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Smartphone-Enabled Web-Based Simulation of Cellular Neurophysiology for Laboratory Course and its EffectivenessTakayuki Yamamoto^{1,2}, Adam Weitemier¹, and Makoto Kurokawa¹¹Department of Biological Sciences, Graduate School of Science, Tokyo Metropolitan University, Tokyo 192-0397, Japan;²Teikyo University High School, Tokyo 192-0361, Japan.<https://doi.org/10.59390/RCVF6232>

The introduction of computer simulations has enhanced the teaching of neurobiology. Many simulators for personal computers are available, but in countries where schools have low school information and communication technology readiness, it is difficult to introduce computer simulations. Even in such countries, however, students often have their own smartphones and are good at operating them. Therefore, we have developed five web-based simulators that cover a wide range of neurophysiology, including single and whole-cell channel currents, membrane potentials and generation and conduction of action potentials using HTML5 and JavaScript. These simulators may be run free of charge on any device, regardless of the model or OS, thereby

enabling schools that have no experience in introducing simulations to introduce them easily. These simulators were especially useful in many schools during COVID-19 restrictions. In this paper, we explain the functions of the simulators we have developed and introduce some practical examples. To verify the usefulness of the simulators, we also conducted a survey in the classrooms in which the simulators were used. Understanding and motivation to learn was shown to increase significantly, indicating that these are useful for neurobiology education.

Key words: neurophysiology; simulator; smartphone; computer; HTML5; JavaScript; COVID-19

Understanding neuronal electrophysiology is an important part of neuroscience education. If possible, high school and undergraduate students in laboratory courses may be able to do extracellular recordings of action potentials using animals such as frogs (Ferragamo and Wotton, 2006), earthworms (Kladt et al., 2010), cockroach (Ramos et al., 2007) or crickets (Dagda et al., 2013). They are generally unable to practice intracellular techniques such as voltage-clamp membrane current recording and patch-clamp channel current recording due to lack of facilities and technical instruction, or the cost and time limitations of training. Since much of this content ends up in a lecture from instructors to the students using textual illustrations, it is difficult to motivate students to learn neuronal electrophysiology. In such cases, it has been reported that computer simulations are educationally effective (Bish and Schleidt, 2008; Rutten et al., 2012). It is difficult, however, to introduce simulations in countries including Japan whose school information and communication technology readiness factor is low (Ma and Qin, 2021; Wu et al., 2023). In such countries, it is not always the case that the number of computers installed in the training room is enough for the number of students, or that all students necessarily have computers. This is one of the biggest barriers to introducing simulations into classroom education.

How can a simulation be done in such a situation? Most students today have smartphones, which are high-performance computers that have a communication environment. If students can run simulations on their smartphones, it will greatly enhance learning neuroscience. Many simulators have been reported, including "NEURON" (Carnevale and Hines, 2001), "SNNAP" (AV-Ron et al.,

2006), "MetaNeuron" (Newman and Newman, 2013), "Neuron in Action" (Moore and Stuart, 2007; Stuart, 2009), "Neurosim" (Heitler, 2022), and "SimBio" (Meir, 2022). All of them, however, are operated by personal computers only and there is no smartphone-enabled simulator yet. Here, we introduce new neuronal electrophysiology simulators that (i) can be operated on smartphones and tablets as well as on personal computers, regardless of the type of device or OS, (ii) may be used for free and without registration, (iii) are web-based and do not require installation, (iv) can be used without confusion by instructors and students unfamiliar with simulation, and (v) can extensively simulate electrophysiological phenomena in neurons.

We also conducted a survey in the classrooms in which the simulators were used to verify their usefulness.

METHODS**Development of New Simulators**

We developed web-based simulators to allow students to run simulations regardless of device model or OS. Since Java and Flash cannot be used on smartphone browsers, the simulators were created using HTML5 and JavaScript. The developed html files were placed on a web server. This makes it possible to easily run simulations in a web browser for free by simply entering a URL (<https://www.biol.se.tmu.ac.jp/neurobio/neuron/sim/index.html>), or by reading a QR code (Figure 1).

