

# Complex Symptomatology Simulated By Unstructured Neural Nets

R. A. CYRULNIK, P. A. ANNINOS\* AND R. MARSH

**SUMMARY** *A neural net model with random interconnections is shown capable of exhibiting the features of Parkinson's disease, including cogwheel rigidity, resting tremor, and dysdiadochokinesis. These properties are simulated uniquely for extrapyramidal disease, with spasticity and hyperreflexia predicted for other upper motoneuron lesions.*

**RÉSUMÉ** *Un modèle de réseau neural, avec d'interconnexions au hasard ("neural net model"), est présenté, pouvant démontrer les manifestations essentielles de la maladie de Parkinson, incluant rigidité de forme roue-dentée, tremblement au repos et dysdiadochokinésie. Ces derniers sont simulés seulement par rapport à la maladie extra-pyramidale; on prévoit spasticité et hyper-reflexie, avec d'autres lésions de neurones motrices supérieures.*

## INTRODUCTION

The pathophysiology of Parkinson's Disease is presumed to involve an imbalance of complex servomechanisms incorporating the alpha motoneurons of the spinal cord, Ward (1968). The nature of such neuronal circuitry and the precise manner in which it generates the characteristic features of the disease have, however, remained unclear. In an attempt to elucidate the organizational features essential to the development of such striking phenomena as cogwheel rigidity and tremor, a neural net model developed by Anninos et al. (1970), Anninos (1970), Anninos and Harth (1971), Anninos (1972a), and Anninos (1972b), is proposed as representative of the alpha motoneuron pool. As will be shown, even though it contains only random interconnections, such a net is capable of exhibiting the characteristic features found in Parkinson's disease.

## THE MODEL

The elements of the net consist of neurons exhibiting all-or-none activity, followed by a refractory period, when their summed inputs from other neurons exceeds a given threshold. It can be shown by probability theory, Anninos et al. (1970), and confirmed by simulation on a computer, Anninos (1970), that the fraction of neurons,  $\alpha \eta$ , in the randomly interconnected net that are active at any discrete time  $t_n$ , will determine the fraction active on the

From the Department of Anatomy and Biostatistics School of Medicine and The Mental Retardation Program, Neuropsychiatric Institute, University of California, Los Angeles, California 90024.

\*Present address: Department of Physics, Dawson College, 350 Selby St., Westmount 215, P.Q.

Reprint Address: Dr. P. A. Anninos, Dept. of Physics, Dawson College, 350 Selby St., Westmount, P.Q., Canada.

next interaction ( $t_{n+1}$ ), as shown in Fig. 2A. When these activity curves cross the 45° line, the activity in each succeeding interaction is the same as in the previous one, so that a steady state of activity is present. In general, there exist three such points for each net: the zero point (0 point, Fig. 2A), an upper steady state point (B point, Fig. 2A), and a lower steady state point (A point, Fig. 2A). Because of the slopes of the curves, non-steady state activity between the A and B points will increase toward the B point, while that below the A point will decrease toward the 0 point, so that the B and 0 points are stable and the A point unstable to an imposed change of activity.

With outside input to the net, the activity at any time depends on that at the preceding time, as before, but the curves are shifted, as shown in Fig. 2B. If the external input is excitatory, the shift is such that there is now always some resulting activity, so that the 0 point moves upward along the 45° line. At the same time, the high steady state B point also is raised, and as can be seen, Anninos (1970) and from the geometry of the curve, the unstable steady state A point is shifted downward toward the 0 point. If a curve is then drawn representing these changes in steady state activity ( $\alpha_{ss}$ ) as a function of excitatory input ( $\sigma_+$ ), the result is shown in Fig. 3 for  $\sigma_2^-$  (which corresponds to little or no inhibitory input from outside the net). Note that with enough external inhibitory input ( $\sigma_2^-$ ) to counterbalance the excitatory input, the curve consists entirely of B points, corresponding to a shift of the activity curves shown in the previous figure (Fig. 2B) downward so that they only touch the 45° line at one point.

