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Modelling in Biology

Assignment 2

Question 1: A one-dimensional model from population dynamics

We are given a non-dimensionalized version of an ecological model of an insect population in a forest below.

$$\dot{x} = rx\left(1 - \frac{x}{k}\right) - \frac{x^2}{1+x^2}$$

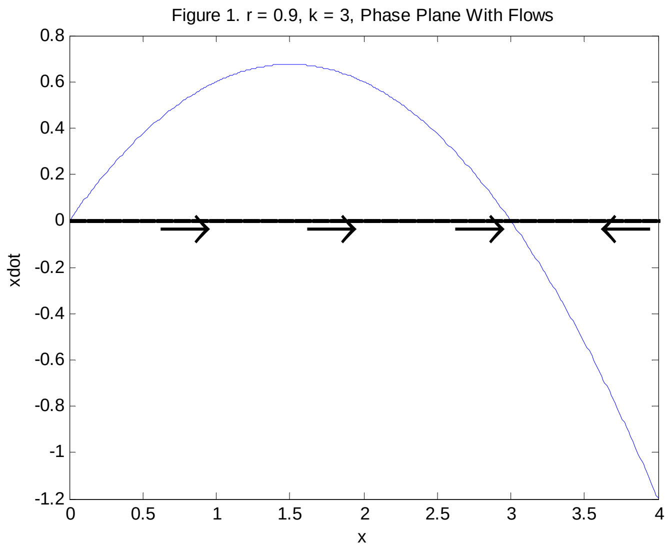
The first source term is the logistic growth of the insects and the second sink term refers to the depletion of the population caused by predation. If we first consider the simple case where there are no predators, we can obtain the following equation.

$$\dot{x} = rx\left(1 - \frac{x}{k}\right)$$

Finding the fixed points of this system is straight forward. First, we set $\dot{x} = 0$, and solve for the values of x^*, which satisfy the equation. The fixed points of the equation are:

$$x^* = 0, k$$

For values between 0 and *k*, the value of $\dot{x}$ is greater than 0, but for values of *x* above *k*, the value of $\dot{x}$ is less than 0, leading to the conclusion that $x^* = k$ is a stable node of the system while $x^* = 0$ is an unstable node. Plotting a graph of the phase plane with the one dimensional flows gives us better intuition of the system.



In figure 1, we can see that if we let *r* = 0.9 and *k* = 3, the system is attracted to $x^* = 3$, the stable fixed point of the system. However, since $x^* = 0$ is also a fixed point, if the initial condition was set to 0, then the population would also continue to be zero. If this value were perturbed, then the population would increase to $x^* = 3$ (the attractor of the system).

Let us now consider the complete system:

$$\dot{x} = rx\left(1 - \frac{x}{k}\right) - \frac{x^2}{1 + x^2}$$

We can do a similar analysis to above to obtain the fixed points by setting $\dot{x} = 0$ and solving for values of x which satisfy the equation. It can also be seen that if x is factored out, $x^* = 0$ is always a fixed point of the system.

$$0 = rx\left(1 - \frac{x}{k}\right) - \frac{x^2}{1 + x^2} = x\left[r\left(1 - \frac{x}{k}\right) - \frac{x}{1 + x^2}\right]$$

To obtain the local stability of the problem, we can look at the gradient of the phase plot close to $x^* = 0$. If we let $\dot{x} = f(x)$, then we differentiate to obtain the following and evaluate it at $x^* = 0$.

$$f'(x) = -\frac{rx}{k} + r\left(1 - \frac{x}{k}\right) + \frac{2x^3}{(1 + x^2)^3} - \frac{2x}{1 + x^2}$$
$$f'(0) = r$$

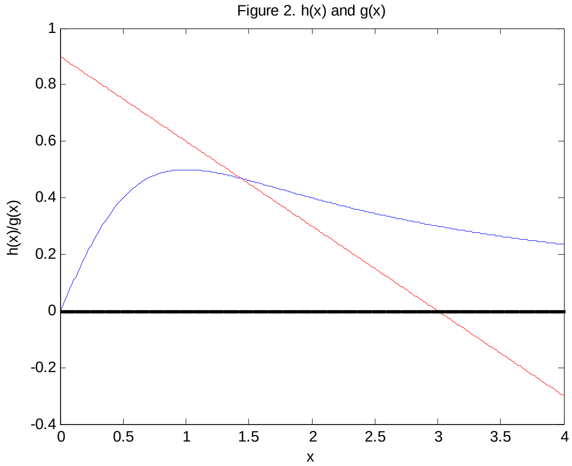
Hence, the stability of the fixed point at $x^* = 0$ depends on the value of r. We assume that r is a positive real value and we can conclude that $x^* = 0$ is an unstable node.

The other fixed points of the system can be obtained through several different methods. The easiest, but least accurate is to use a geometric approach by looking at the intersection of two lines. We make the following substitutions to our complete system:

$$h(x) = r\left(1 - \frac{x}{k}\right) \text{ and } g(x) = \frac{x^2}{1 + x^2}$$

If the value of h is above the value of g, then we can conclude that the value of $\dot{x}$ is positive and the flows are in the positive direction. The reverse holds true when the value of g is greater than h. Plotting h and g on the same graph we obtain figure 2.

Figure 2. h(x) and g(x)



By zooming in closer to where the intersection occurs, we can deduce that the other fixed point occurs when $x^* = 1.44$ to three digits of accuracy (3sf).

A more accurate method would be to allow the computer to do a numerical solution to find where the two curves intersect (i.e. when $h - g = 0$). For this method, we can use the `fsolve` function.