To simplify the operation, five independent simulators were developed each with a single screen fitted for smartphones: "Membrane Potential," "Membrane Current", "Channel Current", "Action Potential" and "Excitatory Conduction" (Figure 1). These can simulate a wide range

phenomenon in neuronal physiology. Of these, "Membrane Potential" is a simulator of the static electrical properties of neurons and the remaining four are simulators of the dynamic electrical properties of neurons. All simulators are designed to be temperature configurable, as electrophysiological phenomena in neurons are related to temperature. Except for "Membrane Potential" simulator, which simulates static properties without change over time, the size of the vertical (voltage, current and/or conductance) and horizontal (time and location) axes of the remaining four simulator graphs can be changed according to the screen size of smartphones, tablets, or personal computers; they can be optimized for any device. The static properties simulator shows results as soon as the input values are changed.— After setting the conditions in the dynamic properties simulators, they can be run when the "Simulate" button is pressed for the time selected with radio buttons. In simulators with an overwrite function, graphs can be cleared with the "CLS" button. In simulators with a "text out" function, if the check box is checked, each value over time will be displayed in text instead of being displayed as a trace. Recording a panel trace is easily possible with a screenshot. Students can also create high-resolution

graphs by copying the text output and pasting it in a spread sheet, or reading it as a CSV file with an application such as GNU R.

Input of parameters specific to each simulator and display of results were designed as follows:

"Membrane Potential" Simulator

By inputting the intramembrane "inside" and extramembrane "outside" ion concentrations of potassium ions, sodium ions, and chloride ions and the ratio of all ion permeabilities, the value and panel of the membrane potential are displayed (Figure 1A).

"Membrane Current" Simulator

The voltage of the "command pulse" (clamp potential) is the stimulus input. The upper panel shows membrane potential, potassium conductance, and/or sodium conductance depending on which "box" is checked. The bottom panel displays membrane currents where the potassium current is displayed if the "TTX" radio button is selected, the sodium current is displayed if the "TEA" radio button is selected, and the total membrane current is displayed if neither is selected (Figure 1B).

