Published in final edited form as:

Neuroimage. 2017 December ; 163: 342–357. doi:10.1016/j.neuroimage.2017.09.043.

Estimating cortical column sensory networks in rodents from micro-Electrocorticograph (μ ECoG) recordings

Ricardo Pizarro^{a,*}, Tom Richner^a, Sarah Brodnick^a, Sanitta Thongpang^a, Justin Williams^a, and Barry Van Veen^b

^aDepartment of Biomedical Engineering, University of Wisconsin-Madison, 1550 Engineering Drive, Madison, WI 53706 USA

^bDepartment of Electrical Engineering, University of Wisconsin-Madison, 1415 Engineering Drive, Madison, WI 53706 USA

Abstract

Micro-Electrocorticograph (μ ECoG) arrays offer the flexibility to record local field potentials (LFPs) from the surface of the cortex, using high density electrodes that are sub-mm in diameter. Research to date has not provided conclusive evidence for the underlying signal generation of μ ECoG recorded LFPs, or if μ ECoG arrays can capture network activity from the cortex. We studied the pervading view of the LFP signal by exploring the spatial scale at which the LFP can be considered elemental. We investigated the underlying signal generation and ability to capture functional networks by implanting, μ ECoG arrays to record sensory-evoked potentials in four rats. The organization of the sensory cortex was studied by analyzing the sensory-evoked potentials with two distinct modeling techniques: (1) The volume conduction model, that models the electrode LFPs with an electrostatic representation, generated by a single cortical generator, and (2) the dynamic causal model (DCM), that models the electrode LFPs with a network model, whose activity is generated by multiple interacting cortical sources. The volume conduction approach modeled activity from electrodes separated $< 1000 \mu\text{m}$, with reasonable accuracy but a network model like DCM was required to accurately capture activity $> 1500 \mu\text{m}$. The extrinsic network component in DCM was determined to be essential for accurate modeling of observed potentials. These results all point to the presence of a sensory network, and that μ ECoG arrays are able to capture network activity in the neocortex. The estimated DCM network models the functional organization of the cortex, as signal generators for the μ ECoG recorded LFPs, and provides hypothesis-testing tools to explore the brain.

Keywords

micro-Electrocorticograph (μ ECoG); sensory cortex; cortical columns; modeling; volume conduction model; dynamic causal model (DCM); DCM Shotgun

*Corresponding author. Phone:+1-514-953-7173.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1. Introduction

Technological developments in electrophysiology have given neuroscientists the freedom to investigate the brain from new perspectives. Scalp electroencephalography (EEG¹) has been used to noninvasively record electrical activity throughout the cortex, facilitating the investigation of frequency components recorded globally; however, EEG is limited in spatial resolution [1, 2]. Penetrating electrodes can record spiking activity from individual neurons [3, 4] or local field potentials (LFPs) from a small population of neurons located within a few hundred μm radius [5, 6, 7]. Intracortical recordings offer precision, specificity, and have been well studied in animals. However, the invasive nature of this technology raises a number of unresolved issues, including reliability, safety, and biocompatibility [8]. Electrocorticographic (ECoG) arrays, also known as intracranial EEG, record LFPs with higher spatial resolution and signal-to-noise ratio (SNR) than scalp EEG [9, 10]. In addition, ECoG arrays record potentials with less cortical damage and less signal variability than intracortical recordings. MicroECoG (μECoG) arrays are ECoG arrays fabricated at a smaller scale, which decreases the craniotomy size required for insertion. MicroECoG arrays can record LFPs with higher SNR than ECoG [11], have been reliably and safely implanted for long periods of time [12], and are adaptable to brain computer interface [13] and optogenetic technologies [14, 15].

Research to date has not provided conclusive evidence as to the neural activity that generates the LFPs recorded from μECoG arrays. Buzsaki et al. [16] argued that the principal contribution to LFPs is the synaptic transmembrane current from collective groups of neurons; however, multiple distinct neuronal states can generate identical LFPs. Mapping LFPs back to the corresponding signal generators (or sources²) is an inverse problem [1, 17], that is mathematically ill-posed, due to the lack of a one-to-one mapping. Investigators commonly undertake a two-step approach to deal with the ill-posed inverse problem. The first step constitutes solving the forward problem; the forward problem involves correlating global and local events, allowing the investigator to determine the contribution of the synaptic and non-synaptic mechanisms to the global LFPs [18, 19]. The second step is to then use the estimated relationship between local and global events to gain insight into the local activity; however, the technical means to undertake this second step are still emerging. Buzsaki et al. suggested using experimentally observed temporal patterns to time-lock neuronal activity and generate LFPs from a network model of neurons as a possible way forward. We undertook the second step, by analyzing μECoG LFPs with a network model of neurons, to gain insight into the local micro-architecture of a sensory cortical region.

The underlying signal generation of the μECoG LFPs resides within the neocortex, whose structure has been determined to be comprised of cortical columns, based on neurophysiological studies of local neuronal connectivity [20, 21, 22]. Columnar

¹Abbreviations: EEG - electroencephalogram, LFP - local field potentials, ECoG - electrocorticograph, SNR - signal to noise ratio, μECoG - micro-electrocorticograph, NITRO - Neural Interface Technology Research and Optimization, DCM - dynamic causal model, NMM - neural mass model, CMC - canonical microcircuit, TDT -Tucker-Davis Technologies, HPF - high-pass filter, SPM - statistical parametric mapping, SD - standard deviation, SEM - standard error of the mean, ii - inhibitory interneurons, sp - superficial pyramidal, ss -spiny stellate, dp - deep pyramidal, NMSE - normalized mean-square error, LRT - likelihood ratio test, GLRT - generalized likelihood ratio test, P_{FA} - probability of false alarm, and VC - volume conduction
²generators and sources are used interchangeably throughout

organization has been established anatomically; however, the disparate definitions of the diameter of a cortical column, shown in Table 1, provide a challenge to determining its functional equivalent [23, 24, 25].

We set out to investigate the underlying signal generation of μ ECoG recorded LFPs to determine if μ ECoG recorded LFPs could capture some of the functional structure of the neocortex. To that end, we recorded sensory evoked LFPs epidurally from the cortical surface, using thin-film bilateral μ ECoG array technology fabricated at the Neural Interface Technology Research and Optimization (NITRO) lab [14]. Each μ ECoG electrode was 200 μ m in diameter, while the center-to-center distance between adjacent electrodes was 750 μ m. The dimensions of this state-of-the-art μ ECoG array provides a means to analyze LFPs recorded over a range of distances and spatial resolutions to address the extent of cortical column connectivity.

We analyzed sensory evoked LFPs recorded from μ ECoG arrays with two distinct computational models: a volume conduction model and a network based model. These computational models use distinct solutions to the forward problem, providing different approaches to gain insight into local activity from global events. The Maxwellian volume conduction model is often used to model potentials from ECoG arrays because of its simplicity and reasonable accuracy in modeling activity in nearby electrodes [26, 27, 28]. The volume conduction model assumes LFPs recorded over the array are produced by a single local cortical generator via electrostatics. The electrode with the highest energy is typically identified as the location for the cortical generator that produces LFPs throughout the array. In contrast, dynamic causal models (DCM) [29] and multivariate auto-regressive models [30] are generative network models of neurons, as recommend by Buzsaki et al. [16], and assume the potentials are generated by multiple interacting sources.

In this manuscript, we compare the single-source volume conduction model with a multiple-interacting-sources DCM-based network model. DCM was developed for EEG and magnetoencephalogram analysis and uses cortical-column-inspired neural mass models (NMMs) to estimate connectivity between modeled sources and predict LFPs in the populations³ and electrodes [31]. NMMs are appropriate for sensory evoked LFPs, since the stimulus is modeled to innervate the spiny stellate population of a specified region, and the cortical circuitry responds with large synchronous spatiotemporal patterns. Bastos et al. [25, 32] established a relationship between local and global activity, rooted in neurophysiological evidence, to develop the canonical microcircuit (CMC) for DCM. They analyzed ECoG potentials over the visual cortex in non-human primates, scaling DCM down to ECoG dimensions, with regions located 6–12 millimeters apart. The CMC incorporates an additional pyramidal population for each source, providing a necessary vertical dimension to model μ ECoG potentials. We employ the CMC in DCM for our network model analysis.

We explored the connectivity and signal generation of cortical sources by comparing the performance of a single-source volume conduction model to a multiple-interacting-sources DCM-based network model in predicting LFPs recorded from a μ ECoG array with

³populations refer to a particular type of cell populations

electrodes located at distances that range 750–3000 μm apart. We investigated the spatial dimensions over which the volume conduction model and DCM accurately predict the recorded electrical potentials. We developed DCM Shotgun, a method that increases the likelihood of converging to a model with high fidelity and can be generalized to analyze other datasets generated from animal brain recordings. We compared the performance of a fully connected DCM to an unconnected DCM version to assess the relevance of the extrinsic network component. We implemented bootstrap methods to assess the stability of the parameters of a sensory network estimated by DCM.

We found that activity from electrodes separated $< 1000 \mu\text{m}$ can be described by the single source volume conduction model with reasonable accuracy, but that electrode separations greater than 1500 μm require a network model, like DCM, to accurately predict the potentials observed. We also found that DCM's extrinsic network is the key component in modeling the potentials over the entire array, strongly suggesting the presence of a network of cortical sources independently interacting. Finally, the sensory network for two cortical sources was estimated with DCM to illustrate the local organization of the sensory cortex and provide likely signal generators responsible for the LFPs recorded from the μECoG array.

This paper is organized as follows. Section 2 describes the data acquisition and preprocessing methods, defines the volume conduction model and the DCM, and presents the objective metrics used for assessing the models. Section 3 presents model performance as a function of electrode separation, identifies the relevance of the network component in DCM, and illustrates the estimated sensory network between two cortical sources. Section 4 discusses the relevance and interpretation of the results. Brief concluding remarks are given in section 5. Notation used throughout the paper is introduced here. Boldface symbols represent vectors, while superscript T denotes vector transpose. Given data $\mathbf{v}$, the sample mean is written as $\bar{\mathbf{v}}$ and model estimate as $\hat{\mathbf{v}}$. $\mathbb{E}[\mathbf{a}]$ denotes the expectation of a random variable $\mathbf{a}$. $\mathbf{x} \sim \mathcal{N}(\mu, \Sigma)$ means the vector $\mathbf{x}$ is normally distributed with mean μ and covariance Σ .

