Journal of Neuroscience Methods 144 (2005) 265–279

JOURNAL OF NEUROSCIENCE METHODS

www.elsevier.com/locate/jneumeth

A method for determining neural connectivity and inferring the underlying network dynamics using extracellular spike recordings

Valeri A. Makarov[a,*], Fivos Panetsos[a], Oscar de Feo[b]

[a] Neuroscience Laboratory, Department of Applied Mathematics, School of Optics, Universidad Complutense de Madrid, Avda. Arcos de Jalon s/n, 28037 Madrid, Spain
[b] Laboratory of Nonlinear Systems, Swiss Federal Institute of Technology Lausanne; EPFL-IC-LANOS, CH-1015 Lausanne, Switzerland

Received 11 October 2004; received in revised form 10 November 2004; accepted 12 November 2004

Abstract

In the present paper we propose a novel method for the identification and modeling of neural networks using extracellular spike recordings. We create a deterministic model of the effective network, whose dynamic behavior fits experimental data. The network obtained by our method includes explicit mathematical models of each of the spiking neurons and a description of the effective connectivity between them. Such a model allows us to study the properties of the neuron ensemble independently from the original data. It also permits to infer properties of the ensemble that cannot be directly obtained from the observed spike trains. The performance of the method is tested with spike trains artificially generated by a number of different neural networks.

Keywords: Neural circuits; Spike trains; Connectivity identification; Network modeling

---

1. Introduction

The qualitative and quantitative analysis of the spiking activity of individual neurons is a very valuable tool for the study of the dynamics and architecture of the neural networks in the central nervous system (Kandel et al., 2000; Moore et al., 1966; Perkel et al., 1967a). Nonetheless, such activity is not due to the sole intrinsic properties of the individual neural cells but it is mostly consequence of the direct influence of other neurons, from a few to hundreds of thousands, which in general leads to dynamical behaviors far beyond a simple combination of those of the isolated neurons. Although any behavior of a neural network depends on the interactions of a high number of neural cells, on their morphology and their entire interconnection pattern, usually we cannot record the activity of each one of these cells but rather we are restricted to a very limited sample of the neurons of the network whose properties we aim to capture. Moreover, deducing the effective connectivity between neurons whose experimental spike trains are observed is of crucial importance in neuroscience: first for the correct interpretation of the electrophysiological activity of the involved neurons and neural networks, and, second and probably more important, for correctly relating the electrophysiological activity to the functional tasks accomplished by the network, being as simple as a response to a sensory stimulus or complex as interpreting a literature text. The above mentioned notion "effective connectivity" is defined as the simplest neuron-like circuit that would reproduce the same temporal relationships between neurons in a cell assembly as those observed experimentally (Aertsen and Preissl, 1991). In other words, by "effective" we mean any observable direct or indirect interaction between neurons that alters their firing activity. Summarizing, when dealing with multiunit extracellular recordings we have the following objectives: (i) inferring the effective connectivity and neuron properties of sub-networks (limiting to neurons experimentally available) and (ii) extrapolating the functionality of the "whole" from the properties of the collected and classified sub-networks.

---

* Corresponding author. Tel.: +34 91 394 6900; fax: +34 91 394 6885.
E-mail address: vmakarov@opt.ucm.es (V.A. Makarov).

0165-0270/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.jneumeth.2004.11.013

To address these problems a common experimental approach is to use extracellular multiunit recordings. In this case spike trains (the time instants of spike occurrences, point events), in general, do not allow any direct insights about the subthreshold and/or intrinsic membrane dynamics of the neurons. Nevertheless, spike trains can be used to identify the functional characteristics and architecture of the neural network they originated from (e.g. Perkel et al., 1967b; Segundo, 2003). Though possible, identifying the effective neural circuits from the spike trains represents a very complex task even for a network of few neurons. The available mathematical methods result undersized with respect to the research exigencies, and the large majority of neurophysiologists restrict their study to the description of the neural activity by means of cross-correlograms (Perkel et al., 1967b), a tool widely understood but which provides very limited knowledge about the functional properties of the neural networks. For instance, in the case of neural ensembles of three or more neurons the cross-correlation may be easily fooled by the presence of indirect connections (via other neuron(s)), or also due to a common input.