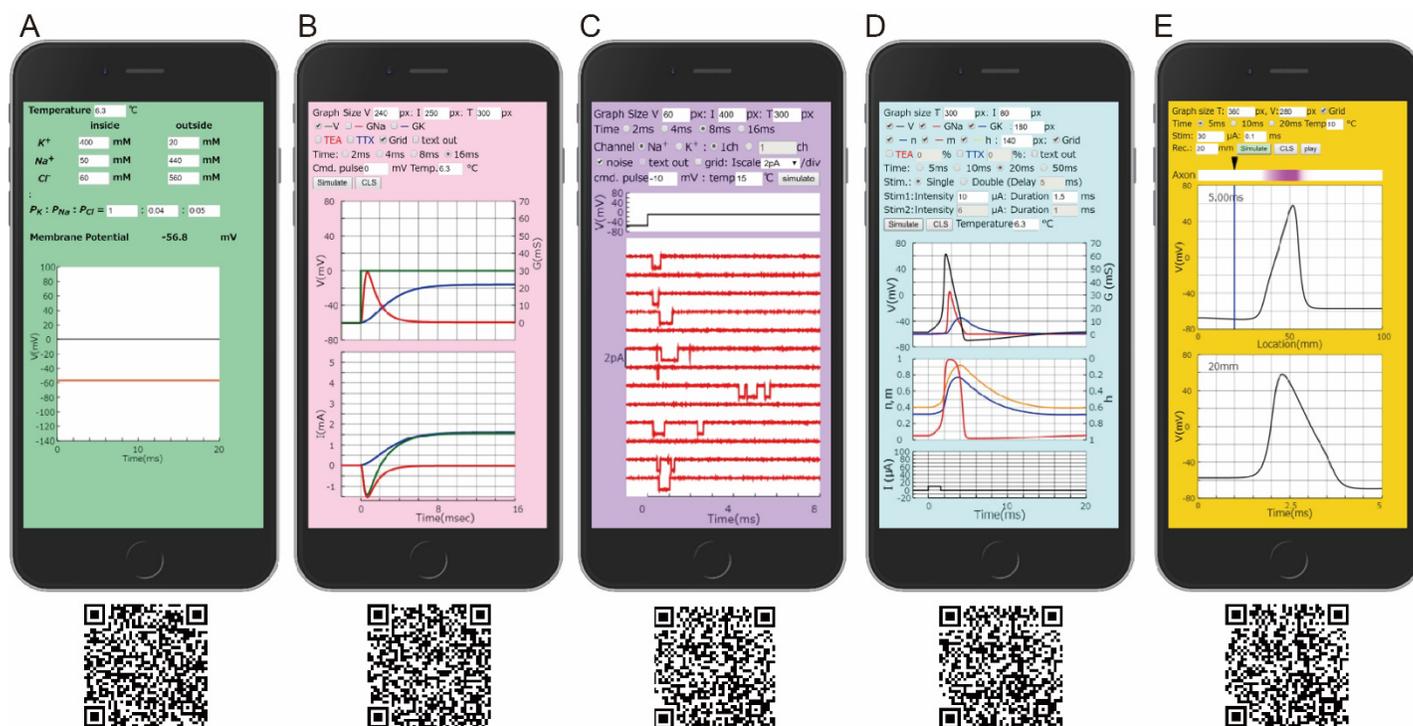


Figure 1. Smartphone screens for each simulator (A-E) and QR code (A-E: each simulator; F: simulators homepage with link to short instruction guide). The examples show (A) "Membrane Potential" simulator - resting membrane potential (red line) at user-set intracellular and extracellular ion concentrations; (B) "Membrane Current" simulator - sodium and potassium membrane conductance (upper panel) and current (lower panel) after a command voltage input; (C) "Channel Current" simulator - single channel currents (sodium in this example) after a command voltage input; (D) "Action Potential" simulator - membrane potential, potassium conductance, and sodium conductance (upper panel) and channel activation/inactivation (lower panel) during an action potential; and (E) "Excitatory Conduction" simulator - propagation (upper panel) and point measurement (lower panel, set at blue line and filled triangle location) of excitatory conduction.



“Channel Current” Simulator

Like the “Membrane Current” simulator, the voltage of the “command pulse” (clamp potential) is the stimulus input. The clamp voltage is shown in the upper panel. Potassium channel currents are displayed when the “K⁺” radio button is selected, and sodium channel currents are displayed when the “Na⁺” radio button is selected (Figure 1C). When the “1ch” radio button is selected, 13 random individual channel currents are displayed. If the radio button for number of channels is selected, the total channel current for the entered number of channels is displayed.

“Action Potential” Simulator

The stimulus current magnitude and pulse duration are the stimulus inputs. Single or double stimulation can be selected with radio buttons. “Delay time” is required to be entered if “Double” stimulation is selected. Stimulation currents are displayed in the bottom panel. In the upper panel, membrane potential, potassium conductance, and/or sodium conductance are displayed depending on which box(es) is/are checked. When the potassium channel activation variable “n”, sodium channel activation variable “m”, and/or sodium channel inactivation variable “h” are checked, each trace is also displayed (Figure 1D).

“Excitatory Conduction” Simulator

Like the “Action Potential” simulator, the stimulus current magnitude and pulse duration are the stimulus inputs. It is required to enter the location (distance from the stimulation electrode) of the recording electrode on the 100 mm long axon, shown by the filled triangle in the axon diagram above the graph. The upper panel shows potentials at 0.5 mm intervals on the axon. The bottom panel displays the intracellular potential at the location of the recording electrode. Each time the “play” button is pressed, the excitation site, where the membrane potential is indicated by color intensity, moves along the axon in slow motion at a speed of 1/1000th, and the graph changes are displayed (Figure 1E).

Survey

The five simulators were presented at the annual meeting of the Japanese Society for Comparative Physiology and Biochemistry in 2018 (Yamamoto and Kurokawa, 2019) and 2019 (Yamamoto and Kurokawa, 2020). The URL has been published so that anyone can use it for free without registration since 2018. In 2020, we asked instructors of undergraduate education for cooperation in implementing practical training using these simulators and conducting comprehension surveys for their students.

The contents of the survey were as follows:

- Degree of understanding of training content before and after simulation training.
- Motivation before and after simulation training
- The usefulness of the simulator used in the training

These were examined on a five-point Likert scale. A comment section was included in all surveys. Before preparing the comprehension survey, we asked the instructors to send us the details of the lesson plan in order

to know which simulator the instructor used and what kind of training was carried out. Comprehension surveys were prepared according to the description (for example, if a refractory period simulation experiment was done, we included the survey item, “understanding of the refractory period”). The survey was created using Google form, and the students accessed the URL after the simulation training. Scores pre- and post-survey were compared by paired t-test.

RESULTS

Practice examples

Using each of the five simulators, that have high flexibility, instructors were able to teach various contents in cellular neurophysiology. Examples of simulation practice using each simulator are shown below.

“Membrane Potential” Simulator

The equilibrium potential of an ion is calculated using by the Nernst equation and the resting membrane potential by the Goldman-Hodgkin-Katz (GHK) equation (Goldman, 1943; Hodgkin and Katz, 1949). That is, the equilibrium potentials of potassium, sodium, and chloride ions can be obtained from concentrations inside and outside the membrane. These concentrations in squid giant axons are given as default. The equilibrium potentials of potassium ions, for example, can be obtained by input of values of the permeability ratio $P_K:P_{Na}:P_{Cl}=1:0:0$, and so forth. The resting potential can be determined from the permeability ratio of all ions.

