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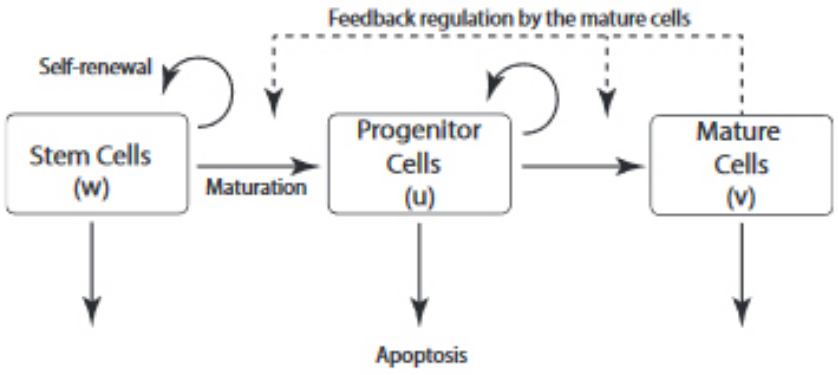
Project II – Neuroendocrine Cells

NEUROENDOCRINE CELLS

Part 1: Describe the problem

The project aims at tracking the three phase transformation of neuroendocrine cells specific to the human colon, which is illustrated in the figure below. A stem cell transforms into a progenitor cell and finally a mature cell through symmetric and asymmetric cell division. Symmetric cell division, also known as self-renewal, occurs when a stem cell divides symmetrically into two identical stem cells. Asymmetric cell division characterizes the maturation process when a stem cell divides into a stem cell and a progenitor cell, or a progenitor cell divides into a progenitor cell and a mature cell. In each phase, cells also experience apoptosis. meaning cell death. With an aim to capture this phenomenon, I want to build a model that track the number of cells in each phase, stem cells, progenitor cells and mature cells.



Part 2: Description of the model

1. Assumptions and notations

First, I denote the total number of stem cells as w, that of progenitor cells as u, and that of mature cells as v.

The model I build in this project is based on these assumptions:

i. Not every cell would follow exactly the process of self-renewing, dividing (symmetric and asymmetric division) or dying. In each phase, there is only some probability of the cells being transformed or die. Mature cells cannot self-renew or divide.
I denote self-renewal rate of a stem cell as a_w and that of a progenitor cell as a_u. I denote a stem cell's division rate as d_w and that of a progenitor cell is d_u.

ii. Symmetric division.

If a stem cell divides symmetrically into two stem cells, the probability of renewal in this case, a_w, would be exactly 1 and the net production of stem cells is exactly 1 stem cell. If the stem cells divide asymmetrically, meaning $a_w = 0.5$, then the net production of stem cells would be 0. Thus, we have the net flux in stem cells due to self-renewal is given by $(2a_w - 1)$. Similarly, we have the net production rate of progenitor cells due to self-renewal is given by $(2a_u - 1)$, where a_u is the probability of symmetric division for a progenitor cell. $(0 < a_u, , a_u < 1)$

Multiplying this rate by the division rate, we have the net change rate in population of stem cells, which is given by $(2a_w - 1)d_w$ and that of a progenitor, given by $(2a_u - 1)d_u$.

iii. Asymmetric division.

In case of asymmetric division, a stem cell would divide into a stem cell and a progenitor cell, and a progenitor cell would divide into a progenitor cell and a mature cell.

If the self-renewal probability of stem cells is a_w, the probability that they divide into progenitor cells is $(1 - a_w)$. Thus, multiplying this rate with the division rate, we have the inflow rate of a stem cell into a progenitor is $2(1 - a_w)d_w$. Similarly, we have the inflow rate of a progenitor cell into a mature cell is $2(1 - a_u)d_u$.

iv. Apoptosis

The cells could die in any phase. The apoptosis rate of each cell is μ_w (for stem cells), μ_u (for progenitor cells) and μ_v (for mature cells).

