Mini-Project in Mathematical and Computational Modeling

École Polytechnique Fédérale de Lausanne, Switzerland

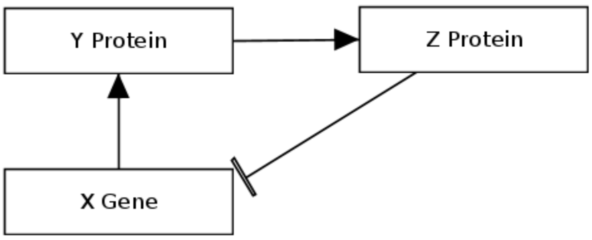
Florian + Dariush

Introduction

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

The Model

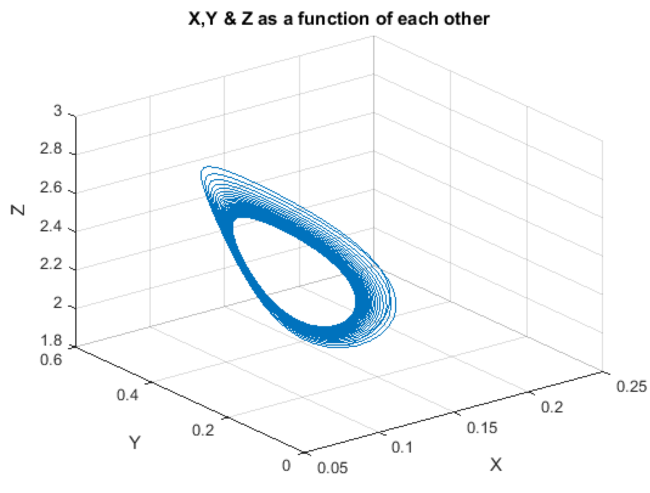
Part A - One-Cell Model



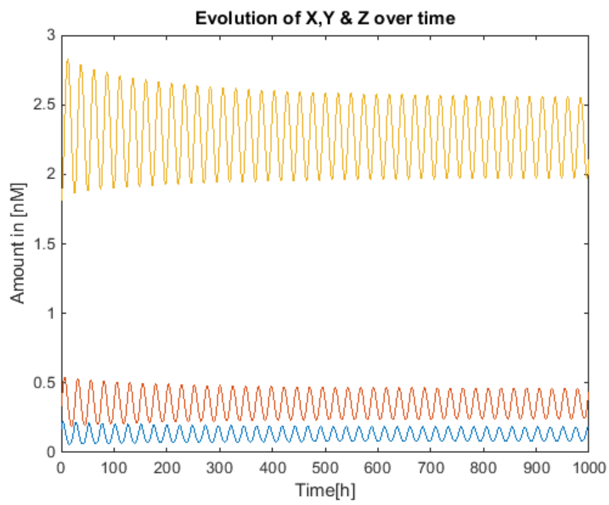
(a) One-Cell Model
The gene mRNA X codes for protein Y which, in turn, activates transcriptional inhibitor Z. The resulting model behaves as a three-variable oscillator.

$$\frac{\delta X}{\delta t} = v_1 \frac{K_1^n}{K_1^n + Z^n} - v_2 \frac{X}{K_2 + X}$$
$$\frac{\delta Y}{\delta t} = k_3 X - v_4 \frac{Y}{K_4 + Y}$$
$$\frac{\delta Z}{\delta t} = k_5 Y - v_6 \frac{Z}{K_6 + Z}$$

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		

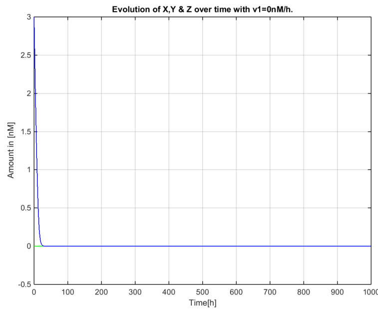


(a) Trajectories
The limit cycle is reached as the variations of $X(t)$, $Y(t)$ and $Z(t)$ become fixed : The trajectories converge, non-lineary (the distance between similar trajectories aren't regular) towards an ellipse (where the blue stripes accumulate)

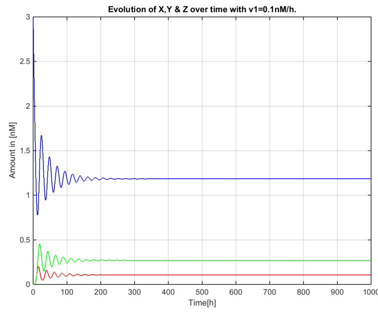


(b) Frequency spectrum
The amplitude of the three variations stabilize after a few hundred hours. The signal are not in phase but have the same, regular, frequencies.

