Morphologic contributions to velocity storage neural integration
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Abstract:
Neurons comprising the velocity storage neural integrator (VSNI) perform a leaky mathematical integration of their inputs. Lacking accurate 3D morphologic representations of their constituent neurons, current network models of vestibular integrators neglect cellular and morphologic mechanisms that could contribute to persistent activity. We present a biophysically plausible model of an electrophysiologically characterized, 3D manually reconstructed neuron from goldfish Area II, a region shown to be necessary, possibly sufficient, for velocity storage. The model reproduces subthreshold electrophysiological responses and firing characteristics recorded in Area II. We demonstrate that morphology is an essential determinant of the response dynamics of the modeled neurons.

1. Introduction

We present a morphologically accurate model of a neuron from Area II (AII) of the goldfish, a region shown to be a necessary, possibly sufficient, component of the velocity storage neural integrator (VSNI) [20]. The VSNI performs a leaky mathematical integration of its input, extending the time constant of input signals from about 4 s to ~20-30s in naïve animals [23]. This integrator works in conjunction with, but independently from, the velocity position neural integrator (VPNI) to sustain compensatory eye movements during head and body motion [20]. Moreover, the VSNI is a critical component in determining spatial orientation of the angular vestibulo-ocular reflex (aVOR) [24,36,37], a reflex crucial to navigation in the 3D environment. Spatial orientation of the aVOR requires the combination of linear and angular acceleration signals, so that humans and animals can orient compensatory oculomotor responses to the gravitational vertical [17,36,37], and the VSNI has been shown to be largely responsible for this [36,37].

Control systems models have proven to be excellent tools for understanding the transfer characteristics of the VSNI [4,17,23,26,37], but have not proposed specific network or single-cell mechanisms to perform the velocity storage. Several recurrent feedback neural network models have successfully captured the dynamics of the VPNI [1,6,31,32], but have suffered from instability and a lack of robustness [5,31,32]. Recent models of vestibular integrators have begun to incorporate single cell properties [9,13,14], which improves the robustness of such network models [9,13]. However, no study has investigated the contribution of realistic 3D morphology of neurons that comprise the integrator, even though dendritic morphology has been shown to be an important determinant of neuronal dynamics [15,35]. Our model, which is based on a manual reconstruction of an AII neuron, demonstrates that morphology plays a critical role in the response dynamics of AII neurons.

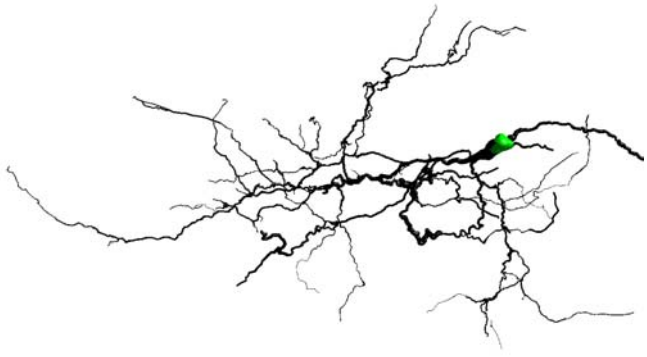

Fig 1: Dendritic tree of an AII neuron reconstructed in 3D using Neurolucida from manually traced light microscope data.

2. Computational Model

2.1 Extracting 3D neuronal morphology

The AII neuron shown in Figure 1 was characterized electrophysiologically [34], and injected with neurobiotin after recording. Using Neurolucida

(Microbrightfield, Colchester, VT), the 3D morphology was traced manually, and reconstructed (Fig. 1).

2.2 Ionic channel kinetics and distributions

At present, no data exist on intrinsic membrane properties of AII neurons. However, Area II has been shown to be analogous to a subset of nucleus prepositus hypoglossi (NPH) neurons in mammals [3,20]. The firing characteristics of NPH neurons are similar to those of medial vestibular nucleus (MVN) neurons [18,30]. In particular, MVN and NPH neurons exhibit a range of action potential profiles and repetitive firing dynamics *in vitro*, categorized broadly into types A and B primarily by their characteristic single and double afterhyperpolarizations, respectively [28,29].