2. Materials and Methods

2.1. Experimental Setup

We recorded sensory evoked potentials using μECoG arrays in four rats, with the following experimental procedure, illustrated in Figure 1. For each rat, we fabricated a platinum μECoG array with the following specifications: 4x4 grid, 200 μm site diameter, 750 μm site-to-site spacing, and 50 kOhms nominal impedance at 1kHz [13]. We then implanted bilateral μECoG arrays in each rat, under isoflurane and buprenorphine. The array was centered at 1.5 mm posterior and 2 mm lateral to bregma, to record from the hindlimb sensory region, as located in [33]. The subject recovered for a week prior to sedated sensory recordings. The rat was sedated with dexmedetomidine (50 $\mu\text{g}/\text{kg}$, SC). The right hindlimb was shaved to remove fur and attach adhesive surface electrodes, ventrally and dorsally. An electrical stimulus was delivered to the sciatic nerve, via the attached surface electrodes. Each electrical stimulus was a monophasic pulse with 1 ms duration, 1.25 mA amplitude, and jittered between 2–4 s. We recorded bilaterally from the sensory cortex, however, for this

study, we focused on the response contralateral to the stimulation site. The response was recorded through the surgically implanted μ ECoG array as potentials in μ Volts as a function of time. We used a multichannel neural-recording system, from Tucker-Davis Technologies (TDT), to sample the signals at 3.05 kHz. The TDT high-impedance headstage introduces a high-pass filter (HPF) with attenuation of 3 dB at 0.3 Hz, and 6 dB at 0.25 Hz. The TDT preamplifier introduces an additional HPF with attenuation of 3 dB at 0.35Hz, and 6 dB at 0.2 Hz. More detailed explanations for the array implantation procedure is found in [34] and data acquisition is found in [14, 15].

2.2. Neural Signal Processing

The recorded potentials were processed in Matlab (Mathworks, v2015 [35]). The data was low pass filtered at 500 Hz to remove noise using an order 20, zero-phase, finite impulse response filter, as in [14]. The potentials were divided into trials by assigning $t = 0$ ms to the stimulus presentation time. Each trial i , from electrode j is denoted as $\mathbf{v}'_{ij}$ and spans 20 ms prior stimulus to 100 ms post stimulus.

An electrical stimulation artifact was observed between 0 and 12 ms post stimulus, due to the electrical equipment and occurs prior to the neurobiological response of interest. This electrical artifact was eliminated using the following procedure [36]. First, a median filter was applied to $\mathbf{v}'_{ij}$ to generate a median filtered trial, $\mathbf{v}^m_{ij}$. The median filter computes the new value as the median over the range of values within a sliding window of 25 samples. A raised cosine window $w[n]$, was then defined for sample n , to isolate the artifact:

$$w[n] = \begin{cases} \frac{1}{2} + \frac{1}{2} \cos \left[\frac{\pi}{6} [nT - 9] \right], & \frac{0}{T} \leq n \leq \frac{12}{T} \\ 0, & \text{otherwise} \end{cases} \quad (1)$$

where T is the sampled interval. The cosine window $w[n]$, was used to define the clean trial $\mathbf{v}_{ij}$, as:

$$v_{ij}[n] = v'_{ij}[n] (1 - w[n]) + v^m_{ij}[n] w[n] \quad (2)$$

The stimulus-triggered average potentials, $\bar{\mathbf{v}}'_j$ and $\bar{\mathbf{v}}_j$, were estimated from trials $i = \{1, \dots, M\}$:

$$\begin{aligned} \bar{v}'_j[n] &= \frac{1}{M} \sum_{i=1}^M v'_{ij}[n] \\ \bar{v}_j[n] &= \frac{1}{M} \sum_{i=1}^M v_{ij}[n] \end{aligned}$$

where M is the total number of trials. We plotted $\bar{v}_j$ and ∇_j versus time, for one representative electrode, in Figure 2, to illustrate the results of the artifact removal procedure.

The data was then downsampled by a factor of four to reduce the size of the dataset and limit the frequency components of interest to < 350 Hz using Matlab's resample command. This downsampling procedure changed the sampling frequency to 762.5 Hz.

The variance σ_j^2 was estimated to quantify the variability in the clean trials, as:

$$\sigma_j^2[n] = \frac{1}{M} \sum_{i=1}^M (v_{ij}[n] - \bar{v}_j[n])^2$$

The standard deviation (SD), and the standard error of the mean (SEM) were then estimated from the variance, as:

$$SD_j[n] = \sqrt{\sigma_j^2[n]}, \quad SEM_j[n] = \sqrt{\frac{\sigma_j^2[n]}{M}}$$

The artifact removal procedure generated clean potentials, defined to target only the neurobiological response of interest. The quality of the clean potentials is illustrated in Figure 3 for two representative electrodes chosen from all four animals. The magnitude of the SEM is minimal compared to the magnitude of the mean and is typical of this data [14]. The shape of the mean potential varies across animals but the positive and negative peaks are consistently located at the same post-stimulus time. There is significant variability in the SD magnitude, correlated to M , the total number of trials acquired in each animal. However, the computational models implemented and defined, in the following two sections, utilize the stimulus-triggered average clean potentials, from electrode j , denoted as ∇_j and referred to, hereon, as average potentials. The average potentials were estimated to remove variability, due to unrelated neural activity or noise, to ensure the computational models analyzed only the neurobiological response of interest. The hypothesis-testing scenario utilizes the individual clean trials, denoted as $\mathbf{v}_{ij}$ and referred to hereon as trials. The hypothesis-testing scenario makes the necessary assumption that the trials' variance can be modeled as a gaussian distribution.

2.3. Volume Conduction

Multiple networks consisting of two nodes $j = \{A, B\}$, from the array were used to implement both the volume conduction model and DCM. Two-node networks provided the necessary structure: (1) to implement a nontrivial volume conduction model and (2) to explore DCM's extrinsic connections. The primary electrode A, was identified as the electrode in the array with the biggest response. The secondary electrode B, was varied across all remaining electrodes in the array, $B = \{1, \dots, 16 | B \neq A\}$. This arrangement resulted in 15 different two-node networks that were predicted with each model.

The volume conduction model assumes LFPs recorded over the array are produced by a single local cortical generator via electrostatics [1, 37]. This assumption results in a simple forward model, consisting of attenuation and offset parameters. Including additional sources translates to multiple regions generating electrical activity in parallel; however, additional sources trivializes the analysis where parameters are estimated to predict the activity exactly. The resulting forward model provides the means to gain insight into the local activity, from globally recorded events, and estimate the location of the cortical generator. For example, neurosurgeons ignore the activity in the remaining electrodes and implement a forward model on ECoG recorded electrical activity to locate the seizure focal point for resection.

In the experiment conducted, the electrical stimulus was relayed via the sciatic nerve, through the thalamus, and terminated in the sensory cortical region. The cortical activity induced by stimulation is modeled as an electric dipole, within a cortical column, in the volume conduction model. The activity from the cortical column dipole is assumed to appear in each μ ECoG electrode due to volume conduction based on the distance between the dipole and the electrode [1, 37]. Thus, there are no temporal shifts or dynamics assumed between electrodes. A graphical model of volume conduction is shown in Figure 4.

Volume conduction model parameters were estimated from the average potentials, $\bar{v}_j$, in the following way. In the volume conduction model, we assumed that the potential at the primary electrode A , $\bar{v}_A$, was equal to the potential of the dipole $\bar{v}_D$, the single local cortical generator. The potential at electrode B was then modeled as $\hat{v}_B$, with attenuation and offset parameters (c_{1B}, c_{2B}), to minimize the squared error, ε_B^2 :

$$\begin{aligned} \min_{c_{1B}, c_{2B}} \varepsilon_B^2 &= \min_{c_{1B}, c_{2B}} \sum_{n=0}^{N-1} (\bar{v}_B[n] - \hat{v}_B[n])^2 \\ &= \min_{c_{1B}, c_{2B}} \sum_{n=0}^{N-1} (\bar{v}_B[n] - (c_{1B} \bar{v}_A[n] + c_{2B}))^2 \end{aligned}$$

where $N = 50 \text{ ms} / T_d$. The method of least-squares was implemented to compute the estimates $\hat{c}_{1B}$ and $\hat{c}_{2B}$, given the potentials $\bar{v}_A$, $\bar{v}_B$:

$$\hat{c}_{1B} = \frac{N \sum_n \bar{v}_A[n] \bar{v}_B[n] - \sum_n \bar{v}_A[n] \sum_n \bar{v}_B[n]}{N \sum_n \bar{v}_A^2[n] - \left(\sum_n \bar{v}_A[n] \right)^2}$$

$$\hat{c}_{2B} = \frac{1}{N} \left(\sum_n \bar{v}_B[n] - \hat{c}_{1B} \sum_n \bar{v}_A[n] \right)$$

2.4. Dynamic Causal Model

DCM as implemented in Statistical Parametric Mapping (SPM) 12 [38] was used for the network analysis. DCM models the brain as a deterministic nonlinear dynamical system involving interactions between multiple neural sources [29]. Effective connectivity is parameterized in terms of coupling between sources. Coupling is then estimated by finding the model parameters that give the best “fit” to the measured data, where “fit” is defined in terms of log-evidence. Log-evidence is an objective function that balances accuracy and complexity of the model [39], rewarding parsimonious models with comparable accuracy. Finding the optimal solution is a nonlinear optimization problem and the number of dimensions to search over is defined by the number of parameters in the model. Convergence to a global optimum is not guaranteed but an appropriate initial guess can result in a high-fidelity model.

In DCM, we employed the neural-mass-model variation, CMC, developed to analyze ECoG potentials over the visual cortex [25, 32]. NMMs are appropriate for sensory evoked potentials, as the stimulus is modeled to innervate spiny stellate population, layer 4, of a cortical column, and the cortical circuitry responds with large synchronous spatiotemporal patterns. Further, NMMs establish a relationship between local and global activity, rooted in empirical neurophysiological data, to gain insight into the local μ -architecture of the investigated cortical region. The CMC models each source as a cortical column comprised of four populations: inhibitory interneurons, superficial pyramidal cells, spiny stellate cells, and deep pyramidal cells. The CMC estimates neurobiological parameters describing the stimulus input, connectivity, synaptic time constants, propagation delay, and pre-synaptic input. The estimated set of parameters comprise DCM’s generative network model. A single pulse is then used as input, to the network model, to predict LFPs in each cortical-column population. The CMC forward model then defines a linear superposition of the local predicted-population LFPs to estimate LFPs, at the global level of the μ ECoG electrodes.

