IMPERIAL

MATH70137

BSc, MSci and MSc EXAMINATIONS (MATHEMATICS)
Summer 2025

This paper is also taken for the relevant examination for the
Associateship of the Royal College of Science

Mathematical Biology 2: Systems Biology

Date: Friday, May 30, 2025

Time: Start time 14:00 – End time 16:30 (BST)

Time Allowed: 2.5 hours

This paper has 5 Questions.

Please Answer All Questions in 1 Answer Booklet

This is a closed book examination.

Candidates should start their solutions to each question on a new sheet of paper.

Supplementary books may only be used after the relevant main book(s) are full.

Any required additional material(s) will be provided.

Credit will be given for all questions attempted.

Allow margins for marking.

DO NOT OPEN THIS PAPER UNTIL THE INVIGILATOR TELLS YOU TO DO SO

1. In this question you will explore 3-component biological circuit topologies, with an input u, output y, and an additional (internal) component, x. A general scheme for these circuits, with Michaelis-Menten kinetics, is given by:

$$\begin{aligned}\dot{x} &= A g^a_{xx}\left(x, K^a_{xx}\right) g^a_{yx}\left(y, K^a_{yx}\right) g^a_{ux}\left(u, K^a_{ux}\right) - B g^b_{xx}\left(x, K^b_{xx}\right) g^b_{yx}\left(y, K^b_{yx}\right) g^b_{ux}\left(u, K^b_{ux}\right)\\ \dot{y} &= C g^a_{xy}\left(x, K^a_{xy}\right) g^a_{yy}\left(y, K^a_{yy}\right) g^a_{uy}\left(u, K^a_{uy}\right) - D g^b_{xy}\left(x, K^b_{xy}\right) g^b_{yy}\left(y, K^b_{yy}\right) g^b_{uy}\left(u, K^b_{uy}\right)\end{aligned} \tag{1}$$

where A, B, C, D and K_{ij} (for $i, j \in \{u, x, y\}$) are positive constants, and the functions g^l_{ij} (for $i, j \in \{u, x, y\}$ and $l \in \{a, b\}$) are each either the inhibitory Michaelis-Menten function:

$$g^l_{ij}(z, K) = \frac{K}{z + K} \tag{2}$$

or the activating Michaelis-Menten function:

$$g^l_{ij}(z, K) = \frac{z}{z + K} \tag{3}$$

Under a certain regime of x, y, u relative to the model constants, Eq. (1) can be simplified and non-dimensionalized into the following form:

$$\begin{aligned}\dot{x} &= x^{\alpha_{xx}} y^{\alpha_{yx}} u^{\alpha_{ux}} - x^{\beta_{xx}} y^{\beta_{yx}} u^{\beta_{ux}}\\ \tau^{-1}\dot{y} &= x^{\alpha_{xy}} y^{\alpha_{yy}} u^{\alpha_{uy}} - x^{\beta_{xy}} y^{\beta_{yy}} u^{\beta_{uy}}\end{aligned} \tag{4}$$

where $\tau > 0$.

(a) Identify the parameter regimes in which Eq. (4) approximates Eq. (1) by replacing the question marks in the statements below with the correct signs (copy the statements to your answer with the correct sign ($\gg, \ll$), instead of ?): **For each $i, j \in \{u, x, y\}$:**

- **If g^a_{ij} is an inhibitory function and $i?K^a_{ij}$ then $\alpha_{ij} = -1$.**
- **If g^b_{ij} is an inhibitory function and $i?K^b_{ij}$ then $\beta_{ij} = -1$.**
- **If g^a_{ij} is an activating function and $i?K^a_{ij}$ then $\alpha_{ij} = 1$.**
- **If g^b_{ij} is an activating function and $i?K^b_{ij}$ then $\beta_{ij} = 1$.**
- **If g^a_{ij} is an inhibitory function and $i?K^a_{ij}$ then $\alpha_{ij} = 0$.**
- **If g^b_{ij} is an inhibitory function and $i?K^b_{ij}$ then $\beta_{ij} = 0$.**
- **If g^a_{ij} is an activating function and $i?K^a_{ij}$ then $\alpha_{ij} = 0$.**
- **If g^b_{ij} is an activating function and $i?K^b_{ij}$ then $\beta_{ij} = 0$.**

(4 marks)

(b) Identify examples of parameters of Eq. (4) where y is regulated by a:

- Coherent Feed-forward loop
- Incoherent Feed-forward loop
- Direct regulation by u with x not regulating y
- Negative feedback on y by x, where u does not directly regulate x but directly activates y.
- Positive feedback on y by x, where u activates x and inhibits y.

