A MODEL FOR RESPONSES TO ACTIVATION BY AXODENDRITIC SYNAPSES

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ABSTRACT A simple mathematical model of synaptic activation shows that the response to synaptic activation depends inversely on the size of the subsynaptic process. This provides a theoretical foundation for: the relationship between excitability and cell size; a possible source of plasticity in nerve cell behavior; and the hypothesis that postsynaptic responses to activation at axodendritic synapses are of large amplitude. The last-mentioned idea provides for flexible nonlinear interaction in dendritic regions because the diminution of postsynaptic potentials (PSPs) by prior potential becomes significant at high levels of depolarization. Digital-computer simulations of nerve cell input-output behavior for axodendritic activation based on these ideas reveal: frequency-transfer curves for axodendritic activation saturate; activations combined on different dendritic branches sum approximately linearly while those on the same branch occlude; simultaneous activation of several synapses on a previously inactive dendritic branch results in a large "peak" response at the onset of stimulation; and such an initial peak may be markedly mitigated by a prior depolarization of the branch. The third-mentioned finding may represent a widespread mode of hypersensitivity to stimulus onset in neural systems and in particular may contribute to the "on" responses of sensory channels, and the fourth suggests that depolarizing synapses at extreme peripheries of dendritic fibers might in some cases serve an inhibitory function.

INTRODUCTION

According to the current concept of nerve cell function, significant integration of electrical activity occurs in dendritic regions of nerve cells in the interaction of graded pulses. What is an adequate model of the mechanisms underlying this integration is not, however, presently clear. Rall's work has suggested that nonlinearity may occur even on linear membrane in the interaction of active synapses (2). However, the properties of this nonlinearity and its implications for nerve cell input-output relations have not been adequately illuminated.

The present paper presents a simple mathematical model of synaptic activation and an analysis of nerve cell input-output behavior for axodendritic activation.

METHODS AND ASSUMPTIONS

The present work assumes that membrane in dendritic regions is linear and that synaptic activation is effected through brief changes in membrane permeability. In particular it is

assumed that Equation 1 expresses the propagation of potentials along the dendritic membrane.

$$C\frac{\partial E}{\partial t} = \frac{1}{(r_e + r_i)2\pi R}\frac{\partial^2 E}{\partial x^2} - \sum g_i(E - E_i) \tag{1}$$

This expression rests on the assumptions that a unit area of membrane may be represented by the electrical circuit shown in Fig. 1, that intra- and extracellular fluids are ohmic, and that one need recognize only longitudinal variations of quantities. E is the transmembrane potential, R is the radius of the equivalent cylinder, and r_e and r_i are the resistances per unit length of the external and internal media, respectively.

It is supposed also that the action of a single synapse may be represented by Equation 2.

$$\left.\begin{aligned}\sum g_i &\equiv \beta + P\delta(x - x^*)\delta(t - t^*)\\ \sum g_iE_i &\equiv PE^*\delta(x - x^*)\delta(t - t^*)\end{aligned}\right\} \tag{2}$$

The quantity, β, represents an average permeability including all ionic species and is assumed to be a constant property of the membrane. The action of a synapse located at the

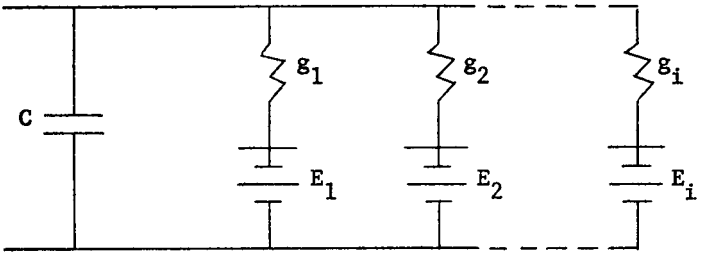

FIGURE 1 Circuit model for unit area of membrane.

position $x = x^*$, activated at the time $t = t^*$, is represented by a brief increase in permeability of the subsynaptic membrane at $x = x^*$ and $t = t^*$. Equation 2 incorporates this assumption with the aid of Dirac delta functions. The magnitude of the permeability change at the synapse is equal to P and the absence of a constant term in the last of Equation 2 means that potentials are measured relative to the resting level.

Equation 3 is the postsynaptic response obtained from Equations 1 and 2 (1, 3, 4). h is the unit step function, and $E(x^*, t^*)$ is the potential across the subsynaptic membrane just before it is activated.

$$E = h(t^*)[E^* - E(x^*, t^*)]\frac{P}{\lambda}\frac{e^{-(t-t^*)-\frac{(x-x^*)^2}{4(t-t^*)}}}{(t - t^*)^{1/2}} \tag{3}$$

λ is the length constant of the equivalent cylinder and is equal to $\sqrt{1/2\pi R(r_e + r_i)\Sigma g_i}$. (The coordinates have been normalized to the length and time constants accordingly.) Fig. 2 shows the spatial and temporal development of this function. For the present purposes we wish to point out three characteristics. First, the function does indeed resemble observed

