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Original contribution

Complex-valued time-series correlation increases sensitivity in FMRI analysis

Mary C. Kociuba [a], Daniel B. Rowe [a,b,*]

[a] Department of Mathematics, Statistics, and Computer Science, Marquette University, Milwaukee, WI, USA
[b] Department of Biophysics, Medical College of Wisconsin, Milwaukee, WI, USA

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ABSTRACT

Purpose: To develop a linear matrix representation of correlation between complex-valued (CV) time-series in the temporal Fourier frequency domain, and demonstrate its increased sensitivity over correlation between magnitude-only (MO) time-series in functional MRI (fMRI) analysis.
Materials and methods: The standard in fMRI is to discard the phase before the statistical analysis of the data, despite evidence of task related change in the phase time-series. With a real-valued isomorphism representation of Fourier reconstruction, correlation is computed in the temporal frequency domain with CV time-series data, rather than with the standard of MO data. A MATLAB simulation compares the Fisher-*z* transform of MO and CV correlations for varying degrees of task related magnitude and phase amplitude change in the time-series. The increased sensitivity of the complex-valued Fourier representation of correlation is also demonstrated with experimental human data. Since the correlation description in the temporal frequency domain is represented as a summation of second order temporal frequencies, the correlation is easily divided into experimentally relevant frequency bands for each voxel's temporal frequency spectrum. The MO and CV correlations for the experimental human data are analyzed for four voxels of interest (VOIs) to show the framework with high and low contrast-to-noise ratios in the motor cortex and the supplementary motor cortex.
Results: The simulation demonstrates the increased strength of CV correlations over MO correlations for low magnitude contrast-to-noise time-series. In the experimental human data, the MO correlation maps are noisier than the CV maps, and it is more difficult to distinguish the motor cortex in the MO correlation maps after spatial processing.
Conclusions: Including both magnitude and phase in the spatial correlation computations more accurately defines the correlated left and right motor cortices. Sensitivity in correlation analysis is important to preserve the signal of interest in fMRI data sets with high noise variance, and avoid excessive processing induced correlation.

1. Introduction

In fMRI, the measured blood oxygen level dependent (BOLD) signal to detect neural activity is spatially Fourier encoded [1,2]. The BOLD fluctuations are measured as a complex-valued fMRI signal over time in the spatial frequency domain, then the *k*-space readout is reconstructed with the inverse Fourier transform (IFT). Before the statistical analysis of the fMRI data, the phase portion of the data is generally discarded, despite physiologically useful information contained in the phase [3]. Previous research suggests that phase-only change arises from large draining vessels [4], or proposes methods to filter phase signal contributions from large vessels [4,5]. Although, other models support the notion that randomly oriented vasculature yield phase change in fMRI studies [6,7]. It has been previously demonstrated that modeling an fMRI time-series with both magnitude and phase increases the power of the activation statistics [8–11] over those from MO models. This manuscript outlines a method to describe correlation between two time-series with both magnitude and phase (equivalently real and imaginary), through exploiting the linear relationship between the image domain and spatial frequency domain. Traditionally both MO and CV models require analysis in the image domain, however, analysis within the frequency domain is also valuable. It has previously been shown how complex-valued temporal frequencies contribute to the correlations between voxels in the cerebral cortex for magnitude-only non-task data [12]. Similarly, in this manuscript the spatial correlation between complex-valued time series is described as a

* Corresponding author at: Department of Mathematics, Statistics, and Computer Science, Marquette University, Milwaukee, WI, USA. Tel.: +1 414 288 5228; fax: +1 414 288 5472.
E-mail addresses: daniel.rowe@marquette.edu, dbrowe@mcw.edu (D.B. Rowe).

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linear combination of second order voxel temporal frequencies. The present study advances the frequency correlation description into a linear matrix framework with an application to a complex-valued simulation demonstrating the strength of the model at low magnitude and phase contrast-to-noise ratio (CNR) values, as well demonstrating its utility in experimental complex-valued fMRI data.

During signal acquisition, unwanted image acquisition artifacts and physiological noise obscure the true underlying signal of interest. To improve the signal-to-noise ratio (SNR), various preprocessing operations, *i.e.* temporal frequency filtering or magnitude image smoothing, are incorporated in the processing and reconstruction pipeline, and physiologic noise sources are commonly regressed out from the signal [13–16]. It is well documented that the application of these operations induces local spatial and temporal correlations into neural regions that were previously uncorrelated [17–19]. The linear framework developed in this manuscript also describes how signal processing alters the structure of the spatial covariance matrix, such that induced correlation is a result of increased overlapping frequency content between voxels after processing. Signal processing will alter the activated voxel's temporal frequency spectrums, by spreading voxel task activated peaks temporally and spatially. Correlation will be induced between voxels as a result of increased overlapping frequency content between the two voxel's Fourier frequency spectrums. This notation for spatial correlation is advantageous since various physiological signals are also confined to specific frequency ranges. Respiratory and cardiac cycle fluctuations are characterized around 0.2–0.3 Hz and 1 Hz in a voxel's temporal frequency spectrum, although they are often aliased to low frequencies in fMRI signal acquisition [13,20,21]. The summation notation of spatial correlation that is described here, allows relative contributions to the correlation to be quantified by segregating the natural partitions in a voxel's temporal frequency spectrum. Compared to magnitude-only correlations, applying this framework with complex-valued data more accurately identifies regions of spatial correlation, and reduces the false positives in correlation maps. This result is most significant in low magnitude CNR data sets since including the phase in the complex-valued correlation results in increased sensitivity of identifying correlated regions.

