

Mathematical Modelling of Parkinsonian Tremor

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Abstract

Parkinson's disease is a complex disorder for which there is no known cure. Nor do we understand fully the origin of one of the disease's cardinal symptoms: tremor. A non-traditional approach to research in Parkinson's disease and in Parkinsonian tremor involves the application of mathematical models. The purpose of this article is to review briefly the contributions of mathematical models to the study of Parkinsonian tremor. There is little evidence that modelling attempts have built on previous ones but there has been a trend to move the focus of modelling from the periphery to the brain, and from abstracted to more physiologically detailed views. We hope that this review will encourage more mathematical modelling in the study of Parkinson's disease and Parkinsonian tremor.

1 Introduction

Tremor in Parkinson's disease¹ is perhaps its most recognizable symptom. In his Essay on the Shaking Palsy of 1817, James Parkinson (1755-1824) described it as,

“Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported;”

Since this tremor occurs in *parts not in action*, that is, in a resting position, Parkinsonian tremor is also thought of as a resting or rest tremor. It is a slow tremor with a typical frequency of 4-6 Hz,² often appearing first in one of the hands or feet, and can be of such a great amplitude as to be quite disabling.

¹Parkinson's disease is a slowly progressive neurodegenerative illness that is associated with a lack of the chemical (neurotransmitter) dopamine in the brain. The symptoms of Parkinson's disease can include: tremor, stiffness (rigidity), slowness of movement (bradykinesia) and difficulty with balance (postural instability).

²The frequency of normal (physiological) tremor is in the range of 8-12 Hz. In a healthy person, the amplitude of the tremor is usually so small that it is barely noticeable (“What?! I don't have a tremor!”).

There is still a lot that we do not understand about Parkinsonian tremor. One fundamental unanswered question is: Where does tremor in Parkinson's disease originate? Two main classes of explanation have emerged early in the study of this question: those involving *central mechanisms* and those involving *peripheral feedback mechanisms*. In the central mechanism theory, it is thought that the oscillations originate in the central nervous system, that is, somewhere in the motor control centres of the brain, such as in the thalamus (Semba et al. 1980; Hirai et al. 1983) or (a more recent hypothesis) in the basal ganglia (Llinas 1984; Plenz and Kital 1999) (Figure 1), and that these abnormal signals are transmitted to the muscles in the extremities which would then result in Parkinsonian tremor. In the peripheral feedback hypothesis, the circuitry of the muscle stretch reflex which would normally act to dampen muscle oscillations somehow becomes unstable³ and leads to Parkinsonian tremor. The instability in the peripheral mechanism could arise, for example, by nonrhythmic inputs above the level of the spinal cord. Parkinsonian tremor could also result from a combination of the two mechanisms (Hua et al. 1998), but the question of the origin of Parkinsonian tremor remains unanswered (Elble 1996; Rodriguez et al. 1998).

This article reviews the contribution of mathematical modelling techniques that complement the traditional neurophysiological approach to research in Parkinsonian tremor and in its control. In particular, we draw your attention to parameter dependence and qualitative behaviour of the mathematical models. The models that we describe here have a common goal: to identify and to examine the effect of parameters that control starting, modulating or stopping of oscillations associated with tremor in Parkinson's disease. Introductions to the mathematical concepts and techniques used in these models, namely those of nonlinear dynamics, can be found in texts such as Thompson and Stewart (1986), Strogatz (1994), Kaplan and Glass (1995), and Beuter et al. (2003). We begin in Section 2 by outlining aspects

³Kandel et al. (2000) describe the stretch reflex loop as a negative feedback loop, in which the regulated variable is muscle length: "Two crucial determinants of the behavior of a feedback system are its *gain* and its *loop delay*. The *gain* of a feedback system refers to its strength or effectiveness. The larger the gain of the stretch reflex, the greater will be the muscle force that results from an imposed change in length. ... The *loop delay* in a feedback system is the time between a disturbance and the compensatory response. For the stretch reflex, the total loop delay is the sum of the sensory and motor conduction times, synaptic delays, and the time required for excitation-contraction coupling. ... When feedback gain is high and a delay is present in the loop, a disturbance may lead to oscillations of the regulated variable."

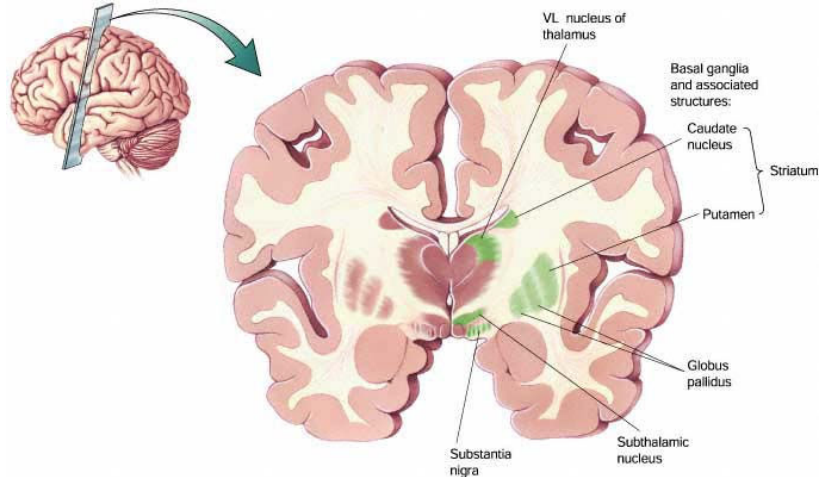


Figure 1: *The main function of the basal ganglia is to initiate and stop movements. The basal ganglia comprise the caudate nucleus and putamen (together called the striatum) and globus pallidus (GP). These telencephalic nuclei function in collaboration with several thalamic nuclei, the substantia nigra (SN) and the subthalamic nucleus (STN). From Bear, Paradiso, and Connors (2002), Fig. 14.11, with permission. Copyright 2002, Lippincott Williams & Wilkins.*

of mathematical modelling in physiology. In Section 3, we present an overview of some mathematical models of tremor in Parkinson’s disease, and then in Section 4, we describe some models put forth to help understand the control of tremor by a surgical technique known as deep brain stimulation. In Section 5, we summarize the differences and the compatibilities of the modelling attempts.

