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Assessing Directional Interactions among Multiple Physiological Time Series: the Role of Instantaneous Causality

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***Abstract*—This paper deals with the assessment of frequency domain causality in multivariate (MV) time series with significant instantaneous interactions. After providing different causality definitions, we introduce an extended MV autoregressive modeling approach whereby each definition is described in the time domain in terms of the model coefficients, and is quantified in the frequency domain by means of novel measures of directional connectivity. These measures are illustrated in a theoretical example showing how they reduce to known indexes when instantaneous causality is trivial, while they describe peculiar aspects of directional interaction in the presence of instantaneous causality. The application on real MV cardiovascular and EEG time series is then reported to investigate the role played by instantaneous causality in the practical evaluation of frequency domain connectivity.**

I. Introduction

EVALUATION of causality is a topic of great importance for the study of physiological time series. While causality is generically intended as the existence of directional interactions between two time series taken from a multivariate (MV) data set, several definitions may be provided leading to different measures which quantify specific aspects of the concept of connectivity. Popular measures of causality are the directed coherence (DC) and the partial DC (PDC), which are derived from the spectral representation of a MV autoregressive (MVAR) model fit on the observed MV series [1,2]. As these measures are defined in the frequency domain, they are widely exploited to assess causality in series exhibiting oscillatory behavior, such as cardiovascular variability and EEG signals [3,4].

An open issue in MVAR-based causality analysis is that the model commonly used to compute DC and PDC forsakes instantaneous effects, i.e. effects occurring between series samples bearing the same time index. Hence, DC and PDC may describe only lagged causality from one series to another in the MV representation. Nevertheless, forsaking instantaneous causality may lead to an ambiguous representation of the MVAR coefficients and of the related frequency domain patterns of causality [4].

In the present study we make use of an extended MVAR (eMVAR) model, describing both instantaneous and lagged effects, to measure causality in the frequency domain. We show that different causality measures can be derived from the spectral representation of the eMVAR model, each reflecting a specific time domain definition of causality. The role played by instantaneous causality in the determination of these measures is illustrated in a theoretical example, and then assessed on cardiovascular and EEG time series.

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II. Methods

A. Time Domain Causality Definitions

According to the framework first introduced by Granger [5], the notion of causality is defined in the context of linear regression models of stochastic processes. Let us consider the MV process $\mathbf{Y}$ composed of M zero-mean scalar processes, $\mathbf{Y}=[y_1,...,y_M]^T$. Denoting as $y_m(n)$ the present value of the scalar process y_m, as $Y_m=\{y_m(n\text{-}1),...,y_m(n\text{-}p)\}$ the set of its p past values, and as $\acute{Y}_m=\{y_m(n),Y_m\}$ the set of its present and p past values, definitions of causality from the process y_j to the process y_i are provided as follows. *Instantaneous causality* exists if $y_j(n)$ is useful to predict $y_i(n)$; *lagged direct causality*, $y_j \rightarrow y_i$, exists if Y_j is useful to predict $y_i(n)$; *extended direct causality*, $y_j \dot{\rightarrow} y_i$, exists if $\acute{Y}_j$ is useful to predict $y_i(n)$; *lagged causality*, $y_j \Rightarrow y_i$, exists if a cascade of direct causality relations occurs such that $y_j \rightarrow y_m \cdots \rightarrow y_i$; *extended causality* from y_j to y_i, $y_j \dot{\Rightarrow} y_i$, exists if a cascade of extended direct causality relations occurs such that $y_j \dot{\rightarrow} y_m \cdots \dot{\rightarrow} y_i$. In the Granger framework, a set of values is useful to predict $y_i(n)$ if its inclusion in the information set reduces the variance of the optimal linear predictor of y_i.

