Neural Networks and Parkinson's Disease

Donald S. Borrett, Tet H. Yeap and Hon C. Kwan

ABSTRACT: A closed-loop or recurrent neural network was taught to generate output discharges to reproduce the prototypical activations in agonist and antagonist muscles which produce the displacement of a limb about a single joint. By introducing a generalized decrease in the excitability of the pre-output layer in the network, the network made the displacement more slowly and also showed an inability to maintain a repetitive movement. These concepts can be applied to the human nervous system in the understanding of the physical basis of movement and its disorders. It is suggested that a movement represents the output of a closed-loop network, such as the cortical-basal ganglia-thalamic-cortical motor loop, which iterates repetitively to its end point or attractor. The model provides an explanation of how the state of thalamic inhibition seen in Parkinson's disease physically may produce bradykinesia and the inability to maintain a repetitive movement.

RÉSUMÉ: Réseaux neuronaux et maladie de Parkinson. Nous avons enseigné à un réseau en boucle fermée, ou réseau neural récurrent, à générer des décharges de sortie pour reproduire les prototypes d'activation dans les muscles agonistes et antagonistes qui produisent le déplacement d'un membre impliquant une seule articulation. En introduisant une diminution généralisée de l'excitabilité de la couche cellulaire précédant la sortie du réseau, le réseau effectuait le déplacement plus lentement et manifestait également une incapacité à maintenir un mouvement répétitif. Ces concepts peuvent être appliqués au système nerveux humain afin d'aider à la compréhension des phénomènes physiques responsables du mouvement et de ses désordres. Nous suggérons qu'un mouvement représente la sortie d'un réseau en boucle fermée, tel le circuit moteur cortex – moyaux gris centraux – thalamus – cortex, qui procède par itération vers son point d'attraction ou terminal. Ce modèle fournit une explication physique de la façon dont l'état d'inhibition thalamique que l'on observe dans la maladie de Parkinson peut produire de la bradycinésie et une incapacité à maintenir un mouvement répétitif.

Can. J. Neurol. Sci. 1993; 20: 107-113

The concept of a dynamical disease was introduced by Mackey and Glass to describe how a change in a control parameter of a physiological system can lead to a pathological state.[1] They applied the techniques of analysis of nonlinear dynamical systems to such areas as hematopoiesis and respiratory control, and were able to model specific pathological conditions by introducing alterations in the value of a control parameter.[2,3] A major difficulty in any similar attempt to model a movement disorder, such as Parkinson's disease, is a currently inadequate conceptualization of the physical basis of normal movement generation. The current view of a movement as the behavioural correlate in time and space of the discharge of neurons in motor cortex and other motor-related regions follows directly from basic and clinical observations, but proves to be incomplete when one asks how the nervous system physically determines a specific neuronal discharge pattern to produce a particular limb trajectory. The concept of a hierarchical motor program or motor plan[4,5] to guide the discharge of lower-order neurons has been introduced to address this dilemma. A motor program, however, is an abstract entity and, although useful conceptually, does not have a physical correlate in the nervous system at the present time. In this paper, we introduce an alternative conceptualization of a movement based on the formalism of neural networks and nonlinear dynamics. It will be shown that this conceptualization of a movement is fruitful not only in addressing how the nervous system may physically determine a specific discharge in producing a normal movement, but also in suggesting a simple underlying mechanism by which some symptoms of Parkinson's disease may arise.

Neural networks are computational structures consisting of individual processing elements (analogous to neurons) and weighted connections between them (analogous to synapses). Architecturally, these networks contain an input layer, hidden layers and an output layer. The objective in most neural network modelling is to determine the set of synaptic weights which will result in a desired output vector upon presentation of a given input vector. If the output of the network, however, feeds back into the input layer with the value of the output layer becoming the new input vector, the network adopts a closed-loop architecture and the computation is repeated. The feedback of the output layer onto the input layer makes the network a discrete-time dynamical system which, if stable, computes in an iterative

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Received May 5, 1992. Accepted in final form November 25, 1992

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fashion until it reaches an equilibrium state. Three possible outcomes may occur which are of physiological significance. The first possibility is that the output of the network evolves from its initial state to a final fixed unchanging state. In this case, the dynamics of the network are said to be characterized by a fixed-point attractor. The second possibility is that the system evolves to an equilibrium where the output repeats a series of state values over a fixed period of time or a fixed number of iterations. In this case, the system is said to relax into a periodic attractor. The third possibility is that the development of the output state is governed by what is referred to as a strange or chaotic attractor, in which the network state becomes unpredictable.[6]

