9 Generation of Action Potential — Hodgkin-Huxley Model

(based on chapter 12, W.W. Lytton, *Hodgkin-Huxley Model*)

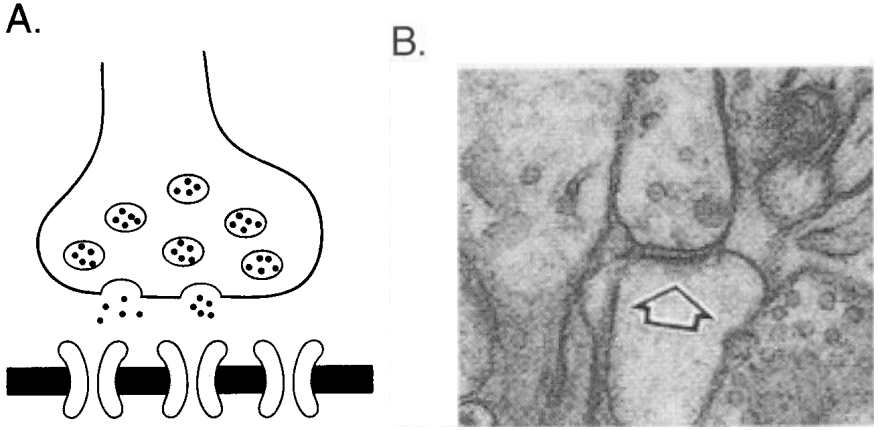
9.1 Passive and active membrane models

- In the previous lecture we have considered a **passive model** of the neuronal **membrane** and applied this model to predict the change of the **Post-Synaptic Potential** in response to pulses arriving at the synapse.
- Now we extend the synapse model to include active elements, namely, **batteries** and **variable resistors/conductors**.
- Such an **active model** will be used to explain generation of pulses known as the **action potential** at the axon of a neuron.
- In the 1950s Alan Hodgkin and Andrew Huxley worked out the ionic basis of the action potential and developed a mathematical model that successfully predicted the speed of spike propagation.
- Their work can be regarded in retrospect as the beginning of computational neuroscience.
- It remains the touchstone for much neural modeling today.

  Since then hundreds have been described and some of the basic parameterization has been updated, but the Hodgkin–Huxley model is still considered to be the standard model.

9.2 Ion channels

- Ion channels (pores) are proteins that span the cell membrane allowing the flow of ions through the membrane.
- Ion channels have three important properties:
  1. They conduct ions,
  2. they recognize and select specific ions, e.g. sodium Na^+ ions
  3. they open and close in response to specific electrical or chemical signals.
- Consider the following example of a neurotransmitter-gated, or chemical-sensitive channels in the dendritic spine:



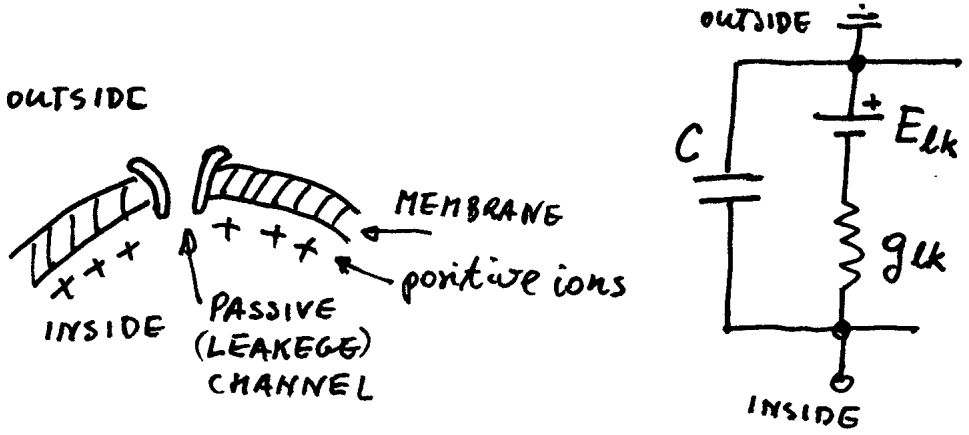
from Trappengberg, *Fundamentals of Computational Neuroscience*

- Schematic illustration of a chemical synapse and an electron microscope photo of a synaptic terminal
- Neurotransmitter-gated ion channels open and close under the regulation of neurotransmitters, such as GABA, glutamite and dopamine.

- The flow of ions results in the **postsynaptic potential** (PSP).
- It is good to remember that the synaptic cleft, that is, the gap between the axon terminal and the dendritic spine is only a few μm wide.

9.3 From passive to the active membrane model

- In the passive model the membrane was modeled as a leakage conductance g_{lk} and a capacitance, C.
- Such a model assumed that the resting membrane potential was 0 mV.
- In reality the **resting membrane potential** (RMP) is negative and approximately equal to -70mV.
- To account for that we have to add a battery E_{lk} associated with the leakage conductance.
- The battery implies that there is a constant excess of positive ions inside the cell.
- These positive ions flow through the always open leakage channel.



- Such a model does not explain the magic of having the excess of positive ions despite of their constant outflow from the cell.

  To understand that we have to consider a few more mechanisms present in the cell.

