HYBRID SYSTEM MODELING AND SIMULATION WITH TUMOR-IMMUNE SYSTEM APPLICATION

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HYBRID SYSTEM MODELING AND SIMULATION WITH TUMOR-IMMUNE SYSTEM APPLICATION

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

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ABSTRACT

HYBRID SYSTEM MODELING AND SIMULATION WITH TUMOR-IMMUNE SYSTEM APPLICATION

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Cancer dynamics exhibits complex behavior due to different factors. Immune system interaction is one of those factors. There exist mathematical models that investigate these interactions. In this thesis, we have used hybrid system modeling that offers several improvements. One of the main advantages of this modeling is that we can investigate through sensitivity analysis the effect of changing the threshold values, which means a point or level at which range changes in model behavior. Hybrid systems provide a promising area in mathematical modeling of many biological and physiological systems. From this point of view, to test the capability of hybrid systems in the sense of simulation is a strong motivation. In this work, we have observed the capability of hybrid system modeling in terms of analysis and computation. We have verified that when we substitute the solvable one, we reduce the complexity in the sense of reasonable computational resources.

Keyword: Piecewise Linear, Hybrid System, Tumor-Immune system, Mathematical Modeling, Simulation.

ÖZ

TÜMÖR-BAĞIŞIKLIK SISTEMI ILE HİBRİT SISTEM MODELLEME VE SIMÜLASYON UYGULAMA

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Yüksek Lisans, Matematik ve bilgisayar bilimleri

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Kanser dinamikleri, değişik faktörlere göre karmaşık davranış gösterir bağışıklık sistemi ilişkisi bu zorluklardan biridir literatürdü, bu ilişkileri inceleyen matematiksel modeller bulun maktadır. Bu tezde çeşitli avantajlar sağlayan hibrit sistem modellemesini kullandık. Bu modelleme başlıca avantajlarından biri, duyarlılık analizi yoluyla örnek davranış değişiklikleri aralığı bir noktaya ya da seviyesi anlamına gelir eşik değerleri, değişen etkisini araştırmak olabilir. Hibrit sistemler, birçok biyolojik ve fizyolojik sistemlerin matematiksel modelleme umut verici bir alanı sağlar. simülasyon duygusu güçlü bir motivasyon bakış Bu açıdan bakıldığında, hibrit sistemlerin yeteneğini test etmek için. Bu çalışmada, analiz ve hesaplama açısından hibrit sistem modelleme yeteneği gözlemledik. Biz çözülebilir bir yerine, biz makul hesaplama kaynaklarının anlamda karmaşıklığını azaltmak olduğunu doğruladıktan.

Anahtar Kelimeler: Parçalı doğrusal, Hibrit sistemler, tümör-bağışıklık sistemi, matematiksel modelleme, simülasyon.

DEDICATION

I would like to dedicate this dissertation to my dear father (Nozad) who has a special place in my heart, I am very thankful for him from the day of my birth to the present day.

I dedicate this dissertation to my mother (Ashwaq) for her constant, unconditional love and support.

I dedicate this dissertation to my uncle (Emad) for his support and encouragement.

I dedicate this dissertation to my aunt (Sudad) for her support and encouragement.

I dedicate this dissertation to my aunt (Sajeda) for her support and encouragement.

I dedicate this dissertation to my lovely husband (Ahmed) for his support and encouragement.

I dedicate this dissertation to my brothers and sisters.