A main differentiation among the definitions provided above may be made on the basis of the role played by instantaneous effects, i.e. effects from one series to another occurring within the same lag. These effects are the basis of instantaneous causality, and are excluded from the definitions of direct causality and causality which consider only lagged effects. On the contrary, instantaneous effects are explicitly accounted for in the extended causality definitions. Note that, in the absence of instantaneous causality, extended direct causality reduces to direct causality and extended causality reduces to causality.

B. Extended Multivariate Autoregressive Modeling

To provide a parametric representation of the various causality definitions, let us define the eMVAR process:

$$\mathbf{Y}(n)=\sum_{k=0}^{p}\mathbf{B}(k)\mathbf{Y}(n-k)+\mathbf{W}(n), \quad (1)$$

where $\mathbf{B}(k)=\{b_{ij}(k)\}$ are $M\times M$ coefficient matrices and $\mathbf{W}(n)=[w_1(n),...,w_M(n)]^T$ is an innovation process with diagonal covariance matrix $\mathbf{\Lambda}=\mathrm{diag}(\lambda^2_i)$. The formulation in (1) represents an extension of strictly causal MVAR modelling where present observations are linearly predicted from past ones [1-3]. The difference stands in the fact that the extended model describes instantaneous effects from one process to another in the form of the coefficient matrix $\mathbf{B}(0)$. As a consequence, this model allows descriptions of all types of causality defined in Sect. IIA: instantaneous causality, lagged direct causality and extended direct causality occur from y_j to y_i when $b_{ij}(0)\neq 0$, $b_{ij}(k)\neq 0$ for at least one $k\geq 1$, and $b_{ij}(k)\neq 0$ for at least one $k\geq 0$, respectively; lagged causality and extended causality occur when nonzero coefficients are present, for at least one lag k, in the positions of $\mathbf{B}(k)$ which identify each direct connection of the cascade linking y_j to y_i.

C. Frequency Domain Causality Measures

The spectral representation of the eMVAR process is obtained taking the Fourier transform (FT) of (1) to yield $\mathbf{Y}(f)=\mathbf{B}(f)\mathbf{Y}(f)+\mathbf{W}(f)$, where $\mathbf{Y}(f)$ and $\mathbf{W}(f)$ are the FTs of $\mathbf{Y}(n)$ and $\mathbf{W}(n)$, and the $M\times M$ frequency domain coefficient matrix is $\mathbf{B}(f)=\sum_{k=0}^{p}\mathbf{B}(k)e^{-j2\pi fk}$. Evidencing the transfer function from $\mathbf{W}(n)$ to $\mathbf{Y}(n)$, the spectral representation becomes $\mathbf{Y}(f)=\mathbf{G}(f)\mathbf{W}(f)$, where $\mathbf{G}(f)=[\mathbf{I}-\mathbf{B}(f)]^{-1}=\overline{\mathbf{B}}(f)^{-1}$ is the $M\times M$ frequency domain transfer matrix. The elements of the coefficient and transfer matrices may be suitably combined to define the *extended DC* (eDC) and *extended PDC* (ePDC):

$$\xi_{ij}(f)=\frac{\lambda_j G_{ij}(f)}{\sqrt{\sum_{m=1}^{M}\lambda_m^2\left|G_{im}(f)\right|^2}} \tag{2}$$

$$\chi_{ij}(f)=\frac{\frac{1}{\lambda_i}\overline{B}_{ij}(f)}{\sqrt{\sum_{m=1}^{M}\frac{1}{\lambda_m^2}\left|\overline{B}_{mj}(f)\right|^2}}. \tag{3}$$