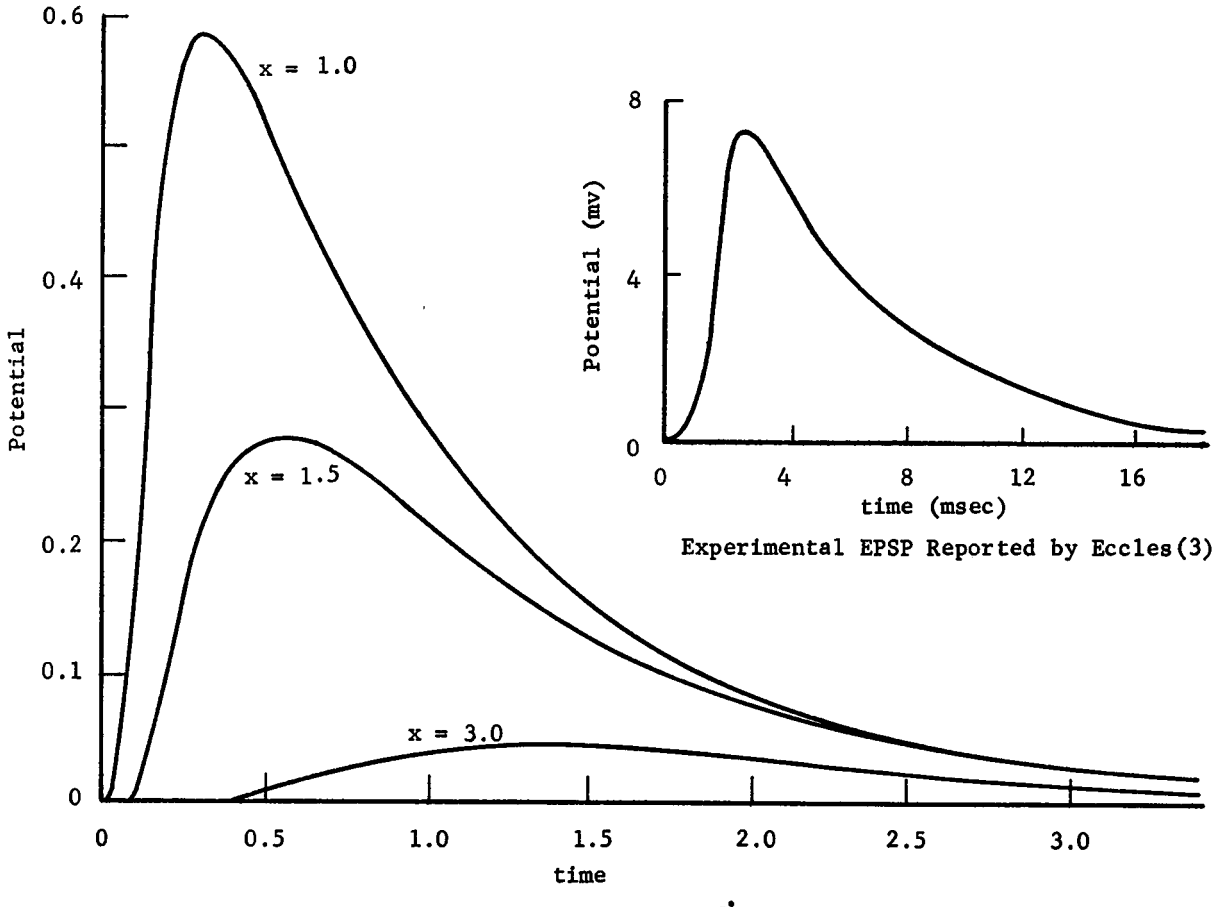

FIGURE 2 The function $\frac{1}{\sqrt{t}} e^{-t-\frac{x^2}{4t}}$ as a PSP.

PSPs (5), at least in a certain range of values.[1] Thus, one can certainly use the function to estimate how postsynaptic potentials propagate and decay on electrotonic membrane. Second, the response amplitude depends on the potential across the subsynaptic membrane at the time of its activation. The simple model used here shows a linear relationship between response diminution and prior potential; the actual data, showing this effect, show only small deviations from linearity (5).

Third, and from the present point of view most important, Equation 3 shows that the response to synaptic activation depends inversely on the size of the equivalent cylinder. This information is contained in the factor λ in the denominator, which is proportional to the square root of the diameter. It is very easy to see why this is happening. Synaptic action according to the above equations is equivalent to adding a branch of conductivity equal to P and a branch containing a current source of amplitude PE^* to the equivalent circuit of each unit of membrane under the synapse, as illustrated in Fig. 3.

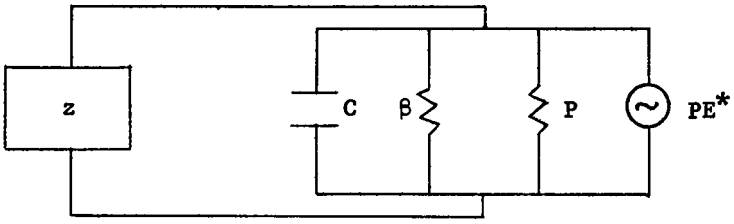

FIGURE 3 Circuit model of activated synapse.

