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Suppression of Anodal Break Excitation by Electrical Stimulation with Down-Staircase Waveform for Distance-Selective Nerve Recruitment*

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***Abstract*— Electrical nerve stimulation using extracellular electrodes is widely performed in clinical medicine as well as basic medical science. It has been reported that selective recruitment of nerve fibers on the basis of the distance between the electrode and the axon is possible without moving the electrode and only by modifying the waveform of electrical stimulation. However, computer simulations have not reproduced the complete nature of the distance-selectivity of the stimulus owing to the difficulty in numerical analysis. In this paper, we propose a minor modification to the myelinated axon model to overcome this difficulty. We confirm that this modification improves the numerical stability of the simulation and enables us to obtain the spatio-temporal dynamics of axons, including the electrode-to-axon distance-dependency. In addition, we propose a novel stimulation method using a down-staircase waveform for distance-selective nerve recruitment. Simulations confirm that the method works well. We show the spatial distribution of axons activated by the down-staircase stimulation, which would be helpful to determine the stimulation parameters for distance-selective nerve recruitment.**

I. Introduction

Electrical nerve stimulation with an extracellular electrode is widely performed in the field of basic medical science as well as clinical medicine. In most cases, a rectangular pulse waveform is adopted. It is believed that rectangular-pulse stimulation tends to activate axons close to the electrode. In addition, thicker axons have a lower threshold for activation [1],[2]. Thus, if one wants to activate specific axons, the stimulation electrode should be located close to the target and the intensity of the stimulation should be adjusted so as not to activate the other axons. To alter the target axons, one should move the stimulating electrode toward the target. However, such movement can cause damage to the neural tissue. Moreover, for a chronically implanted electrode, the position cannot be changed very easily.

If the target of stimulation can be altered just by changing the waveform of electrical stimulation and without moving the electrode, the functional capability of electrical stimulation would be significantly improved. For this purpose, several stimulation waveforms have been proposed, such as pulses with an exponentially falling edge [3], up-staircase waveforms [2], and exponentially rising waveforms [4]. These waveforms were evaluated mainly in terms of the axonal diameter-selectivity, both by experiments and computer simulations [2],[3],[5]. Compared with the diameter-selectivity, few studies have focused on spatial selectivity, i.e., the selectivity to the distance between the electrode and the axon [2],[6]–[8]. This could be because numerical simulation of axon response becomes significantly difficult when the stimulation electrode is located very close to the axon; in this case, the numerical solution frequently diverges. Therefore, obtaining the spatial distribution of axons responding to the extracellular stimulation becomes difficult. Hence, it is essential to overcome the difficulty in numerical simulations to elucidate the characteristics of distance-selective nerve stimulation.

In this study, we propose a minor modification to the myelinated axon model. We show that this modification improves the numerical stability. By using the modified model, we compare the response properties of axons to several stimulus waveforms. In addition, we propose a novel stimulation method using down-staircase waveforms for distance-selective stimulation. We show the spatial distribution of the recruitment of axons in response to stimulation in clinical applications.

II. Model and Simulation Method

The spatio-temporal dynamics of rabbit myelinated axon in response to extracellular stimulation were investigated by numerical simulation. The axon model consists of 21 nodes of Ranvier, which are connected with resisters imitating the internodes. The dynamics of the membrane potential at the *i*-th node are described as follows [2],[7]–[10]:

$$C_{\mathrm{m}}\frac{dV(i)}{dt}=I_{\mathrm{axial}}(i)-\pi dl\left\{G_{\mathrm{Na}}m^{2}h\left(V(i)-E_{\mathrm{Na}}\right)+G_{\mathrm{L}}\left(V(i)-E_{\mathrm{L}}\right)\right\}, \tag{1}$$

where C_{m}, d, and l are the capacitance, diameter (15 μm), and length of the node (1.5 μm), respectively. G_{Na} is the maximum sodium conductance and G_{L} is the leak conductance. E_{Na} and E_{L} are the sodium and leak current equilibrium potentials, respectively. I_{axial} is the axial current passing through the internodes, which is described as follows [2],[7]–[10]:

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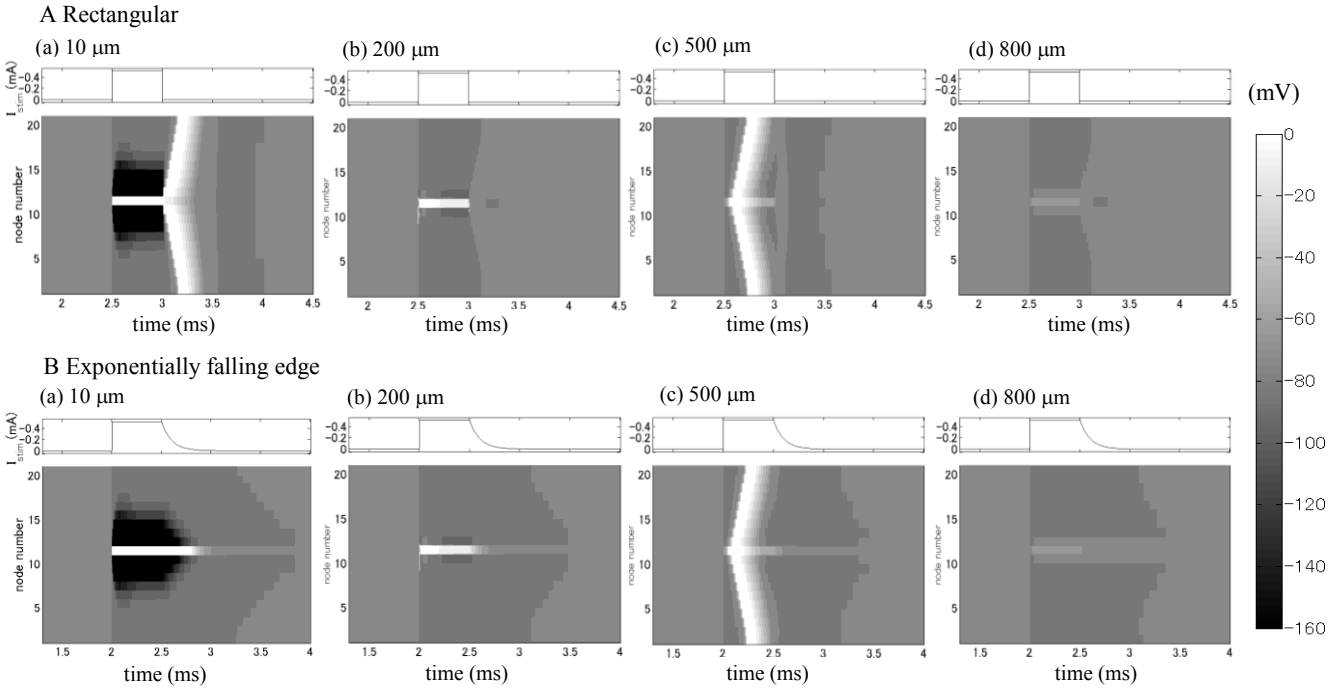

Fig. 1. A: Response pattern of myelinated axon to single pulse stimulation depending on distance between electrode and axon. Vertical axis is the node number, and horizontal axis represents time. Membrane potential at each node is represented by gray scale (unit: millivolt), truncated from –160 mV to 0 mV. Diameter of the axon is 15 μm. Amplitude and duration of pulses are –0.5 mA and 500 μs, respectively. The distance between the electrode and axon is 10 μm (a), 200 μm (b), 500 μm (c), and 800 μm (d), respectively. B: Suppression of anodal break excitation at axons very close to the stimulation electrode by a stimulation pulse with exponentially falling edge. The falling time constant is 100 μs. Other parameters are the same as in A.

$$I_{\text{axial}}(i) = G_a\{V(i-1)+\phi(i-1) - 2\big(V(i)+\phi(i)\big)+V(i+1)+\phi(i+1)\}, \quad (2)$$

where G_a is the internodal conductance and $\phi(i)$ is the extracellular potential at the i-th node. The variables m and h are the gate variables of the sodium channel, whose dynamics are described as follows [2],[7]–[10]:

$$dm/dt = \alpha_m(1-m) - \beta_m m, \quad (3)$$

$$dh/dt = \alpha_h(1-h) - \beta_h h. \quad (4)$$

It has been reported that voltage-dependent potassium channels are almost entirely absent on the rabbit myelinated nerves unlike squid and frog nerves [11]. Therefore, the potassium channels are not included in the model.

