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Parkinsonian Tremor and Simplification in Network Dynamics

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We explore the behavior of richly connected inhibitory neural networks under parameter changes that correspond to weakening of synaptic efficacies between network units, and show that transitions from irregular to periodic dynamics are common in such systems. The weakening of these connections leads to a reduction in the number of units that effectively drive the dynamics and thus to simpler behavior. We hypothesize that the multiple interconnecting loops of the brain's motor circuitry, which involve many inhibitory connections, exhibit such transitions. Normal physiological tremor is irregular while other forms of tremor show more regular oscillations. Tremor in Parkinson's disease, for example, stems from weakened synaptic efficacies of dopaminergic neurons in the nigro–striatal pathway, as in our general model. The multiplicity of structures involved in the production of symptoms in Parkinson's disease and the reversibility of symptoms by pharmacological and surgical manipulation of connection parameters suggest that such a neural network model is appropriate. Furthermore, fixed points that can occur in

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the network models are suggestive of akinesia in Parkinson's disease. This model is consistent with the view that normal physiological systems can be regulated by robust and richly connected feedback networks with complex dynamics, and that loss of complexity in the feedback structure due to disease leads to more orderly behavior.

1. INTRODUCTION

The principal site of cell damage in Parkinson's disease (PD) is in the substantia nigra pars compacta (SNc). Loss of dopaminergic neurons here, which project mainly to the striatum, prevents or weakens the modulatory effect of the SNc on the striatum. The main treatment for PD is the administration of levodopa which temporarily replenishes the supply of dopamine in the nigro–striatal pathway. These structures are part of a complex circuitry within the basal ganglia and through the thalamus and motor cortex, involving several loops with multiple inhibitory connections. Parkinson's disease is characterized by several types of change in motor function, such as tremor, rigidity, bradykinesia and akinesia, which are associated with this circuit (Wichmann and DeLong, 1993; Elble, 1996). Exactly why these particular changes occur is not known, though it seems clear that they must be an indirect result of the cell destruction in the SNc.

We propose that the mechanism by which symptoms of PD arise is one of a simplification in a dynamical process that is always active, but changes when parameters such as the amount of dopamine in the nigro–striatal pathway decrease. We investigate a general mathematical model that has many of the properties of the motor circuitry involved in the generation of parkinsonian motor signs. Using this model, we show by numerical simulation and by analysis that weakening of synaptic efficacies of a subset of units in the model can lead to changes in dynamical regime like those observed in PD. Normal physiological tremor, which is irregular in character, gives way to regular oscillations, or else approaches a fixed point, which is suggestive of akinesia.

The idea of parkinsonian symptoms arising from a parameter change in a network has been suggested before in other mathematical models. Borrett *et al*. (1993) used a simple perceptron-type network with feedback to simulate changes in voluntary movement that occur in PD (movement about a single joint, including repetitive oscillatory movements), and Grossberg (1987, p. 135) suggests explanations of difficulties in initiating and terminating movements in PD as well as the 'bracing' phenomenon using gated dipole networks. Contreras-Vidal and Stelmach (1995) model basal ganglia modulation of voluntary movement and note that dopamine depletion in their model leads to decreased modulatory range of the network. None of the above deal with tremor, *per se*.

We put forward our hypothesis in Section 2 and present some examples of tremor in control subjects and in patients with PD, showing the differences in dynamics. Then in Section 3 we briefly motivate our modeling approach. In Section 4 we describe the neural network model in general and simulations with relatively many units (50 or 20) showing the change from aperiodic to periodic behavior. In Section 5 we analyze the origin of the changes in dynamics in the model and this process is illustrated in Section 6 by means of a particular 6-unit network, where the mechanism is apparent. In Section 7 we describe aspects of the physiology of the motor ciruitry that justify our model. Finally, in Section 8 we discuss interesting aspects of the model, both mathematically and in relation to PD.

2. THE HYPOTHESIS

We propose that an appropriate model for the motor circuitry involved in the production of tremor is a neural network in which connections are rich enough to involve multiple interacting loops and in which many of the connections are inhibitory. Furthermore, the change that occurs in PD should be modeled as a weakening in synaptic efficacies in one part of the network (simulating dopamine deficiency in the nigro–striatal pathway).

If one takes this approach, the analysis described in this paper leads to the hypothesis that the onset of a regular oscillation in PD 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. This implies that tremor in PD and normal physiological tremor are produced by the same motor circuitry, but operating in different parameter ranges. It also implies that normal physiological tremor is the output of an aperiodic regime in the network, i.e., that it is deterministic but aperiodic. It is, of course, possible that there are other sources of noise in the final generation of movement at the periphery, such as stochastic properties of ion channels, so that normal physiological tremor need not be strictly deterministic. However, this hypothesis is different from what might be presented as an alternative hypothesis: that normal physiological tremor corresponds to a fixed point perturbed slightly by noise, and that regular tremor arises from it by a Hopf bifurcation.

The model also displays a stable fixed point for certain parameter values. This is suggestive of another common symptom of PD, namely, difficulty with initiation of movement. This symptom is at least one form of what is clinically known as akinesia, although it is perhaps better considered as one aspect of a complex set of symptoms in PD whose relationships are not fully understood, including akinesia, the 'freezing phenomenon', bradykinesia and rigidity (Delwaide and Gonce, 1993). Once a dynamical system is attracted to a fixed point, it requires an external force of some magnitude to dislodge it. The model suggests that this akinesia may simply be another mode of operation of the same dynamical system with another value of the altered parameter.

