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by

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Multivariate construction of effective computational networks from observational data

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Abstract

We introduce a new method for inferring effective network structure given a multivariate time-series of activation levels of the nodes in the network. For each destination node in the network, the method identifies the set of source nodes which can be used to provide the most statistically significant information regarding outcomes of the destination, and are thus inferred as those source information nodes from which the destination is computed. This is done using incrementally conditioned transfer entropy measurements, gradually building the set of source nodes for a destination conditioned on the previously identified sources. Our method is model-free and non-linear, but more importantly it handles multivariate interactions between sources in creating outcomes at destinations, rejects spurious connections for correlated sources, and incorporates measures to avoid combinatorial explosions in the number of source combinations evaluated. We apply the method to probabilistic Boolean networks (serving as models of Gene Regulatory Networks), demonstrating the utility of the method in revealing significant proportions of the underlying structural network given only short time-series of the network dynamics, particularly in comparison to other methods.

Keywords: computational neuroscience, effective networks, information transfer, information theory

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I. INTRODUCTION

A key objective of computational neuroscience is to infer a network which underpins the observed activity levels between individual sources in brain imaging data. Typically this process begins by pre-processing the raw recorded data in some way to form a multivariate time series for the *source node* variables; e.g. the source node time-series could be the result of beamforming applied to MEG recording variables, with artifact removal, etc. The idea then is to take the multivariate time series representing the activity level of each source node, and translate this into a network structure revealing the (directed) connections between the nodes and ideally an explanation for how the dynamics of each node results from their inputs elsewhere in the network. There are three fundamentally different notions of the type of network one may try to infer: *functional*, *structural* and *effective* networks.

Functional network inference constructs such networks using a measure of correlation between nodes to infer connectivity [1]. This can certainly highlight relationships between nodes, but only reveals undirected relationships, and provides no explanation for how the relationship manifests.

Structural network inference seeks to find which nodes in the system have physical, directed connections. While one can infer direct causal links between source variables under certain limited circumstances [2], in general one needs to be able to intervene in the network to produce such insights [3, 4]. Indeed, to properly do this one needs to be intervene on a large scale (beyond what can be done in the brain using localised interventions of TMS) and under general circumstances the task is simply impossible from multivariate time-series observations alone [5, 6]. Furthermore, knowing the structural network alone does not tell us about time or experimentally modulated changes in how the network is interacting [1], nor how information processing takes place.

Effective network analysis seeks to bridge between these two approaches. This approach examines directed relationships between nodes (across time) and seeks to infer the minimal neuronal circuit model which can replicate and indeed explain the recorded activity patterns [1, 7]. Friston states that effective connectivity is closer than the functional connectivity approach "to the intuitive notion of a connection and can be defined as the influence on neural system exerts over another" [1]. Certainly the effective network should reflect the underlying structural network, however it is not intended to give a unique solution to the "inverse problem" of inferring the structural network from time series, and indeed it should be experimentally and time dependent (to capture the result of external modulations) [1].

In this paper, we focus on effective network inference as the most meaningful and useful way of capturing and explaining the observed interactions between nodes given the multivariate time-series of their activity levels. While we should not interpret an effective network as directly inferring the underlying neural structure, it should be interpreted as attempting to provide the best explanation of how the source nodes appear to interact to produce their next states, which reflects the underlying structural network. Directed measures such as the transfer entropy [8] and Granger causality [9] are popularly used for effective network inference. This is because they capture the directed, dynamic *predictive* effect of a source on a destination variable, provide some explanation regarding how the dynamics are created from these interactions, and are readily testable against null models of no source-destination interaction to allow robust statistical testing of whether a directed link should be inferred [10–15]. The transfer entropy is model-free and captures non-linear interactions (due to its underlying information-thereotic formulation), while the Granger causality is faster and simpler to measure. While the intuition behind these measures suits the task of effective network inference very well, the generally used pairwise form of these measures (which examine the univariate effect of a source on a destination) are susceptible to missing outcomes created by collective interactions between multiple nodes, and to inferring superfluous connections due to correlations of one strong source to other apparent sources (e.g. common cause or pathway effects). Certainly multivariate forms of these measures exist and are known to address these problems (e.g. the conditional transfer entropy [16, 17]), however an obvious brute force approach in applying them for effective network inference suffers combinatorial explosion in evaluating all potential groupings of candidate sources.

In this paper, we present a systematic algorithm employing the use of multivariate directed dependence measures to infer effective networks. The method properly captures collective interactions and eliminates false positives, while remaining computationally efficient. Our approach seeks to find the simplest network which can statistically capture dependencies in the data set in terms of how the next state of each variable is *computed* from the other variables (see Fig. 1). We view each node as a computing unit: computing its next state at each time step using the its own previous states and those of other nodes in the network. Our method infers where the information in the next state of the node comes

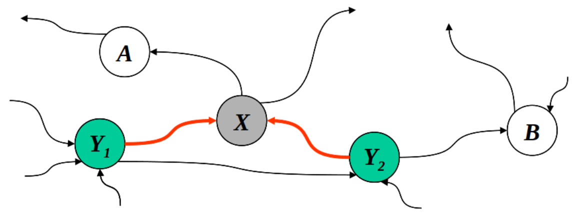


FIG. 1. Central question: how to infer the set of nodes $\mathbf{V}_X = \{Y_1, Y_2\}$ which can be used to infer the computation of the next state of X, for each node X in the network?

from, and assigns incoming links to the node accordingly. In describing the computation at each node, our method also provides a simple explanation of how the dynamics are created, in terms of probability distributions of the destination node in terms of its sources.

Our method is rooted in information theory, and as such is model-free and captures non-linear relationships. It is specifically designed to capture both uni- and multivariate relationships between sources in creating the outcomes in the destinations. Crucially, it does not suffer combinatorial explosion in the number of possible source sets considered, while it automatically tailors the power of inference (in terms of how much of the network can be inferred) to the support supplied by the amount of available data. The less observational data we have, the more conservative the method is in terms of inferring effective connections.

