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MODELING ELECTRICAL ACTIVITY OF A NEURON: A BOND GRAPH APPROACH

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INTRODUCTION

Neurons, which are the center part of the nervous system, are electrically excitable cells that transmit information mostly within themselves via synapses through electrochemical process [1]. This electrical and chemical stimulus of neurons is called action potential [2]. Each neuron integrates the incoming signals, and when the stimulation reaches a certain threshold, action potential as an output signal will be activated [3]. Therefore, the comprehension of how the synaptic inputs interact in time is momentous to characterize input-output attributes of the neuron.

One of the most striking models for the analysis of conduction of action potential sequences in nerve fiber is Hodgkin–Huxley model (H-H) in that not only does it provide electrical and physical characteristics of membrane of axon, but also it specified nerve conduction properties [4-7]. Studies regarding Hodgkin-Huxley model are a central pillar of modern neuroscience research ranging from molecular investigations of the structural basis of ion channel function including understanding the conditions that control both the rate and timing of action potentials, to the computational implications at circuit level which is used to describe both neuronal integration and circuit level information processing [8]. This model in which the proteins are resistances and the membrane is a capacitance, is based on the assumption that the membrane contains proteins that selectively conduct sodium and potassium ions in a time- and voltage-dependent manner [4].

In order to understand how exactly current travels from one point to the next along dendrites and axons, the cable theory was developed by Rall [9, 10]. Cable theory is one of the most significant contributions of theoretical neuroscience and has been extremely useful to explain a large range of phenomena [11]. This theory derives a mathematical model that describes how membrane potential spreads along the dendritic trees and axons. The one-dimensional cable theory of neurons describes current flow using partial differential equations. These equations can be transformed to an equivalent cylinder leading to analytical solutions for transient current inputs. The steady-state solution of the cable equation, which is defined when steady current or voltage is applied, is a significant reference for understanding general solution. Computer simulations and modeling are quite considerable tools for neuroscientists on comprehensive understand of nervous system physiology and its functioning [12]. Likewise, the models are used to investigate the specifications of neurons that are not inaccessible or not conveniently controlled in both experiments and mathematical approaches [13]. In this context, a number of computer software [14, 15] is accessible for neural modeling, but there is no comprehensive and tangible method for modeling the neural function.

In this study, bond graph method, which is one of the best tools to model bioelectrical stimulation of neuron characteristics, was applied for exploring the action potential that has been made along the neuron for initial step and square function excitations based on the

cable theory. Bond graphing is a unified graphical approach for modeling the storage, dissipation, and transformation of energy within a dynamic system. The structure of the bond graph has been designed to facilitate systematic derivation of differential equations governing the dynamic response of the system model. The bond graph approach leads directly to a computer simulation of the both transit and steady-state response. In addition, bond graph modeling can be developed profoundly to consider other complex aspects of nervous system.

MATERIALS AND METHODS

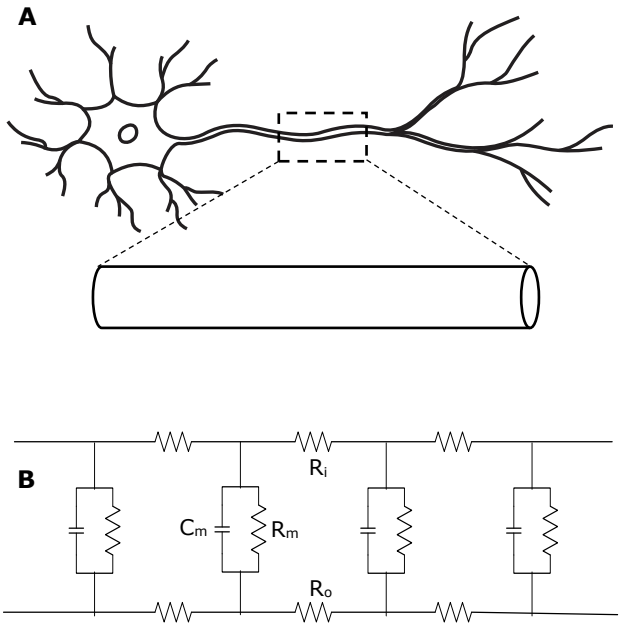
The axons and dendrites of the neurons consist of thin tubes of nerve membranes. In cable theory, the numerous of mutually parallel resistances and capacitances are used in order to define the membrane that contains two resistances, which are indicative of intracellular and extracellular resistance, locating in series way above and beneath them respectively as shown in Figure 1-B.

