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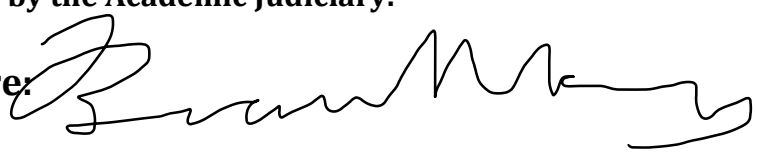
Homework # (Unit): 1

Instructions: In the space below, list *all* resources that were used in the completion of this assignment. This must include any books, websites or other reference materials that were consulted, as well as a list of any people that you discussed the problems with. Please note that all resources that were consulted in trying to answer any of the problems on the assignment must be included, even if you do not feel that the resource helped. *Note, if the only resources you used were the class text(s) and lectures, list those; do not leave this page blank.*

By signing below, I attest that the statements made above represent a complete accounting of the materials I used in completing this assignment. I understand that the failure to disclose the use of any resource is an act of academic dishonesty subject to penalty by the Academic Judiciary.

Signature: 

Date:

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Written Homework #1

Part A: Defining Concepts

1. **Provide a one sentence definition of each of the following classes of proteins**
   (a) **Enzyme** – a class of protein that catalyzes reactions, enabling reactions to happen at a rate faster than what is natural.
   (b) **Receptor** – a class of protein that is used in cellular signaling, through the binding of a extracellular ligand to drive a cellular response.
   (c) **Transcription Factor** – another class of protein that regulates the rate of DNA transcription to mRNA.
2. **Provide a one sentence definition of each of the following aspects of cellular physiology**
   (a) **Anabolism** – Building larger molecules from smaller molecules using energy.
   (b) **Catabolism** – The breakdown of molecules into smaller molecules to be released as energy or to be used in anabolic reactions.
   (c) **Transport** – The movement of molecules or individual atoms through a cell membrane using transport proteins.
3. **Provide a detailed description of each of the following cellular physiological processes:**
   (a) **Signal Transduction -** signal transduction is the process in which a cell reacts to the binding of a ligand to a receptor on the cell surface. The process begins when a ligand binds to a receptor on the cell. The receptor changes it's conformation in response to the docking of the ligand. The change in the protein's shape will change the protein's activation state, either activating or deactivating it. The change in activation state will impact down stream effectors to induce a cellular response.
   (b) **Transcription** – Transcription is the process of creating mRNA copied of DNA for translation outside of the cell nucleus. The process can be likened to taking what someone said and writing down what they said mRNA and DNA are similar in that they both have 4 bases C, A, G and depending on whether it is DNA or RNA will either have T or U respectively. The protein that unwinds the DNA and transcribes the DNA is called an RNA polymerase and the direction of transcription is from 5' to 3'.
   (c) **Translation –**Translation is the process of converting mRNA into Proteins through ribosomes. Multiple proteins can be created from a single mRNA allowing for the amplification of effects. The step-by-step translation of mRNA into a protein occurs in 3 base groups called codon. Each combination of 3 base for each codon represents a specific amino acid. There are some amino acids that has multiple codons coding for it, allowing for some redundancy in case the mRNA was incorrectly translated or the DNA was damaged. For the chain to begin building the correct anti-codon must attach itself to it's corresponding codon.
4. **Provide a brief description of each of the following mathematical concepts:**
   (a) **System of ordinary differential equations** – A group of equations that represents the rate of change of some equation.
   (b) **Null cline –** a line defined by where a specific variable's rate of change is 0, to change the signs of a variable the trajectory must cross this line
   (c) **Stationary Point –** a point in which the rate of change in all variables in the system is 0. For a system of two variables this is where the nullclines of the two variables intersect.
5. **Provide a detailed description of the following computational method.**
   (a) **The forward Euler Algorithm** – The trajectory of a function based on time can be approximated using its derivative and a small time step. We start with an initial value for all the variables. We then calculate the rate of change for each variable based on the current value of the variable. We then add the rate of change multiplied by a delta time to get the approximated value at $(current\ time + \Delta t)$. We then repeat this process for a variable duration to get the value at that time as well as the time in between.

