On Modeling the Neuronal Activity in Movement Disorder Patients by using the Ornstein Uhlenbeck Process

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***Abstract*— Mathematical models of the neuronal activity in the affected brain regions of Essential Tremor (ET) and Parkinson's Disease (PD) patients could shed light into the underlying pathophysiology of these diseases, which in turn could help develop personalized treatments including adaptive Deep Brain Stimulation (DBS). In this paper, we use an Ornstein Uhlenbeck Process (OUP) to model the neuronal spiking activity recorded from the brain of ET and PD patients during DBS stereotactic surgery. The parameters of the OUP are estimated based on Inter Spike Interval (ISI) measurements, i.e., the time interval between two consecutive neuronal firings, by means of the Fortet Integral Equation (FIE). The OUP model parameters identified with the FIE method (OUP-FIE) are then used to simulate the ISI distribution resulting from the OUP. Other widely used neuronal activity models, such as the Poisson Process (PP), the Brownian Motion (BM), and the OUP whose parameters are extracted by matching the first two moments of the ISI (OUP-MOM), are also considered. To quantify how close the simulated ISI distribution is to the measured ISI distribution, the Integral Square Error (ISE) criterion is adopted. Amongst all considered stochastic processes, the ISI distribution generated by the OUP-FIE method is shown to produce the least ISE. Finally, a directional Wilcoxon signed rank test is used to show statistically significant reduction in the ISE value obtained from the OUP-FIE compared to the other stochastic processes.**

***Index Terms*— Neuronal Activity Modeling, Inter-Spike Interval, Ornstein-Uhlenbeck Process, Fortet Integral Equation, Poisson Process, Inverse Gaussian Distribution.**

I. Introduction

Essential Tremor (ET) and Parkinson's Disease (PD) are progressive, chronic neurological disorders of the central nervous system that impair motor skills. The exact underlying pathophysiology of these diseases is unknown. The treatment of these diseases consists of either medication therapies or surgical procedures such as Deep Brain Stimulation (DBS). DBS involves high frequency electrical stimulation through implanted electrodes to the ventral intermediate nucleus (VIM) of the thalamus in case of ET/PD, or to the internal segment of the Globus Pallidus (GPi) or Subthalamic Nucleus (STN) in case of PD. DBS helps to control some of the most debilitating symptoms of these diseases but its underlying mechanisms are still unclear. In our group, we aim to design the next generation of DBS systems in which the stimulation is continuously adapted to the patients' condition [1]. One step towards this ambitious goal is to develop a simple yet accurate mathematical model of the neuronal activity in the part of the brain where DBS is applied [2]. Mathematical modeling of the spiking activity in ET and PD patients could also be useful in understanding the pathophysiology of these diseases as well as the underlying mechanism of DBS.

In this work we use the Ornstein Uhlenbeck Process (OUP) to model the neuronal spiking activity recorded during DBS stereotactic surgery from the VIM and STN of ET and PD patients, respectively. The OUP is a modified Wiener Process based on leaky integration assumption [3] that can model the randomness of the Inter Spike Interval (ISI), the time interval between two consecutive neuronal firings. It captures the spike generation mechanism, which is ignored in a simplistic model like the Poisson Process (PP), and also accounts for the change in membrane potential between two firing events, unlike in Brownian Motion (BM) models [4]. The OUP requires only two dynamic parameters, together with three intrinsic parameters of the neuron, which reduces the computational complexity compared to other models (please refer to [2] and references therein).

The OUP has been successfully applied to model the neuronal activity in animal and human models [5]. In [2], [6], the OUP was used to model the spiking activity recorded from VIM and STN of an ET and a PD patient, respectively. Although, the study considered very limited patients data, to the best of our knowledge, it was the first to show that OUP can be used to model the spiking activity measured in-vivo from PD and ET human subjects. In [2], [6], the measured ISI was used to estimate the first two moments of the First Passage Time (FPT) distribution, i.e., the distribution of the first time the neuron membrane potential exceeds a certain threshold starting from some initial resting state at which point the neuron generates an action potentials or spike [7]. The OUP with the parameters extracted with this "moment method" method (indicated in the rest of the paper as OUP-MOM) was simulated and the resulting ISI distribution estimated. To quantify whether the simulated ISI distribution well approximates the measured ISI distribution, an Integral Square Error (ISE) criterion was adopted. The resulting ISI distribution from the OUP-MOM was shown to produce the smallest ISE compared to PP and BM. A Kolmogorov-Smirnoff test further showed a higher likelihood that the measured ISI samples were drawn from the simulated ISI distribution based on the OUP-MOM, than from the simulated ISI distribution based on PP or BM.

