Multiple Frequencies in the Basal Ganglia in Parkinson's Disease

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Abstract. *In recent years, the authors have developed what appears to be a very successful phenomenological model for analyzing the role of deep brain stimulation (DBS) in alleviating the symptoms of Parkinson's disease. In this paper, we extend the scope of the model by using it to predict the generation of new frequencies from networks tuned to a specific frequency, or indeed not self-oscillatory at all. We have discussed two principal cases: firstly where the constituent systems are coupled in an excitatory-excitatory fashion, which we designate by "+/+"; and secondly where the constituent systems are coupled in an excitatory-inhibitory fashion, which we designate "+/−". The model predicts that from a basic system tuned to tremor frequency we can generate an unlimited range of frequencies. We illustrate in particular, starting from systems which are initially non-oscillatory, that when the coupling coefficient exceeds a certain value, the system begins to oscillate at an amplitude which increases with the coupling strength. Another very interesting feature, which has been shown by colleagues of ours to arise through the coupling of complicated networks based on the physiology of the basal ganglia, can be illustrated by the root locus method which shows that increasing and decreasing frequencies of oscillation, existing simultaneously, have the property that their geometric mean remains substantially constant as the coupling strength is varied. We feel that with the present approach, we have provided another tool for understanding the existence and interaction of pathological oscillations which underlie, not only Parkinson's disease, but other conditions such as Tourette's syndrome, depression and epilepsy.*

Keywords

Computational model, control theory, Parkinson's disease, pathological oscillations.

1. Introduction

Over the last ten years, some of the authors' research on external assistive technology have been reported in this journal. The first steps taken in internal assistive technology, deep brain stimulation for the relief from symptoms of Parkinson's disease, have also been published here [1], and elsewhere [2], [3].

In [2], [4], a computational model of Parkinsonian pathological oscillatory activity and its suppression with the application of high-frequency stimulation is presented. The model is a macroscopic neural-mass type model and aims to capture the key features of a synchronized group of neurons in a mathematically tractable manner. The model has been shown to produce theoretical results that provide a fit in close agreement with clinical data published in [5], [6] and also provided by the University of Oxford.

In this study, the model presented in [2] is used as the basis with which to explore the oscillatory activity in self-oscillating and non-self-oscillating coupled loops. This is inspired by the observation that pathological basal ganglia oscillations in the range 3–300 Hz have been recorded in Parkinsonian patients. We suggest that the interaction between distinct loops either tuned to a particular frequency or inherently non-oscillatory can give rise to this range of oscillatory frequencies. We explore this hypothesis using two inter-coupled loops set to produce oscillations in the tremor range of frequencies, although this could easily be extended to encompass a wide range of frequencies such as appear in the Parkinsonian basal ganglia LFP recordings [7], [8], [9], [10]. Concepts from control theory, in particular the use of root locus analysis, are applied to analyze the model.

2. Methods

In this paper we present results obtained in our studies so far of the generation of the multitude of frequencies observed in the basal ganglia from the inter-coupling of our basic model shown in Fig. 1. For $g_1 = g_2 > 0$ we have "+/+" coupling and for $g_1 = -g_2 < 0$ we have "+/−" coupling.

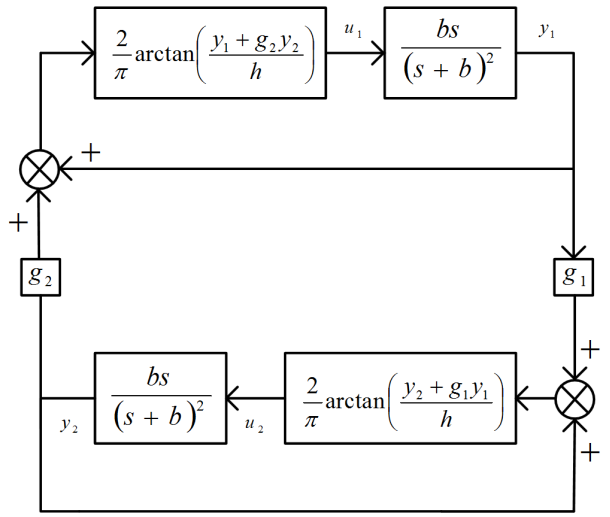

Fig. 1: The basic system considered. +/+ coupling has $g_1 = g_2 > 0$; +/- coupling has $g_1 = -g_2 < 0$.

