Mini-Project in Mathematical and Computational Modeling

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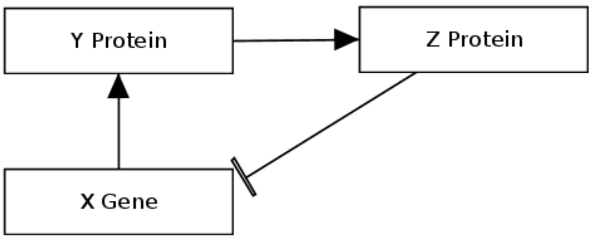
Introduction

Introduction to the article goes here Introduction to the article goes here

The Model

Part A - One-Cell Model



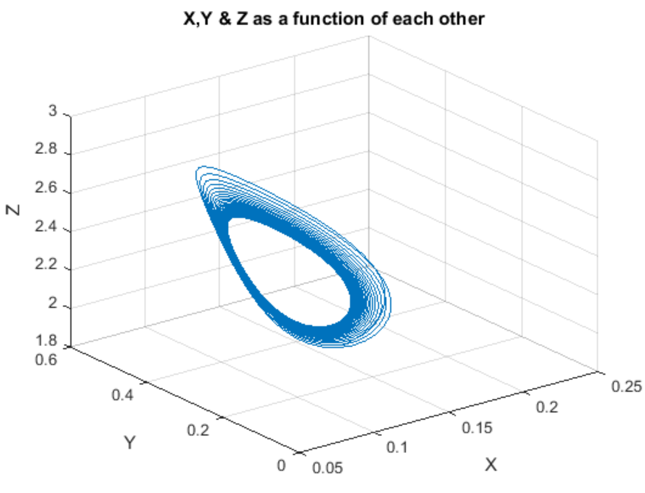
(a) One-Cell Model
The gene mRNA X codes for protein Y which, in turn, activates transcriptional inhibitor Z. The resulting model behaves as a three-variable oscillator.

$$\frac{\delta X}{\delta t} = v_1 \frac{K_1^n}{K_1^n + Z^n} - v_2 \frac{X}{K_2 + X}$$

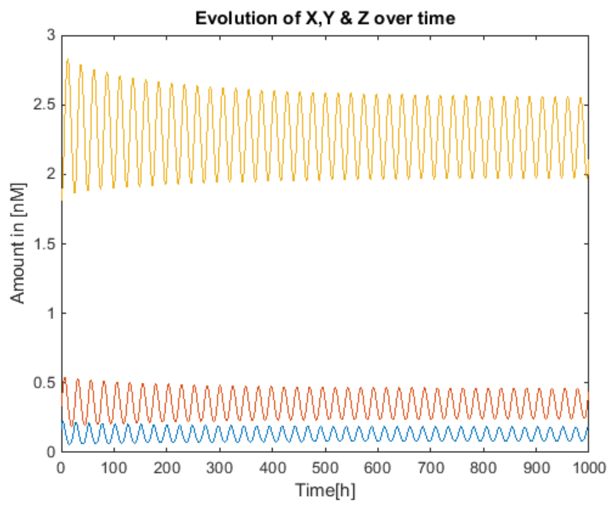
$$\frac{\delta Y}{\delta t} = k_3 X - v_4 \frac{Y}{K_4 + Y}$$

$$\frac{\delta Z}{\delta t} = k_5 Y - v_6 \frac{Z}{K_6 + Z}$$

v_1	translation rate of X	K_1	Michaelis constant of X
v_2	degradation rate of X	K_4	Michaelis constant of Y
v_4	degradation rate of Y	K_6	Michaelis constant of Z
v_6	degradation rate of Z		
k_3	transcription rate of X		
k_5	transcription rate of Z		

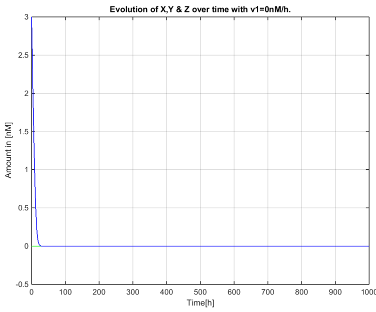


(a) Trajectories
The limit cycle is reached as the variations of $X(t)$, $Y(t)$ and $Z(t)$ become fixed : The trajectories converge, non-lineary (the distance between similar trajectories aren't regular) towards an ellipse (where the blue stripes accumulate)

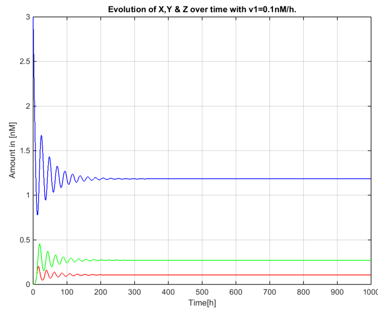


(b) Frequency spectrum
The amplitude of the three variations stabilize after a few hundred hours. The signal are not in phase but have the same, regular, frequencies.