You need to find a single example for each case. For each parametrization, write-down the equations of the dynamics and draw an arrow scheme of the circuit. (5 marks)

(C) Consider the circuit where:

* $\alpha_{xx} = \alpha_{yx} = \alpha_{ux} = \alpha_{xy} = \alpha_{yy} = 0$
* $\alpha_{uy} = 1$
* $\beta_{ux} = \beta_{uy} = 0$
* $\beta_{xx} = 1, \beta_{yx} = -1$
* $\beta_{xy} = 1, \beta_{yy} = 1$

Write down the dynamics of the circuit, identify its fixed point(s) and analyze their stability. (6 marks)

(D) Fixing $\alpha_{uy} = \alpha_{xy} = \beta_{yy} = 1$ and $\alpha_{ux} = \beta_{ux} = \beta_{uy} = \alpha_{yy} = \alpha_{xx} = 0$, and assuming $\beta_{xy} \neq -1$, identify necessary and sufficient conditions on the other parameters for there to be exact adaptation of y to $y = 1$ with respect to changes in u (that is, enumerate all the circuits that provide this exact adaptation). (5 marks)

(Total: 20 marks)

2. Dense Associative Memories are dynamical systems that can encode for many stable fixed points. In our setting, there are K distinct patterns, $Z_i = (z_{i,1}, \dots, z_{i,N})$ for $i \in \{1, \dots, K\}$. Each pattern is of magnitude unity:

$$\|Z_i\| = \sqrt{\sum_{l=1}^{N} z_{i,l}^2} = 1$$

Let $\mathbf{x} = (x_1, \dots, x_N)$ denote the state of the dynamical system, and we also consider a weight vector on the patterns $\mathbf{w} = (w_1, \dots, w_K)$. The dynamics are given by:

$$\dot{x}_j = \sum_{i=1}^{K} z_{i,j} \frac{e^{w_i + \beta \sum_{l=1}^{N} z_{i,l} x_l}}{\sum_{k=1}^{K} e^{w_k + \beta \sum_{l=1}^{N} z_{k,l} x_l}} - x_j \tag{1}$$

where $\beta \geq 0$.

(a) Identify the fixed point(s) of the dynamics at $\beta = 0$ and analyze their stability.

(3 marks)

(b) Show that when $\beta \to \infty$, each pattern $(z_{i,1}, \dots, z_{i,N})$ is a fixed point of the dynamics. You do not need to test for stability. Hint: Recall that for two vectors $\mathbf{u}, \mathbf{v}$, we have that:

$$\sum_i u_i v_i = \|\mathbf{u}\| \, \|\mathbf{v}\| \cos \theta_{\mathbf{u},\mathbf{v}}$$

where $\theta_{\mathbf{u},\mathbf{v}}$ is the angle between $\mathbf{u},\mathbf{v}$. Also, use the fact that, when $\beta \to \infty$, and for any collection of distinct values $a_1, \dots, a_K$, the value of $\frac{e^{w_i + \beta a_i}}{\sum_{k=1}^{K} e^{w_k + \beta a_k}}$ is 1 if a_i is the maximal value in the collection, or 0 otherwise.

(5 marks)

(c) Consider the case where $\mathbf{x}$ is one dimensional ($\mathbf{x} = x$) and set $Z_1 = 1, Z_2 = -1$. Write down the dynamics and show that they are invariant to a transformation of $w_1 \to w_1 + \Delta, w_2 \to w_2 + \Delta$ for any constant Δ, and use this observation to reduce the number of parameters in the dynamics.

(2 marks)

(d) Show that in the dynamics derived in (c), when $w_1 = w_2$, the point $x = 0$ is always a fixed point, and identify the critical value of β where its stability properties change.

(5 marks)

(e) Use the fact that $\frac{e^{\beta x} - e^{-\beta x}}{e^{\beta x} + e^{-\beta x}}$ has its maximal slope at $x = 0$ to plot, schematically, the bifurcation diagram of the dynamics derived in (d), taking $w_1 = w_2$. Annotate the critical β and the fixed points at $\beta \to \infty$. Explain how you derived the bifurcation diagram, including using graphical arguments.

(5 marks)

(Total: 20 marks)

3. Here we will consider the following biological circuit, where u is an input, y is the output, and x is an internal variable:

$$\begin{aligned} \dot{y} &= a + f(u) - x - y \\ \dot{x} &= b(y - y_0) \end{aligned} \tag{1}$$

where f is a general differentiable function and a, b, y_0 are positive constants.

(a) For a fixed u, identify the fixed point of the dynamics. What type of feedback does x provide on y?

(5 marks)

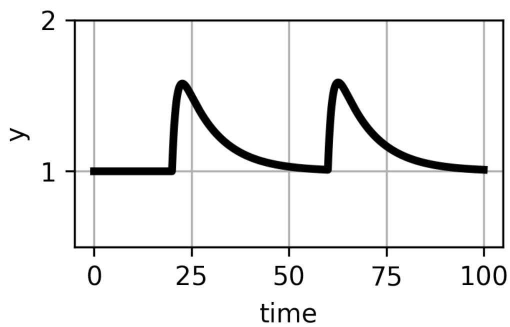
(b) Prove that if, for every u and every scalar λ, we have that $f(\lambda u) = f(\lambda) + f(u)$, then the system has fold-change detection of its output with respect to its input.

(6 marks)

(c) Prove that $f(\lambda u) = f(\lambda) + f(u)$ entails that $f(u) = k \log u$ with $k = f'(1)$.

(4 marks)

(d) Taking $f(u) = k \log u(t)$, with $k > 0$, consider the following dynamics of y:



Considering that $b \ll 1$, plot schematically the dynamics of (a) the input u and (b) the variable x. Annotate the plots including explaining the absolute/relative changes in the variables.

