Action potential backpropagation in a model thalamocortical relay cell.

Nada A.B. Yousif* and Mike Denham

Centre for Theoretical and Computational Neuroscience, University of Plymouth, UK

*Corresponding Author: Email nada.yousif@plymouth.ac.uk

Abstract

Thalamocortical (TC) cells relay most sensory information to the neocortex. Sensory and cortical afferents are segregated in TC cells, and the way these inputs are integrated is important to understanding the role of TC cells in sensory processing. Experimental results indicate that backpropagating action potentials effect synaptic integration. We investigate backpropagation in a previously described multi-compartment model of a TC cell, and compare simulation results with experimental results. The model does not replicate the results well, and we suggest changes that improve these results but affect the firing modes of the model. This has repercussions for models of thalamocortical signalling.

Keywords: Thalamocortical, multi-compartment model, backpropagation

Introduction

Thalamocortical (TC) cells are the basic components that relay almost all sensory information, with the exception of olfactory, to the neocortex [12]. This gives the thalamus a vital role that is not yet fully understood. One interesting fact is that thalamocortical relay cells do not receive most of their synaptic inputs from sensory afferents [15]. The cortical innervation of the thalamus is a much greater source of input, with TC cells in sensory nuclei receiving feedback from the same areas of cortex to which they project [5]. Furthermore, there is a clear spatial segregation of these inputs in the dendritic arbour of TC cells, with cortical inputs located mainly in distal dendrites and sensory inputs mainly in proximal dendrites [10]. Knowledge of the way that TC cells integrate these inputs is crucial for accurate modelling of thalamocortical circuits and hence to understanding the role of TC cells in these circuits.

It has been shown that the shunting of EPSPs by backpropagating action potentials (APs), which was investigated in a recent paper by Häusser et al [6], can play a part in synaptic integration. Their results indicated that due to this shunting, distal synapses may contribute to

synaptic integration to a far greater extent than proximal synapses. If the same mechanisms are at play in TC cells, then the spatial segregation of afferents will be of functional relevance.

This paper investigates action potential backpropagation in a multi-compartment model of a TC cell as described by Destexhe et al [3]. The results from simulations of this model are compared with recent experimental results of Williams and Stuart [17]. In [17], simultaneous whole-cell current-clamp recordings were made from the dendrites and soma of TC neurons, in slices of the rat dorsal lateral geniculate nucleus (LGN), which preserve the dendritic morphology, and the amplitude of backpropagated action potentials through successive branch points of a single dendrite were measured. The APs demonstrated a significant attenuation of amplitude. They then measured AP amplitudes at various dendritic locations throughout the cell. By considering stem dendrites and higher order dendrites separately, they showed a clear dependence of AP amplitude on the dendritic recording location.

Consistent with other studies [16] these results indicated that there is a strong influence of dendritic morphology on the action potential propagation. This means that APs may fail to propagate into the most distal parts of the dendritic tree. Further results in [17] indicated that AP backpropagation is an active process, dependent on the activation of dendritic sodium channels, of which there is a non-uniform distribution throughout the extent of the TC cell. The results also pointed to an on-average uniform density of potassium channels across the cell.

In this paper, we show that this model does not reproduce Williams and Stuart's [17] results well. We then apply a number of biophysically plausible changes to the model and show that these result in a closer match between the behaviour of the model and the experimental results. Finally, we investigate the conditions under which burst and tonic firing is evoked in the model, with and without the changes, and compare our results with those reported in [4].

The Model

The original cell morphology [3] used in these simulations was obtained from a TC cell from the rat ventrobasal nucleus. The cell was stained, reconstructed and incorporated into

NEURON [7]. The model has a total of 206 compartments, which includes 11 dendrites with varying numbers of sections. The model contains Hodgkin Huxley type sodium and potassium currents located solely in the soma, a passive leak current and I_T, the low-threshold Ca^{2+} current to which burst activity is attributed [2]. The T-current has an uneven somatodendritic distribution throughout the cell, as described in [3] and as reported in [17].

