



Estimation of neural connections from partially observed neural spikes



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ABSTRACT

Plasticity is one of the most important properties of the nervous system, which enables animals to adjust their behavior to the ever-changing external environment. Changes in synaptic efficacy between neurons constitute one of the major mechanisms of plasticity. Therefore, estimation of neural connections is crucial for investigating information processing in the brain. Although many methods have been proposed for this purpose, most of them suffer from one or all the following mathematical difficulties: (1) only partially observed neural activity is available; (2) correlations can include both direct and indirect pseudo-interactions; and (3) biological evidence that a neuron typically has only one type of connection (excitatory or inhibitory) should be considered. To overcome these difficulties, a novel probabilistic framework for estimating neural connections from partially observed spikes is proposed in this paper. First, based on the property of a sum of random variables, the proposed method estimates the influence of unobserved neurons on observed neurons and extracts only the correlations among observed neurons. Second, the relationship between pseudo-correlations and target connections is modeled by neural propagation in a multiplicative manner. Third, a novel information-theoretic framework is proposed for estimating neuron types. The proposed method was validated using spike data generated by artificial neural networks. In addition, it was applied to multi-unit data recorded from the CA1 area of a rat's hippocampus. The results confirmed that our estimates are consistent with previous reports. These findings indicate that the proposed method is useful for extracting crucial interactions in neural signals as well as in other multi-probed point process data.

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1. Introduction

One of the most important properties of the brain is its ability to modify its architecture on the basis of experience. This phenomenon, which is known as plasticity, enables living organisms to flexibly adjust their behavior to the external environment and improve their chances of survival. Various studies have shown that changes in synaptic connections constitute the primary mechanism of plasticity, in which many types of neurotransmitters and receptors are involved. Although the detailed processes of how synaptic efficacy is modified are complex, detecting the overall change in neural connections is essential for investigating information processing in the brain. Recent advancements in experimental technologies, such as multi-electrode recording from a freely behaving animal, enable us to record the activities of a large number

of neurons simultaneously for extended periods (Tatsuno, Lipa, & McNaughton, 2006). After spike sorting of the multi-unit activity (MUA) data, sorted single-unit activity (SUA) data are obtained. SUA represents the timing of spike occurrence of each neuron, and it can be considered as a point process. Many studies have investigated the correlational properties of SUA data with the objective of understanding system-level information processing in the brain (Brown, Kass, & Mitra, 2004; Gerstein & Perkel, 1969; Hino, Takano, & Murata, 2015; Perkel, Gerstein, & Moore, 1967; Shimazaki, Amari, Brown, & Grün, 2012; Takano, Hino, Yoshikawa, & Murata, 2015). Toward this end, methods based on pairwise neuronal correlations, such as cross-correlation (Barthó et al., 2004; Wilson & McNaughton, 1994) and joint peristimulus time histogram (Aertsen, Gerstein, Habib, & Palm, 1989; Ito & Tsuji, 2000) have been widely adopted. For instance, in the context of memory consolidation, Wilson and McNaughton (1994) estimated functional neural interactions in the CA1 area of the hippocampus by means

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of cross-correlation functions. They showed that pairwise correlations induced during a behavior task epoch were sustained during a post-task non-REM sleep epoch, thereby supporting the conjecture that reactivation of behaviorally induced neural activity during sleep (memory reactivation) plays an important role in memory consolidation. Other approaches based on graph structure estimation methods, such as sparse inverse covariance selection (SICS), have been also adopted (Banerjee, Ghaoui, & dAspremont, 2008; Friedman, Hastie, & Tibshirani, 2008; Scheinberg & Rish, 2009). SICS assumes that observed data are generated from a Gaussian distribution and estimates a graph structure as its inverse covariance matrix. Efficient algorithms for SICS have been proposed, and they can estimate the functional connections of a network composed of numerous neurons. However, the above-mentioned methods suffer from several mathematical difficulties. First, owing to their focus on pairwise relationships, they cannot capture high-order correlations that might result in pseudo-correlations with pairwise measurements. Second, they generally provide functional correlations, which lack directional properties as a fundamental feature; therefore, it is difficult to discuss the direction of connections. Third, they usually do not consider the fact that only a limited number of neurons are recorded in experiments. Unobserved neurons affect the activity of observed neurons, but existing methods do not include a systematic treatment for interference from unobserved neurons. Recently, several attempts have been made to overcome the above-mentioned difficulties. For instance, some studies have adopted the information-theoretic approach to investigate high-order correlations (Nakahara & Amari, 2002; Nie & Tatsuno, 2012; Tatsuno, Fellous, & Amari, 2009). Assuming that spikes are generated from an exponential family of distributions, the method based on information geometry models the probability of coincident multi-neuronal firings, p_{x_1, x_2, \dots, x_k} , by a log-linear model:

$$\ln p_{x_1, x_2, \dots, x_k} = \sum_i \theta_i x_i + \sum_{i < j} \theta_{ij} x_i x_j + \dots + \theta_{12 \dots k} x_1 x_2 \dots x_k - \psi, \quad (1)$$