(5 marks).

(Total: 20 marks)

4. In this question we will study the evolution of two species whose abundance is given by a and b. The abundances of a, b change according the (per-individual) replication rate λ and the death rate μ. The death rate μ is a positive constant ($\mu > 0$) while the replication rate depends on a, b according to:

$$\lambda(a,b) = \mu + c[K^2 - (a+\delta b)^2]$$

Where c, K, δ are parameters such that $c > 0, K > 0, \delta > 1$. Note that at all time points $a \geq 0, b \geq 0$.

(a) Write a deterministic ODE system for the time evolution of the abundances of a and b.

(2 marks)

(b) Recall that the carrying capacity of a species is defined as its population size at steady-state, when it is in isolation. What are the carrying capacities of each of the two species? Which has the larger carrying capacity?

(3 marks)

(c) Consider the fraction of individuals of each species $f_a = \frac{a}{a+b}, f_b = \frac{b}{a+b}$. Prove that these fractions do not change with time.

(3 marks)

(d) From here onward, we will focus on a stochastic version of the system:

$$\begin{aligned} A &\xrightarrow{\mu} \varnothing \\ B &\xrightarrow{\mu} \varnothing \\ A &\xrightarrow{\lambda(a,b)} A+1 \\ B &\xrightarrow{\lambda(a,b)} B+1, \end{aligned} \tag{1}$$

where $\lambda(a, b)$ is the same as before. The above means that, at any given time, an individual of species A or B can die (with rate μ) or replicate (with rate $\lambda(a, b)$). Assume that events occur as a memoryless (Poisson) process.

Write down the stoichiometry matrix and and the corresponding array of rates for Eq. (1) as you would when preparing a stochastic system for simulation by the Gillespie algorithm.

(2 marks)

(e) Alice wrote down a simulation of Eq. (1) using the Gillespie algorithm. She used the parameter values $\mu = 0.07, c = 0.05$, $K = 800, \delta = 5$. Initial population sizes were $a_0 = 300, b_0 = 100$. She ran a very large number of simulations, each until she observed that the population consisted of either only a or only b. What was the relative frequency of each outcome?

(4 marks)

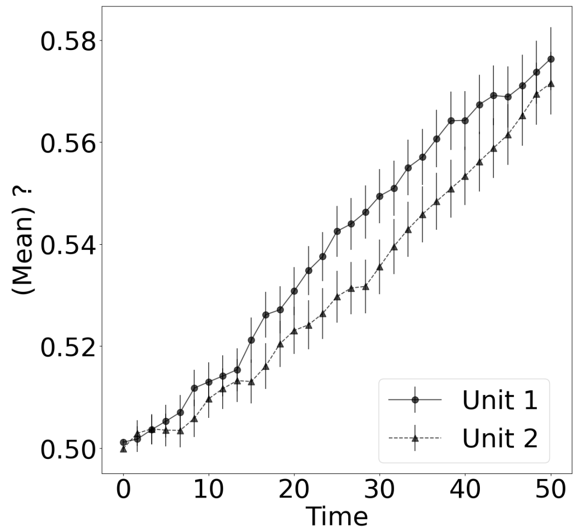
(f) Estimate (approximately) the values of the ensemble averages (averages across all simulations) $\langle a(t)\rangle, \langle b(t)\rangle, \langle f_a(t)\rangle, \langle f_b(t)\rangle$ that Alice observed at the end of her simulations.

(2 marks)

(g) Now consider a system made up of two units, both with an internal dynamics defined by Eq. (1) and with stochastic hopping of individuals between the two units, with constant hopping rate $\gamma > 0$. The replication rate λ has the same form in both units and same as above, which is

$$\lambda(a_i, b_i) = \mu + c[K^2 - (a_i + \delta_i b_i)^2],$$

with $i = 1, 2$ for each unit. The parameter values are $\mu = 0.07, c = 0.05, \gamma = 0.1$ (in units of time), $K = 600, \delta = 5$. The figure below represents the outcomes of a Gillespie simulation of this system; we report ensemble averages over 10^3 iterations, with error bars being standard error of the mean. Each curve corresponds to one of the two units.



What is plotted in the figure?

- a_1, a_2
- f_{a1}, f_{a2}
- f_{b1}, f_{b2}
- b_1, b_2

Motivate your answer.

(2 marks)

(h) What is the crucial parameter that determines which population is likely to take over in this composite system?

(2 marks)

(Total: 20 marks)

5. In this question, we will consider a population of cells which can divide or die. Each cell has a biological circuit, whose dynamics are captured by the deterministic normal form of the saddle-node bifurcation:

$$\dot{x} = x^2 + \mu \tag{1}$$

where, until stated otherwise, we assume that $\mu > 0$.

(a) Assuming that, at time $t = 0$, we have that $x \ll 0$, and define τ as the time elapsed until x changes sign from negative to positive. Prove that $\tau(\mu) = \frac{\pi}{2\sqrt{\mu}}$.