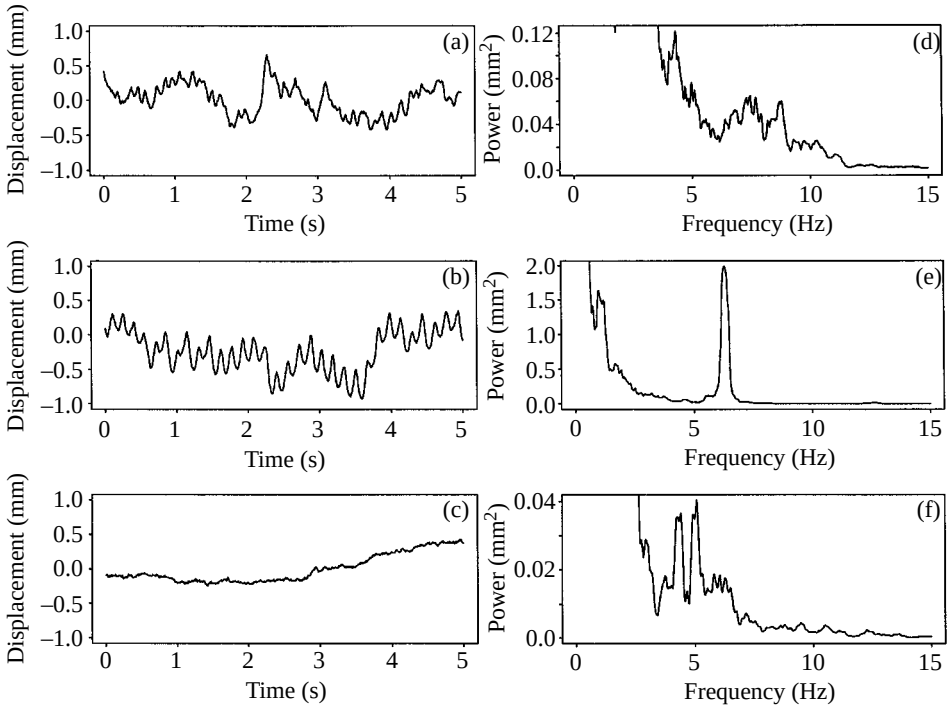

Figure 1. Displacement recordings of postural tremor in a control subject and two patients with PD, sampled at 200 Hz. On the left are 5-s segments of the time series; on the right are corresponding power spectra for the full 29.5-s recordings (estimated by smoothing with an 11-point Daniell filter). The large amount of power at low frequencies arising from the drift in finger position is not shown. Note that the scales on the power spectra are different. (a),(d) Normal physiological tremor in a control subject. (b),(e) Typical parkinsonian tremor, with a frequency of 6.3 Hz, though the amplitude is relatively small compared with many PD patients. (c),(f) Unusually low amplitude tremor (compared with control subjects) of another patient with PD known to have rigidity, as shown by a neurological exam, and difficulty with initiating and sustaining rapid alternating movements, as shown by other motor tests. Although the amplitude is very low, there does seem to be some oscillation at about 5 Hz, typical of PD.

Figure 1 shows displacement recordings and power spectra of postural tremor in a control subject and in two patients with PD. The first [Fig. 1 (a),(d)] is typical of normal physiological tremor. It is irregular and has a broad spectrum. The frequency of normal physiological tremor is usually cited as being between 8 and 12 Hz, but in displacement (rather than acceleration) lower frequencies are relatively more enhanced and the power between about 6 and 11 Hz seen here is typical. The second [Fig. 1 (b),(e)] is typical of tremor in PD, with a frequency of 6.3 Hz, though the amplitude is relatively small compared with that of some patients with PD. The third [Fig. 1 (c),(f)] shows the tremor of the affected hand of another patient with PD having an unusually low amplitude. This patient had clinically diagnosed rigidity and other motor tests showed difficulties with initiation and maintenance of smooth movement. There is, however, evidence of some oscillation around 5 Hz despite the low amplitude.

3. MODELING APPROACH

Ideally, one would want to construct a mathematical model that described faithfully the essential aspects of the brain's motor circuitry. However, the dynamics of the interactions between the structures involved in the motor circuits, and indeed the exact set of structures that are essential, are not known in detail. We know where there are inhibitory and excitatory connections for the most part, but it is not possible yet to quantify reliably the strengths of these connections, or to ascertain the importance of time delays present in all neural systems, or of internal dynamics of a single structure.

We therefore take a general approach and ask whether simple models that share some basic properties with the network of brain structures involved in the motor circuits show the type of dynamical changes in behavior that we see in PD when a similar parameter is changed. We do not argue that our particular model is exactly right, but that the types of behavior observed are generic in systems of this type. It is clear from the description above that the relevant motor circuitry involves a network of multiple interacting loops in which many of the connections are inhibitory. Though in principle this could apply on a fine scale, where the units of the network are individual neurons, we have in mind a coarse description, in which anatomical structures (or functional substructures of them) are considered as individual units, e.g., Vop in thalamus, SNc, striosomes and matrisomes as substructures within striatum (Graybiel, 1991). Our network is intended to include all the relevant structures for involuntary motor control, including those in the basal ganglia thalamo–cortical loops, the cerebellar loops and possibly descending pathways and feedback from the periphery.

We expect the input–output (response) function for a unit to be one that sums inputs and that saturates: beyond a certain level of stimulation the unit does not become more active, and similarly, below a certain level it does not become less active. To the extent that cells within a structure simply act in parallel, they may be lumped into a single unit having properties like those of a single neuron. Though this is a simplification, it is a reasonable first approximation. According to Bergman *et al*. (1998), 'The neural networks of the basal ganglia are organized as single-layered elements that are connected by sequential feed-forward connections. Most neurons in the nuclei of the basal ganglia are projection neurons with interneurons forming only a small fraction of the total neuronal population. Even the numerous lateral interconnections in the striatum are functionally weak.'

Therefore, standard Hopfield-type neural network models with sigmoidal response functions and inhibitory connections are an appropriate framework for this investigation (Hopfield, 1984). Complex behavior in such networks appears common, especially in high dimensions (Kürten and Clark, 1986; Sompolinsky *et al*., 1988; Das *et al*., 1991; Lewis and Glass, 1991, 1992). We study the effects of changes of connectivity in networks of this type. To find *typical* effects, we run simulations with *random* networks. We have chosen to make all our connections

inhibitory, but essentially the same results are found if excitatory connections are included, as long as inhibition is abundant. We require inhibitory loops, but a simple loop can be inhibitory even if only one of its links is inhibitory (any odd number will do the trick).

