Deep Brain Stimulation and its Possible Effect on Information Transfer in the Thalamus

J.E. Rubin and D. Terman

1 Introduction

Deep brain stimulation of the subthalamic nucleus (STN) or globus pallidus (GPi) has recently gained great importance in the treatment of Parkinson's disease (PD) and other neurological disorders (for recent reviews and results, see e.g. [27, 5, 4, 16, 17, 30]). The basic mechanisms underlying DBS remain mysterious, however. It is not known whether DBS acts to enhance or suppress neuronal activity within a given structure, which areas and which neurons within these areas are acted upon by DBS, or how the geometry and orientation of neurons modulate the effect of the electric field generated by the DBS. These issues present a daunting challenge for theoreticians hoping to use computational models to gain insight into the mechanisms underlying DBS.

There are several reasons why it is believed that the primary action of DBS is to suppress neuronal activity. One argument is that because the clinical effects of DBS are similar to those of ablative surgeries, the mechanisms underlying these treatments must be similar [8, 27, 5, 26]. Numerous experimental studies have demonstrated that in PD, the output nuclei of the basal ganglia become overactive, thereby increasing the level of inhibition sent onto the thalamus. This may in turn inhibit the thalamus from passing along sensorimotor signals to the cortex. Ablative surgery clearly eliminates this over-activity; indeed, this is the explanation usually given for why it works. By analogy, one may expect that DBS somehow has an inhibitory effect that reduces the increased activity of the GPi. This inhibitory effect may arise through a variety of mechanisms (reviewed in [3, 8, 24, 6, 5, 4, 26, 15]).

Alternatively, it is not at all clear how to explain the beneficial effects of DBS if its action is to enhance neuronal activity. Recall that Parkinson's disease is associated with increased firing of GPi. If DBS enhances activity, then DBS would further increase the firing of GPi neurons. This seems contradictory. *The goal of this paper is to demonstrate, with a computational model, that this is, in fact, not contradictory.*

We note that the above arguments are phrased in terms of the firing rates of neurons. Several authors have pointed out that the pattern of neuronal activity, not just the rate, may be important [11, 23, 19, 22, 24, 31, 13, 36, 37]. In particular, numerous studies have demonstrated that neurons within both the STN and GPi show an increased level of synchrony and bursting activity during Parkinsonian states [11, 23, 19, 31, 13]. Using a computational model, we demonstrate that while synchronous and patterned output of GPi (corresponding to a Parkinsonian state) may disrupt the thalamic ability to relay sensorimotor information, high frequency, tonic output of GPi (corresponding to DBS) may restore thalamic relay capabilities.

Our computational model includes neurons within STN, GPe, GPi, the thalamus and the cortex. We assume that the thalamus receives two sources of input. One is from GPi and the other input corresponds to ascending signals, possibly relating to sensorimotor activity. Here, we view the thalamus simply as a relay station whose role is to pass sensorimotor signals faithfully to the cortex.

We consider three states of the basal ganglia. In a "normal" state, output from GPi is irregular and uncorrelated. This has a minimal effect on the thalamic cells; in particular, the thalamus is able to transmit ascending sensorimotor signals accurately. In a "parkinsonian" state, GPi neurons fire bursts of action potentials at a tremor frequency of 4-8 Hz. The bursts are synchronized among subpopulations of GPi neurons. The resulting effect on thalamic cells

is significant and the thalamus is no longer able to transmit ascending signals faithfully. Finally, we simulate DBS of STN neurons. We assume that DBS provides a high frequency, excitatory input to STN neurons. We find that this input leads to increased activity of STN neurons which in turn excite GPi cells, inducing them to fire tonically at high frequency. Our main result is that this may restore the ability of the thalamus to relay its sensorimotor input faithfully.

2 The Model

The network model consists of five neuronal structures; these are the thalamus, cortex, STN, GPe and GPi. The network architecture is illustrated in Figure 1. The thalamus receives synaptic inhibition from GPi and excitatory ascending input, which we consider to relate to sensorimotor activity. The cortex receives excitation from the thalamus. GPi and GPe both receive excitatory input from STN, and GPe receives a constant applied current corresponding to input from the striatum. Moreover, there is interpallidal inhibition among the GPe neurons. Finally, STN receives inhibition from GPe, as well as a periodic applied current corresponding to high frequency stimulation (ie DBS).

