Excitable membranes and Fitzhugh-Nagumo equations

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0.1 Introduction

In neuronal and cardiac tissue, momentary membrane potential impulses are called action potentials and are caused by electrical currents of an ionic nature, which flow through the cell channels of these membranes. The cellular currents examined are divided into two different types, depending on their ionic composition:

1. The 'fast' current (fast-response excitatory variable u) increases as the con- ductance of the membranes increases, by means of the positive ions of Na and Ca. Ergo, these positive ions increase the intensity of the current and thus depotentiate the membrane potential difference (which we assume to be negative).
2. The 'slow' current (slow-response inhibotory variable v) is caused by the delayed response of K- channels, which allow these negative ions to leave the cell, thus causing the recovery phase. Physically, these ion pumps act as batteries to maintain ion concentration gradients between cells.

From a purely mathematical-computational perspective, the equations, and its parameters, that are suitable for describing a system of two variables for the excitation of neuronal and cardiac membranes are the Fitzhugh-Nagumo equations:

$$\frac{du}{dt} = u(u - a)(1 - u) - v + s(t)$$

(0.0)

$$\frac{dv}{dt} = e(u - bv)$$

(0.1)

With the following parameters chosen: $a = 0.15$, $b = 2.5$, $e = 0.01$ (this parameter must be small to represent the slow inhibitory response), $s(t) = 0.01 - 0.06$ (variable source term that within this range simulates a self-stimulated impulse).

From the biological phenomenon of neuronal and cardiac membrane excitations, parallels can be drawn with electronic circuits.

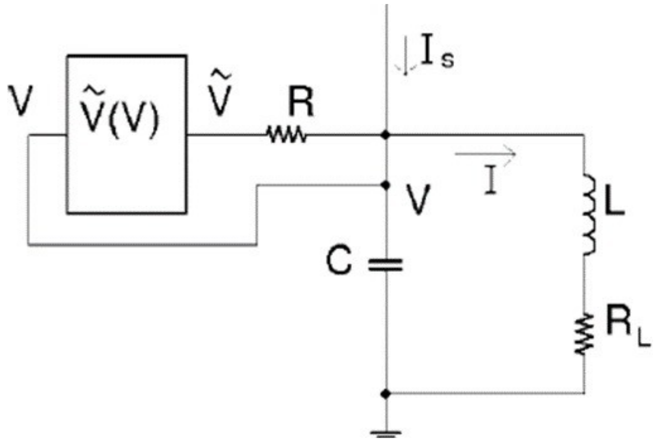
In fact, the aim of this paper will be to describe, in sections 0.2 and 0.3, the excitation of membranes and thus to derive cardiac/neuronal action potentials, by means of two cir- cuital models that differ structurally but are equivalent in their description: the Nagumo circuit and the three-transistor circuit.

To do this, the modus operandi will be to relate the mesh laws of such circuits to the mathematical Fitzhugh-Nagumo equations, emphasising the importance of the choice of parameters, but above all the initial conditions, for the stability of such a model. It should be noted that the practical approach for the realisation of model-circuits, although algorithmically similar, is very different and allows different nuances relating to the same biological topic to be highlighted.

In the last part of the paper, the way in which these cardiac/neuronal impulses are diffused is described, with the analysis of a unit segment of a transmission line between two nodes with different power (to continue the circuit analogy), by means of the well-known diffusion equation.

0.2 Nagumo Circuit

0.2.1 circuit description



1. *C*, the capacitor represents the ability of the cell membrane 'to charge and discharge';
2. *V,*the fast variable *u* , at a fixed membrane resistance, is the capacitor voltage analogous to the membrane potential due to currents charging the capacitor (with Na+ and Ca+ ions);
3. *I*, proportional to the slow variable u, represents the currents discharging the condenser, analogous to the outward potassium membrane currents;
4. *R*,resistance of cellular channels;
5. *L,*represents the solenoid that establishes the induction current *I*.Its value is chosen to make and small;
6. V_g , represents a *V-regulator* circuit. The circuit for generating V_g will not be dealt with computationally, (circuit consisting of two MLT04 multipliers and two ground multipliers) as it is not relevant to the physics of the problem, but is only part of the construction physics of the circuit. What is important to know is that: 1.Produce the voltage V_g , which is a cubic function of the voltage *V*; 2. for reasons of construction and proper delivery of V_g , the Values of *R* and *C* are chosen;

7. *Is, is* a scaling current so that the parameter $s(t)$ is a self-stimulated source term, compatible with the stability and efficiency of the N-F equations, i.e. such that $s(t)$ is between 0.00 and 0.06;
8. R_l , the resistance of the inductor, chosen ad hoc such that b = 2.5.

