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Heck, A.

**DOI**

[10.1088/1742-6596/1286/1/012054](https://doi.org/10.1088/1742-6596/1286/1/012054)

**Publication date**

2019

**Document Version**

Final published version

**Published in**

Journal of Physics. Conference Series

**License**

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**Citation for published version (APA):**

Heck, A. (2019). In action with action potentials. *Journal of Physics. Conference Series*, 1286, [012054]. <https://doi.org/10.1088/1742-6596/1286/1/012054>

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# In action with action potentials

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**Abstract.** The subject of bioelectricity is for many life science students the first encounter with biophysics. The transfer of knowledge on electricity from the context of physics to the context of physiology is not without difficulty. Use of computer simulations is expected to enhance the students' understanding and interest, and to promote critical and integrative thinking. This paper discusses models, simulations, and activities designed for life science students that help them come to grips with biophysical processes underlying action potentials of a single neuron through 'virtual labs'. Key models and computer simulations are presented, including their use in exploring phenomena such as firing threshold, spike train and refractory period. Experiences and opinions of biomedical students regarding the virtual labs have been collected and are discussed in this paper.

## 1. Introduction

Physics becomes more and more important in other disciplines, such as life sciences. For example, electrical concepts are needed to describe and explain electrophysiological processes in the human body. In textbooks, students come across concentration gradients, electric potential difference across a cell membrane, polarization and depolarization of the membrane, and voltage-dependent ion channels playing a central role in the generation of an action potential as a result of an electric stimulus. An analogy with electric circuits is used to explain models of cell excitation, such as the Hodgkin-Huxley model (henceforth abbreviated as HH model) of an action potential in a neuron.

Although the life science textbooks and supplemental materials contain a lot of pictures and animations of the processes taking place, many students have difficulties in

- understanding the analogy between electric circuits and neural models;
- grasping all of the required physics concepts;
- realizing how the physics-based models help them mastering the fundamentals of neurophysiology.

One reason might be that prior physics courses focussed on other contexts, irrelevant for life sciences. Another plausible reason is that a textbook with accompanying lectures alone is insufficient to mediate transfer from physics to life science. To address the students' needs, an inquiry and/or quantitative approach to study the basics of neuroscience is often promoted. Roth and Robbie [1] propose solving well-designed homework problems as lesson activities that help students learn and understand the subject matter. Authors [2-6] propose simulating neural computer models.

Various neural computer simulation tools are already available for use in education. They are

- professionally designed as hyperlinked tutorials and interactive simulations such as *Neurons in Action* [6], in which one can specify parameters to run virtual experiments;
- created and deployed by the end user with a friendly user interface. Examples are *NeuroLab* [5], *Neurophysiology Virtual Lab* [6], the Java-based *Computational Neuroscience Package* [8], *MATLAB*-based simulations [9] and this set of JavaScript-based simulations;



- set up as adaptable programs in a suitable computer language such as *MATLAB* [10] or *Python* [11].

Interaction ranges from adapting parameters only, like in *Neurons in Action* [7] to setting up and simulating neural networks via a plug-and-play interface like in *SimBrain* [12] and *Neuronify* [13].

At introductory level, many of the professional tools, especially the *GENESIS Simulation System* [14] and the *NEURON Simulation Environment* [15], overwhelm students with a lot of parameter choices, details not yet dealt with, and/or sophisticated user interfaces. The tools often do not give students easy access to simple models, because they are mainly intended for use at higher undergraduate level. The goals of the current study were to design easy-to-use graphical user interfaces of basic neural models, of which the underlying code can be inspected and changed if needed, and that are JavaScript-based so that they run anytime, anywhere, and on any device that supports web browsing.