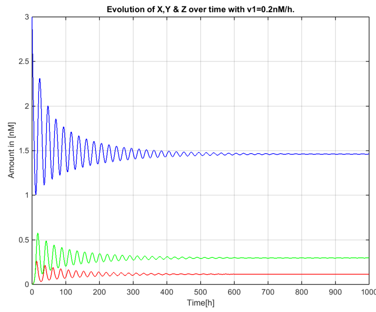
Figure 3:
Trajectories of $X(t)$, $Y(t)$ and $Z(t)$ with initial conditions : $X_0 = 0.16$, $Y_0 = 0.33$, $Z_0 = 1.8$ [nM]
We observe on both graphs that $Z(t)$ has the bigger amplitude of variation whereas $X(t)$ and $Y(t)$ have small amplitudes. Additionaly, the convergence towards a single loop in (a) indicate that the frequencies of the signals are equal; this is illustrated as well in (b)



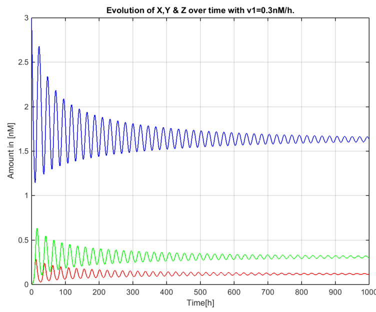
(a) $v_1 = 0$ nM/h



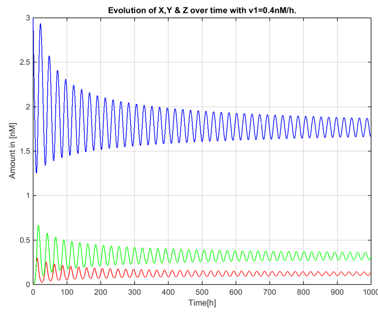
(b) $v_1 = 1$ nM/h



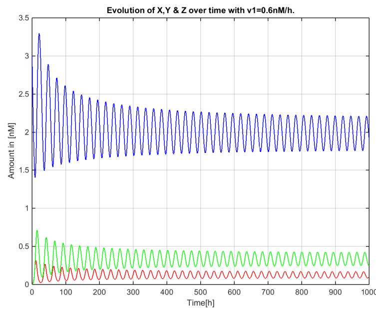
(c) $v_1 = 2$ nM/h



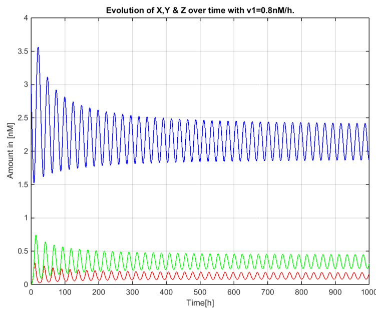
(d) $v_1 = 3$ nM/h



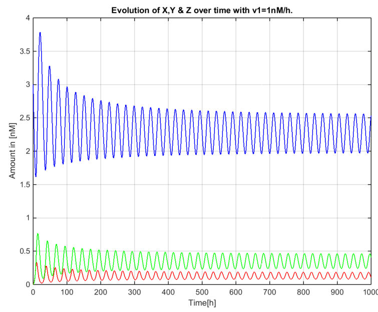
(e) $v_1 = 4$ nM/h



(f) $v_1 = 6$ nM/h

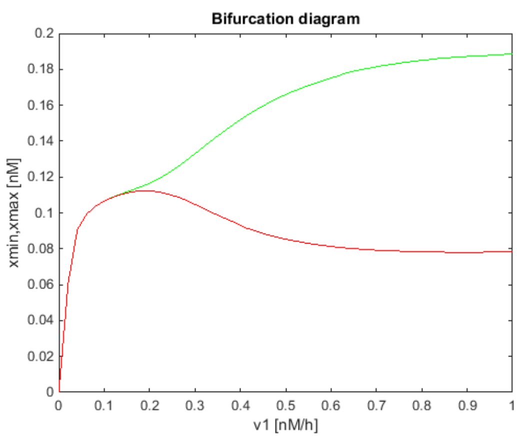


(g) $v_1 = 8$ nM/h

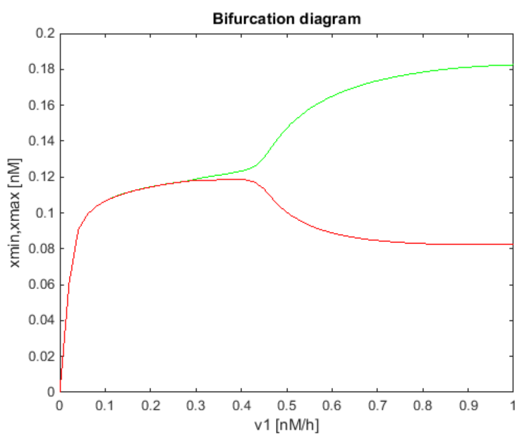


(h) $v_1 = 10$ nM/h

