Synchronization of Two Cellular Circadian Rhythms

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Abstract

ABSTRACT

1 Introduction

Almost all animals have innate biological clock that controls various timing inside the body. Negative feedback of gene expression is one typical generator for a mammalian circadian clock. One simple model of the circadian rhythm is to consider the clock gene expression in a particular cell. This has been shown in Wang and Peskin's work. Building upon their work, we investigate the coupling of two cells with different periods, and study the possible interactions among them.

The model for one cellular circadian oscillator consists of the following: the mRNA and the corresponding proteins encoded by the gene. First, mRNA molecules are synthesized through transcription and enter the cytoplasm. Then, protein molecules are generated in the cytoplasm through translation. Some protein molecules will enter the nucleus and bind to some activating transcription factor on the DNA, thus inhibiting the transcription. This provides a negative feedback that can lean to oscillations in the amount of substances in the cell, provided the parameters are well-chosen.

In this paper we build two such cellular circadian oscillators with different periods. To simulate the information exchange between the two cells, we take a simplified approach that allows protein molecules to directly flow between two cells through diffusion. Both deterministic version and stochastic version of the model are utilized to compare the results.

In the rest of the paper, we first use the deterministic version to find suitable parameters that will generate two oscillations with different periods. Next, we use the deterministic model to study the case when two cells are coupled. Finally, the stochastic version of the model is investigated. Comparisons and analysis are also stated at the end.

2 Mathematical Modeling

2.1 A Simple Cellular Circadian Oscillator

We construct a four-variable model to simulate the mammalian circadian clock in a cell. This is achieved by the expression of clock gene, e.g. the clock gene *per* in *Drosophila*.

The pathway is shown in Figure 1. The *per* gene is transcribed into *Per* mRNAs in the nucleus, which are then exported to the cytoplasm to be translated to PER protein and to degrade. Some

PER proteins enter the nucleus where they inhibit the transcription of the *per* gene and degrade in the nucleus. We assume that the PER proteins inhibit the transcription by binding to the DNA molecules on several pre-determined sites. The transcription continues if and only if none of the sites are occupied.

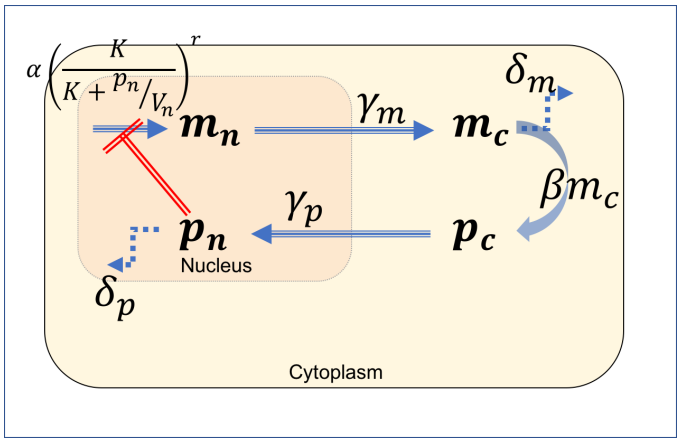


Figure 1: a schematic cellular clock

The variables and parameters that describe the process is the following:

- m_n: number of mRNAs inside the nucleus;
- m_c: number of mRNAs in the cytoplasm;
- p_n: number of protein molecules inside the nucleus;
- p_c: number of protein molecules in the cytoplasm;
- α: transcription rate when no proteins are binding;
- β: translation rate from mRNA to protein molecule;
- r: total number of sites on which the protein can bind;
- K: the equilibrium constant of the reaction of protein binding to DNA molecules;
- γ_m: the rate at which mRNAs inside the nucleus are transported to cytoplasm;
- δ_m: the degradation rate of mRNAs in cytoplasm;
- γ_p: the rate at which the protein molecules in the cytoplasm are transported into nucleus;
- δ_p: the degradation rate of this protein inside nucleus;
- V_n: the volume of the nucleus.

Using the above notations, we can define the six reactions involved in the model in Table 1. One remark is that the rate of transcription is $\alpha\{\frac{K}{K+p_n/V_n}\}^r$. We can think of $\frac{K}{K+p_n/V_n}$ as the possibility that one particular site is not occupied, so it being raised to r^{th} power is the probability that all sites are not occupied. The deduction of this expression can be found in Wang and Peskin's work.

The model consists of two versions.

Reaction	Reaction Name	Rate (Probability)	Result
1	Transcription of the gene	$\alpha\{\frac{K}{K+p_n/V_n}\}^r$	$m_n \to m_n + 1$
2	Export of mRNA from nucleus to cytoplasm	$\gamma_m m_n$	$m_n \to m_n - 1$, $m_c \to m_c + 1$
3	Translation of the mRNA	βm_c	$p_c \to p_c + 1$
4	Import of protein into nucleus	$\gamma_p p_c$	$p_c \to p_c - 1$, $p_n \to p_n + 1$
5	Degradation of mRNA in cytoplasm	$\delta_m m_c$	$m_c \to m_c - 1$
6	Degradation of protein in nucleus	$\delta_p p_n$	$p_n \to p_n - 1$

