

ASSESSING THE PROJECT OBJECTIVES

As mentioned in the introduction and overview, the major objectives of the *Neurons in Action Version 2: Understanding the Behavior of Normal and Abnormal Neurons* (NIA2) project were:

Specific Aim #1. To restructure, refine, and add features to the existing tutorials.

Specific Aim #2. To extend the range of NIA downward to the chatter of single channels and upward to the behavior of simple circuits.

Specific Aim #3. To add new tutorials to the original prototype.

Each objective above will be addressed separately. The individual sections contain detailed analyses of each Specific Aim's sub-goals as they were described in the NSF proposal. However, it should be noted that early in the project, feedback from users of the prototype NIA and drafts of NIA2 led the PIs to realize that the existing interface was limiting the ability of both students and instructors to work with the NIA materials. If left unmodified, it would almost certainly have created significant barriers to effectively accessing the more advanced materials being developed under the grant. To avoid having interface-related difficulties and frustrations draw focus away from the concepts being presented in the tutorials and decreasing the overall utility of NIA2, the PIs made the decision to reallocate project time and resources to create a more user-friendly interface. Thus, some of the original project objectives were not fully realized within the timeline of this grant. They have not been abandoned, just delayed in completion. After the Specific Aims are discussed in this section, we will look at student and instructor reactions to NIA2's new interface and include their suggestions for future changes in this regard.

The following assessment was based on the various data outlined in the *Data Collection Method 1: Review of project materials* section above. While we have a variety of computational science education evaluation experiences, neuroscience is not our native discipline. We have portrayed the current state of NIA2 as accurately as we possibly could within these multiple data sources and the extent of our own knowledge of neuroscience concepts.

Specific Aim #1. To restructure, refine, and add features to the existing tutorials. Within the *Detailed Project Plan* section of the NSF proposal, this objective was broken down into eight different sub-goals. We will begin with the current status of these sub-goals and then extend beyond to work done in the project that was not explicitly mentioned in the proposal.

- (a) **Restructuring**: Below we have given the list of the proposed tutorials (Figure 1) as they are listed in the NSF proposal and the current tutorials (Figure 2) as they are listed in the *Tutorials* section of the NIA2 CD. Specific discussions of revised and new tutorials are included in subsequent sub-goal sections.

| |
|---|
| <p><u>Basic Level</u></p> <ul style="list-style-type: none"> • Patch: Signals That Don't Move <ul style="list-style-type: none"> ○ The Membrane Tutorial ○ Patch Resting Potential Tutorial ○ *Patch Chattering Ion Channels Tutorial ○ Patch Na Action Potential Tutorial ○ *Patch Ca Action Potential Tutorial ○ *Patch Neuromuscular Junction Tutorial ○ *Patch Neuron-Neuron Synapse Tutorial • Axons: Signals That Move <ul style="list-style-type: none"> ○ Passive Axon Tutorial ○ Unmyelinated Axon Tutorial ○ Myelinated Axon Tutorial ○ Partial Demyelination Tutorial ○ *Extracellular Stimulating and Recording <p><u>Advanced Level</u></p> <ul style="list-style-type: none"> • Patch: <ul style="list-style-type: none"> ○ Patch Voltage Clamp Tutorial ○ *Interpreting Voltage Clamp Results Tutorial: Don't be Misled! ○ Patch Threshold Tutorial: To Fire or Not to Fire? ○ Patch Refractoriness Tutorial: How Fast Can a Neuron Fire? ○ Patch Postsynaptic Interactions Tutorial: What Happens When Inputs Coincide? • Axons <ul style="list-style-type: none"> ○ Axon Diameter Change Tutorial: Easy and Difficult Paths for the Traveling Spike ○ Non-Uniform Channel Density Tutorial: How Do Anesthetics Block Nerves? • Cells <ul style="list-style-type: none"> ○ Site of Impulse Initiation Tutorial: The Motoneuron ○ Synaptic Integration Tutorial: A Motoneuron with Passive Dendrites ○ Presynaptic Terminal Tutorial: Invasion of the Action Potential • Networks <ul style="list-style-type: none"> ○ *Temporal Resolution Tutorial: Detecting Coincident Inputs with Precision <p><u>Specialized Level</u></p> <ul style="list-style-type: none"> ○ *Ca dynamics ○ *Active Dendrites ○ *Oscillations |
|---|

Figure 1: Planned Tutorials as Stated in NSF Proposal

| <u>BASIC Level Tutorials</u> | <u>ADVANCED Level Tutorials</u> |
|---|--|
| <p><u>Patch: Stationary Signals</u></p> <p>Introduction to Neurons in Action The Membrane Tutorial Equilibrium Potentials The Na Action Potential Threshold: To Fire or Not to Fire Voltage Clamping a Patch Chattering Ion Channels The Ca Action Potential The Neuromuscular Junction Postsynaptic Inhibition Interactions of Synaptic Potentials</p> <p><u>Axons: Signals That Move</u></p> <p>The Passive Axon The Unmyelinated Axon The Myelinated Axon Partial Demyelination</p> | <p><u>Patch: Stationary Signals</u></p> <p>Extracellular Ca Sensitivity of the Na Channel A Dynamical View of Threshold Na and K Channel Kinetics</p> <p><u>Axons: Signals That Navigate</u></p> <p>Axon Diameter Change Non-uniform Channel Density</p> <p><u>Cells</u></p> <p>Site of Impulse Initiation Synaptic Integration Impulse Invasion of the Presynaptic Terminal Coincidence Detection "Voltage Clamping" Intact Cells</p> |

Figure 2: NIA2 Current Tutorials

In the matrix below (Figure 3), the Restructuring sub-goals are listed in left column and the current status of each of those sub-goals is discussed in the right column.

| NSF Proposal Restructuring Sub-Goals | Current Status of Those Sub-Goals |
|--|---|
| <i>In the proposed new structure, the NIA1 tutorials will be grouped into Basic and Advanced categories, and a Specialized category will be added.</i> | As is illustrated in Figure 2 above, there are currently only BASIC Level and ADVANCED Level Tutorials. |
| <i>All of the NIA1 tutorials will be updated with respect to references and hyperlinked material ...</i> | In the current version of NIA2, hyperlinked materials include reference papers, reference to various textbook treatments of a particular concept, further explanations of processes, answers to conceptual understanding questions posed by authors within the tutorial, reference to related ideas in other tutorials, equations, and definitions. |
| <i>In the Advanced level, descriptive subtitles have been added to the terse terminology of NIA1 so that the naive student might know the substance of the tutorial.</i> | The descriptive subtitles have been removed from all the tutorials in the main List page of tutorials on the CD. However, there is a link off this List page to Goals (see APPENDIX A). This page gives the user a rich description of the substance of each tutorial. |

Figure 3: Current Status of Proposed Restructuring Sub-Goals

As we can see above, the authors did not include the Specialized category in NIA2. However, this is one of the parts of the project that was put on temporary hold in order to create NIA2’s new interface. This new interface helped the PIs fully realize the restructuring of the existing tutorials and create a more conducive environment for the user to explore neurobiology concepts. We will discuss this project “detour” in detail at the end of the Specific Aim #1 section.

The other two restructuring objectives, hyperlinked materials and descriptions of the tutorial goals, have been met and have been of great value to the education community. We actually used both of these ourselves during the course of the project evaluation. The detailed descriptions in the Goals sections helped us easily locate specific information that was mentioned in the evaluation interviews. We also know that various instructors used these descriptions to think about project ideas for students outside of the tutorials covered in the classroom. It will be a valuable asset to instructors in the future.

The hyperlinked materials provided us with great resources while we attended the NIA2 “crash course” at Woods Hole. It was easy to quickly look up definitions, explanations of equations, referenced papers, and detailed discussions of what we were seeing in the tutorials. These extra materials truly aided us in getting a better understanding of the project’s content. During our site visits, we saw students using the hyperlinked materials as a regular part of the doing the tutorials. In particular,

students were interested in the authors' in-depth discussions of electrophysiological mechanisms behind what they were observing in the graphs. We observed students taking notes by hand, taking pictures with their cell phones, or doing screen captures of these materials so they could study them at home.