Figure 4: $X(t)$, $Y(t)$ and $Z(t)$ with initial conditions $X_0 = 0.16$, $Y_0 = 0.33$, $Z_0 = 1.8$ [nM]
The first signal to fade is $Y(t)$ and its oscillatory stability predicts stability of the system. We also observe that the signals converge towards null or the limit cycle in a non-linear fashion. At the opposite, it is rather difficult to predict the threshold value of v_1 using those plots ?

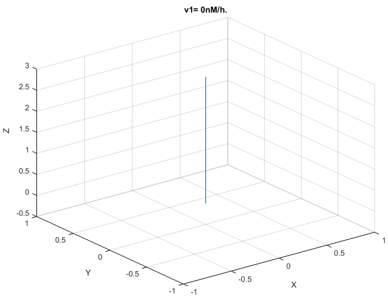


(a) at $h_{max} = 1000$ h

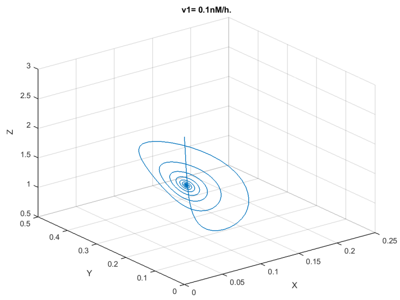


(b) at $h_{max} = 10\ 000$ h

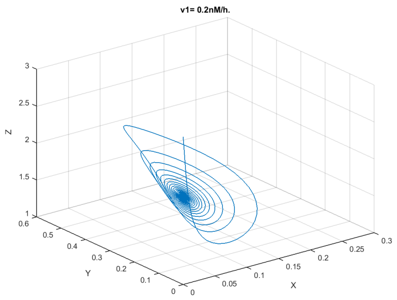
Figure 5: Bifurcation Diagram : X_{min} and X_{max} plotted at time intervals $[9/10; 1]$ of h_{max}
A limit cycle might be reached when $X_{min} \neq X_{max}$. However, the system needs to be run for enough time for the cycle to be reached, as the (a) suggests. (b) illustrates the non-linear convergence of the system; also the threshold for v_1 seems to be around 4.5