We define our function in a separate m file as shown below.

```
function F = myfun(x)
global r k
F = r*x.*(1-(x./k)) - ((x.^2)./(1+x.^2));
```

Then we can call the `fsolve` function as shown below supplying our initial guess in the second argument of the function.

```
B = fsolve(@myfun, 1)
```

This yields the solution B = 1.4373, the second fixed point in our system. Although zooming into the function gave us a pretty good estimate of the value of the fixed point, `fsolve` is much faster, more elegant, and the value is reusable in Matlab. To analyze the stability of this fixed point, we can again find the slope of the phase plane as above.

$$f'(1.4373) = -0.27$$

As this is a negative value, this shows that our new found fixed point is stable. But have we really found all the fixed points of the system? One method is to use the solve function to find all values for which $\dot{x} = 0$. This function finds all of the roots of the equation without having the need for initial guesses. Multiplying out the function, it can be seen that we get a quartic term meaning that we should be getting 4 different fixed points to our system.

```
A = solve('0.9*x*(1-(x/3))-((x^2)/(1+x^2))');
```

Which when run gives:

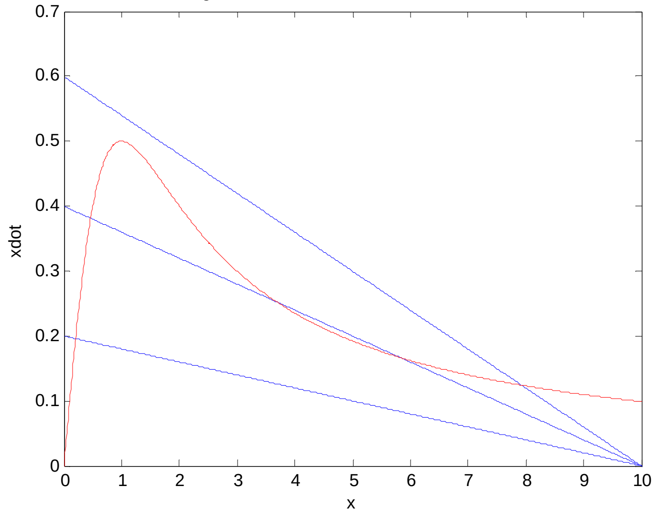
```
A =

                                                                   0.
                                        1.4372866581082433838758550746653
 .78135667094587830806207246266737+1.2152152275843732767755856584891*i
 .78135667094587830806207246266737-1.2152152275843732767755856584891*i
```

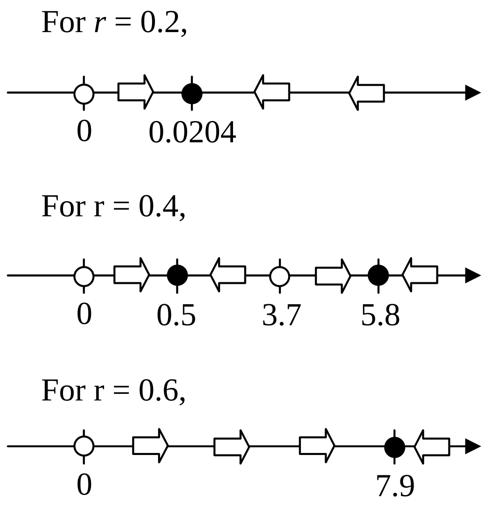
As expected, there are 4 fixed points; however, two of them are imaginary and would not be found using the `fsolve` method. After analysis of the only two real fixed points, we can conclude that for almost all initial conditions (except for 0), the value of the population will approach x^* = 1.4373, the only stable fixed point in our system. This is less than the value we obtained in the absence of predators as expected. Predation limits the growth of a population and the equilibrium value would be expected to be less than without predation.

To further continue our stability analysis, we can perturb the values of k and r to see changes in the behavior of our system. First if we fix the value of k to be 10 and see changes to the behaviour when we increase the value of r (0.2, 0.4, and 0.6), we can see that the number of fixed points increases from two to a maximum of 4 (including the one at $x^* = 0$) and decreases again to two fixed points as r is increased even further (figure 3).

Let us consider each value of r separately and sketch the flows on the line. First, when r = 0.2, there are two fixed points at 0 and 0.0204 (obtained using `solve` function). They are unstable and stable respectively and we can plot this on the line as shown below.

Figure 3. Phase Plane with various r values

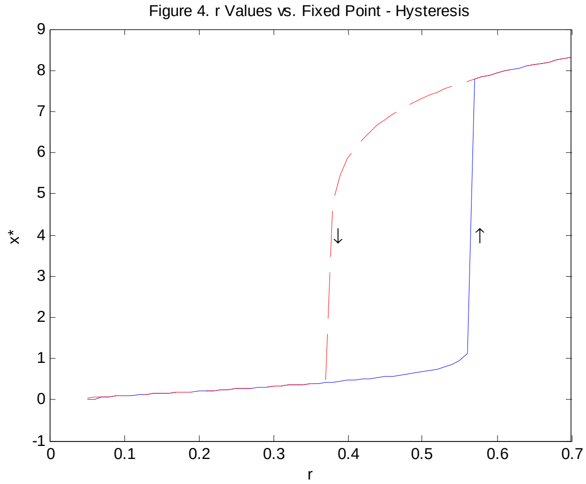




Calculating for the fixed points can also be done by `fsolve`, knowing *a priori* how many fixed points we expect. Interpreting the results of our stability analysis, we can infer that if $r = 0.2$, then for all initial conditions not at $x = 0$, then the value of the population will be attracted to $x^* = 0.02$. For $r = 0.4$, there are four fixed points and starting at any of the fixed points will cause the population to remain at the point. However, for all initial conditions between 0 and 3.7, then the population will move to the stable 0.5 fixed point. For initial conditions above 3.7, the population will tend to the stable 5.8 fixed point. For $r = 7.9$, this is again similar to when we were considering $r = 0.2$, and for all initial conditions except 0, the population will tend to 7.9, the only stable fixed point of the system.

An important feature of this system is that it exhibits hysteresis, or that perturbation of a parameter in one direction does not yield the same results as perturbation of the same parameter in a different direction. We shows this by simulating a slow drift of the growth rate of *r*, which could be the result of natural selection, weeding out the slower less virile insects, leaving the faster insects to replicate, speeding up the growth rate.

Figure 4. r Values vs. Fixed Point - Hysteresis



In figure 4, we can see the result of the hysteresis. The blue solid line reflects the only fixed point found when $r = 0.05$. Increasing the values of *r* slowly using the x^* value calculated as the next guess, will cause us to track the fixed point as we increase the value of *r*. However, at approximately $r = 0.6$, we see that the `fsolve` function loses the fixed point and finds the fixed point near $x^* = 8$ (also a stable fixed point). Upon return (red crosses), the `fsolve` function finds the only fixed point at around $x^* = 8$ and tracks that fixed point. A bifurcation occurs and the fixed point is lost. The `fsolve` function picks up again on the original fixed point until reaching $r = 0.05$ again.

