



The effect of feedback inhibition on throughput properties of the dorsal lateral geniculate nucleus

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Abstract

The effect of feedback inhibition from thalamic reticular cells on retinogeniculate transmission by thalamocortical neurons of the dorsal lateral geniculate nucleus is analyzed using a minimal integrate-and-fire-or-burst network model. Potassium leakage conductances control the neuromodulatory state of the network and eliminate rhythmic bursting in the presence of spontaneous input. During oscillatory full-field stimulation, feedback inhibition from thalamic reticular neurons leads to thalamocortical relay neuron burst responses. Depending on average input rate, contrast level, and temporal frequency of modulation, the response of the aroused network may or may not be phase-locked to the visual stimulus.

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1. Introduction

Like other sensory thalamic nuclei, the dorsal lateral geniculate nucleus (dLGN) controls the flow of sensory information to cortex, acting as a state-dependent gateway between the sensory periphery and higher cortical centers [4]. During sleep the principle cells of the dLGN exhibit rhythmic bursts of action potentials (APs) which do not reflect the excitatory glutamatergic drive they receive from

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spontaneously active retinal ganglion cells (RGCs). These emergent network properties of the sleeping thalamus require the interaction between excitatory (glutamatergic) thalamocortical (TC) cells and inhibitory (GABAergic) thalamic reticular (RE) neurons, as well as the low-threshold Ca^{2+} current (I_T) that both TC and RE cells express. During arousal thalamocortical relay neurons of the dLGN cease rhythmic bursting, enter tonic mode, and respond with conventional APs that faithfully relay EPSPs received from spontaneously active or visually stimulated RGCs.

We present and analyze a minimal network model of retinogeniculate transmission by the dLGN that includes feedback inhibition from RE cells of the associated perigeniculate nucleus (PGN). We thus test the hypothesis that feedback inhibition from RE cells can significantly modify TC cell responses to visually driven RGC input. The dLGN/PGN network is constructed from TC and RE-like integrate-and-fire-or-burst (IFB) neuron models and is consequently more idealized than Hodgkin–Huxley-type models of thalamic oscillations and waves with [1] or without [3] AP generating currents. These simulations are novel in that the input/output properties—as opposed to autonomous network rhythms—of the dLGN/PGN model are characterized and, importantly, the sleep/awake transition occurs in the context of spontaneous retinal input.

2. Model

Simulations were performed using a minimal dLGN/PGN network model composed of TC-like and RE-like IFB neuron models [5]. Briefly, an IFB model is constructed by adding a slow variable to a classical integrate-and-fire neuron,

$$C \frac{dV}{dt} = - \underbrace{g_{\text{KL}}(V - V_{\text{KL}})}_{I_{\text{KL}}} - \underbrace{g_{\text{NL}}(V - V_{\text{NL}})}_{I_{\text{NL}}} - \underbrace{g_{\text{T}}\Theta(V - V_h)h(V - V_{\text{T}})}_{I_{\text{T}}},$$

$$\frac{dh}{dt} = \begin{cases} -h/\tau_h^- & (V > V_h), \\ (1 - h)/\tau_h^+ & (V < V_h), \end{cases}$$

where the leakage current $I_{\text{L}} = I_{\text{KL}} + I_{\text{NL}}$ is the sum of potassium and non-specific components. A spike occurs when V reaches the threshold V_{θ} , and an absolute refractory period of length t_{R} is imposed during which $V = V_{\text{reset}}$. The slow variable h represents de-inactivation of I_{T} and the Heaviside function $\Theta(V - V_h)$ is an idealization of I_{T} activation. The TC-like IFB model originally presented in [5] reproduces the salient response features of TC cells to sinusoidal current injection.

A subtle change in parameters converts the TC-like IFB model into an RE-like version (see Fig. 1A and B). In the TC model, the resting membrane potential (V_{L}^{TC} , filled circle) is more depolarized than V_h^{TC} (vertical branch of h -nullcline, dotted line), while in the RE model $V_{\text{L}}^{\text{RE}} < V_h^{\text{RE}}$. Thus, the TC neuron exhibits tonic spiking when depolarized and post-inhibitory rebound bursts, while the resting RE model is primed to burst because I_{T} is de-inactivated ($h = 1$) when $V^{\text{RE}} = V_{\text{L}}^{\text{RE}}$.

