LECTURE 6

The behavior of the ion channels of a generic type S (e.g., $S = K^+$, or $S = Na^+$, etc.) can be described by using the following class of models:

$$I_S = N g_S(V,t) \varphi_S(V)$$

where: $I_S \triangleq$ current density

$\varphi_S(V) \triangleq$ I-V curve of a single ion channel of type S

$N \triangleq$ number of channels for unit of surface

$g_S(V,t) \triangleq$ proportion of open channels in the population of N channels

* How do we model $g_S(V,t)$ and $\varphi_S(V)$?

To model $\varphi_S(V)$ we can either use electrodiffusion arguments or energy-barrier arguments - The outcome of this effort is:

a) If the cell has long channels or high concentrations of ions:

$$\varphi_S(V) \cong \mu (V - V_S) \qquad V_S \triangleq \text{Nernst potential}$$

$\Downarrow$

This is the case for cells in invertebrates

It is linear

b) If the cell has short channels:

$$\varphi_S(V) \cong \frac{(zF)^2 V}{RT} \mu \frac{[S]_i - [S]_e e^{-\left(\frac{zF}{RT}V\right)}}{1 - e^{-\left(\frac{zF}{RT}V\right)}}$$

$\Downarrow$

This is the case for cells in vertebrates

It is GHK-approximation

Both models do not depend on time t

In case a) it is usually written:

$$I_s = \hat{g}_s \, g_s(V,t) \, (V - V_s)$$

$\hat{g}_s \triangleq N\mu$ - max conductance density

In case b) it is usually written:

$$I_s = \hat{p}_s \, \frac{(zF)^2 V}{RT} \, g_s(V,t) \, \frac{[S]_i - [S]_e \, e^{-\left(\frac{zF}{RT}V\right)}}{1 - e^{-\left(\frac{zF}{RT}V\right)}}$$

$\hat{p}_s \triangleq N\mu$ - max permeability

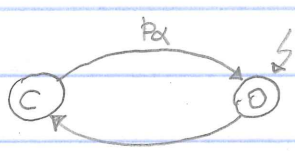
To model $g_s(V,t)$ we can consider:

- The conversion of channels from one state to one another $\Rightarrow$ Ex.: $[C] \underset{\beta(V)}{\overset{\alpha(V)}{\rightleftarrows}} [O]$

($\alpha(V)$: it is a rate; it is a fraction of N channels)

The complexity of this approach grows with the number of states; and functions $\alpha(V)$ and $\beta(V)$ need to be estimated anyway

- A probabilistic characterization of the transition from one state to one another $\Rightarrow$ Ex:



(p_α: it is the condition of a single channel; p_β: it is the probability of going from "open" to "closed")

We study the probability of one channel to be open under voltage V and - since N is very big - we assume a good matching between probability and fraction of open channels

• A data-driven approach ⇒ For instance, if the model template is:

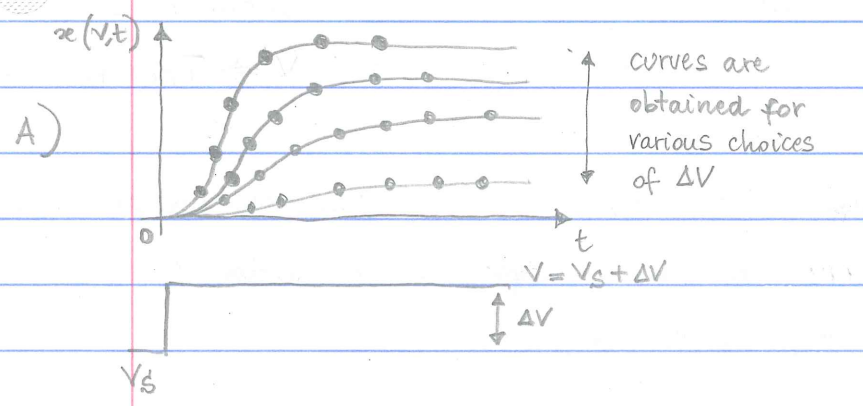
$$I_S = \hat{g}_S \, g_S(V,t) \, (V - V_S)$$

we consider the ratio:

