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ROBUSTNESS, VARIABILITY, PHASE DEPENDENCE, AND LONGEVITY OF INDIVIDUAL SYNAPTIC INPUT EFFECTS ON SPIKE TIMING DURING FLUCTUATING SYNAPTIC BACKGROUNDS: A MODELING STUDY OF GLOBUS PALLIDUS NEURON PHASE RESPONSE PROPERTIES

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Abstract—A neuron's phase response curve (PRC) shows how inputs arriving at different times during the spike cycle differentially affect the timing of subsequent spikes. Using a full morphological model of a globus pallidus (GP) neuron, we previously demonstrated that dendritic conductances shape the PRC in a spike frequency-dependent manner, suggesting different functional roles of perisomatic and distal dendritic synapses in the control of patterned network activity. In the present study we extend this analysis to examine the impact of physiologically realistic high conductance states on somatic and dendritic PRCs and the time course of spike train perturbations. First, we found that average somatic and dendritic PRCs preserved their shapes and spike frequency dependence when the model was driven by spatially-distributed, stochastic conductance inputs rather than tonic somatic current. However, responses to inputs during specific synaptic backgrounds often deviated substantially from the average PRC. Therefore, we analyzed the interactions of PRC stimuli with transient fluctuations in the synaptic background on a trial-by-trial basis. We found that the variability in responses to PRC stimuli and the incidence of stimulus-evoked added or skipped spikes were stimulus-phase-dependent and reflected the profile of the average PRC, suggesting commonality in the underlying mechanisms. Clear differences in the relation between the phase of input and variability of spike response between dendritic and somatic inputs indicate that these regions generally represent distinct dynamical subsystems of synaptic integration with respect to influencing the stability of spike time attractors generated by the overall synaptic conductance.

Key words: phase response curve (PRC), high conductance state, stochastic synaptic background, spike time attractor, dendrite, small-conductance calcium-activated potassium (SK).

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Abbreviations: cPRCs, cumulative phase response curves; GP, globus pallidus; PRC, phase response curve; PRVCs, phase response-variance curves; STN, subthalamic nucleus.

INTRODUCTION

Neurons *in vivo* are subjected to a constant barrage of excitatory and inhibitory synaptic inputs that are distributed throughout the neuronal morphology, thus putting the neuron in a state of high membrane conductance. Such high conductance states (Destexhe and Pare, 1999; Rudolph and Destexhe, 2001, 2003a,b; Destexhe et al., 2003) are capable of switching the class of excitability by which a neuron initiates action potentials (Hodgkin, 1948; Prescott et al., 2008), the resonant properties of a neuron (Fernandez and White, 2008), and can affect conductance-based mechanisms of synaptic integration (Rudolph and Destexhe, 2001).

In neuronal systems the phase response curve (PRC) describes how inputs to a neuron at different times during the spike cycle affect the timing of subsequent spikes (Winfree, 2001; Smeal et al., 2010; Schultheiss et al., 2012). Type I PRCs are composed predominantly of positive values indicating that depolarizing inputs nearly always advance the timing of the next spike, whereas type II PRCs contain a significant negative lobe indicating, paradoxically, that *excitatory* inputs can *delay* spiking when delivered at some phases (typically early phases) of the spike cycle. PRC shape is dependent on the species and spatial distribution of membrane currents that a neuron possesses (Gutkin et al., 2005; Goldberg et al., 2007; Stiefel et al., 2008, 2009; Schultheiss et al., 2010; Ermentrout et al., 2012; Schultheiss, 2012) as well as on the neuron's spike frequency (Gutkin et al., 2005; Schultheiss et al., 2010; Schultheiss, 2012), and PRC shapes reflect neuronal excitability dynamics (Hodgkin, 1948; Rinzel and Ermentrout, 1998; Brown et al., 2004) and modulation state (Stiefel et al., 2008, 2009; Stiefel and Gutkin, 2012). PRCs are also powerful and efficient predictors of patterned network behavior, and type II PRCs are typically well suited to support synchronization phenomena in coupled networks (Hansel et al., 1995; Ermentrout, 1996; Acker et al., 2003) and entrainment of spiking to fluctuating or oscillatory input patterns (Rinzel and Ermentrout, 1998; Galan et al., 2006, 2007a,b; Marella and Ermentrout, 2008; Abouzeid and Ermentrout, 2009). Weak-coupling within a neural network is only sufficient to achieve synchronization if the individual oscillators have similar frequencies (Ermentrout and Kopell, 1991; Dodla and Wilson, 2009), but strong-coupling can result in destabilization of phase-locked states under some conditions (Ermentrout and

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Kopell, 1991; Oh and Matveev, 2009). Furthermore, phase dependent variance in the PRC can affect the degree and stability of network synchrony (Ly and Ermentrout, 2010; Ermentrout et al., 2011). However, PRC analysis can be used to predict near synchronous states under strong-coupling conditions (Maran and Canavier, 2008), and synchronization resulting from type II phase response dynamics can generalize to the strong-coupling case (Bogaard et al., 2009). To date, the effects on PRCs of high conductance states and high spike time variability due to considerable synaptic input fluctuations characteristic of *in vivo* conditions have not been addressed.

