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An Active Method for Tracking Connectivity in Temporally Changing Brain Networks

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***Abstract*— The inference of connectivity in brain networks has typically been performed using passive measurements of ongoing activity across recording sites. Passive measures of connectivity are harder to interpret, however, in terms of causality – how evoked activity in one region might induce activity in another. To obviate this issue, recent work has proposed the use of active stimulation in conjunction with network estimation. By actively stimulating the network, more accurate information can be gleaned regarding evoked connectivity. The assumption in these previous works, however, was that the underlying networks were static and do not change in time. Such an assumption may be limiting in situations of clinical relevance, where the introduction of a drug or of brain pathology, might change the underlying networks structure. Here, an extension of the evoked connectivity paradigm is introduced that enables tracking networks that change in time.**

I. INTRODUCTION

An emerging technique in neural medicine is the use of brain stimulation [1], [2], [3], [4], [5]. Currently, these techniques are used in an empirically-driven manner, whereby different stimulation sites and parameters are tested until a desired behavioral effect is achieved. An important step in improving the use of these techniques will be incorporating better knowledge of the underlying brain network *connectivity* and, specifically, how stimulating at one site may affect neuronal activity in another, neighboring, location.

The prevailing methods for assessing neuronal connectivity are passive, that is, they do not involve perturbing the brain. The result of these methods is a *functional connectivity* network consisting of nodes (e.g., brain regions or electrodes) and edges representing the strongest statistical associations between nodes (see [6], [7] and the references contained therein). Since these functional connectivity networks are passive they do not necessarily clarify how stimulation at a network region might affect surrounding regions, nor do they disambiguate whether brain regions are truly coupled or driven by a common source.

Brain stimulation provides a means to *actively* probe the network, thus enabling disambiguation of causality from simple correlation. Consider, for example, the situation illustrated in Figure 1. Here, several nodes in a brain network (as measured by, for instance, spatially disparate electrodes) produce ongoing oscillations. By measuring passively and using a metric such a correlation, one would infer a highly connected network. Conversely, by stimulating, one could identify which nodes actually evoked activity in other nodes. To this end, recent work has introduced a method for actively perturbing a brain network using stimulation in an effort to elucidate evoked connectivity [8]. The evoked network returned in that case was assumed to be static, i.e., the evoked network did not change in time.

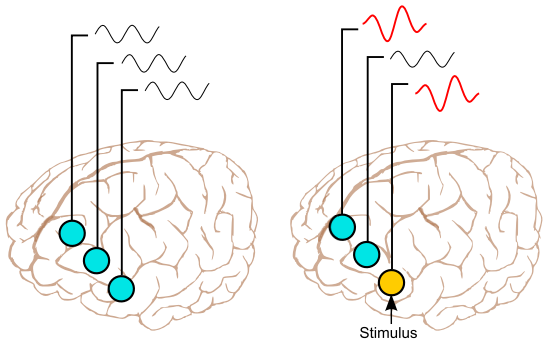

Fig. 1. Passive vs. Active network inference. (Left) Passive measurement cannot disambiguate the origin of certain endogenous brain activity, for example, ongoing oscillations. (Right) By using active stimulation, it is possible to eluciated which regions evoke activity in others – so-called evoked connectivity.

In this note we introduce a generalization to the method of [8] that allows tracking of temporally changing evoked brain networks. Such capability may be useful in clinical situations in which the underlying neuronal network changes in character due to the introduction of a drug, or through some other endogenous physiological change. The paper is organized as follows: In Section II we provide background on evoked connectivity in brain networks and present mathematical preliminaries; In Section III we introduce the generalization for temporal tracking and show its efficacy in several simulation studies; finally, in Section IV, we discuss potential applications and formulate conclusions.

II. BACKGROUND

The evoked network inference method of [8] uses a Bayesian inferential framework to update a prior probability mass function over all possible networks after each successive stimulation of a network node. The stimulus may be, for example, an electrical current applied to the brain through a stimulating electrode. The stimulus affects the neuronal activity in the vicinity of the electrode, i.e, the node, and the activity of any brain regions to which that node is connected.

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These changes in activity can be detected through electrode recordings from connected regions.

