34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

"Stim-eLab": a Simulation Tool to Enhance Education of Bioelectrical Mechanisms of Electrical Stimulation

Mohammad Reza Mohagheghi-Nejad, Amin Mahnam

Abstract— **Mechanisms of electrical stimulation of neural tissue are among the basic concepts in neural engineering and it is necessary for students who are going to work in the field of neural engineering or neuroscience to have a good understanding of these concepts. A program was developed based on Graphical User Interface toolbox of MATLAB software to help students of Biomedical Engineering and Physiology disciplines to more easily learn the concepts and mechanisms of electrical stimulation. The software provides students a virtual laboratory where they can study the behavior of neural fibers in response to intracellular or extracellular stimulations. Different stimulus waveforms can be applied and various parameters of the fiber and the membrane model can be modified to study their effects on the behavior of the fiber. The software provides an easy to use environment for the students to get a deep understanding of the electrophysiological concepts related to electrical stimulation via a problem solving or study-based approach.**

I. Introduction

Electrophysiology is the study of the electrical properties of biological cells and tissues [1]. It is the basis for the neuroscience and a variety of its branches including cognitive neuroscience, and also the newly emerged field of neural engineering: a discipline within biomedical engineering that uses engineering techniques to understand, repair, replace, enhance, or otherwise exploit the properties of neural systems [2]. Although, electro-physiological studies have been interested researchers for more than a hundred years, we are now witnessing a rapid expansion of the understanding about the complex behavior of the brain, and at the same time, the exciting engineering applications of this knowledge. Therefore, the related graduate courses are lectured in almost all the well-known biomedical engineering departments around the world, and even as courses in BSc programs.

Since the effective electrophysiology laboratories are too expensive for educational purposes, various simulation programs are developed and are in use in many departments, helping students to better understand the mechanisms behind the rest membrane potential, action potential formation, and the contribution of different ion channels on these phenomena.

HHSim is a free package implemented in MATLAB, to simulate a patch of excitable membrane based on HH model [3]. It provides an environment to simulate intracellular stimulation of the membrane and study the underlying gating mechanisms as well as the effect of Na and K blockers.

NERVE is a web-based program in Java that simulates an unmyelinated nerve fiber using HH model, and propagating action potential [4]. The application of these programs are limited to the understanding of the mechanisms of action potential formation in response to intracellular stimulation, which may be adequate for physiology students, but not for those in biomedical engineering disciplines, where the concepts like the mechanisms of extracellular stimulation, the effects of stimulus waveform, multi-electrode stimulation and nerve block are also of great interest.

NEURON is a comprehensive simulating environment providing a specialized programming language and also a graphical interface for simulating neurons and neuronal networks [5]. Virtually any neural structure can be implemented in this environment, and its completeness and flexibility has attracted many researchers in neuroscience and neural engineering, to use this environment for neural modeling and simulations. However, it takes a considerable time for the students to learn working with this software, and it exposes students to many details of the models and simulations which is confusing for learning purposes.

Neurons in Action (NIA) is a set of interactive tutorials that are based on NEURON software, prepared specially for education, by leading the students through a series of laboratory experiments [6]. However, these tutorials should be purchased for 50$ by each student.

However, there is no simulation tool available specialized for study and education of electrical stimulation. The need for such environment is increasing in recent years by expanding the therapeutic and rehabilitation applications of electrical stimulation, and emergence of the new field of neural engineering.

We have developed a virtual laboratory of electrophysiology with appropriate tools to learn and study the concepts related to electrical stimulation and block, for students of biomedical engineering and neuroscience. The program allows for intracellular and extracellular multi-electrode stimulation of neural fibers, using McNeal model of the fiber. HH, CRRSS or a user-defined model of the membrane may be adopted for the simulations. The program provides appropriate visualization tools to design the desired stimulations and view the response of the fiber.

M. R. Mohagheghi-Nejad was with the University of Isfahan, Isfahan, Iran. He is now with the School of Electrical and Computer Engineering, University of Tehran, Tehran, Iran (e-mail: m.mohagheghi@ut.ac.ir).

A. Mahnam, is with the department of Biomedical Engineering, School of Engineering, University of Isfahan, Isfahan, Iran (Corresponding Author; e-mail: mahnam@eng.ui.ac.ir).

