Course 67562 | Spring 2025

Dynamics, Networks and Computation

Homework Exercise #2

Prof. Mor Nitzan | *TA: Hagai Rappeport*

1 Submission Guidelines

Submission deadline is Thursday, the 9th of May 2025, at 23:59

1.1 Submission

Submit a single .ipynb file (Jupyter notebook) with your answers to the questions. (Python code cells for code questions, MarkDown cells for text/math) If there are any other files required to run the code in the notebook, supply them as well.

If you wish to submit in any other way (e.g. want to use another language), Okay it with me (Hagai) first.

1.2 Working in Groups

Your'e allowed to discuss questions and code implementations with other students, but the final answers should be yours alone. In particular, you should write all code yourself.

2 Fluctuations in Growth

Consider a population of bacteria growing. Starting at t_0 from an initial population size N_0, each bacterium samples a time from an exponential distribution with rate μ, and this growth continues until the bacteria reach a population size of $C \cdot N_0$.

2.1 Behavior of The mean

Write the differential equation describing the *mean* number of bacteria as a function of time $\langle N(t) \rangle$, and solve for T, the time where the population reaches its final size $C \cdot N_0$

2.2 Adding Stochasticity

Write a simulation of the stochastic process described above. Specifically, implement a function which given values for N_0, μ and C, returns T, the time to reach the threshold $C \cdot N_0$, based on the results of a single realization of the process.

Hint: What property of exponential distributions did we discuss that might simplify this simulation?

2.3 Fluctuations Around the Mean

Analyze the fluctuations in time to reach the threshold, T, as a function of N_0. Specifically, set $\mu = 1$ and $C = 100$, choose 5 different N_0 values in the range 1 to 10,000 (you may want to space them logarithmically) and for each run 200 realizations of the random process and store the resulting threshold times T. What do the histograms of these times look like? How does their mean compare to your results from 2.1? Can you fit a function for the standard deviation in T as a function of N_0?

3 Dynamics of The Feed Forward Loop

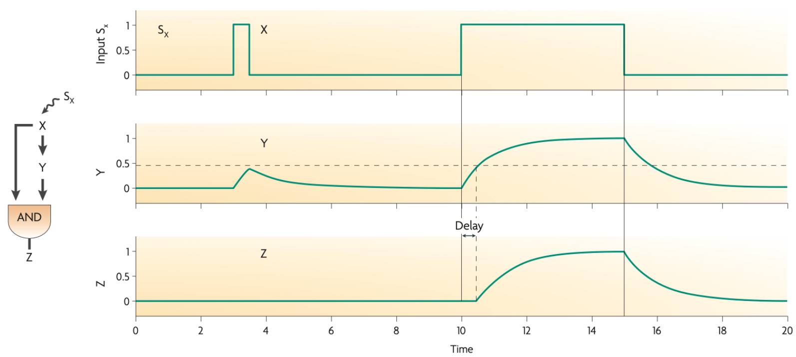
In class, we have described a dynamical model where X and Y are both required to fully generate some resource Z, and in addition Y is positively regulated by X. We named this arrangement a *Type 1 Coherent Feed Forward Loop*, and analytically reasoned that it generates dynamical behavior where Z is only generated for sufficiently long pulses of X.

Note: In this and the following sections, you'll be asked to numerically solve ODEs. To this end, you can use any ODE solver you'd like. You can also write a simple one yourself (this will probably be quicker) - Namely, given an initial condition $\vec{x}(0)$ and an expression for its time derivative $\dot{\vec{x}} = f(x,t)$, simply choose some small Δt and iteratively advance $x(t+\Delta t) = x(t) + \Delta t \cdot f(x,t)$

3.1 FFL Versus Regular Activation

3.1.1 Simulating the FFL With an AND Gate

We'll start by assuming that Z is generated iff both X and Y exceed some critical level K_{XZ} and K_{YZ} respectively (as we did in class), and Y is produced iff $X > K_{XY}$. Write the relevant ODEs and solve them with parameter values which will give (qualitatively) the following behavior:



Namely, you should choose production rates, degradation rates, critical activation values and pulse durations such that starting from an all 0 state, an initial short pulse of X will cause a noticeable increase in Y, but will not suffice to activate Z, whereas a second longer pulse will cause activation.

