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A mathematical model of interaction between regulatory proteins in bacterial flagellum

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Abstract

In this paper we present a basic mathematical model for interaction between key regulatory proteins involved in the construction and assembly of bacterial flagellum. We make reasonable assumptions about the model and conduct a linear stability analysis. We construct direction field for the model and provide the numerical solution.The results are presented graphically and the conclusion is drawn that the interaction between the two proteins is significantly influenced by the parameters involved.

Keywords: regulatory proteins, bacterial flagellum, flagella-dependent-motility, *salmonella*, expression, transcription, hook-basal body, linear stability analysis.

1.0 Introduction

Bacterial flagellum is a whip-like structure extending from the cytoplasm to the exterior of the cell (see Figure 1). The tail of the flagellum is made up of a protein called flagellin.Flagella provide motility (i.e. movement) to the bacteria and contribute to disease outcomes by affecting the bacterium's fitness by being a target of host immune responses [1].Flagella-dependent motility is advantageous for bacteria since it allows cells to seek and acquire nutrients and escape unfavourable environmental conditions [2, 3].

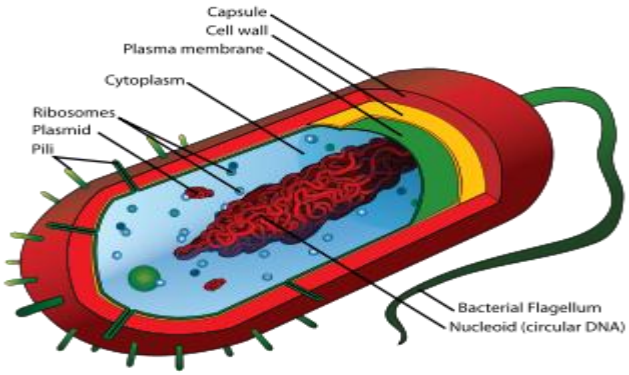

Figure 1: Intercellular bacterial cell structure

The flagellum of *Salmonella typhimurium*is composed of three structural parts, a basal body, a hook and a filament, and is constructed in this order [4]. More than 50 genes are required for flagellar formation and function. These flagellar genes constitute at least 14 different operons, and most of them are clustered in four regions on the chromosome[4, 5]. Transcription of these operons forms a highly organized cascade called the flagellar regulon, and is coordinated with the

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flagellar assembly hierarchy [6, 7]. According to the relative positions in the transcriptional hierarchy, the flagellar operons are grouped into three classes, 1, 2 and 3. Class 1 contains only one operon, FlhD, consisting of two genes, FlhD and FlhC, whose products are both required for class 2 expression. Class 2 contains the operons responsible for formation of the flagellar basal structure, the hook-basal body (HBB) complex. Class 2 also contains the FliA gene, which encodes an alternative sigma factor, σ^{28}, needed for class 3 expression [8]. Class 3 contains operons responsible for filament formation, flagellar rotation and chemotaxis. FliA-dependent expression of class 3 is under negative control from an anti-sigma factor, FlgM[9 - 12]. The FlgM geneis expressed from both class 2 and class 3 promoters [13, 14]. In addition to class 3 expression, the FliA-FlgM regulatory system is known to be involved in regulation of class 1 and class 2 expression[7]. The role of the FlgM regulatory protein is to prevent σ^{28}-dependent transcription of class 3 promoters prior to HBB completion. This ensures that structural subunits needed late in assembly are not produced until the earlier assembly stage (HBB completion) is finished. Once the hook-basal body is completed, FlgM is secreted out of the cell through the partially completed flagellum.

Ding et al. [15] described the functional characterization of the FlgM gene in *Yersinia pseudotuberculosis*. Direct interaction of FlgM with the alternative sigma factor σ^{28} (FliA) was first confirmed. Ikebe et al. [16] analysed the transcription in vivo and in vitro of the FliA gene encodes the flagellum-specific sigma factor σ^{28} in *Salmonella typhimurium.*

This paper presents a mathematical model examining the relationship between the proteins FlgM and FliA. To simulate the relationship we make reasonable assumptions about the model and conduct a linear stability analysis. We provide numerical solution of the model.