In this setting, time-series from n nodes are obtained in a recording epoch, leading to a network containing

$$\mathrm{N_{edge}} = (\mathrm{n}^2 - \mathrm{n})/2$$

undirected pairwise connections. The method for performing inference over these connections is described in [8]. The operational details are summarized below.

A. Stimulus and Detector Design

The method begins by defining a stimulus, $\mathbf{s}$, which is a vector over all $\mathrm{N_{edge}}$ edges where

$$(\mathbf{s})_\mathrm{j} = \begin{cases} 1 & \text{if the edge involves a stimulated node} \\ 0 & \text{otherwise} \end{cases}$$

The detector, intended to identifiy stimulated edges, is assumed to possess some probability of false alarm, $\mathrm{p_{fa|s}}$ missed detection, $\mathrm{p_{md|s}}$. Note that the detector will either detect correspondence between two nodes that are stimulated or will not; hence the detector response is also binary.

This formulation is, clearly, very general. The stimulus vector $\mathbf{s}$ encodes which edges are stimulated, but does not describe how that stimulation (or detection) is performed. For the purposes of this paper, the method is operationalized by assuming that (i) the stimulus is an electrical current impulse, applied to the brain through an electrode; and (ii) the detector is a spectral binary discriminator that compares the power within a specific frequency band to a predfiend threshold [8]. In general, however, quite abstract notions of evoked networks are possible, depending on the definition of node, stimulus and detector.

B. Active Network Inference

Prior to formulating the inferential procedure, consider the following definitions:

Definition 1 (Network)**.** *A network consists of two vectors,* $\mathbf{v}$*,* $\mathbf{e}$*, of dimension* $\mathrm{N_{edge}}$*. The vector,* $\mathbf{v}$ *specifies all possible pair-wise connections, where the* j^{th} *element,* v_j *specifies a possible connection between two nodes. The vector,* $\mathbf{e}$*, contains elements* $(\mathrm{e})_\mathrm{j}$ *where*

$$(\mathbf{e})_\mathrm{j} = \begin{cases} 1 & \text{if a connection is inferred in } v_j \\ 0 & \text{otherwise} \end{cases}$$

Definition 2 (Detector)**.** *The detector consists of a vector* $\mathbf{d}$ *of dimension* $\mathrm{N_{edge}}$ *consisting of elements* $(\mathrm{d})_\mathrm{j}$*, where*

$$(\mathbf{d})_\mathrm{j} = \begin{cases} 1 & \text{if an evoked response is detected in } v_j \\ 0 & \text{otherwise} \end{cases}$$

Active network inference is performed by applying the Chapman-Kolmogorov equation [9] to the problem of updating the posterior probability distribution of the edges,

$$\mathrm{P}(\mathbf{e}^{(\mathrm{k})} | \mathbf{d}^{(\mathrm{k})}, \mathbf{s}^{(\mathrm{k})}, \mathrm{H_k}),$$

at stimulus-index k, where

$$\mathrm{H_k} = \left\{ \mathbf{d}^{(\mathrm{a})} \mid \mathrm{a} < \mathrm{k} \right\},$$

is the set of observations resulting from the past stimulations. Note that the notation $^{(\mathrm{k})}$ is used to indicate the realization of a particular vector or element at stimulation index k. It follows that the edge posterior at stimulus index k can be related to the posterior at stimulus index $\mathrm{k}-1$:

$$\begin{aligned} \mathrm{P}\left((\mathbf{e}^{(\mathrm{k})})_\mathrm{j} | (\mathbf{d}^{(\mathrm{k})})_\mathrm{j}, (\mathbf{s}^{(\mathrm{k})})_\mathrm{j}, \mathrm{H_k}\right) \propto \\ \mathrm{P}\left((\mathbf{d}^{(\mathrm{k})})_\mathrm{j} | (\mathbf{e}^{(\mathrm{k})})_\mathrm{j}, (\mathbf{s}^{(\mathrm{k})})_\mathrm{j}\right) \times \\ \sum_{c_j=0}^{1} \mathrm{P}\left((\mathbf{e}^{(\mathrm{k})})_\mathrm{j} | (\mathbf{e}^{(\mathrm{k}-1)})_\mathrm{j} = \mathrm{c_j}\right) \times \\ \mathrm{P}\left((\mathbf{e}^{(\mathrm{k}-1)})_\mathrm{j} = \mathrm{c_j} | (\mathbf{d}^{(\mathrm{k}-1)})_\mathrm{j}, (\mathbf{s}^{(\mathrm{k}-1)})_\mathrm{j}, \mathrm{H_{k-1}}\right), \end{aligned} \tag{1}$$