In the present study we evaluated how high conductance states composed of fluctuating synaptic background activity influence the effects of additional single synaptic inputs on spike timing using measures of spike train perturbations, including PRCs, from simulations with different background characteristics and input locations. First, we extended our previous analysis of a morphologically reconstructed globus pallidus (GP) neuron model (Schultheiss et al., 2010) to address the consequences of high conductance states for neuronal PRCs. Having previously demonstrated that dendritic SK current can cause type II PRCs for dendritic inputs even when the somatic PRC is type I (Schultheiss et al., 2010; Schultheiss, 2012), we specifically investigated whether this mechanism can persist in the high-conductance state. Using average PRCs derived across many trials with each of several synaptic backgrounds spanning the physiological range, we tested how driving the model with stochastic spatially distributed conductance backgrounds, rather than with tonic somatic current, affects the shape and spike frequency dependence of somatic and dendritic PRCs.

In the second part of this study, we analyzed on a trial-by-trial basis how phasic synaptic input can perturb spike timing away from attractors generated by the stochastic background input patterns. To accomplish this we used several measures of spike timing perturbations including the incidence and phase dependence of added or skipped spikes elicited by PRC stimuli, the extent to which average PRCs were able to predict input effects in individual trials, i.e. PRC variance, and the longevity across spike cycles of perturbations of spike timing. Finally, we developed a new type of PRC plot, the cumulative PRC, for describing the phase response properties of neurons during high conductance states. The cumulative PRC captures how perturbations of spike timing evolve across subsequent spike cycles and distinguishes intrinsic effects from the effects of synaptic background activity.

EXPERIMENTAL PROCEDURES

All simulations were run using the GENESIS software platform (www.genesis-sim.org/GENESIS) on Emory University High Performance Compute Clusters (Sun Microsystems, Santa Clara, CA, USA). A fixed time step of 20 μs was used for all simulations using the implicit Crank–Nicholson integration method. Custom Matlab (The MathWorks, Natick, MA, USA) routines were used for analysis of voltage, current, conductance, and spike time data.

In order to address theoretical propositions from the PRC literature based largely on analyses of reduced models or experimental preparations under highly idealized circumstances, we incorporated considerable physiological realism both in the GP neuron model itself (Hanson et al., 2004; Gunay et al., 2008; Edgerton et al., 2010; Schultheiss et al., 2010; Edgerton and Jaeger, 2011) and in the synaptic backgrounds applied to it, as described in the following sections.

GP neuron model

Morphology and passive electrical properties. The morphology and passive electrical properties of the baseline model (GP_{base}) have been previously described in detail (Hanson et al., 2004; Gunay et al., 2008). In brief, using Neurolucida (MicroBrightField, Inc., Williston, VT, USA) we reconstructed the morphology of a GP neuron for which a battery of electrophysiological recordings had been made and created a GENESIS morphology file using CVAPP software (http://www.compneuro.org). Passive biophysical parameters of the model were set so that voltage responses to current injection stimuli reproduced those measured in the recorded neuron (Hanson et al., 2004). To allow axonal spike initiation and realistic axonal current sources and sinks, a standard axon consisting of a highly excitable axon initial segment and nodes of Ranvier separated by myelinated inter-node segments, was adapted from Shen et al. (1999) and attached to the soma (Gunay et al., 2008).

Active conductances and model tuning. One calcium-activated conductance, the small-conductance calcium-activated potassium current (SK), modeled using the Hill equation, and eight voltage-gated membrane conductances, modeled using the Hodgkin–Huxley formalism, were implemented in the model based on experimental evidence of their presence in GP neurons. The voltage-gated conductances include: fast-transient and persistent sodium currents, NaF and NaP; fast and slow delayed-rectifier (K_{dr}) potassium currents, K_V3 and K_V2; an A-type potassium current, K_V4; an M-type potassium current, KCNQ; the hyperpolarization-activated mixed cation current, or h-current; and a high-voltage-activated calcium current (Ca_{HVA}) representing a mixture of L-, N-, and P/Q-type currents and which acts as the calcium source for SK activation.

Each conductance was distributed uniformly throughout the dendrite with the exception of Ca_{HVA}, which had a greater density in thinner, distal dendritic compartments (Hanson and Smith, 2002). During the tuning process, conductance densities were determined using a semi-automated process comparing model behaviors with physiological recordings, and a thorough exploration of parameter space was performed (Gunay et al., 2008; Schultheiss et al., 2010). As described in our previous studies, GP_{base} sits within a wide parameter basin across which considerable parameter variations result in smoothly varying electrophysiological features and falls well within the physiological variability for the following electrophysiological measures: spontaneous spike waveform, spontaneous spike frequency, somatic FI curve, spike frequency adaptation, spike height attenuation during positive current steps, voltage 'sag' during negative current steps, and latency to the first spike following the offset of negative current steps. The full GENESIS model is available from ModelDB (http://www.senselab.med.yale.edu/ModelDB/). In order to specifically test the role of dendritic SK in shaping responses to phasic synaptic stimuli, we also generated a version of the model lacking dendritic SK conductance (GP_{NDSK}).

PRC analysis during high conductance states

Synaptic backgrounds. In order to generate spiking in the model that reproduced many of the essential features of GP neuronal activity *in vivo*, it was necessary to determine how synaptic background parameters influenced the frequency (Fig. 1) and regularity of spiking (Fig. 2). The synaptic backgrounds were composed of individual dual exponential conductance injections