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Local field potential driven Izhikevich model predicts a subthalamic nucleus neuron activity

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***Abstract*—An interesting question has been raised recently regarding the relationship between the local field potentials (LFPs) and the single unit spiking activity. In this study, we investigate whether a linear modification of the LFPs, acquired from microelectrode recordings inside the subthalamic nucleus (STN) of Parkinson's disease patients, can provide input to an appropriately parameterized Izhikevich model to predict the spikes of an STN neuron. We show that the model is able to predict both the exact timing and the rhythm of the recorded spikes with high accuracy in 5 out of 7 intranuclear single neuron recordings. For the rest of the models, one model shows a lower accuracy in predicting the rhythm and the second one shows a lower accuracy in predicting the timing of the spikes. Overall, the results dictate that the LFPs can reliably predict the occurrence of spikes.**

I. Introduction

THE predictive relation between local field potentials (LFPs) and neuronal firing, *per se*, has been firstly examined in the primary visual cortical area (V1) using extracellular microelectrode recordings (MERs) in anesthetized monkeys [1]. A recent study in the primary somatosensory cortical area (S1) of rats using a combination of intracellular and extracellular recordings reveals an analogous interconnection between LFPs and the spikes [2]. In addition to proving that spikes can be predicted by the area's LFP, research studies are also suggesting the opposite. A linear relationship is revealed that connects the spikes to the LFPs in the V1 of anesthetized monkeys [3]. With the use of recordings from the same electrode and nearby electrodes, it is proven that some of the local properties of the LFPs can be predicted by the spiking activity of a few or even a single neuron [3]. Until now, spikes have been inferred from LFPs in recordings acquired from the cortex of animals, mainly due to the accessibility of the area and the easiness of the surgical procedure. In addition, the highly organized topography of the cortex constitutes the LFPs to be regarded as the best indicators of integrative activity in a neural area.

The relationship between LFP and spiking signals recorded in areas where neurons are positioned in a less ordered manner is more controversial. Almost no relation was found between the LFPs acquired from the dorsolateral area of the geniculate nucleus of monkeys and the spiking activity inside that nucleus [1]. Contrarily to this finding, we provided evidence that the LFPs recorded inside the subthalamic nucleus (STN) of Parkinson's disease (PD) patients undergoing deep brain stimulation (DBS) surgery, reflect synchronized aggregate activity. A nonlinear, Hammerstein-Wiener model was found to predict the spiking activity of the neural area near the microelectrode ([4]-[6]). In addition, a mathematical model that is physiologically inspired by the temporal summation of action potentials (APs) observed in neurons, was also found to predict the spikes and the spiking rhythm in the same recordings [7].

This paper describes a modification of an Izhikevich model to receive the LFPs as its input. The model is then used, for the first time, to predict the spiking activity of single neuron recordings, acquired from the motor area of the STN of PD patients.

II. Processing and Analysis of Raw Signals

A. Data Handling

Raw data acquisition, processing and analysis are analytically described elsewhere ([4]-[7]). Briefly, electrophysiological data were recorded from three awake, un-medicated PD patients, during DBS operation. Recordings were acquired during spontaneous STN activity, prior to the implantation of the DBS lead using an array of five electrodes ("Ben Gun" formation). Only single neuron signals acquired around the final stimulation point (+/- 1mm) inside the STN were included in this study. Each recording, lasting 10 s, was digitized at 24 kHz and, after appropriate anti-alias filtering, downsampled to 12 kHz, for computational convenience. In total, 7 single neuron recordings were used in this study. Recordings were named as S*X*-D*YZ*'*sign*''*mm*', where *X* was the sequential number of each patient (*X*={1,2,3} in this study), *Y* was the identifier of the hemisphere (*Y*={7,8} for left and right, respectively), *Z* was the anatomical position of the recording electrode (*Z*={1,2,3,4,5} for central, medial, lateral, posterior, and anterior electrodes, respectively), '*sign*' was a string named as {'plus','min'} for recording locations below or above the theoretical target, respectively and '*mm*' was a number denoting the distance, in mm, between the recording location and the theoretical target. Models are named after the corresponding recordings.

Off-line data processing and analysis were conducted by custom-made MATLab (The MathWorks, Natick, MA) code. An FIR equiripple low-pass (LP) filter of order of

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2100 samples, with a pass-band of [0 100] Hz and a stop-band of [0.15 12] kHz and p-p rippling in passband equal to 2 x 10^{-6} db was used to acquire the LFP signal. To acquire the spike signal, we used an FIR generalized equiripple band-pass (BP) filter with stop-bands of [0 450] Hz and [2.55 6] kHz, a pass-band of [0.5 2.5] kHz, of the same order and p-p rippling equal to 2 x 10^{-6} db. Signals were visually inspected, and only epochs free from artifacts following the typical waveform of an STN glutamatergic projection neuron activity (low noise and high amplitude spikes) were used for the analysis.