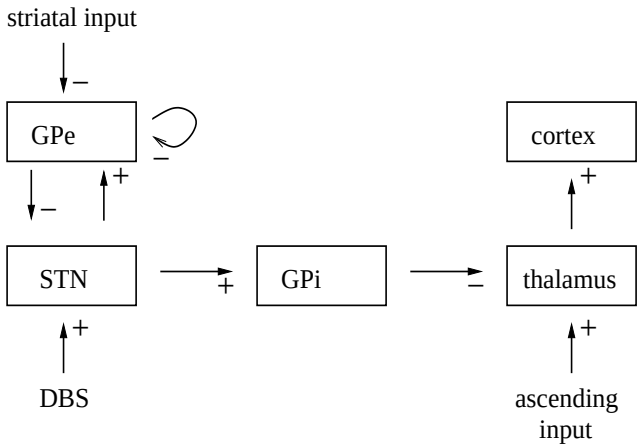

Figure 1: The network architecture.

The network includes single-compartment conductance-based biophysical models for each cell-type. Here we briefly describe firing properties of each cell-type.

The model for the thalamic cells is similar to that of [34]. These cells are silent at rest and respond to a constant depolarizing current with rapid continuous firing. Moreover, they display a strong rebound burst following sustained hyperpolarizing input. In what follows, the hyperpolarizing current will correspond to input from GPi and the rebound bursts correspond to tremor-like oscillations that may disrupt the flow of sensorimotor input to the thalamus.

We model sensorimotor input to the thalamus as a periodic step function. The model thalamic neurons will faithfully follow this periodic input over a wide range of input strength and frequency. This sensorimotor input is then relayed onto the cortex.

The model for the cortical cells was introduced in [38]. These cells respond to constant excitatory input with continuous spiking. Larger applied currents elicit faster responses.

The model STN and GPe neurons were introduced in [37]. We model the GPi cells precisely as GPe neurons. The model STN cells fire intrinsically at approximately three Hz and exhibit high frequency sustained firing with sufficient excitatory input. They also display a long afterhyperpolarization after sustained firing and strong rebound bursts after release from hyperpolarizing

current. The pallidal cells can fire rapid periodic spikes with sufficient applied current. They also display bursts of activity with a small amount of hyperpolarizing current, as well as an AHP following sustained firing.

The synaptic current $I_{\alpha\to\beta}$ from structure α to structure β is given as

$$I_{\alpha\to\beta} = g_{\alpha\to\beta}(v_\alpha - E_{\alpha\to\beta})\sum_j s_\alpha^j$$

Here, $g_{\alpha\to\beta} > 0$ is the maximal synaptic conductance and $E_{\alpha\to\beta}$ is the reversal potential. The sum is over presynaptic cells. Each synaptic variable s_α^j satisfies a first order differential equation of the form

$$s'_\alpha = A_\alpha(1 - s_\alpha)H_\infty(v_\alpha - \theta_\alpha) - B_\alpha s_\alpha$$

H_∞ is an approximation of the Heaviside step function.

3 Main Results

Our main objective is to study how thalamic cells respond to excitatory signals, representing sensorimotor input, during both "normal" and "parkinsonian" states, with and without high frequency stimulation. Here we define what is meant by each of these states.

As shown in [29], the STN and GPe neurons form an excitatory/inhibitory network that can oscillate in the absence of input from other structures. In [37], we describe several different types of activity patterns that may be generated by isolated the STN/GPe network (but with a constant level I_{app} of striatal inhibition to GPe), along with a detailed description of how the activity patterns depend on parameters. We demonstrated that this network can produce both irregular asynchronous activity and synchronous tremor-like activity as shown in Figure 2. We note that both of the patterns shown in Figure 2 are generated for a network with exactly the same architecture. In order to switch from the pattern shown in Figure 2A to that shown in Figure 2B, we increased I_{app} and decreased $g_{Ge\to Ge}$. These parameters correspond to the level of striatal input to GPe and interpallidal inhibition, respectively. Note that experimental results show an increase in striatal inhibition to GPe (e.g., [1]) and a decrease in intrapallidal inhibition [35, 25] in parkinsonian conditions.

By a "normal state", we mean that the parameters are chosen so that the STN/GPe network produces the irregular pattern shown in Figure 2A. By a "parkinsonian state", we mean that the parameters are chosen so that the STN/GPe network produces the more regular, synchronous activity shown in Figure 2B.

Figures 3A and 3B illustrate the response of the full network during the normal and parkinsonian states, respectively, when there is no DBS. During the normal state, the thalamus responds to the excitatory sensorimotor input and faithfully transmits these signals to the cortex. In this case, the uncorrelated, irregular input from GPi is too weak to disrupt thalamic relay; the firing pattern of a typical GPi cell sending input to the TC cell shown appears in the bottom row of the plot.

