

ARTICLE

Simulated *in vivo* Electrophysiology Experiments Provide Previously Inaccessible Insights into Visual Physiology

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Lecture content and practical laboratory classes are ideally complementary. However, the types of experiments that have led to our detailed understanding of sensory neuroscience are often not amenable to classroom experimentation as they require expensive equipment, time-consuming surgeries, specialized experimental techniques, and the use of animals. While sometimes feasible in small group teaching, these experiments are not suitable for large cohorts of students. Previous attempts to expose students to sensory neuroscience experiments include: the use of electrophysiology preparations in invertebrates, data-driven simulations that do not replicate the experience of conducting an experiment, or simply observing an experiment in a research laboratory.

We developed an online simulation of a visual neuroscience experiment in which extracellular recordings

are made from a motion sensitive neuron. Students have control over stimulation parameters (direction and contrast) and can see and hear the action potential responses to stimuli as they are presented. The simulation provides an intuitive way for students to gain insight into neurophysiology, including experimental design, data collection and data analysis. Our simulation allows large cohorts of students to cost-effectively “experience” the results of animal research without ethical concerns, to be exposed to realistic data variability, and to develop their understanding of how sensory neuroscience experiments are conducted.

Key words: neurophysiology, simulation, virtual experiment, online learning, motion sensitivity, tuning curves, statistical analysis, extracellular recording, vision

Science education in the biomedical sciences complements lecture-based instruction with “hands-on” practical classes, facilitating learning through direct experience and observation of scientific phenomena. In practical classes, students often manipulate biological tissue or processes, and record data or observations for subsequent analysis and interpretation. These classes have parallel aims, for example, to: (1) train students in experimental techniques useful in their professional careers as scientists or health practitioners; (2) reinforce and consolidate theoretical concepts introduced in lectures or in textbooks; and (3) motivate student-driven inquiry and exploration.

Despite the educational benefits of conducting experiments within laboratory classes (Olson and Loucks-Horsley, 2000), their wide-spread use is limited by time, cost, and feasibility. Inexorable increases in student numbers continually force us to rethink how to allocate our limited face-to-face teaching time in order to maximize teaching quality and learning outcomes. As some courses move to online delivery, it becomes logistically challenging to run classes that require physical attendance. In addition, while animal experimentation has been the basis of many insights in neuroscience, both students and animal ethics committees are becoming less comfortable with the use of animals for learning purposes, despite the educational advantages (Ra’anan, 2005).

Developing the research-teaching nexus is commonly promoted as a way of enhancing both student learning and teacher engagement in education. However, the increasing specialization of many fields makes it

challenging to design experiments for practical classes that replicate or even approximate experiments done in the research lab. For example, most scientific fields increasingly collect and process large data sets. However, in a typical biomedical science degree, students may not have time to collect large data sets, and are rarely exposed to the associated analytical and conceptual challenges. In our opinion, simply providing data for analysis without the experimental context is inappropriate from a teaching and learning standpoint. In many cases, ethical implications and regulations restricting animal use make it difficult for students to conduct experiments with animals, or animal tissue. This problem is acutely felt in visual neuroscience, where *in vivo* experiments are quite common. The complex neurosurgeries necessary to perform electrophysiological recordings, and the long hours required for the collection of reliable data mean that students will never experience the type of experiments that underlie much of the sensory neuroscience literature.

We designed and developed a web-based, interactive simulation that allows students to make extracellular recordings from motion sensitive neurons, as commonly found in the retina, primary visual area (V1) and the middle temporal area (MT/V5) of primates (Born and Bradley, 2005; Price and Born, 2009; Bear et al., 2016). A classic description of these types of experiments is found in Hubel and Wiesel (1959). Specifically, the simulation explores how neurons in MT respond to moving stimuli as they are varied in direction and contrast. This simulation provides an intuitive and optionally self-directed way for students to gain insight into neurophysiology, including experimental

design, data collection and data analysis. Critically, the simulations are scalable, allowing practical classes to be run in the same way regardless of student numbers or classroom layout. Finally, our simulation allows students to “experience” the results of animal research without ethical concerns, and without compromising on the realism of the data, including its inherent variability.

