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Modeling synaptic facilitation and depression in thalamocortical relay cells

A thesis submitted in partial fulfillment of the requirement for the degree of Bachelor of Science in Interdisciplinary Studies from The College of William and Mary

by

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Abstract

Thalamocortical relay (TC) neurons in the lateral geniculate nucleus receive both retinal and cortical input; however, the two pre-synaptic signals are filtered in significantly different ways. Using a three-compartment model of a TC cell, with distinct equations for the proximal and distal dendrites, we model the synaptic plasticity of feedback signals from the cortex (corticogeniculate facilitation) and feedforward retinal input (retinogeniculate depression). We discuss the use of model-generated cross-correlograms in lending insight into the interplay of the driving and modulating afferents.

1 Introduction

1.1 The thalamus

Centrally located in the diencephalon, the thalamus plays a major role in the relaying of signals from ascending sensory pathways and descending cortical pathways to numerous locations across the cortex. While the function of the thalamus is not entirely known, it is evident that the structure plays significant roles in a number of cognitive processes such as sensory perception, awareness, and attention, among many others.

The thalamus is divided into a dorsal and ventral thalamus; however, most use of the term thalamus refers exclusively to the dorsal thalamus, while distinguishing the “ventral thalamus” as a separate body through which fibers from the dorsal thalamus pass on their way to the telencephalon. The dorsal thalamus is itself divided into a number of nuclei that can be generally categorized as anterior, medial, and ventrolateral. Anterior nuclei typically involve sensory and motor information; medial nuclei concern visceral, emotional, and limbic systems, while ventrolateral nuclei appear to be involved in learning and memory processes, as well as alertness.

Nuclei in the thalamus can also be categorized as relay, association, or nonspecific: relay nuclei have defined inputs and project to functionally distinct areas of the cerebral cortex, association nuclei both receive input and output to the association areas of the cortex, and nonspecific nuclei project diffusely throughout the cortex. These projections are achieved by glutamatergic relay neurons in the nuclei, the principle cells of the thalamus; GABAergic interneurons are an important component of dorsal relay nuclei [1]. A summary of inputs and outputs of the thalamus is provided in Figure 1.

S. Murray Sherman goes further in classifying the inputs to the relay neurons in the nuclei as driving or modulatory, a distinction that reflects the effect of the input on the post-synaptic thalamic neurons. Drivers are less common than modulators, act on ionotropic post-synaptic receptors, have a fast and short-lived effect, and the information transmitted corresponds the receptive field properties of the sensory periphery. Modulators are more numerous, act on metabotropic post-synaptic receptors with G-protein coupled receptors, have a slower and more diffuse effect, and act to alter the probability of certain aspects of sensory relay [5].
The difference in the quantity of driving and modulatory afferents synapsing on a thalamic cell is not to be understated: in the case of cells in the lateral geniculate nucleus of the thalamus (LGN), responsible for transmitting vision information, only 10–20% of afferents to relay neurons correspond to the ascending retinal input, while 40% correspond to descending cortical feedback, 30% are from ascending brain stem inputs, and 10–20% come from interneurons and other inhibitory sources. Those 10–20% of retinal afferents are the only drivers of the cell; all other inputs are modulatory. The location at which drivers and modulators synapse on the thalamic cell is also key: driving afferents synapse at dendrites very close to the soma, while modulatory inputs synapse at more removed dendrites, leading to distinct patterns of electrical loss and diffusion from the dendrites. Drivers, furthermore, have “local sign” while modulators do not; e.g. driving visual input to the LGN is retinotopically
mapped.

From an anatomical perspective, drivers seem to have large boutons, with so-called RL-type (round, large) synaptic vesicles and well-localized terminal zones; in contrast, modulators have longer, thinner branches with swollen, stub-like shoot-offs and RS-type (round, small) vesicles. Unfortunately, these distinctions are often not enough to make a conclusive identification of an input as driving or modulatory [1].

Distinguishing between driving and modulatory inputs to a cell is much simpler when the input corresponds to a clearly defined receptive field (for instance, vision, as opposed to proprioception) as loss of driving input yields a measurable effect (i.e. loss of center-surround receptive field properties). Nonetheless, drivers and modulators can also be differentiated by their distinctive cross-correlograms, which here refers to a graphical measure of correlation between two spike trains. Driving inputs have a pronounced spike in the correlogram that is present for a short time interval, while modulatory inputs have a less pronounced spike that acts over a significantly longer period of time, as can be seen in Figure 3 [5]. Further background on correlograms and a mathematical basis for cross-correlation is discussed in Section 1.3.

