
INFERRING LARGE-SCALE STRUCTURAL CONNECTIVITY FROM LOCAL ACTIVITY IN A MODEL OF THE MOUSE LARGE-SCALE CORTICAL NETWORK

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ABSTRACT

1 Inferring the structural connectivity from electrophysiological measurements is a
2 fundamental challenge in systems neuroscience. Directed functional connectivity
3 measures, such as the Generalized Partial Directed Correlation (GPDC), provide
4 estimates of the causal influence between areas. However, such methods have a limi-
5 tation because their estimates depend on the number of brain regions simultaneously
6 recorded. We analyzed this problem by evaluating the effectiveness of GPDC to
7 estimate the connectivity of a ground-truth, data-constrained computational model of
8 a large-scale mouse cortical network. The model contains 19 cortical areas modeled
9 using spiking neural populations, and directed weights for long-range projections
10 were obtained from a tract-tracing cortical connectome. We show that the GPDC
11 estimates correlate positively with structural connectivity. Moreover, the correlation

between structural and directed functional connectivity is comparable even when using only a few cortical areas for GPDC estimation, a typical scenario for electrophysiological recordings. Finally, GPDC measures also provided a measure of the flow of information among cortical areas.

1 Introduction

The communication between brain regions is often analyzed through structural and functional connectivity [1]. The former refers to anatomical connections between brain regions generally quantified using tracer injections or diffusion magnetic resonance imaging [2]. The map of these connections is called “connectome” [3], whose analysis includes methods to evaluate the networks defined by nodes (brain regions) and edges (synapses) [4, 5]. Functional connectivity evaluates brain communication from statistical relations between recorded brain signals [6, 1]. Particularly, directed functional connectivity methods use the concept of causality to infer both the intensity and the direction of the connections between brain regions [7]. Even though there is some association between structural and functional connectivity, the relationship between them is not straightforward [1]. While the former is practically static and compose the map of possible pathways for information flow between brain regions, the latter changes continuously and depends, for example, on the dynamical states of brain regions, noise, and strength of structural connections [8].

During electrophysiological procedures, researchers typically record brain signals using electrodes positioned in different depths of brain regions. Even with the improvement in technologies for recording signals, it is usually possible to record signals only from a few areas compared to the number of sources of activity in the brain [9, 10, 11]. Thus, the functional connectivity analysis presents a problem because many regions that may perform as common inputs [7], and influence indirectly other regions [12, 6] are not recorded. Therefore, the comparison between structural and functional connectivity is problematic since spurious inferred causality relations can lead to misinterpretations of electrophysiological data.

Some simulation studies evaluated the relation between directed functional connectivity and structural connections [8, 13, 14, 15]. However, most of these studies used either autoregressive models for the dynamics of each node [16] or rate-based models [13]. These studies provided important steps towards evaluating the reliability of causality measures, but they are still distant from laboratory experimental conditions.

In this work, we investigated the relationship between directed functional connectivity and structural connectivity in a large-scale spiking neuronal network model of the cortex, derived from a cortical connectome of the mouse obtained using tracer injections [17]. Causality measures obtained using GPDC explained most of the variance of structural connection strengths. The mean correlation remained high ($r > 0.6$) even when only a few cortical areas were considered in the GPDC calculation, indicating that this causality measure provides reliable results in typical experimental conditions in which only recordings from a subset of areas are available.

2 Methods

2.1 Neuron model

We modeled the neurons using a single-compartment Hodgkin–Huxley-type model, where the membrane potential of the i -th neuron described by,

$$C_m \frac{dV_i}{dt} = -g_{Na} m_i^3 h_i (V - E_{Na}) - g_K n_i^4 (V - E_K) - g_L (V - E_L) + I_{ext,i} + I_{syn,i}, \quad (1)$$

the membrane capacitance C_m is 0.50 nF (0.125 nF) for excitatory (inhibitory) neurons. The maximal conductances values were $g_{Na} = 12.5 \mu\text{S}$, $g_K = 4.74 \mu\text{S}$ and $g_L = 0.025 \mu\text{S}$. The reversal potentials $E_{Na} = 40 \text{ mV}$, $E_K = -80 \text{ mV}$, and $E_L = -65 \text{ mV}$ correspond to the sodium, potassium and leakage channel, respectively [18]. The dynamics of the voltage-gated ion channels are described by activation and inactivation variables m , n , and h , where m and n accounts for the

58 dynamics of Na channels and h for K channels. The probability that an ion channel is open evolves
59 according to a set of ordinary differential equations [19],

$$\frac{dm}{dt} = \alpha_m(V)(1 - m) - \beta_m(V)m, \quad (2)$$

$$\frac{dh}{dt} = \alpha_h(V)(1 - h) - \beta_h(V)h, \quad (3)$$

$$\frac{dn}{dt} = \alpha_n(V)(1 - n) - \beta_n(V)n, \quad (4)$$

60 where,

$$\alpha_m(V) = 0.1 \frac{(V+16)}{1 - \exp(-(V+16)/10)}, \quad (5)$$

$$\beta_m(V) = 4 \exp(-(V + 41)/18), \quad (6)$$

$$\alpha_h(V) = 0.07 \exp(-(V + 30)/20), \quad (7)$$

$$\beta_h(V) = [1 + \exp(-V/10)]^{-1}, \quad (8)$$

$$\alpha_n(V) = 0.01 \frac{(V+20)}{1 - \exp(-(V+20)/10)}, \quad (9)$$

$$\beta_h(V) = 0.125 \exp(-(V + 30)/80), \quad (10)$$

61 The parameters used in this neuron model was previously reported and applied in some studies that
62 modeled cortical neuronal populations. [20, 19, 21]