According to the definition of a current source, the amount of current supplied is fixed while the potential across its terminals accommodates itself to the electrical characteristics of the rest of the circuit. In particular, the bigger the total impedance seen from the terminals of the current source, the larger the potential. Another way to look at this is indicated in Fig. 3. The larger the "downstream" impedance, Z, the larger the percentage of current which flows back through the other branches of membrane at the synapse and therefore, the larger the potential at the synapse. It is clear that since smaller fibers present larger longitudinal resistances than larger ones, responses should be larger in smaller fibers.

This idea has been presented earlier by Katz and Thesleff (7) who also provide experimental recordings of miniature end plate potentials in the frog which corroborate the idea.

This relationship between synaptic response amplitude and neural size is significant with regard to a distinction between axodendritic and axosomatic activation, to the relation between excitability and cell size, and to plasticity in single cells.

It is clear, for example, that we should expect much larger responses in dendritic regions than in somatic regions to comparable synaptic action. For example, for a ratio of somatic to dendritic diameter of about 100, a response differential of the order of a factor of 10 is expected. This would suggest dendritic PSPs of the order of 50 mv.

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[1] It should be clear that Equation 3 is only a first approximation to the response to synaptic activation. This expression can be regarded as a valid solution only when Equation 1 holds for values of x extending infinitely away in both directions, or in only one direction if x^* is the origin of the cylinder. Furthermore, the approximation neglects the finite time course of synaptic action. Thus, Equation 3 approaches a Dirac delta function at $x = x^*$ as t approaches t^*. Such problems have been treated in detail by Rall (2, 6). Equation 3 is, however, a reasonable approximate solution and illustrates the fundamental physical processes.

RESULTS

The general picture of electrical activity which arises from these basic considerations consists of very large amplitude PSPs in dendritic regions which propagate and decay approximately like Equation 3.

The immediate and most significant implication of large amplitude dendritic depolarizations is that dendritic PSPs may be markedly diminished by prior activity. This factor provides for a high degree of nonlinear interaction in axodendritic activation in both spatial and temporal summation which is not present for axosomatic activation.

Fig. 4 shows[2] subthreshold activity at the soma corresponding to activation of a

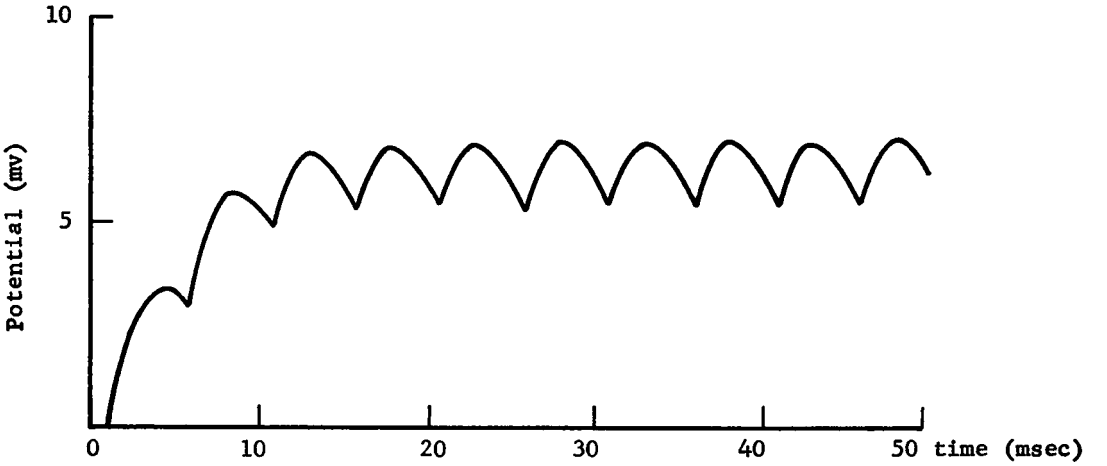


FIGURE 4 Subthreshold potential for regular axodendritic input.

single axodendritic synapse. As the dendritic depolarization level increases through temporal summation of PSPs, subsequent PSPs are diminished in amplitude. Fig. 5 shows how steady-state PSP amplitude depends on input frequency for a single dendritic synapse firing regularly.

Because of this diminution of PSPs, frequency transfer curves for axodendritic activation saturate. For single synapses, the saturation value depends only on the electrotonic distance of the synapse from the soma since the saturation potential at the synapse is 70 mv. Fig. 6 shows a typical transfer curve from a single regularly-firing synapse.

Frequency transfer curves utilizing several dendritic synapses also tend to saturate, but the degree of the effect depends upon the spatial separation of the synapses

[2] The results presented in the remainder of this section have been obtained with the help of the computation scheme described in the Appendix. The calculations used 50 mv as the peak amplitude of a control PSP and 5 msec for the membrane time constant. It is clear, however, that the properties described here are by and large independent of these particular numbers.

and on the temporal distribution of input pulses among them. Fig. 7 illustrates this dependence with frequency transfer curves for several combinations of input in a single dendritic branch.

