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DEPARTMENT OF MATHEMATICS

MATHEMATICAL MODELING

(18G6E16)

Experiential Learning

Report *on*

MATHEMATICAL MODELLING OF CARDIAC DYNAMICS WITH A SYSTEM OF NON LINEAR ORDINARY DIFFERENTIAL EQUATIONS

Submitted by:

DEEKSHA SANU	1RV19EC048
PRAGYA SEN	1RV19EC126

Submitted to:

Mrs. Nivya Muchikel
Assistant Professor

Department of Mathematics
RV College of Engineering

RV College of Engineering®, Bengaluru

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Department of Mathematics

CERTIFICATE

Certified that the **Mathematical Modeling**(18G6E16) work titled **MATHEMATICAL MODELLING OF CARDIAC DYNAMICS WITH A SYSTEM OF NON LINEAR ORDINARY DIFFERENTIAL EQUATIONS** is carried out by **Deeksha Sanu** (**1RV19EC048**) and **Pragya Sen(1RV19EC126)** who are bonafide students of RV College of Engineering, Bengaluru, in partial fulfilment of the requirements for the course of **Bachelor of Engineering** in **Electronics and Instrumentation** of the Visvesvaraya Technological University, Belagavi during the year 2021- 2022. It is certified that all corrections/suggestions indicated for the Internal Assessment have been incorporated in the report deposited in the departmental library.

MARKS ALLOTTED:

DEEKSHA SANU	1RV19EC048	
PRAGYA SEN	1RV19EC0126	

Signature of the faculty

MATHEMATICAL MODELLING OF CARDIAC DYNAMICS WITH A SYSTEM OF NON LINEAR ORDINARY DIFFERENTIAL EQUATIONS

Deeksha Sanu
deekshasanu.ec19@rvce.edu.in

Pragya Sen
pragyasen.ec19@rvce.edu.in

Abstract: Cardiac Arrhythmia, or irregular heart beat, is a name for a large family of cardiac behaviors that show abnormalities in the electrical behavior of the heart. A heartbeat that is too fast ("tachycardia") or too slow ("bradycardia") can be fatally dangerous. Other examples of arrhythmias include heart palpitations, stroke, and embolism. The natural pacemaker of the heart is called the sino atrial node. Pacemaker cells are polarized. When the cells generate an electrical impulse (a cardiac action potential), voltage gated channels open to allow charge to move through the cell, creating heartbeats. These cardiac dynamics can be modeled with the help of a system of nonlinear ordinary differential equations. With the help of MATLAB, required graphs are generated to visualize the problem

Keywords: *Mathematical Modelling, MATLAB, Cardiac Dynamics, nonlinear ordinary differential equations*

1. Introduction:

In this paper for modelling cardiac dynamics, a two variable system is used to study the voltage flux across cardiac cell membranes. This gives us an insight of how and why arrhythmias form.

$$\frac{dv}{dt} = -kv(v-a)(v-1) - vh + S(t)$$

$$\frac{dh}{dt} = (\varepsilon_0 + \frac{\mu_1 h}{v+\mu_2})(-h - kv(v-a-1))$$

v = voltage across the cell membrane
h = gating variable
When h=0, voltage can pass freely and when h>0, the gate reduces the voltage passing into the cell. If h happens to be an extremely large value, the gate is essentially closed.

S(t) = Electrical impulse generated by the pacemaker
a, k, ε ,μ1, μ2 are positive, unitless constants.
a = the threshold excitation,
k controls the magnitude of the electric current across the cell membrane,
vh describes the repolarization current in the recovery process

$\varepsilon_0 + \frac{\mu_1 h}{v+\mu_2}$ = relationship between cell's excitation and recovery time scales

2. The Basic Model:

First, let us assume that S(t) = 0, now the equation becomes,

$$\frac{dv}{dt} = -kv(v-a)(v-1) - vh$$

$$\frac{dh}{dt} = (\varepsilon_0 + \frac{\mu_1 h}{v+\mu_2})(-h - kv(v-a-1))$$

v-nullclines occur when,

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

$$-kv(v-a)(v-1) - vh = 0$$

h-nullclines occur when,

$$\frac{dh}{dt} = 0$$

$$\varepsilon_0 + \frac{\mu_1 h}{v+\mu_2} = 0\,,\ -h - kv(v-a-1) = 0$$

Looking at the above equation, there is only one non-negative equilibrium solution (v_0,h_0). The only non-negative equilibrium point occurs when v_0= 0 and h_0=0, at the point (0, 0).