MATERIALS AND METHODS

The Visual neuroscience simulation website (accessible at <http://ilearn.med.monash.edu.au/physiology/>) has four main sections, containing: (1) theoretical, background material; (2) instructions for running the stimulation; (3) the interactive simulation; (4) a way to download data. For flexibility, specific learning outcomes are not detailed on the website, allowing the simulation itself to be used for a range of purposes (e.g., simple demonstrations in lectures, qualitative explorations in tutorial classes, and detailed quantitative analyses in practical classes or for student assignments).

The simulation website opens to a **Background** tab (Figure 1), which gives historical context to physiological studies of neurons in the visual system, and describes the

general properties of neurons in the middle temporal area (MT). A YouTube video of one of the pioneering electrophysiology experiments from the laboratory of David Hubel and Torsten Wiesel in the 1960’s is embedded so that students may appreciate how a “real” experiment is conducted. Note that this recording was made in V1, where the hallmark feature of neurons is their orientation tuning.

Neurons in MT receive the majority of their inputs from V1, and physiologically, they are characterized by their strongly direction-selective responses to stimuli that move through their spatial receptive fields (Maunsell and Van Essen, 1983). Critically, activity of neurons in MT is correlated with the perception of motion (Born and Bradley, 2005). Each neuron has a “preferred” direction, which causes the highest mean spike rate to be evoked. Motion in directions opposite the preferred (commonly referred to as the anti-preferred or non-preferred direction) evoke the lowest mean spike rate. Near-preferred directions evoke intermediate levels of spiking, such that many neurons respond to a range of directions spanning 90-180° around the preferred direction (see Figure 4).

The **Instructions** tab gives basic instructions on how to operate the simulation. How students explore the

Visual neuroscience *experiments*

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Background

Simulation

Visual cortical neurons

Sensory neurons encode information about stimuli in the timing, and rate, of action potentials. Neurons in different areas of the brain are sensitive to different stimulus properties. For example, in primary visual cortex (V1), neuronal responses are strongly affected by the orientation of a stimulus. For a single neuron, different orientations evoke different rates of spiking; and different neurons have different “preferred” orientations. The video on the right shows recordings made in the 1960s from the laboratory of David Hubel and Torsten Wiesel, who first demonstrated orientation selectivity in V1, and won a Nobel prize for related work on the visual system. You can hear the amplified ‘spiking’ activity of a single cortical neuron, and see the visual stimulus that has evoked that activity. As you watch the video, think about the properties of the stimulus that evokes the weakest and strongest neuronal responses.

In the middle temporal area (MT), neuronal responses are strongly affected by orientation, but also by the direction and speed of moving objects. While each direction evokes a different average spiking rate, the responses to repetitions of the same stimulus are surprisingly variable. A further complication is that responses scale with contrast – larger responses are seen at higher contrasts.

This means that given the spiking responses of just one neuron, it is impossible to determine what stimulus was presented. For example, a spiking rate of 30 spikes in a second might be evoked by a fast, high contrast stimulus moving upwards, or a slow, low contrast stimulus moving to the right. The brain therefore relies on populations of neurons to reliably encode stimulus features.

In this simulation, you will quantify how the responses of a typical neuron in MT depend on motion direction, contrast, and some other unrevealed factors. This can be used to assess how much information a neuron conveys about the stimulus, and the reliability of that information. We can then infer how populations of neurons work together to accurately encode a diverse range of stimuli.



Figure 1. Background tab. Background information is complemented by an embedded YouTube video of an experiment by David Hubel and Torsten Wiesel in the 1960s, which shows the procedure for mapping characteristics of the receptive fields and tuning properties of neurons in cat primary visual cortex.

simulation depends on the formative or summative questions provided by their instructor, thus the online instructions only describe what students can directly control and see – not how they should think about the results.

