

Bachelor's thesis



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JANUARY 30, 2013

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Introduction

The brain consists of about 10¹¹ of neurons. Each of these neurons is connected to about 7000 of other neurons, creating a complex and sophisticated network. Simulating such an enormous network, is computationally almost impossible, certainly when taking into account all the different parameters of each neuron. These parameters include the concentration of ions such as sodium, potassium, calcium and chloride, potentials of all the synapses and the potentials of each membrane (of each neuron).

With the help of so called "neural mass models" however, properties of this network can still be researched. By combining the mean behaviour of groups of neurons the influence of ionic concentrations on patterns in the EEG can be explained. This can then be used to simulate the effect of a heart attack on the brain, in this context the research was also setup.

During a heart attack the energy supply to each neuron is limited, causing the sodium-potassium pumps to stop. This in turn causes the extracellular potassium concentration to rise inside the brain; this chain of events will be explained in the chapter "single neuron behaviour". This brings us to the goal of this thesis; finding the response of groups of neurons under various conditions for the concentrations of sodium and potassium.

The task of this thesis is to calculate the behaviour of such a neural mass population. In order to do this the thesis starts with the theoretical analysis of the behaviour of a neuron in normal conditions and how neural mass models are constructed. The next step is to model this neuron, the chapter "Setup: model of the neuron" describes the numerical model that is used to investigate the electrical behaviour of a single cell. As the numerical model is finished, four experiments are conducted with it, as described in the chapter "Experiments/Simulations". This results in linearized behaviour of the populations under varying ion concentrations.

Theory

Single Neuron Behaviour

To understand the electrical behaviour of a single neuron, first the structure of a neuron is discussed. Then the generation of action potentials is explained, together with the role of the various ion concentrations in this process.



Figure 1: Schematic of a neuron

In figure 1, the structure of a neuron is shown. There are three different parts: the dendrites, the cell body with the nucleus and the axon.

The dendrites are responsible for receiving inputs of all the neurons that are connected to this neuron. These dendrites are connected to the cell body. This cell body is basically a membrane filled with water, a nucleus and other structures and various ions such as potassium (K^+) , sodium (Na^+) , calcium and chloride.

The membrane consists of a lipid bi-layer, as seen in figure 2. Between these lipids, large protein structures can be found. These proteins serve as gates. The behaviour of each gate depends on the voltage across the membrane, the membrane potential, and the ion-concentrations. There are different types of gates, groups of different gates are explained in the chapter called "The Hodgkin-Huxley model".

Molecular ion pumps keep the concentration of K^+ inside the cell at about 20 times higher than the concentration of K^+ outside the cell. The concentration of Na^+ is kept 10 times lower inside the cell than the concentration of Na^+ outside the cell.



Figure 2: Schematic of the gates in the membrane

The cell body then responds to the input by the dendrites. The input changes the membrane voltage and this causes the gates to react. This generates an action potential, which is propagated by the axon.

Now that the structure is exposed and we have a global idea of what is going on in the neuron, we will as promised take a closer look at the behaviour of the gates whilst generating a pulse/ an action potential.

Inside the cell, as told, potassium is kept at a relatively high level, and sodium at a relatively low level. External stimuli entering via the dendrites change the permeability of the membrane for sodium, because the gates behave differently. This results in an inflow of sodium, causing the membrane to depolarize. When the membrane depolarizes the permeability of potassium changes, this is due to the changed membrane potential. This results in an outflow of potassium, causing the membrane to hyperpolarize. This chain of events is called an Action Potential, as shown in figure 3. The concentrations are now slowly being pumped back to their original levels.

The action potentials repeat at a certain rate under constant conditions, this is called the firerate/spikerate. It can be easily determined by measuring the time between two action potentials and taking the inverse of this number.



Figure 3: An action potential of a neuron.

The electrical behaviour of the biological neuron concerning action potentials is now clear. The model of a neuron can now be researched, constructed and analysed. This will be done in the next chapter, but first we will continue with the theory about neural masses.

Neural Mass Models

The brain consists of billions of neurons and each of these neurons has thousands of connections to other neurons. This creates such a big and complex network that is almost impossible computes its exact behaviour. With the help of Neural Mass Modeling this is possible in some way. In Neural Mass Modelling, the average behaviour of a group of neurons is used. These so called populations are connected in some way in each model. By giving each other feedback almost any rhythmic pattern of the brain can be simulated, making it a powerful tool in the computational neurophysiology. In figure 4, schematic images of Neural Masses are shown.