More detailed calculations involving activity in several dendritic branches are presented in reference 1. The general finding (in agreement with earlier calculations for subthreshold activity made by Rall (2)) is that responses to combinations of

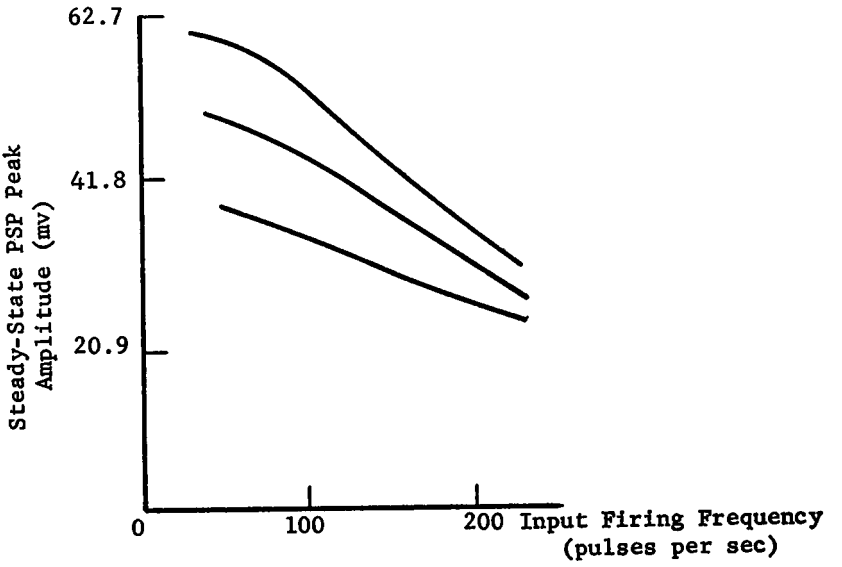


FIGURE 5 Decrease of PSP amplitude with frequency in one axodendritic synapse (the three curves correspond to three different control values of PSP amplitude).

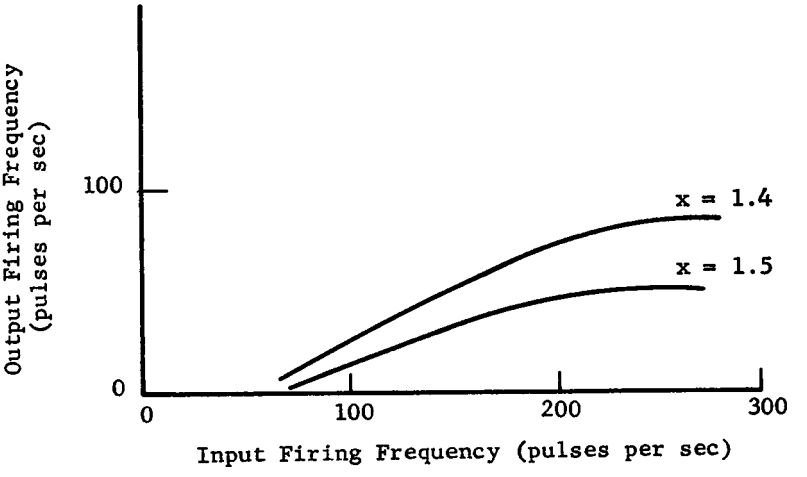


FIGURE 6 Frequency transfer for regular axodendritic input. In this and subsequent figures, x denotes the distance of the synapse from the soma.