We will now define the following equations:
$v' = f(v, h)$
$h' = g(v, y)$

In order to calculate the eigenvalues of the Jacobian matrix J(v, h) evaluated at the non-negative equilibrium point (v_0,h_0)=(0,0), we must calculate the following partial derivatives: $f_v(0,0)$, $f_h(0,0)$, $g_v(0,0)$ and $g_h(0,0)$:

$f_h(v,h) = -kv^2 + 2kav + 2kv - ak - h$
$f_h(0,0) = -ak$
$f_h(v,h) = -v$
$f_h(0,0) = 0$
$g_v(v,h) = (-\frac{\mu 1 h}{(v+\mu 2)^2})(-h - kv(v - a - 1)) + (\epsilon_0 + \frac{\mu_1 h}{v+\mu_2})(-2kv + ak + k)$
$g_v(0,0) = \epsilon_0 (ak + k)$
$g_h(v,h) = (\frac{\mu_1 h}{v+\mu_2})(-h - kv(v - a - 1)) + (-1)(\epsilon_0 + \frac{\mu_1 h}{v+\mu_2})$
$g_h(0,0) = -\epsilon_0$

Evaluating the Jacobian results in $\lambda_1 = -ak$ and $\lambda_2 = -\epsilon_0$
Both the eigenvalues are negative. This implies that the point (0,0) is asymptotically stable. If the solution starts close enough to an asymptotically stable equilibrium point, then the solution will converge to that equilibrium point as $t \to \infty$.
This means that the voltage across the cell membrane has a tendency to go towards zero, and the gating variable also approaches zero, in which voltage will able to pass freely through the gate.

Now, we will assume the following numbers for the constants a, k, ϵ_0, μ_1, *and* μ_2

$a = 0.15$
$k = 8$
$\epsilon_0 = 0.002$
$\mu_1 = 0.2$
$\mu_2 = 0.3$

Now, the equations become,
$\frac{dv}{dt} = -8v(v - 0.15)(v - 1) - vh$
$\frac{dh}{dt} = (0.002 + \frac{0.2h}{v+0.3})(-h - 8v(v - 16))$

The graph of the nullclines for these equations is as follows:

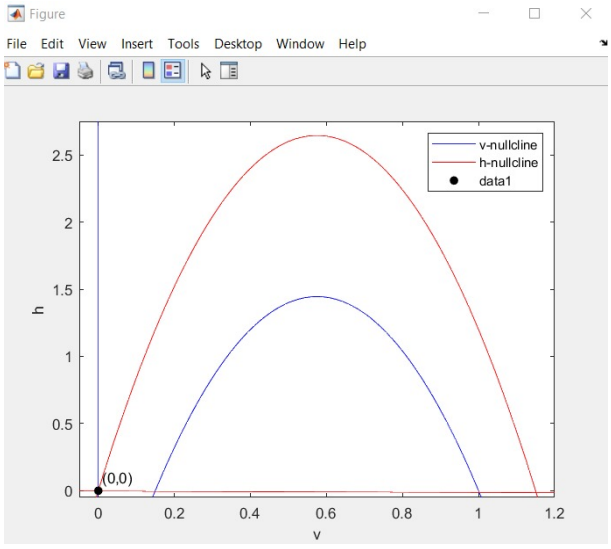

Figure 1: A graph of the nullclines of and dt/dv and dt/dh

It is seen that the only positive equilibrium solution occurs at $(v_0,h_0)=(0,0)$.
The next graphs contain the vector field of the equations for dv/dt and dh/dt on the domain
$v = [-0.05, 1.2]$, $h = [-0.05, 2.75]$.
A sample solution curve in the vector field is plotted with the starting point $(v_0,h_0)=(0.5,0.2)$ which is marked in black.