Table 1: Reaction Table

2.1.1 Deterministic Version

If we view the number of molecules of each substance as large numbers, the fact that them being integers will have little influence on the model. In this way, we can set up the model using differential equations. Notice that the rate of change of the amount of one substance is equal to the rate that it is produced (imported) minus the rate that it is degraded (exported). This gives us the following:

$$\frac{dm_n}{dt} = \alpha\{\frac{K}{K + p_n/V_n}\}^r - \delta_m m_n, \tag{1}$$

$$\frac{dm_c}{dt} = \gamma_m m_n - \delta_m m_c, \tag{2}$$

$$\frac{dp_c}{dt} = \beta m_c - \gamma_p p_c, \tag{3}$$

$$\frac{dp_n}{dt} = \gamma_p p_c - \delta_p p_n. \tag{4}$$

If we write $k = KV_n$, then the first equation becomes $\frac{dm_n}{dt} = \alpha\{\frac{k}{k+p_n}\}^r - \delta_m m_n$. Hence the set of differential equations can also be written as

$$\frac{dm_n}{dt} = \alpha\{\frac{k}{k + p_n}\}^r - \delta_m m_n, \tag{5}$$

$$\frac{dm_c}{dt} = \gamma_m m_n - \delta_m m_c, \tag{6}$$

$$\frac{dp_c}{dt} = \beta m_c - \gamma_p p_c, \tag{7}$$

$$\frac{dp_n}{dt} = \gamma_p p_c - \delta_p p_n. \tag{8}$$

Here we state that, besides modeling, the set of equations can also give insight on the choice of parameters in order to yield an expected oscillation. This is discussed later.

2.1.2 Stochastic (Microscopic) Version

On the other hand, we can also look at the microscopic version, keeping track of the number of each molecules when each reaction happens. Recall that if an event has probability per unit time r to happen, and let T denote the time this event first happens, then

$$\mathbb{P}(T > t) = \lim_{n\to\infty} \prod_{j=1}^{n} (1 - \frac{rt}{n}) = \lim_{n\to\infty} (1 - \frac{rt}{n})^n = e^{-rt}. \tag{9}$$

So T follows an exponential distribution with parameter r. Since T is continuous, it follows that $F(T)$, the distribution function acting on T, is uniformly distributed on the interval $(0, 1)$. Hence,

$$-\frac{\log(U)}{r},$$

with U being a random variable uniformly distributed on the interval $(0, 1)$, would generate a realization of T.

In the stochastic approach, given initial amount of each substances, six reaction times (each follows an exponential distribution with the parameter being the reaction's probability per unit time, respectively) are generated. We assume only the first reaction actually happens. Then the numbers of molecules are adjusted correspondingly and the above process is repeated.

2.2 Stability Analysis and Choice of Parameters for Single Cell Oscillator Model

In order to judiciously choose parameters so that the system defined by equations (5)-(8) can sustain a periodic oscillation, we perform a stability analysis of the system. The steady state is defined to be the case when the amount of each substance is not changing with respect to time, i.e. the left hand side of the four equations (5)-(8) are all zeros. This yields

$$\alpha\{\frac{k}{k + p_n^0}\}^r = \delta_m m_n^0, \tag{10}$$

$$\gamma_m m_n^0 = \delta_m m_c^0, \tag{11}$$

$$\beta m_c^0 = \gamma_p p_c^0, \tag{12}$$

$$\gamma_p p_c^0 = \delta_p p_n^0. \tag{13}$$

Here the superscript 0 denotes the value of the variable in its steady state. Multiplying all the four equations will give us

$$\alpha\beta\{\frac{k}{k + p_n^0}\}^r = \delta_m \delta_p p_n^0. \tag{14}$$

By plotting this we can assure that there is a unique positive steady state, as expected.

Next, we linearize the four equations around the steady state. This gives us

$$\frac{d\widetilde{m_n}}{dt} = -\eta\widetilde{p_n} - \gamma_m\widetilde{m_n}, \tag{15}$$

$$\frac{d\widetilde{m_c}}{dt} = \gamma_m \widetilde{m_n} - \delta_m \widetilde{m_c}, \tag{16}$$

$$\frac{d\widetilde{p_c}}{dt} = \beta \widetilde{m_c} - \gamma_p \widetilde{p_c}, \tag{17}$$

$$\frac{d\widetilde{p_n}}{dt} = \gamma_p \widetilde{p_c} - \delta_p \widetilde{p_n}, \tag{18}$$

where

$$\eta = r \frac{\delta_m \delta_p}{\alpha\beta} \frac{p_n^0}{p_n^0 + k} \alpha, \tag{19}$$

and the variables with tildes are the deviations from the steady state values, e.g. $\widetilde{p_n} = p_n - p_n^0$. Equations (15)-(18) hold when the deviations are small. A typical case is that after the system reaching equilibrium, there is some small perturbation.

