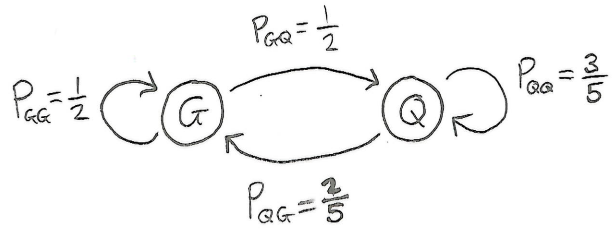
M.B 2012 (Faisal Questions)

1. → Half of the growing cells turn quiescent overnight $\therefore P_{GQ} = \frac{1}{2}$
→ Two out of five quiescent cells turn into growing cells overnight $\therefore P_{QG} = \frac{2}{5}$
→ Other cells remain in their respective state.

Two states:
- Growing (G)
- Quiescent (Q)

a) i) Markov process diagram:



✓

ii) Transition probability matrix $\underset{\approx}{P}$:

$$\underset{\approx}{P} = \begin{array}{c} \\ \\ \end{array} \begin{array}{cc} G & Q \end{array}$$
$$\underset{\approx}{P} = \begin{array}{cc|c} G & Q & \\ \end{array}$$

$$\begin{array}{c} \\ \underset{\approx}{P} = \end{array} \begin{array}{c} \begin{array}{cc} G & Q \end{array} \\ \begin{pmatrix} \frac{1}{2} & \frac{2}{5} \\ \frac{1}{2} & \frac{3}{5} \end{pmatrix} \end{array} \begin{array}{c} \\ G \\ Q \end{array}$$

✓ (collum-to-row form. i.e. collumns sum to 1)

iii) In the long run, what proportion of cells will be in each state?

- 'In the long run' ⇒ stationary (steady state) distribution. π.
- To find this distribution, we can utilise the probability condition for the steady state distribution; $\pi_1 + \pi_2 = 1$, and the forward-kolmogorov equation; $\underset{\approx}{P}\underset{\sim}{\pi} = \underset{\sim}{\pi}$.
- We can now solve for π_1 and π_2:

$$\begin{pmatrix} \frac{1}{2} & \frac{2}{5} \\ \frac{1}{2} & \frac{3}{5} \end{pmatrix} \begin{pmatrix} \pi_1 \\ \pi_2 \end{pmatrix} = \begin{pmatrix} \pi_1 \\ \pi_2 \end{pmatrix} \Rightarrow \begin{cases} \frac{1}{2}\pi_1 + \frac{2}{5}\pi_2 = \pi_1 & \therefore \frac{2}{5}\pi_2 = \frac{1}{2}\pi_1 \\ \frac{1}{2}\pi_1 + \frac{3}{5}\pi_2 = \pi_2 & \therefore \frac{1}{2}\pi_1 = \frac{2}{5}\pi_2 \end{cases} \Bigg\} \; \pi_1 = \frac{4}{5}\pi_2 \quad ① \text{ (same)}$$

Also: $\pi_1 + \pi_2 = 1$ ②

- sub ① into ②:

$$\therefore \overset{①}{\left(\frac{4}{5}\pi_2\right)} + \pi_2 = 1 \quad \therefore \pi_2 = \frac{5}{9} \quad \therefore \pi_1 = \frac{4}{9} \quad \therefore \pi = \begin{pmatrix} \frac{4}{9} \\ \frac{5}{9} \end{pmatrix} \begin{matrix} \leftarrow \pi_G \\ \leftarrow \pi_Q \end{matrix}$$ ✓

important to comm

- Hence in the long run, $\frac{4}{9}$ of the cells will be growing and $\frac{5}{9}$ of the cells will be quiescent.

MiB - 2012 (Guy-Bart Stan Questions)

2. b) i) List the different attractors that a (continuous time, non-linear ODE) model of the form $\dot{x} = f(x)$ can have when x is:

A) 1D:

(Slide 64 notes)

→ fixed points

→ $\pm\infty$

B) 2D:

→ fixed points

→ $\pm\infty$

→ limit cycles

C) 3D and higher:

→ fixed points

→ $\pm\infty$

→ limit cycles

→ quasi-periodic attractors

→ chaotic attractors.

ii) explain the concept of 'bifurcation' of a dynamical system. (slide 26 notes)

- A bifurcation occurs when a change in the parameter(s) of the model produce qualitative (or large) changes in the long term behaviour (of the attractors) of the system, eg:

↳ (i.e the number or stability of the attractors of a dynamical system.)