Bernstein (1902) proposed the hypothesis that the resting potential is caused by the concentration ratio of potassium ions inside and outside the membrane, and equal to the equilibrium potential of potassium ions. This is mostly correct. Depending on the hypothesis, students can obtain a linear-relationship curve of the membrane potential versus log extracellular K⁺ concentration by changing the value of extracellular K⁺ concentration (Fig 2). It is known, however, that a real cell membrane has a permeability to sodium that ranges between 1 and 10% of its permeability to potassium (Nicholls et al., 2001). By drawing a curve of the resting potential depending on the GHK equation, $P_K:P_{Na}:P_{Cl}=1:0.04:0.45$ (Hodgkin and Katz, 1949), it can be seen that as concentrations of potassium decrease, the membrane potential depolarizes away from the equilibrium potential of potassium ions (Figure 2), as shown experimentally by Hodgkin and Keynes (1955). At the peak of the action potential there is an instant in time when membrane potential does not change and the GHK equation uses the following permeability rate, $P_K:P_{Na}:P_{Cl}=1:20:0.45$ (Hodgkin and Katz, 1949). Students also learn that higher sodium ion permeability results in more depolarized membrane potential, which simulates “overshoot” potential of impulses.

“Membrane Current” Simulator

Using this simulator, whole-cell voltage-clamp experiments can be simulated. Larger biphasic current responses can be obtained to the more depolarizing command pulses. Potassium current, which is a late steady current, is displayed when TTX, which inhibits voltage-gated sodium

channels, is applied. Applying TEA, which inhibits voltage-gated potassium channels, displays sodium current, which is an early transient current. A current-voltage (I-V) curve (Hodgkin, Huxley and Katz, 1952; Raman and Ferster, 2022) can be obtained by reading the peak value of each current change against the step voltage (Figure 3). Under voltage-clamp conditions, the current response to voltage steps reflects changes in membrane conductance. A conductance-voltage curve can also be drawn by reading the peak value of each conductance change in response to the command voltage pulse (Hodgkin and Huxley, 1952a). Students can learn much about properties of voltage-dependent ion channels through discussions about why the sodium and potassium current in the I-V curve appear different, while their conductance changes are similar.

“Channel Current” Simulator

Commonality and differences in the gating properties between sodium and potassium ion channels involved in the generation of action potentials, such as voltage dependency of both channels, inactivation only in sodium channels and delayed response of only potassium channels etc. can be visually observed, while all 13 channels displayed on one screen have different aperture patterns in a single-channel simulation. The I-V curve of each single ion channel can be compared with the curve obtained using the “Membrane Current” simulator. As shown by Strassberg and DeFlice (1993), as the channel population is increased, for both the potassium channel current (left) and the sodium channel current (right), the sum of discrete channel currents converges to the continuous whole-cell membrane current (Figure 4).

“Action Potential” Simulator

Hodgkin and Huxley (1952b) showed the time course of action potentials and conductance. Inward current stimulation depolarizes the membrane potential. Depolarization in membrane potential increases the open probability of voltage-gated sodium and potassium channels, as simulated in “Channel Current” simulator, that causes an increased conductance of each ion. Conductance changes of each ion are simulated during generation of action potentials, in which activation of sodium conductance begins earlier than that of potassium conductance (Figure 5 left).

Action potentials are generated when positive feedback of depolarization and sodium channel activation occurs before repolarization by sodium channel inactivation and potassium channel activation. Stimulus threshold can be inquired by stimulus intensity, which is the minimum intensity required for positive feedback. An all-or-none action potential can be seen by varying the intensity of the stimulus (Figure 5, middle and right).

The stimulation threshold is determined by the strength and duration of the stimulation current. Guttman (1966) showed that the product of threshold intensity and duration is nearly constant, while rheobase increases with increasing temperature. The temperature dependency of the strength-duration curve can also be simulated (Figure 6).

The stimulus threshold changes during the refractory

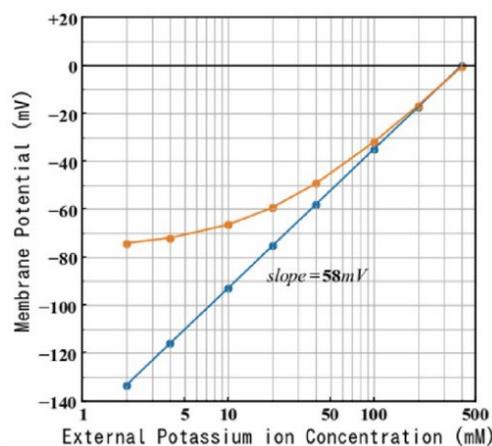


Figure 2. The effects of extracellular K⁺ concentration on the membrane potential. The orange curve is given by the GHK equation for K⁺, Na⁺, and Cl⁻, and the blue line is given by the Nernst equation for K⁺ in a semi-logarithmic graph.