Let $\widetilde{\mathbf{x}} = \begin{bmatrix} \widetilde{m_n} \\ \widetilde{m_c} \\ \widetilde{p_c} \\ \widetilde{p_n} \end{bmatrix}$ and $A = \begin{bmatrix} -\gamma_m & 0 & 0 & -\eta \\ \gamma_m & -\delta_m & 0 & 0 \\ 0 & \beta & -\gamma_p & 0 \\ 0 & 0 & \gamma_p & -\delta_p \end{bmatrix}$. It follows that

$$\frac{d\widetilde{\mathbf{x}}}{dt} = A\widetilde{\mathbf{x}}. \tag{20}$$

This is a system of ordinary differential equations, and the behaviour of $\widetilde{\mathbf{x}}$ is characterized by the eigenvalues of matrix A. The characteristic equation of matrix A is given by

$$0 = \det(\lambda I - A) \tag{21}$$

$$= \det\left(\begin{bmatrix} \lambda + \gamma_m & 0 & 0 & \eta \\ -\gamma_m & \lambda + \delta_m & 0 & 0 \\ 0 & -\beta & \lambda + \delta_p & 0 \\ 0 & 0 & -\gamma_p & \lambda + \delta_p \end{bmatrix} \right) \tag{22}$$

$$= (\lambda + \gamma_m)(\lambda + \delta_m)(\lambda + \gamma_p)(\lambda + \delta_p) + \eta\beta\gamma_m\gamma_p \tag{23}$$

$$= (\lambda + \gamma_m)(\lambda + \delta_m)(\lambda + \gamma_p)(\lambda + \delta_p) + G\gamma_m\delta_m\gamma_p\delta_p, \tag{24}$$

where

$$G = \frac{\eta\beta}{\delta_m\delta_p} \tag{25}$$

$$= \left(r \frac{\delta_m\delta_p}{\alpha\beta} \frac{p_n^0}{p_n^0 + k} \alpha \right) \frac{\beta}{\delta_m\delta_p} \tag{26}$$

$$= \left(\frac{p_n^0}{k + p_n^0} \right) r. \tag{27}$$

The second equality follows from (19).

We claim that the best case for oscillation is that

$$\gamma_m = \delta_m = \gamma_p = \delta_p = \nu, \tag{28}$$

in the sense that they generate oscillation with the smallest G. Proof of this claim can be found in Peskin's work [1]. Now, it follows from (24) that

$$0 = (\lambda + \nu)^4 + G\nu^4 \tag{29}$$

$$(\lambda + \nu)^4 = -G\nu^4 \tag{30}$$

$$(\lambda + \nu) = (-1)^{\frac{1}{4}} G^{\frac{1}{4}} \nu \tag{31}$$

$$\lambda = \mu(-1 + (-1)^{\frac{1}{4}} G^{\frac{1}{4}}) \tag{32}$$

We see that there are four solutions to λ and each is a complex number. In order for the system of ODEs (20) to have oscillating solutions, the real part of at least one λ must be greater than 0. This implies that $G^{\frac{1}{4}} > \sqrt{2}$, or equivalently, $G > 4$. By (27),

$$\left(\frac{p_n^0}{k + p_n^0}\right) r > 4. \tag{33}$$

Since $\left(\frac{p_n^0}{k+p_n^0}\right) < 1$, it must be that $r \geq 5$. Setting $r = 5$ and Substituting this into the steady state equation, with some simple algebra we have

$$\alpha\beta > \nu^2 k \cdot 4(1+4)^5. \tag{34}$$

This sheds some light on how the parameters shall be chosen.

2.3 Multi-Cellular Oscillator

In this section, we propose three ways of modeling interactions among multiple cells. The simplest approach would be to allow direct diffusion of "information" between every two cells. A demonstration of this approach can be seen in Figure 2.

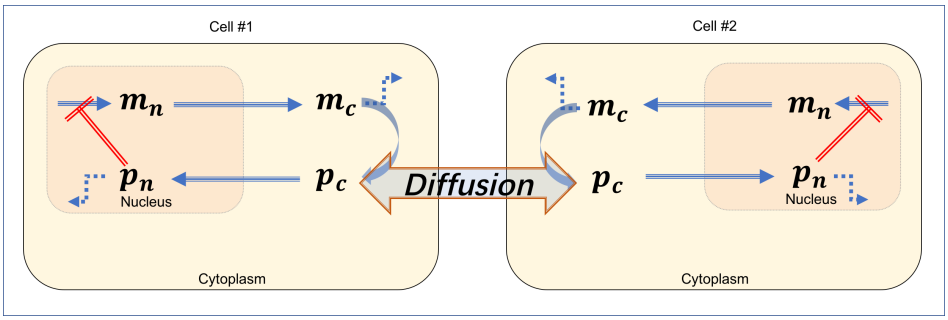


Figure 2: Protein diffusion between two cellular oscillators

2.3.1 Direct flow of protein

This is the easiest version. Assume there is a pipe connecting the two cells and these two cells have the same volume. Protein molecules in one cell can move to the other cell through the pipe. The speed of diffusion is proportional to the difference in the number of protein molecules in the two cells, i.e.

$$\frac{dp_c^1}{dt} = -F(p_c^1 - p_c^2), \tag{35}$$

$$\frac{dp_c^2}{dt} = -\frac{dp_c^1}{dt}. \tag{36}$$

Here the superscripts 1 and 2 indicate cell 1 and cell 2.

Observe that although this method is simple and concise, it has a limitation that it can only be applied in the case when the two cells are identical in volume. When the volumes are different, it is the concentration, instead of the number of molecules that shall be considered. Also, communicating "information" among cells of a multi-cellular organism are usually through a media called extra-cellular fluid rather than a direct diffusion among cells. Hence some alternative methods are discussed below.

2.3.2 Direct Diffusion with ECF

ECF stands for extra-cellular fluid, by which cells live and communicate "information" with each other. We consider the case where, instead of connecting two cells with a pipe directly, there are only pipes between each cell and ECF. It means that, every time a protein molecule would like to go from one cell to another, it must go through ECF as a transportation media.

