Inference of topology and the nature of synapses, and the flow of information in neuronal networks

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The characterisation of neuronal connectivity is one of the most important matters in neuroscience. In this work, we show that a recently proposed informational quantity, the causal mutual information, employed with an appropriate methodology, can be used not only to correctly infer the direction of the underlying physical synapses, but also to identify their excitatory or inhibitory nature, considering easy to handle and measure bivariate time-series. The success of our approach relies on a surprising property found in neuronal networks by which non-adjacent neurons do “understand” each other (positive mutual information), however this exchange of information is not capable of causing effect (zero transfer entropy). Remarkably, inhibitory connections, responsible for enhancing synchronisation, transfer more information than excitatory connections, known to enhance entropy in the network. We also demonstrate that our methodology can be used to correctly infer directionality of synapses even in the presence of dynamic and observational Gaussian noise, and is also successful in providing the effective directionality of inter modular connectivity, when only mean fields can be measured.

Many real systems have been modelled by complex networks with different topological characteristics. Network theory has been applied in a large number of examples and different research fields, such as biology [1], economics [2] and physics [3]. In neuroscience, the application of network theory provides a way to analyse the structure and the functional behaviour of neuronal systems [4]. A fundamental research topic in neuroscience is the determination of the structure of the brain, to better understand its functioning. Some neuronal networks had their structure directly mapped by means of diffusion tensor imaging tractography [5].

Inference of topology and the nature of synapses is the inference of its topology, that is, the determination of the underlying synaptic connectivity by indirect means, based on functional measurements of time-series of the membrane potential [6, 7]. There are works that infer the topology based on functional measures such as correlation [8, 9] and synchronisation [10], or functional magnetic resonance imaging [11]. And there are those based on informational quantities [12, 14, 17, 18]. Infer- ence based on functional measures requires a threshold analysis that establishes a link between the measurement and the physical connection [12, 19, 20]. Rubido et al. [17] showed that a threshold can be calculated whenever a functional measure between nodes (cross correlation (CC) or mutual information) in a network is dissimilar. Higher functional values correspond to a pair of adjacent nodes, lower functional values to non-adjacent nodes. Bianco-Martinez et al. [18] used the mutual information rate (MIR) to successfully infer the connectivity of a network composed of Hindmarsh-Rose (HR) neurons [21] connected by electrical synapses. Both works in Refs. [17, 18] have shown that the threshold technique could surprisingly provide an inferred network that matched exactly with the real network. These works have consid- ered undirected networks, where nodes were connected bidirectionally with the same intensity.

This work considers HR networks with chemical synapses. Unlike electrical synapses that are undirected, chemical synapses are directed [22]. Whereas undirected networks can have their topologies properly inferred by CC and MIR, directed networks require methodologies capable of detecting the directionality of the physical influence [12, 19, 22]. Granger causality [12] is a concept construct on the idea that one can obtain optimal fittings of mathematical models about the measured time-series that provide the structure and direction of the connectivity. These models are statistically optimised to improve the predictability of events in one time-series based on observations of other time-series and have been shown to be a powerful tool to infer [24]. Informational quantities have also been demonstrated to provide a framework that is at the frontier to infer. In Ref. [17] it was shown that inference based on mutual information is more reliable than those based on correlational measurements. In Ref. [22] it was shown that directed information had advantages over Granger causality for quantifying effective connectivity in the brain. One question that remains open is whether information measures can reliably infer the connectivity of complex neuronal networks for all existing synapses by only accessing bivariate measurements, in
contrast to more complex and computational demanding techniques such as multivariate analysis based on informational analysis \[14, 15\], a technique that takes into consideration time-series from more than two neurons, or modelled-based multivariate approaches such as those that employ compressive sensing \[16\].

