A Mathematical Investigation of Cardiac Dynamics

Nicole Dong | Mohammed Alshehri

Introduction

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 hard. 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 sinoatrial 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 a system of nonlinear ordinary differential equations. We will use a two-variable system to study the voltage flux across cardiac cell membranes, which can give insight to how and why arrhythmias form:

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

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

The variable v represents the voltage across the cell membrane.

The variable h is the gating variable. If $h = 0$, voltage can pass freely. If $h > 0$, then the gate reduces the voltage passing into the cell. It h is an extremely large value, the gate is essentially closed.

The function $S(t)$ represents the electrical impulse generated by the pacemaker.

The letters $a, k, \varepsilon_0, \mu_1, \mu_2$ are positive, unitless constants. a represents the threshold excitation in the system, k controls the magnitude of the electric current across the cell membrane, vh describes the repolarization current in the recovery process, and $\varepsilon_0 + \frac{\mu_1 h}{v+\mu_2}$ is the relationship between the cell's excitation and recovery time scales.

The Basic Model

First, we will assume that $S(t) = 0$, so that the equations become:

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

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

The v-nullclines occur when:

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

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

The h-nullclines occur when:

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

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

As can be seen, 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 $(0, 0)$.

Next, we will 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 $g_h(0, 0)$:

$f_v(v, h) = -kv^2 + 2kav + 2kv - ak - h$

$f_v(0, 0) = -ak$

$f_h(v, h) = -v$

$f_h(0, 0) = 0$

$g_v(v, h) = (-\frac{\mu_1 h}{(v+\mu_2)^2})(-h - kv(v-a-1)) + (\varepsilon_0 + \frac{\mu_1 h}{v+\mu_2})(-2kv + ak + k)$

$g_v(0, 0) = \varepsilon_0(ak + k)$

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

$g_h(0, 0) = -\varepsilon_0$

Evaluating the Jacobian results in $\lambda_1 = -ak$ and $\lambda_2 = -\varepsilon_0$

Both of the eigenvalues are negative. This means 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 $t \to \infty$.

Biologically, 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.

Next, we will assume the following numbers for the constants a, k, ε_0, μ_1, and μ_2 :

$$a = 0.15$$

$$k = 8$$

$$\varepsilon_0 = 0.002$$

$$\mu_1 = 0.2$$

$$\mu_2 = 0.3$$

The equations become:

$$\frac{dv}{dt} = -8v(v - 0.15)(v - 1) - vh$$

$$\frac{dh}{dt} = (0.002 + \frac{0.2h}{v+0.3})(-h - 8v(v - 16))$$

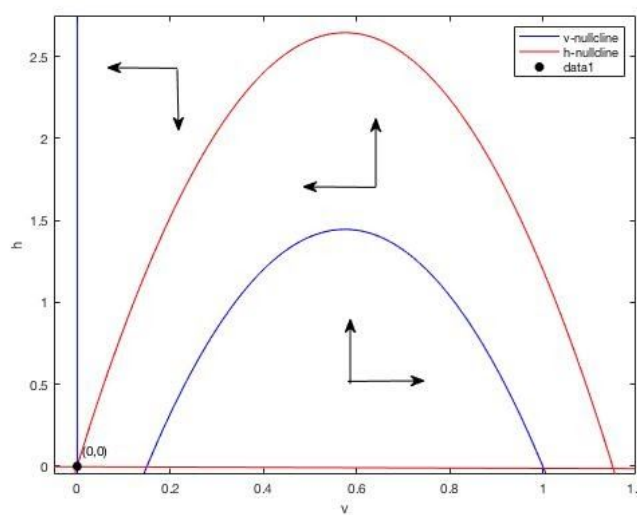The graph of the nullclines for these equations is as follows:

Figure 1: A graph of the nullclines of $\frac{dv}{dt}$ and $\frac{dh}{dt}$

As can be seen, the only positive equilibrium solution occurs at $(v_0, h_0) = (0, 0)$.

The next graphs contain the vector field of the equations for $\frac{dv}{dt}$ and $\frac{dh}{dt}$ on the domain $v = [-0.05, 1.2], h = [-0.05, 2.75]$.

