Systems Biology Project 2

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1 Activator Cascade

1. Write down the ODEs that describe the system:

$$\begin{aligned} \frac{dY}{dt} &= V_{Ymax}\left(\frac{X^{*nY}}{K_Y^{nY}+X^{*nY}}\right) - Ydy \\ \frac{dZ}{dt} &= V_{Zmax}\left(\frac{Y^{nZ}}{K_Z^{nZ}+Y^{nZ}}\right) - Zdz \end{aligned}$$

2. Plot of Activator Cascade: See Figure 1

3. Explore the effects of signal strength (i.e. the magnitude of X*) on the profile of Z. When does a stronger signal fail to yield a higher response? Why?

   When we increase the magnitude of X*, the profile of Z does not change, but the ratio of the steady state of Y to Z increases. That is, the steady state of Y increases until it is closer to that of Z. The biggest change happens from $X* = 1$ to $X* = 2$. This is because the value of $X*$ is squared when it is used, which has no effect on 1 but does affect 2. Further, that first step is the biggest ratio step (times 4). See Figure 2 for graphs with values of $X*$ from 1 to 9.

4. If we increase the Hill coefficient, how does the answer to (4) change? Why?

   Nothing really changes as we increase the Hill coefficient because we always rely on an equation that contains the protein concentration in the numerator and the denominator.

5. What is the relationship between the response time of Z and the onset of the signal? Numerically determine Zs response time by estimating its steadystate ZSS and the time it takes for Z to become ZSS/2 (in the original configuration and others if you would like to explore further).

   The response time of Z in the original configuration is 8.0 seconds.

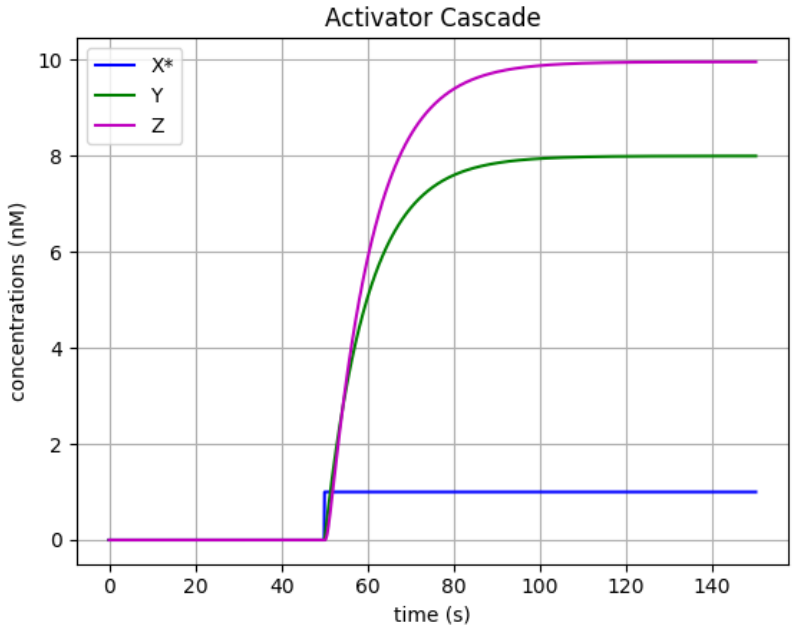
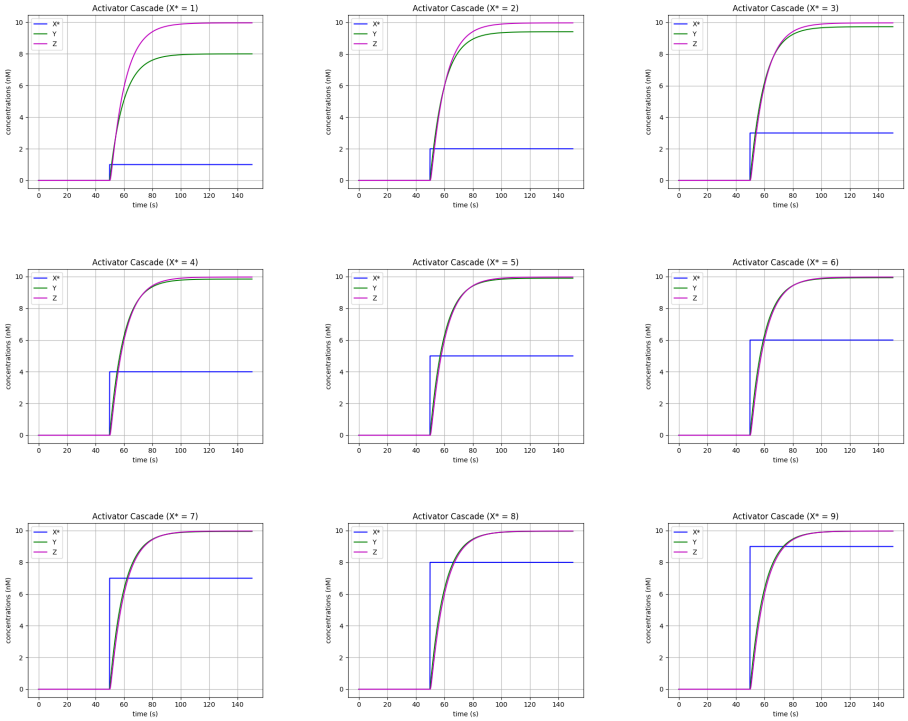