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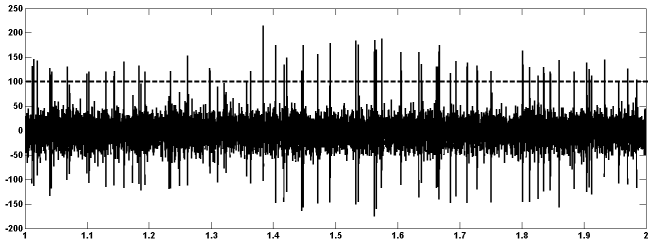

Fig. 1: Sample of recorded data set over a window of 1 sec with spike thresholding. The dotted line represents the threshold set by the physician.

The goal of this paper is two-fold: (1) propose an estimation method for the OUP parameters that reduces the ISE compared to the OUP-MOM method [2], [6] and (2) show that this ISE reduction is statistically significant by examining a large number of human subjects. In this paper we use the OUP to model the ISI distributions of 19 VIM and 10 STN neuronal firings measured during DBS surgery from 5 ET and 6 PD patients, respectively. We propose to extract the two dynamic parameters of the OUP by means of the Fortet Integral Equation (FIE), which is based on the minimization of maximum Kolmogorov Smirnov statistical error for the integral equation [8], [9]. In the rest of the paper, OUP-FIE will indicate the OUP with the parameters extracted using this FIE method. We then proceed as in [2], [6] to compare OUP-FIE, OUP-MOM, PP and BM based on the ISE criterion. The ISE is calculated as the sum of the squared error between measured ISI distribution and numerically simulated ISI distribution at each bin. We show that the model parameter estimated based on the FIE method gives overall better results compare to the moments method. Statistical comparison of the performance of OUP-FIE, OUP-MOM, PP and BM by using the directional Wilcoxon signed rank test [10] shows that the OUP-FIE provides the best curve fit to measured ISI distributions in both ET and PD patients.

The paper is organized as follows. Section II describes the data set and outlines the parameter extraction for the OUP-FPT, followed by a discussion on parameter identification for OUP-MOM, PP and BM. Section III shows the superior performance of OUP-FPT according to the ISE criteria and the directional Wilcoxon signed rank test. Section IV concludes the paper.

II. Modeling

A. Data Set

Pre-DBS, during-DBS and post-DBS micro-electrode recordings (MER), performed to precisely locate an optimal DBS target by assessing neuronal spiking activity at different depths in the brain, were obtained from surgeries done at the University of Illinois at Chicago and the Rush University in Chicago, with respective IRB approvals. MER measures the electrical potential differences across the cell membrane to analyze the high-frequency activities of a single neuron. There are two major sources of noise in recordings: one is due to the cellular activities of neighboring neurons, which cannot be removed, and the other is due to the stimulation artifact present in MER data when a train of high frequency DBS pulses is applied through the macro contact of the micro-electrode assembly. The artifact template was subtracted from recorded signals to recover the neuronal activities but the spiking activities embedded inside the artifact could not be recovered due to saturated signal amplification. The occurrence of spike timestamps was calculated based on visual threshold determined by the physician as shown in Fig. 1. Finally, the ISIs were calculated as the difference between two consecutive spike timestamps.

Our modeling of the spiking activity in the brains of PD and ET patients is performed based on the estimate of the distribution of the ISIs, which we shall refer to as the measured ISI distribution. The measured ISI distributions is obtained by binning the ISIs, where the bin width is calculated using the Freedman Diaconis rule [11] given by

$$h = \frac{\mathsf{IQR}(x)}{(n)^{1/3}}, \tag{1}$$

where, x is the ISI's, h is the bin width, $\mathsf{IQR}(x)$ is the inter-quartile range of x and n is the number of data samples.

