Inheritable epigenetic states
Dynamical modelling of living systems 7.5hp

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INTRODUCTION

The DNA is like a digital memory, but unlike computers that work with zeros and ones, DNA code has four letters A, C, T, and G. The combination of all letters — billions in humans — is our genetic code. This code stores the blueprints of all proteins (which you studied in the first lab) in the form of genes that are about 10^3–10^4 letters long. These genes are wrapped around nucleosomes, which can control if a gene is active or inactive by methylation and acetylation.

As cells grow and divide, the DNA is copied so that mother and daughter cells have the same genes. However, this is not the full story, as the inactive or active state of several genes also carries on to the daughter cells. To achieve this, cells use so-called epigenetic mechanisms. If these fail, cells start malfunctioning that may trigger cancers.

In this lab, you will simulate a simple epigenetic system in Yeast. The model you will use comes from a cross-disciplinary collaboration between Kim Sneppen (modeling) and Geneviève Thon (cell biology). Their work was published in Cell — one of the most prestigious journals in biology — and is one of the seminal papers in epigenetic modeling [1].

Note: In this lab, we will often refer to 'The book'. This is of course the course book Models of Life by Kim Sneppen [2].

Lab report

You will write a lab report for this lab that, without including figure captions, should consist of a maximum of 1500 words (roughly 3–5 pages). You are allowed one figure panel per task, but each figure panel can consist of more than one figure. Ensure that your plots are well-formatted in a vector format with clear axis labels and legends, and proper font size.

TASKS

Task 1: Standard model for Yeast epigenetics

To start our understanding of how epigenetic mechanisms work, we will be implementing the model outlined in chapter 7.2.1 (Model of a system with L nucleosomes) in the book. The model has two key ingredients. First, active conversion by epigenetic proteins from one state to another, *e.g.* $M \to U$. Second, stochastic conversion where, *e.g.*, M or A falls of by chance.

The important parameter that balances these two types of conversion is the so-called feedback-to-noise ratio F

$$\frac{P_{\text{active conversion}}}{P_{\text{random conversion}}} = \frac{\alpha}{1-\alpha} = F.$$

Depending on F, the system may switch stochastically between M-dominated to A-dominated states. This is called bistability, *i.e.* when two states co-exist over time.

Goals

- First, theory. Look at Eq. 7.1 and 7.2 in the book and solve them to recreate the middle plot in Fig. 7.7. Also, find $F_c = 1/(\sqrt{(2)}-1)$, the point where the system becomes bistable. *Hint: Solve for m and a when both equations are in a steady-state for the cases where $m = a$ and $m \neq a$. I will not judge you if you use some kind of symbolic solver like Wolfram Alpha [3]. To find F_c, think about when the bistable solutions hold.*

- Implement the stochastic A-U-M model on page chapter 7.2.1 in the book. The time step is a constant $\Delta t = 1$. Using $F = 2, 4, 6$ simulate the system and recreate Fig. 7.6 and 7.8 (middle figures). *Note the number of steps in Fig 7.6!* Comment on the results. Why does the system become more bistable as F increases?

Task 2: Epigenetics and cooperativity

In the last model, a switch between A and M indirectly required two other nucleosomes to be picked. This is visualised as model 0 in Fig 1. During active conversion, one nucleosome could only reach the other state by being actively chosen with two other nucleosomes (which could of course be the same both times). This cooperativity is the main reason for bistability, which we will now test.

If we remove one of the active conversions, as shown in model 1 in Fig 1, we get a significantly simpler model. In this case, the only way to for a nucleosome to go unmethylated is by random conversion. We will now see that this simplicity yields no bistability.

