Computer Model for Action Potential Propagation Through Branch Point in Myelinated Nerves

LEI ZHOU AND SHING YAN CHIU
Department of Physiology, University of Wisconsin School of Medicine, Madison, Wisconsin 53706

Received 7 June 2000; accepted in final form 20 September 2000

Zhou, Lei and Shing Yan Chiu. Computer model for action potential propagation through branch point in myelinated nerves. J Neurophysiol 85: 197–210, 2001. A mathematical model is developed for simulation of action potential propagation through a single branch point of a myelinated nerve fiber with a parent branch bifurcating into two identical daughter branches. This model is based on a previously published multi-layer compartmental model for single unbranched myelinated nerve fibers. Essential modifications were made to couple both daughter branches to the parent branch. There are two major features in this model. First, the model could incorporate detailed geometrical parameters for the myelin sheath and the axon, accomplished by dividing both structures into many segments. Second, each segment has two layers, the myelin sheath and the axonal membrane, allowing voltages of intra-axonal space and periaxonal space to be calculated separately. In this model, K ion concentration in the periaxonal space is dynamically linked to the activity of axonal fast K channels underneath the myelin in the paranodal region. Our model demonstrates that the branch point acts like a low-pass filter, blocking high-frequency transmission from the parent to the daughter branches. Theoretical analysis showed that the cutoff frequency for transmission through the branch point is determined by temperature, local K ion accumulation, width of the periaxonal space, and internodal lengths at the vicinity of the branch point. Our result is consistent with empirical findings of irregular spacing of nodes of Ranvier at axon branches, suggesting that branch points of myelinated axons play important roles in signal integration in an axonal tree.

INTRODUCTION

The extensive neuronal connections through axons or dendrites provide the structural basis for signaling and information processing in the nervous system. Branching in the axonal tree greatly enriches spatial information processing. Both nonmyelinated and myelinated nerve fibers in the CNS and peripheral nervous system (PNS) exhibit extensive branching. For example, before the sensory fiber reaches the dorsal column, there is a single branch that leads to the dorsal root ganglion neuron. Branching also occurs as the terminal is reached, as in the case of the nerve terminals of motor and sensory fibers, and the terminal axonal arbors in thalamocortical and pyramidal fiber tracts (Deschenes and Landry 1980; Quick et al. 1979). Do all impulses faithfully invade branch points or nerve terminals? Physiological experiments have shown that the safety factor for action potential propagation is usually lowered at branch points (Stockbridge 1988; Stockbridge and Stockbridge 1988). This could be manifested by either branch point failures or differential conduction into one of several daughter branches. These mechanisms allow a branch point to be actively involved in action potential routing and temporal editing of neuronal information, which could provide a structural basis for some forms of plasticity. A well-characterized example is the T-junction in the dorsal root ganglion, where a myelinated sensory fiber branches and bifurcates to the spinal cord and the dorsal root ganglion (DRG) neuron. Experimental results have shown that not all afferent action potentials could reach the DRG cell body (Luscher et al. 1994; Stoney 1990), with the branch point at the T-junction of the DRG functioning like a switch or a low-pass filter, protecting the soma from excessive input.

Branch points in myelinated and nonmyelinated nerve fibers are very different. In the nonmyelinated nerve fibers, branches could bifurcate from any point along the axon. For myelinated nerve fibers, however, branches only emerge from the nodes of Ranvier (Quick et al. 1979). The myelin sheath enwrapping the axon not only forms an electrical insulation for the axon, but also alters the axonal membrane properties including ion channel distribution. In mammalian myelinated nerve fibers, the specific conductance of the nodal membrane is much higher than that of the internodal axonal membrane. In the nonmyelinated nerve fibers, ion channels appear to be evenly distributed on the axonal membrane. In contrast, in the mammalian myelinated nerve fibers, most sodium channels, and slow K channels are concentrated at the nodes of Ranvier, whereas fast K channels are concealed underneath the myelin in the juxtaparanodal region. Based on these morphological and physiological differences, the propagation of action potentials on myelinated nerve fibers is fast and salutary and incurs low metabolic costs, which is in contrast to the slower and continuous nature of propagation in the nonmyelinated fibers. In a recent computer simulation of the myelinated fiber (Halter and Clark 1991), during saltatory conduction, most of the voltage drop in the internode occurs across the myelin sheath with little or no voltage drop across the internodal axolemma.

There have been many empirical and theoretical studies on action potential propagation through axonal branch points, but all of them have focused on nonmyelinated nerve fibers (Hines 1984; Mascagni and Sherman 1998; Parnas and Segev 1976). Even though there exist many excellent modeling programs...
(NEURON, SPICE, etc.) available for simulation of very complex neuronal structures such as dendritic trees, all of these are single compartmental models, with each compartment (segment) having only one layer that represents the axonal membrane (Segev et al. 1998). For realistic simulation of the myelinated nerve, we need a model with at least two layers for each computer segment, one for the axonal membrane and the other for the myelin sheath.

No computer model is yet available for simulating branch points in a myelinated fiber. Considering the basic differences between the myelinated and nonmyelinated nerve fibers, it is important to provide a mathematical model for bifurcations in myelinated nerve that allows a study to be made of the role played by the branch point in action potential propagation. To provide a realistic simulation of branch points in myelinated fibers, it is essential to uncouple the calculation of intra-axonal voltage signal from peri-axonal voltage in a two-layer model. Such a distributed-parameter compartment mathematical model was published by Halter and Clark (1991) for a single unbranched myelinated nerve fiber. In that model, each segment has multiple layers, and the electrical activity in the periaxonal space was calculated separately from that of the axonal signal. In this paper, we developed a computer model for a single branch point in a myelinated fiber with one parent branch and two daughter branches, based on Halter and Clark’s unbranched model (Halter and Clark 1991). We then used our model to examine various factors that might affect local excitability at the branch point, including geometrical parameters such as internodal length, myelin thickness and periaxonal space thickness, as well as K ion accumulation at the paranodal regions.

