ANALYSIS OF TWO TYPES OF CYCLIC BIOLOGICAL SYSTEM MODELS WITH TIME DELAYS

A THESIS

SUBMITTED TO THE DEPARTMENT OF ELECTRICAL AND

ELECTRONICS ENGINEERING

AND THE GRADUATE SCHOOL OF ENGINEERING AND SCIENCE

OF BILKENT UNIVERSITY

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

MASTER OF SCIENCE

By

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July 2011

I certify that I have read this thesis and that in my opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science.

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ABSTRACT

ANALYSIS OF TWO TYPES OF CYCLIC BIOLOGICAL SYSTEM MODELS WITH TIME DELAYS

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July 2011

In this thesis, we perform the stability analysis of two types of cyclic biological processes involving time delays. We analyze the genetic regulatory network having nonlinearities with negative Schwarzian derivatives. Using preliminary results on Schwarzian derivatives, we present necessary conditions implying the global stability and existence of periodic solutions regarding the genetic regulatory network. We also analyze homogenous genetic regulatory network and prove some stability conditions which only depend on the parameters of the nonlinearity function. In the thesis, we also perform a local stability analysis of a dynamical model of erythropoiesis which is another type of cyclic system involving time delay. We prove that the system has a unique fixed point which is locally stable if the time delay is less than a certain critical value, which is analytically computed from the parameters of the model. By the help of simulations, existence of periodic solutions are shown for delays greater than this critical value.

Keywords: Stability Analysis, Periodic Solutions, Monotone Dynamical System, Schwarzian Derivatives, Gene Regulatory Networks, Erythropoiesis, Poincaré Bendixson Theorem, Hill Functions, Time Delay.

ÖZET

ZAMAN GECİKMELİ İKİ DÖNÜŞSEL BİYOLOJİK SİSTEM MODELİNİN ANALİZİ

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Temmuz 2011

Bu tezde zaman gecikmeli iki farklı biyolojik sistem modelinin kararlılık analizi yapılmıştır. Zaman gecikmesi içeren gen düzenleyici sistem modelinin kararlılık analizi yapılmıştır. Bu modelde doğrusal olmayan öğelerin negatif Schwarz türevleri olduğu varsayılmıştır. Schwarz türevleri hakkında elde edilen sonuçlar kullanılarak, gen düzenleyici sistem modelinin kararlılığıyla ilgili sonuçlar ispatlanmıştır. Ayrıca periyodik çözümlerin oluşmasını sağlayan koşullar elde edilmiştir. Homojen gen düzenleyici sistem modeli incelenip kararlılığıyla ilgili sonuçlar bulunmuştur. Ayrıca zaman gecikmesi içeren doğrusal olmayan Eritropoez modelinin kararlılık analizi yapılmıştır. İlk önce belirtilen sistemin tek bir denge noktası olduğu ispatlanmış, daha sonra sistem bulunan denge noktası etrafında doğrusallaştırılmıştır. Sistemin gecikme değeri belli bir kritik değerin altında olması koşuluyla yerel kararlı olduğu gösterilmiştir. Simulasyonlar gecikmenin bu kritik değerden yüksek olduğunda periyodik çözümler üretmiştir.

Anahtar Kelimeler: Kararlılık Analizi, Monoton Dinamik Sistemler, Schwarz Türevi, Gen Düzenleyici Sistemler, Poincaré Bendixson Teoremi, Hill Fonksiyonları, Eritropoez, Zaman Gecikmesi.

ACKNOWLEDGMENTS

I would like to express my deep gratitude to my supervisor Prof. Dr. Hitay Özbay for his unlimited support, patience and guidance. I benefited a lot from his deep knowledge on the topics discussed in this work.

I would like to thank Prof. Dr. Ömer Morgül and Assist. Prof. Coşku Kasnakoğlu for reading and commenting on this thesis and for being on my thesis committee.

I would also like to express my deep gratitude to Dr. Silviu-lulian Niculescu, my co-advisor in the Bosphorus project, for his inspiring ideas and guidance.

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Dedicated to my Grandfather

Chapter 1

Introduction

1.1 Cyclic Biological Processes

The process of creating images of the human body is called medical imaging. After Wilhelm Conrad Röntgen discovered X-Rays in 1895, they have been widely used for the purpose of creating various images of the human body. Although there are side effects due to exposure to radiation, medical imaging has saved thousands of lives by early diagnosis of disease. Creating machines for medical imaging purposes not only requires medical knowledge but also requires advanced knowledge of engineering and physics. This lead to the birth of a new interdisciplinary field called Biomedical Engineering, which also deals with mathematical modeling of biological processes.

Since 1970s various models have been introduced for many different biological processes. Mathematical modeling of biological processes not only helps us to understand the underlying mechanisms better, but it also gives us a way of controlling them. For example, an effective and reliable model of a disease may help us determine correct therapeutic actions, e.g. the right amount of drug, or delivery time of the drug. In 1965, Goodwin has put forward a low-order dynamical system that became the milestone example of biochemical oscillatory networks under negative feedback [1]. In this thesis we deal with the analysis of two different biological systems (a) gene regulatory networks, and (b) formation of red blood cells in the human body (erythropoiesis).

By means of genes we pass our traits to our offspring. Gene expression is the process by which the gene information is converted. It has two main processes known as transcription and translation. In transcription, genes are copied into messenger RNA after which mRNA is decoded to make the corresponding protein. The transcription process is effected by the activities of regulatory proteins. The combination of these processes and interactions between regulatory proteins and mRNA are referred as gene regulatory network. Gene regulatory networks may be used to control various functions of living organisms since they play a very important role in the process of protein synthesization. In the first part of this thesis we will consider gene regulatory networks, which have the following general mathematical model:

$$\begin{aligned}
\dot{p}_1(t) &= -k_{p1}p_1(t) + f_{p1}(g_m(t-\tau_{gm})) \\
\dot{g}_1(t) &= -k_{g1}g_1(t) + f_{g1}(p_1(t-\tau_{p1})) \\
&\vdots \\
\dot{p}_m(t) &= -k_{pm}p_m(t) + f_{pm}(g_{m-1}(t-\tau_{g_{m-1}})) \\
\dot{g}_m(t) &= -k_{g1}g_m + f_{gm}(p_m(t-\tau_{pm})), \qquad (1.1)
\end{aligned}$$

where p_i and g_i represent the concentrations of protein and mRNA respectively and the constants k_i represent the degradation rates for mRNAs and proteins. This model has been first analyzed by Goodwin in [1]. It has a cyclic pattern which one can encounter in other fields of science as well. In [2], Townley *et al.* considered a model similar to (1.1). The early results regarding oscillatory behavior of the model (1.1) has been put forward by Hasting *et al.* [3]. These results have been generalized by Mallet-Paret in [4]. Their result basically says that the solution of the model (1.1) either converges to the equilibrium point or it is a nonconstant periodic solution. Basically, their result rules out any chaotic behavior. Then, Allwright presented a simple condition regarding the global attractivity of the unique equilibrium point, [5]. By using the results presented in [4] and [5], we will try to make an analysis of the model (1.1). We will analyze the system (1.1) with nonlinearities having negative Schwarzian derivatives. The concept of Schwarzian derivatives has been widely used in the analysis of nonlinear difference equations [6] as well as in projective geometry [7]. We will show in Chapter 2 that functions with negative Schwarzian derivatives have very special forms. By using the results from Chapter 2, in Chapter 3 we will present conditions regarding the stability and existence of oscillatory behavior of the model (1.1).

In Chapter 4, we will consider another vital biological process namely *erythropoiesis* which is the process of production erythrocytes known as red blood cells. The red blood cells are responsible of transporting oxygen to our body tissues, which is needed for energy production in our cells. We will consider a recent model of Erythropoiesis proposed by Lai *et al.* in [8]. We will show that the system in [8] has a unique equilibrium point which is locally stable for some values of the delay. A global analysis of the model is still an open problem.

The models studied in Chapters 3 and 4 fall into the category of cyclic nonlinear systems with time delays. Analysis of such systems have been investigated extensively in the literature [9], [10], [11] and [12]. There are various technique developed depending on the type of nonlinearity and interaction of the time delay with the nonlinearities. Here we use methods from [5], [4], [13] and [14] to analyze gene regulatory networks and erythropoiesis. Both systems have a feedback mechanism so techniques from feedback stability analysis are also used.

1.2 Literature Review

Note that we can rewrite the model (1.1) as follows:

$$\begin{aligned}
\dot{z}_1(t) &= -\lambda_1 z_1(t) + g_1(z_2(t-\tau_1)) \\
\dot{z}_2(t) &= -\lambda_2 z_2(t) + g_2(z_3(t-\tau_2)) \\
&\vdots \\
\dot{z}_n(t) &= -\lambda_n z_n(t) + g_n(z_1(t-\tau_n)).
\end{aligned} \tag{1.2}$$

If we do the following change of variables

$$x_i(t) := z_i(t-h_i), \qquad h_i = \sum_{k=1}^{i}(\tau_k), \tag{1.3}$$

we obtain the mathematical model (1.4) which is equivalent to (1.2):

$$\begin{aligned}
\dot{x}_1(t) &= -\lambda_1 x_1(t) + g_1(x_2(t)) \\
\dot{x}_2(t) &= -\lambda_2 x_2(t) + g_2(x_3(t)) \\
&\vdots \\
\dot{x}_n(t) &= -\lambda_n x_n(t) + g_n(x_1(t-\tau)),
\end{aligned} \tag{1.4}$$

where

$$\tau = \sum_{k=1}^{n}(\tau_k) = h_n. \tag{1.5}$$

In Chapter 3, we analyze the gene regulatory network (1.4) and present some results regarding its stability. In [15], Wang *et al.* analyzed a generalized version of the system (1.4) and by using the result of [4] they prove some conditions implying delay independent unstability of equilibrium points, for which case the system (1.4) has periodic solution for all positive values of the delay. In [10], Enciso considered the gene regulatory network (1.4) under negative feedback. He presented a global stability result by using the methods of [9], [16] and [17]. Moreover, by using a Hopf bifurcation approach he showed existence of periodic solutions for some cases. In [14], Muller *et al.* introduced a general model for repressilator and analyzed the model using the fact that Hill functions have negative Schwarzian derivatives. In the present work, we first prove that bounded functions with negative Schwarzian derivatives can only have two special forms and they can have at most three fixed points. Then by using the results of [4] and [5], we get the same global stability result of [10]. Different from [10] we will prove results regarding the stability of the linearized system. We will show that if the linearized system is unstable then system (1.4) has periodic solutions. Moreover, we give upper and lower bounds for possible periodic solutions of the system (1.4) under negative feedback. We also consider the homogenous genetic regulatory network under negative feedback with nonlinearities in the form of Hill functions and prove a result regarding the global stability of the homogenous system. Furthermore, we analyzed the system (1.4) under positive feedback which is to the author's knowledge has not been considered in the literature yet. We proved a global stability result regarding the positive feedback case by using the results presented in [18]. In [18], Smith makes a general analysis regarding the stability of monotone systems which includes the general regulatory network model we consider as a subcase. His results lead us conclude that the general solution of the system (1.4) under positive feedback converges towards an equilibrium point of it [18], [19]. We also analyzed the homogenous genetic regulatory network under positive feedback as a subcase.

In Chapter 4, we analyze the Erythropoiesis model proposed by Lai *et al.* in [8]. To the author's knowledge the model has not been investigated in the literature. In the present work we prove a local stability result regarding the Erythropoiesis model. But the nonlinearities involved in the model does not possess special patterns which makes it hard to make a global analysis of the model.

Chapter 2

Preliminary Results

2.1 Definitions and Notations

In this section we will try to present some basic definitions and notations that are frequently used in the thesis. Although most of the results presented in this chapter can be generalized to any inner product space, we will concentrate on $\mathbb{R}^n$ equipped with the usual Euclidean norm defined as

$$||x|| = \sqrt{x_1^2 + ... + x_n^2}, \qquad \text{for } x = (x_1, ..., x_n)^T \in \mathbb{R}^n. \tag{2.1}$$

A subset K of the vector space $\mathbb{R}^n$ over the field $\mathbb{R}$ is called a convex cone if for any scalars $\alpha\ , \beta\ \in\ \mathbb{R}_+$ and vectors x, $y \in K$ we have

$$\alpha x + \beta y \in K. \tag{2.2}$$

Since the biological parameters such as number of genes, enzymes, mRNA take positive values, we will analyze our systems in the cone $\mathbb{R}^n_+$ which is defined as

$$\mathbb{R}^n_+ = \{x \in \mathbb{R}^n : x_i \geq 0 \quad \forall i = 1, 2, ..., n\}. \tag{2.3}$$

The symbol $\mathbb{C}$ will denote the set of complex numbers and the set $\overline{\mathbb{C}}_+$ is defined as

$$\overline{\mathbb{C}}_+ = \{s \in \mathbb{C} : Re(s) \geq 0\}. \tag{2.4}$$

For a function

$$g(x) : K \to K, \tag{2.5}$$

where K is any set, $g^n(x)$ will denote the function which is the composition of $g(x)$ with itself n times. Given an interval $I \subseteq \mathbb{R}$, $D^n(I)$ will denote the set of n times continuously differentiable functions defined on the interval I. A function $f(x)$ defined from the normed linear space X to the normed linear space Y is bounded if

$$\exists M \geq 0 \quad \text{such that} \quad ||f(x)||_Y \leq M||x||_X \quad \forall x \in X. \tag{2.6}$$

A complex valued function f is said to belong to the set $\mathcal{H}^\infty$ if it is analytic and bounded in $\mathbb{C}_+$. The set $\mathcal{H}^\infty$ is a commutative ring with unity over itself [13]. For a function $f \in \mathcal{H}^\infty$, the infinity norm of f denoted as $||.||_\infty$ is defined as follows:

$$||f||_\infty = \text{ess} \sup_{s \in \mathbb{C}_+} |f(s)|. \tag{2.7}$$

Note that this definition makes sense since f is bounded and analytic in $\mathbb{C}_+$. Let $x(t)$ be a vector function depending on the variable t. A point $y \in \mathbb{R}^n$ is said to be an omega point of $x(t)$ if there is an increasing sequence $0 < t_i \to \infty$ and we have

$$\lim_{t_i \to \infty} (x(t_i)) = y.$$

The omega limit set of the solution $x(t)$ is the set of omega points of $x(t)$.

2.2 Linear Time Invariant Systems

Linear systems are commonly encountered in engineering, mathematics and economics. This chapter will present some basic results from Linear System Theory that will be used frequently in Chapters 3 and 4 of the thesis. A retarded linear time invariant (LTI) system with a single delay has the following state space representation:

$$\dot{x}(t) = A_0 x(t) + A_1 x(t-\tau), \qquad \tau > 0, \tag{2.8}$$

where $A_0,\ A_1 \in \mathbb{R}^{n\times n}$ and $x(t) \in \mathbb{R}^n$. Although the results we have in this section can easily be generated to multiple delay case, we will concentrate on single delay case as the mathematical models we will analyze in Chapters 3 and 4 have single delays.

Definition 1. *The characteristic function* $\chi(s)$ *associated with the system* (2.8) *is given by*

$$\chi(s) = det(sI - A_0 - A_1 e^{-\tau s}). \tag{2.9}$$

Definition 2. *The characteristic function* (2.9) *is said to be stable if*

$$\chi(s) \neq 0, \qquad \forall s \in \overline{\mathbb{C}}_+. \tag{2.10}$$

The system (2.8) *is said to be stable if its characteristic function is stable. The system* (2.8) *is said to be stable independent of delay if it is stable for all* $\tau \geq 0$.

For constant matrices A_0, A_1, *the characteristic equation of the system* (2.8) *will be in the following form:*

$$\chi(s) = p_0(s) + p_1(s)e^{-\tau s} = 0, \tag{2.11}$$

where $p_0(s)$, $p_1(s)$ *are polynomials of degree* n *and* $n-1$ *respectively.*

Notice that when $p_0(s)$ and $p_1(s)$ in (2.11) do not have a common zero in $\overline{\mathbb{C}}_+$, we have

$$\chi(s_0) = 0 \quad \text{for some } s_0 \in \overline{\mathbb{C}}_+ \qquad \Leftrightarrow \qquad 1 + \frac{p_1(s_0)e^{-\tau s_0}}{p_0(s_0)} = 0. \tag{2.12}$$

We will now present a Lemma which is commonly known as the Small-Gain Theorem.

Lemma 1. *Let* $g(s), h(s) \in \mathcal{H}^\infty$ *such that*

$$||gh||_\infty < 1.$$

Then, the characteristic function

$$\chi(s) = 1 + g(s)h(s)e^{-\tau s}$$

is stable for all $\tau \geq 0$.

Proof. For fixed τ, we know that the characteristic function

$$\chi(s) = 1 + g(s)h(s)e^{-\tau s}$$

is stable if

$$\chi(s) \neq 0, \qquad \forall s \in \mathbb{C}_+.$$

Suppose for some $s_0 \in \mathbb{C}_+$, we have

$$\begin{aligned} \chi(s_0) = 1 \quad &+ \quad g(s_0)h(s_0)e^{-\tau s_0} = 0 \\ &\Rightarrow \quad g(s_0)h(s_0)e^{-\tau s_0} = -1 \\ &\Rightarrow \quad |g(s_0)h(s_0)| \geq 1 \\ &\Rightarrow \quad ||gh||_\infty \geq 1, \end{aligned}$$

which contradicts the fact that $||gh||_\infty < 1$. □

As a corollary of Lemma 1, we have the following result.

Lemma 2. *Let* $G \in \mathcal{H}^\infty$, *then for all* $|k| < ||g||_\infty^{-1}$ *the characteristic equation*

$$\chi(s) = 1 + kG(s)e^{-\tau s} \tag{2.13}$$

is stable independent of delay.

Proof. Let $h(s) = k$, then we have

$$||Gh||_\infty < 1$$

and the result follows from Lemma 1. □

Consider a characteristic function of the form (2.13), then $\omega_c > 0$ is called a gain crossover frequency of the characteristic equation if we have

$$|kG(j\omega_c)| = 1. \tag{2.14}$$

Similarly, we call ω_g a phase crossover frequency of the characteristic equation if

$$cos(\angle k + \angle G(j\omega_g)) = -1. \tag{2.15}$$

Let us now analyze a characteristic function of the following form:

$$\chi(s) = 1 + \frac{ke^{-\tau s}}{(s+a_1)...(s+a_n)} = 0 \qquad k \in \mathbb{R}, \qquad a_i \in \mathbb{R}_+. \tag{2.16}$$

We will now present a Lemma regarding the stability of a characteristic equation in the form (2.16). The proof of the Lemma will require the famous Nyquist criteria in control theory. One may check [20] or any other introductory material on control theory for a proof of the Nyquist result. Basically, Nyquist criteria says that the characteristic equation (2.16) is stable if its Nyquist plot does not encircle the point -1.

