# QUANTITATIVE COMPARISON OF SIGNAL ANALYIS METHODS FOR CHARACTERIZATION OF BRAIN FUNCTIONAL CONNECTIVITY

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**Abstract: Brain functional connectivity can be characterized by the temporal evolution of correlation between signals recorded from spatially-distributed regions. It is aimed at explaining how different brain areas interact within networks involved during normal (as in cognitive tasks) or pathological (as in epilepsy) situations. Numerous techniques were introduced for assessing this connectivity. Recently, some efforts were made to compare methods performances but mainly qualitatively. In this paper, we go further and propose a comprehensive comparison of some different methods (linear and nonlinear regressions, phase synchronization (PS), and generalized synchronization (GS)) based on relevant simulation models. For this purpose, quantitative criteria are used: in addition to mean square error (MSE) under null hypothesis (independence between two signals) and mean variance (MV) computed over all values of coupling degree, we devised a new criterion for comparing performances. Results show that the performances of the compared methods are highly depending on the hypothesis regarding the underlying model for the generation of the signals. Moreover, none of them outperforms the others in all cases and the performances hierarchy is model-dependent**

## Introduction

Brain functional connectivity can be characterized by the temporal evolution of correlation between signals recorded on spatially-distributed regions. It is aimed at explaining how different brain areas interact within networks involved during normal (as in cognitive tasks) or pathological (as in epilepsy) situations. Numerous techniques were introduced for assessing this connectivity. In early fifties, first methods were proposed to address these questions [1]. They were based on temporal cross-correlation and its counterpart in the frequency domain, the coherence function [2, 3], after the introduction of the fast Fourier transformation (FFT) [4]. Some other methods based on these two techniques were later introduced by using time-varying model [5, 6] for characterizing the functional interactivity in the time or/and frequency domain between brain structures.

As these methods are mostly linear, recently a considerable number of researches have been dedicated to the development of new nonlinear approaches [7], because of the nonlinear nature of EEG signals. A family of methods based on mutual information [8] or on nonlinear regression [9, 10] was first introduced in the EEG field. Another family is currently developing, based on works related to the study of nonlinear dynamical systems and chaos [11, 12]. The latter family is divided into two groups: PS methods [13, 14] which first estimate the phase of each signal and secondarily compute an index to determine the degree of relationship based on covariation of extracted phases; and GS methods [15, 16], also consisting of two steps, first reconstruct the state space and then compute an index of similarity which represents how much the behaviors of time series are similar in the state space.

Considering the diversity and number of methods introduced for characterizing brain signal couplings, there is a need for identifying objectively, among all these methods, those applicable to a given clinical condition and which approach performs better. Recently, some efforts were made for comparing methods performances but mainly qualitatively [17] and for particular application [18].

In this paper, based on relevant simulation models, we go further and propose a comprehensive comparison of classes of methods (linear and nonlinear regressions, phase synchronization, and generalized synchronization). For this purpose, quantitative criteria are used: in addition to mean square error (MSE) under null hypothesis (independence between two signals) and mean variance (MV) computed over all values of coupling degree, we devised a new criterion for comparing performances.

## Materials and Methods

We have investigated some of the widely used methods for characterizing interactions between systems. They are belonging to three categories:

*(i)* Linear and nonlinear regression: Pearson correlation coefficient ($R^2$); coherence function (CF); nonlinear regression ($h^2$).

(*ii*) Phase synchronization: Hilbert phase entropy (HE); Hilbert mean phase coherence (HR); wavelet phase entropy (WE); wavelet mean phase coherence (WR).

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(*iii*) Generalized synchronization: three similarity indexes (S, H, N); synchronization likelihood (SL).

Here we review succinctly their definitions.

i) Pearson coefficient of correlation, for two time series $x(t)$ and $y(t)$, is defined in the time domain as follows [19]

$$R^2(t) = \max_{\tau} \frac{\operatorname{cov}^2\left(x(t), y(t+\tau)\right)}{\operatorname{var}\left(x(t)\right) \cdot \operatorname{var}\left(y(t+\tau)\right)}$$

where *var*, *cov*, and $\tau$ denote respectively variance, covariance, and time shift between the two time series. The variance and covariance are computed within a sliding window centered at time *t*.

