Published in final edited form as:
Conf Proc IEEE Eng Med Biol Soc. 2011 ; 2011: 757–760. doi:10.1109/IEMBS.2011.6090173.

Using point process models to describe rhythmic spiking in the subthalamic nucleus of Parkinson's patients

Uri T. Eden,
Department of Mathematics and Statistics, Boston University, Boston, MA 02215 USA (phone: 617-353-9553; tzvi@bu.edu)

Ramin Amirnovin, and
Al-Rohdan Laboratories – MGH-HMS Center for Nervous System Repair, Department of Neurosurgery, Massachusettes General Hospital, Boston, MA 02114

Emad N Eskandar
Al-Rohdan Laboratories – MGH-HMS Center for Nervous System Repair, Department of Neurosurgery, Massachusettes General Hospital, Boston, MA 02114

Abstract

Neurological disease is often associated with changes in firing activity in specific brain areas. Accurate statistical models of neural spiking can provide insight into the mechanisms by which the disease develops and clinical symptoms manifest. Point process theory provides a powerful framework for constructing, fitting, and evaluating the quality of neural spiking models. We illustrate an application of point process modeling to the problem of characterizing abnormal oscillatory firing patterns of neurons in the subthalamic nucleus (STN) of patients with Parkinson's disease (PD). We characterize the firing properties of these neurons by constructing conditional intensity models using spline basis functions that relate the spiking of each neuron to movement variables and the neuron's past firing history, both at short and long time scales. By calculating maximum likelihood estimators for all of the parameters and their significance levels, we are able to describe the relative propensity of aberrant STN spiking in terms of factors associated with voluntary movements, with intrinsic properties of the neurons, and factors that may be related to dysregulated network dynamics.

I. Introduction

Abnormal neural firing in the subthalamic nucleus (STN) of patients with Parkinson's disease (PD) is postulated to play a role in the pathogenesis of the tremor, rigidity, and akinesia that characterize the disorder [1]–[3]. Modifying neuronal firing patterns in the STN using deep brain stimulation (DBS) significantly reduces the severity of these symptoms [4]–[5]. However, the mechanisms by which DBS achieves its effects remain unclear.

Analyses of spike train data from STN typically employ separate descriptive statistical techniques to characterize distinct features of the data. Short-term history dependence is often analyzed with interspike interval histograms [6], while long-term history dependence related to neural oscillations is often analyzed using spectral estimators [7]. Separately, tuning curves are often estimated to relate STN spiking rates to features of voluntary movements, such as the direction of an arm reach [8]–[10].

An alternate approach to characterizing the statistical properties of neural spike train data is the construction of point process probability models [11]–[13]. Point process models have been used successfully to model and decode neural firing in rat hippocampus during a

spatial navigation task [14], [15], in primate hippocampus during learning tasks [16], [17], and in primate motor cortex during arm reaching tasks [13], [18], among others.

A central component of point process neural modeling is the specification of the conditional intensity function, which defines the probability of a spike in any small time interval as a function of the biological covariates to which neural firing is tuned and as a function of the neuron's past firing history [11]. Here, we present a point process generalized linear model (GLM) for characterizing the spiking activity of STN neurons, recorded from PD patients, that relates spiking probability simultaneously to factors such as the time course of movement planning and execution, directional selectivity, refractoriness, bursting and oscillatory dynamics. We illustrate the application of this model to a sample dataset recorded from STN during a voluntary movement task.

II. Methods

We constructed conditional intensity models for neurons in the STN that describe the probability of spiking at each instant as a function of the time relative to the start of a reaching movement and of the recent spiking history of the neuron in the past 150 ms. Given the observation interval, $[0, T]$, let $N^i(t)$ be a counting process signifying the total number of spikes fired by the i^{th} neuron in the recorded population in the interval $[0, t]$, for $t \leq T$. The conditional intensity for this neuron is defined as:

$$\lambda^i(t|H_t) = \lim_{\Delta t \to 0} \frac{\Pr(N^i(t+\Delta t) - N^i(t) = 1 | H_t)}{\Delta t}, \quad (1)$$

where H_t is the past spiking history of all observed neurons up to time t.