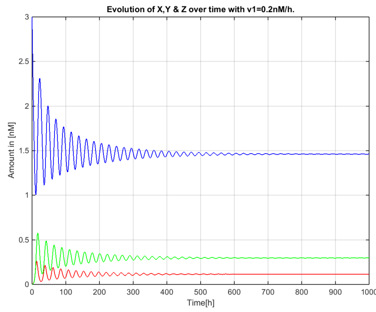
Figure 3:
Trajectories of $X(t)$, $Y(t)$ and $Z(t)$ with initial conditions : $X_0 = 0.16$, $Y_0 = 0.33$, $Z_0 = 1.8$ [nM]
We observe on both graphs that $Z(t)$ has the bigger amplitude of variation whereas $X(t)$ and $Y(t)$ have small amplitudes. Additionaly, the convergence towards a single loop in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



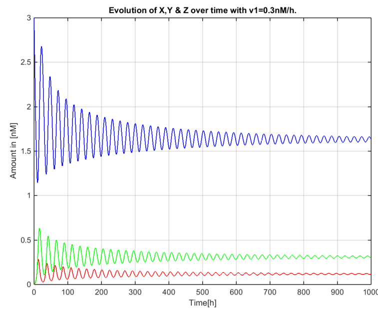
(a) $v_1 = 0$ nM/h



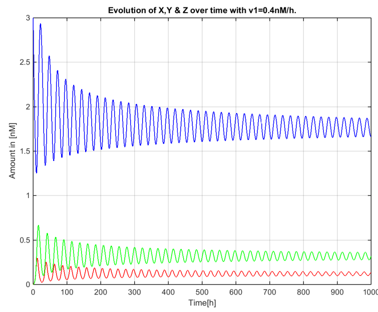
(b) $v_1 = 1$ nM/h



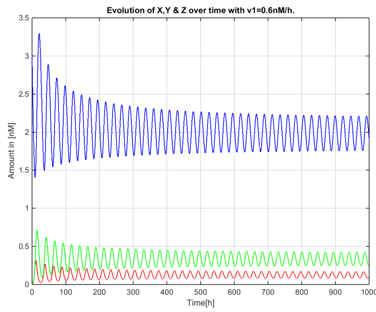
(c) $v_1 = 2$ nM/h



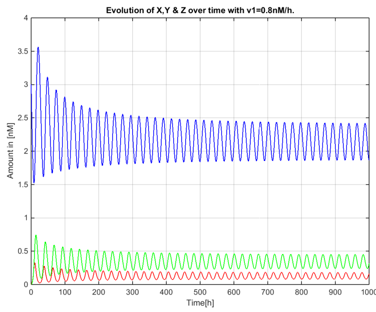
(d) $v_1 = 3$ nM/h



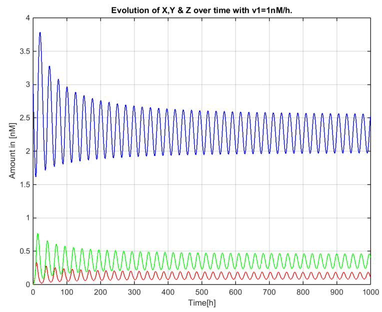
(e) $v_1 = 4$ nM/h



(f) $v_1 = 6$ nM/h