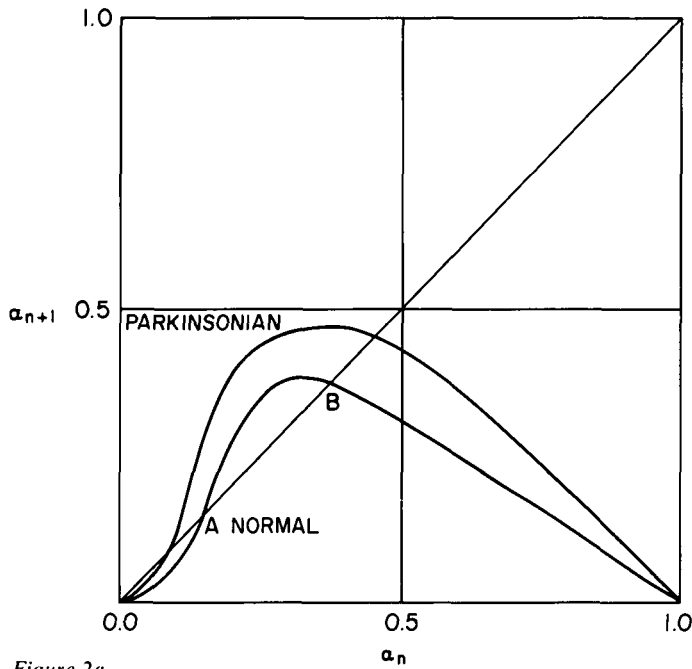


Figure 2a.

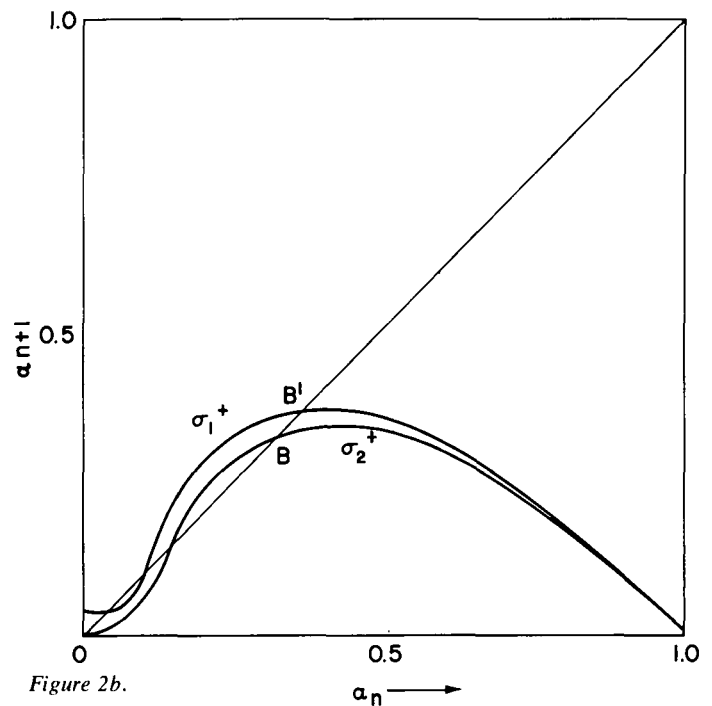


Figure 2b.

Dependence of activity of net on that of preceding iteration. (a) Parkinsonian net has higher steady state (point B) than normal. (b) Effect of increasing input ( $\sigma$ ) in raising the B point.  $\sigma_1 + > \sigma + \alpha_n$  fraction of active neurons at nth iteration.

PHYSIOLOGICAL CORRELATES OF THE MODEL

In the model proposed, we let the neural net correspond to the alpha motoneuron pool of the spinal cord (Fig. 1). There are both excitatory and inhibitory influences acting upon this pool. Peripheral inputs via the dorsal roots constitute excitatory input originating in muscle spindles upon stretch, Patton (1965). From higher centers in the central nervous system (CNS), the resultant input is inhibitory, Ward (1968), at least from extra-pyramidal sites, Mettler (1942) although there is evidence that the pyramidal tracts themselves are excitatory, Tower (1949). There are also peripheral inhibitory connections from antagonistic stretch receptors, Liddell and Sherrington (1925).

