Inferring network properties from time series via transfer entropy and mutual information: validation of bivariate versus multivariate approaches

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Functional and effective networks inferred from time series are at the core of network neuroscience. Since it is common practice to compare network properties between patients and controls, it is crucial for inferred network models to reflect key underlying structural properties. However, even a few spurious links severely distort the shortest-path length and derived measures including the small-world coefficient, providing misleading insights into the macroscopic topology of the network. This poses a challenge for functional connectomes based on correlation, whose transitivity necessarily induce numerous false positives. We assess the extent to which false positives bias the properties of the networks inferred by bivariate and multivariate algorithms. Mutual information, bivariate transfer entropy, and multivariate transfer entropy are respectively used for inferring functional, directed-functional, and effective networks. The validation is performed on synthetic ground truth networks with 100–200 nodes and various topologies (regular lattice, small-world, random, scale-free, modular), as well as on a real macaque connectome. The time series of node activity are simulated via simple autoregressive dynamics. We find that multivariate transfer entropy is able to capture the key properties of all network structures for longer time series. Bivariate methods can achieve higher recall (sensitivity) for shorter time series under some circumstances; however, as available data increases, they are unable to control false positives (lower specificity). This leads to overestimated clustering, small-world, and rich-club coefficients, underestimated shortest path lengths and hub centrality, and fattened degree distribution tails. Caution should therefore be used when interpreting network properties of functional connectomes obtained via correlation or pairwise statistical dependence measures, rather than more holistic (yet data-hungry) multivariate models.

I. INTRODUCTION

Functional and effective network inference in neuroscience typically involves pre-processing the data, defining the parcellation, extracting the time series, inferring the links in the model network, and measuring network properties, e.g. to compare patients and controls or to predict phenotype $^1$ $^2$. Each step in the pipeline requires making modelling and analysis choices, whose influence on the final results is the subject of ongoing research $^3$ $^6$. As part of this effort, we study how the choice of different inference algorithms affects the properties of the resulting network model in comparison to the underlying structural network, and whether the ability to accurately reflect these properties changes across different underlying structural networks.

The structure (or topology) of a network can be described at multiple scales $^1$: from the microscopic (individual links), to the mesoscopic (modules and motifs) and the macroscopic (summary statistics, such as average shortest-path length and measures of small-worldness) $^7$. At each scale, the structure is associated with development, ageing, cognition, and neuropsychiatric diseases $^8$. Previous studies have assessed the performance of different network inference algorithms in identifying the structural links at the microscale $^9$ $^{12}$. The goal of this work is to extend the assessment to all scales and to a variety of topologies, across a range of related network inference algorithms. We link the performance at the microscale to the resulting network properties at the macroscale, and describe how this changes as a function of the overall topology.

We compare bivariate and multivariate approaches for inferring network models, employing statistical dependence measures based on information theory $^14$. These approaches include functional network inference, which produces models of networks of pairwise or bivariate statistical relationships between nodes, and can either quantify undirected statistical dependence, in the case of mutual information (MI) $^14$, or directed dependence, in the case of transfer entropy (TE) $^{15}$ $^{16}$. These approaches also include effective network inference, which is intended to produce the simplest possible circuit models that explain the observed responses $^{17}$. In this class, we evaluate the use of multivariate TE, which, in contrast to the bivariate approaches, aims to minimise spurious links and infer minimal models of the parent sets for each target node in the network.

All of these inference techniques seek to infer a network model of the relationships between the nodes in a system. Different methods capture different aspects of these relationships and don’t necessarily seek to replicate the underlying structural topology, nor do we expect them to in general (particularly in neuroimaging experiments, where aspects of the structure may be expressed more or less or not at all, depending on the cognitive task). Why do we then seek to evaluate these methods in inferring microscopic, mesoscopic and macroscopic fea-
nature of the underlying network structure? Under certain circumstances, we do expect effective network inference methods to replicate underlying structure: in the absence of hidden nodes (and other simplifying assumptions, including stationarity), networks inferred via multivariate TE are proven to converge to the underlying structure for sufficiently long time series [18, 19]. It is important to validate that these algorithms perform to that expectation where it is applicable; in doing so, we also address the recent call for more extensive model diversity in testing multivariate algorithms: “To avoid biased conclusions, a large number of different randomly selected connectivity structures should be tested [including link density as well as properties such as small-worldness]” [19]. Outside of these circumstances though, it is at least desirable for functional and effective networks to recognise important features in the underlying network structure: to track overall regime changes in that structure reliably, and to reflect the properties of distinctive nodes (or groups of nodes) in the structure.

This motivates our validation study, which is primarily based on synthetic datasets involving ground truth networks of 100–200 nodes with different topologies, from regular lattice to small-world and random (Section III), scale-free (Section IV), and modular (Section V). Many of these structural properties are incorporated in the macaque connectome analysed in Section VI. At the macroscale, we measure several fundamental and widely-used properties, including shortest-path length, clustering coefficient, small-world coefficient, betweenness centrality, and features of the degree distributions [7]. These properties of the inferred network models are compared to those of the real underlying structural networks in order to validate and benchmark different inference algorithms in terms of their ability to capture the key properties of the underlying topologies. At the microscale, the performance is assessed in terms of precision, recall, and specificity of the inferred model in classifying the links of the underlying structural network. As above, whilst we do not expect all approaches to strictly capture the microscale features, these results help to explain their performance at the macroscale.

