MATH 723 Mathematical Neuroscience Spring 2008
Instructor: Georgi Medvedev

1 Lecture 1. The Hodgkin-Huxley model.

1.1 Derivation of the model

In a classical series of papers, Hodgkin and Huxley studied electrical properties of the giant squid axon (see [HH, HI], and references therein). They developed a framework for modeling electrical activity in excitable cells, which forms a basis for a wide class of neuronal models, so-called conductance based models.

1.1.1. The current balance equation. Imagine a cylindrical membrane, which separates intracellular space from the extracellular. We assume that the properties of membrane are spatially uniform and consider a small patch of the membrane. The membrane is covered with sufficiently large number of ionic channels. These channels can be in one of the two states "open" or "closed". The ions from extracellular space can enter the cell (and vice versa, the ions from intracellular space can leave the cell) through open channels (Fig. 1). The net currents through ionic channels are called ionic currents or conductances. The dynamics of the Hodgkin-Huxley (HH) model is generated by three ionic conductances: sodium (I_{Na}), potassium (I_K) and a passive linear conductance, (I_L). The latter is called the leak current. In addition, to describe many experimental results, it is convenient to include an additional current, I, the applied current, which can be controlled during the experiment. The dynamical state of the system is determined from the current balance equation

$$I = I_{Na} + I_K + I_L + I', \tag{1.1}$$

where the last term on the right hand side denotes the capacitative current generated by the electrical properties of the membrane. By the Faraday's law,

$$I' = C\dot{V} \ (C = 1\mu F/cm^2) \tag{1.2}$$

where C is the membrane capacitance, $V(t)$ is the membrane potential (or voltage), and $\dot{V}(t)$ denotes the time derivative of $V(t)$. By plugging in (1.2) into (1.1), we have

$$C\dot{V} = -I_{Na} - I_K - I_L + I. \tag{1.3}$$

Next, we describe the individual conductances I_{Na}, I_K and I_L. In modeling excitable cell membranes, one encounters a variety of different ionic conductances (even for the same ionic species). However, they may differ in the quantitative description, most of them admit the same formalism suggested by Hodgkin and Huxley for the giant squid axon in [HH]. The transient sodium conductance, I_{Na}, is modeled in the following way:

$$I_{Na} = g_{Na} p \, (V - E_{Na}) \tag{1.4}$$

where E_{Na} ($E_{Na} = 120mV$) is *the reversal potential*, $g_{Na}(g_{Na} = 120mS/cm^2)$ is *the maximal conductance*, and p is the probability of an ionic channel to be open at time t. The reversal potential, E_{Na}, is the value of the membrane potential, for which the net current through the Na channels is zero (i.e., when the

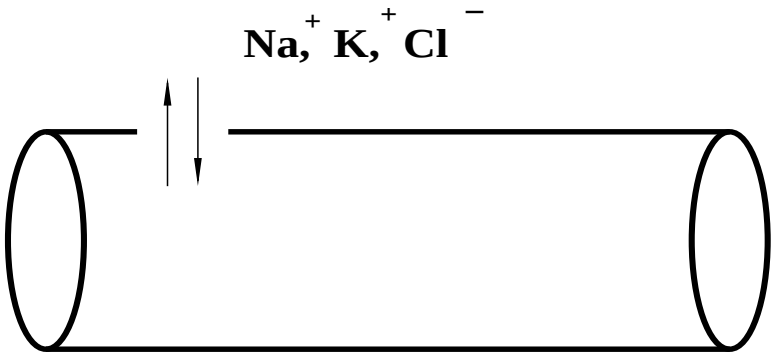

Figure 1: An illustration to the assumptions underlying the HH model.

current flowing into the cell balances that flowing out of the cell). The maximal conductance g_{Na} is determined by the density of Na channels. To compute probability p, one assumes that the state of the channel is determined by two independent processes: the activation and the inactivation. For modeling transient sodium current we assume that there are three activation and one inactivation gates per channel. Let m and h denote the probabilities of the "activation" and "inactivation" gates to be open, respectively. Then

$$p = m^3 h, \tag{1.5}$$

where m is called an activation gating variable and h is called an inactivation gating variable. The dynamics of the voltage-gated potassium current is modeled, similarly:

$$I_K = g_K n^4 (V - E_K), \tag{1.6}$$

where g_K ($g_K = 36mS/cm^2$) is the maximal conductance, E_K ($E_K = 12mV$) is the reversal potential and n is the activation variable. The description of I_K does not involve inactivation. Finally, the leak current is modeled by

$$I_L = g_L (V - E_L), \tag{1.7}$$

where g_L($g_L = 0.3mS/cm^2$) is the ohmic leak conductivity and E_L($E_L = 10.6mV$). Note that this current depends linearly on V and, therefore, it is called a passive current. The leak current is introduced to approximate the contribution of typically smaller ionic currents not taken into account by I_{Na} and I_K. By combining (1.1)-(1.7), we arrive at the following equation

$$C\dot{V} = -g_{Na} m^3 h (V - E_{Na}) - g_K n^4 (V - E_K) - g_L (V - E_L) + I. \tag{1.8}$$