2. Differential equations

Knowing the inflow and death rate of each cell in each phase, we could build a system of differential equations that captures the change in their population.

Stem cells (w).
Because it is the first phase, the rate of change of stem cells' population over time will depend only its self-renewal rate and division rate of stem cells over time will depend only on its self-renewal rate, division rate and death rate:

$$\frac{dw}{dt} = [(2a_w - 1)d_w]w - \mu_w w$$

Progenitor cells (u)

As the second phase, the inflow rate of progenitor cells depends not only on its own self-renewal, division and death rate, but also the asymmetric division rate of stem cells.

$$\frac{du}{dt} = [(2a_u - 1)d_u]u + [2(1 - a_w)d_w]w - \mu_u u$$

Mature cells (v)

As the last phase, the inflow rate of mature cells solely depends on the asymmetric division rate of progenitor cells and its outflow rate is its death rate.

$$\frac{du}{dt} = [(2(1 - a_u)d_u]u - \mu_v v$$

We could rewrite the system as:

$$\frac{dw}{dt} = [(2a_w - 1)d_w - \mu_w]w$$

$$\frac{du}{dt} = [(2a_u - 1)d_u - \mu_u]u + [2(1 - a_w)d_w]w$$

$$\frac{du}{dt} = [(2(1 - a_u)d_u]u - \mu_v v$$

3. Overall goal

   Given the system of differential equations that captures the rate of change in the population of cells during the three phase transformation, I want to track the total population of cells over time and seek the find the equilibrium for each phase. Furthermore, I want to perform the stability analysis for the equilibria with varying parameters, meaning different rates of symmetric and asymmetric division and death of these cells, to see how they affect the equilibria.

4. Implement the model in Matlab

Solve the system of differential equations

I use ode45 – a numerical-method solver provided by Matlab to solve this 3-D system of linear differential equations. In order to do that, I create a separate function file that defines the system and provide the values for all the parameters. On the main operating file, I provide the initial values of the system, define the time period I want to track and use ode45 for the previously defined function. Lastly, I use the Matlab's plot to give a trajectory of the population of cells over time. Below is the function file.

```
function dYdt = RHS_Function(t,Y)

% Define variables:
w = Y(1);
u = Y(2);
v = Y(3);

% Define paramters:
aw = .1;
au = .2;
dw = .3;
du = .4;
```

```
mu = .01;
mw = .02;
mv = .03;

% Define equations:
dwdt = ((2*aw - 1).*dw).* w - mw.*w;
dudt = ((2*au - 1).*du).*u + (2*(1 - aw).*dw).*w - mu.*u;
dvdt = (2*(1 -au).*du).*u - mv.*v;

% Assemble equations into a single column vector:
dYdt = [dwdt; dudt; dvdt];

end
```

The method I use for stability analysis will be explained in part II.

Part 3: Stability Analysis

1. Equilibria
   To find the equilibria for the system, we set all functions equal to 0:

(1) $\frac{dw}{dt} = [(2a_w - 1)d_w - \mu_w]\, w = 0$

(2) $\frac{du}{dt} = [(2a_u - 1)d_u - \mu_u]\, u + [2(1 - a_w)d_w]\, w = 0$

(3) $\frac{dv}{dt} = [2(1 - a_u)d_u]\, u - \mu_v\, v = 0$

(1) $\Leftrightarrow w^* = 0$ (or $(2a_w - 1)d_w = \mu_w$)
(2) $\Leftrightarrow u^* = 0$ (or $(2a_u - 1)d_u = \mu_u$)
(3) $\Leftrightarrow v^* = 0$ (or $\mu_v = 0$)

We have (0,0,0) is the only equilibrium for the system if the inflow rate of each cell type differs from its death rate. In contrast, we will have an infinite number of equilibria if the inflow rate of each cell type equals to its death rate.

2. Stability analysis

In order to perform the stability analysis, we need to rewrite the system into matrix form.

