

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 effective connectivity structure than transfer entropy.

I. INTRODUCTION

By using microelectrode technology to record the spikes of many neurons simultaneously, neuroscientists are able to investigate how cortical neurons interact with one another to encode sensory stimuli or behavioral output. These interactions can be analyzed to determine the structure of *functional* or *effective* connections among the recorded population of neurons. Functional connections are identified using symmetric measures of statistical dependence, whereas effective connections are identified using asymmetric measures of causality [1]. Although there are a number of ways to evaluate causality [2], effective connections between neurons are 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]–[5], which detects whether the state transition probabilities of neuron X depend on the recent past state of neuron Y . If so, it is presumed that information flows from neuron Y to neuron X . Previous studies have found that transfer entropy more accurately detects effective connectivity than measures such as cross-correlation or mutual information [3], [4].

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 [6], [7]. Our proposed method operates by computing the total and noise entropies of neuron X 's response to a spike in neuron Y . This allows us to determine whether neuron X 's spike train conveys information about a recent spike in neuron Y , indicative of an effective connection from neuron Y to neuron X .

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 transmitted 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 spike train immediately following a spike in neuron Y and the portion of this entropy that is attributable to noise [7]. 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 binary state of 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 [8], IT is a non-negative quantity.

The computation of IT mirrors the direct method for quantifying the stimulus-response properties of neurons [6], [7], with key differences that: a) the response distributions of neuron X are estimated following neuron Y spikes as opposed to concurrent with a presented stimulus, b) the response distributions of neuron X define the random variable denoting the presence/absence of a spike at time lag τ rather

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than binary words representing response patterns, and c) the responses of neuron X are allowed to overlap when the interspike 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 , are 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 are defined by the presence or absence of a spike in the interval $[t-1\text{ms}, t]$. By evaluating transfer entropy in this manner, we measure the effect of the recent binary state of neuron Y on the spike-count state 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 [9]. The conditional intensity function, $\lambda_i(t|\mu_i, \alpha_i, k)$, for each neuron was defined as:

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

where μ_i is the mean firing rate of neuron i , $\alpha_i(t)$ 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, $\alpha_i(t)$, were defined as random walks over a range of ± 15 sps, starting at 0 sps at time zero (Fig. 1c). The connectivity kernels, k_{ji} , were defined as random walks over lags ranging from 1-10 ms, starting with a weight of 0 at 1 ms lag and constrained to a range of ± 1 (Fig. 1d). Refractory effects, k_{ii} , were modeled as exponential decays from a weight of -5 at 1ms lag to 0 at 10ms lag (Fig. 1e). For each neuron, the number of spikes occurring at each millisecond time step was determined by drawing from a Poisson distribution with rate, $\lambda_i(t|\mu_i, \alpha_i, k)$.

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 $\alpha_i(t)$ equal, producing firing rate co-variation [10]. The network structure of the simulated ensemble is shown schematically in Fig. 1a. Arrows indicate the presence

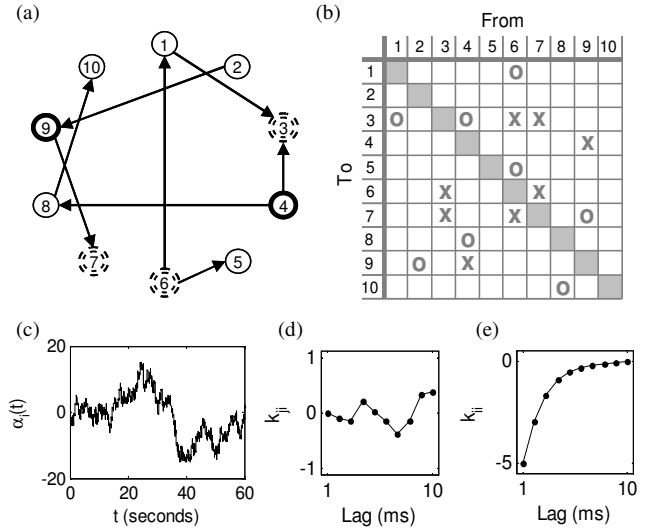


Fig. 1. A 10-neuron ensemble was simulated using a Poisson generative model. The structure of simulated network connections is shown in (a). Arrows indicate the presence/direction of effective connections. Firing rate co-variation was simulated between neurons 4 and 9 and between neurons 3, 6, and 7. b) The neuron connectivity matrix corresponding to (a). Circles mark effective connections and exes mark functional connections. c) Example firing rate variation, $\alpha_i(t)$. d) Example effective connection, k_{ji} . e) Refractory effect, k_{ii} .

and direction of effective connections. Firing rate co-variation occurred between neurons 4 and 9 and between neurons 3, 6, and 7. The corresponding connectivity structure matrix is shown in Fig. 1b. Effective connections between neurons, where k_{ji} is nonzero, are indicated with circles. Refractory effects are shown in gray. Functional connections, 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 was then 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 recorded throughout a 30 minute experimental session.

III. RESULTS

The significance of information transmission, IT , and transfer entropy, TE , between any pair of neurons X and Y was evaluated by comparing the measured IT and TE values with IT and TE values obtained using shuffled data. Shuffled data were generated by randomly shuffling the inter-spike intervals of neuron X , eliminating any effective or functional connection 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

Figs 2A and 2B show the effective connections (shown in black) identified by IT and TE , respectively, for the simulated ensemble defined in Fig. 1. Information transmission correctly identified all eight simulated effective connections (indicated with circles) and erroneously identified an effective connection from neuron 9 to neuron 2. Transfer entropy correctly identified seven out of eight simulated effective connections, but incorrectly identified six functional interactions (indicated with exes) as effective connections.

