

The Role of Corticothalamic Feedback in the Response Mode Transition of Thalamus

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Abstract—Thalamus is the relay station for most sensory information between peripheral receptors and the cortical areas. There is cumulative evidence showing that thalamus actively gates information flow. An important issue about this role is that thalamus adjusts its response mode according to the sensory information arrived. The corticothalamic feedback signal has been suggested to be essential for such adjustment. In this paper, we pieced together the experimental evidence in a realistic multi-layer network model of the thalamocortical circuit and examined its behavior in response to sinusoidal inputs. The results reproduced the burst/tonic responsive modes and feedback signal's role in mode transition.

Keywords—thalamus; cortex; feedback; response mode.

I. INTRODUCTION

While sensory signals are detected in peripheral receptors, cortical processing of such signals is responsible for the perceptual experience. On the passage from periphery to cortex, there is the relay station of thalamus. Cumulating evidence has shown that the relay function of thalamus is not simply “passing by” but active processing. This processing is modulated by various inputs to thalamus other than those from the peripheral sensory organs. These inputs, including those from cerebral cortex and brainstem, modulate the thalamic nuclei's state and control their gating properties in neuronal information processing.

Since 1990s, the thalamic relay cells have been shown to exhibit two distinct modes, burst and tonic, in responding to the sensory inputs [3]. Neurons in burst mode are shown to be more efficient in signal detection and found mostly when the animal is in drowsy or sleeping state. In contrast, in tonic mode neurons have higher fidelity in signal transmission and tonic mode is related to alert and behaving states. The transition between burst and tonic modes is suggested to be dependent on the recent membrane potential history before the coming of sensory information. Based on such results and the reciprocal connection between thalamic relay nuclei and their related cortical areas, there emerges the “wake-up call” hypothesis that the feedback information from cerebral cortex can switch the relay cells from burst mode to tonic mode by depolarization. This hypothesis is attracting since it offers a versatile transfer function dealing with various stimuli and brain states like a self-adapting filter. The evidence supporting this hypothesis is still being gathered and in need of tidying up. Murray Sherman and his

colleagues have illustrated the kinetics of low threshold calcium channel (I_T) [4] and shown that it may contribute to the transition between burst and tonic modes of thalamic relay cells in an integrate-and-fire-or-burst model [5].

Based on their work, we want to test the “wake-up call” hypothesis in a multi-layered network with integrate-and-fire-or-burst neurons. The model is focused on the interaction between thalamus and cortex. Neocortex is composed of 6 layers in which layer IV and layer VI receive thalamic inputs. While the signal to layer IV are passed through layer II/III, layer V, and then to higher thalamic nuclei and brainstem, layer VI sends feedback afferent to the thalamic relay nuclei from which it receives input. Given this specific connection of layer VI and our simulation resource limit, we omitted the cortical layers other than layer VI and higher thalamic nuclei from our current model. Our results showed that feedback is essential in controlling the relay cells' mode transition. We also explored the input frequency's role in shaping the stimulation-response mode relationship and proposed that this supports that the mode transition is essential in controlling the animal states.

In the contribution below, we first introduce the network structure of our model, then list parameters employed in the simulation, and finally show simulation results about the network under various stimulation paradigm. The significance of the results is discussed finally.

II. METHODS

A. Network structure

The network comprises two layers, one thalamic and one cortical. There were five populations in thalamic layer, resembling cells in a barrel-like structure of relay nucleus, with various tuning on stimulation features, such as directions and velocity of whisker reflection. Each relay cell population (resting potential, V_{relay}) was reciprocally and specifically connected with a neuron population in the cortical layer. The reciprocal connection was assigned according to the anatomical features of layer VI excitatory neurons (resting potential, V_{pyr}), which offer the corticofugal feedback signals [6]. The specific one-to-one connection was assigned since the stimulation features are preserved in the thalamocortical projections. There was a representative homogenous population of layer VI inhibitory interneuron, basket cell (resting potential, V_{bask}), in the cortical layer. According to Swadlow et al [7], the thalamocortical inputs to

the layer IV interneurons are divergent and convergent, blurring the stimulation features. Similarly we assigned layer VI inhibitory interneuron with inputs from all thalamic relay cells and outputs to all cortical excitatory cells, sharing the same number with thalamic cells. The 1 from 6 ratio of inhibitory interneurons is near the general proportion, 20~30 % in cerebral cortex [8].

