

## 6.1 Synaptic Interactions

### 6.1.1 Hyperpolarizing inhibition

The line you need to add to `synsim.m` is:

$$dV = -dt/C * ( g_i*(V(t)-E_i) + g_e*(V(t)-E_e) + V(t)/R );$$

1. See Fig. 1.

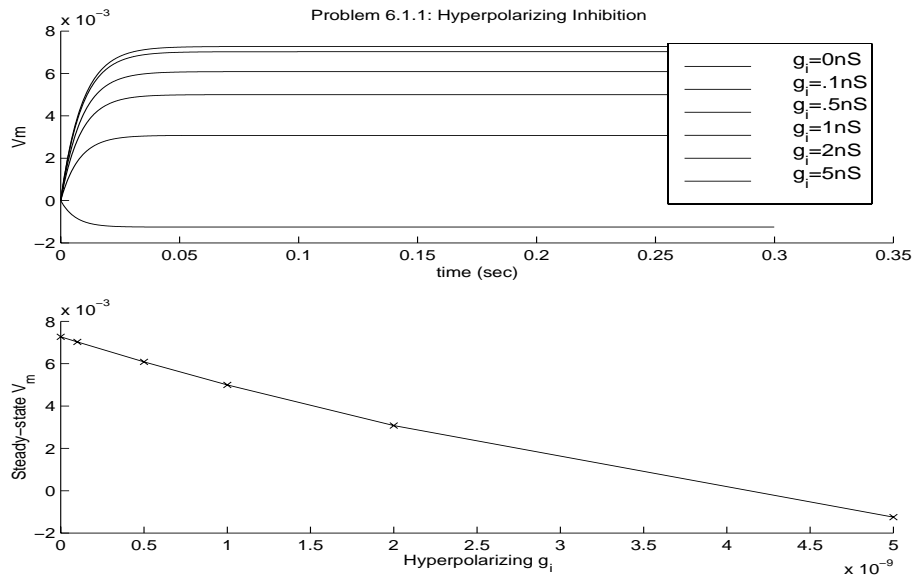


Figure 1: Hyperpolarizing inhibition. Top: the membrane potential as a function of  $t$  for a range of  $g_i$  values. The topmost curve is for  $g_i = 0$ , the next for  $g_i = 0.1nS$ , and so on. Bottom: steady state voltages as a function of  $g_i$ .

2. At steady state, the voltages have reached equilibrium values. Thus, current may be flowing through the resistor  $R$  and possibly through  $g_i$  and  $g_e$ , but no current flows through the capacitor  $C$ . This allows us to ignore the capacitor in our calculation of the input resistance. So if you look at the circuit now, notice that the total input conductance is just the sum of the conductances  $g_i$ ,  $g_e$ , and  $1/R$ . The input resistance, then, is:

$$R_{in} = \frac{1}{g_i + g_e + 1/R} \quad (1)$$

which makes the time constant:

$$\tau = R_{in}C = \frac{C}{g_i + g_e + 1/R} \quad (2)$$

With no synaptic inputs, the  $R_{in}$  is larger than with synaptic input (either excitatory or inhibitory). We can see this from the equation. When we set  $g_i = 0$  and  $g_e = 0$ ,  $R_{in}$  is larger than for any other values of  $g_i$  and  $g_e$  (keep in mind that conductances can only be positive). Intuitively, any time an ion channel opens, the conductance of the cell membrane increases. Increased conductance implies decreased resistance. The membrane time constant  $\tau$  changes proportionally to  $R_{in}$ . In the presence of excitation or inhibition,  $\tau$  is smaller than without synaptic input.

3. First, notice that in our steady-state plot of voltage vs.  $g_i$  in Fig. 1 the relationship looks close to linear. But why is this? The hand-waving argument is that excitation causes an influx of positive charge (e.g.  $Na^+$ ) while hyperpolarizing inhibition causes an efflux of positive charge (e.g.  $K^+$ ). The total number of charges that enter/exit the cell are simply a linear sum of the two, since a single (singly-charged) cation cancels out exactly one (singly-charged) anion.  $E_i$  and  $E_e$  determine the magnitude of the linear scaling, since they determine how many ions cross the membrane for a given  $g_i$  and  $g_e$ .

In equation form, consider the membrane equation. Realize that at steady-state  $dV_m/dt = 0$ , and solve for  $V_m$ :

$$C \frac{dV_m}{dt} + g_i(V_m - E_i) + g_e(V_m - E_e) + \frac{V_m}{R} = 0 \quad (3)$$

$$g_i(V_m - E_i) + g_e(V_m - E_e) + \frac{V_m}{R} = 0 \quad (4)$$

$$V_m = \frac{(g_i E_i + g_e E_e) R}{1 + R(g_i + g_e)} \quad (5)$$

For small synaptic inputs,  $g_i + g_e \ll 1/R$  and the right half of the denominator is smaller than 1. (For example for  $g_i = 0.1 nS$ ,  $R(g_i + g_e) = 0.11$ .) Then:

$$V_m = (g_i E_i + g_e E_e) R \quad (6)$$

which is linear in hyperpolarizing input and excitatory input. For larger values of  $g_i$  and  $g_e$  this is no longer true, and we can in fact see the curve in Fig. 1 become less linear for larger values of  $g_i$ .

