Simulation of action potential propagation in complex terminal arborizations

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ABSTRACT Action potential propagation in complex terminal arborizations was simulated using SPICE, a general purpose circuit simulation program. The Hodgkin-Huxley equations were used to simulate excitable membrane compartments.

Conduction failure was common at branch points and regularly spaced boutons en passant. More complex arborizations had proportionally more inactive synapses than less complex arborizations. At lower temperature the safety factor for impulse propagation increased, reducing the number of silent synapses in a particular arborization.

Small structural differences as well as minute changes in the discharge frequency of the action potential resulted in very different activation patterns of the arborization and terminal boutons.

The results suggest that the structural diversity of terminal arborizations allows a wide range of presynaptic information processing. The results from this simulation study are discussed in the context of experimental results on the modulation of synaptic transmission.

INTRODUCTION

In the preceding publication (Lüscher and Shiner, 1990) evidence was presented that within the given geometrical constraints the terminal boutons of nerve fibers may be activated in a complex temporal sequence or may not be activated at all because the afferent impulse fails to propagate beyond branch points. In this paper the simulations have been extended to more complex arborizations in order to evaluate the possibility that complex terminal arborizations may be involved in presynaptic information processing.

Probably the best studied synapse in the mammalian central nervous system is the synaptic contacts made between the Ia muscle spindle afferent fibers and the motoneurons in the spinal cord of the cat. These fibers form complex arborizations giving off several terminal boutons and boutons en passant to the motoneurons (Brown and Fyffe, 1981; Burke et al., 1978, 1979). The current concepts of transmission at these synapses have recently been reviewed extensively (Redman, 1990). One important postulated feature of these synapses is that the probability of releasing a quantum of transmitter varies at each bouton. Some or all boutons may almost always release transmitter (Jack et al., 1981*a*, *b*; Clamann et al., 1989), but others may almost never release transmitter (Redman and Walmsley, 1983; Clamann et al., 1989; Lüscher, 1990) leading to transmission failure and thus silent synapses (Henneman et al., 1984).

One possible mechanism for transmission failure could be failure of the afferent impulse to invade the arborization (Edwards et al., 1976; Lüscher et al., 1979; 1983*a*), but other hypotheses have been advanced. In particular the absence of detectable latency fluctuations in the components of single-fiber excitatory postsynaptic potentials has been used as an argument against the branch point failure hypothesis (Jack et al., 1981*a*; but see Cope and Mendell, 1982*a*, *b*). In addition, it has been argued that failure of the action potential to invade short terminal branches should have no effect on transmitter release because electrotonic conduction should suffice to depolarize the synaptic boutons above the threshold for transmitter release (Redman and Walmsley, 1983). However, as we have shown in the preceding paper (Lüscher and Shiner, 1990), this is a misunderstanding of the branch point failure mechanism because the action potential can fail while approaching the branch point, arriving at the critical site with an amplitude already very much depressed. At present, there is no direct experimental demonstration of conduction failure at axon inhomogeneities leading to silent synapses in the mammalian central nervous system. It is possible that transmission failure may reflect a very low intrinsic release probability at certain synapses (Jack et al., 1981*a*, *b*; Redman, 1990).

It has long been known from theoretical studies that axonal branch points can be regions of low safety for impulse propagation due to impedance mismatch between

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0006-3495/90/12/1389/11 $2.00

the parent and the daughter branches (Goldstein and Rall, 1974; Ramón et al., 1975; for reviews see Waxman, 1972, 1975; Swadlow et al., 1980). Conduction failure at axonal branch points has been observed in the motor axons of various animals (Krnjević and Miledi, 1959; Parnas, 1972; Hatt and Smith, 1976), and in the central nervous system of the leech, branch point failure accounts for silent synapses (Macagno et al., 1987). Due to the small size of terminal arborizations and individual synapses in the mammalian central nervous system, it is at present impossible to record from them to experimentally explore the possibility of conduction failure. No direct experimental evidence is therefore available which could prove or disprove either of the two hypotheses mentioned above.

In this paper we have turned to computer simulations of propagating action potentials in complex terminal arborizations to investigate how temperature, structural details of the arborization and spike frequency influence impulse invasion. Because no data are available on the membrane properties of terminal arborizations in the central nervous system, a standard Hodgkin-Huxley model (Hodgkin and Huxley, 1952) was used with the assumption of uniform membrane properties. Due to this limitation the simulation of action potential in a single selected structure may not be physiologically relevant. What is important, however, is the observation that small differences in the architecture of the terminal structure have a profound effect on impulse propagation and synapse activation. Furthermore, small differences in the discharge frequency of the action potential or in temperature lead to different activation patterns in the terminal arborization. The simulations clearly indicate that action potentials may fail at branch points and boutons en passant, leading to silent synapses. The results suggest that an intimate relation exists between structure and function in the terminal arborization and that the structural variability seen in central terminations offers an enormous potential for presynaptic information processing.

Some of these results have been presented in abstract form (Lüscher and Shiner, 1989).

MATERIALS AND METHODS

Our approach to the simulation of the propagation of action potentials in complex terminal arborizations has been described in detail in the preceding paper (Lüscher and Shiner, 1990). Only a short summary of the technique will be given here. Our approach is based primarily on the work of Segev et al. (1985) and Bunow et al. (1985) who used a general purpose electrical circuit simulation program called SPICE (Vladimirescu et al., 1981) to simulate the electrical behavior in complex dendritic trees. We developed a software package which takes as input a list of the axon segments describing the architecture of the branching structure. These segments must be specified in terms of dimension, their connections to other segments, and whether they consist of excitable or passive membrane. The Spice code for excitable membrane compartments is based on the equations of Hodgkin and Huxley (1952). In addition, information on how the action potentials are to be initiated at the initial compartment of the branching scheme must be input. The SPICE code is generated from this input list and SPICE called as a subroutine. Output consists of the time course of the membrane potential and the various currents in each compartment.

