1. In this problem we will compare the model with single methylation site vs. double methylation sites. The model with a single methylation site is given by:

\[
\frac{d(X + X_*)}{dt} = V_R R - \frac{V_B B X_*}{K + X_*}
\]

where the activity is given by \( A = X_* \). The model with two methylation sites is given by

\[
\frac{d(X_2 + X_2\text{*})}{dt} = \frac{R V_R X_1}{X_1 + X_0} - B V_B X_2\
\frac{d(X_1 + X_1\text{*})}{dt} = B V_B X_2\text{*} + \frac{R V_R X_0}{X_1 + X_0} - \frac{R V_R X_1}{X_1 + X_0} - B V_B X_1\text{*}
\]

\[
\frac{dX_0}{dt} = -\frac{R V_R X_0}{X_0 + X_1} + B V_B X_1\text{*}
\]

and the activity is given by \( A = X_1\text{*} + X_2\text{*} \). Let \( K = 10, V_R R = 1, V_B B = 2 \). Derive the parameter sensitivities of the activities \( \left( \frac{dA}{dp_i} \right) \) for both the single and double methylation models. Comment on which parameter each model is most robust and most sensitive to.

2. Consider a toy model of protein production:

\[
\frac{dm}{dt} = f(p) - \gamma m
\]

\[
\frac{dp}{dt} = g(p) - \delta p
\]

a) Assume that there is transcriptional self-regulation \( f(p) = \frac{\alpha}{K + p} \). We now know that the mRNA transcription process and thus we want to understand the sensitivity with respect to the mRNA transcription rate \( \alpha_0 \). Compute the transfer function from \( \alpha \) to \( p \). Plot this transfer function for \( \alpha = 0.002, \beta_0 = 0.1, \gamma = 0.005, \delta = 0.001, K = 0.002 \). Compare it with the transfer function from \( \alpha_0 \) to \( p \) without regulation \( (f(p) = \alpha_0 = 0.001) \). (Note: As a reminder on how to compute these transfer functions, see BFS chapter 3 page 3-11).

b) Now assume that there is no transcriptional regulation \( f(p) = \alpha_0 \) but there is translational self-regulation such that \( g(p) = \frac{\beta m}{K + p} \). Compute the transfer function from \( \alpha_0 \) to \( p \) when \( \beta = 0.2 \). Compare again with the case with no regulation.
3. Consider a simple model of chemotaxis:

\[
\frac{dX_m}{dt} = k_R R + k_f^f(L)X^*_m - k_s X_m
\]

\[
\frac{dX^*_m}{dt} = -k_B B^p \frac{X^*_m}{K_{X^*_m} + X^*_m} - k_f^f(L)X^*_m + k_s X_m
\]

where \(X_m\) is the concentration of methylated receptor complex, and \(X^*_m\) is the concentration of activated, methylated receptor complex. Ligand concentration enters into the equation through the rate \(k_f^f(L)\). In this model, \(C\text{heR}(R)\) and \(C\text{heB}^p(B^p)\) concentrations are constant. (BFS, Section 5)

a) Pick parameter values such that \(k_B B^p > k_R R\) and plot the dynamics, doubling the ligand concentration at time \(t=20\). Compare to figure 5.12 in BFS.

b) Now assume that CheR no longer acts in saturation. Rederive the dynamics and plot. Comment on how this assumption affects adaptation.