Lemma 3. *Consider a characteristic equation in the form* (2.16) *and let*

$$K_l = \prod_{i=1}^{n}(a_i). \tag{2.17}$$

Then one of the following holds:

1. *If* $0 < k < K_l$*, then* $\chi(s)$ *is stable independent of delay.*
2. *If* $K_l \leq k \leq K_u$*, then* $\chi(s)$ *is stable* $\forall \tau < \tau_m$ *and unstable* $\forall \tau \geq \tau_m$*, where* τ_m *is smallest positive number satisfying*

$$\tau = \frac{1}{\omega_c}\left(2\pi h + \pi - \sum_{i=1}^{n}\arctan(\frac{\omega_c}{a_i})\right), \qquad h \in \mathbb{Z}$$

where $\omega_c > 0$ *is the unique gain crossover frequency satisfying the following equation:*

$$\prod_{i=1}^{n}(\omega_c^2 + a_i^2) = k^2$$

and K_u is given by the following formula

$$K_u \quad = \quad \sqrt{\prod_{i=1}^{n}(\omega_g^2 + a_i^2)},$$

where $\omega_g > 0$ is the smallest ω satisfying

$$cos\left(\prod_{i=1}^{n}\left(arctan\left(\frac{\omega}{a_i}\right)\right)\right) = -1.$$

3. *If $k \geq K_u$, then $\chi(s)$ is unstable independent of delay.*

4. *If $-K_l < k < 0$, then $\chi(s)$ is stable independent of delay.*

5. *If $k \leq -K_l$, then $\chi(s)$ is unstable independent of delay.*

Proof. For fixed $a_i \in \mathbb{R}_+$, let $\chi(s)$ be a characteristic equation in the form (2.16). We have

$$\begin{aligned} \left|\frac{ke^{-\tau j\omega_c}}{(j\omega_c + a_1)......(j\omega_c + a_n)}\right| &= 1 \\ &\Leftrightarrow \prod_{i=1}^{n}(\omega_c^2 + a_i^2) = k^2. \end{aligned}$$

But $h(\omega) = \prod_{i=1}^{n}(\omega^2 + a_i^2)$ is an increasing function of ω and

$$h(0) = \prod_{i=1}^{n}(a_i^2), \qquad h(\infty) = \infty.$$

Therefore if $k \geq K_l$, we have unique ω_c satisfying

$$\prod_{i=1}^{n}(\omega_c^2 + a_i^2) = k^2.$$

Let $G_\tau(s)$ be defined as

$$G_\tau(s) = \frac{e^{-\tau s}}{\prod_{i=1}^{n}(s + a_i)}.$$

If k satisfies the condition given in Part 1 and 4, then we

$$||kG_\tau(s)||_\infty < 1 \qquad \forall \tau \geq 0$$

and the result follows from Lemma 2. For the proof of part 2 and 3, suppose that we have

$$k \geq \prod_{i=1}^{n}(a_i) = K_l$$

and consider the delay free system

$$f(s) = 1 + kG_0(s). \tag{2.18}$$

Since the roots of the characteristic function $f(s)$ depends continuously on the parameter k, we conclude that $f(s)$ is stable for all $k < K_u$ where K_u is the smallest positive number such that the characteristic equation

$$1 + K_u G(s) = 0 \tag{2.19}$$

has a root on the imaginary axis [21]. That is $\exists\ \omega_g > 0$ such that

$$\begin{aligned} 1 + K_u G_0(j\omega_g) &= 0 \\ &\Rightarrow K_u = -\prod_{i=1}^{n}(j\omega_g + a_i) \\ &\Rightarrow K_u = \sqrt{\prod_{i=1}^{n}(w_g^2 + a_i^2)}, \end{aligned}$$

where ω_g is the smallest positive number satisfying

$$cos\left(\prod_{i=1}^{n}\left(arctan\left(\frac{\omega_g}{a_i}\right)\right)\right) = -1.$$

If $k \geq K_u$ then we have

$$kG_0(j\omega_g) \leq -1$$

so the Nyquist plot of the delay free system encircles the point -1 and the delay free system is unstable by Nyquist criteria. Hence, if we have

$$K_l \leq k \leq K_p$$

then the delay free system is stable. By the continuous dependence of the roots on the parameter τ, we know that the system will be stable for all $\tau < \tau_m$ where at τ_m is the smallest positive number such that for $\tau = \tau_m$ the characteristic function $\chi(s)$ has a root on the imaginary axis [21]. That is $\exists\ \omega_c \geq 0$ satisfying

$$1 + \frac{ke^{-j\tau_m\omega_c}}{\prod_{i=1}^{n}(j\omega_c + a_i)} = 0,$$

where ω_c is the unique frequency satisfying

$$\prod_{i=1}^{n}(\omega_c^2 + a_i^2) = k^2$$

and τ_m is the smallest positive number satisfying

$$\tau_m = \frac{1}{\omega_c}\left(2\pi h + \pi - \sum_{i=1}^{n} arctan(\frac{\omega_c}{a_i})\right), \qquad \text{for some } h \in \mathbb{Z}.$$

Note that τ_m depends on k and we have

$$\tau_m(K_u) = 0 \qquad \tau_m(K_l) = \infty. \tag{2.20}$$

If $\tau \geq \tau_m$, we have

$$\angle(ke^{-\tau j\omega_c}G(j\omega_c)) < -\pi \tag{2.21}$$

since both

$$\tau\omega, \qquad \sum_{i=1}^{n} arctan(\frac{\omega}{a_i}) \tag{2.22}$$

are increasing functions of ω. But (2.21) and (2.22) implies that for $\tau \geq \tau_m$ the Nyquist plot of $\chi(s)$ will encircle the point -1 more than once so $\chi(s)$ is unstable for $\tau \geq \tau_m$. For part 3 of the Lemma, we have shown that if

$$k \geq K_p,$$

then the delay free characteristic function is unstable and with the same arguments as part 2 of the Lemma, the characteristic function will remain unstable as we increase delay. For the proof of part 5 of the Lemma, note that for $k \leq -K_l$ and any positive delay we have

$$\chi(0) \leq 0, \qquad \chi(\infty) = 1 \qquad \forall \tau \geq 0.$$

Intermediate theorem implies that $\exists\ y \in \mathbb{R}_+$ such that

$$\chi(y) = 0 \quad \forall \tau \in \mathbb{R}_+. \tag{2.23}$$

Equation (2.23) proves that the characteristic function is unstable independent of delay. □

Although the systems we will consider in Chapters 3 and 4 are nonlinear, we need Lemma 3 to determine the stability of the linearized systems. We will use the fact that the linearized system and nonlinear system have similar local behavior around the vicinity of an equilibrium point of the nonlinear system.

2.3 Functional Differential Equations

Most of the processes we observe in the nature can not be accurately modeled by means of linear systems. Some processes involve nonlinearities, other processes involve both nonlinearities and time delays at the same time. Such systems are modeled by the help of functional differential equations. The biological systems we will consider in Chapters 3 and 4 are nonlinear and also have lumped delays. Therefore, we need to present some results that are widely used in the analysis of Functional Differential Equations. A general model for a nonlinear process is given by

$$\dot{x} = f(t, x(t), x(t-\tau)), \qquad t \in \mathbb{R}_+,\ x(t) \in\ \mathbb{R}^n,\ f : \mathbb{R}^n \to \mathbb{R}^n. \tag{2.24}$$

Most of the physical systems that are modeled are casual. Therefore, we assume in (2.24) that

$$\tau \geq 0. \tag{2.25}$$

If the function $f(t, x(t), x(t-\tau))$ in (2.24) does not explicitly depend on t, the system (2.24) is called autonomous. Otherwise, it is called nonautonomous. In Chapters 3 and 4, we will deal with autonomous systems. Therefore, in this section we will concentrate on autonomous systems. For the rest of the thesis we will assume that our system has the following general form:

$$\dot{x} = f(x(t), x(t-\tau)), \qquad x(t) \in\ \mathbb{R}^n,\ \tau \geq 0,\ f : \mathbb{R}^n \to \mathbb{R}^n. \tag{2.26}$$

To find a solution of a functional differential equation (2.26), we need to know initial values of the states. It is clear that for a system without a delay to find a solution for $t > t_0$ we need to know a single vector $x(t_0)$, where $t_0 \in \mathbb{R}$ is our initial time. For systems with a delay to find a unique solution of the system, we need to know the value of x not only at present but we also need a knowledge of the past. That is we need to know

$$x(\theta) \qquad \text{for} \qquad t_0 - \tau \leq \theta \leq t_0, \tag{2.27}$$

where t_0 is the initial time. An excellent book on the analysis of functional differential equations is [22] and it also contains results on the existence, uniqueness and continuous dependence of the solutions on initial conditions which is beyond the scope of this work. The systems we will consider in Chapters 3 and 4 satisfy the technical conditions given in [22] so that the systems we will analyze have unique solutions which depend continuously on initial conditions. Let us move to another concept related to the analysis of functional differential equations which is the concept of an equilibrium point. The constant vector 0 is called an equilibrium point of the system (2.26), if $f(0,0) = 0$. The linearization of system (2.26) around the equilibrium point 0 given by the following:

$$\dot{x} = Ax(t) + Bx(t-\tau), \qquad x(t) \in \mathbb{R}^n,\ A,\ B\ \in \mathbb{R}^{n\times n}, \tag{2.28}$$

where

$$A_{i,j} = \left.\frac{\partial f_i}{\partial x_j}\right|_{x=0},\ B_{i,j} = \left.\frac{\partial f_i}{\partial x_j(t-\tau)}\right|_{x=0}. \tag{2.29}$$

The linearization of the system around its equilibrium points play an important role in the analysis of functional differential equations. In fact, we know that if the characteristic equation of the linearized system (2.28) is stable, then the equilibrium point around which the linearization is done is locally stable. In other words, the solutions with initial conditions in some neighborhood of the equilibrium point will converge to the equilibrium point. In some special cases one can conclude satisfactory information regarding the general behavior of a system by just looking the linearization of it around its equilibrium points.

2.4 Schwarzian Derivatives

The concept of Schwarzian derivative is widely used in predicting the periodic orbits of nonlinear difference equations [6]. It is also commonly used in Projective differential geometry with a proper generalization to $\mathbb{R}^n$[7]. In this work, we will only need some basic properties of the Schwarzian derivatives of functions defined on an interval.

Let f be a continuous, three times differentiable function from $I = (a, b)$ with $-\infty \leq a < b \leq \infty$ to an interval $J \subseteq \mathbb{R}$. The Schwarzian derivative of the function f [6], denoted by $Sf(x)$, is defined as

$$Sf(x) = \begin{cases} -\infty & \text{if } f^{'}(x) = 0 \\ \dfrac{f'''(x)}{f'(x)} - \dfrac{3}{2}\left(\dfrac{f''(x)}{f'(x)}\right)^2 & \text{if } f^{'}(x) \neq 0 \end{cases} \tag{2.30}$$

In this work, we are dealing with functions satisfying one of the following conditions:

$$f^{'}(x) > 0 \quad \text{or} \quad f^{'}(x) < 0 \quad \forall x \in (0, \infty). \tag{2.31}$$

Therefore, $Sf(x) > -\infty$ for the class of functions we are interested in. Some immediate results which can be deduced from definition (4) are as follows:

Lemma 4. *[6] Let $I \subseteq R$ be an interval and suppose $f,\ g \in D^3(\mathbb{R}_+)$ such that the function $f \circ g(x)$ is well-defined. Suppose also that we have*

$$f^{'}(x) \neq 0 \qquad \forall x \in (0, \infty), \tag{2.32}$$

then the following hold:

1. *For any $c \in \mathbb{R}$ and $d \in \mathbb{R}\backslash\{0\}$, $Sf(x) = S(f(x)+c)$ and $Sf(x) = S(df(x))$.*

2. *$S(f \circ g)(x) = Sf(g(x)) \cdot g^{'}(x)^2 + Sg(x)$.*

3. *If $Sf(x) \leq 0$, $Sg(x) < 0$ then $S(f \circ g)(x) < 0$.*

4. *If* $Sf(x) < 0 \ \ \forall x \in int(I)$*, then* $f^{'}$ *cannot have positive local minima nor negative local maxima.*

Proof. 1. Observe that $f^{'}(x) = (f(x)+c)^{'}$ which proves $Sf(x) = S(f(x)+c)$. We also have

$$\begin{aligned} f^{'''}(x)/f^{'}(x) &= (df^{'''}(x))/(df^{'}(x)) \\ f^{''}(x)/f^{'}(x) &= (df^{''}(x))/(df^{'}(x)). \end{aligned}$$

Therefore $Sf(x) = S(df(x))$.

2. The following set of equations will give us the desired result:

$$\begin{aligned} (f\circ g)^{'}(x) &= f^{'}(g(x))g^{'}(x) \\ (f\circ g)^{''}(x) &= f^{''}(g(x))g^{'}(x)^2 + f^{'}(g(x))g^{''}(x) \\ (f\circ g)^{'''}(x) &= f^{'''}(g(x))(g^{'}(x))^3 + 3f^{''}(g(x))g^{''}(x)g^{'}(x) + f^{'}(g(x))g^{'''}(x) \\ S(f\circ g)(x) &= \frac{(f\circ g)^{'''}}{(f\circ g)^{'}(x)} - \frac{3}{2}\left(\frac{(f\circ g)^{''}(x)}{(f\circ g)^{'}(x)}\right)^2 \\ &= \frac{g^{'''}(x)}{g^{'}(x)} + 3\frac{f^{''}(g(x))g^{''}(x)}{f^{'}(g(x))} + \frac{f^{'''}(g(x))g^{'}(x)^2}{f^{'}(g(x))} \\ &- \frac{3}{2}\left(\frac{f^{''}(g(x))g^{'}(x)}{f^{'}(g(x))} + \frac{g^{''}(x)}{g^{'}(x)}\right)^2 \\ &\Rightarrow S(f\circ g)(x) = Sf(g(x))g^{'}(x)^2 + Sg(x). \end{aligned}$$

3. Since we have

$$Sf \leq 0, \quad Sg < 0 \quad \text{and} \quad g^{'}(x)^2 \geq 0 \ \ \forall x \in int(I), \tag{2.33}$$

part 2 of the Lemma implies that

$$S(f\circ g)(x) = Sf(g(x))g^{'}(x)^2 + Sg(x) < 0. \tag{2.34}$$

4. Suppose $f^{'}$ has a positive local minima at $x \in int(I)$, then we have

$$\begin{aligned} f^{'}(x) &> 0, \quad f^{''}(x) = 0, \quad f^{'''}(x) \geq 0 \\ &\Rightarrow Sf(x) > 0 \end{aligned}$$

which is a contradiction. Similarly, suppose that $f^{'}$ have negative local maxima at x, and let

$$h(x) = -f(x).$$

Then, the function $h^{'}$ will have a positive local minima at x and from part 1 we have

$$Sh(x) = Sf(x) < 0. \tag{2.35}$$

We have shown that $h^{'}$ can not have positive local minima so $f^{'}$ can not have negative local maxima.

□

Let us now calculate Schwarzian derivatives of some functions which are commonly seen as nonlinearities in the modeling of physical systems, which includes the Hill functions. Hill functions appear as nonlinearities in the gene regulatory network we will consider in Chapter 3.

Example 2.4.1. Let us start with the exponential function

$$\begin{aligned} S(e^{ax}) &= -\frac{a^2}{2}. \\ S(e^{-ax}) &= -\frac{5a^2}{2}. \end{aligned}$$

In real life problems, we commonly encounter Hill function type nonlinearities. Hill functions have the following general form:

$$f(x) = \frac{a}{b + x^m} + c, \qquad g(x) = \frac{ax^m}{b + x^m} + c \quad a, b > 0 \quad c \geq 0 \quad m \in \mathbb{N}. \tag{2.36}$$

We will now calculate Schwarzian derivatives of Hill functions in the interval $(0, \infty)$. From Lemma 4, we know addition and multiplication with a constant does not change the value of the Schwarzian derivative, so we will, without loss of generality, calculate the Schwarzian derivative of the following functions

$$f(x) = \frac{1}{b + x^m}, \quad g(x) = \frac{x^m}{b + x^m} \qquad b > 0. \tag{2.37}$$

Notice that

$$f(x) = \frac{1}{b+x^m} = -\frac{1}{b}\left(\frac{x^m}{b+x^m} - 1\right) = -\frac{1}{b}\left(g(x) - 1\right).$$

Then from Lemma 1, we have

$$Sf(x) = Sg(x) = S\left(\frac{1}{b+x^m}\right).$$

Therefore, without loss of generality, we will only calculate $Sf(x)$. For this purpose, let

$$h_1(x) = b + x^m, \quad h_2(x) = \frac{1}{x}.$$

Then, we have

$$\begin{aligned} f(x) &= h_2 \circ h_1(x), \\ &\Rightarrow Sf(x) = S(h_2 \circ h_1)(x) = Sh_2(h_1(x))h_1^{'}(x)^2 + Sh_1(x) \\ &\quad Sh_1(x) = -\frac{(m^2-1)}{x^2}, \quad Sh_2(x) = 0 \\ &\Rightarrow Sf(x) = -\frac{(m^2-1)}{x^2}. \end{aligned}$$

Lastly, let us calculate the Schwarzian derivative of the tangent hyperbolic function defined as

$$f(x) = a\ \tanh(bx) = a\left(\frac{e^{2bx}-1}{e^{2bx}+1}\right) \qquad a, b \in \mathbb{R}_+.$$

For this purpose, let

$$g(x) = e^{2bx}, \qquad h(x) = \frac{x-1}{x+1}, \tag{2.38}$$

then $f(x) = h \circ g(x)$ and we have

$$\begin{aligned} Sg(x) &= -2b^2 \\ Sh(x) &= 0 \\ &\Rightarrow Sf(x) = S(h \circ g)(x) = -2b^2 < 0. \end{aligned}$$

As a corollary of Example 2.2.1, we have the following result.

Lemma 5. *Let a,b > 0, $c \geq 0$ and $m \in \mathbb{N}$ be constants. Suppose f and g are Hill functions of the form* (2.36). *Then one of the followings holds:*

1. *If $m = 1$, then $Sf(x) = Sg(x) = 0$.*
2. *If $m > 1$, then $Sf(x) = Sg(x) < 0$.*
3. *If $h(x) = a$ tanh(bx), then S(h(x))< 0.*

The most important property of functions having negative Schwarzian derivatives is presented in part 4 of Lemma 4. There we proved that the derivatives of functions with negative Scwarzian derivatives can not possess positive local minima or negative local maxima.

2.5 Fixed Points

Fixed points of functions play very important role in the analysis of nonlinear systems. In this section we first state some easy remarks regarding fixed points of functions, then we will concentrate on determining fixed points of functions having negative Schwarzian derivatives. Let us start with the definition of a fixed point.

Definition 3. *Let $f(x) : X \to Y$ be a function, then the point $x \in X$ is called a fixed point of f, if*

$$f(x) = x.$$

The functions of interest in this thesis are defined from $X \subseteq \mathbb{R}^n$ to $Y \subseteq \mathbb{R}^n$. When $n = 1$, we will assume that f is defined on an interval $X = (a, b) \subseteq \mathbb{R}$ and $f \in D^3(I)$. Let us present two basic results regarding the fixed points of functions:

Lemma 6. *Let $f : I \to K$ be a decreasing function, where I and K are intervals. Then, f can have at most one fixed point. Moreover, if $I = \mathbb{R}_+ = [0, \infty)$ and $f(0) \geq 0$, then f has a unique fixed point.*

Proof. Suppose that there exists $x < y$ such that $f(x) = x$ and $f(y) = y$. Since f is a decreasing function $x = f(x) \geq f(y) = y$ which is obviously a contradiction. For the second part of the Lemma, let

$$g(x) = x - f(x).$$

Then, g is increasing and we have

$$g(0) = -f(0) \leq 0, \quad g(\infty) = \infty,$$

so by intermediate value theorem $\exists x_0 \in [0, \infty)$ satisfying

$$\begin{aligned} g(x_0) &= f(x_0) - x_0 = 0 \\ &\Rightarrow f(x_0) = x_0. \end{aligned}$$

Hence, f has at least one fixed point. The uniqueness follows from the first part of the Lemma. □

Lemma 7. *Let $f : I \to K$ be a differentiable function, where I and K are intervals. If we have*

$$|f'(x)| < 1 \qquad \forall x \in I,$$

then f can have at most one fixed point.

Proof. Suppose there exists $x < y$ such that $f(x) = x$ and $f(y) = y$. Then, by mean value theorem, there exists $z \in (x, y)$ satisfying

$$f'(z) = \frac{f(y) - f(x)}{y - x} = 1.$$

But this contradicts the assumption that

$$|f'(x)| < 1.$$

Hence, f can have at most one fixed point. □

After these two basic Lemmas, we present the following result which reduces the process of finding the fixed points of some multidimensional functions defined on the cone $\mathbb{R}_+^n$ to find the fixed points of a function defined on $\mathbb{R}_+$:

Lemma 8. *Let* $h(x) : \mathbb{R}_+^n \to Y \subseteq \mathbb{R}_+^n$ *be defined as*

$$h(x_1, x_2, ..., x_n) = \begin{pmatrix} h_1(x_2) \\ \vdots \\ h_{n-1}(x_n) \\ h_n(x_1) \end{pmatrix},$$

where

$$h_i(z_i) : \mathbb{R}_+ \to Y_i \subseteq \mathbb{R}_+ \qquad \forall i = 1, 2, ..., n.$$

Let the function $q(t)$ *from* $\mathbb{R}_+$ *to* $Y_1 \subseteq \mathbb{R}_+$ *be defined as*

$$q(t) = h_1 \circ h_2 \circ ... \circ h_n(t). \tag{2.39}$$

The number fixed points of the functions h *and* q *have the same cardinality. In particular, if* q *is a decreasing function or we have*

$$|h_i^{'}(z)| < 1 \quad \forall z \in \mathbb{R}_+ \quad \forall i = 1, ..., m$$

then the function h *has a unique fixed point.*

Proof. Let $x = (x_1, x_2, ..., x_n)$ be a fixed point of h. Then, the following holds:

$$\begin{aligned} x_1 &= h_1(x_2) \\ x_2 &= h_2(x_3) \\ &\vdots \\ x_n &= h_n(x_1) \\ &\Rightarrow x_1 = h_1(x_2) = h_1 \circ h_2(x_3) = ... = h_1 \circ h_2 \circ ... \circ h_n(x_1) = q(x_1) \end{aligned}$$

Hence, x_1 is a fixed point of q. Conversely, assume that

$$q(x_1) = x_1,$$

and let

$$u = (x_1, h_2 \circ ... \circ h_n(x_1), h_3 \circ ... \circ h_n(x_1), ..., h_n(x_1)).$$

It is easy to check that this special u satisfies $h(u) = u$. Note that if x, y are fixed points of h such that $x_1 = y_1$, then we have

$$\begin{aligned} x_n &= h_n(x_1) = h_n(y_1) = y_n \\ x_{n-1} &= h_{n-1}(x_n) = h_{n-1}(y_n) = y_{n-1} \\ &\vdots \\ x_2 &= h_2(x_3) = h_2(y_3) = y_2, \end{aligned}$$

which implies that

$$x = y.$$

So for any fixed point of q, we can find a unique fixed point of h. Therefore, the number of fixed points of h and q can be bijectively mapped to each other and has the same cardinality. Assume that q is a decreasing function and we have

$$q(0) \geq 0.$$

By Lemma 6, g has a unique fixed point. Since the fixed points of h have the same cardinality as the fixed points of the function q, h has a unique fixed point. Also note that

$$|h_i^{'}(z_i)| < 1 \quad \forall i = 1, ..., n \Rightarrow |q^{'}(t)| < 1 \quad \forall t \in \mathbb{R}_+,$$

so q has a unique fixed point which implies that h has a unique fixed point. $\square$

Lemma 9. *Let*

$$h(x) = \frac{a(x)}{b(x)},$$

where a and b are polynomials with

$$k = max(deg(a)), deg(b)) + 1.$$

Then, h has at most k fixed points.