We have $\frac{d\vec{y}}{dt} = \begin{bmatrix} \frac{dw}{dt} \\ \frac{du}{dt} \\ \frac{dv}{dt} \end{bmatrix}$, $\vec{y} = \begin{bmatrix} w \\ u \\ v \end{bmatrix}$ and $A = \begin{bmatrix} (2a_w - 1)d_w - \mu_w & 0 & 0 \\ 2(1 - a_w)d_w & (2a_u - 1)d_u - \mu_u & 0 \\ 0 & 2(1 - a_u)d_u & -\mu_v \end{bmatrix}$

Thus, we have: $\frac{d\vec{y}}{dt} = A\vec{y}$

The stability of the equilibria of this system depends on the Eigen values of the matrix A. They are stable if the Eigen values of A have negative real parts and vice versa. I use Matlab to find the Eigen values of the system for a given set of parameters. The command I use is “eig(A)”.

If all the Eigen values have negative real parts, the equilibrium point (0,0,0) of the system is stable.

3. Bifurcation analysis

Furthermore, I am interested in seeing how the varying parameters would affect the equilibria and stability of the system. To analyze the impact of the parameters, I create a vector for these parameters, which allows them to take on multiple different values and hold the others constant. For this analysis, I will vary 2 parameters at a time and plot a surface to see how these changes lead to different Eigen values and thus impact the stability of the equilibrium. I then plot the corresponding Eigen values and the two parameters.

For this report, I only focus the third Eigen value (eval(3)).

```
% Changes in the parameters for stem cells
eigenvalues = zeros(1,N);
aw_vec = linspace(lowbound, upbound, N);
au = .2
dw_vec = linspace(lowbound, N, N);
du = .4;
mu = .01;
mw = .02;
mv = .03;

% use for loop to create matrix A for each value of aw and dw

for i =1:N
    aw = aw_vec(i);
    for j = 1:N
        dw = dw_vec(j);
     %    w                              u                v
     A = [(((2*aw - 1).*dw)-mw)       0                 0;
        2*(1 - aw).*dw      (2*au - 1).*du-mu       0;
         0                    2*(1 -au).*du          -1*mv];
    eval = eig(A);
    eigenvalues(i,j)= eval(3); % try trace and det instead!
    end
end

% Plot
[Aw, Dw] = meshgrid(aw_vec, dw_vec)

figure(1);
surf(Aw, Dw,eigenvalues)
title('Illustration of Eigen values','fontsize',20)
xlabel('Aw','fontsize',20)
ylabel('Dw','fontsize',20)
zlabel('Eigen Values','fontsize',20)
```

To see the bifurcation values of d_w, a_w that leads to a zero Eigen values, I plot only the contour of the surface, where the Eigen values are 0. From there, we will know the range for d_w, a_w that determines the critical points where the system changes from being unstable to stable.

```
% Plot the contour for values of aw, dw where eig(A) = 0
figure(2);

[Aw, Dw] = meshgrid(aw_vec, dw_vec)
```

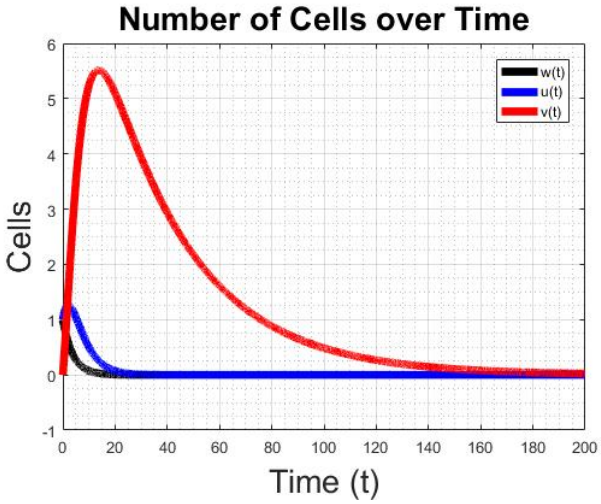
```
contour(Aw, Dw,eigenvalues,[0 0])
xlabel('Aw','fontsize',20)
ylabel('Dw','fontsize',20)
```

The results will be reported in part 4.

