BT612 Systems Biology

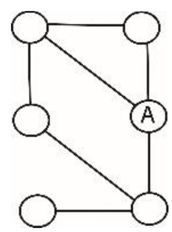
Total Marks: 50 **End-semester Examination** **Time: 3 hr.**

July-November 2024

Instructions: 1) Preferably write the answers following the order of questions. 2) You MUST SHOW ALL the relevant steps of your calculation/derivation. **3)** Clearly MARK the FINAL answer. 4**)** Use standard mathematical notations/symbols only. **5)** All graphs should be suitably labelled and axes marked. **6)** Marks will be deducted for irrelevant calculations/derivations. **7)** No marks will be given for a partially correct answer.

Q1. We have a protein-protein interaction network with 13000 nodes and 6600 edges. We deleted 600 edges and then added 500 new edges to the network. What is the average degree of this modified network? [3]

Q2. Calculate the clustering coefficient of node A in the following graph. [3]



Q3. We are generating a random graph of 4 nodes using the Erdös–Rényi (ER) algorithm. The probability of having two nodes connected in this graph is 0.1. What is the probability of getting a graph where all nodes are connected to each other? [3]

Q4. The macroscopic rate constant for the following reaction is K. Calculate the mesoscopic rate constant for this reaction following Gillespie's algorithm. If required, assume any constant but declare those constants. The reaction: $A + B + D \rightarrow 2C$ [3]

Q5. The following ODE represents an autocatalytic system: $\frac{dx}{dt} = \frac{x}{1+x} - x$. Find the steady state. [3]

Q6. X and Y are two cell types that divide and die. X cells also differentiate into Y cells. The following system of ODE represents the dynamics of the system. Identify all possible steady states and characterize their stabilities. Here x = number of X cells; y = number of Y cells. [5]

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

Q7. The dynamics of a system is represented by an autonomous ODE $\frac{dx}{dt} = f(x)$, where $f(x)$ is a nonlinear function of *x*. Prove that this dynamical system is not oscillatory. [5]

Q8. In a population of bacteria, mutations occur randomly over time. Suppose that in a certain bacterial strain, mutations occur at an average rate of 3 mutations per hour. Simulate this process numerically and calculate the number of mutations over a 2.5 hour period. If you need uniformly distributed random numbers between 0 and 1, use the list of numbers given below. Use these numbers sequentially from left to right: 0.5, 0.2, 0.01, 0.1, 0.25, 0.9, 0.95, 0.85, 0.8, 0.001, 0.6, 0.75, 0.02, 0.15.

Note that we are not following or counting mutations in individual cells. We are counting mutations in the population as a whole. The rate given above is also a population-level rate. [5]

Q9. Draw the bifurcation diagram for the ODE $\frac{dx}{dt} = x - \beta x(1-x)$. Here, β is the bifurcation parameter. Both x and β are real numbers. The bifurcation diagram must show the stability of the steady states. Show all the calculations, including the stability analysis. [5]

Q10. Let $f(x) = kx(1-x)$ for $x \in [0,1]$, where *k* is a constant. Find the value of *k* so that $f(x)$ is a valid PDF for *x* on the interval $[0,1]$. [5]

Q11. Consider the reaction 2X → Y as a Poisson process with a rate of 10 molecules of Y per sec. At t = 0, the number of X = 1000 and the number of Y = 20. We simulated this reaction and recorded the time (end-point) when the reaction stopped. We repeated this simulation a large number of times. What will be the mean and variance of the end-point in this simulated data? Show all steps of calculations with reasoning. [5]

Q12. Prove that in the Erdös–Rényi (ER) model of a random network, the mean degree of a node is $\langle k \rangle = pN$. Here, p: the probability of having a node between a node pair and N: the number of nodes.

Also, what will be the variance of the degree of a node in this network? [5]

Q1.

Number of nodes, $N = 13000$

Number of edges, $L = 6600 - 600 + 500$

$= 6500$

$\therefore$ Avg degree, $\langle k \rangle = \frac{2L}{N} = \frac{2 \times 6500}{13000}$

$= 1$

Ans

Q2.

Number of neighbours, $K = 3$

Number of edges between the neighbours, $n = 1$

$\therefore$ Clustering co-efficient,

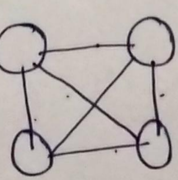
$$C_A = \frac{n}{{}^{K}C_2} = \frac{1}{{}^{3}C_2} = \frac{1}{3}$$

Ans

Q3. $N = 4$

$p = 0.1$

$L = {}^{N}C_2 = 6$



$\therefore$ Probability of the graph $= p^L = (0.1)^6$

$= 10^{-6}$

Ans

Q4. Na: Avogadro number

V = Volume in L. This is crucial.

the volume must be considered only in L for the following relation. If you miss to consider this in L, your answer is wrong.