Since the patient with disease of the basal ganglia manifests increased tone, we start with the assumption that at rest the steady state motoneuron activity (B point, Fig. 2a) is higher in Parkinsonians than in normals. The pathology in Parkinson's disease is in the basal ganglia, Hassler (1937). Since dorsal

PHYSIOLOGICAL CORRELATES OF THE MODEL

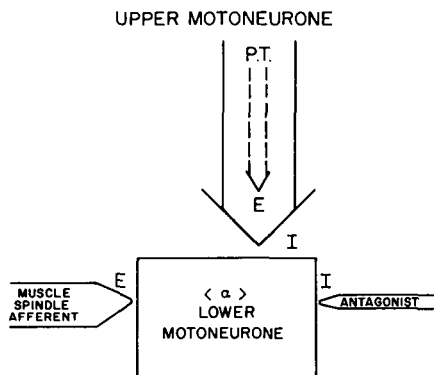


Figure 1. Physiological correlates of the model. The neural net corresponds to the alpha motoneuron pool of the spinal cord having indicated excitatory (E) and inhibitory (I) inputs.  $\langle \alpha \rangle$  fraction of active neurons, corresponding to tone. P.T. = pyramidal tract.

rhizotomy abolishes the rigidity, Pollock and Davis (1930), it is presumed that the pathology causes a resultant decrease in inhibitory influence upon the alpha motoneuron pool rather than a primary increase in excitation in producing the increase of tone.

DISCUSSION

The clinical manifestations of extrapyramidal disease to be simulated consist of cogwheel rigidity, resting tremor, and difficulty in initiating and terminating movements, Merritt (1967). In addition, these features should not be predicted in other cases, such as the normal or the patient with spasticity from an upper motoneuron lesion.

A. COGWHEEL RIGIDITY

Rigidity describes the reaction to passive stretch of the limb innervated by the net. Since such muscular stretch would produce increased excitatory input to the net, an increase in instantaneous activity would result, displacing the resting activity from the B point (Fig. 2a).

As this is not only a steady state point but a stable one, the system normally tends to return to that level of activity in a series of damped oscillations. However, if the stretch is continued, we essentially have a new level of steady input, Anninos et al (1970) so that the steady state resting activity (B point) is raised (Fig. 2b;

point B to B<sup>1</sup>). If activity at the resting point is of sufficient magnitude, as could be the case in Parkinson's disease, the same increase in excitatory input would result in activation of such a large fraction of the total neuronal population, that on the following iteration there would exist mostly refractory neurons, resulting in a very low level of activity at that time (Fig. 4). A net in this situation will return not to the original level of activity, but to the lower steady state. This would correspond to a sudden transition from a high steady state point in the Parkinsonian (Fig. 3, point B<sub>p</sub>) to a lower steady state (Fig. 3, point O<sub>p</sub>) when a given level of input, Anninos (1972) is reached, which cannot happen on the normal curve. In other words, if the resting activity is high enough, and the inhibition low enough, the additional input due to passive muscle stretch can cause a sudden "give" in tone. At this point, however, there are now many non-refractory neurons, so that once achieved any additional input will cause the net to go to the higher steady state level of activity (Fig. 2a, point B) resulting in a "catch" (Fig.

