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System Identification of Local Field Potentials under Deep Brain Stimulation in a Healthy Primate

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Abstract

High frequency (HF) Deep Brain Stimulation (DBS) in the Sub-Thalamic Nucleus (STN) is a clinically recognized therapy for the treatment of motor disorders in Parkinson Disease (PD). The underlying mechanisms of DBS and how it impacts neighboring nuclei, however, are not yet completely understood. Electrophysiological data has been collected in PD patients and primates to better understand the impact of DBS on STN and the entire Basal Ganglia (BG) motor circuit. We use single unit recordings from Globus Pallidus, both pars interna and externa segments (GPi and GPe) in the BG, in a normal primate before and after DBS to reconstruct Local Field Potentials (LFPs) in the region. We then use system identification techniques to understand how GPe LFP activity and the DBS signal applied to STN influence GPi LFP activity. Our models suggest that when no stimulation is applied, the GPe LFPs have an inhibitory effect on GPi LFPs with a 2-3 ms delay, as is the case for single unit neuronal activity. On the other hand, when DBS is ON the models suggest that stimulation has a dominant effect on GPi LFPs which mask the inhibitory effects of GPe.

I. Introduction

DBS is a neurosurgical treatment that stimulates the brain with electrical signals, and is used to treat PD and other neurological disorders such as Essential Tremor and dystonia [1]. The DBS signal consists of a sustained train of voltage-controlled, constant-amplitude, current pulses which are delivered to a specific sub-cortical target nucleus through surgically implanted electrodes and a neural stimulator [2]. Currently, the mechanisms of action of DBS are not fully understood, although several hypotheses have been formulated. Some hypothesize that HF stimulation acts as a transient electrical inactivation or reversible lesion to block the output of dysfunctional targets [3]. Alternatively, stimulation may “jam” signal flow out of abnormally functioning structures, thereby facilitating movement [4]. Data gathered from Basal Ganglia (BG) via microelectrode recordings in both primate and

patients, provide an extraordinary source of information about PD and DBS [5] allowing us to perform both statistical and system analysis.

In this paper, we use recordings from GPi and GPe in a normal primate before and during DBS applied to STN to reconstruct and analyze LFP activity in the GPi as a function of LFP activity in the GPe with and without HF DBS. See Fig. 1 for a schematic of the pallidal-subthalamic circuit. Whereas LFPs have been proposed as a useful tool to investigate the behavior before and after stimulation [6,7,8], we reproduce them from single Spike Unit Recordings (SURs) from 20 neurons in GPi and GPe. A least squares approach is then used to define an input-output autoregressive model of BG. Finally, a pole-zeros map analysis is done in both conditions.

We found that, when DBS is OFF, the GPi LFPs receive an inhibitory action by GPe LFPs with a 2 ms delay. When DBS input is applied, the model suggests that GPi LFPs have a stronger influence from the stimulation signal which masks the GPe inhibitory effect. In order to validate this result, we show that when a constant DBS train is applied, GPi LFPs have dominant rhythm with a strong periodicity.

This study is useful in understanding how neighboring BG nuclei react to stimulus applied to STN. It's a preliminary analysis to understand how estimate a model from data to make a controlled DBS. Closed-loop DBS strategies may eliminate manual and lengthy postoperative programming of the DBS signal and may enable the DBS system to adapt to patient needs.