Concrete examples of learning activities of first-year biomedical students with neural computer models are discussed in this paper. These activities introduce the students to passive electrical properties of cell membranes, active electrical responses, and the ionic basis of the action potential. The HH model is the principle model of action potential. It can be reduced (under assumptions) to a system of two state variables: the so-called Krinsky-Kokol-Rinzl model. The FitzHugh-Nagumo model and the Izhikevich model are other examples of two-variable systems that are simple and essentially behave like the HH model [see, for example 16-18]. Students can actually implement these simpler models themselves with a suitable modelling tool. We use the computer learning environment *COACH* [19] and the *Easy JavaScript Simulations* (EjsS) modelling toolkit [20] for the purpose of creating and simulating models of spiking neurons.

## 2. Materials and methods

In this section we present an overview of how first-year students in biomedical sciences are introduced to bioelectricity at the University of Amsterdam, and the digital lecture notes that include simulations of neural models and linked tasks.

### 2.1. Introducing students in biomedical sciences to bioelectricity

Two bachelor programmes at the University of Amsterdam contain courses in which bioelectricity is discussed: psychobiology and biomedical sciences. The first-year biomedical sciences students participate in the course *Human Physiology*, in which they study the function of cells, tissues and organs in the human body. One week in this 8-weeks course is spent on neurophysiology. It consists of 4 hours lectures, 9 hours e-lectures (PowerPoint presentations with spoken explanation), reading of eight chapters of the textbook *Medical Physiology* [21] and participating in a digital interactive course on bioelectricity and mathematical modelling of an excitable cell in the SOWISO computer learning environment [22], which includes randomized exercises with automated feedback. In 2017, computer simulations were implemented via the *Easy JavaScript Simulations* (EjsS) modelling toolkit [20] and added to the course. In this paper we present the first experiences with these simulations in the study year 2016-2017 with 109 freshmen (76 female / 33 male) in biomedical sciences.

The SOWISO lecture notes in neurophysiology consist of three parts: (1) basic principles of electricity; (2) an electrical model of a neuron; and (3) action potentials and the HH model. The first part gives students the opportunity to brush up basic notions of electricity from secondary school such as electric charge, electric potential energy, voltage, current, resistor, and electric circuits with parallel and sequential components. In the context of bioelectricity, important notions are capacitance, the capacitor in an electric circuit, and the charging and discharging of a capacitor. But these notions are new to the Dutch freshmen and therefore treated in the first part of the digital lecture notes in great detail. Figure 1 is a screen shot of a course page with practice tasks, which illustrates a computer generated exercise and automated feedback on responses entered by a student.

Bioelectricity: Core principles

Practising the core principles

We consider the following section of an electrical circuit

$\text{---} \parallel \text{---} \text{---} \parallel \text{---} \text{---}$   
 $C_1 \quad C_2$

It consists of two capacitors in series with  $C_1 = 12 \text{ mF}$  and  $C_2 = 36 \text{ mF}$ .  
 These can be replaced by a single capacitance  $C$ .  
 Calculate the replacement value.

$C = 12 + 36 \text{ mF}$  ✗ You mistakenly used the replacement formula for parallel capacitors.

$C = \frac{1}{\frac{1}{12} + \frac{1}{36}} \text{ mF}$  ✔ Simplify.

$C = 9 \text{ mF}$  ✔ Great

next > stop redo ? ask question

**Figure 1.** Screen shot of a SOWISO page illustrating a randomized exercise and automated feedback.

The other two parts of the digital lecture notes and student activities are described in the next two subsections. They provide a brief summary of the electrophysiology taught. The interested reader is referred to neuroscience textbooks [see, for example, 23] for further details.