Thus, in the above figure (4), we can see that the behavior of the function depends on which path is taken. Two bifurcations occur on this interval, corresponding to the jumps seen in figure 4. We can approximate these values by asking matlab to print the value of r when the exitflag = -2 (referring to when no convergent solutions are found). Unfortunately, this only works when we are sampling r values on return. To get the bifurcation on the upward direction, we can make the assumption that the x^* value that we find will not be less than the previous value. This is implemented in the code below. The r values at which the bifurcations occur are at r = 0.37 and 0.57.

```
k1 = 10;
rvals = 0.05:0.01:0.7;
x0 = 0.5; %The initial guess
E(1) = x0;
for i = 2:length(rvals)+1
    r1 = rvals(i-1);
    [E(i),fval,exitflagup(i)] = fsolve(@myfuna, x0);
    if E(i) < E(i-1)
        x0 = 8;
        upbif = r1 %Finds first bifurcation
    else
        x0 = E(i);
    end
end
figure;
plot(rvals,E(2:length(rvals)+1))
title('Figure 4. r Values vs. Fixed Point - Hysteresis')
xlabel('r')
ylabel('x*')
hold on;
rvals1 = 0.7:-0.01:0.05;
x0 = 8; %The initial guess
for i = 1:length(rvals1)
    r1 = rvals1(i);
    [K(i),fval,exitflagdown(i)] = fsolve(@myfuna, x0);
    if exitflagdown(i) == -2
        x0 = 0.8;
        downbif = r1 %Finds second bifurcation
    else
        x0 = K(i);
    end
end
plot(rvals1,K, 'xred')
hold off;
```

For the bifurcation that occurs at r = 0.37, we can see that one stable and another unstable node collide and annihilate each other. The same is seen for the bifurcation that occurs at r = 0.57. Thus we can conclude that both bifurcations are saddle nodes.

For all models, it is necessary to bring it back to the biology to interpret our results. Outbreaks occur when we the population resides at a high fixed point value. Following the plot of figure 4, we can see that the r value can be perturbed substantially before the fixed point is lost. From this, we can infer that an outbreak does not readily occur so long as the r value is below 0.57. Once the growth rate increases past this value, an outbreak occurs and the population jumps to a higher fixed point. However, once an outbreak occurs, the r values must again be perturbed to r = 0.37 for the outbreak to be controlled again. So once a relatively rare outbreak occurs, it takes long to disappear.

Question 2: A two-dimensional (two-species) population model

In this problem, we now look at the two-dimensional model of rabbits and sheep competing for the same food resources. The two equations governing the growth of each species is shown below.

$$\dot{x} = 3x\left(1-\frac{x}{3}\right)-2xy$$
$$\dot{y} = 2y\left(1-\frac{y}{2}\right)-xy$$

The population of rabbits is given by the variable *x* and the population of sheep by the variable *y*.

If we first consider growth of both species without the competition (*xy*) term, then we can see that it follows a logistic growth curve. We can differentiate the logistic growth curve and see which one has the higher maximum to determine which species reproduces faster by the model.

$$\dot{x} = 3x - x^2 \Rightarrow \ddot{x} = 3-2x = 0 \Rightarrow x = \frac{3}{2} \Rightarrow \dot{x}\left(\frac{3}{2}\right) = 2.25$$
$$\dot{y} = 2y - y^2 \Rightarrow \ddot{y} = 2-2y = 0 \Rightarrow y = 1 \Rightarrow \dot{y}(1) = 1$$

So rabbits are capable of reproducing 2.25 times faster than sheep (under the right conditions). In the absence of competition, we can also determine the maximum population level (which is also equal to the carrying capacity for each species) and conclude which population would be larger. By solving the differential equations, we can get functions of the population of rabbits and sheep as a function of time with c_1 and c_2 being constants of integration. The solution was done using the matlab commands shown below:

```
eqns = dsolve('Dx = 3*x - x^2')
eqns1 = dsolve('Dy = 2*y - y^2')
```

$$\dot{x} = 3x - x^2 \Rightarrow x(t) = \frac{3}{1+3c_1e^{-3t}}$$
$$\dot{y} = 2y - y^2 \Rightarrow y(t) = \frac{2}{1+2c_2e^{-2t}}$$

The maximum value of the population will occur as the value of t approaches infinity.

$$\lim_{t\to\infty} x(t) = 3$$
$$\lim_{t\to\infty} y(t) = 2$$

Here we can see that the population of rabbits reaches at equilibrium without competition is higher than the population of sheep. Now let's consider the competition term *xy* in both equations. We can see that the population of rabbits decreases twice as fast as the population of sheep since the ratio of the two competing term is 2. Presumably, the rabbits die faster when there is less food available (which is related to the amount of competition). This sink term is biologically interpreted as the rate of change of either the sheep or rabbits is dependent on the number of that species and the number of the other species while the numerical factor attenuates the effect of the competition depending on how quickly the competition takes effect.

Proceeding onto the linear analysis of the system, we can find the fixed points of the system again using the solve function of matlab.

```
A = solve('3*x*(1-x/3) - 2*x*y = 0','2*y*(1-y/2) - x*y = 0');
for i = 1:length(A.x)
    fp(i,:) = [A.x(i) A.y(i)];
end
fp
```

The fixed points found were:

```
fp =

[ 0,  0]
[ 0,  2]
[ 3,  0]
[ 1,  1]
```

We can also calculate the Jacobian of the system with matlab and evaluate the Jacobian at the fixed points to find the eigenvalues and eigenvectors. First, we calculate the Jacobian analytically.

```
syms x y
F = [3*x*(1-x/3)-2*x*y; 2*y*(1-y/2)-x*y];
v = [x,y];
jac = jacobian(F,v)

jac =

[ 3-2*x-2*y,       -2*x]
[         -y,    2-2*y-x]
```

And now evaluating it at each point to determine the stability of the 4 fixed points:

