Mini-Project in Mathematical and Computational Modeling

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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.

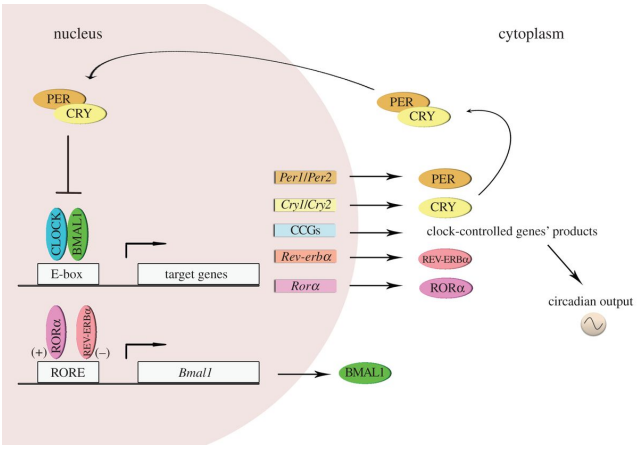
The Model

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.

Circadian clock in mammals

The oscillator can be modeled following the molecular circadian clock in mammals :
Model proteins Y and Z act like the PER/CRY complex were PER is the product of the genes Per1 and Per2 and CRY of Cry1 and Cry2. This complex is built in the cytoplasm and re-enters the nucleus to inhibit an activator of Per1, Per2, Cry1 and Cry2 : CLOCK and BMAL1 (equivalent of X), both activating the upstream promoter sequence E-Box. This whole process concludes a negative feedback loop.
Furthermore, BMAL1 activates itself by the mean of proteins Rorα and REV-ERBα (mimicked by V in our model) which link to a promoter of Bmal1.
The following figure (taken from [1]) represents this one.



PER, CRY and BMAL1 pathways

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

[1] "Minutes, days and years: molecular interactions among different scales of biological timing" 2014, by Diego A. Golombek et al.

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

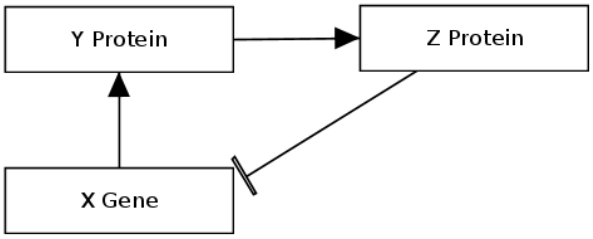
In the third section we will attempt to do justice to the geometry of the situation, and introduce a coupling matrix A, that ideally would tell us exactly how much connection there is between every cell. We did not attempt to create a perfect model, where a greater distance would result in linear falloff, 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.

In the following url you can find the collection of .gif files that we made to show the evolution of X in all N cells over time.
`https://github.com/Afanc/mini-pro-model/tree/Florian/Miniprojet%202.0/Part%20C`
In C_2_gif_1 until C_2_gif_6 we see the evolution of the complexity of our system. The titles in the .gif files give the indication as to what part of the model was added. A is the reference to the correlation matrix between the cells. Lambda refers to the multiplier of the period.
N is the number of cells simulated. A gradient of lambdas is introduced to emulate wave-like propagation of the signal in the SCN. In the last two heat maps, we simulate synhcronisation between he two halves of the SCN, with no connection between the wo at first and different base periods to see if they could synchcronise of they were out of sync. In the second one there is a very strong connection between the two halves, and synchronisation takes place again.

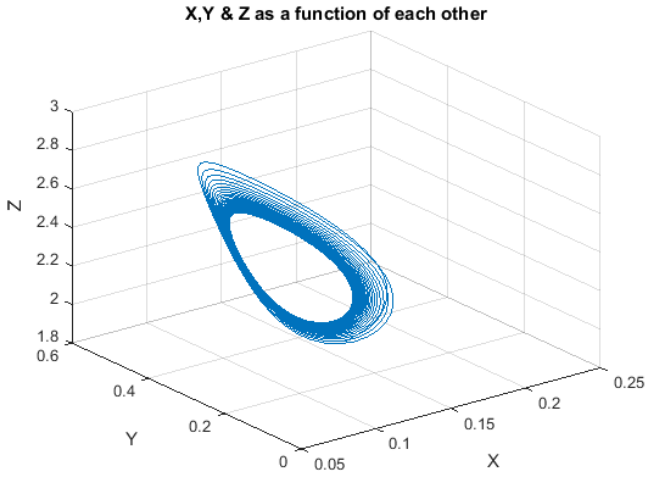
Part A - One-Cell Model



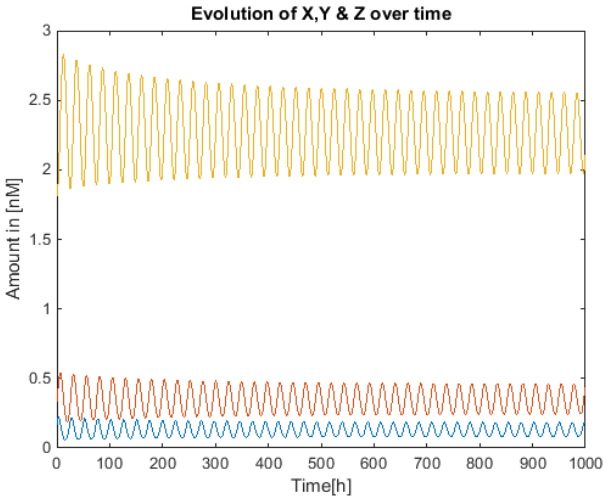
(a) One-Cell Model
The gene mRNA X codes for protein Y which, in turn, activates transcriptional inhibitor Z. The resulting model behaves as a three-variable oscillator.

