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STUDENT VERSION

Coincidence detection in the integrate-and-fire neuron

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Abstract: In this activity students will study a linear, first order, one-dimensional ordinary differential equation (ODE) and learn how it can be used to understand basics of neural dynamics. The modeling framework is known in the mathematical neuroscience literature as the "integrate-and-fire" neuron. The form of the model is equivalent to the linear ODE used to describe the RC circuit. This activity assumes familiarity with solving linear first order ODEs, for instance using the integrating factor method. Students are asked to set up and solve a homogeneous version of the equation and a nonhomogeneous version (constant forcing term). Students are asked to set up ODEs (select initial values), solve the ODEs, and perform some related algebraic calculations. Throughout, students are asked to interpret their results in light of biological experiments and biological terms that are explained in the activity. There is a focus throughout on solving the ODE in the presence of unspecified parameters and interpreting how parameter values may affect response characteristics of biological neurons. Outcomes of the project include: improved skill setting up and solving linear first order ODEs (including with unspecified parameters) and demonstrating how mathematical models can improve understanding of dynamic biological systems. There is no requirement or expectation that students have experience with biology or neuroscience.

SCENARIO DESCRIPTION

The human brain is composed of billions of cells called *neurons*. The electrical activity of neurons is the basis for our behaviors, perceptions, thoughts, dreams, and so much more. Mathematical models of this electrical activity can help us understand how the brain works, how to treat brain diseases, and how to unravel the mysteries of cognition and consciousness.

A starting point for understanding the brain is to model the activity of a single neuron. The quantity that describes the electrical activity of neurons is the voltage difference between the inside and outside of the cell. This voltage, typically referred to as *membrane potential* is expressed in units of millivolts (mV). Figure 1 shows an example of the membrane potential of a neuron. Striking

features of the membrane potential of a neuron are the rapid and large swings in voltage (labelled as *spikes in* $V(t)$) and smaller fluctuations near a "resting" value of the voltage (labelled as $V(t)$ *near rest*). Since membrane potential is a quantity that changes over time, ordinary differential equations are a natural mathematical language for describing the time-course of $V(t)$. Modeling $V(t)$ in all its detail requires systems of nonlinear differential equations [1], but in this activity you will learn that much about a neuron can be learned by describing $V(t)$ with a linear, first order, one-dimensional ordinary differential equation (ODE).

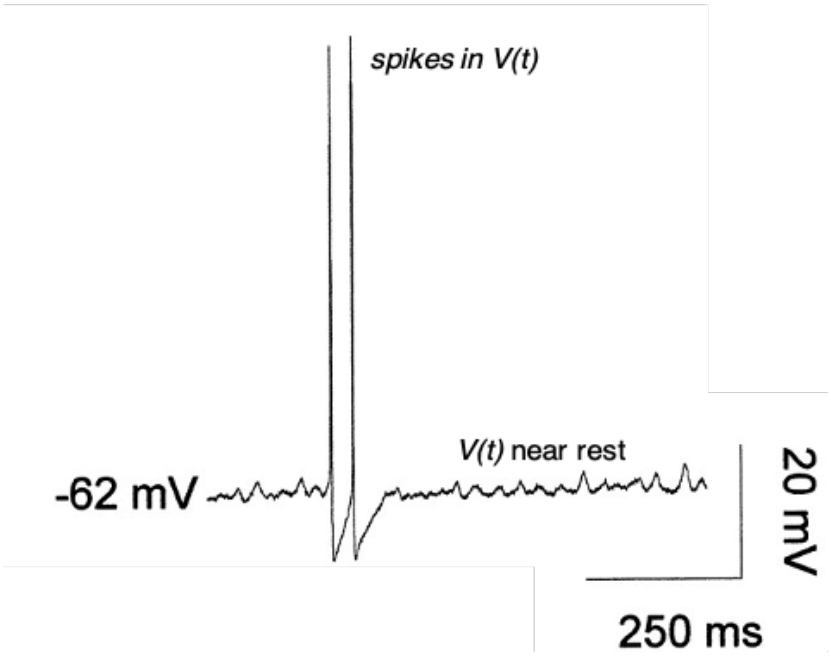

Figure 1. Voltage in a neuron exhibiting large and sudden spikes and small fluctuations near rest. This voltage time-course was recorded from a slice of a rat's brain taken from a region that is involved in the perception of smell (the olfactory bulb) [4].

The membrane potential changes when electrically-charged particles, called *ions*, flow into and out of the cell. For example, a flow of positively-charged ions into the cell will increase the membrane potential. The idea behind most mathematical models of neurons is to treat flow of current into and out of a cell as you would the flow of current around an electrical circuit. An important example of a mathematical model that uses this electrical circuit idea to describe a neuron's voltage is the *integrate-and-fire model* [2, 3]. It is one of the first models used to describe neural voltage and is still used by many researchers. This model was created by assuming that the membrane of a cell acts the same as an electrical circuit composed of a capacitor in series with a resistor. The ODE

associated with this model is:

$$C\frac{dV}{dt} = -\frac{1}{R}(V(t) - E) + I(t). \tag{1}$$

The following parameters are constants: C is the membrane capacitance (units: picoFarad), R is the membrane resistance (units: megaOhm), and E is the resting potential of the neuron (units: milliVolts). The term $I(t)$ is an input current (units: nanoAmps). This term can represent, for example, current injected into the neuron by a neuroscientist who has inserted an electrode into the cell, or the natural flow of current between two neurons that are coupled together in the brain through a structure called a "synapse."