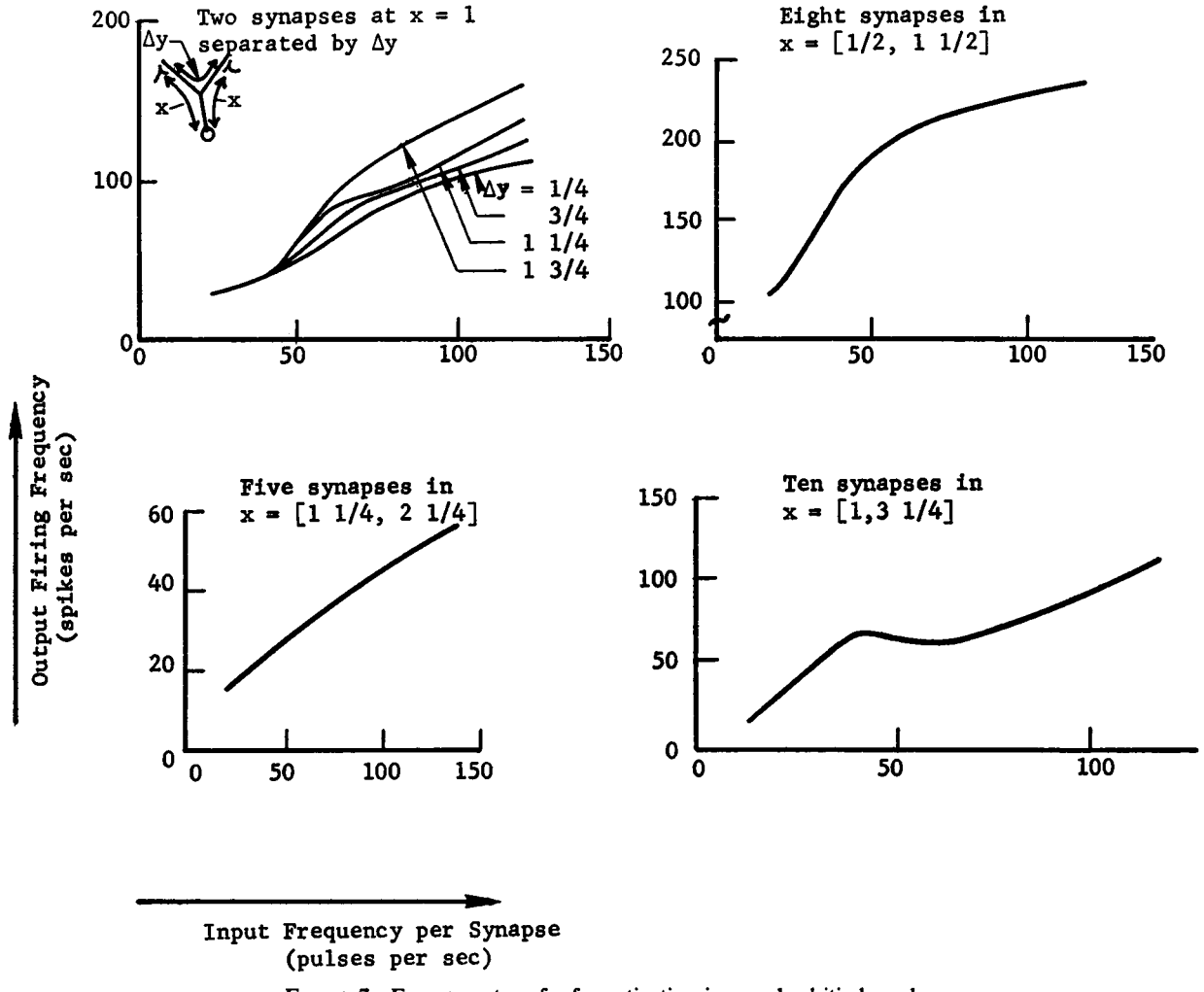


FIGURE 7 Frequency transfer for activation in one dendritic branch.

input tend to be about equal to the sum of the responses to the individual inputs when the individual components are effected on different dendritic branches, whereas if the inputs are combined on the same branch the combined response is less than the sum of the individual responses. That is, activations on different branches sum approximately linearly, while those on the same branch occlude.

The diminution of dendritic PSPs by prior depolarization also provides a mechanism whereby the onset of activity may be emphasized. This is illustrated by the

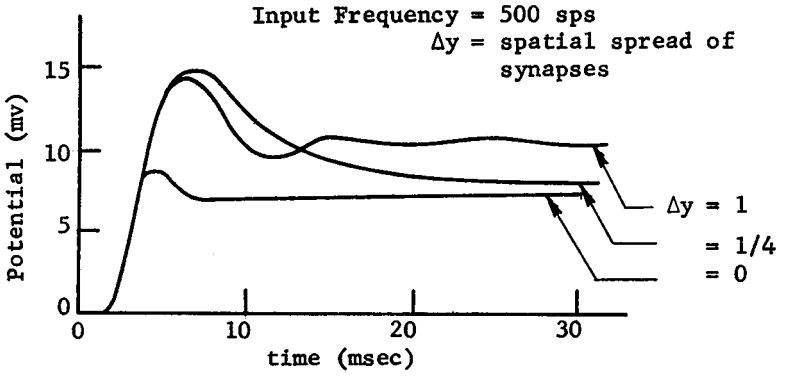


FIGURE 8 Subthreshold potential with activity in one dendritic branch.

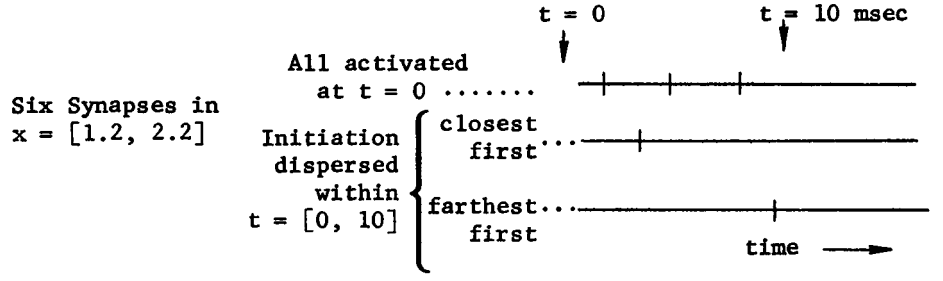


FIGURE 9 Dependence of response on dispersion of input initiation times.

time course of subthreshold activity shown in Fig. 8. The number of initial large PSPs depends on the number of synapses which are activated prior to the inhibiting effect of PSPs from other synapses.