63 2.2 Spiking neuronal population model

64 Each spiking neuronal population was composed of 2000 neurons, 1600 excitatory and 400 in-
65 hibitory. Neurons within each spiking neuronal population were randomly connected with proba-
66 bility $p_{\text{intra}} = 10\%$. The synaptic current I_{syn} that arrives to postsynaptic neuron i is modeled by,

67

$$I_{\text{syn},i}(t) = \sum_{j \in \text{presyn}} g_{\text{syn},i,j}(t) [E_{\text{syn}} - V_i(t)], \quad (11)$$

68 where the index j represent a presynaptic neuron connected to neuron i and the sum over j accounts
 69 for all the synapses that impinge on neuron i . E_{syn} is the synaptic reversal potential which is 0 mV
 70 for excitatory and -70 mV for inhibitory synapses. The dynamics of synaptic conductance $g_{\text{syn},i,j}$
 71 is described by an exponential function as follows [22],

$$\frac{dg_{\text{syn},i,j}}{dt} = -\frac{g_{\text{syn},i,j}}{\tau}. \quad (12)$$

72 When a presynaptic neuron j fires a spike, a synaptic weight w is added on the synaptic conductance
 73 $g_{\text{syn},i,j}$ after the axonal delay, which was set as 1 ms [19]. The value of w depends on the excita-
 74 tory/inhibitory nature of the presynaptic and postsynaptic neurons. The synaptic time constant τ is
 75 2 ms and 8 ms for excitatory and inhibitory synapses, respectively. Furthermore, all neurons receive
 76 a background input given by a heterogeneous Poisson-process spiking activity with a rate of 7.3
 77 kHz [19]. The effect of the background input in each neuron is an excitatory synaptic current. To
 78 add heterogeneity in our model, all synaptic weights w for recurrent connections and background
 79 input were taken from a Gaussian distribution (Table 1).

Table 1: Synaptic weights for intra-areal connections. Mean synaptic weight \bar{w} and standard deviation σ_w for all possible synapses. E, I, and Input represent excitatory neurons, inhibitory neurons, and external input, respectively. The arrow indicates the direction of the connection.

Synapses	\bar{w} (nS)	σ_w (nS)
$E \rightarrow E$	2.5	1.0
$E \rightarrow I$	2.5	1.0
$I \rightarrow E$	240	10
$I \rightarrow I$	240	10
$Input \rightarrow E$	3.2	1.0
$Input \rightarrow I$	3.2	1.0

2.3 Mouse large-scale cortical network

The mouse cortex's large-scale network model comprises 19 cortical areas where a spiking neuronal population models each area with long-range and recurrent synapses. Parameters related to recurrent synapses were described in the previous session. Neurons from different areas are randomly connected with probability $p_{\text{inter}} = 5\%$. The synaptic weights between cortical areas are based on the recently published anatomical connectivity dataset for the mouse cortex [17] obtained by retrograde tracer injections [23]. This technique consists in injecting a tracer that flows from the target area to the cell bodies, allowing to identify neurons projecting to the target area. The Fraction of Labeled Neurons (FLN) was measured as the ratio of the number of labeled neurons in a source area to the total quantity of labeled neurons in all source areas [24, 25]. The synaptic weights for directed long-range connections are the FLNs scaled by the global scaling parameters $\mu_E = 50$ and $\mu_I = 25$,

$$w_{\text{lr},E}^i = \mu_E \sum_j^N \text{FLN}_{i,j} \quad (13)$$

$$w_{\text{lr},I}^i = \mu_I \sum_j^N \text{FLN}_{i,j}. \quad (14)$$

Long-range connections as excitatory, targeting either excitatory or inhibitory neurons with synaptic weight, $w_{\text{lr},E}^i$, and $w_{\text{lr},I}^i$, respectively. The index j represents the source area, i the target area, and N is the total number of simulated cortical areas. The axonal delay for long-range connections is given by the ratio between the anatomical distance estimates between cortical areas and the conduction speed set as 3.5 m/s [26].

2.4 LFP signal

We computed the local field potential (LFP) signal as a sum of the currents' absolute values acting upon excitatory neurons in a spiking neuronal population [27, 28]. Thus, for a cortical area in our

100 model, the LFP signal will be given by,

$$\text{LFP} = R \frac{\sum_i^{N_E} (|I_{E,i}| + |I_{I,i}| + |I_{\text{bkg},i}|)}{N_E}, \quad (15)$$

101 $I_{E,i}$ accounts for both the local (within population) and global (inter-areal projections) excitatory
 102 synaptic currents, while $I_{I,i}$ corresponds to the local inhibitory current. $I_{\text{bkg},i}$ is the synaptic current
 103 related to the background Poisson input. R represents the resistance of a typical electrode used for
 104 extracellular measurements, here chosen to be 1 M Ω [19]. N_E is the number of excitatory neurons
 105 in each neuronal population.

106 The mean was subtracted from the simulated LFP signal. The resultant signal was filtered using a
 107 low-pass filter in 1 kHz to avoid aliasing and downsampled to 1 kHz.