In all simulations the model axons and synaptic boutons have uniform membrane properties and accumulation or depletion of ions in the periaxonal space is not taken into account. Excitable membrane compartments were used with standard Hodgkin-Huxley parameters (Hodgkin and Huxley, 1952). Resting membrane potential is 0.0 mV. The simulations were run at temperatures between 16° and 22°C.

All simulations were carried out on either a μVAX II, μVAX 3500, or a VAX 6000-310 running under VMS. The results of a number of tests of the program are given in the preceding paper (Lüscher and Shiner, 1990). Similar tests were carried out by Segev et al. (1985) and Bunow et al. (1985). From these tests we have concluded that SPICE provides a sufficiently accurate solution to the equations of propagated action potentials in complex arborizations.

RESULTS

We first present the results of our simulations of single propagating action potentials and of trains of action potentials in simple and complex bifurcations at different temperatures. After that, simulations of propagating action potentials through regularly spaced boutons en passant will be presented.

Action potential propagation in complex terminal arborizations

Fig. 1 illustrates the propagation of a single action potential and the associated membrane currents along an asymmetrically bifurcating axon termination. At each bifurcation the axon, which has a uniform diameter of 0.1 μm throughout the whole structure, divides into two branches of unequal length (8.5 μm and 19 μm). This is very short when compared to the resting length constant of 71.5 μm. The arborization carries four terminal boutons designated *A*, *B*, *C*, and *D*. The terminal boutons at the long and the short branch are of equal diameter (4.0 μm), but their lengths are 5.0 and 6.0 μm, respectively. The length of the parent axon is 200.0 μm. The dimensions of the terminal boutons are taken from reconstructed Ia-terminal arborizations in the cat which have been filled intracellularly with horseradish peroxidase (Brown and Fyffe, 1978), and from an EM-study of Ia-terminal arborizations which also demonstrated that the unmyelinated terminal branches have diameters as small as 0.1 μm (Fyffe and Light, 1984). The building block of the arborization corresponds to the arborization analyzed in detail in the preceding paper (Lüscher and Shiner, 1990). The action potential is initiated in the first

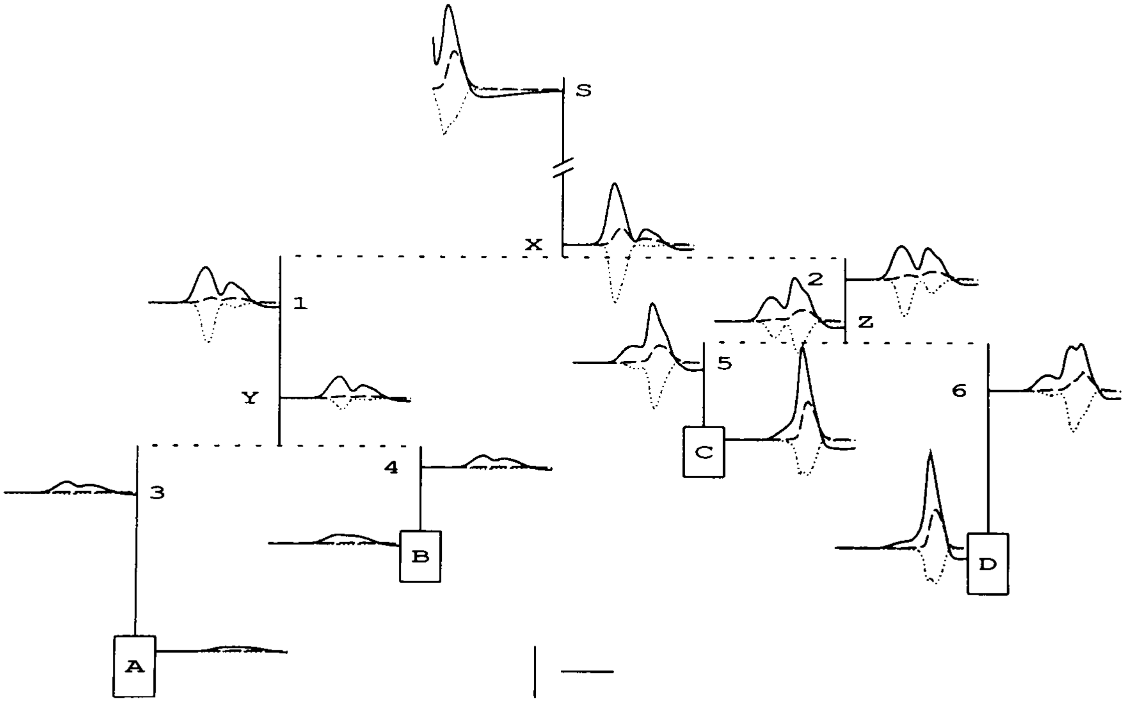

FIGURE 1 Propagation of a single action potential (membrane potential: *solid line*) and the associated Na$^+$ (*dotted line*) and K$^+$ (*dashed line*) currents along an asymmetrically bifurcating terminal arborization and the complex activation pattern of its terminal boutons. The action potential is initiated at the first segment at site S. The action potential fails to propagate beyond branch point y and z. The electrotonically conducted potential is reflected at the sealed end of bouton C, increasing the membrane potential above threshold and evoking a new action potential in bouton C. This action potential is antidromically conducted to branch point z and beyond to branch point x where it fails to propagate further. At branch point z it also spreads into the long branch leading to bouton D which develops an action potential. Boutons A and B are not activated. Horizontal scale bar, 2.0 ms; vertical scale bar, 50.0 mV or 1,000 μA/cm^2, respectively. The arborization is drawn to scale; as a reference the size of bouton A corresponds to 4.0 × 6.0 μm. The horizontal dashed lines simply separate the various branches; they do not represent length.

compartment of the parent axon at point S by setting the membrane potential initially to 50.0 mV ($V_{\text{rest}} = 0$ mV). Temperature is 16.0°C.

