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Modelling Hodgkin-Huxley

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Chapter 1

Introduction

The Hodgkin Huxley equations are until today the single most influential findings in the biophysical description of excitable membranes and have sparked numerous other models, always trying to adopt the current research in neurosciences. This essay describes the original Hodgkin Huxley equations and their implementation in Mathematica. The model is used to describe some of the key features of action potentials involved in axonal excitation: threshold, refractoriness, repetitive spiking and temperature dependence. In order to give the reader a broader perspective, short descriptions of the biological background and the experimental methods involved are provided.

Chapter 2

Neurophysiological and neurobiological properties of the brain

2.1 Composition of the brain and its building units: neurons

The brain, contained within the skull, is part of the central nervous system. It is the major organ for processing of all conscious and unconscious stimuli, thought and feelings, learning and memory. It is also responsible for controlling numerous other organs, as well as breathing, heart beat and temperature regulation. The brain's building unit is the neuron. The human brain contains about 10^{11} neurons, the space in between containing glial cells that build up the myelin coating as Schwann's cells. Neurons are highly differentiated cells

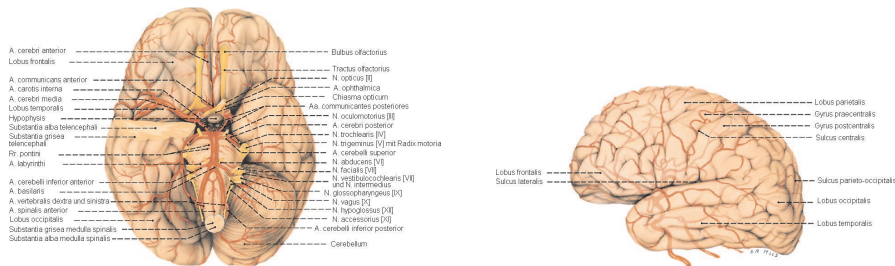


Figure 2.1: The brain

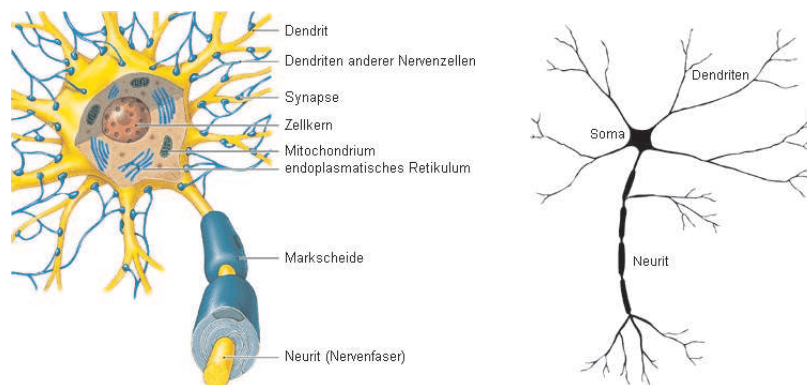


Figure 2.2: Pictures of a neuron

that are capable to receive, process and send out neuronal excitation. A neuron consists of a cell body, dendrites and axon (=neurite).

2.2 The cell membrane

Since the lipid bilayer comprising the cell membrane is unpolar, small polar molecules and ions are not able to pass the membrane by themselves. This characteristic is crucial for the cell to maintain distinct concentrations of solutes, different from the cells surroundings, within the cell. Cells have various mechanisms at hand to allow for transport across the plasma membrane, but only ionic channels will be of concern here. Ion channels' primary function is to allow inorganic ions such as Na^+ , K^+ , Ca^{2+} , Cl^- to diffuse down their electrochemical gradient. Ion channels differ from mere aqueous pores due to their ion specificity. The diffusion speed is limited and saturates because the ions pass the so called *selectivity filter* single file. The selectivity filter is a part of the ion channel where protein loops (*selectivity loops*) reach into the opening and narrow it considerably, therefore providing for specific binding and transport of the respective ion. Ion channel proteins therefore are, other than pores, gated (i.e. voltage or ligand gated channels).

A single neuron contains numerous different ion channels (usually more than ten types) that are assembled in domains over the plasma membrane. The K^+ -leak channel is the most abundant one in animal cells.

