MA508 – Worksheet 1

In 1965, the Nobel prize for physiology and medicine was awarded to Jaques Monod and François Jacob for their study of the *lac* operon. This is a series of genes that produces proteins involved in lactose metabolism in bacteria. Some of these proteins bind to and regulate the genes in the *lac* operon. Since the *lac* operon is complex, here we will analyze a simpler system – a single gene that is regulated by its protein product. You will see that, even in this simple system, complex behaviors can arise.

As you probably know, a gene is a section of DNA that codes for a single protein. To turn the DNA into protein, an enzyme called RNA polymerase binds to a region of DNA called the promoter, and then transcribes the following DNA into RNA. Then, this RNA is translated into a protein (see Fig. 1).

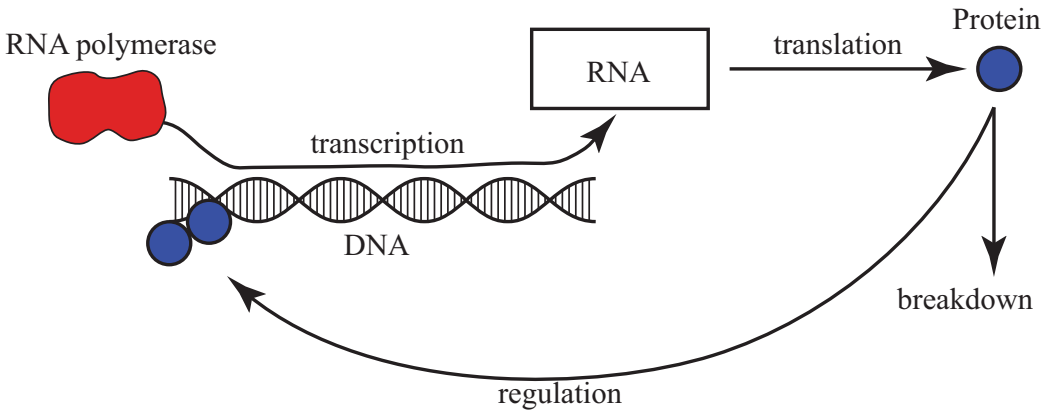

Figure 1: A cartoon showing the experimental system

Proteins can bind to the promoter region and affect how easily RNA polymerase binds. In this way, the formation of the protein can be regulated. Proteins, once made, do not last forever but are eventually broken down and destroyed. Thus, by regulating the formation of protein, the amount of protein can be controlled.

Here, we will study a single gene that is regulated by its own protein product. In particular, RNA polymerase cannot bind to the promoter unless two of the protein molecules are bound (see Fig. 1). Mathematically, the system can be expressed with the following equation

$$\dot{p} = -kp + A\frac{p^2}{p^2 + B^2}$$

where k, A, and B are positive constants that determine how quickly the protein is destroyed, how quickly it is formed, and how strongly the protein affects its formation, respectively. For simplicity, assume $k = B = 1$.

Answer the following questions.

Here, again, is the governing equation

$$\dot{p} = -p + A\frac{p^2}{p^2+1}$$

1a) Draw the phase line for the case where $A = 6$ (i.e., plot $\dot{p}$ vs. p, indicate any fixed point(s) and indicate the stability of each. On the horizontal axis (p) indicate the flow directions).

1b) Without solving the equation, sketch $p(t)$ as a function of t for several initial conditions for $A = 6$.

1c) Draw the phase line for the case where $A = 1$.

1d) Without solving the equation, sketch $p(t)$ as a function of t for several initial conditions for $A = 1$.

1e) Suppose that you wanted to maintain a non-zero steady-state concentration of protein in one of your cells. Would you choose $A = 1$ or $A = 6$? What else would you have to do to ensure a non-zero steady-state?

I have uploaded a couple movies showing simulations of this system. In each movie, on the left, the protein molecules "dance" randomly due to Brownian motion. When they are near either of two binding sites on the DNA molecule, they bind. When one protein molecule is bound to DNA, the protein turns yellow. If a second protein molecule then binds, they turn red and more protein is formed. All the while, the protein is being destroyed.

Watch the two movies (N10_start.mov, and N60_start.mov), which show what happens when we initially have 10, or 60 protein molecules. On the right is a plot of the number of molecules as a function of time, $p(t)$. Time is measured in milliseconds, so the entire experiments occurs over five seconds.

2) Based on these movies, and assuming that the system at least approximately obeys the differential equation, what can you say about the parameter A in the system? This is maybe a hard question, but think about what makes the system behave differently for $A = 1$ than for $A = 6$, and then think about what would be required to get the behavior you observe in the movies.