Parametric changes may be introduced into the network and may result in an alteration of the dynamics of the network. Excitability is a network parameter which is relevant to the nervous system, and is related to the input-output relationship of the individual elements of the network. It is a property of nonlinear dynamical systems that the attractor dynamics remain unchanged over a range of parametric values. At a critical parametric value, however, a qualitative change in network dynamics may be induced (e.g., from a periodic attractor to a fixed-point attractor). This qualitative change in dynamics is referred to as a bifurcation.[3,6,7]

If the output of the network not only feeds back onto the input layer but also projects to lower order structures directly responsible for movement generation, then a mechanism is established whereby the repetitive iterations of the network can produce a physical movement. As the network relaxes into the attractor, the descending collateral projections drive the physical limb to its end point.

In modelling the execution of a movement about a single joint, the well-defined sequence of EMG activation must be employed. This sequence is principally characterized by an initial agonist activity which brings about acceleration of the limb, followed by antagonist activation leading to deceleration of the limb to the target position, and then a smaller, second agonist burst.[8,9] In Parkinson's disease, it has been suggested that the biphasic or triphasic agonist-antagonist burst does not generate sufficient limb momentum to reach the desired end point and additional bursts are required.[10] Several hypotheses have been proposed to explain this abnormality. Hallett and Khoshbin[10] proposed an explanation of this phenomenon by introducing the concept of energization of specific muscles to facilitate movement and postulating a defect in energization in Parkinson's disease. Similarly, the inability of Parkinsonian patients to maintain repetitive movements may be postulated to be secondary to a defect in energization. The introduction of the concept of energization, however, still leaves open the question of its physical correlate. As we have previously suggested,[11,12] a movement can be conceptualized as the physical correlate of the output of a recurrent neural network, such as the cortical-basal ganglia-thalamic-cortical loop, as it relaxes into a fixed point attractor. With this conceptualization, bradykinesia and inability to maintain repetitive movements can be seen to arise from the increased inhibitory input to the thalamus[13] seen in Parkinson's disease.

Methods

Since the neural network is required to generate a temporal sequence of output discharge appropriate for the movement, we employed a triphasic temporal sequence (Figure 1A) for single movement generation, and an alternating sequence (Figure 1B) for repetitive movement generation. The simplifying assumption was that these temporal patterns of discharge frequency from the output nodes of the network (Figure 2) would produce the same pattern of muscle activation necessary for the production of movements. It should be noted, however, that this is not a necessary assumption. More complex nonlinear relation between the output discharge and muscle activation could be employed, at a cost of additional computational load during simulation.

The desired output of the network is shown in Figure 1A. There is an initial agonist burst, followed by an antagonist burst and then a final smaller agonist burst which accompanies the displacement shown. This triad of activity at the output nodes (Figure 2) will produce the appropriate muscle activation for a movement about a single joint. The desired activities shown in Figure 1A are displayed as a trajectory in phase space with the 3 axes representing agonist node activity, antagonist node activity and displacement (Figure 1B). This trajectory was divided into 12 segments. With the first 2 points of this trajectory as its initial input, a learning algorithm (see below) would permit the network to find a set of synaptic weights that resulted in an output equal to the 3rd point in the trajectory. Then with the second and 3rd point in the trajectory, the algorithm had to search for the synaptic weights that resulted in an output equal to the fourth point in the trajectory. This procedure was repeated to encompass the entire trajectory, shown in Figure 1B, including the fixed-point attractor "a" (cf. ref. 11). The final set of synaptic weights chosen had to satisfy all these input-output pairings. The use of two previous points as the input resulted in a network model which can be described analytically as a second-order difference equation.

A four layer network was employed in the modelling. The network consisted of an input layer, 2 hidden layers and an output layer as illustrated in Figure 2. Each processing element or node in one layer interacted with every processing element of the next layer. To form a closed-loop architecture to allow repetitive iterations, each element of the output layer fed back onto its corresponding element in the input layer. At this level of feedback, discrete delays (T) were introduced so that the input to the network consisted not only of the last output state but also the output just prior to the last. In the output layer were three elements whose activities represented those of the agonist node, antagonist node and the displacement node. The input layer was composed of six nodes to receive the corresponding delayed feedback. The two hidden layers consisted of three elements each. The output layer not only fed back onto the input layer but also projected to elements physically responsible for the movement (e.g., at the brain stem and spinal cord levels). As well, to reduce the network dimension and complexity, the initial value for the limb angular velocity variable was always zero in the movements to be learned.