1.1.2. The equations for the gating variables. To complete the description of the HH system, we introduce the equations for the gating variable m, h, and n. We sketch the scheme used for deriving the equation for n. The equations for other variables are treated similarly. Assume that each of four gates involved in the activation of the potassium channel can be in either open (O) or closed state (C). Also assume that the switching from O to C (and vice versa) is a Poisson process with transition probabilities:

$$P_{\mathbf{C}\to\mathbf{O}} = \alpha_n(V) \quad \text{and} \quad P_{\mathbf{O}\to\mathbf{C}} = \beta_n(V).$$

Therefore,

$$\text{Prob}\left(\mathbf{C} \mapsto \mathbf{O}, \text{in time } [t, t+\Delta t]\right) = \alpha_n(V)\Delta t + o(\Delta t),$$
$$\text{Prob}\left(\mathbf{O} \mapsto \mathbf{C}, \text{in time } [t, t+\Delta t]\right) = \beta_n(V)\Delta t + o(\Delta t),$$

where voltage-dependent functions $\alpha_n(V)$ and $\beta_n(V)$ are called opening and closing rates, respectively. Also, recall that the probability of the gate to be open at time t is given by $n(t)$. Therefore,

$$\begin{aligned}\text{Prob}\left(\mathbf{O}, \text{at time } t+\Delta t\right) &= \text{Prob}\left(\mathbf{O}, \text{at time } t\right)\left(1 - \text{Prob}\left(\mathbf{O} \mapsto \mathbf{C}, \text{in time } [t, t+\Delta t]\right)\right) \\ &+ \text{Prob}\left(\mathbf{C}, \text{at time } t\right)\text{Prob}\left(\mathbf{C} \mapsto \mathbf{O}, \text{in time } [t, t+\Delta t]\right),\end{aligned}$$

or,

$$n\left(t+\Delta t\right) = n(t)\left(1-\beta\Delta t\right) + \left(1-n(t)\right)\alpha\Delta t + o(\Delta t). \tag{1.9}$$

By rearranging terms in (1.9), we have

$$\frac{n(t+\Delta t) - n(t)}{\Delta t} = -\beta(V)n + (1-n)\alpha + \frac{o(\Delta t)}{\Delta t},$$

and, by taking the limit as $\Delta t \to 0$

$$\dot{n} = \alpha_n(V)(1-n) - \beta_n(V)n. \tag{1.10}$$

In complete analogy, we obtain the equations for m and h

$$\dot{m} = \alpha_m(V)(1-m) - \beta_m(V)m, \tag{1.11}$$
$$\dot{h} = \alpha_h(V)(1-h) - \beta_h(V)n. \tag{1.12}$$

It is important to note that functions $\alpha(V)$ and $\beta(V)$ (for m, n, h) can be measured experimentally. The system of equations (1.8), (1.10)-(1.12) is called *the Hodgkin-Huxley model*. For convenience, we rewrite (1.10) in the following form

$$\dot{n} = \frac{n_\infty(V) - n}{\tau_n(V)},$$

where

$$n_\infty(V) = \frac{\alpha_n(V)}{\alpha_n(V) + \beta_n(V)}, \tag{1.13}$$
$$\tau_n(V) = \frac{1}{\alpha_n(V) + \beta_n(V)}. \tag{1.14}$$

Function $n_\infty(V)$ and $\tau_n(V)$ are called *the steady state function* and *the time constant* of the activation of K channels, respectively. Similarly, we define functions

$$m_\infty(V) = \frac{\alpha_m(V)}{\alpha_m(V) + \beta_m(V)},\ \tau_m(V) = \frac{1}{\alpha_m(V) + \beta_m(V)}, \tag{1.15}$$

$$h_\infty(V) = \frac{\alpha_h(V)}{\alpha_h(V) + \beta_h(V)},\ \tau_h(V) = \frac{1}{\alpha_h + \beta_h}. \tag{1.16}$$