On the other hand, during the parkinsonian state, the thalamus is no longer able to relay sensorimotor input faithfully. The synchronous, bursting output of GPi is now powerful enough to influence thalamic activity and this is clearly reflected in both the thalamic and cortical responses.

We now introduce deep brain stimulation (DBS) of the STN. We model this as

$$I_{DBS} = i_D H(\sin(2\pi t/\rho_D))(1 - H(\sin(2\pi(t+\delta_D)/\rho_D))\,,$$

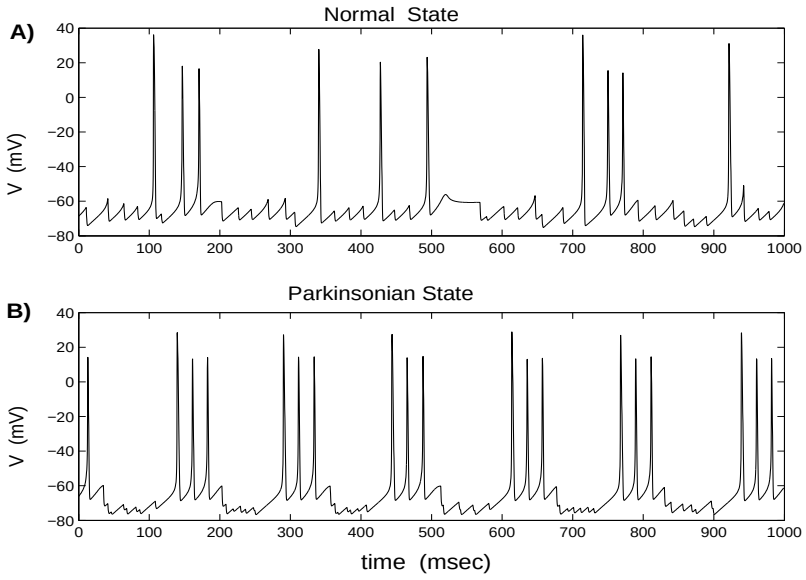

Figure 2: Membrane potential of STN neuron for (A) normal and (B) parkinsonian states. The STN displays irregular activity during the normal state and a more regular, synchronous activity during the parkinsonian state.

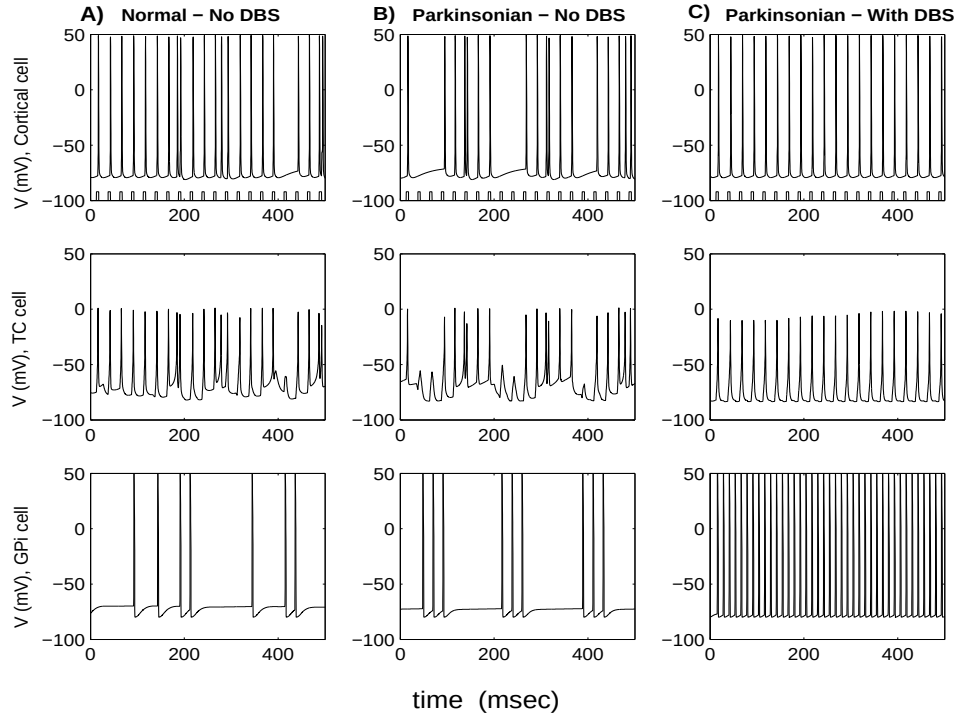

Figure 3: Response of the network to sensory motor input. The three columns show the normal, parkinsonian without DBS, and parkinsonian with DBS cases, respectively. The sensorimotor input is indicated at the bottom of the top panels in each column. Note that the cortex responds faithfully to sensorimotor input for the normal and parkinsonian with DBS cases; however, the cortex does not respond faithfully for the parkinsonian without DBS case.

