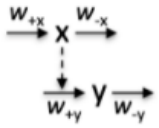
CELLULAR AND SYSTEMS MODELING - HW5

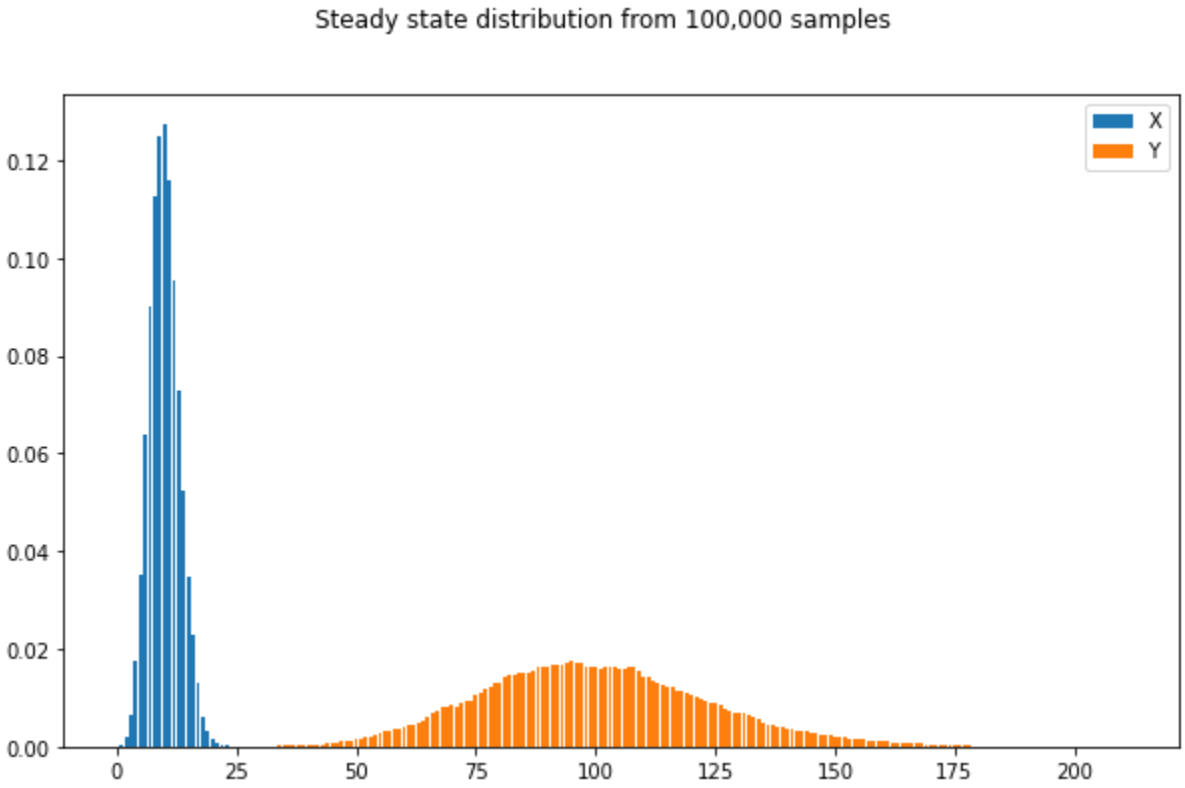
Student: Shu-Ting Cho (shc167@pitt.edu)

1. Stochastic simulation of transcription and translation. (15 points)



Consider the above mechanism to model production of a gene's transcript (x) and protein (y). The w's are rate constants for production and degradation. Assume the the rate of protein synthesis is linear with respect to x. Assume the following values for the rate constants: $w_{-x} = w_{-y} = 1\ \mathrm{s}^{-1}$ and $w_{+x} = w_{+y} = 10\ \mathrm{s}^{-1}$.

(a) Perform stochastic simulations to determine the steady state distributions for both x and y. Show that you obtain the correct means and variances for each. (Note that $\mathrm{var}(y) = \bar{y}\left(1 + \frac{w_{+y}}{w_{-x}+w_{-y}}\right)$).



Mean:
X: 10.023164; Y: 99.795677
(E[X]=10, E[Y]=100)
Var:
X: 9.66858343; Y: 559.24653511
(var(X)=10, $var(y) = \bar{y}\left(1 + \frac{10}{1+1}\right) = 99.795677 * 6 = 598.774062$)
The mean and variance values that I obtained are correct because they are close to the expected values.

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(b) Compute the CV and Fano factor for three different sets of parameters (w_{+x}, w_{+y}): (10,10) (same as above), (100,1), and (1,100). Explain your results.

