Neural Networks 95 (2017) 29–43

Contents lists available at ScienceDirect

Neural Networks

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

A multivariate extension of mutual information for growing neural networks☆

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ARTICLE INFO

Article history:
Received 28 December 2016
Received in revised form 26 May 2017
Accepted 7 July 2017
Available online 24 July 2017

Keywords:
Mutual information
Shannon information theory
Multivariate mutual information
Multiinformation
Total correlation
Neural network development
MEA

ABSTRACT

Recordings of neural network activity in vitro are increasingly being used to assess the development of neural network activity and the effects of drugs, chemicals and disease states on neural network function. The high-content nature of the data derived from such recordings can be used to infer effects of compounds or disease states on a variety of important neural functions, including network synchrony. Historically, synchrony of networks in vitro has been assessed either by determination of correlation coefficients (e.g. Pearson's correlation), by statistics estimated from cross-correlation histograms between pairs of active electrodes, and/or by pairwise mutual information and related measures. The present study examines the application of Normalized Multiinformation (NMI) as a scalar measure of shared information content in a multivariate network that is robust with respect to changes in network size. Theoretical simulations are designed to investigate NMI as a measure of complexity and synchrony in a developing network relative to several alternative approaches. The NMI approach is applied to these simulations and also to data collected during exposure of in vitro neural networks to neuroactive compounds during the first 12 days in vitro, and compared to other common measures, including correlation coefficients and mean firing rates of neurons. NMI is shown to be more sensitive to developmental effects than first order synchronous and nonsynchronous measures of network complexity. Finally, NMI is a scalar measure of global (rather than pairwise) mutual information in a multivariate network, and hence relies on less assumptions for cross-network comparisons than historical approaches.

1. Introduction

Recordings of electric potential over time from electrodes embedded in neural tissues enable the observation of neural firing activity from neurons within a given proximity of each electrode, depending on the manufacture (Obien, Deligkaris, Bullmann, Bakkum, & Frey, 2015). While neural spiking is the underlying mechanism that gives rise to broader functional activity like cortical rhythms (Fries, Nikolić, & Singer, 2007; Wang, 2010), there is also interest in the underlying information content of spiking patterns via a variety of hypotheses of neural encoding (Kumar, Rotter, & Aertsen, 2010; Reyes, 2003; Rullen & Thorpe, 2001). Microelectrode arrays (MEAs) allow examination of neural spiking, bursting and coordinated neural activity in cultures of neural tissues in vitro (Nam & Wheeler, 2011; Pine, 2006). Examination of neural network function using MEAs has been proposed as an approach to evaluate the impacts of drugs, chemicals, and disease states (Johnstone et al., 2010) on network development and function, and the recent availability of multi-well MEA (mwMEA) formats have facilitated such studies (Brown et al., 2016; Crossley et al., 2014; Valdivia et al., 2014; Wainger et al., 2014; Woodard et al., 2014). The focus of this work involves the inference of network development effects resulting from chemical exposures, although the methods for measuring network properties described here may have broader applications. In particular, a new normalization of Shannon mutual information (extended to multivariate networks) is used to measure effects in growing neural networks.

In the MEA experimental paradigm, electric potentials are recorded over time using extracellular electrodes positioned in brain structures (in vivo) or embedded into a surface upon which neural cells are cultured (in vitro). While the amplitude and shape of individual action potentials can be assessed, most often the

☆ Preparation of this document has been funded in part by the U.S. Environmental Protection Agency. This document has been reviewed by the National Health and Environmental Effects Research Laboratory and approved for publication. Approval does not signify that the contents reflect the views of the Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

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http://dx.doi.org/10.1016/j.neunet.2017.07.009
0893-6080/

action potential spikes are reduced to time-stamps and analyzed as spike trains on each individual electrode (or "units") if multiple signals are observed on a single electrode. These spike trains can then be compared across time and space (different electrodes) to examine network characteristics. A variety of measures of network information may be extracted from spike train data derived from MEA recordings that are indicative of network development and/or function (Bove, Genta, Verreschi, & Grattarola, 1996; Brown et al., 2016; Chiappalone, Bove, Vato, Tedesco, & Martinoia, 2006; Cotterill et al., 2016). This includes measures that assess the synchrony of activity in the network.

Synchrony is a useful concept that is associated with increasing network complexity; however, measures and definitions of synchrony differ widely in the literature. From the tissue-level viewpoint of a large neural network, it is suggested synchronous neural firing and associated potential oscillation is relevant to sensory awareness (Engel & Singer, 2001), attention (Gregoriou, Gotts, Zhou, & Desimone, 2009; Gross et al., 2004; Ward, Doesburg, Kitajo, MacLean, & Roggeveen, 2006), memory (Jensen, Kaiser, & Lachaux, 2007; Palva, Monto, Kulashekhar, & Palva, 2010; Tallon-Baudry, Bertrand, & Fischer, 2001) and other high level cognitive processes (Buzsáki & Draguhn, 2004; Eckhorn, Reitboeck, Arndt, & Dicke, 1990; Engel, Fries, & Singer, 2001; Uhlhaas et al., 2009; Uhlhaas & Singer, 2006). Synchronous activity is observed in both in vivo and in vitro neural network recordings, and arises spontaneously in networks grown in vitro, indicating that it is an intrinsic property of neural networks, and as noted above, is important to neural function. Thus, assessment of effects of neuroactive/neurotoxic compounds or disease states on the development or maintenance of synchrony is important.