2. Theory

A $p_{row} \times p_{col}$ complex-valued k-space readout is reconstructed to a single image with the discrete inverse Fourier transform (IFT). With a real-valued isomorphism representation [22] of the Fourier reconstruction operator, Ω, and the k-space readout in vector form, s_t, an image vector, y_t, for a single image time point, t, is reconstructed as

$$y_t = \Omega s_t. \tag{1}$$

Equivalently, with the forward Fourier Transform $\Omega^{-1} = \overline{\Omega}$, the k-space readout is written as

$$s_t = \overline{\Omega} y_t. \tag{2}$$

In Eqs. (1) and (2), the signal and image vectors are $2p \times 1$, where $p = p_{row}p_{col}$ is the number of voxels, and the real parts are stacked over the imaginary parts, so $s_t = (s_R', s_I')'$ and $y_t = (y_R', y_I')'$. The real parts in each vector are organized as $s_R = (s_{R1}, \ldots, s_{Rp})'$ and $y_R = (y_{R1}, \ldots, y_{Rp})'$, and the imaginary parts in each vector are organized as $s_I = (s_{I1}, \ldots, s_{Ip})'$ and $y_I = (y_{I1}, \ldots, y_{Ip})'$. To build up the real-valued matrix framework, consider the representation of the inverse Fourier reconstruction.

$$\Omega = \begin{bmatrix} \Omega_R & -\Omega_I \\ \Omega_I & \Omega_{R.} \end{bmatrix}$$

where Ω_R and Ω_I are constructed with the Kronecker product, $\Omega_R = [(\Omega_{yR} \otimes \Omega_{xR}) - (\Omega_{yI} \otimes \Omega_{xI})]$

and $\Omega_I = [(\Omega_{yR} \otimes \Omega_{xI}) + (\Omega_{yI} \otimes \Omega_{xR})]$. The jkth element of the $p_{col} \times p_{col}$ Fourier matrix Ω_x is $(\Omega_x)_{jk} = w^{(-\frac{pcol}{2}+j)(-\frac{pcol}{2}+k)}$ where j and k have indexing values from 0 to $p_{col} - 1$ with $w = \frac{1}{N} e^{i2\pi/p_{col}}$ for the IFT and $w = e^{-i2\pi/p_{col}}$ for the forward Fourier transform (FT), [22].

To reconstruct images over n time repetitions (TRs), the complex-valued spatial frequencies are represented in the real-valued $2pn \times 1$ vector s, with each successive TR concatenated to the vector. An analogous explanation describes the organization of the real-valued image $2pn \times 1$ vector, y, which is reconstructed with the Kronecker product,

$$y = (I_n \otimes \Omega)s. \tag{3}$$

A $2pn \times 2pn$ permutation matrix, P, reorders the elements of vector y so the real-valued time-series $2pn \times 1$ vector $v = Py$ is now ordered by voxel rather than ordered by image. The voxel ordered time-series is Fourier transformed into the temporal frequency domain, with the $2n \times 2n$ temporal forward Fourier transform (FT) matrix, Ω_T, as opposed to the $2p \times 2p$ spatial Fourier operations. The real-valued $2pn \times 1$ vector f consists of the temporal frequencies of each voxel stacked upon the corresponding imaginary temporal frequencies is represented,

$$f = \left(I_p \otimes \overline{\Omega}_T\right) Py. \tag{4}$$

For voxel α, the $2n \times 1$ real-valued voxel time-series is denoted v_α, with real parts stacked over imaginary parts $v_\alpha = (v_{\alpha R}', v_{\alpha I}')'$ so the real and imaginary parts in each vector are organized as $v_{\alpha R} = (v_{\alpha R1}, \ldots, v_{\alpha Rn})'$ and $v_{\alpha I} = (v_{\alpha I1}, \ldots, v_{\alpha In})'$, with a mean and covariance structure of $\mu_{R\alpha}$ and $\mu_{I\alpha}$., $\sigma^2_{R\alpha} I_n$ and $\sigma^2_{I\alpha} I_n$.The corresponding temporal frequencies for voxel α are denoted in the $2n \times 1$ vector f_α, where $v_\alpha = \Omega_T f_\alpha$ and $f_\alpha = \Omega_T v_\alpha$, are organized similarly to the time-series equivalent. With an analogous description of another voxel β, the spatial covariance between the two voxels is simply written, $\mathrm{cov}(v_\alpha, v_\beta) = (v_\alpha - \mu_\alpha)^T (v_\beta - \mu_\beta)/(2n)$.

Assuming the time-series is demeaned, then the covariance between two voxels in terms of temporal frequencies is represented as,

$$cov\left(v_\alpha, v_\beta\right) = \left(v_\alpha^T v_\beta\right)/(2n) = \left(\overline{\Omega}_T f_\alpha\right)^T \left(\overline{\Omega}_T f_\beta\right) = \left(f_\alpha^T f_\beta\right)/4 \tag{5}$$

The spatial covariance in Eq. (5) is expanded to a $p \times p$ spatial covariance matrix, Σ, such that the entry (α, β) in Σ represents the spatial covariance between the two demeaned real-valued voxel time-series of voxel α and voxel β. By defining D as the diagonal matrix consisting of the diagonal elements of Σ, a $p \times p$ spatial correlation matrix is written as,

$$R = D^{-1/2} \ \Sigma \ D^{-1/2}. \tag{6}$$

By aggregating the second order temporal frequencies into biologically meaningful or experimentally relevant bands, the influence preprocessing steps have on each voxel temporal frequency spectrum can be quantitatively measured. In an fMRI study, the frequency corresponding to the activation is considered when dividing the spectrum into bands. To understand the contribution each temporal frequency band yields to spatial correlation, the