PREDICTIONS IN ABSENCE EPILEPSY WITH THE USE OF COMPUTER MODELS OF NEURONAL NETWORKS

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Abstract A computer model of a thalamic network was used in order to understand the rhythmic activity that characterizes absence epilepsy. The model was constructed using a Hodgkin Huxley framework. Results from the model confirm the hypothesis that an isolated augmentation of the maximum conductance of the low threshold calcium current (I_T) in the reticular thalamic nucleus may be conducive to the occurrence of autorhythmicity and hence epilepsy. The model predicts that higher values of this I_T can cause the transition of the network to an intermittent state. This intermittency increased monotonically with the increase of I_T in the reticular nucleus. The model was also used to investigate electrophysiological methods of bringing about a transition of the network to a subthreshold state. Methods that were successful at bringing about a phase shift that resulted in the reticular thalamic neurons firing before the thalamocortical neurons were found to lead to subthreshold activity in the network. This sort of phase shift was attained either by the application of periodic excitatory pulses to the reticular thalamic neurons or the application of a constant hyperpolarization to the thalamocortical neuron.

KEYWORDS absence epilepsy, thalamus, computer models, oscillations.

1. INTRODUCTION

The previous years have seen the increasing use of computer models in the investigation of the nervous system. One of the reasons for this is the availability of mathematical equations which describe the activity of a neuron with a level of detail that the neuroscientist finds essential. Equations that incorporate such detail in neuronal behavior, cannot be solved analytically. The widespread use of mathematical models in neuroscience therefore only became possible after the availability of powerful computers. Computer models of thalamic networks have been found to reproduce several important results that have been observed experimentally (Lytton and Thomas, 1977). It would therefore be productive now, to use the models to make predictions for experimental work. Areas where experimental work does not corroborate prediction from the model could be used as an opportunity for the improvement of the model. Such a collaboration between the work of the theoretician and experimentalist, could lead to the improvement of the models and in turn, a decrease in the number of unnecessary experiments.

Absence epilepsy is a generalized epilepsy inflicting children. It is characterized by the presence of spike and wave discharges in the electroencephalogram of the patient. Studies of

the disease have been greatly facilitated by the development of animal models of absence epilepsy. One such successful model has been the Genetic Absence Epilepsy Rat of Strasbourg (GAERS). Neurophysiological, behavioral, pharmacological and genetic studies have demonstrated that the GAERS rat is a good animal model for the problem of human absence epilepsy (Marescaux et al., 1992).

Investigations with GAERS have demonstrated that the thalamocortical system is the brain area primarily involved in the generation and maintenance of the spike and wave discharges which appear in the electroencephalogram during a seizure (Marescaux et al., 1992). Many of the investigations into the basic mechanisms underlying the seizures have focused on the thalamus. The spike and wave discharges have been found in some cases to appear in the thalamus before making their appearance in the cortex (Williams, 1953; Vergnes and Marescaux, 1992). Experiments by Morison and Bassett (1945) showed that the thalamus isolated from neocortical input was still capable of rhythmic activity. Many attempts to understand the rhythmic activity of the thalamocortical system during epileptic seizures have therefore focused on the rhythmic activities of the thalamus (von Krosigk et al., 1993; Huguenard et al., 1990; Crunelli et al., 1994; Steriade et al., 1988).

Investigations on the generation of rhythmic activity within the thalamus have revealed the relay nuclei and the reticular thalamic nucleus to be crucially involved in the activity (Steriade et al., 1990; von Krosigk et al., 1993). For the purpose of this investigation, we constructed a unit circuit in which the important connections within and between these areas were represented. The network consisted of two reticular thalamic (RE) neurons and one thalamocortical (TC) neuron (Figure 1).

The spike and wave discharges seen in the EEG of a patient during a seizure is due to synchronous, rhythmic activity in the concerned neural networks. As we are only investigating a three neuron network, the question of synchrony cannot be addressed. We will instead be looking at the factors that affect the rhythmic behavior of the network. We will first describe the consequences to network activity, of an isolated augmentation in the I_T conductance in the reticular thalamic (RE) nucleus of the model. The reason for carrying out this investigation was an isolated increase that has been observed in the RE nucleus of the epileptic rat (GAERS rat) when compared to the normal rat. The second part of the paper will focus on how the phenomenon of phase shifting observed in several biological oscillators can be used to make the activity of the TC neurons subthreshold.

