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COMPARATIVE NEUROSPORA BIORHYTHM ON LIGHT VS LIGHT WITH FRQ PROTEIN

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Abstract: The Neurospora biorhythm model is based on the negative feedback auto regulation of gene expression. This research is about the comparative mathematical model for Neurospora process which specific effects on light only and on light with the FRQ protein. The models are analyzed by a differential equation theory, to find equilibrium points, the stability and the limit cycle state. The Routh-Hurwitz criterion is used for finding the parameters that confirm each state. Besides, we can verify all values of the parameters by using numerical method and solution curves.

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1. Introduction

The abilities of some bacteria are that they can adapt themselves to their environment which result of this changing is the circadian rhythm [1]. This depends on the period of light and dark [2]. The molecular mechanism of circadian rhythm, especially in Neurospora has been studied by many researchers [3, 4]. The biorhythm model or system has been explained by mathematical models [5, 6]. The first model was presented by Goodwin [7] where the result came from negative feedback on the gene expression. The purpose of the present article is to examine both the biochemical variables and the light/dark cycle in the settings of differential equation system [8].

In the recent years, the mathematical models for circadian rhythm in Neurospora have been formulated by D. Gonze, J. Leloup and A. Goldbeter. They considered the transcription of FRQ protein which negatively regulates the expression of the FRQ gene in the experiment, [9].

In this paper, the mathematical model for Neurospora is modified according to specific effects on light and on light with the FRQ protein. The equilibrium points are found and the Routh-Hurwitz criterion is used to confirm the limit cycle and stability state [17, 18].

2. Model Formula

2.1. Mathematical Model

The results of the previous model studying oscillations Drosophila [5, 10] were the sole negative regulations. In this, the role of the PER-TIM complex is done by FRQ in neurospora [11]. A further differential was controlled by TIM degradation in the fly that is effective by light [12, 13, 14, 15]. Applying the model in the work of Gonze et. al [16], the modified mathematical model system of Neurospora biorhythm differential equations with the light effect is:

$$\frac{dM}{dt} = v_s \frac{K_l^n}{K_l^n + F_N^n} - v_m \frac{M}{K_m + M} + L, \tag{1}$$

$$\frac{dF_C}{dt} = k_s M - k_1 F_C + k_2 F_N - k F_C, \tag{2}$$

$$\frac{dF_S}{dt} = k F_C - v_d \frac{F_S}{K_d + F_S}, \tag{3}$$

$$\frac{dF_N}{dt} = k_1 F_C - k_2 F_N - v_{dN} \frac{F_N}{K_{dN} + F_N}. \tag{4}$$

In this system of equations (1)–(4), if changing the eq. (1) to be eq. (5), the system produces that eq. (5), eq. (1), eq. (3) and eq. (4), are the modified Neurospora biorhythm model on light with FRQ protein effectives,

$$\frac{dM}{dt} = v_s \frac{K_l^n}{K_l^n + F_N^n} - v_m \frac{M}{K_m + M} + LF_N. \tag{5}$$

The four variables M, F_C, F_S and F_N in eq. (1)–(5) denote the concentrations of the *frq* mRNA, the cytosolic, stable and nuclear forms of FRQ respectively. $F_t = F_C + F_S + F_N$ is the total concentration of FRQ protein which is denoted F_t. The parameter denotes the rate of *frq* transcription, the constant K_l related to the threshold of the *frq* transcription before nuclear FRQ represses this process. The constant n is the Hill coefficient, v_m is the maximum rate of *frq* mRNA degradation and the Michaelis constant K_m related to *frq* mRNA degradation and eventually L is the illuminance which is its unit is *lux* or *lx*.

In Eq. (2), the constant k_s is the rate of FRQ protein synthesis, the constant k_1 and k_2 denote the transport of FRQ protein into and out of the nucleus of Neurospora.

