

# Project 3 - TMA4320

Simulating the action potential with random walk of ions

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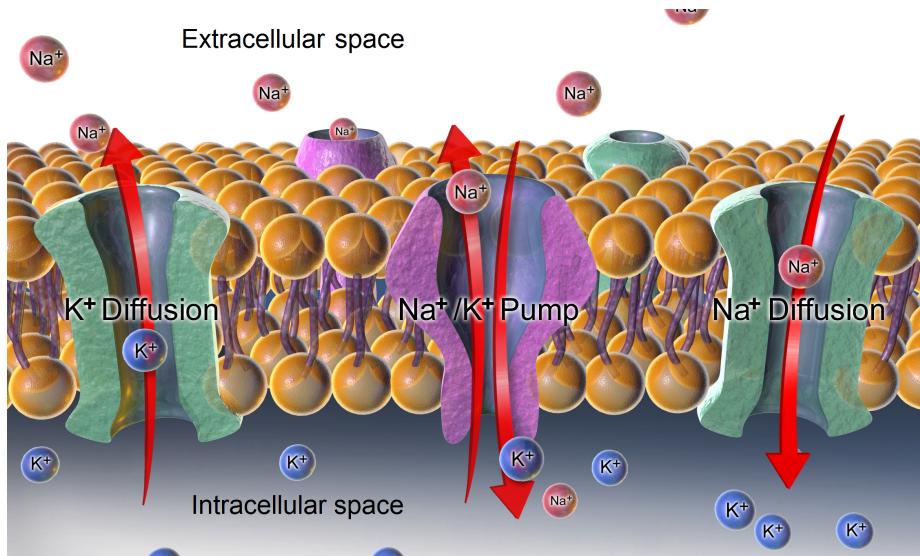


Figure 1: Illustration of the sodium-potassium pump and ion flow in and out of a cell. Credits: "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2).

This project description consist of 8 numbered sections. Of these sections, three sections ([1](#), [4](#) and [6](#)) are pure theory sections where you will find all necessary background information in order to do the exercises. Sec. [2](#) consist of analytical exercises which are meant to give you insight into diffusion processes. The remaining 4 sections ([3](#), [5](#), [7](#) and [8](#)) consist of programming exercises where you will do simulations. The overall goal is to be able to simulate the action potential, which give cells the ability to generate electrical signals (more about the action potential in Sec. [6](#)). I suggest to do the programming in python, as this is the only programming language in which you are guaranteed to get help

from the student assistants. However, you are welcome to use e.g. C++ if you fancy obscure debugging without receiving syntax help.

You should submit a report where you answer each exercise in the same order as given in this project description. The report should either be a .pdf-file written in L<sup>A</sup>T<sub>E</sub>X, or handed in as a Jupyter notebook accompanied with a .html- or -pdf-file which is easily printable for me. Use the exercise numbers given here to mark your answers. You should only give explicit answers and discussions to the exercises. Do not include an introduction, methods, conclusion or any additional sections which you might be used to include in lab reports etc..

Your grade will be determined by the correctness of your results, your discussion of the results, and how you relate the computational results to real world physics. In general, the last exercises will weigh more on your final grade than the first exercises. Your code in itself will generally not be subject to grading. Since tiny syntax errors may have huge qualitative impact on your results, a certain degree of mercy will be given to those with erroneous results. That is, you will not be given the maximum score if your results are obviously physically incorrect, but your discussion viewed in light of the results will be judged in your favour. If you understand that the results are physically incorrect, you will be awarded for pointing out what is wrong, and why this is wrong, as this shows physical intuition and insight into the involved physics. That said, the final grade will be based on the overall impression of your report. In rare cases, your code might be used in the evaluation, so you should submit your code alongside the report (if you hand in a Jupyter notebook with all your code, you need not hand in a separate file containing your code).

