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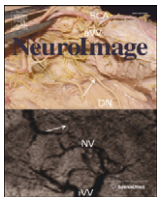

Comments and Controversies

Nonlinear connectivity by Granger causality

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ABSTRACT

The communication among neuronal populations, reflected by transient synchronous activity, is the mechanism underlying the information processing in the brain. Although it is widely assumed that the interactions among those populations (i.e. functional connectivity) are highly nonlinear, the amount of nonlinear information transmission and its functional roles are not clear. The state of the art to understand the communication between brain systems are dynamic causal modeling (DCM) and Granger causality. While DCM models nonlinear couplings, Granger causality, which constitutes a major tool to reveal effective connectivity, and is widely used to analyze EEG/MEG data as well as fMRI signals, is usually applied in its linear version. In order to capture nonlinear interactions between even short and noisy time series, a few approaches have been proposed. We review them and focus on a recently proposed flexible approach has been recently proposed, consisting in the kernel version of Granger causality. We show the application of the proposed approach on EEG signals and fMRI data.

Introduction

Exploring long-range interactions of neuronal assemblies at different temporal and spatial scales is an important issue in human brain research. The concept of brain functional connectivity, defined as the statistical dependence between neuronal activities in distant regions, is central for the understanding of the organized behavior of cortical regions which constitute distributed functional networks typically engaged in cognitive and perceptive processing (Friston et al., 1996). Activity in a neural system can directly or indirectly exert influence over that in another (Friston, 1994, 2011-this issue). This influence is modeled as the effective connectivity in the brain, and has been extensively investigated with multi-modal functional neuroimaging studies (Breakspear, 2004; Brovelli et al., 2004; David et al., 2008; Seth, 2005). The state of the art to understand the communication between brain systems are dynamic causal modeling (DCM) (Friston et al., 2003; Stephan et al., 2008) and Granger causality analysis (GCA).

Granger causality analysis (Granger, 1969; Wiener, 1956) is an approach that measures the causal association and effective connectivity and can provide information about the dynamics and directionality on both electroencephalography (EEG) (Brovelli et al., 2004; Guo et al., 2008; Kaminski et al., 2001; Wang et al., 2008) and functional magnetic resonance imaging (fMRI) (Chen et al., 2009; Gao et al., 2008; Goebel et al., 2003; Londei et al., 2007; Roebroeck et al., 2005; Seth, 2005; Sridharan et al., 2008; Uddin et al., 2009; Upadhyay et al., 2008; Wilke et al., 2009; Zhou et al., 2009a,b). In this issue, Bressler and Seth give the details of Wiener–Granger causality (Bressler and Seth, 2011-this issue).

Despite good results obtained with GCA based on linear models, in order to interpret the amount of transmission of nonlinear information between brain regions and its functional role, it is important to consider the physiological basis of the signal, which is likely to be mainly nonlinear. Furthermore, there is wide evidence that the hemodynamic processes associated with changes in physiological states in fMRI experiments, including cerebral blood flow, cerebral blood volume and total deoxyhemoglobin content caused by neuronal activity, are examples of nonlinear functions of physiological parameters (Buxton et al., 2004; Johnston et al., 2008; Lahaye et al., 2003).

Regarding DCM, a nonlinear extension that models nonlinear couplings of neuronal population activity in fMRI data has been developed (Stephan et al., 2008). For a critical review on DCM, see Daunizeau et al. (2011-this issue). Regarding GCA, several studies have proposed a nonlinear version. Freiwald et al. (1999) described a general framework that encompasses both linear and nonlinear modeling of neurophysiological time series data by means of Local Linear Nonlinear Autoregressive models (LLNAR); Gourevitch et al. (2006) presented and reviewed some usual approaches to detect linear and nonlinear causality between signals; in Bezruchko et al. (2008), the autoregression model is constructed in the form of a polynomial of order p to evaluate nonlinear Granger causality. In order to capture nonlinear interactions between brain regions even

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in short fMRI time series, two approaches have been recently proposed, one consisting in an extended autoregressive model (Li et al., 2010) and one based on the kernel version of Granger causality (Liao et al., 2009b).

In this paper, we review the nonlinear approaches to Granger causality which have been proposed so far and then focus on a comprehensive approach based on Kernel methods. This review could complete the table in Friston (2009) on the presence of nonlinear approaches to Granger causality. The paper is organized as follows: in the next section, we describe the theory behind Granger causality and recall some approaches that have been proposed for its extension to nonlinear case. Then we review Kernel Granger causality (KGC) as a simple approach to nonlinear Granger causality which in principle can handle all the orders of nonlinearity. In the Results section, we report its application to neural data, namely an EEG data set from a visual task, and an fMRI data set for a motor imagery task. In the Discussion section, we approach some issues related to Granger causality in general, and nonlinear Granger causality in particular, when we apply it to the analysis of neural data.

Granger causality: from the definition to the nonlinear extension

To understand nonlinear approaches to Granger causality as generalizations of the linear case, we first review the linear case briefly. The temporal dynamics of a stationary time series$\{\xi(t)\}_{t=1,..N+\ m}$, can be described using an autoregressive model based on the past m values of the time series.