Part 4: Data and results

1. Trajectory of the population of cells

Given the plot of the cells' population growth, we could see that in the long run, the number of cells all decay to 0. This confirms our stability analysis in which we predict that there is a unique and stable equilibrium for this system, (0,0,0) as long as the inflow rate differs from death rate in each phase.



2. Stability and bifurcation analysis
    a. Eigen values and stability of the system

What we have found in the plot is also consistent with the Eigen values we have found, given these specific values for our parameters (see the above function file).

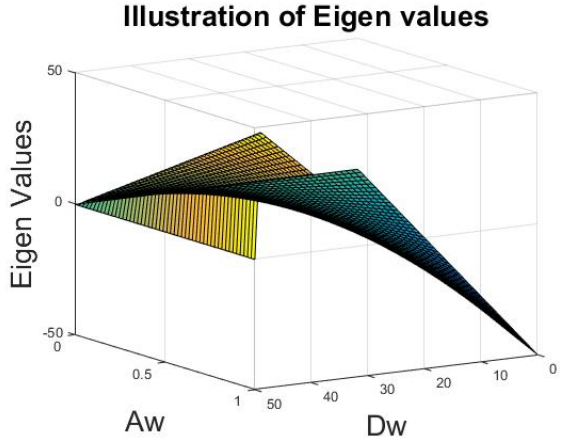
$\lambda_1 = -0.0300$, $\lambda_2 = -0.2500$ and $\lambda_3 = -0.2600$

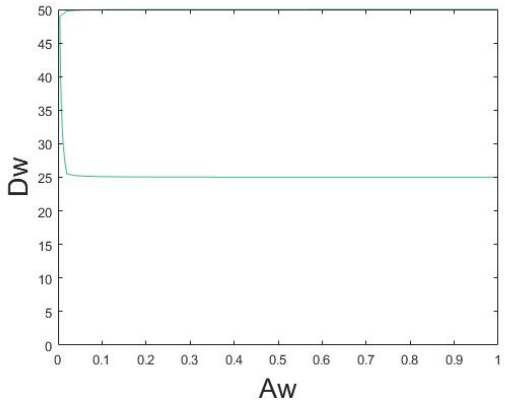
The Eigen values are all negative, indicating that the equilibrium (0,0,0) of the system is stable (a sink).

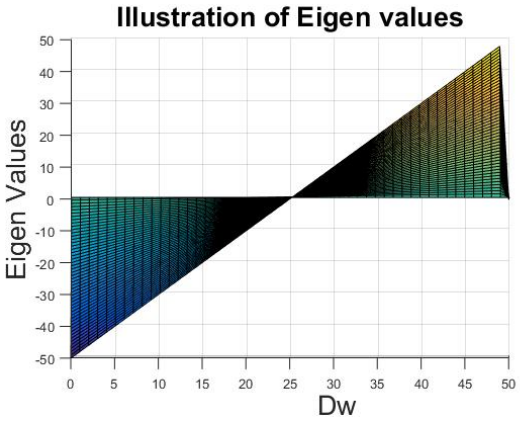
    b. Bifurcation analysis

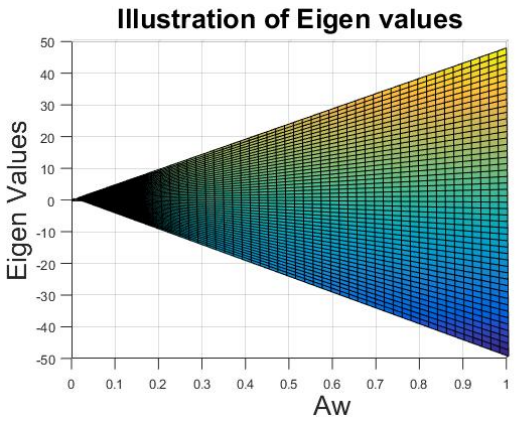
First, I focus on finding the bifurcation values for d_w, a_w, the division rate and self-renewal rate for stem cells. The result is presented by the plot. From these plots, we can see that bifurcation occurs when the division rate of a stem cell, d_w, = 25. The 'contour plot' provides a clearer illustration of this critical value, $d_w^* = 25$.

