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# Model-based estimation of intra-cortical connectivity using electrophysiological data

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ABSTRACT

This paper provides a new method for model-based estimation of intra-cortical connectivity from electrophysiological measurements. A novel closed-form solution for the connectivity function of the Amari neural field equations is derived as a function of electrophysiological observations. The resultant intra-cortical connectivity estimate is driven from experimental data, but constrained by the mesoscopic neurodynamics that are encoded in the computational model. A demonstration is provided to show how the method can be used to image physiological mechanisms that govern cortical dynamics, which are normally hidden in clinical data from epilepsy patients. Accurate estimation performance is demonstrated using synthetic data. Following the computational testing, results from patient data are obtained that indicate a dominant increase in surround inhibition prior to seizure onset that subsides in the cases when the seizures spread.

## Introduction

The human brain is arguably nature's most complex system. The development and validation of a theory that underpins its function is one of the greatest challenges faced by scientists today. This great challenge is being addressed by both the experimental and theoretical neuroscience communities. The experimental neuroscience community is generating an ever increasing number of facts, describing the interaction between manipulations and observations. The theoretical neuroscience community is developing mathematical models that can explain generators of data and make non-trivial predictions about system behavior (to be validated by experiments). To date, neither approach has been successful in developing an understanding of high-level brain function. Continuously accumulating more facts has not brought us closer to an understanding of what appears to be emergent phenomena in the brain. Understanding such phenomena requires the development and acceptance of theory. However, theoretical developments have been limited by the inability to accurately measure model parameters and account for inter-subject variability. This has led to mathematical models that are either over-parameterized or overly-simplified. Over-parameterized models often provide ambiguous explanations of data leading to misleading theories. Overly-simple models can be useful in certain applications, but can often neglect important aspects of the underlying biology.

An opportunity to overcome the challenges mentioned above has arisen with the advent of data-driven neural modeling. Data-driven modeling is a process of a creating a subject-specific mathematical model of a particular subject or experimental preparation. The model is constrained by known relationships and general principles that are described by mathematical functions, where the parameters of the functions are considered unknown. For example, an excitatory post-synaptic potential will have a fast rise time (from synaptic dynamics) and a slower decay time (from membrane dynamics) that is described by

$$h(t) = \alpha\left(exp\left(-\frac{t}{t_s}\right)-exp\left(-\frac{t}{t_m}\right)\right), \tag{1}$$

where $\alpha$ is a synaptic gain parameter and $t_s < t_m$ are the synaptic and membrane time constants, respectively. The form of the synaptic response function (or kernel due to the convolution in time) is well accepted. However, the parameters are known to vary across subjects, brain regions, and neural population types and thus need to either measured or inferred from data to create accurate models.

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Similarly, the probability that a neuron at position $\mathbf{r}$ connects with a neighbor at position $\mathbf{r}'$ decreases as the distance, $\mathbf{r} - \mathbf{r}'$, increases. This motivates the shape of connectivity functions (or kernels due to the convolution in space) that are used to describe neural fields, such as Amari's model (Amari, 1977) that has the form

$$w(\mathbf{r} - \mathbf{r}') = \sum_n \theta_n \, exp\left(-\frac{(\mathbf{r} - \mathbf{r}')^T(\mathbf{r} - \mathbf{r}')}{\sigma_n}\right), \tag{2}$$

where $\theta_n$ are the parameters that describe the effective connectivity strength of excitatory ($n = e$) and inhibitory ($n = i$) connections, and $\sigma_n$ specifies the axonal–dendritic range. The form of the connectivity function is well accepted in the literature and gives rise to important phenomena, such as tuning of cortical regions to receptive fields. However, as for the case with the post-synaptic response function in Eq. (1), the parameters are subject-specific.

There are several data-driven frameworks recently presented in the literature (Friston et al., 2003; Schiff and Sauer, 2008; Ullah and Schiff, 2010; Sedigh-Sarvestani et al., 2012; Pinotsis et al., 2013; Gorzelic et al., 2013; Turner et al., 2013; Aram et al., 2012; Freestone et al., 2011, 2013, 2014). These frameworks utilize system identification techniques to solve the problem of inferring parameters from data. They have demonstrated great potential in furthering our understanding of the function and structure of neural circuits. Moreover, data-driven models provide new opportunities in the field of neural engineering to incorporate control and systems theory to optimize therapeutic bionic devices (Schiff, 2011).

Perhaps the most limiting factor in the widespread adoption of data-driven modeling frameworks is the high level of complexity of the estimation algorithms. It is often the case with complicated algorithms that the results are clouded by a lack of understanding of the methods involved. Furthermore, the high level of complexity has led to the inappropriate application of data-driven methods to certain problems. Therefore, the development of methods that do not rely on complicated, iterative algorithms represents a significant contribution to neuroscience.

This paper provides a method for data-driven neural field modeling that does not rely on complicated, computationally intense estimation algorithms. The output of the method is an estimate of an intracortical connectivity function that can be computed in closed-form from local field potential or other high-resolution electrophysiological measurements. The estimated connectivity function is based on the assumption that the mean field dynamics of the cortex is governed by Amari-style neural field equations (Amari, 1977), where the parameters are not known. The dynamics of this model are governed by the connectivity function, which physically describes the statistics of the axonal–dendritic projections. Computationally, the shape of the connectivity function strongly dictates the type of dynamics that the cortical field can exhibit.