B. The Ornstein Uhlenbeck Process (OUP)

The OUP, X_t is a modified Wiener Process, which can be thought of as the continuous-time analogue of the discrete-time AR(1) process. It is described by the following Langevin standard stochastic differential equation that can be solved using Ito calculus [2] thus giving

$$X_t = \mu\tau + (x_0 - \mu\tau)e^{-t/\tau} + \sigma \int_0^t e^{-(t-s)/\tau} dW_s \tag{2}$$

$$\sim \mathcal{N}\left(\tau\mu + (x_0 - \mu\tau)e^{-t/\tau}, (1 - e^{-2t/\tau})\frac{\sigma^2}{2}\right), \tag{3}$$

where W_t is the standard Wiener Process, $\tau > 0$ is a time constant, $\mu\tau > 0$ is equilibrium mean value, $\sigma > 0$ is diffusion coefficient, and x_0 is initial condition of the process. Here $\mathcal{N}(\mu, \sigma^2)$ indicates a Gaussian distribution with mean μ and variance σ^2. A neuron generates an action potential/spike when its membrane potential, X_t exceeds a certain threshold, y_0; then it resets to its resting potential, $x_0 < y_0$. Mathematically, the time between two spikes, i.e., the ISI, is described by the FPT random variable T defined as

$$T = \inf\{t \geq 0 : X_t \geq y_0,\ X_0 = x_0 < y_0\}. \tag{4}$$

The probability density function of the random variable T, indicated as $f_{\mathrm{OUP}}(t; \mu, \sigma)$[1], depends on the three intrinsic parameters (τ, x_0, y_0), and the two dynamic parameters (μ, σ). A closed form for $f_{\mathrm{OUP}}(t; \mu, \sigma)$ is unknown, but its moment generating function is known, from which $f_{\mathrm{OUP}}(t; \mu, \sigma)$ can be efficiently numerically estimated. Parameters are estimated as follows:

[1]Here, as in the following, $f_{\mathrm{RP}}(x; \cdots)$ indicates the probability density function of the ISI generated when the neuronal activity is modeled by the random process "RP", and where the parameters listed in "$\cdots$" are estimated from the measured ISI data.

- The intrinsic parameters (x_0, y_0) are set to plausible physical values. In particular, without loss of generality, we set $x_0 = 0$ (a non zero value for x_0 can be incorporated in the long-term mean value that depends on μ and τ) and $y_0 = 15\text{mV}$ (where 15mV is the difference between the neuron firing threshold and the neuron resting potential).
- The dynamic parameters (μ, σ) are extracted by: (1) *moment method*: the first two moments of the FPT are equated to the first two moments of the measured ISI distribution as done in [2], and (2) *FIE method*: two different expressions of the probability density function of the dimensionless form of the OUP are equated to the estimate μ and σ.
- The time constant τ is chosen within the interval $[1 : 25]$ ms in steps of 0.2 ms according to the following criteria. For each τ we estimate the parameters (μ, σ) according to one of the two methods described in the above point, from which we obtain the ISI distribution $f_{\text{OUP}}(t; \mu, \sigma)$. We then evaluate the Integral Square Error (ISE) as the sum of the squared error between the measured ISI distribution and $f_{\text{OUP}}(t; \mu, \sigma)$. The τ that gives the lowest ISE is chosen.

Next we describe the two methods to obtain estimates for the pair (μ, σ).

1) The moment method: Let m_1 and m_2 be the first two moments of the measured ISI distribution. Let $M_1(\eta|\xi)$ and $M_2(\eta|\xi)$ be the first two moments of the FPT in (4) for the OUP in (3) (whose expressions can be found in [7] but are not reported here for sake of space), where

$$\xi = \sqrt{\frac{2}{\sigma^2\tau}}(x_0 - \mu\tau), \quad \eta = \sqrt{\frac{2}{\sigma^2\tau}}(y_0 - \mu\tau). \tag{5}$$

In [2] the authors solved

$$\tau M_1(\eta|\xi) = m_1, \quad \tau^2 M_2(\eta|\xi) = m_2, \tag{6}$$

to obtain the estimates $(\hat{\xi}, \hat{\eta})$, from which they computed the OUP parameter estimates as

$$\mu_{\text{mm}} = \frac{1}{\tau}\frac{\hat{\eta}x_0 - \hat{\xi}y_0}{\hat{\eta} - \hat{\xi}}, \quad \sigma_{\text{mm}} = \sqrt{\frac{2}{\tau}}\frac{y_0 - x_0}{\hat{\eta} - \hat{\xi}}. \tag{7}$$

With the parameters in (7), the resulting ISI distribution is denoted by $f_{\text{OUP}}(t; \mu_{\text{mm}}, \sigma_{\text{mm}})$.

