Practice

Action Potential of purkinje fibers

Jesús Carro

Modeling with ODEs

ThinkBS

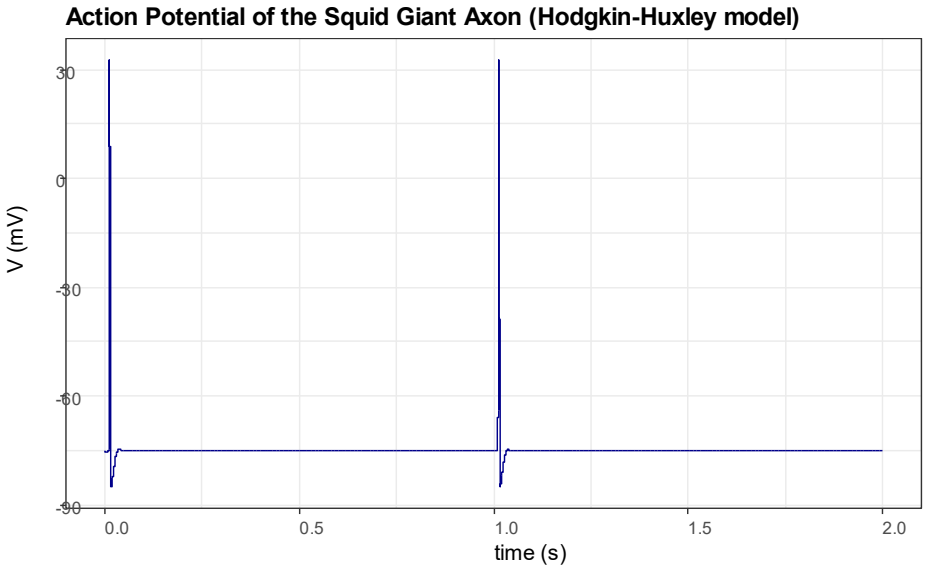
INTRODUCTION

We are in 1960. A research group in experimental electrophysiology, lead by Denis Noble, has been able to isolate mammalian purkinje fibers and to study their electrophysiological properties. They want to develop a new mathematical model, like the one proposed by Hodgkin and Huxley in 1952 for the squid axon. They want to be able to test different hypothesis with it, before performing new experiments in cells. They perfectly understand the results of the experiments, and their knowledge of the experimental part is enough to transform their results into equations, but they are not able to simulate them in a computer (they are in 1960).

After several steps of data analysis and experimental test, the research group of Denis Noble has the model of the Purkinje fibers. In this practice you will put all the information together to create the new model and you will use ODE solvers to analyze it.

> ***Important**: Remember that you are using a very simple model developed in the sixties. Be careful with the conclusions you obtain from your model to understand how these cells work.*
>
> *The model used is the one developed by Denis Noble in 1960. The model and its limitations are described in https://models.cellml.org/e/2a6*
> *and the paper can be found in*
> *https://physoc.onlinelibrary.wiley.com/doi/pdf/10.1113/jphysiol.1962.sp006849*

On the ThikBS platform, you can get a file that simulates the Hodgkin and Huxley model (`HH_model.R`). You can use this model as start point for your Purkinje model. The Action potential obtained with the model proposed by Hodgkin and Huxley is graphically represented in the Figure 1.



FIRST PART: MODEL DEVELOPMENT

The AP of a purkinje cell and the one of an axon have different properties, but the structure of the model is very similar. We will use the same structure, but you will need to add more currents to the model. Save the `HH_model.R` file with a new name to modify it; after several modifications of this file, you will get the AP model of the purkinje cells.

1.1. The cell capacity

The experimentalists have measured the cardiac conductance of the purkinje cells, and it differs from the axon cells. For purkinje cells, $C_m = 12\ \mu F$. Modify the capacity in your model. After this modification, your model won't be able to generate APs. Do not worry about this until the end of this part.

1.2. The leakage current (I_L)

You must modify this current to use the values of E_L and G_L obtained this type of cell: -60 and 75 respectively.

1.3. The sodium currents

With the information of the experiments, other researchers deduced that there are two sodium currents: one similar to the one detected in the axon, and another background current.

Add the $I_{Na,bk}$ background current (remember to include this current when $\frac{dV}{dt}$ is calculated):

$$I_{Na,bk} = G_{Na,bk} \cdot (V - E_{Na})$$

$$G_{Na,bk} = 140$$

Modify the I_{Na} current to the new one developed by the other group:

$$I_{Na} = G_{Na} \cdot m^3 \cdot h \cdot (V - E_{Na})$$

$$G_{Na} = 400000$$

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

$$\alpha_m = -100 \cdot \frac{V + 48}{e^{-\frac{V+48}{15}} - 1}$$

$$\beta_m = 120 \cdot \frac{V + 8}{e^{\frac{V+8}{5}} - 1}$$

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

$$\alpha_h = 170 \cdot e^{-\frac{V+90}{20}}$$

$$\beta_h = \frac{1000}{e^{-\frac{V+42}{10}} + 1}$$

1.4. The potassium currents

The purkinje cells have two potassium currents. You need to transform I_K in the addition of these two ones: $I_K = I_{K1} + I_{K2}$.

Set E_K to the value of -100.

The I_{K1} is defined by:

$$I_{K1} = G_K \left(e^{\frac{-V-90}{50}} + 0.0125 \cdot e^{\frac{V+90}{60}} \right) \cdot (V - E_K)$$

$$G_K = 1200$$

The I_{K2} is defined by:

$$I_{K2} = G_K \cdot n^4 \cdot (V - E_K)$$

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

$$\alpha_n = -0.1 \cdot \frac{V + 50}{e^{-\frac{V+50}{10}} - 1}$$

$$\beta_n = 2 \cdot e^{-\frac{V+90}{80}}$$

1.5. The stimulation current

After all the modifications, the model should be self-stimulated. Under control conditions, the stimulation current is not necessary. You can set it to 0. Do not remove it, under some conditions, it could be useful. We will use it in the last practice.