for $\mathrm{j} = 1, \ldots, \mathrm{N_{edge}}$, noting that the binary variable $\mathrm{c_j}$ encodes whether a connection exists. In Eqn. (1), the posterior at the previous stimulus index, $\mathrm{k}-1$, is updated via multiplication of a user-specified one-step edge update probability mass function, $\mathrm{P}\left((\mathbf{e}^{(\mathrm{k})})_\mathrm{j} | (\mathbf{e}^{(\mathrm{k}-1)})_\mathrm{j}\right)$, prior to marginalization and multiplication by the likelihood, $\mathrm{P}\left((\mathbf{d}^{(\mathrm{k})})_\mathrm{j} | (\mathbf{e}^{(\mathrm{k})})_\mathrm{j}, (\mathbf{s}^{(\mathrm{k})})_\mathrm{j}\right)$ to yield the posterior probability mass function of the edges at the current stimulus index, k.

It is assumed that the initial probability mass function, $\mathrm{P}\left(\mathbf{e}^{(0)}\right)$, is set to .5 for all edges. The likelihood is expressed in terms of the probability of missed detection, $\mathrm{p_{md|s}}$, given stimulus s, and the probability of false alarm, $\mathrm{p_{fa|s}}$, given stimulus s,

$$\mathrm{p_{md|s}} = \mathrm{P}\Big((\mathbf{d}^{(\mathrm{k})})_\mathrm{j} = 0 \mid (\mathbf{e}^{(\mathrm{k})})_\mathrm{j} = 1, (\mathbf{s}^{(\mathrm{k})})_\mathrm{j} = \mathrm{s}\Big), \tag{2}$$

and

$$\mathrm{p_{fa|s}} = \mathrm{P}\Big((\mathbf{d}^{(\mathrm{k})})_\mathrm{j} = 1 \mid (\mathbf{e}^{(\mathrm{k})})_\mathrm{j} = 0, (\mathbf{s}^{(\mathrm{k})})_\mathrm{j} = \mathrm{s}\Big), \tag{3}$$

where $\mathrm{p_{md|s}}$, and $\mathrm{p_{fa|s}}$, are assumed to be the same for all j. The likelihood can thus be written as:

$$\mathrm{P}\big((\mathbf{d}^{(\mathrm{k})})_\mathrm{j} = \mathrm{d} \mid (\mathbf{e}^{(\mathrm{k})})_\mathrm{j}, (\mathbf{s}^{(\mathrm{k})})_\mathrm{j} = \mathrm{s}\big) = \begin{cases} \mathrm{d}\,(1 - \mathrm{p_{md|s}}) + (1-\mathrm{d})\,\mathrm{p_{md|s}} & , \quad (\mathbf{e}^{(\mathrm{k})})_\mathrm{j} = 1 \\ \mathrm{d}\,\mathrm{p_{fa|s}} + (1-\mathrm{d})\,(1 - \mathrm{p_{fa|s}}) & , \quad (\mathbf{e}^{(\mathrm{k})})_\mathrm{j} = 0 \end{cases}$$

C. Stimulation Policy

The selection of which node to stimulate is determined on the basis of 'node variance,' defined as the sum of the variances associated with each of the connection probabilities. That is, if the ℓ^{th} edge connecting node i to the other nodes exists with an estimated probability of $\hat{p}_{i,\ell}$, the node variance, $\mathrm{v_i}$, is computed according to,

$$\mathrm{v_i} = \sum_{\ell=1}^{\mathrm{N_{nodes}}-1} \hat{\mathrm{p}}_{\mathrm{i},\ell}\,(1 - \hat{\mathrm{p}}_{\mathrm{i},\ell}), \tag{4}$$

where

$$\hat{\mathrm{p}}_{\mathrm{i},\ell} = \mathrm{P}\left((\mathbf{e}^{(\mathrm{k})})_\mathrm{j} | (\mathbf{d}^{(\mathrm{k})})_\mathrm{j}, (\mathbf{s}^{(\mathrm{k})})_\mathrm{j}, \mathrm{H_k}\right). \tag{5}$$