2.3 Transmembrane voltage

One of the key aspects of neuronal activity is the membrane potential. It is due to a difference in the electrical charge on both sides of the cell membrane caused by an excess of positive ions over negative ones on one side and a deficit on the other. This state is maintained by the cell through active pumping (esp. by the Na⁺/K⁺-Pump) and passive diffusion. The Na⁺/K⁺-Pump is an ATPase that functions as an antiport to move three sodium ions out of the cell against their electrochemical gradient, whereas two potassium ions are pumped inside. The Na⁺/K⁺-Pump is responsible for the low content of Na⁺ within the cell. Therefore other ions have to compensate the generally negative charge presented by proteins and nucleic acids. This role is mostly performed by K⁺-ions that get into the cell via antiport by the Na⁺/K⁺-Pump and the function of K⁺-leak channels (which provides for free movement in and out of the cell). Since the large amount of negatively charged anions attracts K⁺-ions into the cell by an electrical force it balances their natural tendency to leave the cell down its concentration gradient allowing K⁺ to come close to its equilibrium value.

The resting membrane potential is a direct result of this equilibrium condition when the net current crossing the membrane is zero. The typical membrane potential of an animal cell lies between -20 and -200mV depending on cell type and organism. As stated, the K⁺ gradient is of major importance. The equilibrium of an ion concentration is generally dependent on its permeability. In the case of K⁺ a higher permeability will result in a membrane potential closer to the equilibrium of K⁺.

2.3.1 The Nernst equation

The Nernst equation can describe the membrane potential quantitatively in good approximation:

$$E = \frac{RT}{zF} \ln \frac{C_o}{C_i} = \frac{k_B T}{q_{\text{ion}}} \ln \frac{C_o}{C_i}$$

with R being the gas constant, ion charge z , Faraday constant F , outside C_o and inside C_i ion concentrations, Boltzmann constant k_B and temperature T .

2.4 Action potentials

Neurons such as the one leading from the human pelvis to the foot can easily extend to one meter. Therefore active signalling is crucial to signal conduction: The neuron will trigger a propagating change in the membrane potential whenever a threshold input excites the cell body. The travelling wave of electrical

excitation is called an *action potential*. Action potentials are brief in nature and travel at constant velocity of about $100 \frac{\text{m}}{\text{s}}$ and constant amplitude.

To measure action potentials a setup of two glass pipettes with inserted wire electrodes and an amplifier are used. One electrode guards the potential outside the cell (reference electrode), the other reports the membrane potential as soon as it penetrates the membrane. The key structural unit for electrically excitable cells (such as egg cells, neurons and muscle cells) are voltage gated channels. Whenever the cell is excited by a sufficient initial depolarisation (through neurotransmitter gated channels) voltage gated Na^+ -channels open. The influx shifts the membrane potential close to the equilibrium potential of Na^+ at $\approx 50\text{mV}$. This depolarisation is counteracted by inactivation of Na^+ -channels and the opening of voltage gated K^+ -channels. The efflux of K^+ ions overwhelms the Na^+ influx and draws the membrane potential back to the equilibrium potential of K^+ .

The currents involved in a locally defined action potential are strong enough to excite neighbouring patches of the membrane, therefore providing for travelling wave propagation along the axon.

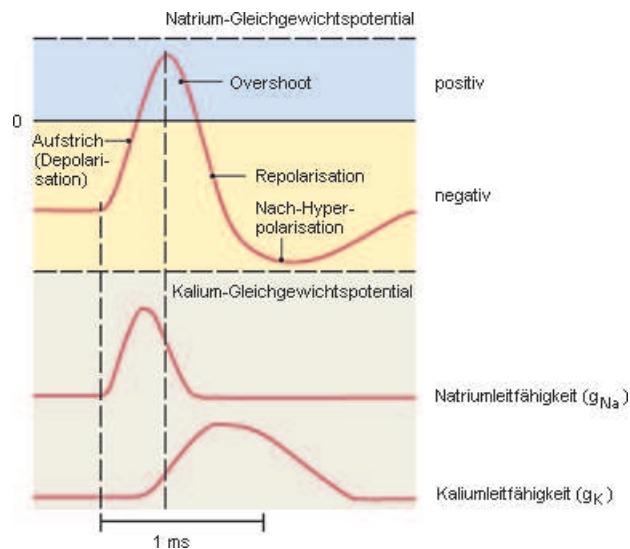


Figure 2.3: A "text book" action potential describing the four phases of an action potential: resting state, polarisation, polarisation and undershoot. Reversal potentials for sodium and potassium are shown, as well as the time course of their conductance.

Chapter 3

Mathematical model of a single neuron

3.1 The Hodgkin Huxley model

3.1.1 A brief history

Since action potentials are the dominant feature of the nervous system, a great deal of scientific research was conducted in deciphering their properties. Alan Hodgkin and Andrew Huxley established a model system in Cambridge 1952 that is until today one of the key achievements in cellular biophysics. Their work on the squid giant axon was awarded a Nobel price in physiology and medicine together with John Eccles in 1963.