From other sources of data, including surveys of graduate students, undergraduate students, and instructors, we found that the linked materials were very popular and helpful. One instructor was very pleased with these updates in NIA2. He said, "...the expanded explanations throughout the tutorials make it much more user friendly. NIA1.5 assumed a lot of insight and grasp of what was going on. Perhaps graduate students could pick up on it. In contrast, NIA2 has filled in a lot of that assumed knowledge; necessary transitions that were not present in NIA1.5 are present in NIA2." We also surveyed several students in a variety of educational contexts. We had 68 respondents, of which approximately two-thirds were graduate students. Some students did not answer all of the questions on the survey. In each of their respective educational contexts, 92% or more of the students responding said that used the linked materials within NIA2. One student said, "The links helped very much. Often I felt like I understood until I realized I didn't! The links were helpful with this." Another student said, "They were VERY helpful. That is what, in my opinion, makes NIA2 so great. I have taken a course on these materials but the linked material took it further, as well as I was happy to be able to "see it happening" instead of just seeing and interpreting some combined graphs on a textbook."

Although helpful, one or two students struggled with understanding these materials. For example, one student said, "They answered questions that I had a hard time answering but the answers weren't always satisfactory and sometimes started at a higher level of explanation than I could comprehend." Such an observation seems reasonable. As pointed out in the introduction to this report, neurobiological concepts are complex, specifically those related to electrophysiology. From our own experiences as neurobiology novices, we know that students often need repeated exposure to these concepts. If they were being introduced to these ideas for the first time via NIA2, it may indeed seem quite overwhelming.

Overall, students really liked these added resources. Almost every student had a comment in that regard. Here are some of the student comments about the linked materials in general:

- *It was a lot of new definitions for me so I found it very useful.*
- *Very useful, especially for beginners to electrophysiology.*
- *Very helpful in explaining things that weren't clear in the main text.*
- *I was not familiar with many of the terms so I was able to look things up in one location.*
- *The links were helpful in explaining things I didn't already know. Also, I liked the links to previous research that related to the experiment we were doing.*
- *I used these often to clarify concepts.*

- *If for any reason I got stuck on a tutorial or aspects that may be unclear, I could easily reference link materials.*
- *Very helpful and good to reinforce the concepts illustrated in the book.*
- *Definitions were helpful but I would add disinhibition to the program list even though it is in the text.*
- *Very helpful, help give background and also explained the more difficult concepts, the equation reminders were also helpful.*
- *I used these because when doing a simulation the links couldn't be seen because they were covered, but by using the book I knew what examples I could reference.*
- *They were very helpful in increasing my understanding of the subject matter. They made what I was seeing in the simulation understandable.*
- *Its just nice to have a historical perspective*
- *Yes, they helped sooo much! If it weren't for those links, I would have been lost.*
- *These were probably more essential to me than the dropdown menus as they provided direct access to the reference material that clarified the points being made. I almost always used the embedded links as they provided concise information that was quite relevant in terms of the concept or answer being sought. Again this has to do with my level of knowledge being very thin in terms of neurophysiology.*
- *The explanations to what was observed in graphics were helpful. They thoroughly explained tough and hard to graph concepts.*
- *I always did. It is great these links exist to provide the user even further information that may not become so obvious as one runs the simulation.*

In most contexts, approximately a half or more of the responding students used links to the pdf papers referenced in the tutorials (one group reported only 27% who used the linked paper). When students did not use the pdf papers, it seemed to be due to lack of time rather than lack of interest. However, students said these papers were “very helpful in understanding the motivation and rationale used to devise the experiments”, “useful for reading up on original resources for lab reports” and that they “helped convey how novel these findings and intuitive leaps were”. Students particularly enjoyed comparing their findings from the tutorial simulations to those found in the experiments referenced in the pdf papers.

- (b) Explaining the equivalent circuit: The PIs planned to take an interactive graphic that “allows the student to click on each circuit element and see the current flowing through that element during the action potential” from an Appendix and put it (or associated diagrams from it) into *The Membrane, Passive Axon, Unmyelinated Axon, and Myelinated Axon Tutorials*. The PIs included a link to a PowerPoint presentation (<http://neuronsinaction.com> under Suggestions for Faculty: Review Sessions) that illustrated the various graphics they wanted to include in NIA2. When comparing the diagrams illustrated in the PowerPoint presentation to those that are in NIA2, we found that the authors were able to incorporate several equivalent circuit diagrams (pp.10, 12, and 13) into *The Membrane* tutorial. These diagrams do seem to help illustrate the process concepts discussed in the tutorial. We did not find any equivalent circuit diagrams in any of the Basic “Axons” Tutorials proper (see current

Basic Tutorials in Figure 2). However, there is a specific link to *Interactive Equivalent Circuit* in the Reference section in the left hand column flanking *each* tutorial page (see Figure 4 below). The diagram accessed by clicking on this link truly is interactive, with associated linked graphs and text explanations of the processes related to membrane capacitance and Na, and K currents (see Figure 5 below).

Neurons in Action : Tutorials Patch... Axons... Cells... History... Equations...

« NIA2 Homepage
« Tutorials List

Current Tutorial

The Passive Axon

- Introduction
- Goals
- Start the Simulation
- Panels & Graphs
- ▼ Experiments...
 - Observe V_m vs time at 4 locations
 - Observe voltage vs space
 - Measure length constant
 - Length constant and R_m
 - Length constant and diameter
 - Length constant and C_m
 - Move the stimulating electrode

Reference

- What is ...
- Interactive Equivalent Circuit
- PDFs of Original Papers

The Passive Axon

How Voltages Spread in Axons Without Voltage-Sensitive Channels

How far do voltages spread without an action potential?

From the experiments in this tutorial on the passive decay of a voltage along an axon illustrated in the diagram below, you will be able to appreciate the necessity for a mechanism to enhance the voltage spread. Nature discovered voltage-sensitive ion channels and with them was able not only to enhance voltage spread but to generate a signal, the action potential, whose shape and amplitude are maintained with high integrity. This integrity will be clear in the next tutorial on propagation in a uniform unmyelinated axon ([Unmyelinated Axon Tutorial](#)).

10 mm
Diam = 10 μm

Are there types of neurons in which voltages spread only passively, without action potentials?

Yes. Two examples in the human body are the rod and cone photoreceptors of the retina, and hair cells—the sensory receptors of the inner ear. These sensory cells are so short that action potentials are not needed to get signals from one end to the other.

Goals of this Tutorial

- To observe the passive spread of a voltage change along an axon in response to injected current
- To measure the "length constant" of the axon

Figure 4: Interactive Equivalent Circuit Link in Axon Tutorials Reference Section

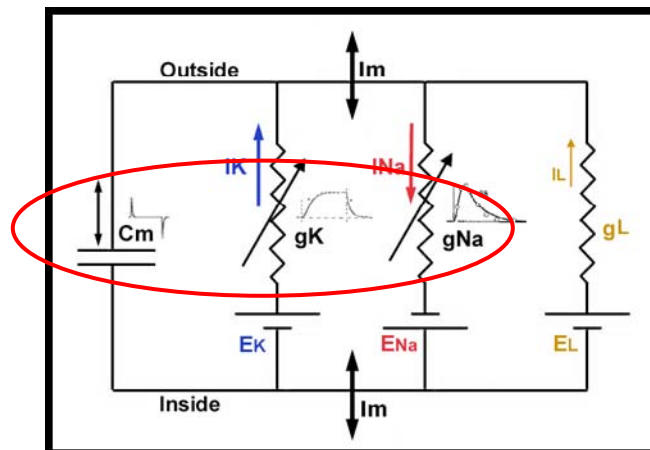


Figure 5: Equivalent Circuit Diagram with Links to Associated Graphs for Membrane Capacitance, Na, and K Currents

- (c) Adding new channel types: According to the NSF proposal, advances in NEURON made it possible to add other channels into NIA2 tutorials. It went on to state that “Adding Ca channels will be a high priority...” The table below (Figure 6) shows the different plans the PIs had for new channel types and the progress made to date.