The simulation allows neurons with unique tuning properties to be generated randomly, reflecting the inter-neuronal variability encountered in real experiments. A second purpose of having each student analyse a unique neuron is to limit the opportunities for collusion. Therefore, before starting the simulation, each student must “Initialize” the neuron they will be recording from by entering a string such as their name into an input box. The string seeds a random number generator, producing a neuron with unique tuning properties. This feature allows students to return to the same neuron hours, days, or weeks later if they need to obtain more data. It also allows the instructor to corroborate a specific student’s neuronal tuning properties if the student runs into problems, or for grading purposes.

The **Experiment** tab introduces students to the experimental design and process of data collection for many visual neurophysiologists, while highlighting the time-consuming and repetitive nature of real-world data collection. It has four panels (Figure 2) showing: (top-left) the visual stimulus “presented” to the animal; (lower-left) a stimulus control panel to move the grating with the specified contrast in the specified direction for one second after the Start button is pressed; (top-right) a visualization of the neuronal response to the one second stimulus, in the form of an oscilloscope display; (lower-right) a summary graph of the spike counts evoked by each stimulus, which automatically updates at the end of each trial.

To generate the neuronal response and spike counts, the simulation has an underlying model of a neuron, which incorporates realistic direction tuning properties and variability based on our own experimental data collected in macaque MT (Price et al., 2005; Price and Born, 2013).

The mean response (R) of the neuron to a given direction (θ) and contrast (c) is given by:

$$\overline{R(\theta, c)} = Gcf(\theta|\theta_{pref}, \kappa) + B \quad (1)$$

where $f(\cdot)$ is the von Mises function

$$f(\theta|\theta_{pref}, \kappa) = e^{\kappa \cos(2(\theta - \theta_{pref}))} \quad (2)$$

θ_{pref} is the neuron’s preferred direction, κ controls the direction tuning bandwidth, G controls the response gain and B reflects the neuron’s spontaneous activity. Note that while this reflects a realistic model of direction selectivity, the linear scaling of responses with contrast is a simplification (Pack et al., 2005). In essence, Equation 2 describes how spiking rate varies with direction, and is often referred to as a circular Gaussian. Equation 1 describes a way to scale (G) and offset (B) these responses. Figure 4 shows the mean tuning curve of a typical neuron. It is not necessary for students or instructors to understand these equations in order to use

the simulation or analyse the resulting data, we have only included them for completeness.

In order to incorporate realistic inter-trial variability, the number of action potentials produced by the neuron on each trial is chosen from a Poisson distribution with mean given by $\overline{R(\theta, c)}$. The precise timing of each action potential within a one second trial is then drawn from a uniform distribution, ensuring at least a one millisecond inter-spike interval (i.e., the absolute refractory period). To additionally illustrate spike rate adaptation, we transformed these spike times using a power function to skew action potentials to have a greater probability of occurring earlier within the trial.

Spike times are converted into a continuous voltage trace by adding Gaussian white noise with an amplitude ~10% of the action potential amplitude. To replicate the feel of a real experiment, when the Start button is pressed, the stimulus moves for one second (Figure 2, top-left), the scrolling oscilloscope window simultaneously displays the recorded voltage trace, where each of the near-vertical lines represents an action potential (Figure 2, top-right), and the voltage trace is played through the computer speakers in auditory form. This is perhaps the most strikingly realistic aspect of the simulation. The instant auditory and visual feedback capture the qualitative stimulus-tuning properties of the neuron, and highlight the inter-trial variability when a stimulus is repeated.

At the end of each trial, the number of spikes fired by the neuron is automatically plotted on a graph below the oscilloscope (Figure 2, bottom right). The data for each contrast is colored differently according to the legend on the right, and can be toggled by clicking on the legend.

In the **Download data** tab (Figure 3) users can “fast-track” the data collection by downloading a data table with specified experimental conditions. Depending on the assessment question, students must choose an appropriate number of stimulus repetitions, and can choose a simple data format with “Spike counts per trial,” or the more complex “Spike times in trial,” which lists the time (in ms) at which each spike occurred in the trial.

The data sets downloaded from the simulation are .csv files with one row for each trial (the number of trials chosen in the input box in Figure 3 multiplied by the number of different conditions). An example data set is shown in Table 1, where two trials were run for each of 12 different orientations and only one contrast value (80%). As in a real experiment, the stimulus properties on each trial are ordered randomly.

