Dendritic Excitation Dependence on Synaptic Democracy in CA1 Pyramidal Neurons

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Abstract

Synaptic democracy is believed to be an important effect that enables distal synapses to contribute information to the soma. Synaptic democracy is found in hippocampal CA1 pyramidal neurons, which is an important area of the brain for learning and memory. Previous computational work by Sterratt et al [1] show that synaptic democracy arises in a model of a CA1 pyramidal neuron when sufficient synapses are synchronously activated given that the calcium concentration is homeostatically maintained. However, in this work only a 5Hz excitatory postsynaptic potential (EPSP) was tested. We explored how different input vectors might affect the dynamics of synaptic democracy and the neuron as a whole. We found that high frequency stimulation compensated for a sub-threshold number of synapses allowing for synaptic democracy. Interestingly, in the cases with supra-threshold synapse numbers, higher frequency synaptic inputs abolished synaptic democracy.

1 Introduction

Neurons communicate with each other via synapses spread across its dendritic tree. Some neurons have relatively long dendritic trees and synapse distance to the soma is an issue. A well-studied class of such neuron is the CA1 hippocampal neuron. CA1 neurons receive inputs across their dendritic trees primarily from CA3 neurons [2]. Once an excitatory synaptic input is received the signal propagates from the dendrite to the soma and if the sum of all the input signals at the soma is above the threshold value, an action potential is generated. If the dendrite is modeled as a leaky cable structure, then the inputs at distal dendrites should not have the same influence on the soma as proximal dendrites, because the input signal will be attenuated [3], but this not the case. Magee and Cook [4] showed that EPSP increases with distance from the soma, thereby compensating for the higher attenuation that occurs with increasing path distance. In compensating for the distance of the synapse to the soma, the "voice" of distal synapses are "heard", this concept is referred to as "synaptic democracy" [1]. Furthermore, Magee and Cook [4] showed that a progressive increase in synaptic conductance is the reason for EPSP amplitude modulation. While an understanding of the exact mechanism governing the change in synaptic conductance is still being elucidated, one

theory suggests that backpropagating action potentials (bAP) play an important role in setting up synaptic democracy.

bAP amplitude decreases with distance from the soma, and activates, to various extents, voltage gated calcium channels, allowing an influx of calcium ions at the dendritic spines. Sterratt et al. [1] hypothesized that calcium transients induced by synaptically-evoked action potentials predict synapse location, thereby providing a scaling mechanism for proximal and distal dendrites to influence the soma equally. Through experimental and computational techniques Sterratt found that peak [Ca] is the best indicator for synapse distance from the soma, moreover, EPSP attenuation is also predicted well by peak [Ca]. Given the aforementioned data, Sterratt built a computational model to study a possible feedback mechanism to increase synaptic conductances to compensate for signal attenuation due to distance. The calcium current contributors in this model were NMDA, AMPA and R-type channels. Because postsynaptic calcium regulates AMPA channels in developing neurons, the synaptic conductance feedback mechanism used in Sterrat's model is mediated by homeostatic regulation of synaptic strength by modifying AMPA conductances of activated synapses[1]. AMPA conductance in the simulation is governed by Equation 1, where $g_{AMPA,i}(r)$ is the conductance of the i^{th} synapse at run r, $[Ca2+]_i(r)$ is the peak calcium concentration, and $[Ca^{2+}]_T$ is the target calcium concentration, a constant obtained by multiplying each synaptic conductance by EPSP attenuation divided by the mean EPSP attenuation of all synapses[1]. Using the AMPA conductance scaling equation Sterratt et al. showed that synaptic democracy could be achieved (Figure 1).

$$g_{AMPA,i}(r+1) = g_{AMPA,i}(r)\left(1 + k\frac{[Ca^{2+}]_T - [Ca^{2+}]_i(r)}{[Ca^{2+}]_i(r)}\right)$$

Equation 1: Update equation from g_{AMPA} that is determined by the difference between the target calcium concentration and the local calcium concentration. This equation reflects the homeostatsis of calcium controlled by g_{AMPA} imposed on the model.