- the number of attractors (e.g. fixed points) changes.
- the type of attractors changes (e.g. from fixed point to limit cycle)
- the stability of attractors (e.g. fixed points) changes.

b) iii) Explain the following types of bifurcations:

A) Transcritical bifurcation:

- A particular kind of local bifurcation in which one of the fixed points is always zero.
- The normal form of the transcritical bifurcation is $\dot{x} = rx - x^2$.
- It is characterised by a merging and subsequent stability reversal of a stable and an unstable fixed point.
- (Exchange of stability properties of the fixed points at the critical bifurcation value)

B) Saddle-node bifurcation: (also known as blue sky bifurcation)

- The normal (common/general?) form of the saddle-node bifurcation is $\dot{x} = r + x^2$ where 'x' is the state variable and 'r' is the bifurcation parameter.
- It is characterised by a merging and subsequent disappearance (or sudden creation depending on how the parameter is varied) of a stable and unstable fixed point.
- (simultaneous appearance or disappearance of a stable fixed point and a saddle (unstable) fixed point at the critical bifurcation value.)

C) Pitchfork bifurcation:

- Change of stability of a fixed point and the simultaneous appearance of 2 new fixed points at the critical bifurcation value.
- The normal forms of the pitchfork bifurcation are: → supercritical case: $\dot{x} = rx - x^3$
  → subcritical case: $\dot{x} = rx + x^3$
- (There is always a fixed point at $x = 0$, and if $r > 0$, there are two other fixed points at $x = \sqrt{r}$ and $x = \sqrt{-r}$)

3. 1D model of gene auto-activation. (Slide 72 notes)

The dynamics of a self-activated gene can be represented by the following model composed of two ODEs:

$$\dot{m} = k_1 \frac{p^2}{K^2+p^2} - d_1 m \quad ①$$

(2nd order model)

$$\dot{p} = k_2 m - d_2 p \quad ②$$

$m(t)$ = mRNA concentration.

$p(t)$ = protein concentration.

k_1 = maximal transcription rate.

k_2 = translation rate

K = activation threshold.

d_1 = mRNA degradation rate.

d_2 = protein degradation rate.

It can be shown that the second order moder ① & ② can be reduced to a first order model of the form:

$$\dot{p} = \alpha \frac{p^2}{K^2+p^2} - d_2 p \quad ③$$

a) First order model ③ and its fixed point(s) analysis.

i) using quasi-steady state approximation $\dot{m}=0$, show how ① & ② reduce to ③ and identify α.

$\dot{m}=0$, $\therefore$ ① $\Rightarrow$ $0 = k_1 \frac{p^2}{K^2+p^2} - d_1 m$ $\quad \therefore d_1 m = k_1 \frac{p^2}{K^2+p^2}$

$$\therefore m = \frac{k_1}{d_1} \frac{p^2}{(K^2+p^2)}$$

sub into ② $\Rightarrow$ $\dot{p} = k_2 \left(\frac{k_1}{d_1} \frac{p^2}{(K^2+p^2)} \right) - d_2 p$

$\therefore \dot{p} = \alpha \frac{p^2}{K^2+p^2} - d_2 p$ where $\alpha = k_2 \frac{k_1}{d_1}$ ✓

ii) Find the analytical expression of the fixed points of ③. Hence show how many fixed points ③ can have, depending [illegible] d_2

– Fixed points of ③ $\left(\dot{p} = \alpha \frac{p^2}{k^2+p^2} - d_2 p\right)$ will occur when $\dot{p} = 0$.

$$\therefore 0 = \alpha \frac{p^2}{k^2+p^2} - d_2 p \qquad \therefore d_2 p = \alpha \frac{p^2}{k^2+p^2} \qquad \therefore d_2 p (k^2+p^2) = \alpha p^2$$

$$\therefore d_2 p k^2 + d_2 p^3 = \alpha p^2$$

$$\therefore d_2 p^3 - \alpha p^2 + d_2 k^2 p = 0$$

$$p = \frac{-b \pm \sqrt{b^2-4ac}}{2a} = \frac{-(-\alpha) \pm \sqrt{(-\alpha)^2 - 4(d_2)(d_2 k^2)}}{2(d_2)}$$

$$\therefore p(\underset{a}{d_2 p^2} \underset{b}{- \alpha p} + \underset{c}{d_2 k^2}) = 0$$

$$\therefore p = \frac{\alpha \pm \sqrt{\alpha^2 - 4 d_2^2 k^2}}{2 d_2}$$

$$\therefore p = 0 \checkmark \quad \text{and} \quad \frac{\alpha \pm \sqrt{\alpha^2 - 4 d_2^2 k^2}}{2 d_2} \checkmark$$

– p represents the concentration of a protein, so p can only be positive and real.

