Journal of Neuroscience Methods 253 (2015) 1–9

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

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

Computational neuroscience

Near-field electromagnetic holography for high-resolution analysis of network interactions in neuronal tissue

Henrik D. Kjeldsen[a,b], Marcus Kaiser[b], Miles A. Whittington[c,*]

[a] University of Newcastle, Institute of Neuroscience, Framlington Place, Newcastle upon Tyne NE2 4HH, UK
[b] University of Newcastle, School of Computing Science, Interdisciplinary Computing and Complex BioSystems Research Group, Claremont Tower, Newcastle upon Tyne NE1 7RU, UK
[c] University of York, Hull York Medical School, York YO10 5DD, UK

HIGHLIGHTS

- We developed a method to estimate electromagnetic field vectors from microelectrode array data.
- The vectors allow high-resolution holographic reconstruction of spatiotemporal activity.
- Separation of electromagnetic source density and dissipation informs on activity structure.
- Electromagnetic flow maps quantify dynamic causal interactions in brain tissue.

ARTICLE INFO

Article history:
Received 20 October 2014
Received in revised form 28 April 2015
Accepted 21 May 2015
Available online 28 May 2015

Keywords:
Electromagnetic field
Holography
Microelectrode array
Dynamic causal interactions

ABSTRACT

Background: Brain function is dependent upon the concerted, dynamical interactions between a great many neurons distributed over many cortical subregions. Current methods of quantifying such interactions are limited by consideration only of single direct or indirect measures of a subsample of all neuronal population activity.

New method: Here we present a new derivation of the electromagnetic analogy to near-field acoustic holography allowing high-resolution, vectored estimates of interactions between sources of electromagnetic activity that significantly improves this situation. In vitro voltage potential recordings were used to estimate pseudo-electromagnetic energy flow vector fields, current and energy source densities and energy dissipation in reconstruction planes at depth into the neural tissue parallel to the recording plane of the microelectrode array.

Results: The properties of the reconstructed near-field estimate allowed both the utilization of super-resolution techniques to increase the imaging resolution beyond that of the microelectrode array, and facilitated a novel approach to estimating causal relationships between activity in neocortical subregions.

Comparison with existing methods: The holographic nature of the reconstruction method allowed significantly better estimation of the fine spatiotemporal detail of neuronal population activity, compared with interpolation alone, beyond the spatial resolution of the electrode arrays used. Pseudo-energy flow vector mapping was possible with high temporal precision, allowing a near-realtime estimate of causal interaction dynamics.

Conclusions: Basic near-field electromagnetic holography provides a powerful means to increase spatial resolution from electrode array data with careful choice of spatial filters and distance to reconstruction plane. More detailed approaches may provide the ability to volumetrically reconstruct activity patterns on neuronal tissue, but the ability to extract vectored data with the method presented already permits the study of dynamic causal interactions without bias from any prior assumptions on anatomical connectivity.

1. Introduction

Neuronal function, from an electrical point of view, originates from the control and utilisation of current flow across biological membranes. A myriad of different proteins are incorporated into membranes to create a baseline 'set point' for neuronal membrane

* Corresponding author. Tel.: +44 1904 328755.
E-mail addresses: hkjeldsen@gmail.com (H.D. Kjeldsen), marcus.kaiser@newcastle.ac.uk (M. Kaiser), miles.whittington@hyms.ac.uk (M.A. Whittington).

http://dx.doi.org/10.1016/j.jneumeth.2015.05.016

current flow and provide an incredibly rich diversity of magnitudes and kinetics of deviations from this. These currents can be quantified directly in individual neurons by invasive techniques utilising direct electrical access to the intracellular environment of individual – or small subsets of – neurons. However, neurons do not act alone: They are embedded in specific local and distributed networks allowing them to influence each other's activity and act in concert to represent external (sensory) events and generate appropriate, patterned outputs (motor).

It is increasingly evident that cortical activity at the level of interacting populations of neurons holds the key to understanding brain function (Wetzel and Stuart, 1976). Therefore, in considering population-level neural behaviour one must consider interaction across the whole neuropil and whatever reciprocal, synaptic interactions with neurons emerge from this (Mitzdorf and Singer, 1979). However, there are two additional fates for the energy associated with changes in neuronal transmembrane current flow: First, changes in charge distribution across membranes lead to electrical potential energy changes organised spatially within the extracellular environment (the local field potential, LFP). These fields can feed-back to influence neuronal activity directly (Taylor and Dudek, 1984); Secondl, the same transmembrane charge distribution changes can give rise to magnetic fields. While these are much weaker than the electric fields they may also feedback to influence neuronal transmembrane current, at least over very short distances (McLean et al., 1995), unless fields are artificially large (Houpt et al., 2003).