1.1.3. The HH system. To sum up the derivation of the HH model system, we rewrite the system of equation (1.8), (1.10)-(1.12) and supply it with the analytical expressions for the steady state functions and the time constants, and with the values of the parameters:

$$\dot{V} = \frac{1}{C}(-g_{Na}m^3h(V-E_{Na}) - g_K n^4(V-E_k) - g_L(V-E_L) + I), \tag{1.17}$$

$$\dot{m} = \frac{m_\infty(V)-m}{\tau_m(V)}, \tag{1.18}$$

$$\dot{h} = \frac{h_\infty(V)-h}{\tau_h(V)}, \tag{1.19}$$

$$\dot{n} = \frac{n_\infty(V)-n}{\tau_n(V)}. \tag{1.20}$$

The rate functions are given by

$$\alpha_n(V) = 0.01\frac{10-V}{\exp\left(\frac{10-V}{10}\right)-1}, \tag{1.21}$$

$$\beta_n(V) = 0.125\exp\left(\frac{-V}{80}\right), \tag{1.22}$$

$$\alpha_m(V) = 0.1\frac{25-V}{\exp\left(\frac{25-V}{10}\right)-1}, \tag{1.23}$$

$$\beta_m(V) = 4\exp\left(\frac{-V}{18}\right), \tag{1.24}$$

$$\alpha_h(V) = 0.07\exp\left(\frac{-V}{20}\right), \tag{1.25}$$

$$\beta_h(V) = \frac{1}{\exp\left(\frac{30-V}{10}\right)+1}. \tag{1.26}$$

The values of the parameters are summarized in

Table 1.

g_{Na}	$120mS/cm^2$	E_{Na}	$120mV$	g_K	$36mS/cm^2$	E_K	$-12mV$
g_L	$0.3mS/cm^2$	E_L	$10.6mV$	C	$1\mu F/cm^2$		

Unless stated otherwise, applied current I is assumed to be 0. The steady state functions and the time constant are calculated by plugging in (1.21)-(1.26) into (1.13)-(1.16). The graphs of these functions are plotted in Figure 2.

1.2 The action potential

1.2.1. The numerical experiments. Next, we reproduce the following numerical experiment described in [IZH]. First, we numerically integrate the HH system with somewhat arbitrary initial condition: $(V_0, m_0, h_0, n_0) = (5, 0.1, 0.2, 0.3)$. The results of this numerical experiment are given in Figure 3.

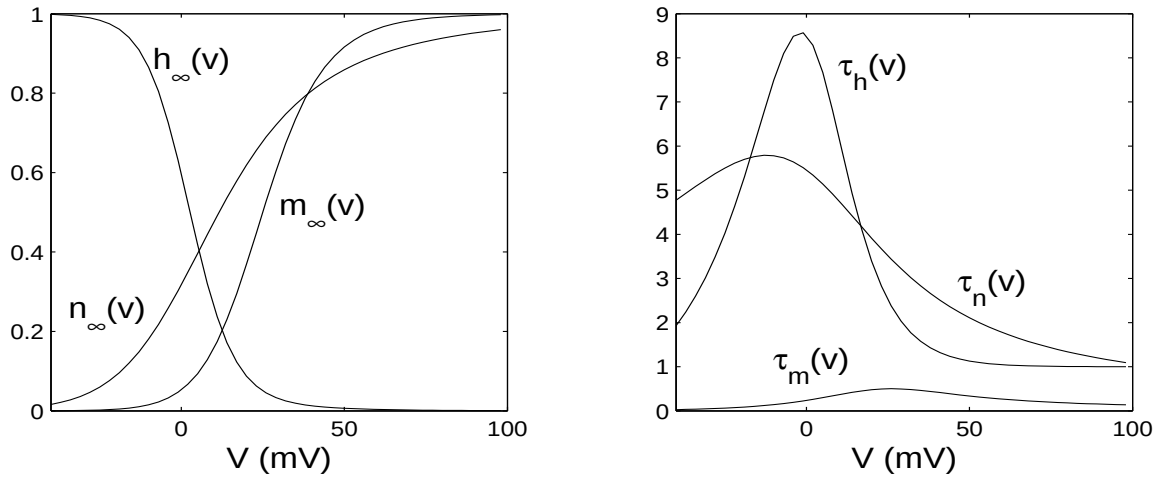

Figure 2: Steady-state (in)activation functions (left) and voltage-dependent time constant (right) are plotted for the Hodgkin-Huxley model.