Simulation Results

Results in the unchanged cell

Williams and Stuart stimulated their cells using somatic current injection, and this was replicated in the model cell. Measuring the AP amplitude decrease through branchpoints, Williams and Stuart report an average decrease of 27.4% for an average electrode separation of 16.5μm (1.66% per μm). In the model cell, it was found that there is a 0.50 ± 0.04% decrease per μm, demonstrating a clear divergence between the results.

The relationship between the AP amplitude and dendritic location is plotted by Williams and Stuart (figure 2B of [17]). The corresponding measurements of AP amplitude from the model are shown in Figure 1. The measurements were taken from 10 of the 11 first-order dendritic sections (one was omitted due to its path distance from the soma being much greater than 65μm), and a further 24 higher order dendrites. The higher-order dendrites were chosen based on 3 criteria, 1) they had to fall into Destexhe et al's [3] classification of distal, 2) they had to be within 65 μm from the soma, to be consistent with plots in [17] and 3) they were 3rd or 4th order dendrites.

For proximal and distal sites, the real cell gives a decrease in AP amplitude of 3.8% per 10μm and 9.0% per 10μm respectively. For the unchanged model these figures come out as 2.1% per 10μm and 3.6% per 10μm. These values are less than in the real cell, especially in the higher order dendrites. As measurements were made at comparable path lengths, it appears that the discrepancy must arise from the passive membrane properties of the model cell dendrites. In order to obtain closer results, a number of changes were applied to the cell, and these are described below.

Changes to the model

Williams and Stuart [17] report the existence of active sodium and potassium channels in the dendrites. The original cell model only contained I_T channels in the dendrites. The first change was to insert active Hodgkin-Huxley type sodium and potassium channels into the dendrites. The sodium conductance was reported in [17] to be highest in the soma relative to the rest of the cell, and this was replicated in the model. However, potassium channels were reported to have an even distribution throughout the cell. These new conductances increased the AP attenuation in the cell, but the effect was not sufficient to reach the reported values.

The next change was to insert I_A channels in the model. This is a rapidly activated potassium current, previously characterized by McCormick and Huguenard [8]. It is reported to have a constant conductance distribution throughout the cell [17]. The introduction of I_A produces a further increase in the attenuation in both the stem and higher order dendrites.

A property that is likely to have a significant effect on the attenuation of signals in a dendritic tree is the axial resistance (Ra). The original model had a uniform value of 260 Ωcm for Ra. Various distributions of axial resistance were investigated and with values of 260 Ωcm in the soma, 660 Ωcm in proximal dendrites and 1060 Ωcm in all other dendrites, attenuation values were much closer to the required levels.

Williams and Stuart [17] discuss a variable concentration of I_T channels throughout the dendritic tree, which was already implemented in the original cell model. However, they also report location dependent variations in the activation and inactivation characteristics of the T-type Ca^{2+} current. From their measurements, the shifts in activation and inactivation properties were applied, and this produced greater attenuation in stem dendrites and but slightly less attenuation in higher-order dendrites.

The full set of percentage decreases in action potential amplitudes are shown in table 1. The increase in attenuation is clearly seen and there is now a 1.1 ± 0.05 % per μm decrease in AP

amplitude through branchpoints. This is of comparable magnitude to the experimentally measured value (1.66% per μm) and much improves upon the result from the original unaltered model cell (0.50 ± 0.04% per μm).

Effects on the firing properties of the cell

In order to observe the effects of these changes on the firing properties of the model TC cell, a study by Destexhe and Sejnowski was used [4]. In this study, the original model from [3] was used to look at how synaptic inputs evoke burst or tonic firing in TC cells. This was investigated at different membrane potentials and the mode of firing at these various potentials (burst or tonic) was reported. Our simulations using the original cell model produced the results in Figure 2a, which approximately agree with those described in [4]. In particular, as in [4], they show a clear switch from burst to tonic firing at a membrane potential of –75mV. We also carried out simulations with a higher leak conductance (figure 2b) as in [4], in order to simulate *in vivo* conditions. Similar results were observed but firing thresholds were higher and a more hyperpolarized membrane potential was required for the shift in firing modes, again as observed in [4].

