Mini-Project in Mathematical and Computational Modeling

École Polytechnique Fédérale de Lausanne, Switzerland

Florian + Dariush

Introduction

The periodic changes that come about due to the day-night cycle to things ranging from visibility to temperature create an environment in which it is advantageous to adapt behaviour to this extrinsic period. Perhaps vision becomes so restricted in the night that basic processes like hunting for food or looking for mates become so inefficient that it's a better strategy to conserve energy when it's dark. Perhaps the opposite is the case and hunting during the night becomes an advantage due to specially evolved senses in animals such as, for example, bats.

For this reason many different lifeforms, from bacteria to animals, have adapted to the 24 hour period that exists around them by synchronising behaviour and processes in different tissues to the day-night cycle by keeping track of time using internal 'clocks'.

In humans this clock works by having a part of the brain, called the suprachiasmatic nuclei (SCN), manage the production of several clock proteins in such a way as to create oscillatory patterns in the concentration of these proteins. These patterns are called circadian when they follow the 24-hour period of the earth's rotation.

Negative feedback loops are used in such a way as to create a periodic rise and fall in the production of proteins that can be influenced by external factors such a light intensity and food uptake to regularly adjust the synchronisation to new environments.

The Model

In this simplified model of the SCN we do not take into account such outside signals and instead focus on behaviours of cells in the SCN all by themselves. The model looks at the production of clock gene mRNA (designated as X), which leads to production of a clock protein(Y). This clock gene protein activates transcription of a third compound (Z), which acts as a transcriptional inhibitor of X, thus creating a negative feedback loop.

In this report we examine several conditions that need to be met for this simple model to exhibit circadian oscillations in the concentrations of the compounds involved. This model is then expanded to investigate synchronisation between cells by taking into account a third protein (V) that is exported and allows the cells in the SCN to talk to each other. First taking into account only 2 cells, this model is expanded to hundreds of cells later on, not reaching the human population of cells in the SCN of 10'000, but at least providing a smaller model that could be scaled up to that number if more processing power was available.

Analysis of the model A

The model under investigation in this report will start out very simple, with a large number of shortcomings and assumptions, which we will attempt to improve upon as analysis progresses. At first we consider a single cell, in a very simple attempt to find conditions under which the concentrations of X,Y and Z will display circadian oscillation. In this first part we will especially focus on the central parameter of the base translation rate of X, the clock gene mRNA. We will vary its value and observe under which conditions circadian behaviour appears. This model obviously looks at one cell in isolation and fails to capture the main usefulness of the system, its ability to integrate information from outside.

Analysis of the model B

In section B we will include multiple cells and the production of the protein V, which allows cells to communicate and synchronise. In this section we will assume that V diffuses so quickly that we can assume its concentration to be the same around all the cells we look at, which is obviously a significant simplification. We would also assume all kinds of delays in its mode of action, depending on how its concentration is sensed by the cells. Of special interest in this section are intrinsic periods of cells. It is sensibly assumed that not all cells will have perfectly identical production rates, and that ultimately the sum of all these differences will be apparent in the period of their oscillations. Next to that we will investigate the coupling factor K, which allows us to manipulate how strongly the cells respond to the average extracellular concentration of V, denoted as F. The strength of the coupling factor, as well as the difference in intrinsic periods of the cells have an impact on whether the cells will synchronise or not, and this section attempts to shed light on these respective conditions.

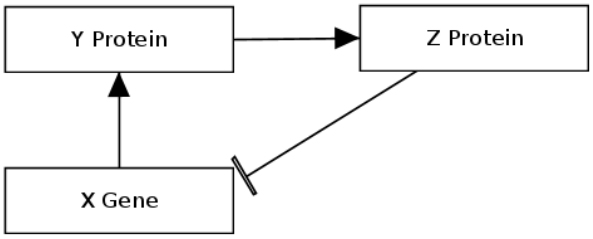
Analysis of the model C

In the third section we will attempt to do justice to the geometry of the situation, and introduce a coupling matrix A, that ideally would tell us exactly how much connection there is between every cell. We did not attempt to create a perfect model, where a greater distance would result in linear falloff, but instead opted to either admit a connection if two cells are neighbours, and deny influence of the cells are removed from each other.

Additionally, we will attempt to emulate a particular behaviour of the SCN, which is that rather than the entire SCN experiencing the same concentrations of clock genes at the same time, those concentrations appear to travel through the SCN in waves, starting at one end, and travelling to the other. This is modelled by introducing a gradient of intrinsic periods going from one end of the cell to the other along what we decided to label the length of the SCN, or the y dimension.

In the very last part we modelled the fact that there are, as the name suggests, two suprachiasmatic nuclei. We will attempt to show that given a certain strength of connection between the two nuclei, simplified with another association matrix, the two nuclei will synchronise to the same circadian behaviour, which in nature is of course the case.