Since new entity ECF are considered and we are more concerned with concentration, it would be better to establish some new notations:

- $M_n^{(i)}$: concentration of mRNAs inside the nucleus for the ith cell;
- $M_c^{(i)}$: concentration of mRNAs in the cytoplasm for the ith cell;
- $P_n^{(i)}$: concentration of protein molecules inside nucleus for the ith cell;
- $P_c^{(i)}$: concentration of protein molecules in cytoplasm for the ith cell;
- P_{ECF}: concentration of protein molecules in extra-cellular fluid;
- $\alpha^{(i)}$: transcription rate when no proteins are binding for the ith cell;
- $\beta^{(i)}$: translation rate from mRNA to protein molecule for the ith cell;
- $r^{(i)}$: total number of sites on which the protein can bind for the ith cell;
- $K^{(i)}$: the equilibrium constant of the reaction of protein binding to DNA molecules for the ith cell;
- $\gamma_m^{(i)}$: the rate at which mRNAs inside the nucleus are transported to cytoplasm for the ith cell;
- $\delta_m^{(i)}$: the degradation rate of mRNAs in cytoplasm for the ith cell;
- $\gamma_p^{(i)}$: the rate at which the protein molecules in the cytoplasm are transported into nucleus for the ith cell;
- $\delta_p^{(i)}$: the degradation rate of this protein inside nucleus for the ith cell;

- λ_{ECF}: the transposition rate at which protein molecules are transported between each cells and ECF;
- $V_n^{(i)}$: volume of the nucleus for the ith cell;
- $V_c^{(i)}$: volume of the cytoplasm for the ith cell;
- V_{ECF}: volume of the ECF;
- n: number of cells in a given organism.

Then, to describe the new dynamical system with ECF as transportation media, we write out a new system of ODE's:

$$\frac{dM_n^{(i)}}{dt} = \frac{\alpha^{(i)}}{V_n^{(i)}}\{\frac{K^{(i)}}{K^{(i)} + P_n^{(i)}}\}^{r^{(i)}} - \gamma_m^{(i)} M_n^{(i)} \tag{37}$$

$$\frac{dM_c^{(i)}}{dt} = \gamma_m^{(i)}(\frac{V_n^{(i)}}{V_c^{(i)}})M_n^{(i)} - \delta_m^{(i)} M_c^{(i)} \tag{38}$$

$$\frac{dP_c^{(i)}}{dt} = \beta^{(i)} M_c^{(i)} - \gamma_p^{(i)} P_c^{(i)} - \lambda_{ECF}(P_c^{(i)} - \frac{V_{ECF}}{V_c^{(i)}} P_{ECF}) \tag{39}$$

$$\frac{dP_n^{(i)}}{dt} = \gamma_p^{(i)}(\frac{V_c^{(i)}}{V_n^{(i)}})P_c^{(i)} - \delta_p^{(i)} P_n^{(i)} \tag{40}$$

$$\frac{dP_{ECF}}{dt} = \sum_i^n \lambda_{ECF}(\frac{V_c^{(i)}}{V_{ECF}} P_c^{(i)} - P_{ECF}) \tag{41}$$

Stability Analysis

With the dynamical system described above, we do analysis on stability of this system by analyzing eigenvalues of the linearized ODE system around steady state. Denote $M_n^{(i)0}, M_c^{(i)0}, P_c^{(i)0}, \widetilde{P_c^{(i)0}}, P_{ECF}^{(i)0}$, for $i \in \{1, ..., n\}$, as the value for variables at a steady state. Then, as before, denote $\widetilde{M_n^{(i)}} = M_n^{(i)} - M_n^{(i)0}$, $\widetilde{P_n^{(i)}} = P_n^{(i)} - P_n^{(i)0}$, and etc.. Therefore, we have a system of linearized equation around steady state:

$$\widetilde{\frac{dM_n^{(i)}}{dt}} = a^{(i)}\widetilde{P_n^{(i)}} - \gamma_m^{(i)}\widetilde{M_n^{(i)}}, \tag{42}$$

$$\widetilde{\frac{dM_c^{(i)}}{dt}} = \gamma_m^{(i)}(\frac{V_n^{(i)}}{V_c^{(i)}})\widetilde{M_n^{(i)}} - \delta_m^{(i)}\widetilde{M_c^{(i)}}, \tag{43}$$

$$\widetilde{\frac{dP_c^{(i)}}{dt}} = \beta^{(i)}\widetilde{M_c^{(i)}} - (\gamma_p^{(i)} + \lambda_{ECF})\widetilde{P_c^{(i)}} + \lambda_{ECF}\frac{V_{ECF}}{V_c^{(i)}}\widetilde{P_{ECF}} \tag{44}$$

$$\widetilde{\frac{dP_n^{(i)}}{dt}} = \gamma_p^{(i)}(\frac{V_c^{(i)}}{V_n^{(i)}})\widetilde{P_c^{(i)}} - \delta_p^{(i)}\widetilde{P_n^{(i)}}, \tag{45}$$

$$\widetilde{\frac{dP_{ECF}}{dt}} = \sum_i^n \lambda_{ECF}\frac{V_c^{(i)}}{V_{ECF}}\widetilde{P_c^{(i)}} - n\lambda_{ECF}\widetilde{P_{ECF}}, \tag{46}$$

where $a^{(i)} = -\frac{\alpha^{(i)}r^{(i)}}{V_n^{(i)}K^{(i)}}\{\frac{K^{(i)}}{K^{(i)}+P_n^{(i)0}}\}^{r^{(i)}+1}$.