Note that the dynamical variables converge to the constant values, the steady state of the system: $(V_s, m_s, h_s, n_s) = (-0.2828, 0.0513, 0.5841, 0.3208)$. In the next experiment, we turn on the applied current for some time, i.e., we set

$$I(t) = I_0 \chi_{[0,T_0]}(t),$$

where

$$\chi_{[0,T_0]} = \begin{cases} 1, \ t \in [0, T_0], \\ 0, \ \text{otherwise}. \end{cases}$$

This time for the initial condition we take (V_s, m_s, h_s, n_s) to avoid transients. The results of this experiment for different values of the amplitude of stimulations, I_0, and its duration, T_0 are plotted in Figure 4.

Note that for weak stimulation, the voltage is slightly increasing and returns to the steady state after the stimulus is removed (Figure 4a). The stimulation, which produces small deviations from the steady state of the membrane potential are called *subthreshold*. A different type of the voltage response is shown in Figure 4b. Here, the voltage changes drastically forming a sharp spike-like profile (*an action potential* (AC) or *a spike*) followed by a gradual decrease in voltage. Before the voltage returns to the steady state, there is a period of time when it takes value below the steady state. This phase in the voltage response to the perturbation of the applied current is called *afterhypolarization* (see Figure 5a). If the stimulation is applied for sufficiently long time, the model generates a train of ACs. (Figure 4c)

1.2.2. The mechanism for the AP generation: a heuristic explanation. Next, we discuss the mechanism of the AP generation. For this, we use the numerical experiment shown in Figure 5. Before the applied current is turned on, the system remains in the steady state. In particular, the right hand side of the equation for voltage (1.17) is equal to zero:

$$-I_{Na} - I_K - I_L + I = 0$$

(see Figure 5d). When I is switched to a positive value as shown in Figure 5e, the right hand side of (1.17) becomes positive and voltage is perturbed in the positive direction. Since $\tau_m \ll \tau_{n,h}$ (see Figure 2), the

