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Assessing causality in brain dynamics and cardiovascular control

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Understanding how different cerebral areas interact to produce an integrated behaviour and disentangling the mechanisms that contribute to cardiovascular control are two of the major challenges of brain and cardiovascular neuroscience. The increasing availability of simultaneous continuous recordings of several variables, resulting from the diffusion of computer-based signal acquisition devices even outside of research laboratories (e.g. in critical care units), as well as the development of fully multivariate signal processing techniques, multiplied in the past decades the efforts aimed at responding to these important issues. Traditionally, fully multivariate approaches are grounded on identification techniques of linear models. For example, approaches based on multivariate autoregressive models are widely used owing to the reliability of model parameter estimation procedures, their rapid convergence towards the optimal solution and the consistency of the estimate under well-defined assumptions. While multivariate model-based linear approaches traditionally aimed at describing the relationships among variables in terms of transfer functions, the focus has recently moved towards the assessment of the strength of the relations and their directionality. Basically, the evaluation of the strength of a linear association between two variables is traditionally performed through the computation of normalized cross-correlation in the time domain and/or the squared coherence in the frequency domain: these functions produce a normalized measure ranging from 0 to 1, where 0 and 1 indicate, respectively, that the two signals are fully uncorrelated and perfectly associated at a given time shift and/or frequency. When the squared coherence is assessed according to a fully multivariate model-based approach describing the interactions among M signals, it has the advantage of accounting for all possible links between two signals. Because these connections

Introduction

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One contribution of 13 to a Theme Issue 'Assessing causality in brain dynamics and cardiovascular control'.

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might be both direct and/or mediated by the remaining $M-2$ signals, the squared coherence is extremely helpful to test the general hypothesis of uncoupling between two signals. However, this approach has an important disadvantage: it is extremely weak when the task is to link the significant strength of association between variables to a specific mechanism. Indeed, the squared coherence (and any other tool for the assessment of the strength of the association between two signals in multivariate recordings) does not account for either the temporal direction of the interactions (i.e. causality) or the temporal sequence of the activation of the mechanisms contributing to the observed association. This lack makes indices based on the assessment of the strength of the association practically useless in clinical settings because of their insufficient specificity.

The primary aim of this Theme Issue is to emphasize approaches to assessing the strength of interactions in multivariate recordings accounting for causality, thus substituting the non-specific concept of association between variables with the notion of correlation in a given temporal direction. These approaches make possible the evaluation of the contribution of specific mechanisms to the overall complexity of brain and cardiovascular dynamics, thus supplementing the traditional univariate assessment of complexity based on the observation of a unique signal [1]. For example, in the field of cardiovascular control analysis, finding a low squared coherence value between heart period and systolic arterial pressure might suggest an inoperative baroreflex (i.e. arterial pressure changes do not provoke any heart period adjustment) and/or an insufficient cardiac mechanics (i.e. modifications of the ventricular filling due to variations of heart period do not lead to arterial pressure changes). Conversely, accounting for causality while assessing the magnitude of the interactions might lead to two distinct tests: the first one for the condition of inoperative baroreflex, and the second one for an insufficient cardiac mechanics, thus being closer to the specific mechanism. Similarly, in the brain, introducing the concept of causality in the study of functional connectivity may be decisive for moving from a purely phenomenological description of the neurophysiological measurements to a mechanistic understanding of the underlying brain processes. For instance, in the visual cortex, including several anatomically connected and hierarchically organized areas, brain connectivity analysis based on the squared coherence or other non-causal measures may only inform about the functional association among these areas. Conversely, a causal approach would be able to separate bottom-up processing of information in the visual system, which is associated with sensation and occurs from the areas of sensory receptors towards hierarchically higher areas, from top-down processing, which is associated with perception and flows in the reverse direction, thus providing lower areas with information about stored knowledge or expectations.

In this Theme Issue, applications to data recorded from two of the most critical and complex human physiological systems (i.e. cardiovascular and cerebral systems) have been intentionally selected to clarify how physiologists and clinicians can take advantage of an approach embedding directionality when assessing interdependences in multivariate recordings. In addition, the proposed approach is fully multivariate, thus offering the possibility of accounting for confounding factors that might fool analysis when carried out according to a bivariate approach.

Practical approaches focusing on the issue of causality were originally postulated in the time domain by Wiener [2] and became popular in the operative formulation given by Granger in the field of multivariate linear stationary stochastic processes [3]. The working definition of Granger causality states that the signal y_j Granger-causes the signal y_i in the set Ω of M signals if a future value of y_i can be predicted significantly better using past and present samples taken from Ω than from Ω after excluding y_j (i.e. $\Omega - \{y_j\}$). This approach has been fully translated into the information domain by exploiting the concept of transfer entropy [4] measuring the reduction of the information carried by y_i in $\Omega - \{y_j\}$ due to the introduction of y_j. The relation between linear causality methods based on predictability improvement in the time domain and the transfer entropy approach in the information domain appears more clearly when considering the close link between predictability and entropy in the case of conditional dependences: the flatter the conditional distribution, the more uncertain the prediction, and the larger the entropy. Owing