The time series of node activity on these networks are generated by vector autoregressive (VAR) dynamics, with linearly coupled nodes and Gaussian noise. Both the VAR process and the inference algorithms are described in detail in Section II.1, where we also discuss how MI and the magnitude of Pearson correlation are equivalent for stationary VAR processes. This implies that the undirected networks obtained via the bivariate MI algorithm are equivalent to the widely employed undirected functional networks obtained via correlation, extending the implications of our results beyond information-theoretic methods. Further, our results based on TE extend to Granger causality, which is equivalent to TE for stationary VAR processes [20]. Networks inferred using bivariate TE are typically referred to as directed functional networks, to emphasise the directed nature of their links. The extension to multivariate TE for effective network inference can also be viewed as an extension to multivariate Granger causality for the stationary VAR processes here.

We find that multivariate TE performs better on all network topologies at all scales, for longer time series. Bivariate methods can achieve better recall with limited amount of data (shorter time series) in some circumstances, but the precision and the ability to control false positives are not consistent nor predictable a priori. On the other hand, thanks to recent statistical improvements, multivariate TE guarantees high specificity and precision regardless of the amount of data available, and the recall steadily increases with more data. We discuss how the mesoscopic properties of the underlying structural network—particularly the network motifs—can influence the precision and recall of the model at the microscale. In turn, we show how the performance at the microscale affects the inferred network properties at the macroscale. We observe that bivariate methods are often unable to capture the most distinctive topological features of the networks under study (including path length, clustering, degree distribution, and modularity), largely due to their inability to control false positives at the microscale.

II. METHODS

A. Networks of linearly-coupled Gaussian variables

We simulate discrete-time, stationary, first-order vector autoregressive processes (VAR) on underlying structural networks of $N$ nodes. A VAR process is described by the recurrence relation

$$Z(t + 1) = Z(t) \cdot C + \varepsilon(t),$$  

where $Z(t)$ is a row vector and $Z_i(t)$ is the activity of node $i$ at time $t$. The Gaussian noise $\varepsilon(t)$ is spatially and serially uncorrelated, with standard deviation $\theta = 0.1$. The $N \times N$ weighted adjacency matrix $C = [C_{ij}]$ describes the network structure, where $C_{ij}$ is the weight of the directed connection from node $i$ to node $j$. The choice of the weights $C_{ij}$ (detailed in the following sections) guarantees the stability of the system, which is a sufficient condition for stationarity [21]. Since stationary VAR processes have multivariate Gaussian distributions, the information-theoretic measures we use can be directly related to Pearson correlation and Granger causality [22].

B. Network inference algorithms

Three algorithms are employed to infer network models from the synthetic time series generated by the VAR processes, using the IDTxl Python package [23].
1. Bivariate mutual information for functional connectivity

Mutual information (MI) is computed between all pairs of nodes independently, in a bivariate fashion, and only the measurements that pass a strict statistical significance test (described below) are interpreted as undirected links.

MI is a measure of statistical dependence between random variables [14], introduced by Shannon in laying the foundations of information theory [13]. Formally, the MI between two continuous random variables $X$ and $Y$ with joint probability density function $\mu(x,y)$ and marginal densities $\mu_X(x)$ and $\mu_Y(y)$ is defined as

$$I(X;Y) := \int \int \mu(x,y) \log \frac{\mu(x,y)}{\mu_X(x)\mu_Y(y)} dx dy,$$

where the integral is taken over the set of pairs $(x,y)$ such that $\mu(x,y) > 0$. The strength of MI lies in its model-free nature, meaning that it doesn’t require any assumptions on the distribution or the variables (e.g., Gaussian). Being able to capture nonlinear relationships, MI is typically presented as a generalised version of the Pearson correlation coefficient. However, since the VAR processes considered here [Eq. (1)] have stationary multivariate Gaussian distributions, the MI between two variables $X$ and $Y$ is completely determined by the magnitude of their Pearson correlation coefficient $\rho$ [14]:

$$I(X;Y) = -\ln(1-\rho^2).$$

Crucially, this one-to-one relationship between MI and the absolute value of $\rho$ implies that the networks inferred via the bivariate MI algorithm are equivalent to the functional networks obtained via cross-correlation—widely employed in neuroscience. Differences may lie in how the raw MI values are transformed into a network structure. Early approaches often used a fixed threshold aimed at obtaining a prescribed link density, while the bivariate MI algorithm used here adopts an adaptive threshold (different for each link) to meet a desired statistical significance level. The statistical significance is computed via null hypothesis testing to reflect the probability of observing a larger MI from the same samples if their temporal relationship were destroyed (the $p$-value is obtained from a chi-square test, as summarised in [24]). The critical level for statistical significance is set to $\alpha = 0.01/N$, where $N$ is the network size. This produces a Bonferroni correction for the inference of parent nodes for each target (i.e., for each target, there is a 0.01 chance under the null hypothesis that at least one spurious parent node is selected).

2. Bivariate transfer entropy for directed functional connectivity

Transfer entropy (TE) is computed between all pairs of nodes independently, in a bivariate fashion, and only the measurements that pass a strict statistical significance test (described below) are interpreted as links.