2 A Mathematical Perspective in Physiological Problems

Mathematical methods are very common in engineering and physics, but not so common in neuroscience and physiology. However, the trend is shifting. The application of mathematical techniques, especially those in dynamics,⁴ to physiological problems is rising in popularity. Mathematical modelling is an integral part of this trend. A model is like a mathematical caricature of the physical (or, here, physiological) problem that one is studying. For interesting discussions on the meaning and process of mathematical modelling, see,

⁴The subject of dynamics as described by Strogatz (1994): “This is the subject that deals with change, with systems that evolve in time. Whether the system in question settles down to equilibrium, keeps repeating in cycles, or does something more complicated, it is dynamics that we use to analyze the behavior.”

for example, Aris (1978) or Casti (1989). We use the term ‘mathematical model’ to describe a set (system) of equations that mimic some aspect of the physiological system, with the number of variables equal to the number of equations in the system. The system of equations can also involve one or many parameters, and by investigating the parameter dependence of the system, one hopes to gain insight into the behaviour of the physiological system it models.

Classification of tremor models may be done in terms of scale of description (macroscopic *vs.* microscopic), scope (global view of entire motor control system *vs.* local view of a small part of it), or level of abstraction (physiological detail *vs.* generic processes). For example, at a coarse level, a variable might reflect overall activity of an anatomical structure in the brain, or the entire sensorimotor feedback system might be modelled by a single equation, while at a microscopic level equations for the membrane potentials of individual neurons might be described in terms of the activity of voltage-gated ion channels. Hoppensteadt and Izhikevich (1997) classify mathematical models used in the neurosciences as *ordinary language models*, *comprehensive models*, *empirical models*, or *canonical models*, the second and third types reflecting the main axis described above: “*Comprehensive Models* are the result of an attempt to take into account all known neurophysiological facts and data. Usually they are cumbersome and are not easily amenable to mathematical analysis ... *Empirical Models*, or caricature models, occur when one tries to construct a model reflecting one or more important neurophysiological observations, often without regard to other neurophysiological facts” However, the criticisms of each extreme can be overstated. On the one hand, detailed models may still be probed by numerical experimentation, and on the other hand, more abstract models can truly capture the essence of a complex process. It can be particularly effective to combine the approaches, by working with both a detailed model and a simplified version of it, especially if it can be shown that behaviour of one is close in some sense to behaviour of the other, but modelling of Parkinsonian tremor has not yet reached this level of sophistication.

In describing the mathematical models of the next two sections, we will attempt only

a general classification of the mathematical models with respect to their level of detail or abstraction. Furthermore, we will discuss key features of the models in terms of: *Description*: What is the level of description of the model? Is it linear or nonlinear? How many equations are in the model? What parameters are in the model?; *Motivation*: What was the motivation for this type of model? Was the model suggested by experimental data? What was the hypothesis to test?; *Analysis*: How was the model analyzed? Were only computer simulations used, or was there an attempt to examine its behaviour analytically? How were appropriate values for parameters chosen?; *Comparison*: How was the model compared to the physical system that it is supposed to characterize? Were there comparisons to experimental data?; *Insight*: What insight is gained by the model? Does the model suggest new experiments? Does the model predict new theories that can be tested by experiment? We have chosen to present a sample of mathematical models of Parkinsonian tremor in more-or-less chronological order of appearance, which shows a general shift in perspective from modelling tremor peripherally to modelling oscillations in the brain. Some of these were discussed in an earlier review paper (Beuter and de Geoffroy 1995).

3 Mathematical Models of Parkinsonian Tremor

In the 1960s, two articles appeared (Austin and Tsai, 1962; Austin et al., 1965) describing a model of Parkinsonian tremor based on the van der Pol oscillator.⁵ The van der Pol equation is of the form

$$\ddot{x} + \alpha(x^2 - 1)\dot{x} + x = 0, \quad (1)$$

where $\alpha \geq 0$ is a constant, and $(\dot{})$ indicates differentiation with respect to time t . This equation is second-order, nonlinear, and depends on one parameter, α . Self-sustained oscillations can arise in the van der Pol oscillator due to its pattern of positive and negative damping (“negative damping” for $|x| < 1$, in which energy is generated at low amplitude; and “positive damping” for $|x| > 1$, in which energy is dissipated at high amplitude).

⁵The original application of this oscillator was as a model of a particular type of electric circuit (van der Pol 1927).

Austin and Tsai (1962) were intrigued by anecdotal evidence from their patients: “In the course of our investigation of Parkinsonian tremor we became impressed with the fact that much of the tremor mechanism was being expressed in the patient’s own history. The majority of patients with Parkinsonian tremor describe that their tremor seems to increase with the amount of emotional excitation.”

Austin et al. (1962, 1965) explored the effects of emotion and fatigue on tremor in Parkinson’s disease with a simple model based on van der Pol’s equation. Theirs is an abstracted model whose main idea is that tremor in Parkinson’s disease results from a change in central input to a peripheral oscillator. They postulate a relationship “between spinal interneurons and motoneurons, with an approximately linear feedback from muscle receptors and the nonlinear feedback going through the brainstem”, assuming that synchronously firing neuronal pools act as integrators (Figure 2). They considered solutions of the van der Pol equation in the limit of weak nonlinearity, that is, when the parameter α is sufficiently small. The small parameter α (their parameter K) measured the degree of “emotional excitation:”

$$\alpha = K \equiv \frac{F}{I} - 1,$$

where F and I represent facilitation (excitation) and inhibition, respectively, in *suprasegmental levels*, i.e., above the spinal cord. They presume that “the downstream paths of excitation are relatively excessive in Parkinsonian tremor,” which would increase the ratio of excitation to inhibition, and hence, would increase the parameter controlling the oscillations.

In the limit of small α , the nonlinearity in Equation (1) acts as a small perturbation to the (linear) harmonic oscillator $\ddot{x} + x = 0$. Using approximation techniques (Kryloff and Bogoliuboff 1943), Austin et al. (1965) obtain an approximate solution to $x(t)$, correct to first order in α . The first-order solution, when α is small, is almost sinusoidal with a slowly varying amplitude and nearly constant phase. They compute solutions for three values of the parameter α : {0.025, 0.05, 0.1}. They compare to electromyographic recordings of tremor under the effect of adrenalin (to simulate emotional excitement) and sodium amytal (to

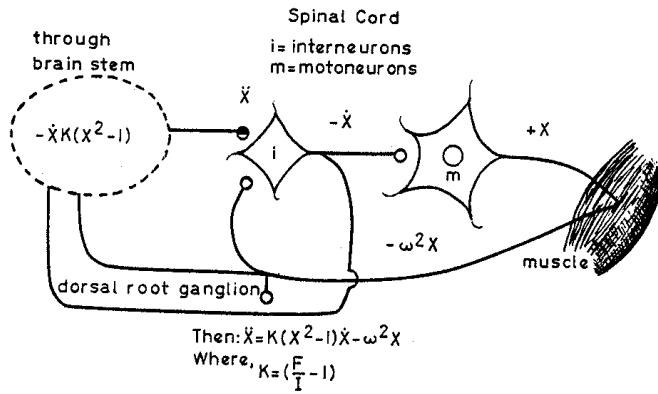


Figure 2: *Austin and Tsai model of tremor mechanism; where i = pool of synchronously firing interneurons; m = pool of synchronously firing motoneurons; X is proportional to the number of synchronously firing motoneurons in a nucleus producing the tremor; $(1 - X^2)$ = oscillatory electrical activity from brain coming downstream, and modulated by $K = (F/I - 1)$. From Austin et al. (1965), Fig. 3, Page 394, with permission. Copyright 1965, S. Karger AG, Basel.*

simulate fatigue) and claim that “both mathematical and analog computer solutions of this model equation result in changes in amplitude similar to the original growth curves derived from experiment.”