We proceed to graph a sample solution curve in the vector field, with the starting point $(v_0, h_0) = (0.5, 0.2)$ marked in black.
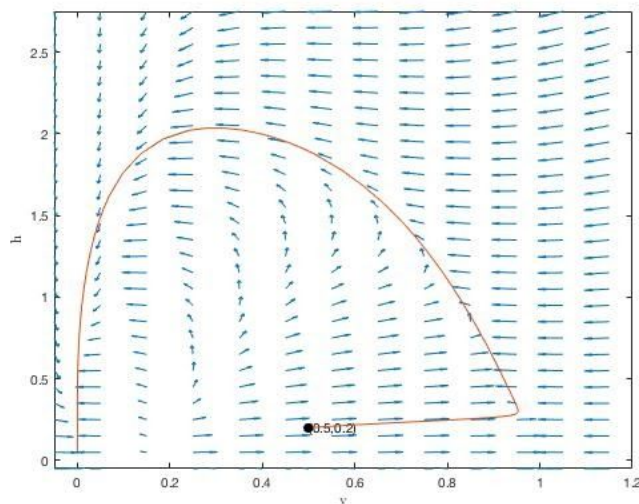
Figure 2: Sample solution curve with initial point (0.5, 0.2) on the vector field of the equations for $\frac{dv}{dt}$ and $\frac{dh}{dt}$

Next, we proceed to graph a sample solution curve in the vector field, with the starting point $(v_0, h_0) = (0.1, 0.2)$ marked in black.
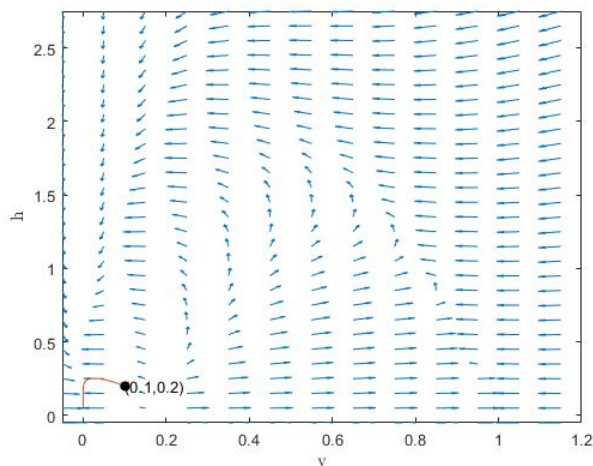
Figure 3: Sample solution curve with initial point (0.1, 0.2) on the vector field of the equations for $\frac{dv}{dt}$ and $\frac{dh}{dt}$

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

Given the nullclines and the vector field, these solutions makes sense. The trajectories of the solution curves follow the directions of the vectors on the vector field.

When the initial value v is to the right of a, the trajectory initially moves in the positive v direction, before rotating counter-clockwise to approach the equilibrium point. On the other hand, when 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 gets closer to zero, the trajectory approaches the equilibrium point quicker.

Model Improvement: Periodic Stimulation

To maintain a steady heartbeat, cardiac cells need to be stimulated periodically. The period of stimulation will be denoted by the parameter *T*, which defines the number of time units that pass between each stimulation. For any time between stimulation times, the cell will not be stimulated.

We assume that the system is initially 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.

We proceeded to plot the nullclines of $\frac{dv}{dt}$ and $\frac{dh}{dt}$ once again.
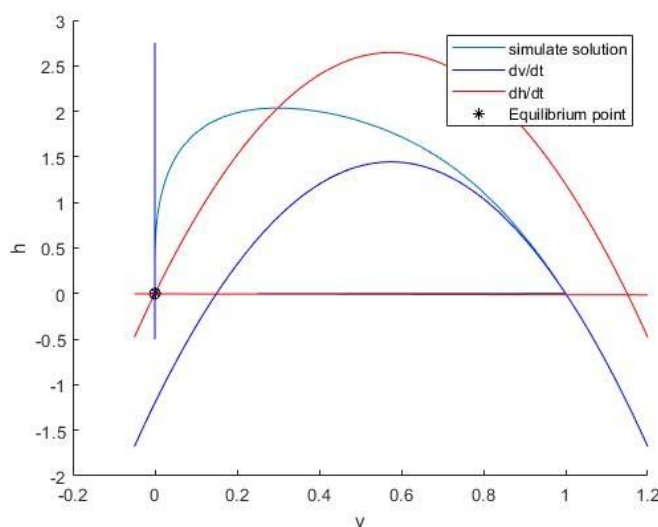

Figure 4: Sample solution curve with initial point (0, 0)

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 agree to what we discussed previously.