Here, j indexes the connection between node i and node ℓ. Thus, the node variance summarizes the uncertainty of the edges that would be involved in a stimulation if the stimulation were applied to node i. The node to stimulate, i^*, is then

$$\mathrm{i}^* = \max_{\mathrm{i}} \mathrm{v_i}. \tag{6}$$

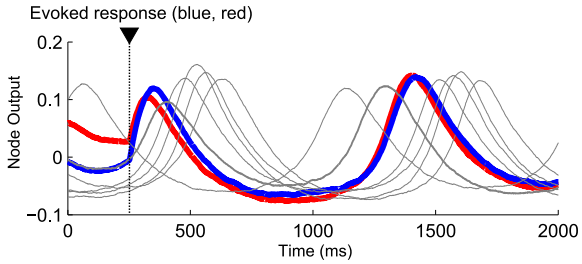

Fig. 2. Example of evoked response in 9 node Wilson-Cowan network. Traces of ongoing oscillations in 8 nodes are shown. A stimulus is delivered to the ninth node at $t = 0$. This subsequently evoked a response in two nodes (the red and blue traces), indicated by the sharp upward deflection. This response can be detected through a power spectral method, as described in [8].

III. TRACKING TEMPORALLY CHANGING NETWORKS

The one-step edge update probability mass function,

$$\mathrm{P}\left((\mathbf{e}^{(\mathrm{k})})_{\mathrm{j}}|(\mathbf{e}^{(\mathrm{k}-1)})_{\mathrm{j}}\right),$$

in (1) controls how smooth the network estimates are as a function of time (and, thus, of stimulation index). Through an appropriate choice of function, it is possible to infer not simply static evoked networks, but also networks that change in time.

Consider the one-step edge update

$$\mathrm{P}\left((\mathbf{e}^{(\mathrm{k})})_{\mathrm{j}} = \mathrm{a}|(\mathbf{e}^{(\mathrm{k}-1)})_{\mathrm{j}} = \mathrm{b}\right) = \begin{cases} a\epsilon + (1-a)(1-\epsilon) & , \quad \mathrm{b} = 0 \\ a(1-\epsilon) + (1-a)\epsilon & , \quad \mathrm{b} = 1 \end{cases}. \quad (7)$$

The user-specified parameter, ϵ, controls the extent to which previous estimates of an edge are thought to be accurate during the current stimulus index, k. In other words, ϵ determines the extent to which the network estimates remain stable with respect to incoming detections. In [8], ϵ was set to a value near zero under the assumption that the networks being inferred did not change temporally. Here, we assume the converse – that the underlying evoked networks could, in fact, exhibit significant and sudden changes.

To demonstrate temporal tracking we perform a simulation study in two settings: probabilistic networks and biophysical neuronal networks.

A. Tracking in Biophysical Neuronal Networks

The first simulation study is performed using a network of Wilson-Cowan mean field neuronal oscillators [10], [11]. In this model, the j^{th} node is described by the nonlinear differential equations:

$$\begin{aligned} \dot{\mathrm{x}_{\mathrm{j}}} &= -x_j + \\ &\left(\mathrm{k_e} - \mathrm{r_e x_j}\right) \mathcal{F}\left(\mathrm{c_1 x_j} - \mathrm{c_2 i_j} + \mathrm{C_e}(\bar{\mathrm{x}}) + \mathrm{P_j(t)}\right) \\ &+ \mathrm{b_j^e u_j(t)} + \mathrm{w(t)} \end{aligned} \quad (8)$$

$$\begin{aligned} \dot{\mathrm{i}_{\mathrm{j}}} &= -\mathrm{i_j} + \\ &\left(\mathrm{k_i} - \mathrm{r_i x_j}\right) \mathcal{F}\left(\mathrm{c_3 x_j} - \mathrm{c_4 i_j} + \mathrm{C_i}(\bar{\mathrm{x}}) + \mathrm{Q_j(t)}\right) \\ &+ \mathrm{b_j^i u_j(t)}, \end{aligned} \quad (9)$$