To analyze the spiking propensity of the STN neurons, we specify the spiking intensity function at each time t as a function of the time relative to the start of a voluntary arm movement and the neuron's spiking history in the preceding 150 ms as follows.

$$\lambda(t|\theta) = \exp\left\{\sum_{d=1}^{4}\sum_{l=t_{start}}^{t_{end}} \alpha_{l,d} g_{l,d}(t) + \sum_{j=0}^{9} \beta_j n_{t-(j+1):t-j} + \sum_{k=1}^{14} \gamma_k n_{t-(10k+9):t-10k}\right\}$$

Here, $g_{l,d}(t)$ is a basis function for a cardinal spline for the movement direction d, $n_{a:b}$ is the number of spikes observed in the interval $(a, b]$ and $\theta = \left[\{\alpha_{l,d}\}_{l=t_{start}}^{t_{end}}, \{\beta_j\}_{j=0}^{9}, \{\gamma_k\}_{k=1}^{14}\right]$ are a set of unknown parameters which relate movement time course and the neuron's spiking history to current spike rate. Cardinal splines are locally defined third order polynomials that can approximate any continuous function [19], making them a flexible class of basis functions for relating movement variables to spiking activity. The times t_{start} and t_{end} are the analysis start and stop times respectively.

It follows from the definition of the conditional intensity function that the probability of a spike in a small time interval $[t, t+\Delta)$ is approximately:

$$\Pr(\text{Spike in} [t, t+\Delta) | \theta) \approx \lambda(t|\theta)\Delta. \quad (2)$$

Hence, the intensity function defines the spiking probability in any small time interval $[t, t+\Delta)$. The $\{\alpha_{l,d}\}_{l=t_{start}}^{t_{end}}$ parameters measure the effect of movement planning and execution on

the spiking probability. The $\{\beta_j\}_{j=0}^{9}$ parameters measure the effects of spiking history in the previous 10 ms to capture the effects of refractoriness and bursting on the spiking probability. The $\{\gamma_k\}_{k=1}^{14}$ parameters measure the effects of the spiking history in the previous 10 to 150 ms, which are most likely associated with both the neuron's individual spiking activity and also that of its local network.

This spiking intensity function defines a point process GLM for the observed spike train data. Such models have concave likelihood surfaces, which allow us to compute maximum likelihood estimates for the model parameters in a straightforward manner [13]. We examined the model fits to the data separately prior to movement onset ($t$start = −1000 ms, $t$end= −500 ms) and during movement ($t$start = 0 ms, $t$end= 500 ms). In order to compare the temporal spiking properties prior to and during movement, we constructed an additional model encompassing the entire trial ($t$start = −1500 ms, $t$end= 1500 ms) where the $\{\beta_j\}_{j=0}^{9}$ and $\{\gamma_k\}_{k=1}^{14}$ parameters were fit separately for these two intervals. Significantly different parameter estimates between these intervals suggest that the temporal neural firing properties change as a function of movement.

III. Results

We illustrate the point process model fit to spiking data from a STN neuron obtained from a patient undergoing DBS implantation surgery. During electrode placement, patients performed a cued joystick movement task. Each trial began with the presentation of a small central fixation point. After a brief delay (250 ms), four small gray targets appeared, arrayed in a circular fashion around the fixation point. After a 1500 ms delay a randomly selected target turned green. At this point the subject used the joystick to guide a cursor from the center of the monitor towards the green target. The methods associated with intraoperative microelectrode recordings and data preprocessing are described in [20].

