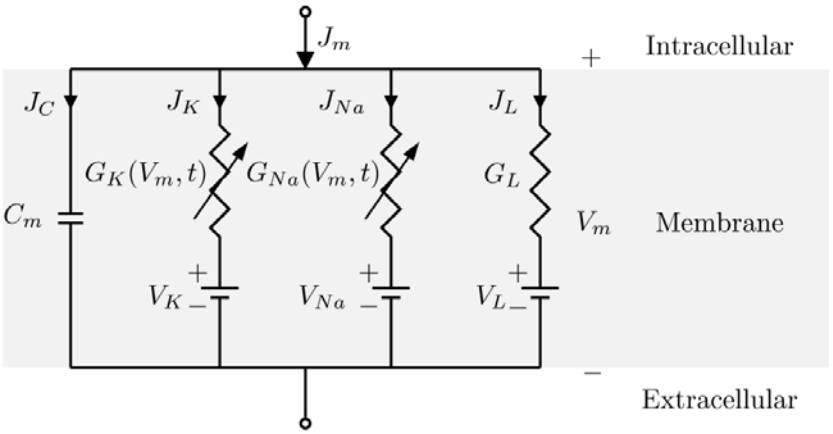
Hodgkin Huxley

The Hodgkin-Huxley (H&H) model of the action potential is perhaps the single most important theoretical achievement in modern neurobiology. It consists of a set of differential equations that describe neuronal "firing". The model, and the experimental work that led up to it, earned its authors the 1963 Nobel Prize, establishing a new framework for thinking about the electrical activity of neurons. The aim in this exercise to model excitable membrane of an axon using H&H network model based on the rate constants for ionic channel conductivities determined by H&H. (You can use MATLAB or Python for simulations)

Let us consider the following model:



The constants of the H&H model are the constant inputs of the model (See Appendix A).

To generate basic HH type neuronal firing:

Step 1: Define an external input current, amplitude and duration for which it is active. Be sure to match the units for the current ($\mu A/cm^2$). A reasonable *dt* (time step) would be 100 times smaller than the duration of an action potential. The total time duration could be, say, 1000msec.
Step 2: Initialize the gating variables *m*, *n*, *h* and find their values at resting state. Set this as the initial condition.
Step 3: Setup the rate constants for the gating variables as a function of the membrane potential. (See Appendix A)
Step 4: Setup the H&H model equations and solve the ODEs i.e., update the 4 state variables for every time step. (See Appendix A)

(You can solve the differential equations using Euler's first order approximation or any of MATLAB's in-built ODE solvers.)

Bioelectronics and Biosensors, Fall 2016
Bonus Programming Exercise

Part 1: Effect of applied current on firing frequency

When a neuron is stimulated, it responds by firing an action potential. The nervous system uses neural firing to relay messages and to process information. For instance, sensory signals are transmitted by sensory neurons that fire sequences of action potentials in various temporal patterns, in the presence of external sensory stimuli, such as light, sound, taste, smell and touch.

Below we will simulate the response to a very basic step current input:

(a) Simulate the behavior for applied step currents of 1, 5, 10, and 500 $\mu A/cm^2$. For each case, **graph** the voltage vs. time, and describe in words the behaviors that you see. **Please note**: The lecture notes in the class includes the term $K_T = 3^{(T-6.3)/10}$, which accounts for the temperature factor in the rate constants. Here we assume the temperature to be 6.3°C so that $K_T = 1$.

(b) You should be observing four qualitatively different behaviors above. Find the three threshold values of the current that separate these four types of behavior. In other words, below a certain value of applied current, behavior 1 occurs; whereas above this, behavior 2 occurs. And so on for the other thresholds. A good current step would be $0.01\mu A/cm^2$ for thresholds 1 and 2, and $1\mu A/cm^2$ for threshold 3. **Indicate** all threshold values on the graph you plot in part a.

(c) One of the four types of behavior you should have described above is convergence to repetitive firing of action potentials that continues indefinitely. What is the minimum and maximum frequency range of such firing as you increase the applied external current? **Include** the maximum and minimum frequency on the graph of part a. Explain why repetitive firing is impossible above this maximum.