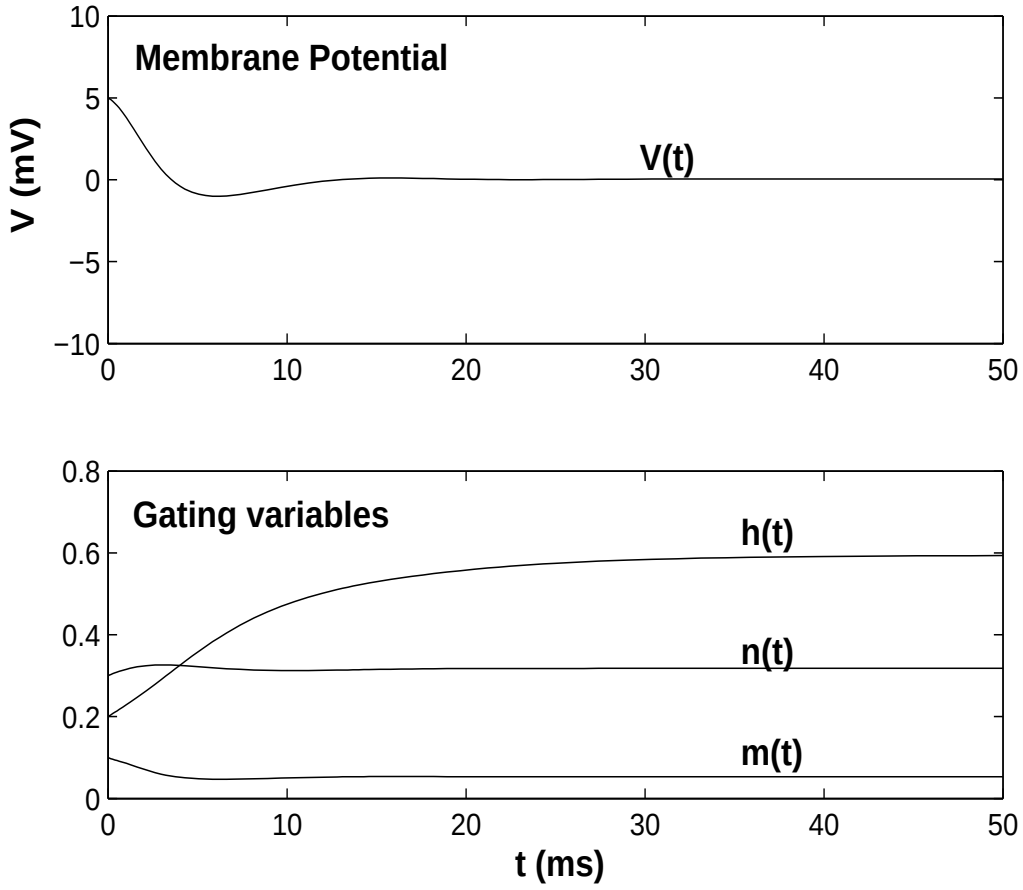

Figure 3: Numerical solution of the HH system of equations with applied current $I = 0$. After brief transients, the trajectory converges to the steady state $(V_s, m_s, h_s, n_s) = (-0.2828, 0.0513, 0.5841, 0.3208)$.

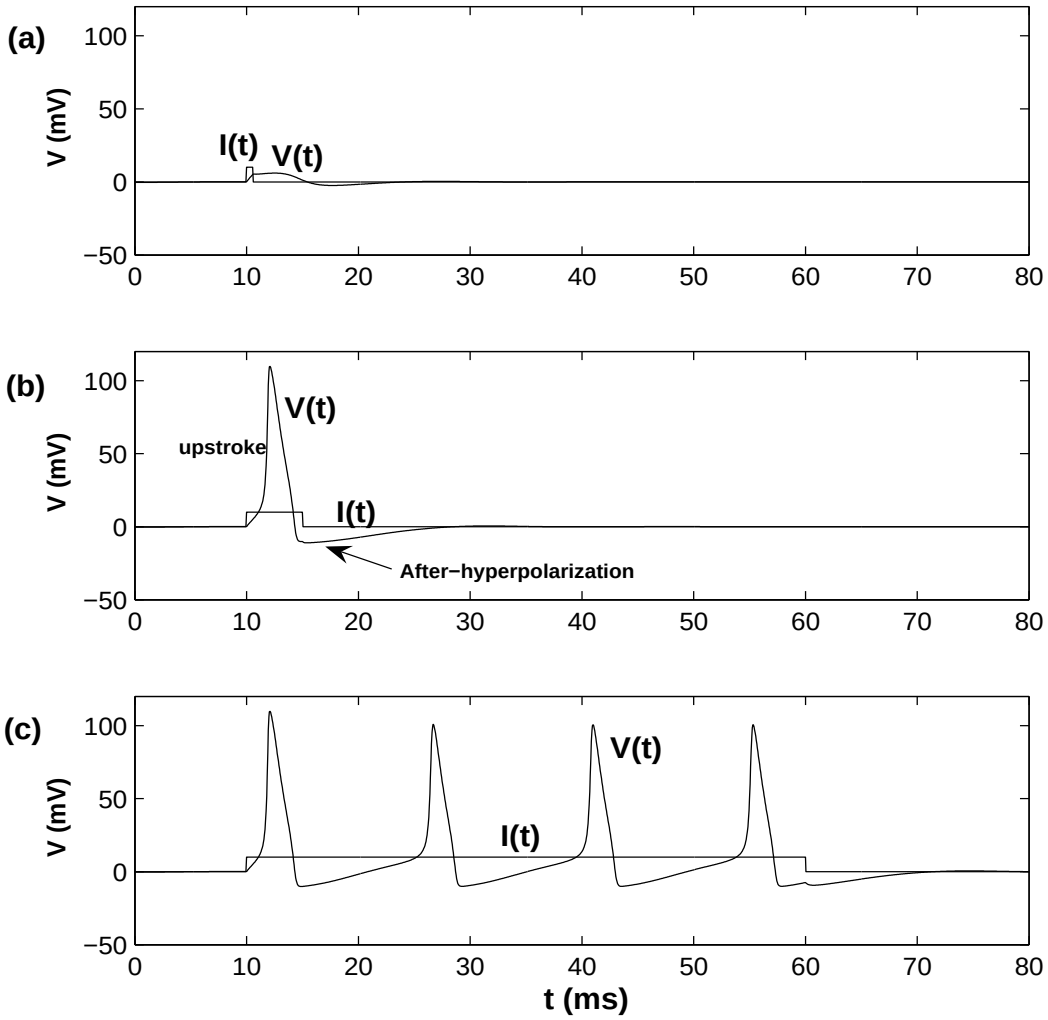

Figure 4: Numerical solutions of the HH equations for different values of the applied current and different periods of stimulation: (a) Subthreshold response (b) suprathreshold response (action potential) (c) periodic discharge.

