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# Assessing uncertainty in dynamic functional connectivity

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ABSTRACT

Functional connectivity (FC) – the study of the statistical association between time series from anatomically distinct regions (Friston, 1994, 2011) – has become one of the primary areas of research in the field surrounding resting state functional magnetic resonance imaging (rs-fMRI). Although for many years researchers have implicitly assumed that FC was stationary across time in rs-fMRI, it has recently become increasingly clear that this is not the case and the ability to assess dynamic changes in FC is critical for better understanding of the inner workings of the human brain (Hutchison et al., 2013; Chang and Glover, 2010). Currently, the most common strategy for estimating these dynamic changes is to use the sliding-window technique. However, its greatest shortcoming is the inherent variation present in the estimate, even for null data, which is easily confused with true time-varying changes in connectivity (Lindquist et al., 2014). This can have serious consequences as even spurious fluctuations caused by noise can easily be confused with an important signal. For these reasons, assessment of uncertainty in the sliding-window correlation estimates is of critical importance. Here we propose a new approach that combines the multivariate linear process bootstrap (MLPB) method and a sliding-window technique to assess the uncertainty in a dynamic FC estimate by providing its confidence bands. Both numerical results and an application to rs-fMRI study are presented, showing the efficacy of the proposed method.

## 1. Introduction

Functional connectivity (FC), the study of the statistical association between two or more anatomically distinct time-series (Friston, 1994, 2011), has become one of the primary areas of research in the field surrounding functional magnetic resonance imaging (fMRI). Although researchers implicitly assumed that FC was stationary across time, particularly in resting-state fMRI (rs-fMRI), it has recently become increasingly clear that the ability to assess dynamic changes in FC is critical for a better understanding of the inner workings of the human brain (Hutchison et al., 2013; Chang and Glover, 2010). The association between changes in connectivity and various diseases has been described in a number of studies (Filippini et al., 2009), and the hope is that this will provide the beginning of a new and deeper understanding of neurodegenerative diseases and neuropsychiatric disorders, such as Alzheimer's disease (Jones et al., 2012) or autism (Starck et al., 2013). The results also support the belief that changes in neural activity patterns associated with dynamically changing FC can provide greater understanding of the fundamental properties of brain networks in both healthy subjects and patients suffering from various mental disorders.

Despite the increased attention, the results of dynamic FC analyses are often difficult to interpret. This is due in part to the inherent low signal-to-noise ratio in the data, physiological artifacts, and variation over time in both the mean and variance of the blood-oxygen-level dependent (BOLD) signal. These issues conspire together to create problems with the interpretation of transient fluctuations in FC (Hutchison et al., 2013), and it is often difficult to determine whether they are in fact due to neuronal activity or simply a byproduct of random noise (Lindquist et al., 2014; Hindriks et al., 2016). In addition, a lack of clear analytical strategy and guidelines for proper interpretation of the results further contribute to this ambiguity. As a consequence, significant research and methodological developments are necessary to move the field forward.

A number of approaches have been proposed to assess dynamic FC in resting-state fMRI data, including independent component analysis, time-frequency coherence analysis (Chang and Glover, 2010), time series models (Lindquist et al., 2014), and change-point detection methods (Cribben et al., 2012, 2013; Xu and Lindquist, 2015). To date, the so-called sliding-window approach (Allen et al., 2012; Chang and Glover, 2010; Handwerker et al., 2012) has been the most common

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analysis strategy, and it is the focus of this work. This approach has a number of benefits, including the fact that it is appealingly simple in both application and intuition. However, in spite of these benefits, the approach has several drawbacks. These include the arbitrary choice of window length and the fact that all observations within the window are weighted equally (Lindquist et al., 2014). However, its greatest shortcoming is possibly the inherent variation present in the estimate, even for null data, which is easily confused with true time-varying changes in connectivity (Lindquist et al., 2014; Hindriks et al., 2016). This can have serious consequences as even spurious fluctuations caused by noise can easily be confused with important signal.

For these reasons, the ability to assess the level of uncertainty in sliding-window correlation estimates is of critical importance. In particular, the introduction of confidence intervals for the correlation estimates could help identify, and screen for, changes in connectivity that are driven purely by random noise. One possible approach towards obtaining such intervals is to use the bootstrap procedure. Standard bootstrap methods are not readably applicable to time series data due to the dependence structure (Kreiss and Paparoditis, 2011). For this reason, in the past few years, new techniques have been proposed for bootstrapping dependent and stationary time series data (see Kreiss and Paparoditis, 2011) for a summary of these methods). To date, this work has primarily focused on estimation of the sample mean and does not consider statistics of order higher than two. To circumvent this problem, Jentsch and Politis (2015) introduced the multivariate linear process bootstrap (MLPB) method. They employ a tapered covariance matrix estimator, which gives higher weights to observations in a close proximity and lower weights to observations farther apart. Application of this procedure results in a stable and consistent estimator of the covariance matrix arising from multivariate time series. These properties of an estimator are critical for accurate estimation of dynamic FC, and standard bootstrap methods do not share them.

