Modeling the bursting behavior of the Hodgkin-Huxley neurons using genetic algorithm based parameter search

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***Abstract*—The Hodgkin-Huxley (HH) model is a widely used biophysically meaningful model that can simulate the action potentials in the nerve axons. It is mainly used to simulate the type 2 behavior of the axon firing. However other types of neuron spiking and bursting have been observed in the literature. This work demonstrates the novelty of showing the optimization of the HH model parameters to simulate neuron bursting behavior. The results of the study demonstrates that it is possible to extend the HH model beyond its intended type 2 behavior and can be modified to simulate more complex neuron firing patterns including neuron bursting. The optimized HH model was able to generate bursting patterns corresponding to the two target bursting patterns used in this study with error values $< 18\%$ for Phasic bursting and $< 6\%$ for Tonic bursting. This work shows by expanding the range of gating variables (m, n and h) beyond the original model range of 0 to 1 can improve the HH model to simulate neuron bursting.**

***Index Terms*—action potential; axon; bursting; genetic algorithm; Hodgkin-Huxley; machine learning; neuron**

I. Introduction

In his 1948 paper, Alan Hodgkin published the results of the experiments on crustacean nerves using constant current stimuli. The results described three classes or types of neuron excitations. Type 1 neurons fired with a wide range of frequencies that depended upon the strength of the stimulus current. Neurons of type 2 fired with a narrow range of frequencies that were relatively insensitive to the stimulus strength. Type 3 neurons that had a higher threshold either failed to repeat or fired once or twice only when the threshold was exceeded [1]. Following the studies on crustacean nerves, Hodgkin and Huxley published a series of papers that describe a physiological model which simulates type 2 behavior of a giant squid axon. The complex model consists of a system of linear and non-linear differential equations along with a set of parametric equations that models the ion channels of the axon [2]–[5]. Since then, the HH model has been widely used to better understand the action potentials in the axons and nervous system.

One of the drawbacks of the model is its inability to simulate the bursting behaviors of the neurons, which is distinct from the spiking patterns mentioned above. Bursting can be defined as the repeated firing of groups of spikes in the neurons. Neuron bursting have been observed, studied and the importance of the bursting behaviors have been discussed in the literature [6]–[8]. Although there exist models that simulate the bursting behavior as well as regular spiking, either they have simulation limitations or they are strictly mathematical and are not biophysically meaningful. It has been theorized that the HH model has the capability to simulate a wide variety of spiking and bursting patterns in addition to its intended type 2 behavior [9]. However, due to the computational complexity these capabilities have not been explored extensively to improve the model. This work is the first to attempt to generate neural bursting

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patterns using the original HH model by converting 23 of its constants to parameters that can be optimized. Here we demonstrate this possibility of extending the HH model by identifying defined constants in the model equations as variables that can be adjusted to get different spiking and bursting patterns. Due to the complex nature of this process and the larger size of the parameter space, a genetic algorithm is used to produce solutions efficiently.

II. Methods

A. The Hodgkin-Huxley model

The HH model consists of four differential equations. It also consists a set of parametric equations [2]. The main equation that relates the membrane potential with the currents is given by (1) as follows.

$$C_m \frac{dV_m}{dt} + I_{ion} = I_{ext} \tag{1}$$

where C_m is the membrane capacitance, V_m is the membrane potential, I_{ion} is the ionic current and I_{ext} is the external current. I_{ion} is the net ionic current flowing across the membrane and is given by the summation of contributions from the currents in the different ion channels.

$$I_{ion} = I_{Na} + I_K + I_L \tag{2a}$$
$$I_{Na} = g_{Na} m^3 h (V_{Na} - V_m) \tag{2b}$$
$$I_K = g_K n^4 (V_K - V_m) \tag{2c}$$
$$I_L = g_L (V_L + V_m) \tag{2d}$$

where I_{Na}, I_K and I_L are the sodium, potassium and the leakage currents respectively. g_{Na}, g_K and g_L are the ionic conductances, and V_{Na}, V_K and V_L are equilibrium potentials. The constants m, n and h are dimensionless variables called gating variables and are given by (3),

$$\frac{dx}{dt} = \alpha_x (1 - x) - \beta_x x \tag{3}$$

where x is m, n or h. α and β values are defined by the parametric equations (4) and (5).