In this paper, our modeling tool was bond graph methodology which can be contemplated as a multidisciplinary modeling language that consists the ability to model various complex heterogeneous systems only by means of a limited number of elements. In bond graph modeling, the elements *C* and *R* represented capacitance and resistance respectively. The electrical current orientation was distinguished by one-way arrows which made the connection between the elements of the model. There were two types of connection; the first type was 1-junction portal indicated common flow (current) points and the other was 0-junction used for common effort (voltage) points. In this model, S_e and S_f symbols have been used to demonstrate the voltage and current sources. In order to model the cable theory appropriately, the parallel resistances and capacitances were modeled as the *R* and *C* elements connected to the 1-junction. Besides, intracellular and extracellular resistances were applied as the *R* elements through the 0-junction port as shown in Figure 1-C. Values for each of the parameters of the developed model, which were educed from the cat motor cortex belonged to the study about cell electrophysiology and experimental form of neuron electrical stimulation, are listed in Table 1 [16].

In our study, only a part of neuron membrane was modeled that contained three extracellular resistances, three intracellular resistances, three membrane resistances and three membrane capacitances (Figure 1-C). The code used for solving mathematical equations, which represent the communication among the system elements, was developed in MATLAB (version 2012b, The Mathworks, Inc.) with assuming steady state. The equations were included three first order differential equations that each of them was related to a membrane capacitance.

Table 1: Parameter values of bond graph model [16].

Parameter	Symbol	Value
Membrane resistant	R_1, R_2, R_3	8200 Ω/cm^2
Membrane capacity	C_1 , C_2, C_3	1 μF/cm^2
Intracellular resistant	R_6, R_7	30 MΩ/cm^2
Extracellular resistant	R_4, R_5	0.0001Ω/cm^2



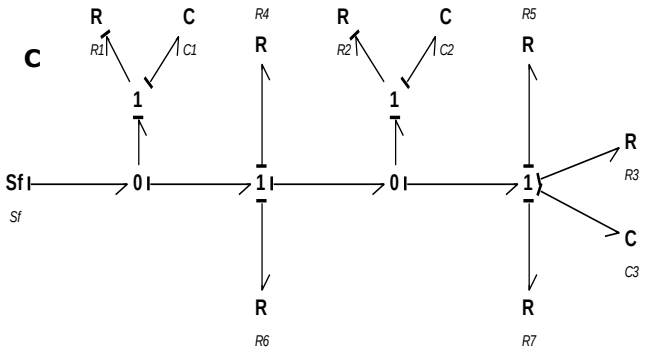
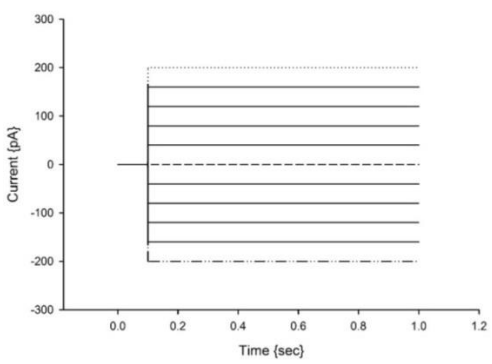


Figure 1: General view of the model. A) The axons and dendrites of a neuron and thin tube of membrane; B) An electrical circuit representing a one-dimensional nerve: R_i and R_e are the intracellular and extracellular resistances per unit length (Ω/m), R_m is the membrane resistance and C_m is the membrane capacitance per unit length (F/m) [17]; C) The bond graph model of the neuron.

RESULT

In this section, a simple simulation cell process is given to illustrate the model. A current source (S_f) was used at the beginning of the model to generate the input step and square functions as shown in Figure 2. Input functions were applied for ten values of 40, 80, 120, 160 and 200 pA in positive and negative form for 0.5 s.



