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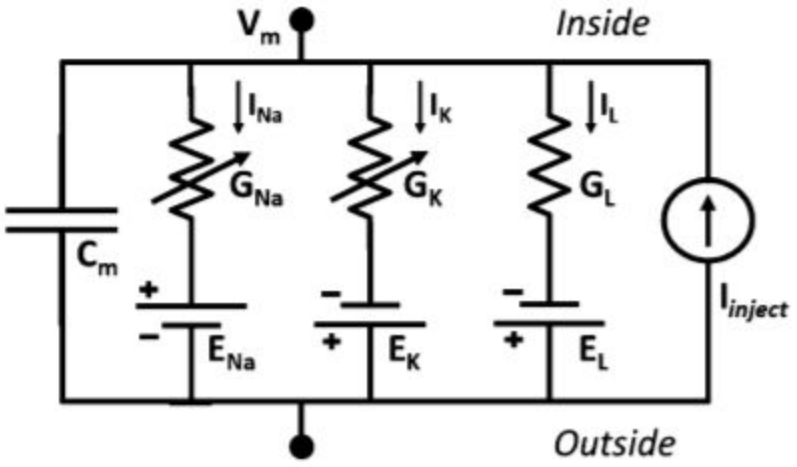
Modeling of the Hodgkin-Huxley Neuron

Introduction

A model was developed in Simulink in order to investigate the dynamics of the circuit derived by Alan Hodgkin and Andrew Huxley in 1952, which they later received a Nobel Prize for.[5] In short, the Hodgkin-Huxley equations are used to model the electrical behavior of a neuron during the firing of an action potential.

The circuit consists of five parallel branches: one branch includes a current source for injected current, which may be from a voltage clamp device, ion pumps, or from the action of neurotransmitter released from a presynaptic neuron; another branch includes the capacitance of the membrane; the final three branches each model different ion channels and consist of a resistor in series with a battery, with the conductance of the resistor determined by the number of open ion channels in the membrane and the voltage of the battery based on the equilibrium (Nernst) potential due to the distribution of the ions across the membrane.[2] In a typical neuron, the action potential is primarily mediated by the action of sodium currents flowing into the cell and potassium currents flowing out of the cell, though chloride, calcium, and other ions also flow through certain channels. Thus, sodium serves to depolarize the membrane, while potassium repolarizes it at the peak of the action potential and, due to the action of potassium channels, briefly hyperpolarizes the cell, leading to an absolute refractory period, during which the cell cannot respond in any way to incoming signals, and a relative refractory period, during which the response is diminished. These behaviors are the result of the gating kinetics of voltage-gated sodium and potassium channels, which make up two of the three remaining branches. The final branch represents the leakage current, due to non-voltage-gated ion channels that are constitutively open. These permit leakage of ions during the resting state, serving to ensure that the Na^+/K^+-ATPase pumps are continuously active to maintain the electrochemical gradients.[4] The circuit is depicted below, from [1].



The above circuit ultimately yields a differential equation in terms of the capacitive, ionic, and injection currents which may then be solved for the membrane potential:[1]

$$C_m \frac{dV}{dt} = g_{Na}(E_{Na} - V) + g_K(E_K - V) + g_L(E_L - V) + I(t)$$

in which the lefthand term represents the capacitive current of the membrane, as capacitive current is proportional to the time derivative of the voltage, the first three righthand terms represent the ionic currents due to sodium, potassium, and leakage, respectively, and the final term represents the injection current. Note that the order of the potentials in the subtraction has been flipped in order to account for the negative sign from moving these terms to the opposite side. This equation can be solved for the membrane voltage by dividing by the membrane capacitance and integrating the righthand side. This version of the differential equation is used in the model, in which the current contributions from each branch except the capacitive are added and integrated to yield the membrane voltage.

