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A method to produce evolving functional connectivity maps during the course of an fMRI experiment using wavelet-based time-varying Granger causality

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Functional magnetic resonance imaging (fMRI) is widely used to identify neural correlates of cognitive tasks. However, the analysis of functional connectivity is crucial to understanding neural dynamics. Although many studies of cerebral circuitry have revealed adaptative behavior, which can change during the course of the experiment, most of contemporary connectivity studies are based on correlational analysis or structural equations analysis, assuming a time-invariant connectivity structure. In this paper, a novel method of continuous time-varying connectivity analysis is proposed, based on the wavelet expansion of functions and vector autoregressive model (wavelet dynamic vector autoregressive-DVAR). The model also allows identification of the direction of information flow between brain areas, extending the Granger causality concept to locally stationary processes. Simulation results show a good performance of this approach even using short time intervals. The application of this new approach is illustrated with fMRI data from a simple AB motor task experiment.

Keywords: fMRI; Connectivity; Dynamic; Time-varying; Wavelets

Introduction

Functional neuroimaging using the BOLD (Blood Oxygen Level Dependent) effect has received considerable attention in the last decade and has become a powerful tool in cognitive neuroscience. Impressive methodological progress has been made since the first description of the effect (Ogawa et al., 1990) and a large number of statistical methods for data analysis have been proposed, although most of them in somewhat ad hoc fashion. So far, image analysis reports in the literature are mainly dedicated to addressing the detection of brain activation. Such approaches ("brain mapping"), though very useful, are unable to address the more fundamental principles that characterize brain dynamics by probing the connectivity information obtainable from the BOLD signal.

Inferring the dynamics of interaction between different neural structures is a crucial step toward understanding neural organization (Sameshima and Baccala, 1999; Friston, 2002). At conceptual level, there is active interest in the formulation of connectivity analysis. Friston has introduced the concept of dynamic causal models (DCM, Friston, 1995; Friston et al., 2003), based on nonlinear input-state-output systems, and a bilinear approximation to dynamic interactions. However, the DCM results rely on the prior connectivity specifications and also on stationarity conditions. A potentially promising approach to addressing some of these issues is the Granger causality concept (Granger, 1969; Sameshima and Baccala, 1999; Baccala and Sameshima, 2001; Roebroeck et al., 2005) which is borrowed from econometrics and based on the notion of the predictability of one signal by another, subject to the time constraint that the effect cannot precede the cause. It is specially suited to study partially ordered linear dependencies in multivariate contexts without assuming any prior connectivity structure. Recently, significant developments have occurred in the analysis of cerebral connectivity. Buchel and Friston (1997) introduced covariance structural equation modeling in fMRI applications. Subsequently, Goebel et al. (2003) and Roebroeck et al. (2005) have proposed the use of vector autoregressive models and shown their utility in the analysis of fMRI experiments. Nevertheless, Granger causality alone is not sufficient to infer effective causal relations, as it is based only on predictive power. Recent developments in

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graphical models have worked towards the identification of effective causal links. Eichler (2005) suggested a graphical representation of multivariate data that allows the inference of effective connectivity, even in the presence of latent variables.

In its original form, Granger causality was defined for linear stationary multichannel signals but, as with most biological signals, there is no unique model for fMRI data and no strong theoretical or experimental basis for the assumptions of stationarity of processes. It is widely recognized that incorrect use of these assumptions can lead to incorrect inferences.

Here, we propose a new method: the wavelet dynamic vector autoregressive (DVAR) process, which can be seen as a generalization of vector autoregressive model (VAR). This approach does not require assumptions about the direction of influence. The DVAR model is a multivariate version of the one proposed by Chang and Morettin (2005) and Dahlhaus et al. (1999). Its novel feature lies in directly modeling time-varying coefficients through wavelet bases with a balance between model complexity and interpretability. Wavelet analysis is an area of intense research in statistical signal analysis because of its wide applicability to model nonstationary signals and its deep relationship to time-frequency representation of a signal. Bullmore et al. (2003, 2004) have demonstrated the value of wavelet analysis applied to the BOLD signal as a means of retaining the colored-noise characteristics of the time series during permutation testing of statistical significance, thus highlighting the use of wavelet techniques in fMRI. Our aim was to combine wavelet analysis and the Granger causality concept given by VAR models to extend the methodology available for the study of brain connectivity. Fitting time-varying coefficients using a wavelet basis allowed us to model nonstationary (locally stationary) and nonlinear (locally linear) multichannel signals using Granger causal (VAR) approaches and make inferences about temporal dynamics of neural interactions. Thus, we can infer the connectivity structure of brain regions in a time-varying way.

In this article, a review of Granger causality theory and connectivity is presented, followed by the methodology underlying the new approach. Simulation results are presented and the usefulness of the method is illustrated in an application involving real fMRI data, in a simple sensorimotor experiment.