We use the following shorthand notations:

$$\begin{aligned} &X_i = (\xi_i, \ldots, \xi_{i+m-1})^T, \\ &Y_i = (\zeta_i, \ldots, \zeta_{i+m-1})^T, \\ &X_i = \xi_{i+m}, \\ &for\, i = 1 \ldots N \end{aligned} \tag{1}$$

We treat these quantities as N realizations of the stochastic variables $\boldsymbol{X}$, $\boldsymbol{Y}$ and $\boldsymbol{x}$.

The temporal dynamics of the time series $\{\xi_i\}_{i=1\ldots N}$ can be described using an autoregressive model based on the past m values of the time series:

$$x = X^T A + e \tag{2}$$

Alternatively, we consider the bivariate autoregressive model which also takes into account the past values of ζ:

$$x = X^T A' + Y^T B + e' \tag{3}$$

The operative definition of Granger causality is that ζ Granger-causes ξ if the variance of residuals $\boldsymbol{e}'$ is significantly smaller than the variance of residuals $\boldsymbol{e}$, as it happen when the coefficients $\boldsymbol{B}$ are jointly significantly different from zero. An index measuring the strength of the causal interaction is then defined as

$$\delta = 1 - \frac{\langle e'^2 \rangle}{\langle e^2 \rangle}, \tag{4}$$

where $\langle\cdot\rangle$ denotes averaging over n (note that $\langle \boldsymbol{e} \rangle = \langle \boldsymbol{e}' \rangle = 0$). This strength is effectively a log likelihood ratio that compares the accuracy of the two models in terms of the sum of squared errors. In classical parametric statistics, it plays the same role as an F-ratio.

Exchanging the roles of the two series, we could evaluate the causality index in the opposite direction ($\xi \to \zeta$). It is worth noting that in general $\delta_{\xi\to\zeta} \neq \pm\delta_{\xi\to\xi}$, that is the causal index is neither symmetric nor antisymmetric, and that we can have nonzero causal relationships in both directions.

In the framework of probabilistic theory, we can approximate the series $\{\xi_i\}_{i=1\ldots N}$ by a Markov process of order m, that is $p(\xi_n|\xi_{n-1},\ldots,\xi_{n-m}) = p(\xi n|\xi_{n-1},\ldots,\xi_{n-m-1})$. The same can be done for $\{\eta_i\}_{i=1\ldots N}$. The generalized Markov property states that $p(x|X,Y) = p(x|X)$. Granger causality implies a violation of the above written property via the concept of transfer entropy. See Barnett et al. (2009) for a complete explanation of the phenomenon.

From the beginning (Granger, 1980; Wiener, 1956) it has been known that if two signals are influenced by third one that is not included in the regressions, this leads to spurious causalities, so an extension to the multivariate case is in order. The conditional Granger causality analysis (CGCA) (Chen et al., 2006; Geweke, 1984) is based on a straightforward expansion of the autoregressive model to a general multivariate case including all measured variables. Other multivariate causality measures, based on the notion of Granger causality, include Partial Directed Coherence (Baccala and Sameshima, 2001), squared Partial Directed Coherence (Astolfi et al., 2006), Direct Transfer Function (Kaminski and Blinowska, 1991), modified Directed Transfer Function (Korzeniewska et al., 2003). For an application to EEG data see for example Blinowska et al. (2004), Chen et al. (2006), and Hesse et al. (2003); for an application to fMRI data see Deshpande et al. (2009), Liao et al. (2009a), and Zhou et al. (2009a,b). The idea of conditional Granger causality implies that all the variables that could have a possible influence in the problem are considered in the analysis. This is not always possible, and a recent study has proposed partial Granger causality to tackle this issue (Guo et al., 2008).

In order to deal with possible nonlinearities in the measured signals, different approaches to nonlinear Granger causality have been proposed. This concern originated first in the field of econometrics (Bell et al., 1996; Hiemstra and Jones, 1994; Teräsvirta, 1998; Warne, 2000). The issue was then transferred to neuroscience in 1999, with a seminal paper by Freiwald et al. (1999), where the extension to the nonlinear case was performed specifying a linear autoregressive model whose coefficients depended on the previous states of the system. In that paper, the authors pointed out that in order to be suitable to evaluate causality a nonlinear model should be matched to the complex characteristics of the system. The issue of detecting causal influences in neural (and thus most probably nonlinear) systems is discussed in Valdes et al. (1999).

A different approach is discussed in Chavez et al. (2003): there the nonlinear Granger causality is seen in probabilistic terms as a violation of the Markov property.

A similar method is discussed in Gourevitch et al. (2006): there the violation of the Markov property is tested by means of the correlation integral (Grassberger and Procaccia, 1983).

A straightforward extension of Eq. (3) to evaluate nonlinear Granger causality is proposed by Bezruchko et al. (2008), in which the autoregression model is constructed in the form of a polynomial of order p. As correctly pointed out by the authors, indeed, for short time series the prevision tends to be unstable when increasing the dimensionality of the model and the order of the polynomial. In the same paper, the authors propose to evaluate nonlinear connectivity looking at the phases, albeit not in the framework of Granger causality.

Kernel Granger causality

Now we focus on a recently proposed approach which tries to condense all the issues above described, introduced in Marinazzo et al. (2008a) and generalized to the nonlinear case and to the issue of network reconstruction in Marinazzo et al. (2008b).