When the changes described above were applied to the model, the pattern of results at control levels of conductances was not dramatically different as seen in figure 3a, although higher levels of input conductance are required. However, the firing pattern at high leak levels is severely affected as shown in figure 3b, as the model cell no longer displays burst firing at any membrane potential or at any level of synaptic conductance. After various investigations this seems to be mainly due to the presence of I_A, and as soon as this current is removed, the model is able to fire bursts of action potentials, as is clearly seen in figure 4.

Discussion

The attenuation of backpropagated action potentials was investigated in a multi-compartment model of a thalamocortical cell [3]. We have shown that this model does not accurately reproduce the experimental results of [17], which show that the attenuation of the amplitude of

APs varies with respect to dendritic location and is generally at a higher level than in the model cell.

A number of changes were made to the model cell, and this resulted in a better replication of the results in [17]. These changes were, 1) addition of Hodgkin and Huxley type sodium and potassium channels, 2) insertion of I_A channels, 3) application of a variable axial resistance distribution and 4) a location dependent shift in I_T activation and inactivation curves. The changes bring the results much closer to the experimental results.

The sodium and potassium conductance values were chosen based on the results in [17]. The higher somatic Na^+ conductance ensures that action potentials are initiated in the soma and not at dendritic sites. The high concentration of potassium channels compared with sodium channels in the dendrites guarantees that there is an increase of attenuation compared with the original passive dendritic situation.

A major influence on the attenuation values, as can be seen from table 1, is the change in the axial resistance. However, it has been proposed previously that TC cells follow Rall's 3/2 power rule [12] and are therefore electronically compact. In this case attenuation of signals would be small [11] as has been reported by experimentalists [1] and modellers [13]. Conversely, there are other reports that TC cells do not obey this rule [9] and Williams and Stuart [17] show that there is difference in the amount of AP attenuation in proximal dendrites compared with in distal dendrites.

The new axial resistance value is a big change from that used in the original cell model. Hence this has a significant effect on the results. Looking at measured values of resistances, Turner et al [14] report a value of 254.4 MΩ for mean peak input resistance and a value of 80.6 MΩ for mean steady-state input resistance. The new applied values do not correspond to these measurements. However, the original value of 260 Ωcm was also outside these values for the dendritic sites.

The changes that were made to the model affect the firing pattern of the cell such that there is a lack of bursting at high leak conditions. This seems to be due to the presence of I_A. This is consistent with the description of I_A as a current that slows the rate of rise and reduces the peak amplitude of the calcium spike in TC cells [8]. It may be that the I_A values in the model are not correct. The combined effect of I_A and the shift in the activation and inactivation kinetics of I_T may cause the abolition of burst firing. This is a point that needs to be investigated further, due to the importance of bursting to the issues of thalamocortical activity.

An additional factor that would influence action potential backpropagation would be cell morphology. The model cell is constructed from a stained rat ventrobasal cell, whereas the cell used in the experimental procedures was a cell from a rat dorsal LGN cell. This may be the cause of the discrepancy between the modelling and experimental results.

If backpropagating action potentials fail to invade distal sites, this will have a profound effect on synaptic integration, since the shunting effect of these action potentials will be less at the distal locations, resulting in synaptic inputs at these locations having a greater effect on synaptic integration than would otherwise be the case. This has implications for sensory processing, as in TC cells there is spatial segregation of sensory afferents and cortical feedback connections. This means that the distally located cortical inputs may have a similar effect on the firing behaviour of the cell as the proximally located sensory inputs. This may give support to the putative role of corticothalamic feedback as one of exercising a strong modulatory effect on the relay of sensory information by TC cells... However, it is clear that accurate modelling of this phenomenon is essential.