Part B: Applying Concept

1. **Consider the following model for the expression of a single gene:**

$$\frac{d[\chi_{prot}]}{dt} = \omega[\chi_{rna}] - \chi_{prot}[\chi_{prot}] \quad \frac{d[\chi_{rna}]}{dt} = \mu - \chi_{\mathrm{rna}}[\chi_{rna}]$$

   a. **Explain these equations. Be sure to define each term and variable, and provide an explanation of the function form for each term.**

   $\omega[\chi_{rna}]$ is the growth term for the rate of change in protein concentration, ω a coefficient that modulates how $[\chi_{rna}]$ impacts the rate of change for protein concentration. $[\chi_{rna}]$ is the RNA concentration. $-\chi_{prot}[\chi_{prot}]$ is the decay term for the rate of change for protein concentration. χ_{prot} is the coefficient that modulates how the concentration of proteins decreases the rate of growth of itself. $[\chi_{prot}]$ is the concentration of proteins. μ is the constant growth term for the rate of change of RNA. $-\chi_{rna}[\chi_{rna}]$ is the decay term for the rate of change in RNA. χ_{rna} is a coefficient that modulates the effect the decay term has on the rate of change in RNA concentration.

   b. **Find all nullclines of the system, and plot them on a plane of $[\chi_{rna}]$ vs $[\chi_{prot}]$.**

   c. **Find all possible steady states of the system and highlight them on the plot made in (b)**

   To find all the nullclines of the system, we'll need to find all the conditions for $\frac{d[\chi_{prot}]}{dt} = 0$ or $\frac{d[\chi_{rna}]}{dt} = 0$.

$$\frac{d[\chi_{prot}]}{dt} = 0 = \omega[\chi_{rna}] - \chi_{prot}[\chi_{prot}]$$
$$0 = \omega[\chi_{rna}] - \chi_{prot}[\chi_{prot}]$$
$$\chi_{prot}[\chi_{prot}] = \omega[\chi_{rna}]$$
$$[\chi_{rna}] = \frac{\chi_{prot}[\chi_{prot}]}{\omega}$$

$$\frac{d[\chi_{rna}]}{dt} = 0 = \mu - \chi_{rna}[\chi_{rna}]$$
$$0 = \mu - \chi_{rna}[\chi_{rna}]$$
$$\chi_{rna}[\chi_{rna}] = \mu$$
$$[\chi_{rna}] = \frac{\mu}{\chi_{rna}}$$

   We can then use MATLAB to visualize how the nullclines will look like. I am not particularly creative so I'm going to set all the constants $\chi_{prot} = \chi_{rna} = \omega = \mu = 1$. The system's steady state will also be highlighted in yellow.