At this point, in order to simplify this dynamical system for the sake of stability analysis and, meanwhile, to keep interesting features of the system, we do the followings:

- Let n = 2, and
- let $\gamma_m^{(i)} = \gamma_p^{(i)} = \delta_m^{(i)} = \delta_p^{(i)} = \lambda^{(i)}$ for $i \in \{1, 2\}$.

Thus, this linear system could also be rewritten as $\dot{X} = AX$, where $A =$

$$\begin{bmatrix}
-\lambda^{(1)} & 0 & 0 & a^{(1)} & 0 & 0 & 0 & 0 & 0 \\
\lambda^{(1)}\frac{V_c^{(1)}}{V_n^{(1)}} & -\lambda^{(1)} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & \beta^{(1)} & -(\lambda^{(1)} + \lambda_{ECF}) & 0 & 0 & 0 & 0 & 0 & \lambda_{ECF}\frac{V_{ECF}}{V_c^{(1)}} \\
0 & 0 & \lambda^{(1)}\frac{V_n^{(1)}}{V_c^{(1)}} & -\lambda^{(1)} & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & -\lambda^{(2)} & 0 & 0 & a^{(2)} & 0 \\
0 & 0 & 0 & 0 & \lambda^{(2)}\frac{V_c^{(2)}}{V_n^{(2)}} & -\lambda^{(2)} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & \beta^{(2)} & -(\lambda^{(2)} + \lambda_{ECF}) & 0 & \lambda_{ECF}\frac{V_{ECF}}{V_c^{(2)}} \\
0 & 0 & 0 & 0 & 0 & 0 & \lambda^{(2)}\frac{V_n^{(2)}}{V_c^{(2)}} & -\lambda^{(2)} & 0 \\
0 & 0 & \lambda_{ECF}\frac{V_c^{(1)}}{V_{ECF}} & 0 & 0 & 0 & \lambda_{ECF}\frac{V_c^{(2)}}{V_{ECF}} & 0 & -2\lambda_{ECF}
\end{bmatrix}$$

, $X^T = \begin{bmatrix}\widetilde{M_n^{(1)}} & \widetilde{M_c^{(1)}} & \widetilde{P_c^{(1)}} & \widetilde{P_n^{(1)}} & \widetilde{M_n^{(2)}} & \widetilde{M_c^{(2)}} & \widetilde{P_c^{(2)}} & \widetilde{P_n^{(2)}} & \widetilde{P_{ECF}}\end{bmatrix}$, and $\dot{X} = \frac{dX}{dt}$.

To get matrix A explicitly, we solve for $a^{(1)}$ and $a^{(2)}$.

With *MatLab*, we could compute all eigenvalues of A and store them in $E = \{e_j\}_{j\in\{1,\ldots,9\}}$, where $e_j \in \mathbb{C}$. Let $e_{max} = argmax_{\{e_j\in E\}}\{real(e_j)\}$, then if $real(e_{max}) > 0$, this system around the steady state is unstable. Otherwise, if $real(e_{max}) \leq 0$, we could conclude that the system around such a steady state is stable.

to write about:

synchronization

limitations

2.3.3 Positive Feedback Transposition with ECF

write something

3 Results

3.1 A Single Cellular Oscillator

We first show the results of one cellular oscillator. The parameters are chosen as following: $r = 5$, $k = 200$, $\alpha = 100000$, $\beta = 10$, $\nu = \gamma_m = \gamma_p = \delta_m = \delta_p = 0.285599$. Here ν is chosen to be 0.285599 as this would give an oscillator whose period is close to 24 hours. r is chosen to be the smallest possible value that allows the model to work. α, β and k are chosen as such that realistic case is mimicked and equation (34) holds. Initial values of p_n, p_c, m_n and m_c do not play an critical role in the oscillation. In fact, as long as the initial values are not set to extremely large or small numbers, given sufficiently long time, the system will settle itself down and converge to a periodic oscillation, with p_n, p_c, m_n and m_c each fluctuating around roughly $1200, 1200, 40$ and 35, respectively. For example, a graph plotting the number of molecules of each substance, with the initial state set to $p_n = 500, p_c = 500, m_n = 500$ and $m_c = 500$, is shown in Figure X.

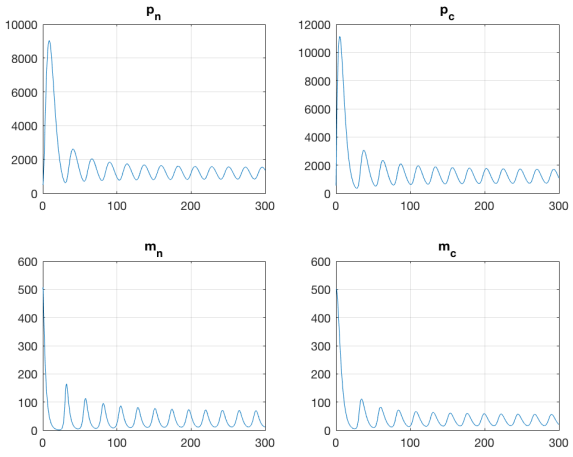


Figure X: Convergence to oscillation ultimately.

