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Development of Distance-Selective Nerve Recruitment for Subcortical Brain Mapping by Controlling Stimulation Waveforms*

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***Abstract*—During brain surgery, it is important to determine the functional brain area and cortico-cortical pathways so as to keep them intact and preserve patients' quality of life. Cortical and subcortical brain mappings are techniques that deliver direct current stimulation to the brain surface and beneath gray matter to identify the brain area and nerve fibers related to higher-order functions. However, because of the non-selective effect of conventional electrical stimulation methods, it has been difficult to obtain precise spatial distribution of nerve fibers in the subcortical region. We investigated the electrical stimulation of subcortical mapping to evaluate axon-to-electrode distance-selectivity. It was clarified that a conventional rectangular biphasic pulse activates axons non-selectively. We propose double exponential waveforms and show that they can recruit targeted fibers and change the location of a target by manipulating stimulus intensity. These results suggest the usefulness of introducing distance-selective stimulation into subcortical brain mapping.**

I. Introduction

During brain surgery, it is important to determine the location of essential cortico-cortical pathways so as to avoid damaging them and negatively affecting the patient's quality of life. To establish their location, cortical mapping and subcortical mapping are usually performed. Cortical mapping constructs a functional mapping of the cortical surface by monitoring the electrophysiological responses to direct electrical stimulation. Subcortical mapping estimates the location of connecting fibers based on the response to direct electrical stimulation. For example, during surgery of the temporal lobe, subcortical mapping is carried out for searching arcuate fasciculus, which connects Wernicke's area and Broca's area and plays an important role in language function [1,2].

If nerve fibers located at a certain distance from the stimulating electrode can be recruited selectively, this would facilitate investigation of the spatial distribution of fibers beneath gray matter, which would help to reduce surgeons' stress and the risks of brain surgery. However, it is difficult to estimate the spatial distribution of fibers by means of conventional subcortical mapping. This problem may be overcome with distance-selective nerve stimulation techniques. Distance-selective stimulation allows only distant axons from the electrode to be recruited without exciting the axons close to the electrode by changing stimulation parameters. If it is possible to manipulate the spatial distribution of recruited fibers by changing the stimulation parameters in subcortical mapping, it would facilitate investigation of the spatial distribution of subcortical fibers.

Many stimulation methods for axon-to-electrode distance- or axonal diameter-selective recruitment have been developed for peripheral nerves. For instance, waveforms such as up and down staircase shapes and a linearly rising pulse have been developed to improve the distance- or diameter-selectivity [3,4,5]. For clinical application, the injected current charge should be balanced to avoid electrolysis of the cerebrospinal fluid, although many of the techniques do not consider this factor. Moreover, it is difficult to apply these methods to cortex stimulation because the peripheral nerve system and the cerebral cortex are morphologically and electrophysiologically different.

In this study, we investigated an electrical stimulation method for subcortical mapping in terms of the distance-selectivity of nerve recruitment. To evaluate the distance-selectivity of stimulation methods, we constructed a multi-layer volume conductor model of the human skull and neocortex, and embedded a mathematical model of a human myelinated axon in the volume conductor. The axonal dynamics in response to an extracellular columned electrode was analyzed by computer simulation when part of the skull and cortex was removed. We found that a conventional biphasic rectangular pulse cannot achieve distance-selectivity between an electrode and an axon. In contrast, a novel stimulation waveform consisting of double exponential curves and a rectangular pulse was found to improve remarkably the distance-selectivity of subcortical nerve recruitment.

II. Model and Simulation Method

We constructed a 3D volume conductor based on anisotropic properties of the human brain, which includes the skull, dura mater, cerebrospinal fluid (CSF), gray matter, and white matter [6,7]. To imitate the resection of gray matter, the layers of skull, dura matter, CSF, and gray matter were partly removed. Thickness and conductivity of each component are listed in Table 1. The extracellular electrode was modeled after a 3-mm diameter columned electrode and located on the surface of white matter. The stimulus was assume to be current stimulation, and the electrical distribution was simulated with COMSOL Multiphysics 4.1 (COMSOL, USA). To estimate the stimulating effect, a mathematical model of the axon was

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embedded in the volume conductor model, and spatio-temporal dynamics of the axon model in response to extracellular stimulation was numerically calculated. We adopted the human mathematical myelinated axon model described in [8,9] and implemented by NEURON (http://www.neuron.yale.edu/neuron/). It consists of 199 nodes and 200 internodes, and the nodes are connected by internodes, which were assumed to be resisters. The diameters of fiber and node were set to 5 μm and 2.2 μm, respectively. The axons were positioned parallel to the surface of the electrode tip. The 99th node (node 99) and the center of the electrode were set to be at the same axis on a longitudinal section. In the following text, the distance between the electrode surface and node 99 is simply called distance. The perspective of the model is depicted in Fig. 1A.

