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Application of Non-linear Control Theory to a Model of Deep Brain Stimulation

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***Abstract*— Deep brain stimulation (DBS) effectively alleviates the pathological neural activity associated with Parkinson's disease. Its exact mode of action is not entirely understood. This paper explores theoretically the optimum stimulation parameters necessary to quench oscillations in a neural-mass type model with second order dynamics. This model applies well established nonlinear control system theory to DBS. The analysis here determines the minimum criteria in terms of amplitude and pulse duration of stimulation, necessary to quench the unwanted oscillations in a closed loop system, and outlines the relationship between this model and the actual physiological system.**

I. Introduction

Deep brain stimulation (DBS) is well established as an effective method of treating the symptoms of medically refractive Parkinson's disease [1]. Its exact mode of action however, remains open to debate. Both patient and animal models of Parkinson's disease demonstrate abnormal, pathological activity in the neurons of the basal ganglia, which is now well established as being due to the depletion of dopamine in the substantia nigra pars compacta, a centre within the basal ganglia of the brain [2]. An increase in the spontaneous firing rate and periodic oscillatory activity has been recorded [3]-[6].

DBS applied to treat Parkinson's disease is typically a high frequency (>100Hz) pulse train applied to the subthalamic nucleus (STN) via surgically implanted electrodes. The choice of stimulation amplitude and pulse duration is usually made based on a trial and error approach for an individual patient with clinically effective amplitudes ranging from 1 – 5 V and pulse durations from 60 – 450 μs [7]-[9].

Within the basal ganglia, the STN forms an important feedback loop with the globus pallidus pars externa (GPe). This loop has been proposed as a possible source of the pathological oscillations that are inherent in Parkinson's disease [10]. This idea is supported by the study of an *in vitro* model by Plenz and Kital [11], which suggests that the STN –Gpe circuit forms a central basal ganglia pacemaker.

The resemblance of DBS quenching pathological oscillations in the STN-GPe loop to the concept of 'high-frequency' dither injection being used to quench 'low-frequency' oscillations in nonlinear control feedback loops has previously been explored using a neural-mass type model of the basal ganglia [10]. The injection of high-frequency dither to modify the properties of a non-linear system is a well established engineering tool. In this study the model developed in [10], which is of fourth order and contains two nonlinearities, is simplified to a feedback loop containing a second order linear system and a single nonlinearity, with positive feedback, as shown in Fig.1. This follows the demonstration by Rosenblum and Pikovsky [3], that the local field potential (LFP) of a family of interconnected neurons, with excitatory interconnections (which is why we use positive feedback in Fig.1), grows in accordance with second order dynamics. The effect of changing DBS amplitude and pulse duration necessary to quench pathological low-frequency oscillations is examined, with the help of describing function (DF) analysis. Although the results obtained are specific to this model, it is suggested that by reducing the complexity of the physiological system, whilst retaining key features, insight can be gained into the mode of action of DBS that will be applicable in a clinical setting.

II. Methods

A. The Model

The basic neural mass model of synchrony in a group of interacting neurons studied here is comprised of a nonlinear sigmoidal element followed by a second order linear block. This combination of sigmoidal nonlinearity and low order linear dynamical system is very common in the field of neural mass modeling [12]. As is usual in these models, the input to the sigmoid is the LFP. In this paper, the output is taken to be the deviation from zero of the total synaptic current injected into the group of neurons. Since this deviation may be positive or negative, the sigmoid is taken

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to be symmetrical about the origin. There are many sigmoids encountered in the literature, but the one which has been found most convenient in the present research is the arctan function given by:

$$u = \left[\frac{2}{\pi}\right] \arctan\left(\frac{y}{h}\right) \quad (1).$$

It is proposed that the parameter *h* decreases steadily as dopamine is depleted by the advance of Parkinson's disease. This means that the slope of *u* vs. *y* evaluated at the origin, which is *2/[πh]*, sharpens steadily as the disease progresses.

The transfer function is of the form

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

where *k* and *b* are constants. This is the simplest transfer function that will generate oscillations in conjunction with the sigmoidal function.

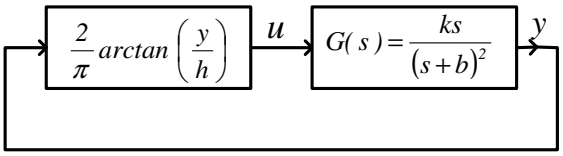

Fig. 1 Simple neural mass model of synchrony within a closed loop of interacting neurons.