108 2.5 Generalized partial directed coherence

109 Generalized partial directed coherence (GPDC) is a frequency-domain method of directed functional
 110 connectivity established on multivariate vector autoregressive (MVAR) model [29]. Considering
 111 that LFP signals from all areas in the model are represented by a set $\mathbf{x}(t) = [x_1(t) \cdots x_N(t)]^T$ of
 112 simultaneously observed time series. The MVAR model for $\mathbf{x}(t)$ is defined as:

$$\mathbf{x}(t) = \sum_{k=1}^p \mathbf{A}_k \mathbf{x}(t-k) + \epsilon(t) \quad (16)$$

113 where p is the MVAR model order. \mathbf{A}_k are coefficient matrices in which the element $a_{ij}^{(k)}$ define the
 114 effect of $x_j(t-k)$ on $x_i(t)$. The term $\epsilon(t)$ is a vector of N white noises with covariance matrix Σ .
 115 The GPDC from the time series x_j to the time series x_i at frequency λ is defined as,

$$\text{GPDC}_{ij}(\lambda) = \left| \frac{\frac{1}{\sigma_i} \bar{A}_{ij}(\lambda)}{\sqrt{\sum_{k=1}^N \frac{1}{\sigma_k^2} \bar{A}_{kj}(\lambda) \bar{A}_{kj}^*(\lambda)}}} \right|^2, \quad (17)$$

116 where

$$\bar{A}_{ij}(\lambda) = \begin{cases} 1 - \sum_{k=1}^p A_{ij,k} e^{-2\pi\sqrt{-1}\lambda k}, & \text{if } i = j \\ - \sum_{k=1}^p A_{ij,k} e^{-2\pi\sqrt{-1}\lambda k}, & \text{if } i \neq j, \end{cases} \quad (18)$$

117 and σ_i^2 refers to the variance of white noise $\epsilon_i(t)$ [29]. λ is a normalized frequency where $\lambda = 0.5$
 118 means one half of the sampling rate f_s [30]. The MVAR model was estimated by the method of
 119 ordinary least squares (OLS) [31]. Akaike's information criterion gave the model order indicated
 120 that the best model order p that was lesser than or equal to 50 [30]. For all analysis it was evaluated
 121 the peak of GPDC.

122 2.6 Weighted FLN and weighted GPDC

123 In order to investigate the propagation of neuronal activity through the links defined by structural
 124 and directed functional connectivity, we defined the weighted FLN (wFLN) and the weighted GPDC
 125 (wGPDC) [32],

$$\text{wFLN}_{ij} = \frac{1}{n} \sum_{j=1}^n \left(\frac{\text{FLN}_{ij} r_j}{\sum_{j \in S} r_j} \right) \quad (19)$$

$$\text{wGPDC}_{ij} = \frac{1}{n} \sum_{j=1}^n \left(\frac{\text{GPDC}_{ij} r_j}{\sum_{j \in S} r_j} \right) \quad (20)$$

126 where FLN_{ij} is the FLN from area j to area i , r_j is the firing rate for area j , GPDC_{ij} is the peak of
 127 GPDC from area j to area i , S is the set of source areas for target area i and finally n is the
 128 cardinality of set S .

129 2.7 Numerical simulations

130 All simulations were performed using the simulator Brian2 [33] applying the exponential Euler
 131 method [34] to integrate the differential equations with an integration step of 0.1 ms. Each simulating
 132 was 30 s long, generating sufficient data points to apply GPDC on the simulated LFP signals [35].

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3 Results

The model of the large-scale cortical network of the mouse is composed of 19 spiking neural populations with recurrent connections and excitatory long-range connections constrained by the directed and weighted structural connectome (Figure 1A and Figure 1B). The dynamical behavior of each simulated cortical area is predominantly asynchronous with transient spike synchronization [36, 37] (Figure 1C). The power spectral density (PSD) of the LFP signal for a cortical area presents a peak in the gamma band (Figure 1D and 1E) [38]. The firing rate of inhibitory neurons is 4.74 ± 0.11 , higher than excitatory neurons rate of 3.64 ± 0.42 (Figure 1F). Differences in population behavior are mostly due to inputs from other areas since we sample their parameters from the same distributions (Section 2.2).

