Computational Systems Biology (BT5240)

Assignment 4

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Problem 1

Sub-Problem (a)

Let A, B, C denote the biomass of species A, B, C in grams. Let X denote the concentration of the metabolite X in millimoles. The differential equations that describe the population dynamics of this system are:

$$\frac{dA}{dt} = g_A A - d_A A + \delta AB - \epsilon AC$$

$$\frac{dB}{dt} = g_B B - d_B B + \beta \eta XB$$

$$\frac{dC}{dt} = g_C C - d_C C + \epsilon AC$$

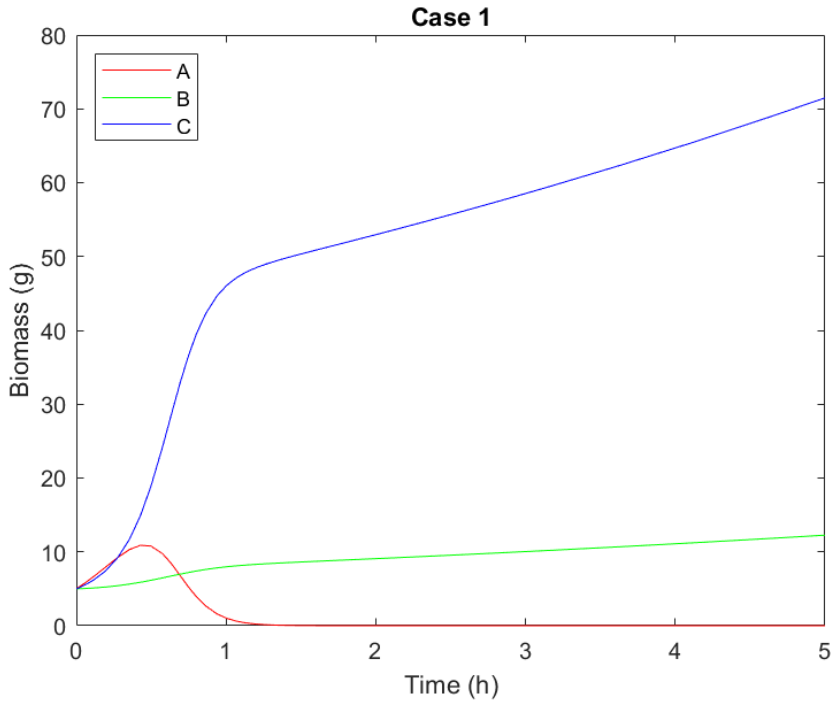
$$\frac{dX}{dt} = \alpha A - \beta XB$$

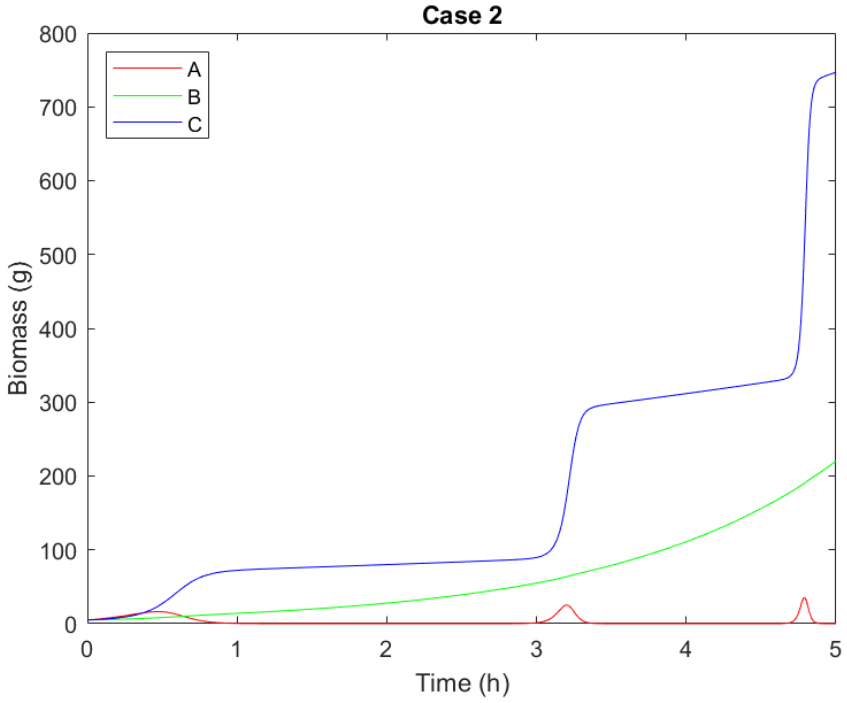
Here,

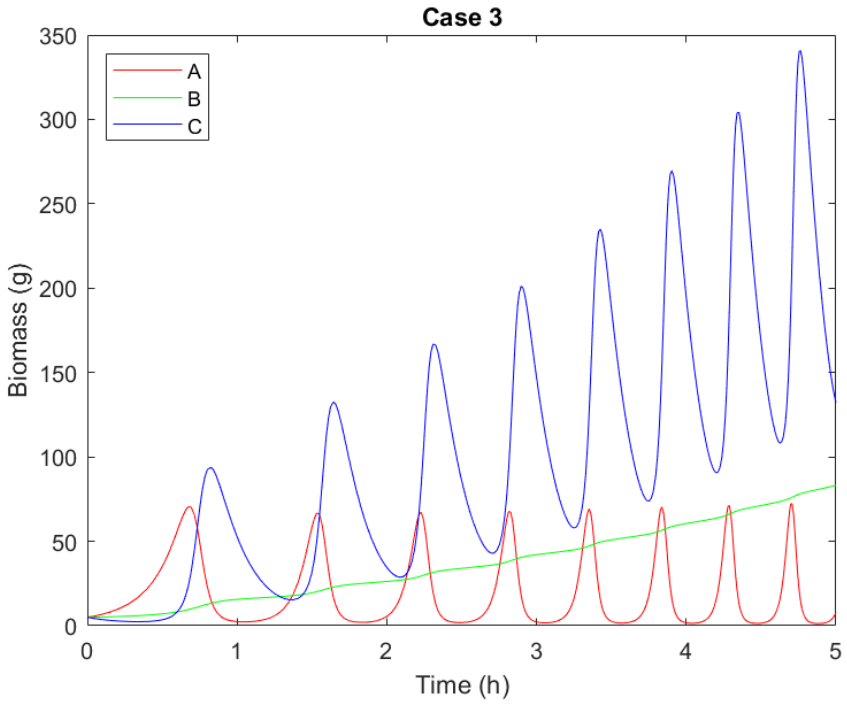
- g_i and d_i denote the growth rate and death rate of species i in h^{-1}.
- α is the rate constant of production of metabolite X by species A, in mmol g_biomass^{-1} h^{-1}.
- β is the rate constant of uptake of metabolite X by species B, in g_biomass^{-1} h^{-1}.
- δ is the rate constant that governs species B's positive influence on the growth of species A, in g_biomass^{-1} h^{-1}.
- ϵ is the rate constant that governs species C's negative influence on the growth of species A, in g_biomass^{-1} h^{-1}.
- η is the rate constant of conversion of metabolite X to biomass by species B, in g_biomass mmol^{-1}.

Sub-Problem (b)

The system was simulated in MATLAB using the formulated ODEs for $t = 5$ hours and the three given parameter sets with initial biomass of 5 grams for each species.







- In Case 1, the system does not reach a steady state in 5 hours. Species A faces extinction.
- In Case 2, the system does not reach a steady state in 5 hours. Species A does not face complete extinction but has short pulses of growth.
- In Case 3, the system shows oscillations in the growth of species A and C. No species face extinction.

In all three cases, species C shows the highest growth while species A shows the least. The growth of species B is monotonically increasing in all cases. Since C is a parasite on A, its growth is tightly coupled to that of A. Since B only relies on a metabolite produced by A, the growth coupling is weaker. The intrinsic growth rates and death rates of the three species greatly affects the dynamics of the system.