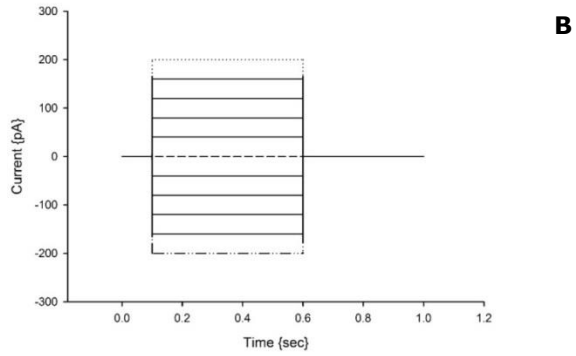
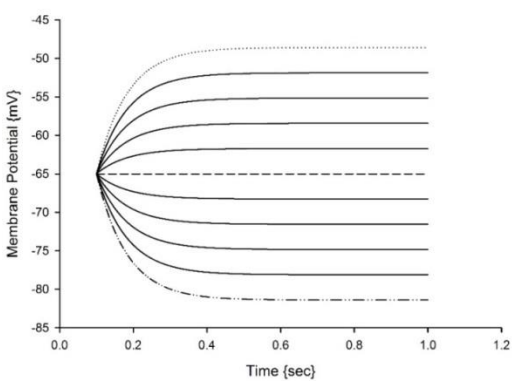


Figure 2: A) Step and B) Square input function.

Consequently, the electrical potential caused by the input excitation functions was estimated as shown in Figure 3.



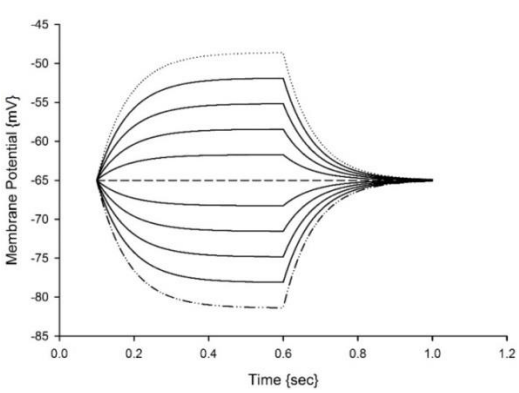


Figure 3: Electrical potential resulted from A) Step input function and B) Square input function.

State space equations could be derived from casual bond graph model. If state variable *q(t)*

represented the capacitance, thus differential equations were attained in equation (1).

$$\begin{bmatrix} \dot{q}_{C_1} \\ \dot{q}_{C_2} \\ \dot{q}_{C_3} \end{bmatrix} = \begin{bmatrix} \frac{1}{R_1 C_1} & 0 & 0 \\ 0 & \frac{1}{C_2}\left(-\frac{1}{R_2}-\frac{1}{R_3}-\frac{1}{R_4}\right) & -\frac{1}{R_3 C_3} \\ 0 & \frac{1}{C_2}\left(-\frac{1}{R_3}-\frac{1}{R_4}\right) & \frac{1}{C_3}\left(-\frac{2}{R_3}-\frac{1}{R_5}-\frac{1}{R_7}\right) \end{bmatrix} \begin{bmatrix} q_{C_1} \\ q_{C_2} \\ q_{C_3} \end{bmatrix} + \begin{bmatrix} 1 \\ 1 \\ 1 \end{bmatrix} [I(t)] \quad (1)$$

DISCUSSION

We focused on neuron activity and creation of action potential in the cell membrane through bioelectrical approach. To this end, the cable theory, which is one of the most prevalent theories about the electrical behavior of neurons, was used. For creating a model of the neuron, the bond graph method, which is a powerful tool for modeling in different disciplines, was applied. This method enabled us to model the neuron's behavior by means of simple elements such as capacitance and resistance.

The overall object of this study was modeling a neuron which serves the higher purpose of modeling a neural tissue that includes a set of neural cells interacting together. A virtual neural tissue is accessible by considering abundant numbers of neurons that raising any changes including changes in the number of cells or changes in physical, chemical and electrical properties of cells, different function of the neural tissue will be visible. To illustrate, increasing or decreasing the number of ion channels, time duration, and value of excitation will cause disorders in normal function of nervous cells which comparing this dysfunction and normal mode facilitates the understanding of disorder mechanisms properly.