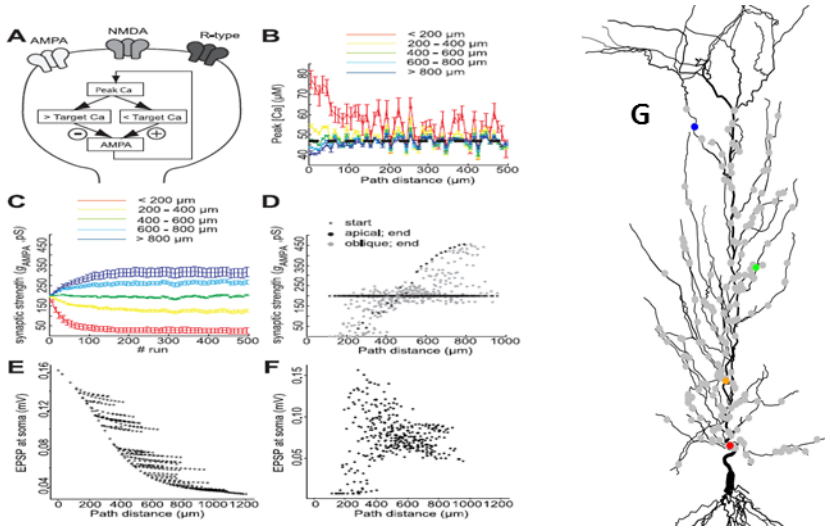

Figure 1 (taken from [1]): **Synaptic democracy established using homeostatic rules based on peak calcium levels**. **A**, Schematic showing the homeostatic regulation of synaptic strength, defined as AMPA conductance, by peak calcium. **B**, Peak calcium in spines during the time-lapse homeostatic simulation. Synapses are colour-coded and grouped according to distance. The black dotted line indicates the target level. **C**, Synaptic strength stabilises during a simulation run of 500 trials. As in B, synapses are grouped and colour-coded according to distance. **D**, Synaptic strength at the beginning (black crosses) and at the end of the scaling simulation (closed circles) plotted against distance. Black circles indicate the apical shaft, grey circles the oblique dendrites. **E**, EPSP

amplitude at the soma of individual synapses plotted against distance at the start of the simulation. **F**, EPSP amplitude at the soma of individual synapses plotted against distance at the end of the simulation. **G**, Morphology under test.

Sterratt's model looked at the effect on synaptic democracy when the synapses were synchronously stimulated with a pulse at 5Hz. In addition, Sterratt et al. used a neuron model which stimulated 240 synapses to achieve consistent action potential generation with each EPSP event provided by the 5 Hz stimulation.

In this paper, we endeavor to study the effects of various neuronal parameters within Sterratt's computational model on synaptic democracy. The major aspects we studied were the effects of changing EPSP frequency, and the effect of EPSP frequency on the number of synapses which need to be activated to elicit a bAP signal to eventually set-up synaptic democracy.

2 Methods and Results

Three experiments were performed and all involved modifying the input vector. The first experiment involved decreasing the synapse number to sub-threshold levels and lower. The second experiment involved increasing the frequency of EPSP spikes that the dendrite was bombarded with. Finally, the last experiment coupled sub-threshold synapse number with higher frequencies.

All simulations were performed on NEURON 7.3 on both personal laptops and supercomputer resources provided generously by *The Neuroscience Gateway* through the NSG Portal [5]. The model explored can be found on Model DB, Ascension Number: 144490 [1].

2.1 Results: Sub-threshold Synapse Number

Sub-threshold simulations should not allow for synaptic democracy in this model because there will be insufficient integration at the soma, and therefore, a bAP will not be produced. bAP's are key to helping set up synaptic democracy as they help to modulate calcium concentration across the dendritic branches appropriately. To test this hypothesis, simulations were performed where the synapse number was reduced to the sub-threshold regime. In Figure 2, results from this experiment are shown. As expected, there is no synaptic democracy from sub-threshold synapse numbers. Furthermore, g_{AMPA} appears to increase across the dendritic branch uniformly.

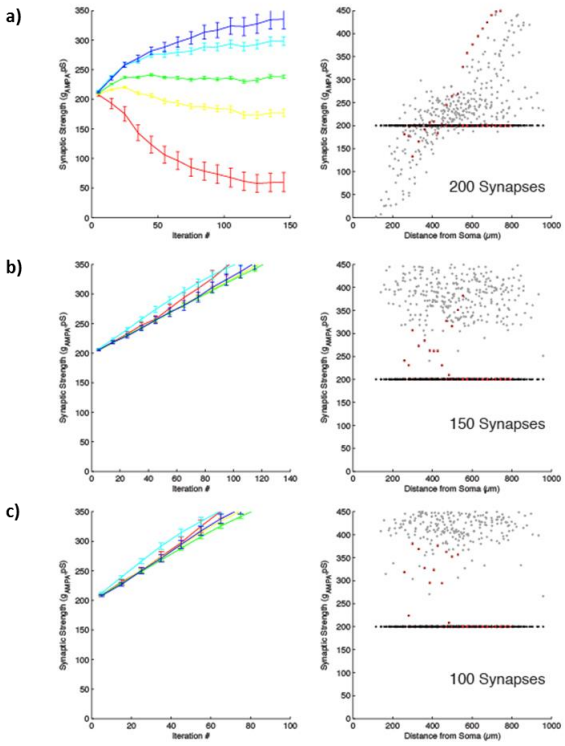

Figure 2: A 5Hz EPSP signal stimulating **a)** 200 synapses, **b)** 150 synapses and **c)** 100 synapses. Figures on the left show the change in AMPA channel conductance for specific synapses (shown in Figure 1). Figures on the right show the synaptic AMPA channel conductance as a function of distance from the soma.