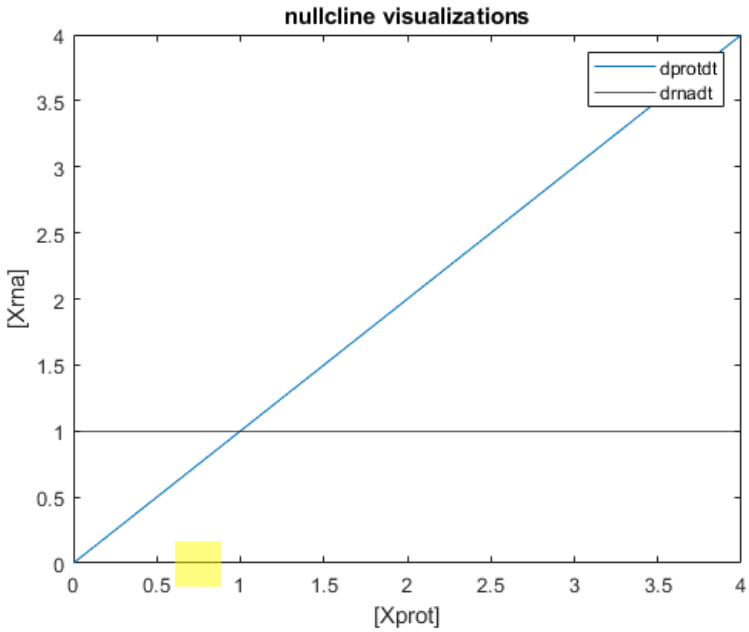


Figure 1. nullclines for the system of two equations. The intersection of the two nullclines represents a stationary point, highlighted in yellow. This particular stationary point is a stable fixed point.

In terms of biology, this system represents a constitutively active gene whose protein that it encodes for is vital to the survival of the cell. Therefore, the system will always ensure that the gene is active and the gene that encodes for the protein is present as well. Even if the system has too high of a concentration of either gene, this system is able to self-regulate and gradually return to this system's stationary point.

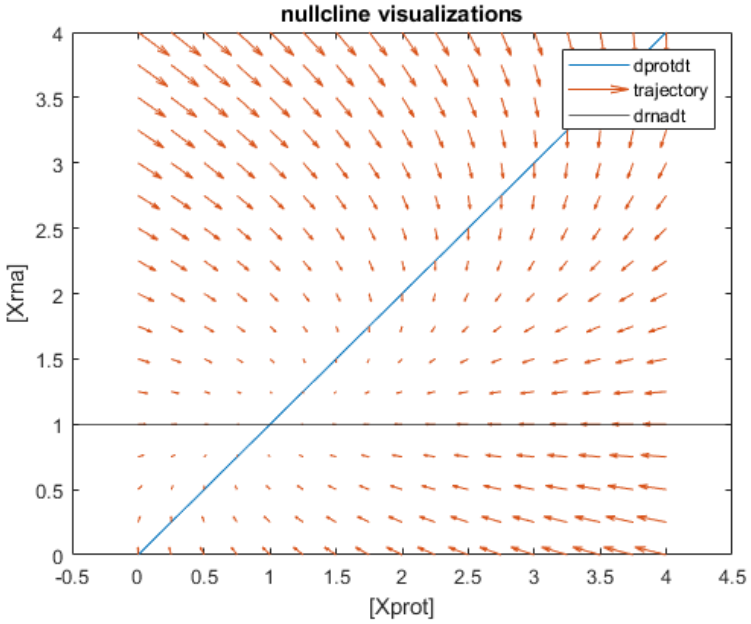


Figure 2. flow field of this system shows that the trajectory of the curve will always approach the stationary point expected of a constitutively active gene.

2. **Proteins Ian and Huang are both transcription factors that control their own production as obligate auto-activators, and both bind DNA without any cooperativity, Protein Ian is blue and protein Huang is yellow**
    a. **Write a system of ordinary differential equations that may be a reasonable model for this system. Be sure to clearly define each term and variable, and provide an explanation of why the functional form you have chosen for each term is appropriate.**

$$\frac{d[l_{prot}]}{dt} = \omega[l_{rna}] - l_{prot}[l_{prot}]$$
$$\frac{d[l_{rna}]}{dt} = \frac{\mu[l_{prot}]}{k_{\frac{1}{2}}[l_{prot}]} - l_{rna}[l_{rna}]$$

$$\frac{d[h_{prot}]}{dt} = \delta[h_{rna}] - h_{prot}[h_{prot}]$$
$$\frac{d[h_{rna}]}{dt} = \frac{\gamma[h_{prot}]}{j_{\frac{1}{2}}[h_{prot}]} - h_{rna}[h_{rna}]$$

Since the two proteins are not going to interact with each other it is sufficient to treat each protein using the basic model for the expression of a single gene. Since the gene is not constitutively active, we cannot have a constant growth term for the rate of change for both variables. Therefore, we'll replace it with the hill equation. We also learn that the proteins "bind DNA without any cooperativity meaning that the h value will be 1.