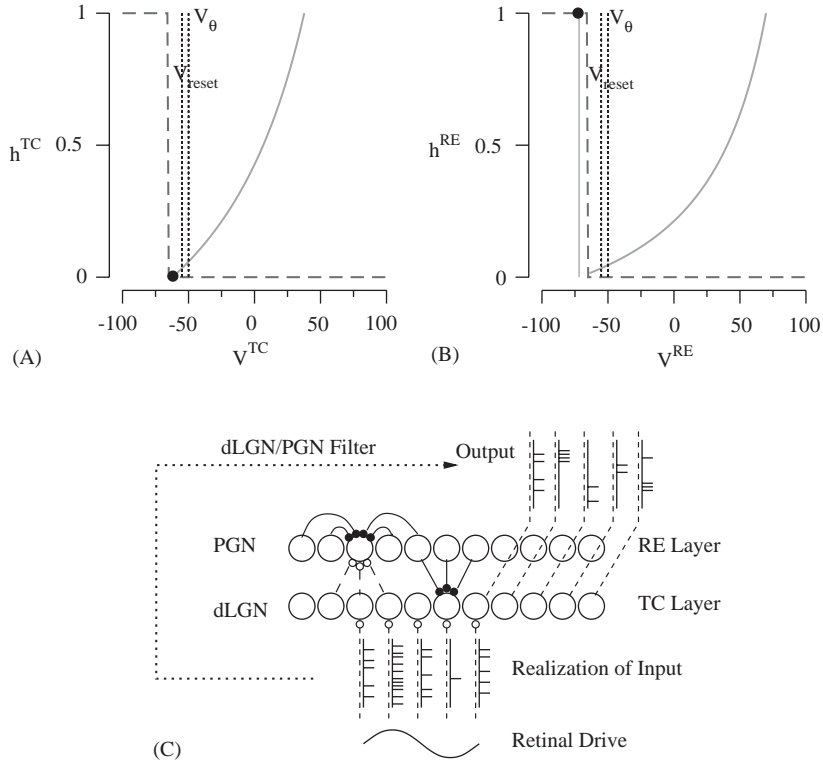


Fig. 1. (A and B) (V, h) -phase planes for the TC-like and RE-like IFB models (solid lines, $\dot{V} = 0$; dashed lines, $\dot{h} = 0$). Filled circles indicate resting membrane potentials, V_L^{RE} and V_L^{TC} . (C) dLGN/PGN network diagram showing excitatory (open circles) and inhibitory (filled circles) synaptic connections. TC parameters in awake state: $C = 1 \mu\text{F}/\text{cm}^2$; in ms: $t_R = 4$, $\tau_h^+ = 100$, $\tau_h^- = 20$; in mV: $V_{\text{KL}} = -100$, $V_h = -65$, $V_{\text{reset}} = -55$, $V_{\text{NL}} = -50$, $V_\theta = -50$, $V_T = 120$; in mS/cm^2 : $g_T = 0.08$, $g_{\text{NL}} = 0.05$, and $g_{\text{KL}} = 0.016$ for V_L^{TC} of -62.1 mV. RE as TC except $g_T = 0.2$, $g_{\text{NL}} = 0.04$, and $g_{\text{KL}} = 0.031 \text{ mS}/\text{cm}^2$ for V_L^{RE} of -71.8 mV.

The dLGN/PGN network is composed of two one-dimensional arrays of TC-like and RE-like IFB models [5] with connectivity following [3] (see Fig. 1C):

$$C \frac{dV_i^{\text{TC}}}{dt} = -I_{\text{MEM}_i}^{\text{TC}} - I_{\text{RET}_i} - I_{\text{GABA}_i},$$

$$C \frac{dV_i^{\text{RE}}}{dt} = -I_{\text{MEM}_i}^{\text{RE}} - I_{\text{AMPA}_i} - I_{\text{GABA}_i}^{\text{RE}},$$

where $I_{\text{SYN}_i} = g_{\text{SYN}} \sum_j w_{ji} s_j (V_i - V_{\text{SYN}})$ and the exponentially decaying synaptic footprint is given by $w_{ij} = \exp(-|x_i - x_j|/\lambda)/2\lambda$ where $\lambda = 0.1$ (one-tenth of the network length). The TC layer receives spontaneous or visually-driven excitatory synaptic conductances (g_{RET}) and feedback inhibition from GABAergic RE cells

(g_{GABA}). The RE layer receives excitatory synaptic conductances (g_{AMPA}) from TC cells and GABAergic inhibition from neighboring RE cells ($g_{\text{GABA}}^{\text{RE}}$). Postsynaptic conductances of form $s_j(t) = \alpha_j^2 t e^{-\alpha_j t}$ are triggered by spiking of presynaptic neurons ($\alpha_{\text{AMPA}} = \alpha_{\text{RET}} = 0.1$ and $\alpha_{\text{GABA}} = \alpha_{\text{GABA}}^{\text{RE}} = 0.05 \text{ ms}^{-1}$) [2].

