BT612 Systems Biology

Total Marks: 40 | **Mid-semester Examination** | **Time: 2 hr.**

July-November 2023

Instructions

1. Preferably write the answers following the order of questions
2. You MUST SHOW ALL the calculation STEPS. MARK the FINAL answer clearly.
3. Use standard mathematical notations/symbols only.
4. All graphs should be suitably labeled and axes clearly marked.

IMPORTANT

Q1. A) What is bimodal gene expression? What is the connection between bifurcation and bimodal gene expression?

B) What are the key assumptions behind the ODE-based modeling of a biochemical system? Explain those very briefly. [2 × 2.5]

Q2. The dynamics of two interacting cell populations are modeled using the following system of ODEs:

$$\frac{dx}{dt} = 4(1-x)x - xy$$

$$\frac{dy}{dt} = 2(1-y)y - xy$$

Find the steady state values of x and y when the initial condition is: $x = 0.2, y = 0.2$ at $t = 0$. Show all relevant calculations to justify your answer. [5]

Q3. A protein positively autoregulates its own expression. The following ODE is used to model its dynamics:

$$\frac{dP}{dt} = \frac{P^2}{1+P^2} - cP$$

Find the condition in terms of c that makes this system bistable. A bistable system has two stable steady states. $P \geq 0$ and $c \geq 0$. [5]

Q4. "For the ODE, $\frac{dx}{dt} = rx + x^3$, r is the bifurcation parameter" – prove this statement using the concept of potential landscape. You must show the diagram of the potential landscape and all the relevant calculations. [5]

Q5. S is an input signal that induces X, and Y. Y inhibits X. This is a feedforward motif. Consider the steady state value of X as the output of this motif. The following ODEs are used to capture the dynamics of this motif:

$$\frac{dX}{dt} = k_1 S(1 - X) - k_2 XY$$

$$\frac{dY}{dt} = k_3 S \frac{(1 - Y)}{K_m + (1 - Y)} - k_4 Y$$

Show that for $K_m \ll 1$ the output of this motif is independent of the input signal. $S > 0$. [5]

Q6. A reversible autocatalytic reaction is shown here,

$$\mathrm{A} + \mathrm{X} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} 2\,\mathrm{X}$$

Create an ODE-based model for this system. Consider that A is present in excess, and therefore, its concentration does not change with time. Use the concept of the Law of Mass Action to create the model. According to the Law of Mass Action, the rate of an elementary reaction is proportional to the product of the concentration of its reactants.

Find all steady states of this system and comment on their stabilities. [5]

Q7. A dynamical system is represented by the following system of ODEs:

$$\frac{dx}{dt} = -3x + 2y \qquad \text{and} \qquad \frac{dy}{dt} = x - 2y$$

What will be the behavior of a trajectory in the phase space when $t \to -\infty$? [5]

Q8. The following system of ODEs represents a mutual repressor circuit involving three molecules. Consider, a = 2, b = c = 0.1 and x, y, z ≥ 0.

$$\frac{dx}{dt} = a - bx - cxz; \quad \frac{dy}{dt} = a - by - cyx; \quad \frac{dz}{dt} = a - bz - czy;$$

Can this system show bifurcation when the rate of production of these molecules, a, is considered as the bifurcation parameter? Consider a is always greater than zero. [5]

Q1.

a) In bimodal gene expression, the distribution of gene expression has two modes. It suggests that there are two subpopulations in the population of cells.

Bistability in gene expression gives rise to bimodality. Genetic circuits with positive feedback can have bifurcation. In a bifurcating system, there could be 2 stable steady states. This is bistability. Through bifurcation a monostable system turns into bistable, giving rise to bimodal gene expression.

b) The key assumptions for ODE-based modeling of biochemical system are:

a) The system is large: The concentrations of molecules are high.

b) The system is homogenous or well mixed.