1.6. Result of the model

Once your model is complete, you should get something like the Figure 2. You could have some differences depending on the results of your dataset.

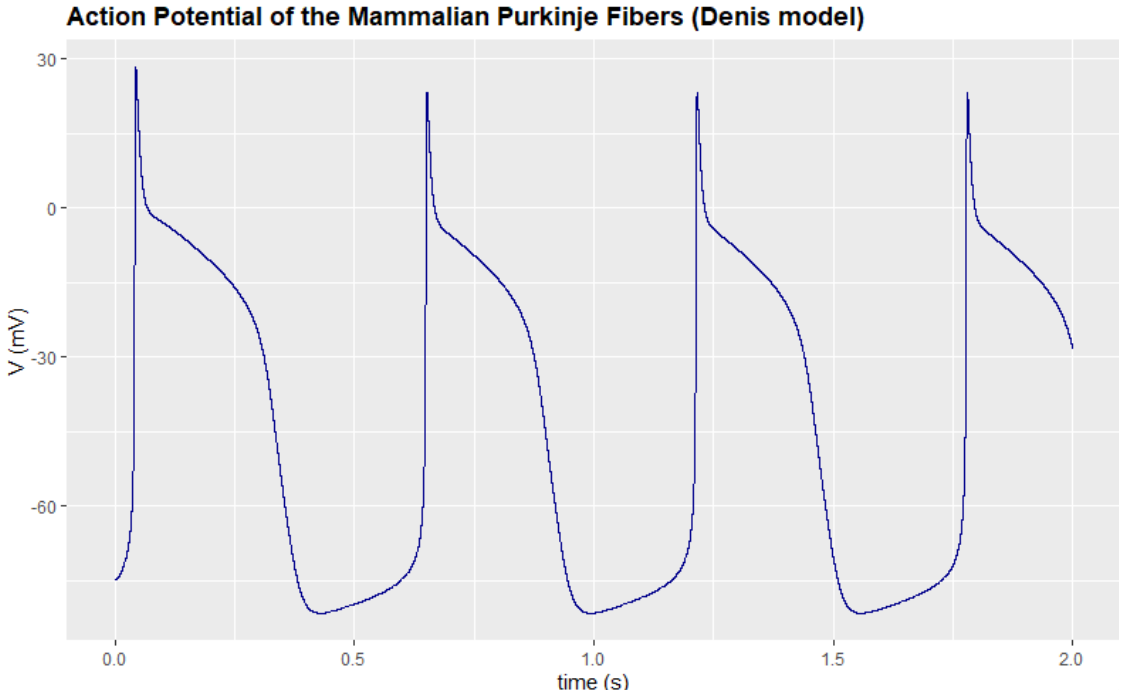


Figure 2. Action potential of the Purkinje cells. Simulated Action potential with the new model.

SECOND PART: MODEL ANALYSIS

Now, you have a new model that can simulate the AP and you can analyze its behavior.

Exercise 1. Evaluate the maximum time step that you can use with the Forward Euler solver. You can calculate it graphically. To do it, calculate the result with one Δt and the half of that Δt. Plot both together, and, if you see differences, divide the first Δt by two and repeat the process until you are not able to see differences.

Exercise 2. Evaluate the maximum time step that you can use with the four-order Runge-Kutta solver. You can calculate it graphically. Comment you result.

Optional – Calculate the maximum time step as the one in which the mean square error of **V** with respect to the previous one is smaller than 0.001. If the error is bigger than 0.001, decrease **dt** by dividing it by two.

1.7. Modification of the current conductances

As you have seen in the previous practice, different cells have different value for the conductances of the currents. To evaluate how it affects to the AP, you need to modify your model:

- Add 3 parameters to the model: $A_K, A_{Na}, A_{Na,bk}, A_L$
- Modify each conductance to include these parameters. E.g.:

```
G_L <- 75 * A_L
```

- By default, this value should be 1. If you change it, you will modify the value of the conductance. E.g. If you set $A_L = 1.05$, you are increasing the conductance of I_L by a 5%.

Exercise 3. Simulate 10 seconds of V by varying one by one the conductance of the current by $\pm 5\%$, $\pm 2.5\%$ and 0%. Plot the simulations of the variations of the same current in the same graph and each different current in a different graph. Comment your results.

1.8. Modification of the extracellular potassium

Action potential models are useful to simulate pathological conditions. For example, we can study what happens under Hyperkalemia (one of the effects of the Ischemia). Modify your model to add a new parameter, $[K^+]_o$. Remember that:

$$E_K = -\frac{RT}{F} ln\left(\frac{[K^+]_i}{[K^+]_o}\right)$$

- Calculate the value of $[K^+]_i$ under control conditions. Remember that under control conditions $[K^+]_o = 5.4$, $R = 8314 \frac{C \cdot mV}{K \cdot mol}, T = 310\ K, F = 96485\ C/mol$
- Modify your model to include the previous equation to calculate E_K.

Exercise 4. Simulate 10 seconds of V for different values of $[K^+]_o$ from 5 to 7 mM in steps of 0.4 mM. Plot all the simulations in the same graph. Comment the results.

OPTIONAL PART: ODE SOLVERS

You can get extra points if you simulate your model with your own solver instead of using the one provided by `deSolve`:

- Fordward Euler solver
- Second-order Runge-Kutta solver.