In Eq. (3), the constant k is the rate of cytosol FRQ which is turned to be stable FRQ, the constant v_d is the maximum rate of stable FRQ degradation and Michaelis constant K_d related to this process.

In Eq. (4), the constant v_{dN} is the maximum rate of nuclear FRQ degradation and Michaelis constant K_{dN} related to this process.

The process is shown in the figure below (Figure 1).

2.2. Model Analysis

We use these functions to find the equilibrium points. The system of eqs. (1)–(4) has two positive steady state $(0, 0, 0, 0)$ and $(M_0, F_{C_0}, F_{S_0}, F_{N_0})$, where

$$M_0 = -\frac{K_m \left(F_{N_0}^n L + K_l^n (L + v_s)\right)}{F_{N_0}^n (L - v_m) + K_l^n (L - v_m + v_s)},$$

$$F_{N_0}^n = \left[K_l^n \left(-1 - \frac{v_s}{L - v_m \frac{M_0}{K_m + M_0}}\right)\right]^{\frac{1}{n}},$$

$$F_{C_0} = \frac{k_s M_0 + k_2 F_{N_0}}{k_1 + k},$$

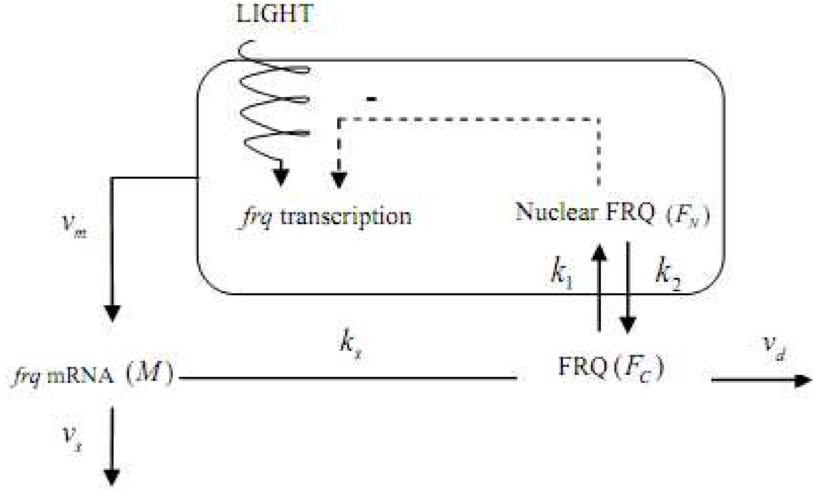

Figure 1: Scheme of the model for circadian oscillations in Neurospora.

and

$$F_{S_0} = -\frac{kK_d\left[k_sM_0 + k_2\left(\left(-K_l^n - \frac{K_l^n v_s}{L - v_m\frac{M_0}{K_m+M_0}}\right)^{\frac{1}{n}}\right)\right]}{(k+k_1)\left[-v_d + \frac{k\left[k_sM_0+k_2\left(\left(-K_l^n - \frac{K_l^n v_s}{L-v_m\frac{M_0}{K_m+M_0}}\right)^{\frac{1}{n}}\right)\right]}{(k+k_1)}\right]}.$$

And the system of eqs. (2)–(5) has two positive steady state $(0,0,0,0)$ and $(M_0, F_{C_0}, F_{S_0}, F_{N_0})$, where

$$M_0 = -\frac{K_m\left(v_sK_l^n + LF_{N_0}K_l^n + LF_{N_0}^{n+1}\right)}{LF_{N_0}K_l^n + LF_{N_0}^{n+1} + K_l^n\left(v_s - v_m\right) - v_mF_{N_0}^n},$$

$$F_{C_0} = \frac{k_s\left[-\frac{K_m\left(v_sK_l^n+LF_{N_0}K_l^n+LF_{N_0}^{n+1}\right)}{LF_{N_0}K_l^n+LF_{N_0}^{n+1}+K_l^n(v_s-v_m)-v_mF_{N_0}^n}\right] + k_2F_{N_0}}{k_1+k},$$

