Assignment 2

Help

The **due date** for this quiz is **Fri 23 May 2014 8:59 PM PDT**.

☐ **In accordance with the Coursera Honor Code, I (bryan) certify that the answers here are my own work.**

Question 1

In this assignment we will work with the model of yeast glycolytic oscillations developed by Bier et al. that was discussed in the lecture. To review, this model calculates concentrations of two chemical species, glucose ([G]) and [ATP], according to the following ODEs:

$$\frac{d[ATP]}{dt} = 2k_1[G][ATP] - \frac{k_p[ATP]}{[ATP]+K_m}$$

$$\frac{d[G]}{dt} = V_{in} - k_1[G][ATP]$$

Part 1 -- Programming

In the lectures, we discussed a very simple Matlab script that uses Euler's method to integrate the differential equation dx/dt = a – bx, x(0) = c. You are provided with this script (euler.m) and should use this as a template to implement the Bier model. These are the steps you will need to take to achieve this.

1. Change the parameters defined at the top of the script from a, b, and c to those relevant to the Bier et al model: V_{in}, k_1, k_p, and K_m. Control values are in the slides. (Use K_m = 13 rather than K_m =20).

2. Replace the statement defining the initial condition for x with statements that assign initial conditions of G and ATP. Good initial values are ATP = 4; G = 3.

3. Replace the differential equation describing dx/dt with two equations describing d[ATP]/dt and d[G]/dt.

4. Replace the statement that updates x at each time step with statements that update ATP and G.

5. Alter the code so that it keeps track of values of G and ATP at all points in time.

6. Change the time of the simulation to one that is long enough to observe interesting behavior such as oscillations. Determine the relevant time scale by trial and error.

7. Remember that Euler's method can "blow up" if the time step is too large. You may need to adjust the time step to make sure you have a stable solution. One way to verify this is to start with a time step that gives "reasonable looking" output, then reduce the time step by a factor of 2. If this gives the same output as the larger time step, then the time step is small enough (Perhaps a mathematician would contend that this statement cannot be proven correct, but this works in practice).

8. Plot G and ATP versus time in different colors on the same plot.

(For answering the following questions use time step=0.2, simulation time=500, Initial ATP=4 and Initial Glucose=3)

Which of the following statements is correct about the behavior of this system if you use the following parameter set?

V_{in} =0.36, k_1 =0.02, k_p =6, and K_m =12.

- ○ The concentration of ATP will reach a stable steady-state level after t=200.
- ○ The concentrations of ATP and Glucose never reach a stable steady-state.
- ○ The concentration of Glucose will reach a stable steady-state level after t=200.
- ○ The concentration of ATP will reach a stable steady-state level after t=1000.

Question 2

If you use the parameters listed below and the initial conditions listed above (Glucose = 3, ATP = 4), what will be the maximum concentration of Glucose and ATP respectively in your simulations? (Round answers to two decimal places)

V_{in} =0.36, k_1 =0.02, k_p =6, and K_m =12.

- 20.98, 18.66
- 40.00,47.75
- 28.19, 22.40
- 16.29, 11.22

Question 3

Which of the following parameter sets will lead to sustained oscillatory behavior in ATP and Glucose concentrations?

- V_{in} =0.36, k_1 =0.02, k_p =6, and K_m =50.
- V_{in} =0.7, k_1 =0.01, k_p =2, and K_m =23.
- V_{in} =0.1, k_1 =0.01, k_p =3, and K_m =12.
- V_{in} =0.01, k_1 =0.01, k_p =6, and K_m =20.

Question 4

Which of the following parameter sets will lead to oscillatory behavior in ATP and Glucose concentrations with higher frequency compared to the other choices?

- V_{in} =0.36, k_1 =0.02, k_p =6, and K_m =10.

- V_{in} =0.36, k_1 =0.02, k_p =6, and K_m =15.
- V_{in} =0.2, k_1 =0.02, k_p =5, and K_m =13.
- V_{in} =0.36, k_1 =0.02, k_p =5, and K_m =5.