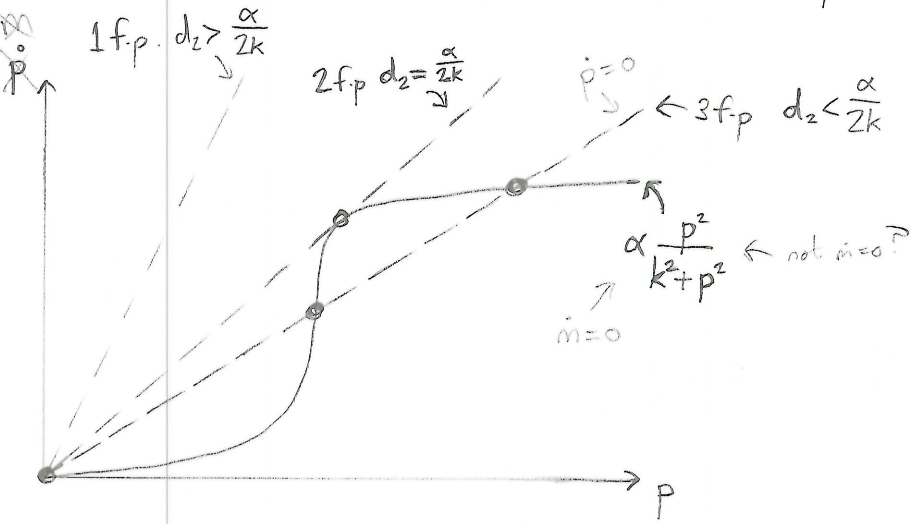
– Then, depending on $d_2 \geq 0$, the model will have a different number of fixed points.

WRITE OUT FULLY.

→ if $\alpha^2 > 4 d_2^2 k^2 \quad \therefore \alpha > \pm 2 d_2 k \quad \therefore d_2 < \frac{\alpha}{2k}$ (3 fixed points, $p=0$ and $p_\pm$)

→ if $\alpha^2 = 4 d_2^2 k^2 \quad \therefore \alpha = \pm 2 d_2 k \quad \therefore d_2 = \frac{\alpha}{2k}$ (2 fixed points, $p=0$ and $p = \frac{\alpha}{2d_2}$)

CHECK → not m? (from notes)



(don't need to draw graph)

→ if $\alpha^2 < 4 d_2^2 k^2 \quad \therefore \alpha < \pm 2 d_2 k \quad \therefore d_2 > \frac{\alpha}{2k}$ (2 complex fixed points & one at $p=0$ ∴ not relevant).

(ii) For the model in (3), show that a bifurcation occurs when d_2 becomes larger than a certain critical value. Calculate the critical value of d_2 at which bifurcation occurs (in terms of parameters of (3)).

- A bifurcation occurs because a (large) change in the parameter d_2 causes qualitative changes in the long term behaviour of the attractor of the system.

- 3 fixed points exist when $d_2 < \frac{\alpha}{2k}$.

- The two fixed points coalesce into one at $d_2 = \frac{\alpha}{2k}$.

- This occurs at the critical value $d_2 = \frac{\alpha}{2k}$, so therefore the bifurcation occurs at $d_2 = \frac{\alpha}{2k}$.

- (Note that at the critical value $d_2 = \frac{\alpha}{2k}$, the two fixed points $p_\pm$ merge into one which has the value $p_{bif} = \frac{\alpha}{2d_2} = k$.)

b) Stability and bifurcation analysis of the first order model (3).