~~of this~~ Molecularity of this reaction, m = 3

∴ The mesoscopic rate constant,

$$\mu = \frac{1}{(N_A V)^{m-1}} K = \frac{1}{(N_A V)^2} K$$

Ans

Q5. At steady state $\frac{dx}{dt} = 0$.

∴ $\frac{x}{1+x} - x = 0$

This equation has only one solution

$x = 0$

∴ The steady state $x^* = 0$ Ans

Q6.

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

This is a linear system of ODEs.

∴ It's co-efficient matrix,

$$A = \begin{vmatrix} -1 & 0 \\ 2 & -2 \end{vmatrix}$$

$\det A = 2 \neq 0$

∴ This system has only one steady state: $(x = y = 0)$ Ans ①

[You can get the same by solving the equations $\frac{dx}{dt} = \frac{dy}{dt} = 0$]

Stability analysis of this steady state,

$\operatorname{tr} A = -3$

$\det A = 2$, $(\operatorname{tr} A)^2 = 9$

$4 \det A = 8$

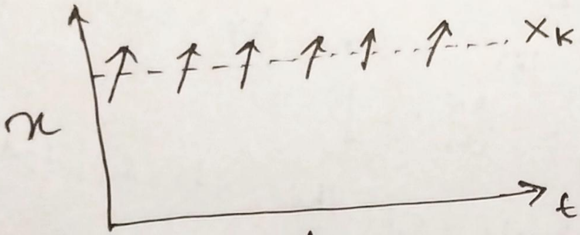
∴ $(\operatorname{tr} A)^2 > 4 \det A$

∴ This steady state is stable and it is a sink node. Ans ②.

Q7.

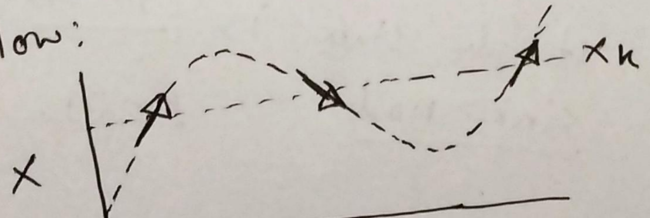
$$\frac{dx}{dt} = f(x)$$

This is an autonomous ODE. Therefore, the slope of an arrow in the direction field is independent of t. So, the arrows (or time evolution vectors) in the direction field, for a particular x are parallel to each other. See the figure:



t

To have oscillation, for some values of x, the arrows in the direction field need to change direction. See the figure below:



t

As the equation is autonomous, such change is not possible. So this system can not have oscillation. Ans

[Your proof may differ, but the proof must be generic and logically correct]

Q8

Rate, $\lambda = 3$ per hr

Time, $T = 2.5$ hr

From the description of the problem it is evident that it is a poisson process. So, we simulate a poisson process with rate $\lambda = 3/\text{hr}$.

Method one: We generate exponentially distributed random numbers using the relation, $\Delta t = -\frac{1}{\lambda} \ln(u)$, $u \sim U(0,1)$

t	Δt	# of mutation
0	$-\frac{1}{3}\ln(0.5) = 0.231$	0
$0+0.231 = 0.231$	$-\frac{1}{3}\ln(0.2) = 0.536$	1
$0.231 + 0.536 = 0.767$	$-\frac{1}{3}\ln(0.01) = 1.535$	$1+1=2$
2.302	$-\frac{1}{3}\ln(0.1) = 0.768$	$1+1+1=3$
3.07 > 2.5		simulation stopped.

∴ Number of mutation in 2.5 hr is 3. Ans

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Method 2

In this case $\Delta t = -\frac{1}{\lambda}\ln(1-u)$,

$u \sim U(0,1)$

t	Δt	# of mutation
0	$-\frac{1}{3}\ln(1-0.5) = 0.231$	
$0+0.231 = 0.231$	$-\frac{1}{3}\ln(1-0.2) = 0.074$	$0+1=1$
$0.231 + 0.074 = 0.305$	0.003	$1+1=2$
0.308	0.035	3
0.343	0.096	4
0.439	0.768	5
1.207	0.999	6
2.206	0.632	7
$2.838 > 2.5$		Simulation stopped

$\therefore$ Total number of mutations in 2.5 hr is 7. <u>Ans</u>.

Q9.