## 2.2. An electrical model of a neuron

Electrical activity of a neuron is mainly driven by differences in ion concentrations in the inside and the outside of the cell, and by ion channels that penetrate the cell membrane and allow the cell to respond on electric, mechanical, or chemical signals. In this summary, only sodium ions ( $\text{Na}^+$ ) and potassium ions ( $\text{K}^+$ ) are taken into account. The extracellular medium has a high concentration of  $\text{Na}^+$  and the intracellular medium has a high concentration of  $\text{K}^+$ . When the cell is at rest, the flow of  $\text{Na}^+$  ions is not significant because the  $\text{Na}^+$  channels is closed, but the flow of  $\text{K}^+$  ions is because the  $\text{K}^+$  channels are open. However, passive ionic redistribution (due to impermeable intracellular anions attracting more  $\text{K}^+$  into the cell) and active transport by the  $\text{Na}^+$ - $\text{K}^+$  pump allow the cell to realize an equilibrium, that is, to maintain the concentration gradients of these positively charged ions.

In the lecture notes, first the situation with one cation is discussed. Two forces drive the ion species through the cell membrane: a diffusion force (due to the concentration gradient) and an electromotive force (due to accumulation of positive and negative charge on the opposite sides of the membrane so that an electric potential difference is created). In other words, the membrane becomes a charged capacitor. When an equilibrium is achieved, the value of the equilibrium potential difference with grounding on the exterior side of the membrane, the so-called Nernst equilibrium potential, depends on the ionic species and can be computed via the Nernst equation:

$$E_{\text{ion}} = \frac{RT}{zF} \ln \left( \frac{C_{\text{out}}}{C_{\text{in}}} \right) \quad (1)$$

Here  $C_{\text{in}}$  and  $C_{\text{out}}$  are the ion concentrations inside and outside the cell, respectively;  $R$  is the universal gas constant;  $T$  is the temperature;  $F$  is Faraday's constant; and  $z$  is the valence of the ion. The Nernst equation is not only important for doing computations, but it can also be used to reason qualitatively about the effects of changes in concentrations. For example, students must learn to reason with the Nernst equation and explain why an increase of the  $\text{K}^+$  concentration outside the cell leads to an increase of the membrane potential. They should also grasp the analogy between an ion channel and an electric circuit component consisting of a battery (with  $E_{\text{ion}}$  as voltage difference) and a resistor (with conductance  $g_{\text{ion}}$ ) in series.

The situation becomes more complicated when two ion species, say  $K^+$  and  $Na^+$ , come into play. Students must learn to understand that in this case the membrane potential  $V_m$  is between the Nernst potentials  $E_K$  and  $E_{Na}$ . The Goldman-Hodgkin-Katz equation can be used to compute the resting membrane potential, but the students learn most from its linearized approximation, which they can derive from basic principles for electric circuits:

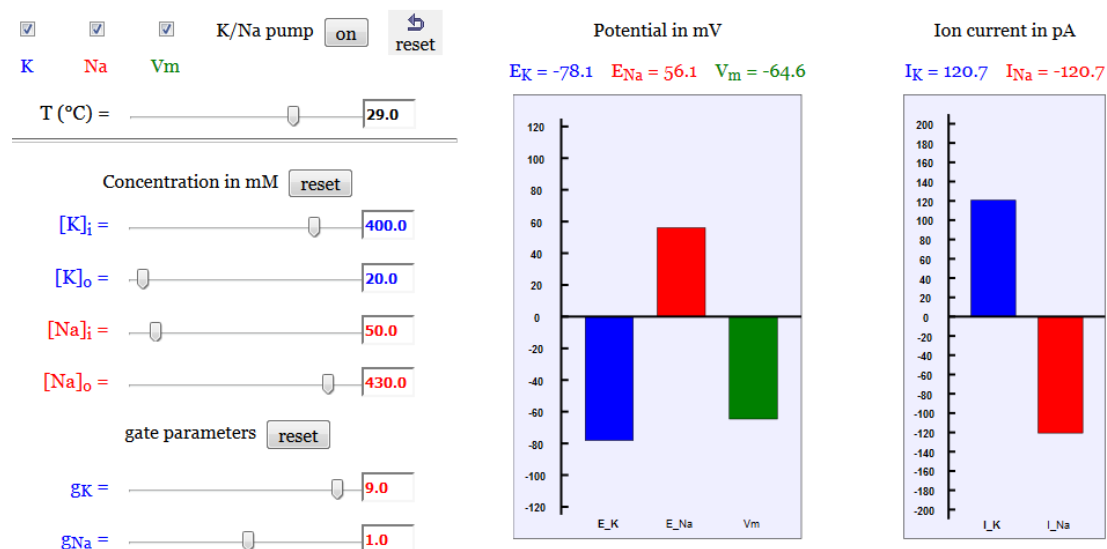
$$V_m = \frac{g_K}{g_K + g_{Na}} E_K + \frac{g_{Na}}{g_K + g_{Na}} E_{Na} \quad (2)$$