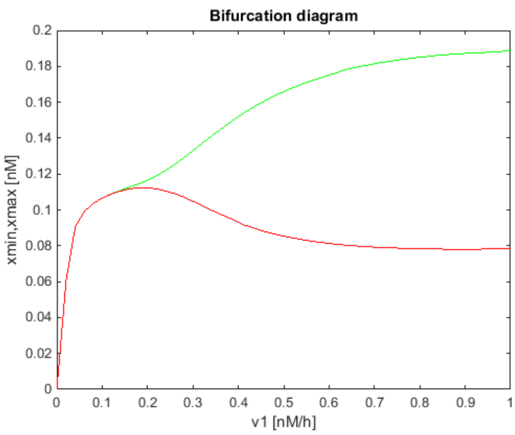


(g) $v_1 = 8$ nM/h

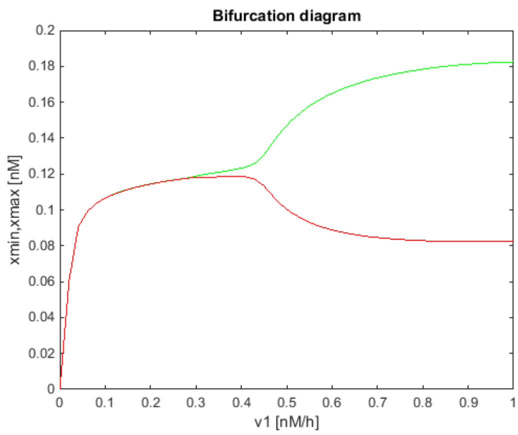


(h) $v_1 = 10$ nM/h

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 ?

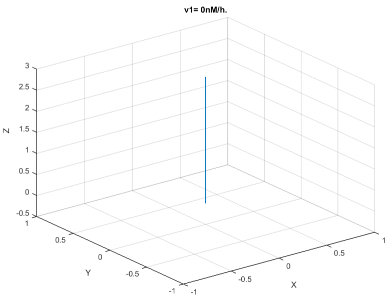


(a) at $h_{max} = 1000$ h

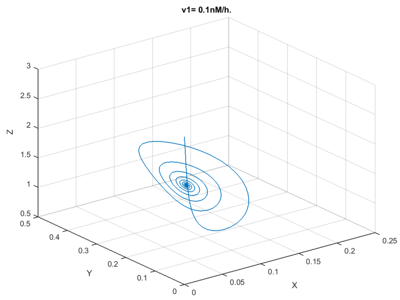


(b) at $h_{max} = 10\,000$ h

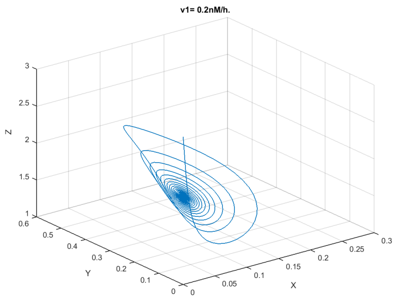
Figure 5: Bifurcation Diagram : X_{min} and X_{max} plotted at time intervals $[9/10; 1]$ of h_{max}
A limit cycle might be reached when $X_{min} \neq X_{max}$. However, the system needs to be run for enough time for the cycle to be reached, as the (a) suggests. (b) illustrates the non-linear convergence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



