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Canonical granger causality between regions of interest

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ABSTRACT

Estimating and modeling functional connectivity in the brain is a challenging problem with potential applications in the understanding of brain organization and various neurological and neuropsychological conditions. An important objective in connectivity analysis is to determine the connections between regions of interest in the brain. However, traditional functional connectivity analyses have frequently focused on modeling interactions between time series recordings at individual sensors, voxels, or vertices despite the fact that a single region of interest will often include multiple such recordings. In this paper, we present a novel measure of interaction between regions of interest rather than individual signals. The proposed measure, termed canonical Granger causality, combines ideas from canonical correlation and Granger causality analysis to yield a measure that reflects directed causality between two regions of interest. In particular, canonical Granger causality uses optimized linear combinations of signals from each region of interest to enable accurate causality measurements from substantially less data compared to alternative multivariate methods that have previously been proposed for this scenario. The optimized linear combinations are obtained using a variation of a technique developed for optimization on the Stiefel manifold. We demonstrate the advantages of canonical Granger causality in comparison to alternative causality measures for a range of different simulated datasets. We also apply the proposed measure to local field potential data recorded in a macaque brain during a visuomotor task. Results demonstrate that canonical Granger causality can be used to identify causal relationships between striate and prestriate cortexes in cases where standard Granger causality is unable to identify statistically significant interactions.

Introduction

An important objective in brain research is to understand how information propagates between different regions (Jirsa and McIntosh, 2007). Electrophysiological measurements of brain activity can be useful for achieving this goal, since they provide rich information about the location and temporal dynamics of spontaneous and task-related brain networks. In particular, invasive local field potential (LFP) and electrocorticography (ECoG) measurements as well as noninvasive electroencephalography (EEG) and magnetoencephalography (MEG) data allow for the modeling of brain connectivity, with wide ranging implications for addressing neuroscientific questions (Astolfi et al., 2007; Bressler et al., 2007; Schoffelen and Gross, 2009), understanding mechanisms of neuropathology (Lin et al., 2009; Wilke et al., 2009) and studying neuropsychological conditions (Hesse et al., 2003). Many connectivity models require assumptions regarding the behavior of the relationship between signals from different regions; for example, autoregressive models try to find areas of the brain whose electrical activity co-varies with past activity in other areas of the brain (Cheung et al., 2010; Hesse et al., 2003).

This paper focuses on models based on Granger causality (GC) (Granger, 1969). Causal models estimate the strength and directionality of signal interactions by analyzing the joint distributions of their time series under appropriate modeling assumptions. Classical methods for causal modeling analyze causality between multiple time series in a pairwise fashion, using bivariate models (Geweke, 1982). However, pairwise analysis is not ideal for functional brain mapping experiments in which multiple time series are available from different sensors, voxels (in a reconstructed source volume), or vertices (from a reconstructed source surface). Usually, such time series can be spatially correlated because of the limited spatial resolution of the mapping techniques or because functional activation is spatially distributed across a larger region of cortex. One approach could be to remove the influence of these confounds via partial measures of causality (Guo et al., 2008), but such partial measures usually require the estimation of a complex parametric model and may be hard to interpret (Eichler, 2006; Kuś et al., 2004; Zhou et al., 2009).

Rather than analyzing causality independently between pairs of time series, in some cases it may be more desirable to analyze causality between multiple regions of interest (ROIs) that each includes multiple correlated time series (d'Alessandro et al., 2003). Grouping multiple time series together can reduce the number of variables to estimate in a parametric model, can improve the signal-to-noise

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ratio of the resulting causality measure, and can help in identifying long-range connectivity that might previously have been obscured by larger apparent short-range connectivity that is artificially introduced by crosstalk within the ROI (Bin et al., 2009).

Many methods have been proposed to assess connectivity between ROIs. One popular method is canonical correlation (Hotelling, 1936), which estimates an undirected model of connectivity by maximizing the correlation between weighted linear combinations of signals from two ROIs. In addition to providing a measure of connectivity, canonical correlation also provides an estimate of the relative contribution of each signal from each ROI to the correlation between the ROIs (Deleus and Van Hulle, 2011; Kuylen and Verhallen, 1981). Canonical correlation analysis, however, is not a causal model and provides no information about the direction of information flow between ROIs.

Models of directed interaction between ROIs often use the concept of GC. Multivariate Granger causality (MGC) (Barrett and Seth, 2010) relies on multivariate autoregressive models of the signals between each ROI. While MGC can be accurate when the data records are sufficiently long, MGC involves substantially more parameters to estimate than do bivariate methods and can be prone to overfitting and sensitive to noise. A possible way to reduce this effect is to use penalized autoregression to promote certain desirable qualities in the estimation of causality such as spatial smoothness or sparse connectivity (Valdés-Sosa et al., 2005). Another approach is Granger canonical correlation analysis (GCCA), (Wu et al., 2011) which aggregates signals in each ROI much like canonical correlation analysis. This approach results in a reduction of the number of parameters to estimate relative to methods like MGC and penalized autoregression, although it does not estimate the amount of causality or the underlying signals responsible for the causal connection (Sato et al., 2010), and can only identify the presence or absence of causality.