Sub-Problem (c)

When species D is introduced into the system, the differential equations are modified to

$$\frac{dA}{dt} = g_A A - d_A A + \delta AB - \epsilon AC$$

$$\frac{dB}{dt} = g_B B - d_B B + \beta \eta XB$$

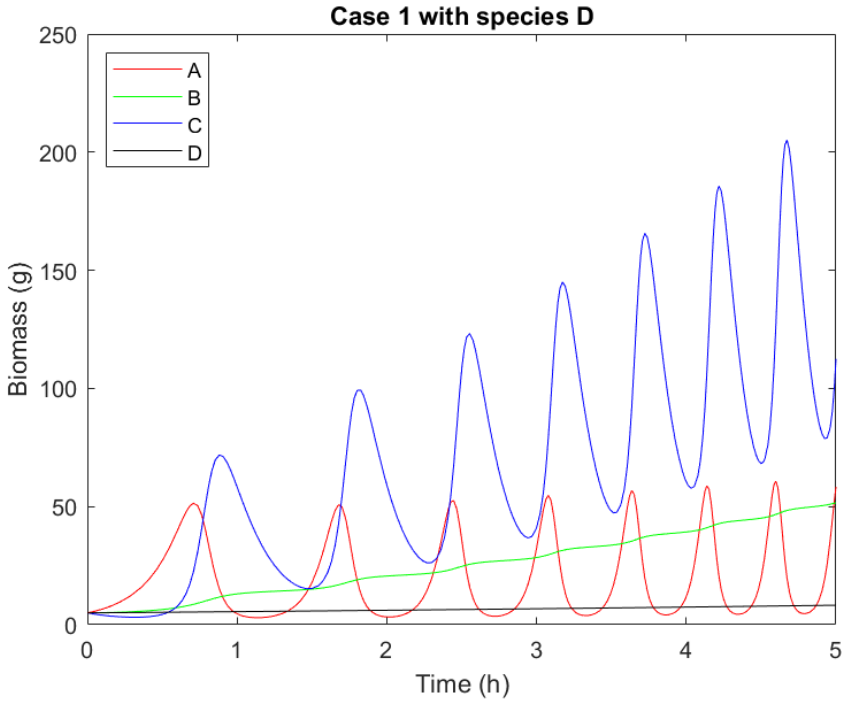
$$\frac{dC}{dt} = g_C C - d_C C + \epsilon AC - \gamma CD$$

$$\frac{dX}{dt} = \alpha A - \beta X B$$

$$\frac{dD}{dt} = g_D D - d_D D$$

Here, three new parameters are introduced - g_D, d_D, and γ. They denote the growth rate constant of species D in h^{-1}, death rate constant of species D in h^{-1}, and the rate constant that governs species D's negative influence on the growth of species C in $g\_biomass^{-1}$ h^{-1} respectively.

When this is simulated for 5 hours using the growth rates and death rates in Case 1 of the previous problem, the system shows a combination of oscillatory, monotonic increase, and steady state behaviour. Species A and C show oscillations. Species B increases monotonically in terms of biomass. Species D stays constant throughout.



Problem 2

Sub-Problem (a)

The Boolean update rules governing the interactions in the tumour regulatory network are:

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P53(t) = MYC(t-1) and not MDM2(t-1)
MYC(t) = not RB(t-1)
MDM2(t) = MDM2(t-1)
RB(t) = not MYC(t-1)
Apoptosis(t) = P53(t) and not MDM2(t)
Proliferation(t) = MYC(t) and not RB(t)
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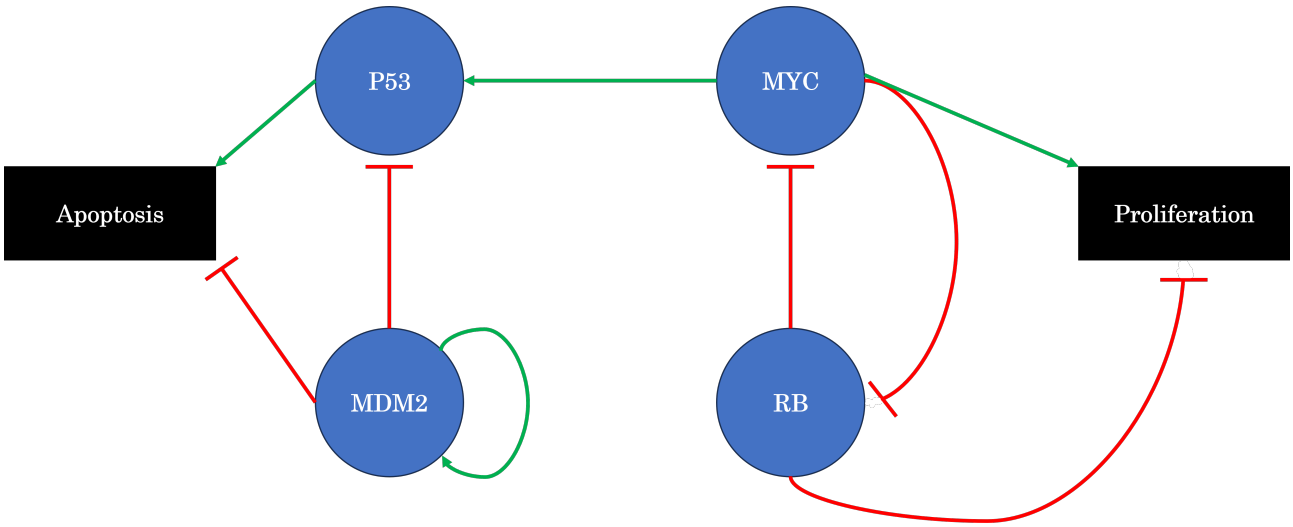