This phenomenon is reflected in output spike trains. Thus, Fig. 9 shows an example of six synapses which, when fired simultaneously elicit a burst of three spikes within the subsequent 10 msec, whereas dispersion of activation times over a period of 10 msec results in only one spike during the same interval. In the case where the saturation level of the PSP summation is suprathreshold, output firing frequency shows an initially high rate of firing, followed by a relatively rapid decrease to a

lower steady-state value. Fig. 10 shows an example of this behavior resulting from simultaneous onset of activity in six synapses on a single dendritic branch. When the PSP summation saturates at a subthreshold level, the output spike pattern shows a burst of pulses at the onset of stimulation and then damps rapidly to silence.

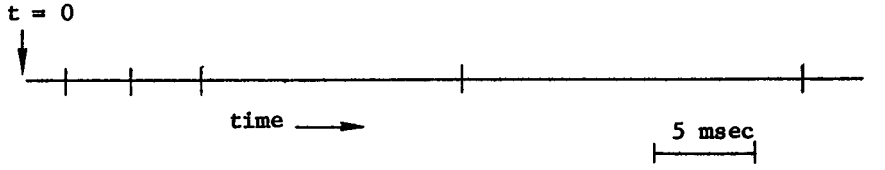
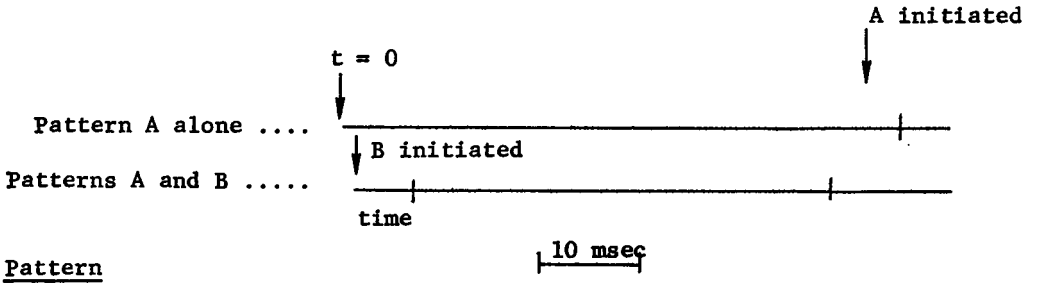


FIGURE 10 Exaggerated response to onset of stimulation.



Pattern

A: 6 synapses in x = [1.2, 2.2]
initiated at t in [50, 60]

B: 3 synapses in x = [1.3, 2.1]
frequency per cell = 100 sps

FIGURE 11 Obliteration of peak response by prior activity.

A point of considerable functional significance is that such a burst at the onset of activation may be markedly mitigated or even obliterated by prior activity in the dendritic branch. Fig. 11, for example, shows a case where a spike resulting from a given activation pattern is completely lost when that activation is superimposed on prior and ongoing activity in the same branch.

DISCUSSION AND CONCLUSIONS

The most fundamental concept in the present work is the idea that the response to synaptic activation depends inversely on neural size. This idea provides an essential key for the interpretation and prediction of nerve cell behavior including a possible source of plasticity. It leads immediately to the idea that PSPs in dendrites are large, which in turn forms the basis of a high degree of flexible nonlinear interaction in dendritic branches.

The theoretical foundation of the first idea is extremely simple and seemingly unassailable and directly corroborated by recordings of miniature end plate poten-

tials (7). Furthermore, other experimental data conform well to the predictions of the idea. For example, if this were not true, then we should expect the larger members of a class of cells subjected to a given stimulation to exhibit higher excitability both because they should have more synapses and because electrotonic decay should be smaller. However, a systematic investigation shows that smaller nerve cells are the more easily excitable (8), as the present concept would predict. It is true that in the special case of activation by only synapses at large electrotonic distances from the soma, the larger spatial decay found in the smaller cell might counterbalance the larger initial amplitude. We expect, however, this situation to be the exception rather than the rule.

Recently several experimental investigations have revealed large amplitude depolarization pulses in dendrites. These have generally been interpreted as a type of all-or-none activity and have been called for example "partial spikes" (9) or "traveling pulses" (10). From the present point of view these potentials are simply the large-amplitude PSPs predicted to occur on smaller neural fibers (dendrites). Also some intracellular recordings have revealed "spikes without prepotentials" (11) associated with certain classes of dendritic activation in hippocampal cells. It is quite reasonable in view of the present work to suggest that such responses might be reflecting large amplitude PSPs. Activations resulting in depolarization peaks of the order of 50 mv at synapses relatively close to the soma will result in peaks well above threshold at the soma. A somatic recording of such an event would resemble a "spontaneous" and continuous rise from the resting potential into an output spike. It must be pointed out, however, that the impedance seen from a synapse on a fine dendrite close to the soma might be considerably different from that seen from a synapse on an infinitely long cylinder. Further work is needed to clarify this point.

