Interaction of segregated resonant mechanisms along the dendritic axis in CA1 pyramidal cells: Interplay of cellular biophysics and spatial structure

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Abstract

Neuronal frequency filters have implications for cognition and motor behavior. Mechanistically, neuronal filters at the network level are generated by the cooperative activity of the participating neurons and synaptic connectivity. Some of these exhibit filtering properties due to negative feedback effects produced by the participating ionic currents (subthreshold resonance), spike discretization (spiking resonance), and history-dependent process (e.g., short-term dynamics; synaptic resonance). The biophysical and dynamic mechanisms of generation of resonance at the single cell level are well understood. However, single-cell studies have mainly focused on point neurons and much little attention has been paid to the complex filtering properties emerging from spatial distribution of dendritic ionic currents, the interplay of the biophysical and dendritic geometric properties, and the preferred dendritic phase frequency responses. In this work, we investigate the dependence of the resonant (amplitude) and phasonant (phase) response properties on the dendritic spatial structure of neurons in the presence of realistic complex ionic current distributions leading to the type of segregated resonances observed in experiments. Our findings reveal a complex interplay between spatial structure and ionic mechanisms leading to a diversity of dendritic amplitude and phase filtering patterns that have implications for the response of neurons to spatially segregated inhibitory inputs arriving from different cell types and ultimately affecting cognitive behaviors.

Keywords: Resonance; phasonance; dendritic filter; neuronal filter; dendritic computation.

Introduction

The processing of synaptic information by neurons is shaped by their intrinsic properties and dendritic geometry, and it occurs in a frequency-dependent manner. *Subthreshold resonance* (STRes) and *phasonance* (STphas) refer to the ability of neurons to exhibit, respectively, a peak amplitude and a zero-phase (-shift) membrane potential response to oscillatory inputs at a preferred (resonant) frequency (Fig. 1) (Hutcheon & Yarom, 2000). STRres and STphas are generated by the interplay of negative and positive feedback effects provided by the participating ionic currents, can be inherited to higher levels of organization (Stark, Levi, & Rotstein, 2022; Richardson, Brunel, & Hakim, 2003; Rotstein, 2017; Hutcheon, Miura, & Puil, 1996), and can be affected by feedback effects and history-dependent process operating at the neuronal network level. Resonance has been proposed to play a key role in the frequency-specific information flow in neuronal networks and to contribute to the generation of brain rhythms , particularly the theta rhythm (4 - 12 Hz) (Buzsaki, 2006; Colgin, 2013; Wang, 2010; Stark et al., 2013).

While the ionic and dynamic mechanisms of generation of resonance in single neurons are well understood, less attention has been paid to the dependence of the resonant properties on the dendritic spatial structure of neurons, and how the interplay of the intrinsic neuronal low- and high-pass filters interact with the dendritic geometric properties to shape the neuronal band-pass filters.

Here, we focus on the dependence of the resonant properties on the dendritic spatial structure of neurons using CA1 pyramidal neurons (PYR) as a case study. We address the general questions of (i) how resonances are communicated along dendrites in the presence of heterogenous distributions of ionic currents and voltage heterogeneities along the cell, and (ii) how resonances generated by biophysically different, spatially segregated ionic mechanisms (Hu, Vervaeke, & Storm, 2002; Hu, Vervaeke, Graham, & Storm, 2009) interact under *in vivo*-like conditions. Understanding this is important because of the spatial segregation of inputs, particularly inhibitory inputs arriving the cell with different frequency content and targeting different portions of the cell's dendrites. Because PV+ interneurons target proximal dendrites (I_M-resonance), while OLM interneurons target distal cells (I_h-resonance) (Udakis, Pedrosa, Chamberlain, Clopath, & Mellor, 2020; Allen & Monyer, 2015; Leão et al., 2012), they have the potential to activate different resonances.

Methods and results

We use a multicompartmental model of CA1-pyramidal neurons (Fig. 2-A) following the Hodgkin-Huxley formalism (Hodgkin & Huxley, 1952). Multicompartmental models have been used to investigate several properties of PYR such as bursting and the coexistence of bursting and single spikes (Kepecs, Wang, & Lisman, 2002; Pinsky & Rinzel, 1994; Golomb, Yue, & Yaari, 2006; Lowett et al., 2023), which are affected by the intrinsic resonant currents. We consider three

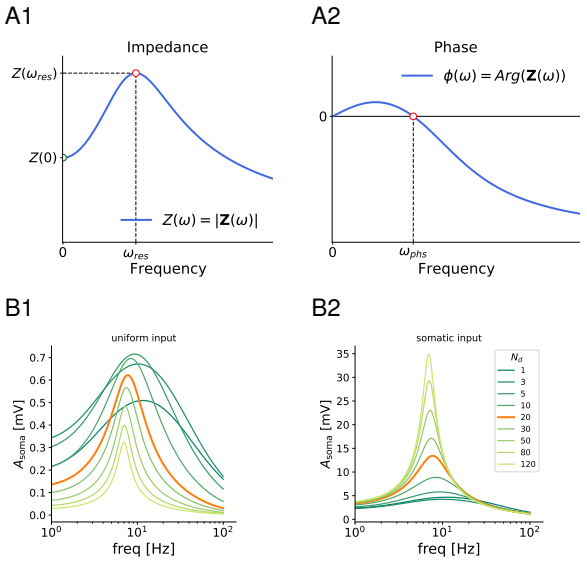

Figure 1: **A.** STres and STphas: representative impedance ($\mathbf{Z}$) amplitude (Z; **A1**) and phase (ϕ; **A2**) profiles. Input frequency (x-axis): ω. Resonant frequency: ω_{res}. Phasonant frequency: ω_{phs}. **B.** Representative examples of the somatic response frequency-dependent amplitude response profiles (N_d dendritic compartments). **B1.** All compartment receive the same sinusoidal input. **B2.** Only the soma receives a sinusoidal input.

well-established properties for the ionic current distributions in CA1 PYR (Migliore & Shepherd, 2002) (Fig. 2). Sinusoidal inputs were applied proximally, distally or at intermediate locations along the dendritic cable. We compute the amplitude and phase profiles for each compartment (e.g., Figs. 3).