For small signal analysis the arctan nonlinearities are replaced by their small signal gains

$$\frac{d}{dz}\left\{\frac{2}{\pi}\arctan\left(\frac{z}{h}\right)\right\}\Bigg|_{z\to 0} = \frac{2}{\pi h}. \tag{1}$$

The small signal equivalent circuit is shown in Fig. 2, where we have introduced the closed loop transfer functions of the two feedback loops.

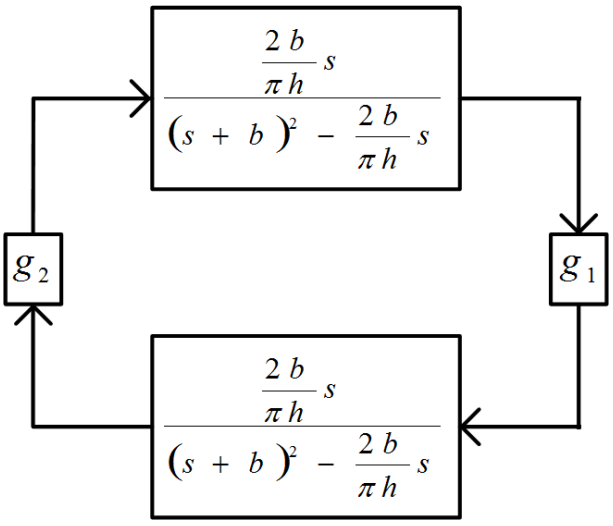

Fig. 2: Small signal (linearized) equivalent of Fig. 1.

The characteristic polynomial of the small signal system is

$$P(s) = \left[(s+b)^2 - \frac{2b}{\pi h}s\right]^2 - \left[\frac{2b}{\pi h}\right]^2 g_1 g_2 \cdot s^2. \tag{2}$$

Our tool for the study of $P(s)$ is the root locus method [11], [12], based here on the observation that $P(s)$ is of the form

$$P(s) = N^2(s) - KM^2(s), \tag{3}$$

with

$$\begin{aligned} N(s) &= (s+b)^2 - \frac{2b}{\pi h}s, \\ M(s) &= s, \\ K &= \left[\frac{2b}{\pi h}\right]^2 g_1 g_2. \end{aligned} \tag{4}$$

Substituting

$$s = \sigma + j\omega, \tag{5}$$

in Eq. (3) and denoting

$$\begin{aligned} N(s) &= A + jB, \\ M(s) &= C + jD, \end{aligned} \tag{6}$$

the roots of the characteristic equation i.e. the values of s for which $P(s) = 0$, are governed by

$$(A + jB)^2 - K(C + jD)^2 = 0. \tag{7}$$

Equating the real and imaginary parts of Eq. (7) separately to zero (noting that K is a real parameter) gives the root locus equation as:

$$[AD - BC] \cdot [AC + BD] = 0, \tag{8}$$

conveniently given here factorized into two parts. The first part, as we shall show below, corresponds to $0 < K < \infty$ (+/+), and the second to $-\infty < K < 0$ (+/−). From Eq. (4) we have, subject to Eq. (5),

$$\begin{aligned} A &= \sigma^2 - \omega^2 + 2b\left[1 - \frac{1}{\pi h}\right]\sigma + b^2, \\ B &= 2\sigma\omega + 2b\omega\left[1 - \frac{1}{\pi h}\right], \\ C &= \sigma, \\ D &= \omega. \end{aligned} \tag{9}$$