TE is a model-free measure of statistical dependence between random variables [15]; however, differently from MI and cross-correlation, it is a directed and not symmetric measure (i.e., the TE from a source node $X$ to a target node $Y$ is not necessarily the same as the TE from $Y$ to $X$), and specifically considers information about the dynamic state updates of the target $Y$. Thus, employing TE has the advantage of generating directed networks and providing a more detailed model of the dynamics of the system under investigation. Formally, the TE from a source stochastic process $X$ to a target process $Y$ is defined as

$$T_{X\rightarrow Y}(t) := I(X_{t-1};Y_t|Y_{<t}),$$

where $I(X_{t-1};Y_t|Y_{<t})$ is the conditional mutual information [14] between the previous sample $X_{t-1}$ of the source and the next sample $Y_t$ of the target, in the context of (the vector of) the target’s past values $Y_{<t}$. The directed and dynamic nature of TE derives specifically from taking the past of the target into account when measuring the lagged statistical dependence between $X$ and $Y$.

In practice, in order to estimate the TE from the time series, $Y_{<t}$ is usually constructed as an embedding vector [25] and a maximum lag must be specified to build a finite embedding of the target’s past (either using uniformly or non-uniformly-spaced variables [26, 27]). Here, using the IDTxl Python package [23], a non-uniform embedding of the target’s past $Y_{<t}$ is built via iterative greedy selection of statistically significant elements of $Y_{<t}$ (as detailed in the next section). Whilst similar multivariate embeddings and lags larger than one time step can be used for the source $X$ in principle, here only a single sample at lag 1 for the source is used in alignment with the chosen VAR model.

Analogously to the MI, the bivariate TE values are transformed into a directed network structure by testing their statistical significance. This is computed (using a theoretical null-distribution, as summarised in [24]) to reflect the probability of observing a larger TE from the same samples if the source samples were temporally decoupled from the target and its past. A critical level of $\alpha = 0.01/N$ is used as per MI.

Bivariate TE has found wide application in studies of directed functional connectivity, e.g., [28–34]. Importantly, TE and Granger causality are equivalent for Gaussian variables [20], which applies to the VAR processes considered here [Eq. (1)]. Therefore, a Gaussian estimator for TE can be employed [16] and the networks inferred via the bivariate TE approach are equivalent to those obtained via Granger causality, which is also widely employed in neuroscience.

3. Multivariate transfer entropy for effective network inference

Differently from the bivariate approaches above, the multivariate TE approach does not consider pairs of nodes
in isolation, but focusses on modelling dynamic updates in each target process in the system by selecting a minimal set of sources that collectively contribute to the computation of the target’s next state. More formally, for each target Y, this method aims at identifying the minimal set of sources X_{<t} that maximise the collective TE to Y, defined as

\[ T_{X \rightarrow Y}(t) := I(X_{<t}; Y_{t}|Y_{<t}). \] (5)

The multivariate TE network inference algorithm is described in full in [9], synthesising together components of [18, 25, 27, 35, 36]. A greedy approach is used to iteratively select the candidate variables to add to X_{<t} from a candidate set \( \{X_{i,t-l}\} \) of lagged variables from the past of each source \( X_i \in \mathbb{Z} \setminus \{Y\} \), up to some maximum lag \( l \leq L \) (\( L = 1 \) for the VAR model used here). Testing the statistical significance of the conditional mutual information for a new candidate source to be included at each step—conditioning on the previously selected sources—provides an adaptive stopping condition for the greedy algorithm. The family-wise error rate for each target is set to \( \alpha = 0.01 \) using the max statistic [9], meaning that there is a 0.01 chance that, under the null hypothesis, at least one spurious parent node is selected for each target. The conditioning on previously selected sources serves to prevent the selection of spurious sources which are correlated with true sources (referred to as holding redundant information only [35]), and also enables capturing multivariate or synergistic effects on the target that cannot be detected by examining individual sources in isolation. Every node is studied as a target (in parallel on a computing cluster, using IDTxl [23]) and the results are then combined into a directed network describing the information flows in the system. Similarly to the bivariate TE discussed above, a non-uniform embedding of the target’s past \( Y_{<t} \) is built first [26], before the second step of selecting sources via the same iterative greedy algorithm [9]. Whilst multiple past samples of any given source can be considered (e.g. as has been done in [9]), only one past value is examined here (\( L = 1 \)), in line with the known structure of the VAR model in Eq. (1) and in order to focus on network structure effects only.

Given that TE and Granger causality are equivalent for Gaussian variables [20], using the Gaussian estimator with the multivariate TE algorithm can be viewed as extending Granger causality in the same multivariate/greedy fashion.

C. Evaluation metrics

At the microscale (individual links), the network inference performance is evaluated against the known underlying network structure as a binary classification task, using standard statistics based on the number of true positives (TP, i.e., correctly classified existing links), false positives (FP, i.e., absent links falsely classified as existing), true negatives (TN, i.e., correctly classified absent links), and false negatives (FN, i.e., existing links falsely classified as absent). The following standard statistics are employed in the evaluation:

**Precision:** \( = \frac{TP}{(TP + FP)} \)

**Recall (true positive rate):** \( = \frac{TP}{(TP + FN)} \)

**Specificity (true negative rate):** \( = \frac{TN}{(TN + FP)} \)

Intuitively, the precision measures how often an inferred link is actually present in the underlying structure, the recall measures the proportion of true links that are detected, and the specificity measures the proportion of absent links that are correctly not inferred. For a properly controlled family-wise error rate \( (\alpha) \), the expected specificity is \( 1 - \alpha \).

At the macroscale, the performance is evaluated in terms of the accuracy in measuring network properties of interest on the inferred network, as compared to their real values when measured on the underlying structural network. These properties include:

**Characteristic path length:** The average shortest distance between all pairs of nodes [7]. A shorter average value is typically interpreted as an indication of the efficiency of the network in propagating information. The characteristic path length is only well defined for connected networks—a problem that is avoided by construction in this study by only generating connected networks. This limitation could be alternatively overcome by replacing the characteristic path length with the analogous global efficiency [37], reported in Appendix A for completeness.