3.1.2 The experimental setup

Hodgkin and Huxley conducted a series of experiments that allowed the determination of the time and voltage dependence of the Na^+ and K^+ conductances. Their set of differential equations is able to model all that was known about action potentials by that time with remarkable accuracy.

To establish the dependences of ionic currents crossing the cell membrane the squid giant axon was used. It has a diameter of half a millimetre (about 1000 times larger than a typical axon) which makes it especially suitable for experimental research.

The key experimental methods used to establish the models were:

- *Space clamp*

The space clamp technique greatly reduces the complexity of the model (leaving out partial differential equations to describe the cable theory). A long thin electrode is inserted into the axon (just like inserting a wire into a tube). As a result the membrane potential is spatially uniform (equal along the complete axon), just as if only a patch of membrane were investigated. After exciting the neuron by a supra threshold stimulus the whole membrane participates in one *membrane action potential* which is of course different from the *propagating action potentials* observed physiologically, but describes the phenomenon in sufficient detail.

- *Voltage clamp*

The membrane potential can be clamped (set) to a specific value by inserting an electrode into the axon and applying a sufficient current to it. A second electrode measures the membrane potential and modulates the applied current in order to remain at the clamped potential.

By shifting the membrane potential and substitution of single ion species with impermeable ones it is possible to examine the conductance involved in action potential creation.

- *Determination of individual ionic currents*

Using the above techniques Hodgkin and Huxley found various currents (capacitive, inward and outward) upon depolarisation of their space and voltage clamped axon. They adjusted the ionic milieu the axon was bathed in to determine which kinds of ions were involved in the phases of an action potential. This rather indirect method was dropped in favor of using radio-labeled potassium and later on substituted impermeable ions or pharmacological blockade of selected ion channels.

3.1.3 The HH model - a set of differential equations

Voltage clamp experiments provided the opportunity to measure ionic currents quantitatively. Hodgkin and Huxley wanted to determine both ionic species and the underlying properties of the axonal membrane regarding excitability. Their model is an empirical approach to the kinetic description of excitable membranes and their goal to predict the properties of action potentials was met with astonishing accuracy.

They were able to fit their research on the squid giant axon into a set of four differential equations (and various supporting functions).

The main equation - describing the membrane in terms of an electric circuit as

we will see later - is a non-linear differential equation, whereas the remaining three describe the properties of ion channels using ordinary, first-order linear differential equations:

$$C_m \frac{dV}{dt} = \bar{G}_K n(t)^4 (E_K - V(t)) + \bar{G}_{Na} m(t)^3 h(t) (E_{Na} - V(t)) + \bar{G}_{leak} (E_{leak} - V(t)) - I_{ext}(t) \quad (3.1)$$

$$\frac{dn}{dt} = \alpha_n(V) \cdot (1 - n(t)) - \beta_n(V) \cdot n(t) \quad (3.2)$$

$$\frac{dm}{dt} = \alpha_m(V) \cdot (1 - m(t)) - \beta_m(V) \cdot m(t) \quad (3.3)$$

$$\frac{dh}{dt} = \alpha_h(V) \cdot (1 - h(t)) - \beta_h(V) \cdot h(t) \quad (3.4)$$

3.1.4 The modelling assumptions

The HH model represents a biophysical modelling attempt. As a result, an electrical equivalent circuit can be constructed in order to describe the membrane with all its relevant properties. Capacitors are used to account for the membrane's ability to store charge. Resistors account for various ion channels that are embedded within and batteries represent the electrochemical forces influencing current (due to the imbalanced ion concentration in- and outside the cell). The resulting circuit is shown in Figure 3.1. Hodgkin and Huxley dis-

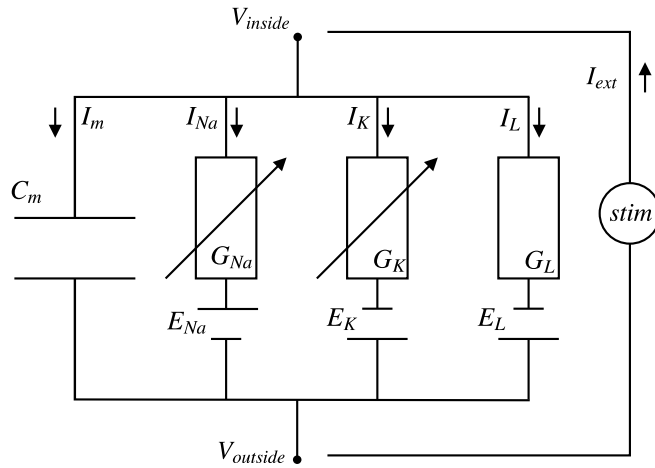


Figure 3.1: The circuit underlying the Hodgkin Huxley model. The branch featuring a capacitor represents the dielectric properties of the axonal membrane, the remaining branches its conductive properties. Resistors with an arrow represent voltage and time dependent conductances that are related to the opening and closing of ion channels.