It can be seen that after about 150 hours of reaction, the system converges to the periodic oscillation as specified above. We manually set the four initial values to be $p_n = 925, p_c = 730, m_n = 32$ and $m_c = 21$ at $t = 0$. We denote this set of values as the initial state for the oscillator. This set of values is (approximately) taken at some time when the system has already started its regular

oscillation, so that our model will not go through the transition to regular oscillation. In fact, for purpose of comparison, this is the state in which p_c starts at its lowest value.

Using the above specification, two types of simulation, the deterministic version as well as the stochastic version, are both implemented. As mentioned above, the deterministic version is described by equations (5)-(8). The stochastic version is described by the last column in Table 1. A code snippet is shown below.

```
[Tmin, kmin] = min(T);
% Tmin is the time it takes for the "happened" reaction to happen.
% kmin is the position (1,2,3,4,5,6) indicating which reaction happens
switch kmin
    case 1
        % transcription happens
        m_n = m_n + 1;
    case 2
        % mRNA enters cytoplasm from nucleus
        m_n = m_n - 1;
        m_c = m_c + 1;
    case 3
        % translation happens
        p_c = p_c + 1;
    case 4
        % protein enters nucleus from cytoplasm
        p_c = p_c - 1;
        p_n = p_n + 1;
    case 5
        % degradation of mRNA
        m_c = m_c - 1;
    case 6
        % degradation of protein
        p_n = p_n - 1;
end
t = t + Tmin;
```

Results from both versions are plotted in Figure X-X. The numbers of molecules of each substance are plotted in each figure. Figure X and X are deterministic version, whose reaction times are set to 40 hours and 150 hours, respectively. Figure X and X are stochastic version, which are stair-case functions, whose reaction times are set to 40 hours and 150 hours, respectively. Observe that the results from the stochastic version resemble those from the deterministic version. Both versions show an oscillating period of about 24 hours. This confirms our expectation.

3.2 Two cellular oscillators with direct flow of protein

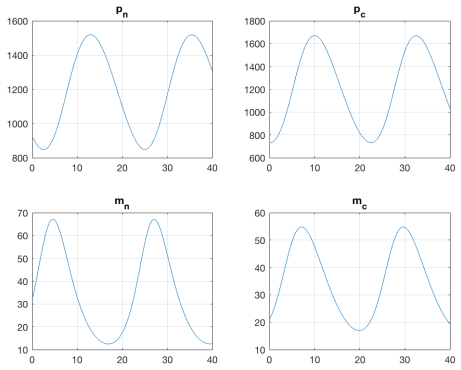


Figure X: Deterministic version, up to $t = 40$.

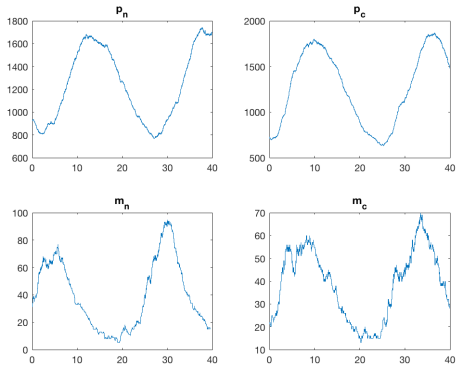


Figure X: Stochastic version, up to $t = 40$.

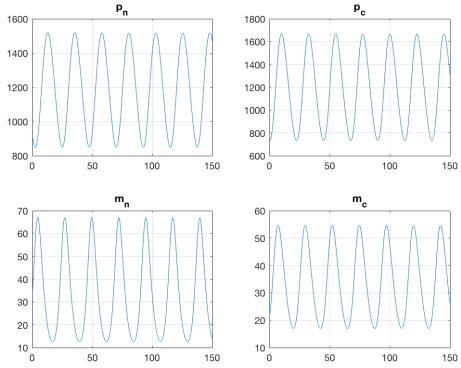


Figure X: Deterministic version, up to $t = 150$.