Linear Granger causality was reformulated, and a new statistical procedure to handle overfitting (Palus and Vejmelka, 2007) was introduced; this new formulation was then generalized to the nonlinear case by means of the kernel trick (Shawe-Taylor and Cristianini, 2004). Kernel algorithms work by embedding data into a Hilbert space, and searching for linear relations in that space (Vapnik,

1998) (for precise information on the geometry of least square regression and projection matrices, see Davidson and MacKinnon, 2004). Hilbert spaces here are spaces of kernel functions, where these functions can be thought of as correlation or covariance functions.

To see how kernels help to evaluate causality, we observe that the predicted values of **x** using only **X** (resp. **Z**) are the projection of the true values of **x** on a space H (resp. $H' = H \otimes H^{\perp}$). In this way the improved prediction which defines Granger causal influence from ζ to ξ resides in $H^{\perp}$, the space of the vectors of H' orthogonal to the vectors of H (that is the information that we can gain on ξ from the values of ζ). It can be shown that $H^{\perp}$ is the range of a matrix constructed from the scalar products of the input variables (**X** or **Z**). These scalar products are contained in a $N \times N$ matrix K, called the Gram matrix, with elements $K_{ij} = k(X_i, X_j)$ (resp. $K_{ij} = k(Z_i, Z_j)$), where k is a kernel function whose spectral representation contains functions of **X** (resp. **Z**).

Since this scalar product is the sole way in which the input variables enter in the model, we can perform Granger causality analysis in spaces constructed by nonlinear functions of the input values characterized only by the Gram matrix of a given kernel k.

Once that the kernel function has been used to create nonlinear mixtures of the original data, the embedding is then performed implicitly, by specifying the inner product between pairs of points; for example, one can use an inhomogeneous polynomial kernel of degree p:

$$K_p(\mathbf{Z}, \mathbf{Z}') = \left(1 + \mathbf{Z}^T \mathbf{Z}'\right)^p,$$

or a Gaussian kernel:

$$K_\sigma(\mathbf{Z}, \mathbf{Z}') = exp\left(-\frac{(\mathbf{Z} - \mathbf{Z}')^T(\mathbf{Z} - \mathbf{Z}')}{2\sigma^2}\right).$$

where **Z** is a $2m \times N$ matrix having vectors $Z_i = (X_i^T, Y_i^T)^T$ as columns in the bivariate case, and a $nobs \times m \times n$ matrix in the multivariate case, where $nobs$ is the number of simultaneously recorded observables.

We thus have a method with the following two main features: (i) the nonlinearity of the regression model can be controlled by choosing the kernel function; (ii) the problem of false-causalities, which arises as the complexity of the model increases, is addressed by a selection strategy of the eigenvectors of a reduced Gram matrix whose range represents the additional features due to the other time series. This effectively reduces the number of unknown model parameters (in our case coefficients of a vector autoregression model) by considering a relatively small number of (possibly nonlinear) mixtures of parameters, thus providing a heuristic approach to bounding model complexity and ensures that the accuracy of different models is a rough approximation to their evidence.

Furthermore, it is worth to recall that KGC is equivalent to performing a linear Granger causality in the feature space of the kernel; it has been demonstrated in Ancona and Stramaglia (2006) that, for polynomial and Gaussian kernels, this nonlinear approach continues to fulfill the following invariance property, necessary to analyze causality and satisfied by linear models:

> "the optimal predictor (i.e. the function which minimizes the risk functional (Papoulis 1985)) does not change when new variables, statistically independent of input and target variables, are added to the set of input variables."

In KGC, the causality between ξ and ζ, conditioned to all the other variables, is assessed comparing the prediction of ξ obtained when ***Z***contains the past values of all the series and the prediction of ξ when ***Z***contains the past values of all the series but ζ (Marinazzo et al., 2008b).

Furthermore, KGC allows also an easy extension to an analysis of the causality between phases (Bezruchko et al., 2008). This is discussed in detail in Angelini et al. (2009a).

The causality index from KGC as described in Marinazzo et al. (2008a), and used in this paper, is a quantity bounded between 0 and 1, which sums up only significant contributions: it follows that it is always significant if the point estimate is nonvanishing.

The application of the kernel approach on simulated autoregressive systems is described in previous papers (Marinazzo et al., 2008a, b) and the performance was very good in terms of statistical power. However, a detailed analysis of the statistical power of our procedure over simulated neural signals will be presented elsewhere.

Results: examples of applications to neural data

Here we show briefly two examples of application of KGC to EEG and fMRI.

EEG data

We considered the human EEG from a visual task contained in the EEGLAB package (Delorme and Makeig, 2004). The data from 32 channels were sampled at 128 Hz. A visual target was presented 80 times. For each trial, we computed the causality between the signals from the 30 channels on the scalp, thus excluding EOG1 and EOG2, for 1 s before the stimulus and 1 s after the stimulus, with $m = 2$, with IP kernel of degrees 1 and 2. About the choice of the model order, application of cross-validation to these data suggested a low value of m; therefore we restricted our analysis to $m = 1$ and $m = 2$.

