Clinical Neurophysiology 121 (2010) 272–273

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Editorial

Do we need to consider non-linear information flow in corticomuscular interaction?

See Article, pages 392–401

The cortex is a mosaic of patches, each with its own cytoarchitectonic and receptor signatures (Zilles et al., 2002). These patches and the sub-cortical areas and nuclei are expected to contribute differentially to specific functions, and evidence for this is already accumulating (Eickhoff et al., 2006). It is however obvious that the operations within each patch cannot depend only on the internal organization. The connectivity between these patches must also play a role. No matter how many complex and refined operations take place within an area, they cannot be performed without input from other areas and the output of these "computations" must be communicated to other areas. These considerations lead naturally to a description of the brain in terms of a network. At the most basic level the description can be thought of as a graph with cytoarchitectonic areas defining the nodes and the white matter pathways connecting these areas describing the edges between them (Young, 1992).

Over the last few decades, neuroimaging methods have yielded glimpses of the way the brain works. First, Positron Emission Tomography (PET) and more recently functional Magnetic Resonance Imaging (fMRI) have provided maps reflecting changes in neural activity. These maps are relatively sluggish because they are indirectly related to neuronal function through the relatively slow hemodynamic changes. More recently, improvements in source estimation methods for EEG and MEG provided direct estimates of local changes in brain activity (Babiloni et al., 2002; Ioannides, 2006). The initial emphasis in neuroimaging studies was placed on identifying the nodes of the neural network through changes in activity under a given task compared to some control condition. This effort has been conceptually satisfying since area specialization was supported by the relatively coarse cytoarchitectonic studies at the beginning of the century and reinforced by the refinements of recent investigations (Zilles et al., 2002). The availability of standard maps and the development of methods to morph one brain on another provided an extra impetus for the cartography of the human brain function. The determination of the "functional" connections, i.e., effective connectivity (Friston, 1994) between these areas was the obvious next step. While the conceptual framework for identifying the nodes of activity is well established, the choice of method for defining the edges and for quantifying their strengths is less obvious. To begin with, the basis of connectivity between areas may be virtual connections between areas mediated by intermediate nodes, e.g., the cerebellum, especially at high frequencies (Ioannides, 2007). A more practical question is what kind of connectivity measure is appropriate for describing the influences of neural areas on each other. The article by Jin et al. in this volume (Jin et al., 2010), addresses in a very direct way one important aspect of this choice, namely the need to consider non-linear measures of connectivity.

Biological systems in general, and the brain in particular, are characterized by multiple feedforward and feedback interconnections between large number of interacting areas, each with its own threshold and non-linear response function. Although non-linearities are therefore almost ubiquitous, many studies use linear methods because of their simplicity and easier interpretation of the results. However, it is evidently important to be able to assess the presence of non-linear interactions and, in the context of understanding the underlying mechanisms, to be able to determine the direction of these interactions in a reliable manner as well.

Correlation and coherence analysis, which quantifies the strength of linear relation between two signals in the frequency domain, have been extensively used to assess functional connectivity in a linear context, whereas – in a non-linear context – non-linear correlation coefficients, phase synchronization and mutual information have been used for the same purpose (Pereda et al., 2005). All these measures do not provide information regarding the *direction* of interaction. Therefore, several approaches to assess the direction of interaction have been proposed, most of them relying on the general concept of Granger causality. Granger causality, which was initially developed in the field of econometrics, states that a time-series x Granger causes a time-series y when y can be predicted better by using past values of x compared to when using past values of y alone (Granger, 1969). Linear methodologies such as directed coherence, directed transfer function and partial directed coherence have been proposed (Baccala and Sameshima, 2001; Pereda et al., 2005); these typically fit multivariate autoregressive models to neurophysiological (EEG, MEG or fMRI) data and obtain descriptions in the frequency domain that are direction-sensitive. Recently, an extension of this concept to non-linear multivariate autoregressive models was proposed (Faes et al., 2008).

Jin et. al. tested for non-linearities in the coupling between neuronal activity and muscle (corticomuscular, CM, coupling). They introduced a novel way to decompose *directed information flow into linear and non-linear components*, based on univariate and bi-variate surrogate data hypothesis testing. First, time-delayed mutual information (TDMI) was used to obtain a measure of the directed information flow between two time-series. Whereas mutual information is a measure that can account for non-linear interactions, it does not provide any information regarding the direction of these interactions, in other words regarding the causal influence of one

1388-2457/$36.00
doi:10.1016/j.clinph.2009.11.005

time-series on the other. TDMI provides this additional information by obtaining the mutual information between the two time-series, after time-lagging one of the two series at a time for different lag values, and keeping the other fixed (Ioannides et al., 2000). Since this measure is non-symmetric (unlike standard mutual information), the direction of information is obtained as the net difference between the TDMI obtained when time-shifting the first time-series minus the TDMI obtained when lagging the second.

In order to decompose into linear and non-linear interactions, the authors use a modification of the method of surrogate data in order to perform statistical hypothesis testing in two stages: first, a standard surrogate data-set is obtained in the frequency domain by obtaining the Fourier transform (FT) of the original time-series, keeping the original amplitudes and randomizing the phase separately for each of the two series. This abolishes any kind of correlation between them; therefore, TDMI is obtained for both the original and surrogate data-sets and used to determine whether there is any (linear or non-linear) interaction. This constitutes the first hypothesis test. When this is the case, i.e., the null hypothesis of no interactions is rejected, a bi-variate surrogate data-set is constructed in the frequency domain by keeping (again) the FT magnitudes, but applying the same phase randomization to both time-series. This preserves any linear correlations that may be present in the data. TDMI is then used to perform hypothesis testing on the bi-variate surrogate data-sets and determine whether there is a non-linear component in the interaction between the two time-series. The proposed methodology was tested in three simulated systems and it was also used to investigate the CM interaction, obtaining measures of linear and non-linear interactions between EEG and sEMG data, with promising results.

