Dendritic Discrimination of Temporal Input Sequences in a Single Hippocampus CA1 Pyramidal Neuron Model

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. Abstract

In integrating synaptic inputs and determining the extent to which action-potential output is generated, dendrites play a critical role. However, the exact computational functions performed by complex dendrites remain unclear. In *Branco T, Clark BA, Häusser M (2010) Dendritic discrimination of temporal input sequences in cortical neurons. Science.*, the authors found the sensitivity to the sequence of synaptic activation single dendrites of cortical pyramidal neurons exhibit by applying patterned, two-photon glutamate uncaging.[1]
In this study, we tried to induce input signals with various temporal sequences into a multi-compartmental single hippocampal CA1 pyramidal neuron model. The outputs generated by the biological-constrained model were compared with results from real-life paper-based biological experiments. This study captured patterns of neuron signals between inputs and outputs of the CA1 pyramidal neuron model, thereby verifying accuracy of the model, providing a conceptual framework for dendritic computation, and approaching the question what dendrites attempt to resolve from synaptic inputs.

. Background

One over-arching goal of systems neuroscience is to understand the relationships between input and output in the brain. Due to the large number of dependencies and interactions in the biological components and environments, the nervous system is complex and high-dimensional. Theoretical analysis and computational modeling are important tools for gaining insight into nervous system function. Three questions what, how, and why the nervous system functions are addressed by three different levels of modeling, descriptive, mechanistic, and interpretive models. Descriptive models summarize large amounts of experimental data, characterizing what neurons and neural circuits do. Mechanistic models address how nervous systems operate on the basis of known anatomy, physiology, and circuitry. Interpretive models explore the behavioral and cognitive significance of nervous system functions using computational principles, addressing why nervous systems operate as they do.[2]
Neurons transform synaptic input into output through dendritic integration. In the dendrites, a single neuron can receive electrochemical signals from up to 100,000 synapses originating from upstream neurons. In classical neuronal models, neurites are considered as bundles of electrical compartments connected together. The plasma membrane of a neurite consists of a bilipid layer that separates ions and charges in the extracellular space from the cytosol, and therefore generates an electrical gradient. Pure lipid membranes can resemble electrical insulators with high resistance, and protein channels and other lipids in membranes can be seen as segments with high conductance. As both the membrane resistance and the membrane capacitance occur over the plasma membrane, they form an electrically parallel circuit known as the RC circuit.[3,4,5] Since the resistance nature of the plasma membrane, a synaptic input naturally becomes weaker as it propagates through the plasma membrane. Thus, dendrites play a critical role in integrating synaptic inputs and determining the extent to which action-potential output is generated.[6,7,8] Therefore, a single neuron can be seen as an independent computational unit which can receive stimulations, process signals with information in space and time, make decisions, and generate responses.
In this study, we extracted and modified a biological-constrained model originally from *Kim Y, Hsu CL, Cembrowski MS, Mensh BD, Spruston N (2015) Dendritic sodium spikes are required for long-term potentiation at distal synapses on hippocampal pyramidal neurons. Elife.*[9] The model was constructed by summarizing large amounts of experimental data and representing biological parts of a single neuron as a combination of independent segments of an electrical circuit. Due to the reusable characteristic of a model, we could apply different experiments to it tentatively. Using this biological-constrained model, we applied various tests and statistical and mathematical methods, and tried to explore and interpret the patterns and behavioral significances of the nervous system functions using computational principles, addressing how and why nervous systems operate as they do.

. Specific Aims

Extracting and modifying a single hippocampus CA1 pyramidal neuron model

We extracted and modified a biological-constrained model originally from *Kim Y, Hsu CL, Cembrowski MS, Mensh BD, Spruston N (2015) Dendritic sodium spikes are required for long-term potentiation at distal synapses on hippocampal pyramidal neurons. Elife.*

Providing inputs with different synaptic structures to the dendrites of a single-neuron model (constrained by experiments)

We randomly fired synaptic inputs with different temporal correlations to a dendrite of the modeled single neuron, and recorded the membrane potential at different positions of the neuron with a voltage plot as the output.[10,11]

Identifying computations of dendritic integration by comparing the outputs to synaptic inputs of the single-neuron model

We applied quantification and statistical analysis to the inputs and outputs of the neuron model, opting to identify computations of dendritic integration. The outputs were used to investigate how biophysical complexity affects the dimensionality complexity of their computational traits.