Those causality indexes were then averaged over all the trials. Fig. 1 reports the results of this analysis. Inspecting the matrices of causal indexes, one can observe that these are not symmetric, nor antisymmetric, as recalled when the causality index was defined above. When a quadratic kernel is used, higher values of the causal indexes appear after the stimulus, and a flow of causality, calculated as described in Seth (2005) toward the occipital electrodes is observed. Of course, these results, obtained for a single subject, are only indicative of a possible trend. Quantitative conclusion could only be drawn after a study involving more subjects and validating the obtained results against the results obtained with a bootstrap method (see for example (Deshpande et al., 2009)). It is also worth to recall that the main result of a causality analysis lies in the matrix of the indexes, and that the causal flow can be calculated, for illustrative purposes, once that the statistical significance of the individual indexes has been assessed.

It is interesting to show the compared performances of the three used kernels in the course of time. We evaluated causality between a frontal (F3) and an occipital (O2) electrode in a moving window of 50 points (0.39 s) (Fig. 2), in order to investigate the change after the stimulus. In this case, we used also a Gaussian kernel with $\sigma = 4$. We can see that the highest increase in causal influence from the frontal to the occipital channel is detected when we use the inhomogeneous polynomial kernel with $p = 2$. In the opposite direction, there is no observable change of causality. As stated above, these results are meant to report the performance of the different kernel; to validate statistically the increase in causality as a phenomenon connected to the visual stimulus, a more comprehensive study is needed.

fMRI data

We use KGC to analyze fMRI data from a motor imagery task (see Liao et al., 2009b, for a complete description of the protocol, results and discussion).

For Granger causality analysis, a seed x was first defined as the average time series of all activated voxels within such a ROI. Then, the seed x was chosen to accomplish effective connectivity assessment of

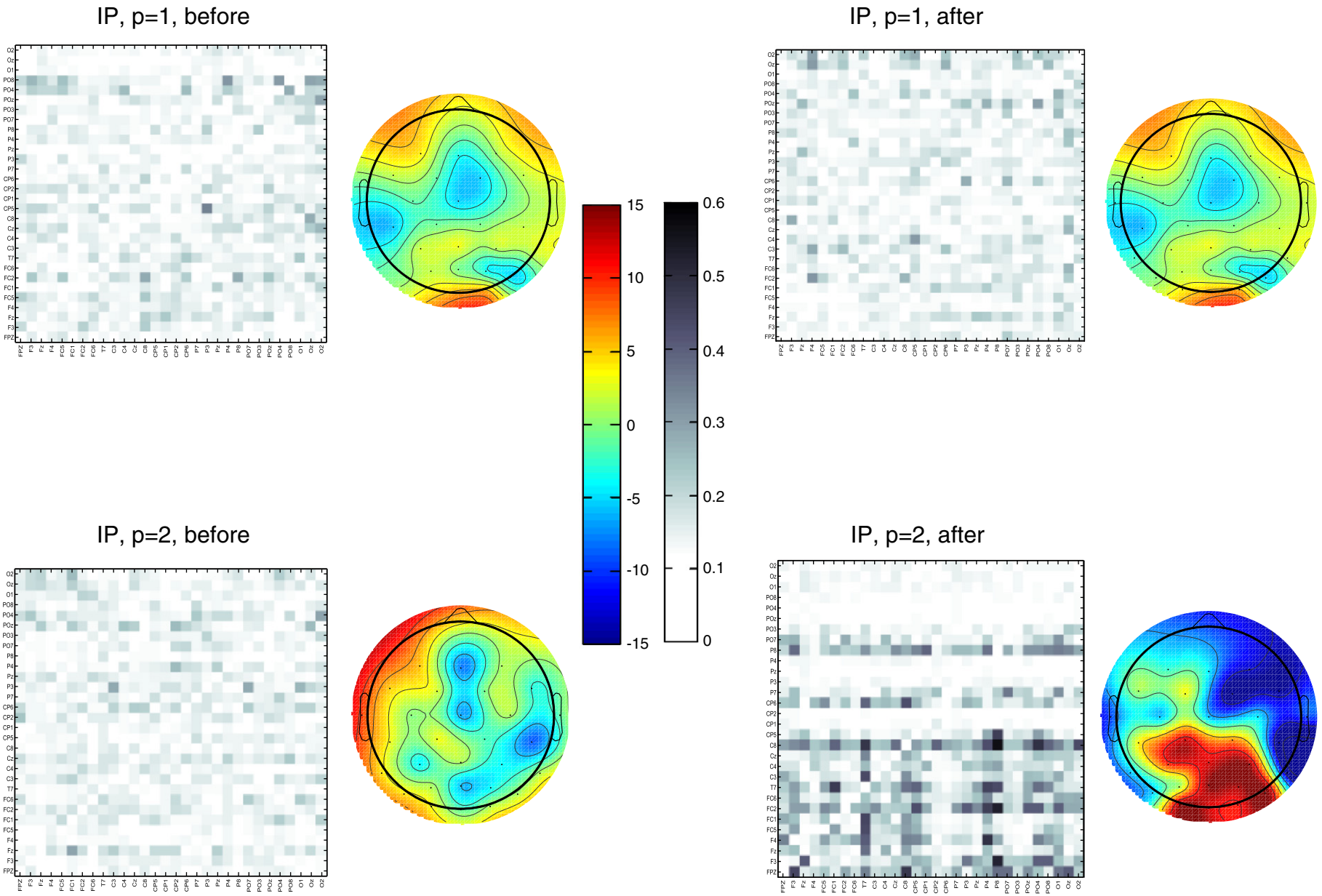

Fig. 1. Analysis of causality for a working memory visual task described in the main text, with two different kernels (linear and quadratic), for 1 s before and 1 s after the presentation of the stimulus. The figure reports the matrices of the causal indexes as well as the causal flow. The matrices of causal indexes are not symmetric, nor antisymmetric, following the definition of the causal index. After the stimulus, when the quadratic kernel is used, an indicative flow toward the occipital electrodes is present.