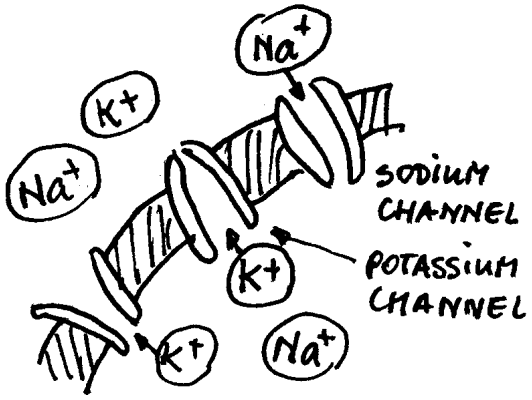
- First, we have to consider the presence of (at least) two types of positive ions:

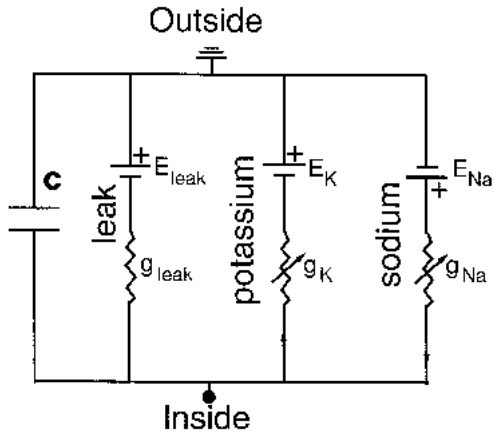
  sodium, Na^+, and **potassium**, K^+, ions.

- There are **voltage-sensitive** channels and related batteries associated with each type of ions.

9.4 Parallel-conductance model of the membrane

- Now we have all elements to form the parallel-conductance model that was first formulated by Hodgkin and Huxley in 1950s





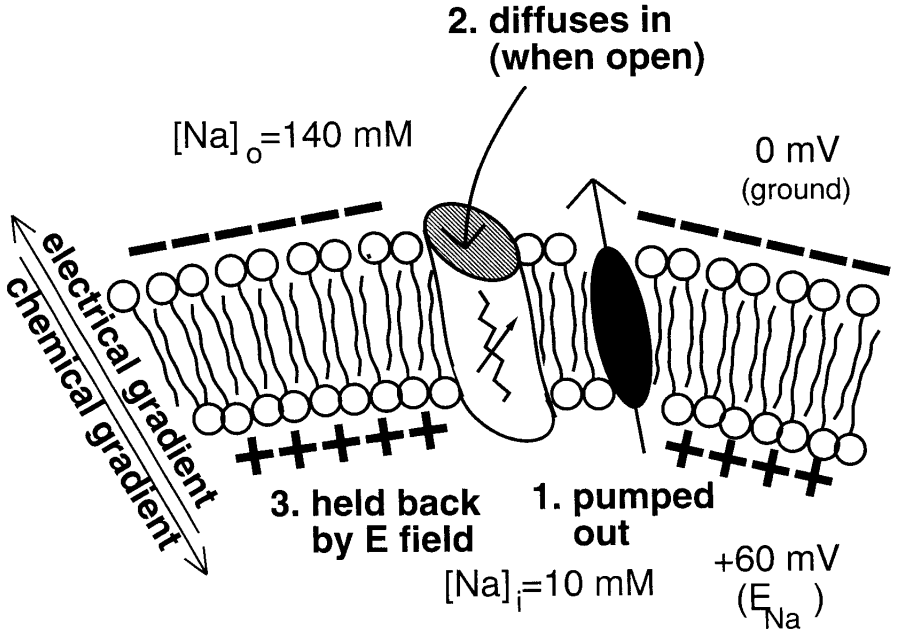
- Note that all points on the inside of the membrane are electrically connected via the cytoplasm. This is the point where we measure potential.
- Similarly the outside of the membrane is connected via the extracellular fluid (horizontal line at top) and is grounded, keeping it at 0 mV.

- The potassium channel is modeled by a variable resistor, g_K and a battery, E_K.
- Similarly, sodium channel is modeled by a variable resistor, g_{Na} and a battery, E_{Na}.
- The variable resistor is voltage-sensitive and varies its conductance depending on the voltage across the resistor.
- Note that the potassium battery pushes the positive potassium ions out off the membrane.
- Conversely, the sodium battery pushes the positive sodium ions inside the cell.
- At rest, the sodium and potassium conductances are zero, that is, the channels are closed and the flow of ions through the respective channels are turned off.

9.5 Where do the batteries come from?

- The batteries are an indirect result of proteins that pump ions across the membrane.
- These ions then try to flow back "downhill," in the direction of their **chemical gradient** from high concentration to low concentration (diffusion process).
- Only a little current has to flow in order to set up an equal and opposite electrical gradient.
- The electrical gradient, opposite in direction to the chemical gradient, is the battery.
- This electrical potential is called the Nernst potential. Each ion has its own Nernst potential.
- It can be precisely calculated by knowing the **concentrations** of a particular ion inside and outside of the cell.
- The value in millivolts of the Nernst potential is the strength of the battery that we use in the circuit diagram.