| NSF Proposal New Channel Sub-Goals | Current Status of Those Sub-Goals |
|--|--|
| <i>(W)e will add a Ca channel (with its ECa) to the Patch Resting Potential Tutorial</i> | The <i>Patch Resting Potential Tutorial</i> from NIA1 was replaced by the <i>Equilibrium Potentials</i> tutorial in NIA2. However, it still only looks at K and Na within this tutorial. To our knowledge, ECa was not included in any of the tutorials. |
| <i>A new tutorial, the Ca Action Potential, will be created...</i> | This new tutorial has been added and does seem to address all the goals set forth by the NSF proposal. A description of <i>the Ca Action Potential</i> tutorial goals can be found in Appendix A. |
| <i>We will also consider giving the student the option of inserting additional channels, in particular a Ca-activated K channel.</i> | To our knowledge, this has not been included in the current version of NIA2. |

Figure 6: Current Status of Proposed New Channel Sub-Goals

- (d) Relating NIA to health and physiology. NIA1 already had tutorials that illustrated how various neurobiological processes underlie our own health (i.e., Myasthenia Gravis and reactions to toxins and anesthesia). The NSF proposal outlined plans for including other health-related topics. The instructors we interviewed seemed to really like the idea of more applications of this kind. In fact, one instructor said that NIA2's strength lies in its real-world examples. The instructor went on to say that kids really "lock in" on these situations. It seems that 18 and 19 year-olds often tend only to care about themselves, and currents are very far removed from what students typically think about. We will investigate this further when we discuss our case studies at the end of the report.

Appendix A lists all goals of the tutorials within NIA2. A quick look at these goals allows the reader to see that NIA2 relates several of the concepts explored to health and physiology. Many of these ideas were specifically mentioned in the NSF proposal. A few of the new health-related or physiology ideas presented are

- mimicking the basic structure of the cardiac action potential (*The Ca Action Potential* tutorial),
- investigating the responses of a muscle fiber to acetylcholine (Ach) (*The Neuromuscular Junction* tutorial),
- mimicking the affect of toxins (TTX, maculotoxin, brevetoxin, BTX) on Na Channel kinetics (*Na and K Channel Kinetics* tutorial),
- exploring the impact of mutations in certain Na channel subtypes on membrane excitability, which could lead to diseases like epilepsy. (*Na and K Channel Kinetics* tutorial),
- exploring the impact of neuron hyperexcitability on pain. (*Na and K Channel Kinetics* tutorial),

- seeing how the sensitivity of the Na channel to Ca affects Na currents, an underlying factor of clinical problems due to hypercalcemia and hypocalcemia (*Extracellular Ca Sensitivity of the Na Channel* tutorial), and
- understanding how small the “coincidence detection windows” are in the auditory system and how this impacts how we hear (*Coincidence Detection* tutorial).

(e) Taking advantage of increased computer speed. In the proposal, the PIs stated,

In NIA1, the effective length of the axons in the various tutorials was limited by computer speeds. With current greatly increased speeds, we will be able, where appropriate in NIA2, to make the axons of the tutorials longer in order to reveal more clearly the movement of the action potential and, in motoneurons, the point of initiation of the action potential. The dendrites of the motoneurons in the Advanced tutorials will also be made longer so that there are more experimental possibilities in the dendritic locations of the synapses.

While no evidence was found that referred to axon length by specifically by name, according to NEURON developer Michael Hines, who collaborated extensively with John Moore, this likely refers in part to extensive work that was done on NEURON in 2008. The revisions were related to “high speed cache efficiency in the context of multithreaded simulations on multicore machines. This had a great impact on serial simulations as well. The [simulation] speed often doubled and certain large models went 10 times faster.” He also noted that the code to implement future tutorial simulations could also be revised to optimize speed. Discussion between NEURON developer Michael Hines and PI John Stuart noted that parallel simulation of large single neurons will probably never be effective on more than 16 processors.

Other examples of NEURON or tutorial-code issues related to speed and efficiency on various levels of computer technology that were addressed by Michael Hines in conjunction with John Moore include

- Adjusting parameters for a transmitter release model.
- Adjust the presentation of a MovieRun to optimize efficiency.
- Discover and remedy an issue in which Mac OS X 10.5 terminal windows stay open after a “Quit” was requested.
- Remaking the nrmmech.dll shared library when upgrading to more recent NEURON.
- Developed strategies to organize the shared objects for Mac, mswin, Linux, address the fact that some Macs are i686 and older ones are PowerPC.
- Changed a mod file so that a shift in rate parameters could be carried out at the user level via a single parameter. (This particular revision required some mathematical analysis.)
- Fixed a problem with NIA on Vista 64 that required more recent version of NEURON that handles the "rebase" problem on Windows.

- Discovered and adjusted the distributions required by older Mac OS X 10.2 and 10.3 versions.
- Addressed a problem with out-of-date xcode installation.
- Discussed that the "Plot what" graph menu item could help select the variable that shows what is happening in the middle of the axon and that developers could use the CellBuilder to define a distribution of dendrites with different lengths and diameters.
- Collaborated extensively on a model that used particularly advanced NEURON idioms to accomplish tutorial goals (i.e., the simulations of the Chandler voltage clamp experiment which demonstrated why the measured voltage of an action potential could be more depolarized than the sodium reversal potential).

Information about the latest developments in NEURON and related discussions can be found at <http://www.neuron.yale.edu/neuron/>.

- (f) Leading students to understand the limits of the voltage clamp technique. The PIs planned to create a new tutorial from information buried in an Appendix of NIA1. This new tutorial, entitled "*Voltage Clamping Intact Cells*", has been included in NIA2 which "reveals the problems of interpreting voltage-clamp or patch-clamp currents when an axon, the dendrites, or the series resistance of the electrode complicate the observations -- common problems when clamping cells in vivo, in slices, or in culture." The voltage clamp technique limitations information is still included as a link in the *Voltage Clamping a Patch* tutorial (see Figure 7 below).

Learn about the limitations of the voltage clamp.

At this point you might want to read the section on [limitations](#) of the voltage clamp technique, caused by the "series resistance" through which the current must flow. In this linked section, [ideal](#), [typical](#), and [out-of-control](#) clamps are illustrated and discussed. In addition, the tutorial on [Voltage Clamping Cells](#) allows you to experiment with series resistance in the electrode and within an intact cell (rather than a patch).

Figure 7: Link to Voltage Clamp Technique Materials within the Voltage Clamping a Patch Tutorial

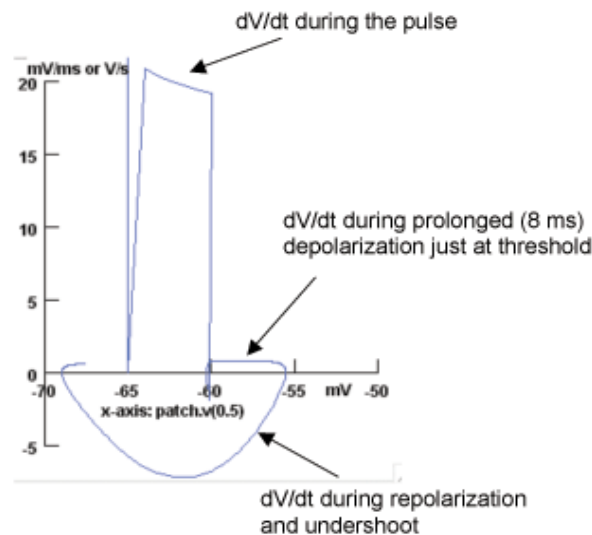
- (g) Major changes to existing threshold and synapse tutorials. There were three major changes to existing NIA1 tutorials that were proposed in this section of the NSF proposal. First, the PIs made plans to change the *Patch Threshold* Tutorial in NIA1.

The Patch Threshold Tutorial at present focuses on leading students to realize that "threshold" cannot be defined as a particular value of membrane voltage (in contrast to the general notion from textbooks) but the new version will also stress the concept of the rate of change of the voltage as the essential feature in bringing a neuron to threshold. A phase

plane graphic window will be added to the tutorial, with the phase plane concept developed in a stepwise fashion so as not to be intimidating.

