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Comments and Controversies

# On spurious and real fluctuations of dynamic functional connectivity during rest

Nora Leonardi, Dimitri Van De Ville*

*Institute of Bioengineering, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland*
*Department of Radiology and Medical Informatics, University of Geneva, Geneva, Switzerland*

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ABSTRACT

Functional brain networks reconfigure spontaneously during rest. Such network dynamics can be studied by dynamic functional connectivity (dynFC); i.e., sliding-window correlations between regional brain activity. Key parameters—such as window length and cut-off frequencies for filtering—are not yet systematically studied. In this letter we provide the fundamental theory from signal processing to address these parameter choices when estimating and interpreting dynFC. We guide the reader through several illustrative cases, both simple analytical models and experimental fMRI BOLD data. First, we show how spurious fluctuations in dynFC can arise due to the estimation method when the window length is shorter than the largest wavelength present in both signals, even for deterministic signals with a fixed relationship. Second, we study how real fluctuations of dynFC can be explained using a frequency-based view, which is particularly instructive for signals with multiple frequency components such as fMRI BOLD, demonstrating that fluctuations in sliding-window correlation emerge by interaction between frequency components similar to the phenomenon of beat frequencies. We conclude with practical guidelines for the choice and impact of the window length.



## Introduction

Functional magnetic resonance imaging (fMRI) has become a key tool to probe the large-scale organization of the brain. Functional connectivity (FC), which is estimated by correlation of BOLD activity, identifies coherent brain activity in distributed and reproducible networks. FC has revealed reorganization of brain networks during cognitive tasks (Ekman et al., 2012; Lewis et al., 2009; Richiardi et al., 2011, 2013; Shirer et al., 2012), but also at rest (Allen et al., 2014; Chang and Glover, 2010; Hutchison et al., 2013b; Kang et al., 2011; Leonardi et al., 2013; Majeed et al., 2011; Smith et al., 2012). To study changes in FC over time sliding-window correlation analysis, where the correlation is estimated for brain activity during multiple, possibly overlapping temporal segments (typically 30–60 s), has been widely deployed (Allen et al., 2014; Chang and Glover, 2010; Hutchison et al., 2013a; Sakoglu et al., 2010). A caveat of analyzing dynamic FC (dynFC) by sliding-window correlation is that the small number of time points renders the estimates unreliable and might lead to spurious variability of dynFC (Hutchison et al., 2013a; Smith et al., 2012). However, there is no systematic account that perspicuously indicates the trade-off that is made by choosing the window length, and its implications for filtering of BOLD activity time series and dynFC itself.

We first break sliding-window correlation into several components to facilitate its study. Then, we present a simple yet instructive analytical model to study the emergence of spurious variability of dynFC in stationary signals. In particular, we investigate the influence of various parameters such as frequency, phase lag, and window length. Next, we introduce a small change to our analytical model to study how real variability of dynFC due to non-stationarity might arise. To provide the best possible insights for signals with many frequency components, we present a frequency-based view on dynFC. This provides an elegant explanation of how fluctuations of dynFC emerge through the interaction between different frequency components. Finally, we illustrate dynFC between two main regions of the default-mode network with experimental fMRI data.

## Breaking down sliding-window correlations

We start by reformulating sliding-window correlation into simpler terms. In particular, we first look at sliding-window *covariance*, which for two time series $x$ and $y$ with sampling period TR is defined as follows at scan $n$:

$$\begin{aligned} c_{xy}[n] &= \operatorname{cov}(x[n-\Delta, n+\Delta], y[n-\Delta, n+\Delta]) \\ &= \frac{\mathrm{TR}}{w}\sum_{i=n-\Delta}^{n+\Delta}(x_i-\bar{x}_n)(y_i-\bar{y}_n), \end{aligned} \tag{1}$$

* Corresponding author at: EPFL/IBI-STI, Station 17, 1015 Lausanne, Switzerland.
*E-mail address:* dimitri.vandeville@epfl.ch (D. Van De Ville).