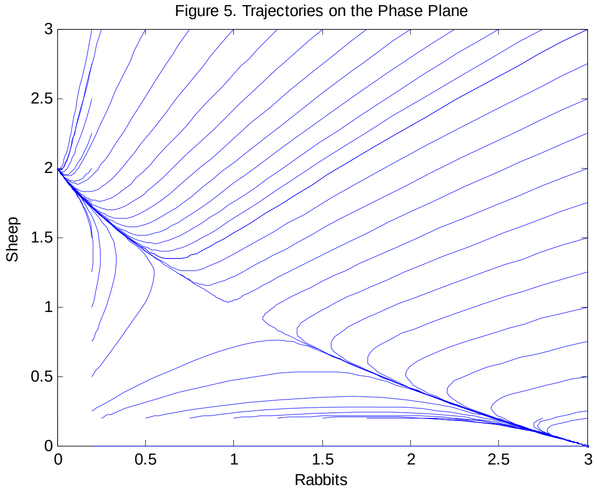
Fixed Point	Jacobian	Trace	Delta	Eigenvalues	Eigenvectors
(0,0)	$\begin{pmatrix} 3 & 0 \\ 0 & 2 \end{pmatrix}$	5	6	2, 3	$\begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}$
(0,2)	$\begin{pmatrix} -1 & 0 \\ -2 & -2 \end{pmatrix}$	-3	2	-2, -1	$\begin{pmatrix} 0 & 1 \\ 1 & -2 \end{pmatrix}$
(3,0)	$\begin{pmatrix} -3 & -6 \\ 0 & -1 \end{pmatrix}$	-4	3	-1, -3	$\begin{pmatrix} -3 & 1 \\ 1 & 0 \end{pmatrix}$
(1,1)	$\begin{pmatrix} -1 & -2 \\ -1 & -1 \end{pmatrix}$	-2	-1	$-1 \pm \sqrt{2}$	$\begin{pmatrix} 1 & 1 \\ -\sqrt{2}/2 & \sqrt{2}/2 \end{pmatrix}$

We calculate the linear stability of the nodes depending on the relative values of the trace and delta from the evaluated Jacobian matrix at the fixed point.

Fixed Point	$\tau^2 - 4\Delta$	**Stability**
(0,0)	1	Unstable Node
(0,2)	1	Stable Node
(3,0)	4	Stable Node
(1,1)	8	Saddle Node

We can also use matlab to draw a flow of trajectories on the phase plane (*x*,*y*) to get an intuition for various initial conditions to get an idea of where the function will tend to.

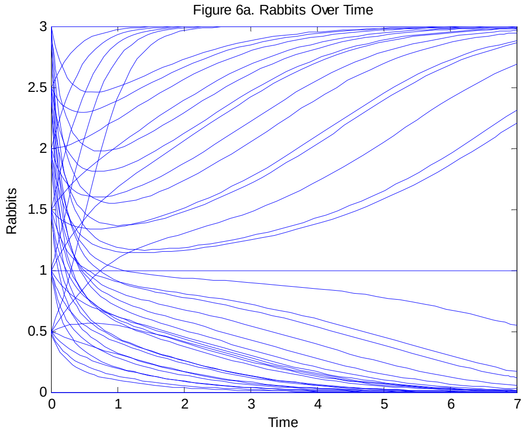
Figure 5. Trajectories on the Phase Plane

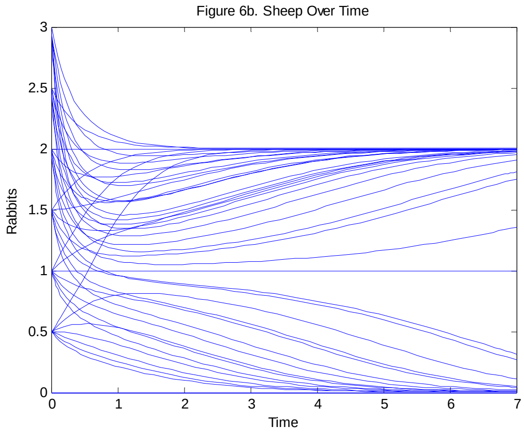


Through looking at figure 5, it can clearly be seen that (0,2) and (3,0) are attracting points of the system. (0,0) is a repelling node and initial conditions move away from that node and approach the other two stable nodes. Although (1,1) is a saddle node and should be stably approachable along one axis, none of the initial conditions presented in figure 5 are exactly on that path. We also notice that the axes also contain straight-line trajectories whereby any value not equal to zero will be driven towards the fixed point (ie the case of population growth without competition as we explored in the first part of the question).

To return to the biology of our model, we can infer that since we have only two stable nodes, most initial conditions will tend to cause the populations to move towards those stable nodes. Unfortunately, the stable nodes only have one species, leading us to conclude that in the end, only one species can survive on any given resource unless the population is controlled very specifically. Here we see the principle of competitive exclusion where two competing species for the same limited resource cannot typically coexist (Strogatz, p. 158). The fixed point (1,1) is the only theoretical stable node where both species can live in harmony, and corresponds to the populations . We can see in figure 6a and 6b this effect of competitive exclusion except for when the initial conditions are both (1,1).

In the management of a farm, one would try to get as close as possible to the (1,1) fixed point to sustain the population of both species for as long as possible. Furthermore, initial conditions along the stable manifold, the special trajectory which dives into the saddle point, the population of the farm would remain stable. With our currently knowledge of systems, it is difficult to say exactly which initial values lie on this stable manifold, but as we can see with our phase diagram, it lies somewhere between the two trajectories flanking a line going closest to the (1,1) fixed point. This fixed point refers to the concentration or density of each species in the farm. Only if we have the density of 1 sheep and 1 rabbit per unit area will be have a stable population of animals. If there would be two sheep and two rabbits per unit area, this would no longer be on the stable manifold and the population would tend to another fixed point and competitive exclusion holds again.





If we slightly change the form of the equations to the ones below, we see a different behaviour altogether.

$$\dot{x} = 3x\left(1 - \frac{2x}{3}\right) - xy$$

$$\dot{y} = 2y\left(1 - \frac{y}{2}\right) - xy$$

In this model, we see that the competition term is the same for both rabbits and sheep meaning that they both will die just as fast for given levels of population. For every one sheep that dies, there will be one rabbit that dies. We also have a slight change in the carrying capacity of the rabbit population. Instead of the fixed point when no competition occurs being at $x^* = 3$, it now occurs at $x^* = 3/2$, or half the previous population. We can do a similar analysis to above and obtain the fixed points and trajectories of the system to become more aware of the consequences of these small changes we have made.