The magnitude-squared coherence function as counterpart of $R^2$ in the frequency domain can be formulated as [20]

$$\left|\rho_{xy}(f)\right|^2 = \frac{\left|S_{xy}(f)\right|^2}{S_{xx}(f) \cdot S_{yy}(f)}$$

where $S_{xx}(f)$ and $S_{yy}(f)$ are respectively the power spectral densities of $x$ and $y$, and $S_{xy}(f)$ is their cross-spectral density .

Different techniques are available for performing nonlinear regression. Here, we concentrate on $h^2$ which fits a nonlinear curve by piece-wise linear approximation [9]

$$h_{xy}^2(t) = \max_{\tau} \left(1 - \frac{\operatorname{var}\left(y(t+\tau)/x(t)\right)}{\operatorname{var}\left(y(t+\tau)\right)}\right)$$

where

$$\operatorname{var}\left(y(t+\tau)/x(t)\right) \triangleq \arg\min_{g}\left(E\left[y(t+\tau) - g\left(x(t)\right)\right]^2\right)$$

here $g$ is an approximation of the mapping function from $x$ to $y$ .

ii) Phase synchronization estimation consists of two steps [13]. The first step is the instantaneous phase extraction of each signal and the second step is the quantification of synchronization degree via an appropriate index. Phase extraction can be done by different techniques. Two of them are used in this work: the Hilbert transform and the wavelet transform. Using the Hilbert transform, analytical signal associated to a real time series $x(t)$ is derived:

$$Z_x(t) = x(t) + i\mathcal{H}\left[x(t)\right] = A_x^H(t) e^{i\phi_x^H(t)},$$

where $\mathcal{H}$, $\phi_x^H$, and $A_x^H$ are respectively the Hilbert transform, the phase, and the amplitude of $x(t)$. Complex continuous wavelet transform can also be used to estimate the phase of signal [21]:

$$W_x(t) = (\psi * x)(t) = \int \psi(t')x(t-t')dt' = A_x^W(t) \cdot e^{i\phi_x^W(t)},$$

where $\psi$ , $\phi_x^W$, and $A_x^W$ are respectively a wavelet function (e.g. Morlet used here), the phase, and the amplitude of $x(t)$. Once phase extraction is performed on two signals, several synchronization indices can be used to quantify phase relationship. In this study, we explored two of them both computed from the shape of the probability density function (pdf) of the phase difference ($\phi = \phi_x - \phi_y$). The first index is stemmed from Shannon entropy and defined as follows [22]

$$\rho = \frac{H_{\max} - H}{H_{\max}}, \quad H = -\sum_{i=1}^{M} p_i \ln p_i ,$$

where *M* is the number of bins used to estimate the pdf, $p_i$ is the probability of finding the phase difference $\phi$ within the *i*-th bin, and $H_{\max}$ is given by $\ln M$ . The second index, which is named mean phase coherence [23], is taken equal to the intensity of the first Fourier mode of the distribution

$$R = \left|\frac{1}{N}\sum_{i=0}^{N-1} e^{i\phi(t)}\right|$$

where *N* is the length of time series. Combining two ways of phase extraction and two indices for quantification of phase relationship, we obtain four different measures of interdependencies: Hilbert entropy (HE), Hilbert mean phase coherence (HR), wavelet entropy (WE), and wavelet mean phase coherence (WR).

iii) Generalized synchronization is also a two step procedure. First, the state space for each time series is reconstructed using a time delay embedding method [24]. This technique makes it possible to investigate the interaction between systems without any knowledge about governing equations. For each time *n* a delay vector corresponding to a point in the reconstructed state space for *x* is defined as

$$X_n = \left(x_n, x_{n+\tau}, \ldots, x_{n+(m-1)\tau}\right), \; n = 1, \ldots, N$$

where $m$ is the embedding dimension and $\tau$ denotes time lag. The state space of *y* is reconstructed in the same way.

