1. A stochastic Lotka-Volterra (predator-prey) model is given by the following equations for the abundance of two species, Y_1 and Y_2,

$$Y_1 \xrightarrow{c_1} 2Y_1$$
$$Y_1 + Y_2 \xrightarrow{c_2} 2Y_2$$
$$Y_2 \xrightarrow{c_3} \emptyset.$$

- Explain why this is called predator-prey model. What is the corresponding ODE model? Given this interpretation, explain whether species 1 or species 2 can exist in isolation, i.e. in the absence of the other species.
- Use the Gillespie algorithm to simulate trajectories from the model. Use $c_1 = 1,\ c_2 = 0.005,\ c_3 = 0.6$.
- Changing which parameter will make it more likely for species 1 to go extinct? What about species 2 ? Change these parameters gradually to verify your hypothesis in simulations.

First Part:
We can consider Y_1 as prey and Y_2 as predator as follows:

$$Y_1 \xrightarrow{c_1} 2Y_1$$

This can be considered as growth equation of prey species Y_1 by rate c_1.

$$Y_1 + Y_2 \xrightarrow{c_2} 2Y_2$$

This explains growth rate of predator species Y_2 by consumption of prey species Y_1 at rate c_2.

And finally,

$$Y_2 \xrightarrow{c_3} \emptyset.$$

is the death rate of predator species Y_2 by rate c_3.
Since there is interdependence between species 1 and species 2 with oscillations, this is a predator-prey model.

For corresponding differential equation
Prey Species: $dY_1 = c_1 Y_1 dt$ and $dY_1 = -c_2 Y_1 Y_2 dt$
Predator Species: $dY_2 = c_2 Y_1 Y_2 dt$ and $dY_2 = -c_3 Y_2 dt$
Hence,

$$\frac{dY_1}{dt} = c_1 Y_1 - c_2 Y_1 Y_2$$
$$\frac{dY_2}{dt} = -c_3 Y_2 + c_2 Y_1 Y_2$$

is the corresponding ODE model.
Species 2 can not remain in isolation as production of species 2 is from species 1. But since there is no direct sink(death rate) for species 1, so species 1 can remain in isolation. If growth rate of species 2 is very low and or death death of species 2 is high then species 1 grows exponentially. Hence species 1 can remain in isolation.

Second Part:

Here, I used Gillespie algorithm to simulate the trajectories for the model. I used the given rates $c_1 = 1,\ c_2 = 0.005,\ c_3 = 0.6$.. Here are 6 different trajectories for different initial values of number of species Y_1 and Y_2.