The total input, u_i, to element i from the other elements is given by:

$$u_i = \sum_j w_{ij} y_j - \theta_i \qquad (1)$$

where y_j is the output of element j, w_{ij} is the synaptic weight from element j to element i, and θ_i is the threshold of the i-th processing element. Each element has an output defined by the

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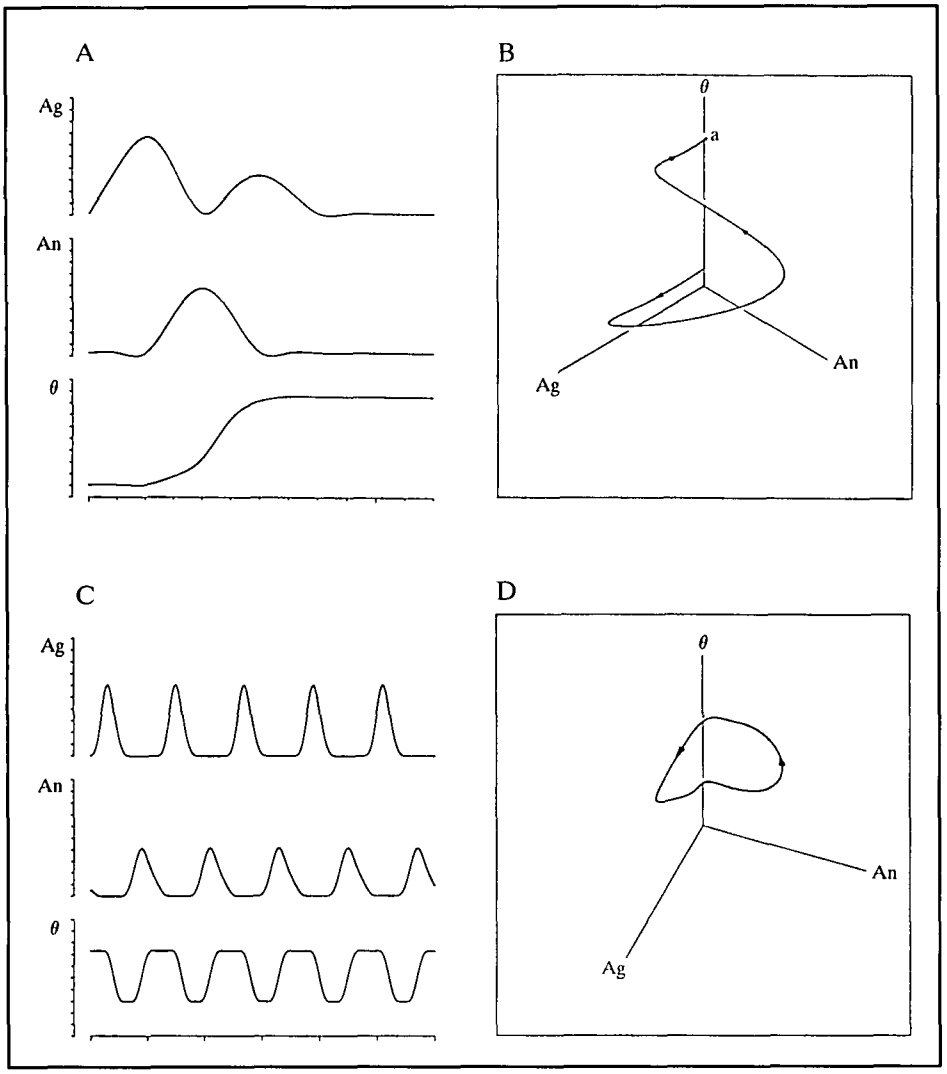

*Figure 1 — **A**. Triphasic discharge pattern for the output agonist node (Ag) and antagonist node (An) necessary for muscle activation for the generation of movement of angular displacement (θ). Each division in the abscissa represents 25 ms. Unless otherwise indicated, in this and subsequent figures, ordinate is in arbitrary units of firing frequency of an output node encoding that variable. As well, data points were fitted to a standard cubic-spine procedure to produce a continuous tracing. **B**. Phase space diagram of Figure 1A. The evolution of these changes describes a trajectory to the fixed-point attractor "a". **C**. Pattern of agonist and antagonist activities that produces a repetitive displacement about a single joint. Each abscissal division represents 150 ms. **D**. Phase space diagram of Figure 1C. The closed loop reflects the agonist and antagonist, activations, and the accompanying cyclic or periodic angular displacement.*

sigmoidal function:

$$y_i = \frac{1}{1 + e^{-u_i}} \qquad (2)$$

This input-output relationship models the firing frequency pattern of a single neuron[14] and is shown in Figure 3.