In current study, we investigated the variation effect of stimulating current function in both step and square initial function by applying eleven different values (0, ±40, ±80, ±120, ±160, and ±200) so that the beginning of all excitations was at time 0.1 s. The potential resulted from the step function showed that for all current values, the initiation time of potential were from 0.1 s with no delay. For 0 current, the value of potential was -65 mv which was the rest potential of the cell. For positive currents, the value of potential was positive and increased from initial value, -65 mv, reached its maximum value and then became constant. Increasing the value of initial current led to an enhancement in the value of potential as well, as for 200 pA the potential reached its maximum at -50 mv which is the threshold value, and with the increase of current the action potential will occur. Similarly for negative currents, diminishing the current value decreased the resulted potential. As an example for input current -200 pA the value of potential reached from -65 mv to minimum value -80 mv.

The potential resulted from the excitation of square current function indicated that for all eleven different current values, which were applied from 0.1 s to 0.6 s, the potential initiation time was from 0.1 s with no delay, then the value of potential reached its maximum at 0.6 s, and regarding to 0 value of input current the potential began to decrease and finally reached 0. For 0 current, the potential was -65 mv as the resting potential of cell which was similar to the result of step current function. For positive currents, the values of potential were positive as well and reached its maximum via the increasing from initial value of -65 mv and later on at the moment 0.6 s started to decrease. The value of potential also increased through the increase of initial value of current value. As for 200 pA the maximum value of potential reached -50 mv, which was the threshold potential, and with the increase of current value the action potential will occur. At the moment 0.6 s the value of current aimed 0, and the potential decreased to its final value. Similarly for negative currents, the generated potential has decreased as the current value diminished. As an illustration, for current -200 pA the value of potential reached from -65 mv to minimum value -80 mv, and when the current has been 0, the value of potential increased and finally at the moment 1 s reached 0.

In order to study the effect of ionic channel density on the variation of cell membrane

potential, six different densities (1, 1.4, 1.8, 2.2, 2.6 and 3) were used. To attain this purpose, the square function was selected as the input current function with the assumed value 200 pA for each of six different density mode as shown in Figure 4.

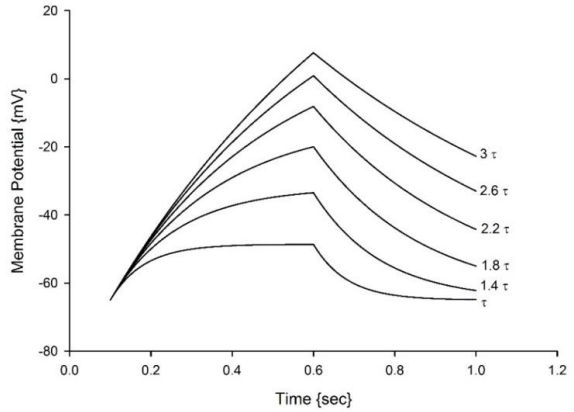


Figure 4: Comparison of time constant and membrane potential among six different ion channel density.

The reason for this choice was due to the ability to observe the effect of density on change of the maximum value of potential and time constant (τ). As shown in equation (2), the time constant is a function of the membrane resistance (R_m) and the membrane capacitance (C_m). The results have revealed that by increasing the channel numbers per surface unit (increase of density), the time constant increased and so did the value of potential regarding to equation (3).

$$\tau = R_m C_m \quad (2)$$

$$V = V_0 \, e^{\frac{-t}{\tau}} \quad (3)$$

Where V_0 is the value of maximum potential. The numerical value used in this modeling, obtained from experimental studies on neurons of cat. Therefore, the results might vary due to the different values of the electrophysiological properties of human cell. Hence, it is suggested to use numerical value of human cell, which can be considered relevant to normal or abnormal human nerve, in future studies to provide striking recognition on neural disorders. The purpose of this paper was only to study the developed model in response of the applied stimuli and attain the similar output with the results of experimental studies on neurons. In that case, using the numerical value related to human or animal cell does not defect the results of the developed model.