    b. **Find all possible steady states of the system, and provide conditions on the parameters necessary for each to exist.**

$$\frac{d[l_{prot}]}{dt} = \omega[l_{rna}] - l_{prot}[l_{prot}] = 0$$
$$\omega[l_{rna}] - l_{prot}[l_{prot}] = 0$$
$$\omega[l_{rna}] = l_{prot}[l_{prot}]$$
$$[l_{rna}] = \frac{l_{prot}[l_{prot}]}{\omega}$$

$$\frac{d[l_{rna}]}{dt} = \frac{\mu[l_{prot}]}{k_{\frac{1}{2}} + [l_{prot}]} - l_{rna}[l_{rna}] = 0$$
$$\frac{\mu[l_{prot}]}{k_{\frac{1}{2}} + [l_{prot}]} - l_{rna}[l_{rna}] = 0$$
$$l_{rna}[l_{rna}] = \frac{\mu[l_{prot}]}{k_{\frac{1}{2}} + [l_{prot}]}$$
$$[l_{rna}] = \frac{\mu[l_{prot}]}{l_{rna}(k_{\frac{1}{2}} + [l_{prot}])}$$

$$\frac{d[h_{prot}]}{dt} = \delta[h] - h_{prot}[h_{prot}] = 0$$
$$\delta[h_{rna}] - h_{prot}[h_{prot}] = 0$$
$$\delta[h_{rna}] = h_{prot}[h_{prot}]$$
$$[h_{rna}] = \frac{h_{prot}[h_{prot}]}{\delta}$$

$$\frac{d[h_{rna}]}{dt} = \frac{\gamma[h_{prot}]}{j_{\frac{1}{2}} + [h_{prot}]} - h_{rna}[h_{rna}] = 0$$
$$\frac{\gamma[h_{prot}]}{j_{\frac{1}{2}} + [h_{prot}]} - h_{rna}[h_{rna}] = 0$$
$$h_{rna}[h_{rna}] = \frac{\gamma[h_{prot}]}{j_{\frac{1}{2}} + [h_{prot}]}$$
$$[h_{rna}] = \frac{\gamma[h_{prot}]}{h_{rna}(j_{\frac{1}{2}} + [h_{prot}])}$$

c. Explain your results from (b) using two annotated plots, one showing the null clines of lan RNA and protein and the other showing the null clines of huang RNA and protein.