Once the synaptic weights were determined and the values of the input layer were set at the initial state, then the values of the remaining elements were calculated including the values in the output layer. The output state was fed back onto the input layer, and the computation was repeated in an iterative fashion.

The determination of the synaptic weights was made through the technique of back propagation.[15] The set of synaptic weights that minimized the mean square error between the ideal trajectory and that produced by the network was chosen for the final synaptic weights.

The same procedure was adopted in modelling a repetitive movement about a single joint with a second network. As shown in Figure 1C, a periodic displacement was accompanied by alternating agonist and antagonist activity. These changes were then described as a closed-loop trajectory in phase space (Figure 1D). The trajectory was divided into 12 segments for network simulation. Again, with the backpropagation method, the set of weights that minimized the mean square error between the ideal trajectory and that produced by the network was chosen as the final synaptic weight.

Once the networks had learned the simple single-joint movement and the repetitive movement, a generalized decrease in the excitability in the pre-output processing elements of the network was introduced. This was accomplished by increasing the threshold term in equation (1) causing a shift to the right in the sigmoidal function in Figure 3. With the network for a single non-repetitive movement, the pre-output layer was subjected to a generalized decrease of excitability. In the network for repetitive movements, a moderate decrease in the excitability was first imposed to see its effect on the network output. The excitability was then further decreased to simulate the effects of a failure to maintain excitability within functional limits, a failure which we assume to exist for the modelling of an inability to perform repetitive movements in Parkinson's disease.

The behaviour of the network subjected to these generalized decreases in the excitability in the pre-output layer was then compared to the changes in motor behaviour seen in a typical Parkinsonian patient (Hoehn and Yahr stage 3[16]) who gave informed consent to the neurophysiological study approved by

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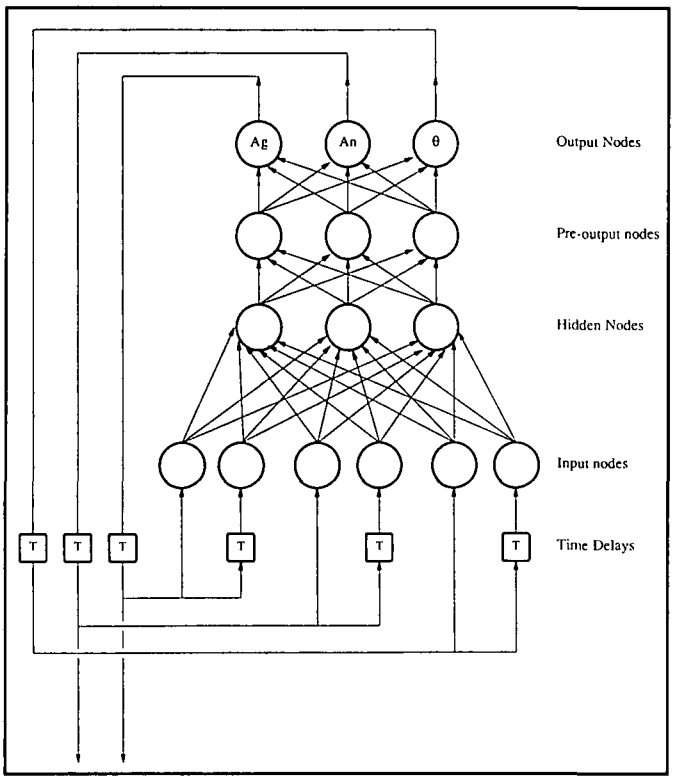

Figure 2 — Network Architecture. The three output nodes for the control of agonist (Ag), antagonist (An) and displacement (θ) activities. In the input layer, there are 2 nodes for each of these variables reflecting both the state transmitted from the output layer through the closed loop plus the state from the precious iterations. Activities in the descending projection may be viewed as those which are required to produce the appropriate EMG activations. T represents a discrete temporal iteration delay.

the Review Committee on the Use of Human Subjects of the University of Toronto. Surface electrodes were placed over the forearm finger flexors (flexor digitorum superficialis) and extensors (extensor digitorum communis) and EMG activity was recorded during simple flexion and extension movements of the index finger, and during repetitive flexion-extension tapping with the index finger. A potentiometric goniometer was used to measure the angular displacement about the metacarpophalangeal joint. To obtain an estimation of the temporal pattern of muscle activation, the EMG was full-wave rectified and smoothed[17,18] to yield a demodulated signal (Figures 4C and 5C).