$$F_{S_0} = \frac{k_s k \left[-\frac{K_m \left(v_s K_l^n + L F_{N_0} K_l^n + L F_{N_0}^{n+1} \right)}{L F_{N_0} K_l^n + L F_{N_0}^{n+1} + K_l^n (v_s - v_m) - v_m F_{N_0}^n} \right] + k k_2 F_{N_0}}{v_d (k_1 + k) - k_s k \left[-\frac{K_m \left(v_s K_l^n + L F_{N_0} K_l^n + L F_{N_0}^{n+1} \right)}{L F_{N_0} K_l^n + L F_{N_0}^{n+1} + K_l^n (v_s - v_m) - v_m F_{N_0}^n} \right] + k k_2 F_{N_0}}.$$

The non-vanishing steady state $(M_0, F_{C_0}, F_{S_0}, F_{N_0})$ is interesting in solving by bifurcation analysis. We apply it for studying a linearization of the system at its steady state, and so we do consider stable and limit cycle analysis.

From Eqs. (1), (2), (3), (4) and (5), we consider the interval of steady state points that satisfy the stability. $(M_0, F_{C_0}, F_{S_0}, F_{N_0})$ is the steady state point, and so we transform the non-linear equations to linearization and use the Taylor expansion. We get $A' = \frac{K_l^n n F_{N_0}^{n-1}}{\left(K_l^n + F_{N_0}^n \right)^2}$, $B' = \frac{K_m}{(K_m + M_0)^2}$, $C' = \frac{K_d}{\left(K_d + F_{S_0} \right)^2}$ and $D' = \frac{K_{dN}}{\left(K_{dN} + F_{N_0} \right)^2}$, which define

$$J = \begin{pmatrix} -v_m B' & 0 & 0 & -v_s A' + L \\ k_s & -(k_1 + k) & 0 & k_2 \\ 0 & k & -v_d C' & 0 \\ 0 & k_1 & 0 & -k_2 - v_{dN} D' \end{pmatrix}.$$

Let $det(I - \lambda J) = 0$. Then we have

$$\begin{vmatrix} -v_m B' - \lambda & 0 & 0 & -v_s A' + L \\ k_s & -(k_1 + k) - \lambda & 0 & k_2 \\ 0 & k & -v_d C' - \lambda & 0 \\ 0 & k_1 & 0 & -k_2 - v_{dN} D' - \lambda \end{vmatrix} = 0.$$

Hence $\lambda^4 + a_1 \lambda^3 + a_2 \lambda^2 + a_3 \lambda + a_4 = 0$ is the characteristic equation for eqs.(1)–(4), where

$$a_1 = k + k_1 + k_2 + C' v_d - D' v_{dN} + B' v_m,$$

$$\begin{aligned} a_2 = &- D' k_1 v_{dN} + B' k_1 v_m + B' k_2 v_m - B' D' v_{dN} v_m \\ &+ C' v_d (k_1 + k_2 - D' v_{dN} + B' v_m) + k(k_2 + C' v_d - D' v_{dN} + B v_m), \end{aligned}$$

$$\begin{aligned} a_3 = &- B' v_m (-k k_2 + D' k v_{dN} + D' k_1 v_{dN}) + C' v_d (B' v_m (k_1 \\ &+ k_2) - D' v_{dN} (k_1 + B' v_m) + k(k_2 - D' v_{dN} + B' v_m)) + A' k_1 k_s v_s, \end{aligned}$$

and

$$a_4 = C'v_d(-B'v_m(-kk_2 + D'kv_{dN} + D'k_1v_{dN}) + A'k_1k_2v_s).$$

We find the stability of steady state points by using the Routh-Hurwitz criterion that we do not have to find the eigenvalues. The conditions are $a_1 > 0$, $a_3 > 0$, $a_4 \geq 0$ and $a_1a_2a_3 > a_3^2 + a_1^2a_4$. If the parameter values satisfy these conditions, the steady state points will be asymptotically stable.