TABLE I. PARAMETERS OF THE VOLUME CONDUCTOR MODEL

Domain name	Value (mm)	Conductivity (S/m)	Reference
Skull	5	0.02	[6]
Dura mater	0.5	0.065	[6,7]
CSF	2.6	1.7	[6,7]
Layer I	0.2	0.14	[6]
Layers II–IV	1.4	0.36	[6]
Layers V–VI	2.1	0.36	[6]
White matter	12	0.083[a], 0.6[b]	[6]
Electrode contact	3[c], 1[d]	100e6	[7]
Substrate	3[c], 4[d]	0.1e–9	[7]

a. Perpendicular to the fibers. b. Parallel to the fibers. c. Diameter. d. Height.

The stimulation waveforms were set to a rectangular biphasic pulse and a double exponential waveform with a rectangular pulse (Fig. 1B). These waveforms were designed such that the total injected charge was zero. The rectangular biphasic pulse is described as a function of time:

$$I(t)=\begin{cases} A, & t_1 < t \le T + t_1, \\ -A, & T + t_1 < t \le 2T + t_1, \\ 0, & otherwise, \end{cases} \quad (1)$$

where I, t_1, and T are intensity, delay, and duration of the stimulus pulse, respectively. In this study, T was set to 0.2 ms.

The exponential waveform with pulse obeys the following equations:

$$I(t)=\begin{cases} 2A\exp((t-t_1)/\tau_1) - A\exp((t-t_1)/\tau_2), & t \le t_1, \\ A, & t_1 < t \le t_1 + T, \\ 0, & t_1 + T < t, \end{cases} \quad (2)$$

where A, τ_1, and τ_2 respectively represent the amplitudes and time constants of the exponential waveform. We set τ_1 to 1 ms, and pulse duration T was set to 0 ms and 0.2 ms. The time constant τ_2 was determined by:

$$\tau_2 = 2\tau_1 + T. \quad (3)$$

The change in membrane potential may also affect the extracellular potential, but we neglected this influence because it is much smaller than that of extracellular stimulation [3,4,5,6,9].

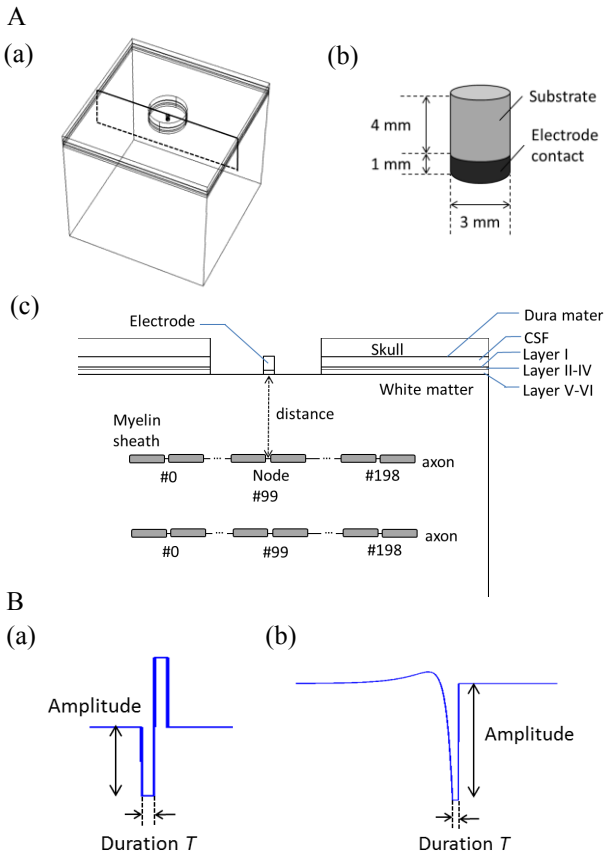

Figure 1. Schematic representation of the model (A) and time course of the stimulus waveforms (B). (Aa), perspective of the volume conductor model, (Ab), a columned electrode, (Ac), a longitudinal section of the model (surrounded by solid line in (Aa)). (Ba), a rectangular biphasic pulse, (Bb), a double exponential waveform with pulse.

III. RESULTS AND DISCUSSION

We investigated the spatial distribution of recruited axons with a rectangular biphasic pulse and a double exponential waveform with pulse (pulse duration T = 0.2 ms). Typical responses are depicted by gray scale images as functions of time and node number (Fig. 2). The white bands observed in Figs. 2Aa–c and Fig. 2Bc denote action potentials propagating along the axons. Dependency diagrams of the spatial distribution on stimulus intensity I in response to each pulse are shown in Fig. 3.