Figure 1: Plot of two molecules with an activator X^*. Parameters: $vYmax = 1\frac{nM}{s}$, $KY = 0.5nM$, $nY = 2$, $vZmax = 1nM/s, KZ = 0.5\frac{nM}{s}$, $nZ = 2$, and $d = 0.1$.



(g)

Figure 2: Plots of two molecules with an activator X^*. Parameters: $vYmax = 1\frac{nM}{s}$, $KY = 0.5nM$, $nY = 2$, $vZmax = 1nM/s, KZ = 0.5\frac{nM}{s}$, $nZ = 2$, and $d = 0.1$. The value of activated X^* was changed between 1 and 9.

2 Feed-Forward Loop

1. Write down the ODEs that describe the system:

$$\begin{aligned} \frac{dY}{dt} &= V_{Ymax}\left(\frac{X^{*nY}}{K_Y^{nY}+X^{*nY}}\right) - Ydy \\ \frac{dZ}{dt} &= V_{Zmax}\left(\frac{X^{*nY}}{K_Y^{nY}+X^{*nY}}\right)\left(\frac{Y^{nZ}}{K_Z^{nZ}+Y^{nZ}}\right) - Zdz \end{aligned}$$

2. Plot of Activator Cascade:

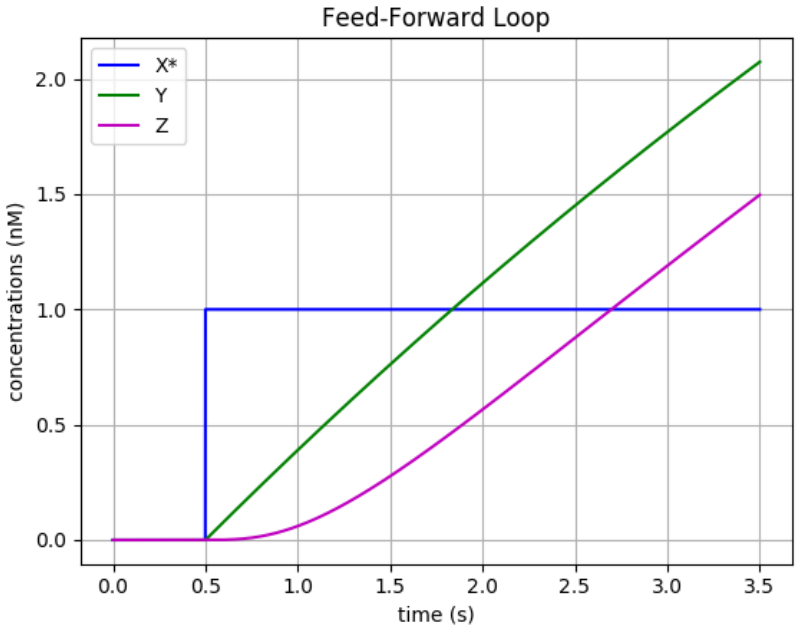