**THEORY**

The branch point is reported by three segments: N0, N1, and N2 (Fig. 1). Segment N0 belongs to the parent branch and is shared by two identical daughter branches. With the application of Kirchoff’s law to segment N0 (Fig. 1C), we obtained Eq. 1, which describes the currents in N0 with second-order temporal accuracy (see Halter and Clark 1991)

\[ \frac{1}{2} (I_{0,j} - I_{1,j} - I_{2,j}) + \frac{1}{2} (I_{b,j+1} - I_{1,j+1} - I_{2,j+1}) = I_{\text{anm}} (1) \]

**Notation**

- \( I_{0}, I_{1}, I_{2} \): intra-axonal current
- \( j \): time index
- \( I_{\text{anm}} \): axonal membrane current

Note that \( I_{\text{anm}} \) has two components: a capacitive component and an ionic component (see the right-hand side of Eq. 2). The ionic component, designated \( I^{\text{ionic}} \), has three components (Na current, K current, and leak current), which has been explicitly explained in Halter and Clark (1991) as well as in our previous work (Zhou et al. 1999).

By substituting the currents with voltage-resistance expression, we obtained Eq. 2 for N0 with second-order spatial and temporal accuracies

\[ I_{\text{anm}} = \frac{1}{2} \left( \frac{V_{0,j} - V_{0,j+1}}{R_{\text{NM}}} + \frac{V_{N1,j} - V_{N1,j+1}}{R_{N01}} + \frac{V_{N2,j} - V_{N2,j+1}}{R_{N02}} \right) \]

\[ + \frac{1}{2} \left( \frac{V_{N0,j} - V_{N0,j+1}}{R_{\text{NM}}} + \frac{V_{N1,j} - V_{N1,j+1}}{R_{N01}} + \frac{V_{N2,j} - V_{N2,j+1}}{R_{N02}} \right) \]

\[ = (V_{0,j+1} - V_{0,j}) - (V_{0,j} - V_{0,j+1}) \frac{C_{\text{anm}}}{\Delta t} + I^{\text{ionic}} \] (2)

**FIG. 1.** Schematic drawing of the simulation model for branch point in myelinated nerve. A: the model describes a single myelinated fiber (parent branch) bifurcating into 2 smaller daughter branches (1 and 2). The arrows showed the direction of action potential propagation. The daughter branch is half the size of the parent branch. All geometrical parameters are in \( \mu \text{m} \). B: the Ranvier node is represented by one segment. The internodal region can be separated into MYSA, FLUT, STIN, FLUT and MYSA. They are represented with 4, 4, 5, 4, and 4 segments, respectively (Zhou et al. 1999). C: the branch point is represented by 3 segments and named as N0, N1, and N2. The intra-axonal voltages of these segments are \( V_{0}, V_{1}, \) and \( V_{2} \). With application of Kirchoff’s law to segment N0, the transmembrane current \( I_{\text{anm}} \) is equal to the difference between \( I_{a} \) and the sum of \( I_{1} \) and \( I_{2} \). MYSA, myelin sheath attachment region; FLUT, fluted internodal region; STIN, stereotype internodal region; \( I_{0} \), intra-axonal current into segment 0; \( I_{1}/I_{2} \), intra-axonal currents flowing from segment N0 to segment N1 or N2; \( p \), periaxonal; \( i \), intra-axonal.
The equation above can be re-organized into

\[ \Psi' V_{n0-1} + \Theta' V_{n0-1} + \Lambda' V_{n0} + \Gamma' V_{n0} + \Phi' = 0 \]  

where

\[ \Phi' = -\left(\Psi' V_{n0-1} + \Theta' V_{n0} + \Lambda' V_{n1} + \Gamma' V_{n2} + \Psi' V_1 + \Theta' V_2 + \Lambda' V_3 + \Gamma' V_4 + \Phi' \right) \]

\[ \Theta'_{n0-1} = -\frac{2R_{NM}R_{N02}}{R_{NM}R_{N01} + R_{NM}R_{N02} + R_{NM}R_{N02}} \]

\[ \Theta'_{n0} = -2 + \frac{2R_{NM}R_{N02}C_{ax}}{R_{NM}R_{N01} + R_{NM}R_{N02} + R_{NM}R_{N02}} \]

\[ \Lambda' = \frac{2R_{NM}R_{N01}}{R_{NM}R_{N01} + R_{NM}R_{N02} + R_{NM}R_{N02}} \]

\[ \Gamma' = \frac{4R_{NM}R_{N01}R_{N02}C_{ax}}{R_{NM}R_{N01} + R_{NM}R_{N02} + R_{NM}R_{N02}} \]

When all the equations for each segment are combined, we obtained the following expression

\[ \begin{pmatrix} A' \, \Gamma' \end{pmatrix} \begin{pmatrix} V'_{n0-1} \, V'_{n0} \, V'_{n1} \, V'_{n2} \end{pmatrix} = \begin{pmatrix} \Phi' \end{pmatrix} \]

where \( V' \) and \( V' \) are the two vectors representing the periaxonal and intra-axonal voltages of all segments.

The above equations are novel to this paper, as they are developed for a single branch point of a myelinated nerve fiber. For equations and matrix for other segments along the parent and daughter branches away from the branch point, we use those already developed for unbranched myelinated fibers by Halter and Clark (1991). To couple both daughter branches with segment N0 of the parent branch, certain modifications have to be made to the matrix according to Eqs. 1–3. \( \Lambda N0 \) and \( \Psi N2 \) were moved to specific position to couple N0 with N2, and the original positions were replaced with 0 (see the following matrix). The following diagram shows the intra-axonal part of the matrix after modification; similar modifications were made for the periaxonal part. In our model, there is only one branch point that connects the parent branch with two daughter branches. This model could be modified in future studies.