Whereas these two individual approaches have been used before, their combination presents an important contribution in order to assess directed information flow in neurophysiological data and decompose it in its linear and non-linear components in an intuitive and relatively simple manner. Specifically, TDMI and other directed information measures have been used to assess effective connectivity, e.g., in (Ioannides et al., 2000; Hinrichs et al., 2006), whereas the bi-variate surrogate data approach was proposed in Prichard and Theiler (1994). The significance of the work of Jin et al. relies in the direct demonstration of non-linearities using a data-driven approach with the minimum of prior assumptions. The choice of CM interaction also allowed the authors to make the computations directly with EEG and EMG records. This choice (rather than studying area-to-area interaction) avoids dealing with the inverse problem directly, thus removing a rather independent layer of complexity. It is of course now important to carry out a similar analysis for time-series representing activity in circumscribed brain areas and thus build up the underlying neural networks. The full potential of the proposed approach, as well as possible extensions to multivariate problems, remain to be seen in future studies.

Finally, this approach will hopefully help to clarify some issues with the application and utility of non-linear measures in general. For example, in the field of epileptic seizure prediction, which is mentioned by the authors, it remains to be proven whether non-linear measures indeed perform better than linear measures, despite the fact that EEG signals may exhibit non-linear characteristics (Mormann et al., 2007), and the initial optimistic results (Martinerie et al., 1998). The reason for this is that non-linear measures are typically affected more in the presence of noise and/or result in the use of more free parameters, which often leads to overfitting to a specific data-set and limits their generalization capability.

References

Babiloni C, Babiloni F, Carducci F, Cincotti F, Rossini PM. High-resolution EEG: modeling time, space and phase of SEPs following upper limb stimulation. International Congress Series 2002;1232:243–6.
Baccala LA, Sameshima K. Partial directed coherence: a new concept in neural structure determination. Biol Cybern 2001;84:463–74.
Eickhoff S, Amunts K, Mohlberg H, Zilles K. The human parietal operculum II. Stereotaxic maps and correlation with functional imaging results. Cereb Cortex 2006;16:268–79.
Faes L, Nollo GD, Chon KH. Assessment of Granger causality by nonlinear model identification: application to short-term cardiovascular variability. Ann Biomed Eng 2008;36:381–95.
Friston KJ. Functional and effective connectivity in neuroimaging: a synthesis. Hum Brain Mapp 1994;2:56–78.
Granger CWJ. Investigating causal relations by econometric models and cross-spectral methods. Econometrica 1969;37:424–38.
Hinrichs H, Heinze HJ, Schoenfeld MA. Causal visual interactions as revealed by an information theoretic measure and fMRI. NeuroImage 2006;31:1051–60.
Ioannides AA, Liu LC, Kwapien J, Drozdz S, Streit M. Coupling of regional activations in a human brain during an object and face affect recognition task. Hum Brain Mapp 2000;11:77–92.
Ioannides AA. Magnetoencephalography as a research tool in neuroscience: state of the art. Neuroscientist 2006;12:524–44.
Ioannides AA. Dynamic functional connectivity. Curr Opin Neurobiol 2007;17:161–70.
Jin S-H, Lin P, Hallet M. Linear and nonlinear information flow based on time delayed mutual information method and its application to corticomuscular interaction. Clin Neurophysiol 2010;121:392–401.
Martinerie J, Adam C, Le Van Quyen M, Baulac M, Clemenceau S, Renault B, et al. Epileptic seizures can be anticipated by non-linear analysis. Nature Medicine 1998;4:1173–6.
Mormann F, Andrzejak RG, Elger CE, Lehnertz K. Seizure prediction: the long and winding road. Brain 2007;130:314–33.
Pereda E, Quiroga RQ, Bhattacharya J. Nonlinear multivariate analysis of neurophysiological signals. Prog Neurobiol 2005;77:1–37.
Prichard D, Theiler J. Generating surrogate data for time series with several simultaneously measured variables. Phys Rev Lett 1994;73:951–4.
Young MP. Objective analysis of the topological organization of the primate cortical visual system. Nature 1992;358:152–5.
Zilles K, Palomero-Gallagher N, Grefkes C, Scheperjans F, Boy C, Amunts K, et al. Architectonics of the human cerebral cortex and transmitter receptor fingerprints: reconciling functional neuroanatomy and neurochemistry. Eur Neuropsychopharmacol 2002;12:587–99.

Andreas A. Ioannides
AAI Scientific Cultural Services Ltd., Laboratory for Human Brain Dynamics, Galaxias Center, 5th Floor Block A, Office 501, 33 Arch. Makarios III Avenue, 1065 Nicosia, Cyprus
E-mail address: a.ioannides@humanbraindynamics.com

Georgios D. Mitsis
Department of Electrical and Computer Engineering, University of Cyprus, P.O. Box 20537, Nicosia 1678, Cyprus

Available online 14 December 2009