SOME THOUGHTS ON ELECTRICAL INTERVENTIONS FOR THE CONTROL OF TREMOR IN PARKINSON'S DISEASE

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Summary Ideas from control theory – state variable feedback, dither injection, the equivalent nonlinearity and the describing function-are applied to models developed to help understand the mechanisms of electrical interventions such as deep brain stimulation (DBS) for the alleviation of Parkinsonian tremor.

1. INTRODUCTION

Pathological synchronisation of neuronal firing in the basal ganglia area of the brain plays a critical role in the emergence of limb tremor in Parkinson's disease. Electrical intervention for suppression of such tremor, which is typically in the 4-6Hz band, was pioneered by Benabid[1], through deep brain stimulation (DBS) by implantable electrodes applying zero-mean voltage pulses, often square waves, at a much higher frequency, typically greater than 100Hz. The phenomenon of suppression of troublesome low frequency oscillations in nonlinear feedback control loops by injection of an auxiliary high frequency "dither" signal has been known since the 1940s, and its explanation in terms of the concept of equivalent nonlinearity [Elgerd, 2] was developed into a powerful general tool by Power and Simpson[3,4]. (It should be mentioned that Power is the accepted English language equivalent of the Irish language surname de Paor, and the Power in question is one of the authors of this paper). One of the contributions of the present paper is to show how the concept of the equivalent nonlinearity, married to another idea from nonlinear control theory – the describing function(DF) – can throw light on tremor suppression within the framework of a model proposed by Haeri et al[5]

We first illustrate, however, another approach to tremor suppression developed by Rosenblum and Pikovsky[6], based on the idea of feedback of the mean field developed by a globally coupled ensemble of neuronal oscillations. This has not yet been applied clinically, but if it could be it holds the promise that after suppression the feedback signal tends towards zero and could therefore have advantages in cases where continuous stimulation eventually loses its efficacy due to adaptation of the brain. In [6] the theoretical treatment is based on a mean field evolution differential equation given in complex number terms. We reformulate this here as two coupled nonlinear ordinary differential equations, which we analyse in polar co-ordinates. These co-ordinates show the inherent dynamics very simply and beautifully, and illustrate in a very direct way the effect of state variable feedback in quenching the mean field oscillation. We also illustrate- for it falls very naturally within the same framework – a possible way to incorporate dither injection into these equations, as an introduction to the more general treatment in connection with the model of Haeri et al.[5].

A third approach to tremor suppression has been suggested by Tass[7]. This is based on an idea inverse to cardiac defibrillation. In the heart there are neuronal oscillators intended to fire in synchronism, but capable of being thrown into the chaotic mode of fibrillation by an electrical accident, i.e. an extraneous pulse at some vulnerable instant from an abnormally firing cell or "ectopic focus". In Parkinson's disease we have a population of neurons firing in synchronisation, but pathologically so. If an extraneous pulse were injected into such a population it is possible that it could throw it out of synchronisation into uncoordinated fibrillation. The great advantage of such an idea is that it would give demand-controlled stimulation, active for instants only when the onset of tremor, or its electrical concomitant in the brain, is detected. This approach is not pursued here, but we hope to illustrate it in the future by developing ideas presented by de Paor [8].

2. ANALYSIS OF THE ROSENBLUM-PIKOVSY APPROACH

The mean field evolution equation to describe dynamics associated with synchronization in a population of globally coupled neuronal oscillators is presented in Eqns (7) and (8) of [6], and is based on ideas developed by Kuramoto [9] and Crawford [10]. We reformulate this equation, given originally as one in complex numbers, in terms of two real state variables x and y, and generalize it by allowing for state variable feedback and a possible avenue for dither injection. With $r = (x^2 + y^2)^{\frac{1}{2}}$ we have:

$$\frac{dx}{dt} = (a-d)x-(b+e)y-c(r+f(t))^2 x$$
$$\frac{dy}{dt} = (b+e)x+(a-d)y-c(r+f(t))^2 y$$
(1)

We have discovered that the dynamics become very transparent when analysed in terms of polar coordinates r and θ, where:

$$x = r\cos\theta$$
$$y = r\sin\theta \qquad (2)$$

Eqns (1) and (2) lead to:

$$\frac{dr}{dt} = r\left[a - d - c(r + f(t))^2\right]$$
$$\frac{d\theta}{dt} = b + e \qquad (3)$$

In equation (3), the case d=e=f(t)=0, a,b,c>0, gives the intrinsic mean field evolution equations. In this case it is clear that the trajectory in the (x,y) plane rotates at b radians per second anticlockwise, while its radius evolves according to $dr/dt=r[a-cr^2]$. For $0<r<\sqrt{(a/c)}$, we have dr/dt>0; for $r>\sqrt{(a/c)}$, we have dr/dt<0; and for $r=\sqrt{(a/c)}$, dr/dt=0. Thus the trajectory settles into a circular limit cycle of radius $\sqrt{(a/c)}$, traversed anticlockwise at b radians per second. The state variables execute simple harmonic motion with period $T=2\pi/b$. This is the period of the observed tremor. The inherent dynamics are illustrated in Fig.1.