Q2.

$$\frac{dx}{dt} = 4(1-x)x - xy \; ; \; \frac{dy}{dt} = 2(1-y)y - xy$$

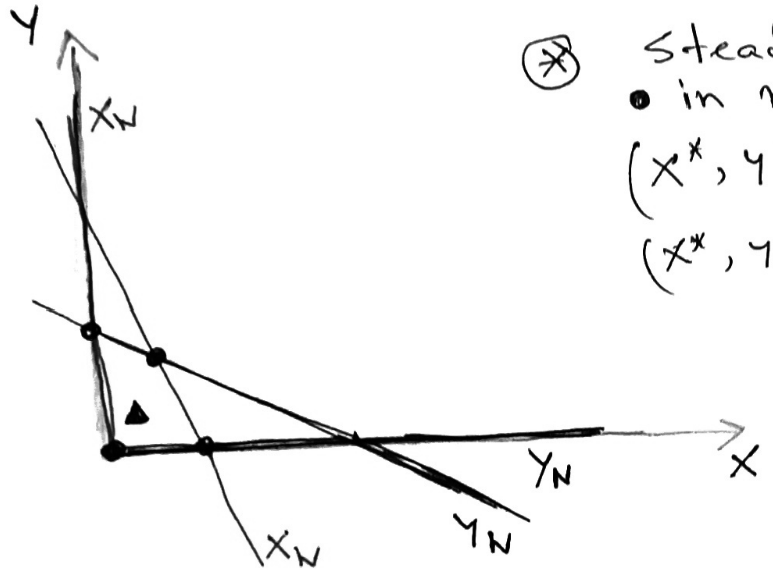
(*) Get the nullclines. Draw nullcline plot. Identify the steady states from the nullcline plot.

(*) X-nullclines: $x = 0$;

$y = 4 - 4x$

(*) Y-nullcline: $y = 0$;

$x = 2 - 2y$



(*) Steady-states (marked by • in nullcline plot)

$(x^*, y^*) = (0, 0)$,

$(x^*, y^*) = (1, 0)$;

$(x^*, y^*) = (0, 1)$

$(x^*, y^*) = \left(\frac{6}{7}, \frac{4}{7}\right)$

$= (0.857, 0.571)$

(*) Jacobian matrix:

$$J = \begin{vmatrix} 4-8x-y & -x \\ -y & 2-4y-x \end{vmatrix}$$

(*) Stability analysis for each steady state

(*) $J_{(0,0)} = \begin{vmatrix} 4 & 0 \\ 0 & 2 \end{vmatrix}$; $\text{tr}\,J = 6$; $\det J = 8$

$\text{tr}J^2 > 4 \det J$

$\text{tr}\,J > 0$, $\det J > 0$

$\therefore (x^*, y^*) = (0, 0)$ is a Nodal Source.

Q2. continued.....

$\circledast$ $J_{(1,0)} = \begin{vmatrix} -4 & -1 \\ 0 & 1 \end{vmatrix}$; $\det J = -4 < 0$

$\therefore (x^*, y^*) = (1, 0)$ is a <u>saddle</u>.

$\circledast$ $J_{(0,1)} = \begin{vmatrix} 3 & 0 \\ -1 & -2 \end{vmatrix}$ $\det J = -6 < 0$

$\therefore (x^*, y^*) = (0, 1)$ is a <u>saddle</u>.

$\circledast$ $J_{\left(\frac{6}{7}, \frac{4}{7}\right)} = \begin{vmatrix} -\frac{24}{7} & -\frac{6}{7} \\ -\frac{4}{7} & -\frac{8}{7} \end{vmatrix} = \begin{vmatrix} -3.428 & -0.857 \\ -0.571 & -1.142 \end{vmatrix}$

$\mathrm{tr}\, J = -\frac{32}{7} = -4.57 < 0$

$\det J = \frac{24}{7} = 3.42 > 0$

$\mathrm{tr}\, J^2 > 4 \det J$

$\therefore (x^*, y^*) = \left(\frac{6}{7}, \frac{4}{7}\right)$ is a <u>Nodal sink</u>.

$\circledast$ The initial position is $x = y = 0.2$. It is shown by ▲ in the nullcline plot. In the phase plane, this position is surrounded by 4 steady states. Only one of this 4 steady states is stable.

Therefore with time the system will converge to this stable steady state.

$\therefore$ steady state value for $t = 0$, $x = y = 0.2$ is

$(x^*, y^*) = \left(\frac{6}{7}, \frac{4}{7}\right) = (0.857, 0.571)$ <u>Ans</u>

Q3. $$\frac{dp}{dt} = \frac{p^2}{1+p^2} - cp \quad ; \quad p \geq 0, \quad c \geq 0$$

By setting $\frac{dp}{dt} = 0$, find all possible steady states. Then find stability of each steady state. Some steady states are semistable. So you have to use correct method for stability analysis. This system has bifurcation. So, you have to do steady state and stability analysis for different values/ranges of c. No need to show the bifurcation plot. But you must show steady states and stability analysis explicitly.