The *Patch Threshold* tutorial no longer exists in NIA2. Appendix A shows that there are two updated *threshold* tutorials. A Basic-level tutorial, *Threshold: To Fire or Not to Fire*, introduces the concept of *threshold* and a new tutorial entitled *A Dynamical View of Threshold: The Rate of Change of the Voltage Determines Firing* now resides in the Advanced section of NIA2. This Advanced tutorial includes the investigations with the phase plane graph, which plots the derivative of the Voltage (dV/dt in mV/ms) over Voltage (mv) (see Figure 8 below).

- o Click the "dV/dt-vs-V, Medium Resolution" button to see the events in more detail. When you run the simulation, you will now see that during the pulse the dV/dt is actually slowly-declining (from 24.3 to 22.2 mV/ms) as the voltage rises. [Why is this?](#)



At the end of the pulse, dV/dt drops to a nearly steady level of about 0.95 mV/ms as the voltage creeps steadily from -60 mV to -56 mV. When the membrane repolarizes, dV/dt becomes negative. Just before the trace ends (at 12 ms on the Voltage-vs-Time plot), the slope once again becomes positive.

Figure 8: Phase Plane Plot Investigation in NIA2 Dynamic View of Threshold Tutorial

From our observations, this is a very novel concept for students at all levels. Most students are used to looking at function graphs. They rarely have opportunities to investigate continuous quantities that are *not* functions in a graphical context. Also, thinking in terms of “rates of change”, while gaining more attention in K-12 and undergraduate education, is still a more advanced level of mathematical thinking. Finally, within most students’ calculus courses, they mostly experience graphs of derivatives over *time*. Here, we see a rate (dV/dt) graphed with respect *voltage*. So, for most users, this sort of plot is a challenge to understand at first. However, it does

provide a different perspective and new insights into understanding the concept of “threshold”.

The second change mentioned in the NSF proposal dealt with the *Patch Postsynaptic Potential* tutorial.

The existing Patch Postsynaptic Potential Tutorial (inappropriately in Level 3 in NIA1) will be divided into a Neuromuscular Junction Tutorial and a Nerve-Nerve Synapse Tutorial so that inhibitory synapses can be treated separately from the neuromuscular junction; both will be moved to the Basic level. Making two synaptic transmission tutorials will permit more experiments to be introduced into each one.

This tutorial has indeed been divided into two different parts. One is the *Neuromuscular Junction* tutorial; however, the other part is now called the *Postsynaptic Inhibition* tutorial. Both of these can be found in the Basic Level tutorials listed in Appendix A. We have had an opportunity to observe students working with both of these tutorials. These observations will be discussed later in the report.

The final change outlined in this section of the proposal was

The Postsynaptic Interactions Tutorial will add a section focused on the detection of coincidence of presynaptic inputs by a postsynaptic cell, and prepare the student for the Simple Networks Tutorial.

As one can see in Appendix A, the *Postsynaptic Interactions* tutorial is no longer in the Basic Tutorials. In its place, we find the *Interactions of Synaptic Potentials* tutorial, which focuses on interactions of excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potential (IPSPs) over time. Students are led to investigate intervals between two interacting subthreshold EPSPs that lead to the second EPSP firing an impulse. This look into interactions of inputs does set the stage for the *Coincidence Detection* tutorial later in the Advanced section.

- (h) Minimovies for faculty to introduce the tutorials to students. NIA2 includes a minimovies link. The minimovies are subdivided into three areas: action potential, axons and synapses. Appendix B shows the list of minimovies available for all three areas. We saw PI Ann Stuart use a minimovie at Woods Hole. They seem to quickly illustrate ideas to the viewer in a dynamic manner. The reactions from instructors were generally positive. From the Initial NIA2 Survey, we found that four out of ten instructors who responded had used the minimovies in class. Here is a break down of usage by movie:

- Increasing Stimulus Amplitude – 2
- Very Near Threshold Stimuli – 2
- Changing External Na Concentration – 3

- Blocking the K Channels – 1
- Ion Conductances Underlying the Action Potential – 3
- Blocking the K Channels: View the Conductances – 2
- Effects of Cooling – 2
- Passive Spread of a Depolarizing Stimulus – 4
- AP Traveling in a 500 μm diam Unmyelinated Axon – 4
- AP Traveling in a 50 μm diam Unmyelinated Axon – 4
- AP Traveling in a Myelinated Axon – 4
- AP Traveling in an Axon with 5 Myelin Wraps – 1
- AP Traveling in a Partially Demyelinated Axon – 2
- AP Initiation in a Motoneuron – 0
- Synaptic Integration – 1
- Postsynaptic Responses to Ach – 0
- Saturation of Ach Response – 0
- Reversal of Ach Response – 1
- IPSP Reversing at Resting Potential – 2.

The movies that were used the most dealt with the Unmyelinated Axon. This does not surprise us. We have heard more about this topic from instructors than almost any other illustrated in NIA2. A detailed discussion of why this has happened can be found in the Project Impact section below.

Only one instructor did not like the format of the minimovies and said, “if they could be more "on line" like and oscilloscope it would be great.” However, others found that the minimovies were particularly good to use when the instructor needed a quick illustration for a lecture or did not have time or room within the course’s existing structure for students to use NIA2 on their own. Most felt they would continue using the minimovies in the future. One instructor wanted more and suggested, “I think more modules with movies about what's happening at the synapse, or within the neuron showing the actual flux of the ions would be useful in conjunction with the 'movies' showing the progression of the current flow and voltage change.”

We received an email from an instructor who just started using the minimovies during the past academic year. The comments were so interesting that we decided to include them all in this report:

The movies worked extraordinarily well in my class of honor's biology undergraduates. For 26 years I have struggled to teach electrophysiology to undergraduates who have a wonderful background in chemistry but a lousy background in physics. Their imaginations are much more quickly captured by dynamic voltage traces, by dynamic representations of the conduction of action potentials.

A few years ago I began to use NIA 1 which was in some ways good but for others it was overwhelming even when I was setting the parameters in front of

the class. One gal told me it had "too many buttons." For me, too, it was a bit cumbersome. One tends to be very busy while lecturing, figuring out what to say next, whether to write on the board or show a slide etc.. Then I had to get all the parameters to show what I wanted to illustrate. I had the students use the simulations but as this was only a 1.5 week part of the course, I could not ask the students to buy NIA. We bought five copies and had students play with NIA during a Discussion section. This short period was not long enough for students to use the program comfortably.

This year I used the movies in lecture. I had students sit in their groups and either showed a movie and asked them to explain what was happening or I asked them to predict what would happen and then showed the movie. The fact that there were no buttons on the screen made it easier for students not to get distracted and for me it was a snap. EVERYONE had fun.

The pedagogical considerations that lead this instructor to this point are worth considering when thinking about future directions for NIA2 and its place in neuroscience education. We applaud the PIs for considering the needs of instructors and making these concepts available in different formats (like the minimovies), so that they can be tailored to fit within different course constraints. We feel that more people need to be made aware of the flexibility of NIA2. Perhaps a venue can be found where instructors can share ideas face to face.

When we began discussion Specific Aim #1 above, we mentioned that the PIs took an unexpected project “detour” because they realized there was a need for changing NIA1’s interface. We followed this detour with the project evaluation. The next section discusses this belated addition to the goal ***To restructure, refine, and add features to the existing tutorials.*** It also assimilates other tutorial-related issues and user ‘wish-list’ ideas we have gathered from all our data sources.