2.0 Model Formulation

The relationship between the proteins FlgM and FliA is described by the following equations:

$$\left.\begin{aligned}\frac{dX}{\partial\tau} &= r_1 + b_1 Y - k_b XY - m_1 X\\ \frac{dY}{\partial\tau} &= r_2 + b_2 Y - k_b XY - m_2 Y\end{aligned}\right\} \tag{2.1}$$

with initial conditions:

$$X(0) = X_0, \quad Y(0) = Y_0, \tag{2.2}$$

where

X is the concentration of FlgM

Y is the concentration of FliA $(\sigma 28)$

r_1 is the constant rate of production for FlgM

r_2 is the constant rate of production for FliA

b_1 is the natural growth rate of FlgM

b_2 is the natural growth rate of FliA

m_1 is the mortality rate of FlgM

m_2 is the mortality rate of FliA

2.1 Non-dimensionalisation

We introduce dimensionless variables for time and concentrations,

$$t = b_1\tau, \qquad x = \frac{k_b X}{b_1}, y = \frac{k_b Y}{b_1} \tag{2.3}$$

to get

$$\left.\begin{aligned}\frac{dx}{\partial t} &= \alpha - \beta x + y(1-x)\\ \frac{dy}{\partial t} &= \sigma - xy - \delta y\end{aligned}\right\} \tag{2.4}$$

with initial conditions:

$$x(0) = \frac{k_b X_0}{b_1} = x_0, \quad y(0) = \frac{k_b Y_0}{b_1} = y_0, \tag{2.5}$$

where

$$\alpha = \frac{k_b r_1}{b_1^2}, \quad \beta = \frac{m_1}{b_1}, \quad \sigma = \frac{k_b r_2}{b_1^2}, \quad \delta = \frac{m_2 - b_2}{b_1}$$

2.2 Simplification

Case 1: In order to perform quantitative analysis, the numbers of parameters are further reduced by making reasonable assumptions about the model. Thus

(a) The rate of production of FlgM is assumed to be the same as rate of its degradation, i.e., $\alpha = \beta$.

(b) The rate of production of FliA is assumed to be the same as one unit more than the rate of its degradation, i.e., $\sigma = 1 + \delta$.

With these assumptions, we arrive at equations (2.6):

$$\left.\begin{aligned} \frac{dx}{\partial t} &= \alpha(1-x) + y(1-x) \\ \frac{dy}{\partial t} &= (1+\delta) - y(x+\delta) \end{aligned}\right\} \tag{2.6}$$

Case 2: Since FlgM get secreted as soon as the hook basal is completed another approach to modeling FlgM-FliA interaction would be by introducing a time dependent degradation rate for FlgM. Thus increasing the secretion rate for FlgM as time increases. This new model will be similar to the above non dimensionalized model with β as a function of time:

$$\left.\begin{aligned} \frac{dx}{\partial t} &= \alpha - \beta(t)x + y(1-x) \\ \frac{dy}{\partial t} &= \sigma - xy - \delta y \end{aligned}\right\} \tag{2.7}$$

The function $\beta(t)$ is assumed here to increase as t increases. $\beta(0) = 1$, $\frac{d\beta(t)}{dt} > 0$ and $\lim_{t\to\infty} \beta(t) = \infty$. We suggest that this is an exponential function $\beta(t) \approx e^{kt}$, where k is a non-negative function.

3.0 Method of Solution

3.1 Stabilility Analysis

The steady states of the system (2.6) satisfy the following algebraic system:

$$\left.\begin{aligned} \alpha(1-x) + y(1-x) &= 0 \\ (1+\delta) - y(x+\delta) &= 0 \end{aligned}\right\} \tag{3.1}$$

From the first equation in (3.1), we have either $x = 1$ or $y = -\alpha$. Thus, it follows from $x = 1$ that we get the equilibrium, $p_1 = (1,1)$. When $y = -\alpha$, we have another equilibrium, $p_2 = \left(\frac{-\delta(\alpha+1)-1}{\alpha}, -\alpha\right)$. Thus the equilibria of (2.6) are $p_1 = (1,1)$ and $p_2 = \left(\frac{-\delta(\alpha+1)-1}{\alpha}, -\alpha\right)$. But only p_1 is biologically meaningful.

