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A stepwise neuron model fitting procedure designed for recordings with high spatial resolution: Application to layer 5 pyramidal cells

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HIGHLIGHTS

- New VSD and Ca^{2+}-imaging techniques allow high-resolution imaging of neurons.
- We present a stepwise model-fitting scheme with possibilities to apply to such data.
- We apply our method to simulated data to construct a reduced-morphology L5PC model.
- Our model is cost-efficient and reproduces the main features of the original model.
- Our model predicts that interconnected L5PCs can amplify low-frequency inputs.

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ABSTRACT

Background: Recent progress in electrophysiological and optical methods for neuronal recordings provides vast amounts of high-resolution data. In parallel, the development of computer technology has allowed simulation of ever-larger neuronal circuits. A challenge in taking advantage of these developments is the construction of single-cell and network models in a way that faithfully reproduces neuronal biophysics with subcellular level of details while keeping the simulation costs at an acceptable level.
New method: In this work, we develop and apply an automated, stepwise method for fitting a neuron model to data with fine spatial resolution, such as that achievable with voltage sensitive dyes (VSDs) and Ca^{2+} imaging.
Result: We apply our method to simulated data from layer 5 pyramidal cells (L5PCs) and construct a model with reduced neuronal morphology. We connect the reduced-morphology neurons into a network and validate against simulated data from a high-resolution L5PC network model.
Comparison with existing methods: Our approach combines features from several previously applied model-fitting strategies. The reduced-morphology neuron model obtained using our approach reliably reproduces the membrane-potential dynamics across the dendrites as predicted by the full-morphology model.
Conclusions: The network models produced using our method are cost-efficient and predict that interconnected L5PCs are able to amplify delta-range oscillatory inputs across a large range of network sizes and topologies, largely due to the medium after hyperpolarization mediated by the Ca^{2+}-activated SK current.

1. Introduction

Automated methods for neuron model fitting have replaced the need for manual tuning of model parameters (Van Geit et al.,

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2008). Due to the ease of their use, they could provide a solution for exploiting computational properties of single neurons and neural circuits (Markram et al., 2015). Novel algorithms and strategies for automated neuron model fitting have been proposed (Keren et al., 2005; Druckmann et al., 2007, 2011; Hendrickson et al., 2011; Bahl et al., 2012; Brookings et al., 2014; Rumbell et al., 2016). These methods span a wide range of types of neurons and their electrophysiological characteristics. Many of these strategies only use voltage traces recorded from the soma, while others rely on electrophysiological recordings at one or more additional dendritic locations in order to reproduce the correct membrane-potential dynamics distributed across the sub-cellular compartments. However, recording with multiple intracellular electrodes is an experimentally demanding procedure ultimately limited by the number of micromanipulators that can fit in a setup, the experimenter's skills, and integrity of the cell in the presence of multiple recording electrodes (Wang et al., 2015). By contrast, recent developments of optical imaging technologies and engineering of novel voltage-sensitive dyes (VSDs) and Ca^{2+} indicators have enabled high-resolution sampling of transmembrane voltage and intracellular Ca^{2+} concentration in single neurons with subcellular resolution (bel and Helmchen, 2007,1; Peterka et al., 2011; Hochbaum et al., 2014; Grienberger et al., 2015; Antic et al., 2016; Lou et al., 2016). In this work, we develop an automated, stepwise procedure for fitting a multicompartmental neuron model to data from somatic patch-clamp recordings in combination with VSD and Ca^{2+}-imaging data.