References

[1] Bloomfield SA and Sherman SM, Dendritic current flow in relay cells and interneurons of the cat's lateral geniculate nucleus, Proc. Natl. Acad. Sci. USA, 86 (1989) 3911-3914.

[2] Deschenes M, Roy JP and Steriade M, Thalamic bursting mechanism: an inward slow current revealed by membrane hyperpolarization, Brain Res. 239 (1982) 289-293.

[3] Destexhe A, Neubig M, Ulrich D, and Huguenard JR, Dendritic low threshold Ca currents in

thalamic relay cells, J. Neurosci. 18 (1998) 3574-3588.

[4] Destexhe A and Sejnowski TJ, The initiation of bursts in thalamic neurons and the cortical control of thalamic sensitivity, Phil. Trans. Roy. Soc. Lond. Series B. 357 (2002) 1649-1657.

[5] Guillery RW, Feig SL and Lozsadi DA, Paying attention to the thalamic reticular nucleus, Trends Neurosci. 21 (1998) 28-32.

[6] Häusser M, Major G and Stuart GJ, Differential shunting of EPSPs by action potentials, Science 291 (2001) 138-141.

[7] Hines ML and Carnevale NT, The NEURON simulation environment, Neural Comput. 9 (1997) 1179-1209.

[8] Huguenard JR and McCormick DA, Simulation of the currents involved in rhythmic oscillations in thalamic relay neurons, J. Neurophysiol. 68 (1992) 1384-1400.

[9] Kniffki K-D, Pawlak M and Vahle-Hinz C, Scaling behavior of the dendritic branches of thalamic neurons, Fractals 1 (1993) 171-178.

[10] Liu XB, Honda CN and Jones EG, Distribution of four types of synapse on physiologically identified relay neurons in the ventral posterior thalamic nucleus of the cat, J. Comp. Neurol. 352 (1995) 69-91.

[11] Rall W, Branching dendritic trees and motoneuron membrane resistivity, Exp. Neurol. 1 (1959) 491-527.

[12] Sherman SM and Guillery RW, Exploring the thalamus, Academic Press, San Diego, 2001

[13] Smith GD and Sherman SM, Detectibility of excitatory versus inhibitory drive in an integrate-and-fire-or burst thalamocortical relay neuron model, J. Neurosci. 22 (2002) 10242-10250.

[14] Turner JP, Anderson CM, Williams SR and Crunelli V, Morphology and membrane properties of neurones in the cat ventrobasal thalamus in vivo, J. Physiol. 505 (1997) 707-726.

[15] Van Horn SC, Erisir A and Sherman SM, Relative distribution of synapses in the A-laminae of the lateral geniculate nucleus of the cat, J. Comp. Neurol. 416 (2000) 509-520.

[16] Vetter P, Roth A and Hausser M, Propagation of action potentials in dendrites depends on dendritic morphology, J. Neurophysiol. 88 (2002) 1924-1932.

[17] Williams SR and Stuart GJ, Action potential backpropagation and somato-dendritic distribution of ion channels in thalamocortical neurons, J. Neurosci. 20 (2000) 1307-1317.

Nada Yousif studied physics at Imperial College, London and graduated in 2001. Since 2002 she has been studying thalamocortical networks using computational modelling techniques, in the Centre for Theoretical and Computational Neuroscience at the University of Plymouth, England.

Mike Denham obtained his PhD in Mathematical Systems and Control Theory in 1972 from Imperial College, London. After five years as a postdoc and then lecturer at Imperial College, he joined Kingston University and from 1984 to 1988 he served as Head of the School of Computing. He joined the University of Plymouth as a Research Professor in 1988. In 1991 he set up the Centre for Neural and Adaptive Systems, and has led the Centre since that time. A new University Research Centre in Theoretical and Computational Neuroscience was established in October 2003 under his leadership. His research interests are in understanding the fundamental principles and mechanisms of information processing in neurons and neuronal networks, using a combination of mathematical analysis and computational modelling.