We explored connectivity, by focusing on the stimulus input and the connectivity parameters, illustrated in Figures 5 and 6. The stimulus input innervates the spiny stellate population of source A, above which the primary recording electrode A is located. Connectivity is estimated with extrinsic and intrinsic parameters. Extrinsic parameters quantify connectivity between cortical columns. The extrinsic feedforward connection starts at the superficial pyramidal population from one cortical column and terminates at both the spiny stellate and deep pyramidal populations of the other cortical column. The extrinsic feedback connection starts at the deep pyramidal population of one cortical column and terminates at both the inhibitory interneuron and superficial pyramidal populations of the other cortical column. Intrinsic parameters estimate connectivity between the four modeled populations within a cortical column. The populations are not all directly connected to each other, rather, some populations can act as mediators. For instance, the spiny stellate population is mediated by the inhibitory interneuron population prior to reaching the deep pyramidal population.

We used DCM to analyze the 15 different two-node networks. Incorporating additional nodes into the analysis could provide a more realistic description of the underlying network. However, additional DCM nodes exponentially increases the number of parameters and the

dimensions defining the hyperplane where the nonlinear optimization is performed. This increase in complexity would decrease our chances of finding an optimal solution. There exists methods to limit the number of parameters at their physiologically plausible average values [40]. However, this is a first study investigating the use of DCM to analyze μ ECoG potentials recorded at sub-mm spatial resolution.

Our initial efforts with DCM led to poor fits, with low-fidelity solutions. We initially implemented DCM with the built-in parameters for two sources [32]. To explore connectivity, we considered all 16 possible networks obtained by toggling each of the four extrinsic connections between the two cortical columns as either “on” or “off.” If a connection is turned “off,” DCM sets the corresponding connection strength to zero. Investigators [41, 42] often use this exploratory approach as a way to determine a winning model based on Bayesian model selection [39]. However, all 16 possible networks yielded solutions with low log-evidence values and poor fits in either electrode A or B.

These unimpressive results, using the built-in parameters, motivated our search for a better initialization scheme. We developed a randomization method, termed DCM Shotgun, to systematically find a good set of initial parameters. DCM Shotgun consists of evaluating a large number of initial parameters for one electrode pair and then using the best solutions as initial parameters for the other electrode pairs. This strategy is motivated by the expectation that good DCM models for different electrode pairs should lie close to each other in parameter space. Obviously, one could choose a large number of independent initial parameters for each electrode pair, but this two-step approach cut the computational burden by a factor of about 14 and proved to be very effective.

The flow of DCM Shotgun is illustrated in Figure 7 and consists of the following sequence. We generated 10,000 initial parameter sets by randomly perturbing each built-in parameter with a random variable, $\Delta \sim \mathcal{N}(0, \sigma_{\Delta}^2)$. The variance σ_{Δ}^2 , was chosen empirically to perturb the values by 50%, in the natural-log scale. We set all four extrinsic connections “on,” denoted hereon as DCM, or connected-DCM, and initialized DCM with the 10,000 different initial parameter sets generated for one example electrode pair, defined to be primary electrode *A* and secondary electrode *B* = 16, located on the opposite side of the array. The converged solutions were then ranked according to DCM’s log-evidence metric [39]. The top 50 converged solutions were subsequently utilized as candidate initial parameter sets to seed DCM for the remaining 14 pairs of electrodes. A winning model for each electrode pair was chosen as the solution with highest log-evidence, resulting in unique estimates for each two-node network, i.e. 15 winning models in each animal.

We investigated the relevance of DCM’s network component, estimated by the CMC extrinsic parameters, in predicting the μ ECoG potentials. To that end, we modeled the data from the electrodes independently. That is, we created an unconnected version of DCM, denoted hereon as unconnected-DCM, by modifying the connected-DCM, as follows. The stimulus input was modified to stimulate the spiny stellate population in each cortical column independently. The extrinsic connections were set to “off,” but all remaining parameters, including the intrinsic connections, were estimated, using an adapted DCM Shotgun, to find a winning solution for the unconnected-DCM. In this unconnected scenario,

the estimated parameters comprise two independent sources. The input independently stimulates the spiny stellate population of each cortical column, to generate LFPs in each population. A forward model is used to predict LFPs at the μ ECoG level from the generated-population LFPs.

2.5. Model assessment

We implemented distinct objective metrics to assess model performance, under various scenarios. The normalized mean-square error (NMSE, [43]) was utilized to estimate the accuracy of the volume conduction model and DCM. NMSE measures the goodness-of-fit of a model-generated waveform $\hat{\mathbf{v}}_j$ to the average potential $\bar{\mathbf{v}}_j$. This metric is inversely proportional to accuracy, meaning the lower the NMSE the higher the accuracy of the model fit. We computed the NMSE as:

$$NMSE_j = \frac{\sum_{n=0}^{N-1} (\bar{v}_j[n] - \hat{v}_j[n])^2}{\sum_{n=0}^{N-1} (\bar{v}_j[n])^2} \quad (3)$$

where $N = 50 \text{ ms}/T_d$. NMSE is normalized by the energy of the average potential $\bar{\mathbf{v}}_j$, hence NMSE is reported as a percent.

We used a hypothesis-testing scenario, to define a composite likelihood ratio test (composite LRT), that determined if the unconnected-DCM could perform as well as the connected-DCM, in predicting the μ ECoG potentials. We implemented Wilks' theorem [44], where the connected and unconnected scenarios were treated as a composite hypothesis testing problem. The null hypothesis, H_0 , was defined to be the unconnected-DCM and the alternative hypothesis, H_1 , was defined to be the connected-DCM:

$$H_0: \mathbf{v}_{1j}, \mathbf{v}_{2j}, \dots, \mathbf{v}_{Mj} \stackrel{iid}{\sim} p(\mathbf{v}_j | \theta_{j,0}),$$

where $\theta_{j,1}, \dots, \theta_{j,l} \in \mathbb{R}^l$ are estimated and $[\theta_{j,l+1}, \dots, \theta_{j,m}]^T = \mathbf{0}^{m-l}$, extrinsic set to 0

$$H_1: \mathbf{v}_{1j}, \mathbf{v}_{2j}, \dots, \mathbf{v}_{Mj} \stackrel{iid}{\sim} p(\mathbf{v}_j | \theta_{j,1}),$$

where $\theta_{j,1} \in \mathbb{R}^m$ are all estimated

and the parametric density $p(\mathbf{v}_j | \theta_{j,h})$ has the same form in either hypothesis, $h = \{0, 1\}$. The null hypothesis, H_0 , estimated l parameters, while the alternate hypothesis, H_1 , estimated m parameters. The family of models in H_0 are a subset of those in H_1 , and the two hypotheses are nested, a key condition that needs to be satisfied in Wilks' theorem.

The generalized likelihood ratio test (GLRT), $\hat{\Lambda}(\mathbf{v}_j)$, is commonly used in composite hypothesis testing to determine if H_0 can be rejected, by comparing to a predetermined threshold γ [45]. In the GLRT, unknown parameters are replaced by estimates, like the maximum likelihood estimate, that maximize the observed potential $\mathbf{v}_j$ [45]. The GLRT was defined in terms of the parametric density as:

$$\hat{\Lambda}(\mathbf{v}_j) = \frac{\max_{\theta_{j,1}} p(\mathbf{v}_j | \theta_{j,1})}{\max_{\theta_{j,0}} p(\mathbf{v}_j | \theta_{j,0})} \underset{H_0}{\overset{H_1}{\gtrless}} \gamma \quad (4)$$

We derived a composite LRT, that was compared to a predetermined threshold, to conclude if we could reject H_0 . Wilks' theorem states that under the nested hypotheses scenario, when the observation is distributed as a model in H_0 , i.e., $\mathbf{v}_j \sim p(\mathbf{v}_j | \theta_{j,0})$, the GLRT has asymptotic distribution [44], to allow us to define *compositeLRT*, as in (A.8). We rejected H_0 , when *compositeLRT* exceeded the threshold γ , whose value was computed *a priori*, to ensure the probability of false alarm (P_{FA}) $< \alpha$, i.e., $P_{FA} = \int_{\gamma}^{\infty} \chi_{m-l}^2[x] dx < \alpha$. The connected-DCM estimated $m = 45$ parameters while the unconnected-DCM estimated $l = 38$ parameters. The threshold was computed with Matlab's function `chi2inv`, $m - l = 7$ degrees of freedom, and $\alpha = 0.05$, to obtain $\gamma = 14.1$.

We implemented a bootstrap with replacement method [46], to compute a distribution of the parameters estimated by DCM. DCM estimates a set of neurobiological inspired parameters. However, the estimates are real numbers and it may be difficult to gain intuition from their numerical value. Modeling different bootstrap subsets of the data generates a distribution of parameter values [46]. The flow of the implemented bootstrap method is illustrated in Figure 8. We incorporated DCM Shotgun to generate 50 candidate initial parameters, in stage I. We then used bootstrap with replacement, to generate 100 subsets containing 0.8M trials. Each bootstrap subset was initialized with the 50 candidate parameter sets, from stage I, and modeled with DCM. We made the assumption that parameter $p \sim \mathcal{N}(\mu_p, \sigma_p^2)$, to summarize the distribution as an illustration and make statistical comparisons between parameters.

3. Results

3.1. Comparing volume conduction to DCM

The NMSE values, defined in (3), were computed between the average potential $\bar{\mathbf{v}}_B$, and the model generated predictions $\hat{\mathbf{v}}_B$, in all secondary electrodes B . The computed NMSE values are plotted, in Figure 9, to summarize model performance, as a function of distance. The Euclidian distance was defined as the center-to-center distance between the primary and secondary electrodes, computed from the dimensions of the μ ECoG array, and the geometric location of B , with respect to A . The NMSE range varies between animals, however, in all animals, volume-conduction-generated NMSE values increased as a function of distance, while DCM-generated NMSE values increased as a function of distance at a lower rate and remained comparatively small throughout.

The model predictions are plotted versus time, in Figure 10, to illustrate the quality of fits generated by volume conduction and DCM. We selected three different electrodes of the array of each animal to demonstrate the fidelity of the model fits as a function of distance. The average potential ∇_A is plotted versus time, in the left panels. Two secondary electrodes ∇_B were selected to represent potentials recorded *near* and *distant* to A , plotted in the middle and right panels, respectively. The volume conduction model fits the *near* potentials better than the *distant* potentials. DCM models the *near* and *distant* potentials with comparable fits.

3.2. DCM network connectivity

Model predictions are plotted versus time, in Figure 11, to illustrate the quality of fits generated by the connected-DCM and unconnected-DCM. We selected the primary electrode of the array of each animal to assess network connectivity. The unconnected-DCM is not able to fit the average potential ∇_A , as well as the connected-DCM, in three of the four animals.