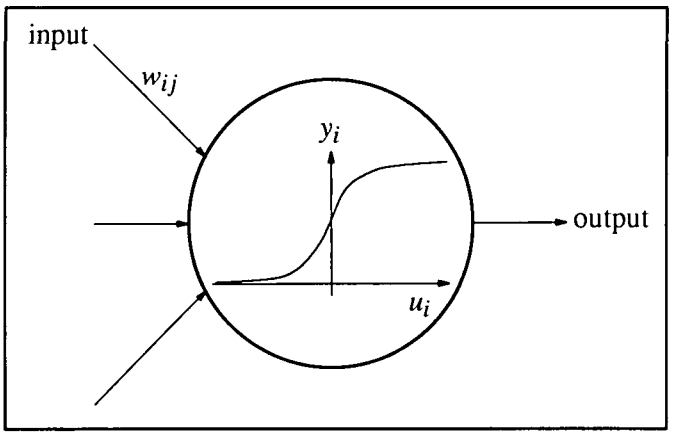

Figure 3 — The input-output relationship of the nodes. The weighted sum of inputs u_i produces an output given by the sigmoidal function shown. A shift to the right in this curve represents a decrease in the excitability of the node.

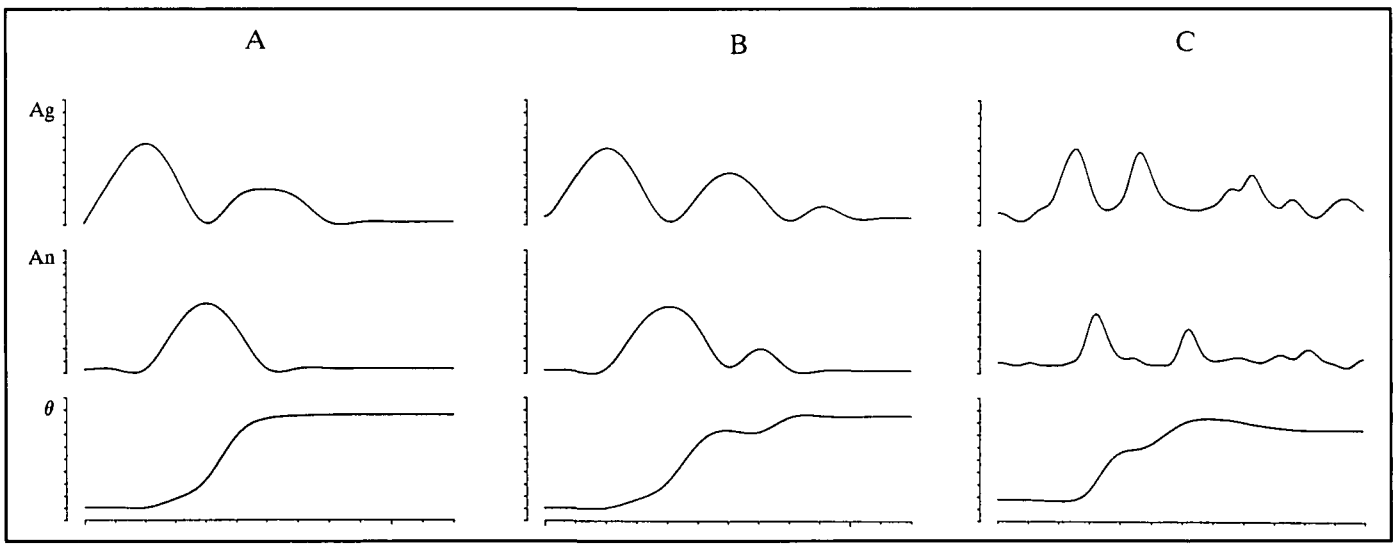

*Figure 4 — **A**. Network output after learning a normal movement. The output nodes reproduce the desired activity shown in Figure. 1A. **B.** Network output after a 30% decrease in the excitability of all nodes in the pre-output layer was introduced. The network shows repetitive agonist and antagonist activation resulting in a displacement which reaches its end point more slowly. In both A and B, each abscissal division represents one iteration, or 25 ms in real time. **C.** Recording from a Parkinsonian patient performing a rapid finger flexion. The first two tracing are rectified and smoothed surface EMG recorded over flexor digitorum superficialis (Ag) and extensor digitorum communis (An) respectively. The third trace represents the angular displacement of the metacarpophalangeal joint of the right index finger. The top tracing shows 2 prominent agonist bursts whereas the 2nd tracing shows 2 unequal antagonist bursts. Abscissa: 50 ms/div. Ordinates: 1.5°/div. for θ; arbitrary integrated EMG units for Ag and An.*