In their discussion (Austin and Tsai 1962), they describe the implications of their modelling study in terms of possible surgeries that could be attempted to reduce the downstream excitation (analogous to the increase in the parameter α): “Parkinsonian tremor is based on an abnormal ratio of suprasegmental facilitation to inhibition, acting downstream on cranial nuclei and spinal interneurons. The abnormal excitatory ratio is due to the predominant destruction of inhibitory regions of the brain by the disease process. This suggests that any surgical procedure which destroys downstream facilitatory paths may decrease the tremor by creating a more balanced level of excitation acting on cranial nerve nuclei and spinal interneurons.” It is interesting to note that their suggestion of a surgical procedure that destroys downstream facilitatory paths appeared some twenty years before the surgical technique of deep brain stimulation was suggested as a treatment for Parkinsonian tremor and the *hypothesis*⁶ that its therapeutic effect is due to inhibition of pathological excitation

⁶The mechanism of deep brain stimulation remains unknown, and one hypothesis is that it acts via

in Parkinson’s disease (see Section 4 for further discussion of tremor control by deep brain stimulation).

In the early 1970s, Gurfinkel and Osovets (1972, 1973) examined the hypothesis of Parkinsonian tremor arising from instabilities in the control of upright stance in the body considered as an inverted pendulum (Gurfinkel and Osovets 1972). To describe the vertical position of the body, “a two-link model was investigated consisting of the foot and knee as an inverted pendulum held by the gastrocnemius muscle” (Figure 3), which they later extended to “other links of the body” (Gurfinkel and Osovets 1973). They wondered if pathological tremor results from passing into a parametric resonance regime from a region of stability upon changing a parameter that represents the magnitude of a periodic change in muscle strength at the frequency of physiological tremor (see ‘amplification coefficient’ below). This is a peripheral mechanism model of tremor, focusing on balance control by muscles.

The idea of a resonance process in their model came from two of their observations in tremor oscillograms (1973, p. 784–785): (1) An *abrupt* change (reduction) in amplitude in the transition between Parkinsonian and physiological tremor, and (2) no higher harmonic components in Parkinsonian tremor, also noting that “the frequency of the Parkinson tremor is almost exactly half the frequency of the physiological tremor (8–12 c/s [cycles/second = Hz]) makes the process similar to that which in the theory of oscillations is called ‘parametric resonance’⁷.”

To study their hypothesis, they analyzed a system that could be expressed by the Mathieu differential equation,⁸ which is of the form

$$\ddot{x} + (a - 2b \cos 2t)x = 0,$$

where $(\dot{})$ represents differentiation with respect to t , and a and b are arbitrary constants.

inhibition (see Section 4 for further discussion of tremor control by deep brain stimulation).

⁷Parametric excitation refers to a situation where a system responds to a variation in one of its parameters, rather than being excited by a direct input. If the parametric variation that drives the behaviour is oscillatory, it may occur that the system variable oscillates at half the driving frequency; this is known as parametric resonance.

⁸The French mathematician Émile Mathieu first studied this equation in 1868 when exploring vibrations of an elliptical membrane [ref: 1947, McLachlan NW, Theory and Application of Mathieu Functions].

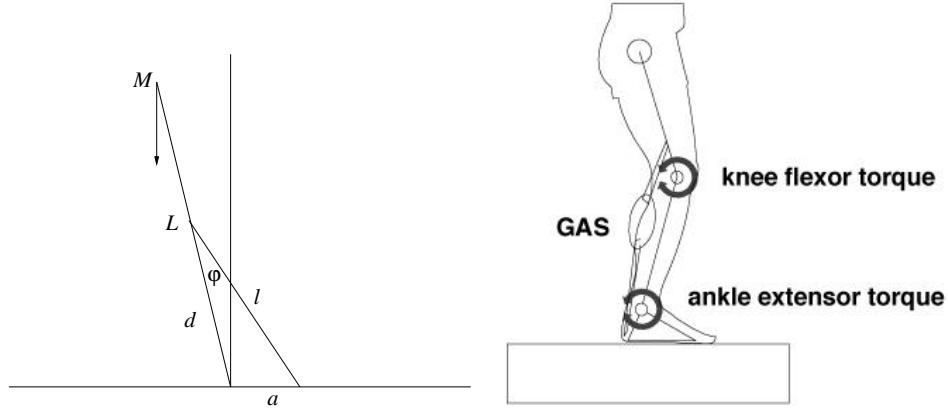


Figure 3: (a) *The vertical position of the body in the form of an inverted pendulum. From Gurfinkel and Osovets (1972), Fig. 1, with permission.* (b) *The biarticular gastrocnemius muscle generates a flexor torque at the knee and an extensor torque at the ankle. Adapted from Zajac (1993), Fig. 2B, with permission.*

This type of equation, in which the term $(b \cos 2t)$ acts as an energy source to the system, i.e., an oscillatory input from spinal motoneurons, is an example of “parametric excitation.” Here, $x = \Delta\phi$ is the (small) angle of deviation from equilibrium of the centre of inertia of the link considered (see Figure 3a), and the parameters a and b involve quantities related to muscle length, natural frequency, etc.

For the two parameters a and b in Mathieu’s equation, there is a transition curve separating unstable and stable solutions. Gurfinkel and Osovets (1973) look for solutions that correspond to stability boundaries (that is, they speak of periodic solutions of the Mathieu equation). They also look for secondary solutions with the fundamental half-frequency, since according to them, Parkinsonian tremor is at half the frequency of physiological tremor. When b is too small, they found that “the system is simply inverted – the pendulum turns over (the subject falls), the raised arm drops, etc” (1973, p. 787). They express the transition from physiological to Parkinsonian tremor in terms of an ‘amplification coefficient’: “for the tremor of the forearm at the elbow joint, the transition to the regime of the parametric resonance occurs when the amplification coefficient becomes about three times greater than is necessary for maintaining the stable vertical position of this link” (1973, p. 789).