Figure 3: Plot of two molecules with an activator X^*, which also feeds forward and activates Z. Parameters: $vYmax = 1\frac{nM}{s}$, $KY = 0.5nM$, $nY = 2$, $vZmax = 1\frac{nM}{s}$, $KZX = 0.5nM$, $nZX = 2$, $KZY = 0.5nM$, $nZY = 2$, and $d = 1$.

3. Demonstrate how this feed-forward system is immune to short signals where as the cascade of activators is susceptible to it. Is a feed-forward loop immune to short signals because it delays the signals off-to-on transition or on-to-off transition? Or both?

3 PER Oscillation

1. Reproduce Figure 2 from "A model for circadian oscillations in the *Drosophila* period protein (PER)": See Figure 6

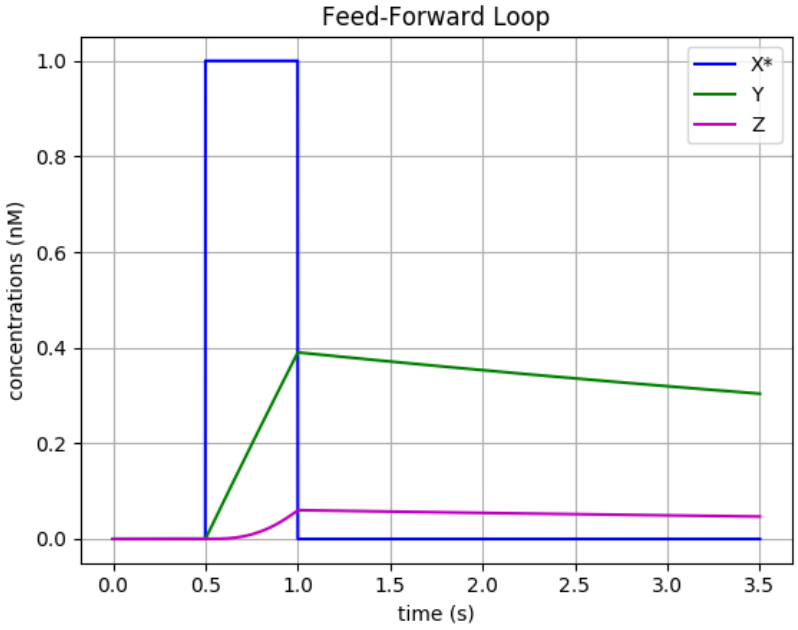


Figure 4: Plot of two molecules with an activator X^*, which also feeds forward and activates Z. In this case, the activator has been cut off after .5 seconds of being on. Parameters: $vYmax = 1\frac{nM}{s}$, $KY = 0.5nM$, $nY = 2$, $vZmax = 1\frac{nM}{s}$, $KZX = 0.5nM$, $nZX = 2$, $KZY = 0.5nM$, $nZY = 2$, and $d = 1$.

