EXPLORING STIMULUS WAVEFORM SPACE FOR SELECTIVE STIMULATION OF NEURAL FIBERS

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Abstract: Rectangular pulses are used in most applications of electrical stimulation, without any evidence for its superiority to other possible waveforms. Special non-rectangular stimulus waveforms have been shown that can change the stimulation pattern of neural fibers in a nerve for selective stimulation of targeted fibers. But the related studies are very limited and mostly based on clues from physiologic insight and trial and error. In this study, a genetic algorithm search tool is used to explore the space of stimulus waveforms for selective stimulation of central fibers of peripheral nerve using a cuff electrode. The search doesn't lead to a perfect desired result, but a waveform with interesting effect on central and lateral fibers is found.

Introduction

Several decades of research on Electrical Stimulation of nervous system, have resulted in various Neural Prostheses [1]. While these devices have enhanced the quality of life for patients with a wide range of different disorders, their functionality is still far from desire. Neural prostheses require an interface that enables selective activation of targeted neurons, in order to provide independent channels of control [2]. However the current interfaces for electrical stimulation provide limited selectivity.

During the last decade, several approaches have been suggested to improve the selectivity of electrical stimulation of neural fibers in peripheral nerves [2].

One of the approaches to improve the selectivity of electrical stimulation is looking for appropriate stimulus waveforms and their parameters based on nonlinear properties of excitable membranes. For example, several researchers have investigated the effect of waveform width and stimulation frequency on the selectivity [3].

Rectangular waveforms have been used in most applications of electrical stimulation. But the reason seems to be nothing but its simplicity and the lack of strong evidences for preference of other waveforms. But the latter is mainly due to our insufficient knowledge about how we can communicate with complex neural elements via electrical stimulation in the most appropriate manner.

During the two last decades, several investigators suggested some non-rectangular waveforms to improve selectivity, in order to provide special selective capabilities or to reduce stimulation drawbacks such as charge injection.

For example, under-threshold depolarizing prepulses followed by an stimulus pulse has been shown that can change the stimulation pattern of neural fibers, based on non-linear properties of excitable membrane and the resulted blocking effect, such that more distant fibers can be selectively activated[4].

We have shown that ramp-shaped under-threshold depolarizing prepulses have wider range of applicability for targeted fibers in different distances from electrode [5].

In a simulation study, we also checked the performance of rectangular and ramp-shaped prepulses for selective stimulation of central neural fibers, but not lateral ones with a cuff electrode (unpublished study).

The results show that the inhomogeneous medium significantly limits the performance of this technique.

We believe that deep insight on dynamics of excitable membrane, and excitation and blocking mechanisms of neural fibers can provide some clues to find the waveforms which can provide selective capabilities. However, It should be noted that inhomogeneous and anisotropic properties of real stimulation medium not only reduces the performance of the suggested methods significantly, but also complicate the use of electrophysiological insight to suggest more appropriate selective waveforms.

On the other hand, the process of finding appropriate waveforms mainly based on trial and error, especially in adjusting the parameters of the waveform for a special application.

Kajimoto has developed a mathematical approach to convert the problem of finding appropriate stimulus waveform and electrode configuration to a classic optimization problem, and then have used linear programming to solve it. He has found stimulation paradigms for selective activation of narrow or distant fibers[6].

But, to find the response of neural fibers, Kajimoto has used a linear model of excitable membrane and a threshold voltage for membrane potential which exceeding that, is interpreted to activation of fiber. He

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also used a homogeneous volume conductor model for stimulating medium.

However, linear models of excitable membranes can not reveal some important behaviors of the membranes which can influence stimulation result significantly[7].

In this study, we have simulated the stimulation of neural fibers in the inhomogeneous and anisotropic volume conductor of a nerve trunk with a cuff electrode around it. Also, we have used a nonlinear model of myelinated neural fibers to find the response of fibers to the stimulations, therefore the model accounts for dynamics of excitable membrane.