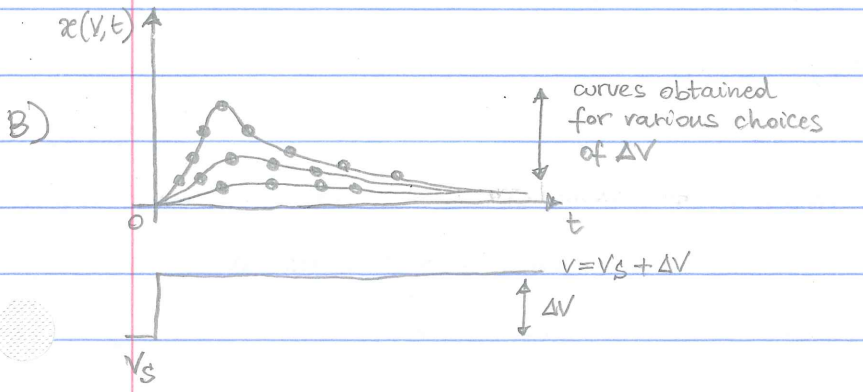
$$x(V,t) = \frac{I_S}{V - V_S}$$

Because I_S, V, and V_S may be measured in a voltage-clamp experiment it turns out that measurements of $x(V,t)$ can be obtained under various settings, e.g.:

- One can fix V and measure the evolution in time of $x(V,t)$:



Black dots are examples of actual measurements while the lines represent their interpolation



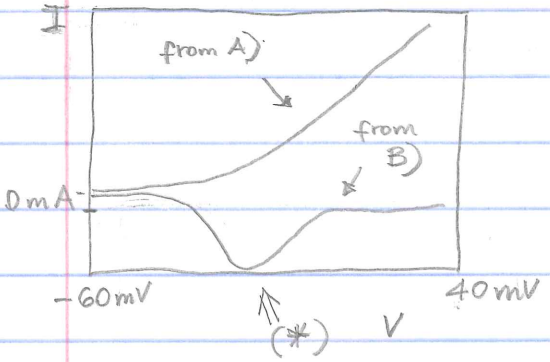
- Plots of type A) are typical of K^+ channels
- Plots of type B) are typical of Na^+ channels

⇓

Fig. 5.3 in your textbook shows the measurements collected in the axon of a squid neuron

- Then, one can consider the value $x_V = \lim_{t \to \infty} x(V,t)$ measured for each choice of V under steady state condition and reconstruct the I-V curve - For instance, from plots A) and B) one obtains I-V curves as in this figure:

c)



(*) Note that a negative current indicates that the direction of the ion flow may be reversed under specific values of V

Note: Plots like A) and B) give information on how channels open and close under a constant membrane voltage V ⇒ They reveal the channel dynamics

Plot C) instead uses $I(V) = x_V (V - V_S)$ ⇒ It is time-independent and solely depends on the number of open channels under voltage V ⇒ It is a "steady-state" I-V curve

Problem: What function can we use to interpolate measurements in plot A)-B)-C)?

In a purely empirical way, one can say that the function for the plots in A) must increase monotonically with t and V, and it must have a saturation as $t \to \infty$ ⇒ Sigmoidal-like functions could work

Similarly, the function for the plots in B) must be the result of 2 opposite

dynamics, one increasing as t and V increases, and one decreasing ⇒ A class of functions $x(V,t) = f_1(V,t) \cdot f_2(V,t)$ with $f_1(\cdot)$ and $f_2(\cdot)$ sigmoidal-like could work

Note: Because we are proceding with no clue on the mechanisms of opening and closing of the channels, we have no insight that can constrain our choice. The only constraints is that we want the functions fit the data as much as we can ⇒ We are doing a black-box model

It was found that - with data coming from the axon of a squid - an excellent fit could be obtained as follow:

For plot A) (k^+ channels):

$$x(V,t) = \hat{g}_K \, n^4(V,t)$$

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

$$\alpha_n(V) = 0.01 \, \frac{10 - \Delta V}{e^{\left(\frac{10-\Delta V}{10}\right)} - 1}$$

$$\beta_n(V) = 0.125 \, e^{\left(-\frac{\Delta V}{80}\right)}$$

$$\Delta V = V - V_{eq}$$

↑ constant

For plot B) (Na^+ channels):

$$x(V,t) = \hat{g}_{Na} \, m^3(V,t) \cdot h(V,t)$$

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

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

$$\alpha_m(V) = 0.1 \, \frac{25 - \Delta V}{e^{\frac{25-\Delta V}{10}} - 1}$$

$$\beta_m(V) = 4 e^{-\left(\frac{\Delta V}{18}\right)} \; ; \; \alpha_h(V) = 0.07 e^{\left(-\frac{\Delta V}{20}\right)}$$

$$\beta_h(V) = \frac{1}{e^{\frac{30-\Delta V}{10}} + 1}$$

A few considerations with these equations:

- What is V_{eq} and how is it determined?