From the 3-D plot, we notice that the Eigen values > 0 for $d_w > 25$. Thus, the system becomes unstable when $d_w > d_w^* = 25$ and is stable when $d_w < d_w^* = 25$.



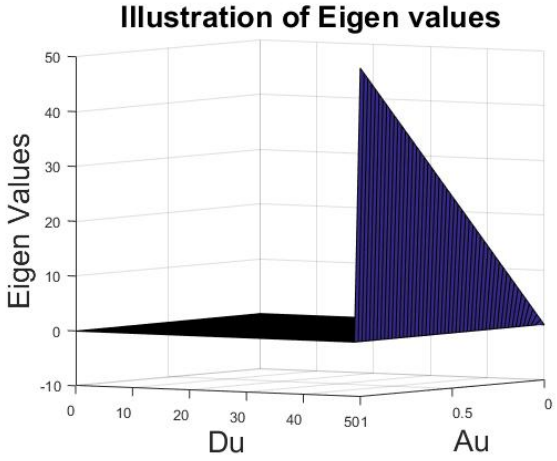


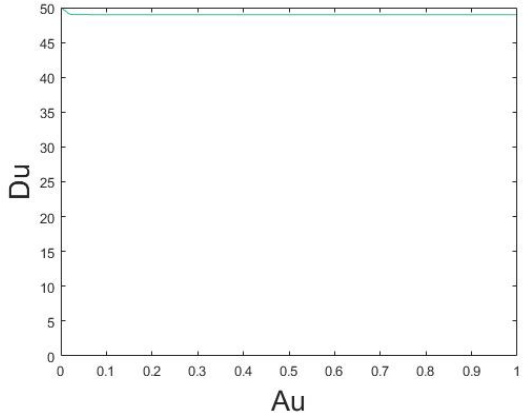


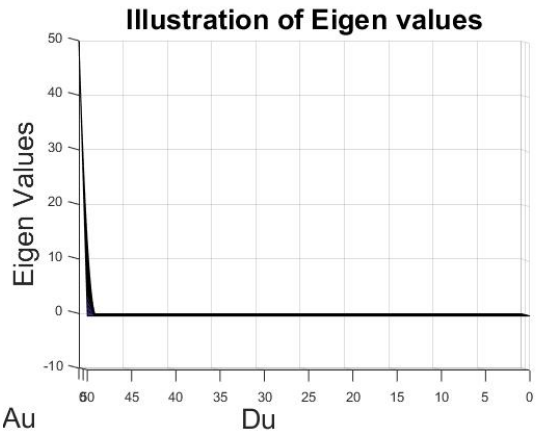


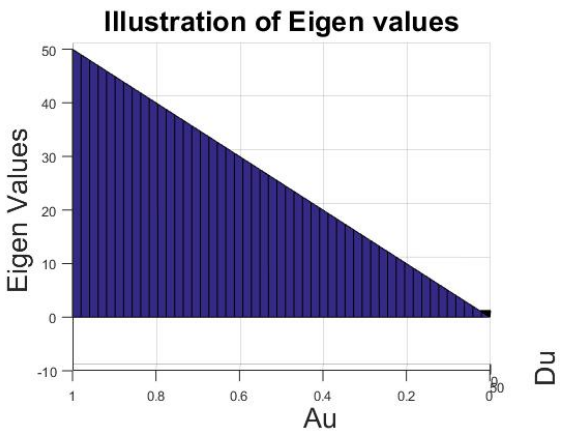
We can apply the same method to examine the critical bifurcation values for parameters of progenitor cells, d_u , a_u. It is interesting to see that when we focus on the second Eigen values only, we get pretty similar plots as we have for d_w, a_w. Thus, I would focus on the first Eigen value instead.

