

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

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Thalamus is the relay station for most sensory information between the peripheral sensors and the cortical areas. There is cumulative evidence showing that thalamus executes the processing role actively (Sherman SM and Guillery RW 2002), instead of letting the information pass by passively. An important issue about this role is that thalamus adjusts its response mode according to the sensory information received. The corticothalamic feedback signal has been suggested to be essential to this strategy (Guido W et al 1995, Sherman SM and Guillery RW 2002). In this report, we pieced together the experimental evidence in a realistic multi-layer network model of the thalamocortical circuit and examined its behavior to sinusoidal inputs. The results reproduced the burst/tonic responsive modes and feedback signal's role in mode transition.

## **Introduction**

Thalamus receives many inputs other than from the peripheral sensory organs. These inputs, including those from cerebral cortex and brainstem, modulate the thalamic nuclei's states and control their gating properties in neuronal information transmission. Since the last decade, the thalamic relay cells have been shown to have two distinct modes, burst and tonic, in responding to the primary sensory inputs (Sherman, SM 2001). The cells in the burst mode are shown to be more efficient in signal detection and abound while the examined animal is drowsy or sleeping state. In contrast, the tonic mode cells have higher signal transmitting fidelity and related with alert and behaving animals. The transition between burst and tonic modes is suggested to be dependent on the initial membrane potential when the sensory information comes. According to this, 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 through leveling up their membrane potentials. The hypothesis is attracting since it offers us an interpretation that the brain can use transfer functions according to different stimuli and behave like a self-adapting filter.

The evidences for this hypothesis are still not enough and in need of tidying up. Murray Sherman and colleagues have illustrated the kinetics of low threshold calcium channel (Zhan XJ et al 1999) and verified that it is capable of assigning the relay cells with burst and tonic modes in an integrate-and-fire model (Smith GD et al 2000). Based on their work, we want to test the whole hypothesis in a multi-layered network comprising teens of integrate-and-fire neurons. For simplicity and simulation resource limit, we omitted the reticular nucleus and cortical layers other

than layer VI. Our results showed that the feedback is really essential in controlling the relay cells' mode transition. We also explored the input frequency's role in shaping the stimuli-response mode relationship and proposed that this is new evidence that the mode transition is essential in controlling the animal states.

## Methods

### Network structure

The network comprises two layers, one thalamic and one cortical. There are five neurons in thalamic layer, assuming to be relay cells in a barreloid, each representing different stimulation features, such as directions of whisker reflection and visual information properties. Each one of the relay cells is reciprocally and specifically connected with a neuron in the cortical layer. The reciprocal connection is assigned since these neurons are representing layer VI excitatory neurons, mainly nontufted, which offer the corticofugal feedback signals (Shepherd GM 2004). The specific one-to-one connection is assigned since the stimulation features are preserved in the thalamocortical projections. There is a representative layer VI inhibitory interneuron, basket cell, in the cortical layer. According to Swadlow et al's work (Swadlow HA 2003), the thalamocortical inputs to the layer IV interneurons are divergent and convergent, blurring the stimulation features, so we assigned it with inputs from all 5 thalamic relay cells and outputs to all 5 cortical excitatory cells. The 1 of 6 ratio is near the general proportion, 20~30% in cerebral cortex (Markram H et al 2004).

### Cellular and synaptic parameters

These parameters are collected from several sources and listed below.

Tab.1 Cellular Parameters for the IFE network

Parameter	value	Unit	Reference
$V_{\theta}$	-35	mV	Smith GD et al 2000
$V_L$	-65	mV	Smith GD et al 2000
$V_{reset}$	-50	mV	Smith GD et al 2000
$C$	2	$\mu F * cm^{-2}$	Smith GD et al 2000
$g_L$	0.035	$mS * cm^{-2}$	Smith GD et al 2000
$V_h$	-60	mV	Smith GD et al 2000
$V_T$	120	mV	Smith GD et al 2000
$\tau_h^-$	20	Ms	Smith GD et al 2000
$\tau_h^+$	100	Ms	Smith GD et al 2000
$g_T$	0.07	$mS * cm^{-2}$	Smith GD et al 2000
$V_{relay}$	$-65 \pm 3.44$	mV	Jahnsen H. and Llinas R. 1984
$V_{nont}$	-67	mV	Shang CF's experimental data
$V_{bask}$	-62	mV	Markram H et al 2004

