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Optimal Stimulus Current Waveshape for a Hodgkin-Huxley Model Neuron

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***Abstract*— Traditionally, rectangular Lilly-type current pulses have been employed to electrically stimulate a neuron. In this paper, we utilize a least squares optimisation approach to assess the optimality of rectangular pulses in the context of electrical current stimulation. To this end, an appropriate cost function to minimise the total charge delivered to a neuron while keeping the waveshape sufficiently smooth, is developed and applied to a Hodgkin-Huxley ionic model of the neural action potential. Cubic spline parameters were utilized to find the optimal stimulation profile for a fixed peak current. Simulation results demonstrate that the optimal stimulation profile for a specified single neuron is a non-rectangular pulse whose shape depends upon the maximum allowable current as well as the stimulus duration.**

I. INTRODUCTION

Neuroprosthetic devices such as cochlear implants, bionic eyes, and deep brain stimulators employ external electrical stimulation of excitable cells to enhance quality of life of thousands of patients suffering from neurological disorders [1], [2], [3].

Efficient electrical stimulation of neuroprosthetic devices can be achieved via two principal approaches. Firstly, it is possible to stimulate a neuron more efficiently through optimising the electrode geometry and location [4], and secondly approach can be through the design of optimal stimulus waveforms [5], [6], [7], [8], [9], [10]. The focus of this paper is on the second approach.

For a leaky membrane, an exponentially increasing current stimulation waveform was shown to be more energy-efficient compared to a traditional rectangular waveform [5]. It was also shown that there exists an optimal stimulation duration for a rectangular stimulus pulse [5]. Sahin and Tie [7] studied the effect of seven different waveforms on the threshold parameters of a mammalian nerve axon using numerical methods. Their simulation results demonstrated that the chronaxie is a function of the applied stimulus waveform. Therefore, non-rectangular pulses may potentially be more efficient compared to rectangular Lilly-type pulses.

Wongsarnpigoon and Grill [8], [11] adopted a genetic algorithm to find the optimal energy-efficient stimulation waveform. Their results for a McIntyre-Richardson-Green (MRG) neuron model showed that a truncated Gaussian function results in an energy efficient stimulus profile. Moreover, they showed that the efficiency of their waveform increased with the stimulus pulse width. In a different work, Wongsarnpigoon *et al.* [12] compared the efficiency of rectangular, rising/decaying exponentials, as well as rising ramp stimulation profiles, and concluded that no waveform can optimise energy, charge, and power simultaneously.

Forger *et al.* [13] used calculus of variations to find an optimal stimulation profile for a Hodgkin-Huxley (HH) model neuron to minimise the L^2 norm of the stimulation current. Their findings indicate that the optimal stimulation waveform highly depends on excitatory/inhibitory post-synaptic currents.

Given that the risk of electrode corrosion and damage to the neural tissue depends on the amount of charge delivered through the electrode [8], we consider the problem of designing a current stimulus waveform that minimizes the total charge delivered, whilst generating an action potential in a HH [14] neural ionic model. Moreover, to minimise the complexity of the electronics of the stimulation device, smooth waveshapes are required. To this end, we have developed an appropriate objective function to minimise the area under the current stimulus waveform applied for a fixed duration, subject to the activation dynamics dictated by the HH equations. The objective function incorporates an additional penalty term to minimise any ripples in the resultant waveshape. Solution to the optimisation problem using cubic splines shows that the optimal stimulus waveform is a non-rectangular, with its shape strongly-dependent on the specified maximum applied current and stimulus duration.

In Section II of this paper, the optimisation problem for minimising the charge delivered to a HH model neuron is formulated, along with our approach to solving this optimisation problem. Simulation results for a typical HH model and a comparison between a rectangular pulse and the optimal waveform are presented in Section III. Discussion of results and conclusion are addressed in Section IV.