We begin by describing the information-theoretic quantities used here (in particular the transfer entropy). We show how the information content in a destination can be fundamentally decomposed in terms of (conditional) information contributions from its causal information sources; this decomposition forms the inspiration for our approach. We then describe existing effective network inference techniques using the transfer entropy, and outline the manner in which they cannot detect collective interactions and may infer spurious links due to source correlations. To address these issue, we present a new criteria for inferring an effective *computational* network by inferring the set of sources for each destination node which makes the destination conditionally independent of all other sources in the network. Constructing this network becomes an optimisation problem, which we propose to address using a greedy algorithm with post-processing (e.g. using the Kernigan-Lin approach). Importantly, our greedy algorithm builds the network using strong information sources first, and then iteratively conditioning on previously selected sources - this allows our technique to capture collective interactions and reject spuriously correlated sources, unlike other approaches. Finally, we demonstrate an application of the method to infer effective networks from short time-series observations of probabilistic random Boolean network dynamics. This test bed is selected since it provides a large state space for the dynamics, highly non-linear interactions, incorporates large noise effects, and is a useful mode for Gene Regulatory Networks [18]. Our application demonstrates the significant improvement that our technique provides over the default univariate application of transfer entropy, and also provides some commentary on parameter settings for the method.

II. INFORMATION-THEORETIC PRELIMINARIES

In this section, we present the fundamental information-theoretic quantities used in this work, then describe how the information in a destination variable may be decomposed into a sum of incrementally conditioned contributions from each of the sources to that destination.

A. Fundamental quantities

In this section we present the fundamental information-theoretic variables used here, as formed for measurements on *time-series data* (i.e. for a variable X with realisations x_n at each time step n in the time series).

The fundamental quantity in information theory [19, 20] is the amount of information required to predict the next state x_{n+1} of an information destination X, i.e. the *entropy* H_X of x_{n+1}:

$$H_X = \langle - \log_2 p(x_{n+1}) \rangle_n \,. \tag{1}$$

Note that the expectation value taken over all realisations/observations n is equivalent to averaging by the observational probability in the full joint space (i.e. $p(x_{n+1})$ here).

The *joint entropy* of two random variables X and Y is a generalization to quantify the uncertainty of their joint distribution: $H_{X,Y} = \langle \log_2 p(x_n, y_n) \rangle_n$. The *conditional entropy* of X given Y is the average uncertainty that remains about x_n when y_n is known: $H_{X|Y} = \langle \log_2 p(x_n|y_n) \rangle_n$.

The *mutual information* between X and Y measures the average reduction in uncertainty about x_n that results from learning the value of y_n, or vice versa: $I_{X;Y} = H_X - H_{X|Y} =$

$\langle \log_2 p(x_n \mid y_n)/p(x_n) \rangle_n$. Of course, we can measure the (time-lagged) mutual information across e.g. one time step: $I(y_n; x_{n+1}) = \langle \log_2 (p(x_{n+1}|y_n)/p(x_{n+1})) \rangle_n$.

The *conditional mutual information* between X and Y given Z is the mutual information between X and Y when Z is known: $I_{X;Y|Z} = H_{X|Z} - H_{X|Y,Z}$. For example, $I(y_n; x_{n+1} \mid z_n) = \langle \log_2 (p(x_{n+1} \mid y_n, z_n)/p(x_{n+1} \mid z_n)) \rangle_n$

Finally, the *entropy rate* is the limiting value of the entropy of the next state x_{n+1} of X conditioned on the previous k states $x_n^{(k)}$ of X: $H_{\mu X} = \lim_{k\to\infty} H\left[x_{n+1}|x_n^{(k)}\right] = \lim_{k\to\infty} H_{\mu X}(k)$.

The *apparent transfer entropy* [8, 16] is the mutual information from realisations y_n of a source variable Y to realisations x_{n+1} of X, conditioned on the history $x_n^{(k)}$ of X (see Fig. 2): $T_{Y\to X} = I(y_n; x_{n+1} \mid x_n^{(k)}) = \left\langle \log_2 \left(p(x_{n+1} \mid x_n^{(k)}, y_n)/p(x_{n+1} \mid x_n^{(k)})\right)\right\rangle_n$. Clearly the value of $T_{Y\to X}$ depends on the history length k: it has been recommended that $k \to \infty$ should be used to properly represent the concept of information transfer, while limiting k to capture the direct causal sources in the past of X (e.g. $k = 1$ in many applications) brings the measure closer to an inference of causal effect [16, 17].

The transfer entropy itself may be conditioned on another potential source variable Z, to provide the *conditional transfer entropy* [16, 17] (see Fig. 2):

$$\begin{aligned} T_{Y\to X|Z} &= I(y_n; x_{n+1} \mid x_n^{(k)}, z_n) \\ &= \left\langle \log_2 \left(p(x_{n+1} \mid x_n^{(k)}, z_n, y_n)/p(x_{n+1} \mid x_n^{(k)}, z_n)\right)\right\rangle_n . \end{aligned} \tag{2}$$

The conditional transfer entropy eliminates the detection of information from Y about X that was redundantly provided by Z, and also captures multivariate interactions between Y and Z which create outcomes in X (e.g. XOR interactions $X = Y \oplus Z$) [16, 17]. It is well known that neither of these properties is provided by the apparent transfer entropy [16]. Finally, we note that if (the in general multivariate) Z captures all of the other causal information contributors to X apart from Y, then we call $T_{Y\to X|Z}$ the *complete transfer entropy* $T^c_{Y\to X}$ [16, 17].

B. Information (de)composition

For the purposes of this work, we are particularly interested in how prediction of the next state of an information destination X can be made from a set of causal information contributors $\mathbf{V}_X$ to X. We consider $\mathbf{V}_X$ to be a subset of some large set of variables or nodes $\mathbf{D}$ which make up the entire network, i.e. $\mathbf{V}_X \in \mathbf{D}$. For simplicity in presenting the mathematics, we assume that $\mathbf{V}_X$ causes X over a lag of one time step, though the extension to variable delays is trivial (one simply expands $\mathbf{V}_X$ to consider not only the potential contribution from nodes at the previous time step, but from several time steps back also - see Section IV B 4).