Using such a model, makes the resulted optimization problem very hard to solve. Considering 30 nodes of Ranvier for one fiber, we will have 60 nonlinear first order differential equations for each considered fiber. It seems that the performance of conventional methods for solving nonlinear optimization problems is poor for solving such complex problem.

In this study, we have utilized a fuzzy genetic algorithm (GA) as a tool to explore the space of possible stimulus waveforms. We have searched for a waveform, able to selectively stimulate neural fibers in the center of the nerve without excitation of lateral fibers.

Method

A 3D volume conductor model of a nerve trunk was used to obtain distribution of electrical potential along the fibers. A view of this model is shown in Figure 1.

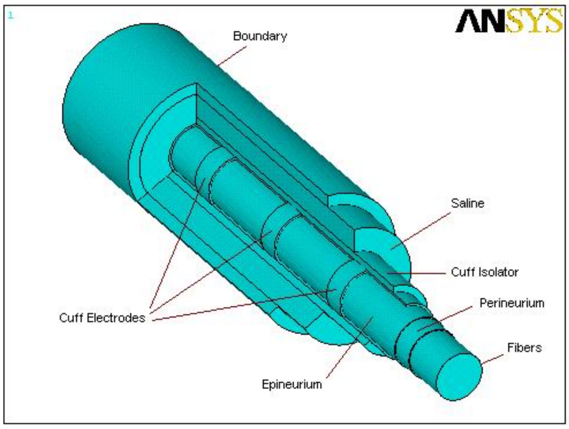

Figure 1: anisotropic and inhomogeneous model of nerve trunk, which a three polar cuff electrode is placed on it.

This model included an anisotropic neural fascicle with the length of 20mm and diameter of 1.9mm covered by perineurium and epineurium layers, each 50um thick. A tri-polar cuff electrode was considered around the nerve. The cuff electrode consisted of three electrode-tips in one row along the fiber with the length of 1mm and thickness of 50um, each covered a 30° Arc of the nerve. An isolating cuff was considered around the electrode tips surrounded by saline. The isolating cuff was 5mm thick and 10mm long. The surrounding saline was considered 0.9mm thick covered by 0.4mm volume for the model of distant medium. The conductivities of the sections were presented in table 1. All the sections were considered purely ohmic. So the volume conductor was linear and without any dynamics [8].

The model was used for simulation of electrical stimulation with unit current amplitude. The required electrical potentials along the fiber for each time step with the corresponding current amplitudes were calculated based on these results. In this part of simulation, the effect of neural fiber itself was neglected.

To model current injection from electrode tips, the total current was distributed uniformly among the nodes of finite element model on the surface of electrode tips.

The model was implemented by ANSYS software and solved by finite element method.

Table 1: Conductivities of different sections of volume conductor.

Section Name	**Conductivity(1/ohm meter)**
Nerve Fascicle	0.5 longitudinal, 0.08 radial
Perineurium	0.00336
Epineurium	0.008
Cuff Isolator	0.0008
Saline	2
Distant medium	0.02
Electrode Tip	20

The computed voltage distribution along the simulation time was fed to fiber models as input and the resulted responses of fibers were obtained.

McNeal model was considered for the neural fibers. The myelinated sections of the fiber were considered ideal isolators. Each fiber model consisted of 30 nodes of Ranvier. The diameter of the fiber is considered to be 10um.

Based on this model the current crossing the membrane in each node due to extracellular stimulation is related to membrane potential and external voltage distribution with this equation:

$$i_{st} = \frac{d\Delta x}{4\rho_i L}\left(\frac{V_{n-1} - 2V_n + V_{n+1}}{\Delta x^2} + \frac{V_{e,n-1} - 2V_{e,n} + V_{e,n+1}}{\Delta x^2}\right) \qquad (1)$$

V_n is the variation of membrane potential from its rest value, $V_{e,n}$ is the extracellular voltage adjacent to the node n, d is the axon diameter, D is the fiber diameter, L is the length of the node of Ranvier, Δx is the internodal distance and ρ_i is the intracellular special resistivity. The values of these parameters are presented in table 2.

