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A biophysically inspired microelectrode recording-based model for the subthalamic nucleus activity in Parkinson's disease

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ABSTRACT

The subthalamic nucleus (STN) plays a central role in movement actuation and manifestation of movement disorders (i.e., tremor, rigidity, akynesia and postural instability) in Parkinson's disease (PD) patients. Moreover, it has been recently revealed that an opportune electrical stimulation of the STN, called deep brain stimulation (DBS), can strongly contribute to the annihilation of the PD-related motor disorders. Currently, a great effort is made both in Medicine, Neurosciences and Engineering for understanding and modeling in details how the STN works, how PD determines its pathological behavior and DBS restores the correct motor function.

The paper is organized in two parts. Firstly some stochastic properties of the STN electrical activity are obtained by analyzing a preliminary set of experimental data coming from microelectrode recordings (MERs) in two PD patients who underwent the surgical implantation of DBS electrodes. Then, a nonlinear, stochastic, continuous-state model describing the global electrical behavior of the STN in PD patients is proposed. It is inspired by the fundamental physiologic features of the subthalamic cells and a fictitious vector state is introduced to represent the main dynamics. Its numerical parameters and stochastic properties are chosen by fitting the available data.

1. Introduction

The subthalamic nucleus (STN) and all the other nuclei of the basal ganglia have received great attention in the last 30 years both under the neuro-anatomic (e.g., [1,2]), neuro-physiologic (e.g., [3–6]) and neuro-functional [7] point of view. In the last decade a great interest by the Neurocomputating community has also grown around such areas in the brain and many efforts have been done in order to numerically replicate the corresponding behavior (e.g., [8–10]). Such interest is due to the fact that the underneath networking mechanisms are still partly unknown and that the extraordinary rich and various range of firing patterns that the basal ganglia cells are able to produce [11] have not yet been faithfully modeled.

But the main reason for the attention given to the STN is surely due to its role in the manifestation of the motor symptoms of some spread neuro-degenerative pathologies, like Parkinson's disease (PD), dystonia and essential tremor. It is quite well demonstrated, in fact, that they produce significant alterations of the STN physiological electrical activity and of the basal ganglia firing patterns (e.g., [12–15]). Such interest is even more increased since it has been observed that the typical Parkinsonian movement disorders (i.e. tremor, rigidity, akynesia and postural instability) considerably reduce when the usually adopted L-dopa based pharmacological therapies are associated with the modulation of the subthalamic activity through a suitable locally applied electrical stimulation. To this aim, the deep brain stimulation (DBS) is the technique currently used in Neurosurgery both for PD and other pathologies [16–18]. Briefly, the DBS consists in square pulse trains provided to selected targets inside the brain and generated by an artificial stimulator surgically implanted in the patient. Frequency and duty cycle of the stimulation are usually fixed in order to guarantee safety for the patients while the amplitude is set by the surgeon during the implantation according to a clinical procedure consisting of the injection of sample stimuli and the evaluation of the correspondingly induced effects on the patient's motor symptoms. Associated with the appropriate pharmacological therapy, the DBS greatly reduces most of the motor symptoms, limits drug-induced dyskinesia and frequently improves patients' ability to perform activities of daily living with less encumbrance from motor fluctuations [19,20]. At a subcortical level, the clinical improvements in Parkinson's disease correlate

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Nomenclature

$B(\delta, \beta)$	beta function with parameters δ and β
C_r^*	r-th contiguous region in D^*
D	$\{0,1, \ldots, N_s-1\}$
D^*	$\bigcup_{g_c \in G} D_c^*$
D_c^*	subset of D for which (4) is satisfied
eCDF_i	empirical CDF for T_i^s
$f(p_f,t)$	Generic CDF with parameters $p_f \in D_f$
f_A^*	optimal fitting $f(p_{f,A}^{\text{MEAN}}, t)$ for A in (15)
f_i^*	optimal fitting $f(p_{f,i}^{\text{MLE}}, t)$ for T_i^s in (13)
$F_B(t)$	beta CDF
g_c	c-th temporal scale
G	$\{g_0, g_1, \ldots, g_J\}$
G_r	$\{g_c \in G : S(c,d) > \Theta_c,\ d \in C_r^*\}$
L_i	number of spikes for the i-th trace
N_c	number of contiguous regions in D^*
N_s	number of temporal translations
$p_{f,A}^{\text{MEAN}}$	optimal parameters for f fitting times in A
$p_{f,i}^{\text{MLE}}$	MLE parameters for f fitting times in T_i^s
$\text{PDF}_f(p_f, t_k^i)$	PDF of f evaluated with parameters p_f at sample t_k^i.
$s(t)$	generic signal to be analyzed
$s_1, \ldots, s_M$	traces available for analysis
$S(c, d)$	wavelet transform coefficient of the signal $s(t)$ with respect to t_d and g_c
t_d	d-th temporal translation
t_k^i	k-th spike arrival time for the i-th trace
Thr	threshold for the Quiroga's algorithm
$T(t)$	time series of the inter-times between consecutive spikes
T_r^c	$\arg\ \max_{t_d, d \in C_r^*}\{S(c,d) : S(c,d) > \Theta_c\}$.
T_i^s	set of the spike arrival times for i-th trace
T_r^*	r-th spike arrival time
u	DBS related input
v	activation level of inhibitory synapses
$w(t)$	white noise with 0 mean, standard deviation σ
x	activation level of excitatory synapses
y	noise-affected signal generated by recorded cells
z	noise-free signal generated by recorded cells
α	rate for x and v
$\gamma, a_i, b_i, \theta_i$	Model parameters (with $i = R, D, H$).
θ	$\arctan(x, v)$
Θ_c	acceptance threshold for the hypothesis that a spike is detectable at scale g_c
σ_n	$\text{median}(\lvert s\rvert/0.6745)$
$\omega(t)$	angular velocity stochastically defined
$\psi(t)$	generic wavelet mother function
$\psi_{c,d}(t)$	wavelet mother function translated of t_d and scaled by g_c according to (3)

