Journal of Neuroscience Methods 269 (2016) 21–32

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

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

Bayesian methods for event analysis of intracellular currents

Josh Merel[a,b,*,1], Ben Shababo[c,1], Alex Naka[c], Hillel Adesnik[c,d], Liam Paninski[a,b,e,f]

[a] Neurobiology and Behavior Program, Columbia University, United States
[b] Center for Theoretical Neuroscience, Columbia University, United States
[c] Helen Wills Neuroscience Institute, University of California, Berkeley, United States
[d] Department of Molecular and Cellular Biology, University of California, Berkeley, United States
[e] Department of Statistics, Columbia University, United States
[f] Grossman Center for the Statistics of Mind, Columbia University, United States

HIGHLIGHTS

- We present a Bayesian approach for automatic event analysis.
- The method was designed and validated for voltage-clamp recordings.
- The method outperforms existing methods on simulated and real data.
- We demonstrate extensions useful for synaptic mapping experiments.

ARTICLE INFO

Article history:
Received 22 March 2016
Received in revised form 13 May 2016
Accepted 16 May 2016
Available online 18 May 2016

Keywords:
Event detection
Postsynaptic current
Calcium imaging
Connectivity mapping
Bayesian methods
MCMC

ABSTRACT

Background: Investigation of neural circuit functioning often requires statistical interpretation of events in subthreshold electrophysiological recordings. This problem is non-trivial because recordings may have moderate levels of structured noise and events may have distinct kinetics. In addition, novel experimental designs that combine optical and electrophysiological methods will depend upon statistical tools that combine multimodal data.
New method: We present a Bayesian approach for inferring the timing, strength, and kinetics of post-synaptic currents (PSCs) from voltage-clamp electrophysiological recordings on a per event basis. The simple generative model for a single voltage-clamp recording flexibly extends to include additional structure to enable experiments designed to probe synaptic connectivity.
Results: We validate the approach on simulated and real data. We also demonstrate that extensions of the basic PSC detection algorithm can handle recordings contaminated with optically evoked currents, and we simulate a scenario in which calcium imaging observations, available for a subset of neurons, can be fused with electrophysiological data to achieve higher temporal resolution.
Comparison with existing methods: We apply this approach to simulated and real ground truth data to demonstrate its higher sensitivity in detecting small signal-to-noise events and its increased robustness to noise compared to standard methods for detecting PSCs.
Conclusions: The new Bayesian event analysis approach for electrophysiological recordings should allow for better estimation of physiological parameters under more variable conditions and help support new experimental designs for circuit mapping.

1. Introduction

Subthreshold neuronal activity provides an unsurpassed richness of information about a single cell's physiological properties. Access to subthreshold activity allows for inference about intrinsic biophysical properties (e.g. membrane and ion channel parameters), circuit level properties (e.g. synaptic connectivity), neural coding (e.g. receptive fields), and synaptic properties (e.g. quantal properties and plasticity). At present, whole-cell patch-clamp stands alone in its ability to reliably access subthreshold activity owing to excellent signal-to-noise ratio (SNR) and very high temporal precision, as opposed to optical subthreshold measurements. At the same time, optical technologies have advanced to the point where we can observe the suprathreshold activity of hundreds of

* Corresponding author at: Neurobiology and Behavior Program, Columbia University, United States
E-mail address: jsmerel@gmail.com (J. Merel).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.jneumeth.2016.05.015
0165-0270/

individual neurons simultaneously with calcium imaging and stimulate neurons by subtype or spatial location (Rickgauer et al., 2014). However, the limits on temporal resolution and the indirectness of the observations make inferring fine-scale network and cellular parameters difficult. Approaches which combine optical tools with electrophysiology offer unique advantages (Scanziani and Häusser, 2009). In this work, we present new statistical techniques useful for analyzing whole-cell data as well as extensions demonstrating how our approach is particularly well-suited to settings where electrophysiology is combined with optical physiology.

1.1. Our setting and approach

Fundamentally, many of the subthreshold-based analyses mentioned above depend on the interpretation of the recorded time series as a sequence of *events*. In this setting, events are the successful transmission of neurotransmitter onto the recorded cell, and when this occurs, a transient current flows into or out of the cell, known as a postsynaptic current (PSC). The analyses of experiments designed to infer properties of evoked or spontaneous inputs to a cell (e.g. monosynaptic mapping or quantal/mini-PSC analyses) require determining when a postsynaptic event happened and describing that event. Estimating PSC properties is most straightforward when recordings are acquired using the voltage-clamp configuration which employs a feedback circuit to hold the membrane potential at a constant value thus mitigating variability in PSC properties due to the intrinsic biophysics of the cell (though see Bar-Yehuda and Korngreen, 2008).

