ANALYSIS OF HYBRID DYNAMICAL SYSTEMS WITH AN APPLICATION IN BIOLOGICAL SYSTEMS

NOURA A. ABDULRAZAQ TAHAR

JANUARY 2017

ANALYSIS OF HYBRID DYNAMICAL SYSTEMS WITH AN APPLICATION IN BIOLOGICAL SYSTEMS

A THESIS SUBMITTED TO

THE GRADUATE SCHOOL OF NATURAL AND APPLIED

SCIENCES OF

ÇANKAYA UNIVERSITY

BY

NOURA A. ABDULRAZAQ TAHAR

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE

DEGREE OF

MASTER OF SCIENCE IN

THE DEPARTMENT OF

MATHEMATICS AND COMPUTER SCIENCE

JANUARY 2017

Title of the Thesis: **ANALYSIS OF HYBRID DYNAMICAL SYSTEMS WITH AN *APPLICATION IN BIOLOGICAL SYSTEMS***

Submitted by NOURA A. ABDULRAZAQ TAHAR

Approval of the Graduate School of Natural and Applied Sciences, Çankaya University.

Prof. Dr. Halil Tanyer EYYUBOĞLU

Director

I certify that this thesis satisfies all the requirements as a thesis for the degree of Master of Science.

Assoc. Prof. Dr. Fahd JARAD

Head of Department

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

Assoc. Prof. Dr. Fahd JARAD

Supervisor

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

Dr. Nurgül GÖKGÖZ KÜÇÜKSAKALLI

Co-Supervisor

Examination Date: 16/01/2017

Examining Committee Members:

Assoc. Prof. Dr. Fahd JARAD	(Çankaya University)	
Assist. Prof. Dr. Dumitru BALEANU	(Çankaya University)	
Assist. Prof. Dr. Tuğba AKMAN	(UTAA)	

STATEMENT OF NON-PLAGIARISM

I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Name, Last Name : NOURA, TAHAR

Signature : 

Date : 16/01/2017

ABSTRACT

ANALYSIS OF HYBRID DYNAMICAL SYSTEMS WITH AN APPLICATION IN BIOLOGICAL SYSTEMS

Tahar, Noura A. Abdulrazaq

M.Sc., Department of Mathematics and Computer Science

Supervisor: Assoc. Prof. Dr. Fahd JARAD

Co-Supervisor: Dr. Nurgül GÖKGÖZ KÜÇÜKSAKALLI

January 2017, 52 Pages

There are many complex dynamics appearing in nature, science, and technology. One of the most useful approaches to model these phenomena is hybrid dynamical systems. Hybrid dynamic systems describe the interactions of continuous and discrete variables regulating each other. In this work, we have looked at different types of hybrid systems that have been used in the modeling of biological systems. We have also looked at the stability analysis of these systems and have given an example of a subclass of hybrid piecewise linear systems and checked the stability of these systems through an example.

Keywords: Hybrid dynamic models, a piecewise linear system of biological systems, the stability of models.

ÖZ

BİYOLOJİK SİSTEMLERDE BİR UYGULAMA İLE HİBRİT DİNAMİK SİSTEMLERİN ANALİZİ

Tahar, Noura A. Abdulrazaq

Yüksek Lisans, Matematik-Bilgisayar Anabilim Dalı

Tez Yöneticisi: Doç. Dr. Fahd JARAD.

Ortak Tez Yöneticisi: Dr. Nurgül GÖKGÖZ KÜÇÜKSAKALLI

Ocak 2017, 52 sayfa

Doğada, bilimde ve teknolojide ortaya çıkan pek çok karmaşık dinamik vardır. Bu olayları modellemek için en kullanışlı yaklaşımlardan biri hibrit dinamik sistemledir. Hibrit dinamik sistemler birbirini düzenleyen sürekli ve süreksiz değişkenlerin etkileşimini tarif eder. Bu çalışmada, biyolojik sistemlerin modellenmesinde kullanılan farklı hibrit sistemlere baktık ve bu sistemlerin bir altsınıfı için örnek verdik, parçalı doğrusal sistemler ve bir örnek üzerinden bu sistemlerin kararlılığını kontrol ettik.

Anahtar Kelimeler: Hibrit dinamik sistemleri modelleri, parçalı doğrusal biyolojik sistemler, modellerin kararlılığı.

TO MY BELOVED FAMILY …

ACKNOWLEDGMENTS

I would like to express my sincere gratitude and appreciation to my supervisor Assoc. Prof. Dr. Fahd JARAD who supported me through the final phase of submission and corrections.

I would like to express my sincere gratitude and appreciation to my co-supervisor Dr. Nurgül GÖKGÖZ KÜÇÜKSAKALLI who encouraged during the period my thesis and guided me throughout my M.Sc.Studies at Cankaya University.

I would like to express my sincere gratitude and appreciation to my father and mother.

I would like to express my sincere gratitude and appreciation to my husband (Gaballa), who was with me, in difficult times and helped me at all times.

I would like to express my sincere gratitude and appreciation to my children Ayat, Abrar and Haneen.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1

INTRODUCTION

1.1 Background to the Study

Constructing mathematical models of biological systems is an important approach to understanding many dynamic systems. They can be used for numerical simulations in order for us to understand the behavior of biological systems in their initial conditions.

Recent developments of the mathematical models of biological systems in [1] have given us the best models for us to be able to investigate the future behavior of biological systems by bifurcation theory. The authors in [1] applied its mathematical model to the complex interactions of the tumor-immune system and [1] explained the construction of the model as a tumor system consisting of killer cells and immune systems consisting of cytotoxic T lymphocytes (CTLs).

The first idea of the mathematic modeling was applied to the logistic equation which shows that the growth of cells is exponential with respect to time. An analogy can investigate the behavior of the Lotika Volterra competition model based on the logistic equation. Hence, our system is the competition model of tumor –immune systems, so we can say that if the size of tumor cells is small, then the growth of tumor cells is slowed, and if the size of tumor cells is large, then the growth of tumor cells is fast.

After the authors in [1] attempted to kill the tumor cells to get to the stages of treatment, which were difficult; however, it is possible to control the growth of the tumor size by enhancing the size of the immune system (injections). This process gave us the term (tumor-dormancy).

There is no specific time to discourage tumor systems. Sometimes, they occur in the early of growth of tumor cells, or they may occur after the treatment state (injection). If this occurs a long time after the increase of the size of the tumor, then the percentage of inhibition will be smaller and it will be called a small dormant tumor. However, if the growth of tumor cells is fast and increasingly uncontrolled, then the tumor cells will escape from the immune system and became killer cells. This stage is known as the sneaking state. There are many complex ideas that explain dormant tumors, and the sneaking state that occurs as the result of non-linear dynamic interactions.

In this thesis, we will investigate the mathematical model and the addition of the delay time for systems to became piecewise linear functions. To understand the behavior of the interactions we must analyze the stability of the result models and then show the stability for the models.

The numerical simulations are very important to prove the stability of the complex systems with respect to delay time.

1.2 Brief Description of the Study

In this thesis, we studied the piecewise linear models applied to tumor-immune systems. Firstly, we started with mathematical models of an immunogenic tumor, which summarized the complex interactions between tumor systems and immune systems by [1]. Then, we presented the general formula for a piecewise linear system, that is, a class of hybrid dynamic systems. We also introduced the construction of hybrid dynamic systems and their types with examples. We started with a competition model that describes the interactions within tumor-immune systems in n-dimensions based on population models. Then, we presented some genetic protein networks in n-dimensions.

We led the hybrid models of a number of biological models and then discussed the stability of the fixed point, equilibrium points and the concepts of stability of piecewise linear systems by of the Lyapunov function.

Finally, we presented some examples with numerical simulations to check the stability of these examples.

1.3 Purpose of the Study

There are many non-linear dynamic systems and biological phenomena in nature that are very complex and which cannot be solved with numerical simulations. Therefore, we have selected a hybrid dynamic model with the addition of a time delay, which means the replacement of the non-linearity of the dynamic system with piecewise linear dynamic systems, after which there will be many methods to solve the differential equations of the linear systems with difference equations.

Piecewise linear functions help us to investigate the behavior of dynamic systems in the future. Predictions of future behavior help us to formulate control theorems. We studied the interactions with tumor-immune systems and with the stability, we came to know the stability of tumor systems. This result has helped scientists to control the growth of tumors.

To sum up, piecewise linear systems give us the control theorems that may contribute to the treatment of diseases.

1.4 Significance of the Study

There are five benefits of this thesis. Firstly, most dynamic systems can be presented as piecewise linear functions with time delays. Secondly, by piecewise linear functions we can produce a simple model describing complex models. Moreover, it becomes easy to find solutions.

And from the genetic networks, we have known that the stability of periodic solutions occurred in the piecewise linear model and it becomes easy to check the stability of genetic networks.

Hybrid models provide us with a simple model for the concentrations of complex interactions, their solutions and a check on their stability with the help of the Lyapunove function.

CHAPTER 2

BACKGROUND INFORMATION

2.1 Introductions of immunogenic tumors system

Tumor cells that die due to, or are discouraged by, immune cells are called the tumor dormant. This means that the growth of tumor cells becomes controlled or discouraged by the immune system and this gives us the biological term (immunogenic tumors system).

In order for cancer to be inhibited by the immune system, there must occur complex and developed interactions. Researchers have conducted a number of studies to enable them to obtain the mathematical model that describes these interactions. One of the best studies was by [1].

2.1.1 The dynamics of immunogenic tumor systems

The dynamics of immunogenic tumor systems are not well understood, but it is known that the behavior of tumor cells is based on the population of immune cells, which means that both are inversely proportional to each other. If the size of the immune system is large, then the size of a tumor decreases and if the size of the immune system is small, then the size of a tumor increases and it may escape the immune system.

The authors in [1] presented a number of effector cells that help tumor cells to escape immune surveillance such that Quality-tainted cells misfortune or concealing of tumor antigens, the loss of MHC class I atoms and tumor-actuated disarrange in immunoregulation.

Let us look at the damper cancer. This one is dormant within the large population of immune cells and it will not grow more than previously. This dormant state may occur after the treatment state or it may occur in the early stages of tumor progression. If the dormant state of the tumor cells occurs late or after an increase in tumor size, and since the tumor cells may escape from the immune system by means of the so-called "sneaking through mechanism [2], then such a tumor is called a small dormant tumor, which is common in animals.

There is diverse clarification for the end of the torpid state of a tumor for the sneaking through of tumors and for safe immune stimulation effects. Often these clarifications depend on the thoughts of insusceptible selection, antigenic modulation, the production by tumor cells of various sorts of invulnerable cell blocking factors, the generation of safe silencer cells, changes in auto-administrative systems in tumor confinement regions and other more confusing concepts that are exceptionally difficult to demonstrate or invalidate tentatively.

The dynamics of nonlinear systems are very complex; however, [1] has studied the non-linear dynamics of the competition between tumor and effectors cells systems.

2.1.2 Mathematical models of immunogenic tumor systems

There are many mathematical models that describe the interactions within tumor-immune system in vivo and in-vitro that tell us that the behavior of tumor cells is exponential, which means if the tumor size population is small, then the growth of tumor cells will be fast, and if the tumor size population is large, then the growth of tumor cells will decrease.