### COGWHEEL RIGIDITY VS. CLASP-KNIFE SPASTICITY

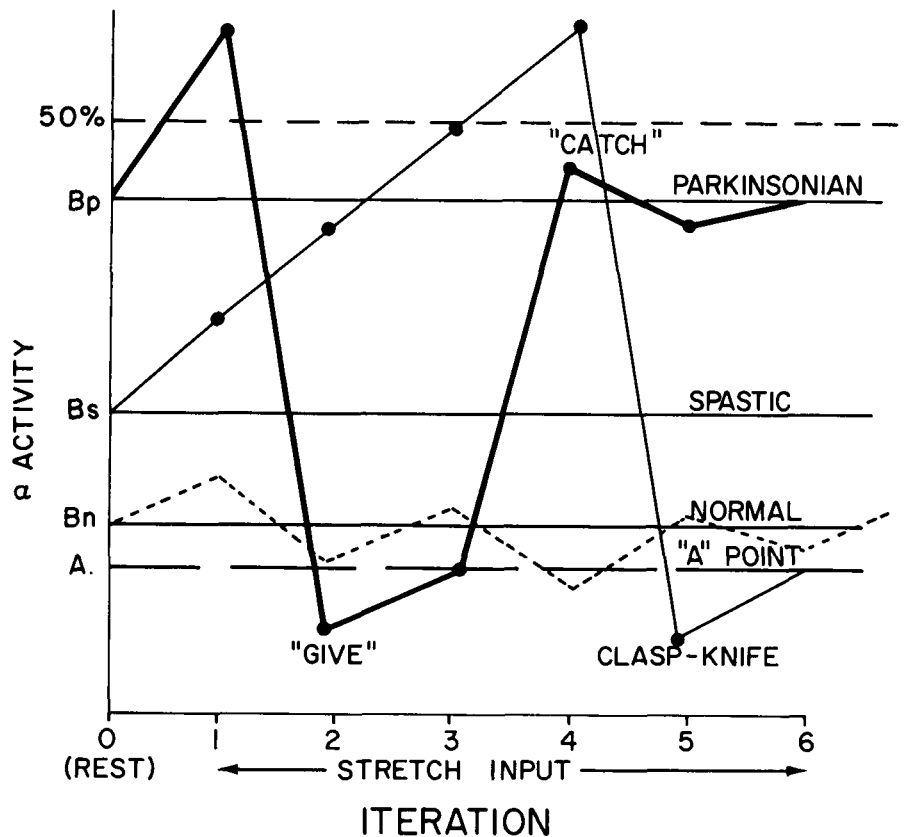


Figure 4. Mechanisms resulting in cogwheel rigidity and in spasticity.

B<sub>p</sub>, B<sub>s</sub>, B<sub>n</sub>, are steady state resting levels of activity ( $\alpha$ ) for Parkinsonian, spastic individual, and normal as have been explained in the text. "A" point is the unstable lower steady state point (see Fig. 2a). If we apply the stretch input, as is indicated with two arrows, and the resting activity is high enough, and the inhibition is low enough, then the input can cause a sudden "give." At this point due to many non-refractory neurons, any additional input will cause the net to go to the higher steady level resulting in a "Catch."

In the spasticity, since there is increasing activity with increasing input, the stretch raises the steady state B, before it achieves the same propensity for a sudden "give" as in Parkinson's and such relaxation in this case is called "Clasp-knife."

Finally, in the same figure we include the normal individual behavior for purpose of comparison as it was explained in the text.

