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Set of Simulators of the Electrophysiology of the A-Type Potassium Current (I_A) in Neurons

Conjunto de Simuladores de la Electrofisiología de la Corriente de Potasio Tipo-A (I_A) en Neuronas

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ABSTRACT

The A-type potassium current (I_A) participates in important brain functions, including neuronal excitability, synaptic integration, and regulation of action potential patterns and firing frequency. Based on the characterization of its electrophysiological properties by current and voltage clamp techniques, mathematical models have been developed that reproduce I_A function. For such models, it is necessary to numerically solve equations and utilize hardware with special speed and performance characteristics. Since specific software for studying I_A is not found on the Internet, the aim of this work was to develop a set of simulators grouped into three computer programs: (1) I_A Current, (2) I_A Constant-V Curves and (3) I_A AP Train. These simulators provide a virtual reproduction of experiments on neurons with the possibility of setting the current and voltage, which allows for the study of the electrophysiological and biophysical characteristics of I_A and its effect on the train of action potentials. The mathematical models employed were derived from the work of Connor *et al.*, giving rise to Hodgkin-Huxley type models. The programs were developed in Visual Basic® and the differential equation systems were simultaneously solved numerically. The resulting system represents a breakthrough in the ability to replicate I_A activity in neurons.

KEYWORDS: A-type potassium current; simulators; virtual experiments.

RESUMEN

La corriente de potasio tipo-A (I_A) tiene importantes funciones cerebrales como: excitabilidad neuronal, integración sináptica y regulación de patrones de potenciales de acción y la frecuencia de disparo. Sus propiedades electrofisiológicas se han caracterizado mediante técnicas de fijación de corriente y de voltaje. A partir de estos conocimientos se desarrollaron modelos matemáticos que reproducen su función. La cantidad de ecuaciones a resolver hace que se requiera de hardware con velocidad y potencia especiales. Un software específico para el estudio propio de la corriente I_A no se ha encontrado en Internet. En este trabajo se presenta un conjunto de simuladores agrupados en tres programas de cómputo: (1) Corriente I_A, (2) Curvas Constante-V y (3) Tren-I_A, que permiten reproducir los experimentos con técnicas de fijación de corriente y de voltaje para estudiar las características electrofisiológicas y biofísicas de la corriente I_A, e investigar el efecto que tiene en el tren de potenciales de acción. Los modelos matemáticos utilizados fueron derivados de los trabajos de Connor *et al*., dando origen a modelos tipo Hodgkin y Huxley. Los programas fueron desarrollados en Visual Basic®. Los sistemas de ecuaciones diferenciales fueron resueltos simultáneamente de forma numérica. Los programas desarrollados contribuyen a solucionar la carencia de este tipo de programas.

PALABRAS CLAVE: Corriente de potasio tipo-A; simuladores; experimentos virtuales.

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INTRODUCTION

The teaching of life sciences is traditionally organized into two parts: theory and lab practice [1] [2]. At the undergraduate level, lab experiments to teach physiology and neurosciences are very expensive. Additionally, it is difficult to carry out experiments for intracellular recording with current and voltage clamp techniques. The need for space, expensive equipment, lab material and experimental animals for educational purposes is out of reach for most universities [3].

Diwakar et al. reported that in India an investment of around 20 million rupees (~267,900 USD) is required for a typical patch clamp configured for lab use, to which other costs such as the animals and facilities must be added [4]. In Mexico, the presence of up to 50 students in each classroom makes this kind of lab practice impossible. One feasible alternative is the development of simulators for teaching. Indeed, simulated patients already form part of the learning environment in different disciplines of the medical field [5] [6] [7] and virtual microscopy practices are employed in histology [8].

Teaching the basic principles of neuroscience is of special interest and can be greatly enhanced by incorporating realistic and interactive simulations of neuronal functioning [9]. Single-neuron computer simulations began with the work of Hodgkin and Huxley [10]. Several simulators are now available to realistically simulate neuronal networks, including GENESIS Simulation System [11], NEURON Simulation Environment [12] and NSL Neural Simulation Language. With the increasing capacity of computational performance, the simulation of the entire brain may ultimately be possible [13].

However, only a few neurosimulators have been adapted to a teaching environment. For example, Hernández and Zurek developed a module of teaching in NEURON, allowing students to examine the properties of biophysics in the axon by using the Hodgkin-Huxley model [14]. A simulator capable of reproducing the classic Hodgkin and Huxley experiments was developed by Reyes-Lazalde *et al.* [15]. The basic study of the passive properties of the axon and dendritic tree can be carried out with an interactive simulator developed for Windows® environment [16]. Brian, a program written in Phyton and found at *http://brian.di.ens.fr*, was developed for quickly coding models of spiking neuronal networks in everyday situations [17]. iCell, an interactive cell modeling tool located at *http://ssd1.bme.memphis.edu/icell/*, integrates research and education for electrophysiology training. It consists of JAVA applets that represent models of a variety of cardiac cells and neurons and provide simulation data on the bioelectric activity of a single cell [18].

Traditional learning media, such as multimedia-based demonstrations, videos, reading and lectures, are passive environments and therefore limit the interactive experience of students [3]. Contrarily, computer simulation enables active learning [3]. The requirements are a computer room, software and an instructor. Several reports have described the pedagogical value of simulators [4]. During a neuroscience course, a comparison was made between traditional teaching and active teaching aided by simulators, finding a greater understanding with the latter [3].

Ribarič and Kordaš tested the effectiveness of a software package for the study of cardiovascular physiology at the undergraduate level of a medical school. The software presented a new approach for teaching physiology, involving active learning and confronting students with multiple ways of simulating basic and clinical physiological phenomena [19]. Reyes-Lazalde *et al.* obtained favorable results when employing software for teaching science [20]. Hence, virtual labs have shown their utility for learning science [21].

During the current pandemic, teaching at a distance has added new relevance to information and communication technology (ICT). In this ICT-induced thrust, there are novel types of teacher-student interactions

and new pedagogical methods. Since all lab practices are now suspended, virtual labs provide an alternative. Due to the high costs of lab practices, the government of India has sponsored an initiative to develop virtual labs, including neurophysiology labs [4].

In the present work, simulators were developed for the teaching and learning of A-type potassium ion current in neurons. They will permit students to perform virtual experiments with a current and voltage clamp. With the help of an instructor, students will be able to appreciate the importance of the A-type potassium current (I_A) and how it modifies the train of action potentials (AP train), and discover other neuronal ion channels in addition to those described in the axon.