The Jacobian of (2.6) is

$$Df(x,y) = \begin{pmatrix} -(\alpha+y) & 1-x \\ -y & -(x+\delta) \end{pmatrix} \tag{3.2}$$

The linearization of (2.6) at p_1 is

$$Df(1,1) = \begin{pmatrix} -(\alpha+1) & 0 \\ -1 & -(1+\delta) \end{pmatrix} \tag{3.3}$$

with eigenvalues $\lambda_1 = -(1+\alpha), \quad \lambda_2 = -(1+\delta)$

By definition, all the parameters are non-negative, hence both the eigenvalues are real and have the same sign $\lambda_1 < 0$ and $\lambda_2 < 0$. Hencethe equilibrium point $(1,1)$ is stable.

3.2 Phase-Plane Analysis

To visualize the complete direction field of system of equation (2.6), we used dfieldplot commands in Maple 13 package. Results are presented in Figures 2 and 3.

3.3 Numerical Procedure

Since, we won't be able to find solution of the model explicitly as a function of time, we solved the system numerically using the Runge-Kutta integration scheme with a modified version of the Newton-Raphson shooting method with α and δ as prescribed parameters. The computations were done using computer symbolic algebraic package MAPLE.

4.0 Results and Discussion

After simplification of the model, we note that when $\alpha = \beta$ and $\sigma = 1 + \delta$,the location of the fixed point which is biologically meaningful is independent of any of the parameters in the model.

The direction fields are presented in Figures 2 – 3. Figure 2 displays the direction field of $x(t)$ against $y(t)$ for certain values of parameters. Figure 3 displays the direction field of $y(t)$ against $x(t)$ for certain values of parameters. From Figures 2 and 3 it seen that the fields are moving toward the equilibrium point $(1,1)$.

For problem in case1, the concentration profiles are presented in Figures 4 –9. Figure 4 displays the graph of $x(t)$ against t for different values of α . It is seen that concentration of FlgM increases as rate of its production increases.Figure 5 displays the graph of $y(t)$ against t for different values of α . It is seen that concentration of FliA decreases as rate of production of FlgM increases. Figure 6 displays the graph of $x(t)$ and $y(t)$ against t for fixed values of parameters. This shows the interaction between the two proteins.

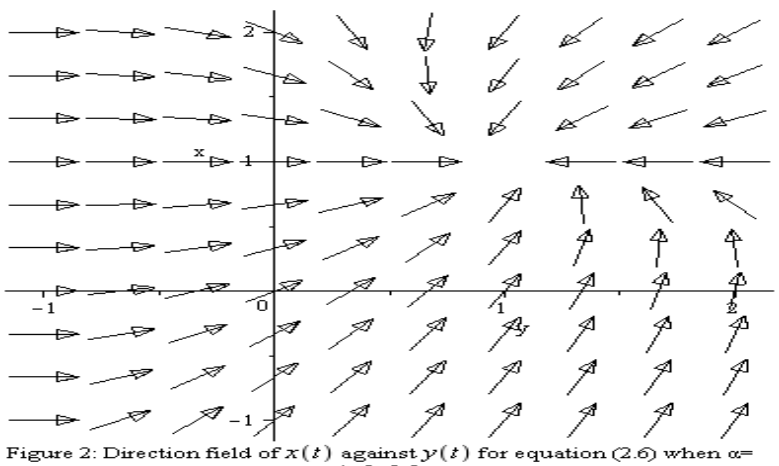

Figure 2: Direction field of $x(t)$ against $y(t)$ for equation (2.6) when α= 1, δ=0.5.

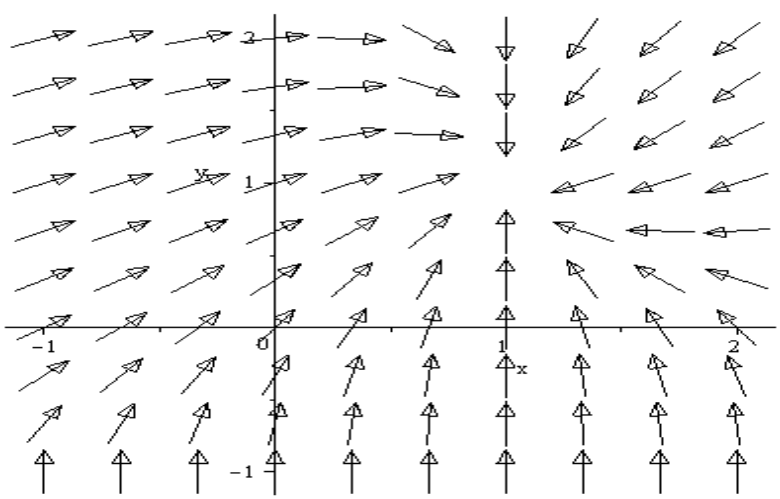

Figure 3: Direction field of $y(t)$ against $x(t)$ for equation (2.6) when α= 1, δ=0.5.