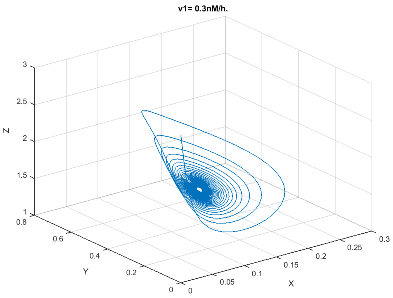
(a) v_1 = 0 nM/h



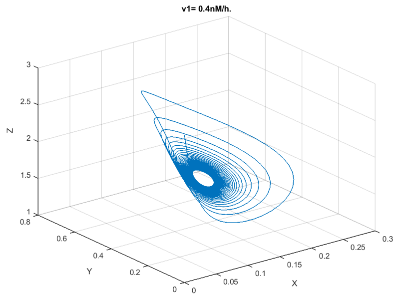
(b) v_1 = 1 nM/h



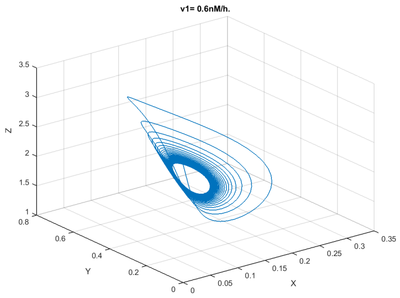
(c) v_1 = 2 nM/h



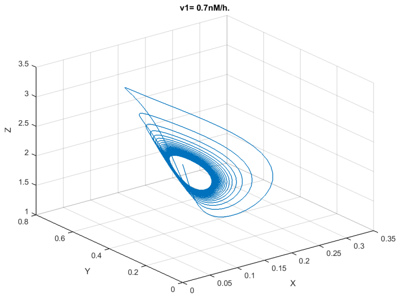
(d) v_1 = 3 nM/h



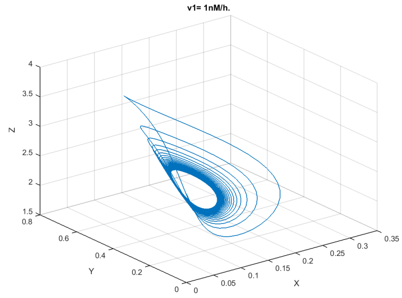
(e) v_1 = 4 nM/h



(f) v_1 = 6 nM/h



(g) v_1 = 8 nM/h



(h) v_1 = 10 nM/h

Figure 6: Trajectories when varying v_1 with initial conditions $X_0 = 0.16$, $Y_0 = 0.33$, $Z_0 = 1.8$ [nM]
v_1 has to reach a certain value for $X(t)$ to be able to compensate its inhibition by $Z(t)$ and therefore for the system to reach a limit cycle. We observe that this value is slightly greater than 4nM/h, as the trajectories still converge to null in (e); there is an 'eye', even though it is smaller than in (f) and (g), since the timescale is not big enough to let the system dissipate completely.

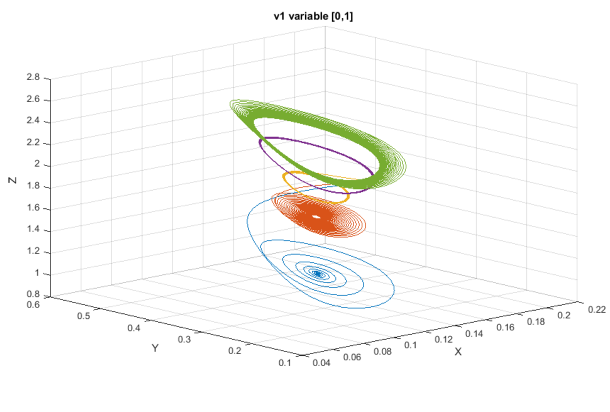
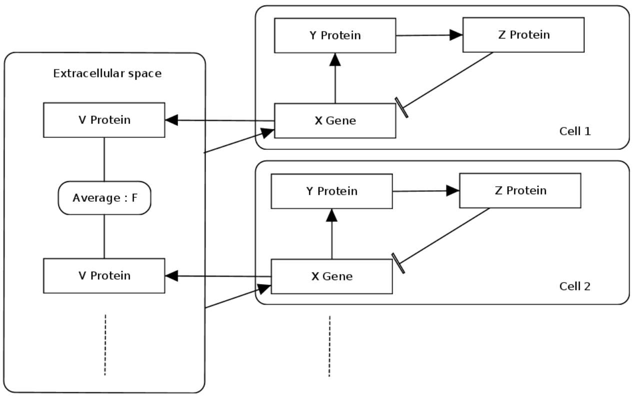


Figure 7: Superimposed trajectories at late timepoints with initial conditions $X_0 = 0.16$, $Y_0 = 0.33$, $Z_0 = 1.8$ [nM] and v_1 = 0.1/0.3/0.5/0.7/0.9 nM/h. We observe here that $Z(t)$ tends to reach greater concentration stability with increasing v_1.

Part B - Multiple Cells Model



(a) Multiple Cells Model
The gene X codes for protein Y which, in turn, activates transcriptional inhibitor Z. In addition, gene X activates a positive feedback loop through the mean concentration of extracellular protein V

$$\frac{\delta X}{\delta t} = v_1 \frac{K_1^n}{K_1^n + Z^n} - v_2 \frac{X}{K_2 + X} + v_c \frac{KF}{K_c + KF}$$

