

013 (Guy-Bart Stan Questions)

I. Model of order 1 for the prevalence of Heterochromia.

Prevalence of Heterochromia can be modelled as:

$$\dot{x} = x(1-x)(x-p), \quad (1) \quad x(0) = x_0 \in [0, 1]$$

$x(t) \in [0, 1]$ \Rightarrow fraction of the population with heterochromia at time t .

x_0 \Rightarrow initial fraction of the population with heterochromia.

$p \in (0, 1) \Rightarrow$ probability of not inheriting heterochromia. (if at least one of the child's parents has it)
 (we assume this probability is neither 0 nor 1).

Hint: remember that x denotes the fraction of the human population that has heterochromia, thus we are only interested in values of x between 0 and 1.

a) Fixed point(s) and phase line analysis of model (1)

i) Find all the fixed points of model (1):

- fixed points of $\dot{x} = x(1-x)(x-p)$ occur when $\dot{x} = 0$

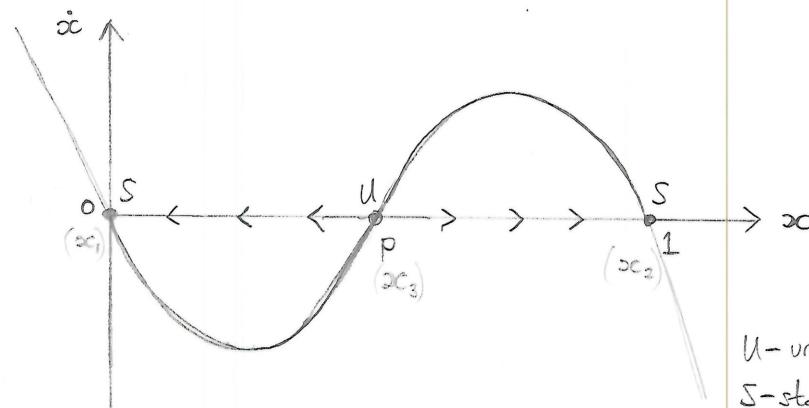
$$\therefore x_1 = 0 \quad x_2 = 1 \quad x_3 = p$$

ii) Draw the phase line: (\dot{x} vs x)

$$\dot{x} = (x-x_1)(x-x_2)(x-x_3) = x^3 - px^2 + px^3 - x^3$$

- $p \in (0, 1)$, so ' p ' has to be between 0 and 1.

- If $x < p$, $x(1-x)(x-p)$ will be negative, so first curve goes downwards.



U-unstable
S-stable.

- x^3 graph:



+ x^3 graph:



b) Stability, basin(s) of attraction and interpretation:

check notation
sheet

i) Classify each of the fixed points as stable or unstable, find the region of attraction of the points.

$x_1: x=0$ is stable (locally attracting). Its region of attraction is $A_1 = [0, p]$. same as $[0, p)$

$x_2: x=p$ is unstable (repelling). Its region of attraction is $A_2 = \{p\}$

could be $(-\infty, p)$

if p want $p \in [0, 1]$
or (p, ∞)

$x_3: x=1$ is stable (locally attracting). Its region of attraction is $A_3 =]p, 1]$ same as $(p, 1]$

ii) Using answers above, what does the model predict about long-term prevalence of heterochromia? (i.e. what are the attractors of D ?)

How do the parameter $p \in (0, 1)$ and the initial condition $x_0 \in [0, 1]$ influence the long term prevalence of heterochromia?
Does this make sense with regards to the meaning of p ?

- If $x_0 = p$, we have that $x(t) = p$ for all time. since $A_2 = \{p\}$

↳ situation: ^{the} fraction of the population with heterochromia is perfectly balanced with the probability that it is transmitted from parent to child such that the percentage of the population with heterochromia remains constant through generations.

- If $x_0 > p$, we have that $x(t) \rightarrow 1$ as $t \rightarrow +\infty$.

↳ This causes each ^{new} generation to have a higher percentage of incidence heterochromia.
Eventually, everyone will have heterochromia.

- If $x_0 < p$, we have that $x(t) \rightarrow 0$ as $t \rightarrow +\infty$.

↳ Every new generation will have a smaller percentage of people with heterochromia, eventually causing the condition to disappear.

NP →

Note that, the larger p , the smaller the chance that a child inherits heterochromia from its parents. Thus the smaller the region of attraction of the fixed point corresponding to the situation in which everyone has heterochromia (α_3), and the larger the basin of attraction of the fixed point corresponding to the situation in which no one has heterochromia (α_1). $\rightarrow \alpha_0 < p \Rightarrow \alpha_0 \rightarrow 0$.