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

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		

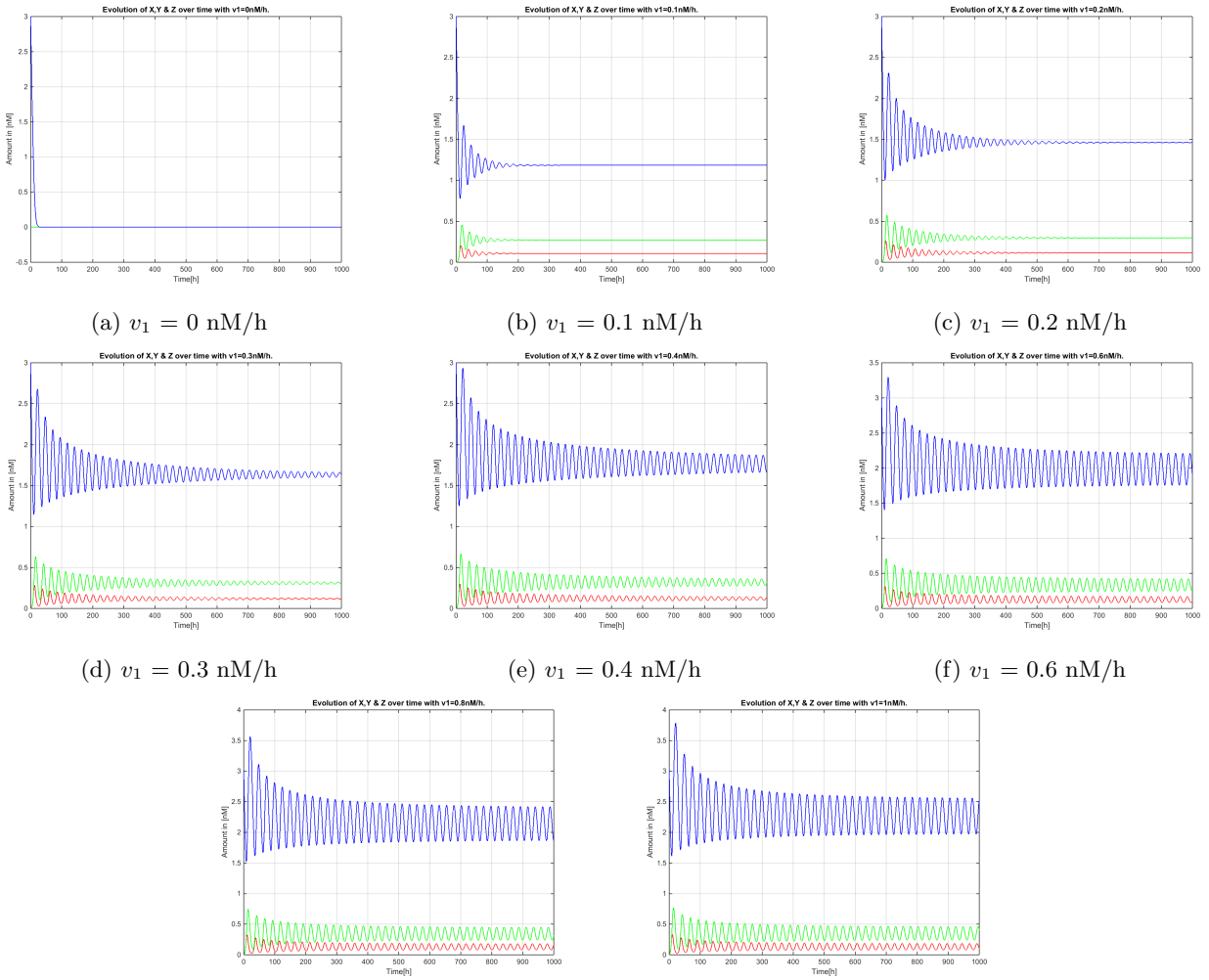


(a) Trajectories
The limit cycle is reached as the variations of $X(t)$, $Y(t)$ and $Z(t)$ become fixed : The trajectories converge, non-linearly (the distance between similar trajectories aren't regular) towards an elliptic limit cycle. The limit cycle is reached quickly due to favorable choice of initial conditions close to final concentrations.



(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 4:
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. Additionally, the convergence towards a single loop in (a) indicate that the frequencies of the signals are equal; this is illustrated as well in (b)