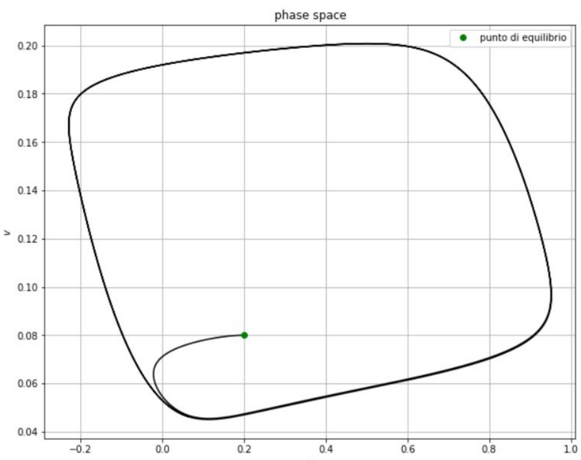
0.2.2 description algorithm applied to the F-N model.

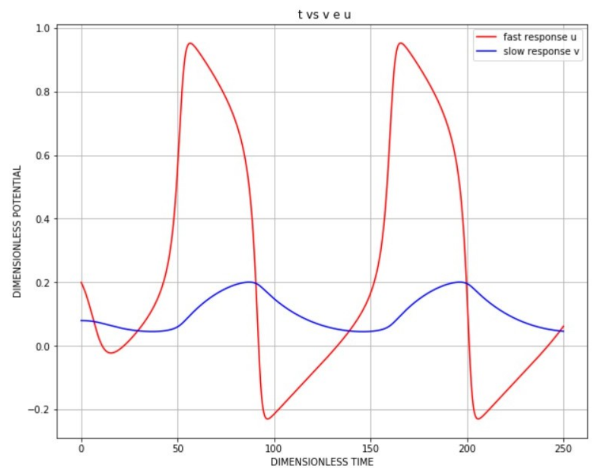
The link equations describing the circuit are as follows:

$$C\frac{dV}{dt} = \frac{Vg - V}{R_s} - I + I_s$$

$$\frac{dI}{dt_s} = \frac{V - IR_l}{L}$$

1. We reconcile these equations, with appropriate parameter changes and substitutions, to the F-N equations $(0.0) and (0.1)$;
2. The values of the circuit components are chosen such that the parameter values of these equations are met (these values are made explicit in the programme);
3. After simplifying the structure of this equation, being a system of first-order coupled differential equations, the Runge-Kutta- Fehlberg algorithm for coupled equations up to sixth order is implemented;
4. After this implementation, plots are made of u Vs v, i.e. the phase space with the fast variable u on the x-axis and the slow variable v on the y-axis;
5. It also plots v VS t and u Vs t , to get a visual image of the impulses related to membrane excitation.





0.2.3 Model stability and initial conditions

This brings us to the heart of the analysis concerning the stability of the F-N equations, relating to the Nagumo circuit. Before doing so, it is only right to recall brief theoretical definitions relating to the concept of equilibrium and stability of a system:

- The equilibrium point of the system is defined as the point of intersection of the trajectories (called nullclines)

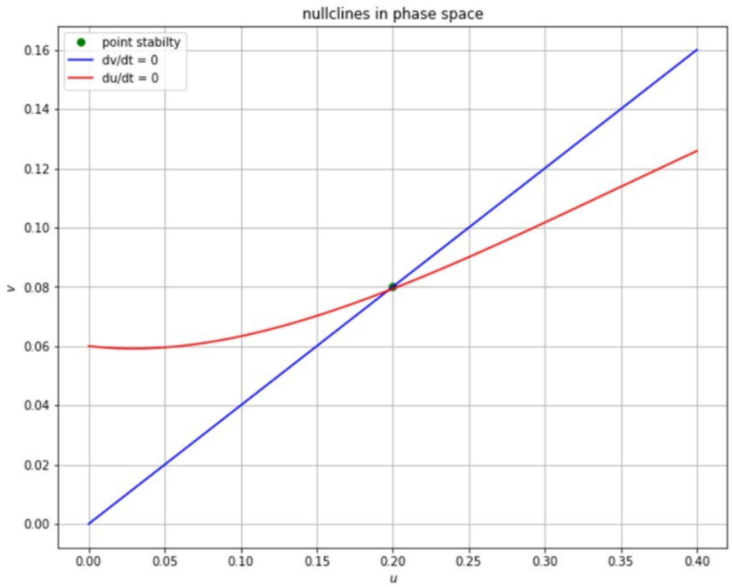
$$\frac{du}{dt} = 0; \frac{dv}{dt} = 0$$