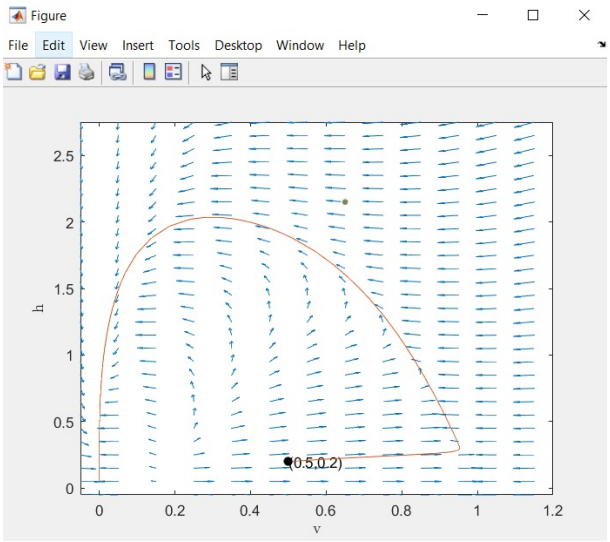

Figure 2: Sample solution curve with initial point (0.5, 0.2) on the vector field of the equations for dv/dt and dh/dt

Next, a sample solution curve in the vector field, with the starting point $(v_0,h_0)=(0.1,0.2)$ marked in black.

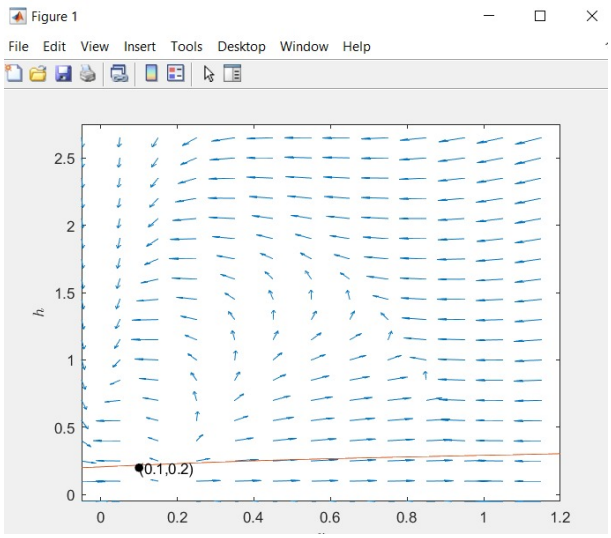

Figure 3: Sample solution curve with initial point (0.1, 0.2) on the vector field of the equations for dv/dt and dh/dt

The solution curve having the starting position (0.5, 0.2) initially moves in the positive v direction, then rotates counter-clockwise and eventually reaches the equilibrium point (0,0). On the other hand, the solution curve having the starting position (0.1, 0.2) initially moves in the negative v direction and reaches the equilibrium point (0,0) much more quickly.

The trajectories of the solution curves follow the directions of the vectors on the vector field.

If the initial value v is to the left of a, the trajectory moves in the negative v direction and directly approaches the equilibrium point. As the initial value v moves closer to zero, the trajectory approaches the equilibrium point faster. But if the initial value v is to the right of a, the trajectory initially moves in the positive v direction, before rotating counter-clockwise to move towards the equilibrium point.

3. Model Improvement: Periodic Stimulation

For maintaining a steady heartbeat, periodic stimulation of cardiac cells is required. The period

of stimulation is denoted by the parameter T, which defines the number of time units that pass between each stimulation. The cell will not be stimulated for any time between stimulation times.