Neural Mass Models can be used in various ways. The neural mass model in figure 4a can be used for reproducing alpha rhythms. The neural mass model in figure 4b can be used to investigate the generation of visual evoked potentials. More complex networks are used for the research of activity during seizures and so forth; this shows how versatile neural mass modelling is.

As told, a population is the average behaviour of a group of neurons. Mostly the mean membrane voltage of the group is used as state-variable; this voltage is then used to calculate the fire rate of the group. In this research however the synaptic input for a single neuron is used; by taking the mean input to a mean group of neurons the population behaviour is calculated. This behaviour is described by the firerate as function of the input. The task of this thesis is to find the influence of ion concentrations on the dynamics of a single neuron and then on the mean behaviour of neurons. This can then be used to determine the population dynamics, as described above.



Figure 4(a) A simple Neural mass model

Figure 4(b): A more complex Neural mass model

Setup: model of the neuron

Over the past decades, various models of the neuron have been constructed. To name just a few: Integrate and fire, Leaky integrate and fire, Hodgkin-Huxley and Moris-Lecar. Each of these models of course has advantages and disadvantages compromising accuracy or computational power.

For this thesis the Hodgkin-Huxley model was picked. The Hodgkin-Huxley model has the advantage that it directly incorporates the effect of ion concentrations, which is important for this research. How these effects are incorporated will be explained later. First we need to know how the Hodgkin-Huxley model works.

The Hodgkin-Huxley model

The Hodgkin-Huxley model was first used in 1952 to study ionic mechanisms during an action potential and received a Nobel Prize for Medicine/Physiology in 1963, making this the standard model for the simulation of a neuron.

The Hodgkin-Huxley model considers the membrane to behave like an electrical capacitor and thus have a certain capacitance. Several currents act on this capacitor, changing the voltage across it. The voltage across this capacitor is called the membrane voltage. In this model there are five currents working on the membrane:

- Potassium-current
- Sodium-current
- "A"-current
- Leak-current
- Applied-current

The first three are gated ion currents, the potassium and the "A" current are related to respectively fast and slow reacting gates for potassium. The sodium current relates to the flow of sodium. The leak current is just the leaking of ions through the membrane. The applied current is the input via the dendrites, as explained before.

In figure 5 the behaviour of each type of gates is shown during an action potential.



Figure 5 Behaviour of gates during an action potential

The Nernst potential

As discussed in the description of the Hodgkin-Huxley model, the ion concentrations are directly linked to the parameters of the model. The ion-currents are all dependent of the membrane voltage and the Nernst potential of each ion. The Nernst potential is a potential that arises between two different ion concentrations. It is defined as:

$$E = \frac{RT}{zF} \ln\left(\frac{[outside]}{[inside]}\right) \qquad (1)$$

With R being the ideal gas constant, T the temperature in Kelvin, z the charge of the ion and F Faradays constant (charge of a mole electrons). The "[]" brackets indicate ion concentration.

Via this Nernst potential, the effect of the intracellular and extracellular ion concentrations on the membrane voltage dynamics are incorporated into the model. The Nernst potentials works linearly on each ion current, this is easy to comprehend looking at Ohm's law (Equation 2, below). The potential in this equation is the difference between the membrane voltage and the Nernst potential.

$$I_n = (V_m - E_n) * g_n \tag{2}$$

With I being a current, V_m being the membrane potential, E_n the Nernst potential for the nth ion and g_n the conductance.

The Hodgkin-Huxley model mathematically

As read above, the Hodgkin-Huxley model takes the behaviour of each gate into account. Each gate can be described using a couple of equations. How these differential equations were obtained can be found in the original paper by Hodgkin and Huxley. Below, first Ohm's law for the current is given and the set of differential equations that apply for each ion-current. Combining these expressions results in an expression for the current.

$$I_n = (V_m - E_n) * g_n \tag{2}$$

$$g_n(V_m) = g_n^* \varphi^\alpha \chi^\beta \tag{3}$$

$$\dot{\varphi}(V_m) = \frac{1}{\tau_{\varphi}}(\varphi_{\infty} - \varphi)$$
 (4)

$$\dot{\chi}(V_m) = \frac{1}{\tau_{\chi}}(\chi_{\infty} - \chi)$$
 (5)

Combining (2) and (3) gives the equation for the n^{th} ion current:

$$I_n = g_n^* \varphi^\alpha \chi^\beta (V_m - E_n)$$
 (6)

 $au_{arphi}, au_{\chi},lpha,eta$ and g_n^* are all constants, $\chi_{\infty}, \varphi_{\infty}$ are functions dependent on V_m .

These constants and functions are all carefully reasoned, as can be read in the papers by Hodgkin and Huxley.

