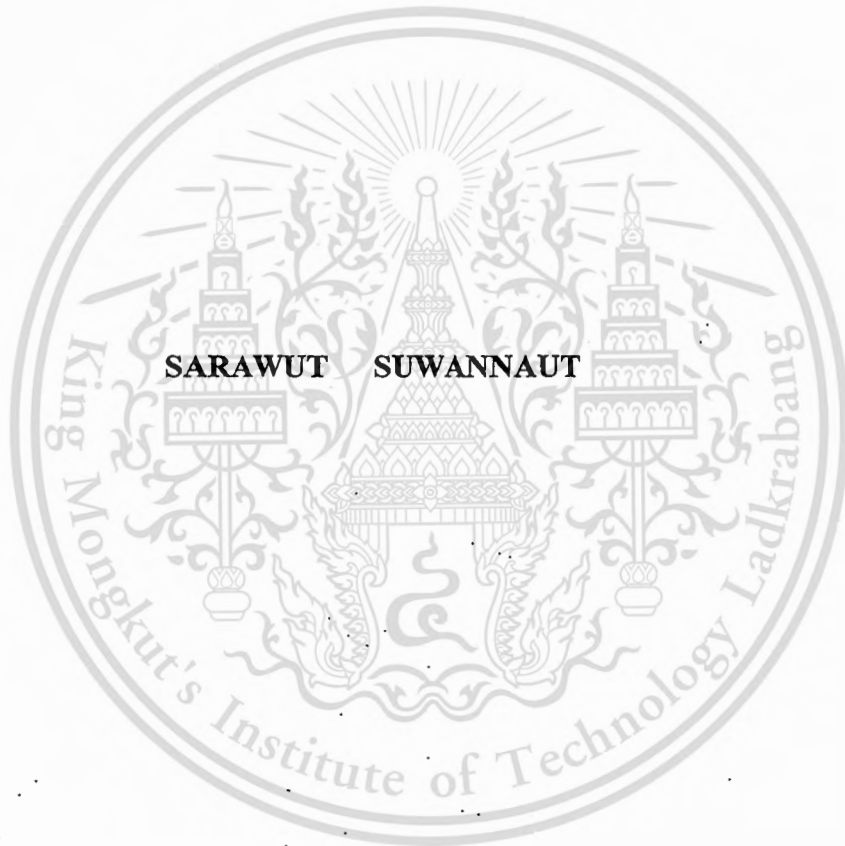


**ANALYSIS OF NEUROSPORA PROCESS MODEL  
WITH LIGHT EFFECTS**



**A THESIS SUBMITTED IN PARTIAL FULFILLMENT  
OF THE REQUIREMENT FOR THE DEGREE OF  
MASTER OF SCIENCE IN APPLIED MATHEMATICS  
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### ABSTRACT

During the last decade, many research have been made on the molecular mechanism of circadian rhythm, especially in Neurospora. Neurospora process model is based on the negative feedback auto regulation of gene expression. This thesis is concerned with the modified mathematical model for Neurospora process with or which includes the effects of light. The differential equation model is analyzed in terms of the stability of the equilibrium solution, and the existence of limit cycles. The Routh-Hurwitz criterion and the Hopf bifurcation theory are used to find the conditions on the model parameters under which different dynamic behaviors may be assured. Moreover, numerical simulations have been carried out to confirm our theoretical predictions.

**Keywords:** Neurospora process, stability, limit cycle, Routh-Hurwitz criterion, Hopf bifurcation

หัวข้อวิทยานิพนธ์	การวิเคราะห์แบบจำลองของกระบวนการทำงานของนิวโรสเปอร์ราที่ได้รับผลกระทบจากแสง
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### บทคัดย่อ

ในช่วงทศวรรษที่ผ่านมา มีงานวิจัยมากมายเกี่ยวกับระบบกลไก โมเลกุลของเวลาวิภูจักรชีวิต โดยเฉพาะอย่างยิ่งนิวโรสเปอร์รา แบบจำลองทางคณิตศาสตร์ของนิวโรสเปอร์รา มีพื้นฐานมาจากวงจรการควบคุมย้อนกลับแบบลบของพฤติกรรมยีน ในงานวิทยานิพนธ์นี้จะเกี่ยวข้องกับแบบจำลองทางคณิตศาสตร์ของกระบวนการทำงานของนิวโรสเปอร์รา ที่ผ่านการพัฒนาแล้วซึ่งพิจารณาถึงผลกระทบที่เกิดจากแสง แบบจำลองที่อยู่ในรูปของสมการอนุพันธ์ดังกล่าวจะถูกนำมาวิเคราะห์สถานะเสถียรของจุดสมดุลและการมีอยู่ของลิมิต ไซเคิล หลักเกณฑ์ของรูท-เฮอร์วิทซ์ และทฤษฎีของฮอฟฟ์ไบเฟอร์เคชันถูกนำมาใช้เพื่อหาเงื่อนไขในรูปของค่าพารามิเตอร์ ซึ่งพฤติกรรมต่างๆ ของแบบจำลองจะถูกนำมาอธิบายผ่านเงื่อนไขข้างต้น นอกจากนี้การหาผลเฉลยเชิงตัวเลขได้นำมาใช้เพื่อยืนยันผลที่ได้จากทฤษฎี

**คำสำคัญ :** กระบวนการทำงานของนิวโรสเปอร์รา เสถียรภาพ ลิมิต ไซเคิล หลักเกณฑ์ของรูท-เฮอร์วิทซ์ ทฤษฎีของฮอฟฟ์ไบเฟอร์เคชัน

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Sarawut Suwannaut

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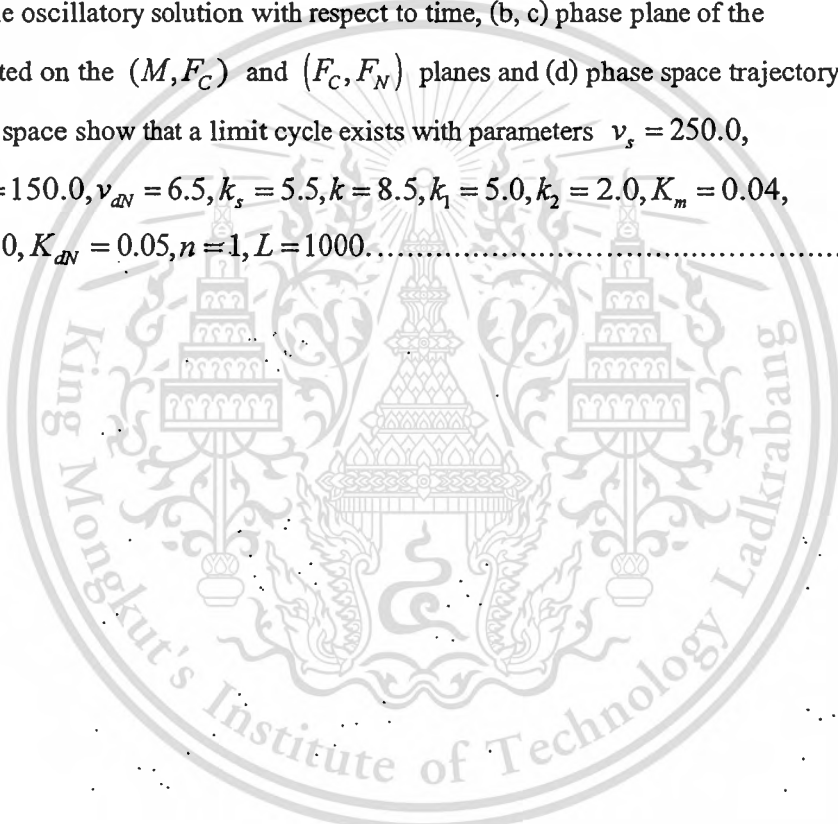
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# Chapter 1

## Introduction

To increase their understanding of natural phenomena, scientists try to describe these phenomena by using mathematical models. Scientists use mathematical models in several branches of science because they can be used to analyze and determine solutions to the problems. Many problems in circadian rhythm, such as a rhythm of melatonin in human body, are very complex and difficult to analyze. Additionally, some scientists have been able to develop and analyze mathematical models for Neurospora and its transcription. In this chapter, we will describe the background on Neurospora, as well as the purpose, scope, method and utilization of this study.

### 1. Background on Neurospora

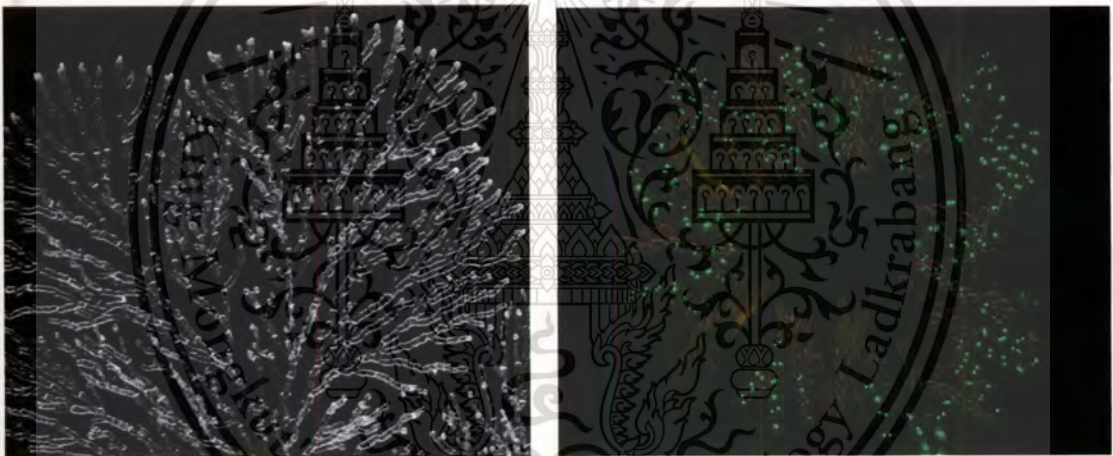


Figure 1.1 Neurospora [1, 3]

Neurospora is the name of a fungal genus containing several distinct species. Fungal generally propagate in one of two basic ways.

- The fungi called yeasts are found as populations of individual cells, and each cell propagates by cell division.
- Filamentous (mycelial) fungi have thread-like cells that propagate by tip extension and branching.

Both yeasts and filamentous fungi have been extensively used as model organisms for the study of genetics. The genus Neurospora is one of the main groups of filamentous fungi that have been used as

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model organisms. There are many features that lend themselves to this use: Neurospora is easy to obtain, grow, do experiment and widely distributed around the world [2].

## **2. Purpose of the Study**

1. To analyze the mathematical model of Neurospora.
2. To find conditions in terms of parameters which consist of stable state conditions and limit cycle condition.
3. To use numerical method to compute approximate solutions to a model of Neurospora for different values of parameters in different illuminations.
4. To illustrate the behaviors of the solution of the model of Neurospora for parameters in each state using Matlab.

## **3. Scope of the Study**

1. Study mathematical models of Neurospora which are first order-non-linear ordinary differential systems.
2. Investigate the behaviors of the models in stable state conditions and limit cycle conditions.
3. Examine the effects of changing light and biochemical parameters of the models

## **4. Method**

1. Study some theoretical backgrounds of ordinary differential equations.
2. Study some numerical methods to compute solutions of our differential equations.
3. Analyze the nonlinear differential system of Neurospora.
4. Find the parameters to support the stability and limit cycle conditions
5. Use numerical methods to create computer programs to confirm the behaviors of solutions of the mathematical model for Neurospora.
6. Illustrate numerical simulations which are carried out to confirm our predictions.
7. Write the thesis.

## 5. Utilization of the Study

1. The model would be useful for examining the effects of changing light and biochemical parameters that are important to the behavior of *Neurospora* and investigating the process of transcription of *Neurospora*.
2. Be able to use some numerical methods and programming to confirm the theoretical results (by investigating the trajectories).

In the next chapter, we will describe about literature review which consists of some research and models about *Neurospora* that involve to this thesis.

In Chapter 3, we first describe our model for *Neurospora* which is a nonlinear differential system. We then analyze the model system using stability theory, Hopf Bifurcation theory, and Routh-Hurwitz criterion to derive conditions that satisfy different dynamic behaviors.

In Chapter 4, we find the proper parameters which satisfy all theoretical stable state conditions, and also limit cycle state conditions with four different cases of illuminances. Next, we verify all parameters by using the Runge Kutta method and we also find all trajectories, phase plane and phase space in each state. Moreover, we show that all parameters described above satisfy stable and limit cycle conditions mentioned in chapter 2.

Finally, in chapter 5, we describe the discussion, conclusion, and the suggestions for further study.

## Chapter 2

### The Mathematical Model for Neurospora

#### 2.1 Literature Review

In 2000, Didier Gonze, Jean-Christophe Leloup, and Albert Goldbeter [7] created a theoretical model for circadian rhythms in Neurospora. A model consists of three compartments which are *frq* mRNA, cytosol FRQ, and nuclear FRQ.

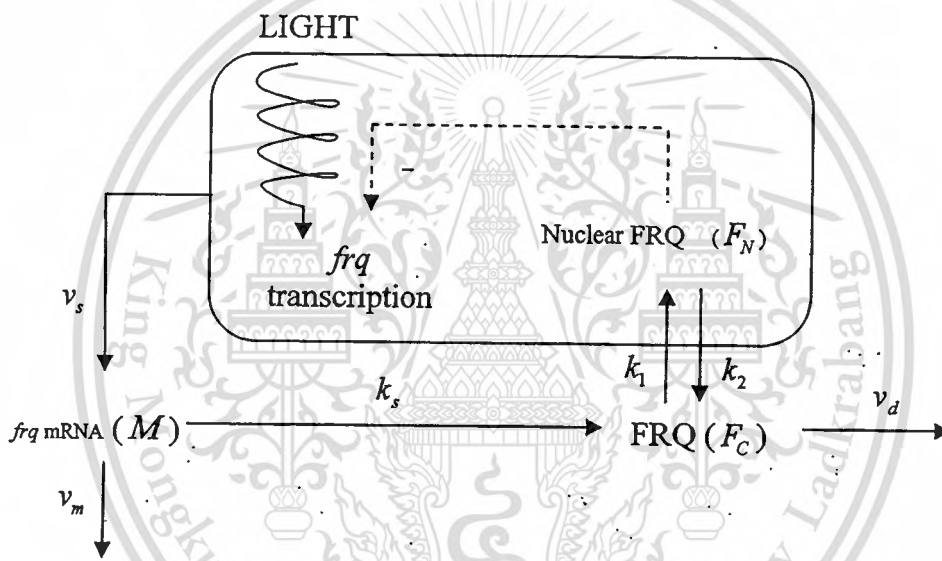


Figure 2.1 Diagram of the model for Neurospora [5].

From the diagram, we obtain

- If there is no light, then the cytosol FRQ protein ( $F_C$ ) will enter to the nucleus. Subsequently, the nuclear FRQ proteins ( $F_N$ ) will repress the transcription of *frq* gene. Moreover, the nuclear FRQ will react to the base sequence of *frq* DNA. Because of this reason, the process will not go on.
- If there is light, then the transcription of *frq* gene will continue. The result of this process is *frq* mRNA ( $M$ ) which will be used in the FRQ protein synthesis. In other words, light indirectly increases the concentration of the nuclear FRQ in the system.

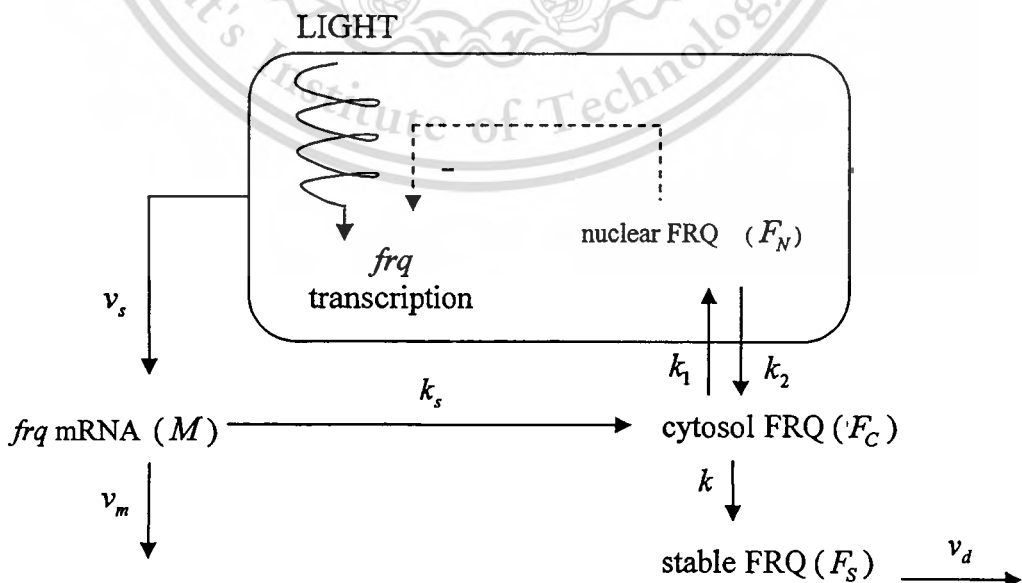
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From this process, we can formulate the system as follows

$$\begin{aligned}\frac{dM}{dt} &= v_s \frac{K_I^n}{K_I^n + F_N^n} - v_m \frac{M}{K_m + M}, \\ \frac{dF_C}{dt} &= k_s M - v_d \frac{F_C}{K_d + F_C} - k_1 F_C + k_2 F_N, \\ \frac{dF_N}{dt} &= k_1 F_C - k_2 F_N,\end{aligned}\quad (2.1)$$

where  $M$  is the concentration of the *frq* mRNA;  $F_C$  is the concentration of the cytosolic form of FRQ;  $F_N$  is the concentration of the nuclear form of FRQ;  $F_t$  denotes the total concentration of FRQ protein where  $F_t = F_C + F_N$ ;  $v_s$  denotes the rate of *frq* transcription; the Michaelis constant  $K_I$  related to the threshold of the *frq* transcription before nuclear FRQ represses this process;  $n$  is the Hill coefficient;  $v_m$  is the maximum rate of *frq* mRNA degradation; the Michaelis constant  $K_m$  related to *frq* mRNA degradation;  $k_s$  is the rate of FRQ protein synthesis;  $v_d$  is the maximum rate of cytosolic FRQ degradation and  $k_1$  and  $k_2$  denote the transport of FRQ protein into and out of the nucleus of *Neurospora*.



**Figure 2.2** Diagram of the model for *Neurospora* with the existence of stable FRQ [5].

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From Figure 2.2, the cytosol FRQ protein  $F_C$  can be transferred to nucleus and can be degraded to the stable FRQ protein,  $F_S$ , under which cannot be transferred to nucleus again. Consequently, the nuclear FRQ protein can be degraded. So they obtain the modified model of *Neurospora* with condition that includes the stable FRQ protein,  $F_S$ , as follows

$$\begin{aligned}
 \frac{dM}{dt} &= v_s \frac{K_I^n}{K_I^n + F_N^n} - v_m \frac{M}{K_m + M}, \\
 \frac{dF_C}{dt} &= k_s M - k_1 F_C + k_2 F_N - k F_C, \\
 \frac{dF_S}{dt} &= k F_C - v_d \frac{F_S}{K_d + F_S}, \\
 \frac{dF_N}{dt} &= k_1 F_C - k_2 F_N - v_{dN} \frac{F_N}{K_{dN} + F_N},
 \end{aligned} \tag{2.2}$$

where  $F_S$  denotes the concentration of stable form of FRQ protein;  $k$  is the conversion rate of cytosol FRQ to stable FRQ;  $v_{dN}$  is the maximum degradation rate of nuclear FRQ; the Michaelis constant  $K_{dN}$  related to degradation of nuclear FRQ and the total concentration of FRQ protein,  $F_t$ , is equal to  $F_C + F_S + F_N$ .

In 2010, Kanchana Kumnungkit, Nipon Wongvisetsirikul, and Sarawut Suwannaut[8, 9] developed the model with stable FRQ by considering quantity of light. Hence, we add the new term called the illuminances or  $L$  in the first equation of (2.2) so that model (2.2) becomes

$$\begin{aligned}
 \frac{dM}{dt} &= v_s \frac{K_I^n}{K_I^n + F_N^n} - v_m \frac{M}{K_m + M} + L, \\
 \frac{dF_C}{dt} &= k_s M - k_1 F_C + k_2 F_N - k F_C, \\
 \frac{dF_S}{dt} &= k F_C - v_d \frac{F_S}{K_d + F_S}, \\
 \frac{dF_N}{dt} &= k_1 F_C - k_2 F_N - v_{dN} \frac{F_N}{K_{dN} + F_N}.
 \end{aligned} \tag{2.3}$$

Then, we write the equilibrium point in terms of parameters. We also found the parameters satisfying stable state with four different values of illuminances by using the Routh-Hurwitz criterion.

## 2.2 The Mathematical Model

In this thesis, we will study the model without the stable FRQ protein and add the illuminances term,  $L$ , into model (2.1) to obtain

$$\begin{aligned}\frac{dM}{dt} &= v_s \frac{K_l^n}{K_l^n + F_N^n} - v_m \frac{M}{K_m + M} + L, \\ \frac{dF_C}{dt} &= k_s M - v_d \frac{F_C}{K_d + F_C} - k_1 F_C + k_2 F_N, \\ \frac{dF_N}{dt} &= k_1 F_C - k_2 F_N,\end{aligned}\tag{2.4}$$

where the variables are defined earlier in the previous section.



## Chapter 3

### Methodology for Analysis of the Model

In this chapter, we will analyze the mathematical models for *Neurospora*, with and without the existence of stable FRQ, described in model (2.3) and (2.4) respectively. Then, we find steady state values in terms of parameters and find conditions satisfying stable state and the existence of limit cycles by using stability theory, Routh-Hurwitz criterion, and Hopf Bifurcation theory. Finally, we will investigate the behavior of models using the numerical method in each state with four different illuminances.

#### 3.1 An Analysis of the Model (2.4)

In this section, we recall and analyze the model (2.4) described in chapter 2. The model is a system of nonlinear differential equations given by

$$\begin{aligned}\frac{dM}{dt} &= v_s \frac{K_l^n}{K_l^n + F_N^n} - v_m \frac{M}{K_m + M} + L, \\ \frac{dF_C}{dt} &= k_s M - v_d \frac{F_C}{K_d + F_C} - k_1 F_C + k_2 F_N, \\ \frac{dF_N}{dt} &= k_1 F_C - k_2 F_N,\end{aligned}$$

where the variables are defined earlier in Chapter 2.

It is clear that the system described above has a positive steady state  $(0, 0, 0)$  with  $L = 0$ . However, we will not consider the behavior of the model at this point.

We define these functions to find the equilibrium points

$$\begin{aligned}\frac{dM}{dt} &= g_1(M, F_C, F_N) = 0, \\ \frac{dF_C}{dt} &= g_2(M, F_C, F_N) = 0, \\ \frac{dF_N}{dt} &= g_3(M, F_C, F_N) = 0.\end{aligned}\tag{3.1}$$

From Eq.(3.1), let  $E^* = (M^*, F_C^*, F_N^*)$  be an equilibrium point and let  $n = 1$  to obtain

$$v_s \frac{K_l}{K_l + F_N^*} - v_m \frac{M^*}{K_m + M^*} + L = 0,$$

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$$k_s M - v_d \frac{F_C^*}{K_d + F_C^*} - k_1 F_C^* + k_2 F_N^* = 0, \quad (3.2)$$

$$k_1 F_C^* - k_2 F_N^* = 0.$$

From the first equation of the model (3.2), we rearrange the first equation of model (3.2) to get

$$M^* = -\frac{-F_N^* K_m L - k_1 K_m L - K_l K_m v_s}{F_N^* L + K_l L - F_N^* v_m - K_l v_m + K_l v_s}. \quad (3.3)$$

Next, consider the second equation of the model (3.2), we have

$$k_s M - v_d \frac{F_C^*}{K_d + F_C^*} - k_1 F_C^* + k_2 F_N^* = 0.$$

So

$$F_N^* = \frac{F_C^* k_1 + F_C^* k_1 K_d - F_C^* k_s M^* - K_d k_s M^* + F_C^* v_d}{k_2 (F_C^* + K_d)}. \quad (3.4)$$

consider the third equation of the model (3.2),

$$k_1 F_C^* - k_2 F_N^* = 0, \quad (3.5)$$

$$F_C^* = \frac{F_N^* k_2}{k_1}.$$

Substitute Eq.(3.5) into Eq.(3.4), we have

$$M^* = \frac{F_N^* k_2 v_d}{F_N^* k_2 k_s + k_1 K_d k_s}. \quad (3.6)$$

From Eq.(3.3) and (3.6), we get

$$F_N^* = -\frac{1}{2k_2 [K_m k_s L + v_d (L - v_m)]} k_1 K_d K_m k_s L + k_2 K_l K_m k_s L + k_2 K_l L v_d - k_2 K_l v_d v_m + k_2 K_l K_m k_s v_s + k_2 K_l v_d v_s \pm [-4k_1 k_2 K_d K_l K_m k_s (K_m k_s L + v_d (L - v_m))(L + v_s) [k_1 K_d K_m k_s L + k_2 K_l (K_m k_s (L + v_s) + v_d (L - v_m + v_s))] ]^{\frac{1}{2}}. \quad (3.7)$$

Since the negative term of Eq.(3.7) is less than zero,

$$-\frac{1}{2k_2 [K_m k_s L + v_d (L - v_m)]} k_1 K_d K_m k_s L + k_2 K_l K_m k_s L + k_2 K_l L v_d - k_2 K_l v_d v_m + k_2 K_l K_m k_s v_s + k_2 K_l v_d v_s - [-4k_1 k_2 K_d K_l K_m k_s (K_m k_s L + v_d (L - v_m))(L + v_s) [k_1 K_d K_m k_s L + k_2 K_l (K_m k_s (L + v_s) + v_d (L - v_m + v_s))] ]^{\frac{1}{2}} < 0,$$

we choose  $F_N^*$  to be the positive term,

$$F_N^* = -\frac{1}{2k_2 [K_m k_s L + v_d (L - v_m)]} k_1 K_d K_m k_s L + k_2 K_l K_m k_s L + k_2 K_l L v_d - k_2 K_l v_d v_m + k_2 K_l K_m k_s v_s + k_2 K_l v_d v_s + [-4k_1 k_2 K_d K_l K_m k_s (K_m k_s L + v_d (L - v_m))(L + v_s) [k_1 K_d K_m k_s L + k_2 K_l (K_m k_s (L + v_s) + v_d (L - v_m + v_s))] ]^{\frac{1}{2}}$$

$$v_d(L-v_m))(L+v_s)(k_1K_dK_mk_sL+k_2K_l[K_mk_s(L+v_s)+v_d(L-v_m+v_s)])]^{1/2}. \quad (3.8)$$

Substituting this  $F_N^*$  into Eq.(3.3) and (3.5),  $M^*$  and  $F_C^*$  can be found as follows

$$M^* = \frac{1}{2k_1K_dk_s(L-v_m)-2k_2K_lk_s(L-v_m+v_s)} \{-k_1K_dK_mk_sL+k_2K_l[K_mk_s(L+v_s)+v_d(L-v_m+v_s)]- [(-4k_1k_2K_dK_lK_mk_s)(K_mk_sL+v_d(L-v_m))(L+v_s)+[k_1K_dK_mk_sL+k_2K_l(K_mk_s(L+v_s)+v_d(L-v_m+v_s))]^2]^{1/2}\}, \quad (3.9)$$

$$F_C^* = -\frac{1}{2k_1[K_mk_sL+v_d(L-v_m)]} k_1K_dK_mk_sL+k_2K_l[K_mk_s(L+v_s)+v_d(L-v_m+v_s)]+[-4k_1k_2K_dK_lK_mk_s(K_mk_sL+v_d(L-v_m))(L+v_s)+[k_1K_dK_mk_sL+k_2K_l(K_mk_s(L+v_s)+v_d(L-v_m+v_s))]^2]^{1/2}. \quad (3.10)$$

More importantly, the equilibrium point  $(M^*, F_C^*, F_N^*) > 0$ .