to the equivalence between predictability improvement based on the linear models and transfer entropy approaches, fully demonstrated in the case of Gaussian variables [5] and also for other probability densities [6], the selection between these two alternative approaches depends on the relevance of nonlinear interactions, on the statistical properties of the estimators when assessed over real data sequences of limited length, and on the robustness of the method against non-stationarities that remain unveiled after the application of traditional tests checking for weak stationarity [7]. Currently, the extension of the Granger causality approach to the frequency domain [8,9] is gaining more and more relevance given the oscillatory nature of physiological variables and the peculiarity of specific control mechanisms of working in accordance to well-defined time scales. Among the set of practical approaches dealing with the issue of causality, it is worth mentioning also methods based on causal coupling [10], nonlinear prediction [11], symbolization [12], synchronization [13] and recurrence analysis [14].

This Theme Issue, collecting together 12 contributions from experts with a consolidated experience in devising methods for the assessment of causality over multivariate time series and in applying them to brain signals and cardiovascular variability series, is designed to provide examples of the evaluation of causality in the time, frequency and information domains. This Theme Issue contains also contributions discussing pitfalls and caveats of Granger causality approaches in relation to the completeness and redundancy of Ω, proposing the monitoring of causality through time-variant procedures to relax the hypothesis of stationarity, and modelling interactions via alternative descriptions to multivariate linear model-based techniques.

Among the contributions covering the issue of assessing causality in the time domain, Eichler [15] reviews the original definition of Granger causality, with special attention to relating it to different concepts of causality, linking the initial time domain approach to more recent extensions in the frequency domain and stressing the issue of spurious causalities that might arise in the presence of latent confounders (i.e. variables omitted in Ω but responsible for a significant portion of the correlation among signals included in Ω). More practically, Porta *et al.* [16] exploit a time domain Granger causality approach to disentangle the mechanisms involved in short-term cardiovascular control during a pharmacological protocol selectively blocking vagal and/or sympathetic branches of the autonomic nervous system.

Among the contributions covering the issue of assessing causality in the frequency domain, Baccalá *et al.* [17] derive a unified asymptotic theory for all the partial directed coherence estimators, thus leading to a formal derivation of confidence intervals and threshold for testing the null hypothesis of absence of a causal link as a function of the frequency. Faes *et al.* [18] address in the frequency domain the theoretically challenging issue of the dependence of causality on the canonical form of the multivariate model necessary to interpret instantaneous links resulting from the inadequate temporal resolution in relation to the latencies among signals. Wen *et al.* [19] propose an efficient method for estimating Granger causality among a subgroup of signals present in Ω starting from the spectral density matrix describing all the causal interactions in Ω. Finally, Ramb *et al.* [20] examine in the frequency domain the effects of the latent confounders on the renormalized partial directed coherence.

Among the contributions covering the issue of assessing causality in the information domain, Schulz *et al.* [21] review nonlinear methods for the estimation of the coupling strength along a specific time direction with special emphasis on those designed in the information domain and exploiting symbolization procedures. Marwan *et al.* [22] propose a novel approach to the assessment of directionality in cardiorespiratory and cardiovascular interactions based on conditional probabilities of recurrences.

Because stationarity is a prerequisite for all the approaches, regardless of the domain where the methods have been devised, a couple of contributions are devoted to possible extensions of the techniques to tackle non-stationarities. Along this line, Blinowska *et al.* [23] turn the original formulation of directed transfer function into a time-variant approach to track the temporal evolution of interactions among brain areas during working memory task. Leistritz *et al.* [24] apply time-variant partial directed coherence to deal with transient interactions in connectivity analyses.

Moreover, with the aim of stressing that all causality approaches strictly depend on the model structure used to describe the interactions among signals, a couple of contributions are included to suggest a representation of signal interactions alternative to the most traditional one based on the multivariate linear model class. Iatsenko *et al.* [25] ground their analysis of cardiorespiratory interactions on a nonlinear model of coupled oscillators. Ramírez Ávila *et al.* [26] check several different schemes of interdependences to find the most helpful one to predict a pregnancy-specific disorder causing maternal and foetal morbidity and mortality (i.e. pre-eclampsia).

Given the close association between mathematical indices and physiological mechanisms, this Theme Issue suggests that causality analysis could be very powerful in identifying pathological subjects characterized by an impairment of a given link or connection among subsystems, in detecting subjects at risk of developing pathology in relation to a particular regulatory mechanism, in predicting the onset of threatening events such as cardiac arrhythmias or epileptic seizures, in typifying the sequence of subsystems that are activated in response to a given stimulus or task, and in providing a more insightful description of the functioning of the autonomic and central nervous systems. Because an impairment of specific cardiovascular mechanisms and an altered connectivity among brain regions may be indicators of pathology, the study of cardiovascular and brain dynamics through causality analysis might suggest parameters helpful in clinics to tailor individual treatments, improve diagnosis and therapy, manage patients and test drugs.

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