9.5.1 Sodium battery — Nernst potential

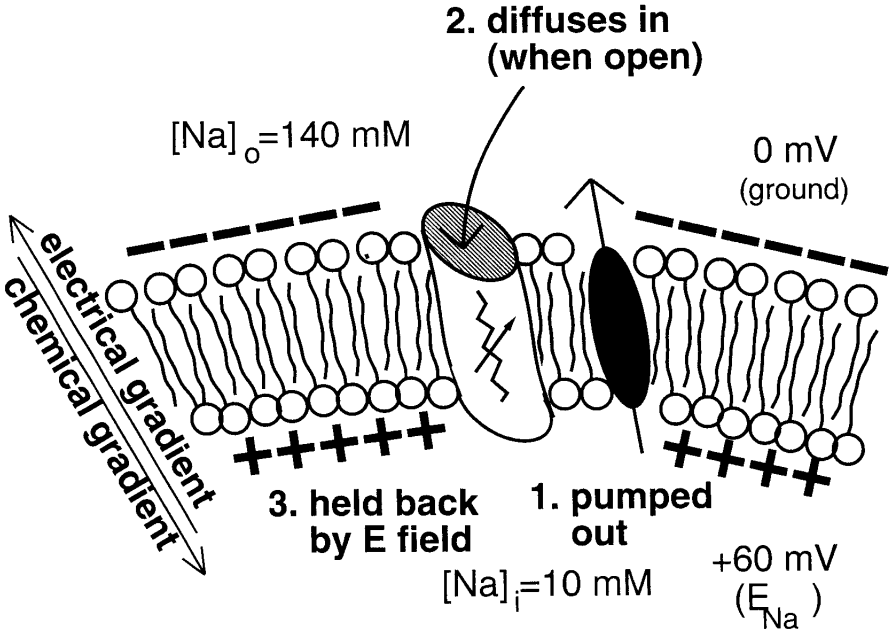


- Concentration of sodium ions Na^+ outside the cell is higher than it is in the cytoplasm, that is, inside the cell.
- The concentration difference creates the chemical gradient forcing the inward diffusion of sodium ions.
- Sodium is pumped from inside to outside (#1 in figure) by a protein that uses energy from ATP (adenosine triphosphate).

- The pumping leaves sodium concentration outside of the cell ($[Na]_o \approx 140$ millimoles) higher than it is in the cytoplasm ($[Na]_i \approx 10$ millimoles).

  (1 mole = $6.02 \cdot 10^{23}$ atoms — the Avogadro number — is a measure of amount of substance)

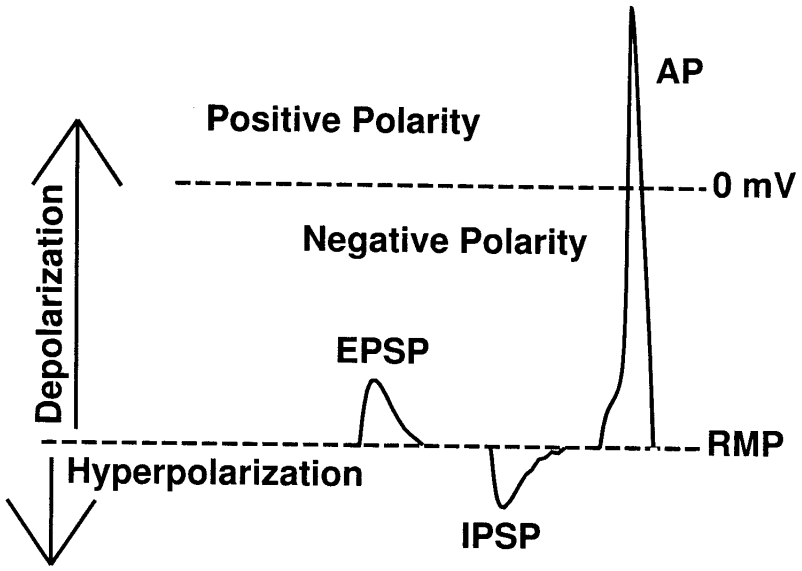
- The concentration difference across the membrane does not in itself lead to any charge separation, since sodium ions on both sides are appropriately matched with negatively charged proteins.
- Since there is more sodium outside, it "wants" to flow inside due to diffusion (#2 in Fig. 12.3).
- (Diffusion is what makes a drop of ink spread out in a glass of water; it wants to go where no ink has gone before.)



- As long as the selective channels for sodium remain closed, sodium cannot diffuse and the sodium concentration gradient has no effect on membrane potential.
- When the sodium channel opens, sodium rushes down its concentration gradient.
- The negative proteins that are paired with the sodium ions cannot follow; they are not allowed through the sodium channel.

- This diffusion of sodium across the membrane leads to charge separation across the membrane, with unmatched sodium ions on the inside and unmatched negative protein molecules on the outside.
- The unmatched sodium ions inside the membrane will stay near the membrane, in order to be close to their lost negative brethren.
- This bunching of positives next to the inside of the membrane, with a corresponding bunching of negatives next to the outside, creates an electric field (#3 in Fig. 12.3) that opposes inward diffusion through the ion channels.
- This outward electric field is the sodium battery.