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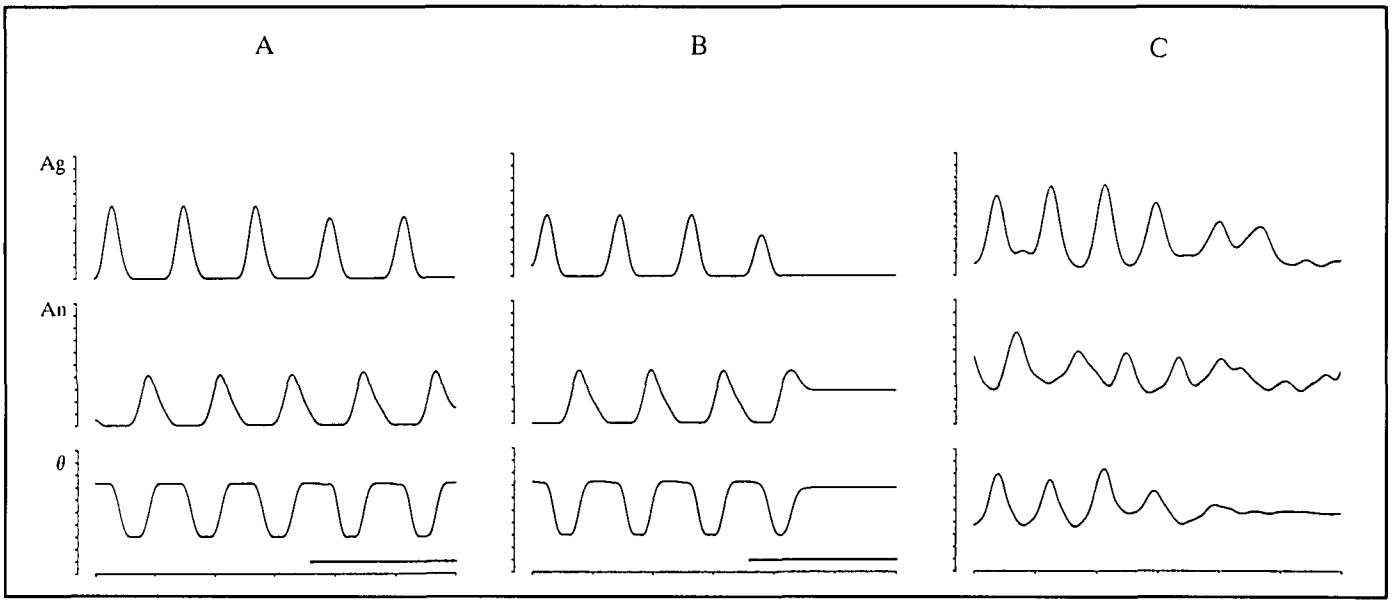

*Figure 5 — **A**. Response of a network after learning a repetitive movement to a moderate decrease in excitability. The first three cycles were generated at normal (100%) excitability, which reproduces the desired output in Figure 1C. When excitability was decreased to 90% of normal (horizontal bar), no substantial changes in the network outputs can be observed. **B**. Network output with a further decrease in the excitability of all nodes of the pre-output layer from 90% to 50% in 4 iterations (horizontal bar). Collapse of the periodic behaviour to a fixed-point attractor results, after which the network outputs do not change with time. In both **A** and **B**, each division on the abscissa represents 10 iterations, or 150 ms in real time. **C**. Recording from a Parkinsonian performing repetitive finger flexion and extension. After several cycles, the patient fails to maintain the repetition, compatible with the interpretation of a collapse of a periodic attractor to a fixed-point attractor shown in **B**. Abscissa: 150 ms/div. Ordinates: arbitrary units of integrated EMG for Ag and An, and 1.5°/div. for θ.*

Results

The network (Figure 2) was first trained to produce the triphasic pattern of activation (Figure 1A) necessary for the generation of a single-joint movement. Figure 4A shows the network output after training, which is in close correspondence to the original pattern (Figure 1A). In Figure 4B is the output of the same network, but in which the excitability of pre-output last layer was decreased by 30%. It can be seen in the displacement tracing that the time to reach the endpoint is longer than in the normal condition in Figure 4A. The displacement itself shows small oscillations rather than the smooth configuration in the normal condition. The slower displacement was accompanied by three agonist and two antagonist bursts rather than the normal triphasic pattern.