Tab.2 Synaptic parameters

Presynaptic	Postsynaptic	Synapse No.	Strength $\mu\text{A}\cdot\text{cm}^{-2}$	in	Synaptic delay in ms	Time constant in ms
Relay cells	Nontufted cells	20 Traub RD et al 2005	3.5 Bannister, NJ 2002		1 Agmon A. and Connors B. 1992	2 Traub RD et al 2005
Relay cells	Basket cells	20 Traub RD et al 2005	5 Agmon A. and Connors B. 1992		1 Porter JT et al 2001	1 Traub RD et al 2005
Basket cells	Nontufted cells	$20 \pm 1.34$ Traub RD et al 2005	1.4 Bannister, NJ 2002		0 Traub RD et al 2005	6 Turner JP and Salt TE 1998
Nontufted cells	Relay cells	20 Traub RD et al 2005	2 Kao C. and Coulter DA 1997		5 Gentet LJ and Ulrich D. 2003	2 Turner JP and Salt TE 1998

Tab.3 Stimulus parameters

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

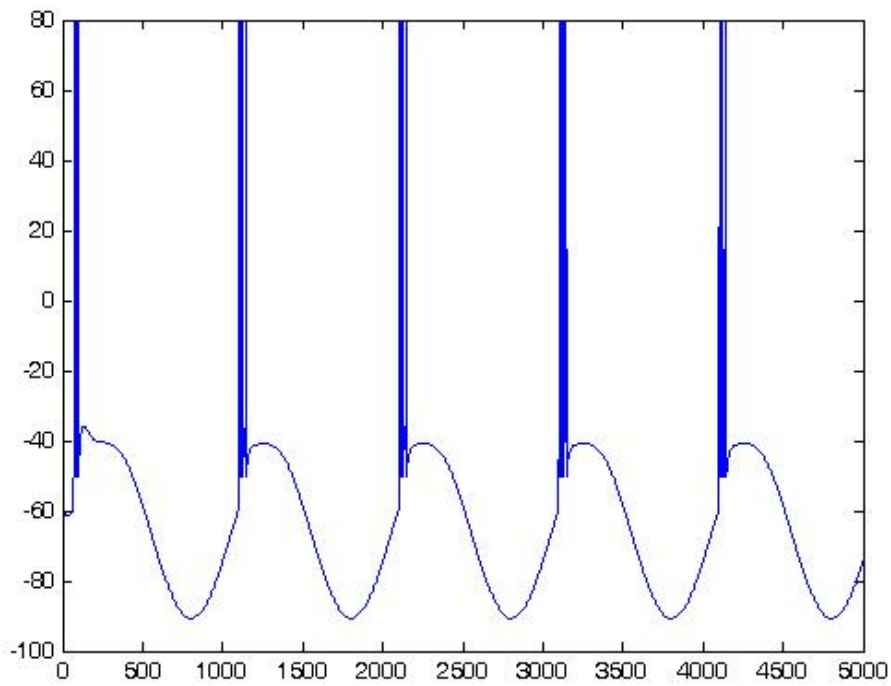
Parameter	Value	Unit
Baseline $I_0$	-0.05/1.1	$\mu\text{A}\cdot\text{cm}^{-2}$
Amplitude $I_1$	0.1~2	$\mu\text{A}\cdot\text{cm}^{-2}$
Frequency $f$	0.25/1/5/10/25	Hz

## Results

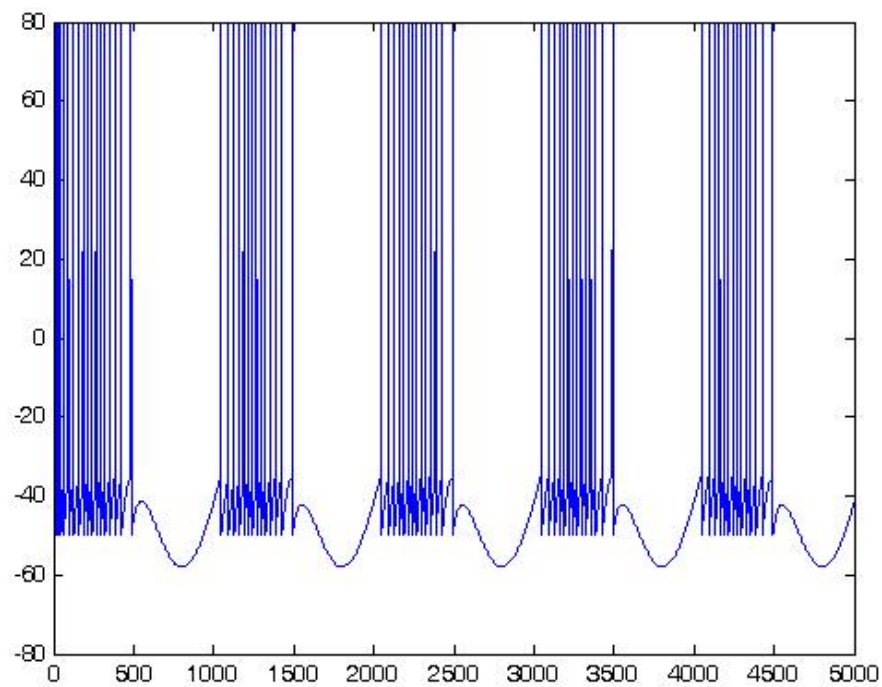
### Burst and tonic modes in relay cells

