This article discusses the physics of the formation of action potentials in nerve cells. In this context it builds mainly on the publications of Hodgkin & Huxley in 1952 in which they experimentally measured and modelled nerve behaviour of squid axons [1]. Thereby it became evident that the formation of action potentials is due to dynamic ionic conductances through the cell membrane. Sodium and potassium channels are composed of voltage sensitive parts that can open and close the channels, controlling the conductance. The probability for gates to be open is then dependent on voltage. This insight made it possible to explain characteristics of nerve behaviour like the refractory period, separation of time scales and even the speed of signal propagation along the nerve. The breakthrough became well-known for its wide variety of applications and it is valid to a large extent until today.

1 Historical overview

Until about 1939 knowledge about the conduction of signals in nerves was very limited. It had been understood that differences in ionic concentrations across the cell membrane were responsible for a membrane potential. One could guess that this potential and the variability of the membrane’s conductance to ionic flows plays an important role, but one had no way to experimentally verify any kind of hypothesis on the formation of action potentials [2]. In 1940, the American study group around Cole and Curtis began to experiment on the squid’s giant axon and the young British scientist Alan Hodgkin learned from them [2]. After World War II Hodgkin worked together with Andrew Huxley using new experimental methods and published a series of papers around 1950 including a complete theory supported by self-conducted experiments [1]. The ionic currents through the membrane were measured in order to study the voltage dependency of the membrane conductance. The excitation model that they formed from their observations predicted nerve behaviour in living organisms extraordinarily well. For this result they were awarded with the Nobel Prize in medicine and physiology only ten years later in 1963. Their electronic model of nerve cells forms the basis for studies of excitable systems until today.

This term paper first addresses the physiological concepts of nerve cells and will then lead through the publications of Hodgkin & Huxley of 1952 [1].

2 Electrical membrane behaviour

Nerve cells are composed of a cell body called soma that receives information through tree shaped extensions, the dendrites. Signals can be transmitted to other nerve cells via the axon, which is a long thin fibre well isolated to its surroundings. This is accomplished by local electric currents through the cell membrane which leads to a potential difference travelling along the axon. In order to understand the results of the research of Hodgkin & Huxley, one needs to understand some key characteristics of excitable cells. Those will be outlined in the following.

2.1 Excitability of cells: All or nothing principle

In a living organism, one is able to distinguish two kinds of cells: Excitable and non-excitable. If the latter kind is irritated by a short electric stimulus, the potential difference through the membrane changes, but falls of quickly towards its resting value. Those cells are found for example in the walls of our intestines [2]. Excitable cells, such as muscle or nerve cells, respond with a strong deflection of the membrane potential, if the stimulus is sufficiently strong, before returning to the resting state again. Through the creation of this Action Potential the cell can reliably conduct information to their neighbouring cells.

2.2 The membrane resting potential

The ability for a stimulus to create an action potential and to conduct this signal through the nervous system is very much dependent on the reaction of the cell membrane to such an impulse [2]. The cell membrane is a semi-permeable barrier to the flow of material into or out of the cell, that means that two types of ions can diffuse through separate channels through the membrane. Those are sodium and potassium cations. Pretending the membrane is only permeable to potassium, any concentration difference of this ion will lead to an equilibrium potential resulting from osmotic forces balanced by a built-up electric field. This Nernst Potential $V_s$ can be calculated if the ionic concentrations on both sides of the cell membrane (i.e. $[S]_i$, $[S]_e$), the temperature $T$ and the charge $z$ of the ion are known [2].

\[ V_s = \frac{kT}{2q} \ln \left( \frac{[S]_e}{[S]_i} \right) \quad (1) \]
Fig. 1. Formation of the membrane equilibrium potential through a selective permeable membrane to potassium ($\text{K}^+$) by balance of osmotic forces and an electric field $\vec{E}$. Other Ions: Sodium Na$^+$, Anions A$^-$ (mainly chloride).

Fig. 2. Electric circuit through a cell membrane [1].

Here $q$ is the elementary charge. In figure 1 one can visualize how the Nernst Potential is created. The situation is actually more complicated since the membrane is permeable to more than one kind of ion. The equilibrium potential will then be dependent on the Nernst Potential of the different ions.

In the resting state of the nerve cell membrane there is a high concentration of potassium inside the cell, while there is a high concentration of sodium on the outside. All ionic channels are closed at this stage and an ionic pump maintains a resting potential of roughly -70mV.