The cells that compose the thalamic nuclei can be themselves divided based on the origin of their driving afferents. A “first order” relay is one that receives its driving input from ascending pathways; a “higher order” relay receives driving afferents from layer 5 of the cortex. Both first order and higher order relays receive modulatory input from layer 6 of the cortex and project primarily to layer 4, although other sources of modulation and targets of the thalamic cells exist. Each thalamic nucleus is composed of a mixture of first and higher order relay neurons in varying proportions. The cell types that are the focus of this paper are first-order relay cells called thalamocortical relay neurons (TC cells); in particular, the focus is on TC cells located in the LGN [1].

Driving and modulatory afferents to thalamocortical relay neurons experience a phenomenon known as short-term synaptic plasticity, discussed in the next section. A central aim of our work was to determine the significance of this synaptic plasticity in influencing the ultimate firing pattern of the TC relay. In order to quantitatively assess its role, we chose to generate and compare cross-correlograms of the spike trains of the system in two states: one in which a form of synaptic plasticity was turned “on” and one with that same plasticity “off.” It was expected that substantial differences would exist between the cross-correlograms of the distinct systems.

1.2 Synaptic plasticity

Synapses are the sites at which neural communication occurs and form at the juncture of a pre-synaptic cell synaptic bouton and a post-synaptic cell dendrite. A signal is transmitted by the release of neurotransmitters into the synaptic cleft by the pre-synaptic cell and the binding of neurotransmitters to post-synaptic receptors.

While often treated as passive vehicles for the transmission of action potentials, synapses can possess a diverse array of dynamic filtering properties, due to modulation
of synapse properties on various time scales, collectively referred to as “synaptic plasticity.” The time scale of plasticity can vary dramatically, as can the role it plays in cognition—long-term plasticity appears to be important for memory and learning, while short-term plasticity, occurring on a time scale of minutes to milliseconds, appears to be responsible for synaptic computation.

Facilitation is a form of short-term synaptic plasticity in which the probability of neurotransmitter release by the pre-synaptic cell is temporarily increased; depression is short-term plasticity in which the probability of release is temporarily decreased, subsequent to a primary release event. A pre-synaptic bouton with a low initial likelihood of neurotransmitter release is one on which facilitation is likely to occur, whereas if the initial probability of neurotransmitter release is high, depression is the more probable phenomenon. Functionally, a facilitating synapse acts as a high-pass filter, transmitting high frequency input signals, while depressing synapses serve as low-pass filters and transmit low frequency signals [2].

A number of studies have implicated Ca\(^{2+}\) as the critical molecule responsible for facilitation and depression. In particular, residual calcium after a pre-synaptic spike is thought to increase the likelihood of further spikes, yielding facilitation [3].

![Figure 2](image)

Figure 2: A. Synaptic current in TC cell after two pulses delivered to fibers of the optic radiation (OR) and optic tract (OT). The two pulses were separated first by a time interval of 10 ms and then by an interval of 25 ms. Figure reproduced from Alexander, G. and Godwin, D. “Presynaptic inhibition of corticothalamic feedback by metabotropic glutamate receptors.” J. Neurophysiol. 94 (2005) pp. 163-175. B. Results of simulation of the same experiment in the model. Scale bars are 10 ms and 10 pA.

The work detailed in this paper involves modeling facilitation and depression in thalamocortical relay (TC) cells. As discussed above, TC cells receive driving, ascending input from the retina via the optic tract (OT) and modulatory, descending
input from the cortex via the optic radiation (OR). The OT afferents synapse near the soma at the *proximal dendrites* and have been demonstrated to exhibit depression. The OR afferents, on the other hand, synapse far from the soma at the *distal dendrites* and exhibit facilitation. It is the aim of this project to model facilitation and depression and to successfully gain insight into their interplay in determining TC cell firing patterns. The mathematical modeling of TC neuron input/output properties mediated by short-term synaptic plasticity is inspired by prior work of an experimental collaborator, Dwayne Godwin of Wake Forest University [4], some of whose data is reproduced by model in Figure 2.

![Figure 3: A and B. Characteristic cross-correlations of TC output and driving retinogeniculate input and modulatory corticogeniculate input, respectively. Figure reproduced from Sherman, S.M. and Guillery, R.W. “On the actions that one nerve cell can have on another: Distinguishing ‘drivers’ from “modulators”.’ PNAS. 95 (1998). 7121-7126.](image)

**1.3 Cross Correlation**

Let $A_1$ and $A_2$ be the two spike trains of zeros and ones, each for a distinct cell, where zeros represent the absence of the cell firing, ones represent the cell firing, and each entry in the train corresponds to a discrete step in time. That is, let $\tilde{t} = (\tilde{t}_1, \tilde{t}_2, \cdots, \tilde{t}_n)$ be the firing times for $n$ distinct action potentials in Cell 1 and define
\[ A_1(t) = \sum_i \delta(t - \bar{t}_i) \]
to be the spike train corresponding to the cell.