Question 5

Which of the following parameter sets will lead to oscillatory behavior in ATP and Glucose concentrations with higher amplitude compared to the other choices?

- V_{in} =0.36, k_1 =0.02, k_p =6, and K_m =7.
- V_{in} =0.2, k_1 =0.02, k_p =5, and K_m =13.
- V_{in} =0.1, k_1 =0.02, k_p =6, and K_m =13.
- V_{in} =0.36, k_1 =0.02, k_p =4, and K_m =15.

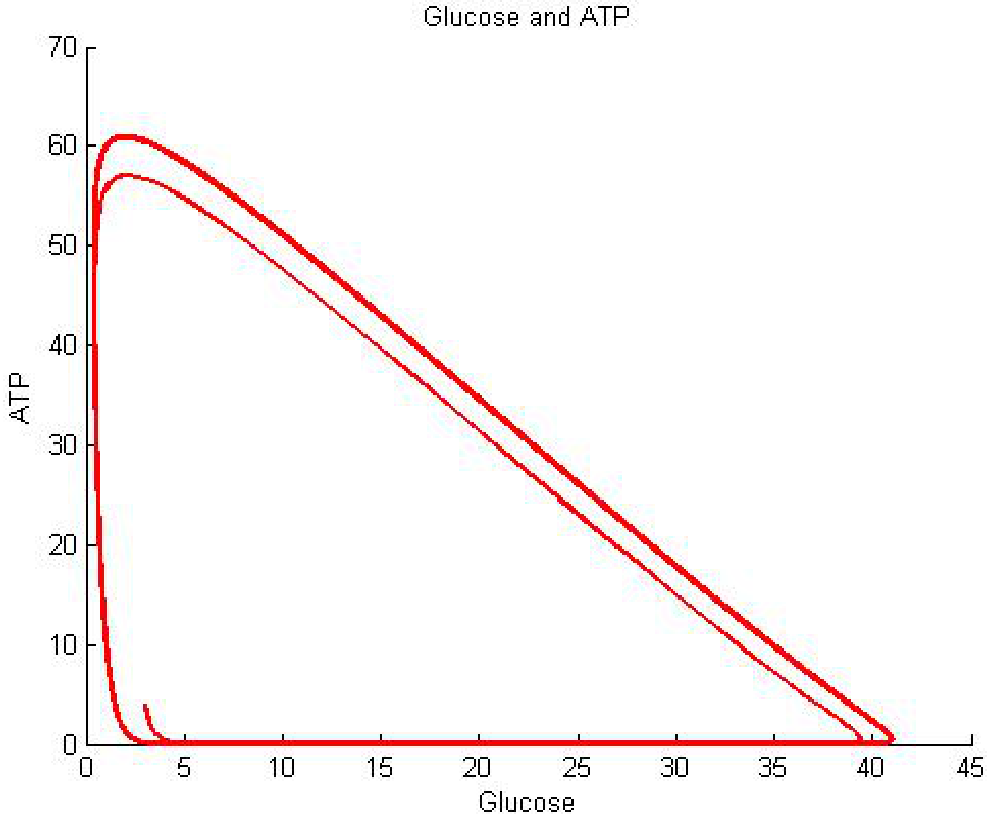