![Diagram of action potential propagation](http://www.jn.physiology.org/doi/10.1152/jn.00990.199)

**Fig. 2.** Action potential propagates across branch point from parent to daughter branches. An action potential was evoked by injecting current into the leftmost node of the parent branch, and propagated from the parent branch to both daughter branches (the arrow shows the direction). Trans-axon membrane voltages at Ranviers near the branch point were shown versus time. Dotted curves showed the responses of 3 segments representing the branch point, N0, N1, and N2 (from top to bottom). Note the time scale is different between left (37°C) and right (20°C).
to simulate multiple branches by adding more couplings to the matrix, an understanding that is similar to the treatment for multiple branches in nonmyelinated nerve fibers (Hines 1984)

\[
A' = \begin{bmatrix}
\Psi' & 0 & 0 & \cdots & 0 & 0 & 0 & 0 & 0 \\
0 & \Psi'_{50} & \Theta'_{50} & \Lambda'_{50} & 0 & 0 & 0 & 0 & 0 \\
0 & \Psi'_{60} & \Theta'_{60} & \Lambda'_{60} & 0 & 0 & 0 & 0 & 0 \\
\cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\
0 & 0 & 0 & \cdots & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \cdots & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \cdots & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \cdots & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \cdots & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \cdots & 0 & 0 & 0 & 0 & 0 \\
\end{bmatrix}
\]

The settings for the morphological and electrophysiological parameters for the parent branch were based on two published papers (Halter and Clark 1991; Zhou et al. 1999). The node of Ranvier was represented by 1 segment, and the internode was responded by 21 segments using the same terminology as in Halter [4 for each myelin sheath attachment region (MYSA) on either end of an internode; 4 for each fluted internodal region (FLUT) on either end of an internode; 5 for stereotype internodal region (STIN), the region in between]. Figure 1B shows the structure of each internode, showing the MYSA, the FLUT, and the STIN. Each daughter branch is half the size of the parent branch (axon diameter, segment length, myelin thickness, etc.). The same physiological parameters were used for the parent branch and the daughter branches (specific axon/myelin membrane conductance/capacitance, Na/Fast K/Slow K channel distributions).

In our model, we assumed that K ion concentration in the periaxonal space is dynamically linked only to K ion efflux through fast K channels on the axonal membrane. The K concentration is calculated according to the volume of periaxonal space and an assumed time constant for potassium clearance (Eq. 4). Based on previous studies, fast K conductance in the mammalian myelinated nerve is assumed to be localized underneath the myelin in the paranodal or juxtaparanodal region in our model (Chiu and Ritchie 1980; Mi et al. 1995). In the present study, these fast K channels provide the major source for the extracellular K ion accumulation. The average thickness of the periaxonal space at the paranodal region is 5 nm in our standard model. Previous theoretical and experimental results provided different values for K clearance in the squid giant axon, ranging from 10 ms (Aston et al. 1988) to 25 ms (Inoue et al. 1997). In our standard model, the time constant for K clearance was set at 10 ms at 37°C or 20 ms at 20°C

\[
\Delta K_{out} = \frac{i_{KF}}{FVol} + \frac{(5.9 - K_{out})}{\tau}
\]

where \(i_{KF}\) is the K current through fast K channels, \(Vol\) is the volume of the periaxonal space at each segment, \(F\) is the Faraday constant, 5.9 is the resting extracellular K concentration (5.9) mM, \(K_{out}\) is the extracellular K concentration, and \(\tau\) is the K ion clearance time constant in the periaxonal space.

**RESULTS**

*Transmission of action potentials from parent branch to daughter branches*

In our model, the branch point is represented by three segments, each having the same specific membrane properties and channel distributions as the nodes of Ranvier along the rest of the fiber. N0 is the last segment of the parent branch as it approaches the branch point. N1 and N2 are the first segment of each daughter branch (Fig. 1C). The diameter of N1 or N2 is equal to that of the node of Ranvier along the rest of the daughter branch. Since the size of the branch point determines the impedance matching between the daughter branches and the parent branch, we adjusted the lengths of the three segments (N0, N1, N2) until a single action potential could successfully invade both daughter branches. At this setting, the total axonal membrane area at the branch point is 27.5 \(\mu m^2\). For comparison, the nodal membrane in the rest of the parent and daughter branches is 23.5 and 5.9 \(\mu m^2\), respectively.

The model was stimulated by injecting a brief current (0.1 A, 25/50 \(\mu s\) at 37/20°C) into the left-most node in the parent branch with eight internodes. This stimulation is large enough to generate an action potential that propagates toward the branch point. In most of the following figures, the voltage signal across the nodal membrane was used to show the activity in the nerve fiber. Temporal responses from several nodes in the parent and daughter branches near the branch point were illustrated in Fig. 2. The shifts between curves reflect the delayed activation of nodes along the nerve fiber in the direction of impulse propagation. The dashed line in each figure

**FIG. 3.** Spatial distribution of propagating impulse on parent and daughter branches. Trans-axon membrane voltage (top) or trans-myelin sheath voltage (bottom) were shown with nerve length as x-axis. Since responses of the 2 daughter branches are identical in the model, only 1 is shown in the figure. The time points selected corresponded to the time just before the action potential reached the branch point and 1 ms later when the impulse passed the branch point. The open arrow shows the position of branch point. \(T = 20°C\).
showed responses of the three segments at the branch point (N0, N1, or N2; from top to bottom). The action potentials of N1 and N2 were identical, suggesting that N1 and N2 were activated simultaneously. As mentioned in theory, expressions for N1 and N2 were physically separated in the matrix, and modifications were made to couple both segments with N0 in the parent branch. The simultaneous activation of N1 and N2 suggested that modifications to the matrix successfully transferred activity from the parent branch to both daughter branches.

One major feature of this model is that the myelin sheath is incorporated into the simulation. In this model of the myelinated nerve fiber, action potential actually travels on the myelin sheath with little or no depolarization occurring on the main part of the internodal axon membrane (Halter and Clark 1991). Using the nerve fiber length as the x-axis, Fig. 3 illustrates a spatial view of action potential distribution on the myelinated nerve fiber at a given time. Trans-axon and trans-myelin sheath voltages were shown along the fiber axis in the figure. Two time points were selected. The first one is chosen just prior to the arrival of the impulse at the branch point, and the second one 1 ms later when the impulse has crossed the branch point. The sharp upward peaks in the trans-axon voltage curve and downward peaks in the trans-myelin voltage curve correspond to the positions of the nodes of Ranvier. Comparing the trans-axon voltage with trans-myelin sheath voltage, it is clear that the impulses are actually jumping from node to node, using the myelin sheath as a bridge (Halter and Clark 1991).