Though the main arguments here apply to any of the variants of the Hopfield model, for the numerical simulations we will make the further simplification of supposing that the response function of the network units is a Heaviside step function, rather than a steep sigmoid, while retaining continuous time dynamics. The class of equations resulting from this simplification preserves the range of qualitative dynamical behaviours of continuous-response networks, though the limiting process has not been rigorously analyzed (Glass and Pasternack, 1978a; Sompolinsky *et al*., 1988; Lewis and Glass, 1991, 1992). The resulting equations are piecewise linear and easily integrated.

These piecewise-linear neural networks form a subset of a larger class of Boolean networks not restricted by the Hopfield model requirement that the combined effect of the inputs to a unit be a linear combination. Such networks have been used to model gene regulation (Thomas, 1973; Mestl *et al*., 1995a) and chemical kinetics (Glass, 1975) as well as neural networks (Lewis and Glass, 1991, 1992). Their equations are also particularly tractable, permitting significant analysis (existence, stability and properties) of fixed points, periodic orbits and aperiodic trajectories (Glass and Pasternack, 1978a; Mestl *et al*., 1995b; Mestl *et al*., 1996). kinds of transitions from irregular to regular behavior that we find here have been observed in Boolean networks when other parameters are changed, namely the probability that a given unit will be biased towards either the 'on' or the 'off' state (Glass and Hill, 1998), and the thresholds in the neural network case (Lewis and Glass, 1992).

4. Periodic and Aperiodic Behavior in Neural Networks

Hopfield-type neural networks (Hopfield, 1982, 1984) can be expressed as

$$\dot{y_i} = -y_i + \sum_{j=1}^{N} w_{ij} g(y_j) - \tau_i, \qquad i = 1, \ldots N, \tag{1}$$

where w_{ij} represents the 'synaptic efficacy' of neuron j acting on neuron i, τ_i is the threshold level of neuron i and g is the response function of a neuron to its input, which may be a sigmoid function, such as $g(y_j) = (1 + \tanh \beta y_j)/2$ where β controls the slope or gain of the sigmoid, or a Heaviside step function, i.e.,

$$g(y_j) = \begin{cases} 0 & \text{if } y_j < 0 \\ 1 & \text{otherwise.} \end{cases} \tag{2}$$

In this formulation y_i represents the amount by which the neuron's membrane potential, x_i, exceeds its threshold, i.e., $y_i = x_i - \tau_i$, so that the threshold for each

y_i is 0. This transformation of variables is mathematically convenient [see, e.g., Lewis and Glass (1991)]. Writing equation (1) in vector form,

$$\dot{\mathbf{y}} = -\mathbf{y} + Wg(\mathbf{y}) - \tau, \tag{3}$$

where g is applied componentwise, emphasizes that the strengths of synaptic connections can be represented by a matrix, W. Negative (positive) elements in W indicate inhibitory (excitatory) connections. Outputs from a unit correspond to columns in W, inputs to rows.

In order to look at the typical effect of reducing the strengths of outputs of a group of units in an inhibitory network, we generated random networks in the form of equation (3) with the binary response function of equation (2), having N units, each unit receiving inputs from K others. That is, for each unit, we randomly selected K of the remaining $N-1$ units to provide inputs to it, and set the corresponding entry in the connection matrix to -1, all other connections being 0. The choice of input units was further restricted to preclude 2-loops, that is, if unit i has an input to unit j, we do not allow an input from unit j to unit i. This is not necessary but is helpful from the point of view of computation, in that it prevents the activity of pairs of units from making many very rapid transitions as they spiral in to the origin. We used as threshold vector τ in equation 3 a slight perturbation of $\tau = -(K - 1.5) \times (1, 1, \ldots, 1)$. The perturbation was small (pseudo-random numbers from a normal distribution with mean 0 and standard deviation 0.001) and was introduced to prevent ambiguities that can arise in integrating the equations when trajectories asymptotically approach the potentially ill-defined situation where the activities of two or more units cross 0 simultaneously. The connection matrix was adjusted by reducing the entries in the first d columns by a factor $\alpha \in [0, 1]$. This corresponds to weakening the output of these d units of the network. As the connection matrices are random, the selection of the first d columns is essentially a random one. Trajectories can easily be computed in terms of points at which units switch state (change sign) (Glass and Pasternack, 1978b). We integrated networks in this way from random initial conditions until the trajectory converged to a fixed point or periodic cycle or for 304 000 steps (switchings), whichever came first. In the process we kept track of the sequence of units that switched, as well as the times of these switchings. Periodicity was determined by looking for at least five consecutive repetitions of a sequence of switching units (up to 2000 steps long) and checking for convergence of the period of this cycle (i.e., the last two circuits taking the same amount of time within 10^{-12} time units).

Figure 2 shows the activity of one of the units in one of these networks over about 150 time units (scaled down to 5 on the plots) with decreasing values of the parameter α. For each simulation, an initial condition was randomly selected and the equations were integrated until convergence to a periodic orbit, or for 304 000 steps if it did not converge, before recording the segments shown. Figure 2(a) shows apparently aperiodic behavior when $\alpha = 1$. Integration for 304 000 steps failed to

