Brain Activity: Connectivity, Sparsity, and Mutual Information

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Abstract—We develop a new approach to functional brain connectivity analysis, which deals with four fundamental aspects of connectivity not previously jointly treated. These are: temporal correlation, spurious spatial correlation, sparsity, and network construction using trajectory (as opposed to marginal) Mutual Information. We call the new method Sparse Conditional Trajectory Mutual Information (SCoTMI).

We demonstrate SCoTMI on simulated and real fMRI data, showing that SCoTMI gives more accurate and more repeatable detection of network links than competing network estimation methods.

I. INTRODUCTION

Resting state brain activity measurements are used to characterise pathological brain states [13, 16, 21], changes in brain function through ageing [19], pharmacological effects [22], or changes due to electrical or magnetic brain stimulation [2, 25].

The advent of resting state brain activity analysis [10, 24, 33, 54, 55, 57, 60, 70] has given a strong impetus to the study of the network aspects of brain structure and function. Brain activity analysis has consequently moved from spatial localisation of task-specific activity responses to a network view of measuring the interactions between brain regions.

In this work we divide the brain into regions representing network nodes using a cortical parcellation as shown in Fig. 1.

Figure 1: A parcellation of the cortical surface into spatial nodes, defined by anatomical boundaries. Although we must account for activity within each brain region, we are interested in finding the activity links between these regions when the brain is resting.

Resting state network analysis is concerned with network function, and has traditionally been broken into two types. Functional connectivity, which measures the strength of connection between nodes with correlation or partial correlation; and effective connectivity which measures the influence that one group of nodes may exert on another group of nodes.

But aside from function there is also structure. So far this has been taken to be synonymous with anatomical networks as probed, for example, with Diffusion Tensor Imaging.

This paper is concerned with functioning and so we will not discuss anatomical networks further. Also we will not be dealing with directional influence and so will not discuss effective connectivity.

However functional networks also have structure. This is most evident in the use of descriptive measures of graph analysis such as path length, node degree and centrality [65, 73]. These are most commonly employed in the search for so-called small world structure [11, 24].

Because the word structure is so closely identified with anatomical networks we will use the word architecture instead to avoid confusion.

We now raise four issues of activity network analysis that need to be jointly dealt with; although all of them have been raised before, no previous work treats them simultaneously.

The current approach to brain activity network analysis is based mostly on static correlation, either explicitly as in seed correlation methods [7] or indirectly via ICA [5] or PCA [39]. There are two problems with this: spurious spatial correlation and temporal correlation.

Firstly, direct spatial interactions cannot be discriminated from spurious (or indirect) spatial interactions if measured by correlation. The activity time series at node A may be correlated with that at node B not because nodes A and B are directly related (or even anatomically linked) to each other but because they are both related to the activity time series at node C. In a static context this problem can be overcome by using partial correlation [71]. Partial correlation has indeed been advanced in recent reviews of fMRI connectivity literature [57, 67], simulation studies [56], and some real data analyses for estimating functional connectivity networks [15, 44, 48].

The network (graph) is constructed from the partial correlation as follows. Two nodes are linked if and only if their partial correlation is non-zero. Nodes that are not linked are thus conditionally independent (CI) of each other (given all the other nodes) if the data is Gaussian. The resulting graphs thus represent conditional independence graphical models (CIGMs) [38, 71].

But then the second problem emerges, since both correlation and partial correlation are static measures that do not acknowledge the temporal correlation present in all brain activity time series [54]. The notion of conditional independence between time series is strongly influenced by the profile of temporal interactions, rather than just zero-lag interactions as for white noise signals. If $x_t$ is white noise and $y_t = x_{t-1}$ then their zero-lag correlation is zero; but cross coherence will pick up the strong dependence between the two time series. So one needs to replace correlation with frequency domain coherence and thus replace partial correlation with partial coherence.

To account for both temporal correlation and spurious spatial correlation we then need to build brain activity networks based on partial coherence [18].

Temporal correlation has been addressed in the brain connectivity literature using vector autoregressive models (VARs) [27, 28, 31, 64]. But these works did not address the spurious spatial correlation issue.

Both issues have already been pursued in an important previous
The remainder of the paper is organised as follows. In Section II we develop SCoTMI as a valid measure of time series network topology in a CIGM framework. Section III contains results and discussion of simulated and real data analyses. We offer conclusions in Section IV.

II. SPARSE CONDITIONAL TRAJECTORY MUTUAL INFORMATION

The method comprises three steps,

A) Sparse Network System Identification. We fit a sparse VAR model at each node, accounting for potential contributions from all other nodes. Network sparsity is induced with a vector $\ell_0$ penalty [52, 53].

B) Network Partial Coherence Spectra. These can be computed analytically from the sparse VAR model.

C) Calculating Trajectory Mutual Information. This is computed from the partial coherences in the frequency domain. It is then used to construct the connectivity network or graph.

A. Sparse Network System Identification

Fitting a VAR model identifies marginal time-lagged interactions between network nodes, where the interaction between each pair of nodes is calculated in the presence of all other node interactions. In this section we are concerned that a full VAR has too many parameters to fit for the network dimensions we are interested in. For example modelling a moderately sized brain activity network of 150 nodes by fitting a 5th order VAR requires estimating 750 parameters, and since fMRI data are often sampled at fewer than 1000 time points, the degrees of freedom for estimation are insufficient to obtain a reliable estimate of true parameters.

A solution to this issue is found by exploiting the underlying sparsity of brain connectivity links to set most VAR parameters to zero. This can be achieved by modifying the least-squares VAR model fitting criterion with a sparsity penalty.

We use a variation of the vector or grouped-parameter $\ell_0$-regularised least squares (gL0LS) cost function [12, 53] to give a sparse estimator where the parameters measuring temporal correlation from one node to another are all zero or all non-zero. The same objective has been pursued using an $\ell_1$ penalty [32, 40] but that induces an amplitude bias in the estimated parameters, and the $\ell_1$ penalised estimate is generally not as sparse as that found using an $\ell_0$ penalty. The grouping is crucial since it enables links between nodes to be completely removed; without grouping (as in [64]) few if any links will be removed.

Note that in [53] a parameterisation different to VAR was used.