The scientists who conducted the experiments and found these functions (Hodgkin and Huxley) neglected the Cl^- ions and assumed that the cell membrane could be modeled as:

H-H model

$$C_m \frac{dV}{dt} + g_{Na}(V - V_{Na}) + g_K(V - V_K) + g_L(V - V_L) = 0$$

where: $g_{Na} \triangleq \hat{g}_{Na} m^3 h$

$g_K \triangleq \hat{g}_K n^4$

$g_L(V - V_L) \triangleq$ leakage current. It is a purely ohmic current that accounts for any other current that does not involve Na^+ or K^+ ions (e.g., Cl^- currents)

In this case, V_{eq} is defined as the membrane voltage at steady-state:

$$\frac{dV}{dt} = 0 \Rightarrow g_{Na}(V_{eq} - V_{Na}) + g_K(V_{eq} - V_K) + g_L(V_{eq} - V_L) = 0$$

$$\Rightarrow V_{eq} = \frac{g_{Na}V_{Na} + g_K V_K + g_L V_L}{g_{Na} + g_K + g_L}$$

- Do n, m, and h have any physiological meaning?

No, they do not. Moreover, n^4 and m^3h were the lowest power of the functions n, m, and h that could fit the data. Hence, the order of the power has no physiological meaning either

However, note this:

$$n_\infty(V) \triangleq \frac{\alpha_n(V)}{\alpha_n(V)+\beta_n(V)}$$

$$\tau_n(V) \triangleq \frac{1}{\alpha_n(V)+\beta_n(V)}$$

$$\Rightarrow \frac{dn}{dt} = \frac{n_\infty(V)-n}{\tau_n(V)}$$

$|n_\infty(V)| \leq 1 \quad \forall V$

for the choice of α_n and β_n it is also $n_\infty \geq 0$

Similarly, one can write:

$$m_\infty(V) \triangleq \frac{\alpha_m(V)}{\alpha_m(V)+\beta_m(V)}$$

$$\tau_m(V) \triangleq \frac{1}{\alpha_m(V)+\beta_m(V)}$$

$$h_\infty(V) \triangleq \frac{\alpha_h(V)}{\alpha_h(V)+\beta_h(V)}$$

$$\tau_h(V) \triangleq \frac{1}{\alpha_h(V)+\beta_h(V)}$$

$$\Rightarrow \frac{dm}{dt} = \frac{m_\infty(V)-m}{\tau_m(V)}$$

$$\frac{dh}{dt} = \frac{h_\infty(V)-h}{\tau_h(V)}$$

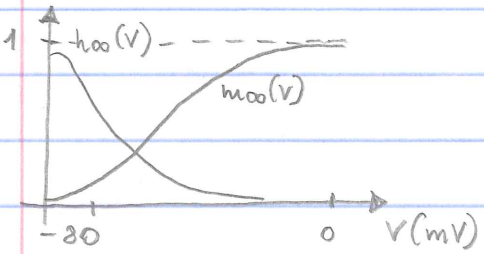
with $m_\infty(V)$ and $h_\infty(V)$ in the range $[0,1]$ for every choice of V

As a result, for every fixed value V, the variables m, h, and n will converge to a value between 0 and 1 with a rate that is described by a first-order linear ODE $\Rightarrow$ $n(V,t)$, $m(V,t)$, and $h(V,t) \in [0,1] \quad \forall t, V \Rightarrow$ They can be interpreted as fractions of open subunits or - equivalently - as probabilities of subunits being open $\Rightarrow$ In this way, we can say:

$g_K = \hat{g}_K n^4 \Rightarrow$ It is mathematically equivalent to a channel with 4 subunits. Each subunit has a probability n to be open and all subunits have the same probability $n \Rightarrow$ The probability of the K^+ channel to be open is n^4

$g_{Na} = \hat{g}_{Na}\, m^3 h \Rightarrow$ It is mathematically equivalent to a channel with 4 subunits, 3 of them being of type 1 and one of them being of type 2. Type-1 subunits have the probability m to be open and Type-2 subunits have the probability h to be open $\Rightarrow$ The probability of the Na^+ channel to be open is $m^3 h$

Note that we are not modeling all the possible combinations of open/closed subunits but we are only modeling the probability of open channels. Also note that, for the Na^+ channels, m and h have an opposite behavior as V increases:



Hence, m is called the "activation" variable and h is called the "inactivation" variable

- What is the rationale for this kind of models?

