BE 159 Spring 2014
Provisional Homework #2
Due at the start of lecture, May 8, 2014.

Problem 2.1 (Independence of the onset of Notch activity on *trans*-Delta (35 pts))**.**
Reproduce Fig. 3h on the Sprinzak, et al. paper by numerically solving the appropriate system of ODEs. When you write down the system of ODEs, indicate the meaning of each term and any approximations that were made in deriving the ODEs. Vary parameters to investigate the robustness of the D_{plate}-independence of onset or reporter fluorescence. *Hint*: Look at Table S3 in the supplementary information for equations and parameter values to set up your calculation.

Problem 2.2 (Dynamics of a *cis-trans* Delta-Notch system (35 pts))**.**
Consider two connected cells the have both *cis* and *trans* Delta-Notch signaling described by the first two equations in Box 1 of the Sprinzak, et al. paper. We assume that the rate of production of Notch (β_N) is the same constant value in both cells. The production rate of Delta, β_D may be different in the two cells. For parts (a) through (d), assume the β's and κ are constants.

a) Show that the equations can be nondimensionalized to be written as

$$\frac{\mathrm{d}n_1}{\mathrm{d}t} = \tilde{\beta}_N - n_1 - \kappa d_1 n_1 - d_2 n_1 \tag{2.1}$$

$$\frac{\mathrm{d}n_2}{\mathrm{d}t} = \tilde{\beta}_N - n_2 - \kappa d_2 n_2 - d_1 n_2 \tag{2.2}$$

$$\frac{\mathrm{d}d_1}{\mathrm{d}t} = \tilde{\beta}_D^{(1)} - d_1 - \kappa d_1 n_1 - d_1 n_2 \tag{2.3}$$

$$\frac{\mathrm{d}d_2}{\mathrm{d}t} = \tilde{\beta}_D^{(2)} - d_2 - \kappa d_2 n_2 - d_2 n_1. \tag{2.4}$$

Going forward, we will drop all tildes and take the variables to be dimensionless.

b) Show that there exists a unique steady state for these equations. I.e., show that there is a unique $\{n_1, n_2, d_1, d_2\}$ that such that all of the time derivatives in equations (2.1) through (2.4) vanish. (This might be challenging. If you are stuck, take the uniqueness of the steady state as given, and proceed.) Explain why it is important to know that the steady state is unique.

c) Numerically compute the steady state and use it to recreate Figs. 4b Sprinzak, et al. paper. Check Table S3 for parameter values.

d) It can be shown that the steady state is linearly stable if the β's are constants. Showing this is challenging and perhaps a bit grungy, so we will now treat the special case of a homogeneous steady state.

   i) First, show that a homogeneous steady state only arises when $\beta_D^{(1)} = \beta_D^{(2)} \equiv \beta_D$.

   ii) Prove that the homogeneous steady state ($n_1 = n_2 = n_0$, $d_1 = d_2 = d_0$) is always linearly stable. *Hint:* You can analytically determine the eigenvalues of the linear stability matrix, but that may not be necessary. You might remember that the following statements are equivalent.

1) A real matrix A has the property $\mathbf{x}^\mathsf{T} \cdot \mathsf{A} \cdot \mathbf{x} > 0$ for all nonzero $\mathbf{x}$. (Such a matrix A is termed positive definite.)
2) A has all positive eigenvalues.
3) The determinants of all upper left submatricies of A are positive.

If you want to use these properties, it may help to remember a property of the determinant of a block matrix composed of square matrices A, B, C, and D.

$$\det \begin{pmatrix} \mathsf{A} & \mathsf{B} \\ \mathsf{C} & \mathsf{D} \end{pmatrix} = \det(\mathsf{A} \cdot \mathsf{D} - \mathsf{B} \cdot \mathsf{C}), \quad \text{provided } \mathsf{C} \cdot \mathsf{D} = \mathsf{D} \cdot \mathsf{C}. \tag{2.5}$$

e) Based on the Sprinzak paper, propose an adjustment to the production rate of Delta, β_D, that would result in the homogeneous state being unstable. Justify your proposal and explain what it means physically. If you are feeling ambitious and curious, analyze the new system, solve the two-cell model numerically, and explore the dynamics. (You do not *have* to do that last bit, but it might be a nice learning experience.)