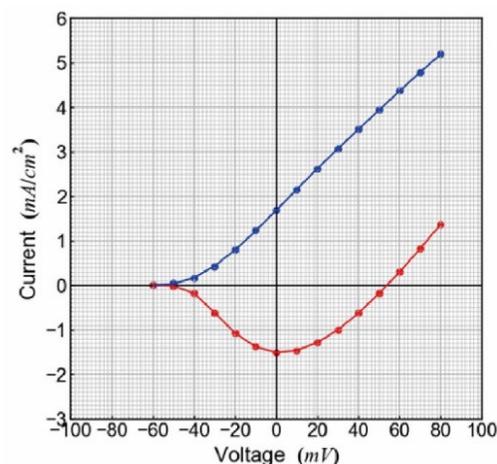


Figure 3. Current-voltage curve obtained using the “Membrane Current” simulator. Potassium current-voltage curve (blue line) and sodium current-voltage curve (red line) are drawn.

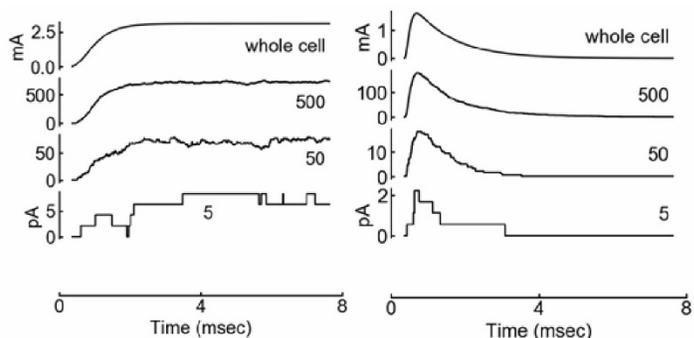


Figure 4. Voltage-clamp step response of channel currents. Potassium current (left) and sodium current (right) at command potential, 80 mV. The top trace is the whole-cell membrane current, and numbers on the waveform in the graph below indicates the number of channels summed are indicated in the lower three traces. These traces were drawn with a CSV file created using the simulator’s “text out” function of the “Membrane Current” (top traces) and the “Channel Current” simulators.

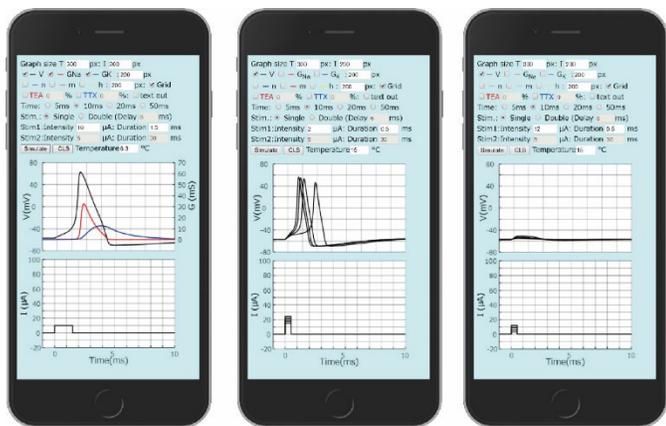


Figure 5. Action potential simulation screen. *Left:* Relationship between conductance change and action potential. In the upper panel, the black trace is the membrane potential, the red trace is the sodium conductance, and the blue trace is the potassium conductance. Lower panel shows stimulation current. *Middle:* Action potential with varying stimulus intensity. *Right:* Stimulation below threshold intensity does not evoke action potential. Stimulus threshold can be inquired by stimulus intensity, which is the minimum intensity to cause the positive feedback. An all-or-none action potentials can be seen by varying the intensity of the stimulus (Figure 5, middle and right).

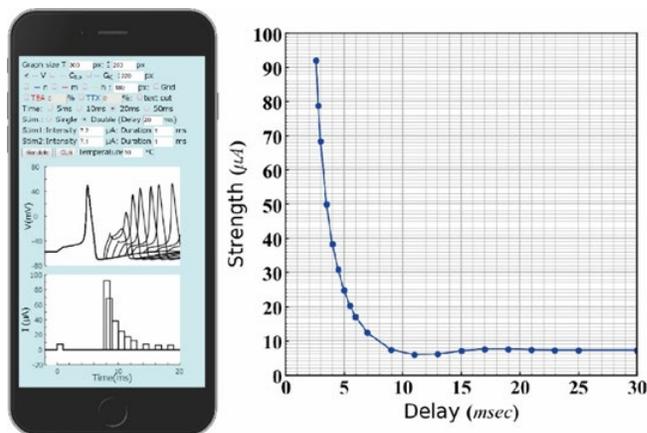


Figure 7. Simulation of refractory period. *Left:* Overlaid waveform of action potential (upper traces) and stimulation current (lower traces). *Right:* delay-strength curve.

