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Parameter Exploration of Staircase-shape Extracellular Stimulation for Targeted Stimulation of Myelinated Axon

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***Abstract*— Spatio-temporal dynamics of a mathematical model of myelinated axon in response to staircase-shape extracellular electrical stimulation, which was developed for selective nerve stimulation, is investigated by the computer simulation. It is shown that the response is classified into four types: subthreshold response, cathodic excitation, anodal block and anodal break excitation. Based on the simulation results, simple diagrams representing the response characteristics of the axon are constructed as functions of stimulation parameters and distance between the axon and electrode. The diagram would be useful for determining simulation parameters for dynamic targeted stimulation of myelinated axon.**

I. Introduction

ELECTRICAL stimulation with an extracellular electrode tends to activate axons near the electrode; thus if one uses a single stimulation electrode, it is necessary to move the electrode to change the target of stimulation. An array of electrodes (multi-site electrode) would allow changing the target without moving the electrode. However, the number of stimulation sites and the spatial resolution of stimulus are strongly limited by the structure of electrode array. In addition, an electrode array with a larger number of stimulation sites and higher spatial resolution can cause more serious damage of neural tissue by implantation of the electrode array.

On the other hand, it has been reported that extracellular stimulation having staircase-shape waveform is possible to inverse the relationship between distance and response of nerve fibers by computer simulation and experiment [1]; it can excite selectively axons distant from the electrode without exciting axons close to the electrode. This stimulation would enable dynamic targeted stimulation by modifying the stimulation parameter in real time. To determine precise stimulation parameters for targeted stimulation, it is necessary to obtain perspective of their stimulation parameter dependency of the system.

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The previous article predicted and demonstrated the selective inactivation of the axon close to the electrode by the staircase-shape stimulation. In this study, we systematically investigated the response pattern and the stimulus parameter dependency of dynamics of a myelinated axon model to the staircase stimulation by the computer simulation to understand the mechanism of selective stimulation.

II. Methods

Spatio-temporal dynamics of membrane potential of a mammalian myelinated axon in response to extracellular electrical stimulation were numerically simulated.

The mathematical model of rabbit peripheral myelinated axon was adopted for the present study. The axon model was consisted of a chain of 21 nodes of Ranvier which were coupled with conductors mimicking internodes. Dynamics of the membrane potential of i-th node $V(i)$ are described as follows [1-4]:

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

where C_{m}, d and l are capacitance, diameter (= 12 μm) and length of the node, respectively. G_{Na} is maximum sodium conductance and G_{L} is leak conductance. E_{Na} and E_{L} are sodium and leak current equilibrium potentials, respectively. I_{axial} is axial current passing through the internode, which is described as follows [1-4]:

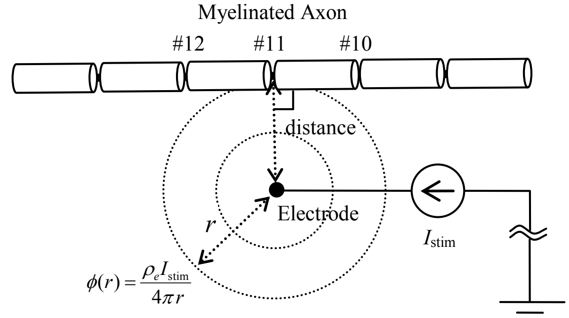


Fig. 1. Schematic representation of the myelinated axon and the stimulation electrode placement.