Since the definitions in (2) and (3) incorporate both $\mathbf{B}(0)$ and $\mathbf{B}(k)$ with $k>0$, eDC and ePDC quantify both lagged ($k>0$) and instantaneous ($k=0$) effects from one process to another. If we want to explore lagged causality in the presence of zero-lag interactions, we have to exclude the coefficients related to the instantaneous effects from the spectral causality measure. Hence, we set $\widetilde{\mathbf{B}}(f)=\overline{\mathbf{B}}(f)+\mathbf{B}(0)=\mathbf{I}-\sum_{k=1}^{p}\mathbf{B}(k)e^{-j2\pi fk}$, $\widetilde{\mathbf{G}}(f)=\widetilde{\mathbf{B}}(f)^{-1}$, yielding the *lagged DC* (lDC) and *lagged PDC* (lPDC) as:

$$\widetilde{\gamma}_{ij}(f)=\frac{\lambda_j\widetilde{G}_{ij}(f)}{\sqrt{\sum_{m=1}^{M}\lambda_m^2\left|\widetilde{G}_{im}(f)\right|^2}} \tag{4}$$

$$\widetilde{\pi}_{ij}(f)=\frac{\frac{1}{\lambda_i}\widetilde{B}_{ij}(f)}{\sqrt{\sum_{m=1}^{M}\frac{1}{\lambda_m^2}\left|\widetilde{B}_{mj}(f)\right|^2}}. \tag{5}$$

The eDC and lDC functions in (2) and (4) and the ePDC and lPDC in (3) and (5) constitute modifications of the well-known DC and PDC introduced respectively in [1] and [2]. The difference with the traditional definitions stands in the fact that the new functions (2-5) are derived from the MVAR model (1) including instantaneous effects rather than from a classic strictly causal MVAR model. As such, they are able to quantify in the frequency domain the causality definitions provided in Sect. IIA: lPDC, ePDC, lDC and eDC quantify respectively lagged direct causality, extended direct causality, lagged causality and extended causality in the frequency domain, meaning that they are nonzero at some frequency if and only if the specific causality definition is met in the time domain. Note that the distinction between lagged and extended measures is due to instantaneous causality, as the absence of instantaneous effects makes ePDC equivalent to lPDC, and eDC equivalent to lDC. Note also that, since the measures defined in (2-5) are complex valued, their squared modulus is commonly used to quantify directional interactions in the frequency domain, and that all squared measures are normalized between 0 and 1.

III. Theoretical Example

To illustrate the role of instantaneous causality on the eMVAR-based evaluation of causality in both time and frequency domains, let us consider the process:

$$\begin{cases} y_1(n)=0.9\sqrt{2}\,y_1(n-1)-0.81y_1(n-2)+w_1(n) \\ y_2(n)=0.5y_1(n-\delta)+y_3(n-1)+w_2(n) \\ y_3(n)=0.5y_2(n-\delta)-0.64y_3(n-2)+w_3(n) \end{cases}, \tag{6}$$

where the innovations w_i are uncorrelated white noises of unit variance. The processes y_1 and y_3 present autonomous oscillations determined by the coefficients of the regression on their own past values. Direct causal effects are set from y_3 to y_2 with lag 1, as well as from y_1 to y_2 and from y_2 to y_3 with lag δ. Here we consider the conditions $\delta=1$ and $\delta=0$, which entail absence and presence of instantaneous causality, respectively. The corresponding causality patterns are shown in Fig. 1a and Fig. 1d. When $\delta=1$, lagged direct causality is set over the directions $y_1\rightarrow y_2$, $y_2\rightarrow y_3$, and $y_3\rightarrow y_2$, entailing the lagged causality relations $y_1\Rightarrow y_2$, $y_2\Rightarrow y_3$, $y_3\Rightarrow y_2$ (direct effects) and $y_1\Rightarrow y_3$ (indirect effect); since instantaneous effects are absent, extended relations coincide with lagged relations (Fig. 1a). When $\delta=0$ the effects from y_1 to y_2 and from y_2 to y_3 are instantaneous, and the only lagged effect is from y_3 to y_2, entailing the relations $y_3\rightarrow y_2$ and $y_3\Rightarrow y_2$; in this case the extended relations are different