  in phase space.
- An equilibrium point is said to be stable (according to Lyapunov) if every orbit of the system in phase space, which starts sufficiently close to the equilibrium point, remains in the vicinity of the equilibrium point.

The system of equations we are analysing is a non-linear system, so we want to check whether it is stable when the initial conditions vary. Previously we solved the system by choosing a particular initial condition: $t_0 = 0$; $u_0 = 0.2$; $v_0 = 0.08$, the reason for this choice is due to the fact that these points are points of stability of the system, information obtained from the graphical intersection of the nullclines provided by the F-N model:

$$u - (u - a) - (1 - u) - v + s = 0$$
$$e - (u - b - v) = 0$$

Computationally, through the intersection of these trajectories, we obtained the coordinates of the stability point.



If one tries to carry out a variation of the initial conditions, in a circle of the point of equi-booko, one obtains the evidence that the equations of F-N. are very sensitive and therefore not stable with respect to a minimal variation of the initial conditions. This is evident as the orbit in the phase space of *Figure2*, deviates from the course of the initial equilibrium condition described above, with reference to *Figure1*; specifically, the trajectory is no longer closed and moves away from the equilibrium point.

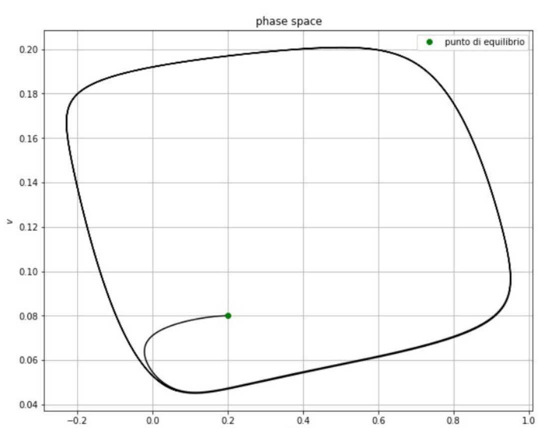


Figure1

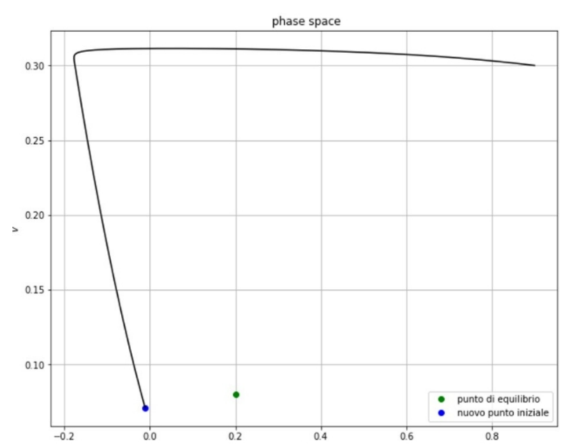
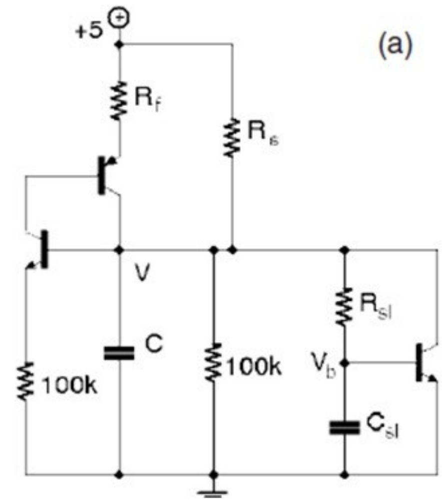