$\frac{dp}{dt} = 0 \Rightarrow$ steady states are

$$p^* = 0$$

* $$p^* = \frac{1 \pm \sqrt{1 - 4c^2}}{2c}$$

For stability analysis;

$$\frac{dp}{dt} = f(p) = \frac{p^2}{1+p^2} - cp$$

* $\therefore f'(p) = \frac{d}{dp} f(p) = \frac{2p}{(1+p^2)^2} - c$

* Important: $f'(p)$ is $\frac{d}{dp} f(p)$, NOT $\frac{d}{dt} f(p)$.

Q3. Continued....

<table>
<tr><th>Value of c</th><th>Steady state</th><th>Stability Analysis</th><th>Stability</th></tr>
<tr><td>$c = 0$</td><td>$p^* = 0$</td><td>$f'(p^*) = 0$
∴ Use the other method<table><tr><th></th><th>dp/dt</th><th></th></tr><tr><td>$p = 0.1$</td><td>+ve</td><td>↑</td></tr><tr><td>$p = 0$</td><td>0</td><td>→</td></tr><tr><td>$p = -0.1$</td><td>+ve</td><td>↑</td></tr></table></td><td>Semi-stable</td></tr>
<tr><td>$c > \frac{1}{2}$</td><td>$p^* = 0$</td><td>$f'(p^*) = -c < 0$</td><td>Stable</td></tr>
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<tr><td></td><td>$p^* = 1$</td><td>$f'(p^*) = 0$<table><tr><th></th><th>dn/dt</th><th></th></tr><tr><td>$p = 1.1$</td><td>-ve</td><td>↓</td></tr><tr><td>$p = 1$</td><td>0</td><td>→</td></tr><tr><td>$p = 0.9$</td><td>-ve</td><td>↓</td></tr></table></td><td>Semi-stable</td></tr>
<tr><td>$0 < c < \frac{1}{2}$</td><td>$p^* = 0$</td><td>$f'(p^*) = -c < 0$</td><td>Stable</td></tr>
<tr><td></td><td>$p^* = \frac{1 - \sqrt{1-4c^2}}{2c}$
< 1</td><td>$f'(p^*) > 0$
You can take a value of c, say $c = 0.4$ to do this calculation</td><td>Unstable</td></tr>
<tr><td></td><td>$p^* = \frac{1 + \sqrt{1-4c^2}}{2c}$
> 1</td><td>$f'(p^*) < 0$
You can take a value of c, say $c = 0.4$ to do this calculation</td><td>Stable</td></tr>
</table>

∴ This system is bistable, when

$0 < c < \frac{1}{2}$ **Ans.**

Q4. This question is on bifurcation analysis. However, as mentioned in the question potential landscape based method has to be used for bifurcation analysis.

Any other method is NOT acceptable.

The plots of potential landscape must be shown.

