Journal of Neuroscience Methods 213 (2013) 43–62

Contents lists available at SciVerse ScienceDirect

Journal of Neuroscience Methods

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

Computational Neuroscience

A procedure for testing across-condition rhythmic spike-field association change

Kyle Q. Lepage [a,*], Georgia G. Gregoriou [b,c], Mark A. Kramer [a], Mikio Aoi [a], Stephen J. Gotts [d], Uri T. Eden [a], Robert Desimone [e]

[a] Boston University, Department of Mathematics & Statistics, Boston, MA, USA
[b] University of Crete, Faculty of Medicine, Department of Basic Sciences, FORTH, Crete, Greece
[c] Institute of Applied and Computational Mathematics, FORTH, Crete, Greece
[d] Laboratory of Brain & Cognition, National Institute of Mental Health, Bethesda, MD, USA
[e] McGovern Institute, Department of Brain & Cognitive Sciences, Massachusetts Institute of Technology, Boston, MA, USA

HIGHLIGHTS

- ► A statistical methodology is introduced capable of studying changes in the coupling between rhythmic local field potential (LFP) and neural spiking times.
- ► The methodology successfully deals with a problematic confounding factor present in more standard analyses based upon spike-field coherence.
- ► The method is capable of studying both per-frequency modulatory effects as well as the tendency of spiking to occur at a specific phase of a sinusoidal (LFP) rhythm.
- ► The method is effective both in simulation and when analyzing real data.

ARTICLE INFO

Article history:
Received 11 August 2012
Received in revised form 19 October 2012
Accepted 19 October 2012

Keywords:
Oscillations
Rhythms
Local field potential
Spikes
Statistical association
Hypothesis testing
coherence
Spike-field coherence
Generalized linear model
Point process

ABSTRACT

Many experiments in neuroscience have compared the strength of association between neural spike trains and rhythms present in local field potential (LFP) recordings. The measure employed in these comparisons, "spike-field coherence", is a frequency dependent measure of linear association, and is shown to depend on overall neural activity (Lepage et al., 2011). Dependence upon overall neural activity, that is, dependence upon the total number of spikes, renders comparison of spike-field coherence across experimental context difficult. In this paper, an inferential procedure based upon a generalized linear model is shown to be capable of separating the effects of overall neural activity from spike train-LFP oscillatory coupling. This separation provides a means to compare the strength of oscillatory association between spike train-LFP pairs independent of differences in spike counts.

Following a review of the generalized linear modelling framework of point process neural activity a specific class of generalized linear models are introduced. This model class, using either a piece-wise constant link function, or an exponential function to relate an LFP rhythm to neural response, is used to develop hypothesis tests capable of detecting changes in spike train-LFP oscillatory coupling. The performance of these tests is validated, both in simulation and on real data. The proposed method of inference provides a principled statistical procedure by which across-context change in spike train-LFP rhythmic association can be directly inferred that explicitly handles between-condition differences in total spike count.

1. Introduction

Many experiments in neuroscience (Fries et al., 2001, 2008; Womelsdorf et al., 2006; Witham et al., 2007; Pesaran et al., 2008; Gregoriou et al., 2009; Jutras et al., 2009; Chalk et al., 2010) have compared the strength of association between the times at which neurons fire and rhythms present in local field potential (LFP) recordings. A measure of association employed in these studies is the "spike-field coherence", a frequency dependent measure of linear association between a point process and a continuous valued LFP signal. Spike-field coherence is shown to respond to overall neural spiking activity (Lepage et al., 2011), making comparison between two pairs of spike-field time series difficult when the average spike-rate differs in the two spike-field pairs.

Existing approaches to dealing with this confound include the employment of neural rate-free measures of association and

* Corresponding author. Tel.: +1 6173531841.
E-mail addresses: lepage@math.bu.edu (K.Q. Lepage), gregoriou@med.uoc.gr (G.G. Gregoriou), mak@bu.edu (M.A. Kramer), mcaoi@bu.edu (M. Aoi), gottss@mail.nih.gov (S.J. Gotts), tzvi@bu.edu (U.T. Eden), desimone@mit.edu (R. Desimone).

0165-0270/$ – see front matter
http://dx.doi.org/10.1016/j.jneumeth.2012.10.010

transformation based techniques, such as neural spike thinning (Mitchell et al., 2009; Gregoriou et al., 2009), a procedure where the overall neural rates are made equal by randomly removing spikes. In this paper, an across-condition test is introduced based upon parametric modelling of the effect of the association of rhythms in field-type time series upon the intensity of the spiking process. By explicitly modelling the dependence of neural spiking activity upon both random, "background", influence and upon field-type rhythmic influence, the relative separation of these effects is made possible.

After a discussion of relevant background in Section 2, an hypothesis test directly comparing the nature of the association between pairs of neural spike times and LFP rhythms is introduced in Section 3. This test, based upon the generalized linear statistical neural modeling framework presented in Truccolo et al. (2005), uses all available data and accounts for differences in firing rate within the maximum likelihood statistical framework. The test provides a statistically principled approach to inferring differences in association across spike-LFP time-series pairs with different spiking rates. In Section 4, the test is demonstrated in simulation and in Section 5, the test is performed on real data. The paper ends with a discussion in Section 6.