Moreover, $\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0$ is the characteristic equation for eqs. (2)–(5), where

$$a_1 = k + k_1 + k_2 + C'v_d - D'v_{dN} + B'v_m,$$

$$\begin{aligned} a_2 = &- D'k_1v_{dN} + B'k_1v_m + B'k_2v_m - B'D'v_{dN}v_m + C'v_d(k_1 + k_2 \\ &- D'v_{dN} + B'v_m) + k(k_2 + C'v_d - D'v_{dN} + B'v_m), \end{aligned}$$

$$\begin{aligned} a_3 = &B'k\left(k_2 - D'v_{dN}\right)v_m + C'v_d\big(B'\left(k_2 - D'v_{dN}\right)v_m + k\big(k_2 - D'v_{dN} + \\ &B'v_M\big)\big) - k_1\left(C'D'v_{dN} - B'C'v_{dN}v_m + B'D'v_{dN}v_m + k_s\left(L - A'v_s\right)\right), \end{aligned}$$

and

$$a_4 = C'v_d\left(-B'k(-k_2 + D'v_{dN})v_m + k_1\left(B'D'v_{dN}v_m + k_s\left(L - Av_s\right)\right)\right).$$

3. The Parameter Values and Numerical Simulations

3.1. The Parameter Values for Neurospora Biorhythm on Light

From eqs. (1), (2), (3) and (4), we consider the illuminance for two values, which is:

1. $L = 400$ *lux*

   The steady state point is $(1.80224, 0.792509, 0.0875122, 0.525576)$, in case of limit cycle. The parameter values of limit cycle state are $v_s = 95, v_m = 470.0, v_d = 65.0, v_{dN} = 4.5, k_s = 5.0, k = 6.6, k_1 = 5.5, k_2 = 1.1, K_m = 0.04, K_l = 0.6, K_d = 1.0, K_{dN} = 0.1, n = 4, L = 400$.

   The steady state point is $(1.41521, 0.880271, 0.199032, 0.541681)$, in case of stable. The parameter values of stable state are $v_s = 95$, $v_m = 470, v_d = 35.0, v_{dN} = 1.5, k_s = 5.0, k = 6.6, k_1 = 1.5, k_2 = 0.1, K_m = 0.04, K_l = 0.6, K_d = 1.0, K_{dN} = 0.1, n = 4, L = 400$.

2. $L = 1000$ *lux*

   The steady state point is $(1.65897, 0.995047, 0.0237696, 0.328634)$, in case of limit cycle. The parameter values of limit cycle state are $v_s = 250, v_m = 1200, v_d = 150, v_{dN} = 6.5, k_s = 5.5, k = 3.5, k_1 = 6.0, k_2 = 1.0, K_m = 0.04, K_l = 0.4, K_d = 1.0, K_{dN} = 0.05, n = 4, L = 1000$.

   The steady state point is $(1.64031, 2.11531, 0.0519199, 0.497184)$, in case of stable. The parameter values of stable state are $v_s = 250, v_m = 1100, v_d = 150.0, v_{dN} = 6.5, k_s = 5.5, k = 3.5, k_1 = 1.0, k_2 = 1.0, K_m = 0.04, K_l = 0.4, K_d = 1.0, K_{dN} = 1.5, n = 4, L = 1000$.

3.2. Numerical Simulations

We can verify all parameter values by using a numerical method, the fourth-order Runge-Kutta method, and solution curves as follows.