$$\frac{dx}{dt} = rx + x^3$$

$\therefore$ If u is the potential, then

$$\frac{dx}{dt} = -\frac{du}{dx}$$

$$\therefore \frac{du}{dx} = -rx - x^3$$

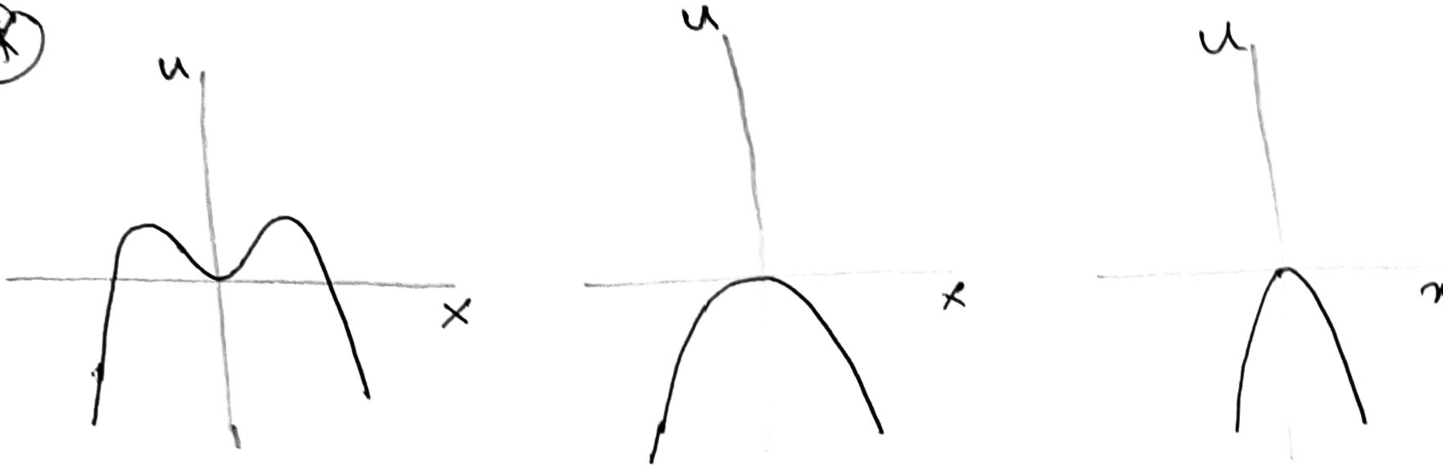
By integration we get,

$$u = -\frac{1}{2}rx^2 - \frac{1}{4}x^4$$

Now investigate the behavior of u for different values of r in u vs. x plot. This plot is the potential landscape

Q4. Continued...

(*)



For $r < 0$
two maxima and one local minimum.
∴ Two unstable steady states. One stable steady state

For $r = 0$
One maximum.
∴ One unstable steady state

For $r > 0$
One maximum
∴ One unstable steady state

This potential landscape plots shows that the number of steady states and there stabilities in this dynamical system changes with the parameter r.

Therefore, this system has bifurcation and r is the bifurcation parameter.

Q5.

$$\frac{dx}{dt} = k_1 S(1-x) - k_2 XY \quad \text{—— (1)}$$

$$\frac{dy}{dt} = k_3 S \frac{(1-y)}{K_m + (1-y)} - k_4 Y \quad \text{—— (2)}$$

$S > 0, \qquad K_m << 1$

As $K_m << 1$, Eq. 2 can be written as

$$\text{(*)} \quad \frac{dy}{dt} = k_3 S \frac{(1-y)}{(1-y)} - k_4 y = k_3 S - k_4 Y \quad \text{—— (3)}$$

At steady state, using (1) & (3),

$$y = \frac{k_1 S(1-x)}{k_2 X} \quad \text{—— (4)}$$

$$y = \frac{k_3}{k_4} S \quad \text{—— (5)}$$

From Eq (4) & (5):

$$\frac{k_3}{k_4} S = \frac{k_1}{k_2} S \frac{(1-x)}{x}$$

$$\Rightarrow X = \frac{k_1 k_4}{k_2 k_3}(1-x)$$

$$\Rightarrow X = C(1-x) \quad \text{where } C = \frac{k_1 k_4}{k_2 k_3}$$

$$\text{(*)} \Rightarrow X = \frac{C}{1+C} = \frac{k_1 k_4}{k_1 k_4 + k_2 k_3}$$

This is the steady state value of X and the steady state value of X is independent of S.

$\therefore$ The output of this motif is independent of input S when $k_m << 1$

(8)

Q6. The ODE-based model for this system is,

(*) $$\frac{dx}{dt} = k_1 A x - k_2 x^2 \qquad \text{—— (i)}$$

[To get this ODE, you may consider x on LHS of the reaction as x_1 and x on RHS as x_2. Write the rate equations for forward and backward reactions using Law of mass action. Then combine the rate equations considering that x_1 and x_2 are the same entity]

A is in excess, so we do not need an ODE for A.

Using Eq. (1), steady states are,

(*) $x^* = 0$ and $x^* = \frac{k_1}{k_2} A$

Do stability analysis:

$$\frac{dx}{dt} = f(x) = k_1 A x - k_2 x^2$$

(*) $\therefore f'(x) = k_1 A - 2k_2 x$

(*) [$f'(x)$ is $\frac{d}{dx} f(x) = \frac{d}{dx}\left(\frac{dx}{dt}\right)$ NOT $\frac{d}{dt} f(x)$ or $\frac{d}{dt}\left(\frac{dx}{dt}\right)$]

(*) $f'(x)\big|_{x=0} = k_1 A > 0$;

$\therefore x^* = 0$ is unstable steady state

(*) $f'(x)\big|_{x=\frac{k_1}{k_2}A} = -k_1 A < 0$;

$\therefore x^* = \frac{k_1}{k_2} A$ is a stable steady state

Q7.

$$\frac{dx}{dt} = -3x + 2y$$

$$\frac{dy}{dt} = x - 2y$$

$\therefore$ The co-efficient matrix is

* $A = \begin{vmatrix} -3 & 2 \\ 1 & -2 \end{vmatrix}$

* Get the eigenvalues of A, $\lambda = \dfrac{trA \pm \sqrt{trA^2 - 4detA}}{2}$

$trA = -5$, $det\,A = 4$,

* $\lambda_1 = -4$, $\lambda_2 = -1$

* Both the eigenvalues are negative. That means the steady state at (0, 0) is asymptotically stable (Nodal sink).