Though the above equation seems rather simplistic at first glance, complexity arises due to the dependence of the sodium and potassium conductances (g_X) on the membrane voltage. As these channels are voltage-gated, they will open in response to membrane depolarization, with the potassium channel taking longer to respond, allowing for the rapid growth phase due to sodium channel opening characteristic of the action potential. The repolarization phase is mediated by the opening of the slower potassium channels and transition of voltage-gated sodium channels to the inactivated state due to the action of a "ball-and-chain" N-terminal domain which closes the channel in a time-dependent manner.[2] The kinetics of these voltage-gated channels can be described by gating parameters, *m, h,* and *n*. The latter describes the gating of the potassium channels while the former two describe the sodium channel. Thus, the conductances of the neuron are modeled by the equations $g_{Na} = g_{Na}^0 hm^3$ and $g_K = g_K^0 n^4$, with the gating parameters described by the differential equation $\frac{dp}{dt} = \alpha_p(1-p) - \beta_p p$, wherein p is *m, h*, or *n*. Finally, the parameters in this equation are given by (from [1]):

$$\alpha_n(V) = \frac{0.01(10 - V)}{\exp\left(\frac{10 - V}{10}\right) - 1} \quad \beta_n(V) = 0.125\exp(-V/80)$$

$$\alpha_m(V) = \frac{0.1(25 - V)}{\exp\left(\frac{25 - V}{10}\right) - 1} \quad \beta_m(V) = 4\exp(-V/18)$$

$$\alpha_h(V) = 0.07\exp(-V/20) \quad \beta_h(V) = \frac{1}{\exp\left(\frac{30 - V}{10}\right) + 1}$$

Note that the variable, V, in the above equations actually corresponds to V_m-V_{RMP}, where V_{RMP} is the resting membrane potential of the neuron.