We developed a hypothesis-testing scenario, to decide if the unconnected-DCM could perform as well as the connected-DCM in predicting μ ECoG potentials. The results of the hypothesis-test are presented in Table 2, for all four animals. The number of trials recorded in each animal is denoted as M . The time window $[t_0, t_1]$, used for each animal, are presented as two rows in Table 2, and labeled in Figure 11, with vertical red lines. The time window defined the number of samples, L . The selected parameters generated the resultant *compositeLRT*. The T value was translated to a p-value, using Matlab's `chi2cdf`, to represent the probability H_0 was being rejected incorrectly. The T value exceeded the predetermined threshold γ in all cases, concluding that the unconnected-DCM hypothesis, H_0 , could be rejected. Further the term $(1-p\text{-value})$ quantifies the certainty of rejection at $>98\%$.

We implemented a bootstrap method, to generate a distribution of parameters and estimate the stability of DCM's predicted network. The summarized network for two connected cortical sources, $j = \{3, 16\}$, is presented in Figure 12. We generated 100 bootstrap subsets, each comprised of 0.8M of the trials, to estimate a distribution of each connectivity parameter p . Parameter distributions were summarized with a mean μ_p and a standard deviation σ_p . The resultant canonical microcircuit illustrates the coupling between two cortical sources, as likely signal generators for the average potentials.

4. Discussion

A results overview is presented in this paragraph, to frame the discussion. Volume conduction did not perform as well as DCM in predicting the LFPs recorded from the μ ECoG array, as presented in Figures 10 and 9. Volume conduction was able to model potentials near the primary electrode with reasonable NMSE, but, as the distance increased, so did the NMSE values. DCM was able to accurately model potentials, with small NMSE values, from all secondary electrodes, regardless of the distance to the primary electrode. The unconnected-DCM appeared to fit potentials from the primary electrode with comparable accuracy to the connected-DCM, reflected in Figure 11. However, we implemented a hypothesis-testing scenario to define a time window $[t_0, t_1]$ in all animals where the *compositeLRT* exceeded the predetermined threshold γ , and concluded that the

unconnected-DCM hypothesis, H_0 , could be rejected with 98% certainty in all animals. Finally, a bootstrap method was implemented to summarize a distribution of sensory network estimates consisting of two neural sources interacting independently.

4.1. Model as a function of distance

We showed that the volume conduction model was able to predict activity, recorded at a distance of 750 μm , reasonably well when compared to DCM; DCM was able to accurately predict activity over any distance. Theoretically, this reasonable comparison can be understood by moving the electrodes closer together. At the trivial distance of 0 μm , two overlapping electrodes would record LFPs generated by the same cortical source, and the potentials would be identical. In this scenario, the volume conduction model could predict activity *exactly*, with parameters: $(c_{1B}, c_{2B}) = (1, 0)$. At a distance of 200 μm , two tangent electrodes, touching on a single point, would record nearly identical potentials generated by the same cortical source; we expect volume conduction to model the potentials at 200 μm with negligible NMSE, δ .

These two inferred additional points can be placed as red stars in the plots of Figure 9, at (0 μm , 0%) and (200 μm , δ), shedding additional light on volume conduction performance as a function of distance. However, it remains unclear at what range $< 750 \mu\text{m}$ volume conduction predicts potentials with $\text{NMSE} < \delta$. In addition, what is a reasonable threshold value for δ ? The two linear fits for each animal in Figure 9 intercept each other around 500–600 μm indicating a range where the two models perform with similar accuracy.

Alternatively, higher-density μECoG arrays, could be fabricated, at interelectrode distance equivalent to the width of a cortical column, 300–400 μm , to aptly sample cortical generators. A higher spatial resolution would provide the means to generate the missing datapoint at a distance of 300–400 μm , in Figure 9, and determine with greater precision the interelectrode distance where volume conduction is able to predict LFPs with NMSE below a threshold, δ .

Slutzky et al. [47] investigated optimal spacing for electrode arrays and concluded that interelectrode spacing for epidural arrays, like μECoG , should be 600–900 μm . They were the first to conduct such a thorough study, and their results provided the dimensional range for our μECoG arrays. However, unresolved issues remain. First, Slutzky et al. used a finite element model, based on volume conduction from a single generator, without considering multiple or interacting sources. Second, high-resolution structural magnetic resonance images were used to account for the shape of the cortex, but Slutzky et al. did not take into account the local layered structure of the neocortex. The optimal spacing suggested by Slutzky et al. would not provide the resolution necessary to determine the distance where volume conduction can predict μECoG potentials with NMSE below δ .

The optimal spacing for electrodes depends *strictly* on the research question being investigated. Moran et al., [42] correlated increasing levels of anesthetic to excitatory and inhibitory synaptic transmission parameters, estimated by DCM, using electrodes located 2000 μm apart over the rat auditory cortex. Moran et al.'s study did not require any higher spatial resolution to accurately observe changes in parameters estimated by DCM, since the regions targeted by anesthetics were located 2000 μm apart. In our study, we showed that the

volume conduction model was less accurate than DCM as the interelectrode distance increased beyond 1500 μm . These results are in agreement with the 300–400 μm width of the cortical column. The transition distance of 1500 μm is theoretically equivalent to lining up 4–5 cortical columns. At distances > 1500 μm , it seems improbable that recorded potentials were generated by a single local cortical generator, as described with the single-source volume conduction model. DCM was able to accurately model potentials, with small NMSE values, from all secondary electrodes, regardless of the distance to the primary electrode. These results suggest that a network type of model is required to accurately predict activity generated by multiple sources, recorded from electrodes located > 1500 μm .

4.2. Model parsimony

We investigated the underlying signal generation of μECoG LFPs by comparing the performance of connected-DCM to two more parsimonious computational models, as determined by the number of estimated parameters. Occam's razor states that, when performance is similar, the simpler model should be selected between competing models [39]. It should be noted that DCM's log-evidence accounts for levels of complexity [39], by measuring the number of estimated parameters and the amount of deviation from the builtin parameter set. DCM's complexity metric cannot be extended to the volume conduction model, so we limit our measure of complexity to the number of estimated parameters.

Our first comparison, between DCM and volume conduction, was biased towards DCM due to the greater number of parameters; however, this comparison revealed great detail with respect to the underlying signal generation. The connected-DCM estimated 45 parameters in a two-node network, while the volume conduction model estimated 2 parameters. We could not expect volume conduction to outperform DCM in fitting the data, due to this drastic difference in parameter quantity. However, we wanted to compare DCM to a simpler, well-accepted model. Had the more parsimonious volume conduction model sufficed, there would be no need for a complex causal network model. The volume conduction model can provide a first-order approximation of the underlying signal generation by identifying the gross location of the signal cortical generator. However, more complex details concerning connectivity, or potentials predicted from sources, can only be revealed with a network model, such as DCM.

The current standard-of-care for performing resection in patients with intractable epilepsy is crude and could benefit greatly from the technological advancements we have presented. Currently, the most specific clinical method to pinpoint the seizure source consists of using volume conduction to model ECoG potentials recorded over the suspected cortical area [48, 49, 50]. The neurosurgeon first identifies the electrode recording abnormal activity, then proceeds with the removal of the underlying cortical region. Using μECoG arrays, instead of ECoG, would reduce the craniotomy size for insertion and reduce the resection size as μECoGs provide higher spatial resolution in identifying the problematic region. Further, it is likely that the underlying seizure generation is not comprised of a single cortical generator, but rather an epileptogenic network [51, 52]. We have shown that to successfully identify a network requires a network model of neurons, like DCM. Rather than identifying a single

region to be removed, DCM could pinpoint a problematic connection, or a problematic population within a cortical region.

Our second comparison, between the connected and unconnected DCM, established that μ ECoG recorded LFPs can capture the underlying sensory network. The connected-DCM required an additional seven degrees-of-freedom when compared to the unconnected-DCM, that comprised of 38 parameters in both regions. It could be argued that the connected-DCM was overfitting when compared to the unconnected-DCM; however, the implemented hypothesis-testing scenario allowed us to reject the null-hypothesis, with > 98% confidence, that the unconnected-DCM predicted the activity equally well. These results provide strong evidence of the existence of a network in the sensory cortex in these four rats. We have conducted a thorough analysis to demonstrate that the rat sensory cortex is comprised of a network, a conclusion that may not be surprising to many investigators. However, our results provide strong evidence that μ ECoG recorded LFPs have the ability to capture the functional structure of the sensory cortex at the level of discretely connected cortical sources.

4.3. Necessity for DCM's complexity

We have argued that in order to accurately characterize the underlying generation of μ ECoG recorded LFPs, a complex network model, like DCM, is needed. However, DCM's complexity comes at a cost. The CMC estimates a set of neurobiologically inspired parameters describing the stimulus input, connectivity, synaptic time constants, propagation delay, and pre-synaptic input. DCM additionally attempts to predict not only the voltage at the electrode level, but also at the population level, something not estimated by volume conduction. The level of detail provided by DCM requires computational time that is longer by orders of magnitude when compared to volume conduction. The computational burden required by DCM would need to be addressed when making the translation to a clinical setting, where results are time sensitive. The amount of time spent by the DCM optimization procedure would have to be reduced significantly in order to perform bedside, real-time modeling on a laptop.

DCM Shotgun increases the likelihood of converging to a model with high fidelity and has the flexibility to be implemented in other datasets recorded from an animal brain. DCM's optimization procedure is sensitive to initial parameters. Using the built-in parameters generated poor fits with low-fidelity, non-convergent solutions. The DCM Shotgun method was developed to generate "enough" initial parameters spanning the parameter space to obtain reliable convergence of the model. The number of initial parameters and the perturbation magnitude required with this dataset were determined empirically. Ten thousand initial parameter sets were utilized in DCM Shotgun. However, it is possible that a different number of initial parameter sets are needed to span the hyperplane in a different scenario or dataset. Additionally, the perturbation magnitude was chosen to perturb the built-in parameter set by 50% on the log-scale. Had the perturbation magnitude been larger, the set of initial conditions would have spanned a larger parameter space; conversely, a smaller perturbation size would result in a smaller, more densely sampled parameter space. Changing the perturbation magnitude allows investigators to either explore a larger parameter space or focus the optimization search in a particular region of the hyperplane.