bled the total membrane current to being the sum of ionic currents and the

capacitive current:

$$I_m(t) = I_{\text{ionic}}(t) + C_m \frac{dV(t)}{dt}$$

Ionic currents

The Hodgkin Huxley (HH) model designed after a series of experiments featured the following characteristics:

The model considers three ionic currents, namely one for sodium, potassium which are voltage and time dependent and a third leak conductance being independent of the membrane potential. The total ionic current is therefore:

$$I_{\text{ionic}} = I_{\text{Na}} + I_{\text{K}} + I_{\text{leak}} \quad (3.5)$$

These currents, though used as point currents in figure [3.1], are actually macroscopic currents that represent a large population of ion channels of the same type with unit $\mu\text{A}/\text{cm}^2$. Each ionic current is dependent on the membrane potential in a linear fashion as described by Ohm's law:

$$\begin{aligned} I &= \frac{U}{R} && \text{with} \\ I &= \text{Current} \\ U &= \text{Voltage} \\ R &= \text{Resistance.} \end{aligned}$$

With the biological background of the equivalent circuit, it is more convenient to talk about conductance instead of resistance:

$$G = \frac{1}{R}$$

The potential the ions experience is expressed by two terms: Driving potential $V(t)$ and the reversal potential given by the Nernst equation of the ionic species E_k , the so called *ionic battery* (see figure [3.1]). As a result, the ionic current of a species k is given by:

$$I_{\text{ionic}} = G_k(E_k - V)$$

Since equation 3.5 states I_{ionic} to be the sum of individual currents, this leads to:

$$I_{\text{ionic}} = \sum_k I_k = \sum_k G_k(E_k - V) \quad (3.6)$$

and in the expanded form for sodium, potassium and leak current considered here:

$$I_{\text{ionic}} = G_{\text{K}}(E_{\text{K}} - V) + G_{\text{Na}}(E_{\text{Na}} - V) + G_{\text{leak}}(E_{\text{leak}} - V)$$

Individual currents can be both positive or negative depending on the membrane potential and the ion species' reversal potential. By the *inward negative* convention, a negative sign will indicate an inward current, a positive one a outward current.

The ionic conductances in Equation 3.6 are both voltage- and time dependend. HH postulated this dependence in order to fit their experimental data. The leakage current however shows a constant form (and is therefore represented as a fixed resistor in Figure 3.1. Although HH did not know the properties of individual ion channels, it is convenient for us to discuss their findings and their postulations in this context.

Gating particles

The macroscopic currents related to numerous ion channels embedded in the cell membrane have been a topic already. These channels are gated by the so called *selectivity filter* (see 2.2) which is comprised of protein loops and effectively controls the flow of ions through the channel. The individual loops (or gates in HH terminology) can be in either permissive or non-permissive state. Only when all gates of an individual channel are permissive, the channel is open and a current can pass.

HH defined the probability for a gate the be found in its permissive state to depend on the membrane potential, therefore incorporating the voltage dependend conductance. A probability p_i ranging from 0 to 1 can be defined for each gate of type i , but since a large population of channels (and therefore gates) has to be considered this leads to:

$$1 - p_i(t) \xrightleftharpoons[\beta_i(V)]{\alpha_i(V)} p_i(t)$$

where $1 - p_i(t)$ is the fraction in non-permissive state and p_i the fraction in permissive state.

Although beeing voltage dependend, α_i and β_i are called *rate constants* (in sec^{-1}). In the HH model the rate constants are described using first-order kinetics:

$$\frac{dp_i}{dt} = \alpha_i(V)(1 - p_i) - \beta_i(V)p_i$$

The rate constants will eventually reach equilibrium when the membrane is set to a fixed potential:

$$p_{i; t \rightarrow \infty} = \frac{\alpha_i(V)}{\alpha_i(V) + \beta_i(V)}$$

The time course for reaching steady-state can be described by:

$$\tau_i(V) = \frac{1}{\alpha_i(V) + \beta_i(V)}$$

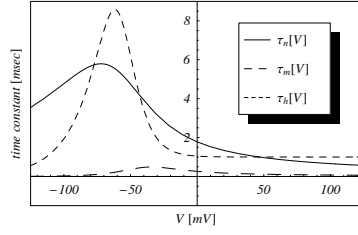


Figure 3.2: Voltage dependent parameters of the HH model: Time constants

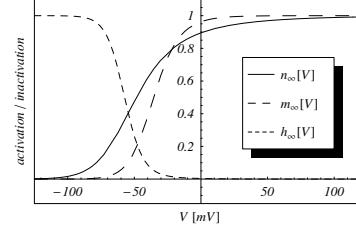


Figure 3.3: Voltage dependent parameters of the HH model: Steady-state values

The above equations allow the time constants and steady-state values to be calculated with respect to the membrane potential. Figure 3.3 shows that a depolarisation will result in an increase of n_∞ and m_∞ , while h_∞ is decreased. Looking at the K^+ -channels this means that tend to be closed at potentials below the resting potential and open up upon depolarisation. Figure 3.2 reveals that parameter n in example changes slowly at low membrane potentials and much more rapidly at higher potentials. In general time constants are highest close to the resting potential and decrease to either side.

Coming back to the description of macroscopic ionic currents in equation 3.6 the above findings have to be implemented. Conductance is proportional to the number of open channels which are in turn proportional to the number of permissive gates. The conductance of channels for ion types k is therefore proportional to the product of probabilities p_i of gate type i :

$$G_k = \bar{G}_k \cdot \prod_i p_i$$

with \bar{G}_k bearing the maximum possible conductance.

The above equations are a general description, HH however only considered channels for sodium, potassium and a leak current. They introduces a gating particle n describing the potassium conductance and two for sodium (m beeing activating and h beeing inactivating).

It is important to notice that h is the probability that the gate is *not* in its inactivating state.

It is now possible to derive specific equations for potassium and sodium conductance:

$$\begin{aligned} G_K &= \bar{G}_K p_n^4 = \bar{G}_K n^4 \\ G_{Na} &= \bar{G}_{Na} p_m^3 p_h = \bar{G}_{Na} m^3 h \end{aligned}$$

and finally

$$I_m(t) = \bar{G}_K n^4 (E_K - V) + \bar{G}_{Na} m^3 h (E_{Na} - V) + \bar{G}_{leak} (E_{leak} - V) + C_m \frac{dV}{dt}$$

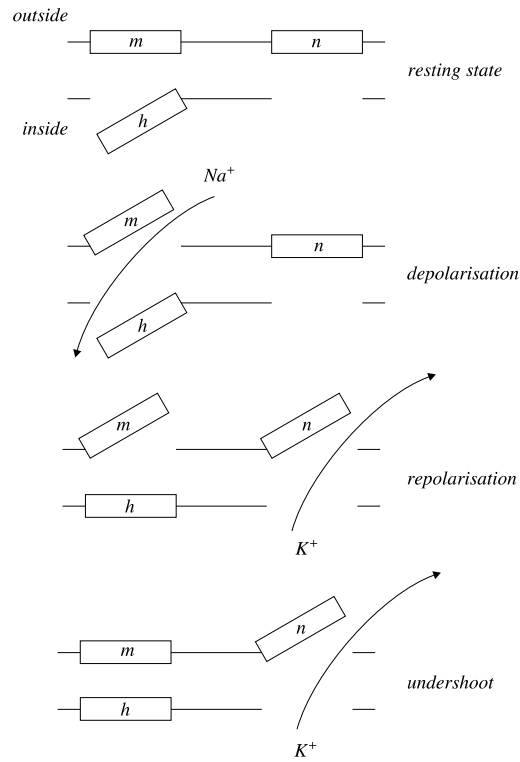


Figure 3.4: Hodgkin and Huxley introduced the gating particles n , m and h to describe the underlying kinetics of the sodium and potassium channels. m and h represent the sodium channel, n the potassium channel respectively.

$$\begin{aligned} \frac{dn}{dt} &= \alpha_n \cdot (1 - n) - \beta_n \cdot n \\ \frac{dm}{dt} &= \alpha_m \cdot (1 - m) - \beta_m \cdot m \\ \frac{dh}{dt} &= \alpha_h \cdot (1 - h) - \beta_h \cdot h \end{aligned}$$

Rate constants

HH used voltage clamp experiments to determine both the number and type of gates necessary for their model, as well as the voltage dependence of the rate constants. By fitting their data, they were able to set up continuous functions of voltage to describe the rate constants. A description can be found in their original publication [1] or in [5].

3.1.5 Recapitulation

The HH model is undoubtedly the most successful empirical model in neuroscience ever since its publication in 1952.

The key feature is the description of sodium and potassium conductances G_{Na} and G_{K} in terms of three activating gating particles m and one inactivating particle h for sodium and four gating particles n for potassium. The dynamics of these particles are described through first-order differential equations featuring two voltage dependent terms: steady state activation and inactivation and the time constants.