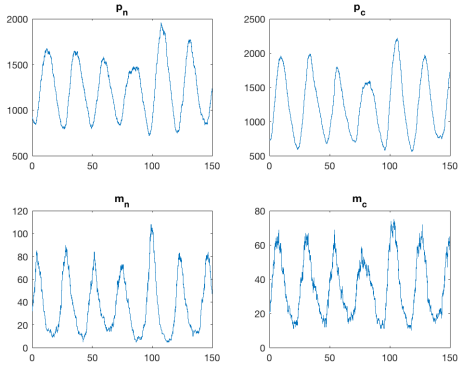
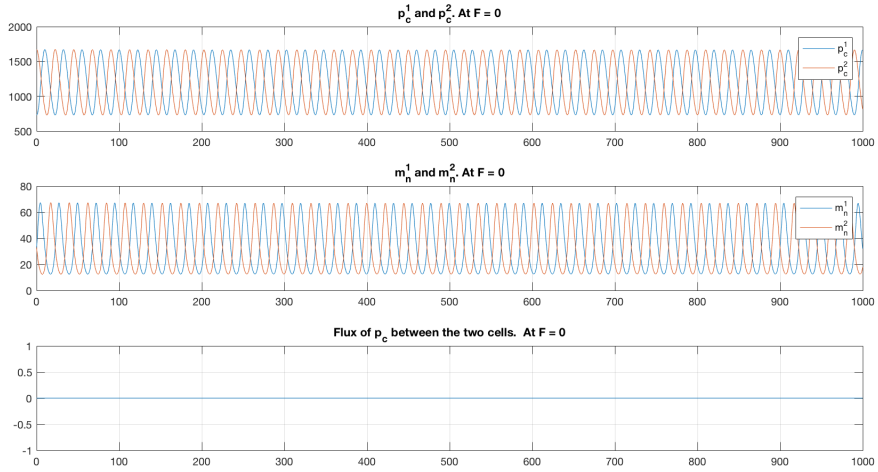
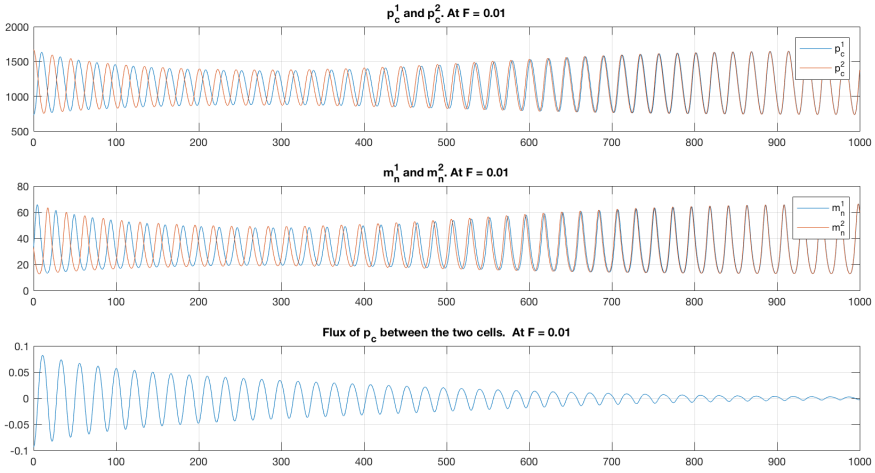


Figure X: Stochastic version, up to $t = 150$.



Figure



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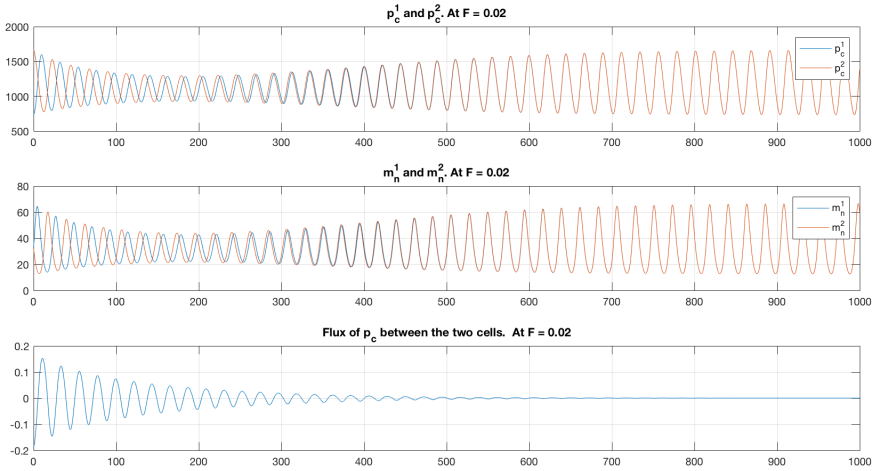

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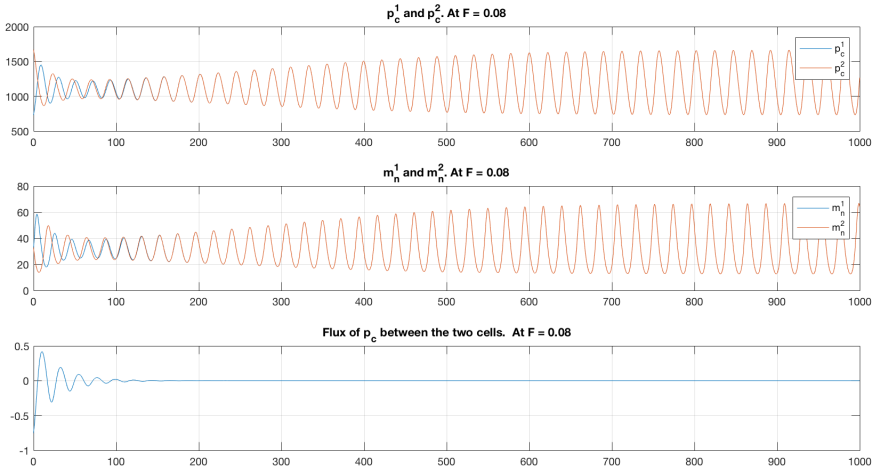