. Methods

The original model constrained by biological experiments we based on is from *Kim Y, Hsu CL, Cembrowski MS, Mensh BD, Spruston N (2015) Dendritic sodium spikes are required for long-term potentiation at distal synapses on hippocampal pyramidal neurons. Elife.*, and can be downloaded on https://github.com/ModelDBRepository/184054. This model requires the simulation platform NEURON which is freely available on https://www.neuron.yale.edu/neuron/. NEURON provides a simulation environment for modeling individual and networks of neurons, with a graphical user interface (GUI), which users with minimal programming experience could easily adjust parameters and gain insights into what the model is showing. Programmers are able to construct neuron models via subdividing parts of neurons into individual compartments, and representing sections as independent segments of electrical circuits with potentially distinct parameters for dimensions and kinetics with predefined functions of the primary scripting language hoc. A Python interface is also available. In this case, programmers can load NEURON as a Python package, and program with Python when being able to access functions defined in NEURON.
All original codes of the model and analysis this study used are uploaded and made available to view publicly on https://github.com/celine-huang/Dendritic-Discrimination-of-Temporal-Input-Sequences. `mosinit.hoc` and `commonFcns` are directly from the original model and contain common functions this model uses. `fullMorphCaLTP8` contains main functions of the model, where `start.hoc` is the entrance interface of the model. C files define ion channels and receptors on membranes, and O files are directly generated out of its corresponding C file when compiled. The upper part (lines 1-49) of `start.hoc` loads functions that initialize the program and load morphology of the single hippocampus CA1 pyramidal neuron model. The lower part (lines 50-59) of `start.hoc` loads the function `doTBSStimCC.hoc` that does simulation tests to the model. `doTBSStimCC.hoc` declares parameters of tests and loads `runTBSCC.hoc`, `analyseTBSCC.hoc`, and `plotTBSCC.hoc`. These functions run experiments, record membrane voltages throughout experiment durations, plot voltage graphs in GUI windows, and save data into csv files. `dataAnalysis` contains Python programs which help analyze simulation data saved in csv files. `check.py` does a quick check for data correctness and preciseness. `sequencesDI.py` generates all possible permutations of an array by heap's algorithm, and then generates directionality index (DI) of each possible permutation using bubble-sort times. `RGBgenerator.py` generates a color palette for colors used for plotting labels. `dataAnalysis.py` generates sorted sequences and DI data by voltage traces heights, plots voltage traces of 5 individual single synapses and their arithmetic sum, plots voltage traces of 120 random-sequence multiple synapses of DI = 0~10 compared with arithmetic sum of single synapses, and plots voltage traces of average of random-sequence multiple synapses of different DI compared with arithmetic sum of single synapses. Apart from the originally downloaded model, `runTBSCC.hoc`, `analyseTBSCC.hoc`, and `plotTBSCC.hoc` in this study are primarily modified by me, and functions in `dataAnalysis` are written independently by me.