CV = std(I)/<I>

Fano factor = var(I)/<I>

Explacted values for Fano factors

1. (10,10)
   X: 10/10=1
   Y: 600/100=6
2. (100,1)
   X: 100/100=1
   Y: 150/100=1.5
3. (1,100)
   X: 1/1=1
   Y: 5100/100=51

	(10,10)	(100,1)	(1,100)
CV(X)	0.32157922	0.09941446	0.99594862
CV(Y)	0.25082382	0.12462607	0.72400138
Fano(X)	1.0327917	0.99217401	1.01870523
Fano(Y)	6.27158188	1.56027787	53.8472019

My results are close to the calculated explacted values.

(c) Now add negative autoregulation to the model by assuming that protein y modulates the rate of x production through a Hill function with half-maximal repression at K = 50 molecules with the same maximal rate of x transcription as you used in part (a). Compute the Fano factor for steady state expression of y for n = 1, 2, and 6. Explain your results.

	n=1	n=2	n=6
Fano(X)	0.85873665	0.76583199	0.72801381
Fano(Y)	4.26908395	3.30302549	2.14468163

They all have the same mean for different n values. Fano factor gets lower for increasing n, which means the variance is smaller. This is because larger n gives a “switch-like” behavior for negative regulation. When the concentration of Y reaches the threshold, X production rate switched off by protein Y if n is big, results in a relatively steady concentration of x.

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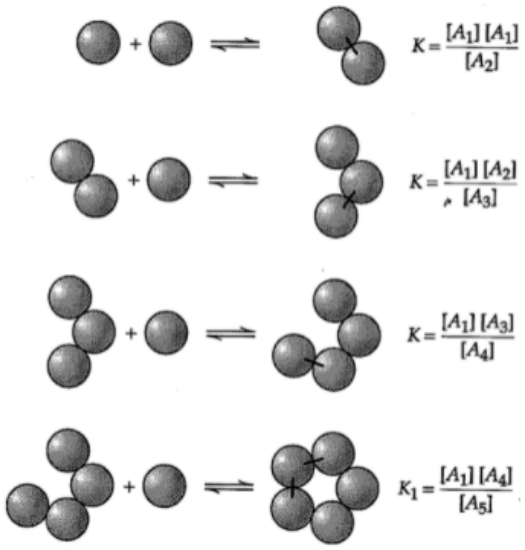
2. One ring to bind them all. (15 points)



In this problem we will consider the ring closure mechanism for a ring composed of five monomers as shown above. The first three binding steps has the same dissociation constant, K, which can be taken as 1 μM. The last step has dissociation constant K1, which can be taken as 10^{-10} μM.

(a) Determine the fraction of monomers that are in rings (the species A_5) when the total monomer concentration is 1 μM.

$$\frac{[A_1][A_1]}{[A_2]} = 1 \Rightarrow [A_2] = [A_1]^2$$

$$\frac{[A_1][A_2]}{[A_3]} = \frac{[A_1][A_1]^2}{[A_3]} = 1 \Rightarrow [A_3] = [A_1]^3$$

$$\frac{[A_1][A_3]}{[A_4]} = \frac{[A_1][A_1]^3}{[A_4]} = 1 \Rightarrow [A_4] = [A_1]^4$$

$$\frac{[A_1][A_4]}{[A_5]} = \frac{[A_1][A_1]^4}{[A_5]} = 10^{-10} \Rightarrow [A_5] = 10^{10} \times [A_1]^5$$

$$Total\ monomer\ conc. = 1\mu M$$

$$= [A_1] + 2[A_2] + 3[A_3] + 4[A_4] + 5[A_5]$$

$$= [A_1] + 2[A_1]^2 + 3[A_1]^3 + 4[A_1]^4 + 5 \times 10^{10} \times [A_1]^5 = 1\mu M$$

$$\Rightarrow [A_1] = 0.00723712$$

$$\Rightarrow \frac{5[A_5]}{[A_1]+2[A_2]+3[A_3]+4[A_4]+5[A_5]} = \frac{5\times10^{10}\times[A_1]^5}{[A_1]+2[A_1]^2+3[A_1]^3+4[A_1]^4+5\times10^{10}\times[A_1]^5} = 99.265698\%$$

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(b) Determine the total monomer concentration at which the fraction of monomers in rings is 0.5. Compare this saturation curve with that of a single-site binding curve with the same half-maximum value.