To emphasize that it is more important to understand the qualitative behaviour of the resting membrane potential upon changes in the environment, the students are provided with a simulation for exploring given scenarios. A screen shot of the simulation is shown in figure 2 and examples of accompanying questions are:

*Depolarization means that the membrane potential increases (strongly). Think up four ways to depolarize the membrane and check the methods that you propose via the simulation.*

*Repolarization means that the membrane potential decreases (strongly). Think up four ways to repolarize the membrane and check the methods that you propose via the simulation.*

*How can you change the membrane potential without changing the ion concentrations and the membrane conductance? Verify your answer via the simulation.*



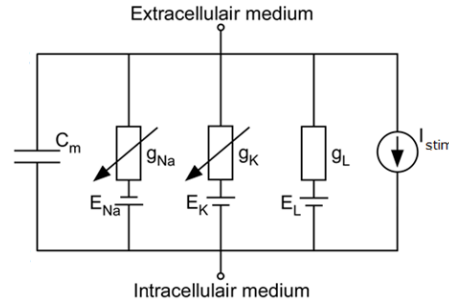
**Figure 2.** Screen shot of the *EjsS* simulation for exploring membrane potential changes when ion concentrations or conductance of ion channels are altered, or when the  $K^+$ - $Na^+$  pump is turned off.

### 2.3. Action potential and the Hodgkin-Huxley model

In the passive cell model, presented in the previous section, membrane properties are constant. But excitable cells, such as nerve cells and muscle cells, can change their potential on a time scale of milliseconds in response to stimuli. An action potential, or spike, is caused by a temporary change of the conductance of ion channels. A small stimulus is not enough to generate a spike, but when a threshold value is reached the sodium channel opens and  $Na^+$  ions enter the cell, causing the membrane potential to change rapidly from a negative to a positive value. This phase of spiking is called depolarization. It is followed by repolarization in which the membrane potential decreases toward the equilibrium potential mainly due to an increase in conductance of the potassium channels, causing more  $K^+$  ions to flow from the inside to the outside of the cell. Undershooting the resting membrane potential, called

hyperpolarization, can occur. See the time-course of the membrane potential of a neuron in Figure 4 for a typical shape of an action potential. The  $\text{Na}^+$ - $\text{K}^+$  pump is needed to restore the equilibrium concentrations of these cations. But it can be ignored initially in modelling because ion concentrations inside and outside of the cell hardly change in one spike (roughly 0.1% of the ions exchange).

Hodgkin and Huxley [24] developed a mathematical model that could explain the spiking behaviour of a squid giant axon on the basis of changes in potassium and sodium conductance. Their work is a cornerstone in mathematical modelling of neural dynamics. The equivalent electric circuit for the HH model is presented in figure 3.



