The recorded Ca2+ fluorescence intensity of a ROI is used to represent the neuron's activity.

The scale of the time series are corresponding to visual stimuli. Shown in **Fig.2**, three different stimuli are shown to the mouse: one artificial movie and two natural movies. The stimuli are separated by grey frames to which the mouse is not sensitive. The artificial movie is composed of moving gratings of various directions. The two natural movies is to mimic the situations of the mouse moving in its living environment. The sequence of visual stimuli is played 20 times for the mouse which forms 20 repeated trials. An example of time series of 20 trials is given in **Fig.3**. We can see that although this neuron is active in almost all trials, the firing pattern seems highly irregular.

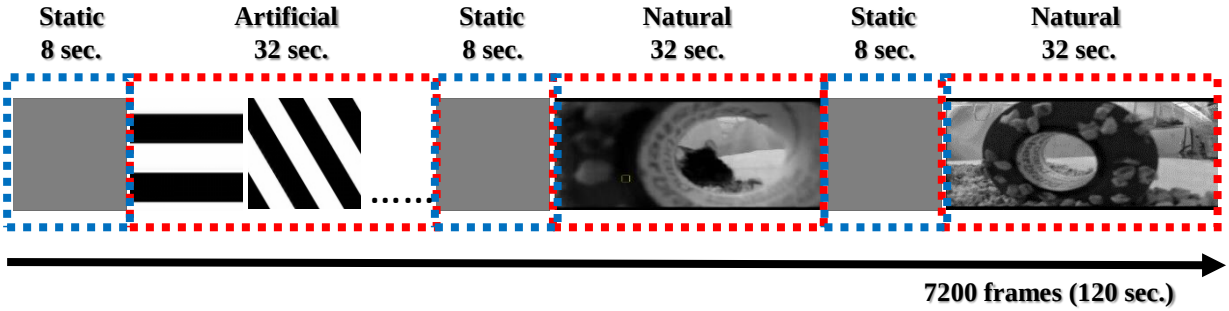

Figure 2. The stimuli presented to the sample mouse. One repeat of the whole video lasts for 120 seconds and has one artificial movie (32 sec.), two natural movies (32 sec. for each one), and three static (gray) frames (8 sec.) in-between and at the beginning of the stimulus. This sequence is played 20 times continuously.

Methods

Causal interaction measure (CIM) [2]:

Our notion of causality is closely related to physical systems responding to interrogation/excitations. The impulse response of the system can be nonlinear and time-varying. Inspired by Takens' delay embedding theorem, it is possible to come up with a data-driven and consistent causality measure between signals. The causality measure we propose is based on a geometrical method. First the delay embedding is designed for multivariate time series data representing *N* neuron activities over time [0,T].

$$X = \{x_{1,1}, \dots, x_{1,T}, x_{2,1}, \dots, x_{2,T}, \dots, x_{N,1}, \dots, x_{N,T}\}$$

Given a pair of signals $\{x_{1,t}\}_t$ and $\{x_{2,t}\}_t$, we have adopted the delay embedding of neuron signal x_1 and x_2 as $\{x_{1,t}, x_{2,t-\tau}\}_t$, where the signal of x_2 is delayed by τ. This delay τ is to be chosen to maximize the causality, and is an estimate of signal delay between two neurons assuming they are causally related. Then we study the intrinsic fractal dimension of the point cloud embedded in $\mathbb{R}^2$, which could be non-integer values. It is a natural assumption that a causality measure could be defined as reversely proportional to the intrinsic dimension. We estimate the *correlation fractal dimension* in practice.

Network construction and analysis:

To construct a causal network of neurons, we compute CIM for each ordered pair of neurons. Specifically we try a range of τ, and pick the one corresponding to the lowest fractal dimension,

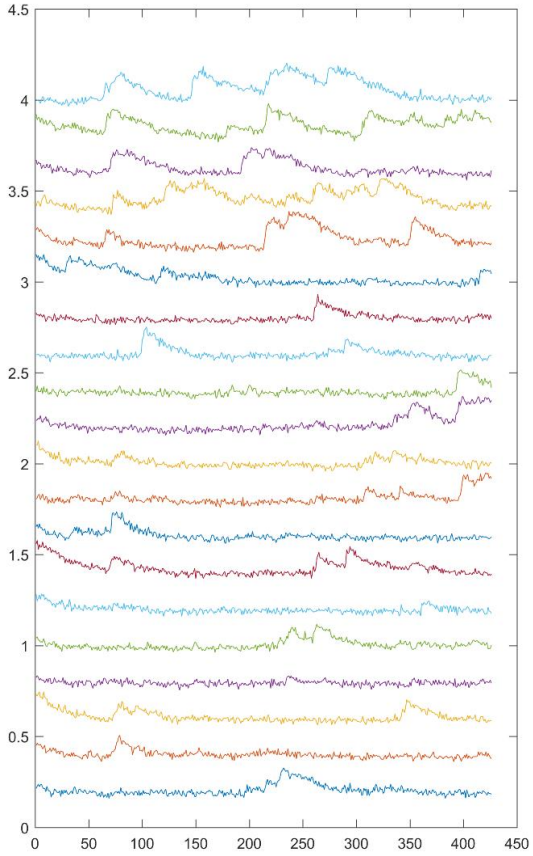

Figure 3. Examples of fluorescence time series of a neuron. This shows the time series of an active neuron (index 238) during the first natural movie stimulus in 20 different trials. Trial order is from bottom (1st) to top (20th).

the reciprocal of which being the CIM. The value of CIM between two neurons can be used as the weight of a directed edge in the network. We adopted a simplifying assumption that two neuronal signals only exhibit one direction of signal transmission or causal interaction, therefore we choose the maximum weight among two directed edges and yield a undirected network.