From Eq.(3.1), we consider the interval of equilibrium points satisfying the stability. Since  $(M^*, F_C^*, F_N^*)$  is the equilibrium point,  $g_i(M^*, F_C^*, F_N^*) = 0$ ;  $i = 1, 2, 3$ .

Because the solution converges to  $(M^*, F_C^*, F_N^*)$ , we transform the nonlinear system by defining new variables, that is,  $m = M - M^*$ ,  $f_C = F_C - F_C^*$  and  $f_N = F_N - F_N^*$ . If  $M, F_C$  and  $F_N$  converge to  $(M^*, F_C^*, F_N^*)$ ,  $m, f_C$  and  $f_N$  converge to zeros. We obtain  $M = m + M^*$ ,  $F_C = f_C + F_C^*$  and  $F_N = f_N + F_N^*$  where  $M^*, F_C^*$  and  $F_N^*$  are constants. Then, the system becomes

$$\begin{aligned} \frac{dm}{dt} &= \frac{d(M - M^*)}{dt} = \frac{dM}{dt} = g_1(M^*, F_C^*, F_N^*) \\ &= g_1(M^* + m, F_C^* + f_C, F_N^* + f_N), \\ \frac{df_C}{dt} &= \frac{d(F_C - F_C^*)}{dt} = \frac{dF_C}{dt} = g_2(M^*, F_C^*, F_N^*) \\ &= g_2(M^* + m, F_C^* + f_C, F_N^* + f_N), \\ \frac{df_N}{dt} &= \frac{d(F_N - F_N^*)}{dt} = \frac{dF_N}{dt} = g_3(M^*, F_C^*, F_N^*) \\ &= g_3(M^* + m, F_C^* + f_C, F_N^* + f_N) \end{aligned}$$

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We expand the right hand side using Taylor series to get

$$\begin{aligned}\frac{dm}{dt} &= g_1(M^*, F_C^*, F_N^*) + \frac{\partial g_1}{\partial M}(M^*, F_C^*, F_N^*)m + \frac{\partial g_1}{\partial F_C}(M^*, F_C^*, F_N^*)f_C + \\ &\quad \frac{\partial g_1}{\partial F_N}(M^*, F_C^*, F_N^*)f_N + O(h), \\ \frac{df_C}{dt} &= g_2(M^*, F_C^*, F_N^*) + \frac{\partial g_2}{\partial M}(M^*, F_C^*, F_N^*)m + \frac{\partial g_2}{\partial F_C}(M^*, F_C^*, F_N^*)f_C + \\ &\quad \frac{\partial g_2}{\partial F_N}(M^*, F_C^*, F_N^*)f_N + O(h), \\ \frac{df_N}{dt} &= g_3(M^*, F_C^*, F_N^*) + \frac{\partial g_3}{\partial M}(M^*, F_C^*, F_N^*)m + \frac{\partial g_3}{\partial F_C}(M^*, F_C^*, F_N^*)f_C + \\ &\quad \frac{\partial g_3}{\partial F_N}(M^*, F_C^*, F_N^*)f_N + O(h).\end{aligned}$$

Since  $g_i(M^*, F_C^*, F_N^*) = 0$ ;  $i = 1, 2, 3$ , the system becomes

$$\begin{bmatrix} \frac{dm}{dt} \\ \frac{df_C}{dt} \\ \frac{df_N}{dt} \end{bmatrix} = \begin{bmatrix} \frac{\partial g_1}{\partial M}(M^*, F_C^*, F_N^*) & \frac{\partial g_1}{\partial F_C}(M^*, F_C^*, F_N^*) & \frac{\partial g_1}{\partial F_N}(M^*, F_C^*, F_N^*) \\ \frac{\partial g_2}{\partial M}(M^*, F_C^*, F_N^*) & \frac{\partial g_2}{\partial F_C}(M^*, F_C^*, F_N^*) & \frac{\partial g_2}{\partial F_N}(M^*, F_C^*, F_N^*) \\ \frac{\partial g_3}{\partial M}(M^*, F_C^*, F_N^*) & \frac{\partial g_3}{\partial F_C}(M^*, F_C^*, F_N^*) & \frac{\partial g_3}{\partial F_N}(M^*, F_C^*, F_N^*) \end{bmatrix} \begin{bmatrix} m \\ f_C \\ f_N \end{bmatrix} + O(h),$$

where the  $3 \times 3$  matrix is called the Jacobian Matrix of the system at  $M^*$ ,  $F_C^*$  and  $F_N^*$ .

We linearize the system at  $(M^*, F_C^*, F_N^*)$ , the above system becomes

$$\begin{bmatrix} \frac{dm}{dt} \\ \frac{df_C}{dt} \\ \frac{df_N}{dt} \end{bmatrix} = \begin{bmatrix} \frac{\partial g_1}{\partial M}(M^*, F_C^*, F_N^*) & \frac{\partial g_1}{\partial F_C}(M^*, F_C^*, F_N^*) & \frac{\partial g_1}{\partial F_N}(M^*, F_C^*, F_N^*) \\ \frac{\partial g_2}{\partial M}(M^*, F_C^*, F_N^*) & \frac{\partial g_2}{\partial F_C}(M^*, F_C^*, F_N^*) & \frac{\partial g_2}{\partial F_N}(M^*, F_C^*, F_N^*) \\ \frac{\partial g_3}{\partial M}(M^*, F_C^*, F_N^*) & \frac{\partial g_3}{\partial F_C}(M^*, F_C^*, F_N^*) & \frac{\partial g_3}{\partial F_N}(M^*, F_C^*, F_N^*) \end{bmatrix} \begin{bmatrix} m \\ f_C \\ f_N \end{bmatrix} \quad (3.11)$$

From the first equation of model (3.1) with  $n = 1$ ,

$$g_1(M, F_C, F_N) = v_s \frac{K_i}{K_i + F_N} - v_m \frac{M}{K_m + M} + L.$$

The partial derivatives of  $g_1(M, F_C, F_N)$  at  $(M^*, F_C^*, F_N^*)$  are

$$\frac{\partial g_1}{\partial M}(M^*, F_C^*, F_N^*) = -v_m \frac{K_m}{(K_m + M^*)^2},$$

$$\frac{\partial g_1}{\partial F_C}(M^*, F_C^*, F_N^*) = 0,$$

$$\frac{\partial g_1}{\partial F_N}(M^*, F_C^*, F_N^*) = -v_s \frac{K_l}{(K_l + F_N^*)^2}.$$

From the second equation of model (3.1),

$$g_2(M, F_C, F_N) = k_s M - v_d \frac{F_C}{K_d + F_C} - k_1 F_C + k_2 F_N.$$

The partial derivatives of  $g_2(M, F_C, F_N)$  at  $(M^*, F_C^*, F_N^*)$  are

$$\frac{\partial g_2}{\partial M}(M^*, F_C^*, F_N^*) = k_s,$$

$$\frac{\partial g_2}{\partial F_C}(M^*, F_C^*, F_N^*) = -v_d \frac{K_d}{(K_d + F_C^*)^2} - k_1,$$

$$\frac{\partial g_2}{\partial F_N}(M^*, F_C^*, F_N^*) = k_2.$$

From the third equation of model (3.1),

$$g_3(M, F_C, F_N) = k_1 F_C - k_2 F_N.$$

The partial derivatives of  $g_3(M, F_C, F_N)$  at  $(M^*, F_C^*, F_N^*)$  are

$$\frac{\partial g_3}{\partial M}(M^*, F_C^*, F_N^*) = 0,$$

$$\frac{\partial g_3}{\partial F_C}(M^*, F_C^*, F_N^*) = k_1,$$

$$\frac{\partial g_3}{\partial F_N}(M^*, F_C^*, F_N^*) = -k_2.$$

Next, we substitute these values into Eq.(3.11), the system (3.11) becomes

$$\begin{bmatrix} \frac{dm}{dt} \\ \frac{df_C}{dt} \\ \frac{df_N}{dt} \end{bmatrix} = \begin{bmatrix} -v_m \frac{K_m}{(K_m + M^*)^2} & 0 & -v_s \frac{K_l}{(K_l + F_N^*)^2} \\ k_s & -v_d \frac{K_d}{(K_d + F_C^*)^2} - k_1 & k_2 \\ 0 & k_1 & -k_2 \end{bmatrix} \begin{bmatrix} m \\ f_C \\ f_N \end{bmatrix}. \quad (3.12)$$

Suppose

$$A' = \frac{K_l}{(K_l + F_N^*)^2},$$

$$B' = \frac{K_m}{(K_m + M^*)^2},$$

$$C' = \frac{K_d}{(K_d + F_C^*)^2},$$

where  $A'$  is the derivative of  $A = \frac{K_l}{K_l + F_N}$  with respect to  $F_N$ ;  $B'$  is the derivative of  $B = \frac{M}{K_m + M}$  with respect to  $M$ ;  $C'$  is the derivative of  $C = \frac{F_C}{K_d + F_C}$  with respect to  $F_C$ , at the equilibrium point  $E^* = (M^*, F_C^*, F_N^*)$ .

After we substitute the values of  $A', B'$  and  $C'$  into the system (3.12), we obtain

$$J = \begin{bmatrix} -v_m B' & 0 & -v_s A' \\ k_s & -v_d C' - k_1 & k_2 \\ 0 & k_1 & -k_2 \end{bmatrix}. \quad (3.13)$$

From  $\det(J - \lambda I) = 0$ ,

$$\begin{vmatrix} -v_m B' - \lambda & 0 & -v_s A' \\ k_s & -v_d C' - k_1 - \lambda & k_2 \\ 0 & k_1 & -k_2 - \lambda \end{vmatrix} = 0,$$

hence, the characteristic equation is

$$\lambda^3 + a_1 \lambda^2 + a_2 \lambda + a_3 = 0, \quad (3.14)$$

where

$$a_1 = k_1 + k_2 + C' v_d + B' v_m,$$

$$a_2 = B' k_1 v_m + B' k_2 v_m + C' k_2 v_d + B' C' v_d v_m,$$

$$a_3 = B' C' k_2 v_d v_m + A' k_1 k_s v_m.$$

We find stability of equilibrium points by using Routh-Hurwitz criterion. The conditions are

$$a_1 > 0,$$

$$a_3 > 0,$$

$$a_1 a_2 > a_3.$$

If the parameters,  $a_1, a_2$  and  $a_3$ , satisfy these conditions, the equilibrium points will be asymptotically stable.

Next, we will find the eigenvalues to analyze this model.

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From Eq.(3.14) , we get the eigenvalues

$$\begin{aligned}\lambda_1 &= -\frac{a_1}{3} - \sqrt[3]{2b_1 + b_2}, \\ \lambda_2 &= -\frac{a_1}{3} + \frac{1+i\sqrt{3}}{\sqrt[3]{4}}b_1 - \frac{1-i\sqrt{3}}{2}b_2, \\ \lambda_3 &= -\frac{a_1}{3} + \frac{1-i\sqrt{3}}{\sqrt[3]{4}}b_1 - \frac{1+i\sqrt{3}}{2}b_2,\end{aligned}$$

where

$$\begin{aligned}b_1 &= \frac{-a_1^2 + 3a_2}{3\sqrt[3]{-2a_1^3 + 9a_1a_2 - 27a_3 + 3\sqrt{3}\sqrt{-a_1^2a_2^2 + 4a_2^3 + 4a_1^3a_3 - 18a_1a_2a_3 + 27a_3^2}}}, \\ b_2 &= -\frac{1}{3\sqrt[3]{2}}\sqrt[3]{-2a_1^3 + 9a_1a_2 - 27a_3 + 3\sqrt{3}\sqrt{-a_1^2a_2^2 + 4a_2^3 + 4a_1^3a_3 - 18a_1a_2a_3 + 27a_3^2}}.\end{aligned}$$

Note that the first eigenvalue  $\lambda_1$  is real. Therefore, if  $\lambda_1$  is negative, that is,

$$-\frac{a_1}{3} - \sqrt[3]{2b_1 + b_2} < 0,$$

then the equilibrium point  $E^*$  will be locally asymptotically stable. On the other hand, if  $\lambda_1$  is positive, that is,

$$-\frac{a_1}{3} - \sqrt[3]{2b_1 + b_2} > 0,$$

the equilibrium point  $E^*$  will be unstable.

Next, we rearrange  $\lambda_2$  and  $\lambda_3$ . Then we let  $\lambda_{2,3} = \left(-\frac{a_1}{3} + \frac{b_1}{\sqrt[3]{4}} - \frac{b_2}{2}\right) \pm i\left(\frac{\sqrt{3}}{4}b_1 - \frac{\sqrt{3}}{2}b_2\right)$  which are a pair of complex eigenvalues. If

$$Re(\lambda_{2,3}) < 0$$

and

$$Im(\lambda_{2,3}) > 0,$$

the equilibrium point  $E^*$  is locally asymptotically stable. However, if

$$Re(\lambda_{2,3}) > 0$$

and  $Im(\lambda_{2,3}) > 0$ , the equilibrium point  $E^*$  is unstable.

We now look for the range of parameters for which the equilibrium point  $E^*$  is locally asymptotically stable. Consider

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$$\operatorname{Re}(\lambda_{2,3}) < 0,$$

which leads us to the following inequality

$$a_1 > \frac{3}{2}(\sqrt[3]{2b_1} - b_2). \quad (3.15)$$

Now, we define  $a_1$  as the bifurcation parameter. Then we will use the Hopf bifurcation theory in order to show that at  $a_1 = R$  where  $R = \frac{3}{2}(\sqrt[3]{2b_1} - b_2)$  the steady state  $E^*$  becomes unstable and the limit cycle, surrounding the equilibrium point, created by the bifurcation which is asymptotically stable.

Consider the real part of the two eigenvalues of the Jacobian matrix in (3.13) and then define the function of bifurcation parameter  $F(a_1)$  and also define  $b_1$  and  $b_2$  as function of  $a_1$ , so we obtain

$$F(a_1) = -\frac{a_1}{3} - \sqrt[3]{2b_1} + b_2. \quad (3.16)$$

From the result above and the inequality (3.15), if  $a_1 > R$ ,  $E^*$  is asymptotically stable and loses its stability at  $a_1 = R$ , at which point (3.13) has a pair of purely imaginary complex eigenvalues.

For Hopf bifurcation to occur, we need parameters such that  $\left. \frac{dF}{da_1} \right|_{a_1=R} \neq 0$ . From (3.16), we get

$$\frac{dF}{da_1} = -\frac{1}{3} - \sqrt[3]{2b_1'} + b_2'$$

and consequently

$$\left. \frac{dF}{da_1} \right|_{a_1=R} \neq 0$$

which is the main condition of Hopf bifurcation theorem.

### 3.2 An Analysis of the Model (2.3)

In this section, we recall and analyze the model (2.3) described in chapter 2. The model is a system of nonlinear differential equations given by

$$\begin{aligned}\frac{dM}{dt} &= v_s \frac{K_l^n}{K_l^n + F_N^n} - v_m \frac{M}{K_m + M} + L, \\ \frac{dF_C}{dt} &= k_s M - k_1 F_C + k_2 F_N - k F_C, \\ \frac{dF_S}{dt} &= k F_C - v_d \frac{F_S}{K_d + F_S}, \\ \frac{dF_N}{dt} &= k_1 F_C - k_2 F_N - v_{dN} \frac{F_N}{K_{dN} + F_N},\end{aligned}$$

where the variables are defined earlier in Chapter 2.

It is clear that the system described above has a positive steady state  $(0, 0, 0, 0)$  with  $L = 0$ . However, we will not consider the behavior of the model at this equilibrium point.

We define these functions to find the equilibrium points

$$\begin{aligned}\frac{dM}{dt} &= g_1(M, F_C, F_S, F_N) = 0, \\ \frac{dF_C}{dt} &= g_2(M, F_C, F_S, F_N) = 0, \\ \frac{dF_S}{dt} &= g_3(M, F_C, F_S, F_N) = 0, \\ \frac{dF_N}{dt} &= g_4(M, F_C, F_S, F_N) = 0.\end{aligned}\tag{3.17}$$

Let  $E^* = (M^*, F_C^*, F_S^*, F_N^*)$  be an equilibrium point and let  $n = 1$ . So we obtain

$$v_s \frac{K_l}{K_l + F_N^*} - v_m \frac{M^*}{K_m + M^*} + L = 0,\tag{3.18}$$

$$k_s M^* - k_1 F_C^* + k_2 F_N^* - k F_C^* = 0,\tag{3.19}$$

$$k F_C^* - v_d \frac{F_S^*}{K_d + F_S^*} = 0,\tag{3.20}$$

$$k_1 F_C^* - k_2 F_N^* - v_{dN} \frac{F_N^*}{K_{dN} + F_N^*} = 0.\tag{3.21}$$

From Eq.(3.17), we get

$$F_N^* = \frac{-K_l K_m L - K_l L M^* + K_l M^* v_m - K_l K_m v_s - K_l M^* v_s}{K_m L + L M^* - M^* v_m}.\tag{3.22}$$

Next, we consider Eq.(3.18)

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$$F_N^* = \frac{F_C^* k + F_C^* k_1 - k_s M^*}{k_s}. \quad (3.23)$$

From Eq.(3.21) and (3.22), we have

$$F_C^* = \frac{1}{(k + k_1)(K_m L + LM^* - M^* v_m)} (-k_2 K_1 K_m L - k_2 K_1 LM^* + K_m k_s LM^* + k_s LM^* + k_2 K_1 M^* v_m - k_s M^2 v_m - k_2 K_1 K_m v_s). \quad (3.24)$$

By solving Eq.(3.19), we get

$$F_S^* = -\frac{F_C^* k K_d}{F_C^* k - v_d}. \quad (3.25)$$

Solving Eq.(3.20) to obtain

$$F_C^* = \frac{F_N^* k_2 + F_N^* k_2 K_{dN} + F_N^* v_{dN}}{k_1 (F_N^* + K_{dN})}. \quad (3.26)$$

From Eq.(3.23) and (3.25), we get

$$F_N^* = \frac{1}{-2k_2(k + k_1) [K_m L + M^*(L - v_m)]} \left[ k k_2 K_{dN} K_m L + k_1 k_2 K_{dN} K_m L + k_1 k_2 K_1 K_m L + k k_2 K_{dN} LM^* + k_1 k_2 K_{dN} LM^* + k_1 k_2 K_1 LM^* - k_1 K_m k_s L M^* - k_1 k_s LM^2 + k K_m L v_{dN} + k_1 K_m L v_{dN} + k LM^* v_{dN} + k_1 LM^* v_{dN} - k k_2 K_{dN} M^* v_m - k_1 k_2 K_{dN} M^* v_m - k_1 k_2 K_1 M^* v_m + k_1 k_s M^2 v_m - k M^* v_{dN} v_m - k_1 M^* v_{dN} v_m + k_1 k_2 K_1 K_m v_s + k_1 k_2 K_1 M^* v_s \pm \{ -4k_1(k + k_1)k_2 K_{dN} (K_m L + M^*(L - v_m)) [-k_s M^*(K_m L + M^*(L - v_m)) + k_2 K_1 (K_m (L + v_s) + M^*(L - v_m + v_s))] + \{ k(k_2 K_{dN} + v_{dN})(K_m L + M^*(L - v_m)) + k_1 [- (k_s M^* - v_{dN})(K_m L + M^*(L - v_m)) + k_2 (K_{dN} (K_m L + M^*(L - v_m)) + K_1 (K_m (L + v_s) + M^*(L - v_m + v_s))] \}^2 \}^{\frac{1}{2}} \right]. \quad (3.27)$$

Since the negative term of Eq.(3.27) is less than zero,

$$\frac{1}{-2k_2(k + k_1) [K_m L + M^*(L - v_m)]} \left[ k k_2 K_{dN} K_m L + k_1 k_2 K_{dN} K_m L + k_1 k_2 K_1 K_m L + k k_2 K_{dN} LM^* + k_1 k_2 K_{dN} LM^* + k_1 k_2 K_1 LM^* - k_1 K_m k_s L M^* - k_1 k_s LM^2 + k K_m L v_{dN} + k_1 K_m L v_{dN} + k LM^* v_{dN} + k_1 LM^* v_{dN} - k k_2 K_{dN} M^* v_m - k_1 k_2 K_{dN} M^* v_m - k_1 k_2 K_1 M^* v_m + k_1 k_s M^2 v_m - k M^* v_{dN} v_m - k_1 M^* v_{dN} v_m + k_1 k_2 K_1 K_m v_s + k_1 k_2 K_1 M^* v_s - \{ -4k_1(k + k_1)k_2 K_{dN} (K_m L + M^*(L - v_m)) [-k_s M^*(K_m L + M^*(L - v_m)) + k_2 K_1 (K_m (L + v_s) + M^*(L - v_m + v_s))] + \{ k(k_2 K_{dN} + v_{dN})(K_m L + M^*(L - v_m)) + k_1 [- (k_s M^* - v_{dN})(K_m L + M^*(L - v_m)) + k_2 (K_{dN} (K_m L + M^*(L - v_m)) + K_1 (K_m (L + v_s) + M^*(L - v_m + v_s))] \}^2 \}^{\frac{1}{2}} \right] < 0,$$

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so we choose  $F_N^*$  to be the positive term,

$$\begin{aligned}
 F_N^* = & \frac{1}{-2k_2(k+k_1)[K_m L + M^*(L-v_m)]} [kk_2 K_{dN} K_m L + k1k2 K_{dN} K_m L + \\
 & k_1 k_2 K_1 K_m L + kk_2 K_{dN} L M^* + k_1 k_2 K_{dN} L M^* + k_1 k_2 K_1 L M^* - k_1 K_m k_s L \\
 & M^* - k_1 k_s L M^{2*} + k K_m L v_{dN} + k_1 K_m L v_{dN} + k L M^* v_{dN} + k_1 L M^* v_{dN} - \\
 & kk_2 K_{dN} M^* v_m - k_1 k_2 K_{dN} M^* v_m - k_1 k_2 K_1 M^* v_m + k_1 k_s M^{2*} v_m - k M^* v_{dN} \\
 & v_m - k_1 M^* v_{dN} v_m + k_1 k_2 K_1 K_m v_s + k_1 k_2 K_1 M^* v_s + \{-4k_1(k+k_1)k_2 K_{dN} \\
 & (K_m L + M^*(L-v_m))[-k_s M^*(K_m L + M^*(L-v_m))] + k_2 K_1 (K_m(L+v_s) + \\
 & M^*(L-v_m+v_s))\} + \{k(k_2 K_{dN} + v_{dN})(K_m L + M^*(L-v_m)) + k_1[-(k_s M^* \\
 & -v_{dN})(K_m L + M^*(L-v_m)) + k_2(K_{dN}(K_m L + M^*(L-v_m)) + K_1(K_m(L \\
 & +v_s) + M^*(L-v_m+v_s)))]\}^{\frac{1}{2}}. \tag{3.28}
 \end{aligned}$$

By solving Eq.(3.24), (3.25), (3.26) and (3.28), we get the equilibrium value  $M^*, F_C^*, F_S^*$  and  $F_N^*$  in terms of parameters and then we obtain the equilibrium point  $(M^*, F_C^*, F_S^*, F_N^*)$ . However, each value of the point are not described in this thesis because it is long and complicated. More importantly,  $M^*, F_C^*, F_S^*$  and  $F_N^*$  are more than zero.

From Eq.(3.17), we consider the interval of equilibrium points satisfying the stability. Because  $(M^*, F_C^*, F_S^*, F_N^*)$  is the equilibrium point,  $g_i(M^*, F_C^*, F_S^*, F_N^*) = 0$  for  $i = 1, 2, 3, 4$ .