**Clustering coefficient:** The clustering coefficient of a node is the fraction of triangles in its neighbourhood, i.e., the fraction of the node’s neighbours that are also neighbours of each other [38]. The mean clustering coefficient hence reflects the average prevalence of clustered connectivity around individual nodes.

**Small-worldness coefficient:** Small-world networks are formally defined as networks that are significantly more clustered than random networks, yet have approximately the same characteristic path length as random networks [38]. The small-worldness coefficient was proposed to capture this effect in a single statistic [29], although improvements on the original measure have been recently suggested [40, 41].

**Degree distribution:** The probability distribution of the in- and out-degree, i.e., the number incoming and outgoing connections of each node.

**Betweenness centrality:** The fraction of all shortest paths in the network that pass through a given node [7].
Modularity: A measure of the separation of a network into specific groups (or modules), defined as the fraction of the edges that fall within the given groups minus the expected fraction if the edges were distributed at random [42].

Rich-club coefficient: The rich-club coefficient measures the extent to which high-degree nodes connect to each other [43].

III. SMALL-WORLD NETWORKS

A. Numerical simulations

The first experiment is aimed at testing the robustness of the three inference algorithms with respect to vast changes in network structure. The Watts-Strogatz model is used to generate a spectrum of topologies, ranging from regular lattices to random Erdős-Rényi networks through a small-world transition [38]. Each simulation starts with a directed ring network of 100 nodes with uniform link weights \( C_{ij} = C_{ji} = 0.15 \) and fixed in-degree \( d_n = 4 \) (i.e., each node is linked to two neighbours on each side, as well as to itself via a self-loop). The source of each link is then rewired with a given probability \( p \in [0, 1] \), so as to change the overall network topology while keeping the in-degree of each node fixed. Only rewiring attempts that keep the network connected are accepted, in order to allow the measurement of the average shortest-path length. The simulations for each \( p \) are repeated 10 times on different network realisations and with random initial conditions.

B. Results

At the microscale, the performance is evaluated in terms of precision, recall, and specificity in the classification of the links (present or absent) in the inferred network compared to the underlying structural network. In the case of bivariate MI, each undirected link in the inferred network is represented as two directed links in opposite directions. For longer time series of 10 000 samples, multivariate TE is the most accurate method, achieving optimal performance according to all metrics on all the network topologies generated by the Watts-Strogatz rewiring model (Figure 1, right column). Bivariate TE also achieves nearly optimal recall and high specificity on all topologies; however, despite the strict statistical significance level, the precision is significantly lower on lattice-like topologies (low rewiring probability) than on random ones (high rewiring probability). The opposite trend is shown by the bivariate MI algorithm, whose precision and recall drastically decrease with increasing rewiring probability. As expected, the recall of all methods decreases when shorter time series of 1000 samples are provided (Figure 1, left column). However, the recall for multivariate TE is consistent across topologies, while it decreases with higher rewiring probability when bivariate methods are used. This results in the bivariate TE having larger recall for lattice-like topologies whilst multivariate TE has larger recall for more random topologies (i.e., for a rewiring probability larger than \( p = 0.2 \)). A further interesting effect is that bivariate TE attains better precision on shorter time series than on longer ones.

At the macroscale, the three algorithms are tested on their ability to accurately measure three fundamental network properties relevant through the small-world transition, using the longer time series of 10 000 samples. Multivariate TE is able to closely approximate the real shortest-path length on all the network topologies generated by the Watts-Strogatz rewiring model, while the bivariate MI and TE algorithms produce significant underestimates, particularly on lattice-like topologies (Figure 2). Similarly, multivariate TE is able to closely match the
FIG. 2. Characteristic path length as a function of the rewiring probability in Watts-Strogatz ring networks \((N=100\) nodes and \(T=10000\) time samples). Multivariate TE is able to closely approximate the characteristic path length of the real topologies (ground truth). On the other hand, bivariate MI and TE produce significant underestimates due to spurious links creating shortcuts across the network, particularly on lattice-like topologies (low rewiring probability). The results for 10 simulations on different network realisations are presented (low-opacity markers) in addition to the mean values (solid markers). For real networks, only the mean values are plotted (cross markers).

FIG. 3. Average clustering coefficient as a function of the rewiring probability in Watts-Strogatz ring networks \((N=100\) nodes and \(T=10000\) time samples). The multivariate TE algorithm closely matches the average clustering coefficient of the real networks (ground truth), which is instead overestimated by bivariate MI and TE. The results for 10 simulations on different network realisations are presented (low-opacity markers) in addition to the mean values (solid markers). For real networks, only the mean values are plotted (cross markers).

FIG. 4. Small-world coefficient as a function of the rewiring probability in Watts-Strogatz ring networks \((N=100\) nodes and \(T=10000\) time samples). The multivariate TE algorithm produces accurate estimates of the small-world coefficient of the real topologies (ground truth), which is instead strongly overestimated by bivariate MI and TE. The results for 10 simulations on different network realisations are presented (low-opacity markers) in addition to the mean values (solid markers). For real networks, only the mean values are plotted (cross markers). Computed instead (not shown).