We can determine the neuronal connectivity by setting a threshold on edge weights. However the degree of a neuron (number of edges connecting to other neurons) is highly sensitive to the threshold chosen, as shown in **Fig. 4**. Given the shape of degree-dimension curves, fixing the degree instead of dimension can better represent and distinguish the roles of different neurons. We chose the nonlinear region (dashed line) as the degree threshold and record the corresponding dimension value for each neuron. The earlier a neuron reaches a certain degree, the more sensitive/active that neuron is. The result is a feature vector capturing the sensitivity of neurons for a stimulus. Finally, we apply the Pearson's Distance

$$D(X,Y) = 1 - corr(X,Y)\,, D \in [0,2]$$

to feature vectors for a dissimilarity measure between the neuronal networks.

Another way we used to characterize weighted networks are Betti curves. Betti curves are results from persistent homology which is an efficient evaluation tool for global network topology at various scales regardless of specific neurons, and this method has been used in brain/neural network studies before [2,3]. In brief, we use Betti 1 curves, which count the number of independent cycles in the network as edge threshold changes. Note the definition of cycles here does not include triangles. For example, a cycle of four nodes will disappear and become two triangles when two diagonal nodes are connected.

Results

Here we averaged time series in every consecutive 3 of 18 trials (excluding the first and the last trial), to reduce noise and obtain 6 experiments. First we use the distribution of τ as a feature of neuron messaging pattern, and compute the Jason-Shannon distance between them. **Fig. 5** shows the distance matrix. We can see this feature is consistent within artificial and natural visual stimuli respectively, and is able to distinguish between the two types of stimuli in most experiments. However two different natural movies do not cause a difference in this feature.

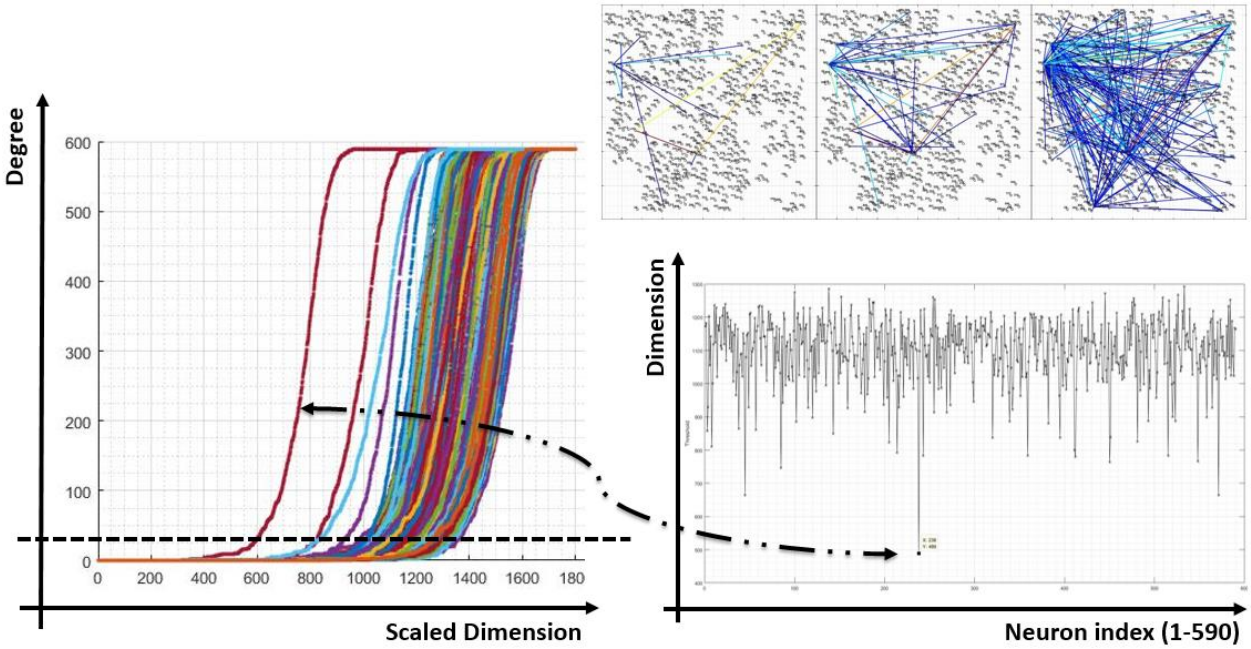

Figure 4. Problem of thresholding dimension/CIM and how to generate a network feature vector. Each curve in the left plot shows how the degree of a neuron in a network increases as the threshold of dimension is relaxed. The plots on the top-right show examples of the binary networks when choosing different dimension threshold. The bottom-right plot shows the corresponding feature vector to the left.