In this work, we use the recently defined causal mutual information (CaMI) \[22, 26\] calculated using an appropriate methodology to infer the direction of chemical synapses in complex neuronal networks without any mistake, by only considering easy to handle and to measure bivariate time-series. Moreover, we show that inhibitory connections are responsible for a considerably larger amount of information transfer than that compared to neurons connected by excitatory synapses. This allows one to infer also the nature of the connection (excitatory and inhibitory), and not only its existence as previous techniques. Furthermore, we will also show that non-adjacent neurons transmit roughly null amount of directed information, indicating that indeed causal information has a direct relationship with the existence of a synapse.

The CaMI was constructed from the idea that if there is a flow of information from a system A to a system B, then longer time-series (or measurements with higher precision) in B should have a positive mutual information to short time-series (or to observations with lower precision) in A. This quantity, measuring the influence from A to B, was shown to be equal to the transfer entropy (TE), and therefore is that it allows one to calculate TE, and therefore is a flow of information from a system A to a system B, then longer time-series (or measurements with higher precision) in B producing the discrete time-series described \(x^n_i = x_i\) \((t = n\Delta t)\). In this way, we obtain the mapping \(X_i = x^0_i, x^1_i, x^2_i, \ldots, x^{T-1}_i\) for neuron \(i\), where \(T\) is the number of points in the mapping. In the following, we will study coupled neurons to determine a time step for which CaMI is maximised, aiming with this maximisation to construct a time Poincaré map that tends to behave as a Markov process, allowing CaMI, MI and TE to express a good approximant of their real values.

Figure 1 shows the normalised membrane potential for two chemical coupled HR neurons with connection from \(x^2\) (red line) to \(x^1\) (black line). The black and red circles correspond to \(X_1\) and \(X_2\), respectively, where the mapping step time \(\Delta t\) is equal to 1ms. With the forward-time trajectory \(X^{L}(n) = x^n_1, \ldots, x^{n+L-1}_i\), where \(L\) is the length of the time-series \(X(n)\) and \(n\) is the discrete time, we generate a symbolic sequence \(S^{L}(n) = s^n_1, \ldots, s^{n+L-1}_i\) (Supplementary Material), where we consider \(s^n_i = 0\) if \(x^n_i \leq 0.5\) and \(s^n_i = 1\) if \(x^n_i > 0\).

Bianco-Martinez and Baptista \[22, 26\] defined a new quantity named CaMI from \(X_i\) to \(X_j\) (CaMI \(X_i\rightarrow X_j\)) as the MI between joint events in \(X_i^{L}\) and the set composed by the joint events of \(X_j^{L}\) and \(X_j^{L}\) as CaMI \(X_i\rightarrow X_j\) = MI(\(X_i^{L} \times X_j^{L}\)) = MI(\(X_i^{L} ; W_j^{2L}\)), where the mutual Information MI(\(X_i^{L}; X_j^{L}\)) is given by MI(\(X_i^{L}; X_j^{L}\)) = \(H(X_i^{L}) + H(X_j^{L}) - H(X_i^{L}; X_j^{L})\), and \(H(X_i^{L})\) is the Shannon entropy of length-\(L\) tra-
tion indexes

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two chemical coupled HR neurons with connection from \(x_2\)
(red line) to \(x_1\) (black line). We consider the coupling strength
\(g_c = 1\) and the mapping time step \(\Delta t = 1\)ms. The black and
red circles correspond to \(X_1\) and \(X_2\), respectively.

FIG. 1. (Colour online) Normalised membrane potential of
two chemical coupled HR neurons with connection from \(x_2\)
(red line) to \(x_1\) (black line). We consider the coupling strength
\(g_c = 1\) and the mapping time step \(\Delta t = 1\)ms. The black and
red circles correspond to \(X_1\) and \(X_2\), respectively.

