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Revealing neuronal functional organization through the relation between multi-scale oscillatory extracellular signals

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ABSTRACT

The spatial organization of neuronal elements and their connectivity make up the substrate underlying the information processing carried out in the networks they form. Conventionally, anatomical findings make the initial structure which later combines with superimposed neurophysiological information to create a functional organization map. The most common neurophysiological measure is the single neuron spike train extracted from an extracellular recording. This single neuron firing pattern provides valuable clues on information processing in a given brain area; however, it only gives a sparse and focal view of this process. Even with the increase in number of simultaneously recorded neurons, inference on their large-scale functional organization remains problematic. We propose a method of utilizing additional information derived from the same extracellular recording to generate a more comprehensive picture of neuronal functional organization. This analysis is based on the relationship between the oscillatory activity of single neurons and their neighboring neuronal populations. Two signals that reflect the multiple scales of neuronal populations are used to complement the single neuron spike train: (1) the high-frequency background unit activity representing the spiking activity of small localized subpopulations and (2) the low-frequency local field potential that represents the synaptic input to a larger global population. The three coherences calculated between pairs of these three signals arising from a single source of extracellular recording are then used to infer mosaic representations of the functional neuronal organization. We demonstrate this methodology on experimental data and on simulated leaky integrate-and-fire neurons.

1. Introduction

The anatomical organization of neuronal elements in the brain, as well as their spatial relationships can provide important clues as to the computational properties of underlying neuronal networks. This spatial organization places constraints on physiological and computational studies targeting the unique features of a neuronal network. By contrast, functional connectivity relates to the correlation between the physiological activities of different neurons (Gerstein and Perkel, 1969; Aertsen et al., 1989; Friston, 1994). Although the term is not well defined across different methodologies such as imaging or extracellular recordings, or even within these methodologies (Horwitz, 2003) it usually refers to the co-activation of several neuronal elements which informs on their connectivity, organization and function. Combining spatial organization and functional connectivity enables the formulation of the functional organization term. For our purposes, functional organization is defined here as the spatial organization of coherent neuronal elements, and does not refer to a specific behavioral function.

Functional organization has been studied over the years using two extreme methodologies: a macroscopic approach that examines large neuronal populations, and a microscopic approach that deals with single neurons. At the macroscopic level, electroencephalography (EEG), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have been used to study inter-region functional organization, both at rest and during task related activities (Barlow and Brazier, 1954; Adey et al., 1961; Gevins et al., 1985; Friston et al., 1993; Biswal et al., 1995; Buchel and Friston, 1997; Pfurtscheller and Andrew, 1999). These macroscopic methodologies have low spatial resolution which prevents them from inspecting local features of the functional organization in a certain region or nuclei. On the other hand, the microscopic approach is based on single neuron activity. The neuronal activity is typically derived from extracellular recordings obtained by using microelectrodes. This approach provides high spatial resolution, but probes an extremely sparse sample of the neuronal population even when using mod-

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ern multi-electrode equipment (Bartho et al., 2004; Buzsaki, 2004).

However, the extracellular signal contains additional information that may be used to bridge the gap between these two extreme approaches and provide multi-scale functional organization information.

The signal picked up by the electrode in the extracellular medium is a summation of a variety of signals derived from many processes and neural elements. These signals include dipoles generated among others by spiking activity (Rall, 1962), postsynaptic potentials (Mitzdorf, 1985) and fluctuations in the membrane voltage (Pedemonte et al., 1998; Goto and O'Donnell, 2001). Spiking activity is reflected primarily in high-frequency changes in the signal (typically >300 Hz), therefore it can be extracted from the raw recorded extracellular signal by a high-pass filter with a cutoff frequency in this range. This time series, termed multi-unit activity (MUA), is the summation of the action potentials of multiple neurons that are in close proximity to the recording electrode. It is based on the principle that the high-frequency spiking signal decays rapidly over distance (Legatt et al., 1980). The distance over which spiking activity may be distinguished from background activity (the summation of more distant neurons) depends on the size and shape of the neurons and on properties of the recording electrode, but is generally on the order of 100–300 μm (Grover and Buchwald, 1970; Henze et al., 2000). The extracellular spike reflects the intracellular action potential but its shape is dependent on multiple properties of the neuron (such as channel concentration, dendritic tree structure) and the location of the electrode relative to the neuron (Henze et al., 2000; Gold et al., 2006).