In 1961, Hagiwara *et al.* [22] recorded I_A for the first time in cells of the marine mollusk *Onchidium verruculatum* and identified it as a K^+ current. The activation and inactivation of the current produces a characteristic "A" profile, which is the reason for the name [23]. The equilibrium potential of I_A is similar to that of the delayed rectifier and is activated with hyperpolarization. The capacity of I_A to trigger action potentials and excitability in various neurons has been extensively studied. The function of I_A in the AP train is to decrease the firing frequency [24]. Gustafsson *et al.* [25] discovered the existence of I_A in CA3 neurons and found it to be decreased by 4-amonopyridine (4-AP), a convulsant, thus resulting in a marked increase in cellular excitability. In rat upper cervical ganglion neurons, I_A was characterized as being very rapidly activated at -60 mV potential, depending on the concentration of external K^+. This activation was reduced with 4-AP [26]. In neostriatal neurons, Bargas *et al.* [27] demonstrated that I_A is responsible for the delayed appearance of the action potential in response to near threshold depolarizing currents.

I_A has been simulated with the aid of specialized programming languages for neuroscience. For example, it was simulated on a typical laterodorsal tegmental neuron with NEURON software [28]. To examine the role of I_A in excitability, network synchronization and epilepsy, Fransén and Tigerholm adopted a modified version of the model by Migliore et al., downloaded from the ModelDB [29] [30] [31]. However, there is no education simulator, to our knowledge, for I_A (*http://senselab.med.yale.edu/senselab/modeldb/*).

The relevance of I_A is evidenced by its participation in several regulatory mechanisms in neurons. The electrophysiological data reported depends on the recording techniques involved [32].

The aim of the present study was to generate educational software to facilitate the teaching and learning of I_A current in undergraduate and graduate programs. A series of simulators were grouped into three computer programs: I_A Current, I_A Constant-V Curves and I_A AP Train. With electrophysiological techniques, they reproduce I_A and allow for an unlimited number of virtual experiments.

MATERIALS AND METHODS

Three interactive computer programs were designed and developed to study I_A: I_A Current, I_A Constant-V Curves and I_A AP Train. For this purpose, the Visual Basic 6.0 programming language for Windows® environment was adopted. The programs were compiled and made executable for Windows, from Windows 7 to Windows 10.

The programs act as simulators. To simulate a neuron, the Hodgkin-Huxley model [9] [10] [11] [12] [13] [14] [15] was employed (equations 1 and 2) and I_A was added in accordance with the model described by Connor *et al.* [24] (equations 3, 4, 5, 6 and 7).

$$C_m \, dV/dt = - \, I_{Na} - I_K - I_A - I_L \quad (1)$$

$$C_m \, dV/dt = - g_{Na} (V - E_{Na}) - g_K (V - E_K) - g_A (V - E_A) - g_L (V - E_L) \quad (2)$$

Where C_m is the membrane capacity per unit area (assumed constant), V is the membrane voltage, and g_{Na}, g_K, g_A and g_L are Na^+, K^+, I_A and leakage conductance, respectively. E_{Na}, E_K, E_A and E_L are the equilibrium potentials for Na^+, K^+, I_A and leakage, respectively. The equations utilized for Na^+, K^+ and leakage conductance and the corresponding velocities were those proposed by Hodgkin and Huxley [10], (see Hodgkin-Huxley equations for I_{Na}, I_K and I_L in Cronin [33] and Sterratt *et at.* [34]).

The equations for I_A are [24] [34]:

$$g_A = G_A\, a^3\, b \tag{3}$$

Where G_A is the maximum conductance of I_A, a is the activating particle and b is the inactivating particle [34].

The kinetics of the activation curves $a_\infty(V)$ and $b_\infty(V)$ (steady state) and time constants $\tau_a(V)$ and $\tau_b(V)$ are:

$$a_\infty = \{[0.0761 \exp(V+99.22 / 31.84)] / [1+ \exp(V+58.3 / 14.54)]\}^{1/3} \tag{4}$$

$$b_\infty = 1 / [1 + \exp(V+58.3 / 14.54)]^4 \tag{5}$$

$$\tau_a = 0.3632 + \{1.158 / [1 + \exp(V-60.96 / 20.12)]\} \tag{6}$$

$$\tau_b = 1.24 + \{2.678 / [1 + \exp(V-55 / 16.027)]\} \tag{7}$$

The parameters used in the model are: C_m = 1 μF cm^{-2}; E_{Na}, E_K, E_A and E_L = 50, -77, -80 and -22 mV, respectively; g_{Na}, g_K and g_L = 120, 20 and 0.3 mS cm^{-2}, respectively; g_A is variable, being selected by the simulators.

I_A Current program

The I_A Current program was designed to generate macroscopic traces for I_A during the voltage clamp technique. It is comprised of four simulators: (1) I_A Current Traces, (2) I_A Inactivation Protocol, (3) I_A Equilibrium Potential and (4) I_A Activation-Inactivation Plots.

The I_A Current Traces simulator, based on the mathematical model reported by Connor and Stevens [24] [35] [36] [37], reproduces the outward currents (I_A).

The I_A Equilibrium Potential simulator, also based on the Connor-Stevens model, examines the equilibrium potential for I_A.

The I_A Inactivation Protocol simulator involves adjusting the voltage holding (VH) to lower and lower negative potential levels before applying the stimulus pulse (voltage command, Vc). The kinetics of the decrease in the peak was derived with a mathematical fit from the experimental data of Connor and Stevens [35] [36] [37].

The I_A Activation-Inactivation Plots simulator consists of mathematical equations describing the rate constants [35] [36] [37], which were also obtained from the experimental data of Connor and Stevens. By employing these equations, the activation and inactivation currents of I_A can be portrayed.

I_A Constant-V Curves program

Based on the Hodgkin-Huxley model [10], this program replicates the voltage dependence of the speed constants.

I_A AP Train program

This program is designed to reproduce the action potentials of neurons with an inward sodium current (I_{Na}), an outward K^+ current (I_K) that does not inactivate (H-H type, Hodgkin and Huxley [10]), and an outward potassium current that inactivates (I_A) (equation 1).

To start the integration, a fourth-order Runge-Kutta method with a step time of dt = 0.01 was used. An algorithm written in basic to solve differential equations with this method is found in Zill [38].

Figure 1 illustrates the flow chart for the implementation of the models in Visual Basic®.