II. Material and Method

A virtual laboratory is developed using MATLAB software to demonstrate the behavior of neural fibers in response to intracellular and extracellular electrical stimulations, and the various related electrophysiological phenomena. The developed software consists of two parts. A neural simulation core and a user interface.

Many parameters of the models may be adjusted by the user, including the fiber's number of nodes of Ranvier (or compartments in an unmyelinated fiber). This is made possible due to vector-based implementation of the model in the SIMULINK environment [9]. The simulations are performed using SIMULINK built-in variable-step ode113 algorithm (Adams-Bashforth-Moulton Method) [10]. Duration of the simulation can be adjusted by the user.

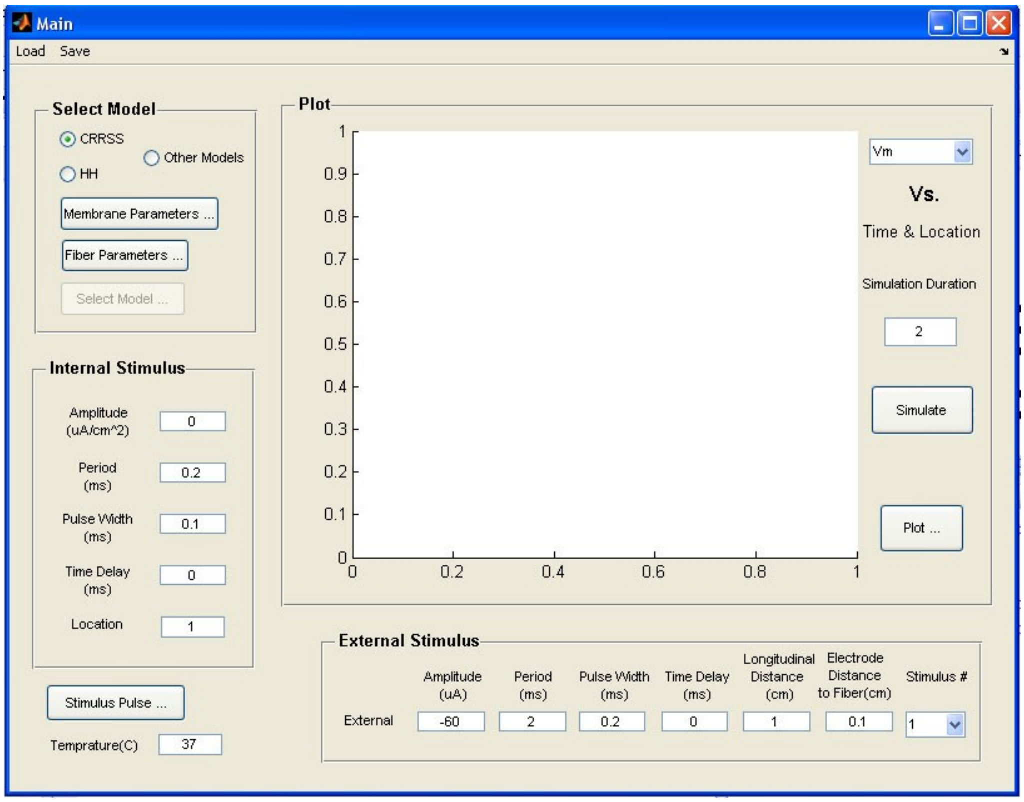

Fig. 1.The main window of the Stim-eLab program. This window provides the basic functionality of the program.

A. Neural Simulation Core

The neural simulation core uses the fiber models implemented in SIMULINK environment to simulate the behavior of the neural fibers. CRRSS and HH based models of neural fibers has already prepared for this virtual laboratory, while other models may also be used if they have implemented in accordance with the software's standard protocol. The SIMULINK models have inputs for intracellular injected current and extracellular distribution of electrical potential along the fiber. The potential distribution is calculated for the user designed stimulus waveforms based on the analytical relationship for infinite homogeneous volume conductor [7].

The already prepared fiber models are based on McNeal model of neural fibers [8]. CRRSS is a model of the excitable membrane developed by Chiu and his colleagues [8] for the nodes of Ranvier of the mammalian peripheral myelinated fibers, while the HH is the famous Hodgkin-Huxley membrane model of unmyelinated giant fibers of squid. These models are the most common models in the neuroscience and neural engineering studies, and are still considered in many studies.