- The inward diffusive force and the outward electrical force reach a steady state (Nernst equilibrium) so that there is no net flow of ions and little need for continued pumping to maintain equilibrium.
- The concentration difference between inside and outside can be directly translated into an electrical potential by using the Nernst equation.
- The resulting battery voltage E_{Na} is approximately +60 mV between the battery plates.
- By contrast, **potassium** is at high concentration inside and low concentration outside.
- The potassium chemical gradient is outward so the electrical gradient is inward.
- The positive inward electrical gradient would be +90 mV if measured from the outside of the membrane, relative to a grounded inside.
- However, we always measure the potential on the inside, relative to ground outside, so the potassium potential (E_K) is about -90 mV.
- Before we write Hodgkin-Huxley equations some comments regarding a standard nomenclature to describe voltage deviations from resting potential

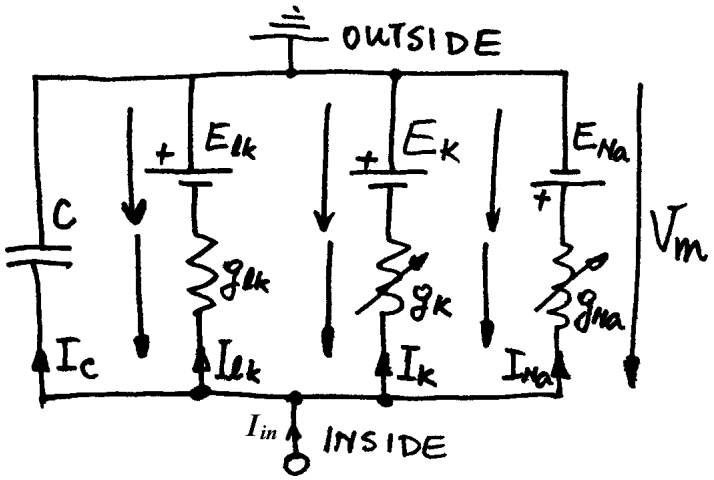


- Resting membrane potential (RMP) is typically about -70 mV (inside negative).
- Negative deviations, which make the membrane even more negative that at rest, are called **hyperpolarizing** (hyper means more).
- Positive deviations, which make the membrane less negative than it is at rest, reducing its polarization, are called **depolarizing**.

- Excitatory postsynaptic potentials (EPSPs) depolarize.

  Inhibitory postsynaptic potentials (IPSPs) hyperpolarize.
- Action potentials (APs) are depolarizations that can overshoot 0 mV, temporarily reversing membrane polarity.
- The membrane can be naturally depolarized by about 120 mV, (approximately the value of the sodium battery) from -70 mV to $+50$ mV
- Natural activity will only hyperpolarize the cell by about 20 to 30 mV (approximatelly the value of the potassium baterry) to -100 mV
- Artificial depolarization with injected current is limited by the tendency of prolonged depolarization to kill the cell.

9.6 The membrane voltage equation



- The calculations for the parallel-conductance model are similar to those for the RC model except that we have to add in the batteries.
- The membrane voltage, V_m, is the same for each parallel branch of the circuit. Hence we can write:

- For the Sodium branch: $V_m = E_{Na} + \dfrac{I_{Na}}{g_{Na}}$. Hence the current: $I_{Na} = g_{Na} \cdot (V_m - E_{Na})$
- For the Potassium branch: $V_m = E_K + \dfrac{I_K}{g_K}$. Hence the current: $I_K = g_K \cdot (V_m - E_K)$
- For the leak branch: $V_m = E_{lk} + \dfrac{I_{lk}}{g_{lk}}$. Hence the current: $I_{lk} = g_{lk} \cdot (V_m - E_{lk})$
- The current through the capacitor is proportional to the time derivative of the voltage across the capacitor

$$I_C = C \cdot \frac{dV_m}{dt}$$

- According to Kirchhoff's law the input current must balance the outgoing currents:

$$I_C + I_{lk} + I_K + I_{Na} = I_{in}$$

- This is typically written in the following form

$$I_C = -I_{lk} - I_K - I_{Na} + I_{in}$$

- Substituting the currents gives the first **Hodgkin-Huxley equation for the membrane voltage**:

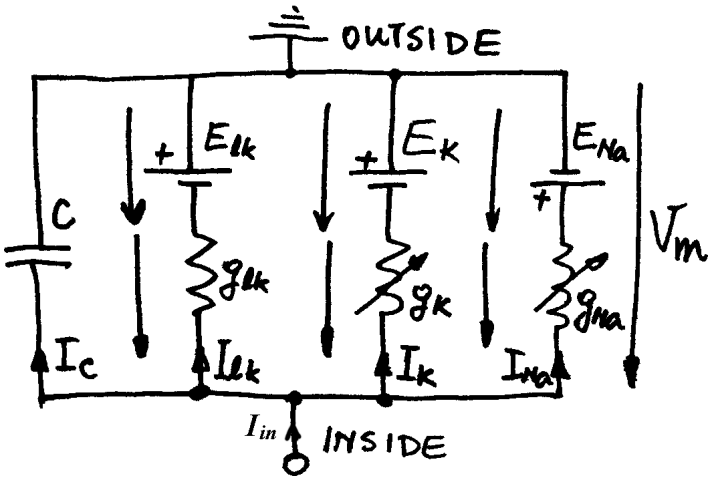
$$C \cdot \frac{dV_m}{dt} = -g_{lk} \cdot (V_m - E_{lk}) - g_K \cdot (V_m - E_K) - g_{Na} \cdot (V_m - E_{Na}) + I_{in} \tag{9.1}$$

- It is a first-order differential equation for the membrane voltage V_m, that can be also written as:

$$C \cdot \frac{dV_m}{dt} = g_{lk} \cdot (E_{lk} - V_m) + g_K \cdot (E_K - V_m) + g_{Na} \cdot (E_{Na} - V_m) + I_{in} \tag{9.2}$$

- The fact that the sodium and potassium conductances also depends on the membrane voltage. This makes the equation difficult to analyze.