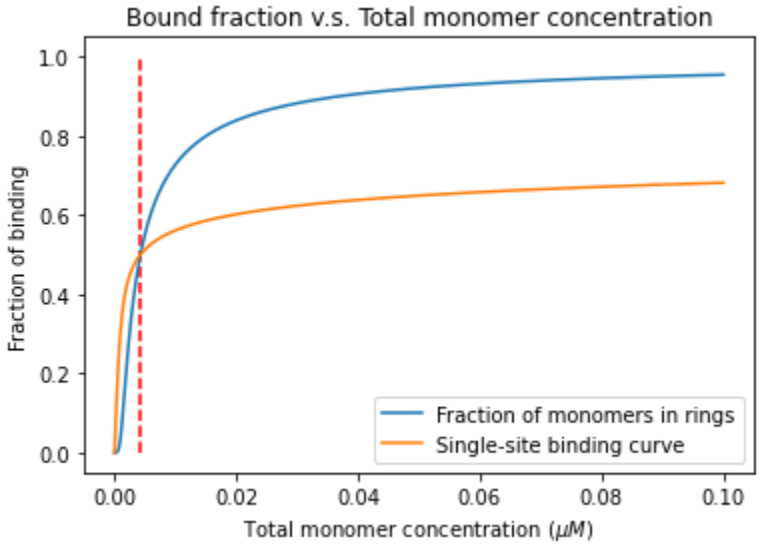
$$0.5 = \frac{5[A_5]}{[A_1]+2[A_2]+3[A_3]+4[A_4]+5[A_5]} = \frac{5\times10^{10}\times[A_1]^5}{[A_1]+2[A_1]^2+3[A_1]^3+4[A_1]^4+5\times10^{10}\times[A_1]^5}$$

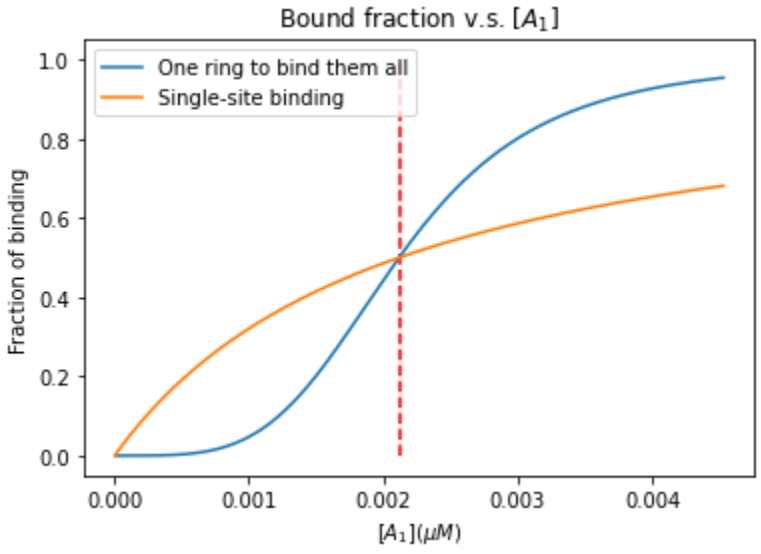
$$\Rightarrow [A_1] = 0.00211698$$

$$Total\ monomer\ conc.$$

$$= [A_1] + 2[A_1]^2 + 3[A_1]^3 + 4[A_1]^4 + 5 \times 10^{10} \times [A_1]^5$$

$$= 0.00425195$$





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(c) Use the relationship between the free energy of binding and the equilibrium constant for binding to rationalize the difference between K and K_1. Does your argument suggest that the value of K_1 should be different than the one given, and if so, state what you think the reason for the difference might be?

Bond Energy is $\Delta G° = -R\ T\ \ln K_{eq}$

$K_{eq} = \exp(-\Delta G°/RT)$

From 4 monomers state to 5 monomers ring will form two bonds, which release more energy than forming one bond. Thus, K_1 for forming two bonds should be larger than K for forming one bond.

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3. Positive autoregulation. (20 points)

In this problem we consider a nonlinear form of positive autoregulation in transcription in which the protein expressed by gene X binds cooperatively to its promoter with an affinity of K and a cooperativity of n.

The differential equation for this system can be written as

$$\frac{dX}{dt} = \beta_1 + \beta_2 \frac{(X/K)^n}{1+(X/K)^n} - \alpha X.$$

(a) Taking $\alpha = \beta_1 = 1\ s^{-1}$, $\beta_2 = 20\ s^{-1}$,, and $K = 10$, find all of the steady states of the system for $n = 1$ and for $n = 6$. [Note that here concentrations are taken to be in units of Molecues and hence can be considered dimensionless.]

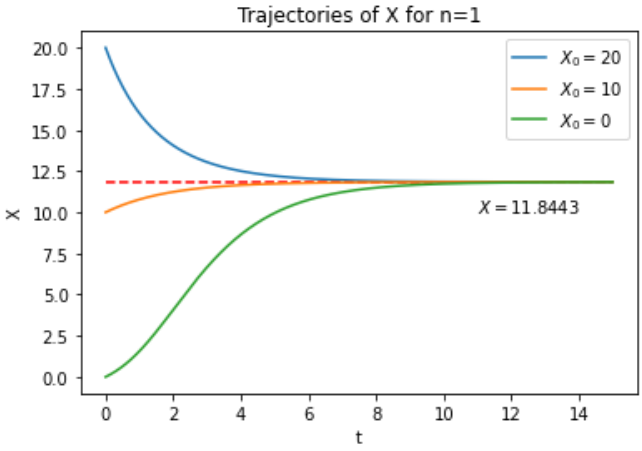
$$\beta_1 + \beta_2 \frac{(X/K)^n}{1+(X/K)^n} - \alpha X = (1) + (20)\frac{(X/(10))^n}{1+(X/(10))^n} - (1)X$$