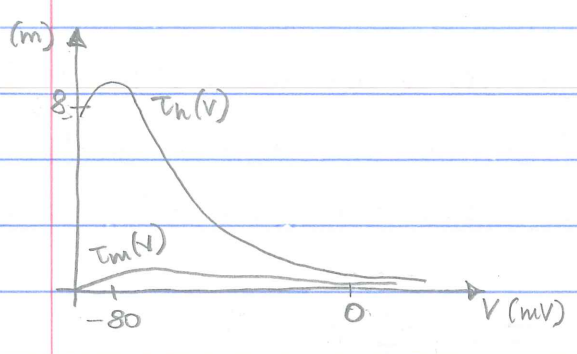
The idea is to modulate the rate of change of these models under different voltages V by having the time constant $\tau = \tau(V)$. In fact, by fixing $V = V^*$ one has:

$$\frac{dn}{dt} = \frac{n_\infty(V^*) - n}{\tau_n(V^*)} \Rightarrow n(V^*, t) = n_\infty(V^*)\left[1 - e^{-t/\tau_n(V^*)}\right]$$

initial conditions: $n(V^*, t) = 0$

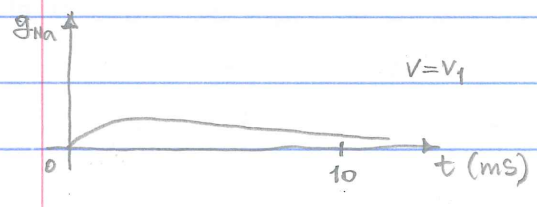
We have a sigmoidal-like function whose slope varies for each value of V

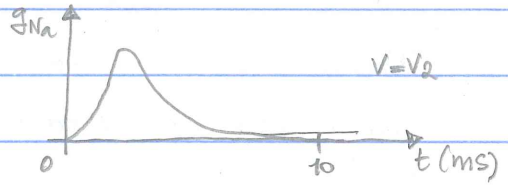
Analogously, time constants τ_h and τ_m have different magnitude at different voltages and their ratio changes with the voltage too:



In particular, $\tau_m(V) < \tau_h(V)$ always, i.e., Na^+ channels activate fast and inactivate slowly $\Rightarrow$ This captures the fact that, at every voltage V, the current first raises and then decays

The ratio τ_m/τ_h varies largely with V $\Rightarrow$ There are voltages at which the channels inactivate very slowly $\Rightarrow$ The amount of ions flowing is larger at these voltages $\Rightarrow$ That's why the peak in the curve $g_{Na}(V,t)$ can change in amplitude and length, e.g.:





$\tau_h/\tau_m\ (V_1) << \tau_h/\tau_m\ (V_2)$

- Why do we spend time on this model?

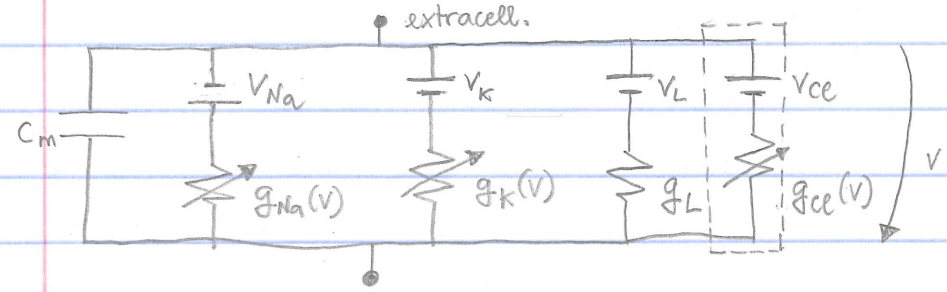
- First, it is a model template that provides results consistent with other, more formal modeling approaches (e.g., modeling the probability of state transition)

