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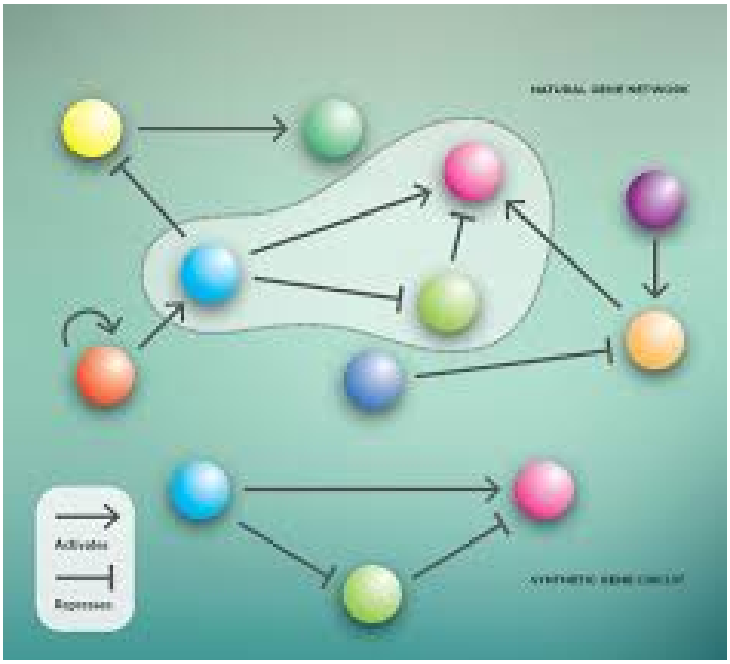
ODE Solving and Gene Networks

Assignment 4



PS1: Dynamic Modelling

Code Overview & Methodology

The code implements a modified Lotka-Volterra framework with metabolite-mediated interactions, organised into:

- Main script: Parameter initialisation, ODE solving (ode15s), and visualisation.
- ODE functions: Modular implementation of species interactions.

Key Assumptions:

- Well-mixed system (no spatial gradients)
- Constant interaction parameters (no adaptation)
- Metabolite X as a sole growth-limiting factor for B
- Immediate metabolite utilisation (no diffusion delays)

System Equations and Biological Significance

$$\frac{dA}{dt} = \underbrace{g_A A}_{\text{Growth}} - \underbrace{d_A A}_{\text{Death}} + \underbrace{\delta AB}_{\text{Mutualism}} - \underbrace{\epsilon AC}_{\text{Parasitism}}$$

$$\frac{dB}{dt} = g_B B - d_B B + \underbrace{\eta\beta BX}_{\text{Cross-feeding}}$$

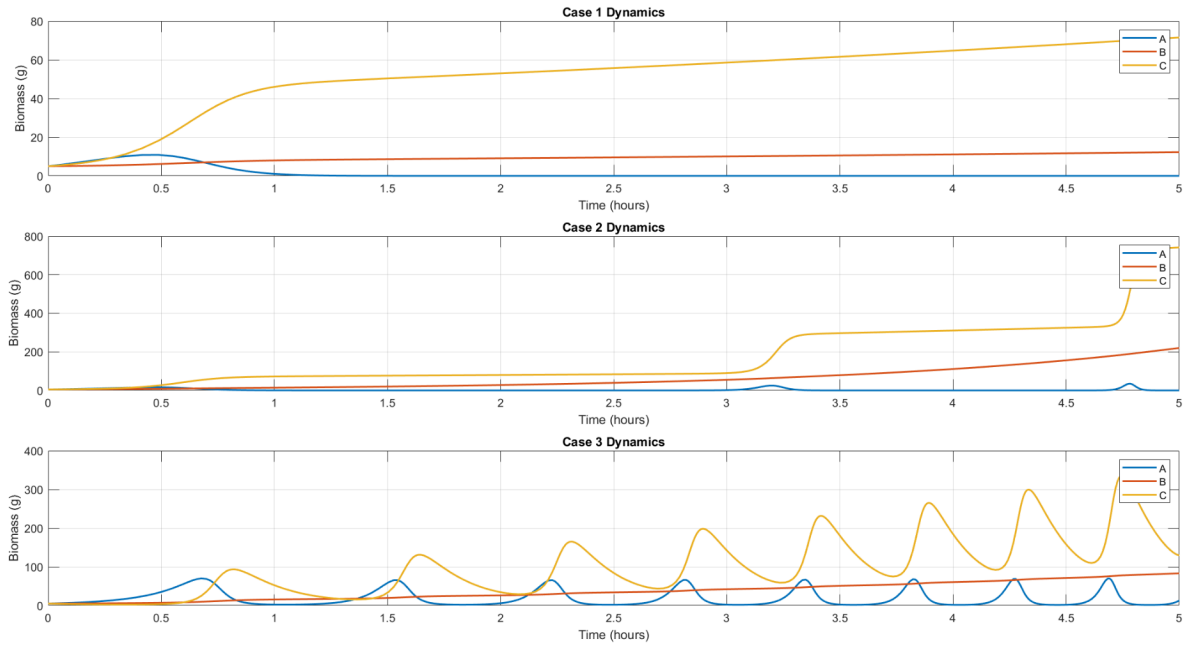
$$\frac{dC}{dt} = g_C C - d_C C + \epsilon AC$$