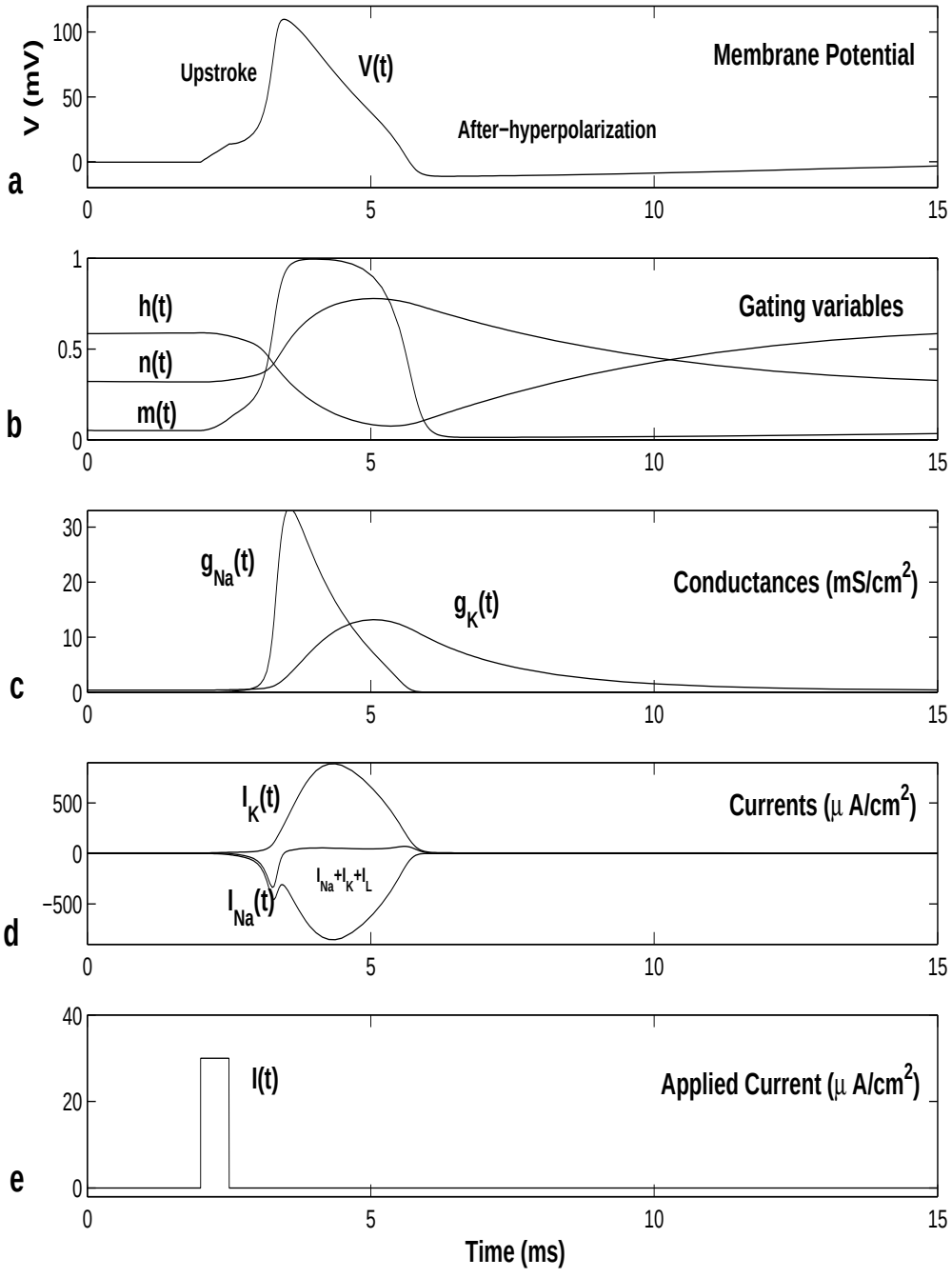

Figure 5: The action potential. The dynamics of the membrane potential (a), gating variables (b), conductances (c), and ionic currents (d), under the perturbations of the applied current (e).