We have incorporated a “hidden” feature to the data, as a column labelled “A,” which has values 0 or 1 (see Table 1). Only upon detailed analysis of the data students can find out that the mean response when A=1 is about 15% higher than the mean response when A=0, all else being equal. This can symbolize, for example, the effects of attentional gain or anesthesia on the neuronal response.

If data is downloaded in the “Spike times in trial” format, the table again includes one row per trial, but the times (in ms) of each action potential are included (so there is a variable number of columns for each row).

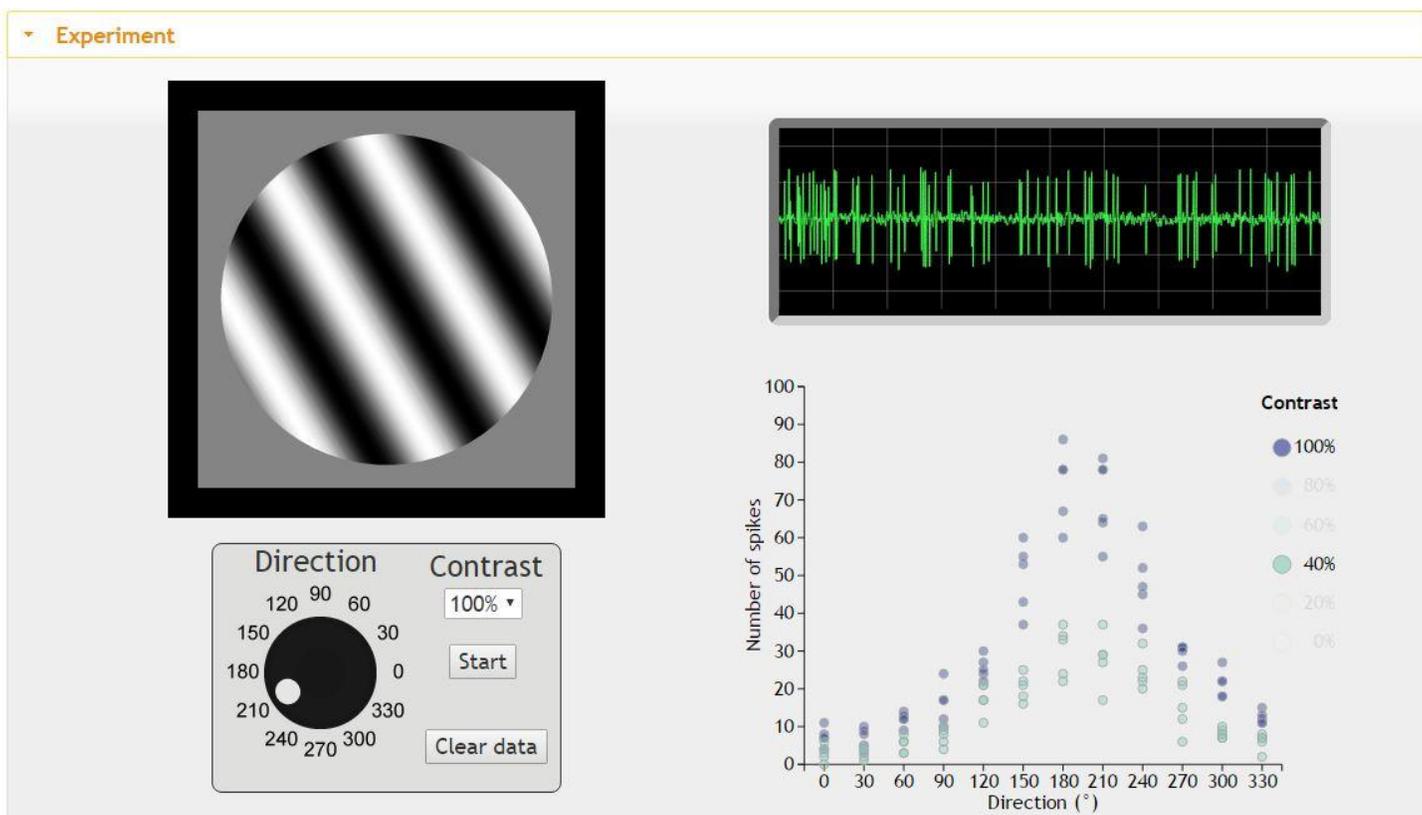


Figure 2. Experiment tab. The left-hand side represents the visual stimulus that the neuron is responding to (drifting grating), and includes the controls for the user to manipulate the properties of the visual stimuli, such as contrast and direction of motion. When the “Start” button is pressed, the grating moves in the specified direction for one second, and the simulated response is shown on the oscilloscope screen (top-right). At the end of the trial, the direction-tuning plot is updated by adding the spike count for the most recent trial.

Figure 3. Download data tab. There are two options for “Type of data”: “Spike counts per trial” or “Spike times in trial.”

Providing flexibility in the format of the data and types of stimuli that are presented was important to us as it allows for varying levels of analysis complexity, according to the student group involved and the instructor’s wishes.

RESULTS

We developed a web-based simulation of electrophysiological recordings from motion-sensitive, direction-selective neurons (Born and Bradley, 2005; Price and

Born, 2009; Bear et al., 2016). The simulation replicates the experience of participating in an experiment, providing both visual and auditory feedback about the recorded neuron’s responses to a range of user-controlled stimuli. Neuronal data can be downloaded for offline analysis. Here, we describe three ways in which we have used the simulation for teaching, and give examples of the types of formative and summative assessment questions that were used in practical classes employing the simulation. An

example Microsoft Excel data file is provided as a supplement, and shows how the data might be reshaped to facilitate basic forms of quantitative analysis and plotting.

Case 1 - Demonstrations