In this work, we propose a new non-parametric model-free approach that combines the MLPB and a sliding-window technique in order to assess the uncertainty in dynamic FC estimates by providing confidence bands. Specifically, we divide time series into adjacent blocks. We use data within each block to generate bivariate time series bootstrap samples. We combine generated data from adjacent blocks into time series. Next, we define a moving time window of size $w$ and use data within that window to calculate the correlation coefficient. Subsequently, the window is moved forward step-wise through time, and the procedure is repeated for each shift. As a result, a time-varying measure of correlation between brain regions is obtained as well as dynamically changing confidence bands. Our algorithm, denoted Dynamic Connectivity Bootstrap Confidence Bands (DCBootCB), provides a valid estimate of the confidence band for the sliding-window estimator of the correlation coefficient.

The properties of the proposed estimator are studied in a series of simulation studies. Our simulations provide evidence that the MLPB approach to bootstrapping correlated time series gives valid model-free time-varying connectivity estimates together with their associated confidence bands. In addition, they show that the theoretical properties of the proposed approach are supported by empirical evidence. We conclude by applying the DCBootCB algorithm to resting state fMRI data.

The article is organized as follows: Section 2 introduces a statistical framework of our problem; Section 3 presents our approach for estimating the time-varying functional connectivity and its confidence bands; Section 4 provides the description and the results of the simulation study; Section 5 presents an application of our method to rs-fMRI data; and Section 6 contains conclusions and a discussion.

## 2. Statistical framework

Our work is concerned with the principled estimation of confidence bands for the time-varying functional connectivity between two time series measured at uniformly sampled time points $t$=1,...,$T$. Let a two dimensional time series be denoted by $\{\mathbf{y}(t),\, t = 1, \ldots, T\}$ with $\mathbf{y}(t) = (y_1(t),\, y_2(t))^\top$, where $\top$ means transpose. Further, assume that:

$$\mathbf{y}(t) = \mu(t) + \varepsilon(t) \tag{1}$$

where $\mu(t)$ is the mean of $\mathbf{y}(t)$ conditioned on all observations obtained up to time $t$, defined by $E(y(t)|y(1), \ldots, y(t-1))$, and $\varepsilon(t)$ is the error term at time $t$ with mean zero and covariance matrix also conditioned on all observations obtained up to time $t$ given by:

$$\Sigma(t) = \begin{pmatrix} \sigma_{11}(t) & \sigma_{12}(t) \\ \sigma_{21}(t) & \sigma_{22}(t) \end{pmatrix}. \tag{2}$$

The diagonal terms of the matrix $\Sigma(t)$ are the time-varying variances of the two time series $y_1(t),\ y_2(t)$. The off-diagonal term is the covariance between the two time series $y_1(t), y_2(t)$. All of these terms are conditioned on all observations obtained till time $t$. Equivalently, the conditional covariance matrix can be expressed as:

$$\Sigma(t) = D(t)R(t)D(t) = D(t)\begin{pmatrix} 1 & \rho(t) \\ \rho(t) & 1 \end{pmatrix}D(t) \tag{3}$$

where the conditional standard deviations of time series are represented in the diagonal matrix $D(t)$; $R(t)$ is the correlation matrix conditioned on all observations obtained till time $t$, and $\rho(t)$ is the correlation coefficient conditioned on the observations collected up to time $t$, which is defined as:

$$\rho(t) = \frac{\sigma_{12}(t)}{\sqrt{\sigma_{11}(t)\sigma_{22}(t)}}. \tag{4}$$

The main goal of this paper is to estimate the confidence bands for $\rho(t)$ by applying a modified sliding-window technique. The general idea behind the basic sliding-window technique is based on calculating the correlation coefficient from the data contained within a window of fixed length $w$. By moving the window, the correlation coefficient can be computed at each time point. This can be expressed as follows:

$$\hat{\rho}(t) = \frac{\sum_{k=t}^{t+w-1}(y_1(k) - \mu_1(k))(y_2(k) - \mu_2(k))}{\sqrt{\sum_{k=t}^{t+w-1}(y_1(k) - \mu_1(k))\sum_{k=t}^{t+w-1}(y_2(k) - \mu_2(k))}} \tag{5}$$

There are a number of potential drawbacks of using the sliding-window approach directly, including its inability to handle sudden changes, the equal weighting of all observations within a window, and the arbitrary selection of window length (Lindquist et al., 2014). Due to these shortcomings, it is important to be able to critically evaluate the uncertainty present in the sliding-window estimate. However, the sliding-window technique does not provide valid and straightforward non-parametric estimates for the confidence bands. The most commonly used approach for computing the confidence interval for the correlation estimator is to use a parametric, asymptotic Fisher approximation for the correlation coefficient. However, as we show in this paper, this approach has a number of shortcomings in practice and is not valid for correlated time series.

## 3. Estimation of time-varying functional connectivity and its confidence bands

In this section, we introduce the DCBootCB algorithm for estimating the time-varying correlation coefficient and its confidence bands. In order to understand the DCBootCB algorithm, we begin by giving a brief summary of statistical concepts used in our study and the MLPB method proposed by Jentsch and Politis (2015).

We start by providing short overview of a number of statistical concepts. A *confidence interval* at a given confidence level, for example 95%, implies that if the same population is sampled on many occasions and interval estimates are calculated each time, the resulting intervals would include the true population parameter in approximately 95 % of the cases.