Second, synchronization is determined via a suitable measure. Four measures are presented in this study based on conditional neighborhood. The principle is to estimate the proximity of neighbor points in the second state space from temporal indices of corresponding neighbors in the first state space. Three measures S, H, and N [15], which are sensitive to the direction of interaction, originate from this principle and use Euclidean distance:

$$S^{(k)}(X|Y) = \frac{1}{N}\sum_{n=1}^{N} \frac{R_n^{(k)}(X)}{R_n^{(k)}(X|Y)},$$

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$$H^{(k)}(X|Y) = \frac{1}{N}\sum_{n=1}^{N}\log\frac{R_n^{(N-1)}(X)}{R_n^{(k)}(X|Y)},$$

$$N^{(k)}(X|Y) = \frac{1}{N}\sum_{n=1}^{N}\frac{R_n^{(N-1)}(X) - R_n^{(k)}(X|Y)}{R_n^{(N-1)}(X)},$$

where $R_n^{(k)}(X)$ and $R_n^{(k)}(X|Y)$ are given by:

$$R_n^{(k)}(X) = \frac{1}{k}\sum_{j=1}^{k}\left(X_n - X_{r_{n,j}}\right)^2$$

$$R_n^{(k)}(X|Y) = \frac{1}{k}\sum_{j=1}^{k}\left(X_n - X_{s_{n,j}}\right)^2$$

where $r_{n,j}, j=1,\ldots,k$ and $s_{n,j}, j=1,\ldots,k$ respectively stand for the time indices of the $k$ nearest neighbors of $X_n$ and $Y_n$.

The fourth measure, referred to as synchronization likelihood (SL) [16], is originally a measure of multivariate synchronization. Here we only focus on the bivariate case. The probability for the distance between embedded vectors $X_n$ to be less than $\varepsilon$ is

$$P_{x,n}^{\varepsilon} = \frac{1}{2(w_2 - w_1)}\sum_{\substack{j=1 \\ w_1 < |n-j| < w_2}}^{N} U\left(\varepsilon - \left|X_n - X_j\right|\right)$$

where $|\cdot|$ is the Euclidean distance, $U$ stands for Heaviside step function, $w_1$ is the Theiler correction, and $w_2$ determines the length of sliding window. Letting $P_{x,n}^{\varepsilon} = P_{y,n}^{\varepsilon} = P_{ref}$ be an arbitrary probability, the above equation for $X_n$ and its analogous for $Y_n$, gives the critical distances $\varepsilon_{x,n}$ and $\varepsilon_{y,n}$ from which we can determine if $X_n$ is close to $X_j$ and $Y_n$ is close to $Y_j$ simultaneously i.e. $H_{n,j} = 2$ in the equation below

$$H_{n,j} = U\left(\varepsilon_{x,n} - \left|X_n - X_j\right|\right) + U\left(\varepsilon_{y,n} - \left|Y_n - Y_j\right|\right)$$

Synchronization likelihood at time $n$ can be obtained by averaging over all values of $j$

$$S_n = \frac{1}{2P_{ref}(w_2 - w_1)}\sum_{\substack{j=1 \\ w_1 < |n-j| < w_2}}^{N}\left(H_{n,j} - 1\right)$$

All these measures, except H, are evolving between 0 and 1. The 0 value means that the two signals are independent. On the opposite, the value 1 means that the two signals are completely synchronized.

In order to comprehensively simulate a wide range of coupled temporal dynamics we used various mathematical models as well as a physiologically-relevant computational model of EEG simulation from coupled neuronal populations. All models share, a common feature: they integrate a parameter which controls the degree of coupling, i.e. increasing this parameter from zero to maximal leads to the generation of signals either independent or highly related (in some cases gives identical signals). The physiological explanation, based on the neuronal populations activities concepts, for choosing these kinds of models are given in our previous work [25].

Model $M_1$ generates two broadband signals ($x_1, x_2$) from the mixing of two independent white noises (*$N_1$*, *$N_2$*) and a common noise (*$N_3$*):

$$x_1 = (1-C)N_1 + CN_3$$
$$x_2 = (1-C)N_2 + CN_3$$

where $0 \le C \le 1$ is the coupling degree; for $C = 0$ the signals are independent and for $C = 1$ they are identical.