$$\alpha_m = \frac{-3.5 - 0.1V_m}{e^{-3.5-0.1V_m} - 1} \tag{4a}$$
$$\alpha_n = \frac{1 - 0.1V_m}{10(e^{1-0.1V_m} - 1)} \tag{4b}$$
$$\alpha_h = 0.07 e^{-\frac{V_m}{20}} \tag{4c}$$
$$\beta_m = 4e^{-\frac{V_m}{18}} \tag{5a}$$
$$\beta_n = 0.125 e^{-\frac{V_m}{80}} \tag{5b}$$
$$\beta_h = \frac{1}{e^{3-0.1V_m} + 1} \tag{5c}$$

A typical membrane potential plot generated using the HH model is shown in the fig.1. The solution of the HH model was found using a fourth order Runge-Kutta (RK4) method in MATLAB. The RK4 method was chosen as it offers a good balance between the computational cost and accuracy of the results. With the help of simulation studies it has been found that, by changing the parameter values in (4) and (5), different membrane potentials can be produced. However, finding the parameters that result in a specific spiking or a bursting pattern can be computationally demanding and difficult. This paper addresses the modeling of bursting behavior and finding the set of parameters to activate it.

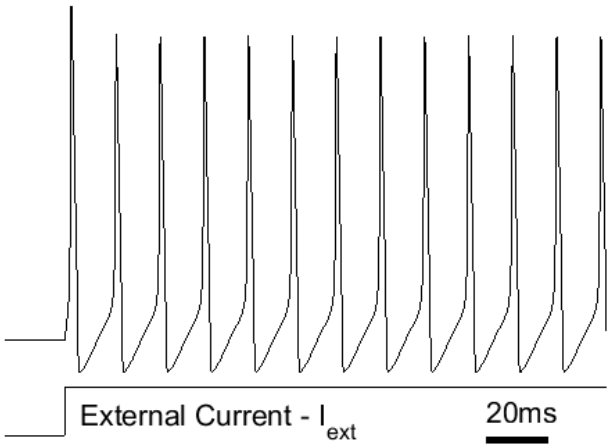


Fig. 1. (a) Typical Hodgkin-Huxley spiking pattern. (b) Phase space plots for the membrane potential displayed in (a). x-axis is the membrane potential and the y axis is the value of the gating variable. (i), (ii) and (iii) corresponds to the gating variables m, n and h respectively

B. Parameters to modify

The concept of this study was to increase the parameter space of the problem so that the solution space was in-

creased. First, the constants in (4) and (5) that can be controlled and would affect the resulting membrane potential were identified. In this process, 23 constants were identified as tunable. Then, the identified 23 constants in the original HH model were transposed to variables than can be varied as shown in (6) and (7). Different sets of parameters could be assigned to these variables to obtain different spiking or bursting patterns. Equations (4) and (5) can be produced by substituting the original set of parameters from Table. I to the variables in (6) and (7).

$$\alpha_m = \frac{\alpha_{m1}(V_m - \alpha_{m2})}{\alpha_{m3} - e^{-\frac{V_m + \alpha_{m4}}{\alpha_{m5}}}} \tag{6a}$$

$$\alpha_n = \frac{\alpha_{n1}(V_m - \alpha_{n2})}{\alpha_{n3} - e^{-\frac{V_m + \alpha_{n4}}{\alpha_{n5}}}} \tag{6b}$$

$$\alpha_h = \alpha_{h1} e^{\alpha_{h2}(V_m + \alpha_{h3})} \tag{6c}$$

$$\beta_m = \beta_{m1} e^{\beta_{m2}(V_m + \beta_{m3})} \tag{7a}$$

$$\beta_n = \beta_{n1} e^{\beta_{n2}(V_m + \beta_{n3})} \tag{7b}$$

$$\beta_h = \frac{\beta_{h1}}{\beta_{h2} + e^{\beta_{h3}(V_m + \beta_{h4})}} \tag{7c}$$

α_{mi}, α_{ni}, α_{hi}, β_{mi}, β_{ni} and β_{hi} represent the 23 parameters that were identified as tunable. External current I_{ext} that is applied to the system can also be treated as a tunable parameter that would affect the output. Therefore, the dimensionality of the optimization problem at hand was set to 24 to match target bursting patterns.