Figure 1 shows the model parameters and their uncertainty for the maximum likelihood fit to this data. Figure 1A shows the spline estimates and 95% confidence bounds of the stimulus related component as a function of time relative to movement onset, with the splines for the four directions plotted in separate colors. In each case, the firing intensity is initially low and begins to increase about 500 ms prior to movement onset. The intensity reaches a peak between 200 ms prior to movement onset to 400 ms after movement onset, and eventually returns to initial firing levels. The shaded areas surrounding each estimate represent 95% confidence regions about the firing rate, which can be used to determine when the estimated rate in one direction is statistically different from another. For example, in the direction indicated by the red line at movement onset, the firing rate is significantly lower that in the directions indicated by the blue and green lines.

Figures 1B and 1C show the short term history components of the model using the data 1500 ms to 1000 ms prior to movement onset and from movement onset to 500 ms into the movement, respectively. In both cases, the value of exp (β_0) is approximately 0.5 and is significantly smaller than one, indicating that the probability of observing a spike in a 1 ms bin is reduced if a spike was observed in the previous 1 ms bin. The values of exp (β_1) and exp (β_2) are significantly larger than one, indicating that the probability of firing increases 2–4 ms after a spike. The temporal spiking properties within the first 10 ms are not significantly different before and during movements.

Figures 1D and 1E show the model parameter estimates related to long-term history effects before and during movement, respectively. In the period prior to movement onset, these

parameters have a distinctive shape. exp (γ_2), the parameter relating to interspike intervals (ISIs) between 20 and 30 ms, is significantly smaller than one while exp (γ_4) and exp (γ_5), relating to ISIs between 40 and 60 ms are significantly larger than one. This pattern consisting of a significantly decreased probability of firing 20–40 ms after the previous spike and a significantly increased probability 40–90 ms after a spike was present in the majority of neurons we examined. During movement, the values of the long-term history parameters indicate virtually no significant effect of past spiking beyond 10 ms, with only exp (γ_2) significantly different from one. Although there is still some inhibition 20–30 ms after a spike during movement, this effect is significantly reduced from the period prior to movement initiation.

III. Discussion

By calculating maximum likelihood estimators for all of the parameters and their significance levels, we were able to simultaneously characterize multiple features previously associated with these neurons such as increased firing as a function of movement planning and execution, directional selectivity, refractoriness, bursting, and oscillatory spiking that is attenuated during movement. We also found that in nearly all of the recorded neurons, the probability of firing a spike was significantly reduced 20–30 ms after a previous spike, suggesting that the previously described oscillatory firing of these neurons is composed of an initial period of inhibition followed by a period of increased firing probability. This model is able to capture the relative propensity of aberrant STN spiking in terms of movement associated factors, factors associated with intrinsic properties of the neurons, and factors that may be related to dysregulated network dynamics.

The mechanism for the oscillatory behavior of STN neurons is not fully understood. The pattern of inhibition and excitation we observed from 20–100 ms after a previous spike suggests possible network mechanisms. One hypothesis is that synchronized firing in the STN feeds back to the globus pallidus pars externa (GPe), which then provides a wave of inhibition back to STN [21]. The timing of the oscillatory spike patterns would therefore be determined by the time course of excitation and inhibition within this recurrent loop.

Point-process analyses provide an elegant approach to determining the contributions of intrinsic dynamics and external stimuli to the propensity of neurons to fire. Future work will focus on characterizing these effects in large, simultaneously recorded populations, on quantifying the relative contributions of these effects in driving neural rhythms, and on developing models for how these aberrant oscillations lead to the observed pathology in Parkinson’s disease.

Acknowledgments

This work was supported in part by the National Science Foundation under Grant IIS-0643995.