B. User Interface

The user interface of the software (Fig. 1) is designed using GUIDE toolkit of the MATLAB software, to provide an easy-to-use graphical interface for the students. The Graphical User Interface Development Environment provides a set of tools to create graphical user interfaces (GUIs) in MATLAB.

The software interface is developed with the aim that a novice student can easily start working with the software, while a skilled student have all the options to adjust parameters of the model and the stimulations. To achieve this goal, the interface is split into different windows. The main window provides the basic tools to apply stimulations and observing the result. However, other windows provide tools to adjust detailed parameters of the membrane and fiber model, and stimulus parameters, and demonstrate the response of the fiber in different ways.

The user can apply stimulations with one internal electrode, and up to three external electrodes to the fiber. Stimulus waveform of mono-phasic, bi-phasic and sinusoidal can be applied. The electrodes are considered by default on the central node (compartment) of the fiber, but the user can adjust the longitudinal position of the electrodes, and the distance of external electrodes. In the "Stimulus Pulse" window, the user can see the designed stimulus pulses and the relative position of the electrodes to the fiber.

The software can demonstrate the response of the fiber to the stimulations in different ways. The default plot in the main window is a three dimensional plot of the interested variable (e.g. membrane potential, gate states or channel conductances) vs. time along the fiber. However, in the "Plot" window, the user can see a fiber variable in certain compartments of the model just along time, or see the spatial plot of the variable for the whole fiber, as a movie along the time. The resulted plots and movies can be saved for further use in a report or presentation.

The user can also use an analysis tool to automatically obtain the stimulus threshold for activation of the fiber, while adjusting the stimulus parameters. The threshold is found using a binary search algorithm [11].

III. RESULT

The developed program provides a convenient environment to study the response of neural fibers to intracellular and extracellular stimulations. Here, the features of the program are demonstrated in a few examples. All the simulations were performed for a fiber 10cm in length and 10μm in diameter. The extracellular resistivity of the volume conductor was 300Ωcm.

Fig. 2 shows the propagation of an action potential along a myelinated fiber, generated by an extracellular stimulation of -100μA. The electrode was in front of the central node of Ranvier (longitudinal position of zero), 1mm from the fiber. A DC anodic intracellular stimulation of -8.5mA/cm^2, at longitudinal position of -3cm, has blocked the propagation of the action potential to the left.

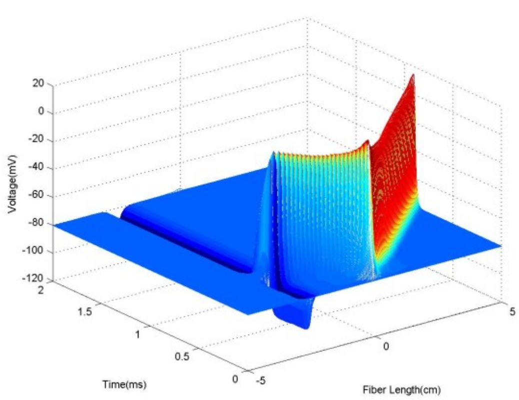

Fig. 2. Action potential propagation was blocked using a DC anodic intracellular stimulation (normal view).

In the "Plots" window, the same plot can be rotated in three-dimensions to obtain a color view of the same phenomena (Fig. 3). In this window the resulted plot can also be saved as a picture to then be used in a report.

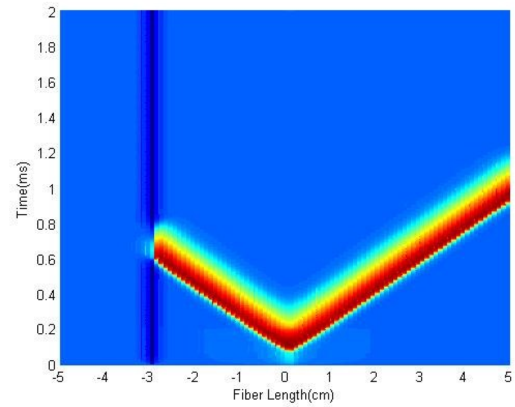

Fig. 3. A color view of the block of a propagating action potential using anodic intracellular DC stimulation (3D plot, rotated to be observed from above).