The brief duration of an AP (about 1 ms) was ignored. Hence, an AP sequence was characterized simply by a binary signal in which the ones represent the times when spikes occurred.

B. The Izhikevich model neuron

The Izhikevich model neuron was developed as an efficient, powerful alternative to the integrate and fire model. The model uses a variable representing voltage potential and a variable representing membrane which accounts for the activation of K^+ ionic currents and inactivation of Na^+ ionic currents. It is a spiking neuron and as such, a spike occurs when the voltage passes a threshold value. Then the voltage and recovery variable are reset. The differential equations that describe the model are:

$$\frac{dv}{dt} = 0.04v^2 + 5v + 140 - u + I \quad (1)$$

$$\frac{du}{dt} = a(bv - u) \quad (2)$$

with the auxiliary after-spike resetting

$$\text{If } v \geq +30 \text{ mV, then } v \leftarrow c \text{ and } u \leftarrow u + d. \quad (3)$$

In the above equations, $a, b, c,$ and d are abstract parameters of the model discussed in [8], v is the membrane voltage potential of the neuron, u represents a membrane recovery variable providing negative feedback to v. After the spike reaches its apex (+30 mV), the membrane voltage and the recovery variable are reset according to eq. (3). In the model, synaptic currents or injected dc-currents are delivered via the variable *I*. Firing patterns of all known types of neurons are simulated with an appropriate choice of the model's parameters $a, b, c,$ and d, as presented in [8].

The main neurophysiological features of STN neurons are (i) a spontaneous spiking activity between 3 and 20 Hz; (ii) increased spiking activity in response to an excitatory input current; and (iii) a post-inhibitory rebound burst followed by a quiescence period, caused by the inactivation of the low-threshold Ca^{2+} current [11]. The Izhikevich model can exhibit a discharge mode that matches an STN glutamatergic projection neuron if its parameter values are set as follows: $a = 0.005,\ b = 0.265, c = -65, d = 1.5$ ([9], [10]).

C. Linear transformation of the LFPs to current

The Poisson's equation for scalar potential, $\Phi(\boldsymbol{r}, t)$, at a vector location, $\boldsymbol{r}$, in time, *t,* in a tissue mass is given by:

$$\nabla[\varepsilon(\boldsymbol{r})\nabla\Phi(\boldsymbol{r}, t)] = -\rho(\boldsymbol{r}, t) \quad (4)$$

where $\rho(\boldsymbol{r}, t)$ is the free (conduction) charge density and $\varepsilon(\boldsymbol{r})$ is the permittivity of the dielectric medium (tissue). If we assume that the source region volume is much smaller than the distance to the microelectrode and that the extracellular fluid is an infinite, homogeneous, isotropic, and purely resistive volume conductor, the potential external to a source region becomes

$$\Phi(\boldsymbol{r}, t) = \frac{1}{4\pi\sigma}\frac{I(t)}{|\boldsymbol{r}|} \quad (5)$$

where $I(t)$ is the monopolar current source, $\boldsymbol{r}$ is the distance of the current source to the microelectrode, and σ is the macroscopic electrical conductivity of the tissue. Equation (5) may be derived with a simple application of Ohm's law if we assume an imaginary surface of radius r surrounding the point source. Since total current is conserved, the current density at this surface must be (current)/(surface area), all in the radial direction. By substituting $\Phi(\boldsymbol{r}, t)$ with the recorded LFP, the current, *I*, injected into the Izhikevich model is described by the linear transformation

$$I = \kappa \cdot LFP \quad (6)$$

where $\kappa = 4\pi\sigma|\boldsymbol{r}|$. In other words, we assume that the sum of the currents in the dendritic sites that results to the recorded LFP is directly proportional to the LFP.

D. Validation methods

In order to verify that the model accurately describes the structure observed in the raw data, we need to compare quantitatively the agreement between the spike train predicted from the LFPs and the spike train detected from the recordings. The first approach is to plot the empirical cumulative distribution function (CDF) of the detected spiking times against the CDF of the predicted spiking times. If the model accurately describes the observed spiking data, then the plot should follow a 45° line. If the model fails to account for some aspect of the spiking behavior, then that lack of fit will be reflected in the plot as a significant deviation from the 45° line.

In addition, we quantify the similarity between the recorded and predicted spike trains using a smoothing process that transforms the binary signals into continuous ones. The two binary spike trains that represent the timing of the spikes, are convolved with a Gaussian function with standard deviation $\hat{\sigma}$, which essentially determines the temporal resolution used in the comparison. A large value means low temporal resolution and vice versa. In this study, $\hat{\sigma}$ varied between 0.5 ms and 6.7 ms. Cross-correlation or correlation coefficient, *r*, can then be calculated as a function of $\hat{\sigma}$.