(4 marks)

(b) We will now assume that after division cells are initialized with $x = x_0 \ll 0$, and that a cell divides when its x changes sign from negative to positive. Denoting by n the number of cells in the population, n_0 the number of cells at $t = 0$, and fixing μ, write a continuous function $n(t)$ that captures the time evolution of n.

(4 marks)

We will now consider that each cell also has an internal variable, y, corresponding to a toxin, that resets upon cell division to a value drawn from some distribution with mean 0 and standard deviation $\sigma > 0$. It then accumulates at a constant rate:

$$\dot{y} = 1 \tag{2}$$

now if the y value of a cell is larger than y_{thresh} (where $y_{\text{thresh}} \gg 1$), the cell will be removed. We will also relax our assumption on μ to allow it to take any value, and we assume that $n_0 > 0$.

(c) Identify the critical value of μ in which, on average, removal and division are balanced. We denote this value as μ_c. Draw schematic plots of the dynamics of n for $\mu < \mu_c$,$\mu = \mu_c$, $\mu > \mu_c$.

(4 marks)

(d) We will now consider a circuit where $\mu = c - 1$ is set by a factor c that is consumed by the cellular population according to

$$\dot{c} = \gamma \left(1 - \frac{1}{K} nc\right) \tag{3}$$

Where $\gamma \gg 1$ and $K \gg 100$. Assuming that the population size remains nonzero, estimate the long-term value of n.

(4 marks)

(e) Finally, we consider a population of cells, each with a value of x initialized at $x = x_0 \ll 0$ which evolves according to Eq. (1), that are not dividing, but are rather removed from the population when their $x > 0$ (now there is no y). We will also assume that new cells arrive at a constant rate λ, and that now $\mu = n/K$. Estimate the long-term value of n in this setting.

(4 marks)

(Total: 20 marks)

Mathematical Biology 2 (Spring 2024): Exam Solutions

Omer Karin

Problem 1. The S-System dynamics:

$$\begin{aligned} \dot{x} &= x^{\alpha_{xx}} y^{\alpha_{yx}} u^{\alpha_{ux}} - x^{\beta_{xx}} y^{\beta_{yx}} u^{\beta_{ux}} \\ \tau^{-1}\dot{y} &= x^{\alpha_{xy}} y^{\alpha_{yy}} u^{\alpha_{uy}} - x^{\beta_{xy}} y^{\beta_{yy}} u^{\beta_{uy}} \end{aligned} \tag{1}$$

a) For each $i, j \in \{u, x, y\}$:

- If g^a_{ij} is an inhibitory function and $i \gg K^a_{ij}$ then $\alpha_{ij} = -1$.
- If g^b_{ij} is an inhibitory function and $i \gg K^b_{ij}$ then $\beta_{ij} = -1$.
- If g^a_{ij} is an activating function and $i \ll K^a_{ij}$ then $\alpha_{ij} = 1$.
- If g^b_{ij} is an activating function and $i \ll K^b_{ij}$ then $\beta_{ij} = 1$.
- If g^a_{ij} is an inhibitory function and $i \ll K^a_{ij}$ then $\alpha_{ij} = 0$.
- If g^b_{ij} is an inhibitory function and $i \ll K^b_{ij}$ then $\beta_{ij} = 0$.
- If g^a_{ij} is an activating function and $i \gg K^a_{ij}$ then $\alpha_{ij} = 0$.
- If g^b_{ij} is an activating function and $i \gg K^b_{ij}$ then $\beta_{ij} = 0$.

b) There are many possible examples for each circuit.

- Coherent Feed-forward loop:

$$\begin{aligned} \dot{x} &= u - x \\ \tau^{-1}\dot{y} &= ux - y \end{aligned}$$

- Incoherent Feed-forward loop

$$\begin{aligned} \dot{x} &= u - x \\ \tau^{-1}\dot{y} &= u/x - y \end{aligned}$$

- Direct regulation by u with x not regulating y

$$\begin{aligned} \dot{x} &= u - x \\ \tau^{-1}\dot{y} &= u - y \end{aligned}$$

- Negative feedback on y by x, where u does not directly regulate x but directly activates y.

$$\begin{aligned} \dot{x} &= y - x \\ \tau^{-1}\dot{y} &= u - x - y \end{aligned}$$

- Positive feedback on y by x, where u activates x and inhibits y.

$$\dot{x} = uy - x$$
$$\tau^{-1}\dot{y} = x/u - y$$

c) The circuit:

$$\dot{x} = 1 - x/y$$
$$\tau^{-1}\dot{y} = u - xy$$

This circuit has a fixed point at $x = y = \sqrt{u}$. Linearizing around the fixed point, we find the Jacobian:

$$J = \begin{pmatrix} -\frac{1}{\sqrt{u}} & \frac{1}{\sqrt{u}} \\ -\tau\sqrt{u} & -\tau\sqrt{u} \end{pmatrix}$$

which has the eigenvalues:

$$\lambda_{1,2} = \frac{-u\tau - 1 \pm \sqrt{\tau u(\tau u - 6) + 1}}{2\sqrt{u}}$$

which has a negative real part and is thus stable. The dynamics are monotonic when $\tau u(\tau u - 6) + 1 \geq 0$ and damped oscillatory otherwise. Denoting $z = \tau u$, we ask when: $z^2 - 6z + 1 = 0$. This occurs at $z = 3 \pm 2\sqrt{2}$. Thus, the dynamics are damped oscillatory when $3 - 2\sqrt{2} < z < 3 + 2\sqrt{2}$.