Proof. Suppose x is a fixed point of h, then we have

$$\begin{aligned} x &= \frac{a_0 + a_1 x + ... + a_n x^n}{b_0 + b_1 x + ... + b_m x^m} = \frac{a(x)}{b(x)} \\ &\Rightarrow \; b_0 x + b_1 x + ... + b_m x^{m+1} - (a_0 + a_1 x + ... + a_n x^n) = 0 \\ &\Rightarrow \; p(x) = c_0 + c_1 x + ... + c_k x^k = 0. \end{aligned}$$

By fundamental theorem of algebra a polynomial of degree k can have at most k zeros, so p can have at most k zeros. Therefore, h has at most k fixed points. $\square$

Lemma 10. *Let $h(x) : \mathbb{R}_+ \to Y \subseteq \mathbb{R}_+$ be a bounded function. Suppose that there exists a function $G(s)$ which is analytic in $\mathbb{C}_+$ and we have*

$$G(x) = h(x) \qquad \forall x \in \mathbb{R}_+.$$

Then, h has finitely many fixed points.

Proof. Suppose that the function h has infinite number of fixed points in $\mathbb{R}_+$. Then, the set of fixed points of h is bounded and contains infinitely many elements. Therefore, by the famous Bolzano-Weirstrass theorem the set of fixed points of $h(x)$ has an accumulation point. Let

$$H(s) = G(s) - s.$$

It can be seen that $H(s)$ is analytic in $\mathbb{C}_+$. For any fixed point x of h we have

$$H(x) = 0.$$

Since the zeros of h has an accumulation point in $\mathbb{R}_+ \subseteq \mathbb{C}_+$, the zeros of the analytic function $H(s)$ has an accumulation point in $\mathbb{C}_+$ which implies that

$$H(s) = 0 \qquad \forall s \in \mathbb{C}_+.$$

Therefore, we have

$$h(x) = x \qquad \forall x \in \mathbb{R}_+, \tag{2.40}$$

which is a contradiction to the boundedness of h. $\square$

Let us give some examples to illustrate this Lemma:

Example 2.5.1. As a first example, let us consider the function e^{-x}. It has an analytic extension e^{-s} so e^{-x} can have finitely many fixed points. In fact, it has a unique fixed point. The functions $\cos x$, $\sin x$, $\tanh x$ have also bounded analytic extensions so they can have finite number of fixed points. In the models of physical process, we encounter rational polynomials, exponentials, hyperbolic functions which have finite number of fixed points. But one can construct interesting functions that are infinitely many times differentiable on the real line but have a Taylor series with a radius of convergence 0 everywhere. As an example of such a function, one may refer to page 418 of [23].

Functions with negative Schwarzian derivatives, which include exponential function, Hill functions and tangent hyperbolic function, are frequently encountered as nonlinearities in the modeling of real life processes. We will now present some interesting results regarding the fixed points of functions having negative Schwarzian derivatives. Let us start with the following two Lemmas:

Lemma 11. *Let h be a three times differentiable function from $\mathbb{R}_+$ to $Y \subseteq \mathbb{R}_+$ and suppose that we have*

$$-\infty < Sh(x) < 0 \qquad \forall x \in (0, \infty).$$

Then $h^{'}$ can not be constant for any $[a, b] \subseteq (0, \infty)$ with $a < b$.

Proof. Suppose on the contrary that there exists positive constants $a < b$ such that $h^{'}$ is constant in $[a, b]$. Let $c \in (a, b)$, then $h^{''}(c) = 0 = h^{'''}(c)$ but this implies that

$$Sh(c) = 0,$$

which is a contradiction. Therefore, $h^{'}$ can not be constant in any subinterval of $\mathbb{R}_+$. □

Lemma 12. *Let h be a three times differentiable function defined from $\mathbb{R}_+$ to $Y \subseteq \mathbb{R}_+$ and suppose that*

$$Sh(x) < 0 \quad \textit{and} \quad h^{'}(x) > 0 \qquad \forall x \in (0, \infty).$$

Then if $h^{''}(c) < 0$ for some $c \in \mathbb{R}_+$ then we have

$$h^{''}(d) \leq 0 \qquad \forall d \geq c. \tag{2.41}$$

Proof. Suppose there exists positive real numbers $c < d$ such that $h^{''}(c) < 0$ and $h^{''}(d) > 0$. Let I be defined as

$$I = [c, d]. \tag{2.42}$$

Since $h^{'}$ is a continuous function and I is a compact set $\exists$ x_1, x_2 $\in I$ such that

$$h^{'}(x_1) \leq h^{'}(x) \leq h^{'}(x_2), \qquad \forall x \in I.$$

But since $h^{''}(c) < 0$, $\exists y \geq c$ satisfying

$$h^{'}(y) < h^{'}(c). \tag{2.43}$$

Similarly, since $h^{''}(d) > 0$ $\quad \exists z \leq d$ satisfying

$$h^{'}(z) < h^{'}(d). \tag{2.44}$$

Equations (2.43) and (2.44) implies that

$$x_1 \neq c \quad \text{and} \quad x_1 \neq d \tag{2.45}$$

and we have

$$h^{'}(x_1) \leq h^{'}(x) \qquad \forall x \in I.$$

Hence, by definition, x_1 is a positive local minima of the function $h^{'}$. But since $Sh(x) < 0$, $h^{'}$ can not have a positive local minima. Therefore, we have

$$h^{''}(d) \leq 0 \qquad \forall d \geq c. \tag{2.46}$$

□

Now suppose that a function h, having the technical assumptions of Lemma 12, satisfies

$$h^{''}(y) = 0, \qquad h^{'}(y) > 0 \tag{2.47}$$

for some $y \in (0, \infty)$. Then we have

$$\begin{aligned} Sh(y) &= \frac{h^{'''}(y)}{h^{'}(y)} - \frac{3}{2}\left(\frac{h^{''}(y)}{h^{'}(y)}\right)^2 && (2.48) \\ &= \frac{h^{'''}(y)}{h^{'}(y)} < 0 && (2.49) \\ &\Rightarrow \; h^{'''}(y) < 0, && (2.50) \end{aligned}$$

which implies that the point y is a positive local maxima of the function $h^{'}$. Combining Lemma 12 and (2.50) we can conclude that if $h^{'}$ will be decreasing in some interval $[a, b]$ then it will be decreasing in $[b, \infty]$. In particular, if $h^{''}(0) < 0$ then $h^{''}(x) \leq 0$ for all $x \geq 0$ which implies that $h^{'}(x)$ is a decreasing function. Combining this fact with Lemmas 11 and 12, we obtain the following result.

Corollary 2.5.1. *Let h be a three times differentiable function defined from $\mathbb{R}_+$ to $Y \subseteq \mathbb{R}_+$ and suppose that we have*

$$Sh(x) < 0 \qquad \text{and} \qquad h^{'}(x) > 0 \qquad \forall x \in (0, \infty)$$

Then $h^{'}$ is a function from $\mathbb{R}_+$ to $Y \subseteq \mathbb{R}_+$ satisfying one of the following properties:

1. *$h^{'}$ is a strictly increasing function on $[0, \infty]$.*
2. *$h^{'}$ is a strictly decreasing function on $[0, \infty]$.*
3. *There exists $a \geq 0$ such that $h^{'}(x)$ is strictly increasing in $(0, a)$ and strictly decreasing in (a, ∞).*

Note that Lemma 11 implies that $h^{'}$ can not be constant in any interval, so the strictly increasing or decreasing function assumptions in the statement of Corollary 2.5.1 are without loss of generality. Although Corollary 2.5.1 is valid for functions having positive derivatives, a symmetric result can be proven for functions with negative derivatives. Corollary 2.5.1 is a general statement also covering unbounded functions, though the functions we are interested in are bounded.

Remark 2.5.1. Let h be a function satisfying the assumptions of Corollary 2.5.1. Moreover, suppose that h is bounded, then $h^{'}$ can not be a strictly increasing function. Because if $h^{'}$ is a strictly increasing function then h can not be bounded. Therefore, for a bounded function h with a negative Schwarzian derivative, either $h^{'}$ is a strictly decreasing function in $[0, \infty]$ or there exists $a \geq 0$ such that $h^{'}$ is strictly increasing in $(0, a)$ and strictly decreasing in (a, ∞).

Remark 2.5.1 leads us to the following Definition:

Definition 4. *For a bounded function h with a negative Schwarzian derivative, we will say h is of type A if $h^{'}$ is a strictly decreasing function, and of type B otherwise. The two types of functions are illustrated by the help of Figures 2.1 and 2.2.*

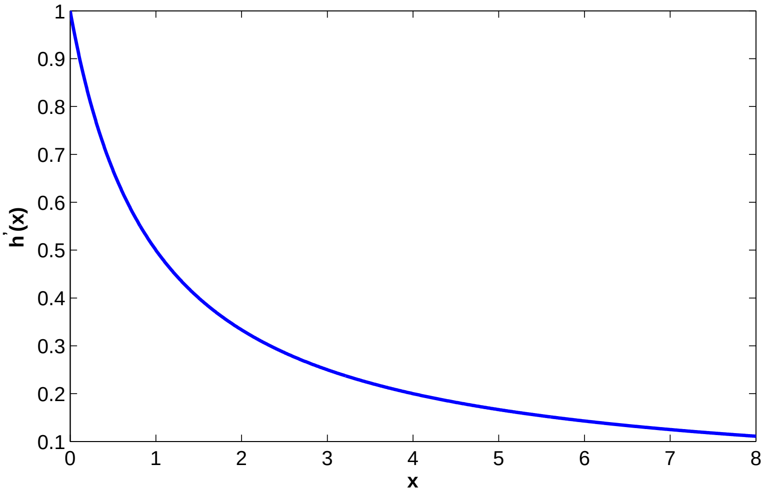

Figure 2.1: A typical x vs $h^{'}(x)$ graph for type A function.

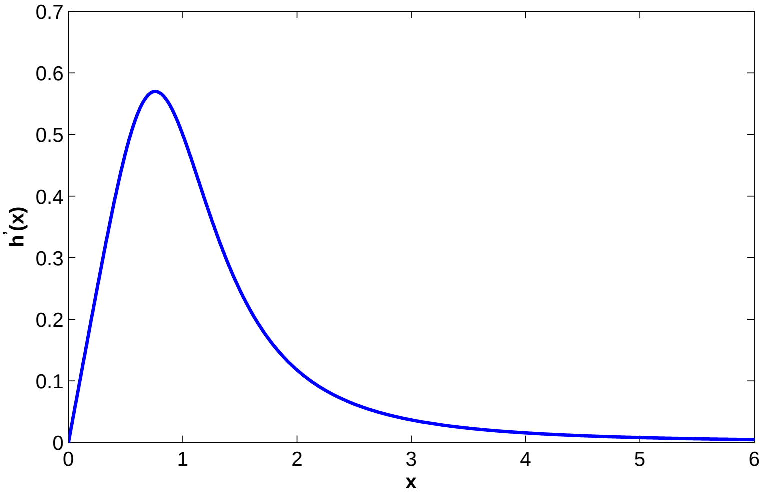

Figure 2.2: A typical x vs $h^{'}(x)$ graph for type B function.

Also note that whether the function h is of type A or B, we always have

$$\lim_{t \to \infty} h^{'}(x) = 0. \tag{2.51}$$

Remark 2.5.2. It is easy to determine whether a function h is of type A or B. If $h^{'}(0) = 0$, then it is clear that the function h is of type B. If we have

$$h^{'}(0) > 0, \tag{2.52}$$

and $h^{''}(0) > 0$ then $h(x)$ is of type B. If (2.52) is satisfied and

$$h^{''}(0) \leq 0, \tag{2.53}$$

then h is of type A.

Remark 2.5.3. Suppose the function h is defined as follows:

$$h(x) = g \circ g(x), \tag{2.54}$$

where g is a function defined from $\mathbb{R}_+$ to $X \subseteq \mathbb{R}_+$ such that

$$Sg(x) < 0 \quad \text{and} \quad g^{'}(x) < 0 \quad \forall x \in (0, \infty). \tag{2.55}$$

Then, by the convolution property of the Schwarzian derivative, we have

$$Sh(x) < 0 \quad \forall x \in (0, \infty). \tag{2.56}$$

Moreover, if x_0 is a fixed point of h, then one of the following holds:

1. x_0 is a fixed point of g.
2. $x_0 < g(x_0)$, so $h(g(x_0)) = g(g(g(x_0))) = g(x_0)$ and h has another fixed point greater than x_0.
3. $g(x_0) < x_0$, so $h(g(x_0)) = g(g(g(x_0))) = g(x_0)$ and h has another fixed point less than x_0.

Two examples of functions satisfying the conditions in 2.5.3 are Hill functions and the tangent hyperbolic function. The gene regulatory network, which we will analyze in Chapter 3, has nonlinearities in the form of Hill functions. Hence, Assumptions in 2.5.3 does not limit us.

Proposition 1. *Let f be a function of the form given in* (2.54) *with g satisfying the assumptions given in Remark 2.5.3 and x_0 be the unique fixed point of g. Then, we have the following:*

1. *If $|g^{'}(x_0)| < 1$, then h has the unique fixed point x_0.*
2. *If h is of type A, then h has the unique fixed point x_0 satisfying*

$$h^{'}(x_0) < 1.$$

3. *If h is of type B and*
   (i) *$h^{'}(x_0) < 1$ then h has the unique fixed point x_0.*
   (ii) *$h^{'}(x_0) > 1$ then h has exactly three fixed points.*

Proof. First note that since g is a strictly decreasing function, we have

$$g(0) > g(x) > 0 \qquad \forall x > 0, \tag{2.57}$$

so g is a bounded function which implies that the function h is bounded. Since g is a decreasing function, it has a unique fixed point x_0. Observe that

$$h^{'}(x) = g^{'}(g(x))g^{'}(x).$$

Since

$$g^{'}(x) < 0 \qquad \forall x \in (0, \infty),$$

we have

$$h^{'}(x) > 0 \qquad \forall x \in (0, \infty).$$

At the unique fixed point x_0 of g, we have the following equality:

$$h^{'}(x_0) = g^{'}(g(x_0))g^{'}(x_0) = (g^{'}(x_0))^2.$$

Therefore, we have

$$\begin{aligned} |g^{'}(x_0)| < 1 \;\; &\Leftrightarrow \;\; h^{'}(x_0) < 1 \\ |g^{'}(x_0)| > 1 \;\; &\Leftrightarrow \;\; h^{'}(x_0) > 1. \end{aligned}$$

We have shown that the function h is either of type A or type B. Therefore, if we prove second and third part of the Proposition then the first part is follows straightforwardl. For the first part of the Proposition assume that the function h is of type A, then $h^{'}$ is strictly decreasing in $\mathbb{R}_+$. Notice that since h is bounded, we have

$$\lim_{x \to \infty} (h^{'}(x)) = 0.$$

If $h^{'}(x_0) \geq 1$, then since $h^{'}$ is a decreasing function we have

$$h^{'}(x) > 1 \qquad \forall x \in [0, x_0].$$

From mean value theorem for some $t \in [0, x_0]$ we have the following:

$$h^{'}(t) = \frac{h(x_0) - h(0)}{x_0} \leq \frac{x_0 - h(0)}{x_0} \leq 1.$$

But on the other hand we have

$$h^{'}(x) > 1, \qquad \forall x \in [0, x_0],$$

so we arrived to a contradiction. Therefore, we have $h^{'}(x_0) < 1$. Now, suppose there exists another fixed point of the function h. We know from Remark 2.5.3 this implies that

$$\exists y \geq x_0 \qquad \text{such that} \qquad h(y) = y.$$

But mean value theorem implies that there exists $t \in [x_0, y]$ such that

$$h^{'}(t) = \frac{h(y) - h(x_0)}{y - x_0} = 1.$$

Since $h^{'}(x)$ is a strictly decreasing function, we have

$$h^{'}(x) < 1 \qquad \forall x \geq x_0. \tag{2.58}$$

Therefore, h has the unique fixed point x_0. For the third part of the Proposition, we assume that h is of type B. We define a new function in the following way:

$$f(x) = x - h(x). \tag{2.59}$$

Then clearly we have

$$f(0) < 0 \quad \text{and} \quad f^{'}(x) = 1 - h^{'}(x). \tag{2.60}$$

Note that the zero crossings of the function f and the fixed points of the function h are the same. Suppose that

$$h^{'}(x_0) < 1. \tag{2.61}$$

Also assume that the function h has a fixed point y which is different from x_0. From Remark 2.5.3, we can safely assume that

$$y < x_0. \tag{2.62}$$

Again from Remark 2.5.3 we have another fixed point of h which is denoted by z and is greater than x_0. For type B functions, we have either

$$h^{'}(x) \;<\; h^{'}(x_0) < 1 \qquad \forall x \in [0, x_0] \tag{2.63}$$

or

$$h^{'}(x) \;<\; h^{'}(x_0) < 1 \qquad \forall x \in [x_0, \infty]. \tag{2.64}$$

If the condition (2.63) is satisfied then we have $f(0) < 0$ and

$$f^{'}(x) > 0 \quad x \in [0, x_0]. \tag{2.65}$$

Then it is clear that $f(y) < 0$; so, in other words, we have

$$f(y) \neq 0 \tag{2.66}$$

which is a contradiction. For the case in equation (2.64) using a similar argument we can show that $f(z) \neq 0$. Hence, if (2.61) is satisfied, then h has the unique fixed point x_0. Now, let us assume that

$$h^{'}(x_0) > 1. \tag{2.67}$$

But for a type B function h, we can have at most two different values such that t_1 and t_2 such that

$$h^{'}(t_i) = 1 \qquad \text{for } i = 1, 2. \tag{2.68}$$

Hence f can have at most three zero crossings which implies that the function h has at most three fixed points. From (2.67) we can deduce the following

$$\exists x_1 > x_0 \quad \text{such that} \quad f(x_1) < 0, \tag{2.69}$$

but since the function h is bounded we have

$$\lim_{t \to \infty} (f(x)) = \infty. \tag{2.70}$$

Therefore, f has a zero crossing greater than x_0, thus h has a fixed point greater than x_0. But we know that the function h has at most three fixed point. From Remark 2.5.3 we can conclude that h has exactly three fixed points. □

The results we obtained in Proposition 1 is vital for our discussion in Chapter 3. Although in Proposition 1 we assumed that the function h is in a special form given by (2.54), the following Corollary gives a more general result.

Corollary 2.5.2. *Let h be a bounded function from $\mathbb{R}_+$ to $Y \subseteq \mathbb{R}_+$ with*

$$Sh(x) < 0.$$

Then, h has at most three fixed points.

Proof. Let $p(x) = x - f(x)$, then from the proof of Proposition 1, p can take the value 0 at most three times. Therefore, the function h can have at most three fixed points. □

Remark 2.5.4. In Corollary 2.5.2, we showed that a function h having negative Schwarzian derivative may have at most 3 fixed point. Suppose that h has exactly 3 fixed points and denote this three fixed points as y_1, y_2 and y_3 which satisfies

$$y_1 < y_2 < y_3. \tag{2.71}$$

From the proof of Proposition 1, we can conclude the following inequalities:

$$h^{'}(y_1)) \leq 1, \quad h^{'}(y_2) \geq 1, \quad h^{'}(y_3) \leq 1. \tag{2.72}$$

In fact, the second item in Proposition 1 is valid for any function h with $Sh(x) < 0$. But we will return to this point in Chapter 3. We close this section with another Corollary of Proposition 1.