## 1 Theory

### *Mathematical introduction*

Diffusion is a process where particles move down the concentration gradient. That is, particles move from areas with high concentration to areas with low concentration. The physical driving force of diffusion is simply random movement of each particle. Diffusion of a substance, of which distribution is given by  $\phi(x, t)$ , is described by the diffusion equation. In one dimension (1D) the diffusion equation takes the form

$$\frac{\partial \phi(x, t)}{\partial t} = \frac{\partial}{\partial x} \left( D(x) \frac{\partial \phi(x, t)}{\partial x} \right), \quad (1)$$

where  $D(x)$  is the (position dependent) diffusion coefficient.

We will now show the correspondence between random walk in 1D and the diffusion equation. Random walk is defined as follows: let  $X(t)$  be a stochastic process in time giving the position of a particle after a time  $t$ . At time  $t = 0$ ,  $X(0) = 0$ . The particle makes a step in every time interval  $\Delta t$ . The particle can move left and right along an axis, or stay put, with the following probabilities

$$X(t + \Delta t) = \begin{cases} X(t) + h & \text{with probability } \frac{d}{2} \\ X(t) & \text{with probability } 1 - d \\ X(t) - h & \text{with probability } \frac{d}{2} \end{cases} \quad (2)$$

We may further define the variable  $\phi(x, t) = P\{X(t) = x\}$ . By conditional probabilities, we may straightforwardly write

$$\phi(x, t + \Delta t) = \frac{d}{2} \phi(x + h, t) + (1 - d) \phi(x, t) + \frac{d}{2} \phi(x - h, t). \quad (3)$$

Slightly rewrite this to

$$\frac{\phi(x, t + \Delta t) - \phi(x, t)}{\Delta t} = \frac{dh^2}{2\Delta t} \frac{\phi(x + h, t) - 2\phi(x, t) + \phi(x - h, t)}{h^2}. \quad (4)$$

Now suppose that  $D = \frac{dh^2}{2\Delta t}$  is a constant. If we then let  $\Delta t$  and  $h^2$  go simultaneously to zero, we find

$$\frac{\partial \phi(x, t)}{\partial t} = D \frac{\partial^2 \phi(x, t)}{\partial x^2}. \quad (5)$$

This is the diffusion equation with constant diffusion coefficient. We have therefore shown that random walk in the limit of infinitesimal steps in time and space corresponds to diffusion.

## 2 Exercises

*The diffusion equation*

### Exercise 2.1

Show that the function

$$\tilde{\phi}(x, t) = \frac{1}{\sqrt{4\pi Dt}} e^{-\frac{(x-\mu)^2}{4Dt}},$$

where  $D$  is a constant, is a solution of the diffusion equation (5).

### Exercise 2.2

#### 2.2.1

Suppose we have an infinite 1D system with constant diffusion coefficient  $D$ . Start with the particle distribution

$$\phi(x, 0) = \delta(x - x_0),$$

where  $\delta(x)$  is the Dirac delta function. Find the time derivative of  $\phi(x, t)$  using the diffusion equation. Use this, as well as the Taylor expansion of  $\phi(x, t)$ ,

$$\phi(x, t) = \phi(x, 0) + \sum_{n=1}^{\infty} \frac{t^n}{n!} \left. \frac{\partial^n \phi(x, t')}{\partial t'^n} \right|_{t'=0}.$$

to show that the particle distribution at time  $t$  is given by the following integral

$$\phi(x, t) = \frac{1}{2\pi} \int_{-\infty}^{\infty} dk e^{-Dtk^2} e^{-ik(x-x_0)}.$$

Compute the integral, and show that this results in

$$\phi(x, t) = \frac{1}{\sqrt{4\pi Dt}} e^{-\frac{(x-x_0)^2}{4Dt}}. \quad (6)$$

This is a normal distribution in  $x$ .

*Hint:* a common representation of the Dirac delta function in physics is  $\delta(x - x_0) = \frac{1}{2\pi} \int_{-\infty}^{\infty} dk e^{-ik(x-x_0)}$ . Strictly speaking, this integral diverges, which any mathematician would surely point out. However, under the right circumstances, it can be used anyhow. In this exercise, you can safely use it!

#### 2.2.2

We have now identified in what kind of systems and after which initial conditions  $\tilde{\phi}$  given in Exercise 2.1 is a solution. Use the results of Exercise 2.2.1 to give a physical interpretation of the diffusion coefficient  $D$ .