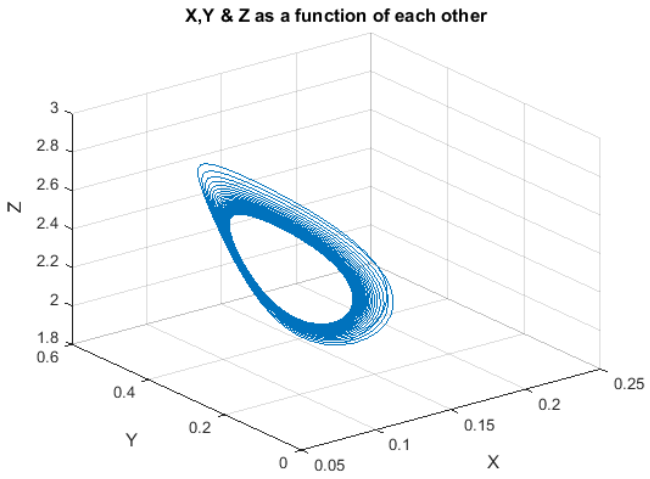
Part A - One-Cell Model



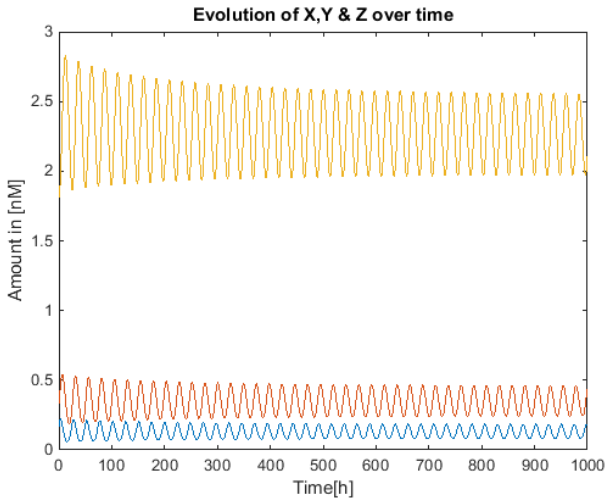
(a) One-Cell Model
The gene mRNA X codes for protein Y which, in turn, activates transcriptional inhibitor Z. The resulting model behaves as a three-variable oscillator.

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

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 Y		
k_5	transcription rate of Z		

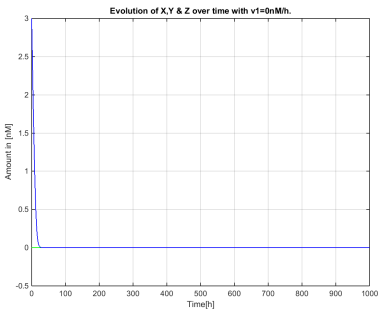


(a) Trajectories
The limit cycle is reached as the variations of $X(t)$, $Y(t)$ and $Z(t)$ become fixed : The trajectories converge, non-lineary (the distance between similar trajectories aren't regular) towards an ellipse (where the blue stripes accumulate)

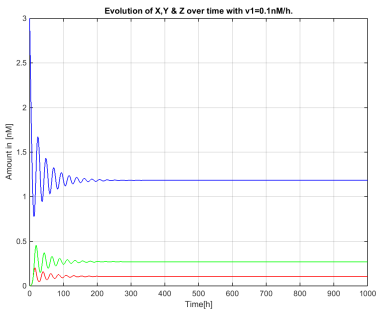


(b) Frequency spectrum
The amplitude of the three variations stabilize after a few hundred hours. The signal are not in phase but have the same, regular, frequencies.

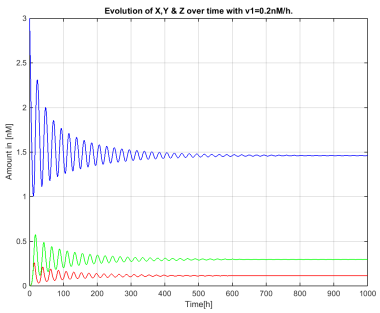
Figure 3:
Trajectories of $X(t)$, $Y(t)$ and $Z(t)$ with initial conditions : $X_0 = 0.16$, $Y_0 = 0.33$, $Z_0 = 1.8$ [nM]
We observe on both graphs that $Z(t)$ has the bigger amplitude of variation whereas $X(t)$ and $Y(t)$ have small amplitudes. Additionaly, the convergence towards a single loop in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