### 6.1.2 Shunting Inhibition

1. See Fig. 2.

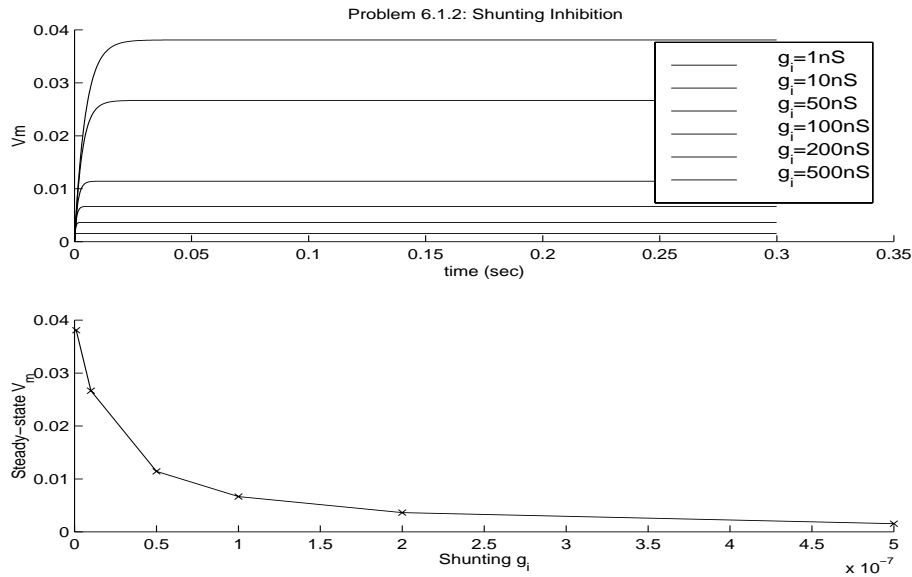


Figure 2: Shunting Inhibition. Top: the membrane potential as a function of  $t$  for a range of  $g_i$  values. The topmost curve is for  $g_i = 1nS$ , the next for  $g_i = 10nS$ , and so on. Bottom: steady state voltages as a function of  $g_i$ .

2. The calculations for effective input resistance  $R_{in}$  and time constant  $\tau$  are as before:

$$R_{in} = \frac{1}{g_i + g_e + 1/R}$$

$$\tau = R_{in}C = \frac{C}{g_i + g_e + 1/R}$$

This time, however, we are using much larger values of  $g_i$ . This is necessary since our  $E_i$  is now 0 rather than  $-20mV$ . In order for  $g_i(V_m - E_i)$  in the membrane equation to yield a large enough value to have an effect in the presence of excitation, since we made the magnitude of  $E_i$  smaller we must increase  $g_i$ . Thus, the input resistance  $R_{in}$  will be smaller than in the case of hyperpolarizing inhibition; and the time constant  $\tau$  will also decrease.

3. We can no longer make the assumption that  $R(g_i + g_e) \ll 1$ . (For example for  $g_i = 100nS$ ,  $R(g_i + g_e) = 10.1$ )  $V_m$  is clearly not a linear function of  $g_i$  nor  $g_e$ . By making the now-valid assumption that  $R(g_i + g_e) \gg 1$ , we

can make some simplifications:

$$\begin{aligned} V_m &= \frac{(g_i E_i + g_e E_e) R}{1 + R(g_i + g_e)} \\ &= \frac{(g_i E_i + g_e E_e) R}{R(g_i + g_e)} \\ &= \frac{(g_i E_i + g_e E_e)}{(g_i + g_e)} \end{aligned}$$

When we notice that  $g_i > g_e$ , we can further make the following approximation. It should be clear now that shunting inhibition has a divisive effect:

$$V_m = \frac{(g_i E_i + g_e E_e)}{(g_i + g_e)} = \frac{(g_i E_i + g_e E_e)}{g_i} \quad (7)$$