Omer: this question is similar to questions given in worksheet and coursework.

d) The dynamics are given by:

$$\begin{aligned} \dot{x} &= y^{\alpha_{yx}} - x^{\beta_{xx}} y^{\beta_{yx}} \\ \tau^{-1}\dot{y} &= u - yx^{\beta_{xy}} \end{aligned} \tag{2}$$

For exact adaptation we must have a steady-state for $y = 1$ for all u and therefore $\beta_{xy} = 1$ and, at s.s,

$$x = u^{1/\beta_{xy}} = u^{\beta_{xy}} = u \tag{3}$$

For $\dot{x} = 0$ at $y = 1$ we have that

$$1 - u^{\beta_{xx}} = 0 \tag{4}$$

and thus we must have $\beta_{xx} = 0$. Since we cannot have that $\dot{x} = 0$ for all y, we must have $\alpha_{yx} \neq \beta_{yx}$. The dynamics are therefore given by

$$\begin{aligned} \dot{x} &= y^{\alpha_{yx}} - y^{\beta_{yx}} \\ \tau^{-1}\dot{y} &= u - yx \end{aligned} \tag{5}$$

Linearizing around $x = u, y = 1$, we have the Jacobian

$$J = \begin{pmatrix} 0 & \alpha_{\mathsf{yx}} - \beta_{\mathsf{yx}} \\ -\tau & -\tau u \end{pmatrix} \tag{6}$$

which has negative trace, and its determinant, $\tau(\alpha_{\mathsf{yx}} - \beta_{\mathsf{yx}})$, is positive when either $\alpha_{yx} = 1$ and $\beta_{yx} < 1$, or $\alpha_{yx} = 0$ and $\beta_{yx} = -1$. The circuits are thus:

$$\begin{aligned} \dot{x} &= y - 1 \\ \tau^{-1}\dot{y} &= u - yx \end{aligned} \tag{7}$$

and

$$\begin{aligned} \dot{x} &= y - 1/y \\ \tau^{-1}\dot{y} &= u - yx \end{aligned} \tag{8}$$

and

$$\begin{aligned} \dot{x} &= 1 - 1/y \\ \tau^{-1}\dot{y} &= u - yx \end{aligned} \tag{9}$$

Omer: exact adaptation has been studied in the worksheets - this question requires more detailed analysis.

Problem 2. Solution:

a) At $\beta = 0$ the dynamics are:

$$\dot{x}_j = \sum_i z_{i,j} \frac{e^{w_i}}{\sum_k e^{w_k}} - x_j \tag{1}$$

which are N decoupled equations whose fixed point is given by:

$$x_j = \sum_i z_{i,j} \frac{e^{w_i}}{\sum_k e^{w_k}} \tag{2}$$

For all j, since the dynamics are decoupled these are effectively N one-dimensional dynamical systems and thus the stability is straightforward since the diagonal of the Jacobian is negative.

Omer: this question is unseen but only requires basic understanding of dynamical systems.

b) This question is unseen and more difficult than other ones. We have that:

$$\begin{aligned}
\dot{x}_j &= \sum_i z_{i,j} \frac{e^{w_i + \beta \sum_l z_{i,l} x_l}}{\sum_k e^{w_k + \beta \sum_l z_{k,l} x_l}} - x_j \\
&= \sum_i z_{i,j} \frac{e^{w_i + \beta \|Z_i\| \|\mathbf{x}\| \cos \theta_{Z_i, \mathbf{x}}}}{\sum_k e^{w_k + \beta \|Z_k\| \|\mathbf{x}\| \cos \theta_{Z_k, \mathbf{x}}}} - x_j \\
&= \sum_i z_{i,j} \frac{e^{w_i + \beta \|\mathbf{x}\| \cos \theta_{Z_i, \mathbf{x}}}}{\sum_k e^{w_k + \beta \|\mathbf{x}\| \cos \theta_{Z_k, \mathbf{x}}}} - x_j
\end{aligned} \tag{3}$$

where the last equality is due the patterns being of unity magnitude. Evaluating the dynamics at a given pattern $\mathbf{x} = Z_m$, (which is also of magnitude unity), we have that:

$$\dot{x}_j = \sum_i z_{i,j} \frac{e^{w_i + \beta \cos \theta_{Z_i, Z_m}}}{\sum_k e^{w_k + \beta \cos \theta_{Z_k, Z_m}}} - z_{m,j} \tag{4}$$

The maximal angle between any two patterns will be $\cos \theta_{Z_m, Z_m} = 1$. Since all patterns are distinct and of magnitude unity, for all $k \neq m$ we have $\cos \theta_{Z_m, Z_k} < 1$. At $\beta \to \infty$ the contribution of the weights $\mathbf{w}$ is negligible, and, thus, as $\beta \to \infty$,

$$z_{i,j} \frac{e^{w_i + \beta \cos \theta_{Z_i, Z_m}}}{\sum_k e^{w_k + \beta \cos \theta_{Z_k, Z_m}}} = \begin{cases} z_{i,j}, & i = m \\ 0, & \text{otherwise} \end{cases} \tag{5}$$

and thus, at $\beta \to \infty$,

$$\begin{aligned}
\dot{x}_j &= \sum_i z_{i,j} \frac{e^{w_i + \beta \cos \theta_{Z_i, Z_m}}}{\sum_k e^{w_k + \beta \cos \theta_{Z_k, Z_m}}} - z_{m,j} \\
&= z_{m,j} - z_{m,j} = 0
\end{aligned} \tag{6}$$

and thus Z_m is a fixed point (for all m).