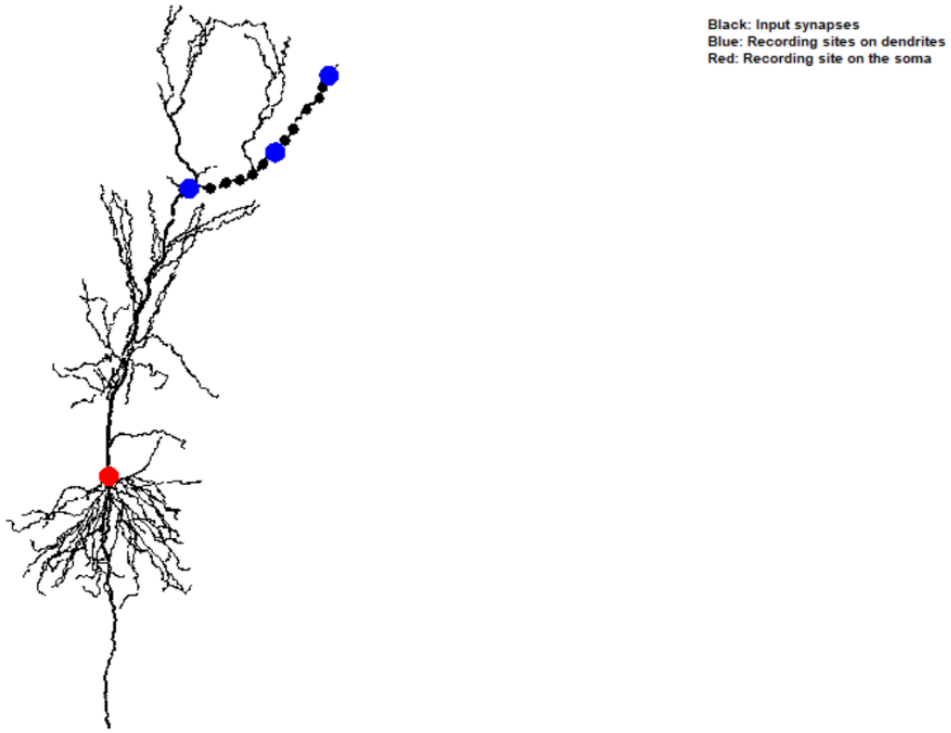

Figure 1. Simulation of a biophysically realistic model of full hippocampal pyramidal neuron morphology. The black dots are where synaptic inputs are fired. The colored dots are where the membrane voltages are recorded.