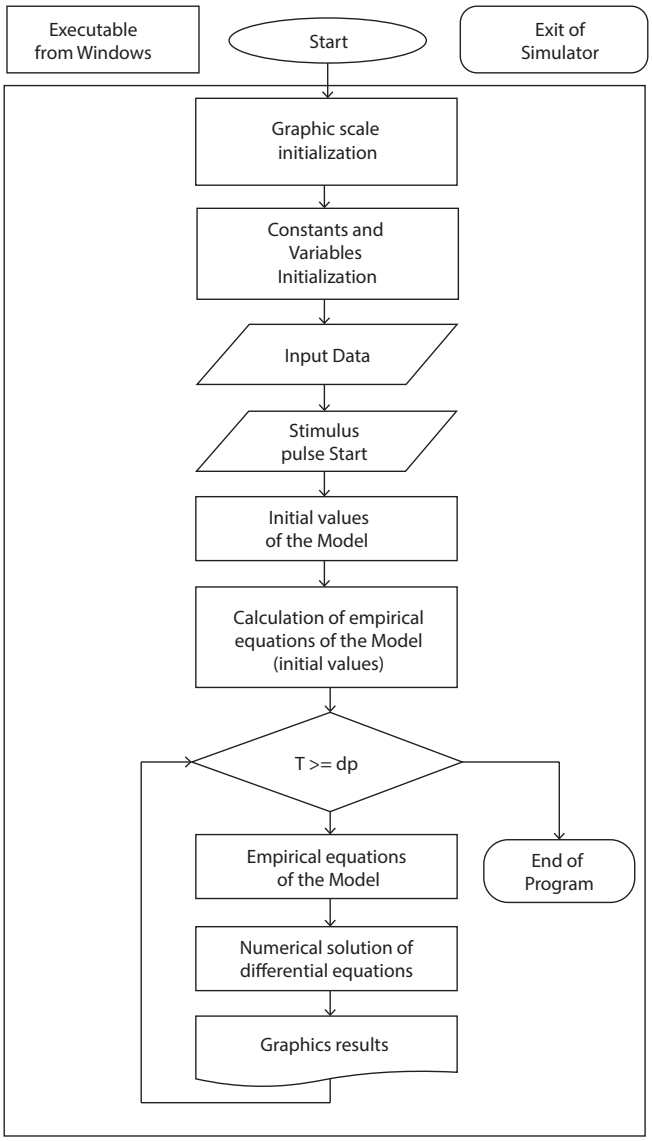

FIGURE 1. Flow chart for implementing the models. For each simulator, the values of the variables and the stimulus pulse are entered. The program initializes the graph scales and the basal values of the model. The differential equations are solved simultaneously, and the results are presented graphically. The iteration time depends on the duration of the stimulus (dp). The user can exit the simulator at any time.

RESULTS AND DISCUSSION

Three interactive computer programs (I_A Current, I_A Constant-V Curves and I_A AP Train) were designed and developed to reproduce the electrophysiology of I_A.

I_A Current program

A-type potassium current simulations

The user interface of the I_A Current simulator has two oscilloscope screens. One shows the macroscopic current traces of the I_A and the other illustrates the stimulus pulse in its voltage clamp mode.

The stimulus voltage to perform the simulations is in the range of -60 to -20 mV, with VH = -93 mV. In the neurons recorded by Connor and Stevens [36], the activation time constant has values from 10-25 ms and the inactivation constant from 220-600 ms. These values vary according to the type of cell. In neurons of the hippocampus of the vertebrate central nervous system, the values are considerably lower. Experimental values from other neurons can also be employed. To simulate and replicate the experimental results in distinct neuronal systems, the user need only enter the time constants of different neurons.

The simulation of the experiments published by Connor and Stevens [35] [36] is depicted in Figure 2.

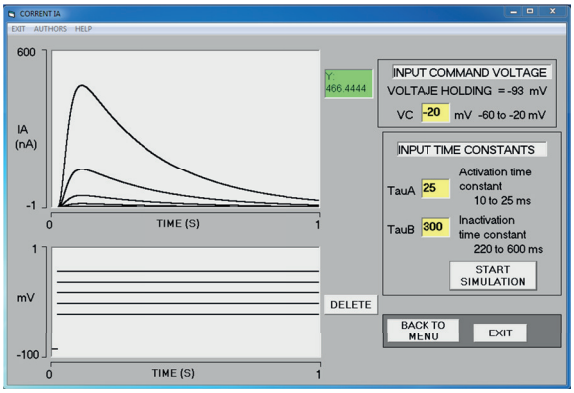

FIGURE 2. The simulation of the experiments carried out by Connor and Stevens were run to study the I_A. The voltage setting pulses are displayed on the lower oscilloscope screen. The upper screen portrays the currents traces corresponding to Vc = -60, -50, -40, -30 and -20 mV (the curves from baseline upwards). The VH was -93 mV and the rise time and decay current constants were 25 and 300 ms, respectively.

Command voltage pulses of -60, -50, -40 and -20 mV were applied. As the command voltage becomes less negative, the amplitude of the current increases [36]. The I_A trace corresponding to each of the stimulus pulses is displayed on the upper oscilloscope screen. For each simulation, the value entered for the time constant was 25 ms for activation and 300 ms for inactivation.

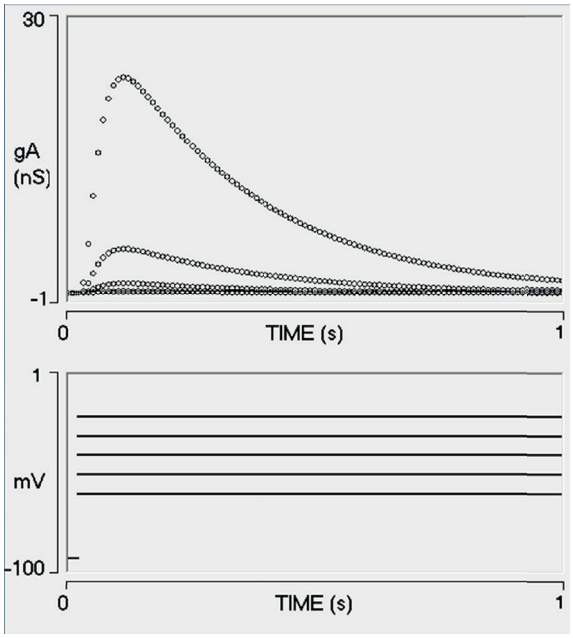

FIGURE 3. Simulations of gA with VH = -93 mV and pulses characterized by a voltage command of -60, -50, -40, -30 and -20 mV. The response is displayed on the upper oscilloscope screen. The trace with the smallest amplitude of conductance corresponds to -60 mV and the highest amplitude to -20 mV.

The simulations generate a classic I_A profile. This is a K^+ output current that starts at hyperpolarized potentials and shows an ascending curve during activation until reaching a maximum, at which point it gradually descends during inactivation. With a new command voltage and VH, there are changes in the channel conductance (g_A) and consequently in the current and peak amplitude of the current. The data correspond to experiments carried out at 5 °C. The currents are very slow in gastropod neurons compared to those in the brain of rats or other vertebrates. I_A is presented directly without considering the total outward potassium current and I_K.