Part 2: Anode Break

One of the properties of neuronal firing is anode break, also known as post inhibitory rebound. It is an electrophysiological phenomenon whereby a neuron fires action potential in response to termination of a hyperpolarizing current. Such a property is observed in different neuronal types, including those in the thalamus. We will simulate that property here.

Experiment with the following stimulation: start with zero applied current, step to a negative value, and then step back to zero. Find an amplitude and duration of the negative step such that the HH model fires an action potential afterwards. **Plot** V, I as a function of time; m, h, and n as a function of time. Explain in words why this phenomenon happens. Hint: Look at the temporal properties of the gating variables.

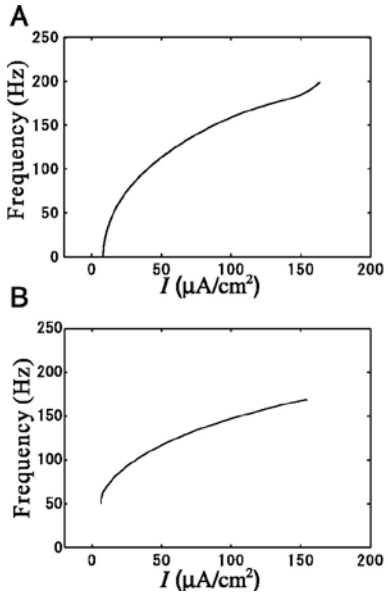
Although the Hodgkin–Huxley model has been tremendously successful, there are limitations. The fact that Hodgkin and Huxley found it expedient to work in the squid giant axon, for example, has had consequences for our understanding of the biophysics and evolution of ion channels. Specifically, the squid giant axon is a highly specialized biological device whose sole purpose is to activate the muscles of the squid's mantle rapidly and reliably to generate its jet propulsion mechanism. As a result, the ion conductances of the axon have evolved for speed. Thus, they are less complex than those found in other neurons. We now know that most other neurons are much more complex, especially with regard to the number and diversity of potassium conductances. Nevertheless, these more complicated conductances are still generally represented computationally using a Hodgkin–Huxley formulation. In the following parts, we will now include additional potassium channels, and see their effects on firing rates of the neuron.

Part 3: *A*-type Potassium channel

Hodgkin (1948) had noticed the two different types of f–I (firing rate vs. Current) curve in axons from the crustacean *Carcinus maenas*. They are depicted in the figure below. Both types of model exhibit a threshold level of current below which the neuron is quiescent. The two different behaviors can be categorized as: those with a continuous frequency-current curve are called Type I (subplot A) whereas those with a discontinuous frequency-current curve are called Type II (subplot B). In part 1 of this exercise we saw that as soon as the threshold is crossed, the model starts firing at a non-zero frequency, depicting type II behavior. It wasn't until Connor and Stevens (1977), who included the A-type potassium current in their model which produced Type I behavior. In the model with the A-type conductance, the firing frequency just above the threshold is very close to zero and increases gradually. The A-type current has also been characterized in mammalian hippocampal CA1 and CA3 pyramidal cells.

Type I

Type II



Connor and Stevens achieved this by adding the A-type potassium channel with conductance g_A and an associated equilibrium potential E_A to a current equation, which includes the modified versions of the Hodgkin–Huxley sodium and potassium, delayed rectifier conductances. In contrast to the standard potassium delayed rectifier current for H&H, the A-type current is inactivating, and has a lower activation threshold. In response to sustained current injection, in the model containing the A-type conductance, the onset of action potentials is delayed compared to the onset of action potentials in the pure HH model. This is because the A-type potassium channel opens earlier as the membrane potential increases towards the spiking threshold, slowing the rise of the membrane potential. However, eventually the A-type current inactivates, reducing the pull on the membrane potential towards the potassium equilibrium and allowing the cell to fire.

