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Stochastic Modeling of the Neuronal Activity in the Thalamus of Essential Tremor patient.

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Abstract— **Several stochastic models, with various degrees of complexity, have been proposed to model the neuronal activity from different parts of the human brain. In this paper, we use an Ornstein-Uhlenbeck Process (OUP) to model the spike activity recorded from the thalamus of a patient suffering from Essential Tremor at the time of implantation of the electrodes for Deep Brain Stimulation. From the recorded data, which contains information about the spike times of a single neuron, we identify the model parameters of the OUP. We then use these parameters to numerically simulate the inter-spike interval distribution. We show that the OUP provides excellent fits to the data recorded both without any external stimulation as well as with stimulation. We finally compare the fits with other stochastic models commonly used and we show the superiority of the OUP model in general.**

I. INTRODUCTION

Essential Tremor (ET) is a progressive neurological disorder characterized by a rhythmic tremor (4-12 Hz) that is present only when the affected muscle is exerting effort and can be in the arms, head (neck), jaw and voice as well as other body regions [1]. Essential tremor is the most common movement disorder. An estimated 5 million Americans suffer from the disease. The pathophysiology of ET is not known. However, clinical, physiological and imaging studies point to an involvement of the cerebellum and/or cerebello-thalamocortical circuits [2]. There is no cure for ET, but there are treatments that give relief and improve quality of life. These include drug therapies and surgical procedures. If the tremor is severely disabling and drugs do not relieve the symptoms, surgery may be an option. Two types of surgery used to treat ET are Deep Brain Stimulation (DBS) [3] and thalamotomy [4]. In thalamotomy, a lesion is placed on a small part of the thalamus and is irreversible. In DBS, an electric probe is placed in the Ventral Intermediate Nucleus (VIN) of the thalamus which is connected to a pacemaker placed near the collarbone. It stimulates the thalamus with pulses of electricity, which are thought to block the brain activity that causes tremor, and is reversible. However, the mechanisms of DBS and its beneficial effects on ET patients are not well understood. This implies that the design of current DBS is somehow heuristic. In order to design the next generation of DBS, an accurate–yet simple–predictive model of the neuronal activity of the brain and of its response to electrical stimulation is necessary. This is the motivation behind the work presented in this paper.

During surgery, for locating the precise target for either DBS or lesioning, the neurosurgeon inserts a micro-electrode and records neuronal activity at different depths from the target. Such recorded neuronal activity, is the potential difference across the membrane of a neuron or of a group of neurons. This variable of interest is stochastically modulated by a wide range of inputs that are both excitatory and inhibitory [5]. Accounting for each and every force that governs its dynamics is highly complicated and involves the specification of many parameters. A stochastic model can serve as a more efficient alternative for modeling such a variable. Such a model should capture in the simplest possible way the physiological phenomenon responsible for the generation of an action potential. The number of model parameters should be limited so that the parameter identification algorithm is neither too cumbersome nor too time consuming.

One of the earliest stochastic models for neuronal spiking used in neurophysiology is the Poisson Process (PP) [6], which involves a single parameter that represents the average inter-spike interval. Unfortunately, the PP does not capture the mechanism of a spike generation [7]. In [7] the authors proposed to use the Wiener Process (WP) to model the neuronal spiking. One main advantage of the WP is that the inter-spike interval distribution has a simple closed form expression. However, the WP does not predict the exponential decay in the membrane potential in between two subsequent input impulses to the neuron that is observed experimentally. An even more general stochastic process model for neural spiking activity appeared in [8], which however requires the estimation of 28 parameters. Another approach in [9] models the neurons as coupled phase oscillators driven by random forces. Although well posed, the model suffers from the drawback of a difficult parameter extraction problem since the neuronal cluster phase is difficult to estimate in practice from the recorded data.