I_A conductance (g_A) simulations

The channel conductance (g_A) is obtained by dividing I_A by the voltage command (V_c). Figure 3 shows the same simulation conditions as Figure 2. The upper oscilloscope screen depicts the g_A value in nS cm^{-2}. The trace duration is 1 s.

Simulation for I_A equilibrium potential

One of the methods to determine the equilibrium potential of an ionic current is to perform voltage clamp experiments and find the command voltage where the current is zero. In the I_A Equilibrium Potential simulator, the equilibrium for the current was -63 mV (Figure 4). The current-voltage relation is not presented.

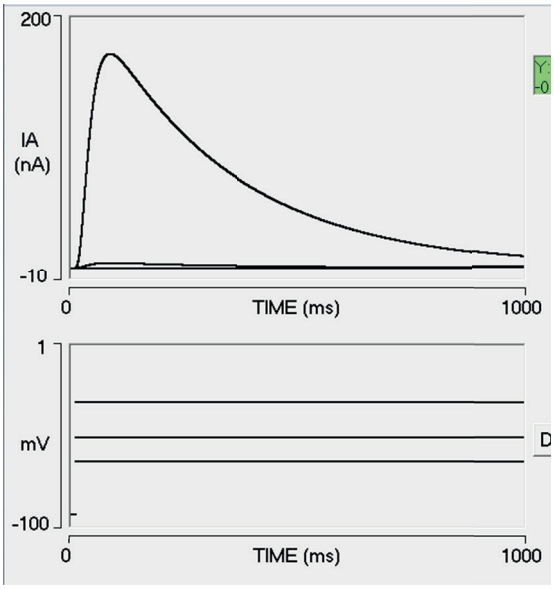

FIGURE 4. Simulation of the equilibrium potential. There was a lack of current at Vc = -63 mV. The upper lines correspond to Vc = -50 and -30 mV.

Inactivation protocol simulation

To simulate the inactivation protocol, the I_A Inactivation Protocol program is provided with the interface depicted in Figure 5. The two oscilloscope

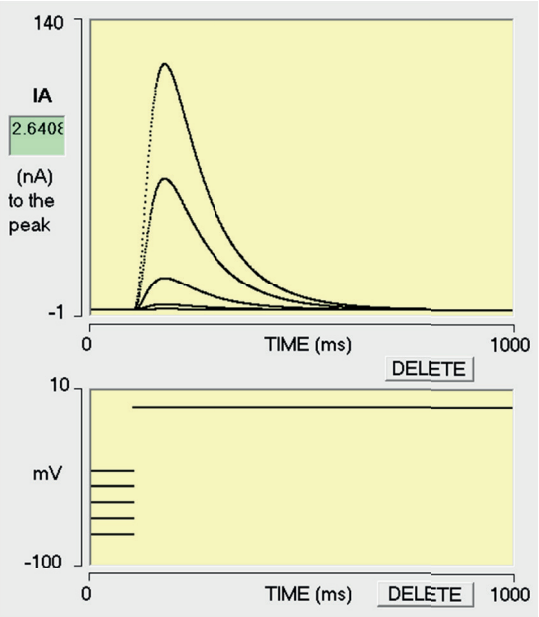

FIGURE 5. Simulations with the inactivation protocol. The voltage holding (VH) was applied at -80, -70, -60, -50 and -40 mV, consecutively. The responses are displayed on the upper oscilloscope screen. The amplitude of the trace was greatest at -80 mV and least (2.6 nA) at -50 mV.

screens on the left side show the current traces of I_A (upper) and the stimulation pulses (lower). The macroscopic I_A current is recorded in a neuron, beginning with a test depolarization at 0 mV and followed by the holding potential that varied from -90 to -50 mV.

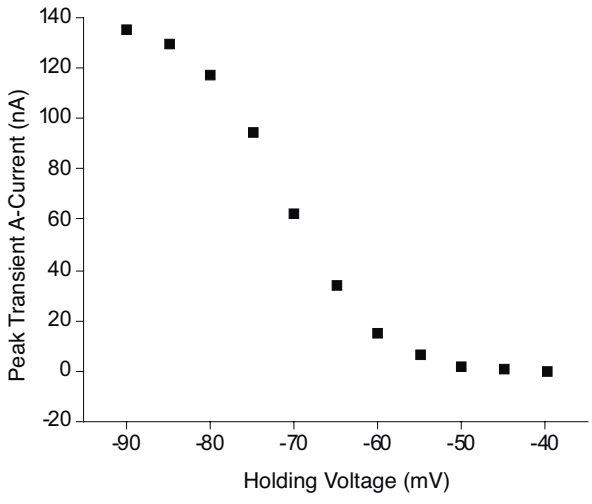

FIGURE 6. Inactivation plot. The peak value of the current decreases as the VH becomes less negative, from -90 to -40, in decremental steps of 5 mV. These results replicate the experimental data [36].

As can be appreciated, the peak value of the current decreases as the holding voltage preceding the stimulus pulse becomes less negative. Figure 6 illustrates how the decline in the peak value follows the pattern of a decreasing curve, as reported by Connor and Stevens [36]. The maximum value of I_A was obtained with a holding potential of -90 mV, and a value near zero was found in the range of -50 to -40 mV.

Simulation of the activation and inactivation curves

Simulations of the activation and inactivation curves are based on the Hodgkin-Huxley model [10]. Figure 7 shows an example of simulation. Curves a(V, ∞) and b(V, ∞) overlap between -30 and -20 mV.

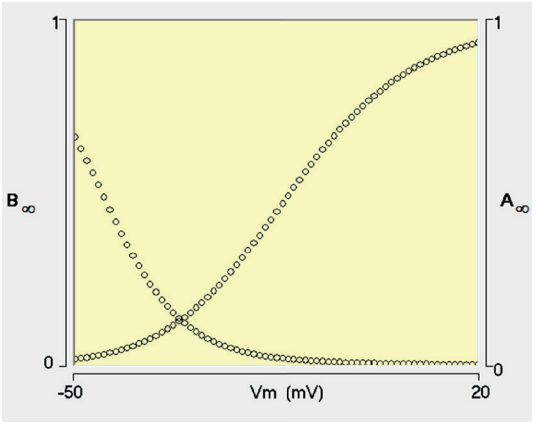

FIGURE 7. Simulation of activation and inactivation curves for the I_A. The decreasing curve corresponds to inactivation and the increasing curve to activation. As the membrane potential becomes less negative, its activation is greater. The simulation is in agreement with the results of Connor *et al.* [37].