The A-type conductance was modelled using independent gating particles: three activating particles *a* and an inactivating particle *b*, described directly in terms of the asymptotic values and τ functions.

$$a_\infty = \left[\frac{0.0761\exp[0.0314(V+94.22)]}{1+\exp[0.0346(V+1.17)]}\right]^{1/3}$$

$$\tau_a = 0.3632 + 1.158/(1+\exp[0.0497(V+55.96)])$$

$$b_\infty = \left[\frac{1}{1+\exp[0.0688(V+53.3)]}\right]^4$$

$$\tau_b = 1.24 + 2.678/(1+\exp[0.0624(V+50)])\,.$$

The rate functions used for the gating variables *n*, *m*, and *h* of the Connor-Stevens model are:

$$\alpha_m = \frac{0.38(V+29.7)}{1-\exp[-0.1(V+29.7)]} \qquad \beta_m = 15.2\exp[-0.0556(V+54.7)]$$
$$\alpha_h = 0.266\exp[-0.05(V+48)] \qquad \beta_h = 3.8/(1+\exp[-0.1(V+18)])$$
$$\alpha_n = \frac{0.02(V+45.7)}{1-\exp[-.1(V+45.7)]} \qquad \beta_n = 0.25\exp[-0.0125(V+55.7)]\,.$$

Finally, the membrane current in the Connor-Stevens model is

$$i_\mathrm{m} = \bar{g}_L(V-E_\mathrm{L}) + \bar{g}_\mathrm{Na}m^3h(V-E_\mathrm{Na}) + \bar{g}_K n^4(V-E_\mathrm{K}) + \bar{g}_\mathrm{A}a^3b(V-E_\mathrm{A}) \tag{6.4}$$

where g_L = 0.3 mS/cm^2 and E_L = -17 mV are the maximal conductance and reversal potential for the leak conductance, and g_{Na} = 120 mS/cm^2, g_K = 20 mS/cm^2, g_A = 47.7 mS/cm^2, E_{Na} = 55 mV, E_K = -72 mV, and E_A = -75 mV

Modify your code to simulate the Connor-Stevens Model and **reproduce** figure below (Figure 6.1, Dayan and Abbott). To debug your code, use the fact that the model should converge to the steady state V = −68 mV, m = 0.0101, h = 0.9659, n = 0.1559, a = 0.5404, and b = 0.2887, if the applied current is zero.

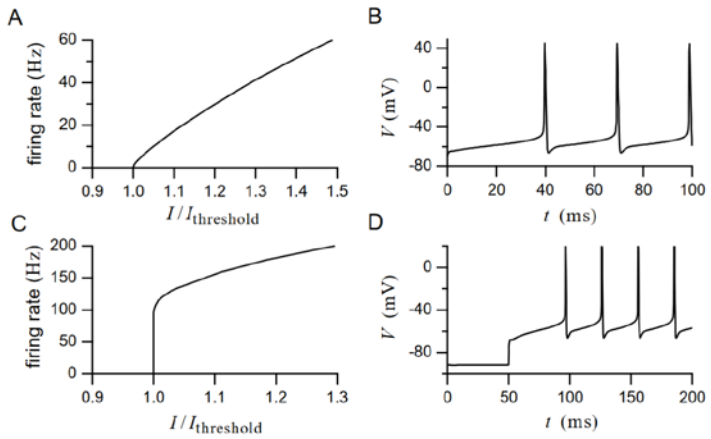
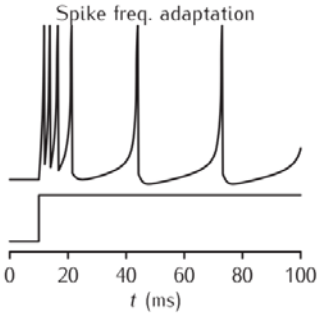


Figure 6.1: Firing of action potentials in the Connor-Stevens model. A) Firing rate as a function of electrode current. The firing rate rises continuously from zero as the current increases beyond the threshold value. B) An example of action potentials generated by constant current injection. C) Firing rate as a function of electrode current when the A-current is turned off. The firing rate now rises discontinuously from zero as the current increases beyond the threshold value. D) Delayed firing due to hyperpolarization. The neuron was held hyperpolarized for a prolonged period by injection of negative current. At $t = 50$ ms, the negative electrode current was switched to a positive value. The A-current delays the occurrence of the first action potential.