In model $M_2$, four lowpass filtered white noises (*$NF_1$*, *$NF_2$*, *$NF_3$*, and *$NF_4$*) are combined in two ways to generate two narrowband signals around a frequency $f_0$. Generated signals share either a phase relationship (PR) or an amplitude relationship (AR), only:

$$PR: \begin{cases} x_1 = A_1\cos\left(2\pi f_0 t + \phi_1\right) \\ x_2 = A_2\cos\left(2\pi f_0 t + C\phi_1 + (1-C)\phi_2\right) \end{cases}$$

$$AR: \begin{cases} x_1 = A_1\cos\left(2\pi f_0 t + \phi_1\right) \\ x_2 = \left(CA_1 + (1-C)A_2\right)\cos\left(2\pi f_0 t + \phi_2\right) \end{cases}$$

where $0 \le C \le 1$, $A_1 = \sqrt{NF_1^2 + NF_2^2}$, $A_2 = \sqrt{NF_3^2 + NF_4^2}$, $\phi_1 = \arctan\left(\frac{NF_2}{NF_1}\right)$, and $\phi_2 = \arctan\left(\frac{NF_4}{NF_3}\right)$. For $C = 0$ two generated signals have independent phase and amplitude and for $C = 1$ they have identical phase or amplitude.

We also evaluated interdependence measures on signals obtained from models of coupled nonlinear oscillators. Here we report one of them: the Rössler coupled systems ($M_3$) [26], in which the driver system is

$$\frac{dx_1}{dt} = -\omega_x x_2 - x_3$$
$$\frac{dx_2}{dt} = \omega_x x_1 + 0.15x_2$$
$$\frac{dx_3}{dt} = 0.2 + x_3\left(x_1 - 10\right)$$

and the response system is

$$\frac{dy_1}{dt} = -\omega_y y_2 - y_3 + C\left(x_1 - y_1\right)$$
$$\frac{dy_2}{dt} = \omega_y y_1 + 0.15y_2$$
$$\frac{dy_3}{dt} = 0.2 + y_3\left(y_1 - 10\right)$$

here $\omega_x = 0.95$, $\omega_y = 1.05$, and C is the coupling degree.

Finally, in order to match some dynamics encountered in real epileptic EEG signals; we considered a physiologically relevant computational model of EEG generation from two coupled populations of neurons. Main model parameters include excitation, inhibition and coupling degree between the two considered populations (model $M_4$) [27]. This model was used to generate two kinds of signal: the background EEG ($M_4$(BKG)) and spiking ($M_4$(SPK)) EEG activity. For both cases, coupling parameter was varied from 0 (independent situation) to a maximum value under which temporal dynamics of signals stay unchanged.

For all models and all values of the degree of coupling parameter, long time-series were generated in order to address some statistical properties of the computed quantities: (i) the mean square error (MSE) under null hypothesis (i.e. independence between two signals), which could be interpreted as bias, defined by $E\left\{\left(\hat{\theta}_0 - \theta_0\right)^2\right\}$ where E is the mathematical expectation, $\theta_0 = 0$ and $\hat{\theta}_0$ is the estimation of $\theta_0$; (ii) the mean variance (MV) computed over all values of the coupling degree and defined as $\frac{1}{I}\sum_{i=1}^{I} E\left\{\left(\hat{\theta}_i - E\left(\hat{\theta}_i\right)\right)^2\right\}$ where $I$ is number of coupling degree points and $\hat{\theta}_i$ is the estimated relationship for the coupling degree $C_i$; (iii) in addition to two above criteria we devised the median of local relative sensitivity (MLRS) as a comparison criterion, it is given by:

$$MLRS = Median\left(S_i/\bar{\sigma}_i\right),\quad S_i = \frac{\hat{\theta}_{i+1} - \hat{\theta}_i}{C_{i+1} - C_i},\quad \bar{\sigma}_i = \frac{\hat{\sigma}_{i+1} + \hat{\sigma}_i}{2}$$

where $S_i$ is the increase rate of the estimated relationship and $\bar{\sigma}_i$ is the average of estimated standard deviations associated to two adjacent values of the coupling degree. This quantity is a reflection of the sensitivity of a method with respect to the change in the coupling degree. We have also retained the median of the distribution of local relative sensitivity instead of its mean because the fluctuation in its estimation may make this distribution very skewed. Unlike MSE and MV, the higher MLRS values indicate the better performances.

For all models and all values of coupling degree, Monte Carlo simulations were conducted to compare interdependence measures provided by aforementioned methods. Each time-series was generated over 20000 samples duration. All estimations were computed in a sliding window (512 points, i.e. 2 seconds as signals sampled at 256 Hz). The overlapping of sliding windows was set to 98%.