jectory points of the discrete mapping. It is also true
that \(\text{CaMI}_{X_i \rightarrow X_j} = \text{MI}(X_i^L, X_j^L) + \text{TE}_{X_i \rightarrow X_j}\). Prob-
abilities to calculate CaMI are constructed considering
the probabilities of the encoded binary symbolic se-
quences. CaMI is thus calculated by \(\text{CaMI}_{X_i \rightarrow X_j} =
\sum_s \sum_{s_j} P(s_i^L, s_j^L) \log \frac{P(s_i^L, s_j^L)}{P(s_i^L)P(s_j^L)}\), where the summa-
tion indexes \(S_i\) and \(S_j\) represent the space of possible
length-\(L\) symbolic sequences coming from neuron \(i\) and
\(S_j\) the space of possible joint events of finding a length-\(L\)
symbolic sequence coming from neuron \(j\) at time \(n – L\)
followed by a length-\(L\) symbolic sequence in this same
neuron at time \(n\), or in other words, of finding a length-
\(2L\) symbolic sequence in neuron \(j\) starting at the time
\(n – L\). \(P(S_i^L)\) is the probability of finding symbolic
sequences \(S_i^L = \{s_i, \ldots , s_i^{L-1}\}\) in \(X_i\), \(P(S_j^L)\) is the prob-
bility of finding a particular length-\(L\) symbolic se-
quences \(S_j^L = \{s_i, \ldots , s_i^{2L-1}\}\) in \(X_j\), and \(P(S_i^L, S_j^L)\) is the joint probability
between length-\(L\)-symbolic sequences in neuron \(i\) and
length-\(2L\) symbolic sequences in neuron \(j\). The directionality
index defined in Ref. [15] in terms of the TE can be calculated by
\(\text{DI}_{X_i \rightarrow X_j} = \text{CaMI}_{X_i \rightarrow X_j} – \text{CaMI}_{X_j \rightarrow X_i}\). For simplicity in notation
we consider that \(\text{DI}_{X_i \rightarrow X_j} \equiv \text{DI}_{ij}\). This index measures the
net amount of directed information flowing from \(X_i\)
to \(X_j\). Thus, if \(\text{DI}_{ij} > 0\), there is a net
amount of information flowing from neuron \(i\) to
neuron \(j\) (from neuron \(j\) to neuron \(i\)). Our hypothesis, also
sustained by the works of [17, 18] and others is that if
there is a directed adjacent connection from neuron \(i\) to
\(j\), thus \(\text{DI}_{ij} > 0\). In the latter case, the directionality
index will be close to zero because the transfer entropy

will be roughly zero for non-adjacent nodes. The
mutual information is a symmetric quantity and therefore
\(\text{MI}(X_j, X_i) = \text{MI}(X_i, X_j)\).

In Fig. 2 we calculate DI as a function of \(g_c\) for
two coupled neurons with one directional connection from \(x_1\)
to \(x_2\). We observe that DI = 0 when the neurons are
uncoupled \((g_c = 0)\), and DI > 0 for \(g_c > 0\). The information
is transmitted from \(x_1\) to \(x_2\), in accordance with the
direction of the connection. We compute DI for \(L = 1\)
(black line), \(L = 2\) (red line), and \(L = 8\) (blue line). For
the following analysis, we fix \(\Delta t = 0.25\)ms, and \(L = 8\)
that maximises DI values.

Next, we build a directed network where the connect-
ions among the neurons are randomly chosen. We con-
sider a random neuronal network with 64 HR neurons
and average degree of connectivities \(K\) equal to 4. As a
consequence, the network has 256 of a total of 4096 di-
rected connections \((ij)\). Figure 3 shows the normalised
directional index, ranked from larger to smaller values,
for 3 different neuronal connectivity configurations: 256
excitatory synapses (black line), 256 inhibitory synapses
(red line), and 128 excitatory and 128 inhibitory synapses
(blue line). In Fig. 3(a) there are 2 regions with \(\text{DI}_{ij} \neq 0\),
that represent the connections from \(i\) to \(j\), while \(\text{DI}_{ij} \approx 0\)
corresponds to the situation in that there is no connection
between \(i\) and \(j\). The magnification (Fig. 3(b)) exhibits
two abrupt transitions. The transition to \(\text{DI}_{ij} \approx h\) allows
the detection of directed connections in the neuronal
network. The transition that occurs for \(\text{DI}_{ij} > h\) allows to
infer the excitatory and inhibitory synapses, as shown
by the blue line, where we observe the existence of 128
excitatory and 128 inhibitory synapses.