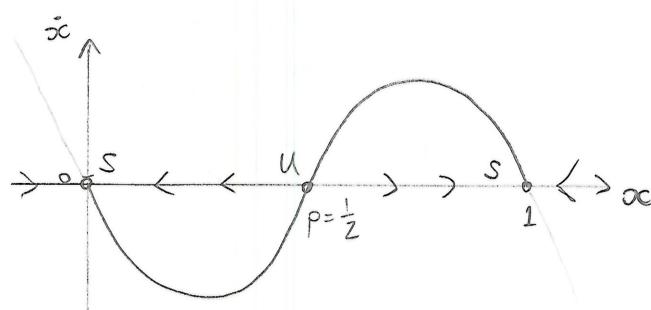
iii) $\alpha_0 = 0.0067$, $p = 0.27$.

$-\alpha_0 < p \therefore \alpha(t) \rightarrow 0$ as $t \rightarrow \infty$ (from part ii)

- the initial condition is well in the region of attraction of α_1 .

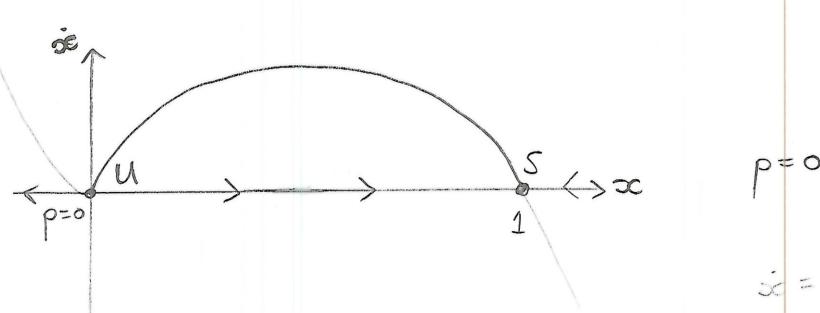
- Thus, heterochromia will die out.

c) Bifurcation analysis consider the model $\dot{\alpha} = \alpha(1-\alpha)(\alpha-p)$ abstractly. Vary p between $-\frac{1}{2}$ and $\frac{1}{2}$:



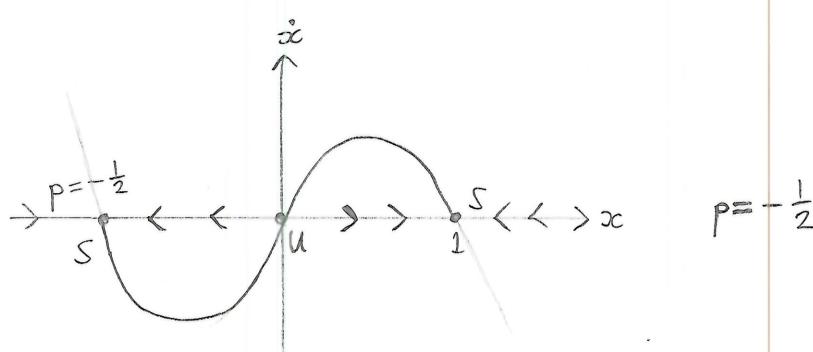
$$\begin{aligned}\dot{\alpha} &= \alpha^2 - p\alpha + p\alpha^2 - \alpha^3 \\ &= \frac{3\alpha^2}{2} - \frac{\alpha}{2} - \alpha^3\end{aligned}$$

$$\begin{aligned}&\equiv -\alpha \left(\alpha^2 - \frac{3\alpha}{2} + \frac{1}{2}\right) \\ &\alpha = 0 \quad \alpha = \frac{3}{2}, 1\end{aligned}$$