## Results

Tables 1 to 3 represent respectively the MSE under null hypothesis, the MV and the MRLS for all methods and simulation models. For each studied situation the best method is highlighted with gray color. Methods that were found to be insensitive with respect to changes in the coupling degree are denoted by symbol "*". From these tables, we deduced that for model M1, R² is the most appropriate estimator based on defined criteria. For model $M_2$, in the case of phase relationship, PS methods (especially WE) perform better than other methods. In the case of amplitude relationship, there is no consensus for the choice of a best method as all methods are more sensitive to the phase of signals than to their envelope. For the coupled Rössler systems (M3), PS methods are more suitable. For Hénon coupled systems, S and N methods had higher performances, on average but R² was found to be more robust in the presence of added noise. For the neuronal population model, in the background activity situation, R² and h² methods detected the presence of a relationship and performed better than other methods; this tendency was also confirmed in the spiking activity situation. However, it was difficult to determine the overall best method in this second case since criteria did not lead to converging results.

To be short, as an example, only curves obtained for model $M_4$ are presented here. The signals generated by this model are very close to those reported in a previous attempt for comparing relationship estimators [17]. In this study, the relationship between two neuronal populations is unidirectional.

For the spiking activity ($M_4$(SPK)) results for all methods are reported in figure 1 (a)-(c). As an interesting result, we observed that WE and CF methods are almost blind to the established relation. Similarly, HE and WR only displayed small increase with increasing of degree of coupling but their variance was low. R², h², S and HR methods exhibited good sensitivity. However, MSE under null hypothesis was found to be high for HR. For background activity ($M_4$(BKG)), results showed that increasing the degree of coupling between neuronal population did not lead to significant increase of computed quantities, as shown in figure 1 (d)-(f). In this situation CF and PS methods but HR do not detect any relationship and the other methods detect a weak relationship.

Table 1: MSE for Different Methods and Models. Best method highlighted with gray color and "*" stands for insensitive method with respect to changes in the coupling degree

| | $M_1$ | $M_2$ | $M_3$ | $M_4$(SPK) | $M_4$(BKG) |
|---|---|---|---|---|---|
| R² | 0.0001 | 0.0764 | 0.1095 | 0.0632 | 0.0015 |
| CF | 0.1045 | 0.1082 | 0.0914 | * | * |
| h² | 0.0010 | 0.1174 | 0.1511 | 0.1038 | 0.0060 |
| HE | 0.0050 | 0.0231 | 0.0638 | 0.0287 | * |
| HR | 0.0030 | 0.1756 | 0.4731 | 0.2493 | 0.0190 |
| WE | 0.0105 | 0.0205 | 0.0765 | * | * |
| WR | 0.0088 | 0.1136 | 0.1615 | 0.0534 | * |
| S | 0.0753 | 0.0284 | 0.0266 | 0.1075 | 0.1200 |
| H | 0.0004 | 2.2281 | 0.4420 | 0.6512 | 0.0042 |
| N | 0.0004 | 0.3782 | 0.1168 | 0.2015 | 0.0049 |
| SL | 0.0043 | 0.1152 | 0.0085 | 0.0413 | 0.0062 |

Table 2: MV for Different Methods and Models. Best method highlighted with gray color and "*" stands for insensitive method with respect to changes in the coupling degree

| | $M_1$ | $M_2$ (PR) | $M_2$ (AR) | $M_3$ | $M_4$(SPK) | $M_4$(BKG) |
|---|---|---|---|---|---|---|
| $R^2$ | 0.0040 | 0.0200 | 0.0367 | 0.0065 | 0.0216 | 0.0021 |
| CF | 0.0055 | 0.0014 | * | 0.0200 | * | * |
| $h^2$ | 0.0040 | 0.0160 | 0.0275 | 0.0060 | 0.0205 | 0.0022 |
| HE | 0.0026 | 0.0057 | * | 0.0019 | 0.0045 | * |
| HR | 0.0096 | 0.0207 | * | 0.0010 | 0.0217 | 0.0066 |
| WE | 0.0016 | 0.0029 | * | 0.0006 | * | * |
| WR | 0.0066 | 0.0119 | * | 0.0018 | 0.0038 | * |
| S | 0.0031 | 0.0058 | 0.0075 | 0.0049 | 0.0184 | 0.0044 |
| H | 0.0107 | 0.2033 | 0.2441 | 0.3408 | 0.2942 | 0.0071 |
| N | 0.0055 | 0.0120 | 0.0142 | 0.0068 | 0.0501 | 0.0060 |
| SL | 0.0492 | 0.0250 | 0.0209 | 0.0254 | 0.0384 | 0.0059 |