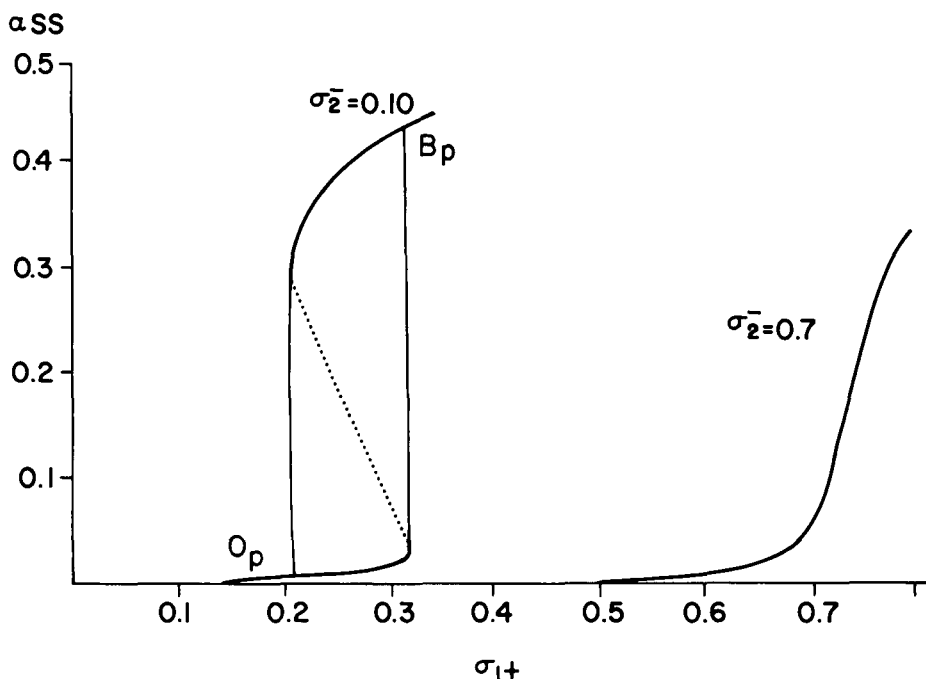


Figure 3. Dependence of steady state activity ( $\alpha_{SS}$ ) on excitatory ( $\sigma_{1+}$ ) and inhibitory ( $\sigma_{2-}$ ) input.

4). The model predicts that the "catch" would be more gradual than the "give" since there is a damped oscillation of activity around the higher steady state as the net approaches it. In spasticity, by definition, there is increasing activity with increasing input. In general, increased input raises the steady state B point (Fig. 2B). There is, however, a theoretical limit on the magnitude of the steady state activity, viz. 50% of the total neuronal population. Therefore, a net with sufficiently high resting activity, as might be seen in Parkinsonism, cannot raise its activity much with increasing input, as would be seen in spasticity.

The question therefore arises why spasticity, rather than rigidity, is present at all in upper motoneuron lesions. As has been shown, Tower (1949), cutting the pyramidal tracts alone results in flaccidity, and it is therefore presumed that the pyramidal tracts themselves are excitatory to the alpha motoneuron as would be expected in order to achieve voluntary motion. However, natural lesions seldom produce isolated pyramidal tract damage but usually also include damage to the extrapyramidal system, Ruch (1965). Thus the steady state resting activity in the model net described above corresponding to the resultant of such a combined lesion, although greater than normal, would actually be lower than in a purely extrapyramidal disease such as Parkinsonism, by virtue of the decrease in facilitatory influence of the pyramidal tract input (Fig. 4). It is therefore conceivable that upon excitatory input as would result from muscle stretch, such a system would have to rise in level of activity before it achieves the same propensity for a sudden "give" as the system in Parkinson's disease, and such a "clasp-knife" type of relaxation is in fact found in cases of clinical pyramidal tract lesions, Ruch (1965). Since it takes longer for the "clasp-knife" phenomenon to occur (Fig. 4) than for the "give" in cogwheeling, it would be expected that the limb would have gone through a good deal of its range of

passive motion, so that cogwheeling would not be seen, but at most a return to the previously hypertonic state would be observed.

B. REFLEXES

The model proposed predicts that the phenomena of "catch" and "give" should be found in the normal individual under appropriate circumstances, as in fact they are. For example, in eliciting a deep tendon reflex, the muscle is stretched, followed after somewhat of a delay by a sudden jerk and then relaxation. Since a monosynaptic arc is involved, it is difficult to explain the apparent delay in the reflex jerk if the latter is due simply to increase in motoneuron activity as a consequence of increased peripheral afferent excitation from muscle stretch. On the other hand, the model proposed predicts that with

enough activity in the motoneuron pool, which would be the immediate consequence of the percussive input, a sudden drop in activity must occur (Fig. 5). This chain of events has the tendency to synchronize the neuronal population at least momentarily, since the large proportion of units made refractory by the percussive input are now all available for activation by the normal tonic influences. Hence one would expect a sudden increase in activity, the reflex jerk, after this relaxation delay, before the net finally settles down to its steady state activity. If inhibitory influences from above are decreased at the time of percussive input, as they presumably are during Jendrassick's maneuver, Hoffman (1951) and Sommer (1940), the synchronized activity producing the reflex jerk would be that much higher.

