Modeling Depolarization Induced Suppression of Inhibition in Pyramidal Neurons

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Abstract

Depolarization-Induced Suppression of Inhibition (DSI) is effectively a mechanism for feedback-inhibition of inhibition. Wilson and Nicoll [4] showed that its effect is mediated through a retrograde endocannabinoid signal. Here, we produced a simple model for DSI which matched the effects and kinetics of DSI found in empirical data. We then explored a possible function for DSI through examining its effects on shaping orientation tuning curves. DSI demonstrated a dramatic effect on the shape of the tuning curve, indicating that it may play a similar role in-vivo.

1 Introduction

1.1 Endocannabinoid-Mediated Depolarization Induced Suppression of Inhibition

Depolarization-Induced Suppression of Inhibition (DSI) is a form of short term plasticity in which the depolarization of a cortical pyramidal cell, for example, due to a train of action potentials, causes a transient suppression of GABA mediated transmission to that pyramidal cell [2]. Wilson and Nicoll [4] demonstrated that DSI is due to a retrograde endocannabinoid signal released from pyramidal cells upon depolarization. When depolarized, buildup of intracellular calcium causes pyramidal cells to release endocannabinoids which bind to G-protein coupled cannabinoid receptor-1 (CB1); these receptors are located on the axon terminals of certain GABAergic cell types. The endocannabinoid binding to CB1 receptors causes a signaling cascade which reduces calcium levels in the presynaptic terminals, thus decreasing the amount of GABA released and effectively suppressing inhibition [5].

1.2 A Role for DSI in Cortical Computation

CB1 receptors are found throughout the cortex, indicating the possibility for DSI to play a role in a variety of cortical computations. In the neocortex, an irregular spiking GABAergic interneuron has been shown to express CB1 receptors [1]. This cell type, located primarily in layer 2/3, can be molecularly identified through its co-expression of the molecular markers cholecystokinin (CCK) and vasoactive intestinal peptide (VIP) [3]. While the presence of this class of interneuron indicates DSI is likely influencing cortical circuit dynamics, its exact role is unclear.

Here, we attempt to model a potential function of DSI in cortical microcircuitry through exploring its possible role in orientation tuning in the visual cortex. First demonstrated by Hubel and Wiesel, orientation tuning is a property of cells in the visual cortex whose firing rates vary as a function of the orientation of a visual stimuli. We created a two neuron model; a pyramidal cell and CCK interneuron were modeled to mimic the effects of DSI seen in literature. To introduce orientation tuning, varying levels of current were injected into the pyramidal cell, as a simplified representation of changes in orientation of a visual stimuli. We examined the shape of the tuning curve with DSI compared to without DSI and saw dramatic changes in both overall firing rates and the shape of the tuning curve, indicating the DSI may play a similar role in vivo.

2 Methods

2.1 Hodgkin-Huxley Model Neuron

A Hodgkin-Huxley model was chosen as the basis for both the pyramidal neuron and the CCK neuron. The Hodgkin-Huxley model has been used extensively since its first description in the 1950s; the computational model behaves and responds well to external current stimuli, as well as offering extensive possibilities for expansion and the introduction of new ions, receptors, and currents. Both the pyramidal neuron and the CCK interneuron shared many of the same parameters, which are detailed below. These parameters generate model cells which accurately reflect the spiking dynamics found in empirical data. The Hodgkin-Huxley model was implemented in Python using the following constants and equations:

Table 1: Hodgkin-Huxley Neuron

Variable	Value
C_m	$1\frac{\mu F}{cm^2}$
g_{Na}	$120\frac{mS}{cm^2}$
g_K	$36\frac{mS}{cm^2}$
g_L	$.3\frac{mS}{cm^2}$
E_{Na}	$45\,mV$
E_K	$-82\,mV$
E_L	$-59.39\,mV$
A_m	$\frac{.1*(V+45)}{1-e^{\frac{-45-V}{10}}}$
B_m	$4e^{\frac{-70-V}{18}}$
A_h	$.07e^{\frac{-70-V}{20}}$
B_h	$\frac{1}{1+e^{\frac{-40-V}{10}}}$
A_n	$\frac{.01(V+60)}{1-e^{\frac{-60-V}{10}}}$

B_n	$.125e^{\frac{-70-V}{80}}$
I_{Na}	$g_{Na} * m^3 * h * (V - E_{Na})$
I_K	$g_K * n^4 * (V - E_K)$
I_L	$g_L * (V - E_L)$

To model the inhibitory synapse from the CCK neuron to the pyramidal cell, a GABA-mediated inhibitory current was introduced. The following parameters include GABA concentration dynamics as well as the GABA channels' opening and closing kinetics:

Table 2: GABA-Mediated Inhibitory Current

Variable	Value
E_{Cl}	$-90\,mV$
α_r	$5mM^{-1}ms^{-1}$
β_r	$.18ms^{-1}$
$[T]_{max}$	$1.5mM$
K_p	$5\,mV$
V_p	$7\,mV$
$\frac{dr}{dt}$	$\alpha_r[T](1-r) - \beta_r r$
$[T]$	$\frac{[T]_{max}}{1 + e^{-\frac{V_{pre} - V_p}{K_p}}}$
I_{Cl}	$g_{GABA_A} r(V_{post} - E_{Cl})$

2.2 Modeling Endocannabinoid Release and DSI

DSI has been shown to be mediated by endocannabinoid release. Thus, it was necessary to introduce a new neurotransmitter to the two-neuron model. The goal of this implementation was to create a transmitter whose effect would inhibit the release of GABA but without affecting the spiking dynamics of the presynaptic inhibitory interneuron. This is because DSI suppresses inhibition through effecting only the axon terminal, rather than the entire presynaptic neuron.

It was also necessary to be able to modify the opening and closing of the endocannabinoid receptor channels, to produce a viable simplified model. Our model does not capture the intracellular signaling details which cause the release of endocannabinoids from the pyramidal cell or the intracellular signaling in the CCK cell which results in the diminished release of GABA transmitter. Instead, we were interested in modeling the effect of DSI at different pyramidal cell firing rates, rather than the detailed mechanism of how DSI was operating intracellularly. We believe our model captures the effect of DSI without needing to model all the intracellular details – evidence for this claim is demonstrated in our results. The following equations and parameters were used for endocannabinoid release and binding:

Table 3: Endocannabinoid Channel Parameters

Variable	Value

$K_{p_{endo}}$	5mV
$V_{p_{endo}}$	0mV
$Ar_{2_{endo}}$	0.004mM-1ms-1
$Br_{2_{endo}}$	0.000045ms-1
$T2_{m_{endo}}$	1.5mM
$\frac{dr_{endo}}{dt}$	$Ar2_{endo}(t) * \left(\frac{T2_{m_{endo}}}{1 + e^{-\frac{V_2 - V_{p_{endo}}}{K_{p_{endo}}}}}\right) * \left(1 - r_{1_{endo}}\right) - Br_{2_{endo}}(t) * r_{1_{endo}}$
$\frac{dr_2}{dt}$	$Ar_{2_{endo}} * \left(\frac{T2_m}{1 + e^{-\frac{V1 - V_p}{K_p}}}\right) * \left(.08 * \left(1 - r_{1_{endo}}\right)\right) * (1 - r_2) - B_{r_2} * r_2$

2.3 Tuning Curves

To stimulate our two neuron model, external current was injected independently into both neurons. For the CCK neuron, a constant current of 10uA was injected. For the pyramidal neuron, a baseline amount of current (7uA) was injected at non-preferred orientations. The amount of current increased in a Gaussian fashion as the stimulus orientation reached preferred orientation (15uA). While a physiological tuning curve is based off the inputs of many excitatory and inhibitory cells, we believe that this simplified model could capture basic elements of tuning curve properties.

4 Results

4.1 Confirming DSI Behavior

First, we confirmed that the interaction between endocannabinoid channels and GABA release produced proper effects on pyramidal cell membrane voltage. Stimulating the presynaptic inhibitory CCK cell produced baseline inhibitory post synaptic potentials (IPSPs) through opening a given amount of GABA channels. However, depolarizing the pyramidal cell before stimulating the CCK cell caused a release of endocannabinoids which bound to their receptors on the CCK axon terminal. The endocannabinoid release upon depolarization caused a decrease in GABA release and reduced IPSP amplitude. Thus, our model was able to replicate the overall effect found in DSI on pyramidal cell membrane voltage.