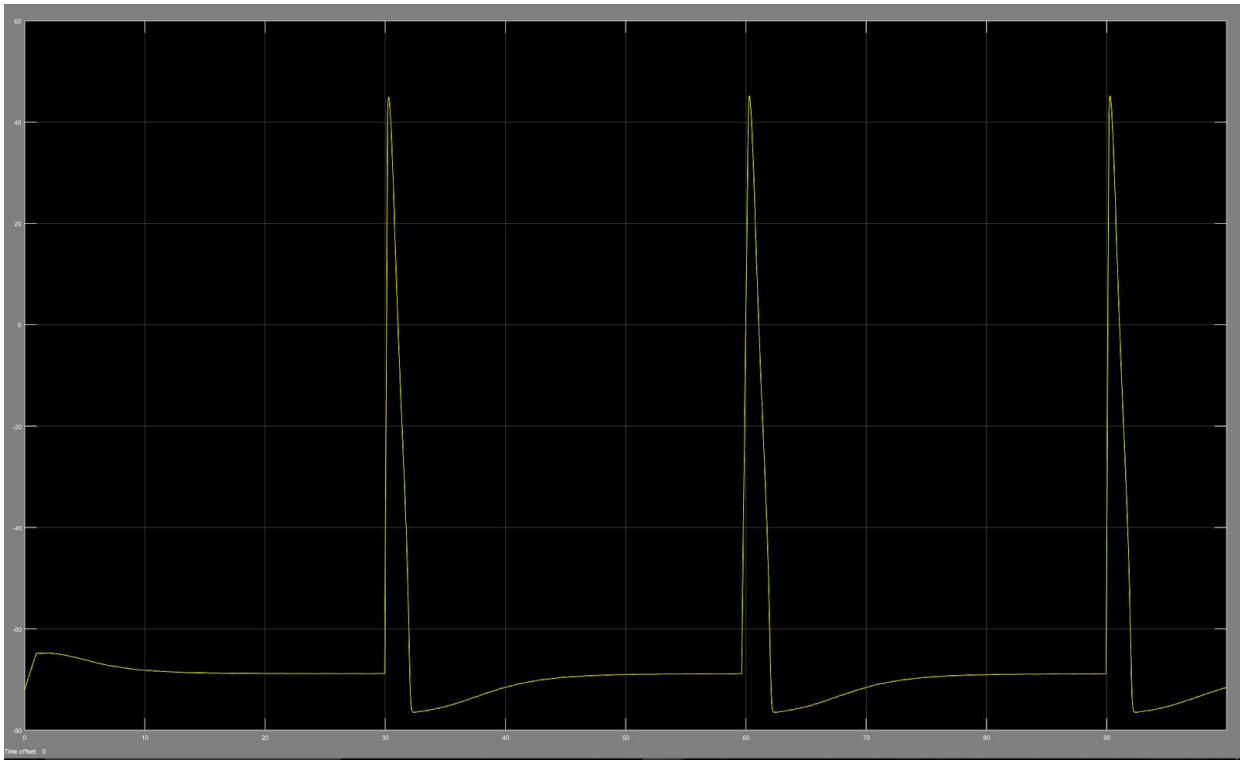
Model

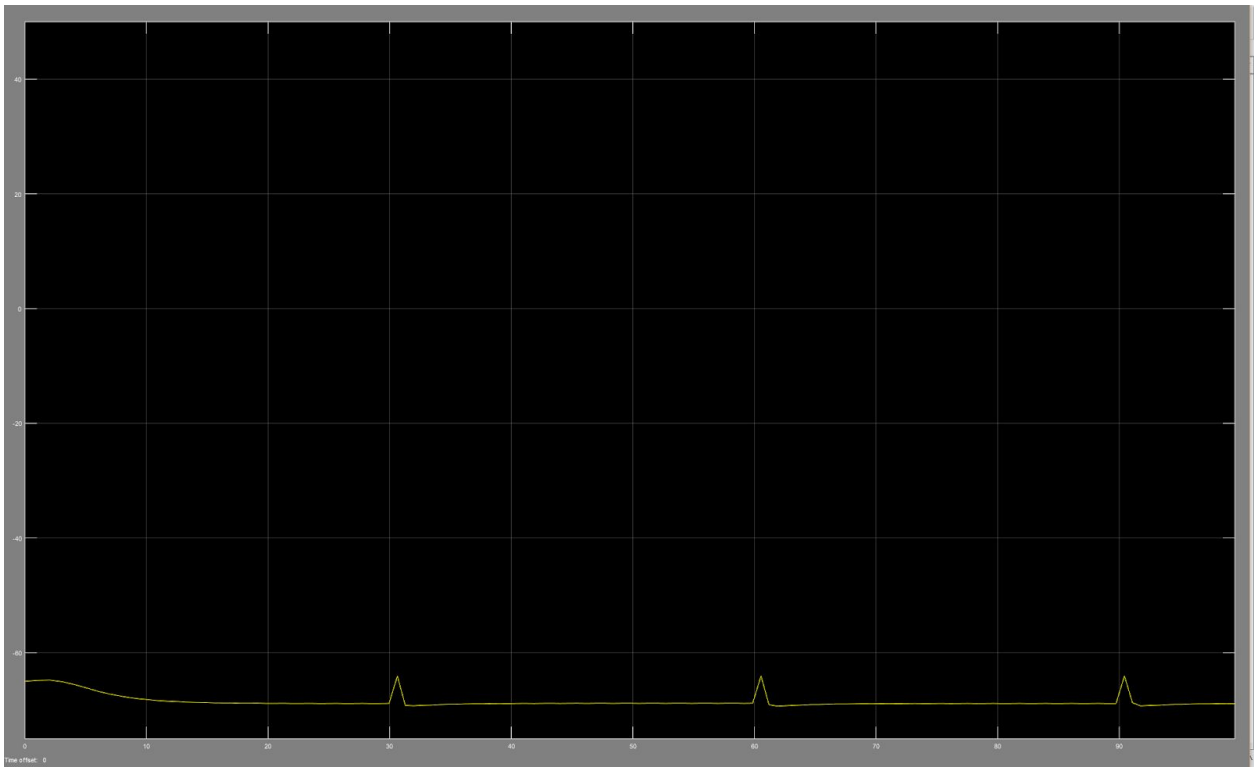
The model consists of three subsections, corresponding to the three branches of ionic currents, which are then added to the pulse generator current, corresponding to the injection current, and the sum is divided by the membrane capacitance and integrated to yield the membrane voltage. The membrane capacitance is taken to be 0.001 mF/cm^2.[3] This voltage is fed back into the required spots (i.e. the calculation for V_m-V_{RMP}, and the E_X-V terms for each ionic current. The resting membrane potential is taken to be -65 mV, as is the initial value of the voltage, in order to reduce the time needed for the conductances to reach their steady-state values.[3] Even so, a 30 msec window is used before the first pulse is generated. Pulses of amplitude 20 μA/cm^2 are injected every 30 seconds with a pulse width of 1 msec.