### 2.2.3

Use the results from Exercise 2.2.1 to find the time evolution  $\phi(x, t)$  given another initial condition  $\phi(x, 0) = g(x)$ , where  $g(x)$  is an arbitrary function.

*Hint:*  $f(x) = \int_{-\infty}^{\infty} dy f(y) \delta(x - y)$ . You can use this straightforwardly to obtain an answer, and no additional complex calculations are needed.

## 3 Programming

### *Random walk in 1D*

Start with 1000 particles at  $x = 0$ . Let each of these particles be subject to a random walk in 100 time steps, where the steps in space are  $h = \pm 1$  and the steps in time are  $\Delta t = 1$  (we use dimensionless time and space axes). Let for simplicity  $d = 1$ , so that there is zero probability for a particle to stay put. The random walk may be simulated by picking a random number between 0 and 1, and choose right (left) if the number is equal to or greater than (less than) 0.5.

Plot the particle distribution along the  $x$ -axis after the simulation. Fit a normal distribution to the resulting particle distribution (use for instance the function `fit` in `scipy.norm`), and explain the results using Theory Section 1 and Exercise 2.

## 4 Theory

### *Random walk in a potential*

An important result from statistical physics is that the probability  $P$  of finding a particle in a state  $(p, x)$ , where  $p$  is the momentum and  $x$  is the position of a particle, is

$$P(p, x) \propto e^{-\beta E(p, x)}, \quad (7)$$

where  $E(p, x)$  is the energy of the particle in the state  $(p, x)$ , and  $\beta = 1/(k_B T)$ . Here,  $k_B$  is the Boltzmann's constant and  $T$  is temperature. The proportionality constant in the equation above is  $1/Z$ , where  $Z$  is the partition function.  $Z$  can be very hard to calculate for all but the simplest systems. However, we do not need to know  $Z$  in our model. The energy of classical particles in the systems we are considering can be written  $E(p, x) = \frac{p^2}{2m} + V(x)$ , where  $V(x)$  is the potential energy. Assume further that all particles have equal momentum  $p$  given a temperature  $T$ , so that we can treat the kinetic terms as a constant. We can then simply use  $V(x)$  as a measure of energy.

Suppose a particle is subject to random walk in 1D. Let the spatial steps be  $\pm h$ , and let the steps in time be  $\Delta t$ . Let  $P^+$  denote the probability of going to the right, and let  $P^-$  denote the probability of going to the left. Let there be zero probability of staying put. Requiring the total probability to be 1 implies

$$P^+ + P^- = 1. \quad (8)$$

Rewrite this to

$$P^+ = \frac{1}{1 + \frac{P^-}{P^+}}. \quad (9)$$

Note that the probability  $P^+$  is simply dependent upon the relative probability of going left and right. We know, using Eq. (7), that

$$\frac{P^-}{P^+} = e^{-\beta[V(x-h) - V(x+h)]}. \quad (10)$$

We thus have everything we need in order to perform a random walk simulation in a potential!

## 5 Programming

### *Random walk in a potential*

In the last section, we derived all theory which is needed to perform a 1D random walk in a potential. Simulate the random walk by picking a random number between 0 and 1, and walk to the right (left) if this number is equal to or greater than (less than)  $P^-$ . Perform the random walk with the same parameters as in Programming exercise 3 (release the particles at  $x = 0$ ), but this time with the following potentials (see further below for which values of  $k$ ):

#### Programming exercise 5.1

$$V(x) = kx$$

This potential could for instance represent the electric potential for charged ions in a constant electric field. This situation is equivalent to random walk with a constant drift.

#### Programming exercise 5.2

$$V(x) = k, \quad \text{for } -3h < x < 3h.$$

$$V(x) = 0 \quad \text{otherwise.}$$

This potential could for instance represent particles moving in two regions ( $x > 3$  and  $x < -3$ ) separated by a membrane potential on the interval  $-3h < x < 3h$ .