$$\dot{\alpha} = \alpha^2 - \alpha^3 = -\alpha^2(\alpha - 1)$$

$$(\alpha-1) = \alpha^2(\alpha-1)$$



$$p = -\frac{1}{2}$$

NP \rightarrow

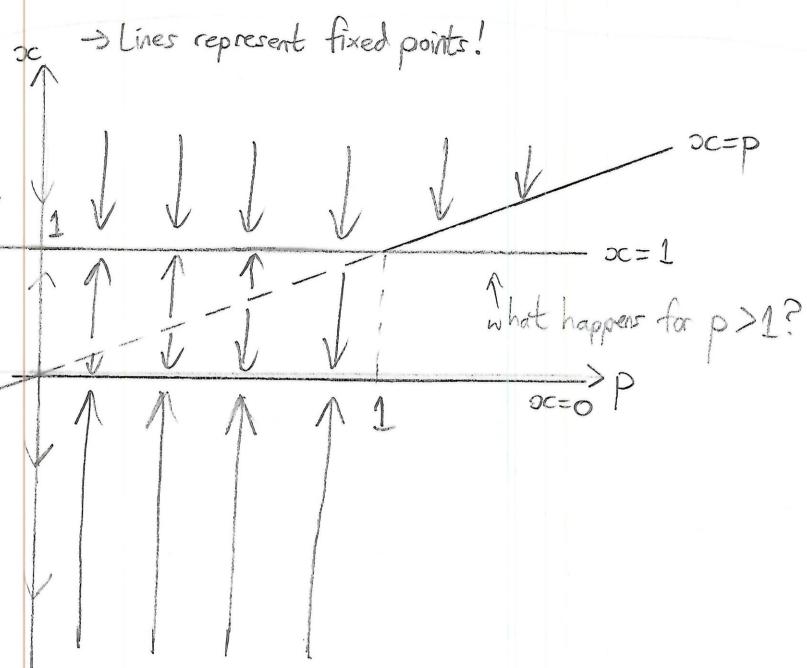
i) Does a bifurcation occur? what kind of bifurcation is it?

- A bifurcation occurs because a change in the parameter p produces a change in the attractors of the system.
- In this case, it is a transcritical bifurcation because there is a merging and subsequent stability reversal of a stable and unstable fixed point.

ii) At what value of p does it occur?

- The bifurcation occurs at $p=0$.

iii) draw the bifurcation diagram:



→ $x_c = 1$ is always stable (look at 3 diagrams on previous page)

→ $x_c = 0$ is:

- stable when p goes from 0 to 1 ($0 \leq p \leq 1$)
- unstable when p goes from $-\infty$ to 0.

→ $x_c = p$ is:

- stable from $-\infty$ to 0
- unstable from 0 to 1

DRAW LINES FOR
FIXED POINTS FIRST.

2. a) Fixed point(s) & Jacobian matrix of a model of order 2:

2nd order model $\begin{cases} \dot{x} = xc - xcy \\ \dot{y} = xcy - y \end{cases}$ ② (in what follows, do not assume that $x(t)$ and $y(t)$ have to be non-negative.)

i) Find all the fixed points of the model ②.

- Fixed points occur when $\dot{x}=0$ and $\dot{y}=0$.

- $\dot{x} = xc(1-y) \therefore 0 = xc(1-y) \therefore \underline{xc=0}, \underline{y=1}$

- When $xc=0$, $\dot{y}=(0)y-y \therefore \dot{y}=-y \Rightarrow$ when $\dot{y}=0$, $y=0$

- When $y=1$, $\dot{y}=xc-1 \Rightarrow$ when $\dot{y}=0$, $xc=1$

- Thus fixed points are at $(0,0)$ and $(1,1)$. ✓

→ or we could do $0=xcy-y=y(xc-1)$
 $\therefore y=0, xc=1$
 but we need to know which coordinates go together!

ii) Compute the analytical expression of the jacobian matrix (also known as the linearisation matrix) of model ②.

$$f_1(x,y) = \dot{x} = xc - xcy$$

$$f_2(x,y) = \dot{y} = xcy - y$$

$$J(x,y) = \begin{bmatrix} \frac{\partial f_1(x,y)}{\partial x} & \frac{\partial f_1(x,y)}{\partial y} \\ \frac{\partial f_2(x,y)}{\partial x} & \frac{\partial f_2(x,y)}{\partial y} \end{bmatrix}$$

$$\therefore J(x,y) = \begin{bmatrix} 1-y & -xc \\ y & xc-1 \end{bmatrix} \quad \checkmark$$

2.b) Local stability and the Hartman-Grobman Theorem (also known as linearisation theorem).

Evaluate the Jacobian matrix at each fixed point.

Using Hartman-Grobman theorem, what can you deduce regarding each of the fixed points of model ②?