. Results

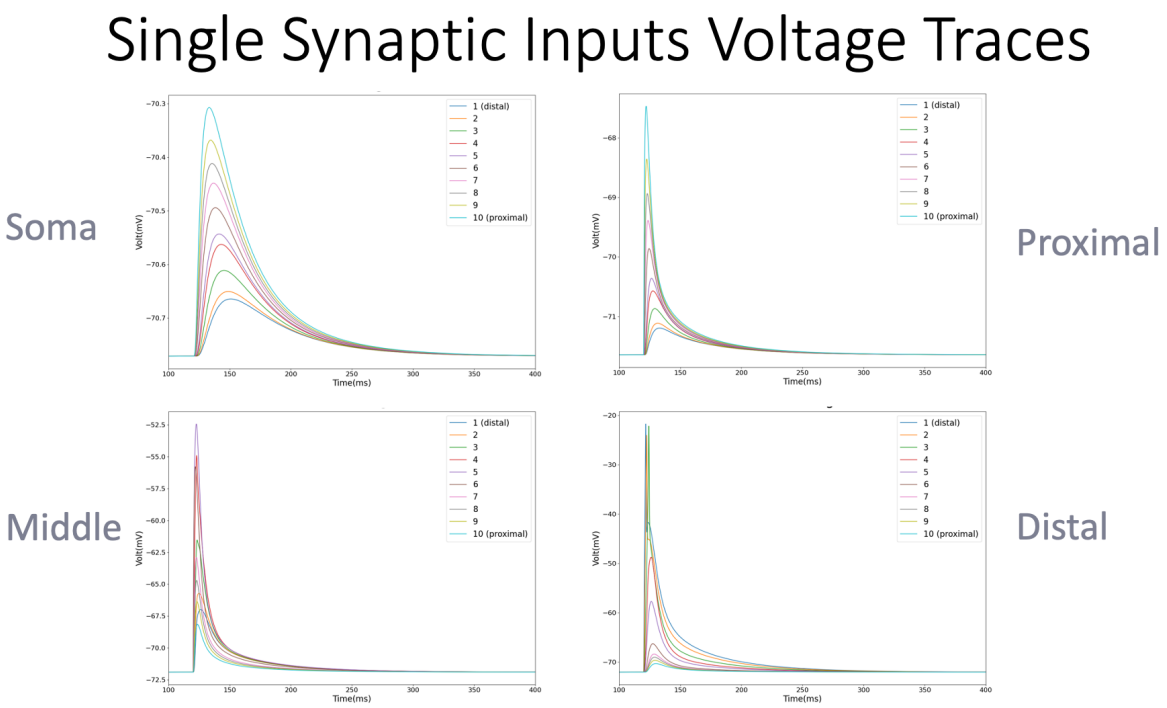

Figure 2. Single Synaptic Input Voltage Traces.
For control group, we first show voltage traces at different recording sites for the ten independent single synaptic input sites. Lines 1~10 each represent a firing site. The firing sites distribute from distal to proximal parts of a dendrite as the index grows. We can observe that peak amplitude increases as the recording site moves from the soma, along the proximal dendrite, to the distal dendrite, and at last dendritic spikes fire in the distal dendrite.
Here we introduce the concept of directionality index (DI). Directionality index indicates the least swapping times needed to get a sequence from an ordered sequence. In our experiments, we fire the ten input locations randomly and therefore get 10! combinations of different temporal and spatial sequences for synaptic inputs. In the results, we use DI to describe directionality of random sequences. Smaller DI describes a more tendency of firing the synaptic inputs from distal to proximal dendrites. Larger DI describes a more tendency of firing from the opposite direction.