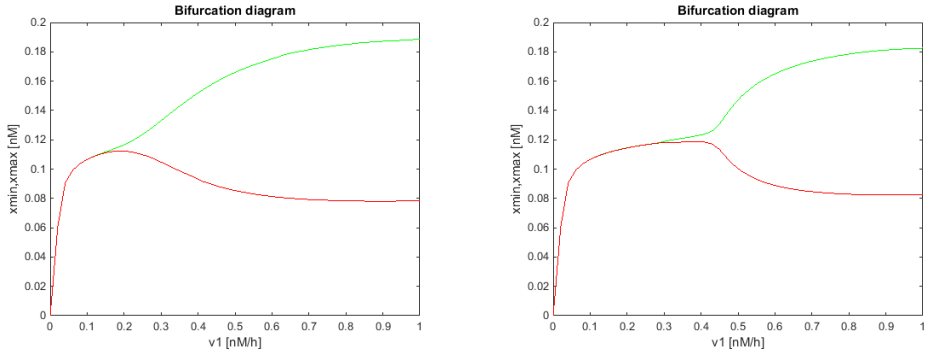


(a) $v_1 = 0$ nM/h (b) $v_1 = 0.1$ nM/h (c) $v_1 = 0.2$ nM/h

(d) $v_1 = 0.3$ nM/h (e) $v_1 = 0.4$ nM/h (f) $v_1 = 0.6$ nM/h

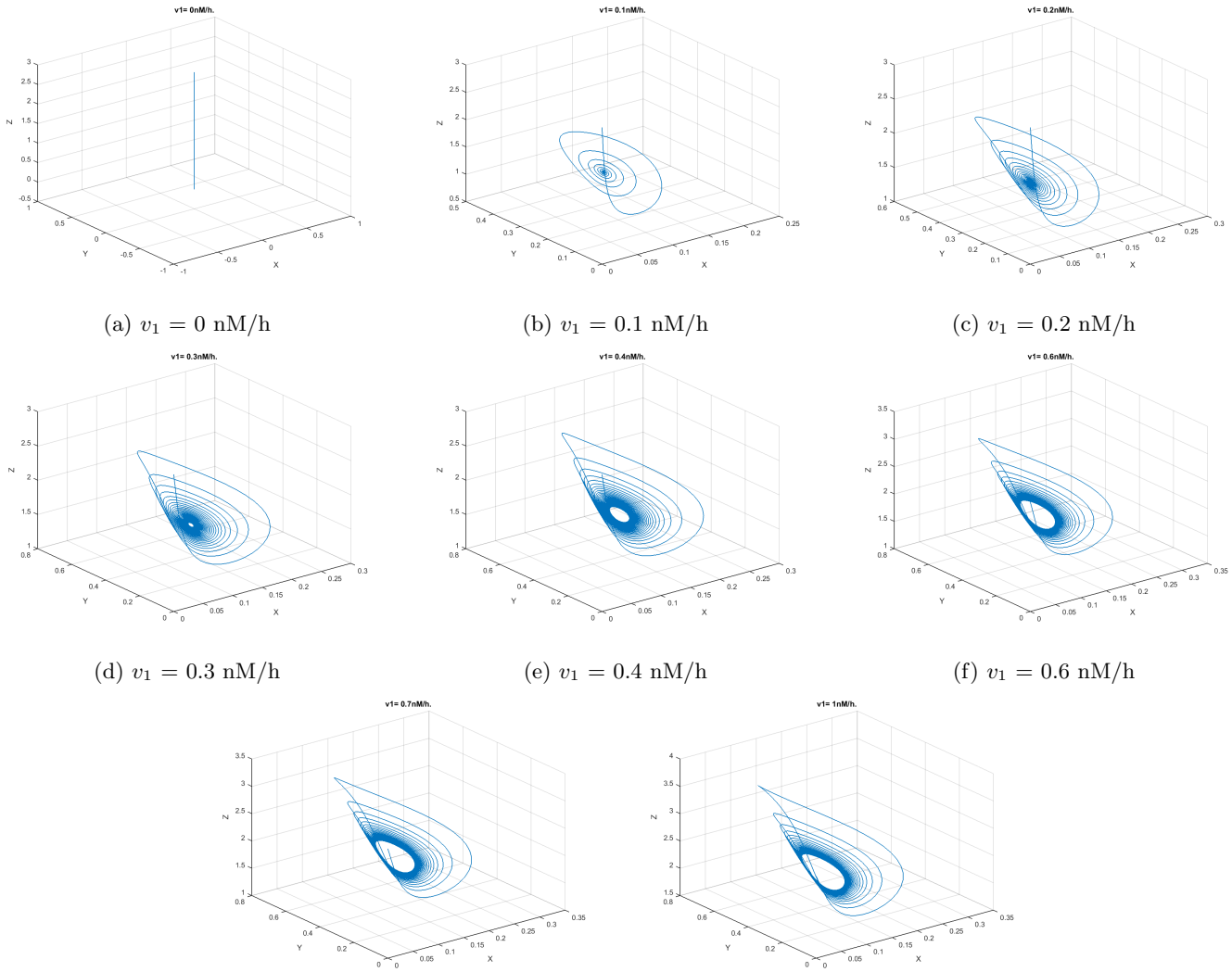
(g) $v_1 = 0.8$ nM/h (h) $v_1 = 1$ nM/h

Figure 5: $X(t)$, $Y(t)$ 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, a fixed point or the limit cycle in a non-linear fashion. It is hard to precisely know the value for v_1 for which the system begins to display circadian behaviour, but it must be somewhere around $v_1 = 0.5$nM/h. A more accurate estimate will be made in the bifurcation diagram that follows. Interesting here is that the concentrations will reach a stable fixed point if v_1 is below a certain threshold.



(a) at $t_{max} = 1000$ h (b) at $t_{max} = 10\,000$ h

Figure 6: Bifurcation Diagram : X_{min} and X_{max} plotted at time intervals $[9/10; 1]$ of t_{max}, meaning it plots the maximum and minimum values in the last tenth of the simulation where we are sure that a either a limit cycle or a stable fixed point has already been reached. 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. In figure (b) the simulation was run for ten times longer, showing that for values of v_1 between 0.2 and 0.4 nM/h, there is very slow oscillatory convergence to a fixed point, which is the same result that is suggested by figure 4 above. The threshold for v_1 for the system to reach circadian oscillation seems to be around 0.4 nM/h