II. METHODS

The equivalent circuit diagram of a space-clamped, single-compartment HH model neuron is represented in Figure 1. In this model, the total membrane current is given by the parallel sum of sodium and potassium membrane currents as well as a leakage current. In this section, we formulate and solve an optimisation problem for HH activation, to challenge the optimality of rectangular Lilly-type pulses which are ubiquitous in the neural stimulation context.

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A. Problem formulation

The dynamical system representing the HH model neuron can be written as

$$\dot{V}_M = -\frac{\bar{g}_L + \bar{g}_K n^4 + \bar{g}_{Na} m^3 h}{C_M} V_M + \frac{\bar{g}_L E_L + \bar{g}_K n^4 E_K + \bar{g}_{Na} m^3 h E_{Na}}{C_M} + \frac{I(t)}{C_M}, \quad \text{(1a)}$$

$$\dot{n} = \alpha_n(V_M)(1-n) - \beta_n(V_M)n, \quad \text{(1b)}$$

$$\dot{m} = \alpha_m(V_M)(1-m) - \beta_m(V_M)m, \quad \text{(1c)}$$

$$\dot{h} = \alpha_h(V_M)(1-h) - \beta_h(V_M)h, \quad \text{(1d)}$$

where V_M represents the membrane potential, C_M is the capacitance of the membrane per unit area, and $\bar{g}$ is the maximum membrane conductance per unit area of the ionic current defined by the relevant subscript. E_{L}, E_{K}, and E_{Na} represent membrane reversal potentials for each ion channels. Gating variables n, m, and h, represent the probability of a subunit gate being open. Coefficients $\alpha(V_M)$ and $\beta(V_M)$ are opening and closing rates of each gate specified by its subscript, respectively. All parameters and rate formulations are given in Table I. Note that these formulations represent a modified version of the original HH equations [14], such that the resting membrane potential is -60mV and outward currents are positive in accordance with modern convention.

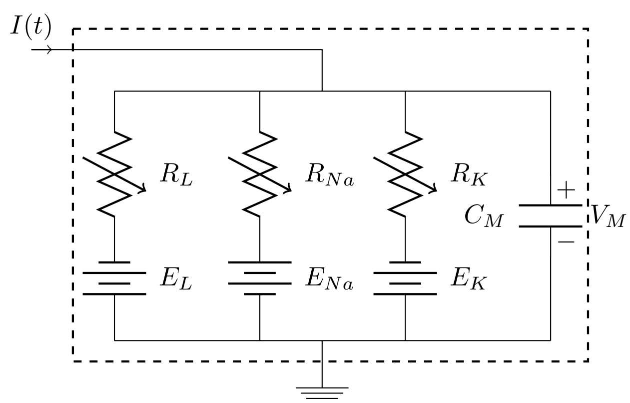

Fig. 1. Hodgkin-Huxley neuron model from a control perspective. Stimulus waveform, $I(t)$, is the input to the system and the membrane voltage, V_M, is the desired output. The dynamics of this nonlinear plant can be expressed by Equations (1).

The objective function which we seek to minimize to find the optimal stimulus profile is defined by

$$\mathcal{J}\big(I(t,\boldsymbol{\theta})\big) = Q + P_1 + P_2, \quad \text{(2)}$$

where

$$Q = \int_{t_{in}}^{t_{in}+\tau_p} I(\tau)d\tau, \quad \text{(3)}$$

is the total charge (per unit membrane area) delivered to the neuron during the period of stimulation, τ_p, initiated at time, t_{in}. P_1 represents a penalty term which is non-zero and positive only when an action potential is not generated by the stimulus. P_2 is a smoothness penalty term to ensure that $I(t)$ is sufficiently smooth. In Equation (2), $\boldsymbol{\theta}$ is a vector representing the parameters defining the cubic spline stimulus waveform, namely the current magnitudes at specified knot points. The overall objective is to find a stimulus, I^*, such that

$$I^* = \underset{\boldsymbol{\theta}}{\operatorname{argmin}}\, \mathcal{J}\big(I(t,\boldsymbol{\theta})\big), \quad \text{(4)}$$

where as noted earlier, the $\boldsymbol{\theta}$ parameters represent cubic spline current values which describe the stimulus waveshape at regularly spaced sample points throughout a specified stimulus duration, τ_p. These spline parameters are updated subject to the activation dynamics indicated by Equations (1) while searching for the minimum value of the objective function using the `fminsearch` simplex optimisation command in MATLAB.