Once the difference between the current voltage and the resting membrane potential is calculated, it is fed into the α and β parameters for each of the three gating variables. These quantities are represented as functions which are manually input according to the forms specified above, and are then multiplied by either *(1-p)* or *p*, subtracted, and integrated in order to yield the gating variable at each point. For *m* and *n*, the values are raised to their respective exponents, and are multiplied together with the electrochemical driving force (the Nernst potential-the current potential) and the constant conductance value. The equilibrium potentials for sodium, potassium, and the leakage channels are taken as +55 mV, -77 mV, and -65 mV, respectively, and the constant conductances are 40 mS/cm^2, 35 mS/cm^2, and 0.3 mS/cm^2.[3] These currents are then fed into the sum with the pulse generator, as discussed above.

Dynamics of the Model

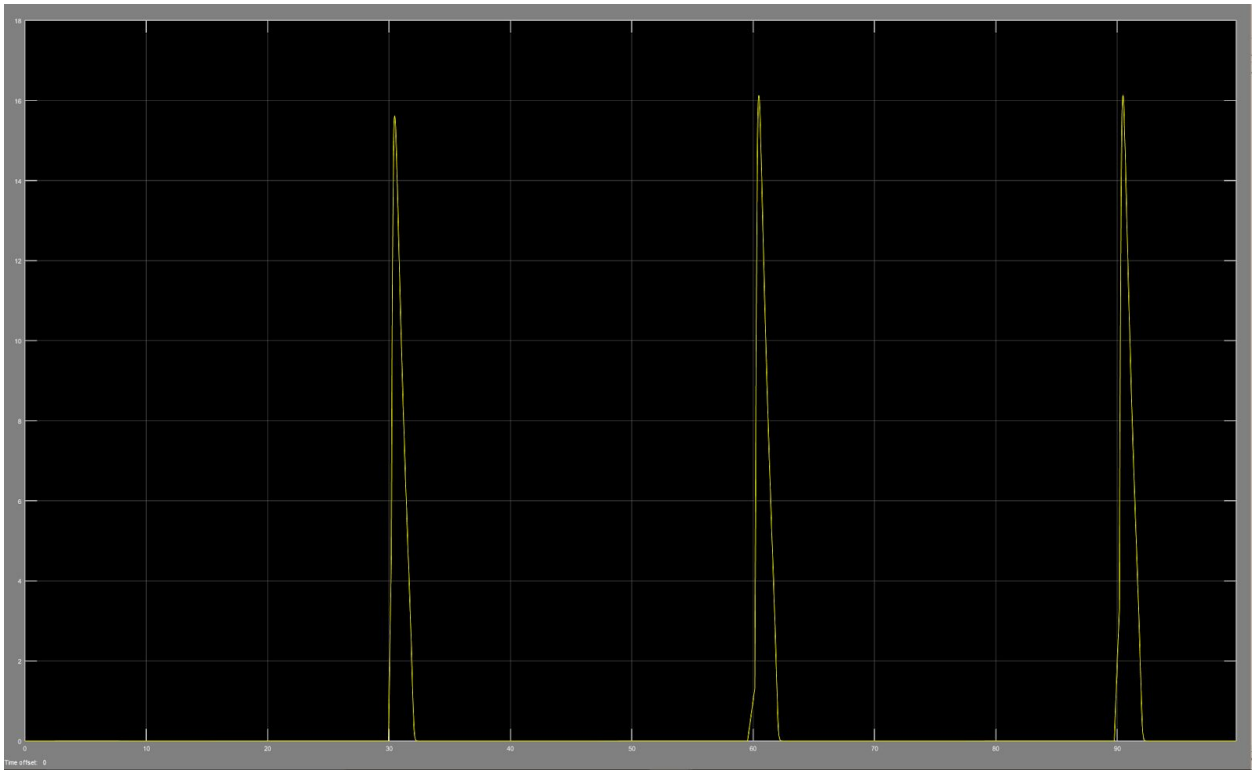
With the above specified parameters, the model yields the following voltage over 100 ms, shown in the first figure on the next page. The action potential, as expected, rapidly depolarizes the membrane, peaking at approximately +45 mV, and then rapidly repolarizing through the hyperpolarizing regime, until the remaining potassium channels eventually close. Each action potential has the same peak value, as the cell has been allowed to return to the resting state before another pulse was introduced. If the pulse amplitude is reduced below the threshold value for action potential generation, then the following image is observed. As expected, the cell does not depolarize, and the injected current is rapidly counteracted, returning the cell to its resting potential. By iteratively changing the pulse amplitude, it was determined that the smallest integer pulse amplitude sufficient to elicit action potential generation is 4 μA/cm^2.