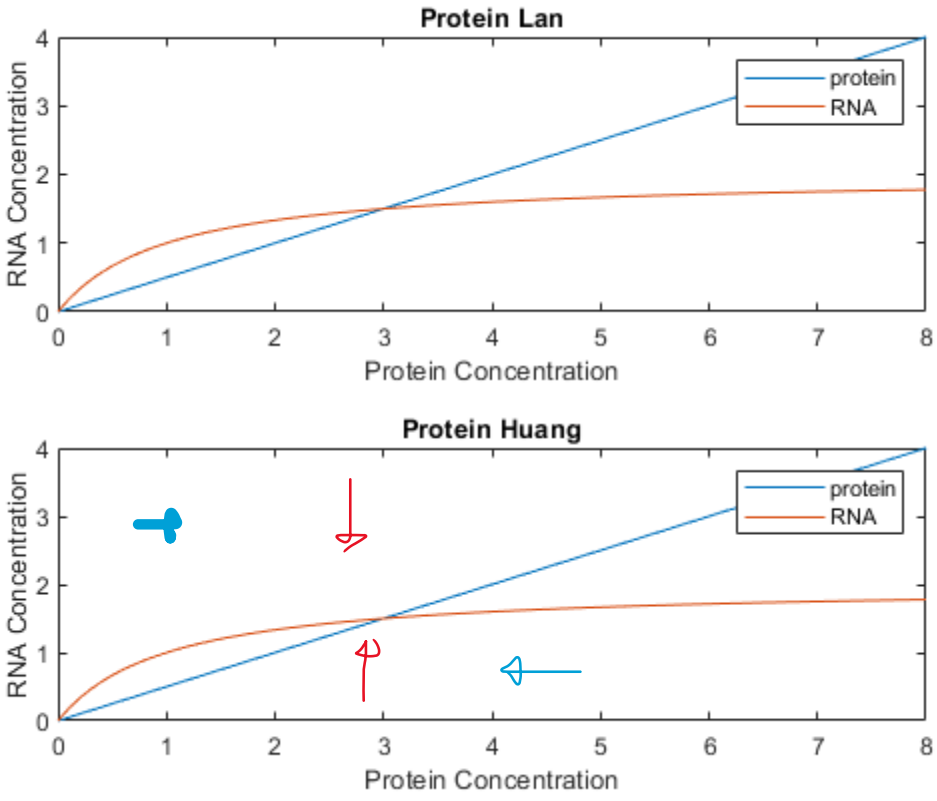


Figure 3. The nullclines of the protein Lan and RNA Lan and of the protein Huang and RNA Huang. The curved figure is the change in RNA concentration for the RNA nullcline while the linear line is the change in RNA

concentration for the Protein nullcline. The intersection of these two nullclines represents a steady state where both the change in RNA concentration and the change in protein concentration are 0. Given an initial protein concentration and RNA concentration, the system will eventually gravitate to either of these two states.

d. Under what conditions would you expect cells that contain the genes for both Lan and Huang to be blue, yellow, green, or colorless.

The conditions for the cells to be any color will be dependent on the initial starting concentration of protein and RNA as these values will eventually gravitate towards either the zero or non-zero steady state. If we take a protein, Lan for example, and input some values that are right and left of the nullclines for each of them, we can get a general trajectory of the nullcline for a given initial starting condition. The values used for the graphs above were $\omega = 1, \mu = 2, k_{1/2} = 1, lprot = 1, lrna = 1$.

Taking a value of $(1, 2)$ left of the protein nullcline, and plugging it into the derivative:

$$\frac{d[l_{prot}]}{dt} = \omega[l_{rna}] - l_{prot}[l_{prot}]$$
$$= 1(2) - 1(1)$$
$$= 1$$

Taking a value of $(3, 1)$ right of the protein nullcline, and plugging it into the derivative:

$$\frac{d[l_{prot}]}{dt} = \omega[l_{rna}] - l_{prot}[l_{prot}]$$
$$1(1) - 1(3)$$
$$= -2$$

This indicates that any value left of the blue line will move towards the right while any value right the blue line will move towards the left.

Taking a value of $(2,1)$ below the RNA nullcline and plugging it into its derivative:

$$\frac{d[l_{rna}]}{dt} = \frac{\mu[l_{prot}]}{k_{\frac{1}{2}} + [l_{prot}]} - l_{rna}[l_{rna}]$$
$$= \frac{2(2)}{1+2} - 1(1)$$
$$= 1/3$$

Taking a value of $(2,2)$ above the RNA nullcline and plugging it into its derivative:

$$\frac{d[l_{rna}]}{dt} = \frac{\mu[l_{prot}]}{k_{\frac{1}{2}} + [l_{prot}]} - l_{rna}[l_{rna}]$$
$$= \frac{2(2)}{1+2} - 1(2)$$
$$= -\frac{2}{3}$$

