

**BE 159 Spring 2015**  
**Homework #2**

Due at the start of lecture, January 29, 2015

**Problem 1** (A simple fold change detector).

As we discussed in class, the Wnt/ $\beta$ -catenin signaling pathway results in a fold change in  $\beta$ -catenin corresponding to that of the Wnt signal. Since  $\beta$ -catenin ultimately enters the nucleus and regulates gene expression, it is important that there also be a fold-change readout of  $\beta$ -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  $\beta$ -catenin) activates expression of Z. X also activates expression of Y, which represses expression of Z.

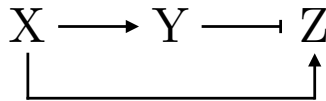


Figure 1: A schematic of a feed forward loop that exhibits a fold change response. This motif is referred to as the incoherent type-1 feedforward loop (I1-FFL).

Because 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  $\alpha_1$  and  $\alpha_2$ , respectively. Those of you who took BE/APh 161 can derive the resulting differential equations for the dynamics of Y and Z. In lieu of deriving them, I write them here.

$$\frac{dY}{dt} = \beta_Y \frac{1 + f \frac{X}{K_1}}{1 + \frac{X}{K_1}} - \alpha_1 Y, \quad (1)$$

$$\frac{dZ}{dt} = \beta_Z \frac{1 + f \frac{X}{K_1}}{1 + \frac{X}{K_1} + \frac{Y}{K_2} + \frac{XY}{K_3}} - \alpha_2 Z, \quad (2)$$

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

a) We can derive, under certain assumptions, that

$$\frac{dY}{dt} = \beta_1 X - \alpha_1 Y \quad (3)$$

$$\frac{dZ}{dt} = \beta_2 \frac{X}{Y} - \alpha_2 Z. \quad (4)$$

Given an intuitive verbal description of each term in these equations.

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

$$\frac{dy}{dt} = F - y \quad (5)$$

$$\frac{dz}{dt} = \frac{1}{r} \left( \frac{F}{y} - z \right), \quad (6)$$

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  $r$ . What is  $r$ ? Given a physical interpretation of its meaning.

- c) 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? *Hint*: When solving for  $y(t)$ , note that you are solving a first order ordinary differential equation and can solve by integrating factor.
- d) Solve for  $z(t)$  for the case where  $r = 1$ . *Hint*: With  $r = 1$ , you are again solving a first order linear differential equation and can solve by integrating factor. The resulting integral may be gnarly, but it is simplified if you do a partial fraction expansion.
- e) In the Goentoro and Kirschner paper we discussed in class, the authors say that “reading fold-changes in  $\beta$ -catenin requires that the cell remembers the basal level of  $\beta$ -catenin before Wnt stimulation.” In this gene circuit, how is the basal  $\beta$ -catenin level “remembered?”
- f) Based on your results, describe how this motif is a fold change detector.
- g) (10 points extra credit) Solve for  $z(t)$  numerically for  $r \neq 1$ . Plot  $z(t)$  for various values of  $r$ . Comment on anything you find from this analysis that you think is significant or interesting.