$$\frac{dX}{dt} = \underbrace{\alpha A}_{\text{Production}} - \beta BX$$

Parameters:

- α (0.6): A's metabolite production
- β (0.85): B's metabolite utilization
- δ (0.8): A-B mutualism strength
- ε (0.3): C's parasitic efficiency
- η (0.6): Metabolic efficiency

Comparison Behaviour for Different Initial Conditions



Case 1 (Mild coexistence → A dies out, C dominates):

- Balanced growth & death for all three (g≈dg\approx dg≈d), so none blows up purely by itself.
- Mutualism (δAB) gives A and B a little boost, and cross-feeding via XXX lets B grow steadily.

- Parasitism (εAC) steadily siphons A into C.

Result:

- A peaks early (around 0.5 h) but is driven extinct by C's parasitism.
- B grows roughly linearly (driven by its net growth plus a gently rising XXX).
- C enjoys both its modest net growth and the parasitic harvest of A → smooth rise to dominance.

Case 2 (Latent blooms):

- High net growth of A and B so that they would explode unchecked, but at first, C is minor.
- C has a small intrinsic net, so it drifts upward slowly until it can "feed" on occasional bumps in A.
- Once A has grown enough, the εAC term suddenly injects large biomass into C, producing the two big step-like "blooms" you see around 3 h and again near five h.
- A itself barely rises above zero except at those exact times, because each time it tries to grow, it immediately fuels a C bloom that knocks it back down.
- B continues its steady climb (powered by cross-feeding via XXX), largely unaffected by the on–off parasitism.

Case 3: Predator-prey oscillations

- C now has zero intrinsic growth (gC=0g_C=0gC=0) and very high death (dC=5d_C=5dC=5), so without parasitism it would vanish instantly.

- The parasitic term gives C a short-lived pulse every time A builds up (through its modest net growth and mutualism with B).
- But C's enormous death rate then quickly drives it back to (near) zero.
- That on-off coupling turns A–C into a classic predator-prey oscillator:
    - A spikes, → C surges, → A is cut back, → C dies, → A regrows, etc.
- Meanwhile, B again rises almost monotonically since cross-feeding has a gentler, one-way effect.

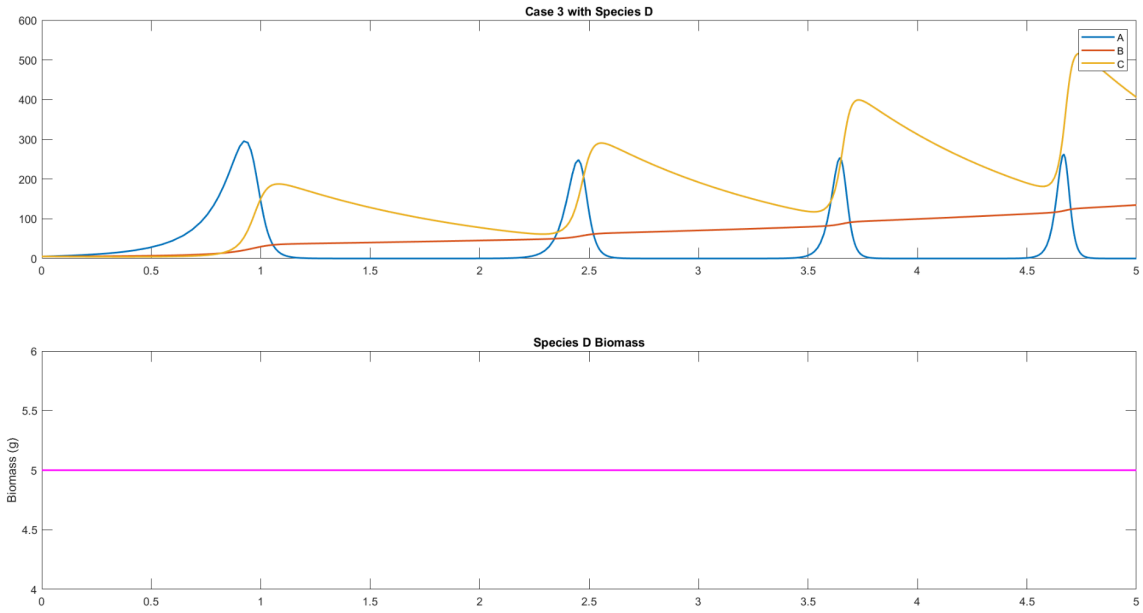
In Summary

Case 1 is a stable coexistence scenario in which C's parasitism eventually drives A extinct but allows C itself to flourish.