Although we are primarily interested in the interactions between nodes, there is nearly always some autoregressive (AR) structure within each fMRI data time series. This suggests we adopt the cost function proposed by [8] which does not penalise the presence of univariate AR characteristics within each node signal.

We denote the new method as gL0LS-SC, mirroring the terminology of [8] since it does not penalise self-connections.

Let $y_t = [y_{(d)}, \epsilon_t]$, be a network with $D$ nodal time series sampled at times $t = 1, \ldots, T$. We denote a particular node with subscript $d$, and a pair of nodes via subscripts $a, b$.

We first note the crucial separability property of VAR fitting, enabling a sparse VAR model fit at each node (see Appendix A). This adds flexibility to the model fitting to allow specification of a different VAR model order for each node, in addition to computational savings due to the separable model fit.
We construct the VAR($p$) regressors as

$$X_t = \left[ X_{(1),t}, \ldots, X_{(D),t} \right]^T$$

$$X_{(d),t} = \left[ y_{(d),t-1}, \ldots, y_{(d),t-p} \right]^T$$

and so the separable VAR($p$) model to fit at node $d$ is

$$y_{(d),t} = X_t^T \alpha_{(d)} + \epsilon_t$$

$$= \sum_i X_{(d),t}^T \alpha_{(d),i} + \epsilon_t$$

where $\alpha_{(d),i}$ is the $p$-vector of parameters corresponding to the VAR model to node $d$ from every node $i \in 1, \ldots, D$. So there are $D$ regressions to fit for the full VAR model.

Optimising at each node separately for $d = 1, \ldots, D$, the cost function to minimise is a sparsity penalised least squares function,

$$J(\alpha_{(d)}) = \sum_{t=1}^{T} \frac{1}{2} \left\| y_{(d),t} - X_t^T \alpha_{(d)} \right\|^2 + h \sum_{i \neq d} I(\|\alpha_{(d),i}\| \neq 0)$$

where $h$ is a tuning parameter to be chosen.

The gLOLS estimate for $\alpha_{(d)}$ can be calculated by cyclic descent [41]. To update the parameters $\alpha_{(d)}$ at the $k$th iteration, we loop through all nodes $i = 1, \ldots, D$ to calculate the sub-vectors of parameters $\alpha_{(d),i}$ separately as,

A) Compute the residual vector $e_k = y_d^t - X \hat{\alpha}_{(d),i}^t$

B) Compute the vector of covariances $\gamma_k = X_{(i),t}^T e_k$

C) $\alpha_{(d),i}^{k+1} = \left\{ \begin{array}{ll} \gamma_k^T + \alpha_{(d),i}^k \| \gamma_k^T + \alpha_{(d),i}^k \| \geq \sqrt{h} & i \neq d \\ \gamma_k^T + \alpha_{(d),i}^k & i = d \end{array} \right.$

and the residual vector is recalculated after every parameter update. Iteration proceeds until $\left\| J(\alpha_{(d)}) - J(\alpha_{(d)}^{k+1}) \right\| < \delta$ for some tolerance $\delta$. The regression sub-matrices $X_{(i)} = [X_{(i),1}, \ldots, X_{(i),T}]^T$ are orthogonalised; although the algorithm can be derived without this assumption, the orthogonality improves numerical conditioning and the unscaled system allows simpler selection of tuning parameters: see Section II-E for further discussion. This method is a variation of the cost function and algorithm introduced in [12, 53].

gLOLS-SC directly discards parameter groups and then uses the least squares estimate for those parameters remaining. $\hat{\epsilon}_t$ regularised estimates by contrast provide biased estimates of the parameters.

Tuning parameter $h$ and model order $p$ are selected using an information criterion; details are in Section II-E.

B. Network Partial Coherence Spectra

Consider a $D$-vector time-series $y_t$ partitioned as $y_t = (y_a^t, y_b^t, z_t)^T$ for two signals of interest $y_a^t$ and $y_b^t$. The temporal correlation is expressed parametrically using a VAR model as

$$A(L) y_t = \epsilon_t \sim N(0, \Sigma)$$

where $L$ is the lag or backshift operator.

Components of the filter transfer function $A(e^{-j\omega})$ (which by an abuse of notation we write as $A(j \omega)$) can be calculated for each node-pair as

$$\alpha_{ab}^\omega(j \omega) = \left\{ \begin{array}{ll} 1 - \sum_{k=1}^{p} \alpha_{ab}^k e^{jkw} & a = b \\ -\sum_{k=1}^{p} \alpha_{ab}^k e^{jkw} & otherwise \end{array} \right.$$

and the parameters can be arranged in columns as $g_d(j \omega) = [\alpha_{dd}^1(j \omega), \ldots, \alpha_{dd}^p(j \omega)]^T$.

Then partial coherence between $y_a$ and $y_b$ is then (see Appendix B)

$$\rho_{y^a y^b|z}^\omega = \frac{-g^H_a(j \omega) \Sigma_{-1} g_b(j \omega)}{\sqrt{g^H_a(j \omega) \Sigma_{-1} g_a(j \omega) \sqrt{g^H_b(j \omega) \Sigma_{-1} g_b(j \omega)}}$$

We have found this key analytical result independently; it was previously stated without proof by [4].

The partial coherence computation can be implemented via the lower diagonal Cholesky factorisation to improve calculation speed and stability. Assuming $\Sigma$ is positive definite,

$$\Sigma^{-1} = \Gamma^{-T} \Gamma^{-1}$$

then we have

$$g^H_a(j \omega) \Sigma^{-1} g_b(j \omega) = g^H_a(j \omega) \Gamma^{-T} \Gamma^{-1} g_b(j \omega)$$

$$= \left( \Gamma^{-1} g_a(j \omega) \right)^H \left( \Gamma^{-1} g_b(j \omega) \right)$$