The root locus equation for the +/+ condition is $AD - BC = 0$, which is readily decomposed into two parts,

$$\omega = 0 \tag{10}$$

and

$$\sigma^2 + \omega^2 = b^2. \tag{11}$$

Equation (10) simply indicates that part of the root locus lies on the real axis. Evans' root locus sketching rules can be applied, and immediately tell us that this is the complete real axis, since there are two real poles or zeros on this axis. The root locus whose equation is

$$AD - BC = 0, \tag{12}$$

is shown in Fig. 3, for $b = 10\pi$, $h = 0.3$ which gives double "poles" (roots of $N^2(s) = 0$) at

$$s = 1.9174 \pm j31.3574. \tag{13}$$

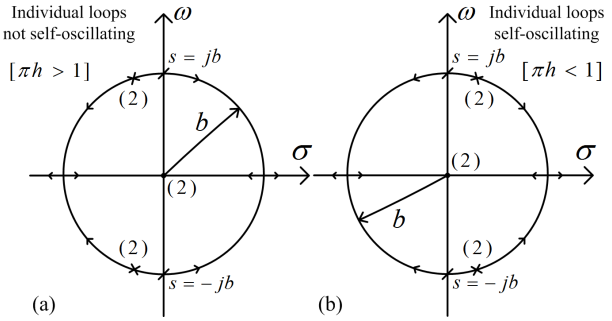

Fig. 3: (a) shows root motion for non-oscillatory system ($\pi h > 1$). As the gain is increased, the system begins to oscillate when a pair of complex conjugate roots cross the imaginary axis. The frequency of oscillation decreases with increasing gain. (b) is for a self-oscillatory system ($\pi h < 1$). As the gain increases one frequency of oscillation increases slightly then disappears as the corresponding complex pair of roots enters the left half plane. The other complex pair move to the right, with frequency decreasing.

If we had $\pi h > 1$, the "poles" would be in the left half plane, but the circle would be followed to the left as well as to the right as K is increased, and the system would be just on the point of oscillation at $s = \pm jb$, and oscillatory beyond that. The "+/−" root locus is described by

$$AC + BD = 0. \tag{14}$$

This gives

$$\omega^2 = \sigma \left[\frac{b^2}{2b\left[\frac{1}{\pi h} - 1\right] - \sigma} - \sigma \right]. \tag{15}$$

Two sketches of the corresponding root locus are shown in Fig. 4. It is noteworthy here that for $\frac{1}{\pi h} < 1$ (e.g. $h = 0.4$) the locus is confined entirely to the left half plane. This shows that oscillations cannot be induced by increasing g_1 or g_2 in the "+/−" situation: the individual loops must be in self-oscillation, as indicated by the right half plane branches in Fig. 4.

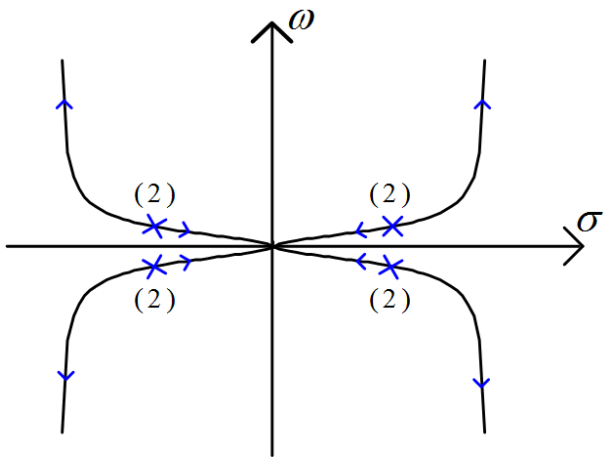

Fig. 4: Root locus sketches for individual loops self-oscillating (right half plane) and not self-oscillating (left half plane). The σ coordinate of the right half plane poles is ζb.

3. Results

Firstly, we studied the onset of oscillations in the "+/+" situation with $\pi h > 1$, taking $h = 0.4$ (individual loops not self-oscillatory). The branches now start from the "poles" shown in the left half plane in Fig. 3, and follow the circle to the right as g is increased. A simple application of the root locus calibration equation

$$|K| = \frac{|N^2(s)|}{|M^2(s)|}, \tag{16}$$

at either crossing point of the imaginary axis, $s = \pm jb$, gives the critical value of $g_1 = g_2$:

$$g_{1,2} = [\pi h - 1]. \tag{17}$$

This is illustrated in Fig. 5.