Sketch the local phase portrait around each fixed point (if appropriate).

$$(A) \quad J(x,y)|_{(0,0)} = \begin{bmatrix} 1 & 0 \\ 0 & -1 \end{bmatrix}$$

$$(A) \quad J(x,y)|_{(1,1)} = \begin{bmatrix} 0 & -1 \\ 1 & 0 \end{bmatrix}$$

- Eigenvalues: $\det(J - \lambda I) = 0$

$$\therefore \det \begin{bmatrix} 1-\lambda & 0 \\ 0 & -1-\lambda \end{bmatrix} = 0$$

$$\therefore (1-\lambda)(-1-\lambda) - (0)(0) = 0$$

$$\therefore \lambda^2 - \lambda + 1 = 0$$

$$\therefore \lambda^2 - 1 = 0$$

$$\therefore \lambda_{1,2} = \pm \sqrt{1} = \pm 1 \quad \checkmark$$

- Eigenvalues: $\det(J - \lambda I) = 0$

$$\therefore \det \begin{bmatrix} -\lambda & -1 \\ 1 & -\lambda \end{bmatrix} = 0$$

$$\therefore (-\lambda)(-\lambda) - (-1)(1) = 0$$

$$\therefore \lambda^2 + 1 = 0$$

$$\therefore \lambda_{3,4} = \pm \sqrt{-1}$$

$$\therefore \lambda_{3,4} = \pm i \quad \checkmark$$

- Eigenvectors: $J \underline{x} = \lambda \underline{x}$, for the fixed point $(0,0)$ (i.e. λ_1 and λ_2)

↓

rearrange: $(J - \lambda I) \underline{x} = 0$

$$\lambda_1 = +1, \quad \begin{pmatrix} 1-(1) & 0 \\ 0 & -1-(1) \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix} = 0$$

$$\begin{cases} 0=0 \\ -2y=0 \end{cases} \quad \therefore y=0$$

$$\therefore \underline{v}_1 = \begin{pmatrix} 1 \\ 0 \end{pmatrix}^x \quad \checkmark$$

↳ since there is no equation governing the choice of x , we are free to choose any value of x (usually 1).

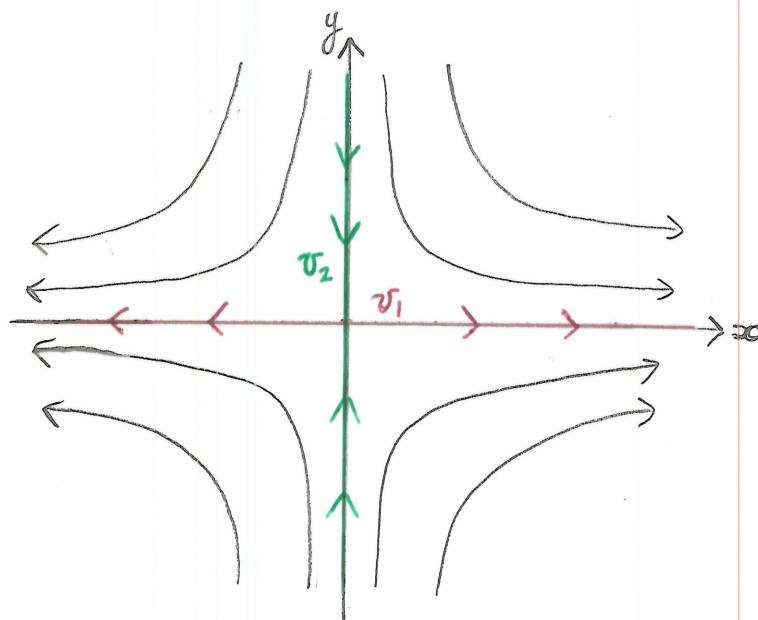
NP →

$$\lambda_2 = -1, \quad \begin{pmatrix} 1-(-1) & 0 \\ 0 & -1-(-1) \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix} \quad \left(J(x,y)|_{(0,0)} = \begin{bmatrix} 1 & 0 \\ 0 & -1 \end{bmatrix} \right)$$

$$\begin{cases} 2x=0 \\ 0=0 \end{cases} \quad \therefore x=0 \quad \therefore v_2 = \begin{pmatrix} 0 \\ 1 \end{pmatrix}$$

at $(0,0)$

- Both eigenvalues have a non-zero real part, so by the Hartman-Grobman theorem, the fixed point behaves locally as a saddle point. (with unstable manifold v_1 (the x axis) and stable manifold v_2 (the y axis)).



$$v_1 e^{\lambda_1 t} + v_2 e^{\lambda_2 t} \quad \lambda_1 = 1 \text{ and } \lambda_2 = -1 \quad \therefore \underbrace{v_1 e^t}_{\rightarrow \infty} + \underbrace{v_2 e^{-t}}_{\rightarrow 0}$$

Youtube video

- Eigenvectors: $(J - \lambda I)v = 0$, for the fixed point $(1,1)$. (i.e. λ_3 and λ_4)

wrong matrix!

