Author's response to reviews

Title: Teaching and learning Hodgkin-Huxley model based on the Software development in NEURON's programming language hoc

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Author's response to reviews: see over
THE FOLLOWING ARE THE CORRECTION FOR THE REVIEWED CONCERNS:

Reviewer: Ted Carnevale

Reviewer's report:

The manuscript describes a program called SENB that the authors wrote to use as an aid in teaching neurophysiology. This reviewer did not receive a copy of SENB for evaluation and is therefore unable to comment on its speed, reliability, or efficiency.

A copy of SENB can be found at:  
http://ylang-ylang.uninorte.edu.co:8080/drupal/?q=node/565

SENB implements a model of a squid axon with a stimulating electrode (presumably a patch electrode), and a graphical user interface that allows users to study spike initiation and conduction and how these phenomena are affected by the anatomical and biophysical properties of the axon, and the stimulus parameters. The graphical user interface (GUI) includes an image of the axon with dots that indicate the location of the location of the stimulus and recording electrodes; it is not clear whether or how a user may change these locations.

Regarding the stimulating electrode:  
The correction has been made in “Tools Details” “Block 3” (page 4).

Regarding the locations of the stimulus and recording electrodes:  
The location of the electrodes cannot be changed.  
The correction has been made in “Tools Details” “Block 3” (page 4).

Like the commercial package NEURONs in Action (NIA), SENB takes advantage of the NEURON simulation environment. However, SENB differs in several ways from NIA. For one thing, SENB is much more limited in scope than NIA because it offers the user only one model (a squid axon) and can only be used for educational purposes that can be accomplished in the context of a squid axon. On the other hand, SENB wraps its entire GUI in a single window, and so may be easier for students to use than NIA, which spawns multiple windows in a way that can clutter a desktop with limited space.

We agree with this comment.

Also, the authors state that SENB is free, but they do not provide a URL from which it can be downloaded or offer to provide it upon request. The use of computational simulations in neuroscience education is not new, nor is the availability of commercial or free software for this purpose. Even so, just as there is no textbook that is perfect in all regards, there is no software package that is perfect for all teaching needs. Also, teaching is at least partly a performing art, and most teachers, like most other performing artists, are always looking for new ways to sharpen their skills and improve their performance. As long as there are students who want to learn about neuroscience, there will be teachers who want to know whether a particular software package might be useful in the classroom.
The URL for downloading the software is:
http://ylang-ylang.uninorte.edu.co:8080/drupal/?q=node/565

Correction made in “Implementation” pages 3 and 4.

Some of them might find SENB to be interesting or even useful, but before that can happen the authors of this manuscript have much work to do. The manuscript needs to be revised to improve its content, its organization and clarity, and its use of English.

Content

The manuscript contains several misstatements and factual errors.

On page 3, the third paragraph begins with a sentence that describes the programming languages that can be used in NEURON. That sentence ends with the statement that “a Python graphic interface [is] also available,” which is untrue. The sentence will also leave readers confused about what the mentioned languages are used for. A correct sentence would read something like the following (note that this example requires renumbering of the papers cited in References):

Users with programming experience can develop software with any combination of hoc (an interpreter with C-like syntax [20] and Python [21], and add new membrane properties with the compiled NMODL language [22].

As per the reviewer suggestion:

Users with programming experience can develop software with any combination of hoc (an interpreter with C-like syntax [20]) and Python [21], and add new membrane properties with the compiled NMODL language [22].

The right hand side of equations 6 and 7 produce results in units of volts, not mV.

The right hand of Equations 6 and 7 have been multiplied by 1000 in order to show the results in units of millivolts.

The right hand side of equation 9 produces results in units of square microns, not cubic microns.

Equation 9 has been fixed as per the reviewer suggestion.

In the right hand side of equation 10, the (um) item in the numerator should be deleted.

Equation 10 has been fixed as per the reviewer suggestion.

The "SECOND EXAMPLE” discussion on page 7 is just wrong, for several reasons. First, fig. 4a does not demonstrate spike propagation.
In order to demonstrate propagation, the axon must be long enough that one can distinguish active from passive spread of the spike waveform, and 50 um is way too short when the length constant is ~437 um (see figures 2 and 5).