This equation can be simplified by introducing a new parameter $\tau = RC$ called the *membrane time constant* (units: milliseconds) and by measuring voltage relative to the resting potential $v(t) = V(t) - E$. The resulting first order linear differential equation for membrane potential is

$$\tau\frac{dv}{dt} = -v(t) + RI(t) \tag{2}$$

In this project you will study solutions to this equation and pay particular attention to the importance of the parameter τ. You will learn how it can be measured in real neurons and how the value of this parameter can determine how neurons respond to different types of inputs.

1 Estimating τ from the voltage dynamics of neurons

The membrane time constant is an important parameter that determines the dynamics of the neuron. A way to measure τ in real neurons is to start an experiment with the membrane potential beginning at a value that is slightly above its resting value. The neuroscientist can then measure $v(t)$ as it decays to 0 mV. If the time-course of $v(t)$ returns to 0 mV in the shape of an exponentially-decaying curve, then the decay rate of this curve can used to estimate the membrane time constant τ.

(a) Set up and solve the initial value problem that would model this experiment. Choose a few different values of τ and sketch the solution. Typical values of τ in real neurons range from around 1 millisecond to 100 milliseconds. A database of values of τ for many different types of neurons can be found at `https://neuroelectro.org/ephys_prop/4/`.

(b) Figure 2 is a graph that was published in a scientific journal article [5]. It shows the voltages in a real neuron measured by neuroscientists (thin black line) and the exponential curves that the neuroscientists fit to these data in order to estimate τ (thick black lines). The membrane time constants estimated from these curves were approximately 0.4 ms and 1.2 ms. Say which curve ("normal" or "DTX-K") goes with which time constant (0.4 ms or 1.2 ms).

(c) The label "DTX-K" refers to a neurotoxin that the scientists applied to the neuron to change its membrane resistance (parameter R in (1)). Did the use of DTX-K increase or decrease membrane resistance? Explain your reasoning briefly (one sentence should be enough).

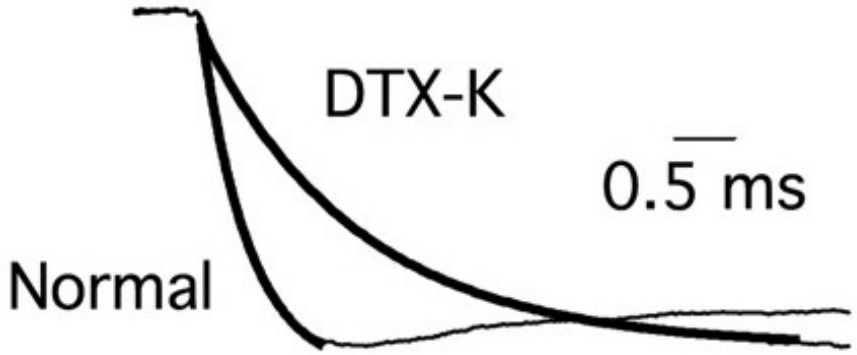

Figure 2. Voltage in a neuron as it returns to rest in a control condition ("normal") and after application of dendrotoxin-K ("DTX-K"). These voltages were recorded from a neuron in a slice of a gerbil's brain taken from a region that is involved in the perception of sound (the medial superior olive) [5]. The scale bar at right represents a time interval of length 0.5 milliseconds. The thicker black curves show the exponential curves that have been fit to the recorded voltage trace.

2 Threshold for spikes and the interspike interval

The linear ODE in (2) cannot produce the large and rapid changes in $V(t)$ that are labelled as *spikes* in Figure 1. Instead, users of this model define some constant voltage value to be the *spike threshold*, often denoted by θ. Any time $v(t)$ reaches this threshold value, the model neuron is said to have produced a spike and the voltage is immediately reset to the resting voltage $v = 0$ mV. This process of $v(t)$ approaching threshold and then spiking (or "firing") when $v(t)$ hits the threshold is why this model model is known as the *integrate-and-fire* neuron.

(a) Consider the case of a neuron receiving a constant, positive input ($I(t) = I$) and set the spike threshold to be $\theta = 1$ mV. Set up and solve an initial value problem in this case.

(b) Suppose a spike has just occurred at time $t = 0$. Use your answer to (a) to find the time to the next spike. You can denote the time to the next spike as T. This quantity is known to neuroscientists as the *interspike interval*. Your final answer should be an equation for T, expressed in terms of the parameters τ, R, and I.

(c) How does the interspike interval depend on τ? In other words, does T increase or decrease with τ?