Figure2

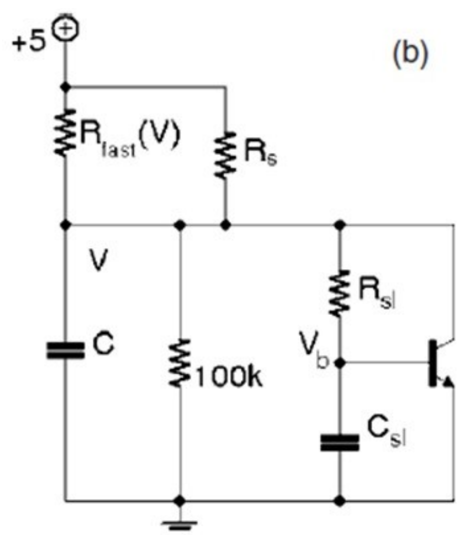
0.3 Three-transistor circuit

0.3.1 Circuit description and link equations

An equivalent model to the Fitzhugh-Nagumo circuit is the three-transistor model shown in the figure:



The circuit can be made simpler by replacing the first two transistors with a resistor $R_{fast}(V)$, which is a function of the voltage V applied to capacitor C.This voltage represents the excitatory variable of the senotrial node. The voltage V_b of the transistor base represents the inhibitory variable.



Applying Kirchoff's laws to the two links gives the following equations:

$$\begin{cases} C\frac{dV}{dt} = \frac{5-V}{R_{fast}(V)} + \frac{5-V}{R_s} - \frac{V}{100k\Omega} - \frac{V-V_b}{R_{sl}} - I_C(V, V_b) \\ C_{sl}\frac{d}{dt}V_b = \frac{V-V_b}{R_{sl}} - I_B(V, V_b) \end{cases}$$

a long charging time of the capacitor C_{sl} characterises the slow response of the self-declared model; the current $\frac{(5-V)}{R_s}$ plays a similar role to the $s(t)$ source term in the F-N model, i.e. it represents the ionic current of sodium and calcium entering the membranes
cells that excite the system. The choice of R_s fixes the period between two excitatory pulses.

I_B and I_C are the base and collector currents of the transistor, their expressions are given by the Ebers-Moll model:

$$I_C(u, v) = -\frac{I0}{\beta_r}\left(e^{200\left(\frac{V}{5}-\frac{Vb}{5}\right)} - 1\right] + I_0\left(e^{200\frac{V}{5}} - e^{200\left(\frac{V}{5}-\frac{Vb}{5}\right)}\right)$$

$$I_B(u, v) = \frac{I0}{\beta_f}\left(e^{200\frac{V}{5}} - 1\right) + \frac{I0}{\beta_r}\left(e^{200\left(\frac{V}{5}-\frac{Vb}{5}\right)} - 1\right)$$

The equations of the two links can be expressed in the form of the F-N equations. by normalising the variables with respect to the polarisation voltage of the transistors, i.e. *5V.*

$$\begin{cases} C\frac{d}{dt}u = (1-u)g_{fast}(u) + (1-u)\frac{R_f}{R_s} - u\frac{R_f}{100k\Omega} - (u-v)\frac{R_f}{R_{sl}} - R_f I_C(u, v) \\ C_{sl}\frac{d}{dt}v = \epsilon[u - v - R_{sl} I_B(u, v)] \end{cases}$$

where $g_{fast}(u)$ is the ratio $\frac{R_{fast}(u)}{R_f}$; ϵ is the parameter governing the slow response of the variable u, and is given by the ratio of the charge times of the two capacitors $\frac{R_f C}{R_{sl} C_{sl}}$.

0.3.2 Choice of parameters for the three-transistor model

For our system of differential equations to describe a fast response and a slow response, it is necessary to fix the values of the capacitances and resistances so that the charging time of capacitor C is faster than the discharging time of capacitor C_{sl} . In particular ϵ which is the ratio between these two quantities, analogous to the case of F-N., is fixed at a value of 0.01. Therefore, we choose the following values for the capacitances and resistances: $C = 0.33\mu f$, $C_{sl} = 1\mu f$, $R_f = 1k\Omega$, $R_{sl} = 33k\Omega$.

In order to have a sufficiently long excitation period that is of the order of magnitude of the senotrial node's excitation period, the value of R_s must be set between [10 kΩ ; 1 MΩ], so R_s is set at 330 kΩ.