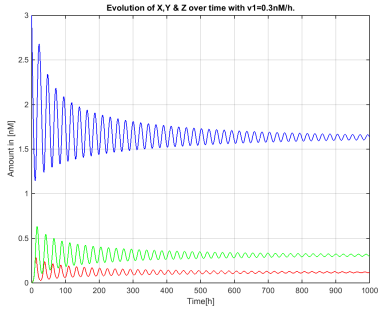
(a) $v_1 = 0$ nM/h



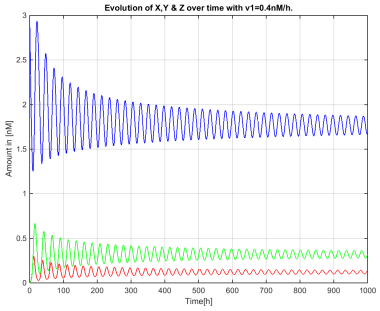
(b) $v_1 = 1$ nM/h



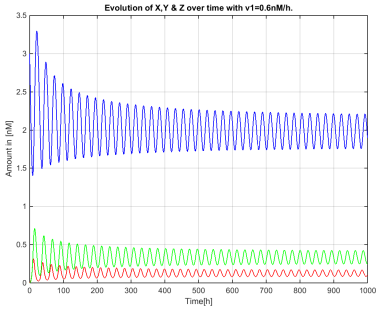
(c) $v_1 = 2$ nM/h



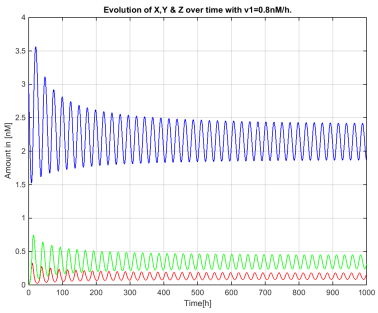
(d) $v_1 = 3$ nM/h



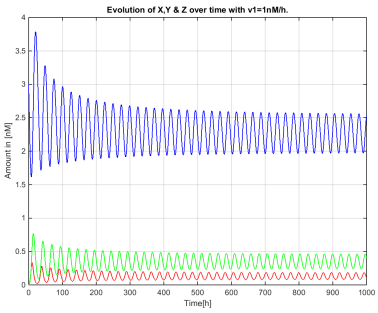
(e) $v_1 = 4$ nM/h



(f) $v_1 = 6$ nM/h

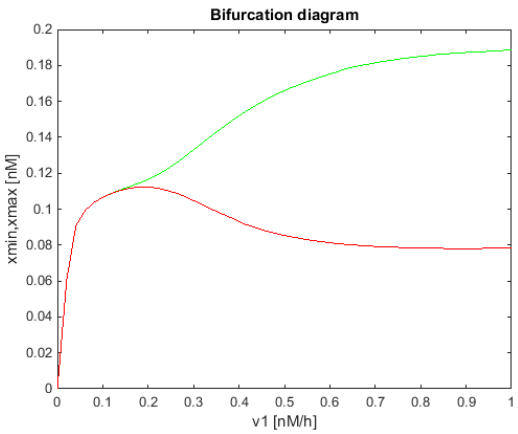


(g) $v_1 = 8$ nM/h

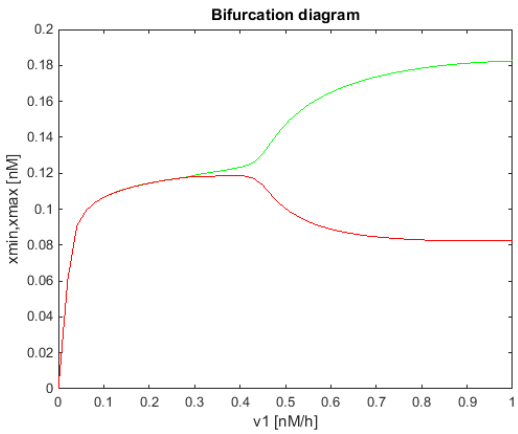


(h) $v_1 = 10$ nM/h

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 ?