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 Fig.1a and 1b. The relays 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.

a)



b)



**Fig.1 Burst and tonic modes in the relay cells**

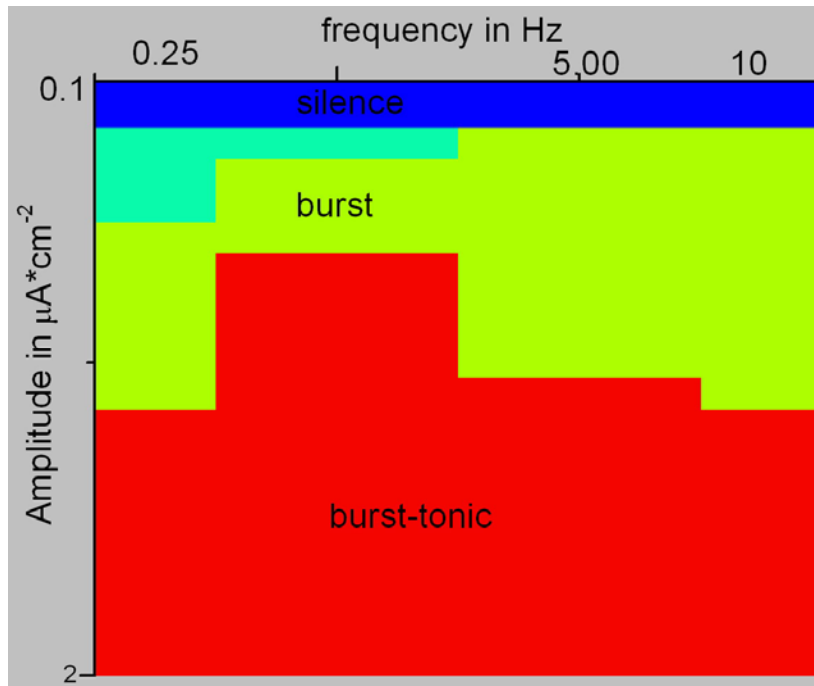
a) the stimulus is  $I_0=0.9*\cos(\pi/500)-0.05$ ;

b) the stimulus is  $I_0=0.9*\cos(\pi/500)+1.1$ .

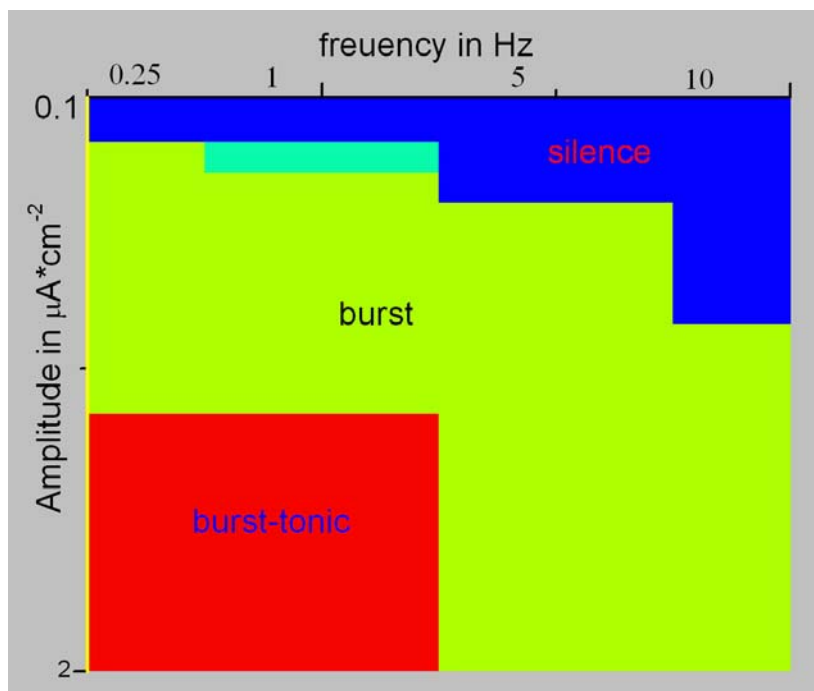
### Frequency dependency of mode transition

The whole sets of data are shown in Fig.2. For both low baseline situations with (Fig.2a) and without feedback (Fig.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 stimulation. The transition from burst mode to tonic mode happens at stimuli higher than  $1 \mu\text{A}\cdot\text{cm}^{-2}$ , but not for all stimulation frequencies. Fig.2c is the high baseline situation with or without feedback.