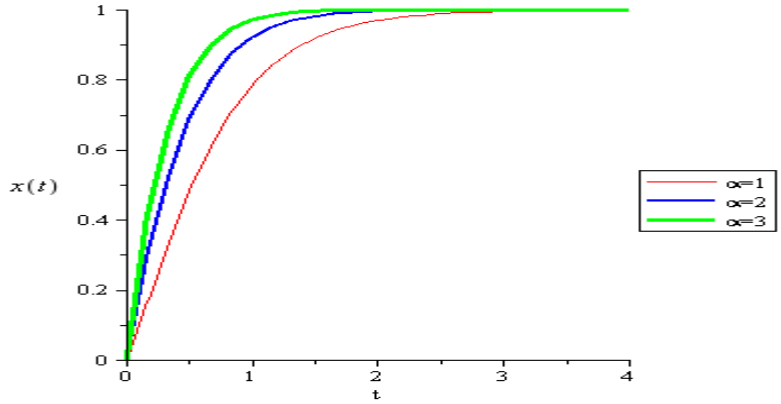

Figure 4: Plots of $x(t)$ against time t for equation (2.6) for different values of α and δ=0.5

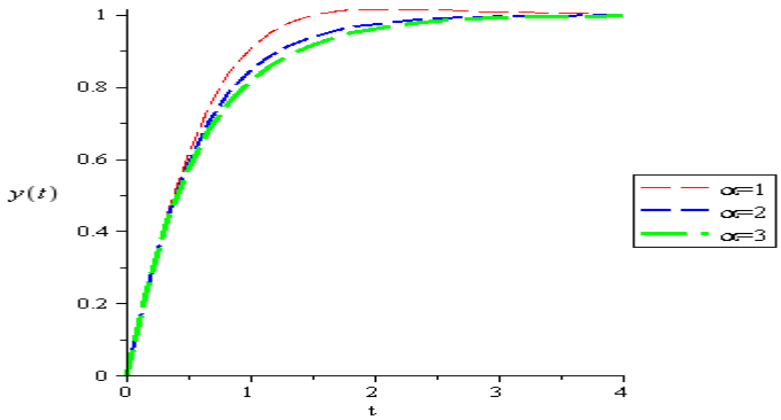

Figure 5: Plots of $y(t)$ against time t for equation (2.6) for different values of α and δ=0.5

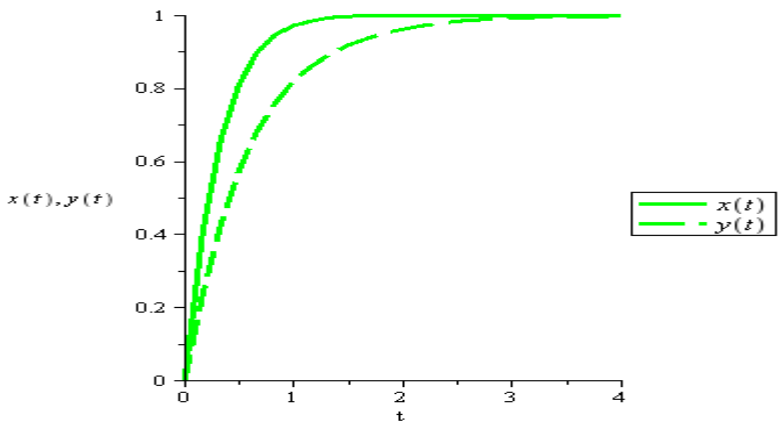

Figure 6: Plots of $x(t)$ and $y(t)$ against time t for equation (2.6) for different values of α and δ=0.5

Figure 7 displays the graph of $x(t)$ against t for different values of δ. It is seen that concentration of FlgM increases as rate of degradation of FliA increases. Figure 8 displays the graph of $y(t)$ against t for different values of δ. It is seen that concentration of FliA increases as rate of its degradation increases. Figure 9 displays the graph of $x(t)$ and $y(t)$ against t for fixed values of parameters. This shows the interaction between the two proteins.