II. METHODS

A. Electrophysiological Data

Recordings from one healthy non human primate (macaca mulatta) are used in this study. The primate was trained using only positive reinforcement to sit quietly in a loosely restraining chair. Prior to recording sessions, it was implanted with a recording chamber. Once the animal prepared, electrical stimulation was applied in the STN via a reduced scale model of the human DBS lead and SURs were obtained from one among GPe, GPi, Striatum, motor or sensorimotor cortex. Stimulation consisted of constant current biphasic square pulses with the cathodic phase preceding the anodic phase. The pulse width was 90 μ S per phase and the amplitude was 80% of the current that produced tonic contraction. Stimulation frequencies ranging from 2 to 130 Hz; during each session, continuous recordings of neuronal activity were made 30 s before and 30 s during stimulation. In this paper, we analyze how LFPs change in GPi and GPe before and after 120 Hz pulse train stimulation. The stimulation we consider is 'Irregular', so that we have 120 impulses in one period but the distance between them is not constant; this characteristic ensures that the signal used for the identification is persistently exciting [10]. Two scenarios for each nucleus are analyzed and 30 s of simulation is performed in MATLAB/Simulink®, with ode-3 (Bagacki-Shampine) solver at 0.1 fixed step size. LFPs were obtained from SURs by the Hodgkin-Huxley model, and sampled at a frequency of 500 Hz, detrended, band-pass filtered at 200 Hz, and then analyzed.

B. Reconstruction of LFPs from SURs

We use the Hodgkin-Huxley model to reconstruct LFP activity of both GPi and GPe neurons from SURs. We need a neurophysiologic model to reconstruct continuous trend for each neuron; this procedure is necessary to obtain Local Field Potentials. Briefly, the membrane potential V_j of the j -th neuron ($j=1,...,20$) is described by the following equation:

$$C\dot{V}_j = - \left(I_j^{Na} + I_j^K + I_j^L \right) + I(t) \quad (1)$$

where C is the equivalent membrane capacity, I_{Na} , I_K and I_L the ionic currents that pass through the cell membrane and we apply for each neuron the corresponding SURs as $I(t)$. As a result, we obtain the continuous valued extracellular voltage signal for each single cell. The ionic currents are

$$\begin{aligned} I_j^{Na} &= g_{Na} m^3 h (V_j - E_{Na}) \\ I_j^K &= g_K n^4 h (V_j - E_K) \\ I_j^L &= g_L (V_j - E_L), \end{aligned} \quad (2)$$

where E_r and g_r , with $r = Na, K$ and L , are respectively the Nernst potential and the maximum conductance [9]. The three variables m , n and h are the gating variables and they evolve according to the differential equations

$$\begin{aligned} \dot{m} &= \alpha_m(V) (1 - m) - \beta_m(V) m \\ \dot{n} &= \alpha_n(V) (1 - n) - \beta_n(V) n \\ \dot{h} &= \alpha_h(V) (1 - h) - \beta_h(V) h. \end{aligned} \quad (3)$$

The various functions α and β , reported in Table I with all model parameters, are empirical functions of V . We compute LFPs through the formula

$$\phi = \sum_{j=1}^N \frac{1}{4\pi\sigma R_j} I_j^{tot} \quad (4)$$

where $I_j^{tot} = I_j^{Na} + I_j^K + I_j^L$ is the net transmembrane current, σ is the extracellular conductance ($\sigma = 0.02 \frac{S}{cm}$, [11]) and R_j is the distance of the j -th neuron from the recording electrode, fixed to $0.005 \frac{cm}{cm}$. This value is constant because the distance between the electrode and each neuron is already encapsulated in data.

C. System Identification

Parametric identification is performed on the reconstructed LFPs. For each scenario, identification is performed in order to analyze the structural changes induced by stimulation in the GPi neural network. In particular, for each scenario and stimulation input, the recorded LFPs are low-pass filtered at 200 Hz to eliminate noise, sampled at $f_s = 333$ Hz to generate fewer samples, detrended to remove the constant component, and split into two non overlapping segments, one for identification and the other one for validation (80 & 20%, respectively). Based on preliminary analysis of the autocorrelation function, ARX model structures were chosen and the model parameters were identified via the RLS algorithm on the identification segments [10]. The general structure

$$y(k) = \sum_{h=1}^p a_h y(k-h) + \sum_{s=0}^q b_s u(k-s-1) + \varepsilon(k) \quad (5)$$

of the ARX model was considered, with $y(k)$, $u(k)$ LFPs and noise input sample respectively, $u(k)$ the input considered, a_h , $h = 1, \dots, p$, and b_s , $s = 0, \dots, q$ parameters to be identified. For each combination of values for p and q such that $p + q$ ranges from 1 to 5, parameters are identified. In particular, the linear structure described in (5) is used to identify the system when no stimulation is applied. In this case, we consider GPe LFPs as input $u(k)$ and GPi LFPs as output $y(k)$. When stimulation is applied to STN, we consider