Corollary 2.5.3. *Let h be a function of the form given in* (2.54) *with g satisfying the conditions given in Remark 2.5.3 and let x_0 be the unique fixed point of the function g. Then, h is either Type A or Type B. If*

$$|g^{'}(0)| > 1, \tag{2.73}$$

then the function h has the unique fixed point x_0 satisfying

$$h^{'}(x_0) \leq 1.$$

Proof. The proof is very similar to the proof of the third part of Proposition 1. If h is of type A, we are done already since it is just part two of Proposition 1. Therefore, suppose that h is of type B. Let

$$f(x) = x - h(x).$$

Then, since we have

$$h^{'}(0) > 1 \tag{2.74}$$

$h^{'}(x) = 1$ just for one point. Therefore, f can take the value 0 only twice, but the function h has either one fixed point or three fixed points. Therefore, h has a unique fixed point. But we know that

$$h(x_0) = g(g(x_0)) = x_0.$$

If we have

$$h^{'}(x_0) > 1,$$

then, from the proof of Proposition 1, we know that the function h has three fixed points, which is a contradiction. Therefore, we have

$$h^{'}(x_0) \leq 1.$$

□

Chapter 3

Gene Regulatory Networks

3.1 Problem Formulation

In this section we will be concerned with the asymptotic stability of a class of biological systems, the so-called gene regulatory networks which contains a feedback loop and time delays. Basically, a gene regulatory network can be described as the interaction of DNA segments with themselves and with other biological structures such as enzymes. Gene regulatory networks can be thought as an indicator of the genes transcription rates into mRNA, which is used to deliver the coding information required for the protein synthesis, [24]. The proteins synthesized have two main duties either they can be used to give stiffness and rigidity to certain biological components such as the cell wall or they are enzymes which has the vital duty of catalyzing chemical reactions that take place in our body. Gene regulatory networks can be modeled by either a Boolean network or a set of continuous differential equations. In this work, we analyze a continuous time cyclic model given in Figure 3.1.

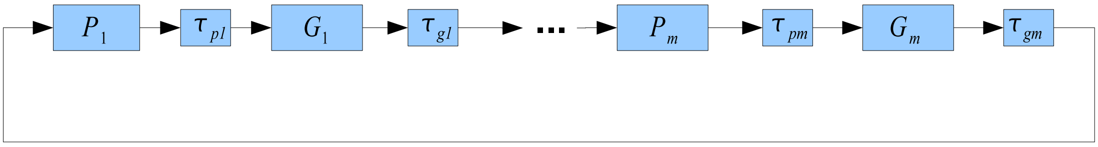

Figure 3.1: A continuous time model of Gene Regulatory System

Here G_i is a stable first order filter whose input is a nonlinear function of the delayed output of P_i. Similarly P_i is a stable first order system whose input is a nonlinear function of the delayed output of G_{i-1} for $1 \leq i < m-1$ and P_1 has an input which is a nonlinear function of the delayed output of G_m.

A continuous time model of the gene regulatory network in Figure 3.1 is proposed in [25]. The model comprises of a set of differential equations given in (1.1). Models similar to (1.1) are frequently encountered in the modeling of biological processes such as mitogen-activated protein cascades and circadian rhythm generator [12], [11], [2] and [26]. In [25], Chen and Aihara analyzed a simplified version of the system (1.1) and proved a local stability result. In the current work, we will assume that the functions $f_i(x)$ are nonlinear and have negative Schwarzian derivatives. In this work, we will analyze system (1.4) which is obtained from (1.2) with the linear transformation given in (1.3). For the sake of clarity, we will rewrite the system model we analyze in this chapter.

$$\begin{aligned}
\dot{x}_1(t) &= -\lambda_1 x_1(t) + g_1(x_2(t)) \\
\dot{x}_2(t) &= -\lambda_2 x_2(t) + g_2(x_3(t)) \\
&\vdots \\
\dot{x}_n(t) &= -\lambda_n x_n(t) + g_n(x_1(t-\tau)).
\end{aligned} \tag{3.1}$$

We suppose that the system (3.1) satisfies the following assumptions:

Assumption 1 For all $i = 1, 2, ..., n$, $\lambda_i > 0$.

Assumption 2 For all $i = 1, 2, ..., n$, the nonlinearity functions g_i satisfy the following conditions:

(i) g_i is a bounded function defined on $\mathbb{R}_+$.

(ii) We have either

$$g_i^{'}(x) < 0 \qquad \text{or} \qquad g_i^{'}(x) > 0 \qquad \forall x \in (0, \infty). \tag{3.2}$$

Assumption 2 simply means that the functions g_i are monotone and take positive values. The nonlinearity functions have $\mathbb{R}_+$ as their domain since their domain represents biological variables which take positive values. Also note that the condition $g_i^{'}(0) = 0$ is allowed, since it does not violate the monotonicity of the functions g_i. Let us define the following function:

$$g = (\frac{1}{\lambda_1} g_1) \circ (\frac{1}{\lambda_2} g_2) \circ ... \circ (\frac{1}{\lambda_n} g_n). \tag{3.3}$$

We say that the gene regulatory network is under negative feedback if

$$g^{'}(x) < 0 \qquad \forall x \in (0, \infty). \tag{3.4}$$

Conversely, the gene regulatory network is said to be under positive feedback if the above inequality is reversed. It can be easily concluded that under negative feedback g defined in (3.4) has a unique fixed point. In system (3.1) the nonlinearities are only due to the functions g_i and in biological systems they often have the Hill function form, which we discussed in Chapter 2. The system (3.1) has been analyzed by Enciso in [10]. In [10], Enciso considered the system 3.1 under negative feedback and based on the results of [9], [16], [17] and [26], he proved that if

$$|g^{'}(x_0)| < 1, \tag{3.5}$$

then the solutions of the system (3.1) converges to the unique equilibrium point. He also proved existence of periodic solutions by a Hopf bifurcation analysis. In this work we get the same global stability result by the help of Theorem 1 of [5]. By using the results of Chapter 2, it is easy to see that the violation of (3.5) implies the local unstability of the linearized system. Combining this fact with the result of [4], we will conclude existence of periodic solutions. Moreover, we also present a result regarding the upper and lower bounds regarding possible periodic solutions. We have also proved a global stability result regarding the homogenous gene regulatory network under negative feedback involving nonlinearities in the form of Hill function. Furthermore, we also considered system (3.1) under positive feedback and proved some global stability results by the help of [18]. Although the nonlinearities in (3.1) are often in the form of a Hill function, the results we obtained is valid for any kind of nonlinearity functions having negative Schwarzian derivatives which includes Hill functions as a subset. For the proofs of the results we will obtain in this section, we will frequently refer to the results we obtained in Chapter 2 regarding the fixed points of functions with negative Schwarzian derivatives.

3.2 Analysis of the Gene Regulatory Network

Let our system be in the form of (3.1) satisfying Assumption 1 and 2. In the previous section we defined the following function:

$$g = (\frac{1}{\lambda_1}g_1) \circ (\frac{1}{\lambda_2}g_2) \circ ... \circ (\frac{1}{\lambda_n}g_n). \tag{3.6}$$

Since the constants λ_i's are positive by Assumption 1, the function g defined in (3.6) is a well defined function on $\mathbb{R}_+$. As a result of Assumption 2 and the chain rule, we have

$$g^{'}(x) < 0 \quad \text{or} \quad g^{'}(x) > 0 \qquad \forall x \in \mathbb{R}_+. \tag{3.7}$$

When $g^{'}(x) < 0$ we will say that the system (3.1) is under negative feedback and $g^{'}(x) > 0$ is referred as the positive feedback case. We will deal with both cases separately and present some results regarding their stability and existence of periodic solutions if any.

3.2.1 Gene Regulatory Networks under Negative Feedback

In this section, we will consider the system (3.1) under negative feedback. That is g defined in (3.6) satisfies:

$$g^{'}(x) < 0 \qquad \forall x \in (0, \infty). \tag{3.8}$$

We start this section with a Lemma regarding the equilibrium points of the system (3.1) under negative feedback.

Lemma 13. *Consider the system in the form* (3.1) *satisfying Assumptions* 1 *and* 2 *under negative feedback. Then, the system has a unique equilibrium point in* $\mathbb{R}^n_+$.

Proof. The function g defined in (3.6) is decreasing and we have

$$g(0) \geq 0.$$

Therefore, by Lemma 6, we conclude that the function g has a unique equilibrium point. Let $x \in \mathbb{R}^n_+$ be an equilibrium point of the system. We have

$$\begin{aligned} x_1 &= \frac{1}{\lambda_1} g_1(x_2) \\ &\vdots \\ x_n &= \frac{1}{\lambda_n} g_n(x_1) \end{aligned}$$

which is in the form of Lemma 8. Therefore, the system (3.1) under negative feedback has a unique equilibrium point in $\mathbb{R}^n_+$. $\square$

Lemma 14. *For the system* (3.1), $\mathbb{R}^n_+$ *is a positively invariant set and for any set of initial conditions the corresponding solution of the system remain bounded.*

Proof. To prove positive invariance, we need only check the direction of the vectors on the boundaries of the region

$$\mathbb{R}^n_+ = \{(x_1, x_2, ..., x_n) \in \mathbb{R}^n : \ x_i \geq 0 \quad \forall i = 1, 2, ..., n\}.$$

The boundaries of the region $\mathbb{R}_+^n$ are just the planes $x_i = 0$. If $x_i = 0$ for some $i = 1, ..., n$, then we have

$$\dot{x}_i = f(x_{i-1}) \geq 0,$$

so it points inside the region $\mathbb{R}_+^n$ which shows that the region $\mathbb{R}_+^n$ is an invariant set of the system (3.1). For each $i = 1, ..., n$, let us define

$$|g_i|_\infty = \sup_{x \in \mathbb{R}_+} g_i(x).$$

Since each g_i is bounded and positive this definition makes sense. For the second part of the lemma, note that

$$x_i(t) > \frac{1}{\lambda_i}|g_i|_\infty \qquad \Rightarrow \quad \dot{x}_i(t) < 0.$$

Therefore, we have

$$\lim_{t\to\infty} x_i(t) \leq |g_i|_\infty \qquad \forall i = 1, ..., n.$$

Hence, the solutions remain bounded for any positive initial condition. □

Let $x_{eq} = (x_1, ..., x_n)$ be the unique equilibrium point of our system. Then, we have the following linearization of system (3.1) around its unique equilibrium point x_{eq}:

$$\dot{x}(t) = A_0 x(t) + A_1 x(t-\tau), \tag{3.9}$$

$$A_0 = \begin{bmatrix} -\lambda_1 & g_1^{'}(x_2) & 0 & \dots & 0 \\ 0 & -\lambda_2 & g_2^{'}(x_2) & \dots & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & 0 & \dots & \dots & -\lambda_n \end{bmatrix} \tag{3.10}$$

$$A_1 = \begin{bmatrix} 0 & \dots & 0 \\ \vdots & \ddots & \vdots \\ g_n^{'}(x_1) & 0 & \dots \end{bmatrix} \tag{3.11}$$

which gives us a characteristic equation of the following form:

$$\begin{aligned} \chi(s) &= \prod_{i=1}^{n}(s+\lambda_i) + ke^{-\tau s} && (3.12)\\ k &= \left(\prod_{i=1}^{n-1} g_i^{'}(x_{i+1})\right) g_n^{'}(x_1). && (3.13) \end{aligned}$$

Since we have $\lambda_i > 0$, the characteristic function $\chi(s)$ defined in (3.12) has all its roots in $\mathbb{C}_-$ if and only if the transfer function

$$G(s) := \left(1 + \frac{ke^{-\tau s}}{\prod_{i=1}^{n}(s+\lambda_i)}\right) \tag{3.14}$$

is stable. Then, we have the following Lemma:

Lemma 15. *Let $G(s)$ be as defined in* (3.14)*, then $G(s)$ is stable independent of delay if*

$$|g^{'}(x_1)| < 1$$

Proof. By applying a Small-Gain argument we see that $G(s)$ is stable independent of delay if we have

$$|k| < (\prod_{i=1}^{n} \lambda_i). \tag{3.15}$$

Note that at the unique equilibrium $x_{eq} = (x_1, ..., x_n)$ of the system (3.1), we have

$$g(x_1) = x_1$$

that is x_1 is the unique equilibrium point of the function $g(x)$. Then, observe that

$$\begin{aligned} |k| &= |(\prod_{i=1}^{n-1} g_i^{'}(x_{i+1}))g_n^{'}(x_1)| \\ &= |g^{'}(x_1)|\, (\prod_{i=1}^{n} \lambda_i). && (3.16) \end{aligned}$$

Note that since the system is under negative feedback, we have $k < 0$. Combining (3.15), (3.16) with a small gain argument, we obtain the desired result. □

Lemma 16. *Let $G(s)$ be a function of the form in* (3.14)*, then $G(s)$ is unstable independent of delay if*

$$|g^{'}(x_1)| > 1 \tag{3.17}$$

Proof. Since the system (3.1) is under negative feedback and

$$|g^{'}(x_1)| > 1, \tag{3.18}$$

we have

$$k < -\prod_{i=1}^{n} \lambda_i < 0. \tag{3.19}$$

If 3.19 is satisfied, by part 5 of Lemma 3 we conclude that $G(s)$ is unstable independent of delay. □

To continue our analysis, we need the following adoption of Theorem 1 in [5]:

Theorem 1. *([5])Consider the system* (3.1) *under assumptions* 1 *and* 2 *and suppose that g defined in* (3.3) *is decreasing. Let x_{eq} be the unique equilibrium point of the system* (3.1)*. If the function $g \circ g$ has a unique positive fixed point, then for any nonnegative initial condition we have*

$$\lim_{t\to\infty} x(t) = x_{eq}. \tag{3.20}$$

If the function $g \circ g$ has more than one but finitely many positive fixed points and l and L are the lower and upper bounds of these fixed points, then for any solution $x(t) = (x_1(t), x_2(t), ..., x_n(t))$ of the system (3.1)*, we have*

$$l < \lim_{t\to\infty} \underline{x_i(t)} \leq \lim_{t\to\infty} \overline{x_i(t)} < L \qquad \forall i = 1, 2, ..., n. \tag{3.21}$$

Theorem 1 leads to the following result.

Proposition 2. *Consider the system* (3.1) *under negative feedback and let Assumptions* 1 *and* 2 *hold. Then, the system* (3.1) *has the unique equilibrium point*

$x_{eq} = (x_1, ..., x_n)$ and g defined in (3.3) *has the unique fixed point x_1 . Let each g_i in* (3.1) *have negative Schwarzian derivatives. If*

$$|g^{'}(x_1)| < 1, \tag{3.22}$$

then for any nonnegative initial condition the solution satisfies

$$\lim_{t \to \infty} x(t) = x_{eq}. \tag{3.23}$$

Proof. From Theorem 1, we get the desired result if we can show that the function

$$f(u) = g(g(u))$$

has unique fixed point. Since the nonlinearity functions g_i have negative Schwarzian derivatives, the functions g and f have negative Schwarzian derivatives by Lemma 4. Then the function f is in the form of Proposition 1. Hence, if we have

$$|g^{'}(x_1)| < 1$$

then by Proposition 1, we conclude that the function f has a unique fixed point which is at the same time the unique fixed point of g. Since f has a unique fixed point, the desired result follows from Theorem 1. □

Note that the condition:

$$|g^{'}(x_1)| < 1$$

also corresponds to the delay independent stability of the linearized system around the unique equilibrium point of it. Therefore, Proposition 2 is consistent with the result of Lemma 15. Most of the nonlinearity functions considered in biological systems do have negative Schwarzian derivatives, including the Hill functions. Therefore, the results we have in Proposition 2 are useful not only for the analysis of gene regulatory networks but also for other biological processes e.g. hematopoiesis [27]. After the global stability condition given in Proposition 1, we will present another result regarding the oscillatory behavior of system (3.1).

For this purpose, we will benefit from a generalized version of the well-known Poincaré-Bendixson Theorem [4].

Theorem 2. *([4])Consider the system* (3.1) *under Assumptions* 1 *and* 2 *with the unique equilibrium point* $x = (x_1, ..., x_n)$ *and suppose that* $g(x)$ *defined in* (3.6) *is decreasing. Let* $x(t)$ *be a solution of the system* (3.1) *which is bounded in* $\mathbb{R}^n_+$*. Then the omega-limit set of* $x(t)$ *consists of either*

(i) *an equilibrium point, or*

(ii) *a nonconstant periodic orbit.*

We showed that the system (3.1) has a unique equilibrium point and all solutions with nonnegative initial conditions are bounded. Therefore, the results presented in Theorem 2 are valid for system (3.1) under negative feedback. Theorem 2 applied to our system leads us to the following.

Proposition 3. *Consider the system* (3.1) *under negative feedback with its unique equilibrium point* $x_{eq} = (x_1, ..., x_n)$*. Suppose that each* g_i *has negative Schwarzian derivative. Then,* g *defined in* (3.3) *has the unique fixed point* x_1*. If we have*

$$|g^{'}(x_1)| > 1 \tag{3.24}$$

then there exists periodic solutions of the system (3.1)*. Moreover, for this case the function*

$$f(u) = g(g(u)) = u$$

has exactly three distinct fixed points. Let y_1 *and* y_2 *be the two fixed points of the function* f *other than* x_1*. Then, if* $x(t) = (x_1(t), ..., x_n(t))$ *is the solution of the system with any positive initial condition, we have*

$$y_1 < \lim_{t\to\infty} \underline{x_i(t)} \leq \lim_{t\to\infty} \overline{x_i(t)} < y_2 \qquad \forall i = 1, 2, ..., n. \tag{3.25}$$

Proof. Theorem 2 implies that a solution $x(t)$ of the system (3.1) either converges to an equilibrium point or it is a nonconstant periodic solution. If we have

$$|g^{'}(x_1)| > 1, \tag{3.26}$$

then

$$k < (\prod_{i=1}^{n} \lambda_i) < 0,$$

which implies that the linearized system is unstable for all positive values of delay by Lemma 3. So the equilibrium point is locally unstable independent of delay. Therefore, for some initial conditions around the unique equilibrium point x_{eq}, the corresponding solution of system (3.1) does not converge to x_{eq}. But for such initial conditions if the solution does not converge to the unique equilibrium point x_{eq}, it can only be a periodic solution by Theorem 2. Therefore, system (3.1) has periodic solutions. It is easy to see that (3.21) implies (3.25). □

Note that Proposition 3 not only gives the conditions on the existence of periodic oscillations but it also gives lower and upper bounds for periodic solutions of the system (3.1). Till now we have dealt with the cases

(i) $|g(x_0)| < 1$

(ii) $|g(x_0)| > 1$.

We will now present a result concerning the $g(x_0) = -1$ case.

Lemma 17. *Let $g(x) : \mathbb{R}_+ \to Y \subseteq \mathbb{R}_+$ be a function with a negative Schwarzian derivative satisfying*

$$g^{'}(x) < 0 \qquad \forall x \in (0, \infty).$$

Then g has a unique fixed point x_0 and

$$g^{'}(x_0) \neq -1. \tag{3.27}$$

Proof. First of all note that g is a nonconstant, positive and strictly decreasing function. Therefore, we have

$$g(0) > 0.$$

Note that if we have $g(0) = 0$ then

$$g(x) < 0 \qquad \forall x > 0$$

which is a contradiction because g takes positive values. Since the function g is monotonic, we have

$$0 < g(x) < g(0) \qquad \forall x \in (0, \infty)$$

so g is bounded. The uniqueness of the fixed point of the function g follows from Lemma 6. Let x_0 be the unique fixed point of g. Since $g(0) > 0$, we have $x_0 > 0$. Let us define

$$f(x) = g \circ g(x). \tag{3.28}$$

Then, since the function g has negative Schwarzian derivative, by Lemma 4 the function f has negative Schwarzian derivative. Also, the boundedness of g implies that the function f is bounded. From Chapter 2, we know that the function f is either of type A or B. Let f be of type A and suppose that

$$g^{'}(x_0) = -1, \tag{3.29}$$

then we have

$$f^{'}(x_0) = (g^{'}(x_0))^2 = 1.$$

We know $0 < x_0$. Therefore, we have

$$f^{'}(x) > 1 \qquad \forall\ x\ \in [0, x_0).$$

Let us define h as

$$h(x) = f(x) - x.$$

Notice the following facts:

$$h(0) = f(0) > 0, \qquad h^{'}(x) = f^{'}(x) - 1 > 0 \quad \forall x \in [0, x_0).$$

Then, by fundamental theorem of Calculus, we have the following inequality:

$$h(x_0) = 0 = h(0) + \int_0^{x_0} h^{'}(x)dx > h(0) > 0$$

which gives us a contradiction. Therefore, we have

$$f^{'}(x_0) < 1 \Rightarrow g^{'}(x_0) \neq -1$$

when the function f is of type A.