In this paper we explore the possibility of using the OUP [10] for modeling thalamic spiking activity recorded during DBS surgery in ET patients. The OUP was first proposed as a model for the neuronal potential dynamics in [11] and is now widely accepted [12] because: a) it accounts for the spike generation mechanism, b) it predicts the exponential decay in the membrane potential in between two subsequent input impulses to the neuron, c) it only involves the specification of two parameters along with a third free parameter, and d) the two model parameters can be easily identified from the recorded data. The OUP thus strikes a balance between an oversimplified model, such as the PP in [6], and a complicated model, such as the ones in [8] and in [9]. However, it was reported in [13] that the OUP might not model satisfactorily every type of neuronal activity in different parts of the brain. We show here that

the OUP can indeed be a simple yet biologically plausible model of the neuronal activity recorded from the thalamus of ET patients and can thus be potentially used to predict the brain neuronal activity in response to electrical stimulations.

The paper is organized as follows: Section II introduces the OUP and relates the neuronal spiking activity to the first passage time problem; Section III discusses the data recordings, the parameter identification methods, and how the OUP compares to existing models; Section IV presents the results of data analysis; finally, Section V concludes the paper and points out interesting directions of future work.

II. The Ornstein-Uhlenbeck Process and the First Passage Time Problem

The neuronal activity as recorded from the VIN consists of neuronal spikes (action potentials) produced by a single cell with superimposed background aggregate activity of neurons in the vicinity and measurement noise. The spike times provide information about the inter-spike interval distribution of the neuron while the background activity is the membrane potential of a group of neurons surrounding the electrode's measuring tip, which is essentially the time varying aggregate input to the neuron. Here we use the OUP to model the membrane potential across a single neuron. When the membrane potential exceeds a certain threshold, the neuron fires. Thus, the spike times, or equivalently the inter-spike intervals, are related to the level crossing problem of the membrane potential process.

The OUP is a stochastic process X_t governed by the following Langevin equation:

$$dX_t = \theta(\mu - X_t)dt + \sigma dW_t, \tag{1}$$

where $\theta > 0$, μ and $\sigma > 0$ are the model parameters, and W_t denotes the standard Wiener process, i.e., dW_t is a zero-mean white Gaussian process with variance dt. The parameter μ represents the equilibrium or mean value; σ represents the diffusion coefficient or the degree of volatility around the mean; θ represents the rate by which the volatility dissipates and the variable reverts towards the mean. The probability density function of X_t in (1), indicated as $f_{OU}(x,t)$ and defined for $t \geq 0$, is given by:

$$f_{OU}(x,t) = \sqrt{\frac{\theta}{[1-\mathrm{e}^{-2\theta t}]\,\pi\sigma^2}}\exp\left\{\frac{-[(x-\mu)-(x_0-\mu)\mathrm{e}^{-\theta t}]^2}{[1-\mathrm{e}^{-2\theta t}]\,\sigma^2/\theta}\right\}$$

This time dependent distribution, in the limit for $t \to \infty$, is a Gaussian density with mean μ and variance $\sigma^2/(2\theta)$.

The OUP in (1) can be assumed to be responsible for the spike generation in a single neuron model, as is described in [12]. Namely, a neuron releases a spike whenever its membrane potential X_t exceeds a threshold y_0, which is assumed to be constant over time. After spiking, the membrane potential is reset to $x_0 < y_0$. Thus the spiking activity is related to the so called *First Passage Time (FPT) problem*. The FPT is a random variable T defined as the time t after time t_0, at which X_t first hits y_0 starting from some initial value $X_{t_0} = x_0$ smaller than y_0, i.e., $T = \inf\{t \geq t_0 : X_{t_0} < y_0 \leq X_t\}$. The FPT distribution function is indicated as $f_T(t;x_0,y_0)$. Although a closed form expression for $f_T(t;x_0,y_0)$ is not available, its moment generating function (i.e., the Laplace transform of $f_T(t;x_0,y_0)$ with respect to t) admits a closed form [14]. From the moment generating function it is thus possible to evaluate all the moments of T.