As mentioned above, various models of the thalamic network have already been constructed. Many of these have been done using a Hodgkin Huxley framework and current clamp data from thalamic neurons (Lytton and Thomas, 1997). These models have been of varying degrees of complexity both in anatomical structure as well as in their physiological activity. The model used for this investigation was a minimal model based on the Hodgkin Huxley framework. The insights gained with using a simpler model can then be used to carry out an investigation using a more complex model.

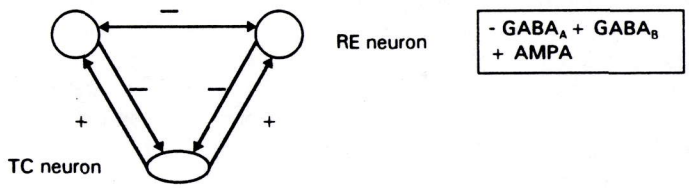

Figure 1: Circuit diagram of network.

2. CONSTRUCTION OF MODEL

Two reticular thalamic (RE) neurons and one thalamocortical (TC) neuron were chosen to create the network (Figure 1). This circuit was chosen because it is representative of the major connections between and within the RE and TC nucleus that are important to the generation of rhythmicity (Steriade et al., 1990, von Krosigk et al., 1993). The physiology of the neurons was constructed using the Hodgkin Huxley formalism. Many of the parameters necessary to describe the ionic currents of the model were obtained from previous models of the thalamic network (Lytton and Thomas, 1997). The RE neurons were constructed using the following intrinsic currents: a low threshold calcium current I_T, the leak current I_l, the fast sodium current I_{Na} and the fast potassium current I_K. Synaptic currents for the RE neurons included I_{GABA_A} and I_{GABA_B} caused by the neurotransmitter γ-Aminobutyric acid (GABA), as well as I_{AMPA} mediated by the fast glutamate receptor amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid (AMPA). The TC neurons were constructed using the low threshold calcium current I_T, the hyperpolarization activated cationic current I_h, the fast sodium current I_{Na}, the fast potassium current I_K and a leak current I_l. The synaptic currents for the TC neurons were the two inhibitory I_{GABA_A} and I_{GABA_B} currents. Simple models of this sort have been used to investigate various aspects of synchronized oscillations in the thalamic network (Wang et al., 1991; Wang and Rinzel 1993; Hutcheon et al., 1994; Destexhe et al., 1996). McCormick and Huguenard (1992) report that the frequency and amplitude of rhythmic Ca^{2+} spike generation in their model TC neurons were most critically dependent on the I_T, I_h and leak currents. Destexhe et al. (1996) also report that currents like the Ca^{2+} mediated potassium current, $I_{K[Ca]}$ and I_{CAN} were found to have very little influence on network behavior.

The equivalent circuit representation for the neuronal membrane comprises a capacitor and several resistors in parallel (Johnston and Wu, 1994). In accordance with this parallel conductance model for ionic currents in a membrane, the following were the equations used to describe the activity of the neurons

$$C_m \dot{V}_{RE} = -I_T - I_{Na} - I_K - I_l - I_{GABA_A} - I_{GABA_B} - I_{AMPA} \quad (1)$$

$$C_m \dot{V}_{TC} = -I_T - I_h - I_{Na} - I_K - I_l - I_{GABA_A} - I_{GABA_B} \quad (2)$$

V_{RE} is the membrane potential of the RE neuron while V_{TC} is the membrane potential of the TC neuron; C_m is the capacitance of the neuron; C_m had a value 1μF/cm^2;

The values of the intrinsic currents were obtained from Ohm's law

$$I = g \times \bar{g} \times (V - E_{eq}) \quad (3)$$

where g is the conductance of the channel, $\bar{g}$ is the maximum conductance of the channel and E_{eq} is the reversal potential of the current.