Since the time of Gurfinkel and Osovets’ model, the data on Parkinsonian tremor and

on its characteristics when suppressed by surgeries (such as deep brain stimulation, see Section 4) throw into question the observations that inspired their hypothesis. Firstly, Parkinsonian tremor data do show higher harmonic components in addition to the main frequency (at around 4–6 Hz) (Scholz and Bacher 1995). Secondly, the characteristic frequency of Parkinsonian tremor “removed” by a successful stereotaxic operation, like deep brain stimulation, may increase but not double (Beuter et al. 2001), or in the case of thalamotomy, physiological as well as Parkinsonian tremor may be eliminated (Duval et al. 2000). Nevertheless, this was one of the first attempts to make a connection between time series data from patients with tremor and the variation of a parameter controlling the stability and nature of the oscillations in a system.

Fukumoto et al. (1985, 1986) attempt to combine in one model the two mechanisms thought to produce Parkinsonian tremor, the ‘central oscillator’ and the ‘peripheral feedback’ mechanisms. To this end, they proposed that “Parkinsonian tremor should be caused from the fatigue of intrafusal muscle fiber,”⁹ and that the fatigue arises from “incessant stimulation by gamma neurons,¹⁰ which are free from [the central nervous system’s] control in Parkinsonian patients.”

The hypothesis of muscle fatigue came from several observations (1985, p. 367): “(A) Firing rate of muscle spindle is reduced after muscle contraction in Parkinsonian patients; (B) Long term physical loading to normal subjects causes a Parkinsonian-like tremor; (C) Parkinsonian patients can suppress the tremor by attention.”

They examined the effect of varying a parameter, analogous to modulating the threshold of the muscle spindle, in an autoregression model¹¹ that they developed from measurements of Parkinsonian tremor.

Using dimensional analysis on acceleration recordings of Parkinsonian tremor, Fukumoto

⁹Intrafusal muscle fiber: one of the contractile muscle fibres found within the muscle spindle (“fusiform-shaped”).

¹⁰Gamma neurons: lower motoneurons responsible for innervating intrafusal muscle fibres of neuromuscular spindles.

¹¹An autoregression model is a type of time series model with linear dynamics in which optimal parameters are chosen, using the autocorrelation function, to minimize the prediction error for a given time series. The time series at a given time is estimated by a linear weighted sum of values of the time series at previous times.

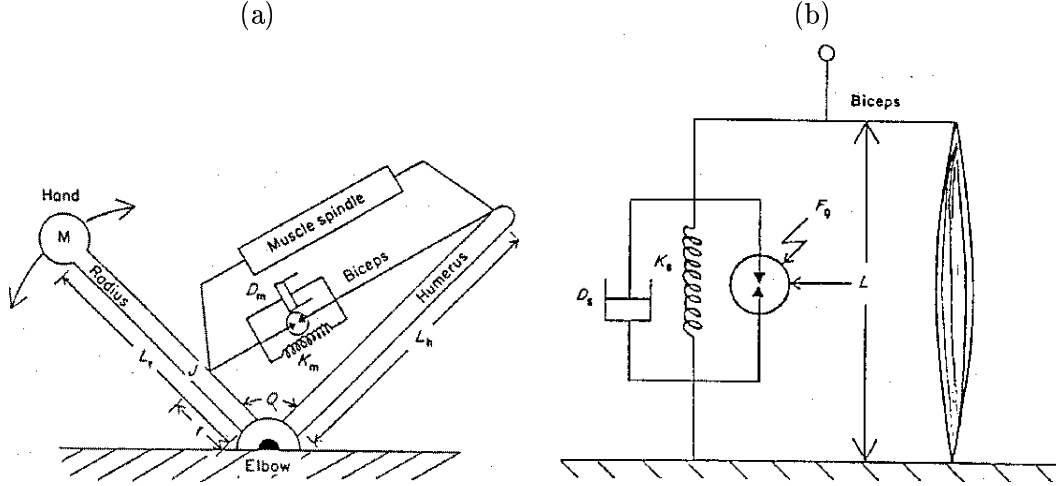


Figure 4: Fukumoto oscillation model of (a) the forearm and (b) the muscle spindle. From Fukumoto (1986), Figs. 6 and 7, page 51, Copyright 1986, with permission from The Institute of Physics and Engineering in Medicine.

et al. concluded that eight independent variables were sufficient to describe the tremor. They proposed a model of the oscillations of the forearm (Figure 4) which Fukumoto describes further in a subsequent paper (Fukumoto 1986). The linear equation governing the deviation, θ , from its initial value of the angle Q between the humerus and the radius (see Figure 4a) of the form

$$\ddot{\theta} + a\dot{\theta} + b\theta = F(t; \alpha),$$

where a and b are constant coefficients that depend on peripheral quantities. The forcing term $F(t; \alpha)$ represents a (time-dependent) torque applied to the forearm, which depends on a parameter α related to the stimulating effect of gamma neurons on the contracting force (the F_g in Figure 4b) of intrafusal muscle fibres. The remaining equations (also linear) in their model, not included here for the sake of brevity, express the relations between lengths and angles in the forearm model.

Computer simulations of the model show that reducing the intrafusal muscle force (by decreasing the parameter F_g in the model below a critical value) results in a frequency of oscillation in the range of Parkinsonian tremor. For higher values of this parameter, the main frequency of oscillation is in the range of physiological tremor. The model is limited in

that it attempts to describe Parkinsonian tremor by linear equations, when there is evidence that it is inherently nonlinear (Timmer et al. 1993; Timmer et al. 2000). As well, their model attributes tremor to a predominantly peripheral mechanism and does not account for oscillations at tremor frequency in various brain structures.