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where $w = (2\Delta + 1)$TR is the odd window length in seconds, $i$ sums only over the scans inside the window, and

$$\bar{x}_n = \frac{\mathrm{TR}}{w}\sum_{i=n-\Delta}^{n+\Delta} x_i$$

is the local average inside the window at position $n$. This calculation is then repeated for all values of $n$ ("sliding" the window across time). After some elementary manipulations, we arrive at the following equality:

$$\begin{aligned} c_{xy}[n] &= \frac{\mathrm{TR}}{w}\sum_{i=n-\Delta}^{n+\Delta}(x_i - \bar{x}_n)(y_i - \bar{y}_n) \\ &= \frac{\mathrm{TR}}{w}\sum_{i=n-\Delta}^{n+\Delta} x_i(y_i - \bar{y}_n) - \mathrm{TR}\frac{\bar{x}}{w}\sum_{i=n-\Delta}^{n+\Delta}(y_i - \bar{y}_n) \overset{(a)}{=} \frac{\mathrm{TR}}{w}\sum_{i=n-\Delta}^{n+\Delta} x_i(y_i - \bar{y}_n) \\ &= \frac{\mathrm{TR}}{w}\sum_{i=n-\Delta}^{n+\Delta} x_i y_i - \bar{y}_n\frac{\mathrm{TR}}{w}\sum_{i=n-\Delta}^{n+\Delta} x_i = \underbrace{\frac{\mathrm{TR}}{w}\sum_{i=n-\Delta}^{n+\Delta} x_i y_i}_{\mathrm{I}} - \underbrace{\bar{y}_n\bar{x}_n}_{\mathrm{II}}, \end{aligned} \tag{2}$$

where $^{(a)}$ simplifies as the second term equals zero. Thus, $c_{xy}[n]$ can be separated into two terms, which are the local average of the cross-product $xy$ (I) minus the product of the local averages of $x$ and $y$ (II).

The sliding-window correlation is then obtained by normalizing at each window by the local variances:

$$\rho_{xy}[n] = \frac{c_{xy}[n]}{\sqrt{c_{xx}[n]c_{yy}[n]}}. \tag{3}$$

Having identified the components that constitute sliding-window correlation, we can now analyze and understand dynFC more easily.

## Spurious fluctuations in dynFC

### *Effect of the window length*

We want to understand how spurious fluctuations of dynFC might arise even for deterministic signals with a fixed relationship; i.e., we consider two pure sinusoidal signals that are phase-locked. Specifically, we take

$$x_i = \sqrt{2}cos(2\pi f i\ \mathrm{TR}), \quad y_i = \sqrt{2}cos(2\pi f i\ \mathrm{TR} + \theta), \tag{4}$$

where the factor $\sqrt{2}$ normalizes both signals for variance equal to one per time unit. This normalization makes the sliding-window covariance comparable to sliding-window correlation as a first approximation; i.e., we have the asymptotic equivalence $lim_{w\to\infty}\rho_{xy}[n] = c_{xy}[n]$.

To investigate the influence of the key parameters frequency $f$, phase lag $\theta$, and window length $w$, we derive the analytical form of $c_{xy}[n]$ for the signals of Eq. (4). First, we approximate $\bar{y}_n$ by integration as follows:

$$\begin{aligned} \bar{y}_n &= \frac{\mathrm{TR}}{w}\sum_{i=n-\Delta}^{n+\Delta}\sqrt{2}cos(2\pi f i\ \mathrm{TR} + \theta) \approx \frac{\sqrt{2}}{w}\int_{(n-\Delta)\mathrm{TR}}^{(n+\Delta)\mathrm{TR}} cos(2\pi f t + \theta)dt \\ &= \frac{\sqrt{2}}{w}\left[\frac{1}{2\pi f}sin(2\pi f t + \theta)\right]_{(n-\Delta)\mathrm{TR}}^{(n+\Delta)\mathrm{TR}} = \frac{\sqrt{2}}{w2\pi f}(sin(2\pi f(n+\Delta)\mathrm{TR} + \theta) \\ &\quad - \quad sin(2\pi f(n-\Delta)\mathrm{TR} + \theta)) = \frac{\sqrt{2}}{w\pi f}cos(2\pi f n\mathrm{TR} + \theta)sin(2\pi f\Delta\mathrm{TR}). \end{aligned}$$