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CHAPTER 1

INTRODUCTION

1.1. Background

Constructing mathematical model of known dynamical process is a fundamental method for many nature science problems. Once a mathematical model for a dynamical phenomenon has been constructed, it used for anticipating the suitable intervention if required or designing a technology system. A promising alternative in this direction is the use of hybrid dynamical systems. Hybrid systems are created by continuous and Boolean variables that regulate each other. Nowadays, hybrid systems offer several advances for various modeling in a natural science. A very useful subclasses of hybrid system is the piecewise linear system. Feature of piecewise linear system is capability of substituting more complex system in to locally solvable system. In these cases, hybrid dynamical systems form a significant tool for this purpose. A regulatory state is a collection of genes has been adjusted or co-regulated throughout one or very familiar transcription factors (TFs). A TF is a protein binding to a cis-regulatory element (for example a reinforce TATA fund) and therefore, in a direct or indirect, positive or negative ways has an impact on the initiation of transcription of organized genes. A cancer related regulatory unite is a group of genes (Carcinogens or tumor suppressor genes) regulating by just one or more common TFs. However, modeling the cancer-related regulatory states of the cell split period existed in cells of human is an important step to understand cancers. There are several kinds of gene transcriptional regulatory related approaches suggested in the past; their nature and synthesis are classified by several factors taking into accounts gene expression values the causal relations between genes, for example with Bayesian analysis or Dynamic Bayesian networks, and the time scope e.g. while continuous or discrete, considering of returns monitoring in regulatory states is decisive. Therefore, some genes have individual characteristics, for example, they regulate themselves or genes in the next further time aspects. Furthermore,

genes could have one or more activators or restraints that co-regulate the cloning grades of genes in regulatory state [1].

1.2 Objectives

Functional dynamical system can be modeled by piecewise linear system, simple models can be used to approximate the complex dynamics. Regulatory gene networks can be divided into subsystems and output of each system can be the external input of other systems. Whole details of the regulatory gene networks can be included in piecewise linear systems by this way.

1.3 Organization of the Thesis

This thesis contains six chapters.

Chapter 1 introduces background about regulatory model by transcription factors with the aim of thesis.

Chapter 2 includes gene regulatory network, how gene is regulated and contain modeling approaches with examples.

Chapter 3 introduces mathematical models and hybrid system with its features and examples.

Chapter 4 includes biological background and parameter estimation.

Chapter 5 presents application of the model and simulation result with sensitivity analysis.

Chapter 6 presents conclusion part.

CHAPTER 2

BACKGROUND

2.1 Gene regulatory network

The genome has a key role to control the processes of cellular, like the rebuttal of cell to circumferential indications, the recognition of cells and set of cells in the detecting of expansion programs, and the duplication of the genome former cell section. A protein that is synthesized from the data containing a coding area of DNA, as an enzyme stimulating a metabolic response, or as a part of a signal transduction aisle. With the presence of little abnormality, overall cells in an organism include the genetic materials itself. This entitles that to know how genes are involved in the control of inside cellular and between cellular process, the objective have be widened from the series of nucleotides encoding protein to regulatory system specifying which gene are explicated, where and when in the creatures, and to what range [2]. Gene expression is a congregation process that is regulated at many cases in the synthesis of protein [2]. A part from DNA transcription regulation, the valuable studied form of regulation, the gene term can be planned through RNA supplying and transfer, RNA transferring and the post-translational amendment of proteins, see Figure 1. The protein achieving these regulatory functions is created by other genes. This produces elevation to genetic regulatory systems constructed by networks of regulatory of interactions between DNA, RNA, protein, and other molecules. Empirical techniques used to explain regulatory interactions on molecular level are decisive to this end. As a matter of reality, the research of genetic regulatory systems received an important motive from the recently development of mechanism, such as microarrays of cDNA and oligonucleotide chips, permitting the spatiotemporal expressions stages of genes to be weighted in a wide analogous path. For more details see [3, 4, 5].
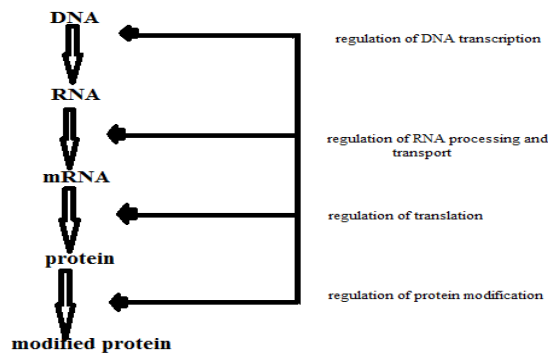
Figure 1: different stages of protein synthesize for regulation of gene expression [3]