We proceed to stimulate solutions to $\frac{dv}{dt}$ and $\frac{dh}{dt}$ 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 $\Delta t = 0.2$.
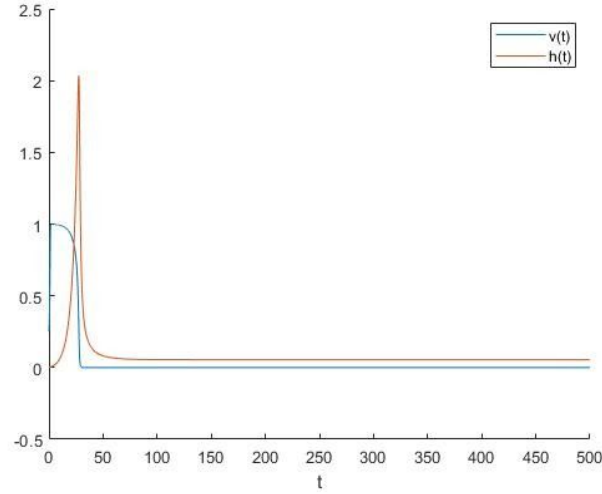

Figure 5: Sample solution curve with initial point (0.25, 0)

Next, we proceed to stimulate solutions to $\frac{dv}{dt}$ and $\frac{dh}{dt}$ 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 $S(t) = 0.25$.
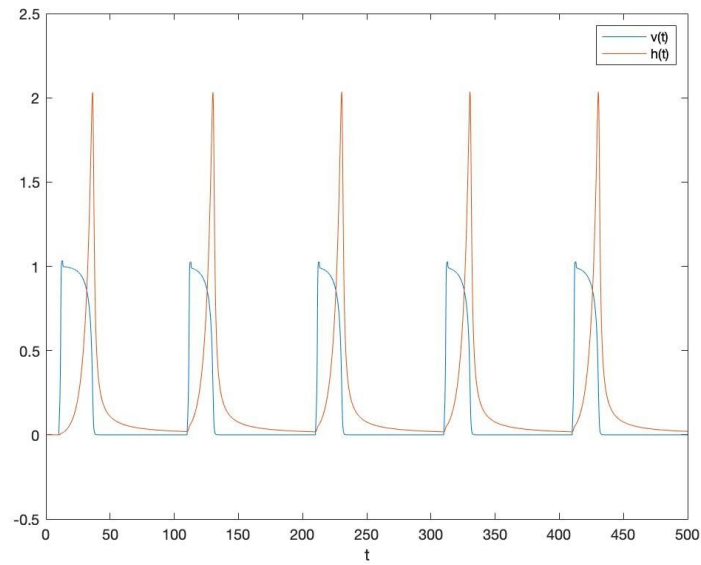

Figure 6: Sample solution curve with initial point (0, 0) with a stimulation period $T = 100$ and a stimulus of $S(t) = 0.25$

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.

Studying the Cardiac Action Potential
The APD 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 $t \in [0, 1000]$ 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:

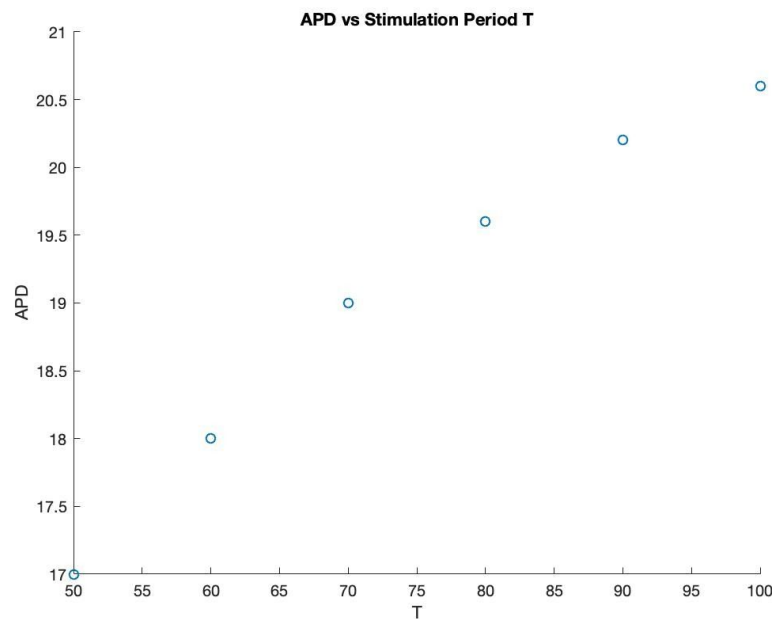| T	APD_0
100	931 - 910.4 = 20.6
90	930.6 - 910.4 = 20.2
80	910 - 890.4 = 19.6
70	939.4 - 920.4 = 19
60	928.4 - 910.4 = 18
50	927.4 - 910.4 = 17