- (i) Project “Detour” – Restructuring the Interface and Other Tutorial-related Issues. As discussed in Ann Stuarts’s 2006 progress report, the first year of the project was devoted to developing the new NIA2 infrastructure to facilitate both use and dissemination. This included the file structure, user interface, and downloading/installation. Significant progress has indeed been made from the prototype NIA1. At the same time, there are some additional issues and a “wish list” of features that users would like to see added

One global change from NIA1 to NIA2 was a switch from an outdated HTML standard to XML, which allows for greater flexibility in content presentation and manipulation. Also, Firefox was chosen to be the browser interface through which all tutorials and simulations would be viewed, because it was free and customizable. However, since that initial decision, Firefox has become a popular general-use browser. This evolution led to some compatibility issues between NIA2 and some users’ established browser preferences and time had to be spent developing a new installer. Furthermore, the installer for Windows presented challenges that required

the assistance of a few programmers to solve. The “NIA Firefox” in the newest version of the program is self-contained and will not interfere with other browsers. Further adjustments were also required for Windows Vista compatibility. This resource investment resulted in the ability to run NIA2 “out of the box” on both Windows and Mac machines. Windows Vista and Firefox patches for older versions of NIA2, as well as a timeline and other pertinent comments or corrections are available online on the NIA2 web site (www.neuronsinaction.com).

Some specific technical changes in NIA2 and their relative advantages are as follows.

- NIA2 adopted a standardized file structure as compared to the somewhat haphazard structure of the prototype. All files were moved and re-linked, which also clarified both the storage of files and which author would have primary domain. Future additions or changes to NIA2 will be quicker and smoother due to this structure.
- The switch to XML versus HTML allows automatic generation of the tutorial outlines, Table of Contents, and so on. It is also flexible for globally modifying the presentation of materials to the user.
- The use of modern HTML code and cascading style sheets (CSS) for supporting files, along with a general clean-up and update, allows for quicker changes in content and formatting. In the prototype, formatting changes were very difficult – page-by-page, versus the global fixes that can be implemented with CSS.
- The development and use of automated scripts during the evolution of NIA2 facilitated rapid, daily updating of NIA2 so that testers and publishers always had the very latest version of the materials.
- The revision of the user interface included, among other things, the outline that appears at the left of each screen and the quick links at the top. The overall goals were to: (1) make it clear to the user exactly where they were in NIA2 at any given time; and (2) create obvious links to materials and other places they might like or need to go.

Currently, further steps are being taken to simplify the XML schema even further, again with the purpose of making future tutorials quicker to develop within the existing framework. Version control is another step that is being taken to facilitate development. A program called Subversion (an open-source version control software package) is used to maintain both current and historical versions of files such as source code, web pages, and documentation. This is particularly useful in a project with multiple authors creating and revising materials.

In addition to the patches and an outline of the various development versions, the NIA2 web site has an author blog that reports how some instructors are using NIA2, links to publications about NIA2, an outline of CD contents, promotional videos, information about Neuron and its creator, information about the NIA2 authors, suggestions for classroom use of NIA2 with different types of student populations, and user endorsements. Users can view the text of four of the tutorials: *The*

Membrane Tutorial, Chattering Channels, Partial Demyelination, and Synaptic Integration.

During the first year, prior to publication of NIA2 by Sinauer Associates, Inc, an undergraduate student was hired to work through all of the tutorials and provided feedback on errors (e.g., links that did not work) and other user issues. This detailed review required about two months of time. Based on this student's detailed recommendations, "Getting Started" and "Background" sections (with graphics) were added to NIA2. A majority of the users surveyed during the evaluation used at least some of these materials, even when they were in a course being led by one of the authors. Some comments from users are as follows.

- *I did use the "Getting Started" pages. This served as a guide and was much needed to understand how to navigate through the program.*
- *The "Getting Started" was not as helpful as I would have liked. It replicated all of the material that appeared on the computer monitor, but did not add much more. I would have liked extra spaces to write notes, or perhaps additional information.*
- *Ann explained everything needed to know. But I would probably have used it otherwise.*
- *They were helpful in learning how to navigate the program when using it for the first time. It provided a good introduction to how the material would be presented, and how to be efficient about using the program.*
- *They were helpful especially with the installation. It was also good to know that all the Firefox windows needed to be closed before the program could run. It didn't work in the beginning because another window was open. [Note: This issue has since been fixed, as noted above.]*

The undergraduate student also produced the first draft of the Windows installation instructions, and suggested a step-by-step set of instructions with screen-capture images. The evaluation team itself can speak to the efficacy of the instructions, which we used when we loaded our own NIA2 programs. Overall, his feedback ran the gamut from technical issues ("a red check appears in the box instead of a red square") to suggestions about clarifying text ("perhaps it would be nice if we had a better explanation of the difference between conductance and voltage") to places where the concepts he was supposed to be seeing in the tutorial were not making themselves clear ("...you tell us that 'the conductances go through a maximum change and then appear to saturate.' I could not really see this by looking at the graph").

The time invested in the detailed, systematic overhaul of the NIA2 structure and interface seems to have been a prudent investment of project resources. Students and faculty interviewed and/or surveyed during the evaluation tended to agree that NIA2 was easy to use, that the interface was visually appealing, and that the instructions were clear. Most disagreed with potentially negative statements like "I had to refer to the help files... many times many times while working through the tutorials" and "I lost focus on what I was supposed to be learning while working through the

simulations.” Responses to the various graphs in NIA2 were mixed, reflecting the widely varied educational backgrounds and experiences of the users.

During the evaluation process, NIA2 users (undergraduates, graduate students, post-docs, and faculty) were asked whether they encountered features, errors, or “glitches” that interfered with their installation or running of NIA2. Most people experienced no issues. Among those that did, several common themes emerged, which are discussed below. Many of these issues appeared to be functions or features of the underlying Neuron program rather than the NIA2 tutorials. Others were within the tutorials’ concepts themselves.

Interface and Systems-Related Issues

- There were issues with the NIA2 version of Firefox and users’ Firefox settings conflicting, and users could not have other Firefox browser windows open while they were using NIA2. This issue had been largely resolved.
- Several student users with Vista machines had trouble with program installation and getting tutorials to start. A free patch is now available on the NIA2 web site to address this issue.
- The instructions for the tutorials are displayed in the browser while the simulations are run in Neuron, which produces multiple control and graph display windows within each simulation. The users often said that working in these multiple windows or going back and forth between simulations and/or instructions was confusing. Some did not like not being able to maximize all of these windows, and we observed users rearranging the windows while they worked. In a survey question asking users about their least favorite part of NIA2, the multiple windows issue is by far the most common response.
- Multiple windows in one tutorial must all be closed before another tutorial is begun, or it results in errors. Some users had difficulty managing this.
- NIA2 is sensitive to mouse placement when changing the parameters in some of the tutorials, so users would type in new values and not have them accepted.
- When deleting lines/traces in graphs, which must be done manually by clicking (e.g., using a right-click type menu on a PC), sometimes more was taken out than the user actually wanted deleted. There is also no “undo” button, even for the most recent action.
- There were issues on some Macs with the “keep lines” feature that allows users to retain the information from previous runs on some graphs in order to compare results for different sets of parameters. According to some users, not having a two-button mouse made it challenging.
- There is no printing option for graphs and other output, so the students whose instructors had them turn in reports with graphs had to take screen captures and save them as images, which then had to be cropped for use. The evaluators also saw students sketching graphs by hand or taking snapshots of the computer screen with cell phone cameras.

- The NIA2 graphs are smooth-looking lines that are actually overlaid on discrete data points. Users can read individual values off graphs using a crosshairs tool, which they are asked to do in some simulations, but they had difficulty when the information they wanted was in a location on a line between two data points.
- Sometimes the HH channel option would not open the HH channel windows when selected.
- The order in which things are selected appeared to make a difference in some tutorials [No specific details were given as to the nature of this problem.]
- Many of the graphs do not have y-axis labels (though the traces themselves may be labeled). This occurs, for example, on the conductance plots of *The NA Action Potential* tutorial. Further, sometimes two different traces with different y-axis units and differing scales are overlaid on one graph. This can be confusing to students. In *The Neuromuscular Junction* tutorial, users are asked, “How do voltage-sensitive channels affect the shape of an EPP or an EPSP?” A plot is presented that includes three traces: the synaptically induced current, the resulting voltage change in a passive muscle fiber and the voltage change with HH channels in the fiber. The scale on the y-axis does not apply to all three traces, and while an explanation is offered (“The traces are plotted from zero so that voltage and current may be plotted together since the point of interest is response shape, not reversal potential.”) this can be confusing for users. An example of this is discussed in the Amherst case study that appears in the following NIA2 Impact section.