$$\lambda_3 = +i, \quad \begin{pmatrix} 1-(+i) & 0 \\ 0 & -1-(+i) \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix} = 0 \quad \rightarrow J(x,y)|_{(1,1)}: \quad \begin{pmatrix} -(+i) & -1 \\ 1 & -(+i) \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix} = 0$$

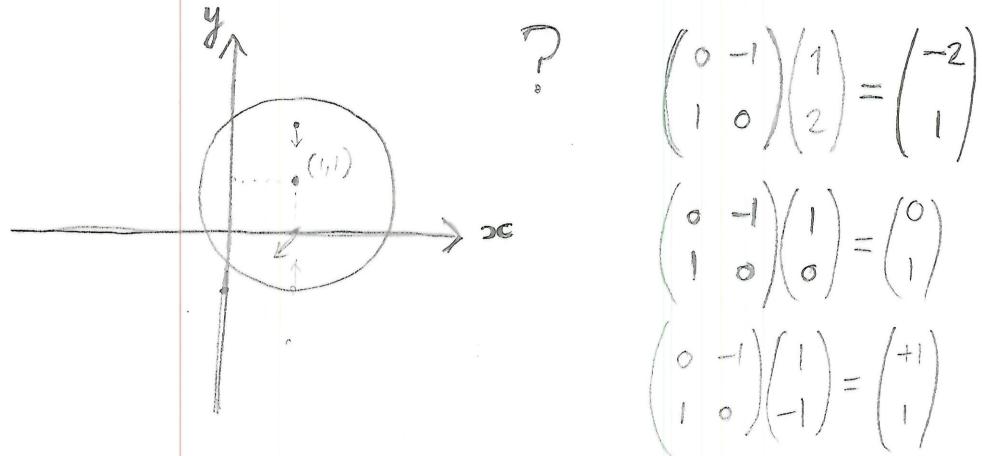
$$\begin{cases} x - ix = 0 \\ -y - iy = 0 \end{cases} \quad \therefore x(1-i) = 0 \quad \therefore -y(1+i) = 0$$

NP →

$$\begin{cases} -ix - y = 0 \\ x - iy = 0 \end{cases} \quad \begin{array}{l} \text{set} \\ ? - y = ix \\ \therefore x = iy \\ x = iy \end{array}$$

- For the fixed point $(1, 1)$: eigenvalues are $\lambda_3 = i$, $\lambda_4 = -i$

- The eigenvalues have zero real part, so Hartman-Grobman Theorem is not applicable and we cannot say anything about the fixed point p_2 . (nevermind sketching the phase portrait).

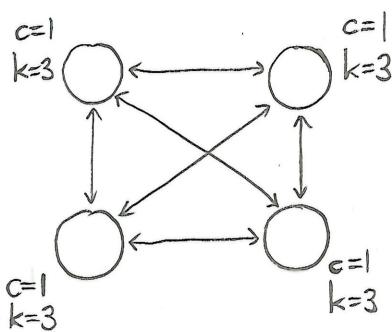


B-2013 (Faisal Questions)

2. c) Biological network analysis : Draw a network of 4 nodes such that:

- each node is at least connected to another node and, (simultaneously)
- each node has a clustering coefficient of 1.

(node degree = number of friends)
(k = neighbours)



- Network of 4 nodes

- Each node has clustering coefficient of 1.

$$C_i = \frac{2n_i}{k_i(k_i-1)} = 1 \rightarrow \text{Thus by trial and error? we can have: } k_i = 3, n_i = 3 \text{ for every node.}$$

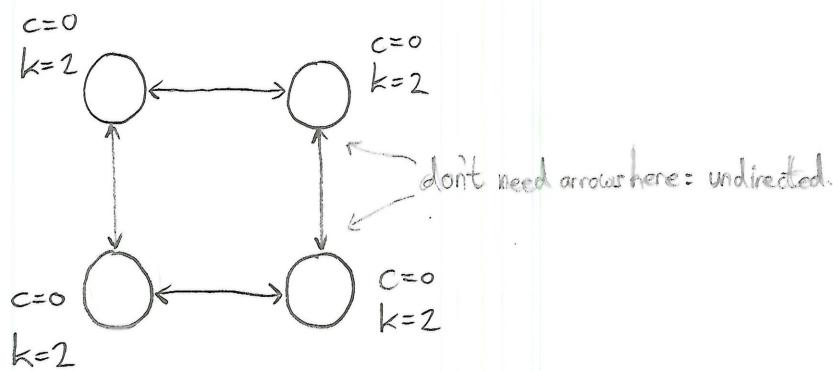
- Where n_i is the number of links connecting the k_i neighbours of node i to each other.

d) Draw a network of 4 nodes such that: - the average node degree is 2 and,

- the average clustering coefficient of the network is 0.