While approaching the first branch point x the amplitude of the action potential decreases (Fig. 1). The small second biphasic deflection is due to decremental reverse conduction of the action potentials initiated in the two terminal boutons C and D. The action potential is actively propagated into both branches as indicated by the large Na-inward currents. The amplitudes of the two action potentials get smaller while approaching branch points y and z, respectively, and fail to propagate actively beyond these branch points. The amplitude of the action potential is smaller at branch point y than at branch point z. Along the branches leading to boutons C and D, it decays electrotonically but is reflected at the sealed ends. The reflection increases the membrane potential in bouton C above threshold, evoking a new action potential; this does not occur in bouton D which resides on a longer branch. The action potential induced in bouton C is propagated back to branch point z and further to branch point x where it fails to propagate further. At the same time it spreads from branch point z into the long branch leading to bouton D, which then develops a full size action potential. The action potential from bouton D cannot actively back-propagate, because it superimposes with the trailing edge and, therefore, with the refractory period of the action potential originating from bouton C. This reverse conducted wave is not actively propagated beyond branch point x, but its decremental decay can be followed down to boutons A and B. Because the amplitude of the action potential is smaller at branch point y than at branch point z, the electrotonic spread into boutons A and B decays too rapidly to evoke an action potential in these terminal boutons. This sequence of events is seen by tracing the time of occurrence of the action potentials in Fig. 1.

Although the pattern of spatial and temporal activation of this terminal arborization involves orthodromic as well as antidromic spike propagation and activation of terminal boutons, the result in terms of transmitter release is simple. Boutons A and B are not depolarized sufficiently to release transmitter because the action potential does not invade them, whereas boutons *C* and *D* both develop action potentials and would release transmitter, although with a considerable temporal dispersion. This dichotomous activation pattern is not due to differential conduction failure, because the nervous impulse is conducted into both daughter branches at branch point *x* and fails at both branch points *y* and *z*. Only in bouton *C*, which is reached first in the branching scheme, does the passively decaying potential depolarize the synaptic bouton above threshold and evoke an action potential. This new action potential is capable of activating bouton *D* with considerable delay. As already demonstrated in an earlier paper (Lüscher and Shiner, 1990) a terminal bouton must not be reached by a propagated action potential in order to be activated, because the reflection of the electrotonic potential at the open-circuit sealed end structure might increase the membrane potential above threshold.

It is important to realize that boutons *A* and *B* are depolarized only very slightly even though they are electrotonically very close to the branch point at which the action potential fails (approximately one tenth of the resting length constant).

In the following (Fig. 2, *A–D*) we will analyze the activation pattern of synaptic boutons in increasingly complex arborizations at different temperatures. The same asymmetrical bifurcation as described above is used as a building block for the different arborizations. All permutations of a first, second and third order branching scheme are analyzed. The temporal and spatial activation patterns of the terminal arborizations are not presented in detail. Regardless of how and when a terminal bouton is activated, it is indicated by a solid symbol. Synaptic boutons which are not activated by an action potential and are depolarized <20 mV above resting potential are indicated with open symbols. With decreasing temperature, more and more terminal boutons are activated. This is expected because with decreasing temperature the safety factor for impulse propagation through branch points increases due to widening of the action potential (Hodgkin and Katz, 1949; Westerfield et al., 1978; Lüscher and Shiner, 1990). A detailed analysis of action potential propagation in the first order, asymmetrical bifurcation is given in the preceding paper (Lüscher and Shiner, 1990). In general, the number of silent synapses is larger in the more complex arborizations than in the simpler branching structures. Except at 16°C (Fig. 2 *D*) the mean number of active synapses is always smaller in the more complex arborization than in the less complex structure. At even lower temperatures, all synaptic boutons would be activated (not shown).

The different permutations at each degree of complexity may show different numbers of activated terminal boutons. For example in Fig. 2 *D*, in the first structure from the left, all terminal boutons are activated, whereas in the fourth structure from the left only a single bouton is activated. Evidently small differences in the structure can have profound effects on the activation pattern of the terminal boutons. Small groups of boutons clustered on short collaterals are most likely to fail because they represent a large electrical load to the approaching action potential.