Problem 2.3 (A simple fold change detector (30 pts))**.**
As we discussed in class, the Wnt/β-catenin signaling pathway results in a fold change in β-catenin corresponding to that of the Wnt signal. Since β-catenin ultimately enters the nucleus and regulates gene expression, it is important that there also be a fold-change readout of β-catenin levels. Goentoro and Kirschner mention a simple motif for gene regulation that gives such a fold-change response, citing the companion paper Goentoro, et al., *Mol. Cell*, **36**, 894–899, 2009. The motif is shown in Fig. 1. In this motif, transcriptional regulator X (which could be β-catenin) activates expression of Z. X also activates expression of Y, which represses expression of Z.

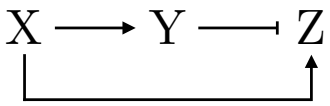

Figure 1: A schematic of a feed forward loop that exhibits a fold change response. This motif is referred to as the incoherent type-1 feedforward loop (I1-FFL).

Because there Y and Z have no effect on X, we can think of X as an input. We will assume that it is somehow set and maintained at a constant level, e.g., as a constantly-produced signaling molecule from a neighboring cell. We are interested in the response of Z as a result of an increase in X. Assume that Y and Z have inherent degradation rates α_1 and α_2, respectively. Those of you who took BE/APh 161 can derive the resulting differential equations for the dynamics of X, Y, and Z. In lieu of deriving them, I write them here.

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = \beta_Y \frac{1 + f\,\frac{X}{K_1}}{1 + \frac{X}{K_1}} - \alpha_1 Y, \tag{2.6}$$

$$\frac{\mathrm{d}Z}{\mathrm{d}t} = \beta_0 \frac{\frac{X}{K_1}}{1 + \frac{X}{K_1} + \frac{Y}{K_2} + \frac{XY}{K_3}} - \alpha_2 Z, \tag{2.7}$$

where the K's, α's, and β's are positive constants. We will investigate the dynamics of this system as the concentration of X is suddenly raise from X_0 to a concentration of $X = FX_0$, where F is the fold change in concentration of X.

a) Give an intuitive description of the physical basis for each of the terms in equations (2.6) and (2.7). If you can (e.g., if you took BE/APh 161 last term and pull out your lecture notes from January 27), you can derive the expressions to help give you a clearer meaning if you are having trouble explaining them with words.

b) Show that when activation of Y by X and repression of Z by Y are very strong, the equations reduce to

$$\frac{\mathrm{d}Y}{\mathrm{d}t} \approx \beta_1 X - \alpha_1 Y \tag{2.8}$$

$$\frac{\mathrm{d}Z}{\mathrm{d}t} \approx \beta_2 \frac{X}{Y} - \alpha_2 Z. \tag{2.9}$$

How are β_1 and β_2 related to the other constants we have already defined?

c) Nondimensionalize the equations, defining y as the dimensionless version of Y and z as the dimensionless version of Z. You should find that

$$\frac{\mathrm{d}y}{\mathrm{d}t} = F - y \tag{2.10}$$

$$\frac{\mathrm{d}z}{\mathrm{d}t} = \frac{1}{r}\left(\frac{F}{y} - z\right), \tag{2.11}$$

where t is now a dimensionless time. Note that these equations demonstrate that the dynamics depend on a single parameter, r, and further that the steady state is independent of r.

d) Imagine we have $F = 1$ and the system has relaxed to a steady state. We then immediately change F. (We will simply call the changed value F, or the fold change in X.) Solve for $y(t)$. How does y depend on F at steady state? How does Y depend on X at steady state?

e) Solve for $z(t)$ for the case there $r = 1$. Solve for $z(t)$ numerically for $r \neq 1$. Plot $z(t)$ for various values of r.

f) Based on your results, describe how this motif is a fold change detector.

Problem 2.4 (Simulations of Delta-Notch signaling on a hexagonal lattice (extra credit))**.**
In coming days, I will post some code that you can use to do simulations of Delta-Notch signaling on a hexagonal lattice, similar to what is seen in developmental systems, e.g., in *Drosophila* development. For extra credit, you can play with the simulation to investigate the patterning dynamics resulting from Delta-Notch-based regulation of gene expression.