Question 6

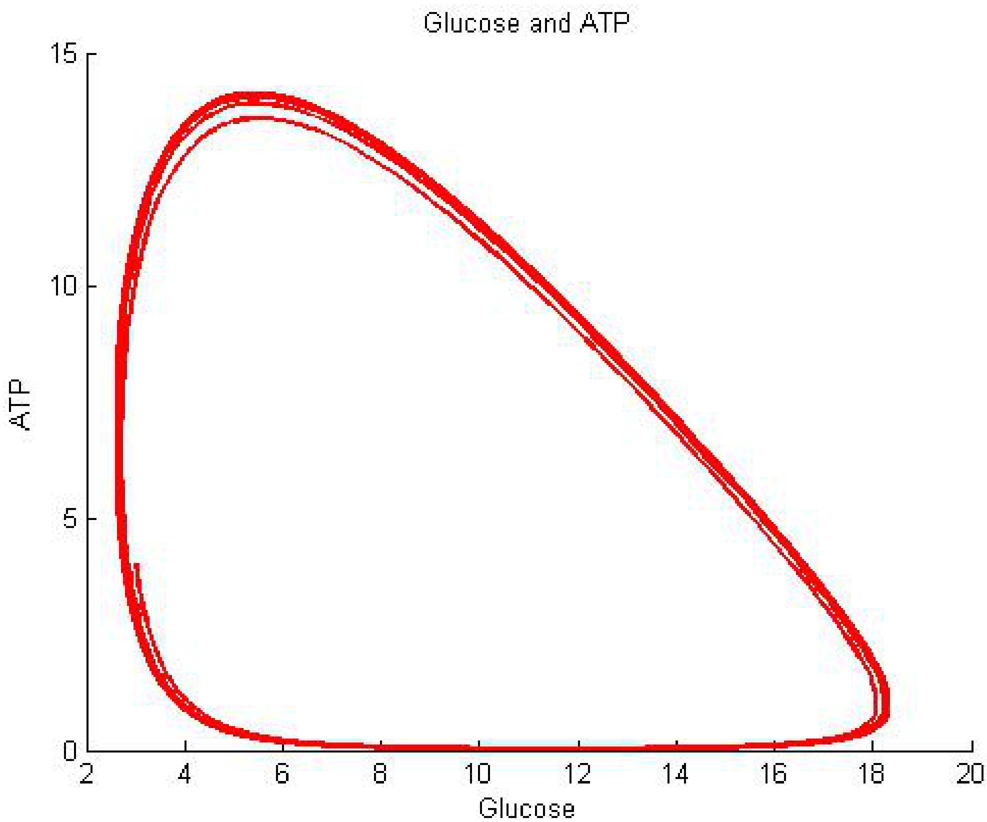
Which of the following parameter sets will lead to damped oscillation in ATP and Glucose concentrations?

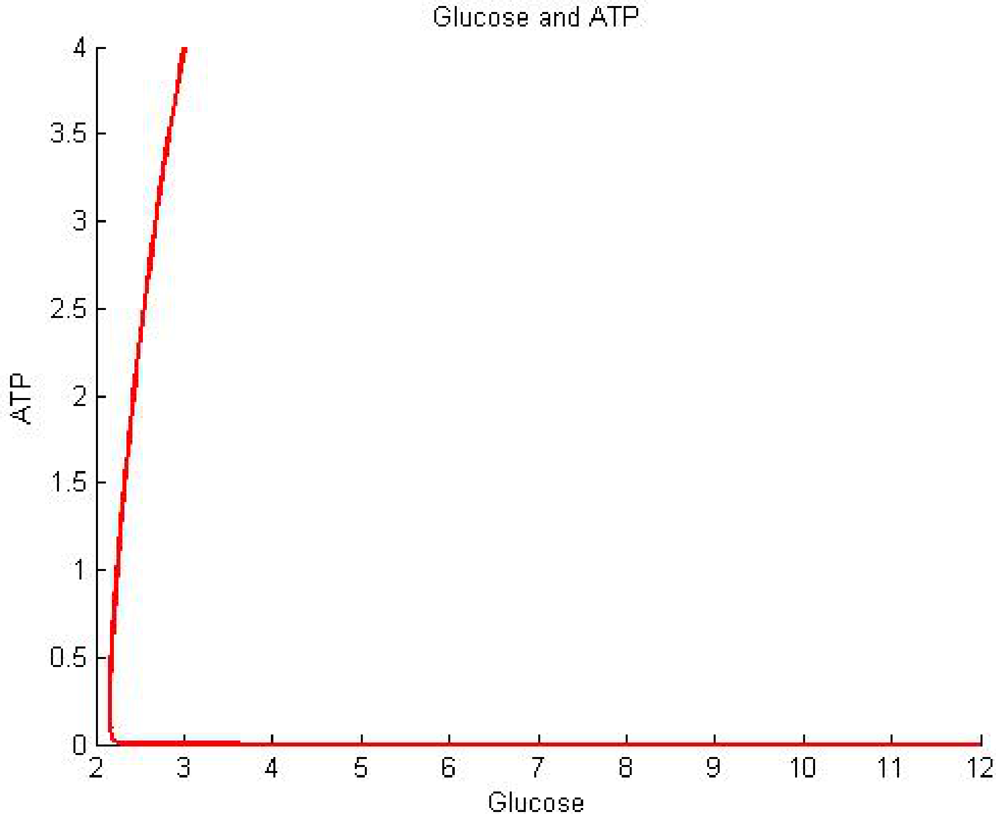
- V_{in} =0.5, k_1 =0.02, k_p =6, and K_m =12.
- V_{in} =0.36, k_1 =0.01, k_p =6, and K_m =13.
- V_{in} =0.3, k_1 =0.02, k_p =6, and K_m =18.
- V_{in} =0.4, k_1 =0.02, k_p =7, and K_m =13.

