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Optimal Stimulus Profiles for Neuroprosthetic Devices: Monophasic versus Biphasic Stimulation

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***Abstract*— Designing stimulation signals for neuroprosthetic devices can be cast as an optimal control problem. Rectangular Lilly-type stimulation waveforms have been used extensively in these devices. In this paper, we rigorously formulate the charge optimization problem from a control perspective and distinguish between monophasic and biphasic stimuli. We show that for a monophasic stimulus, the important factor in stimulating a neuron is the total delivered charge per unit cell membrane. This factor is a consequence of the subthreshold linear behavior of the neural membrane. On the other hand, biphasic pulses, which are ubiquitous in the neuron stimulation context, can stimulate a neuron in its non-linear range, thereby challenging the finding that total charge delivery is the only critical factor. As a result, there may be even more optimal stimulus profiles than Lilly-type rectangular waveforms for biphasic stimulation. Furthermore, solving the charge minimization problem also will reduce the risk of electrode corrosion, which is an important factor in improving the performance of neuroprosthetic devices.**

I. INTRODUCTION

Electrical stimulation of excitable cells by injecting current waveforms through micro-electrodes is crucial to the function of neuroprosthetic devices such as prosthetic limbs, deep brain stimulators for the treatment of epilepsy, as well as retinal and cochlear implants [1], [2], [3], [4], [5]. The design of appropriate current waveforms to stimulate neurons has gained considerable attention [6], [7]. Rectangular Lilly-type pulses have been widely used in the context of electrical stimulation of neurons [8], [3], [4], [5].

Among the methods that can improve the performance of neuroprosthetic devices, the design of optimal stimuli has attracted considerable attention recently [9], [10], [11], [12], [13], [14], [15], [16], [17].

Jezernik and Morari showed that in order to minimize the required energy for generating an action potential, a current stimulation waveform whose magnitude increases exponentially can be used [9]. Computer simulations for different waveforms presented in [10] suggest that non-rectangular pulses can be more energy efficient compared to rectangular pulses if applied at optimal pulse width.

Genetic algorithms have revealed that for a McIntyre-Richardson-Green model neuron, a truncated Gaussian stimulus is more energy efficient compared to rectangular pulses [18], [12]. They also showed that it is not possible to optimize total delivered charge, energy, and power at the same time [19].

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The model for a single neurite developed by Reilly [20] suggests that a higher threshold is required for biphasic stimulation due to the fact that the second anodic phase opposes depolarization of the action potential. Based on this model, as the interphase gap increases, the required threshold for generating action potentials would decrease. Field-Fote *et al.* [21] found that there was a considerable difference between monophasic and biphasic stimulus thresholds. Their experimental results, however, contradicted the model based approach proposed by Reilly.

Foutz *et al.* [16] have shown that centred-triangular waveforms are more energy efficient compared to traditional rectangular pulses. They performed *in vivo* experiments on rats to investigate the energy efficiency of non-rectangular pulses. Furthermore, they showed that the varying compliance voltage as well as the pulse width of the stimulation had a significant effect on reducing the amount of energy required to activate a neuron.

Since electrode corrosion depends upon the amount of charge it delivers to the neural tissue, our aim in this paper is to formulate the charge optimization problem for a Hodgkin-Huxley (HH) neural model [22], [23]. Given that contradictory differences between monophasic and biphasic stimuli have been reported in the literature [20], [21], we formulate the optimization problem such that these two cases will be considered and can be compared. We illustrate that there is a difference between these two types of stimulus waveforms from an optimal control point of view.

The rest of the paper is organized as follows. In Section II the optimization problem to minimize the total delivered charge to a HH model neuron is formulated. In our formulation we consider monophasic as well as biphasic stimuli. Moreover, in case of biphasic stimulation, we consider the effect of the interphase gap. Primary results for monophasic and biphasic stimulation are presented in Section III, where we show that nonlinearities should be taken into account for biphasic stimulation. Conclusions and future work are addressed in Section IV.