2. Background

Coherence, analogous to cross-correlation in the time domain, is a theoretical quantity linking two time series in the frequency domain. Non-parametric coherence estimators are common and have been successfully employed in diverse sciences. In neuroscience, background material on field-field coherence (coherence between two field-type time-series) and spike-field coherence includes: Brillinger (1975), Brillinger (2001), Rosenberg et al. (1998), Halliday et al. (1995), Amjad et al. (1997), Jarvis and Mitra (2001), Mitra and Bokil (2008), and Lepage et al. (2011). Coherence in the neuroscience setting has been used to characterize neural population activity (Bullock et al., 1995; Towle et al., 1999; Zaveri et al., 1999; Bruns and Eckhorn, 2004; Kristeva et al., 2007; DeCoteau et al., 2007a,b; Montgomery and Buzsáki, 2007; Sirota et al., 2008; Bollimunta et al., 2008), and the relationship between neuron spiking and field potentials (spike-field coherence) (Fries et al., 2001, 2008; Womelsdorf et al., 2006; Witham et al., 2007; Pesaran et al., 2008; Gregoriou et al., 2009; Jutras et al., 2009; Chalk et al., 2010). The spike-field coherence, $C_{ny}(f)$, can be defined in a fashion analogous to the definition of the "field–field", or more standard coherence between random processes modelling field-type recordings. This definition, discussed in more detail in Lepage et al. (2011), is summarized in the following. Let dn_t be the number of spiking events that occur in the time interval, $[(t-1)\Delta, t\Delta)$. Here Δ is the time between field measurements, and t is the time-index associated with the tth bin. The collection of these counts is a time-series and can be usefully modelled as a truncated realization[1] of a discrete-time point process, $\mathbf{dn}$. Here, dn_t, is the tth element of $\mathbf{dn}$, and is a random variable whose realization is the number of spiking events that occur in the interval $[(t-1)\Delta,\ t\Delta)$. To avoid multiple events in an observation interval, Δ is chosen sufficiently small such that the probability of multiple spiking events in any one observation interval is negligibly small. Note that this is possible for single neuron recordings due to the refractory period immediately following a neuron spiking event. During this refractory period, subsequent neuron spiking is greatly suppressed (Koch, 1999). A point process is completely characterized by its conditional intensity, Λ_t,

$$\Lambda_t = \lim_{\Delta \to 0} \frac{P(dn_t = 1|H_t)}{\Delta}, \tag{1}$$

where H_t is the spike history process (Daley and Vere-Jones, 2003). Intuitively, the probability of an event at time t equals $\Delta \cdot \Lambda_t$, up to negligible corrections due to the small non-zero probability of multiple events in any one increment (Daley and Vere-Jones, 2003). When the increments, dn_t, do not depend on either past or future increments, the point process is called Poisson, and the conditional intensity, Λ_t, is equal to the rate of occurrence of spiking events. While sometimes convenient, this model is physiologically inaccurate due to dependence on past spiking. As described in Lepage et al. (2011), a spike-field coherence consistent with the more standard field–field coherence is defined in terms of weak-sense stationary random processes. Thus, the first two moments of dn_t must be independent of absolute time. Time-dependent firing activity, while maintaining stationary first and second moments can be attained by generalizing the discrete-time point-process to a doubly-stochastic discrete-time point process. That is, let the conditional intensity, Λ_t, be itself a weak-sense stationary random process such that $\Lambda_t \geq 0$. With this stipulation, both the point process modeling the spikes and the intensity, which determines the probability of a spike in each time-step, are both random processes. Let the centered increments of the discrete-time point process, dn_t be $d\tilde{n}_t$ such that,

$$d\tilde{n}_t = dn_t - E\{dn_t\}, \tag{2}$$

where E denotes the expectation operator. This ensures that $E\{d\tilde{n}_t\} = 0$. In analogy with the standard discrete-time Fourier transform, define the discrete-time Fourier transform of the centered increments, $d\tilde{n}_t$, evaluated at frequency f, as,

$$N_T(f) = \frac{\Delta}{T} \sum_{t=0}^{N-1} e^{-i2\pi ft\Delta} d\tilde{n}_t. \tag{3}$$

Here T is the duration of the time-series and Δ is the duration between samples. Let the local-field potential recording be represented by the weak-sense stationary random process y_t, with an associated discrete-time Fourier transform, $Y_T(f)$,

$$Y_T(f) = \frac{\Delta}{T} \sum_{t=0}^{N-1} e^{-i2\pi ft\Delta} y_t. \tag{4}$$

The spike-field coherence between the spiking and the local-field potential, $C_{\tilde{n}y}(f)$, is

$$C_{\tilde{n}y}(f) = \lim_{T \to \infty} \frac{E[N_T(f) Y_T^*(f)]}{\sqrt{E[|N_T(f)|^2] E[|Y_T(f)|^2]}}. \tag{5}$$

If the relevant spectra exist, Eq. (5) can be re-written,

$$C_{\tilde{n}y}(f) = \frac{S_{\tilde{n}y}(f)}{\sqrt{S_{\tilde{n}\tilde{n}}(f) S_{yy}(f)}} \tag{6}$$

where $S_{\tilde{n}y}(f)$ is the cross-spectrum between $d\tilde{n}_t$ and y_t, $S_{\tilde{n}\tilde{n}}(f)$ is the spectrum of $d\tilde{n}_t$ and $S_{yy}(f)$ is the spectrum of y_t. Through the Cauchy–Schwartz inequality, $0 \leq |C_{\tilde{n}y}(f)| \leq 1$ and $|C_{\tilde{n}y}(f)| = 1$ when there is a linear relation between $N_T(f)$ and $Y_T(f)$.

[1] Random processes which begin and end are not weak-sense stationary. That is, the dependence changes at the beginning and end of the random process and hence there is dependence on absolute time. Actual recordings begin and end, and are typically handled by realizing an infinite time-series and then truncating this realization to the recording duration.