III. Simulation Results

We ran the optimisation problem for a HH model neuron whose parameters are specified in Table I. The penalty terms we have utilized are

$$P_1 = k_1\Big(|V_{M_{max}} - 20| - (V_{M_{max}} - 20)\Big), \quad \text{(5a)}$$

$$P_2 = k_2 \int_{t_{in}}^{t_{in}+\tau_p} |\ddot{I}(\tau)|d\tau, \quad \text{(5b)}$$

in which $V_{M_{max}}$ is the maximum membrane potential generated by the current stimulus, and will be zero if an action potential is generated (i.e. $V_{M_{max}} > 20$mV). The coefficients k_1 and k_2 are scalars defining the weight of each penalty term. Coefficient k_1 should be sufficiently large to guarantee the action potential generation and k_2 depends on the required level of smoothness. Assuming that the maximum applicable current is limited to $I_{max} = 6 \times 10^4 \mu$A/cm^2, the optimal stimulation waveshape, for $k_1 = 10$ and $k_2 = 1$, will be a non-rectangular pulse, as shown in Figure 2. In this simulation, we have set the stimulus to begin at $t_{in} = 1$ms, with duration is limited to $\tau_p = 1$ms. Figure 2(a) shows the generated action potential as well as the optimal stimulus waveshape (not to scale) to provide an indication of the timing of the stimulus relative to the action potential. In Figure 2(b), the optimal stimulus is zoomed to between 1ms and 2ms with the correct scale on the ordinate. The total charge per unit membrane area delivered to the neuron in this case is calculated to be 14.2μC/cm^2.

Relaxing the smoothness constraint by setting $k_2 = 0$ results in the stimulus waveshape shown in Figure 3. This stimulus waveshape has three peaks, and is less smooth compared to the case when $k_2 = 1$. However, the total charge per unit membrane area is now 6.2μC/cm^2, 60% less than the smooth waveshape of Figure 2(b). Another remarkable difference between these two waveshapes is the long latency between the stimulus and the action potential upstroke when the delivered charge is minimal, as shown in Figure 3(a). This is due to the fact that we are reducing the stimulus charge until the neuron just fires.

We have solved the optimisation problem for different values of I_{max} within the typical range reported for retinal

TABLE I

PARAMETERS AND VARIABLES OF THE HH MODEL NEURON.

Parameters and Variables	Value
C_M	$1[\mu$F/cm$^2]$
$\bar{g}_L$	$300[\mu$S/cm$^2]$
$\bar{g}_K$	$36000[\mu$S/cm$^2]$
$\bar{g}_{Na}$	$120000[\mu$S/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]

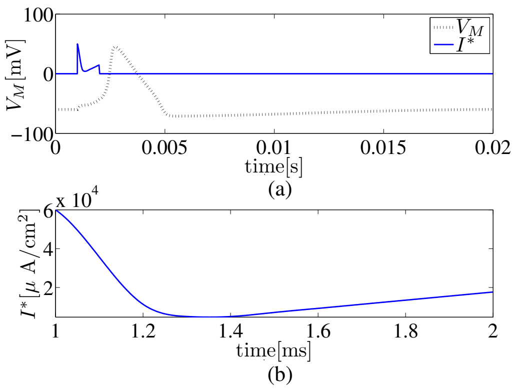

Fig. 2. Optimal stimulation profile and the resultant action potential for the HH model neuron specified in Table I. In this simulation, $t_{in} = 1$ms, $\tau_p = 1$ms, $k_1 = 10$, $k_2 = 1$, and $I_{max} = 6 \times 10^4\mu$A/cm^2. (a) Generated action potential and the optimal stimulus waveshape (not to scale), (b) The optimal stimulus zoomed to between 1ms and 2ms. The area under this stimulus which represents the total charge per unit cell membrane area is 14.2μC/cm^2.