2.3 Membrane electric circuit

Current can be carried through the membrane in different ways that can be modelled as electric connections between the inside and the outside of the cell operated in parallel (see figure 2). It can either charge the membrane capacity $C_m$ or it can be carried through ionic channels that are permitting either sodium or potassium flow, $I_{Na}$ or $I_K$. A small proportion of current is leaking through the membrane labelled $I_l$. To restore the resting potential after excitation or leakage, the Sodium-Potassium-Pump can bring ions back to the other side against the concentration gradient by usage of energy. The electric behaviour can be modelled by

$$C_m \frac{dV}{dt} + I_{\text{ion}}(V) = I_{\text{app}}, \quad (2)$$

$$I_{\text{ion}} = I_{Na} + I_K + I_l. \quad (3)$$

Fig. 3. Experimental results for potassium (l) and sodium (r) conductances as a function of time for various depolarisation voltages. The number on the graph represents the depolarisation value in mV that was applied at time $t=0$. [1]

By assuming Ohm’s law the ionic currents can be written as a product of a constant conductance $g_i$ and the perturbation of the Voltage $V$ from the Nernst Potential $V_i$ ($i = \text{Na, K, I}$). Thereby the circuit equation is obtained:

$$C_m \frac{dV}{dt} = -g_{Na}(V-V_{Na}) - g_{K}(V-V_{K}) - g_{l}(V-V_{l}) + I_{\text{app}}. \quad (4)$$

But experimental results yield a surprise. For a sufficiently large current $I_{\text{app}}$ the voltage behaviour is highly nonlinear. Therefore one has to allow the conductances to be dynamic, say a function $g(V)$. The achievement of Hodgkin & Huxley was to measure the ionic current in dependence of voltage in order to predict the behaviour of the ionic conductances.

3 The Hodgkin & Huxley theory

In the 1950s Alan Hodgkin and Andrew Huxley conducted their experiments on the squid’s giant axon which was convenient because of its size. It is striking that they formed their model without any understanding of the molecular composition of the cell membrane and still predicted its behaviour with outstanding precision.

3.1 Measuring techniques

For determination of the ionic conductances Hodgkin & Huxley used the combination of two experimental techniques developed by Marmont and Cole. The space clamp technique assured the voltage to be spatially constant along the axon [3]. As a result the underlying equation reduces from a partial differential to a ordinary differential equation, since any spatial voltage derivatives vanish. For measuring the conductances characteristic for each depolarisation voltage, the voltage clamp was used to keep the potential constant in time [4]. For measurements of the sodium conductance $g_{Na}$ the potassium channels were blocked and vice versa. The results can be seen in figure 3.
3.2 Forming of a model

The idea of Hodgkin & Huxley was to model the conductance by introducing three so called gating variables \( m, n \) and \( h \) that each follows the simple differential equation

\[
\dot{z} = \alpha_z (1-z) - \beta_z z \quad \text{with} \quad z = n, m, h.
\]

The gating variables can vary between 0 and 1. The crux of these equations is to allow the rate constants \( \alpha \) and \( \beta \) to be voltage dependent. The scientists further proposed that the potassium and sodium conductances \( g_K \) and \( g_{Na} \) should follow the relation

\[
g_K = \bar{g}_{Na} n^4 \quad \text{and} \quad g_{Na} = \bar{g}_{Na} m^3 h,
\]

with the constants \( \bar{g}_{Na,K} \). Through this formalism any voltage perturbation will influence the rate constants and therefore the gating variables which then determine the conductances. The change of conductance will in turn alter equation 4 which determines further voltage developments. This circle of dependencies explains the non-linear behaviour of nerve excitation. The system of equations 4, 5 and 6 is called the Hodgkin & Huxley model.

Hodgkin & Huxley gave a biological interpretation for their ansatz [1, p.507/512]. They suggested that the variables \( m \) and \( n \) might correspond to the probability of two kinds of particles to be present at a certain place in the membrane, for example on the inside of it. The variable \( h \) then is the probability of a third kind of particle not to be present on the inside. The rate constant \( \alpha_{m,n} \) represents the transfer rate for each particle from the outside to the inside and \( \beta_{m,n} \) vice versa, while \( \alpha_h \) and \( \beta_h \) have the opposite directionality.

As it is known today, the sodium and potassium channels are indeed composed of four parts that can each be either in an active or inactive state. In the case of sodium even the so called inactivating particle \( h \), that is blocking the flow of sodium while in its active state, could be identified.

In order to complete the model the rate constants \( \alpha(V) \) and \( \beta(V) \) had to be determined. One can rewrite equation 5 by introducing new variables defining a time constant \( \tau_z \), a stationary value \( z(t \to \infty) = z_\infty \) and a resting value \( z(t = 0) = z_0 \)

\[
z_0 = \frac{\alpha_{z,0}}{\alpha_{z,0} + \beta_{z,0}}, \quad z_\infty = \frac{\alpha_z}{\alpha_z + \beta_z}, \quad \tau_z = \frac{1}{\alpha_z + \beta_z}.
\]

It is important to realize that since the rate constants are functions of \( V \), so are \( \tau_z, z_\infty \) and \( z_0 \). The new differential equation now reads

\[
\tau_z \dot{z} = z_\infty - z
\]

with the solution for a constant voltage

\[
z(t) = z_\infty - (z_\infty - z_0) e^{-t/\tau_z}.
\]