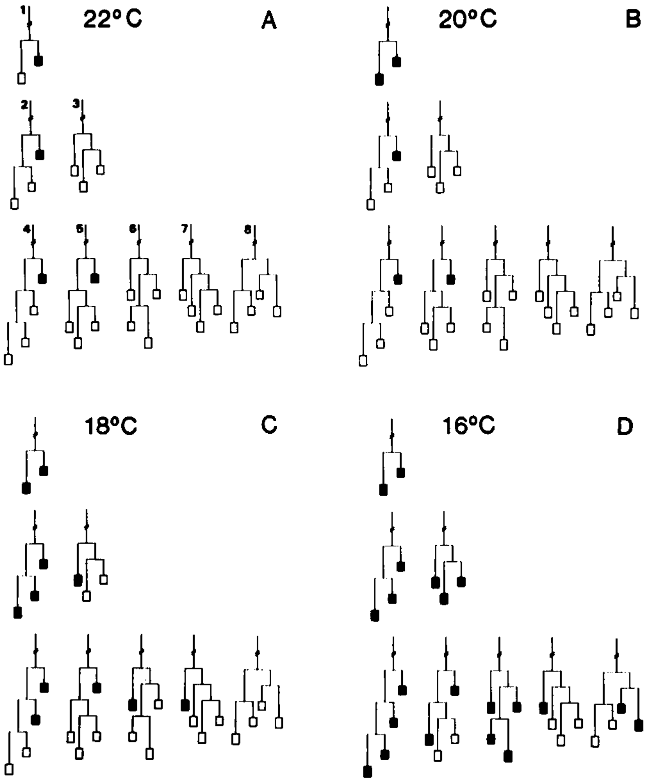

FIGURE 2 Activation pattern of terminal boutons by a single action potential in eight different arborizations of increasing complexity at different temperatures. Boutons which are not depolarized more than 20 mV above resting potential are indicated with open symbols.

Trains of action potentials in complex terminal arborizations

Because information is coded in sequences of action potentials rather than in single spikes, we have simulated the propagation behavior of spike trains in selected arborizations. Fig. 3 illustrates such a case. Fig. 2 *D* shows that a single action potential is capable of activating all four synaptic endings at 16°C. In Fig. 3, the simulations were also performed at 16°C and the action potentials were elicited by short (100 μs) suprathreshold current pulses at the first compartment of the parent axon (site *S*). The interpulse intervals in columns *1*, *2*, *3*, and *4* are 10.0, 8.0, 6.0, and 4.0 ms, respectively. The voltage transients are illustrated for boutons *A*, *B*, *C*, and *D* and the branch points *x*, *y*, and *z*. Simulations were carried out for 50 ms.

A train of action potentials with an interpulse interval of 10 ms (Fig. 3, column *1*) is capable of activating all four boutons without a single failure. If the spike interval is shortened by 2.0 ms to 8.0 ms, boutons *A* and *B* are activated without failure whereas only the first two spikes activate boutons *C* and *D*. These two synaptic boutons remain silent thereafter (Fig. 3, column *2*). If the spike interval is once more shortened by 2.0 ms to 6.0 ms, bouton *A* is no longer activated by every impulse. Every second action potential fails to activate bouton *A*. The remaining three terminal boutons respond only to the first action potential of the spike train (Fig. 3, column *3*). At a spike interval of 4.0 ms all four boutons respond only to the first action potential of the spike train and remain completely silent thereafter (Fig. 3, column *4*).

In Fig. 2 we have shown that different permutations of arborizations of the same degree of complexity may behave differently in terms of activation of the terminal boutons. In Fig. 4 we test whether the two permutations of a second order branching structure behave differently for regular trains of action potentials. At 16°C, the three boutons in the two structures illustrated in Fig. 4, *A* and *B*, are all activated by a single action potential (cf. Fig. 2 *D*). A different activation pattern of the synaptic boutons can be seen for different, but regular trains of action potentials.

The action potentials are elicited by short (100 μs) suprathreshold current pulses delivered to the first compartment of the parent axon at site *S*. The spike intervals in columns *1*, *2*, and *3* are 8.0, 6.0, and 4.0 ms, respectively. The voltage transients are illustrated for boutons *A*, *B*, and *C* and for branch points *x* and *y*.

For spike intervals of 8.0 ms all three boutons in both structures are activated without failure (Fig. 4, *A* and *B*, column *1*). At a higher spike frequency (6.0 ms spike interval) the two structures behave differently. In Fig. 4 *A* (column *2*) bouton *A* is activated without failure, whereas in Fig. 4 *B* (column *2*) bouton *A* is activated only by every second action potential. Boutons *B* and *C* in Fig. 4 *A* are activated by the first two action potentials and thereafter by every second spike only. The same synaptic boutons are activated only by the first action potential of the train in the structure illustrated in Fig. 4 *B*. If the spike interval is shortened by 2.0 ms to 4.0 ms, boutons *A*, *B*, and *C* are