Second, regardless of how long or short the axon might be, a response like the one shown in fig. 4b does not demonstrate failure of spike propagation.

The sharp rise of membrane potential during the stimulus current can only occur in the near vicinity of the stimulating electrode. The voltage response in 4b is simply a failure of spike initiation. Doubling or tripling the stimulus current amplitude would elicit a spike, and probably also a propagating spike (if the axon is long enough).

But it would be better for the authors to leave the stimulus current unaltered, and chop the axon into smaller compartments. By comparing the initial charging transients in 4a and 4b, one can predict that multiplying the axon’s nseg parameter by a factor of 3 would restore spike initiation. Increasing L to 1000 um, and nseg to something between 40 and 60 would allow a clear demonstration of spike propagation. The discussion of “axial dissipation of energy” is irrelevant and should be dropped. The citation of ModelDB is also irrelevant; it doesn’t even refer to a particular model, and sheds no light on what is going on.

The “SECOND EXAMPLE” has been changed and new case is presented: Test of Repetitive Spiking when a long-lasting current step of constant amplitude is injected into the axon.

Organization and clarity

The reader does not discover what SENB is until finally, in a paragraph near the bottom of page 3, the authors say what it does (the paragraph just before the Implementation section). One would have expected a clear statement of purpose in the very first paragraph on page 1. The second sentence in the first paragraph on page 1 would have been a good place to come right out and say this. In the current manuscript, this sentence begins

"This software allows changing the geometric and biophysical neuronal properties in a simple . . . "


The suggestions have been applied, and the first paragraph in page 1 has been modified.

The term "virtual models" in the first sentence in the Background section is a tautology. A model is, by definition, not the same as the original. It is already "virtual."

The word “virtual” have been removed from the Background section.

In the absence of source code, readers will gain little understanding of SENB from the list of "functional blocks" that is presented on pages 4 and 5. However, the diagram in Figure 1 adds
nothing at all to the manuscript and should be omitted, regardless of whether source code is provided or not.

Figure 1 has been removed.

Gfuga appears in equations 2-4 but is not defined.

Gfuga should be replaced by GL (specific leak conductance) in equations 2 to 4.

None of the terms in equation 8 are defined.

There was a typing error in equation 8, and $N_0\text{Est}$ should be replaced by $N_0\text{Stim}$

Page 5 contains many items that need clarification.

What is the "security button" that is mentioned in the description of figure 2?

The “security button” is described in “Block 7” page 4.

Can users change the locations of the "Measuring point" and "Stimulus point"? How?

The users cannot change the locations of the "Measuring point" and "Stimulus point".

The legend for figure 2 says "note the asterisk on the left of the calculated values" but nowhere in the paper does one find out what this asterisk is supposed to signify.

The sentence has been fixed following the suggestions:
“And the values of $fe$, $\text{Lambda}$, $\text{Tau}$, $v$, $EL$, $E\text{Na}$, $E\text{K}$, $Ac$, $Vc$ are calculated.”

The reader should not have to guess whether the graphs of Vm and ionic currents display the time courses of these variables at the location indicated by the "Measuring point."

Figure 1 has been fixed following the suggestions.

On page 6 the following items need to be fixed:

Parametros pasivos
(ej.
time o tstop
Also, what is tintp (next to last line of next to last paragraph on this page)?

On page 7:
In the legend for fig. 3 what do the authors mean by the sentence "For the same reasons . . . ". For what same reasons?

Figures 1 and 2 are mislabeled.
In the real figure 2, what are the purposes of the "RESET" and "DEFAULT PARAMETERS"
buttons?

Note that in figures 3, 4, and 5, the membrane potential does not begin at a stable resting level but instead starts to hyperpolarize from the very beginning of the simulation. This means that the model is not properly initialized. The standard HH model has a resting potential of -65 mV at 6.3 deg. C. Perhaps the authors changed one of the ionic conductance densities or ionic equilibrium potentials to a nonstandard value, or maybe some additional mechanism was also inserted into the model. A common mistake is to insert both hh and the pas mechanism; the latter has a reversal potential of -75 mV. Whatever the cause, it should be found and corrected, and new figures should be generated.