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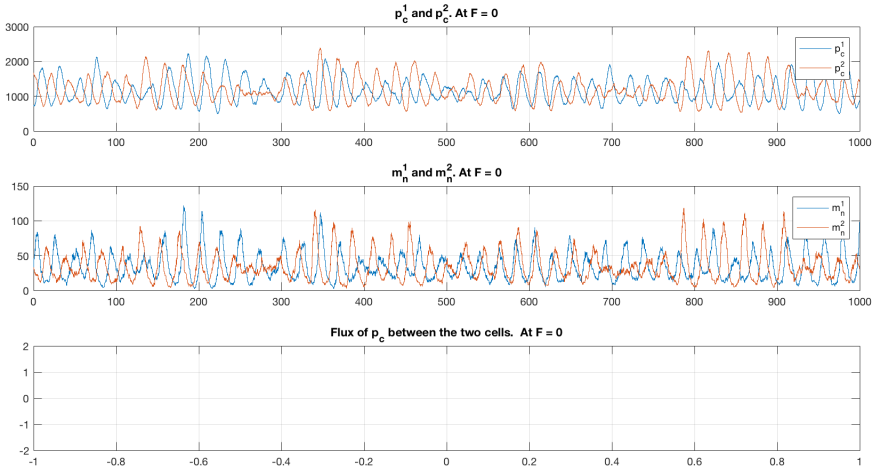

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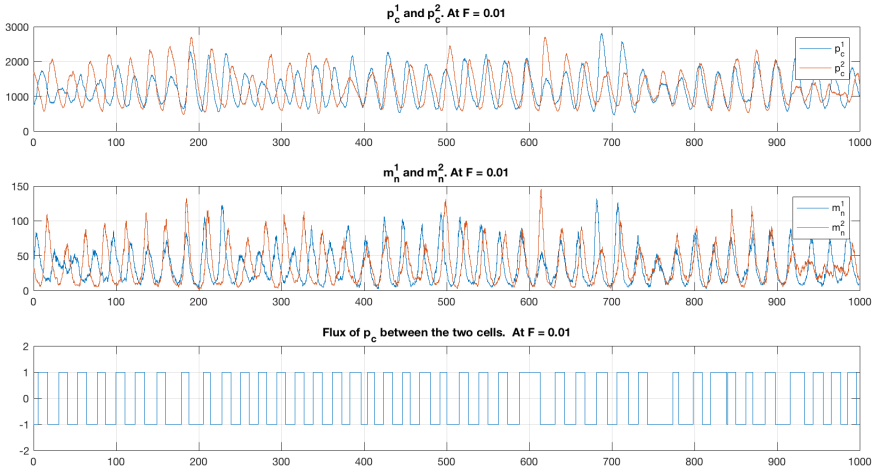

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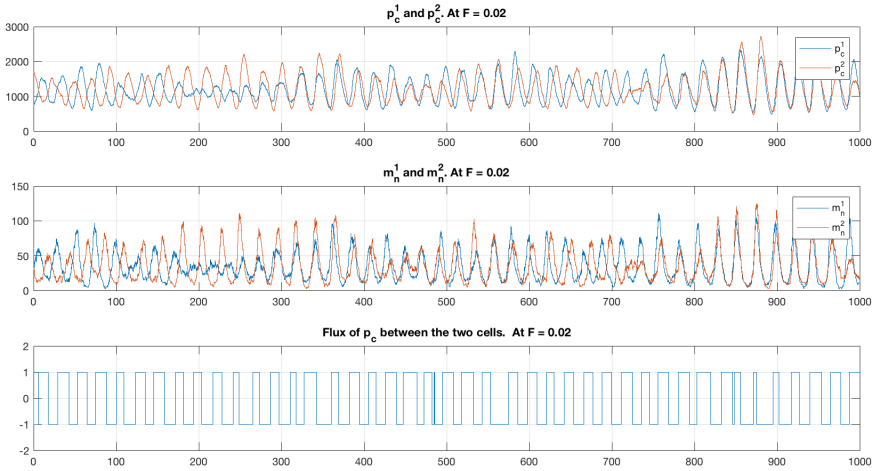

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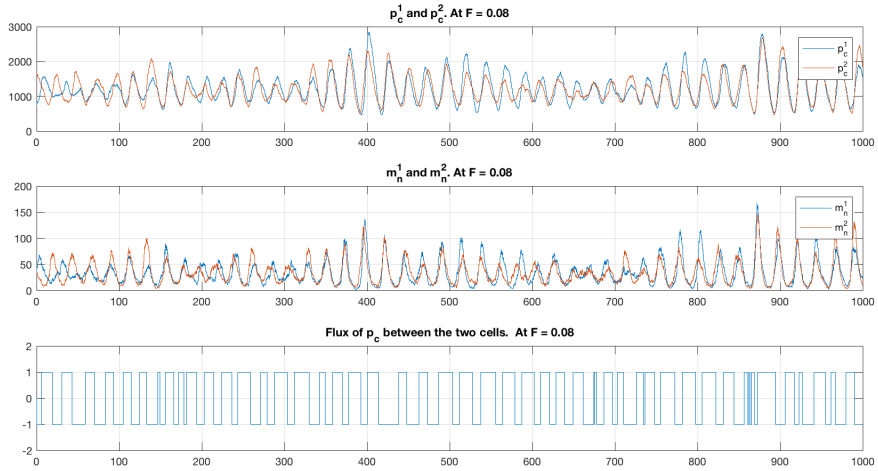
p_c^1 and p_c^2. At F = 0.08
3000
2000
1000
0
0
100
200
300
400
500
600
700
800
900
1000
p_c^1
p_c^2
m_n^1 and m_n^2. At F = 0.08
200
150
100
50
0
m_n^1
m_n^2
Flux of p_c between the two cells. At F = 0.08
2
1
0
-1
-2

Figure