The new fixed points are:

```
nfp =

[    0,    0]
[    0,    2]
[ 3/2,    0]
[    1,    1]
```

And the stability analysis of these points using the Jacobian matrix:

```
jac1 =

[ 3-4*x-y,        -x]
[       -y,  2-2*y-x]
```

Fixed Point	Jacobian	Trace	Delta	Eigenvalues	Eigenvectors
(0,0)	$\begin{pmatrix} 3 & 0 \\ 0 & 2 \end{pmatrix}$	5	6	2, 3	$\begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix}$
(0,2)	$\begin{pmatrix} 1 & 0 \\ -2 & -2 \end{pmatrix}$	-1	-2	1, -2	$\begin{pmatrix} -3/2 & 0 \\ 1 & 1 \end{pmatrix}$

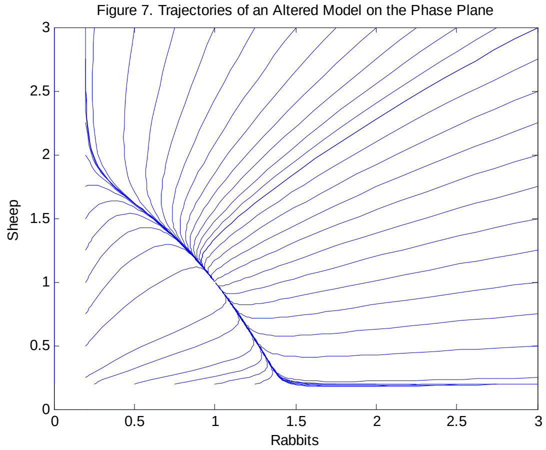
(3/2,0)	$\begin{pmatrix} -3 & -\frac{3}{2} \\ 0 & -2 \end{pmatrix}$	$-\frac{5}{2}$	$-\frac{3}{2}$	$\frac{1}{2}, -3$	$\begin{pmatrix} 1 & 1 \\ -\frac{7}{3} & 0 \end{pmatrix}$
(1,1)	$\begin{pmatrix} -2 & -1 \\ -1 & -1 \end{pmatrix}$	-3	1	$-\frac{1}{2} \pm \frac{\sqrt{5}}{2}$	$\begin{pmatrix} 1 & 1 \\ -\frac{1}{2} - \frac{\sqrt{5}}{2} & -\frac{1}{2} + \frac{\sqrt{5}}{2} \end{pmatrix}$

We calculate the linear stability of the nodes depending on the relative values of the trace and delta from the evaluated Jacobian matrix at the fixed point.

Fixed Point	$\tau^2 - 4\Delta$	**Stability**
(0,0)	1	Unstable Node
(0,2)	9	Saddle Node
(3/2,0)	$\frac{49}{4}$	Saddle Node
(1,1)	5	Stable Node

From the stability analysis, we see that (1,1) has now become a stable node while (3/2,0) and (0,2), the nodes corresponding to only rabbits or only sheep existing, are saddle nodes. We can guess that the stable manifold to these saddle nodes would be along the axes where there is exclusively one species in the population. Otherwise, we expect the population approach the stable node at (1,1). In this case, both populations can coexist harmoniously so long as the initial conditions are correct. Below in figure 7 we see a phase portrait of the system with a few trajectories.

Figure 7. Trajectories of an Altered Model on the Phase Plane



In figures 8a and 8b below, we can see the effect over time of the model. Although there are trajectories over time going to 1.5 for rabbits and 2 for sheep, this corresponds to the other population being set to 0. All other trajectories over time will converge to 1 (except of course when both populations are zero). In this model, the management of a farm is simple as the population of both species will tend to (1,1) equilibrium over time.

Figure 8a. Rabbits Over Time for Altered Model

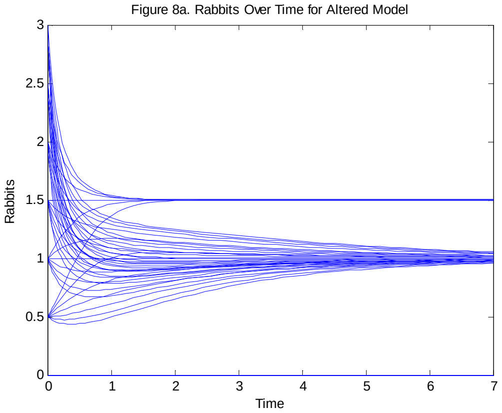
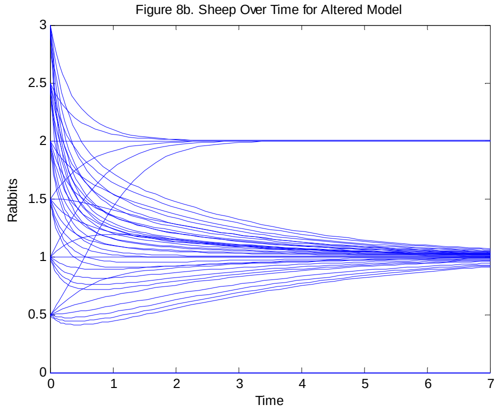


Figure 8b. Sheep Over Time for Altered Model



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Question 3: The production of energy in yeast: a model for glycolysis

In this problem we attempt to analyze one section of the metabolism of glucose, specifically the energy input stage of glycolysis or the conversion of glucose first into glyceraldehyde-3-phosphate (G3P) and then into pyruvate, the final product of glycolysis. In the first reaction, glucose (B) is converted to F6P (fructose-6-phosphate) (Y) by a hexokinase enzyme. The next enzyme in the pathway, phosphofructokinase, is a rate limiting step for glycolysis and hydrolyses ATP (C) into ADP (X) and transferring the phosphate group to F6P making F1,6BP (fructose-1,6-bisphosphate) (D). This step is one of the rate limiting steps of glycolysis as it synthesizes a high energy intermediate which can then undergo a series of exothermic reaction to release energy ultimately in the form of ATP. Later in the glycolysis pathway, F6P is converted to 2 molecules of G3P. The G3P is then converted to pyruvate, each G3P molecule releasing 2 molecules of ATP, and is the final product of glycolysis.