We can see that $d_u^* \approx 50$ is a bifurcation value. The system becomes unstable when $d_u > d_u^* = 50$ and is stable when $d_u < d_u^* = 50$. Interestingly, the second Eigen value seems to remain around 0 for all values of $d_u < 50$.









Part 5: Improvements

1. Introduce the new assumption
   v. An improvement to the model is taking into account the effects of number of mature cells on the overall division rates. It is known that as the number of mature cells increase, the division rates of stem and progenitor cells decrease. Thus, we could have their division rates, d_w and d_u, as a function of v, the total number of mature cells.

To demonstrate the decaying function $d_w(v)$ and $d_u(v)$, we can use a linear function ($d_w(v) = (k - v)(v <= k)$), a decaying exponential function ($d_w(v) = ve^{-t}$) or fractional function ($d_w(v) = \frac{k}{av+b}$)

For this project, I would choose the fractional function to express the relationship between d_w, d_u and v.

2. Implement the change
   a. Numerical solution to the system

We now have d_w, d_u as functions of v, not constants:

$d_w(v) = \frac{k1}{av+1}$ (while a,b,c,d ≥ 0)

$d_u(v) = \frac{k2}{bv+1}$

We have a non-linear system:

$$\frac{dw}{dt} = [(2a_w - 1)\frac{k1}{av+1} - \mu_w]\, w$$

$$\frac{du}{dt} = [(2a_u - 1)\frac{k2}{bv+1} - \mu_u]\, u + [2(1 - a_w)\frac{k1}{av+1}]\, w$$

$$\frac{du}{dt} = [(2(1 - a_u)\frac{k2}{bv+1}]\, u - \mu_v\, v$$

Implementing this change in Matlab, I replace the constant value assigned to d_w, d_u with the new expressions, $d_w(v)$ and $d_u(v)$. The remaining part is kept the same.

```
function dYdt = RHS_Function_New(t,Y)
```

```
% Define variables:
w = Y(1);
u = Y(2);
v = Y(3);


% Define parameters:
k1 = 2;
k2 = 2.5;
a = 0.2;
b = 0.7;


aw = .1;
au = .2;
dw = k1./(a*v + 1);
du = k2./(b*v + 1);
mu = .01;
mw = .02;
mv = .03;

% Define equations:
dwdt = ((2*aw - 1).*dw).* w - mw.*w;
dudt = ((2*au - 1).*du).*u + (2*(1 - aw).*dw).*w - mu.*u;
dvdt = (2*(1 -au).*du).*u - mv.*v;

% Assemble equations into a single column vector:
dYdt = [dwdt; dudt; dvdt];

end
```

b. Equilibria and stability analysis

To find the equilibria for the system, we set all functions equal to 0:

(1) $\frac{dw}{dt} = [(2a_w - 1)\frac{k1}{av+1} - \mu_w]\, w = 0$

(2) $\frac{du}{dt} = [(2a_u - 1)\frac{k2}{bv+1} - \mu_u]\, u + [2(1 - a_w)\frac{k1}{av+1}]\, w = 0$

(3) $\frac{du}{dt} = [2(1 - a_u)\frac{k2}{bv+1}]\, u - \mu_v\, v = 0$

(1) $\Leftrightarrow w^* = 0$

or $(2a_w - 1)\frac{k1}{av+1} = \mu_w \Leftrightarrow (2a_w - 1)\frac{k1}{\mu w} = av + 1$

$\Leftrightarrow v^* = (2a_w - 1)\frac{k1}{a\mu_w} - \frac{1}{a}$

#1 When $w^* = 0$;

(2) $\Leftrightarrow u^* = 0$

or $(2a_u - 1)\frac{k2}{bv+1} = \mu_u$

$\Leftrightarrow v^* = (2a_u - 1)\frac{k2}{b\,\mu_w} - \frac{1}{b}$

i. When $u^* = 0$:

(3) $\Leftrightarrow v^* = 0$

ii. When $v^* = (2a_u - 1)\frac{k2}{b\,\mu_w} - \frac{1}{b}$:

(3)$\Leftrightarrow (2a_u - 1)\frac{k2}{bv+1} - \mu_u = 0 \Leftrightarrow \mu_v\, v = 0 \Leftrightarrow v^* = 0$. Contradict!