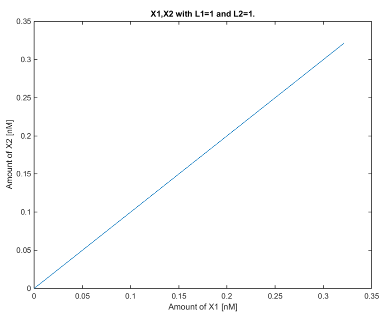
$$\frac{\delta Y}{\delta t} = k_3 X - v_4 \frac{Y}{K_4 + Y}$$

$$\frac{\delta Z}{\delta t} = k_5 Y - v_6 \frac{Z}{K_6 + Z}$$

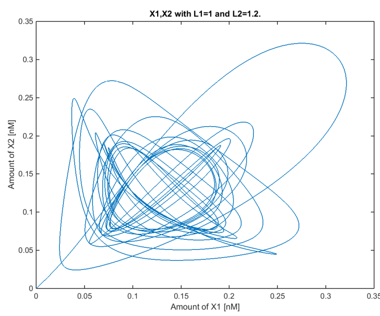
$$\frac{\delta V_i}{\delta t} = k_7 X_i - v_8 \frac{V_i}{K_8 + V_i}$$

$$\text{where } F = \frac{1}{N} \sum_{i=1}^{N} V_i$$

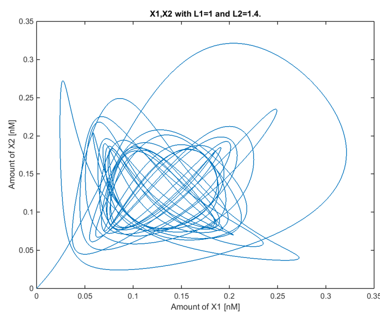
v_1	translation rate of X	k_1	transcription rate of X
v_2	degradation rate of X	K_1	Michaelis constant of X
v_4	degradation rate of Y	K_4	Michaelis constant of Y
v_6	degradation rate of Z	K_6	Michaelis constant of Z
v_8	degradation rate of V	K_8	Michaelis constant of V
k_3	transcription rate of X	K_c	Michaelis constant of X by F
k_5	transcription rate of Z	v_c	Activation rate of X by F
k_7	transcription rate of V	K	Coupling Constant



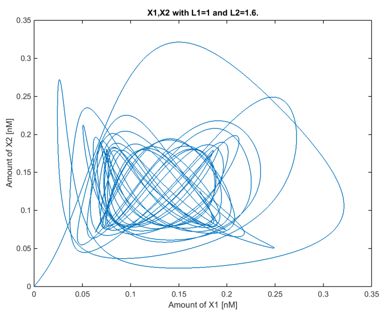
(a) $\lambda_1 = 1,\ \lambda_2 = 1\ [h^{-1}]$



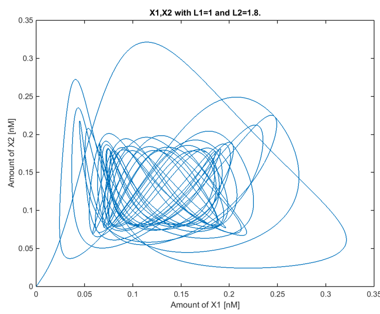
(b) $\lambda_1 = 1,\ \lambda_2 = 1.2\ [h^{-1}]$



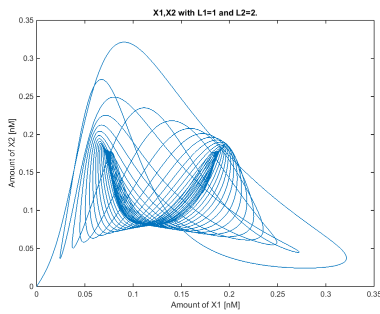
(c) $\lambda_1 = 1,\ \lambda_2 = 1.4\ [h^{-1}]$



