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An Information Transmission Measure for the Analysis of Effective Connectivity among Cortical Neurons

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Abstract

We present a methodology for detecting *effective* connections between simultaneously recorded neurons using an information transmission measure to identify the presence and direction of information flow from one neuron to another. Using simulated and experimentally-measured data, we evaluate the performance of our proposed method and compare it to the traditional transfer entropy approach. In simulations, our measure of information transmission outperforms transfer entropy in identifying the effective connectivity structure of a neuron ensemble. For experimentally recorded data, where ground truth is unavailable, the proposed method also yields a more plausible connectivity structure than transfer entropy.

I. Introduction

Microelectrode arrays allow neurophysiologists to investigate interactions among populations of simultaneously recorded cortical neurons and address questions about the role of these interactions in encoding sensory stimuli or behavioral output. Interactions between neurons are often classified as either *functional*, if the dependency is symmetric, or *effective*, if the dependency is causal [1]. Though there are a variety of methods for detecting and evaluating interactions between neurons [2], effective connectivity among neurons is typically identified by detecting the presence and direction of information flow [1].

The standard measure of information flow between two neurons x and y is transfer entropy [3–6], which measures the deviation from the Markov property that $p(x_F|x_P,y_P) = p(x_F|x_P)$, where the subscripts P and F represent past and future, respectively. More specifically, transfer entropy detects whether the transition probabilities of neuron x depend on the state of neuron y . If so, it is presumed that information is flowing from neuron y to neuron x .

Previous studies have found that transfer entropy more accurately detects effective connectivity than measures such as cross-correlation and mutual information [4,5].

In this paper we introduce an alternative information transmission measure for identifying effective connections between neurons, which builds upon the direct method for quantifying how much information a neuronal response carries about a stimulus [7–9]. Our proposed method operates by computing the so-called total and noise entropies of a neuron's response to the spikes in another neuron, rather than to a presented stimulus. This allows us to quantify the average information that neuron x 's spike train transmits about neuron y 's spikes.

Using simulated and experimentally-measured data, we evaluate the performance of our proposed method for inferring effective connectivity between neurons and compare its performance against the traditional transfer entropy approach. In simulations, our measure of information transmission outperforms transfer entropy in identifying the effective connectivity structure of a neuron ensemble. For experimentally recorded data, where ground truth is unavailable, the proposed method also yields a more plausible connectivity structure than transfer entropy.

II. Methods

A. Information Transmission

To measure the information transmission from neuron y to neuron x , we use the difference $IT = H_{total} - H_{noise}$ where H_{total} and H_{noise} respectively denote the total entropy of neuron x 's response to a spike in neuron y and the portion of this entropy that is attributable to noise [8]. The total and noise entropies are defined as

$$H_{total} = - \sum \langle p(x_\tau | y=1) \rangle_\tau \log_2 \langle p(x_\tau | y=1) \rangle_\tau \quad (1)$$

$$H_{noise} = - \left\langle \sum p(x_\tau | y=1) \log_2 p(x_\tau | y=1) \right\rangle_\tau \quad (2)$$

where τ denotes a positive time lag, $p(x_\tau | y=1)$ denotes the empirically estimated probability distribution of the presence/absence of a spike in neuron x , evaluated in 1ms bins, at lag τ following a spike in neuron y , and $\langle \dots \rangle_\tau$ denotes an average over all lags, ranging from one to ten milliseconds. By Jensen's inequality [10], IT is a nonnegative quantity.

The computation of IT mirrors the direct method for quantifying the stimulus-response properties of neurons [6,7], with the key differences that: a.) the response distributions of a neuron are estimated post-spike as opposed to concurrent with a presented stimulus, b.) the response distributions of a neuron define the random variable denoting the presence/absence of a spike at time lag τ rather than the random variable denoting the neuron's response patterns [7], and c.) the responses in neuron x are allowed to overlap when the inter-spike intervals of neuron y are less than $\tau_{max} = 10\text{ms}$.

