Signal processing in nervous system
- Hodgkin Huxley Model -

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Abstract

Alan Lloyd Hodgkin and Andrew Huxley investigated the ion mechanisms in the huge giant axon of squids in order to describe the generation of an action potential with mathematical methods. For a better understanding of initiation and propagation of neuronal signals they built a biophysical model. In that model every part of the nerve cell can be represented by an electronic component. Furthermore this model consists of ordinary differential equations, which are based on the electric features of following electric variables: current, conductance, capacitance and battery. They introduced gating variables for the ion channels, which describes the opening and closing kinectis of ion channels.
After all the two investigators developed the Hodgkin Huxley Model, which fits very well to the measured voltage data from the voltage clamp experiment with the squid giant axon. So this model gives a good approximation for the electric characteristics of excitable cells.

1 Introduction

In this paper the signal processing in nervous system will be shown on the basis of the Hodgkin-Huxley model. Hodgkin and Huxley tried to understand with the help of an voltage clamp experiment the mechanism of action potential generation. So they examined the huge axon from squids in order to characterize the initiation and propagation of neuronal signals. With the aid of an equivalent circuit and a set of nonlinear ordinary differential equations, they worked out a mathematical model, the Hodgkin Huxley model. With this model they could explain how the experimental results emerge. The Hodgkin Huxley model is a good way for approximating the electrical features of excitable cells.
Their experiment, the "voltage clamp experiment", is the origin of most neuron models. By dint of the Hodgkin Huxley model you are able to test dynamic behaviour of ion channels in neuronal cells and you can make predictions about stimuli responses of excitable cells.

Before the idea of the Hodgkin-Huxley model will be presented, the structure of nerve cells and its generation of action potentials will be illustrated. Afterwards their voltage clamp experiment will be shown, where a huge suqid axon was analysed in order to obtain some experimental data. With these experimental data of action potential generation they build an biophysical model.

It will be explained how the biophysical model and the mathematical equations can simulate the voltage events in neuronal cells. Afterwards some dynamic behaviour of a Hodgkin Huxley modeled neuron will be presented.

2 Nerve cell and action potential

Neurons or nerve cells are electrically excitable cells in the nervous system. The main tasks of a nervous system are collecting information, processing information and eliciting a response to the information. In order to fulfill these functions, a huge number of linked neurons are essential. Alone the human brain, being one of the two part in central nervous system, has about 100 billions neurons, which are highly connected with each other.

2.1 Structure of nerve cells

Neuronal cells consists of a cell body, the so-called soma, furthermore of dendrites, axon and the axon foot. The dendrites receive the chemical messages from other neuronal cells. The axon transmits the electro-chemical signal, the action potential, to other neurons. If the action potential reached the axon foot, the electro-chemical message will be again transformed into a chemical message. We will only focus on the electro-chemical signal, the action potential.

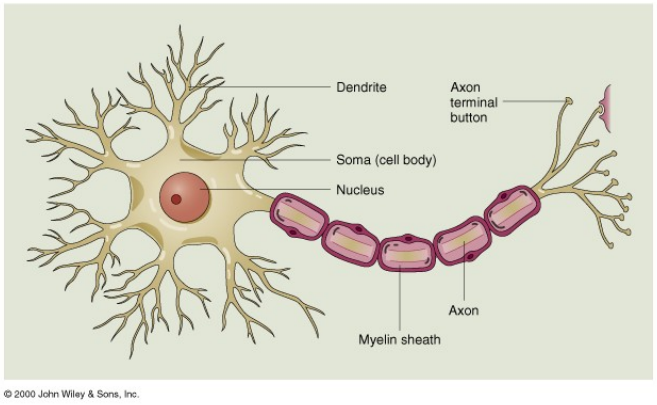

Figure 1: structure of a neuronal cell [1]

2.2 Action potential generation

Nerve signals are changes in membrane voltage, also called membrane potential, which are caused by ion movements through the cell membrane. The cell membrane has different charges on both sides. Inside from the cell membrane (in the cytoplasm) there are a lot of negative charged proteins and RNA, as you can see in the figure 2. In the inside there are also a high concentration of potassium ions, which plays a different role in generating an action potential. Besides this the potassium ions also have a counter ion function for the

negative charged proteins and RNA. But the concentration of negative charged ions overbalances, therefore the inside is negatively charged. Outside from the cell membrane (in the extracellular fluidity) a high concentration of sodium ions and a high concentration of chloride ions can be found, which is lower then the sodium ion concentration. Thus the outside is mainly positive charged.