Suppose now the function f is of type B, and we have

$$f^{'}(x_0) = 1.$$

We know that f can either have a unique fixed point or three fixed points. Since f is of type B, we have either

$$f^{'}(x) < 1 \quad \forall x \in [0, x_0) \quad \text{or} \quad f^{'}(x) < 1 \quad \forall x \in (x_0, \infty).$$

If $f^{'}(x) < 1$ in $[0, x_0)$, we have

$$h(x_0) = 0 = h(0) + \int_0^{x_0} h^{'}(x)dx > h(0) > 0,$$

which gives us a contradiction. For the other case assume that $f^{'}(x) < 1$ in (x_0, ∞). Then, for any $x > x_0$ we have

$$h(x) = h(x_0) + \int_{x_0}^{x} h^{'}(x)dx < 0 + x - x_0 < x$$

which implies that the function f can not have a fixed point x greater than x_0. Also if we have

$$f^{'}(x) < 1 \qquad \forall x \in [0, x_0),$$

we get the following equality:

$$h(x_0) = 0 = h(0) + \int_0^{x_0} h^{'}(x)dx > h(0) > 0,$$

which is again a contradiction. Therefore, considering the shape of type B function $f(x)$, we see that there $\exists\ t < x_0$ such that

$$f^{'}(x) > 1 \qquad \forall x \in (t, x_0).$$

As a result we have the following

$$\begin{aligned} h(x_0) &= 0 = h(t) + \int_t^{x_0} h^{'}(x)dx = h(t) - a \\ &\Rightarrow \ h(t) = -\int_t^{x_0} h^{'}(x)dx < 0. \end{aligned}$$

Since we have

$$h(0) > 0 \qquad \text{and} \qquad h(t) < 0,$$

intermediate value theorem implies that $\exists\ k \in (0, t)$ such that

$$h(k) = 0.$$

Therefore, the point $k < x_0$ is a fixed point of f. Then, we should have another fixed point of the function f which is larger than x_0. But we showed that f can not have a fixed point larger than x_0 which gives us another contradiction. Therefore, we get the desired result that is

$$f(x_0) = (g^{'}(x_0))^2 \neq 1.$$

□

Remark 3.2.1. In Proposition, 2 we assumed that all the nonlinearity functions g_i satisfy

$$Sg_i(x) < 0 \qquad \forall x \in (0, \infty). \tag{3.30}$$

But it is enough to have one nonlinearity function g_i satisfying (3.30). The rest of the nonlinearities may have

$$Sg_i(x) \leq 0. \tag{3.31}$$

One interesting case is if the all the nonlinearity functions are in the following form

$$g_i(x) = \frac{a}{b+x} + c. \tag{3.32}$$

Then, we have

$$Sg(x) = Sg_i(x) = 0 \qquad \forall i = 1, ..., n. \tag{3.33}$$

Then, f is in the following form:

$$f(x) = g \circ g(x) = \frac{p+x}{q+x} \qquad p, q > 0 \tag{3.34}$$

and has always a unique positive fixed point.

3.2.2 Homogeneous Gene Regulatory Network with Hill Functions

In this section we consider the homogenous gene regulatory network under negative feedback with Hill function type nonlinearities. In other words, we will analyze the following system:

$$\begin{aligned} \dot{x}_i(t) &= -x_i(t) + f(x_{i+1}(t)) \qquad i = 1, 2, ..., n-1 \\ \dot{x}_n(t) &= -x_n(t) + f(x_1(t-\tau)) \qquad (3.35) \\ & \qquad (3.36) \end{aligned}$$

where the function f in (3.35) has the following form:

$$f(x) = \frac{a}{b + x^m} \qquad a, b > 0 \quad m = 1, 2, 3, ... \tag{3.37}$$

Notice that f satisfies

$$f^{'}(x) < 0 \qquad \forall x \in (0, \infty).$$

Also note that to have negative feedback, we should have odd number of interactions between genes. That is n should be an odd number.

Since $f(0) > 0$ and f is decreasing, we conclude that f has a unique fixed point, x_0, satisfying

$$x_0 = f(x_0) = \frac{a}{b + x_0^m}. \tag{3.38}$$

Then, the unique equilibrium point of system (3.35) is $x_{eq} = (x_0, ..., x_0)$. Notice that we have

$$f^{'}(x_0) = -\frac{m\ a\ x_0^{m-1}}{(b + x_0^m)^2} = -\frac{m\ x_0^{m+1}}{a}. \tag{3.39}$$

From (3.38) we get the following equation:

$$x_0^{m+1} = a - bx_0. \tag{3.40}$$

Let us define a new function $h(x)$ as

$$h(x) = f^n(x). \tag{3.41}$$

Then from Proposition 2, system (3.35) is stable if we have

$$|h^{'}(x_0)| < 1 \quad \Leftrightarrow \quad (|f^{'}(x_0)|)^n < 1. \tag{3.42}$$

Combining (3.38) and (3.39), we get the following set of equations:

$$\begin{aligned}
(|f^{'}(x_0)|)^n < 1 &\Rightarrow |(f^{'}(x_0))| < 1. \\
&\Rightarrow \frac{mx_0^{m+1}}{a} < 1 \\
&\Rightarrow mx_0^{m+1} < a \\
&\Rightarrow m(a - bx_0) < a \\
&\Rightarrow \frac{(m-1)a}{mb} < x_0.
\end{aligned}$$

Let us define

$$p(x) = x^{m+1} + bx - a. \tag{3.43}$$

Clearly $p(x_0) = 0$ and we have

$$p^{'}(x) \quad = \quad (m+1)x^m + b > 0 \quad \forall x \in (0, \infty) \tag{3.44}$$

and

$$p(0) \quad = \quad -a < 0. \tag{3.45}$$

Since $p(x_0) = 0$ and p is strictly increasing, we have

$$p\left(\frac{(m-1)a}{mb}\right) < 0 \Leftrightarrow \frac{(m-1)a}{b} < x_0. \tag{3.46}$$

We then have the following identities:

$$\begin{aligned}
p\left(\frac{(m-1)a}{mb}\right) &= \left(\frac{m-1}{m}\right)^{m+1}\left(\frac{a}{b}\right)^{m+1} + \frac{m-1}{m}a - a \\
&= \left(\frac{m-1}{m}\right)^{m+1}\left(\frac{a}{b}\right)^{m+1} - \frac{a}{m}.
\end{aligned} \tag{3.47}$$

Combining (3.46) and (3.47), we arrive at the following set of inequalities:

$$\begin{aligned}
p\left(\frac{(m-1)a}{mb}\right) &< 0 \\
\Leftrightarrow \quad & \left(\frac{m-1}{m}\right)^{m+1}\left(\frac{a}{b}\right)^{m+1} < \frac{a}{m} \\
\Leftrightarrow \quad & \left(\frac{a}{m}\right)^{m} < \left(\frac{b}{m-1}\right)^{m+1}.
\end{aligned} \tag{3.48}$$

If the constants a, b and m satisfy the inequality (3.48), then from Proposition (2) the unique equilibrium point of system (3.35) is globally attractive. The arguments we had so far are valid for $m > 1$ case. For $m = 1$ the Hill functions do not have negative Schwarzian derivative. Now let $m = 1$ and a and b arbitrary positive real numbers. Then, the system (3.35) has the unique equilibrium point $x_{eq} = (x_0, ..., x_0)$ satisfying

$$\begin{aligned} x_0 &= \frac{a}{b + x_0} \\ &\Rightarrow x_0^2 = a - bx_0 \end{aligned}$$

From Proposition 2, the unique equilibrium point of (3.35) is globally attractive if

$$\begin{aligned} g'(x_0) &= \frac{a}{(b + x_0)^2} = \frac{x_0^2}{a} < 1 \\ &\Rightarrow a - bx_0 < a \\ &\Rightarrow 0 < x_0. \end{aligned} \tag{3.49}$$

Equation (3.49) shows that for $m = 1$ the unique equilibrium point of (3.35) is globally attractive regardless of the values of the positive constants a and b. Thus the following result has been established.

Proposition 4. *Consider system* (3.35) *and let* $x_{eq} = (x_0, ..., x_0)$ *be its equilibrium point.*

(i) If $m = 1$*, then* x_{eq} *is globally attractive for all positive constants* a, b.

(ii) If $m = 2, 3, ...$ *and* a, b, m *satisfy*

$$(\frac{a}{m})^m < (\frac{b}{m-1})^{m+1},$$

then x_{eq} *is globally attractive.*

(iii) The system (3.35) *has periodic solutions for cases other than (i) and (ii).*

In this section we considered the gene regulatory network under negative feedback with nonlinearities having negative Schwarzian derivatives. The results we obtained regarding the global attractivity of the unique fixed point of the system are compatible with the delay independent stability condition of the linearized system around its unique equilibrium point. We also analyzed the homogenous gene regulatory network which has Hill type of nonlinearities commonly encountered in biological models.

3.2.3 Gene Regulatory System under Positive Feedback

In this section, we will consider the system (3.1) exposed to positive feedback. As in the previous section let g be defined as

$$g(x) = g_1 \circ g_2 \circ \dots \circ g_n(x) \quad g : \mathbb{R}_+ \to I \subseteq \mathbb{R}_+ \tag{3.50}$$

where I is a bounded interval. For positive feedback, we require that g satisfies

$$g^{'}(x) > 0 \quad \forall x \ \in (0, \infty). \tag{3.51}$$

We start this section with the following Theorem adopted from [18]:

Theorem 3. *Consider system* (3.1) *under positive feedback. Then, any solution of system* (3.1) *with any nonnegative initial conditions converges to one of its equilibrium points.*

Like in the negative feedback case, we will assume that the nonlinearity functions have negative Schwarzian derivatives and Assumptions 1 and 2 are satisfied. But to ensure positive feedback only even number of nonlinearity functions may have negative derivative. Another important point is that unlike the negative feedback case, this time we may have $g(0) = 0$ which makes 0 a fixed point of g. We start our analysis with a Corollary of Theorem 3.

Corollary 3.2.1. *Consider system* (3.1) *under positive feedback. If the function g defined in* (3.50) *has a unique fixed point, then the system* (3.1) *has a unique equilibrium point x_{eq} and any solution of the system with a nonnegative initial condition will converge to its unique equilibrium point x_{eq}.*

Proof. If g has a unique equilibrium point, then by Lemma 8 the system has a unique equilibrium point. The global convergence result follows directly from Theorem 3. □

To continue the analysis, we will assume that each g_i has negative Schwarzian derivative. This leads us to the following result:

Proposition 5. *Consider the system* (3.1) *under positive feedback and assume that each* g_i *has negative Schwarzian derivative. Then,* g *defined in* (3.3) *has negative Schwarzian derivative and the following results hold:*
(i) The function g *has at most three fixed points.*
(ii) If

$$g^{'}(x) < 1 \quad \forall x \geq 0, \tag{3.52}$$

then g *has a unique fixed point. In this case, the system defined by* (3.1) *has a unique equilibrium point* x_{eq} *which is globally attracting.*
(iii) If $g^{'}(0) > 1$ *then* g *has a unique positive fixed point.*

Proof. (i) and (ii) follows from Lemma 1. For the third part if we have

$$g^{'}(0) > 1, \tag{3.53}$$

then whether the function g is of type A and type B it has a unique equilibrium point from Corollary 2.5.3. Here the only point of confusion is that except for a nonzero fixed point of the function g, 0 may also be a fixed point of it. Therefore, it can have two fixed points. □

Remark 3.2.2. In Proposition 5 the function g is not of the form $g(x) = f \circ f(x)$. Therefore, g does not have to have odd number of fixed points. As an example, one may consider the following function:

$$g(x) = \frac{4x}{1+x} \tag{3.54}$$

which has the fixed points 0 and 3.

3.2.4 Homogenous Gene Regulatory Network under Positive Feedback

In this section we will deal with homogenous gene regulatory network under positive feedback. Consider system (3.1) under positive feedback with

$$g_i(x) = f(x), \qquad \lambda_i = 1, \qquad \forall i = 1, 2, ..., n, \tag{3.55}$$

where f is defined from $\mathbb{R}_+$ to $\mathbb{R}_+$ Notice that we did not assume any special form for f yet. We start our analysis with the following lemma:

Lemma 18. *Let* $k(x) : \mathbb{R}_+ \to I \subseteq \mathbb{R}_+$ *be a three times continuously differentiable function satisfying*

$$k^{'}(x) > 0 \qquad \forall x \in (0, \infty). \tag{3.56}$$

Let h *be defined on* $\mathbb{R}_+$ *as*

$$h(x) = k^m(x). \tag{3.57}$$

Then, any fixed point of h *is a fixed point of* k*.*

Proof. Suppose that $h(0) = 0$ and $k(0) > 0$, then we have

$$h(0) = k^n(0) > ... > k(k(0)) > k(0) > 0 \tag{3.58}$$

which is contradiction. Therefore, $k(0) = 0$ and 0 is a fixed point of the function k. Let $x > 0$ be a fixed point of the function h and suppose $k(x) \neq x$. Then, we have either

$$x < k(x) \qquad \text{or} \qquad k(x) < x. \tag{3.59}$$

If $x < k(x)$, then since k is a strictly increasing function we have

$$h(x) = k^n(x) > ... > k(x) > x. \tag{3.60}$$

But we know that $h(x) = x$ so (3.60) gives us a contradiction. Similarly, if we have $k(x) < x$ then

$$h(x) = k^n(x) < ... < k(x) < x$$

which is again a contradiction. Therefore, we should have $k(x) = x$. Also, it is easy to see that any fixed point x of k is a fixed point of h. Thus, we conclude that the functions k and h have the same fixed points. □

Remark 3.2.3. The homogenous system is under positive feedback either if
(i) $f^{'}(x) > 0$ for all $x \in (0, \infty)$ or
(ii) $f^{'}(x) < 0$ for all $x \in (0, \infty)$ and $n = 2m$ for some positive integer m.

We will first deal with the case (ii) of Remark 3.2.3. From linear algebra, we know that every positive number has a unique prime decomposition. We also know that n is an even integer. Then, we have either
(i) $n = 2^k$ for some positive integer k or
(ii) $n = 2^{k_1} p_1^{k_2} .... p_n^{k_n}$, where $p_1, p_2, ..., p_n$ are distinct prime numbers and $k_i > 0$.
We have the following Lemma regarding case (ii) of Remark 3.2.3:

Lemma 19. *Consider the homogenous gene regulatory network* (3.1) *under positive feedback with*

$$f^{'}(x) < 0. \tag{3.61}$$

Moreover, suppose that f has negative Schwarzian derivative. Then, f has a unique fixed point, say $x_0 > 0$, and one of the following holds:
(i) *We have $n = 2^k$. In this case*

$$g(x) = f^n(x) \tag{3.62}$$

has the unique fixed point x_0 provided that

$$|f^{'}(x_0)| < 1. \tag{3.63}$$

If $|f^{'}(x_0)| > 1$, then g has exactly three equilibrium points.
(ii) *When $n = 2^{k_1} p_1^{k_2} .... p_n^{k_n}$, we define h as*

$$h(x) = f^{(\prod_{i=1}^{n} p_i^{k_i})}(x). \tag{3.64}$$

In this case h has a unique fixed point x_0 which is also the unique fixed point of f. If

$$|f^{'}(x_0)| < 1 \tag{3.65}$$

then we have $|h^{'}(x_0)| < 1$ *and* g *defined in* (3.62) *has the unique fixed point* x_0*. If we have*

$$|f^{'}(x_0)| > 1, \tag{3.66}$$

then $|h^{'}(x_0)| > 1$ *and* g *defined in* (3.62) *has exactly three equilibrium points.*

Proof. Firstly, since f is monotonically decreasing we know that it has a unique fixed point x_0 by Lemma 6. Suppose $n = 2^k$ and let

$$g(x) = f^n(x). \tag{3.67}$$

Now, let $h_1(x) = f^{2^{k-1}}(x)$, then we have

$$g(x) = h_1(h_1(x)) \qquad \text{and} \qquad h_1^{'}(x) > 0 \quad \forall\ x\ \in (0, \infty). \tag{3.68}$$

From Lemma 18 with $m = 2$, we conclude that any fixed point x of g is a fixed point of the function h_1. Let $h_2(x) = f^{2^{k-2}}(x)$, then we have

$$h_1(x) = h_2(h_2(x)) \tag{3.69}$$

and again from Lemma 18 we conclude that any fixed point of h_1 is a fixed point of h_2. Since $n = 2^k$ we know that g has as many fixed points as h_{k-1} which is defined as

$$h_{k-1}(x) = f(f(x)). \tag{3.70}$$

If we have

$$|f^{'}(x_0)| < 1 \tag{3.71}$$

at the unique equilibrium point x_0 of f, we conclude that h_{k-1} has a unique equilibrium point. Therefore, from Lemma 18 we deduce that g has a unique fixed point. Lemma 3 also implies that if

$$|f^{'}(x_0)| > 1, \tag{3.72}$$

then the function $h_{k-1}(x)$ has exactly three fixed points. Therefore, from Lemma 18 the function g has three fixed points.

Now for the second part, consider $n = 2^{k_1} p_1^{k_2} .... p_n^{k_n}$ and let

$$k = p_1^{k_2} .... p_n^{k_n}.$$

and

$$h(x) = f^k(x).$$

Since k is an odd number, we have

$$h^{'}(x) < 0 \qquad \forall x \in (0, \infty).$$

We also know that h has a negative Schwarzian derivative from Lemma 4. Therefore, h has a unique fixed point by Lemma 1. Since f is decreasing it has a unique fixed point x_0. Also note that

$$h(x_0) = f^k(x_0) = x_0. \tag{3.73}$$

From (3.73) we conclude that the unique fixed point x_0 of f is the unique fixed point of h. Also note that

$$|h^{'}(x_0)| < 1 \quad \Leftrightarrow \quad |f^{'}(x_0)| < 1.$$

Similarly, we have

$$|h^{'}(x_0)| > 1 \quad \Leftrightarrow \quad |f^{'}(x_0)| > 1.$$

Notice that

$$g(x) = h^{2^{k_1}}(x). \tag{3.74}$$

Then the rest of the arguments are the same as the proof of the first part. □

We will continue our analysis with case (i) of Remark 3.2.3. We consider the homogenous gene regulatory under positive feedback with the nonlinearity function f satisfying

$$f^{'}(x) > 0 \quad \forall x \in (0, \infty). \tag{3.75}$$

Lemma 20. *Consider the homogenous gene regulatory network* (3.1) *under positive feedback with the nonlinearity function f satisfying* (3.75)*. Then, the function*

$$g(x) = f^n(x) \tag{3.76}$$

has as many fixed points as f. In particular, if f has a unique fixed point, then system (3.1) *has a unique equilibrium which is globally attractive.*

Proof. A direct application of Lemma 18 and Proposition 3 leads to the desired result. □

We are interested in the fixed points of the function f. If, further, f has a negative Schwarzian derivative, we know that it has one, two or three fixed points. As an example, let us consider the following Hill type of functions and try to find some conditions regarding its fixed points. The type of functions we will consider is given by

$$f(x) = \frac{ax^m}{b + x^m} + c, \quad a,\ b,\ c > 0 \tag{3.77}$$

so we rule out zero as a fixed point by taking the constant c strictly positive. Then $x > 0$ is a fixed point of the function defined in (3.77) if x is a root of the following polynomial:

$$h(x) = x^{m+1} - (a + c)x^m + bx - bc. \tag{3.78}$$

Some interesting cases regarding the function (3.78) may occur. Let us consider one such interesting example. Let $a = 3.6$, $b = 5$, $m = 2$ and $c = 0.4$, then we have

$$h(x) = x^{m+1} - (a + c)x^m + bx - bc = (x - 1)^2(x - 2)$$

which implies that the function f has exactly two fixed points. We will try to find a sufficient condition depending on the parameters a, b, c and m so that the function f defined in (3.77) has a unique equilibrium point. First note that for arbitrary positive constants a, b, c and m, we have

$$h(0) = -bc < 0. \tag{3.79}$$

Therefore, if we have

$$h^{'}(x) \geq 0 \qquad \forall x \in \mathbb{R}_{+}, \tag{3.80}$$

then h can have at most one positive root so f has a unique fixed point. For $m > 1$, we have

$$\begin{aligned} h^{'}(x) &= (m+1)x^{m} - (m)(a+c)x^{m-1} + b \\ &= x^{m-1}((m+1)x - m(a+c)) + b = h_1(x) + b. \end{aligned}$$

In order to guarantee (3.80) , we should have

$$h_1(x) \geq -b \qquad \forall x \in \mathbb{R}_{+}. \tag{3.81}$$

But h_1 takes its minimum at the point y where

$$h_1^{'}(y) = 0. \tag{3.82}$$

As a result of (3.82), we get the following equations:

$$\begin{aligned} h_1^{'}(x) &= (m+1)(m)x^{m-1} - (m)(m-1)(a+c)x^{m-2} \\ &= x^{m-2}(m)(m+1)(x - \frac{m-1}{m+1}(a+c)) \\ &\Rightarrow h_1^{'}(y) = 0 \Leftrightarrow y = \frac{m-1}{m+1}(a+c) \\ &\Rightarrow \min(h_1(x)) = h_1\left(\frac{m-1}{m+1}(a+c)\right) \\ &= -\left(\frac{m-1}{m+1}\right)^{m-1}(a+c)^{m}. \end{aligned} \tag{3.83}$$

Combining this with (3.80) and (3.82), we arrive at the following result:

$$\left(\frac{m-1}{m+1}\right)^{m-1}(a+c)^{m} \leq b \Rightarrow h_1(x) \geq -b \Rightarrow h^{'}(x) \geq 0.$$

Hence the following result has been established.

Lemma 21. *Let f be given as a function in the form* (3.77)*. Then the following holds:*

(i) *If $m = 1$, then for any positive constants a, b and c, the function f has a unique fixed point.*

(ii) *If $m = 2,\ 3, \ldots$ and the positive constants a, b and c satisfy*

$$\left(\frac{m-1}{m+1}\right)^{m-1} (a+c)^m \leq b, \tag{3.84}$$

then f has a unique fixed point.