Question 7

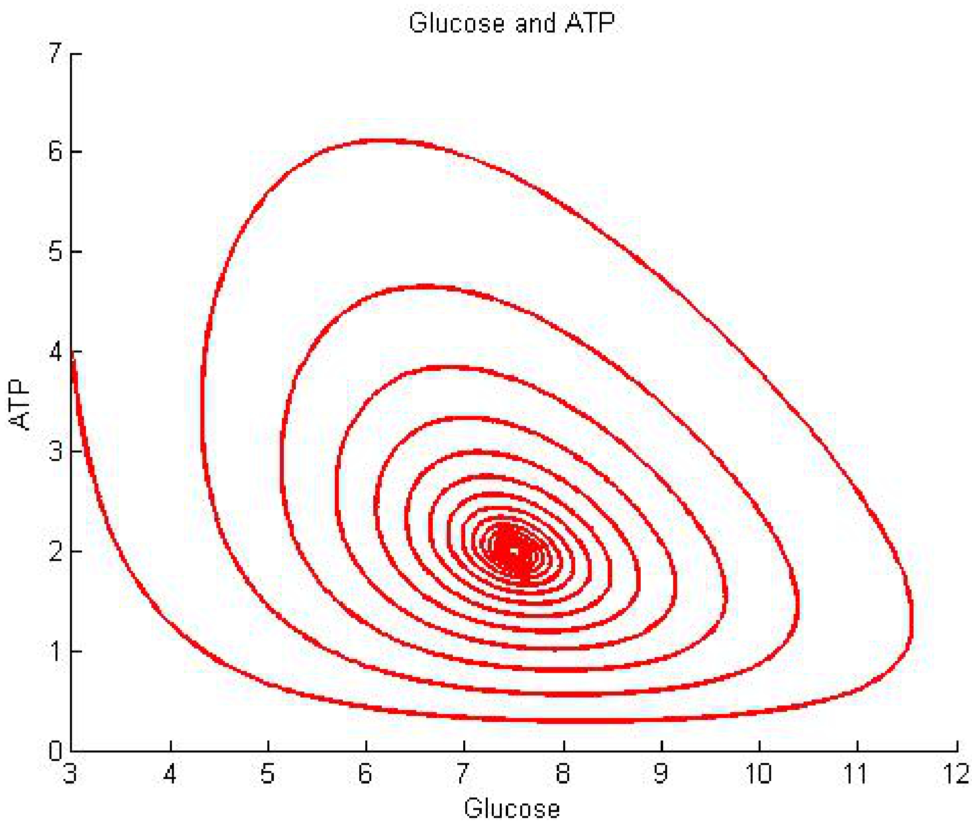
Visualize the trajectory in the phase plane, i.e. generate a plot of ATP versus G. Which of the following phase plane trajectories can represent damped oscillatory behavior in Glucose and ATP concentrations?