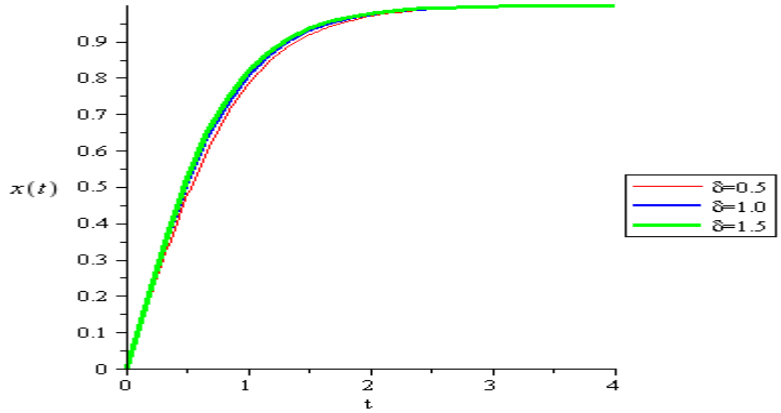

Figure 7: Plots of $x(t)$ against time t for equation (2.6) for different values of δ and α=1

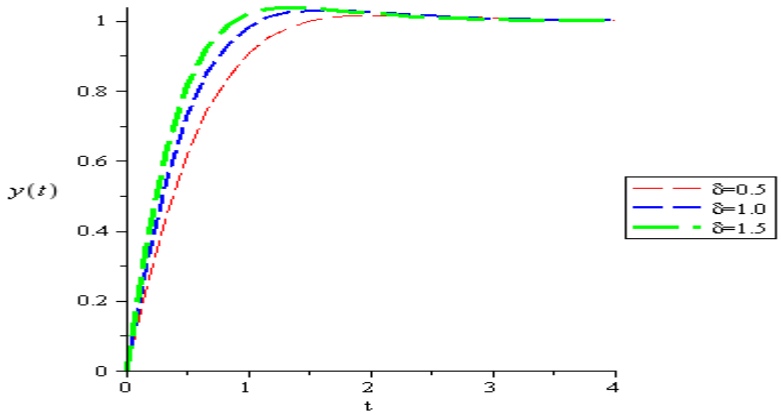

Figure 8: Plots of $y(t)$ against time t for equation (2.6) for different values of δ and α=1

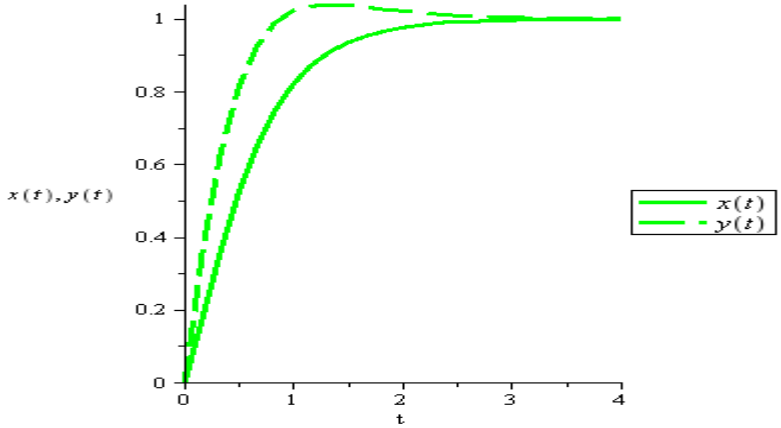

Figure 9: Plots of $x(t)$ and $y(t)$ against time t for equation (2.6) for different values of δ and α=1

For problem in case 2, the concentration profiles are presented in Figures 10 – 18. Figure 10 displays the graph of $x(t)$ against t for different values of α. It is seen that concentration of FlgM increases as rate of its production increases. Figure 11 displays the graph of $y(t)$ against t for different values of α. It is seen that concentration of FliA decreases as rate of production of FlgM increases. Figure 12 displays the graph of $x(t)$ and $y(t)$ against t for fixed values of parameters. This shows the interaction between the two proteins.

