BE 159 Winter 2018
Homework #1
Due at the start of lecture, January 17, 2018

Problem 1.1 (A simple fold change detector).
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.

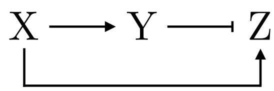

Figure 1: A schematic of a feed forward loop that exhibits a fold change response. This motif is referred to as the incoherent type-1 feedforward loop (I1-FFL).

Because 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 γ_1 and γ_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.

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = \beta_Y \frac{1 + f\frac{X}{K_1}}{1 + \frac{X}{K_1}} - \gamma_1 Y, \tag{1.1}$$

$$\frac{\mathrm{d}Z}{\mathrm{d}t} = \beta_Z \frac{1 + f\frac{X}{K_1}}{1 + \frac{X}{K_1} + \frac{Y}{K_2} + \frac{XY}{K_3}} - \gamma_2 Z, \tag{1.2}$$

where f and the K's, γ's, and β'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

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = \beta_1 X - \gamma_1 Y \tag{1.3}$$

$$\frac{\mathrm{d}Z}{\mathrm{d}t} = \beta_2 \frac{X}{Y} - \gamma_2 Z. \tag{1.4}$$

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

$$\frac{\mathrm{d}y}{\mathrm{d}t} = F - y \tag{1.5}$$

$$\frac{\mathrm{d}z}{\mathrm{d}t} = \frac{1}{r}\left(\frac{F}{y} - z\right), \tag{1.6}$$

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 β-catenin requires that the cell remembers the basal level of β-catenin before Wnt stimulation." In this gene circuit, how is the basal β-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.