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

This system has two steady states,

$x = 0$ and $x = \left(1 - \frac{1}{\beta}\right)$

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For stability analysis

$$\frac{dx}{dt} = f(x) = x - \beta x(1-x)$$

$$\therefore f'(x) = 1 - \beta + 2\beta x$$

[Important $f'(x)$ is not $\frac{d^2x}{dt^2}$ or $\frac{d}{dt}\frac{dx}{dt}$]

. For steady state, $x = 0$

$$f'(x)\Big|_{x=0} = 1 - \beta$$

$\therefore$ when, $\beta > 1$, $f'(x)\Big|_{x=0} < 0$,

so, $x = 0$ is stable

when, $\beta < 1$, $f'(x)\Big|_{x=0} > 0$

So, $x = 0$ is unstable

For steady state $x = 1 - \frac{1}{\beta}$

$$f'(x)\Big|_{x=1-\frac{1}{\beta}} = \beta - 1$$

$\therefore$ when $\beta < 0$, $f'(x)\Big|_{x=1-\frac{1}{\beta}} < 0$,

so, $x = 1 - \frac{1}{\beta}$ is stable

when $0 < \beta < 1$, $f'(x)\Big|_{x=1-1/\beta} < 0$,

So, $x = 1 - \frac{1}{\beta}$ is stable.

when $\beta > 1$, this steady state is unstable

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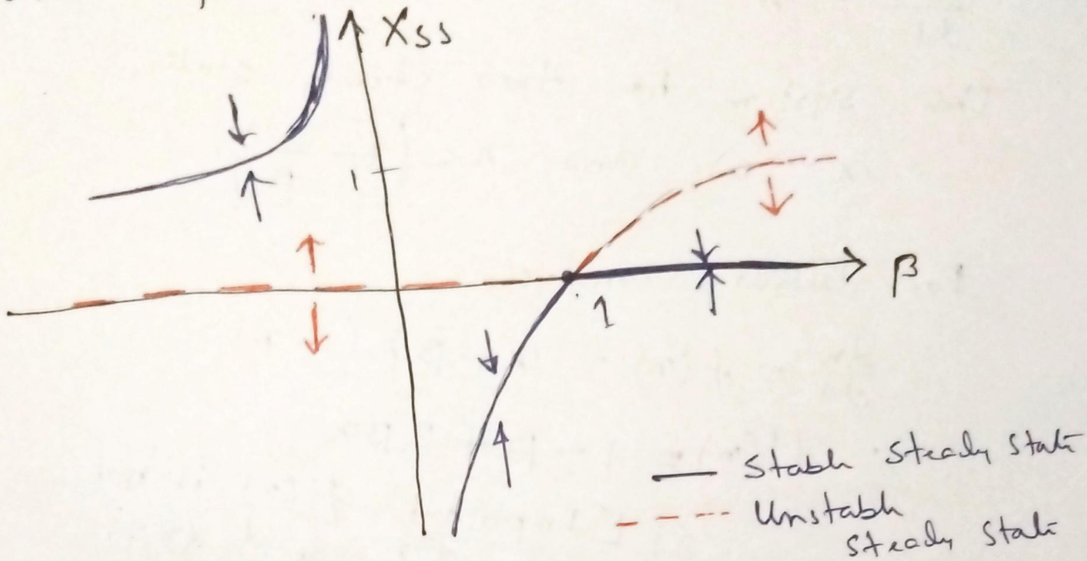
$\therefore$ The bifurcation diagram (the answer):



Q10.

$$f(x) = kx(1-x) \quad , \quad x \in [0, 1]$$

For $f(x)$ be a valid PDF, the following conditions must be met:

a) $f(x)$ is a positive function.
So $k > 0$.

b) $\int_0^1 f(x)\,dx = 1$ ——— (1)

$$\int_0^1 f(x)\,dx = k\int_0^1 x(1-x)\,dx = \frac{k}{6} \quad \text{——— (2)}$$

Eq (1) = Eq (2)

$\therefore$ $k = 6$. Ans

Q11

The simulation should stop when X is exhausted. In each reaction event 2 molecules of X is used. So, the reaction will stop after $n = 500$ reaction events.

It is a poisson process with rate $\lambda = 10/s$.

$\therefore$ Mean of the waiting time for nth reaction/event.

$$E(S_n) = \frac{n}{\lambda} = \frac{500}{10} = 50\ s. \quad \underline{\text{Ans}}$$

$\therefore$ Variance of the waiting time for the nth reaction/event,

$$var(S_n) = \frac{n}{\lambda^2} = \frac{500}{100} = 5\ s \quad \underline{\text{Ans.}}$$

Note that in this question, end-point or stop time for simulation is same as waiting time for nth reaction or 500-th reaction.

Q12

In an E-R graph,
total number of edges,

$$L = p\,{}^{N}C_{2}$$

$\therefore$ Mean degree,

$$\langle k \rangle = \frac{2L}{N} = \frac{2p\,{}^{N}C_{2}}{N}$$

$$= p(N-1)$$

$$\simeq pN \quad (\text{for } N >> 1)$$

Ans (A)

We know degree distribution of ER network follows Poisson distribution with mean $\langle k \rangle$. In Poisson distribution mean and variance are equal.

$\therefore$ variance of degree of a node in this graph $= \langle k \rangle = pN$. Ans.