As a rule of non-exponential tumor growth, the energy is very much portrayed by the logistic equation [3, 4].

By focusing on the fact that the effector cells (EC) of immune cells consist of (CTL or NK cells), we can describe the interaction between (EC-TC) in vitro as described by the kinetic scheme as [1]

$$E + T \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \overset{k_2}{\rightarrow} E + T^* \overset{}{\rightarrow} T^* + E$$

Then we can present the mathematical model of the interactions between effectors cells and the immunogenic tumor in vivo as [1]

$$\frac{\mathrm{dE}}{\mathrm{dT}} = \mathrm{s} + \mathrm{F(C,T)} - \mathrm{d_1 E} - \mathrm{k_1 ET} + (\mathrm{k_{-1}} + \mathrm{k_2})\mathrm{C}, \quad (2.1.2.1)$$

$$\frac{\mathrm{dT}}{\mathrm{dt}} = \mathrm{aT}(1 - \mathrm{bT_{tot}}) - \mathrm{k_1 ET} + (\mathrm{k_{-1}} + \mathrm{k_3})\mathrm{C}, \quad (2.1.2.2)$$

$$\frac{\mathrm{dC}}{\mathrm{dt}} = \mathrm{k_1 ET} - (\mathrm{k_{-1}} + \mathrm{k_2} + \mathrm{k_3})\mathrm{C}, \quad (2.1.2.3)$$

$$\frac{\mathrm{dE^*}}{\mathrm{dt}} = \mathrm{k_3 C} - \mathrm{d_2 E^*}\ , \quad (2.1.2.4)$$

$$\frac{\mathrm{dT^*}}{\mathrm{dt}} = \mathrm{k_2 C} - \mathrm{d_3 T^*}. \quad (2.1.2.5)$$

Where E equals the concentrations of effector cells, T equals the concentration of tumor cells, C is the complex conjugate of $(\mathrm{E} - \mathrm{T})$. $\mathrm{E^*}$, $T^*$are the inhibition of the effector and tumor cells respectively, k_1 is a non-negative parameter that describes the connecting of EC to TC. k_{-1} is a non-negative parameter that describes the separation of EC from TC. k_2 is a positive parameter that describes the death of tumor cells, and k_3 is a positive parameter that describes the death of immune cells.

We assume that the immunogenic tumor in the spleen $T_{tot} = T + C$ is the normal (non-improved by TC nearness) rate that describes the complex interaction $(EC - TC)$,and d_1, d_2, d_3 are positive constants that describe the rates of the end of E, E^* and T^* cells respectively.

We also assume that the tumor cells do not leave the TC or $EC - TC$ complexes and a is a rate of maximal growth of $TC. b^{-1}$ which is a rate of the maximal carrying capacity of the organic environment for TC.

The region TC that consists of tumor cells will stimulate EC; moreover, there are a number of cells near the tumor region such as (nearby lymph nodes), that will enhance migration of EC into this region. This process will contribute to the stimulated accumulation of effectors cells. [5], [6], [7] gave us the function that consists of the parameter which plays a role in the accumulation process as [1]:

$$F(C, T) = \frac{fC}{g + T} \qquad (2.1.2.6)$$

where $f, \text{and } g$ are positive constants. The function $F(C, T)$ depends on $C \approx EC - TC$ complexes, but C does not depend only on the effector cells. This function is not predictable with a model in which one assumes that the accumulation of effectors cells due to the presence of signals. However, it is predictable with the acumination of ($C \approx$ KET) which limits the rate of transport of effectors cells to the tumor. This rate does not occur in the circulation.

From equations 2.1.2.4 and 2.1.2.5, T^* and E^* do not have any effect on the other variables or no effect on each other; therefore, it is not necessary to analyze them. We focus on equation 2.1.2.1 and 2.1.2.3 that manages the behavior of this system.

It is not easy to form and dissociate the C complex conjugates since this work needs to select accurately the appropriate time before the beginning of the decomposition of tumor cells. The motivation of the effector's cells occurs on a much slower timescale,

which implies an approximate, the equation 2.1.2.5, i.e. $(\frac{dC}{dt} = 0)$ that gives the following result as [1]

$$C \approx KET, \tag{2.1.2.7}$$

where [1]

$$k = \frac{k_1}{k_2 + k_3 + k_{-1}}.$$

The authors in [1] have stated that $EC - TC$ conjugates in most of the cases comprise a small concentration of effectors cells or tumor cells which approximate $T_{tot} \approx T$ along with Equations 2.1.2.6 and 2.1.2.7. We can rewrite the equations 2.1.2.1 and 2.1.2.2 as [1]:

$$\frac{dE}{dt} = s + \frac{pET}{g + T} - mET - dE \ , \tag{2.1.2.8}$$

$$\frac{dT}{dt} = aT(1 - bT) - nET, \tag{2.1.2.9}$$

where

$p = fK, m = Kk_3, n = Kk_2$, and $d = d_1$.

2.2 Hybrid Dynamic System Model

2.2.1 Definition of Hybrid Dynamic System

Hybrid dynamic systems describe the complex dynamic systems by a function that consists of the coexistence of continuous and discrete time.

This means that the dynamical systems may take the values from a continuous set (real numbers) or they may take the values from a discrete set of symbols $\{q_1, q_2, \ldots., q_n\}$.

The mathematical modeling of hybrid dynamic systems will help us to understand the behavior and analyses of complex nonlinear dynamics of biological systems. In addition

to the model of the hybrid dynamic, we can find solutions and check, the stability of these biological systems.

Hybrid models correspond to any interaction or coupling between two or more models that are not based on the same formalism: for example deterministic and stochastic, global and local, phenomena logical and physically based.

2.2.2 Mathematical Models of Hybrid Dynamic Systems

There are many forms for a model of hybrid dynamic systems; however, the most common of them is from the viewpoint of a deterministic dynamic, which is summarized as follows [8].

$$\frac{dx(t)}{dt} = F_{i(t)}(x(t), u(t), \mu)\ , \qquad (2.2.2.1)$$

$$i(t) = G(i(t\_), x(t\_), u(t), \mu), \qquad (2.2.2..2)$$

$$x(t) = R(i(t\_), x(t\_), u(t), \mu), \qquad (2.2.2..3)$$

$$y(t) = O(i(t), x(t), u(t), \mu), \qquad (2.2.2..4)$$

where $x(t) \in R^n$ is the continuous state at time $t \in R$

$i(t) \in \{1,2,3,\ldots..N\}$ is the discrete state at t; $F_i(t)$ is the vector-valued smooth function.$u(t) \in R^m$ is the external input, $\mu \in R^L$ is the system (bifurcation) parameters: G is a map of the discrete-state move from $i(t\_)$ to $i(t)$ with $i(t\_) \equiv \lim_{\tau \to t-0} i(\tau)$; R is a reset map of continuous state accompanying a discrete-state move and $y(t) \in R^k$is the output, and O is the yield work(the output function).

2.2.3 Types of Hybrid Dynamic System

There are three types of hybrid dynamic system in [9].

2.2.3.1 Decoupled Models

Theses describe the same phenomena that are divided into independent levels. Then we can model and find the solutions for each one. Moreover, in this model, we can compare the models that describe the same phenomena but based on different hypotheses; therefore this model is the best [10].

2.2.3.2 Coupled Models

This case studies two or more different models that are coupled through input/output variables. It describes the concentrations of biochemical substances in plasma [11].

2.2.3.3 Intricate Models

This model describes the strong and complex concentration of non-linear dynamic systems. Moreover, the model is, in actuality, interesting; however, its modeling potential changes relying upon the setting under the type of breaking points, thresholds, switches (Hills function) or Peaks (Dirac's function). It is not easy to build and solve this model because the formalism selected is fundamentally and exclusively mathematical, which is a strong constraint [12]. Construction for three types, see Figure 1.

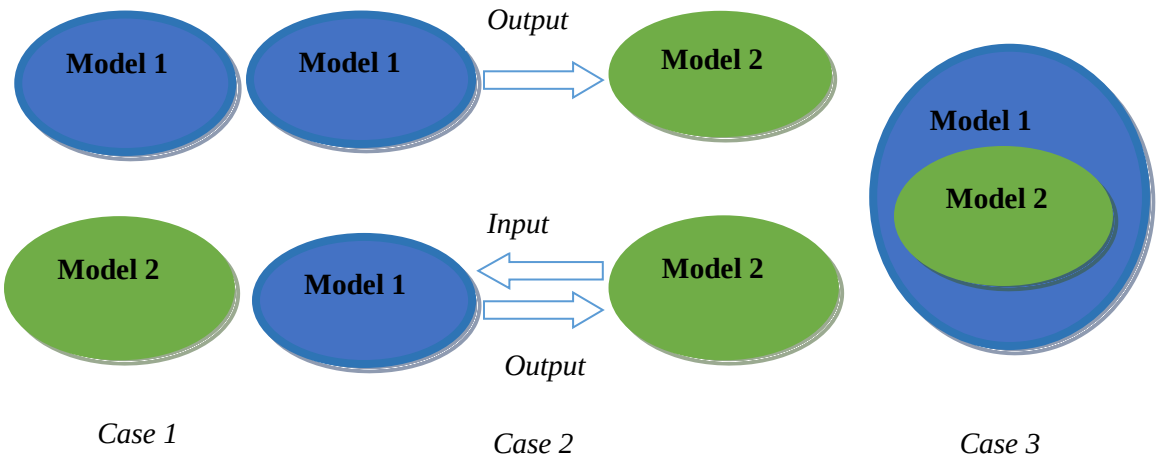

Figure 1: Construction of three types of hybrid dynamic system [9]

2.2.4 The main articles of the applications of hybrid dynamic system

1. Gene regulatory networks
2. Tumor and its treatment
3. Complex Neural systems

CHAPTER 3

DIFFERENTIAL EQUATIONS WITH PIECEWISE CONSTANT ARGUMENT

Piecewise constant arguments are a discrete class of hybrid dynamical system and they are presented by difference equations.They help us to use numerical simulations and build the hybrid control theory of differential equations.

3.1. Logistic equation with piecewise constant arguments

Gave us and the applied new model on a population or logistic equation in a single species with continuous and discrete time as [13]

$$\frac{dN(t)}{dt} = rN(t)\{1 - aN(t) - bN(⟦t⟧)\} \tag{3.1.1}$$

where $N(t)$ is the population concentration and a, b, r are positive parameters.$⟦t⟧$ is the infinite interval and the discrete part and $t \in (0, \infty)$ is the contiguous part.

By model (3.1.1), it is easy to investigate the competitions models of diseases with respect to time such as [13] having modeled the piecewise constant argument of the competition model of bacteria cells with respect to time as [13]

$$\frac{dx(t)}{dt} = rx(t)\{1 - \propto x(t) - \beta_0 x(⟦t⟧) - \beta_1 x(⟦t-1⟧)\} \tag{3.1.2}$$

Since every single tumor-immune system presents the population or logistic equation as [13]

$$\begin{cases} \dfrac{dN_1}{dt} = r_1 N_1\left(1-\dfrac{N_1}{k_1}\right) - \dfrac{r_1 \propto_{12i}}{k_1} N_1 N_2 + \dfrac{r_1 \propto_{12S}}{k_1} N_1 N_2, \\ \dfrac{dN_2}{dt} = r_2 N_2\left(1-\dfrac{N_2}{k_2}\right) - \dfrac{r_2 \propto_{21}}{k_2} N_1 N_2. \end{cases} \tag{3.1.3}$$

N_1, N_2 present the tumor and immune populations respectively; however, it (the equation) consists only continuous time situations.