$$= h^H_a(j \omega) h_b(j \omega)$$

where we precompute as

$$\Gamma^{-1} A(j \omega) = \Gamma^{-1} (g_1(j \omega), \ldots, g_D(j \omega))$$

$$= [\Gamma^{-1} g_1(j \omega), \ldots, \Gamma^{-1} g_D(j \omega)]$$

$$= Q(j \omega)$$

$$= [q_1(j \omega), \ldots, q_D(j \omega)]$$

C. Calculating Trajectory Mutual Information.

When conditional independence (CI) graphs are phrased in terms of scalar random variables [38, 71], then CI is equivalent to zero partial correlation or equivalently zero partial scalar mutual information [71]. But the theory can handle vectors, allowing us to account for temporal dependencies; then CI is equivalent to the vanishing of a partial correlation matrix between two nodes. We will first show this is equivalent to the vanishing of a Conditional Mutual Information (CMI). The classic reference on Mutual Information is [17]. We just remind the reader that the MI between two random vectors $x_a, x_b$ is $I(x_a; x_b) = \int p(x_a, x_b) \log \left( \frac{p(x_a, x_b)}{p(x_a)p(x_b)} \right) \, dx_a dx_b$ where $p(x_a)$ is the marginal probability density of $x_a$ and $p(x_a, x_b)$ is the joint probability density between $x_a, x_b$; in the zero mean Gaussian case this is $I(x_a; x_b) = - \frac{1}{2} \ln(\|\Sigma_a/\Sigma_{ab}\|\Sigma_b))$ where the $\Sigma$ denote corresponding variance matrices. If $x_a, x_b$ are scalar random variables this can be written as $I(x_a; x_b) = - \frac{1}{2} \ln(1 - \rho_{ab}^2)$ where $\rho_{ab}$ is the correlation between $x_a$ and $x_b$.

1) Mutual Information and Partial Correlation Matrices: Let $x_a^t, x_b^t, t = 1, \ldots, T$ denote (scalar) time series at two nodes of interest. Collect the time series into $T$-vectors $x_a, x_b$. Then we are interested in the Conditional Independence of these node random vectors. Let $z_{ab}$ (or just $z$) denote the vector of time series at other nodes.

Then we have,

a) Theorem CMI: $x_a, x_b$ are CI given $z_{ab}$, if and only if $I(x_a; x_b|z_{ab}) = 0$; i.e. conditional mutual information (CMI) vanishes.

b) Theorem MIPC: The partial correlation matrix between $x_a, x_b$ given $z$ vanishes if and only if $I(x_a; x_b|z_{ab}) = 0$.

These results are well known and can be found in classic references [17, 71] but also [59]. For completeness we give a proof in Appendix C.

To continue we represent the CMI in the frequency domain.

2) CMI in the Frequency Domain: If $x_a^t, x_b^t, z_t$ are jointly stationary then as $T \rightarrow \infty$

$$\frac{1}{T} \int_{-\pi}^{\pi} I(x_a^t; x_b^t|z_t) \, d\omega \rightarrow -\frac{1}{2} \int_{-\pi}^{\pi} \ln \left( 1 - |\rho_{ab}(\omega)|^2 \right) \frac{d\omega}{2\pi}$$
where the partial coherence \( \rho_{ab|z}(\omega) \) is

\[
\rho_{ab|z}(\omega) = \frac{F_{ab|z}(\omega)}{\sqrt{F_{a|z}(\omega) F_{b|z}(\omega)}},
\]

and \( F_{a|z}(\omega) \) is the conditional spectrum of \( x^a \). \( F_{b|z}(\omega) \) is the conditional spectrum of \( x^b \), and \( F_{ab|z}(\omega) \) is the conditional cross-spectrum between \( x^a \) and \( x^b \). These conditional spectra can be interpreted such that, e.g., \( F_{a|z}(\omega) \) is the spectrum of the stationary residual obtained after \( x^a_\tau \) is regressed on \( z_\tau \).

This result, due to [29], is quoted in [50] without proof; for completeness we sketch a proof in Appendix D.

3) Computation of CMI: We calculate conditional trajectory Mutual Information by discretisation as

\[
I(\mathbf{y}^a; \mathbf{y}^b | \mathbf{y}^z) = -\frac{T - P}{2K} \sum_{k=1}^{K} \ln \left( 1 - \left| \rho_{ab|z} \left( 2\pi \frac{k}{K} \right) \right|^2 \right)
\]

where \( K \) is the number of samples of the DFT and \( p \) is the maximum estimated VAR order.

D. Conditional Independence Graph from SCoTMI

Now we can construct a CI graph.

We calculate the SCoTMI between each pair of nodes and then thin out the graph by thresholding.

The null hypothesis of no active links is

\[ H_0: I(x_a; x_b | z_{ab}) = 0, \ a \neq b \]

and we refer to the model under the null hypothesis hereafter as the null hypothesis model. The univariate AR structure of the null hypothesis model \( I(x_a; x_b | z_{ab}) \neq 0 \) for \( a = b \) under \( H_0 \) means the analytic behaviour of the SCoTMI statistic is difficult to characterise; so we calculate empirical null distributions by simulation, and standardise the SCoTMI scores via mean subtraction and dividing by the standard deviation to generate an appropriate threshold.

This is a crucial step since, as [72] has recently emphasised, the large number of voxels versus small number of time points makes connectivity measures extremely noisy and simulations show the sobering result that even white noise data can exhibit substantial structure because of this.

The threshold is adjusted with Bonferroni correction for multiple comparisons.

E. Implementation Details

1) Model Conditioning: The gLOLS-SC algorithm requires each column group of regressor variables \( X(d) \) to be orthogonal, as \( X(d)^T X(d) = I_p \). This is easily imposed from raw unscaled variables \( \tilde{X}(d) \) via the Cholesky factorisation as \( X(d) = \tilde{X}(d) \tilde{X}^T(d) \tilde{X}(d) \). The problem is therefore solved for scaled VAR parameters \( \alpha(d) = \left( \tilde{X}(d)^T \tilde{X}(d) \right)^{\frac{1}{2}} \hat{\alpha}(d) \) and is similarly unscaled to calculate the final estimates \( \hat{\alpha}(d) \).

2) Initial Estimate: Non-convex optimisation is highly dependent on initial conditions. We initialise the gLOLS-SC algorithm with an \( \ell_2 \) regularised parameter estimate, where the corresponding initialisation tuning parameter \( h_2 \) is chosen using Stein’s Unbiased Risk Estimator (SURE) [61]. Some advantages of SURE over other model selection methods are that SURE is unbiased, does not assume that the fitted model is the same as the operating model, and does not use approximations such as linearisation or series expansions [58]. Alternately an \( \ell_1 \) regularised initial solution could be used, but we find results are largely identical and the \( \ell_1 \) calculation is slower.