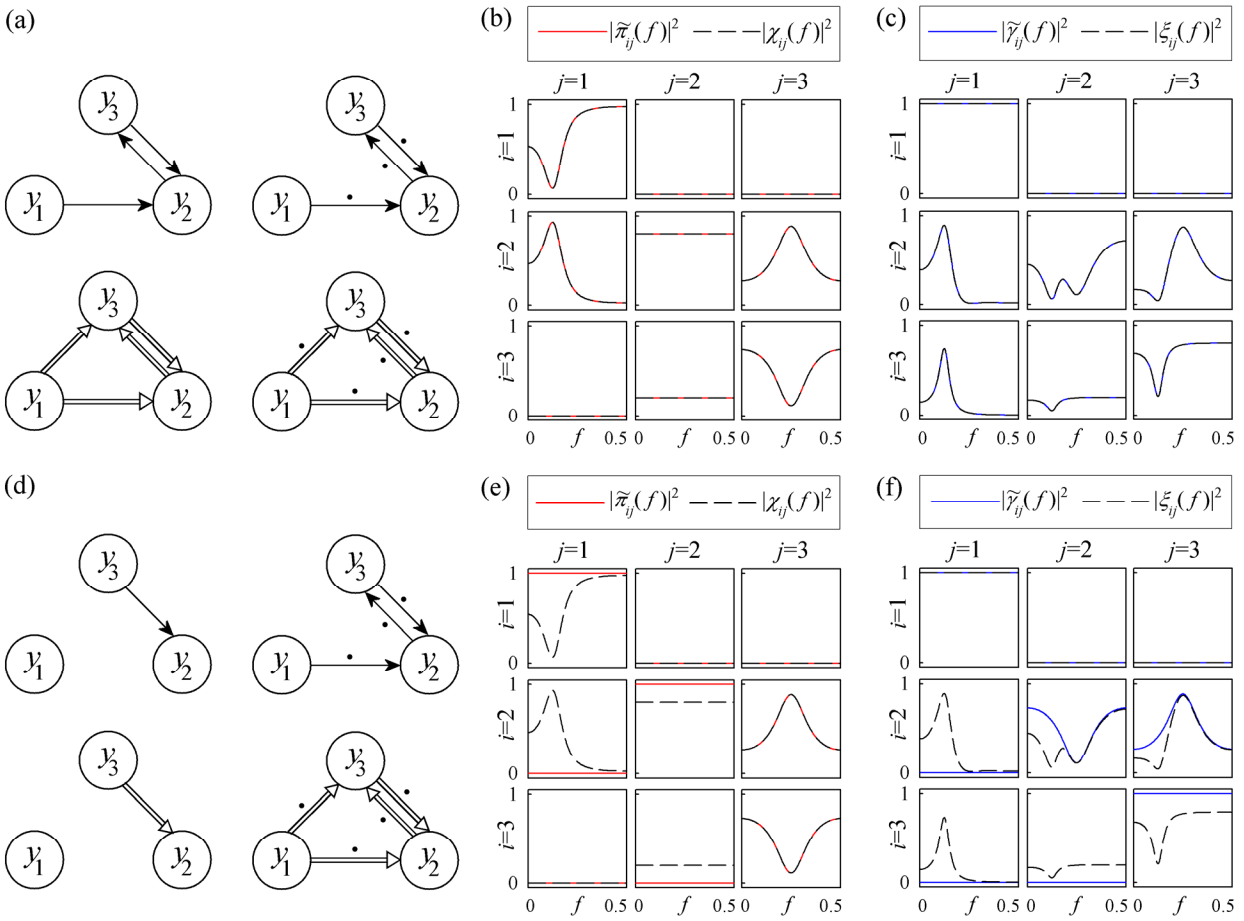

Fig. 1. Graphical models depicting the lagged direct causality ($y_j \rightarrow y_i$), extended direct causality ($y_j \dashrightarrow y_i$), lagged causality ($y_j \Rightarrow y_i$), and extended causality ($y_j \dashrightarrow y_i$) relations imposed for the theoretical process (6), and corresponding squared lPDC, ePDC, lDC and eDC functions computed in the absence of instantaneous causality (δ=1, a,b,c) and in the presence of instantaneous causality (δ=0, d,e,f).