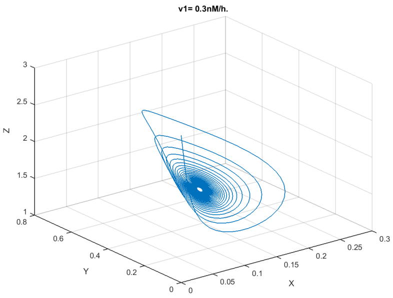
(a) v_1 = 0 nM/h



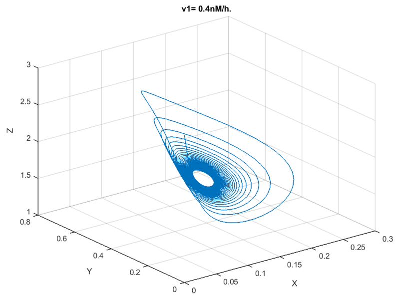
(b) v_1 = 0.1 nM/h



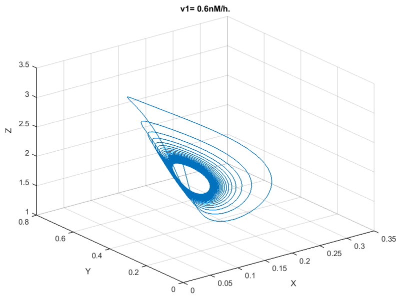
(c) v_1 = 0.2 nM/h



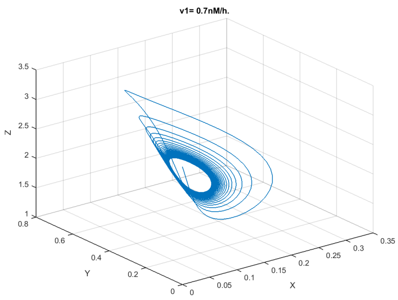
(d) v_1 = 0.3 nM/h



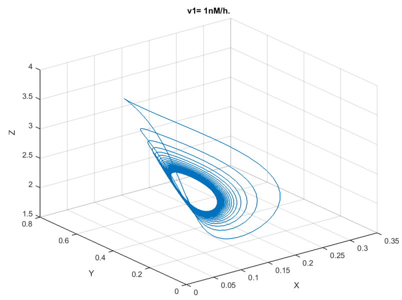
(e) v_1 = 0.4 nM/h



(f) v_1 = 0.6 nM/h



(g) v_1 = 0.8 nM/h



(h) v_1 = 1 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.

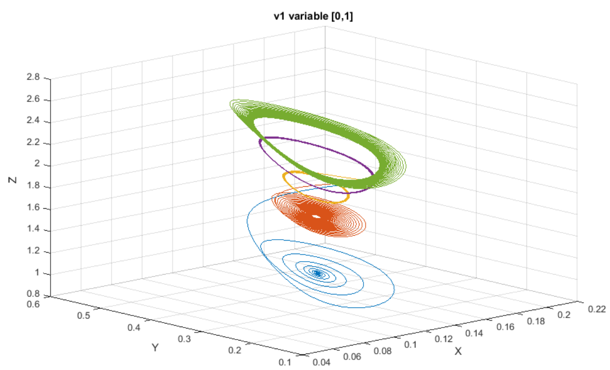
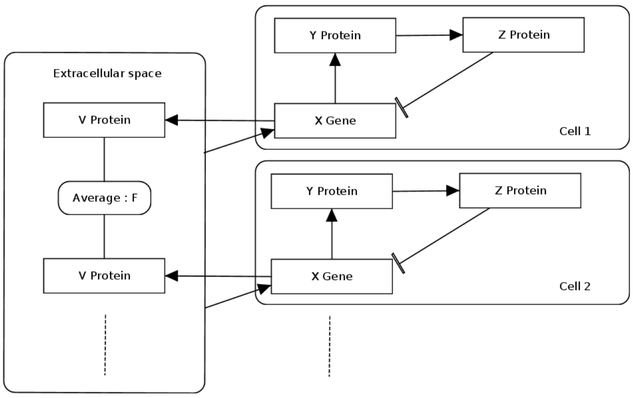


Figure 7: Superimposed trajectories at late timepoints with initial conditions $X_0 = 0.16$, $Y_0 = 0.33$, $Z_0 = 1.8$ [nM] and v_1 = 0.1/0.3/0.5/0.7/0.9 nM/h. We observe here that $Z(t)$ tends to reach greater concentration stability with increasing v_1.

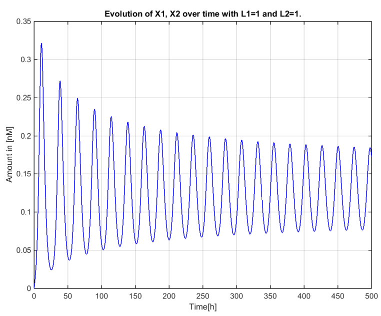
Part B - Multiple Cells Model



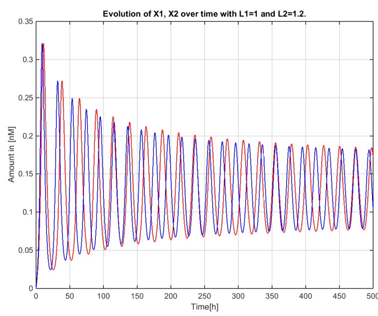
(a) Multiple Cells Model
The gene X codes for protein Y which, in turn, activates transcriptional inhibitor Z. In addition, gene X activates a positive feedback loop through the mean concentration of extracellular protein V

$$
\begin{aligned}
\frac{\delta X}{\delta t} &= v_1 \frac{K_1^n}{K_1^n + Z^n} - v_2 \frac{X}{K_2 + X} + v_c \frac{KF}{K_c + KF} \\
\frac{\delta Y}{\delta t} &= k_3 X - v_4 \frac{Y}{K_4 + Y} \\
\frac{\delta Z}{\delta t} &= k_5 Y - v_6 \frac{Z}{K_6 + Z} \\
\frac{\delta V_i}{\delta t} &= k_7 X_i - v_8 \frac{V_i}{K_8 + V_i} \\
\text{where } F &= \frac{1}{N} \sum_{i=1}^{N} V_i
\end{aligned}
$$

