Signal integration on the dendrites of a pyramidal neuron model

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Abstract This paper studied the synaptic and dendritic integration with different spatial distributions of synapses on the dendrites of a biophysically-detailed layer 5 pyramidal neuron model. It has been observed that temporally synchronous and spatially clustered synaptic inputs make dendrites perform a highly nonlinear integration. The effect of clustering degree of synaptic distribution on neuronal responsiveness is investigated by changing the number of top apical dendrites where active synapses are allocated. The neuron shows maximum responsiveness to synaptic inputs which have an intermediate clustering degree of spatial distribution, indicating complex interactions among dendrites with the existence of nonlinear synaptic and dendritic integrations.

Keywords Integration · Nonlinear · Cluster · Synchronous · Dendrites

Introduction

Recently it was observed that synchronous and spatially clustered synaptic input makes a single dendrite perform a highly nonlinear integration, while asynchronous or highly distributed input could only produce a linear relationship between the input and the output of somatic membrane potential (Gasparini and Magee 2006; Gasparini et al. 2004; Losonczy and Magee 2006; Spruston and Kath 2004; Polsky et al. 2004; Yoneyama et al. 2011). The temporally and spatially concentrated synaptic input could effectively

activate the sodium channels and thus produce dendritic spikes which are responsible for the observed nonlinearity. The nonlinear dynamics of the firing rates of neurons populations would also be responsible for the priming shift assessed at the behavioral level (Lavigne et al. 2012; Wang et al. 2012). Besides the synaptic integration on a single dendrite, extensive dendritic trees also integrate synaptic inputs nonlinearly and exhibit dendritic integration with dendritic spikes propagating forward to the soma or backward to distant dendritic locations. However, there is rare experimental evidence supporting the nonlinear characteristics of dendritic integration, due to the difficulty of controlling a large number of synaptic inputs to a single pyramidal cell. Thus compartmental modeling is necessary. But to our knowledge, few computational study have so far focused on investigating the interactions between distributed top distal branches, which is quite important for understanding the intrinsic mechanisms of neuronal computation.

In this paper both synaptic integration and dendritic integration were investigated by allocating synaptic inputs on a single dendrite or several distal/basal dendrites in a biophysically-detailed layer 5 pyramidal neuron model. The results show that both temporally synchronous and spatially clustered synaptic input makes the dendrite perform a highly nonlinear integration, which is consistent with experimental observations (Gasparini and Magee 2006). NMDA current also improves the ability of nonlinear integration of synaptic inputs, which is consistent with the experimental results observed in (Yoneyama et al. 2011). Moreover, when synapses are distributed over several different branches where dendritic integration is involved, intermediate clustering degrees of synaptic distribution could produce the maximal neuronal outputs in response to mild synaptic inputs. Either too compact or

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broadly distributed inputs would impair the ability of nonlinear synaptic and dendritic integration.

Methods

In this paper, simulations were performed using NEURON version 7.0 (Hines and Carnevale 2001), which is used to model the morphologically detailed layer V pyramidal neuron. It has multicompartments which are established with each compartment's dynamics simulated by a Hodgkin-Huxley model and then coupled via conductances. Besides the spike generation, this morphologically detailed compartmental model has extensive dendritic trees that integrate synaptic inputs nonlinearly and exhibit complex dendritic integrations. Here, the layer V neocortical pyramidal neuron model was obtained from the ModelDB section of the Senselab database (<http://senselab.med.yale.edu>). The detailed morphology of this neuron is as follows (Mainen and Sejnowski 1996): the diameter and length of the soma were 25 and 35 μm respectively, with a membrane area of 2,747.9 μm^2 . There were 11 primary neurites and 87 branches totaling 17,667.6 μm in length and 52,996.2 μm^2 in area, which were divided into 164 segments. All dendritic branches were divided into cylindrical compartments each with a maximum length of 20 μm . This realistic cell model includes five voltage-dependent currents: fast Na^+ (INa), fast K^+ (IKv), slow, non-inactivating K^+ (IKm), and high-threshold Ca^{2+} (ICa), as well as one Ca^{2+} -dependent potassium current (IKCa). Values of channel densities are given in Table 1. Each pre-synaptic input was modeled by using AMPA and NMDA conductances for excitation. The unitary AMPA conductance transient was implemented using the built-in function Exp2Syn of NEURON, with 0.5 and 2 ms rise and decay time constants respectively, a reversal potential of 0 mV, and a peak conductance of 0.1 nS. The NMDA conductance was implemented based on the asymmetric trapping block model of NMDA receptors (Vargas-Caballero and Robinson 2004). This model reproduces the spatiotemporal properties of sodium, calcium and NMDA receptor spikes found experimentally. The time step was 50 μs .

Table 1 Channel densities for simulations in this report except for special remark

Conductance ($\text{pS}/\mu\text{m}^2$)	g_{Na}	g_{Kv}	g_{Ca}	g_{KCa}	g_{Km}
Soma	54	600	3	6.5	0.2
Dendrites	50	1	10	3.25	0.1
Axon hillock and initial segment	80	3,000	0	0	0
Nodes Ranvier	30,000	0	0	0	0

Results

Spatial and temporary input patterns on a single dendrite

In this section, AMPA type synaptic inputs with different temporal and spatial patterns are located on a single distal dendrite (shown in Fig. 1a). Recordings are membrane potentials collected at the soma. Here action potential is blocked by removing the sodium channel at the soma. Figure 1b reproduces the result of synaptic integration on single dendrite reported in the Fig. 2e of the paper (Gasparini and Magee 2006). For the four input patterns, only synchronous and clustered input can trigger dendritic spikes and produce the nonlinear synaptic integration.