### 6.1.3 Normalization

1. See Fig. 3.

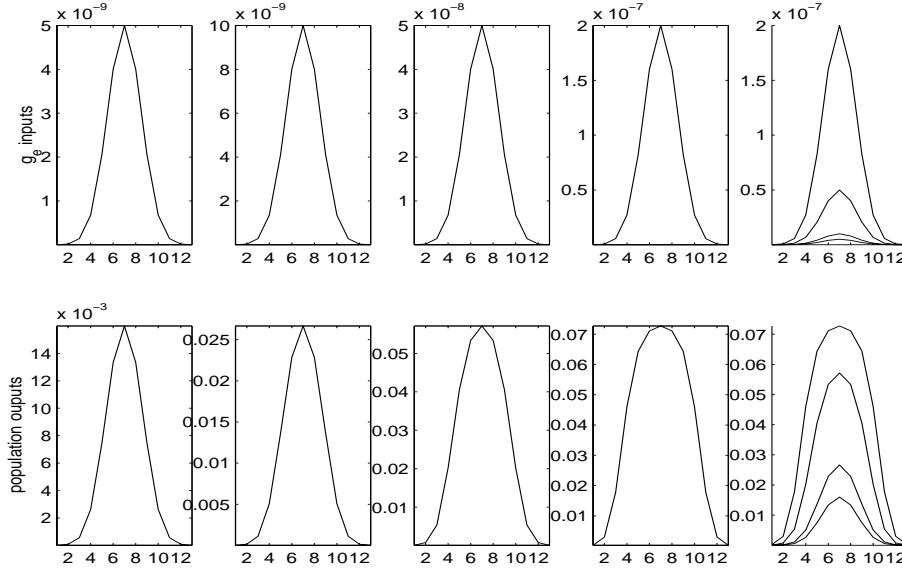


Figure 3: Gaussian input (top row) and corresponding population outputs (bottom row) for different input magnitudes. All inputs and outputs are superimposed in the right-most plots.

2. We can recall the equation from Eq. 5:

$$V_m = \frac{(g_i E_i + g_e E_e) R}{1 + R(g_i + g_e)}$$

and notice that in this case, we've set  $g_i = 0$ . The equation becomes:

$$V_m = \frac{g_e E_e R}{1 + R g_e} \quad (8)$$

For small input signals (peak of Gaussian at 5nS, for example),  $R g_e \ll 1$  and  $V_m = g_e E_e R$ . The population output is just a linearly scaled version of the input.

For large input signals, the relationship between a neuron's input and its output is no longer linear. The neurons receiving the largest input (from the middle of the Gaussian) saturate at some value, and the population output becomes flatter in the middle.

- Now, we need to calculate the `scale` factor. We're just looking for an order-of-magnitude estimate. We're dealing with 13 neurons here, and a reasonable neuron output is around  $40mV$ . So the sum of the population output will be  $13 * 40 * 10^{-3} = 0.5$ . We would like the inhibitory inputs to be on the order of  $100nS$ , so the scaling factor should be about `scale` =  $\frac{100 * 10^{-9}}{0.5} = 2 * 10^{-7}$ .
- For the same inputs to the population as before, we've now added normalizing inhibition. See Fig. 4. Notice that all the population output plots

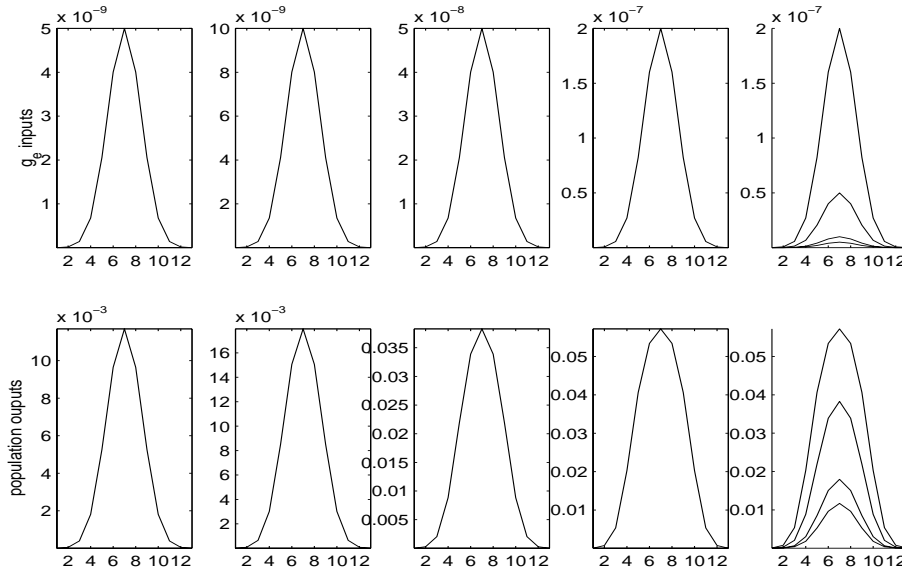


Figure 4: The effects of shunting inhibition for normalization. Gaussian input (top row) and corresponding population outputs (bottom row) for different input magnitudes. All inputs and outputs are superimposed in the right-most plots.

are shaped much more like Gaussians than without normalization (Fig. 3). The saturation behavior has been reduced by normalization.