The magnitude of the current depends on the state of the gates controlling the channels. The opening of these gates are voltage dependent processes. Most of the equations describing the

nature of this dependence was obtained from experimental work. With the exception of the fast sodium and fast potassium, it was not necessary to obtain the forward and reverse rate constants for the gates. Instead, the state of the gate at time infinity $gate_{\infty}$, and the gate time constant τ_{gate} were directly obtained from available experimental results. It was then possible to compute the state of the activation or inactivation gate via the following equation (Hodgkin and Huxley, 1952)

$$gate_t = gate_{\infty} - (gate_{\infty} - gate_{t-1}) \exp[-\Delta t / \tau_{gate}] \quad (4)$$

The gate controlling a channel could be an activation gate m or an inactivation gate h. The conductance of a gate g depended on the state of these gates

$$g = m^N h \quad (5)$$

3. ISOLATED AUGMENTATION OF THE LOW THRESHOLD CALCIUM CONDUCTANCE IN THE RE NUCLEUS

3.1. EXPERIMENTAL OBSERVATION OF INCREASE IN I_T

The availability of the GAERS model of epilepsy allows for the comparison of neuronal membrane properties between the epileptic and non-epileptic rats. A study by Tsakiridou et al. (1995) found in comparing the voltage-dependent calcium channels of both rats, that the amplitude of the low threshold calcium current of the GAERS rat was higher. The whole-cell patch clamp analysis revealed that the amplitude of the low threshold calcium current (I_T) in the RE neurons of the GAERS rat was -198+/- 19 pA as opposed to -128 +/- 14 pA for the non-epileptic rat. This augmentation was found to be isolated to particular areas of the thalamus. While the I_T current was found augmented in the reticular thalamic nucleus, the I_T in the TC neurons of both rats were not found significantly different. No significant differences were found in the high threshold Ca^{2+} current, I_L between the non-epileptic and GAERS rat. More detailed tests were conducted to understand the reason for the increased amplitude of I_T in the GAERS rat. These tests revealed no significant differences in the activation and inactivation curves for I_T between the normal and epileptic rat. The kinetics of the current for the two rats were also similar. The augmentation of the I_T current therefore reflected an increase in the number of T-type Ca^{2+} channels or an increase in single channel conductance.

3.2. BIFURCATION TO RHYTHMIC ACTIVITY

The purpose of this investigation was to examine if such an isolated augmentation of I_T in the RE nucleus could lead to activity that was characteristic of epilepsy i.e. autorhythmicity. The increase in the I_T current of the RE neurons in the model was implemented with a gradual increase in the maximum conductance of the I_T channels. The conductance of I_T in the TC neurons was kept constant as it was gradually increased for the RE neurons. An investigation of the system as we varied the amplitude of I_T in the RE neurons revealed that it is an important control parameter in the behavior of the system (Thomas and Grisar, 1996). Most significantly, the amplitude of I_T was able to determine if the system acted in an autorhythmic manner. Figure 2 displays the activity of the TC neuron as the I_T conductance was varied in