This is only true when v* = $(2a_u - 1)\frac{k2}{b\,\mu_w} - \frac{1}{b} = 0$ (this depends on the parameters)

Thus, the equilibrium is (0,0,0).

#2 When v* = $(2a_w - 1)\frac{k1}{a\mu_w} - \frac{1}{a}$:

(2) $\frac{du}{dt} = [(2a_u - 1)\frac{k2}{bv+1} - \mu_u]\,u + [2(1 - a_w)\frac{k1}{av+1}]\,w = 0$

(3) $\frac{du}{dt} = [2(1 - a_u)\frac{k2}{bv+1}]\,u - \mu_v\,v = 0$

It is interesting that if we plug in v* and solve for u* and w*, there may exist another equilibrium point (w*, u*, v*) which are functions of the parameters. However, for this project, I'm only interested in the trivial equilibrium, (0,0,0) and its stability.

We know that (0,0,0) is one equilibrium for the system if the inflow rate of each cell type differs from its death rate.

3. Stability and bifurcation analysis

In order to perform the stability analysis, we need to rewrite the system into matrix form.

We have $\frac{d\vec{y}}{dt} = \begin{bmatrix} \frac{dw}{dt} \\ \frac{du}{dt} \\ \frac{dv}{dt} \end{bmatrix}$, $\vec{y} = \begin{bmatrix} w \\ u \\ v \end{bmatrix}$ and the matrix B:

$$B = \begin{bmatrix} (2a_w - 1)\frac{k1}{av+1} - \mu_w & 0 & 0 \\ 2(1 - a_w)\frac{k1}{av+1} & (2a_u - 1)\frac{k2}{bv+1} - \mu_u & 0 \\ 0 & 2(1 - a_u)\frac{k2}{cv+d} & -\mu_v \end{bmatrix}$$

Thus, we have: $\frac{d\vec{y}}{dt} = B\vec{y}$

The stability of the equilibria of this system depends on the Eigen values of the matrix B. They are stable if the Eigen values of B have negative real parts and vice versa. However, it is hard to implement the change in the parameters in Matlab. It is because a matrix is defined in Matlab if it consists of all constant value. In this improved model, the division rates are unknown because they depend on v, the number of mature cells. Thus, to examine the Eigen values of this system, I use the "for" loop to find the Eigen values for a few values of v.

```
v_vec = linspace(0, 10, N)
eigenvalues = zeros(3,N)

for i = 1:N
    v = v_vec(i)

% Matrix A
%    w                          u                v
    A = [((2*aw - 1).*dw)-mw      0                    0;
```

```
        2*(1 - aw).*dw      ((2*au - 1).*du)-mu   0;
     0                    2*(1 -au).*du      -1*mv]

    eigenvalues(:,i)= eig(A)
end
```