Average X-type RGC responses to oscillatory full-field stimulation were modeled as

$$\rho(t) = \rho_{\text{DC}} + \rho_{\text{AC}} \cos(2\pi ft) = \rho_{\text{DC}}[1 + c \cos(2\pi ft)],$$

where ρ_{DC} and ρ_{AC} are DC and AC spike rates, $c = \rho_{\text{AC}}/\rho_{\text{DC}}$ is the stimulus contrast, and f is the temporal frequency of modulation. Event times for spontaneous or visually driven retinal excitatory postsynaptic conductances are modeled as a modulated gamma process of rate $\rho(t)$ [6].

3. Simulation results

The neuromodulatory state of the dLGN/PGN network is determined by g_{KL} for each cell type. In the sleep state ($g_{\text{KL}}^{\text{TC}} = 0.02$, $g_{\text{KL}}^{\text{RE}} = 0.027 \mu\text{S}/\text{cm}^2$) the network exhibits sleep rhythm activity in the presence of a 30 Hz spontaneous retinal input (not shown), while in the awake state ($g_{\text{KL}}^{\text{TC}} = 0.016$, $g_{\text{KL}}^{\text{RE}} = 0.031 \mu\text{S}/\text{cm}^2$) rhythmic bursting is not sustained (Fig. 2B). Though some cells exhibit several bursts,

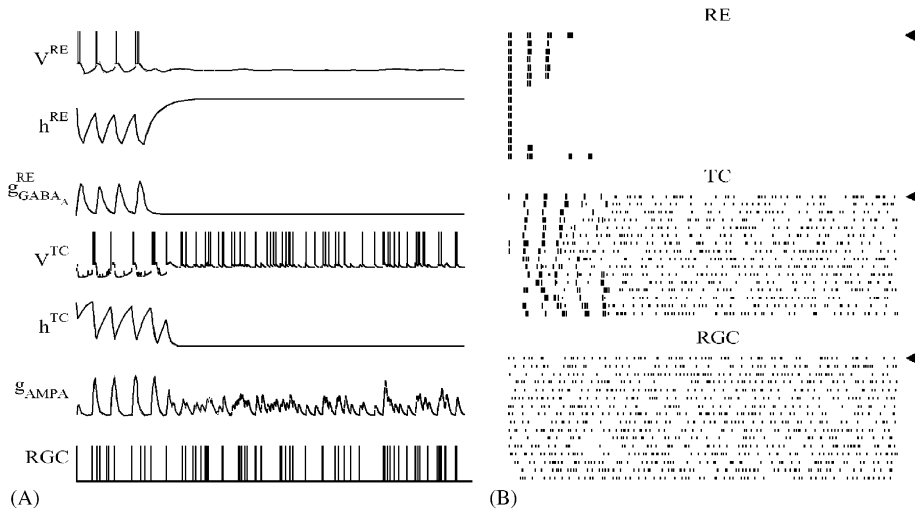


Fig. 2. Aroused network ($g_{\text{KL}}^{\text{TC}} = 0.016$, $g_{\text{KL}}^{\text{RE}} = 0.031 \mu\text{S}/\text{cm}^2$) driven by 30 Hz spontaneous input. (A) Response of neurons in the network (filled triangle in B) and (B) Raster plots show network activity under full-field spontaneous stimulation. Short and long vertical lines indicate burst and tonic spikes, respectively. Network parameters as in Section 2 and in mV: $V_{\text{AMPA}} = 0$, $V_{\text{RET}} = 0$, $V_{\text{GABA}} = -85$, $V_{\text{GABA}}^{\text{RE}} = -85$; in mS/cm^2 : $g_{\text{AMPA}} = 0.1$, $g_{\text{RET}} = 0.3$, $g_{\text{GABA}} = 15$, $g_{\text{GABA}}^{\text{RE}} = 1$.