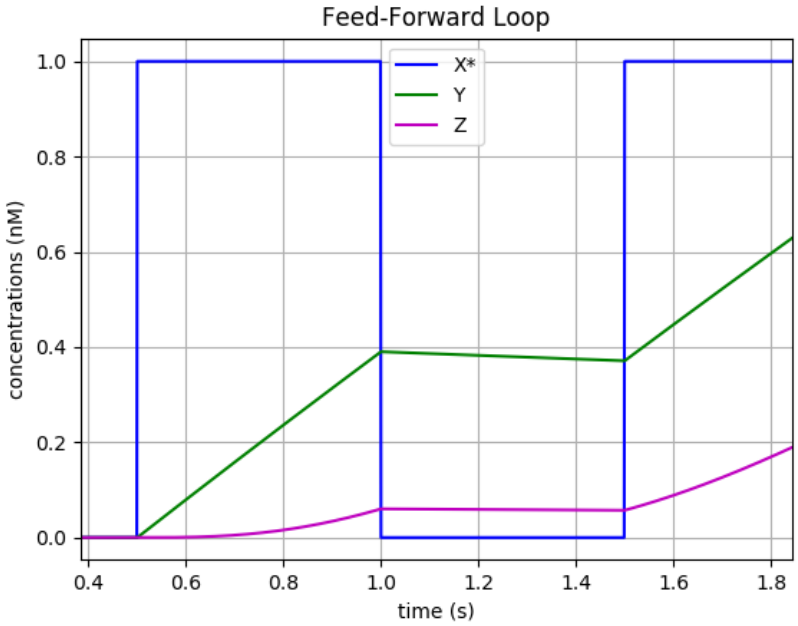


Figure 5: Plot of two molecules with an activator X^*, which also feeds forward and activates Z. In this case, the activator has been cut off after .5 seconds of being on, and then put on again after another .5 seconds. Parameters: $vYmax = 1\frac{nM}{s}$, $KY = 0.5nM$, $nY = 2$, $vZmax = 1\frac{nM}{s}$, $KZX = 0.5nM$, $nZX = 2$, $KZY = 0.5nM$, $nZY = 2$, and $d = 1$.