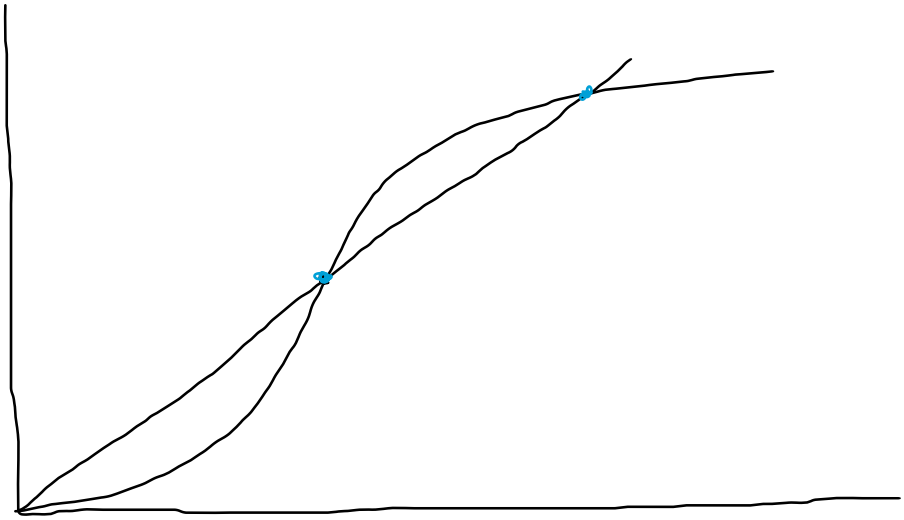
This indicate that any value below the RNA nullcline will go up and any value below the nullcline will go down.

With this information we will have a blue cell if the Lan protein has a non-zero starting condition for both of its variables while Huang as a zero concentration starting condition for both of its variables. For a green cell, both lan and haung have a non-zero starting condition for it's variables. For a yellow cell, huang has a non-zero starting condition while lan has a zero-starting condition. For a color-less cell there will be a 0 protein and RNA concentration for both proteins.

3. **Consider a general model for an auto-regulatory gene:**

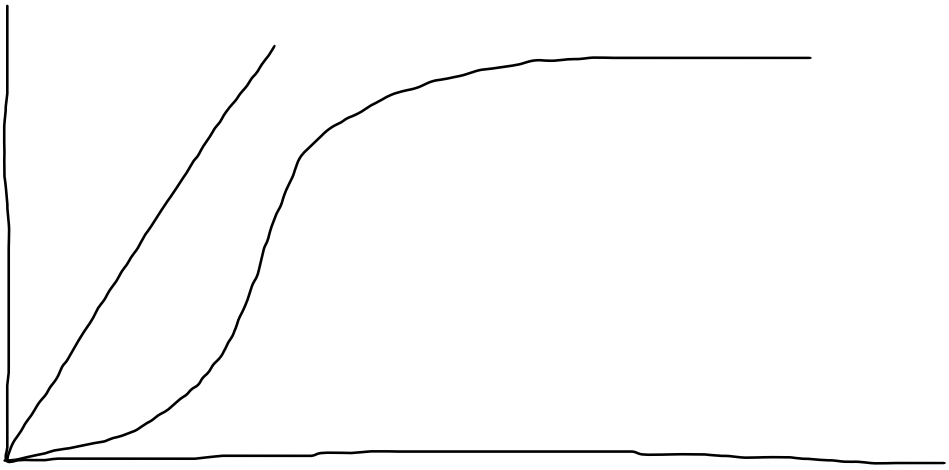
   a. **Demonstrate why cooperative binding, represented by h > 1 is necessary for this system to have two equilibrium states (i.e. two stable stationary points).**

   The stationary point at $(0,0)$ is an unstable stationary point. Having a h > 1 will change the RNA nullcline such that it will intersect the protein nullcline at two points.



   b. **Explain why cooperative binding alone does not guarantee the existence of two equilibrium states.**

   The protein nullcline is linear and does not necessarily have to intersect the RNA nullcline twice if the slope of the protein nullcline is high enough



   c. **Will a model of this form always have at least one equilibrium states?**
   no, it is dependent on the slope of the protein nullcline.

see above

Sources Used

1. Chapter 5, Mass Action Kinetics
2. https://byjus.com/biology/differences-between-catabolism-and-anabolism/
3. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/signal-transduction
4. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/transcription
5. https://www.khanacademy.org/science/ap-biology/gene-expression-and-regulation/translation/a/translation-overview
6.