- Average node degree = 2 → thus all nodes should have 2 neighbours.

- Average clustering coefficient = 0. → thus all local clustering coefficients must be zero.



NP →

2.e) Biological network synthesis: What class of networks does the model by Barabasi-Alberts capture and how?

- It was developed to capture the scale-free properties of real-life networks.
- We start with a small network and grow it by connecting new nodes to already existing nodes with a probability proportional to the existing node's (connectivity) degree k .
- The highly connected nodes that already exist in the network are more likely to obtain links to newcomer nodes and this makes them even more highly connected.

f) (more biological network synthesis): What generative features renders the Barabasi-Alberts model attractive in the context of protein networks.

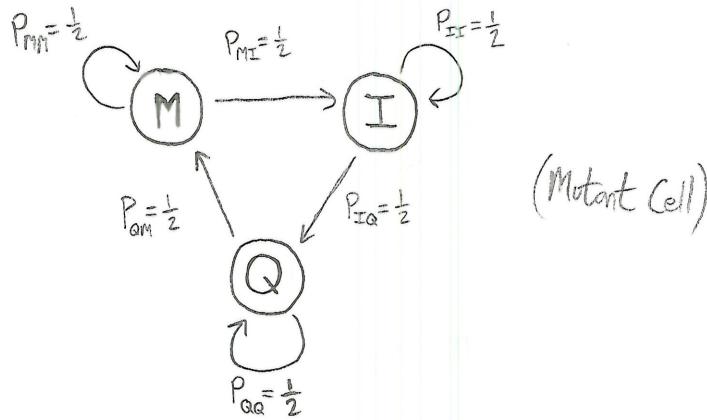
- Growth and preferential attachment have a common origin in protein networks that is probably rooted in gene duplication - a genetic implementation of the preferential attachment model.
(PCR)
- Duplicated genes produce identical proteins that interact with the same protein partners.
- Therefore, each protein that is in contact with a duplicated protein gains an extra link.
- Highly connected proteins have a natural advantage: it is not that they are more (or less) likely to be duplicated, but they are more likely to have a link to a duplicated protein than their weakly connected cousins, and therefore they are more likely to gain new links if a randomly selected protein is duplicated.
- The most important feature of this explanation is that it traces the origin of scale-free topology back to a well-known biological mechanism: gene duplication.

Markov processes of cell cycles in healthy and mutant cells:

(3-state) Transition probability matrix P :

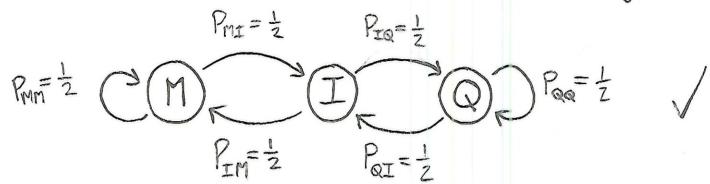
$$P_{\text{wild type}} = \begin{pmatrix} Q & I & M \\ \frac{1}{2} & \frac{1}{2} & 0 \\ \frac{1}{2} & 0 & \frac{1}{2} \\ 0 & \frac{1}{2} & \frac{1}{2} \end{pmatrix} \quad \begin{array}{l} (\text{column-to-row form i.e. columns sum to 1}) \\ (\text{Wild type Cell}) \end{array}$$

(3-state) Markov process model for mutation cell:



a) Markov Process Basics

i) Sketch Markov process diagram for Wild type cell.



ii) Write out the (labelled) Markov transition probability matrix for the mutant cell.

$$P_{\text{mutant}} = \begin{pmatrix} Q & I & M \\ \frac{1}{2} & \frac{1}{2} & 0 \\ 0 & \frac{1}{2} & \frac{1}{2} \\ \frac{1}{2} & 0 & \frac{1}{2} \end{pmatrix} \quad \checkmark$$

NP →

iii) Briefly, state the Markov property and explain the meaning of this assumption in the context of these cells and their life-cycle.

- The Markov property states that the transition probability for the current cell state transition does not depend on previous history of states visited.
- In this case the cell-cycle history of the cell does not matter (e.g. how often the cell had already divided itself), but only on the current cell state.

b) Steady states of Markov Processes

i) In the long run, what proportion of time does a wild-type cell spend in each state?