3.2 Tumor-immune system with piecewise constant arguments

Now, by using time -delay inclusion of [14], we have the piecewise constant argument of the tumor-immune competition model as follows [13]

$$\begin{cases} \dfrac{dx}{it} = r_1 x(t)\left(1-\dfrac{x(t)}{k_1}\right) - \propto_1 x(t)y([\![t]\!]) + \propto_2 x(t)y([\![t-1]\!], \\ \dfrac{dy}{dt} = r_2 y(t)\left(1-\dfrac{y(t)}{k_2}\right) + \propto_1 y(t)x([\![t]\!] - \propto_2 y(t)x([\![t-1]\!] - d_1 y(t). \end{cases} \tag{3.2.1}$$

where $[\![t]\!]$ is the discrete time and $t \in [0, \infty)$ is the continuous time. The behavior that the system has taken to investigate the piecewise linear function is explained as follows:

The tumor cells consist of killer cells, and immune cells consist of resting and Cytotoxic T lymphocytes (CTLs); however, the latter (CTLs) are more important than the resting cells in our studies because they have the great effect of killing tumor cells.

It is known that immune cells have discrete time to increase in order to kill tumor cells, so a delay is added to the discrete time $[\![t]\!]$ for the immune cells $\propto_1 x(t)y([\![t]\!])$.Moreover, the immune cells need the time discrete delay in order to build up a reasonable reaction acknowledgment of tumor cells $y([\![t-1]\!]$. Similarly to the tumor cells, it needs a discrete time to decrease by providing the immune cells $\propto_1 y(t)x([\![t]\!]$; it also it needs in a delay discrete time in order to proliferate $\propto_2 y(t)x([\![t-1]\!]$. In the end, the immune cells (CTLs) need to continuous time to death $d_1 y(t)$.And the positive parameters r_1, r_2 present the growth rates of $x(t), y(t)$ respectively, k_1, k_2 equals the carrying capacities of $x(t), y(t)$ respective, and d_1 presents the death rate of $y(t)$.

3.3 Genetic regulatory networks

We will study a simple form for a continuous dynamic system of genetic regulatory networks that describes the interactions between two genes (a and b) that code by two proteins (A and$B$). Since the interactions between genetic networks are very complex and it is not easy to understand the behavior of these networks, we use a discrete approximation method with a piecewise constant argument function to simplify networks to produce a new model such that it becomes easy to analyzes. The dynamics of genetic regulation networks is given as [15].the dynamic of a genetic regulatory network of two genes (a and b) that coding a regulatory protein (A and B) ,see Figure 2.

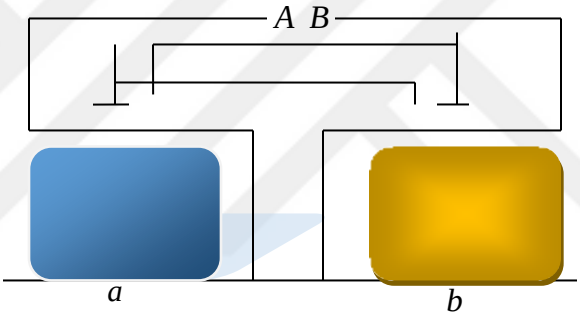

Figure 2: The transcription of two genes [15]

$$\dot{x}_i = f_i(x) - \gamma_i x_i, \qquad 1 \le i \le n, \tag{3.3.1}$$

Where $x = (x_1, x_2, \dots\dots, x_n)^t > 0$ is the population of proteins. $f_i(x)$ is the synthesis rate for each protein x_i and $\gamma_i x_i$ is the decay rate of each protein x_i

We rewrite (3.3.1) in the general case as [15]

$$\dot{x} = f(x) - \gamma x, \tag{3.3.2}$$

where $f(x) = (f_1(x), f_2(x), \dots\dots, f_n(x))^t$ and $\gamma = \mathrm{diag}(\gamma_1, \gamma_2, \dots\dots, \gamma_n)$ is a constant diagonal matrix.

If we consider to any gene i on the concentration x of a protein in the cell, then $f_i: IR_+^n \rightarrow IR_+$ is the dependence of the synthesis rate of a protein that is encoded by i. Therefore,[15]

$$f_i(x) = \sum_{i \in I} \kappa_{il} b_{il}(x), \tag{3.3.3}$$

Where $\kappa_{il} > 0$ is a rate parameter, $b_{il}: IR_+^n \rightarrow \{0, 1\}$ is a Boolean-valued regulation function, I is an index set and b_{il} catches and controls the conditions that are under the protein encoded by gene i synthesized at a rate κ_{il} .

Given the step function [15]

$$s^+, s^-: K \times IR_+ \rightarrow \{0,1\}$$

The conditions that control the step are [15]

$$h^+(x_i, \theta_i) = s^+(x_i, \theta_i) = \begin{cases} 1, & x_i > \theta_i, \\ 0, & x_i < \theta_i. \end{cases}$$
$$s^-(x_i, \theta_i) = 1 - s^+(x_i, \theta_i), \tag{3.3.4}$$

Where $K \subseteq IR_+$. A step function leads a dynamic system for genetic- protein and it controls the activity of the gene changes in a switch-like (inhibition-activation) manner at the networks of a regulatory protein. Note that the step function does not consider$x_i = \theta_i$; therefore, they are not the regulatory functions.

-$\{\theta_i^j\}, \{\gamma_i\}, \{\kappa_{il}\}$ are the parameters of the discrete part of the hybrid dynamic system of (3.3.2) and our simple example for two genes-proteins is [15]

$$\dot{x}_a = \kappa_a s^+(x_b, \theta_b^1) s^-(x_a, \theta_a^2) - \gamma_a x_a \ , \tag{3.3.5}$$

$$\dot{x}_b = \kappa_b s^+(x_a, \theta_a^1) s^-(x_b, \theta_b^2) - \gamma_b x_b \ . \tag{3.3.6}$$

Where the discrete part can be defined by the difference equation $s^+ = 1 - s^-$. The rate κ_a presents the gene a if the concentration x_b of protein B, is greater than θ_b^1,

and x_a from protein A is less than θ_a^2. Similarly, the rate κ_b presents the gene b if the concentration x_a from protein A is greater than θ_a^1, and x_b forming protein B is less than θ_b^2.

Now, we see the concentration of the gene-protein in n −dimensions that are defined on the region Ω as domains$D \subset \Omega$, so firstly, we present the properties of the domains in the phase space.

3.3.1 Domains in phase space

For n −dimensions, the phase space is $\Omega = \Omega_1, \ldots\ldots, \Omega_n$ where every Ω_i is defined by $\Omega_i = \{x_i \in IR_+ | 0 \leq x_i \leq max_i\}$ where max_i is a positive parameter with $max_i > max_{x\in\Omega}\left(\frac{f_i(x)}{\gamma_i}\right)$.

The protein encoded by the gene will change in a different interaction at a different concentration; therefore, for every x_i $\exists p_i$ such that [15]

$$\{\theta_i^1, \ldots\ldots, \theta_i^{p_i}\},$$

We let D be the domain in the region Ω, which means $D \subset \Omega$ such that $D = D_1, \ldots\ldots, D_n$ where every D_i is defined by the following equations as [15]

$$D_i = \{x_i \in \Omega_i | 0 \leq x_i \leq \theta_i^1\},$$

$$D_i = \{x_i \in \Omega_i | x_i = \theta_i^1\},$$

$$D_i = \{x_i \in \Omega_i | \theta_i^1 \leq x_i \leq \theta_i^2\},$$

$$D_i = \{x_i \in \Omega_i | x_i = \theta_i^2\},$$

$$\vdots$$

$$D_i = \{x_i \in \Omega_i | x_i = \theta_i^{p_i}\},$$

$$D_i = \{x_i \in \Omega_i | \theta_i^{p_i} \leq x_i \leq max_i\}.$$

If we work on n-dimensions then the general form of the domains is defined by [15]

$$\prod_{i=1}^{n}(2p_i + 1).$$

3.3.2 Types of domains

3.3.2.1 Regulatory domain

This domain has the variables x_i that does not belong to D and it is defined by D_r.

3.3.2.2 Switching domain

In this domain, at least one of the variables x_i has a value belonging to D and it is defined by D_s.

Definition 3.1: The order $k \in N$ of a domain $D \in D_s$ is equal to the numbers of switching domains [15]

$$\text{order}(D) = k,$$

Definition 3.2: If $k \geq 1$ is the order of the domain and $\text{supp}(D) \subset \Omega$, then

- For the regulatory domain $D \in D_r$,$\text{supp}(D) = \Omega$,
- For the switching domain$D \in D_s$, $\text{supp}(D) = (n - k)$dimensions.

If we define the boundary of D in $\text{supp}(D)$ to be the set ∂D for all values $x_i \in \text{supp}(D)$ by following sets [15]

$$A(D) = \{D' \in D \backslash D' \subseteq \partial D\},$$

The set $A(D)$ has the domains in the boundary of D that are switching domains [15]

$$R(D) = \{D' \in D_r \backslash D \subseteq \partial D'\}.$$

$R(D)$ has the regulatory domains that have D in their boundary.

The domain D of order k such that $k \geq 1$ and I is the subset of k , such that $I \subset k$ then domain are presented as [15]

$D = \{x \in \Omega | x_i = \theta_i^{q_i} < x_i < \theta_i^{q_i+1} \text{ if } i \notin I\}$,

Where we have the tradition that $\theta_i^0 = 0$ and $\theta_i^{p_i+1} = \max_i$, and $\theta_i^0 \leq x_i$ and $x_i \leq \theta_i^{p_i+1}$, if $i \notin I$, in order to incorporate the bounds of the domain Ω.

Now, our simple example is a two-gene network in the two-dimensional phase space Ω, as in Figure 3.

The phase space has 9 regulatory domains and 16 switching domains, and we find D^1, D^2 because the protein concentration has two thresholds each, as in the following sets [15]

$D^1 = \{(x_a, x_b) \in \Omega | 0 \leq x_a < \theta_a^1, 0 \leq x_b < \theta_b^1\}$, is a regulatory domain.

$D^2 = \{(x_a, x_b) \in \Omega | 0 \leq x_a < \theta_a^1, x_b = \theta_b^1\}$ is a switching domain. Here, only x_b is a switching variable. Therefore the order of the switching domain is 1 and $\text{supp}(D^2)\{(x_a, x_b) \in \Omega | x_b = \theta_b^1\}$, see Figure 3.