Because the solution converges to  $(M^*, F_C^*, F_S^*, F_N^*)$ , we transform the nonlinear equations by defining new variables, that is,  $m = M - M^*, f_C = F_C - F_C^*, f_S = F_S - F_S^*$  and  $f_N = F_N - F_N^*$ . If  $M, F_C, F_S$  and  $F_N$  converge to  $(M^*, F_C^*, F_S^*, F_N^*)$ ,  $m, f_C, f_S$  and  $f_N$  converge to zeros. So we obtain  $M = m + M^*, F_C = f_C + F_C^*, F_S = f_S + F_S^*$  and  $F_N = f_N + F_N^*$  where  $M^*, F_C^*, F_S^*$  and  $F_N^*$  are constants. Then, the system becomes

$$\begin{aligned}\frac{dm}{dt} &= \frac{d(M - M^*)}{dt} = \frac{dM}{dt} = g_1(M^*, F_C^*, F_S^*, F_N^*), \\ &= g_1(M^* + m, F_C^* + f_C, F_S^* + f_S, F_N^* + f_N);\end{aligned}$$

$$\begin{aligned}\frac{df_C}{dt} &= \frac{d(F_C - F_C^*)}{dt} = \frac{dF_C}{dt} = g_2(M^*, F_C^*, F_S^*, F_N^*), \\ &= g_2(M^* + m, F_C^* + f_C, F_S^* + f_S, F_N^* + f_N);\end{aligned}$$

$$\begin{aligned}\frac{df_S}{dt} &= \frac{d(F_C - F_C^*)}{dt} = \frac{dF_S}{dt} = g_3(M^*, F_C^*, F_S^*, F_N^*), \\ &= g_3(M^* + m, F_C^* + f_C, F_S^* + f_S, F_N^* + f_N);\end{aligned}$$

$$\begin{aligned}\frac{df_N}{dt} &= \frac{d(F_N - F_N^*)}{dt} = \frac{dF_N}{dt} = g_4(M^*, F_C^*, F_S^*, F_N^*), \\ &= g_4(M^* + m, F_C^* + f_C, F_S^* + f_S, F_N^* + f_N);\end{aligned}$$

Expanding the right hand side of the above system using Taylor approximation, we get

$$\begin{aligned}\frac{dm}{dt} &= g_1(M^*, F_C^*, F_S^*, F_N^*) + \frac{\partial g_1}{\partial M}(M^*, F_C^*, F_S^*, F_N^*)m + \frac{\partial g_1}{\partial F_C}(M^*, F_C^*, F_S^*, F_N^*) \\ &\quad f_C + \frac{\partial g_1}{\partial F_S}(M^*, F_C^*, F_S^*, F_N^*)f_S + \frac{\partial g_1}{\partial F_N}(M^*, F_C^*, F_S^*, F_N^*)f_N + O(h), \\ \frac{df_C}{dt} &= g_2(M^*, F_C^*, F_S^*, F_N^*) + \frac{\partial g_2}{\partial M}(M^*, F_C^*, F_S^*, F_N^*)m + \frac{\partial g_2}{\partial F_C}(M^*, F_C^*, F_S^*, F_N^*) \\ &\quad f_C + \frac{\partial g_2}{\partial F_S}(M^*, F_C^*, F_S^*, F_N^*)f_S + \frac{\partial g_2}{\partial F_N}(M^*, F_C^*, F_S^*, F_N^*)f_N + O(h), \\ \frac{df_S}{dt} &= g_3(M^*, F_C^*, F_S^*, F_N^*) + \frac{\partial g_3}{\partial M}(M^*, F_C^*, F_S^*, F_N^*)m + \frac{\partial g_3}{\partial F_C}(M^*, F_C^*, F_S^*, F_N^*) \\ &\quad f_C + \frac{\partial g_3}{\partial F_S}(M^*, F_C^*, F_S^*, F_N^*)f_S + \frac{\partial g_3}{\partial F_N}(M^*, F_C^*, F_S^*, F_N^*)f_N + O(h), \\ \frac{df_N}{dt} &= g_4(M^*, F_C^*, F_S^*, F_N^*) + \frac{\partial g_4}{\partial M}(M^*, F_C^*, F_S^*, F_N^*)m + \frac{\partial g_4}{\partial F_C}(M^*, F_C^*, F_S^*, F_N^*) \\ &\quad f_C + \frac{\partial g_4}{\partial F_S}(M^*, F_C^*, F_S^*, F_N^*)f_S + \frac{\partial g_4}{\partial F_N}(M^*, F_C^*, F_S^*, F_N^*)f_N + O(h),\end{aligned}$$

but  $g_i(M^*, F_C^*, F_S^*, F_N^*) = 0; i = 1, 2, 3, 4$ , the system becomes

$$\begin{bmatrix} \frac{dm}{dt} \\ \frac{df_c}{dt} \\ \frac{df_s}{dt} \\ \frac{df_N}{dt} \end{bmatrix} = \begin{bmatrix} \frac{\partial g_1}{\partial M}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_1}{\partial F_C}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_1}{\partial F_S}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_1}{\partial F_N}(M^*, F_C^*, F_S^*, F_N^*) \\ \frac{\partial g_2}{\partial M}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_2}{\partial F_C}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_2}{\partial F_S}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_2}{\partial F_N}(M^*, F_C^*, F_S^*, F_N^*) \\ \frac{\partial g_3}{\partial M}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_3}{\partial F_C}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_3}{\partial F_S}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_3}{\partial F_N}(M^*, F_C^*, F_S^*, F_N^*) \\ \frac{\partial g_4}{\partial M}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_4}{\partial F_C}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_4}{\partial F_S}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_4}{\partial F_N}(M^*, F_C^*, F_S^*, F_N^*) \end{bmatrix} \begin{bmatrix} m \\ f_c \\ f_s \\ f_N \end{bmatrix}$$

+O(h),

where the  $4 \times 4$  matrix is called the Jacobian Matrix of the system at  $M^*, F_C^*, F_S^*$  and  $F_N^*$ . Then, the linearized system at  $(M^*, F_C^*, F_N^*)$  is

$$\begin{bmatrix} \frac{dm}{dt} \\ \frac{df_c}{dt} \\ \frac{df_s}{dt} \\ \frac{df_N}{dt} \end{bmatrix} = \begin{bmatrix} \frac{\partial g_1}{\partial M}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_1}{\partial F_C}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_1}{\partial F_S}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_1}{\partial F_N}(M^*, F_C^*, F_S^*, F_N^*) \\ \frac{\partial g_2}{\partial M}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_2}{\partial F_C}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_2}{\partial F_S}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_2}{\partial F_N}(M^*, F_C^*, F_S^*, F_N^*) \\ \frac{\partial g_3}{\partial M}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_3}{\partial F_C}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_3}{\partial F_S}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_3}{\partial F_N}(M^*, F_C^*, F_S^*, F_N^*) \\ \frac{\partial g_4}{\partial M}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_4}{\partial F_C}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_4}{\partial F_S}(M^*, F_C^*, F_S^*, F_N^*) & \frac{\partial g_4}{\partial F_N}(M^*, F_C^*, F_S^*, F_N^*) \end{bmatrix} \begin{bmatrix} m \\ f_c \\ f_s \\ f_N \end{bmatrix} \quad (3.29)$$

From the first equation of model (2.3) with  $n = 1$ ,

$$g_1(M, F_C, F_S, F_N) = v_s \frac{K_l}{K_l + F_N} - v_m \frac{M}{K_m + M} + L,$$

the partial derivatives of  $g_1(M, F_C, F_S, F_N)$  at  $(M^*, F_C^*, F_S^*, F_N^*)$  are

$$\frac{\partial g_1}{\partial M}(M^*, F_C^*, F_S^*, F_N^*) = -v_m \frac{K_m}{(K_m + M^*)^2},$$

$$\frac{\partial g_1}{\partial F_C}(M^*, F_C^*, F_S^*, F_N^*) = 0,$$

$$\frac{\partial g_1}{\partial F_S}(M^*, F_C^*, F_S^*, F_N^*) = 0,$$

$$\frac{\partial g_1}{\partial F_N}(M^*, F_C^*, F_S^*, F_N^*) = -v_s \frac{K_l}{(K_l + F_N^*)^2}.$$

From the second equation of model (2.3),

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the partial derivatives of  $g_2(M, F_C, F_S, F_N)$  at  $(M^*, F_C^*, F_S^*, F_N^*)$  are

$$\begin{aligned}\frac{\partial g_2}{\partial M}(M^*, F_C^*, F_S^*, F_N^*) &= k_s, \\ \frac{\partial g_2}{\partial F_C}(M^*, F_C^*, F_S^*, F_N^*) &= -(k_1 + k), \\ \frac{\partial g_2}{\partial F_S}(M^*, F_C^*, F_S^*, F_N^*) &= 0, \\ \frac{\partial g_2}{\partial F_N}(M^*, F_C^*, F_S^*, F_N^*) &= k_2.\end{aligned}$$

From the third equation of model (2.3),

$$g_3(M, F_C, F_S, F_N) = kF_C - v_d \frac{F_S}{K_d + F_S},$$

the partial derivatives of  $g_3(M, F_C, F_S, F_N)$  at  $(M^*, F_C^*, F_S^*, F_N^*)$  are

$$\begin{aligned}\frac{\partial g_3}{\partial M}(M^*, F_C^*, F_S^*, F_N^*) &= 0, \\ \frac{\partial g_3}{\partial F_C}(M^*, F_C^*, F_S^*, F_N^*) &= k, \\ \frac{\partial g_3}{\partial F_S}(M^*, F_C^*, F_S^*, F_N^*) &= -v_d \frac{K_d}{(K_d + F_S^*)^2}, \\ \frac{\partial g_3}{\partial F_N}(M^*, F_C^*, F_S^*, F_N^*) &= 0.\end{aligned}$$

From the fourth equation of model (2.3),

$$g_4(M, F_C, F_S, F_N) = k_1 F_C - k_2 F_N - v_{dN} \frac{F_N}{K_{dN} + F_N},$$

the partial derivatives of  $g_4(M, F_C, F_S, F_N)$  at  $(M^*, F_C^*, F_S^*, F_N^*)$  are

$$\begin{aligned}\frac{\partial g_4}{\partial M}(M^*, F_C^*, F_S^*, F_N^*) &= 0, \\ \frac{\partial g_4}{\partial F_C}(M^*, F_C^*, F_S^*, F_N^*) &= k_1, \\ \frac{\partial g_4}{\partial F_S}(M^*, F_C^*, F_S^*, F_N^*) &= 0, \\ \frac{\partial g_4}{\partial F_N}(M^*, F_C^*, F_S^*, F_N^*) &= -k_2 - v_{dN} \frac{K_{dN}}{(K_{dN} + F_N^*)^2}.\end{aligned}$$

Next, we substitute these values into Eq.(3.29), the system becomes

$$\begin{bmatrix} \frac{dm}{dt} \\ \frac{df_C}{dt} \\ \frac{df_S}{dt} \\ \frac{df_N}{dt} \end{bmatrix} = \begin{bmatrix} -v_m \frac{K_m}{(K_m + M^*)^2} & 0 & 0 & -v_s \frac{K_l}{(K_l + F_N^*)^2} \\ k_s & -(k_1 + k) & 0 & k_2 \\ 0 & k & -v_d \frac{K_d}{(K_d + F_S^*)^2} & 0 \\ 0 & k_1 & 0 & -k_2 - v_{dN} \frac{K_{dN}}{(K_{dN} + F_N^*)^2} \end{bmatrix} \begin{bmatrix} m \\ f_C \\ f_S \\ f_N \end{bmatrix} \quad (3.30)$$

Suppose

$$A' = \frac{K_l}{(K_l + F_N^*)^2},$$

$$B' = \frac{K_m}{(K_m + M^*)^2},$$

$$C' = \frac{K_d}{(K_d + F_S^*)^2},$$

$$D' = \frac{K_{dN}}{(K_{dN} + F_N^*)^2},$$

where  $A'$  is the derivative of  $A = \frac{K_l}{K_l + F_N}$  with respect to  $F_N$ ;  $B'$  is the derivative of  $B = \frac{M}{K_m + M}$  with respect to  $M$ ;  $C'$  is the derivative of  $C = \frac{F_S}{K_d + F_S}$  with respect to  $F_S$ ;  $D'$  is the derivative of  $D = \frac{K_{dN}}{(K_{dN} + F_N)}$  with respect to  $F_C$ , at the equilibrium point  $E^* = (M^*, F_C^*, F_S^*, F_N^*)$ .

After we substitute  $A', B', C'$  and  $D'$  into the system (3.30), we obtain

$$J = \begin{bmatrix} -v_m B' & 0 & 0 & -v_s A' \\ k_s & -(k_1 + k) & 0 & k_2 \\ 0 & k & -v_d C' & 0 \\ 0 & k_1 & 0 & -k_2 - v_{dN} D' \end{bmatrix} \quad (3.31)$$

From  $\det(J - \lambda I) = 0$ ,

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

therefore, the characteristic equation is

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$$\lambda^4 + c_1\lambda^3 + c_2\lambda^2 + c_3\lambda + c_4 = 0, \quad (3.32)$$

where

$$\begin{aligned} c_1 &= k + k_1 + k_2 + C'v_d - D'v_{dN} + B'v_m, \\ c_2 &= -D'k_1v_{dN} + B'k_1v_m + B'k_2v_m - B'D'v_{dN}v_m + C'v_d(k_1 + k_2 - D'v_{dN} + B'v_m) + k(k_2 + C'v_d - D'v_{dN} + B'v_m), \\ c_3 &= -B'v_m(-kk_2 + D'kv_{dN} + D'k_1v_{dN}) + C'v_d[B'v_m(k_1 + k_2) - D'v_{dN}(k_1 + B'v_m) + k(k_2 - D'v_{dN} + B'v_m)] + A'k_1k_s v_s, \\ c_4 &= C'v_d[-B'v_m(-kk_2 + D'kv_{dN} + D'k_1v_{dN}) + A'k_1k_2v_s]. \end{aligned}$$

Using Routh-Hurwitz criterion, the conditions are

$$\begin{aligned} c_1 &> 0, \\ c_3 &> 0, \\ c_4 &\geq 0, \\ c_1c_2c_3 &> c_3^2 + c_1^2c_4. \end{aligned}$$

If the parameters,  $c_1, c_2$  and  $c_3$ , satisfy these conditions, the equilibrium points will be asymptotically stable.

By factorizing the characteristic equation Eq.(3.32), we obtain

$$(\lambda + C'v_d)(\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3) = 0,$$

where

$$\begin{aligned} a_1 &= k + k_1 + k_2 - D'v_{dN} + B'v_m, \\ a_2 &= B'v_m(k_1 + k_2) - D'v_{dN}(k_1 + B'v_m) + k(k_2 - D'v_{dN} + B'v_m), \\ a_3 &= -B'v_m(-kk_2 + D'kv_{dN} + D'k_1v_{dN}) + A'k_1k_s v_s. \end{aligned}$$

Note that the first eigenvalue  $\lambda_1 = -C'v_d$  is real. Therefore, if  $\lambda_1$  is negative, that is,

$$-C'v_d < 0,$$

the equilibrium point  $E^*$  will be locally asymptotically stable. On the other hand, if  $\lambda_1$  is positive, that is,

$$-C'v_d > 0,$$

the equilibrium point  $E^*$  will be unstable.

Next, other roots or the eigenvalues of Eq.(3.32) are

$$\lambda_2 = -\frac{a_1}{3} - \sqrt[3]{2b_1 + b_2},$$

$$\lambda_3 = -\frac{a_1}{3} + \frac{1+i\sqrt{3}}{\sqrt[3]{4}}b_1 - \frac{1-i\sqrt{3}}{2}b_2,$$

$$\lambda_4 = -\frac{a_1}{3} + \frac{1-i\sqrt{3}}{\sqrt[3]{4}}b_1 - \frac{1+i\sqrt{3}}{2}b_2,$$

where

$$b_1 = \frac{-a_1^2 + 3a_2}{3\sqrt[3]{-2a_1^3 + 9a_1a_2 - 27a_3 + 3\sqrt{3}\sqrt{-a_1^2a_2^2 + 4a_2^3 + 4a_1^3a_3 - 18a_1a_2a_3 + 27a_3^2}}},$$

$$b_2 = -\frac{1}{3\sqrt[3]{2}}\sqrt[3]{-2a_1^3 + 9a_1a_2 - 27a_3 + 3\sqrt{3}\sqrt{-a_1^2a_2^2 + 4a_2^3 + 4a_1^3a_3 - 18a_1a_2a_3 + 27a_3^2}}.$$

Note that the second eigenvalue  $\lambda_2$  is real. Therefore, if  $\lambda_2$  is negative, that is,

$$-\frac{a_1}{3} - \sqrt[3]{2}b_1 + b_2 < 0,$$

the equilibrium point,  $E^*$ , will be locally asymptotically stable. On the other hand, if  $\lambda_2$  is positive, that is,

$$-\frac{a_1}{3} - \sqrt[3]{2}b_1 + b_2 > 0,$$

the equilibrium point,  $E^*$ , will be unstable.

Next, we rearrange  $\lambda_3$  and  $\lambda_4$ . Then we let  $\lambda_{3,4} = \left(-\frac{a_1}{3} + \frac{b_1}{\sqrt[3]{4}} - \frac{b_2}{2}\right) \pm i\left(\frac{\sqrt{3}}{\sqrt[3]{4}}b_1 - \frac{\sqrt{3}}{2}b_2\right)$  which are a pair of complex eigenvalues. If

$$Re(\lambda_{3,4}) < 0$$

and

$$Im(\lambda_{3,4}) > 0,$$

the sum of eigenvalues is negative and the real parts of both eigenvalues must be negative. Hence, if all three of the eigenvalues of the Jacobian matrix  $J$  are negative and the equilibrium point,  $E^*$ , is locally asymptotically stable. However, if

$$Re(\lambda_{3,4}) > 0$$

and  $Im(\lambda_{3,4}) > 0$ , at least one eigenvalue has a positive real part and the equilibrium point  $E^*$  is unstable.

We now look for the range of parameters for which the equilibrium point  $E^*$  is locally asymptotically stable. Consider

$$Re(\lambda_{3,4}) < 0,$$

which leads us to the following inequality

$$a_1 > \frac{3}{2}(\sqrt[3]{2b_1 - b_2}). \quad (3.33)$$

Now, we define  $a_1$  as a bifurcation parameter. Then we will use the Hopf bifurcation theorem in order to show that at  $a_1 = R$  where  $R = \frac{3}{2}(\sqrt[3]{2b_1 - b_2})$  the steady state  $E^*$  becomes unstable and the limit cycle, surrounding the equilibrium point, created by the bifurcation which is asymptotically stable.

Consider the real part of the two eigenvalues of the Jacobian matrix in (3.31) and then define a function of bifurcation parameter  $F(a_1)$  and also define  $b_1$  and  $b_2$  as function of  $a_1$ , we obtain

$$F(a_1) = -\frac{a_1}{3} - \sqrt[3]{2b_1 + b_2}. \quad (3.34)$$

From the inequality (3.33), if  $a_1 > R$ ,  $E^*$  is asymptotically stable and loses its stability at  $a_1 = R$ , at which point (3.31) has a pair of purely imaginary complex eigenvalues. For Hopf bifurcation to occur, we need parameters such that  $\left. \frac{dF}{da_1} \right|_{a_1=R} \neq 0$ . From (3.34), we get

$$\frac{dF}{da_1} = -\frac{1}{3} - \sqrt[3]{2b_1' + b_2'}.$$

Consequently,

$$\left. \frac{dF}{da_1} \right|_{a_1=R} \neq 0$$

which is the main condition of the Hopf bifurcation theorem.

## Chapter 4

### Numerical Results

In this chapter, we will use the modified mathematical model developed in Chapter 2 to determine numerical solutions for concentrations of *frq* mRNA, cytosol FRQ, stable FRQ and nuclear FRQ. To do this, we have to first find reasonable estimates for the parameters. More importantly, we considered the example of illuminances [4] as follows:  $L = 0.002$  lux, for example, is moonless clear night sky with airflow;  $L = 1$  lux, for example, is full moon overhead at tropical latitudes;  $L = 400$  lux, for example, is sunrise or sunset on a clear day;  $L = 1000$  lux, for example, overcast day or typical TV studio lighting.

#### 4.1 Parameters and Numerical Solutions for the Model (2.4)

In this section, we find the proper parameters which satisfy all theoretical stable state conditions and also limit cycle state conditions by using mathematical program with copyright from KMITL called MATLAB version 7.6 and equilibrium points by using MATHEMATICA version 7. Here are the results for all four different cases of illuminances described above.

- $L = 0.002$  lux
  - For the stable state, the parameters used in the simulation are  $v_s = 3.5$ ,  $v_m = 1.0$ ,  $v_d = 3.0$ ,  $k_s = 1.2$ ,  $k_1 = 2.0$ ,  $k_2 = 2.0$ ,  $K_m = 0.5$ ,  $K_l = 1.7$ ,  $K_d = 0.2$ ,  $n = 1$ ,  $L = 0.002$  and  $(2.41229, 5.50065, 5.50065)$  is the equilibrium point.
  - For the limit cycle, the parameters used in the simulation are  $v_s = 3.5$ ,  $v_m = 1.0$ ,  $v_d = 3.0$ ,  $k_s = 1.2$ ,  $k_1 = 2.0$ ,  $k_2 = 2.0$ ,  $K_m = 0.005$ ,  $K_l = 1.7$ ,  $K_d = 0.05$ ,  $n = 1$ ,  $L = 0.002$  and  $(2.47109, 4.27401, 4.27401)$  is the equilibrium point.
- $L = 1$  lux
  - For the stable state, the parameters used in the simulation are  $v_s = 4.0$ ,  $v_m = 3.5$ ,  $v_d = 3.0$ ,  $k_s = 1.0$ ,  $k_1 = 3.5$ ,  $k_2 = 3.25$ ,  $K_m = 0.02$ ,  $K_l = 1.0$ ,  $K_d = 0.05$ ,  $n = 1$ ,  $L = 1$  and  $(2.75895, 0.572265, 0.616285)$  is the equilibrium point.
  - For the limit cycle, the parameters used in the simulation are  $v_s = 4.0$ ,  $v_m = 3.5$ ,  $v_d = 3.0$ ,  $k_s = 1.2$ ,  $k_1 = 3.5$ ,  $k_2 = 3.25$ ,  $K_m = 0.01$ ,  $K_l = 2.0$ ,  $K_d = 0.02$ ,  $n = 1$ ,  $L = 1$  and  $(2.45657, 1.13125, 1.21827)$  is the equilibrium point.

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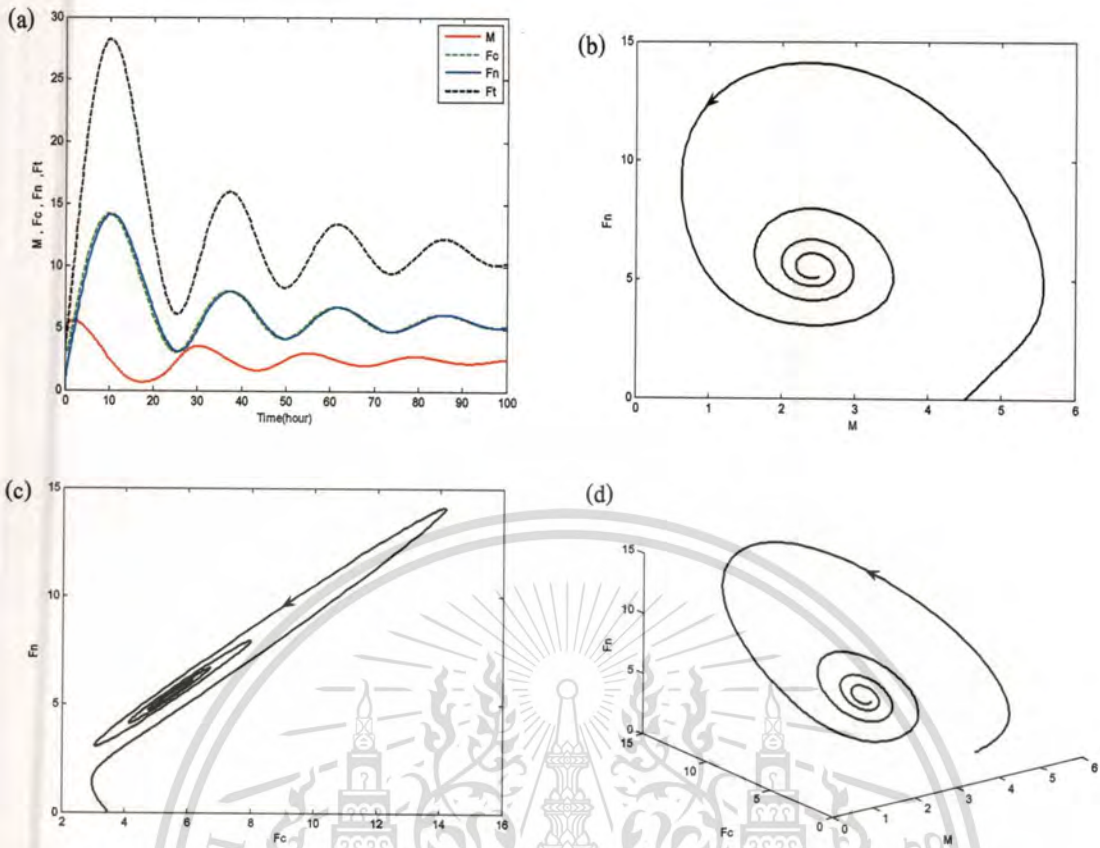
3.  $L = 400$  lux

- For the stable state, the parameters used in the simulation are  $v_s = 55.0$ ,  $v_m = 410.0$ ,  $v_d = 5.0$ ,  $k_s = 1.5$ ,  $k_1 = 3.5$ ,  $k_2 = 1.1$ ,  $K_m = 0.01$ ,  $K_l = 1.2$ ,  $K_d = 0.01$ ,  $n = 1$ ,  $L = 400$  and  $(3.31666, 1.98873, 6.32777)$  is the equilibrium point.
- For the the limit cycle, the parameters used in the simulation are  $v_s = 55.0$ ,  $v_m = 410.0$ ,  $v_d = 5.0$ ,  $k_s = 0.5$ ,  $k_1 = 3.5$ ,  $k_2 = 3.1$ ,  $K_m = 0.001$ ,  $K_l = 1.6$ ,  $K_d = 0.004$ ,  $n = 1$ ,  $L = 400$  and  $(9.99376, 6.40925, 7.23625)$  is the equilibrium point.

4.  $L = 1000$  lux

- For the stable state, the parameters used in the simulation are  $v_s = 250.0$ ,  $v_m = 1200.0$ ,  $v_d = 20.0$ ,  $k_s = 2.5$ ,  $k_1 = 3.0$ ,  $k_2 = 3.0$ ,  $K_m = 0.2$ ,  $K_l = 5.5$ ,  $K_d = 0.1$ ,  $n = 1$ ,  $L = 1000$  and  $(7.70431, 2.60555, 2.60555)$  is the equilibrium point.
- For the limit cycle, the parameters used in the simulation are  $v_s = 250.0$ ,  $v_m = 1200.0$ ,  $v_d = 20.0$ ,  $k_s = 2.5$ ,  $k_1 = 3.0$ ,  $k_2 = 3.0$ ,  $K_m = 0.01$ ,  $K_l = 3.5$ ,  $K_d = 0.1$ ,  $n = 1$ ,  $L = 1000$  and  $(7.20923, 0.911666, 0.911666)$  is the equilibrium point.

Next, we verify all parameters by using Runge Kutta method, by applying MATLAB toolbox, ode45. All trajectories, phase plane and phase space in each state are also illustrated. Moreover, we show that all parameters described satisfy stable and limit cycle conditions mentioned in chapter 2.



**Figure 4.1** (a) The stable solution with respect to time, (b, c) the phase plane projected on the  $(M, F_N)$  and  $(F_C, F_N)$  planes and (d) phase space trajectory in  $M - F_C - F_N$  space of the model (2.4) with stable state parameters  $v_s = 3.5, v_m = 1.0, v_d = 3.0, k_s = 1.2, k_1 = 2.0, k_2 = 2.0, K_m = 0.5, K_l = 1.7, K_d = 0.2, n = 1, L = 0.002$ .