Synchrony of signals at the tissue-level follows from the temporal coincidences in aggregated firing of many neurons, and is measured in terms of rate and phase by binning signals into temporal and/or spatial windows. Temporal synchrony at the neural spiking level is a lower level phenomenon, and while the classical view of neural coding emphasizes rate synchrony, temporal synchrony of the firing of individual neurons at a millisecond-level resolution may drive both higher level synchronous behavior and associated cognitive processes (Diesmann, Gewaltig, & Aertsen, 1999; Riehle, Grün, Diesmann, & Aertsen, 1997). Some form of temporal synchrony will arise as a result of temporally causal relationships between the firing patterns of pairs of neurons, relationships which are integral to the study of synaptic interactions in the nervous system (Bologna et al., 2010; Salinas & Sejnowski, 2001). Inferring the developmental state of synaptic relationships between neurons through temporal synchrony of their observed firing patterns – and quantifying this synchrony – is one avenue for investigating developmental neurotoxicity by making comparisons between populations of cultures under different experimental conditions.

A simple measure of synchrony between the binary spike trains of two firing neurons is Pearson's correlation coefficient, which returns the cross-correlation between spike trains derived from two neurons. The signal from a given neuron/electrode may be time lagged relative to another at various time lag intervals to return more general multi-dimensional cross-correlograms and auto correlations when a single spike train is compared relative to a time lagged version of itself (Knox, 1981; Rieke, Warland, van Steveninck, & Bialek, 1996). There are theoretical deficiencies to using linear correlation as a measure of temporal neural synchrony in pairwise interactions. First and foremost, linear correlation relates little about the information content of a coincident binary signal: two perfectly correlated neurons may fire once or one-hundred times in a given time interval and the correlation coefficient will be the same. Second, correlation is not well defined for zero-valued signals, i.e. when no firing is observed by an electrode embedded in a neural culture.

Shannon's mutual information (MI) is a higher order information theoretic measure of temporal synchrony that has been used as a measure of information encoding in stimulus response experiments (Bologna et al., 2010; Borst & Theunissen, 1999) in the sense that MI depends on higher orders of the joint probability distribution than linear correlation (Li, 1990). Pairwise MI accounts for both linear correlation of two firing neurons and the shared information content of the two spike trains, and hence represents a more robust measure of temporal synchrony as a mechanism of neural information coding. Other pairwise measures of temporal synchrony include transfer entropy (Gourévitch & Eggermont, 2007; Schreiber, 2000) and joint entropy (Garofalo, Nieus, Massobrio, & Martinoia, 2009) which are nonsymmetric measures that allow for inference of directional causality in networks. Cutts and Eglen (2014) review and benchmark a large number of pairwise correlation measures. Measures of pairwise mutual information are considered in their benchmarking but rejected as inconsistent measures of *linear* correlation because of non-invariance with respect to spiking rates (which is an attractive property of such measures in the present case).

All of the described synchrony measures may be useful for investigating the pairwise connections of a multi-node neural network, from which connectivity properties between neurons may be inferred. However, further assumptions and processing on connectivity maps or the multivariate comparison structures (cross-correlation and pairwise MI matrices, etc.) are required if an experimenter desires a scalar measure of overall network complexity in a network of neurons/electrodes with more than two nodes. A scalar measure of neural network complexity that does not rely on aggregating many pairwise temporal synchrony measures would provide a more natural framework to make population comparisons between observed network activity in the form of multi-dimensional (e.g. recorded from multiple electrodes) spike trains recorded in neural cultures. MI has previously been extended to the multivariate case of a multi-node network in at least two different forms, which are described in detail below. The hypothesis tested in this paper is that one of these multivariate extensions to MI – when coupled with a novel normalization term that is motivated by a self-consistency property of the function – is useful as a scalar measure of the information content of a *developing* neural network via simulations of binary spike train recordings. The proposed normalized mutual information measure is demonstrated (by examining concentration—responses in real experiments) to be more sensitive than aggregated linear correlation and other neural spiking parameters as a discriminant feature for the effects of compounds on network function tested in vitro in Sections 3 and 4.

In Section 2, the proposed function is shown to be justified in the context of Shannon information theory as an asymptotically consistent measure of shared information as connection strength increases. Also in Section 2, bounding properties of the function are stated and proved in the case of a network that is growing in size.

For the purposes of this study, mutual information measures are applied to multichannel spike recordings without prior knowledge of the generative neural network topology underlying those recordings. The network is assumed to be (possibly) fully connected (without self-connections), and all possible pairwise and higher order interactions are considered. In practice there is some topology to biological neural networks; in order to generate simulations in 3 a series of feed-forward partially connected neural networks are generated that have directed connections. However, the analyses on spike train recordings make no specific assumptions about network topology.