Several models of MVN neurons have been developed [2,22,27]. Quadroni and Knöpfel [22] presented multi-compartment models of type A and B MVN neurons, comprising primary dendrites which branch symmetrically into two daughter branches. The type A (B) model consisted of 3 (4) dendrites divided into 46 (61) compartments. The models, which included nine conductances known to exist in MVN neurons, reproduced the firing characteristics of both neuron types. Both ion channel kinetics and densities were constrained by intracellular studies of MVN neurons, including data on deep cerebellar nuclei and hippocampal CA3 pyramidal cells when MVN neuron studies were not available. Channel densities varied for the somatic, proximal dendritic, and distal dendritic compartments. (In general, channel densities and intracellular calcium concentration were greatest at the soma, reduced in the proximal dendrites, and minimal (or zero) in the distal dendrites.) Modeled calcium dynamics included diffusion, fast uptake, binding to proteins, and buffering.

Av-Ron and Vidal [2] constructed a minimal model consisting of a single compartment, which still captured the dynamics of both MVN neuron types. Traditional Hodgkin-Huxley formalism [12] was used to incorporate six active currents, and a leak current. These currents included sodium I_{Na}, potassium I_K (delayed rectifier), transient potassium I_A, persistent sodium I_{Nap}, high threshold calcium I_{Ca}, and calcium-dependent potassium I_{KCa}. The Fitzhugh-Nagumo simplification [8,19] was used, which compresses the sodium activation variable and delayed rectifier potassium inactivation variable into a single recovery variable.

Our interest lies in a constructing a minimal model of AII neurons which includes conductances necessary to reproduce recorded dynamics, but also applies biophysically plausible, spatially extended channel densities and calcium dynamics to our morphologic data. As a first approximation, therefore, we adopt the ion channel types and kinetics presented in Av-Ron and Vidal [2], with channel distributions and calcium dynamics similar to those employed by Quadroni and Knöpfel [22]. Our computational model is implemented in NEURON [11].

2.3 Synaptic input

A detailed study incorporating electrophysiology, immunohistochemistry, and electron microscopy [10] determined the probable distribution of excitatory and inhibitory synaptic input from vestibular pathways to oculomotor neurons in goldfish. This study found that excitatory synapses are located primarily on dendrites, and inhibitory synapses are located on the soma and proximal dendrites. In the absence of data elucidating synaptic distributions in AII neurons, we assume a similar distribution for our model.

2.4 Network model of VSNI

Single neuron recordings and selective lesion experiments [20] have shown that AII is necessary, possibly sufficient, for velocity storage neural integration in the goldfish. The connectivity established between AII and VN indicates that a circuit linking VN and AII may be a sufficient

mechanism for velocity storage [16]. For simplicity we discuss the mechanism for velocity storage during rightward eye velocities. During rightward eye velocities, the right VN and left AII are largely silent [3,33]. Because the spontaneous firing rate of AII neurons averages 12.07 spikes per second (s/s) in light [3], but can be more than 100 s/s during sinusoidal stimulation, it is unlikely that reciprocal inhibition provides an effective positive feedback mechanism.

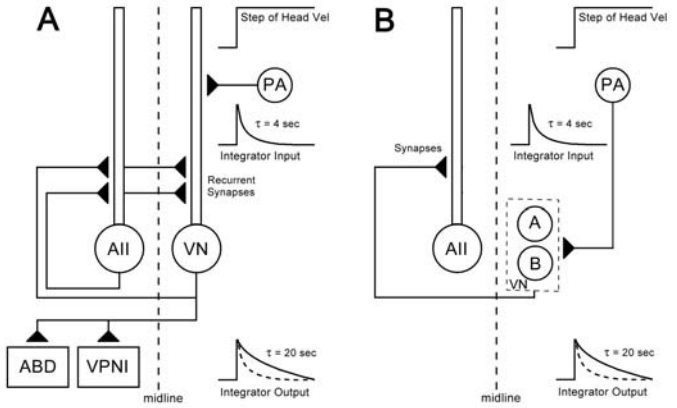

Fig. 2: Schematic of (A) the full proposed network model and (B) simplified model used in this study. PA: primary afferent; VN: vestibular nucleus; ABD, abducens nucleus A: Type A MVN neuron. B: Type B MVN neuron. See text for description.

The only circuit with upregulated neuronal activity that might subserve rightward velocity storage is the excitatory pathway from right AII to left VN and the return path across the midline from VN to AII [33]. Oculomotor behavioral studies involving velocity storage [3,20] have shown that AII neurons encode eye velocity with the time constant of velocity storage, and exhibit negligible position sensitivity; therefore, AII has the appropriate signaling properties for eye velocity generation and storage. Further, inactivating AII by bilateral lidocaine injections, while leaving VN intact, abolished velocity storage [20]. This illustrates that AII is necessary for velocity storage, and that circuits within VN cannot provide the integration independently of AII. Behavioral studies have shown that unidirectional adaptation of the VSNI time constant can be produced by monocular visual stimuli [7]. Additionally, midline commissural section between the two VN nuclei, which includes any pathway between the two AII nuclei, did not abolish velocity storage [16,20]. These facts together demonstrate that a unidirectional mechanism for integration exists either within a single AII nucleus, or as a result of the VN-AII pathway. Because the inhibitory ipsilateral VN-AII circuit is largely silent during sustained rightward eye velocities [33], we conclude that it does not play a significant role in the corresponding velocity storage. Finally, although AII neurons project to the cerebellum [33,34], lesions of the vestibulocerebellum increase, not abolish, velocity storage [16]; therefore these projections are not causal for the integration mechanism.