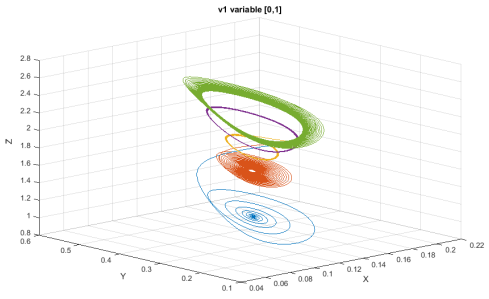


(a) $v_1 = 0$ nM/h (b) $v_1 = 0.1$ nM/h (c) $v_1 = 0.2$ nM/h

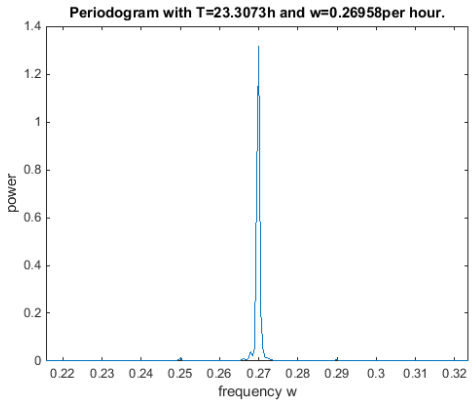
(d) $v_1 = 0.3$ nM/h (e) $v_1 = 0.4$ nM/h (f) $v_1 = 0.6$ nM/h

(g) $v_1 = 0.8$ nM/h (h) $v_1 = 1$ nM/h

Figure 7: 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 around 0.4 nM/h, as the trajectories still converge close to zero in (e); there is an 'eye', even though it is smaller than in (f) and (g). It is possible that the simulation time is not long enough to let the system dissipate completely.



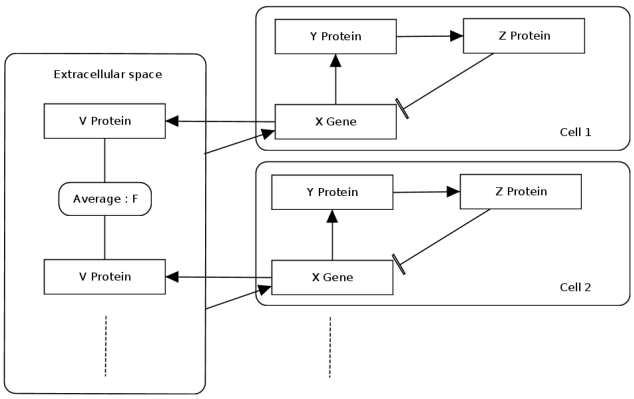
(a) Superimposed trajectories at late timepoints with initial conditions $X_0 = 0.16$, $Y_0 = 0.33$, $Z_0 = 1.8$ [nM] and $v_1 = 0.1/0.3/0.5/0.7/0.9$ nM/h. We observe here that $Z(t)$ tends to reach greater concentration stability with increasing v_1.



(b) Periodogram of the oscillations above with v_1 =0.7nM/h.

Figure 8: This analysis of the trajectories allows to sample for frequencies that are strongly represented in a set of data points. The simulations above appear to have a strong representation around a frequency that corresponds to a period of 23.4 hours, which is close to the 24 hour circadian rhythm that is observed in nature.

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

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

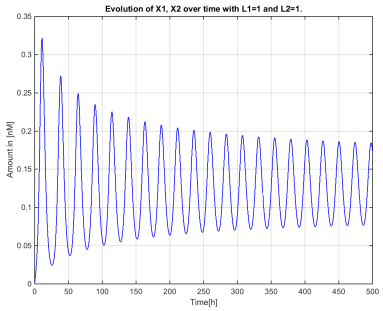
$$\frac{\delta Y}{\delta t} = k_3 X - v_4 \frac{Y}{K_4 + Y}$$

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

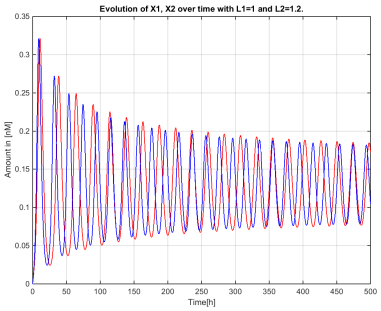
$$\frac{\delta V_i}{\delta t} = k_7 X_i - v_8 \frac{V_i}{K_8 + V_i}$$

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

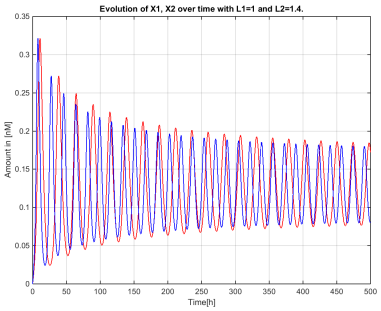
v_1	translation rate of X	k_1	transcription rate of X
v_2	degradation rate of X	K_1	Michaelis constant of X
v_4	degradation rate of Y	K_4	Michaelis constant of Y
v_6	degradation rate of Z	K_6	Michaelis constant of Z
v_8	degradation rate of V	K_8	Michaelis constant of V
k_3	transcription rate of Y	K_c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



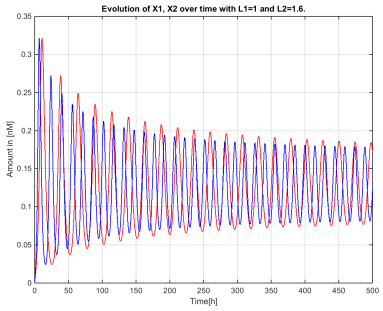
(a) $\lambda_1 = 1$, $\lambda_2 = 1$ $[h^{-1}]$



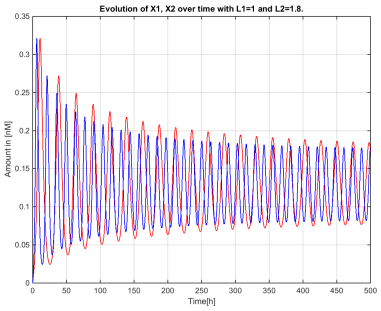
(b) $\lambda_1 = 1$, $\lambda_2 = 1.2$ $[h^{-1}]$