On similar grounds, we also find $\bar{x}_n = \frac{\sqrt{2}}{w\pi f}cos(2\pi f n\mathrm{TR})sin(2\pi f\Delta\mathrm{TR})$. Therefore, the second term $\bar{x}_n\bar{y}_n$ of Eq. (2) reverts to

$$\bar{x}_n\bar{y}_n = \frac{2}{w^2\pi^2 f^2}cos(2\pi f n\mathrm{TR})cos(2\pi f n\mathrm{TR} + \theta)sin^2(2\pi f\Delta\mathrm{TR}).$$

To estimate the first term of Eq. (2), we use the product-to-sum trigonometric identity

$$2cos(2\pi f i\mathrm{TR})cos(2\pi f i\mathrm{TR} + \theta) = cos(4\pi f i\mathrm{TR} + \theta) + cos(\theta),$$

which, after integration, leads to

$$cos(\theta) + \frac{1}{w\pi f}cos(2\pi f n\mathrm{TR} + \theta)sin(2\pi f\Delta\mathrm{TR}).$$

By combining both terms, we retrieve the expression

$$\begin{aligned} c_{xy}[n] = cos(\theta) &+ \frac{1}{w\pi f}cos(2\pi f n\mathrm{TR} + \theta)sin(2\pi f\Delta\mathrm{TR}) \\ &- \frac{2}{w^2\pi^2 f^2}cos(2\pi f n\mathrm{TR})cos(2\pi f n\mathrm{TR} + \theta)sin^2(2\pi f\Delta\mathrm{TR}). \end{aligned} \tag{5}$$

As a sanity check, we see that in the limit of stationary covariance (i.e., infinite window length), we have

$$\lim_{w\to+\infty} c_{xy}[n] = cos(\theta).$$

We now use this expression to efficiently trace $c_{xy}[n]$ as function of frequency $f$, phase lag $\theta$, window length $w$, and window position $n$. In Fig. 1a, $c_{xy}[n]$ is plotted for $f = 0.025$ Hz and zero phase lag, as a function of window length $w$. The dashed lines are for different window positions $n$, and the thick line corresponds to the mean $\bar{c}_{xy} = E[c_{xy}[n]]$. We observe considerable fluctuations of $c_{xy}[n]$ for short window lengths, and crossings with the true value (i.e., 1) exactly for multiples of the window length because the term $sin(2\pi f\Delta\mathrm{TR})$ in Eq. (5) vanishes for $2\Delta\mathrm{TR} = 1/f$. Importantly, only when the window length is larger than the first crossing, which corresponds to the wavelength $1/f = 40$ s, fluctuations of $c_{xy}[n]$ diminish and converge to the true value of $cos(\theta)$.

The same observations can be made from Figs. 1b and c, where we plot $\bar{c}_{xy}$ for various frequencies, and the difference between maximal and minimal $c_{xy}[n]$ in Fig. 1d. Spurious fluctuations of $c_{xy}[n]$ occur when the window length is too short with respect to the underlying frequency component. We propose the following rule of thumb for minimal window length when observing underlying frequencies of $f_{\min}$ or higher:

$$w \geq \frac{1}{f_{\min}}.$$

Therefore, high-pass filtering that removes frequency components below $1/w$ can be recommended; see also Smith et al. (2012) and Hutchison et al. (2013a) for similar recommendations. The cut-off frequency $f_{\min}$ is indicated in Fig. 1. It should be noted that these plots only depend on the window length in seconds, not in TRs.

Sliding-window correlation $\rho_{xy}[n]$ (and its fluctuations) can be obtained by normalizing $c_{xy}[n]$ according to Eq. (3). In the ideal case with zero phase lag, sliding-window correlation clamps to 1; however, even a small phase lag is sufficient to introduce the same spurious fluctuations as we observed for sliding-window covariance. In Fig. 2, we plot sliding-window correlation and its extrema for phase lags of $\theta = \pi/16$ and $\theta = \pi/4$, respectively. The variability of sliding-window correlation is decreased compared to sliding-window covariance, but still the true correlation of $cos(\theta)$ is recovered only for window lengths above $w_{\min}$, in accordance with the previous rule of thumb.