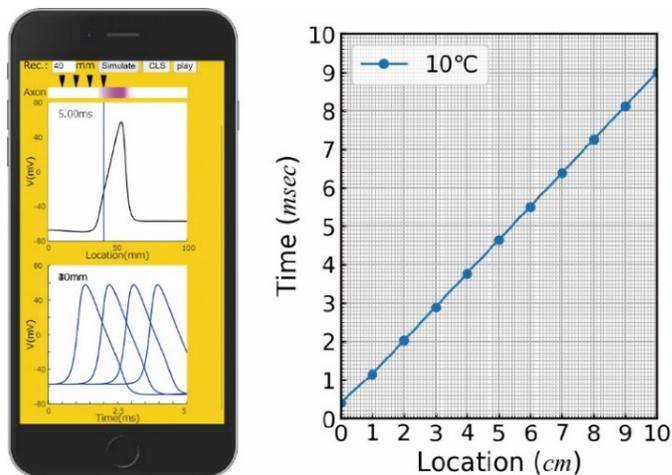


Figure 8. Simulation of excitatory conduction. *Left:* The top trace shows the membrane potential along the axon at various times (5 ms in this graph) and the bottom traces show the membrane potential over time at four different recording electrode positions, which are indicated by filled triangles. *Right:* Relationship between the distance from the stimulation site to the recording electrode and the arrival time of excitation.

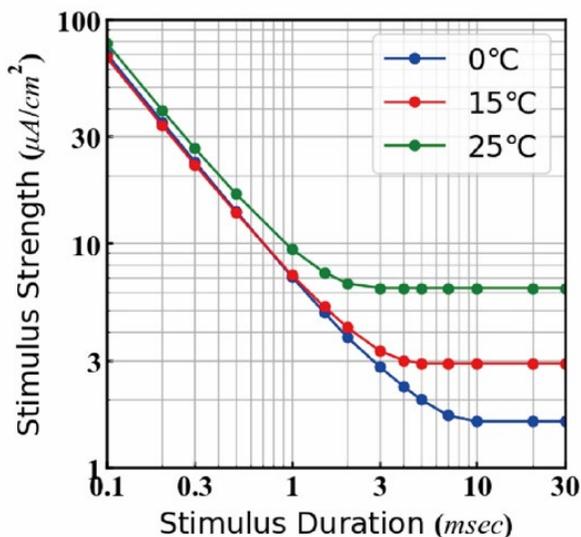


Figure 6. Threshold stimulation strength-duration curve in a double-logarithmic graph. Blue, red and green traces are obtained at 0°C, 15°C and 25°C respectively.

period of a previous action potential. The refractory period can be found using double stimuli on the simulator (Figure 7). During the absolute refractory period, the threshold intensity is infinity (i.e., when a second stimulation cannot generate an action potential no matter how strong the stimulation). During the relative refractory period, the threshold is higher, but can be reached. This can be understood by drawing a graph of stimulus thresholds after varying stimulus delays. Some students may find that just after the period, the threshold becomes lower than that of the first stimulation, referred to as the super normal period (Khurana and Khurana, 2020).

“Excitatory Conduction” Simulator

In excitatory conduction, the membrane potential changes not only temporally but also spatially, making action potential conduction sometimes difficult for students to understand. Cooley and Dodge (1966) performed this simulation used an IBM7094 mainframe computer, but now this can be achieved with a smartphone (Figure 8 left). By changing the position of the recording electrode, reading the arrival time of the action potential, and graphing it, the conduction velocity is indicated as the slope of the graph (Figure 8, right). When the play button is pressed, the movement of the excitable region and changes in the membrane potential are displayed in animation (after numerical calculation); this helps students grasp visually how an action potential conducts. By changing the position of the recording electrode, reading the arrival time of the

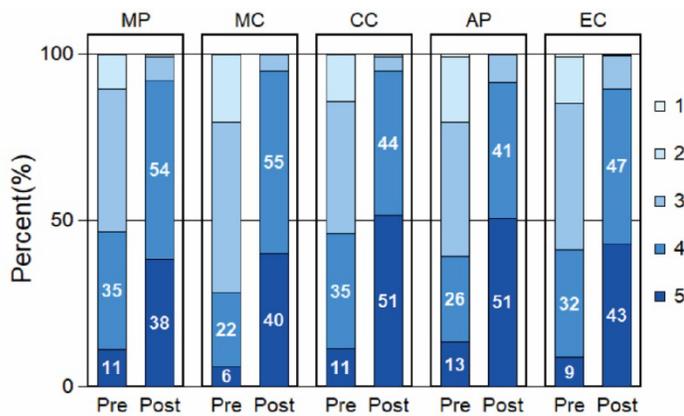


Figure 9. Survey results for understanding before and after the simulation experiments with a five-level Likert scale. Likert scale: 1, I do not understand at all.; 2, I do not understand much.; 3, I understand a little.; 4, I understand somewhat.; 5, I understand very well. Pre: Survey response obtained before simulation experiments, Post: after simulation experiments. MP, Membrane Potential; MC, Membrane Current; CC, Channel Current; AP, Action Potential; EC, Excitable Conduction simulator experiments. Numbers indicate the percentages replying, "I understand very well" and "I understand somewhat." Significant differences were shown using paired t-test in all simulators.