Fukumoto defends the model despite its limitations:

“Our model cannot explain all the mechanisms of tremor, but it is interesting that such a simple model can explain two wholly different types of tremor with only one changing parameter; this may explain the instability of Parkinsonian tremor.” (1986, p. 54)

Beuter and Vasilakos (1995) describe Parkinson’s disease in the context of a dynamical disease.¹² They observed fluctuations occurring over seconds or minutes in tremor recordings from subjects with Parkinson’s disease. These short-term fluctuations “are felt to be mainly due to the disease itself, while the other two (medium and long term) are believed to be caused by the treatment” (1995, p. 36). In keeping with the idea of Parkinson’s disease as a dynamical disease, they present the hypothesis that “changes in tremor correspond to changes in some critical parameter(s) in the equations governing the system” and that “these changes may be associated with changes in other physiological systems” (1995, p. 36). These short-term fluctuations suggested a pattern “produced by the beat phenomenon that occurs when two independent oscillations appear with frequencies in close proximity” (1995, p. 37). Also, they explored the role of mechanical disturbances, such as heart beat and breathing, on the modulation of tremor amplitude. Their mathematical model involved a linear combination of two nonlinear coupled oscillators representing the contribution of central (x_1) and peripheral (x_2) control loops to finger position, p . The equation for the finger position is of the form

$$p = ax_1 + bx_2,$$

where the constants a and b are the relative weights and $\{x_1, x_2\}$ are the intended finger

¹²From Mackey and Glass (1979): “by *dynamical disease* we mean a disease that occurs in an intact physiological control system operating in a range of control parameters that leads to abnormal dynamics and human pathology.”

positions of each loop. Each x_i satisfies a nonlinear differential equation modelling negative feedback of the form

$$\dot{x} = -S(\alpha, P_\tau, x_\tau) - x.$$

Here, S is a nonlinear negative feedback term depending on a parameter α , which determines the degree to which each loop is controlled by its own activity, via $x_\tau = x(t - \tau)$, or by the finger position, via $P_\tau = P(t - \tau)$, and τ represents the time delays of transmission for each loop. The coupling of the equations appears through the time-delayed ultimate finger position P . Although theirs is an abstracted global model, it includes the central and peripheral mechanisms explicitly. They compare the ideas of the beat phenomenon and amplitude modulation by varying certain parameters in their model. In particular, they modify the weights a and b of each loop, modulating the central loop weight by blood pressure and by respiration rate, while generally keeping the weight of the peripheral loop ten times larger than the weight on the central loop. As well, they increased the degree by which each loop is controlled by its own activity (through the parameter α), which resulted in a simulated finger position whose power spectrum would indicate the beat phenomenon. Though too simplistic to describe the observations consistently, the results of their model “demonstrate a working example of the principal idea of the concept of a dynamical disease. Simply, the change in one parameter has led to the disappearance and appearance of a symptom in a pathological range” (1995, p. 41). To sum up, they describe quite succinctly the importance of modelling: “If we are successful, it will become possible to develop therapeutic strategies to reposition the system (mechanically, electrically, or pharmacologically) in a range of parameter space associated with ‘healthy’ dynamical behavior” (1995, p. 41).

Edwards et al. (1999) examine a neural network model under parameter changes that weaken the connection between the network units. This is a global model, abstracted from physiological detail, but that allows central and peripheral loops to be involved. They were inspired by the observation in tremor data that “[n]ormal physiological tremor is irregular while other forms of tremor show more regular oscillations” (1999, p. 157), which seems analogous to transitions from irregular to periodic dynamics that occur in neural networks

as the connections are weakened. Since Parkinson’s disease is associated with a loss of the neurotransmitter dopamine, Edwards et al. proposed “the hypothesis that the onset of a regular oscillation in [Parkinson’s disease] is a change in dynamical regime of the network from a normally aperiodic one to a more regular one as the parameter corresponding to dopamine efficacy decreases” (1999, p. 159). They explored their hypothesis using a piecewise linear approximation to a nonlinear neural network of the form:

$$\dot{\mathbf{x}} = -\mathbf{x} + A\mathbf{f}(\mathbf{x}) - \mathbf{b}.$$

Here, A is an $n \times n$ matrix containing the strengths of the connections between the n units of the network, $\mathbf{f}(\mathbf{x})$ is an $n \times 1$ vector function of the sigmoidal (or step-function) response of each unit, and \mathbf{b} is an $n \times 1$ vector containing the threshold of each unit. Each x_i represents the amount by which the unit’s value exceeds its threshold, b_i . This is an additive neural network model,¹³ in which the variables are thought of as overall activity in an entire anatomical structure in the brain or functionally independent subpopulations of cells in an anatomical structure, and the network as a whole is a caricature of the global motor circuitry, with its many feedback loops. The essential feature is that activity of a ‘unit’ increases with input and saturates at minimum and maximum levels. Positive or negative connection strengths correspond to excitation and inhibition respectively. Here, the thresholds are taken to be sharp, so that there is an instantaneous jump from minimum to maximum activity.

The components, a_{ij} , of the matrix A are taken to be:

$$a_{ij} = \begin{cases} 0 & \text{if units } i \text{ and } j \text{ are not connected, } i \neq j; \text{ or if } i = j, \\ 1 & \text{units } i \text{ and } j \text{ are connected at full strength, } i \neq j, \\ \alpha \in (0, 1) & \text{if the connection between units } i \text{ and } j \text{ is weakened, } i \neq j. \end{cases}$$

By decreasing the parameter α , analogous to weakening connections in the motor circuitry

¹³This type of additive neural network model is sometimes called a Cohen-Grossberg or Hopfield network, though the symmetry of those networks is not required here (Cohen and Grossberg 1983; Hopfield 1984).

due to dopamine loss, it is demonstrated that the dynamics of the network can change from irregular oscillations (like that of normal tremor) to regular periodic oscillations (Parkinsonian tremor). A limitation of the model as presented in this paper is that “it does not reproduce the increase in amplitude along with transition to periodicity that is usually associated with tremor in Parkinson’s disease” (1999, p. 174). This issue was addressed in a subsequent paper (Edwards and Gill 2003) in which the network is replaced by many parallel copies, as are thought to be present in basal ganglia – largely independent subpopulations of cells in each structure project to similar subpopulations in other structures, with little cross-talk between the resulting separate loops (Graybiel 1991; Bergman et al. 1998). In this paper, Edwards and Gill show that, under certain conditions on the weak cross connections between separate loops, synchronization of loops occurs naturally when they are each in a regular oscillation, but not when their activity is irregular. Thus, when each parallel copy of the network is put into an oscillatory regime, they automatically synchronize, which could account for the increase in tremor amplitude.

The work of Edwards et al. (1999, 2003) suggests the possibility that tremor in Parkinson’s disease “does not result simply from a particular group of tremorigenic cells,” but that “it arises from normal tremor via bifurcations in a dynamical process” (1999, p. 172). Oscillations may result from *global* network dynamics in a rate model, as well as from the initiation or synchronization of activity in local (such as single-cell) oscillators.

Terman et al. (2001, 2002) have developed a cell-level model of the external segment of the globus pallidus and the subthalamic nucleus, and their interactions. They propose that conductance-based cellular models, rather than firing-rate models, are required to capture the dynamic activity of these structures and that reciprocal connections between the external globus pallidus and the subthalamic nucleus, along with lateral inhibition within the external globus pallidus and input from the striatum, could generate the oscillations seen in Parkinsonian tremor.