C. Discussion

At the microscale, the results concerning the bivariate TE can be explained in the light of the recent theoretical derivation of TE from network motifs \([45]\). For a fixed in-degree, the TE decreases with the rewiring probability, making it harder for candidate links to pass the statistical significance tests when only short time series are available. This explains why the recall for the bivariate TE slightly drops with higher rewiring probability for \(T=1000\) (Figure 1). We can speculate that a similar mechanism could be responsible for the more drastic drop in the recall for the bivariate MI (via evidence from derivations for covariances from network structure for similar processes \([46]\)). The fact that bivariate TE is larger for regular lattice structures also explains why its recall is slightly higher than for multivariate TE here: the redundancy between close sources that elevates their bivariate TE is explicitly conditioned out of the multivariate TE. On the other hand, as the rewiring increases, the higher recall for multivariate TE must be due to this method capturing synergistic effects that (more disparate) multiple sources have on the target, which the bivariate method does not.

Comparing the results between shorter and longer time series raises another question: why is the precision of the bivariate TE worse for longer time series than for shorter ones, especially for lattice-like topologies? More complex motifs involving common parents and multiple walks, which are more prevalent in regular lattice topologies, can result in nonzero TE on spurious links. These indirect effects are typically weak; however, for long enough time series, the low TE values can be distinguished from noise and thus pass the statistical significance tests. The result-
ing spurious links (false positives) decrease the precision and the specificity as the time series length is increased, with the effect being stronger in regular lattice topologies. In other words, the Bonferroni correction of the statistical significance level (i.e., dividing α by the network size N) does not result in a well calibrated test for bivariate inference methods—the sources are correlated, and the tests on them are not independent. The differences in the specificity on the plots are subtle because the networks are sparse; however, they manifest in large differences in the precision. Crucially, this effect is not seen for the multivariate TE, which maintains specificity consistent with the requested α for all topologies and time series lengths. Thus, lower recall achieved by multivariate TE on regular lattice networks for short time series (compared to bivariate TE) can be viewed as a compromise to control the specificity in a consistent fashion. A compelling argument in favour of controlling the specificity is provided by Zalesky et al. [4], who conclude that “specificity is at least twice as important as sensitivity [i.e., recall] when estimating key properties of brain networks, including topological measures of network clustering, network efficiency and network modularity”. Unfortunately, there is currently no consistent a priori way (nor a reasonable candidate) to determine the optimal time series length for bivariate TE to attain high precision.

Moving to the macroscale results, it is clear that the ability to control the false positives while building connectomes is a crucial prerequisite for the application of complex network measures. Adding only a few spurious links leads to significant underestimate of the average shortest-path length—an effect that has previously been reported for lattice-like networks using MI [17] and extended here to TE and across a range of topologies (Figure 2). Together with the clustering coefficient, the shortest-path length is a defining feature of small-world networks. Although evidence of small-world properties of functional networks obtained from fMRI recordings have been provided in several studies (e.g. [18]), whether or not the brain is a small-world network is still being debated [49, 50]. Following Papo et al. [50], the question addressed here is of a pragmatic rather than an ontological nature: independently of whether the brain is a small-world network or not, to what extent can neuroscientists using standard system-level neuroimaging techniques interpret the small-world construct in the context of functional brain networks? An indication that the interpretation is problematic was provided by Hlinka et al. [51], who showed that functional connectivity matrices of randomly coupled autoregressive processes show small-world properties. The effect is due to intrinsic properties of correlation rather than just to the finite sample size problem or spatial oversampling. Specifically, correlation has a transitivity property: for any node X with neighbours Y and Z (and respective correlations ρXY and ρXZ), a lower bound can be derived for the correlation between the neighbours [52]:

$$\rho_{YZ} \geq \rho_{XY} \rho_{XZ} - \sqrt{1 - \rho_{XY}^2} \sqrt{1 - \rho_{XZ}^2}.$$

In particular, a strong positive correlation between two pairs of them implies a positive correlation within the third pair: $\rho_{XY}^2 + \rho_{XZ}^2 > 1$ implies $\rho_{YZ}^2 > 0$ [52]. The problem was further investigated by Zalesky et al. [53], who showed that functional connectivity matrices of independent processes also exhibit small-world properties and that—in practice—the correlation between neighbours is much higher than the theoretical lower bound in Eq. [4]. These considerations on correlation extend to bivariate MI, given the one-to-one relationship between MI and the absolute value of Pearson’s correlation coefficient for the Gaussian variables considered in this study (see Section II B 1). This transitivity property results in more triangular cliques in functional networks, i.e., an inflated clustering coefficient across the whole spectrum of networks in Figure 3. Together with the underestimate of the shortest-path length discussed above, the outcome is an overestimate of the small-worldness coefficient (Figure 4). As shown, the limitations of bivariate methods can be overcome by multivariate TE, to a large degree for shorter time series and certainly when sufficiently long time series are available.

IV. SCALE-FREE NETWORKS

A. Numerical simulations

The preferential attachment algorithm [54] is used to generate undirected scale-free networks of 200 nodes. Starting with two connected nodes, a new node is added at each iteration and linked bidirectionally to two existing nodes, selected with probability proportional to their current degree. This preferential mechanism makes high-degree nodes more likely to be selected and further increase their degree—a positive feedback loop that generates few highly-connected hubs and many low-degree nodes. A constant uniform link weight $C_{XY} = C_{XX} = 0.1$ is assigned to all the links, achieving strong coupling but ensuring the stationarity of the VAR dynamics. For robustness, each simulation is repeated 10 times on different network realisations and with random initial conditions.