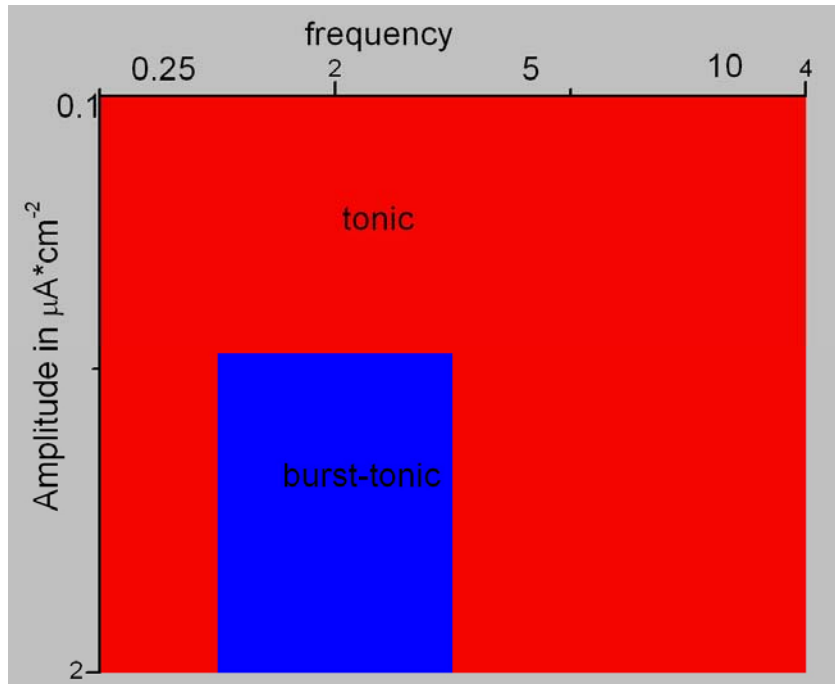
a)



b)



c)



**Fig.2 Mode transition**

The response modes to various stimuli are represented in colorgram. The low baseline situation is sensitive to feedback connections while the high baseline situation is resistant to it. a) and b) respectively shows the response modes of relay cells with or without feedback connections to low baseline stimuli. c) shows the response modes of relay cells to high baseline stimuli.

### Feedback connection shapes the mode Transition

The burst-tonic transition is essential to the “wake-up call”, representing that the feedback signal is really playing its role and the relay cells are switched into the high fidelity transferring mode from the high detectability mode. For 5Hz and 10Hz stimuli with low baseline, the burst-tonic mode transition happens only if there is the feedback connection. While controversially the transition is only postponed to higher 1Hz stimuli with low baseline if the feedback connection is turned off. And for the 0.25Hz stimuli with low baseline the stimulation-response mode relationship is not strongly dependent on the existence of feedback connection. The high baseline stimuli raise the relay cells already to tonic mode, so the relay cells are mostly resistant to remove of feedback connections. While the 1Hz stimuli with high baseline shows unique feature that the burst-tonic transition mode evoked when the stimuli is up to  $0.9\mu\text{A}\cdot\text{cm}^{-2}$ .

### $I_T$ 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.  $m = H(V - V_h)$ , and  $H(*)$  is the Heaviside step function. Consistent with the physiological result, the active periods are mostly about 100ms when the stimuli are capable of evoking burst-tonic transition.

## Discussion

1. Although the model is really simple and incomplete, the essential role of feedback is significant. To incorporate more components, especially the reticulus nucleus and cortical columnar constructions should make the model more concrete and precise in temporal structure. The feedforward inhibition is proposed to be efficient to shape 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 (Choe Y 2003).
2. The stimuli frequencies are respectively related to different brain states: 0.25Hz are slow waves related with drowsiness and slow-wave sleep, 1Hz are  $\delta$ -wave related with slow-wave sleep, 5Hz are  $\theta$ -wave related with certain behavioral activities, and 10Hz are  $\alpha$ -wave related with restful attentiveness. (Connors, BW 1997). The slow-wave and  $\delta$ -wave are related with similar brain states, and so are the  $\delta$ -wave and  $\theta$ -wave. Consistently, the former two frequencies evoke similar response mode and show similar response to the existence of feedback connections. So are the later two. This offers us a new point of view to consider the role of feedback connections. Maybe the burst-tonic transition in feedback-removed relay cells to low frequency stimuli reflects the higher sensitivity to silent signals during the drowsy states.

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