2.2 Results: Increasing Frequency

In Figure 3 we show the effect on synaptic conductance, by measuring g_{AMPA} values, due to a change in synaptic stimulation frequency.

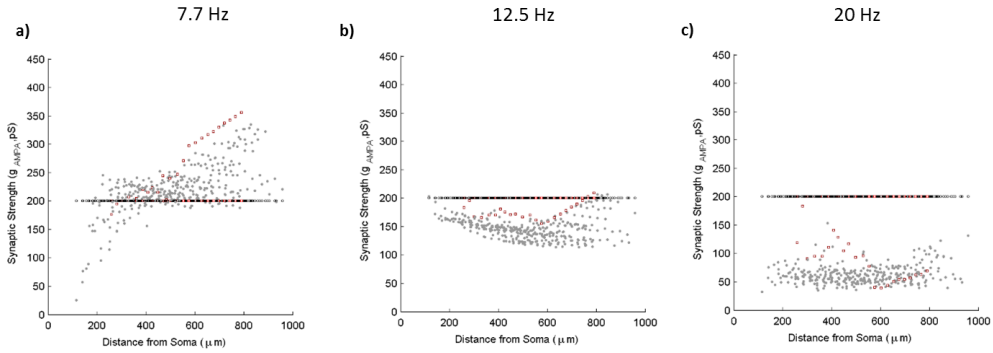

Figure 3: g_{AMPA} behavior for increasing input frequency. 200 synapses are simulated in each case. Each figure shows the g_{AMPA} weight as function of distance from the soma. The grey dots represent oblique dendrites and the red dots represent apical dendrites. In **a)**, synaptic democracy is clearly illustrated as synapses closer to the soma have lower g_{AMPA} than those that are farther away. In **b)**, synaptic democracy is no longer present and average g_{AMPA} value is lower. In **c)**, the trend of decreasing g_{AMPA} continues as most values fall between 50 to 100 pS.

Note, that the stimulation across target number of synapses is synchronous. When asynchronous synaptic inputs were simulated (data not shown), the action potential was not generated (i.e. sub-threshold stimulation), thus preventing a change in conductances and the establishment of synaptic democracy. Although asynchronous inputs may be a more physiologically representative, as they model the stochastic nature of noise present in dendritic stimulation, it is more difficult to characterize the interaction effect between various levels of asynchronous inputs and stimulation frequency. Thus, we chose to model sub-threshold stimulation by modulating the number of active synapses.

2.3 Results: Sub-threshold synapse number coupled with high frequency

To determine how a train of multiple EPSP events would influence an axon with less than the threshold value of activated synapses, the CA1 neuron was simulated to receive continuous rounds of EPSP excitation at varying frequencies. We expected that the added number of EPSP events and their increasing frequencies would provide a means for the neuron to compensate for the lowered number of active synapses. In this sense, a neuron that has a limited number of inputs can still respond to trains of stimuli to potentially establish synaptic democracy through bAPs. As expected, synaptic scaling occurred with a general trend, with a higher number of synapses and/or a higher frequency of stimulation resulting in an overall decrease in AMPA receptor conductances (Figure 4). However, the distribution of conductance values exhibited a nonlinear dependence on the synapses' distances from the soma. In particular, instead of the conductances generally increasing monotonically with distance, conductance minimums were observed at distances ~ 500 µm. Interestingly, this effect was more pronounced in the cases with higher synapses and/or stimulus frequencies. We suspect that the increased stimulation may have resulted in synapses proximal to the soma receiving saturating levels of input during the refractory periods that follow preceding stimulus events. At saturation, a synapse would not be able to base scaling responses on a bAP; thus, the proposed scaling mechanism may not contribute to synaptic democracy in this regime.