action potential, and graphing it, the conduction velocity is indicated as the slope of the line (Figure 8, right). Temperature dependency of the conduction velocity can also be explored.

Survey

In 2020, we distributed the URL of the simulators and asked for cooperation in conducting practical training using the simulator we developed and a survey. The simulators have been introduced in many neurophysiology classes at universities and high schools across Japan. Two national universities, two public universities, two private universities, and one private high school in Japan cooperated with the survey in total. A total of 1146 students (1055 undergraduate students and 91 high school students) responded to the survey for experiments using five types of simulation experiments. Of these, 199 students used Membrane Potential simulator; 156, Membrane Current simulator; 150, Channel Current simulator; 403, Action Potential simulator and 238, Excitatory Conduction simulator. The simulators were used in a laboratory neurobiology course where most of the undergraduates were biology majors. In high school, the simulators were used in biology classes.

Changes in Understanding due to Simulation Experiments

The understanding of the phenomenon before the simulation experiment (pre) and after the simulation experiment (post) were graphed on a five-level Likert scale (Figure 9). In the graph, the ratio of "understand very well" and "understand somewhat" was indicated as a numerical value. The results show that in simulation experiments using every type of simulator, the combined ratio of "understand very well" and "understand somewhat" was less than 50% before the simulation experiments but

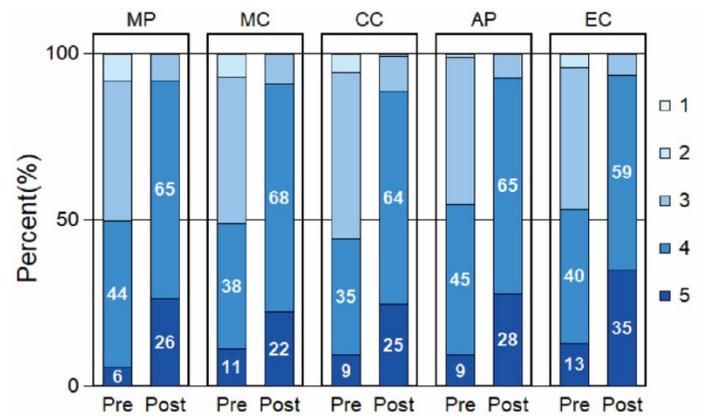


Figure 10. Survey results for motivation before and after the simulation experiments with a five-level Likert scale. Likert scale: 1, I have no motivation to learn.; 2, I do not have study motivation much.; 3, I have motivation to learn a little.; 4, I have study motivation somewhat.; 5, I have study motivation strongly. Pre: Survey response obtained before simulation experiments, Post: after simulation experiments. MP, Membrane Potential; MC, Membrane Current; CC, Channel Current; AP, Action Potential; EC, Excitable Conduction simulator experiments. Numbers indicate the percentages replying, "I have study motivation very well" and "I have study motivation somewhat." Significant differences were shown using paired t-test in all simulators.

increased to over 90% after the simulation experiments. Significant differences were shown using paired t-test in all simulators with $p < 0.01$.

Changes in Motivation through Simulation Experiments

The motivation to learn before the simulation experiment (pre) and the motivation after the simulation experiment (post) were graphed on a five-level Likert scale (Figure 10). In the graph, the ratio of "strongly have" and "somewhat have" was indicated as a numerical value. The results show that in simulation experiments using every type of simulators, the combined ratio of "strongly have" and "somewhat have" was around 50% before the simulation experiment but increased around 90% after the simulation experiments. Significant differences were shown using paired t-test in all simulators with $p < 0.01$.

Usefulness of These Simulators

Survey results for the rate of usefulness were graphed on a five-level Likert scale, in which the ratio of "extremely useful" and "useful to somewhat" was indicated as a numerical value (Figure 11). The results show that in simulation experiments using every type of simulators, the combined ratio of "extremely useful" and "useful to somewhat" was over 80%.