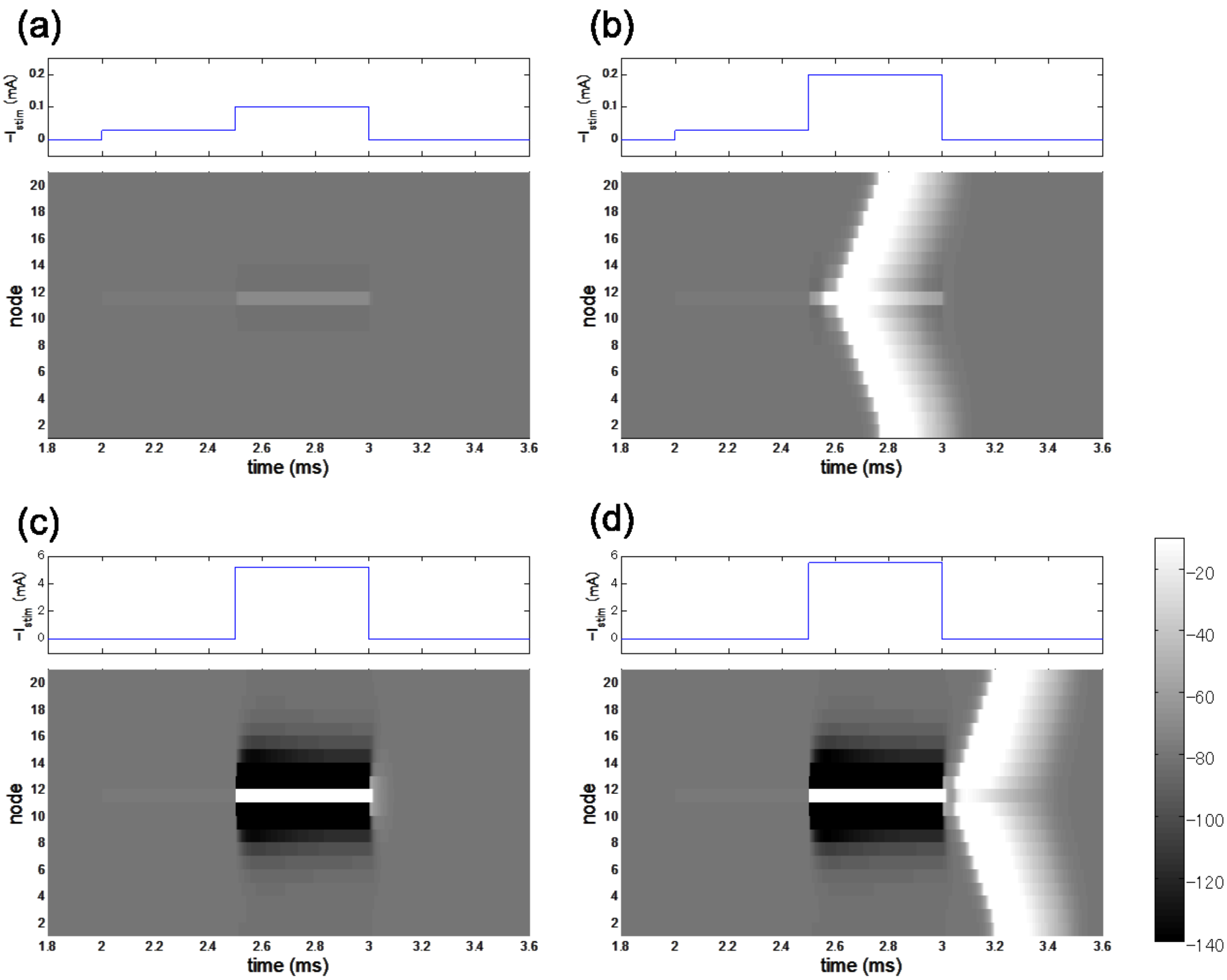


Fig. 2. Changes of response of axon to staircase stimulation depending on amplitude of the second pulse. Membrane potential of node is represented by gray scale (unit: mV) (a) Subthreshold response (amplitude of second pulse = -0.1 mA). (b) Cathodic excitation (-0.2 mA). (c) Anodal block (-5.2 mA). (d) Anodal break excitation (-5.5 mA). Parameters: distance = 0.25 mm. amplitude of the first pulse = -0.03 mA, pulse duration = 0.5 ms, gap between first and second pulse = 0 ms.

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

where G_a is internodal conductance and $\phi(i)$ is extracellular potential at i-th node. Variables m and h are the gate variables of the sodium channel whose dynamics are described as follows [3, 4]:

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

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

where α and β are rate functions defined as follows:

$$\alpha_m(V) = (126.04 + 0.363V)/(1+\exp((-V-49)/5.3)) \quad (5)$$

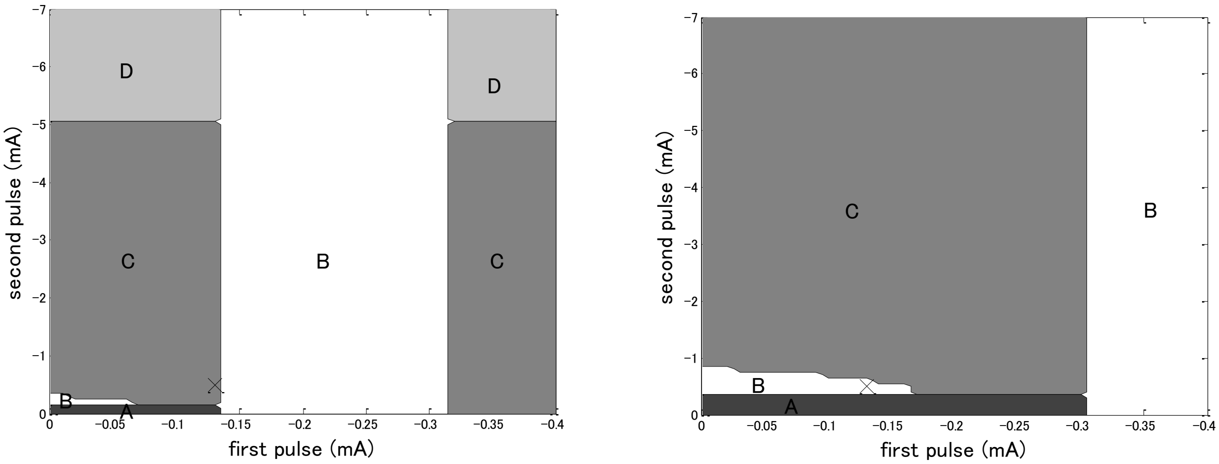
$$\beta_m(V) = \alpha_m(V)/\exp((V+56.3)/4.17) \quad (6)$$

$$\alpha_h(V) = \beta_h(V)/\exp((V+74.5)/5) \quad (7)$$

$$\beta_h(V) = 15.6/(1+\exp((-V-56)/10)). \quad (8)$$

The set of differential equations were numerically solved using MATLAB function ode15s.

An electric stimulation was assumed to be applied from a small spherical electrode located near the axon and the ground electrode is located relatively far away from the stimulation electrode. The extracellular space was assumed to be isotropic and homogeneous volume conductor. In addition, the influence of the membrane current on the extracellular potential is neglected because the influence is generally much smaller than the extracellular electrical stimulation [3]. In this



(a) (b)

Fig. 3. Diagrams of response pattern as functions of intensities of first and second pulse of staircase stimulation. The parameter region A-D represent subthreshold response (A), cathodic excitation (B), anodal block (C) and anodal break excitation (D), respectively. Distance from the electrode was (a) 250μm and (b) 500μm.

case, the extracellular potential at i-th node $\phi(i)$ is given by the following equation [1-3, 5]:

$$\phi(i) = \rho_e I_{stim} / 4\pi r(i) \tag{9}$$

where I_{stim} is amplitude of stimulation current, and ρ_e ($=55\,\Omega\text{cm}$) is resistivity of the extracellular space. $r(i)$ is distance between the centers of electrode and i-th node. The stimulation electrode was located closest to 11-th node (Fig. 1).

The stimulation current is composed of successive two current pulses, each of which the duration is 0.5 ms. Interval between the first and second pulses is set to zero.

III. Results and Discussion

A. Classification of the response to extracellular stimulation

The response of the myelinated axon to the extracellular staircase stimulation was investigated as functions of first and second pulse amplitudes and distance between the electrode and axon. Figures 2a-d show typical response of the myelinated axon model. In these simulations, the second pulse amplitude changed from -0.1 mA to -5.5 mA whereas the first pulse amplitude was fixed to -0.03 mA.

Cathodic excitation

When a weak cathodic stimulation was applied (e.g. (I_1, I_2) = (-0.03 mA, -0.2 mA), the nodes of Ranvier near the stimulation electrode were depolarized, whereas surrounding nodes were hyperpolarized. The spatial profile of the membrane potential had "Mexican hat"-like shape (subthreshold response, Fig. 2a) [5, 6]. In the case that membrane potential of the node closest to the stimulation electrode exceeded a *threshold* level for excitation; an action potential was generated and propagated in both directions along the axon (cathodic excitation, Fig. 2b).

Anodal block

When the intensity of second pulse was increased to -5.2 mA, an action potential was generated at the node closest to the electrode (node #11). However, propagation of the action potential was blocked at neighbor nodes (#10 and #12) due to the strong hyperpolarization at the nodes (anodal block, Fig. 2c) [6].

Anodal break excitation

Figure 2d shows the case of (I_1, I_2) = (-0.03 mA, -5.5 mA). Similar to the anodal block response, an action potential was initiated at the closest node (#11) but blocked at neighbor nodes (#10 and #12) during the stimulation period. However, after stopping the stimulation, action potentials were generated at the neighbor nodes (#10 and #12) and propagate along the axon (anodal break excitation) [1, 5, 6]. It is noteworthy that the spike generating mechanism is quite different from the cathodic excitation as just described.