because they include also the non-negligible instantaneous effects: besides $y_3 \dashrightarrow y_2$ and $y_3 \dashrightarrow y_2$ we note also $y_1 \dashrightarrow y_2$ and $y_2 \dashrightarrow y_3$, as well as $y_1 \dashrightarrow y_2$, $y_2 \dashrightarrow y_3$ and $y_1 \dashrightarrow y_3$ (Fig. 1d).

The corresponding squared measures of frequency domain causality are reported in Fig. 1b,c,e,f. In the absence of instantaneous causality, ePDC overlaps with lPDC reflecting an unique definition of direct causality (Fig. 1b), while eDC overlaps with lDC reflecting an unique definition of causality (Fig. 1c). In the presence of instantaneous causality the four measures are all different to each other, reflecting the different causality definitions; specifically, we note that, for each pair of processes y_i and y_j, $\widetilde{\pi}_{ij}(f)\neq 0$ when $y_j \rightarrow y_i$ and $\chi_{ij}(f)\neq 0$ when $y_j \dashrightarrow y_i$ (Fig. 1e), and $\widetilde{\gamma}_{ij}(f)\neq 0$ when $y_j \Rightarrow y_i$ and $\xi_{ij}(f)\neq 0$ when $y_j \dashrightarrow y_i$ (Fig. 1f).

IV. Real Data Applications

A. Cardiovascular variability

The beat-to-beat variability of the heart period (t), systolic arterial pressure (s) and respiratory flow (r) was measured (M=3 series, N=300 points) in ten young healthy subjects, breathing spontaneously and standing in the 60° upright position after passive head-up tilt [6]. For each subject, the model order p was set according to the Akaike Information Criterion (AIC), and the eMVAR model (1) was identified through a procedure which sets *a priori* the directions of the instantaneous effects, based on the knowledge that $r(n)$ was measured in real time before $s(n)$, which in turn was measured before $t(n)$ [4]. After model validation checking whiteness and independence of the residuals w_i, the squared eDC and lDC were computed and averaged within the low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, ±0.04 Hz around the respiratory frequency) bands.

Results shown in Fig. 2 evidence well-interpretable patterns of causality related to the generation of cardiovascular and cardiorespiratory oscillations, such as the closed-loop interaction between t and s in the LF band (both $|\xi_{st}|^2, |\widetilde{\gamma}_{st}|^2$ and $|\xi_{ts}|^2, |\widetilde{\gamma}_{ts}|^2$ are significant, Fig. 2a) and the unidirectional interaction from r to s and from r to t in the HF band ($|\xi_{sr}|^2, |\widetilde{\gamma}_{sr}|^2$ and $|\xi_{tr}|^2, |\widetilde{\gamma}_{tr}|^2$ are very high but $|\xi_{rs}|^2$, $|\widetilde{\gamma}_{rs}|^2$ and $|\xi_{rt}|^2, |\widetilde{\gamma}_{rt}|^2$ are very low, Fig. 2b). Instantaneous causality seems to play a role in determining these regulatory mechanisms, as the squared eDC is significantly higher than the squared lDC when evaluated from s to t at LF (baroreflex mechanism) and from r to t and to s at HF (effects of respiration on cardiovascular variables) [4,7].