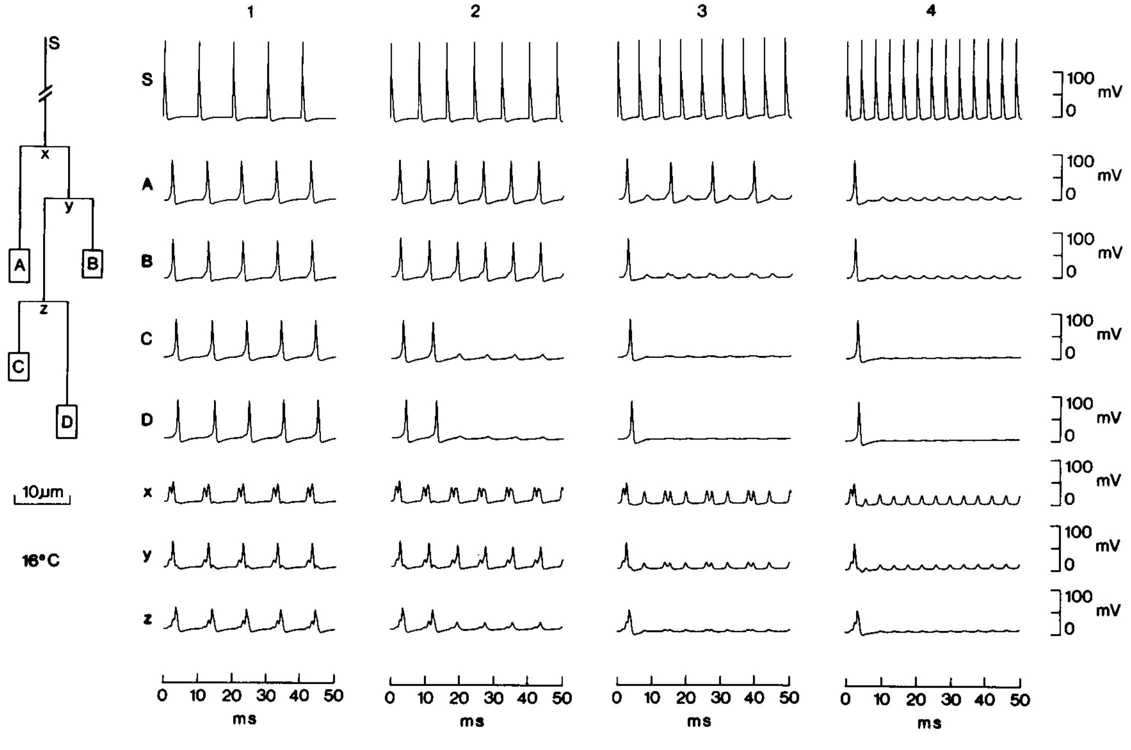

FIGURE 3 Propagation of a train of action potentials in a complex terminal arborization. This arborization pattern corresponds to pattern number 6 in Fig. 2. The interpulse intervals in columns *1*, *2*, *3*, and *4* are 10.0, 8.0, 6.0, and 4.0 ms, respectively. The voltage transients are illustrated for the site of stimulation *S*, for boutons *A*, *B*, *C*, and *D*, and for the branch points *x*, *y*, and *z*.

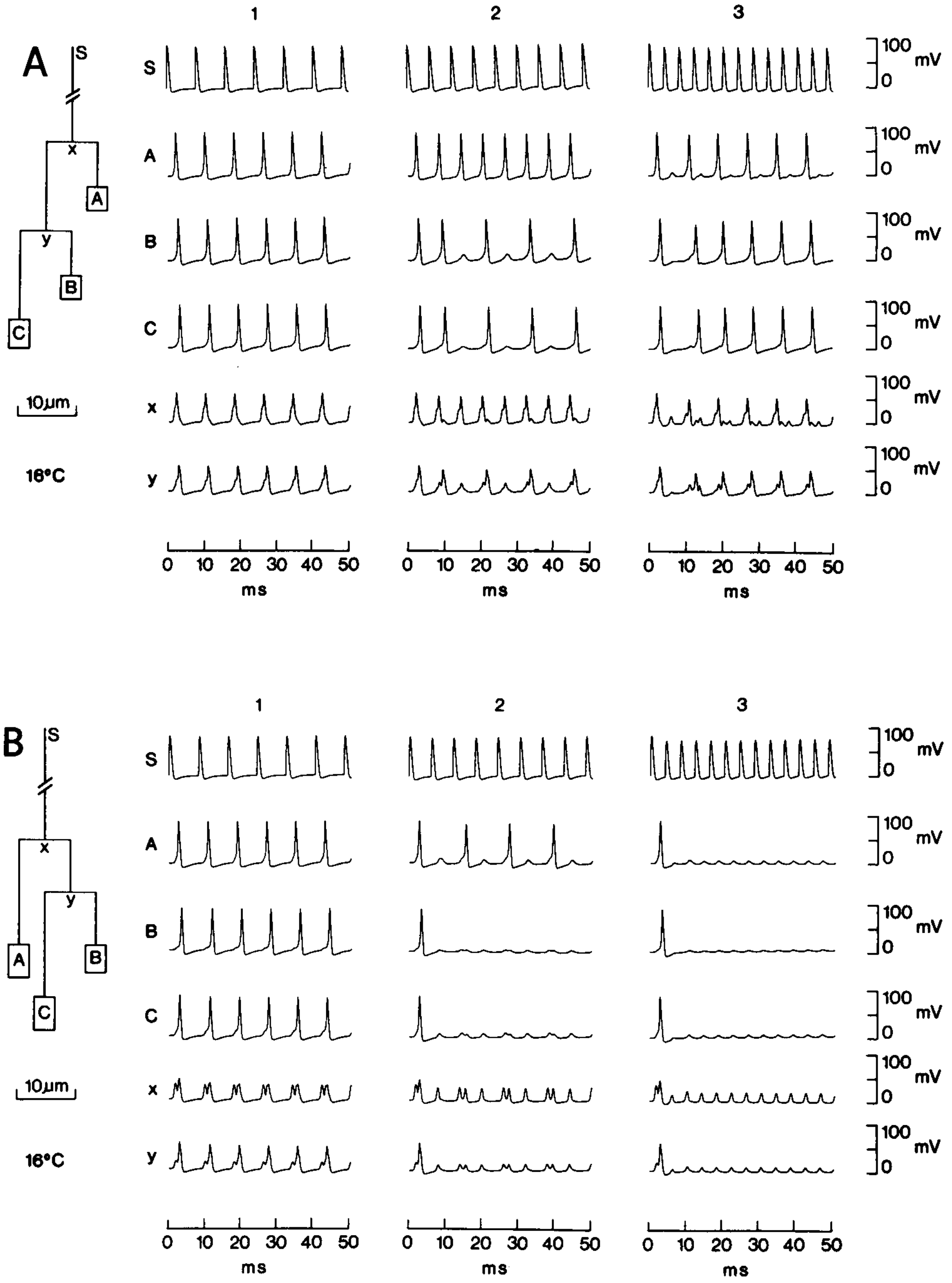

FIGURE 4 Propagation of trains of action potentials and activation pattern of synaptic boutons in two similar terminal arborizations. The interpulse intervals are 8.0, 6.0, and 4.0 ms in columns *1*, *2*, and *3*, respectively. In *A*, the second bifurcation is connected to the long branch of the first order bifurcation. This branching pattern corresponds to number 2 in Fig. 2. In *B*, the second order bifurcation is connected to the short branch. This pattern corresponds to number 3 in Fig. 2. The voltage transients are illustrated for the site of stimulation *S*, for the boutons *A*, *B*, and *C*, and for the branch points *x* and *y*. Different activation patterns can be seen in the two quite similar structures.

activated by every second impulse in Fig. 4 *A* (column *3*), in Fig. 4 *B* only the first spike is capable of activating the synaptic boutons (column *3*).