In Figure 4.1, we plot the stable solution with respect to time, phase plane, and phase space trajectory of the model (2.4) starting from initial point  $(M_0, F_{C_0}, F_{N_0}) = (3.5, 4.5, 0)$  with stable state parameters described above. When time increases, the variables  $M, F_C$  and  $F_N$  approach to the steady state value  $E^* = (M^*, F_C^*, F_N^*) = (2.41229, 5.50065, 5.50065)$  as theoretically expected.

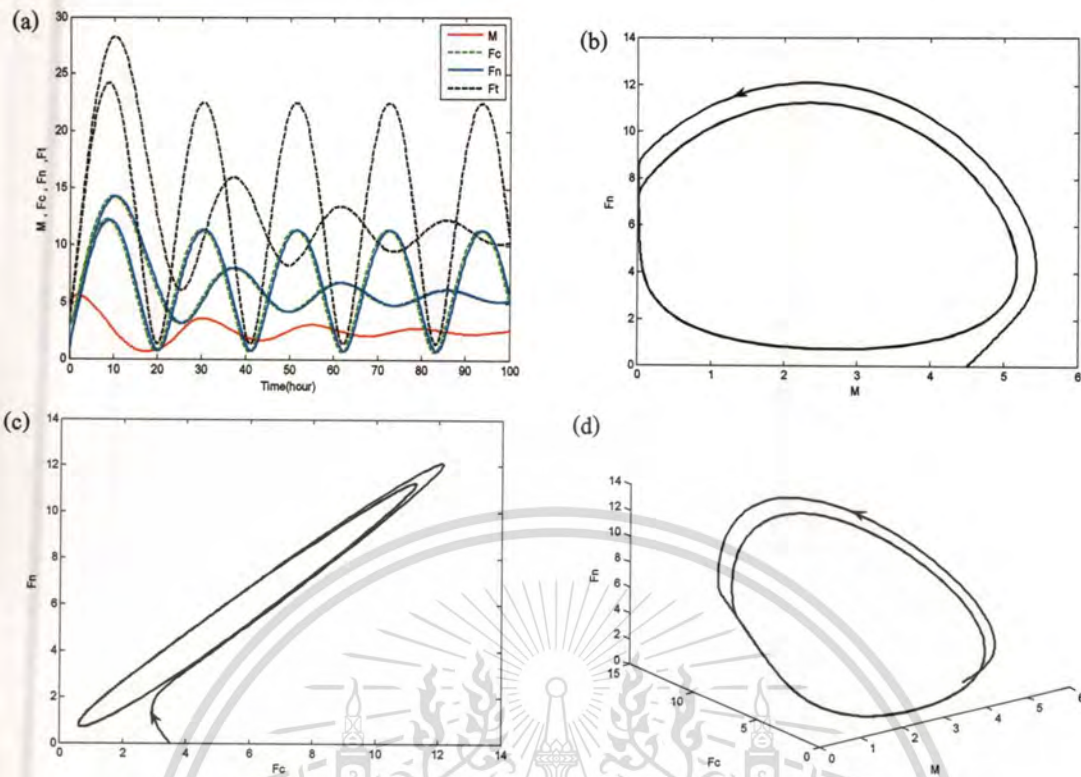
In the case of  $L = 0.002$  lux with stable state parameters shown in Figure 4.1, the coefficients of the characteristic equation are satisfied the Routh-Hurwitz criterion which are

$$a_1 = 4.07742, a_3 = 0.27759, a_1 a_2 = 1.11649 > a_3.$$

Then, real part of eigenvalues  $\lambda_1$  and  $\lambda_{2,3}$  are negative, that is,

$$-\frac{a_1}{3} - \sqrt[3]{2} b_1 + b_2 = -4.02653, \quad -\frac{a_1}{3} + \frac{b_1}{\sqrt[3]{4}} - \frac{b_2}{2} = -0.0254417$$

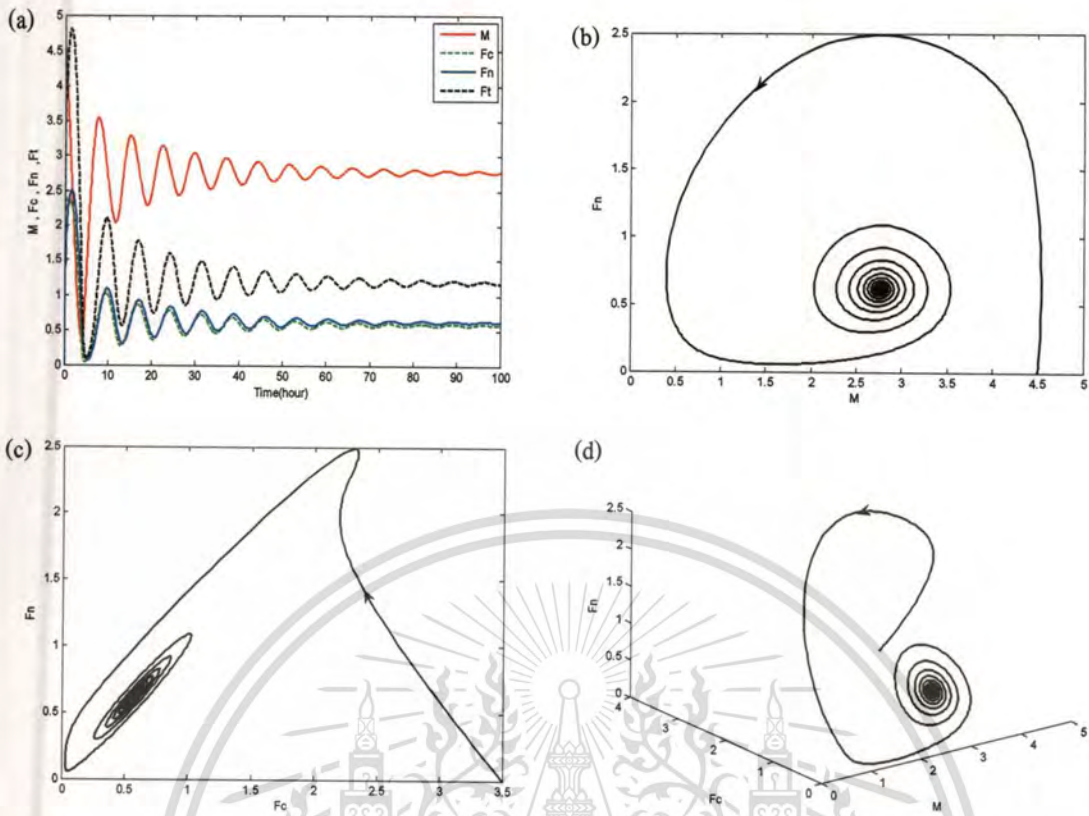
where  $b_1 = 1.17831$  and  $b_2 = -1.18282$ .



**Figure 4.2** (a) The oscillatory solution with respect to time, (b, c) phase plane of the model (2.4) projected on the  $(M, F_N)$  and  $(F_C, F_N)$  planes and (d) phase space trajectory in  $M - F_C - F_N$  space show that a limit cycle exists with parameters  $v_s = 3.5, v_m = 1.0, v_d = 3.0, k_s = 1.2, k_1 = 2.0, k_2 = 2.0, K_m = 0.005, K_l = 1.7, K_d = 0.05, n = 1, L = 0.002$ .

In Figure 4.2, we plot the time series, phase plane, and phase space trajectory of the model (2.4) starting from initial point  $(M_0, F_{C_0}, F_{N_0}) = (3.5, 4.5, 0)$  with parameters chosen to satisfy the condition under which a limit cycle will occur. When time increases, the trajectory is tended toward to stable limit cycle at the steady state value  $E^* = (M^*, F_C^*, F_N^*) = (2.47109, 4.27401, 4.27401)$  as theoretically predicted.

In the case of  $L = 0.002$  lux with limit cycle parameters shown in Figure 4.3 and 4.4, the condition at critical value  $R = 4.03863$  is  $a_1 < R$  and eventually,  $\frac{dF}{da_1}|_{a_1=R} = -3.58983 \neq 0$  so the function  $F$  is decreasing at  $a_1 = R$ . Due to the fact that the equilibrium point  $E^*$  is locally asymptotically stable if  $a_1 > R$  then  $E^*$  loses its stability and the system undergoes a Hopf bifurcation at  $a_1 < R$  calculated from the theoretical value of  $R$ . Moreover, this bifurcation  $a_1$  under condition of  $L = 0.002$  lux is a supercritical Hopf bifurcation.



**Figure 4.3** (a) The stable solution with respect to time, (b, c) the phase plane projected on the  $(M, F_N)$  and  $(F_C, F_N)$  planes and (d) phase space trajectory in  $M - F_C - F_N$  space of the model (2.4) with stable state parameters  $v_s = 4.0, v_m = 3.5, v_d = 3.0, k_s = 1.0, k_1 = 3.5, k_2 = 3.25, K_m = 0.02, K_l = 1.0, K_d = 0.05, n = 1, L = 1$ .

In Figure 4.3, we plot the stable solution with respect to time, phase plane, and phase space trajectory of the model (2.4) starting from initial point  $(M_0, F_{C_0}, F_{N_0}) = (3.5, 4.5, 0)$  with stable state parameters described above. When time increases, the variables  $M, F_C$  and  $F_N$  approach to the steady state value  $E^* = (M^*, F_C^*, F_N^*) = (2.75895, 0.572265, 0.616285)$  as theoretically expected.

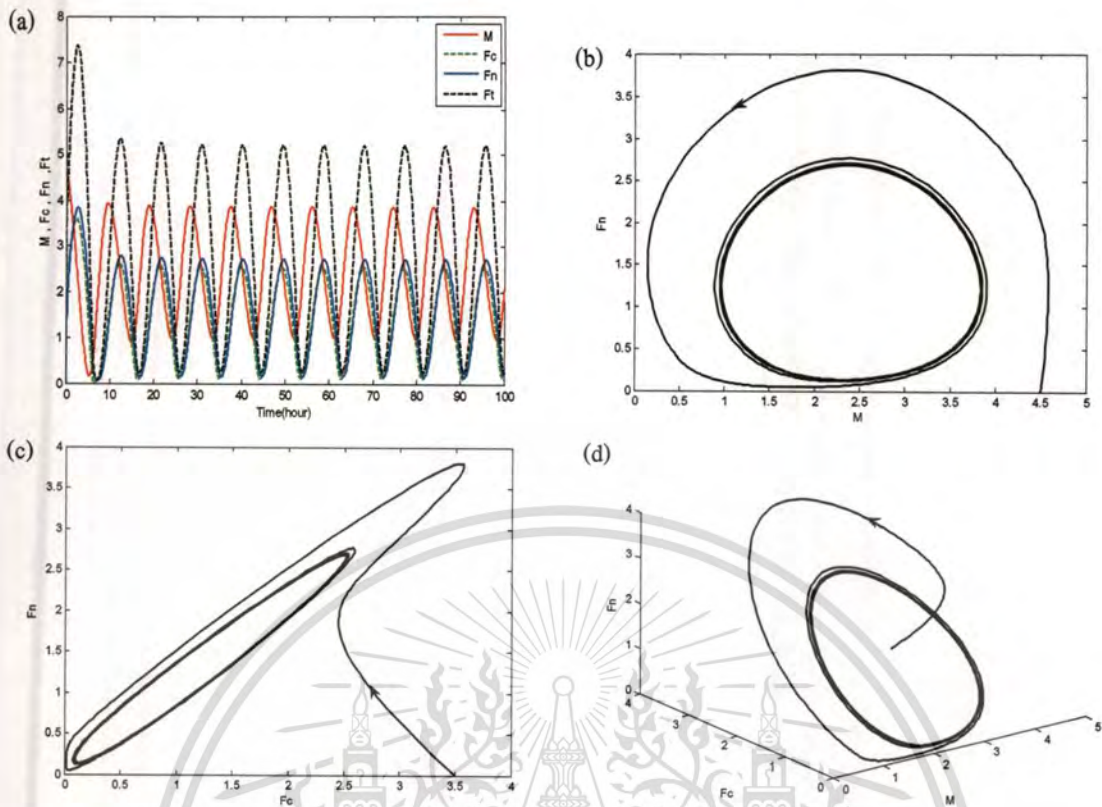
In the case of  $L = 1$  lux with stable parameters shown in Figure 4.3, the coefficients of characteristic equation are satisfied the Routh-Hurwitz criterion which are

$$a_1 = 7.14645, a_3 = 5.37051, a_1 a_2 = 9.45969 > a_3.$$

Then, real part of eigenvalues  $\lambda_1$  and  $\lambda_{2,3}$  are negative, that is,

$$-\frac{a_1}{3} - \sqrt[3]{2b_1 + b_2} = -7.06668, \quad -\frac{a_1}{3} + \frac{b_1}{\sqrt[3]{4}} - \frac{b_2}{2} = -0.0398853$$

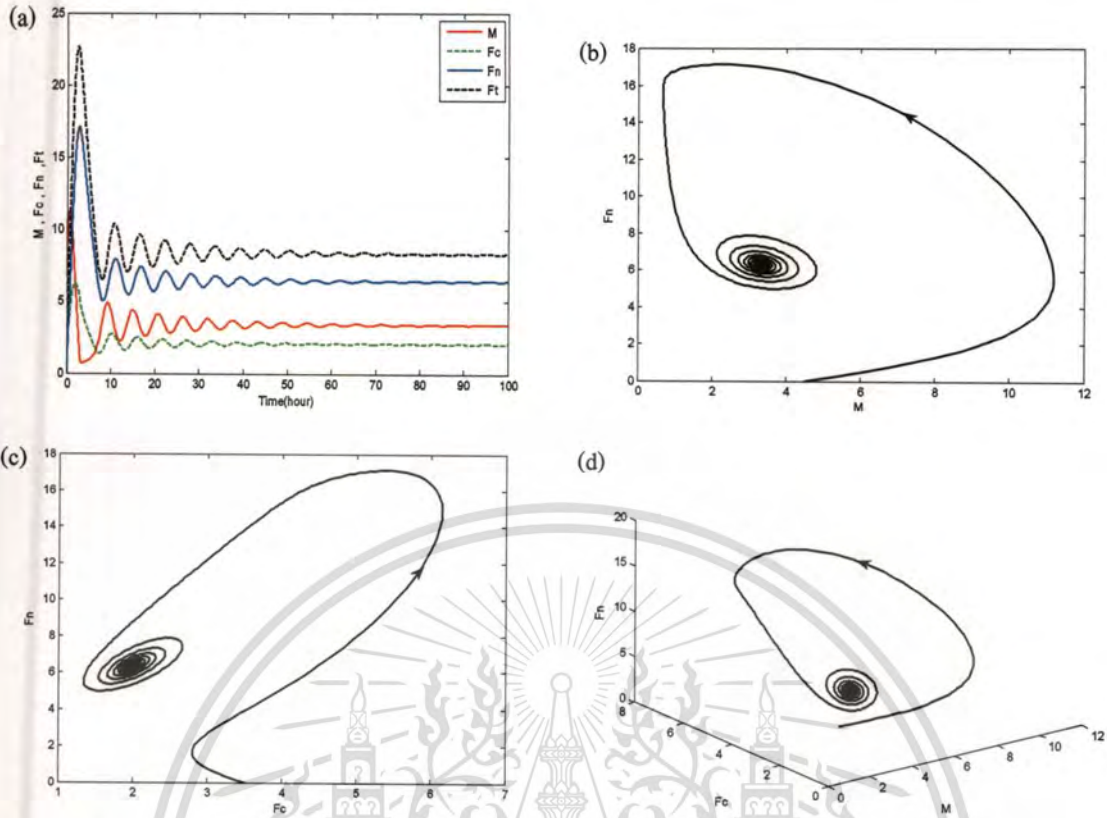
where  $b_1 = 2.25812$  and  $b_2 = -1.83948$ .



**Figure 4.4** (a) The oscillatory solution with respect to time, (b, c) phase plane of the model (2.4) projected on the  $(M, F_N)$  and  $(F_C, F_N)$  planes and (d) phase space trajectory in  $M - F_C - F_N$  space show that a limit cycle exists with parameters  $v_s = 4.0, v_m = 3.5, v_d = 3.0, k_s = 1.2, k_1 = 3.5, k_2 = 3.25, K_m = 0.01, K_l = 2.0, n = 1, L = 1$ .

In Figure 4.4, we plot the oscillatory solution with respect to time, phase plane, and phase space trajectory of the model (2.4) starting from initial point  $(M_0, F_{C_0}, F_{N_0}) = (3.5, 4.5, 0)$  with parameters chosen to satisfy the condition under which a limit cycle will occur. When time increases, the trajectory is tended toward to stable limit cycle at the steady state value  $E^* = (M^*, F_C^*, F_N^*) = (2.45657, 1.13125, 1.21827)$  as theoretically predicted.

In the case of  $L = 1$  lux with limit cycle parameters shown in Figure 4.4, the condition at critical value  $R = 6.86415$  is  $a_1 < R$  and eventually,  $\frac{dF}{da_1}|_{a_1=R} = -3.97632 \neq 0$  so the function  $F$  is decreasing at  $a_1 = R$ . Due to the fact that the equilibrium point  $E^*$  is locally asymptotically stable if  $a_1 > R$  then  $E^*$  loses its stability and the system undergoes a Hopf bifurcation at  $a_1 < R$  calculated from the theoretical value of  $R$ . Moreover, this bifurcation  $a_1$  under condition of  $L = 1$  lux is a supercritical Hopf bifurcation.



**Figure 4.5** (a) The stable solution with respect to time, (b, c) the phase plane projected on the  $(M, F_N)$  and  $(F_C, F_N)$  planes and (d) phase space trajectory in  $M - F_C - F_N$  space of the model (2.4) with stable state parameters  $v_s = 55.0, v_m = 410.0, v_d = 5.0, k_s = 1.5, k_1 = 3.5, k_2 = 1.1, K_m = 0.01, K_l = 1.2, K_d = 0.01, n = 1, L = 400$ .

In Figure 4.5, we plot the stable solution with respect to time, phase plane, and phase space trajectory of the model (2.4) starting from initial point  $(M_0, F_{C_0}, F_{N_0}) = (3.5, 4.5, 0)$  with stable state parameters described above. When time increases, the variables  $M, F_C$  and  $F_N$  approach to the steady state value  $E^* = (M^*, F_C^*, F_N^*) = (3.31666, 1.98873, 6.32777)$  as theoretically expected.

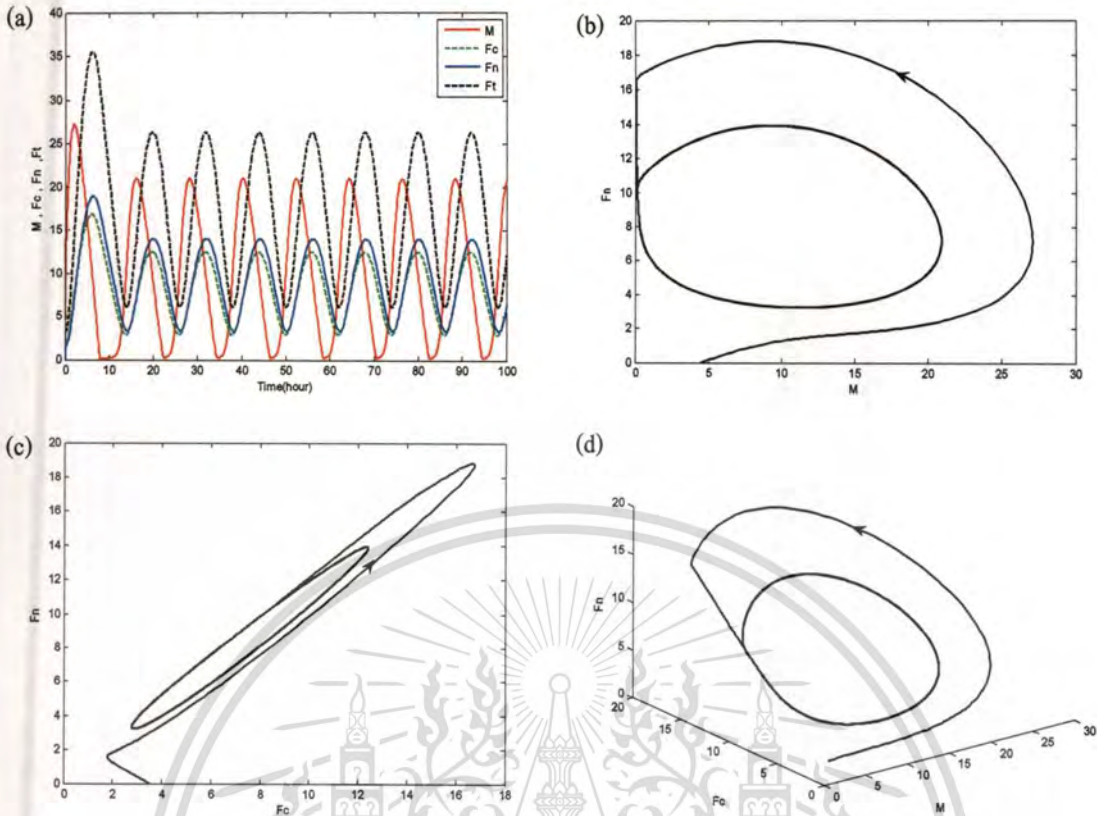
In the case of  $L = 400$  lux with stable parameters shown in Figure 4.5, the coefficients of characteristic equation are satisfied the Routh-Hurwitz criterion which are

$$a_1 = 4.983, a_3 = 6.11973, a_1 a_2 = 8.58384 > a_3.$$

Then, real part of eigenvalues  $\lambda_1$  and  $\lambda_{2,3}$  are negative, that is,

$$-\frac{a_1}{3} - \sqrt[3]{2b_1 + b_2} = -4.88676 =, -\frac{a_1}{3} + \frac{b_1}{\sqrt[3]{4}} - \frac{b_2}{2} = -0.0481215$$

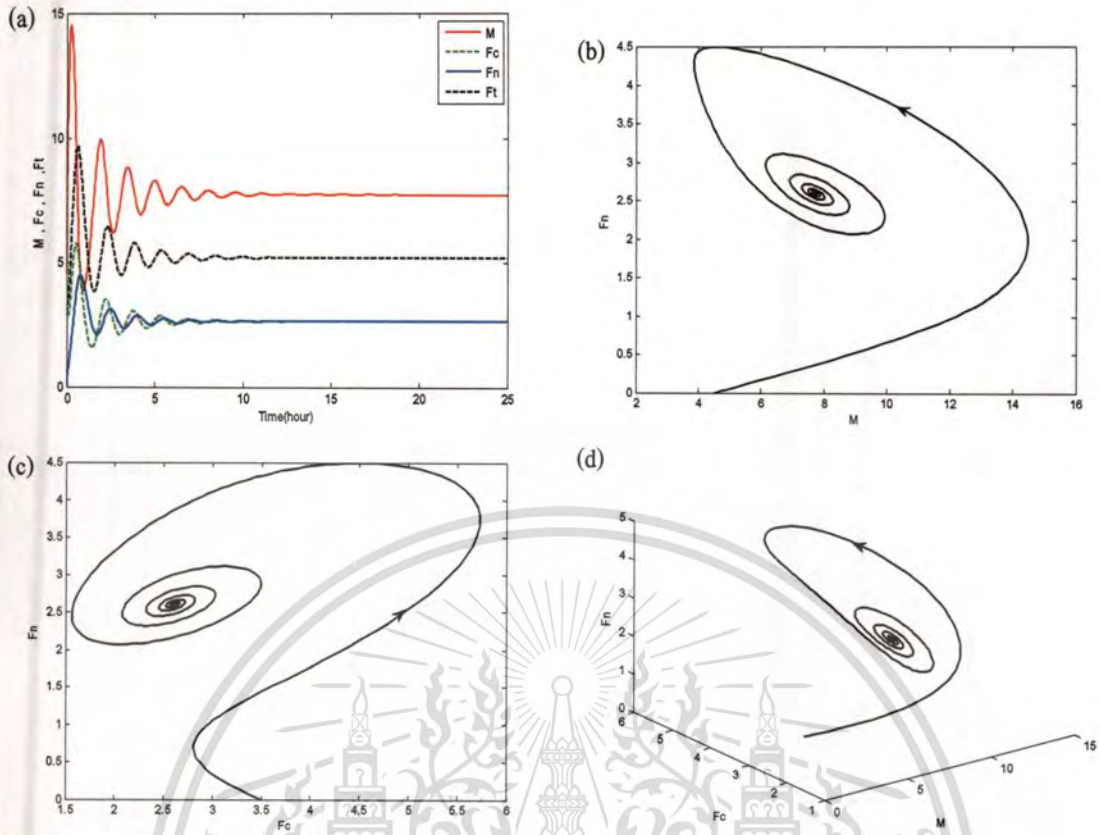
where  $b_1 = 1.79247$  and  $b_2 = -0.967383$ .



**Figure 4.6** (a) The oscillatory solution with respect to time, (b, c) phase plane of the model (2.4) projected on the  $(M, F_N)$  and  $(F_C, F_N)$  planes and (d) phase space trajectory in  $M - F_C - F_N$  space show that a limit cycle exists with parameters  $v_s = 55.0, v_m = 410.0, v_d = 5.0, k_s = 0.5, k_1 = 3.5, k_2 = 3.1, K_m = 0.001, K_l = 1.6, K_d = 0.004, n = 1, L = 400$ .

In Figure 4.6, we plot the oscillatory solution with respect to time, phase plane, and phase space trajectory of the model (2.4) starting from initial point  $(M_0, F_{C_0}, F_{N_0}) = (3.5, 4.5, 0)$  with parameters chosen to satisfy the condition under which a limit cycle will occur. When time increases, the trajectory is tended toward to stable limit cycle at the steady state value  $E^* = (M^*, F_C^*, F_N^*) = (9.99376, 6.40925, 7.23625)$  as theoretically predicted.

In the case of  $L = 400$  lux with limit cycle parameters shown in Figure 4.6, the condition at critical value  $R = 6.66514$  is  $a_1 < R$  and eventually,  $\frac{dF}{da_1}|_{a_1=R} = -3.78378 \neq 0$  so the function  $F$  is decreasing at  $a_1 = R$ . Due to the fact that the equilibrium point  $E^*$  is locally asymptotically stable if  $a_1 > R$  then  $E^*$  loses its stability and the system undergoes a Hopf bifurcation at  $a_1 < R$  calculated from the theoretical value of  $R$ . Moreover, this bifurcation  $a_1$  under condition of  $L = 400$  lux is a supercritical Hopf bifurcation.



**Figure 4.7** (a) The stable solution with respect to time, (b, c) the phase plane projected on the  $(M, F_N)$  and  $(F_C, F_N)$  planes and (d) phase space trajectory in  $M - F_C - F_N$  space of the model (2.4) with stable state parameters  $v_s = 250.0, v_m = 1200.0, v_d = 20.0, k_s = 2.5, k_1 = 3.0, k_2 = 3.0, K_l = 5.5, K_d = 0.1, n = 1, L = 1000$ .