3.1.6 Generating an action potential

In 2.4 the ability of action potential generation was described. The HH model offers a tool to demonstrate this aspect of the membrane. Whenever a short (msec range) inward current pulse (nA range) is applied to a patch of axonal membrane, the membrane capacitance is charged and the membrane potential depolarizes. As a result n and m are increased. If the current pulse is sufficient in strength the generated I_{Na} will exceed I_{K} resulting in a positive feedback loop between activation m and I_{Na} . Since τ_m is very small at these potentials, the sodium current shifts the membrane potential beyond 0mV. As sodium inactivation h and I_{K} kick in the membrane potential returns to its resting potential and even undershoots a little due to the persistent potassium current.

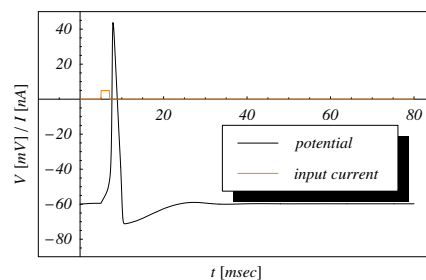


Figure 3.5: Generation of an action potential by a small but sufficient input current of 5nA for 2ms.

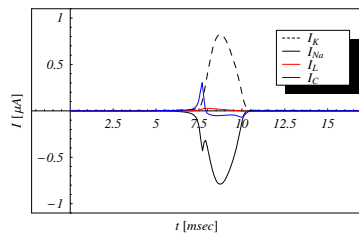


Figure 3.6: Plot of the individual currents involved in an action potential. By the "inward negative" convention, the inward sodium current is negative, the outward potassium current positive.

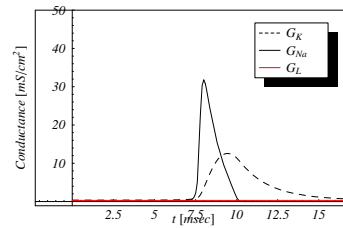


Figure 3.7: Time course of individual conductances. After a depolarising stimulus, the sodium conductance rises rapidly (fast activation) and relaxes slowly (slow inactivation) to its initial value. The potassium conductance shows considerably slower kinetics.

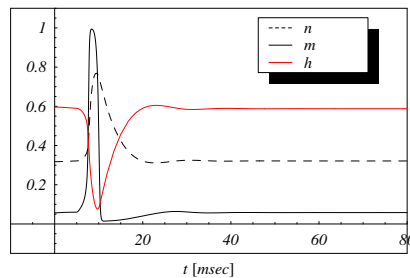


Figure 3.8: Sodium activation m charges more rapidly compared to the other two gating particles. Potassium activation takes considerably longer to return to its initial value, therefore causing a temporary undershoot below the membrane's resting potential

3.1.7 Modelling neuronal properties

Threshold

One of the key phenomena already discussed in the biological background is the all-or-nothing principle of action potential generation. Only a large enough (*supra threshold*) stimulus leads to depolarization beyond a membrane potential of 0mV. A *sub-threshold* stimulus cannot trigger an action potential. The difference in input stimulus strength between the two is narrow: Figure 3.9 shows a sub-threshold stimulus of 2.8nA for 2ms, whereas supra-threshold behavior is initiated by a 2ms stimulus of 2.85nA.

Refractory Period - absolute and relative

HH neurons - just like actual neurons - show a phenomenon called refractoriness. As a result, no second action potential can be generated regardless of the provided stimulus in the phase called *absolute refractory period*. Figure 3.10

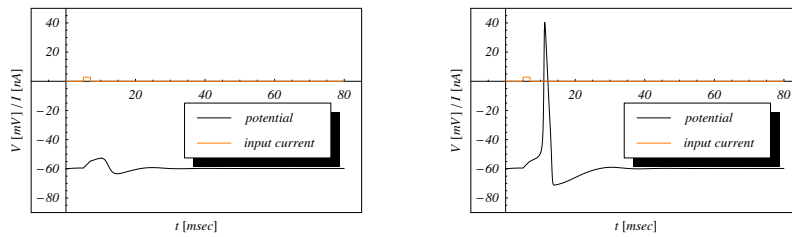


Figure 3.9: Plots of a sub-threshold and a supra-threshold stimulation.

shows that a second ten-fold stimulus cannot create an action potential after a delay of 5ms. However, after 10ms a three-fold stimulus is sufficient. This phase is referred to as *relative refractory period*.