Omer: this question is unseen, and, while the calculation is slightly elaborate, only requires basic understanding of what is a fixed point.

c) The dynamics are now given by:

$$\dot{x} = \frac{e^{w_1+\beta x} - e^{w_2-\beta x}}{e^{w_1+\beta x} + e^{w_2-\beta x}} - x \tag{7}$$

where the transformation $w_1 \to w_1 + \Delta, w_2 \to w_2 + \Delta$ is equivalent to multiplying the numerator and denominator of the first term by a constant and thus does not change the dynamics. We can therefore take $\Delta = -w_1$, denote $w = w_2 - w_1$, rewrite:

$$\dot{x} = \frac{e^{\beta x} - e^{w-\beta x}}{e^{\beta x} + e^{w-\beta x}} - x \tag{8}$$

d) when $w_1 = w_2$, the dynamics are:

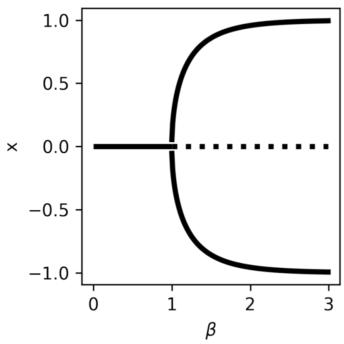
$$\dot{x} = \frac{e^{\beta x} - e^{-\beta x}}{e^{\beta x} + e^{-\beta x}} - x = \tanh \beta x - x \tag{9}$$

where $x = 0$ provides a fixed point solution for the dynamics. For $x = 0$ to be a stable fixed point, we need $\frac{d\dot{x}}{dx} = 0$ at $x = 0$:

$$\frac{d\dot{x}}{dx} = -\frac{\left(e^{\beta x} - e^{-\beta x}\right)\left(\beta e^{\beta x} - \beta e^{-\beta x}\right)}{\left(e^{-\beta x} + e^{\beta x}\right)^2} + \frac{\beta e^{-\beta x} + \beta e^{\beta x}}{e^{-\beta x} + e^{\beta x}} - 1 \tag{10}$$

which, evaluated at $x = 0$, is equal to $-1 + \beta$. Thus $x = 0$ is stable for $\beta < 1$.

e) The function $\tanh \beta x$ is a symmetric sigmoid with slope β around $x = 0$. As this is the maximal slope, for $\beta < 1$ there are no more fixed points, while, for $\beta > 1$, there are two more intersections corresponding to stable fixed points (this is straightforward to show with graphical arguments), which asymptote towards $x \pm 1$. The bifurcation diagram is then:



Omer: this question is 'seen' in the sense that the main difficulty, which is understanding bifurcations for a sigmoid, has been studied in class and in the worksheets.

Problem 3. Solution:

a) The dynamics:

$$\begin{aligned} \dot{y} &= a + f(u) - x - y \\ \dot{x} &= b(y - y_0) \end{aligned} \tag{1}$$

have a fixed point at $y = y_0$ and $x = a + f(u) - y_0$. x provides integral feedback on y.

b) To prove fold-change detection, we consider an input λu:

$$\begin{aligned} \dot{y} &= a + f(\lambda u) - x - y = a + f(u) + f(\lambda) - x - y \\ \dot{x} &= b(y - y_0) \end{aligned} \tag{2}$$

setting $\hat{y} = y, \hat{x} = x - f(\lambda)$, we have that:

$$\begin{aligned} \dot{\hat{y}} &= \dot{y} = a + f(u) + f(\lambda) - x - y = a + f(u) - \hat{x} - y \\ \dot{\hat{x}} &= \dot{x} = b(\hat{y} - y_0) \end{aligned} \tag{3}$$

and thus the dynamics, and their fixed point, are independent of λ, proving fold-change detection.