DCM Shotgun could be refined by reducing the complexity of the model. The number of initial parameters and the perturbation magnitude in DCM Shotgun were constrained by the number of dimensions in the hyperplane, defined by the number of model parameters. Reducing the number of parameters that need to be optimized would facilitate the search for a high-fidelity solution. To that end, the model could be explored to lock down parameters at specific values. For example, we bootstrapped the data to estimate a distribution of parameters, illustrated in Figure 12, for one animal. Going forward, the variance of the parameter distribution could be used to determine each parameter's perturbation magnitude in DCM Shotgun. Minimal variance would indicate that a parameter could be locked down at the mean of the distribution. Alternatively, large variance values indicate that a particular parameter should be explored in other datasets. Exploring initial conditions, using the DCM Shotgun, could be valuable when little is known about the particular region of the animal's cortex being investigated.

Finally, DCM's forward model, as defined by the selected NMM, could be adapted for distinct neurophysiological recordings. DCM's forward model quantifies the contribution each local predicted-population LFP makes to the global μ ECoG electrode LFP. The forward model is estimated as part of the DCM optimization procedure, culminating in parameter variability across animals and electrodes. Going forward, investigators may choose to lock down these parameters to a set of values determined empirically or theoretically. The distribution mean estimated from each animal could be used to empirically determine a parameter set for the forward model. Alternatively, the properties of the brain tissue could be explored to theoretically estimate the forward model, as in [53]. For other research purposes, investigators may need to optimize the parameters in transforming experiments. The CMC was developed for non-human primates; in order to implement this NMM, we required the forward model to be estimated for rats. In addition, it has been shown that the neural implants, like μ ECoG arrays, elicit meningeal tissue responses [12], altering the effective electrode impedance [54, 55], which suggests that the forward model may not be static and needs to be re-estimated over time.

4.4. Sensory micro-architecture

The estimated sensory network model for two cortical sources is consistent with previous published results. Douglas and Martin [56] investigated the cat visual cortex and demonstrated how to reproduce the intracellular responses by using a conductance-based model comprised of three neural populations: inhibitory, deep pyramidal, and superficial pyramidal, clumped together with spiny stellate. In their model, the inhibition to the deep pyramidal population was stronger than the inhibition to the spiny stellate. Also, the inhibition to the deep pyramidal was stronger than the feedback to the inhibitory population. Both observations, are consistent with the resulting canonical microcircuit, estimated for all animals with DCM and illustrated in Figure 12, for one animal. The DCM-estimated relative connection strengths matched those reported by Douglas and Martin, culminating in high log-evidence, i.e., high prediction accuracy and low model complexity [39].

In order to implement DCM, many assumptions were made about the structure of the neocortex. However, the network model provides a valuable hypothesis-testing tool. We

showed that DCM accurately modeled the μ ECoG LFPs for two nodes, pointing to the existence of an underlying sensory network comprised of interacting cortical sources. A two-node network was implemented to adapt and develop the model methodology. A more complex network, comprising of additional nodes, could be implemented with DCM and could potentially better explain the underlying sensory network. However, additional DCM nodes exponentially increases the number of parameters and the dimensions defining the hyperplane where the nonlinear optimization is performed. This increase in complexity would decrease our chances of finding an optimal solution. Regardless, it would be naive to think that the rat sensory cortex is connected in such a discrete manner. The sensory cortex may be better explained as a complex distributed network. Nevertheless, DCM does provide a means to gain insight into the local μ -architecture from global events, culminating in a valuable tool that can be used to assess future hypotheses.

NMMs in DCM define a forward model in order to gain insight into the local activity from globally recorded events. DCM's implementation illustrates the second step in the two-step approach suggested by Buzsaki et al. [16], used to circumvent the ill-posed inverse problem. Boulay et al. [57] conducted an experiment that exemplifies the first step, where the forward problem is solved to establish a relationship between global and local events. Boulay et al. correlated μ ECoG LFPs to penetrating electrode LFPs recorded from the rat sensory cortex, while applying a gamma-aminobutyric acid (GABA)-A receptor antagonist to isolate excitatory components and block inhibitory connections. Boulay et al. attributed the N1 peak increase in amplitude to the depolarization of pyramidal cells and the N2 peak disappearance to corticocortical inhibition by GABA-A receptor activation. In a different experiment, Moran et al. [42] demonstrated how a network model of neurons, as suggested by Buzsaki et al., might be used to undertake the second step and use an established forward model to gain insight into local activity from global LFPs. Moran et al. applied increasing levels of anesthetic over the rat auditory cortex and simultaneously recorded the steady-state response using epidural electrodes. Moran et al. modeled the response with DCM to estimate a decrease in excitatory synaptic transmission parameters and an increase in inhibitory synaptic transmission parameters.

Using the tools we have contributed to the field, investigators will be able to efficiently undertake the second step, and make confident inferences about underlying functional networks from measurements recorded from the cortical surface. DCM-based studies [42, 32], like ours, assume the cortical-column-inspired NMMs estimate the relationship between local and global events. Using drugs as antagonists or anesthetics provides a controlled method to manipulate the brain and determine if DCM is able to predict the corresponding changes. In addition, optogenetic technology is an emergent tool that can be used to manipulate the brain in a controlled manner to determine if DCM can predict the expected changes. Our work demonstrates that μ ECoG arrays have the ability to capture the functional network structure of the sensory cortex and provides the tools necessary to investigate the underlying signal generation from μ ECoG recorded LFPs.

5. Conclusion

Sensory evoked potentials were recorded with thin-film μ ECoG arrays, and modeled using a single-source volume conduction model and a multiple-interacting-sources DCM-based network model. The volume conduction model could perform with reasonable accuracy close to the source, but failed to predict activity located more than 1500 μ m from the source. DCM was able to predict activity over the entire array with minimal error, suggesting a network model is needed to accurately predict activity. Using a criterion to evaluate model performance that is different from the one used to optimize the model gives a more diverse and robust view of the model performance. We rejected the null hypothesis of an unconnected version of DCM, with a confidence of $> 98\%$, by implementing Wilks' Theorem, under a nested hypothesis scenario. These results suggest the presence of a sensory network and that μ ECoG arrays are able to capture network activity from the neocortex.

DCM Shotgun was developed to properly initialize DCM, and can be extended to other datasets that have not yet been explored. DCM employs a complex network model of neurons that requires multiple assumptions. However, DCM can provide a valuable hypothesis testing method to explore controlled manipulation of the brain. We used DCM, under a bootstrap method, to estimate a sensory network between two cortical sources, whose structure matched previous neurophysiological modeling results. The estimated network describes the local organization of the cortex, at the level of functionally connected sources, providing a method to describe signal generators for the μ ECoG recorded LFPs.

Acknowledgments

The authors would like to acknowledge the members of the NITRO lab for their assistance in performing the surgery and collecting data. In particular, Jared Ness, for his assistance in collecting sensory evoked potentials in animals S2 and S3.

The corresponding author would like to thank the Computation and Informatics in Biology and Medicine (CIBM) funds, training and support that make it possible to conduct this work. Ricardo Pizarro is supported by the CIBM Training Program, funded by the NLM training grant 5T15LM007359.

The corresponding author would like to thank the SPM listserv for their help with troubleshooting the SPM software. In particular, we would like to thank Karl Friston, for the tireless correspondence over email that greatly helped the progress of this work.

This research was performed using the compute resources and assistance of the UW-Madison Center For High Throughput Computing (CHTC) in the Department of Computer Sciences. The CHTC is supported by UW-Madison, the Advanced Computing Initiative, the Wisconsin Alumni Research Foundation, the Wisconsin Institutes for Discovery, and the National Science Foundation, and is an active member of the Open Science Grid, which is supported by the National Science Foundation and the U.S. Department of Energy's Office of Science.

References

1. Nunez, PL., Srinivasan, R. Electric fields of the brain: the neurophysics of EEG. Oxford university press; 2006.
2. Niedermeyer, E., da Silva, FL. Electroencephalography: basic principles, clinical applications, and related fields. Lippincott Williams & Wilkins; 2005.
3. Nicolelis MA, Baccala LA, Lin R, Chapin JK. Sensorimotor encoding by synchronous neural ensemble activity at multiple levels of the somatosensory system. Science. 1995; 268(5215):1353–1358. URL <http://www.sciencemag.org/content/268/5215/1353.short>. [PubMed: 7761855]