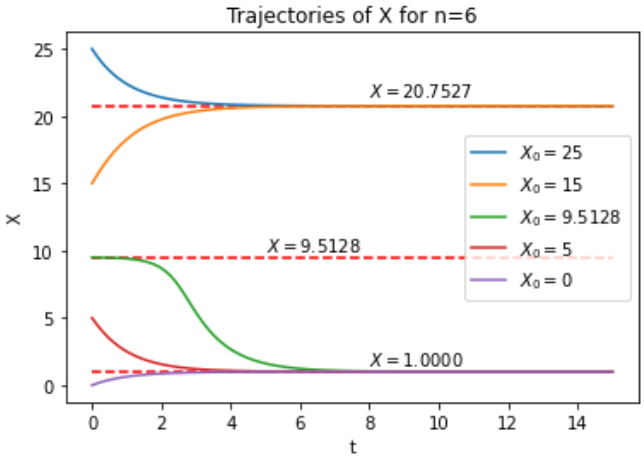
n=1: $$(1) + (20)\frac{(X/(10))^1}{1+(X/(10))^1} - (1)X = 0 \Rightarrow X = \frac{11}{2} + \frac{\sqrt{161}}{2} \approx 11.84428877022472$$

n=6: $$(1) + (20)\frac{(X/(10))^6}{1+(X/(10))^6} - (1)X = 0$$

$$\Rightarrow X = 1.000020002380401\ or\ 9.51284349619874\ or\ 20.752727408104253$$

(b) Plot representative trajectories of X to reach each steady state for both values of n.





Unstable steady-state at x=9.5128

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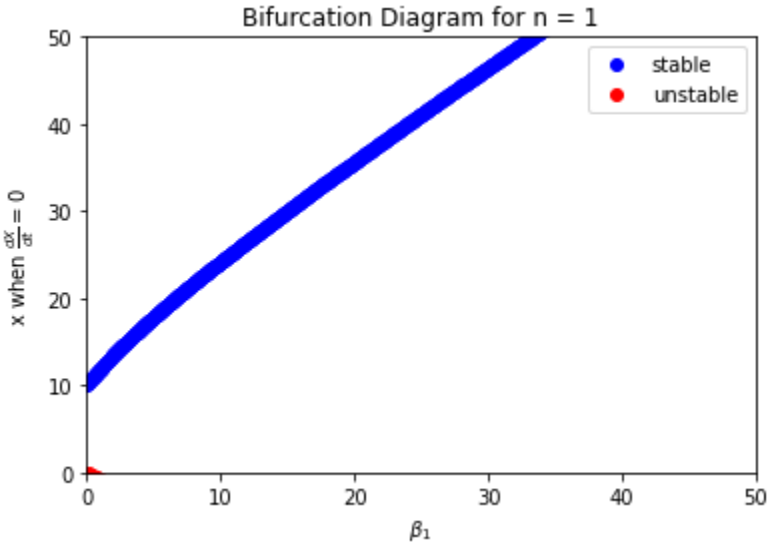
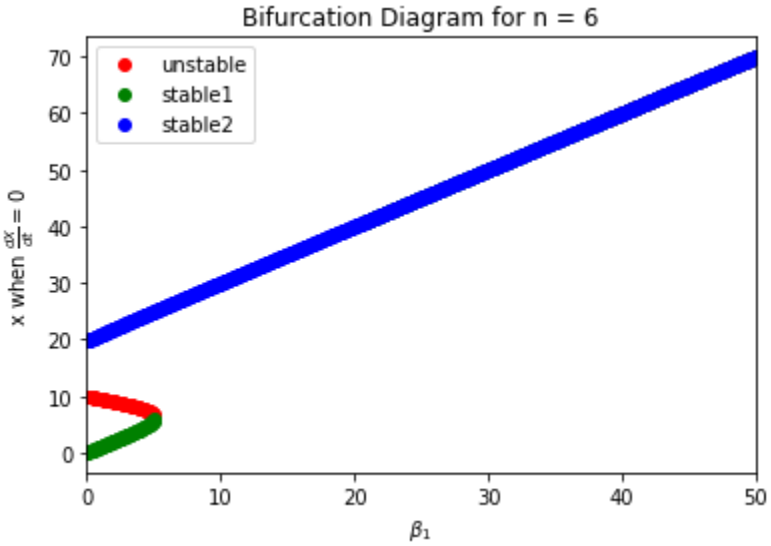
(c) Using β_1 as a bifurcation parameter, make a bifurcation plot with respect to the steady state X amount for both values of n.