Notice that the DI values between adjacent and non-
adjacent neurons are notably dissimilar, meaning that
a small threshold \(h\) can be chosen such that \(\text{DI}_{ij} > h\)
implies a directed connection from neuron \(i\) to neuron
\(j\). For the network whose neurons are connected by
both inhibitory and excitatory synapses, we notice in the
blue line of Fig. 3 two ranges of DI dissimilar values.
For \(h < \text{DI}_{ij} < 0.4\), the connection is excitatory and for
\(\text{DI}_{ij} > 0.4\) the connection is inhibitory. In Fig. 3(c) we
see the adjacency matrix, where the coloured elements
of the matrix indicate if the pairs of neurons are connected.

FIG. 2. (Colour online) Directional index (DI) as a function
of the coupling strength \((g_c)\) for the mapping step time \(\Delta t =
0.25\)ms. We consider \(L = 1\) (black line), \(L = 2\) (red line),
and \(L = 8\) (blue line).
in Fig. 4 We verify that the inference for the existence of a synapse is robust to dynamic noise in the membrane potential. However, for \( \sigma_d \gtrsim 3.5 \) it is not possible to infer whether the synapse is excitatory or inhibitory. Therefore, the inference of the connectivities is more robust than the inference of its nature of the synapses. CaMI-based inference is also robust to additive noise of moderate amplitude (Supplementary Material).

In the literature, there are many works that consider C. elegans neuronal network to study nervous system [35, 36]. The C. elegans is a soil worm with body size about 1mm and a simple nervous system [37]. We consider in our study the connectome of the large somatic nervous system according to Ref. [38] that consists of 277 neurons. To test our inference approach, we consider approximately 50\% of excitatory and 50\% of inhibitory synapses in the C. elegans network with 1731 directed connections. The directed adjacency matrix \((\varepsilon_{ij})\) is obtained from the brain connectivity of the C. elegans. Figure 5 exhibits the DI values, where the two discontinuities transitions in the DI values correspond to the excitatory and inhibitory synapses. In Fig. 5 it is possible to identify the connected neurons of the C. elegans, where from \( i = 1 \) to \( i = 138 \) and from \( i = 139 \) to \( i = 277 \) there are 850 inhibitory synapses and 881 excitatory synapses, respectively.

In conclusion, we propose a successful methodology based on CaMI to infer, characterise and investigate the transmission of information in neuronal networks with chemical synapses. Through the CaMI, we show not only how to infer the existence of synapses, but also to identify the nature of the synapse. Our technique can be applied to time-series generated with Gaussian dynamical noise inbuilt in the neuron equations, or to time-series contaminated by observational noise (Supplementary Material). Moreover, we also showed that when access to the neuron potential is not possible, but rather only local mean fields can be measured, such as those coming from EEG signals, our CaMI-based technique can correctly determine the effective net directed connectivity between different neuronal clusters. This work also shows that excitatory connections are not so efficient to transfer information as inhibitory connections, and that non-adjacent neurons transfer roughly zero amount of information. This latter

We analyse the noise effect in the inference of the connections. Neuronal noise can be related to several sources, such as synaptic noise [33] and ion conductance noise [34]. In the action potential equation, we add a Gaussian noise with zero mean and variance \( \sigma_d \). We calculate the DI\(_{ij} \) values for the neuronal network with \( \sigma_d = 3 \) (black line) and \( \sigma_d = 4 \) (green line), as shown

The uncoupled pairs of neurons are indicated in black, while the coupled pairs are in colour scale according to the normalised directional index. We consider the same parameters used to calculate the blue line in Fig. 3. For DI\(_{ij} < 0.4 \) the colour scale shows the excitatory synapses and for DI\(_{ij} \geq 0.4 \) the synapses are inhibitory.