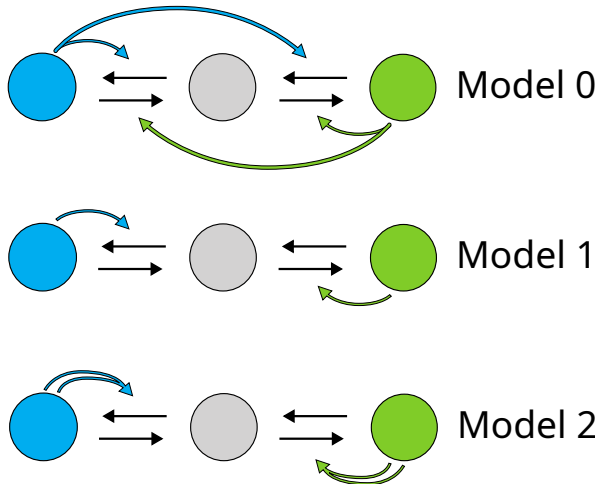

FIG. 1. The three variants of the A-U-M model. In **model 0**, each state can affect both the conversion to U and to its own state. In **model 1 and 2** the nucleosomes can only convert an unmethylated nucleosome to their own states, requiring either 1 or 2 to make a successful conversion.

Goals

- Based on Eqs. 7.1 and 7.2 in the book, formulate new equations that describe model 1 in Fig 1. As before, solve these equations to find the stable states. Are there bistable states?
- Implement model 1 in Fig 1 and simulate using $F = 10$. Plot the histogram as before. How does this compare to the simulations you did earlier?
- In Fig 1 we show a variant of model 1 — model 2 — which requires two nucleosomes to make a successful active conversion. Code-wise, this means that if the chosen nucleosome is U, then it goes to another state if the two other nuclesomes randomly chosen are both either A or M. Implement this model and simulate using $F = 10$. Plot the histogram in the same figure as before. Explain using your most intuitive language why this model change has such drastic effects to the stability of the system.

Task 3: Epigenetics and local vs. non-local interactions

In the models implemented thus far, the contact between two nucleosomes is completely distance-independent. Biologically this means that any part of the chromatin is in contact with all other parts simultaneously. In reality, the distance between sections of chromatin (simplified — nucleosomes) falls off as a power law. *I.e.* the probability that two nucleosomes separated by a distance d are in contact goes as

$$P(d) \sim d^{\gamma}$$

where $\gamma < 0$ is some parameter.

We want to study how this contact probability affects bistability. But first we need to formulate a way to pick the next nucleosome based on this probability. Given a vector of all distances $\mathbf{d}$ from a randomly chosen nucleosome n_1 to any other nucleosome $n_2 \neq n_1$ and the corresponding probability vector $\mathbf{P} = \mathbf{d}^{\gamma}$, the algorithm for choosing a value from $\mathbf{P}$ is as follows;

1. Calculate the cumulative probability vector $\mathbf{P}_c = [p_1, p_1 + p_2, p_1 + p_2 + p_3, \dots]$.
2. Pick a random number r from the uniform distribution $U[0, \sum P)$.
3. Using r, pick the first index i from $\mathbf{P}_c$ where $r \leq P_c[i]$.

Use this index i to get n_2.

Goals

- Using model 0, implement the power-law distance dependence. With $F = 6$ and 3–6 values for $\gamma \in [-1.0, -3.0]$, simulate the system for a reasonable amount of time. Plot the corresponding histograms as in Fig. 7.8 next to $P(d)$ with $d \in [1, L]$. Explain what happens as γ changes. Roughly, at what γ does the system show bistability? Compare this to the results from model 0 without any distance-dependency.

Task 4: Can epigenetic states survive cell division?

One of the essential roles of epigenetics is to ensure that the state of the genes — on or off — is maintained as cells grow and divide. As cells divide, the epigenetic state of the nucleosomes change. In fact, half of all nucleosomes loses their acetylation and/or methylation.

Adding cell division to one of the models is dead simple. Every time t_{div} simply change 50% of the acetylated and methylated nucleosomes to the unmodified state.

Goals

- Using $F = 6$ and $\gamma = -1.0$ simulate the model in task 3 but now with a cell division event that occurs ten times during the simulation. Plot the number of A and M nucleosomes versus time, with the division events clearly marked on the plot. Also plot the histogram as before. Does the system's state remain? Explain why this happens.

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[1] I. B. Dodd, M. A. Micheelsen, K. Sneppen, and G. Thon, Theoretical analysis of epigenetic cell memory by nucleosome modification, Cell **129**, 813 (2007).

[2] K. Sneppen, *Models of life* (Cambridge University Press, 2014).

[3] W. A. LLC, Wolfram—alpha, https://www.wolframalpha.com/ (2009), accessed: 2022-07-01.