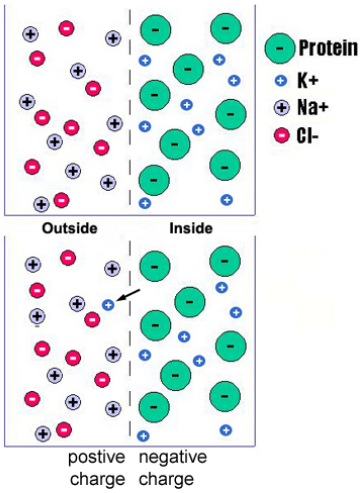

Figure 2: different ion concentrations inside and outside [2]

The upper part of the figure 2 represents the resting membrane with is steady state concentration, negatively charged, that means the inside is negative and the outside is positive and the cell membrane has a resting potential of -70mV (see upper part of figure 3). That means, that inside has in comparison to the outside a negative potential of -70 mV. But if a stimuli by chemical transmitter or electric signal occurs, than the balance of ions between inside and outside will be influenced (see lower part of figure 2 where ions pass the cell membrane). Consequently the ion concentration steady state will be disturbed. If the strength of this disturbance is high enough and the membrane voltage exceeds the threshold of -55mV, then an action potential at the axon hillock will be generated and will moves along the axon, see middle and lower part of figure 3. The response to a stimulus follows the all-or-none principle. If the membrane potential stays below -55mV nothing will happens. But if the membrane voltage reach the -55mV, an action potential will be fired immediately.

2.3 Phases of action potential

All phases of an action potential are illustrated in figure 4. If no stimuli occurs the axon is in steady state with a membrane potential of -70mV, and the ion conductance for Na^+ is very low. Firing of an action potential occurs if the membrane voltage exceeds the threshold of -55mV. In the depolarization phase, when the membrane voltage increase more and more, up to + 50mV, the voltage dependent ion channels for Na^+ becomes active and a high Na^+ influx into the inside takes place. After that the repolarization starts, where the Na^+ channels close and the also voltage-dependent ion channels for K^+ open

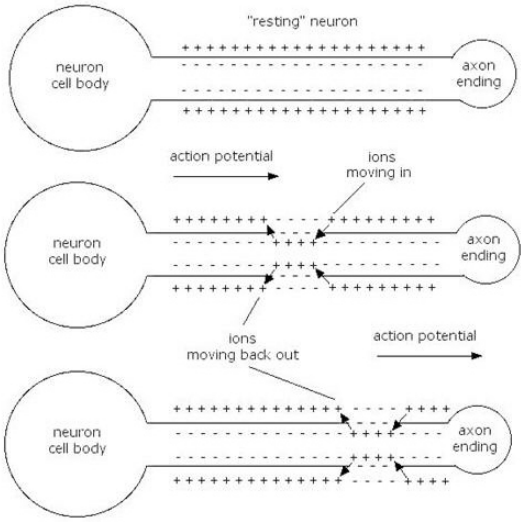

Figure 3: membrane potential [3]

and the membrane potential falls. Afterwards the hyperpolarization enters. Because there are shortly more K^+ outside, so that the outside is much more positive charged then the inside, the membrane voltage decrease to -85mV. The hyperpolarization happens at the same time of the refractory period, where a new firing of action potential is not possible. Furthermore the Na^+/K^+ pump restores the membrane potential to -70mV. Finally the resting phase reenters and the neuron is ready for new firing of action potentials.

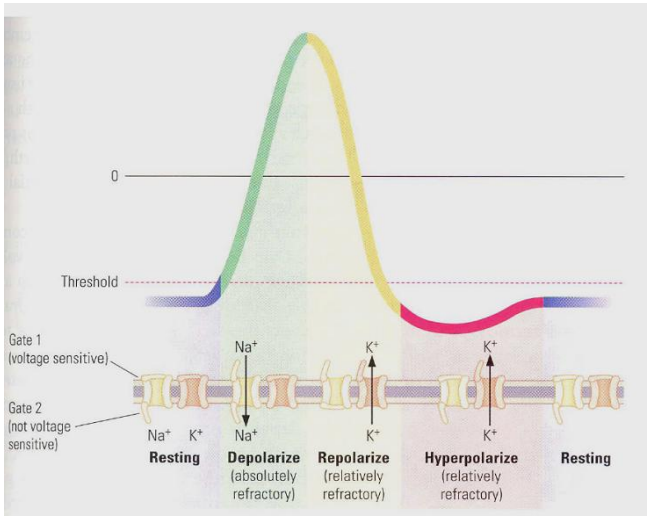

Figure 4: phases of action potential [4]

3 Hodgkin-Huxley model

The Hodgkin-Huxley model was developed in 1953 by Alan Lloyd Hodgkin and Andrew Huxley and they received for this 1963 the Nobel prize. This model characterizes the initiation and propagation of neural signals in giant axons of squids and describe very well the dynamic behaviour of channel kinetics. These two man established a mathematic model in order to explain the experimental results of the voltage clamp experiment. With this mathematic model the prediction of stimuli response is possible.