Thus, in the context of neuronal activity the FPT is the time in between two consecutive spikes, or inter spike interval (ISI). The density of the FPT, or of the ISI, thus depends on five parameters: μ, σ, θ, y_0 and x_0. The first two parameters (the drift μ and the diffusion σ) are related to the neuronal membrane potential dynamics and are to be extracted from recorded data. The last three parameters (the membrane time constant $1/\theta$, the firing threshold y_0 and the membrane resting potential x_0) are intrinsic parameters of the neuron and are set to biologically plausible values. In the following, we discuss how μ and σ can be identified.

III. Methods

For data analysis we use data obtained at the University of Illinois at Chicago (UIC). This recording was performed during surgical implantation of DBS electrode into VIN of thalamus of an adult (awake) ET patient at the UIC Medical Center as an IRB-approved research project. The surgery was performed on both sides of the patient's brain in one session. Recording of neuronal electrical activity was performed before, during and immediately after applying test electrical stimulation to the VIN. We used standard microrecording electrodes (Alpha-Omega Engineering, Nazareth Illit, Israel) that allow delivering stimulation through the tip of the microelectrode (microstimulation) or through the tip of the integrated guiding cannula (macrostimulation) located 3 mm above the microelectrode tip [15]. The procedure of stimulation/recording was performed on both sides, first on the left, and then on the right side. During the surgical mapping process, two identical microelectrodes were inserted at a distance of 2mm from each other (referred as Electrodes 1 and 2). Both of them were used for simultaneous recording while the macrostimulation was delivered from Electrode 1, with effective distance between recording and stimulation sites of 3mm and 3.6mm for Electrodes 1 and 2, respectively.

Theoretically, a macroelectrode records the low frequency local field potential while a microelectrode records the high frequency firing activity from a single neuron. However, when either of them is used for stimulating, the same contact cannot record; the recording from the other contact of same electrode is saturated due to the high stimulus voltage. Hence, when stimulating, the other neighboring electrode is used for recording. In this case, the microelectrodes served to continuously record the neuronal activity of the thalamus before, during and after stimulation. The recording was made using NeuroNav device (Alpha-Omega Engineering), at a sampling rate of 24kHz. Stimulation was applied at two pulse rates, namely, at 130Hz and at 160Hz and with a pulse width of 60 microseconds. Pulse trains of durations of 15, 30 and 40sec were applied at varying intervals between trains on both the left and right VIN.

In the absence of an external stimulus, the timestamps of spike occurrences were detected by setting a threshold that was determined by the neurosurgeon by visual inspection of the recorded data. When a train of high frequency pulses was applied, spikes could be extracted from the voltage recorded by the electrode adjacent to the stimulating electrode. The recording still had stimulation artifacts. By subtracting the artifacts, the spikes in between stimulus pulses could be recovered. In the latter case, only the time interval when there was no stimulus artifact was considered since it is not possible to determine if there were spikes embedded in the artifacts. We obtain the ISI required for the parameter extraction from the detected spike timings as the difference between the consecutive spike timings.

The parameters of the model $\mu_{ou} = \mu \times \theta$ (the drift coefficient) and σ (the diffusion coefficient) can be estimated for fixed values of $\tau = 1/\theta$, x_0 and y_0 following the method proposed in [16]. We assume that $x_0 = 0$ (the resting membrane potential), $y_0 = 15$mV (the firing threshold). The physiological value of θ can be $1-20$ms [5] and can serve as a guide to choose τ. However, it is a free parameter in the model and uniquely determines μ and σ to match the first two moments as calculated from the recorded data. Once the parameters are identified, we use them to calculate the cumulative distribution function (CDF) from simulated ISIs following (1) and compare it with the one estimated from the recorded data.