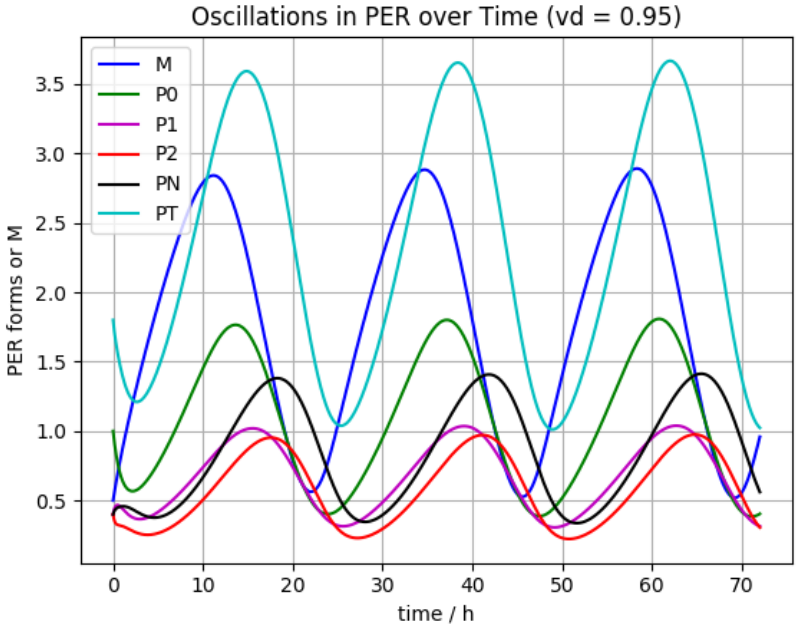
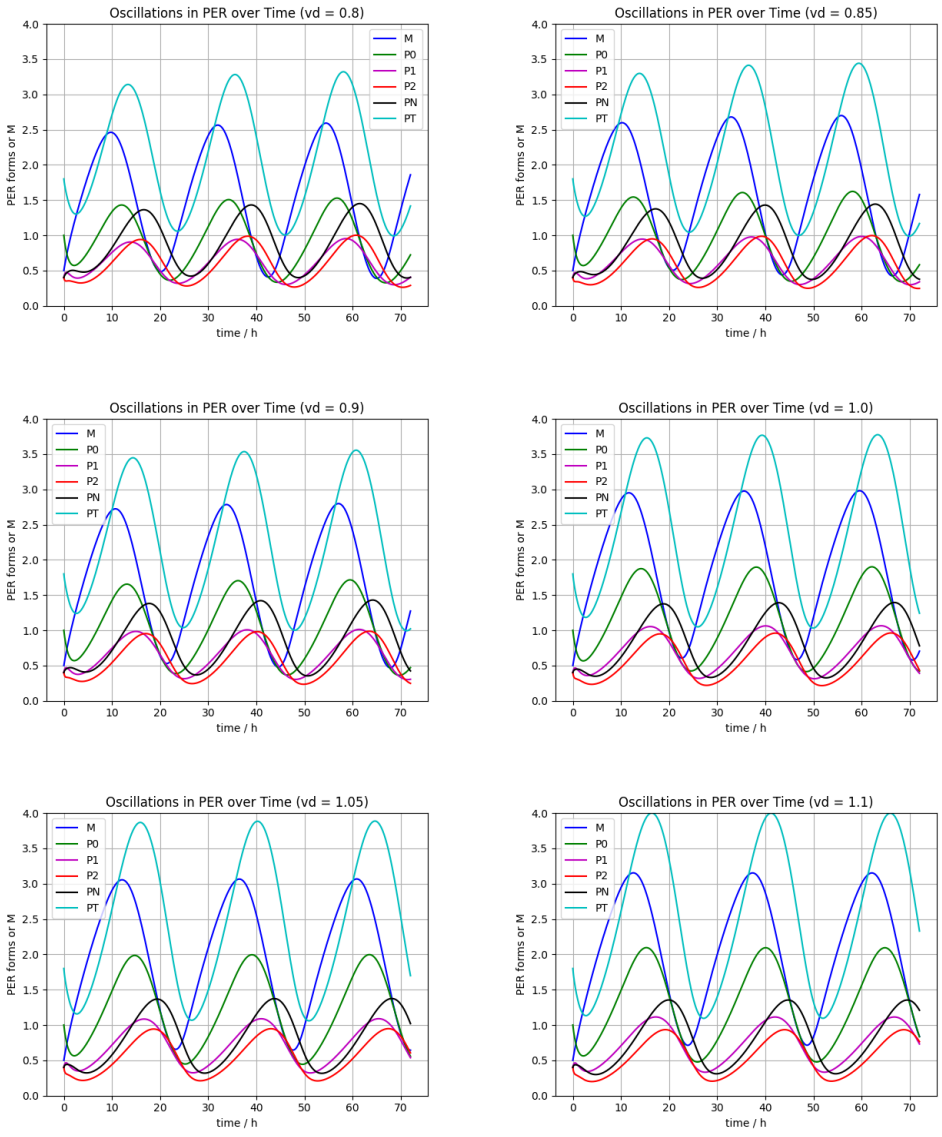


Figure 6: Reproduction of Figure 2 from "A model for circadian oscillations in the *Drosophila* period protein (PER)", by Albert Goldbeter.