Table 3: MLRS for Different Methods and Models. Best method highlighted with gray color and "*" stands for insensitive method with respect to changes in the coupling degree

| | $M_1$ | $M_2$ (PR) | $M_2$ (AR) | $M_3$ | $M_4$(SPK) | $M_4$(BKG) |
|---|---|---|---|---|---|---|
| $R^2$ | 57.6 | 3.94 | 0.41 | 1.38 | 0.0013 | 0.00012 |
| CF | 56.4 | 1.30 | * | 2.20 | * | * |
| $h^2$ | 35.6 | 4.06 | 0.36 | 0.98 | 0.0018 | 0.00011 |
| HE | 40.9 | 6.58 | * | 15.5 | 0.0012 | * |
| HR | 42.5 | 6.5 | * | 8.87 | 0.0012 | 0.00007 |
| WE | 47.0 | 6.69 | * | 13.8 | * | * |
| WR | 46.6 | 6.76 | 0.08 | 8.83 | 0.0012 | * |
| S | 31.1 | 2.23 | 0.84 | 6.91 | 0.0009 | 5e-6 |
| H | 30.3 | 2.84 | 0.77 | 3.53 | 0.0007 | 9e-5 |
| N | 29.0 | 3.02 | 0.60 | 3.46 | 0.0004 | 9e-5 |
| SL | 8.32 | 0.772 | 0.41 | 3.52 | 0.0013 | 7e-7 |

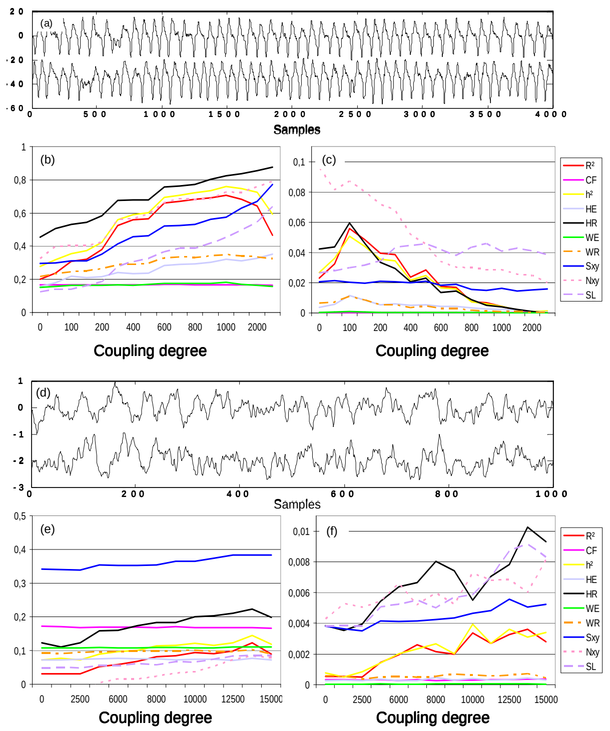


Figure 1: Results obtained for $M_4$ (neuronal population model). (a) A pairs of signals generated by model $M_4$ (SPK) (b) Estimated relationship, and (c) variances of estimation, as a function of coupling degree, estimated for all methods using Monte-Carlo simulation in the spiking activity. (d)-(f) Results obtained for the case of background activity .

## Conclusions

In this work, we have compared the performances of some widely used estimators of statistical coupling for characterizing the interaction between brain structures. Three statistical criteria of performance were computed using sufficiently large simulated data.

To sum up we can say the evaluation of signal interdependencies is not straightforward. Generally speaking, there is no "best" method. Results are sensitive to assumptions about processes involved in the generation of analyzed signals. It appears that the most common estimators $R^2$ and $h^2$ perform more or less well in all situations. Therefore, they should be used as the first tools towards the characterization of signal interdependencies before applying other methods.

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