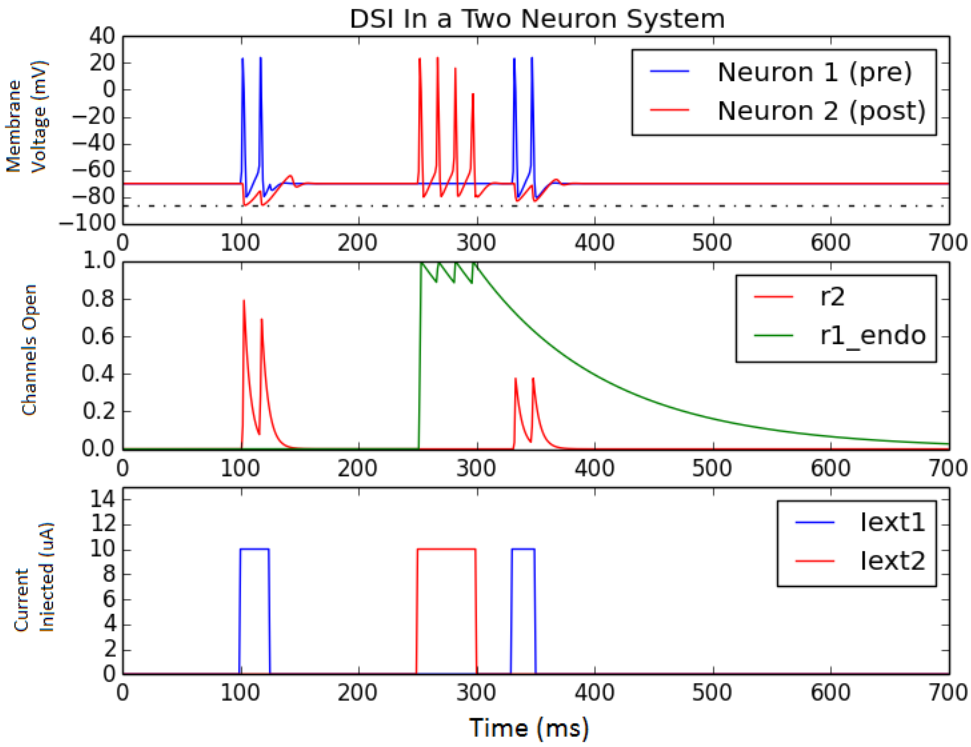

Figure 1: Eliciting DSI in Post-Synaptic Cell

Top Panel – Voltage Traces of CCK neuron (blue) and pyramidal cell (red)

Middle Panel – Portion of Endocannabinoid (green) and GABA (red) channels open

Bottom Panel – Current injected into CCK neuron (blue) and pyramidal cell (red)

However, the DSI parameters needed further fine tuning to replicate the kinetic of DSI found physiologically.

4.2 Physiological DSI

To demonstrate that this simplified model of DSI could be relevant in examining potential interactions between DSI and small neural networks, we verified that the variables could be modified to reproduce the physiological kinetics of DSI observed in in-vivo and in-vitro preparations. To produce physiological kinetics, we modified the opening and closing gating variables of the endocannabinoid receptor: Ar2endo and Br2endo. As demonstrated in Figure 2, decreasing the opening variable Ar2endo produced the slow buildup of endocannabinoids that mimicked the kinetics found in Zachariou et al [5]. That is, longer depolarization of the pyramidal cell released more endocannabinoids, up to a maximum level achieved through five seconds of depolarization. Similarly, decreasing the Br2endo closing variable yielded endocannabinoid decay similar to that shown in Wilson and Nicoll [4].

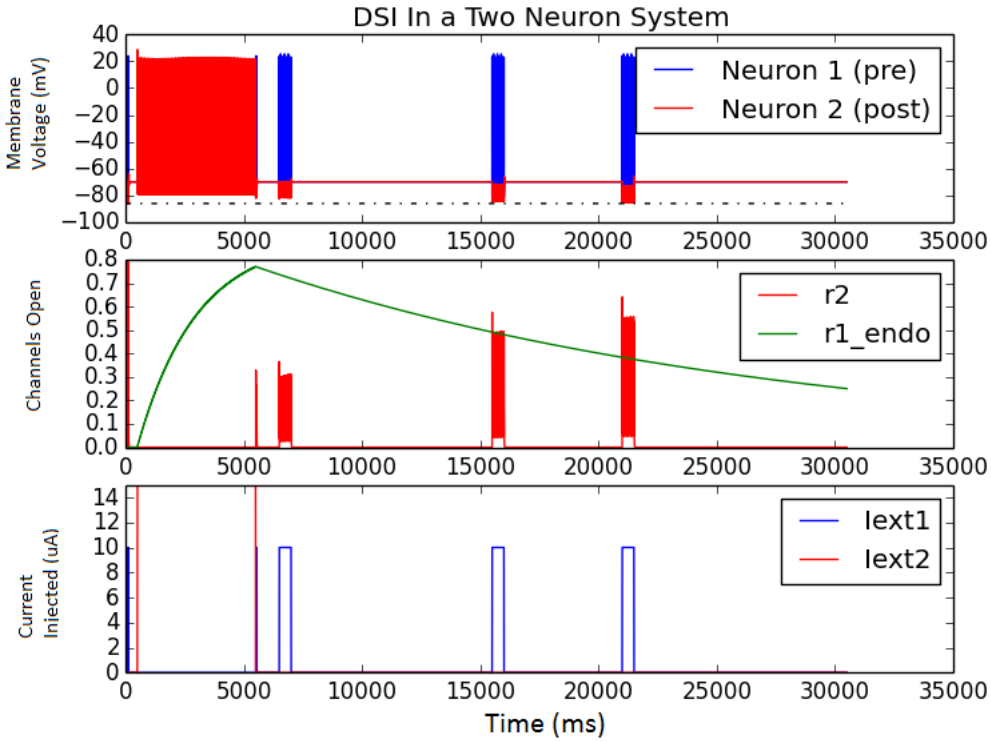

Figure 2: Replicating Physiological DSI Kinetics

Top Panel – Voltage Traces of CCK neuron (blue) and pyramidal cell (red)