I_A Constant-V Curves program

This program allows the user to observe the voltage dependence of the opening and closing speed constants for I_A. In the first simulation, the values entered were those reported for gastropod cells (Figure 8).

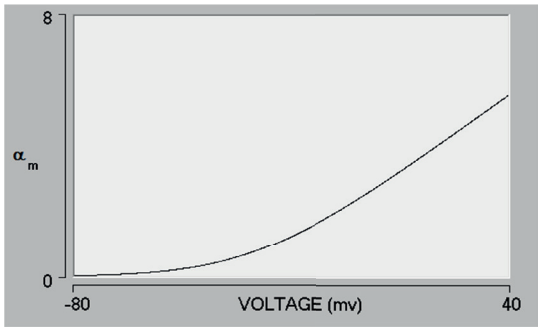

FIGURE 8. Simulation carried out to portray the kinetics of the velocity constant α_m with respect to the voltage.

I_A AP Train program

The Train I_A program simulates a neuron with the sum of the currents I_A, I_{Na} and I_K. It reproduces action potentials when the neuron is stimulated by a current pulse lasting from 50-200 ms at an intensity of 8 nA cm^{-2}. A test simulation to study the effect of I_A on the AP train is shown in Figure 9.

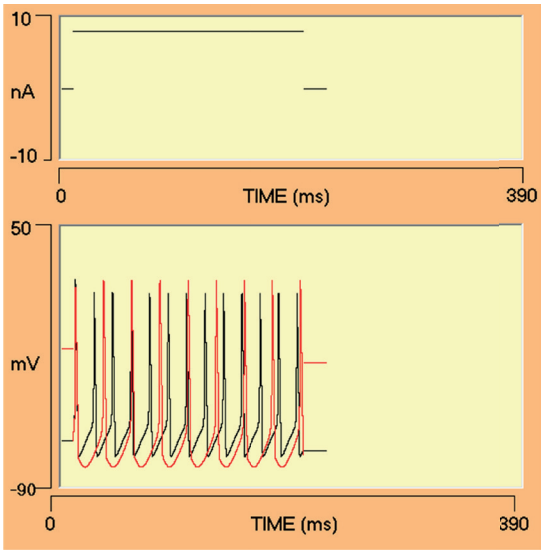

FIGURE 9. Simulation of the effect of I_A on the AP train. With g_A = 50 mS cm^{-2}, it is clearly observed how this current hyperpolarizes the neuron and decreases the AP frequency [39]. Control action potentials (utilizing Na^+ and K^+ channels) in black, I_A action potentials in red.

Two simulations were performed in a row with g_A set at 50 mS cm^{-2}. In the first, the AP was generated in a neuron with only Na^+ and K^+ channels (trace in black). In the second, the AP was triggered in a neuron that also has A-type potassium channels (red line). Note how the time between APs increases in the second. Hence, I_A delays the appearance of the AP and the frequency of the AP train decreases.

The overall model

A-type potassium channels are found in the neurons of mollusk and of the central and peripheral nervous system of mammals. The physiological implications of this type of channel reveal its importance for the appropriate functioning of neurons and the brain as a whole.

Programs for simulating I_A, such as NEURON and GENESIS, are freely accessible (*https://www.neuron.yale.edu/neuron/download*; *http://genesis-sim.org/*). For their proper use, however, it is necessary for the operator to undergo specialized training. Moreover, a high-speed, high-performance computer may be required, depending on the number of compartments simulated and the complexity of the model. Examples of special equipment with these specifications are a workstation or parallel supercomputer system.

Simulations of I_A have been carried out for research purposes. For example, Huguenard and McCornick [40] reported simulating I_A in the rhythmic oscillation of thalamic neurons.

Nevertheless, the tools employed imply considerable drawbacks for teaching purposes. They are very large and a substantial investment of time is required to learn how to manage them [15].

Due to the pandemic affecting us today and in the near future, online education has assumed increasing importance. The development of simulators with limited extension facilitates their usage, handling and transport. Furthermore, they can be easily adapted to remotely support teaching practices [15].

In the present work, a series of educational simulators were combined to reproduce the fundamental electrophysiology of I_A under experimental conditions of current and voltage clamp. The simulators were validated with the mathematical models developed by the experiments of Connor and Stevens [35] [36] [37]. The programs that group the simulators are compatible with on any personal computer having the minimum characteristics to run Windows® 7 to Windows® 10.

Thus, the software package developed presently will allow students to perform the experiments of Connor *et al.* [35] [36] [37]. The results and implications of I_A in the electrophysiology of the neuron can then be discussed with the instructor. The mathematical model currently employed for I_A was the one published by Connor *et al.* [24]. A description of the mathematical models proposed for I_A is found in Rush and Rinzel [39]. The numerical solution of differential equations enabled the reproduction of reported experimental data. Operation of the programs does not require specialized training. The user need only rely on scientific articles or on an instructor for an explanation of the biophysics and electrophysiology of I_A.

Since experiments involving organic tissue remain costly, despite efforts to decrease the cost of electrophysiological recording [32], simulators provide a practical alternative for study and research in neuroscience. They have the advantage of permitting changes in the biophysical factors of the neuron in order to observe their influence on neuronal functioning, a capacity not shared by experimental animal models. In the case of the model described herein, the simulators enable students and teachers to vary the conductance of the A-type potassium channel or the time constants for the generation and decline of I_A.

The development of simulators requires validation with experimental data. In regard to the simulators developed in the current investigation, real experimental values were entered for the variables, finding that the model reproduced the experimental results. Hence, the variables can be modified to analyze their consequences in a reliable model.

CONCLUSIONS

The three interactive computer programs described herein were able to replicate the biophysical characteristics of I_A and provide a virtual reproduction of the electrophysiological processes involved in activating and inactivating an ion current.

The corresponding oscilloscope screens showed voltage-dependent curves. The I_A AP Train program simulates the influence of I_A on an AP train, revealing how it decreases the AP trip frequency in the trace. With this simulator, the effect can be observed of increasing or decreasing g_A (channel conductance), modifying time constants, and altering the kinetics of the speed constants, among other phenomena. The simulators should be considered a teaching tool and do not replace the professor.

AUTHOR CONTRIBUTIONS

A.R.L. provided advice in neurosciences and programming, he was in charge in mathematical modeling and its numerical solution. M.E.P.B. provided advice in physiology and oversaw simulations and validation of the model. M.R.M. provided advice in education and oversaw programming, interface design and figures. M.F.P.E. oversaw the programming and compilation of the simulators. All authors participated in the structural analysis, review, and correction of the work.