The system is initially assumed to be at $(v_0, h_0)=(0,0)$ and a large positive stimulus is added to the voltage. Based on previous plots, the trajectory will initially move in the positive v direction. The maximum value that v will attain is 1.
The nullclines of dv/dt and dh/dt are plotted:

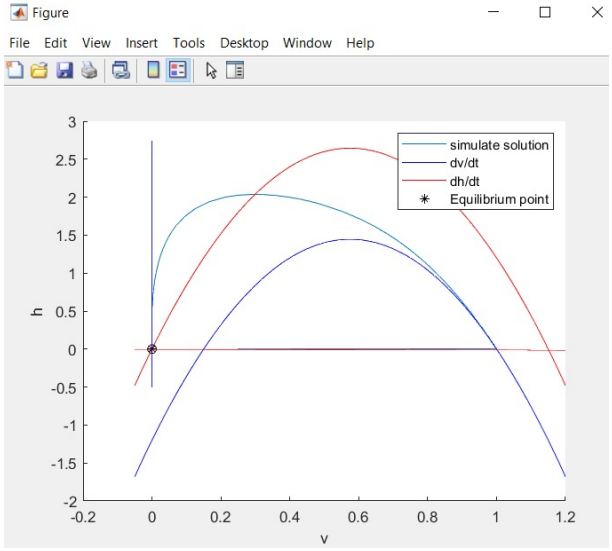

Figure 4: Sample solution curve with initial point (0,0)

The solution starts at $(v_0, h_0)=(0,0)$ and a positive stimulus S=0.25 of voltage is added.
The flow is counter-clockwise. If no more stimuli are given after the initial push, then as $t \to \infty$ the system will approach the equilibrium solution (0,0). It basically starts at (0.25,0) and goes to max v of 1, then it rotates counterclockwise approaching the equilibrium point (0,0). Which is in agreement with what was discussed previously.

The solutions to dv/dt and dh/dt are simulated starting from the initial condition $(v_0,h_0)=(\beta,0)$ in which $\beta = 0.25$ over the time interval $t \in [0, 500]$ with a time-step of $\Delta t = 0.2$.

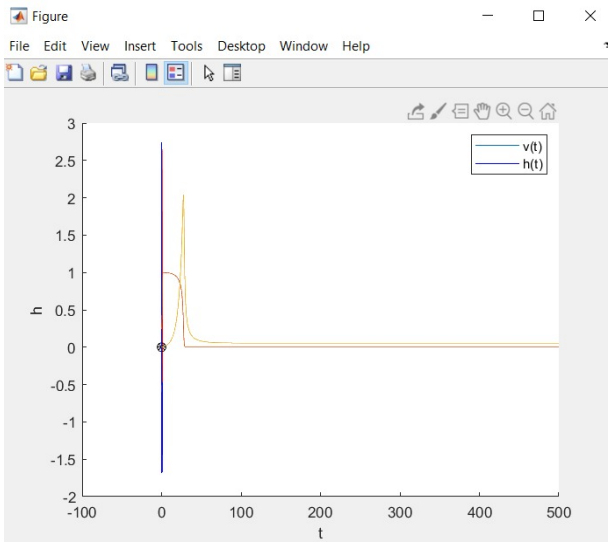

Figure 5: Sample solution curve with initial point (0.25, 0)

Next, the solutions to dv/dt and dh/dt are simulated starting from the initial condition $(v_0,h_0)=(0,0)$ over the time interval $t \in [0, 500]$ with a time-step of $\Delta t = 0.2$ with a stimulation period T = 100 and a stimulus of S(t) = 0.25.

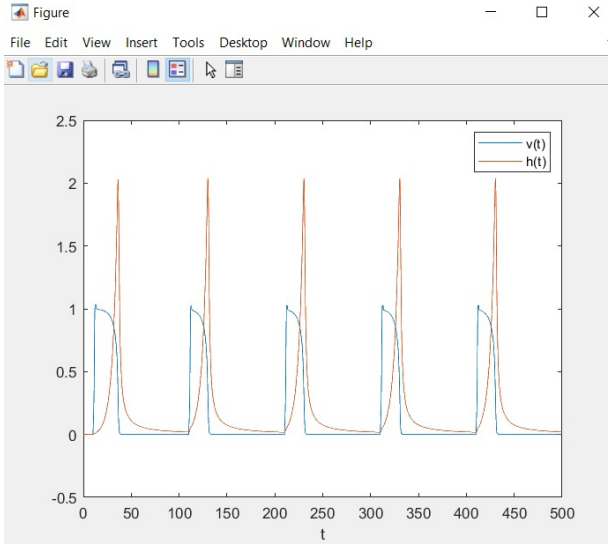

Figure 6: Sample solution curve with initial point (0,0) with a stimulation period T=100 and a stimulus of S(t)=0.25