Identifying the key steps in this pathway, we come up with the 4 chemical equations below.

$$B \xrightarrow{k_1} Y$$
$$C + Y \xrightarrow{k_2} X + D$$
$$2X + Y \xrightarrow{k_3} 3X$$
$$X \xrightarrow{k_3} E$$

Where B, C, D, and E are metabolites in the pathway we assume to be in equilibrium, and we are only concerned with the concentrations of ADP (X) and F6P (Y). Utilizing the law of mass action, we can come up with rate equations governing the system below.

$$\frac{dY}{dt} = k_1 B$$
$$\frac{dY}{dt} = -k_2 CY, \frac{dX}{dt} = k_2 CY$$
$$\frac{dY}{dt} = -k_3 X^2 Y, \frac{dX}{dt} = k_3 X^2 Y$$
$$\frac{dX}{dt} = -k_3 X$$

Now, gathering the equations together, we get the governing relationships below (ie the system of differential equations describing the system).

$$\frac{dY}{dt} = k_1 B - k_2 CY - k_3 X^2 Y$$
$$\frac{dX}{dt} = k_2 CY + k_3 X^2 Y - k_3 X$$

To non-dimensionalize the equations, we first divide both equations by k_3 and we make the following substitutions.

$$y = Y,\ x = X,\ b = \frac{k_1 B}{k_3},\ a = \frac{k_2 C}{k_3}, \text{ and } \tau = k_3 t$$

We get now the non-dimensionalized form of the equations found below.

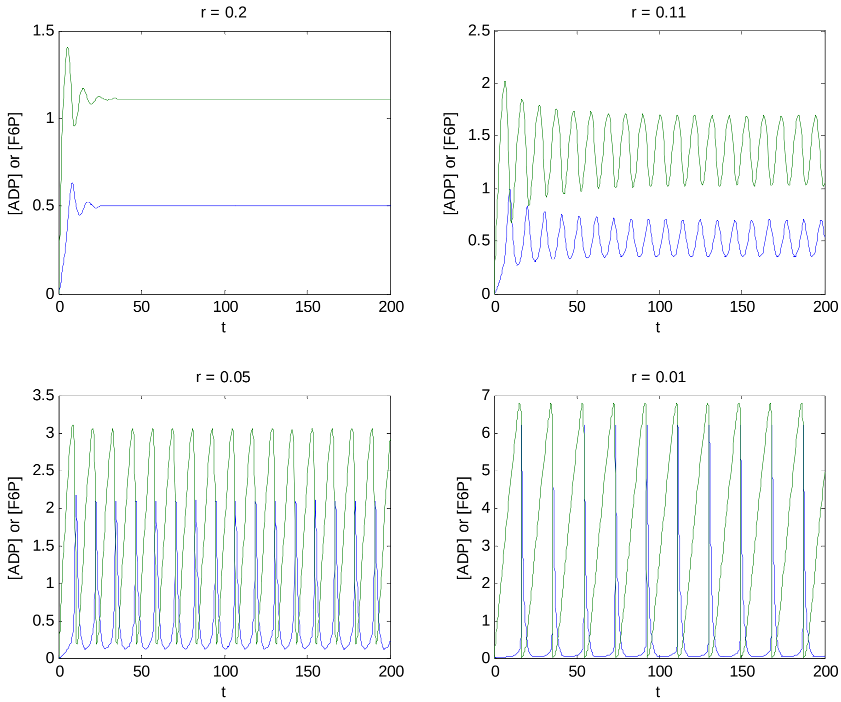
$$\dot{y} = \frac{dy}{d\tau} = b - ay - x^2 y$$
$$\dot{x} = \frac{dx}{d\tau} = ay + x^2 y - x$$

To get a feel of this function, we can first solve the differential equations numerically with ode45 and plot the value of ADP (*x*) and F6P (*y*) as a function of time. We defined the matlab function with the equation as shown below.

```
function dx = adpfun(t,x)
global a b
dx = zeros(2,1);
dx(1)  = a*x(2)  +  (x(1)^2).*x(2)  - x(1);
dx(2)  = b - a*x(2)  -  (x(1)^2).*x(2);
```

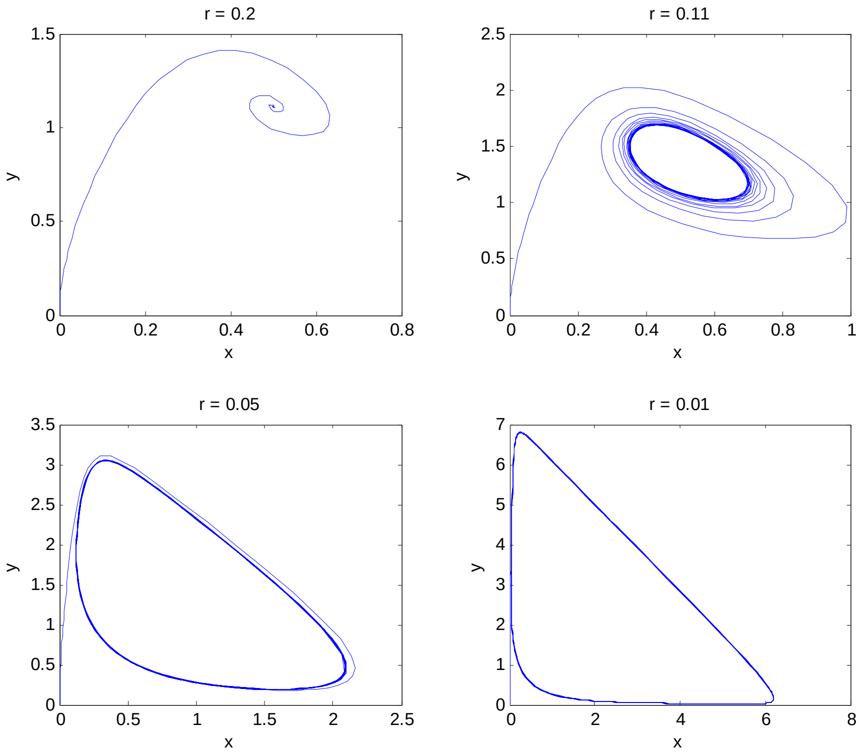
Fixing b = ½, we can obtain different trajectories for different values of a as shown in the next four plots (figure 9).