2) The FIE method: We set $x_0 = 0$ and consider the dimensionless form of OUP given by

$$Y_s = \frac{X_{s\tau}}{y_0}, \ \alpha = \frac{\mu\tau}{y_0}, \ \beta = \frac{\sigma}{y_0}\sqrt{\frac{\tau}{2}}, \ s = \frac{t}{\tau}. \tag{8}$$

Then $Y_s \sim \mathcal{N}\big(\alpha(1 - e^{-s}), \beta^2(1 - e^{-2s})\big)$ and, by writing the density of Y_s in two different ways [9], we have

$$\text{LHS}(s) = \Phi\left(\frac{\alpha(1 - e^{-s}) - 1}{\sqrt{\beta^2(1 - e^{-2s})}}\right) = \tag{9}$$

$$= \int_0^s f(u)\Phi\left(\frac{\alpha - 1}{\beta}\frac{1 - e^{-(s-u)}}{\sqrt{1 - e^{-(s-u)}}}\right)du = \text{RHS}(s) \tag{10}$$

TABLE II: Performance comparison of different processes by using directional Wilcoxon signed rank tests.

ET	FIE<BM	FIE<PP	FIE<Mom	PP<BM
Results	Yes	Yes	Yes	Yes
p-value	0.0001	0.0001	0.0001	0.0392
PD	FIE<BM	FIE<PP	FIE<Mom	BM<PP
Results	Yes	Yes	Yes	Yes
p-value	0.0485	0.0027	0.0314	0.007

where $\Phi(\cdot)$ and $f(\cdot)$ are the cumulative distribution function and the probability density function, respectively, of the random variable $\mathcal{N}(0, 1)$. We use the approximate solution for $\text{RHS}(s)$ in (10) as in [9] (indicated as $\text{RHS}_{\text{app}}(s)$) and estimate $(\hat{\alpha}, \hat{\beta})$ as

$$(\hat{\alpha}, \hat{\beta}) = \arg\min_{\alpha,\beta} \max_{s\in\mathbb{R}_+} |\text{RHS}_{\text{app}}(s) - \text{LHS}(s)|, \tag{11}$$

which represents the minimization of maximum Kolmogorov Smirnov statistical error for the integral equation (10). Finally, we obtain the OPU parameter estimates

$$\mu_{\text{fie}} = \frac{\hat{\alpha}y_0}{\tau}, \quad \sigma_{\text{fie}} = \frac{\hat{\beta}y_0}{\sqrt{2\tau}}. \tag{12}$$

With the parameters in (12), the resulting ISI distribution is denoted by $f_{\text{OUP}}(t; \mu_{\text{fie}}, \sigma_{\text{fie}})$.

We conclude the section by revising two other well known models for the neuronal activity, PP and BM, and the resulting ISI distribution.

C. The Poisson Process (PP)

When the spiking activity is modeled as a PP, the resulting ISI has a Negative Exponential (NE) distribution. Let μ_{ne} be the maximum likelihood estimate of the mean of a NE random variable from the measured ISI distribution. Then, the resulting ISI distribution is

$$f_{\text{PP}}(t; \mu_{\text{ne}}) = \frac{1}{\mu_{\text{ne}}}e^{-t/\mu_{\text{ne}}}, \quad t \geq 0.$$

