BE 150 Spring 2018
Homework #4
Due at the start of lecture, May 2, 2018.

Problem 4.1 (Kinetic proofreading in the immune system, 50 pts)**.**
In class, we talked about kinetic proofreading in the context of translation. In this problem, we will consider a model for kinetic proofreading in the immune system. T cells recognize specific agonist major histocompatibility complexes (MHC) on an antigen presenting cell (APC). The APCs also have many endogenous MHCs that should not trigger T cell activation. It has been proposed that T cells are able to distinguish agonist MHCs (which should trigger T cell activation) and endogenous MHCs (which should not trigger T cell activation) via a kinetic proofreading mechanism. Such a mechanism is shown in Fig. 1.

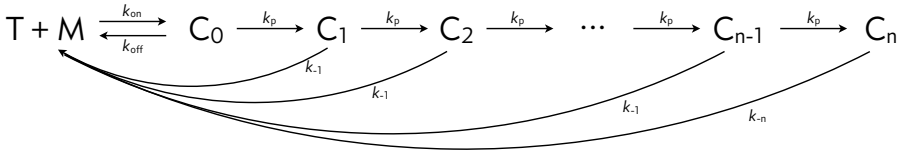

Figure 1: A mechanism for kinetic proofreading in T cell activation. M = MHC; T = T cell receptor (TCR). The complexes C_i denote MHC-TCR complexes with various stages of phosphorylation. In this model, all complexes may dissociate and "reset" to an unbound MHC and TCR. The rate of activation of T cells is proportional to the concentration of complex C_n. We say that C_n is the "active form."

In this problem, we will provide a bit less guidance than usual in the analysis and leave you to think carefully about what plots and what limits are useful for analyzing the system and making conclusions about it. This is meant to help train you think carefully and creatively about new circuits you encounter. Specifically, you will think about the competing needs of the T cell activation system:

> The system must be **selective**. That is, T cells should only be activated upon interaction with an agonist MHC, and not with endogenous MHCs.
>
> The system must be **sensitive**. That means it should get considerable T cell activation when the agonist MHC is present.

a) Assuming mass action kinetics, write down a system of ODEs for the concentrations of all chemical species. Until part (e), consider only a single MHC species.

b) Until part (e), assume that $k_{-n} = k_{-1}$. Show that at steady state, the fraction of complexes that are in the active form is α^n, where

$$\alpha = \frac{1}{1 + k_{-1}/k_p}. \tag{4.1}$$

Hint: Recall the sum of the first n terms of a geometric series,

$$\sum_{k=0}^{n-1} x^k = \frac{1-x^n}{1-x}, \tag{4.2}$$

provided $0 < x < 1$.

c) Compute the fraction of MHC that is bound to active TCR complexes.

d) Discuss, with plots, limits, and/or words, how these results relate to the selectivity and sensitivity of the system. You can compute other quantities in our arguments if you like, such as the ratio of active complexes that are bound to agonist and endogenous MHCs.

e) It has been argued that k_{-n} can be tuned to get better performance of the system in terms of sensitivity without a comparable sacrifice in selectivity. Evaluate this claim.

f) If you are feeling curious and motivated, investigate other modifications to the kinetic proofreading mechanism. You might want to postulate about how the fact that the interactions between MHCs and TCRs are happening on cell membranes. This part of the problem has no points associated with it, but is meant to provide something to think about and possibly to spark conversations among students and the course staff.

Problem 4.2 (Coupled repressilators, 50 pts)**.**
In this problem, we further study the dynamics of the repressilator, with the interesting twist that we will consider two coupled respressilators. A schematic of the repressilator is shown in Figure 2a. Consider now two repressilators, which we will label x and y, that are coupled as in Fig. 2b. For this coupling, we have chosen that gene A in the respective circuits repress their counterparts in the other. A_x and A_y have two repressors acting on them, and we assume if one or both of the repressors are bound (with their respective cooperativity), the polymerase is occluded.

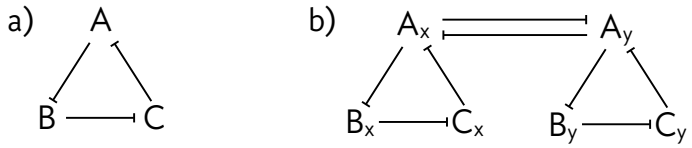

Figure 2: a) The repressilator. b) Two coupled repressilators.

For simplicity, we will consider only the dynamics of the protein products and neglect the mRNA dynamics. We will further assume that each gene in the "x" repressilator has the same unregulated rate of production β_x and the same rate of

dilution/decay, γ_x. Each repressor acts on the other repressors within its repressilator with activation constant k and Hill coefficient n. The same holds for the "y" repressilator; each gene has the same unregulated rate of production β_y, the same rate of dilution/decay, γ_y, and repress other genes within the "y" repressilator with Hill coefficient n and activation constant k. We assume that the repressors in the "x" and the "y" repressilators have the same unregulated steady state level, which is to say that $\beta_x/\gamma_x = \beta_y/\gamma_y$. Repression *between* repressilators (in this case, A_x repressing A_y and A_y repressing A_x) operate with Hill coefficient n_c and activation constant k_c.

a) Show that the dynamical equations of the circuit can be written in dimensionless form as

$$\dot{x}_a = \frac{\beta}{1 + x_c^n + (\kappa y_a)^{n_c}} - x_a, \tag{4.3}$$

$$\dot{x}_b = \frac{\beta}{1 + x_a^n} - x_b, \tag{4.4}$$

$$\dot{x}_c = \frac{\beta}{1 + x_b^n} - x_c, \tag{4.5}$$

$$\gamma^{-1}\,\dot{y}_a = \frac{\beta}{1 + y_c^n + (\kappa x_a)^{n_c}} - y_a, \tag{4.6}$$

$$\gamma^{-1}\,\dot{y}_b = \frac{\beta}{1 + y_a^n} - y_b, \tag{4.7}$$

$$\gamma^{-1}\,\dot{y}_c = \frac{\beta}{1 + y_b^n} - y_c. \tag{4.8}$$

b) Show that if the two repressilators are completely uncoupled (achievable by setting $\kappa = 0$), the ratio of the periods of steady oscillation is $T_x/T_y = \gamma$.

c) Write a code to solve for the dynamics of the coupled repressilators. Use parameters $n = 3$, $n_c = 2$, $\beta = 20$, and $\gamma = 3/2$. Solve for the dynamics for $\kappa = 0.1$ and $\kappa = 1$ and generate plots. Comment on what you see.

d) Compute the period of steady oscillation for species B_x and B_y for the parameter values in part (c), but with κ ranging from zero to ten. Plot T_x and T_y versus κ. Comment on the results. Specifically, comment on sychronization and where you see qualitative changes in the period as κ increases. *Hint: There are many ways to compute the period of oscillation. You could use power spectra, or you could detect where peaks are. To do the latter, the* `scipy.signal.argrelmax()` *function is useful.*

e) This system is fun to play with. Invent another way to couple the represillators (i.e., change which species are coupled and whether or not the coupling is via repression or activation). Perform a similar set of analyses and comment on what you see.