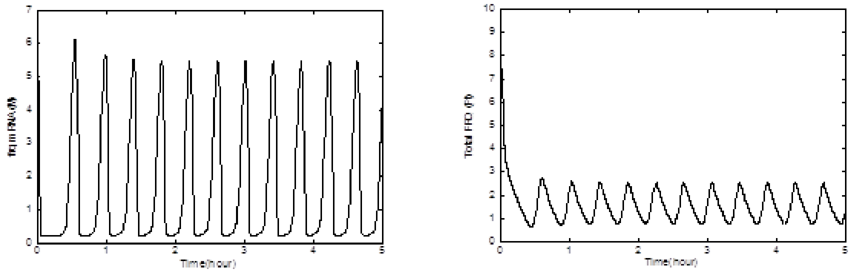

Figure 2: In case of limit cycle state, *frq* mRNA and total FRQ protein vs time in 5 hours with $L = 1000$ *lux*.

3.3. The Parameter Values for Neurospora Biorhythm on Light with FRQ Protein

From eqs. (5), (2), (3) and (4), we consider the illuminance L for two values, which is:

1. $L = 400$ *lux*

   The equilibrium point is $(3.00438, 0.628211, 0.478054, 0.0183893)$, in case of limit cycle. The parameter values of limit cycle state are $v_s = 470.5, v_m = 300.5, v_d = 5.0, v_{dN} = 3.2, k_s = 0.5, k = 1.6, k_1 = 0.8, k_2 = 0.3, K_m = 0.2, K_l = 0.02, K_d = 1.9, K_{dN} = 0.1, n = 4, L = 400$.

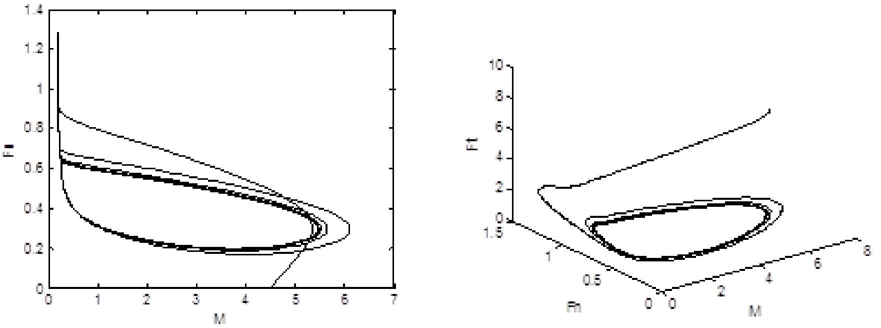

Figure 3: In case of limit cycle state, *frq* mRNA vs. nuclear FRQ in 2-dimension and *frq* mRNA vs. nuclear FRQ vs. total FRQ protein in 3-dimension with $L = 1000$ *lux*.

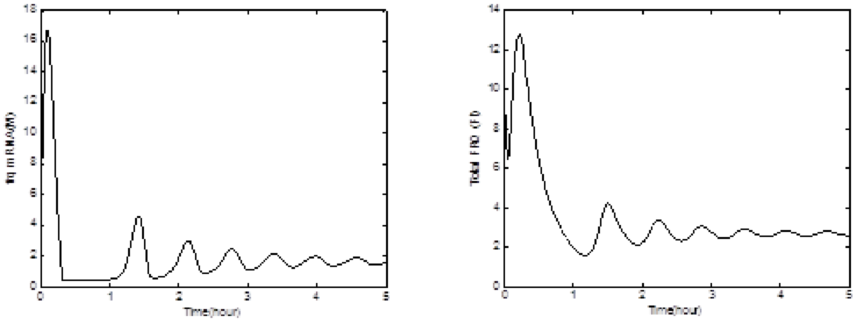

Figure 4: In case of stable state, *frq* mRNA and total FRQ protein vs. time in 5 hours with $L = 1000$ *lux*.

The equilibrium point is $(1.34309, 0.311199, 0.0204605, 0.0192226)$, in case of stable. The parameter values of stable state are $v_s = 470.5, v_m = 300.0, v_d = 7.0, v_{dN} = 3.2, k_s = 0.5, k = 0.5, k_1 = 1.8, k_2 = 2.3, K_m = 0.2, K_l = 0.02, K_d = 0.9, K_{dN} = 0.1, n = 4, L = 400$.