The equation for the membrane potential of each neuron is of the form $C\dot{v} = -I(v)$, where C is capacitance, v is voltage and I is current. The current term, $I(v)$, depends on

voltage nonlinearly and is of the form

$$-I(v) = -I_L - I_K - I_{Na} - I_T - I_{Ca} - I_{AHP} - I_{syn} + I_{app},$$

where the main terms follow the Hodgkin–Huxley formalism,¹⁴ but include also a low-threshold T-type calcium current I_T , a high-threshold calcium current I_{Ca} , and a calcium-activated, “afterhyperpolarization” potassium current I_{AHP} . The term, I_{app} , models inhibitory (negative) inputs from the striatum to the external globus pallidus as a constant applied current (for subthalamic neurons, I_{app} is set to zero). The term, I_{syn} , represents the current due to synaptic inputs from other cells, with conductances depending on the type of connection: $g_{S \rightarrow G}$ for subthalamic nucleus (STN) to external globus pallidus (GPe) connections; $g_{G \rightarrow S}$ for GPe to STN; $g_{G \rightarrow G}$ for lateral connections within GPe. The slow T-type calcium current is designed to produce the post-inhibition rebound bursts seen in subthalamic neurons, and this seems to be a crucial aspect of the model for the generation of oscillations.

Networks of just a few (8 to 20) cells of each type (from subthalamic nucleus and external globus pallidus) were used in simulations, and three different connection architectures were investigated: random, sparsely connected; structured, sparsely connected; and structured, tightly connected (Figure 5). The cells of the subthalamic nucleus and the external globus pallidus form parallel layers (modelled as one-dimensional arrays) with equal numbers of cells.

Different sets of activity patterns are found numerically with the three styles of connection architecture as two parameters are varied, the synaptic conductances $g_{S \rightarrow G}$ and $g_{G \rightarrow G}$ ($g_{G \rightarrow S}$ is held constant). The paper attempts to extract from the numerical simulations the mechanisms and features that determine the type of behaviour and the frequencies involved.

The relevant details are the type of architecture, the strengths of synaptic interactions, the

¹⁴The Hodgkin–Huxley model is a four-dimensional system of ordinary differential equations that describes the three main currents (leak current I_L , potassium current I_K , and sodium current I_{Na}) underlying the action potential of many neurons, originally the giant axon of the squid [ref: 1952, Hodgkin AL, Huxley AF, Journal of Physiology]. The current terms for each type of ion channel are of the form $I = w^p(v - v_r)$, where w is a voltage-dependent ion channel gating variable with its own differential equation.

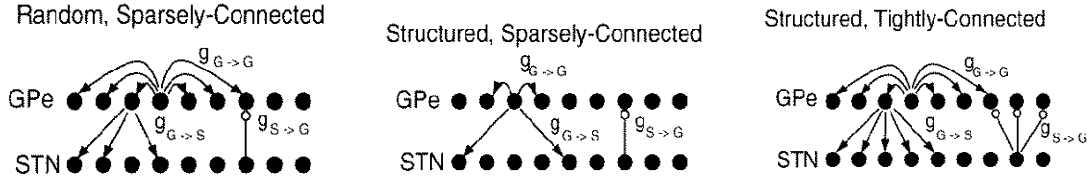


Figure 5: *Terman, Rubin, Yew and Wilson model network arrangement of cells of the subthalamic nucleus (STN) and the external globus pallidus (GPe) in (a) random, sparsely-connected, (b) structured, sparsely-connected, and (c) structured, tightly-connected architectures. From Terman et al. (2002), Fig. 3a, page 2968, Fig. 5a, page 2970, and Fig. 7a, page 2972, with permission. Copyright 2002 by the Society of Neuroscience.*

strength of the constant input from striatum, as well as intrinsic properties of the cells, particularly the time scale of the calcium build-up and rebound excitation. Most relevant for Parkinsonian tremor are the clustered rhythms and propagating waves that occur with the more structured architectures. With the parameter values used in the sparsely connected structured network, periods of bursting for each cluster occur at a frequency of 4 to 6 Hz (with much more rapid spiking within bursts).

Clustered rhythms or travelling waves occur if the synaptic conductance of the projections from the subthalamic nucleus to the external globus pallidus is sufficiently high and if the intrapallidal synapses have sufficiently low conductances (though waves can give way to continuous spiking if lateral pallidal conductance is too low). It is suggested that enhanced inhibitory input from striatum in Parkinson's disease has the effect of weakening the lateral pallidal connections and thus promoting clustered rhythms or travelling waves. The clustered rhythms are essentially a result of the post-inhibitory rebound excitation of subthalamic cells and the timing of alternating bursts is governed primarily by the rate of deinactivation of the I_T current, which produces the rebound excitation, preventing an inhibited cluster from remaining quiescent.

This model is consistent with recent experimental results, which suggest that the traditional idea of decreased activity in the external globus pallidus and increased activity in the subthalamic nucleus in Parkinson's disease is not accurate, but instead that there is increased correlation of firing between cells within both these structures (Bergman et al.

1998). The number of clusters that can form will determine the number of different phases present (e.g., antiphase with two clusters), which could account for the variety of phases seen in recordings from these structures in Parkinson's disease and the variety of phases seen in tremor oscillations of different body segments.

The implication of this approach is that the subnetwork formed by the external globus pallidus and the subthalamic nucleus, along with a constant input from striatum, is enough to explain the onset of partially synchronized rhythmic activity in both structures under the conditions thought to arise in Parkinson's disease. Oscillations seen in thalamus and other structures would then have to be driven by the oscillations between the subthalamic nucleus and the external globus pallidus. It is not clear whether ignoring other structures within and outside of basal ganglia is reasonable, though the authors only claim that their model is sufficient to produce the observed behaviour. This is probably the most convincing model for the origin of tremor in Parkinson's disease so far.

4 Control of Tremor by Deep Brain Stimulation

The models we described in the previous section consider the effect of parameters that start or modulate oscillations associated with tremor in Parkinson's disease. In this section, we turn to models that examine how tremor oscillations are stopped or controlled by a surgical treatment known as deep brain stimulation. In this treatment, an electrode is surgically implanted in the patient's brain for long-term electrical stimulation of subcortical structures at high frequencies. The procedure has an interesting history (see Benabid et al. 1998 for a review), including its use to treat chronic pain, up to the surge in attention it received since the early 1990s when a group in Grenoble (Benabid et al. 1991) suggested it as a treatment for tremor in Parkinson's disease. The motivation for applying deep brain stimulation to treat movement disorders such as Parkinson's Disease seems to have been based on empirical observations and very little theory.