Tutorial Content-Related Issues

- There are occasional discrepancies between the printed and online versions of the tutorials. For example, the default parameter settings in one tutorial did not match what was stated in the printed book. [The user wasn’t sure at the time of the survey which tutorial it was.] Also, information such as definitions that are linked in the online version of NIA2 does not appear in the printed materials.
- The users felt that some of the questions in the tutorials were confusing and that some of the terms were not easily defined. In one specific example, students were unclear about the exact meaning of “node,” which affected the way they constructed independent experiments based on the tutorials. The instructor contacted the authors, and this particular issue was resolved. Another example of this was that one instructor felt that clearer explanations were needed of h, n and m probabilities associated with ion channels.
- There are also occasional discrepancies between specific tutorial language and students’ prior experiences with mathematics and graphs. For example, “The Na Action Potential” tutorial asks students to examine graphical output and answer the question, “Why is I_{Na} so ‘kinky’ with two phases.” They are instructed to use the I_{Na} graph (see the red graph in Figure 9 below) to find where the minimum I_{Na} occurs. The tutorial discusses the fact that I_{Na} (a current) is increasing and decreasing over time. However, the terms minimum,

increasing, and decreasing in this context are the *opposite* of what students would have learned in earlier mathematics classes about minima and maxima of a graph. This caused a great deal of confusion in one observed lab session in which this tutorial was used, and at least two other instructors commented on it specifically. This issue was discussed face-to-face with the PIs during SPINES 2008.

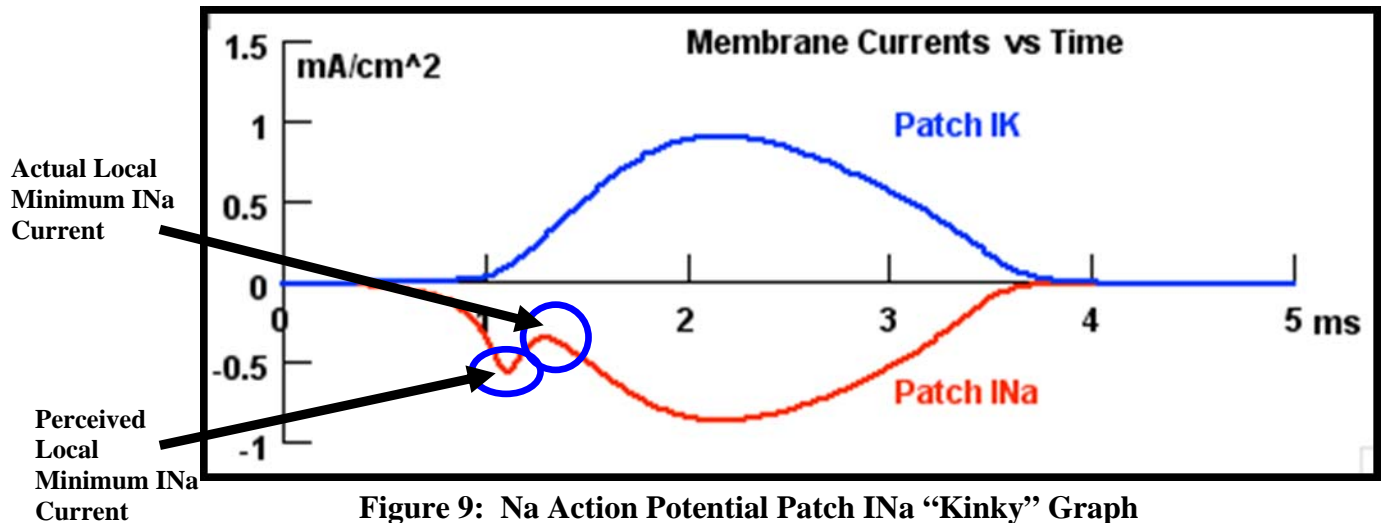


Figure 9: Na Action Potential Patch INa “Kinky” Graph

Overall, despite the issue cited above, the user response to NIA2 was highly enthusiastic. In fact, in many cases people have learned so much that users would like to see even more functionality, like more integrated systems-level tutorials, to expand the foundation offered by NIA2. Some of these are no doubt functions of the underlying Neuron simulator rather than NIA2 specifically. A “wish list” of items from users is shown below.

Interface and Systems-Related Wish-list Items

- An “undo” button that can be used when running simulations and making graphs (as opposed to the current delete function for traces).
- A better way to take measurements directly from the graphs (besides the crosshairs tool).
- A better way to color or label traces from multiple scenarios on a graph when using the “keep lines” feature, before the line is generated.
- A way to download the data for further analysis, modeling, or graphing in another program, such as Matlab.
- A way to print the graphs or to save them as figure files that can be imported into a word processing program like MS Word.
- The ability to generate a report. [The specific details of what a report should contain were not given by the respondent.]
- A single simulation interface rather than multiple windows.
- A consistent panel added to every tutorial that gives the option to dig deeper into Neuron’s capabilities. This way, users would to be able to vary even more

parameters than are already possible, perhaps via some sort of “advanced options” button.

Tutorial Content-Related Wish-list Items

- More interpretation of graph results.
- Links to mathematical resources would be useful for students that do not have a strong life-science background (e.g. most psychology undergraduates).
- Written answers to the questions asked in the tutorials.
- A “Stop and Reflect” section with graduated learning questions to help direct students toward why things happened (as opposed to just what happened) during the tutorial.
- A more formal conclusions section included at the end of each tutorial to make sure that no pertinent points intended to be discovered during explorations were missed.
- Incorporate more static screen shots with explanatory arrows and text (e.g., for the “kinky” graph discussed above) to clarify what students need to be looking at. Alternatively, put in some sort of scroll-over function with pop-up explanations that serves the same purpose.
- Suggest alternate paths through the tutorials for those who choose to do them “backwards” with respect to the NIA2 layout (e.g., start with channels and then go to membranes). This is for individuals who prefer to look at larger systems first, then the components, rather than building upward from the smaller units.
- Expand the tutorials even further to model new conditions and systems. For example, users suggested systems-level tutorials on receptive fields (retina), surround inhibition (as in the thalamus), epilepsy (cortical network), and central pattern recognition (lobster ganglion). Neuromodulation and second-messenger cascades were two other proposals. [The users who wanted the latter two topics additions are using a custom-made WinPP program to do these sorts of simulations. Students dislike the program, especially compared to the ease of NIA2.]
- One user said specifically, “It would be nice to have a tutorial where channel dynamics could be altered both at the single channel level and at the whole cell level. Steady state activation and inactivation can be altered in "Na and K Channel Kinetics" but the dynamics (time constants) cannot. In chattering channels no aspect of kinetics/dynamics can be altered.
- An instructor who used NIA2 in an undergraduate course stated, “I also wanted to suggest some pharmacology exercises – such as adding imaginary drugs that close or open K, Cl, Na, Ca or mixed ion channels – and get students to find whether the drug opened or closed the channels (using Ohm’s law with constant low amplitude current pulses) and to figure out reversal potentials for the responses which would point to ions involved. They could then test their notions by changing ion concentrations. This would be an exercise that sort of broadened the neuromuscular junction tutorial.”

- The undergraduate who reviewed the whole of NIA2 said: “I have an idea for NIA 5.2. Your tutorials do an amazing job of really explaining why things are happening the way they do in a neuron. I feel that one way you could really help students using your course is to provide a "take home notes" section at the end of each tutorial, which would outline the conclusions discovered during that tutorial. This section would make a great reference section and would make it easier for students to go back and review what they have already learned.”