### Programming exercise 5.3

$$V(x) = -k, \quad \text{for } x < -3h.$$

$$V(x) = k \left( -1 + 2 \frac{x + 3h}{6h} \right), \quad \text{for } -3h < x < 3h.$$

$$V(x) = k, \quad \text{for } x > 3h.$$

This potential could for instance model the electrical potential felt by ions moving in two regions ( $x > 3$  and  $x < -3$ ) separated by a membrane ( $-3h < x < 3h$ ) with constant electrical resistance.

*Info for all programming exercises:*

The quantity  $\beta k$  gives the ratio between the potential energy and thermal energy<sup>1</sup>. Plot the particle distribution after the random walk simulation for a range of values of  $\beta k$  (minimum 3, maximum 5) between 0.1 and 10 for each potential, so that the effect of the ratio  $\beta k$  becomes apparent. Explain why the results make physical sense. Explain the differences between the results from the different values of  $\beta k$  using your knowledge of the involved physics.

## 6 Theory

### *A simplified model for ion transport through cell membranes*

Each human cell consist of an interior encapsulated by a cell wall (or membrane). The main job of the cell wall is to stop the interior of the cell from leaking out of the cell, as well as to stop random molecules from entering the cell and disturb the cell activity. However, the cell wall cannot be a fully non-penetrable wall, as this would hinder any kind of flow into and out of the cell - which is a condition for life.

The cell wall consist of mostly lipids. Lipids are molecules which are amphiphilic, meaning that they have one polar end (soluble in water) and one non-polar end (not soluble in water). For the cell to be able to move through the body, which hosts an environment dominated by water, the outer cell wall needs to be polar. As the cell interior is also filled up with water, a polar inner cell wall secures the stability and functionality of the cell. An effective method of stopping water-soluble molecules to penetrate the cell wall is to make the interior of the cell wall non-polar. Indeed, this is exactly how our cells are built up. The cell wall consists namely of a double layer of lipids, with the non-polar ends meeting within the cell wall, and with the polar ends forming both the inner and outer surface of the cell wall.

For the cells to be able to efficiently transport molecules through the membrane, the cell wall also consists of a variety of proteins. These proteins facilitate

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<sup>1</sup>Remember that we operate with dimensionless position  $x$ , so that  $k$  is given in units of energy.

transport of specific molecules or ions through the cell membrane, by providing a polar environment across the membrane. Look at Fig. 1 for reference. There are two main types of transport processes across a cell membrane, **facilitated diffusion** where the specific molecules or ions move in the direction dictated by the concentration gradient, carried on by channel or carrier proteins, and **active transport** where molecules and ions are moved up the electrochemical gradient, which requires an input in energy such as ATP hydrolysis. In facilitated diffusion, the opening of both channels and carriers can be controlled by external factors such as a voltage across the membrane.

## 6.1 The action potential

All animal cells have the ability to generate a membrane potential, which is a voltage between the interior and exterior of the cell. Some cells also have the ability to rapidly regulate this potential by depolarizing and repolarizing. These include muscle cells and nerve cells. This sudden voltage pulse is known as the action potential. The sudden depolarization may cause adjacent cells to depolarize as well, enabling the transportation of an electric signal. The mechanism for generating the potential is as follows (a bit simplified, in order not to provide you with a huge overload of unnecessary information):

1. *Resting potential:* The cell plasma (interior liquid) contains an enzyme called sodium-potassium adenosine triphosphatase. Given one ATP molecule (the basic energy transporter in our body,  $ATP \rightarrow ADP + \text{phosphate}$  releases energy), this enzyme transports three  $\text{Na}^+$  ions out of the cell, while two  $\text{K}^+$  ions are simultaneously pumped into the cell. This is called the sodium-potassium pump (SPP). The SPP works more or less in a constant pace. If you give the SPP sufficient time to do its job, it results in: 1) a concentration gradient of  $\text{K}^+$  and  $\text{Na}^+$  across the cell wall. 2) A voltage difference between the interior and exterior of the cell, due to exporting three positively charged ions while importing only two. The cell interior therefore has a lower potential than the cell exterior. The resting potential is about  $-70 \text{ mV}$ .
2. *Depolarization:* Given an external electric stimulus, at a given threshold, about  $-55 \text{ mV}$ ,  $\text{Na}^+$  channels through the cell membrane open.  $\text{Na}^+$  flows into the cell due to two effects: 1) The electric potential favours charge flow into the cell. 2) Diffusion causes  $\text{Na}^+$  to flow inwards, as the concentration inside the cell is much lower than outside. Due to there being two effects favoring an inflow of  $\text{Na}^+$ , the inflow will actually last even after the voltage has flipped, so that the interior of the cell will end up being positively charged. The  $\text{Na}^+$  channels close when the voltage between the interior and the exterior of the cell is about  $+30 \text{ mV}$ .
3. *Repolarization:* After depolarization, and after the sodium channels close, the potassium channels open. Both the voltage and the  $\text{K}^+$  gradient favour an outflow of  $\text{K}^+$ . Since the concentration of  $\text{K}^+$  is so much larger inside