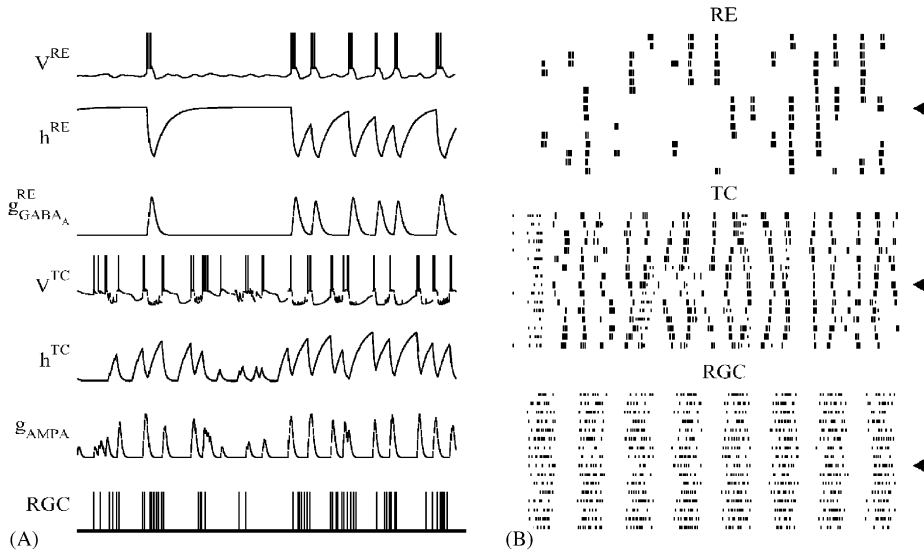


Fig. 3. Aroused network ($g_{KL}^{TC} = 0.016$, $g_{KL}^{RE} = 0.031 \mu S/cm^2$) stimulated at 2.5 Hz, with $\rho_{DC} = 30$ and $\rho_{AC} = 60$ Hz. (A) Response of TC and RE neurons in the same retinotopic position (filled triangle in B) and (B) Raster plots of network activity under full-field oscillatory stimulation. Though the network is awake, RE cells are active and population rhythm is phase-locked to RGC input.

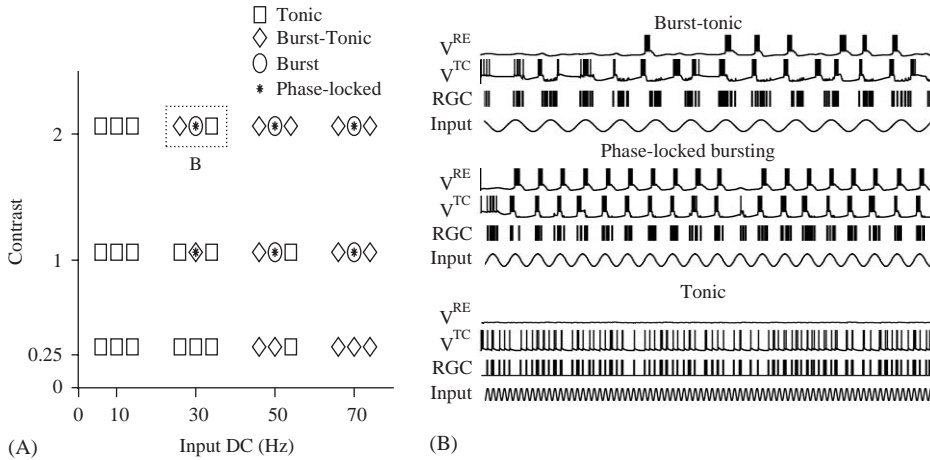


Fig. 4. (A) Parameter study of IFB network response to stimuli with different mean firing rate and contrast. Symbol shape indicates the burst fraction (percentage of spikes occurring with $h_{TC} > 0.05$): tonic (< 0.15), burst-tonic ($0.15-0.85$), and burst (> 0.85). Asterisks indicate burst responses that appeared phase-locked to the stimulus. Groups of symbols correspond to input frequencies of 4, 6.25 and 25 Hz. (B) Representative membrane potential and RGC spike times for three network response types in A. Temporal frequency of stimulus is 4 (top), 6.25 (middle) and 25 Hz (bottom).

ultimately the RE cells are quiescent and TC cells respond in tonic mode faithfully relaying retinal input.

Fig. 3 shows the response of the awake network to full-field, sinusoidally modulated input. With cellular and network parameters identical to Fig. 2, modulated stimulation leads to active RE cells and both burst and tonic TC responses. Fig. 4 presents a parameter study showing the increased burst fraction of TC cell response depending on the average input rate, contrast level, and temporal frequency of modulation. These TC cell PIR bursts are due to feedback inhibition from RE cells and may or may not be *phase-locked* to the visual stimulus (*asterisks*). Fig. 4B shows the three types of responses in simulations identical except for temporal frequency of retinal input (4, 6.25 and 25 Hz, respectively).

4. Conclusions

The neuromodulatory state of the dLGN/PGN network is determined by g_{KL} for each cell type. In the sleep state, the network exhibits sleep rhythm activity in the presence of a 30 Hz spontaneous retinal input. When g_{KL}^{TC} and g_{KL}^{RE} are chosen to represent the awake state, the network model presented here is unable to sustain sleep rhythm activity: the RE cells are ultimately quiescent and TC cells respond in tonic mode faithfully relaying RGC input. However, in the presence of modulated stimulation with sufficiently high mean firing rate, the RE cells exhibit phase-locked bursts and modify (through feedback inhibition) the response of TC cells and network throughput. Parameter studies indicate three response types depending on mean firing rate, contrast level, and temporal frequency of the stimulus.

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