The simplest way to use the simulation and related videos is to demonstrate the practicalities of running an electrophysiology experiment and illustrate how the tuning properties of sensory neurons are characterized. After a brief introduction, we show students a video of an electrophysiology experiment, followed by the responses to multiple stimulus trials in the simulation. In this scenario, students do not have the opportunity to change stimulus parameters themselves, but are provided with the link to the simulation for later exploration. This provides a rapid method for illustrating what an experiment looks like, spike timing variability, tuning of neurons, and the variability in neuronal responses to repeated stimulation. Due to the animations and audio, this is an engaging method of illustrating concepts that are routinely presented in introductory lectures on sensory neuroscience.

Case 2 - Supporting qualitative analysis

In small group teaching where students have access to computers, the simulation has been used to promote and substantiate discussions about *qualitative* aspects of neuronal responsiveness and tuning. Guided by a facilitator, students have the opportunity to explore the effects of changing stimulus parameters, and to engage in discussions about neuronal tuning, neuronal variability, experimental design, and even the ethical considerations associated with running such an experiment.

Both before and during exploration of the simulation, students discuss:

- What is involved in setting up an electrophysiology experiment, with both awake and anesthetised animals. This extends from practical issues such as conducting surgeries, setting up life-support systems, electrode design, signal amplification, and data storage - through to ethical considerations.
- Referring to complementary lecture material, what are the known tuning properties of neurons in V1 and MT?

Students explore, via guided inquiry, concepts such as:

- How do neuronal responses depend on stimulus direction?
- How do neuronal responses depend on contrast? How do the simulated contrast response functions differ from classically reported responses?
- What is the nature of the inter-trial variability in spike timing? Where might this variability originate?
- What is the nature of the inter-trial variability in evoked spike count when a stimulus is repeated, and what implications might this variability have for accurate perception?
- What happens to the probability of spiking throughout a trial? What effect might this phenomenon of adaptation have on perception, and how might it be beneficial from a

neuronal coding perspective?

- Given the observed neuronal variability, what requirements does the brain have for population coding to ensure reliable and accurate perception?