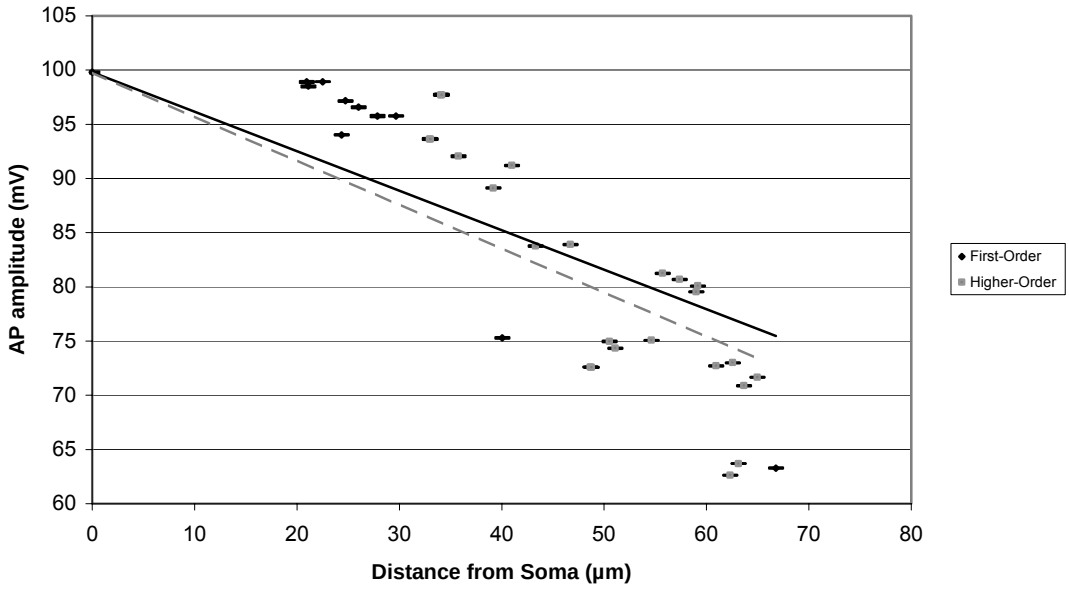

Figure 1: Data showing relationship between dendritic location and action potential amplitude, for first-order (black) and higher–order (grey) dendrites separately in the unchanged model TC cell. All distances are measured from the soma-dendrite junction to the point of recording.

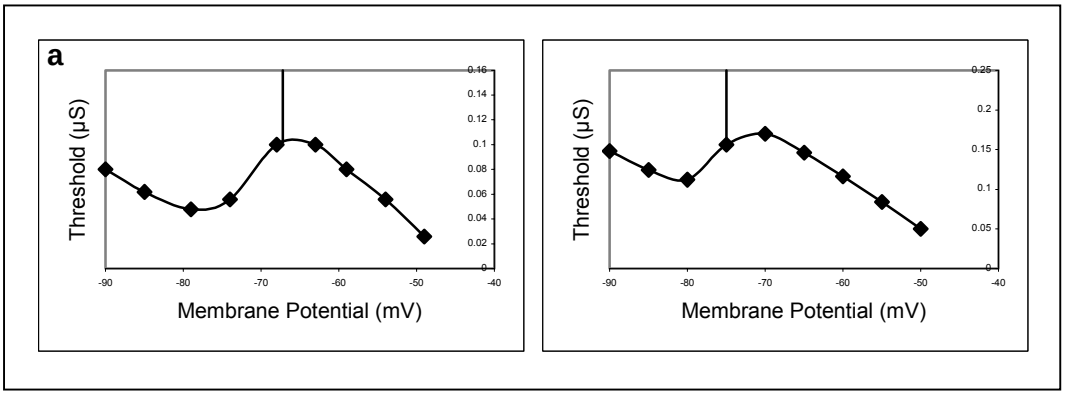

Figure 2: Replication of results in [4]. (a) Excitation of TC cell through AMPA and NMDA synapses, at various membrane potentials requires the shown threshold levels of AMPA conductance. The switch

from tonic mode firing to burst mode firing occurs at –68mV. (b) Similar results are obtained using a higher value for leak conductance to simulate *in vivo* recording conditions. The thresholds are higher and the switch between firing modes occurs at a more hyperpolarized level.