2. $L = 1000$ *lux*

   The equilibrium point is $(3.56273, 0.63821, 0.651308, 0.0187361)$, in case of limit cycle. The parameter values of limit cycle state are $v_s = 470.5, v_m = 300.5, v_d = 5.0, v_{dN} = 3.2, k_s = 0.5, k = 2.0, k_1 = 0.8, k_2 = 0.3, K_m = 0.2, K_l = 0.02, K_d = 1.9, K_{dN} = 0.1, n = 4, L = 1000$.

   The equilibrium point is $(8.57433, 1.60625, 0.104969, 0.0142019)$, in case

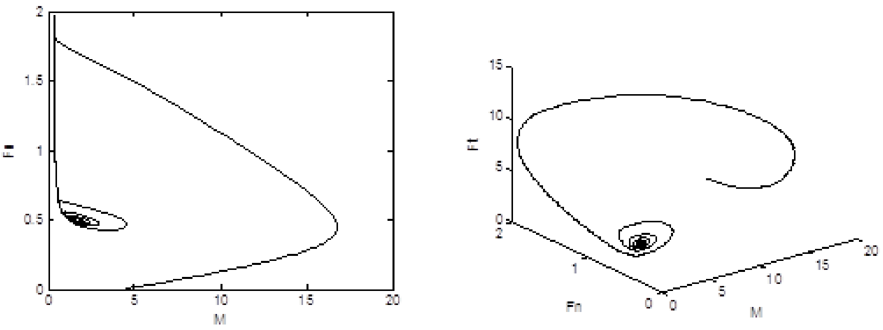

Figure 5: In case of stable state, *frq* mRNA vs. nuclear FRQ in 2-dimension and *frq* mRNA vs. nuclear FRQ vs. total FRQ protein in 3-dimension with $L = 1000$ *lux*.

of stable. The parameter values of stable state are $v_s = 350.5, v_m = 300.5, v_d = 7.0, v_{dN} = 3.2, k_s = 0.5, k = 1.5, k_1 = 1.2, k_2 = 3.5, K_m = 0.2, K_l = 0.02, K_d = 0.2, K_{dN} = 0.01, n = 4, L = 1000.$

3.4. Numerical Simulations

We can verify all parameter values by using numerical method, the fourth-order Runge-Kutta method, and solution curves as follows.

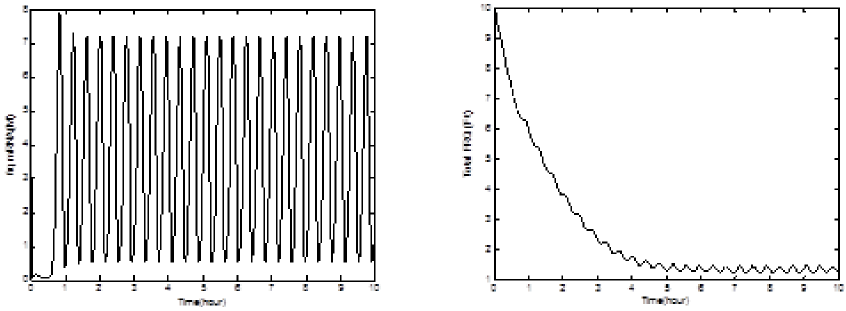

Figure 6: In case of limit cycle state, *frq* mRNA and total FRQ protein vs. time in 10 hours with $L = 1000$ *lux*.