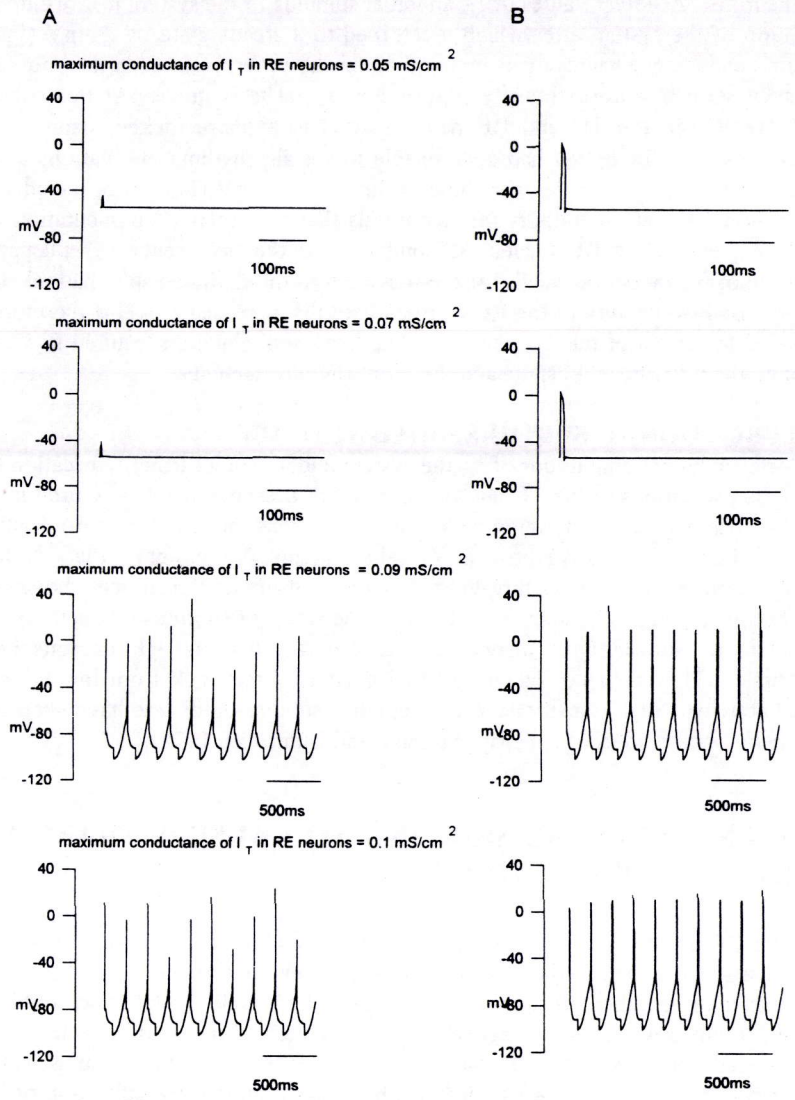

Figure 2. Activity of the network with changes in the maximum I_T conductance of the RE neurons. The resting membrane potential was set at approximately -55 mV. This was done to reflect the relatively depolarized resting membrane potentials found the RE neurons during the wake state. Lower values of $\bar{g}_T$ in the RE neurons were unable to bring about oscillatory activity in the network A) an RE neuron B) a TC neuron.

the RE neurons. At lower values of I_T, an initial stimulus to the system just resulted in a small perturbation of the system after which it returned to a steady state of -55mV (figure 2a, b). Maximum conductance values for I_T higher than this however, resulted in the bifurcation of the system to a state of autorhythmicity (figure 2 c, d). The frequency of this oscillation was about 5 Hz. Both the TC and RE neurons fired in a phase locked manner. Maximum conductance values for I_T that had been unable to sustain rhythmic oscillations at the resting membrane potential of -55 mV, were able to do so at -70 mV (figure not included). Results from the model therefore support the hypothesis that the isolated augmentation of the low threshold current in the RE nucleus is conducive to the occurrence of epilepsy. Further examination of the model revealed that the transition to the rhythmic state had taken place due to the increased excitability of the RE neurons with the increased I_T. This therefore results in an increased inhibition of the TC neurons. The increased inhibition resulted in a greater ease for evoking the low threshold spike and therefore rhythmic activity.

3.3. BIFURCATION TO SUBTHRESHOLD ACTIVITY

At even higher amplitudes of I_T, the system underwent a further bifurcation into a state in which the oscillations of the TC neuron became subthreshold and it now fired intermittently (figure 3). The degree of intermittence in the TC neurons increased monotonically as I_T was increased. Figure 3 displays how at I_T values below 0.6 mS/cm^2, the TC neuron still undergoes some activity above threshold. At the I_T value of 0.6 mS/cm^2 however, the TC activity becomes completely subthreshold. In these states of subthreshold activity, the system continued in an autorhythmic manner due to the fact that the RE neurons had become autorhythmic. They then no longer required excitatory feedback from the TC neurons for sustained activity. Such transitions to a completely subthreshold state have been observed in some experimental models of epilepsy (Steriade and Contreras, 1995).

4. THE USE OF PHASE SHIFTING TO CAUSE A TRANSITION TO SUBTHRESHOLD ACTIVITY

The effects of both single as well as periodic stimuli on oscillatory activity in various excitable tissue have been studied (Winfree 1977, 1987). A stimulus was frequently found to either shorten or lengthen the period of the perturbed cycle. The exact outcome of the perturbing stimulus was found to depend on factors such as the phase at which the stimulus was introduced, the amplitude of the stimulus and whether or not the stimulus was excitatory or inhibitory. In this section we will describe how phase shifts were utilized in order to make the oscillations in our model subthreshold. One of the methods which was successful at converting the oscillations of the TC neurons to subthreshold activity, were low amplitude periodic pulses to the RE neurons. These periodic pulses were found to be effective at various values of phase, amplitude and period, thus ensuring the possibility of success in an experimental situation which includes limiting factors such as noise and limited resolution. Another successful method was the application of a constant low amplitude hyperpolarizing current in the TC neuron. This method too, was found to be effective for a range of input amplitudes.