Initial Values for Y_1 and Y_2

Y_1	25	50	100	100	200	200
Y_2	50	100	100	200	100	400

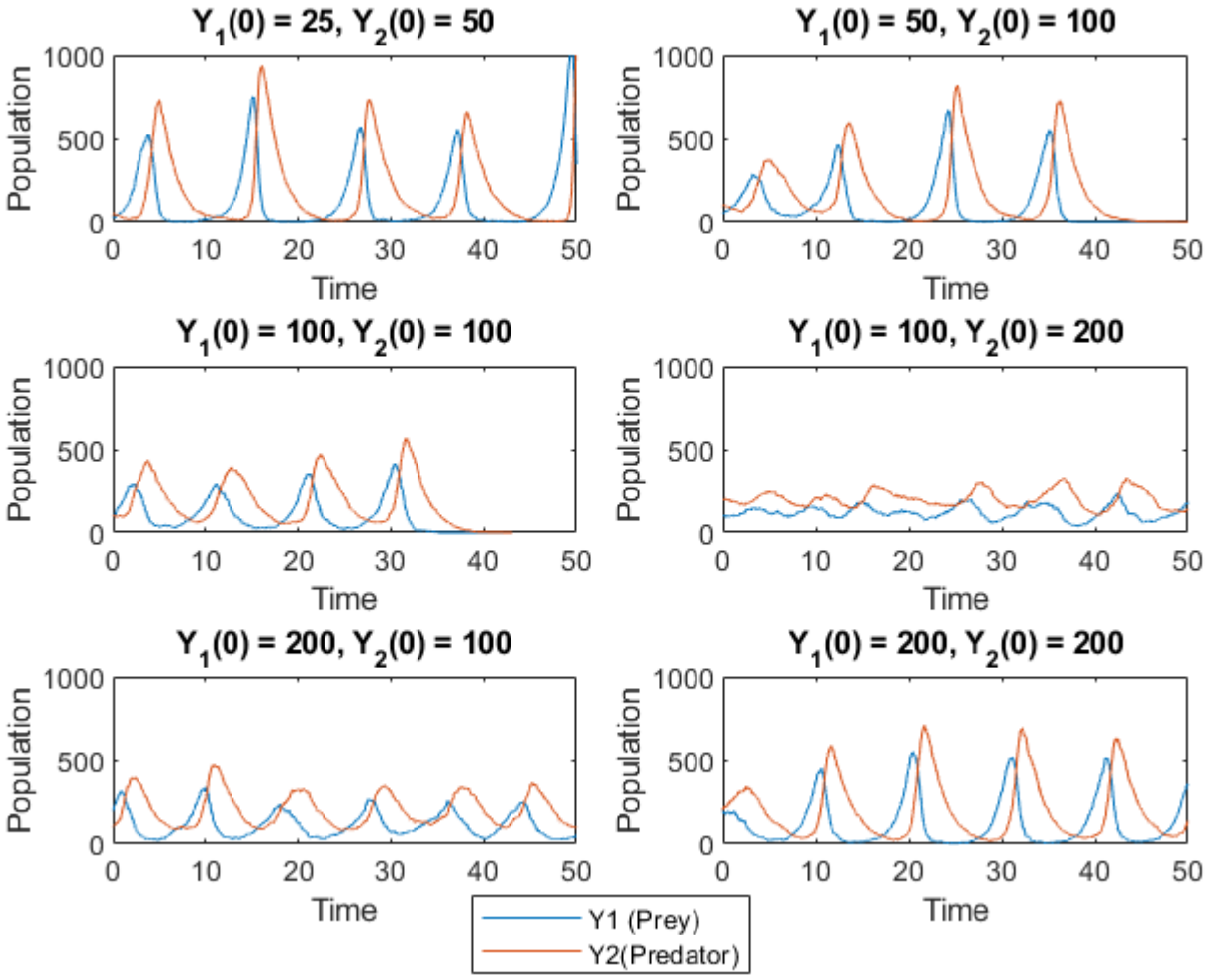

Figure 1: Trajectories for different initial values of number of species Y_1 and Y_2 with $T = 50$.

Third Part:
Here, the effect of changing c_1, c_2, c_3 on species 1 and species 2 are analysed.

Following table shows the change of rates c_1, c_2 and c_3. One at a time, one of the rates was changed keeping other two unchanged. It was seen from the simulation that when c_2 was changed, then species 1 and species 2 go extinct quickly. For smaller c_2, species 2 goes extinct fast whereas for larger c_2 species 1 goes extinct.(2nd row on following figure)
Though by decreasing c_1, increasing c_2 and decreasing c_3, species 1 goes extinct. But effect of change in c_2 is quick and noticeable.

c_1	0.001	0.01	0.05	0.1	0.5	1	1.2	1.5
c_2	0.0001	0.001	0.005	0.01	0.05	0.1	0.2	0.5
c_3	0.001	0.01	0.05	0.1	0.6	1	1.2	1.5