Although still in their infancy, these techniques have become prominent experimental tools, by opening up a window on dynamics of gene expression. In addition to experimental tools, computer tools will be dispensable. As most genetic regulatory systems of interest involve many genes connected through interlocking feedback loops, an intuitive understanding of their behavior is hard to be obtain. By explicating hypotheses on the topology of regulatory network in the form of computer model, the behavior of possibly large and complex regulatory systems can be predicated and explained in a systematic way. Figure 2 shows the combined application of experimental and computational tools. Starting from an initial model, suggested by knowledge on regulatory mechanisms and expression data, the behavior of the system is simulated at a variety of experimental conditions, comparing the predications with the observed temporal evolution of genes expression levels gives an indication of the adequacy of the model. If the predicted and observed behavior does not match, and the experimental data is considered reliable, the model must be revised. The activities of modeling a regulatory network, simulating the behavior of the system and testing the resulting predictions are repeated until an adequate model is obtained [2].
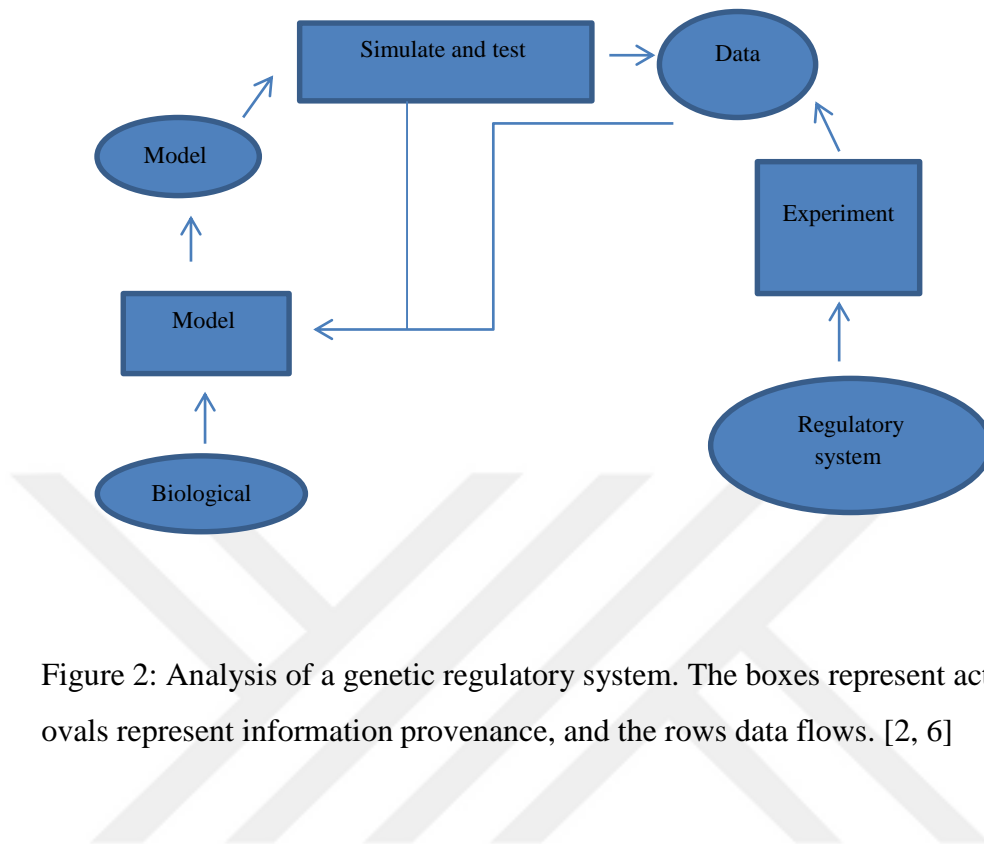
Figure 2: Analysis of a genetic regulatory system. The boxes represent activates, the ovals represent information provenance, and the rows data flows. [2, 6]