These differential equations were numerically solved using a built-in numerical solver for stiff differential equations in MATLAB (ode15s). However, divergence of the numerical solution sometimes occurred when the electrode was very close to the axon or the intensity of the stimulation was very strong. This is due to the significant stiffness of the system when the absolute value of the membrane potential is large. To avoid this, we modified the rate functions for the gate variables [8]. In short, we set lower limits for the time constant of the gate variables ($1/(\alpha+\beta)$) to suppress the stiffness of the system. We mathematically and numerically confirmed that this modification does not qualitatively change the dynamical properties of the system.

The extracellular stimulation is assumed to be applied from a small spherical electrode located relatively close to the axon, and the ground electrode is located far away from the stimulating electrode. The extracellular medium is assumed to be an isotropic and homogeneous volume conductor. For simplicity, the interaction between the axons through the extracellular potential generated by them is neglected, because this effect is estimated to be much smaller than the extracellular stimulation. In this case, the extracellular potential of the i-th node is given by the basic solution of Poisson's equation [2],[7]–[10]:

$$\phi(i) = \rho_e I_{\text{stim}}/4\pi r(i), \quad (5)$$

where I_{stim} is the amplitude of the stimulation current and ρ_e (55 Ω cm) is the resistivity of the extracellular space. $r(i)$ is the distance between the center of the electrode and the i-th node. The stimulation electrode was located closest to the 11-th node, and the distance between them is simply called *the distance between the electrode and the axon*.

For rectangular pulse stimulation, the pulse duration is set to 500 μs. The pulse waveform with an exponentially falling edge consists of a rectangular pulse with a 500 μs duration and the following exponential function: $\exp(-t/\tau)$, where τ is the time constant (100 μs). The waveform of the down-staircase stimulation consists of two consecutive rectangular pulses, 500 μs in duration each, with no gap between them. The intensity of the first and second pulses is denoted by I_1 and I_2, respectively.