- Second, it works surprisingly well when it comes to model g_{Na} and g_K in a variety of neurons (not only the squid axon) - Parameters may change,

functions $\alpha_*(V)$ and $\beta_*(V)$ may have different forms but the modeling process does not change

- Third, it can be extended to other types of ion channels (e.g., Cl^-, Ca^{2+}, etc.) which means that the model of the membrane can be a (nonlinear) electric circuit with ion currents that are added in parallel one at the time:

(**)



- Fourth, these models are defined for a large range of V and, depending on the value of V, may have significantly different temporal dynamics ⇒ They are of the outmost interest to model those cells that can experience large variations in the membrane voltage. Cells like:

* neurons
* cardiac cells
* muscle cells
* pancreatic cells
* hypothalamic cells
* etc.

} If properly stimulated, they can experience a large excursion (e.g., 60 mV or more) in the membrane potential in a finite time (range: 4 ÷ 150 ms)

⇓

These cells are called "excitable"

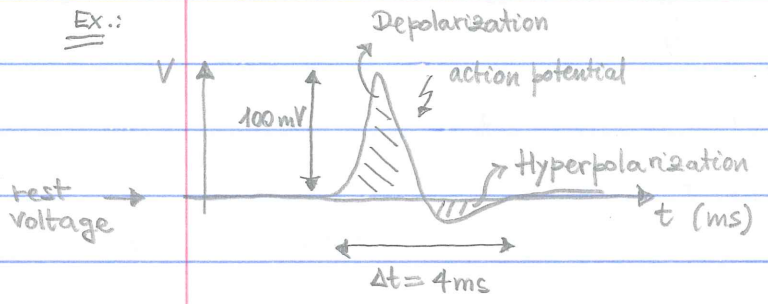
Note that two features define an excitable cell:

a) The excursion in membrane voltage (a.k.a. "action potential" or "spike") does not imply that large I_K or I_{Na} occurs. For instance, the flux of

Na^+ and k^+ ions in the squid axon during an action potential is $< 10^{-11}$ moles/cm^2

b) The action potential initiates in one point of the membrane and propagates along the membrane. It eventually transfers to a nearby cell via electro-chemical reactions

Ex.:



- The hyperpolarization is a phase at the end of the spike during which V is lower than the rest value

⇓

No further spikes can be initiated in this phase

i) The action potential is threshold-based, i.e., V must reach a critical value in order to make the whole excursion

ii) The action potential is a all-or-nothing phenomenon, i.e., if V reaches the threshold, then the spike occurs with probability $\cong 1$; if V is below the threshold, the probability of turning into a spike is $\cong 0$

iii) The mechanisms of initiation and termination of an action potential can be explained by using the H-H model and looking at the dynamics of Na^+ and k^+ channels:

Let us assume that some exogenous input increases V above the rest value (V_{rest})

⇑

KICK-OFF EVENT

⇒

$h(V_{rest}, 0) \cong 1$ (usually)

$n(V_{rest}, 0) \cong 0$ (usually)

$\tau_m(V_{rest}) \ll \tau_n(V_{rest}), \tau_h(V_{rest})$

Hence, "m" will start increasing from its initial value $m(V_{rest}, 0)$ with a pace faster than the changes of "h" and "n" (Na^+ CHANNELS ACTIVATION)

⇓

I_{Na} starts entering the cell membrane and that increases the value of V (MEMBRANE DEPOLARIZATION)

⇓

As V increases, we have: $\tau_h(V) \downarrow$ $h_\infty(V) \downarrow$

$\tau_n(V) \downarrow$ $n_\infty(V) \uparrow$

As a result, I_{Na} starts decreasing because of $h(V,t)$ (Na^+ CHANNELS INACTIVATION) and I_K starts increasing but I_K flows toward the extracellular environment

