Project 2 for INF 5610 fall 2007

October 8, 2008

Goals for the project

This project consists of two parts. In Part one we will examine the effect of changing parameters in the models for electrical activity in the cells. The model used will be the Beeler-Reuter model, which was the first model for electrical activity in ventricular cells. In Part two we will study how the cells react to repeated electrical stimuli. These properties are central both in development and treatment of a number of heart arrhythmias.

One must deliver a detailed written report with figures describing the most important results.

Deadline: 17.11.2008 at 12.00.

Questions about the project goes to `sundnes@simula.no`.

Description of the Beeler-Reuter model

In this section we give a complete specification of the Beeler-Reuter model. It is not necessary to understand all details of the model in order to complete the project.

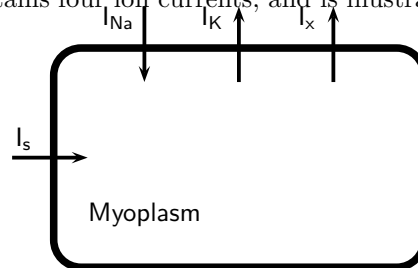The model contains four ion currents, and is illustrated in Figure 1.

Figure 1: Ion currents in the Beeler-Reuter model.

The equations for the model are

$$-C_m \frac{dV}{dt} = I_{\text{Na}} + I_{\text{K}} + I_x + I_s + I_{app}$$

$$\frac{dc}{dt} = 0.07(1 - c) - I_s$$

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m$$

$$\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h$$

$$\frac{dj}{dt} = \alpha_j(1 - j) - \beta_j j$$

$$\frac{dk}{dt} = \alpha_k(1 - k) - \beta_k k$$

$$\frac{df}{dt} = \alpha_f(1 - f) - \beta_f f$$

$$\frac{dx}{dt} = \alpha_x(1 - x) - \beta_x x$$

$$(1)$$

The ion currents are given by

$$I_{\text{Na}} = (4m^3 hj + 0.003)(V - 50),$$

$$I_{\text{K}} = 1.4 \frac{\exp(0.04(V + 85)) - 1}{\exp(0.08(V + 53)) + \exp(0.04(V + 53))},$$

$$I_x = 0.8x \frac{\exp(0.04(V + 77)) - 1}{\exp(0.04(V + 35))},$$

$$I_s = 0.09fk(V + 66.18 + 13.0287\ln[\text{Ca}]_i),$$

and all the rate functions (α and β) are of the form

$$\alpha_m = \frac{C_1 \exp(C_2(V - V_0)) + C_3(V - V_0)}{1 + C_4 \exp(C_5(V - V_0))}.$$

The constants $C_1, \ldots, C_5$ and V_0 for each of the functions are specified in Table 1.

Part 1

Exercise 1: Upstroke velocity

We want to study how the action potential in the Beeler-Reuter model depends on the different parameters in the model. We are especially interested in how the maximum upstroke velocity changes when we change equilibrium potentials E_K and E_{Na}, as well as the maximum conductance values $\bar{g}_K$ and $\bar{g}_{Na}$. The upstroke

	C_1	C_2	C_3	C_4	C_5	v_0
α_m	0	-	1.0	-1.0	-0.1	-47.0
β_m	40	-0.5599	0	0	-	-72
α_h	0.126	-0.25	0	0	-	-77
β_h	1.7	0	0	1	-0.082	-22.5
α_j	0.055	-0.25	0	1	-0.2	-78.0
β_j	0.3	0	0	1.0	-0.1	-32
α_k	0.095	-0.01	0	1.0	-0.0719	5.0
β_k	0.07	-0.0171	0	1.0	0.05	-44
α_f	0.012	-125.0	0.0	1.0	0.15	-28.0
β_f	0.0065	-0.02	0	1.0	-5.0	-30.0
α_x	0.0005	-0.0833	0	1.0	0.0571	-50.0
β_x	0.0013	-0.06	0	1.0	0.04	-20.0

Table 1: Constants for the rate functions in the Beeler-Reuter model

velocity is defined as the time derivative of the transmembrane potential in the upstroke phase of the action potential.

On the course web-page you will find the matlab functions run_single.m and ds_dt.m. The command to run in matlab is run_single.m, while the model is specified in ds_dt.m. The equilibrium potentials E_K and E_{Na} and conductance values $\bar{g}_K$ and $\bar{g}_{Na}$ are input parameters to the function run_single.m. Normal choices for these parameters are

$$E_{Na} = 50, \quad \bar{g}_{Na} = 4.0,$$
$$E_K = -85, \quad \bar{g}_K = 0.35,$$

which are obtained with the following matlab command
[u,t,s] = run_single(50,-85,4,0.35);
Here u is the maximum upstroke velocity, t is time and s are the state variables of the model. The command plot(t,S(:,1)) gives a plot of variable 1 (the transmembrane potential).

(a) Make changes in the equilibrium potentials E_K and E_{Na} (eK and eNa in run_single.m). Make figures that show the connection between each of the parameters and the upstroke velocity.

(b) Make similar changes in the conductance values $\bar{g}_K$ and $\bar{g}_{Na}$. Again make figures showing the changes in upstroke velocity as the two values are altered.

(c) Discuss briefly the results from exercise a) and b). Try to explain the relations between the different parameters and the upstroke velocity.