Two points need to be stressed. First, our simulation result can only be achieved by completely separating the myelin sheath from the axon membrane in our two-layer model for each segment, a major advantage of our model. Second, the sharp voltage peaks at the nodes of Ranvier have a certain spatial spread to them, suggesting that the depolarization at the node passively spreads into the paranodal region. This depolarization of the paranodal axon membrane will lead to activation of fast K channels at the paranodal region, a conclusion corroborated by intracellular recordings in rat myelinated axons (Barrett and Barrett 1982; David et al. 1995). The electrotonic coupling between the nodal and the paranodal membranes becomes important as factors affecting branch point excitability are explored, as will be evident below.

**Branch point failures at high frequency**

The active role of branch points in filtering neural information was tested with a train of high-frequency impulses (Fig. 4). Comparing spikes on the parent branch upstream from the branch point with spikes on both daughter branches (*) downstream from the branch point, it can be seen that there is a certain failure in the parent-to-daughter branch when the frequency of stimulation was increased. In other words, intermittent failures were found on the daughter branches. At 37°C (left), 400-Hz action potentials could propagate on the parent branch without failures. After the branch point, about 60% of the impulses are seen on the daughter branches (calculated with a time window of 50 ms as shown in Fig. 4). At 20°C, the daughter branch can only follow ∼50% of the 250-Hz stimulation delivered to the parent branch. There are two possible origins of this intermittent failure in the daughter branches.

**FIG. 4.** Intermittent branch point failures occurred at high frequency. The simulation model was tested with a train of stimulus at different frequencies (400 Hz at 37°C, 250 Hz at 20°C) to the parent branch. Responses of the last node in parent branch and the 3rd node after the branch point in one of the daughter branches are shown. Intermittent conduction failures could be detected by comparing the responses of parent branch to those of daughter branches.
One possibility is that the daughter branch, being of a smaller diameter than the parent branch, has a correspondingly longer refractory period. Thus, whereas the parent branch can follow high-frequency stimulation, the daughter branch cannot, even though there is 100% transmission at the branch point. To examine this possibility, we directly stimulated the daughter branch at the same frequency as applied to the parent branch (400 Hz at 37°C, 250 Hz at 20°C). The results showed that the daughter branch could follow this high rate of stimulation with no conduction failures (data not shown). This suggests that the intermittent failures in the daughter branches are due to failures of transmission at the branch point. We now used our model to examine several factors that might affect the transmission efficacy at the branch point.

**K accumulation in the periaxonal space**

In mammalian myelinated axons, virtually all of the kinetically fast K channels are localized underneath the myelin in the paranodal or juxtaparanodal region. Considering the very restricted space between the myelin sheath and the axonal membrane, a small amount of K ion efflux through these channels might dramatically increase local K ion concentration (Chiu 1991). Is there any functional significance for this local K accumulation? We used our model to examine the effect of K accumulation on branch point excitability. We treated the intra-axon [K] as constant (150 mM). In our standard model, we assumed that the K clearance time constant in the periaxonal space is 10 ms at 37°C or 20 ms at 20°C. We first examined the effect of K accumulation in electrogenesis on the unbranched portion of the nerve. Figure 5A shows that for the standard model subjected to a single stimulation, the periaxonal K concentration rises to a peak of 15 mM at 37°C and to 38 mM at 20°C. Comparing the nodal action potentials with (—) and without (…) K accumulation, it can be seen that K accumulation leads to a small afterdepolarization that is more pronounced at 20°C (Fig. 5B). One mechanism by which local K accumulation affects excitability is by altering the Nernstian K equilibrium potential for the fast K channels, which is −82.3 mV at 20°C and −86.6 mV at 37°C. While the potassium current typically flows outward during an action potential because the K equilibrium potential is always more negative than the membrane potential, this situation becomes different when there is K accumulation, which makes the K equilibrium potential more depolarized. In our simulations, we found that during an action potential, there is actually a period during which the K equilibrium potential (solid line) is higher (i.e.,

![Diagram](http://jn.physiology.org/)

**FIG. 5.** Activity-dependent K ion accumulation in the periaxonal space between axon membrane and myelin sheath. K ion clearance time constant is set as 10 ms at 37°C (left) or 20 ms at 20°C (right) in the standard model. All simulations were carried out in the parent branch. A: periaxonal K concentration in the 1st segment of FLUT region. Dotted line shows the resting K ion level (5.9 mM). B: trans-axon membrane potential at the Ranvier node with (—) or without (…) K accumulation in the simulation. C: K equilibrium potential was calculated according to the Nernst equation based on the periaxonal [K] curve in A, as shown by solid line. Dashed line shows the resting K equilibrium potential (−82.3 mV at 20°C, −86.6 mV at 37°C) and the local trans-axon membrane potential (pointed by arrow). D: potassium current density in the 1st segment of FLUT region with or without K ion accumulation in the simulation (37°C, left; 20°C, right).
more depolarized) than the local axon membrane potential (dashed line; Fig. 5C). During this period, K current becomes inward at 20°C (Fig. 5). Around 5 ms after the peak of action potential, fast K channels quickly deactivated, leading to an abolishment of this inward current even though the driving force for the fast K current still remains in the inward direction. At 37°C, this inward driving force does not produce an inward K current, since the fast K channels are rapidly deactivated (Fig. 5D).