A. Rectangular Biphasic Pulse

When a rectangular biphasic pulse was used, all axons located within 2.2 mm from the electrode were recruited (Fig. 2Aa–c). When the distance from the electrode was greater than 2.2 mm, none of the nodes reached sufficient depolarization and no action potential was generated (Fig. 2Ad). As the stimulus intensity was greater, the position of recruited axons was deeper, but excitation of axons close to the electrode was always observed regardless of the stimulus

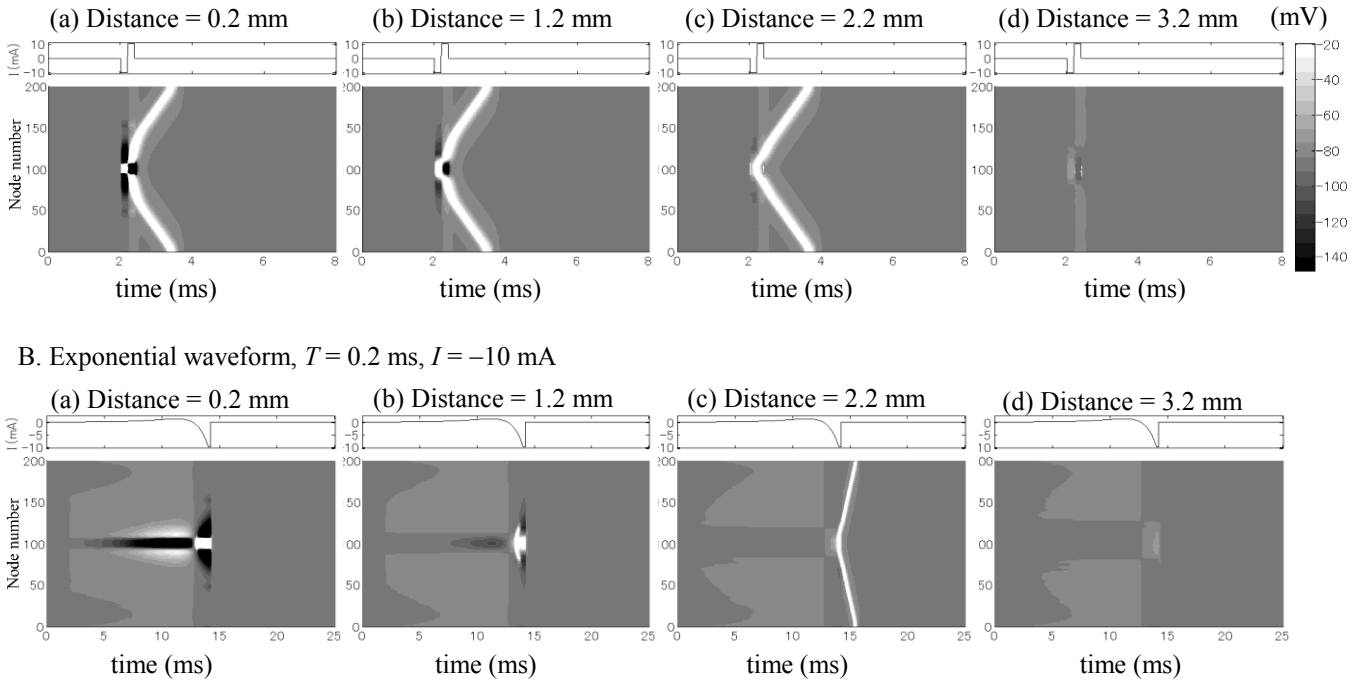

Figure 2. Changes of the membrane potential in response to a rectangular biphasic pulse (A) and a double exponential waveform (pulse duration $T = 0.2$ ms) (B). Time course of stimulus current intensity I is shown in the top row of each waveform. Membrane potential is represented by gray scale (unit: millivolts) and truncated within the range −148 to −20 mV (bottom). $I = -10$ mA. Distances are 0.2 mm (a), 1.2 mm (b), 2.2 mm (c), and 3.2 mm (d).

intensity (Fig. 3A). Therefore, a rectangular biphasic pulse cannot recruit axons distance-selectively.