II. METHODS

Figure 1 shows the block diagram of a neuron from a control perspective. In this system, the input is the current stimulus waveform, represented by I_{stim}, and the system output is the membrane potential. The main equation governing this dynamical system is the well-known Hodgkin-Huxley formulation of neural activation [22], [23]. The states and

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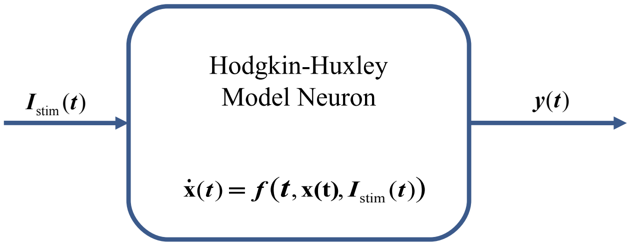

Fig. 1. Representation of a neuron under electrical stimulation from a control perspective. I_{stim}, representing the electrical stimulation, is the input to the system. The vector $\mathbf{x}(t) = [V_M(t)\ n(t)\ m(t)\ h(t)]^T$ represents the states of the system and $\mathbf{f}\big(t, \mathbf{x}(t), I_{\text{stim}}(t)\big)$ is a nonlinear function described by the Hodgkin-Huxley (1952) equations [22]. The desired output of the system is the membrane potential.

the output of the system are

$$\mathbf{x}(t) = [V_M(t)\ n(t)\ m(t)\ h(t)]^T, \tag{1}$$
$$y(t) = V_M(t), \tag{2}$$

where $V_M(t)$ is the membrane potential, and n, m, and h are gating variables. The state space realization of the system may be written as

$$\dot{\mathbf{x}}(t) = \mathbf{f}\big(t, \mathbf{x}(t), I_{\text{stim}}(t)\big), \tag{3}$$

where

$$\mathbf{f} = \begin{bmatrix} g_1 V_M + g_2 \\ \alpha_n(V_M)(1-n) - \beta_n(V_M)n \\ \alpha_m(V_M)(1-m) - \beta_m(V_M)m \\ \alpha_h(V_M)(1-h) - \beta_h(V_M)h \end{bmatrix} + \frac{1}{C_M}\begin{bmatrix} I(t) \\ 0 \\ 0 \\ 0 \end{bmatrix} \tag{4}$$

in which

$$g_1 = -\frac{\bar{g}_L + \bar{g}_K n^4 + \bar{g}_{Na} m^3 h}{C_M}, \tag{5}$$
$$g_2 = \frac{\bar{g}_L E_L + \bar{g}_K n^4 E_K + \bar{g}_{Na} m^3 h E_{Na}}{C_M}. \tag{6}$$

In the above equations, C_M represents the capacitance of the membrane per unit area, E_{L}, E_{K}, and E_{Na} are reversal potentials for the different ion channels. $\bar{g}_L$, $\bar{g}_K$, and $\bar{g}_{Na}$ are maximum conductances per unit area of the relevant ionic current. Coefficients $\alpha(V_M)$ and $\beta(V_M)$ are nonlinear functions of V_M which determine the closing and opening rates for each gate.

In our optimization problem, we consider two types of stimulation waveforms, monophasic and biphasic stimuli.

A. Monophasic Stimulus

The objective for a monophasic stimulus is to generate an action potential while keeping the total delivered charge at its lowest possible value. Therefore, the cost function can be written as

$$\mathcal{J}_{\text{m}} = \int_{\tau_p} I_{\text{stim}}(\tau) d\tau, \tag{7}$$

where τ_p is the period that the stimulation has been applied. The objective is to find the optimal stimulation waveform, $I^{\text{m}}_{\text{stim}}$, such that

$$I^{\text{m}}_{\text{stim}} = \underset{I_{\text{stim}}}{\text{argmin}}\, \mathcal{J}_{\text{m}}\big(I_{\text{stim}}(t)\big), \tag{8}$$

subject to the dynamics expressed by Equation (3) and while making sure that the neuron fires an action potential, which is guaranteed if the membrane potential reaches a threshold voltage, V_T, at some point in time. Therefore, the following constraint must additionally be satisfied:

$$\max_{\tau_p}(V_M) \geq V_T. \tag{9}$$

B. Biphasic Stimulus

For biphasic stimuli the cost function to be minimized is

$$\mathcal{J}_{\text{b}} = \int_{\tau_s} |I_{\text{stim}}(\tau)| d\tau, \tag{10}$$

where τ_s is the total stimulation time for both phases. To keep the charge-balanced condition, the following constraint applies:

$$\int_{\tau_s} I_{\text{stim}}(\tau) d\tau = 0. \tag{11}$$

Moreover, the threshold requirement indicated by Equation (9) needs to be satisfied. We consider four different cases for solving the above optimization problem:

- Case I: We assume that the applied waveform consists of two rectangular equal pulses with different polarities. Therefore, in this case the objective is to find the optimal values of the pulse magnitude, A, its duration, τ_p, and the interphase gap, τ_{ig}. In other words,

$$\boldsymbol{\theta}^{\text{b}}_{\text{I}} = \underset{\boldsymbol{\theta}_{\text{I}}}{\text{argmin}}\, \mathcal{J}_{\text{b}}\big(I_{\text{stim}}(\boldsymbol{\theta}_{\text{I}}, t)\big),$$
$$\boldsymbol{\theta}_{\text{I}} = [A\ \tau_p\ \tau_{ig}]^T. \tag{12}$$

- Case II: We assume that the applied waveform consists of two rectangular nonequal pulses with different polarities as shown in Figure 2a. In this case the objective is to find $\boldsymbol{\theta}^{\text{b}}_{\text{II}}$ such that

$$\boldsymbol{\theta}^{\text{b}}_{\text{II}} = \underset{\boldsymbol{\theta}_{\text{II}}}{\text{argmin}}\, \mathcal{J}_{\text{b}}\big(I_{\text{stim}}(\boldsymbol{\theta}_{\text{II}}, t)\big),$$
$$\boldsymbol{\theta}_{\text{II}} = [A_+\ \tau_{p+}\ A_-\ \tau_{p-}\ \tau_{ig}]^T. \tag{13}$$

- Case III: We assume that the applied waveform consists of a rectangular positive pulse and an arbitrary negative polarity as shown in Figure 2b. In this case the objective is to find $\boldsymbol{\theta}^{\text{b}}_{\text{III}}$ such that

$$\boldsymbol{\theta}^{\text{b}}_{\text{III}} = \underset{\boldsymbol{\theta}_{\text{III}}}{\text{argmin}}\, \mathcal{J}_{\text{b}}\big(I_{\text{stim}}(\boldsymbol{\theta}_{\text{III}}, t)\big),$$
$$\boldsymbol{\theta}_{\text{III}} = [A_+\ \tau_{p+}\ I_-(t)\ \tau_{ig}]^T. \tag{14}$$

- Case IV: We assume that the applied waveform consists of two arbitrary waveforms with different polarities as