3.1 Voltage clamp experiment

In this voltage clamp experiment Hodgkin and Huxley measured the membrane voltage V_m by using an intracellular micropipette electrode and an electrode in the extra cellular fluid. They were able to control the V_m , also insert an external current for the purpose of generating an action potential in squid axons. They only could measure potential changes, that means they could not detect influx or efflux currents.

3.2 Equivalent electric model

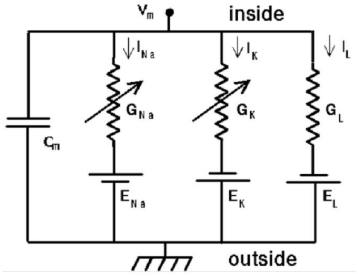

Figure 5: equivalent eletric model [5]

Each component of an excitable cell has a biophysical analog, as shown in figure 5.

3.2.1 Electric analog for cell membrane

The ions inside and outside a neuronal cell are separated through the cell membrane, the membrane behaves here like a capacitor. Discharging the capacitor corresponds to influx currents and charging to efflux currents. Because of the different ionic concentrations inside and outside the cell, which are separated through the membrane and the closed ion channels, there will be established an electric potential difference between inside and outside, here called V_m ,the membrane potential.

3.2.2 Electric analog for ion flows and ion concentrations

The ion flow through open ion channels because of different ion concentrations corresponds to electric flows. In squid axons ion flows for sodium ions, for

potassium ions and a leakage ion flow exist, which are labeled with I_{Na}, I_K and I_L. The level of ion currents is membrane-voltage-dependent, so the ion currents also obeys the Ohms law. The higher the current is, the higher the electric conductance is. The g_{Na} is equal to the inward Na^+ influx and g_{Na} is equal to outward K^+ efflux and g_L stands for the leakage conductance. The currents and conductances are also shown in figure 5. Furthermore in figure 5 the symbol E is displayed. E stands for an electric battery and represents the electrochemical gradient of the ion concentration and potential. Because this electrochemical gradient is the driving force for the ions it can be replaced with a battery E.

3.3 Mathematic model

The following mathematic model approximates the electric features of excitable cells very well and consists of a set of nonlinear ordinary differential equations.

For the capacitive behaviour of cell membranes you can write following equation (1) for C_m. The "q" in equation (1) is equal to the charge density on both sides of the membrane, V_m is the membrane voltage.

$$C_m = \frac{q}{V_m} \tag{1}$$

$$I_{Ion} = \frac{-dq}{dt} \tag{2}$$

$$I_{Ion} = \sum_{ion\ species\ i} I_i \tag{3}$$

The equation (2) says that the ion current I_{ion} appears as a loss of charge. Equation (3) sums up all specific ion currents like ion currents for K^+, Na^+ and leakage ion current to one total current I_{ion}. After combining these equations you get the following equation (4):

$$\frac{dV_m}{dt} = -\frac{1}{C_m}\left(\sum_i I_i\right) \tag{4}$$

So the time derivative of the potential across the membrane is proportional to the sum of the currents. Following assumptions are made, that ionic currents obey Ohms law like in equation (5), where V stands for voltage, R for resistance and g for conductance. Second assumption is that driving force for current is the difference between V_m and V_i , shown in equation (6) where V_i is V for each ion, V_i is equal to E_{Na}, E_K, E_L (battery from electric model) and corresponds to the Nernstian equilibrium potential of corresponding ion species.

$$I = \frac{V}{R} = g * V \tag{5}$$

$$DrivingForce = V_m - V_i \tag{6}$$

So now the current can be calculated like in equation (7) and that yields finally the equation (8):

$$I_i = g_i\,(V_m - V_i) \tag{7}$$

$$\frac{dV_m}{dt} = -\frac{1}{C_m}\left(\sum_i g_i \left(V_m - V_i\right)\right) \tag{8}$$