Figure 9. Trajectories for Various r values



For low values of r, there seems to be a very periodic motion over time of both concentrations of ADP and F6P. As the values of r increase, we still get a periodic function but the function begins to decay over time until when r = 0.2, we don't see any sustained periodicity in the plot. To get a better idea of the function, we can also plot each case on the phase plane (figure 10).

Figure 10. Phase Plane for Various *r* Values with b = ½



When $r = 0.01$ and 0.05, we can clearly see a limit cycle appearing, correlating with the fact that we see oscillations and periodicity in the trajectories as a function of time in figure 9. As r is increased to 0.11, the limit cycle is still visible but in a slightly different shape to what is seen with smaller values of r, but when r is increased to 0.2, we obtain a stable spiral correlating with the eventual diminishing of the trajectories in figure 9.

If we now go through the stability analysis of the system, we can obtain a better understanding of the type of behavior seen in figures 9 and 10. First, we find the fixed points of the system by solving for x and y in the following simultaneous equations.

$$0 = b - ay - x^2 y$$
$$0 = ay + x^2 y - x$$

Adding the two equations, and re-substituting our result, we obtain that the fixed point of the system occurs at:

$$(x^*, y^*) = \left(b, \frac{b}{a + b^2} \right)$$

Now for the linear stability analysis of the fixed point we first obtain the Jacobian matrix:

$$Jacobian(x, y) = \begin{pmatrix} -1 + 2xy & a + x^2 \\ -2xy & -(a + x^2) \end{pmatrix}$$

Evaluating the trace and determinant of the Jacobian matrix will ultimately determine the stability of our fixed point.

$$\tau = -1 + 2xy - a - x^2$$
$$\Delta = -(-1 + 2xy)(a + x^2) + 2xy(a + x^2) = a + x^2$$

Evaluating the trace and determinant at the fixed point, $(x^*, y^*) = \left(b, \frac{b}{a + b^2}\right)$:

$$\tau = -1 + 2b\left(\frac{b}{a + b^2}\right) - a - b^2$$
$$\Delta = a + b^2$$

We assume that both *a* and *b* are greater than zero, so our determinant will always be positive. Thus, we will either have a stable or unstable node/spiral. The point at which the behavior will flip from being stable to unstable and vice versa is when $\tau = 0$. This change in stability is referred to as the Hopf bifurcation. We now solve for *b* to determine at which value of *a* this will occur for any given value of *b*.

$$0 = -1 + 2b\left(\frac{b}{a + b^2}\right) - a - b^2$$
$$2b^2 = (1 + a + b^2)(a + b^2)$$
$$0 = a + a^2 + (2a - 1)b^2 + b^4$$

Let $x = b^2$ and by solving the quadratic equation, we obtain:

$$x = b^2 = \frac{1 - 2a \pm \sqrt{1 - 8a}}{2}$$

From the above equation, we can see that to maintain *a* and *b* positive and real, *a* is bounded on the interval [0, 1/8]. Furthermore, the value of *b* is also bounded on the interval [0, 1], corresponding to values when *a* = 0. In our values above, for *b* = ½, we can solve for the value of *a* at which the bifurcation occurs. This point is at *a* = 0.1160. If we plot the boundary for the values of *a* and *b* for when the system moves from a stable limit cycle to a stable spiral (i.e. values for *a* and *b* at which the bifurcation occurs), we get the plot obtained in figure 11.

Exploring further, we can now select values to check if the behaviour is what we predicted in our analysis by taking values of *a* and *b* and looking at the phase plane plot. In figures 12a and 12b, we can see that indeed, the values on the left side of the boundary in figure 11 lead to stable limit cycles while values on the right side of the boundary lead to stable fixed points (or spirals to a single point).

Figure 11. Values of a and b

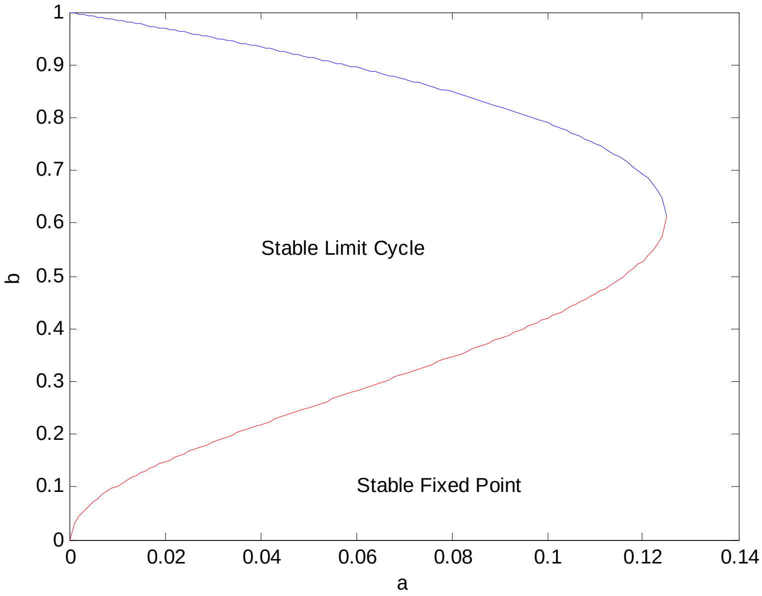


Figure 12a. a = 0.14 b = 1

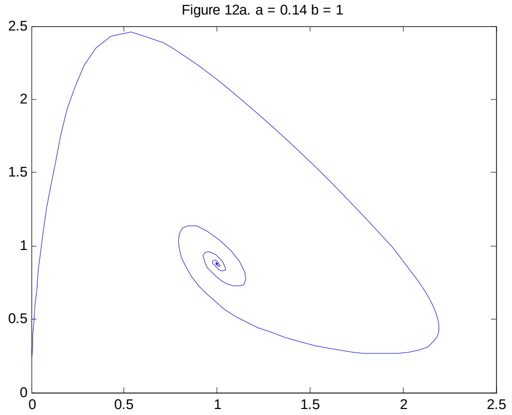
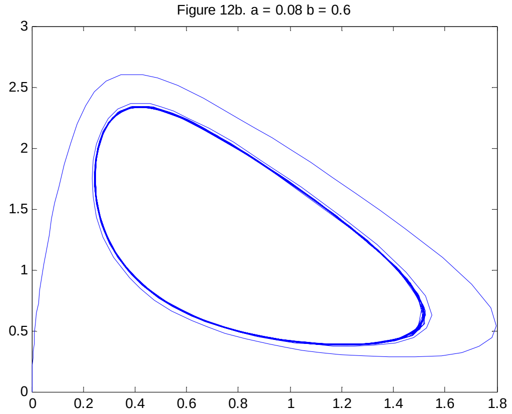
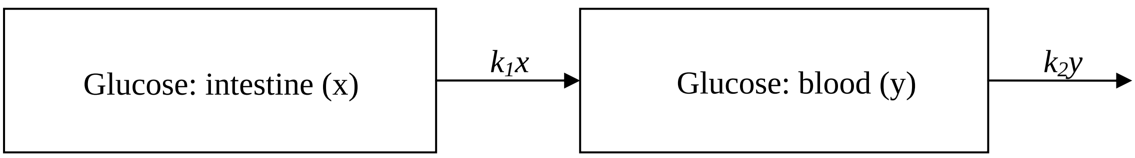