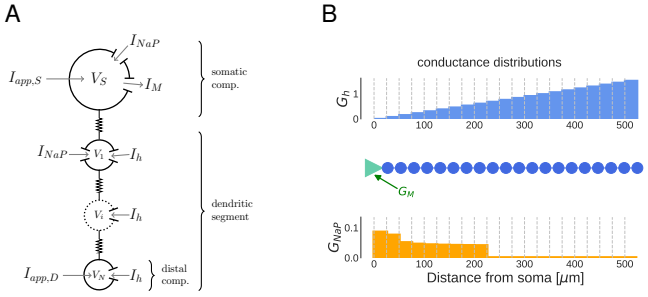

Figure 2: Schematic diagram of the multicompartmental model. **A.** The dendritic segment is divided into N_d compartments of equal length. **B.** Spatial distribution of the ionic currents along the cable.

Experimental work has shown the presence of theta subthreshold resonance and phasonance in PYR *in vitro* (Pike et al., 2000; Leung & Yu, 1998; Zemankovics, Káli, Paulsen, Freund, & Hájos, 2010; Hu et al., 2002, 2009). In (Hu et al., 2002, 2009), the authors demonstrated the existence of two different types of theta STres in CA1 pyramidal cells (PYR) *in vitro*: (i) perisomatic, generated by an M-type potassium current (I_M) and amplified by a persistent sodium current (I_{Nap}), and (ii) dendritic, generated by a hyperpolarization-activated (h-, sodium/potassium) current (I_h).

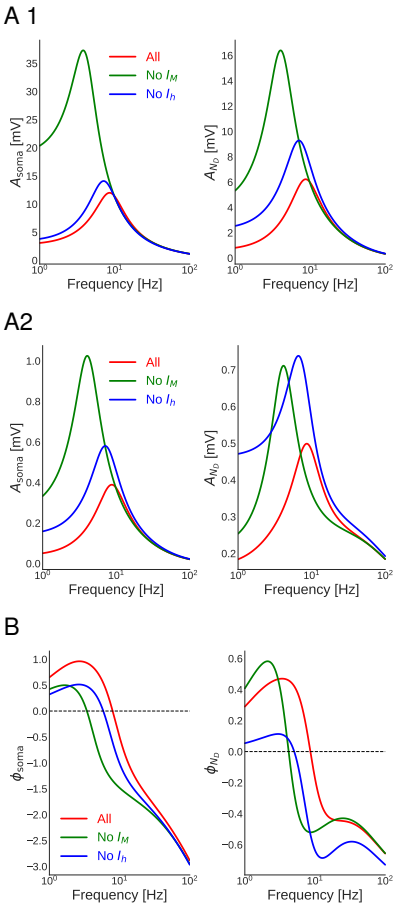

Figure 3: **Segregation and interaction between resonant mechanisms.** Color lines: presence of all currents (red), suppression of I_M (green) and suppression of I_h (blue). Responses of somatic (left) and most distal (right) compartments to an oscillatory input applied to the soma (A1) and to the most distal dendrite (A2 and BB). The baseline resting potential distribution varies between ~ -80mV (most distal dendrite) and ~ -58mV (soma).

A CA1 PYR minimal ball-and-stick model captures the coexistence of h- and M-current-based resonances. However, two-compartment models fail to reproduce the segregation between the two mechanisms due to the partial overlapping of the activation/inactivation ranges of the resonant currents (I_h and I_M). This creates an interference between the two resonances when independently activated in the soma and dendrites. Addition of one or more passive dendritic compartments would violate the presence of active dendritic ionic currents. Our model includes a number of dendritic compartments with a realistic distribution of active ionic currents (Fig. 2) and at the same time preserves the segregation between the two resonant mechanisms.

We found conditions under which the two mechanisms interact. This includes strong voltage variations along the dendritic cable that differentially activate the different ionic channels distributed along the dendrite. We also describe how the spatial structure gives the neuron enough flexibility to support these scenarios. We selectively inhibited the different currents

and analyzed how the joint activation of the resonant mechanisms produces responses with different attributes than those produced in the classical scenarios where only one resonant current is active (e.g., Fig. 3-A). We then extended our results to the analysis of the phase profiles (e.g., Fig. 3-B) finding similar segregation and interaction mechanisms of phasonance along the dendritic cable. Finally, we showed how the interplay of background noise and the resonant mechanisms generates sustained oscillations along the cable and how they are modulated by the cable's ionic and geometric properties.

Conclusion

Neuronal frequency filters are believed to have implications for cognition and motor behavior in health and disease. Our findings reveal a complex interplay between spatial structure and ionic mechanisms leading to a diversity of dendritic resonant and phasonant responses through the interaction of spatially distributed ionic currents and segregated resonances. This flexible neuronal filtering properties have significant implications for individual neuron contributions to network rhythms. The joint interaction of resonant and phasonant mechanisms and the diversity of associated patterns reveal the ways in which neurons regulate their activity and the response to structured and non-structured inputs during network activity.

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