REFERENCES

[1] Randall C, Burkholder T. Hands-on laboratory experience in teaching-learning physiology. Adv Physiol Educ. 1990;259(4):S4-7. https://doi.org/10.1152/advances.1990.259.6.S4

[2] Woodhull-McNeal AP. Project labs in physiology. Adv Physiol Educ. 1992;263(6):S29-32. https://doi.org/10.1152/advances.1992.263.6.S29

[3] Bish JP, Schleidt S. Effective use of computer simulations in an introductory neuroscience laboratory. J Undergrad Neurosci Educ. 2008;6(2):64-7.

[4] Diwakar S, Parasuram H, Medini C, Raman R, Nedungadi P, Wiertelak E, et al. Complementing Neurophysiology Education for Developing Countries via Cost-Effective Virtual Labs: Case studies and Classroom Scenarios. J Undergrad Neurosci Educ. 2014;12(2):130-9.

[5] Maran NJ, Glavin RJ. Low to high-fidelity simulation - A continuum of medical education? Med Educ Suppl. 2003;37(1):22-8. https://doi.org/10.1046/j.1365-2923.37.s1.9.x

[6] Oriol NE, Hayden EM, Joyal-Mowschenson J, Muret-Wagstaff S, Faux R, Gordon JA. Using immersive healthcare simulation for physiology education: Initial experience in high school, college, and graduate school curricula. Am J Physiol - Adv Physiol Educ. 2011;35(3):252-9. https://doi.org/10.1152/advan.00043.2011

[7] Harris DM, Ryan K, Rabuck C. Using a high-fidelity patient simulator with first-year medical students to facilitate learning of cardiovascular function curves. Am J Physiol - Adv Physiol Educ. 2012;36(3):213-9. https://doi.org/10.1152/advan.00058.2012

[8] Anyanwu GE, Agu AU, Anyaehie UB. Enhancing learning objectives by use of simple virtual microscopic slides in cellular physiology and histology: Impact and attitudes. Am J Physiol - Adv Physiol Educ. 2012;36(2):158-63. https://doi.org/10.1152/advan.00008.2012

[9] Av-Ron E, Byrne JH, Baxter DA. Teaching basic principles of neuroscience with computer simulations. J Undergrad Neurosci Educ. 2006;4(2):40-52.

[10] Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in Nerve. J Physiol. 1952;117(4):500-44. https://doi.org/10.1113/jphysiol.1952.sp004764

[11] Segev I. Temporal Interactions Between Post-Synaptic Potentials. In Bower J, Beeman D (eds.). The book of GENESIS, 2nd ed. New York: Springer-Verlag; 1998. 79-96p. https://doi.org/10.1007/978-1-4612-1634-6_6

[12] Carnevale NT, Hines ML. The NEURON Book. Cambridge: Cambridge University Press; 2006. 480 p.

[13] Izhikevich EM, Edelman GM. Large-scale model of mammalian thalamocortical systems. PNAS. 2008;105(9):3593-8. https://doi.org/10.1073/pnas.0712231105

[14] Hernández OE, Zurek EE. Teaching and learning the Hodgkin-Huxley model based on software developed in NEURON's programming language hoc. BMC Med Educ. 2013;13(70):1-9. https://doi.org/10.1186/1472-6920-13-70

[15] Reyes-Lazalde A, Reyes-Monreal M, Pérez-Bonilla ME. Desarrollo de un simulador de los experimentos clásicos y actualizados de fijación de Voltaje de Hodgkin y Huxley. Rev Mex Ing Biomed. 2016;37(2):135-48. https://doi.org/10.17488/rmib.37.2.1

[16] Reyes Lazalde A, Pérez-Bonilla ME, Funchs-Gómez OL, Reyes-Monreal M. Interactive simulators to study the passive properties of the axon and the dendritic tree. Rev Mex Ing Biomed [Internet]. 2012;33(1):29-40. Available from: http://www.rmib.mx/index.php/rmib/article/view/226

[17] Goodman D, Brette R. Brian: a simulator for spiking neural networks in Python. Front Neuroinform. 2008;2(NOV):1-10. https://doi.org/10.3389/neuro.11.005.2008

[18] Demir SS. Simulation-Based Training In Electrophysiology By iCELL. In 2005 IEEE Engineering in Medicine and Biology 27th Annual Conference. Shangai: IEEE-EMBS;2005:851-4. https://doi.org/10.1109/IEMBS.2005.1616549

[19] Ribarič S, Kordaš M. Teaching cardiovascular physiology with equivalent electronic circuits in a practically oriented teaching module. Am J Physiol - Adv Physiol Educ. 2011;35(2):149-60. https://doi.org/10.1152/advan.00072.2010

[20] Reyes Lazalde A, Reyes Monreal M, Pérez Bonilla ME. Experimentación virtual con el simulador dosis-respuesta como herramienta docente en biología. Apertura. 2016;8(2):22-37. http://dx.doi.org/10.32870/Ap.v8n2.855

[21] Vega OA, Londoño-Hincapié SM, Toro-Villa S. Laboratorios virtuales para la enseñanza de las ciencias. Informática. 2016;(35):97-110. https://doi.org/10.30554/ventanainform.35.1849.2016

[22] Hagiwara S, Kusano K, Saito N. Membrane changes of *Onchidium* nerve cell in potassium-rich media. J Physiol. 1961;155(3):470-89. https://doi.org/10.1113/jphysiol.1961.sp006640

[23] Cai S-Q, Li W, Sesti F. Multiple modes of A-type potassium current regulation. Curr Pharm Des. 2007;13(31):3178-84. https://doi.org/10.2174/138161207782341286

[24] Connor JA, Walter D, McKown R. Neural repetitive firing: modifications of the Hodgkin-Huxley axon suggested by experimental results from crustacean axons. Biophys J. 1977;18(1):81-102. https://dx.doi.org/10.1016%2FS0006-3495(77)85598-7

[25] Gustafsson B, Galvan M, Grafe P, Wigström H. A transient outward current in a mammalian central neurone blocked by 4-aminopyridine. Nature. 1982;299(5880):252-4. https://doi.org/10.1038/299252a0

[26] Galvan M, Sedlmeir C. Outward currents in voltage-clamped rat sympathetic neurones. J Physiol. 1984;356(1):115-33. https://doi.org/10.1113/jphysiol.1984.sp015456

[27] Bargas J, Galarraga E, Aceves J. An early outward conductance modulates the firing latency and frequency of neostriatal neurons of the rat brain. Exp Brain Res. 1989;75(1):146-56. https://doi.org/10.1007/BF00248538