where $(\mathrm{x_j}, \mathrm{i_j})$ denote, respectively, the activity in excitatory and inhibitory cell populations in a cortical macrocolumn. The connectivity between macrocolumns arises through the functions $\mathrm{C_e}(\cdot)$ and $\mathrm{C_i}(\cdot)$, where

$$\mathbf{x}^{\mathrm{T}} = [\mathrm{x_1}\ \mathrm{x_2}\ \ldots\ \mathrm{x_N}]^{\mathrm{T}}. \quad (10)$$

The specific coupling function considered is

$$\mathrm{C_{x,i}}(\mathbf{x}) = \mathrm{k_s} \sum_{\mathrm{k} \in \mathcal{N}} \mathrm{c_k x_k}, \quad (11)$$

where $\mathcal{N}$ denotes the set of all nodes, $\mathrm{k_s}$ is a coupling coefficient and $\mathrm{c_k} = 1$ in the presence of a connection. The term $\mathrm{u_j(t)}$ is the exogenous input, used to locally stimulate a given node in the network. Note that each parameter in (9) corresponds to a neurophysiologic quantity, the details of which can be found in [8].

Here, a nine node network is considered with parameterization

$$\begin{aligned} &\mathrm{c_1} = 16, c_2 = 12, c_3 = 15, c_4 = 3, a_e = 1.3, a_i = 2 \\ &\theta_{\mathrm{e}} = 4, k_d = 2, \theta_i = 3.7, r_e = r_i = 1, \\ &\mathrm{k_e} = k_i = 1, b_j^e = b_j^i = 1, P_j(t) = 1.25, Q_j(t) = 0 \end{aligned} \quad (12)$$

and $w(t)$ taken as a Gaussian random process of variance 0.1. As shown in Figure 2, with this parameterization, each node produces ongoing oscillations. As in [8], we assume that stimulations and detections take place every 2000ms, and that the detector operates by identifying signals that exhibit unexpectedly large power in high frequencies. The underlying assumption is that such high frequency activity is evoked only when a connection is present between the stimulated and detected nodes. A schematic of the simulation setup is shown in Figure 2.

Figure 3 illustrates the performance in a Monte Carlo simulation when $\epsilon = 0.0005$, the same value chosen in [8]. Here, the true network connectivity is generated randomly by assigning each edge ($\mathrm{c_k}$ in (11)) a value of 0 or 1 with equal probability. After 50 stimulation epochs ($50 \times 2000ms$), the network is randomly changed, i.e., edges are reset to 0 or 1 with equal probability. The correctness of the inferred networks is measured in terms of the Jaccard error, defined as

$$\text{Jaccard Error} = 1 - \frac{|\mathrm{E_{True}} \cap \mathrm{E_{Inferred}}|}{|\mathrm{E_{True}} \cup \mathrm{E_{Inferred}}|}, \quad (13)$$

where $\mathrm{E_{True}}$ and $\mathrm{E_{Inferred}}$ are the collection of true and inferred edges, respectively. The error takes the value 0 when the inferred network is correct and matches exactly the true network. As shown in Figure 3, in the simulation, the inferred connectivity converges to a value of 0.1, i.e., nearly correct, within 50 stimulations. At $t = 50$ stimulations, the underlying network changes, resulting in a large increase in Jaccard error. The active method recovers as designed and reconverges to a correct estimate of the new network within 50 simulations.