Granger causality and dynamic connectivity

Granger causality (Granger, 1969) is a concept that originated in the area of econometrics, focusing on understanding the relationships between two time series. Granger (1969) defined the causality in terms of predictability, based on the fact that the effect cannot come before the cause. Subsequently, Goebel et al. (2003) applied Granger causality to the description of interregional connectivity in fMRI data and to detection of the direction of information flow between brain regions.

Formally, consider a k-dimensional multivariate time series $\mathbf{y}_t$

$$\mathbf{y}_t = [y_{1t}\ y_{2t}, \ldots,\ y_{kt}]',$$

composed by k time series measured on time t. The Granger causality identification is based on the improvement in predictions of future values of the series $\mathbf{y}_t$, using the information of a collection of p past values of the series $(\mathbf{y}_{t-1}, \mathbf{y}_{t-2}, \ldots, \mathbf{y}_{t-p})$. Hence, consider a k-dimensional vector autoregressive model (VAR) of order p, defined by

$$\mathbf{y}_t = \mathbf{v} + \mathbf{A}_1\mathbf{y}_{t-1} + \mathbf{A}_2\mathbf{y}_{t-2} + \ldots + \mathbf{A}_p\mathbf{y}_{t-p} + \boldsymbol{u}_t,$$

where $\boldsymbol{u}_t$ is an error vector of random variables with zero mean and covariance matrix $\boldsymbol{\Sigma}$ given by

$$\sum = \begin{bmatrix} \sigma_{11}^2 & \sigma_{21} & \cdots & \sigma_{k1} \\ \sigma_{12} & \sigma_{22}^2 & \cdots & \sigma_{k2} \\ \sigma_{13} & \sigma_{23} & \cdots & \sigma_{k3} \\ \vdots & \vdots & \ddots & \vdots \\ \sigma_{1k} & \sigma_{2k} & \cdots & \sigma_{kk}^2 \end{bmatrix},$$

and $\mathbf{v}$ and $\mathbf{A}_i$ ($i = 1,2, \ldots, p$) are coefficient matrices given by

$$\mathbf{v} = \begin{bmatrix} v_1 \\ v_2 \\ \vdots \\ v_k \end{bmatrix} \qquad \mathbf{A}_i = \begin{bmatrix} a_{11i} & a_{21i} & \cdots & a_{kl1} \\ a_{12i} & a_{22i} & \cdots & a_{k2i} \\ a_{13i} & a_{23i} & \cdots & a_{k3i} \\ \vdots & \vdots & \ddots & \vdots \\ a_{1ki} & a_{2ki} & \cdots & a_{kki} \end{bmatrix}.$$

The VAR model allows an easy way of identifying Granger causality. An important result of the VAR model, is that the series y_{jt} noncauses y_{lt}, if and only if, the coefficient $a_{jli} = 0$ for any i. In other words, the past values of y_{jt} aid the prediction of future values of y_{lt}. Hence, Granger causalities can be identified simply looking for the VAR representation, and the direction of causality can be interpreted as the direction of information flow. Furthermore, Granger causality relationship is not necessarily reciprocal, for example, y_{jt} may Granger cause the signal y_{lt}, without any implication that y_{lt} Granger causes y_{jt}.

This approach can be extended to the analysis of time series of BOLD signals in functional magnetic resonance imaging data (Goebel et al., 2003). Let k-dimensional time series represent the regions of interest BOLD signal. Using the concept of Granger causality, the VAR modeling makes possible the identification of functional connectivity between brain areas by simply testing the significance of the estimates of the components of the matrix $\mathbf{A}_t$. However, as the Granger causality is defined in terms of predictability, the VAR modeling can indicate only functional relationships. In other words, this approach points out the links between signals, but does not, per se, indicate neurophysiologic mechanisms (effective connectivity).

There are two widely used approaches to assigning significance to the elements of matrices $\mathbf{A}_i$. The first is based on a Wald test for the statistical significance of the causality coefficients of a VAR model (Lütkepohl, 1993). The second one is based on the computation of F statistics by considering the ratio of residual variances and is described in detail by Geweke (1982).

According to Roebroeck et al. (2005), there are two main obstacles to the application of Granger causality mapping in fMRI. The first obstacle is that the BOLD response is not a direct measure of neural activity, and then, the connectivity relationships cannot be identified due to hemodynamic blurring. Furthermore, the low temporal resolution of fMRI may not provide enough information for inferring connectivity. Despite these apparent problems, the above authors were able to show by simulations that the Granger causality can be useful for inferring brain functional connectivity.

However, VAR modeling is an adequate approach only in cases of stationary time series, i.e., the autoregressive coefficients and error matrix covariance are time-invariant. In fact, most connectivity studies of fMRI data to date have used correlation analysis or structural equations models, assuming stationarity conditions. In