B. Transfer Entropy

Transfer entropy from neuron y to neuron x is the Kullback-Leibler divergence between the probability distributions $p(x_F|x_P, y_P)$ and $p(x_F|x_P)$ [5], defined as:

$$TE_{Y \rightarrow X} = \sum p(x_F, x_P, y_P) \log_2 \frac{p(x_F|x_P, y_P)}{p(x_F|x_P)} \quad (3)$$

Consequently, if the Markov property holds that $p(x_F|x_P, y_P) = p(x_F|x_P)$, transfer entropy is zero. Using an approach similar to that described by Gourévitch and Eggermont [3], the past and future states of neuron x , x_P and x_F , were defined by counting the number of spikes in the intervals $[t-10\text{ms}, t]$ and $[t, t+10\text{ms}]$, respectively. The past states of neuron y were defined by the presence or absence of a spike the interval $[t-1\text{ms}, t]$. By evaluating transfer entropy in this manner, we measured the effect of neuron y 's binary state on the spike-count transition probabilities of neuron x .

C. Ensemble Simulation

To evaluate information transmission as a measure of effective connectivity between neurons, and to compare its performance to that of transfer entropy, we simulated a 10-neuron ensemble using a Poisson generative model [11]. The conditional intensity function, $\lambda_i(t|\mu_i, a_i, k)$, for each neuron was defined as:

$$\lambda_i(t|\mu_i, a_i, k) = [\mu_i + a_i(t)] \cdot \exp \left[\sum_{j=1}^N \sum_{\tau=1}^{10} k_{ji}(\tau) \beta_j(t-\tau) \right] \quad (4)$$

where μ_i is the mean firing rate of neuron i , $a_i(t)$ is the firing rate variation of neuron i , $k_{ji}(\tau)$ is the effective connection from neuron j to neuron i at time lag τ , and $\beta_j(t-\tau)$ is the binary state of neuron j at time t minus τ .

The mean firing rate, μ_i , of each neuron in the ensemble was 20 spikes per second (sps). The firing rate variations, $a_i(t)$, were defined as random walks over a range of ± 15 sps, starting at 0 sps at time zero (Figure 1C). The connectivity kernels, k_{ji} , were defined as random walks over lags ranging from 1–10 ms, starting at 0 at 1ms lag and constrained to a range of ± 1 (Figure 1D). Refractory effects, k_{ii} , were modeled as exponential decays from -5 at 1ms lag to 0 at 10ms lag (Figure 1E). For each neuron, the number of spikes occurring at each millisecond time step was determined by drawing from a Poisson distribution with rate, $\lambda_i(t|\mu_i, a_i, k)$.

To determine if our information transmission measure could distinguish between functional and effective connectivity, we modeled functional interactions between selected neurons by setting their firing rate variation parameters $a_i(t)$ equal, producing firing rate co-variation [12]. In our simulation, firing rate co-variation occurred between neurons 4 and 9 and between neurons 3, 6, and 7. The network structure of the simulated ensemble is shown schematically in Figure 1A. Arrows indicate the presence and direction of effective connections. The corresponding connectivity structure matrix is shown in Figure 1B. Effective connections between neurons, where k_{ji} is nonzero, are indicated with circles.

Refractory effects are shown in gray. Functional interactions, modeled as firing rate co-variations where $\alpha_i(t) = \alpha_j(t)$, are indicated with exes. Twenty minutes of simulated data were used for analysis.

D. Data Collection

Experimental data was collected from a single Rhesus macaque monkey implanted with a 16-channel floating microelectrode array (Microprobes for Life Science, Inc., Gaithersburg, MD) in the upper extremity region of left hemispheric primary motor cortex (M1). The monkey performed a center-out, reach-to-manipulate task with its right upper extremity. Each trial in this task consisted of the monkey initially grasping and holding a centrally-located pull-object for a duration of 500 ms. The monkey would then be cued to reach for and manipulate one of three peripherally-located objects (rotational knob, pull handle, push button) within an allowed response time of 500 ms. Trials were separated by 1000 ms intertrial intervals.