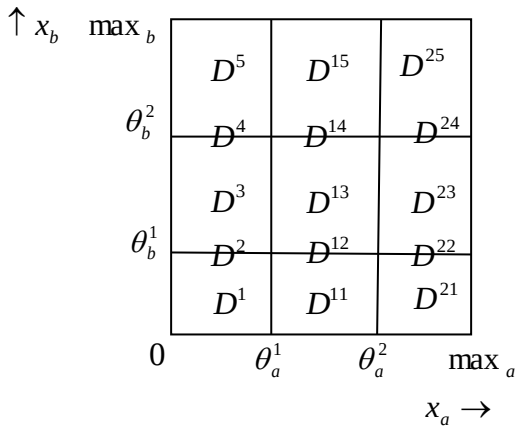

Figure 3: Phase space for a two-gene network with PWL model [15]

The focal point $\emptyset(D^{13})$ for $the\ regulatory\ domain\ D^{13}.x_a, x_b$ is attracted to $\emptyset(D^{13})$ $by \frac{\kappa_a}{\gamma_a} and \frac{\kappa_b}{\gamma_b}$, respectively, see Figure 4

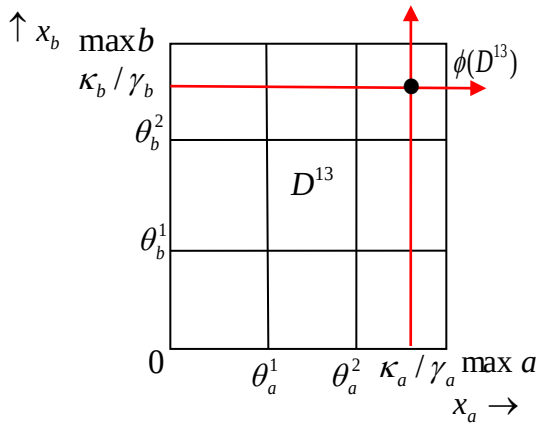

Figure 4: The focal point

There are a number of boxes and every box has a solution in the phase space. We explain the method to find the solution of boxes by focal points

3.3.3 Classical solutions and focal points

The simple linear system for (3.3.2) can be written as [15]

$$\dot{x} = f^D - \gamma x, \quad x \in D \tag{3.3.3.1}$$

Where $f^D = f_i(x_1, \ldots, x_n)$ is the value of the synthesis rate f_i in the box B_s Thus the solutions in the box are easy to compute by [15]

$$x(t) = \emptyset(D) + e^{\gamma(t_0 - t)}\big(x(t_0) - \emptyset(D)\big), \tag{3.3.3.2}$$

Where $\emptyset(D)$ satisfies the linear system $\gamma\emptyset(D) = f^D$ inside each boxB_s , and the solutions are monotonical as $t \to \infty$; Additionally, all solutions that tend to a stable equilibrium are called the focal point of the box.

Definition 3.3: if we let $D \in D_r$ be a regulatory domain, there exists a focal point for the flow in D defined by [15]

$\emptyset(D) = \gamma^{-1} f^D \in \Omega.$

Suppose that $\emptyset(D) \in \text{supp}(D')$ for all $D' \subseteq \partial D$; this means the trajectories will take the contiguous time to reach the focal point, which is a special case. From Figure 3.2, we have a regulatory domain $D^{13}$by [15]

$$\dot{x_a} = \kappa_a - \gamma_a x_a,$$

$$\dot{x_b} = \kappa_b - \gamma_b x_b.$$

Hence the focal point for D^{13} is $\emptyset(D) = (\frac{\kappa_a}{\gamma_a}, \frac{\kappa_b}{\gamma_b})$, which lies when the solution leaves the domain $D^{13}$and enters another domain, such as D^{25}. Therefore, there will be two different focal points in different domains. The problem occurs when the trajectories continuously flows and enters a switching domain because the vector field for the switching domain is unknown and since the step functions are not defined when the variable x_i takes some threshold value $\theta_i^{q_i}$, it will be difficult to know the new solutions of in the switching domain. Therefore, Filippov's approach will help us to find the solution to the switching domains.

3.3.4 Filippov solutions and focal sets

The piecewise linear function (3.3.2) is defined in a regulatory domain; however, the switching domain is not defined because $k \geq 1$ where k presents variables assuming a threshold value.

If the solutions for the different regulatory domains such as D^1, D^{11} enter a switching domain D^6, that appear as transparent walls. However, if D^{13}, and D^{15} go toward the same switching domain as D^{14}, then the switching domain is referred to as black walls and we use the Filippov approach to solving it.

The focal points $\emptyset(D^1) = (0,0), \emptyset(D^{11}) = \left(0, \frac{\kappa_b}{\gamma_b}\right), \emptyset(D^{13}) = \left(\frac{\kappa_a}{\gamma_a}, \frac{\kappa_b}{\gamma_b}\right)$ and $\emptyset(D^{15}) = \left(\frac{\kappa_a}{\gamma_a}, 0\right)$. D^6 is a transparent wall and D^{14} is a black wall ,see Figure 5.

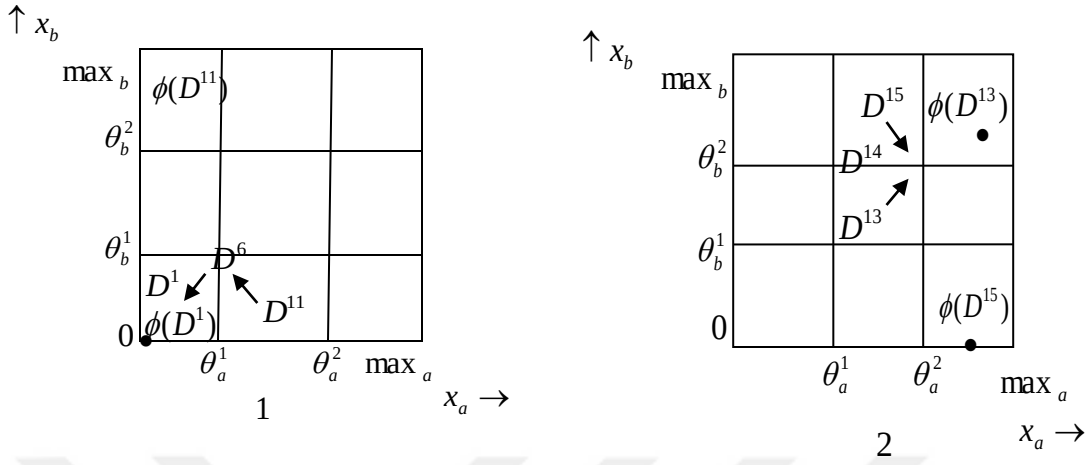

Figure 5: Behavior of two gene networks with the PWL model [15]

The theory control concludes the Filippov approach when the solution to switching domains is called sliding modes. The approach contains the numerical simulation of piecewise linear functions by Euler's method or other methods that explain the behavior of the solution.

The Filippov approach develops system (3.3.3.1) to become [15]

$$\dot{x} \in H(x)\,, \tag{3.3.3.3}$$

Where $H: \Omega \to 2^{R^n}$ a set is valued function and is defined by [15]

$$H(x) = \{f^D - \gamma x). \tag{3.3.3.4}$$

D is a regulatory domain.

Definition 3.4: Let $\xi_t(x_0)$ be an absolutely continuous function that is the solution of system (3.3.3.4) on the interval $[0, T]$in the sense of Filippov, such that $\xi_0(x_0) = x_0$ and $\dot{\xi}_t \in H(\xi_t)$ for most of $t \in [0, T]$.

CHAPTER 4

THE STABILITY OF HYBRID DYNAMIC SYSTEM

4.1 Concepts of the stability of fixed points

Firstly, we will present the stability of the one-dimensional system, which can be described by [16].In a one-dimensional system, we suppose that the real phenomena are described mathematically by discrete dynamic systems. Every discrete dynamic system has fixed points $f(x^*) = 0$, where x^* is a fixed point; however, their proprtries are not similar.This means that if the neighborhood point of a fixed point is attracted to the fixed point, then the fixed point is stable. If the neighborhood or trajectories point goes away from the fixed point, then the fixed poin is unstable. The convergence and divergence can be seen in the phase planes of the systems.

Let us consider the stability of 2-dimensions. In this case, we will use the Jacobian matrix A as [16]

$$A = \begin{pmatrix} \frac{\partial \dot{x}}{\partial x} & \frac{\partial \dot{x}}{\partial y} \\ \frac{\partial \dot{y}}{\partial x} & \frac{\partial \dot{y}}{\partial y} \end{pmatrix}$$

Then, we compensate for all fixed points in matrix A and find the eigenvalues:

- if $Rel\ \lambda_1, \lambda_2 > 0$, then the fixed point is unstable,
- if $Rel\ \lambda_1, \lambda_2 < 0$, then the fixed point is stable.

4.2 Concepts of the stability of piecewise linear systems

4.2.1 The Lyapunov-Razumikhin method

The Lyapunov method is one of the main methods that help us to design and analyzes the controller of dynamic systems, be they linear or non-linear systems. This method is based on the sufficient conditions [17, 18], namely those which are set up for (stability, uniform stability, and uniform asymptotic stability) of the zero solutions [19]

This section studies the comparison of values of a solution in different parts that will help us to check the stability for of the systems with an argument function that has a discontinuity.

Stability Theorems [19]:

Let N be the natural numbers, i.e., $N = \{0,1,2, \dots .\}$ and R^+be the positive real numbers, i.e., $R^+ = [0, \infty)$

R^n are an n-dimensional real space for $n \in N$ and the Euclidean norm for R^n is$\|. \|$.

Suppose that θ_i is a real-valued sequence such that [19]:

$$0 = \theta_1 < \theta_2 < \cdots < \theta_i < \cdots < \cdots with\ \theta_i \to \infty \text{ as } i \to \infty$$

Let we then let a piecewise linear function [19]

$$x'(t) = f\Big(t, x(t), x\big(\beta(t)\big)\Big) \tag{4.1}$$

Here $x \in s(\rho) = \{x \in R^n : \|x\| < \rho\}, t \in R^+$[12]

$$\beta(t) = \theta_i, \text{if } t \in [\theta_i, \theta_{i+1}), i \in N$$

with these assumptions, we can check the stability [19]

(C_1) $f(t, y, z) \in C\big(R^+ \times s(\rho) \times s(\rho)\big)$,

(C_2) If $y = z = 0$ then $f(t, 0, 0) = 0\ \forall t \geq 0$,

(C_3) $f(t, y, z)$ satisfies the Lipchitz equation as:

$$\|f(t, y_1, z_1) - f(t, y_2, z_2)\| \leq \ell(\|y_1 - y_2\| + \|z_1 - z_2\|), \quad (4.2)$$

For all$t \in R^+$and $y_1, y_2, z_1, z_2 \in S(\rho)$ where $L > 0$ is a Lipchitz constant,

(C_4) There is a positive number θ such that $\theta_{i+1} - \theta_i \leq \theta, \forall i \in N$,

$(C_5)\ell\theta[1 + (1 + \ell\theta)e^{\ell\theta} < 1$,

(C_6) $3\ell\theta e^{\ell\theta} < 1$,

(C_7) $\acute{K} = \{a \in C(R^+, R^+)\}$ a is entirely expanding and $a(0) = 0\}$,

(C_8) $\Omega = \{b \in \{C(R^+, R^+)\}, b(0) = 0, b(s) > 0\ for\ s > 0\}$.