[28] Sanchez RM, Surkis A, Leonard CS. Voltage-clamp analysis and computer simulation of a novel cesium- resistant a-current in guinea pig laterodorsal tegmental neurons. J Neurophysiol. 1998;79(6):3111-26. https://doi.org/10.1152/jn.1998.79.6.3111

[29] Fransén E, Tigerholm J. Role of A-type potassium currents in excitability, network synchronicity, and epilepsy. Hippocampus. 2010;20(7):877-87. https://doi.org/10.1002/hipo.20694

[30] Migliore M, Hoffman DA, Magee JC, Johnston D. Role of an A-type K^+ conductance in the back-propagation of action potentials in the dendrites of hippocampal pyramidal neurons. J Comput Neurosci. 1999;7(1):5-15. https://doi.org/10.1023/A:1008906225285

[31] Hines ML, Morse T, Migliore M, Carnevale NT, Shepherd GM. ModelDB: A Database to Support Computational Neuroscience. J Comput Neurosci. 2004;17(1):7-11. https://doi.org/10.1023/B:JCNS.0000023869.22017.2e

[32] Lemus-Aguilar I, Bargas J, Tecuapetla F, Galárraga E, Carrillo-Reid L. Diseño modular de instrumentación virtual para la manipulación y el análisis de señales electrofisiológicas. Rev Mex Ing Biomédica [Internet]. 2006;27(2):82-92. Available from: http://www.rmib.mx/index.php/rmib/article/view/359

[33] Cronin J. Mathematical Aspects of Hodgkin-Huxley Neural Theory. Cambridge: Cambridge University Press; 1987. 261p.

[34] Sterratt D, Graham B, Gillies A, Willshaw D. Principles of Computational Modelling in Neuroscience. Cambridge: Cambridge University Press; 2011. 300 p.

[35] Connor JA, Stevens CF. Inward and delayed outward membrane currents in isolated neural somata under voltage clamp. J Physiol. 1971;213(1):1-19. https://doi.org/10.1113/jphysiol.1971.sp009364

[36] Connor JA, Stevens CF. Voltage clamp studies of a transient outward membrane current in gastropod neural somata. J Physiol. 1971;213(1):21-30. https://doi.org/10.1113/jphysiol.1971.sp009365

[37] Connor JA, Stevens CF. Prediction of repetitive firing behaviour from voltage clamp data on an isolated neurone soma. J Physiol. 1971;213(1):31-53. https://doi.org/10.1113/jphysiol.1971.sp009366

[38] Zill DG. Ecuaciones diferenciales con aplicaciones. 2nd Ed. México: Grupo Editorial Iberoamérica; 1988. 516 p.

[39] Rush ME, Rinzel J. The potassium A-current, low firing rates and rebound excitation in Hodgkin-Huxley models. Bull Math Biol. 1995;57(6):899-929. https://doi.org/10.1007/BF02458299

[40] Huguenard JR, McCormick DA. Simulation of the currents involved in rhythmic oscillations in thalamic relay neurons. J Neurophysiol. 1992;68(4):1373-83. https://doi.org/10.1152/jn.1992.68.4.1373

COMPLEMENTARY MATERIAL

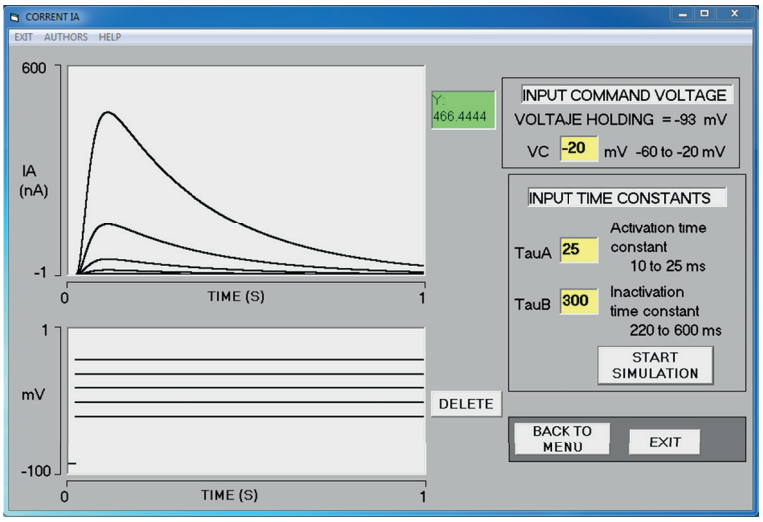

FIGURE 1. User interface of the I_A Current Traces simulator. The variable input module is shown on the right side: command voltage (-60 to -20 mV), activation time constant (10-25 ms) and inactivation time constant (220-600 ms). On the left side, the I_A macroscopic current is depicted on the upper monitorand the command voltage on the lower monitor.

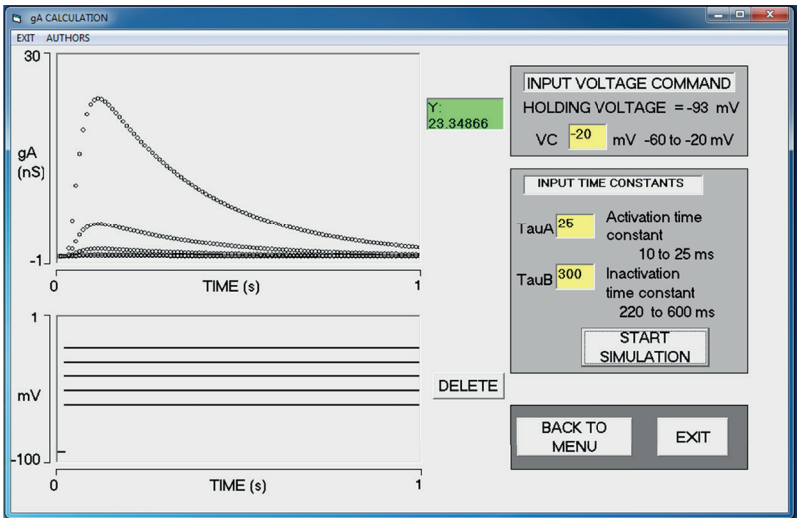

FIGURE 2. User interface for the g_A conductance simulation. The user enters the value of the variables and starts the simulation. The maximum amplitude of the conductance is measured with the cursor inside the upper monitor display and the value appears in the green box.

