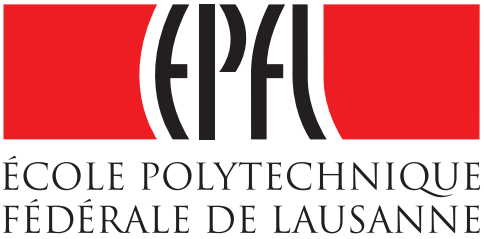


ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

EPFL Semester Project – Spring 2016

0.8cm

Explicit stabilized methods for numerical integration of Neuron's equations[0.4cm]

Author:
[1.5cm] Nicolò Ripamonti
Sciper n. ??????

Supervisors:
Prenom1 Nom1
Prenom2 Nom2

Responsible:
Prof. Prenom Nom

May 3, 2016

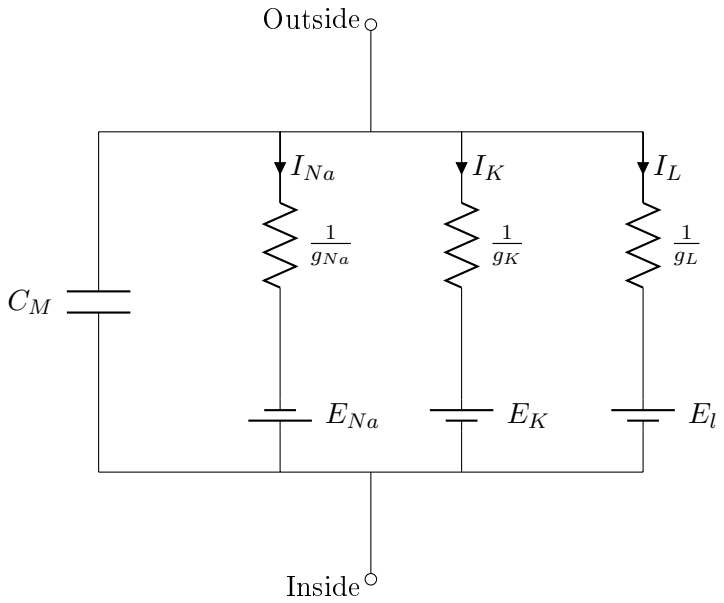
Contents

Chapter 1

Biological model

1.1 Hodgkin-Huxley work

Experimental results show that the process of depolarization of the surface membrane of a nerve fibre could be described by an equivalent electrical circuit.



It is important to underline that Hodgkin and Huxley come to this model not by describing the molecular events related to changes in permeability but they were driven by some questions regarding the general behaviour of cellular membrane[**main_paper_HH**]. Their starting assumption, verified later by data, was that membrane permeability is influenced by membrane potential and not by membrane current: a straightforward consequence is that the main contribution is the effect of electric fields on distribution of

charged particles. This result makes clear the importance of describing the mechanism of ions crossing of the membrane, in particular sodium and potassium: unfortunately, at their time, they were only able to reject previously accepted assumptions and models but thanks to a exaustive study of nerve cells of squid giant axon, they got a more in-depth view of some properties of the membrane, like the steep relation between its potential and the ionic conductance. Basically what happens is that even a small change in the potential is followed by a e-fold increase in g_{K} and g_{Na} (ionic conductances of sodium and potassium): the effect of this phenomena is of great importance since it affects the difference in ionic concentration between the inside of the cell and the extracellular liquid which in its turn generates a Nerst's potential that could be represented as a battery in the simplified circuit. Another observed property is the behaviour of the membrane with respect to an imbalance between input and output current, i.e. more positive charges enter the cell than leave it or viceversa, which made them think that capacitive effects come into play to change membrane potential, which polarise or depolarise according to the change in the total charge. All these observations, combined with their previous hypothesis, were used to build a solid theoretical framework from which a set of equations could be developed.