2.2 Gene Regulation

Expression of a gene relies on the activation of operon sequences. Activating and depredating of operon sequences are regulated by the promoter region [7]. Hence, there are two main regions in promoter repressor and activator operators. A repressor operator is an essential element in the inhibition of protein synthesis, since if a repressor protein binds to this region; protein synthesis will be deactivated as a result. Activator proteins, on the other hand, exist in the cell used to break this bond and activate the transcription. An activator operator in promoter has many different functions. It helps RNA polymerase to bind to promoter region, activates the operon and makes transcription possible, if the synthesized material quantity reaches to a critical value; the operon that is responsible for the synthesis of this material inhibited by a negative feedback mechanism breaks the bonds between activator protein and operator or binds repressor protein to repressor operator. In both cases, the operon is deactivated and the protein synthesis controlled. Figure 3 includes

genes X, Y and Z encoding for three proteins, β−galactosidase, galactoside permease and thiogalactosidase transacetylase for lactose metabolism in E.coli and the regions regulating the expression of these genes Although the regulatory gene is not a part of the lactose operon, it encodes repressor protein inhibiting transcription of the lac operon. Promoter region is put as control sides, whereas activator and repressor regions, P and O, in the promoter are drawn in a separate in the Figure 3.

Figure 3: Lac operon in E.coli [8]
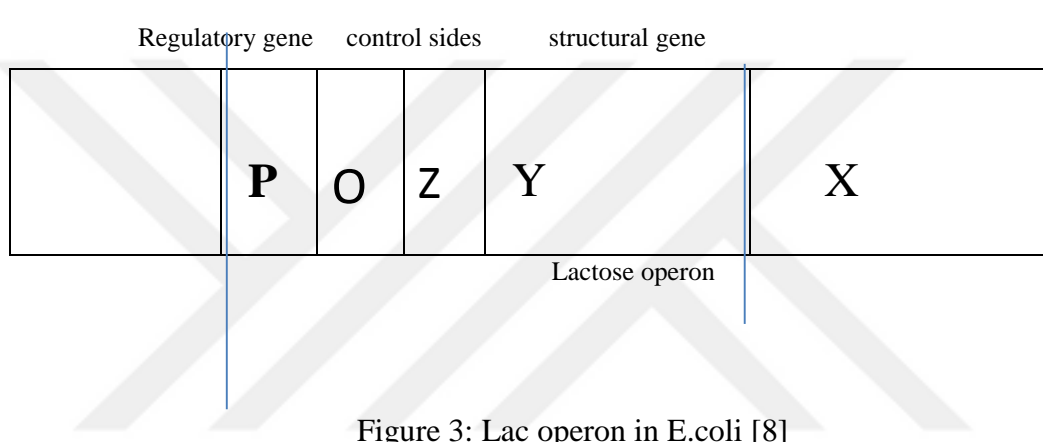
Synthesis and regulation mechanisms in complex systems result in a hierarchical organization, differentiation and increased functionality [9,10] in prokaryotic genomes, genes having related functions are often located in the same operon, as it is shown in the figure, and transcribed collectively, while in eukaryotes, most of the protein coding genes are transcribed individually.