We next examined the effects of K accumulation on branch point transmission. In our standard model with a K clearance time constant of 10/20 ms at 37/20°C, we have shown that intermittent failures at the branch point occur at high frequency (400 Hz at 37°C or 250 Hz at 20°C). How does hastening or slowing K clearance affect the branch point transmission? To address this issue, we apply the same fixed high frequency of stimulation, but vary the K clearance time constant to 1 ms, 10 ms (standard model), and 100 ms. The simulations showed that varying the K clearance time constant produced complex patterns of excitability changes at the branch point (Fig. 6A). At 37°C, progressively slowing K clearance (from 1 to 10 to 100 ms) progressively reduces the transmission rate through the branch point (transmission is 100% pass at 1 ms, 60% pass at 10 ms, and 58% pass at 100 ms). Thus at 37°C, more K accumulation leads to more branch point failures. The results at 20°C were similar. As the K clearance time constant is progressively increased from 1 to 20 ms, the branch point transmission was depressed (from 100% transmission at 1 ms to 50% transmission at 20 ms). Further retarding K clearance time to 100 ms leads to no further branch point failures. Figure 6B shows the paranodal K accumulation corresponding to these simulations. With fast K clearance rate (1 ms), there was no sustained K ion buildup at both temperatures. With very slow K clearance rate (>100 ms), local K concentration increases quickly and reaches a ceiling (~35 mM). The existence of a ceiling level of [K] accumulation is consistent with experimental results in the cerebral cortex (Heinemann and Lux 1977) and the optic nerves (Connors et al. 1982).

Impedance mismatch

As suggested by previous studies (Swadlow et al. 1980; Waxman 1975), a low safety factor for action potential propagation at branch point might be due to impedance mismatch. In other words, if the combined electrotonic loading of the two daughter branches is bigger/smaller than that of parent branch, the threshold for action potential to propagate forward is higher/lower at the site of nonuniform geometry. We therefore examined the effects of several geometrical adjustments that might affect the impedance matching between the parent branch and the daughter branches. All manipulations were tested in the standard model with an impulse train (400 Hz at 37°C, or 250 Hz at 20°C).

![Fig. 6](http://jn.physiology.org/)

**Fig. 6.** Effects of local K ion accumulation in branch point excitability. The effects of K ion accumulation were tested with impulse train at 400 Hz (37°C, left) or 250 Hz (20°C, right). Three different time constants for K ion clearance were tested [1 ms, 10 ms at 37°C or 20 ms at 20°C (standard model), 100 ms]. A: responses of the 3rd node after branch point in a daughter branch at different K clearance time constants. From top to bottom, τ = 1 ms, standard model (10 ms at 37°C, 20 ms at 20°C), and 100 ms. B: periaxonal K ion concentrations in the paranodal region near branch point in the parent branch. The number at the right of each curve shows the corresponding K ion clearance time constant.
INTERNODAL LENGTH. Shortening the internodal length is one common solution to overcome impedance mismatch in sites of abrupt morphological changes, as in the case of the transition zone from myelinated to demyelinated axons (Waxman and Brill 1978) and the motor axon terminal region (Zhou et al. 1999). It would be interesting to examine whether a foreshortening of the internodal length on the parent branch prior to the branch point facilitates impulse propagation through the branch point. We therefore shortened the length of the last internode in the parent branch just before the branch point by half. This internodal shortening dramatically eliminates branch point failures, allowing 100% transmission from the parent branch to the two daughter branches at both 37°C and 20°C (Fig. 7, middle). Interestingly, this reduction of internodal length proximal to the branch point improves transmission through the branch point without penalizing the conduction latency for the arrival time of the first action potential at the daughter branch. Thus when the simulation traces for the preinternodal shortening in Fig. 7 are examined more closely at expanded time scale, the first action potential was found to arrive at the daughter branch slightly sooner than in the case of the standard model, at both 37°C and 20°C. Shortening the internodes in the daughter branches, just after the branch point, has the opposite effects of reducing the transmission rate through the branch point (Fig. 7, bottom).

PERIAXONAL SPACE. Besides internodal length, another factor that may affect impedance matching between the parent branch and the daughter branches is how tightly the myelin is wrapped around the axons, i.e., the thickness of the periaxonal space. During development and even in adulthood, myelinated nerve structure undergoes continuous modification apparently to adapt to different functional requirements (Kleitman and Bunge 1995; Schroder 1986). It has been reported that the distance between myelin sheath and axon is smaller in adult mice than in younger ones. Intuitively, a tight wrapping (reduced periaxonal space) will reduce the excitation membrane area, which may affect impedance matching between parent and daughter branches. Further, a consequence of the tiny volume of the paranodal periaxonal space is that any variation in the thickness of the periaxonal space could have significant impact on the periaxonal K accumulation. We therefore examined the effects on branch point transmission when the periaxonal space thickness was selectively varied on either the parent branch (Fig. 8) or the daughter branches (Fig. 9).

When the periaxonal space in the parent branch was made narrower by a factor of 2 from the standard model (from 5 to 2.5 nm), there is an increase in branch point transmission. There is a slight increase in the ceiling for the periaxonal K accumulation from ~27 mM to ~31 mM. When the periaxonal space was widened from the standard model by a factor of 2 (to 10 nm), more failures at the branch point occurred. A more dramatic effect on the branch point transmission results when the periaxonal space of the daughter branches is altered. On narrowing the periaxonal space by a factor of 2, transmission failure through the branch point is completely eliminated. When the daughter branch periaxonal space was widened by a factor of 2, dramatic enhancement of transmission failure results. There is a correspondingly larger change in the periaxonal K accumulation, probably due to the smaller sizes of the daughter branches compared with the parent branches.

![FIG. 7. Effects of internodal length irregularities on branch point transmission. Top: standard model with regular internodal lengths in both parent and daughter branches. Middle: the parent branch internodal just before the branch point was shortened by half. The shortened internode was marked by the open arrow. Bottom: the daughter branch internodal length just after the branch point was shortened by half. The shortened internode was marked by the open arrow.](http://jn.physiology.org/longtable/ oustedSite)
Temperature

Empirical studies have shown that in both nonmyelinated axons (Westerfield et al. 1977) and myelinated axons (Stoney 1990), conduction failures at branch points are very sensitive to small changes in temperatures. The general consensus is that warming increases branch point conduction failures, and cooling improves conduction through branch points (Luscher et al. 1983; Swadlow et al. 1980). We therefore examined the effects of changing the temperature on branch point failures, with particular attention paid to small temperature changes around the physiological operating point of 37°C. Figure 10 shows the relationship between transmission through the branch point versus temperature when the parent branch was driven at 400 Hz. For the standard model (○), ~60% of the action potentials are transmitted through the branch point into the daughter branches at 37°C. As the temperature is increased from 37 to

FIG. 8. Effects of varying periaxonal space width in the parent branch. The distances between the axon membrane and the myelin sheath at the paranodal region (MYSA and FLUT) were either decreased (left) or increased (right) by a factor of 2 from the standard model (5 nm). The system was tested with an impulse train of 400 Hz at 37°C. The response of the 3rd node after the branch point in a daughter branch was shown in the top. The corresponding paranodal [K] in the periaxonal space near the 4th node of Ranvier in parent branch was shown in the bottom.