We conclude that there are two possible substrates for velocity storage integration, which we will test using the network illustrated in Fig. 2A. The first possibility (I) is a VN-AII loop, whereby both right AII and left VN are activated. The second possibility (II) is that velocity storage is produced within a single AII nucleus. Because no axon collaterals from ipsi- or contralateral AII neurons have been observed in AII [33], this mechanism could be due to intrinsic cellular properties and/or dendro-dendritic connections between AII neurons within a single nucleus. Because both these mechanisms require AII, we are particularly interested in modeling this nucleus.

To test these two mechanisms, ultimately we will propose the recurrent feedback neural network shown in Fig. 2A. This figure represents input-output connections of the proposed network for a rightward head velocity step. AII and VN represent multiple neurons from Area II and vestibular nucleus, respectively. These neurons are all-to-all connected by excitatory recurrent synapses, without autapses. The VN neurons receive feedforward excitatory primary afferent input from the ipsilateral horizontal canal. Contralateral abducens (ABD) and VPNI receive integrated network

output from VN neurons. The network as shown allows us to test mechanism I, that velocity storage arises from the dynamics of VN, AII, and the recurrent feedback loop between them. Further, if we neglect hypothesized recurrent synapses across the midline from AII to VN, we can test mechanism II: whether AII is capable of velocity storage independently of feedback through VN, either by intrinsic cellular properties, or dendro-dendritic connections, realized in the model by the recurrent synapses from AII onto itself.

The simplified model we test here is shown in Fig. 2B. Here we evaluate the neuronal dynamics which arise from the interaction of excitatory synaptic input from VN with the intrinsic cellular properties, including morphology, of a single AII neuron. The simplified model consists of 3 components: the primary afferent (PA), vestibular nucleus (VN), and AII. Rather than representing multiple neurons, here AII is modeled as a single neuron, and VN as two independent neurons described below. Following Robinson [25] and Raphan et al. [23], we combine the dynamics of the semicircular canals and primary afferents into a simple first order leaky integrator with a time constant of 4s. The ipsilateral VN receives the PA signal as excitatory input.

Modeling studies have provided strong evidence that Types A and B neurons correspond respectively to tonic and phasic neurons recorded *in vivo* [2,27], and show that these neurons have different responses to the same stimulus. Assuming that tonic and phasic neurons exert different influences upon their targets, in our work the VN is modeled as two single-compartment neurons, types A and B, as in [2]. Action potentials of the VN are recorded as excitatory events presynaptic to the AII neuron, which is modeled using the fine-scale model described above in 2.1, 2.2, and 2.3. Of the MVN neurons that were readily identified as one of the two types in experiments, about 40% were Type A, and 60% Type B [28]. Synaptic input from these two cell types onto our AII neuron are weighted similarly.

Results

In recent neurophysiological experiments [3], a goldfish was exposed to controlled changes in optokinetic and vestibulo-ocular stimulus velocity. The stimuli included velocity step modulations as well as sinusoidal velocity modulation at a range of frequencies. We first restrict our model neuron to a single compartment and compare its response to the AII neurons reported by Beck et al. [3]. We then show how the response dynamics of the model neuron are changed when the morphologic and spatially extended properties are included. Further, we emulate the responses of AII neurons with varied morphology, by modifying morphologic parameters (e.g. diameter, dendritic field extent) in the model according to the range of morphologic types of AII neurons observed in [34].

Discussion

Our fine-scale model of an AII neuron allows us to consider, for the first time, intrinsic cellular properties involved in the functionality of the VSNI. We are able to reproduce recent experimental results [3,34], and show that variations in the dendritic morphology are important determinants of the resulting neuronal response. In future work, we plan to develop a coarse-scale representation (as in Pinsky and Rinzel [21]) of the fine-scale model presented here, which will be incorporated into the full network model of the VSNI (Fig. 2A) described above. We will study the effects of single-cell morphology on the output characteristics, stability, and robustness of the resulting network.

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