ganglion cells [15], to ascertain how the optimal waveshape changes with maximum current. The results of this simulation are presented in Figure 4. In these simulations, the pulse duration is fixed to $\tau_p = 1$ms, and the weighting factors in the cost function are $k_1 = 10$ and $k_2 = 1$. As can be observed, the initiation of the action potential slightly depends on the maximum magnitude of the stimulus. For the larger maximum applicable current, the action potential upstroke occurs earlier. The amount of charge per unit area associated with each of these optimal stimulus waveshapes is presented in Table II. An interesting point is that the total charge per unit membrane area for $I_{max} = 9 \times 10^4\mu$C/cm^2 is lower than the total charge when $I_{max} = 6 \times 10^4\mu$C/cm^2 or $I_{max} = 12 \times 10^4\mu$C/cm^2.

Simulation results for different values of pulse duration, τ_p, are shown in Figure 5. The total delivered charge per unit membrane area for the optimal stimuli shown in Figure 5 is presented in Table III.

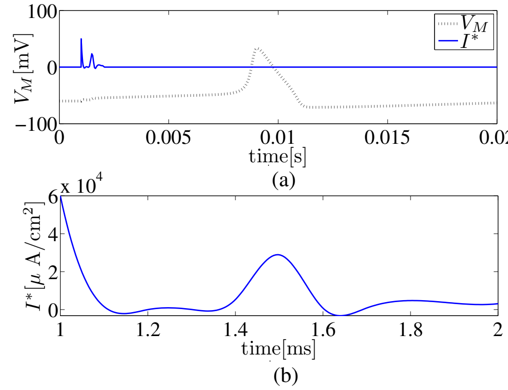

Fig. 3. Optimal stimulus profile and resultant action potential for the HH model neuron specified in Table I. In this simulation, $t_{in} = 1$ms, $\tau_p = 1$ms, $k_1 = 10$, $k_2 = 0$, and $I_{max} = 6 \times 10^4\mu$A/cm^2. (a) Generated action potential and optimal stimulus waveshape (not to scale), (b) The optimal stimulus zoomed to between 1ms and 2ms. The total delivered charge per unit cell membrane area in this case is 6.2μC/cm^2.

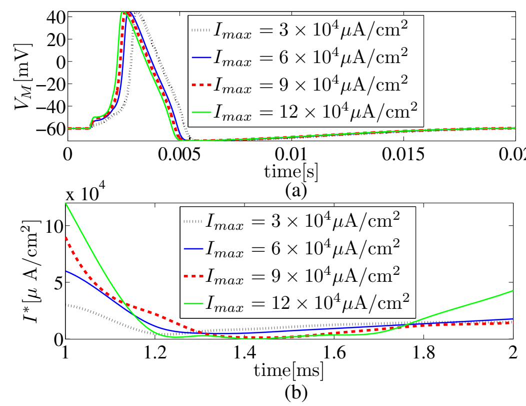

Fig. 4. Optimal current stimulus profile and resultant action potential for different values of I_{max}. In these simulations, the pulse duration is fixed to $\tau_p = 1$ms, $k_1 = 10$, and $k_2 = 1$. The maximum applicable current, I_{max}, varies from $3 \times 10^4\mu$A/cm^2 to $12 \times 10^4\mu$A/cm^2. (a) Generated action potential for different values of I_{max}, (b) The optimal stimulus zoomed to between 1ms and 2ms. The total delivered charge per unit membrane area for these stimulus profiles are presented in Table II.