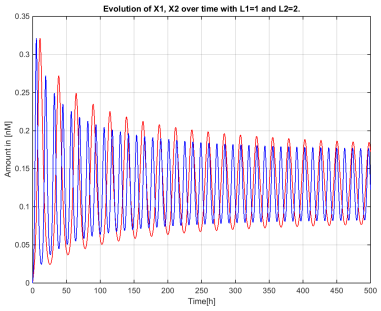
(c) $\lambda_1 = 1$, $\lambda_2 = 1.4$ $[h^{-1}]$



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

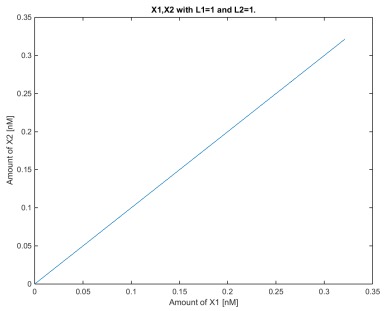


(e) $\lambda_1 = 1$, $\lambda_2 = 1.8$ $[h^{-1}]$

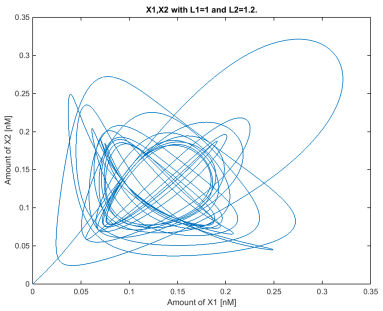


(f) $\lambda_1 = 1$, $\lambda_2 = 2$ $[h^{-1}]$

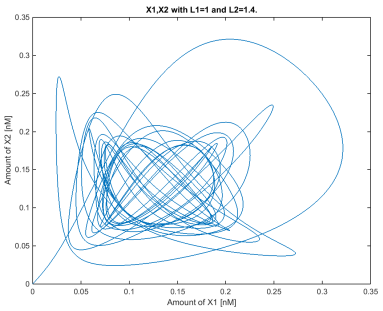
Figure 11: $X_1(t)$ and $X_2(t)$ trajectories in a two-cells Model with $K = 0$ ($\leftrightarrow$ no coupling)
Figure (a) has both signals perfectly aligned. We observe no synchronisation, as expected These figures mainly serve to show whether the signals are in or out of phase, to help interpret figure 11 more easily.



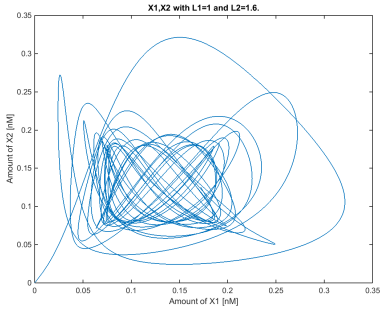
(a) $\lambda_1 = 1$, $\lambda_2 = 1$ $[h^{-1}]$



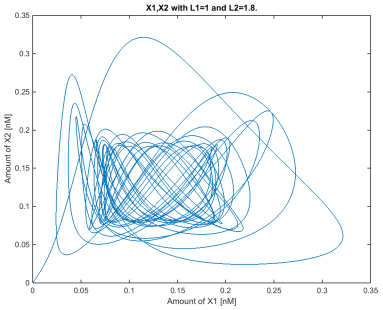
(b) $\lambda_1 = 1$, $\lambda_2 = 1.2$ $[h^{-1}]$



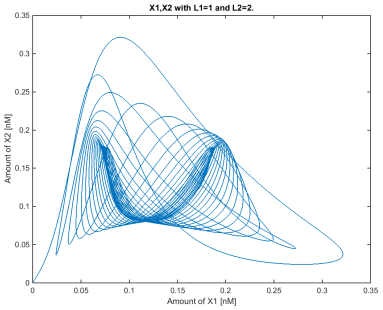
(c) $\lambda_1 = 1$, $\lambda_2 = 1.4$ $[h^{-1}]$



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



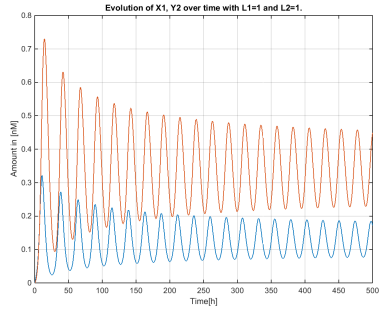
(e) $\lambda_1 = 1$, $\lambda_2 = 1.8$ $[h^{-1}]$



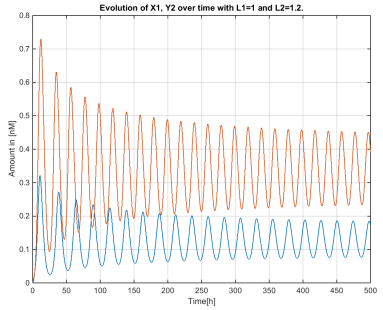
(f) $\lambda_1 = 1$, $\lambda_2 = 2$ $[h^{-1}]$

Figure 12: X_1 and X_2 trajectories with varying λ_i in a two-cells Model with $K = 0$

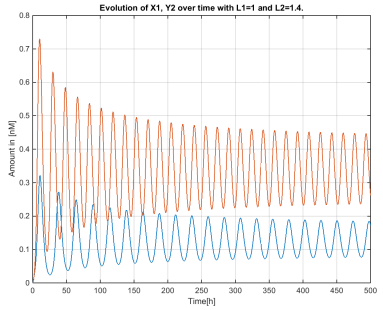
Figure (a), the control, makes perfect sense since the two cells have the same period, hence the exact same signal. With unequal periods, the limit cycles of both cells aren't in phase and form these '8' patterns. The fluctuations at the beginning of trajectories come from the inner adjustment of the cells (see Figure 7). The sides of the rectangles that appear represent the variation of X_1 and X_2 between their minimal and maximal values and receiving a rectangle shows us that we reach a limit cycle. (f) gives us a different pattern due to the two periods being a multiple of each other. We expect the phase difference not to vary greatly over time, as in the other figures.