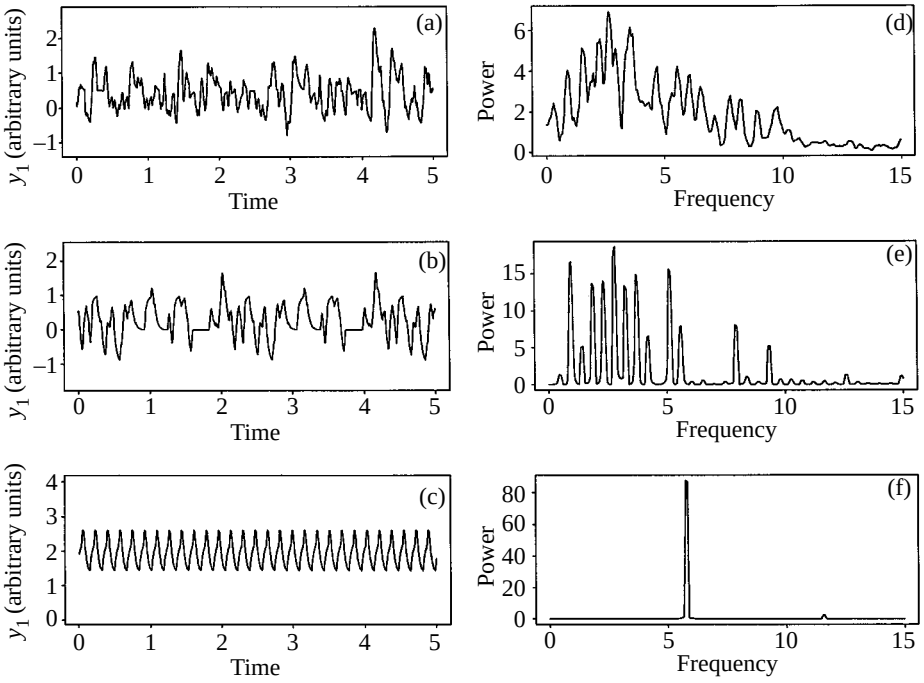

Figure 2. Interpolated time series from one unit of each of three random networks ($N = 50$, $K = 10$, $d = 8$) with different values of α, after transients have died away (after 304 000 integration steps when aperiodic). On the left are segments of the time series; on the right are the corresponding power spectra, based on all 6000 points (estimated by smoothing with an 11-point Daniell filter). The time scale is arbitrary and has been divided by 30 for the plots, so that the frequencies in the spectra are similar to those in the tremor examples. (a),(d) $\alpha = 1.0$, aperiodic, all units switching; (b),(e) $\alpha = 0.5$, period = 64.304 62 time units (562 integration steps); (c),(f) $\alpha = 0.2$, period = 5.18061 time units (40 integration steps).

reveal any periodicity. It is likely that the behavior of this network is aperiodic, but we cannot rule out very long periods or very long transients. Figure 2(b) shows an example when $\alpha = 0.5$ with a long period (64.30 time units). The behavior still appears irregular over short times. Figure 2(c) shows an example when $\alpha = 0.2$ with a short period (5.18 time units).

One way to compare time series from the model with recordings of tremor is to calculate their power spectra. Figure 2 also shows the power spectra of the simulations from the model in the regular and irregular regimes. None of the simulations have the low-frequency drift that is seen in recordings of postural tremor, but this is not usually considered as part of the tremor, *per se*. The short-period example [Fig. 2(f)] has a single dominant peak like that of the parkinsonian tremor example. The aperiodic example [Fig. 2(d)] has a broad range of power extending to higher frequencies than that of the short-period one, similar to the normal physiological tremor with power above the parkinsonian frequency. The long-period example

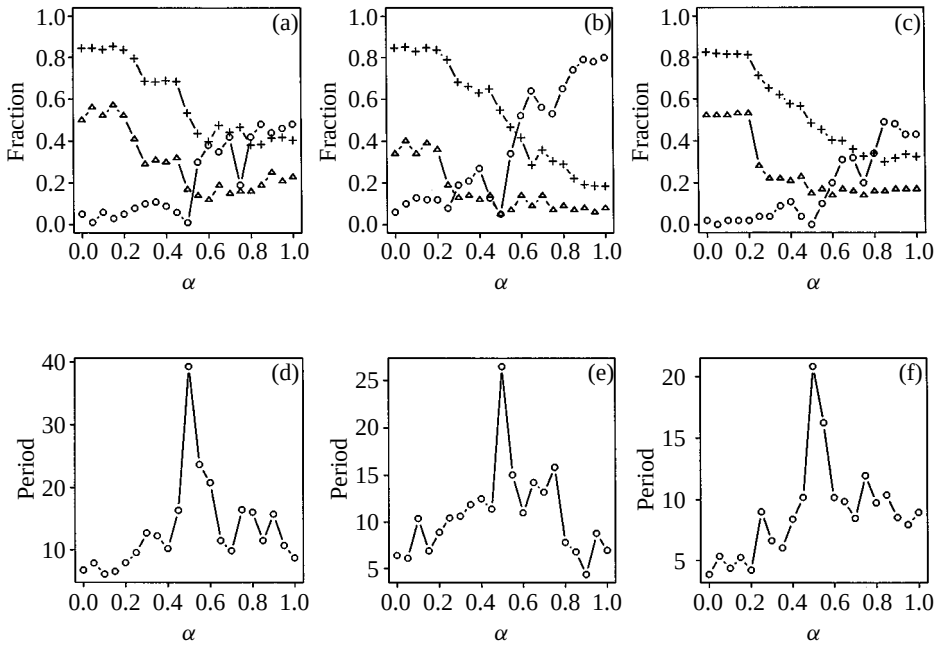

Figure 3. Average behavior of 100 random networks each of which is weakened by various values of the parameter, α. The fraction of networks that had aperiodic behavior ('$\circ$'), the fraction of networks that had fixed point behavior ('$\triangle$'), and the average fraction of units that were fixed (not switching) after transients had died away ('$+$') are all indicated on the upper graphs. The average period of the periodic orbits is indicated on the lower graphs. (a),(d) $N = 50$, $K = 5$, $d = 10$; (b),(e) $N = 50$, $K = 10$, $d = 8$; (c),(f) $N = 20$, $K = 5$, $d = 5$.

[Fig. 2(e)] has power in the same range as the aperiodic one, but more isolated in equally spaced peaks. The time and therefore frequency scale of the simulations is arbitrary, of course, and in this study we have not attempted to deal with the complex issue of transformation of neural signals through muscle contractions to finger displacement.