Table 2: Value of the parameters of the fiber model.

Parameter	Value	Unit
ρ_i	55	ohm.cm
L	1.5	um
L/D	100	
d/D	0.6	
Δx	500	um

The nonlinear dynamics of the membrane of each node of Ranvier was simulated by CRRSS model. This model was based on the data from experimental studies on nodes of Ranvier of myelinated axons of rat. The equations of this model are as follows. The parameter values are presented in table 3[9].

$$\frac{dV}{dt}=\frac{-g_{Na}m^2h(V-E_{Na})-g_L(V-E_L)+I_{St}}{c} \qquad (2)$$

$$\frac{dm}{dt}=k(\alpha_m(1-m)-\beta_m m) \qquad (3)$$

$$\frac{dh}{dt}=k(\alpha_h(1-h)-\beta_h h) \qquad (4)$$

$$k=Q_{10}^{\frac{T-T_0}{10}} \qquad (5)$$

$$\alpha_m=\frac{97+0.363V_m}{1+\exp\left(-\frac{V_m-31}{5.3}\right)} \quad \beta_m=\frac{\alpha_m}{\exp\left(\frac{V_m-23.8}{4.17}\right)} \qquad (6,7)$$

$$\beta_h=\frac{15.6}{1+\exp\left(-\frac{V_m-24}{10}\right)} \quad \alpha_h=\frac{\beta_h}{\exp\left(\frac{V_m-5.5}{5}\right)} \qquad (8,9)$$

The Model was implemented by Matlab-Simulink software. The simulations were run on a 500MHz Pentium III computer.

In this study, monopolar stimulation method is considered and simulated.

The width of stimulus waveform was considered 1mSec and divided into ten 0.1mSec parts. The current amplitude was considered constant in each part, so each waveform in the space of defined stimulus waveforms can be represented by 10 real numbers. The amplitude of the waveform in each part was considered to be between -800 to 800 uA.

The response of two fibers, one at the center of the nerve trunk and the other at the lateral distance of 0.9mm from the center was evaluated for each waveform, to find the waveform that can produce action potentials in the central fiber, but not in the lateral one.

At first, production of action potential was considered as the criteria for GA search. But due to inappropriate results, it was changed to a more variable parameter, the maximum entrance of sodium to the cell from the last node of Ranvier during the stimulation

Table 3: Parameter values for CRRSS model of excitable membrane.

Parameter	Value	Unit
V_r	-80	MV
C_m	2.5	uF/cm^2
g_{Na}	1445	mS/cm^2
E_{Na}	115	mV
g_L	128	mS/cm^2
E_L	-0.01	mV
m(t=0)	0.003	
h(t=0)	0.75	
T_0	37	°C
Q_{10}	3	

While during action potential initiation a large amount of sodium ions enters the cell, this criteria seemed to be relevant.

A fuzzy genetic algorithm was used to search for appropriate waveform. This was a real-valued genetic algorithm implemented with GAToolbox, a toolbox provided for MATLAB software. The specifications of this algorithm are as follows.

The chromosomes consisted of 10 real numbers between -800 to 800, as its genes. The number of chromosomes in each population was 100. The parent selection method used was "Stochastic Universal Sampling". Ranking method was used to generate fitness values. Generation gap was considered 0.45. A set of fuzzy rules were used to change the mutation rate in the population as a means to preserve the population diversity along the generations and avoiding premature convergence.

Results

The evolutionary algorithm could not find any waveform in the defined search space which was able to stimulation central neural fibers of the nerve trunk selectively. But the result of its effort to find such a waveform was still valuable and noticeable. Figure 2 shows the waveform found by the algorithm after 100 generations (The best chromosome in the population).

Figure 3 shows the response of central neural fibers to this special waveform, while figure 4 shows the response of lateral neural fiber under the study. These figures present the membrane voltage along the fiber during the simulation time. The stimulus waveform although could not induce action potential in the central fiber, had a special still interesting effect. It resulted in production of two propagating action potentials per period of stimulation in the central fiber, but only one in the lateral fiber. This is not a perfect, but still interesting and usable result. It means that central fibers respond to this waveform twice the lateral ones in frequency which is still appropriate in FNS applications in comparison to existing methods.