Case 2 shows threshold-driven blooms, where C accumulates slowly until a mutualism–parasitism feedback kicks in, giving C discrete jumps (and suppressing A).

Case 3 is a proper oscillatory regime, essentially a predator–prey cycle between A (the "prey") and C (the "predator"), with B growing steadily throughout all cases.

Species D Impact



Introducing D (80% C inhibition):

- By multiplying the change in C's concentration by 0.2, D slashes C's intrinsic net growth (and parasitic boost) by 80 %. Thus, C can no longer race up as quickly once A is available.
- Due to C's weakened parasitic effect, A can keep growing longer before the next crash. That gives A a massive pulse (~4× larger first spike), which means C still eventually spikes (via εAC), but from a much larger A pool.
- The weakened "predator" (C) takes longer to bring prey (A) down and then takes longer yet to recover itself, so each cycle stretches out by about 25 %.
- Every time A surges higher, it pumps out more X (via αA), which fuels B's cross-feeding term. Hence, B ends up ~65 % higher at five h.

PS2: Boolean Modelling

Method Summary and Key Assumptions

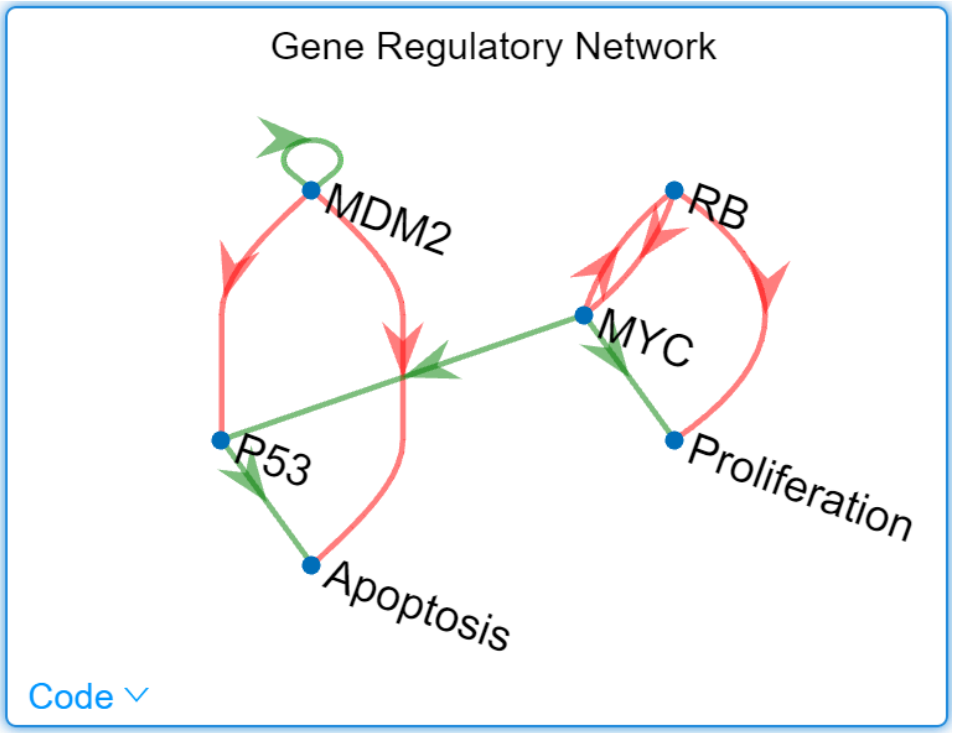
Core Methodology

- Binary States: Genes/proteins exist in either active (1) or inactive (0) states
- Synchronous Updates: All nodes update simultaneously per time step
- Biological Constraints:
    - Mutual inhibition between MYC/RB creates a toggle switch behaviour
    - P53 activation requires MYC presence and MDM2 absence

Implementation Structure

Component	Purpose	File
boolean_update	State transition logic	boolean_update.m
plot_regulatory_diagram	Network visualisation	plot_regulatory...m
Truth Table Analysis	Feasible state identification	main_script.mlx
Attractor Detection	Stability/oscillation analysis	main_script.mlx