We verify that the inference for the existence of a synapse is robust to dynamic noise in the membrane potential. However, for \( \sigma_d \gtrsim 3.5 \) it is not possible to infer whether the synapse is excitatory or inhibitory. Therefore, the inference of the connectivities is more robust than the inference of its nature of the synapses. CaMI-based inference is also robust to additive noise of moderate amplitude (Supplementary Material).

![Graph showing the normalised directional index for different values of \( \sigma_d \).](image)

**FIG. 4.** (Colour online) Normalised directional index, ordered from larger to smaller values, for a random neuronal network with \( N = 64 \) HR neurons, \( K = 4 \), \( \Delta t = 0.25 \), \( L = 8 \), \( T = 4 \times 10^6 \), and \( g_c = 0.1 \). We consider 3 cases for the connectivity: 256 excitatory synapses (black line), 256 inhibitory synapses (red line), and 128 excitatory and 128 inhibitory synapses (blue line). (b) Magnification of (a). (c) Matrix of the normalised directional index (DI\(_{ij} \)) of latter case.

![Graph showing the normalised directional index for different values of \( \sigma_d \).](image)

**FIG. 5.** Normalised directional index, ordered from larger to smaller values for \( N = 277 \) HR neurons. We consider \( \sigma_d = 1 \), \( g_c = 0.035 \), \( \Delta t = 0.25 \), and \( L = 8 \).

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observation suggests that a pre-synaptic neuron (a neuron that has an adjacent connection to the post-synaptic one) not only exchange information (positive mutual information), but is also capable of using information to cause an effect in a post-synaptic neuron (positive transfer entropy). Non-adjacent neurons only exchange information. This one-to-one relationship between structure and information transmission remains valid for a wide range of the coupling strength $g_c$, constraint within an interval with not so small (to prevent full decorrelation) and not so large (to prevent full synchronization) bounds. For an inference with no mistakes, time-series should be sufficiently long, more specifically, their size in seconds (i.e., $t$) should scale with the size of the network, and it is a function of the coupling strength, a relationship that was studied in much detail in Ref. [17].

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**INFERENCE OF TOPOLOGY AND THE NATURE OF SYNAPSES, AND THE FLOW OF INFORMATION IN NEURONAL NETWORKS: SUPPLEMENTARY MATERIAL**

**ENCODING THE TRAJECTORY INTO SYMBOLIC SEQUENCES**

Figure 1 (in the paper) shows the normalised membrane potential for two neurons coupled from $x_2$ (red line) to $x_1$ (black line). In Table I we show some mapped values of $x_1^t$ and $x_2^t$ with their respective length-1 symbolic values $s_1^l$ and $s_2^l$, and also the length-2 and length-4 symbolic sequence $S_1^{2L} = 2(n)$ and $S_2^{2L} = 4(n)$, respectively.

| n  | $x_1^t$ | $s_1^l$ | $S_1^{2L}(n)$ | $x_2^t$ | $s_2^l$ | $S_2^{2L}(n)$ |
|----|---------|---------|-------------|---------|---------|-------------|
| 285| 0.163043| 0       | 0           | 0.374431| 0       | 0.0110      |
| 286| 0.161350| 0       | 0           | 0.500448| 1       | 1.1000      |
| 287| 0.274266| 0       | 0           | 0.886941| 1       | 1.0000      |
| 288| 0.265589| 0       | 0           | 0.213396| 0       | 0.0000      |
| 289| 0.279589| 0       | 0           | 0.174788| 0       | 0.0000      |
| 290| 0.306991| 0       | 0           | 0.174349| 0       | 0.0000      |
| 291| 0.349396| 0       | 0           | 0.173966| 0       | 0.0000      |
| 292| 0.427650| 0       | 0           | 0.173642| 0       | 0.0000      |
| 293| 0.645130| 1       | 1           | 0.173384| 0       | ...         |
| 294| 0.725724| 1       | 1           | 0.173200| 0       | ...         |
| 295| 0.180110| 0       | ...         | 0.173100| 0       | ...         |