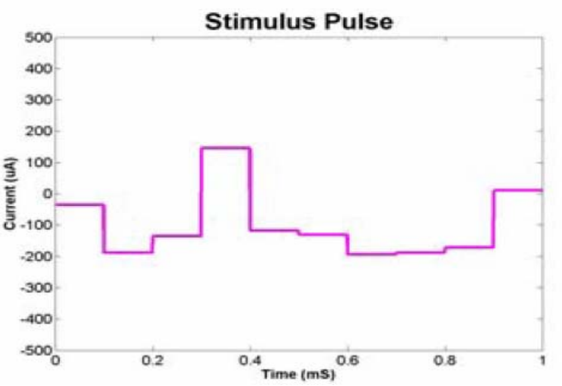

Figure 2: The stimulus waveform found by Genetic Algorithm search.

Conclusions

We implemented an anisotropic and inhomogeneous model of peripheral nerve volume conductor in addition to nonlinear model of neural fibers to look for a stimulus waveform which can selectively stimulate some central neural fibers without activation of lateral ones with a monopolar cuff electrode.

A genetic algorithm has used to explore the space of stimulus waveforms for this purpose.

The previous studies have shown that some waveform-base selective techniques tested in homogeneous medium represent poor performance using this more realistic model.

Genetic Algorithm as a stochastic-based search algorithm, although could not find the desired waveform, but could suggest a waveform, that can fire central fibers twice the lateral ones.

This is an acceptable result in comparison with some selective stimulation methods used in clinical applications (e.g. post stimulus voiding).

It seems that the use of maximum sodium entrance as the criteria for genetic algorithm is the key reason which leads us to such interesting result

This technique can also be used to find more appropriate waveforms for stimulation of neural cells in central nervous system where selectivity is more valuable and desirable.

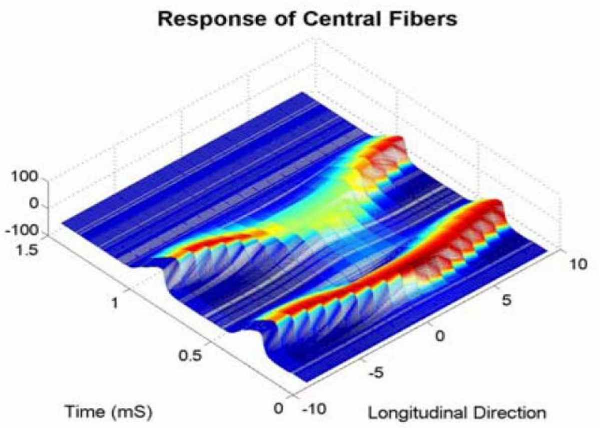

Figure 3: The response of central neural fiber to the waveform shown in figure 2 along the time.

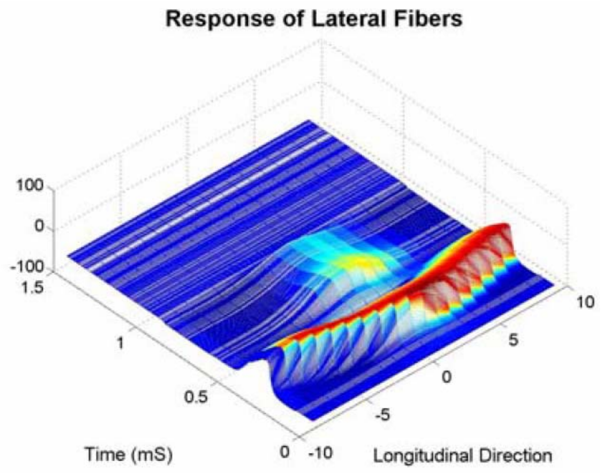

Figure 4: The response of lateral neural fiber to the waveform shown in figure 2 along the time.

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