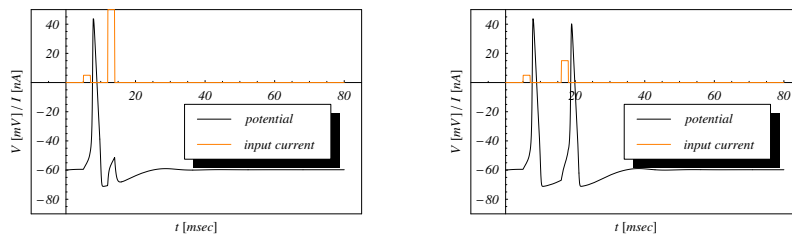


Figure 3.10: During the *absolute refractory period* no second action potential can be generated regardless of the stimulus strength. During the *relative refractory period* the stimulus has to be stronger than the initial one.

Repetitive spiking

A persistent stimulus will result in an ongoing firing of action potentials. The frequency of action potential generation is governed by the stimulus' strength. The amplitude is also stimulus dependent. Subsequent action potentials show a decreasing amplitude. A very strong stimulus will result in a *depolarisation block* (see Figure 3.11).

Temperature dependence of rate constants

Hodgkin and Huxley performed their voltage clamp experiments at 6.3°C. Higher temperatures affect the reversal potentials since the Nernst equation is temperature dependent, but by far more dramatic are their influence on the rate constants. Higher temperatures lead to lower time constants (compare Figure 3.5 and Figure 3.12) and decreased amplitudes. In correlation to the phenomenon

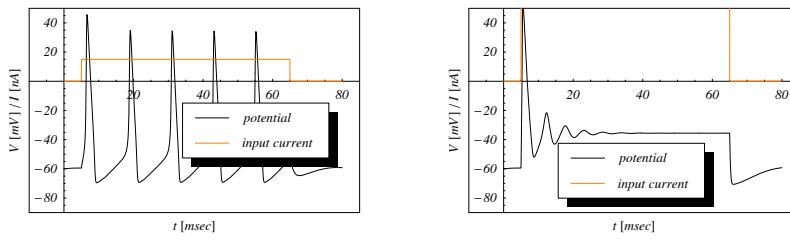


Figure 3.11: If a supra-threshold stimulus is applied over a long period, *repetitive spiking* can be observed. A very strong stimulus (i.e. 200nA) will block action potential generation.

of depolarisation blocking, a temperature at which no further action potential can be generated can be determined (see Figure 3.13).

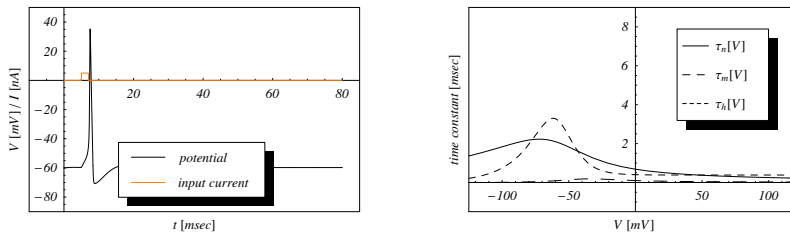


Figure 3.12: Action potential generation can be influenced by increased temperatures. HH originally worked at 6.3°C. A temperature of 10°C leads to a fastend time course and lower amplitudes.

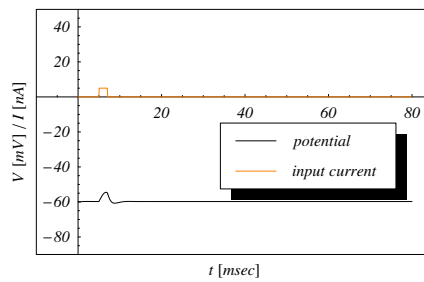


Figure 3.13: If the temperature is set to 25°C no action potential is generated, a phenomenon called *temperature block*.

Chapter 4

Appendix

4.1 Parameters of the Hodgkin Huxley model

The parameters were taken from [4] and [7]:

Param.	value	unit
V_0	0	mV
C_m	1	$\mu\text{F cm}^{-2}$
\bar{G}_{Na}	120	mS cm^{-2}
\bar{G}_{K}	36	mS cm^{-2}
\bar{G}_{leak}	0.3	mS cm^{-2}
E_{Na}	55	mV
E_{K}	-72	mV
E_{leak}	-49.387	mV
T	6.3	C

$$\begin{aligned}\frac{dn}{dt} &= \alpha_n(V) \cdot (1 - n) - \beta_n(V) \cdot n \\ \alpha_n(V) &= \phi \cdot \frac{a_n(V - V_{\alpha_n})}{1 - e^{-(V - V_{\alpha_n})/K_{\alpha_n}}} \\ \beta_n(V) &= \phi \cdot b_n \cdot e^{-(V - V_{\beta_n})/K_{\beta_n}}\end{aligned}$$