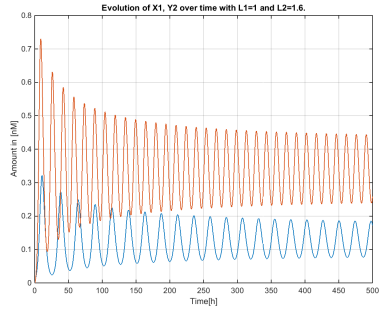
(a) $\lambda_1 = 1$, $\lambda_2 = 1$ $[h^{-1}]$



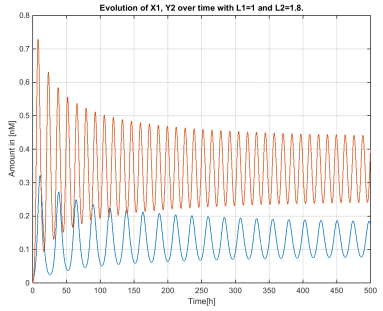
(b) $\lambda_1 = 1$, $\lambda_2 = 1.2$ $[h^{-1}]$



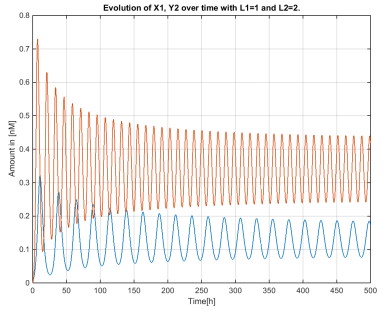
(c) $\lambda_1 = 1$, $\lambda_2 = 1.4$ $[h^{-1}]$



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

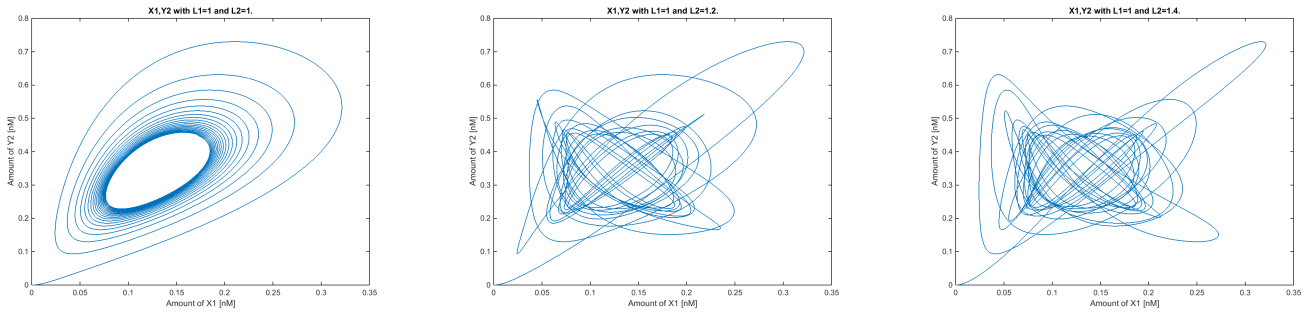


(e) $\lambda_1 = 1$, $\lambda_2 = 1.8$ $[h^{-1}]$

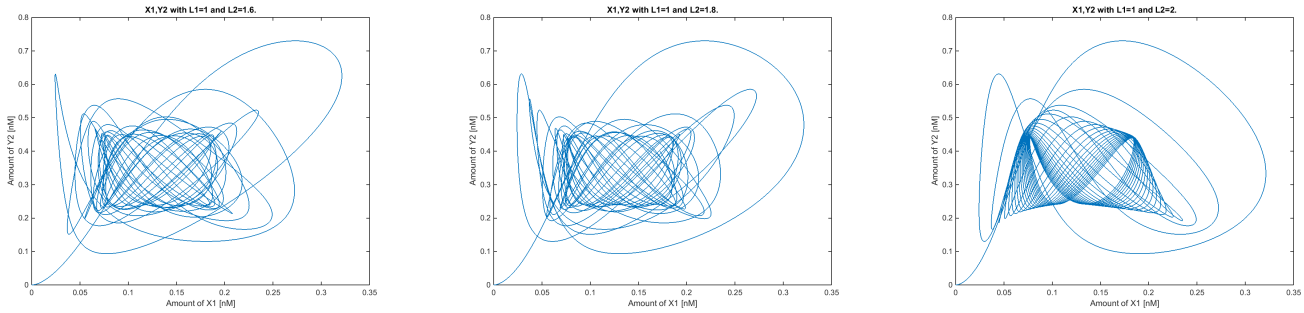


(f) $\lambda_1 = 1$, $\lambda_2 = 2$ $[h^{-1}]$

Figure 13: $X_1(t)$ and $Y_2(t)$ trajectories in a two-cells Model with $K = 0$ (no synchronisation). The key observation to make here is that the signal of Y(t) is always slightly delayed to X(t).



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



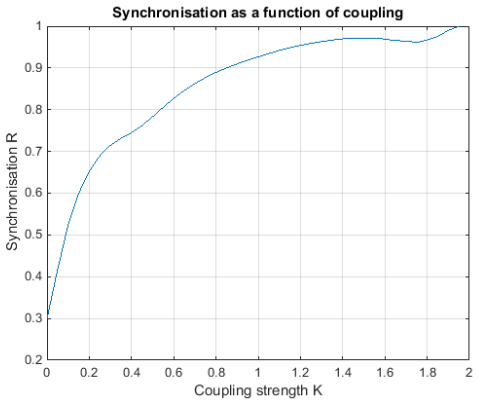
(d) $\lambda_1 = 1$, $\lambda_2 = 1.6$ $[h^{-1}]$ (e) $\lambda_1 = 1$, $\lambda_2 = 1.8$ $[h^{-1}]$ (f) $\lambda_1 = 1$, $\lambda_2 = 2$ $[h^{-1}]$

Figure 14: 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 12 can be made, except for the key difference in figure (a), where the fact that the two cells share the same period but are partially out of phase creates a limit cycle instead of a linear interaction.