3) Tuning Parameter Selection: The choice of sparsity parameter \( h \) and VAR model order \( p \) is crucial for the gLOLS-SC algorithm. We unscale the model via an initial estimate of the noise variance, then choose \( h \) and \( p \) using the Extended Bayesian Information Criterion (EBIC) [14]. EBIC adjusts BIC for large dimension bias; for selecting two parameters we must find the minimum of the EBIC surface for the penalised regression at each node. We find EBIC tuning parameter \( \tau = 0.5 \) is effective for the models we consider, and our results are robust to the choice of \( \tau \). We use an iterative window search for \( h \), giving an efficient traverse of the parameter space, then optimisation proceeds using an active set algorithm such as in [47].

III. Results

We demonstrate the efficacy of SCoTMI using simulated data and real data examples.

The detection performance of SCoTMI is compared against that of two alternative methods: Sparse Partial Correlation Estimation (SPACE) [47], and the non-parametric conditional trajectory Mutual Information method of [49, 50] which we refer to as nCTMI to distinguish it from other conditional Mutual Information measures.

SPACE has the equivalent aim to SCoTMI of finding sparse network links via Conditional Independence between nodes, but does not account for temporal characteristics. We use the implementation from the authors (cran.r-project.org/package=space), and for rigorous choice of tuning parameter we use the suggested BIC-type model selection criterion defined by the authors in [47]. We expect the results from SPACE to be largely equivalent to other \( \ell_1 \) penalised sparse correlation methods, such as the penalised likelihood methods of [26, 48]; SPACE uses a penalised regression framework (asymptotically equivalent to penalised likelihood for \( \ell_1 \) regularisation), similar to SCoTMI.

The nCTMI method requires specification of spectral tuning parameters; we use the implementation from the authors of [50], setting the tuning parameter \( \tau_{nCTMI} \) to be constant as \( \tau_{nCTMI} = (255(T^{1/5}) + T^{4/5})/256 \). The key difference between nCTMI and SCoTMI is that nCTMI uses a non-parametric calculation of partial coherence, whereas the parametric approach of SCoTMI allows the imposition of a sparse linking assumption to improve model conditioning.

We use the same null thresholding method for nCTMI and SPACE as we do for SCoTMI (described below in section III-A1) in order to provide principled comparison, given that no thresholding procedure is specified in [50], and the standard SPACE thresholding as described in [47] is via the shrinkage threshold from the \( \ell_1 \) penalty.

We select the SCoTMI tuning parameter and model order using the Extended Bayesian Information Criterion as described in Section II-E. Network graph thresholds are adjusted using Bonferroni correction for multiple comparisons.

A. Simulations

We must first establish the behaviour of the model under the null hypothesis where there is no interaction between node channels. This allows a principled estimate of the null distribution, to set appropriate link thresholds.

We then use two models of simulated data:

- A physiologically motivated generative model, and
- A model constructed from real data network topologies and connectivity profiles

to demonstrate the performance of SCoTMI in comparison to SPACE and nCTMI.
autocorrelated noise to each node time series similarly to our null hypothesis. Within each channel, we augment the white noise structure by adding self-interactions that have significant temporal correlation aspects in the intermediate step of sparse VAR modelling. This shows that results are consistent under the conditions we will examine, and allows fast and accurate estimation of thresholds for real data analysis without any computational problems due to large dimensionality.

2) Physiologically Motivated Simulation: To demonstrate identification of links generated from a physiologically motivated network model we use the publicly available NetSim simulation data from [56], where signals are generated using the non-linear balloon model to simulate a Blood Oxygenation Level Dependent (BOLD) response to neural activity.

The raw data has additive white noise rather than autoregressive noise; [24] cites this as a possible reason that lag-based measures of interaction are less effective in the original study [56]. But our intermediate step of sparse VAR modelling shows that only the node self-interactions have significant temporal correlation aspects in the raw (white-noise) data. Although there is already temporal correlation within each channel, we augment the white noise structure by adding autocorrelated noise to each node time series similarly to our null hypothesis model simulations described earlier. This does not affect the interactions between nodes, but simulates some characteristics of physiological noise within each channel.

We use the 7 simulation cases with ≥ 10 network nodes (simulations 2, 3, 4, 6, 11, 12, 17 from [56]); smaller networks cannot represent realistic whole-brain network topologies, and lack the characteristics of sparse linking topologies of larger networks. Simulation conditions are described in Table I.

Results from 50 repetitions of each simulation case in Fig. I show excellent detection for all methods when the number of time points is much larger than the number of system nodes (simulation case 6). Otherwise, SCoTMI outperforms both competing methods in all other cases. In particular, simulation case 4 (Fig. 3b) has the closest dimensionality to the real data we analyse, with 50 nodes; then the SCoTMI method consistently outperforms SPACE and nCTMI.

3) Simulations with Network Topologies from Real-data Interactions: In this section we compare the performance of SCoTMI, SPACE and nCTMI for identification of simulations representing real network dimensions and topologies. These networks are larger than can be stably simulated using non-linear physiologically motivated models, so we use a sparse VAR model with off-diagonal noise covariance to represent network links.

A problem is then how to construct the sparse VAR network to be adequately representative of real fMRI resting state networks. The sparse VAR filter network poles estimated from the real data we analyse in the next Section III-B are jointly distributed throughout the region of convergence (the complex unit circle), whereas constructing a VAR network with network filter poles distributed from a univariate Gaussian has those poles clustered within the region of convergence. So randomly assigned VAR network poles are artificially better conditioned than those from real data, leading to unrealistic simulation results. Since it is not possible to simulate a stable VAR network with hundreds of nodes from pre-specified pole positions, we must then use the VAR poles and network topologies derived from real data.

The simulations use the VAR network poles estimated by the gl0LS-SC algorithm on the real data as described below in Section III-B, with 167 nodes. To provide a robust estimate, we perturb each of the non-zero VAR poles by a small amount as $a_{k_{\text{SIM}}}^{ab} = a_{k_{\text{SIM}}}^{ab} + \epsilon$, $\epsilon \sim N(0, \sigma_{\text{pert}}^2)$, then repeat the simulation for multiple perturbations. We use $\sigma_{\text{pert}}^2 = 10^{-4}$ for this work and unstable perturbations of the VAR network poles are discarded.