- First, some comments on the directions of current and voltages involved in the model:



- Typically the conventional direction of currents is towards the ground, that is, zero potential.
- If the current is positive, than it indicates the direction of movement of positive charges.
- The conventional direction of voltages is “against the current”. Such voltages can be positive or negative.

- In the literature, the phrase “membrane current” is used as a synonym for conductive (ionic) current.
- Therefore, negative current flows in and depolarizes; positive current flows out and hyperpolarizes.

9.6.1 Calculating the resting potential

- The resting potential can be calculated assuming that there is voltage change, that is, the time derivative of the membrane voltage is zero.
- In addition the external current $I_{in} = 0$.

  Now eqn (9.1) can be re-written as:

$$g_{lk} \cdot (V_m - E_{lk}) + g_K \cdot (V_m - E_K) + g_{Na} \cdot (V_m - E_{Na}) = 0 \tag{9.3}$$

- Solving equation (9.3) for V_m gives the **resting membrane potential** (RMP):

$$V_m = \frac{g_{lk} \cdot E_{lk} + g_K \cdot E_K + g_{Na} \cdot E_{Na}}{g_{lk} + g_{Na} + g_K} \tag{9.4}$$

- This is a version of the Goldman-Hodgkin-Katz (GHK) equation.
- It says that steady-state membrane voltage is the weighted sum of the batteries, weights being the conductances associated with respective batteries.
- Since g_{lk} is the dominant conductance at rest, it will have the greatest effect on determining RMP.
- If a conductance is turned off completely (e.g., $g_{Na} = 0$), the corresponding battery has no influence.
- If, on the other hand, a conductance is very high, then the other batteries will have very little influence, e.g., if $g_{Na} \gg g_K$ and $g_{Na} \gg g_{lk}$, then $V_m \approx \frac{g_{Na} \cdot E_{Na}}{g_{Na}} = E_{Na}$

9.7 Modelling the active channels

- To complete the Hodgkin-Huxley model, we have to describe the behavior of the **sodium** and **potassium** channels.
- These channels are modeled as voltage-sensitive conductances controlled by **three types of "activation particles"**.
- These conceptual activation particles are voltage-dependant time-evolving quantities describing gradual switching on and off the potassium and sodium channels.
- These quantities associated with the conceptual particles change their values between 0 (channel off) and 1 (channel fully on).

9.7.1 The potassium channel — n particles

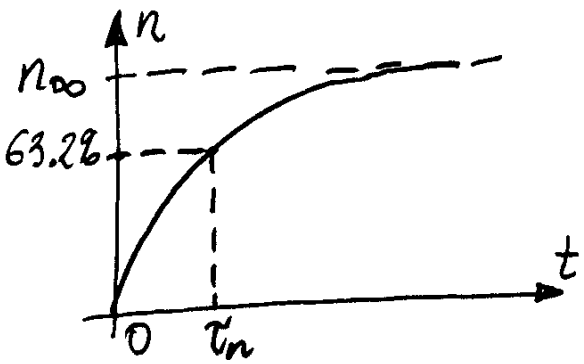
- The variation of the conductance of the potassium channel, g_K, is modeled by one type of time-varying activation particles called n.
- Firstly, there is the following non-linear relationship between the channel conductance and the activation particles

$$g_K = G_K \cdot n^4 \tag{9.5}$$

where G_K is the maximum value of the conductance, for $n = 1$.

- Secondly, the particles vary in time between 0 and its maximum, or steady-state value, n_∞

$$\tau_n \frac{dn}{dt} = n_\infty - n \tag{9.6}$$



Assuming that n_∞ is constant (which it is NOT), this equation would have a well-known solution in the form of a saturating exponential growth

$$n(t) = n_\infty(1 - e^{-\frac{t}{\tau_n}}) \tag{9.7}$$

governed by the time constant τ_n.

- Thirdly, the time constant, τ_n and the steady-state value n_∞ depends on the membrane voltage through the following experimentally verified equations:

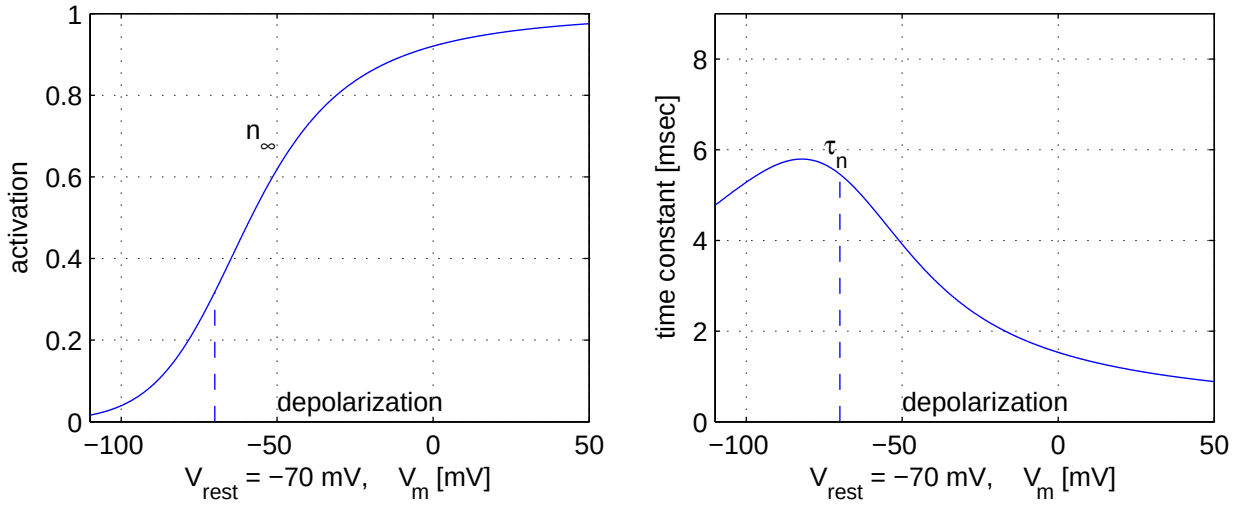
$$\tau_n = \frac{1}{\alpha_n + \beta_n}\ , \qquad n_\infty = \alpha_n \cdot \tau_n = \frac{\alpha_n}{\alpha_n + \beta_n} \tag{9.8}$$