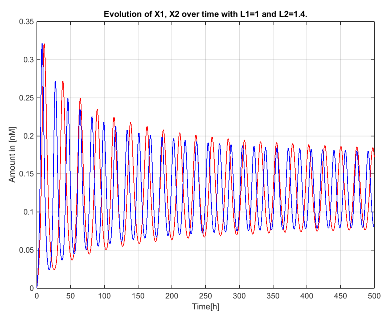
v_1	translation rate of X	k_1	transcription rate of X
v_2	degradation rate of X	K_1	Michaelis constant of X
v_4	degradation rate of Y	K_4	Michaelis constant of Y
v_6	degradation rate of Z	K_6	Michaelis constant of Z
v_8	degradation rate of V	K_8	Michaelis constant of V
k_3	transcription rate of X	K_c	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



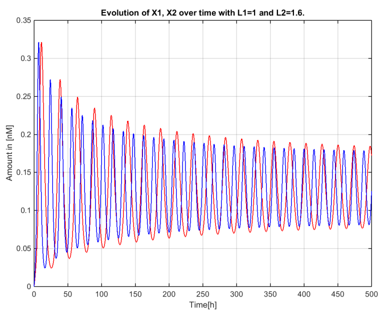
(a) $\lambda_1 = 1$, $\lambda_2 = 1$ $[h^{-1}]$



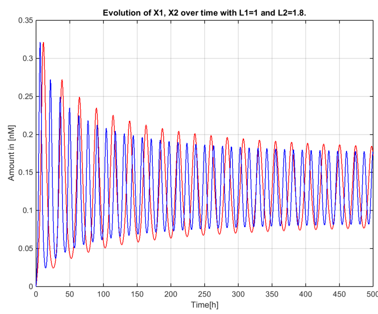
(b) $\lambda_1 = 1$, $\lambda_2 = 1.2$ $[h^{-1}]$



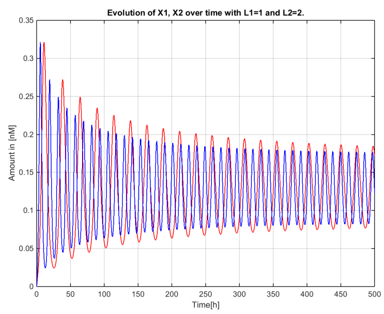
(c) $\lambda_1 = 1$, $\lambda_2 = 1.4$ $[h^{-1}]$



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

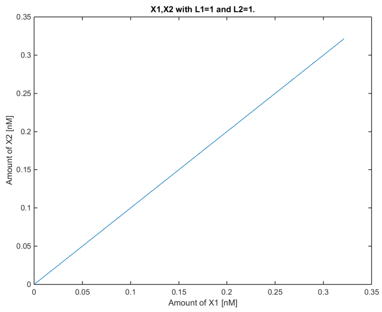


(e) $\lambda_1 = 1$, $\lambda_2 = 1.8$ $[h^{-1}]$

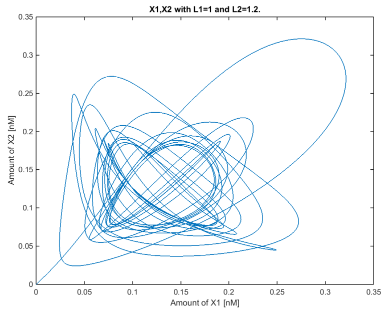


(f) $\lambda_1 = 1$, $\lambda_2 = 2$ $[h^{-1}]$

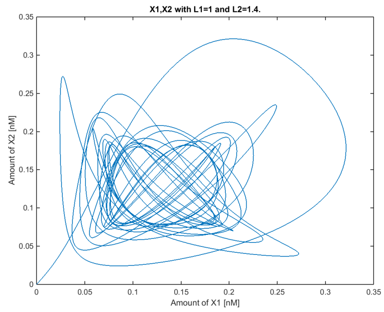
Figure 10: $X_1(t)$ and $X_2(t)$ trajectories in a two-cells Model
Figure (a) has both signals perfectly aligned. We observe that what ? Different periods ? aaa