the cell, diffusion enables the restoration of the resting potential at about  $-70$  mV.

The SPP runs more or less throughout the entire cycle. Note however that while the long-term behaviour of the action potential cycle is a result of the SPP, the short term behaviour is not. That is, the SPP stores energy in a concentration gradient of sodium and potassium, and a resulting electric potential. However, once this energy is stored, the cells manage firing off many action potentials before this energy is drained.

Take a brief moment to reflect on the magnificence of this process! By storing energy in a concentration gradient, the cells manage to fire off electric signals. These electric signals are, among others, responsible for keeping your heart pumping blood, which keeps you alive!

## 7 Programming

### *Interplay between diffusion and voltage*

We will soon model a simplified action potential cycle using a random walk simulation in a potential. Before doing so, we of course need to simplify our model. The simplifications involve: 1) We explore a one-dimensional system. 2) We assume that the extracellular volume is infinite<sup>2</sup>, meaning that the ion concentrations are constant outside the cell. 3) We include only  $\text{K}^+$  and  $\text{Na}^+$  ions in the simulation (in reality, other ions also play a role). 4) We neglect the SPP in this exercise. That is, we do not pump ions through the cell wall. Diffusion and voltage are therefore the only driving forces. 5) The ion channels have two states: open and closed.

Define the system between  $x = -L/2$  and  $x = L/2$ . The cell membrane is located inside  $-h \leq x \leq h$ . The cell interior is located to the left of the membrane, and the cell exterior is located to the right. In the random walk simulation, use step sizes  $h = 1$ ,  $\Delta t = 1$ , and  $L = 50$ . If a particle reaches the system edges, it can only move into the system in the next time step.

We need to define a number of potentials in order to model the physics in this problem. For simplicity, we will in this exercise assume that the membrane potentials (which model the  $\text{Na}^+$  and  $\text{K}^+$  channels) are constant in time. We will wait until the next section to let them open and close. Therefore, define the membrane potentials as

$$V_{\text{Na}}(x) = \begin{cases} V_{\text{Na}}^0 & -h \leq x \leq h \\ 0 & \text{otherwise} \end{cases}, \quad (11)$$

and

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<sup>2</sup>Note that we define a finite system below, which we have to do in order to do a computational simulation. The only practical implication of this assumption is that the exterior ion concentrations are constant throughout the simulation.

$$V_K(x) = \begin{cases} V_K^0 & -h \leq x \leq h \\ 0 & \text{otherwise} \end{cases}. \quad (12)$$

Note the membrane potential  $V_{Na}$  is only felt by the sodium ions, while  $V_K$  is only felt by the potassium ions. That is, if we for instance set  $V_{Na} \rightarrow \infty$  and  $V_K \rightarrow 0$ , sodium ions are completely blocked from passing through the membrane, whereas the potassium ions flow through the membrane as if the interior and exterior made up one homogenous region.