**Figure 3.** Equivalent electric circuit for the Hodgkin-Huxley model.

Mathematically, this circuit diagram represents the five terms in the differential equation (3) that describes the currents involved in the behaviour of the cell membrane: from left to right, the membrane capacitance  $C_m$ , the variable sodium conductance  $g_{\text{Na}}$ , the variable potassium conductance  $g_{\text{K}}$ , the constant leakage conductance  $g_{\text{L}}$ , and the stimulus current  $I_{\text{stim}}$ .

$$C_m \frac{dV_m}{dt} + I_{\text{Na}} + I_{\text{K}} + I_{\text{L}} = I_{\text{stim}} \quad (3)$$

where

$$I_X = g_X \cdot (V_m - E_X) \quad (4)$$

for  $X = \text{Na}, \text{K},$  or  $\text{L}$ , according to Ohm's law for conductance. Hodgkin and Huxley suggested to model the voltage-dependent sodium and potassium conductance through a number of gates controlled by activation and inactivation gating particles. Pioneering experimental techniques of that time allowed them to determine that the voltage-gated  $\text{K}^+$  current has 4 activation gating particles (leading to the term  $n^4$  in equation (5) below, where  $n$  is the activation variable for  $\text{K}^+$ ) and that the voltage-gated  $\text{Na}^+$  current has three activation gating particles (with activation variable  $m$ ) and one inactivation gating particle (with inactivation variable  $h$ ; hence the term  $m^3h$  below). The equations for the sodium and potassium conductance are:

$$g_{\text{Na}} = x_{\text{Na}} \bar{g}_{\text{Na}} m^3 h \quad \text{and} \quad g_{\text{K}} = x_{\text{K}} \bar{g}_{\text{K}} n^4 \quad (5)$$

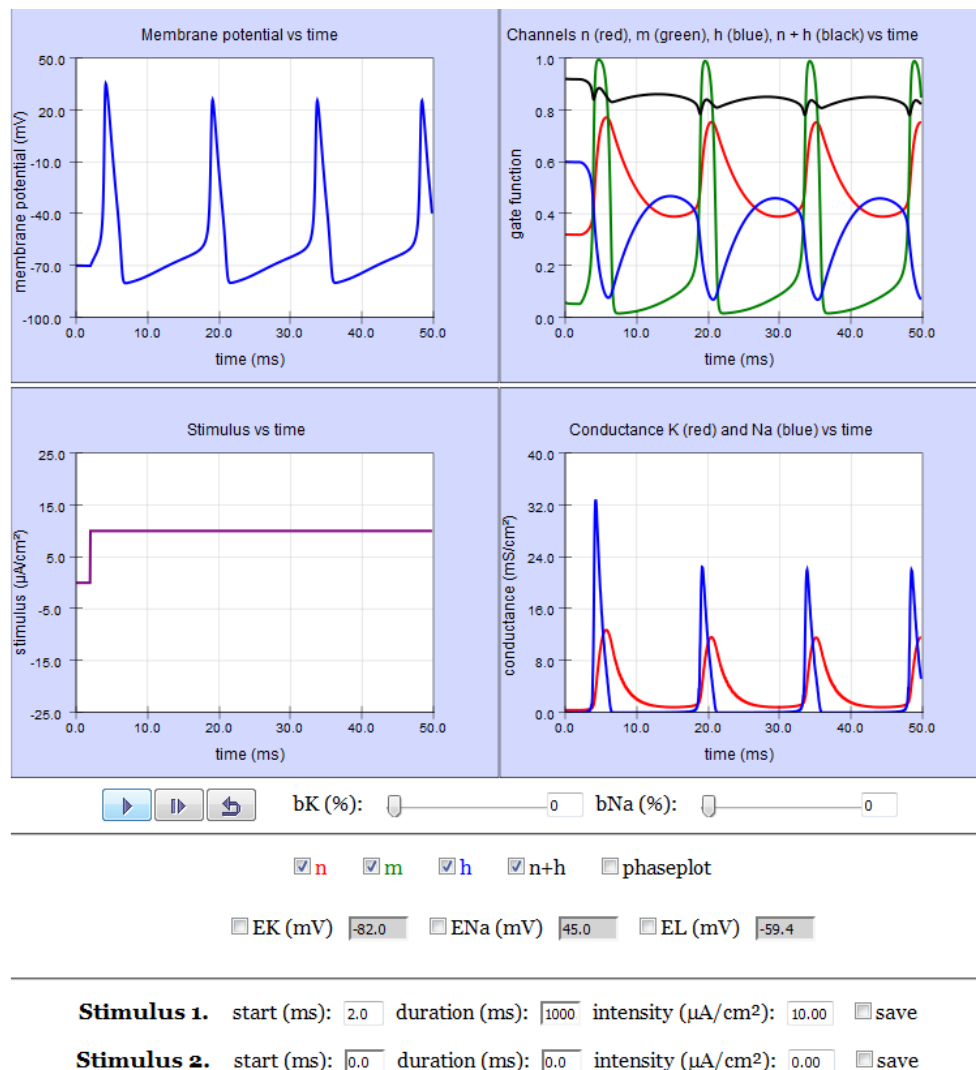
$$\frac{dm}{dt} = \alpha_m (1 - m) + \beta_m m, \quad \frac{dh}{dt} = \alpha_h (1 - h) + \beta_h h, \quad \frac{dn}{dt} = \alpha_n (1 - n) + \beta_n n$$