B. Parameter space analysis

Figures 3a and 3b show the response properties of the myelinated axons at 250 μm and 500 μm apart from the electrode, respectively. As shown, the stimulation parameter space is divided into several regions according to the type of response and the regions changes depending on the distance between the electrode and the axon. The border line between

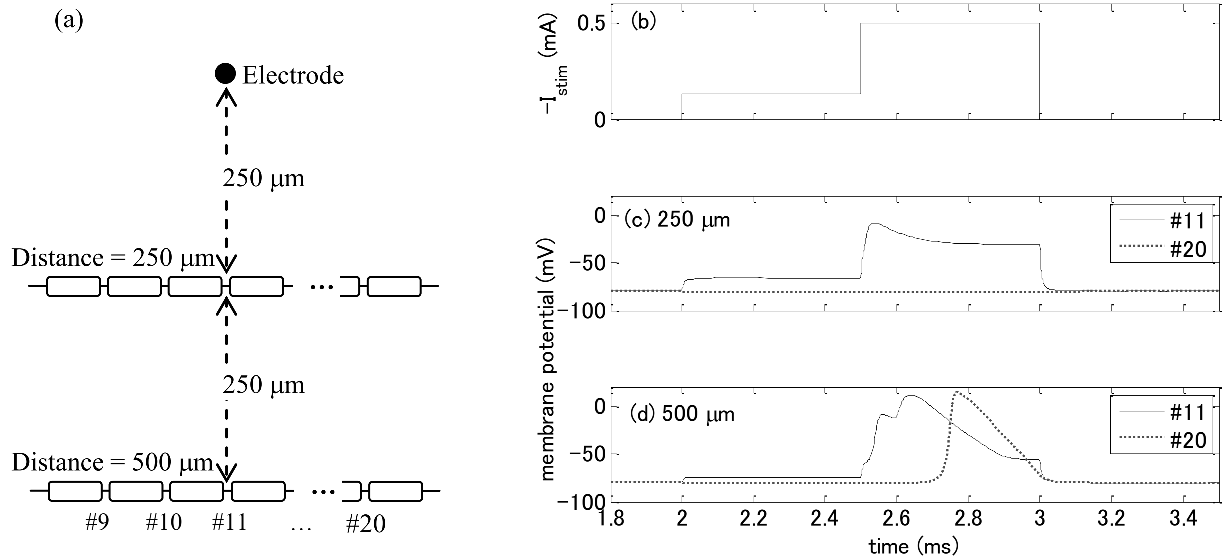


Fig. 4. An example of the distance-selective recruitment of myelinated axons by the staircase-shape stimulation. The stimulation parameter set is (I_1, I_2) = (-0.13 mA, -0.5 mA) indicated by X in Fig. 3. (a) Spatial arrangement of the stimulation electrode and the axons. (b) The waveform of the stimulation current. (c) The response of the axon at 250 μm apart from the electrode. (d) The response of the axon at 500 μm apart from the electrode.

cathodic excitation (region B) and anodal block (region C) is downward sloping, whereas the border line between cathodic excitation and subthreshold response (region A) is horizontal. The parameter region for cathodic excitation becomes shrinking and disappears with increasing distance between the amplitude of the first stimulation pulse. In addition, the border line shifts rightward as increasing the distance between the axon and electrode. These characteristics enable the inversion of distance-response relationship.

By using these diagrams, one can easily determine the stimulation parameters for selective stimulation. The parameter margins as well as the combination of possible response patterns are easily obtained. For example, if one adopt stimulation parameter of (I_1, I_2) = (-0.13 mA, -0.5 mA) indicated by X in the diagrams, *cathodic excitation* is induced in the axon at 500 μm apart from the electrode, whereas *anodal block* occurs in the axon at 250 μm. Figure 4 shows the time course of the membrane potentials in this case. We can confirm that the action potential is induced at the nodes closest to the electrode in both axons, propagating action potential is observed only in the axon at 500 μm (Fig. 4d). As a result, synaptic terminals of the axon at 500 μm would be selectively activated by the staircase-shape stimulation.

IV. Conclusion

We constructed a simple diagram representing the response characteristics of a myelinated axon model as functions of stimulation parameters, and distance between the axon and electrode. The diagram would be useful for determining simulation parameters for dynamic targeted stimulation of myelinated axon.

Grill and his colleagues have confirmed that staircase-shape stimulation actually works as selective sciatic nerve stimulation in cats [1]. Thus, it is suggested the robustness of staircase-shape stimulation against parameter variations and fluctuations inherent in living organisms.

In this study, stimulation selectivity was limited to the distance between the electrode and axon. However neural system has axons with wide diameter distribution; for more precise control of neural system it is necessary to develop a stimulation method selective to not only distance from the electrode but also thickness of the axons.

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