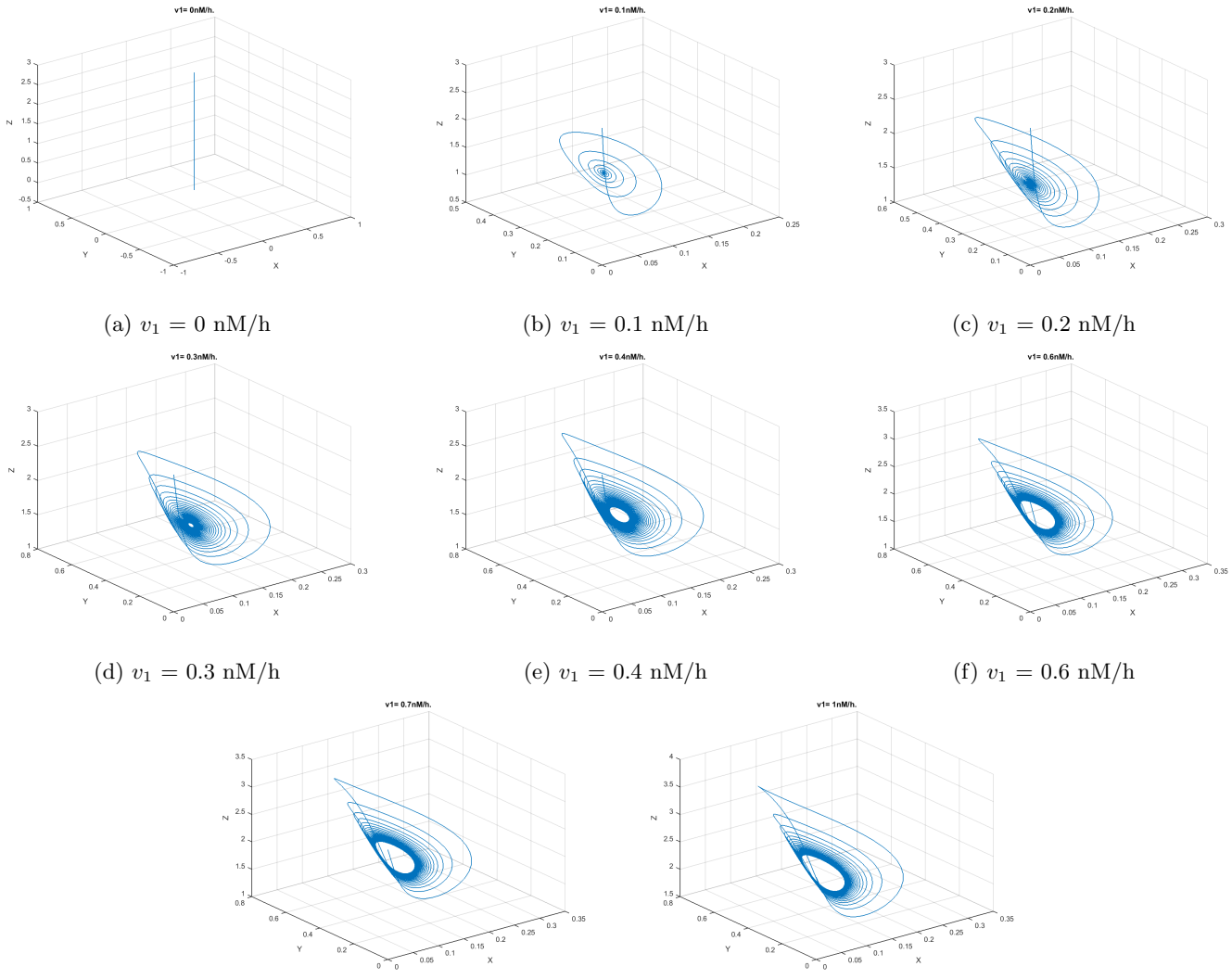


(a) at $h_{max} = 1000$ h



(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.

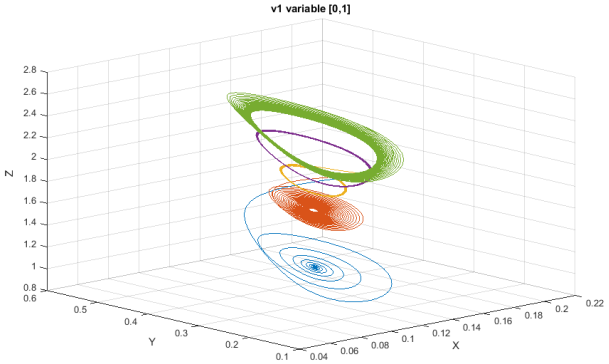
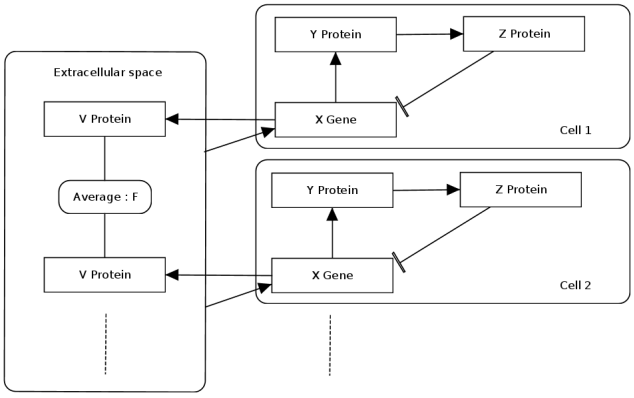


Figure 7: Superimposed trajectories at late timepoints with initial conditions $X_0 = 0.16$, $Y_0 = 0.33$, $Z_0 = 1.8$ [nM] and $v_1 = 0.1/0.3/0.5/0.7/0.9$ nM/h. We observe here that $Z(t)$ tends to reach greater concentration stability with increasing v_1.

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

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

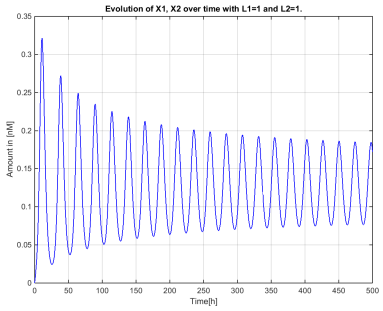
$$\frac{\delta Y}{\delta t} = k_3 X - v_4 \frac{Y}{K_4 + Y}$$

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

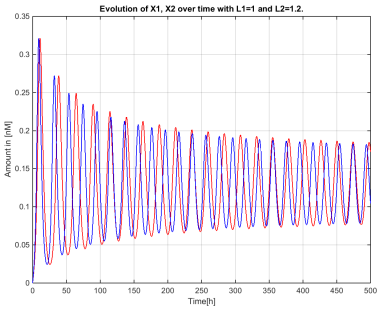
$$\frac{\delta V_i}{\delta t} = k_7 X_i - v_8 \frac{V_i}{K_8 + V_i}$$

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

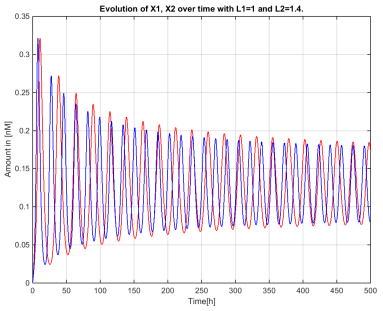
v_1	translation rate of X	k_1	transcription rate of X
v_2	degradation rate of X	K_1	Michaelis constant of X
v_4	degradation rate of Y	K_4	Michaelis constant of Y
v_6	degradation rate of Z	K_6	Michaelis constant of Z
v_8	degradation rate of V	K_8	Michaelis constant of V
k_3	transcription rate of Y	K_c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



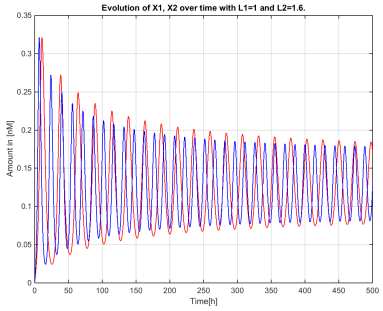
(a) $\lambda_1 = 1$, $\lambda_2 = 1$ $[h^{-1}]$