Figure 3 shows the results of simulations of a large number of networks each with several values of the parameter α, for several choices of N, K and d. The fraction of networks that were aperiodic after 304 000 integration steps, the fraction that reached a fixed point and the average fraction of 'fixed' units are all plotted. A unit is considered fixed if it does not switch once a periodic cycle is reached (in the sense that the sequence of units which do switch have settled down to a periodic pattern, though of course the trajectory itself only approaches a limit cycle asymptotically). In the case of aperiodic behavior, we counted 'fixed' units over the last 10 000 steps after a 294 000 step transient. Figure 3 also shows the average period of the networks that were periodic (not counting networks that approached fixed points).

In general, as α decreases, the behavior becomes more regular. The number of fixed units clearly tends to increase as the parameter decreases. Note that the fraction

of fixed units is usually much larger than the fraction of units weakened — the dynamical effect of the damage is widespread. The fraction of aperiodic networks clearly decreases with the parameter, with a dip at $\alpha = 0.5$. The proportion of fixed points increases slightly as α is decreased with a big jump at $\alpha \approx 0.25$. The average period of the periodic solutions does not seem to vary in any simple way with the parameter, except that at around $\alpha = 0.5$ we tend to have very long periods. At this parameter value, there seems to be a dearth of aperiodic networks but these are replaced by an abundance of very long-period ones. There may be a smaller but similar effect at $\alpha = 0.75$. In general, in these examples, when $\alpha > 0.5$ we tend to find aperiodic behavior, but if it is periodic, the period tends to be short or intermediate in length, and fixed points are rare. For $0.25 < \alpha < 0.5$, there are few aperiodic networks, still not too many fixed points, and we usually obtain periodic behavior of intermediate length. When $\alpha < 0.25$ we find more fixed points, short-period oscillations and very few aperiodic networks.

5. Dynamical Simplification

Equation (3) has many parameters (all the entries of the matrix W and of the vector τ), which allow for a wide variety of behaviors. However, there are clearly comprehensible effects of moving to boundaries of the region of parameter space where all variables can actively change state. A kind of dynamical simplification occurs, wherein the effective dimension of the dynamics is reduced as units become stuck in the 'on' or 'off' state.

This is true even in more general contexts. The response function, g, may be a continuous sigmoid, and the decay terms may have coefficients other than 1. In fact, even if the sigmoid (or step function) takes on extremal values of anything other than 0 and 1, the equations can nevertheless be rewritten with our standard g with range [0,1], by adding another term to the threshold and scaling the connection matrix. Similarly, adding an external input vector, $\mathbf{I}$, to the equation is mathematically equivalent again to changing the thresholds (τ is replaced by $\tau - \mathbf{I}$). We continue to work with equations (2) and (3) for simplicity, but realize that the comments of this section apply equally in a much broader context.

After crossing such a 'boundary' in parameter space, the sum of the inputs to a particular unit cannot cross threshold, regardless of the configuration of inputs. For example, this is the case if, for some i in equation (1),

$$\max_{\mathbf{y}} \left(\sum_{j=1}^{N} W_{ij} g(y_j) \right) < \tau_i . \tag{4}$$

The left-hand side here is

$$\sum_{j=1}^{N} \max\{w_{ij}, 0\},$$

the sum of the positive entries in the ith row of W, because g takes on values in $\{0, 1\}$. In this case, for any value of the vector $\mathbf{y}$, we have

$$\sum_{j=1}^{N} W_{ij} g(y_j) - \tau_i < 0,$$

and y_i will become negative in finite time and remain negative thereafter. This means that, even though y_i continues to change, its effect on other variables becomes fixed at 0 (as $g(y_i) = 0$ when $y_i < 0$) and the behavior of the system becomes essentially $(N-1)$-dimensional.

Similarly, if

$$\min_{\mathbf{y}} \left(\sum_{j=1}^{N} W_{ij} g(y_j) \right) = \sum_{j=1}^{N} \min\{w_{ij}, 0\} > \tau_i, \tag{5}$$

then y_i will become positive in finite time after which $g(y_i)$ is fixed at 1. If one of these two conditions holds for every variable, $i = 1, \ldots, N$, then the network is forced to a fixed point.

If each row of W has K entries and entries in the i^{th} row are bounded by $\pm\alpha_i$, $\alpha_i > 0$, then the above conditions become

$$|\tau_i| > \alpha_i K,$$

in which case $g(y_i)$ becomes fixed. It is clear that these extremes can be reached by manipulating any of the three parameters: decreasing K, the number of inputs, decreasing α_i, the strength of the inputs, or increasing the magnitude of τ_i, the threshold. Adding an external input will have a similar effect as discussed above.

From the point of view of modeling parkinsonian tremor, rather than rows of W (i.e., α_i or K above) or the thresholds, it is more appropriate that columns of W are weakened, as this corresponds to weakening the outputs of damaged units. This is the approach taken in the 50- and 20-unit examples of the previous section. We now turn to an example that makes clear how this process can lead us to a 'boundary' in parameter space.

6. A SIX-DIMENSIONAL EXAMPLE

We wish to address the question of how networks of complex inhibitory loops can show the type of transition from irregular to regular behavior that we see in Parkinson's disease by means of weakening of synaptic connections. To this end, we focus here on a particular 6-unit inhibitory network (Fig. 4), namely equation (3)

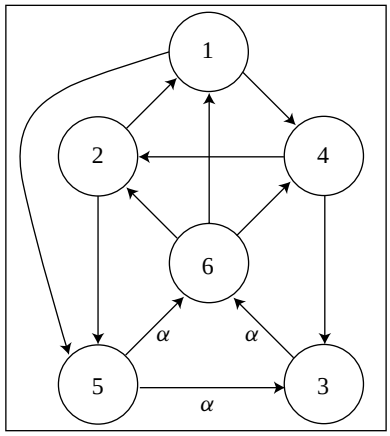

Figure 4. The connection structure of the example 6-unit network. All connections are inhibitory with weight 1 except the three labeled α, which are weakened as α decreases.

with

$$W = \begin{pmatrix} 0 & -1 & 0 & 0 & 0 & -1 \\ 0 & 0 & 0 & -1 & 0 & -1 \\ 0 & 0 & 0 & -1 & -\alpha & 0 \\ -1 & 0 & 0 & 0 & 0 & -1 \\ -1 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\alpha & 0 & -\alpha & 0 \end{pmatrix},$$

and

$$\tau = -\frac{3}{2}(1, 1, 1, 1, 1, 1)^T.$$

The parameter α will be varied. This network with $\alpha = 1$ is a slight modification of one considered in Lewis and Glass (1991) and further investigated by Bersini and Calenbuhr (1997), which appeared to display chaotic behavior.