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

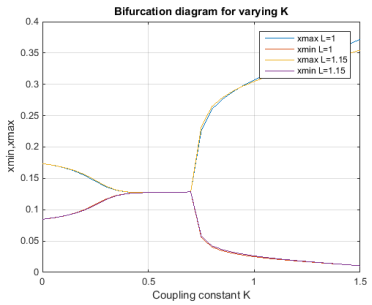
The Coefficient of Synchronization R is as the name suggests a measure of the synchronisation between N different cells. This ratio can take any value between 0 and 1 as the variance of F cannot exceed the mean value of the individual variances of V_i.
$R = 1$ means very high synchronisation whereas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



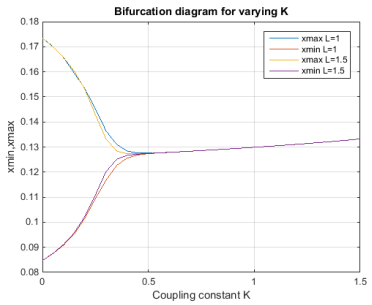
(b) Value of R depending on the Coupling Constant K

Figure 15: We introduce the Coefficient of Synchronization R

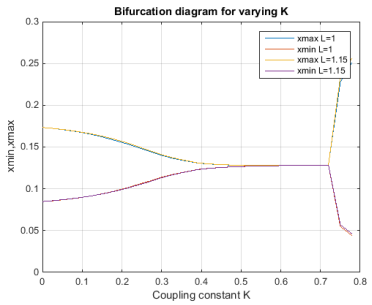
The plot shows some irregularity, but shows a clear trend. The higher the strength of the signal of V is (denoted by the factor K), the more the cells begin to oscillate in synchronisation.



(a) $\lambda_1 = 1$ $\lambda_2 = 1.15$
and initial conditions
$X_{i,0} = 0$ $Y_{i,0} = 0$ $Z_{i,0} = 3$ $V_0 = i, 0$

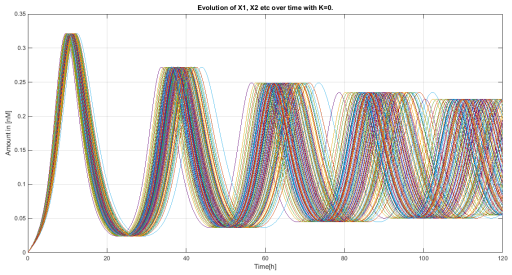


(b) $\lambda_1 = 1$ $\lambda_2 = 1.5$
and initial conditions
$X_{i,0} = 0$ $Y_{i,0} = 0$ $Z_{i,0} = 3$ $V_0 = i, 0$

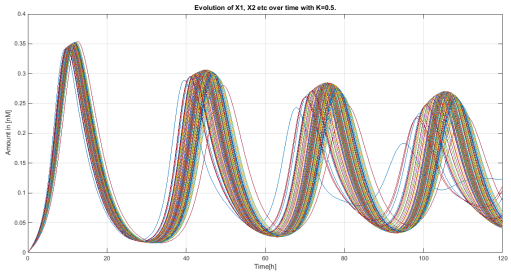


(c) $\lambda_1 = 1$ $\lambda_2 = 1.15$
and initial conditions
$X_{i,0} = 0$ $Y_{i,0} = 0$ $Z_{i,0} = 0$ $V_{i,0} = 0$

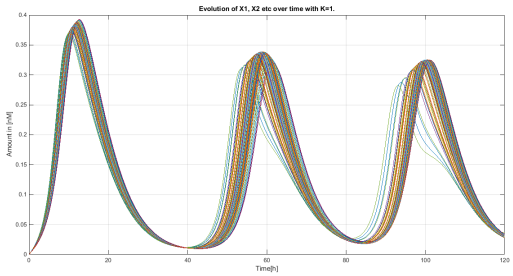
Figure 16: Bifurcation diagram in a two-cells Model X_{min} and X_{max} plotted at time intervals $[9/10; 1]$ of $h_{max} = 2000$h. We observe that if $K >$ a threshold value and if the difference in the periods of the two cells is high enough, the circadian behaviour of both cells dies. The reason for 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. This behaviour is further noticeable when the initial conditions are far from those of their limit cycles, as the cells enter tighter limit cycles ($\Delta X_{(c)} < \Delta X_{(a)}$)



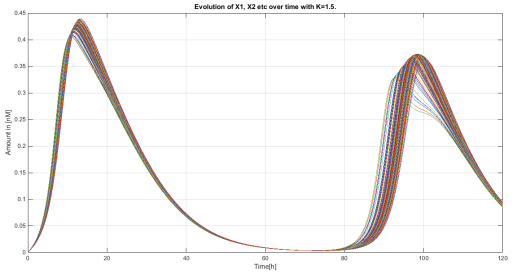
(a) $K = 0.0$



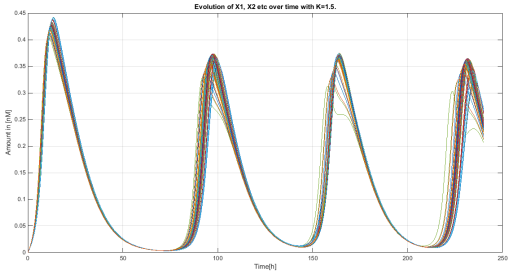
(b) $K = 0.5$



(c) $K = 1.0$



(d) $K = 1.5$



(e) $K = 1.5$

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Figure 17: $X_i(t)$ trajectories in a 100-Cells Model with initial conditions $X_{i,0} = 0$ $Y_{i,0} = 0$ $Z_{i,0} = 3$ $V_{i,0} = 0$ and $\lambda_i \sim N(0, 0.05)$. As excepted, with no coupling the cells are unable to synchronize leading to the loss of the signal in (a). Furthermore, with increasing K the population synchronizes in 2-5 periods and in a decreasing period length pattern u know talk english?.