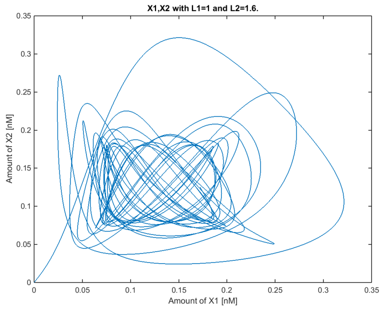
(a) $\lambda_1 = 1,\ \lambda_2 = 1\ [h^{-1}]$



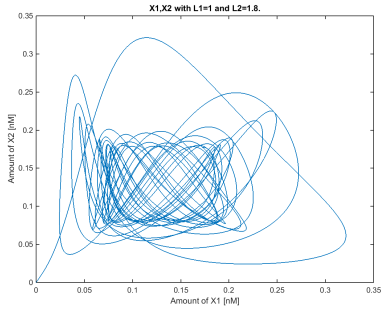
(b) $\lambda_1 = 1,\ \lambda_2 = 1.2\ [h^{-1}]$



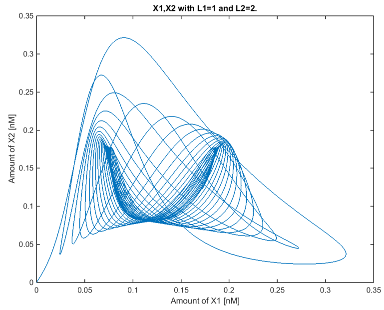
(c) $\lambda_1 = 1,\ \lambda_2 = 1.4\ [h^{-1}]$



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

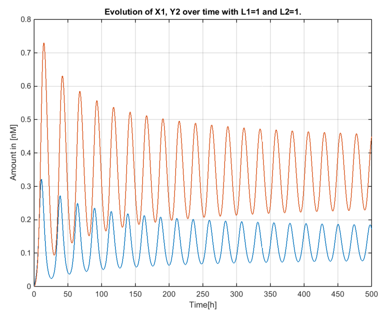


(e) $\lambda_1 = 1,\ \lambda_2 = 1.8\ [h^{-1}]$

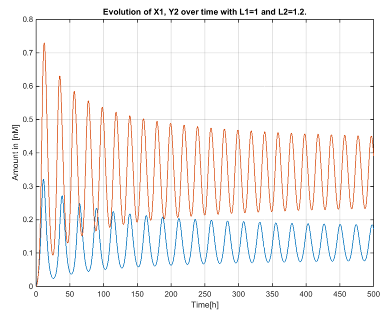


(f) $\lambda_1 = 1,\ \lambda_2 = 2\ [h^{-1}]$

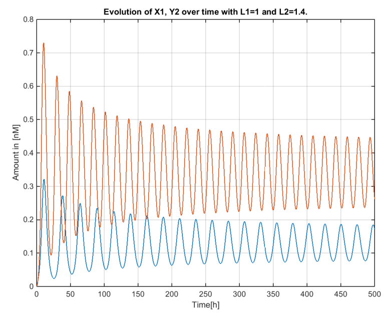
Figure 11: X_1 and X_2 trajectories with varying λ_i in a two-cells Model
Figure (a), the control, makes perfect sense since the two cells have the same period, hence the exact same signal. With unequal periods, the limit cycles of both cells aren't in phase and form these '8' patterns. The box that appears represent the variation of X_1 and X_2 and therefore directly gives us their minimal and maximal values. (f) gives us weird shit ?what can we say bout (f) ?