This network, though simple, still shares some features with the network thought to be involved in the production of tremor in Parkinson's disease. In particular, there are several units that participate in more than one inhibitory loop each. The parameter α represents the modulation of outputs from two of the units (the third and fifth) which might be considered as synaptic efficacies (in a global sense) of signals emanating from neurons in these units.

This network also changes from irregular to regular behavior as α decreases. When $\alpha = 1$, its behavior seems irregular as shown in Fig. 5(a). However, if $\alpha < \frac{3}{4}$ it is easy to show that the behavior must be periodic [Fig. 5(b)]. In this case, the sixth unit, which receives inputs only from the third and fifth, receives a total (inhibitory) input of at most $2\alpha < 1.5$ so that

$$\Lambda_6 \equiv w_{6,3}g(y_3) + w_{6,5}g(y_5) - \tau_6 \geq 1.5 - 2\alpha > 0.$$

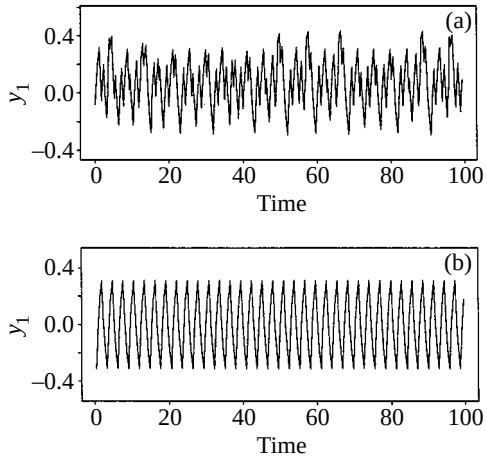

Figure 5. Behavior of one unit of the 6-unit network when (a) $\alpha = 1.0$, aperiodic and (b) $\alpha = 0.7$, period = 2.88727 time units.

Now the equation driving the sixth unit at any time is

$$\dot{y}_6 = -y_6 + \Lambda_6,$$

where $\Lambda_6 = 1.5, 1.5 - \alpha,$ or $1.5 - 2\alpha$, depending on the signs of y_3 and y_5, i.e., on which orthant (the n-dimensional analog of a quadrant in two dimensions) of phase space the trajectory is in. As Λ_6 is always positive, in a finite time y_6 will become positive, and from then on, $g(y_6)$ will be fixed at 1. In other words, the system can be reduced to five dimensions with input from unit 6 incorporated into τ. The equation for unit 1, for example, becomes

$$\dot{y}_1 = -y_1 - g(y_2) - g(y_6) + \frac{3}{2} = -y_1 - g(y_2) + \frac{1}{2}.$$

The net has reached a 'boundary' in parameter space, where unit 6 ceases to contribute to the dynamics of the system. Furthermore, under these circumstances, units 1, 2 and 4 receive a constant input from unit 6 and behave as an isolated network, i.e., the resulting 5×5 W matrix is reducible. Amongst themselves, these three units now form the simple inhibitory cycle of Glass and Pasternack (1978b), which is known to oscillate periodically. Units 3 and 5 are then driven by the periodic oscillation of units 1, 2 and 4 and follow the same rhythm.

In fact, even for α somewhat larger than $\frac{3}{4}$ the network has this same behavior. The bifurcations that occur as α is increased again from 0.75 up to 0.8 are shown in Fig. 6 for one of the units (y_6). Note that as α increases, stable cycles disappear, causing the network to fall into another stable cycle until at about $\alpha = 0.796$ the behavior appears not to settle onto a periodic cycle but remains irregular. Analysis of these bifurcations is in progress and will appear in a future publication.

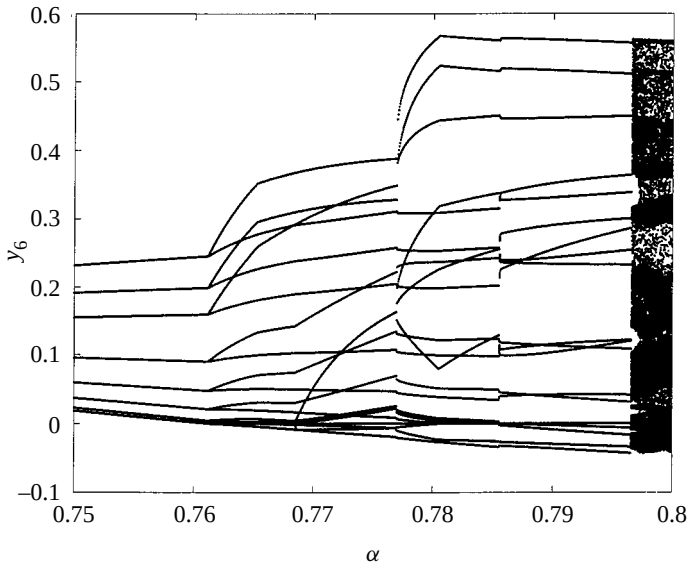

Figure 6. Bifurcation diagram for the 6-unit network as α is varied. For each value of α, the network was integrated for 1000 steps (points on trajectories where one variable crosses zero), the value of unit 6 at the last 500 steps being plotted. After choosing a random initial condition for the smallest value of α, the final state of the system at each value of α is used as initial condition for integration at the next incremented value.