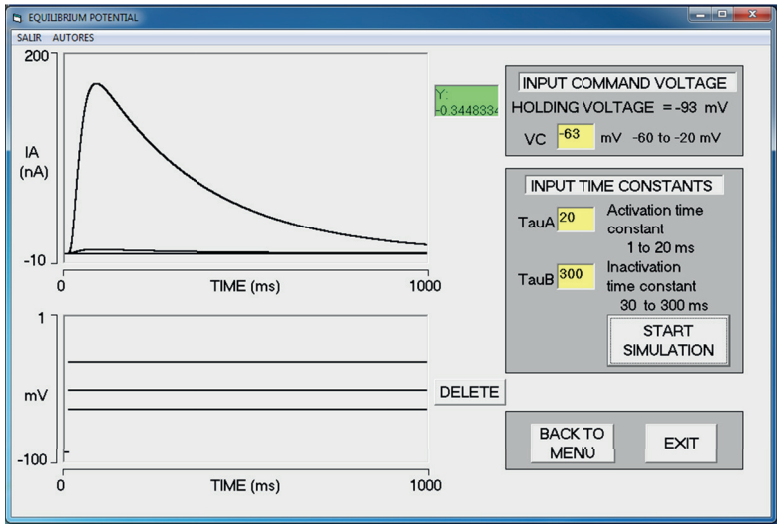

FIGURE 3. User interface of the I_A Equilibrium Potential simulator. The user enters the value of the time constants. Several simulations are performed with different values of the command voltage until the voltage that produces zero I_A current is found. The current is measured with the cursor and its value appears in the green box.

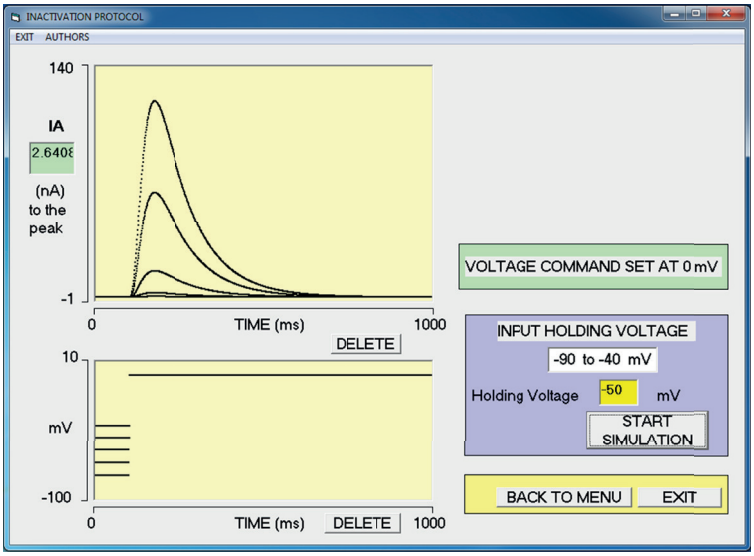

FIGURE 4. User interface of the I^A Inactivation Protocol simulator. Enter the holding voltage (prepulse) (-90 to -40 mV) on the right side. The macroscopic I_A current is displayed on the upper monitor. The peak value of the current appears in the green box. The stimulation protocol is shown on the bottom monitor.

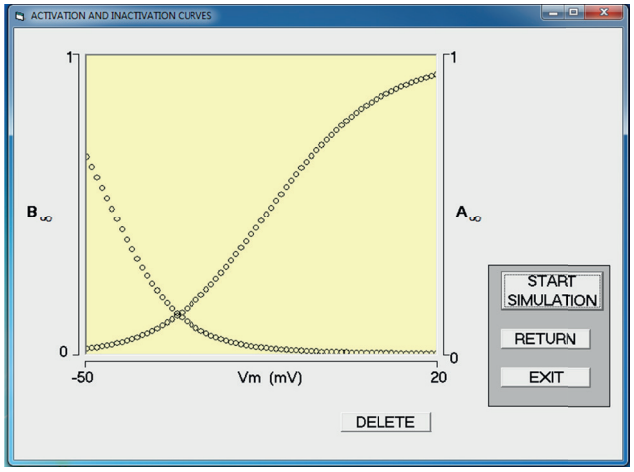

FIGURE 5. User interface of the I_A Activation-Inactivation Plots. The monitor portrays the activation curve (ascending trace) and the inactivation curve (descending trace).

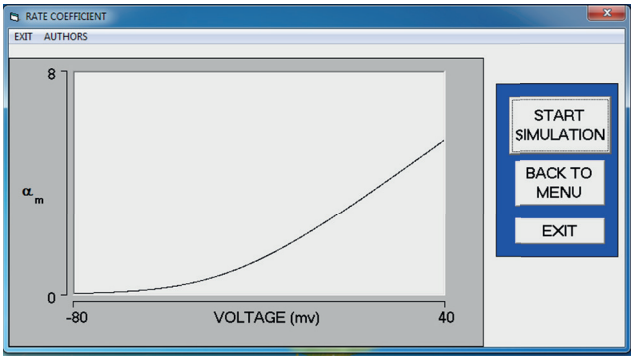

FIGURE 6. User interface of the I_A Constant-V Curves program. The monitor illustrates α_m.

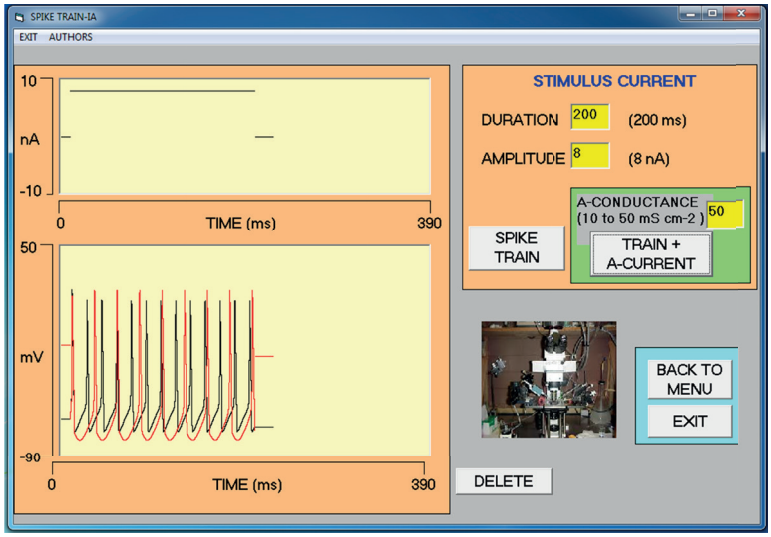

FIGURE 7. **User interface of the I_A AP Train program. The duration and amplitude of the stimulus current pulse and the value of conductance g_A (10-50 mS/cm^2) are entered on the right side. The stimulus pulse is depicted on the upper monitor and the train of action potentials on the lower monitor. The << Spike Train >> button produces the control simulation (black line). The << Train + A-Current >> button produces the simulation of a neuron that has type-A potassium channels (red line).**