Exercise 2: Propagation velocity

In this exercise we will study how changes in the upstroke velocity affect the conduction velocity for the electric signal. We look at a monodomain model of the form

$$\frac{\partial V}{\partial t} + I_{ion} = \nabla \cdot (\sigma \nabla V), \tag{2}$$

where the ionic current I_{ion} is calculated using the Beeler-Reuter model. Matlab code for this model is found in the file run.m, which can be found on the course web site. Download the file to the same directory as ds_dt.m. In addition to plotting the solution for every time step, a time series is plotted from the point (0,0). (Since the action potential lasts about 300ms we need to run the simulation quite long to get plots of the complete action potential. For this project we are mostly interested in the activation, and we save a lot of computing time by just simulating a part of the interval.)

(a) A simulation with standard parameter choices is started with the command

    v = run(50,-85,4,0.35)

    Make changes in the conductances and equilibrium potentials, and observe how this changes the solution. Illustrate the changes with plots of the membrane potential V at different time steps. (In order to save these plots you need to edit the matlab code, either by changing the end time of the simulation or by adding a couple of lines that writes the plots to a file at given time steps.)

(b) The time series from the point (0,0) can be used to estimate the activation time for this point. To have a precise definition of the activation time, we can use the time point when the membrane potential turns positive. Use the activation time and the distance from the center of the computational domain to estimate the conduction velocity. The unit for distance is centimeters, while time is given in milliseconds. The simulations will not give physiologically realistic conduction velocities. Show figures where the conduction velocity is plotted against the two parameters from (a). Discuss the results.

Part 2

In this part of the project we will study the refractory period of the cells. The refractory period is the interval after electrical activation where it is not possible to initiate a new action potential. The refractory period is important for rythm disturbances in the heart. Conditions such as ischemic heart disease change the refractory period in parts of the muscle, and this is important for the development of arrhythmias during ischemic heart disease and acute infarctions. Anti-arrhythmic drugs also frequently work by changing the refractory period of the cells.

As for the first part of the project we will first do experiments for single cells, and then look at some results in 2D. The model and Matlab code to be used is the same as in Part 1.

Exercise 3: Refractory cells

In the program code `run_single.m` it is possible to specify two stimulus currents; $s1$ and $s2$.

(a) Do experiments with different time points for the $s2$ current, and find an estimate for the refractory period of the cell. To do this you also need to change the end time for the simulation in `run_single.m`, for instance to 1000 ms. Plot the values of the state variables of the models, and see if you can relate the refractory period to the dynamics of these variables. (Hint: The excitability of the cell is mostly related to the fast sodium current.)

(b) Try to increase the maximum conductance for potassium ($\bar{g}_K$). What effect do you see on the action potential duration? What about the refractory period.?

Exercise 4: Re-entry

Normal heart rythm depends on each signal to propagate from the sinoatrial (SA) node, activate the complete heart muscle, and then vanish, to leave the heart ready for a new activation from the SA node. This means that each signal must only activate a specific region of the heart once. The opposite may, however, occur, and is called re-entry. The 2D simulations in Excercise 1 showed an example of normal activation. An even simpler activation pattern is obtained by replacing the lines
```
Q = round(3*n/8):round(5*n/8);
q = length(Q)
S(Q,Q,1) = -20*ones(q,q); % adds a peak in v in the center
mesh(S(:,:,1))
```

in the Matlab code with
```
Q = round(n/2):n;
q = length(Q)
S(Q,Q,1) = -20*ones(q,q); % adds a peak in the upper right corner
mesh(S(:,:,1))
```

(a) Run experiments with this initial condition. What happens? What will you see if you run the simulation longer (> 500ms)? (It is not recommended that you actually do this simulation, as it will be very time consuming, but it should be possible to guess the answer.)

5

(b) Certain heart conditions, such as ischemia, results in a refractory period that is markedly different in different parts of the heart. We can simulate the effect of this by adding the lines

```
R = 1:round(n/2);
r = length(R)
S(R,:,6) = zeros(r,n); % sets state var 6 to zero for x < 0.5
figure(2)
mesh(S(:,:,6))
figure(1)
```

at a suitable place in the file `run.m`. Run a simulation with the parameter choices

```
v = run(50,-85,8,1) .
```

What happens? To see any interesting effects you will have to change the end time for the simulation, for instance to 30 or 50 ms. (Or preferably even longer if you are using a fast computer or have a good portion of patience.) Show plots of V at suitable time points.

Try to explain what happends with the signal from what you know about the refractory period. (Hint: For $v \approx v_{eq}$, $j = 0$ is not an equilibrium condition for the gate variable j. When v is close to the resting potential j will therefore approach 1 fairly quickly, so that the cell is no longer refractory.)

(c) What you saw (or should have seen) in (b) was the start of a spiral wave, which is a simple form of re-entry. Instead of activating the whole domain once and thereafter dying, this wave will go on for ever and activate the tissue repeatedly. In a real heart such a wave may give a condition known as *flutter*, which typically gives a heart rate of 200-400 beats per minute. The spiral wave may also break up into smaller waves and give a condition known as *fibrillation*. This is a condition where the electrical activity is completely chaotic, with multiple spiral waves continuously being generated and extinguished.

The acute treatment for fibrillation is to apply a strong electric shock (*defibrillation*) to the heart. This shock will often extinguish the chaotic activity, and leave the heart able to be activated from the SA node. Re-entrant arrhythmias can also be treated with drugs that change the electrical properties of the cells and the tissue. Discuss what kind of changes you would expect ot see from the following changes:

- Increase or reduction of the refractory period of the cell.

- Changes in the conduction velocity, for instance as a consequence of altered upstroke velocity or changes in the conductivity.