- 'In the long run' \Rightarrow stationary/steady state distribution π .
- To find this distribution, we utilise the steady state distribution $\pi_1 + \pi_2 + \pi_3 = 1$, and the forward-kolmogorov equation $\tilde{\pi}\pi = \pi$.
- For the wild type cell:

$$\begin{matrix} Q & \xrightarrow{M} \\ \begin{pmatrix} \frac{1}{2} & \frac{1}{2} & 0 \\ \frac{1}{2} & 0 & \frac{1}{2} \\ 0 & \frac{1}{2} & \frac{1}{2} \end{pmatrix} & \begin{pmatrix} \pi_1 \\ \pi_2 \\ \pi_3 \end{pmatrix} = \begin{pmatrix} \pi_1 \\ \pi_2 \\ \pi_3 \end{pmatrix} \end{matrix} \Rightarrow \begin{cases} \frac{1}{2}\pi_1 + \frac{1}{2}\pi_2 + 0 = \pi_1 & (1) \\ \frac{1}{2}\pi_1 + 0 + \frac{1}{2}\pi_3 = \pi_2 & (2) \\ 0 + \frac{1}{2}\pi_2 + \frac{1}{2}\pi_3 = \pi_3 & (3) \end{cases} \begin{array}{l} \therefore \pi_1 = \pi_2 \\ \therefore \pi_1 + \pi_3 = 2\pi_2 \\ \therefore \pi_2 = \pi_3 \end{array}$$

$$\text{Also: } \pi_1 + \pi_2 + \pi_3 = 1 \quad (4)$$

- sub ① and ③ into ④:

$$\begin{matrix} \textcircled{1} & \textcircled{3} \\ (\pi_2) + \pi_2 + (\pi_2) & = 1 \end{matrix} \quad \therefore 3\pi_2 = 1 \quad \begin{matrix} \checkmark & \textcircled{2} & \textcircled{1} \\ \therefore \pi_2 = \frac{1}{3} & = \pi_3 = \pi_1 \end{matrix}$$

$$\therefore \pi = \begin{pmatrix} \frac{1}{3} \\ \frac{1}{3} \\ \frac{1}{3} \end{pmatrix}$$

- So the wild type cell will spend $\frac{1}{3}$ of time in each state.

iii) in the long run, what proportion of time does a mutant cell spend in each state?

- For the mutant cell:

$$\begin{pmatrix} \frac{1}{2} & 0 & \frac{1}{2} \\ \frac{1}{2} & \frac{1}{2} & 0 \\ 0 & \frac{1}{2} & \frac{1}{2} \end{pmatrix} \begin{pmatrix} \pi_1 \\ \pi_2 \\ \pi_3 \end{pmatrix} = \begin{pmatrix} \pi_1 \\ \pi_2 \\ \pi_3 \end{pmatrix} \Rightarrow \begin{cases} \frac{1}{2}\pi_1 + 0 + \frac{1}{2}\pi_3 = \pi_1 & \text{(x1)} \\ \frac{1}{2}\pi_1 + \frac{1}{2}\pi_2 + 0 = \pi_2 & \text{(x2)} \\ 0 + \frac{1}{2}\pi_2 + \frac{1}{2}\pi_3 = \pi_3 & \text{(x3)} \end{cases} \therefore \begin{aligned} \pi_3 &= \pi_1 & \text{①} \\ \pi_1 &= \pi_2 & \text{②} \\ \pi_2 &= \pi_3 & \text{③} \end{aligned}$$

$$\text{Also: } \pi_1 + \pi_2 + \pi_3 = 1 \quad \text{④}$$

- sub ① & ② into ③:

$$\therefore \pi_1 + (\overset{\text{②}}{\pi_1}) + (\overset{\text{①}}{\pi_1}) = 1 \quad \therefore 3\pi_1 = 1$$

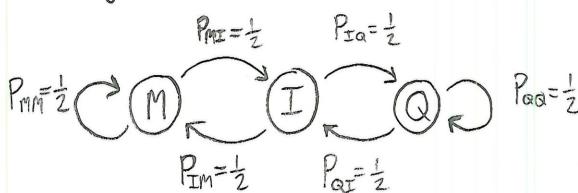
$$\therefore \pi_1 = \frac{1}{3} \stackrel{\checkmark \text{ ② } \text{ ①}}{=} \pi_2 = \pi_3$$

$$\therefore \pi = \begin{pmatrix} \frac{1}{3} \\ \frac{1}{3} \\ \frac{1}{3} \end{pmatrix}$$

- so the mutant cell also spends $\frac{1}{3}$ of the time in each state.

c) First/one-Step analysis of Markov Processes.

i) Calculate the average number of hours it takes to go around the cycle from when a cell leaves mitosis to when it returns to mitosis for the wild type cell. (Hint: self transitions do not count for departures and arrivals in the Mitosis state (M)).