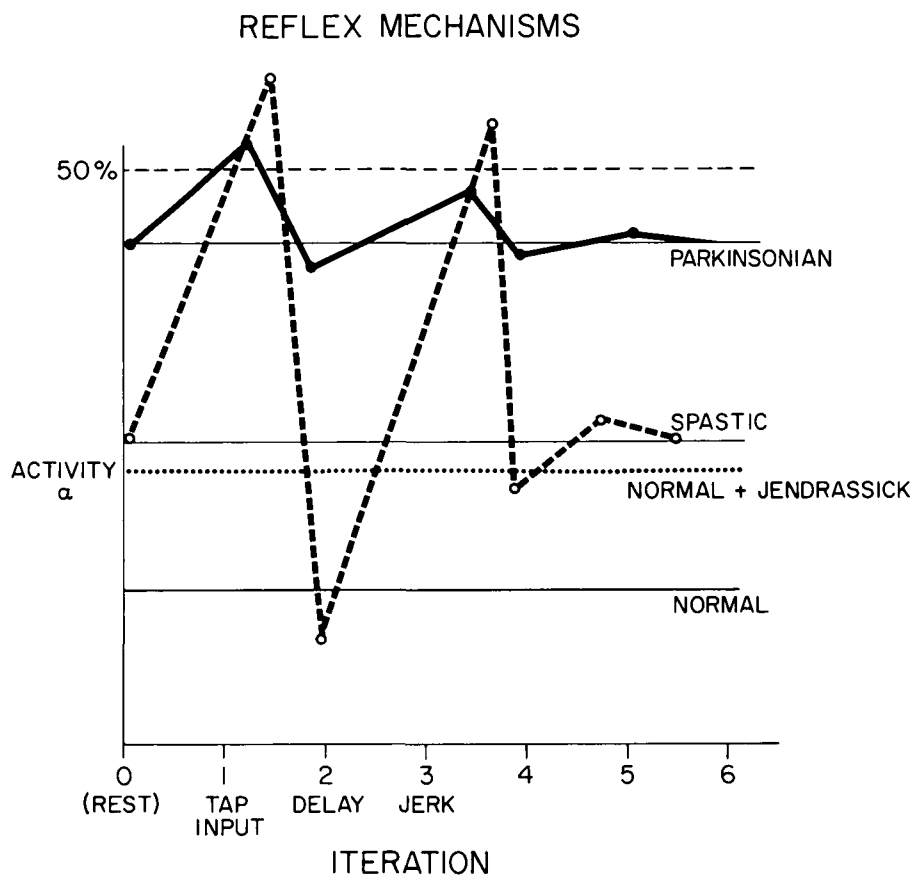


Figure 5. Activity (a) upon momentary percussive input. In Parkinsonian, percussion of the reflex hammer has little effect because the high resting activity keeps a large fraction of the neurons refractory, whereas in the spastic individual the resting activity is lower, so that there are enough non-refractory neurons available to effect a larger than normal hyperactive reflex.

From this perspective, one can also understand another characteristic of Parkinsonism, viz. the failure of Jendrassick's maneuver (reinforcement) to increase deep tendon reflexes, Jung and Hassler (1960). Referring to Fig 5, since we assume the resting activity (time 0) to be higher for the Parkinsonian than for either the normal or spastic individual, the increase in activity due to the percussion of the tendon is limited because so many neurons are refractory. This would remain true even if further decrease in the inhibition from above could be effected via Jendrassick's maneuver. In the spastic individual, on the other hand, the resting activity is lower than in pure extrapyramidal syndromes, as explained above, so that there are enough non-refractory neurons available for the resultant decrease in inhibition from above due to his disease to effect a larger than normal hyperactive reflex (even without reinforcement). In other words, in the Parkinsonian, percussion of the reflex hammer has little effect because the high resting activity keeps a large fraction of the neurons refractory, whereas it can bring out the hyperactivity present in pyramidal lesions because these still leave a group of neurons available for this outside influence. The resultant hypersynchronization may be so large in the spastic individual as compared to the normal, that the net enters a state in which most of its neurons become alternately refractory and then synchronously active, resulting in what corresponds to the phenomenon of clonus seen in spasticity. In this event, the resting activity of the spastic individual has been effectively raised by the percussive input to the level of the Parkinsonian, showing the cogwheel phenomenon.