sodium channel activation variable m responds to this perturbation faster than other gating variables. For increasing values of V, $m_\infty(V)$ takes larger values (see Figure 2), therefore, m is increasing under the perturbation of the applied current. As a result, the sodium conductance

$$g_{Na}(t) = g_{Na} m^3 h$$

is increasing (see Figure 5c) and so is

$$-I_{Na} = -g_{Na}(t)\,(V - E_{Na})\,.$$

This destroys the balance of the ionic currents:

$$-I_{Na} - I_K - I_L + I > 0.$$

The voltage continues to increase. The perturbation of the applied current has a similar effect on the dynamics of n, the activation variable of the potassium channels: n is increasing for the increasing values of voltage, and so is

$$g_K(t) = g_K n^4(t)$$

(see Figure 5b). However, the potassium conductance is changing more slowly, because of the difference of the time constants $\tau_n \gg \tau_m$. Therefore,

$$-I_K = -g_K(t)\,(V - E_K)$$

is decreases and counteracts the effect of increasing $-I_N a$. In addition, for increasing values of V, $h_\infty(V) \to 0$ (see Figure 4). Therefore, as V continues to increase, h is gradually decreasing and so is

$$g_{Na}(t) = g_{Na} m^3 h.$$

The combination of these two effects, the increase of the magnitude of I_K and decrease of that of I_{Na}, results in the dominating effect of I_K. Therefore, after certain interval of time, V starts to decrease and eventually returns to the steady state. This sequence of events provides a heuristic description of the mechanism for the AP generation. We emphasize the role of the separation of the time scales ($\tau_n \ll \tau_{n,h}$): the AP is generated, because the sodium conductance responds much faster than the potassium conductance to the perturbation of the applied current.

1.3 The Morris-Lecar model

In [ML], Morris and Lecar formulated a differential equation model to explain different patterns of electrical activity observed in the barnacle muscle fiber. The model was derived using HH formalism for modeling excitable cells. Unlike the HH system of equations, the ML system consists of only two differential equations, which makes it more amenable to mathematical analysis. The ML system exhibits many features common to a wide class of the HH type models. Because of that and since it is convenient for analytical studies, it is often used as a phenomenological model of a typical neuron. The ML model is given by the following system of equations:

$$\begin{aligned} C\frac{dV}{dt} &= -g_{Ca} m_\infty (V - E_{Ca}) - g_K n (V - E_K) - g_L (V - E_L) + I, \\ \frac{dn}{dt} &= \phi \frac{n_\infty(V) - n}{\tau(V)}, \end{aligned}$$

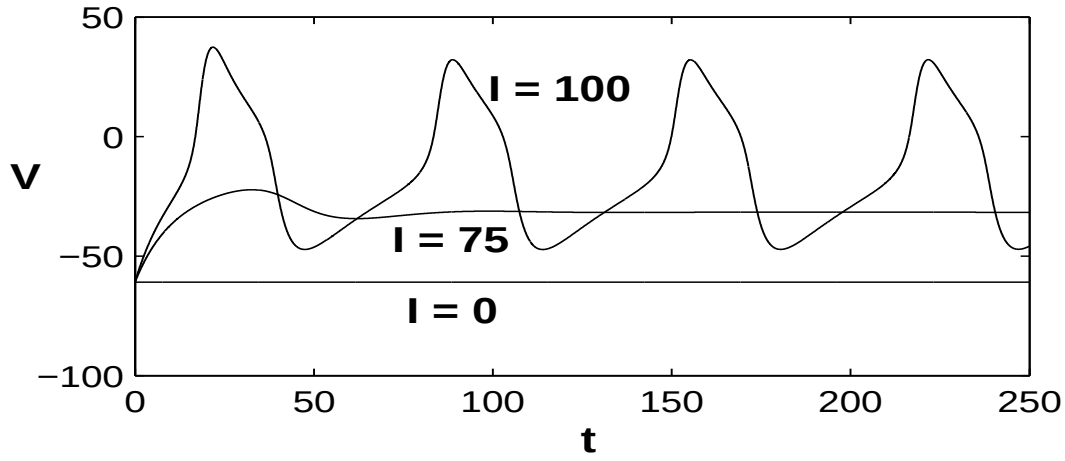

Figure 6: Numerical simulations of the Morris-Lecar model.

where

$$m_\infty(V) = 0.5\left(1 + \tanh\left(\frac{V-\nu_1}{\nu_2}\right)\right),$$

$$n_\infty(V) = 0.5\left(1 + \tanh\left(\frac{V-\nu_3}{\nu_4}\right)\right),$$

$$\tau(V) = \frac{1}{\cosh\left(\frac{V-\nu_3}{2\nu_4}\right)},$$

and the values of the parameters are summarized in

Table 2.

g_{Ca}	$4.4mS/cm^2$	E_{Ca}	$120mV$	g_K	$8mS/cm^2$	E_K	$-84mV$
g_L	$2mS/cm^2$	E_L	$-60mV$	C	$20\mu F/cm^2$	ν_1	$-1.2mV$
ν_2	$18mV$	ν_3	$2mV$	ν_4	$30mV$	ϕ	$0.04mS^{-1}$

In the ML model, we encounter a new conductance: a voltage-dependent Ca^{2+} current. It plays the same role in the spike generating mechanism of the ML model as the Na^+ current in the HH system.