Figure 7: A graph of T versus APD_0

As can be seen, APD_0 increases as T increases. From a biological viewpoint, as the heart cell is stimulated more frequently, the time period between consecutive beats decreases.

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

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

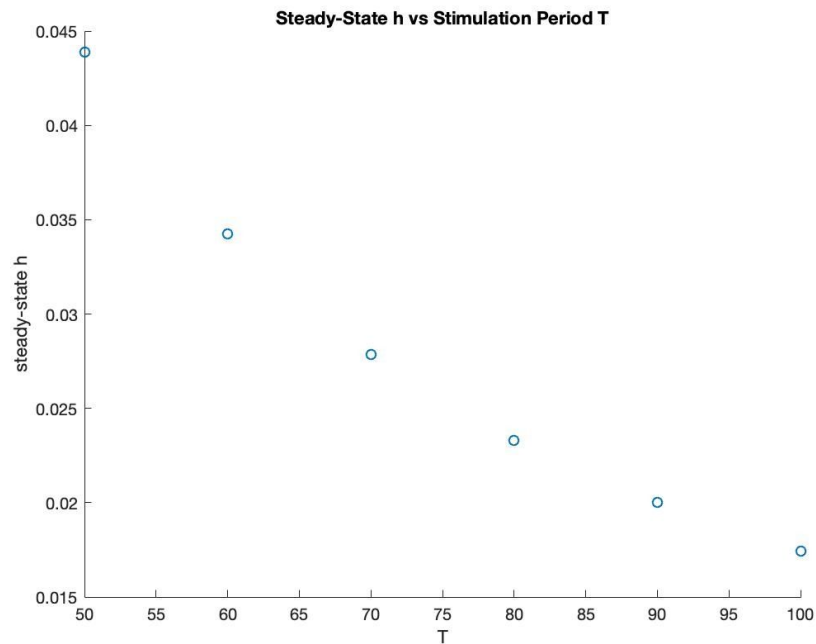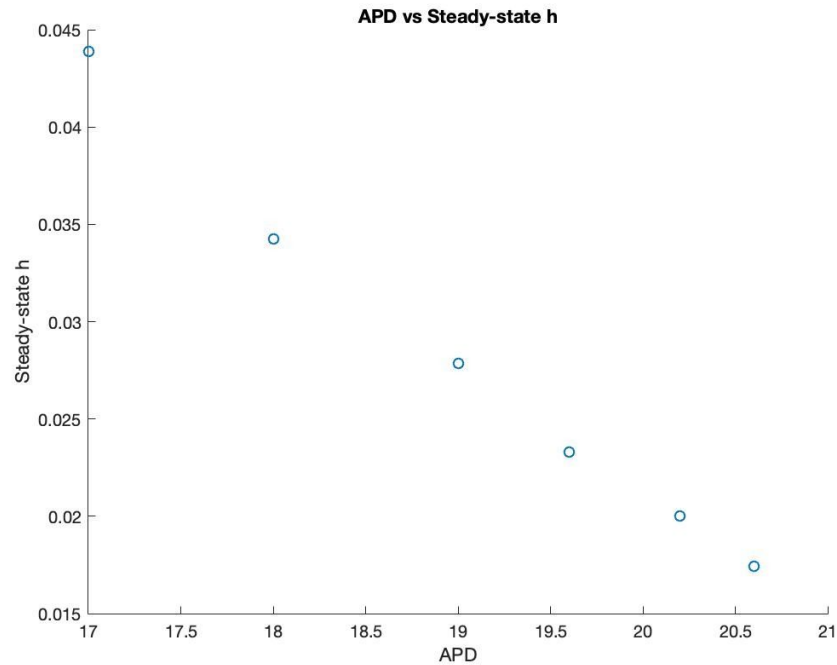| T	$\bar{h}$
100	0.017442
90	0.020004
80	0.023303
70	0.027845
60	0.034229
50	0.043878

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

As can be seen, the steady-state $\bar{h}$ 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 $\bar{h}$

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

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. We assume 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 $\bar{h}$, 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 hearneat 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.