Recently, more sophisticated statistical methods have been introduced for the identification of effective connectivity in relatively large neural networks. Nevertheless, to extract the interactions among neurophysiological data from two or more neural elements, or brain sites, all these methods always recur to the evaluation of some kind of covariance or correlation between the multiple signals. In fact, even the methods that go beyond simple correlation (e.g., regression analysis, principal components analysis and multidimensional scaling) conceptually embody the notion of co-variation in activity (Horwitz, 2003). In this framework a method based on linear partialization (conditional probability) in frequency domain has been proposed in (Brillinger et al., 1976; Dahlhaus et al., 1997; Rosenberg et al., 1989). Although this approach allows distinguishing direct from indirect (trough other neurons) connections, it does not differentiate between excitatory and inhibitory synapses, a problem solved by Eichler et al. (2003) by adopting a similar approach based on partialization in time domain. Another approach, called partial directed coherence (e.g. Sameshima and Baccala, 1999), uses Granger causality (Granger, 1969) to expose the direction of information flow. Further two more methods: direct causality (Kaminski et al., 2001), and direct directed transfer function (Korzeniewska et al., 2003) have been introduced. These methods allow identifying the presence of feedback between two or more neurons, but coupling polarities are not directly accessible. Although these methods have been successfully applied on simulated networks of randomly spiking coupled neurons, their application to real data is basically limited because: (i) they do not allow resolving mutual couplings between neurons and/or do not distinguish the type of such couplings; (ii) as a rule their application assumes the use of relatively large spike trains with constant statistical properties, a condition difficult to be satisfied in the experiments; (iii) they usually fail when applied to excessively rhythmic neural assemblies, a rather common situation which may just represent an objective of the research. An additional very important remark is that all these methods assume a stochastic nature of the spike trains generated by neurons. Consequently, no considerations are made about the dynamics of the involved neurons or about the nature of the intrinsic processes that are responsible for such behavior, with the consequent enormous difficulties in subsequent steps of the study: assigning of functional and/or neurochemical properties of the neurons, determination of anatomical correlates, etc. Furthermore, all these methods deal only with the connectivity patterns, i.e. only presence and sometime type and direction of the couplings between neurons can be estimated. No knowledge about absolute values of couplings or other parameters of the network can be drawn.

In contrast to a purely statistic approach, a deterministic one can be considered. The main advantage of deterministic methods is the use of mathematical models for inferring single neuron or neural network properties (indirect method) especially useful where direct observation of the neural dynamics (experimental procedures) is very difficult or even impossible. In general, in the literature, the indirect inference of network properties from models is approached in a very abstract manner, considering relatively simple, usually vaguely biophysically meaningful, neuron models (like phase oscillators (e.g. Ermentrout, 1982), Fitzhugh-Nagumo (FitzHugh, 1961), Plant (Plant, 1981), Hindmarsh-Rose (Hindmarsh and Rose, 1984), etc.) connected in networks which are either large and extremely regular (chains, rings, lattices, global or random couplings) or composed of only few (two) neurons. Alternatively, the Hodgkin–Huxley formalism (Hodgkin and Huxley, 1952) for modeling the dynamics of an individual neuron can be adopted. However, the need of a priori investigations of the channel dynamics of each particular neuron and the synaptic transduction properties, together with the computational complexity of its integration, restrict as well its use to the cases of very regular networks or of only a few neurons. Whilst these approaches allowed studying many phenomena experimentally observed in the central nervous system (like partial synchronization, phase or frequency locking, different types of waves, clustering, etc.), they lack direct biophysical interpretation and, the study of the dynamics of intermediate size networks, having biophysically supported effective connectivity patterns, is still a challenging problem. In this direction, a method for extracting a dynamical system out of the interspike intervals (ISIs) has been proposed (Racicot and Longtin, 1997; Sauer, 1994). This method allows concluding, for instance, about the possible chaotic nature of the spike timings of a neuron (e.g. Pavlov et al., 2001). Recently another approach taking into account the deterministic dynamics of a single neuron activity has been introduced (Paninski, 2004; Paninski et al., 2003; Pillow and Simoncelli, 2003). This approach provides a biophysically more realistic alternative to the models based on Poisson (stochastic) spike generation. It was shown that the leaky integrate and fire cell driven by a noisy stimulus demonstrates an adaptive behavior