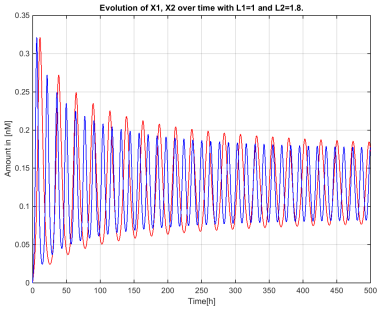
(b) $\lambda_1 = 1$, $\lambda_2 = 1.2$ $[h^{-1}]$



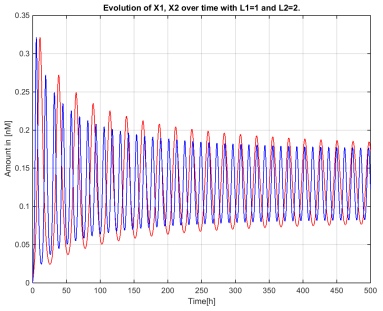
(c) $\lambda_1 = 1$, $\lambda_2 = 1.4$ $[h^{-1}]$



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

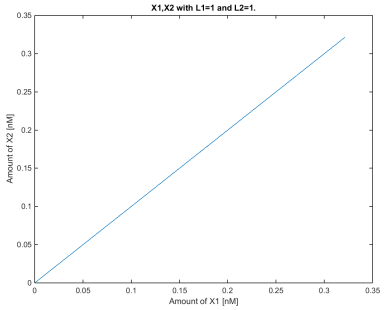


(e) $\lambda_1 = 1$, $\lambda_2 = 1.8$ $[h^{-1}]$

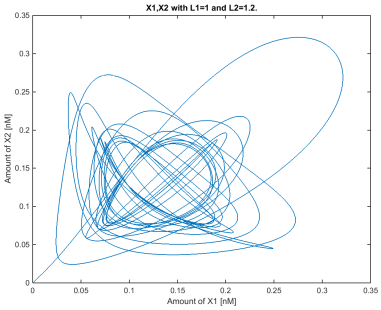


(f) $\lambda_1 = 1$, $\lambda_2 = 2$ $[h^{-1}]$

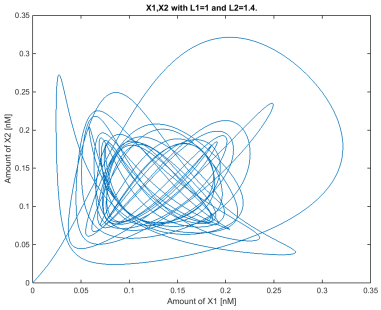
Figure 10: $X_1(t)$ and $X_2(t)$ trajectories in a two-cells Model with $K = 0$ ($\leftrightarrow$ no coupling)
Figure (a) has both signals perfectly aligned. We observe no synchronisation, as excepted.



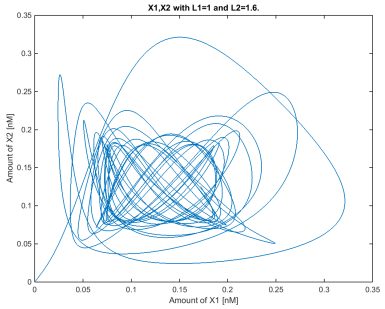
(a) $\lambda_1 = 1$, $\lambda_2 = 1$ $[h^{-1}]$



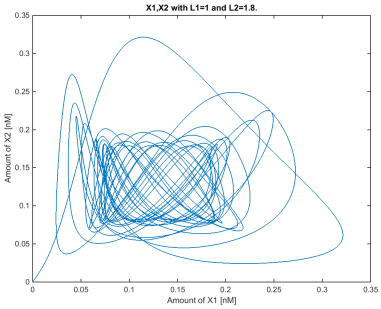
(b) $\lambda_1 = 1$, $\lambda_2 = 1.2$ $[h^{-1}]$



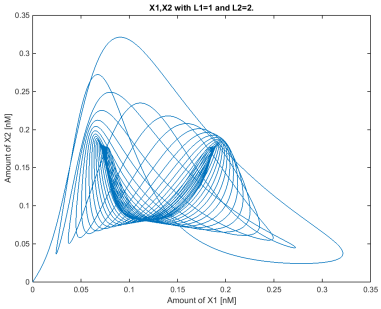
(c) $\lambda_1 = 1$, $\lambda_2 = 1.4$ $[h^{-1}]$