### C. TREMOR

The genesis of tremor in Parkinson's disease is ascribed by some to rhythmical cellular discharge in the thalamus, Jasper and Bertrand (1966). Such oscillatory change in input to the neural net model proposed to represent the alpha motoneuron pool of the spinal cord

would produce a waxing and waning of the level of activity, at the same frequency. The question remaining unanswered, however, is how neuronal pools, be they in the thalamus or spinal cord, could undergo such regular rhythmical alterations in activity as are seen in the Parkinsonian, and what features of connection are necessary to achieve this. Andersen (1966) has proposed a model involving organized recurrent collateral feedback which produces rhythmical changes in activity. In Parkinson's disease, however, the tremor is extremely regular in frequency. Surprisingly, the model proposed here, despite its random interconnections, is capable of undergoing a highly regular cycling phenomenon. This arises under the following conditions. If the state vector representing the specific neurons active and not active at a given time is ever repeated in the net's history, the activity during interactions following that repetition must also be the same as during the interactions following the initial appearance of that state vector, since the connections between the neurons are unchanged. Therefore a cycle of interactions will occur leading to eventual re-repetition of that state vector, *ad infinitum*. (Note that, in general, a return to a former level of activity is not necessarily equivalent to a return to the same state vector, since the same numerical level of activity could result from excitation of a completely different group of neurons.)

In fact, this model not only is capable of cycling, Anninos (1972), but predicts that such phenomenon would be more likely to occur in Parkinsonism than in the normal individual. Fig. 3 shows the effect on the steady state level of activity for varying excitatory and inhibitory input, Anninos (1972). With enough inhibitory input, there is no inflection point, and increased excitatory input merely increases steady-state activity, which is always stable (B point, Fig. 2). If there is lowered inhibition, as would be seen in Parkinson's disease, the curve is S-shaped, with the steady-state levels

below the upper inflection point being unstable (A point, Fig. 2). As was seen in the discussion of cogwheel rigidity, the tendency in Parkinson's disease is for the net to go from the stable steady state to the unstable one and then return to the former, with the minimal variation in input that would only cause the normal individual to oscillate about his stable steady-state activity. Because such a large fraction of neurons are active and thus synchronized in the Parkinsonian, there is a great tendency for the state vector to be repeated upon return to the original resting state, which is the necessary and sufficient condition for cycling, at least of two states, to take place. This condition, however, is immediately destroyed if any additional input increases the level of activity, since the state vector at that point becomes non-repetitious. Therefore, the model predicts that the tremor will be present at rest, but not on activity, which is the case in Parkinsonism. Another prediction of the model concerning the tremor is that once established, the cycle should be unaffected by procedures which do not directly excite or inhibit the net from outside, since the cycling is regenerated internally within the net. Therefore, this explanation of the tremor is consistent with the observation that dorsal rhizotomy does not affect the tremor in Parkinsonism, which would be difficult to explain if the tremor were due to oscillatory peripheral feedback mechanisms, Pollock and Davis (1930).

### D. DYSDIADOCHOKINESIS

Difficulty in initiating and terminating movements is simply explained by our model as being due to the large number of refractory cells because of the high level of activity. Regardless of whether the outside input is then changed in a resultant excitatory or inhibitory direction, most of the input connections are wasted going to cells that cannot respond, so that both initiation of increased activity of the net and inhibition of ongoing activity are more difficult than in the normal individual.