Please note: The relevant parts of chapter 6 from Dayan and Abbott are uploaded. Along with the equations and constants, it also provides a detailed explanation for the figure 6.1. The conductances are expressed in terms of mS/mm^2 instead of mS/cm^2. For subplot C, you can substitute the graph you obtained in part 1, which is slightly different than given here: The firing rate may not be the same as in the figure, but you should still be able to see the desired effect.

Part 4: Adaptive Current

So far, we have looked at type I and type II neural excitability. In both these cases, for a given current injection, the firing rate remains constant. However, in many types of neurons, the firing rate in response to a sustained current injection decreases throughout the spike train, as shown below. The standard HH model described so far cannot exhibit this behavior. However, it is possible to incorporate this behavior into HH model by incorporating an extra conductance I_{adapt} that depends on the neuronal spiking.



There is a large variety of mechanisms responsible for spike-frequency adaptation. Ionic currents that influence spike generation are of particular importance. Three main types of such adaptation currents are known: M-type currents, which are caused by voltage-dependent, high threshold potassium channels (Brown & Adams, 1980); AHP-type currents, mediated by calcium-dependent potassium channels (Madison & Nicoll, 1984); and slow recovery from inactivation of the fast sodium channel (Fleidervish, Friedman, & Gutnick, 1996). In this example, we will concentrate on the M-type currents.

B. Ermentrout in "Linearization of F-I curves by adaptation", Neural Comput. 10:1721-9 (1998) gives an example of such a M-type current. It is inspired by Traub's model of hippocampal neurons. The adaptation current can be interpreted in several ways. Ermentrout calls it an M-current, after the muscarine-sensitive potassium current. It could also be interpreted as a slow inhibitory autapse with a time constant of 100 ms. An autapse is a synapse made by a neuron onto itself. Finally, it could be regarded as a simplified model of calcium-dependent potassium current. In that case, the variable z would represent calcium concentration. An explicit model for the accumulation of calcium is given in Section 4.2 of the paper.

In this case, the M-current is a non-inactivating current. Because of their low time constant at rest, each action potential simply increases the activation by a more or less fixed amount. If the neuron is stimulated by a constant depolarizing current, each action potential increases the amount of open M-channels and the corresponding potassium current subtracts from the applied stimulus, thus causing a decrease in the firing frequency.

In the paper, they add the adaptation current by:

$$I_{adapt} = gz(V - E_K),$$

where,

$$\frac{dz}{dt} = 0.01(1/(1 + \exp(-(V + 20)/5)) - z).$$

In the model, the membrane current is given by

$$i_m = \bar{g}_L(V - E_L) + \bar{g}_{Na}m^3h(V - E_{Na}) + \bar{g}_K n^4(V - E_K) + gz(V - E_K)$$

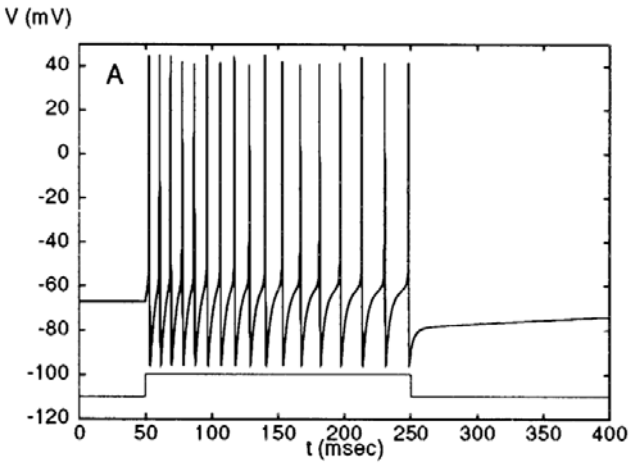
where,
$\bar{g}_{Na} = 100mS/cm^2; \bar{g}_K = 80mS/cm^2; \bar{g}_L = 0.1mS/cm^2; g = 5mS/cm^2$
$E_{Na} = 50mV; E_L = -67mV; E_K = -100mV$

The injected current pulse is 5μA/cm^2.