where the  $\alpha$ 's and  $\beta$ 's are voltage-dependent functions;  $\bar{g}_{\text{Na}}$  and  $\bar{g}_{\text{K}}$  are the maximum  $\text{Na}^+$  and  $\text{K}^+$  conductance, respectively, and  $x_{\text{ion}}$  is the fraction of non-blocked gates for a given ion species. This term is introduced here to explore the effect of drugs such as tetrodotoxin (TTX) and tetraethylammonium (TEA), which block sodium and potassium channels, respectively.

#### 2.4. Computer simulations of the Hodgkin-Huxley model

One of our goals was to explore the feasibility of using a JavaScript-based simulation of the HH model with a user-friendly graphical user interface in educational practice. For example, it was not clear upfront whether computations would not be too complex to let simulations run smoothly. The *Easy JavaScript*

*Simulations* (EjsS) modelling toolkit [20] was selected for implementing the HH model because Thomson [8] had demonstrated that well-functioning Java-based simulations of neural models could be built with it. A screen shot of a simulation of the HH model with parameter choices for the squid axon is shown in figure 4. The diagram windows display time-courses of (1) the membrane potential; (2) the stimulus, in this case a constant current injection after 2 ms; (3) the sodium and potassium conductance of; and (4) the gating variables  $n$ ,  $m$ , and  $h$ , plus the sum  $n + h$ .



**Figure 4.** *EjsS* simulation of the Hodgkin-Huxley model for the squid axon.

What students are expected to learn from this simulation is that

- an action potential is generated when the membrane potential reaches some threshold;
- the action potential is generated by ionic currents through voltage-gated channels. In particular, the generation of a spike (firing of the neuron) consists of a depolarization phase, in which the sodium conductance rapidly increases, and a repolarization phase, in which the potassium conductance increases and the sodium conductance decreases to its initial value so that the membrane potential is close to the resting level;
- the potassium conductance decreases slowly to its initial value after repolarization;
- the constant current stimulus generates an oscillatory behaviour (a spike train);
- the sum  $n + h$  is nearly constant;

- the gating variable  $m$  changes relatively fast, because its time scale is small compared to the time scales of  $n$  and  $h$  in the relevant voltage range.