B. The integrate-and-fire-or-burst model

The neurons in our network were described by the integrate-and-fire-or-burst (IFB) model taken from [5] and [9]. The IFB model was constructed by adding a slow variable to a classical integrate-and-fire neuron model. The neuronal model contains two equations, one for voltage and one for calcium current:

$$C \times dV/dt = -I_L - I_T - I_S - I_D \quad (1)$$

$$dh/dt = -h/\tau_h^-, \text{ if } V \geq V_h;$$

$$(1-h)/\tau_h^+, \text{ if } V < V_h \quad (2)$$

where $I_L = g_L \times (V - V_L)$ is a constant conductance leakage current, I_T is the low threshold Ca^{2+} current, and I_S and I_D are two synaptic currents. An action potential occurred whenever the membrane potential reaches the firing threshold (V_{theta}). There was an absolute refractory period τ_{rp} (4 ms) during which the voltage of neurons remains at V_{reset} . The low-threshold Ca^{2+} current was described as $I_T = g_T \times m_\infty \times h \times (V - V_T)$, where $m_\infty = \Theta(V - V_h)$ represents instantaneous voltage-dependent activation, and Θ is the Heaviside step function.

The input to the network was as following: (1) simulation begins with a pre-cue time interval lasting for 500 ms, during which the network receives only noise and will exhibit spontaneous activity; (2) in the stimulus presentation period, the input of sinusoidal current $I_0 + I_1 \sin(f)$ lasted for 5000 ms was applied to the thalamic cells besides for noises from outside.

C. Synaptic input

The last two terms in (1), I_S and I_D , were synaptic currents attributable to excitatory spontaneous input and excitatory or inhibitory drive. Each synaptic potential received by the neuron in the network was modeled as an α function [10] of conductance. An individual EPSP occurring at $t=0$ would be given by:

$$\alpha(s) = q/\tau_s \times \exp(-s/\tau_s) \times \Theta(s) \quad (3)$$

where q is the total charge that is injected in a postsynaptic neuron via a synapse with efficacy $w_{ij} = 1$. More realistically, the postsynaptic current α should have a finite duration, e.g., as in the case of an exponential decay with time constant τ_s . As usual, Θ is the Heaviside step function with $\Theta(s) = 1$ for $s > 0$ and $\Theta(s) = 0$ else.

All calculations were performed using the Matlab program and a time step of 0.1 ms.

D. Cellular and synaptic parameters

These parameters were collected from several sources and listed below, as table 1, 2, and 3.

III. RESULTS

A. Burst and tonic modes in relay cells

We thoroughly tested the model's response to several sets of parameters including baseline current, amplitude of sinusoidal inputs and sinusoidal frequency. Two representative results are showed in Figure 1a and 1b. The baseline current strongly determines the response mode of relay cells, consistent with Sherman et al's results that the low and high baseline current lead to burst and tonic mode, respectively.

B. Frequency dependency of mode transition

The whole sets of results are shown in Figure 2. For both low baseline situations with (Figure 2a) and without feedback (Figure 2b), the response mode transition is dependent on input frequency. At both situations, the emergence of burst mode response from originally silent cells are relatively transiently as the stimulus increases for the high frequency stimulation and smoothly for the low

TABLE I. CELLULAR PARAMETERS

Parameters	Values and Sources		
	Value	Unit	Reference
V_θ	-35	mV	[5]
V_L	-65	mV	[5]
V_{reset}	-50	mV	[5]
C	2	$\mu F \cdot cm^{-2}$	[5]
g_L	0.035	$mS \cdot cm^{-2}$	[5]
V_h	-60	mV	[5]
V_T	120	mV	[5]
τ_h^-	20	Ms	[5]
τ_h^+	100	Ms	[5]
g_T	0.07	$mS \cdot cm^{-2}$	[5]
V_{relay}	-65 ± 3.44	mV	[11]
V_{pyr}	-67	mV	[12]
V_{bask}	-62	mV	[8]

TABLE II. SYNAPTIC PARAMETERS

Presynaptic	Postsynaptic	Values and References			
		Synapse Number	Strengt h ($\mu A \cdot cm^{-2}$)	Synaptic delay(ms)	Time constant (ms)
Relay cells	Pyramidal cells	20 [13]	3.5 [14]	1 [15]	2 [13]
Relay cells	Basket cells	20 [13]	5 [15]	1 [16]	1 [13]