Use of English

The manuscript needs to be revised for fluency.

Discretionary Revisions, Minor Essential Revisions, and Major Compulsory Revisions:

The issues raised about Content, Organization and clarity, and Use of English are to be regarded as Major Compulsory Revisions.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
This manuscript raises no conflict of interest issues for me. Without reservation, I can answer "no" to all of the screening questions.

Reviewer: RAMON RF FAYAD

Reviewer's report:

The authors present a simple and didactic software that can be easily used as a tool to simulate some of the electric properties of a typical axon. Even though there is software available that performs this task, the authors develop an approach that is an understandable simplification of more sophisticated simulation programs, such as NEURON. In this sense, it is possible to say that the software developed can be considered if not a novelty as such, it is at least original. The manuscript describes how the software is implemented, the operating requirements and, as the authors state, that can be freely used.

A copy of SENB can be found at: http://ylang-ylang.uninorte.edu.co:8080/drupal/?q=node/565
Despite of these positive considerations, the manuscript requires both minor and major compulsory revisions. One can consider some minor revisions. Because English is not the native language of the authors, the final version approved by them must be corrected by an expert in grammar, particularly in punctuation and the label of some graphs where English and Spanish are mixed. In addition, the use of commas and dots in the numbers (parameters and results) in consideration are not only inconsistent but confusing (see equation (6), for example). The use of these symbols in Spanish and in English is different. For instance, 273,15 in Spanish is equivalent to 273+15/100 while in English it is absolutely different and it could be meaningless.

The numbers has been written using dots instead of commas. The manuscript writing has been reviewed by an expert.

Among the major and compulsory revisions, it is important to stress that it is absolutely necessary to include at least a paragraph where the starting points and the basic electrophysiological properties of the Hodgkin-Huxley axon are considered in the simulations by using the software.

A description of the Hodgkin-Huxley parameters has been included.

Even for an expert in neurophysiology it could be difficult to identify what are the authors trying to simulate with the software. It is not enough to emphasize the importance and value of computer simulations of electrophysiological phenomena. It is absolutely necessary to describe the situation one tries to simulate.

A paragraph has been included describing the scope of the software, and the aim of the examples.

In equations (1) to (10) there are symbols (Gfuga, for example) and parameters that are not explained in the text. If one knows Spanish, “Gfuga” may be means “Gleak” (making reference to the conductance in the leak currrets) but it is not described in the text. One can suppose that the numbers make reference to the universal gas constant, Faraday’s constant and Kelvin but they are not explained in the text and are written with commas as in Spanish. These are a serious omissions and shows that it is not clear what the simulation makes reference to. Maybe the authors are supposing that any reader must know and guess the ideas they have in mind and do not explain the central points in the text. It is not enough to make reference to a software that is available and that they make some generalization or simplification of it. It is absolutely necessary to describe what the software performs.

The suggestions have been taken in account and the corrections have been made in the document.

Some calculations, such as those for m3, n2 and h do not have any meaning if the equations of Hodgkin-Huxley are not described with the proper identification of each variable and the
justification that allow the inclusion of some terms in the equations.

The suggestions have been taken in account and the corrections have been made in the document.

Electrophysiology is a very wide field. The title of the manuscript is very suggestive but the case in consideration is too specific. For this reason it is suggested that the title must be limited to the phenomena that is going to be simulated.

New title:
Teaching and learning Hodgkin–Huxley model based on the Software development in NEURON's programming language hoc

The abstract sections are more or less understandable. It is recommend that a sentence similar to that of the conclusion be included in the “Background” and in the “Results”.

The suggestions have been taken in account and the corrections have been made in the document.

In the references it is recommended to be consistent in the way to cite the journals and periodic publications.

The suggestions have been taken in account and the corrections have been made in the document.

Because the implemented software can be used as an adequate tool that can improve the understanding of some properties of the Hodgkin-Huxley axon in a simple way, the authors must rewrite the manuscript. They must describe explicitly and with more detail the properties in consideration, the phenomena to be simulated, the importance and meaning of each variable. Of course, it is necessary to be clear and consistent in the to write the numbers and units to be reported. The language correction of the version must be done before the final paper be submitted for evaluation and possible publication.