Proof. We already proved the case (ii). For the case where $m = 1$, let a, b and c be arbitrary positive constants. If y is a fixed point of the function f, we have

$$h(y) = y^2 + (b - a - c)y - bc = 0.$$

But h can have at most two roots. Since

$$h(0) < 0 \qquad h(-\infty) = \infty, \tag{3.85}$$

h has only one positive root; so, f has a unique fixed point. $\square$

We have said in Theorem 3 that under positive feedback, the solution converges to one of the equilibrium points independent of delay, see also [18]. Therefore, there should always exist at least one equilibrium point which is locally stable for all values of delay. The following result establishes this property.

Lemma 22. *Consider the system* (3.1) *under positive feedback, i.e., g defined in* (3.50) *satisfies:*

$$g^{'}(x) > 0 \qquad \forall x \in \mathbb{R}_+.$$

Suppose that g is bounded and continuously differentiable, then g has a fixed point $x_1 \in \mathbb{R}_+$ such that

$$g^{'}(x_1) \leq 1.$$

Thus, the system is locally stable around the equilibrium point $x_{eq} = (x_1, x_2, ..., x_n)$, *where*

$$x_n = g_n(x_1)/\lambda_n, \ldots, x_2 = g_2(x_3)/\lambda_2.$$

Proof. Since the function g is bounded, the following supremum is well-defined:

$$a = \sup_{x \in \mathbb{R}_+} (g(x)). \tag{3.86}$$

It is clear that if x is a fixed point of g, then $x \leq a$. Let the set S be defined as

$$S = \{x \in \mathbb{R}_+ : g(x) = x\}, \tag{3.87}$$

then, because of (3.86), $b = \sup(S)$ exists. Note that since g is bounded and positive, the set S is nonempty. Since $b = \sup(S)$, there exists a sequence $x_i \in S$ such that

$$g(x_i) = x_i \quad \text{and} \quad \lim_{i \to \infty} (x_i) = b. \tag{3.88}$$

Since g is continuous, we have

$$g(b) = b.$$

Suppose that for all fixed points x of g, we have

$$g^{'}(x) > 1.$$

Then, $g(b) = b$ and $g^{'}(b) > 1$, but since g bounded then $\exists z > b$ such that

$$g(z) = z. \tag{3.89}$$

But this is contradiction to (3.86), so there exists some $x_1 \in \mathbb{R}_+$ such that

$$g^{'}(x_1) \leq 1. \tag{3.90}$$

The stability of the linearized system follows from the structure of the transfer function given in (3.14) and using the result of Lemma 15. □

3.3 Simulation Results

We now illustrate the theoretical results obtained in previous sections by examples.

Example 3.3.1. We consider system (3.1) with $n = 3$, $\lambda_1 = \lambda_2 = \lambda_3 = 1$, and the nonlinearity functions are given by

$$g_1(x) = \frac{1}{1+x} \qquad g_2(x) = \frac{2}{2+x} \qquad g_3(x) = \frac{1}{3+x}. \tag{3.91}$$

The unique equilibrium point of the system can be found as $x_{eq} = (0.83, 0.4, 0.45)$ and at the unique fixed point of g we have

$$g^{'}(0.83) = 0.0173 < 1. \tag{3.92}$$

Therefore, by Proposition 2 we expect that the solution converges to x_{eq} independent of delay. Figure 3.2 shows the solution of the system with $x(0) = (1, 0.9, 0.8),\ \tau = 0$. As expected the solution converges to x_{eq}. Figure 3.3 is the solution of the same system with $x(0) = (0.4, 2, 0.6),\ \tau = 4$. The solution again converges to x_{eq}.

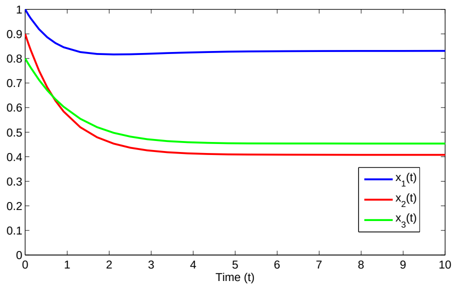

Figure 3.2: $x_1(t)$, $x_2(t)$ and $x_3(t)$ vs t graphs of system with $x(0) = (1, 0.9, 0.8),\ \tau = 0$

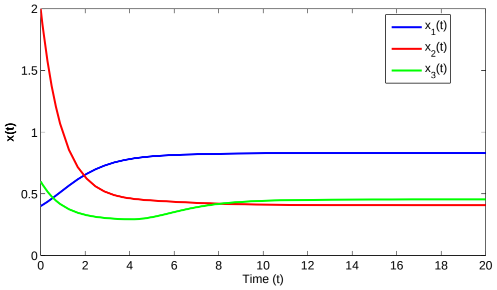

Figure 3.3: $x_1(t)$, $x_2(t)$ and $x_3(t)$ vs t graphs of system with $x(0) = (0.4, 2, 0.6)$, $\tau = 4$

Example 3.3.2. (Homogenous Negative Feedback Case) In this example we will try to illustrate the results of Proposition 4. Consider the homogenous negative feedback case with $a = 2$, $b = 0.25$, $m = 3$, $n = 3$ and f is given by

$$f(x) = \frac{2}{0.25 + x^3} \tag{3.93}$$

Note that

$$(\frac{a}{m})^m = 0.2963 > (\frac{b}{m-1})^{m+1} = 0.00024. \tag{3.94}$$

The function h defined as

$$h(x) = f \circ f(x),$$

has three fixed points given by $y_1 = 0.0039$, $y_2 = 1.1442$ and $y_3 = 8$. From Proposition 4 and Theorem 1 we expect oscillatory solutions of the system and the following inequality to be satisfied:

$$0.0039 = y_1 < \underline{\lim_{t\to\infty} x_i(t)} \leq \overline{\lim_{t\to\infty} x_i(t)} < y_3 = 8 \qquad \forall i = 1, 2, 3. \tag{3.95}$$

The simulation results, with initial conditions $x_1(0)$=1, $x_2(0) = 3$, $x_3(0) = 4$ and $\tau = 0$, are shown in Figure 3.4. We have periodic solutions as expected and the inequality in (3.95) is satisfied.

Now consider the same problem with $a = 2$, $b = 2$, $m = 3$, $n = 3$, then we have

$$f(x) = \frac{2}{2 + x^3} \quad \text{which implies} \quad (\frac{a}{m})^m = 1 < (\frac{b}{m-1})^{m+1} = 8. \tag{3.96}$$

In this case the unique equilibrium point can be calculated as

$$x_{eq} = (0.7709, 0.7709, 0.7709). \tag{3.97}$$

From Proposition 4, we expect the solution of the system to converge to x_{eq} for any initial condition. The simulation result with three sets of initial conditions and time delays are shown in Figures 3.5, 3.6 and 3.7. The simulation results confirms the theory: $x(t)$ converges to x_{eq} independent of delay in all the cases studied above.

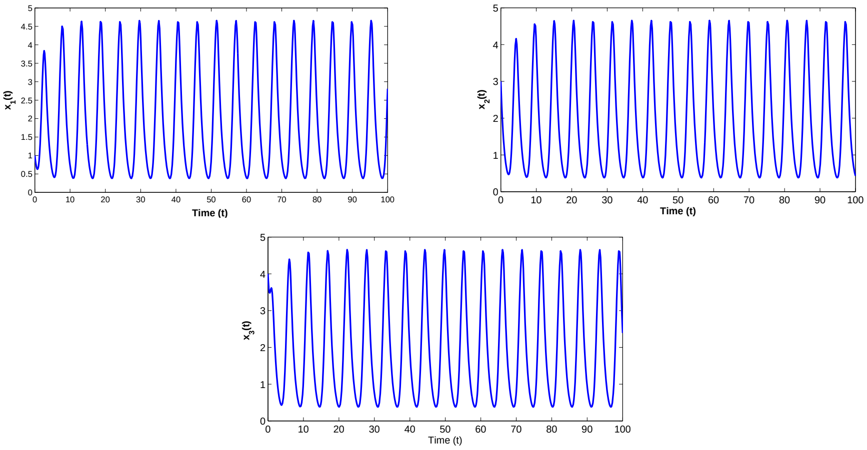

Figure 3.4: $x_1(t)$, $x_2(t)$ and $x_3(t)$ vs t graph of system with $x(0) = (3, 3, 4), \tau = 0$

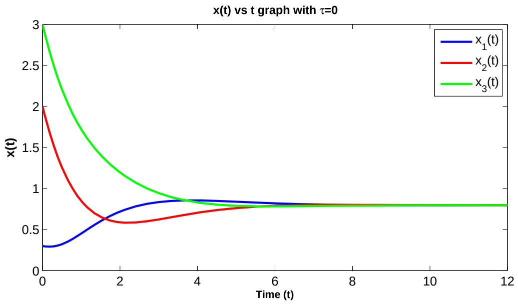

Figure 3.5: $x_1(t)$, $x_2(t)$ and $x_3(t)$ vs t graphs of system with $x(0) = (0.3, 2, 3),\ \tau = 0$

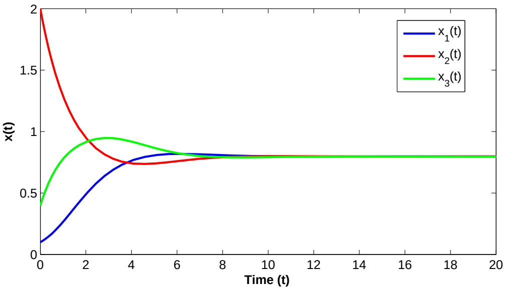

Figure 3.6: $x_1(t)$, $x_2(t)$ and $x_3(t)$ vs t graphs of system with $x(0) = (0.1, 2, 0.4)$, $\tau = 1$

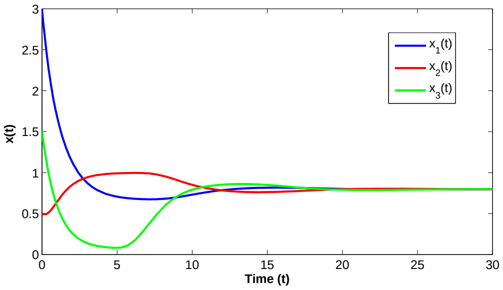

Figure 3.7: $x_1(t)$, $x_2(t)$ and $x_3(t)$ vs t graphs of system with $x(0) = (3, 0.5, 1.5)$, $\tau = 5$

Example 3.3.3. In this example, we will consider the homogenous gene regulatory network under positive feedback. For this purpose, let the function f be in the following form:

$$f(x) = \frac{3.6x^2}{5 + x^2} + 0.4. \tag{3.98}$$

Let $n = 3$, in this case the system has two equilibrium points

$$e_1 = (1, 1, 1), \qquad e_2 = (2, 2, 2). \tag{3.99}$$

From Theorem 3, we expect the general solution of the system either to converge to e_1 or to e_2. First, let us simulate the system with $x_1(0) = 0.9$, $x_2(0) = 0.95$ and $x_3(0) = 0.85$ and $\tau = 0$. We get the simulation results shown in Figure 3.8. As can be seen from Figure 3.8, the solution converges to the equilibrium point e_1. Let us simulate the same system with initial conditions $x_1(0) = 1$, $x_2(0) = 3$, $x_3(0) = 4$ and $\tau = 2$. The simulation results is shown in Figure 3.9. When we change the initial conditions, the system converges to the other equilibrium e_2 which is compatible with the theoretical results we obtained.

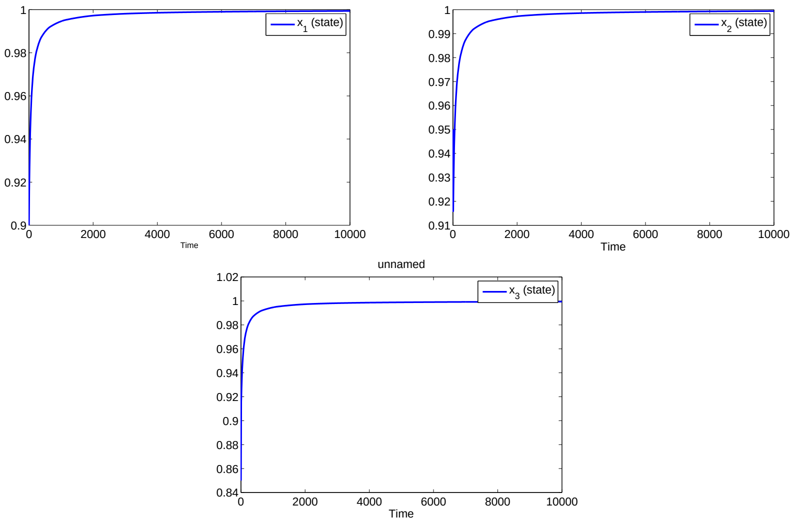

Figure 3.8: $x_1(t)$, $x_2(t)$ and $x_3(t)$, $\tau = 0$ vs t graph for the homogenous gene regulatory network under positive feedback

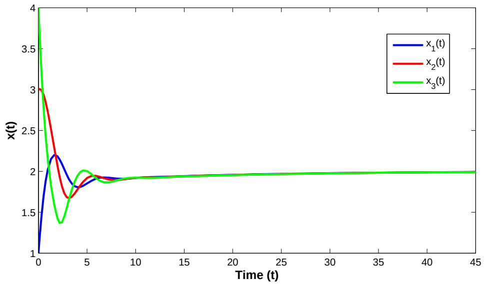

Figure 3.9: $x_1(t)$, $x_2(t)$, $x_3(t)$ and $\tau = 2$ vs t graph with $x(0) = (0.9, 0.95, 0.85),\ \tau = 0$

Example 3.3.4. In this example we will investigate the positive feedback with $n = 3$ and having the following nonlinearity function

$$f(x) = \frac{2x}{2+x} + 1. \tag{3.100}$$

This gives the unique equilibrium point $x_{eq} = (2, 2, 2)$, so we expect the solutions to converge to x_{eq} for any arbitrary initial condition. Figures 3.11 and 3.10 show the simulation results of the system corresponding to the initial conditions $x(0) = (3, 0.5, 4),\ \tau = 0$ and $x(0) = (5, 3, 0.7), \tau = 5$ respectively. As we expect the solution converges to the unique equilibrium point x_{eq}.

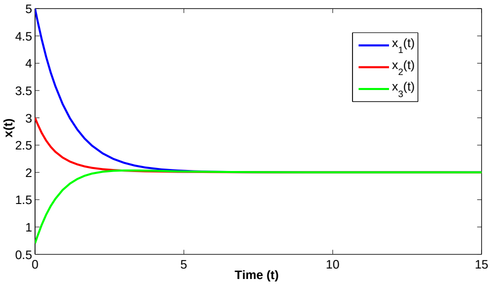

Figure 3.10: $x_1(t)$, $x_2(t)$ and $x_3(t)$ vs t graph with $x(0) = (5, 3, 0.7),\ \tau = 5$

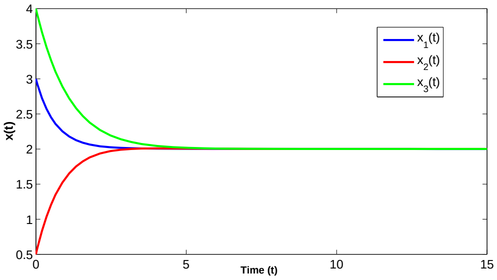

Figure 3.11: $x_1(t)$, $x_2(t)$ and $x_3(t)$ vs t graph with $x(0) = (3, 0.5, 4),\ \tau = 0$

Example 3.3.5. In this example, we will again investigate the homogenous positive feedback case but this time the system has three fixed points. Namely, consider the system (1.4) with $\lambda_i = 1$ and $g_i(x) = f(x)$ is given by

$$f(x) = g \circ g(x), \tag{3.101}$$

where g has the following form:

$$g(x) = \frac{2}{0.25 + x^3}. \tag{3.102}$$

The function g has the unique fixed point $y_2 = 1.1442$ and the function f has $y_1 = 0.0039$, $y_2 = 1.1442$ and $y_3 = 8$ as its three fixed points. Therefore, the system has three equilibrium points $z_1 = (y_1, y_1, y_1)$, $z_2 = (y_2, y_2, y_2)$ and $z_3 = (y_3, y_3, y_3)$. If we calculate the derivative of f at its fixed points, we get the following results:

$$f'(y_1) = 2.13 \cdot 10^{-6} < 1 \qquad f'(y_2) = 6.6096 > 1 \qquad f'(y_3) = 2.14 \cdot 10^{-6} < 1. \tag{3.103}$$

The characteristic equation $H^i_\tau(s)$ of the linearized system around each z_i is given by the following formula:

$$H^i_\tau(s) = 1 + \frac{(f(y_i))^3 e^{-\tau s}}{(s+1)^3} \qquad i = 1, 2, 3. \tag{3.104}$$

Since we have

$$(f(y_i))^3 < 1 \qquad \text{for} \quad i = 1, 3,$$

the system is locally stable independent of delay around z_1 and z_3. The linearized system around z_2 has the following characteristic equation:

$$H^2_\tau(s) = 1 + G_\tau(s) = 1 + \frac{288 e^{-\tau s}}{(s+1)^3}.$$

For $\tau = 0$, $G_0(s)$ has the Nyquist diagram shown in Figure 3.14. Since $G_0(s)$ encircles the point -1 twice, $H^2_\tau(s)$ has two zeros in $\mathbb{C}_+$. As we increase the delay value the first negative real axis crossing of $H^2_\tau(s)$ will always be less than -1, so the the Nyquist diagram encircles the point -1 more than once for all positive values of the delay. Therefore, the linearized system is locally unstable independent of delay around z_2. Therefore, we expect the solution to converge to either z_1 or z_3. Figure 3.12 shows the solution of the system with $x(0) = (1, 1.2, 1.4)$, $\tau = 0$. Although $x(0)$ is near to z_2 the solution converges to z_3. Figure 3.13 shows the simulation results of the system with $x(0) = (1, 0.9, 0.8)$ and $\tau = 2$. Again, $x(0)$ is near to z_2 but the solution converges to z_1 which confirms our theoretical expectations.

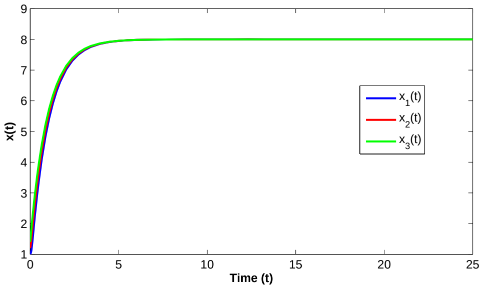

Figure 3.12: $x_1(t)$, $x_2(t)$ and $x_3(t)$ vs t graph with $x(0) = (1, 1.2, 1.4)$, $\tau = 0$

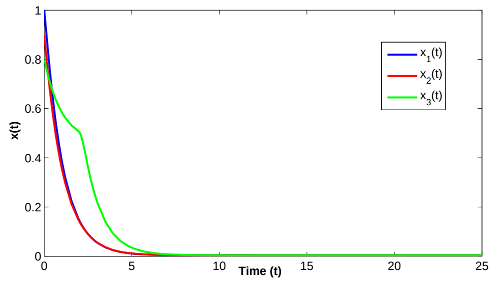

Figure 3.13: $x_1(t)$, $x_2(t)$ and $x_3(t)$ vs t graph with $x(0) = (1, 1.2, 1.4),\ \tau = 0$

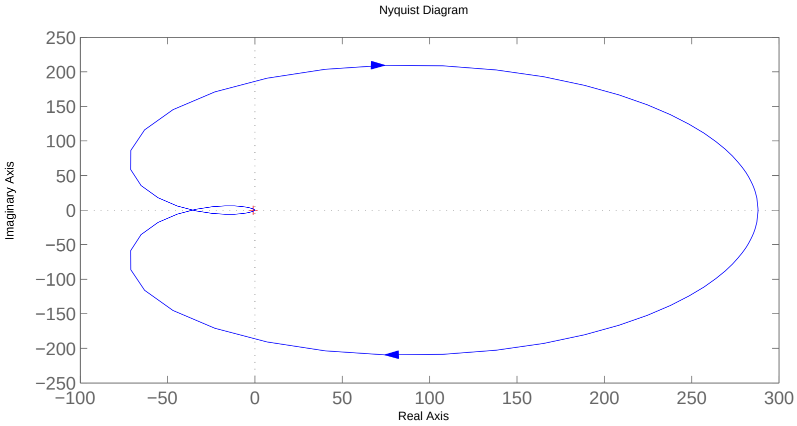

Figure 3.14: Nyquist Diagram of of $G_0(s)$

Chapter 4

A model of erythropoiesis

4.1 Erythropoiesis

In the paper [8], Lai *et.al.* proposed a dynamical model accounting for the process of murine erythropoiesis. In this chapter, we will consider the proposed model and develop some local stability results. Before starting the analysis, let us give a brief introduction to the process of erythropoiesis.

Erythrocytes, commonly known as red blood cells, are the most common type of blood cell in the human body which are responsible for the delivery of the oxygen to our tissues. This vital duty of red blood cells make them indispensable for human. In human body, nearly 2 million new erythrocytes are produced per second and at a given time a human may have approximately 20 trillion red blood cells. The new red blood cells are developed in the bone narrow and do have a life time of 100 days [28]. Erythrocytes have a red color due to the fact that it contains hemoglobin which is the iron-containing protein used for the oxygen transport.