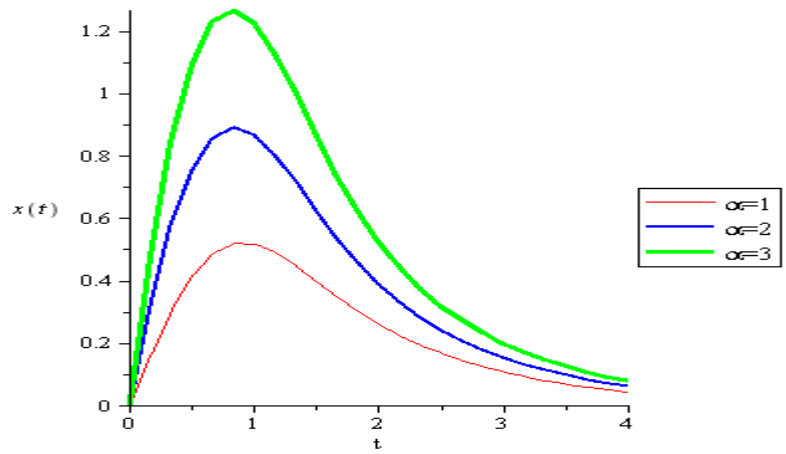

Figure 10: Plots of $x(t)$ against time t for equation (2.7) for different values of α and δ=0.5, k=1, σ=1.

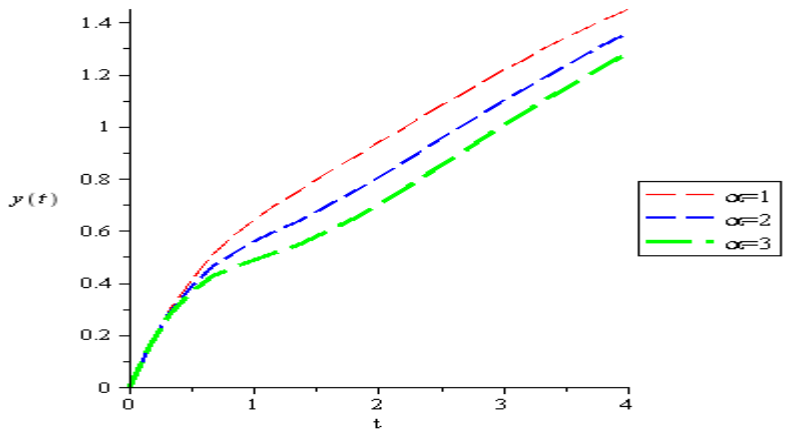

Figure 11: Plots of $y(t)$ against time t for equation (2.7) for different values of α and δ=0.5, k=1, σ=1.

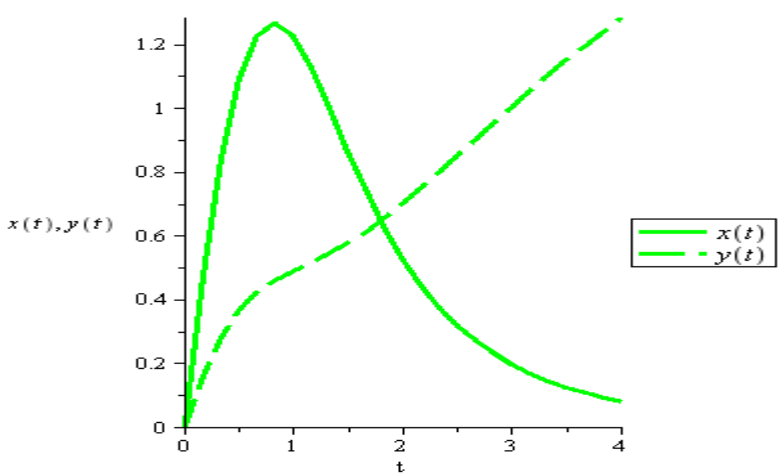

Figure 12: Plots of $x(t)$ and $y(t)$ against time t for equation (2.7) for different values of α and δ=0.5, k=1, σ=1.

Figure 13 displays the graph of $x(t)$ against t for different values of δ. It is seen that maximum concentration of FlgM decreases as rate of degradation of FliA increases. Figure 14 displays the graph of $y(t)$ against t for different values of δ. It is seen that concentration of FliA decreases as rate of its degradation increases. Figure 15 displays the graph of $x(t)$ and $y(t)$ against t for fixed values of parameters. This shows the interaction between the two proteins.