The cross correlation of \( A_1 \) and \( A_2 \) is a function of the possible time interval between two spikes (\( \tau \)), given by the equation

\[ C(\tau) = \langle A_1(t)A_2(t-\tau) \rangle_t \]

where \( \langle \cdot \rangle_t \) denotes the average over all \( t \). It can be quickly seen that this is not a symmetric function. For our purposes, so that a spike in the post-synaptic cell after a time interval of \( \tau \) has passed since the pre-synaptic cell fired increments \( C \) at positive \( \tau \), let \( A_1 \) be pre-synaptic and \( A_2 \) be post-synaptic.

Functionally, the cross correlation provides a measure of the probability of a post-synaptic spike given that a certain amount of time has passed since a pre-synaptic spike. If the pre-synaptic cell is inhibitory, for instance, the value of \( C(\tau) \) for positive \( \tau \) would be expected to be less than \( C(\tau) \) at negative \( \tau \), with the exact form of the correlation dependent on the time scale of the inhibition. Similarly, for a pre-synaptic input that has a fast-acting, significant, excitatory impact of the post-synaptic cell, \( C(\tau) \) would be expected to have a substantial positive peak for positive \( \tau \) near 0.

Experimentally-generated cross-correlograms of drivers and modulators are shown in A and B of Figure 3.

2 Model formulation

Thalamocortical relay neurons can experience two types of spiking: tonic and bursting. While the regime under which our model operated did not typically hyperpolarize the cells enough to activate the low-threshold calcium current (\( I_T \)) responsible for bursting behaviors, a model including \( I_T \) was still selected in order to reproduce cell behavior as accurately as possible. Furthermore, because the different location of the facilitating and depressing synapses was important in the analysis, a model of a TC cell in which soma, proximal dendrites, and distal dendrites were separated and treated as three distinct compartments was employed.

2.1 Three-compartment TC cell model

A three-compartment model of a thalamocortical relay neuron by Zomorrodi, Kröger, and Timofeev [7] was adapted for our purposes, as depicted in Figure 4. In the Hodgkin-Huxley style equations for this model,
Figure 4: A visualization of the adapted three compartment model, showing the soma ($V_1$), proximal dendrites ($V_2$), and distal dendrites ($V_3$), with OT and OR inputs.

\[
C \frac{dV_1}{dt} = -I_L - I_{Na} - I_K - I_T - g_{12}^*(V_1 - V_2) + I_{inj}
\]

\[
C \frac{dV_2}{dt} = -I_L - I_T - I_{syn}^D - g_{12}^*(V_2 - V_1) - g_{23}^*(V_2 - V_3)
\]

\[
C \frac{dV_3}{dt} = -I_L - I_T - I_{syn}^E - g_{23}^*(V_3 - V_2),
\]

$V_1$ refers to the somatic voltage, $V_2$ to the proximal dendritic voltage, and $V_3$ to the distal dendritic voltage. The membrane capacitance is $C$ and the conductance $g$ between two compartments is identified by its subscripts (e.g. $g_{12}^*$ refers to the conductance between the soma and proximal dendrites). Present in the model but not in the equations above are the areas $A$ of the three compartments, included in the $g^*$ terms, and a “dendritic correction term” included by the original authors.

The sodium ($I_{Na}$), potassium ($I_K$), and leak ($I_L$) currents are modeled in standard ways by gating variables, and the low-threshold calcium current ($I_T$) is generated using a form of the GHK equation. To verify that the model could reproduce TC-cell specific behaviors, its behavior was simulated in the presence of a constant applied current ($I_{inj}$) and both tonic and burst-type spiking were observed (Figure 5).
2.2 Synaptic plasticity equations

Several models of facilitation and depression exist; ours is a generalization of a previous model, modified to make symmetric equations for the two forms of plasticity. The synaptic currents for the OR and OT inputs are denoted by $I_{syn}^F$ and $I_{syn}^D$ respectively. These in turn are defined by the equations $I_{syn}^F = g_F w(V_3 - V_{syn})$ and $I_{syn}^D = g_D s(V_2 - V_{syn})$. Because the reversal potential for the synaptic currents is zero, $V_{syn} = 0$ mV.