B. Results

At the microscale, the performance is evaluated in terms of precision and recall in the classification of the links. The outcome is qualitatively similar to the small-world case presented above: for longer time series (10 000 samples), multivariate TE is the most accurate method, achieving optimal performance according to all metrics (Figure 5, right column). Bivariate TE also achieves optimal recall, however, despite the strict statistical significance level, the precision is significantly lower than multivariate TE. The bivariate MI algorithm scores comparatively very poorly both in terms of precision and recall (< 40% on average). As expected, the recall of all methods decreases...
Multivariate TE
Bivariate TE

Inferred in-degree
Frequency

0 10 20 30 40 50

Real in-degree

Bivariate MI
Bivariate TE
Multivariate TE

T = 1000

T = 10000

Precision

Recall

FIG. 5. Precision (top row) and recall (bottom row) in scale-free networks obtained via preferential attachment (N=200 nodes). Multivariate TE guarantees high precision regardless of the amount of data available (T = 1000 in the left column and T=10000 in the right column). Bivariate TE can achieve slightly better recall than multivariate TE for shorter time series (bottom left panel) but its precision drops substantially for longer time series (top right panel) and the optimal time series length cannot be determined a priori. Bivariate MI has lower precision and recall than TE-based methods, both for T=1000 and T=10000. The box-whiskers plots summarise the results over 10 simulations on different network realisations, with median values indicated in colour.

when shorter time series of 1000 samples are provided (Figure 5, left column). Once more, bivariate TE attains better precision on shorter time series than on longer ones, and for these networks attains slightly better recall than multivariate TE on the shorter time series.

At the macroscale, the three algorithms are tested on their ability to accurately measure several relevant properties of scale-free networks. It is well known that the degree distribution of networks generated via the preferential attachment algorithm follows a power-law, with theoretical exponent \( \beta = 3 \) in the limit of large networks [54]. Fitting power-laws to empirical data requires some caution, e.g. adopting a logarithmic binning scheme [55], and the dedicated powerlaw Python package is employed for this purpose [54]. For sufficiently long time series (\( T = 10000 \) in this study), multivariate TE is able to accurately recover the in-degrees of the nodes in our scale-free networks, while the bivariate MI and TE algorithms produce significant overestimates (Figure 6). As a consequence, the (absolute value of the) exponent of the fitted power-law is underestimated by the latter methods, as shown in Figure 7.

Hubs are a key feature of scale-free networks and have high betweenness centrality, since most shortest paths pass through them. However, their centrality is highly underestimated by bivariate methods, often making it indistinguishable from the centrality of peripheral nodes (Figure 5, left column). Once more, bivariate TE attains

As in the small-world case, multivariate TE is able to very closely approximate the real mean clustering coefficient, while the bivariate MI and TE algorithms consistently overestimate it (Figure 7). The related measure of local efficiency [37] is reported in Appendix A. A closer examination of the clustering of individual nodes (instead of the average) reveals that low clustering values are consistently overestimated by bivariate methods, while high clustering values are underestimated (Appendix B). Finally, bivariate methods overestimate the rich-club coefficient (Appendix C).
C. Discussion

Echoing the discussion of small-world networks in Section III, the ability to control the false positives while building connectomes—exhibited only by multivariate TE—is also crucial for correctly identifying fundamental features of scale-free networks, such as the power-law degree distribution and the presence of hub nodes. Hubs are characterised by high degree and betweenness centrality. Unfortunately, the centrality of hubs is not robust with respect to false positives: the addition of spurious links cause strong underestimates of the betweenness centrality of real hubs, since additional links provide alternative shortest paths. For bivariate TE, the effect is so prominent that the inferred centrality of real hubs can be indistinguishable from the centrality of peripheral nodes, as shown in Figure 8. The in-degree is in principle more robust with respect to false positives; however, bivariate methods infer so many spurious incoming links into non-hubs that they become as connected (or more) than real hubs (Figure 6). Taken together, these effects on the in-degree and centrality greatly hinder the identification of real hubs when bivariate MI or TE are employed. The inflation of the in-degree of peripheral nodes also fattens the tail of the in-degree distribution (Figure 7), resulting in an underestimate of the exponent of the fitted power-law with respect to the theoretical value $\beta = 3$ [54]. This has severe implications for the synthetic networks used in this study, erroneously providing evidence against the simple preferential attachment algorithm used to generate them. The third distinct characteristic of these networks is their low average clustering, which is also induced by the preferential attachment algorithm, whereby each new node is only connected to two existing ones. However, bivariate methods fail to capture this feature, producing a strong overestimate of the average clustering coefficient (Figure 9). This can be attributed to the transitivity property of Pearson’s correlation, which produces overabundant triangular cliques in functional networks (as already discussed in Section III). Given the significant biases affecting all the distinctive properties of scale-free networks—in addition to the small-world networks presented above—it is evident that great caution should be used when applying bivariate inference methods (cross-correlation, MI, TE) to draw conclusions as to topological properties of real-world networks. In contrast, again, the multivariate TE was demonstrated to produce network models with microscopic and macroscopic topological properties consistent with those of the underlying structural scale-free networks.