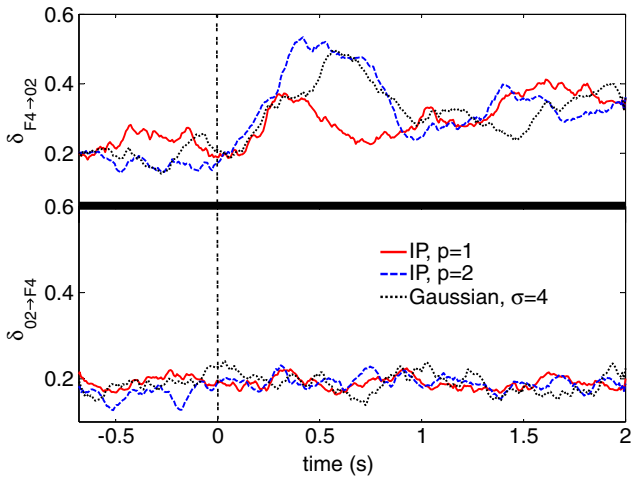

Fig. 2. Averaged causal indexes evaluated on a moving window between a frontal and an occipital electrode for different kernels before and after the presentation of the preferred visual stimulus in the working memory task described in the text.

the supplementary motor areas (SMA) against the rest of the voxels in whole brain separately for each subject using the bivariate IP and Gaussian KGC and GCA (Gao et al., 2008; Goebel et al., 2003; Roebroeck et al., 2005; Upadhyay et al., 2008) method.

The detailed results of this analysis are explained in Liao et al. (2009b). We report here the comparisons of the causal connectivity results showing the $F_{x\to y}$ and $F_{y\to x}$ maps between those obtained from KGC (IP kernel with $p=2$) and GCA method. In Fig. 3, we display three Granger causality sub-maps: brain regions found only by KGC (shown in red), brain regions found only by GCA (shown in green), and common brain regions (the regions found by KGC intersecting the regions found by GC) (shown in yellow). In the map of the regions influenced by the (SMA) (Fig. 3A), we find that the significant causal influences from the SMA to the bilateral cingulate motor area (CMA), superior parietal lobule (SPL), paracentral lobule, putamen and the contralateral postcentral were found by KGC only. Significant influences from the seed to the bilateral inferior parietal lobule (IPL) and SMA were detected only with GC. Regarding the regions influencing the seed (SMA) (Fig. 3B), KGC detected strong influences from the bilateral SPL and the contralateral postcentral and precentral gyrus. GC only found that the part of SMA extensively influenced the seed.

In order to explain the causal influences revealed by GCA but not by KGC (green regions in Fig. 3), we can say that when we add to the model the nonlinear features, in particular for those short and noisy time series, the threshold for significance is raised, and so some weak linear influences are no longer detected in the nonlinear KGC analysis (see below in the Discussion section).

Discussion

In the following we will address some specific points, either related to nonlinear Granger causality in particular, or to Granger causality in general.

