Problem Set 5

- You may use your course materials and/or any literature resources to formulate your solutions.
- Homework should be submitted by email to the teaching assistant. Each collaborating team member name should be listed on the first page of the submitted homework.
- Problem Set 5 is due on **Tuesday, May 4th, 2021** by **11:59 PM**.

Problem 1: Lateral inhibition through Notch-Delta signaling

In lecture, we considered the dynamics of Notch and Delta in a two-cell system by taking the limit in which the decay rate of Delta is much greater than that of Notch. Here you are asked to examine the same problem in the opposite limit.

(a) Argue that in the limit $\nu = \gamma_D/\gamma_N << 1$, the Notch activity in the two cells quickly settles into a steady state. What are the resulting dynamical equations for the evolution of Delta that follow from the complete system presented in lecture?

(b) Using the functional forms for the Notch and Delta activation rates, F(D') and G(N) (See lecture), obtain a phase portrait for the dynamics of Delta in the two cells. Compute and plot the nullclines for the system (plot can be on a separate plot than the phase portrait). Based on the phase portrait and nullclines, show that in the long-time limit, the system will settle into a steady state in which one cell assumes the primary fate while the other cell assumes the secondary fate. Discuss whether lateral inhibition works similarly as the case discussed in lecture (i.e. limit in which the decay rate of Delta is much greater than that of Notch). (***Note: example code for constructing a streamplot in Julia is provided on Slack;*** Streamplots or quiver plots can also be constructed in Matlab, Mathematica, and many other numerical computing environments)

Problems 2 – 3: Receptor signaling and adaptation. In the following problems, we will explore signal amplification and adaptation with the simple model of bacterial chemotaxis described in the following papers and texts:
- N. Barkai, U. Alon & S. Leibler, Robust amplification in adaptive signal transduction networks. C. R. Acad. Sci. Paris, t. 2, Série IV, p. 871–877 (2001). (**complete description of model**)
- U. Alon, M. G. Surette, N. Barkai & S. Leibler, Robustness in bacterial chemotaxis. *Nature*, 397, 168-171 (1999).
- Alon, Ch. 7 (**textbook chapter; will be posted on Slack**)

For problems 2-3, READ Barkai et al, 2001

2) Answer the following questions briefly, in words and sketches:

a) Why are both amplification and adaptation required for chemotaxis? Consider a bacterium as it successfully navigates up a gradient in chemoattractant.
b) What are the mechanisms for amplification in the proposed models of this signaling pathway? Consider the level of description of the network that is shown in Box 1 of Alon et al.
c) What are the mechanisms of adaptation in the proposed models?
d) What is the "robustness" with which Barkai et al. are concerned and why?

3) The complete equations for the mass action kinetics for inhibition-based adaptation are provided in Barkai et al., 2001 (page 876).

- Consider only two methylation states (m = 0, 1).
- Allow only the m = 1 state to be activated (i.e., set $\alpha_0^+ = 0$).
- Allow methylation to be zeroth order.
- Include the deactivation paths mediated by B and B_p (B acting as an "inhibitor").

Then the mass action kinetics are given by:

$E_0 \rightarrow E_1$	V_{max}^R	(1)
$E_1^* \leftrightarrow E_1$	α_1^-, α_1^+	(2)
$E_1^* + B_p \leftrightarrow \{E_1^* B_p\} \rightarrow E_0 + B_p$	a_{bp}, d_{bp}, k_{bp}	(3)
$E_1^* + B \leftrightarrow \{E_1^* B\} \rightarrow E_0 + B$	a_b, d_b, k_b	(4)
$\{E_1^* B_p\} \rightarrow E_1 + B_p$	β_1	(5)
$\{E_1^* B\} \rightarrow E_1 + B$	β_1	(6)
$B \leftrightarrow B_p$	$k_{1+} \times A$, k_{1-}	(7)

a) Express the balances in (a) as a series of ODEs for the seven species: E_0, E_1, E_1^*, B, B_p, $\{E_1^* B\}$, $\{E_1^* B_p\}$.
b) Using the parameter values (p. 877 of Barkai et al., 2001), justify the zeroth order approximation for methylation, give an expression for this rate, and find its numerical value for this rate.
c) Explore the adaptation of two-state version of the model by generating same responses as in Fig. 3 of Barkai et al. 2001. How does the response of the two-state model differ from that of the three-state model used in the paper? Use Julia (DifferentialEquations.jl), Matlab (ode23/ode23t), or programming environment of choice to integrate the system of equations from 3(b). Example code for DifferentialEquations.jl is provided on Slack.