To combine all the formulas; the change in the membrane voltage is calculated with (7)

$$\dot{V_m} = \frac{I_{app} + \sum_n g_n^* \chi^\beta (V_m - E_n)}{C}$$
(7)

In this equation (7) the currents are summed and the change in the membrane voltage is calculated, taking into account the capacitance of the membrane.

Solving the differential equations

The simulations that were written for this thesis make use of the Euler method to solve the various differential equations. The Euler method is a first order routine to solve Ordinary Differential Equations and was published around 1770. This method calculates the derivative, multiplies it with a chosen time constant and adds it to the previous value. This solving method is far from flawless; it is known to suffer from stability problems and is relatively not precise. It is a trade-off between computation time and accuracy. In order to conduct a better experiment the time step should be reduced. This method however is quite easy to implement for this set of differential equations and gives good results in decent computation time.

Experiments/Simulations

Now that the model is explained, a couple of experiments were set-up. The first experiment is just to model the single neuron in normal conditions; this is done in two steps. By doing this experiment, the used code could be tested; it is also used to test the scripts that analyze the simulations.

The second experiment is designed to investigate the influence of the Nernst potential of potassium on the spiking behaviour of the neuron. Both steps of experiment one are repeated, in each repetition the Nernst potentials of potassium is varied. This gives an indication of the influence of potassium.

Then the spiking-threshold and the spiking-slope are found by repeating the simulation in varying ion concentrations, these results are then linearized.

In the fourth experiment the mean behaviour of a variation of neurons is calculated, paving the way for a neural mass population, as discussed in the theory on neural masses.

Experiment 1: Single neuron

The first experiment is solving the single neuron in normal conditions (standard concentrations of chemicals).

Figure 6: A neuron generating action potentials.

The results of this simulation can be seen above in figure 6. The model seems to behave nicely. The membrane voltage rises by the input current and at a certain point the neuron starts to spike, completely in line with the theory.

In the next step of the experiment the input current was swept over a range of 0 to $2 \frac{\mu A}{cm^2}$, using a step-size of: $0.005 \frac{\mu A}{cm^2}$. For each applied current the firerate, the action potentials per second, of the neuron was determined. The fire rate is plotted against the applied input current, giving a fire rate-input curve. This fl-curve determines the behaviour of the neuron. The results of this next step are given in figure 7.

FIGURE 7, this figure shows a fl-curve. At a Nernst potential of -80 mV the applied current is swept over a range of 0 to 2 μ A/cm^2.

Experiment 2: Effect of ion concentrations on the neuron

To determine the effect of changes in ion concentrations, the experiment as in experiment one was repeated. This time the Nernst potential for potassium was changed. For three different Nernst potentials the fl-curve, in the range of 0 to $2 \frac{\mu A}{cm^2}$, was determined. So basically for each Nernst potential, an input current is picked from 0 to $2 \frac{\mu A}{cm^2}$, for each input current and Nernst potential the spike rate is determined.

Figure 8: Spike rate vs. applied current for various Nernst Potential of potassium.

The figure above shows, that at a higher Nernst Potential for potassium the spike rate at a certain current increases absolutely. Note also that the neuron starts to spike at a lower applied current, as the Nernst potential gets higher; In figure 8 one can see that at a Nernst potential for potassium of -85 mV the threshold current for spiking is $1.04 \frac{\mu A}{cm^2}$, at -75 mV this is reduced to about $0.26 \frac{\mu A}{cm^2}$.

To get a better idea of the behaviour over bigger ranges of applied currents the same experiment was repeated, now with an applied current between 0 and 500 $^{\mu A}/_{cm^2}$. The results can be seen below in figure 9.

In figure 9 we see that the beginning, about 0 to $100 \frac{\mu A}{cm^2}$, of the fl-curves behave in a square root like fashion. The biggest part however, from 75 $\frac{\mu A}{cm^2}$ until it collapses, is almost linear. The linear part is also the interesting part; one can see that as the Nernst potential changes, the slope of these lines also changes. This dependence of the slope on the Nernst potentials is interesting to linearize, as will be done in the next experiment.

So we can basically extract two interesting sets of data: the slope of each curve and the threshold current for which spiking begins to occur.

To be able to get some sound results, this specific simulation will be performed again, using a large number of varying Nernst potentials for not only potassium but also sodium.

Experiment 3: Generate more data and linearization of the data

In this experiment the exact same procedure as in experiment 2 was followed as said, the only difference is that apart from only varying the Nernst Potential for potassium, also sodium was changing.

Linearization of this data leads to figure 9 and figure 10. Figure 9 shows the linearization of the spiking-threshold current. Figure 10 shows the linearization of the slope.