As such, we can express the entropy of X in terms of the information $I(\mathbf{v}_{x,n}; x_{n+1})$ from the set of causal information contributors $\mathbf{V}_X$ at the previous time step n, plus any intrinsic uncertainty or stochasticity U_X remaining in the destination after considering these sources:

$$H_X = I(\mathbf{v}_{x,n}; x_{n+1}) + U_X, \tag{3}$$

$$U_X = H(x_{n+1} \mid \mathbf{v}_{x,n}). \tag{4}$$

We can make an alternative decomposition of the entropy H_X by taking a computational perspective: we consider H_X in terms of how much information is contributed by the past of X and the remaining uncertainty after considering that past. The information from the past of X is captured by the *active information storage* [17, 21], $A_X = I(x_n^{(k)}; x_{n+1})$ where $x_n^{(k)} = x_{n-k+1}, \ldots, x_{n-1}, x_n$ is the joint vector of the past k values of X, up to and including x_n. The remaining uncertainty after considering the past of X is the entropy rate $H_{\mu X}$. The decomposition is then given by:[22]

$$H_X = I(x_n^{(k)}; x_{n+1}) + H(x_{n+1} \mid x_n^{(k)}), \tag{5}$$

$$H_X = A_X + H_{\mu X}. \tag{6}$$

We then further partition the information from the causal contributors in order to align Eq. (3) and Eq. (5) [17]:

$$H_{\mu X} = I(\mathbf{v}_{x,n}; x_{n+1} \mid x_n^{(k)}) + U_X, \tag{7}$$

$$H_X = A_X + I(\mathbf{v}_{x,n}; x_{n+1} \mid x_n^{(k)}) + U_X, \tag{8}$$

$$H_X = A_X + T_{\mathbf{V}_X \to X} + U_X. \tag{9}$$

Here, $T_{\mathbf{V}_X \to X} = I(\mathbf{v}_{x,n}; x_{n+1} \mid x_n^{(k)})$ is the *collective transfer entropy* [17], and represents the (multivariate) information transfer from the set of joint sources $\mathbf{V}_X$ to X. As such, Eq. (9) shows how the information in the next state is a sum of information storage, information transfer, and intrinsic uncertainty.

We can still further expand the collective transfer entropy by [17] "*incrementally* taking account of the contribution of each causal information source". That is, we consider an *arbitrary* ordering (using index g) of the causal sources to X in $\{\mathbf{V}_X \setminus X\}$, writing these in order as $Z_1, Z_2, ..., Z_G$. We can then write an arbitrarily ordered subset of $g-1$ sources as:

$$\mathbf{V}_X^{<g} = \{Z_c \mid \forall c : 1 \leq c < g\}, \tag{10}$$

$$\mathbf{v}_{x,n}^{<g} = \{z_{c,n} \mid \forall c : 1 \leq c < g\}, \tag{11}$$

and then make the decomposition:

$$T_{\mathbf{V}_X \rightarrow X} = \sum_g I(z_{g,n}; x_{n+1} \mid x_n^{(k)}, \mathbf{v}_{x,n}^{<g}). \tag{12}$$

This equation produces a sum of *incrementally conditioned mutual information* terms [17]: each term is the information added by the given source Z_g that was not contained either in the past of the destination or in the previously inspected sources $\mathbf{V}_X^{<g}$. Each of these terms is a transfer entropy [8] itself, and if we expand this sum:

$$\begin{aligned} T_{\mathbf{V}_X \rightarrow X} =& I(z_{1,n}; x_{n+1} \mid x_n^{(k)}) + \\ & I(z_{2,n}; x_{n+1} \mid x_n^{(k)}, z_{1,n}) + \\ & I(z_{3,n}; x_{n+1} \mid x_n^{(k)}, z_{1,n}, z_{2,n}) + \ldots + \\ & I(z_{G,n}; x_{n+1} \mid x_n^{(k)}, \mathbf{v}_{x,n}^{<G}), \end{aligned} \tag{13}$$

we see that the first term is the apparent transfer entropy from source Z_1, the last term is the complete transfer entropy from source Z_G (since all other causal sources are conditioned on), and the intermediate terms are conditional transfer entropies (see Fig. 2). The collective transfer entropy captures (while accounting for redundancies) all transfers from the sources to the destination, incorporating both single-source effects and multiple source effects (i.e. interaction-based transfers such as an XOR outcome from two variables). Importantly, it is not a simple sum of the apparent TE from each source, nor the sum of the complete TE from each source.

Finally, we combine Eq. (9) with Eq. (12) to obtain:

$$H_X = A_X + T_{\mathbf{V}_X \rightarrow X} + U_X, \tag{14}$$

$$H_X = A_X + \sum_g I(z_{g,n}; x_{n+1} \mid x_n^{(k)}, \mathbf{v}_{x,n}^{<g}) + U_X. \tag{15}$$

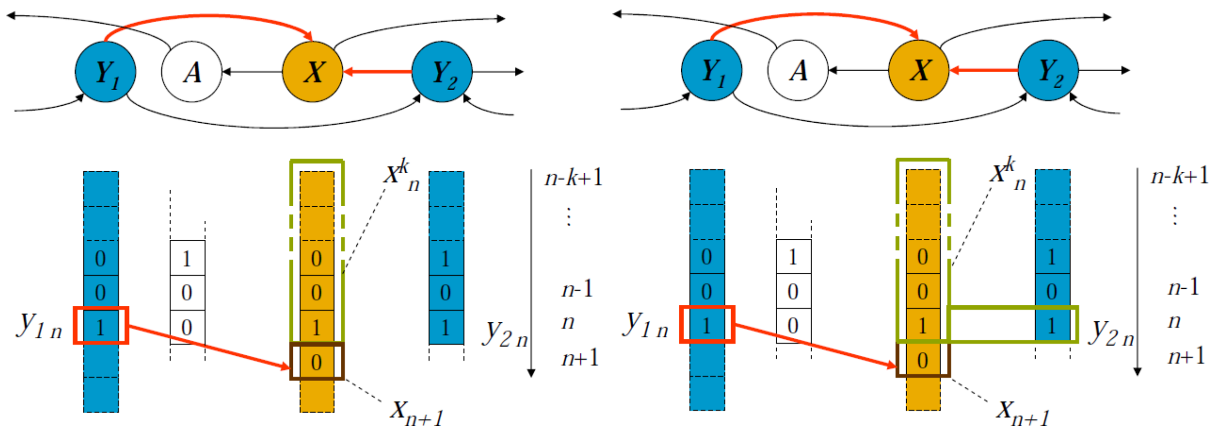


FIG. 2. Transfer entropy between nodes in networks: left, apparent transfer entropy $T_{Y_1 \to X}$ from Y_1 to X; right, conditional transfer entropy $T_{Y_1 \to X|Y_2}$ from Y_1 to X, conditioned on the other source Y_2

As such, we see that the information in the next state of the destination X can be viewed as a sum of the stored information from its past, plus the incremental contribution of each source in the set $\mathbf{V}_X$, plus any remaining uncertainty after all these sources have been considered.