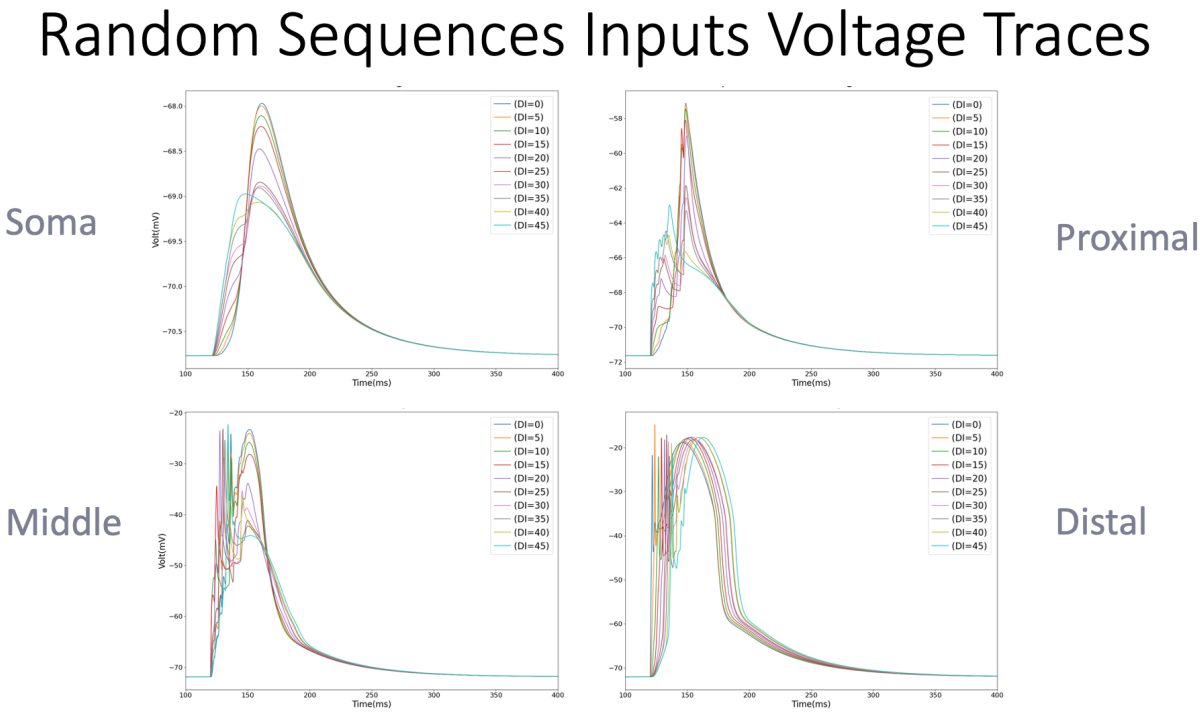

Figure 3. Random Sequences Input Voltage Traces.
We simulate membrane voltage traces at different recording sites in which ten input sites are fired in different random sequences, shown as DI. We can observe that voltage traces with smaller DI has a larger peak amplitude than the ones with larger DI. Similar voltage traces at the soma and the proximal dendrite, with a spiking component on the latter. Dendritic spikes fire on all parts of the dendrite, and a large slow component appears on the distal dendrite.

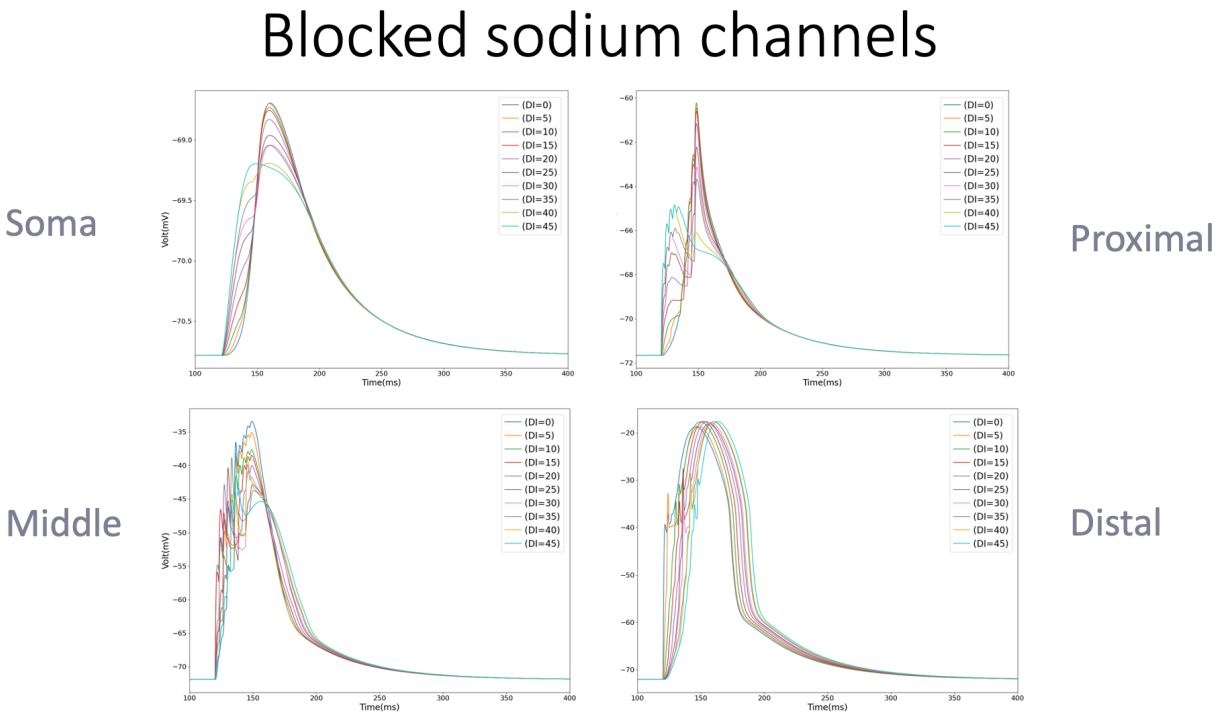

Figure 4. Random Sequences Input Voltage Traces where sodium channels are blocked.
We simulate firing of input signals of random sequences with blockage of sodium channels with TTX, and compare the results to the none-blockage to observe how sodium channels function in dendritic integration. We can see that the overall spiking rate and amplitude decreases.