2.3 Transcription

In most cases, synthesis of the protein are being in the cytoplasm, while the creatures, such as eukaryotes that contain their DNA and chromosomes situated in the nuclei of cells and consequently ,RNA maybe utilized as a mold for installation. The vicarious consequence of DNA through RNA is the prime aspect of the main dogma [11]. One strand of DNA is named the sense or noncoding strand in which the template is used to encode information. This operation starts with linking of RNA polymerase to promoters that are the distinctive areas of the noncoding strand where transcription beginning it will be easy reach for gene. RNA polymerase hydrogen strains to be broken and the snail strands to be UN wind. Then, for an unlock one-pair, the complementary base-pairs are related by hydrogen bonds creating RNA (mRNA) messenger for more details [12].Once RNA polymerase reaches the termination area on the strand, the operation is ends and the DNA turns to the original form. The molecule mRNA is one the three types of RNA taking part in the protein synthesis. In most molecules, a high proportion of the RNA nucleotides are used for encoding. For this reason, in experiments usually mRNA levels are measured to determine future predictions.

2.4 Translation

There is another operation in protein composition it called Translation where mRNA carries the genetic information to the ribosomes from the chromosomes; a cell structure contains ribosomal RNA (rRNA) and protein base pairs. Similar to transcription, translation has also three parts, inception, base-paring and ending. Nucleotide sequences are transferred into triplets and each of those triplets is linked to a specific amino acid. Each three mRNA nucleotides are called as codons; these codons are together from units of genetic code DNA or RNA while the identical ones in tRNA are named its anticodons. It can be shown in ribosomes, the codon AUG specifying the amino acid methionine, launches the polypeptide composition and,

throughout hydrogen bonds, the rule pairs on mRNA are corresponded to the ones on transmit RNA (tRNA). Hence, tRNA is a tiny one-stranded RNA molecule to the length between seventy four till seventy nine nucleotides [13]. Consequently, every tRNA holds just single amino acid. Transcription and translation processes result in proteins which are the most functional life molecules because of catalyzing a wide variety of chemical reactions and also serving as building blocks for cellular structures like muscles, skin, and enzymes. The tissue, metabolic state of the cell, specifies the amount of protein that a cell expresses.

2.5 Modeling approach

2.5.1 Modeling by Graphs

Generally speaking, Gene regulatory networks have been modeled through considering them as directed graphs. A tuple $G = (V; E)$ of a directed graph is, in which V is the group of (genes) and E is a collection of edges (relationships). In fact, the edges can be perceived as guide in such a way that the rows of vertexes (v_i, v_j), usually in short (i, j), with the head (v_i) and thetail (v_j) of the edge. These edges have the potentiality to bear some weights and they enable be described. For epitome, the energizing or restraint of gene by other may be showed as (i; j; +) or (i; j ;-), One after the other. An easy directed shape impersonation of regulatory network of three V={1,2,3}; E={(1,2,+),(1,3,-),(3,2,-),(2,3,+),(3,3,+)}, see Figure 4.
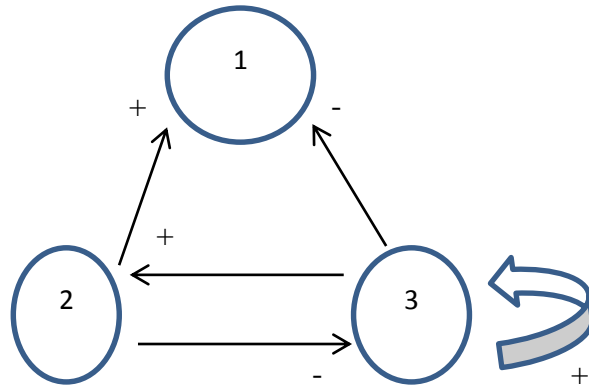
Figure 4: A graph represent simple regulatory network [2].