CONCLUSION

While biological systems contain so many inherent complications, using sophisticated methods for modeling, deriving and solving the differential equations expressing the system performance adequately will make the process more difficult. Bond graph method advantage compared to other methods is that in addition to possess the ability to model such a system, also benefits from greater convenience. To illustrate, instead of solving a high order differential equation, several first order differential equations can be considered by means of bond graph method. Using bond graph method for modeling the electrical activity of nerve cell based on cable theory demonstrates fine qualitative and quantitative accommodation with the results of experimental studies. Additionally, the result of the density of ion channels alteration in the bond graph model of nerve cell matched with the results of theoretical potential functions and time constants. Hence, the neuron model presented in this study creates the action potential similar to real nerve cell, and its changing is proportional with the density of ion channels alteration which reflects the ability of this model to study deficiency of the nervous system in a virtual neural tissue.

REFERENCES

[1] Segev I. "Cable and compartmental models of dendritic trees", *The Book of Genesis*, pp. 51-77, Springer, New York, USA, 1998.

[2] Hodgkin AL, Huxley AF. "Action potentials recorded from inside a nerve fibre", *Nature*, vol. 144(3651), pp. 710-711, 1939.

[3] Dumas J-G, Rondepierre A. "Modeling the electrical activity of a neuron by a continuous and piecewise affine hybrid system", *Hybrid Systems: Computation and Control*, pp. 156-171, Springer, New York, USA, 2003.

[4] Appali R,Van Rienen U, Heimburg T. "A Comparison of the Hodgkin–Huxley Model and the Soliton Theory for the Action Potential in Nerves",

Advances in Planar Lipid Bilayers and Liposomes, vol. 16, pp. 275-299, 2012.

[5] Deng B. "Conceptual circuit models of neurons", *J. Integr Neurosci.*, vol. 8(3), pp. 255-297, 2009.

[6] Wang J, Chen L, Fei X. "Analysis and control of the bifurcation of Hodgkin–Huxley model", *Chaos, Solitons & Fractals*, vol. 31(1), pp. 247-256, 2007.

[7] Hodgkin AL, Huxley AF. "A quantitative description of membrane current and its application to conduction and excitation in nerve", *J. Physiol. (Lond),* vol. 117(4), pp. 500-544, 1952.

[8] Catterall WA, Raman IM, Robinson HP, Sejnowski TJ, Paulsen O. "The Hodgkin-Huxley heritage: from channels to circuits", *J. Neurosci.,* vol. 32(41), pp. 14064-14073, 2012.

[9] Rall W. "Membrane time constant of motoneurons", *Science,* vol. 126(3271), pp. 454, 1957.

[10] Rall W. "Membrane potential transients and membrane time constant of motoneurons", *Exp. Neurol.,* vol. 2(5), pp. 503-532, 1960.

[11] Bédard C, Destexhe A. "Generalized cable theory for neurons in complex and heterogeneous media", *Phys. Rev. E Stat. Nonlin. Soft. Matter Phys.,* vol. 88(2), pp. 022709, 2013.

[12] Sacchi O, Belluzzi O, Canella R, Fesce R. "A model of signal processing at a mammalian sympathetic neurone", *J. Neurosci. Methods,* vol. 80(2), pp. 171-180, 1998.

[13] Yamada WM, Koch C, Adams PR. "Multiple channels and calcium dynamics", In *Methods in neuronal modeling*, MIT Press, Cambridge, 1998.

[14] Brown AM. "Simulation of axonal excitability using a Spreadsheet template created in Microsoft Excel", *Comput. Methods Programs Biomed.,* vol. 63(1), pp. 47-54, 2000.

[15] Ozer M, Isler Y, Ozer H. "A computer software for simulating single-compartmental model of neurons", *Comput. Methods Programs Biomed.,* vol. 75(1), pp. 51-57, 2004.

[16] Connors B, Gutnick M, Prince D. "Electrophysiological properties of neocortical neurons in vitro". *J. Neurophysiol.,* vol. 48(6), pp. 1302-1320, 1982.

[17] Roth BJ. "The electrical conductivity of tissues", In *Biomedical Engineering Handbook,* 2nd Edn., CRC Press LLC, 2000.