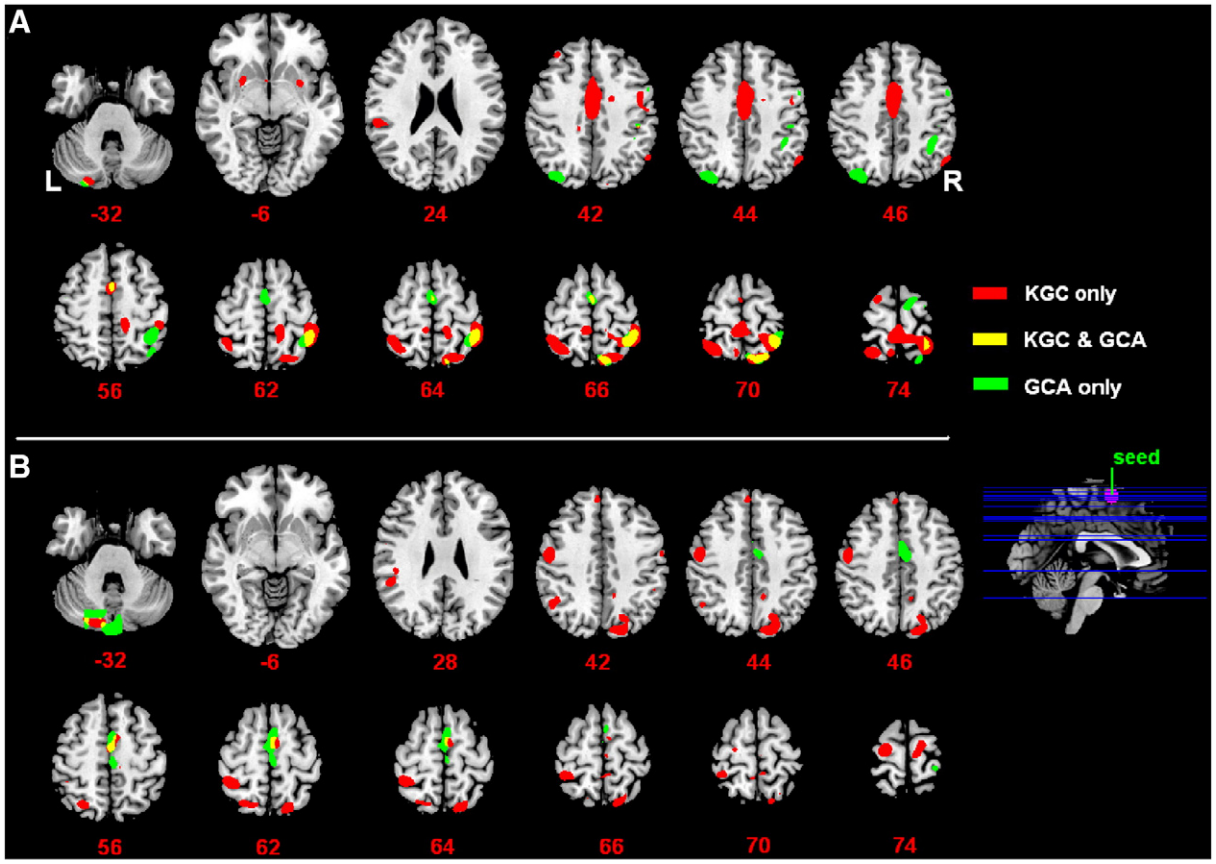

Fig. 3. Granger causality map of the regions influenced by the supplementary motor areas (SMA) (A) and the regions influencing the SMA (B) in fMRI data from a motor imagery task. Three Granger causality sub-maps: brain regions found only by KGC (shown in red), brain regions found only by GCA (shown in green), and common brain regions (the regions found by KGC intersecting the regions found by GCA) (shown in yellow). Adapted from Fig. 6 in Liao et al. (2009b). © IEEE 2009, used with permission.

Choice of the model order

There are several recipes for the choice of the optimal value of the autoregressive model order *m* (Lütkepohl, 2005). In machine learning based approaches, this is usually done using the standard cross validation scheme (Shawe-Taylor and Cristianini, 2004) or the embedding dimension (Kantz and Schreiber, 1997). Alternatively, one can use the Bayesian information criterion (BIC) (McQuarrie and Tsai, 1998), or other order selection criteria (Akaike Information criterion, Hannan-Quinn criterion). These last criteria (AIC and BIC) are usually considered as approximations to the log evidence or log marginal likelihood for a model. The model evidence is simply the probability of observing the data given some model. The log-evidence includes an accuracy term and a complexity term and is a crucial quantity in comparing models. In the example above, it can be used to optimize the value of m. However, one could also use an implicit approximation to the model evidence to compare the model with the extra time-series *y* and those without *y*, thus assessing causality. As it is possible to upper bound the complexity (see, e.g. Cherkassky and Ma, 2003), we can conclude that the accuracy, as measured by the unexplained variance or residual sum of squares (after filtering), is a good approximation to the model evidence.

High dimensionality and ill-posedness

One of the major issues when we deal with high dimensional and even short fMRI data is that the problem becomes ill-posed (number of variables comparable with, or bigger than, the number of observations). A recent paper (Zhou et al., 2009a) has introduced a way to overcome this problem, by means of reduction of dimensionality in reference regions of interest (ROI) with principal component analysis (PCA). This approach, applied to fMRI, could be more correct and more efficient than methods based on averaging or *a priori* definition of ROIs.

For sparse connectivity and small number of samples, methodologies based on L1 norm minimization have been proposed (Napoletani and Sauer, 2008). Even if KGC proves more efficient (i.e. it shows higher statistical power for a given size) than those methodologies in reconstructing network connectivity (i.e. bigger number of true connections revealed, with fixed number of false connections, see Marinazzo et al., 2008b), also in this case a dimensionality reduction is in order. A method already rooted in this framework has been proposed (Angelini et al., 2009b), based on the concept of redundant and synergetic variables (Schneidman et al., 2003), which looks for connectivity patterns between groups of redundant variables.

Model comparison

One of the most important issues that need to be addressed within our framework is how to compare different models. Model comparison is the most important aspect of inference with causal models and allows one to test different hypotheses by comparing different models in terms of their (log) evidence. In the context of Granger causality, this has been approximated by comparing models in terms of their accuracy under bounded complexity (using the filtered Granger Causal Index introduced in Marinazzo et al., 2008a).

However, it will be important to check whether the issue of model comparison could be further improved by use of approaches using more than only the accuracy, like e.g. writing down nested models and using likelihood ratio tests. Moreover, the availability of likelihood-ratio tests would remove the need for the filtering of eigenvalues to control the complexity, and one could directly assess the influence of the second time series on the first. This requires the kernel model, employed by KGC, to be expressed in a maximum likelihood framework: it is a matter for further work. We refer the reader to Mak et al. (2009) for a recent attempt to generalize in a nonlinear fashion the maximum-likelihood linear regression.