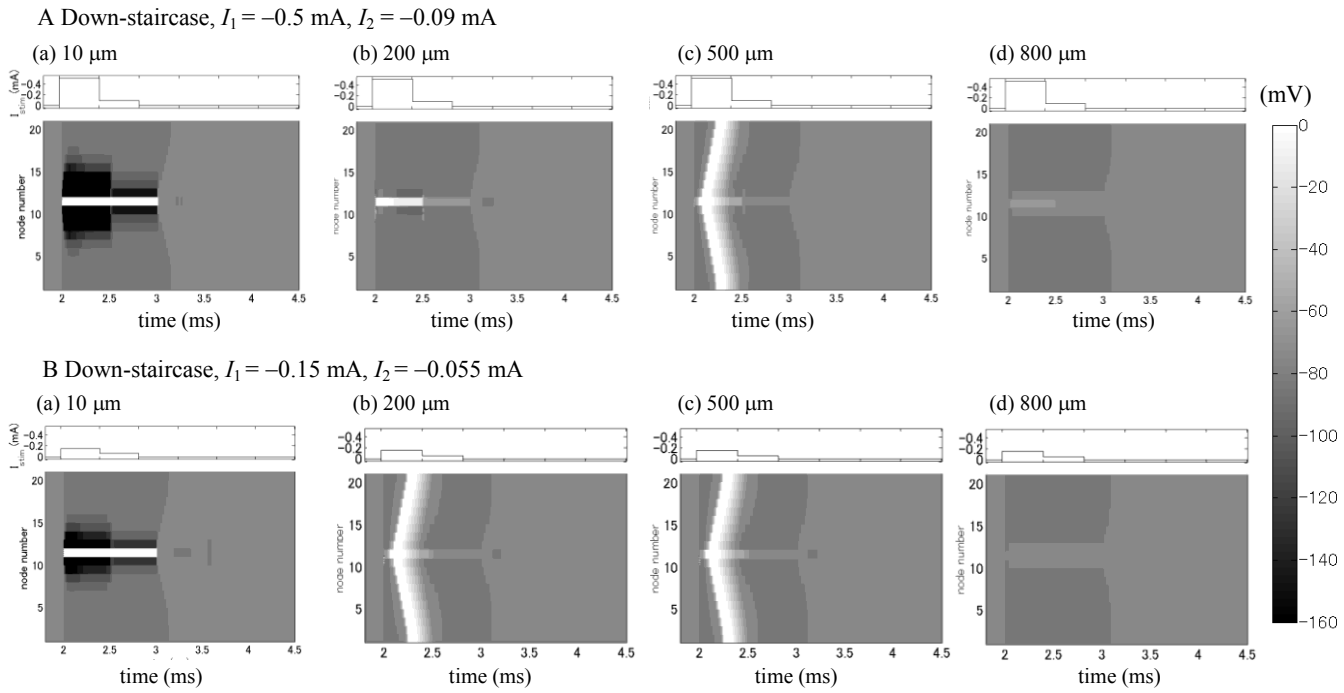

Fig. 2. Suppression of anodal break excitation and distance-selective stimulation by down-staircase stimulation. Vertical axis is the node number, and horizontal axis represents time. Membrane potential at each node is represented by gray scale. (unit: millivolt), truncated from –160 mV to 0 mV. Diameter of the axon is 15 μm. Durations of the pulse is 500 μs. The distance between the electrode and axon are 10 μm (a), 200 μm (b), 500 μm (c) and 800 μm (d), respectively. Stimulation parameters: (A) (I_1, I_2) = (–0.5 mA, –0.09 mA), (B) (–0.15 mA, –0.055 mA).

III. Results and Discussion

As is well known, the responses of myelinated axon to extracellular electrical pulse stimulation are classified into four types: *subthreshold response* (Fig. 1Ad), *cathodic excitation* (Fig. 1Ac), *anodal block* (Fig. 1Ab), and *anodal break excitation* (Fig. 1Aa) [7],[8]. The *subthreshold response* occurs at axons very far from the stimulation electrode. In this case, depolarization at the node closest to the electrode (node #11) and slight hyperpolarization at the surrounding nodes (e.g., nodes #10 and #12) are observed (Fig. 1Ad). Since the membrane potential of any node does not reach the threshold for excitation, no action potential is generated in the axon. *Cathodic excitation* occurs at axons over a range of distances from the stimulation electrode called the *activating zone* (Fig. 1Ac). As shown, an action potential is initiated at node #11 and spreads on both sides of the axon. The spatial distribution of the activating zone is dependent on the intensity of the stimulation and the spatial profile of conductivity in the tissue. If an axon is in the region closer than the activating zone, even though the node closest to the electrode is strongly depolarized and generates an action potential, the action potential cannot propagate along this axon due to the strong hyperpolarization at the surrounding nodes (*anodal block*) [10]. Interestingly, when the axon is very close to the electrode, a propagating action potential cannot be generated during the stimulation due to the *anodal block*; however, after stopping the stimulation, action potentials are initiated at nodes surrounding the node closest to the electrode (e.g., #10 and #12) and propagate on both sides of the axon (*anodal break excitation*). This phenomenon could not be reproduced by numerical simulation with the original model due to the divergence of numerical solution.

As a result, there are two populations of axons responding to the stimulation by a microelectrode: axons in the activating zone (at a certain distance from the electrode), and those very close to the electrode. These results clearly indicate the necessity for suppression of anodal break excitation to achieve distance-selective activation. It has been reported that the anodal break excitation can be suppressed by modifying the waveform of the stimulation, e.g., pulses with steep rise front and slow exponential decay [3] or square pulses with a slow exponential decay [5]. Figure 1B shows the responses of myelinated axons to stimulation with pulses having slow exponential decay. It can be confirmed that the anodal break excitation is blocked at the axons close to the electrode (Fig. 1Ba).

The exponentially decaying waveform can be generated by the combination of a general-purpose pulse generator and an electrical circuit comprising a diode, resistors, and a capacitor [3]. This circuit is simple and easy to operate manually in a laboratory experiment. However, because this circuit is not embedded in available electrical stimulators intended for clinical use, it has rarely been used in clinical medicine.