The students get accompanying tasks in which they vary the current stimulus to discover that

- a sufficiently large stimulus is needed to reach the threshold for spike generation;
- a greater strength of the stimulus translates into a higher firing rate;
- there is a maximum firing rate (the main reason is that temporary inactivation of sodium channels in a cell makes it impossible to fire again for about 1 ms);
- due to hyperpolarization it is relatively difficult to initiate another spike during a certain time;
- two short stimuli must be separated in time long enough to lead to two spikes and this so-called relative refractory period can be determined quantitatively;
- a short negative stimulus, or more precisely, turning off a negative stimulus causing hyperpolarization, can also generate an action potential (the reason is that the firing threshold is not a fixed value, but is lowered because hyperpolarization removes inactivation of sodium channels and closes potassium channels that are open at rest);
- administration of channel blockers like TTX and TEA influences the shape of action potentials and may even stop the firing process;
- firing may occur even without a stimulus; for example, when one administers a potassium channel blocker and reduces the number of open  $K^+$  channel to about 65%.

The above tasks and other experiments that students can do via adjustments of parameters in the simulation of the HH model, but in particular the students' thinking and peer discussion about reasons for observed phenomena are expected to enhance the students' understanding of core neurophysiological principles behind the firing of neurons and to promote their curiosity.

### 3. Results and discussion

We asked students via an on-line questionnaire for feedback on the ease of use and the usefulness of the simulations, and on their feelings during their work with them. Ninety-five students (87% of all students in the course) filled out the questionnaire and some of them added suggestions for improvement of the graphical user interface of the simulation of HH model. Cronbach' alpha value of 0.92 indicates a very high internal consistency amongst the items of the instrument. A formal assessment of the effectiveness of the instruction has yet to be conducted.

The results of the questionnaire are comparable to opinions found in the literature (see, for example, [25]). However, the results presented in table 1 show a split of the student population into two clusters: cluster 1, consisting of 34 students having rather negative opinions about the simulations, and cluster 2, consisting of 61 students with positive opinions. The division into two clusters could just reflect that some students (cluster 1) felt the burden of having more work to do irrelevant in their eyes for the written multiple-choice exam or found the graphical user interfaces complicated and/or the tasks unclear. Others (cluster 2) were more positive and only commented on the user interface: in the version used by the students, all parameters got their default values again after a reset of the simulation. This was annoying, especially in the task to determine the refractory period. In the version shown in figure 4, save buttons have been added to optionally store new default parameter values for the current stimuli. Positive reactions are mainly about enhanced understanding and the ease of use, and they match the finding that in the exam most students could explain and apply the physics principles with regards to neurophysiology.

**Table 1.** Results from the questionnaire about the use of simulations. Items are on a 5-point Likert scale (strongly disagree-disagree-neutral-agree-strongly agree)

<i>Questions</i>	<i>Cluster 1</i>	<i>Cluster 2</i>
The simulations... made the contents more attractive	2.2 ± 1.0	3.7 ± 0.7



were easy to use	$2.4 \pm 1.0$	$3.5 \pm 1.0$
gave results that could easily be interpreted	$2.4 \pm 0.9$	$3.6 \pm 0.6$
motivated me extra for study	$1.7 \pm 0.8$	$3.0 \pm 0.8$
made me better understand the contents	$2.2 \pm 1.0$	$3.7 \pm 0.6$
increased my confidence	$1.7 \pm 0.8$	$3.1 \pm 0.7$
made the contents more difficult instead of clearer	$3.9 \pm 0.8$	$2.4 \pm 0.8$
increased my understanding of the electric model of a membrane	$2.2 \pm 0.7$	$3.6 \pm 0.7$
increased my understanding of the Hodgkin-Huxley model	$2.0 \pm 0.8$	$3.7 \pm 0.6$

Simulations of other models of action potentials of a single neuron can be created and used in a similar style. For example, the observation in the simulation outcomes of the HH model that  $n + h$  is nearly constant and that the gating variable  $m$  changes relatively fast leads to a reduction into a dynamic system of two variables, named the Krinsky-Kokol-Rinzl model. Even simpler two-dimensional dynamical systems have been developed that essentially behave like the HH model [14 -16]. Famous is the FitzHugh-Nagumo model, in which the equations contain a fast excitation variable  $V$  and a slow recovery variable  $W$ :

$$\frac{dV}{dt} = f(V) - W + I_{\text{stim}} \quad \text{and} \quad \frac{dW}{dt} = \varepsilon \cdot (V + \beta - \gamma W) \quad (6)$$