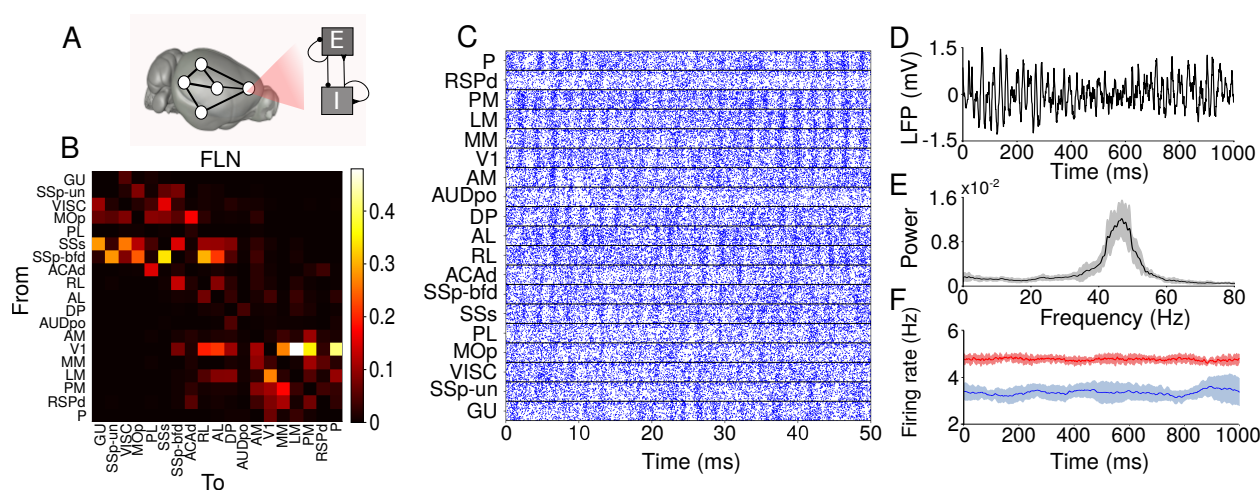


Figure 1: Large-scale cortical network. (A) Local neuronal population where E and I are populations of spiking neurons. (B) Map of structural connectivity given by the FLNs. These values define the strength of long-range projections in the large-scale network model. (C) Raster plot of 50ms of activity for each cortical area. (D) Simulated LFP signal for an area in the large-scale network model. (E) Power spectral density for simulated LFP signals from one area. Continuous black line corresponds to the average over ten simulations, and the gray shaded area delimits its standard deviation. (F) Firing-rate for excitatory (blue) and inhibitory (red) populations computed using a sliding window of 100ms. The continuous line corresponds to an average firing-rate over ten simulations, and the shaded area is the standard deviation. To exemplify, we used data from area MOp in (D), (E), and (F).

We first compared the FLN values to the average GPDC over ten simulations of the model. Many medium to strong connections from the structural connectome were also captured by the directed

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functional connectivity (Figure 2A and Figure 2B). We used the GPDC largest value (peak), but other approaches such as the average of GPDC over frequencies and area under the GPDC curve (Supplementary Figure S1) produced similar results.

Although the graph density of structural connectome is 97% [17], most structural connections are weak, which leads to a prevalence of weak average GPDC values. Weak structural connections are characteristics shared by connectomes from different mammals, with FLNs varying by several orders of magnitude, log-normally distributed [23, 39, 17, 40]. To evaluate the relation between structural and directed functional connectivity, we plotted GPDC values from ten simulations against FLNs and fit a linear model, obtaining the Pearson correlation r (Figure 2C). The scatter plot presents most points close to the origin due to the predominance of small values for the GPDC and FLN. Interestingly, for some FLNs, there is a high variation of GPDC values over different simulations. The Pearson correlation between FLN and GPDC is 0.73, and GPDC explains approximately 54% of the variance in FLN. This value similar to those obtained by other works that analyzed different structural connectomes using functional connectivity applied to empirical data [41, 42] or firing-rate models [43].

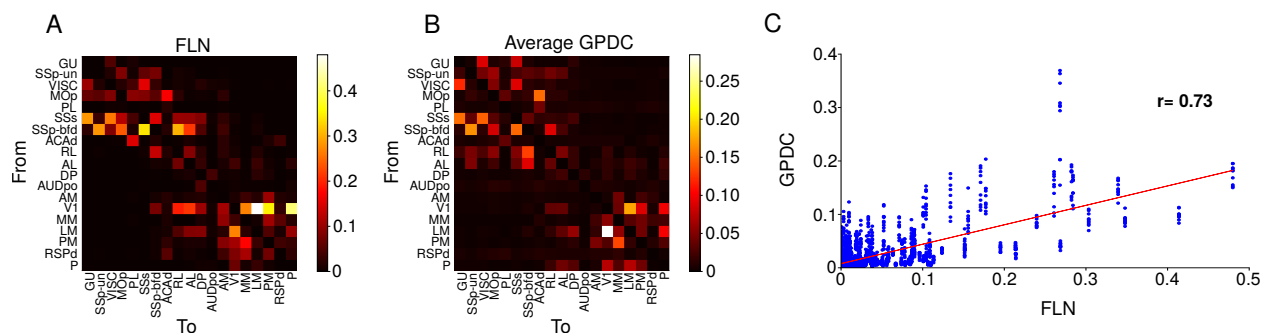


Figure 2: Relation between structural and directed functional connectivity. (A) Map of structural connectivity given by the FLNs. (B) Map of directed functional connectivity given by the average of GPDC peaks over ten simulations. (C) Scatter plot of FLNs *versus* GPDC peak. The red line corresponds to the linear fit. The Pearson correlation between FLNs and GPDC is 0.73.

We also investigated the propagation of activity between cortical areas through the pathways defined by structural and directed functional connectivity. The propagation of activity in the cortex is constrained by direct anatomical connections between areas and indirect paths [44], with

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the propagation of activity occurring mainly through the strongest long-range projections [24]. The weighted FLNs are strongly correlated to the target areas' firing rate (Figure 3A), while the correlation with the weighted GPDC and firing rate was 0.54 (Figure 3B). This indicates that neural activity propagation is directly dependent on the strength of structural connections and that GPDC can capture part of this activity propagation.