III. STANDARD INFORMATION-THEORETIC INFERENCE OF EFFECTIVE NETWORKS

The task of effective network construction is to select which nodes from the whole network $\mathbf{D}$ should be considered to be the sources $\mathbf{V}_X$ for each destination node X - see Fig. 1.

In the information-theoretic domain, while the mutual information is often used to infer functional networks, it is the apparent (or univariate) transfer entropy (TE) which is widely used to infer effective networks, e.g. in [10–12]. This is because it provides a directional, dynamic, model-free measure of dependence of a source on a destination variable [8], which aligns with the philosophy behind effective network analysis. Importantly, the actual TE value is not directly used in these studies; what is used is the inference of whether the TE value was statistically significant [14, 15], i.e. whether the dynamic source-destination relationship was significant given their marginal distributions. The statistical significance of the actual TE value is evaluated by comparing it to a distribution of TE measurements where there is no source-destination temporal relationship. This is done by shuffling or rotating[23] the source values to generate many surrogate source time series, and generating a surrogate TE value from each one. One then tests whether the null hypothesis that there was no directed source-destination temporal relationship is supported by the actual TE value (rejecting this null hypothesis and concluding the actual TE value statistically significant if there is a probability less than α of the actual TE value being observed by chance under the null hypothesis). Such statistical significance has been evaluated for performing effective connectivity analysis with the transfer entropy in several applications to neural data; e.g. [10–13].

This use of the transfer entropy provides model-free and non-linear capabilities, and the statistical significance approach adds objectivity in determining whether a connection should be inferred, and robustness to low amounts of data [12]. As alluded to in Section II A however, a particular problem however is that it ignores multivariate effects in only considering univariate sources. In the context of effective network inference, this means that:

- it can miss inferring links whose effect is only manifested via interactions (e.g. XOR functions);
- it can infer redundant links, e.g. adding potential sources whose information contribution is only due to their being correlated with a true information source, or adding links which are only manifested due to indirect causes through other variables in the data. For example, the method is susceptible to inferring redundant links $Y \to X$ due to either *pathway relationships* $Y \to Z \to X$, or *common cause relationships* $Z \to Y$ and $Z \to X$

One can directly take a multivariate approach, e.g. by examining Granger causality from each variable, conditioning out the whole remainder of the system [24]. And indeed, this could be mirrored in theory via the *complete transfer entropy* [16], which provides advantages of non-linearity and model-freedom over the Granger causality approach, but is in fact impossible in practise due to the limitations of available observations. Although Granger causality can be computed with less data, going directly to condition out all other variables is still undesirable. This is because where information is held redundantly by two potential sources, both will reduce the conditioned contribution of the other to zero when the measure is made conditioning out all variables in the system. Such a situation becomes increasingly likely in large neural data sets, where the brain's massive redundancy comes into play, and also in short data sets where undersampling in large multivariate spaces begins to mask real information contributions.

We need an approach between these two extremes, which can infer links whether they are involved in uni- or multivariate interactions creating information in the destination, and appropriately handles redundancy in the data set. We will consider how to do this in the next section, building on our information-theoretic view of the information (de)composition of destination variables provided in Section II.

IV. MULTIVARIATE EFFECTIVE SOURCE SELECTION

Our goal, as previously stated, is to find the simplest network which can statistically capture dependencies in the data set in terms of how the next state of each variable is computed from the other variables. This means that we wish to find the simplest set of sources $\mathbf{V}_X$ in the network $\mathbf{D}$ which can make X *conditionally independent* from the remaining sources $\mathbf{D} \setminus \mathbf{V}_X$, given its own past $x_n^{(k)}$ also. To restate this in the notation of Section II, we seek to infer the simplest set of sources $\mathbf{V}_X$ in the network $\mathbf{D}$ from which the greatest amount of information about a destination X can be statistically-significantly predicted (minimizing remaining uncertainty, see Eq. (3)).

Since $I(\mathbf{v}_{x,n}; x_{n+1})$ monotonically increases with the size of the set $\mathbf{V}_X$, then the prediction of the next state (from the observed data set) can be trivially maximized by including all of the potential sources $\mathbf{D}$ in $\mathbf{V}_X$. However, a large proportion of this increase is because the measurement becomes more and more biased with the size of the set $\mathbf{V}_X$, and the increase does not mean that all of those sources actually provide statistically-significant information about x_{n+1}. So we clarify our **goal** as:

> To identify the set of source variables $\mathbf{V}_X \in \mathbf{D}$ for X which *maximises* the collective transfer entropy $T_{\mathbf{V}_X \to X}$ to X, subject to the condition that each source Z in $\mathbf{V}_X$ incrementally adds information to X in a *statistically significant* fashion (i.e. that $T_{Z \to X | \mathbf{V}_X \setminus Z}$ is statistically significant $\forall Z \in \mathbf{V}_X$).

We point out that the goal cannot be satisfied by the following approaches:

- Maximising the number of sources in $\mathbf{V}_X$ is not sound, since (in all likelihood) many of the sources in the complete data set will not provide a statistically significant amount of information to the destination in addition to that provided by other sources.

- Selecting sources which have individually large *univariate* transfer entropies or lagged mutual information values to X will not address the goal either, since this ignores the contributions from sources involved in multivariate interactions, and does not discriminate out redundant contributions.

- Selecting sources which contribute large amounts of information conditioned on all other potential sources in $\mathbf{D}$ will not address the goal, since this is impractical with short data sets and wilfully eliminates all redundant contributions (even though the observer requires one copy of that redundant information to help with predicting the destination).

Selecting the set of sources $\mathbf{V}_X$ to meet the above goal is a non-trivial *optimisation problem*, since we have $\sum_{m=1}^{|\mathbf{D}|} \binom{|\mathbf{D}|}{m} = 2^{|\mathbf{D}|}$ potential solutions; clearly this is an NP-hard problem as the size of the solution space expands exponentially with the problem size, and we cannot directly evaluate whether a given candidate solution is optimal. We have a quality function for potential solutions $\mathbf{V}_X$ to the optimisation problem, being the amount of information they are able to predict about the next state of X, subject to the condition that every source in $\mathbf{V}_X$ contributes a statistically significant amount of information conditioned on all other sources in $\mathbf{V}_X$.

In the following sections, we present an efficient algorithm to address this optimisation problem, then discuss its properties and parameter settings.