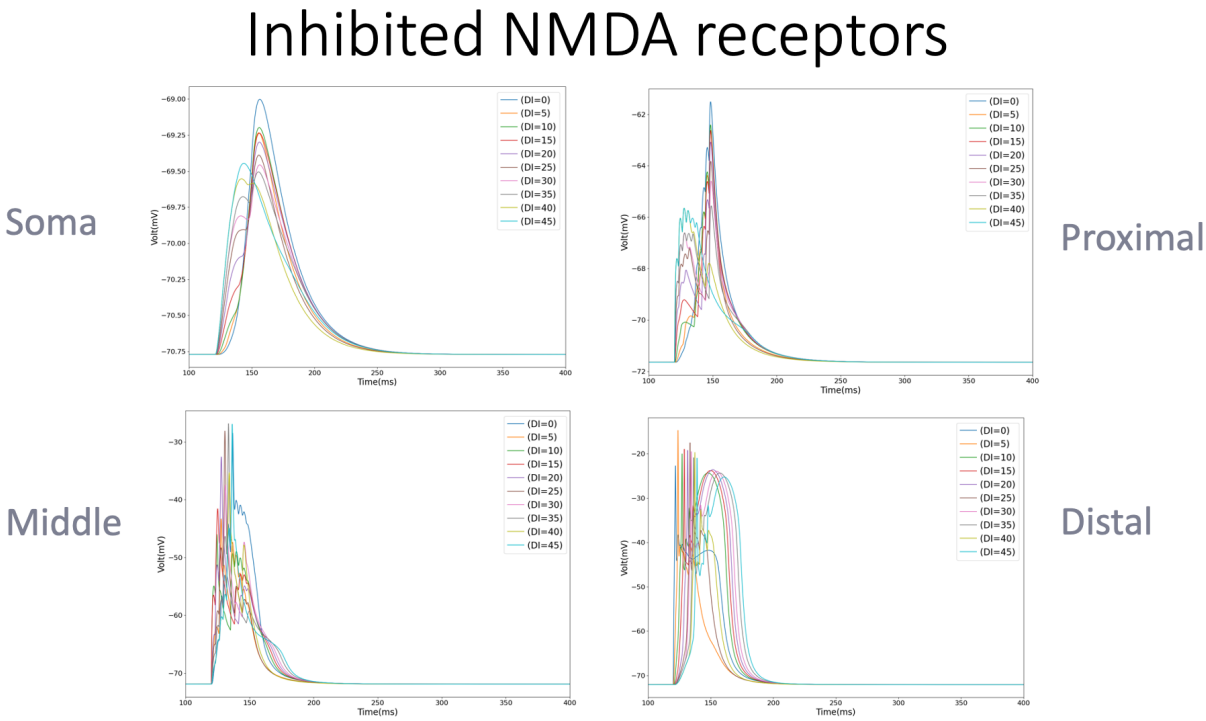

Figure 5. Random Sequences Input Voltage Traces where NMDA receptors are inhibited.
We simulate firing of input signals of random sequences with inhibition of NMDA receptors with AP5, and compare the results to the none-blockage to observe how NMDA receptors function in dendritic integration. We can observe that the area of the slow component reduces.