Given the gl0LS-SC derived links and associated network poles are from only a half-way point in our SCoTMI algorithm for network identification, these chosen active links do not correspond exactly to the estimated true active links from the SCoTMI method, but do still comprise a principled representation of the underlying physiological system. Each simulation had filter orders up to 167, with 167 nodes. To provide a robust estimate, we perturb each of the non-zero VAR poles by a small amount as $a_{k_{\text{SIM}}}^{ab} = a_{k_{\text{SIM}}}^{ab} + \epsilon$, $\epsilon \sim N(0, \sigma_{\text{pert}}^2)$, then repeat the simulation for multiple perturbations. We use $\sigma_{\text{pert}}^2 = 10^{-4}$ for this work and unstable perturbations of the VAR network poles are discarded.

<table>
<thead>
<tr>
<th>NetSim</th>
<th># Nodes</th>
<th>Time points</th>
<th>Noise (%)</th>
<th>Other</th>
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<tbody>
<tr>
<td>2</td>
<td>10</td>
<td>200</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>200</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>200</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>1200</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>10</td>
<td>200</td>
<td>1.0</td>
<td>Bad ROIs (Time series mixed)</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>200</td>
<td>1.0</td>
<td>Bad ROIs (Spurious added time series)</td>
</tr>
<tr>
<td>17</td>
<td>10</td>
<td>200</td>
<td>0.1</td>
<td></td>
</tr>
</tbody>
</table>

Table I: NetSim simulation conditions; further details of the simulation framework are in [56].
off-diagonal terms $\sigma_{ij}$, $i \neq j$ uniformly distributed over the interval $-1 < \sigma_{ij} < 1$, rather than being constrained as $0.5 < |\sigma_{ij}| < 1$ which produces unrealistically optimistic results.

We simulated 5 perturbations using filter orders $\geq 2$ of the VAR system from each of 40 real data sets. 34 of those gave stable simulations (assessed as stable network filter poles and a positive definite noise covariance matrix) once perturbed to give a total of 170 simulations.

Results in Fig. 4 show all network identification methods are erratic when the number of true links is small. Realistic networks (Section III-B) have $> 100$ links, as detected by all methods, so we regard the results for $< 100$ links as uninformative in practice. We do note though that nCTMI performs well in this unrealistic regime.

For short recording periods with 200 time points nCTMI fails catastrophically, finding no links at all, whereas SCoTMI consistently finds a substantial network. SCoTMI consistently outperforms nCTMI for simulated networks with 500 time points. For a longer recording periods of 1200 time points the performance of nCTMI improves, doing a little better than SCoTMI.

The SPACE method is uncompetitive in all cases.

Results show the area calculated under the Receiver Operating Characteristic curve for false positive rate $\leq 0.2$, and results are consistent for the same cases calculating area under the entire ROC curve.

**B. Real Data**

We demonstrate SCoTMI on publicly available resting-state fMRI data from the Human Connectome Project [66]. The echo-planar imaging data has spatial resolution of $2 \times 2 \times 2$mm voxels and 1200 time samples at a temporal sampling rate of 0.7 seconds. We use the minimally preprocessed data from 10 subjects, comprising four separate scanning sessions for each subject to give a total of 40 individual data sets.

We use only grey matter voxels, collated into 167 non-overlapping regions of interest (ROIs). This provides a comprehensive decomposition of the brain and includes the right and left cortical hemispheres (shown in Fig. 1) as well as subcortical structures and cerebellum. We summarise each ROI using the temporal singular vector corresponding to the largest singular value of the ROI data vector-matrix, to give the representative signal at each network node.

Further data acquisition and preprocessing details are described in [30, 55] (using HCP preprocessing pipeline v3.0).

We first show representative results from the four scanning sessions of a single subject, then we show summary results showing the consistency of link detection for the multiple scanning sessions within a single subject, and between all subjects.

1) Single Scanning Session: Results for a single scanning session (Fig. 5) show some SCoTMI connections are significantly stronger than the others, as represented by line thickness. Commonly cited patterns are discernible, such as the characteristic links between frontal and parietal lobes comprising the default mode network. SCoTMI shows minimal detection of links. The distributions of these links are shown in Fig. 6.

2) Repeatability of Results From a Single Subject: In isolation, it is difficult to objectively claim that networks estimated from a single scanning session using a particular method (SCoTMI, SPACE, or nCTMI) are more or less valid than results from using the other methods. Also, single session results are generally difficult to interpret [10] due to variations in brain activity between scans. But for a
method to have any validity it must be capable of consistently finding (more or less) the same links across multiple scanning sessions for the same person, so we examine results from 40 scanning sessions from 10 separate subjects.

Appropriate comparison can be made by examining two measures:

- The consistency of the distribution of links, between different hemispheres and lobes within the brain.
- The rate that particular links are repeatedly detected across multiple scanning sessions for the same subject.

The distribution of the type of links for all datasets is shown in Fig. 7. Of particular note, SCoTMI detects a more consistent number of links than SPACE within most subjects, and in total across all subjects. The types of links detected by nCTMI are almost exclusively intra-lobe or intra-hemispheric. Contralateral links between the two brain hemispheres are essentially undetected by nCTMI; that is physiologically and anatomically implausible for normal functioning brain activity [46].

Fig. 8 shows that SCoTMI detects far more links repeatedly in 4/4 sessions than either of SPACE or nCTMI methods, for all subjects. Crucially, the higher overall number of links detected for most SPACE results (Fig. 7) does not correspond to a higher rate of repeatedly detected links than estimated by SCoTMI (Fig. 8).

Summary results from four scanning sessions of a single subject are presented in Fig. 9, showing the links detected as active in more than one session; thicker lines denote links detected more often.

Although architectural analysis is not the focus of this paper, key differences in the overall arrangement of SCoTMI, SPACE, and nCTMI results are apparent when the links are shown grouped within and between brain lobes. The grouping of nodes into lobes is only for visualisation and interpreting results, and is not in any way constrained in the modelling process; so any apparent architecture is entirely data-driven.
Although anatomical and activity networks are not necessarily equivalent [63], the pattern of SCoTMI activity links detected in Fig. 9a is consistent with bulk anatomical connections [46] showing strong repeatability for linkage within each cortical lobe, links between the hemispheres and both subcortical structures [51] and cerebellum [36], and some bilateral links between frontal, parietal, and occipital lobes.