2.5.2 Bayesian Networks

To analyze the interactions among genes, statistical information is used by Bayesian networks. Due to the fact that the regulatory elements are not the only genes, other expression levels of regulatory factors, like protein concentrations and experimental conditions, are also adopted in most the Bayesian approaches. According to Markov assumption, that is given a finite set of experimental data, the dynamics of these factors are modeled by a directed acyclic graph [14], where vertices of the regulatory factors, which (1, 2... n) represents the corresponding to the random variables $x_1, x_2, \ldots, x_n$, respectively. These random variables are the expression levels of the genes. The corresponding regulatory factor, [14]. On the other hand, is a gene with a conditionally distribution $(x_i \mid$ parents $(x_i))$ where parents (X_i) represents the regulatory factors having a direct influence on i , all edges that have an outgoing edge directed towards x_i .The outcome of the conditional distributions produces a joint probability distribution [15, 16].

$$\text{P} (x_1, x_2, \ldots x_n).\text{P} (x_1, x_2, \ldots x_n)=\prod_{i=1}^{n} \text{p}(x_i \mid \text{parents}(x_i)) , \qquad (1)$$

Bayesian approach, on the other hand, gives a certain result for the possible networks and searches for the best network matching the given data most, or equivalence class of networks deducing the underlying network [14] .Furthermore, Bayesian networks provide a valuable outcome concerning the interactions instead of seeking for a network or a category of networks. Bayesian networks and statistical methodologies are activated to accord with the random sides and measurements of gene expression. Although Bayesian networks are not computationally practical, expectation of the gene regulations and sets of genes with the same functions can easily be useful into the field [17].

2.5.3 Boolean network

Boolean networks are one of the most studied discrete approaches. The classical logical description of regulatory relations is explained by Somogyi and Sniegoski in [18].The Boolean approach represents the regulatory relations by stepwise functions the genes in a regulatory network are assumed to be logical variables, i.e., their expressionism either on or off [19]. In other words, enzymes are said to be present, if the expression levels lie in a predefined interval which is identified by the threshold values for the enzymes and absent otherwise, the considered gene is inactive before threshold value, e, and is activated after the concentration achieves the threshold concentration , see Figure 5 .
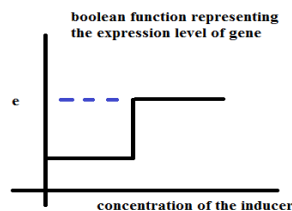

Figure 5:   Boolean approach [18]

Then, the Boolean function elated to the figure looks like:

$$\omega\,(x) := \begin{cases} 0, if\ x < t_i \\ 1, if\ x\ \geq t_i \end{cases} \tag{2}$$

At a particular time, some of the genes in a cell are active while others are inactive. All active and inactive genes construct a collection of Boolean variables, usually called the metabolic situation of the cell. Gene expressions for the next time point are described by Boolean logical rules and updated synchronously in the classical description [20]. Liang, Fuhrman and Somogyi describe an algorithm called REVEAL for inferring gene regulatory network from state transmission table which corresponds to the time- chain expression profiles. Given a finite set of gene expression the algorithm searches for the Boolean logical rules to infer the underlying regulation network. Small number of state transitions, input/output pairs is used in the algorithm, which results in a reduced search space. If the number of regulator variables for each vertex is bounded, then the algorithm identifies the network in polynomial time, but still not efficiently. Akutsu, Miyano and Kuhara propose a simpler algorithm to infer the underlying regulation network with an assumption that the numbers of regulatory genes are limited by a constant. They formally define the identification trouble as given number of variables and expression patterns, to decide whether there exists an unparalleled Boolean network, and to give the output if it exists [21]. The algorithm uses an easy exhaustive seeking for each duet of vertices and all possible Boolean functions. Unfortunately, the algorithm works less efficiently than REVEAL and allocates more space [21]. Akutsu et al. also state that the network cannot be identified uniquely when real expression scores are given to the algorithm, because the number of different expression patterns generated by the algorithm is so small, if the data are not random, i.e., the periodic solution problem is encountered.