Finally, to compare the OUP model with existing stochastic models, we also fit the measured ISI distribution to the exponential distribution arising from a Poisson process and to an Inverse Gaussian (IG) distribution arising from a random walk model [7]. The Poisson model of neuronal membrane potential would generate ISIs distributed according to the following exponential distribution

$$f_{PP}(x;\mu_{ex}) = \frac{1}{\mu_{ex}} \mathrm{e}^{-\frac{x}{\mu_{ex}}}, \quad x \geq 0, \tag{2}$$

where μ_{ex} is the mean value and can be estimated from the sample ISIs as the maximum likelihood (ML) estimate. The random walk model, which is essentially a (Gaussian) Winer process, generates ISIs that are distributed according to the following IG distribution [7]

$$f_{IG}(x;\mu_{ig},\lambda) = \sqrt{\frac{\lambda}{2\pi x^3}} \exp\left\{\frac{-\lambda(x-\mu_{ig})^2}{2(\mu_{ig})^2 x}\right\}, \quad x \geq 0, \tag{3}$$

where μ_{ig} is the mean and $(\mu_{ig})^3/\lambda$ is the variance, whose ML estimates can be obtained as in [17]. The results of our comparison are reported next.

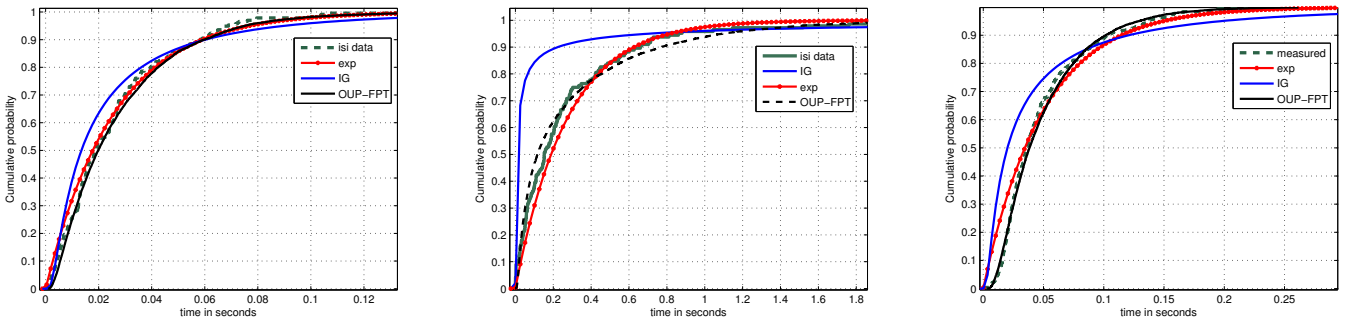
IV. Results

Here we present the analysis on the data recorded from the thalamus of an ET patient: (a) before, during and after 30s train of stimulus on the left side, and (b) during and after 40s train of stimulus on the right side. In both cases the stimulation was at 160Hz and was applied through the outer macroelectrode 1 while the data was recorded by microelectrode 2. For each set of data, ISIs were calculated from the spike times and the CDF was estimated (with the Matlab function `ecdf`). From the estimated CDF, the mean and standard deviation were computed. The OUP parameters μ_{ou}, σ and τ were estimated as in [16] by matching the first two moments of the recorded ISI with the first two moments of the FPT. These parameters are tabulated in Table I together with the mean and standard deviation of the recorded data. The parameters of the IG (μ_{ig}, λ) and of the exponential (μ_{ex}) distribution were ML estimated as in [17]. In order to establish which distribution best fit the recorded data, a Kolmogorov-Smirnoff (KS) test was performed between the measured ISI samples and the simulated CDF of the three distributions. This tested the null-hypothesis that the recorded data are from the simulated distribution against the hypothesis that the samples are not from the simulated distribution. The p-values obtained from the test corresponding to each distribution are tabulated in Table II. A higher p-value indicates a greater probability of the simulated samples and the recorded data having the same underlying distribution. Hence the p-value is an indicative of the goodness of fit. Fig. 1 shows the simulated CDF for the three distributions fitted to ISIs measured from the right VIN (similar results are obtained for the left side but we do not report it here for sake of space).