3) Repeatability of Results From All Subjects: Summary results, for all 40 scanning sessions from 10 subjects, in Fig. 10 show the SCoTMI method finds a higher proportion of repeatedly detected links than the competing SPACE and nCTMI methods. The repeatedly detected SCoTMI links are anatomically and physiologically plausible [46], being predominantly intra-lobe, intra-hemisphere and contralateral lobe (homotopic connections); this corroborates and substantiates the similar patterns shown for the single subject summary graphs in Fig. 9. The default mode connections between contralateral frontal and parietal lobes are particularly apparent.

SPACE shows a lower rate of repeatability, as indicated by line thickness in Fig. 10, despite detecting more links overall than SCoTMI, and has a proportionally higher detection rate for contralateral links to a different lobe (heterotopic connections) than is found by SCoTMI.

The nCTMI method is inconsistent and fails to find many of the bilateral links expected to be detected in healthy resting brain activity across cortical commissures.

C. Discussion

We have developed Sparse Conditional Trajectory Mutual Information as a valid means of constructing brain activity networks, dealing with the characteristics that the underlying network is sparse and has temporal correlation between data within and across nodes. The absence of a link between two nodal time series indicates independence between the two nodal time series, given all the other nodal time series in the network.

The results from simulations and real data analysis show that SCoTMI gives consistent and valid estimates of network topology and strength of active links (as measured by conditional mutual information), under conditions of sufficient recording time and model dimensions.

SCoTMI strongly outperforms static sparse partial correlation estimation (SPACE) on simulated data having both static and time-delayed correlations, where network dimensions, link structure and strengths correspond to real fMRI data. SCoTMI also strongly outperforms the non-parametric nCTMI method on physiologically motivated simulated network data.

In our simulations the number of temporal time points has a significant influence on network detection for a given number of nodes, agreeing with existing empirical research [6]. Specifically, the simulations show significantly improved detection when increasing from short recording (200 time points) to long recording (1200 time points). This effect extends to the relative dimensions of the network, reducing detection performance as the number of nodes approaches or exceeds the number of temporal samples.

The detection rate is influenced by short recording (i.e. fewer time points) in two ways. Firstly, there is some loss of degrees of freedom for parameter estimation, when the number of parameters approaches or exceeds the number of time points. The sparse VAR model alleviates but does not completely solve this problem, especially for higher-order VAR models when the vector of time-lagged parameters is significant and there are multiple links from each node.

The second main reason that short recording causes lower detection stems from the null hypothesis condition. We expand on our preliminary discussion of this issue from Section II-D, first discussing the Gaussian case and then the case of null distributions for time series networks.

When the number of nodes exceeds the number of time points, it has been shown empirically [72] that substantial spurious architecture is detected for correlation graphs calculated from static white noise. An explanation for this behaviour in the static case stems from...
Random Matrix theory (RMT) [3]. RMT characterises the system singular values when the number of network nodes is of the same order as the number of time points, as is the case here (we call this the RMT regime). This results (in the purely white noise case) in the singular values following the Marchenko-Pastur distribution [43]. Classical behaviour occurs on the other hand when the number of temporal observations is far greater than the number of network nodes; then the cumulative distribution of white noise singular values asymptotically approaches a unit step function at 1.

It is easily shown (by repeated simulation) that for the example of [72] with 90 nodes of independent white noise, the distribution of system singular values does not converge to classical behaviour until there are thousands of time points. Consequently, severe undersampling by using only hundreds (or fewer) of time points will give spurious detection of network links, which manifests in the architectural measures reported by [72]. So the problem is not one of normalising architectural measures, but of being in the RMT regime which makes it difficult to set an appropriate threshold for identification of the active links; and all this is again dependent on using a valid method for topological discovery.

Due to being in the RMT regime we must determine null distributions by simulation, since analytic derivations do not yet exist dealing with the temporal correlation aspect of time series data. Hence we use empirical (i.e. obtained by massive simulation) null distributions to set thresholds for detection of active links. Such approximations are sufficient for our method, as demonstrated by the tight bounds in the null estimates (Fig. 2) for the model dimensions corresponding to the real data we use. Analytic characterisation of the influences of network dimensions on time-series network activity is a separate issue and will be addressed in future work.

From our simulations, it is practicable to use SCoTMI to estimate network activity for the real data we have analysed with 167 nodes and 1200 time points. Real data results, using resting state fMRI data from multiple scanning sessions of the same person, show the SCoTMI method outperforms the static equivalent SPACE and non-parametric nCTMI methods by:

- Calculating a more consistent overall number of links between sessions,
- More repeatable detection of particular links between sessions and between subjects, and
- Estimating a more anatomically plausible arrangement of links within and between brain lobes, measured as a higher repeatability for detecting intra-lobe links, intra-hemisphere links and homotopic links to the contralateral same lobe.

The gL0LS method underlying SCoTMI is valid for underdetermined inverse problems, as per its original formulation for a different application [12]. We find in practice that allowing self-connections without penalty, using the gL0LS-SC cost function, has a negligible impact on most analyses.

SCoTMI can handle large networks with thousands of nodes. The computation time is dominated by the gL0LS-SC algorithm for sparse VAR, rather than the partial coherence or Mutual Information estimates. The iterations for each specific model fit are fast since the gL0LS-SC algorithm discards most parameters on the first pass. Most of the computation is spent searching the model tuning parameter spaces for sparsity $h$ and VAR order $p$, via the EBIC surface described in Section II-E.

IV. Conclusion

In this paper we have developed a method SCoTMI for constructing sparse Conditional Independence Graphs for temporally correlated activity networks.

The method consists of three stages. Firstly a sparse network system identification stage, in which an $\ell_0$ penalised group sparse VAR is fitted jointly to all nodes. The vector or group $\ell_0$ penalty induces maximally sparse networks. Secondly a partial coherence spectrum stage, where the partial coherences are obtained analytically from the sparse VAR model. Finally the partial coherence spectra are used to compute undirected conditional Mutual Information from which the CI graph can be assembled via thresholding. The CI graph is then interpreted statistically.

We have demonstrated that SCoTMI outperforms the alternative methods of sparse partial correlation (SPACE) and non-parametric Mutual Information (nCTMI), by detecting a more consistent total number of network links, more repeatedly for particular links, from real resting state fMRI data.