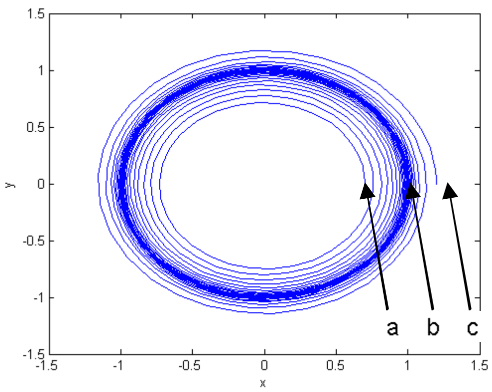

Fig 1. Initial conditions for trajectory. (a)(x,y)=(0.7,0), (b)(x,y)=(1,0), (c) (x,y)=(1.2,0)

With state variable feedback –dx-ey added to the dx/dt equation and ex-dy to the dy/dt equation, with d>0 and e≥0, the period changes to $T=2\pi/(b+e)$ while the equation for the evolution of r becomes $dr/dt=r[a-d-cr^2]$. This immediately shows that for d≥a the oscillation is quenched and r=0 becomes a stable equilibrium value.

To illustrate the effect of dither injection we consider d=e=0 and let f(t) be a zero mean high frequency dither signal where "high" is relative to the inherent frequency of the system. The equation for evolution of r now becomes:

$$\frac{dr}{dt} = r\left[a - cr^2 - 2crf(t) - cf^2(t)\right] \qquad (4)$$

If the frequency of f(t) is sufficiently high, it and the zero mean components of $f^2(t)$ are effectively filtered out. Denoting the mean value of $f^2(t)$ by k, the effective equation for evolution of r becomes:

$$\frac{dr}{dt} = r\left[a - ck - cr^2\right] \qquad (5)$$

It is seen that, provided ck>a, r=0 becomes a stable equilibrium and the oscillation is quenched. This is illustrated in Fig.2. The crossings of the trajectory seen here are not unexpected, as the system is no longer autonomous.

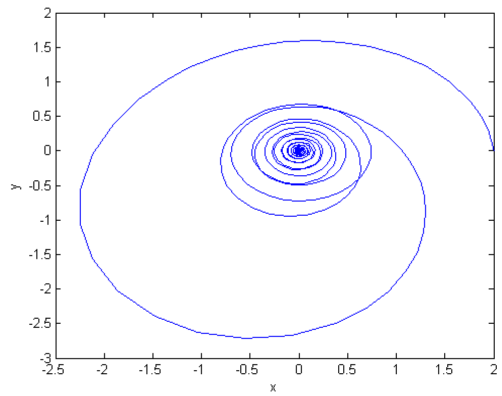

Fig 2. Effect of dither on the trajectory

3. ANALYSIS OF THE MODEL OF HAERI ET AL.

The only physiologically based model of Parkinsonian tremor with which the authors are familiar is that of Haeri et al. [5]. This considers the interactions between various parts of the basal ganglia area of the brain. There are two feedback loops involved, one comprising the substantia nigra pars compacta and the striatum, the other the globus pallidus externus and the subthalamic nucleus. Our familiarity with control theory tells us immediately that the oscillation arises in the first mentioned loop. This is shown in Fig.3(a),where in [5] f(t)=0. Haeri et al. [5] assume that DBS decreases certain gains, g, in the system.

We illustrate what would happen if the DBS signal f(t) acts at the input to the "ideal relay" or "bang-bang" element in the feedback loop.

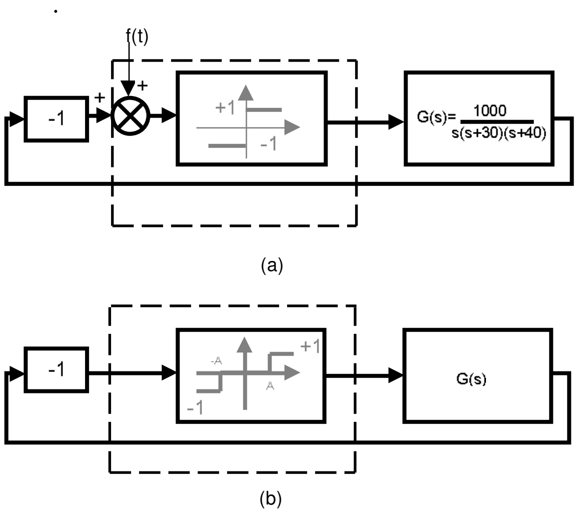

Fig 3. (a)Injection of dither into original non-linear element,(b)dither source and original ideal relay replaced by the equivalent non-linearity relay with dead-zone.