$$\begin{aligned}\frac{dm}{dt} &= \alpha_m(V) \cdot (1 - m) - \beta_m(V) \cdot m \\ \alpha_m(V) &= \phi \cdot \frac{a_m(V - V_{\alpha_m})}{1 - e^{-(V - V_{\alpha_m})/K_{\alpha_m}}} \\ \beta_m(V) &= \phi \cdot b_m \cdot e^{-(V - V_{\beta_m})/K_{\beta_m}}\end{aligned}$$

$$\begin{aligned}\frac{dh}{dt} &= \alpha_h(V) \cdot (1 - h) - \beta_h(V) \cdot h \\ \alpha_h(V) &= \phi \cdot \frac{a_h(V - V_{\alpha_h})}{1 - e^{-(V - V_{\alpha_h})/K_{\alpha_h}}} \\ \beta_h(V) &= \phi \cdot b_h \cdot e^{-(V - V_{\beta_h})/K_{\beta_h}}\end{aligned}$$

with ϕ regulating the temperature dependence by:

$$\phi = Q_{10}^{(T-6.3)/10} \quad \text{and} \quad Q_{10} = 3$$

Param.	n	m	h	unit
a	0.01		0.1	$0.0.7 \text{ ms}^{-1}$
b	0.125	4	1	ms^{-1}
V_{α}	-50	-36	-60	mV
V_{β}	-60	-60	-30	mV
K_{α}	10	10	20	mV
K_{β}	80	18	10	mV

4.2 Implementation of the Hodgkin Huxley model with Mathematica

The implementation in Mathematica utilised the equations listed in the above chapters and sections. However I would like to provide some of the key code lines:

Indeterminate rate functions

The expression for α_n can be indeterminate for certain parameter choices. Using L'Hopitals rule it can be shown that $\alpha_n(V) = 0.1$ at $V(t) = V_0$:

■ Rate functions:

```
(* potassium current *)
If[V_0 == Vα_n, α_n[V_] = Which[V == V_0, φ * .1, True, φ *  $\frac{a_n (V - V_{\alpha_n})}{1 - e^{-(V - V_{\alpha_n})/K_{\alpha_n}}}$ ],
  α_n[V_] = φ *  $\frac{a_n (V - V_{\alpha_n})}{1 - e^{-(V - V_{\alpha_n})/K_{\alpha_n}}}$ ;
β_n[V_] = φ * b_n * e^{-(V - V_{\beta_n})/K_{\beta_n}};

(* sodium current *)
If[V_0 == Vα_m, α_m[V_] = Which[V == V_0, φ * 1, True, φ *  $\frac{a_m (V - V_{\alpha_m})}{1 - e^{-(V - V_{\alpha_m})/K_{\alpha_m}}}$ ],
  α_m[V_] = φ *  $\frac{a_m (V - V_{\alpha_m})}{1 - e^{-(V - V_{\alpha_m})/K_{\alpha_m}}}$ ;
β_m[V_] = φ * b_m * e^{-(V - V_{\beta_m})/K_{\beta_m}};

α_h[V_] = φ * a_h * e^{-(V - V_{\alpha_h})/K_{\alpha_h}};
β_h[V_] = φ *  $\frac{b_h}{1 + e^{-(V - V_{\beta_h})/K_{\beta_h}}}$ ;
```

Figure 4.1:

Input current

The external input current was implemented through a discontinuous function:

■ External input current

```
t1 := 5;
dur1 := 2;
stim1 := 5;
delay1 := 0;
t2 := t1 + dur1;
t3 := t1 + dur1 + delay1;
dur2 := 0;
stim2 := 0;
t4 := t3 + dur2;
extinput[t_] := Which[t1 <= t < t2, stim1, t3 <= t < t4, stim2, True, 0];
```

Figure 4.2:

Solving the differential equations

■ Solving the differential equations

```
ODE1 = v'[t] == -INa[t] - IK[t] - IL[t] + extinput[t];
ODE2 = n'[t] ==  $\alpha_n$ [v[t]] * (1 - n[t]) -  $\beta_n$ [v[t]] n[t];
ODE3 = m'[t] ==  $\alpha_m$ [v[t]] * (1 - m[t]) -  $\beta_m$ [v[t]] m[t];
ODE4 = h'[t] ==  $\alpha_h$ [v[t]] * (1 - h[t]) -  $\beta_h$ [v[t]] h[t];

sol = NDSolve[{ODE1, ODE2, ODE3, ODE4, v[0] == v0, n[0] == n0, m[0] == m0, h[0] == h0},
{v, n, m, h}, {t, 0, 100}, MaxSteps -> 10000]
```

Figure 4.3:

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