1.2 Mathematical description

The total membrane current could be divided into a capacity current (modeled with a perfect condenser without dielectric loss) and an ionic current. Thus

$$I = C_M \frac{\partial V}{\partial t} + I_i, \tag{1.1}$$

where

- I is the total membrane current density
- I_i is the ionic current density
- V is the displacement of membrane potential from its resting value
- C_M is the membrane capacity per unit area
- t is the time

The choice of model the currents in parallel is due to the similarity between ionic current when $\frac{dV}{dt} = 0$ and the capacity current when $I = 0$. This model is enriched by identifying the different contributions for the ionic current as follow

$$I_i = I_{\mathrm{Na}} + I_{\mathrm{K}} + I_{\mathrm{L}},$$

where I_{Na},I_{K} and I_{L} are the components carried by different ions channels. Using Ohm's law, expressed in term of conductance (i.e. $I = gV$), results in

$$I_i = g_{\mathrm{Na}}(V - V_{\mathrm{Na}}) + g_{\mathrm{K}}(V - V_{\mathrm{K}}) + g_{\mathrm{L}}(V - V_{\mathrm{L}}),$$

in which V,V_{Na},V_{K} and V_{L} are the displacements from resting potentials. One thing to notice is that the individual ionic contribution can be positive or negative depending on the relation between the membrane voltage and the ionic potential: this can be a problem of sign conventions, which is solved by setting positive a ionic current flowing out of the cell. As said before, the conductance of sodium and potassium channel show a strong dependence on membrane potential, while G_{L} is usually taken as a constant: this is called leakage conductance and its value is smaller than the voltage-dependent conductances. Although Hodgkin and Huxley did not know the complex mechanism behind the rise and fall of ionic conductances, they were were able to reconstruct this relation by fitting their experimental results.

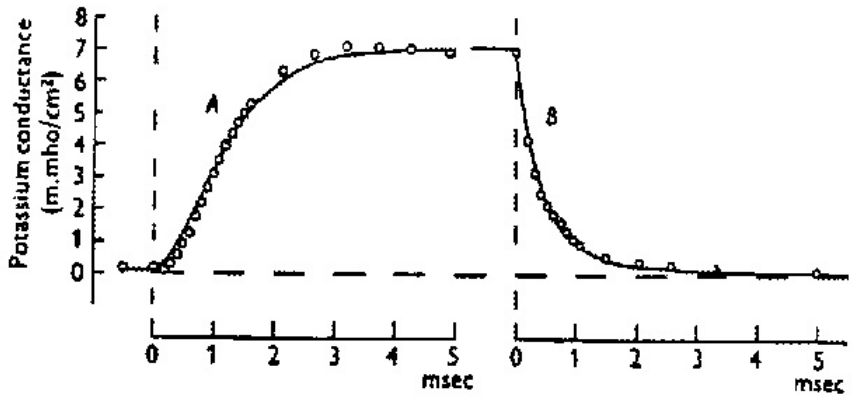


Figure 1.1: Rise and fall of potassium conductance associated with a depolarization and a polarization of 25mV

Without any first principles avalaible they noticed that the potassium conductance is proportional to the fourth power of the solution of a first order equation in the following sense

$$\begin{aligned} g_{\mathrm{K}} &= \bar{g}_{\mathrm{K}} n^4, \\ \frac{dn}{dt} &= \alpha_n(1-n) - \beta_n n, \end{aligned} \tag{1.2}$$

where $\bar{g}_{\mathrm{K}}$ has the dimension of a conductance/cm^2, α_n and β_n are constant with respect to time but depend on membrane potential, n is a dimensionless variable constrained between 0 and 1. In the resting state, i.e. V = 0, n has the value

$$n_0 = \frac{\alpha_n|_{V=0}}{\alpha_n|_{V=0} + \beta_n|_{V=0}}.$$

In order to obtain an explicit formulation for α_n and β_n, a lot of their measuraments had been taken in different temperatures, ionic concentrations

and membrane potential configurations and then plotted against the resting potential V to give the following result

$$\alpha_n = 0.01 \frac{\mathrm{V}+10}{e^{\frac{\mathrm{V}+10}{10}} - 1},$$
$$\beta_n = 0.125 e^{\frac{\mathrm{V}}{80}},$$