where i_D corresponds to stimulation amplitude, ρ_D to stimulation period, and δ_D to the duration of each impulse. In Figure 3C, we add DBS to the system. Note that DBS completely restores the thalamic ability to transmit sensorimotor information.

4 Discussion

In this paper, we use a computational model to consider how DBS of the STN may affect firing patterns in the basal ganglia and in some of the cells affected by basal ganglia outputs. Our simulations support the paradoxical-seeming idea that DBS may enhance the firing rate of inhibitory GPi cells, and that this may actually *improve* the responsiveness to excitatory inputs of the TC cells that GPi targets. More specifically, we find that the increased rhythmicity of STN firing in parkinsonian conditions leads to rhythmic GPi firing, and thus *phasic* inhibition of TC cells, which can compromise their responsiveness. High-frequency stimulation induces high-frequency, tonic firing of STN, and thus of GPi, which results in strong but *tonic* inhibition of TC cells. This tonic inhibition may have a much weaker effect on TC responsiveness, through mechanisms that our simulations and analysis explain. Thus, the key point of our results is that DBS may be effective at reducing motor symptoms of parkinsonism because it eliminates the oscillatory nature of the inhibition to TC cells. Although this argument runs counter to much of the existing theorization on what mechanisms underlie the efficacy of DBS, it is quite natural from the perspective of oscillatory networks.

Some experimental studies have suggested that DBS somehow silences STN firing. Benazzouz et al. [9, 7] found that HFS of STN in rats suppresses activity of cells in pallidal areas, as well as near the stimulation site in STN. These studies compare firing before HFS with that after HFS, however; they cannot establish how firing changes during HFS. Moreover, Boraud et al. [12] found that HFS of GPi in MPTP-treated monkeys restored GPi firing rates from their MPTP-induced elevated states back to normal levels, but did not in fact block GPi activity.

There is also experimental evidence that DBS enhances neuronal activity, however. It has been shown that HFS of STN in normal rat leads to an increase in extracellular glutamate in the GP and SNr [39, 28]. Given that the STN is the primary source of excitatory afferents in these areas, this suggests that HFS of STN may not suppress STN activity. Moreover, Anderson et al. [2] have recently shown that HFS of GPi produces a reduction in discharge frequency of thalamic neurons that GPi cells inhibit.

We have made the simplifying assumption that GPi outputs and ascending sensorimotor signals impinge on common cortically-projecting thalamic areas. There is some experimental support for overlap between the thalamic targets of the GPi and of the cerebellum [18, 20, 33, 32]. Even if these targets are disjoint sets, however, the strong, synchronized rebound bursts from TC cells that receive GPi inputs (e.g. in VLo) would disrupt cortical responsiveness to sensorimotor signals from other (e.g. Vim) TC cells [21, 10] in cortical areas on which the TC inputs converge. It is even possible that the TC rebound bursts would induce cortical bursts, through recruitment of cortical interneurons [14], although we have not explored this in our simulations.

We have made numerous other simplifying assumptions as well. We have assumed that the role of the GPi is simply to relay input from STN; we have ignored direct inputs from GPe to GPi; and we have not considered how the basal ganglia might play a functional role in modulating sensorimotor signals to the thalamus. We have also taken an extremely simplistic view of the effect of DBS on neuronal activity, ignoring, for example, any field effects or variations due to the differential positioning of a stimulating electrode relative to different cells that it affects. Finally, we have treated individual cells as single compartment units. Nonetheless, the mechanism that we have elucidated is based on a small number of properties, such as rhythmicity of indirect pathway activity in PD and TC rebound burst firing in response to phasic inhibition, that have

been experimentally observed in basal ganglia and TC cells and that do not depend on the specifics of our approach.

References

[1] R. Albin, A. Young, and J. Penney. The functional anatomy of basal ganglia disorders. *Trends Neurosci.*, **12**:366–375, 1989.