Definition 4.1

Let V be function denoting $\{R^+ \times S(\rho) \to R^+\}$ and $V \in \mathbb{Q}$ if:

i. V is continuous on $R^+ \times S(\rho)$, where$V(t, x) \equiv 0$ for all $x = 0$ and $t \in R^+$;
ii. $V(t, x)$is continuous on the interval $(\theta_i, \theta_{i+1}) \times S(\rho)$ and for each where there exists the derivative for the right side at $t = \theta_i, i \in N$.

Definition 4.2

If we let $V \in \mathbb{Q}$, there exists the derivative of *V* that satisfies definition (4.1) in [19]

$$V'(t, x, y) = \frac{\partial V(t,x)}{\partial t} + \text{grad}_x^T\, V(t, x) f(t, x, y) \quad (4.3)$$

For all$t \neq \theta_i$ in R^+ and $x, y \in S(\rho)$.

Note:

We let (C_1 – C_6) are be satisfied; then the zero solution of the piecewise linear system (4.1) has stability. To checking the stability of the piecewise linear model (4.1), we have to use the Lyapunov-Razumikhin method. We present the concepts of the stability in the following theorems. This is approach is identical to that of the Lyapunov method with ordinary differential equations.

Theorem 4.1

Let $V \in \mathfrak{Q}, u \in \mathfrak{K}$ if [12]

i. $u(\|x\| \leq V(t,x) \leq v(\|x\|)$ on $R^+ \times s(\rho)$
ii. $V'(t,x,y) \leq 0$ for all $t \neq \theta_i$ in R^+ and $x,y \in S(\rho)$ such that $V(\beta(t),y) \leq v(t,x)$,

Then the zero solution of (4.1) is uniformly stable.

Proof: we assume that $v(\delta_1) \leq u(\varepsilon)$such that $\varepsilon > 0$ and $\delta_1 = \delta\, K(\ell) > 0$, we therefore prove the stability in two parts in [19]

1. $t_0 = \theta_j$

Hence, $j \in N$ and satisfies $\|x(\theta_j)\| < \delta$. Since the zero solution is stable, then the condition $V\left(\theta_j, x(\theta_j)\right) \leq v(\delta) < v(\delta_1) \leq u(\varepsilon)$ is satisfied and gives us $V(t, x(t)) \leq u(\varepsilon)\ \forall t \geq \theta_j$. Here $\|x(t)\| < \varepsilon\ \forall t \geq \theta_j$, which means the change of $j \in N$ does not effect in the change of δ.

2. $t_0 \in IR^+$

Hence, $t_0 \neq \theta_I$ for all $i \in N$;

We assume $j \in N$ such that $\theta_j < t_0 < \theta_{j+1}$.Solutions of (4.1) satisfy $\|x(t_0\| < \delta$.by follow same steps of case 1 we have$\|x(\theta_j)\| < \delta_1$ leads for$\|x(t)\| < \varepsilon$ for$t \geq \theta_j$. Also it is true for all $t \geq t_0$ where $t_0 \in R^+$.

Theorem 4.2:

Let $V \in \mathfrak{Q}, u \in \acute{K}$ if [19]

i. $u(\|x\| \leq V(t,x) \leq v(\|x\|)$ on $R^+ \times S(\rho)$
ii. $V'(t,x,y) \leq -w(\|x\|$ for all $t \neq \theta_i$ in R^+ and $x,y \in S(\rho)$ such that $V(\beta(t),y) < \psi(V(t,x))$ such that $\psi(s) > s\ \forall s > 0\ \ such\ that\ \psi\ > 0\ \ and\ w \in \Omega$

Then the zero solution for (4.1) is uniformly asymptotically stable

Proof: we assume that the zero solution of (4.1) is uniformly stable from theorem (4.3). Our aim is to prove "uniform" asymptotic stability with $\theta_i, i \in N$.

We assume $j \in N$ and $\rho_1 \in (0,\rho)$.we prove the stability in two parts as

(1) $t_0 = \theta_j$ and $\delta > 0$ Satisfies $v(K(l)\delta) = u(\rho_1)$ssuch that $K(\ell) > 1$, from theorem (4.1) we have $V(t,x(t)) \leq v(\delta) \leq v(K(\ell)\delta) \forall t \geq \theta_j$ and exactly the $\|x(t)\| < \delta$,now we want to prove that this δ can be taken as δ_0 in the discussion of uniform asymptotic stability. We want to prove that there exists a $aT = T(\varepsilon) > 0$ for the arbitrary $\varepsilon > 0$ such that $0 < \varepsilon < \rho_1$ and satisfies [19]

$$\|x(t)\| < \varepsilon\ \forall t \geq \theta_j + T \quad \text{if } \|x(\theta_j)\| < \delta.$$

Let a set of function [19]

$\gamma = \inf\{w(s): v^{-1}(u(\varepsilon)) \leq s \leq \rho_1\}\ such\ that\ \varepsilon < \rho_1\ and\ \ u,v \in k\ gives\quad u(\varepsilon) < v(\rho_1)$ that leads $v^{-1}(u(\varepsilon)) < \rho_1$.

It is known that $\delta_1 = K(\ell)\delta$,by definition of $\psi(s)$,

We have [19]

$$\psi(s) - s > a\ for\ a > 0\ and\ \ u(\varepsilon) \leq s \leq v(\delta_1)$$

let $u(\varepsilon) + Na \geq v(\delta_1)$ such that N is the smallest positive integer.

Assume that [19]

$$t_k = k\left(\frac{v(\delta_1)}{\gamma} + \theta\right) + \theta_j, k = 1,2, \dots, N. \text{We shalll show that this[4]}$$

$$V(t, x(t)) \leq u(\varepsilon) + (N - k)a \text{ for } t \geq t_k, \quad k = 0,1,2, \dots, N \tag{4.4}$$

We have [19]]

$$V\big(t, x(t)\big) \leq v(\delta_1) \leq u(\varepsilon) + Na \ \forall t \geq t_0 = \theta_j,$$

(4.4) is true for all $0 \leq k < N$.we can show that at $k = k + 1$ in [19]

$$V\big(t, x(t)\big) \leq u(\varepsilon) + (N - k - 1)a \ \forall t \geq t_{k+1}, \tag{4.5}$$

To proving (4.5);

We let $I_k = [\beta(t_k) + \theta, t_{k+1}]$. Firstly, to prove that $t^* \in I_k$such that [19]

$$V\big(t^*, x(t^*)\big) \leq u(\varepsilon) + (N - k - 1)a, \tag{4.6}$$

Otherwise, $V\big(t, x(t)\big) > u(\varepsilon) + (N - k - 1)a \ \forall t \geq I_k$,

$$\text{and } V\big(t, x(t)\big) \leq u(\varepsilon) + (N - k)a \quad \forall t \geq t_k, \tag{4.7}$$

We take $\beta(t)$ for all $t \geq I_k$ in (4.7) in [19]

$$V\left(\beta(t), x\big(\beta(t)\big)\right) \leq u(\varepsilon) + (N - k)a \ \forall t \geq \beta(t_k) + \theta \tag{4.8}$$

By applying condition (ii) in Theorem (4.2), we get [19]

$$\psi\left(V\big(t, x(t)\big)\right) > V\big(t, x(t)\big) + a > u(\varepsilon) + (N - k)a \geq V\left(\beta(t), x\big(\beta(t)\big)\right) \text{ for all } t \in I_k,$$

Also by [19],

$$V'\left(t, x(t), x\left(\beta(t)\right)\right) \leq -w(\|x(t)\|) \leq -\gamma \text{ for all } t \neq \theta_m \text{ in } I_k,$$

We get [19]

$$v^{-1}\left(u(\varepsilon)\right) \leq \|x(t)\| \leq \rho_1 \text{ for } t \in I_k,$$

Since the function V is continuous and x(t) is solution for (4.1), then [19]

$$V\left(t_{k+1}, x(t_{k+1})\right) \leq V\left(\beta(t_k) + \theta, x(\beta(t_k) + \theta)\right) - \gamma(t_{k+1} - \beta(t_k) - \theta)$$

$< v(\delta_1) - \gamma(t_{k+1} - t_k - \theta) = 0$,which is a contradiction.

(4.6) is proved.

(2) $t^* \in I_k$, wheret^* satisfies that [19]

$$V\left(t^*, x(t^*)\right) \leq u(\varepsilon) + (N - k - 1)a$$

We consider that [19]

$$V\left(t, x(t)\right) \leq u(\varepsilon) + (N - k - 1)a \; \forall \; t \in [t^*, \infty), \qquad (4.9)$$

If (4.9) is not true for t^*, then we assume that there are $\bar{t} \in (t^*, \infty)$ such that [19]

$V(\bar{t}, x(\bar{t})) > u(\varepsilon) + (N - k - 1)a \geq V(t^*, x(t^*))$,

If there exist $\tilde{t} \in (t^*, \bar{t})$ such that $\tilde{t} \neq \theta_m$,then by (4.9), we have [12]

$$\{ V'\left(\tilde{t}, x(\tilde{t}), x\left(\beta(\tilde{t})\right)\right) > 0 \; and \; V\left(\tilde{t}, x(\tilde{t})\right) > u(\varepsilon) + (N - k - 1)a\}.$$

However, if $\tilde{t}$ did not exist$\tilde{t}$, then we have only $t \in \left(t^*, \bar{t}\right)$ such that $t \neq \theta_m$, which satisfies [19]

$$V'\left(t, x(t), x\left(\beta(t)\right)\right) \leq 0 \text{ or } V\left(t, x(t)\right) \leq u(\varepsilon) + (N - k - 1)a.$$

Notes [19]:

1. If $V'\left(t, x(t), x(\beta(t))\right) \leq 0$ then $V\left(\bar{t}, x(\bar{t})\right) \leq V(t^*, x(t^*))\forall$ (contradiction)
2. If $V(t, x(t)) \leq u(\varepsilon) + (N - k - 1)a$ then $V(t, x(t)) \leq V(\bar{t}, x(\bar{t}))$ (contradiction)

So there exists $\tilde{t}$ and it satisfies Theorm (4.2)) in [19]

$$\psi\left(V(\tilde{t}, x(\tilde{t}))\right) > V(\tilde{t}, x(\tilde{t})) + a > u(\varepsilon) + (N - k)a \geq V\left(\beta(\tilde{t}), x(\beta(\tilde{t}))\right)$$

which gives[19]

$$V(t, x(t)) \leq u(\varepsilon) + (N - k - 1)a \; \forall\, t \geq t^* \text{and } \forall\, t \geq t_{k+1}.$$

The proof of (4.2) is complete.