A. Iterative greedy method

We propose the use of a *greedy method* to avoid evaluating all possible source combinations, by instead *incrementally* building the source set $\mathbf{V}_X$ making a *greedy* choice at each selection step about which new source to add to $\mathbf{V}_X$. The method seeks to incrementally add sources Z to $\mathbf{V}_X$, taking inspiration from the information decomposition in Eq. (12) and Eq. (15), by adding the source at each selection step which adds the most information about the destination X conditioned on the previously selected sources.

The steps of the *basic iterative greedy method* are as follows:

1. Initialise $\mathbf{V}_X = \emptyset$.

2. Evaluate $T_{Z \to X|\mathbf{V}_X}$ for every source $Z \in \mathbf{D} \setminus \mathbf{V}_X$.

3. Select the source $Z \in \mathbf{D} \setminus \mathbf{V}_X$ which provided the largest incremental information contribution $T_{Z \to X|\mathbf{V}_X}$ about the next state of X, while that the information was statistically significant against null models.

4. Repeat steps 2 and 3 until no source Z can be found to be added to $\mathbf{V}_X$. Termination of the algorithm occurs because either there is no more information in X left to account for, or no source Z provides a statistically significant information contribution $T_{Z \to X|\mathbf{V}_X}$ which could account for part of the remaining uncertainty in X.

We make several comments on these steps as follows.

To evaluate the statistical significance of a *conditional* transfer entropy $T_{Z \to X|\mathbf{V}_X}$, one follows the known algorithm [11, 12, 14, 15] for the apparent transfer entropy with a slight modification: shuffling or rotating the source only, but not the destination or conditioned time series (this preserves the temporal ordering within the destination and with respect to the conditioned time series). The null hypothesis is altered to suggest that there is no temporal relationship from the source to the destination state change, conditioned on the other sources.

We note that the statistical significance need not be evaluated for the conditional TE from every potential source Z at step 3; one simply should evaluate statistical significance for the sources in descending order of the conditional TE they provide until identifying a source which provides a statistically significant incremental information contribution. We must explore beyond the source with the largest conditional TE value if it did not prove to be statistically significant, because a source with a lower conditional TE may provide this in a statistically significant fashion and consequently be selected. This could happen where the lower TE source had a lower entropy but was more strongly correlated with the activity in the destination variable. While this is possible, it is likely that the algorithm would only evaluate the statistical significance for a large proportion of sources when none of them become selected at step 3. Thus, the average runtime of the algorithm is likely to be better than the asympototic worst case performance.

Next, note that we called step 3 a *greedy selection*, and hence we have a *greedy method*, because the selection may not be optimal. It could make a non-optimal choice if:

- the selected source Z_1 contributes a large amount of information redundantly with another non-selected source Z_2, and another separate amount of information redundantly with another non-selected source Z_3. Z_2 and Z_3 won't be selected at a later step because the information they each appear to provide is redundant with Z_1; and
- Z_2 and Z_3 actually provide a large amount of joint or interaction-based transfer to X, which cannot be detected for either in isolation by step 2 unless the other source has already been included in $\mathbf{V}_X$.

In this case, the extra information from Z_2 and Z_3 will not be detected.

This situation, and indeed the simpler situation where two sources provide an interaction based outcome in the destination but neither provide a detectable information contribution on their own, can be addressed by the following enhancement:

5. When no source Z can be found providing a statistically significant information contribution $T_{Z \to X|\mathbf{V}_X}$, repeat steps 2 and 3 considering **joint pairs** of sources $\mathbf{Z} = \{Z_a, Z_b | Z_a, Z_b \in \mathbf{D} \setminus \mathbf{V}_X\}$ instead of single sources Z.

We note that this enhancement costs computational time, i.e. $O\left(|\mathbf{D} \setminus \mathbf{V}_X|^2\right)$ transfer entropy evaluations (not including statistical significance calculations). As such, the user must weigh up the computational cost of including this step against the potential benefit gained from capturing multivariate interactions where neither source makes a detectable information contribution on its own. Of course, step 5 can be extended to triplets $\mathbf{Z} = \{Z_a, Z_b, Z_c | Z_a, Z_b, Z_c \in \mathbf{D} \setminus \mathbf{V}_X\}$ (and so on) when no variables are identified as adding contributions at the pair level (or so on), if one has enough computational time (or conversely if the available data set $|\mathbf{D}|$ is small enough), though it is unlikely that the computational time cost would justify any additional benefit here.

Additionally, we suggest a pruning/partition optimisation step as an enhancement:

6. Once we have finalised the determination of $\mathbf{V}_X$ after the above (i.e. no further sources add statistically significant information to the destination X), then check whether each $Z \in \mathbf{V}_X$ adds a statistically significant amount of information $T_{Z \to X|\mathbf{V}_X \setminus Z}$ given all of

the other sources selected for $\mathbf{V}_X$. Where a source fails this test it is removed from $\mathbf{V}_X$. Importantly, if multiple sources fail the test, then we remove only the source Z which provided the least amount of information $T_{Z \to X|\mathbf{V}_X \setminus Z}$, then repeat this step with the remaining $\mathbf{V}_X$. The partitioning of $\mathbf{D}$ into $\mathbf{V}_X$ and $\mathbf{D} \setminus \mathbf{V}_X$ could be further explored here using the Kernighan-Lin optimisation algorithm [25], which uses several steps to test not only the aforementioned pruning, but also a local-maxima avoidance strategy to explore whether other additional sources in $\mathbf{V}_X$ may provide a better solution.

We refer to the algorithm including steps 5 and 6 as the *enhanced iterative greedy method*.

Certainly, the most recently selected source in $\mathbf{V}_X$ has already passed the pruning test of step 6. Each other source passed the test at the time they were selected, however they were selected when $\mathbf{V}_X$ contained less other sources. As such, there is a possibility that sources selected later by the algorithm (say Z_2 and Z_3 in the previous example) are able to provide all of the information provided by an earlier selected source (i.e. source Z_1 in the previous example). This step serves to make sure that we have identified the *simplest* set $\mathbf{V}_X$ that can be used to maximally, statistically significantly predict X. As such, it ensures that our selection $\mathbf{V}_X$ meets the goal we articulated at the start of Section IV. The removal of only one source at a time is important, since this avoids a situation where all sources providing redundant information are removed, leaving no sources in $\mathbf{V}_X$ containing this information about X (which is a key problem with the exclusive use of the analogue of complete transfer entropy in [24]). Crucial also is that this pruning step will not remove sources which provide significant joint interaction-based outcomes with other sources in $\mathbf{V}_X$, since the interaction-based contribution is captured in $T_{Z \to X|\mathbf{V}_X \setminus Z}$. Furthermore, this step helps to add some robustness against spurious source selection: were a spurious source to be selected at an early step simply due to statistical fluctuations, there is the opportunity to remove it here if the real sources providing the same plus more information were discovered at a later step.