But we still not know how the conductance for the individual currents looks like or how they are calculated. Now let us have a closer view to the currents for ion species Na^+ and K^+:

$$I_{Na} = g_{Na}\left(V_m - E_{Na}\right) \tag{9}$$

$$I_K = g_K\left(V_m - E_K\right) \tag{10}$$

In order to fit the experimental results from the voltage experiment Hodgkin and Huxley added some new variables, the so called gating variables ("m","n" and "h"). The resulting equations are shown in equation (11) and (12). $\overline{g}_{Na}$ and $\overline{g}_K$ denote the maximal conductivity of the individual ion channels. The meaning of gating variables will be explained in chapter 3.3.1.

$$I_{Na} = \overline{g}_{Na} \cdot m^3 \cdot h \cdot \left(V_m - E_{Na}\right) \tag{11}$$

$$I_K = \overline{g}_K \cdot n^4 \cdot \left(V_m - E_K\right) \tag{12}$$

[6]

3.3.1 Gating variables

The gating variables stand for the probabilistic dynamic of ion channels and represents the fraction of open channels. The experimental leads the both scientists to introduce three gating variables m, h and n. Years later other investigators found out that the postulated gating variables typify the structure properties of ion channels. The sodium ion channel has 4 gates, 3 activation or "m" gates and one inactivation or "h" gate. Only when all gates are open the ion can flow through the channel. In the resting polarized membrane state only the activation gates are closed, shown in figure 7 (upper right part). Hence this ion channel is indeed closed but available, because the inactivation gate is open. In the lower right part the depolarization state is shown, where the inactivation gate is closed. Even if the activation gates are open, this channel is now closed and not available. After a certain time of repolarizing the channel returns to the resting state. The left side of the figure 7 shows that the variables m and n are strongly connected with conductance g_{Na} and that g_{Na} is equal to the product of $m * h^3$ (see equation (11)).

The gating variable "n" for K^+ stands for the independent gating of four channel-subunits. The variable "n" gives the fraction of subunits in active status and there is no gate for inactivation. The "n" gates in the potassium ion channel open with a time delay after increasing of membrane voltage.
Now we have the main equations for simulating a neuronal action potential. As you can see in figure 6 the action potential generated with the Hodgkin Huxley Model approximates the real action potential in a neuronal cell like in figure 4 very well.

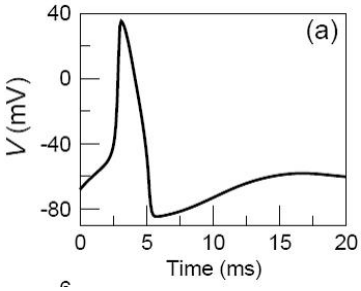

Figure 6: Action potential generated with Hodgkin Huxley model [7]

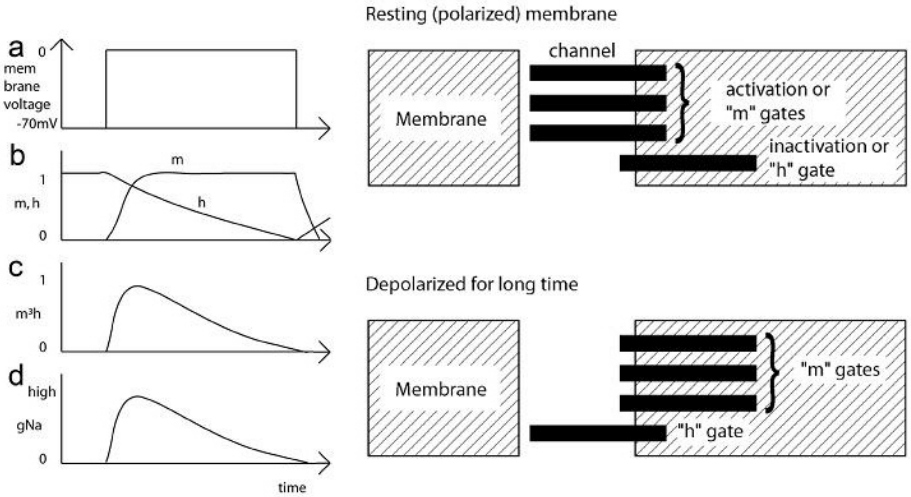

Figure 7: gating variables for sodium ion channel [8]

3.4 Dynamic behaviour of Hodgkin Huxley model

In conclusion you can say that the Hodgkin Huxley model reproduces the initiation and propagation of action potential very well. Therefore this mathematical model can be used as basis for investigating dynamic behaviour of neuronal cells and spares yourself time-consuming experiments with real neuronal cells. Now some example of stimuli response will be shown, which were derived from the Hodgkin Huxley model.