To demonstrate why the information transmission and transfer entropy measures give different results, in Fig. 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 dotted 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 (indicated by solid red lines which show the across-lag average spike probabilities) on the recent past of neuron Y is significantly different from chance (red dotted lines mark the 99th percentile of across-lag spike probability averages for shuffled data).

Fig. 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 (red solid line) lies below the range for shuffled data (demarcated by red dashed lines). 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.

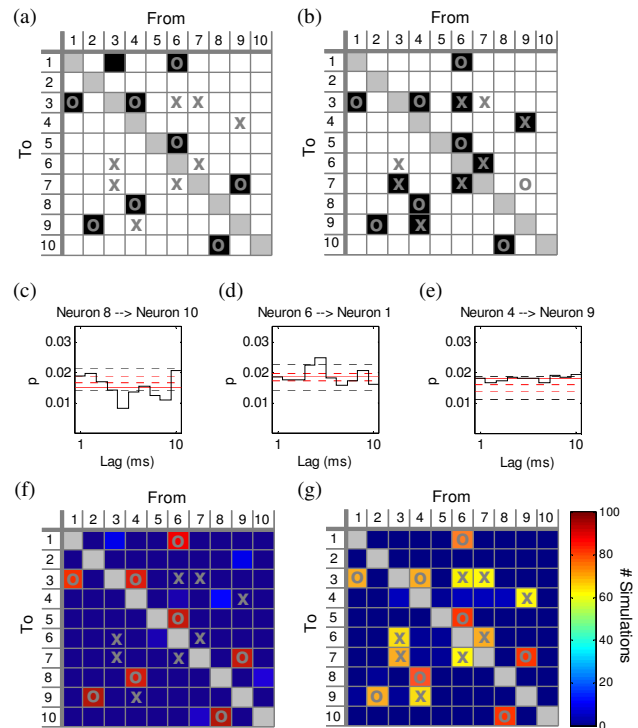


Fig. 2. Simulated ensemble results. a) Effective connections (marked in black) identified by information transmission. b) Effective connections identified by transfer entropy. c-e) Across-lag spiking probabilities for neurons 10, 1, and 9, following spikes in neurons 8, 1, and 4, respectively. f-g) Incidence of detecting a neuronal interaction as effective over 100 simulations using information transmission and transfer entropy, respectively.

Fig. 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, Fig. 2e shows that the average spiking probabilities of neuron 9 are elevated (due to firing rate co-variation) but not modulated following a spike in neuron 4. Information transmission therefore does not detect an effective connection between these neurons. It might be expected that transfer entropy would likewise not detect an effective connection here, given that the spiking probabilities of neuron 9 are elevated both before and after a spike in neuron 4, and transfer entropy operates in part by conditioning the future state of neuron 9 on its own past. However, due to firing rate co-variation, the presence of a neuron 4 spike 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 neuron 4 spike 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.

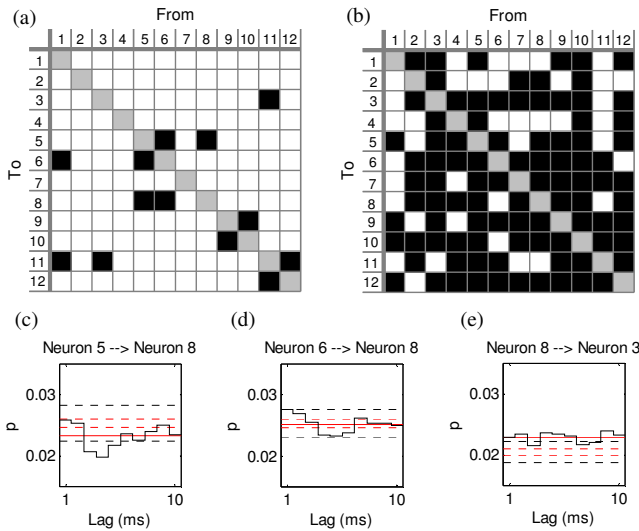


Fig. 1. Motor cortex ensemble results. a) Effective connections (marked in black) identified by information transmission. b) Effective connections identified by transfer entropy. c-e) Across-lag spiking probabilities for neurons 8, 8, and 3, given a spike in neurons 5, 6, and 8, respectively.

To confirm that the results shown in Fig. 2a-b are not just specific to a particular set of simulated connectivity kernels and firing rate co-variations, we repeated the simulation 100 times. Though each simulation used the connectivity structure shown schematically in Fig. 1a, new connectivity kernels, k_{ji} , and firing rate variation parameters, $\alpha_i(t)$, were generated for each simulation. Fig. 2f-g 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. Transfer entropy correctly identified $76.4 \pm 6.1\%$ of simulated effective connections and misidentified $65.8 \pm 4.5\%$ of simulated functional connections.

B. Motor Cortex Data

Fig. 3a-b 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. Fig. 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 between the first and second neuron pairs (Fig. 3c-d), whereas identified effective connections between the first and third pairs (Fig. 3c and Fig. 3e). Overall, information transmission identified 13 effective connections between 132 neuron pairs, whereas transfer entropy identified 93 effective connections. This difference in result could be attributable to the fact that transfer entropy detects firing rate co-variation as effective connectivity (see Fig. 2g) 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 (the volume sampled by the

microelectrode array) is likely very high, given that these neurons likely represent similar motor outputs [11].

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 information theoretic method for identifying causal interactions 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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