with α_n and β_n measured in ms and V in mV. What they noticed is that during the depolarisation phase the change in g_{K} has sigmmoid shape, while the polarisation phase behaves as a decaying exponential: this situations are captured very well by α_n and β_n respectively. The fourth power that relates n to g_{K} is related to the number of first-order processes that have to occur in order to have the desired curvature of the sigmoid function: more numerous they are, more steep the shape will be. This is compatible with their educated guess (verified several years later) that each ionic channel contains several gates, and all of them have to be open in order to have an open channel (and so a sigmoid depolarisation) but it is enough that one of them is closed to shut the channel (and so an decaying exponential polarisation). After this physical explanation, n can be interpreted as the probability for a given gate to be open: if we extend this to the more realistic case of a large number of channels, it becomes the fraction of the total number of gates that are in the permessive state (N.B. The definitiion of permissive/non-permissive state of the gate is a little bit different from the definition of open/close and it was given later than [**main_paper_HH**], but still today α and β represents the transition between this two states).
Regarding the sodium conductance, the procedure followed was only slightly different from the one adopted for the potassium. As before the idea is that the conductance is related to a certain number of first order process, but while for the potassium these processes are all of the same kind, described by the gate state n, now we have two different variables that come into play. This led them to the following assumptions:

$$g_{\mathrm{Na}} = m^3 h \bar{g}_{\mathrm{Na}},$$
$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m, \tag{1.3}$$
$$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h h, \tag{1.4}$$

where $\bar{g}_{\mathrm{Na}}$ is a constant and the α's and β's depend on V but not on time. Here h plays the opposite role of what is n for the potassium case: for it being open means that the channel is inactive and we have the polarisation phase. m instead behaves exactly as n, with the only difference that here we have that the experimental steepness of the relation between gate conductance and membrane potential is reached by considering only 3 of this gates instead of 4 as before. However, even if all these "activating" gates m are open, if the

"inactivating" gate h is open the channel stays closed. The initial states for the first-order equations describing the transition rates are again

$$m_0 = \frac{\alpha_m|_{V=0}}{\alpha_m|_{V=0} + \beta_m|_{V=0}},$$
$$h_0 = \frac{\alpha_h|_{V=0}}{\alpha_h|_{V=0} + \beta_h|_{V=0}}.$$

Now that we have all the coefficients, we can rewrite (1.1) as

$$I = C_M \frac{\partial V}{\partial t} + \bar{g}_{\mathrm{K}} n^4 (V - V_{\mathrm{K}}) + \bar{g}_{\mathrm{Na}} m^3 h (V - V_{\mathrm{Na}}) + \bar{g}_{\mathrm{L}} (V - V_{\mathrm{L}}). \quad (1.5)$$

For the cable approximation of the axon, which is surrounded by a large amount of conducting fluid, the membrane current, in the case of a propagated action potential, is related to V by the following electrostatical relation

$$I = \frac{1}{2aR} \frac{\partial}{\partial x} \left(a^2 \frac{\partial V}{\partial x} \right),$$

where R is the cytoplasmatic resistivity and a the axon radius, which can vary along the cable. Hence, after rearranging equation (1.5) to take into account unit measures used for experimental setting, we get to

$$\begin{aligned} 10^{-3} C_M \frac{\partial V}{\partial t} =& \frac{10^4}{2aR} \frac{\partial}{\partial x} \left(a^2 \frac{\partial V}{\partial x} \right) \\ & - \bar{g}_{\mathrm{K}} n^4 (V - V_{\mathrm{K}}) - \bar{g}_{\mathrm{Na}} m^3 h (V - V_{\mathrm{Na}}) - \bar{g}_{\mathrm{L}} (V - V_{\mathrm{L}}) \\ & - \frac{10^2 g_{syn} y}{2\pi a} \delta_{syn}(x)(V - V_{syn}), \end{aligned} \quad (1.6)$$

in which the most simple modelization of synaptic interaction is considered ($g_{syn}(y)$), depending only on the synaptic receptor state y evolving as

$$y(t) = \frac{t - t_{off}}{\tau} e^{\left(-\frac{t - t_{off} - \tau}{\tau}\right)}$$

This is a simple, yet effective, description of an incoming spike in the potential, able to capture the substance of synaptic mechanisms, but also to allow a fast and efficient computation, required in the case of a large neural networks.