In Figure 4.7, we plot the stable solution with respect to time, phase plane, and phase space trajectory of the model (2.4) starting from initial point  $(M_0, F_{C_0}, F_{N_0}) = (3.5, 4.5, 0)$  with stable state parameters described above. When time increases, the variables  $M, F_C$  and  $F_N$  approach to the steady state value  $E^* = (M^*, F_C^*, F_N^*) = (7.70431, 2.60555, 2.60555)$  as theoretically expected.

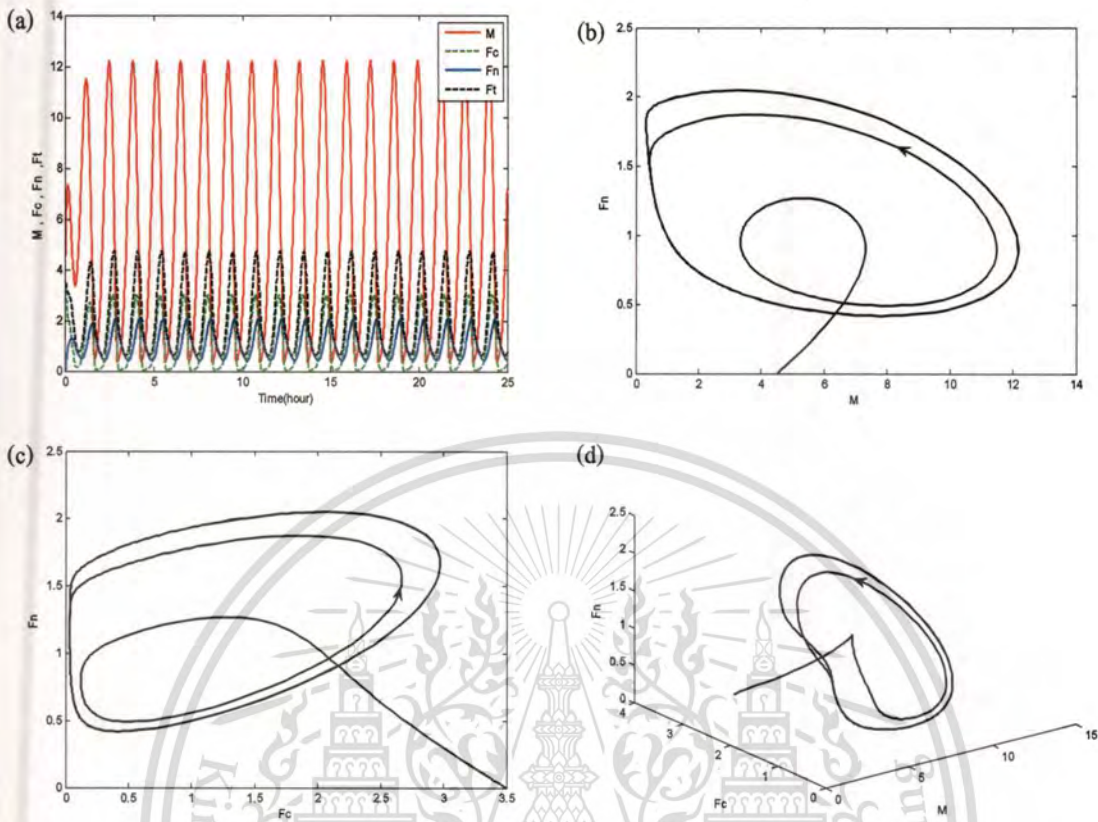
In the case of  $L = 1000$  lux with stable parameters shown in Figure 4.7, the coefficients of characteristic equation are satisfied the Routh-Hurwitz criterion which are

$$a_1 = 10.1146, a_3 = 160.112, a_1 a_2 = 252.027 > a_3.$$

Then, real part of eigenvalues  $\lambda_1$  and  $\lambda_{2,3}$  are negative, that is,

$$-\frac{a_1}{3} - \sqrt[3]{2b_1 + b_2} = -9.28785, \quad -\frac{a_1}{3} + \frac{b_1}{\sqrt[3]{4}} - \frac{b_2}{2} = -0.413357$$

where  $b_1 = 4.24106$  and  $b_2 = -0.572932$ .



**Figure 4.8** (a) The oscillatory solution with respect to time, (b, c) phase plane of the model (2.4) projected on the  $(M, F_N)$  and  $(F_C, F_N)$  planes and (d) phase space trajectory in  $M-F_C-F_N$  space show that a limit cycle exists with parameters  $v_s = 250.0, v_m = 1200.0, v_d = 20.0, k_s = 2.5, k_1 = 3.0, k_2 = 3.0, K_m = 0.01, K_l = 3.5, n = 1, L = 1000$ .

In Figure 4.8, we plot the oscillatory solution with respect to time, phase plane, and phase space trajectory of the model (2.4) starting from initial point  $(M_0, F_{C_0}, F_{N_0}) = (3.5, 4.5, 0)$  with parameters chosen to satisfy the condition under which a limit cycle will occur. When time increases, the trajectory is tended toward to stable limit cycle at the steady state value  $E^* = (M^*, F_C^*, F_N^*) = (7.20923, 0.911666, 0.911666)$  as theoretically predicted.

In the case of  $L = 1000$  lux with limit cycle parameters shown in Figure 4.15 and 4.16, the condition at critical value  $R = 11.6798$  is  $a_1 < R$  and eventually,  $\frac{dF}{da_1}|_{a_1=R} = -15.5944 \neq 0$  so the function  $F$  is decreasing at  $a_1 = R$ . Due to the fact that the equilibrium point  $E^*$  is locally asymptotically stable if  $a_1 > R$  then  $E^*$  loses its stability and the system undergoes a Hopf bifurcation at  $a_1 < R$  calculated from the theoretical value of  $R$ . Moreover, this bifurcation  $a_1$  under condition of  $L = 1000$  lux is a supercritical Hopf bifurcation.

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#### 4.2 Parameters and Numerical Solutions for the Model (2.3).

In this section, we find the proper parameters by using the same method described in previous section. Here are the results for all four different cases of illuminances.

1.  $L = 0.002$  lux

- In case of stable state, the parameters are  $v_s = 4.0, v_m = 1.0, v_d = 3.5, v_{dN} = 1.7, k_s = 1.1, k = 0.4, k_1 = 1.8, k_2 = 0.5, K_m = 0.02, K_l = 1.2, K_d = 1.5, K_{dN} = 0.25, n = 1, L = 0.002$  and the equilibrium point is (2.21446, 2.07536, 0.466399, 4.25979).

- In case of limit cycle, the parameters are  $v_s = 4.0, v_m = 1.0, v_d = 3.5, v_{dN} = 1.7, k_s = 1.1, k = 0.4, k_1 = 1.8, k_2 = 0.15, K_m = 0.02, K_l = 1.2, K_d = 0.5, K_{dN} = 0.25, n = 1, L = 0.002$  and the equilibrium point is (1.87908, 1.18915, 0.078639, 3.66091).

2.  $L = 1$  lux

- In case of stable state, the parameters are  $v_s = 4.0, v_m = 2.0, v_d = 4.0, v_{dN} = 2.2, k_s = 0.9, k = 0.6, k_1 = 1.7, k_2 = 0.25, K_m = 0.3, K_l = 0.8, K_d = 1.7, K_{dN} = 0.05, n = 1, L = 1$  and the equilibrium point is (3.5461, 1.71277, 0.58776, 2.99148).

- In case of limit cycle, the parameters are  $v_s = 4.0, v_m = 2.0, v_d = 4.0, v_{dN} = 2.2, k_s = 0.9, k = 0.5, k_1 = 1.5, k_2 = 0.01, K_m = 0.3, K_l = 0.8, K_d = 1.7, K_{dN} = 0.04, n = 1, L = 1$  and the equilibrium point is (3.22846, 1.46809, 0.382085, 3.05563).

3.  $L = 400$  lux

- In case of stable state, the parameters are  $v_s = 95.0, v_m = 470.0, v_d = 50.0, v_{dN} = 7.5, k_s = 5.0, k = 2.6, k_1 = 3.5, k_2 = 3.5, K_m = 0.05, K_l = 5.5, K_d = 3.0, K_{dN} = 0.5, n = 1, L = 400$  and the equilibrium point is (3.62004, 4.52551, 0.923242, 2.71582).

- In case of the limit cycle, the parameters are  $v_s = 95.0, v_m = 470.0,$

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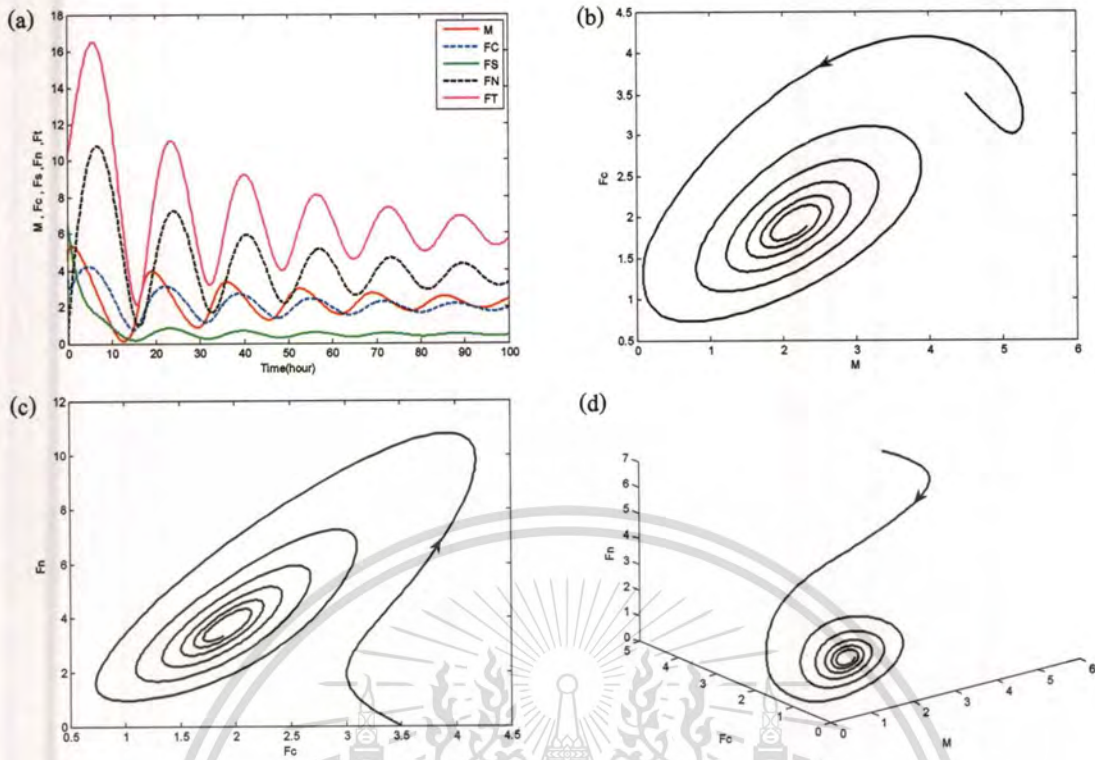
$v_d = 35.0, v_{dN} = 5.5, k_s = 5.0, k = 6.6, k_1 = 3.5, k_2 = 1.5, K_m = 0.01, K_l = 0.6,$   
 $K_d = 1.0, K_{dN} = 0.1, n = 1, L = 400$  and the equilibrium point is (2.36955,  
 1.20838, 0.295112, 0.237929).

4.  $L = 1000$  lux

- In case of stable state, the parameters are  $v_s = 250.0, v_m = 1200.0,$   
 $v_d = 150.0, v_{dN} = 8.5, k_s = 5.5, k = 3.5, k_1 = 5.0, k_2 = 2.0, K_m = 0.07, K_l = 0.7,$   
 $K_d = 1.0, K_{dN} = 0.05, n = 1, L = 1000$  and the equilibrium point is (2.96822,  
 2.30746, 0.056904, 1.64408).

- In case of the limit cycle, the parameters are  $v_s = 250.0,$   
 $v_m = 1200.0, v_d = 150.0, v_{dN} = 6.5, k_s = 5.5, k = 8.5, k_1 = 5.0, k_2 = 2.0,$   
 $K_m = 0.04, K_l = 0.7, K_d = 1.0, K_{dN} = 0.05, n = 1, L = 1000$  and the equilibrium  
 point is (2.82542, 1.18887, 0.072236, 0.254987).

Next, we verify all parameters by using the same method described previous section and we also find all trajectories, phase plane and phase space in each state as follows. Moreover, we show that all parameters described above satisfy stable and limit cycle conditions mentioned in chapter 2.



**Figure 4.9** (a) The stable solution with respect to time, (b, c) the phase plane projected on the  $(M, F_C)$  and  $(F_C, F_N)$  planes and (d) phase space trajectory in  $M - F_C - F_N$  space of the model (2.3) with stable state parameters  $v_s = 4.0, v_m = 1.0, v_d = 3.5, v_{dN} = 1.7, k_s = 1.1, k = 0.4, k_1 = 1.8, k_2 = 0.5, K_m = 0.02, K_l = 1.2, K_d = 1.5, K_{dN} = 0.25, n = 1, L = 0.002$ .

In Figure 4.9, we plot the stable solution with respect to time, phase plane, and phase space trajectory of the model (2.3) starting from initial point  $(M_0, F_{C_0}, F_{S_0}, F_{N_0}) = (3.5, 4.5, 6.5, 0)$  with stable state parameters described above. When time increases, the variables  $M, F_C, F_S$  and  $F_N$  approach to the steady state value  $E^* = (M^*, F_C^*, F_S^*, F_N^*) = (2.21446, 2.07536, 0.466399, 4.25979)$  as theoretically expected.

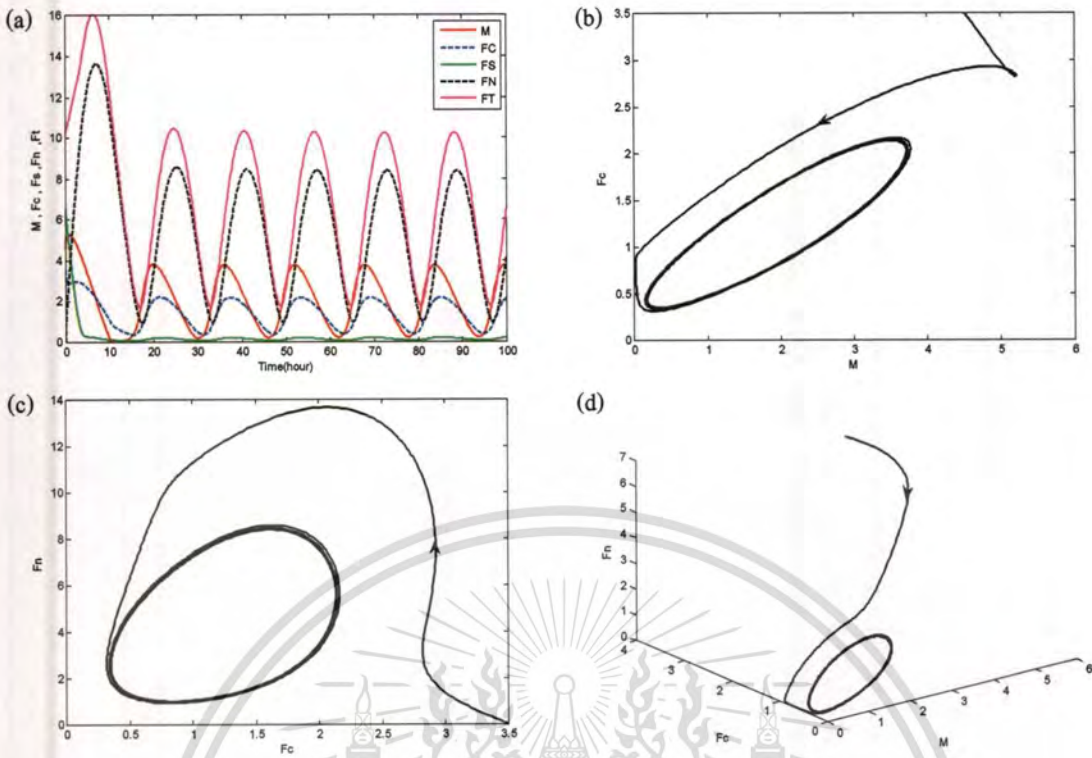
In the case of  $L = 0.002$  lux with stable parameters shown in Figure 4.9, the coefficients of characteristic equation are satisfied the Routh-Hurwitz criterion which are

$$c_1 = 4.04085, c_3 = 0.582997, c_4 = 0.222198, c_1 c_2 c_3 = 8.97023 > c_3^2 + c_1^2 c_4 = 3.96804.$$

Then, real part of eigenvalues  $\lambda_1, \lambda_2$  and  $\lambda_{3,4}$  are negative, that is,

$$-C'v_d = -1.35774, -\frac{a_1}{3} - \sqrt[3]{2b_1 + b_2} = -2.67178, -\frac{a_1}{3} + \frac{b_1}{\sqrt[3]{4}} - \frac{b_2}{2} = -0.00566673,$$

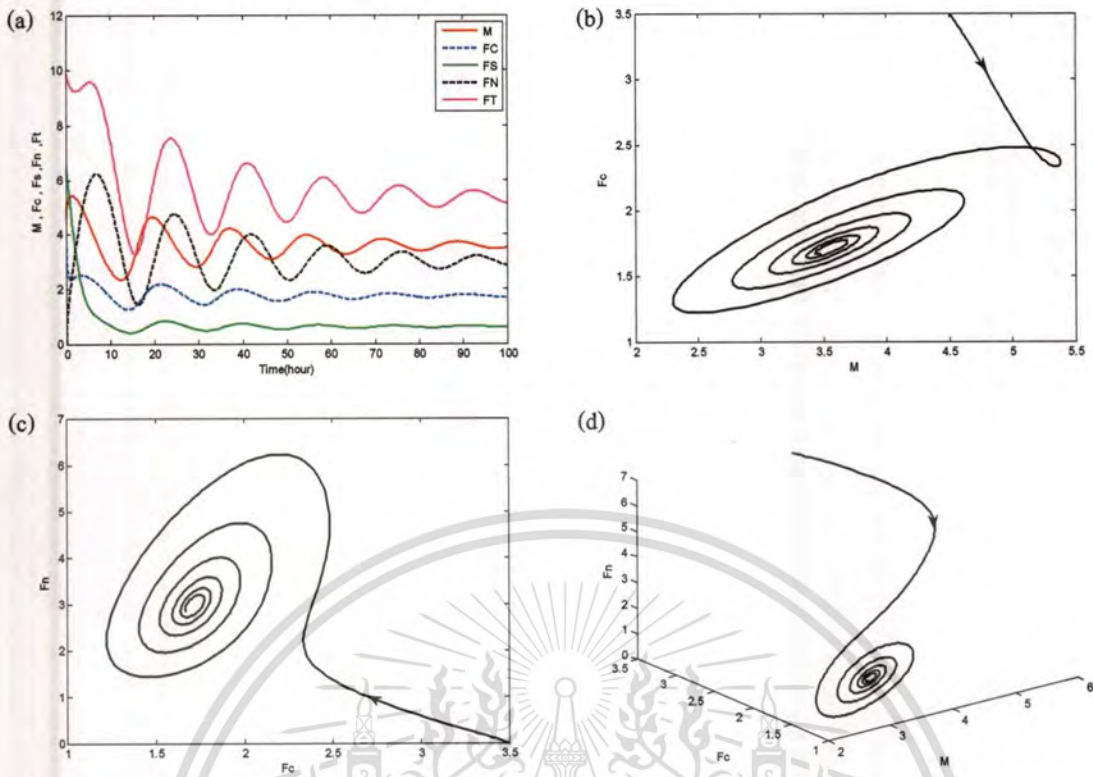
where  $a_1 = 2.68311, a_2 = 0.164759, a_3 = 0.359297, b_1 = 0.873388$  and  $b_2 = -0.677006$ .



**Figure 4.10** (a) The oscillatory solution with respect to time, (b, c) phase plane of the model (2.3) projected on the  $(M, F_C)$  and  $(F_C, F_N)$  planes and (d) phase space trajectory in  $M - F_C - F_N$  space show that a limit cycle exists with parameters  $v_s = 4.0, v_m = 1.0, v_d = 3.5, v_{dN} = 1.7, k_s = 1.1, k = 0.4, k_1 = 1.8, k_2 = 0.15, K_m = 0.02, K_I = 1.2, K_d = 0.5, K_{dN} = 0.25, n = 1, L = 0.002$ .

In Figure 4.10, we plot the oscillatory solution with respect to time, phase plane, and phase space trajectory of the model (2.3) starting from initial point  $(M_0, F_{C_0}, F_{S_0}, F_{N_0}) = (3.5, 4.5, 6.5, 0)$  with parameters chosen to satisfy the condition under which a limit cycle will occur. When time increases, the trajectory is tended toward to stable limit cycle at the steady state value  $E^* = (M^*, F_C^*, F_S^*, F_N^*) = (1.87908, 1.18915, 0.078639, 3.66091)$  as theoretically predicted.

In the case of  $L = 0.002$  lux with limit cycle parameters shown in Figure 4.10, the condition at critical value  $R = 2.42575$  is  $a_1 < R$  and eventually,  $\frac{dF}{da_1}|_{a_1=R} = -4.09654 \neq 0$  so the function  $F$  is decreasing at  $a_1 = R$ . Due to the fact that the equilibrium point  $E^*$  is locally asymptotically stable if  $a_1 > R$  then  $E^*$  loses its stability and the system undergoes a Hopf bifurcation at  $a_1 < R$  calculated from the theoretical value of  $R$ . Moreover, this bifurcation  $a_1$  under condition of  $L = 0.002$  lux is a supercritical Hopf bifurcation.



**Figure 4.11** (a) The stable solution with respect to time, (b, c) the phase plane projected on the  $(M, F_C)$  and  $(F_C, F_N)$  planes and (d) phase space trajectory in  $M - F_C - F_N$  space of the model (2.3) with stable state parameters  $v_s = 4.0, v_m = 2.0, v_d = 4.0, v_{dN} = 2.2, k_s = 0.9, k = 0.6, k_1 = 1.7, k_2 = 0.25, K_m = 0.3, K_l = 0.8, K_d = 1.7, K_{dN} = 0.05, n = 1, L = 1$ .

In Figure 4.11, we plot the stable solution with respect to time, phase plane, and phase space trajectory of the model (2.3) starting from initial point  $[M_0, F_{C_0}, F_{S_0}, F_{N_0}] = (3.5, 4.5, 6.5, 0)$  with stable state parameters described above. When time increases, the variables  $M, F_C, F_S$  and  $F_N$  approach to the steady state value  $E^* = (M^*, F_C^*, F_S^*, F_N^*) = (3.5461, 1.71277, 0.58776, 2.99148)$  as theoretically expected.

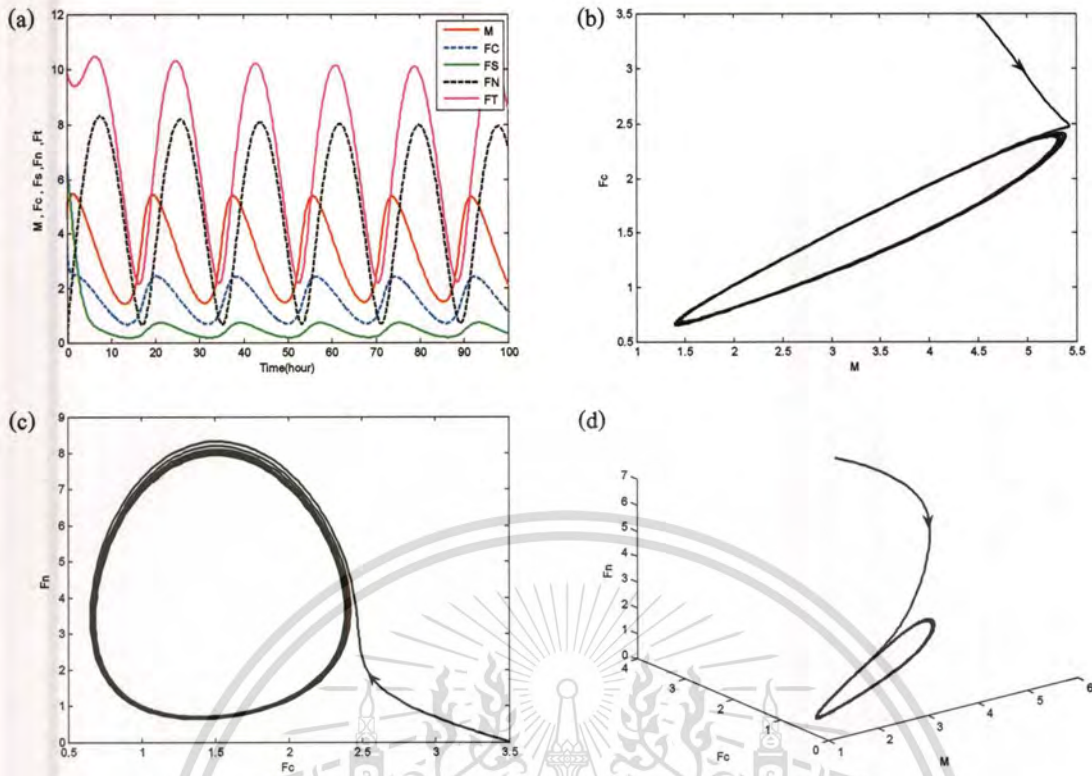
In the case of  $L = 1$  lux with stable parameters shown in Figure 4.11, the coefficients of characteristic equation are satisfied the Routh-Hurwitz criterion which are

$$c_1 = 3.87791, c_3 = 0.638665, c_4 = 0.12938, c_1 c_2 c_3 = 8.85637 > c_3^2 + c_1^2 c_4 = 2.35353.$$

Then, real part of eigenvalues  $\lambda_1, \lambda_2$  and  $\lambda_{3,4}$  are negative, that is,

$$-C' v_d = -1.29924, -\frac{a_1}{3} - \sqrt[3]{2b_1 + b_2} = -2.54339, -\frac{a_1}{3} + \frac{b_1}{\sqrt[3]{4}} - \frac{b_2}{2} = -0.0176405,$$

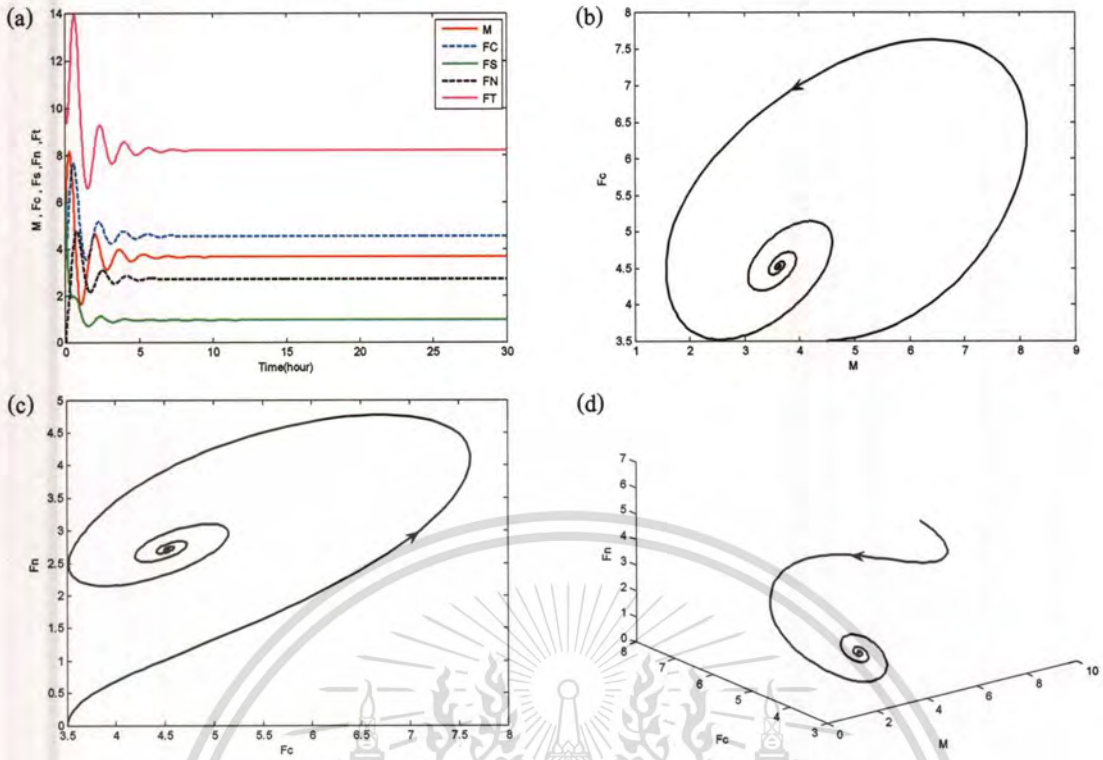
where  $a_1 = 2.57867, a_2 = 0.225599, a_3 = 0.345559, b_1 = 0.836944$  and  $b_2 = -0.629349$ .