[2] M. Anderson, N. Postpuna, and M. Ruffo. Effects of high-frequency stimulation in the internal globus pallidus on the activity of thalamic neurons in the awake monkey. *J. Neurophysiol.*, **89**:1150–1160, 2003.

[3] P. Ashby. What does stimulation in the brain actually do? *Prog. Neurol. Surg.*, **15**:236–245, 2000.

[4] A. Benabid, A. Koudsie, A. Benazzouz, B. Piallat, P. Krack, N. V. Blerkom, V. Fraix, and P. Pollak. Subthalamic nucleus deep brain stimulation. In A. Lozano, editor, *Movement Disorder Surgery*. S. Karger AG, Basel, 2001.

[5] A. Benabid, A. Koudsie, A. Benazzouz, B. Piallat, P. Krack, P. Limousin-Dowsey, J. Lebas, and P. Pollak. Deep brain stimulation for Parkinson's disease. In D. Calne and S. M. Calne, editors, *Advances in Neurology, Volume 86: Parkinson's Disease*. Lippincott Williams & Wilkins, Philadelphia, 2001.

[6] A. Benabid, A. Koudsie, A. Benazzouz, L. Vercueil, V. Fraix, S. Chabardes, J. Lebas, and P. Pollak. Deep brain stimulation of the corpus luysi (subthalamic nucleus) and other targets in parkinson's disease. Extension to new indications such as dystonia and epilepsy. *J. Neurol.*, **248**, Supp. 3:S37–S47, 2001.

[7] A. Benazzouz, D. Gao, Z. Ni, B. Piallat, R. Bouali-Benazzouz, and A. Benabid. Effect of high-frequency stimulation of the subthalamic nucleus on the neuronal activities of the substantia nigra pars reticulata and the ventrolateral nucleus of the thalamus. *Neuroscience*, **99**:289–295, 2000.

[8] A. Benazzouz and M. Hallett. Mechanisms of action of deep brain stimulation. *Neurology*, **55**, Supp. 6:S13–S16, 2000.

[9] A. Benazzouz, B. Piallat, P. Pollack, and A. Benabid. Responses of the substantia nigra pars reticulata and globus pallidus complex to high frequency stimulation of the subthalamic nucleus in rats: electrophysiological data. *Neurosci. Lett.*, **189**:77–80, 1995.

[10] H. Bergman and G. Deuschl. Pathophysiology of Parkinson's disease: From clinical neurology to basic neuroscience and back. *Mov. Disord.*, **17**, Suppl. 3:S28–S40, 2002.

[11] H. Bergman, T. Wichmann, B. Karmon, and M. DeLong. The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. *J. Neurophysiol.*, **72**:507–520, 1994.

[12] T. Boraud, E. Bezard, B. Bioulac, and C. Gross. High frequency stimulation of the internal globus pallidus (GPi) simultaneously improves parkinsonian symptoms and reduces the firing frequency of GPi neurons in the MPTP-treated monkey. *Neurosci. Lett.*, **215**:17–20, 1996.

[13] P. Brown, A. Oliviero, P. Mazzone, A. Insola, P. Tonali, and V. D. Lazzaro. Dopamine dependency of oscillations between subthalmaic nucleus and pallidum in Parkinson's disease. *J. Neurosci.*, **21**:1033–1038, 2001.

[14] A. Destexhe, D. Contreras, and M. Steriade. Mechanisms underlying the synhronizing action of corticothalamic feedback through inhibition of thalamic relay cells. *J. Neurophysiol.*, **79**:999–1016, 1998.

[15] J. Dostrovsky and A. Lozano. Mechanisms of deep brain stimulation. *Mov. Disord.*, **17**, Supp. 3:S63–S68, 2002.

[16] C. Gross. Stimulation of the globus pallidus internus. In A. Lozano, editor, *Movement Disorder Surgery*. S. Karger AG, Basel, 2001.

[17] T. he Deep Brain Stimulation for Parkinson's Disease Study Group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. *New England J. Med.*, **345**:956–963, 2001.

[18] G. Macchi and E. Jones. Toward an agreement on terminology of nuclear and subnuclear divisions of the motor thalamus. *J. Neurosurg.*, **86**:670–685, 1997.

[19] M. Magnin, A. Morel, and D. Jeanmonod. Single-unit analysis of the pallidum, thalamus, and subthalamic nucleus in partkinsonian patients. *Neuroscience*, **96**:549–564, 2000.

[20] A. Mason, I. Ilinsky, S. Maldonado, and K. Kultas-Ilinsky. Thalamic termial fields of individual axons from the ventral part of the dentate nucleus of the cerebellum in Macaca mullata. *J. Comp. Neurol.*, **421**:412–428, 2000.