$\beta_1 + \beta_2 \frac{(X/K)^n}{1+(X/K)^n} - \alpha X$, changing β_1





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4. Analysis of a 2D ODE system. (20 points)

Consider the following 2D equations for a model describing an enzyme substrate and its product.

$$\frac{dS}{dt} = v_0 - k_1 P^2 S$$
$$\frac{dP}{dt} = k_1 P^2 S - k_2 P$$

(a) Find an expression for the fixed point(s) of the system as a function of k_1, k_2, and v_0.

$$\frac{dS}{dT} = v_0 - k_1 P^2 S = 0$$
$$\frac{dP}{dT} = k_1 P^2 S - k_2 P = 0$$

$$\Rightarrow k_1 P^2 S = v_0 \Rightarrow P^2 = \frac{v_0}{Sk_1} \Rightarrow P = \sqrt{\frac{v_0}{Sk_1}}$$

$$k_1 P^2 S - k_2 P = k_1 \frac{v_0}{Sk_1} S - k_2 \sqrt{\frac{v_0}{Sk_1}} \Rightarrow v_0 = k_2 \sqrt{\frac{v_0}{Sk_1}}$$

$$\Rightarrow v_0 = \frac{k_2^2}{Sk_1} \Rightarrow S = \frac{k_2^2}{k_1 v_0}$$

$$v_0 - k_1 P^2 S = v_0 - k_1 P^2 \frac{k_2^2}{k_1 v_0} = v_0 - P^2 \frac{k_2^2}{v_0} = 0 \Rightarrow v_0 = P^2 \frac{k_2^2}{v_0}$$

$$\Rightarrow v_0^2 = P^2 k_2^2 \Rightarrow P = \pm \frac{v_0}{k_2}$$

$$fixed\ points(S, P) = \left(\frac{k_2^2}{k_1 v_0}, \pm \frac{v_0}{k_2}\right)$$

(b) Write an expression for the Jacobian evaluated at the fixed point(s).

Jacobian matrix:

$$\begin{pmatrix} \frac{\partial \dot{S}}{\partial S} & \frac{\partial \dot{S}}{\partial P} \\ \frac{\partial \dot{P}}{\partial S} & \frac{\partial \dot{P}}{\partial P} \end{pmatrix} = \begin{pmatrix} -k_1 P^2 & -2k_1 SP \\ k_1 P^2 & 2k_1 SP - k_2 \end{pmatrix}$$

fixed point $(S, P) = \left(\frac{k_2^2}{k_1 v_0}, \pm \frac{v_0}{k_2}\right)$

$$\Rightarrow \begin{pmatrix} -k_1 \frac{v_0^2}{k_2^2} & -2k_1 \frac{k_2^2}{k_1 v_0}\left(\pm \frac{v_0}{k_2}\right) \\ k_1 \frac{v_0^2}{k_2^2} & 2k_1 \frac{k_2^2}{k_1 v_0}\left(\pm \frac{v_0}{k_2}\right) - k_2 \end{pmatrix}$$

$$= \begin{pmatrix} -\frac{k_1 v_0^2}{k_2^2} & \pm 2k_2 \\ \frac{k_1 v_0^2}{k_2^2} & k_2 \text{ or } -3k_2 \end{pmatrix}$$

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(c) Taking $k_1 = v_0 = 1$, analyze the stability of the fixed point(s) as a function of k_2. How many different stability classes do you find?

$k_1 = v_0 = 1$

$fixed\ points(S, P) = (k_2^2, \pm \frac{1}{k_2})$

Jacobian Matrix $= \begin{pmatrix} -\frac{k_1 v_0^2}{k_2^2} & \pm 2k_2 \\ \frac{k_1 v_0^2}{k_2^2} & k_2 \text{ or } -3k_2 \end{pmatrix} = \begin{pmatrix} -\frac{1}{k_2^2} & \pm 2k_2 \\ \frac{1}{k_2^2} & k_2 \text{ or } -3k_2 \end{pmatrix}$

eigen value λ for $P = -\frac{1}{k_2} \Rightarrow \begin{matrix} -2k_2 \\ k_2 \end{matrix}$

$\det|J - I\lambda| = 0 \Rightarrow (-\frac{1}{k_2^2} - \lambda)(k_2 - \lambda) + 2k_2 \cdot \frac{1}{k_2^2} = 0$

$\Rightarrow -\frac{1}{k_2} + \frac{\lambda}{k_2^2} - k_2\lambda + \lambda^2 + \frac{2}{k_2} = 0$

$\Rightarrow \lambda^2 + (\frac{1}{k_2^2} - k_2)\lambda + \frac{1}{k_2} = 0$

$\Rightarrow k_2^2\lambda^2 + (1 - k_2^3)\lambda + k_2 = 0$

$\lambda = \frac{k_2^3 - 1 \pm \sqrt{k_2^6 - 2k_2^3 + 1 - 4k_2^3}}{2k_2^2}$

$= \frac{k_2^3 - 1 \pm \sqrt{k_2^6 - 6k_2^3 + 1}}{2k_2^2}$ ※

λ for $P = \frac{1}{k_2} \Rightarrow \begin{matrix} 2k_2 \\ -3k_2 \end{matrix}$

$\Rightarrow (-\frac{1}{k_2^2} - \lambda)(-3k_2 - \lambda) - 2k_2 \cdot \frac{1}{k_2^2} = 0$