Omer: while the form is different, similar FCD analysis has been conducted in class and in the worksheets.

c) Taking $f(\lambda u) = f(\lambda) + f(u)$, we have:

$$\frac{df(\lambda u)}{d\lambda} = uf'(\lambda u) \tag{4}$$

and

$$\frac{d}{d\lambda}\left(f(u) + f(\lambda)\right) = f'(\lambda) \tag{5}$$

and thus $uf'(\lambda u) = f'(\lambda)$. In particular, for $\lambda = 1$, we have that $uf'(u) = f'(1)$, i.e.,

$$f'(u) = \frac{f'(1)}{u} \tag{6}$$

and thus,

$$f(u) = f'(1)\log u + C \tag{7}$$

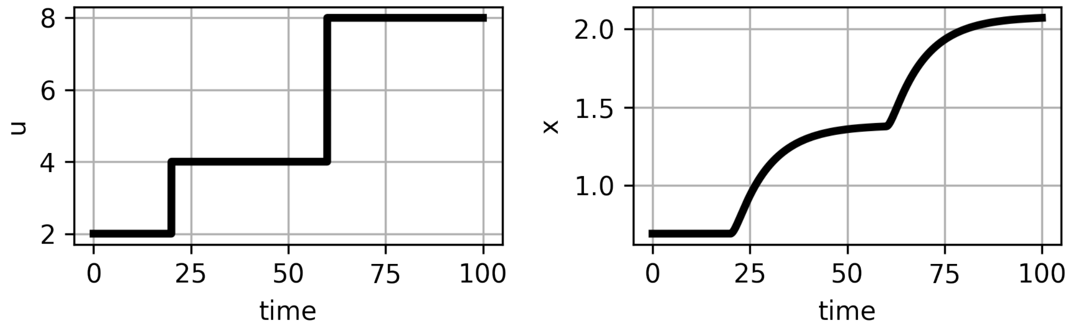
Noting that also for $\lambda = 1$ we have that $f(u) = f(1) + f(u)$ we have that $f(1) = 0$, and therefore,

$$0 = f(1) = f'(1)\log 1 + C = C \tag{8}$$

and thus $C = 0$. We thus have that $f(u) = f'(1)\log u$.

Omer: unseen.

d) The dynamics of the input u corresponds to increases in constant folds (e.g. 2 fold), while x tracks the logarithm of the input, since at steady-state $x = a + f(u) - y_0$:



Omer: here the students should reason that, from knowledge of the FCD property, the input should increase by identical fold changes to produce identical output pulses, and they can estimate x. Similar analysis has been conducted in class.

Problem 4. a) The time derivative is given by the difference between replication and death rate, multiplied by population size. The difference is:

$$\lambda(a, b) - \mu = c[K^2 - (a + \delta b)^2].$$

So the system of ODE is:

$$\begin{aligned} \dot{a} &= ca[K^2 - (a + \delta b)^2] \\ \dot{b} &= cb[K^2 - (a + \delta b)^2]. \end{aligned} \tag{9}$$

b) To find the carrying capacity of a species, let us consider it in isolation and ask when $\lambda(a, b) = \mu$ For the carrying capacity of a, we set $b = 0$ and $\lambda(a, b) = \mu$, which yields the carrying capacity $a = K$. Similarly, the carrying capacity of b is K/δ. As $\delta > 1$ for our purposes, b has a lower carrying capacity.

c) To prove that the quantities are constant, we calculate the time derivative of

$$\frac{a(t)}{a(t) + b(t)},$$

Thus,

$$\begin{aligned} \dot{f}_a &= \frac{b\dot{a} - a\dot{b}}{(a + b)^2} \\ &= \frac{ab[K^2 - (a + \delta b)^2] - ab[K^2 - (a + \delta b)^2]}{(a + b)^2} \\ &= 0 \end{aligned} \tag{10}$$

with an equivalent derivation for f_b. *Note*: Discussed in lectures and the same exercise given in worksheet, for linear λ.

d) With the notation explained in the lectures and lecture notes, the stoichiometry matrix is given by:

$$\begin{bmatrix} -1 & 0 & 1 & 0 \\ 0 & -1 & 0 & 1 \end{bmatrix}. \tag{11}$$

The columns correspond to event types - death of a, death of b, birth of a, birth of b. The rates of array, with same ordering of possible reactions/events is:

$$(\mu a, \mu b, \lambda(a, b)a, \lambda(a, b)b).$$

e) The fixation probability of each species is given by their initial proportion, so a fixes with probability $\frac{3}{4}$ and b with probability $\frac{1}{4}$. The outcomes that Alice will observe will be fluctuations around $K = 800$ when a fixes (with prob. $3/4$) and fluctuations around $K/\lambda = 160$ with when b fixes (with prob. $1/4$). *Note*: More advanced, but a similar question was in worksheet. In that case, it was a linear λ, but they should be able to infer that here the fixation probabilities work the same way, as the two species have still same death and replication rates μ, λ, and the notes and lectures make it explicit. So, more advanced question but still easy to answer if they followed the material.

f) Answer:

$$\begin{aligned}\langle a(t)\rangle &\approx \frac{3}{4}\cdot 800 = 600\\ \langle b(t)\rangle &\approx \frac{1}{4}\cdot 160 = 40\end{aligned} \tag{12}$$

For the fractions, they can reason that they do not change, on average, as the two species have same rates. Or, by direct calculation based on fixation probability, they can prove that the "final" ($t \to \infty$) fractions are, on average, equal to the initial ones.

Note: More advanced and detailed understanding, but a similar question was in worksheet. So still easy if they understood the worksheets.

g) The answer is f_{a1}, f_{a2}.