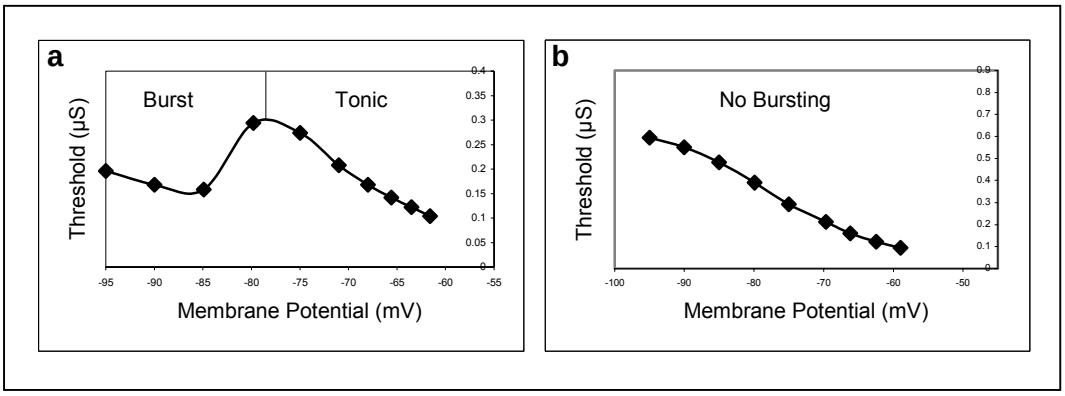

Figure 3: Replication of results in [4] using the modified TC cell model.

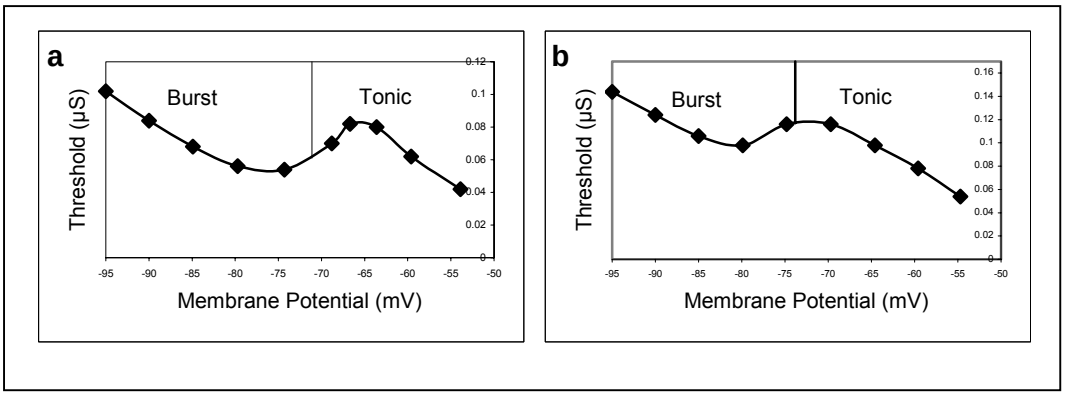

Figure 4: Replication of results in [4] using the modified TC cell model, without I_A channels.

	% Decrease in AP amplitude per 10µm	
	First-order dendrites	Higher-order dendrites
Control	2.05 ± 0.06	3.65 ± 0.04
+ Na and K channels	2.36 ± 0.11	4.19 ± 0.08
+ I_A channels	2.40 ± 0.05	4.21 ± 0.06
+ Variable Ra distribution	3.48 ± 0.07	6.57 ± 0.05
+ Shift in I_T activation curves	3.50 ± 0.08	6.50 ± 0.06

Table 1: Effect of subsequent changes on the values of decrease in AP amplitudes, as measured in stem and higher-order dendrites.