In this work, we present a Bayesian approach for inferring the timing, strength, and kinetics of postsynaptic currents from voltage-clamp recordings, and we demonstrate on simulated and real data that this method performs better than standard methods for detecting PSCs. The improvement in single-trial accuracy with our method should allow for better estimation of physiological parameters with less data and under more variable conditions (e.g. when the exact timings of stimuli or its effects are unknown). In addition, the quantification of uncertainty over PSC features provided by Bayesian inference enables new experimental designs (e.g. Shababo et al., 2013).

Bayesian approaches are naturally extensible, so the intuitive, generative model and straightforward inference procedure flexibly extend to include structure relevant to the analyses mentioned above. Specifically, we extend the core single-trial model to include types of data obtained in monosynaptic mapping experiments which may involve optical stimulation artifacts or combine voltage-clamp recordings and optical recordings. For this latter extension, we combine the single trace model presented in this work with related work on calcium imaging (Pnevmatikakis et al., 2013) to demonstrate a Bayesian approach to analyzing mapping experiments consisting of simultaneous population calcium imaging and single cell voltage-clamp recordings (Aaron and Yuste, 2006).

1.2. Review of other approaches

To the best of our knowledge, all previous methods for inferring PSCs have relied on first inferring the timing of single events (i.e. event onsets), and then sometimes fitting per-event kinetics given that event time. These methods have tended to fall into two categories. The superficially simpler of the two approaches is to find events by thresholding the trace or its first derivative (i.e. finite difference). In practice, such methods have extra parameters for smoothing, computing the appropriate offset, or post-processing. Implementations tend to over-detect candidate events and then evaluate candidates based on analysis of per event kinetics (Jonas et al., 1993; Ankri et al., 1994; Hwang and Copenhagen, 1999; Kudoh and Taguchi, 2002). For concreteness, consider a two-stage approach wherein a threshold is used to identify initial candidates, and then a model is fit to the transient dynamics in order to confirm or reject candidate events by comparison of the parameters of the dynamics against pre-determined criteria (Ankri et al., 1994). Even with post-processing, such methods can be non-selective and tend not to exploit all of the available information (i.e. the transient dynamics are not used to detect the events initially).

Threshold methods have been largely superseded by the second class of approaches, template-based methods (Clements and Bekkers, 1997; Pernía-Andrade et al., 2012). In these methods, templates are usually learned by averaging event-responses collected by a simpler method (e.g. thresholding and/or hand-curation). While template methods are straightforward, initial attempts to apply these methods failed when the amplitude of the events varied or where events overlapped – both common scenarios. The first commonly used algorithm for PSC detection that attempted to avoid issues related to amplitude variability introduced the idea of rescaling a fixed template at each time step (Clements and Bekkers, 1997). Following this trend, template-matching approaches have gradually shifted towards deconvolution methods, which are a more well-founded way to use templates (Pernía-Andrade et al., 2012). Deconvolution generally refers to methods that assume the observed trace is the result of convolving a template with unobserved events (of varying amplitude), and such methods invert this model to estimate the times from the template. Both of these template-based methods produce inferred events with different amplitudes and a threshold can then be used to screen out small events (see Guzman et al. (2014) for a Python implementation of Clements and Bekkers (1997) and Pernía-Andrade et al. (2012), and see Richardson and Silberberg (2008) for deconvolution of current clamp traces).

Methods that rely on fixed-shape templates can work very well when the shape of the event is consistent across events, but postsynaptic events can vary in shape and amplitude, especially for events from different pre-synaptic sources due to different dendritic filtering, issues with space-clamp, or different receptor subunit distributions. Indeed, a core rationale behind the initial preference for threshold based approaches was the recognition that events may vary too much for a single template. While it is possible to use approaches that employ multiple templates (Li et al., 2007; Shi et al., 2010), there are still potential issues related to the stage-wise separation between learning the template and subsequent detection causing a sub-optimal use of information.

We take a Bayesian approach, rooted in a probabilistic, generative model. Broadening the taxonomy, this approach is a type of deconvolution method. However, we do not consider a single template (or a handful of templates), but instead a distribution over templates through the use of prior distributions on the kinetics and amplitudes of individual PSCs. Importantly, we also model event timing in continuous time (i.e. without binning), and we incorporate an autocorrelated, AR(p) noise process (Chib and Greenberg, 1994), which provides a more accurate description of the data. This leads to more precise detection of event times and inference that is more robust (i.e. less susceptible to noise). As such, our inference better leverages all available information (i.e. all events and full timecourse of each event). Given this probabilistic formulation of the noise process and the inclusion of priors on the PSC features, we can then perform posterior inference in this model using Markov chain Monte Carlo (MCMC, see Section 2).

A tradeoff is that the proposed approach is more computationally intensive than previous approaches. Nevertheless, we believe the flexibility and robustness that this approach affords makes up for this in many settings. Beyond handling overlapping events and variation in the shape of events, our method inherits advantages of probabilistic modeling. The method is extensible and amenable to serving as a modular component of hierarchical models, as we