CHAPTER 5

STABILITY ANALYSIS OF SOME MODELS

5.1 The logistic equation

5.1.1 Stability of the logistic equation with a piecewise argument constant

We have studied in Chapter 3 the logistic equation with a piecewise constant argument for the single species in [20]

$$\frac{dN(t)}{dt} = rN(t)\{1 - bN(t) - aN(t)\} \tag{5.1.1.1}$$

The solution for (5.1.1.1) is [20]

$$N(t) = N(n)\exp\{r\int_{n}^{t}\big(1 - aN(s) - bN(n)\big)ds\} \tag{5.1.1.2}$$

$$n \le t < n + 1$$

The logistic equations before adding the time delay are [20]

$$\frac{d}{dt}\{\frac{1}{N(t)}\exp\{r[1 - bN(n)]t\} = ar\exp\{r[1 - bN(n)]t\}, t \in [n, n + 1) \tag{5.1.1.3}$$

Then by integrating Equation (5.1.1.3) on the intervals $[n, n + 1)$, we get [20]

$$N(t) = \frac{N(n)\exp\{r[1-bN(n)](t-n)\}}{1+aN(n)\left(\frac{\exp\{r[1-bN(n)](t-n)\}-1}{1-bN(n)}\right)}$$

$$n \leq t < n + 1 \tag{5.1.1.4}$$

Suppose $t \to n + 1$ in (5.1.4)

$$N(n+1) = \frac{N(n)\exp\{r[1 - bN(n)]\}}{1 + aN(n)\left(\frac{\exp\{r[1 - bN(n)]\} - 1}{1 - bN(n)}\right)} \quad , n = 0,1,2, \ldots \tag{5.1.1.5}$$

By setting $f(x) = x$ we can get the fixed points of (5.1.1.5) in [20]

$$f(x) = x(n+1) = \frac{x(n)\exp P\{r[1 - x(n)]\}}{1 + \propto x(n)\left((\exp\{r[1 - x(n)]\} - \frac{1}{1 - x(n)})\right)}$$

$$n = 0,1,2, \ldots \tag{5.1.1.6}$$

where $b \neq 0$ because if b = 0 it will be the trivial dynamics of (5.1.1.1) in [20]

$$x = \frac{x\exp[r(1 - x)]}{1 + \propto x(\frac{\exp[r(1 - x)] - 1}{1 - x})} \tag{5.1.1.7}$$

By rewrite (5.1.7) as [20]

$$x[x(1 - \propto) - 1]\left(\frac{\exp[r(1 - \propto)] - 1}{1 - x}\right) = 0, \tag{5.1.1.8}$$

the fixed points become in [20]

$$x^* = 0 \quad \text{and} \quad x^* = \frac{1}{1 + a} \tag{5.1.1.9}$$

Then, we check the eigenvalues of $f(x^*) = 0$, and if $|\lambda_i| > 0$ $then\ x^*$ is unstable. If $|\lambda_i < 0|$ then x^* is stable.

5.1.2 Stability Hybrid dynamic model of logistic equation

We take the general case of logistic equation by replacing $[t]$ in (5.1.1.1) with $\beta(t)$ such that in [19]

$$N'(t) = rN(t)\left(1 - aN(t) - bN\left(\beta(t)\right)\right) \quad t > 0$$

By the following setting of the positive equilibrium, N^* is denoted by the origin:

$$x = b(N - N^*)$$

We then have [19]

$$x'(t) = -r[x(t) + \frac{1}{1+\propto}][\propto x(t) + x\left(\beta(t)\right)]$$

Here [19]

$f(x,y) = -r\left(x + \frac{1}{1+\propto}\right)(\propto x + y)$ is a continuous function for all derivatives $x, y \in s(\rho)$

Take the derivative once of $f(x,y)\ \forall x, y$. And we get [19]

$\left|\frac{\partial f}{\partial x}\right| \leq r\left(2 \propto \rho + \rho + \frac{\propto}{1+\propto}\right), \left|\frac{\partial f}{\partial y}\right| \leq r\,(\rho + \frac{1}{1+\propto})$ for $x, y \in S(\rho)$.

We assume that $r(2 \propto \rho + 2\rho + 1) = \ell$ satisfies the Lipchitz equation. $(C_1) - (C_3)$ are satisfied for sufficient small. Also, $(C_5) - (C_6)$ is satisfied.

We assume that $\propto \geq 1$ and $p < \frac{1}{1+\propto}$.

We let a Lyapunov function $V(x) = x^2$ where $x \in s(p)$ and $t \neq \theta_i$;

Therefore, we have [19]

$V`\left(x(t), x\left(\beta(t)\right)\right) = -2rx(t)(x(t) + \frac{1}{1+\propto})(\propto x(t) + x\left(\beta(t)\right))$,

$\leq -2r(x(t)+\frac{1}{1+\propto})(\propto x^2(t)-|x(t)||x(\beta(t))|,$

$$\leq -2r\left(x(t)+\frac{1}{1+\propto}\right)(\propto -1)x^2(t)\leq 0,$$

Where [19]

$V(x(\beta(t)))\leq V(x(t)).$

By Theorem 4.1, we say the zero solution is uniformly stable. This means that the positive equilibrium N^* is uniformly stable.

From theorem 4.2, it could check the uniformly asymptotic stability by following steps

We assume that $\rho_1 \in (0,\rho)$ such that $x(t)\in S(\rho_1)$ for all $t\geq t_0$ where $|x(t_0)|<\delta$ *and* $\delta>0$.

We assume that $q \in R^+$ such that $1<q<\propto$, which satisfies [19]

$$\psi(s)=q^2 s,$$

$$w(s)=2r(\propto -q)\eta s^2,$$

$$\eta=\frac{1}{1+\propto}-p_1,$$

$$V(x)=x^2,$$

$V`\left(x(t),x(\beta(t))\right)\leq -2r\left(x(t)+\frac{1}{1+\propto}\right)(\propto -q)x^2(t)\leq -w(|x(t)|, t\neq \theta_i.$

whenever [19]

$$V\left(x(\beta(t))\right)<\psi(V(x)).$$

It means the zero solution convergence to the positive equilibrium N^*. Therefore, N^* is uniformly asymptotically stable as per Theorem 4.2.

5.2 Competitions Model of Tumor-Immune System

5.2.1 Stability of the competition model with a piecewise argument constant

Chapter 3 presents the mathematical model for the interaction among tumor-immune cells with piecewise constant arguments of delay as [13]

$$\begin{cases} \dfrac{dx}{dt} = r_1 x(t)\left(1 - \dfrac{x(t)}{k_1}\right) - \propto_1 x(t)y([\![t]\!]) + \propto_2 x(t)y([\![t-1]\!]), \\ \dfrac{dy}{dt} = r_2 y(t)\left(1 - \dfrac{y(t)}{k_2}\right) + \propto_1 y(t)x([\![t]\!]) - \propto_2 y(t)x([\![t-1]\!]) - d_1 y(t). \end{cases} \quad (5.2.1.1)$$

Where $[\![t]\!]$ is the continuous part, $t \in [0, \infty)$ denotes the discrete state, $x(t)$ equals the size of tumor cells, r_1 is the growth rate of $x(t)$ and k_1 is the carrying capacity of (t).

We now assume that every one of (5.2.1.1) is based on the logistic equation since they describe the competition of everyone with respect to time. Moreover, we let the capacity of the tumor cells larger than the immune system [14].

The parameter values are given in [13] in terms of consistency with the biological facts and they are given in Table 5.1.

To check the stability, we must find the solution to every one of the systems (5.2.1.1) by integrating every one of them in (5.2.1.1) on an interval of the form $t \in [n, n+1)$ as [13]

$$\begin{cases} x(t) = x(n)e^{\int_n^t x(s)(r_1(1-x(s)k_1) - \propto_1 y(n) + \propto_2 y(n-1)ds,} \\ y(t) = y(n)e^{\int_n^t y(s)(r_2(1-y(s)k_2) + \propto_1 x(n) - \propto_2 x(n-1) - d_1)ds} \end{cases} \quad (5.2.1.2)$$

Table 1: Parameters values used for numerical analysis [13]

Parameters	Values
r_1(growth rate of tumor cells)	$0.18\ \text{day}^{-1a}$
r_2(growth rate of CTLs)	$0.1045\ \text{day}^{-1a}$
k_1(carrying capacity of tumor cells)	$5.0\times10^{6}\text{cells}^{a}$
k_2(carrying capacity of CTLs)	$3.0\times10^{6}\text{cells}^{a}$
$\propto_1$(decay rate of tumor cells by CTLs)	$4.401\times10^{8}\text{cells}^{1}\text{day}^{1b}$
$\propto_2$(decay rate of CTLs by tumor cells)	$3.422\times10^{-9}\text{cells}^{-1}\text{day}^{-1a}$
d_1(death rate of CTLs)	$0.0412\ \text{day}^{1a}$

where $k_1 = \frac{1}{k_1}, k_2 = \frac{1}{k_2}$.if $x(n), y(n) > 0 then\ x(t), y(t) > 0$.

If $t \to n+1$, then $x(n+1), y(n+1) > 0$ and if assume initial condition of $x(n)$and $y(n)$ then we find the time of (2.2).

If $t \in [n, n+1)$, then we have [13]

$$\begin{cases} \frac{dx}{dt} - \{r_1 - \propto_1 y(n) + \propto_2 y(n-1)\}x(t) = -r_1 k_1 \big(x(t)\big)^2, \\ \frac{dy}{dt} - \{r_2 + \propto_1 x(n) - \propto_2 x(n-1) - d_1\}y(t) = -r_2 k_2 \big(y(t)\big)^2. \end{cases} \qquad (5.2.1.3)$$

Everything in (5.2.1.3) represents the Bernoulli differential equation, which can obtain [13]

$$\begin{cases} \dfrac{d}{dt}\left[\dfrac{1}{x(t)}e^{[r_1-\propto_1 y(n)+\propto_2 y(n-1)]t}\right] = r_1k_1e^{[[r_1-\propto_1 y(n)+\propto_2 y(n-1)]t} \\ \dfrac{d}{dt}\left[\dfrac{1}{y(t)}e^{[r_2+\propto_1 x(n)-\propto_2 x(n-1)-d_1]t}\right] = r_2k_2e^{[[r_2+\propto_1 x(n)-\propto_2 x(n-1)-d_1]t}, \end{cases} \quad (5.2.1.4)$$

by integrating (5.2.1.4) on the [13]

$$\begin{cases} x(n+1) = \dfrac{x(n)[r_1-\propto_1 y(n)+\propto_2 y(n-1)]}{[r_1-\propto_1 y(n)+\propto_2 y(n-1)-r_1k_1x(n)]e^{-[r_1-\propto_1 y(n)+\propto_2 y(n-1)-r_1k_1x(n)]}}, \\ y(n+1) = \dfrac{y(n)[r_2+\propto_1 x(n)-\propto_2 x(n-1)-d_1]}{[r_2+\propto_1 x(n)-\propto_2 x(n-1)-d_1-r_2k_2v(n)]e^{-[r_2+\propto_1 x(n)-\propto_2 x(n-1)-d_1]}+r_2k_2y(n)]} \end{cases} \quad (5.2.1.5)$$

interval $t \in [n, n+1)$, so [13]

Now, we have a system of two-dimensions of difference equation; then we find the equilibrium points to check their stability.