FIG. 9. Effects of varying the periaxonal space width of the daughter branches. The distances between the axon membrane and the myelin sheath at the paranodal region (MYSA and FLUT) were either decreased (left) or increased (right) by a factor of 2 from the standard model (5 nm). The system was tested with the same impulse train as in Fig. 8. The response of the 3rd node after the branch point in a daughter branch was shown in the top. The corresponding paranodal [K] in the periaxonal space near the 4th node of Ranvier in daughter branch was shown in the bottom.
Transmission through the branch point becomes totally temperature sensitive when the branch point was preceded by a shortened internode, thus validating the conclusion that transmission in Fig. 10 could follow 400-Hz action potentials when they are directly stimulated, 4°C, both the parent and daughter branches can follow 400-Hz stimulations with no failures when stimulated directly, results from the standard model with uniform internodal lengths for all branches (see Fig. 7); ○, results when the parent branch has a preshortened internode just preceding the branch point (see Fig. 7).

40°C, the transmission is sharply reduced to zero. On the other hand, simply lowering the temperature by 2°C, from 37 to 35°C, greatly improved transmission through the branch point from ~60% to near 100%. This improvement subsides as the temperature is further reduced, so that by 27°C, the transmission falls back to ~60%. In control simulations (data not shown), we found that over the temperature range from 27 to 40°C, both the parent and daughter branches can follow 400-Hz action potentials when they are directly stimulated, thus validating the conclusion that transmission in Fig. 10 reflects transmission through the branch point. Interestingly, when the branch point was preceded by a shortened internode, transmission through the branch point becomes totally temperature insensitive, remaining at 100% over the entire temperature range (27–40°C).

**DISCUSSION**

In this paper we provided the first computer simulation of action potential propagation through a single branch point in myelinated nerve fibers. The model is based on a previously published multiple-layer compartmental model for an unbranched myelinated nerve fiber (Halter and Clark 1991). Our model successfully simulates action potential propagation from a parent myelinated branch through a single branch point to two identical, but smaller, myelinated daughter branches. Since in our model each segment has two layers representing the axonal membrane and the myelin sheath, a very realistic description to the action potential propagation across branch point in a myelinated nerve fiber is achieved. Through independent and separate calculation of the intra-axonal and periaxonal signals, it is possible to theoretically examine various subtle changes in geometrical and physiological parameters important for modulating branch point excitability in a myelinated fiber, such as longitudinal currents in the periaxonal space thickness, internodal length, and K accumulation in the periaxonal space.

Most neuronal information conducted through an axon is encoded in the pattern of impulses. In addition to passive transfer of information from the parent branch to the daughter branches, a branch point might also actively process the information by differential routing, frequency filtering, and pattern editing. One major focus of this paper is the morphological basis by which branch point excitability and frequency filtering is affected. A future application of our model is to study branch points in sensory fiber terminals, in which afferent impulses propagate retrogradely from daughter to parent branches. The results obtained in this paper on branch point regulation may shed light on how afferent signal is processed as it originates from the sensory endings. One major result of our theoretical analysis is that the branch point in a myelinated fiber acts like a low-pass filter, with the cutoff frequency for high-frequency transmission critically determined by various factors related to the local geometry in the vicinity of the branch point.

**K accumulation in the periaxonal space affects frequency filtering of branch point**

Electrical activity in nerve fibers could have short-term or long-term effects on nerve fibers, allowing nerve fibers to adapt to certain functional requirements. K accumulation in the space between the myelin sheath and axolemma has been suggested to mediate signaling between axons and glial cells, and this could be an important factor affecting local excitability near branch points (Nicholson 1995). Activation of fast K channels on the paranodal axon leads to K accumulation in the periaxonal space (Chiu 1991). In our standard model (Fig. 6A), when the parent branch is driven at 400 Hz at 37°C, only 60% of the impulses are transmitted to the daughter branches. What is the basis of these transmission failures? This failure cannot be explained by the inability of the daughter branches (which are smaller) to follow 400-Hz stimulation, since direct stimulation of the daughter branches with 400 Hz revealed no failures. Hence, failures occur at the branch point. What is the cause of the branch point failure? Our computer simulations suggest that K accumulation in the periaxonal space is one main reason for this failure. Hence, when the K clearance in the standards model is hastened to τ = 1 ms, branch point failures disappear (Fig. 6A). When the K clearance is retarded to τ = 100 ms, branch point failures increase (Fig. 6A). Notice that varying K clearance time constant affects only the branch point transmission; the conduction on either the parent or daughter branches is unaffected. The reason for the branch point failures may be that the paranodal depolarization induced by K ion accumulation passively spreads to the nodal region and inactivates nodal Na channels. This causes a conduction block at the branch point, a site of low safety factor. Figure 6A shows that a branch point not only can act like a low-pass filter, but that the branch point may edit the information by altering the impulse pattern, as shown in Fig. 6 (37°C). For example, the responses of the daughter branches at τ = 10 ms and τ = 100 ms have similar transmission rate (~60%) but have different patterns.

Our finding that branch point transmission is highly sensitive to K accumulation in the periaxonal space suggests that information flow in axon arbors of myelinated fibers with multiple
branching is very vulnerable to disregulation of K homeostasis under the myelin sheath. It is noteworthy that the internodal axon is heavily stained for Na/K ATPase (Mata et al. 1991), suggesting that K homeostasis under the myelin sheath is critical for normal signaling in myelinated axons, particularly at branch points.