**Figure 4.12** (a) The oscillatory solution with respect to time, (b, c) phase plane of the model (2.3) projected on the  $(M, F_C)$  and  $(F_C, F_N)$  planes and (d) phase space trajectory in  $M - F_C - F_N$  space show that a limit cycle exists with parameters  $v_s = 4.0, v_m = 2.0, v_d = 4.0, v_{dN} = 2.2, k_s = 0.9, k = 0.5, k_1 = 1.5, k_2 = 0.01, K_m = 0.3, K_I = 0.8, K_d = 1.7, K_{dN} = 0.04, n = 1, L = 1$ .

In Figure 4.12, we plot the oscillatory solution with respect to time, phase plane, and phase space trajectory of the model (2.3) starting from initial point  $(M_0, F_{C_0}, F_{S_0}, F_{N_0}) = (3.5, 4.5, 6.5, 0)$  with parameters chosen to satisfy the condition under which a limit cycle will occur. When time increases, the trajectory is tended toward to stable limit cycle at the steady state value  $E^* = (M^*, F_C^*, F_S^*, F_N^*) = (3.22846, 1.46809, 0.382085, 3.05563)$  as theoretically predicted.

In the case of  $L = 1$  lux with limit cycle parameters shown in Figure 4.12, the condition at critical value  $R = 2.0899$  is  $a_1 < R$  and eventually,  $\frac{dF}{da_1}|_{a_1=R} = -4.14026 \neq 0$  so the function  $F$  is decreasing at  $a_1 = R$ . Due to the fact that the equilibrium point  $E^*$  is locally asymptotically stable if  $a_1 > R$  then  $E^*$  loses its stability and the system undergoes a Hopf bifurcation at  $a_1 < R$  calculated from the theoretical value of  $R$ . Moreover, this bifurcation  $a_1$  under condition of  $L = 1$  lux is a supercritical Hopf bifurcation.



**Figure 4.13** (a) The stable solution with respect to time, (b, c) the phase plane projected on the  $(M, F_C)$  and  $(F_C, F_N)$  planes and (d) phase space trajectory in  $M - F_C - F_N$  space of the model (2.3) with stable state parameters  $v_s = 95.0, v_m = 470.0, v_d = 50.0, v_{dN} = 7.5, k_s = 5.0, k = 2.6, k_1 = 3.5, k_2 = 3.5, K_m = 0.05, K_l = 5.5, K_d = 3.0, K_{dN} = 0.5, n = 1, L = 400$ .

In Figure 4.13, we plot the stable solution with respect to time, phase plane, and phase space trajectory of the model (2.3) starting from initial point  $(M_0, F_{C_0}, F_{S_0}, F_{N_0}) = (3.5, 4.5, 6.5, 0)$  with stable state parameters described above. When time increases, the variables  $M, F_C, F_S$  and  $F_N$  approach to the steady state value  $E^* = (M^*, F_C^*, F_S^*, F_N^*) = (3.62004, 4.52551, 0.923242, 2.71582)$  as theoretically expected.

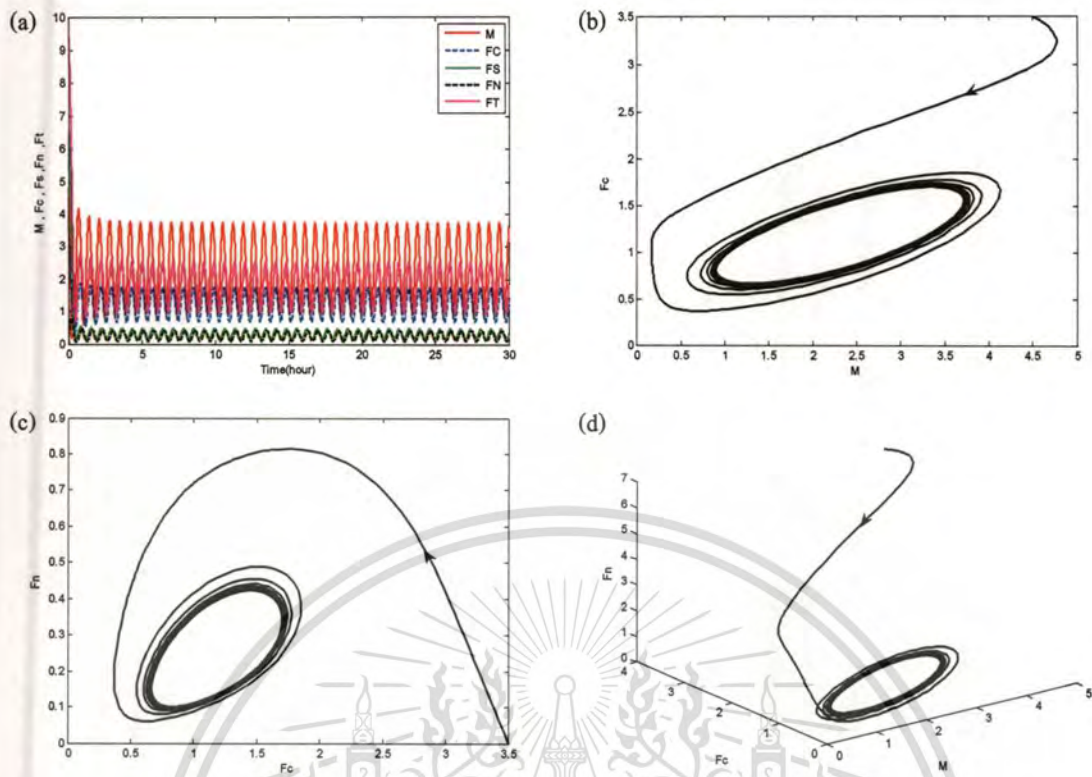
In the case of  $L = 400$  lux with stable parameters shown in Figure 4.13, the coefficients of characteristic equation are satisfied the Routh-Hurwitz criterion which are

$$c_1 = 18.7275, c_3 = 226.639, c_4 = 438.916, c_1 c_2 c_3 = 432291 > c_3^2 + c_1^2 c_4 = 205302.$$

Then, real part of eigenvalues  $\lambda_1, \lambda_2$  and  $\lambda_{3,4}$  are negative, that is,

$$-C' v_d = -9.74543, -\frac{a_1}{3} - \sqrt[3]{2} b_1 + b_2 = -8.50361, -\frac{a_1}{3} + \frac{b_1}{\sqrt[3]{4}} - \frac{b_2}{2} = -0.239245,$$

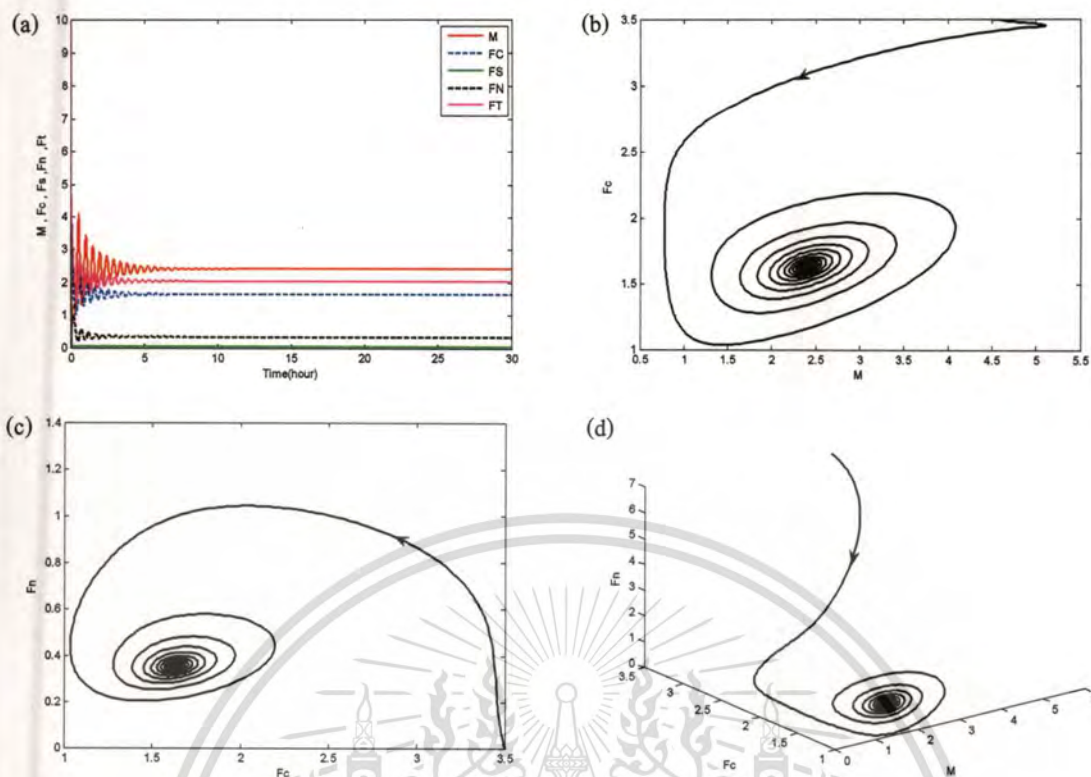
where  $a_1 = 8.98211, a_2 = 14.3153, a_3 = 87.1311, b_1 = 3.64921$  and  $b_2 = -0.911864$ .



**Figure 4.14** (a) The oscillatory solution with respect to time, (b, c) phase plane of the model (2.3) projected on the  $(M, F_C)$  and  $(F_C, F_N)$  planes and (d) phase space trajectory in  $M - F_C - F_N$  space show that a limit cycle exists with parameters  $v_s = 95.0, v_m = 470.0, v_d = 35.0, v_{dN} = 5.5, k_s = 5.0, k = 6.6, k_1 = 3.5, k_2 = 1.5, K_m = 0.01, K_l = 0.6, K_d = 1.0, K_{dN} = 0.1, n = 1, L = 400$ .

In Figure 4.14, we plot the oscillatory solution with respect to time, phase plane, and phase space trajectory of the model (2.3) starting from initial point  $(M_0, F_{C_0}, F_{S_0}, F_{N_0}) = (3.5, 4.5, 6.5, 0)$  with parameters chosen to satisfy the condition under which a limit cycle will occur. When time increases, the trajectory is tended toward to stable limit cycle at the steady state value  $E^* = (M^*, F_C^*, F_S^*, F_N^*) = (2.36955, 1.20838, 0.295112, 0.237929)$  as theoretically predicted.

In the case of  $L = 400$  lux with limit cycle parameters shown in Figure 4.14, the condition at critical value  $R = 19.4667$  is  $a_1 < R$  and eventually,  $\frac{dF}{da_1}|_{a_1=R} = -6.74102 \neq 0$  so the function  $F$  is decreasing at  $a_1 = R$ . Due to the fact that the equilibrium point  $E^*$  is locally asymptotically stable if  $a_1 > R$  then  $E^*$  loses its stability and the system undergoes a Hopf bifurcation at  $a_1 < R$  calculated from the theoretical value of  $R$ . Moreover, this bifurcation  $a_1$  under condition of  $L = 400$  lux is a supercritical Hopf bifurcation.



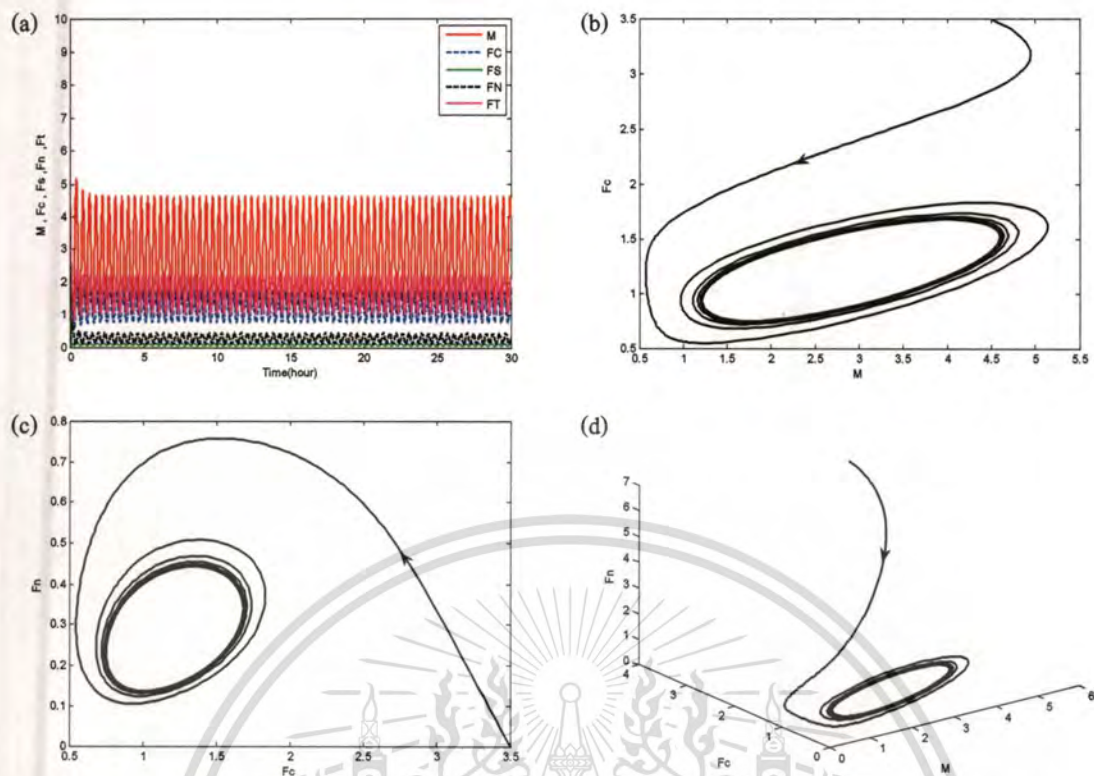
**Figure 4.15** (a) The stable solution with respect to time, (b, c) the phase plane projected on the  $(M, F_C)$  and  $(F_C, F_N)$  planes and (d) phase space trajectory in  $M - F_C - F_N$  space of the model (2.3) with stable state parameters  $v_s = 250.0, v_m = 1200.0, v_d = 150.0, v_{dN} = 8.5, k_s = 5.5, k = 3.5, k_1 = 5.0, k_2 = 2.0, K_m = 0.07, K_l = 0.7, K_d = 1.0, K_{dN} = 0.05, n = 1, L = 1000$ .

In Figure 4.15, we plot the stable solution with respect to time, phase plane, and phase space trajectory of the model (2.3) starting from initial point  $(M_0, F_{C_0}, F_{S_0}, F_{N_0}) = (3.5, 4.5, 6.5, 0)$  with stable state parameters described above. When time increases, the variables  $M, F_C, F_S$  and  $F_N$  approach to the steady state value  $E^* = (M^*, F_C^*, F_S^*, F_N^*) = (2.96822, 2.30746, 0.056904, 1.64408)$  as theoretically expected.

In the case of  $L = 1000$  lux with stable parameters shown in Figure 4.29 and 4.30, the coefficients of characteristic equation are satisfied the Routh-Hurwitz criterion which are  $c_1 = 152.976, c_3 = 13290.3, c_4 = 49198.5, c_1 c_2 c_3 = 5.29576 \times 10^9 > c_3^2 + c_1^2 c_4 = 1.32796 \times 10^9$ . Then, real part of eigenvalues  $\lambda_1, \lambda_2$  and  $\lambda_{3,4}$  are negative, that is,

$$-C'v_d = -134.283, \quad -\frac{a_1}{3} - \sqrt[3]{2}b_1 + b_2 = -16.5048, \quad -\frac{a_1}{3} + \frac{b_1}{\sqrt[3]{4}} - \frac{b_2}{2} = -1.09439,$$

where  $a_1 = 18.6936, a_2 = 92.0932, a_3 = 923.735, b_1 = 7.46839$  and  $b_2 = -0.864006$ .



**Figure 4.16** (a) The oscillatory solution with respect to time, (b, c) phase plane of the model (2.3) projected on the  $(M, F_C)$  and  $(F_C, F_N)$  planes and (d) phase space trajectory in  $M - F_C - F_N$  space show that a limit cycle exists with parameters  $v_s = 250.0, v_m = 1200.0, v_d = 150.0, v_{dN} = 6.5, k_s = 5.5, k = 8.5, k_1 = 5.0, k_2 = 2.0, K_m = 0.04, K_l = 0.7, K_d = 1.0, K_{dN} = 0.05, n = 1, L = 1000$ .

In Figure 4.16, we plot the oscillatory solution with respect to time, phase plane, and phase space trajectory of the model (2.3) starting from initial point  $(M_0, F_{C_0}, F_{S_0}, F_{N_0}) = (3.5, 4.5, 6.5, 0)$  with parameters chosen to satisfy the condition under which a limit cycle will occur. When time increases, the trajectory is tended toward to stable limit cycle at the steady state value  $E^* = (M^*, F_C^*, F_S^*, F_N^*) = (2.82542, 1.18887, 0.072236, 0.254987)$  as theoretically predicted.

In the case of  $L = 1000$  lux with limit cycle parameters shown in Figure 4.16, the condition at critical value  $R = 28.0237$  is  $a_1 < R$  and eventually,  $\frac{dF}{da_1} \Big|_{a_1=R} = -18.761 \neq 0$  so the function  $F$  is decreasing at  $a_1 = R$ . Due to the fact that the equilibrium point  $E^*$  is locally asymptotically stable if  $a_1 > R$  then  $E^*$  loses its stability and the system undergoes a Hopf bifurcation at  $a_1 < R$  calculated from the theoretical value of  $R$ . Moreover, this bifurcation  $a_1$  under condition of  $L = 1000$  lux is a supercritical Hopf bifurcation.

## Chapter 5

### Discussion and Conclusion

#### 5.1 Discussion and Conclusion

The mathematical models used in this thesis are systems of nonlinear differential equations, model (2.3) and (2.4), including concentration of *frq* mRNA ( $M$ ), cytosol FRQ ( $F_C$ ), stable FRQ ( $F_S$ ) and nuclear FRQ ( $F_N$ ). In the first model (2.4), we do not consider the existence of stable FRQ protein. On the other hand, we also investigate the existence of stable FRQ protein in the second model. We have analyzed the stability properties of both models by two methods. In the first method, we have used an analytical method in which we linearized the nonlinear equations. In the second method, we used a mathematical program called Matlab to compute numerical solutions for both models in order to investigate the behaviors of the model with four different illuminations.

First, we consider the first model (2.4). In case of stable state, we analyzed the model that has a positive equilibrium,  $E^* = (M^*, F_C^*, F_N^*)$ . We linearized the equations about this equilibrium point and used a mathematical package of Mathematica to find the coefficients  $a_1, a_2$  and  $a_3$  of the cubic characteristic equations of the linearized equations. We then used the Routh-Hurwitz criterion to find the range of parameters of these coefficients that correspond to asymptotically stable of the equilibrium point. Eventually, we also investigate the first eigenvalue ( $\lambda_1$ ) and the real part of the second and third eigenvalues ( $\lambda_{2,3}$ ). If  $\lambda_1 < 0$  and  $Re(\lambda_{2,3}) < 0$ , then the equilibrium point  $E^*$  will be asymptotically stable. Additionally, if  $\lambda_1 > 0$  and  $Re(\lambda_{2,3}) > 0$ , then the equilibrium point will be unstable. Moreover, we find that the stable parameters with four different illuminances satisfy all conditions of stable state described section 4.

In the case of existence of limit cycle, we use the same method described above. By considering the eigenvalues  $\lambda_{2,3}$ , we define  $a_1$  as the bifurcation parameter and the critical value  $R$  by which at  $a_1 = R$  the real part of  $\lambda_{2,3}$  is equal to zero. Consequently, we find the parameters that satisfy  $\frac{dF}{da_1} \Big|_{a_1=R} \neq 0$  which we found that  $\frac{dF}{da_1} \Big|_{a_1=R} < 0$  for all of illuminations. Eventually, the condition at the critical value  $R$  is  $a_1 < R$ . Due to the fact that  $a_1 > R$  the equilibrium point will be asymptotically stable such that the bifurcation parameter  $a_1$  is a supercritical Hopf bifurcation with all illuminances.

Finally, we consider the second model (2.3). In the case of stable state, we analyze the model that has a positive equilibrium  $E^* = (M^*, F_C^*, F_S^*, F_N^*)$ . We linearized the equations about this

equilibrium point and used the Mathematica program to find coefficients  $c_1, c_2, c_3$  and  $c_4$  in the fourth-order characteristic equations of the linearized equations. We then used the Routh-Hurwitz criterion to find the range of parameters of these coefficients that correspond to asymptotically stable of the equilibrium point. Next, we factorize the characteristic equation then we have the first eigenvalue and the cubic equations where  $a_1, a_2$  and  $a_3$  are coefficients. Eventually, we also investigate the first eigenvalue ( $\lambda_1$ ), the second eigenvalue ( $\lambda_2$ ) and the real part of the third and fourth eigenvalues ( $\lambda_{3,4}$ ). If  $\lambda_1 < 0, \lambda_2 < 0$  and  $Re(\lambda_{2,3}) < 0$ , then the equilibrium point  $E^*$  will be asymptotically stable. Conversely, if  $\lambda_1 > 0, \lambda_2 > 0$  and  $Re(\lambda_{3,4}) > 0$ , then the equilibrium point will be unstable. Moreover, we found that the stable parameters with four different illuminances satisfy all conditions of stable state described section 4.

In the case of existence of limit cycle, we did the same method described above. By considering the eigenvalues  $\lambda_{3,4}$ , we also define  $a_1$  as the bifurcation parameter and the critical value  $R$  by which at  $a_1 = R$  the real part of  $\lambda_{3,4}$  is equal to zero. Consequently, we find the parameters that satisfy  $\frac{dF}{da_1} \Big|_{a_1=R} \neq 0$  which we found that  $\frac{dF}{da_1} \Big|_{a_1=R} < 0$  for all of illuminations. Eventually, the condition at the critical value  $R$  is  $a_1 < R$ . Due to the fact that  $a_1 > R$  the equilibrium point will be asymptotically stable such that the bifurcation parameter  $a_1$  is a supercritical Hopf bifurcation with all of illuminances.

Then, we used Matlab program to find numerical method by using the Runge Kutta method of the system of nonlinear differential equation. We also plot the time series of *frq* mRNA ( $M$ ), cytosol FRQ ( $F_C$ ), stable FRQ ( $F_S$ ) and nuclear FRQ ( $F_N$ ), the phase plane and phase space. Furthermore, we conclude that light is the incentive of the transcription of *frq* mRNA. When illuminances increases, the frequency of four variables,  $M, F_C, F_S$  and  $F_N$ , will be increased and the period of them will be decreased. This corresponds to the behavior of *Neurospora* with high illuminances inducing the transcription of *frq*. We have found that the equilibrium point is asymptotically stable when  $a_1 > R$  which conform to the theoretical results. For  $a_1 < R$ , the numerical solutions show that oscillations occurs in *frq* mRNA ( $M$ ), cytosol FRQ ( $F_C$ ), stable FRQ ( $F_S$ ) and nuclear FRQ ( $F_N$ ) and also show a limit cycle in the phase plane and phase space.

## 5.2 Suggestions for Further Study

In the analysis of the model in this thesis, we make an assumption by assuming the Hill coefficient  $n$  is equal to 1 in order to make it simple to find analytical equilibrium point in terms of parameters. In general, if we do not assume  $n = 1$ , it should be realistic and complicated. For those

who would like to extend these results, we suggest that the modified mathematical model with delay would be better. In addition, in a real *Neurospora*'s life, if other factors are included, the model will be a system of partial differential equations, the analysis of which would become more complicated.



## References

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**APPENDIX A.****THE RESEARCH PAPER**

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# Analysis of Effective Neurospora Process Model

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## Abstract

Neurospora process model is based on the negative feedback auto regulation of gene expression. This research is concerned with the modified mathematical model for Neurospora process which considers the effects of light. The differential equation model is analyzed in terms of the stability of the equilibrium solution, and the existence of limit cycles. The Routh-Hurwitz criterion and the Hopf bifurcation theory are used to find the conditions on the model parameters under which different dynamic behavior may be assured. Moreover, numerical simulations have been carried out to confirm our theoretical predictions.

*Keywords:* neurospora process, circadian rhythm, stability, limit cycle, Routh-Hurwitz criterion, Hopf bifurcation.