In order to validate the model in terms of rhythm prediction, we calculated the number of spikes present in adjacent, non-overlapping bins. The bin width, for this study, was kept equal to 5 ms. Then, the mean squared error (MSE) between the predicted and recorded rhythm was estimated.

III. Results

The spiking activity of a recorded STN neuron predicted by the Izhikevich model is shown in Fig. 1. Data (S3-

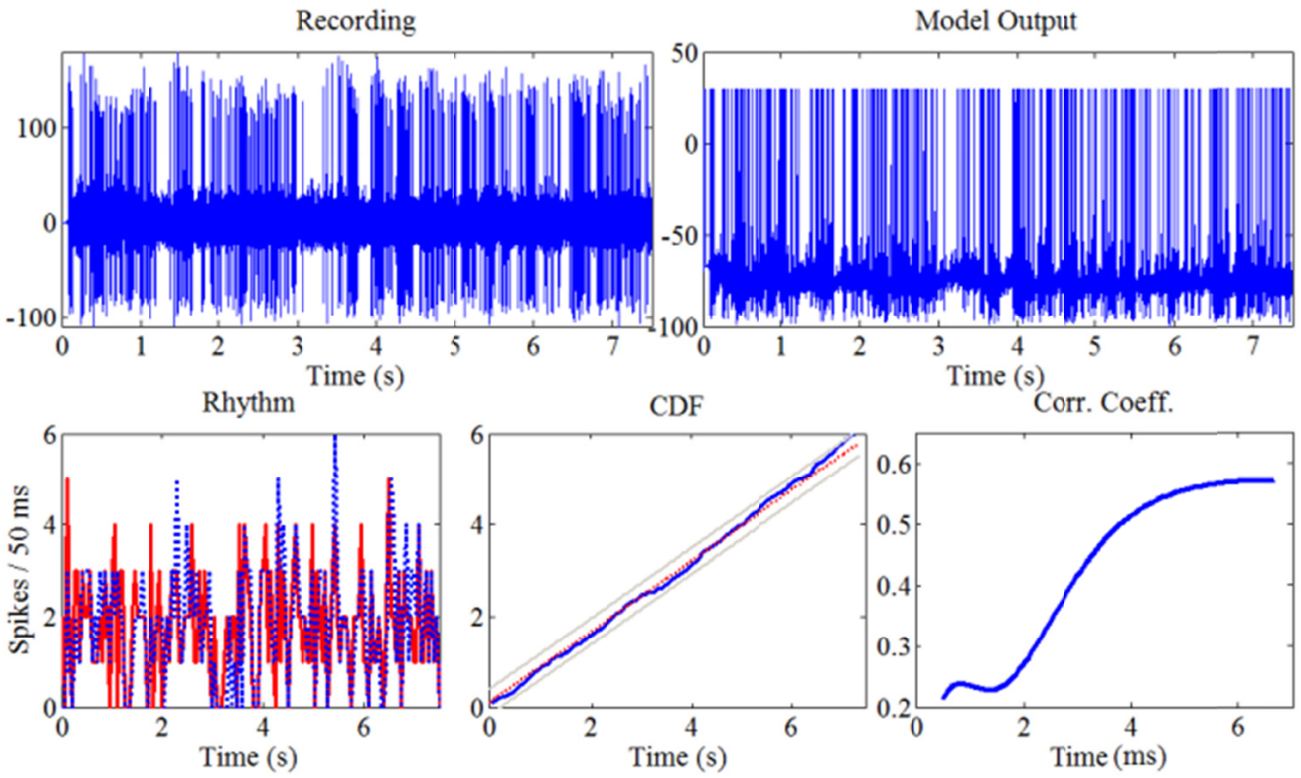

Fig. 1. Prediction of the single neuron spiking activity using the local field potentials as input to an Izhikevich model. Recording S3-D75min15. Upper panel: Raw recording (left) and model's output (right). Bottom panel: (Left) The prediction of the spiking rhythm. The recorded rhythm, calculated every 50 ms, is shown in continuous red line. The prediction is shown in dotted blue line. (Center) The calculated CDF, shown in blue. The 45° line is shown in dotted red line. Grey continuous lines define the 95% confidence interval. (Right) The curve of the correlation coefficient for various values of $\hat{\sigma}$.

D75min15) were received from Subject 3. For the Izhikevich neuron model, the parameters were set as defined in Section II.B and κ was chosen equal to 3.8 as it resulted in minimum rhythm MSE. The model was able to simulate the presence and the absence of individual spikes and spike bursts with high accuracy. This was reflected into the estimated MSE of the rhythmic activity (MSE = 1.0). In addition, the estimated CDF curve was maintained inside the 95% confidence interval and approach the 5% borders only in the last 0.5 s. The correlation coefficient was estimated as 0.5727 (for $\hat{\sigma} = 6.6$ ms).