As shown by simulations at 20°C, K accumulation causes the K reversal potential to be higher than the membrane potential during part of the repolarizing phase. This, coupled with a slowing down of fast K channel deactivation by cooling, allows a time window during the action potential when inward K currents are generated (Fig. 5). This inward K current may even enhance the excitability of the system, allowing K accumulation in this special instance to actually facilitate transmission through the branch point. Experimental results have shown that under certain conditions, such as postischemic or posttetanic firing, K accumulation in the periaxonal space can generate inward, regenerative potassium currents (Bostock et al. 1991; Kierman et al. 1997). Collectively, these experimental results and our theoretical results suggest that it is quite possible that K accumulation at the periaxonal space will show significant and unexpected physiological impact on branch point excitability.

Since the fast K channels concealed underneath the myelin are the major source of K accumulation, our model suggests that these myelin-concealed K channels may exert profound control on branch point transmission via modulating periaxonal K accumulation in the branch point vicinity. Our previous analysis of Kv1.1-null mice, where one K channel subtype under the myelin was deleted, suggested that myelin-concealed K channels are important modulators of transition zone excitability at the motor nerve terminal (Zhou et al. 1998, 1999). Whether Kv1.1 plays an important role in branch point excitability is an open question. Preliminary experimental results on the sciatic nerve–DRG preparation showed that in the Kv1.1-null mice, the percentage of high-frequency spikes reaching the DRG neuron soma is higher than the wild type (unpublished observations). Our theoretical study here suggests that Kv1.1 may modulate branch point failures via periaxonal K accumulation. In the CNS, A-type fast K channels have been shown to play a critical role in gating action potential propagation in CA3 pyramidal axons (Debanne et al. 1997; Kopytsova and Debanne 1998).

**Role of impedance mismatch in branch point failure**

It has been shown that the safety factor for action potential propagation is usually lower at regions of geometrical heterogeneity, such as sites of abrupt change in axonal diameter and axon bifurcation (Parnas et al. 1976). How does geometrical heterogeneity affect action potential propagation? A key factor is impedance mismatch (Rall 1959; Swadlow et al. 1980). For the case of nonmyelinated axons, the GR ratio of the two daughter branches ($d_1$, $d_2$) to the parent branch $(d)$ is $(d_1^{3/2} + d_2^{3/2})/d^{3/2}$. If this ratio is larger than 1, invasion of the daughter branches is slowed down or may even fail. If this ratio is smaller than 1, invasion of the daughter branches is secure and without failures. In our model, the two daughter branches each have half the diameter of the parent branch, which yields a GR ratio of 0.71 if our axons were nonmyelinated. However, other factors come into play in branch point of myelinated fibers. For example, we found that the nodal area $(N_0 + N_1 + N_2)$ at the branch point is critical. If it is too small, action potential cannot invade the daughter branches. In our standard model, the area was adjusted to give successful invasion of the daughter branches.

Our simulations also identified other important determinants of branch point transmission. One of them is the internodal length of the parent branch just prior to the branch point. By replacing the single internode prior to the branch point with two half-size short internodes, transmission failure is completely eliminated, allowing the branch point to dramatically increase its cutoff frequency for high-frequency signals. Reduction of the internodal length just proximal to the branch point also dramatically abolished the temperature sensitivity of conduction failures at the branch point. With uniform internodal lengths, warming abruptly block transmission through the branch point, and cooling first improves transmission then reduces it (Fig. 10). With a single prebranch point internodal shortening, fidelity of branch point transmission stays constant at 100% over a broad temperature range (27–40°C). In unbranched myelinated fibers, previous theoretical and experimental studies have confirmed that internodal shortening can dramatically increase the safety factor at the transition zone near demyelinated regions (Waxman 1972). Our present study extends these results to branch points of myelinated fibers and shows that a shortened prebranching internodal length could improve the safety factor at the branch point and increase the cutoff frequency for high-frequency signal transmission. Interestingly, shortening the internodes in the daughter branches immediately after the branch point has the opposite effect of shifting the cutoff frequency to a lower value, screening the daughter branches from receiving high-frequency signals from the parent branch (Fig. 7).

Our finding that internodal length irregularity around a branch point can shift the cutoff frequency for signal transmission in opposite direction, depending on the pre- or postbranching location of the irregularity, clearly has significance in terms of signal integration in an axonal tree. In a detailed analysis of the morphology of the terminal arborization of thalamic and cortical neurons, Deschenes and Landry (1980) found that irregular spacing is the rule, rather than the exception, for nodes of Ranvier near branch points of these CNS myelinated fibers. They noted examples where the parent branch undergoes internodal shortening just prior to the branch point, which according to our simulations would shift the cutoff frequency for parent-to-daughter transmission to the high-frequency spectrum. Interestingly, internodal lengthening in the parent branch prior to the branch point can also occur (Deschenes and Landry 1980), which might suggest a functional requirement to reduce high-frequency, parent-to-daughter, transmission in certain areas of the axon arbors. Likewise, shortening of postbranch internodes has also been observed in daughter branches, which according to our analysis should be another mechanism for limiting high-frequency, parent-to-daughter transmissions. As Deschenes and Landry (1980) have remarked, the regular and predictable spacing of nodes of Ranvier on the basis of axonal diameter according to the Rushton’s Law (Rushton 1951) for optimal conduction appears to undergo a breakdown on arborization. Our theoretical analysis suggests that internodal length irregularity and its deviation from Rushton’s Law at branch point vicinity may serve an important functional role in...
filtering neural information in the spatial and temporal domain in an axonal tree (Deschenes and Landry 1980).