Finally, we note that our basic iterative greedy algorithm could viewed as analogous to *forward feature selection* in the domain of machine learning, where the "features" here are the source nodes and one is trying to learn/predict the destination node. An important distinction though is that our algorithm seeks to limit its inference as a function of the amount of available data (as detected by the statistical significance tests), whereas feature selection typically includes as many features as one is able to process. Furthermore, we note that the idea of iteratively constructing source nodes for a given destination is considered by Faes et al. [26]. The perspective of the algorithm is different, seeking to judge whether a single link should be inferred rather than considering how to infer a network, yet the end result is somewhat equivalent. The algorithm presented in that study also seeks to limit inference as a function of statistical power, and uses bias correction to check that newly added sources are reducing the remaining entropy beyond the bias level. This is weaker than a test of statistical significance used here, since a source could appear to reduce entropy beyond the bias level, but still not do so in a statistically significant fashion. This could also lead to spurious sources with high entropy but low statistical significance being included instead of lower entropy actual sources.

B. Comments on the technique and parameter setting

Before testing the algorithms, we explore parameter setting options and provide comments on the properties of the technique.

1. History length to condition on

We have three available choices regarding how to handle the history length k of the destination variable X in the transfer entropy measurements, and consequently our interpretation of *self-links* in the network:

- Set k to a large value, implicitly including $x_n^{(k)}$ in $\mathbf{V}_X$. This takes a *computational perspective* of the information in the next state, properly decomposing it into stored and transferred information. This is advantageous if one wishes to understand the emergent computation taking place on the network (i.e. akin to describing computation in cellular automata in terms of blinkers, gliders and glider collisions [16, 17, 21]). It specifically ensures that effective connections are inferred where new information is transferred from the source to the destination. This approach may be closer to the spirit of effective network inference in seeking a minimal network to replicate the dynamics.

- Minimise k to include only the $x_n^{(k)}$ which are (or at least are thought to be) direct causal sources to x_{n+1} (implicitly including $x_n^{(k)}$ in $\mathbf{V}_X$). In many systems this would result in setting $k = 1$. Such a setting brings the measures closer to approximating the *causal* influence of sources on the destination [5].

- Set $k = 0$ in relevant transfer entropy equations, making them simply mutual information or conditional mutual information measurements. This makes no assumption about self-links in the data set, and is the most model-free approach. In following this approach, one should then allow the previous step of the destination x_n to itself be selectable for $\mathbf{V}_X$ from the set of sources, such that self-links can be inferred if they are statistically significant.

Each of these options could be justified from certain perspectives, and so the choice between them depends on precisely how the user wishes to interpret the effective network.

2. False detection rate

In theory, one should correct for multiple comparisons, e.g. the common Bonferonni correction by correcting the threshold for the statistical significance tests from the original α to $\alpha_c = \alpha/L$ where L is the number of possible connections evaluated. This allows one to interpret the selected α as the (upper limit on the) probability that we infer at least one connection in the network due to statistical fluctuations (if the source and destination actually had no relationship under the null hypothesis).

In performing statistical tests with the apparent transfer entropy only, it is clear that one makes $|\mathbf{D}|(|\mathbf{D}| - 1)$ comparisons, and computing a correction is straightforward. With multiple rounds of comparisons in our approach, it is possible that one may compare the same source-destination pair multiple times (i.e. if a source Z_1 were rejected initially, with another source Z_2 selected, then the source Z_1 is tested again using a transfer entropy conditioned on Z_1). It is unclear how many times the pair may be tested, since we do not know a priori how many sources will be selected for each destination (and therefore how many times a source might be tested). As such, it is difficult to judge what correction should be made here. However, we observe that:

1. the algorithm will not make a statistical test for each source $Z \in \mathbf{V_X}$ until the final selection round when no source is found to be significant, and it is likely that when

a significant source is found that only very few sources were previously evaluated for statistical significance in that round;

2. the comparisons for the same source in different rounds (with more other sources conditioned on in later rounds) are not independent, and indeed we conjecture that a spurious source with high statistical significance (due to correlations to actual sources) in an early round is likely to have reduced statistical significance in later rounds once the actual sources are discovered.

As such, we conjecture that the multiple rounds of comparisons in our approach are not likely to lead to a higher false discovery rate for spurious sources than in the baseline apparent transfer entropy approach.

Of course, we note that one could simply view the α in use as adjusting the sensitivity and hence the true-positive/false-alarm trade-off (e.g. driving the locus of the receiver/relative operating characteristic or ROC curve), and not rely so much on directly interpreting its numerical meaning.

3. A pluggable general algorithm

In the preceeding description, we have not made any description of how the transfer entropies are measured here. This is because the iterative greedy algorithm(s) are applicable to any type of entropy estimation techniques, i.e. using discrete-valued variables or otherwise discretising continuous valued data, or using kernel estimation with static [8, 27] or variable [28] kernel widths for continuous-valued data, etc.

We also note that the iterative greedy algorithm(s) presented here for the conditional transfer entropy could be applied identically to with partial correlations / Granger causality as the directional measure. Clearly one loses the advantages of nonlinearity and model freedom of the transfer entropy technique, though if the underlying time-series are Gaussian with linear relationships the two measures are equivalent anyway [29], and the linear methods require much less data and can be evaluated much more quickly (indeed there are analytic alternatives to the use of bootstrapping for the statistical significance testing).

4. *Consider variable time-lag for all sources*

As previously stated, to simplify the mathematics above we have assumed that direct influences on x_{n+1} come from potential source variables z_n for $Z \in \mathbf{D}$ at time step n only. Of course, we could consider all source variables $z_{n+1-\lambda}$ for some other known source-destination time lag λ instead of simply using $\lambda = 1$. More generally though, the source-destination time lag could be unknown and different for each interaction. This is known to be the case in real neuro data sets, and indeed other authors have examined how to select the appropriate delay from one source to a destination [10, 11].