The curves cannot represent a or b, as the y axis ranges from 0.50 to 0.58, so the answer can only be f_{a1}, f_{a2} or f_{b1}, f_{b2}. In this system, the species a has higher carrying capacity, because $\delta = 5$ and the same argument as for part b) of the question holds. In a stochastic system with hopping between two units, the species with the larger carrying capacity has a higher fixation rate, its fraction increases. Therefore the proportion of species a increases.

Note: Based on lecture notes.

h) The crucial parameter is δ, as the difference in carrying capacities of the two species is modulated by it. In a setting where $0 < \delta < 1$, the answer to the previous question would be f_{b1}, f_{b2}, as in that case the species b would have the higher carrying capacity.

Note: Based on lecture notes.

Problem 5. Solution:

a) As in the lecture notes, we can solve this by simple integration,

$$\tau = \int_0^\tau dt = \int_{-\infty}^0 \frac{dx}{x^2+\mu} = \mu^{-1/2} \tan^{-1} \frac{x}{\sqrt{\mu}}\bigg|_{x=-\infty}^0 = \frac{\pi}{2\sqrt{\mu}} \tag{1}$$

b) Cellular growth will be of the form $n(t) = n_0 e^{\nu t}$. The doubling time is given by $\frac{\pi}{2\sqrt{\mu}}$, that is, $e^{\nu \frac{\pi}{2\sqrt{\mu}}} = 2$, and therefore $\nu = \frac{2\log 2}{\pi}\sqrt{\mu}$. Taken together, we have that:

$$n(t) = n_0 e^{\frac{2\log 2}{\pi}\sqrt{\mu} t} \tag{2}$$

c) The critical value of μ is that in which cell division and cell removal are balanced. That is, every birth of a cell is equally likely to conclude in either a division (producing 2 cells) or removal (producing 0 cells). Since cells are born with an average value of $y = 0$, The time τ in which this would occur is $\tau = y_{\text{thresh}}$, corresponding to

$$\mu_c = \frac{\pi^2}{4y_{\text{thresh}}^2} \tag{3}$$

d) At s.s. we have $c = K/n$ and thus the control parameter is given by $\mu = K/n - 1$. When n is very small compared with K, the control parameter will be large and the population is rapidly dividing. When $n = K$ there is no progression beyond $x = 0$ and cells die. The dynamics are balanced occurs when $K/n - 1 = \mu_c = \frac{\pi^2}{4y_{\text{thresh}}^2}$, that is, when

$$n = \frac{K}{1+\mu_c} \tag{4}$$

e) In this case, from Little's law, we have that:

$$n = \lambda\tau \tag{5}$$

since now

$$\tau = \frac{\pi}{2\sqrt{\mu}} = \frac{\pi}{2\sqrt{n/K}} \tag{6}$$

we have the equation:

$$n\sqrt{n} = \frac{\pi\lambda\sqrt{K}}{2} \tag{7}$$

and thus

$$n = \left(\frac{\pi\lambda\sqrt{K}}{2}\right)^{2/3} \tag{8}$$

MATH70137 Mathematical Biology 2: Systems Biology Markers Comments

Question 1	a. Most students did reasonably well. The question merely required considering how the activating / inhibiting functions behave far away from the half-way activation/inhibition point. b. Most students did well but some were confused with regarding to the meaning of "negative feedback" and merely placed inhibiting arrows, without any feedback. c. Most students identified the fixed point and knew how to correctly perform stability analysis. d. Most students, while generally understanding the meaning of exact adaptation, did not perform the full analysis correctly.
Question 2	a. This was straightforward and most students did this correctly. b. Following the hint, this question required the students to realize that the inner product is maximal when the vectors are aligned (and, in this case, identical). This turned out to be challenging, with most students 'getting' the right direction but not fully proving the question. c. This was straightforward for most students. d. The first part was straightforward. The second part (critical beta) was more challenging as it required a more elaborate calculation. e. This was the most challenging part, as it required the students to draw a bifurcation diagram building on (a-d). The bifurcation diagram was different from the saddle node bifurcation diagram shown in class and required the use of graphical reasoning. Most students did not complete it correctly.
Question 3	a. Straightforward analysis and answered correctly by the majority of students. b. This was more challenging but most students were familiar with the proof approach and answered (broadly) correctly, although some had a mistake in the transformation. c. This was very challenging and most students tried to prove the converse. d. This question tests understanding of the concepts of exact adaptation and fold-change detection. Almost no students identified the correct answer - a step-like input that results in adaptation.

Question 4

a. Most students got this correctly, with some forgetting to scale by population size.
b. Most students got this correctly.
c. Most students got this correctly, with some making mistakes during the technical calculation.
d. Many students did not answer this correctly as they did not remember what the stoichiometry matrix was.
e+f. Students generally succeeded here, although there was some confusion with respect to the carrying capacity.
g. Most students succeeded here.
h. Most students succeeded here.

Question 5

a. Similar to lecture notes and most students completed it correctly.
b. Many students failed to notice that growth should be exponential, rather than linear.
c. This question requires identifying the point in which differentiation and self-renewal are balanced. While conceptually more advanced, those who identified the right approach performed the calculation generally well.
d. Almost no student attempted or succeeded this question.
e. Those that attempted this question identified that Little's law should be used.