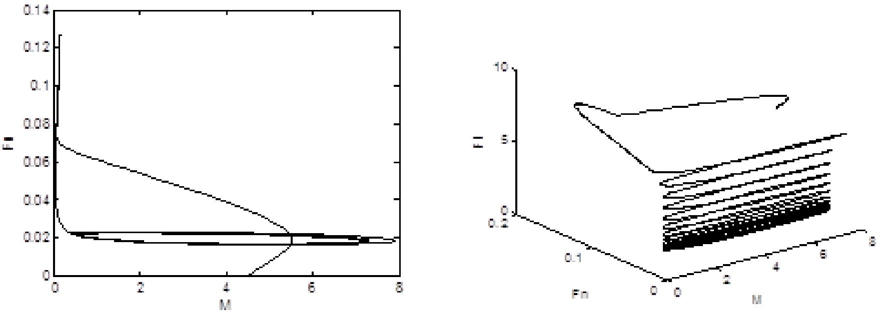

Figure 7: In case of limit cycle state, *frq* mRNA vs. nuclear FRQ in 2-dimension and *frq* mRNA vs. nuclear FRQ vs. total FRQ protein in 3-dimension with $L = 1000$ *lux*.

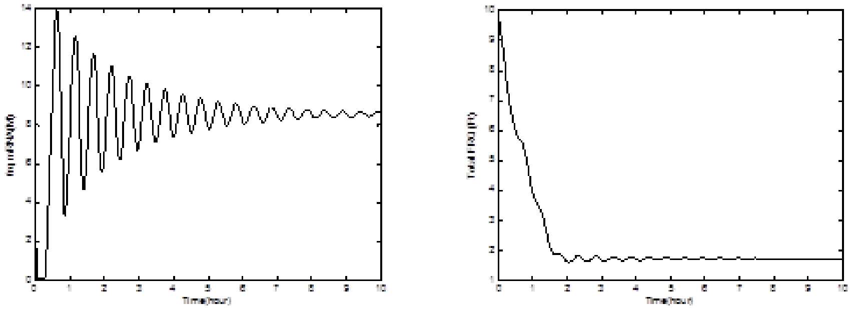

Figure 8: In case of stable state, *frq* mRNA and total FRQ protein vs. time in 10 hours with $L = 1000$ *lux*.

4. Conclusions

We consider the model for Neurospora and Drosophila, and we modify the new Neurospora model on light and the new Neurospora model on light with FRQ protein. These are the incentive which is the system (eqs. (1), (2), (3) and (4)) and the system (eqs. (5), (2), (3) and (4)), respectively. More importantly, we consider the illuminance as follows:

(i) $L = 400$ *lux*, for example, is sunrise or sunset on a clear day.

(ii) $L = 1000$ *lux*, for example, overcast day or typical TV studio lighting.

From the system, we can find the steady state points and parameters which

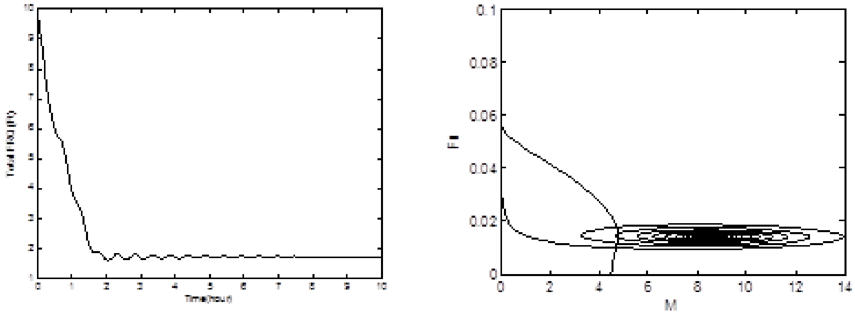

Figure 9: In case of stable state, *frq* mRNA vs. nuclear FRQ in 2-dimension and *frq* mRNA vs. nuclear FRQ vs. total FRQ protein in 3-dimension with $L = 1000$ *lux*.

satisfy limit cycle state and stable state as follow in Section 3. These values can be verified by using the fourth-order Runge-Kutta method and solution curves that show in previous section. Moreover, all parameters will be very useful for scientists or researchers who would like to restrain the growth of Neurospora because it always grows in their laboratory and experiments.

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