Figure 9: Real Data: Summary graph from four scanning sessions of a single subject, showing links repeatably detected as active for multiple sessions using SCoTMI (a), SPACE (b), and nCTMI (c). Thin, medium and thick lines represent link detection in 2, 3 and 4 out of a total of 4 scanning sessions. Subcortical links are shown in purple; neocortical links are blue. Results shown are for Subject 1 from Fig. 7 and 8. Node labels are unabbreviated in [34].
Figure 10: Real Data: Multiple-subject results, summarising 4 scanning sessions from each of 10 subjects. Networks represent the repeated detection, at the inter-subject level, of links detected more than once at the intra-subject level. Line width is proportional to the number of subjects with repeated detection of a particular link. These graphs summarise the full results of Fig. 8. Node labels are unabbreviated in [34].
Future work could involve non-stationary analysis via windowing methods or similar.

**APPENDIX A**

**The VAR Model is Separable by Node**

We show the separability of the Vector Autoregression model into a regression at each node.

Let \( x_t = [x_{dt}, t = 1, \ldots, T \) be a \( d \)-dimensional network time-series; i.e. one time series is at each of the \( d \) nodes of a network.

Consider fitting a (network) VAR(\( p \)) by maximum likelihood, \( \min_A \mathcal{L}(A) \)

\[
\mathcal{L}(A) = \frac{1}{T} \sum_{t=1}^{T} e_t^T \Sigma^{-1} e_t + \frac{T}{2} \ln |\Sigma|
\]

\[
e_t = x_t - \sum_{r=1}^{p} A_r x_{t-r}
\]

\[
X_t = \left[ x_{T-1}^T, x_{T-2}^T, \ldots, x_{T-p}^T \right]^T
\]

\[
A_{D \times D} = [A_1, \ldots, A_p]
\]

Now optimising first over \( \Sigma \) gives

\[
\hat{\Sigma} = \frac{1}{T} \sum_{t=1}^{T} e_t e_t^T
\]

The log-likelihood now becomes \( \hat{\mathcal{L}} = \frac{T}{2} \ln |\hat{\Sigma}|. \)

Now perturb \( A \) to find its first order

\[
\delta \mathcal{L} = \frac{T}{2} \text{tr} \left( \hat{\Sigma}^{-1} \sum_{t=1}^{T} (X_t^T \delta A^T) (x_t - AX_t) \right)
\]

\( \Rightarrow 0 = \sum_{t=1}^{T} (x_t - AX_t) X_t^T \)

\( \Rightarrow S_{xx} = \hat{A} S_{xx} \hat{A}^T \)

\[
S_{xx} = \frac{1}{T} \sum_{t=1}^{T} X_t X_t^T
\]

\[
S_{sx} = \frac{1}{T} \sum_{t=1}^{T} x_t X_t^T
\]

\[
S_{xx} A^T = S_{sx}^T
\]

since \( \delta A \) is arbitrary.

Let \( a_{dt} \) be the \( d \)-th column of \( A^T \) and let \( S_{sd} = \frac{1}{T} \sum_{t=1}^{T} x_t a_{dt} \) be the \( d \)-th column of \( S_{sx} \). Then the MLEs are

\[
S_{xx} a_{sd} = S_{sx}, \quad d = 1, \ldots, D
\]

i.e. one equation for each node.

So the fitting is separable into a regression at each node

\[
\min_{a_{d}} \sum_{t=1}^{T} e_{d,t}^2 : e_{d,t} = x_{d,t} - X_t a_{d}; \quad d = 1, \ldots, D
\]

**APPENDIX B**

**Partial Coherence from the VAR Filter**

Consider the \( D \)-vector time series \( y_t \) which we partition as

\[
y_t = \left( \begin{array}{c} y_t^a \\ y_t^b \\ z_t \end{array} \right) = \left( \begin{array}{c} u_t \\ z_t \end{array} \right)
\]

where we have reorganised the entries of \( y_t \) if necessary so that \( y_t^a, y_t^b \) are two time series of interest.

Suppose we have a joint vector autoregressive (VAR) model,

\[
A(\L) y_t = \epsilon_t, \quad E(\epsilon_t) = 0, \quad \text{var}(\epsilon_t) = \Sigma
\]

\[
A(\L) = I - \Sigma_p A_p L^{p}
\]

where \( L \) is the lag or backshift operator. Then if \( F_y(\omega) \) is the spectrum of \( y_t \) we have

\[
y_t = A^{-1}(\L) \epsilon_t \Rightarrow F_y(\omega) = A^{-1}(j\omega) \Sigma A^{-H}(j\omega)
\]

where superscript \( H \) for Hermitian denotes complex conjugate transpose.

We wish to calculate the partial coherency between \( y_t^a, y_t^b \), eliminating (or regressing out) the effects of other time series. This is given by

\[
\rho_{y^a y^b | z} (\omega) = \frac{F_{y^a y^b | z}(\omega)}{\sqrt{F_{y^a y^a | z}(\omega)} \sqrt{F_{y^b y^b | z}(\omega)} \sqrt{F_{z z}(\omega)}}
\]

where the partial spectra are the entries of the \( 2 \times 2 \) matrix \( F_{zz} (\omega) \) is the \( 2 \times (p - 2) \) cross spectrum

\[
F_{zz} (\omega) = F_{aa} (\omega) - F_{az} (\omega) (F_z (\omega))^{-1} F_{za} (\omega) H
\]

From a standard partitioned matrix inversion formula \([42]\), \( F_{zz} (\omega) \) is the upper \( 2 \times 2 \) block element of \( F_y (\omega)^{-1} \). But from above we see that

\[
F_y (\omega)^{-1} = A(j\omega)^H \Sigma^{-1} A(j\omega)
\]

Now denote the columns of \( A(j\omega) \) by \((g_1(j\omega), \ldots, g_D(j\omega))\) so that

\[
[(F_y(j\omega))^{-1}]_{a,s} = g^H_s (j\omega) \Sigma^{-1} g_s (j\omega)
\]