Figure 12b. a = 0.08 b = 0.6



Question 4: Compartmental models in biology and physiology

We first consider the compartmental model of glucose moving from the intestine to the blood stream and from the blood to the other cells in the body as shown in the diagram below.



The compartmental system above can be modelled with the following equations:

$$\frac{dx}{dt} = -k_1 x$$

$$\frac{dy}{dt} = k_1 x - k_2 y$$

Through experimental data, it was shown that the rate constants are similar in all subjects, so we assume that $k_1 = k_2 = k$, yielding the equations below.

$$\frac{dx}{dt} = -kx$$
$$\frac{dy}{dt} = k(x - y)$$

To solve the system of differential equations, we first solve the above and substitute in the second to get the following.

$$x(t) = Ae^{-kt}$$
$$\frac{dy}{dt} + ky = kAe^{-kt}$$

To solve for y(t), we make the assumption that the solution is in the form below.

$$y(t) = Bte^{-kt} + C$$

From our initial condition $y(0) = 0$, we can immediately conclude that $C = 0$. Solving for the value of B by differentiating and substitution, we get:

$$-kBte^{-kt} + Be^{-kt} + kBte^{-kt} = kAe^{-kt}$$
$$B = kA$$

Giving our general solution:

$$y(t) = kAte^{-kt}$$

Matlab can also give us the solution of the differential equations with the code below.

```
[x y] = dsolve('Dx = -k*x', 'Dy = k*(x-y)', 'y(0) = 0')
```

Yielding the solution that we expected:

```
x =
C2*exp(-k*t)
y =
exp(-k*t)*k*C2*t
```

Now we know the general solution to the model, we need to see if it is a good fit to the data provided in the files subject1.dat and subject2.dat. We first import the data into matlab with the code below.

```
data1 = load('subject1.dat');
data2 = load('subject2.dat');
```

And defining the data imported as variables to fit the curve to:

```
T = data1(:,1);
```

```
Y = data1(:,2);
T2 = data2(:,1);
Y2 = data2(:,2);
```

We then define a function in matlab to which we want to fit our curve to, utilizing two variables matlab will solve for.

```
function yhat = glucfun(beta,t)
c1 = beta(1);
c2 = beta(2);
yhat = c1*c2*t.*exp(-c1*t);
```

Using the least squares method (function `lsqcurvefit`), we can find the values of c1 and c2 with the code below.

```
%Curve fitting for subject 1
c0 = [0.01 10]; %Initial guess
n = length(T);
limT = T(1:n);
limY = Y(1:n);
foo = lsqcurvefit(@glucfun,c0,limT,limY)
Z = foo(1)*foo(2)*limT.*exp(-foo(1)*limT);
figure;
plot(T,Y)
hold on;
plot(limT,Z,'red')
hold off;
title('Subject 1 Data and Fit')
xlabel('Time')
tsub1 = 1/foo(1) %Calculate characteristic time constant
```

The out values of k and A respectively are given below:

```
foo =

     0.0167    9.9981
```

Where k = 0.0167 and A = 9.9981 from the general analytical solution solved above. We can further derive the characteristic time constant 1/k = 60.0123 for the first subject.

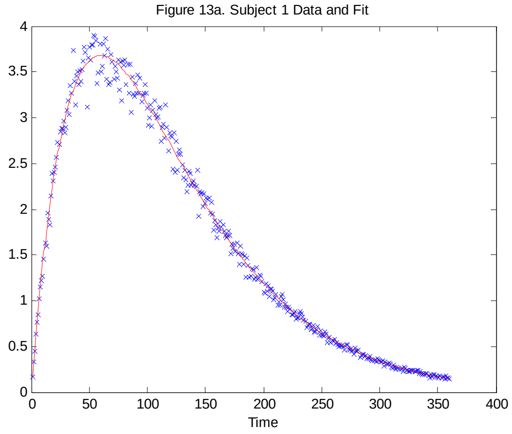
The same method can be done to fit a curve to the data for subject 2. The output values of k and A respectively for subject 2 are given below:

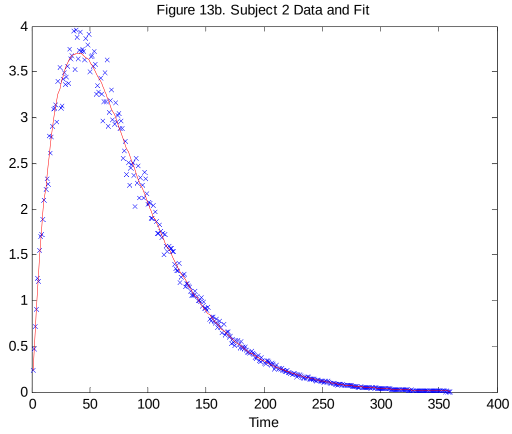
```
foo1 =

  0.250 10.0744
```

With the characteristic time constant of 40.0303.

The plots with the original data (in blue) and the curve fits (in red) are shown below in figures 13a and 13b.





With the calculated time characteristic, we can determine that subject 1 is positive for GDM and subject 2 is healthy. Our calculated T value for subject 1 was 60 min, which falls within the range of 58 ± 6 min characteristic of patients with GDM. The calculated T value for subject 2 was 40 min, falling within the range of 42 ± 4 min, suggesting that this patient is healthy.