Hint: You don't need to tune all of the parameters, some are redundant. You can decide that the steady state values of all three components is 1, which in turn will eliminate some of the other parameters.

3.1.2 Regular Activation

Using the same parameters, remove the double regulation on Z and retain only the X regulation. What's different?

3.2 Robustness to Noise in Signal

3.2.1 Random Flipping of Signal

Using the FFL with the same parameters, add random noise to X in the form of flipping its value at random at each time point independently with probability p. How high can p get with the system still reacting qualitatively as before? (Z is near 0 until shortly after the long signal starts, then increases to its steady state value and starts decreasing once the signal is off)

3.2.2 Other Types of Noise

Suggest a different type of noise in the system and analyze the FFLs robustness against it as a function of some noise parameter of interest.

3.3 Hill Functions and Soft Activation

In class we described the Hill activation function of a gene X as a function of the concentration of some signal S_X,

$$\beta_X \frac{S_X^n}{K_X^n + S_X^n}$$

Where β_X, as before, is the maximal production rate, K_X is the value of S_X at which we reach half of this maximal rate (analogous to the threshold value in the step function) and n is a parameter which controls the steepness of the transition between 0 and β_X.

This expression is derived from a model for the probability that a transcription factor F_X molecule is bound at its regulatory site, as a function of the concentration of S_X

$$\mathcal{P}(F_X \text{ is bound}) = \frac{S_X^n}{K_X^n + S_X^n}$$

Using this interpretation, derive an equivalent expression for the production rate of a gene X which requires *two* transcription factors F_X and F'_X which in turn are active as a function of the concentrations of *two* signals S_X and S'_X. Assume that production happens iff both F_X and F'_X are bound, and that their binding probabilities are independent.

3.4 FFL With a Soft AND Gate

Rerun your FFL simulation from Q3.1.1 with the same parameters, only this time use the activation function you derived in Q3.3 using X and Y as the signals and both with $n = 1$, what changed? How robust is this system against your noise mechanism from Q3.2.2?

4 From Lac to NAND

Two common carbon sources for bacteria are the sugars *glucose* and *lactose*. While Bacteria can use both of these sugars as an energy source, glucose is preferred when it is present, and only in its absence will they switch to utilizing lactose. Bacteria have an efficient regulatory system controlling the activation of the machinery necessary to metabolize lactose, the *lac operon*.

In this question we'll use a simplified model of this regulation which only considers:

1. The concentration of lactose, which acts as an activator.
2. The concentration of glucose, which acts as a repressor.

4.1 Soft NAND

Generalize your derivation of the soft AND gate from Q 3.4 to describe the production rate of a gene as a function of both activator and repressor concentrations, where we allow non-zero activation when the repressor is bound or the activator is not (or both).

More specifically, we have a repressor X and an activator Y, both of which have (independent) Hill binding probabilities, and we consider four possible scenarios,

1) Both X and Y bound,
2) Only X is bound
3) Only Y is bound
4) Neither are bound

Each of these has its associated production rate (which should be lowest when the repressor is bound and the activator is not and highest when the activator is bound and the repressor is not).

4.2 The Lac Operon

Next, we will use this model to design a lactose regulatory system with the following design goals:

- When lactose is absent, we want minimal *lac* production.
- When lactose is present but glucose is also present, a small amount of *lac* is produced.

- When lactose is present and glucose is absent, we want *lac* to be produced at maximal rate.

Choose parameter values for the model which will produce, qualitatively, this desired behavior. Visualize the rate of production of lac as a function of both lactose and glucose levels with these parameters (as a contour map or 3D plot).

4.3 NAND

We'll now use the model you developed in Q4.1, but will interpret X and Y as general regulators of Z (not necessarily an activator and repressor respectively)

In what parameter limits does your model describe a logical NAND gate? Explain and provide a plot to support.

Good Luck!