Given the conditions [13]

$$\propto_1 > \propto_2, r_2 > d_1 \text{ and } r_1 > \frac{(\propto_1-\propto_2)(r_2-d_1)}{k_2r_2} \quad (5.2.1.6)$$

The positive equilibrium [13]

$$(\bar{x}, \bar{y}) = \left(\frac{k_2r_1r_2+(\propto_2-\propto_1)(r_2-d_1)}{k_1k_2r_1r_2+(\propto_1-\propto_2)^2}, \frac{k_1r_1(r_2-d_1)+r_1(\propto_1-\propto_2)}{k_1k_2r_1r_2+(\propto_1-\propto_2)^2}\right) \quad (5.2.1.7)$$

Now, we apply the following setting to get the linear system of (5.2.61.5) about the positive equilibrium points [13]

$$w(n+1) = Bw(n)$$

where B is [13]

$$B = \begin{pmatrix} e^{-k_1 r_1 \bar{x}} & 0 & -\frac{(1-e^{-k_1 r_1 \bar{x}})x_1}{k_1 r_1} & \frac{(1-e^{-k_1 r_1 \bar{x}})x_2}{k_1 r_1} \\ 1 & 0 & 0 & 0 \\ \frac{(1-e^{k_2 r_2 \bar{y}})x_1}{k_2 r_2} & -\frac{(1-e^{k_2 r_2 \bar{y}})x_1}{k_2 r_2} & e^{-k_2 r_2 \bar{y}} & 0 \\ 0 & 0 & 1 & 0 \end{pmatrix}$$

Then check the eigenvalues of the matrix. If $|\lambda_{ij}| < 1$, then r_1 is stable but if $|\lambda_{ij}| > 1$, then r_1 is unstable [21].

5.2.2 Stability of Hybrid model of competition model

The interactions between tumor and immune cells is based on the Lotika-Volterra model as prey and predator models that are represented by x, y in [22]

$$\frac{dx}{dt} = ax - bxy,$$

$$\frac{dy}{dt} = cxy - dy.$$

where x is the populations of tumor cells and y is the populations of immune cells.

By adding the stochastic parameter β for distribution the function $\beta(t)$ to the pervious model as [22]

$$\frac{dx}{dt} = ax - \beta xy,$$

$$\frac{dy}{dt} = cxy - dy.$$

β(t) is defined by [22]

$$\beta(t) = 1 - \frac{e^{-4\eta t}}{2\pi}$$

Therefore,we get [22]

$$\frac{dx}{dt} = ax - (1 - \frac{e^{-4\eta t}}{2\pi})xy,$$

$$\frac{dy}{dt} = cxy - dy.$$

If we lead the positive equilibrium points as[22]

$$x = \frac{d}{c}, y = \frac{a}{b(1 - \frac{e^{-4\eta t}}{2\pi})}$$

And we take limit for the equilibrium points at $t \to \infty$ as [22]

$$\lim_{t\to\infty} \frac{a}{b(1 - \frac{e^{-4\eta t}}{2\pi})} = \frac{a}{b} > 0$$

Therefore, the simplest model is stable and it makes a small circle on the positive equilibrium where η= $\frac{1}{4}$, see Figure 6.

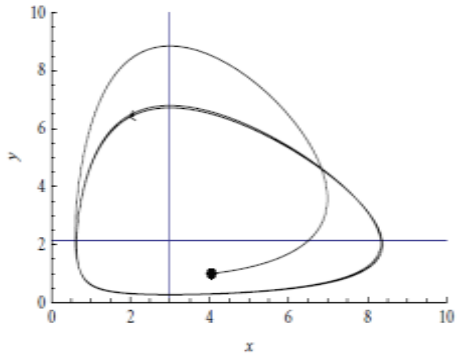

Figure 6: Evolutions of interaction of competition model where $a = 2, b = c = 1, d = 3$ *and* $\eta = \frac{1}{4}$.[22]

5.3 Gene-protein networks

A analysis of the behavior of regulatory genetic networks is difficult because the solutions of phase spaces lie in the switching domains and they have become undefined. Therefore, we will study the solutions of PWL systems for every box of the phase space in domains by built on the hypercube. The threshold is the domains that do not take their values from threshold values as a regulatory domain. The intersections of the domains occurring at the least value have a threshold value as the switching domain.

To study the solutions in switching domains, we have to study the equilibrium points of the PWL system that lies in the regulatory domains. Its stability is asymptotic, and the stability of the equilibrium points of the PWL is important in the control theory of hybrid dynamic systems.

The paper [15] studies the construction of the equilibrium points of PWL systems and their stability. Firstly we will explain the types of equilibrium points then followed by the stability for them.

5.3.1 Types of Equilibrium Points

5.3.1.1 Regulatory Equilibrium Points

The solutions x of a focal point $\emptyset(D)$ where D equals regulatory domain which is asymptotically stable.

5.3.1.2 Singular Equilibrium Points

Singular equilibriums points are found by the focal points $\emptyset(D)$ and their solutions are founded by the Filippove method, which uses the terms of weakly stable. This is the opposite of the Lyapunove method, which uses the terms of stable the same differential equation .So [15] has presented the concepts of stable and weakly stable in the following section.

5.3.2 Stability of genetic regulatory networks with piecewise linear function

The stability of genetic regulatory networks with piecewise a linear function is based on the equilibrium points as follows [15]

1. If the equilibrium set E which is a subset of neighborhoods V such that $E \subseteq V$, there exists a point U such that $E \subseteq U \subseteq V$ and every solution ξ_t of Equation (3.5.3.3) where $\xi_0(x) = x$ for all points $x \in U$ then equilibrium set E is stable.
2. If the equilibrium set E which is a subset of neighborhoods V such that $E \subseteq V$, there exists point U such that $E \subseteq U \subseteq V$ .and some solution ξ_t of Equation (3.5.3.3) where $\xi_0(x) = x$ for all points $x \in U$,then equilibrium set E is weakly stable.
3. If the first case is satisfied in addition to the following conditions[15]

   i. $\xi_t(x) \in V, \forall t \geq 0,$

   ii. $\lim_{t \to \infty} \xi_t(x) \in E.$

Then equilibrium set E is asymptotically stabl

4-If the second case is satisfied in addition to the following conditions [15]

i. $\xi_t(x) \in V, \forall t \geq 0,$

ii. $(ii) \lim_{t \to \infty} \xi_t(x) \in E.$

Then equilibrium set E is weakly asymptotically stable.

By the following numerical example, the stability of genetic networks will be clear.

5.3.3 Examples

Given the simplest model of piecewise linear as [23]

$$\frac{dE}{dt} = \mu^E_{s(t)} E + K^E_{s(t)},$$

$$s(t) = \begin{cases} s_1 \quad if\ (E \geq e), \\ s_2\ if\ (E < e). \end{cases}$$

$$K^T_{S1} = 400, K^T_{S2} = 0, e = 3, \mu^T_{s1,s2} = -1.$$

We start with E_1 as [6]:

$$\frac{dE_1}{dt} = \mu^{E}_{s_1(t)} E_1(0) + K^{E}_{s_1(t)},$$

$$\frac{dE_1}{dt} = -1E_1(0) + 400.$$

The solutions of E_1 are given by [23]:

$$\vec{E}_1(0) = (-E_1(0) + 400)e^{-t},$$

We assume initial condition according to $(E \geq e)$,

$$E_1(0) = 3{,}3.5,$$

$$\vec{E}_1(0) = (-1(3) + 400)e^{-t} = 397 > 0\ (stable),$$

$$\frac{d\vec{E}_1}{dt} = (-1(3.5) + 400)e^{-t} \overset{t=0}{\Longrightarrow}\ 396.5 > 0(stable).$$

Let check E_2 is [23]:

$$\frac{d\vec{E}_2}{dt} = \mu^{E}_{s_2(t)} E_2(0) + K^{E}_{s_2(t)},$$

We assume the initial conditions according to $(E < e)$ in [23]

$$E_2(0) = 0.5,$$

$$\vec{E}_2(t) = (-1(0.5) + 0)e^{-t} \overset{t=0}{\Longrightarrow} -0.5 < 0(unstable).$$

Example:

Let the general form of concentrations of RNA molecules and proteins with piecewise linear function for n of genes in [24]:

$$\frac{\mathrm{dy}}{\mathrm{dx}} = \mathrm{M}_{\mathrm{s(t)}}\mathrm{x(t)} + \mathrm{k}_{\mathrm{s(t)}},$$

where $M_{s(t)}$ is a constant matrix[24]

$$s_i(t) = F_i\left(q\left(\left[y_1(t-\tau_{1,i}), y_2(t-\tau_{2,i})\right], \dots, y_n(t-\tau_{ni})\right)\right),$$

$$Q_i(y(t)) = \begin{cases} 1 & \text{if } x_i(t) > h_i \\ 0 & \text{if } x_i(t) \le h_i \end{cases},$$

where $y(t) \in R^n$ is the vector that presents the continuous variables. By the state space of the system, we can investigate as $s_i\binom{t+}{t-} \in R^n$, This presents the switching matrix . $M: s \to R^{n\times n}$ as a diagonal matrix of eigenvalues, $k: s \to R^n$ is the switching vectors that present the state of the system and $F_i: \{0,1)^n \to \{0,1\}$ is a step function for the state spaces $s_i(t)$.

For two-dimensions, we have four state spaces (regions) ,see Figure 7. Since $n! = 2! = 4$ state spaces and the solutions will remove (converge or discourage) the state spaces finally to form a square shape. The convergence occurs when the eigenvalues are negative, however, the divergence occurs when the eigenvalues are positive [16]

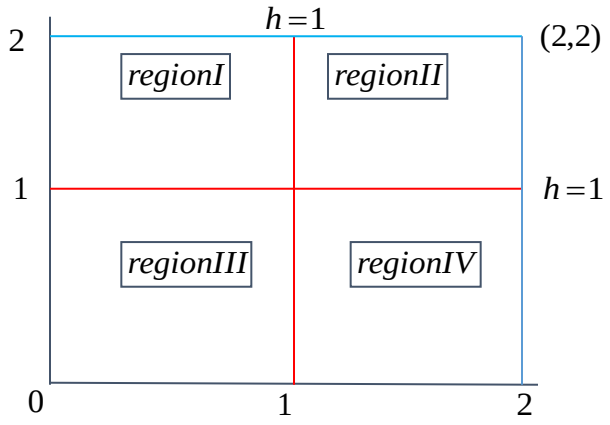

Figure 7*:* State space, Thresholds of example [16]

Here [11]

$$s_i(t) = F\big(q([y_1(t), y_2(t)])\big),$$

The state spaces $s_i(t) = (0,0),(0,1),(0,0),(1,1)$ and we can get $M_{s(t)}$ as [16]

$$M_{0,0} = M_{0,1} = M_{1,0} = M_{1,1} = \begin{bmatrix} -1 & 0 \\ 0 & -1 \end{bmatrix}$$

and [11]

$$k_{s(t)} = k_{0,0}, k_{0,1}, k_{1,0}, k_{1,1}$$

where

$$k_{0,0} = \begin{pmatrix} 0 \\ 2 \end{pmatrix}, k_{0,1} = \begin{pmatrix} 2 \\ 2 \end{pmatrix}, k_{1,0} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}, k_{1,1} = \begin{pmatrix} 2 \\ 0 \end{pmatrix},$$

And $h_1 = h_2 = 1$.