If we compare the activation patterns of the terminal boutons in columns *2* and *3* of Fig. 4 *A* an additional interesting observation can be made. In column *2* propagation failures occur at branch point *y* leading to failure of every second impulse. In column *3*, however, propagation failure has already occurred at branch point *x*. Therefore, only every second impulse reaches branch point *y*, which is able to pass the reduced frequency without introducing additional failures. This clearly indicates that higher discharge frequencies must not necessarily introduce a higher failure rate. Depending on where intermittent failure occurs first in serially interconnected branch points, different activation patterns can be observed for different spike train frequencies.

Propagation of action potentials through boutons en passant

In the central nervous system synapses are often arranged in a linear sequence and are then called boutons en passant. Long strings of boutons en passant have been observed on the parallel fibers of the cerebellum (Fox and Barnard, 1957), the Schaffer collaterals of the hippocampus (Andersen, 1975), on the muscle spindle afferent fibers of the frog, and, with fewer synapses, on the muscle spindle afferent fiber of the cat spinal cord (Grantyn et al., 1984; Brown, 1981; Burke et al., 1978). These synapses are connected by short axon segments and, depending on the number of synapses, represent a large electrical load to the approaching action potential.

In Fig. 5 the simulation of the propagating action potential through an increasing number of boutons en passant is illustrated. In the center of the long branch of a simple asymmetrical bifurcation 1, 2, 3, 4, or 5 boutons en passant are present. The length of the parent axon is 250 μm. The uniform diameter of the axon is 0.2 μm. The dimensions of all synaptic boutons are 5.0 × 5.0 μm. The length of the axon segments connecting the boutons en passant is 2.0 μm. The action potential is elicited at the first compartment of the parent axon by setting the initial condition to 50 mV. The voltage transients are illustrated (*from top to bottom in each column on the left side*) for the first compartment of the parent axon (site of stimulation), the first compartment of the long branch immediately after the bifurcation, the compartment just before the first bouton en passant, the boutons en passant (labeled *1* to *5*) and the terminal boutons *A* and *B*. The simulation was carried out at 22°C.

As the number of boutons en passant is increased (up to 4), propagation into the string of synapses is increasingly delayed, but all boutons en passant are activated together. At the first bouton en passant the action potential is reflected (*arrows*), leading to a decremental reverse conduction of the action potential. Its potential spread can be followed back into bouton *B* which resides on the short branch of the bifurcation. If there are more than four boutons en passant the action potential fails to propagate beyond the first bouton. Because the action potential fails gradually while approaching the first bouton, the whole string of boutons en passant is depolarized only slightly, probably not sufficiently to release transmitter. It is important to realize that the action potential either fails at the first bouton, rendering all the connected boutons silent, or it does not fail, and instead activates all synaptic boutons in the string together. For the structure illustrated in Fig. 5, it is not possible for the action potential to fail at any one of the interconnected boutons.

Fig. 6 illustrates the propagation of high frequency trains of action potentials through a string of boutons en passant. The dimensions of the terminal arborization are the same as for the structure illustrated in Fig. 5. Four boutons en passant are present at the long branch. Action potentials are elicited by injecting short suprathreshold current pulses into the first compartment of the parent axon. The spike intervals for the three simulations differed only by 0.1 ms. The intervals were 3.8, 3.9, and 4.0 ms in columns *1*, *2*, and *3*, respectively. The voltage transients are illustrated for the first compartment of the parent axon (site of stimulation, *S*), the branch point *x*,

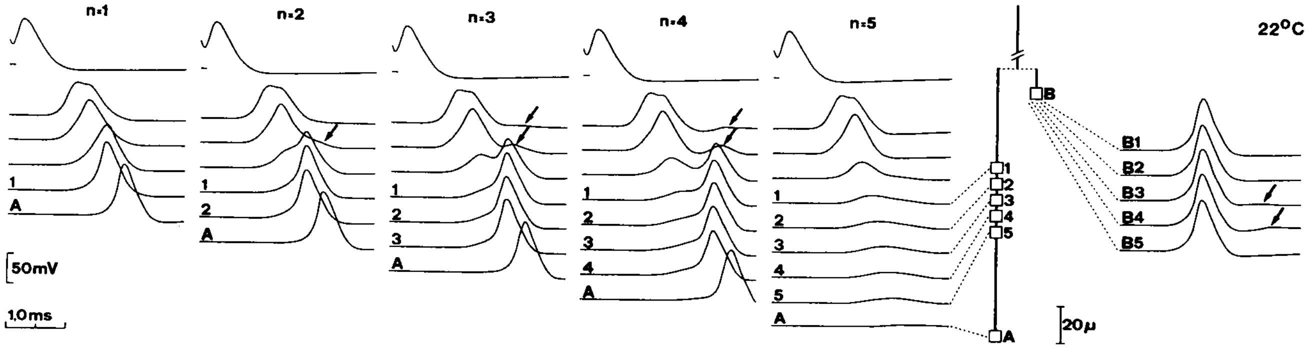

FIGURE 5 Propagation of a single action potential through an increasing number (1 to 5) of boutons en passants. The voltage transients are illustrated for the site of stimulation, the first compartment of the long branch immediately after the bifurcation, the compartment just before the first bouton en passant, the boutons en passant (labeled *1–5*), and the terminal boutons *A* and *B*. If more than four boutons are connected in a row, the action potential fails to propagate past the first bouton. Arrows point to decremental reverse conducted action potentials.