ACKNOWLEDGEMENTS

The authors would like to express their thanks and appreciation to Dr. Rafael Elul for many stimulating discussions on the topics covered by this presentation.

This research has been supported by NSF grant GB-30498 and by NIH grant NS-8498. Dr. Cyrulnik is supported by NIH Special Fellowship No. 2 F11 NS 2276-03.

REFERENCES

1. ANDERSEN, P. (1966). "Rhythmic 10c/sec activity in the Thalamus," in: *The Thalamus*, New York: Columbia University Press (Purpura, ed.).
2. ANNINOS, P. A., BEEK, B., CSERMELY, T. J., HARTH, E. M., and PERTILE, G. (1970). Dynamics of Neural structures. *Journal of Theoretical Biology*, 26, pp. 121-148.
3. ANNINOS, P. A. (1969). "Dynamics and function of neural structures," Ph.D. Thesis, University Microfilms, Ann Arbor, Michigan, 1970.
4. ANNINOS, P. A. and HARTH, E. M. (1971). Hysteresis Effects in Artificial Neural Nets, 24th ACEMB, 13, pp. 121.
5. ANNINOS, P. A. (1972a). Mathematical model of memory trace and forgetfulness. *Kybernetik*, 10, pp. 165-167.
6. ANNINOS, P. A. (1972b). Cyclic modes in artificial neural nets. *Kybernetik*, 11, pp. 5-14.
7. HASSLER, R. (1937). Zur pathologie der paralysis agitans und des postencephalitische parkinsonismus. *J. Psychol.*, 48, 367.
8. HOFFMAN, P. (1951). Die Aufklärung der Wirkung de Jendrassik-schen Handgriffsdurch de Arbeiten von Sommer und Kuffler. *Dtsch. Z. Nervenheilk*, 166, pp. 60-64.
9. JASPER, H. H. and BERTRAND, G. (1966). "Thalamic Units involved in somatic sensation and voluntary and involuntary movements," in: *The Thalamus*, New York: Columbia University Press (Purpura, D., ed.), pp. 365-390.
10. JUNG, R. and HASSLER, R. (1960). The extrapyramidal motor system, in: *Handbook of Physiology*, 2, pp. 863-927.
11. LIDDELL, E. G. T. and SHERRINGTON, C. S. (1925). Further observations on myotatic reflexes. *Proc. Roy. Soc. B.*, 97, pp. 267-283.
12. MERRITT, H. H. (1967). "A Textbook of Neurology," Philadelphia, Lea and Febiger, pp. 473-482.
13. METTLER, F. A. (1942). Relations between pyramidal and extrapyramidal function. *Res. Publ. Ass. Nerv. Ment. Dis.*, 21, pp. 150-227.
14. PATTON, H. D. (1945). "Reflex regulation of movement and posture," in: *Neurophysiology*, Philadelphia: W. B. Saunders (Ruch, T. C., Patton, H. D., Woodbury, J. W., and Towe, A. L., eds.), 184-195.
15. POLLOCK, L. G. and DAVIS, L. (1930). Muscle tone in parkinsonian states. *Arch. Neurol. and Psychiat.* (Chicago), 23, pp. 303-317.
16. RUCH, T. C. (1965). "The cerebral Cortex: Its Structure and Motor Function," in: *Neurophysiology*, Philadelphia: W. B. Saunders (Ruch, T. C., Patton, H. D., Woodbury, J. W., and Towe, A. L., eds.), 273.
17. SOMMER, J. "Periphere bahnung von muskeleigenreflexen als wesen des jendrassik-schen phenomena." *Dtsch. Z. Nervenheilk*, 150, pp. 249-269.
18. TOWER, S. S. (1949). Chapter 6 in: *The precentral motor cortex*, 2nd ed. (Bucy, P. C., ed.), Univ. of Ill. Press, Urbana, XIV, 615.
19. WARD, A. J. (1968). "The function of the basal ganglia," in: *Handbook of clinical Neurology* (Vinken, P. J. and Bruyn, G. W., eds.), North-Holland Publishing Co., Amsterdam.