B. Double Exponential Waveform with Pulse

In the case of a double exponential waveform with a 0.2-ms duration pulse, only those axons located at a depth 2.2 mm from the electrode were recruited (Fig. 2B). As shown in Fig. 3C, as the stimulus intensity was greater, axons located deeper were recruited, whereas the axons close to the electrode were not recruited. Moreover, the recruited area shifted when the stimulus intensity was adjusted. Therefore, a double exponential waveform with pulse was able to excite targeted axons at a certain axonal distance from the electrode only by adjusting the stimulus parameters. Compared with a waveform with no pulse (Fig. 3B), a waveform with a 0.2 ms pulse (Fig. 3C) needed slightly less intensity to activate axons far from the electrode surface, and the parameter region narrowed. By adding a pulse to a double exponential waveform, the distance-selectivity was improved.

C. Mechanism of Distance-Selective Stimulation by a Double Exponential Waveform

In the case of a rectangular biphasic pulse, initiation sites of action potentials were dependent on the electrode-to-axon distance. When the axon was located far from the electrode, an action potential was initiated at nodes 95–105 (Fig. 2Ac). When the axon was close to the electrode, no action potential was propagated at nodes 95–105. After stopping the depolarization at nodes 95–105, their neighboring nodes (nodes 70–94, 106–130) strongly depolarized and generated action potentials (Figs. 2Aa,b). These excitations were induced by *virtual cathodes* [10] at nodes 70–94 and 106–130 during a positive counter pulse for charge balance (in 2.2–2.4 ms).

In contrast, a double exponential waveform did not recruit axons close to the electrode. A positive pulse with a gentle slope preceding a negative pulse also induced *virtual cathodes*, but their intensities were not sufficiently strong to generate action potentials. In the following negative pulse, strong depolarization at nodes 93–108 was blocked by *virtual anodes* induced at the neighboring nodes (Figs. 2Ba,b) [10,11]. In the case of the distant axon, an action potential was generated by a negative pulse. A *virtual anode* induced by a negative pulse was not sufficiently strong to prevent action potential being propagated, and the axon was recruited (Fig. 2Bc). Therefore, a double exponential waveform is able to accomplish distance-selective stimulation.

Fig. 3 shows the responsiveness of the axons as functions of stimulus intensity and axon depth. By using the diagrams in Fig. 3B and C, we can easily estimate the distance between the electrode and the recruited axon. For example, if we apply a double exponential waveform with –20 mA and obtain the axonal response, it means that there are axons approximately 2 mm from the electrode. When I is high, rebound excitation occurs close to the electrode surface, which reduces the distance-selectivity. Therefore, stimulus intensity should be set within a range such that rebound excitation does not occur.

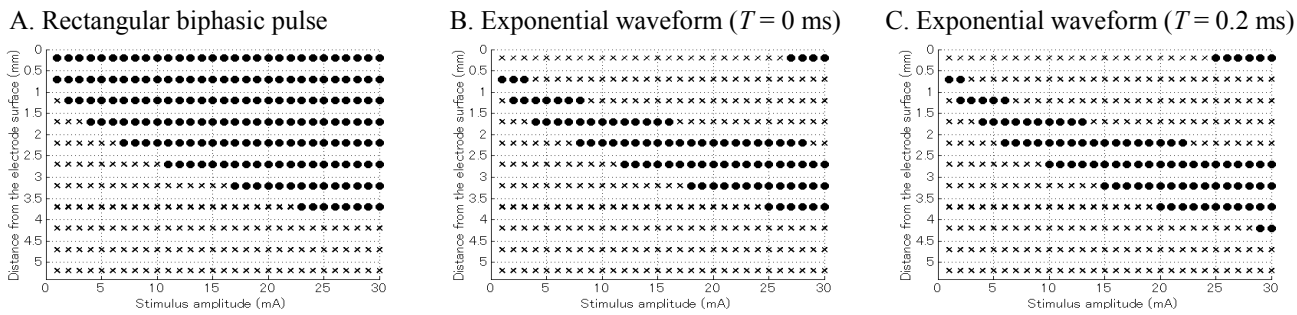

Figure 3. Diagrams as functions of stimulus amplitude and distance between the electrode and the axon. Axons generating action potentials and no action potentials are represented by black circles and crosses, respectively. Stimuli waveforms are a rectangular biphasic pulse (A), a double exponential waveform (T = 0 ms) (B), and T = 0.2 ms (C).

We presumed that large fibers exist in the shallow white matter area [12], and so we adopted the 5-μm diameter axon model. Axons with large diameters are mainly recruited by extracellular electrical stimulation because large axons have a lower threshold than small axons. When the diameters of axons are smaller than 5 μm, higher stimulus intensity is needed to recruit axons at the same depth as axons with 5-μm diameters [3,13].