(d) $\lambda_1 = 1,\ \lambda_2 = 1.6\ [h^{-1}]$

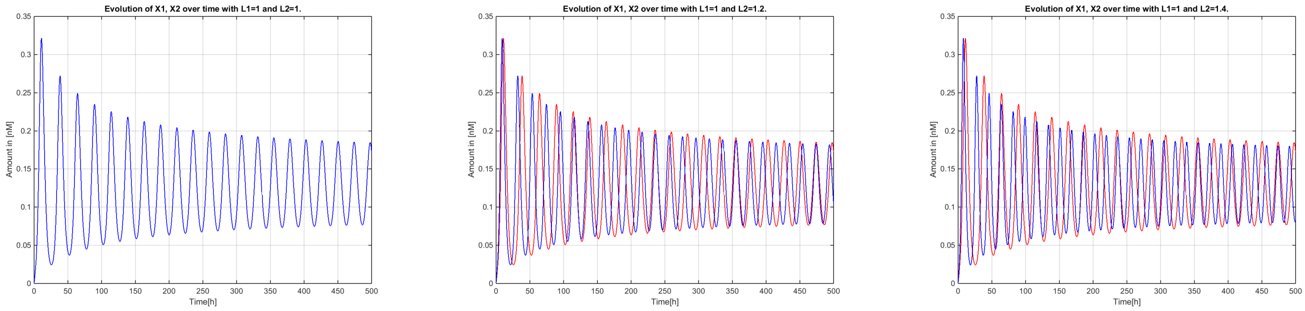


(e) $\lambda_1 = 1,\ \lambda_2 = 1.8\ [h^{-1}]$

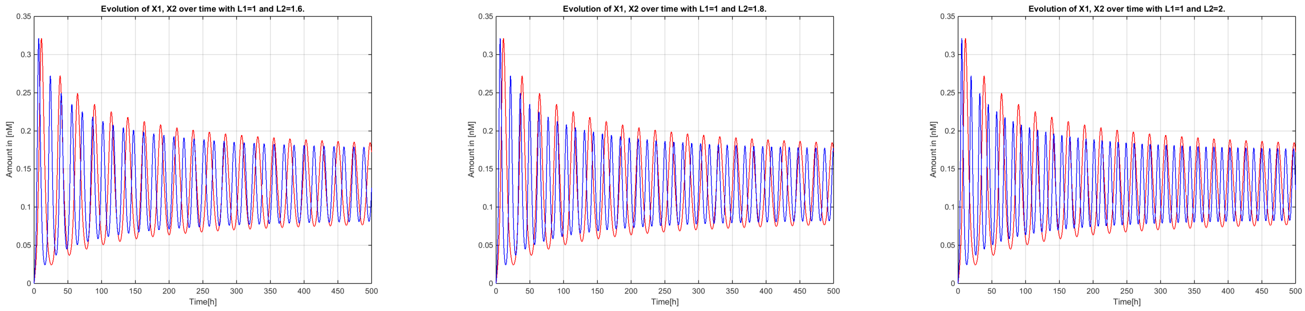


(f) $\lambda_1 = 1,\ \lambda_2 = 2\ [h^{-1}]$

Figure 10: X_1 and X_2 trajectories with varying λ_i in a two-cells Model
I don't really know what to say except 'wow it's cool' + square is max/min of Xs

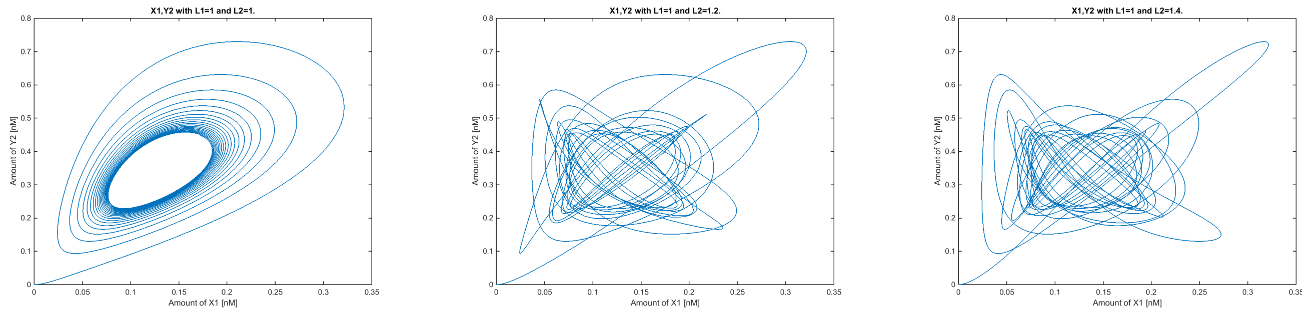


(a) $\lambda_1 = 1,\ \lambda_2 = 1\ [h^{-1}]$ (b) $\lambda_1 = 1,\ \lambda_2 = 1.2\ [h^{-1}]$ (c) $\lambda_1 = 1,\ \lambda_2 = 1.4\ [h^{-1}]$

