Analysis of a Fourth Order Model of Neural Synchrony and Applied Stimulation using Control Theory

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Abstract—Deep brain stimulation (DBS) effectively suppresses the pathological neural activity associated with Parkinson’s disease, with a parallel improvement in motor symptoms of the disease observed. However, its exact mode of action is not fully understood. This study explores a fourth order computational model of neural synchrony and applied stimulation using established nonlinear control systems theory. A novel method of combining two describing functions is developed, which allows the amplitude of oscillations in the model to be studied as the applied stimulation parameters vary. The theoretical model parameters are fitted to experimental data recorded in a patient with Parkinson’s disease for a range of stimulator settings.

Index Terms—neural synchrony, Parkinson’s disease, control theory, deep brain stimulation.

I. INTRODUCTION

DEEP brain stimulation is a clinically available treatment option for a number of neurological disorders including medically refractive Parkinson’s disease. The subthalamic nucleus (STN) and the globus pallidus interna (GPI) are the most common targets. Although successful, its exact mode of action is not clearly understood. The primary symptoms of Parkinson’s disease occur as a result of a decrease in the level of dopamine in the brain caused by the death of dopamine-secreting cells in the substantia nigra pars compacta region. The motor symptoms of the disease, bradykinesia and akinesia, have been shown to correlate with synchronous beta-band (12-30 Hz) oscillatory activity in the basal ganglia [1], [2]. DBS suppresses these pathological oscillations, with a parallel improvement in the motor symptoms of Parkinson’s disease observed [1], [3], although a direct causal link remains yet to be established.

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Computational modeling of the basal ganglia and DBS is an important tool in the exploration of possible therapeutic mechanisms of electrical stimulation on the brain [4]. Models devised vary from complex biophysical cellular level models [5] to simplified mean-field based models [6]. Mean field models enable the system level response of a neural population to be studied in a mathematically simplified manner due to the reduced number of parameters. This can be advantageous as it allows comparison with clinical data which reflects the activity of a neural ensemble, where recordings from individual neurons are not possible [7].

The second order mathematical model of neural synchrony presented in [8] is one such mean-field model, and describes one of the simplest possible feedback loops that will generate and sustain oscillations. It is comprised of a nonlinear element and a transfer function. The nonlinear element is chosen as a sigmoidal arctan function, and the transfer function as second order. The analysis described explores the suitability of this model as a representation of a neuronal circuit in the cortico-basal ganglia network which demonstrates increased synchronized oscillatory activity in Parkinson’s disease. The methods employed in the analysis, specifically describing function analysis, are based on techniques used in nonlinear control engineering. The application of high frequency stimulation, representing deep brain stimulation, is included in the model. The effects of changing the parameters of this stimulation, amplitude, frequency and pulse duration, was studied and compared with clinical data published in [9].

This current study extends the analysis of the second order model to a fourth order model representing two distinct interconnected nuclei exhibiting synchronous oscillatory activity, similar to that presented in [10]. Although the focus in [10] is on the STN-GPe loop, the model described can typify

Figure 1. Schematic diagram of the second order model of neural synchrony as explored in [8].
II. METHODS

A. Theoretical analysis

A fourth order computational model representing a neuronal circuit that demonstrates pathological oscillatory activity, as is observed in Parkinson’s disease, is outlined in [10]. It is essentially comprised of two reciprocally connected second order models, and represents two distinct neural ensembles. Each ensemble is represented by a nonlinear element in series with a transfer function. The output from each non-linearity represents the deviation from zero of the total synaptic current averaged over all cells in the ensemble, with the output from the \( G(s) \) block being the deviation from zero of the ensemble averaged mean-field output of all cells in the area. For each nucleus, the nonlinear element is modeled by a sigmoidal arctan function of the form:

\[
u = \frac{2}{\pi} \arctan \left( \frac{y}{h} \right)
\]

(1)

where \( y \) is the input to the block, and the parameter \( h \) sets the sharpness of the characteristic, and thus the responsiveness of the feedback loop. \( h \) in \( NL_1 \) represents the effect of a change in dopamine concentration on the system, and \( h_2 \) is set to a fixed value. The transfer function is given by:

\[ G(s) = \frac{k}{(s + b)^2} \]

(2)

where \( k \) and \( b \) are constants. The form chosen for \( G(s) \) sets the angular frequency of oscillation at \( b \) radians per second, and also provides the low-pass filtering necessary to justify use of the Describing Function [11].

The DBS stimulation is modeled in this study as a biphasic, rectangular waveform, with an amplitude of stimulation \( a \) and pulse duration \( \alpha \), and is applied additively at the input to a nonlinear element, Fig. 2.

Describing function analysis is a common technique in the area of control engineering. The describing function is the effective gain relating a sinusoidal input to the fundamental sinusoidal component of the resulting output of a nonlinear element [12]. In general, the describing function of a nonlinear element with a sinusoidal input is a function of both the amplitude \( (Y_m) \) and frequency \( (\omega) \) of the input. Following the techniques outlined in [13] the describing function of the nonlinear element, a sigmoidal arctan function, \( NL_2 \) in Fig. 2, is evaluated as:

\[
D(Y_m, \omega) = \frac{4h_2}{\pi Y_m^2} \left( \frac{Y_m^2}{h_2^2} + 1 - 1 \right)
\]

(3)

where

\[
f = \frac{(c^2 + 1 - b^2) \sqrt{(c^2 + 1 - b^2) + 4b^2c^2}}{2}
\]

and

\[
b = \frac{a}{Y_m} \quad , \quad c = \frac{h_1}{Y_m}
\]