Besides internodal length irregularities, we also found that the width of the periaxonal space is critical. We found that selectively altering the periaxonal space in the daughter branches dramatically alters the efficacy of high-frequency invasion of the daughter branches. Tightening the myelin wrappings around the daughter branches (decreasing the width of the periaxonal space) greatly enhances the passage of high-frequency signal from the parent to the daughter branches. Loosening the myelin wrapping (widening the periaxonal space) screens the daughter branches from receiving high-frequency signals. One reason for this effect of periaxonal space is that the thickness of this space determines the electronic coupling between the nodal and the internodal axon and hence the capacitative load of the daughter branches as seen by an invading parent branch. For example, widening the periaxonal space in the daughter branches would allow increased electrotonic coupling between the nodal and the internodal axolemma. Since the internodal axolemma has few sodium channels to support conduction, this would have the effect of increasing the capacitative load in the daughter branches, thereby reducing the chances of successful parent-to-daughter branch invasion. Using periaxonal space geometry to control information flow into daughter branches could have functional significance, particularly during development where immature myelinated axons may have a slightly wider periaxonal space than adult nerves. In a developmental study by Yamamoto et al. (1996), the axoglial junctions where the terminal myelin loops attach to the paranodal axolemma was examined in 10- and 31-day-old rats. When the terminal loops attach to the axolemma, the extracellular distance between the loop and the axolemma (i.e., the periaxonal space) is 4.0 nm. This distance widens to 5.5 nm when the terminal loops do not attach to the axolemma. Yamamoto et al. (1996) further found that even though the paranodal length remains unchanged during development, the frequency of terminal loops with attachment increased with fiber grow. Hence, there is a progressive reduction in the overall width of the periaxonal space as myelination proceeds. Other examples of periaxonal space alteration can be found in various demyelinating diseases. For example, a widening of the periaxonal space was detected in myelinated fibers in the peripheral demyelinating neuropathy associated with the toxins of the buckthorn shrub (Heath et al. 1982). One could imagine that the looser periaxial space in new branches formed during either development or regeneration may screen them from potential excitotoxicity due to high-frequency signaling in the parent branches.

Another possible function of a branch point is differential routing of impulses into one and not the other daughter branches. In nonmyelinated axons, this differential routing occurs in daughter branches of different sizes, suggesting that the input impedance of individual daughter branches is an important determinant of differential routing. In our model, we used two identical daughter branches and therefore have not systematically investigated the conditions for differential routing at branch points of myelinated fibers. Nevertheless, we have performed preliminary studies on differential routing with our model and found that differential routing only occurs when the two daughter branches are of very different morphological parameters. Another essential requirement for differential routing is that the initial node of two daughter branches at the branch point (N1 and N2) should have different sizes (data not shown), otherwise the activities of the two daughter branches are always coupled together, activating or failing at the same time. This scenario is quite different from branch points in nonmyelinated nerve fibers, in which differential routing could be achieved easily without dramatic geometrical difference between the two daughter branches. Indeed, even random channel noise could affect differential routing in branch points of nonmyelinated axons (Horikawa 1993). Our computer simulations highlight the importance of the membrane properties of the nodal membrane at the branch point (N0, N1, N2) in determining branch point transmission. There is little or no direct measurement of the membrane properties of the special node at the branch point. It is possible that the node of Ranvier at the branch point may have specialized properties adapted for branch point transmission.

**Comparison with empirical studies on branch points of myelinated axons**

As discussed in the Introduction, a large body of work already exists on empirical and theoretical analysis of conduction at branch points in invertebrate nonmyelinated axons, including crayfish and the squid giant axons (Grossman et al. 1973, 1979; Parnas and Segev 1979; Smith 1980, 1983). These studies of nonmyelinated branch points all show that K accumulation, temperature, frequency of stimulation, and local geometry affect conduction failures at the branch point. Our study shows that branch point of myelinated axons are similarly affected by these factors, but with new features unique to regulating branch point excitability being the internodal length in the vicinity of the branch point and the differentiation of the paranodal structure. How does our paper compare with previous work? There is no theoretical work on branch point excitability in myelinated axons prior to our work. Empirical analysis of branch point transmission in myelinated axons started with the work of Knjizevic and Miledi (1958, 1959), who inferred, rather than directly proved, that failure of neuromuscular transmission in the phrenic nerve–diaphragm preparation during high-frequency stimulation is due to branch point failure. Subsequent empirical work on branch point excitability of myelinated axons has relied on both using the dorsal root ganglion preparation where three myelinated axons form the T-junction, and the neuromuscular junction preparation (Sieck and Prakash 1995). The empirical study of Stoney (1990) on adult frog DRG is the closest to which our theoretical work can be compared. Here, Stoney (1990) observed that the T-junction starts to block transmission into the dorsal root at frequency above 363 Hz (21–23°C). Interestingly, Stoney (1990) demonstrated that in the frog, moderate warming above 22°C improves the ability of branch points of myelinated axons to follow brief, high-frequency action potentials. Further warming to above 37°C blocks branch point transmission (Stoney 1990). Thus both empirical analysis (Stoney 1990) and our theoretical analysis are in qualitative agreement in demonstrating that branch point transmission has a bell-shaped dependence on temperature in myelinated axons. The quantitative difference between the empirical data on frog and our model may lie in the physiological operating temperature, which is room temperature in frog and 37°C in this study. In another empirical...
study on the T-junction in dorsal root ganglion, Stoney (1985) has noticed the frequency filtering action of the branch point and has suggested that internodal shortening in the immediate vicinity of the branch point may be a mechanism for extending the useful frequency range of the T-junction in information flow. Indeed, as Stoney (1985) has pointed out, some dorsal root ganglion in both amphibians (Ito and Takahashi 1960) and mammals (Lieberman 1976) have unusually short perifascicular internodes that may represent a functional adaptation in extending the useful frequency range of the branch point. This is dramatically confirmed in our computer simulations: a single short internode proximal to the branch point confers not only high-frequency following ability to the branch point, but allows this frequency following ability to be maintained over a broad temperature range. Finally, in the soleus nerve muscle preparation, Schiller and Rahamimoff (1989) observed neuromuscular transmission failure during high-frequency stimulation that they attributed to axonal conduction failures, presumably at branch points of these myelinated axons. Interestingly, they found that diabetes rats have less failure than normal ones. Further, elevating extracellular potassium increases tetanic muscular transmission failure during high-frequency stimulation, which they attributed to axonal conduction failures, presumably at branch points of these myelinated axons: mechanism of the depolarizing afterpotential. J Physiol (Lond) 323:117–144, 1982.