To understand the behavior and dynamic of the system, we apply the above results to the given piecewise linear model and check the convergence of all points as:

The first state IV that characterizes [16]

$$(x_1(t) > h = 1, x_2(t) \leq h = 1),$$

By the operation $Q_i\big(y(t)\big)$, it will note that the chosen point is $s_i(t) = (1,0)$ by [16]

$$\frac{dy}{dt} = M_{1,0}y(t) + k_{1,0},$$

$$\begin{pmatrix} \frac{dx_1}{dt} \\ \frac{dx_2}{dt} \end{pmatrix} = \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \end{pmatrix}.$$

By solving the linear system, we get [16]

$$\begin{pmatrix}\vec{x}_1(t)\\ \vec{x}_2(t)\end{pmatrix} = \begin{pmatrix}x_1(0)e^{-t}\\ x_2(0)e^{-t}\end{pmatrix}.$$

If we let $t = 0$ and assume the initial values [16]

$$\big(x_1(0), x_2(0)\big)^T = (1.5,1)^T$$

Then $(\vec{x}_1(0), \vec{x}_2(0)^T = (1.5,1)^T > 0$, the stability for the solution in region IV which is stable.

Region III is characterized by [16]

$$\{x_1, x_2 \le h = 1\},$$

By the operation $Q_i\big(y(t)\big)$,it selects the point $(0,0)$ by [16]

$$\frac{dx}{dt} = M_{(0,0)}x(t) + k_{0,0},$$

$$\begin{pmatrix}\frac{dx_1}{dt}\\ \frac{dx_2}{dt}\end{pmatrix} = \begin{pmatrix}-1 & 0\\ 0 & -1\end{pmatrix}\begin{pmatrix}x_1\\ x_2\end{pmatrix} + \begin{pmatrix}0\\ 2\end{pmatrix},$$

By solving the linear system, we get [16]

$$\begin{pmatrix}x_1\\ x_2\end{pmatrix} = \begin{pmatrix}x_1(0)e^{-t}\\ 2-(2-x_2(0))e^{-t}\end{pmatrix},$$

If we let $t = 0$ and assume the initial values

$$\big(x_1(0), x_2(0)\big)^T = (1,1)^T,$$

Then $(\vec{x}_1(0), \vec{x}_2(0)^T = (1,1)^T > 0$, and the stability for the solution in Region IV is stable.

Region II that characterizes [16]

$$\{x_1, x_2 \ge h = 1\},$$

By the operation $Q_i(y(t))$ will select the point $(1,1)$ as [16]

$$\frac{dx}{dt} = M_{(1,1)}x(t) + k_{1,1},$$

$$\begin{pmatrix} \frac{dx_1}{dt} \\ \frac{dx_2}{dt} \end{pmatrix} = \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} + \begin{pmatrix} 2 \\ 0 \end{pmatrix},$$

By solving the linear system we get [11]

$$\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} 2-(2-x_1(0))e^{-t} \\ x_2(0)e^{-t} \end{pmatrix},$$

If we let $t = 0$ and assume the initial values

$$\big(x_1(0), x_2(0)\big)^T = (1.2,1.5)^T,$$

Then $(\vec{x}_1(0), \vec{x}_2(0)^T = (1.2,1.5)^T > 0$, the stability for the solution in region IV is stable.

The region II that characterizes [16]

$$\{x_1 \leq h = 1, x_2 > h = 1\},$$

By the operation $Q_i(y(t))$ it will choose the point $(0,1)$ as [16]

$$\frac{dx}{dt} = M_{(0,1)}x(t) + k_{0,1},$$

$$\begin{pmatrix} \frac{dx_1}{dt} \\ \frac{dx_2}{dt} \end{pmatrix} = \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} + \begin{pmatrix} 2 \\ 2 \end{pmatrix},$$

By solving the linear system we get in [16]

$$\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} 2-(2-x_1(0))e^{-t} \\ 2-(2-x_2(0))e^{-t} \end{pmatrix},$$

If we let $t = 0$ and assume the initial values

$$\left(x_1(0), x_2(0)\right)^T = (1,1.5)^T,$$

Then $(\vec{x}_1(0), \vec{x}_2(0)^T = (1,1.5)^T > 0$,the stability for the solution in Region II is stable.

Every region is stable.

CHAPTER 6

CONCLUSION AND DISCUSSION

In this study, piecewise linear systems with time-delay, which are a class of hybrid dynamic systems, were is investigated in terms of mathematical modeling of dynamic systems.The most important piecewise linear part was the analysis stability of models with time- delay, which was take in long simulations. We started with a population model that concluded all concepts of stability theorems (fixed points, equilibrium points, periodic solutions and phase spaces) in two-dimensions and n-dimensions.Next, we were able to investigate the competition models that were based on population equations, In this way, we can check the stability for competition models of using numerical simulations. furthermore, the study has shown the dynamic of complex networks, such as gene regulatory networks. Piecewise linear systems helped us to produce the simplest model that is easy to check. Constructing piecewise linear systems of complex phenomena has contributed to investigating the future behavior of theses problems because they have the time-delay parameter with piecewise linear functions.The stability of networks was according to sufficient conditions.

Then, we have to lead the hybrid model for some biological systems.The hybrid models were more stable than piecewise linear models by eigenvalues of the fixed and equilibrium points.

At the end of this work, we investigated the construction of dynamic systems in two-dimensions and n-dimensions as hyperplane maps with an example for each one.

In our work, we collected a number of non-linear biological systems and analyzed them with PWL function, then proved the stability of complex genetic networks with piecewise linear functions in numerical simulations.

REFERENCES

[1] **Vladimir A. Kuzenetsov and Iliya A. Makalin. (1994),** *"Nonlinear Dynamics of Immunogenic Tumors: Parameters Estimation and Global Bifurcation Analysis",* Laboratory of Mathematical Immunogenic, Vol. 56, No. 2, pp. 295-301.

[2] **Uyttenhove, C., J.Maryanski, and T.Boon.(1983),**"*Escape of Mouse Mastocytoma P815 After Nearly Complete Rejection is Due to Antigen-loss Variants Rather than Immunosuppression"*.J.Expl Med.157,1040-1052.

[3] **Emanuel,N.M.(1981)**,"*Chemical and Biological Kinetics"*. Russian Chem.Rev.50,901-947.

[4] **Wheelock, E.and M.K.Robinson.(1983)**,"*Biology of Disease"*. Endogenous Control of The Neoplastic Process.Lab.Investigation 48,pp 120-139.

[5] **Kuznetsov, V.A. (1979),**"*The dynamics of Cellular Immunological Antitumor reactions.I.Synthesis of Multi-Level Model"*. In Mathematical Methods of Systems Theory (in Russian), Vol.1, pp.57-71.

[6] **Kuznetsov, V.A.(1991)**," *A mathematical Model for The Interaction Between Cytotoxic Lymphocytes and Tumor Cells. Analysis of The Growth, Stabilization, and Regression of The B-cell ymphoma in Mice Chimeric with Respect to The Major Histocompatibility Complex."* Biomed.Sci.2, pp 465-476**.**

[7] **Kuznetsov, V.A.(1992)**,"*Dynamics of Immune Processes During Tumor Growth"* (in Russian) Moscow: Nauka.

[8] **Aihara K., Suzuki H. (2010),** *"Theory of Hybrid Dynamical Systems and Its Applications to Biological and Medical Systems",* Institute of Industrial Science, Tokyo Japan, pp. 4893-4896.

[9] **Stephanu A., Volbert V. (2016),** *"Hybrid Modelling a Classification Review",* Institute of Numerical Mathematics, Vol. 11, No. 1, pp. 40-44.

[10] **Fisher, N. Piterman.(2010),** *"The Executable Pathway to Biological Networks. Briengs in Functional genomics"*,pp.79-92.

[11] **B.S. Brooks, S.L. Waters.(2008),**" *Mathematical Challenges in Integrative Physiology", pp 893-896*.

[12] **Nomura T.(2010)**," *Toward an Integration of Biological and Physiological Functions at Multiple Levels".* Frontiers in Physiology.pp 1-164.

[13] **Gurcan F, Kartal S., Bozkurt F. (2014),** *"Stability and Bifurcation Analysis of A Mathematical Model for Tumor-Immune Interaction with Piecewise Constant Arguments of Delay",* Article in Chaos Solitons and Fractals, Ankara-Turkey, pp. 16-20.

[14] **Sarkar R. R., Banerjee S. (2006),** *"A Time Delay Model for Control of Alignment Tumor Growth", a* Third National Conference on Nonlinear Systems and Dynamics, Ankara, Turkey, pp. 20-27.

[15] **Gouze J. L, Jong H. D, Casey R. (2004),** *"Piecewise-Linear Models Of Genetic Regulatory Networks: Equilibria and Their Stability",* Tokyo, Japan, pp. 4-16.

[16] **Kahraman M. (2007),** *"Modelling Functional Dynamical Systems by Piecewise Linear Systems with Delay",* Master Thesis, Ankara-Turkey, pp. 51-57.

[17] **Hale J. K. (1977),** *"Theory of Functional Differential Equations"*, Springer-Verlag, pp. New York, USA, pp. 12-19.

[18] **Razumikhin B. S. (1956),** *"Stability of Delay Systems"*.Berlin, Germany, pp. 12-21.

[19] **Akhmet M.(2009),**"*Nonlinear Hybrid Continuous/Discrete-Time Models",* Vol. 8, Master Thesis, Atılım University, Ankara-Turkey, pp. 70-79.

[20] **Gopalsmay K., Liu P.(1996),** *"Persistence and Global Stability in a Population Model",* The Flinders University of South Australia, pp. 59-61.

[21] **Li X, Mou C, Niu W, Wang D.(2011),**" *Stability Analysis for Discrete Biological Models using Algebraic Methods*". Math Comput ,pp.247–62

[22] **Cattani C., Ciancio A. (2011),** *"Separable Transition Density in the Hybrid Model for Tumor-Immune System Competition"*, Messina, Italy, pp.1-7.

[23] **Al-windawi., H.(2016),"***Hybrid System Modeling and Simulation with Tumor-Immune System Application*", Master Thesis, Cankaya University, Ankara-Turkey, pp. 30-32.

[24] **Oktem H., Karasozen B., Kahraman M. (2009),** *"A Model of Angiogenesis by Hybrid Systems With Delay on the Piecewise Constant Part",* Article in Journal of Process Control, Ankara, Turkey, pp. 5-7

APPENDICES

Curriculum Vitae

PERSONAL INFORMATION:

Full Name: Noura A. Abdulrazaq Tahar

Nationality: Libyan

Gender: Female

Date of Birth: November ^{20th} 1988

Marital Status: Married

Mobile: 05438999512

Email: Haneenmohammed2012@gmail.com

EDUCATION:

Degree	**Institution**	**Year of Graduation**
B.sc in mathematics science	Omar Al- Mukhtar University	2012
M.sc in mathematics and computer science	Çankaya University	2017

LANGUAGES:

Arabic: native

English

HOBBIES:

Reading

Playing sports

WORK EXPERIENCE:

1-Libyan high school (Lecturer for two years (mathematics lessons))