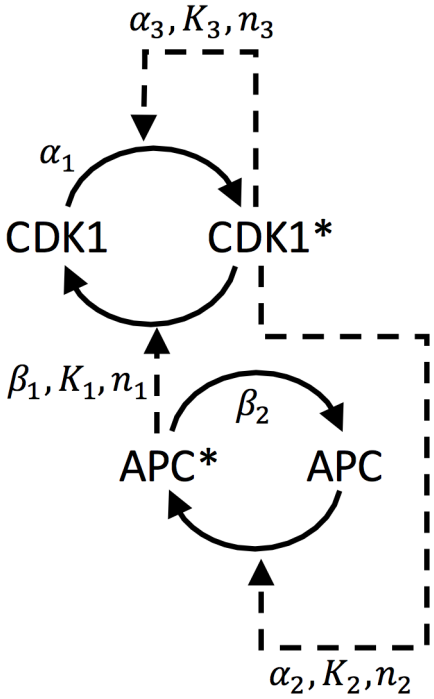
CSM2024 Take-Home Exam (100 points)

1. (50 points) Consider the following model for the interactions between two key components that regulate the cell cycle. Each constant or set of constants represents a single reaction in the model. The starred version of each protein represents the active form. The dashed lines represent the Hill function for positive regulation in the form $\alpha \cdot \frac{x^n}{K^n + x^n}$ for input x. For the activation of CDK1 to CDK1*, assume a linear contribution of first order activation with rate α_1 in addition to the Hill function for positive activation .



   (a) (10 points) Write a set of differential equations for the model (Hint: You only need two equations.)

   (b) (10 points) Make a schematic diagram that indicates positive and negative feedbacks. (Hint: There should be two nodes.)

   (c) (10 points) Take the parameter values to be $\alpha_1 = 0.02$, $\alpha_2 = \alpha_3 = 3$, $\beta_1 = 3$, $\beta_2 = 1$, $K_1 = K_2 = K_3 = 0.5$, and $n_1 = n_2 = n_3 = 3$. Plot the nullclines, flow fields, and a representative set of trajectories in the phase plane. Describe the dynamics.

   (d) (10 points) Change the parameter to $n_1 = n_2 = n_3 = 8$ while keeping everything else the same. Plot the nullclines, flow fields, and a representative set of trajectories in the phase plane. Describe the dynamics.

   (e) (10 points) What happens to the stability of the fixed points when as the parameters changed? Comment on the eigenvalues of the Jacobian matrix that describe the system. (Extra points for numerically determining the eigen values for the two cases.)

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2. (50 points) Consider a simple network of two interacting proteins X and Y that form the following network, where X, Y, and XY represent the amounts of X, Y and their complex XY respectively:

$$X \xrightarrow{\lambda_X} X+1 \qquad X \xrightarrow{X} X-1$$
$$Y \xrightarrow{\lambda_Y} Y+1 \qquad Y \xrightarrow{Y} Y-1$$
$$X,Y,XY \xrightarrow{c\cdot X\cdot Y} X-1,Y-1,XY+1 \qquad XY \xrightarrow{XY} XY-1$$

Protein X is a transcription factor that acts as a repressor for the expression of a third protein Z, which we will add to the model in part (d). Protein Y binds to X to form a complex XY that is transcriptionally inactive. The production rates λ_X and λ_Y can be taken to be 50 molecules/s and 30 molecules/s respectively, and c is 50 /molecule/s.

(a) (10 points) Compute the mean steady state values of X, Y, and XY and compare these with the expected mean values of X and Y in the absence of complexation. How would you describe Y's regulation of X?

The production and degradation of X, Y, and the complex XY can be described by the following equations:

$$\frac{dX}{dt} = \lambda_X - X - c\cdot X\cdot Y$$
$$\frac{dY}{dt} = \lambda_Y - Y - c\cdot X\cdot Y$$
$$\frac{dXY}{dt} = c\cdot X\cdot Y - XY$$

At steady state, the rates are 0:

$$0 = \lambda_X - X - c\cdot X\cdot Y \implies \lambda_X = X + c\cdot X\cdot Y$$
$$0 = \lambda_Y - Y - c\cdot X\cdot Y \implies \lambda_Y = Y + c\cdot X\cdot Y$$
$$0 = c\cdot X\cdot Y - XY \implies XY = c\cdot X\cdot Y$$

In the absence of complexation:
From above, we know that $XY = c\cdot X\cdot Y$. Substituting this in the equations for X and Y gives:

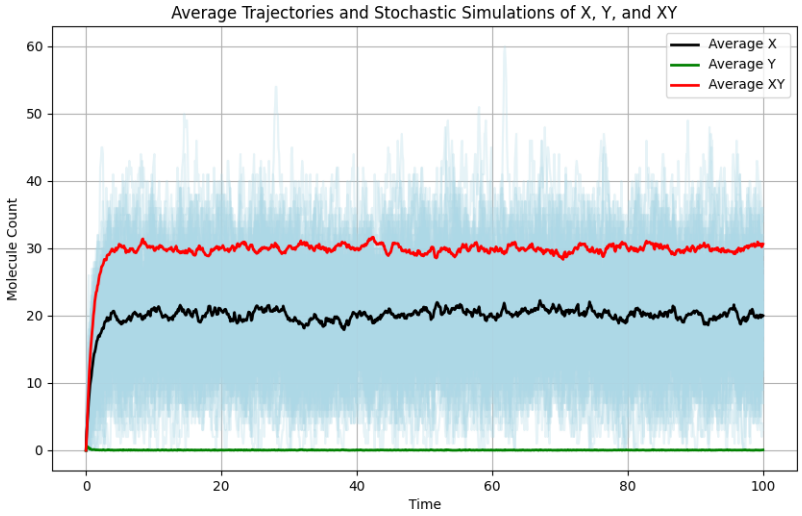
$$\lambda_X = X + XY$$
$$\lambda_Y = Y + XY$$

In the absence of complexation, we have that $XY = 0$:

$$\lambda_X = X = 50$$
$$\lambda_Y = Y = 30$$

So, the expected mean steady state values of X, Y, and XY with no complexation are $\langle X_{ST}\rangle = 50, \langle Y_{ST}\rangle = 30$, and $\langle XY_{ST}\rangle = 0$. Running both a Gillespie simulation and ODE solver confirms these values for this scenario, with the mean values of X, Y, and XY computed at $49.98 \approx 50$, $29.99 \approx 30$, and 0, respectively, for both methods.

With complexation:
Using our model steady state equations from above, we can simulate the mean values for X, Y, and XY using a Gillespie algorithm. As an additional check, the equations can be solved using an ODE solver. The plot of the simulation is below, with the mean values of X, Y, and XY with complexation calculated to be 20.0, 0.03, and 29.9, respectively, with both methods.



Y's regulation of X:
When complexation is present, we see a decrease in the amounts of both X and Y, and an increase in the amount of XY. Since Y binds to X to form the complex XY, this means that Y is decreasing the amount of available X and thus Y is acting as a negative regulator for X.

(b) (10 points) Compute the steady state variances in X, Y, and XY, and compare them to what would be expected from a simple birth-death process with the same mean value.

With complexation:
The Gillespie algorithm simulation gave variances of $\text{var}_X = 49.3$, $\text{var}_Y = 0.04$, and $\text{var}_{XY} = 30.2$.
Without complexation/ Simple birth-death process:
Removing complexation reduces the complexity of the model to a simple birth-death process for X and Y. The variances in this case are approximately $\text{var}_X = 50$ and $\text{var}_Y = 30$.
Comparison:
So, we see that var_X stays about the same between both cases, although there is a slight decrease in the variance of X when complexation is present. This decrease is most likely due to the fact that the formation of the complex XY reduces the fluctuations in the free X molecules, since some X is bound in the complex.
We see a more substantial decrease in var_Y in the presence of complexation, which is most likely because Y is mostly consumed in the complex XY, leaving very few free Y molecules that can fluctuate.

(c) (5 points) Compare the observed probability that $X < 4$ from your stochastic trajectory with the expected probability from a simple birth-death process with the same mean value of X. How is this result related to your findings in (b)?
With complexation, we have that the observed probability of $X < 4$ is 0.0108. However, with the simple birth-death process, this probability is 0.013. So, the observed probability of $X < 4$ is greater in the absence of complexation. This relates to the previous finding, as since there is higher variance and fluctuation in X in the absence of complexation, since there is more free X, then the probability of X being in a state farther away than the mean makes sense.

(d) (10 points) Now consider an additional component Z, whose production is regulated in an all-or-none fashion by X:

$$Z \xrightarrow{f(X)} Z + 1 \qquad\qquad Z \xrightarrow{Z} Z - 1,$$

where $f(X) = \lambda_Z \Theta(X < 4)$ and Θ is the Heaviside function, which evaluates to 1 if the argument is True and 0 if the argument is False. Take λ_Z to be 1000 molecules/second. Compute a stochastic

trajectory of the system of about 1000 time units and plot the amount of Z vs. time. Describe your observations. (*Hint:* In case you are trying to use BNGL for problem 2 on the Long Answer section, here is a BNGL model that implements a Heaviside function for a stochastic model along with a Jupyter notebook that can run it).

(e) (10 points) Suppose that Z is itself a transcription factor that induces expression of genes that switches the cell to a different phenotype. We will refer to the phenotype with low Z expression as A and the phenotype with high Z expression as B. Assume that phenotype B persists as long as $Z > 4$. Run a trajectory of at least 20,000 time units and determine the distribution of lifetimes for each phenotype. Plot the resulting distributions and compute the mean lifetime of each state. For each state what type of distribution is observed?

(f) (5 points) What are the biological implications of the distributions for each state?