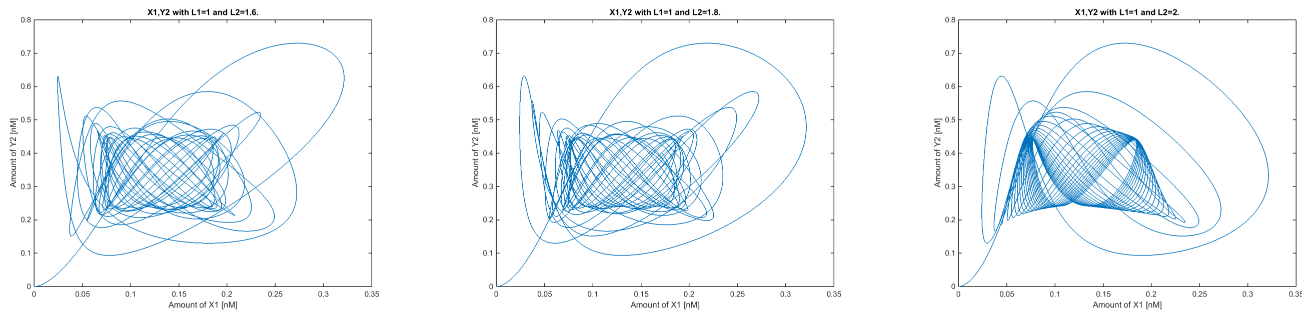


(d) $\lambda_1 = 1,\ \lambda_2 = 1.6\ [h^{-1}]$ (e) $\lambda_1 = 1,\ \lambda_2 = 1.8\ [h^{-1}]$ (f) $\lambda_1 = 1,\ \lambda_2 = 2\ [h^{-1}]$

Figure 11: $X_1(t)$ and $X_2(t)$ trajectories in a two-cells Model
We observe that

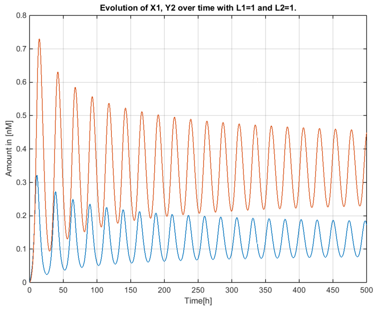


(a) $\lambda_1 = 1,\ \lambda_2 = 1\ [h^{-1}]$ (b) $\lambda_1 = 1,\ \lambda_2 = 1.2\ [h^{-1}]$ (c) $\lambda_1 = 1,\ \lambda_2 = 1.4\ [h^{-1}]$

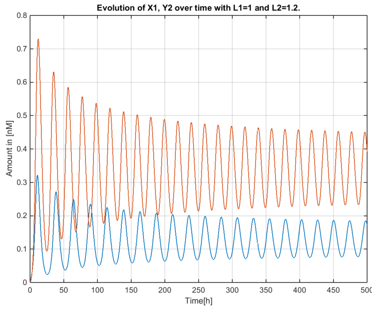


(d) $\lambda_1 = 1,\ \lambda_2 = 1.6\ [h^{-1}]$ (e) $\lambda_1 = 1,\ \lambda_2 = 1.8\ [h^{-1}]$ (f) $\lambda_1 = 1,\ \lambda_2 = 2\ [h^{-1}]$

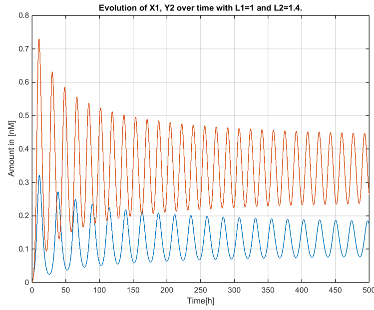
Figure 12: X_1 and Y_2 trajectories



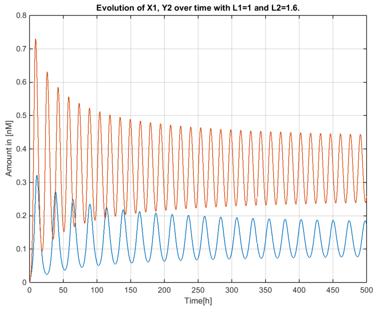
(a) $\lambda_1 = 1,\, \lambda_2 = 1\ [h^{-1}]$



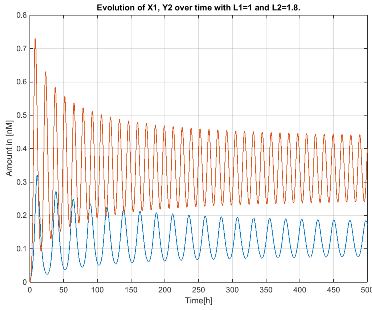
(b) $\lambda_1 = 1,\, \lambda_2 = 1.2\ [h^{-1}]$



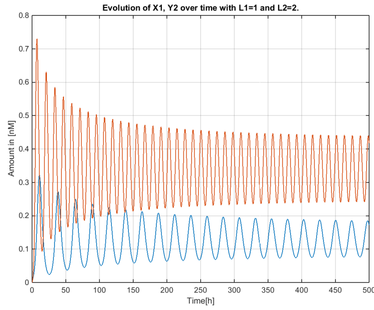
(c) $\lambda_1 = 1,\, \lambda_2 = 1.4\ [h^{-1}]$