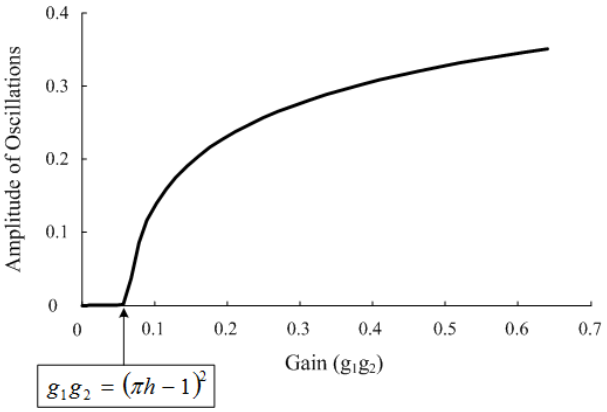

Fig. 5: Amplitude of oscillation as a function of gain ($g_1 g_2$) for a value of $h = 0.4$ (system is not self-oscillatory). The curve is derived by simulation of the system shown in Fig. 1.

The angular frequency of oscillation of y_1 as a function of g_1, derived by simulating the system in Fig. 1, also with $h = 0.4$, is plotted in Fig. 6.

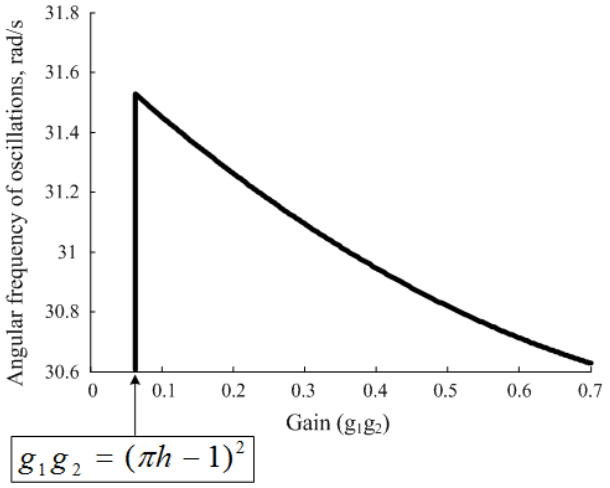

Fig. 6: The angular frequency of oscillation of $y_1$as a function of gain (g_1g_2) derived by simulating the system shown in Fig. 1 for the "+/+" case. The loops are not self-oscillatory, with $h = 0.4$.

The decrease in frequency with increase in coupling strength g_1g_2 is notable. What we show here is that such a decrease in frequency could arise from "+/+" coupling of closely coupled neurons in the basal ganglia, or indeed other centers of the brain.

We now turn to "+/−" coupling, for which the root loci, in self-oscillatory and non self-oscillatory modes, are shown in Fig. 4. These root loci are described by the equation

$$AC + BD = 0, \tag{18}$$

which leads to

$$\omega^2 + \sigma^2 = \frac{b^2\sigma}{(2b\zeta - \sigma)}, \tag{19}$$

where

$$\zeta = \frac{1}{\pi h} - 1. \tag{20}$$

One of the equations for root locus gain which follows from the prescription given earlier in Eq. (16) is

$$K = \frac{B^2}{C^2}. \tag{21}$$

This leads very readily to the expression

$$K = \frac{4\omega^2}{\sigma^2}\left[\sigma - \zeta b\right]^2, \tag{22}$$

substituting for ω from Eq. (19), setting

$$\sigma = \zeta b \pm \delta, \tag{23}$$

where δ is the deviation from the pole σ coordinates of ζb.

$$K = 4\left\{\frac{b^2}{(\zeta^2 b^2 - \delta^2)} - 1\right\}\delta^2. \tag{24}$$

The important feature here is that K is an even function of δ, i.e. values of K are evenly distributed about $\sigma = \zeta b$. The interesting feature here is that not only can frequencies less than that of tremor (our basic oscillator frequency) be generated, but also frequencies much higher. This agrees with the observations of Foffani et. al [7], [8], who have observed frequencies up to 300 Hz in the human STN.