5. See Fig. 5.

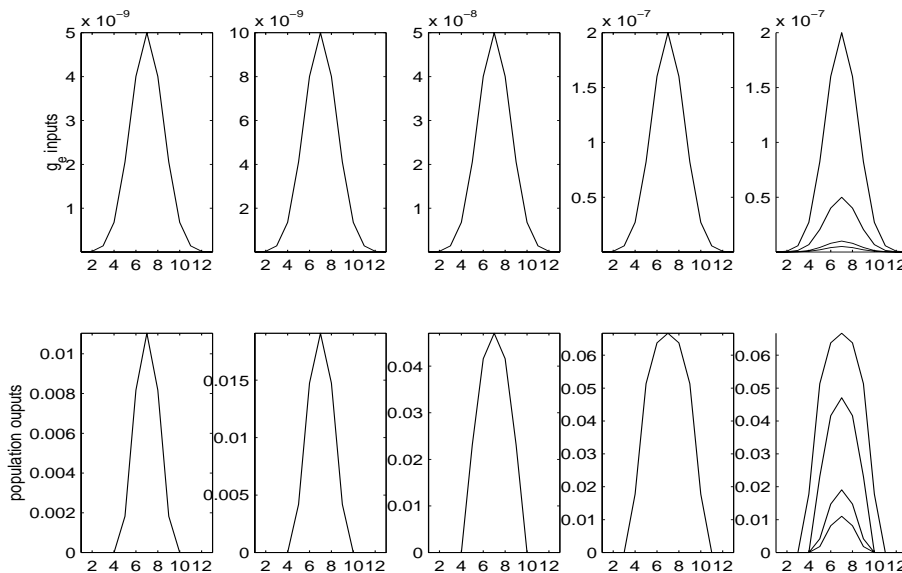


Figure 5: The effects of current as feedback. Gaussian input (top row) and corresponding population outputs (bottom row) for different input magnitudes. All inputs and outputs are superimposed in the right-most plots.

6. Most of this has already been explained in the text above. In the first case (no feedback), for small inputs (small  $g_e$ ) the output is almost linear in the input. So the population output is shaped the same as the input. As the excitatory input becomes bigger, the neurons no longer respond linearly to their input and saturate. The peak in the population output becomes flatter. Normalizing inhibition helps to keep the neurons from saturating in this manner. As the total population response increases due to a large input, the shunting inhibition also increases and keeps the neurons away from saturation. For this reason, we see that the population output is shaped like the input Gaussian even for large inputs for neurons with recurrent shunting inhibition. The unbiological case of feedback with current is... unbiological and weird. There's no point in trying to make up an answer about what it might represent – we just wanted you to see that current injection is not equivalent to changing the input conductance (the latter being what ion channels in a neuron membrane actually do). Current feedback distorts the shape of the input.

The time until stabilization is markedly shorter (faster) for both cases of inhibition. Recall that in our calculations of the time constant  $\tau$  of the membrane we found that  $\tau$  decreases with increasing synaptic input. Thus, it is not surprising that when we add feedback (more synaptic input),  $\tau$

decreases and the voltages stabilize more quickly.

7. Local inhibition is a biologically valid phenomenon, and very useful. Consider the following example: the input into your population of cells comes from a visual scene, such that input from nearby points in the visual field comes into nearby cells. On the left side of the visual field is a very brightly lit object in a patch of sunlight; on the right side is a dimly lit object standing in the shadow. If all cells normalized their output to the average of the entire population, the bright object might push the cells on the left into saturation, while the dark object might be insufficient to activate the cells on the right. The population of cells would be unable to say much about the details of either object. However, if the normalization is local, the cells on the left half of the visual field will normalize their output such that they can pick out the details of the bright object and convey the clear image of a harmless white dove. The cells in the right half of the visual field will normalize to much lower light levels, allowing the animal to realize there's a hungry black hawk staring straight at it.

## 6.2 The Hodgkin-Huxley Model

It is remarkable feat of ingenuity and insight that the Hodgkin-Huxley model was developed even before the nature of ion transport across nerve membranes was well understood. Hodgkin and Huxley's analogy to explain macroscopic membrane current in terms of gating particles was validated when the patch-clamp technique was developed by Sakmann and Neher. It allowed experimentalists to study and record microscopic currents through single ion channels for the first time and settle the question about the origin of membrane excitability once and for all.

### 6.2.1 H-H equations under Voltage Clamp

1. The total current which flows across the membrane is composed of the sodium current  $I_{Na}$ , the potassium current  $I_K$  and the leak current  $I_L$ . Since we are interested in steady-state values, the dynamics of  $n$ ,  $m$  and  $h$  can be ignored. The steady-state  $K^+$  and  $Na^+$   $i-v$  curves are graphed in **Figure 6**. Notice that  $I_K$  is a monotonically increasing function of the membrane voltage and is positive for  $V > E_K$ . According to our sign convention, all positive currents represent the outward flow of cations. Thus, as the membrane is depolarized, more potassium ions move down their electrochemical gradient from the inside the membrane to the outside. For large  $V$ ,  $I_K$  becomes a linear function of  $V$  since  $g_K$  saturates at high voltages.