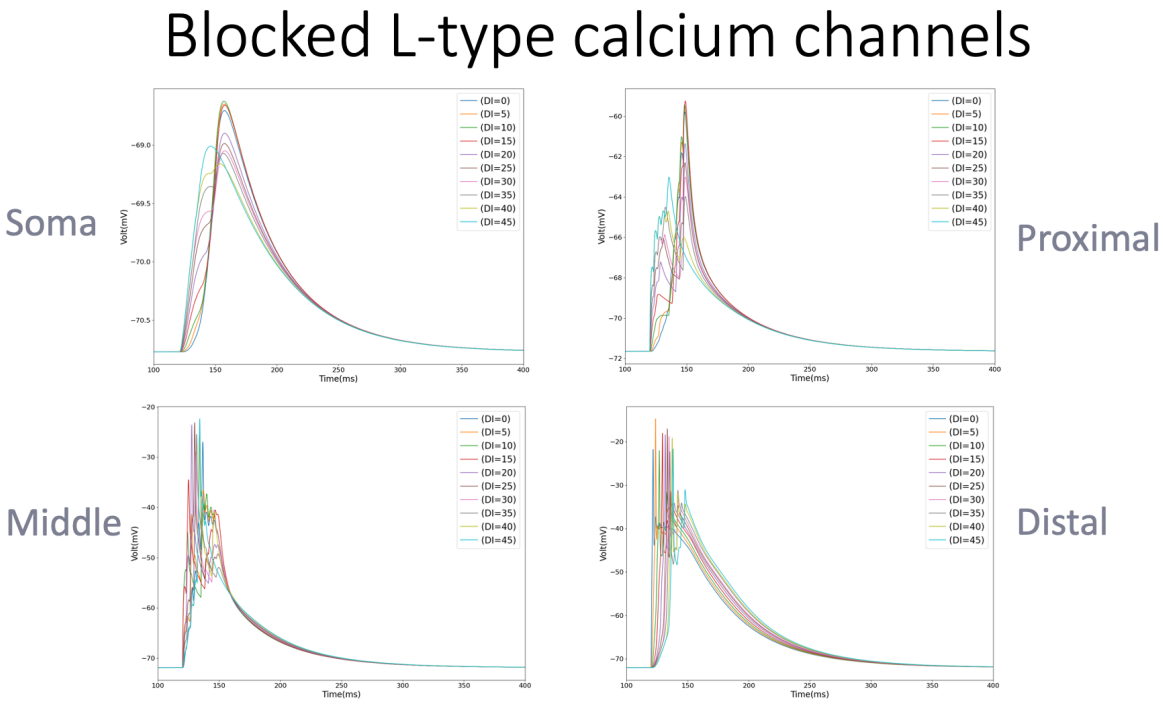

Figure 6. Random Sequences Input Voltage Traces where L-type calcium channels are blocked.
We simulate firing of input signals of random sequences with blockage of L-type calcium channels with nimodipine, and compare the results to the original to observe how L-type calcium channels function in dendritic integration. We observe that the area of the slow component reduces.

. Discussions

From our results in **Figure 3.**, we can observe that peak amplitude of membrane voltages recorded at the soma and proximal dendrites has a negative correlation to the directionality index, which shows that sequential activation from the dendritic branch to the soma (IN direction) produces a larger somatic response than that of the opposite direction (OUT direction) in single dendrites of cortical pyramidal neurons. This correlates with experimental results in *Branco T, Clark BA, Häusser M (2010) Dendritic discrimination of temporal input sequences in cortical neurons. Science.* (**Figure 7. (a)**). The

experimental results generated by applying patterned, two-photon glutamate uncaging show that when stimulating same numbers of synaptic inputs, the somatic responses of IN direction are always larger than the ones of OUT direction. This is because of the overlapping of membrane voltage responses. When sequentially activating synaptic inputs from the dendritic branch to the soma (IN), the further activated inputs tend to propagate to the soma earlier, and the closer activated inputs tend to propagate to the soma later. This results in the compactness of the total response, leading to a larger somatic response while activating by IN direction.

By blocking and inhibiting different ion channels and receptors, we show that blocking sodium channels with TTX reduces overall spikings, and inhibiting NMDA receptors with AP5 and blocking L-type calcium channels with Nimodipine reduce the total area of the slow component. This correlates with experimental results in *Hsu, C. L., Zhao, X., Milstein, A. D., & Spruston, N. (2018). Persistent Sodium Current Mediates the Steep Voltage Dependence of Spatial Coding in Hippocampal Pyramidal Neurons. Neuron.*, where results are generated by in vitro recording.[12] From the bottom part of **Figure 7. (b)-(d)**, we can see that only TTX blockage affects peak amplitude of somatic responses significantly, showing its direct effect on bursts of neurons. While all drug blockages affect the integral of somatic responses, showing their effect on total opening of ion channels.