⇓

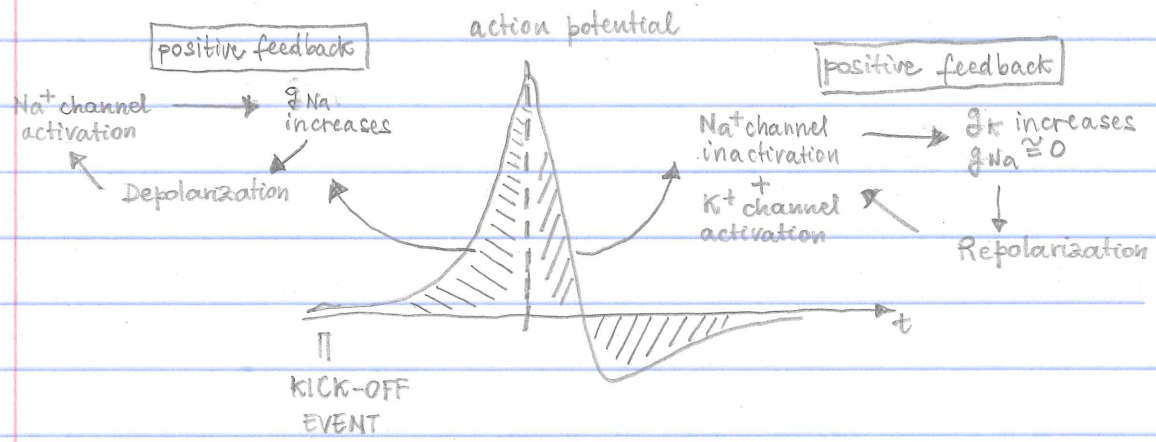
I_K contributes to decrease V (MEMBRANE REPOLARIZATION)

⇓

As $V \cong V_{rest}$: $n_\infty(V) \cong 0$ and $h_\infty(V) \cong 1$ again. However, $\tau_n(V)$ and $\tau_h(V)$ are large, so it takes a while to $h(V,t)$ and $n(V,t)$ to return to the rest value. In the meantime, V keeps decreasing and goes below V_{rest} (MEMBR. HYPERPOLARIZATION)

⇓

As $V < V_{rest}$, $n(V,t)$ reaches 0 and $h(V,t)$ reaches 1 eventually, while I_{Na} begins growing ⇒ V repolarizes to V_{rest}



Note that, during hyperpolarization, we have:

$h(V,t) \cong 0 \Rightarrow I_{Na} \cong 0$

$n(V,t) \cong 1 \Rightarrow I_K$ is large

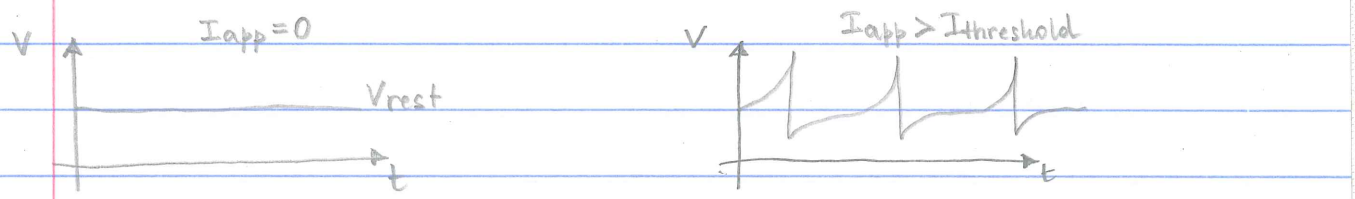
$\Rightarrow$ Na+ channels cannot compensate for I_K. Hence there cannot be another action potential, i.e., hyperpolarization defines a "refractory period"

- How do we model an exogenous input in the equivalent circuit (**)?

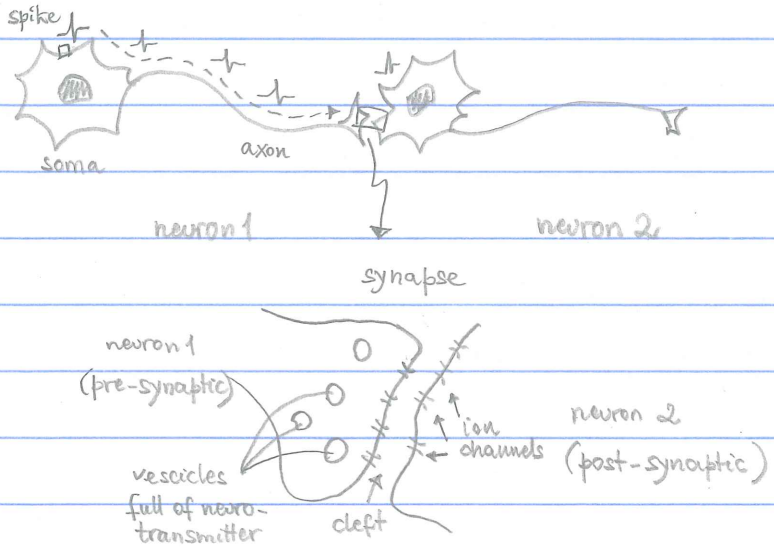
$$C_m \frac{dV}{dt} + \hat{g}_K n^4 (V - V_K) + \hat{g}_{Na} m^3 h (V - V_{Na}) + g_L (V - V_L) = I_{app}$$