Effect of NMDA currents

In the previous section where only AMPA type synapses are applied, the concentrated integration of inputs is essential for the nonlinearity. In order to investigate how the slow excitatory postsynaptic potentials (EPSPs) produced by NMDA receptors affect synaptic integration, a detailed model of NMDA receptor (Vargas-Caballero and Robinson 2004) is applied. It is shown that NMDA current could help enhance the integration of temporally asynchronous or spatially distributed synaptic inputs and make the nonlinear input–output relationship (Fig. 2). Due to the existence of sustained slow NMDA current, most of the individual inputs that arrive at different time and different location could be summated together and activate dendritic spikes. This is consistent with the result shown in (Gasparini et al. 2004); Fig. 3 gives a comparison of the recordings with and without NMDA currents when the inputs are synchronous and clustered on the single dendrite. Note that the second peak of membrane potential is generated by the NMDA current.

Dendritic integration when synapses are distributed over distal/basal dendrites

In this section spatial distribution of synapses over all of the distal dendrites is studied (Fig. 4a). A single stimulus is added to each synapse at the same time. Synapses are allocated to a different number of randomly selected distal dendrites (The total number of distal dendrites is 56 for this neuron). Each selected dendrite can be seen as a cluster and synapses are equally distributed on each cluster. In order to give a smooth curve of the membrane potential with the increase of number of allocated dendrites, sodium current is blocked at the soma and axon in order to avoid the generation of action potentials (APs). In each case, simulations are conducted for 20 times.

Fig. 1 **a** Layer V pyramidal neuron model and simulation strategy. Input stimulus is generated from the integration of several synapses which are located on one of the distal dendrites. Output is the peak value of membrane potential recorded at the soma. Synapses with synchronous or asynchronous single stimulus are either spatially

clustered or distributed on the dendrite. **b** Linear and nonlinear input–output relationships for clustered/distributed and synchronous/asynchronous input patterns. Note that action potential is blocked by removing the sodium channel at the soma

Fig. 2 Effect of NMDA synapses on the nonlinear integration of spatially distributed or temporally asynchronous synaptic inputs

Fig. 3 Recordings from the stimulated dendrite (red lines) and the soma (black lines) with increasing stimulus when there are (a) no NMDA synapses or (b) there are NMDA synapses. Here synaptic inputs are synchronous and clustered on the stimulated dendrite

Previous study shows that when stimulus is applied on a single dendrite, clustered inputs are contributive to triggering dendritic spike which is responsible for the generation of APs at the soma. Similarly, when activated synapses are distributed among all the distal dendrites, an

intermediate degree of clustering is needed to produce APs at the soma (Fig. 4b), especially for the small number of synapses. As dendritic spikes generated on far tuft dendrites are difficult to be transferred to the soma, too high degree of clustering (e.g. concentrated on a single dendrite)

Fig. 4 Effect of clustering degree of synaptic distribution on somatic responsiveness. **a** Distributed synaptic inputs on the distal or basal dendrites. A single stimulus is added to each synapse at the same

time. **b** Activated synapses are distributed on the distal dendrites. **c** Activated synapses are distributed on the basal dendrites

Fig. 5 Effect of basal synaptic distribution on somatic responsiveness to Poisson input. **a** Average firing rate for 10 times of realizations versus number of allocated basal dendrites, where the number of synapses is 400 and each synapse is stimulated by a Poisson-

distributed spike train with the mean spiking rate of 10 Hz; **(b)** Different degree of synaptic clustering can modulate the input-output relationship. Here sodium current is resumed so that action potentials could be generated

will not always cause APs due to the dependence of cluster's location. If synaptic inputs are loosely distributed over distal dendrites, much information is lost during the transmission along separated dendrites, causing the failure of effective integration of dendritic spikes. However, when the number of synaptic inputs is increased, intensive dendritic spikes could be generated on each allocated dendrite and depolarize the other neighboring branches, thus spreading information to all the dendrites and further

transferring to the soma (Fig. 4b). Qualitatively similar phenomenon can be obtained on the basal dendrites (totally 102 basal dendrites) (Fig. 4c).

We also examined neuronal firing rate with the increase of number of allocated basal dendrites, where the number of synapses is 400 and each synapse is stimulated by a Poisson-distributed spike train with the mean spiking rate of 10 Hz. The firing rate decreases dramatically when synapses are distributed over about 20 basal dendrites (Fig. 5a).

Based on this sensitive dependence of neuronal response on synaptic distribution, Fig. 5b shows that an effective gain modulation of the input–output relationship could be achieved by changing the clustering degree of synapse distribution.

Conclusions

In this paper, signal integrations on the branches of a biophysically-detailed layer 5 pyramidal neuron model have been investigated. The results show that both temporally synchronous and spatially clustered synaptic inputs can make a single dendrite performing highly nonlinear synaptic integrations. NMDA current also improves the ability of nonlinear integrations of synaptic inputs. Moreover, when synapses are distributed over several different branches where dendritic integrations are involved, intermediate clustering degrees of synaptic distributions could produce the maximal neuronal response, especially for weak synaptic inputs. Either too compact or too broadly distributed synapses would impair the ability of nonlinear signal integration of the pyramidal neuron.

This study about the generation of nonlinear signal integration from synapses and dendrites would provide insights into understanding the detailed mechanisms of temporal coding and neural binding problems (Singer 2009; Feldman 2013; Li et al. 2011). Moreover, it has been reported that calcium current and NMDA conductance plays a significant role in the signal integration of real brain (Mel 1993; Schiller et al. 2000; Nevian et al. 2007) and spike-timing dependent plasticity (Cutsuridis 2012), so further investigations regarding the effects of calcium and NMDA currents would be necessary to understand the complex interactions between different dendritic branches of pyramidal neurons.

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