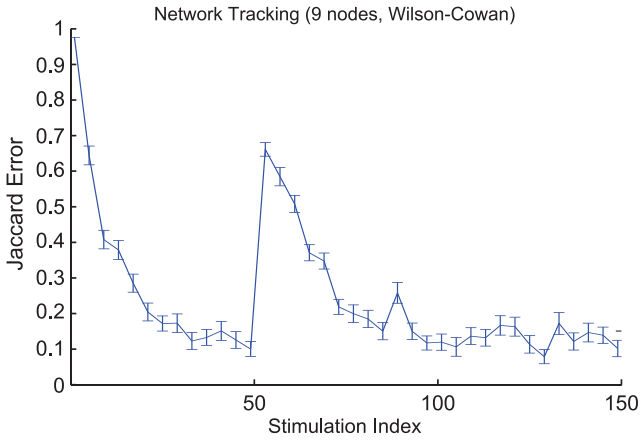

Fig. 3. Jaccard error in simulation of 9-node Wilson-Cowan neuronal oscillator network. The network estimate quickly converges to a small value, indicating correct estimation. At $t = 50$ stimulations, the network changes in structure, leading to a rapid increase in Jaccard error. The inference scheme recovers and reconverges to a correct estimate of the new network. Mean and standard error for $n = 50$ simulations.

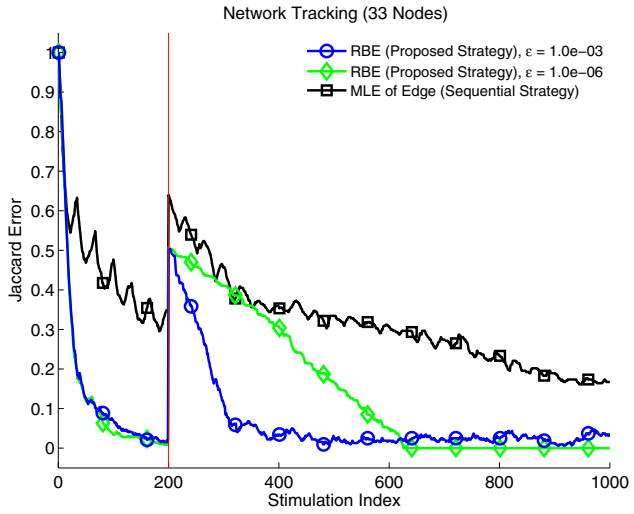

Fig. 4. Tracking a network with sudden connectivity change. The evoked connectivity estimate converges rapidly and correctly, as evidenced by the Jaccard error. At $t = 200$ stimulations, the underlying network changes in structure, and the estimation scheme recovers quickly, again converging to an accurate estimate of the new network. Mean of $n = 100$ simulation shown.

B. Tracking in Probabilistic Networks

To investigate the performance in more detail and with a larger scale, a probabilistic network of 33 nodes is considered. Neither the nodes nor the connections possess dynamics – that is, a stimulation to a node evokes a '1' or a '0' in neighboring nodes according to the presence or lack of a connection (see [8] for complete details). Detections follow specified distributions for $\mathrm{p}_{\mathrm{fa}|\mathbf{s}}$ and $\mathrm{p}_{\mathrm{md}|\mathbf{s}}$.

To study the performance of our scheme in this more abstract setting, the following simulation is performed. First, a network is generated where all except 10% are present (the first '10%' of $\mathbf{s}$ is set to '0'). Within 200 stimulations (see Figure 4) the estimate converges accurately, as evidenced by a low Jaccard error. At $t = 200$ stimulations the underlying network structure changes, undergoing a reconnection of the first 10% of edges, while simultaneously disconnecting the last 40% of edges. This rather large structural change leads to a dramatic jump in the Jaccard error. Nevertheless, the adaptive scheme recovers and the estimate reconverges. Figure 4 illustrates this recovery for two different values of ϵ. The higher value of 1×10^{-3} leads to a more rapid recovery, while the lower value of 1×10^{-6} exhibits a slower recovery but, eventually, more accurate convergence (the Jaccard error becomes 0). Both parameterizations drastically outperform a naive scheme based on a sequential round-robin approach, in which each node is stimulated according to the repeating sequence $1, 2, ..., N$. The round-robin scheme exhibits significantly slower convergence and recovery as measured by the maximum likelihood.

IV. CONCLUSIONS

In this note we have established the temporal tracking capability for estimating evoked connectivity in brain networks. Our results show that evoked connectivity remains effective, even if the underlying brain networks exhibit sudden changes. The overall scheme is highly general and can be adapted to a range of stimulation and recording modalities. Translation of the methodlogy to experimental applications is, naturally, a desired goal and is the subject of ongoing and future work.

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