where the rate constants are:

$$\alpha_n(V) = \frac{10 - V}{100(e^{(10-V)/10} - 1)}\ , \qquad \beta_n(V) = 0.125e^{-V/80} \tag{9.9}$$

where V is the membrane potential relative to to the axon's resting potential in millivolts.

- The voltage dependance of n_∞ and τ_n is illustrated by the following plots



- Note that when the membrane is depolarized $(V_m > V_r)$ the steady-state value of the activation particles n increases, and the time constant decreases.

9.7.2 The sodium channel — m and h particles

- The variation of the conductance of the sodium channel, g_{Na}, is modeled by two types of activation particles, m and h also called inactivation particle due to its role of switching off the channel.
- The relationship between the channel conductance and the activation particles is now as follows

$$g_{Na} = G_{Na} \cdot m^3 \cdot h \tag{9.10}$$

  where G_{Na} is the maximum value of the conductance, for $m = 1$ and $h = 1$.

- As for the potassium channel there is a differential equation for each particle:

$$\tau_m \frac{dm}{dt} = m_\infty - m \qquad \tau_h \frac{dh}{dt} = h_\infty - h \tag{9.11}$$

- The time constants and steady state values are defined in terms of the rate constants:

$$\tau_m = \frac{1}{\alpha_m + \beta_m} \qquad \tau_m = \frac{1}{\alpha_m + \beta_m} \tag{9.12}$$

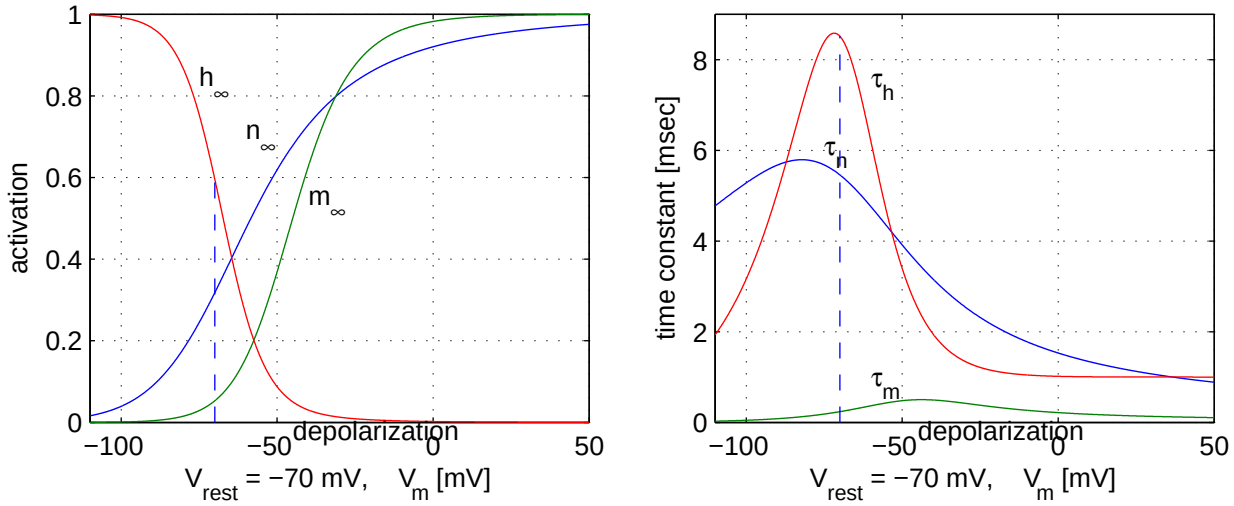
$$m_\infty = \alpha_m \cdot \tau_m = \frac{\alpha_m}{\alpha_m + \beta_m} \qquad h_\infty = \alpha_h \cdot \tau_h = \frac{\alpha_h}{\alpha_h + \beta_h} \tag{9.13}$$

- The voltage-dependant rate constants are experimentally derived to be equal to

$$\alpha_m(V) = \frac{25 - V}{10(e^{(25-V)/10} - 1)} \qquad \alpha_h(V) = 0.07e^{-V/20} \tag{9.14}$$

$$\beta_m(V) = 4e^{-V/18} \qquad \beta_h(V) = \frac{1}{e^{(30-V)/10} + 1}$$

- The voltage dependance of the steady-state values and time constants are illustrated by the following plots. The potassium parameters are included for comparison.