We also observed that for small decreases in excitability, the slowing of movement was insignificant. Significant slowing occurred only when the excitability approached a 30% decrease. Figure 4C shows the typical results produced by finger extension in a Parkinsonian patient. The displacement shows a prominent alteration in slope approximately halfway to the endpoint of the displacement (cf. Figure 4B). This displacement was the result of three agonist and two antagonist bursts, similar to the behaviour of the neural network model for bradykinesia shown in Figure 4B.

Figure 5A shows the response of a second network trained to reproduce the repetitive movement when excitability of the pre-output layer was reduced by 10%. The beginning three cycles show the normal learned output at 100% excitability. A 10% decrease in excitability, as indicated by the horizontal bar below the displacement trace, did not substantially alter the output dynamics of the network except for a minor reduction in the amplitude of AG, and a slight change in the durations of the two phases of displacement (θ).

Figure 5B shows the output of the network in which the excitability of the pre-output layer was systematically decreased further from the 90% level to 50% over four iterations (horizontal bar). It can be seen that the alternating agonist-antagonist activation occurs in association with the repetitive displacement but at a critical level of excitability diminution, to 60% in this instance, repetitive displacement and agonist and antagonist activation cease. In the language of nonlinear dynamics, at a critical value of the excitability parameter, the dynamics of the network changed qualitatively, or collapsed, from a periodic attractor to a fixed-point attractor.

In Figure 5C are the results produced by repetitive flexion-extension finger movements in a Parkinsonian patient. As demonstrated in the network model, the patient's alternating agonist-antagonist activation accompanying the repetitive displacement ceases after several alternations despite encouragement to continue moving.

Discussion

Neural network modelling has been successfully applied to the neurosciences, cognitive psychology and artificial intelligence.[19] In clinical medicine, neural network models of language abnormalities[20] and seizure activity[21] have been developed, and provide support for hypotheses concerning pathophysiological mechanisms. Similarly, the techniques in analysis of nonlinear dynamical systems have been applied to such diverse areas as meteorology,[22] physics[23] and physiology.[1,3,6,24] With a recurrent or closed-loop structure, the present network evolves dynamically over time, and can be subjected to

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analysis by nonlinear dynamical techniques. This dynamical configuration seems most plausible for modelling movement and movement disorders. Once the synaptic weights of the network are learned, the network output evolves in a predetermined fashion with no moment-to-moment supervisory entities required to control its evolution. It is suggested that with this conceptualization of movement generation, a motor program can be embedded by an attractor and the configuration of its basin of attraction in phase space, which, in turn, are determined by the configuration of synaptic weights within the network. Changes in the input values or parametric changes to the network itself (e.g., excitability in the present case) may be sufficient to allow the network to demonstrate a diversity of output characteristics such as speed, direction or force of movement. If a parametric change reaches a critical level, network stability may no longer be guaranteed, and a pathological dynamic may emerge allowing the modelling of movement disorders. In our case, bradykinesia was modelled as a *near-bifurcation phenomenon* with the excitability of the pre-output layer representing the parameter that was varied. In the case of repetitive movement, the Parkinsonian abnormality represented a true bifurcation in network dynamics with a periodic attractor collapsing into a fixed-point attractor once a critical parametric value was exceeded.

In the present and many other neural network models, a number of features found in biological neurons, such as membrane channel dynamics, compartmental characteristics of dendritic arborizations, dendritic spikes and differential excitability of neuronal membrane, are not explicitly taken into consideration. For this reason, it may be argued that these neural networks, with simple properties of excitation and inhibition, synaptic modification, sigmoidal input-output relations, and feedback, are not relevant to biological computation. However, as eloquently stated by Hopfield and Tank,[14] these latter properties are *not* the results of approximation. They are real properties of biological networks, and a neural network with these properties "retains two important aspects for biological computation: dynamics and nonlinearity".[14] Additional neuronal features, though not essential for computation per se, will certainly enrich the computational capacity of neural networks.