The late 1990s marked the first appearance of mathematical and computer models that examine hypotheses of stopping tremor oscillations by deep brain stimulation. One model

of tremor control by deep brain stimulation, proposed in a text called *Phase Resetting in Medicine and Biology* (Tass 1999) and further developed in subsequent articles (Tass 2000; Tass 2001; Tass 2002), consists of clusters of interacting phase oscillators¹⁵ subjected to random forces whose activity can synchronize (representing pathological oscillations) and can be *de*-synchronized by a stimulation pulse of appropriate intensity, duration and phase. The motivation for this model is from studies suggesting “that Parkinsonian resting tremor is caused by a cluster of neurons located in the thalamus and the basal ganglia which fire synchronously at a frequency similar to that of tremor” (2001, p. 243). It assumes that the origin of tremor in Parkinson’s disease (and essential tremor) is abnormally synchronized neuronal activity, and attempts to develop the theory for ‘desynchronizing’ or modulating the activity “so that it comes close to an uncorrelated firing; where the latter is in the physiological mode” (2001, p. 343).

Tass extends his original model of an appropriately-timed single-pulse stimulation to a more effective ‘double pulse’ to desynchronize the pathologically synchronized clusters of neurons, and suggests this as a new stimulation technique which, instead of *chronic* deep brain stimulation, need only be applied when the group of neurons become synchronized. Though not yet tested in humans at the time of the article, Tass states that “the double-pulse techniques will soon be applied to tremor patients” (2001, p. 353).

Montgomery and Baker (2000) present computer simulations of a model three-neuron network, one neuron of which having an abnormal discharge of information that interferes with the transfer of information between the other two. Their motivation for this work was to provide an alternative hypothesis to one stating that “[deep brain stimulation] of a neural structure acts by inhibiting that structure, either by depolarization blockade¹⁶ or by release of inhibitory neurotransmitters”(2000, p. 259). In this article, they examine the notion of ‘noise’ as a pathological mechanism and how “suppression of it may play a role

¹⁵Phase oscillator: a model of a single neuron in which firing or bursting is assumed to depend only on the phase (and not on the amplitude).

¹⁶Depolarization blockade: a neuron is constantly depolarized but below the threshold needed to produce an action potential, which increases the threshold for producing an action potential, and thus makes it more difficult for neurons to fire.

in [deep brain stimulation] therapeutic effect” (2000, p. 259). Their model is not specific to the pathology of Parkinson’s disease, nor only to its symptom of tremor. It is a coarse level view of information transfer in the presence of abnormal neuronal activity to explore how stimulation might override this abnormal activity. They discuss this in the context of movement disorders such as Parkinson’s disease, essential tremor and multiple sclerosis. Their results indicate that regular high frequency deep brain stimulation can lessen the impact of irregular abnormal neuronal activity on information transfer.

In their discussion on deep brain stimulation in the future, Montgomery and Baker (2000) expressed quite well the need for new approaches to the theory: “The future of [deep brain stimulation] will depend on advances in the electrophysiological study of complex systems. In view of this complexity, new conceptual and mathematical approaches are necessary and explanations will have to be built on models and simulations, which have not been the usual approach in the medical sciences” (2000, p. 266). See also the paper by Montgomery in the present issue.

Titcombe et al. (2001) present a model in which high frequency deep brain stimulation results in a gradual change in network properties controlling the generation of tremor. In particular, they examine the hypothesis that deep brain stimulation induces a qualitative change in the dynamics so that the stable oscillations are destabilized as a parameter affecting the oscillation is modified. A possible qualitative change in the dynamics is a *supercritical Hopf bifurcation*: as the control parameter crosses a critical value, the dynamics change from a stable fixed point (no oscillations) to a stable limit cycle (oscillations). Their focus on the supercritical Hopf bifurcation was suggested by experimental data of rest tremor in subjects with Parkinson’s disease receiving high frequency stimulation. These data showed a gradual increase and decrease of tremor amplitude after switching the stimulation off and on respectively, which is typical of oscillatory transitions displaying a supercritical Hopf bifurcation. Titcombe et al. explored this hypothesis with a schematic network model that illustrates how an oscillating system can interact with periodic stimulation. Since “there is not general agreement about the detailed structure of the network or the abnormalities that

lead to Parkinsonian tremor” (2001, p. 766–767), they chose to examine their hypothesis at a macroscopic level. The equations of the network model are

$$\frac{dx_1}{dt} = S_I(x_3) - x_1, \quad \frac{dx_j}{dt} = S_E(x_{j-1}) - x_j, \quad j = 2, 3. \quad (2)$$

Here, $S_I(x)$ is an inhibitory response function and $S_E(x)$ is an excitatory response function, typically sigmoidal in form. This network model is an example of feedback inhibition: x_1 excites x_2 , x_2 excites x_3 , and x_3 inhibits x_1 . The specific form of response functions they used are

$$S_I(x) = \frac{0.5^\mu}{x^\mu + 0.5^\mu}, \quad S_E(x) = \frac{x^\mu}{x^\mu + 0.5^\mu}, \quad (3)$$

where μ is the bifurcation parameter of the system. The system has undergoes a Hopf bifurcation when $\mu = \mu_c$: for $\mu < \mu_c$, the solution has a stable fixed point, and for $\mu > \mu_c$, the solution has a stable limit cycle. They model deep brain stimulation as a periodic train of short pulsatile stimuli of two parameters: the stimulation pulse amplitude and the stimulation period. The network given in (2)–(3) depends on the control parameter μ , and has an inherent time constant of recovery from each stimulation pulse. Thus, they model the control parameter as a function of time as

$$\mu(t) = \mu_0 - z(t), \quad \frac{dz}{dt} = -\frac{1}{t_c}z,$$

where $z(t)$ represents the change in μ due to stimulation from its baseline value μ_0 . Here, t_c is the time constant of the network. In this way, Titcombe et al. hypothesize that the periodic stimulation leads to a time-dependent decrease in the control parameter μ such that oscillation is destabilized. The results of simulations of the model with two different time constants for the change of the controlling parameter. Varying the time constant leads to dynamics that appears qualitatively similar to what is observed in the patients. As well, their theory predicts the curve separating the effective and ineffective stimulation regimes for different time constants. Comparing the theoretical predictions with clinical data for thalamic stimulation, they found good agreement between theory and experiment.