C. Target bursting patterns

In order to compute values for the identified parameters it was decided to use two target bursting patterns. Izhikevich identifies large number of spiking and bursting patterns in his 2004 paper [9]. The phasic bursting and the tonic bursting patterns were selected as the targets for this study. The simulated data for these two target bursting patterns shown in fig.2 were generated using the the mathematical model created by Izhikevich [10]. The goal of this study is to adapt these two target bursting patterns to the HH model because it is considered biophysically meaningful.

D. Parameter optimization

It was decided to employ an algorithm in the class of evolutionary algorithms to optimize the model parameters identified in section II-B. To better suit the specific problem of optimization, a genetic algorithm was chosen. The use of a genetic algorithm is critical for a problem of this magnitude to improve the efficiency of finding a solution. If it was assumed there are only ten possibles values per tunable parameter, that would indicate the existence of 10^{24}

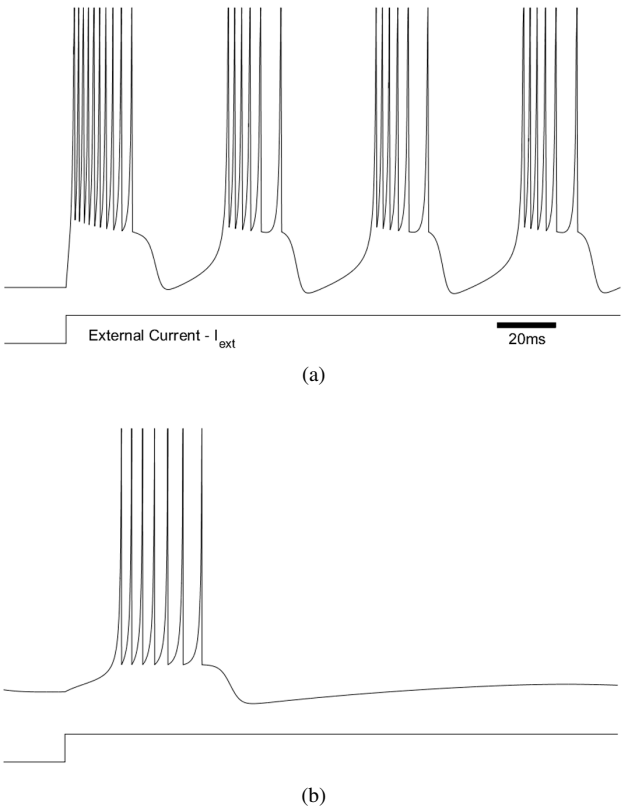


Fig. 2. Two target bursting patterns used in the study. (a) Tonic bursting. (b) Phasic bursting. Each plot shows the action potential response to an external step current input. Time resolution is $0.04ms$. [10].

possible permutations of parameter sets and solutions. A brute force approach would take too long to go through all permutations. An algorithm like gradient descent is not viable for this specific case since the solution space is highly non-linear and contains large number of local minima.

Decimal values of the 24 parameters were used as the chromosome for the algorithm. A population of randomly generated 200 data samples was used to initialize the problem. The size of the initial population is a significant characteristic of genetic algorithms that determines the quality of the solution found as well as the computational resources required to find it [11], [12]. Although this can be subjective and dependent upon various factors, the initial population size is often selected to be ten times the number of dimensions in the problem [13].

To create the initial population, first a chromosome was generated randomly. Upper and lower bounds for the randomly generated chromosome were set using an offset from the initial values of the parameters. The selection of this chromosome for the initial population was done based on the fact that its error function was below a predefined maximum. This process was repeated until the initial population was filled with 200 chromosomes.

The error function (typically identified as the fitness

function) for the problem was chosen to indicate a measure of how close a resulting membrane potential pattern was to one of the targets we have chosen in section II-C (fig. 2). In this case, the error function was the relative difference between the target pattern and the pattern that was obtained by modifying the 24 parameters. The genetic algorithm minimized this relative difference until it reached a predefined minimum difference.

The calculation of the relative error was done in parts. The mean squared error between the reference data set and the obtained data set from the modified HH model was the major component of this calculation and is shown in (8).

$$e = \frac{1}{q}\sum_{i=1}^{q}(V_{mi} - V_{refi})^2 \tag{8}$$

where V_{mi} is the membrane potential obtained from the Hodgkin-Huxley model, V_{refi} is the reference potential shown in fig. 2 and q is the number of time samples in the V_m data array.