Interactions between synaptic inputs to the dendrites and firing of the soma are a hallmark of neural computation (Smith et al., 2013). This is especially true for L5PCs, which are characterized by a long apical dendrite that spans across cortical layers and receives inputs from various neuron populations in different parts of the dendritic tree (Larkum, 2013). The apical dendrite is rich in voltage-gated Ca^{2+} channels that contribute to the generation of a dendritic Ca^{2+} spike (Schiller et al., 1997). This Ca^{2+} spike plays an important role in integration of synaptic inputs to the apical tuft, communication of these signals to the soma, and coincidence detection in the form of the back-propagating action potential-activated Ca^{2+} spike (BAC) firing (Larkum, 2013). L5PCs express many types of voltage-gated ion channels (Korngreen and Sakmann, 2000; Christophe et al., 2005; Almog et al., 2009), and a number of computational models have been developed accounting for these biophysical properties (Keren et al., 2005, 2009; Bahl et al., 2012; Mainen and Sejnowski, 1996; Durstewitz et al., 2000; Hay et al., 2011; Almog and Korngreen, 2014). The multitude of types of voltage-gated ion channels, however, represents a challenge for modeling of the membrane-potential dynamics: unless specific care is taken, the role of a specific ion-channel species may be assigned to another ion-channel species when both conductances are fitted simultaneously, i.e., constrained by the same objective functions (Achard et al., 2006). To tackle this problem, in Keren et al. (2009), a parameter peeling experimental procedure was introduced, in which specific types of ion channels in L5PC are blocked sequentially using drugs, and the neuron response to different stimuli are recorded at each stage. The ion-channel conductances are then fitted step-by-step to these data. Another strategy was explored in Bahl et al. (2012), where experimental data from L5PCs with and without apical dendrite (occluded using a "pinching" method (Bekkers and Häusser, 2007)) were used during one of the three stages of fitting. In this case, the data for different stages of fitting were obtained from separate experiments. Both techniques facilitate the optimization procedure by reducing the number of free parameters that are fitted simultaneously.

Reduced-morphology models may be crucial in simulations of large networks due to the lighter computational load they impose. While the level of detail in the morphologies obtained from 3D reconstructions is high, the electrophysiological properties of the distal dendritic segments, as well as the heterogeneity of ion-channel populations between different dendritic branches, remain elusive (Häusser et al., 2000) and are generally not taken into account in the models. However, in many neuron types, dendritic electrophysiological properties vary monotonically with the distance from the soma (Migliore and Shepherd, 2002), which favors the use of simplified (yet multi-compartmental) morphologies. These simplified models should reproduce the experimentally observed properties of communication between perisomatic and (proximal to mid-distal) dendritic sections of the considered neuron while reducing the computational load in comparison to full-morphology models.

In this work, we use the experimentally validated model introduced in Hay et al. (2011) ("Hay model") to generate simulated VSD and Ca^{2+}-imaging data as well as simulated electrophysiological recordings in a L5PC. We simulate the parameter peeling procedure by sequentially setting channel conductances of different ion-channel species to zero in the Hay model and measuring the neuron responses to different stimuli under these blockades. We then fit the channel conductances in a four-compartment model to reproduce these data. We propose and apply a four-step scheme, where the three first steps utilize information on voltage and intracellular Ca^{2+} concentrations along the dendrites with high spatial resolution. The first step fits the parameters of reduced morphology, in a similar fashion as in Bahl et al. (2012), and parameters controlling passive membrane properties. The second step fits the non-specific ion-channel conductances. These are important for correctly describing the distal dendritic excitability. The third step fits the Ca^{2+} channel conductances and SK channel conductances and the parameters describing Ca^{2+} dynamics. The fourth step fits the rest of the active conductances, including the conductances responsible for the spiking behavior. We show that the obtained reduced-morphology L5PC model is cost-efficient and faithfully reproduces the membrane dynamics and spiking behavior, including the BAC firing. Furthermore, we test our method for fitting a neuron model with a full, reconstructed morphology, and find that acceptable fitting results are obtained also when using this complex dendritic morphology.

The obtained reduced-morphology model is especially useful in network simulations due to its lighter requirements of random access memory and computation time. We validated our model by introducing it in a biophysically detailed L5PC microcircuit model (Hay and Segev, 2015), which originally included the full-morphology Hay model neurons, and showing that the two models yielded similar network dynamics. Our circuit model of reduced-morphology L5PCs predicts that interconnected L5PCs amplify certain delta-range frequencies due to the large contributions of the Ca^{2+}-activated K^+ currents (SK currents) to the cell electrophysiology.

2. Materials and methods

2.1. The L5PC model

The Hay model of an L5PC, as well as the reduced-morphology model developed here, include the following ionic currents: fast inactivating Na^+ current (I_{Nat}), persistent Na^+ current (I_{Nap}), non-specific cation current (I_h), muscarinic K^+ current (I_m), slow inactivating K^+ current (I_{Kp}), fast inactivating K^+ current (I_{Kt}), fast non-inactivating K^+ current ($I_{Kv3.1}$), high-voltage-activated Ca^{2+} current (I_{CaHVA}), low-voltage-activated Ca^{2+} current (I_{CaLVA}), small-conductance Ca^{2+}-activated K^+ current (I_{SK}), and finally, the passive leak current (I_{leak}). The current balance equation of each segment