$I_{Na}$  on the other hand is a non-monotonic function of  $V$ .  $I_{Na}$  is negative for  $V < E_{Na}$  which happens to be the physiologically relevant range for neurons. Thus, as the membrane is gradually depolarized,  $Na^+$  ions flow inwards causing  $I_{Na}$  to increase in magnitude with  $V$ . This represents

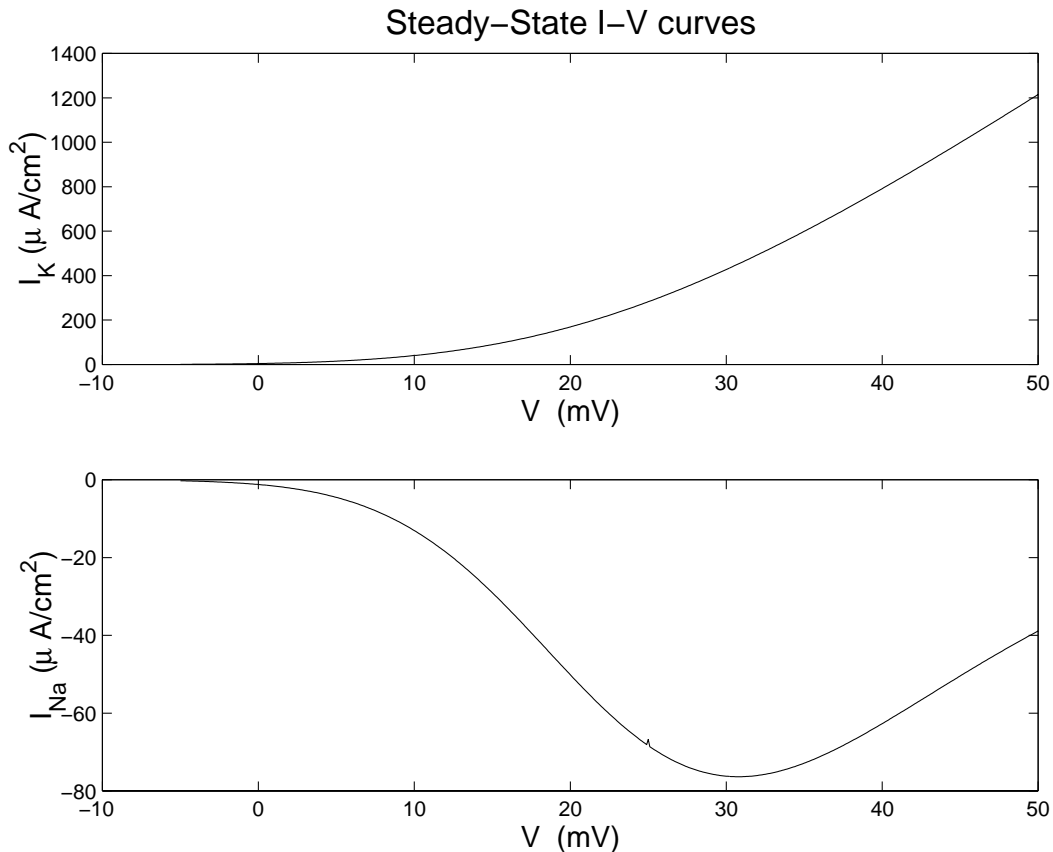


Figure 6: Steady state  $i - v$  curves for the Hodgkin-Huxley currents.  $I_K$  (a) is a monotonic function of the membrane voltage  $V$  (w.r.t. the resting potential), whereas  $I_{Na}$  (b) is not.

the activation part of the  $i - v$  curve. During the activation phase, the slope of the  $i - V$  curve is negative which means the larger the voltage, the larger is the inward sodium current which would in turn increase the membrane voltage further (assuming that  $I_K = 0$ ). During activation, the increase in  $g_{Na}$  with  $V$  outweighs the linear decrease in the driving potential ( $E_{Na} - V$ ). Thus, for moderate depolarization,  $I_{Na}$  represents a positive feedback mechanism. This, incidentally is the reason for action potential generation. For large  $V$ , inactivation dominates and  $I_{Na}$  goes to zero and becomes positive for  $V > E_{Na}$ . Notice that because of inactivation, the steady-state value of  $I_{Na}$  is much smaller than  $I_K$ .