Appendix

Figure 1

```
% graphing the v-nullcline: dv/dt = 0
fimplicit(@(va,ha) (-8*va)*(va-0.15)*(va-1)-(va*ha),'b')
hold on

% graphing the h-nullclines: dh/dt = 0
fimplicit(@(vb,hb) (0.002 +(0.2 * hb/(vb + 0.3))),'r')
hold on
fimplicit(@(vc,hc) (-8*vc.^2 + 9.2*vc - hc), 'r')
hold on

% setting the axis boundaries:
% x-axis: -0.05 to 1.2
% y-axis: -0.05 to 2.75
axis([-0.05 1.2 -0.05 2.75])

% labeling the graph's axes
xlabel('v')
ylabel('h')
legend('v-nullcline','h-nullcline');

% plotting the equilibrium point
plot(0,0,'.black','MarkerSize', 20)
text(0.01,0.1,'(0,0)');
```

Figure 2

```
close all;
clear all;
clc;

% Set the axis limits
% v: -0.05 to 1.2
% h: -0.05 to 2.75
vmin = -0.05; vmax = 1.2;
hmin = -0.05; hmax = 2.75;

%set step size for v and h
vstep = 0.5; hstep = 0.5;

%generate mesh for plotting
[v, h] = meshgrid(vmin:0.1:vmax, hmin:0.1:hmax);

% set parameter values
%(note: the value(s) of S(t) are defined in the file F.m)
a = 0.15; k = 8; ep = 0.002; m1 = 0.2; m2 = 0.3;

% Define the system of equations dv/dt = f(v,h) and dh/dt = g(v,h)
dv = -k*v.*(v-a).*(v-1) - v.*h;
dh = (ep + (m1*h)./(v+m2)).*(-h-k*v.*(v-a-1));

%normalize vectors (to help plotting)
dv = dv./sqrt(dv.^2 + dh.^2);
dh = dh./sqrt(dv.^2 + dh.^2);

% Generate the vector field
quiver(v, h, dv,dh,'AutoScaleFactor',0.5)

%change axes limits, add labels
axis([vmin vmax hmin hmax])
xlabel('$v$','Interpreter','latex')
ylabel('$h$','Interpreter','latex')

% this plots the solution to the system, with (v0,h0)=(0.5,0.2)
hold on

% plotting (v0,h0)=(0.5,0.2)
plot(0.5,0.2,'.black','MarkerSize', 20)
text(0.5,0.2,'(0.5,0.2)');

% this function plots the solution to the system of diffeq's
f = @(t,x) [-k*x(1)*(x(1)-a)*(x(1)-1)-x(1)*x(2);(ep+((m1*x(2))/(m2+x(1)))*(-x(2)-8*x(1)*(x(1)-a-1)))];
[t,xa] = ode45(f,[0 500],[0.5 0.2]);
hold on
plot(xa(:,1),xa(:,2))
plot(xa(1,1),xa(1,2),'k*','LineWidth',2)
xlabel('v'), ylabel('h')
```

Figure 3

```
close all;
clear all;
clc;

% Set the axis limits
% v: -0.05 to 1.2
% h: -0.05 to 2.75
vmin = -0.05; vmax = 1.2;
hmin = -0.05; hmax = 2.75;

%set step size for v and h
vstep = 0.1; hstep = 0.15;

%generate mesh for plotting
[v, h] = meshgrid(vmin:vstep:vmax, hmin:hstep:hmax);

%set parameter values %(note: the value(s) of S(t) are defined in the file F.m)
a = 0.15; k = 8; ep = 0.002; m1 = 0.2; m2 = 0.3;

% Define the system of equations dv/dt = f(v,h) and dh/dt = g(v,h)
dv = -k*v.*(v-a).*(v-1) - v.*h;
dh = (ep + m1*h./(v+m2)).*(-h-k*v.*(v-a-1));

%normalize vectors (to help plotting)
dv = dv./sqrt(dv.^2 + dh.^2);
dh = dh./sqrt(dv.^2 + dh.^2);

% Generate the vector field
quiver(v, h, dv,dh,'AutoScaleFactor',0.5)

%change axes limits, add labels
axis([vmin vmax hmin hmax])
xlabel('$v$','Interpreter','latex')
ylabel('$h$','Interpreter','latex')

% this plots the solution to the system, with (v0,h0)=(0.5,0.2)
hold on
[v,h] = ode45(@system_ex,[-0.05,1.2],[0.5,0.2]);
plot(v(:,1),h(:,2))

% plotting (v0,h0)=(0.5,0.2)
plot(0.1,0.2,'.black','MarkerSize', 20)
text(0.1,0.2,'(0.5,0.2)');

% this function plots the solution to the system of diffeq's
function yprime = system_ex(t,y)
yprime = zeros(2,1);
yprime(1) = -8*y(1).*(y(1)-0.15).*(y(1)-1) - y(1).*y(2);
yprime(2) = (0.002 + 0.2*y(2)./(y(1)+0.3)).*(-y(2)-8*y(1).*(y(1)-0.15-1));
end
```