As $|\lambda_1| > |\lambda_2|$, let's call λ_1 as the FAST eigenvalue and λ_2 as SLOW eigenvalue. Similarly $\vec{v}_1$, the eigenvector of λ_1 is the FAST eigenvector. ~~and~~ The eigenvector $\vec{v}_2$ of λ_2 is the SLOW eigenvector.

The general solution of this system is,

* $\vec{x} = c_1 e^{\lambda_1 t} \vec{v}_1 + c_2 e^{\lambda_2 t} \vec{v}_2$ —— (1)

When, $t \to -\infty$, $|x| \to \infty$

PTO.

Q7. continued....

As, $t \to -\infty$,

$$e^{\lambda_1 t} >> e^{\lambda_2 t}$$

Therefore eq. (1) becomes.

$$\vec{x} \sim c_1 e^{\lambda_1 t} \vec{v}_1$$

$\therefore$ When $t \to -\infty$, trajectories will be nearly parallel to $\vec{v}_1$, the fast eigenvector.

In other words, when $t \to -\infty$, the trajectories will be parallel to the eigenvector of $\lambda_1 = -4$.

[Extra: This eigenvector (FAST one) is $(-0.89, 0.44)$]

Q8. First find all possible steady state of this system.

At steady state,

$$a - bx - cxz = 0 \quad \text{——— (1)}$$

$$a - by - cy\cancel{x} = 0 \quad \text{——— (2)}$$

$$a - bz - czy = 0 \quad \text{——— (3)}$$

From (1), we get,

$$z = \frac{a - bx}{c\cancel{x}} \quad \text{——— (4)}$$

From (3), we get

$$z = \frac{a}{b + cy} \quad \text{——— (5)}$$

Equating (4) & (5),

$$ab - b^2x + acy - acx - bcxy = 0 \quad \text{——— (6)}$$

Multiply Eq (2) by b and then subtract from (6) : This gives,

$$(y - x)(b^2 + ac) = 0$$

As, b, a, c > 0

(*) $\therefore y - x = 0 \Rightarrow y = x$

Using similar stratagy we can show,

$y = z$.

$\therefore$ At steady state,

(*) $$x = y = z \quad \text{——— (7)}$$

PTO

Q8. continued ...

Using Eq ① & ⑦, we get

$$cx^2 + bx - a = 0$$

$\therefore$ At steady state,

$$x = y = z = \frac{-c + \sqrt{b^2 + 4ac}}{2c} \quad \text{—— ⑧}$$

[As $x, y, z \geq 0$]

For the given values of a, b, and c, using Eq ⑧ we get at steady state,

$$x = y = z = 4$$

~~Note that if we change the value of a~~

Note that for any value of a, where $a > 0$, the system has only one steady state.

So, value of a does not affect number of possible steady states.

Now check the effect of a on the stability of the steady state.

PTO.

Q8. Continued....

The Jacobian of the system,

$$J = \begin{vmatrix} -b-cz & 0 & -cx \\ -cy & -b-cx & 0 \\ 0 & -cz & -b-cy \end{vmatrix}$$

For any value of a $(a>0)$, ~~~~ at steady state, $x=y=z$.

So, let,

$-b-cz = -b-cx = -b-cy = p$

$-cx = -cy = -cz = q$

Now rewrite the Jacobian at the steady state using p & q,

$$J = \begin{vmatrix} p & 0 & q \\ q & p & 0 \\ 0 & q & p \end{vmatrix}$$

The sign of p and q remain same for any value of a. The numerical value may change with a, but as the J is symmetric and signs of p & q are constant, the sign of eigenvalues will not change.

$\therefore$ Signs of eigenvalues of J will remain same for all values of a

PTO...

Q8. Continued....

- So, the stability of the steady state does not change with a.

- As the value of a does not affect number of steady state and the stability of the steady state, this system does not have bifurcation with respect to a.