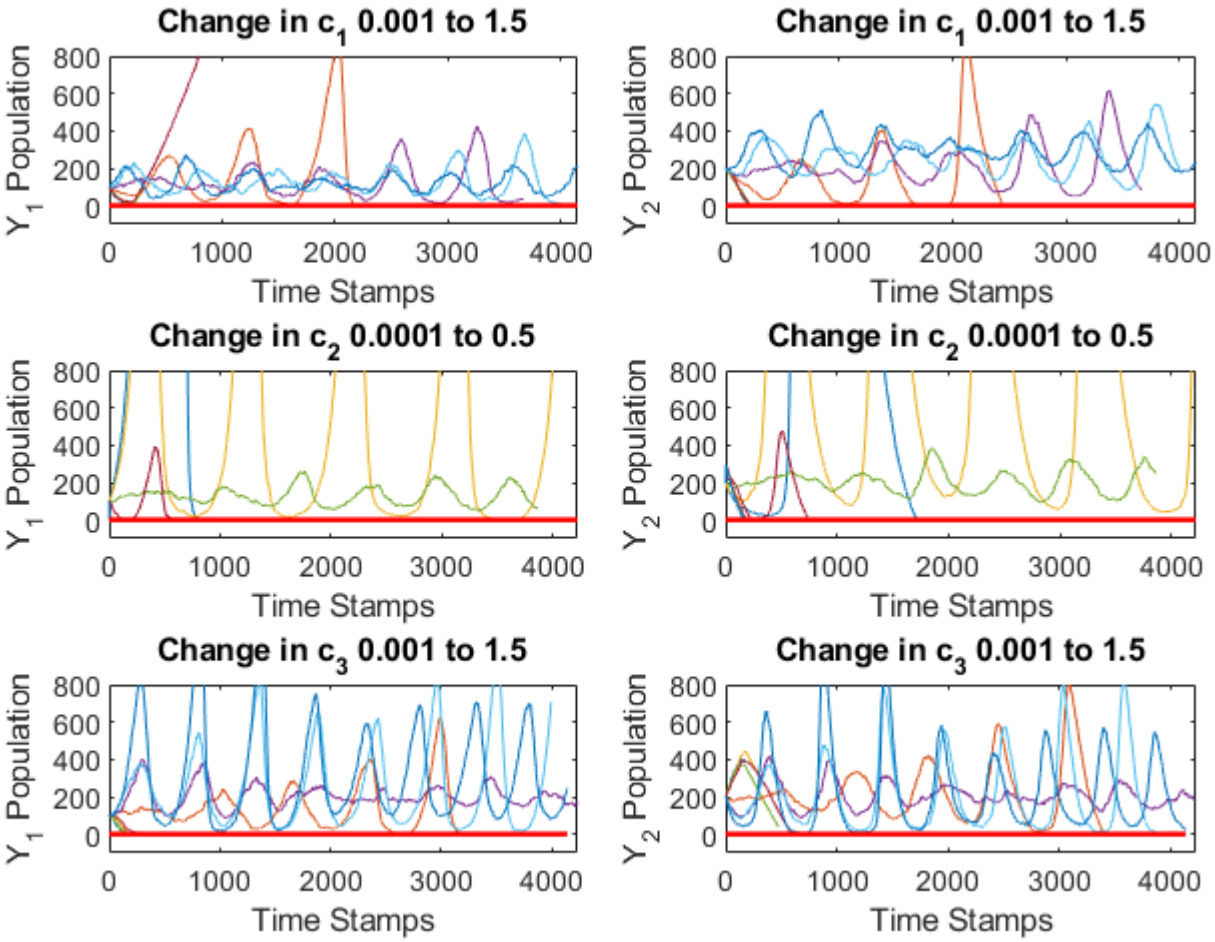

Figure 2: 1st column: Population of species 1 with changing rates, 2nd column: population of species 2 with changing rates, Red line : $Y = 0$. Most of the trajectories with change in c_2 go extinct (see 2nd row).

2. Consider the following chemical reaction

$$A \xrightarrow{k} X \xrightarrow{\alpha_1} \emptyset$$
$$B \xrightarrow{k} Y \xrightarrow{\alpha_1} \emptyset$$
$$X + Y \xrightarrow{k_\alpha} C.$$

The deterministic set of equations describing this reaction has the form

$$\frac{d[X]}{dt} = k - \alpha_1 [X] - k_\alpha [X][Y]$$
$$\frac{d[Y]}{dt} = k - \alpha_2 [Y] - k_\alpha [X][Y]$$

where $[\,\cdot\,]$ denotes concentration.

- Find the fixed points of the deterministic system. Show that for the values

$$k = 10 \qquad \alpha_1 = 10^{-6} \qquad \alpha_2 = 10^{-5} \qquad k_\alpha = 10^{-5}$$
$$k = 10^3 \qquad \alpha_1 = 10^{-4} \qquad \alpha_2 = 10^{-3} \qquad k_\alpha = 10^{-3}$$

  the fixed points are the same.
- Run the Gillespie algorithm and show that the behavior is very different in the two cases. Compute the stationary distributions in the two cases.
- Can you give an argument why the behavior in the two cases is so different?