4. O'Keefe J, Dostrovsky J. The hippocampus as a spatial map. preliminary evidence from unit activity in the freely-moving rat. *Brain research*. 1971; 34(1):171–175. URL <http://www.sciencedirect.com/science/article/pii/0006899371903581>. [PubMed: 5124915]
5. Mitzdorf U. Current source-density method and application in cat cerebral cortex: investigation of evoked potentials and EEG phenomena. *Am Physiological Soc*. 1985
6. Katzner S, Nauhaus I, Benucci A, Bonin V, Ringach DL, Carandini M. Local origin of field potentials in visual cortex. *Neuron*. 2009; 61(1):35–41. [PubMed: 19146811]
7. Lindén H, Tetzlaff T, Potjans TC, Pettersen KH, Grün S, Diesmann M, Einevoll GT. Modeling the spatial reach of the lfp. *Neuron*. 2011; 72(5):859–872. [PubMed: 22153380]
8. Nicolelis MA, Lebedev MA. Principles of neural ensemble physiology underlying the operation of brain-machine interfaces. *Nature Reviews Neuroscience*. 2009; 10(7):530–540. URL <http://www.nature.com/nrn/journal/v10/n7/abs/nrn2653.html>. [PubMed: 19543222]
9. Crone NE, Miglioretti DL, Gordon B, Sieracki JM, Wilson MT, Uematsu S, Lesser RP. Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. i. alpha and beta event-related desynchronization. *Brain*. 1998; 121(12):2271–2299. URL <http://brain.oxfordjournals.org/content/121/12/2271.short>. [PubMed: 9874480]
10. Leuthardt EC, Schalk G, Wolpaw JR, Ojemann JG, Moran DW. A brain-computer interface using electrocorticographic signals in humans. *Journal of neural engineering*. 2004; 1(2):63. URL <http://iopscience.iop.org/1741-2552/1/2/001>. [PubMed: 15876624]
11. Viventi J, Kim DH, Moss JD, Kim YS, Blanco JA, Annetta N, Hicks A, Xiao J, Huang Y, Callans DJ, et al. A conformal, bio-interfaced class of silicon electronics for mapping cardiac electrophysiology. *Science translational medicine*. 2010; 2(24):24ra22–24ra22. URL <http://stm.sciencemag.org/content/2/24/24ra22.short>.
12. Schendel AA, Nonte MW, Vokoun C, Richner TJ, Brodnick SK, Atry F, Frye S, Bostrom P, Pashaie R, Thong-pang S, et al. The effect of micro-ecog substrate footprint on the meningeal tissue response. *Journal of neural engineering*. 2014; 11(4):046011. URL <http://iopscience.iop.org/1741-2552/11/4/046011>. [PubMed: 24941335]
13. Thongpang S, Richner TJ, Brodnick SK, Schendel A, Kim J, Wilson JA, Hippensteel J, Krugner-Higby L, Moran D, Ahmed AS, et al. A micro-electrocorticography platform and deployment strategies for chronic bci applications. *Clinical EEG and Neuroscience*. 2011; 42(4):259–265. URL <http://eeg.sagepub.com/content/42/4/259.short>. [PubMed: 22208124]
14. Richner TJ, Thongpang S, Brodnick SK, Schendel AA, Falk RW, Krugner-Higby LA, Pashaie R, Williams JC. Optogenetic micro-electrocorticography for modulating and localizing cerebral cortex activity. *Journal of neural engineering*. 2014; 11(1):016010. URL <http://iopscience.iop.org/1741-2552/11/1/016010>. [PubMed: 24445482]
15. Park D-W, Schendel AA, Mikael S, Brodnick SK, Richner TJ, Ness JP, Hayat MR, Atry F, Frye ST, Pashaie R, et al. Graphene-based carbon-layered electrode array technology for neural imaging and optogenetic applications. *Nature communications*. :5.
16. Buzsaki G, Anastassiou CA, Koch C. The origin of extracellular fields and currents eeg, ecog, lfp and spikes. *Nature reviews neuroscience*. 2012; 13(6):407–420. [PubMed: 22595786]
17. Alifanov O. Solution of an inverse problem of heat conduction by iteration methods. *Journal of Engineering Physics and Thermophysics*. 1974; 26(4):471–476.
18. Einevoll GT, Pettersen KH, Devor A, Ulbert I, Halgren E, Dale AM. Laminar population analysis: estimating firing rates and evoked synaptic activity from multielectrode recordings in rat barrel cortex. *Journal of neurophysiology*. 2007; 97(3):2174–2190. [PubMed: 17182911]
19. Li X, Ascoli GA. Effects of synaptic synchrony on the neuronal input-output relationship. *Neural computation*. 2008; 20(7):1717–1731. [PubMed: 18254692]
20. Mountcastle VB. The columnar organization of the neocortex. *Brain*. 1997; 120(4):701–722. [PubMed: 9153131]
21. Hubel DH, Wiesel TN. Sequence regularity and geometry of orientation columns in the monkey striate cortex. *Journal of Comparative Neurology*. 1974; 158(3):267–293. [PubMed: 4436456]
22. Oroquieta F, Markram H, Rockland KS, et al. The neocortical column. *Frontiers in Neuroanatomy*. 2012; 6(22):1–2. [PubMed: 22291620]

23. Horton JC, Adams DL. The cortical column: a structure without a function. *Philosophical Transactions of the Royal Society B: Biological Sciences*. 2005; 360(1456):837–862.
24. da Costa NM, Martin KA. Whose cortical column would that be? *Frontiers in neuroanatomy*. :4.
25. Bastos AM, Usrey WM, Adams RA, Mangun GR, Fries P, Friston KJ. Canonical microcircuits for predictive coding. *Neuron*. 2012; 76(4):695–711. [PubMed: 23177956]
26. Nunez PL, Srinivasan R, Westdorp AF, Wijesinghe RS, Tucker DM, Silberstein RB, Cadusch PJ. Eeg coherency: I: statistics, reference electrode, volume conduction, laplacians, cortical imaging, and interpretation at multiple scales. *Electroencephalography and clinical neurophysiology*. 1997; 103(5):499–515. URL <http://www.sciencedirect.com/science/article/pii/S0013469497000667>. [PubMed: 9402881]
27. Towle VL, Carder RK, Khorasani L, Lindberg D. Electrographic coherence patterns. *Journal of Clinical Neurophysiology*. 1999; 16(6):528. URL http://journals.lww.com/clinicalneurophys/Abstract/1999/11000/Electrographic_Coherence_Patterns.5.aspx. [PubMed: 10600021]
28. Robinson P. Neurophysical theory of coherence and correlations of electroencephalographic and electrographic signals. *Journal of theoretical biology*. 2003; 222(2):163–175. URL <http://www.sciencedirect.com/science/article/pii/S0022519303000237>. [PubMed: 12727452]
29. Friston KJ, Harrison L, Penny W. Dynamic causal modelling. *Neuroimage*. 2003; 19(4):1273–1302. URL <http://www.sciencedirect.com/science/article/pii/S1053811903000207>. [PubMed: 12948688]
30. Chang J-Y, Pigorini A, Massimini M, Tononi G, Nobili L, Van Veen BD. Multivariate autoregressive models with exogenous inputs for intracerebral responses to direct electrical stimulation of the human brain. *Frontiers in human neuroscience*. :6.
31. David O, Kiebel SJ, Harrison LM, Mattout J, MKilner J, Friston KJ. Dynamic causal modeling of evoked responses in eeg and meg. *NeuroImage*. 2006; 30(4):1255–1272. URL <http://www.sciencedirect.com/science/article/pii/S1053811905008013>. [PubMed: 16473023]
32. Bastos LV, MR, BCA, FP, FKJ. A dcm study of spectral asymmetries in feedforward and feedback connections between visual areas v1 and v4 in the monkey. *NeuroImage*. 2015; 108
33. Hall RD, Lindholm EP. Organization of motor and somatosensory neocortex in the albino rat. *Brain Research*. 1974; 66(1):23–38.
34. Gage GJ, Stoetzn CR, Richner T, Brodnick SK, Williams JC, Kipke DR. Surgical implantation of chronic neural electrodes for recording single unit activity and electrographic signals. *Journal of visualized experiments: JoVE*. (60)
35. Guide, MU. The mathworks, Inc; Natick, MA: p. 5
36. Bloomfield, P. Fourier analysis of time series: an introduction. John Wiley & Sons; 2004.
37. He, B., Musha, T., Okamoto, Y., Homma, S., Nakajima, Y., Sato, T. Electric dipole tracing in the brain by means of the boundary element method and its accuracy; *Biomedical Engineering, IEEE Transactions on BME-34*. 1987. p. 406-414. URL http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=4122562
38. Friston, KJ. *Neuroscience Databases*. Springer; 2003. Statistical parametric mapping; p. 237-250. URL http://link.springer.com/chapter/10.1007/978-1-4615-1079-6_16
39. Penny WD, Stephan K, Mechelli A, Friston K. Comparing dynamic causal models. *Neuroimage*. 2004; 22(3):1157–1172. URL <http://www.sciencedirect.com/science/article/pii/S1053811904001648>. [PubMed: 15219588]
40. Babajani-Feremi A, Soltanian-Zadeh H. Multi-area neural mass modeling of eeg and meg signals. *Neuroimage*. 2010; 52(3):793–811. [PubMed: 20080193]
41. Leff AP, Schofield TM, Stephan KE, Crinion JT, Friston KJ, Price CJ. The cortical dynamics of intelligible speech. *The Journal of Neuroscience*. 2008; 28(49):13209–13215. [PubMed: 19052212]
42. Moran RJ, Jung F, Kumagai T, Endepols H, Graf R, Dolan RJ, Friston KJ, Stephan KE, Tittgemeyer M. Dynamic causal models and physiological inference: a validation study using isoflurane anaesthesia in rodents. *PloS one*. 2011; 6(8):e22790. [PubMed: 21829652]
43. Haykin, S., Van Veen, B. *Signals and systems*. John Wiley & Sons; 2007.

44. Wilks SS. The large-sample distribution of the likelihood ratio for testing composite hypotheses. *The Annals of Mathematical Statistics*. 1938; 9(1):60–62.
45. Kay, SM. *Fundamentals of statistical signal processing, volume II: detection theory*. Prentice Hall; 1998.
46. Efron, B., Tibshirani, RJ. *An introduction to the bootstrap*. CRC press; 1994.
47. Slutzky MW, Jordan LR, Krieg T, Chen M, Mogul DJ, Miller LE. Optimal spacing of surface electrode arrays for brain–machine interface applications. *Journal of neural engineering*. 2010; 7(2):026004.
48. Burneo JG, Steven DA, McLachlan RS, Parrent AG. Morbidity associated with the use of intracranial electrodes for epilepsy surgery. *Canadian Journal of Neurological Sciences/Journal Canadien des Sciences Neurologiques*. 2006; 33(02):223–227. [PubMed: 16736735]
49. Krakow K. Imaging epileptic activity using functional mri. *Neurodegenerative Diseases*. 2008; 5(5):286–295. [PubMed: 18520163]
50. Pizarro R, Nair V, Meier T, Holdsworth R, Tunnell E, Rutecki P, Sillay K, Meyerand M, Prabhakaran V. Delineating potential epileptogenic areas utilizing resting functional magnetic resonance imaging (fmri) in epilepsy patients. *Neurocase*. doi.
51. Stead M, Bower M, Brinkmann BH, Lee K, Marsh WR, Meyer FB, Litt B, Van Gompel J, Worrell GA. Microseizures and the spatiotemporal scales of human partial epilepsy. *Brain*. 2010;awq190.
52. Viventi J, Kim DH, Vigeland L, Frechette ES, Blanco JA, Kim YS, Avrin AE, Tiruvadi VR, Hwang SW, Vanleer AC, et al. Flexible, foldable, actively multiplexed, high-density electrode array for mapping brain activity in vivo. *Nature neuroscience*. 2011; 14(12):1599–1605. [PubMed: 22081157]
53. Foutz TJ, Arlow RL, McIntyre CC. Theoretical principles underlying optical stimulation of a channelrhodopsin-2 positive pyramidal neuron. *Journal of neurophysiology*. 2012; 107(12):3235–3245. [PubMed: 22442566]
54. Williams JC, Hippensteel JA, Dilgen J, Shain W, Kipke DR. Complex impedance spectroscopy for monitoring tissue responses to inserted neural implants. *Journal of neural engineering*. 2007; 4(4): 410. [PubMed: 18057508]
55. Sillay KA, Rutecki P, Cicora K, Worrell G, Drazkowski J, Shih JJ, Sharan AD, Morrell MJ, Williams J, Wingeier B. Long-term measurement of impedance in chronically implanted depth and subdural electrodes during responsive neurostimulation in humans. *Brain stimulation*. 2013; 6(5): 718–726. [PubMed: 23538208]
56. Douglas RJ, Martin K. A functional microcircuit for cat visual cortex. *The Journal of Physiology*. 1991; 440(1):735–769. [PubMed: 1666655]
57. Boulay, CB. PhD thesis. University at Albany, State University of New York; 2011. The interactions between motor cortex and spinal cord during acquisition and performance of simple motor skills and their implications for rehabilitation.