Glucose and ATP
ATP
Glucose
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
45


Glucose and ATP
ATP
Glucose
15
10
5
0
2
4
6
8
10
12
14
16
18
20



Glucose and ATP
ATP
Glucose
4
3.5
3
2.5
2
1.5
1
0.5
0
2
3
4
5
6
7
8
9
10
11
12



Glucose and ATP
ATP
Glucose
7
6
5
4
3
2
1
0
3
4
5
6
7
8
9
10
11
12

Question 8

Once the model is working, you can simulate biologically meaningful changes to the system. For instance, results presented in the lectures showed the effects of changes in the Michaelis constant of ATPase activity. Here we will simulate a potentially important perturbation and investigate how this alters the behavior of the model.

Simulate increases and decreases in the glucose transport rate (V_{in}) .Use the default values of parameters. How do these changes affect the amplitude and frequency of glycolytic oscillations? If glucose transport rate becomes large enough, oscillations will cease. Plot time courses, and trajectories in the phase plane, under both oscillating and non-oscillating conditions. Which of the following statements is correct?

- When V_{in} is higher than 1 no sustained oscillations will be observed.
- Increased V_{in} can suppress the oscillation and at the end increases the steady-state concentration of glucose.
- Increased V_{in} can suppress the oscillation and at the end decreases the steady-state concentration of ATP
- Regardless of the value V_{in} , the system always has an oscillatory behavior.

Question 9

Which of the following statements is correct? (using the following parameter set: V_{in} =0.36, k_1 =0.02, k_p =6)

- For K_m <16 we will always see oscillations in Glucose and ATP concentrations.
- For K_m >16 we will always see oscillations in Glucose and ATP concentrations.
- For 4< K_m <12 we will always see oscillations in Glucose and ATP concentrations.
- For K_m >12 we will always see oscillations in Glucose and ATP concentrations.

Question 10

Which of the following statements is correct? (V_{in} =0.36, k_1 =0.02, k_p =6)

- If we fix all parameters, the system shows sustained oscillations in some ranges of K_m .
- The oscillation in the system just depends on K_m and V_{in} .
- K_m is the only parameter which determines if the system shows oscillations.
- The oscillation in the system does not depend on V_{in} .

Question 11

Part 3 – More complex programming

To answer Part 2, you can manually test different values for V_{in} , and then report which cause oscillations and which do not. A more complete and rigorous way to do this is to generate a bifurcation diagram such as the one shown in the lecture.

To generate this plot, I simply created a for loop to cycle through different values of V_{in} .At each value of V_{in} , I determined the minimum and maximum values of glucose or ATP that were achieved after a certain time interval (to avoid effects of transient oscillations at the beginning), and then plotted these.
(Hint: Try values of V_{in} in range of 0.1-1.6 and for your simulations use time step= 0.05 and simulation time=2000).

How do you interpret these results in the context of the role of glucose transport rate?

- After oscillation is ceased by increasing glucose transport rate , steady-state concentration of glucose will be increased due to increased rate of its transportation to the yeast cell.
- Glucose transport rate is the only parameter that controls the oscillations in ATP and Glucose concentrations.
-

After oscillation is ceased by increasing glucose transport rate, steady-state concentration of glucose will be decreased due to increased steady-state level of ATP.

After oscillation is ceased by increasing glucose transport rate , steady-state concentration of glucose will be increased due to decreased steady-state level of ATP.

In accordance with the Coursera Honor Code, I (bryan) certify that the answers here are my own work.

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