Homework project.

The matlab code for the numerical experiments with the HH system of the previous subsection is given in the Appendix to this lecture. Modify this code to study the voltage responses in the ML system. For the ML system, use $(V_0, n_0) = (-60.855, 0.01495)$ as the initial condition. Find the values for the amplitude and the duration of stimulation which yield sub- and superthreshold responses, as well as trains of AP. Repeat this numerical experiment for $\phi = 0.02$. Describe the effect of changing ϕ on the trains of AP generated

for prolonged stimulation. To make sure, that you entered the parameters correctly, compare your numerics with that in Figure 6 for the same values of parameters.

Appendix: Matlab codes.

Matlab function for integrating the HH system of equations:

```
%                          The Hodgkin-Huxley Model

function xdot = hh_syst(t,x)

I = inp(t);

v=x(1);
n=x(2);
m=x(3);
h=x(4);


an = 0.01*(-v+10)/(exp(-0.1*v+1)-1);
bn = 0.125*exp(-v/80);


am = 0.1*(-v+25)/(exp(-0.1*v+2.5)-1);
bm = 4*exp(-v/18);


ah = 0.07*exp(-v/20);
bh = 1/(exp(-0.1*v+3)+1);


dv = I + 36*n^4*(-12-v) ...
+ 120*m^3*h*(120-v) ...
+ 0.3*(10.6-v);

dn = an*(1-n)-bn*n;
dm = am*(1-m)-bm*m;
dh = ah*(1-h)-bh*h;


xdot = [dv dn dm dh]';
```

Matlab code for the numerical experiment with the HH model for different values of the applied current and different durations of the stimulation.

```
%=========================================================================
```

```
%   HH_stimulate.m:  HH system with stimulation current
%
%  Example:  HH_stimulate(10, 1, 5)
%
%    It means:  we applied a dc current in HH model, and
%    1.  current amplitude = 10 (uA/cm2̂)
%    2.  current duration = 1 (ms)
%    3.  delay or beginning time of current = 5 (ms)
%=========================================================================


function[]=HH_stimulate(intensity, duration, delaytime)

global  howstrong howlong delay

howstrong = intensity;   % intensity of applied current
howlong = duration;   % duration of applied current
delay = delaytime;   % delaytime (or beginning time) of applied current


T_MAX = 50;
step = 0.05;
tspan=0:step:T_MAX;

x0 =[-0.2828, 0.3208, 0.0513, 0.5841];

[t,x]=ode15s(@hhF, tspan, x0);

v=x(:,1);
n=x(:,2);
m=x(:,3);
h=x(:,4);


figure(1)
subplot(2,1,1)
plot(t,v);
axis([0 T_MAX -20 120]);
title(sprintf('HH MODEL with I (applied current)', num2str(howstrong)))
ylabel ('V (mV)')


for i=1:length(t)
current(i)=inp(t(i));
end
```

```
subplot(2,1,2)
plot(t, current)
axis([0 T_MAX 0 max(current)+1]);
xlabel ('t (ms)')
ylabel ('I (μA/cm2)')


%%%%%%%%%%%%%%%%%%%%%%%%%%%%

function xdot = hhF(t,x)

I = inp(t);

v=x(1);
n=x(2);
m=x(3);
h=x(4);


an = 0.01*(-v+10)/(exp(-0.1*v+1)-1);
bn = 0.125*exp(-v/80);

am = 0.1*(-v+25)/(exp(-0.1*v+2.5)-1);
bm = 4*exp(-v/18);

ah = 0.07*exp(-v/20);
bh = 1/(exp(-0.1*v+3)+1);

dv = I + 36*n^4*(-12-v) ...
+ 120*m^3*h*(120-v) ...
+ 0.3*(10.6-v);

dn = an*(1-n)-bn*n;
dm = am*(1-m)-bm*m;
dh = ah*(1-h)-bh*h;

xdot = [dv dn dm dh]';

%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function I=inp(t)


global  howstrong howlong delay
```

```
I = 0;

t_end = delay+howlong;

if (t >= delay) & (t<=t_end)
I = howstrong;
end;
```

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