LFPs from the STN (which is the stimulation target) as a further input (see figure 1). For this scenario, the system structure is

$$y(k) = \sum_{h=1}^p a_h y(k-h) + \sum_{s=0}^q b_s u(k-s-1) + \sum_{r=0}^z c_r w(k-r-1) + \varepsilon(k) \quad (6)$$

where $w(k)$ is the second stimulation input considered; for each combination of values for p , q and r such that $p+q+r$ ranges from 1 to 5, parameters are identified.

III. RESULTS

20 neurons from both GPe and GPi were recorded before and during a STN DBS. SURs from GPe and GPi are given as inputs to the Hodgkin-Huxley network cellular model to obtain LFPs. When no stimulation is applied (DBS-OFF), GPe LFPs is the only input; in our stimulation condition (DBS-ON) STN LFPs are obtained from the Hodgkin-Huxley model, considering $I(t)$ in the eq.(1) the stimulation signal (120 Hz Irregular pulse-train), because recordings from STN are not available. For this nucleus, we hypothesize that neurons are on a square lattice with a distance 1 μm between each neuron, and the recording electrode is at the center of the network, as shown in Fig. 3. So for the STN network R_j in eq.(4) is calculate as

$$R_j = \sqrt{d_i^2 + d_q^2} \quad (7)$$

where d_i and d_q are distances respectively on rows and columns from each neuron by the electrode (see Fig. 3).

In the first scenario, we identify an ARX model for the GPi from recorded LFPs. The order of the system is chosen on the basis of recent studies on GPi [12], in which the inhibitory effect of a single neuron of GPe on GPi has 5-6 ms of delay. In Fig.4a and 4b we show the poles-zeros map respectively for DBS-OFF and DBS-ON condition.

In the first scenario, the 15-th order linear structure is chosen with ten poles $(-0.6661 \pm 0.5130i, -0.3339 \pm 0.7096i, 0.0764 \pm 0.7559i, 0.4694 \pm 0.5747i, 0.6983 \pm 0.2053i)$ and five zeros $(0.2224 \pm 0.1664i, -0.1423 \pm 0.2281i, -0.1662)$. In DBS-ON condition, a structure with ten poles $(-0.7388 \pm 0.4483i, -0.2662 \pm 0.7385i, 0.1076 \pm 0.6504i, 0.5431 \pm 0.5490i, 0.6101 \pm 0.1959i)$ and ten zeros $(-0.2433 \pm 0.2283i, 0.2357 \pm 0.2632i, 0.0175, -0.4520 \pm 0.6287i, 0.3366 \pm 0.5761i, 0.4818)$ is identified. Both systems are stable and the correlation of residuals says that the error is a white noise. One way to see how models fit data is to determine the estimate output writing the model in form of predictor:

$$\hat{y}(t|t-1) = (1 - A(z))y(t) + B(z)u(t-1) + C(z)w(t-1) \quad (8)$$

where $A(z)$, $B(z)$ and $C(z)$ are z-domain polynomials of identified systems, $u(t)$ and $w(t)$ are respectively GPe and STN input, $y(t)$ is output data and $\hat{y}(t)$ is the estimated model output. For As reported in fig. 5, both models give a good fit of data. Further, in the DBS-ON condition, parameters of DBS input (c_r) are two orders of magnitude larger than b_s parameters. This could be explained by the dominant effect of DBS which overrides activity in the region with no DBS. These results are consistent with frequency analysis: as proved in [13], the Power Spectrum Density (PSD), (Welch's method with data split in to 300 segments, 100 ms long each, and 50% overlap. Hamming window applied) is a useful tool to evaluate synchrony between cells detecting in this way LFPs periodicity. PSD reported in Fig. 6b confirms that the GPi LFPs have a prominent oscillation at the stimulation frequency, as the ARX structure parameters reveal. In the DBS-OFF condition, the LFPs

spectrum covers the frequency range (0-200 Hz) with a lower amplitude than the DBS-ON scenario, demonstrating that every neuron has a unique spiking frequency.