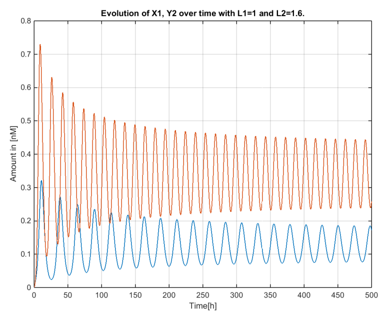
(a) $\lambda_1 = 1,\ \lambda_2 = 1\ [h^{-1}]$



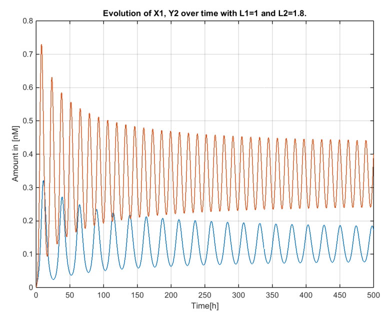
(b) $\lambda_1 = 1,\ \lambda_2 = 1.2\ [h^{-1}]$



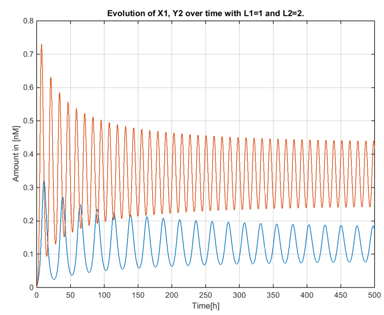
(c) $\lambda_1 = 1,\ \lambda_2 = 1.4\ [h^{-1}]$



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

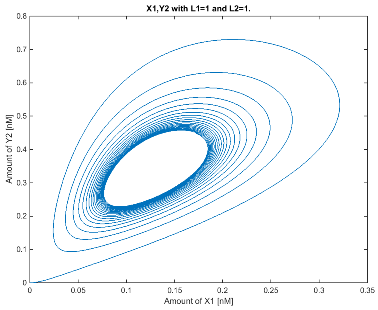


(e) $\lambda_1 = 1,\ \lambda_2 = 1.8\ [h^{-1}]$

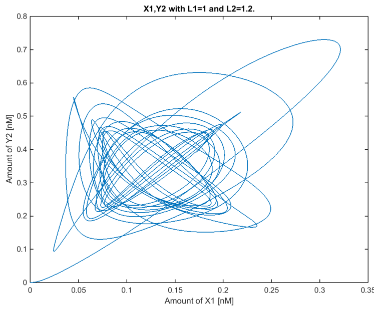


(f) $\lambda_1 = 1,\ \lambda_2 = 2\ [h^{-1}]$

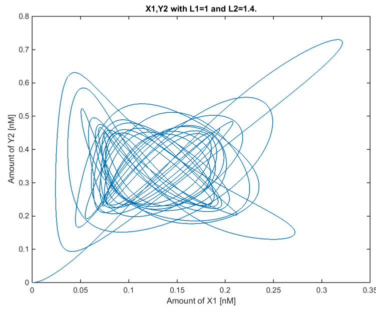
Figure 12: raraara



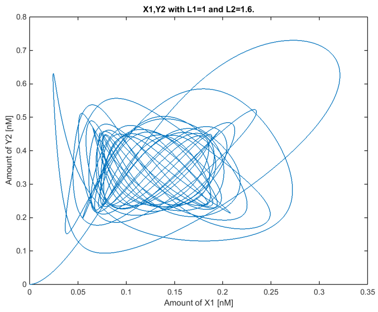
(a) $\lambda_1 = 1$, $\lambda_2 = 1$ $[h^{-1}]$



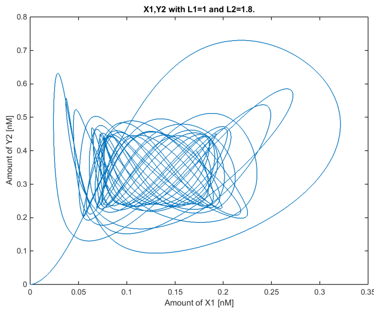
(b) $\lambda_1 = 1$, $\lambda_2 = 1.2$ $[h^{-1}]$



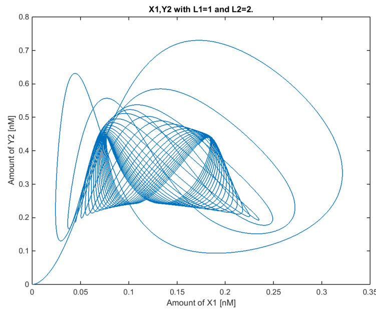
(c) $\lambda_1 = 1$, $\lambda_2 = 1.4$ $[h^{-1}]$