Neural data was recorded using a Plexon acquisition system and sorted offline using OfflineSorter software (Plexon Inc, Dallas, TX). The data analyzed in this paper is from a single experimental session in which 12 well-isolated neurons were simultaneously recorded for the full duration of an experimental session lasting 30 minutes.

III. Results

The significance of information transmission, IT , and transfer entropy, TE , between any pair of neurons, x and y , was evaluated by comparing values obtained for IT and TE with values obtained using shuffled data. Shuffled data were generated by randomly shuffling the interspike intervals of neuron x , eliminating any effective or functional connectivity between neuron y and neuron x . This procedure was repeated 1000 times, providing bootstrapped estimates of the distributions of IT and TE values based on chance alone. Values obtained for unshuffled data that fell outside the range of these distributions thus could be considered significant at the $p < 0.001$ level.

A. Simulated Data

Figures 2A and 2B show the effective connectivity structure (shown in black) identified by IT and TE , respectively, for the simulated ensemble defined in Figure 1. Information transmission correctly identified all eight simulated effective connections (indicated with circles) and erroneously identified an effective connection from neuron 3 to neuron 1. Transfer entropy correctly identified seven out of eight simulated effective connections, but incorrectly identified all eight functional interactions (indicated with exes) as effective connections.

To demonstrate why the information transmission and transfer entropy measures give different results, in Figures 2C–E we show the across-lag spiking probabilities for neurons 8, 6, and 4, following spikes in neurons 10, 1 and 9, respectively. Information transmission detects an effective connection if the spikes of neuron y evoke a modulation in the across-lag spiking probabilities of neuron x (solid black lines) that is significantly different from chance (black dashed lines mark the 99th percentile of spiking probabilities for shuffled

data). Conversely, transfer entropy detects an effective connection if the dependence of neuron x 's future state (proportional to the across-lag average spike probabilities indicated by solid red lines) on the recent past of neuron y is significantly different from chance (red dashed lines mark the 99th percentile of across-lag spike probability averages for shuffled data).

Figure 2C shows that the spikes of neuron 8 evoke a significant modulation in the across-lag spiking probabilities of neuron 10; that is, the average response of neuron 10 to spikes in neuron 8 is significantly different than what might be observed by chance alone.

Consequently, information transmission correctly detects an effective connection from neuron 8 to neuron 10. In addition, the future state of neuron 10, given a spike in neuron 8, is significantly lower than chance; that is, the across-lag average spiking probability for neuron 10 lies below the range of these averages for shuffled data. This indicates that the spike-count transitions of neuron 10 depend on the state of neuron 8 – for example, $p(x_F=0|x_P=1, y_P=1) > p(x_F=0|x_P=1)$, and transfer entropy also identifies an effective connection from neuron 8 to neuron 10.

Figure 2D shows that the spiking probabilities of neuron 1 are significantly modulated by spikes in neuron 6, and, as expected, information transmission detects effective connectivity between these neurons. However, the future state for neuron 1, given a spike in neuron 6, is not significantly different from chance, and transfer entropy therefore does not identify the effective connection that exists between these neurons.

Most interestingly perhaps, Figure 2E shows that the spiking probabilities of neuron 9 are elevated but not modulated by spikes in neuron 4. Information transmission therefore does not detect an effective connection between these neurons. One might expect that transfer entropy would likewise not detect an effective connection here, given that the future state of neuron 9 is conditioned on its own past, and, due to firing rate co-variation, the spiking probabilities of neuron 9 are elevated both before and after a spike in neuron 4. However, due to firing co-variation, a spike in neuron 4 likely coincides with neuron 9 transitioning between high states (e.g., $p(x_F=2|x_P=3, y_P=1) > p(x_F=2|x_P=3)$) and, conversely, the absence of a spike in neuron 4 likely coincides with neuron 9 transitioning between low states (e.g., $p(x_F=0|x_P=0, y_P=0) > p(x_F=0|x_P=0)$). Consequently, transfer entropy incorrectly identifies firing rate co-variation between neurons 4 and 9 as an effective connection.