The characteristic parameters of the base and emitter currents of the transistor obviously depend on the type of transistor used. For the study of this circuit, a 2N3904 was used, with the following parameters associated with it:

$$I_0 = 6.7 - 10^{-15} A;$$

$$\beta_r = 0.737$$

$$\beta_f = 416$$

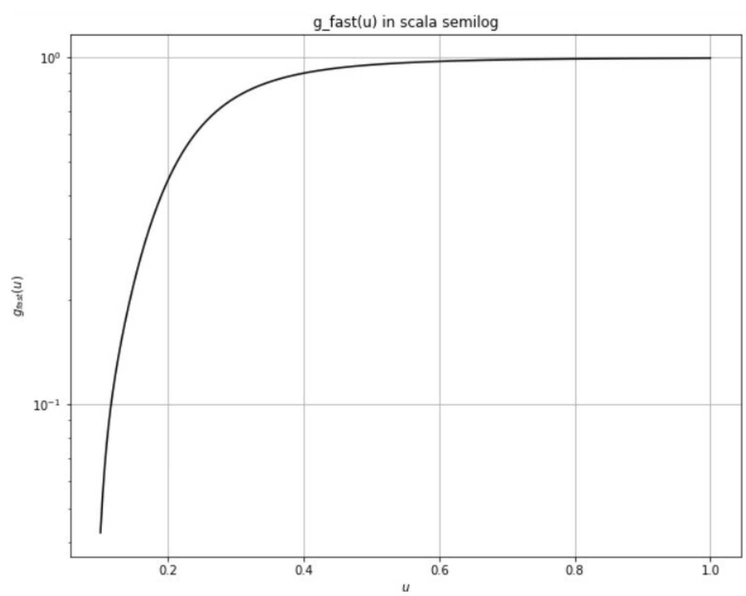
All that remains is to find an expression for the function $g_{fast}(u)$; When V increases from zero and passes through a certain threshold value, the two transistors are switched on, allowing current to flow through the series combination of Rf and the transistor pnp. This current acts as a positive feedback trigger that rapidly charges the capacitor. Therefore $R_{fast}(V)$ must have a steep transition until Rf is reached. Based on these considerations, the ratio $\frac{Rf\ ast}{Rf} = g_{fast}$ can be expressed with this function:

$$g_{fast}(u) = \frac{1}{[1 + e^{w1\,(Vt1\,-5u)}] - [1 + (\frac{V\,t2}{5u})^{w2}]}$$

From the experimental data, it is possible to obtain a best fit and the parameters within $g_{fast}(u)$, this procedure was carried out in the article by Jarrett L. Lancaster and Edward H. Hellenb, obtaining the following values:

$$w_1 = 30;\ w_2 = 3.5;\ V_{t1} = 0.48;\ V_{t2} = 1.25$$

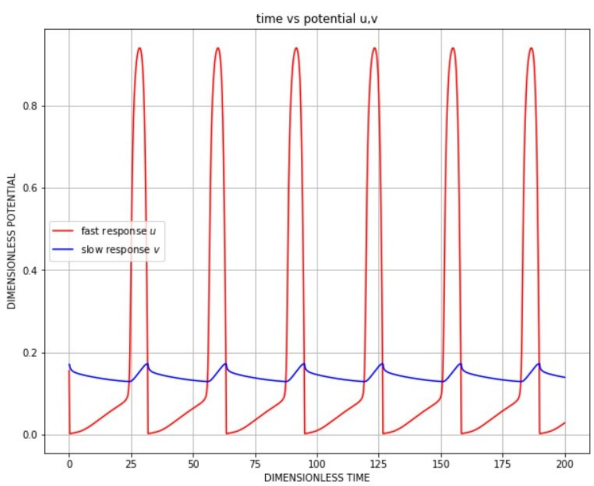
Follow the trend of $g_{fast}(u)$ on a semilogarithmic scale:

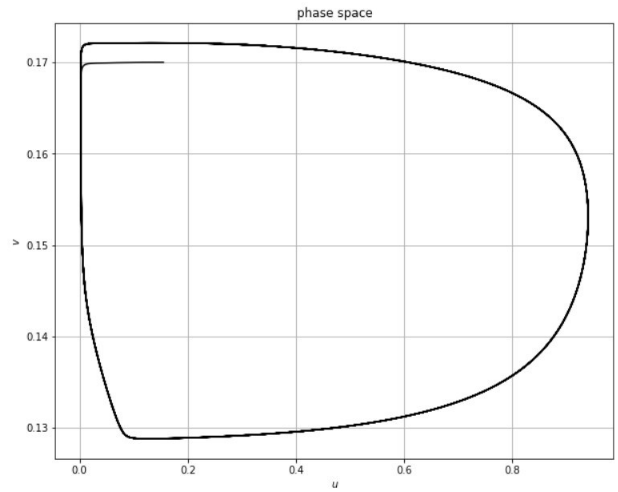


From the graph, we note that $g_{fast}(u)$ grows rapidly until it reaches the asymptotic value 1.