As such, our algorithm can be generalised by considered potential sources $z_{n+1-\lambda}$ for $Z \in \mathbf{D}$ for various delays say $\lambda = 1 \ldots l$. There is certainly no problem in selecting contributions from two or more lags from the one source Z to X; obviously this does not alter the inferred effective network structure, but does provide additional information to explain the dynamics. Furthermore, we note that widening our consideration for l possible delays simply linearly increases the time complexity of the algorithm by a factor l. The consideration of various source-destination lags is included in the approach of Faes et al. [26].

V. APPLICATION TO PROBABILISTIC RANDOM BOOLEAN NETWORKS

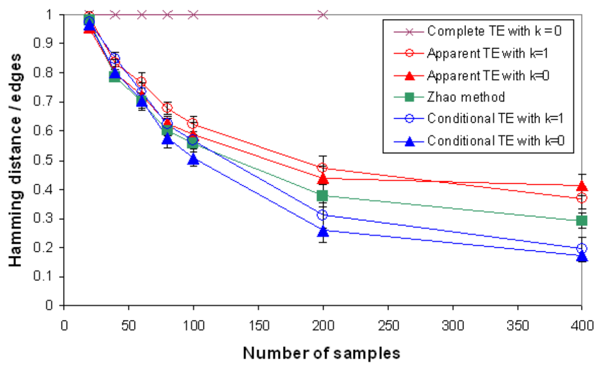
To explore the performance of our technique, we test it using time series observations of *probabilistic random Boolean networks* (pRBNs). These models are chosen for testing for several reasons. RBNs provide a very large sample space of dynamics, including highly non-linear behaviour and the inclusion of collective interactions, making the task of effective network inference here particularly challenging. Adding to this challenge is the inclusion of stochasticity on the Boolean functions (i.e. the "p" in pRBNs). Importantly, RBNs (and pRBNs) are an important model for Gene Regulatory Networks [18], a domain where researchers face similar challenges to computational neuroscientists in inferring underlying network structure, and pRBNs have been used to test such inference methods in this domain (see e.g. [30]).

Here, we use software from Zhao et al. [30] to generate pRBN networks and dynamics to test our method against. We simulate pRBNs with 20 nodes, and 40 directed edges randomly assigned subject to a maximum of 3 incoming edges per node (self-links are allowed). Each node has a random Boolean function assigned from its inputs (subject to each node being an information contributor to that function[31]) and then fixed for the experiment. Dynamics are generated by starting the network in a random state, and then each node executes its update function synchronously for each time $n+1$ using the values of the input nodes at time step n. The rule executions at each time step for each node are subject to a 0.20 probability of bit-flipping (i.e. noise). The inclusion of only rules where each node contributes (making collective interactions more prominent than in ordinary RBNs) and the addition of noise makes the inference task more challenging here.

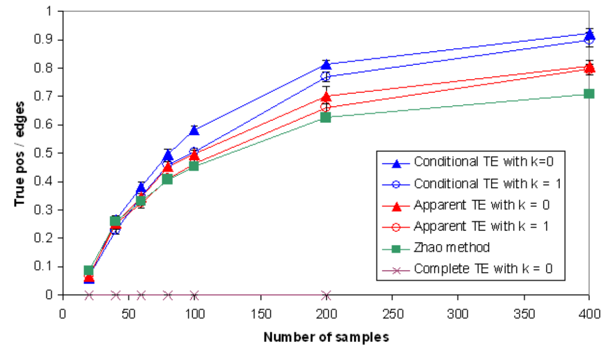
We evaluate the performance of our technique and standard apparent TE inference by comparing the inferred effective network to the known underlying structural network. We have discussed previously that effective network inference should not necessarily be to reproduce the underlying structural network, but must certainly reflect it. Indeed, in this example where the network performs a random exploration of the state space of possible dynamics (due to the random initial state, and noise at each step) as opposed to being driven by task-related inputs, and we ensure that the causal inputs occur in step with the time-series observations we have, then we should expect good effective network inference to closely reflect the underlying structure, given enough observations. Evaluation against the underlying structural network also provides insight into how well our method improves on the apparent transfer entropy technique in terms of detecting true collective interactions and avoiding inferring spurious connections due to correlations only.

We investigate these methods using several different numbers of time-series observations ($N = 20$ to 400), and set the threshold for the tests of statistical significance at $\alpha = 0.01$ (no adjustment for multiple comparisons; we are viewing α as a sensitivity parameter for ROC performance). We present the results in terms of Hamming distance of the inferred effective network from the underlying structural network, true positive count and false positive count in Fig. 3 (note all counts are normalised by the total number of actual causal edges here, 40). The Hamming distance measure is simply the sum of the other two measures.

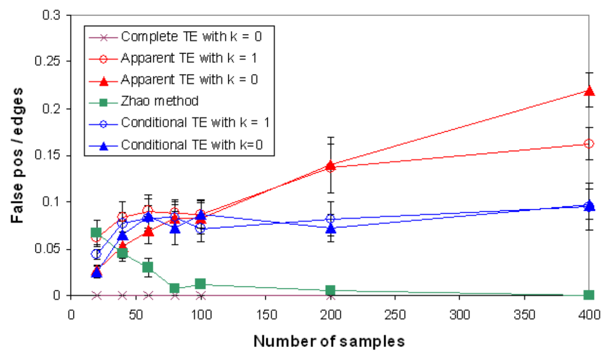
First, the plots show that inferring effective networks using the complete TE (i.e. conditioning on all other nodes in the network) has no utility from the finite number of samples here - it is not able to statistically significantly infer any connections, so has no false positives but no true positives either. This was as expected when we discussed the proposal of this method by Quinn et al.[24] in Section III.



(a)Hamming distance



(b)True positives



(c)False positives

FIG. 3. Comparison of the effective networks produced by our technique (Conditional TE) as compared to other techniques (Apparent TE, Complete TE and Zhao's method), as evaluated by (a) Hamming distance to the underlying structural network, (b) true positive and (c) false positive count (all normalised by the actual number of edges in the structural network), versus the number of time-series observations N used.

Next, the Hamming distance plot in Fig. 3(a) shows that both the established apparent transfer entropy technique and our iterative conditional transfer entropy technique (with the basic greedy method) are able to produce inferences which are reasonably close to the underlying structural network, when enough observations are used. In particular, both exhibit strong performance increase as the number of observations increases.