Experimental or endogenous inputs

As with all current implementations of Granger causal analyses, we have neglected experimental or exogenous inputs that correspond to stimulus functions in conventional neuroimaging experiments. These are an important source of variance and call for an extension of the vector autoregression models used in Granger causality so that they can be incorporated gracefully. This is particularly important in our application because we could, in principle, consider bilinear interactions between exogenous inputs and the data (states). This would be equivalent to an experimentally mediated change in the coupling or autoregression coefficients and would address the key issue of context-sensitive coupling in the same way that DCM does. A few Granger causality studies including both linear and nonlinear models (Guo et al., 2008; Li et al., 2010) have addressed this issue, taking into account experimental or exogenous inputs to brain regions.

Bivariate aspect of KGC approach

Note that even in the context of a kernel approach with a full (multivariate) vector autoregression model, our inferences are still about bivariate coupling. In other words, we are not testing sparse architectures or different models of coupling; rather we are simply testing two models where one model does not have a particular connection. This means that the Granger causal index should not be interpreted in terms of a dependency graph. It is a measure of the statistical dependence between the two regions, allowing for complete coupling elsewhere. In principle, there is no reason why we could not extend our approach to explore any arbitrary connectivity by comparing models with and without subsets of connections. However, this would depend upon the model comparison framework as mentioned above.

Distinction between function and effective connectivity

Granger causal analysis occupies an interesting and intermediate position between functional and effective connectivity (Friston, 2011-this issue). It should be noticed that our approach does not need to refer explicitly to estimates of the autoregression coefficients that quantify the coupling between brain areas. All we need to do is examine the observed and predicted data under different models. The measure of coupling is based upon an inference (the comparison of model accuracies); this is the Granger causal index. This means that our measure of coupling is inferential and reflects the statistical dependencies between two brain areas. This means that it measures functional connectivity (Friston, 2011-this issue). However, because the models impose temporal precedence; this functional connectivity can be considered as directed (given the qualifications about hemodynamic latency variations above). This measure of coupling is different from effective connectivity which, in our model, corresponds to the estimates of the autoregression matrices $\boldsymbol{A}$ and $\boldsymbol{B}$ in the first two equations. In principle, having estimated the Granger causality we could now return and examine the effective connectivity in terms of the regression coefficients in the usual way.

Application to fMRI

First of all, we should note that there are some controversies about the opportunity of applying GCA to fMRI data (Friston, 2009, 2011-this issue; Roebroeck et al., 2011-this issue). Some reasons have been indicated to justify why GCA might not be the method of choice for fMRI data. For example, the causal interactions are mediated at the neuronal level and the vector autoregression models used by GCA have

no hidden neuronal states (Friston, 2009). Anyway, efforts are being made in order to provide GCA with the approximating features of DCM (Ge et al., 2009). Another concern is the fact that GCA rests upon uncorrelated prediction errors, although random fluctuations in fMRI data are smooth because of the hemodynamic response function (HRF) convolution. Finally, regional variations in the latency of the HRF would violate the assumptions of temporal precedence upon which GCA is based. In some current application, we can appeal to the fact that we are looking at the coupling amongst distributed modes, where any variations in hemodynamic latency will average out.

As discussed in Roebroeck et al. (2005), the straightforward application of GC to hemodynamically filtered and sub-sampled time series, can lead to bias toward false positive causalities, even before considering differences in hemodynamics between different regions. This bias is present also when KGC is used, and also KGC can be modified to contrast its effect, with the same the strategy proposed by Roebroeck et al. (2005), or with other strategies which will hopefully be explored in the future.

Still about deconvolution, we must know two out of the three signals in the equation $y(t)=s(t)\otimes h(t)+e(t)$, where $y(t)$ is the observed signal, $s(t)$ is the activity of the underlying neural population, and $h(t)$ is the HRF. One has then to make assumptions on $s(t)$ and $h(t)$. In this issue, Roebroeck et al. (this issue) state that "undoing the effect of hemodynamics on fMRI data (by deconvolution) can be an important tool. However, it is crucially dependent upon assumptions that need to be verified." Nonlinearity is certainly another assumption that we should make, but it is not clear if this nonlinearity should reside in $s(t)$ or in the HRF $h(t)$. A biologically inspired model has to answer precisely to this question. In the application of KGC on fMRI data (Liao et al., 2009b), this aspect was not considered; furthermore it did not consider one of the crucial problems, that is the differences in nonlinear $h1(t)$ and $h2(t)$ that convolve $s1(t)$ and $s2(t)$, respectively (differences that were underlined in Roebroeck et al., this issue). In Logothetis et al. (2001), it is suggested that, like in neural responses, fMRI blood oxygenation level-dependent (BOLD) contrast signal is also a nonlinear function of stimulus contrast (Boynton et al., 1996, 1999), however, a linear systems analysis on the fMRI responses predicted a linear relationship between the BOLD and neural activity. So, many of the more recent effective connectivity approaches are based on stochastic or deterministic dynamic models, and capable of capturing temporal structure. Volterra series representation (Friston and Buchel, 2000) characterizes interactions in a nonlinear convolution model relating multiple inputs to a single output. Thus, dynamic nonlinear influences on a single region can be characterized. For future work, aimed to detect interactions in a nonlinear convolution model in which multiple inputs are fed to a single output, more physiologically motivated models will be needed (Balloon, Windkessel or Volterra models).