The activity of individual neurons may be extracted from the MUA and transformed into multiple point processes, where each of the time series represents a separable single-unit spike train (SU-ST) or a non-separable multi-unit spike train (MU-ST). In other words, whereas the MUA is a time series of the sampled and filtered signal representing the overall activity recorded extracellularly from nearby neurons, the MU-ST is a set of point processes which represent spike times of multiple units. Research on the properties of spike trains such as rate, synchronization and patterns has played a major role in furthering our understanding of neuronal processing (Abeles, 1991). The MUA is made up of spiking activity of large or nearby neurons that can be transformed into spike trains (either SU-ST or MU-ST), and background unit activity (BUA). The BUA represents smaller sub-noise level spikes generated by the surrounding neuronal population. By separating the BUA from the MUA small and local neuronal populations can be studied without the bias of larger dominant spikes (Moran et al., 2008).

The low-frequency (typically <300 Hz) changes in the extracellular signal recorded by the microelectrode are termed the local field potential (LFP). This signal is derived from multiple slower processes and is less attenuated over large distances because of its lower frequency. Thus, it can reflect remote processes in the range of 0.5–3.0 mm away from the microelectrode tip (Mitzdorf, 1987; Juergens et al., 1999). Historically, LFP was assumed to arise from excitatory and inhibitory postsynaptic potentials (Mitzdorf, 1985). The LFP was thought to reflect the summation of the input to the local network, as opposed to the MUA which represents the output of the local network (Freeman, 1975; Legatt et al., 1980). However, other slow processes contributing significantly to the LFP have been identified such as membrane oscillations (Pedemonte et al., 1998; Goto and O'Donnell, 2001) and spike hyperpolarization (Buzsaki, 2002). The relationship between the LFP and the various representations of spiking information is complex. In some cases there is significant mutual information between spiking activity and the LFP recorded on the same electrode (Rasch et al., 2008). Other behavioral events can be reflected in only one of the signals, either in the LFP or in the spiking activity (Buchwald et al., 1965).

Periodic oscillations play a cardinal role in the normal function of the nervous system (for a review see Engel et al., 2001; Hutchison et al., 2004; Buzsaki and Draguhn, 2004). Early studies suggested that the oscillatory electroencephalogram (EEG) reflected behavioral states of the brain (Adrian and Matthews, 1934; Brazier, 1949). More recently, oscillations have been identified in different brain areas in the LFP (Bragin et al., 1995; Murthy and Fetz, 1996; Brown and Williams, 2005), MUA (Gray and Singer, 1989; Eeckman and Freeman, 1990), and spike trains (Baker et al., 2003; de Solages et al., 2008). In addition to their normal expression, pathological oscillations have also been found in several cognitive and motor disorders such as epilepsy (Bragin et al., 2002), essential tremor (Halliday et al., 2000; Deuschl and Bergman, 2002), and Parkinson's disease (PD) (Lenz et al., 1988; Bergman et al., 1994; Levy et al., 2002; Brown, 2003).

In this manuscript we present a data analysis method which utilizes the differential manifestation of oscillations in different extracellular signals. This method may be used to shed light on the functional organization of multiple scales of the environment surrounding the microelectrode. A specific implementation of a subset of this analysis method has recently been used by us to characterize the local functional organization of the subthalamic nucleus in Parkinson's disease patients (Moran et al., 2008). The methodology presented below describes the general framework and demonstrates its use on both simulated and experimental data. This broad approach enables the deployment of the techniques on diverse neurophysiological signals recorded in different brain structures during diverse experimental paradigms.

2. Methods

2.1. Animal recordings

The neuronal recordings are from a Cynomologus monkey (*Macaca fascicularis*, male, 4 kg), that underwent 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) injections leading to a Parkinsonian state. All procedures were in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and Bar Ilan University Guidelines for the Use and Care of Laboratory Animals in Research and were approved and supervised by the Institutional Animal Care and Use Committee (IACUC). Full details of the experimental protocol appear elsewhere (Erez et al., 2009). Briefly, data were acquired via multiple microelectrodes extended to different nuclei of the basal ganglia through a recording chamber. Extracellular recording was performed via glass-coated tungsten microelectrodes (impedance, 0.25–0.7 MΩ at 1 kHz). The electrode signal was amplified with a gain of 1000 and band-pass filtered with a 2–8000 Hz four-pole Butterworth filter (MCP+ 4.10, Alpha–Omega Engineering, Nazareth, Israel). The signal was continuously sampled at 40 kHz with 14-bit resolution (Alphamap 10.10, Alpha–Omega Engineering) yielding a ~0.5 μV recording amplitude resolution. The continuous digitized signal was later sorted offline (OFS-2.8.4, Plexon, Dallas, TX) to produce SU-STs.

2.2. Simulations

Following earlier work by Zeitler et al. (2006), we constructed a simulated leaky integrate-and-fire (LIF) neuronal environment with partially correlated input. The environment was expanded to control the phase of the correlated oscillatory common drive. Three main components were defined for the single neuron model: (1) The LFP, which forms the total input to the neuron (Fig. 1A,