In the system without constant stimulus, v and h both approach zero. In the system with constant stimulus, v and h approach the equilibrium point

zero, but then proceed to increase in magnitude periodically.

4. Studying the Cardiac Action Potential

The APD(Action Potential Duration) is the duration from the time a cell is stimulated to the time it repolarizes. The APD is calculated as follows:

$$APD_{beat} = t_{down} - t_{up}$$

In which t_{up} is the time at which the voltage v passes a constant critical voltage v_c on the way up, and t_{down} is the time at which the voltage v passes that same constant critical voltage v_c on the way down.

We let the critical voltage be $v_c = 0.1$

The APD for the last full beat of the v(t) solution curve corresponds to the steady state APD, and is denoted APD_0.

We proceed to use the initial condition $(v_0, h_0) = (0,0)$ over the time interval $\in [0, 1000]$ with a time-step of $\Delta t = 0.2$ and stimulus $S(t) = 0.25$ to stimulate solutions to $\frac{dv}{dt}$ and $\frac{dh}{dt}$ to find the APD_0 for $T_1 = 100$, $T_2 = 90$, $T_3 = 80$, $T_4 = 70$, $T_5 = 60$ and $T_6 = 50$.

The following is a table of the data points that we have gathered:

T	APD_0
100	931 - 910.4 = 20.6
90	930.6 - 910.4 = 20.2
80	910 - 890.4 = 19.6
70	939.4 - 920.4 = 19
60	928.4 - 910.4 = 18
50	927.4 - 910.4 = 17

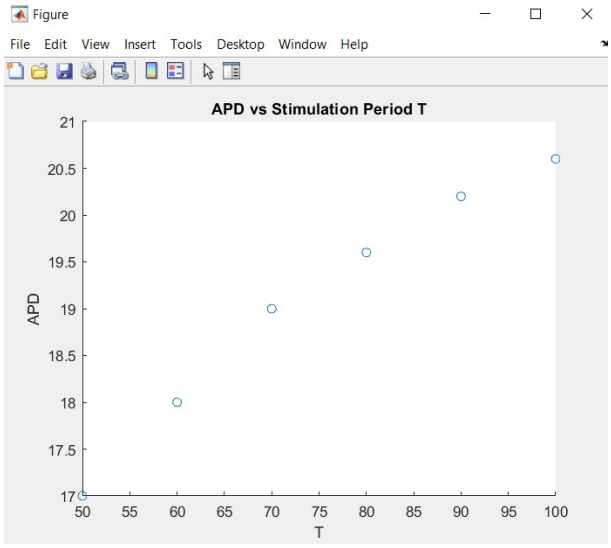

Figure 7: A graph of T vs APD_0

It is seen that APD_0 increases as T increases. From a biological viewpoint, as the heart cell is 0 stimulated more frequently, the time period between consecutive beats decreases.
An important feature of cardiac tissue is that the APD needs to be long enough, especially for large animals. The heartbeats of large animals are longer, because they have larger hearts, and so the voltage gated channels in their hearts need more time to allow charge to move through the cell to create heartbeats.

The minimum value of h between two beats is denoted $\overline{h}$, and is a measure of how much the heart cell has been allowed to relax before the next stimulation. A smaller $\overline{h}$ means that the heart cell is more relaxed. The value of the last $\overline{h}$, between the last two beats, corresponds to the steady-state $\overline{h}$.