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

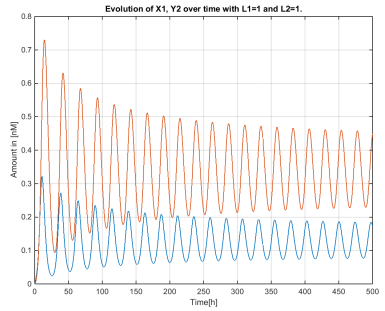


(e) $\lambda_1 = 1$, $\lambda_2 = 1.8$ $[h^{-1}]$

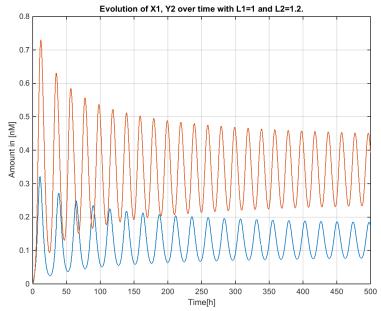


(f) $\lambda_1 = 1$, $\lambda_2 = 2$ $[h^{-1}]$

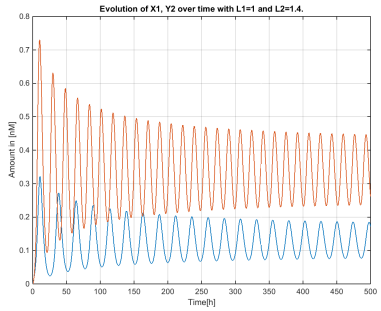
Figure 11: X_1 and X_2 trajectories with varying λ_i in a two-cells Model with $K = 0$
Figure (a), the control, makes perfect sense since the two cells have the same period, hence the exact same signal. With unequal periods, the limit cycles of both cells aren't in phase and form these '8' patterns. The fluctuations at the beginning of trajectories come from the inner adjustment of the cells (see Figure 6). 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) ?



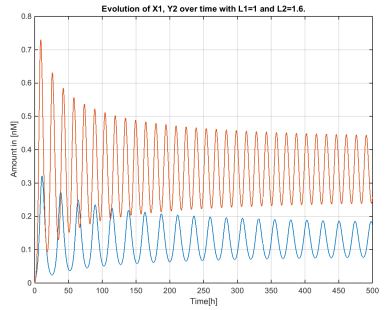
(a) $\lambda_1 = 1$, $\lambda_2 = 1$ $[h^{-1}]$



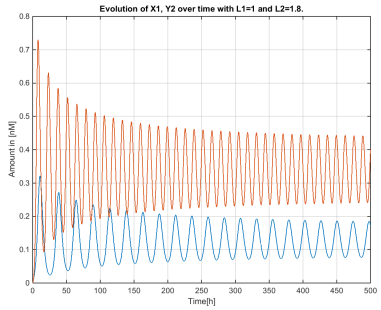
(b) $\lambda_1 = 1$, $\lambda_2 = 1.2$ $[h^{-1}]$



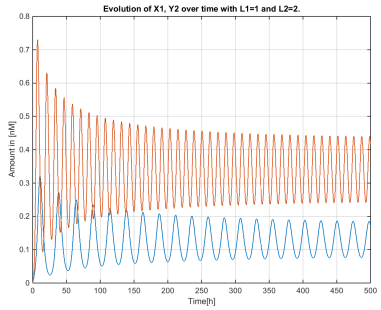
(c) $\lambda_1 = 1$, $\lambda_2 = 1.4$ $[h^{-1}]$



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

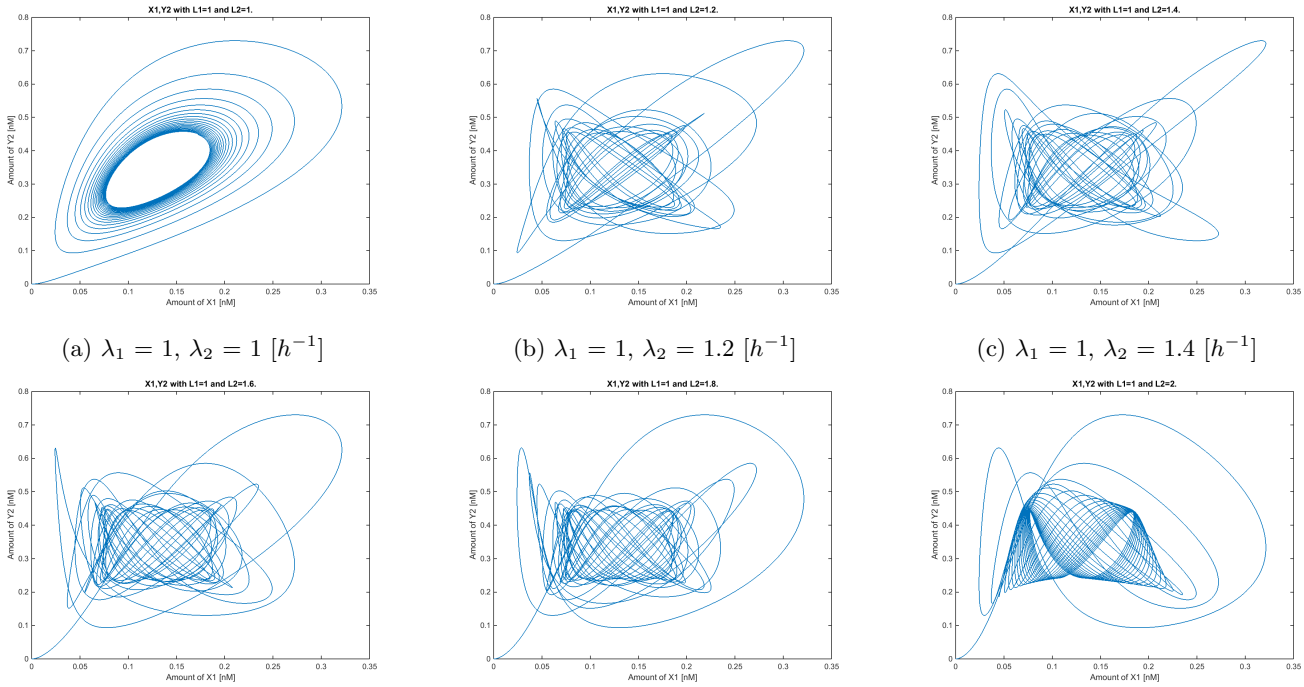


(e) $\lambda_1 = 1$, $\lambda_2 = 1.8$ $[h^{-1}]$



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

Figure 12: $X_1(t)$ and $Y_2(t)$ trajectories in a two-cells Model with $K = 0$
We observe no synchronisation, as excepted. nothing else to say ? :(