Presynaptic	Postsynaptic	Values and References			
		Synapse Number	Strength ($\mu A \cdot cm^{-2}$)	Synaptic delay (ms)	Time constant (ms)
Basket cells	Pyramidal cells	20 ± 1.34 [13]	1.4 [14]	0 [13]	6 [17]
Pyramidal cells	Relay cells	20 [13]	2 [18]	5 [19]	2 [17]

TABLE III. STIMULUS PARAMETERS

Parameters	Values and Units	
	Value	Unit
Baseline I_0	-0.05 / 1.1	$\mu A \cdot cm^{-2}$
Amplitude I_1	0.1~2	$\mu A \cdot cm^{-2}$
Frequency f	0.25 / 1 / 5 / 25	Hz

a. The stimuli are $I = I_0 + I_1 \cdot \cos(2\pi f t)$

frequency stimulation. The transition from burst mode to tonic mode happens at stimuli higher than $1 \mu A \cdot cm^{-2}$, but not for all stimulation frequencies. Figure 2c is the high baseline situation with or without feedback.

C. Feedback connection shapes the mode Transition

The burst-tonic transition was essential to the “wake-up call”, suggesting that the feedback signal was playing its role and the relay cells were switched into the high fidelity transferring mode from the high-efficacy detecting mode. For 5 Hz and 25 Hz stimuli with low baseline, the burst-tonic mode transition happens only if there is the feedback connection. For the 0.25 Hz stimuli with low baseline the

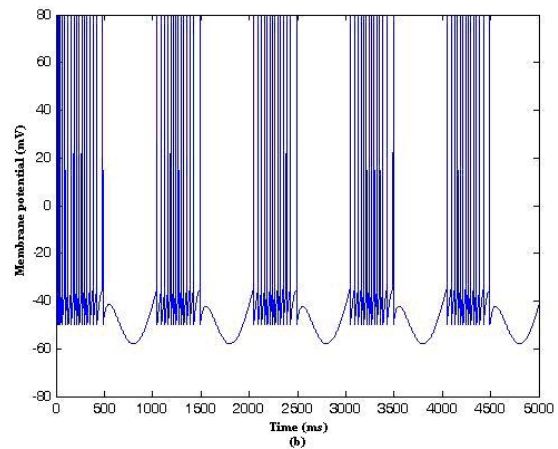
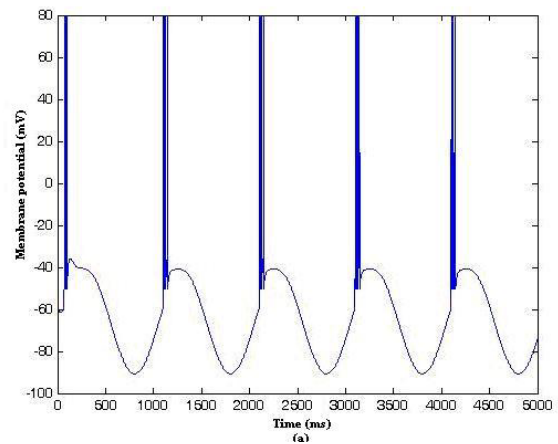
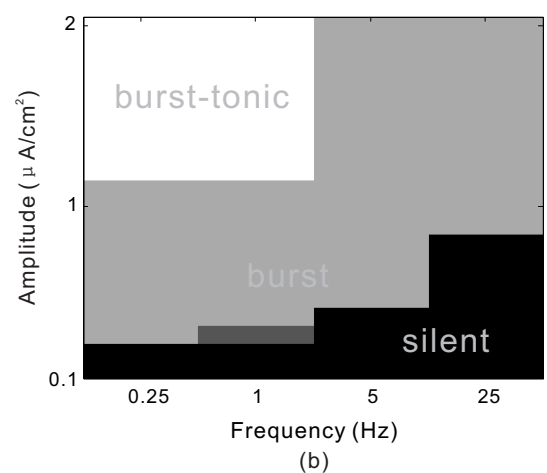
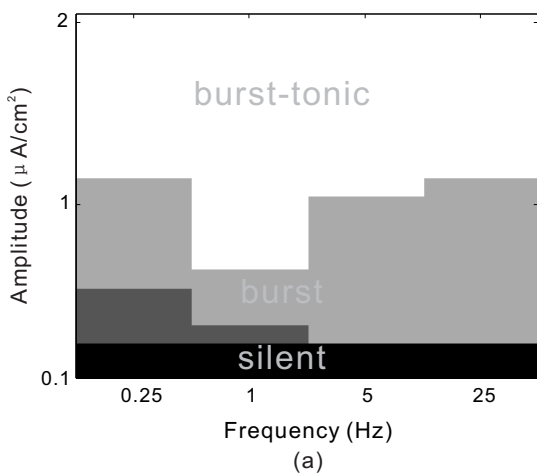


Figure 1. Burst and tonic modes in the relay cells: (a) burst mode, the stimulus is $I_0=0.9 \cdot \cos(\pi/500) - 0.05$. (b) tonic mode, the stimulus is $I_0=0.9 \cdot \cos(\pi/500) + 1.1$.