It should be emphasized that the network model should not be interpreted as an attempt at establishing exact correspondences between components in the model with specific anatomical regions of the CNS. Rather, it is employed to examine *qualitative correspondences* between the generic behaviours of the biologically-relevant network model and movement generation. Despite these reservations, the suggestion that the cortical-basal ganglia-cortical motor loop may be responsible for the iterations that generate a movement is a plausible hypothesis, and represents a starting point in the development of a biologically realistic neural network model of movement generation. This suggestion is consistent with findings in the basic and clinical sciences. There is increasing evidence that the circuitry of the basal ganglia maintains a parallel and modular architecture throughout the cortical-basal ganglia-thalamic-cortical loop and that the loop structure may be defined more precisely as being composed of "mini-loops" emanating and ending in a single cortical column or possible a small subset of columns.[25-28] This anatomical substrate, plus the physiological observation that there is virtually complete overlap of neuronal discharge activity at the cortical and basal ganglia[29] levels is consistent with the interpretation that repetitive iterations in the loop co-evolves with the movement.

The generalized alteration in excitability of the pre-output layer of the network introduced to model Parkinsonism is consistent with experimental evidence. Experimental studies suggest that dopamine deficiency produces symptomatology by causing increased inhibition at the thalamic (pre-output) level of the cortical-basal ganglia-cortical loop. The globus pallidus interna (GP_i), the main output nucleus of the basal ganglia, exerts a predominantly inhibitory effect on its target nuclei in the thalamus.[27,30] MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) treated primates with Parkinsonian symptoms show increased tonic neuronal discharge in GP_i and this is felt to be at least partially due to increased activity in the subthalamic nucleus which exerts an excitatory drive on GP_i.[31] The fact that lesions of the subthalamic nucleus in MPTP-treated primates reverse their Parkinsonism[13] suggests that dopamine deficiency produces its symptomatology because of the increased inhibitory output from GP_i to the thalamus. This is consistent with the decreased excitability introduced to the pre-output layer of the present neural network to model Parkinsonism.

Neural network modelling teaches us that any observable, behavioural variable of a movement is a network phenomenon, and cannot be reduced to the activity of a single neuron or a particular group of neurons (also cf. ref. 14). This suggests the need for a shift in emphasis in studies of motor physiology and pathophysiology. Rather than attempting to correlate the activity of a neuron or group of neurons to a single observable movement variable, a more fruitful approach may, ironically, be that of classical neurology, the clinico-pathological correlation. By observing the behavioral deficits resulting from a structural or biochemical lesion to the motor system, and reproducing these deficits in a network model, the actual neural network architecture and dynamics in the human nervous system may be developed. For example, in this study, we have evidence that if a recurrent or feedback structure, such as the cortical-basal ganglia-cortical loop, iterates to produce a movement, then the bradykinesia and inability to maintain a repetitive movement in Parkinson's disease can be understood in terms of an increased inhibitory input, or a generalized excitability change to a component, such as the thalamus, in the loop. This strengthens the plausibility of the proposed model and suggests that the model can be successfully expanded further.

The present study also suggests a conceptualization of movement disorders in general. We may hypothesize that the CNS symptomatology is a manifestation of near-bifurcation network behaviour. In our network simulation we have observed that stable output behaviour of the network can be sustained over a moderate range of excitability change (Figure 5A). This is an important property for biological networks since parameters such as excitability are constantly influenced by factors such as electrolyte and neuromodulator concentrations. However, when parametric variation approaches a critical value, as may be the case in disease states, network stability can no longer be guaranteed. This instability is illustrated by the collapse of the periodic attractor into a fixed-point (Figure 5B) and the emergence of damped oscillatory or repetitive agonist-antagonist bursts (Figure 4B). Thus, in the context of nonlinear network dynamics, a disease state would not produce frank symptomatology

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until the parametric change induced by the disease state approaches a critical value for bifurcation. The use of recurrent neural networks in the conceptualization of movement generation would thus allow the important idea of dynamical disease[1] to be extended to movement disorders.

Certainly, much work is needed in the further development of these nonlinear dynamical models. Issues concerning postural tone and movement initiation as well as the explicit incorporation of a physical manipulandum or limb which is driven by the network need to be addressed, and will add increased complexity to the architecture and dynamics of the network used. The role of the bereitschaftspotential[32,33] in this model of movement generation and its disorders, the mechanisms of learning and the role of the cerebellar motor loop[4] in this formulation are further problems which need to be pursued. The hope is that with further study, a more comprehensive network model of the motor system may be developed, which not only demonstrates the physical basis of many features of movement generation, but may also bridge the gap in our understanding between cellular or molecular pathology and the spectrum of movement disorders.

Acknowledgements

We thank Mr. Hoi Nguyen for his assistance in neural network programming and computation, and computer graphics. We gratefully acknowledge the support of a grant from the Toronto East General Hospital Research Foundation.

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