Case 3 - Supporting quantitative analysis

Finally, in practical classes, the simulation has been used as a background to qualitative discussions (as above), followed by quantitative data analysis. In this case, students are required to “design” an experiment that will give insight into some aspect of neuronal tuning, download an appropriate data set, and analyze it (e.g., in Microsoft Excel, GraphPad Prism, or Matlab). We have run this practical in two ways: first, as a single two-hour session, with a requirement for data analysis and literature searching as part of the summative assessment; second, as multiple two-hour sessions across a semester, allowing progressive acquisition of analytical skills and discussion of

Trial number	Direction	Contrast	A	Spike counts
1	180	80	0	63
2	150	80	0	33
3	120	80	0	23
4	90	80	0	10
5	0	80	1	9
6	60	80	0	7
7	330	80	0	11
8	120	80	1	24
9	30	80	0	6
10	270	80	1	23
11	150	80	1	63
12	270	80	0	27
13	90	80	1	13
14	240	80	0	50
15	210	80	0	59
16	180	80	1	67
17	60	80	1	11
18	330	80	1	13
19	30	80	1	10
20	240	80	1	51
21	300	80	1	15
22	210	80	1	71
23	0	80	0	8
24	300	80	0	18

Table 1. Example data downloaded from simulation. In this case, “Spike counts per trial” was selected as the type of data, and two trials were downloaded for each direction of motion for a grating with 80% contrast.

background material. In the latter case students were assessed via separate literature reviews and reports containing their quantitative analysis.

Before downloading data, students are prompted to discuss how many trials or repetitions of each unique stimulus are required to characterize the neuronal responses. In a real-world experiment, researchers may be concerned not just with direction and contrast, but a range of other factors such as stimulus position, size and speed. Students are forced to consider the infeasibility of looking at the responses to all unique stimulus combinations; for example, in an experimental design with 10 directions, 10 contrasts, 10 positions, 10 speeds and 10 sizes, there might be 10^5 unique conditions. Clearly, it is not possible to show every condition the multiple times necessary to characterize a mean response and its associated variability.

Therefore, students are required to design meaningful “experiments” and download appropriately sized data sets that will allow them to perform statistical analyses addressing questions such as:

- How does direction affect neuronal responses? In different scenarios, they may be required to plot direction tuning, fit a function to the data, find the preferred direction, or in conjunction with literature search, define and calculate common metrics of direction selectivity (Figure 4).
- How does contrast affect neuronal responses? Again, this will require plotting, data fitting, and calculation of common metrics found in the literature.
- How do contrast and direction interact (i.e., are they independent)?
- Use significance tests (e.g., t-test; ANOVA) to support arguments about whether direction and contrast have a significant influence on neuronal responses.
- Apply measurements of effect size (e.g., d' ; ROC) to illustrate the discriminability of the responses to two directions (or contrasts).
- Quantify and illustrate how neuronal responses adapt over time in response to a sustained stimulus.
- How does response variability relate to mean firing rate? E.g., calculate and interpret a Fano factor for multiple directions. Note that the Fano factor is the ratio of the response variance to the mean (similar to the coefficient of variation, which uses the standard deviation). For a Poisson process, which describes spike counts quite well, Fano factor = 1.
- Assume the parameter A represents an experimental manipulation; quantify its effect on neuronal responses and tuning. Note that the parameter A simply implements a small gain change, but this will only be evident if responses to dozens of trials are compared. This can be used to support discussion of effects such as anaesthesia and attention.

Desired Learning Outcomes

We typically commence lectures and laboratory classes by providing students with a list of 4-6 learning outcomes or objectives (e.g., “After this lecture, students should be able

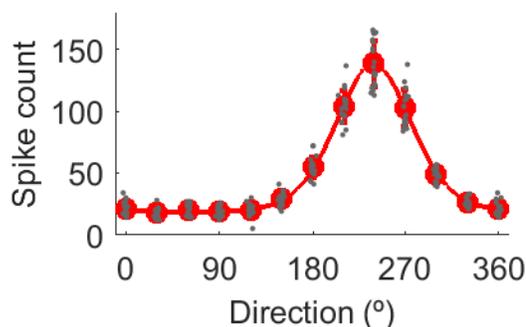


Figure 4. Direction tuning of a single neuron. Red markers and error bars show mean (SD) across 20 repetitions of each direction. Grey data points show responses on individual trials, with a small amount of horizontal jitter to avoid overlapping data points. Data are fit using least-squares regression with a von Mises function (Eq. 1). Based on the fit, the preferred direction is 240° .