The rate functions used for the gating variables *n*, *m*, and *h* are:

$\alpha_m(V) = .32(54 + V)/(1 - \exp(-(V + 54)/4))$
$\beta_m(V) = .28(V + 27)/(\exp((V + 27)/5) - 1)$
$\alpha_h(V) = .128 \exp(-(50 + V)/18)$
$\beta_h(V) = 4/(1 + \exp(-(V + 27)/5))$
$\alpha_n(V) = .032(V + 52)/(1 - \exp(-(V + 52)/5))$
$\beta_n(V) = .5 \exp(-(57 + V)/40)$.

Write a code to simulate the above model (described in Section 4.1 of the paper), and reproduce Figure 2A, shown below. **Plot** z versus time.



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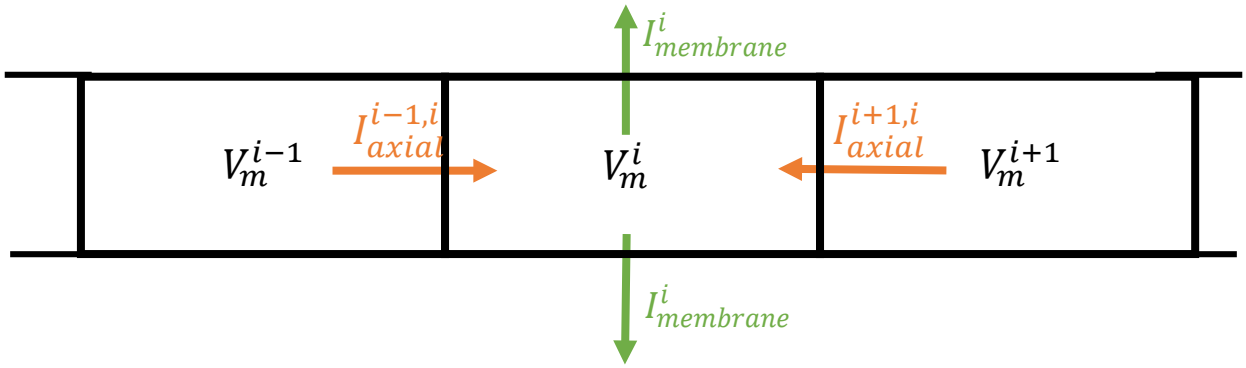
Part 5: Action Potential Propagation

As the soma begins to depolarize, the membrane potentials are summed up and an action potential is generated in and around the axonal hillock, after which the action potential is conducted through the axon. It propagates down the axon, depolarizes the presynaptic terminal and causes neurotransmitter release into the synaptic cleft. These neurotransmitters then bind to postsynaptic receptors and depolarize or hyperpolarize the postsynaptic neuron. This is how neurons communicate with each other, and modelling the conduction through axon can help us understand the neuronal communication better.

Now that we have learnt how to generate an action potential, next we would like to learn how the action potential is propagated down the axon. For that, we will implement a multi-compartmental axon model.

Model:
One can model the axon to be consisting of cylindrical compartments of small length that are added right next to each other. In this model, the membrane of each compartment is assumed to be isopotential. The action potential will be generated at each consequent compartment for its propagation.



At each compartment, there will be the axial current that are coming from the neighboring compartments and transmembrane current that runs through the cell membrane through the mechanisms that are described in the earlier parts of this exercise. In this part of the exercise, we will also inject a stimulus current into the first compartment of the axon.