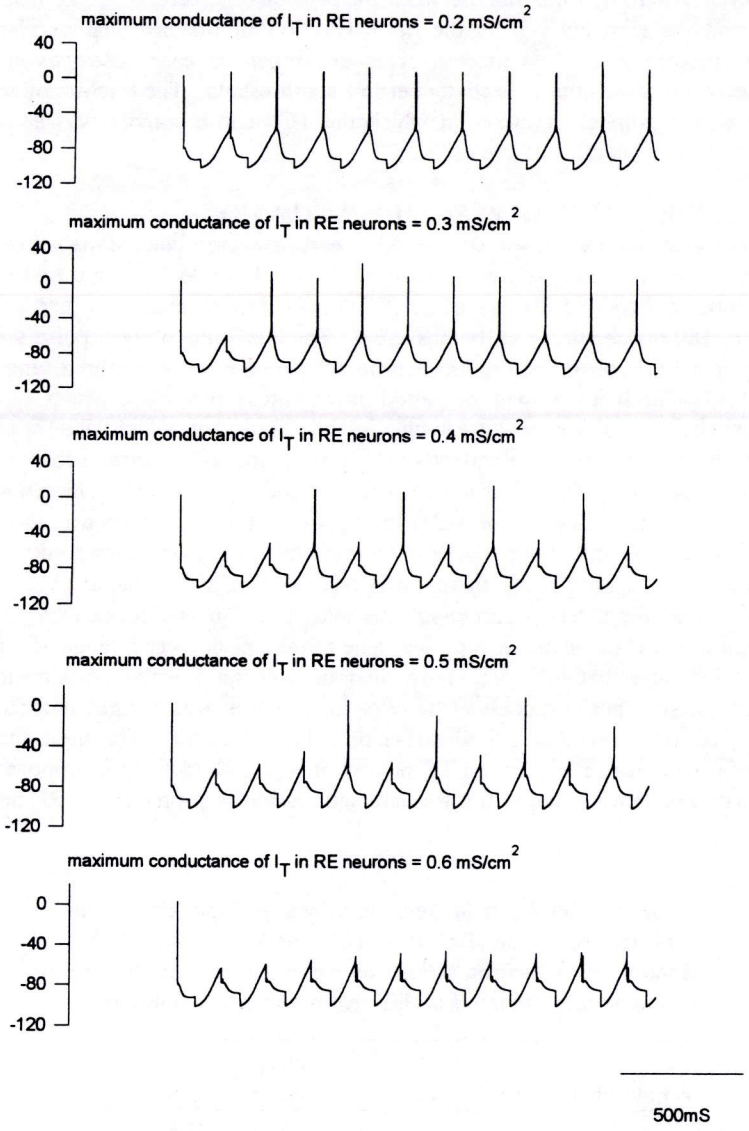

Figure 3. At higher values of $\bar{g}_T$ in the RE neurons, the activity of the TC neurons remained oscillatory but became subthreshold.

The phase as reported in this paper has a value between 0 and 1. It was computed as the ratio δ/T_o. Where δ is the time between the previous marker event (the neuron reaching threshold) and the stimulus. T_o is the normal period of the neuronal oscillatory activity without any perturbation. The success of an experiment in each case was judged by the number of cycles in which the TC activity became subthreshold. The fraction of activity above threshold was the number of cycles in which the TC neuron activity was above threshold compared to the total number of cycles.

4.3. PHASE SHIFTING WITH PERIODIC EXCITATION

Periodic excitatory pulses to the RE neurons were found capable of completely suppressing threshold activity in the TC neuron (Figure 4, Table 1). Figure 4b demonstrates the completely subthreshold activity of the TC neuron as the result of a periodic excitation applied every 180 ms beginning at the phase 0.9. The amplitude of each pulse was 5 $\mu A/cm^2$ lasting for 1 ms. The period of the TC neuron activity in the subthreshold range was about 180 ms. This is slightly lower than the period of the unperturbed cycle which is 200 ms. The lowered periodicity was due to the stimulus in the RE neuron which slightly advanced the firing of the RE neuron and consequently the firing of the TC neuron. Table 1 displays the results obtained with periodic pulses at different amplitudes and phases. The reported value in each case is the fraction of cycles for which the activity of the TC neuron was above threshold. While all the displayed stimuli were able to increase the degree of intermittency in TC firing, some were more successful than others. It is obvious that a stimulus at phase 0.9 was the most successful at completely suppressing threshold activity in the TC neuron. The fact that the suppression of TC threshold activity was able to take place over a range of amplitude and phase values indicates that such procedures may be successful in the experimental situation. Of critical importance in the success of these periodic pulses, was a slight shift forward in the firing of the RE neuron so that it fired earlier than the TC neuron. The slight increase in the frequency of oscillatory activity in the TC neuron of figure 4b (5.5 Hz as opposed to 5 Hz in the unstimulated system), is due to this forward shift in the firing time of the RE neuron.