2. During a voltage step from a holding voltage  $V_{hold}$  to a clamp voltage  $V_{clamp}$ , the dynamics of  $n$ ,  $m$  and  $h$  can be obtained by solving the corresponding first-order differential equations. They can be summarized as,

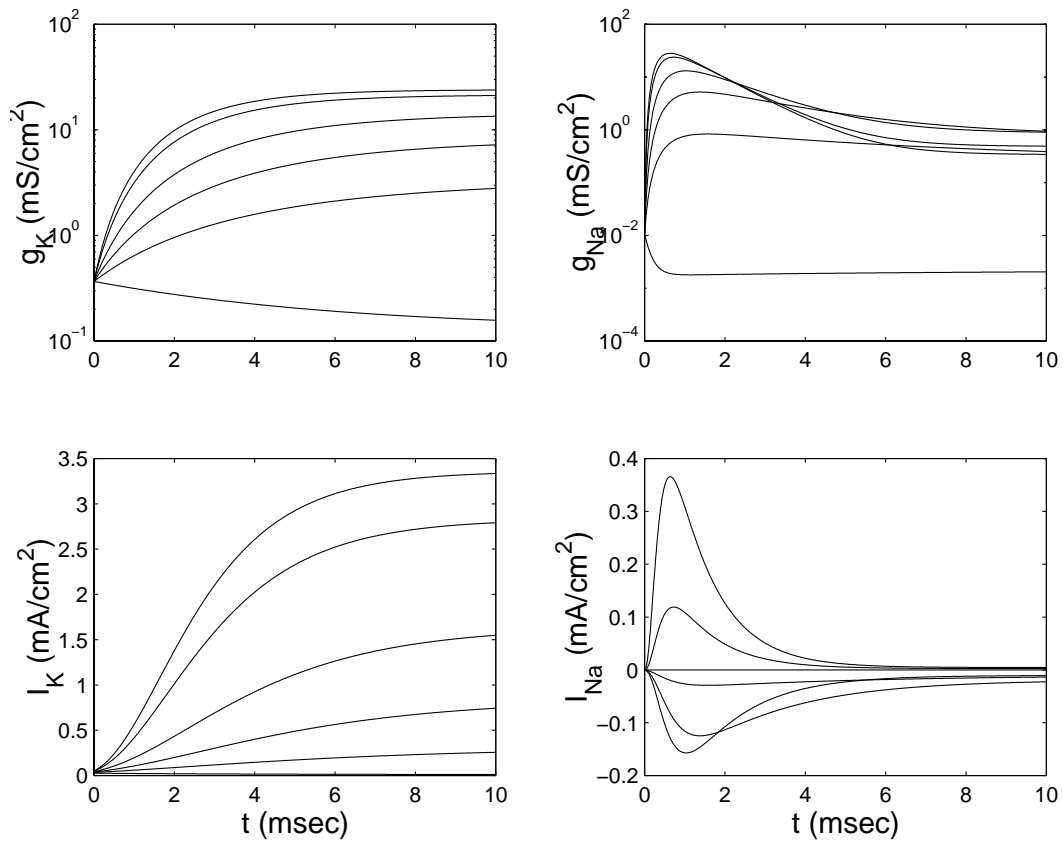


Figure 7: Hodgkin-Huxley conductances and currents during voltage clamp.

$$n(t) = n_{\infty}(V_{clamp}) + [n_{\infty}(V_{hold}) - n_{\infty}(V_{clamp})] e^{-t/\tau_n(V_{clamp})} \quad (9)$$

$$m(t) = m_{\infty}(V_{clamp}) + [m_{\infty}(V_{hold}) - m_{\infty}(V_{clamp})] e^{-t/\tau_m(V_{clamp})} \quad (10)$$

$$h(t) = h_{\infty}(V_{clamp}) + [h_{\infty}(V_{hold}) - h_{\infty}(V_{clamp})] e^{-t/\tau_h(V_{clamp})} \quad (11)$$

These can be used to obtain the conductances ( $g_K$  and  $g_{Na}$ ) and the currents ( $I_K$  and  $I_{Na}$ ) as functions of time. These are plotted in **Figure 7**. For the plots  $V_{hold} = 0$  and  $V_{clamp} \in \{-5, 15, 26, 38, 55, 63\}$  mV with respect to the resting potential.  $n$  evolves from its old value to its new one with a time constant  $\tau_n$  and as a result  $g_K$  activates during a depolarizing step. On the other hand,  $g_{Na}$  is a product of  $m^3(t)$  and  $h(t)$ , and it first increases and reaches its peak then decreases to a much lower steady-state value. This is because the time constant of activation ( $\tau_m$ ) is much smaller than the time constant of inactivation ( $\tau_h$ ).