- The steady-state value, m_∞, of the sodium activation particle m behaves similarly to its potassium counterpart: when the membrane voltage increases, m_∞ also increases.
- The steady-state value, h_∞, of the sodium in-activation particle h behaves in the opposite direction: when the membrane voltage increases, h_∞ decreases, switching off the sodium channel.

- **Four first-order differential equations** (9.2), (9.6) and (9.11) together with the supporting algebraic equations for the **potassium conductance** (9.5), (9.8), (9.9) and for the **sodium conductance** (9.10), . . . , (9.14) form the **complete Hodgkin-Huxley model of action potential genetration.**

9.7.3 Action potential — the pulse

- The Hodgkin-Huxley equations cannot be solved analytically due to non-linear relationship between the conductances and the unknown membrane voltage, and must be solved using recursive approximation of derivatives.

- Each first-order differential equation of the form $\frac{dx}{dt} = f$ approximated by $\Delta x = \Delta t \cdot f$

  is replaced with the recursive relationship for the next value of the unknown variable x in the following form: where Δt is the time step, and k is the time step number.

  $$x(k+1) = x(k) + \Delta t \cdot f$$

- Now we can calculate the membrane voltage and associated quantities step by step.

- To calculate the membrane voltage (action potential) we have used the following parameters:

  Membrane capacitance: $C = 1\mu$F/cm^2

  Potassium battery: $E_K = -12$ mV relative to the resting potential of the axon.

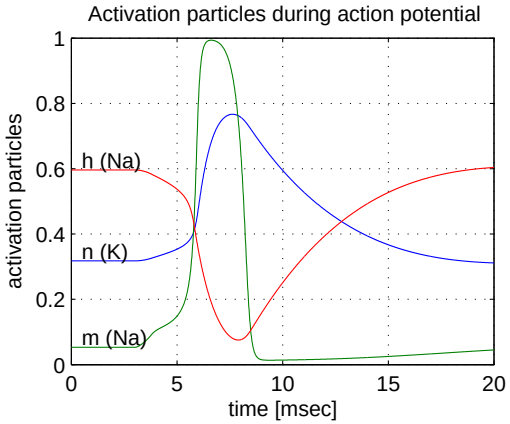
  Maximal Potassium conductance: $G_K = 36$ mS/cm^2

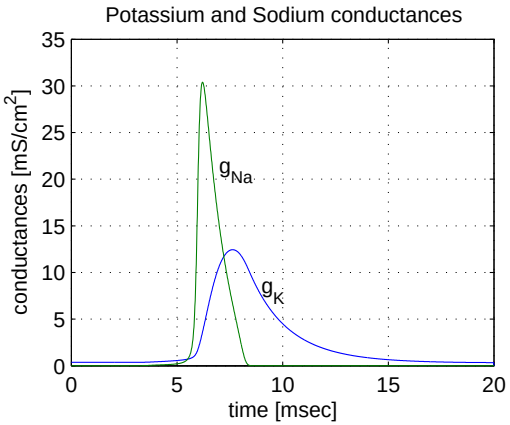
  Sodium battery: $E_{Na} = 115$ mV sodium reversal potential relative to the resting potential of the axon.

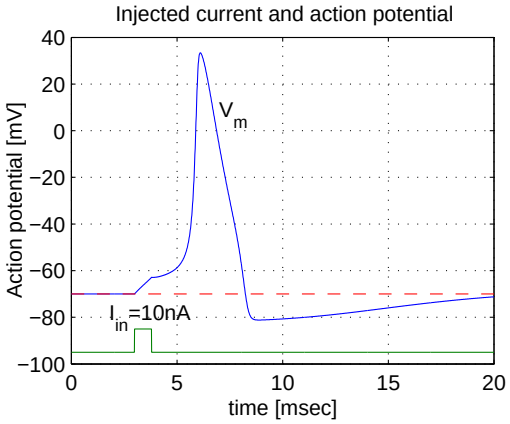
  Maximmu Sodium conductance: $G_{Na} = 120$ mS/cm^2

  Leakage conductance: $g_{lk} = 0.3$ mS/cm^2 is voltage-independent.

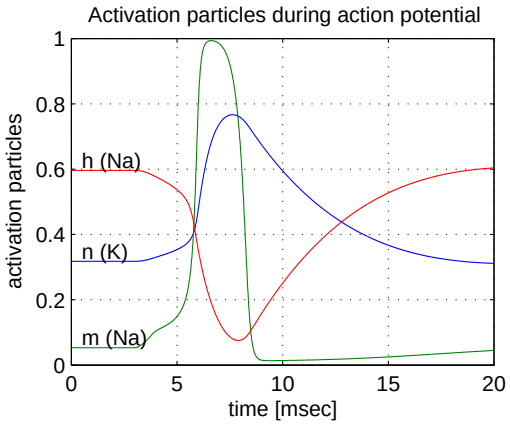
  Leakage battery $E_{lk} = 10.613$ mV is calculate from the membrane equilibrium condition.