The possible effect of a 'lesion' can be understood by considering a slight alteration of this example. Suppose that a seventh unit has threshold $-\frac{3}{2}$ and has excitatory connections to units 5 and 6 with strength β, and that the thresholds for units 5 and 6 are $-\frac{1}{2}$, instead of $-\frac{3}{2}$. Suppose that unit 7 is fixed in the 'on' state. Now

$$\Lambda_6 = \beta g(y_7) - \alpha g(y_3) - \alpha g(y_5) + \frac{1}{2}.$$

If $\beta = 1$, this reduces to the situation we had before. Suppose now that units 3 and 5 are damaged to the point where $\alpha = 0.7$. Then

$$\Lambda_6 = \beta - 0.7(g(y_3) + g(y_5)) + \frac{1}{2} \geq 0.1,$$

as before. Unit 6 is fixed 'on' and the loop of units 1, 2 and 4 goes periodic. But now a lesion in the structure represented by unit 7 will decrease the total strength, β, of its output connections. If $\beta < 0.9$,

$$\Lambda_6 < 1.4 - 0.7(g(y_3) + g(y_5)),$$

which is negative when units 3 and 5 are both 'on', so that unit 6 can switch states again. If we damage unit 7 by the right amount, unit 5 (which had also stopped switching) starts again, too. In simulations with $\beta = 0.89$, the aperiodic behaviour re-emerges, and the 'lesion' has eradicated the regular periodic tremor.

In our 20- and 50-unit examples in Section 4, the number of fixed units increased as the parameter decreased (Fig. 3) suggesting that the same type of dynamical simplification is occurring as in the 6-unit example above. The phenomenon can be understood in terms of the approach to boundaries of the central region in parameter space, where even before leaving the central region, the probability of a unit becoming fixed in the 'on' or 'off' state (though not fixed in level of internal activity) increases. The number of units contributing to the dynamics (and therefore the effective dimension of the dynamics) decreases as synaptic efficacies in parts of the network are weakened. This is a probabilistic statement: it clearly depends to some extent on the particular structure and the particular trajectory.

7. Physiological Plausibility of the Model

It is evident that the brain's motor circuitry is a network. Several subcortical loops involving many anatomical structures are involved in motor function in general and tremor in particular [schematics of these may be found in, e.g., Graybiel (1991) and Elble (1996)]. A cerebellar circuit involves the pontine nuclei, the inferior olive and the thalamus, as well as motor cortex. The motor circuit of the basal ganglia, which is directly implied in PD, also involves the thalamus and motor cortex. Yet another circuit involves spinal cord neurons and feedback from the periphery, to the cerebellum and thalamus, for example. If the details of the connections and structures involved are still debated, the overall picture of a complex network with multiple interacting loops is clear. It is also clear that many of the connections in this network are inhibitory.

The input structure (putamen) and output structures (internal segment of the globus pallidus and substantia nigra pars reticulara) of the basal ganglia are connected by an inhibitory direct pathway and an indirect pathway that is excitatory in net effect (involving two inhibitory links). These conflicting pathways are modulated by the SNc, apparently by both excitation and inhibition of subpopulations of cells in the putamen (Wichmann and DeLong, 1993). This modulation is weakened in PD by loss of dopaminergic neurons in the SNc that project to the striatum (including putamen). Thus, the particular damage that occurs in PD weakens the synaptic efficacies of a part of the network. The net effect seems to be that the output structures of the basal ganglia become overactive, and therefore keep the thalamus inhibited. But how parkinsonian tremor arises in these circuits is still not clear.

Thalamic cells in the ventralis intermedius (Vim) have been observed to oscillate at the frequency of the tremor observed in hands, feet and jaw in PD. Destruction of a part of Vim often leads to a dramatic and long-lasting reduction in tremor. However, cells have also been observed to fire in correlation with tremor in another part of the thalamus, the ventralis oralis posterior (Vop), in the subthalamic nucleus, the internal part of the globus pallidus and in motor cortex and the pyramidal tracts. Vim, where surgical interventions are most effective, does not even receive inputs

directly from the basal ganglia, but is really part of the cerebellar motor circuit. Moreover, interventions involving a lesion of the globus pallidus or the subthalamus can also suppress parkinsonian tremor (Elble, 1996).

This critical and proven involvement of several separate structures and circuits in the production of the tremor suggests that it does not result simply from a particular localized group of tremorgenic cells. Rather, it seems to result from abnormal operation of an existing control system that involves interactions in a network of brain structures. Feedback loops involving inhibition can produce oscillatory behavior in dynamical systems, and the existence of such loops in the brain's motor circuitry is well established. Thus, it seems plausible that PD is a 'dynamical disease' in the sense that it arises from normal tremor via bifurcations in a dynamical process. This was previously suggested by Beuter and Vasilakos (1995b), where the reversibility of symptoms in PD by pharmacological and electrical interventions were also argued to support the idea, though the model presented there was different.

The normal dynamical regime in the network discussed above should be one of irregular activity. Everyone has a normal physiological tremor that is usually quite small in amplitude and irregular in character, involving what seems to be random firing of motor neurons (Fig. 1). Of course, amplitude generally increases when tremor develops in PD, though the regular oscillations can sometimes be seen even when amplitude is not abnormally large (Edwards and Beuter, 1996).

Tremor in subjects with PD can undergo changes over periods of minutes or seconds. The higher amplitude regular oscillations can appear and disappear suddenly or gradually (Gurfinkel and Osovets, 1973; Beuter and Vasilakos, 1995a; Edwards and Beuter, 1996). This suggests that the parameters determining the dynamical regime are also fluctuating, or that additional inputs are being given to the network from other areas (voluntary commands or anxiety, for example, can alter tremor), or that other systemic variables such as the ballistocardiogram are modifying the dynamics via peripheral feedback (Beuter and Vasilakos, 1995b).

Of course, there are other types of regular tremor, such as essential tremor, that have different etiologies. However, it is not unreasonable to suppose that these types of tremor could also arise from changes in dynamical regime, but due to alterations of different parameters. We do not consider this question further here.