This problem falls into the category of constrained optimization because there are large sections of the solution space that carry infeasible solutions. Therefore, to avoid having these infeasible solutions in the population and in-turn to improve the effectiveness of the optimization process, additional penalties were attributed to the error function by comparing features of V_m with V_{ref}. These features include the number of local and global extrema and the values and the positions of the extrema.

During each successive generation by the genetic algorithm, 5% of the best chromosomes survive. While an 80% of the entire next generation is created using crossover, the remaining 15% is created with mutation. The above percentages used in the genetic algorithm were chosen arbitrarily.

The number of generations the genetic algorithm goes through varies between the trials. The accuracy of the results and the number of generations passed by to get to a certain result is highly dependent on the initial population. When a significant improvement of the error function is not observed and the error function is plateaued, the genetic algorithm is restarted with a new initial population.

Multiple computers were used to run simulations because of the time complexity of the problem. However, majority of the simulations were run on a computer with an Intel Core i7-4790 processor running at 3.6GHz and 24GB DDR3 memory under Windows 7 Enterprise (64bit) edition. Evaluation of a single generation of the genetic algorithm with 200 chromosomes under the described platform took about 42 seconds on average. Therefore, to run a simulation for about 10000 generations, it takes approximately 5 days.

III. Results

A genetic algorithm based parameter search method was employed to explore the possibility of using HH model to simulate busting behavior of the neurons. 23 constants in the HH model was converted to parameters that can be modified and the genetic algorithm was used to optimize these parameters to obtain two neuron bursting patterns. Results from the genetic algorithm shown in fig.3 displayed membrane potential patterns that have the characteristics of bursting behaviors similar to the references used for the optimization. All the simulations were performed with an external current that takes the shape of a step function. The optimized parameters found in the study are listed in the tonic and phasic columns in the Table I. One can produce fig.3 by substituting the tonic and phasic values from the Table I in the equations (6) and (7) and solving the HH model. The absolute percentage error values of the two resulting bursting patterns with respect to the target bursting patterns are listed in the Table II. The equation (9) was used to calculate the absolute percentage error.

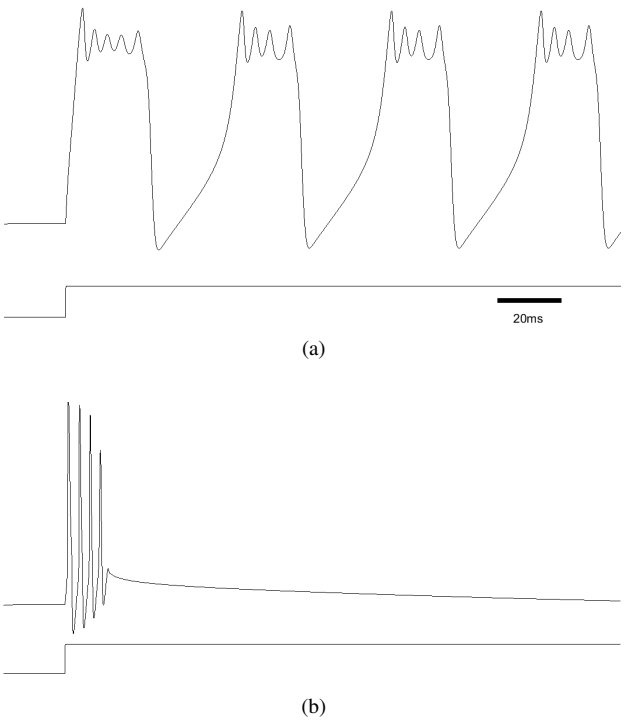
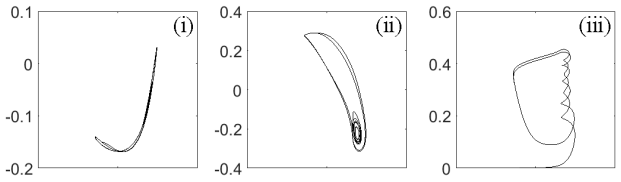


Fig. 3. Two bursting patterns found form the genetic algorithm corresponding to the used references. (a) Tonic bursting. (b) Phasic bursting.