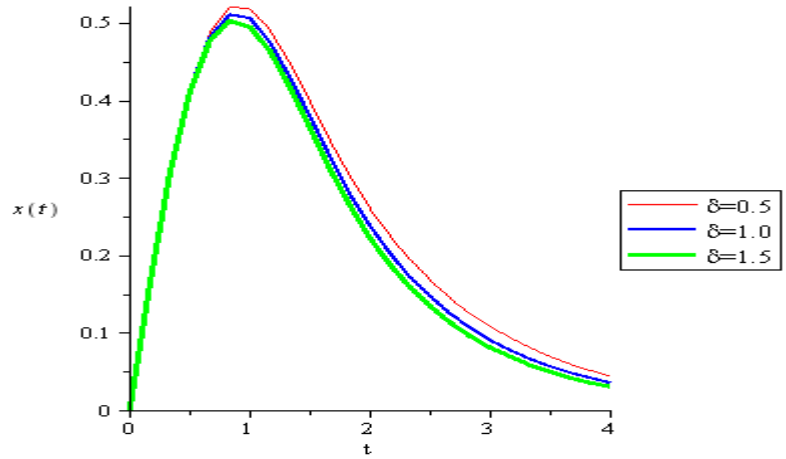

Figure 13: Plots of $x(t)$ against time t for equation (2.7) for different values of δ and α=1, k=1, σ=1.

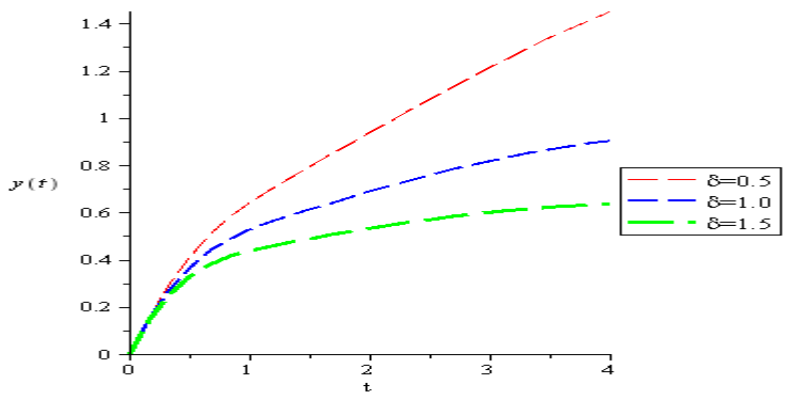

Figure 14: Plots of $y(t)$ against time t for equation (2.7) for different values of δ and α=1, k=1, σ=1.

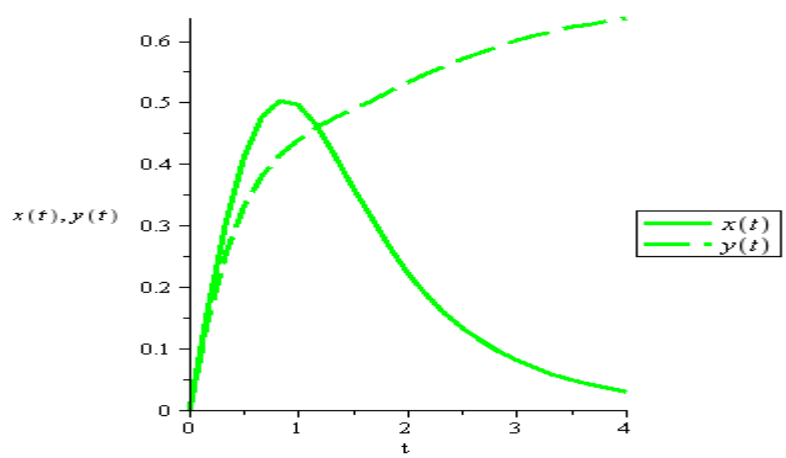

Figure 15: Plots of $x(t)$ and $y(t)$ against time t for equation (2.7) for different values of δ and α=1, k=1, σ=1.

Figure 16 displays the graph of $x(t)$ against t for different values of σ. It is seen that maximum concentration of FlgM increases as rate of production of FliA increases. Figure 17 displays the graph of $y(t)$ against t for different values of σ. It is seen that concentration of FliA decreases as rate of its production increases. Figure 18 displays the graph of $x(t)$ and $y(t)$ against t for fixed values of parameters. This shows the interaction between the two proteins.