DISCUSSION

It has been reported that computer simulations are educationally effective, especially in neuroscience (Bish and Schleidt, 2008). Computer simulations, however, have not been introduced effectively in neuroscience education in Japanese high schools and undergraduate institutions since there are often not enough computers for all students. Nevertheless, the simulators we developed were proactively

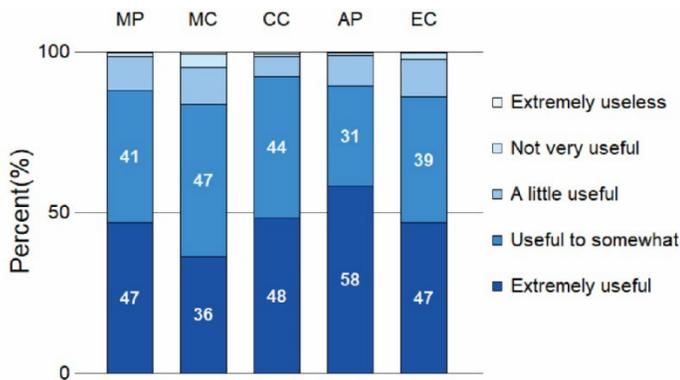


Figure 11. Survey results for usefulness with a five-level Likert scale. MP, Membrane Potential, 199 students; MC, Membrane Current, 156 students; CC, Channel Current, 150 students; AP, Action Potential, 403 students; EC, Excitable Conduction, 238 students. Numbers indicate the percentages replying, “Extremely useful” and “Useful to somewhat.”

introduced in many schools in 2020 and 2021, when the Covid-19 pandemic forced most schools to implement distance learning urgently and for the first time.

Several factors made these easy to implement. Unlike commercial packages such as *Neurons In Action* (Moore and Stuart, 2007), *Neurosim* (Heitler, 2022), and *Action Potentials* (Meir, 2022), these simulators are provided free for anyone to use without registration. These simulators are web-based, can be run by simply accessing a URL, and are very easy to operate. NEURON is a free and advanced simulator, but as Northcutt (2021) stated, “Approximately half of the students in the undergraduate class had problems either downloading NEURON or running simulations once it downloaded.” Since the web-based simulators do not require installation and can be run simply by visiting a URL, we avoided download problems. Most simulators, such as SNNAP (AV-Ron et al., 2006) and MetaNeuron (Newman and Newman, 2013), can only be used on personal computers, but these new simulators are smartphone-enabled in addition to computer-enabled. Students are good at using smartphones, so even instructors who were not familiar with computers had no problem in teaching operation. These simulators could demonstrate a wide range of neuronal phenomena depending on what educational content was taught. Instructors could incorporate their own contents into remote experiments using any simulator.

The most striking impetus for introduction of the simulators was the Covid-19 pandemic. Since the simulators were considered to be educationally effective in each simulation experiment, these continued to be used even after face-to-face experiments resumed. At these schools, there were cases where simulation experiments were conducted instead of animal experiments, and where simulation experiments were conducted in combination with animal experiments. In the case of simulations combined with animal experiments, many students commented that the simulation experiments helped them to better understand and run experiments on animals. Therefore, it can be said that the simulators reduce or even replace the

need for experimental animals.

Most of the student comments on the simulators were positive. Many said that they were able to deepen their understanding through the lectures on the basic principles of cellular neurophysiology before or after simulation experiments. This indicates that this simulator is an educational tool, but not a textbook. Because these simulators are simple, in many cases it is necessary for students to think about the conditions, repeat the simulation, and create graphs based on the values. Some commented that activities such as creating logarithmic graphs based on the values that students read from simulations were useful in improving their scientific skills. In addition, there were many comments such as, “I deepened my understanding by doing it in a group.” Indeed, the portability of smartphones and tablets allow flexible and easy student-student and student-teacher interaction. The ability to share information over the Internet using smartphones and conduct group experiments while communicating with each other was also thought to have contributed to enhancing the educational effect.

Due to lack of comparison of groups taught with and without simulators in the survey, objectivity may be insufficient in verification of educational effects of the simulators. It is obvious, however, that at least the students thought that their understanding had deepened subjectively. Many commented that these simulation experiments had increased their interest in the phenomena of cellular neurophysiology. The usefulness of these simulators was also highly evaluated, indicating that these were actually easy for students to understand and use. It appears that the motivation of most of students increased by actively conducting these simulation experiments due to ease of operation.

One of the advantages of web-based simulators is that, unlike simulators that require installation, when we update the simulator, these updates are seamless for users who do not need to download a new program. These simulators we developed are licensed under the MIT license and are free for anyone to use, copy, modify, etc.

We believe the smartphone-based web-based simulators that we have developed are useful for high schools and undergraduates in neuroscience education.

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