0.3.3 Algorithm description applied to the three-transistor model.

The modus operandi of this algorithm is the same as in the first section: after rewriting the mesh equations in the form of the F-N equations, a Runge-Kutta-Fehlberg algo- ry for coupled equations up to sixth order is implemented again. After this implementation, plots of u vs v, v vs t and u vs t *are* performed.





0.3.4 Model stability and initial conditions

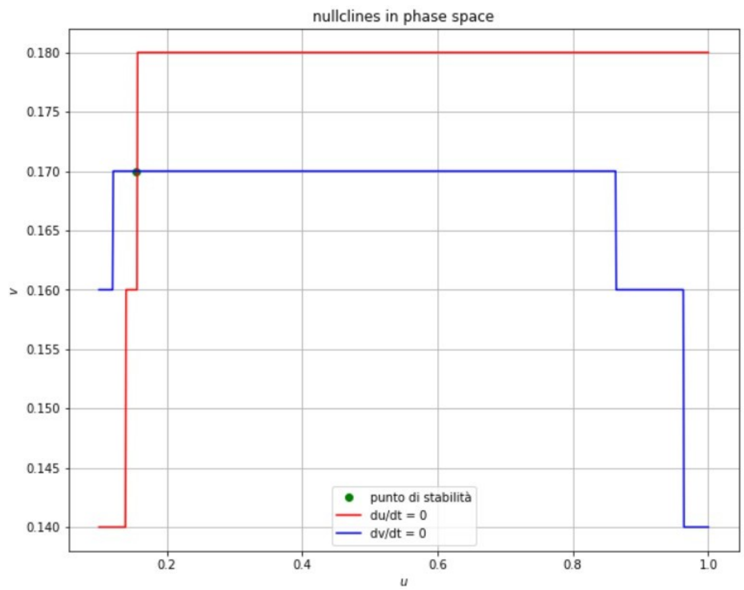
Similar to the circuit model of F-N. we want to verify the Ljapunov stability of the three-transistor model. The equations of the trajectories associated with $\frac{du}{dt} = 0$ and $\frac{dv}{dt} = 0$ appear to be:

$$\begin{cases} (1-u)g_{fast}(u) + (1-u)\frac{Rf}{R_s} - u\frac{Rf}{100k\Omega} - (u-v)\frac{Rf}{Rsl} - \frac{Rf}{Rsl}I_{C_3}(u,v) = 0 \\ u - v - \frac{Rf}{Rsl}I_B(u,v) = 0 \end{cases}$$

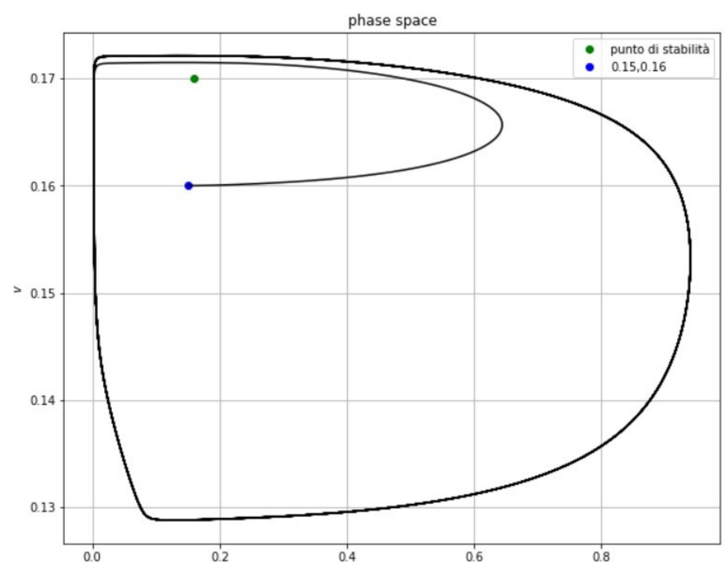
The solution of the system can be obtained by applying the bisection method to the two trajectories. Having chosen the initial point vi and final point vf of the domain on which to search for zero and ϵ1 ϵ2 arbitrarily small quantities, the algorithm proceeds as follows: for a given value of u and chosen the interval on which to search for zero [vi,vf]:

1. We calculate $vn = \frac{vi+vf}{2}$;
2. Calculate $f(u, vn)$
3. If $(f(u, vn) < e\ e_1$ $|v_f - v_i| < e_2$ the cycle stops: vn is the approximate zero value of the function. If vn does not fulfil this condition then:
4. the algorithm calculates f(u,vn) - $f(u, vi)$.
5. if f(u,vn) - $f(u, vi) > 0$, vn is substituted for vi and returns to Step 1, otherwise it substitutes vn a vf and return to Step 1.

the algorithm was repeated a number of i times as the variable u varied.



The point obtained from the intersection has co-ordinates (0.16,0.17) corresponding to the initial condition we assigned in the search for model solutions. If we repeat the RKF algorithm by varying the initial condition, we have that:



The equilibrium point of the three-transistor model is stable. In fact, if an initial condition other than the stability condition is chosen, the new trajectory given follows the same points as the trajectory given by the equilibrium condition. Regardless of the initial condition, the trajectories of the system tend towards the same curve.

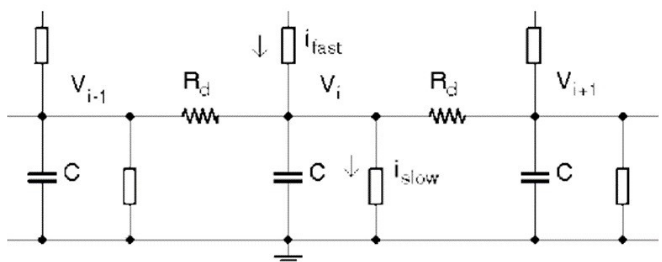
0.4 Diffusion of the cardiac impulse

0.4.1 Biological process description

The self-exciting systems we described above are analogous to the sinoatrial node, the heart's natural pacemaker, located in the upper part of the right atrium. The source terms $s(t)$ and $(1 - u)Rf/Rs$ in the equations of the two models correspond to the calcium currents flowing in the cells of the sinoatrial node. These currents are responsible for the increase in the membrane potential, generating the pacemaker impulse. The heartbeat signal generated by the sinoatrial node propagates through the muscle cells of the atria, causing them to contract and send blood into the ventricles. At the same time, the signal travels through the cell membranes of the cardiac conduction system to the atrioventricular node, located between the right atrium and the ventricle.

0.4.2 Process description as transmission network

Heartbeat and nerve signals propagate as action potentials (impulses) in an excitable medium. This medium is modelled by coupling the cells of the excitable circuit with a resistor Rd,simulating the structure of a transmission network as shown in the following figure:



Signal diffusion is described by the one-dimensional diffusion equation:

$$\frac{dV}{dt} = D\frac{d2V}{dx2}$$

0.4.3 Algorithm for solving the 1D diffusion equation

Before describing, the algorithm, it was decided, for simplicity's sake, to choose a unitary transmission section ($L = 1cm$) and to draw 10 nodes in this range, each with its own potential $V[i]$:

1. Since node number 1 (indexed with Phyton with 0), does not communicate with node $V[-1]$ in the following algorithm, and similarly, node number 10, $V[n - 1]$, with the subsequent node $V[n]$, two initial conditions were chosen with values that are plausible and compatible with the results obtained in section 2 of the paper:

$V[-1]$ = V1s =

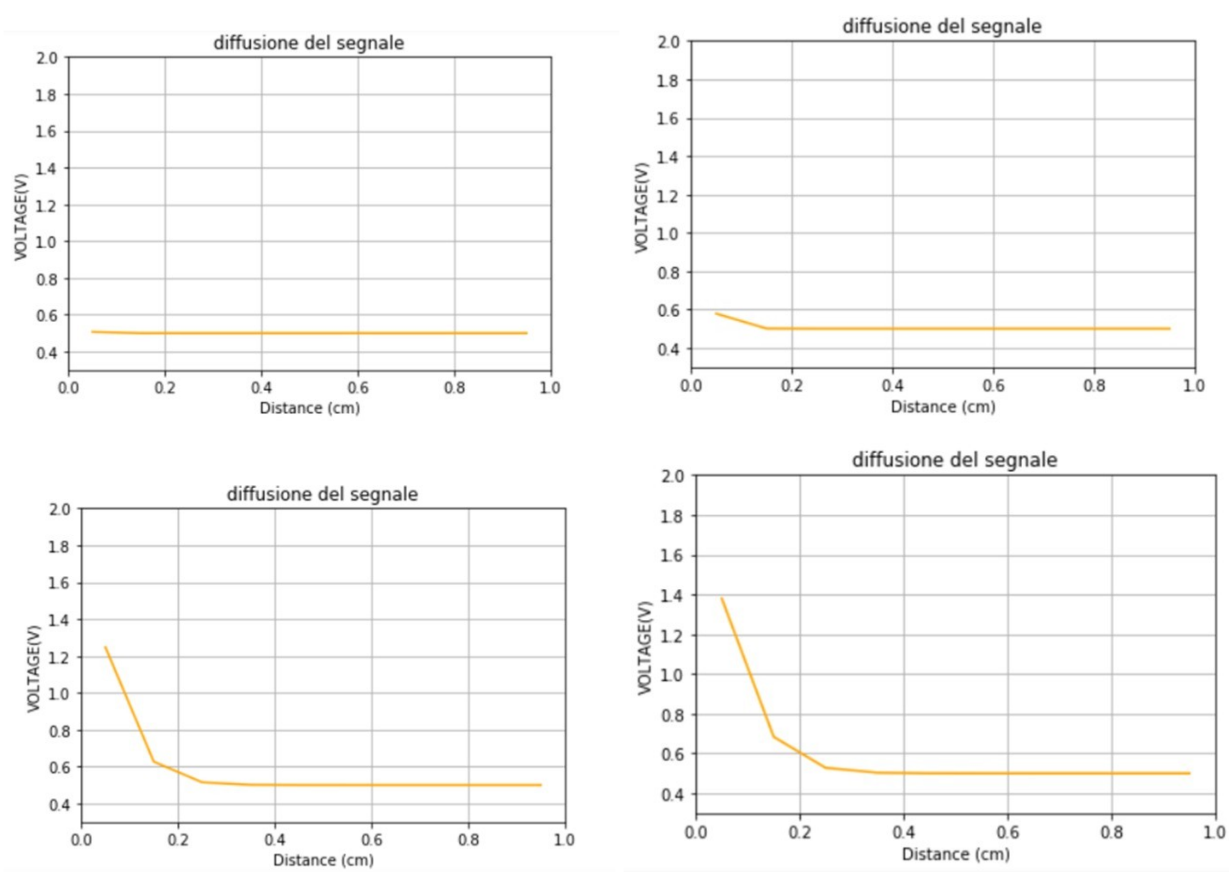
3.2V $V[n]$ = V2s =

$0.5V$

2. V was chosen$_0$ consistent with a stability value of u_0 , obtained in section 2, knowing that $V = 5u$;
3. A characteristic time step of cardiac diffusion was used, of $\Delta t = 2.5\mu s$ and as diffusivity coefficient $D = 10\text{-}5cm2/\mu s$;
4. The centre of the unit network L was chosen as the origin of the x-axis and dx/2 intervals were defined to make this axis an equispaced string. The objective is to vectorise the spatial component.
5. V has also been vectorised, understood as a vector that always repeats V_0 if it is not subject to variation.
6. The change dV - dt is defined as the change in potential for dt and, at this point, a cycle *f or* the time intervals defined by the step time in step 2 has been started.
7. Within such a *f or* loop, another *f or* loop is defined, running a l o n g spatial nodes, where a discrete second derivative is defined, in space, of the potential *V,* as the variation of the potential with respect to the immediately preceding and following node:

$$D\frac{V_{i+1} - V_i}{dx2} - D\frac{V_i - V_{i-1}}{dx2}$$

8. This contribution is added to the V value$_0$ and the process is iterated over the arbitrarily defined time interval.



This trend, without going into the details of the technique used, nor any further subtleties, is also confirmed by the experimental results of cardiac diffusion using the of Magnetic Resonance Imaging (MRI).FIG.3.3 of the publication: https://link.springer.com/chapter/10.1007/978-3-319-53001-7_3.

Also a other paper confirms the the following trend for the spread cardiac: https://www.semanticscholar.org/paper/Cardiac-diffusion-tensor-imaging-based-on-sensing- Huang-Wang/c2d1210a2329dcdc4fe8eb61cf6cef2fa3265f4f.