Erythropoiesis is a 7 day process of production of erythrocytes which take place in the red bone marrow of our bones. Erythropoiesis is stimulated by the decrease of oxygen delivery to the kidney. A feedback loop involving erythropoietin (Epo) regulates the erythropoiesis. For normal times, the production of erythrocytes should be equal to the destruction of it and the total number of erythrocytes present in our body should be enough to satisfy the need of oxygen of our tissues. Figure 4.1 is presented for the visualization of the feedback mechanism involved in erythrocytes:

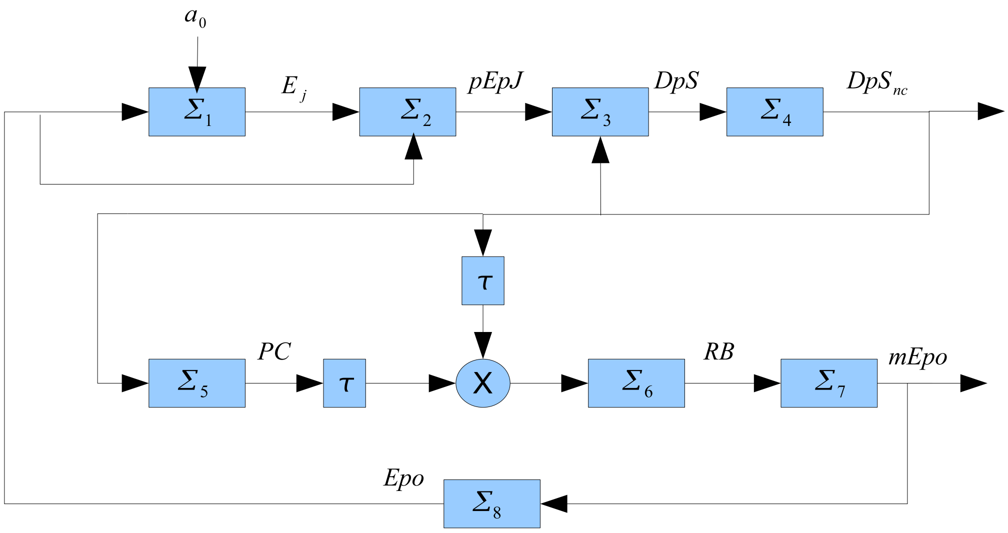

Figure 4.1: The feedback loop involved in the process of Erythropoiesis.

The Epo has the primary duty of protecting red blood cells from apoptosis which is the programmed cell death in organisms. One role of Epo during the formations of erythropoiesis is when Epo binds EpoR in non-differentiated cells of the bone marrow, the protein JAK2, which is responsible for DNA transcription and activity in the cell, is activated and promotes the activation of EpoR through the phosphorylation of several tyrosine which residues in the receptor. Then the transcription factor STAT5 is recruited to the activated EpoR, is phosphorylated, dimerised and gets activated. Once activated, dimerised STAT5 translocates into the nucleus and promotes the transcription of several essential genes involved in the modulation of erythropoiesis. The adequate function of the

JAK2-STAT5 signalling during erythropoiesis is crucial to ensure the success in the differentiation and maturation of red blood cells and recent results suggest that the pathway appears deregulated in certain kinds of leukaemia [8]. Hence, we see that Epo plays the major role for the process erythropoiesis to start.

4.2 Mathematical Model for Erythropoiesis

For the analysis of the model given in [8], we will assume zero Epo injection. After changing the symbols of variables of the mathematical model in [8], we have the following mathematical model:

$$\begin{aligned}
\frac{d}{dt}x_1(t) &= -a_1x_1(t) - a_2x_1(t)x_8(t) + a_0 \\
\frac{d}{dt}x_2(t) &= -a_3x_2(t) + a_2x_1(t)x_8(t) \\
\frac{d}{dt}x_3(t) &= -a_6x_3(t) + a_5(1 - 2x_3(t) - 2x_4(t))x_2(t) \\
\frac{d}{dt}x_4(t) &= -a_4x_4(t) + a_6x_3(t) \\
\frac{d}{dt}x_5(t) &= a_7x_5(t) - a_8x_5(t)x_4(t) - a_9x_5(t)^2 \\
\frac{d}{dt}x_6(t) &= -a_{11}x_6(t) + a_{10}x_5(t-\tau)x_4(t-\tau) \\
\frac{d}{dt}x_7(t) &= -a_{13}x_7(t) + \frac{a_{12}}{x_6^g(t)} \\
\frac{d}{dt}x_8(t) &= -a_{15}x_8(t) + a_{14}x_7(t). \qquad (4.1)
\end{aligned}$$

The values of the positive constants a_i and the biological parameters corresponding model states x_i are given in Appendix A. As the biological model variables x_i make sense when they take positive values, we will analyze the system (4.1) in the cone $\mathbb{R}^8_+$. As we said in Chapter 2, equilibrium points play an important role in the analysis of dynamical systems. For that reason we start the analysis of the system (4.1) by determining the equilibrium points of it in $\mathbb{R}^8_+$. We present the following Lemma regarding the equilibrium points of the system (4.1):

Lemma 23. *The system* (4.1) *has a unique equilibrium point in* $\mathbb{R}^8_+$.

Proof. Let $x = (x_1, ..., x_8) \in \mathbb{R}^8_+$ be an equilibrium point of the system (4.1). Firstly, note that

$$x_i \neq 0 \qquad \forall i = 1, 2, ..., 8.$$

Because if $x_6 = 0$ we have

$$x_7 = \infty$$

or if $x_i = 0$ for $i \neq 6$ we have

$$x_6 = \infty.$$

Therefore, $x_i \neq 0$ for all $i = 1, 2, ..., 8$. After this little remark, we can safely say that at an equilibrium point x the following equations are satisfied:

$$\begin{aligned}
x_1 &= \frac{a_0}{a_1} - \frac{a_2}{a_1} x_1 x_8 \\
x_2 &= \frac{a_2}{a_3} x_1 x_8 \\
x_3 &= \frac{a_5}{a_6} (1 - 2x_3 - 2x_4) x_2 \\
x_4 &= \frac{a_6}{a_4} x_3 \\
x_5 &= \frac{a_7}{a_9} - \frac{a_8}{a_9} x_4 \\
x_6 &= \frac{a_{10}}{a_{11}} x_5 x_4 \\
x_7 &= \frac{(a_{12}/a_{13})}{x_6^g} \\
x_8 &= \frac{a_{14}}{a_{15}} x_7, \qquad (4.2)
\end{aligned}$$

where

$$x_i > 0 \qquad \forall i = 1, 2, ..., 8. \qquad (4.3)$$

By carefully organizing the equations in (4.2), we get the following set of equations:

$$\begin{aligned}
x_1 &= \frac{a_0}{a_1 + a_2 x_8} = g_1(x_8)\\
x_2 &= \frac{a_2}{a_3} x_1 x_8 = \frac{a_2}{a_3} x_1 \left(\frac{a_0 - a_1 x_1}{a_2 x_1} \right) = g_2(x_1)\\
x_3 &= \frac{a_5}{a_6}(1 - 2x_3 - 2x_4) x_2 = \frac{(a_5 a_4) x_2}{a_6 a_4 + (2a_5(a_6 + a_4)) x_2} = g_3(x_2)\\
x_4 &= \frac{a_6}{a_4} x_3 = g_4(x_3)\\
x_5 &= \frac{a_7}{a_9} - \frac{a_8}{a_9} x_4 = g_5(x_4)\\
x_6 &= \frac{a_{10}}{a_{11}} x_5 x_4 = \frac{a_{10}}{a_{11}} x_5 \left(\frac{a_7 - a_9 x_5}{a_8} \right) = g_6(x_5)\\
x_7 &= \frac{(a_{12}/a_{13})}{x_6^g} = g_7(x_6)\\
x_8 &= \frac{a_{14}}{a_{15}} x_7 = g_8(x_7), \qquad (4.4)
\end{aligned}$$

Notice that for $t > 0$ the functions $g_i(t)$ in (4.4) are well defined functions from $\mathbb{R}_+$ to $\mathbb{R}$. In fact, the only problematic function is g_7 since for $t < 0$ the function

$$g_7(t) = (t)^{6.19} \qquad (4.5)$$

may take complex values. But for biological reasons we are interested in equilibrium points with positive coordinates. Note that except for g_2 and g_6, we have functions that are well-defined from $\mathbb{R}_+$ to $Y_i \subseteq \mathbb{R}_+$. Now, suppose that we have two equilibrium points x, $y \in \mathbb{R}^n_+$. If for some $i \in \{1, 2, ..., 8\}$ we have

$$x_i = y_i, \qquad (4.6)$$

then from (4.6) and (4.4) we get the following set of equations:

$$x_{i+1} = y_{i+1} = g_i(x_i) = g_i(y_i) \qquad \forall i = 1, 2, ..., 7. \qquad (4.7)$$

Equation (4.7) implies that $x_8 = y_8$, so we have

$$x_1 = g_1(x_8) = g_1(y_8) = y_1. \qquad (4.8)$$

Therefore, we have $x = y$. In other words, if two equilibrium points of the system (4.1) have the same value for some coordinate, then these two equilibrium points are equal to each other. Since we are interested only in the equilibrium points with positive coordinates, we have to find the intervals $I_i \subseteq \mathbb{R}_+$ such that $g_i(I_i) \subseteq \mathbb{R}_+$. Now, notice the following facts:

$$\begin{aligned}
g_1 &: \mathbb{R}^+ \to [0, a_0/a_1],\ g_1^{'} < 0 \\
g_2 &: [0, a_0/a_1] \to [0, a_0/a_3],\ g_2^{'} < 0 \\
g_3 &: [0, a_0/a_3] \to \left[0, \frac{a_0a_4a_5}{a_0a_4a_6 + 2a_5(a_4+a_6)}\right],\ g_3^{'} > 0 \\
g_4 &: \left[0, \frac{a_0a_4a_5}{a_0a_4a_6 + 2a_5(a_4+a_6)}\right] \to Y_4,\ g_4^{'} > 0 \\
g_5 &: \left[0, \frac{a_0a_5a_6}{a_0a_4a_6 + 2a_5(a_4+a_6)}\right] \to Y_5,\ g_5^{'} < 0 \\
g_6 &: \left[b, \frac{a_7}{a_9}\right] \to \left[0, \frac{a_{10}b(a_7 - a_9b)}{a_8a_{11}}\right],\ g_6^{'} > 0 \\
g_7 &: \mathbb{R}^+ \to \mathbb{R}^+,\ g_7^{'} < 0 \\
g_8 &: \mathbb{R}^+ \to \mathbb{R}^+,\ g_8^{'} > 0,
\end{aligned} \tag{4.9}$$

where $b > a_7/(2a_9)$, Y_4 and Y_5 are given by

$$\begin{aligned}
b &= \frac{a_7(a_0a_4a_6 + 2a_5(a_4+a_6)) - a_0a_5a_6}{a_9(a_0a_4a_6 + 2a_5(a_4+a_6))} \\
Y_4 &= \left[0, \frac{a_0a_5a_6}{a_0a_4a_6 + 2a_5(a_4+a_6)}\right] \\
Y_5 &= \left[\frac{a_7(a_0a_4a_6 + 2a_5(a_4+a_6)) - a_0a_5a_6a_8}{a_9(a_0a_4a_6 + 2a_5(a_4+a_6))}, \frac{a_7}{a_9}\right].
\end{aligned} \tag{4.10}$$

Note that by constructing the domains and ranges of the functions g_i, we have made related calculations so that the following function is well-defined:

$$g(y) = g_6 \circ g_5 \circ g_4 \circ g_3 \circ g_2 \circ g_1 \circ g_8 \circ g_7(y). \tag{4.11}$$

From (4.9), we see that g is a well defined function from $\mathbb{R}_+$ to $\left[0, \frac{a_{10}b(a_7-a_9b)}{a_8a_{11}}\right]$ and by chain rule we have the following equality:

$$\begin{aligned}
g^{'}(y) &= g_6^{'}(g_5(g_4(g_3(g_2(g_1(g_8(g_7(y)))))))) \times g_5^{'}(g_4(g_3(g_2(g_1(g_8(g_7(y))))))) \\
&\times g_4^{'}(g_3(g_2(g_1(g_8(g_7(y)))))) \times g_3^{'}(g_2(g_1(g_8(g_7(y))))) \times g_2^{'}(g_1(g_8(g_7(y)))) \\
&\times g_1^{'}(g_8(g_7(y))) \times g_8^{'}(g_7(y)) \times g_7^{'}(y) \quad \forall y \in \mathbb{R}_+.
\end{aligned}$$

From equation (4.9), we have

$$g^{'}(y) < 0 \qquad \forall y \ \in \mathbb{R}_+ \tag{4.12}$$

Notice that for any equilibrium point $x = (x_1, ..., x_8)$ of the system (4.1), we have the following equality:

$$x_6 = g(x_6).$$

In other words, for every equilibrium point of the system (4.1), we have a fixed point of the function g. But we have also shown that, two different equilibrium points have different coordinates. Therefore, the system (4.1) has as many equilibrium points as the fixed points of g. Since g is a function from $\mathbb{R}_+$ to $\left[0, \frac{a_{10}b(a_7-a_9b)}{a_8a_{11}}\right]$, by Lemma 6 we conclude that g has a unique fixed point, which implies that the system (4.1) has a unique equilibrium point. $\square$

To find the unique equilibrium point of the system (4.1), we need only to find the unique fixed point of g defined in the proof of Lemma 23. The unique fixed point of g gives us the sixth coordinate x_6 of the unique equilibrium point x of the system (4.1). To find other coordinates of the equilibrium point, we just use the relation in (4.9). We conclude this section with the following result.

Proposition 6. *For any $\tau \geq 0$, the system* (4.1) *has a linearization around its unique equilibrium point with a characteristic function in the following form:*

$$\chi(s) = P(s) + Q(s)e^{-\tau s}, \tag{4.13}$$

where $P(s)$, $Q(s)$ are polynomials with $deg(P) > deg(Q)$ and the function $P(s)$ has no zeros in $\mathbb{C}_+$. The characteristic equation $\chi(s)$ is stable $\forall\tau < \tau_m$ and unstable $\forall\tau > \tau_m$, where τ_m is the smallest positive integer such that $\exists\ \omega_m \geq 0$ satisfying

$$\chi(j\omega_m) = P(j\omega_m) + Q(j\omega_m)e^{-\tau j\omega_m} = 0.$$

Proof. For the proof of this Lemma, we will first linearize the system (4.1) around its unique equilibrium point and then show that the characteristic equation of the linearized system is stable $\forall\tau < \tau_m$, which in turn implies that the system (4.1) is locally stable around its unique equilibrium point $\forall\tau < \tau_m$. Let

$$x_{eq} = (x_1, ..., x_8) \quad \in \ R_+^8$$

be the unique equilibrium point of the system (4.1), then the linearization of the system (4.1) around x_{eq} will give us the following linear system:

$$\dot{x} = A_0 x(t) + A_1 x(t-\tau), \tag{4.14}$$

where A_0, A_1 are $R^{8\times 8}$ constant matrices in the following form:

$$A_0 = \begin{bmatrix} -k_1 & 0 & 0 & 0 & 0 & 0 & 0 & -k_2 \\ k_3 & -k_4 & 0 & 0 & 0 & 0 & 0 & k_2 \\ 0 & k_5 & -k_6 & -k_7 & 0 & 0 & 0 & 0 \\ 0 & 0 & k_8 & -k_9 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -k_{10} & -k_{11} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -k_{12} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -k_{13} & -k_{14} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & k_{15} & -k_{16}, \end{bmatrix} \tag{4.15}$$

$$A_1 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & k_{17} & k_{18} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0, \end{bmatrix} \tag{4.16}$$

and k_i's are positive constants given by:

$$\begin{array}{llllll}
k_1 = & a_2x_8 + a_1 = \dfrac{a_0}{x_1} & k_2 = & a_2x_1 & k_3 = & a_2x_8 \\
k_4 = & a_3 & k_5 = & a_5(1 - 2x_3 - 2x_4) = \dfrac{a_6x_3}{x_2} & k_6 = & 2a_5x_2 + a_6 \\
k_7 = & 2a_5x_2 & k_8 = & a_6 & k_9 = & a_4 \\
k_{10} = & a_8x_5 & k_{11} = & a_9x_5 & k_{12} = & a_{11} \\
k_{13} = & ga_{12}x^{-g-1} = \dfrac{ga_{13}x_7}{x_6} & k_{14} = & a_{13} & k_{15} = & a_{14} \\
k_{16} = & a_{15} & k_{17} = & a_{10}x_5 & k_{18} = & a_{10}x_4.
\end{array}$$

The characteristic equation of the linearized system (4.14) can be calculated by the following formula:

$$\chi(s) = det(sI - A_0 - A_1e^{-\tau s}). \tag{4.17}$$

Let us now seperate the matrix $(sI - A_0 - A_1e^{-\tau s})$ into four submatrices as following:

$$(sI - A_0 - A_1e^{-\tau s}) = \begin{bmatrix} B_1 & B_2 \\ B_3 & B_4, \end{bmatrix} \tag{4.18}$$

where $B_i \in \mathbb{R}^{4\times4}$ are the four sub-matrices of $(sI - A_0 - A_1e^{-\tau s})$. By the the result given in Appendix B, we have the following equality:

$$\chi(s) = det(sI - A_0 - A_1e^{-\tau s}) = det(B_4)det(B_1 - B_2B_4^{-1}B_3). \tag{4.19}$$

Before moving further, let us write the matrices B_1, B_2, B_3 and B_4 explicitly:

$$B_1 = \begin{bmatrix} s+k_1 & 0 & 0 & 0 \\ -k_3 & s+k_4 & 0 & 0 \\ 0 & -k_5 & s+k_6 & k_7 \\ 0 & 0 & -k_8 & s+k_9 \end{bmatrix} \qquad B_2 = \begin{bmatrix} 0 & 0 & 0 & k_2 \\ 0 & 0 & 0 & -k_2 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$B_4 = \begin{bmatrix} s+k_{11} & 0 & 0 & 0 \\ -k_{18}e^{-\tau s} & s+k_{12} & 0 & 0 \\ 0 & k_{13} & s+k_{14} & 0 \\ 0 & 0 & -k_{15} & s+k_{16} \end{bmatrix} \qquad B_3 = \begin{bmatrix} 0 & 0 & 0 & k_{10} \\ 0 & 0 & 0 & -k_{17}e^{-\tau s} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \tag{4.20}$$

Notice that

$$\det(B_4) = (s + k_{11})(s + k_{12})(s + k_{14})(s + k_{16}),$$

which obviously has no roots in $\mathbb{C}_+$. To continue our analysis, we need to calculate $det(B_1 - B_2 B_4^{-1} B_3)$. Firstly, notice the following:

$$\begin{aligned}
(B_2 B_4^{-1} B_3) &= B_2 \begin{bmatrix} x_1 & 0 & 0 & 0 \\ x_2 & x_5 & 0 & 0 \\ x_3 & x_6 & x_8 & 0 \\ x_4 & x_7 & x_9 & x_{10} \end{bmatrix} B_3. && (4.21)\\
&= B_2 \begin{bmatrix} 0 & 0 & 0 & x_1 k_{10} \\ 0 & 0 & 0 & x_2 k_{10} - x_5 k_{17} e^{-\tau s} \\ 0 & 0 & 0 & x_3 k_{10} - x_6 k_{17} e^{-\tau s} \\ 0 & 0 & 0 & x_4 k_{10} - x_7 k_{17} e^{-\tau s} \end{bmatrix} && (4.22)\\
&= \begin{bmatrix} 0 & 0 & 0 & k_2 c(s) \\ 0 & 0 & 0 & -k_2 c(s) \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0, \end{bmatrix} && (4.23)
\end{aligned}$$

where $c(s)$ is given by the following equation:

$$c(s) = (x_4 k_{10} - x_7 k_{17} e^{-\tau s}) = k_{13} k_{15} k_{17} (s + k_{11} - \frac{k_{10} k_{18}}{k_{17}}).$$

Then, we have the following equality:

$$\begin{aligned}
det(B_1 - B_2 B_4^{-1} B_3) &= det\left(\begin{bmatrix} s + k_1 & 0 & 0 & -k_2 c(s)) \\ -k_3 & s + k_4 & 0 & k_2 c(s) \\ 0 & -k_5 & s + k_6 & 0 \\ 0 & 0 & -k_8 & 0 \end{bmatrix}\right) \\
&= (s + k_1)(s + k_4)(s^2 + (k_6 + k_9)s + k_6 k_9 + k_7 k_8) \\
&+ k_2 k_5 k_8 c(s)(s + k_1 - k_3).
\end{aligned}$$