1.3 Domain and boundary conditions

The problem described in the previous chapter is solved on a domain which can be schematized on a domain as the one represented in figure 1.2. The unbranched sections of the neuron are represented as 1D segments, an approximation due to the difference between length and thickness of each branch:

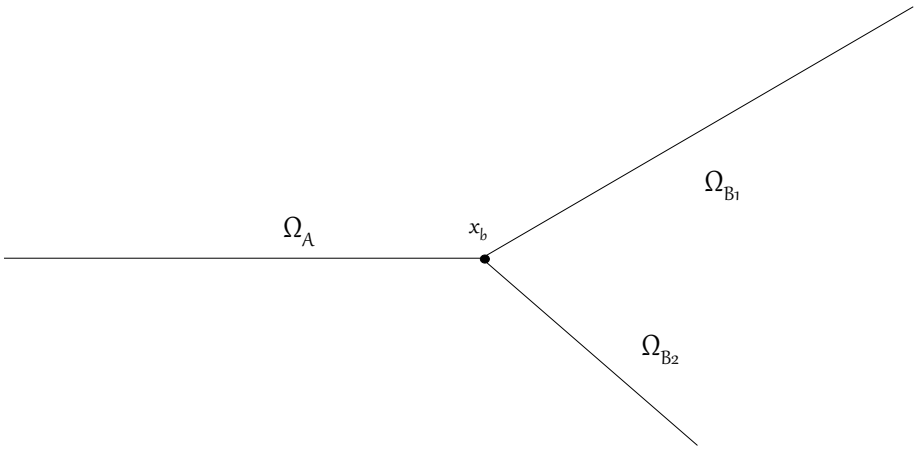


Figure 1.2: Dendritic tree with a branching node.

this involves that all the variables considered are function of the axial abscissa along the cable but not of the radial distance from the center. This model is acceptable if the real radius, even if variable, show only relative deviations with respect to its mean value: some problem may occur if, for instance, we consider a tapered dendrite.
To set the boundary conditions and so complete the definition of the problem, electrostatic consideration are needed: the current between two points x and $x + \Delta x$ is proportional to the voltage difference and the inverse of membrane resistance, thus

$$I(x) = \frac{\pi a^2}{R} \frac{V(x - \Delta x) - V(x)}{\Delta x},$$

and by taking the limit $\Delta x \to 0$ we have

$$I(x) = \frac{\pi a^2}{R} \frac{\partial V}{\partial x}.$$

In the branching node, Kirchoff's law regarding conservation of the current states that

$$\sum_{x_b} I = \left(a^2 \frac{\partial V}{\partial x} \right) \Big|_{x=x_b}^{A} - \left(a^2 \frac{\partial V}{\partial x} \right) \Big|_{x=x_b}^{B_1} - \left(a^2 \frac{\partial V}{\partial x} \right) \Big|_{x=x_b}^{B_2} = 0,$$

which is chosen as boundary condition in the branching node x_b.
On the terminal points is assumed that no current flows outside or inside, giving Neumann homogenous conditions

$$\frac{\partial V}{\partial x} = 0.$$

Chapter 2

Spatial discretization

2.1 Finite differences

The partial differential equation (1.6),(1.2),(1.3) and (1.4) are replaced by a system of ODEs, using the technique called method of lines. The idea is to approximate the spatial derivatives of the problem with algebraic approximations. First we need to define a mesh: on the unbranched regions of the dendrite a uniform mesh with spacing h is used, except for the elements near the boundary for which is reduced to $\frac{h}{2}$ (TODO: spiega perchè è più fine sul bordo, motivi di convergenza e chiedi a Francesco il motivo bio).

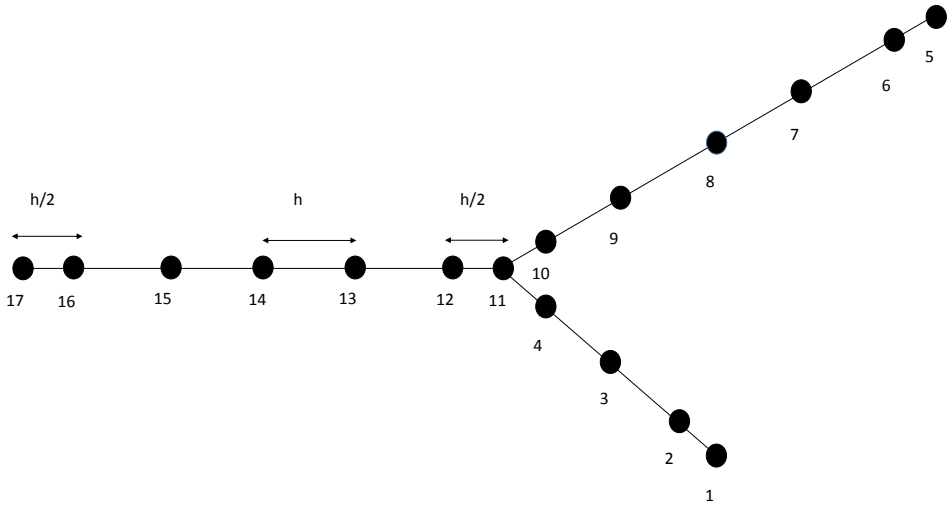


Figure 2.1: Example of mesh used

A possible starting point for the discretization is to look at finite differences centered at each point x_j of the mesh: for the points far from