IV. CONCLUSION

LFPs are a useful to analyze the influence of DBS to BG nuclei. We reconstructed LFPs from SURs recorded from a healthy primate. We then applied a standard system identification technique to construct input-output models of GPi LFPs as a function of GPe LFPs and the DBS signal. Our models suggest that when no stimulation is applied, the GPe LFPs have an inhibitory effect on GPi LFPs with a 2 ms delay, as is the case for single unit neuronal activity. On the other hand, when DBS is ON the models suggest that stimulation has a dominant effect on GPi LFPs which mask the inhibitory effects of GPe. Using recordings from Striatum, cortex and GPe, an identification procedures would be used to see how those nuclei influence GPi. An identification procedure will be used to see what happens for the primate with Parkinson's disease, in same conditions of an healthy one. It would be interesting to close a DBS control loop for the PD primate to restore GPi and GPe LFPs spectrum to the values of the healthy one.

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Fig 1.
The different pathways for the effects from STN to reach GPi neurons

Fig. 2.
Identification scheme. a) DBS-OFF. b) DBS-ON

Fig. 3.
STN neurons network configuration

Fig. 4. Poles-zeros map of the identified structures. The symbol 'x' represents poles and the symbol 'o' is for zeros. a) DBS-OFF: one input is considered. b) DBS-ON: two inputs are considered.

Fig. 5.

a) Data fitting of identified ARX model – DBS-OFF. b) Data fitting of identified ARX model – DBS-ON

Fig. 6.

a) GPi LFPs in DBS-OFF and -ON conditions. b.1) Power Spectrum Density of LFPs. b.2) Zoom of b.1

TABLE I

Hodgkin-Huxley model parameters

Symbol	Value	Unit
E_{Na}	55	[mV]
E_K	-72	[mV]
E_L	-50	[mV]
g_{Na}	120	[mS/cm ²]
g_K	36	[mS/cm ²]
g_L	0.3	[mS/cm ²]
n	$\frac{(0.1 - 0.01 V)}{\exp(1 - 0.1 V) - 1}$	[V/mV]
m	$\frac{(2.5 - 0.01 V)}{[\exp(2.5 - 0.1 V) - 1]}$	[V/mV]
h	$0.07\exp(-V/20)$	[V/mV]
n	$0.125\exp(-V/80)$	[V/mV]
m	$4\exp(-V/18)$	[V/mV]
h	$\frac{1}{\exp(3 - 0.1 V) + 1}$	[V/mV]

Parameters and empirical functions of V according to Hodgkin-Huxley model; these functions have been adjusted by Hodgkin-Huxley to fit data of the giant axon of the squid [9].

TABLE II

arx systems coefficients

Parameters	DBS-OFF	DBS-ON
a_1	-4.80	-0.512
a_2	0.56	0.345
a_3	-0.54	-0.231
a_4	0.48	0.305
a_5	-0.42	-0.174
a_6	0.34	0.222
a_7	-0.26	-0.252
a_8	0.18	0.188
a_9	-0.12	-0.119
a_{10}	0.07	0.489
b_1	0.005	-0.002
b_2	-0.004	0.006
b_3	-0.006	0.008
b_4	0.004	0.013
b_5	0.0009	-0.0002
c_1	-	-0.251
c_2	-	0.325
c_3	-	-0.211
c_4	-	0.267
c_5	-	-0.129

The a_h coefficients are parameters for the output regressors, b_s and c_f the input regressors parameters, respectively for GPe and STN LFPs.