Many of the extensive changes (XLM, CSS, version control, etc.) made to the NIA2 structure and interface were done to streamline development of future tutorials and to ensure that NIA2 keeps up with modern technology. In the future, the NIA2 tutorials may adopt yet another face that concurrent with the latest innovations in interactive technology for education. There is discussion between the PIs and Sinauer about the possibility of utilizing iTunes rather than CDs to disseminate new NIA2 tutorials, including those currently under development. In this iTunes model, NIA2 users would download a tutorial or package of tutorials in the same way other songs, albums/CDs, and movies are downloaded. A free tutorial player would allow users to read the tutorial and run the simulations on their computers.

Specific Aim #2. To extend the range of NIA downward to the chatter of single channels and upward to the behavior of simple circuits. Once again, within the *Detailed Project Plan* section of the NSF proposal, this objective was broken down into list of different sub-goals. This section addresses the current status of these sub-goals.

(a) New tutorial in single channel behavior. In the NSF proposal the PIs stated,

We will introduce a Chattering Channels Tutorial that will permit students to move intellectually from a knowledge of channels as proteins in the membrane to an understanding of how the gating of these channels by changes in membrane voltage underlies impulses.

This tutorial has become a reality in NIA2. It is a Basic-level tutorial called *Chattering Ion Channels*. One of the objectives behind the creation of this tutorial was to “lead the student to an understanding of Ohm’s Law through experimenting with how it is applied to currents through channels”. Figure 10 below shows that the PIs were able to include this in the *Chattering Ion Channels* tutorial. We observed this investigation in action at Woods Hole with the SPINES participants in summer 2008. PI Ann Stuart wrote the Ohm’s Law equation on the board in her introduction and continued to refer to it as the entire class observed and explored the relationships between current, conductance and driving force. A couple participants marveled that this experiment was so different from just memorizing the Ohm’s Law equation, like they had done in previous classes.

2. What determines the amplitude of the current flowing through the K channel when it opens?
- Prepare to measure the current as a function of voltage.

When you do this you will discover, experimentally, that channel currents obey Ohm's law.

 - Measure the current flowing through the open channel at each voltage. (Click on the current trace and observe the y-axis value in the top bar of the graph).
 - Record the value of the current and the voltage step (on paper). Remember that you are only examining the current through a single K channel—your Na channel is blocked with tetrodotoxin. Does the K current through the channel become larger or smaller as the step voltage moves farther away from the value of E_K ($E_K = -77\text{mV}$: see Patch Parameters panel)?
 - Plot your values of current versus the voltage step values. Current should be on the y-axis and voltage should be on the x-axis. Are your values in a straight line? If they are, why is the line [straight](#)? Extrapolate the line to see where it crosses the voltage axis (current = 0). What is the significance of the voltage value is this crossing point?
 - So did the current get bigger as the voltage moved away from E_K or moved closer to E_K ? As you clamp to a voltage closer to E_K , the "driving force" on the K ion (V_m minus E_K) will decrease. You can play with this concept by changing the value of E_K as well in the Parameters Menu.
 - Questions:
 - Do you understand why you observe a [smaller amplitude](#) of current at the offset of the pulse if the channel opening outlasts the pulse?
 - What should you [observe](#) if you step the voltage to a value negative to E_K ?
 - Will the single channel conductance [change](#) with voltage?
 - Is [conductance](#) a value you determine by measurement or by calculation?

Figure 10: Investigating Ohm's Law in the Chattering Ion Channels Tutorial

Interesting to note, the initial copies of NIA2 actually contained an error in Ohm's Law that has since been corrected, as noted in Ann Stuart's blog on the NIA2 web site, shown below.

*Apologies for embarrassing error found in NIA 2.0
Oct 1, 2008 • Posted by Ann Stuart*

*The representation of Ohm's Law is incorrect at the top of the page that comes up when selecting this equation from the Equations pull-down menu. **Correct: $E = I \cdot R$. Incorrect: E does NOT equal I/R .** Probably others have seen this error and cluck-clucked. The authors welcome emails pointing out errors so that they may be corrected on the next CD batch. Please email me at stuart@med.unc.edu.*

Another objective of the *Chattering Ion Channels* tutorial is to get students to think about concept of *conductance*. As stated in the NSF proposal,

They will see that when the channel is open, it has a fixed, measurable conductance: that is, the channel is either open or closed. (A common misconception of a pore slowly widening and narrowing to let through more or fewer ions can be dispelled). The conductance plot will show that, in response to a large step depolarization, the number of openings of the channel increases so that the channel is almost always open. The concept of channel opening as a probability will be stressed in this approach (and, for the inquisitive student, linked to Hodgkin and Huxley's ideas about probability in

the NIA2 Appendix). The student will next be directed to increase the number of channels (in the parameters menu) and plot on a second graph the frequency of channel openings versus time. Clearly as the number of channels is increased there will also be double and triple amplitudes as two or three channels open simultaneously. With larger channel numbers, an S-shaped plot should emerge; the text will point out that a similar plot can be obtained by delivering the voltage step to one channel over and over (of course the student can confirm this).

In many ways this is a very ambitious goal. One of the evaluators is a statistician, and she can attest to the fact that probability concepts are often the most difficult to teach to undergraduate students, because in many ways the fundamental rules of probability run directly counter to the deterministic way in which the human brain naturally tries to organize information about the world. The first potential barrier is the difficulty of translating the behavior of a single member of a population observed many times (here, a single channel) into a concept of the aggregate or “average” behavior of the whole population of interest (here, a large number of channels). This leads directly into a second major challenge of making the connections between a discrete relative frequency distribution derived from an experiment on a sample and the theoretical or large-scale probability of events within a population. These concepts are often not obvious to students with little experience, even in a dynamic simulation environment. For example, the fact that the smooth S-curve for current (the culmination of this tutorial) is the result of the summation of individual probabilistic channel openings and closings as the number of channels gets very large (approaching infinity or the population), particularly when events are observed over time. These connections are fundamental to achieving the stated objectives.

In the text of the *Chattering Ion Channels* tutorial, one of the goals is, “To appreciate the stochastic nature of the gating of single channels by voltage.” The term stochastic is also used in a linked explanation later when students are posed the question, “Does the depolarizing step ‘open the channel’?” The response is as follows.

No. The depolarizing step increases the probability that the channel will open. This probability is a function of membrane potential such that for larger depolarizations the probability that the channel will open is greater.

Because the opening of the channels upon depolarization is stochastic, for repeated trials you will see the channel open at random times after the onset of the step -- or perhaps not at all in any given trial.

In neither place, nor anywhere else in the tutorial, is the term “stochastic” defined in and of itself. The meaning is implied by association with the term probabilistic, but most undergraduate students have likely had little formal exposure to the concepts of stochastic processes. Given the focus on the understanding of the probabilistic nature of channels stated for this tutorial, users would benefit from even a brief introduction or definition of the term *stochastic* to cement the idea that the *process* is governed by

underlying probabilistic phenomena. Further, while the proposal states that Hodgkin and Huxley’s ideas about probability will be included in an NIA2 Appendix (“for the inquisitive student”), this appendix does not exist. The information about probability is found in the tutorial in separate bits via the various links, such as the one quoted above. Another example, under the heading, “What are three important observations about the K current as you increase the amplitude of the depolarizing steps?” says:

(2) *Why does the channel tend to open earlier?*

When the patch is stepped to more and more positive values, the opening probability increases for the K channel. Thus it tends to open earlier in the step. Also, remember there is only one channel in the patch in this experiment, yet there can be several openings and closings. So we learn that the single channel may open, close, then open again, perhaps even several times during the depolarization.

Another instance where the tutorial would benefit from additional interpretation of terms is the normalized current versus time plot that comes at the end of the tutorial, shown below in Figure 11. This is the plot that demonstrates the key principle of the collective, probabilistic nature of channel opening. In this example, even with 200 channels (which students tend to think is a rather large number) there is a noticeably “jagged” look to the experimental current, whereas smoothed curves represent what happens with a large population of channels (>10,000). Here, the term “normalized” represents the standardizing the y-axis scale of the graph achieved by dividing the generated current by the number of channels. However, the word “normal” has many different meanings. In the context of probability it would be easy to confuse it with the normal probability distribution (often called the Gaussian probability distribution in electrical applications), which is the classic bell-shaped curve. If students have had prior exposure to normal distributions in mathematics or statistics, this terminology may confuse them. They may look for the bell curve shape rather than what they are supposed to be seeing: the S-curve.