Then the characteristic equation of the linearized is given by the following:

$$\begin{aligned} \chi(s) &= det(sI - A_0 - A_1 e^{-\tau s}) = det(B_4) det(B_1 - B_2 B_4^{-1} B_3) \\ &= (s + k_1)(s + k_4)(s^2 + (k_6 + k_9)s + k_6 k_9 + k_7 k_8) \\ &\times \ (s + k_{11})(s + k_{12})(s + k_{14})(s + k_{16}) \\ &\times \ (1 + K e^{-\tau s} G_1(s) G_2(s) G_3(s)), \end{aligned}$$

where K, $G_1(s)$, $G_2(s)$ and $G_3(s)$ are given by

$$\begin{aligned} K &= (k_2 k_5 k_8 k_{13} k_{15} k_{17}) \\ G_1(s) &= \frac{s + k_1 - k_3}{s + k_{11}} \\ G_2(s) &= \frac{(s + k_{11} - \frac{k_{10} k_{18}}{k_{17}})}{s + k_{12}} \\ G_3(s) &= \frac{1}{(s + k_1)(s + k_4)(s + k_{14})(s + k_{16})(s^2 + (k_6 + k_9)s + k_6 k_9 + k_7 k_8)}. \end{aligned}$$

For any $s_0 \in \mathbb{C}_+$ the following condition is satisfied:

$$\chi(s_0) = 0 \Leftrightarrow (1 + K e^{-\tau s} G_1(s_0) G_2(s_0) G_3(s_0)) = 0. \tag{4.24}$$

When we do the related calculations, we observe the following equations:

$$\begin{aligned} (k_1 - k_3) = 0.15 &> 0.009 = k_{11} \\ (k_{11} - \frac{k_{10} k_{18}}{k_{17}}) = 0.00899 &> k_{12} = 0.00016. \end{aligned}$$

But this implies that the functions

$$|G_1(j\omega)|, \quad |G_2(j\omega)|, \text{ and } \quad |G_3(j\omega)| \qquad \omega \in [0, \infty] \tag{4.25}$$

are decreasing. Let us define the following function:

$$G(s) = G_1(s) G_2(s) G_3(s). \tag{4.26}$$

For

$$\tau > \frac{1}{k_1 - k_3} + \frac{1}{k_{11} - \frac{k_{10} k_{18}}{k_{17}}} = 118, \tag{4.27}$$

$$\angle(G(j\omega) e^{-j\omega}) \tag{4.28}$$

is a decreasing function of ω. But then we have a very similar situation like in Lemma 3. In fact, the results we obtained in Lemma 3 are valid here. The function G defined in (4.26) belongs to $\mathcal{H}^\infty$, and $|G(j\omega)|$ is a decreasing function of $\omega \in [0, \infty]$. Note that the characteristic function of the linearized system is stable if and only if the characteristic equation

$$H_\tau(s) = 1 + Ke^{-\tau s}G(s) = 0$$

has no roots in $\overline{\mathbb{C}}_+$. For $\tau = 0$, we will prove in simulation part that the delay free characteristic equation $H_0 = 1 + KG(s)$ is stable. We also have $KG(0) > 1$, hence we do not have stability independent of delay condition. Note that $G(s)$ has no poles in $\mathbb{C}_+$. Increasing delay will make the linearized system unstable since the functions

$$|G(j\omega)|, \qquad \angle(G(j\omega)e^{-j\omega})$$

are decreasing functions of ω and we have

$$KG(0) > 1.$$

Therefore, if we increase the delay value enough, the first negative axis crossing of the Nyquist plot of the function $H_\tau(s)$ will be at a value less than -1 so the Nyquist plot of the function $H_\tau(s)$ will encircle the point -1 at least once so the characteristic equation will be unstable as a result of the Nyquist criteria. To find the critical value τ, we will use the fact that the roots of the characteristic function of the linearized system depends continuously on the parameter τ which means that the characteristic function of the linearized system will be stable for all $\tau < \tau_m$ where τ_m is the smallest positive number such that the function

$$H_\tau(s) = 1 + Ke^{-\tau s}G(s)$$

has a root on the imaginary axis. Since $|G(j\omega)|$ is a decreasing function of ω, we can find the critical value of τ_m by the following formula:

$$\tau_m = \frac{PM}{\omega_m}, \tag{4.29}$$

where PM denotes the phase margin of the characteristic function $KG(s)$ [20]. As $|G(j\omega)|$ is a decreasing function, when we increase $\tau > \tau_m$ the Nyquist plot of the function

$$Ke^{-\tau s}G(s) \tag{4.30}$$

will encircle -1 more than once since if τ is increased first negative real axis crossing of the Nyquist plot will happen at a lower frequency. Hence, $|G(j\omega)|$ at this low frequency will be greater than 1. This completes our proof that the system will be stable for all $\tau < \tau_m$ and it will be unstable for all $\tau > \tau_m$. In (4.29), we have shown that the calculation τ_m will require the value of the gain margin of some characteristic function which can be calculated by simulation programs easily. For analytic calculation, we will use the fact that the function $|G(j\omega)|$ is decreasing. We know that

$$|G(0)K| > 1,$$

and $|G(j\omega)K|$ is a strictly decreasing function of ω and we have

$$\lim_{\omega\to\infty} |G(j\omega)K| = 0.$$

By the intermediate value theorem $\exists\omega_m > 0$ such that

$$|G(j\omega_m)K| = 1.$$

Since $|G(j\omega)K|$ is strictly decreasing function of ω we have a unique gain crossover frequency, which can be found by the solution of the roots of a polynomial. To see this note that

$$|G(j\omega)K| = \left|\frac{P(j\omega)}{Q(j\omega)}\right| = \frac{P_m(\omega)}{Q_m(\omega)},$$

where $P_m(\omega)$ and $Q_m(\omega)$ are polynomials. Hence, we have the following equality:

$$\begin{aligned} P_m(\omega_m) - Q_m(\omega_m) &= 0 \\ &\Rightarrow \omega_m \text{ is the positive root of the polynomial } P_m(\omega) - Q_m(\omega). \end{aligned}$$

Then, τ_m is given by the following equation:

$$\tau_m = \frac{\pi + \angle(G(j\omega_m))}{\pi}.$$

□

We have shown the local stability of the equilibrium point of the system (4.1) for some values of the delay. Note that since the nonlinearities involved in the system (4.1) are somehow arbitrary, we could not estimate the domain of attraction of the unique equilibrium point of the system (4.1). If $x_i = 0$ for some $i = 1, 2, ..., 8$, then we have $\dot{x}_i \geq 0$, which means that $\mathbb{R}^8_+$ is an invariant set of the the system (4.1). But due to the shape of nonlinearities, the system can not be categorized as a monotone dynamical system, which makes it hard for us to make a complete analysis of the system (4.1). Therefore, the global analysis of system (4.1) is still an open question.

4.3 Simulation Results

In this section we will try to verify results obtained in the previous section by means of simualtions. We calculated the coordinates unique x_{eq} equilibrium of the system (4.1) as following:

$$\begin{array}{llll} x_1 = 0.997928 & x_2 = 0.000296 & x_3 = 0.000236 & x_4 = 0.000229 \\ x_5 = 3 & x_6 = 0.4957 & x_7 = 0.007329 & x_8 = 0.062302 \end{array}$$

To calculate τ_m, we first show that the linearized delay free system is stable. We do this by drawing the Nyquist graph of the function $KG(s)$. The graph we obtained is presented in Figure 4.2.

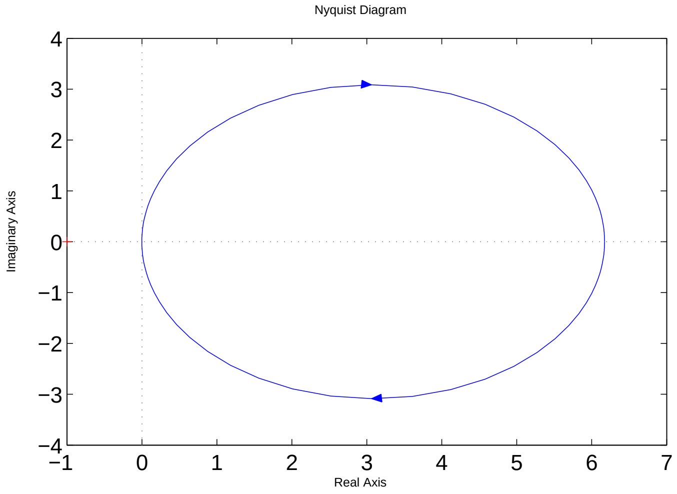

Figure 4.2: Nyquist Plot of the function $KG(s)$.

As we can see from Figure 4.2 the Nyquist plot does not encircle -1, therefore $1 + KG(s)$ is stable. We also see that increasing delay may make the system unstable. For the calculation of τ_m, we will benefit from the Bode plot of $KG(s)$. Figure 4.3 shows the Bode plot of the function $KG(s)$; we can conclude from this plot that the undelayed system is stable. The phase margin and crossover frequency of the system are calculated as

$$PM = 1.73 \text{ rad}, \qquad \omega_m = 0.01 \text{ rad}h^{-1}. \tag{4.31}$$

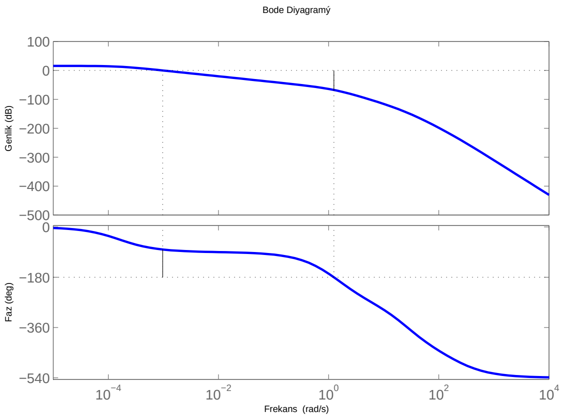

Figure 4.3: Bode plot of the function $KG(s)$.

Then, the critical τ_m can be calculated as:

$$\tau_m = PM/\omega_m = 1.73/0.01 = 1730 \ h. \tag{4.32}$$

The biologic variable x_6, which represents the red blood cell levels, is biologically more important than the other variables. Therefore, we only show the simulation results corresponding to x_6. The unit of time in the simulations are hours (h). The sixth coordinate of the output of system with initial conditions $y = (0.3, 0.4, 1.5, 1.2, 2, 0.2, 0.2, 0.2)$ and delay value $\tau = 1000 \ h < \tau_m$ are given in Figure 4.4. As we can see in Figure 4.4 x_6 converges to the sixth coordinate of x_{eq}, which is compatible the theoretical results.

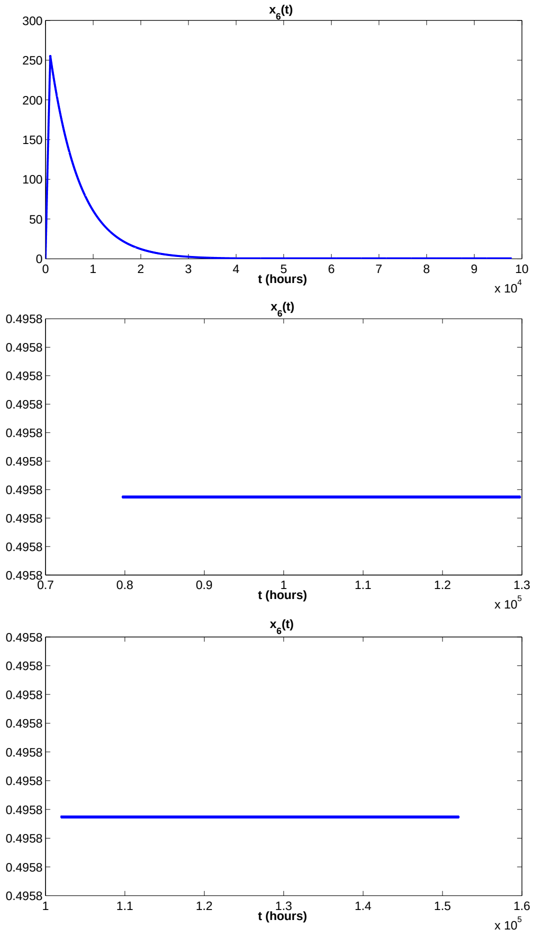

Figure 4.4: Output of the sixth coordinate x_6 with initial conditions y and $\tau = 1000h$.

Figure 4.5 shows the simulation results corresponding to the initial condition $y_\nu = (1.3, 0.03, 0.03, 0.03, 3.2, 0.6, 0.01, 0.01)$ and a time delay of

$$\tau = 5000\ h > \tau_m. \tag{4.33}$$

From equation (4.33), we can conclude that the equilibrium point is locally unstable for this value of delay. From Figure 4.5 we see that x_6 has an oscillatory behavior, which confirms the local unstability of x_{eq}.

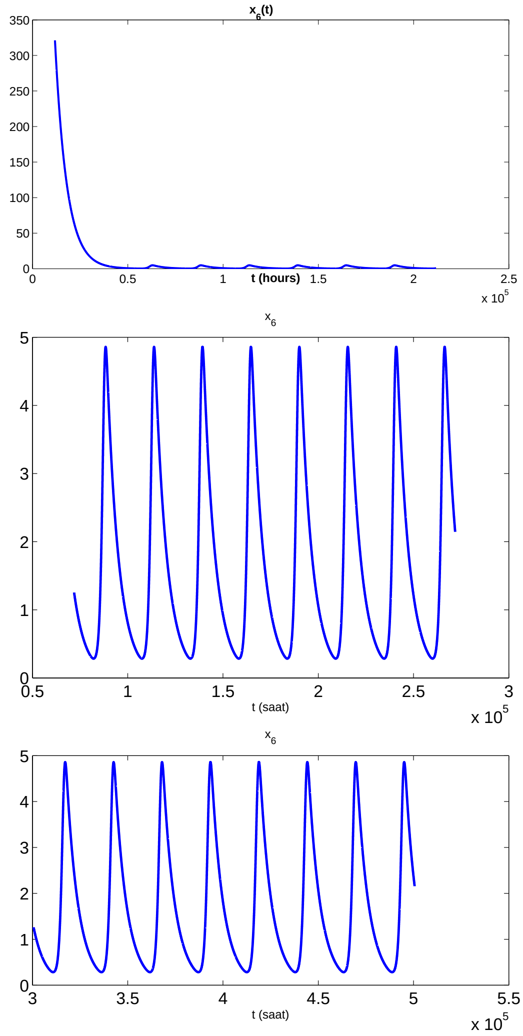

Figure 4.5: Output of the sixth coordinate x_6 with initial conditions y_ν and $\tau = 5000h$.

Although after looking Figures 4.4 one may be tempted to conclude that the general solution of the system (4.1) converges to x_{eq}, it may not be the case since the result we proved in the previous section is just a local stability result. Therefore, there may exists some initial conditions such that the solutions corresponding to these initial conditions may not converge to x_{eq}. The system can have periodic solutions or it may even show chaotic behavior. A global analysis will more likely require some advanced results from differential topology[29]. So further work is required to prove the observation that the unique equilibrium x_{eq} of the system (4.1) is a global attractor.

Chapter 5

Conclusions

In this work, we analyzed two cyclic nonlinear biological models with time delays, namely, the genetic regulatory network and the erythropoiesis model. For the analysis of the genetic regulatory network, we assume that the nonlinearity functions have negative Schwarzian derivatives and by the help of the results presented in [4], [5], and [18], we performed a detailed analysis of the genetic regulatory feedback. For the erythropoiesis model, we proved a delay dependent local stability result.

In Chapter 2, we gave the required mathematical background and some preliminary results which are needed for our analysis in Chapters 3 and 4. We also recalled some basic results for the analysis of linear time delay systems. Another important concept from Chapter 2 is the Schwarzian derivative. We proved that functions having negative Schwarzian derivatives can only have two forms. Based upon this classification, we proved some results about the fixed points of such functions.

In Chapter 3, we considered gene regulatory networks modeled as cyclic nonlinear dynamical systems with time delayed feedback. We analyzed negative feedback and positive feedback cases separately. We assumed that the nonlinearity functions have negative Schwarzian derivatives.

For the negative feedback case we obtained global stability conditions independent of delay. Also derived is a condition for instability independent of delay (leading to oscillatory behavior); the computation of a general expression for the period of oscillations is the subject of a future study. As a special case of the negative feedback, we considered the homogenous gene regulatory network where all nonlinearity functions are equal to a Hill function. For this case, we proved a delay independent global stability result depending only on the parameters of the Hill function. A similar result is given for the existence of oscillatory solutions.

For positive feedback case, we derived conditions for single positive equilibrium point, which is asymptotically stable independent of delay. In some cases there are more than one equilibrium point. For these cases, we demonstrated how to compute these equilibrium points and whether they are stable or not. For the case with more than one locally stable equilibrium, one interesting problem can be the calculation of the radius of convergence of each stable equilibrium point. Furthermore, homogenous network is considered as a special case and some easy result to check existence of single equilibrium point is proven.

In Chapter 4, we analyzed a mathematical model of Erythropoiesis proposed in [8]. We first showed that the model has a unique fixed point in $\mathbb{R}^8_+$. Then, the linearization of the system around this unique fixed gave us a locally stable system for some values of delay. We also found the critical delay value and showed, by the help of simulations, for delay values larger than this critical value, the system has oscillatory behavior.

APPENDIX A

Erythropoiesis Model

A.1 Model Variables

Variable Symbol	Variable Name	Variable Definition
x_1	Ej	Non-activated receptor complex EpoR/JAK2
x_2	pEpJ	Epo-bound activated EpoR/JAK2 complex
x_3	DpS	Activated cytosolic STAT5
x_4	DpS_{nc} (pEpj)	Activated nuclear STAT5
x_5	PC	Red blood progenitor cell levels
x_6	RB	Cells levels
x_7	mEpo	Levels of Epo messenger RNA in the renal cortices
x_8	Epo	Blood levels of erythropoietin, Epo

Table A.1: Model variables of Erythropoiesis

A.2 Model Parameters

Parameters	Definition	Value
a_0	Synthesis rate of non-activated receptor complex (Ej)	0.15 h^{-1}
a_1	Degradation rate of Ej	0.15 h^{-1}
a_2	Activation rate of Epo	0.005 h^{-1}
a_3	Degradation rate of activated EpoR/JAK2 (pEpj)	1.05 h^{-1}
a_4	Degradation rate of nuclear STAT5 (DpS_{nc})	28.02 h^{-1}
a_5	Synthesis rate of activated cytosolic STAT5 (DpS)	21.78 h^{-1}
a_6	Degradation rate of DpS	27.23 h^{-1}
a_7	Synthesis rate of proliferation cells (PC)	0.009 h^{-1}
a_8	Activation rate of DpS_{nc}	2.06×10^{-7} h^{-1}
a_9	Degradation rate of PC	0.03 h^{-1}
a_{10}	Synthesis rate of red blood cells (RB)	0.115 h^{-1}
a_{11}	Degradation rate of RB	0.00016 h^{-1}
a_{12}	Synthesis rate of Epo messenger RNA (mEpo)	0.02 h^{-1}
a_{13}	Degradation rate of mEpo	210 h^{-1}
a_{14}	Synthesis rate of Epo	15.3 IU/mL h
a_{15}	Degradation rate of Epo	1.8 IU/mL h
g	Kinetic order	6.19

Table A.2: Model parameters for Erythropoiesis

APPENDIX B

Matrix Equalities

Lemma 24. *Let A and B be square matrices. Then the following equality holds:*

$$det(K) = det \begin{bmatrix} A & 0 \\ C & B \end{bmatrix} = det(A)det(B)$$

Proof. If A or B is singular then $det(A)det(B) = 0$, but also the matrix K has linearly dependent rows if $det(A) = 0$ or it has linearly dependent columns if $det(B) = 0$ in both cases giving us $det(K) = 0$. Now, suppose both A and B are nonsingular, then notice that

$$\begin{aligned} K &= \begin{bmatrix} A & 0 \\ C & B \end{bmatrix} = \begin{bmatrix} A & 0 \\ 0 & I \end{bmatrix} \begin{bmatrix} I & 0 \\ 0 & B \end{bmatrix} \begin{bmatrix} I & 0 \\ B^{-1}C & I \end{bmatrix} \\ &\Rightarrow \; det(K) = det(A)det(B)1 = det(A)det(B). \end{aligned}$$

□

Lemma 25. *Let A and D be square matrices and D is nonsingular, then the following equality holds:*

$$det(K) = det \begin{bmatrix} A & B \\ C & D \end{bmatrix} = det(D)det(A - BD^{-1}C).$$

Proof.

$$\begin{aligned}\begin{bmatrix} A & B \\ C & D \end{bmatrix} &= \begin{bmatrix} I & 0 \\ 0 & D \end{bmatrix} \begin{bmatrix} A & B \\ D^{-1}C & I \end{bmatrix} \\ &= \begin{bmatrix} I & 0 \\ 0 & D \end{bmatrix} \begin{bmatrix} A - BD^{-1}C & B \\ 0 & I \end{bmatrix} \begin{bmatrix} I & 0 \\ D^{-1}C & I \end{bmatrix}.\end{aligned}$$

By using Lemma 24, we get the desired equality. □

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