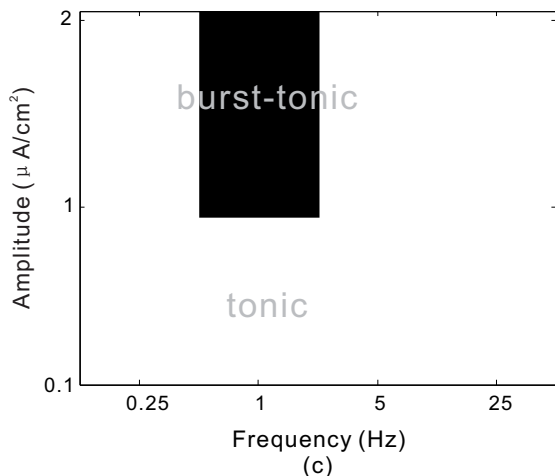


Figure 2. Mode transition. The response modes to various stimuli represented in colorgram. The low baseline situation is sensitive to feedback connections while the high baseline situation is resistant to it. (a, b) the response modes of relay cells with or without feedback connections to low baseline stimuli. (c) the response modes of relay cells to high baseline stimuli.

stimulation-response mode relationship was not strongly dependent on the existence of feedback connection. The high baseline stimuli raised the relay cells already to tonic mode, so the relay cells were mostly resistant to removal of feedback connections. The 1 Hz stimuli with high baseline showed unique feature that the burst-tonic mode transition was evoked when the stimuli were up to $0.9 \mu\text{A}\cdot\text{cm}^{-2}$.

D. I_T current is underlying the transition

To verify the essential role of low threshold calcium channel we compared the mode transition graph and the activation states of I_T . Since the activation states of I_T is governed by membrane potential and the slow variable h , and the time constant of h is invariable, we plotted the duration length in which h is positive. $m_\infty = \Theta(V - V_h)$, and $\Theta(*)$ is the Heaviside step function. Consistent with the physiological result, the active periods were mostly about 100 ms when the stimuli are capable of evoking burst-tonic transition.

IV. DISCUSSION

Although the model is really simple and incomplete, the essential role of feedback is significant. To incorporate more components, especially the reticular nucleus and cortical columnar constructions should make the model more concrete and more precise in temporal structure. The feedforward inhibition is proposed to be efficient in shaping the receptive field spatially and temporally. Since it is incorporated in the model, it is possible to study that in the multi-layered neuronal network instead of in pure feedforward triad. In fact there has been work on this idea [20].

The stimuli frequencies are related to different brain states: 0.25 Hz are slow waves related with drowsiness and slow-wave sleep, 1 Hz are δ -wave related with slow-wave sleep, 5 Hz are θ -wave related with certain behavioral

activities, and 25 Hz are α -wave related with restful attentiveness [21]. The slow-wave and δ -wave are related with similar brain states, and so are the δ -wave and θ -wave. Consistently, stimuli of the former two frequencies evoke similar response mode and show similar response to the existence of feedback connections. Similar comparison applies to the later two. This offers us a new point of view to consider the role of feedback connections. The burst-tonic transition in feedback-removed relay cells to low frequency stimuli may reflect the higher sensitivity to silent signals during the drowsy states.

Because the neuronal model of this work is a single-compartmental model, there is a limitation that some results may not expand to situations involving temporally or spatially patterned synaptic input distributed over dendritic arbors. Nevertheless, this kind of single-compartmental model is appropriate in some situations, and the statistics for the stochastic responses is satisfied. However, a model with multi-compartment may have more fruitful results.

ACKNOWLEDGMENT

This work is supported by the China Postdoctoral Science Foundation funded project under Grant No. 20100470593 and the 973 Program under Grant No. 2011CB302201.

We are very grateful of Santa Fe Institute to offer us the opportunity to study in the Complex System Summer School in Beijing 2005 and make us known. We thank Zhang Jiang and Li Jing-jing for fruitful discussion, prof. John Holland, prof. Han Jing, prof. Cosma Shalizi for valuable suggestions.

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