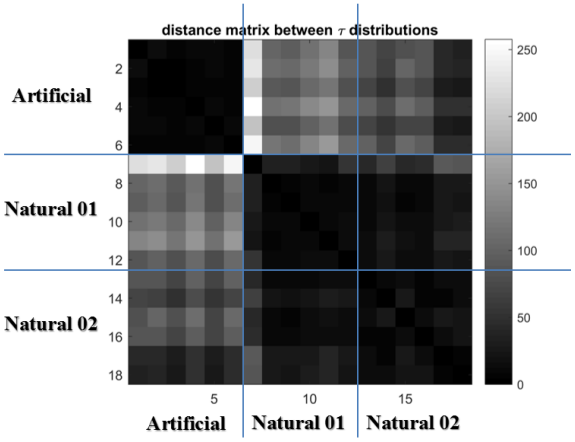

Figure 5. Distance matrix of τ distributions. The rows and columns are order to put experiments for the same stimulus together.

Next, based on the same averaged data, we calculated the distance matrix of the networks. The results in **Fig. 6** show that, for the same stimulus, the causal networks are generally less dissimilar compared to those with different stimulus. Especially by using network feature vector shown in **Fig. 4**, two natural movies are now distinguishable, compared to using τ distributions, although now the consistency within each stimulus is worse, indicating a high variability regarding neuron-based features.

Last, for each of 20 trials, we calculated Betti 1 curves for the networks of neurons in AL and V1 regions respectively, and plot the averages of the curves for different stimuli. From the error bars we can tell there is still high variance of network topology. However Betti 1 curves for V1 show a clear distinction between artificial and natural movies. Betti curves were proposed as invariants in presence of nonlinearity in neural systems [3]. We find the topological features of networks is associated with geometry in visual stimuli, which in turn supports our network construction approach and the feasibility of using CIM to infer causal

relations from neuronal signals. Moreover, the causality pattern shows the potential to discover the underlying biological neural network.

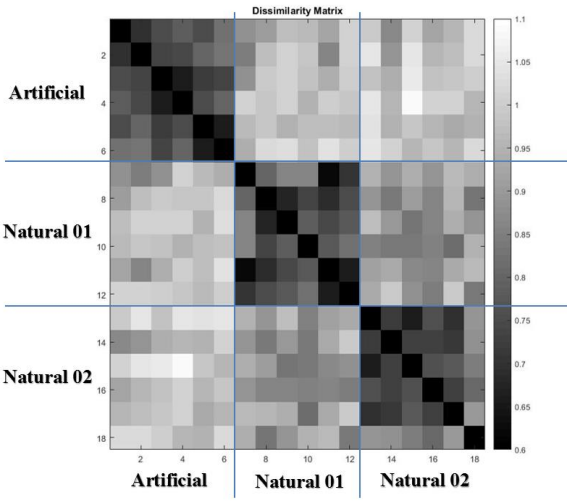

Figure 6. Distance matrix of causal networks. The rows and columns are order to put experiments for the same stimulus together.

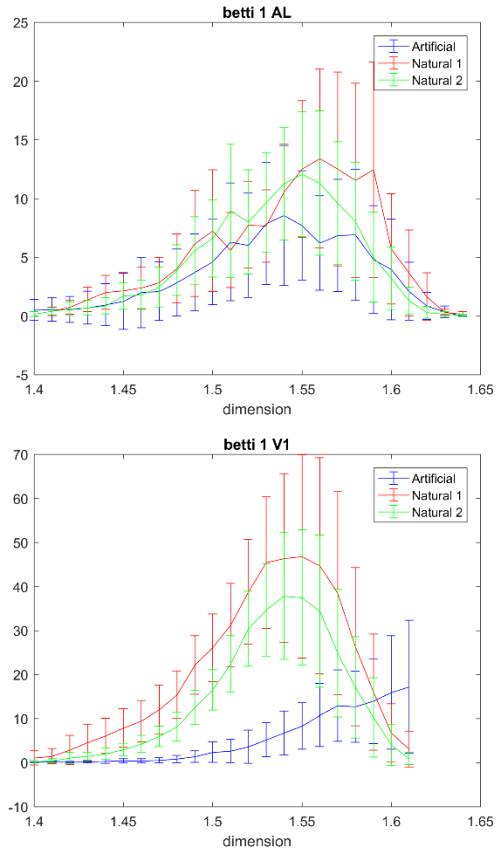

Figure 7. Average Betti 1 curves of networks for different stimuli. The top plot shows Betti 1 curves of causal network of neurons in AL, and the bottom one shows that in V1. Each curve is an average of 20 curves calculated from 20 trials of networks. Error bars show the standard error.

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