(d) $\lambda_1 = 1,\, \lambda_2 = 1.6\ [h^{-1}]$

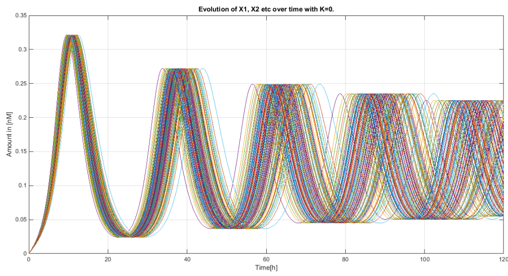


(e) $\lambda_1 = 1,\, \lambda_2 = 1.8\ [h^{-1}]$

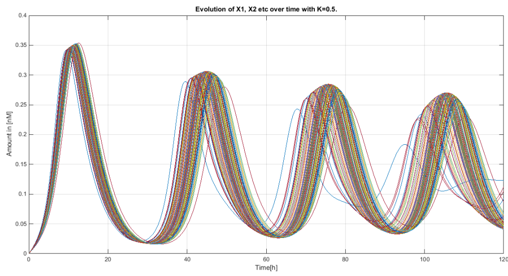


(f) $\lambda_1 = 1,\, \lambda_2 = 2\ [h^{-1}]$

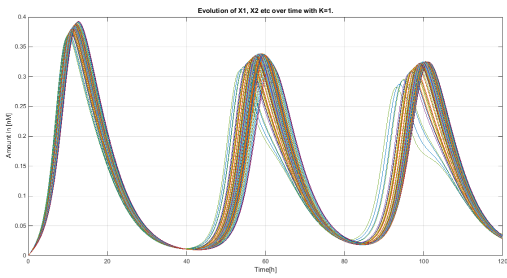
Figure 13: raraara



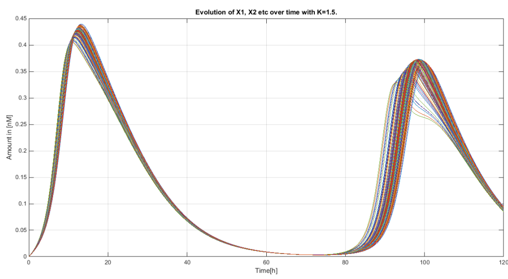
(a) $K = 0.0$



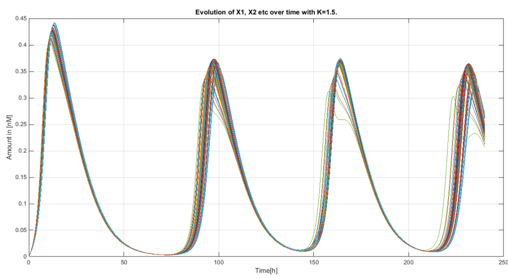
(b) $K = 0.5$



(c) $K = 1.0$

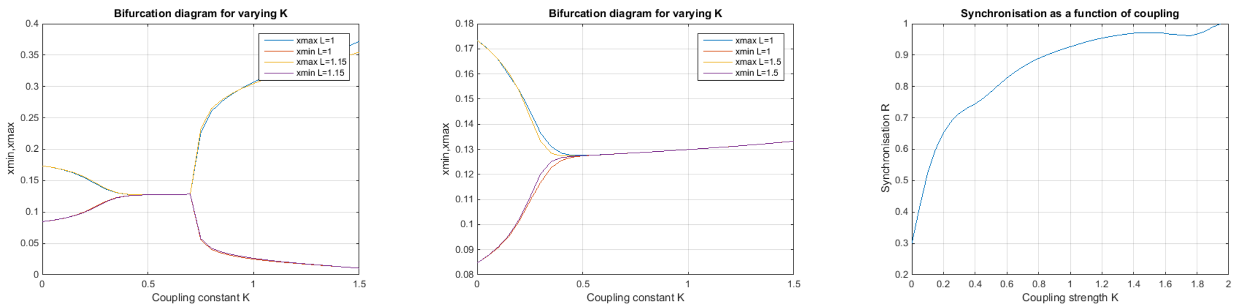


(d) $K = 1.5$



(e) $K = 1.5$

Figure 14: raraara



(a) $K = 0.0$

(b) $K = 0.3$

(c) $K = 1.0$

Figure 15: raraara