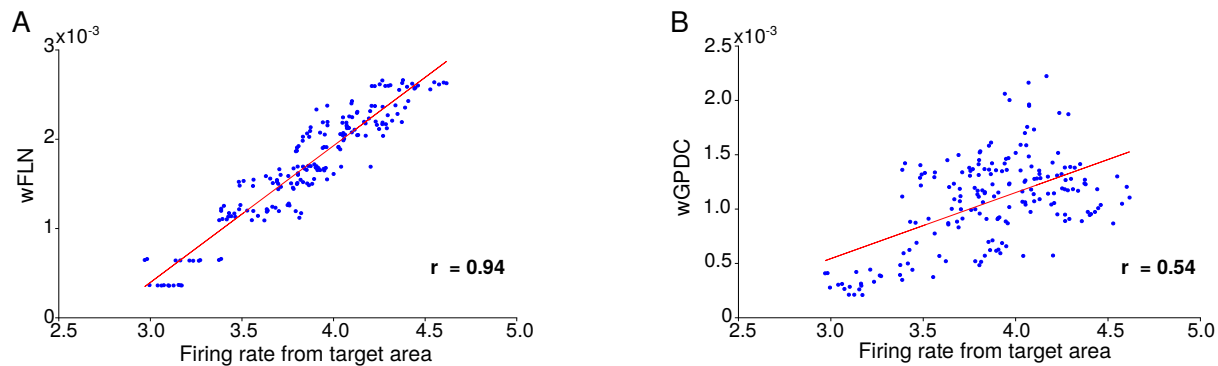


Figure 3: Propagation of activity through structural and directed functional pathways. (A) Weighted FLN *versus* the firing-rate for target areas. The Pearson correlation between Weighed FLNs and firing-rate for target areas is 0.94. (B) Weighted GPDC *versus* the firing-rate for target areas. The Pearson correlation between Weighed GPDC and firing-rate for target areas is 0.54. Red lines are linear fit.

We analyzed the behavior of GPDC estimates when considering a reduced number of areas, reproducing typical experimental setups. We considered a visual and a frontoparietal cluster, both composed of 7 cortical areas [17]. We evaluated the GPDC estimates between all areas of each cluster (Figures 4C and 4F), conditioned on the whole connectome (Figures 4B and 4E), conditioned on the areas in each cluster, and using only pairwise (bivariate) estimates (Figures 4D and 4G). This analysis simulates the situations where an electrophysiologist only has information from a single cluster of cortical areas or a pair of areas. The highest correlations between the GPDC and FLN occurred when we conditioned GPDC to the whole connectome, followed by GPDC conditioned to the cluster area, and pairwise GPDC. Also, in all cases, the correlation for the frontoparietal cluster was higher in all scenarios.

We extended the analysis to evaluate the effect of cluster size on GPDC correlation to FLN. We used cluster sizes ranging from 2 to 15 areas. We created 150 random clusters sampled from all

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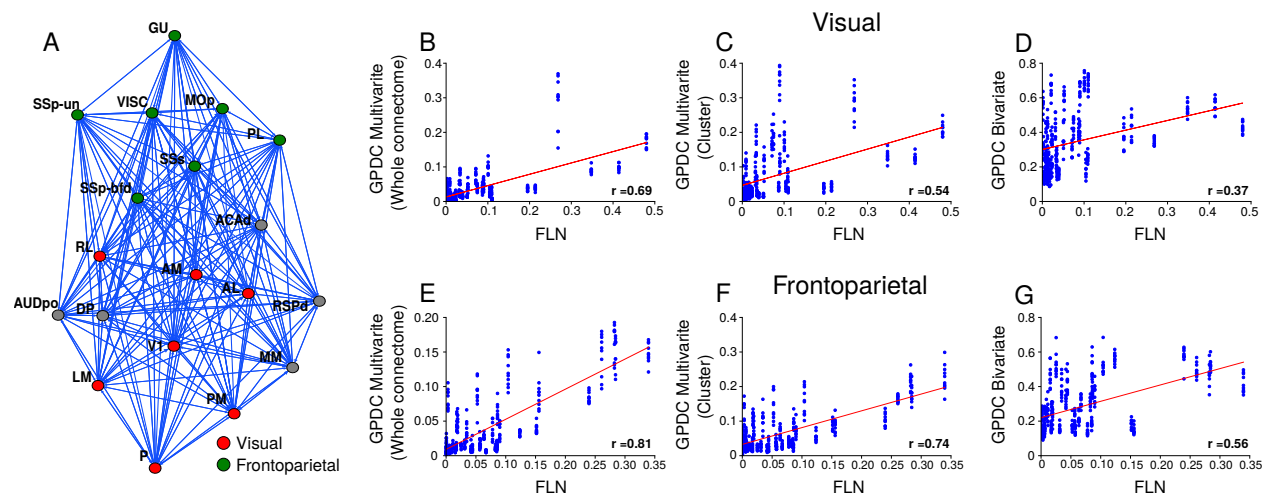


Figure 4: Correlation between FLN and GPDC for the visual and frontoparietal clusters. (A) Graph representing the mouse cortical connectome. Nodes represent cortical areas and edges, directed long-range projections between them. Green nodes are cortical areas belonging to the frontoparietal cluster. Red nodes are cortical areas belonging to the visual cluster. Both clusters are composed of 7 cortical areas. (B-D) FLN *versus* GPDC for the visual cluster. The GPDC was computed in (B) conditioned to the whole connectome, (C) conditioned to the areas in the cluster and (D) bivariate approach. (E-G) FLN *versus* GPDC for the frontoparietal cluster. The GPDC was computed in (E) conditioned to the whole connectome, (F) conditioned to the areas in the cluster and (G) bivariate approach. Red lines are linear fit and r is the Pearson correlation.