## 1 Introduction

Some bacteria have the ability to adapt themselves to their environment which result of this changing is the circadian rhythm. This rhythm is depended on the period of light and dark[5]. During the last decade, many research have been made on the molecular mechanism of circadian rhythm, especially in Neurospora[3,7].

Mathematical model has been used to simply explain the biological system[9,16]. Goodwin made the first model which its result was come from negative feedback on gene expression[10]. Later, this model was used to examine properties of circadian rhythm as well as efficiency of light[6].

In 2000, D.Gonze, J.Leloup and A.Goldbeter have formulated the mathematical model for circadian rhythm in Neurospora. They considered in the transcription of FRQ protein which it negatively regulates the expression of the frq gene[9].

In 2010, K.Kumnungkit, N.Wongvisetsirikul and S.Suwannaut have modified the mathematical model for Neurospora under the condition that considered the stable FRQ protein which specific effects on light and the FRQ protein. They also find equilibrium points and used the Routh-Hurwitz criterion to confirm the stability and limit cycle state.

In this paper, we modified the mathematical model for Neurospora under the condition that not considered the stable FRQ protein which specific effects on light. We also used the Routh-Hurwitz criterion and the Hopf bifurcation theory to confirm the stability and limit cycle state.

## 2 Model formulation

Because of the negative autoregulation of gene expression, the circadian rhythm of Neurospora can happen. The FRQ protein enters the nucleus where it represses the transcription of its gene frq[1,3]. Conversely, light control the circadian system by inducing the transcription of frq[4]. From the scheme, we obtain

- If there is no light, then the cytosol FRQ protein ( $F_C$ ) will enter to the nucleus. Subsequently, the Nuclear FRQ proteins ( $F_N$ ) will repress the transcription of frq gene. Moreover, the nuclear FRQ will react to the base sequence of frq DNA. Because of this reason, the process will not go on.

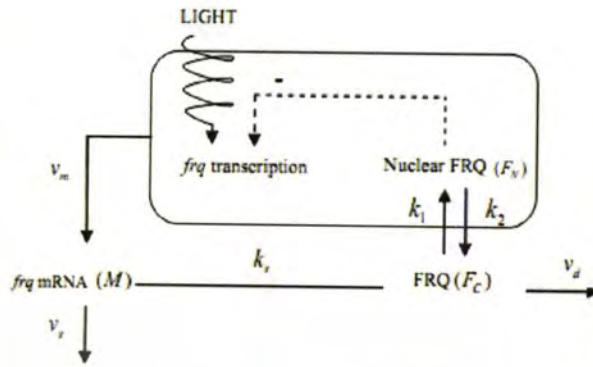


Figure 1: Scheme of the model for circadian rhythm on Neurospora

- If there is light, then the transcription of *frq* gene will continue. The result of this process is *frq* mRNA ( $M$ ) which is material of the FRQ protein synthesis. Besides, light is the incentive of this process which it will react to the nuclear FRQ.

From this process, we can formulate to be three differential equations below

$$\frac{dM}{dt} = v_s \frac{K_I^n}{K_I^n + F_N^n} - v_m \frac{M}{K_m + M} + L \quad (1)$$

The three variables  $M$ ,  $F_C$  and  $F_N$  denote the concentrations of the *frq* mRNA and the cytosolic and nuclear forms of FRQ respectively. The total concentration of FRQ protein is equal to  $F_t = F_C + F_N$  which is denoted  $F_t$ . In the first equation  $v_s$  denotes the rate of *frq* transcription and the constant  $K_I$  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 *kw*.

$$\frac{dF_C}{dt} = k_s M - v_d \frac{F_C}{K_d + F_C} - k_1 F_C + k_2 F_N \quad (2)$$

In the second equation, the constant  $k_s$  is the rate of FRQ protein synthesis, the constant  $v_d$  is the maximum rate of cytosolic FRQ degradation.

$$\frac{dF_N}{dt} = k_1 F_C - k_2 F_N \quad (3)$$

In the third equation, the constant  $k_1$  and  $k_2$  denoted the transport of FRQ protein into and out of the nucleus of Neurospora.

We define these functions to find the equilibrium points

$$\frac{dM}{dt} = g_1(M, F_C, F_N) = 0 \quad (4)$$

$$\frac{dF_C}{dt} = g_2(M, F_C, F_N) = 0 \quad (5)$$

$$\frac{dF_N}{dt} = g_3(M, F_C, F_N) = 0 \quad (6)$$

Let  $E^* = (M_0, F_{C_0}, F_{N_0})$  is the equilibrium point. So we obtain

$$v_s \frac{K_I^n}{K_I^n + F_N^n} - v_m \frac{M}{K_m + M} + L = 0 \quad (7)$$

$$k_s M - v_d \frac{F_C}{K_d + F_C} - k_1 F_C + k_2 F_N = 0 \quad (8)$$

$$k_1 F_C - k_2 F_N = 0 \quad (9)$$

Then, we consider Eq.(7) and let  $n = 1$  we get

$$v_s \frac{K_l}{K_l + F_N} - v_m \frac{M}{K_m + M} + L = 0$$

Hence

$$M_0 = -\frac{-F_{N_0} K_m L - k_1 K_m L - K_l K_m v_s}{F_{N_0} L + K_l L - F_{N_0} v_m - K_l v_m + K_l v_s} \quad (10)$$

Next, we consider Eq.(8)

$$k_s M - v_d \frac{F_C}{K_d + F_C} - k_1 F_C + k_2 F_N = 0$$

So

$$F_{N_0} = \frac{F_{C_0} k_1 + F_{C_0} k_1 K_d - F_{C_0} k_s M_0 - K_d k_s M_0 + F_{C_0} v_d}{k_2 (F_{C_0} + K_d)} \quad (11)$$

We consider Eq. (9) So that

$$\begin{aligned} k_1 F_C - k_2 F_N &= 0 \\ F_{C_0} &= \frac{F_{N_0} k_2}{k_1} \end{aligned} \quad (12)$$

And then we substitute Eq.(12) to Eq.(11), that is

$$M_0 = \frac{F_{N_0} k_2 v_d}{F_{N_0} k_2 k_s + k_1 K_d k_s} \quad (13)$$

From Eq.(10) and (13), we get

$$F_{N_0} = -\frac{1}{2k_2 (K_m k_s L + v_d(L - v_m))} \frac{(k_1 K_d K_m k_s L + k_2 K_l K_m k_s L + k_2 K_l L v_d - k_2 K_l v_d v_m + k_2 K_l K_m k_s v_s + k_2 K_l v_d v_s \pm (-4k_1 k_2 K_d K_l K_m k_s (K_m k_s L + v_d(L - v_m))(L + v_s)(k_1 K_d K_m k_s L + k_2 K_l (K_m k_s (L + v_s) + v_d(L - v_m + v_s))))^{\frac{1}{2}})}{(k_1 K_d K_m k_s L + k_2 K_l (K_m k_s (L + v_s) + v_d(L - v_m + v_s)))^{\frac{1}{2}}}$$

By using this value, we can find  $M_0$  and  $F_{C_0}$  and then the Equilibrium Point is  $(M_0, F_{C_0}, F_{N_0})$ . More importantly, it is under the fact that  $M_0, F_{C_0}$  and  $F_{N_0}$  are more than zero.

From Eqs. (1), (2) and (3), we consider the interval of equilibrium points that satisfy the stability. Due to  $(M_0, F_{C_0}, F_{N_0})$  is the equilibrium point so  $g_i(M_0, F_{C_0}, F_{N_0}) = 0; i = 1, 2, 3$ .

$$\text{Let } A' = \frac{K_l}{(K_l + F_{N_0})^2}, B' = \frac{K_m}{(K_m + M_0)^2} \text{ and } C' = \frac{K_d}{(K_d + F_{C_0})^2}$$

After we linearized system and find the Jacobian matrix at  $E^*$ , we obtain

$$J = \begin{pmatrix} -v_m B' & 0 & -v_s A' \\ k_s & -v_d C' - k_1 & k_2 \\ 0 & k_1 & -k_2 \end{pmatrix} \quad (14)$$

Suppose that  $\det(J - \lambda I) = 0$

$$\begin{vmatrix} -v_m B' - \lambda & 0 & -v_s A' \\ k_s & -v_d C' - k_1 - \lambda & k_2 \\ 0 & k_1 & -k_2 - \lambda \end{vmatrix} = 0 \quad (15)$$

Hence, the characteristic equation is

$$\lambda^3 + a_1 \lambda^2 + a_2 \lambda + a_3 = 0 \quad (16)$$

Where

$$a_1 = k_1 + k_2 + C' v_d + B' v_m \quad (17)$$

$$a_2 = B' k_1 v_m + B' k_2 v_m + C' k_2 v_d + B' C' v_d v_m \quad (18)$$

$$a_3 = B' C' k_2 v_d v_m + A' k_1 k_s v_m \quad (19)$$

We find the stability of equilibrium points by using Routh-Hurwitz criterion that we don't have to find the eigenvalues. The conditions are  $a_1 > 0, a_2 > 0, a_3 > 0$  and  $a_1 a_2 > a_3$ . If the parameter values satisfy these conditions, the equilibrium points will be Asymptotically Stable.

As you can see the Characteristic equation, it cannot factorize. Consequently, we have to find the Eigenvalues to analyze this model.

From Eq(16) , we get the Eigenvalues

$$\lambda_1 = -\frac{a_1}{3} - 2^{\frac{1}{3}} b_1 + b_2 \quad (20)$$

$$\lambda_2 = -\frac{a_1}{3} + \frac{1+i\sqrt{3}}{2^{\frac{2}{3}}} b_1 - \frac{1-i\sqrt{3}}{2} b_2 \quad (21)$$

$$\lambda_3 = -\frac{a_1}{3} + \frac{1-i\sqrt{3}}{2^{\frac{2}{3}}} b_1 - \frac{1+i\sqrt{3}}{2} b_2 \quad (22)$$

Where

$$b_1 = \frac{-a_1^2 + 3a_2}{3 \left( -2a_1^3 + 9a_1 a_2 - 27a_3 + 3\sqrt{3} \sqrt{-a_1^2 a_2^2 + 4a_2^3 + 4a_1^3 a_3 - 18a_1 a_2 a_3 + 27a_3^2} \right)^{\frac{1}{3}}} \quad (23)$$

$$b_2 = -\frac{1}{3 \cdot 2^{\frac{1}{3}} \left( -2a_1^3 + 9a_1 a_2 - 27a_3 + 3\sqrt{3} \sqrt{-a_1^2 a_2^2 + 4a_2^3 + 4a_1^3 a_3 - 18a_1 a_2 a_3 + 27a_3^2} \right)^{\frac{1}{3}}} \quad (24)$$

We note that the first eigenvalue  $\lambda_1$  is real value. Therefore, if  $\lambda_1$  is negative, that is,  $-\frac{a_1}{3} - 2^{\frac{1}{3}} b_1 + b_2 < 0$ , then the equilibrium point  $E^*$  will be locally asymptotically stable. On the other hand, if  $\lambda_1$  is positive, that is,  $-\frac{a_1}{3} - 2^{\frac{1}{3}} b_1 + b_2 > 0$ , the equilibrium point  $E^*$  will be unstable.

Next, we expand  $\lambda_2$  and  $\lambda_3$ . Then we let  $\lambda_{2,3} = \left( -\frac{a_1}{3} + \frac{b_1}{2^{\frac{2}{3}}} - \frac{b_2}{2} \right) \pm i \left( \frac{\sqrt{3}}{2^{\frac{2}{3}}} b_1 - \frac{\sqrt{3}}{2} b_2 \right)$  which are a pair of complex Eigenvalues. If  $Re(\lambda_{2,3}) < 0$  and  $Im(\lambda_{2,3}) > 0$ , then the sum of eigenvalues is negative and thus the real parts of both eigenvalues must be negative. Hence, if all three of the eigenvalues of the Jacobian matrix  $J$  are negative and the equilibrium point  $E^*$  is locally asymptotically stable. However, if  $Re(\lambda_{2,3}) > 0$  and  $Im(\lambda_{2,3}) > 0$ , then at least one eigenvalue has a positive real part and the equilibrium point  $E^*$  is unstable.

We now look for the range of parameter values for which the equilibrium point  $E^*$  is locally asymptotically stable. Consider

$$Re(\lambda_{2,3}) < 0$$

which leads us to the following inequality

$$a_1 > \frac{3}{2} \left( 2^{\frac{1}{3}} b_1 - b_2 \right) \quad (25)$$

Now, we define  $a_1$  as the bifurcation parameter. Then we will use the Hopf bifurcation theorem in order to show that at  $a_1 = R$  where  $R = \frac{3}{2} \left( 2^{\frac{1}{3}} b_1 - b_2 \right)$  the steady state  $E^*$  becomes unstable and the limit cycle, surrounding the equilibrium point which created by

the bifurcation is asymptotically stable.

Consider the real part of the two eigenvalues of the Jacobian matrix in (19) and then define function of bifurcation parameter  $F(a_1)$  and also define  $b_1$  and  $b_2$  as function of  $a_1$ , so we obtain

$$F(a_1) = -\frac{a_1}{3} - 2^{\frac{1}{3}} \cdot b_1 + b_2 \quad (26)$$

From the result above and inequality (28), if  $a_1 > R$ ,  $E^*$  is asymptotically stable and loses its stability at  $a_1 = R$ , at which point (19) has a pair of purely imaginary complex eigenvalues. For Hopf bifurcation to occur, we need parameters values such that  $\frac{dF}{da_1}|_{a_1=R} \neq 0$ . From (29), we get

$$\frac{dF}{da_1} = -\frac{1}{3} - 2^{\frac{1}{3}} \cdot b'_1 + b'_2 \quad (27)$$

And consequently  $\frac{dF}{da_1}|_{a_1=R} \neq 0$  which is the main condition of the Hopf bifurcation theorem.

### 3 Numerical Solutions

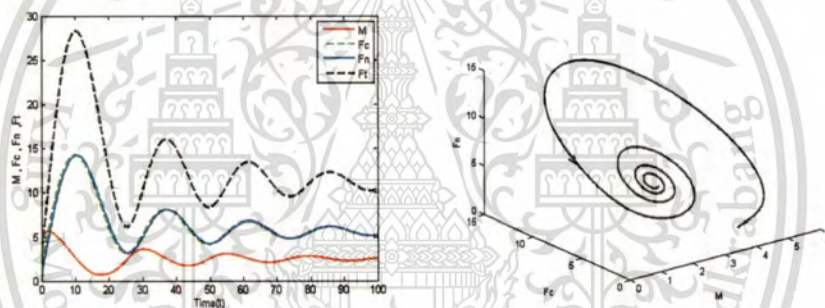


Figure 2: The solution with respect to time ( $t$ ) and 3d-trajectory in the  $M - F_C - F_N$  space of the system eqs (1)-(3) which the parameter values are  $v_s = 3.5, v_m = 1.0, v_d = 3.0, k_s = 1.2, k_1 = 2.0, k_2 = 2.0, K_m = 0.5, K_l = 1.7, K_d = 0.2, n = 1, L = 0.002$  and the equilibrium point is  $E^* = (M_0, F_{C_0}, F_{N_0}) = (5.58075, 2.41351, 5.58075)$

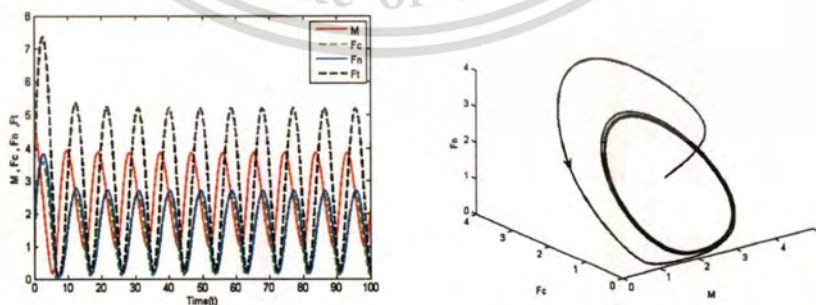


Figure 3: The solution with respect to time ( $t$ ) and 3d-trajectory in the  $M - F_C - F_N$  space of the system eqs (1)-(3) which the parameter values are  $v_s = 4.0, v_m = 3.5, v_d = 3.0, k_s = 1.2, k_1 = 3.5, k_2 = 3.25, K_m = 0.01, K_l = 2.0, K_d = 0.02, n = 1, L = 1$  and the equilibrium point is  $E^* = (M_0, F_{C_0}, F_{N_0}) = (2.45657, 1.13125, 1.21827)$

From the former figure, we plot the solution with respect to time ( $t$ ) and 3d-trajectory in the  $M - F_C - F_N$  space of the system eqs (1)-(3). Afterward, we suppose the initial solution as  $(4.5, 3.5, 0)$  and considered time ( $t$ ) on 0 to 100. Furthermore, we find the parameter values with  $v_s = 3.5, v_m = 1.0, v_d = 3.0, k_s = 1.2, k_1 = 2.0, k_2 = 2.0, K_m = 0.5, K_l = 1.7, K_d = 0.2, n = 1, L = 0.002$  that satisfy all theoretical stable conditions. As you can see from Fig.2, the values of  $M, F_C$  and  $F_N$  are converged to the equilibrium point at  $E^* = (M_0, F_{C_0}, F_{N_0}) = (5.58075, 2.41351, 5.58075)$

In the latter figure, we also plot the solution with respect to time ( $t$ ) and 3d-trajectory in the  $M - F_C - F_N$  space of the system eqs (1)-(3). Afterward, we suppose the initial solution and time as the same values that we did in Fig 2. Therefore, we find the parameter values with  $v_s = 4.0, v_m = 3.5, v_d = 3.0, k_s = 1.2, k_1 = 3.5, k_2 = 3.25, K_m = 0.01, K_l = 2.0, K_d = 0.02, n = 1, L = 1$  that satisfy all theoretical stable limit cycle conditions. As you can see from Fig.3, the values of  $M, F_C$  and  $F_N$  are converged to the equilibrium point at  $E^* = (M_0, F_{C_0}, F_{N_0}) = (2.45657, 1.13125, 1.21827)$

## 4 Conclusion

From the mathematical model for Neurospora, we modified the new model with light is the incentive which is Eqs. (1), (2) and (3). More importantly, we considered the illuminance as follows

- $L = 0.002$  lux , for example, is moonless clear night sky with airflow.
- $L = 1$  lux , for example, is full moon overhead at tropical latitudes.
- $L = 400$  lux , for example, is sunrise or sunset on a clear day.
- $L = 1000$  lux , for example, overcast day or typical TV studio lighting.

From the system, we can find the equilibrium points and parameters which satisfy limit cycle state and stable state as follow by some examples in section 3 which all conditions were found by using the Routh-Hurwitz criterion and the Hopf Bifurcation Theory. 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 scientist or researcher who are interested in the transcription of Neurospora and its circadian rhythm.

## 5 Acknowledment

We are grateful to Nipon Wongvisetsirikul, Wongvisarut Khuangsatung and Chompunut Pakdeecharoen for several enlightening remarks and discussions, and the referees for useful comments and suggestions. Significantly, this research was support by King Mongkut's Institute of Technology Ladkrabang and Science Achievement Scholarship of Thailand.

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**APPENDIX B.****EQUILIBRIUM POINTS AND LINEARIZATION**

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### Equilibrium Points and Linearization [6, 13]

**Definition 1.** A point  $X_e \in R^n$  is an equilibrium point (or fixed point, stationary point, singular point, critical point or rest point) of

$$\frac{dX}{dt} = f(t, X) \quad (\text{B-1})$$

if  $f(t, X) = 0$  for all  $t \geq t^*$ .

If  $X_e$  is an equilibrium point of (1) at  $t^*$ , then it is an equilibrium point for all  $t \geq t^*$ .

**Definition 2.** The equilibrium point  $X = 0$  of (B-1) is stable if for every  $\delta > 0$  and any  $t_0 \in R^+$  there is a  $\omega(\delta, t_0) > 0$  such that

$$|u(t, t_0, \gamma)| < \delta \text{ for every } t \geq t_0$$

whenever  $|\gamma| < \omega(\delta, t_0)$  where  $u(t, \gamma)$  is a solution of (B-1).

**Definition 3.** The equilibrium point  $X = 0$  of (B-1) is asymptotically stable if

1. it is stable and
2. for every  $t_0 \geq 0$  there is an  $\varepsilon(t_0)$  such that

$$\lim_{t \rightarrow \infty} u(t, t_0, \gamma) = 0 \text{ whenever } |\gamma| < \varepsilon.$$

**Definition 4.** The equilibrium point  $X = 0$  of (B-1) is unstable if it is not stable. In this case there is a  $t_0 > 0$  and a sequence  $\gamma_m > 0$  of initial points and a sequence  $t_m$  such that  $|u(t, t_0, \gamma)| \geq \gamma$  for every  $m, t_m \geq 0$ .

For more general setting, consider a system of three autonomous first-order differential equation :

$$\begin{aligned} \frac{dX}{dt} &= g_1(X, Y, Z), \\ \frac{dY}{dt} &= g_2(X, Y, Z), \\ \frac{dZ}{dt} &= g_3(X, Y, Z), \end{aligned} \quad (\text{B-2})$$

where  $g_1, g_2$  and  $g_3$  are nonlinear functions. We let  $x_s = (\bar{X}, \bar{Y}, \bar{Z})$  be the equilibrium point, then

$$g_1(\bar{X}, \bar{Y}, \bar{Z}) = g_2(\bar{X}, \bar{Y}, \bar{Z}) = g_3(\bar{X}, \bar{Y}, \bar{Z}) = 0.$$

Setting the solution at any time in the form

$$X(t) = \bar{X} + x(t), \quad (\text{B-3})$$

$$Y(t) = \bar{Y} + y(t), \quad (\text{B-4})$$

and

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$$Z(t) = \bar{Z} + z(t). \quad (\text{B-5})$$

This method is called perturbation of equilibrium point. We substitute  $X(t), Y(t)$  and  $Z(t)$  in (B-3), (B-4) and (B-5) into the system (B-2),

$$\begin{aligned} \frac{dX}{dt} &= g_1(\bar{X} + x(t), \bar{Y} + y(t), \bar{Z} + z(t)) \\ \frac{dY}{dt} &= g_2(\bar{X} + x(t), \bar{Y} + y(t), \bar{Z} + z(t)) \\ \frac{dZ}{dt} &= g_3(\bar{X} + x(t), \bar{Y} + y(t), \bar{Z} + z(t)) \end{aligned}$$

We expand  $g_1, g_2$  and  $g_3$  in Taylor series about the equilibrium point  $(\bar{X}, \bar{Y}, \bar{Z})$ . Then, we obtain

$$\begin{aligned} \frac{d(\bar{X})}{dt} + \frac{dx}{dt} &= g_1(\bar{X}, \bar{Y}, \bar{Z}) + g_{1x}(\bar{X}, \bar{Y}, \bar{Z})x + g_{1y}(\bar{X}, \bar{Y}, \bar{Z})y + g_{1z}(\bar{X}, \bar{Y}, \bar{Z})z \\ &\quad + \text{terms of order } x^2, y^2, z^2, xy, xz, yz \text{ and higher,} \end{aligned} \quad (\text{B-6})$$

$$\begin{aligned} \frac{d(\bar{Y})}{dt} + \frac{dy}{dt} &= g_2(\bar{X}, \bar{Y}, \bar{Z}) + g_{2x}(\bar{X}, \bar{Y}, \bar{Z})x + g_{2y}(\bar{X}, \bar{Y}, \bar{Z})y + g_{2z}(\bar{X}, \bar{Y}, \bar{Z})z \\ &\quad + \text{terms of order } x^2, y^2, z^2, xy, xz, yz \text{ and higher,} \end{aligned} \quad (\text{B-7})$$

$$\begin{aligned} \frac{d(\bar{Z})}{dt} + \frac{dz}{dt} &= g_3(\bar{X}, \bar{Y}, \bar{Z}) + g_{3x}(\bar{X}, \bar{Y}, \bar{Z})x + g_{3y}(\bar{X}, \bar{Y}, \bar{Z})y + g_{3z}(\bar{X}, \bar{Y}, \bar{Z})z \\ &\quad + \text{terms of order } x^2, y^2, z^2, xy, xz, yz \text{ and higher,} \end{aligned} \quad (\text{B-8})$$

where  $g_{1x}(\bar{X}, \bar{Y}, \bar{Z})$  is  $\frac{\partial g_1}{\partial x}$  calculated at  $(\bar{X}, \bar{Y}, \bar{Z})$  and similarly for  $g_{1y}(\bar{X}, \bar{Y}, \bar{Z})$ ,  $g_{1z}(\bar{X}, \bar{Y}, \bar{Z})$ ,  $g_{2x}(\bar{X}, \bar{Y}, \bar{Z})$ ,  $g_{2y}(\bar{X}, \bar{Y}, \bar{Z})$ ,  $g_{2z}(\bar{X}, \bar{Y}, \bar{Z})$ ,  $g_{3x}(\bar{X}, \bar{Y}, \bar{Z})$ ,  $g_{3y}(\bar{X}, \bar{Y}, \bar{Z})$ ,  $g_{3z}(\bar{X}, \bar{Y}, \bar{Z})$  and other terms.

By the definition of the equilibrium point, we have  $\frac{d(\bar{X})}{dt} = \frac{d(\bar{Y})}{dt} = \frac{d(\bar{Z})}{dt} = 0$  and  $g_1(\bar{X}, \bar{Y}, \bar{Z}) = g_2(\bar{X}, \bar{Y}, \bar{Z}) = g_3(\bar{X}, \bar{Y}, \bar{Z}) = 0$ . We consider only linear terms. Thus, from (B-6), (B-7) and (B-8), we obtain

$$\begin{aligned} \frac{dx}{dt} &= a_{11}x + a_{12}y + a_{13}z \\ \frac{dy}{dt} &= a_{21}x + a_{22}y + a_{23}z \\ \frac{dz}{dt} &= a_{31}x + a_{32}y + a_{33}z \end{aligned} \quad (\text{B-9})$$

We denote the Jacobian matrix of the system (B-2) by  $J$  which is given by

$$J(\bar{X}, \bar{Y}, \bar{Z}) = \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix} = \begin{bmatrix} \frac{\partial g_1}{\partial x} & \frac{\partial g_1}{\partial y} & \frac{\partial g_1}{\partial z} \\ \frac{\partial g_2}{\partial x} & \frac{\partial g_2}{\partial y} & \frac{\partial g_2}{\partial z} \\ \frac{\partial g_3}{\partial x} & \frac{\partial g_3}{\partial y} & \frac{\partial g_3}{\partial z} \end{bmatrix}_{(\bar{X}, \bar{Y}, \bar{Z})}$$

**Definition 5.** An equilibrium point  $x_s = (\bar{X}, \bar{Y}, \bar{Z})$  of a system of ordinary differential equations is hyperbolic if none of the eigenvalues of  $J(x_s)$  have zero real part.