The following is a table of the data points that we have gathered:

T	$\overline{h}$
100	0.017442
90	0.020004
80	0.023303
70	0.027845
60	0.034229
50	0.043878

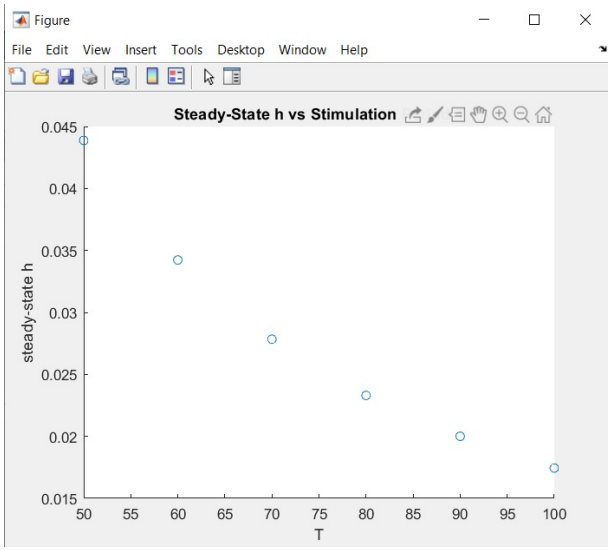

Figure 8: A graph of T versus $\overline{h}$

It is seen that the steady-state $\overline{h}$ decreases as T increases. From a biological point of view, if the heart cell is stimulated less frequently, it will return closer to a resting state, thus will be closer to zero.

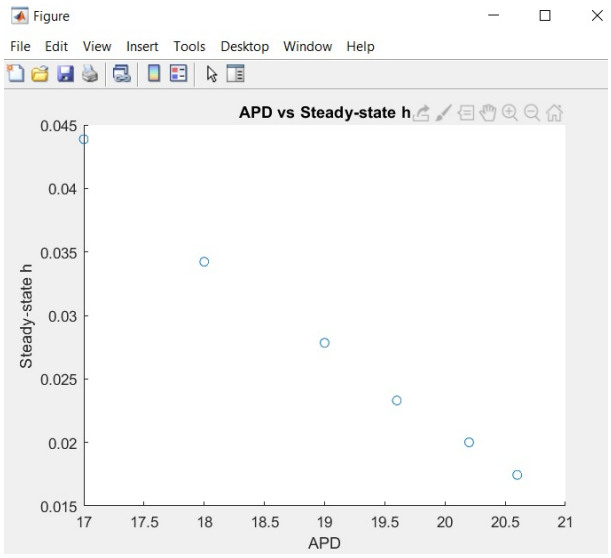

Figure 9: A graph of APD versus $\overline{h}$

As can be seen, the steady-state $\overline{h}$ decreases as APD increases. This is because there will be a longer resting period between consecutive heartbeats if a heartbeat takes a longer amount of time, which means that the steady-state $\overline{h}$ will decrease (since it has more time to reach a resting state).

5. Conclusion

We used a two-variable system to study the voltage flux across cardiac cell membranes, in order to give insight as to how and why arrhythmias form. We determined that the system has a tendency to go towards the equilibrium point $(v_0, h_0) = (0,0)$.

To maintain a steady heartbeat, cardiac cells need to be stimulated periodically. For any time between stimulation times, the cell will not be stimulated. It is assumed that the system is initially at $(v_0, h_0) = (0,0)$, and a large positive stimulus S(t) is added to the voltage. Thus, we created graphical models of heartbeats.

We determined from our data that $\overline{h}$, a measure of how much the heart cell has been allowed to relax

before the next stimulation, decreases as the APD, which is the duration from the time a cell is stimulated to the time it repolarizes, increases.

Basically, if a heartbeat takes longer, the heart cell also needs to relax more. This helps explain why a heartbeat that is too fast ("tachycardia") or too slow ("bradycardia") can be fatally dangerous. If a heartbeat is too fast, the heart cell may not have enough time to relax. On the other hand, if a heartbeat is too slow, the heart cell may relax too much, since it will tend towards the equilibrium resting state, so it may not be able to recover quickly enough.

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