- I_{app} can be an external input applied through an electrode to modify the electrical behavior of the cell membrane:

Ex.:



- In case of neurons, I_{app} can be provided by the electrochemical interface (synapse) with another neuron:



Description of the synapse

a) The arrival of an action potential in the termination (button) of the axon depolarizes the membrane and opens Ca^{2+} channels in the pre-synaptic neuron

⇓

b) The influx of Ca^{2+} ions causes the vesicles to open and release the neurotransmitters, which pass the cell membrane and diffuse in the cleft. Neurotransmitters are molecules that can bind with the proteins of ion channels and open the channels despite the membrane voltage

⇓

c) Neurotransmitters in the cleft bind with receptors on channels in the post-synaptic neuron and open the channels, letting the current I_{app} flows in the post-synaptic neuron

* How to model the synapse?

a) and b): For our cases, we neglect the dynamics of the Ca^{2+} ions and we lump the whole process occurring in the pre-synaptic neuron as a delay Δt between when the action potential is generated and when the neurotransmitter is released in the cleft. We also assume that the diffusion of the neurotransmitter in the cleft is impulsive, i.e.:

$$[L]_t = L_{max}\,\delta(t-\Delta t)$$

$L \triangleq$ neurotransmitter (a.k.a., "ligand")

$L_{max} \triangleq$ max concentration of L in the cleft

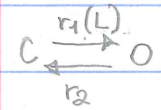
$\delta \triangleq$ Dirac's delta function

c): There are several types of neurotransmitters (e.g., Ach, GABA, Glt, etc.) and each type may interact with one type of ion channels (either anion or cation channels) ⇒ Neurotransmitters can cause either depolarizing currents (e.g., Glt) or hyperpolarizing currents (e.g., GABA).
Also, even though neurotransmitters interact with voltage-gated channels (e.g., Cl^-, Na^+, etc.), the effects of the neurotransmitter can mask the effects of voltage ⇒ It make sense to model the resultant ion current as an exogenous input to the post-synaptic cell membrane:

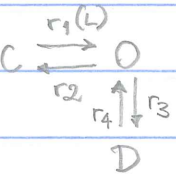
$$I_{syn} = g_{syn}(V - V_{syn})$$

g_{syn}: ligand-dependent conductance
V_{syn}: synapse reverse potential

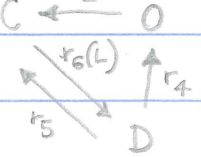
We can model the synaptic conductance by using the formalism seen for the ion channels. Typically one of the following schemes is considered:

A) 

C ≜ closed state
O ≜ open state
$r_1(L) \triangleq r_1 \cdot [L]$
r_1, r_2 ≜ rate constants

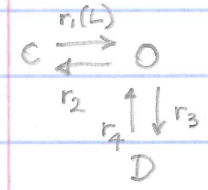
B) 

D ≜ desensitized state. It models a condition when the current flow decreases in time or is blocked even though the neurotransmitter opens the channels

C) 

$r_6(L) \triangleq r_6 \cdot [L]$

Example: To model B) we have:



$o \triangleq$ fraction of channels in open state

$d \triangleq$ fraction of channels in desensitized state

$c \triangleq 1 - o - d$

$$\begin{cases} \dfrac{do}{dt} = r_1[L](1-o-d) + r_4 d - (r_2 + r_3) o \\ \dfrac{dd}{dt} = r_3 o - r_4 d \\ I_{syn} = g_{syn}^{max} o \cdot (V - V_{syn}) \end{cases}$$

REFERENCE:

Textbook (volume 1): chapter 5, sec. 5.1; 5.1.1; 5.1.2
chapter 8, sec. 8.1; 8.1.5; 8.1.6

E.M. Izhikevich "Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting", The MIT Press, 2009 - chapter 2

A copy of the chapter of this additional book is available on Husky CT. Please, download it.