areas in the connectome for each cluster size and computed the Pearson correlation for (A) the GPDC conditioned on the whole connectome, (B) conditioned on the cluster areas, and (C) pairwise (bivariate). For cases (A) and (B), the Pearson correlation increases, and the standard variation decreases as we increase the cluster size (Figure 5A-B), showing that it is advantageous to include more areas in the GPDC calculation. Surprisingly, the results for scenarios A and B are similar, indicating that using signals measured in a few cortex areas is similar to using signals from the whole cortex, at least regarding the correlation between structural and directed functional connectivity. The correlation between whole connectome GPDC and cluster GPDC estimates increases for large clusters, as expected (Supplementary Figure S2). When considering the bivariate GPDC (Figure 5C), the average Pearson correlation decreases for a range of cluster sizes and remain stable in a low value, which shows that pairwise estimates of directed functional connectivity are affected by interference from ignored signals.

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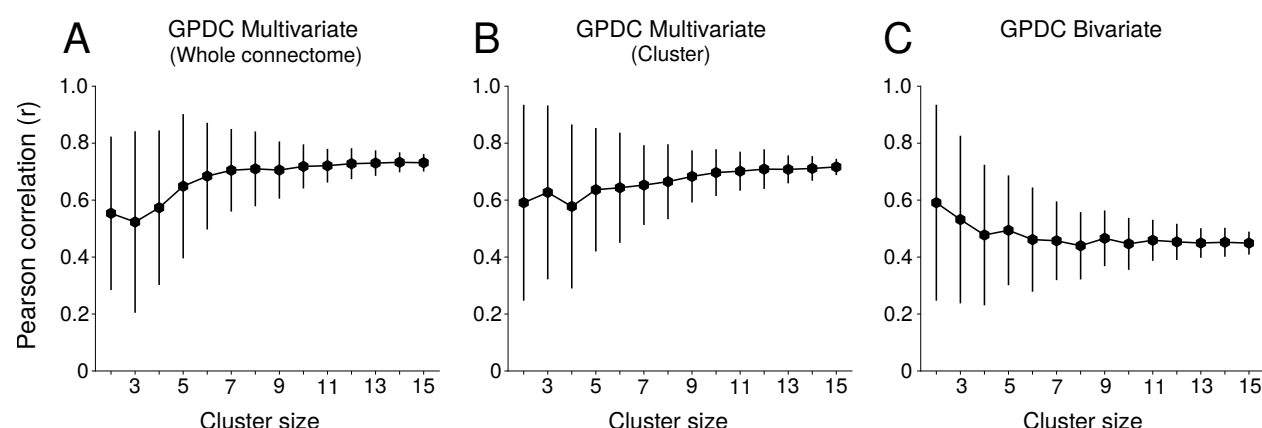


Figure 5: Correlation between FLN and GPDC for the different cluster size with randomly chosen areas.. Average (black dots) and standard deviation (error bars) of Pearson correlation for different cluster size. (A) GPDC is conditioned to the whole connectome. (B) GPDC is conditioned only to areas in the cluster. (C) GPDC bivariate.

4 Discussion

We evaluated the inference of directed functional connectivity applying GPDC on simulated LFP signals generated from a large-scale network model for the mouse cortex. Our main result demonstrates that when GPDC is conditioned to a reduced number of areas or the whole connectome, the average Pearson correlation between structural and directed functional connectivity for both cases are comparable. This result provides evidence that it is possible to obtain a reliable relationship between structural and directed functional connectivity in electrophysiological experiments even when signals are recorded from few areas.

Pearson correlation between structural and directed functional connectivity considering the whole connectome and all possible connections in our model is in the range of values obtained in experimental works comparing structural connectivity obtained by tracers and (undirected) functional connectivity [45]. Specifically, previous studies comparing structural and functional connectivity in mice cortex obtained a lower Pearson correlation coefficient than ours [46, 47]. However, besides the undirected functional connectivity adopted in both studies, structural connectivity was set as undirected in one of them (long-range projection weights were given by the average of weights in 2

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directions [46]). Also, recordings suffer the influence of the unrecorded source of activities what can affect the relationship between structural and functional connectivity [48].

Although large-scale network models have been used to investigate and predict brain activity observed in electrophysiology and neuroimage [24, 25, 49, 50], as far as we know, the relationship between structural and functional connectivity has been almost unexplored through large-scale network models [51]. Besides, most works in this subject used neural mass description (rate models) to describe each area's activity in the large-scale network model [52, 53]. However, the information propagated between brain regions can be characterized not only by the rate code but also by the temporal code [54, 55, 56, 57, 58]. Additionally, there are hypotheses pointing to spike-timing and spike coherence as essential components of cortical communication [59, 36, 60]. Thus, in our large-scale network model, a spiking neuronal population describes each cortical area's activity [24, 61]. Although spiking neuronal populations are computationally expensive and sometimes prohibitive for large-scale network models simulating many connected brain areas, they present a rich possibility of dynamical behaviors that are not possible using rate models.