5 Discussion and Conclusions

We have presented an overview of mathematical modelling and computer simulations related to tremor in Parkinson's disease. There has been a remarkable variety of approaches to the problem. Most modelling attempts have been at the macroscopic level, and most have tried to include both central and peripheral components. Recent models attempting a microscopic description of aspects of the basal ganglia might be a reflection of the increase in available anatomical and experimental information over the years. However, it is still not clear what components of the motor circuitry are essential to include in a model for Parkinsonian tremor.

The earliest studies attempted to model the oscillation of body parts themselves using simplistic and abstracted equations capable of oscillation. Thus, they focus on the peripheral manifestation of the disorder, though in some cases (the Fukumoto model and the Austin and Tsai model) the change in Parkinson's disease was modelled as a change in input from the suprasegmental levels (i.e., from the brain), though not an oscillatory input. Beuter and Vasilakos also use abstract equations but explicitly including central and peripheral feedback loops whose interactions could account for some aspects of tremor recordings. The model of Edwards, Beuter and Glass again uses abstract equations at a macroscopic level, but attempts to capture in a generic way the structure of interactions in the brain's motor circuitry. Tass uses a pool of generic oscillators that can synchronize as the basic material in his model, again a loose representation of clusters of potentially oscillating real neurons within a range of brain structures.

What do the models have to say about the origin of tremor oscillations in Parkinson's disease? Gurfinkel and Osovets deal only with a peripheral oscillator. The Fukumoto model and the Austin and Tsai model suggest only that tremor of body parts results from increase in a particular stimulus from the brain, without giving any information about the source of this input. Beuter and Vasilakos suggest that certain pathological features of tremor, such as beats, arise from changes in feedback loop parameters, involving other physiological variables such as blood pressure and respiration rate. This model still does not attempt to

pinpoint the ultimate origin of the tremor oscillations, however. The Edwards, Beuter and Glass model explains the origin of tremor oscillations as a dynamical response to weakened units and connections in a coarse-scale network model. It presents the possibility that tremor comes from a global change in network activity as a result of local damage, in contrast to the alternative possibility that tremor arises locally from cells whose activity is upset, so that they become tremorgenic. In both cases cells oscillating at tremor frequency would be expected, the difference being in the cause of this oscillation. The amplitude of tremor is suggested to result from synchronization that occurs naturally when the circuits go into regular oscillation. The model of Terman, Rubin, Yew and Wilson attributes the oscillation to patterns of inhibition and excitation between the cells of the subthalamic nucleus and the external globus pallidus, combined with crucial details of the cell dynamics, particularly post-inhibitory rebound resulting from slow calcium build-up. The high amplitude of tremor results from synchronization of clusters of cells that can occur because of the particular network structures hypothesized. The crucial change in Parkinson's disease here is increased inhibitory input from striatum, which is a plausible effect of damage to the nigro-striatal pathway, though this is not explicitly modelled here.

We also outlined some mathematical models that describe the suppression of Parkinsonian tremor by deep brain stimulation. Tass assumes the presence of oscillators to begin with and, as did Terman et al., deals with the question of synchronization as the means by which high-amplitude tremor builds up. Montgomery and Baker run computer simulations on an abstract network model to focus on the effect of stimulation, rather than on the specific motor disorder, on the activity and information exchange between neurons representing structures involved in motor control. Titcombe, Glass, Guehl and Beuter consider an abstract global model to illustrate how an oscillating system can interact with periodic stimulation. The numerical simulations of this model can reproduce the behaviour seen in tremor data, but it does not represent the output of any specific structures in the motor system. Another phenomenon relating to deep brain stimulation that could be explored theoretically is the rebound in tremor observed in some patients with Parkinson's disease

after stimulation arrest (Hariz et al. 1999).

The general idea of the models presented here is that there is some change in dynamical behaviour due to parameter or input change. Over time, we can see the shift in perspective from models that try to capture oscillations in the periphery to models that reflect oscillations in the brain. It is unclear whether tremor is generated by a small set of cells in one particular location or by network interactions involving a couple of structures (such as Terman et al. propose) or whether it is a large scale network effect across much of the motor circuitry (as in the model of Edwards, Beuter and Glass). However, it seems evident that a successful model of Parkinsonian tremor should account for the observed oscillation in many brain structures. It is also difficult to determine the role of synchronization of neuronal activity within the basal ganglia in Parkinsonian tremor, since there is some evidence to suggest that, at therapeutically relevant frequencies, deep brain stimulation increases synchronized neuronal activity while also improving Parkinsonian symptoms (Garcia et al. 2003). We should point out, though, that entrainment at high frequency induced by stimulation does not preclude the possibility that there was already synchronized activity at a lower frequency associated with Parkinsonian tremor, but this remains unclear.

Mathematical models have also been proposed attempting to describe tremor in a context broader than that of Parkinson's disease, for example, by Stein and Oğuztöreli (1976). Others have considered symptoms of Parkinson's disease beyond that of tremor. The model of Edwards et al. (1999, p. 159) "suggests that akinesia may simply be another mode of operation of the same dynamical system with another value of the altered parameter," and Borrett et al. (1993) also relate akinesia to a fixed point in the dynamics of their network model for Parkinsonian bradykinesia. Nakamura et al. (1978a, 1978b) study a model concerning what they call the 'hastening phenomenon', that is, a quickened tapping response of patients with Parkinson's disease in a tapping test to follow a periodic signal. Connolly et al. (2000) use a network model of potential functions in an attempt to explain the presence of both hypokinetic and hyperkinetic¹⁷ symptoms. From the microscopic view,

¹⁷The terms *hypokinetic* and *hyperkinetic* are usually applied to disorders. Thus, Parkinson's disease is described as a hypokinetic disorder of the basal ganglia, even though tremor generally is increased.

Porenta (1986) modelled neuronal pathways of the basal ganglia circuitry in the context of Parkinson's disease.

Finally, we comment on the impact of these models of tremor in Parkinson's disease. In the early modelling attempts we have described here, there is little evidence that new models were constructed from previous ones, i.e., there are few (if any) citations between articles to indicate an awareness of other modelling approaches. It is also unlikely that mathematical models have yet had a significant impact on mainstream research on Parkinson's disease or tremor, but as the quality of physiological information relevant to Parkinson's disease is improving, modelling is becoming more focused on the known changes in neuronal activity in the brain and therefore more relevant. In fact, since the dynamics of the neuronal networks involved in the motor circuitry in the brain are clearly complex, mathematical models may prove to be essential to understanding fully the origin and treatment of symptoms like tremor. It is our hope that this review article will promote interest in more collaboration between mathematicians and physiologists to understand the complexity of Parkinson's disease and Parkinsonian tremor.

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