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

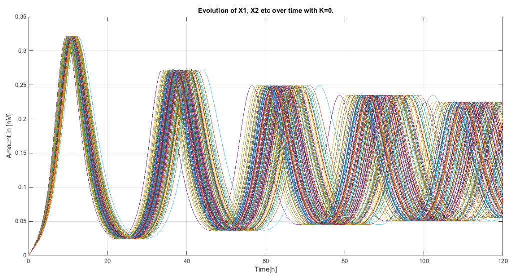


(e) $\lambda_1 = 1$, $\lambda_2 = 1.8$ $[h^{-1}]$

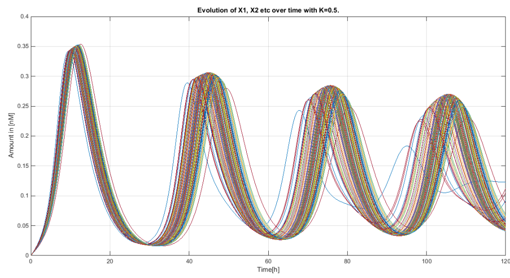


(f) $\lambda_1 = 1$, $\lambda_2 = 2$ $[h^{-1}]$

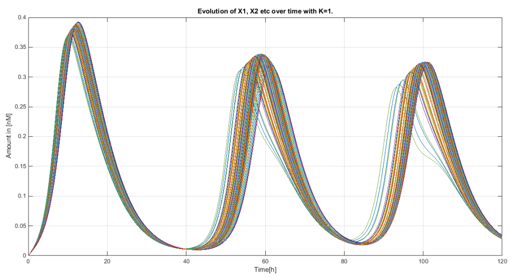
Figure 13: X_1 and Y_2 trajectories



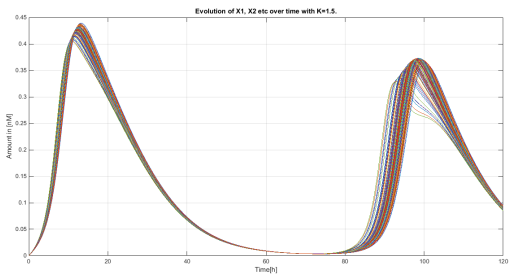
(a) $K = 0.0$



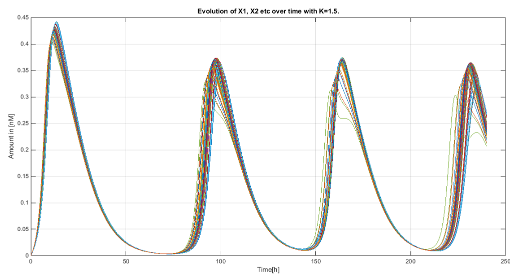
(b) $K = 0.5$



(c) $K = 1.0$

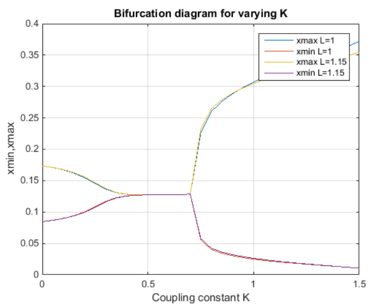


(d) $K = 1.5$

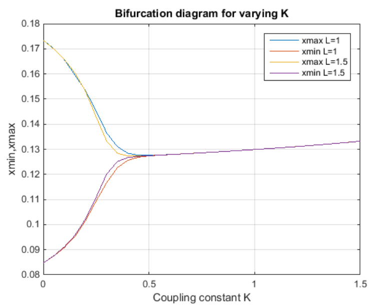


(e) $K = 1.5$

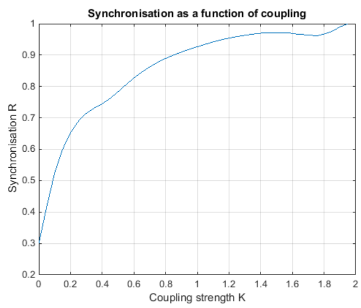
Figure 14: raraara



(a) $K = 0.0$



(b) $K = 0.3$



(c) $K = 1.0$

Figure 15: raraara