Here  $\varepsilon$  is a small parameter and  $f$  is a suitable function. Traditional choices are:

$$f(V) = V - \frac{1}{3}V^3, \quad \varepsilon = 0.08, \quad \beta = 0.7 \quad \text{and} \quad \gamma = 0.8 \quad (7)$$

Other extension possibilities for instruction are the integrate-and-fire models, mostly used for simulating neural networks. But of course they can also be applied to a single neuron. In this case, the neuron generates an action potential when the membrane potential  $V$  reaches the threshold potential  $V_{\text{thresh}}$ . Hereafter, the membrane potential is reset to its initial value, or even lower. In the model of Izhikevich [26], the subthreshold phase is modelled as follows:

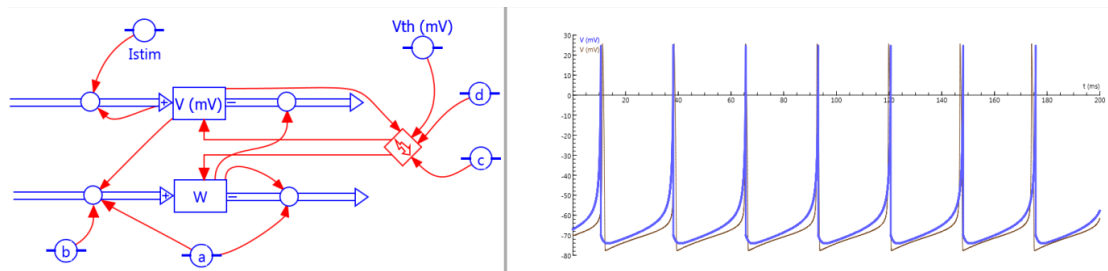
$$\frac{dV}{dt} = 0.04V^2 + 5V + 140 - W + I_{\text{stim}} \quad \text{and} \quad \frac{dW}{dt} = a \cdot (bV - W) \quad (8)$$

The parameter  $a$  describes the time scale of the recovery variable  $W$  and the parameter  $b$  describes the sensitivity of the recovery variable to the subthreshold fluctuations of the membrane potential. When the membrane potential  $V$  reaches a threshold value, say at time  $t$ , it is reset to the value  $c$  and the value of  $d$  is added to the recovery variable  $W$ :

$$V(t + \delta) \rightarrow c \quad \text{and} \quad W(t + \delta) \rightarrow W + d \quad \text{and} \quad \delta \rightarrow 0 \quad (9)$$

Izhikevich [26] showed that this model can describe various forms of neural behaviour (regular and fast spiking, intrinsically bursting and chattering) by different choices of its parameters. This opens the eyes of students for the importance of quality of neural models. By the way, all JavaScript implementations of the models presented so far run smoothly on a modern laptop computer: only one student complained about the speed of running the simulations

Alternatively, students could easily implement the Izhikevich model [26] and other two-variable models in a system dynamics based modelling tool such as *COACH* [19]. Figure 5 is a screen shot of the model and a simulation, with the spike train of the HH model graphed in the background. Such implementations are expected to enhance the students' understanding of the models and the modelling process.



**Figure 5.** COACH implementation and simulation of the Izhikevich model for the squid axon.

#### 4. Conclusions

In conclusion, our experiment supports the commonly shared expectations that simulating neural models, even simple ones, is good for:

- observing, exploring, and understanding neural phenomena via immediate feedback;
- letting textbook pictures come to life in ‘virtual labs’;
- enhancing students’ learning and practising with multiple representations;
- illustrating how computer models are used in the science field;
- preparing and engaging students toward modelling of neural networks;
- making students more enthusiastic and eager for studying challenging problems in neurophysiology.

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