To say that akinesia equals a fixed point attractor in the dynamics of the network would no doubt be an oversimplification. However, the need for a large input to dislodge a dynamical system from a deep basin of attraction at a fixed point is one possible explanation for difficulty with initation of movement in PD. PD has been classified into one predominantly tremorous type and one predominantly akinetorigid type. The distinction is not always very clear, however, and when levodopa is given to patients with the latter type, they sometimes pass through a period of tremor before the symptoms are relieved (Findley, 1993). This argues for an interrelationship between the symptoms and suggests the presence of a dynamical regime corresponding to tremor and another corresponding to akinesia, but does not mean that these symptoms will react identically to treatment.

8. DISCUSSION

Recent reviews have underlined the necessity of network models for understanding basal ganglia functions [e.g., Alexander (1995) and Graybiel (1991)]. The model presented here, though somewhat abstracted from the details of connections of the basal ganglia and related structures, responds to this need. A number of recent network models of the basal ganglia and motor function (Kwan *et al*., 1990; Mitchell *et al*., 1991; Borrett *et al*., 1993; Contreras-Vidal and Stelmach, 1995; Suri *et al*., 1997) have concentrated on voluntary movement and learning, whereas we tackle an involuntary movement for the first time from a network perspective. In this context, too, we take the approach that basal ganglia functions are understandable as part of a larger motor network.

The simulations and analysis in the above sections provide a plausible mechanism for dynamical changes in the motor circuitry of the brain that lead to regular tremor and possibly even akinesia in PD. The basic observation is that as synaptic efficacies of a group of units in the system are weakened (as for the dopaminergic neurons of the SNc in PD), then dynamical simplification can take place. Network activity that is normally irregular can become regular periodic oscillation or can stop altogether, going into a fixed state.

Aspects of the model that seem necessary for transitions from irregular to regular behavior are: the presence of inhibition, which is needed to prevent (by means of frustration) approach to a fixed point; several interconnecting loops [which seem to be necessary for aperiodic behavior to exist, see Mestl *et al*. (1996)]; saturation of activity in units (which is necessary to keep behavior bounded, and is completely plausible physiologically). These conditions are not very restrictive. The summing of inputs by a unit to determine output is part of the neural network framework, but in the context of general Boolean networks where this assumption is relaxed, similar behavior and transitions are seen (Glass and Hill, 1998).

The irregular regime in the model resembles recordings of normal physiological tremor at the periphery. The periodic regime looks increasingly like the regular oscillations of tremor in PD as the period shortens. Long period behavior still looks irregular over short intervals. It is estimated that the symptoms of PD emerge only when 80–90% of the cells in the SNc are damaged (Hornykiewicz and Kish, 1987). It could be argued that our simulations show a similar robustness in that short period behavior, which really looks like tremor, becomes common only when the α parameter is decreased below about 0.25.

Recordings of finger position in patients with PD who have rigidity or akinesia but not the typical tremor may sometimes resemble fixed point behavior, as much as can be expected in such a complex physiological system. Also, the difficulty in initiating movement in PD is suggestive of the necessity to provide a strong external input to a dynamical system stuck in a stable fixed state. Interestingly, the neural network model of Borrett *et al*. (1993) for parkinsonian bradykinesia also associates akinesia with a fixed point of its dynamics. The presence of transitions in patients

with PD between regular and irregular tremor suggests that a fluctuating parameter or an external input is causing a bifurcation in the motor circuit network's dynamics, which is understandable in terms of the model.

We know that other structures besides the SNc and other neurotransmitters besides dopamine are affected by PD. We also pointed out above that the model ignores many complexities. These facts do not undermine the observation that the features of the physiological network which are retained produce behavior resembling in many respects the physiologically observed behavior. A weakness of this model, however, 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.

The implication of this model that normal physiological tremor is the output of an aperiodic but deterministic dynamical system (and there is evidence for 'chaos', strictly speaking, in models of this type) is provocative. It has been argued that normal hand tremor is a result of uncorrelated firing of motor neurons driving a damped linear oscillator (Gantert *et al*., 1992; Timmer *et al*., 1993). Our model suggests that this uncorrelated firing may be deterministic. This does not rule out the possibility that other influences could be at work simultaneously in normal physiological tremor, including stochastic ones, but it does suggest that there is an aperiodic deterministic component to it. It is different from other potential models of the transition such as a Hopf bifurcation from a fixed point (normal) to a periodic orbit (parkinsonian). Transitions from fixed point to periodic behavior also occur in our network model and it might be suggested that these transitions better reflect the appearance of parkinsonian tremor. However, such transitions correspond to an *increase* in the synaptic efficacies, rather than a decrease, and though the increase in amplitude in parkinsonian tremor would be accounted for, other factors such as akinesia would not and normal physiological tremor would then have to originate elsewhere.

The current work places into focus fundamental questions concerning the nature of normal physiological function. One view is that the normal state reflects a stable steady state which is stabilized and maintained by numerous feedbacks. Here, the steady state would reflect the targeted position of the finger (Fig. 1), but in other settings the steady state would reflect the blood pressure, expired carbon dioxide, cell count, etc. However, controlled physiological variables are not constant in time, but display fluctuations about some mean value. Although it has been argued that such fluctuations reflect deterministic chaos (Goldberger *et al*., 1990), data analysis methods used to demonstrate the idea present formidable challenges and claims based on them have been contested (Kaplan and Glass, 1993). Whether or not normal functioning reflects deterministic chaos, Goldberger has observed that loss of complex dynamics is a common feature of human disease (Goldberger, 1996). The current work proposes a hypothesis by which such loss of complexity can occur.

Key physiological systems are regulated by multiple feedback circuits, and chaotic dynamics have been observed in this type of system (Glass and Malta, 1990; Mestl

et al., 1996). Changes in the structure of the system can lead to transitions from chaos to periodicity and steady states (Glass and Pasternack, 1978a). In identifying the changes in Parkinson's disease with dynamical simplification in a dynamical system we make the implicit assumption that the normal behavior may be associated with deterministic chaos (operating in a range that might be typified by low amplitude high-dimensional fluctuations). Loss of the complex feedback structure through disease leads to bifurcations to more orderly dynamics.

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