The describing function of the original non-linearity, \( NL_2 \), is denoted \( D_o \), with \( D_s \) the notation assigned to the describing function of the equivalent non-linearity, \( NL_1 + DBS \). The amplitude of the oscillations is described at each given point in the loop in terms of the describing function as follows:

\[
|y| = Y_m
\]

(6)

\[
|X_1| = D_o(Y_m) \cdot Y_m
\]

(7)

\[
|X_2| = D_o(Y_m) \cdot Y_m \cdot |G(jb)|
\]

(8)

\[
|X_3| = D_o(Y_m) \cdot Y_m \cdot |G(jb)| \cdot D_e(D_o(Y_m) \cdot Y_m \cdot |G(jb)|)
\]

(9)

\[
|X_4| = D_o(Y_m) \cdot Y_m \cdot |G(jb)| \cdot D_e(D_o(Y_m) \cdot Y_m \cdot |G(jb)|) \cdot |G(jb)|
\]

(10)

From Fig. 2, it is clear that in (10) \( |X_4| = Y_m \), and so, equating (6) and (10) yields:

\[
D_o(Y_m) \cdot D_e(D_o(Y_m) \cdot Y_m \cdot |G(jb)|) = \frac{1}{|G(jb)| \cdot |G(jb)|}
\]

(11)
The transfer functions are chosen to be equal, and the simplest form of $G(s)$ to support oscillations is second order and taken as:

$$G(s) = \frac{k}{(s + b)^2}$$

(12)

This is evaluated at angular frequency $b$ as:

$$|G jb)| = \frac{k}{2b^2}$$

(13)

This sets the critical value of the composition of describing functions shown on the left hand side of (11) to the critical value for which oscillations will occur in the model as $\frac{45}{\pi}$. Taking $k = b^2$ sets the threshold equal to 4. For oscillations to occur in the system, the phase condition must also be satisfied: the phase difference around the feedback loop must sum to zero. Each transfer function contributes a phase difference of $-\frac{\pi}{2}$, and when combined with the negative feedback in the model yields zero.

In order to examine the effects of changing the parameters of the model and the stimulation applied to the model on the amplitude of the oscillations, the intersection point between the describing function and the threshold for generation of oscillations is calculated for a range of parameter values. This allows the amplitude of oscillations, denoted $Y_m$, to be calculated as a function of $h_1$, the parameter modeling the effect of dopamine on the system, $\alpha$, the amplitude of applied stimulation and $\beta$, the pulse duration of the applied stimulation.

**B. Clinical data**

In order to assess the validity of the theoretical model, a fit to experimental data using a least mean squares error minimization routine was examined. LFP data was recorded from the STN of a patient with Parkinson’s disease using a quadripolar implanted stimulation lead (Medtronic, DBS Lead Model 3389) during stimulation with an external stimulator device (Medtronic), for a range of amplitudes and pulse durations. The data was recorded at the Department of Clinical Neurology, University of Oxford. The data was band pass filtered in Spike2 (Cambridge Electronic Design Ltd., Cambridge, UK) using an FIR filter with cut off frequencies $10 < f < 30Hz$. Two samples of this LFP data are shown in Fig. 3 - both without stimulation and with $130Hz$ stimulation applied at an amplitude of $3V$ and a pulse duration of $400\mu s$. To calculate the amplitude of the oscillations for each stimulation setting the root mean square value of a 10 second epoch was calculated. Each epoch began 10 seconds after the adjustment to the stimulation took place. The amplitude of the beta band oscillations in the LFP data for each stimulation setting was normalized with respect to the DBS-off data recorded during that trial, and the squared error between the clinical and the theoretical data was minimized for each data set to fit the theoretical curve to the data.

**III. Results**

The amplitude of oscillations $Y_m$, occurring in the unstimulated system is presented in Fig. 4 as a function of $h_1$, the parameter representing the effect of a decreased dopamine concentration on the system.

![Figure 4](image)

**IV. Conclusions**

This study describes a novel method of applying describing function analysis to a fourth order system model. The model can represent any two distinct, interconnected nuclei, and here is used to represent the pathological oscillatory neural activity that occurs in Parkinson’s disease. Describing function analysis allows the relationship between the applied stimulation and the amplitude of oscillations to be derived. The use of a mean-field model such as the simplified one...
Figure 5. Amplitude of oscillations plotted as a function of the amplitude of applied stimulation calculated for the theoretical fourth order model of synchronous neural activity, with $h_1 = 0.09$ and $h_2 = 1$. Clinical data is from a single data set with the rms amplitude value for each setting of stimulation amplitude calculated from a 10 second epoch and normalized with respect to the DBS-off data recorded during that trial.

Figure 6. Amplitude of oscillations plotted as a function of the pulse duration of applied stimulation calculated for the theoretical fourth order model of synchronous neural activity, with $h_1 = 0.09$ and $h_2 = 1$. Clinical data is from a single data set with the rms amplitude value for each setting of pulse duration calculated from a 10 second epoch and normalized with respect to the DBS-off data recorded during that trial.

described, and the application of describing function analysis, provides a means of fitting clinical data, which can be recorded from the basal ganglia, to the theoretical model in a straightforward manner as the number of parameters is low. Using experimental LFP data recorded from a Parkinsonian patient allowed the model parameters to be optimized. Although a good agreement was observed between the theoretical and clinical data for this single patient, further analysis with more extensive data, for a broader range of parameters, would allow the model behavior and the appropriateness of the model across a wider population to be examined. It is also envisaged that the analysis could be extended to evaluate models of higher orders representing a larger number of interconnected nuclei.

REFERENCES