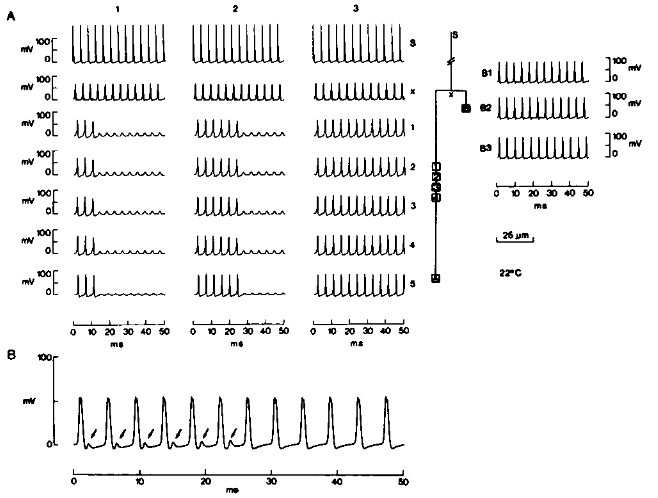

FIGURE 6 (*A*) Propagation of high-frequency trains of action potentials through a string a four bottoms en passant. The interpulse intervals in columns *1*, *2*, and *3* are 3.8, 3.9, and 4.0 ms, respectively. The voltage transients are illustrated for the site of stimulation *S*, for the boutons 1, 2, 3, 4 *A* and *B* and for the branch point *x*. Very small differences in action potential frequency lead to very different propagation patterns. (*B*) Enlargement of the voltage transient recorded at branch point *x* (column *2*) illustrating the decremental reverse conducted potentials (*arrows*) up to the point of propagation failure at bouton *1*.

and all the synaptic boutons labeled from *1* to *4*, and *A* and *B*.

For a spike interval of 4.0 ms (column *3*), all boutons are activated. A very small reverse propagated potential, reflected at bouton *1* can be observed at the branch point and at bouton *B*. If the spike interval is shortened by only 0.1 ms (column *2*), the first six action potentials propagate without failure through the string of boutons en passant, but the following action potentials fail to activate the synaptic boutons. If one carefully inspects the small reverse propagated potential (column *2*, branch point *x*, enlarged in Fig. 6 *B*) one can observe a gradual increase of its amplitude after each action potential up to the point where the action potential fails at the first bouton en passant. This is probably due to the fact that each action potential falls into the relative refractory period of the preceding spike. This gradually increasing antidromically conducted potential interacts with the orthodromically conducted action potential leading to a gradual reduction of its amplitude, which in turn leads to an increase of the reverse conducted wave. If the amplitude of the action potential falls below a critical level, it is no longer capable of overcoming the impedance mismatch at the first synapse en passant. Exactly the same sequence of events can be observed in column *1*, where the spike interval is shortened by an additional 0.1 ms. Failure, however, occurs much sooner (after the third spike), because the action potentials fall earlier into the relative refractory period of the preceding spikes. This simulation illustrates that minute changes in the discharge frequency have profound effects on the activation pattern of boutons en passant.

DISCUSSION

A large body of literature exists on the simulation of action potential propagation in myelinated and unmyelinated axons (for review see Swadlow et al., 1980). More recently these simulations have been extended to bifurcating axons with one short collateral (Stockbridge, 1988). In our preceding paper we went one step further by attaching terminal boutons and axon swellings to bifurcating axons with short collaterals (Lüscher and Shiner, 1990). There we could demonstrate that an action potential need not propagate in a continuous, uninterrupted manner along the arborization into the terminal boutons. This paper is a continuation of the preceding study in which more complex arborizations are analyzed. It demonstrates that, depending on the architecture of the arborization and the frequency of the spike train, a varying number of synaptic boutons are invaded by the action potential. The action potential may fail at bifurcations or strings of boutons en passant, leading to silent synapses. However, if the synaptic boutons are electrotonically close to the failing branch point, the passively propagated potential which is reflected at the open-circuit, sealed end of the synaptic bouton can increase the membrane potential above threshold, initiating a new action potential which is back-propagated into the arborization and interacts with the orthodromically conducted impulses. Clearly, small structural differences have dramatic effects on the activation pattern of the synaptic boutons.

Because the mechanisms leading to failure have been discussed in detail in the previous paper (Lüscher and Shiner, 1990), we would like to focus the present discussion on the possible integrative properties of terminal arborizations and relate them to experimental observations.

Sensitivity of conduction failure to temperature

The first publication dealing with intermittent conduction in the vertebrate spinal cord was by Barron and Matthews (1935). They found that warm Ringer solution increased the number of conduction failures, whereas a drop of cold Ringer solution applied to the dorsal columns was sufficient to relieve this propagation block. Barron and Matthews were not able to identify the exact location of the block, but inferred that it was probably located at sites of collateral branchings. Forty years later, Westerfield et al. (1978) showed experimentally in the squid giant axon that conduction through branch points is very sensitive to temperature. From computer simulations Westerfield et al. (1978) concluded that "the shape, particularly the duration of the action potential, is the primary effector of propagation success at branch points."