**TABLE I. Mappings for $\Delta t = 1ms$ and $L = 2$.**

Considering the symbolic sequences $S_1^{2L}$ and $S_2^{2L}$ is possible to find the probabilities $P(S_1^{2L})$, $P(S_2^{2L})$ and $P(S_1^{2L}, S_2^{2L})$. These probabilities are used to calculate the Casual Mutual Information

$$CaMI_{X_i \rightarrow X_j} = \sum_{s_i} \sum_{s_j} P(S_i, S_j^{2L}) \log \frac{P(S_i^{2L})}{P(S_i^{2L})}$$

and Directional Index

$$DI_{X_i \rightarrow X_j} = CaMI_{X_i \rightarrow X_j} - CaMI_{X_j \rightarrow X_i}. \quad (2)$$

**INFORMATIONAL QUANTITIES FOR ADJACENT NEURONS**

The $CaMI_{ij}$, measuring the influence from $i$ to $j$, was shown to be equal to $CaMI_{ij} = MI_{ij} + TE_{ij}$, where $MI_{ij} = MI_{ji}$ is the mutual information, and $TE_{ij}$ is the transfer entropy from $i$ to $j$. In Fig. 6 we compare the values of $DI_{ij}$, $CaMI_{ij}$, and $MI_{ij}$, as a function of $g_c$, for two coupled neurons with one directional connection from $x_i$ to $x_j$. We observe that $CaMI_{ij} \approx MI_{ij}$, therefore $TE_{ij} \approx DI_{ij}$.

In Fig. 7 we show the values of $DI_{ij}$, $CaMI_{ij}$, and $MI_{ij}$, for $o$ neuron $i = 1$ in a network with $N = 64$ neurons. There are connections from $i = 1$ to $j = 29, 46, 54,$ and $65$. In these case, we observe that $CaMI_{ij} \approx MI_{ij}$, therefore $TE_{ij} \approx DI_{ij} > 0$. Moreover, there are connetions from $j = 3, 5,$ and $19$ to $i = 1$, where $DI_{ij} < 0$. Finally, we can observe $DI_{ij} \approx 0$ when there are no connections.

**DELAY ANALYSIS**

In Table 1, we show the case where no mapping delay is considered. We can insert a time delay by generating the symbol $s_t^n$ using the values of $x_2^{n+delay}$. In Fig. 1 we show the Directionality Index (DI) as a function of mapping step time $\Delta t = 0.5ms$ and $L = 6$. For the dynamical model used, we find that the DI is higher if $L = 6$ than if $L = 2$. In addition, the DI values are higher in the region where $\Delta t < 1.0$ and delay $< 6ms$. This shows that a possible delay in connections can be neglected in this case.
FIG. 8. Directionality index \((DI)\) as a function of mapping step time \(\Delta t\) and delay in this mapping. (a) \(L = 2\) and (b) \(L = 6\).

**ADDITIVE NOISE**

The additive noise is related to the imprecision of the equipment responsible for capturing the electrical signals in the neural membrane, so in our simulations we add to the values of \(p(t)\) a noise with zero mean and standard deviation \(\sigma_a\). In Figs. 9(a) and 9(b) we observe the change in the dynamics of the membrane potential of a network neuron under the application of additive noise with \(\sigma_a = 0.1\) and \(\sigma_a = 0.35\), respectively. The difference between the minimum and maximum values reached by the membrane potential of the HR model is approximately 3.5, so \(\sigma_a = 0.35\) corresponds to 10% of this value. For \(\sigma_a = 0.1\) the observed dynamics remains very similar to the case with no noise observed in Fig. 1, however, when \(\sigma_a = 0.35\) the noise intensity can change the values of the symbolic sequence \(S^n_i(n)\). In Fig. 9(c) we see that the DI calculation does not present significant changes when considering the additive noise with \(\sigma_a = 0.1\) (black line). For \(\sigma_a = 0.35\) (green line) it is no longer possible to distinguish excitatory connections from inhibitory ones, but all 256 connections are detected.