Specific problems of nonlinear GC

For every nonlinear generalization of GC, the most important problems to be solved are:

(i) Fix the degree of nonlinearity of the model
(ii) Deal adequately with overfitting, so that the introduction of more features due to nonlinearity results in a minimal loss of statistical power

Every approach comes with a possible answer to these two problems, but a lot of work still needs to be done to establish the best recipes in the field of neural systems.

When choosing the kernel for the model, it is important that the model itself will be matched to the dynamical characteristics of the signal, as correctly pointed out in Pereda et al. (2005). In KGC, we deal with problem (i) performing a preliminary analysis in which we look how the causality indices change with the order p of the polynomial kernel, or with the σ of the Gaussian kernel, and the parameter is chosen according to the stability of the results. Our approach to overfitting lays in the framework of sparsification through statistical testing, discussed for example in Haufe et al. (2008). This strategy is of proven efficacy, but of course is not able to completely eliminate the problem. In spite of our efforts, we can always run into some situations in which linear GCA detects influences which are not considered significant in KGC. This is what happens in the green regions in Fig. 3. To illustrate better this point, we have generated two time series as follows:

$$x(t) = 0.95\sqrt{2}x(t-1) - 0.9025x(t-1) + 0.5\tau_1(t),$$
$$y(t) = ax(t-1) + bx(t-1)^2 + c\tau_1(t), \quad (5)$$

where the τ's are unit variance Gaussian noise terms. We evaluated the bivariate causality for two pairs of maps for 100 trials using KGC with IP kernel with $p=1$ and 2, and Gaussian kernel with $\sigma=6$.

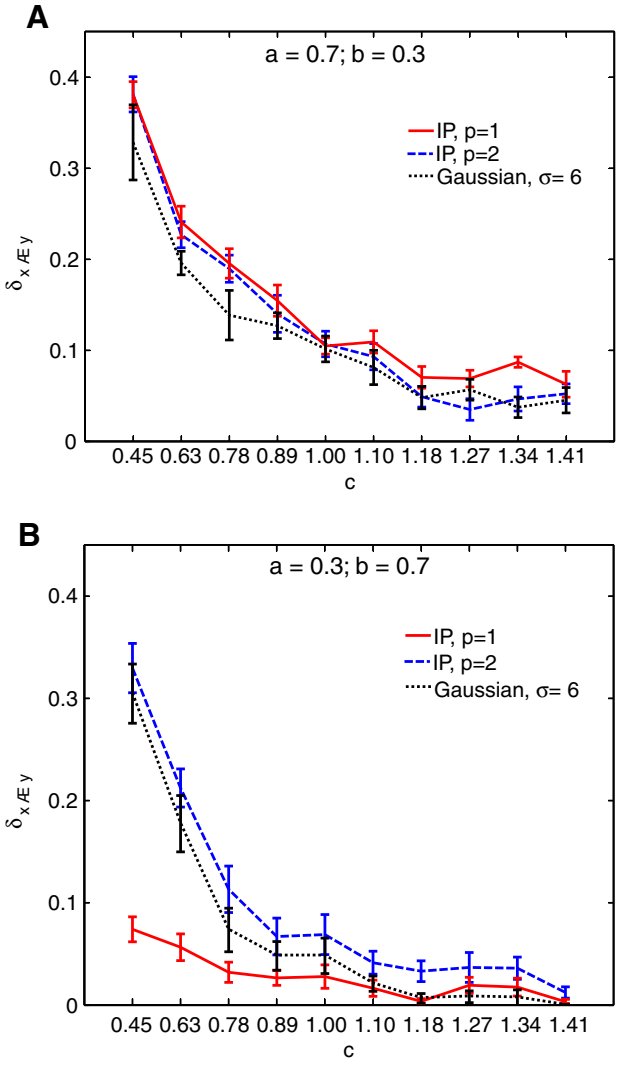

Fig. 4. Causal influences for the model in Eq. (5) calculated with different kernels for increasing levels of noise. (A) Case of stronger linear influence ($a=0.7$) and weaker nonlinear influence ($b=0.3$). The linear kernel is slightly more robust. (B) Case of weaker linear influence ($a=0.3$) and stronger nonlinear influence ($b=0.7$). In this case the usefulness of nonlinear kernels for the detection of nonlinear influences decreases when the noise increases.

As shown in Fig. 4, all the causal influences decrease with increasing noise. When linear influences are stronger (left panel), the linear kernel is slightly more robust (for example when $c = 1.34$); when nonlinear influences are stronger (right panel), the usefulness of nonlinear kernels for the detection of nonlinear influences decreases when the noise increases.

Stationarity and noise

The framework of Granger causality assumes stationarity of signals: further work should deal with the effects of nonstationarities on nonlinear estimates of causalities (see Dhamala et al., 2008; Fujita et al., 2007; Sato et al., 2006, for a promising strategy in the linear case).

We expect that the proposed method will provide a statistically robust basis to assess nonlinear drive–response relationships in many fields of science, wherever collected data form time series; it works for deterministic and stochastic systems, provided that noise is not so high as to obscure the deterministic effects.

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