Using linear control theory [13], it is readily shown that almost sinusoidal oscillations at angular frequency *ω=b* set in as soon as the small signal loop gain at *ω=b* exceeds unity, i.e.

$$\frac{2}{\pi h} > \frac{2b}{k} \quad (3a)$$

For later use it is convenient to rearrange this as

$$1 - \frac{\pi b h}{k} > 0 \quad (3b)$$

It is clearly shown by (3b) that dopamine depletion (leading to progressive decrease in *h*), must eventually result in the onset of oscillations. The output *u* from the sigmoid represents the deviation from zero of the total synaptic current of the group of neurons, whilst *y*, the output from the transfer function block is the deviation from zero of the LFP [9], [14].

The DBS waveform (or dither), is modeled as a biphasic, rectangular pulse, with amplitude *a*, period *T* and fractional pulse duration *α* for both positive and negative excursions. It is applied additively at the input to the sigmoidal function. The dither pass-band is well above the pass-band of G(s).

B. The Equivalent Nonlinearity

It is assumed that *y* remains approximately constant over a DBS or dither cycle. The signal *u* consists of a slowly varying component superimposed on a series of harmonics of the dither frequency. However, these harmonics are filtered out by G(s), so that *y* responds essentially to the low frequency component of *u*. Under these conditions [13], the original nonlinearity and the applied DBS may be replaced by a single equivalent nonlinearity, which is the function *û* versus *y*, where *û* is the mean value of *u* over a dither cycle. Simulations have confirmed the validity of this concept [10]. In this case the result is

$$\hat{u} = \left[\frac{2}{\pi}\right]\left[(\alpha)\arctan\left(\frac{y+a}{h}\right) + (\alpha)\arctan\left(\frac{y-a}{h}\right) + (1-2\alpha)\arctan\left(\frac{y}{h}\right)\right] \quad (4)$$

For later use, the slope at the origin of this equivalent nonlinearity is evaluated as

$$\left.\frac{d\hat{u}}{dy}\right|_{x=0} = \frac{2}{\pi h}\left[1 - \frac{2\alpha a^2}{a^2 + h^2}\right] \quad (5)$$

The increase in the term *2/[πh]* is offset by the decrease of the term in square brackets in (5), as the DBS amplitude is increased.

C. The Describing Function

In order to further examine, on a theoretical basis the effect of changing the amplitude of stimulation, a concept from control engineering – DF analysis - can be applied [10],[13]. DF analysis enables the approximate calculation of the response of a particular non-linear system to a given input. In (4), it is assumed that

$$y = Ym \sin\theta, (\theta = bt) \quad (6)$$

where *Ym* is the amplitude of the sinusoidal oscillation and *t* represents time. Using the approach to calculation of DF given in [13], it has proved possible in this project to evaluate the DF as

$$DF = \frac{4h}{\pi Ym^2}\left(\sqrt{\frac{Ym^2}{h^2}+1}-1\right) - \frac{8\alpha h}{\pi Ym^2}\left(\sqrt{\frac{Ym^2}{h^2}+1} - \frac{Ym}{h}(f)\right) \quad (7)$$

where f is

$$\sqrt{\frac{(c^2+1-b^2)+\sqrt{(c^2+1-b^2)^2+4b^2c^2}}{2}} \quad (8)$$

with

$$b = \frac{a}{Ym} \quad (9)$$

and

$$c = \frac{h}{Ym} \quad (10)$$

It is planned to give the derivation of these equations in an extended paper. For present purposes, it is sufficient to state that, as *Ym* goes to zero, DF reaches a maximum value, which is equal to the slope at the origin of the equivalent nonlinearity, as given in (5). The DF is plotted as function of *Ym* in Fig.2, which shows simulated conditions for a healthy system, dopamine depletion and when DBS is applied to the system.

III. RESULTS

Equation (5) permits calculation of the range of values of *a* necessary for quenching by the counterpart of (3a), where *2/[πh]* is replaced by the expression given on the right hand side of (5). The result is

$$\left(\frac{\pi bh}{k}\right)\left(\frac{1}{1-\frac{2\alpha a^2}{a^2+h^2}}\right) > 1 \quad (11)$$

which leads directly to

$$a > h\sqrt{\frac{\left(1-\frac{\pi bh}{k}\right)}{\left(2\alpha-\left(1-\frac{\pi bh}{k}\right)\right)}} \quad (12)$$

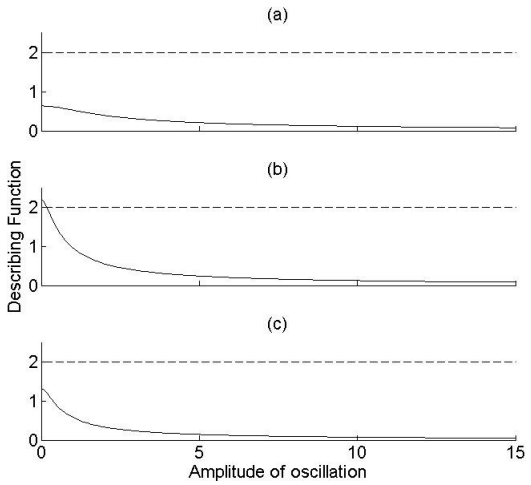

Fig. 2 The DF plotted as a function of the amplitude of oscillation, *Ym*. The ordinate 2 which has been emphasized in this figure is just *2b/k* with *b* = *k*. (a) depicts a non-oscillating (healthy) system. (b) shows the intersection that occurs with a decreased value of *h* due to dopamine depletion. (c) is when DBS is applied to the system, counteracting the decrease in *h* and thereby quenching the oscillations.