Since we consider each compartment as an isopotential node, Kirchoff's Current Law applies as the following:

$$I_{stim} + I_{axial} - I_{membrane} = 0$$

Assuming the intracellular resistance between each compartment is R_i, we can calculate the axial current running from the neighbor on the left and the neighbor on the right by using Ohm's Law as the following:

$$I^{i-1,i}_{axial} = \frac{V_m^{i-1} - V_m^{i}}{R_i}$$
$$I^{i+1,i}_{axial} = \frac{V_m^{i+1} - V_m^{i}}{R_i}$$

Thus the total axial current that runs into the i[th] compartment will be:

$$I_{axial}^{i} = I_{axial}^{i+1,i} + I_{axial}^{i-1,i} = \frac{V_m^{i+1} - 2V_m^i + V_m^{i-1}}{R_i}$$

Let the intracellular longitudinal resistivity be ρ_i (Ω.cm). In this case, the resistance between the two neighboring compartments of the axon will be:

$$R_i = \frac{\rho_i \Delta z}{\pi a^2}$$

where a is the radius of the axon (cm) and Δz is the length of one compartment.

The transmembrane current consists of the capacitive current and the ionic currents, and can be written as the following:

$$I_{membrane}^{i} = C\frac{dV_m^i}{dt} + I_{ion}^{i}$$

In this equation, C is the capacitance of the membrane (µF). The ionic current term is calculated via the Hodgkin-Huxley model as follows:

$$I_{ion}^{i} = \bar{g}_{Na} m^3 h\left(V_m^i - E_{Na}\right) + \bar{g}_K n^4\left(V_m^i - E_K\right) + g_l\left(V_m^i - E_L\right)$$

where m, h and n are functions of V_m^i. We will use the similar model constants and rate constant equations as basic HH dynamics for Part 1 (Appendix A). Including this information into the initial equation from Kirchoff's Current Law, we find:

$$I_{stim}^{i} + \pi a^2 \frac{V_m^{i+1} - 2V_m^i + V_m^{i-1}}{\rho_i \Delta z} - C\frac{dV_m^i}{dt} - I_{ion}^{i} = 0$$

Since we would like to work on a model that is independent of the surface area of the membrane, similar to the earlier parts of this exercise, we can divide all the terms with the surface area of the cylindrical compartment, $2\pi a \Delta z$. In this case, we would obtain:

$$i_{stim}^{i} + \frac{a}{2\rho_i}\frac{V_m^{i+1} - 2V_m^i + V_m^{i-1}}{(\Delta z)^2} - c_m\frac{dV_m^i}{dt} - i_{ion}^{i} = 0$$

In this equation, i_{ion} is the ionic current per unit area (µA/cm^2), c_m is the membrane capacitance per unit area (µF/cm^2) and i_{stim}^{i} is the stimulating current per unit area (µA/cm^2). To implement this equation numerically, you need to discretize it time also.

$$i_{stim}^{i} + \frac{a}{2\rho_i}\frac{V_m^{i+1} - 2V_m^i + V_m^{i-1}}{(\Delta z)^2} - c_m\frac{\Delta V_m^i}{\Delta t} - i_{ion}^{i} = 0$$

This is the discretized cable equation written for the i[th] compartment of the axon. For the first and last compartments, the above equation will be slightly different. How would you need to

implement those two compartments? (Hint: How many neighbors do these compartments have? How will it affect the equation for the axial current?)

Thus, for an axon with N compartments, you will have a system of N equations. To solve this system of equations, you can use any of the following numerical methods: forward Euler, backward Euler, Crank-Nicholson, 4th order Range-Kutta etc. Although forward Euler is easier to implement, backward Euler will give you a more accurate and stable result. If you choose to implement an implicit numerical method, instead of implementing a for-loop that would go through each compartment, you will need to solve the system of equations all at once at each time step. Make sure that you understand why this is the case for implicit methods and not the explicit methods.

With the help of these reductions, implement the propagation of an action potential through the axon. Let the length of the axon be 2 cm. Define length of the compartment. (Hint: For forward Euler, the length of each compartment should be 0.1 cm. For other methods, they can be smaller (up to 10µm)). The diameter of the axon is 500 µm, and the total time duration is 10ms. You apply a stimulation current of 100 µA/cm^2. To begin with, let's say the longitudinal resistivity of the intracellular medium is 354 Ω.mm, and the temperature is 6.3°C. **What** is the velocity of the action potential propagating through the axon?