V. MODULAR NETWORKS

A. Numerical simulations

In order to study the performance of the three inference algorithms on modular topologies, networks of 100 nodes are generated and equally partitioned into five groups of 20. Initially, each node is directly linked to 10 random targets within its own group, such that the five communities are completely disconnected. The initial density is thus 50% within each group and 10% overall. Link targets are then gradually rewired from within to between groups, weakening the modular structure but preserving the overall density and keeping the out-degrees fixed. Eventually, the concepts of “within” and “between” groups are no longer meaningful—the links are equally distributed and the topology resembles a random Erdős-Rényi network of equal overall density. This happens when the rewiring is so prevalent that only 2 links are left within the initial groups and 8 out of 10 links are formed between them (for each node). Going even further, when all 10 links are formed between the initial groups and
none within, the network becomes multipartite, i.e., the nodes are partitioned into five independent sets having no internal connections. A constant uniform link weight $C_{XY} = C_{XX} = 0.08$ is assigned to all the links, achieving strong coupling but ensuring the stationarity of the VAR dynamics. Each simulation is repeated 10 times on different network realisations and with random initial conditions.

### B. Results

At the microscale, we find that bivariate MI and TE infer more spurious links within the initial groups than between them for smaller between-group densities (Figure 10, left column). As the between-group density increases though, we find more spurious links between the initial groups than within them. The normalised false-positive rate is also significantly higher within groups for smaller between-group densities (right column), however the normalisation sees the false-positive rate becoming comparable between and within group as the between-group density increases. The number of false positives produced by multivariate TE is comparatively negligible.

At the mesoscale, the modularity of the partition corresponding to the five disconnected communities is maximal in the absence of rewiring and decreases as more and more links are formed between groups rather than within them (Figure 11). Bivariate and multivariate TE produce accurate estimates of the real modularity, while bivariate MI often underestimates it, particularly for shorter time series ($T=1000$) and intermediate between-group densities.

### C. Discussion

Our results on modular networks confirm and extend previous findings on correlation-based functional connectivity, stating that “false positives occur more prevalently between network modules than within them, and the spurious inter-modular connections have a dramatic impact on network topology” [1]. Indeed, the left column of Figure 10 shows that bivariate MI and TE infer a larger number of false positives between the initial groups than between them, once we have a mid-range between-group link density in the underlying structure (which induces the transitive relationships). However, the same does not apply to the false positive rate (i.e., the normalised number of false positives) shown in the right column of Figure 10 where an edge does not actually exist, it is more likely to be inferred if it is within rather than across group (for up to mid-range between-group link densities). As such, the higher number of false positives between modules is mostly due to the larger number of potential spurious links available between different communities compared to those within them. Nonetheless, the key message is that the modular structure (at the mesoscale level) affects the performance of bivariate algorithms in inferring single links (at the microscale level). This provides further empirical evidence for the theoretical finding that bivariate TE—despite being a pairwise measure—does not depend solely on the directed link weight between a single pair of nodes, but on the larger network structure they are embedded in, via the mesoscopic network motifs [15]. In particular, the abundance of specific “clustered motifs” in modular structure increase the bivariate TE, making links within each group easier to detect but also increasing the false positive rate within modules. Other studies have related also the correlation-based functional connectivity to specific structural features, such as search information, path transitivity [57], and topological similarity [58].
VI. MACAQUE CONNECTOME

A. Numerical simulations

Finally, the three inference algorithms are compared on a real macaque brain connectome obtained via tract-tracing [60]. This directed network consists of 71 nodes and 746 links and incorporates multiple properties investigated above, including a small-world topology and the presence of hubs and modules. With the structure fixed, we investigate the scaling of the performance as a function of the cross-coupling strength (i.e., the sum of incoming link weights into each node, denoted as \( C_{in} \) and formally defined as \( C_{in} = \sum_X C_{XY} \) for each node \( Y \)). We vary \( C_{in} \in [0.3, 0.7] \), making \( C_{XY} \) constant for each parent \( X \) for a given \( Y \) to achieve this, and keep the self-link weights constant at \( C_{XX} = 0.2 \) to ensure the stationarity of the VAR dynamics. For robustness, each simulation is repeated 10 times with random initial conditions.

B. Results

At the microscale, the results summarise the main findings presented so far. There exists an optimal window—characterised by low cross-coupling strength and short time series—where bivariate TE attains similar or better performance compared to multivariate TE in terms of recall, specificity, and precision. For stronger coupling or longer time series, the recall of all methods increase, but the precision and specificity of the bivariate methods substantially drop whilst those of multivariate TE remain consistently high (Figure 12). The macroscale results concerning the local and global efficiency are reported in Appendix A.

C. Discussion

Interestingly, Figure 12 shows how similar outcomes are produced by either stronger coupling (link weights) or longer time series. An explanation is readily available in the simple case of VAR dynamics used in this study, since the bivariate TE on spurious links is typically lower than the TE on real links, and it increases with the coupling strength [61]. Therefore, spurious links can only pass statistical significance tests when sufficiently long time series are available (in order for their weak TE values to be distinguished from noise); for the same reason, for shorter time series, spurious links can only be detected in the presence of strong enough links. Unfortunately, for real datasets, there is no consistent way to determine these optimal windows for bivariate TE a priori.

VII. CONCLUSION

In this paper, we have sought to evaluate how well network models produced via bivariate (directed and undirected) and multivariate network inference methods capture features of underlying structural topologies. We evaluated the performance of these methods at the microscopic and macroscopic scales of the network. As outlined in the Introduction, these inference techniques seek to
Yet we should expect all of the methods to identify relevant features in the underlying network structure, both in the network regime overall as well as in identifying distinctive nodes or groups of nodes in the structure. For longer time series, multivariate TE performs better on all network topologies (lattice-like, small-world, scale-free, modular, and the real macaque connectome). This enhanced performance is very clear at the microscale of single links, achieving high precision and recall, and consequently at the macroscale of network properties, accurately reflecting the key summary statistics of the ground truth networks used for validation.