From Table II we can see that the OUP-FPT has either comparable or much higher p-values than the other two distributions for ISI samples measured from both sides and under all conditions. The exponential performs relatively better for samples during stimulus while the IG has a good performance for samples without stimulus on the left side. The IG however has very poor performance for the right side with very low p-values. The better performance of the OUP can be explained as follows: the free parameter τ has the power of tuning the OUP parameters to obtain a good fit. τ also offers a good indication of the presence and absence of stimulus, or the transition from ON to OFF stimulation states (notice the wide difference in the values of τ for data with and without stimulus in Table I). The exponential and the IG have comparable performances for selected cases but in general cannot produce good fits for all ranges of the recorded data. Fig. 1 corroborates these facts and we can see a direct correlation between a high p-value and a good visual fit. We notice that the IG has an unsatisfactory performance, the exponential has a good fit for the data before and during stimulus while the OUP-FPT has a good fit for all three cases. Thus, from the numerical p-values and the visual fit, we conclude that the OUP can serve as a good model for neuronal activity in the thalamus of ET patients in general with and without stimulus.

V. Conclusion and Future Work

In this paper, we showed that the OUP can serve as a simple yet accurate model for spike generation in the VIN neurons of ET patients, which was never shown before. We tested the OUP model on patient data sets and we showed excellent agreement between the recorded data and the simulated one according to the OUP model. We also showed



(a) Before stimulation. (b) During stimulation. (c) After stimulation.

Fig. 1. Comparison between IG, exponential and OUP-FPT CDFs fitted to the ISIs from the right side. (a): Before applying any stimulus. (b): During a train of 160 Hz pulses for 40s. (c): Immediately after the stimulus over a period of 25s.

TABLE I

OUP PARAMETERS.

Data type	μ_{ou} [mV/s]	σ [mVs$^{-1/2}$]	τ [sec]	mean±std
Left VIN				
Before stim.	656.33	82.92	0.0167	0.0336±0.0272
During stim.	201.77	92.54	0.1218	0.0609±0.0726
After stim.	860.64	62.13	0.0241	0.0241±0.015
Right VIN				
Before stim.	754.69	125.47	0.0085	0.0256±0.0228
During stim.	2.57	65.98	0.2720	0.2720±0.3718
After stim.	360.59	63.90	0.0500	0.0498±0.0415

TABLE II

P-VALUES FROM THE KS TEST FOR DIFFERENT DISTRIBUTIONS.

Data type	Exponential	IG	OUP-FPT
Left VIN			
Before stim.	0.42×10^{-16}	0.20	0.23
During stim.	0.05	0.53×10^{-41}	0.04
After stim.	0.57×10^{-15}	0.74×10^{-45}	0.835
Right VIN			
Before stim.	0.034	6.87×10^{-7}	0.568
During stim.	0.087	0.373×10^{-41}	0.130
After stim.	0.112×10^{-15}	0.73×10^{-45}	0.170

the superiority of the OUP compared to existing models. We expect the OUP model to fit different patients, each with its particular parameters to be identified as described in this paper. The used parameter identification method is not optimized according to any criterion and is simply a matching of the first two moments. The OUP performs better or as good as other simple models with optimized parameters. We are currently working on determining a biological-inspired optimization criterion and deriving identification algorithms for the OUP model. Another direction of future work is to correlate the OUP parameter changes with the state of the patient's tremor. This will enable the design of time-adaptive DBS stimulation (switching stimulation on and off) tailored to the needs of each individual patient. We envisage that the variation of one or more OUP parameters extracted from the measured signal can be used as an indicator of the return of tremor in the stimulation off state.

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