In this paper we formulate, develop, and apply a novel directed causal connectivity measure called canonical Granger causality (CGC) that combines the strengths of canonical correlation with the directionality of GC. Our CGC measure combines the strengths and overcomes the disadvantages of GC and MGC by using an optimized weighted linear combination of the time series to parsimoniously represent each ROI with a single time series. This is similar to the idea of canonical correlation, where the signal dimensionality is reduced by considering the weighted sum of signals (Correa et al., 2010). Subsequently, CGC computes standard bivariate GC between the two representative time series.

While CGC and MGC both summarize causal influences between ROIs, CGC is a more parsimonious model and thus is more stable for short time series as shown in the following sections. CGC and penalized autoregression both estimate causal models with low complexity, but CGC uses the a priori information to select regions of interest while penalized autoregression simply looks for sparse causal interactions without addressing problems related to crosstalk between signals. Finally, similar to GCCA, CGC also uses weighted sums to represent each region when estimating causality. However, CGC estimates the strength of causality between those regions; results from our simulations will show that CGC can thus better estimate the underlying connectivity between the signals of interest in each region (Fig. 1).

A preliminary version of CGC was presented by Ashrafulla et al. (2012). This paper expands substantially upon the results presented in that work, presenting a refined procedure for computing CGC, using extensive simulations to evaluate and characterize the approach relative to methods like MGC and GCCA, and applying the method to identify causality in real LFP data.

The paper is organized as follows. First, we review GC and MGC to establish the groundwork for CGC, and we describe GCCA for comparison. We then present the CGC measure and associated algorithm. We follow with a simulation study illustrating the advantages and disadvantages of the proposed measure. CGC is then applied to real brain data acquired from a macaque performing a visuomotor task (Bressler et al., 1993). We show that for this data, CGC can identify causal interactions between striate and prestriate regions of the occipital lobe.

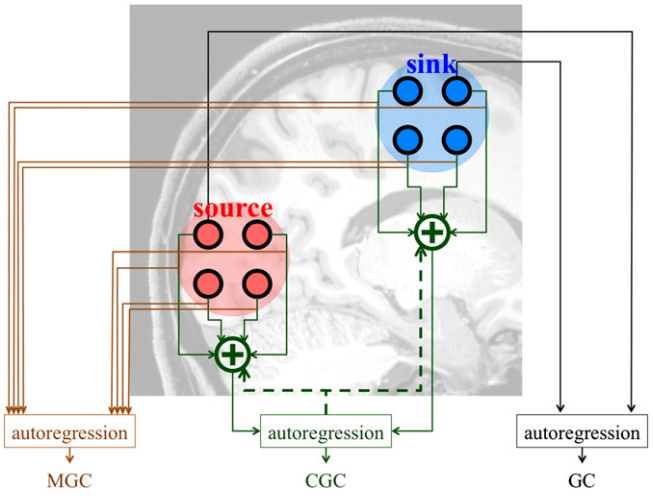

Fig. 1. We want to estimate the causality from the source region to the sink region via the time series recordings (represented by dark circles) from each region. GC analyzes the causality between pairs of recordings using univariate and bivariate autoregressive models. MGC fits much larger parametric autoregressive models to collections of time series. CGC parsimoniously represents each ROI using a single signal formed through an optimized weighted linear combination of signals from the ROI. CGC then applies standard GC analysis to these parsimonious representations.

Review of Granger causality measures

Granger causality (GC)

Let x_1 and x_2 be two time series of length N. If the past values of x_2 substantially improve the prediction of x_1, then x_2 is said to "Granger cause" x_1 (Granger, 1969). GC thus attempts to measure the extent to which past values of x_2 can be used to predict the present value of x_1 (Sims, 1972). Mathematically, calculation of GC from x_2 to x_1 considers two different Pth order autoregressive (AR) models given by:

$$x_1[n] = \sum_{p=1}^{P} b[p]x_1[n-p] + r_1[n] \tag{1}$$

$$\begin{bmatrix} x_1[n] \\ x_2[n] \end{bmatrix} = \sum_{p=1}^{P} \mathbf{A}[p] \begin{bmatrix} x_1[n-p] \\ x_2[n-p] \end{bmatrix} + \begin{bmatrix} s_1[n-p] \\ s_2[n-p] \end{bmatrix} \tag{2}$$

$$n = 1, \ldots, N$$

where the AR coefficients $b[p] \in \mathbb{R}$ and $\mathbf{A}[p] \in \mathbb{R}^{2\times 2}$, $p = 1,\ldots,P$, are estimated by minimizing the variance or 2-norm of the prediction errors $r_1[n]$ and $[s_1[n]\ s_2[n]]^T$ in Eqs. (1) and (2) respectively. The quantities

$$\rho_1^2 = \frac{1}{N-1}\sum_{n=1}^{N}(r_1[n])^2 \text{ and } \sigma_{2\to 1}^2 = \frac{1}{N-1}\sum_{n=1}^{N}(s_1[n])^2 \tag{3}$$

measure the total AR prediction errors under the two different models. ρ_1^2 is a measure of how well the past of x_1 can be used to predict its future values, while $\sigma_{2\to 1}^2$ is a measure of how well the past