with the modulation of the oscillatory activity induced by the DBS along the basal ganglia [21]. It is proved, in fact, that the DBS in the STN increases the subthalamic low-frequency oscillations (i.e., 1–1.5 Hz, [22]), modulates the beta ones [21], forces the pallidal neuronal elements to synchronize at frequencies greater than 70 Hz [23], and spreads its effects until the motor thalamus due to the central role of the STN in the coordination of the basal ganglia function [24]. Such results suggest that the DBS works at the cellular level by modifying the firing patterns running from the extrapyramidal system toward the cortical areas, i.e., it reduces the oscillations of the dopamine-depleted pathways in the tremor band (i.e., 2–7 Hz), reshapes those in the beta ones (i.e., 13–35 Hz), and enhances high frequency oscillation (>70 Hz). Thus, it is supposed to introduce a regularization in the firing patterns and an informational lesion of the stimulated nucleus [25].

However, a detailed and exhaustive description of the modifications induced by PD in the firing patterns of the basal ganglia and of the dynamics according to which DBS affects both STN behavior and its pallidal and nigral projections is unfortunately still far to come, even if important results and interesting models have been reported in Neurosciences (e.g., [26–28]) and Neuroengineering [29]. The great variety of synaptic connection shapes, projection fibers, dendritic arborizations and ionic currents involved in the functional interactions of the basal ganglia is a challenging hurdle toward a full comprehension of such mechanisms since it introduces a level of complexity hard to manage or represent through simplified models. Moreover, while it is quite clear how the single subthalamic cell electro-chemically behaves (see [3,4,30]) and different dynamical models have been proposed in correspondence (e.g., [31–33]), a lot of work is still required to understand how cells generate the macroscopic subthalamic activity, as it results from in vivo microelectrode recordings (MERs) during DBS devices implantation (see Fig. 1, Trace 1). To this aim a signal processing approach has been recently proposed in literature to characterize the intraoperative local potentials [34] and to analyze the inter-spike intervals (ISIs) distribution [35] of the MERs, but few information have been extracted, while great efforts have dealt with finite-elements models reproducing the effect of DBS at the cellular level [29]. Such results may be helpful in analysis but cannot be used for DBS control tasks, which are now emerging as fundamental topics in Biomedical Engineering. It should be considered, in fact, that the subthalamic response to DBS stimuli changes in time either physiologically or as a consequence of the electrodes corrosion or other external events, making the stimulation no more suited or effective and, consequently, the comfort for the patient and the device energy management not optimal. In that case, it would be hopeful to automatically tune the parameters of the stimulation in order to recover the best possible effect. To this aim a sufficiently fast model of STN activity can be

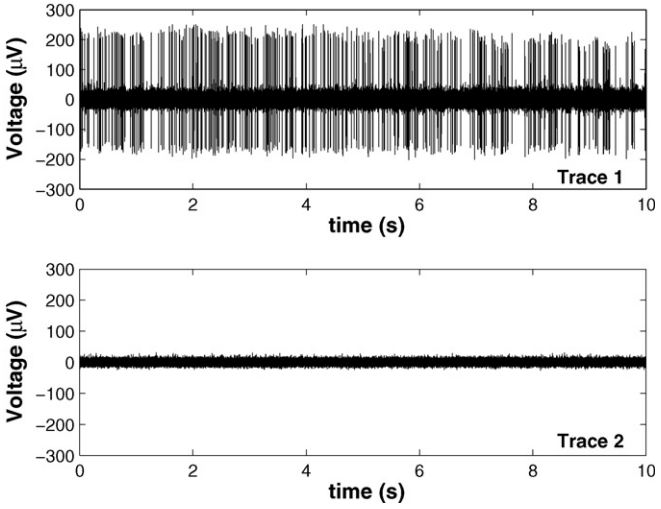

Fig. 1. Typical shape of intraoperative microelectrode traces both far and close to the STN. Trace 1 has been recorded at the planned theoretical target. Trace 2 4.0 mm before it. Data are from Patient 1, hemisphere "right", electrode A.