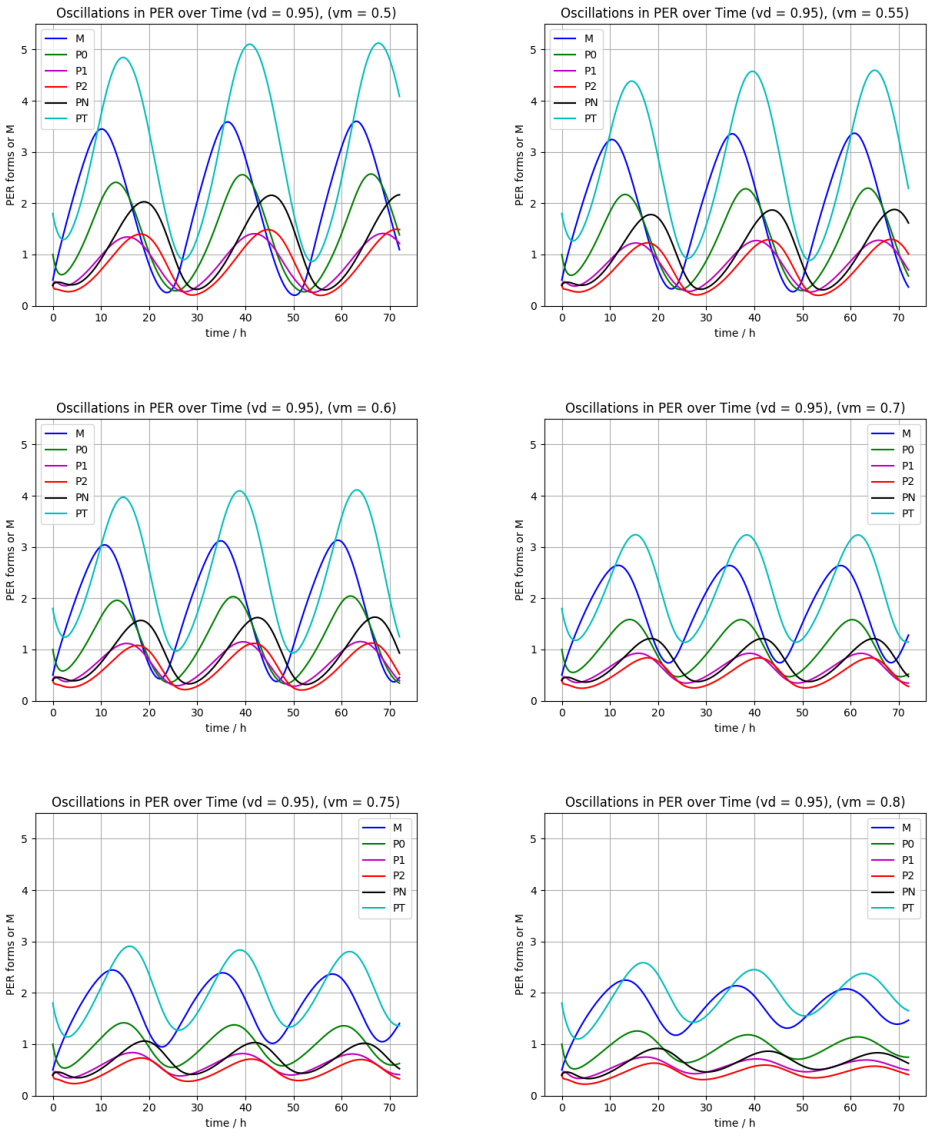
2. Varying the PER degradation rate: See Figure 7

3. Varying the mRNA degradation rate: See Figure 8



(e)

Figure 7: Plots with standard y-axis showing effect of changing v_d (the PER degradation rate) on PER oscillations. As we can see, lower values of v_d correspond to lower maximum levels of total PER (PT), while higher values of v_d correspond to higher maximum levels of total PER. As Goldbeter points out, this is counterintuitive because v_d is the degradation rate of PER, and yet increasing it also increases the maximum value of PT.



(e)

Figure 8: Plots with standard y-axis showing effect of changing v_m (the mRNA degradation rate) on mRNA oscillations. As we can see, lower values of v_m correspond to higher maximum levels of total mRNA (M), while higher values of v_m correspond to lower maximum levels of total PER. This does not follow the same pattern as varying the PER degradation rate - in fact, it is more intuitive, since higher degradation rate leads to lower maximum mRNA levels.