Table 1: Results from tests in which periodic excitation was applied to the RE neurons. The table displays the fraction of TC neuron activity above threshold with the use of the periodic stimulus at different phases and amplitudes.

	Phase		
Amplitude ($\mu A/cm^2$)	0.9	0.925	0.95
2	0	0.6	0.6
3	0	0.6	0.6
4	0	0.6	0.6
5	0	0.6	0.6

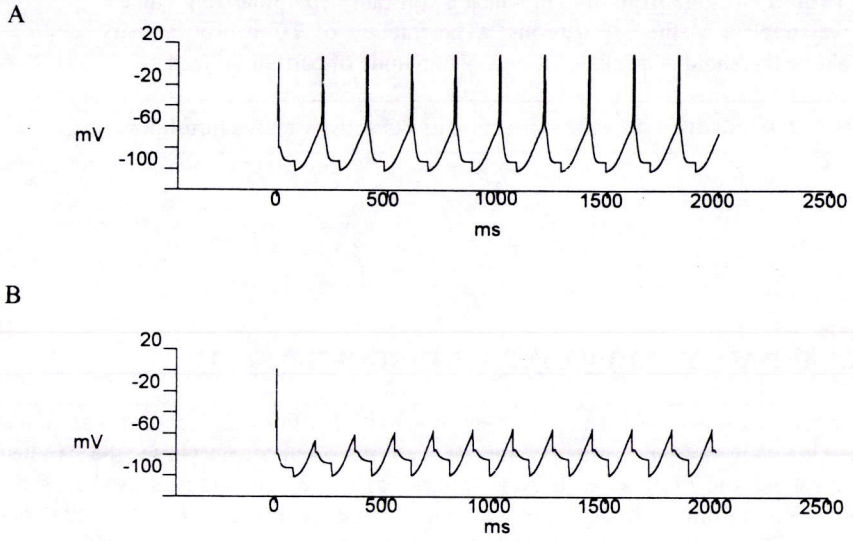

Figure 4: A) Activity of the TC neuron without any perturbing inputs. B) Excitatory pulses to the RE neuron results in the transition of the TC neuron to subthreshold oscillations.

4.4. PHASE SHIFTING WITH CONSTANT HYPERPOLARIZATION OF TC NEURON

The success of the method described above, was based on shifting the activity of the RE neuron ahead of the TC neuron activity so that it fired before the TC neuron. It stood to reason then, that the same thing could be achieved by delaying the firing time of the TC neurons with the use of a hyperpolarizing pulse to the TC neurons. We found however, that the use of a periodic hyperpolarizing input to the TC neuron, was not significantly successful at preventing threshold activity. A constant low amplitude hyperpolarizing current however, was able to accomplish this task. Wang (1994) had demonstrated how a constant hyperpolarizing current was successful at decreasing the firing frequency of a single model TC neuron. In our model, we made use of this property to make the firing frequency of the TC neuron slightly lower than that of the RE neuron. An isolated constant hyperpolarizing current to the TC neuron was able to prevent any threshold activity in the TC neuron. Table 2 displays the low amplitudes of hyperpolarizing currents delivered to the TC neurons and the fraction of TC activity above threshold. The critical mechanism for the success of this method once again, was the same as what had made the excitatory pulse to the RE neurons work. It was shifting the firing of the TC neuron with respect to the RE neuron so that the RE neuron consistently fired first (figure 5c). Since the RE neuron is inhibitory, it prevented the TC neuron from firing. Unlike the case with delivering excitatory pulses to the RE neuron, the period of pertubed network activity had increased to 220 ms.

Table 2: Results from tests in which a constant hyperpolarizing current was applied to the TC neurons. The fraction of TC neuron activity above threshold is displayed for each amplitude of current utilized.