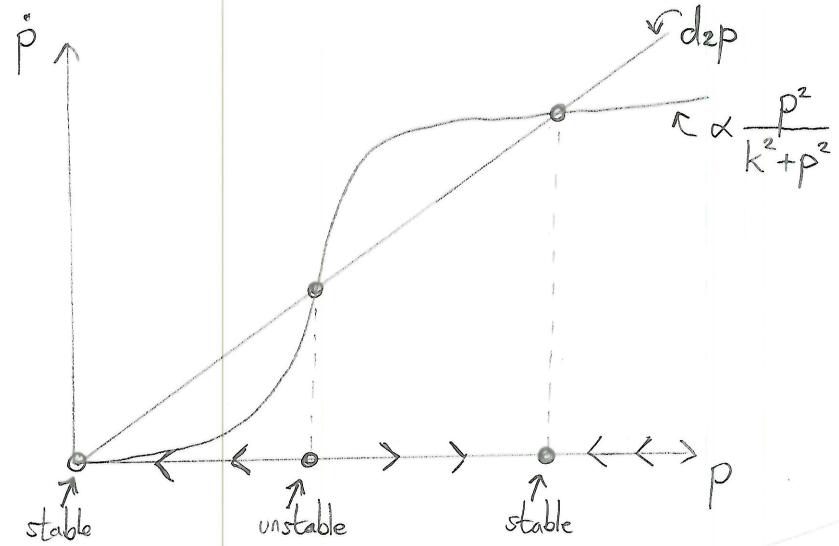
i) Using a graphical approach (nullcline) explain the stability of each fixed point for the model given in (3), show the flow on the p axis.

- The fixed point $p=0$ is stable, p_- is unstable and p_+ is stable.

- Graphically:
  - → The equation $\dot{p} = \alpha \frac{p^2}{k^2+p^2} - d_2 p$ allows us to easily evaluate flow along the real line of protein concentrations p.
  - → For $\dot{p}$ to be positive, we need to have $\alpha \frac{p^2}{k^2+p^2} - d_2 p > 0 \therefore \alpha \frac{p^2}{k^2+p^2} > d_2 p$ (i.e. $\dot{p}$ is positive when the curve $\alpha \frac{p^2}{k^2+p^2}$ lies above the curve $d_2 p$).
  - → For $\dot{p}$ to be negative, we need to have $\alpha \frac{p^2}{k^2+p^2} - d_2 p < 0 \therefore \alpha \frac{p^2}{k^2+p^2} < d_2 p$ (i.e. $\dot{p}$ is negative when the curve $\alpha \frac{p^2}{k^2+p^2}$ lies below the curve $d_2 p$).

NP →

- This allows us to draw the direction of the flow on the horizontal axis p:



- <u>Algebraically</u>:

  → The stability of the fixed points can be established by looking at the Jacobian evaluated at each fixed point.

  ? → one equation.

  → The <u>Jacobian here is scalar</u> and given by:

$$\frac{\partial}{\partial p}\left(\alpha\frac{p^2}{k^2+p^2}-d_2p\right) = \frac{\alpha(k^2+p^2)2p-2\alpha p^3-d_2(k^2+p^2)}{(k^2+p^2)^2} = \frac{\alpha k^2 2p-d_2(k^2+p^2)}{(k^2+p^2)^2}$$

→ At $p_0=0$, we have $\left.\frac{\partial}{\partial p}\left(\alpha\frac{p^2}{k^2+p^2}-d_2p\right)\right|_{p_0=0} = -\frac{d_2}{k^2} \leq 0$ $\therefore$ the f.p. $p_0=0$ is stable.

→ At $p=p_\pm$, we have by definition that $d_2(p_\pm^2+k^2)-\alpha p=0$,

Thus $$\left.\frac{\partial}{\partial p}\left(\alpha\frac{p^2}{k^2+p^2}-d_2p\right)\right|_{p=p_\pm} = \frac{\alpha k^2 2p_\pm-d_2(k^2+p_\pm^2)^2}{(k^2+p_\pm^2)^2} = \frac{d_2(k^2-p_\pm^2)}{(k^2+p_\pm^2)}$$

→ The Jacobian is zero at **$p=k$**; positive for $p<k$, and negative for $p>k$.

→ Since $p_-<k$ and $p_+>k$, we have that p_- is unstable and p_+ is stable.

NP→

→ (Note that, imposing that the Jacobian is zero, also corresponds in this case to imposing that the two curves touch tangentially, i.e. slopes of the curves are equal.)

→ This means that the two fixed points merge into one when $p = k$.

→ This is coherent with what we said before.

iii) what type of bifurcation occurs when d_2 becomes larger than the critical bifurcation value?

– When d_2 becomes larger than the critical bifurcation value $\left(d_2 > \frac{\alpha}{2k}\right)$, a stable and unstable fixed point merge and then disappear.

– This means it is a saddle-node or blue sky bifurcation.

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