- First-step analysis for each transient state: (τ_i is the time it takes to reach state M from state i)

$\tau_m = 0$ ^① (not $P_{mm}(1 + \tau_m)$ because the time it takes to reach state M from M is zero, see Hint also)

$$\tau_I = P_{IM}(1 + \tau_m) + P_{IQ}(1 + \tau_Q) \quad \text{②}$$

$$\tau_Q = P_{QI}(1 + \tau_I) + P_{QM}(1 + \tau_m) \quad \text{③}$$

$$\therefore \text{② } \tau_I = \frac{1}{2}(1 + \overset{\text{①}}{\tau_m}) + \frac{1}{2}(1 + \tau_Q) = \frac{1}{2} + \frac{1}{2} + \frac{\tau_Q}{2}$$

NP →

$$\therefore \tau_I = 1 + \frac{\tau_Q}{2} \quad \text{④}$$

$$③ \tau_Q = \frac{1}{2}(1 + \tau_Q) + \frac{1}{2}(1 + \tau_I) = \frac{1}{2} + \frac{\tau_Q}{2} + \frac{1}{2} + \frac{\tau_I}{2}$$

$$\text{(x2)} \therefore 2\tau_Q = 2 + \tau_Q + \tau_I$$

$$\therefore \tau_Q = 2 + \tau_I$$

- sub in ④:

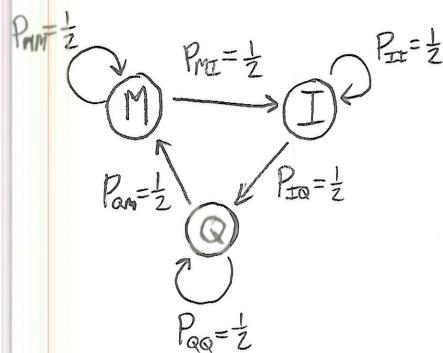
$$\tau_Q = 2 + \left(1 + \frac{\tau_Q}{2}\right) = 3 + \frac{\tau_Q}{2}$$

$$\therefore \frac{\tau_Q}{2} = 3 \quad \therefore \tau_Q = 6 \quad \checkmark$$

$$\therefore \tau_I = 1 + \frac{6}{2} = 4 \quad \checkmark \quad \boxed{\therefore \tau = 4}$$

- Thus, the average number of hours it takes to go around the cycle from when a cell leaves mitosis to when it returns again is 4.

ii) Calculate the average number of hours it takes to go around the cycle from when a cell leaves Mitosis to when it returns to Mitosis for the mutant cell. (Hint: self-transitions do not count for departures and arrivals in the Mitosis state (M)).



- First-step analysis for each transient state: (τ_i is the time it takes to reach state M from state i)

$$\tau_M = 0 \quad ① \quad (\text{it takes zero steps to reach } \underline{M} \text{ from } \underline{M})$$

$$\tau_I = P_{II}(1 + \tau_I) + P_{IQ}(1 + \tau_Q) \quad ②$$

$$\tau_Q = P_{QQ}(1 + \tau_Q) + P_{QM}(1 + \tau_M) \quad ③$$

$$\therefore ② \tau_I = \frac{1}{2}(1 + \tau_I) + \frac{1}{2}(1 + \tau_Q) = \frac{1}{2} + \frac{\tau_I}{2} + \frac{1}{2} + \frac{\tau_Q}{2} \quad (\text{x2}) \quad \therefore 2\tau_I = 2 + \tau_I + \tau_Q$$

$$\therefore \tau_I = 2 + \tau_Q \quad ④ \quad \text{NP} \rightarrow$$

$$\textcircled{3} \quad \tau_Q = \frac{1}{2}(1 + \tau_Q) + \frac{1}{2}\left(1 + \overset{\textcircled{1}}{\gamma_M}\right) = \frac{1}{2} + \frac{\tau_Q}{2} + \frac{1}{2}$$

$$(x^2) \quad \therefore 2\tau_Q = 2 + \tau_Q$$

$$\therefore \tau_Q = \underline{\underline{2}} \quad \checkmark$$

$$\textcircled{4} \quad \therefore \tau_I = 2 + (2) = \underline{\underline{4}} \quad \checkmark$$

$$\boxed{\therefore \tau = 4}$$

- The (surprising) finding is that despite the very different Markov process structure, the cycle times (and stationary distributions) are identical, hence the inter mitosis cycle time is not an indicator for cancerous growth.