Results from data-driven mesoscopic neural modeling frameworks must be interpreted with care. A common misconception is that the variables that are estimated have a direct one-to-one correspondence to the actual brain. This is not the case. The resultant models are far less complex than the actual brain. Accordingly, parameter estimates must be interpreted as being constrained by the models. This is not to say that the models are not related to actual neural dynamics or that valuable insights cannot be gained. In actual fact, mesoscopic models are leading to new hypotheses about many types of phenomena. Furthermore, the constraints that the models place on the data facilitate the estimation of variables that are normally hidden in experimental observations.

The rest of this paper is set out as follows. In the Methods section, the stochastic Amari neural field model is briefly reviewed. Then necessary formulations for the intra-cortical connectivity estimator are provided. This is followed by the data collection approach and the pre-processing steps. The Results section provides examples using synthetic data that demonstrate the estimation performance with known parameters. Following this, results using recorded intracranial electroencephalogram (iEEG) data over normal, seizure, and post-seizure periods are presented. Finally, in the Discussion section, the implications and limitations of this method as well as possible future extensions are discussed. All frequently used symbols in the following sections are given in Table 1.

## Methods

### *Neural field model*

This manuscript presents a new method for inferring the underlying connectivity structure of cortex with the assumption that the cortical dynamics of interest are governed by physical laws described by the neural field model of Amari (1977). The single layer Amari neural field model is

$$v(t, \mathbf{r}) = \int_{-\infty}^{t} h(t - t')\left(\int_{\Omega} w(\mathbf{r} - \mathbf{r}')f(v(t', \mathbf{r}'))\,\mathrm{d}\mathbf{r}' + p(t', \mathbf{r})\right)\mathrm{d}t'. \tag{3}$$

The spatial dynamics are governed by the connectivity function, $w(\mathbf{r})$, that collects all the presynaptic firing rates that drive the field of postsynaptic potentials, $v(t, \mathbf{r})$, and $\mathbf{r} \in \Omega \subset \mathbb{R}^n$ are spatial locations in $n$-dimensional physical space, $n \in \{1, 2, 3\}$. The temporal dynamics are governed by the post-synaptic response function, $h(t)$, acting on action potentials and the external inputs arriving from other neural populations. The term $p(t, \mathbf{r})$ denotes external inputs. The relationship between the presynaptic mean membrane potential, and the presynaptic mean firing rate is typically described by a sigmoid function in generative neural population models. The sigmoidal relationship is

$$f(v(t, \mathbf{r})) = \frac{f_{\max}}{1 + exp(\varsigma(v_0 - v(t, \mathbf{r})))}, \tag{4}$$

where $f_{\max}$ is the maximum firing rate, $v_0$ describes the mean firing threshold relative to the resting membrane potential and the parameter $\varsigma$ defines the steepness of the sigmoid at $v_0$ (also specifies variability of firing thresholds).

**Table 1**
Notation. The symbols, description of the quantity, and the SI units where relevant.

| Symbol | Quantity | Units |
|---|---|---|
| *Domain* | | |
| $\mathbf{\Omega}$ | Spatial domain | n.a. |
| $\mathbb{Z}^+$ | Non-negative integers | n.a. |
| $\mathbb{R}^n$ | $n$-Dimensional real numbers | n.a. |
| $\mathbf{r}$ | Spatial location | [mm, mm] |
| $t$ | Time | s |
| *Model* | | |
| $\mathbf{y}_t(\mathbf{r}_{ij})$ | Electrophysiological measurement | mV |
| $v_t(\mathbf{r})$ | Mean membrane potential field | mV |
| $f(v(\mathbf{r}))$ | Activation function | spike $s^{-1}$ |
| $\hat{f}(v(\mathbf{r}))$ | Linearized activation function | spike $s^{-1}$ |
| $e_t(\mathbf{r})$ | Field disturbance, with covariance function $\gamma(\mathbf{r})$ | mV |
| $\varepsilon_t(\mathbf{r}_{ij})$ | Observation noise, with covariance matrix $\Sigma_\varepsilon$ | mV |
| $m(\mathbf{r}_{ij})$ | Observation function, where $i = 1, \ldots, I$ and $j = 1, \ldots J$ | n.a. |
| $w(\mathbf{r})$ | Connectivity function | mV $\text{spike}^{-1}$ |
| $\psi_i(\mathbf{r})$ | Connectivity basis functions | n.a. |
| $\theta_i$ | Weights of the connectivity basis functions | mV $\text{spike}^{-1}$ |
| $\mu_i$ | Centers of the connectivity basis functions | mm |
| $\sigma_i$ | Widths of the connectivity basis functions | mm |
| *Estimation* | | |
| $\boldsymbol{\tau}$ | Spatial shift | mm |
| $\boldsymbol{\nu}$ | Spatial frequency | cycles/mm |
| $\mathbf{y}_t^d$ | Differential re-referenced observations along j-direction | mV |
| $R(\boldsymbol{\tau})$ | Spatial correlation | $\text{mV}^2$ |
| $\mathcal{S}(\boldsymbol{\nu})$ | Power spectral density | $\text{mV}^2$ mm/cycles |

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