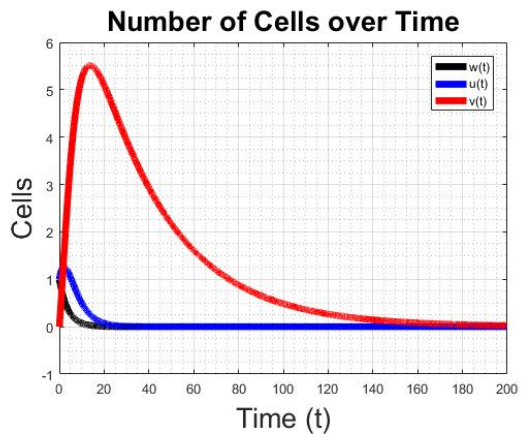
4. Bifurcation analysis

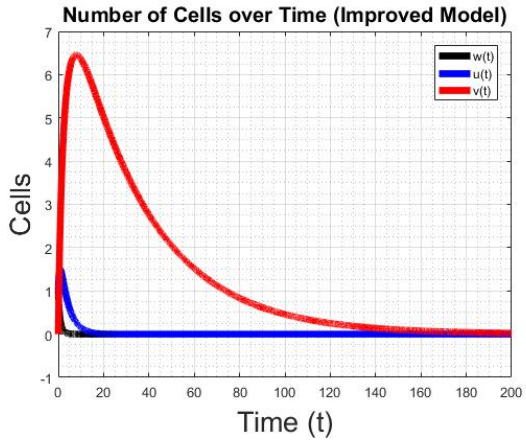
I am interested in seeing how the varying parameters would affect the equilibria and stability of the system. To analyze the impact of each parameter, I create a vector for this parameter, which allows it to take on multiple different values and hold others constant. I then plot the corresponding Eigen values of B resulting from this change.

5. Comparison with the original system
   a. Solutions to the system

I don't see a huge different between the two models in terms of the plot of numerical solutions. In both model, the number of cells all converge to 0 in the long run. Thus, both systems show that (0,0,0) is a stable equilibrium.

From the plot, we could see that when the division rates depend on number of mature cells, the growing and decaying process of mature cells takes place faster. v(t) has a "steeper" peak.





b. Stability analysis.

With this set of parameters (see the function file above), we find that the Eigen values are:

```
eigenvalues =


  Columns 1 through 7

   -0.0300   -0.0300   -0.0300   -0.0300   -0.0300   -0.0300   -0.0300

   -0.1975   -0.1975   -0.1975   -0.1975   -0.1975   -0.1975   -0.1975

   -0.5533   -0.5533   -0.5533   -0.5533   -0.5533   -0.5533   -0.5533


  Columns 8 through 10

   -0.0300   -0.0300   -0.0300

   -0.1975   -0.1975   -0.1975
```

```
   -0.5533   -0.5533   -0.5533
```

From these results, we can see that all of the Eigen values are negative (for these specific values of v). As we see from the plot, given this set of parameters, the maximum value of mature cells is around 8 while the results above are for v in (0, 10). Thus, we can generalize this result and say that Eigen values are always negative in this system. The equilibrium (0,0,0) is always stable. This conclusion is consistent with our original model.

Part 6: Conclusion

The project is designed to track the transformation of neuroendocrine cells specific to the human colon, which consist of three phases: stem cells, progenitor cells and mature cells. These transformations result from symmetric cell division (self-renewing) and asymmetric cell division (a cell dividing into two cells of different kinds). This project uses differential equations to mathematically represent the changes in number of each type of cells due to its transformation or death, and provides qualitative analysis for this model.

Using Matlab to solve this system of differential equations numerically, I have found that the number of cells will eventually decay to zero, which is consistent with the stability analysis I have constructed mathematically by working on the system of differential equations. (0,0,0) is a unique and stable equilibrium for the original model, in which I assume all the parameters and variables are independent of one another. To further explore the effects of changes in division rates or probabilities, I perform bifurcation analysis that focuses on the self-renewing and division rate of stem cells and those of progenitor cells. It is interesting to see that bifurcation does occur when the division rate of each cell gets too big. For stem cell, the critical value of division rate is 25, and that of progenitor cell is around 50. These values are valid to explain the bifurcation of only one of the three Eigen values of the system.

Given these findings, the model still has limitations and room for improvements. The first limitation of the model is to assume that all parameters and variables are independent of one another. In reality, it is known that the division rates of stem cells and progenitor cells are greatly affected by the number of mature cells. This notation is included in my improved model, which implies a possibility of having another equilibrium point other than (0,0,0). The stability analysis for the trivial equilibrium is consistent with our finding in the original model. Further explorations to this model could include continuing the bifurcation analysis for the improved model, changing the initial values for stem cells and progenitor cells or exploring the relationship among the parameters (stem cells' division and self-renewal rate vs. those of progenitor cells).