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

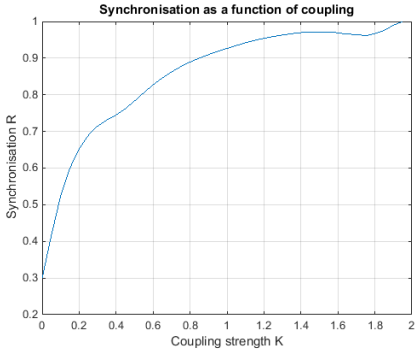
(d) $\lambda_1 = 1$, $\lambda_2 = 1.6$ $[h^{-1}]$ (e) $\lambda_1 = 1$, $\lambda_2 = 1.8$ $[h^{-1}]$ (f) $\lambda_1 = 1$, $\lambda_2 = 2$ $[h^{-1}]$

Figure 13: X_1 and Y_2 trajectories with varying λ_i in a two-cells Model with $K = 0$

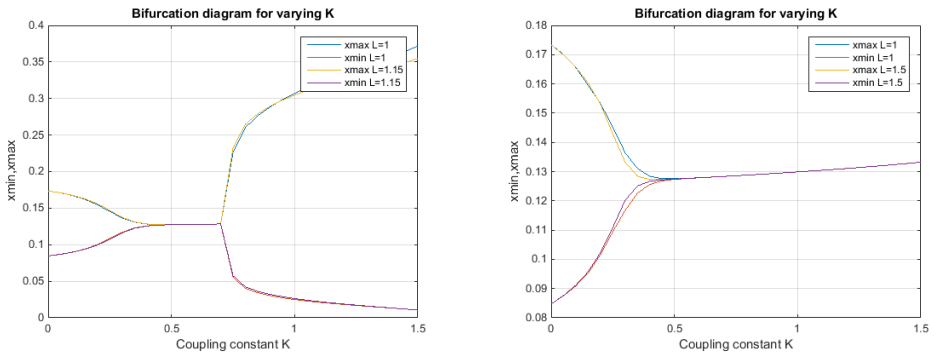
Once again, both cells tend to reach their limit cycles without any kind of interaction. The same observations as in Figure 11 can be made.

$$R = \frac{\langle F^2 \rangle - \langle F \rangle^2}{\frac{1}{N}\sum_{i=1}^{N}(\langle V_i^2 \rangle - \langle V_i \rangle^2)}$$

The Coefficient of Synchronization R is - obviously - a measure of the synchronisation between N different cells. This ratio can take any value between 0 and 1 as the variance of F cannot exceed the mean value of the individual variances of V_i.
$R = 1$ means very high synchronisation rate as $R = 0$ means no synchronisation at all.



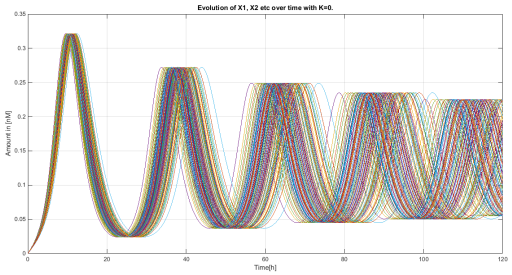
(b) Value of R depending on the Coupling Constant K



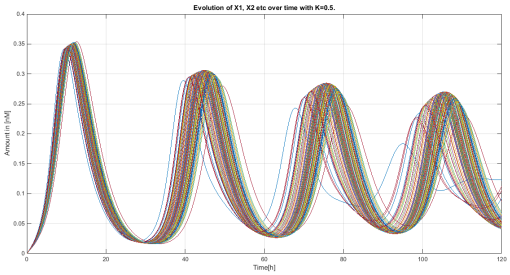
(c) eeeh (d) eeeh

Figure 14: The Coupling Constant K has an impact on the synchronisation of the population.

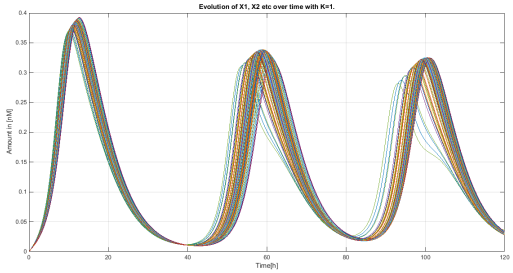
We observe that $K > 0.5$ or high ? has a disastrous effect on both cells cycles. The reason for this is that the positive feedback loop has high sensitivity and tends to overload concentrations of Z_i which in turn inhibit any production of X_i.