boundaries the following standard results for uniform grid can be used

$$\frac{\partial f}{\partial x} = \frac{f(x + \frac{\Delta x}{2}) - f(x - \frac{\Delta x}{2})}{\Delta x} + \mathcal{O}((\Delta x)^2),$$

which is a second order centered approximation of the first order derivative of a function. By applying this form twice in the diffusive term of (1.6) we get to

$$\frac{\partial}{\partial x}\left(a^2 \frac{\partial V}{\partial x}\right) \approx a^2 \frac{V(x + \Delta x) - 2V(x) + V(x - \Delta x)}{(\Delta x)^2},$$

in the case of a constant.
Near the terminal and ending nodes the situation is more subtle because of the nonuniformity of the grid and so we need to go more in depth with Taylor series: we report, as example, the case of the last node of the branch Ω_A.

Figure 2.2: Local region in the middle of the mesh (left) and near the terminal point of the branch Ω_A (right)

Consider

$$f(x_{j+\frac{1}{2}}) = f(x_j) + \frac{\partial f}{\partial x}(x)\bigg|_{x=x_j} \frac{\Delta x}{2} + \frac{\partial^2 f}{\partial x^2}(x)\bigg|_{x=x_j} \left(\frac{\Delta x}{2}\right)^2 + \mathcal{O}((\Delta x)^3),$$

$$f(x_{j-\frac{1}{2}}) = f(x_j) - \frac{\partial f}{\partial x}(x)\bigg|_{x=x_j} \frac{\Delta x}{4} + \frac{\partial^2 f}{\partial x^2}(x)\bigg|_{x=x_j} \left(\frac{\Delta x}{4}\right)^2 + \mathcal{O}((\Delta x)^3),$$

and by combining them you get

$$\frac{\partial f}{\partial x}(x)\bigg|_{x=x_j} = \frac{f(x_{j+\frac{1}{2}}) + 3f(x_j) - 4f(x_{j-\frac{1}{2}})}{\frac{3}{2}\Delta x} + \mathcal{O}((\Delta x)^2)$$

2.2 Node enumeration

Chapter 3

Setting of the problem

Cable equation:

$$\begin{aligned} 10^{-3} C_M \frac{\partial V}{\partial t} =& \frac{10^4}{2aR} \frac{\partial}{\partial x} \left(a^2 \frac{\partial V}{\partial x} \right) \\ & - \bar{g}_{\mathrm{K}} n^4 (V - V_{\mathrm{K}}) - \bar{g}_{\mathrm{Na}} m^3 h (V - V_{\mathrm{Na}}) - \bar{g}_{\mathrm{L}} (V - V_{\mathrm{L}}) \\ & - \frac{10^2 g_{syn} y}{2\pi a} \delta_{syn}(x)(V - V_{syn}), \end{aligned}$$

Boundary conditions:

- Branching node

$$\left(a^2 \frac{\partial V}{\partial x} \right) \Big|_{x=x_b}^{A} = \left(a^2 \frac{\partial V}{\partial x} \right) \Big|_{x=x_b}^{B_1} + \left(a^2 \frac{\partial V}{\partial x} \right) \Big|_{x=x_b}^{B_2}$$

- Terminal nodes

$$\frac{\partial V}{\partial x} = 0$$

Initial condition:

$$V \Big|_{t=0} = V_0$$

Gate states:

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

Initial conditions

$$n_0 = \frac{\alpha_n|_{V=0}}{\alpha_n|_{V=0} + \beta_n|_{V=0}}$$
$$m_0 = \frac{\alpha_m|_{V=0}}{\alpha_m|_{V=0} + \beta_m|_{V=0}}$$
$$h_0 = \frac{\alpha_h|_{V=0}}{\alpha_h|_{V=0} + \beta_h|_{V=0}}$$