### 6.2.2 Action Potential Generation

1. The code needed for `hhsim.m` to output  $I_K$  is as follows:

```
I_K = G_K*Y(:,2).^4.*(Y(:,1) - E_K);
```

The Hodgkin-Huxley equations demonstrate a threshold behavior with respect to current injection. For short current pulses, when the magnitude of the pulse is small as in the two top panels of **Figure 8** ( $I$  is a 0.5 msec pulse of magnitude 0.15 nA), the membrane voltage depolarizes in response to the current, causing both  $m$  and  $n$  to increase, but  $h$  to decrease. Because the time constant of sodium activation is more than one order of magnitude faster than  $\tau_n$  and  $\tau_h$  at these voltages, we can consider the later two for the moment to be stationary. But the sodium conductance,  $G_{Na}$  increases somewhat. Because the membrane is depolarized from rest, the driving potential for the potassium current,  $V - E_K$  also increases. The concomitant increase in  $I_K$  outweighs the increase in  $I_{Na}$  due to the increase in  $G_{Na}$  and the overall current is outward, driving the membrane potential back toward the resting potential. The potential will slightly undershoot and then overshoot until it finally returns to  $V_{rest}$ . The oscillatory response around the resting potential can be attributed to the small-signal behavior of the potassium conductance acting phenomenologically similar to an inductance.

If the amplitude of the current pulse is increased to 0.4 nA (bottom two panels of **Figure 8**, the depolarization due to the voltage-independent currents reaches a point where the amount of  $I_{Na}$  generated exceeds the amount of  $I_K$ . At this point, the membrane voltage triggers a positive feedback mechanism, the additional  $I_{Na}$  depolarizes the membrane, further increasing  $m$  that in turn increases  $I_{Na}$  leading to further membrane

depolarization. Given the almost instantaneous dynamics of sodium activation ( $\tau_m$  is  $\approx 0.1$ - $0.2$  msec), the sodium current raises the membrane potential rapidly to 0 mV and beyond. In the absence of sodium inactivation and potassium activation, this positive feedback process continues until  $V$  equals  $E_{Na}$ . However, after some delay both the slower sodium inactivation variable  $h$  as well as the potassium activation  $n$  kick in. Sodium inactivation decreases the amount of sodium conductance available, while potassium activation brings the membrane potential towards  $E_K$ . Since the sodium current quickly falls to zero after 1 msec but  $I_K$  persists longer, the membrane potential falls to below its resting level. At this low voltage, the potassium activation switches off, returning the system to its initial configuration as  $V$  approaches the resting potential.

### 6.2.3 The f-I curve

1. The line needed in the program to compute the firing rate is given by

```
freq = spikes/tmax * 1000;
```

The f-i curve for the H-H model can be computed by injecting a long-lasting current step of constant amplitude and counting the number of action potentials generated in a given time interval. If the magnitude of the current is too small, it gives rise to a persistent sub-threshold depolarization. However, if the input is of sufficient amplitude to exceed the threshold, the membrane generates one action potential. As the current amplitude is increased a second action potential is initiated. At around 0.18 nA (for our conditions) the membrane generates an indefinite train of spikes at fixed intervals: the membrane potential between action potentials always slowly creeps past  $V_{th}$  and the cycle begins anew: the system travels on a stable limit cycle. In a noiseless situation, the interval between consecutive spikes is constant and the cell behaves as a periodic oscillator with constant frequency.

2. An important feature of the Hodgkin and Huxley model is that the frequency at the onset of repetitive activity has a well-defined non-zero minimum. The membrane is not able to sustain oscillations at lower frequencies. This behavior, generated by a so-called *Hopf bifurcation* mechanism, is generic to a large class of oscillators occurring in nonlinear differential equations. This property distinguishes the f-I curve of the H-H model from the curves for the Integrate & Fire neuron which we will see in problem set 7. This behavior can be eliminated by adding random noise to  $I$  before injection. Noise can linearize the f-I curve like in the I & F case, giving rise to a sigmoidal f-I curve which can be approximated by an I & F model by choosing the right parameters. Notice that as the amount of noise is increased, the curve becomes first sigmoidal, and then more and more linear. When the noise gets too high, the shape of the curve will be dominated by the noise and lose its smooth shape.