Figure 7, corresponding to the right half plane root locus branches in Fig. 4, shows the increasing and decreasing frequencies which can be generated by varying $g_1 = -g_2$ in the "+/−" situation. The geometric mean of these two frequencies, follows fairly readily as

$$\sqrt{\omega_1\omega_2} = \sqrt{b^2\left(1 - \zeta^2\right) + \delta^2}. \tag{25}$$

Typical figures arising from coupling tremor band oscillations are $b = 10\pi$, $\zeta = \left[\frac{1}{\pi h} - 1\right] = 0.061$ and δ going from 0 to ± 1.197. Thus, the geometric mean of ω_1 and ω_2 is almost constant, at a value very close to b. This feature has been noted by colleagues in a more complex model based on the actual layout of the basal ganglia [13] . It is fascinating to see it emerge here also, in our much simpler phenomenological model of LFPs, observed in the neighborhood of oscillating neurons, without explicit reference to their anatomical arrangement.

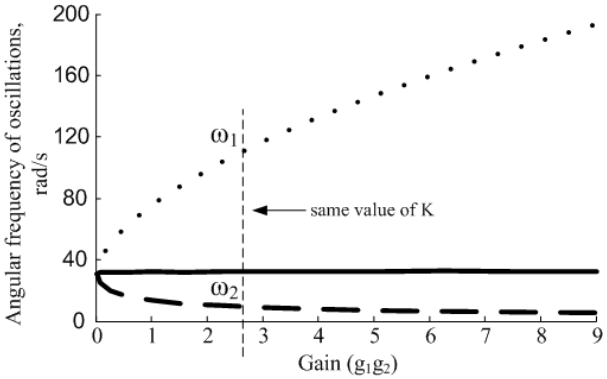

Fig. 7: The angular frequencies of oscillation of $y_1$as a function of gain (g_1g_2) derived by simulating the system shown in Fig. 1, for the "+/−" case, with $h = 0.3$ (system self-oscillatory). The geometric mean of the two frequencies, which remains almost constant, is also included.

4. Discussion

In this paper we have followed an observation made in [9] that "neurons exhibiting oscillatory activity at tremor frequency (typically 4–6 Hz) are located in the

dorsal region of the STN, where neurons with beta activity (typically 15–30 Hz) are observed." This suggested to us that a study of interactions of our basic oscillator which has proved of great value in matching DBS results from [5] and [6], might throw light on the variety of frequencies observed in the basal ganglia of Parkinsonian patients. We have found that "+/+" coupling can generate all frequencies below tremor. The higher frequency bands most often observed in Parkinson's disease are beta (15–30 Hz) and gamma (35–80 Hz), but frequencies up to 300 Hz have been observed [7], [8]. The beta band oscillations are implicated in the seizure of gait, whereas the gamma band oscillations are considered pro-kinetic. However, we have shown that gamma and other higher frequencies, can be generated by "+/−" coupling of neurons tuned to much lower frequencies, illustrated here by a typical tremor frequency, 5 Hz ($=10\pi$ rad·s^{-1}). It seems possible that "+/−" coupling of neurons tuned to tremor (or other) frequencies could generate the whole gamut of frequencies observed in disease states correlated with pathological oscillations in the basal ganglia and other centers.

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Madeleine LOWERY is an Associate Professor in the School of Electrical, Electronic and Communications Engineering, University College Dublin. Her research involves the exploration of nerve and muscle activity through mathematical modelling, analysis, and experimentation, to increase understanding of neu-romuscular activity in healthy and diseased states and develop novel and improved rehabilitation strategies. Her research interests include electromyography, myoelectric prosthetic control, bioelectromagnetics, electrical stimulation, deep brain stimulation and neural control of movement. She received the B.E. and Ph.D. degrees from the Department of Electronic and Electrical Engineering, University College Dublin, Dublin, Ireland, in 1996 and 2000, respectively. Between 2000 and 2005, she was a Postdoctoral Fellow then Research Assistant Professor at the Rehabilitation Institute of Chicago and the Department of Physical Medicine and Rehabilitation, Northwestern University.