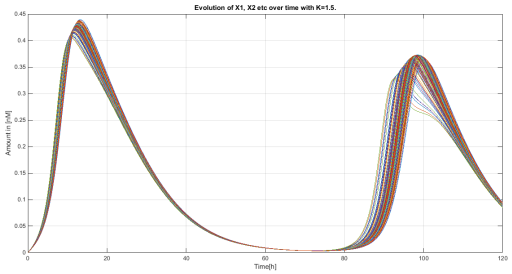
(a) $K = 0.0$



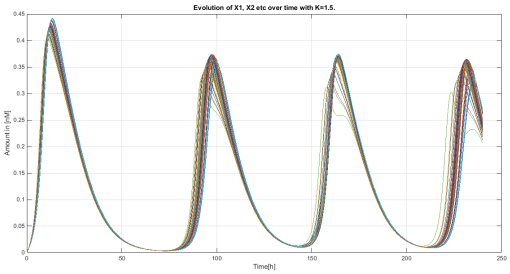
(b) $K = 0.5$



(c) $K = 1.0$

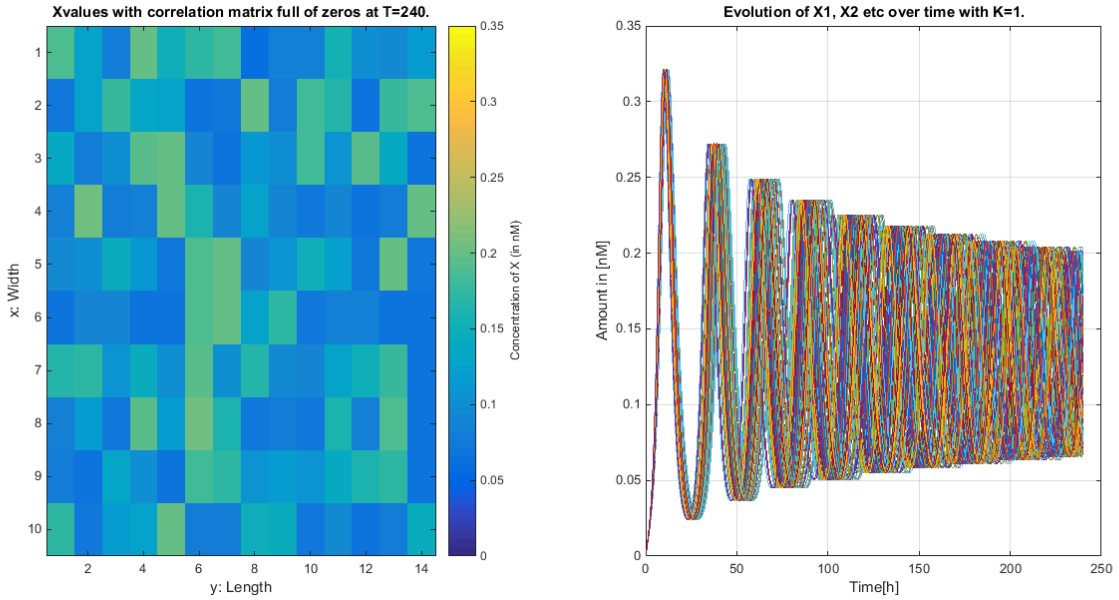


(d) $K = 1.5$

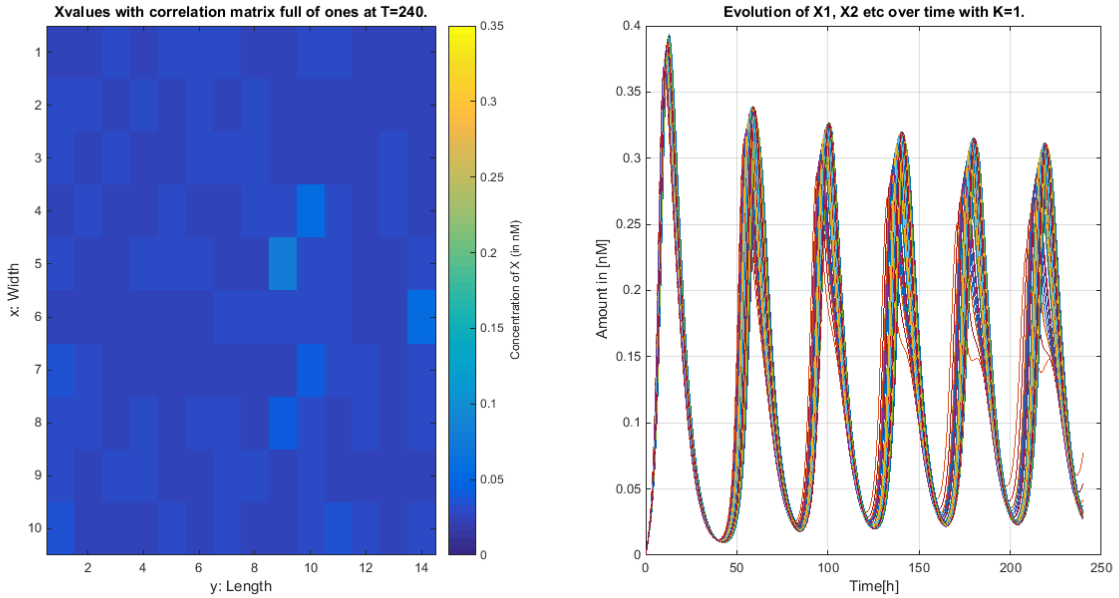


(e) $K = 1.5$

Figure 15: raraara



(a) $K = 0.0$



(b) $K = 0.3$

Figure 16: raraara