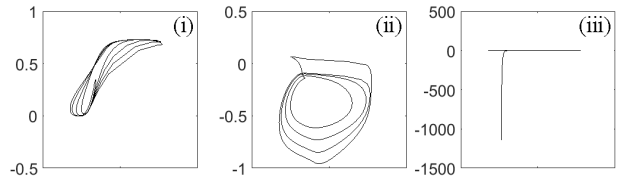
$$absolute\ percentage\ error = \left|\frac{V_m - V_{ref}}{V_{ref}}\right| \times 100\% \tag{9}$$

IV. Discussion

One of the important observations made while studying the results is the behavior of the gating variables in the phase space as shown in the fig.4. When the HH model was originally developed in 1952, the authors had to come up with some postulates about the existence of three fictional



(a)



(b)

Fig. 4. Phase space plots corresponding to the bursting patterns shown in figure 3. (a). Tonic bursting. (b). Phasic bursting. (i), (ii) and (iii) corresponds to the gating variables m, n and h respectively

TABLE I
OPTIMIZED PARAMETER VALUES THAT PRODUCE FIG. 3 COMPARED WITH THE ORIGINAL PARAMETERS THAT PRODUCE FIG. 2

Parameter	Original	Tonic	Phasic
α_{m1}	0.100	−0.160	−0.113
α_{m2}	35.000	26.450	50.790
α_{m3}	1.000	0.200	−0.241
α_{m4}	35.000	33.000	36.560
α_{m5}	10.000	11.301	6.307
α_{n1}	0.010	0.086	0.013
α_{n2}	50.000	35.573	38.338
α_{n3}	1.000	−2.745	−1.200
α_{n4}	50.000	50.116	43.679
α_{n5}	10.000	12.608	14.799
α_{h1}	0.070	0.007	−0.077
α_{h2}	−0.050	0.220	−0.028
α_{h3}	60.000	38.500	64.935
β_{m1}	4.000	5.450	4.404
β_{m2}	−0.056	0.046	0.013
β_{m3}	60.000	52.420	58.466
β_{n1}	0.125	0.993	0.828
β_{n2}	60.000	55.346	50.960
β_{n3}	80.000	89.568	79.297
β_{h1}	1.000	0.140	−0.748
β_{h2}	1.000	2.044	−1.901
β_{h3}	0.100	−0.116	0.740
β_{h3}	30.000	39.537	29.871
I_{ext}	0.100	0.115	0.207

particles that would describe the states of the Sodium and Potassium channels in the axon. n,m and h are the dimensionless quantities that are associated with the activation of the Potassium channel, activation of the Sodium channel and the inactivation of the Sodium channel respectively. The values of n, m and h were such that $0 \leq n, m, h \leq 1$. In order to fit the data they obtained from the experiments, Hodgkin and Huxley chose (2b) and (2c) among many possible solutions to explain Potassium and Sodium channel activation. The behavior of the gating variables in phase space for the parameters in the original model is shown in the fig.1b and it can be noted that the values range between 0 and 1. However, when simulating the bursting behavior the values of gating variables exceed these limits.

TABLE II
ABSOLUTE PERCENTAGE ERROR VALUES OF THE TWO RESULTING BURSTING PATTERNS WITH RESPECT TO THE TARGET BURSTING PATTERNS

	Tonic	Phasic
Absolute percentage error	5.88%	17.91%

The observation of having gating variables that exceed the original limits can be due to the limitations of the HH model. Studies have found the existence of additional channels in the neuronal membranes. The presence of these additional channels has implications on the membrane potentials [14], [15]. Further, as stated before the equations associated with the gating variables lack a physical basis. Hence the known limits of the gating variables may only suit the specific pattern or patterns of membrane potentials for which the original model was intended for. However, this study explores the possibilities of the model beyond its intended capabilities.

Although the results that perfectly matched the target patterns that were used could not be produced in a reasonable time period, the results of the genetic algorithm demonstrated the ability to modify the HH model to simulate bursting behavior. While the proposed HH model seems more complex compared to a simple mathematical model like Izhikevich model that offers more flexibility, it has been demonstrated that HH model is comparable to Izhikevich model in computational cost [16]. Therefore, it is worth exploring the possibility of expanding the HH model beyond its original model parameters to simulate the bursting behavior because the equations of the HH model have a biophysical meaning unlike a pure mathematical model.

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