First Part:
For fixed point of the deterministic system, we have,

$$0 = k - \alpha_1 [X] - k_\alpha [X][Y]$$
$$0 = k - \alpha_2 [Y] - k_\alpha [X][Y]$$

subtracting

$$\alpha_2 [Y] - \alpha_1 [X] = 0 \Longrightarrow [Y] = \frac{\alpha_1}{\alpha_2} [X]$$

so

$$k - \alpha_1 [X] - k_\alpha [X] \frac{\alpha_1}{\alpha_2} [X] = 0$$

or,

$$k_\alpha \; \alpha_1 [X]^2 + \alpha_1 \alpha_2 [X] - k \; \alpha_2 = 0$$

Hence fixed points;

$$\begin{pmatrix} [X] \\ [Y] \end{pmatrix} = \begin{pmatrix} \frac{-\alpha_1\alpha_2 \; + \; \sqrt{\alpha_1^2\alpha_2^2 + 4k_\alpha k \alpha_1 \alpha_2}}{2k_\alpha \alpha_1} \\ \frac{-\alpha_1\alpha_2 \; + \; \sqrt{\alpha_1^2\alpha_2^2 + 4k_\alpha k \alpha_1 \alpha_2}}{2k_\alpha \alpha_2} \end{pmatrix}$$

Since $[X]$ and $[Y]$ are concentrations of reactants in chemical reaction, we discards negative values for fixed point.

Finding fixed points for give rates;

$$k = 10 \qquad \alpha_1 = 10^{-6} \qquad \alpha_2 = 10^{-5} \qquad k_\alpha = 10^{-5}$$

Solving system of non-linear equations:

```
syms k a1 ka a2 x y
solve(k-a1*x-ka*x*y==0,k-a2*y-ka*x*y==0)
k=10;
a1=1e-6;
a2=1e-5;
ka=1e-5;
%%%%%%%discarding negative values%%%%
  x: [3.1618e+03]
  y: [316.1778]
```

and finding fixed points for give rates;

$$k = 10^3 \qquad \alpha_1 = 10^{-4} \qquad \alpha_2 = 10^{-3} \qquad k_\alpha = 10^{-3}$$

```
syms k a1 ka a2 x y
solve(k-a1*x-ka*x*y==0,k-a2*y-ka*x*y==0)
k=1000;
a1=1e-4;
a2=1e-3;
ka=1e-3;
  x: [3.1618e+03] = [3162] %%(approximately)%%
  y: [316.1778]=[316] %%(approximately)%%
```

We conclude that even-though the rates are different, fixed points are the same.

Second Part:
Gillespie Algorithms with first set of rate constants:

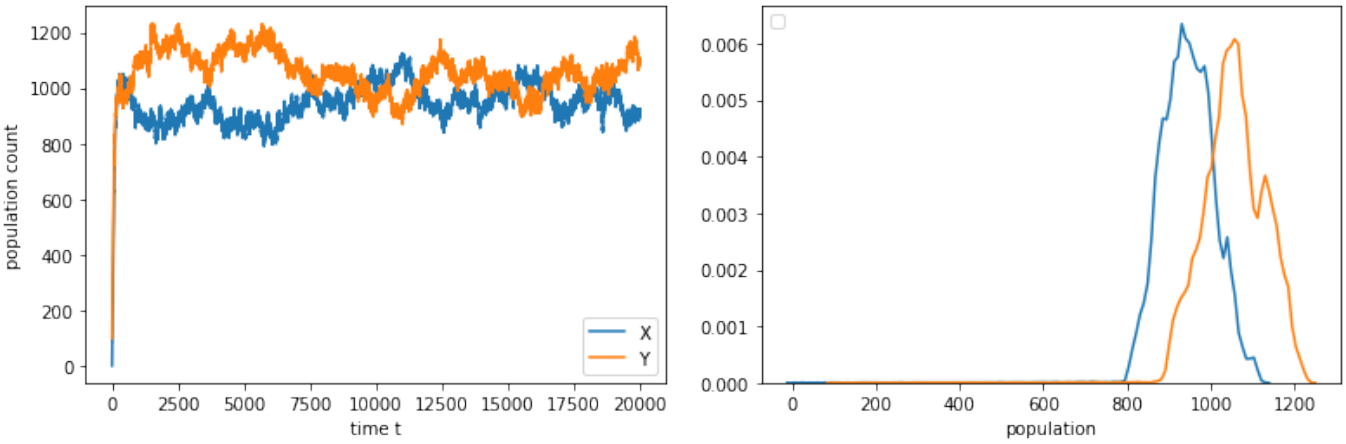

Figure 3: Behaviour of chemical reaction with first set of rate constants. Here the stationary distribution is achieved only after few thousand time steps(slow). 1st figure: trajectory of concentrations. 2nd figure: kernel densities.
Stationary Distribution: X [mean = 976.66 , Std= 85.45], Y [mean = 1090.66 , Std= 80.23]

For next set of rate constants, since $k = 10^3$ and other rate constants are larger as compare to previous case, the process is very fast growing within same time frame. In first case I was able to run simulation for $t = 100000$ or more. But in 2nd case it took really long time so I was able to run only for $t = 100$.