Spatial plots are also available in the "Plot" window, where the selected variable is shown along the fiber in each time instant. The repetition of these plots during the time, create a movie which shows the changes of the variable during the time along the fiber. Fig. 4 and 5 demonstrates these plots before and after the collision of two approaching action potentials.

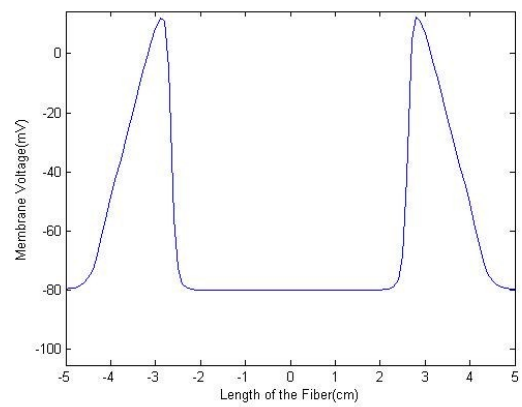

Fig. 4. A frame of the movie demonstrating two action potentials propagating toward each other, before collision.

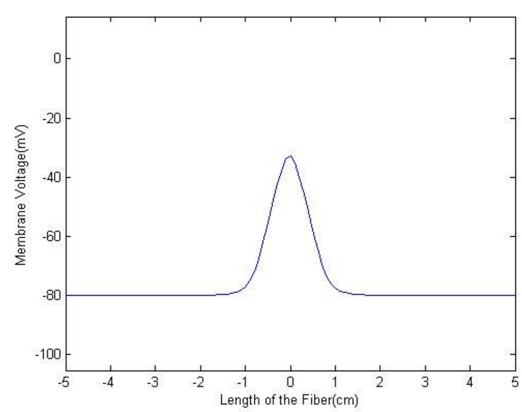

Fig. 5. A frame of the movie demonstrating two action potentials propagating toward each other, during collision.

The action potentials were generated by extracellular stimulations with two electrodes 1mm from the fiber. The position of the electrodes may be viewed in the "Stimulus Pulse" window by clicking on "Electrodes Relative Positions" pushbutton (Fig. 6).

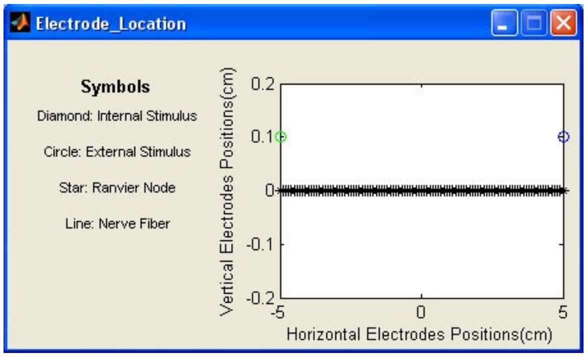

Fig. 6. Position of electrodes, shown for the example of action potential collision (Fig. 4 and 5).

Fig. 7 demonstrates the gating dynamics of the sodium channels for unmyelinated HH fiber model, during an anode break excitation in the "Plot" window. The gating parameters are plotted for the central node where a long anodic current is injected by the intracellular electrode. The plot helps students to understand the mechanism underling this interesting phenomenon and learn about importance of dynamics in the behavior of excitable membrane.

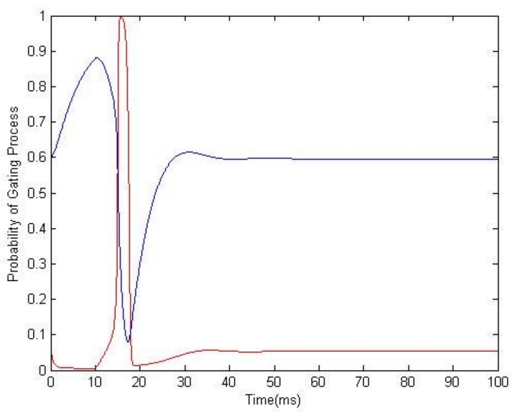

Fig. 7. The gates' state m (red line) and h (blue line) of the sodium channels are plotted when an anode block excitation is occurred after an anodic intracellular stimulation of 10ms duration.