The general picture of nerve cell function which has been expressed here then seems quite compatible with these experimental reports of large amplitude pulses in dendritic regions. Furthermore, the concept quite adequately accounts for the results of a systematic investigation of the electrical properties of synaptic transfer in frog motoneurons (12). These results show input-output relations at both the subthreshold and output spike level for both axodendritic and axosomatic activation which are compatible in all respects with the results of the present work. For example, Fig. 12 shows the dependence of steady-state PSP amplitude on input frequency for a case of axodendritic activation.

This investigation indicates that the fundamental mechanism discussed in the present work—that is, large amplitude PSPs in dendrites and therefore, a large role played by diminution of PSPs by prior potential—is indeed operative in frog motoneurons.

Perhaps the most significant of the transfer properties obtained in the present work are first, that there exists a brief elevated level of activity following simultaneous

activation of several synapses on a previously inactive branch and second, that this peak may be markedly diminished by prior activity in the branch.

It seems quite reasonable to suggest that the former may be a widespread mode of hypersensitivity to stimulus onset in neural systems. Such hypersensitivity is, of course, well-known. In particular this mechanism should be directly applicable to the so-called "on" responses (13) in primary afferents.[3] Since these cells typically exhibit dense dendritic arborizations and are typically excited by a group of receptors all of which are excited simultaneously by the stimulus, the necessary conditions for the effect are indeed "built into" the neural apparatus. The mechanism should be effective on more central nerve cells as well.

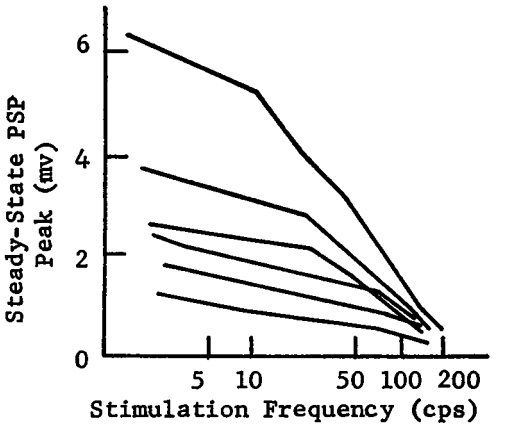


FIGURE 12 Dependence of PSP amplitude on stimulation frequency (12).

That these peaks at the onset of stimulation are markedly diminished by prior activity in the branch adds an interesting dimension to the interpretation of the function of synapses at extreme periphery of dendritic branches. It is not difficult to see that such synapses do not contribute greatly to exciting the cell. They might very well, however, contribute significantly to the cell function by preventing peaks of activity at the onset of stimulation at other synapses in the branch. That is, the initial peak response should be reduced from the control value whereas the steady-state level should be augmented. Because of nonlinear interaction among synapses, however, the steady-state augmentation can be very small. In such a case a depolarizing synapse could be serving a primarily inhibitory function.

Such an interpretation could provide resolution of the otherwise anomalous report of Willis et al. that very small depolarizations were observed in cat motoneurons upon stimulation of heteronymous fibers (15). These depolarizations look like the function of Fig. 2 after propagation over some two length constants.

[3] It is necessary to assume that receptors excite primary afferents by a synaptic mechanism to attribute "on" responses to this mechanism. The present writer has partially developed this concept in reference 1 and 14.

At least two independent investigations have shown that the diameters of neural elements have increased following a high level of electrical activity in the elements (16, 17). Through the mechanism described above—namely, the dependence of synaptic response amplitude on impedance as seen from the synapse—it is clear that such size changes can bring about changes in electrical behavior. An increase in neural size in the course of function should mean both that the initial synaptic response should diminish in amplitude and that the amount of spatial decay should diminish. Thus, depending on the location of the synapse and other parameters, either a decrease or an increase in sensitivity may ensue. Potentiation should be most likely to apply to the case where synapses are on dendrites relatively far from the soma for it is in this case that the spatial decay factor might be the more important. On the other hand, for synapses closer to the soma, habituation or accommodation clearly should ensue. Thus, that post-tetanic potentiation often has been reported to be associated with dendritic activation (18) is quite consistent with the present hypothesis. (Rall has recognized that increasing cell size would decrease the spatial decrement of PSPs and discussed potentiation on this basis (19)).

The experimental reports have indicated size changes of the order of 10%. This would suggest, according to the above analysis, an electrical response diminution to about 83% the control size. Clearly this is a significant fraction. It is not clear what mechanism is causing the size changes. It seems quite plausible to suggest that osmotic pressure brought about by differing concentrations engendered by ongoing ionic fluxes might be the key factor.

It would seem then that the extremely simple concept investigated here does provide for a great deal of flexibility. There is a good deal of evidence to suggest that it does indeed provide an adequate representation of the behavior of real nerve cells and, as far as the present writer can see, none to show that it does not. At the very least its capacities with regard to any particular set of data should be considered prior to the presentation of ad hoc hypotheses and assumptions.

APPENDIX

The computation scheme utilized here simulates electrical behavior produced by synaptic activation.[4] An arbitrary number of synapses may be accommodated and these may be dispersed in an arbitrary number of dendritic branches.