Linearization of the spiking threshold

The first task was to find and linearization of the input offset/threshold for which the neuron begins to spike. For this the Nernst potential for potassium was swept over a range of -84 to - 76 mV and the Nernst potential for sodium was swept over a range of 50 to 60 mV. The input current at which the neuron starts to spiked is recorded for each combination of Nernst potentials. The linearization is

 $I_{threshold} = -3.3 - 0.05 * E_{potassium} - 0.00 * E_{sodium}$, with both Nernst potentials in mV. Spiking threshold vs. Nernst potentials

Figure 10a: Spiking threshold, the spiking threshold in μ A/cm² is plotted vs. the Nernst potential of sodium and potassium, giving a nice plane.

Figure 10b: Relative error of the linearization. The results as seen in figure 10a are linearized. The error of this linearization is shown above.

Linearization of the slope of the spiking rate

First the slope was determined in the f-I curve for every Nernst Potential combination (of sodium and potassium). The slope is the slope of the linear part of figure 9. In the next step the data was linearly approximated. The formula that was found is:

 $\frac{spikerate}{applied current} = 5.021 + 0.03409 E_{potassium} - 0.00918 E_{sodium}$, with both Nernst potentials in mV.

The original results give figure 11a:

Figure 11a Surface plot of the measurements.

To clearly show how close the approximation is the relative error between the two surfaces is plotted below in figure 11b.

Figure 11b: Relative error of the measurements and the linearization.

Experiment 4: Mean behaviour

In the final experiment, an attempt was made to simulate a population. In order to do this a single neuron was simulated multiple times, each time slightly changing the parameters. In 81 steps, all the relevant parameters of the neuron were varied +/-10%.

Figure 12 Mean behaviour of varying neurons. The image shows in blue the behaviour of a single neuron, in red the mean of all these blue lines is shown.

In figure 12 we see that the offset is now blurred out, this is as expected. Every individual neuron starts to spike at a certain offset, because we have combined a lot of neurons the reaction to a certain input is smoothened. The slope itself shows nothing special, it is just the mean. It is very close to the original (compare it with the red line in figure 8). This would suggest that if you smooth out the beginning (around threshold) of each curve, one can just use the normal curve further on to simulate the behaviour of a group of neurons, responding to a certain input.

Conclusion

In this research, first a numerical model of the neuron was constructed. For this the Hodgkin-Huxley model was used, a widely known and used model for simulating neurons. Using a straight forward experiment, the model was tested and proved to work. The first fl-curve could now be determined. In the next experiment the behaviour of neurons under the influence of the intercellular and extracellular concentration of potassium was researched. This showed that neurons spike faster as the Nernst potential of potassium gets higher. The threshold is also lower for the neurons to start spiking. In the experiment that followed we have been able to linearize this behaviour of fl-curves.

In the third experiment 81 different Nernst potential combinations have been used, this resulted in the results, shown in figure 10a and 11a. These results could be approximated with the following linearizations; figure 10a can be described with $I_{threshold} = -3.3 - 0.05 * E_{potassium} - 0.00 * E_{sodium}$. Showing no dependence of the threshold current to the Nernst potential of sodium; figure 11a can be described with $\frac{spikerate}{applied current} = 5.021 + 0.03409 E_{potassium} - 0.00918 E_{sodium}$. The approximations are relatively good as can be seen in figures 10b and 11b. The spiking threshold has a really small relative error, indicating that the measurements are almost perfectly linear. The linearization of the slope of the fl-curves has a bigger error, when compared to the linearization. Therefore the quality of this approximation reduces as the concentration differences become bigger.

Experiment four showed that the mean behaviour of a group of neurons causes the threshold to be blurred out. The slope however does not change as much as compared to the various neurons, which is expected

In short, we have been able to calculate the dependence of the input-firing rate curve of neural cells on intercellular and extracellular ion concentrations of potassium and sodium. With the results of experiment 4 we also showed that this behaviour can be extrapolated to the behaviour of a group of neurons by smoothing out the fl-curve around the threshold current, thus the mean group behaviour can be described as a result of this thesis.

Discussion/Recommendations

The Hodgkin-Huxley model that was used leaves out the influence of chloride and calcium for example. However in a complete neural mass model of the brain, they might be important as ion concentrations change drastically. So this research could be repeated with taking into account chloride and calcium.

Other follow-up research can also be done to examine an even wider range of ion concentrations. Also the simulation time could be increased, combined with reducing the applied current step size the threshold currents can be determined more precisely. However, as they are blurred out for calculating the mean group behaviour this is of smaller significance.

References

Figures

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