Finally, Fig. 8 shows the action potentials created at longitudinal positions of 0cm and 1cm, when the density of the potassium channels is reduced to zero. This may illustrate the behavior of the fiber in the presence of tetraethylammonium (TEA) as the potassium channel blocker.

IV. Conclusion

An electronic laboratory was developed for students of biomedical engineering in order to improve their understanding about neural activation in response to intra and extra cellular electrical stimulation. However, it can also be used by researchers while exploring new concepts and ideas.

The program provides an easy to use graphical user interface, to help students focus on the electrophysiological concepts.

Several extracellular and intracellular electrodes are available for electrical stimulation, and the program is quite flexible in defining different stimulation patterns and waveforms. Both myelinated and unmayelinated fiber models have been implemented in the program with the ability to adjust their parameters, and the program allows for using a user-defined fiber model. These features makes this program specifically useful for engineering student, which may be interested on the mechanisms and phenomena related to electrical stimulation, nerve block, selective stimulation, and the effect of different parameters on these techniques.

We are currently working to improve the usability of the software by allowing the user to study the response of a population of fibers.

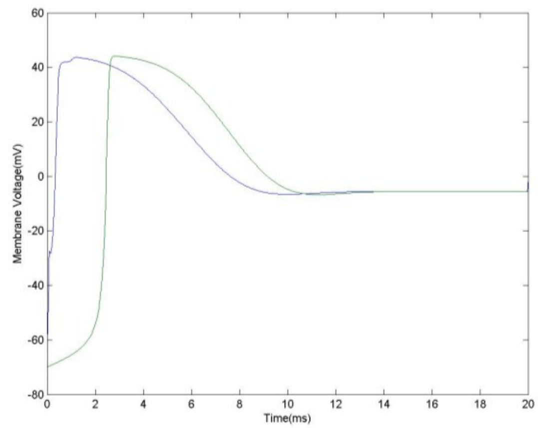

Fig. 8. Membrane potential is shown for compartments in 0 and 1cm of the fiber length in the presence of TEA that causes action potential not to be constructed.

References

[1] Wikipedia contributors. "Electrophysiology." *Wikipedia, The Free Encyclopedia*, 8 Jul. 2011. Web. 10 Sep. 2011.

[2] Wikipedia contributors. "Neural engineering." *Wikipedia, The Free Encyclopedia*. Wikipedia, The Free Encyclopedia, 28 Aug. 2011. Web. 10 Sep. 2011.

[3] D. S. Touretzky, M. V. Albert, N. D. Daw, A. Ladsariya, M. Bonakdarpour. (2008, Oct 24). HHsim: graphical Hodgkin-Huxley simulator [Online]. Available: http://www.cs.cmu.edu/~dst/HHsim.

[4] F. Bezanilla. NERVE [Online]. Available: http://nerve.bsd.uchicago.edu/nerve1.html.

[5] M. L. Hines, N. T. Carnevale, " The NEURON simulation environment," *J. Neural Comp*., vol. 9, Aug. 1997, pp. 1179-1209.

[6] J. W. Moore, A. E. Stuart. (2011). Neurons in Action [Online]. Available: http:// www.neuronsinaction.com.

[7] F. Rattay, "Analysis of models for extracellular fiber stimulation," *IEEE Trans. Biomed. Eng.*, vol. 2, July 1989, pp. 676-682.

[8] F. Rattay, M. Aberham, "Modeling axon membranes for functional electrical stimulation," *IEEE Trans. Biomed. Eng.*, vol. 40, Sep. 1993, pp. 1201-1208.

[9] M. R. Mohagheghi-Nejad, "Designing an educational software for extracellular stimulation," B.S. thesis, Dept. Biomed. Eng., University of Isfahan, Isfahan, Iran, 2011.

[10] Shampine, L. F. and M. K. Gordon, *Computer Solution of Ordinary Differential Equations: the Initial Value Problem*, SanFrancisco, W. H. Freeman, 1975.

[11] T. H. Cormen, C. E. Leiserson, R. L. Rivest, C. Stein, *Introduction to Algorithms,* 2nd ed. MIT Press, 2001, pp. 253–272.