Figure 4

```
k=8;
a=0.15;
mu1=0.2;
mu2=0.3;
sigma0=0.002;
tspan = [0 500];
f = @(t,x) [-k*x(1)*(x(1)-a)*(x(1)-1)-x(1)*x(2);
(sigma0+((mu1*x(2))/(mu2+x(1))))*(-x(2)-8*x(1)*(x(1)-a-1)))];
[t,xa] = ode45(f,tspan ,[0.25 0]);
hold on
plot(xa(:,1),xa(:,2))

v=-0.05:.01:1.2;
h=-0.05:.01:2.75;

ha = -k.*(v-a).*(v-1);
hb=((-sigma0 .*(v+mu2)) ./mu1);
hc= -k .*v .*(v-a-1);

x2=zeros(1,10);

y=linspace(-0.5,2.75,10);

axis = ([-0.05 1.2 -0.05 2.75]);
plot(v,ha, 'b');
hold on;
plot(v,hc,'r');
hold on;
plot(0,0,'k*')
plot(0,0,'ko')
hold on;
plot(v,hb,'r');
plot(x2,y,'b');

hold off;

legend('simulate solution','dv/dt','dh/dt','Equilibrium point');
xlabel('v')
ylabel('h')
```

Figure 5

```
k=8;
a=0.15;
sigma0=0.002;

tspan = [0 500];
f = @(t,x) [-k*x(1)*(x(1)-a)*(x(1)-1)-x(1)*x(2);
   (sigma0+((0.2*x(2))/(0.3+x(1)))*(-x(2)-8*x(1)*(x(1)-a-1)))];

[t,xa] = ode45(f,tspan ,[0.25 0]);
hold on

plot(t,xa(:,1))
plot(t,xa(:,2))
xlabel('t')
legend('v(t)','h(t)')
```

Figure 6

```
function output =  f(t)
T=100;
if  ( mod(t,T) >= 10.0) && (mod(t,T) <= 13.0 )

    output = 0.25;
else
    output = 0;
end

end
--------
function y = g(t,x)
mu1 = 0.2;
mu2=0.3;
sigma0=0.002;
v = x(1);
h = x(2);
y = [-8.*v.*(v-0.15).*(v-1)-v.*h+f(t);((sigma0+((mu1.*h)./(mu2+v))).*((-h)-8.*v.*(v-(0.15)-1)))];

end
------
X0 = [0, 0];
tspan = 0:0.2:500;
[t,xa] = ode45(@g,tspan,X0);
plot(t,xa(:,1));
hold on
plot(t,xa(:,2));

xlabel('t')
legend('v(t)','h(t)')
```

Figure 7

T=[100,90,80,70,60,50];
APD=[20.6,20.2,19.6,19,18,17];

scatter(T,APD);
xlabel('T')
ylabel('APD')
title('APD vs Stimulation Period T')

Figure 8

T=[100,90,80,70,60,50];
h=[0.017442,0.020004,0.023303,0.027845,0.034229,0.043878];

scatter(T,h);
xlabel('T')
ylabel('steady-state h')
title('Steady-State h vs Stimulation Period T')

Figure 9

APD=[20.6,20.2,19.6,19,18,17];
h=[0.017442,0.020004,0.023303,0.027845,0.034229,0.043878];

scatter(APD,h);
xlabel('APD')
ylabel('Steady-state h')
title('APD vs Steady-state h')