To compare the charge delivered to a HH model neuron through optimal stimulation and a traditional rectangular Lilly-type pulse, we determined the minimum required duration for a rectangular pulse to generate an action potential with the same stimulus magnitude. Table IV presents the total charge for an optimised stimulus with maximum magnitude, I_{max}, and minimum duration, τ_{opt}, as well as the equivalent rectangular pulse with the same magnitude and minimum duration, τ_{rect}. In this table, Q_{opt} represents the total charge per unit membrane area for an optimal stimulus and Q_{rect}

TABLE II

TOTAL DELIVERED CHARGE PER UNIT AREA FOR STIMULI SHOWN IN FIGURE 4.

$I_{max}[\mu$A/cm$^2]$	3×10^4	6×10^4	9×10^4	12×10^4
Q[μC/cm^2]	12	14.2	14	17.2

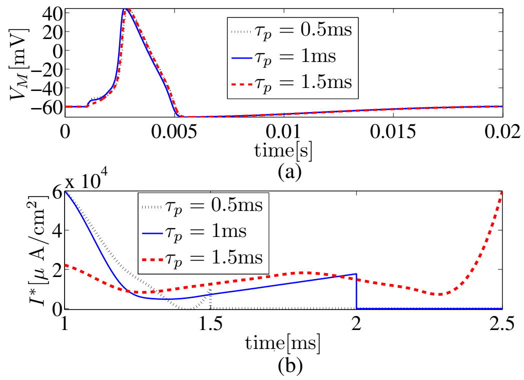

Fig. 5. Optimal stimulation profile and the resultant action potential for different values of τ_p. In this simulation, the maximum pulse magnitude is set to $I_{max} = 6 \times 10^4 \mu$A/cm^2, $k_1 = 10$, and $k_2 = 1$. (a) Generated action potential for different values of τ_p, (b) The optimal stimulus zoomed to between 1ms and 2ms. The total delivered charge per unit cell membrane area for these stimulation profiles are presented in Table III.

TABLE III
TOTAL DELIVERED CHARGE PER UNIT MEMBRANE AREA FOR STIMULI SHOWN IN FIGURE 5.

τ_p[ms]	0.5	1	1.5
Q[μC/cm^2]	9.5	14.2	21.4

represents the analogous charge for the rectangular pulse. This table shows that the optimal stimulus profile delivers less charge to the neuron. Furthermore, as the magnitude of the stimulus increases the optimal waveshape becomes more efficient.

IV. DISCUSSION, CONCLUSIONS AND FUTURE WORK

In this paper, we have developed an optimisation framework to seek an optimal stimulation profile for a HH model neuron that minimizes the total charge delivered. Simulation results suggest that the optimal stimulus profile is non-rectangular, whose shape depends not only on the neuron model but also on the maximum applicable current and the required level of smoothness. The results presented here demonstrate that there is a trade-off between pulse smoothness and total delivered charge.

A remarkable observation from our results is that there is a rise in the tail of the optimal stimulus profiles for various values of the maximum applicable current as well as the pulse duration. From this observation, it can be inferred that an additional amount of charge is required near the end of stimulation to fire the neuron, which appears to be the result of nonlinearity in the HH equations.

TABLE IV
COMPARISON OF TOTAL CHARGE DELIVERED TO HH MODEL NEURON THROUGH AN OPTIMAL STIMULUS AND AN EQUIVALENT RECTANGULAR PULSE.

I_{max} [μA/cm^2]	τ_{rect} [μs]	τ_{opt} [μs]	Q_{rect} [μC/cm^2]	Q_{opt} [μC/cm^2]
3×10^4	210	300	6.33	5.77
6×10^4	110	200	6.66	5.63
9×10^4	101	100	9.18	4.90
12×10^4	101	75	12.12	4.63

It is worth mentioning that we optimised our stimulus spline values for positive values, meaning that only monophasic optimal stimulus profiles were considered here. However, for safety reasons charge-balanced stimuli, also known as biphasic pulses, are very popular in electrical stimulation of neurons. An additional charge-balanced constraint can be achieved by adding an extra penalty term to the cost function. We will revisit optimal stimulus design for a HH model neuron under charge-balanced conditions in our future work.

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