If more and more synapses are activated with decreasing temperature, one would expect to observe a corresponding augmentation in the amplitude of the postsynaptic potentials and as a consequence, an increased monosynaptic reflex. This, in fact, has been reported from a number of experiments. Grundfest observed an augmentation of the reflex discharge in the cooled spinal cord of the cat as early as 1941. Later, Koizumi et al. (1954) and Brooks et al. (1955) studied spinal reflexes at different temperatures and found an increased reflex response after cooling the spinal cord. Pierau et al. (1976) reported an inverse relationship between spinal cord temperature and amplitude of postsynaptic potentials in motoneurons. They ascribed this effect to an increase in input resistance of the motoneurons with cooling. Lüscher et al. (1983*b*) found a similar inverse, approximately linear relationship between spinal cord temperature and amplitude of the postsynaptic population potential. All these observations are consistent with the result presented in Fig. 2, demonstrating that in our simulation more and more synapses are activated in a complex terminal arborization with decreasing temperature.

Spike broadening may not only improve conduction in the terminal arborization but may lead to increased transmitter release as well. Such a mechanism has been proposed for the activation of silent synaptic connections on the Mauthner cell (Lin and Faber, 1988). The shape and duration of the action potential certainly control transmitter release through modulation of calcium influx, but may also determine the extent of propagation into the terminal arborization as well, as our simulations suggest. These two mechanisms may operate in parallel for efficient presynaptic control of synaptic transmission.

Complexity of arborization and silent synapses

About 10 years ago we proposed that the afferent impulses invade the simple ramifications of fibers going to small motoneurons more completely than the extensive arborizations going to large cells. This would result in activation of a higher percentage of the synapses on small cells, leading to larger excitatory postsynaptic potentials in them. Similarly, large and, therefore, more complex arborizations should carry more inactive or silent synapses than small arborizations (Lüscher et al., 1979; Lüscher et al., 1983*a*). Anything that facilitates invasion of the arborization should lead to a larger postsynaptic potential, and this increase should be larger in large cells because they are approached by more complex arborizations than small cells. The experimental findings that posttetanic potentiation was more effective in large than in small motoneurons (Lüscher et al., 1979; Lüscher et al., 1983*a*) was consistent with this idea, and our simulations presented in this paper support it further.

Spike train frequency and conduction failure in complex arborizations

Honig et al. (1983) demonstrated that the mean amplitude of single-fiber excitatory postsynaptic potentials in motoneurons of the cat declined at some connections when the frequency of stimulation of single Ia-fibers was raised above 50 Hz, but at others it failed to decline or even increased. At still other connections a steep decline in the amplitude of the postsynaptic excitatory potential was noticed at the onset of a high-frequency train. These findings were interpreted as being due to a graded depression of transmitter release from each of the numerous boutons given off by the Ia afferent fiber to the motoneuron under investigation. Alternatively, receptor desensitization has also been proposed as a possible mechanism for depression at higher frequencies. Because the authors noted that different connections on different motoneurons showed different frequency sensitivities, but were similar on the same motoneuron, they were forced to assume that the amount of desensitization or depletion of transmitter varied at different connections, apparently depending on some property of the motoneuron.

Our simulations indicate that conduction failure in the presynaptic arborization could account for all these observations. The precipitous drop in the amplitude of the excitatory postsynaptic potential at the onset of a high-frequency train can be explained by the abrupt blockage of the afferent impulse at boutons en passant after the first few impulses have passed, as illustrated in Fig. 6. Increasing the stimulus frequency usually leads to an increase in conduction failure as illustrated in Fig. 3, but this need not always be the case. The distal branch points are usually more susceptible to conduction failure due to the electrical load presented by the terminal boutons. They start to fail at relatively low frequencies. If the action potential starts to fail intermittently at a proximal branch point at a higher frequency (Fig. 4 *A*, column *3*), the now reduced frequency may pass through the distal branch points without additional failures. Such a mechanism would show up as facilitation on the postsynaptic site (Fig. 4 *A*, column *3*). Depending on when and where the action potential starts to fail in a branching structure, different frequency sensitivities could be observed. Because an enormous structural variability exists, the possible activation pattern of synaptic endings would be similarly diverse. However, if a motoneuron influences the structural complexity of its impinging axonal arborizations in any way, the frequency sensitivities of the impinging arborizations would be expected to be similar, as the results of Honig et al. (1983) suggests they are.

Concluding remarks

Whereas the simulation study presented in this paper clearly indicates that the presynaptic arborization may offer a broad range of possibilities for information processing and that the activation patterns of the synaptic endings described are capable of explaining many of the experimentally observed synaptic modulations, it can of course not prove that similar mechanisms operate in the real world. Even very small changes in the density and composition of ionic channels in the terminal arborizations would greatly modify impulse conduction in these structures. Myelinization of terminal branches would similarly affect impulse propagation. The available experimental information on these questions is not sufficient to decide whether the structure of the terminal arborizations are designed for optimal and safe impulse conduction, or whether the central nervous system takes advantage of the possibilities offered by the structural complexity for presynaptic information processing. It is, however, an attractive proposition for giving the structural complexity and diversity of terminal arborizations a functional meaning.

We are grateful to the Informatikdienste and the Institut für Informatik und angewandte Mathematik of the University of Bern for the use of their computing facilities. We wish to thank Dr. H. P. Clamann for reading the manuscript.

This work was supported by the Swiss Multiple Sclerosis Society and the Swiss National Science Foundation (Grant No. 3.265-0.85).

Received for publication 25 June 1990 and in final form 13 August 1990.

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