In attempting to further understand the entirety of the electromagnetic interactions between brain regions, and link this to the causal dynamics of the system we noticed that similar problems have been addressed in acoustic imaging, specifically in near-field acoustic holography (NAH) (Maynard et al., 1985; Thomas et al., 2010). We therefore set out to explore whether analogies between acoustics and electromagnetics could be used to generalize this technique to the neuro-electromagnetic case, i.e. to near-field electromagnetic holography (NEH). The idea of NEH goes further than considering the activity recorded in electrodes used to study neuronal populations: By considering recorded activity as a map of the electromagnetic interference between signals originating from a set of sources an estimate of these original sources can be reconstructed via holographic methods. This method has potential advantages over existing source localisation methods for neural electrical activity. Whilst this approach has been shown to be valid for a few coexistent sources (Alqadah et al., 2014) it needs to be applied to sensory (microelectrode) arrays to be useful in localising and characterising the many multiples of activity sources that typify population neuronal activity. For example, conventional current source density (CSD) estimates map the origin of activity by considering only the *average* of sources in a given locale. In contrast, a holographic reconstruction, by being dependent on interference between sources may not suffer as much from this inherent averaging effect—thus a greater spatial resolution of multiple source structures should be possible (see Maynard et al., 1985).

In addition, source reconstruction using acoustic holography works through the reconstruction of acoustic energy flow (Hald, 2001). The electromagnetic analogy of this is the Poynting vector, where the scalar is the electromagnetic energy flux density and the direction represents the flow from source to sink. That is for a given source region the vector points in the direction of the mean, largest recipient of the electromagnetic energy estimated (Williams and Maynard, 1980). Considering that causal effects of one population of neurons on another must reasonably be carried by physical energy flow, whatever the conduit, we propose that electromagnetic energy flow vectors can be used to infer causal effects in neural tissue with fewer of the biological and statistical assumptions required for methods used presently.

However, for accurate reconstruction of sources nearfield holography requires back-propagation of recorded signals through a homogeneous, source-free medium (i.e. no additional sound or electromagnetic generators between the electrode array and the reconstruction plane of interest (Valdivia and Williams, 2007)). While compensation for lack of homogeneity can improve CSD estimates of electrical sources (Łęski et al., 2011), it forms a major problem with acoustic sources (Williams and Valdivia, 2010; Bi et al., 2015). This suggests a uniquely appropriate application for NEH on cortical tissue: Brain electromagnetic sources have no 'physical' structure in the sense that they do not overtly modify the signal conduction properties of the medium unless they become excessive (for example in epilepsy). Resistivity in neuronal tissue *does* change with activity, but with a relatively slow timeconstant (5–10 s, Fox et al., 2004; Lopez-Aguado et al., 2001)—far slower than even the slowest brain activity studied with conventional EEG and local field potential recordings. In addition, permittivity has been shown not to change at all during intense periods of electrical activity (Yoon et al., 1999).

The problem of holographic reconstruction in media with multiple sources requires inhomogeneous wave equations to be used to reach a precise, accurate answer. While this approach works numerically with known additional sources this luxury is not afforded by studies of brain tissue: here each microscopic component of the neuropil may constitute a source at any given time. The down-side of this is that any reconstruction will only ever reflect an *estimate* of the true nature of sources present. On the other hand, the ubiquitous, distributed nature of additional sources provides a blanket 'forcing' of the wave equations required. As a consequence the holographic reconstruction becomes probabilistic, with only the largest, most spatially focal sources of activity surviving the process. An additional implementation problem arises owing to the fact that the electrode arrays used for invasive recording are effectively embedded within such a heterogeneous, spatially-distributed source. This invalidates the use of holographic reconstruction in terms of providing *absolute* physical quantities such as electric and magnetic fields. However, the use of estimates of orthogonal partners to the measured electrical field (the estimated magnetic field) still provides a valid means to vectorise the activity present and therefore attempt to improve spatial resolution of source distribution through NEH. Thus the myriad potential sources present in active neuronal tissue, and the relatively static, homogeneous nature of the transmission properties of neuropil (even with active sources) on physiologically relevant timescales suggests that NEH may provide an improved means to estimate spatiotemporal activity patterns in the brain.

Here we test this hypothesis and present a method for analysing extracellular microelectrode array recordings. We utilise the Poynting vector to estimate the electromagnetic energy transfer per unit area of neuronal tissue. In doing so we are able to consider a direct analogy of current source density—the *electromagnetic energy source density* alongside *electromagnetic energy dissipation* (the proportion of charge distribution that is dissipated rather than contributing to the magnetic field) to provide a 'super-resolution' estimate of energy flow between brain sub-regions as a vector. We test this method by demonstrating the improved spatial detail and highly directional behaviour of a known, highly laminarly organised spatiotemporal dynamic phenomenon—the sleep-associated slow wave oscillation in an in vitro experimental model.

2. Methods

NAH typically involves the use of planar arrays of microphones (Paillasseur et al., 2011). For an implementation with electromagnetic sources from brain tissue the following precedented analogies