Crucially though, *our iterative conditional TE technique provides substantially better performance than the apparent TE technique.* This could be summarised in that from 400 time-series observations, our iterative conditional technique provides an effective network with approximately half the deviation from the underlying structural network than the apparent TE method does. From another perspective, the iterative conditional TE method is able to produce an effective network closer than the structural network as the apparent TE method does with 400 time-series observations, but with half the number of observations.

This is as expected from the advantages of the conditional TE discussed in Section II A, which are properly utilised by our technique as discussed in Section IV. In particular, we know that the conditional TE detects collective interactions that the apparent TE cannot, and this is demonstrated in the significantly larger true positive rate for our technique in Fig. 3(b) (approaching an impressive 90% of the network with 400 time series observations). Furthermore, the conditional TE dismisses spurious connections due to correlations where the apparent TE cannot, and this is demonstrated in the significantly smaller false positive rate for our technique in Fig. 3(c).

Interestingly, the false positive rate for the apparent TE technique appears to be increasing with the number of time-series observations in Fig. 3(c). This may be due to spurious correlations (e.g. between Z and X due to a pathway relationship $Z \rightarrow Y \rightarrow X$) appearing to have more statistical significance with regards to apparent TE when they are measured over a larger number of time-series observations. In contrast, the false positive rate for our technique remains stable with the number of time-series observations used. In part this is because our conditional TE based technique is better able to properly ignore such spurious correlated sources by conditioning out the actual primary sources (since by the data processing theorem these sources should be selected first, at least in the absence of noise, and should be more likely to be selected in the presence of noise). Indeed, the false positive rate remains stable around the level at which one would expect from the given $\alpha = 0.01$ (i.e. at $0.1 * 40 = 4$ false inferences out of 360 non-existent edges, giving a false positive rate of 0.011). This may seem surprising, since as discussed in Section IV B 2 more statistical tests are made with our technique, and an increase in false positives could be expected. As suggested there however, it seems that no increase in false positives is observed since there are generally not many more statistical tests actually made with the technique in practice, and indeed when they do occur they are not independent of the tests at the preceding step.

Note that we have plotted results for both setting $k = 0$ and 1. For $k = 0$, the network can infer self-links where it seems they exist, whereas with $k > 0$ these cannot be inferred: in both cases we normalise by the number of links that could be inferred by that technique. As discussed regarding the choice of this parameter in Section IV B 1, we could expect the performance with $k = 0$ to be closer to the underlying structural network - since the nodes do not in general have a causal influence on their next state, so this approach is a better model to the causal process. Certainly, this expectation bears out to an extent. We see that for an intermediate number of observations, the inference with $k = 0$ out-performs that with $k = 1$ for both the apparent TE technique and our conditional TE technique. The performance gap seems to close at larger numbers of observations though, and for the apparent TE it is reversed due to a significantly larger false positive rate with $k = 0$. It seems then that conditioning on the history of the destination, even if it is not a causal source, may provide some stability against false positive inference. As previously discussed Section IV B 1, the choice between these parameter settings largely comes down to what the user wants the effective network to represent. The performance gap for matching the structural network is not as large as one may expect, and indeed it seems $k > 0$ adds some stability, as well as the ability to interpret the results as representing computation on the network.

Finally, note that we have included the inference results from the technique presented by Zhao et al. [30], as calculated using the software distributed for that paper. The method of [30] uses pairwise, cross-time mutual information measurements across the network, then explores all of the different thresholdings of these to see which minimises a cost function combining the description length of the network (i.e. the number of links) and unexplained uncertainty in the state of the nodes. We note that our conditional TE technique significantly outperforms that of [30] in terms of the Hamming distance and true positive rate, though does have a larger false positive rate. It is important to note that the sensitivity parameter for the technique from [30] used here $\Gamma = 0.4$ cannot be tuned to provide a better true positive or Hamming distance here.

VI. DISCUSSION AND CONCLUSION

We have presented an iterative greedy method to infer effective networks from multivariate time-series observations using incremental conditional transfer entropy measurements. Our technique is consistent with the original intention of effective network analysis, in that it seeks to infer the simplest network to explain the observed dynamics. In particular, it does so by considering how the dynamics of each node are *computed* as a function of the source nodes, and hence our approach infers effective *computational* networks.

In being information-theoretic, and based on the transfer entropy, our technique provides inference of directional, non-linear relationships, using model-free analysis. We provide a crucial improvement to effective connectivity analysis over standard apparent transfer entropy analysis by using (iteratively) conditional TE, which is known to capture collective multivariate interactions (e.g. XOR relationships) and ignore spurious correlations (e.g. from pathway or common cause effects). Importantly, we structure an iterative greedy algorithm (with enhancements) in such as way as to avoid combinatorial explosions in the number of source combinations considered, while avoiding conditioning out all redundant contributions (only removing them when the redundant information has already been included in the network). Furthermore, in employing rigorous tests of statistical significance, we avoid overfitting and limit the inference to the statistical power in our data set. Importantly also, our technique infers an effective network which is usefully able to explain the dynamics of the nodes using (conditional) probability distributions; such explanation is a key goal of effective network inference.

While our effective connectivity approach does not explicitly seek to infer the causal or structural network underpinning the data, it should reflect this network, and given a large ensemble of input distributions to the network or sampling across many types of biases, it may indeed also provide useful inference of the structural network from the observational data. Indeed, we have demonstrated the validity of the technique using the particularly challenging example of probabilistic random Boolean networks, showing in particular that our conditional TE based approach significantly outperforms standard apparent TE effective network inference (when evaluated against the underlying structural network).

In future work, we seek to apply the technique to various types of brain recordings. In doing so, we will certainly need to incorporate several practical considerations, including variable source-destination lags as discussed in Section IV B 4. We shall also seek to refine the steps of our algorithm, in particular the post-processing optimisation steps.

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[2] For example, using the "back-door" approach (as discussed in [3, 5]), though this requires a priori knowledge of where all other causal links are to the given node, defeating the purpose of general inference.

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[22] Note that the correctness of these equations is independent of k; altering k merely changes the proportions of information that is attributed to either the information storage or the entropy rate.

[23] Rotation is required where one is considering multiple past values of the source, e.g. performing an embedding of l past values to obtain a state vector of the source $y_n^{(l)}$, or otherwise requires the entropy rate of the source to be preserved. Otherwise, if considering a single past source value y_n only, investigation of the null hypothesis to destroy the relationship $p(x_{n+1} \mid x_n^{(k)}, y_n)$ is facilitated by shuffling alone.

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