(d) Based on your answer to (c) and your observations in Question 1, would you describe a neuron with a small membrane time constant as "fast" or "slow"?

3 Neural coincidence detection

The billions of neurons in the brain exhibit a wide variety of dynamics and have a wide variety of "jobs." As a result, neurons can have very different electrical properties from one another. Membrane time constants, for instance, are smaller than 1 ms in some neurons and larger than 100 ms in other neurons.

For this problem, you will think about neurons that have the specialized capability to generate spikes only when inputs arrive close together in time, and to not generate spikes when inputs do not arrive close together in time. Neurons with this property are called *coincidence detectors*. You will use your understanding of (2) to predict whether coincidence detector neurons should have small or large membrane time constants.

Suppose $I(t)$ consists of two pulses of current that are infinitesimally-narrow in time. Mathematically such instantaneous events can be described by something called the Dirac delta function. We say the first current pulse occurs at time t_1 and the second occurs some time later at time t_2. Each of these inputs causes the voltage of the neuron to instantaneously increase ("jump up") by an amount that we will call Δv. Figure 3 shows examples of the voltage response to these inputs (solid black curve with two peaks). In this example, a first input arrives at $t_1 = 0$ ms and increases the voltage by $\Delta v = 2/3$ mV and a second input of the same strength arrives at $t_2 = 1$ ms. Thus the two inputs are separated by $t_2 - t_1 = 1$ ms. These inputs do not increase the voltage enough to bring $v(t)$ across the threshold (shown as a dashed black line at the top of the figure). If the inputs were closer together in time, then the voltage responses to each input may sum up and cross threshold. The instantaneous input pulses described in this problem can be thought of as a simple way to model how neurons are connected to one another in the brain through structures called *synapses*.

(a) Set up and solve the initial value problem that models the voltage of a neuron immediately after the second of the two instantaneous inputs. In other words, set up and solve the initial value problem to calculate $v(t_2)$. To do this, you will first set up and solve an initial value problem that described $v(t)$ in the time interval $t_1 \leq t < t_2$. Then you will add Δv to your solution to get the value of v after it has been instantaneously increased by the second input.

Your final answer will be an equation for $v(t)$ in terms of the parameters $t_2 - t_1$ (the time between inputs), τ (the membrane time constant), and Δv (the voltage increase caused by each input). To simplify your calculations you can assume the first input arrives at $t_1 = 0$ ms.

(b) Using your answer to (a), find an equation for the largest value of $t_2 - t_1$ for which the neuron's voltage crosses threshold. This quantity is called *coincidence detection window* of the neuron. If inputs arrive closer together in time than that value, the neuron will spike (its voltage will cross threshold). If inputs arrive further apart in time, voltage will remain below threshold.

(c) How does the coincidence detection time window depend on τ?

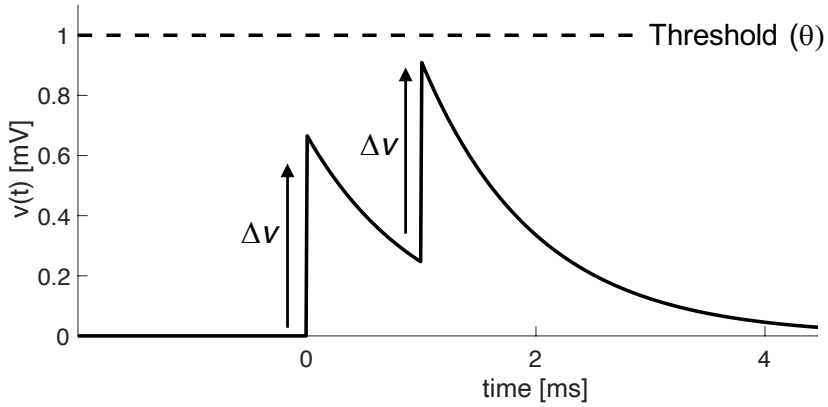

Figure 3. Voltage trace of the integrate-and-fire model in response to instantaneous inputs that displace voltage by an amount $\Delta v = 2/3$ mV. In this figure the first input is at $t_1 = 0$ ms and the second is at $t_2 = 1$ ms, resulting in a time difference of $t_2 - t_1 = 1$ ms. Other parameters used for this figure: membrane time constant is $\tau = 1$ ms and spike threshold is $\theta = 1$ mV (horizontal dashed line).

(d) A good coincidence detector neuron should spike only when inputs arrive close together in time and not spike when inputs arrive far apart in time. Based on your calculations, do you predict that coincidence detector neurons are "fast" or "slow" neurons (small or large time constants)?

(e) Coincidence detectors can be found at several locations in the brain involved in the processing of sounds. Two such regions are the *cochlear nucleus (ventral) octopus cell* and the *medial superior olive ventral cell*. Explore the database of time constant measurements at `https://neuroelectro.org/ephys_prop/4/` and determine if the time constants of neurons in these regions match what you predicted in (c). Explain (briefly) what you find.

Tip: Click the blue button "view data in table form" to search the table more easily.

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