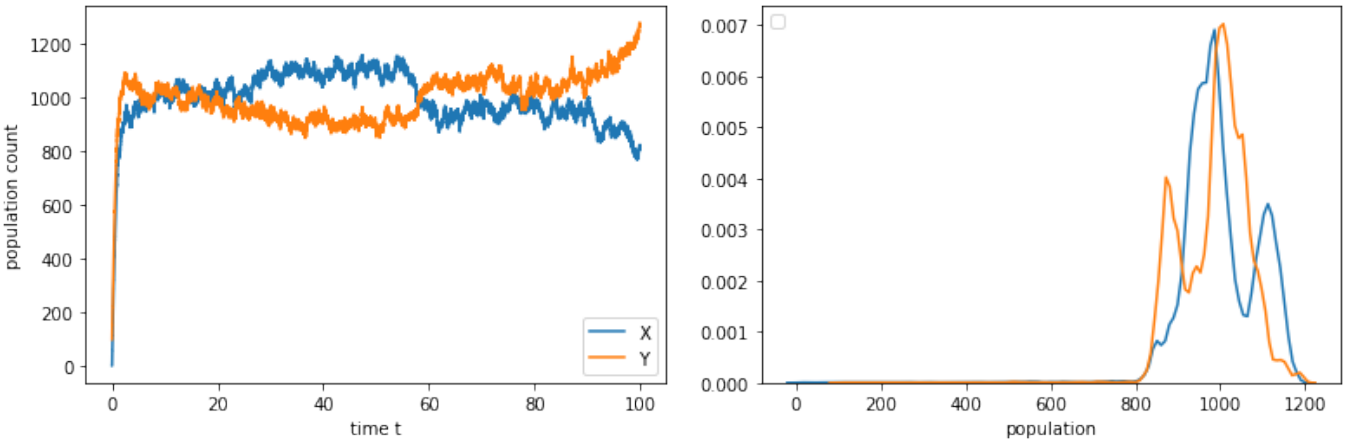

Figure 4: Behaviour of chemical reaction with 2nd set of rate constants. Here the stationary distribution is achieved quickly and more stable(fast). 1st figure: trajectory of concentrations. 2nd figure: kernel densities. **Stationary Distribution: X [mean = 997.66 , Std= 94.56], Y [mean = 986.13 , Std= 84.67]**

Third Part:

The behavior in these two cases is so different because of the rate constants. In 2nd case rate constants are bigger as compared to 1st case. Due to which there are many more reactions occurring within the same time frame. So the simulation also takes very long time to to run. We can see on this figure 5 that within t=2, they already attend high population (red and green trajectories).

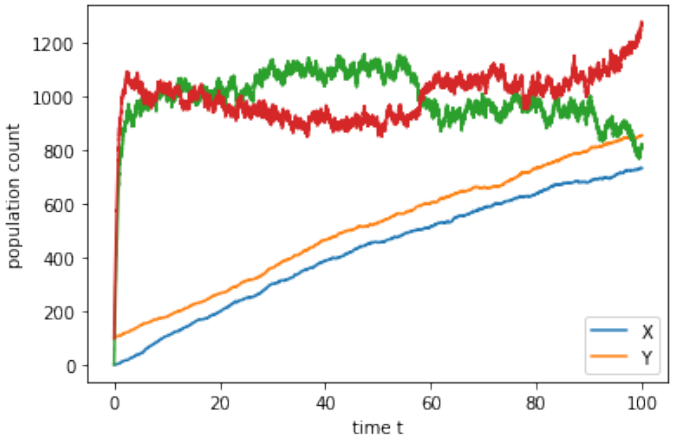

Figure 5: Blue and Orange trajectories: First case with smaller values of rate constants.
Red and Green trajectories: second case with bigger values of rate constants.

3. Consider a gene whose product regulates its own transcription (autoregulation). The deterministic set of equations describing mRNA (r) and and protein (p) expression level are given by:

$$\frac{dr}{dt} = k_l + \phi(p) - \gamma_r r,$$

$$\frac{dp}{dt} = r k_p - \gamma_p p, \tag{1}$$

where $\phi(p)$ is a function that describes how the rate of mRNA transcription depends on the protein concentration p.