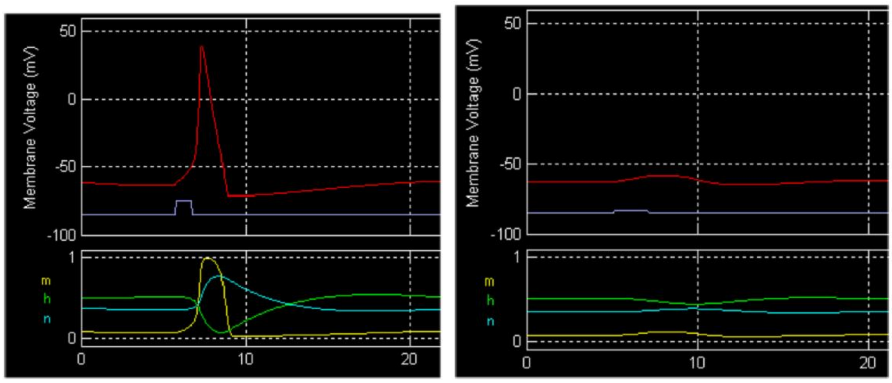

Figure 8: left: firing an action potential, right: no firing [9]

On the left side of figure 8 an example of firing an action potential is illustrated. The stimulus process of neuron (gray/violet rectangular signal) is strong enough and the membrane potential (red line) exceeds the threshold, consequently an action potential will be fired. At First the variable "m" increases (yellow line) and with a time delay the "h" variable (green line) decreases. So at first the Na^+ ion channel is open and then with a time delay the inactivation gate "h" close this channel and no more Na^+ can flow into the inside of a neuronal cell. At the same moment as the inactivation gate "h" closes the sodium ion channel, the potassium channels open (increase of n-variable, see turquoise line) and K^+ can flow from the inside to the outside and will lower again the membrane voltage. The right side of figure 8 shows how the membrane potential react to the stimulus in the first instance. But the stimulus is too weak and the membrane voltage does not overstep the threshold of -55mV and therefore no action potential will be generated and the membrane voltage returns to resting state. This illustration also shows how opening probability of the "m" gates rises for a short while, but it is not strong enough to influence the Na^+ ions. So the gating variables values does not changes a lot.

On the left side of figure 9 an example of an continuous stimulus is pictured. The Hodgkin Huxley model predict in a continuous stimulus case a repeating sequence of action potentials. On the left side of figure 9 the second stimulus takes place in the refractory phase, and this model says that no action potential will be fired during second stimulus. The second stimulus occurs where the inactivation gate "h" is still smaller then in resting state. So the Na^+ channel is still closed and not available. Consequently no Na^+ can flow into the neuronal cell in order to increase the voltage membrane. In addition to that the gating variable "n" is still high, so the K^+ efflux is still high and avoid a new

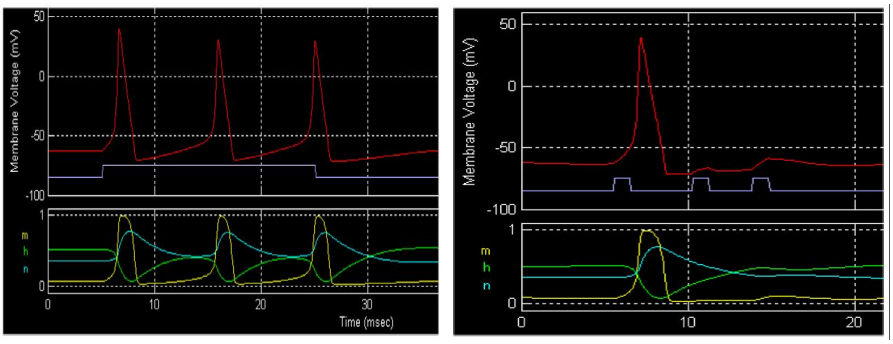

Figure 9: left: continuous stimulus, right: stimulus during refractory phase [9]

action potential generation. That means the voltage membrane stays below the threshold and no action potential can be fired. This predicted stimulus response reflects indeed the real stimulus response of neuronal cells.

These examples prove that the Hodgkin Huxley model can be used for predicting different stimuli responses of neuronal cells. But this Hodgkin Huxley model is too complex for making mathematical analysis. That is why a a lot of investigators simplified this mathematical model. But the most mathematical models for generating action potentials in neurons are based on the model from Hodgkin and Huxley. So after all the Hodgkin Huxley model remains an important tool for neuronal cell investigation at the computer.

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