Middle Panel – Portion of Endocannabinoid (green) and GABA (red) channels open

Bottom Panel – Current injected into CCK neuron (blue) and pyramidal cell (red)

Thus, we have shown that this model of DSI, although simplified, can be used to model physiological kinetics of endocannabinoid release, decay, and decreases in IPSP.

4.3 DSI-Mediated Spike Rate Modification

To show that this model of DSI could potentially affect the fine-tuning of an orientation tuning curve, we examined whether DSI could modify spike rates of the pyramidal cell during stimulus orientations. These different orientation were modeled by varying levels of current injections (See methods for more details).

As shown in Figure 3, without DSI, at non-preferred orientations of 0 to 30 degrees the pyramidal cell has a constant firing rate. This firing rate then begins to increase at orientations of 30 degrees. On the other hand, with the introduction of DSI, a graded response to orientation immediately emerges at non-preferred orientations. Interestingly, the cell firing rates saturates at 45 degrees. It should be noted that GABA conductance was increased to produce this effect, as low GABA conductance did not produce enough inhibition to for DSI to play a role in pyramidal cell firing rates. Thus, DSI could potentially be exploited in producing spike-rate dependent orientation preferences.

DSI in Orientation Tuning

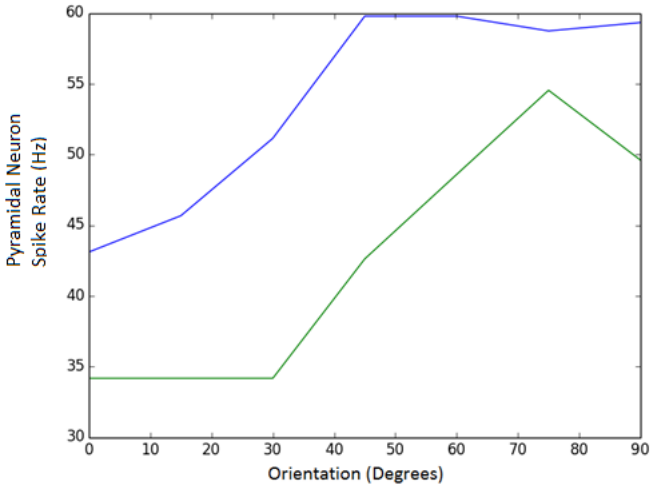

Figure 3: DSI-Mediated Spike Rate Modification

Spike rates of pyramidal neuron shown with DSI (blue) and without DSI (green)

Preferred orientation of the pyramidal neuron is 90 degrees

5 Discussion

Here, we have shown that our model was effective at reproducing the effects of DSI on pyramidal cell inhibition. Our modeled DSI produced robust effects on IPSPs and spike rates, and was tailored to match the kinetics of reports of DSI in literature. Additionally, we were able to demonstrate that DSI could possibly play an important role in orientation tuning. DSI was shown to dramatically change the shape of the tuning curve. However, this result comes with several caveats.

First, our model of DSI merely modeled the effects of DSI. The intracellular mechanisms required to produce the effects of DSI were not modeled here. While we were able to mimic the effects of DSI compared to previous literature, it is possible that certain mechanistic elements of DSI would have unforeseen consequences in tuning curve properties. Modeling more intracellular elements which are critical for DSI, such as calcium ion concentrations, would likely produce a more realistic model.

Second, the orientation tuning of the pyramidal cell was modeled through artificial means. Injecting varying levels of current likely does not accurately reflect why a pyramidal neuron has higher firing rates at preferred orientation. Ideally, a model of many (>10,000) neurons would be used. Tuning curves arise due to the inputs of many different excitatory and inhibitory cells onto a pyramidal neuron. The balance of excitation and inhibition is critical in producing a tuning curve. Nevertheless, because CCK interneurons make up a population of inhibitory neurons in the cortex which do synapse onto pyramidal cells, it seems likely that DSI could still play an important role in orientation tuning. Thus we believe our initial hypothesis has been somewhat validated – it is likely DSI plays a role in shaping tuning curve, however, this role is probably much more subtle than the effect presented here.

References

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