D. The Brownian Motion (BM)

When the spiking activity is modeled as a BM with positive drift, the resulting ISI has an inverse Gaussian (IG) distribution. The maximum likelihood estimates of the IG model parameters are a function of the measured sample mean and variance of the ISI. The IG model parameter, μ_{ig} can be estimated as the measured mean ISI and λ_{ig} can be estimated as the ratio of the cube of the mean and variance. Then, the resulting ISI distribution is

$$f_{\text{BM}}(t; \mu_{\text{ig}}, \lambda_{\text{ig}}) = \sqrt{\frac{\lambda_{\text{ig}}}{2\pi t^3}} \ \exp\left\{\frac{-\lambda_{\text{ig}}(t - \mu_{\text{ig}})^2}{2\mu_{\text{ig}}^2 t}\right\}, \ t \geq 0.$$

III. Results

A. Performance Comparison based on Statistical Analysis

The quantitative statistical performance comparison of the different stochastic processes is summarized in Table I for both ET and PD patients. Table I reports several statistical dispersion parameters: the median, the first quartile Q_1, the

TABLE I: Quantitative performance comparison of different processes.

Process, Disease	Median $\times 10^{-3}$	First Quartile (Q_1) $\times 10^{-3}$	Third Quartile (Q_3) $\times 10^{-3}$	Inter-Quartile Range $\times 10^{-3}$	Standard Deviation [w/o outliers] $\times 10^{-3}$	Median Absolute Deviation $\times 10^{-3}$
OUP-FIE, ET	0.1507	0.0559	0.2704	0.2145	0.1295	0.0974
OUP-MOM, ET	0.1759	0.0820	0.3112	0.2292	0.1393	0.1201
PP, ET	0.5009	0.2460	0.7872	0.5412	0.3116	0.2883
BM, ET	1.0319	0.1309	2.9752	2.8443	1.7873	0.9698
OUP-FIE, PD	0.0396	0.0163	0.1166	0.1003	0.0782	0.0294
OUP-MOM, PD	0.0742	0.0326	0.2128	0.1802	0.1140	0.0552
PP, PD	0.4428	0.3898	0.7082	0.3184	0.2493	0.1867
BM, PD	0.0686	0.0228	0.2220	0.1992	0.1369	0.0572

third quartile Q_3, the inter quartile range $Q_1 - Q_3$, the standard deviation without outliers, and Median Absolute Deviation. All of these values for each stochastic model were calculated across all recordings of all ET and PD patients separately. For each of the parameters, the OUP-FIE method gives the minimum value. The maximum statistical parameter values are obtained from the BM and PP for ET and PD patients respectively. This shows that the OUP-FIE method provides the best curve fit to measured ISI distribution, according to the ISE criteria, among the four proposed models. We also notice that OUP-MOM, although inferior to OUP-FIE, performs better than BM and PP, according to the ISE criteria.

In order to determine whether the ISE values obtained with OUP-FIE were significantly less than those obtained with other stochastic processes, we performed a series of directional Wilcoxon rank tests over all recordings from PD and ET patients. In Table II the results of the first three tests show that there is statistically significant reduction in ISE values obtained with OUP-FIE compared to those obtained with the other stochastic processes for both ET and PD patients. This shows that the OUP, when its parameters are estimated by the FIE method, provides a good model for the neuronal activity. The last test in Table II compares PP and BM. For ET patients, it shows that that PP is superior to BM, while for PD patients, it shows that that BM is superior to PP.

IV. Conclusions

In this work we demonstrated that the OUP can be used to model the neuronal spiking activity in the STN of 10 PD patients and in the VIM of 19 ET patients. The OUP requires less parameters compared to a deterministic model for neuronal activity, therefore it is a computationally efficient method to model the neuronal activities. To extract the OUP parameters from the measured ISI distribution, we used the FIE method. We compared the performance of OUP-FIE with that of BM, PP and OUP-MOM and concluded that the OUP distribution in which the model parameters were extracted using the FIE method provides the best fit for both PD and ET patients data sets. We also performed different directional Wilcoxon rank tests to statistically compare the performance of different stochastic process. We concluded that the overall performance of FIE method is best amongst all stochastic processes, i.e., it provides the best fit to all measured ISI distributions for both PD and ET patients.

This type of stochastic modeling of the neuronal activity might be helpful in determining the effect of DBS on the input dynamic parameters of the OUP model. By determining a relationship between the DBS parameters an the OUP model parameters, we might be able to find a DBS paradigm that correlates to the most optimal clinical effects on a patient.

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