Physica A 441 (2016) 121–130

Contents lists available at ScienceDirect

Physica A

journal homepage: www.elsevier.com/locate/physa

Theory of feedback controlled brain stimulations for Parkinson's disease

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HIGHLIGHTS

- We derive an effective model for the dynamics of the subthalamic nucleus.
- The phase diagram of the neural network activity is analysed.
- Tremor-related activity is ascribed to an instability in the network.
- We propose a stimulation protocol to avoid the unstable region, and hence tremor.

ARTICLE INFO

Article history:
Received 7 May 2015
Received in revised form 6 August 2015
Available online 5 September 2015

Keywords:
Computational neuroscience
Dynamic model
Active deep brain stimulation
Parkinson's disease

ABSTRACT

Limb tremor and other debilitating symptoms caused by the neurodegenerative Parkinson's disease are currently treated by administering drugs and by fixed-frequency deep brain stimulation. The latter interferes directly with the brain dynamics by delivering electrical impulses to neurons in the subthalamic nucleus. While deep brain stimulation has shown therapeutic benefits in many instances, its mechanism is still unclear. Since its understanding could lead to improved protocols of stimulation and feedback control, we have studied a mathematical model of the many-body neural network dynamics controlling the dynamics of the basal ganglia. On the basis of the results obtained from the model, we propose a new procedure of active stimulation, that depends on the feedback of the network and that respects the constraints imposed by existing technology. We show by numerical simulations that the new protocol outperforms the standard ones for deep brain stimulation and we suggest future experiments that could further improve the feedback procedure.

1. Introduction

The basal ganglia circuit plays a central role in humans movements. In Parkinson's disease, the death of dopaminergic neurons in the substantia nigra causes movement disorders such as tremor, rigidity, slowness of movement, and postural instability [1,2]. At the neural level, this degenerative process modifies the activity in the basal ganglia. In ill individuals, the neurons in the subthalamic nucleus show an oscillatory discharge pattern that is coherent at the frequency of the limb tremor [3]. Such activity is suppressed by treatment with the dopamine prodrug, levodopa, and by dopamine agonists [4]. The effect of treatment with these drugs is a reduction in the severity of the symptoms. These observations suggest that the anomalous discharge pattern is correlated to the motor disfunction.

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http://dx.doi.org/10.1016/j.physa.2015.08.019
0378-4371/

Another strategy to reduce the symptoms associated with Parkinson's disease is deep brain stimulations on the basal ganglia [5–7]. In deep brain stimulation, electrodes implanted in the brain stimulate neurons in the subthalamic nucleus with electrical impulses at a constant frequency of about 100 Hz. Although the therapy has been shown to be effective in reducing the motor symptoms of the disease, it is far from optimal. In fact, the treatment delivers constant electrical stimulations independent of the state of the patient. Conversely, in brain disorders, and in particular in the case of Parkinson's disease, symptoms are highly variable, depending on factors such as cognitive and motor load and concurrent drug therapy [8]. A feedback control that modifies the stimulation parameters depending on the current state of the neural network would clearly be more appropriate and indeed solutions in this direction have been shown to be more efficient in alleviating parkinsonian motor symptoms than the standard deep brain stimulations [9–11] but, to the best of our knowledge, no general protocol has been found yet.

In this paper we derive a mathematical model that describes the dynamics of the subthalamic nucleus. We ascribe the onset of tremor-related activity in Parkinson's disease to a region of unstable activity in the phase diagram of the neural network. Based on this premise, we show that the main symptoms of the disease are reproduced as a consequence of the degradation of neural stimulation from the striatum and we propose a novel feedback based stimulation protocol to avoid the unstable region, and hence tremor. We also show that our procedure can be implemented with current technology and we finally test the efficiency of the protocol by numerical simulations of the dynamics in the basal ganglia.