where x_i is a binary variable representing the spikes of neuron i , θ is a parameter representing neural interactions, ψ is a normalization factor for the integral to be 1, and k is the number of observed neurons, following the same notation as that in the original paper. Further, θ_{ij} represents the interaction between neurons i and j . Although this model mitigates the problem of pseudo-correlations, it suffers from two drawbacks. First, its computational cost increases with k . Second, it assumes that connections are symmetric. For the problem of directionality, a method based on Granger causality has been proposed to extract information regarding the direction of connections (Arnold, Liu, & Abe, 2007; Hu, Li, & Liang, 2015; Kim, Putrino, Ghosh, & Brown, 2011; Quinn, Coleman, Kiyavash, & Hatsopoulos, 2011). Suppose that the activities of two neurons, x_i and x_j , are observed. If x_j provides statistically significant improvements of the future values of x_i , the directed influence from x_j to x_i is estimated, and it is said that there is Granger causality from x_j to x_i . However, it is difficult to capture higher-order correlations with this approach, which focuses on two spike trains. To overcome the problems of high-order correlations and directionality simultaneously, Noda, Hino, Tatsuno, Akaho, and Murata (2014) recently proposed the graph structure estimation method based on the graph Laplacian. They modeled the correlations between nodes i and j , including higher-order ones, by

$$\xi_{ij} = c_0 + c_{ij} \theta_{ij} + \sum_k c_{ij}^k \theta_{ik} \theta_{kj} + \sum_{k, j} c_{ij}^{kl} \theta_{ik} \theta_{kl} \theta_{lj} + \dots \quad (2)$$

for $i \neq j$,

where θ_{ij} is the connection from j to i and c is a decay coefficient, following the same notation as that in the original paper. Assuming

that the influence deteriorates as it propagates to other neurons, the method models the propagation of influence on the basis of random walk. However, this method is inadequate for estimating inhibitory connections because the influence can take only positive values. Finally, regarding the problem of unobserved neurons, to the best of our knowledge, no existing method can explicitly deal with the influence of unobserved neurons. In this study, we develop a novel mathematical framework that can systematically address the problems of pseudo-correlations, directed connections, and the influence of unobserved neurons.

2. Problem setting

In this section, we introduce the notations used and corresponding assumptions.

Suppose that N neurons out of many are observed. Let $X_i(t) \in \{1, 0\}$ be a random variable representing the state of neuron $i \in \{1, 2, \dots, N\}$ at time t (i.e., 1 denotes firing and 0 denotes non-firing). These neurons' activities are recorded at time $t = 1, 2, \dots, T$ discretely, and the spike data are given by

$$\mathcal{D} = \{X_1(t), X_2(t), \dots, X_N(t)\}_{t=1}^T. \quad (3)$$

Neural connections are represented as a graph structure. Let V be a set of nodes $\{1, 2, \dots, N\}$ and E be a set of edges $\{(i, j), i, j \in V\}$. Neural connections are characterized by a graph (V, E) , where V corresponds to a set of neurons and E corresponds to a set of synaptic connections. The graph is also represented by a matrix $W \in \mathbb{R}^{N \times N}$. Let w_{ij} be element (i, j) of W . Here, w_{ij} represents the strength of a connection from neuron j to neuron i . Connections are classified into two types, namely excitatory and inhibitory connections. According to neuroscience, a neuron is known to have only one type of connection; thus, neurons are either excitatory or and inhibitory. Excitatory neurons promote firing of the neurons to which they connect. On the other hand, inhibitory neurons suppress firing of the connected neurons. Therefore, w_{ij} is classified as follows:

$$\begin{cases} w_{ij} > 0, & \text{excitatory connection from } j \text{ to } i, \\ w_{ij} = 0, & \text{no connection from } j \text{ to } i, \\ w_{ij} < 0, & \text{inhibitory connection from } j \text{ to } i. \end{cases} \quad (4)$$

We assume that observed neurons do not have self-connections and that the strength of connection w_{ij} remains unchanged during the observed period $[1, T]$.

3. Stochastic firing model

We assume that firing of neuron i at time t is determined by its internal state $U_i(t)$ that corresponds to the membrane potential:

$$\Pr(X_i(t) = 1) = \Phi(U_i(t)), \quad (5)$$

where Φ is the cumulative distribution function of probability density function ϕ ,

$$\Phi(x) = \int_{-\infty}^x \phi(z) dz. \quad (6)$$

In this study, for mathematical simplicity, we assume that the probability density function ϕ is a Gaussian distribution with mean 0 and variance σ^2 . The Gaussian distribution function is denoted by ϕ_{σ^2} and the cumulative distribution function is denoted by Φ_{σ^2} :

$$\Phi_{\sigma^2}(x) = \int_{-\infty}^x \phi_{\sigma^2}(z) dz, \quad (7)$$

$$\phi_{\sigma^2}(z) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(-\frac{z^2}{2\sigma^2}\right). \quad (8)$$

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