A. Wilks' Theorem

A hypothesis-testing scenario was implemented, to define a composite LRT, that determines if the unconnected-DCM could perform as well as the connected-DCM, in predicting the μ ECoG potentials. We implemented Wilks' theorem [44], where the connected and unconnected scenarios are treated as a composite hypothesis testing problem. The null hypothesis, H_0 , was defined to be the unconnected-DCM and the alternative hypothesis, H_1 , was defined to be the connected-DCM:

$$H_0: \mathbf{v}_{1j}, \mathbf{v}_{2j}, \dots, \mathbf{v}_{Mj} \stackrel{iid}{\sim} p(\mathbf{v}_j | \theta_{j,0}),$$

where $\theta_{j,1}, \dots, \theta_{j,l} \in \mathbb{R}^l$ are estimated and $[\theta_{j,l+1}, \dots, \theta_{j,m}]^T = \mathbf{0}^{m-l}$, extrinsic set to 0

$$H_1: \mathbf{v}_{1j}, \mathbf{v}_{2j}, \dots, \mathbf{v}_{Mj} \stackrel{iid}{\sim} p(\mathbf{v}_j | \theta_{j,1}),$$

where $\theta_{j,1} \in \mathbb{R}^m$ are all estimated

and the parametric density $p(\mathbf{v}_j | \theta_{j,h})$ has the same form in either hypothesis, $h = \{0, 1\}$. The family of models in H_0 are a subset of those in H_1 , and the two hypotheses are nested, a key condition that needs to be satisfied in order to implement Wilks' theorem.

The generalized likelihood ratio test (GLRT), $\hat{\Lambda}(\mathbf{v}_j)$, is commonly used in composite hypothesis testing to determine if H_0 can be rejected, by comparing to a predetermined threshold γ [45]. In the GLRT, unknown parameters are replaced by estimates, like the maximum likelihood estimate (MLE), that maximize the observed potential $\mathbf{v}_j$ [45]. The GLRT was defined in terms of the parametric density as:

$$\hat{\Lambda}(\mathbf{v}_j) = \frac{\max_{\theta_{j,1}} p(\mathbf{v}_j | \theta_{j,1})}{\max_{\theta_{j,0}} p(\mathbf{v}_j | \theta_{j,0})} \underset{H_0}{\overset{H_1}{\gtrless}} \gamma \quad (\text{A.1})$$

To estimate the parametric density $p(\mathbf{v}_j | \theta_{j,h})$, we made the following assumption. The trial $\mathbf{v}_{ij}$ can be written as a sum of the model estimate from hypothesis h , $\hat{\mathbf{v}}_{j,h}$ plus some gaussian distributed noise $\mathbf{W}_i$:

$$v_{ij}[n] = \hat{v}_{j,h}[n] + W_i[n] \quad (\text{A.2})$$

where $n = [\frac{t_0}{T_d}, \frac{t_1}{T_d}]$ is a time window defined *a priori*, the noise $\mathbf{W}_i \sim \mathcal{N}(0, \sigma_{j,h}^2 \mathbb{I}_L)$, and $L = \frac{t_1 - t_0}{T_d}$, is the number of samples in the time window. Assuming the noise is gaussian distributed, permitted the parametric density to have the same form in each hypothesis and be estimated for hypothesis h , as a product of gaussians:

$$\begin{aligned} p(\mathbf{v}_j | \theta_{j,h}) &= p(\mathbf{v}_{1j}, \dots, \mathbf{v}_{Mj} | \theta_{j,h}) = \prod_{i=1}^M p(\mathbf{v}_{ij} | \theta_{j,h}) \\ &= \left(\frac{1}{2\pi\sigma_{j,h}^2} \right)^{\frac{ML}{2}} e^{-\frac{1}{2\sigma_{j,h}^2} \sum_i (\mathbf{v}_{ij} - \hat{\mathbf{v}}_{j,h})^T (\mathbf{v}_{ij} - \hat{\mathbf{v}}_{j,h})} \end{aligned} \quad (\text{A.3})$$

The formulation of the parametric density in (A.3) was substituted into (A.1) to obtain an explicit form of the GLRT:

$$\begin{aligned}
\hat{\Lambda}(\mathbf{v}_j) &= \frac{\max_{\theta_{j,1}} p(\mathbf{v}_j | \theta_{j,1})}{\max_{\theta_{j,0}} p(\mathbf{v}_j | \theta_{j,0})} \\
&= \left(\frac{\sigma_{j,0}^2}{\sigma_{j,1}^2} \right)^{\frac{ML}{2}} \frac{e^{-\frac{1}{2\sigma_{j,1}^2} \sum_i (\mathbf{v}_{ij} - \hat{\mathbf{v}}_{j,1})^T (\mathbf{v}_{ij} - \hat{\mathbf{v}}_{j,1})}}{e^{-\frac{1}{2\sigma_{j,0}^2} \sum_i (\mathbf{v}_{ij} - \hat{\mathbf{v}}_{j,0})^T (\mathbf{v}_{ij} - \hat{\mathbf{v}}_{j,0})}} \quad (\text{A.4})
\end{aligned}$$

All parameters in (A.4) are either known or have been estimated, except for $\sigma_{j,h}^2$. In the GLRT, unknown parameters are replaced by the MLE, $\hat{\sigma}_{j,h}^2$, derived to be:

$$\hat{\sigma}_{j,h}^2 = \frac{1}{ML} \sum_{i=1}^M (\mathbf{v}_{ij} - \hat{\mathbf{v}}_{j,h})^T (\mathbf{v}_{ij} - \hat{\mathbf{v}}_{j,h}) \quad (\text{A.5})$$

Plugging (A.5) back into (A.4), reduces the GLRT to:

$$\begin{aligned}
\hat{\Lambda}(\mathbf{v}_j) &= \left(\frac{\sigma_{j,0}^2}{\sigma_{j,1}^2} \right)^{\frac{ML}{2}} \frac{e^{-\frac{1}{2\sigma_{j,1}^2} \sum_i (\mathbf{v}_{ij} - \hat{\mathbf{v}}_{j,1})^T (\mathbf{v}_{ij} - \hat{\mathbf{v}}_{j,1})}}{e^{-\frac{1}{2\sigma_{j,0}^2} \sum_i (\mathbf{v}_{ij} - \hat{\mathbf{v}}_{j,0})^T (\mathbf{v}_{ij} - \hat{\mathbf{v}}_{j,0})}} \\
&= \left(\frac{\sigma_{j,0}^2}{\sigma_{j,1}^2} \right)^{\frac{ML}{2}} \frac{e^{-\frac{ML}{2} \frac{\sum_i (\mathbf{v}_{ij} - \hat{\mathbf{v}}_{j,1})^T (\mathbf{v}_{ij} - \hat{\mathbf{v}}_{j,1})}{\sum_i (\mathbf{v}_{ij} - \hat{\mathbf{v}}_{j,1})^T (\mathbf{v}_{ij} - \hat{\mathbf{v}}_{j,1})}}}{e^{-\frac{ML}{2} \frac{\sum_i (\mathbf{v}_{ij} - \hat{\mathbf{v}}_{j,0})^T (\mathbf{v}_{ij} - \hat{\mathbf{v}}_{j,0})}{\sum_i (\mathbf{v}_{ij} - \hat{\mathbf{v}}_{j,0})^T (\mathbf{v}_{ij} - \hat{\mathbf{v}}_{j,0})}} \\
&= \left(\frac{\sigma_{j,0}^2}{\sigma_{j,1}^2} \right)^{\frac{ML}{2}} \frac{e^{-\cancel{ML/2}}}{e^{-\cancel{ML/2}}} \\
&= \left(\frac{\hat{\sigma}_{j,0}^2}{\hat{\sigma}_{j,1}^2} \right)^{\frac{ML}{2}} \quad (\text{A.6})
\end{aligned}$$

We implemented Wilks' theorem to derive a composite LRT that is compared to a predetermined threshold, to conclude if we can reject H_0 . Wilks' theorem states that under the nested hypotheses scenario, when the observation is distributed as a model in H_0 , i.e., $\mathbf{v}_j \sim p(\mathbf{v}_j | \theta_{j,0})$, the GLRT has the following asymptotic distribution:

$$2 \log \hat{\Lambda}(\mathbf{v}_j) \stackrel{D}{\sim} \chi_{m-l}^2 \quad (\text{A.7})$$

where m and l are the number of parameters estimated under each hypothesis. We plugged (A.6) into (A.7) to define *compositeLRT*:

$$compositeLRT = ML \log \frac{\hat{\sigma}_{j,0}^2}{\hat{\sigma}_{j,1}^2} \stackrel{D}{\sim} \chi_{m-l}^2 \quad (\text{A.8})$$

We reject H_0 , when *compositeLRT* exceeds the threshold γ , whose value was computed *a priori*, to ensure the probability of false alarm (P_{FA}) $< \alpha$, i.e., $P_{FA} = \int_{\gamma}^{\infty} \chi_{m-l}^2[x] dx < \alpha$. The connected-DCM estimated $m = 45$ parameters while the unconnected-DCM estimated $l = 38$ parameters. The threshold was computed with Matlab's function `chi2inv`, $m - l = 7$ degrees of freedom, and $\alpha = 0.05$, to obtain $\gamma = 14.1$.

B. DCM shotgun results

We summarized the results generated by the proposed DCM shotgun in concert with bootstrapping approach into two tables. Providing these values can be useful for future studies looking to explore similar techniques or brain regions explored in this manuscript. Table B.3 summarizes the forward model as generated by DCM shotgun and bootstrapping. The forward model parameters are the forward model by layer, the gain by each of the two channels, and finally the resulting gain obtained by multiplying the first two values. Table B. 4 summarizes the initial parameters as generated by DCM shotgun and bootstrapping. These parameters generated potentials at the sensor level with small NMSE, high log evidence and can provide a good starting point for future studies.