We can conclude that directionality of activation sequences of dendritic inputs has an impact on the firing of somatic response. Among the involved ion channels, sodium channels affect the most on depolarization in a short period of time which generates a spike.

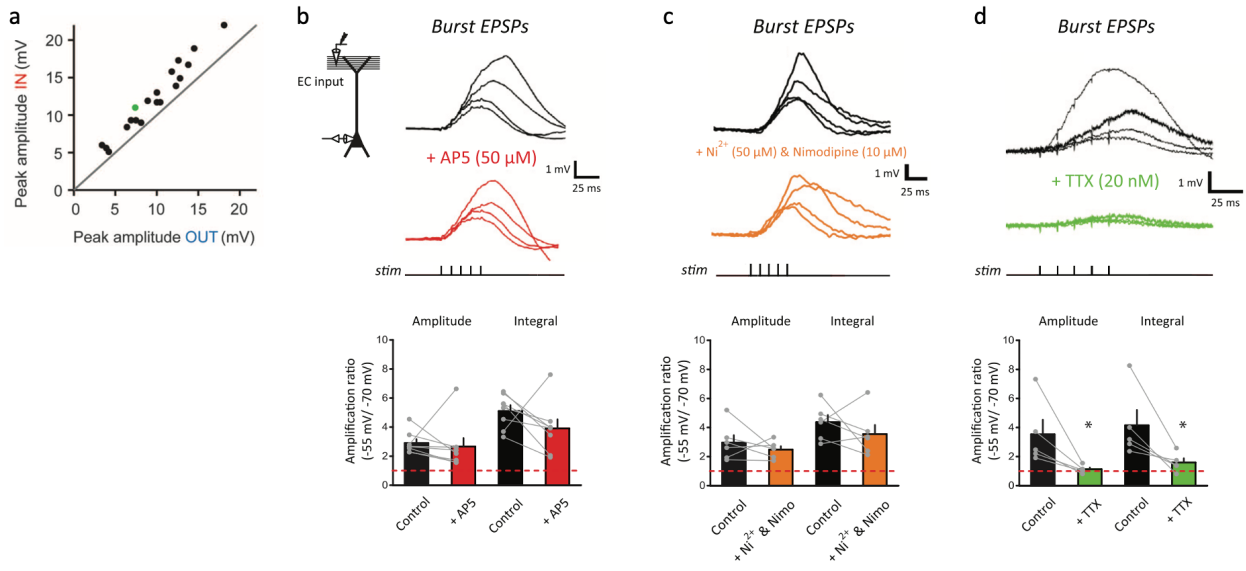

Figure 7. Experimental Results from other papers. (a) Plot comparing peak amplitudes for sequential activation from the dendritic branch to the soma (represented as IN direction) and from the soma to the dendritic branch (represented as OUT direction) from *Branco T, Clark BA, Häusser M (2010) Dendritic discrimination of temporal input sequences in cortical neurons. Science.* (b)-(d) Voltage dependence of small, high frequency burst EPSPs in the control (top), bath application of 50uM AP5, 50uM Ni^{2+}+10uM Nimodipine, and 20nM of TTX (middle colored), and summary of their amplification ratios (bottom) from *Hsu, C. L., Zhao, X., Milstein, A. D., & Spruston, N. (2018). Persistent Sodium Current Mediates the Steep Voltage Dependence of Spatial Coding in Hippocampal Pyramidal Neurons. Neuron.*

. Significance

By creating principles of analyzing quantitative models, our analyses show that our model correlates with real-life experiments, proving the correctness and preciseness of a potentially useful single hippocampus CA1 pyramidal neuron model. We conclude that directionality of activation sequences of dendritic inputs has a significant impact on the firing of somatic response, and sodium channels affect the most while generating a spike, could be shown in a single hippocampus CA1 pyramidal neuron model. Our study reveals potential relationships between the biophysical complexities and dimensionality of computational traits in dendritic integration, thereby providing a more analytical framework for conceptualizing future computational goals of neurons.

. References

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