$\Rightarrow \frac{3}{k_2} + \frac{\lambda}{k_2^2} + 3k_2\lambda + \lambda^2 - \frac{2}{k_2} = 0$

$\Rightarrow k_2^2\lambda^2 + (3k_2^3 + 1)\lambda + k_2 = 0$

$\lambda = \frac{-3k_2^3 - 1 \pm \sqrt{9k_2^6 + 2k_2^3 + 1}}{2k_2^2}$ ※

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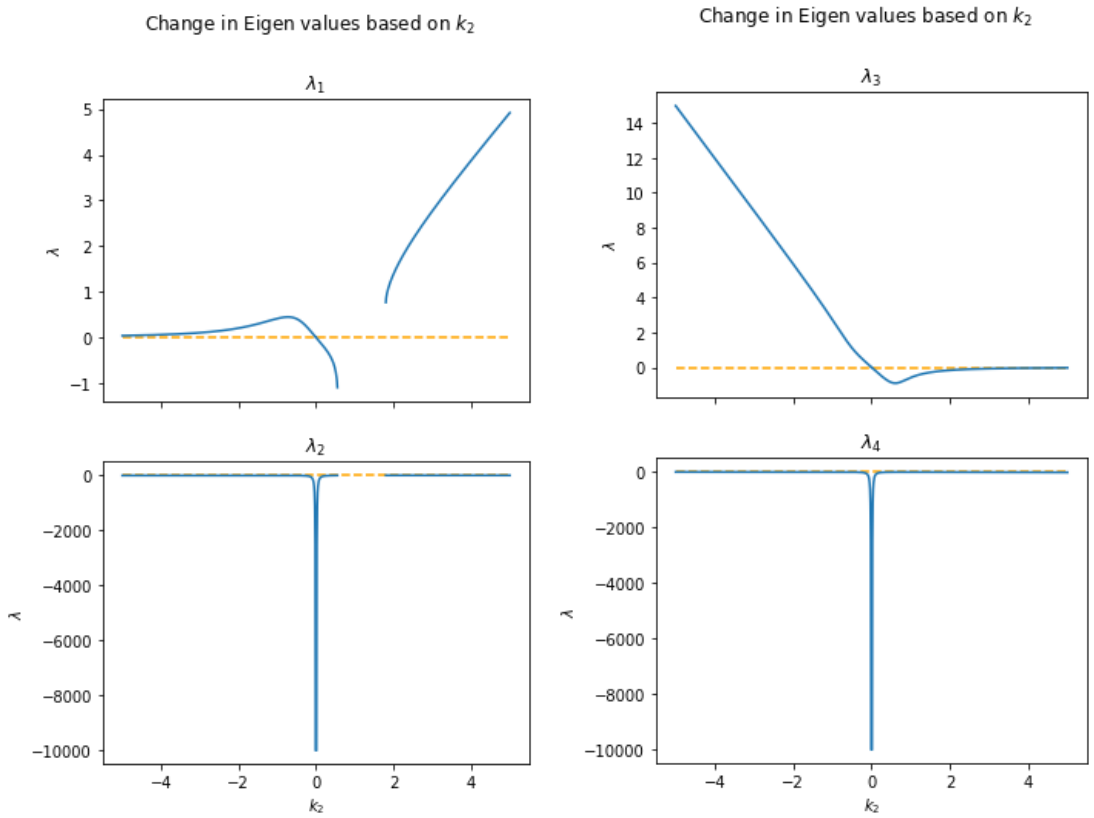
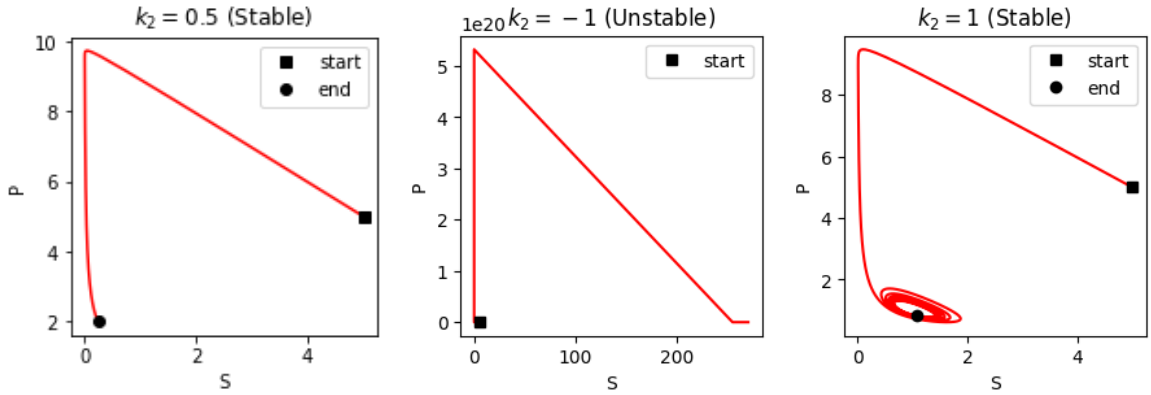