The resulted rhythm MSE (for 50 ms bin width) and the corresponding maximum correlation coefficient are shown in Fig. 2. The model can predict the rhythm and the timing of the single neuron spiking activity if both of these measures result in a point inside the right bottom corner of the graph. A model was unable to locate a spiking burst, although its correlation coefficient measure was large enough; that resulted to an increment of the rhythm MSE (S1-D83min10). On the contrary, the rhythm prediction of a model could be well above average but its correlation coefficient was at the same time very low (S2-D84min05). This means that the model cannot detect well the timing of the spikes; rather, its spiking rhythm follows accurately the recorded rhythm. The rest of the models detected the presence and the rhythm of the spikes very accurately. Often, equivalent or even more accurate results could be produced even if other parameter values were set. By introducing into the model other parameter values, than the ones defined in Section II.B, a more general neuron type is modeled. The estimation of the rhythm MSE for recording S3-D75min15 hypothesizing various types of Izhikevich neuron models can be seen in Table I. The parameter values of the Izhikevich model for each neuron type shown in Table I, are defined in [8].

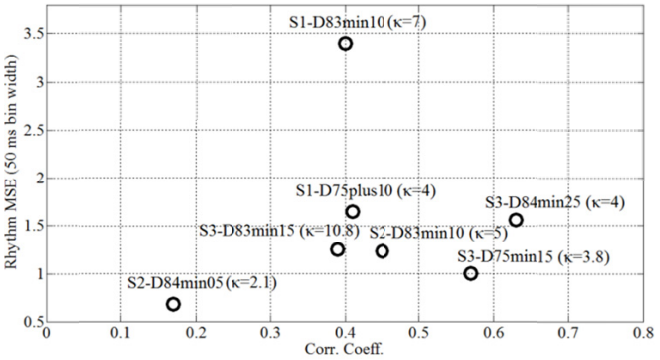

Fig. 2. Validation results for 7 single neuron intranuclear recordings. Recordings from 5 nuclei (3 Subjects) are used. The value of parameter κ, found empirically to give optimal results, is included in the parenthesis, next to each model's name.

TABLE I
MSE AS A FUNCTION OF K FOR DIFFERENT TYPES OF SPIKING NEURON MODELS (RECORDING S3-D75MIN15)

Type of spiking neuron	Rhythm MSE	κ
tonic spiking	0.91	6
phasic spiking	1.05	5
tonic bursting	1.26	3
mixed mode	0.88	5
spike frequency adaptation	1.08	9
Class 1 excitable	0.99	10
Class 2 excitable	0.96	1
spike latency	0.91	6
subthreshold oscillations	0.88	1
resonator	0.80	1
integrator	0.98	10
rebound spike	1.13	3
threshold variability	1.13	2

IV. DISCUSSION

It is well established that information is coded in the population activity of neurons, especially in sensory, motor and other higher cortical brain regions. Any neuron responds primarily to a combination of chemical and electrical signals, some of which are believed to influence (if not dominate) the LFP. Here we introduced a modification of an Izhikevich model that predicts the output temporal pattern of AP events as a function of an input electrophysiological pattern of LFPs for an STN neuron.

However, the strengths of modeling are tempered by the necessary simplifications made in any reasonable model This approach is only valid for single neuron recordings. What is more, finding a single neuron recording acquired during the implantation procedure of a deep brain stimulator is a challenging task to achieve. Most of the recordings inside the STN are either noisy or the received spikes come from two or more neurons.

Nonetheless, the model can expand to include more neurons randomly interconnected. This will allow research on the dynamics of an STN neuron network. In the future, such a model can become a test bed for the various proposed effects of DBS. This will enable the design of time-adaptive DBS stimulation that can be tailored to the needs of individual PD patients. Of course, to reach this goal and test the DBS effects on the firing activity, the model must be modified accordingly.

V. CONCLUSION

In this paper, we showed that the LFPs, recorded from an area inside the STN of PD patients, can be linearly transformed and then inserted into an Izhikevich model of an STN neuron to predict the timing and rhythm of a single neuron's spikes. We tested the proposed modeling approach to 7 single neuron recordings acquired from 5 nuclei (3 Subjects). Six out of the 7 models were able to predict very accurately the spiking rhythm calculated in 50 ms bins or the spike timing. Five out of 7 models predicted both the rhythm and the timing of the spikes with high accuracy. Our proposed model allows for high level functional views that are still consistent with low level ideas of operation. Our approach can be used as the test bed for current and future theories on the STN and even shed some light on the effect that the DBS has on the STN function.

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