For clinical application, it would be useful to recruit deeper axons and axons running perpendicular to the brain surface [14]. We adopted a single-site columned electrode with a flat surface, but developing the spatial pattern of the electrode would improve the efficacy of stimulation. In addition, a waveform which consists of rectangular pulses would be easy to use, since an exponential waveform is not able to be generated by pulse generators. Finding a pulse-based waveform which can be substitution of an exponential waveform is also remained to be studied.

IV. Conclusion

We numerically simulated the responses of axons to an extracellular columned electrode and compared the spatial distribution of recruited axons with a biphasic rectangular pulse and a double exponential waveform. We found that the region of axons recruited by a conventional rectangular biphasic pulse was monotonously broadened by increasing the stimulus intensity. Therefore, it is not able to achieve distance-selective nerve recruitment. We proposed double exponential waveforms and showed that these are able to selectively recruit axons at a certain distance from the electrode, which is dependent on the stimulus intensity. As the intensity was changed from 0 mA to −30 mA, the area of recruited axons changed from 0.5 mm to 4 mm. These results suggest that this may be applied to subcortical brain mapping. The recruitment of axons in the inner part of white matter remains an important issue requiring further research.

References

[1] H. Duffau, L. Capelle, D. Denvil, N. Sichez, P. Gatignol, L. Taillandier, M. Lopes, M. C. Mitchell, S. Roche, J. C. Muller, A. Bitar, J. P. Sichez, and R. Effenterre, "Usefulness of intraoperative electrical subcortical mapping during surgery for low-grade gliomas located within eloquent brain regions: functional results in a consecutive series of 103 patients," *J. Neurosurg.*, vol. 98, pp. 764–778, April 2003.

[2] N. Sanai and M. S. Berger, "Intraoperative stimulation techniques for functional pathway preservation and glioma resection," *Neurosurg. Focus*, vol. 28, no. 2, Feb. 2010.

[3] W. M. Grill and J. T. Mortimer, "Inversion of the current-distance relationship by transient depolarization," *IEEE Trans. on BME*, vol. 44, no. 1, Jan. 1997.

[4] A. Ueno, N. Katayama, A. Karashima, and M. Nakao, "Spatio-temporal dynamics of a myelinated nerve fiber model in response to staircase-shape extracellular electrical stimulation," *JBMES*, vol. 49, no. 6, pp. 896–903, 2011 (in Japanese).

[5] K. Hennings, L. A. Nielsen, S. S. Christensen, and O. K. Andersen, "Selective activation of small-diameter motor fibres using exponentially rising waveforms: a theoretical study," *Med. Biol. Eng. Comput.*, vol. 43, pp. 493–500, 2005.

[6] L. Manola, B. H. Roelofsen, J. Holsheimer, E. Marani, and J. Geelen, "Modelling motor cortex stimulation for chronic pain control: electrical potential field, activating functions and responses of simple nerve fibre models," *Med. Biol. Eng. Comput.*, vol. 43, pp. 335–343, 2005.

[7] A. Wongsarnpigoon and W. M. Grill, "Computational modeling of epidural cortical stimulation," *J. Neural Eng.*, vol. 5, pp. 443–454, 2008.

[8] J. R. Schwarz, G. Reid, and H. Bostock, "Action potentials and membrane currents in the human node of Ranvier," *Eur. J. Physiol*., vol. 430, pp. 283–292, 1995.

[9] W. A. Wesselink, J. Holsheimer, and H. B. K. Boom, "A model of the electrical behaviour of myelinated sensory nerve fibres based on human data," *Med. Biol. Eng. Comput.*, vol. 37, pp. 228–235, 1999.

[10] F. Ratty, *Electrical Nerve Stimulation –Theory, Experiments, and Applications*. Wien: Springer-Verlag, 1990, chs. 7 & 8, pp. 122–156.

[11] J. Holsheimer, G. G. Heide, and J. J. Struijk, "Anodal block of myelinated nerve fibers: a modeling study," *IEEE Trans. on BME*, vol. 12, no. 5, 1990.

[12] G. Meyer, P. Wahle, A. C. Perdomo, and R. F. Torres, "Morphology of neurons in the white matter of the adult human neocortex," *Exp. Brain Res*., vol. 88, pp. 204–212, 1992.

[13] N. J. M. Rijkhoff, J. Holsheimer, F. M. J. Debruyne, and H. Wijkstra, "Modeling selective activation of small myelinated nerve fibers using a monopolar point electrode," *Med. Biol. Eng. Comput.*, vol. 33, pp. 762–768, 1995.

[14] M. Catani and M. T. Schotten, "A diffusion tensor imaging tractography atlas for virtual in vivo dissections," *Cortex*, vol. 44, pp. 1105–1132, May 2005.