Sub-Problem (b)

For a given state to be feasible, the cell fate must be biologically plausible. Thus, states that give rise to both apoptosis and proliferation are considered infeasible. As MDM2 is not regulated by the other proteins, its presence guarantees that P53 is inactivated. Hence, any states where both P53 and MDM2 are present must be biologically infeasible.

The truth table for the system is shown below:

State	P53	MYC	MDM2	RB	Fate	Feasibility
1	0	0	0	0		Feasible
2	0	0	0	1		Feasible
3	0	0	1	0		Feasible
4	0	0	1	1		Feasible
5	0	1	0	0	P	Feasible
6	0	1	0	1		Feasible
7	0	1	1	0	P	Feasible
8	0	1	1	1		Feasible
9	1	0	0	0	A	Feasible
10	1	0	0	1	A	Feasible
11	1	0	1	0		Infeasible
12	1	0	1	1		Infeasible
13	1	1	0	0	A/P	Infeasible
14	1	1	0	1	A	Feasible
15	1	1	1	0	P	Infeasible
16	1	1	1	1		Infeasible

Sub-Problem (c)

The system was simulated for three different initial conditions.

Condition 1: All proteins absent initially

Time	P53	MYC	MDM2	RB	Apoptosis	Proliferation
1	0	0	0	0	0	0
2	0	1	0	1	0	0
3	1	0	0	0	1	0

In this case, the cell undergoes apoptosis and the simulation ends. This means that this initial condition leads to cell death and prevents the growth of the tumour.

Condition 2: All proteins present initially

Time	P53	MYC	MDM2	RB	Apoptosis	Proliferation
1	1	1	1	1	0	0
2	0	0	1	0	0	0
3	0	1	1	1	0	0
4	0	0	1	0	0	0

In this case, the cell state oscillates between two states. This means that the cell does not actively proliferate or undergo apoptosis but simply maintains its metabolism for survival. This could imply that the cell is healthy or the tumour cell is not metastasizing.

Condition 3: Only RB present initially

Time	P53	MYC	MDM2	RB	Apoptosis	Proliferation
1	0	0	0	1	0	0
2	0	0	0	1	0	0

In this case, the cell reaches a steady state. This also means that the cell does not actively proliferate or undergo apoptosis but simply maintains its metabolism for survival.

Sub-Problem (d)

The system was then simulated in the presence of three different drugs that affected different proteins. The initial condition was set such that the cell fate is proliferation, allowing the tumour to be actively growing when the drug is introduced.

Drug A: Inhibits MDM2

Time	P53	MYC	MDM2	RB	Apoptosis	Proliferation
1	0	1	0	0	0	1
2	1	1	0	0	1	1
3	1	1	0	0	1	1

In this case, the cell reaches a steady state. This means that the drug does not allow the cell to proliferate but does not kill it either.

Drug B: Inhibits MYC

Time	P53	MYC	MDM2	RB	Apoptosis	Proliferation
1	0	1	0	0	0	1
2	1	0	0	0	1	0

In this case, the cell undergoes apoptosis. Thus, the drug is effective in killing the tumour.

Drug C: Activates RB

Time	P53	MYC	MDM2	RB	Apoptosis	Proliferation
1	0	1	0	0	0	1
2	1	1	0	1	1	0

In this case, the cell undergoes apoptosis. Thus, the drug is effective in killing the tumour.