[21] F. Middleton and P. Strick. Basal ganglia and cerebellar loops: motor and cognitive circuits. *Brain Res. Rev.*, **31**:236–250, 2000.

[22] E. Montgomery, Jr. and K. Baker. Mechansism of deep brain stimulation and future technical developments. *Neurol. Res.*, **22**:259–266, 2000.

[23] A. Nini, A. Feingold, H. Slovin, and H. Bergman. Neurons in the globus pallidus do not show correlated activity in the normal monkey, but phase-locked oscillations appear in the MPTP model of parkinsonism. *J. Neurophysiol.*, **74**:1800–1805, 1995.

[24] J. Obeso, M. Rodriguez-Oroz, M. Rodriguez, R. Macias, L. Alvarez, J. Guridi, J. Vitek, and M. DeLong. Pathophysiologic basis of surgery for Parkinson's disease. *Neurology*, **55**, Supp. 6:S7–S12, 2000.

[25] M. Ogura and H. Kita. Dynorphin exerts both postsynaptic and presynaptic effects in the globus pallidus of the rat. *J. Neurophysiol.*, **83**:3366–3376, 2000.

[26] W. Olanow and M. Brin. In D. Calne and S. M. Calne, editors, *Advances in Neurology, Volume 86: Parkinson's Disease*. Lippincott Williams & Wilkins, Philadelphia, 2001.

[27] W. Olanow, M. Brin, and J. Obeso. The role of deep brain stimulation as a surgical treatment for Parkinson's disease. *Neurology*, **55**, Supp. 6:S60–S66, 2000.

[28] G. Paul, T. Reum, W. Meissner, A. Marburger, R. Sohr, R. Morgenstern, and A. Kupsch. High frequency stimulation of the subthalamic nucleus influences striatal dopaminergic metabolism in naive rats. *NeuroReport*, **11**:441–444, 2000.

[29] D. Plenz and S. Kitai. A basal ganglia pacemaker formed by the subthalamic nucleus and external globus pallidus. *Nature*, **400**:677–682, 1999.

[30] P. Pollak, V. Fraix, P. Krack, E. Moro, A. Mendes, S. Chabardes, A. Koudsie, and A. Benabid. Treatment results: Parkinson's disease. *Mov. Disord.*, **17**, Supp. 3:S75–S83, 2002.

[31] A. Raz, E. Vaadia, and H. Bergman. Firing patterns and correlations of spontaneous discharge of pallidal neurons in the normal and tremulous 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine vervet model of parkinsonism. *J. Neurosci.*, **20**:8559–8571, 2000.

[32] S. Sakai, M. Inase, and J. Tanji. The relationship between MI and SMA afferents and cerebellar and pallidal efferents in the macaque monkey. *Somatosens. & Mot. Res.*, **19**:139–148, 2002.

[33] S. Sakai, I. Stepniewska, H. Qi, and J. Kaas. Palladial and cerebellar afferents to presupplementary motor area thalamocortical neurons in the owl monkey: a multiple labeling study. *J. Comp. Neurol.*, **417**:164–180, 2000.

[34] V. Sohal and J. Huguenard. Reciprocal inhibition controls the oscillatory state in thalamic networks. *Neurocomp.*, **44**:653–659, 2002.

[35] I. Stanford and A. Cooper. Presynaptic μ and δ opioid receptor modulation of $GABA_a$ IPSCs in the rat globus pallidus *in vitro*. *J. Neurosci.*, **19**:4796–4803, 1999.

[36] D. Terman, J. Rubin, A. Yew, and C. Wilson. Synchronous parkinsonian rhythms in a model for the indirect pathway of the basal ganglia. *Neurocomp.*, **39-40**:973–982, 2001.

[37] D. Terman, J. Rubin, A. Yew, and C. Wilson. Activity patterns in a model for the subthalamopallidal network of the basal ganglia. *J. Neurosci.*, **22**:2963–2976, 2002.

[38] R. Traub and R. Miles. *Neuronal Networks of the Hippocampus*. Cambridge University Press, Cambridge, UK, 1991.

[39] F. Windels, N. Bruet, A. Poupard, N. Urbain, G. Chouvet, C. Feuerstein, and M. Savasta. Effects of high frequency stimulation of subthalamic nucleus on extracellular glutamate and GABA in substantia nigra and globus pallidus in the normal rat. *Eur. J. Neurosci.*, **12**:4141–4146, 2000.