Hodgkin & Huxley realized that for sodium the value \( m_0 \) for a resting membrane can be neglected just like the stationary value \( h_\infty \). Inserting the solutions into equation 6 one attains

\[
g_K = \left\{ (g_{K_\infty})^\frac{1}{4} - [(g_{K_\infty})^\frac{1}{4} - (g_{K_0})^\frac{1}{4}] e^{-t/\tau_z} \right\}^4
\]

\[
g_{Na} = \bar{g}_{Na} m_0^3 h_0 \left[ 1 - e^{-t/\tau_z} \right]^3 e^{-t/\tau_h}
\]

with the stationary potassium conductance \( g_{K_\infty} \) and the conductance at \( t=0 \) labelled \( g_{K_0} \). This behaviour is exactly the outcome of the measurements in figure 3. For potassium an instant change in voltage (\( V = 0 \to V = V_{dep} \) at \( t = 0 \)) results in a sigmoidal conductance curve flattening to a steady state. Sodium shows a transient amplitude with growing intensity for increasing depolarisation values.

For each individual depolarisation the curves in figure 3 were fitted assuming a behaviour as derived in equation 10 and 11. The steady state value and the time constant that gave the best fit could be used to attain the rate constants

\[
\alpha_z = n_\infty/\tau_z \quad \text{and} \quad \beta_z = (1 - z_\infty)/\tau_z
\]

as a function of voltage. The resulting data was fitted (example for potassium in figure 4) which made it possible to solve equation 5 for every depolarisation value. In the following the results of this model will be examined.

3.3 Testing of the model

An important effect of the model is the separation of time scales for the gating variables \( m, n, h \) that explains the behaviour of the sodium and total conductance. The time constants are plotted in figure 5. It can be seen that especially the sodium gating variable \( m \) is moving on a very fast timescale while the inactivating particle \( h \) is rather slow, especially at low voltages. Therefore the blocking of the sodium channel becomes increasingly relevant at long times, while the three activating parts open the sodium channels almost instantly. This behaviour is exactly what one sees in figure 3, where the sodium conductance shows an initial
Fig. 5. Time constants for sodium and potassium gating variables as a function of voltage. [2]

Fig. 6. Time dependence of membrane action potential after depolarisation (number on solid lines in mV). Upper Graph: Model; lower Graph: Experimental data. [1]

sigmoidal increase followed by an exponential decrease.

Computation of time course of the action potential itself after depolarisation shows an excellent match with experimental measurements as seen in figure 6. Only minor differences are observable. All three phases of the action potential can be reproduced: The depolarisation phase (increasing slope), the repolarisation phase (decreasing slope) and hyperpolarisation (phase restoring the resting potential)

The Hodgkin & Huxley model also explains the refractory period after the action potential has decayed. It can be seen that when the action potential is in hyperpolarisation, the probability for the inactivating particles to block the sodium flow is still high while the potassium conductance is high. This forces the potential to the potassium Nernst Potential and the creation of a new signal will not be possible in this period. The propagation of action potentials in only one direction is due to this property.

3.4 Propagated action potential

The obtained model reproduces space clamped measurements well as seen in the previous section. But matter of interest is rather the propagation behaviour of action potentials, since this is what is actually happening in living organisms. Hodgkin & Huxley used Lord Kelvin’s cable equation to introduce a current driven by spatial voltage curvature to their equation. Assuming the signal travels with a constant velocity c, the expression is

\[ I = \frac{a}{2R} \frac{\partial^2 V(x,t)}{\partial x^2} \bigg|_{x_0}^{x_0+ct} = \frac{a}{2Rc^2} \frac{\partial^2 V(x(t))}{\partial t^2} \]  (13)

with a being the diameter of the axon and R the specific membrane resistance. Using this term in equation 4 instead of \( I_{app} \) and assuming the conductances \( g_i(V) \) that were computed by space clamped measurements one can numerically solve for the voltage behaviour. Results are again a good match with experimental results. The signal velocity c was obtained by the best fit with experimental measurements which resulted in a value of approximately 20 m/s.

4 Summary

To conduct information as potential differences through an organism nerve cells have developed a very effective mechanism. The basis of this mechanism is a semi-permeable cell membrane that is conducting sodium and potassium ionic current through separate channels. The conductances are dependent on changes of the membrane resting potential, that is maintained by anionic pump that brings sodium ions to the outside of the cell and potassium ions to the inside. Stimuli creating a local perturbation of the membrane potential of sufficient size cause the ionic conductances to increase rapidly before they fall back to their resting values. The complicated interplay between voltage dependent sodium and potassium conductances lead to a transient potential increase of fixed amplitude called action potential that is able to travel through the nerve system in one direction. In the publications of Hodgkin & Huxley in 1952 the exact behaviour of the nerve was quantitatively studied and modelled. Striking is the fact that they used unphysiological measuring techniques by holding voltage across the membrane constant in space and in time. Through this they were able to formulate a model which also successfully predicts the propagation of action potentials removing space and time clamps. This is a non-trivial result which is owed to the clever modelling ideas of the team combined with their experimental endurance and which was awarded with the Nobel Prize in 1963.

References