Amplitude ($\mu A/cm^2$)	Fraction of TC activity above threshold
0.5	1
1.0	0
1.5	0
2.0	0

4.5. MECHANISM FOR PRODUCING SUBTHRESHOLD STATE

The mechanism by which the TC neuron activity became subthreshold was similar in each case. Without any input, the TC and RE neurons oscillated in phase, the TC neuron reaching threshold and firing at each cycle (figure 5a). The stimulus was used to shift the phase of RE neuron firing with respect to TC neuron firing, so that the RE neuron fired before the TC neuron. This could be done either by making the RE neuron fire ahead with the use of an excitatory pulse (figure 5b), or using hyperpolarization to make the TC neuron fire later (figure 5c). Since the RE neuron is inhibitory, when it fired, it prevented the TC neuron from reaching threshold. The stimulus in either case was a low amplitude stimulus because success depended only on a small phase shift and because the threshold of a Ca^{2+} mediated spike in the thalamus is low.

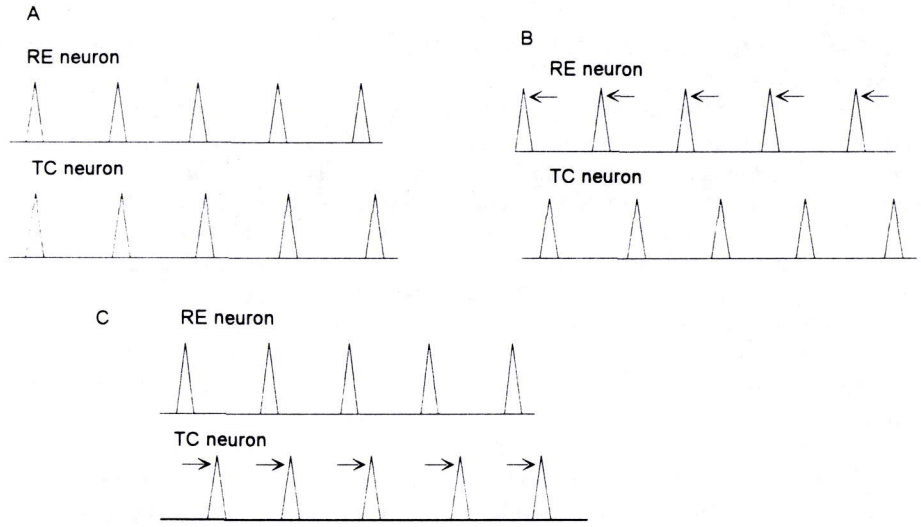

Figure 5: Mechanisms of transition to subthreshold activity A) Without any perturbing inputs, TC and RE neurons fire in phase B) One mechanism for making TC activity subthreshold was the use of periodic excitatory pulses to the RE neurons so they fired earlier than the TC neurons. C) Another mechanism for making TC neuron activity subthreshold was the use of a constant hyperpolarizing current on the TC neurons so they oscillated at a lower frequency.

5. FUTURE WORK

The results from the investigations carried out above, have been carried out on a minimal model of the thalamic network. While, the use of such models have been instructive concerning the mechanism involved in rhythmic activity in the thalamus (Lytton and Thomas, 1997), it would be important in future work to carry out the same investigation using more detailed models. A more biologically realistic model would include features such as the Ca2+ mediated channels like $I_{K[Ca]}$ and I_{CAN}.

A second important question to be addressed with regards to epilepsy is the question of synchrony. The high amplitude activity seen in the EEG during a seizure is due to the synchronous activity of the neurons in the network. A bigger network will have to be constructed in order to investigate how factors like the isolated increase of I_T in the RE nucleus could affect network synchrony. Such a model will have to take into account the natural occurrence of heterogeneity in the properties of neurons.

Winfree (1987) has reported the presence of singularities in vaious models of biological oscillators. Such singularities result in the capability of single pulses to terminate the rhythmic activity of the oscillator. These singularities have been called *black holes* by Winfree. In many cases, the termination of the rhythm has been found to depend very sensitively on the amplitude and phase of the pulse delivered. This high degree of sensitivity has in many cases, made the possibility of finding such a black hole extremely difficult in the experimental situation which includes noise and limited resolution. For these reasons, we did not commit ourselves immediately to the search for a *black hole* in the network, but opted instead to look for a more stable periodic mechanism that would create subthreshold activity. Future work will include the use of the theoretical work that has been developed concerning these nonlinear oscillators to investigate if such a black hole exists in the network.

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