The structural connectivity obtained by tracer injections has the advantage that the FLNs between areas are not reciprocal [62], i.e., they are directional. Thus, the best approach to compare structural connectivity and functional connectivity was using a measure that provides the direction of influence from one signal to another. The mouse cortical connectome used in our large-scale network model was obtained through tracer injections [17]. For this reason, GPDC was a suitable choice for evaluating functional connectivity measures. GPDC is a frequency domain measure [29, 30]. However, to have only one value representing the directed functional connectivity, we choose the peak of GPDC, which presented a better correlation with structural connectivity compared to other approaches (Figure S1).

In our results, although the GPDC peak is positively correlated with FLNs, there are several GPDC values that do not correspond to strong FLNs. There are some justifications for these mismatches between GPDC and FLNs. First, in some situations investigated using systems of

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few neuronal populations, the direction and weight of directed functional connectivity estimates can be influenced by the phase relation between signals [36, 63, 64]. In large-scale network models, the system's heterogeneity, mainly due to axonal delays for long-range projections, can arise several phase differences between regions [65]. Thus, the relationship between structural and directed functional connectivity can be altered. Second, GPDC classifies the intensity of the connection regarding a signal source [30, 15], what is problematic for comparing with strength of structural connectivity [66]. Therefore, there might be cases where the functional coupling is strong concerning a particular source even though the synaptic projections are not.

The propagation of activity between simulated cortical areas is strongly correlated with weighted FLNs and moderately correlated with weighted GPDC estimates. There are several ways to analyze the propagation of activity in the cortex; some of them can be based only on structural connectivity [44], in amplification caused by changes in projections weights [24] and some based on alterations in firing rates [67]. However, to the best of our knowledge, no studies explore how to acquire signal propagation paths based on directed functional connectivity. Here, we based our analysis on the idea proposed by Cole et al. of activity flow [32]. As we verified in our results, the mean GPDC peak weighted by the firing rate from a source area is positively correlated to the target area's firing rate. Results are better when, instead of considering the GPDC peak, we considered the FLNs. This result suggests that signal propagation pathways are better determined by structural connectivity than by directed functional connectivity. The use of directed functional connectivity to infer signal propagation is not straightforward because several aspects of the model dynamics and some characteristics of the method applied can affect the inference of connections for directed functional connectivity.

The relationship between structural and directed functional connectivity is better when GPDC is conditioned to all areas in the connectome. However, when it is conditioned to few areas in a cluster, structural and directed functional connectivity are moderately correlated. Gămănut et al. identified 6 cluster in the connectome (prefrontal, frontal, parietal, cingulate, temporal and visual) [17] based on the same approach used to investigate the macaque cortex [68]. We joined prefrontal, frontal

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and parietal clusters in a single cluster called frontoparietal. The regions AUDpo, and DP, which compose the temporal cluster and ACAd, RSPd, and MM, which belong to the cingulate cluster were excluded from these calculations because they form clusters with small number of regions [17]. The idea was to evaluate the relationship between GPDC and FLNs in specific clusters with the same cluster size. The general results were the same for frontoparietal and visual clusters. For frontoparietal clusters, the range of values for FLN and GPDC is smaller than for visual cluster. The correlation between GPDC and FLN was better in the frontoparietal cluster, where even for the bivariate approach, GPDC and FLNs are moderately correlated.

The correlation between GPDC considering the whole connectome and GPDC considering the cluster increases with the number of areas considered in the measurement (Supplementary Figure S2A). Besides that, the difference between GPDC estimates for those two approaches decreases with the cluster size (Supplementary Figure S2B). It is well known that pairwise estimates of directed functional connectivity present false connections compared to structural connectivity, caused by common input or indirect connections [7, 14, 6]. Novelli et al. showed that the relation between structural and directed functional connectivity in a large-scale network model for the macaque brain is more accurate when the multivariate approach is applied to infer directed functional connectivity than for bivariate approach [52]. Nevertheless, it is uninvestigated the reliability of directed functional connectivity estimates according to the number of areas considered. With our results, we evaluated not only the relationship between structural and directed functional connectivity (Figure 4 and Figure 5) for different cluster sizes but also the directed functional connectivity estimates when a reduced number of areas are considered (Figure S2).

Our large-scale network model has some limitations related to the similarity in different cortical areas' dynamical behavior and the connectome. First, modeled neuronal populations are practically homogeneous excepted by synaptic currents caused by long-range projections. However, in realistic approaches, several biologically based features can be added to the model, for example, cell types, spatial scales, and density of excitatory and inhibitory populations [69, 70, 71]. Second, still related to the homogeneity between cortical areas, the simulated LFP for areas in our large-scale network

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model oscillates in gamma band (Figure 1). It is known that the activity of cortical areas in mice can oscillate in different bands [72, 73]. Also, oscillatory activity in the mouse cortex is related to density and type of inhibitory neurons [74, 75]. Recently, it has been shown that the relationship between structural and functional connectivity in the macaque cortex is frequency dependent [76]. Third, it is shown that functional connectivity is dependent on network states [77]. Also, studies in computational neuroscience have been exploring multistability and temporal patterns of functional connectivity [78, 79, 80]. In our model, we did not explore network states and dynamics of directed functional connectivity. The computation of directed functional connectivity is dependent on the data length [35]. Thus, the evaluation of directed functional connectivity patterns in short windows of data can be untrustworthy because of the number of samples considered. Finally, we considered only cortical areas in our large-scale network model. It would be interesting to integrate subcortical areas into the model and verify their impact on the relationship between structural and functional connectivity. Future studies can overcome these limitations by creating more detailed models with biologically plausible neuronal features and connectome composed of cortical and subcortical areas [69, 81].