to ...”). When using the simulation as a demonstration or for Qualitative analysis (Cases 1 and 2, above), some specific learning objectives are:

- Describe how sensory neurons can represent the properties of environmental stimuli.
 - Sketch the tuning curve of a direction-selective neuron.
 - Describe the origins and nature of variability in neuronal spiking, and how this variability may affect the reliability of sensory coding.
- In addition, when using the simulation to support Quantitative analysis (Case 3), some specific learning objectives are:
- Illustrate the tuning properties of a direction-selective neuron and use common metrics to quantify the strength of tuning
 - Apply and interpret common statistical tests used to assess the significance and effect size of population-level differences.

DISCUSSION

We designed and developed a web-based interactive simulation that allows students to explore how a visual neuron responds to moving stimuli. This simulation fills a gap in biomedical sciences education, by allowing students to “perform” an experiment that they wouldn’t otherwise be able to do because of financial, temporal and ethical constraints. Further, the simulation gives students the opportunity to analyse complicated data sets to answer questions that they have posed themselves. The simulation described in this paper can be used at a range of conceptual levels, including instructor-led demonstrations, the basis of qualitative discussions about neuronal tuning and electrophysiology experiments, and the basis of quantitative, analytical projects.

Numerous online demonstrations and computer-based simulations such as MetaNeuron (Newman and Newman, 2013), Neurons in Action 2 (Moore and Stuart, 2007), and MemPot (Barry, 1990) are available to illustrate the principles of cellular electrophysiology, however, fewer

attempts have been made to simulate sensory neurophysiology experiments. One advantage that our approach has over similar systems-level neuroscience simulations (Grisham et al., 2008; Grisham, 2009) is that it works within a browser, and therefore can be used on almost all computers, tablets, and smartphones without requiring installation of any additional software.

While the simulation incorporates realistic variability, it also always “works.” This is advantageous in that students know the data analysis will be tractable, however, there is also no requirement for students to apply rigorous experimental techniques. This can be a problem in that it doesn’t expose students to the common failures and frequent difficulties of real experimentation. Related to this, all simulations are lacking in the development of practical skills, but may also conceal from students the tactile pleasures of hands-on experimentation. To combat this, we believe that it is important to complement the use of simulations with hands-on experimentation. For example, electrophysiology experiments using sensory and motor nerves in the cockroach leg are relatively simple and cheap, although they rarely generate large amounts of quantitative data for analysis (Marzullo and Gage, 2012; Dagda et al., 2013).

Finally, the code underlying our visual neuroscience simulation is easily adapted to other scenarios, both in the area of vision (e.g., visual coding of attributes such as orientation, color, faces), and of audition (coding of frequency, space, or timing); as well as other types of sensory coding. All that is required is an underlying model of the relationship between stimulus and mean spike count, and a visualization of the experiment itself. For example, we have recently developed a simulation on spatial auditory tuning (Quiroga and Rajan).

To date, we have used the simulation in three units at Monash University. In BMS1052 (Human Neurobiology), which had 540 Biomedical Science students enrolled, we used it as a demonstration within a lecture on the visual system. In PSY3310 (Introduction to Computational Neuroscience), which had 100 psychology students enrolled, we used it as the basis of qualitative discussions within a lecture and quantitative analyses within a two-hour tutorial. In PHY3111 (Sensory and Cognitive Neuroscience), we used it as the basis of one of five mini-projects extending over eight weeks, in which 16 students majoring in Physiology developed detailed analyses and wrote a report answering the questions described in “Case 3 - Supporting quantitative analysis,” above. In all cases students responded positively to the activity, showing great engagement and enthusiasm.

The code underlying all of our simulation is freely available for non-profit, educational use, under a creative commons license: CC-BY-NC-4.0.

The direct link to the simulation is:
<http://ilearn.med.monash.edu.au/physiology/Neurophysiology/visualNeuroscience.html>

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