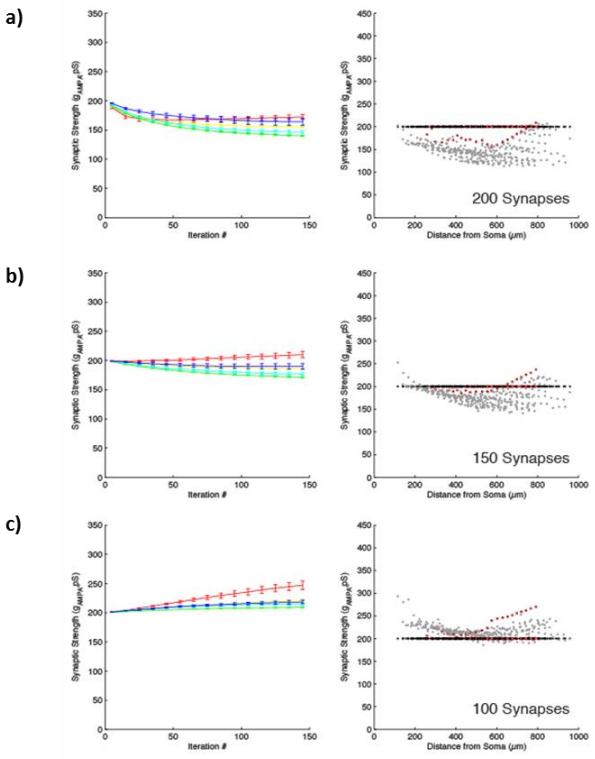

Figure 4: Influence of higher frequency stimulus events for various synaptic populations. (a) At a stimulation frequency of 12.5 Hz, the synaptic conductances scaled to lower values for neurons with higher active synapses, as compared to neurons with fewer synapses (b) and (c). A non-linear distribution of conductances across distances from the soma is observed across the varying synapse numbers, with a more pronounced effect for higher synapse numbers.

3 Discussion of results

The results obtained in large part appear to be expected and consistent with Sterratt et al. [1]. The number of synapses and the frequency of synchronous EPSP's were varied and then AMPA synaptic conductances (g_{AMPA}) were analyzed across the dendritic branches. In sub-threshold regimes (< 190 synapses according to [1]), no synaptic democracy is observed because bAPs are not triggered. However, the results show that increasing frequency can compensate for fewer synapses. Interestingly, synaptic democracy is not observed when frequency is increased and the number of synapses are in the supra-threshold regime.

Frequent synaptic excitation, which was modeled up to 20 Hz, a markedly higher input vector than the 5 Hz used in Sterratt et al., not only causes synaptic democracy to be abolished, but also causes g_{AMPA} channels across the dendrite to approach zero. Regardless of dendritic location, all g_{AMPA}'s converged to zero in a uniform fashion with increasing excitation frequency.

One potential explanation for the diminishing g_{AMPA} values is provided by the mechanisms involved in modulating local calcium concentration. Specifically, Equation 1 shows that the difference between the target calcium and local calcium concentrations determine g_{AMPA}. This model is representative of a neuron where calcium concentration is homeostaticly maintained through dynamic g_{AMPA} – the model is motivated by an extensive literature review discussed in [1]. By overly exciting the dendrites, levels of calcium are elevated disrupting the homeostasis. The neuron model attempts to compensate by decreasing g_{AMPA}'s until they are minimized.

From a neurophysiological perspective, diminishing g_{AMPA}'s reflect a down regulation in AMPA receptors (AMPAR). According to [6], "... increasing neural network activity by membrane depolarization or by unbalancing excitatory and inhibitory input to favor excitation [7] result in reductions in synaptic receptor accumulation through receptor internalization…" Receptor internalization (also known as endocytosis) is a process by which the synapse consumes receptors effectively reducing the coupling between pre and post-neurons. Receptor internalization can be expressed quantitatively by g_{AMPA} approaching zero, and therefore, seems quite compatible with the results. Furthermore, consistently with these neurophysiological studies helps to validate Sterrat's et al. model.

It is enticing to speculate on the role of the AMPAR internalization due to excessive excitation with regard to neuropathology. One hypothesis as to the role of AMPAR internalization may be as a stabilizing mechanism for neurons in overly excited networks. Relevant work on an epileptic rat model of the limbic system is described in [8], where they found that rats that have chronic seizures tend to have more AMPAR's. Applying the AMPAR hypothesis to the results found in [8], we theorize that rats that suffer from chronic seizures are unable to internalize AMPAR's causing them to lack this apparent stabilizing mechanism in the limbic circuits.

Two future directions for this project which inform each other include 1) adding more mechanistic detail to this model, 2) reducing the neuron model to only the most impactful compartments. The model still lacks basic neuronal compartments such as inhibitory synapses, which may also contribute to synaptic democracy or g_{AMPA} convergence to zero. To study synaptic democracy in larger networks, the detailed neuron modeled considered in this paper may help to elucidate which are the most impactful compartments. Eventually, given a sufficiently large network, circuits in

the limbic system can be modeled to potentially be used in the study of neuropathologies such epilepsy, memory loss and more.

4 Citations, figures, tables, references

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