In view of (3b), which applies to a patient with Parkinson's disease, (12) predicts that quenching can only be obtained for

$$\alpha > \frac{\left(1-\frac{\pi bh}{k}\right)}{2} \quad (13)$$

Fig. 3 shows the theoretical curve of the minimum DBS amplitude necessary for quenching oscillations as a function of α, for the illustrative value of the quantity on the left hand side of (3b), taken as 0.01 (for $b = k$ and $h = 0.99/\pi$).

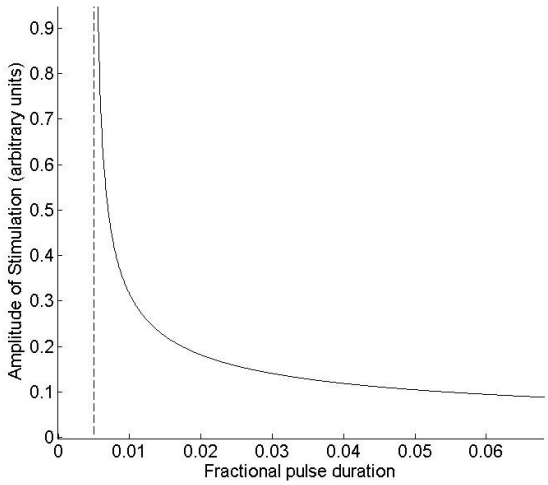

Fig. 3: Theoretical curve of the amplitude of DBS signal for quenching, as a function of fractional pulse duration.

The parameter a is in normalized units. These can be converted to volts using clinical data such as provided in [1], as will be done in a later extended paper.

The illustration in Fig.3, that quenching of oscillations can be achieved at lower stimulation amplitudes when the pulse duration is increased is supported by clinical observations [1],[7]–[9].

For the stimulation waveform considered, the mean square amplitude is readily shown to be $2a^2\alpha$. This quantity is directly proportional to the power injected by the stimulating electrodes. A graph of $a^2\alpha$ vs. α is shown in Fig. 4. This shows that the power needed to quench oscillation decreases monotonically with fractional pulse duration. The maximum possible value of fractional pulse duration is 0.5. However, clinical considerations must dictate the maximum value which can be used in practice.

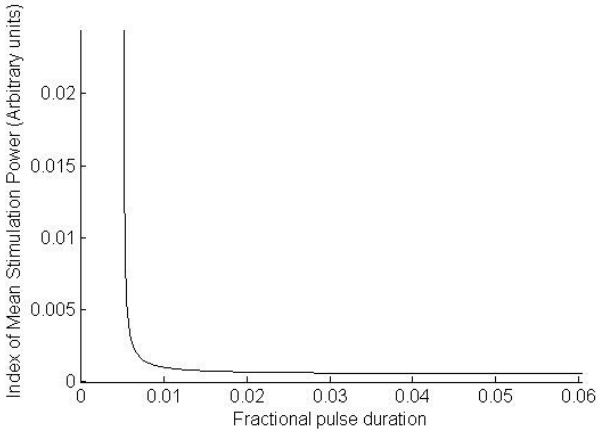

Fig. 4: Theoretical curve of the mean square amplitude of stimulation as a function of fractional pulse duration.

IV. DISCUSSION

Control theory and concepts most commonly applied to the theory of non-linear feedback systems are used in this study to provide a framework in which to explore the effects of DBS. The first exposition of this approach presented in [10] is further developed and analyzed.

The DF analysis enables the identification of the conditions under which oscillations are present in the feedback loop considered, the determination of the minimum amplitude of stimulation and the mean DBS power needed to quench these oscillations, both as a function of fractional pulse duration. The translation and application of these parameters to a clinical environment will facilitate the choice of settings necessary to quench the pathological oscillations in patients, potentially providing an improvement on the current trial and error approach followed.

The model examined here is the simplest that has so far been discovered to model the onset and quenching of oscillations in a group of mutually excitatory neurons. The specific structure of the basal ganglia, along with cortical and striatal inputs and outputs, will be incorporated at a later date. Volume conduction effects of the tissue will also be taken into account.

In summary, the analysis outlined here provides an initial platform from which more in depth and physiologically complete models and analyses can be developed.

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