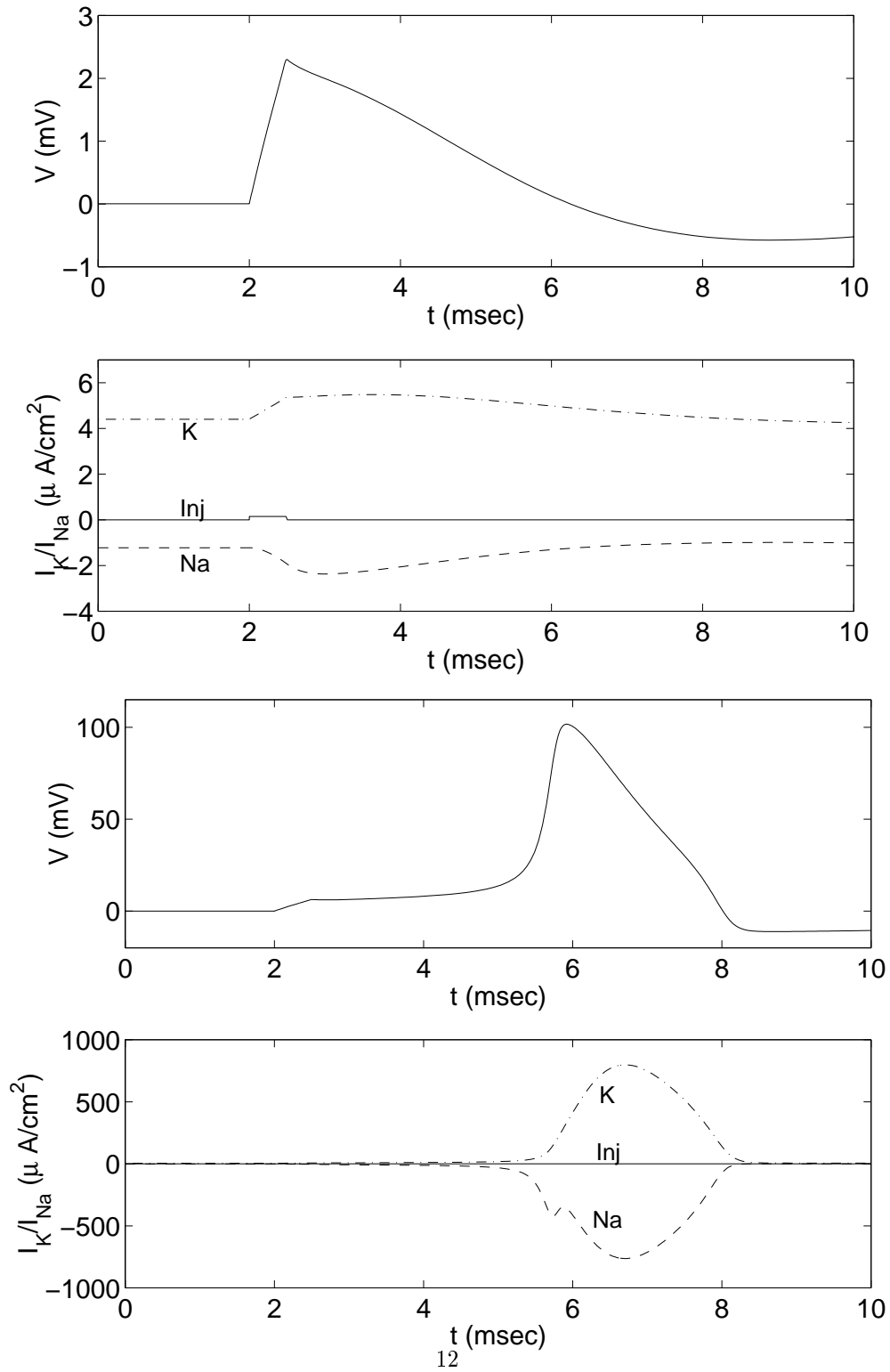


Figure 8: The response of the H-H model to current injection.

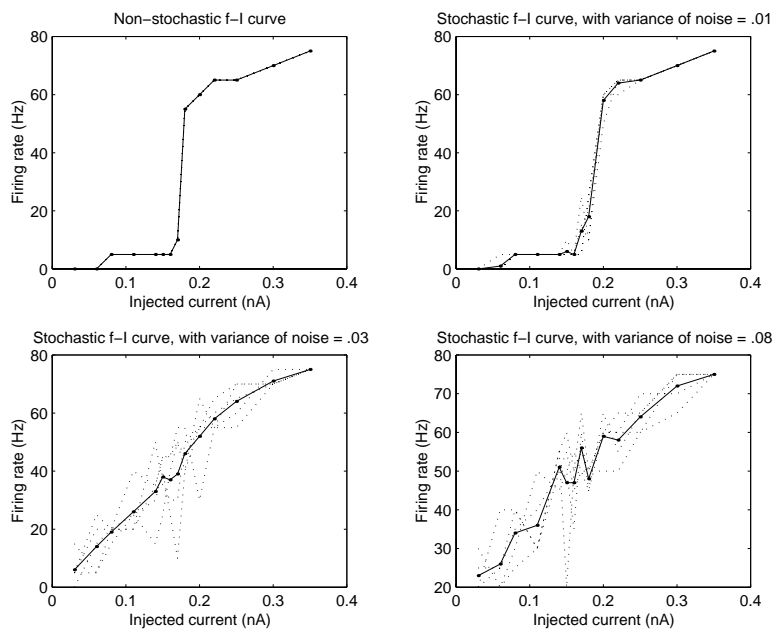


Figure 9: f-I curve of the H-H model. The first plot shows the f-I curve for constant current injection, whereas the latter three plots include the addition of Gaussian noise. The solid line is an average of 5 runs of 200ms each, and the dotted curves are the individual 200ms curves.