Let  $V(t)$  be the (time-dependent) electric potential difference between the interior and exterior of the cell. This potential is felt by both types of ions. Inside the cell membrane, the potential is assumed to be linear in  $x$  (that is, a constant electric field inside the membrane), connecting the two potentials within and outside the cell. We can model the cell membrane as an effective circuit consisting of a capacitor in parallel with one resistor and a switch for each ion channel. The switch turns the gate on/off, while the resistor determines the rate in which charges are allowed to flow through the cell membrane. The gate potentials already defined model the resistors. We use our knowledge of capacitors to find the membrane voltage.  $V(t)$  can therefore be expressed as

$$V(t) = \frac{Q(t)}{C}, \quad (13)$$

where  $C$  is the capacitance of the cell membrane, and  $Q(t)$  is the charge difference on each side of the effective capacitor. The capacitance is assumed to be constant. We can therefore calculate it at for instance the resting potential, and use this value at all times  $t$ . We now slightly rewrite this equation to a more suitable form for our problem, which involves an aqueous solution of ions. Suppose that we can define  $C_c$  as the concentration capacitance, so that the voltage can be rewritten into the following form:

$$V(t) = \frac{[Q(t)]^+}{C_c}, \quad (14)$$

where  $[Q(t)]^+$  is the charge concentration difference on both sides of the cell membrane. At the resting potential, the intracellular ion concentrations are about  $[Na^+]_{\text{outside}} = 145 \text{ mM}$  ( $\text{mM} = \text{millimole per litre}$ ),  $[K^+]_{\text{outside}} = 5 \text{ mM}$ , while the inside concentrations are approximately  $[Na^+]_{\text{inside}} = 5 \text{ mM}$  and  $[K^+]_{\text{inside}} = 140 \text{ mM}$ . The resting potential is  $-70 \text{ mV}$ . We use these numbers to find

$$C_c = \frac{[Q(t)]_{\text{rest}}^+}{V_{\text{rest}}} = \frac{-5e \text{ mM}}{-70 \text{ mV}} \approx 0.07e \text{ M/V}, \quad (15)$$

where  $e$  is the elementary charge.

To illustrate how the voltage changes when the concentrations change, we look at an example. How much should  $[Q(t)]^+$  change to increase the membrane voltage by  $\Delta V = 100 \text{ mV}$ ? We straightforwardly find  $\Delta[Q(t)]^+ = C_c \Delta V =$

$0.07e \text{ M/V} \times 100 \text{ mV} = 7e \text{ mM}$ . This corresponds to  $\Delta[\text{Na}^+]_{\text{inside}} + \Delta[\text{K}^+]_{\text{inside}} = 7 \text{ mM}$ , given that the outside ion concentrations are constant.

Note that we only have three adjustable parameters in our model,  $V_{\text{Na}}^0$ ,  $V_{\text{K}}^0$  and  $\beta = 1/k_B T$ , where we set  $T$  to  $T_0 = (273+37) \text{ K}$  in all following simulations. We now normalize all energies to the thermal energy, so that we effectively only have two adjustable parameters,  $\beta V_{\text{Na}}^0$  and  $\beta V_{\text{K}}^0$ , both of which are dimensionless parameters. The electric energy potential for the sodium and potassium ions is given as  $eV(t)$ , where  $e$  is the elementary charge. We may also normalize this with the thermal energy, so that  $\beta eV(t)$  is the dimensionless (relative) energy.

### 7.1 Programming exercise 7.1

You will now do a random walk simulation. Let each particle in the simulation represent 0.1 mM inside the cell. That is, start with 1450  $\text{Na}^+$  ions and 50  $\text{K}^+$  ions outside the cell (release them at  $x = L/4$  at  $t = 0$ ). Start with 50  $\text{Na}^+$  ions and 1400  $\text{K}^+$  ions inside the cell (release them at  $x = -L/4$  at  $t = 0$ ). Set the membrane potentials to a constant  $V_{\text{Na}}^0 = V_{\text{K}}^0 \equiv V^0$ . Run the simulation for (at least) 500 time steps with three different values of  $\beta V^0$ ,  $\beta V^0 \in \{0, 1, 3\}$ . In each time step, calculate the voltage  $V(t)$  across the cell wall, and use this potential in the next time step. Plot the voltage  $V(t)$  as function of the time steps for all three membrane potential strengths, and compare the results. Where does the voltage settle? Why should this result (the value at which the voltage settles) be anticipated?