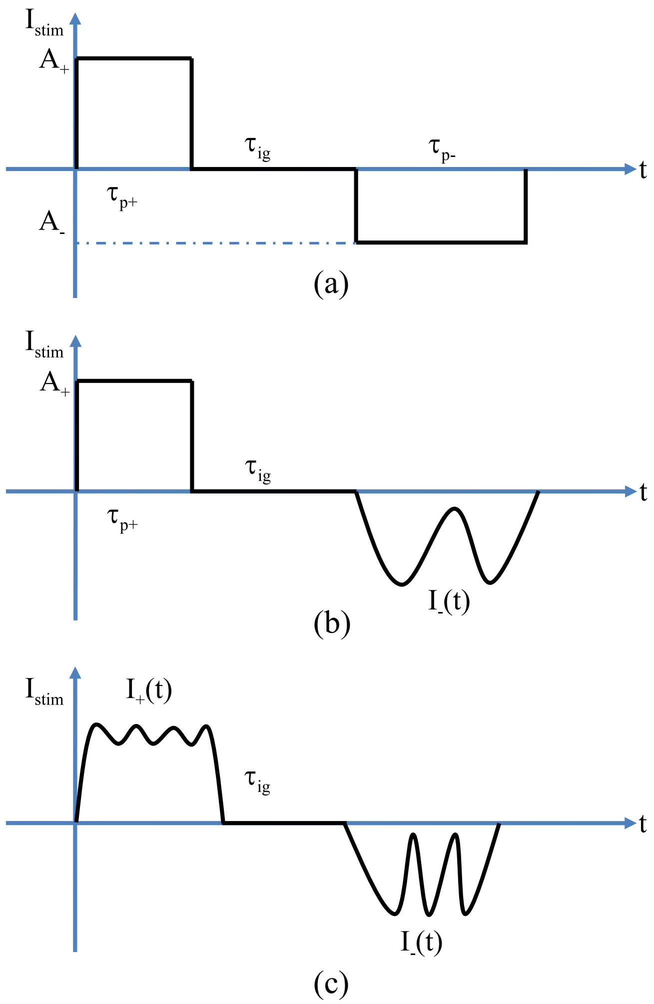

Fig. 2. Different scenarios considered for a biphasic stimulus. (a) The positive and negative parts are both rectangular, and optimal τ_{ig} is to be determined. (b) The first phase is a rectangular pulse and the second phase has an arbitrary shape to be determined. (c) Both phases have arbitrary shapes and are to be determined such that the optimization conditions are met.

shown in Figure 2c. In this case the objective is to find $\boldsymbol{\theta}_{\mathrm{IV}}^{\mathrm{b}}$ such that

$$\boldsymbol{\theta}_{\mathrm{IV}}^{\mathrm{b}} = \underset{\boldsymbol{\theta}_{\mathrm{IV}}}{\operatorname{argmin}} \, \mathcal{J}_{\mathrm{b}}\big(I_{\mathrm{stim}}(\boldsymbol{\theta}_{\mathrm{IV}}, t)\big),$$
$$\boldsymbol{\theta}_{\mathrm{IV}} = [I_{+}(t) \; I_{-}(t) \; \tau_{ig}]^{T}. \tag{15}$$

III. Results

We have run simulations for a HH model neuron with parameters and variables listed in Table I. Simulation results for rectangular and triangular monophasic stimuli are shown in Figure 3. In both cases, the action potential upstroke has occurred at the same point in time. The amount of charge for the rectangular pulse is 7μC/cm^2 and for the triangular pulse is 6.9μC/cm^2. This observation shows that when the system operates in its linear region, the amount of charge determines the occurrence of an action potential. It is worth noting that up to threshold, the neuron can be considered as a simple RC element, which is a linear system.

TABLE I
Parameters and variables of the HH model neuron.

Parameters and Variables	Value
C_M	1[μF/cm^2]
$\bar{g}_L$	300[μS/cm^2]
$\bar{g}_K$	36000[μS/cm^2]
$\bar{g}_{Na}$	120000[μS/cm^2]
E_L	-49.4[mV]
E_K	-72[mV]
E_{Na}	55[mV]
$\alpha_n(V_M)$	$\frac{10(V_M+50)}{1-e^{-(V_M+50)/10}}$[1/s]
$\alpha_m(V_M)$	$\frac{100(V_M+35)}{1-e^{-(V_M+35)/10}}$[1/s]
$\alpha_h(V_M)$	$70\,e^{-(V_M+60)/20}$[1/s]
$\beta_n(V_M)$	$125\,e^{-(V_M+60)/80}$[1/s]
$\beta_m(V_M)$	$4000\,e^{-(V_M+60)/18}$[1/s]
$\beta_h(V_M)$	$\frac{1000}{1+e^{-(V_M+30)/10}}$[1/s]

Simulation results illustrated in Figure 4 show the difference between a traditional rectangular pulse with 0.5ms of interphase gap and a non-traditional triangular pulse with 0.95ms interphase gap. The delivered charge to the neuron during each phase of the rectangular biphasic pulse is approximately 20.3μC/cm^2 while this value for the triangular biphasic stimulus is approximately 17.1μC/cm^2 which indicates that there is a 20% difference in the delivered charge between these two waveforms that generate the same action potential. Therefore, from an optimization point of view, there is considerable difference between monophasic and biphasic stimulation. This is due to the fact that in biphasic stimulation, nonlinearities of the system have a significant effect in the response of the system to the input compared with monophasic stimulation. In order to find the optimal stimulation waveform for an HH model neuron, the optimization problems addressed in Section II should be solved using available optimization methods.