Bivariate methods can exhibit higher recall (sensitivity) for shorter time series for certain underlying topologies; however, as available data increases, they are unable to control false positives (lower specificity). At the macroscale, this leads to overestimated clustering, small-world, and rich-club coefficients, underestimated shortest path lengths and hub centrality, and fattened degree distribution tails. Caution should therefore be used when interpreting network properties of functional connectomes obtained via correlation or pairwise statistical dependence measures. Their use is only advisable when the limited amount of data doesn’t allow the use of the more sophisticated but more accurate multivariate TE, which more faithfully tracks trends in underlying structural topology.

Further research is required to try to reliably identify a priori the situations where bivariate TE will exhibit higher precision and recall (particularly in terms of time series length), as there is no clear candidate approach to do so at present. In the current status quo, the key strength of the multivariate approach lies in its ability to appropriately control the false positive rate to meet the requested values. Avenues for future research also include assessing the ability of inference algorithms to capture key network features when only a subset of nodes is observed. Finally, while we focus on functional brain networks, our conclusions and methods also apply to anatomical brain networks in which connectivity is measured using correlation in cortical thickness or volume [62]. Beyond neuroscience, they also extend to metabolite, protein and gene correlation networks [63] (a similar validation study using synthetic networks was carried out in gene regulatory networks using bivariate MI and TE [64]).

**SUPPORTING INFORMATION**

The network inference algorithms described in this paper are implemented in the open-source Python software package IDTxl [23], which is freely available on GitHub (https://github.com/pwollstadt/IDTxl). The code used for the systematic exploration of network structures and inference methods is also publicly available (https://github.com/LNov/infonet).

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APPENDIX A: LOCAL AND GLOBAL EFFICIENCY

The crucial limitation of shortest path length measures (and of the derived small-world coefficient) is being only defined for connected networks. Therefore, the analogous global efficiency measure [37] is often used to overcome this shortcoming (also see [41] for an alternative measure of small-worldness based on global efficiency). The related local efficiency measure can instead be regarded as analogous to the clustering coefficient [37]. Complementing the results in the main text, we report the global and local efficiency of small-world networks (Figure 13), scale-free networks (Figure 14), and the macaque connectome (Figure 15).

APPENDIX B: CLUSTERING COEFFICIENT OF SCALE-FREE NETWORKS

Plotting the clustering coefficient values of individual nodes instead of the average shows that the low clustering values are consistently overestimated by bivariate methods (which is the most prominent effect affecting the average), while high clustering values are underestimated (Figure 16).

APPENDIX C: RICH-CLUB COEFFICIENT AND ASSORTATIVITY OF SCALE-FREE NETWORKS

The rich-club coefficient measures the extent to which high-degree nodes connect to each other [43]. Instead of choosing a specific threshold to define high-degree nodes, the rich-club coefficient is plotted in Figure 17 for a range of thresholds (non-normalised values). The rich-club coefficient is overestimated by bivariate MI and TE across all thresholds, although the effect is less prominent than on other network properties.

Assortativity (or assortative mixing) is a preference for nodes to attach to others with similar degree. The in-degree assortativity coefficient is the Pearson correlation coefficient of degree between pairs of linked nodes. Positive values indicate a correlation between nodes of similar in-degree, while negative values indicate relationships between nodes of different in-degree. As shown in Figure 18, the scale-free networks obtained via preferential attachment are disassortative (i.e., they have negative assortativity coefficients). Bivariate and multivariate TE accurately reproduce the assortativity of the real networks (ground truth), while bivariate MI consistently underestimate it.
FIG. 14. Global and local efficiency in scale-free networks obtained via preferential attachment (N=200 nodes and T=10000 time samples). Multivariate TE is the only algorithm able to preserve the efficiency of the real networks (ground truth), while bivariate TE and MI consistently overestimate it. The box-whiskers plots summarise the results over 10 simulations, with median values indicated in colour.

FIG. 15. Global and local efficiency as a function of coupling weight in a real macaque connectome (N=71 nodes and T=10000 time samples). All inference algorithms produce underestimates for low coupling. For stronger coupling, multivariate TE converges to the real global and local efficiency of the underlying networks (ground truth), while bivariate TE and MI consistently overestimate both measures. For each value of the cross-coupling weights, the results for 10 simulations from random initial conditions are presented (low-opacity markers) in addition to the mean values (solid markers).

FIG. 16. Inferred vs. real clustering coefficient of individual nodes in scale-free networks obtained via preferential attachment (N=200 nodes and T=10000 time samples). Multivariate TE accurately reproduces the clustering coefficient of the real networks (ground truth), while bivariate methods overestimate low clustering values and underestimate high clustering values. The results are collected over 10 simulations on different network realisations.

FIG. 17. Rich-club coefficient in scale-free networks obtained via preferential attachment (N=200 nodes and T=10000 time samples). Multivariate TE accurately reproduces the rich-club coefficient of the real networks (ground truth) for lower in-degree thresholds, while bivariate TE and MI consistently overestimate it. Mean values over 10 simulations.

FIG. 18. In-degree assortativity coefficient in scale-free networks obtained via preferential attachment (N=200 nodes and T=10000 time samples). Bivariate and multivariate TE accurately reproduce the assortativity of the real networks (ground truth), while bivariate MI consistently underestimate it. The black dashed line represents the identity between real and inferred values. The results are shown for 10 different network realisations.
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