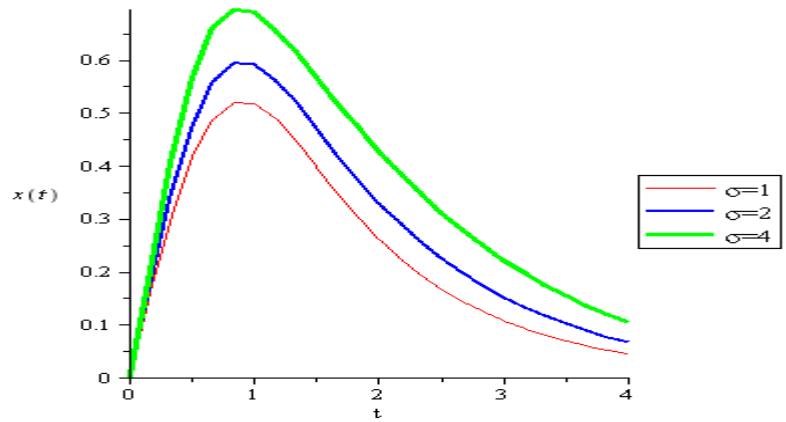

Figure 16: Plots of $x(t)$ against time t for equation (2.7) for different values of σ and α=1, k=1, δ=0.5.

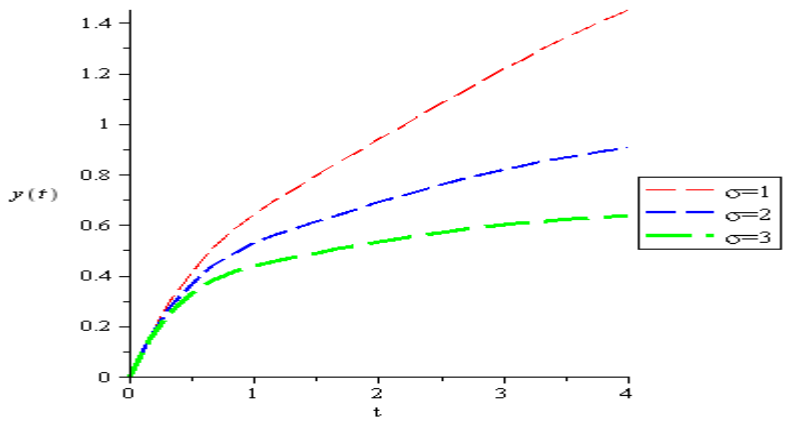

Figure 17: Plots of $y(t)$ against time t for equation (2.7) for different values of σ and α=1, k=1, δ=0.5.

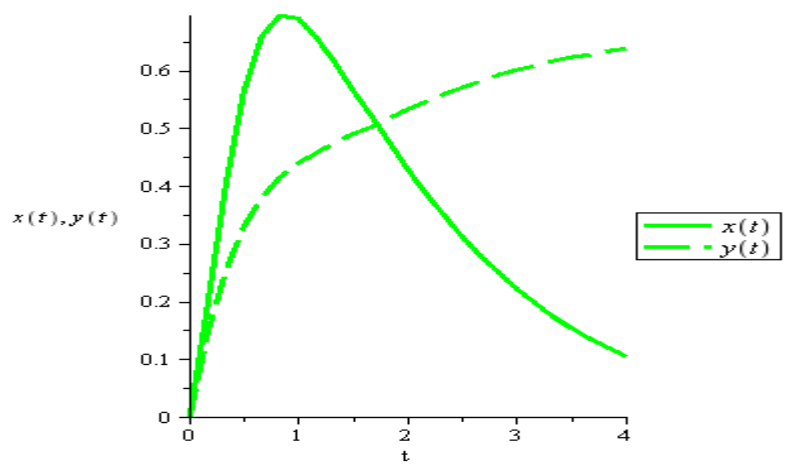

Figure 18: Plots of $x(t)$ and $y(t)$ against time t for equation (2.7) for different values of σ and α=1, k=1, δ=0.5.

5.0 Conclusion

For the relationship between the proteins FlgM and FliA, a linear stability analysis has been presented. The governing parameters of the problem are the rate of production of FlgM (α), rate of degradation of FlgM (β), rate of production of FliA (σ), and rate of degradation of FliA (δ). A computer symbolic algebraic package, MAPLE was used to numerically calculate the value of the FlgM and FliA with different parameter values using Runge-Kutta scheme with a modified version of the Newton-Raphson shooting method. Since the role of the FlgM regulatory protein is to prevent σ^{28}-dependent transcription of class 3 promoters prior to HBB completion. The results obtained in the work showed that this interaction between the two proteins is significantly influenced by the parameters involved.

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