IV. Discussion, Conclusions and Future Work

In this paper we addressed and rigorously formulated the charge optimization problem for monophasic and biphasic stimulation. We demonstrated that in the case of monophasic stimulation, it is sufficient to deliver a certain amount of charge in a fixed period of time to activate the neuron. As long as the system operates in its linear phase, or equivalently in its subthreshold regime, this argument is valid.

However, for biphasic stimulation, nonlinearities of the system play an important role in its response, and therefore, the profile of the applied stimulus becomes an important factor in activating the neuron under electrical stimulation. We illustrated the difference between rectangular and non-rectangular stimuli through a numerical example. In our future work, we will solve the charge optimization problem and will validate the result via *in vitro* experiments. We believe that the results can be used to improve the performance of

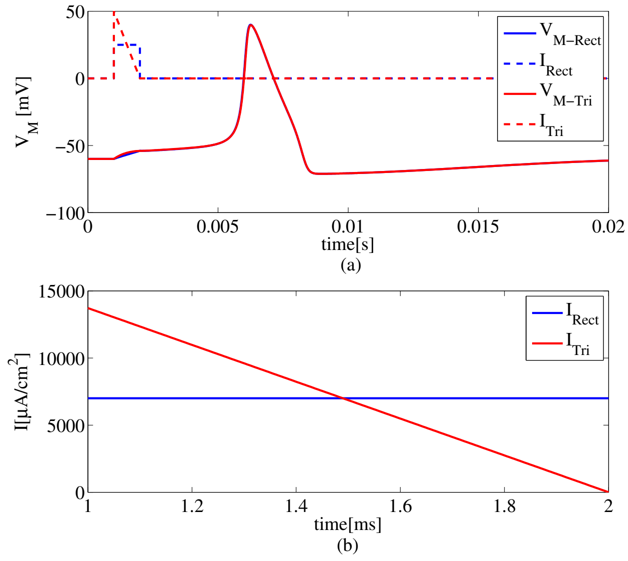

Fig. 3. Simulation results for the HH Model neuron specified in Table I. Simulations results are shown for rectangular and triangular monophasic waveforms. (a) Generated action potential for both stimuli along with stimulus waveforms (not to scale), (b) Rectangular and triangular waveforms applied to the neuron.

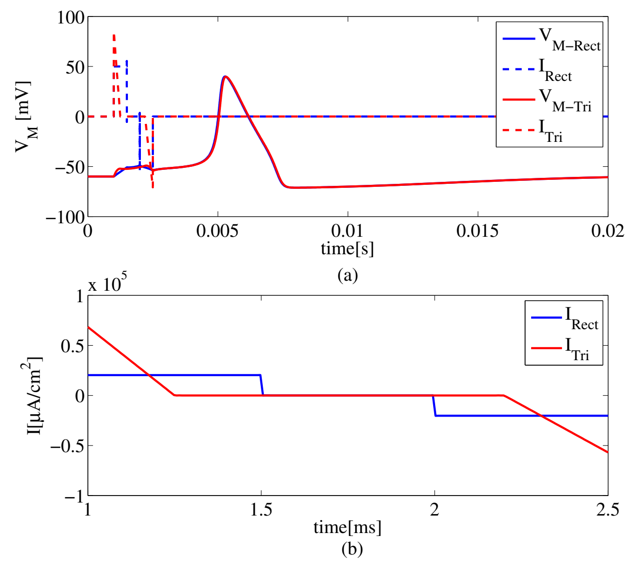

Fig. 4. Simulation results for the HH Model neuron specified in Table I. Simulations results are shown for rectangular and triangular biphasic charge balanced waveforms. (a) Generated action potential for both stimuli along with stimulus waveforms (not to scale), (b) Rectangular and triangular charge balanced waveforms applied to the neuron.

neuroprosthetic devices through optimizing the total charge delivered per phase.

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