**Theorem 1. (Principle of Linearized Stability)** If  $x_s$  is a hyperbolic equilibrium solution of (B-2), then  $x_s$  is either unstable or asymptotically stable, and its stability type (with respect to (B-2)) matches the stability type of  $x_s$  as an equilibrium solution of (B-9).

**Example 1** Linearize the non-linear system:

$$\frac{dx}{dt} = xy - 2, \quad \frac{dy}{dt} = x - 2y$$

**Sol<sup>n</sup>** Find the equilibrium points by solving this system,

$$\frac{dx}{dt} = xy - 2 = 0,$$

$$\frac{dy}{dt} = x - 2y = 0.$$

We obtain the equilibrium points are  $(2, 1), (-2, -1)$ .

Use the Jacobian matrix to change each equilibrium point  $(x_0, y_0)$  in the x-y plane to the origin in the u-v plane:

$$\begin{bmatrix} \frac{du}{dt} \\ \frac{dv}{dt} \end{bmatrix} = \begin{bmatrix} y & x \\ 1 & -2 \end{bmatrix} \begin{bmatrix} u \\ v \end{bmatrix}.$$

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At (2,1), we get

$$\begin{bmatrix} \frac{du}{dt} \\ \frac{dv}{dt} \end{bmatrix} = \begin{bmatrix} 1 & 2 \\ 1 & -2 \end{bmatrix} \begin{bmatrix} u \\ v \end{bmatrix}.$$

At (-2,-1), we get

$$\begin{bmatrix} \frac{du}{dt} \\ \frac{dv}{dt} \end{bmatrix} = \begin{bmatrix} -1 & -2 \\ 1 & -2 \end{bmatrix} \begin{bmatrix} u \\ v \end{bmatrix}.$$

The eigenvalues at each equilibrium point determine the stability of that point:

At (2,1), we get

$$\begin{vmatrix} 1-\lambda & 2 \\ 1 & -2-\lambda \end{vmatrix} = 0$$

$$\therefore \lambda = 1.56, -2.56$$

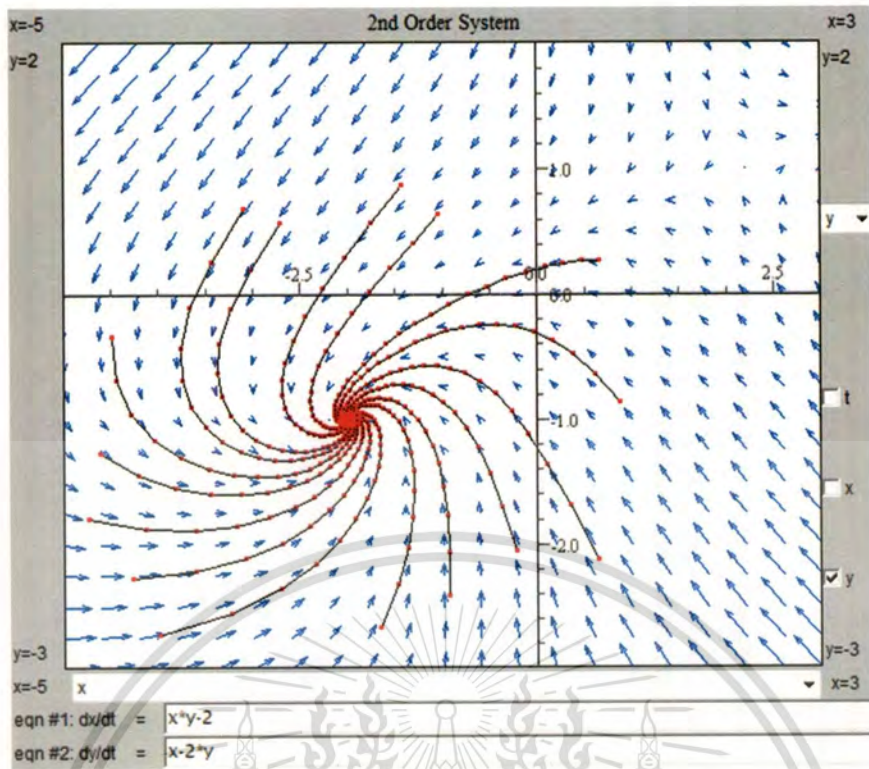
So the equilibrium point (2,1) is saddle point.

At (-2,-1), we have

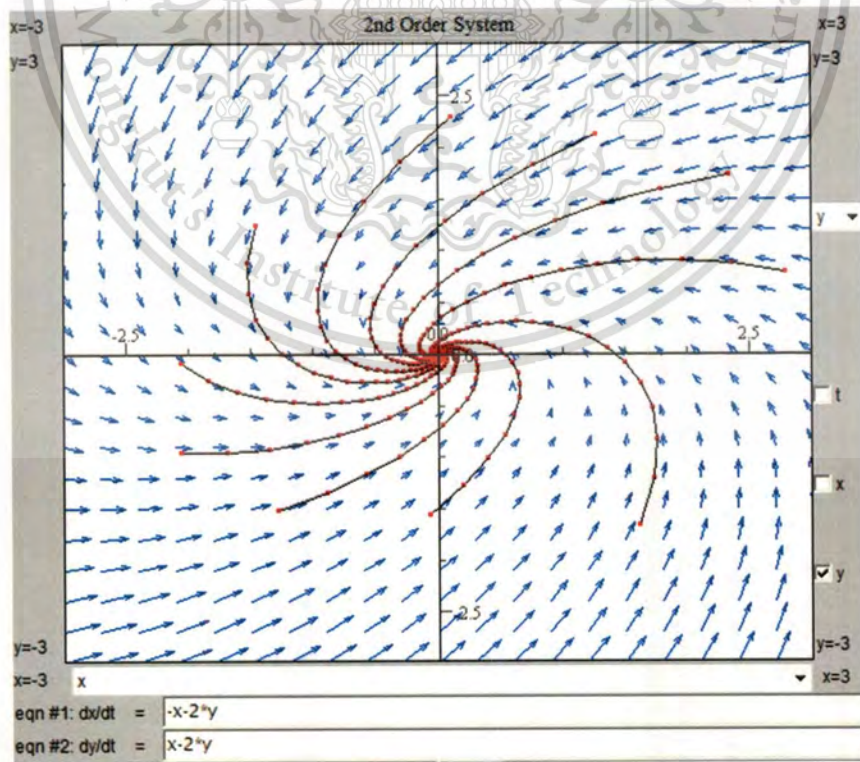
$$\begin{vmatrix} -1-\lambda & -2 \\ 1 & -2-\lambda \end{vmatrix} = 0$$

$$\therefore \lambda = -1.5 \pm 1.32i$$

So the equilibrium point (-2,-1) is spiral sink.



**x-y phase plane**



**u-v phase plane**

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**Example 2** Linearize the non-linear system:

$$\frac{dx}{dt} = y - (x^2 + y^2)x, \quad \frac{dy}{dt} = -x - (x^2 + y^2)y$$

*Sol<sup>n</sup>* Find the equilibrium points by solving this system,

$$\begin{aligned} \frac{dx}{dt} &= y - (x^2 + y^2)x = 0, \\ \frac{dy}{dt} &= -x - (x^2 + y^2)y = 0. \end{aligned}$$

We obtain the equilibrium points are  $(0, 0)$ .

Use the Jacobian matrix to change each equilibrium point  $(x_0, y_0)$  in the  $x$ - $y$  plane to the origin in the  $u$ - $v$  plane:

$$\begin{bmatrix} \frac{du}{dt} \\ \frac{dv}{dt} \end{bmatrix} = \begin{bmatrix} -(3x^2 + y^2) & 1 - 2xy \\ -1 - 2xy & -(x^2 + 3y^2) \end{bmatrix} \begin{bmatrix} u \\ v \end{bmatrix}$$

At  $(0,0)$ , we get

$$\begin{bmatrix} \frac{du}{dt} \\ \frac{dv}{dt} \end{bmatrix} = \begin{bmatrix} 0 & 1 \\ -1 & 0 \end{bmatrix} \begin{bmatrix} u \\ v \end{bmatrix}$$

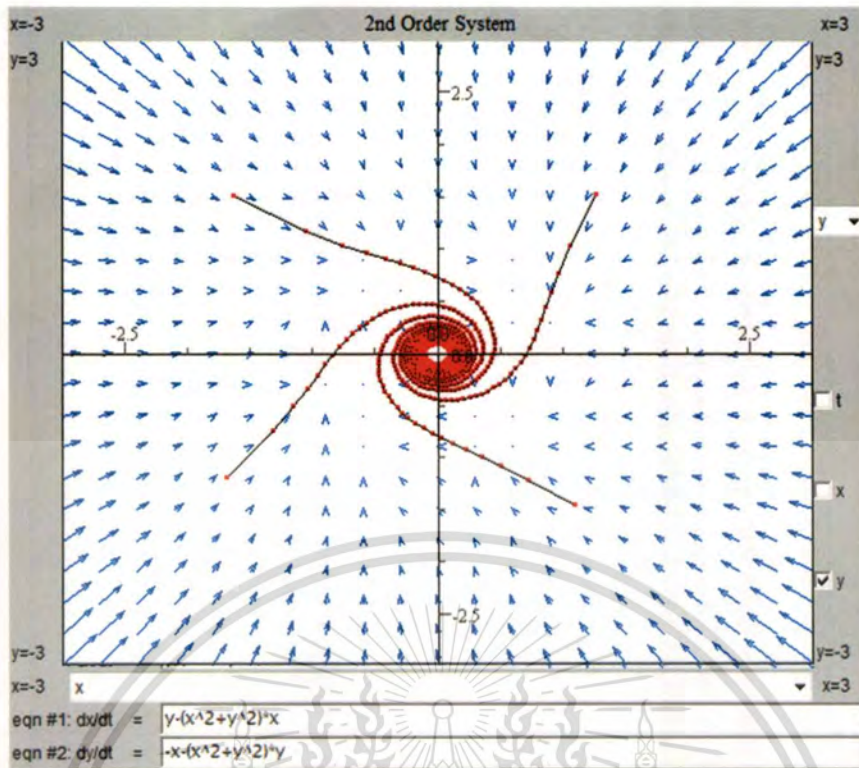
The eigenvalues at each equilibrium point determine the stability of that point:

At  $(0,0)$ , we obtain

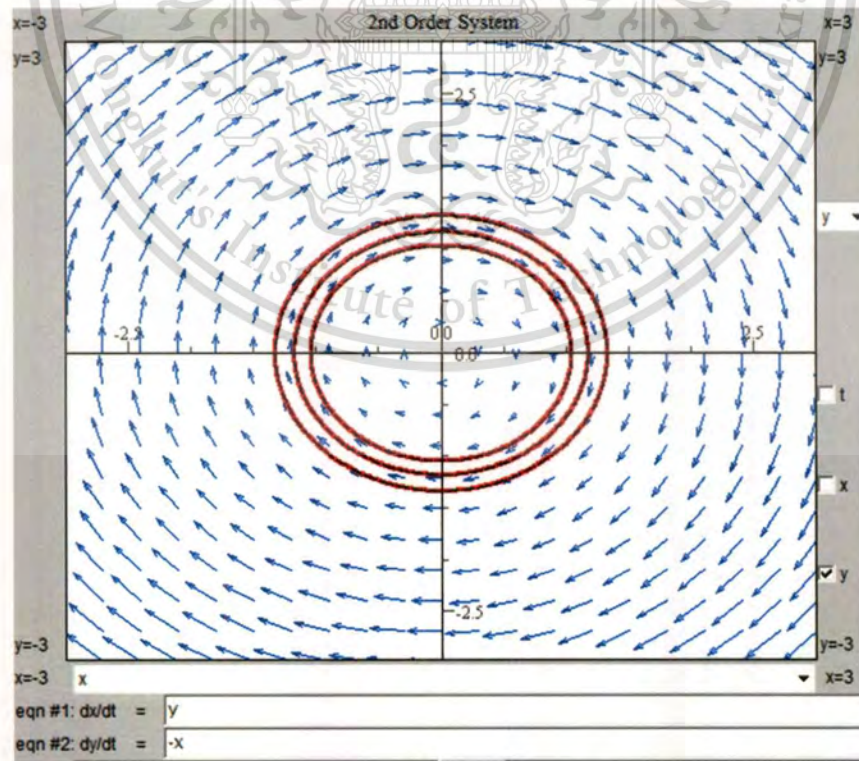
$$\begin{vmatrix} \lambda & 1 \\ -1 & \lambda \end{vmatrix} = 0$$

$$\therefore \lambda = \pm i$$

So the equilibrium point  $(0,0)$  is center



x-y phase plane



u-v phase plane

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## APPENDIX C.

### THE ROUTH-HURWITZ CRITERIA FOR LOCAL ASYMPTOTICAL STABILITY



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### The Routh-Hurwitz Criteria for Local Asymptotical Stability [10, 11]

We obtain a characteristic equation in the form

$$\lambda^k + b_1\lambda^{k-1} + \dots + b_k = 0. \quad (C-1)$$

The stability of the equilibrium point can be determined without solving for the actual values of the eigenvalues by using the Routh-Hurwitz criteria.

**Definition 1.** (Routh-Hurwitz criteria for local asymptotical stability)

Given the characteristic equation (C-1), define  $k$  matrices as follow:

$$\begin{aligned}
 H_1 &= [b_1] \\
 H_2 &= \begin{bmatrix} b_1 & 1 \\ b_3 & b_2 \end{bmatrix} \\
 H_3 &= \begin{bmatrix} b_1 & 1 & 0 \\ b_3 & b_2 & b_1 \\ b_5 & b_4 & b_3 \end{bmatrix}, \dots \\
 H_j &= \begin{bmatrix} b_1 & 1 & 0 & 0 & \dots & 0 \\ b_3 & b_2 & b_1 & 1 & \dots & 0 \\ b_5 & b_4 & b_3 & b_2 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ b_{2j-1} & b_{2j-2} & b_{2j-3} & b_{2j-4} & \dots & b_j \end{bmatrix}, \dots \\
 H_k &= \begin{bmatrix} b_1 & 1 & 0 & 0 & \dots & 0 \\ b_3 & b_2 & b_1 & 1 & \dots & 0 \\ b_5 & b_4 & b_3 & b_2 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & \dots & b_k \end{bmatrix}
 \end{aligned}$$

where the  $(l, m)$  term in the matrix  $H_j$  is

$$(l, m) = \begin{cases} b_{2l-m} & \text{for } 0 < 2l - m < k \\ 1 & \text{for } 2l = m \\ 0 & \text{for } 2l < m \text{ or } 2l > k + m \end{cases}$$

Then, all eigenvalues have negative real parts. This means that the equilibrium point  $\bar{X}$  is stable if and only if the determinants of all Routh-Hurwitz matrices are positive which is

$$\det H_j > 0 \text{ for } j = 1, 2, 3, \dots, k.$$

Next, we show conditions of Routh-Hurwitz criteria for case  $k = 3$  which are appeared in the thesis.

For  $k = 3$ ; We need to show that  $\det H_j > 0$  for  $j = 1, 2$  and  $3$

$$H_1 = [b_1]; \det H_1 = b_1,$$

$$H_2 = \begin{bmatrix} b_1 & 1 \\ b_3 & b_2 \end{bmatrix}; \det H_2 = b_1 b_2 - b_3,$$

$$H_3 = \begin{bmatrix} b_1 & 1 & 0 \\ b_3 & b_2 & b_1 \\ b_5 & b_4 & b_3 \end{bmatrix}; \det H_3 = b_1 b_2 b_3 - b_3^2 - b_1^2 b_4 + b_1 b_5.$$

Since coefficient  $b_4$  and  $b_5$  in  $3^{\text{rd}}$  order characteristic polynomial equation equal to zero then we have

$$\det H_1 = b_1,$$

$$\det H_2 = b_1 b_2 - b_3,$$

$$\det H_3 = b_1 b_2 b_3 - b_3^2 = b_3 (b_1 b_2 - b_3).$$

So, the three conditions which correspond to  $\det H_j > 0$  for  $j = 1, 2$  and  $3$ , are  $b_1 > 0, b_3 > 0$  and  $b_1 b_2 > b_3$ .

Therefore, the three conditions of Routh-Hurwitz criteria for local asymptotically stable for a  $3^{\text{rd}}$  order characteristic polynomial equation are

1.  $b_1 > 0$ ,
2.  $b_3 > 0$ , and
3.  $b_1 b_2 > b_3$ .

Finally, we show conditions of Routh-Hurwitz criteria for case  $k = 4$  which are also appeared in the thesis.

For  $k = 4$ ; We need to show that  $\det H_j > 0$  for  $j = 1, 2, 3$  and  $4$

$$H_1 = [b_1]; \det H_1 = b_1,$$

$$H_2 = \begin{bmatrix} b_1 & 1 \\ b_3 & b_2 \end{bmatrix}; \det H_2 = b_1 b_2 - b_3,$$

$$H_3 = \begin{bmatrix} b_1 & 1 & 0 \\ b_3 & b_2 & b_1 \\ b_5 & b_4 & b_3 \end{bmatrix}; \det H_3 = b_1 b_2 b_3 - b_3^2 - b_1^2 b_4 + b_1 b_5,$$

$$H_4 = \begin{bmatrix} b_1 & 1 & 0 & 0 \\ b_3 & b_2 & b_1 & 1 \\ b_5 & b_4 & b_3 & b_2 \\ b_7 & b_6 & b_5 & b_4 \end{bmatrix};$$

$$\det H_4 = b_1 b_2 b_3 b_4 + b_2 b_3 b_5 + 2b_1 b_4 b_5 + b_1^2 b_2 b_6 + b_3 b_7 - b_1^2 b_4^2 - b_1 b_2^2 b_5 - b_5^2 - b_1 b_3 b_6 - b_1 b_2 b_7.$$

Since coefficient  $b_5, b_6$  and  $b_7$  in 4<sup>th</sup> order characteristic polynomial equation equal to zero then we get

$$\det H_1 = b_1,$$

$$\det H_2 = b_1 b_2 - b_3,$$

$$\begin{aligned} \det H_3 &= b_1 b_2 b_3 - b_3^2 - b_1^2 b_4 \\ &= b_3 (b_1 b_2 - b_3) - b_1^2 b_4, \end{aligned}$$

$$\begin{aligned} \det H_4 &= b_1 b_2 b_3 b_4 - b_3^2 b_4 - b_1^2 b_4^2 \\ &= b_3 b_4 (b_1 b_2 - b_3) - b_1^2 b_4^2 \\ &= b_4 (b_3 (b_1 b_2 - b_3) - b_1^2 b_4). \end{aligned}$$

Hence, the four conditions which correspond to  $\det H_j > 0$  for  $j=1,2,3$  and 4, are  $b_1 > 0, b_3 > 0, b_4 \geq 0$  and  $b_1 b_2 b_3 > b_3^2 + b_1^2 b_4$ .

Therefore the four conditions of Routh-Hurwitz criteria for local asymptotically stable for a 4<sup>th</sup> order characteristic polynomial equation are

1.  $b_1 > 0,$
2.  $b_3 > 0,$
3.  $b_4 \geq 0,$  and
4.  $b_1 b_2 b_3 > b_3^2 + b_1^2 b_4.$

**APPENDIX D.****THE HOPF BIFURCATION THEOREM**

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### The Hopf Bifurcation Theorem [12]

Let the following be a nonlinear system of  $n$  equations in  $n$  variables that contains a parameter  $\nu$ ,

$$\frac{dX}{dt} = f(X, \nu), X \in R^n \quad (D-1)$$

where  $X \in R^n$  and  $\nu$  is a real valued parameter on an interval  $J$ .

Let the equilibrium point of the system in equation (D-1) be  $X = X^*(\nu)$  and the Jacobian matrix be

$$A(\nu) = D_x f(X^*(\nu), \nu) = \frac{\partial f_i}{\partial X_j}(X^*(\nu), \nu), i, j = 1, 2, \dots, m$$

Suppose that

1.  $A(\nu)$  has a pair of complex conjugate eigenvalues  $\lambda_1$  and  $\lambda_2$  such that
 
$$\lambda_1(\nu) = \lambda_2(\nu) = \alpha(\nu) \pm i\omega(\nu)$$
 such that for some number  $\nu = \nu_c \in J$ , where  $\nu_c$  is called a critical value of  $\nu$ ,
 
$$\omega(\nu_c) = \omega_0 > 0, \alpha(\nu_c) = 0 \text{ and } \alpha'(\nu_c) \neq 0$$
2. The remaining  $n-2$  eigenvalues of  $A(\nu)$  all have strictly negative real parts. Then, the equation (D-1) has a family of periodic solutions near the critical point  $\nu_c$ . The appearance of periodic solutions out of an equilibrium point is called a *Hopf Bifurcation*.
3. There are two possibilities for the periodic solutions. Without loss of generality we can assume that the equilibrium point is asymptotically stable for  $\nu < \nu_c$ . Then,
  - (a) If the equilibrium point is asymptotically stable at  $\nu = \nu_c$ , then the periodic solution occurs for  $\nu > \nu_c$  and is asymptotically stable sufficiently near the critical point. This is called a *supercritical periodic solution*.
  - (b) If the equilibrium point is not asymptotically stable at  $\nu = \nu_c$ , then the periodic solution occurs for  $\nu < \nu_c$  and is not asymptotically stable. This is called a *subcritical periodic solution*.

The periodic solution which results from a Hopf bifurcation from the critical point  $X^*(\nu)$  corresponds to a trajectory on a closed curve or orbit about the critical point in the phase plane. Such closed trajectories in the neighborhood, of which all trajectories are spiral, are called *limit cycles*.

## APPENDIX E.

### HILL EQUATION



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### Hill Equation [5]

In biochemistry, the binding of a ligand to a macromolecule is often enhanced if there are already other ligands present on the same macromolecule (this is known as Cooperative binding). The **Hill coefficient**, named for Archibald Vivian Hill, provides a way to quantify this effect.

It describes the fraction of the macromolecule saturated by ligand as a function of the ligand concentration; it is used in determining the degree of cooperativeness of the ligand binding to the enzyme or receptor. It was originally formulated by Archibald Hill in 1910 to describe the sigmoidal O<sub>2</sub> binding curve of hemoglobin.

A coefficient of 1 indicates completely independent binding, regardless of how many additional ligands are already bound. Numbers greater than one indicate positive cooperativity, while numbers less than one indicate negative cooperativity. The Hill coefficient was originally devised to explain the cooperative binding of oxygen to Hemoglobin.

$$\text{Hill equation: } \theta = \frac{[L]^n}{K_d + [L]^n} = \frac{[L]^n}{(K_A)^n + [L]^n} = \frac{1}{\left(\frac{K_A}{[L]}\right)^n + 1}$$

$\theta$  - fraction of occupied sites where the ligand can bind to the active site of the receptor protein.

$[L]$  - free (unbound) ligand concentration

$K_d$  - Apparent dissociation constant derived from the law of mass action (equilibrium constant for dissociation)

$K_A$  - ligand concentration producing half occupation (ligand concentration occupying half of the binding sites), that is also the microscopic dissociation constant.

$n$  - Hill coefficient, describing cooperativity (or possibly other biochemical properties, depending on the context in which the Hill equation is being used).

Taking the reciprocal of both sides, rearranging, inverting again, and then taking the logarithm on both sides of the equation leads to an alternative formulation of the Hill equation:

$$\log\left(\frac{\theta}{1-\theta}\right) = n \log [L] - \log K_d.$$

When appropriate, the value of the Hill coefficient describes the cooperativity of ligand binding in the following way:

- $n > 1$  - **Positively cooperative reaction:** Once one ligand molecule is bound to the enzyme, its affinity for other ligand molecules increases.
- $n < 1$  - **Negatively cooperative reaction:** Once one ligand molecule is bound to the enzyme, its affinity for other ligand molecules decreases.
- $n = 1$  - **Noncooperative reaction:** The affinity of the enzyme for a ligand molecule is not dependent on whether or not other ligand molecules are already bound.



Example of Matlab program to find numerical solutions, phase plane and phase space of model (2.4) with parameters satisfying limit cycle conditions and  $L = 1$  lux.

```

function f = model_m1(t,x)
    m = x(1);
    fc = x(2);
    fn = x(3);

    % stable
    %vs = 4.0;
    %vm = 3.5;
    %vd = 3.0 ;
    %ks = 1.0 ;
    %k1 = 3.5 ;
    %k2 = 3.25 ;
    %km = 0.02 ;
    %k1 = 1.0 ;
    %kd = 0.05 ;
    %n = 1 ;
    %L = 1.;

    % limit cycle
    vs = 4.0;
    vm = 3.5;
    vd = 3.0 ;
    ks = 1.2 ;
    k1 = 3.5 ;
    k2 = 3.25 ;
    km = 0.01 ;
    k1 = 2.0 ;
    kd = 0.02 ;
    n = 1 ;
    L = 1 ;

    eq1 = vs*((k1^n)/((k1^n)+(fn^n))) - vm*(m/(km+m)) + L ;
    eq2 = ks*m - vd*(fc/(kd+fc))- k1*fc + k2*fn ;
    eq3 = k1*fc - k2*fn ;

    f = [eq1 ; eq2 ; eq3 ];
```

```

function cal_model_m1
tspan = [0 100];
init = [4.5 3.5 0]; % M FC FS FN
options = odeset('RelTol',1e-5,'AbsTol',[1e-5 1e-5 1e-5]);
[t , x] = ode45(@model_m1,tspan,init,options)

figure(7)
plot(t, x(:,1),'k','LineWidth',1.5)
xlabel('Time (hour)');
ylabel('frq mRNA (M)');

figure(8)
plot(t, x(:,2),'k','LineWidth',1.5)
xlabel('Time (hour)');
ylabel('Cytosol FRQ (Fc)');

figure(10)
plot(t, x(:,3),'k','LineWidth',1.5)
xlabel('Time (hour)');
ylabel('Nuclear FRQ (Fn)');

figure(11)
plot(t, x(:,2)+x(:,3),'k','LineWidth',1.5)
xlabel('Time (hour)');
ylabel('Total FRQ (Ft)');

figure(2)
plot(x(:,1), x(:,2),'k','LineWidth',1.5)
xlabel('M');
ylabel('Fc');

figure(3)
plot(x(:,1), x(:,3),'k','LineWidth',1.5)
xlabel('M');
ylabel('Fn');

figure(4)
plot(x(:,2), x(:,3),'k','LineWidth',1.5)
xlabel('Fc');
ylabel('Fn');

figure(12)
plot3(x(:,1),x(:,2),x(:,3),'k','LineWidth',1.5)
xlabel('M');
ylabel('Fc');
zlabel('Fn');

```

## BIOGRAPHY

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