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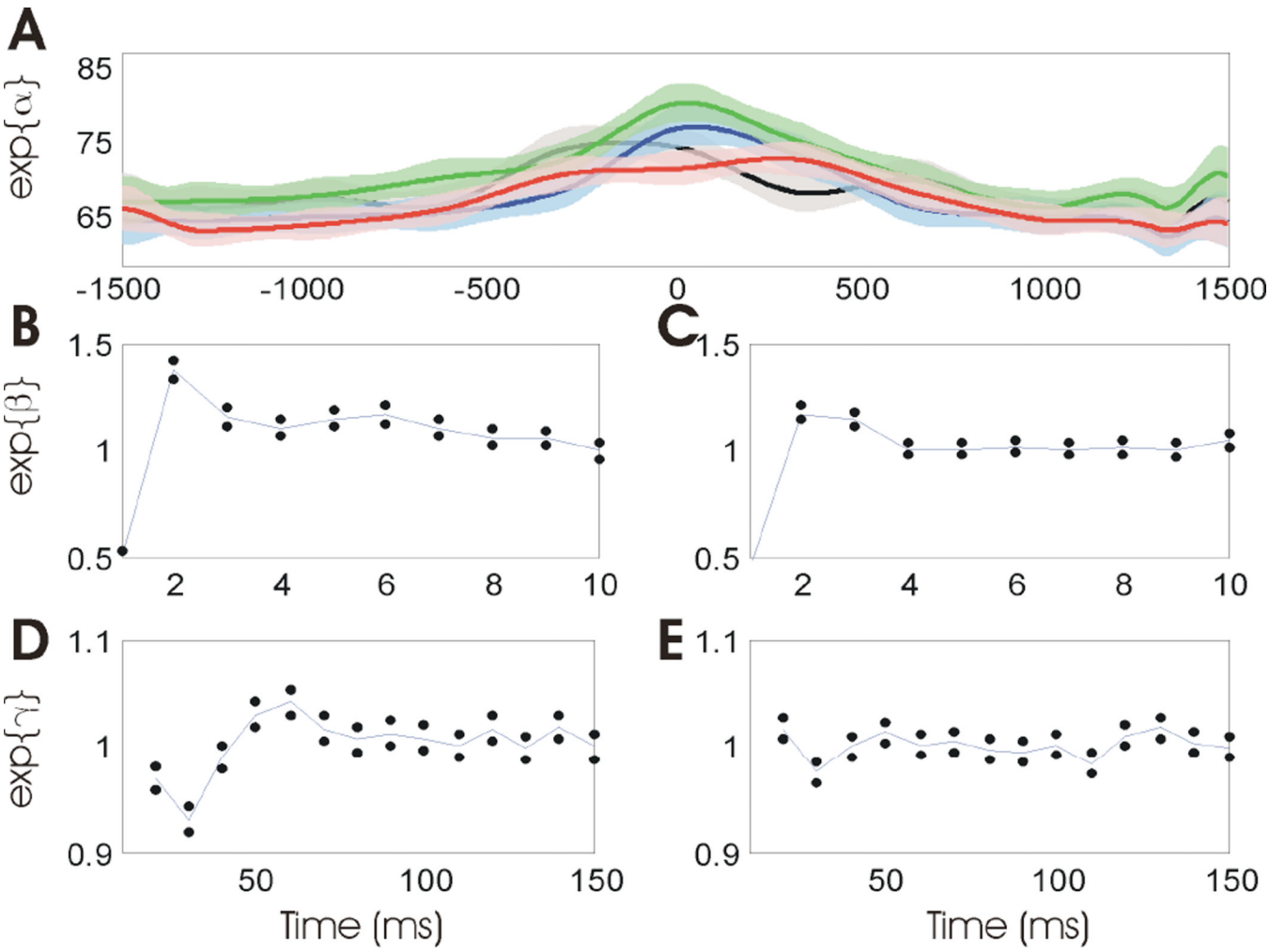

Fig. 1.

A) Stimulus related firing intensity estimates in each of four movement directions. B) Short term history (0–10ms) parameters prior to movement. Blue line represents parameter estimates, black dots represent confidence intervals. C) Short term history parameters during movement. D) Long-term history parameters (10–150ms) prior to movement. E) Long-term history parameters during movement.