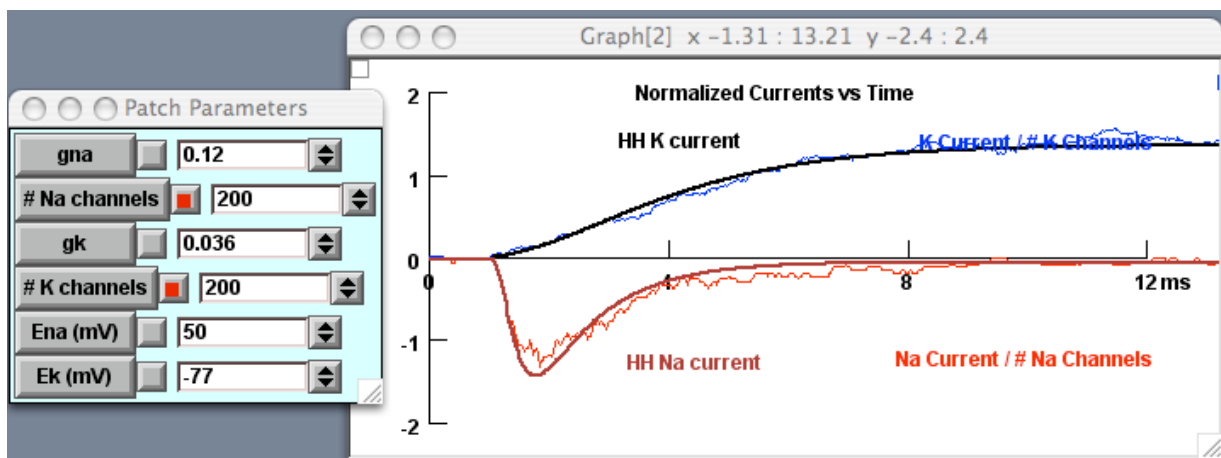


Figure 11: Normalized Current versus Time Plot in the Chattering Ion Channels Tutorial

We had the opportunity to observe Ann Stuart teach this tutorial at SPINES 2008. Her verbal introduction and setup of the materials was excellent, and addressed many of the concepts and concerns addressed above, and participants in the SPINES program appeared to be making exactly the connections stated in the tutorial goals. However, not all instructors will have the capability to provide a similar expository introduction to their students. Future users would benefit if some of this were translated into some kind of introductory text or link within the NIA2 book and CD.

(b) New tutorial for modeling a simple network. The PIs proposed the following:

We will focus on a well-known sensory problem: the localization of a sound in space (Carr and Konishi, 1988; Oertel, 1999). Sound localization is essentially a problem of "tuning": the tutorial will lead the students to discover the various ways in which a simple neuronal circuit can achieve tuning. The students will build on their knowledge of how to achieve a window for coincidence detection, developed in the Postsynaptic Interactions Tutorial.

As stated before in the discussion of Specific Aim #1, students are given an introduction to coincidence detection in the *Interactions of Synaptic Potentials* tutorial. They are able to identify a “window” (or “interval” as it is called this tutorial) where an impulse is generated as a result of two subthreshold EPSPs. It might be a good idea to actually use the words “*coincidence detection*” in this *Interactions of Synaptic Potentials* tutorial. This could help students explicitly make the connection for themselves when they reach the new *Coincidence Detection* tutorial included in the Advanced tutorials section. We observed a class working on the *Coincidence Detection* tutorial during our site visits. Their instructor did a fantastic job helping students make that connection and setting up the physiological context for the tutorial. He even made specific references to recent auditory research. More details will be provided in the Impact section below.

In regard to explicit connections, we feel this tutorial would benefit from an explicit introductory discussion of the auditory context as a simple *network*. This idea seemed to be strongly emphasized in the proposal (emphasis added by the evaluators in bold).

*The students will consider how **a model circuit** would solve the problem of detecting input from the two ears whose timing with respect to one another indicates the spatial position of the sound. One solution to this problem is described in the literature (Carr and Konishi, 1988) but it is not the only solution. **We will set up circuits involving two presynaptic stimulus detector (SD) cells, each providing subthreshold input to a postsynaptic coincidence detector (CD) cell.** Students will control the length, diameter, and degree of myelination of the axons of the presynaptic SD cells and the location of their synapses on two dendrites of the CD cell. **They will experiment with various circuit designs that can cause the postsynaptic cell to fire.** For example,*

students will have learned in preceding tutorials that the time to propagate a signal is a function of the length and the diameter of an axon but is much more sensitive to the diameter; they will be able to control the time of arrival of a signal at the CD dendrite by varying such parameters. The students will discover, simply using the one coincidence detector, that nature has an enormous array of possibilities for executing a particular task.

Neither of the words “network” or “circuit” appears in the *Coincidence Detection* tutorial. In fact, it was difficult for us to see the “network” when we were working with this tutorial. However, we feel after spending time really looking at the NSF proposal, the *network* concept is one that deserves a stronger emphasis in this tutorial.

Specific Aim #3. To add new tutorials to the original prototype. The NSF proposal outlined plans for a third category of tutorials, *Specialized* tutorials, to be added to the Basic and Advanced level tutorials already included in NIA2. The PIs discussed four different tutorials that they wanted to include in this category:

- *Extracellular stimulation and recording*
- *Ca dynamics*
- *Active dendrites*
- *Oscillations in hair cells*

In the current version of NIA2, these tutorials do not exist. In fact, there is no *Specialized* level of tutorials (see Figure 2 in the discussion of Specific Aim #1 for a current list of NIA2 tutorials). This is not unexpected. As stated earlier, the project “detour” of creating a new structure and interface simply delayed progress on this front. We have been in communication with PI Ann Stuart regarding this part of the project. In her April 3, 2009 email she updated us on the progress that is being made on Specific Aim # 3.

We are well along on Extracellular Recording and John has made the simulations for a tutorial on A-type K channels (something I think is an important tutorial). People have requested a network tutorial (within the capability of NEURON) and I have enthusiasm for an Active Dendrites tutorial, although neither of these are being worked on yet. What John really wants to complete after the Extracellular tutorial, and before going on to other tutorials, is a set of tutorials on "Calcium in Action" that would be in the same format as NIA2 but would be focused on calcium instead of on action potentials, and so with different history, "What is?" files, and other links. John has five of these tutorials completely outlined and the simulations essentially done--he is waiting for me to get free enough to throw myself into it (probably this summer). We have not discussed with Sinauer how this set of tutorials would be marketed or combined in some way with NIA2.

NEURON developer Michael Hines also told us

I'm enthusiastic about helping [John] and Ann develop a tutorial that exhibits inhibitory synchronization of a network of simple spiking cells where each cell has an intrinsic firing rate and the cells are connected all to all with inhibitory connections and leads the

user to an understanding of why delay is necessary and also why it is necessary that inhibition delays the generation of a spike more when one is close to threshold and hardly delays it at all when the cell is far from threshold.

Overall, we are very pleased with what Ann and John have accomplished during the period that was covered by grant funding, as well as what they are working on for future updates to NIA2. As we noted earlier, this is simply the latest piece in an ongoing, lifelong aim to bring the visual component to neuroscience education in a realistic, usable way. Our conversations with John Stuart at Woods Hole made abundantly clear that the ideas of *Neurons in Action* have been around for a long time; they have simply been waiting for the technology to make them possible on a larger scale. Further, the PIs enthusiasm appears to thrive rather than wane as the project progresses. The undergraduate student who reviewed the NIA2 program made what was likely a humorous reference to “NIA 5.2.” Given the passion the PIs have for what has essentially been a lifelong project for them, it is not unreasonable to believe this could actually happen. Couple that drive with the growing “wish-list” of neuroscience topics that the education community would like Ann and John to tackle in this dynamic way, there should be plenty to keep them busy for years to come. We, as well as the neuroscience undergraduate education community, are looking forward to seeing the new tutorials currently under development and any future offerings Ann and John create.