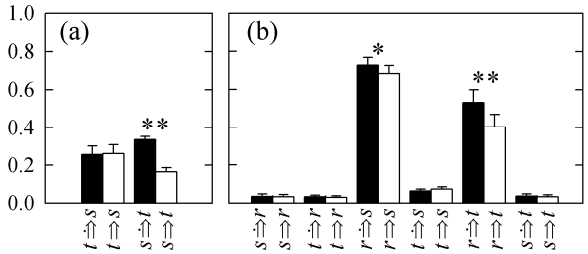

Fig. 2. Relations of extended causality ($y_j \Rightarrow y_i$) and lagged causality ($y_j \Rightarrow y_i$), measured respectively by the squared eDC (black) and squared lDC (white) for the cardiovascular variability series (t: heart period; s: systolic pressure; r: respiration), averaged in the LF band (a) and in the HF band (b). Values are mean+std.err. over 10 subjects. **, p<0.001, * p<0,01 eDC vs lDC (Student t-test for paired data).

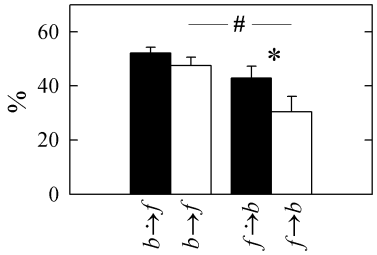

Fig. 3. Relations of extended direct causality ($b \rightarrow f$, $f \rightarrow b$) and lagged direct causality ($b \rightarrow f$, $f \rightarrow b$), measured respectively by the squared ePDC (black) and squared lPDC (white) for the EEG recordings. Values are the percentage of relations (mean+std.err. over 10 subjects) resulted as significant within the alpha band for back-to-front and front-to-back directions. *, p<0.001, ePDC vs lPDC; #, p<0.01 back-to-front vs. front-to-back (Student t-test for paired data).

B. EEG propagation

Multichannel EEG recordings were acquired through the standard 10-20 system (256 Hz sampling rate, Fpz common reference) in ten healthy subjects with eyes closed in the relaxed awake state [8]. Signals were band-pass filtered, downsampled to 64 Hz, and divided in 5 subsets describing front-to-back directions in the scalp (left-lateral: electrodes O1, T5, T3, F7; left-central: P3, C3, F3, Fp1; central: Pz, Cz, Fz; right-central: P4, C4, F4, Fp2; right-lateral: O2, T6, T4, F8). Signals of each subset were re-referenced by subtraction of the average signal from all other subsets, and were then modeled as in (1). Extended MVAR identification was performed using the AIC for model order selection and a novel method based on non-gaussianity for coefficient estimation [9]. For each subject, frequency domain analysis was performed only on the subsets fulfilling the requirements of whiteness, independence and non-gaussianity of the residuals w_i. The squared ePDC and lPDC were computed between each pair of signals, and their significance was assessed by means of a statistical test based on surrogate data [10].

Results were collected quantifying the percentage of back-to-front connections and front-to-back-connections for which ePDC and lPDC resulted as statistically significant within the alpha band of the frequency spectrum (8-12 Hz). As shown in Fig. 3, the percentage of significant direct connections was balanced over the back-to-front and front-to-back directions when assessed by ePDC, and was prevalent over the back-to-front direction when assessed by lPDC. This result shows that instantaneous causality, which in this application is likely related to non-physiological phenomena such as volume conduction effects, may mask the detection of a preferential direction of propagation of the alpha EEG waves. Such a direction is expected to occur from the posterior visual cortex towards central and anterior cortical regions [9,10] and is evidenced by the patterns of lagged direct causality measured by the lPDC.

V. CONCLUSION

Utilization of the framework presented in this study for the evaluation of frequency-domain causality is recommended whenever the interactions among the observed MV time series cannot be fully explained in terms of lagged effects. In such a case, the significance of instantaneous causality determines a distinction between the concepts of lagged (direct) causality and extended (direct) causality, which can be quantified in the frequency domain respectively by the lDC (lPDC) and the eDC (ePDC) measures defined in this paper. This differentiation is demonstrated by the reported theoretical example, and its potential impact on the interpretation of physiological mechanisms is illustrated by the applications on real MV cardiovascular variability series and EEG signals.

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