Here, we propose a novel stimulation waveform for selective nerve recruitment: a down-staircase waveform (Fig. 2). The down-staircase waveform comprises two successive pulses with different amplitudes. This waveform is designed on the basis of the following concept: the first pulse activates the axons in the activating zone and the second pulse

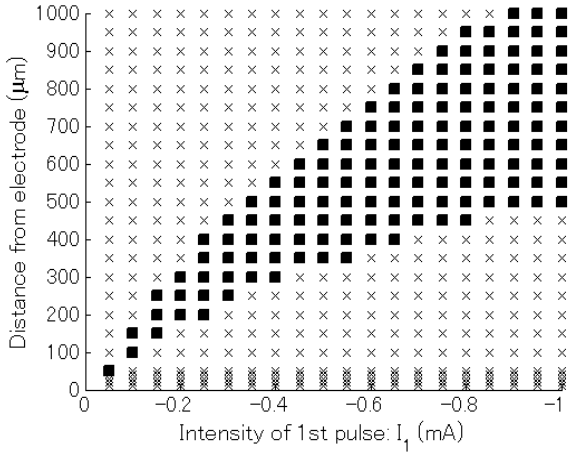

Fig. 3 Spatial distribution of axons (diameter = 15 μm) responding to down-staircase stimulation as function of intensity of stimulation. Vertical axis is the distance between axon and electrode. Horizontal axis is the intensity of the first pulse I_1. The intensity of second pulse is given by (6). Filled squares indicate that propagating action potentials are observed (excited) at the parameter set; crosses indicate that the parameter set cannot recruit the axon (not excited).

suppresses the anodal break excitation in the neighborhood of the electrode. Figure 2A shows the responses of myelinated axons to the down-staircase stimulation with (I_1, I_2) = (−0.5 mA, −0.09 mA). We can confirm that the anodal break excitation is certainly suppressed. As a result, only the axons ~500 μm away from the electrode respond by generating propagating action potentials (Fig. 2Ac). By modifying the intensities of the first and the second pulses, the target axons that are be recruited can be altered. As shown in Fig. 2B, for (I_1, I_2) = (−0.15 mA, −0.055 mA), the distribution of activated axons is moved to 200 μm away from the electrode.

Figure 3 shows the spatial distribution of the myelinated axons activated by the down-staircase stimulation as a function of the intensity of the first pulse I_1. In the simulation, the second pulse intensity I_2 is given as a function of I_1 defined as follows:

$$I_2 = a\, I_1 + b, \tag{6}$$

where $a = 0.1$ and $b = -0.04$ mA. These parameter values were obtained heuristically. It was confirmed that this stimulation protocol faithfully suppresses anodal break excitation. As shown in the figure, the region of recruitment moves as the first pulse intensity is varied. In other words, the target axons are altered without moving the stimulating electrode. By using this diagram, it is easy to determine the stimulation parameters necessary to selectively recruit a target region.

It is important to note that Fig. 3 also shows the limitations of this stimulation protocol. For example, when the target is set 200 μm away from the electrode, axons in the range of 200 ± 50 μm are also recruited. Distance-selectivity becomes worse with increasing distance between the target axon and electrode. Thus, this protocol should be used for thin neural tissue. However, this limitation will be alleviated by using a multiple-site stimulation electrode. Nevertheless, improvement in the distance selectivity is an important issue to be studied.

IV. Conclusion

In this paper, we proposed a minor modification to the myelinated axon model from the viewpoint of physiological findings and dynamical system theory to overcome the difficulty in numerical analysis under certain stimulating conditions. We observed that the modified axon model exhibited anodal break excitation in response to rectangular pulse stimulation for axons very close to the stimulation electrode. We confirmed that the anodal break excitation can be suppressed by altering the stimulus waveform from a rectangular pulse to a pulse with an exponentially falling edge. We proposed a novel stimulation method using a down-staircase waveform and showed that it enables distance-selective nerve stimulation. In addition, we obtained the stimulus intensity-dependency of the spatial distribution of the axons responding to the down-staircase stimulation. It would be helpful to determine the stimulation parameters for distance-selective stimulation. Because the down-staircase stimulation can be generated by a conventional pulse-based electric stimulator, it would be useful in clinical application. Improvements in distance-selectivity for recruitment remain an important issue for future study.

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