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Mutual information in the frequency domain for the study of biological systems

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ABSTRACT

Many biological systems are comprised of multiple components that are interacting nonlinearly and producing multiple outputs of distinct frequency characteristics. Quantitative analysis of the observable outputs to identify the dependencies among components is imperative to increase the understanding of the underlying mechanism of the system. In this work, quantification of nonlinear dependencies in terms of mutual information between time series with respect to frequency characteristics is explored. A new model-free methodology is developed and tested on simulated data from coupled nonlinear systems. The results indicate that the proposed framework performs better than a conventional method for quantifying interactions. Application on real-world electrophysiological data from an emotional state assessment experiment reveals specific brain areas that are associated with levels of emotional responses.

1. Introduction

Applying system approaches in the study of problems arising in engineering, biology, ecology and psychology is a natural approach [1]. In biomedical research, individuals (e.g. cells, tissue, organ systems) and cross-individuals as suggested by scientific holism [2] (e.g. cardiac-respiratory system, nervous-cardiac system) could both be treated as complex systems comprised of multiple components. These components are typically interacting nonlinearly [3], each producing some observable outputs.

Without exact knowledge of the underlying mechanism of the system, we are confined to the study and quantitative analysis of the observable outputs (i.e. biological signals) to gain understanding of the system. Biological signals are usually recorded through some sensor or device and can represent very diverse aspects of the systems characteristics, ranging from electrical activity, to chemical concentrations, or any other characteristic that has dynamic properties (i.e. changes over time). Commonly observed biological signals in research are: the electrical potential difference between two electrode sensors, e.g. electroencephalogram (EEG) and electrocardiogram (ECG); the magnetic fields changes produced by electrophysiological activity, e.g. magnetoencephalogram (MEG) and magnetocardiogram (MCG); the brain blood flow activity, i.e. functional magnetic resonance imaging (fMRI); galvanic skin response (GSR); potential of hydrogen (pH); arterial blood pressure, etc. Although these signals are inherently very different from each other, a nearly universally common characteristic is their quasi-periodic (oscillatory) structure due to specific frequency components [4]. Biological signals have been employed in research extensively, e.g. to detect distinct frequency components from the human brain [5,6], to help with the diagnosis of Alzheimer's disease [7–9], to study epilepsy [10], to estimate flow velocity and Doppler spectra of arterial disease [11] and to understand the anesthetic drug effect [12].

The most interesting and important biological system to study is the human brain, due to its complexity and the plethora of signals that produces. The brain contains approximately 86 billion connected neuronal cells [13]. To execute different brain functions simultaneously, subsets of neurons work together under particular/individual tasks [14], and, furthermore, the different subsets may interact with each other. Researchers from a broad range of background study EEG as multivariate time series through quantitative methods for disease diagnosis, or in general for the study of brain connectivity [15–21]. Kaminski and Blinowska studied the frequency content with relation to the direction of electrical activity spread [15], and Nolte et al. using the coherency measure showed that brain activity at a specific frequency band is associated with the communication in the motor areas across hemisphere [16]. Schindler et al. demonstrated that a correlation structure could show a dynamic evolution during focal onset seizures [17]. Salvador

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et al. applied the partial coherency spectrum for multivariate time series and constructed frequency-dependent graphs of the brain functional networks [18]. Sherman et al. developed a bicoherence gain function for an application of tracking thalamo-cortical nonlinear interactions in epilepsy patients with or without antiepileptic drugs [19]. Ince et al. proposed a general framework to analyze neuroimaging data using mutual information [22], and Jeong et al. and Na et al. developed time-domain mutual information variants to characterize the complexity and the information transmission between cortical areas in patients with Alzheimer's disease [20] and schizophrenics [21]. However, in most studies, either linear measures (e.g. correlation and coherence) are employed to study the nonlinear interacting mechanism [17,16,18], or interactions are quantified only within the time domain [20,21].

A better measure of interaction that could be used to study nonlinear interactions with respect to specific frequencies remains of interest in neuroscience research. Salvador et al. considered functional connectivity based on mutual information in the frequency domain to describe the covariability between brain regions with application to schizophrenia studies [23–25]. However, the multivariate normality they assumed and the assumption of linear interactions limits the applicability of the methodology and even becomes contrary to the original problem. A similar approach was used by Cassidy at al. [26] where again mutual information in the frequency domain was employed under the assumption of normality to develop a new approach for functional brain connectivity analysis. Brillinger proposed a statistical nonparametric approach to study the dependence of bivariate time series by means of the mutual information in the frequency domain, and he showed its superiority compared with correlation and coherence in an example studying ambient seismic noise data [27]. In his paper, the mutual information was quantified between bivariate stationary time series in terms of the real and imaginary part of their Fourier transform at each frequency. Another application-driven frequency-dependent neural connectivity method, called Time-Frequency Cross Mutual Information, was developed initially for MEG and sEMG-MEG multi-modality dataset [28] and then naturally extended to EEG to study brain functional organization under real motor vs imaginary motor tasks [29,30].