Our results shed light on the relationship between structural and directed functional connectivity in the circumstances near to those faced by electrophysiologists. We concluded that the reliability of directed functional connectivity estimates and the relationship with structural connectivity relies on the number of areas considered. Despite the limitations of our large-scale network model, our findings can support analysis based on electrophysiological recordings, and our model can be used for other investigations regarding cortical communication.

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Supplementary Material

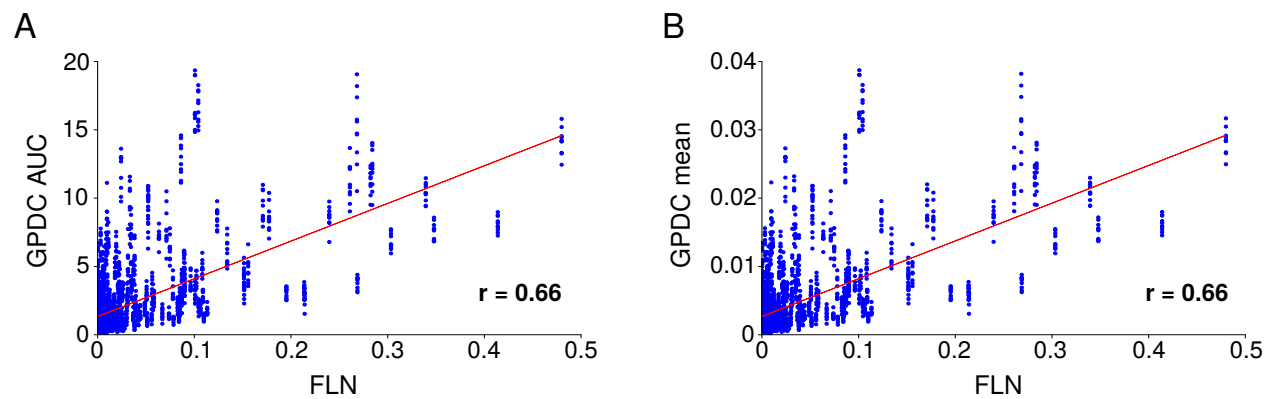


Figure S1: **Area Under Curve (AUC) and mean of GPDC estimates** . (A) GPDC AUC *versus* FLN. (B) GPDC mean *versus* FLN. In both cases, the Pearson correlation between GPDC mean or AUC and FLN is 0.66. Red lines are linear fit.

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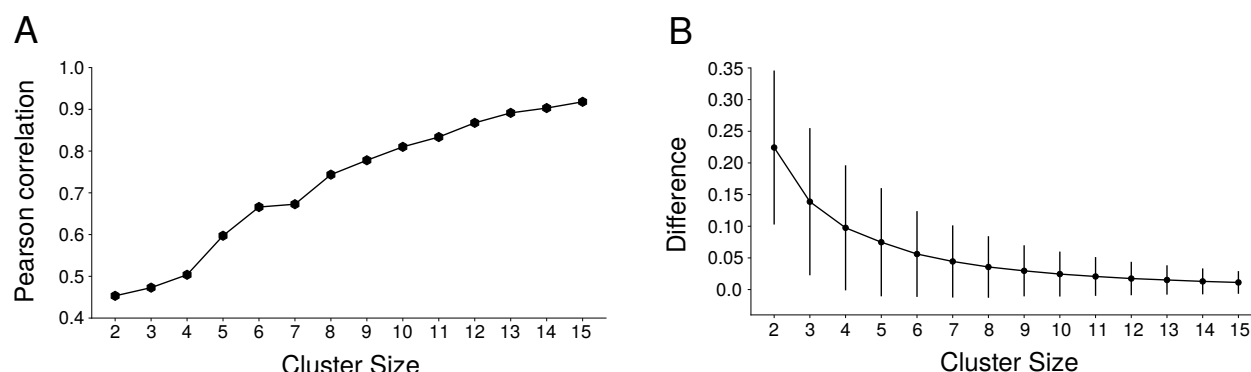


Figure S2: Correlation and difference between GPDC estimates conditioned to the whole connectome and GPDC estimates conditioned to the cluster areas. A) Pearson correlation increases with the cluster size. Each bullet represents the average pearson correlation over 150 clusters composed of randomly chosen areas. Comparing all clusters size, the highest value for standard deviation of pearson correlation 0.07. B) Average difference between GPDC estimates conditioned to the whole connectome and GPDC estimates conditioned to the cluster areas. Average and standard deviation decrease with the cluster size.

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Table S1: **Name of areas in mouse cortical connectome.** Adapted from Gămănut et. al., 2018.

Abbreviations	Areas
ACAd	Anterior cingulate area dorsal part
AL	Anterolateral area
AM	Anteromedial area
AUDpo	Auditory cortex posterior area
DP	Dorsal posterior area
GU	Gustatory area
LM	Lateromedial area
MM	Mediomedial area
MOp	Motor cortex primary
P	Posterior area
PL	Prelimbic area
PM	Posteromedial area
RL	Rostrolateral area
RSPd	Rostroplenial area dorsal part
SSp-bfd	Somatosensory cortex primary barrel field
SSp-un	Somatosensory cortex primary unassigned
SSs	Somatosensory cortex secondary
V1	Primary visual area
VISC	Visceral area