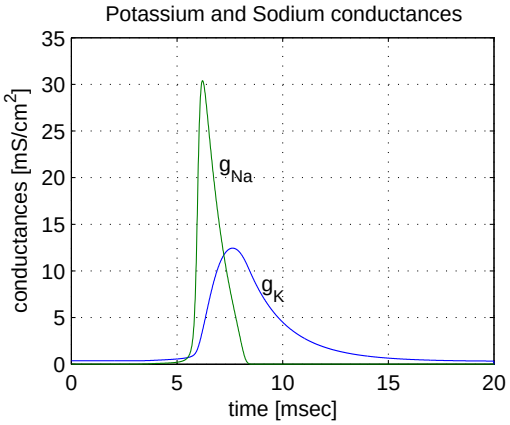


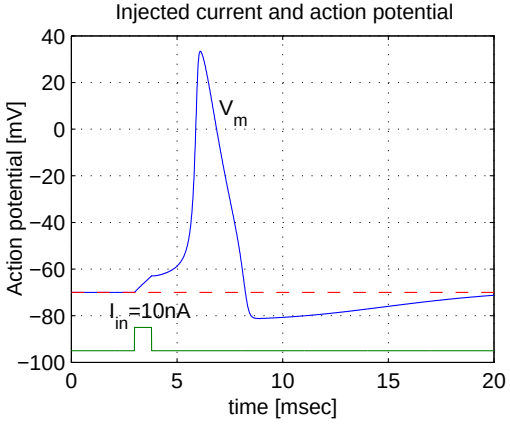




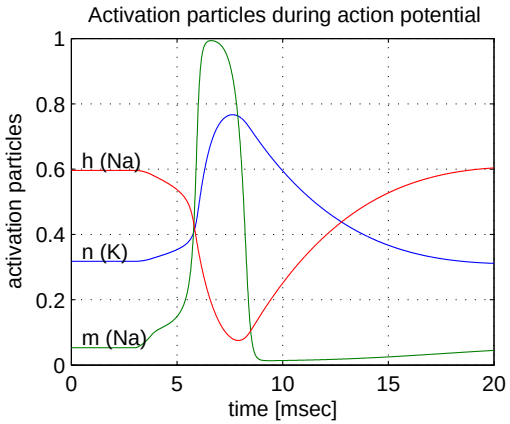
- At rest, the membrane potential is $V_r = -70$mV.
- Both potassium and sodium channels were almost completely switched off as indicated be the small values of potassium and sodium conductances.
- Note the resting values of particles: K: $n = 0.32$, Na: $m = 0.05, h = 0.6$.
- At some stage the injected current pulse ($I_{in} = 10$nA in the example) that emulates the Post-Synaptic Potential (PSP) **depolarizes** the cytoplasm, that is, the inside of the cell.
- This initial depolarization (before 5ms in the example) results in a slow increase of the membrane potential, which results in the increase of the values of the particles m (Na) and n (K) and decrease of the value of h.
- As a result both sodium and potassium channels start to open up.
- At some stage, (just after 5ms when all particle values are equal) the **conductance of the sodium channel increases rapidly**.
- The rapid increase of the sodium channel conductance results in **rapid depolarization**, that is, increase of the voltage potential, creating the **rising edge of the action potential**.

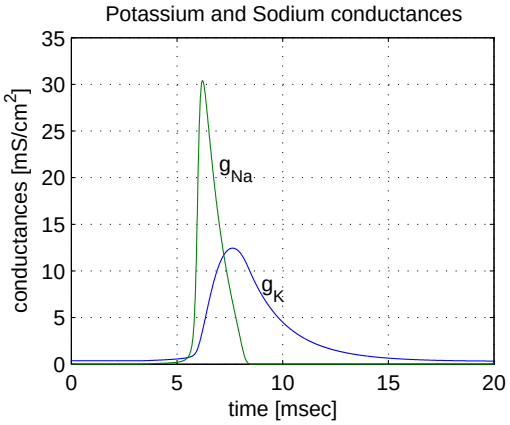


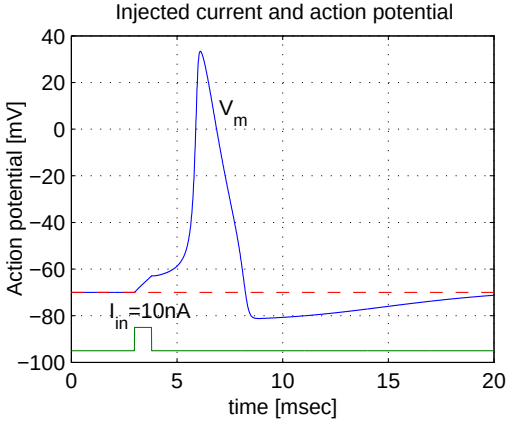




- **During the rising edge of the action potential**, the slower process of opening the potassium channel begins.
- This process is driven by the slow increase of the value of m particles and corresponding increase of the potassium channel conductance.
- At the same time the sodium channel conductance increases to its maximum value due to increase of the value of the n particles and the decrease of the value of the h particles.
- **After the action potential reaches its maximum**, the opening of the potassium channel and closing of the sodium channel starts the **rapid process of re-polarization** when the membrane voltage goes quickly towards the resting potential.
- Switching off the sodium channel (its conductance is close to zero) with the potassium channel being still open and supplying the outward current, results in **hyperpolarization** when the membrane voltage drops below the resting potential.







- After the membrane voltage reaches its minimum, a slow process of **After-HyperPolarization** (AHP) begins.
- During after-hyperpolarization the potassium channel slowly switches off as indicated by reduced channel conductance g_K and corresponding particle n.
- In addition a very slow process of partial opening of the sodium channel takes place as indicated by the channel particles h and m slowly moving towards their resting values.
- The after-hyperpolarization is always present after the neuron fires.
- It reflects a short term firing history and, as we will investigate it further, provides immediate inhibition.