Table B.3

DCM Shotgun generated forward model for the CMC in animal S2 in electrodes $\{A, B\} = \{3, 16\}$

Gain parameter	value $\pm$ std
Forward model by layer	
ss	0.20 $\pm$ 0.00
sp	0.16 $\pm$ 0.01
dp	-0.90 $\pm$ 0.20
Gain by channel	
A	17.06 $\pm$ 5.04
B	-19.69 $\pm$ 7.02
Resulting gain by layer	
A (ss)	3.41 $\pm$ 1.01
B (ss)	-3.94 $\pm$ 1.40
A (sp)	2.69 $\pm$ 0.73
B (sp)	-3.10 $\pm$ 1.02
A (dp)	-16.20 $\pm$ 6.83
B (dp)	18.92 $\pm$ 8.78

sp - superficial pyramidal, ss - spiny stellate, dp - deep pyramidal

NOTE: inhibitory interneurons do not contribute to potential at sensor level

Table B.4

DCM Shotgun generated initial parameters for the CMC in animal S2 in electrodes $\{A,B\} = \{3,16\}$

CMC parm #	location detail	value± std
A2 *	A (sp) ==> B (ss)	1.14 ±0.02
A3 *	B (sp) ==> A (ss)	1.60 ±0.23
A6 *	A (sp) ==> B (dp)	0.79 ±0.25
A7 *	A (sp) ==> B (dp)	1.31 ±0.60
A10 *	B (sp) <= A (dp)	1.34 ±0.34
A11 *	A (sp) <= B (dp)	0.84 ±0.29
A14 *	B (ii) <= A (dp)	1.14 ±0.40
A15 *	A (ii) <= B (dp)	1.16 ±0.36
C1	A input	1.82 ±0.19
T1	A ss	1.33 ±0.23
T2	B ss	1.61 ±0.16
T3	A sp	0.62 ±0.02
T4	B sp	1.43 ±0.08
T5	A ii	1.00 ±0.27
T6	B ii	1.14 ±0.12
T7	A dp	0.71 ±0.13
T8	B dp	0.83 ±0.02
D1		1.19 ±0.03
D2		1.11 ±0.11
D3		1.59 ±0.18
D4		1.64 ±0.03
S1		1.59 ±0.10

CMC parm#	location detail	value± std
R1		1.21 ±0.00
R2		0.17 ±0.00
	A ss—	
G1	>ss	0.59 ±0.10
G2	B ss—>ss	1.05 ±0.18
G3 *	A sp—>ss	0.67 ±0.03
G4 *	B sp—>ss	0.86 ±0.10
G5 *	A ii—>ss	0.86 ±0.07
G6 *	B ii—>ss	1.14 ±0.18
G7	A ii—>ii	0.72 ±0.20
G8	B ii—>ii	1.25 ±0.38
G9 *	A ss—>ii	1.04 ±0.15

CMC parm#	location detail	value± std
G10 *	B ss→ii	1.86 ±0.40
G11 *	A dp→ii	1.06 ±0.11
G12 *	B dp→ii	1.12 ±0.16
G13	A sp→sp	0.96 ±0.07
G14	B sp→sp	0.72 ±0.06
G15 *	A ss→sp	1.29 ±0.29
G16 *	B ss→sp	1.78 ±0.60
G17 *	A ii→dp	1.58 ±0.80
G18 *	B ii→dp	1.98 ±0.16
G19	A dp→dp	0.87 ±0.12
G20	B dp→dp	1.38 ±0.34

The numbering for the parameters follows the SPM convention, e.g.,

$$A = \left\{ \begin{bmatrix} A1 & A2 \\ A3 & A4 \end{bmatrix}, \begin{bmatrix} A5 & A6 \\ A7 & A8 \end{bmatrix}, \begin{bmatrix} A9 & A10 \\ A11 & A12 \end{bmatrix}, \begin{bmatrix} A13 & A14 \\ A15 & A16 \end{bmatrix} \right\}, D = \begin{bmatrix} D1 & D2 \\ D3 & D4 \end{bmatrix}$$

and so on.

* displayed in Figure 12, ==> feedforward connection, <= = feedback connection, -> intrinsic connection, sp - superficial pyramidal, ss - spiny stellate, dp - deep pyramidal, ii - inhibitory interneurons, A - extrinsic connections, C - stimulus input, T - synaptic time constant, G -intrinsic connections, D - propagation delays, S - sigmoid activation function, R - slope of sigmoid

NOTE: electrode A and extrinsic connection parameter A are two separate concepts

Highlights

- Activity at electrodes located $< 1000 \mu\text{m}$ can be predicted using the single source volume conduction model with acceptable error, but DCM more accurately describes the potentials observed at electrode distances greater than $1500 \mu\text{m}$.
- An initialization strategy called DCM Shotgun was developed to find a set of initial parameters that result in high probability of obtaining a high-fidelity DCM.
- The relevance of the network component in DCM was assessed to be key in modeling the recorded LFPs, strongly pointing to the presence of a network, and that μECoG arrays can capture network activity from the neocortex.
- The estimated sensory network model illustrates the local organization of the cortex and provides possible signal generators for the μECoG recorded LFPs.

Figure 1. MicroECoG arrays were surgically implanted on the sensory cortex of the rat brain for recordings and a surface electrode was attached to the right leg for stimulation.

Figure 2.

An electrical stimulation artifact is removed, using a procedure defined in (2), that uses a median filter and a raised cosine window.

Figure 3.

Stimulus-triggered average clean potentials from two electrodes are plotted versus time with the standard deviation (SD) and the standard error of the mean (SEM) from all four animals. The inset in the bottom left corner of each plot identifies the electrode from the animal's grid. The electrode with the strongest response was chosen in the left column. Electrode #16 was chosen, in the right column, to represent a weak response.

Figure 4.

The volume conduction model is a static representation of the activity, with no temporal dynamics. Activity in the two electrodes are a linear representation of the activity generated by a single local cortical generator, graphically represented by an electric dipole within a cortical column.

Figure 5.

Extrinsic connections of the CMC are shown for two sources, modeled as cortical columns. The feedforward and feedback connections are illustrated as solid and dashed lines, respectively. The potentials in electrodes A and B are estimated with a forward model from the potentials in each population: *ii* - inhibitory interneurons, *sp* - superficial pyramidal, *ss* - spiny stellate, and *dp* - deep pyramidal. The spiny stellate population of cortical column A is the stimulus input location, highlighted in pink.

Figure 6.

Intrinsic connections of the CMC are estimated for each independent source, modeled as a cortical column. The populations are not all connected to each other directly and some populations can act as mediators. Self connected parameters are not shown, for simplicity.

Figure 7.

The full parameter space was explored using the two part method named dynamic causal model (DCM) Shotgun: (I) 10,000 sets of parameters were generated to initialize DCM for one example electrode pair, defined to be primary electrode A and secondary electrode $B = 16$, located on the opposite side of the array. (II) The top 50 solutions were used as candidate initial parameter sets, for the remaining 14 electrode pairs. This procedure generated a unique winning model for each two-node network, 15 winning models in total for each animal.

Figure 8.

This flowchart illustrates how bootstrapping was utilized to assess the stability of the dynamic causal model (DCM) parameter estimates: (I) DCM Shotgun (Figure 7) was employed to find top 50 solutions on entire dataset from one electrode pair (II) The data was bootstrapped 100 times and the top 50 solutions from stage I was utilized to initialize DCM in stage II

Figure 9.

The normalized mean-square error (NMSE) values computed from model fits in all secondary electrodes are plotted above versus the physical center-to-center distance between the primary and secondary electrodes. Volume conduction (VC) generated NMSE are denoted with red stars, and dynamic causal model (DCM) generated NMSE are denoted with black open circles, for animals: (a) S1, (b) S2, (c) S3*, and (d) S4. A linear fit was computed and plotted for both volume conduction and DCM in corresponding colors.

* two VC datapoints in (c) are > 100% NMSE.

Figure 10.

Stimulus-triggered average potentials along with volume conduction fits and connected-DCM fits are plotted above versus time, from three different electrodes of the array for each animal, shown as rows: (a) S1, (b) S2, (c) S3, and (d) S4. (left column) Average potential from the primary electrode ∇_A , is plotted in yellow. The DCM fit is shown in black to highlight quality of fit. (center column) Average potential from a secondary *near* electrode ∇_B , located $750 \mu m$ from the primary electrode is shown in green. The volume conduction model fit is depicted in red and DCM fit in black. (right column) Average potential from a secondary *distant* electrode ∇_B , located over $2000 \mu m$ from the primary electrode is shown in blue. The NMSE defined in (3) computed for both models is shown on the bottom right corner of the secondary electrode plots. The inset in each plot identifies the electrode used as primary (yellow), secondary *near* (green) and secondary *distant* (blue). Mean - average

potential, VC - volume conduction, DCM - dynamic causal model, and NMSE - normalized mean-square error

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 11.

The dynamic causal model (DCM) generated waveforms are plotted versus time for the connected-DCM (Conn) and the unconnected-DCM (Unconn) along with the average potentials from the primary electrode in all animals. The connected-DCM model fits were generated from one example electrode pair, defined in Figure 7. The average potential ∇_A , is plotted in yellow, as a function of time. The two DCM fits are plotted in different colors and line types, denoted in the legend. The inset on the bottom left identifies the electrode from the animal's grid. The *compositeLRT* was defined in (A.8) between $[t_0, t_1]$. The normalized mean-square error (NMSE) is reported for each model at the bottom right of each figure.

Figure 12.

Resultant canonical microcircuit between primary, *A*, and secondary, *B*, cortical sources estimated as $\mu_p \pm \sigma_p$ from 100 bootstrap subsets from animal S2. (a) Primary and secondary electrodes, highlighted as yellow and blue, respectively, in the inset grid at the top center. The strength of extrinsic connections μ_p are weighted on a greyscale bar on the right side. Feedforward connections are illustrated as solid lines and feedback connections as dashed lines. The strength of intrinsic connections μ_p are shown for the (b) primary and (c) secondary electrodes and weighted with the line thickness. The spiny stellate population of cortical column A, highlighted in pink, indicates the location of the input stimulus into the network.

Table 1

Cortical column classified by diameter [25]

Column type	diameter (μm)
minicolumn	50 – 60
cortical column	300 – 400
hypercolumn	500 – 1000

Table 2

Hypothesis-testing results presented for the *compositeLRT*, defined in (A.8), and computed between $[t_0, t_1]$

<i>animal</i>	S1	S2	S3	S4
<i>M</i>	55	1000	191	82
t_0 (ms)	10	10	10	10
t_1 (ms)	100	60	40	60
<i>L</i>	69	38	23	38
<i>compositeLRT</i>	16.9	141	1116	164
p-value	0.0182	$<10^{-10}$	$<10^{-10}$	$<10^{-10}$

M - # of trials, t_0 - start time, t_1 - end time,

L - # of samples, and *compositeLRT* - composite likelihood ratio test