- Write down the transition matrix for the Markov process describing this system.
- Consider the case of *positive autoregulation*:

$$\phi(p) = \frac{k_0 \left(\frac{p}{K}\right)^n}{1 + \left(\frac{p}{K}\right)^n}$$

Setting $k_l = 0,\ \gamma_p = \gamma_r = k_p = k_0 = 1$ and $K = 0.5$ in Eq. 1 above, determine the number of fixed points for $n = 1$ and $n = 10$. . Determine the stability of the fixed points.

- Consider the case of *negative autoregulation*:

$$\phi(p) = \frac{k_0}{1 + \left(\frac{p}{K}\right)^n}$$

Use the Gillespie algorithm to find and plot the stationary distribution of protein for the stochastic process you wrote down above. Use transition rates $k_l = 0.001s^{-1}$, $k_r = 0.01s^{-1}$, $k_p = 0.17s^{-1}$ and $\gamma_p = 0.00028s^{-1}$, $\gamma_r = 0.00833s^{-1}$ with $n = 10$. Do this for the case of (i) strong regulation, $K = 100$ and (ii) weak regulation, $K = 10000$. Calculate the ratio of the standard deviation to the mean of the distribution for both cases.

First Part: Here we use transition probabilities for the Markov process describing the system:

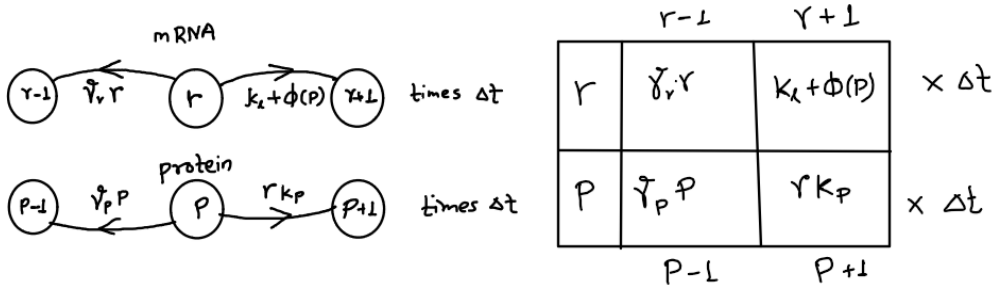

Figure 6: transition probabilities for Markov Process:

Second Part:
In the case of *positive autoregulation*:

$$\phi(p) = \frac{k_0 \left(\frac{p}{K}\right)^n}{1 + \left(\frac{p}{K}\right)^n}$$

Setting $k_l = 0,\ \gamma_p = \gamma_r = k_p = k_0 = 1$ and $K = 0.5$
For $n = 1$, $\phi(p) = \frac{p}{0.5+p}$, so equation (1) becomes;

$$\frac{dr}{dt} = \frac{p}{0.5 + p} - r$$

$$\frac{dp}{dt} = r - p$$

The equilibrium points for this system are $(0, 0)$ and $(0.5, 0.5)$

$$Jacobian(J) = \begin{pmatrix} -1 & \frac{0.5}{(0.5+p)^2} \\ 1 & -1 \end{pmatrix}$$

For fixed point $(0, 0)$; Eigen-value for Jacobian: $\lambda_1 = 0.4142$ and $\lambda_2 = -2.4142 \implies$ **Unstable**
For fixed point $(0.5, 0.5)$;Eigen-value for Jacobian: $\lambda_1 = -0.2929$ and $\lambda_2 = -1.7071 \implies$ **Stable**

For $n = 10$, $\phi(p) = \frac{p^{10}}{(0.5)^{10}+p^{10}}$, so equation (1) becomes;

$$\frac{dr}{dt} = \frac{p^{10}}{(0.5)^{10} + p^{10}} - r$$

$$\frac{dp}{dt} = r - p$$

The equilibrium points for this system are $(0, 0)$, $(0.5, 0.5)$ and $(0.999015, 0.999015)$.

$$Jacobian(J) = \begin{pmatrix} -1 & \frac{10p^9(0.5)^{10}}{((0.5)^{10}+p^{10})^2} \\ 1 & -1 \end{pmatrix}$$

For fixed point $(0, 0)$; Eigen-value for Jacobian: $\lambda_1 = -1$ and $\lambda_2 = -1 \implies$ **Stable Fixed Point.**

For fixed point $(0.5, 0.5)$;Eigen-value for Jacobian: $\lambda_1 = 1.2361$ and $\lambda_2 = -3.2261 \implies$ **Unstable**.