Using elementary theory expounded by Power and Simpson[4], the combination of bang-bang element and dither signal, taken to be a symmetrical zero-mean square wave of amplitude A, is replaced by the equivalent nonlinearity shown in Fig.3(b)- an ideal relay with a deadzone extending from –A to +A. We initially assume the loop to be in a state of oscillation with positive and negative pulses, interspersed with zero values, appearing at the output of the equivalent nonlinearity. The G(s) block is a lowpass filter and the oscillation observed at its output is essentially sinusoidal. Subject to this, the equivalent nonlinearity may be represented by its describing function (DF), which is the effective gain relating its sinusoidal input of amplitude E to the fundamental component of its output. As given for example by Phillips and Harbor [11]:

$$DF = 0 \qquad , E \le A$$

$$= \frac{4}{\pi E}\sqrt{1-\left(\frac{A}{E}\right)^2} \qquad , E \ge A$$

(6)

The essential feature of this is that it has a peak value 2/(πA) at A√2. A graph is given in fig.4. in the (E/A,DF.A) plane. The condition for oscillation is:

$$G(j\omega) = -\frac{1}{DF}$$

(7)

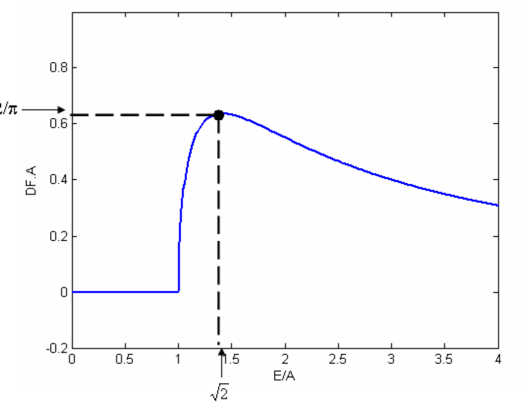

Fig 4 The describing function

This is illustrated graphically in Fig.5, for A<1/(42π). For E<A, -1/DF is out at -∞, on the negative real axis. As E increases above A, -1/DF comes in along that axis, reaches a turning point of -Aπ/2 for E = A√2, and then goes out to -∞ again. As shown, there are two intersections with the G(jω) locus, both at the point (-1/84,0) and both corresponding to ω=√1200.

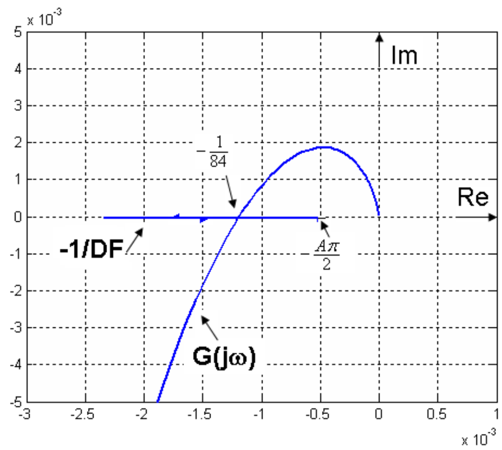

Fig 5.Intersection of loci of -1/DF and G(jw)

Application of the Nyquist criterion [3] shows that only the higher value of E represents a stable oscillation-the tremor observed at ω=√1200, i.e. frequency 5.51Hz. We see immediately that as the dither amplitude A is increased, intersection of the loci ceases to be possible for (Aπ/2)>1/84, i.e. for:

$$A > \frac{1}{42\pi}$$

(8)

Equation (8) defines the range of dither amplitudes for which the tremor is quenched.

4. DISCUSSION

The approaches of Rosenblum and Pikovsky [6] and Haeri et al. [5] have been analysed using approaches suggested by control theory. It has been shown how state variable feedback (but without the delay considered in [6]) can quench the tremor and how dither injection could work if it could be incorporated in the manner shown. The model of Haeri et al. [5] has been subjected to analysis using the concepts of equivalent nonlinearity and describing function. It is hoped that our analysis will help throw light on possible mechanisms for electrical intervention for the relief of Parkinsonian tremor, mechanisms which, as indicated by Benabid [1], "are still to be deciphered". Benabid, however, suggests that jamming of a feedback loop is probably involved, and that is exactly what is done by square wave dither introducing a sufficiently wide deadzone in the equivalent nonlinearity.

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