Based on the plot we can see

1. k_2 region (e.g., k_2=0.5) that will give real and negative values for both λ, thus is stable.
2. k_2 regions (e.g., k_2=-1) that will give real and mixed positive and negative values for the two λ, thus is unstable.
3. k_2 regions (e.g., k_2=1) that will give complex and negative values for the two λ, thus is stable.

(d) Plot a representative trajectory for each region of stability along k_2.



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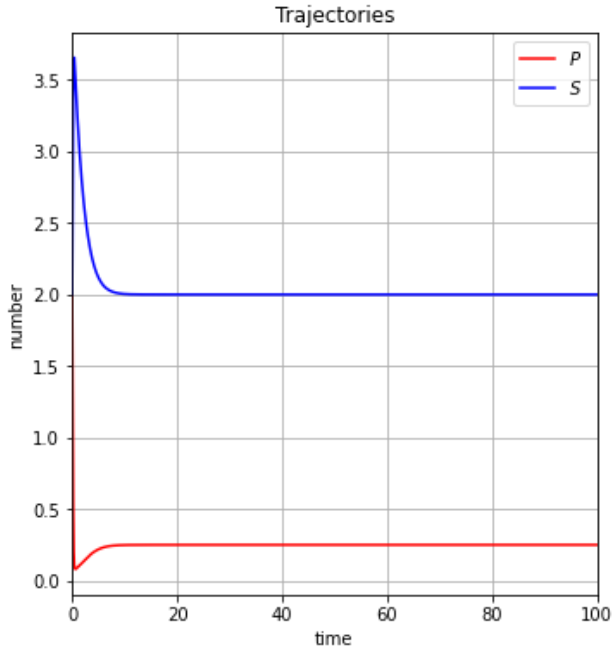
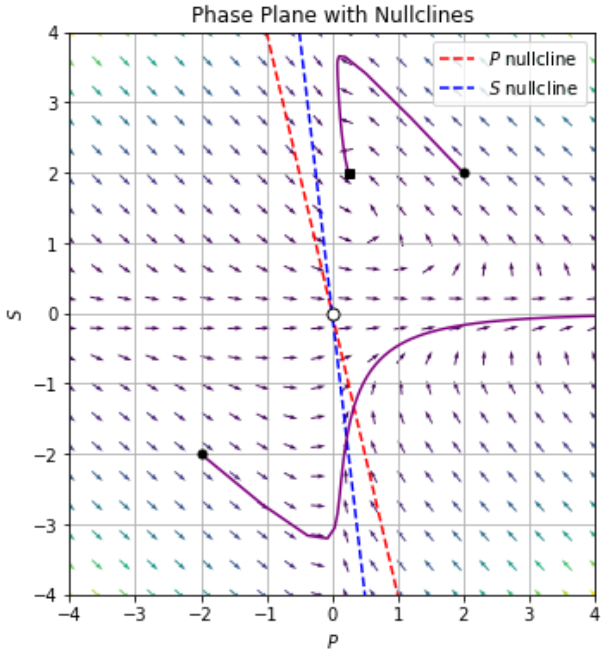
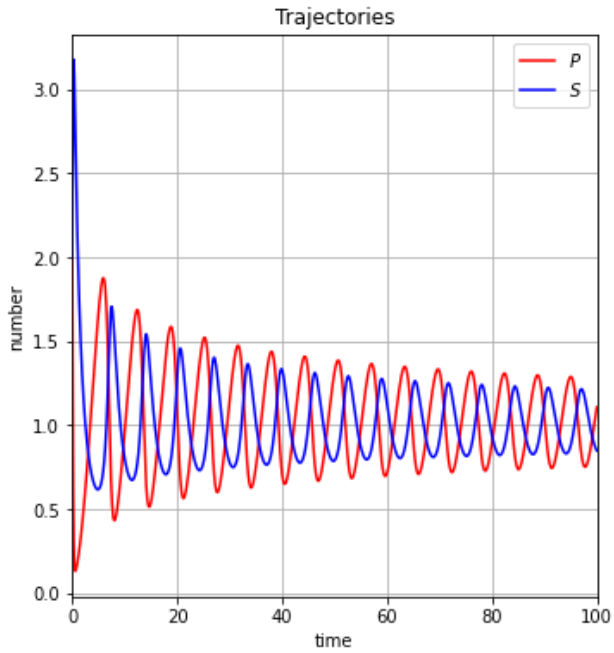
(e) Plot the nullclines for a representative point in each region.