PSPs propagate and decay according to Equation 3. The response at the synapse is the function of Equation 3 evaluated at $x = x^* + 1$. The amplitude of the PSP is diminished in proportion to the potential extant at the synapse at the time of its activation. The diminution of PSP amplitude incorporates also an approximation to the propagation of output spikes back into dendritic regions. Equation 4, which is the solution to Equation 1 with the boundary and initial conditions of Equation 5, has been utilized for this effect. This function is shown in Fig. 13.

[4] This model is an extension of the nerve cell simulation presented in reference 20.

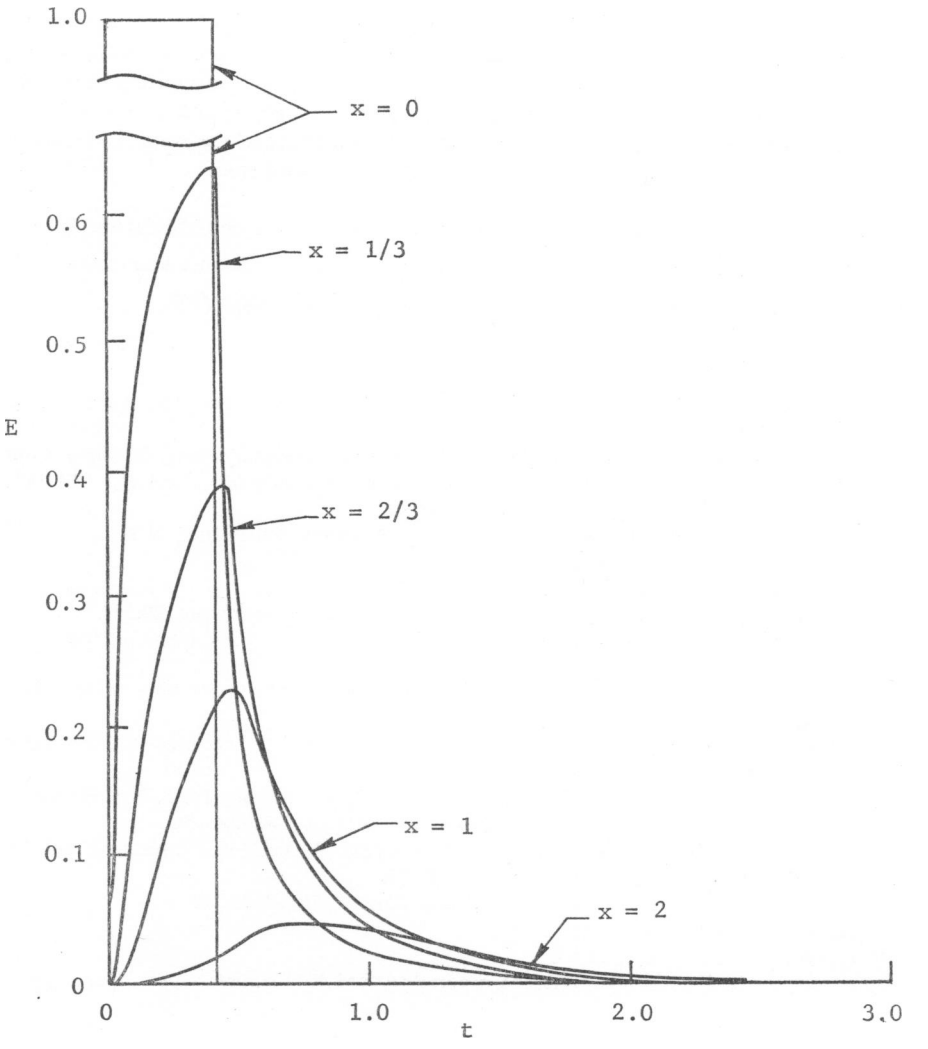


FIGURE 13 Model for propagation of spike potential into dendrites.

$$E(x, t) = \frac{A}{2}\left\{e^{x}\left[\operatorname{erf} c\left((t)^{1/2} + \frac{x}{2(t)^{1/2}}\right) - \operatorname{erf} c\left((t - t^*)^{1/2} + \frac{x}{2(t - t^*)^{1/2}}\right)\right]\right.$$
$$\left. - e^{-x}\left[\operatorname{erf} c\left((t)^{1/2} - \frac{x}{2(t)^{1/2}}\right) - \operatorname{erf} c\left((t - t^*)^{1/2} - \frac{x}{2(t - t^*)^{1/2}}\right)\right]\right\} \quad (4)$$

$$E(x, 0) = 0$$

$$E(0, t) = \begin{cases} A, \ t \epsilon [0, t^*] \\ 0, \text{ otherwise} \end{cases} \quad (5)$$

Output spike trains are produced by a threshold rule. Refractoriness is determined by three factors: (*a*) the threshold increases instantaneously at the occurrence of an output spike and then decays exponentially; (*b*) output spikes propagate backward into dendritic regions and thereby diminish the amplitudes of subsequent PSPs; and (*c*) prior to testing against the threshold rule, the amplitude of the total potential at the soma is decreased by the factor $1 - e^{-K(t-T)}$ where T is the time of the last output spike.

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