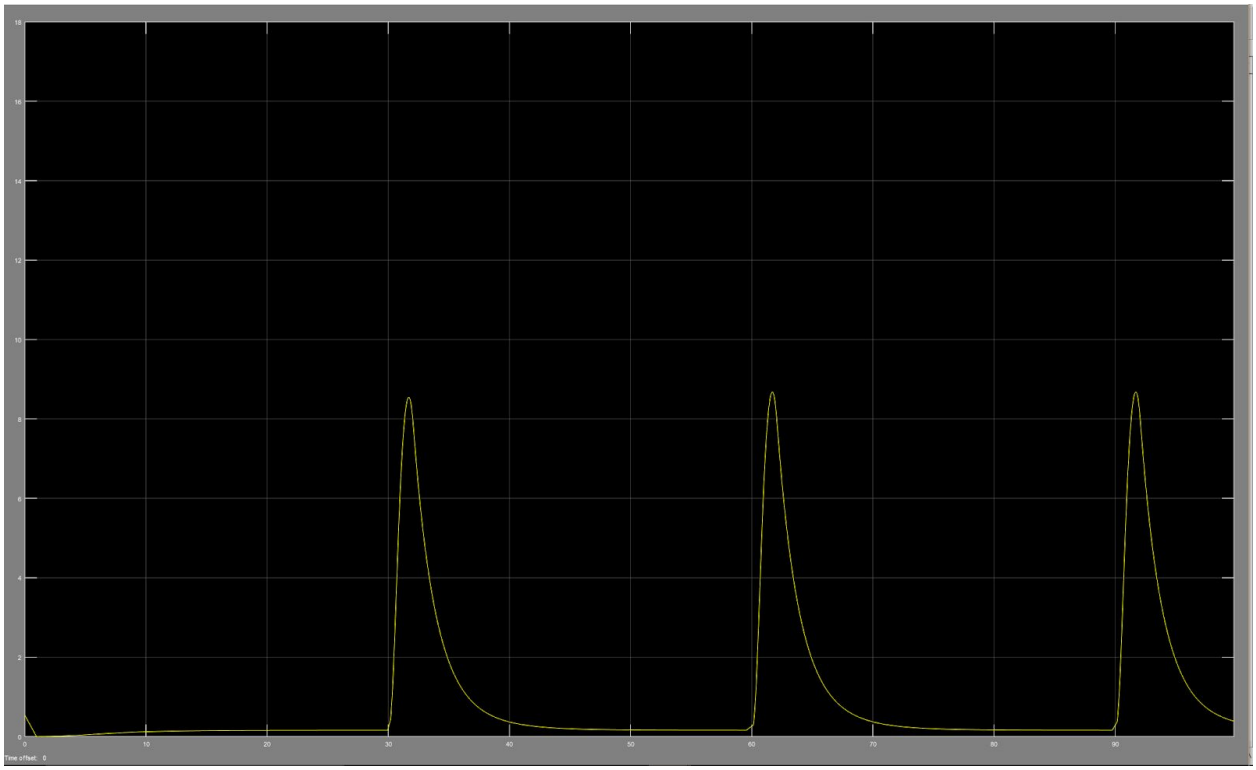




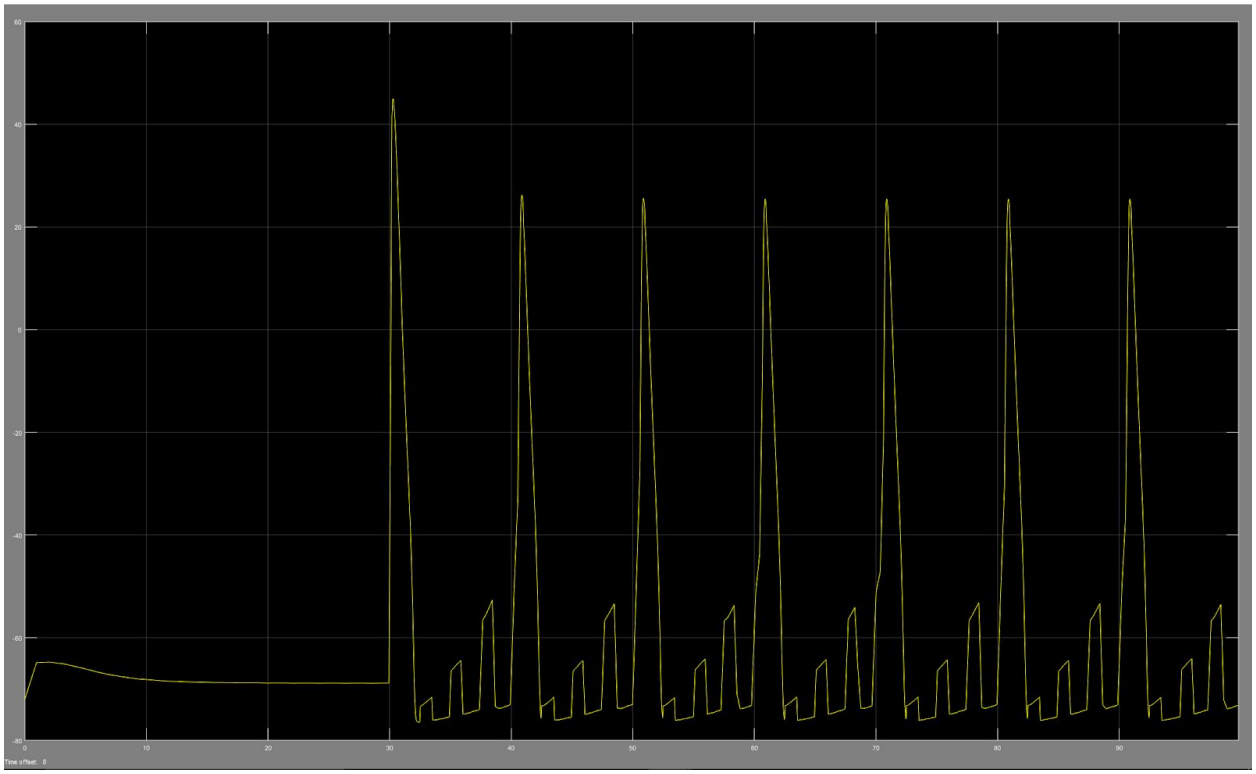
For the case in which a depolarization was elicited, the membrane conductances due to the voltage-gated sodium and potassium channels are depicted below with the sodium channel on

top. The sodium conductance is approximately a factor of two larger than the potassium conductance, and peaks earlier.





If, instead, the pulses were rapidly administered at the same pulse amplitude and width but every 2.5 msec, the pattern depicted below is obtained as a result of the refractory period of the neuron. During this period, not enough sodium channels have returned to their closed state from the inactive state to support the generation of a complete action potential, leading to the small graded depolarizations seen between the action potentials. It may also be noted that the cell has not yet returned completely to its resting state upon the generation of the second action potential, as the peak amplitude is nearly 20 mV smaller than that of the normal action potential from the resting state.



Conclusion

Based on the above observations, the model appears to accurately depict the dynamics of the action potential. Numerous examples exist in literature which contain plots of the above behaviors, including refractory and non-refractory action potentials, above- and below-threshold responses, and conductances of voltage-gated sodium and potassium channels, including those in [2] and [6], which are consistent with this model.

References

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4. Kandel, Eric R., et al. *Principles of Neural Science* 5th ed. New York: The McGraw-Hill Companies, Inc., 2013. Print.
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