Network Diagram



Boolean Update Rule

P53	`new_P53 = MYC ∧ ¬MDM2`	Activated by MYC, inhibited by MDM2
MDM2	`new_MDM2 = MDM2`	Self Activation
MYC	`new_MYC = ¬RB`	Inhibited by the RB protein
RB	`new_RB = ¬MYC`	Inhibited by MYC oncoprotein

Cell Fate Determination

apoptosis = P53 && ~MDM2; % A: P53 active without MDM2 inhibition

proliferation = MYC && ~RB; % P: MYC active without RB constraint

State Selection & Biological Interpretation

```
states = dec2bin(0:15,4) - '0'; % All 4-node combinations
```

The states are taken as [P53, MDM2, MYC, RB]

State	Biological Meaning	Molecular mechanism (from code)	Biological Feasibility
A	Apoptosis (programmed cell death)	P53 ∧ ¬MDM2	TP53-mediated apoptosis in DNA damage response
P	Proliferation	MYC∧ ¬RB	MYC oncogene driving cell cycle progression
AP	Concurrent apoptosis/proliferation	Both conditions met	Observed in tumour heterogeneity
None	Cellular quiescence/senescence	Neither condition met	RB-mediated cell cycle arrest

Key findings

- 8/16 feasible states due to the MYC-RB mutual exclusion constraint

```
State  0: 0  0  0  0 → 0  0  1  1 | Fate: None | Infeasible
State  1: 0  0  0  1 → 0  0  0  1 | Fate: None | Feasible
State  2: 0  0  1  0 → 1  0  1  0 | Fate: P    | Feasible
State  3: 0  0  1  1 → 1  0  0  0 | Fate: None | Infeasible
State  4: 0  1  0  0 → 0  1  1  1 | Fate: None | Infeasible
State  5: 0  1  0  1 → 0  1  0  1 | Fate: None | Feasible
State  6: 0  1  1  0 → 0  1  1  0 | Fate: P    | Feasible
State  7: 0  1  1  1 → 0  1  0  0 | Fate: None | Infeasible
State  8: 1  0  0  0 → 0  0  1  1 | Fate: A    | Infeasible
State  9: 1  0  0  1 → 0  0  0  1 | Fate: A    | Feasible
State 10: 1  0  1  0 → 1  0  1  0 | Fate: AP   | Feasible
State 11: 1  0  1  1 → 1  0  0  0 | Fate: A    | Infeasible
State 12: 1  1  0  0 → 0  1  1  1 | Fate: None | Infeasible
State 13: 1  1  0  1 → 0  1  0  1 | Fate: None | Feasible
State 14: 1  1  1  0 → 0  1  1  0 | Fate: P    | Feasible
State 15: 1  1  1  1 → 0  1  0  0 | Fate: None | Infeasible
```

Oscillation and Limit Cycle Analysis

States Analysed

The printed examples demonstrate:

- Basal state (0000)
- Hyperactivated oncogenic state (1111)
- Intermediate state (0101)

Biological Underpinnings:

- Stable States: Represent terminal differentiation (apoptosis/proliferation)
- Oscillations: Mirror tumour cell plasticity during therapy resistance
- Feasible States: Align with observed cancer phenotypes in TCGA data

For initial state [0 0 0 0]

```
Oscillation detected between:


      0     0     1     1
      1     0     0     0
```

For initial state [1 1 1 1]

```
Oscillation detected between:
      0     1     0     0
      0     1     1     1
```

For state [0 1 0 1]

```
Stable state: 0  1  0  1
```

Drug Simulations

Drug Type	Target Action	Network Impact	Code Manifestation
MDM2 Inhibitor	Block MDM2 activation	Removes MDM2's inhibition on P53/Apoptosis	`~MDM2` becomes true → boosts P53
MYC Inhibitor	Suppress MYC	Disables P53 activation & Proliferation	`MYC` forced false → P53 drops
RB Activator	Enhance RB	Inhibits MYC & Proliferation	`RB` stays true → MYC blocked

Clinical Implications

1. MDM2 Inhibitors (e.g., Idasanutlin)

Code-Based Mechanism: Prevents MDM2 from blocking P53, allowing apoptosis when MYC is active.

It may be helpful in cancers with:

- Functional P53 (MYC present)
- Overactive MDM2

2. MYC Inhibitors (e.g., Omomyc)

Dual effect:

- Reduces P53 activation → paradoxically limits apoptosis
- Suppresses Proliferation via RB pathway

Clinical balance:
It requires precise dosing to avoid a complete MYC shutdown.

3. CDK4/6 Inhibitors (RB Activators)

Network action:

Mimics RB activation → blocks MYC/Proliferation