Vary the temperature from 4°C to 24°C, in steps of 1°C, and **plot** the velocity of propagation (y-axis) vs. temperature (x-axis). Vary the axonal resistivity from 200 Ω.mm to 1200 Ω.mm, in steps of 100 Ω.mm and **plot** the velocity of propagation (y-axis) vs. axonal resistivity (x-axis). Vary the diameter of the axon from 100 µm to 1000 µm, in steps of 100 µm and **plot** the velocity of propagation (y-axis) vs. diameter (x-axis). Explain the underlying reasons of the trend that you observe in the results.

Hint for implementing implicit methods: As you may remember from your linear algebra courses, such a system of equations can be written in a matrix format with N rows. In order to obtain the last term in the discretized cable equation, you will need to find an NxN matrix ($[\xi]$) to be multiplied with the matrix that consists of the membrane potential of each compartment. For example, if you are using backward Euler method for integration, you should obtain an equation in the form of:

$$[\xi][v_m]^t = \mu([i_m]^t + [i_{stim}]^t) - [v_m]^{t-1}$$

Furthermore, since you will not know the membrane current at time step t, at each time step you will first need to calculate a temporary value for $[v_m]^t$ by using $[i_m]^{t-1}$. Then you would calculate a temporary value for $[i_m]^t$ by using this temporary value of $[v_m]^t$. Now you have a temporary value for $[v_m]^t$, you can use it to calculate a more accurate estimate for $[i_m]^t$ and so on. You would need to repeat this process until your $[v_m]^t$ converges. Then you can proceed to the next time step.

For further reference, check Hines & Carnevale, 1997.

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Appendix A.

The constants for the Hodgkin Huxley model are:

Membrane Capacitance (C_m) = 1 µF/cm².
Resting Membrane Potential (V_m) = -60.045 mV.
Sodium Channel Nernst Potential (V_{Na}) = ((T+273)/279.3 K) x 55.17 mV.
Potassium Channel Nernst Potential (V_K) = -((T+273)/279.3 K) x 72.14 mV.
Leakage Channel Nernst Potential (V_L) = -((T+273)/279.3 K) x 49.42 mV.
Maximum Sodium Channel Conductance (G_{Na}) = 120 mS/cm².
Maximum Potassium Channel Conductance (G_K) = 36 mS/cm².
Maximum Leakage Channel Conductance (G_L) = 0.3 mS/cm².

The model can be summarized neatly into 4 separate ODE's. These are the state variables.

$$\frac{dv}{dt} = \frac{1}{C_m} \cdot \underbrace{[I - g_{Na} m^3 h(v - E_{Na}) - g_K n^4 (v - E_K) - g_l (v - E_l)]}_{i_m}$$

$$\frac{dn}{dt} = \alpha_n(v)(1 - n) - \beta_n(v) n$$

$$\frac{dm}{dt} = \alpha_m(v)(1 - m) - \beta_m(v) m$$

$$\frac{dh}{dt} = \alpha_h(v)(1 - h) - \beta_h(v) h$$

The rate constants for the gating variables, as a function of voltage are given by the following equations.

$$\begin{aligned}
\alpha_m &= \frac{-0.1(V_m + 35)}{e^{-0.1(V_m+35)} - 1} K_T \\
\beta_m &= 4e^{-(V_m+60)/18} K_T \\
\alpha_h &= 0.07e^{-0.05(V_m+60)} K_T \\
\beta_h &= \frac{1}{1 + e^{-0.1(V_m+30)}} K_T \\
\alpha_n &= \frac{-0.01(V_m + 50)}{e^{-0.1(V_m+50)} - 1} K_T \\
\beta_n &= 0.125e^{-0.0125(V_m+60)} K_T
\end{aligned}$$

where V_m is expressed in mV and all the α's and β's are expressed in $1/\text{ms}$.

Please feel free to email on ashah@ethz.ch (Parts 1-4); yasart@ethz.ch (Part 5) in case of any questions.