Based on the work of Brillinger [27], we herein present a method to quantify interactions between time series with respect to frequency, by studying directly the spectral characteristics of the time series both individually and jointly. Measures of dependency in the time domain, such as correlation (linear measure) and mutual information (nonlinear measure) do not provide any information regarding the frequencies where the dependency may exist. Given that typical biological signals contain multiple frequency components, estimation of dependency in the time domain is biased towards the components/frequencies in the signal that have the highest amplitude (most energy), while dependency at other components/frequencies may be masked. On the other hand, study of signals in the frequency domain by linear measures (e.g. coherence and its derivatives) can indeed capture dependency at specific frequencies, but by construction are accurate only for the case of a linear relation. Our aim is to bridge this gap and provide a model-free method to quantify nonlinear dependency in the frequency domain. In the following sections, we first give detailed description of the methodology framework including spectral characteristics of time series, probabilistic dependence, density estimation and various implementation details. We test the proposed methodology on simulated data from a variety of coupled nonlinear systems and compare the results with those obtained from application of a traditional dependency measure. Finally, we apply our methodology to a real-world electrophysiological dataset to study the brain's response to emotional stimuli.

2. Methods

The measure of Mutual Information (MI) stems from Information Theory and is a reliable metric of the statistical dependency of two random variables [31,27]. Our aim is to derive appropriate formulations of MI between two signals as functions of frequency using the representation of the signals in the frequency domain. The core idea of our approach is that the observed signal (time series) values in the time domain are less informative than the spectral characteristics we observe in the frequency domain.

2.1. Spectral characteristics

Biological signals are nonlinear, nongaussian and nonstationary stochastic processes [32,33]. Given a signal $x(t)$ the Fourier transform $X(f) = \int_{-\infty}^{\infty} x(t)e^{-i2\pi ft}dt$ decomposes the signal into a sum of complex exponentials (frequency domain representation) [34], allowing us to estimate the magnitude and phase for each frequency component in the signal. The magnitude represents the intensity of each frequency component (1) (magnitude spectrum), while the phase refers to its offset from the origin (2) (phase spectrum).

$$X^A(f) = \sqrt{Re(X(f))^2 + Im(X(f))^2}, \tag{1}$$

$$X^\phi(f) = \arctan\left\{\frac{Im(X(f))}{Re(X(f))}\right\}. \tag{2}$$

For two signals $x(t)$ and $y(t)$, the magnitude-squared coherence function (MSC) [35] is defined as

$$C_{XY}(f) = \frac{|P_{XY}(f)|^2}{P_{XX}(f)P_{YY}(f)}, \tag{3}$$

where $P_{XY}(f)$, $P_{XX}(f)$ and $P_{YY}(f)$ are the cross- and auto-spectral densities of $x(t)$ and $y(t)$, derived from their Fourier transforms $X(f)$ and $Y(f)$. Due to its simplicity in estimation, MSC is one of the most commonly used measures of dependency. It quantifies the linear dependency of the two signals at frequency f, taking value 0 when they are linearly independent and 1 when there is a perfect linear relation. Unfortunately, when the relation between the two signals is nonlinear, MSC can produce totally misleading results.

2.2. Dependency in the frequency domain

In order to estimate a more general measure of dependency, capable of capturing nonlinear relations, we employ the well known measure of Mutual Information, and we define the mutual information between the magnitudes of $x(t)$ and $y(t)$ at frequency f as

$$I_{XY}^{AA}(f) = \mathbf{E}\left[\ln\frac{p(X^A(f), Y^A(f))}{p_X(X^A(f))p_Y(Y^A(f))}\right], \tag{4}$$

where $\mathbf{E}$ is the expectation operator, and $p(X^A(f), Y^A(f))$ and $p_X(X^A(f))$, $p_Y(Y^A(f))$ are the joint and marginal probability densities of $X^A(f)$, $Y^A(f)$. This is the traditional definition of MI [31], where we treat the magnitudes at frequency f as random variables. We can similarly define $I_{XY}^{\phi\phi}(f)$ for the mutual information between phases and $I_{XY}^{A\phi}(f)$ for the magnitude-phase mutual information. We note the similarity between Eqs. (4) and (3), where the spectral densities in the fraction are replaced with probability densities. MI is by construction non-negative and can take values from 0 to $+\infty$. The formulations for $I_{XY}^{AA}(f)$, $I_{XY}^{\phi\phi}(f)$ and $I_{XY}^{A\phi}(f)$ allow for more flexibility in estimating dependencies, since they do not assume a pre-specified type of relation, and they are estimated on the basis of the joint distributions. We note that this also makes the measures potentially