**INFORMATION FLOW BETWEEN NETWORKS**

In many experimental cases it is not possible to directly measure the membrane potential of each neuron, but only an average field of a group of them, or a brain region. Through the analysis of the mean field between two neural networks, we show that it is possible to infer if distinct networks are connected to each other, and identify the direction of the effective connectivity by the direction of the flow of information.

In order to do this analysis, we considered two random networks with \(N = 64\) neurons each, with average degree of intra connections within the networks \(K_{\text{intra}} = 24\) and average degree of inter connections between networks \(K_{\text{inter}} = 12\). To study the flow of information between the two networks, we consider that there are only directed connections from neurons of network 1 to neurons of network 2. In each of the networks we calculated the mean field of the membrane potential and made the symbolic sequence using this time series. The process of calculating \(DI\) was performed in the same way as in the case of isolated neurons.

FIG. 9. Membrane potential for the neuron \(i = 32\) for additive noise standard deviation (a) \(\sigma_a = 0.1\) and (b) \(\sigma_a = 0.35\). (c) Normalised Directionality index for \(\sigma_a = 0.1\) (black line) and \(\sigma_a = 0.35\) (green line). We consider \(\Delta t = 0.5\), \(L = 4\), and \(g_c = 0.1\).

In Fig. 10(a) we show the values obtained from the \(DI\) as a function of the intensity of the coupling \(g_c\). For \(\Delta t = 0.25\) ms, where \(L = 1\) (black line), \(L = 2\) (red line), \(L = 4\) (green line), and \(L = 8\) (blue line). Time evolution of the Normalised Mean Field (NMF) for network 1 (black line) and network 2 (red line), both with (b) \(g_c = 0.025\), (c) \(g_c = 0.175\), and (d) \(g_c = 0.275\).

In Fig. 10(a) we show the values obtained from the \(DI\) as a function of the intensity of the coupling \(g_c\), where we set \(\Delta t = 0.25\) ms and we evaluate different sizes for
the symbolic trajectory: \( L = 1 \) (black line), \( L = 2 \) (red line), \( L = 4 \) (green line) and \( L = 8 \) (blue line). We find that, as in the case of two neurons, the highest \( DI \) values are observed when using symbolic trajectories of size \( L = 8 \). In this case, we observed that when the coupling is low, the \( DI \) values are small, since the influence of the network dynamics 1 on the network 2 is smaller. For a coupling around \( g_c = 0.175 \) we have the highest calculated value of \( DI \) and for \( g_c > 0.275 \) the value of \( DI \) decreases, tending to a constant value. This happens when the neurons of both networks are roughly completely synchronous. The neurons had been completely synchronous, thus the Transfer Entropy would be zero, resulting in a DI of zero. To understand more about the dynamical behaviour leading to the curve presented by the blue line in Fig. 10(a), we analyse the temporal evolution of the normalised mean field (NMF) for three values of the coupling. In Fig. 10(b) we have \( g_c = 0.025 \) and we observe that the NMF of network 1 (black line) and network 2 (red line) show that the neurons of these networks present the behaviour of bursting synchronisation, when neurons start the bursting of firing activities roughly simultaneously. Firings are asynchronous. In Fig. 10(c) we have \( g_c = 0.175 \) and the NMF of network 1 and 2 show that not only intra but also inter neurons are roughly synchronous. Firings spikes in the NMF indicates intra synchronisation. Inter synchronisation is evidenced by the fact that the curves are roughly identical. These both factors are responsible for the high DI values. Finally, in Fig. 10(d) we have \( g_c = 0.275 \) which is intense enough to make the networks to almost fully synchronise.

Therefore, even in the case when we have only the data of the average field of networks, we show that it is possible to infer the effective directionality of the connections in a similar way to the case between two neurons only. This method may be thus suitable to be considered for information flow studies in different regions of the brain, analysing data obtained from several experimental sources such as structural and functional MRI, diffusion tensor imaging, magnetoencephalography, and electroencephalography.