2. Materials and methods

Current evidence mentioned in the Introduction indicates that the death of the dopaminergic cells produces oscillatory neural activity in the basal ganglia and causes the tremor characteristic of Parkinson's disease. A priori, the complete circuit could be involved in the generation of the oscillations. However, experiments on *in vitro* cultures demonstrate that a suitable subcircuit shows spontaneous oscillatory activity analogous to that observed in the basal ganglia in patients affected by Parkinson's disease [12]. The subcircuit is formed by the external globus pallidus and the subthalamic nucleus together with external currents coming from the cortex and from the striatum. Motivated by this experimental observation, we will analyse here the dynamics of that subcircuit and show that its dynamics is indeed sufficient to explain the raise of the anomalous oscillation in the basal ganglia.

Our first goal is to give a microscopic description of the basal ganglia and to derive their effective dynamics. We consider a neural network with N neurons, $N_S = fN$ of which belong to the subthalamic nucleus and $N_G = (1-f)N$ to the external globus pallidus. To each neuron i we associate two continuous variables: the membrane potential $h_i(t)$ and the firing rate $F_i(t) \geq 0$, that are related by

$$F_i(t) = \phi_i(h_i(t)), \tag{1}$$

with ϕ_i sigmoidal functions, e.g.

$$\phi_i(x) = \frac{\phi_i^{\infty}}{1 + \exp\left[-g_i(x - h_i^*)\right]}. \tag{2}$$

The constants g_i measure the amplification of the neural response ($g_S = 0.3\ \mathrm{mV}^{-1}$ [13], $g_G = 0.2\ \mathrm{mV}^{-1}$ [14]), h_i^* is the activation potential ($h_S^* = 15$ mV [13], $h_G^* = 10$ mV [14]) and ϕ_i^{∞} is the maximal firing rate ($\phi_S^{\infty} = 0.5$ kHz [15,16], $\phi_G^{\infty} = 0.1$ kHz [14]).

The dynamics of the network is governed by the equation

$$\tau_i \dot{h}_i = -h_i + \sum_{k=1}^{N} R_{ik}\phi_i(h_k) + \eta_i + I_i, \tag{3}$$

where $\eta_i(t)$ are independent, Gaussian white noises $\langle \eta_i(t)\eta_j(t')\rangle = \Omega_i^2\delta_{ij}\delta(t-t')$ and I_i are the external currents coming form the striatum (STR) and the cortex (CTX). The time constants τ_i are $\tau^S = 6$ ms [15,16] and $\tau^G = 14$ ms [17], respectively. The matrix elements of the synaptic matrix R are Gaussian random variables. We suppose for simplicity the absence of self synapses, i.e. $R_{ii} = 0$. Note though that this biologically motivated assumption could be removed as it becomes irrelevant in the limit of a large number of neurons. The off-diagonal elements of the matrix R are

$$\langle R_{ij}\rangle = \mu_{ij}; \quad \langle R_{ij}R_{ln}\rangle - \langle R_{ij}\rangle\langle R_{lk}\rangle = \delta_{il}\delta_{jk}\sigma_{ij}^2. \tag{4}$$

The mean and the variance take four distinct values depending on the indices i and j belonging either to the subthalamic nucleus or to the external globus pallidus:

$$\begin{aligned}
&\mu_{ij} = m_{SS}, \quad && \sigma_{ij} = \sigma_{SS}, \quad && i = 1,\dots,N_S,\ j = 1,\dots,N_S,\\
&\mu_{ij} = m_{SG}, \quad && \sigma_{ij} = \sigma_{SG}, \quad && i = 1,\dots,N_S,\ j = 1,\dots,N_G,\\
&\mu_{ij} = m_{GS}, \quad && \sigma_{ij} = \sigma_{GS}, \quad && i = 1,\dots,N_G,\ j = 1,\dots,N_S,\\
&\mu_{ij} = m_{GG}, \quad && \sigma_{ij} = \sigma_{GG}, \quad && i = 1,\dots,N_G,\ j = 1,\dots,N_G.
\end{aligned} \tag{5}$$