For fixed point $(0.999, 0.999)$;Eigen-value for Jacobian: $\lambda_1 = -0.9007$ and $\lambda_2 = -1.0993 \implies$ **Stable**.

Third Part: Negative autoregulation:

- Strong Regulation $K = 100$

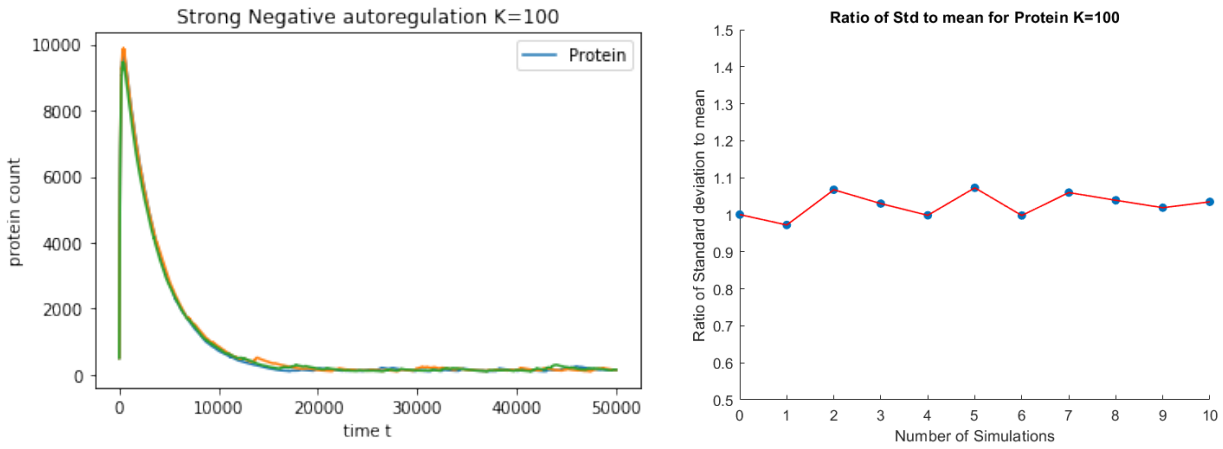

Figure 7: Trajectories of protein count in strong autoregulation. Ratio of standard deviation to mean plot for many simulations $K = 100$.

- Weak Regulation $K = 10000$

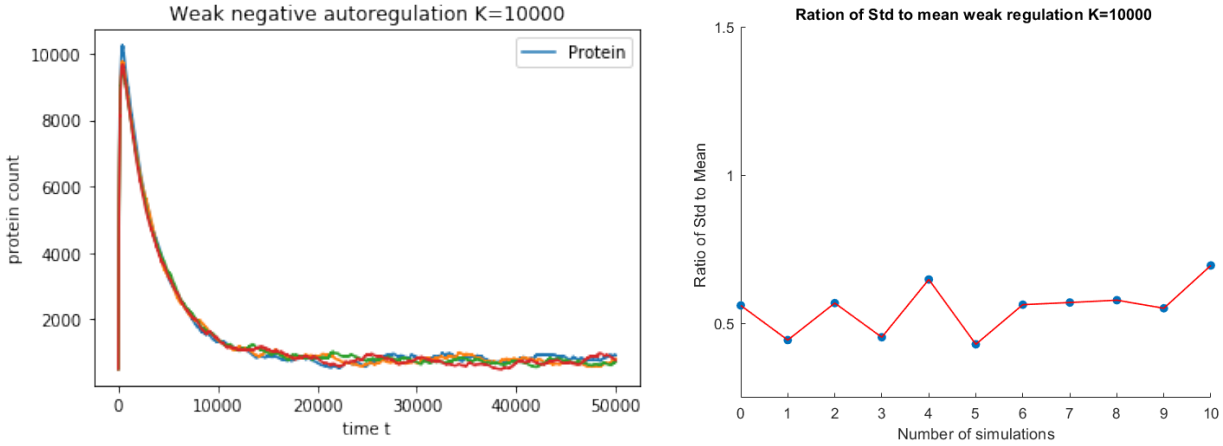

Figure 8: Trajectories of protein count in weak autoregulation. Ratio of standard deviation to mean plot for many simulations $K = 10000$.