To confirm that the results shown in Figures 2A–B are not just specific to a particular set of simulated connectivity kernels and firing rate co-variation parameters, we repeated the simulation 100 times. Though each simulation used the same connectivity structure shown schematically in Figure 1A, new connectivity kernels, k_{ji} , and firing rate variation parameters, $\alpha_i(t)$, were generated for each simulation. Figures 2F and 2G show the incidence of classifying any pairwise interaction as effective, using information transmission and transfer entropy, respectively, over the 100 ensemble simulations. Information transmission correctly identified $91.0 \pm 3.8\%$ of simulated effective connections and misidentified 0% of simulated functional connections as effective. Transfer entropy correctly identified $76.4 \pm 6.1\%$ of simulated effective connections and misidentified $65.8 \pm 4.5\%$ of simulated functional connections as effective.

B. Motor Cortex Data

Figures 3A and 3B show the effective connectivity structure identified by information transmission and transfer entropy, respectively, for the population of neurons recorded from M1 in an awake, behaving monkey. Information transmission identifies 13 effective connections, whereas transfer entropy identifies 93 effective connections, out of 132 possible connections. Figures 3C–E show the across-lag spiking probabilities for neurons 8, 8, and 3, following spikes in neurons 5, 6 and 8, respectively. Information transmission identified effective connections for the first and second pairs (Figures 3C–D). Transfer entropy, however, identified effective connections between the first and third pairs (Figures 3C and 2E). This difference in result is likely attributable to the fact that transfer entropy detects firing rate co-variation as effective connectivity (see Figure 2F) whereas information transmission does not. Furthermore, the incidence of firing rate co-variation between neurons recorded in a 2mm x 2mm x 4mm region of motor cortex (dimensions of microelectrode array) is likely very high, given that these neurons are likely to represent similar motor outputs [13]. This may explain why transfer entropy identified so many effective connections among the recorded neurons (Figure 3B).

IV. Conclusion

This study presents a novel approach for identifying effective connections between cortical neurons. Using simulated neuronal ensembles, we show that this method, which measures information transmission between neurons, is more sensitive to and selective for effective connectivity than the standard method for identifying information flow between neurons, transfer entropy. We also use our method to identify effective connections between motor cortical neurons recorded on a microelectrode array implanted in an awake, behaving monkey and show that our measure of information transmission yields a more plausible effective connectivity structure than what is obtained using transfer entropy. Future work aims to extend this method to measure information transmission using the frequency distributions of a neuron's response patterns (i.e., binary words) given a spike in another neuron. We believe that the information transmission measure introduced here provides more accurate identification of the effective connectivity structure among simultaneously recorded neurons, which may provide insight into how ensembles of neurons collectively encode behavior.

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Figure 1.

Neuronal ensemble simulation. (A) Ensemble network structure. (B) Connectivity matrix.

(C) Example firing rate variation, $\alpha_i(t)$. (D) Example connectivity kernel, k_{ji} . (E) Example

refractory kernel, k_{ii} .

Figure 2.

Ensemble simulation results. (A) Effective connections (marked in black) identified by information transmission. (B) Effective connections identified by transfer entropy. (C–E) Across-lag spiking probabilities for neurons 10, 1, and 9, following spikes in neurons 8, 1, and 4, respectively. (F–G) Incidence of detecting a neuronal interaction as effective over 100 simulations using information transmission and transfer entropy, respectively.

Figure 3.

Motor cortex ensemble results. (A) Effective connections (marked in black) identified by information transmission. (B) Effective connections identified by transfer entropy. (C–E) Across-lag spiking probabilities for neurons 8, 8, and 3, given a spike in neurons 5, 6, and 8, respectively.