In the event of a pre-synaptic spike from OR input, the following changes instantaneously occur:

\[ w \leftarrow w + f(1 - w) \]
\[ f \leftarrow f + \delta f(f_{max} - f) \]

Similarly, in the event of a spike from the OT afferent:
\[ s \leftarrow s + p(1 - s) \]

\[ p \leftarrow p + \delta_p(p_{\text{min}} - p) \]

The differential equations governing behavior of these variables in the absence of a spike are:

\[
\frac{dw}{dt} = -\frac{w}{\tau_w} \\
\frac{df}{dt} = \frac{(f_{\text{min}} - f)}{\tau_f} \\
\frac{ds}{dt} = -\frac{s}{\tau_s} \\
\frac{dp}{dt} = \frac{(p_{\text{max}} - p)}{\tau_p}
\]

The standard model assumes \( p_{\text{max}} = 0.9, p_{\text{min}} = 0.1, f_{\text{max}} = 0.9, f_{\text{min}} = 0.1 \) as the max and min parameters. The time constants \( \tau_s = 25 \text{ ms}, \tau_d = 300, \tau_w = 30 \text{ ms}, \) and \( \tau_f = 325 \text{ ms} \) were determined from the Alexander-Godwin two-pulse protocol data. Using the modeling equations and further data from the two-pulse experiment, it was determined that \( \delta_p = 0.735 \) and \( \delta_f = 0.147 \). Model results are compared to experimental results in Figure 2.

3 Analysis

A central aim in our work was understanding the significance of the facilitation and depression dynamics (and any interplay between them) in determining a relay cell’s input/output properties. To assess this, we developed a scheme in which depression and facilitation could be turned “off” by removing the plasticity but keeping the transfer ratio of input spikes to output spikes constant. For the depressing OT input, this was achieved by setting \( \delta_p = 0 \) and adjusting \( p_{\text{max}} \) to a lesser value (\( p_{\text{max}} = 0.45 \)). For facilitation in the OR input, \( \delta_f \) was set to zero and \( f_{\text{min}} \) was increased (t) \( f_{\text{min}} = 0.4 \). Figure 6 illustrates the differences between the synaptic gating variables with plasticity “on” and “off.”
Figure 6: A. The $s$ gating variable and depressed synaptic current from the OT for with depression plasticity “on.” B. The $s$ gating variable and depressed synaptic current from the OT for with $\delta_p = 0$ and $p_{\text{max}} = 0.45$. In A, the amplitude of the initial current spikes is larger, but subsequent responses are depressed. In B, the spikes are relatively constant in magnitude.

3.1 1-D Correlograms

One dimensional cross correlograms (described in Section 1.3) were generated using MATLAB’s `xcorr` function.

Qualitatively, all figures matched the form predicted by the one-dimensional cross correlograms presented in Figure 3 and [1]; however, quantitative differences existed between the cases with plasticity on or off. Specifically, compared to the cross-correlation with both facilitation and depression turned on, the case where facilitation plasticity is turned off demonstrates less correlation (lower instantaneous firing rate) for the depressing input for $\tau$ slightly greater than zero and more correlation (higher instantaneous firing rate) for the facilitating input at the same $\tau$. This can be partially explained by the fact that each individual facilitation spike imparts more current in the model when facilitation is turned off (explaining the rise in correlation for the modulatory OR input), and that the effect of several OR input spikes, not being facilitated, will be less, decreasing the time interval over which they can alter the probability that a driving spike from the OT yields an output spike in the TC cell (explaining the decrease in correlation for the driving input).

The correlograms with depression plasticity turned off, surprisingly, looked very similar to the correlograms both plasticities turned on. An expected difference between the two was that depression plasticity being turned on would cause a slight decrease in correlation for positive $\tau$ very close to zero, as the second of two OT input spikes in rapid succession would impart almost no current to the post-synaptic cell and therefore would not be correlated with a spike. It is possible that this phenomenon is obscured by comparison to the case with depression turned off due to the adjustments made to preserve the transfer ratio.

Taken as a whole, the 1-D correlograms suggest a negative result: synaptic plasticity, as interpreted by our model, does not appear to have a significant effect on the
firing rate probabilities that are reflected by a 1-D cross-correlogram, although it is possible that other analytical techniques could be better suited to elucidate plasticity’s role. As has been mentioned, the result for cross-correlograms may be due in part to the scheme by which plasticity was turned on and off by holding transfer ratio constant and altering the amplitude of initial response. It is unclear, however, what alternatives exist for arresting plasticity while still keeping the model parameters in a physiologically realistic range.

3.2 2-D Correlograms and future directions
To gain further insight into the dynamics of the TC relay system— in particular, to gain an added level of definition that 1-D correlograms lack—the concept of a two-dimensional cross correlation was developed in which the correlation gave the
probability of a spike in the TC cell, given that a spike from the OT input occurred \( \tau_1 \) ms ago and a spike from the OR occurred \( \tau_2 \) ms ago. That is,

\[
C^{(2)}(\tau_1, \tau_2) = \langle A_1(t - \tau_1)A_2(t - \tau_2)A_3(t) \rangle_t
\]

where \( A_1 \) and \( A_2 \) are pre-synaptic inputs and \( A_3 \) is the post-synaptic TC cell. While code capable of generating two-dimensional cross correlograms has been written and implemented, work towards understanding and appropriately interpreting the model’s output is still ongoing.

References


4 Appendix: Larger Figures

A. 

B. 

C. 

D. 

E. 

F.