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Figure 18: $X_i(t)$ trajectories in a 100-Cells Model with initial conditions $X_{i,0} = 0$ $Y_{i,0} = 0$ $Z_{i,0} = 3$ $V_{i,0} = 0$ and $\lambda_i \sim N(1, 0.05)$. As expected, with no coupling the cells are unable to synchronize leading to the loss of the signal in (a). Furthermore, with increasing K the population synchronizes in longer periods. But the higher the strength of the inter-cellular signal, the more synchronisation we observe.

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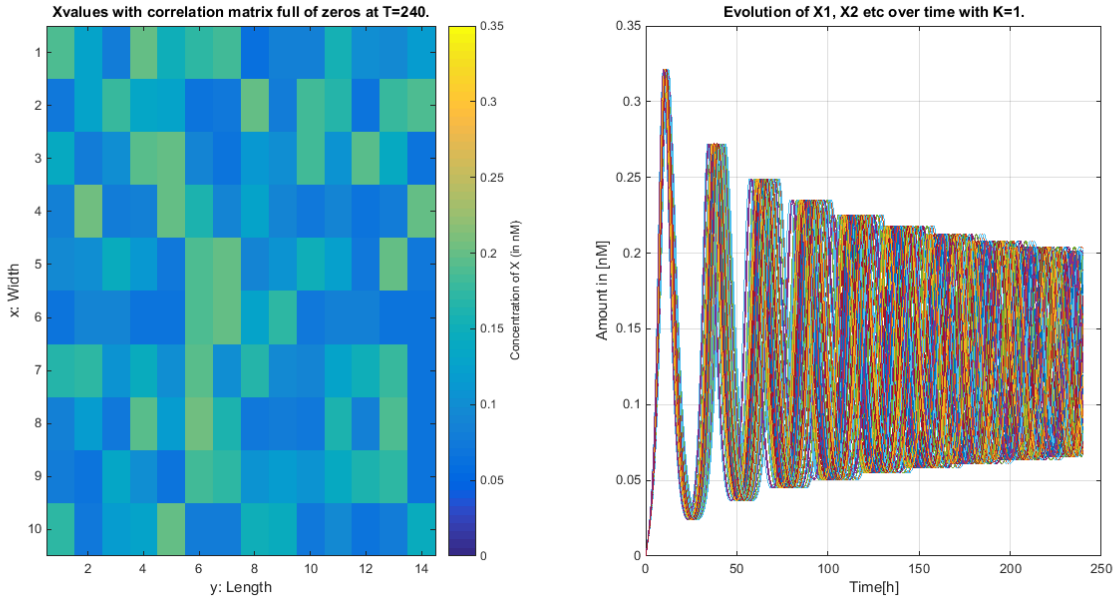
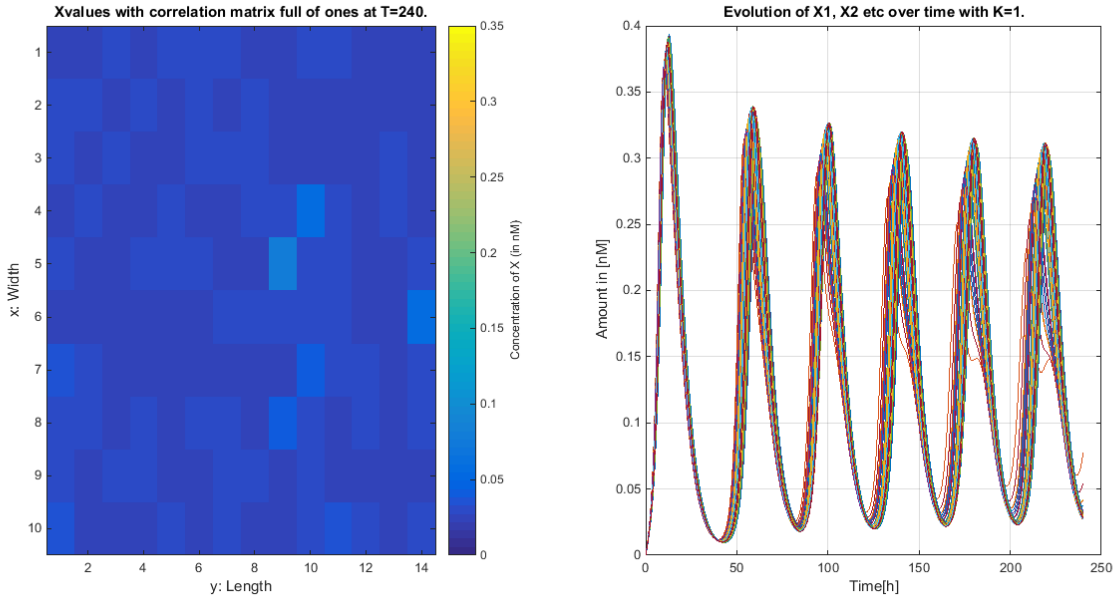
Part C - Circadian Behaviour in the Brain



(a) $K = 0.0$



(b) $K = 0.3$

Figure 20: raraara