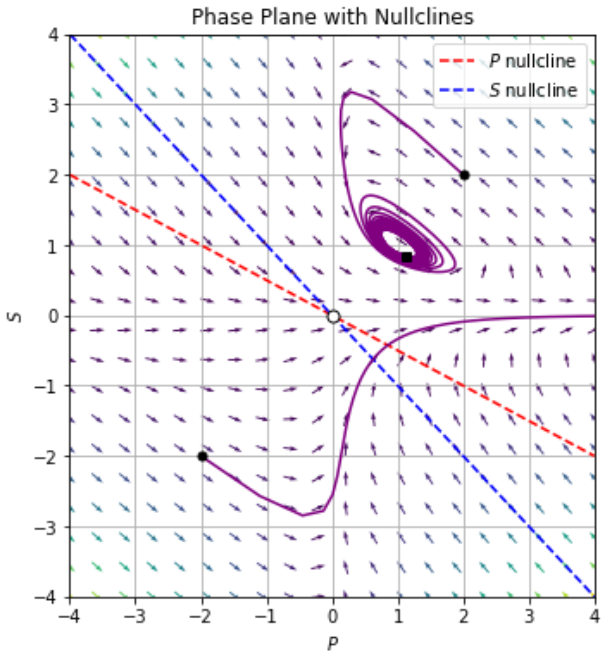
k_2=0.5, eigenvalues are [-2.78077641, -0.71922359]





k_2=1, eigenvalues are [-9.71445147e-17+1.j, -9.71445147e-17-1.j]





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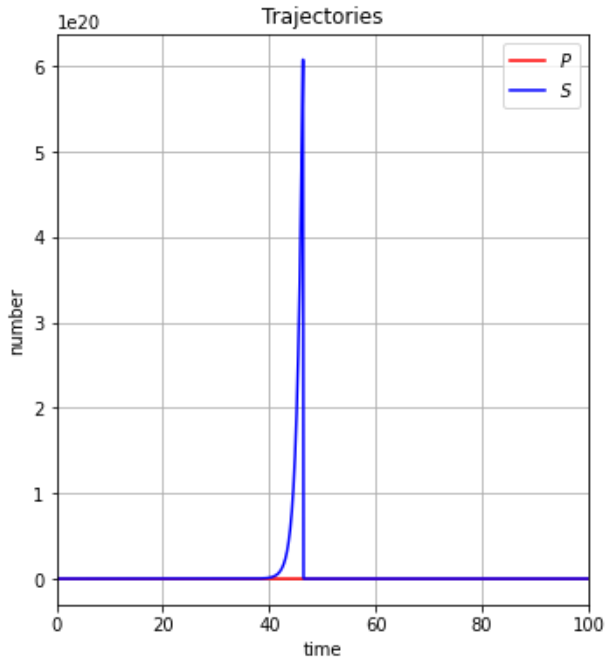
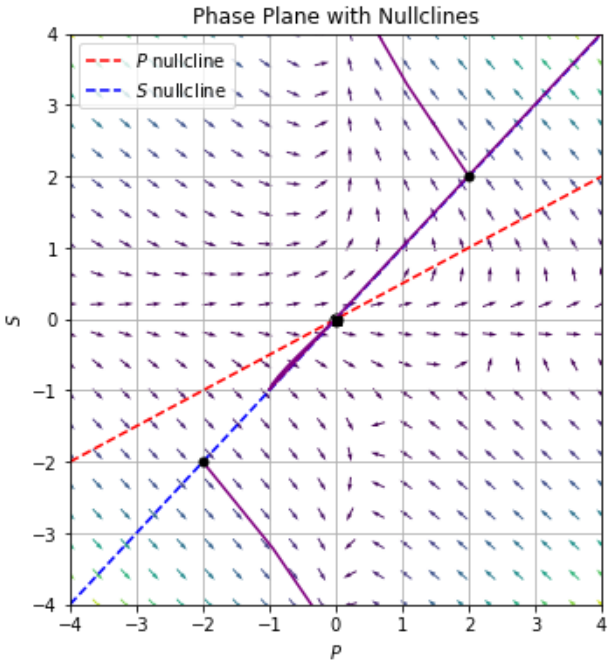
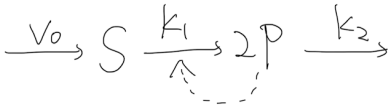
k_2=-1, eigenvalues are [0.41421356 -2.41421356]





(f) Draw a diagram of this system using the conventions in which solid arrows represent chemical transformations and dashed arrows represent catalysis. What types of feedback are evident from your diagram and how to these give rise to the dynamics you observe?



Based on my diagram, the production of P is a positive feedback loop.
When the degradation of P is low (small k_2), the amount of P will be high, and that will stimulate the production of P more.
When k_2 is high, the degradation of P will be fast, and the amount of P will decrease because of lower stimulation from P.