Thus we see

\[
F_{zz} (\omega) = \begin{pmatrix} \alpha (\omega) & \beta (\omega) \\ \beta^* (\omega) & \gamma (\omega) \end{pmatrix}^{-1}
\]

\[
= \frac{1}{\Delta (\omega)} \begin{pmatrix} \gamma (\omega) & -\beta (\omega) \\ -\beta^* (\omega) & \alpha (\omega) \end{pmatrix}
\]

\[
\Delta (\omega) = \alpha (\omega) \gamma (\omega) - |\beta (\omega)|^2
\]

\[
\alpha (\omega) = g^H_s (j\omega) \Sigma^{-1} g_s (j\omega)
\]

\[
\beta (\omega) = g^H_s (j\omega) \Sigma^{-1} g_b (j\omega)
\]

\[
\gamma (\omega) = g^H_b (j\omega) \Sigma^{-1} g_b (j\omega)
\]

and we can obtain the partial coherency

\[
\rho_{a|z} (\omega) = \sqrt{\frac{F_{aa} (\omega) F_{bb} (\omega)}{F_{ab} (\omega) F_{ba} (\omega)}} \frac{\beta (\omega)}{\alpha (\omega) / \Delta (\omega)}
\]

\[
= \frac{\gamma (\omega)}{\gamma (\omega) / \alpha (\omega) / \Delta (\omega)}
\]

\[
= -\frac{\beta (\omega)}{\gamma (\omega) / \alpha (\omega)}
\]

\[
= \sqrt{\frac{g^H_b (j\omega) \Sigma^{-1} g_b (j\omega)}{g^H_a (j\omega) \Sigma^{-1} g_a (j\omega) g^H_b (j\omega) \Sigma^{-1} g_b (j\omega) \Sigma^{-1} g_b (j\omega)}}
\]

without any spectral inversion.

We can thus compute all the partial coherencies for all pairs of time series from the single VAR model, requiring only \( D \) regressions rather than \( D^2 \), as shown in Appendix A.
Adding Gaussianity and zero means we have [17]

\[ I (x_a; x_b | z_{ab}) = \frac{1}{2} \ln |\Sigma_{a|z}| + \frac{1}{2} \ln |\Sigma_{b|z}| - \frac{1}{2} \ln |\Sigma_{(ab)|z}| \]

where the covariance matrices are the relevant conditional covariance matrices. But using partitioned determinant formulæ [42],

\[
\begin{align*}
|\Sigma_{(ab)|z}| & = \left| \begin{bmatrix}
\Sigma_{a|z} & \Sigma_{az}^T \\
\Sigma_{bz} & \Sigma_{bz}^T
\end{bmatrix}
\right| \\
& = |\Sigma_{a|z}| |\Sigma_{b|z} - \Sigma_{bz} | |\Sigma_{a|z}^{-1} \Sigma_{az}^T| \\
\Omega_{abz} & = \Sigma_{a|z}^{-1} \Sigma_{ bz} | |I - \Omega_{abz}|
\end{align*}
\]

Thus

\[ I (x_a; x_b | z_{ab}) = -\frac{1}{2} \ln |I - \Omega_{abz}| \]

It now follows that \( I (x_a; x_b | z_{ab}) \) vanishes if and only if \( \Omega_{abz} \) vanishes. \( \Omega_{abz} \) is in fact the partial correlation matrix.

**APPENDIX D**

**MI in the Frequency Domain**

If \( x_t^a, x_t^b, z_t \) are jointly stationary then as \( T \to \infty \)

\[
\frac{1}{T} I (x_a; x_b | z_{ab}) \to -\frac{1}{2} \int_{-\pi}^{\pi} \ln \left( 1 - |\rho_{ab}|^2 (\omega) \right) \frac{d\omega}{2\pi}
\]

**Proof sketch.** We have from Appendix C

\[ I (x_a; x_b | z_{ab}) = -\frac{1}{2} \ln |I - \Omega_{abz}| \]

Since \( x_t^a \) is stationary the variance matrix \( \Sigma_a \) of \( x_a \) is Toeplitz. This means it has a time invariance property and so its eigenvectors are almost complex exponentials. The eigenvalues are approximately the values of the spectrum as follows [9]

\[ \Sigma_a \approx O \Lambda_a O^H \]

where \( O_{T \times T} \) is a unitary Discrete Fourier Transform matrix \( [O^H O = I] \) of complex exponentials. And

\[ \Lambda_a = \text{diag} \left[ \left| F_a \left( 2\pi \frac{k}{T} \right) \right| \right]_{k=1, \ldots, T} \]

Similarly

\[ \Sigma_b = O \Lambda_b O^H \quad \text{and} \quad \Sigma_{bz} = O \Lambda_{bz} O^H \]

We thus find

\[
\begin{align*}
\Sigma_{b|z} & = \Sigma_b - \Sigma_b \Sigma_{bz}^{-1} \Sigma_{bz}^T \\
& \approx O \Lambda_b O^H - O \Lambda_{bz}^{-1} O^H \left( O \Lambda_b O^H \right)^{-1} O \Lambda_{bz} O^H \\
& = O \left[ \Lambda_b - \Lambda_{bz}^{-1} \Lambda_b^* \right] O^H \\
& = O \Lambda_{bz} O^H \\
\Lambda_{b|z} & \approx \text{diag} \left[ \left| F_{bz} \left( 2\pi \frac{k}{T} \right) \right| \right]
\end{align*}
\]

Continuing in a similar way delivers

\[
\begin{align*}
\Omega_{abz} & \approx O^{-H} \Lambda_{bz}^{-1} O^{-1} O \Lambda_{bz} O^H \\
& \times O^{-H} \Lambda_{bz}^{-1} O^{-1} O \Lambda_{bz} O^H \\
& = O \Lambda_{bz}^{-1} O^H \\
D_{ab|z} & = \text{diag} \left[ \left| F_{bz} \left( 2\pi \frac{k}{T} \right) \right| \right]^{2} \left[ F_a \left( 2\pi \frac{k}{T} \right) \right]
\end{align*}
\]

Finally then

\[
\begin{align*}
\frac{1}{T} \ln |I - \Omega_{abz}| & \approx \frac{1}{T} \ln |O| \left| I - D_{ab|z} \right| O^H | \\
& = \frac{1}{T} \sum_{T} \ln \left( 1 - |\rho_{ab}| \left( 2\pi \frac{k}{T} \right) \right)^2 \\
& \to \int_{0}^{\pi} \ln \left( 1 - |\rho_{ab}| \right)^2 \frac{d\omega}{2\pi}
\end{align*}
\]

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