*NB! When calculating the potential  $V(t)$ , you need to input the ion concentrations. Recall that the exterior ion concentrations are fixed to the initial concentrations throughout the whole simulation. The interior concentrations are however given as the number of particles inside the cell times 0.1 mM.*

### 7.2 Programming exercise 7.2

You are now going to do almost the same simulation as in Exercise 7.1, only with different membrane voltages for the two types of ions. Run the simulation first with  $\beta V_{\text{Na}}^0 = 1$  and  $\beta V_{\text{K}}^0 = 10$ , and thereafter with  $\beta V_{\text{Na}}^0 = 10$  and  $\beta V_{\text{K}}^0 = 1$ . Plot the voltage  $V(t)$  as function of the time steps for each situation. What do you observe? Why doesn't the voltage settle at the same place as in Exercise 7.1? (*The answer to this last question is a nice place to show your understanding of the involved physics, and I suggest that you answer this question as detailed as you can manage.*)

## 8 Programming

### *Simulating the action potential*

We will now include voltage-controlled membrane potentials in our model. Let  $V_{\text{Na}}(x, t)$  and  $V_{\text{K}}(x, t)$  now be time-dependent potentials modelling the voltage-

controlled  $\text{Na}^+$  and  $\text{K}^+$  gates. We describe the time dependence of the potentials with the following text:

The starting voltage is about  $-70$  mV (use the initial ion concentrations given above). Both channels are initially closed, enforced by setting  $V_{\text{Na}}(x) = V_{\text{Na}}^0$  and  $V_{\text{K}}(x) = V_{\text{K}}^0$  inside the cell wall,  $-h < x < h$ . However, when  $V(t) \leq -70$  mV (that is, instantaneously), the sodium gate potential is lowered to  $V_{\text{open}}$  within the membrane, allowing sodium ions to stream into the cell interior. When the membrane voltage reaches  $30$  mV, the sodium channels are closed by setting  $V_{\text{Na}} = V_{\text{Na}}^0$  inside the membrane. Simultaneously, the potassium gates are opened  $V_{\text{K}}(x) = V_{\text{open}}$  between  $-h \leq x \leq h$ . Potassium ions flow out and lower the membrane voltage, until it reaches  $-70$  mV, at which point the potassium gates close and the sodium gates open<sup>3</sup>. The process now starts over again, and runs in a cycle. To start with, we do not include the SPP.

### 8.1 Exercise 8.1 (programming)

Set the closed gate potentials to  $\beta V_{\text{Na}}^0 = \beta V_{\text{K}}^0 = 50$ , and the opened gate potentials to  $\beta V_{\text{open}} = 1$ . Start with the initial concentrations as given in Exercise 7. Follow the description above on how to control the potential. Run the system for 1000 time steps, and plot  $V(t)$ . How many cycles does your system go through before it stops shooting voltage signals? Why does it stop to shoot voltage signals?

### 8.2 Exercise 8.2 (programming)

Now do the simulation in Exercise 8.1 over again, but this time add the sodium-potassium pump. Do this by transporting 2 potassium ions<sup>4</sup> from outside the cell membrane to inside the cell membrane, and 3 sodium ions from the inside the cell membrane to outside the cell membrane, for every 10th time step. Run the simulation for 5000 time steps. Does the cycle stop now, or does it seem to continue to run? Why? *Note that if there are too few potassium ions outside the cell ( $< 2$ ), or too few sodium ions inside the cell ( $< 3$ ), you have to make sure that the SSP does not run. That is, if there for instance are too few available sodium ions, you should stop pumping potassium ions as well. In this case, wait until there are sufficient amounts of ions at the right place to run the pump, and then wait for another 10 time steps to run the pump again.*

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<sup>3</sup>In reality, the sodium gates open at about  $-55$  mV, and the cell therefore requires electric stimuli for the action potential to be released. In order not to overcomplicate the model, we have chosen not to include an external electric stimuli in the model. Instead, we program the cells to auto-fire the action potential as soon as the resting potential is reached. This can therefore be viewed as a toy model for a pacemaker cell.

<sup>4</sup>Strictly speaking, one particle in your simulation does not represent an ion, but rather it represents  $0.1$  mM. In other words, when simulating the SPP, transport  $0.3$  mM sodium out of the cell and  $0.2$  mM potassium into the cell.