2.5.4 Models with Piecewise-Linear Differential Equations

Changing in the concentration is considered an approximated way functions in Boolean networks. By using piecewise-linear differential equations we will gain a substitution approximation. See Figure 6. However, it is clear that the averages of degradation of some mRNA molecules and the possible extreme number of regulating genes for a single gene could be inclusive into the model known as parameters as well. An easy shape of this ways declared in [21, 22, 23]

$$\frac{dxj}{dt} = g_j(x) - \gamma_j x_j \quad (j = 1,2,3, ...,n)$$ (3)

Whereas x_j denotes to the cellular concentration of gene i and γ_j is the degradation is the degradation x_j
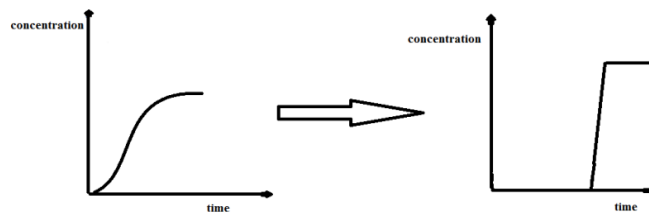

Figure 6**:** Approximation with piecewise-linear equations [21]

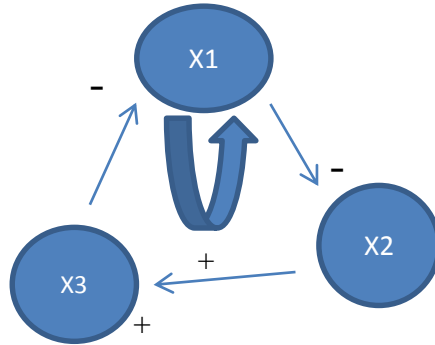[24, 25, 26] concentrated on the model acted by Figure 7 which is mathematically subedit as

Figure 7: A model taken from PLDE

$$\dot{x}_1 = k_{1,1}.\,h^+(x_1,\theta_{1,1},m_{1,1}) + k_{1,3}.\,h^-(x_3,\theta_{1,3},m_{1,3}) - \gamma_1 x_1$$

$$\dot{x}_1 = k_{1,1}.\,h^-(x_1,\theta_{2,1},m_{2,1}) - \gamma_1 x_1$$

$$\dot{x}_1 = k_{3,2,1}.\,h^+(x_1,\theta_{3,1},m_{3,1})\,.\,h^+(x_2,\theta_{3,2},m_{3,2}) - \gamma_3 x_3$$

Adopting single variable for the mRNA concentricity and supposing that the proteins are shown near to be look as by this variable might result in an unfavorable bad approximation, while the part of post-transcriptional regulations prokaryotes is minimal than those with eukaryote.

2.6 Immune system

While a strange tissue, an organism or tumor cells is shown at the period in a body, the immune system trying to distinguish them and, if it passes, it attempts to remove them. The immune system reply has pair of various interacting replies the cellular response and the hum oral replay. The first one has been hold by T lymphocytes. Other one hum oral replay is connected to another group of cells, called B lymphocytes. These helper cells have not the ability to murder tumor cells; they give accelerated biochemical hints to a private kind of T lymphocytes named normal killers (NKs). T cells start to double and emancipation different cytokines that

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moreover catalyze additional T cells, B cells and NK cells. As long as the B cells accretion, T helper cells transmit a sign to begin the operation of the produce of antibodies. Antibodies spread in the blood and are tied to tumor cells, implying that they are extra speedily that are killed by normal killer cells. Like all T cells, NK cells are being trained to characterize one given type of an infected cell or a cancer cell. NK cells are lethal. They represent a ticklish streak of the protection [27].

CHAPTER 3

MATHEMATICAL MODELS

As above- mentioned, gene regulatory networks become gradually useful tool for analyzing and getting knowledge for the arrangement and the dynamisms of their cells. In gene regulatory networks the better understanding to the complex process is many mathematical models of these systems are expanding. Mathematical models are considered so essential to predict the impact of nonlinear interactions and may yield insight to understand systems of regulation of operations existed inside the cell. In fact, gene regulatory networks have been modeled as networks comprised of nodes that represent genes, metabolites or proteins and brims that represent molecular interactions (protein, DNA-protein or relations among genes). The most challenges matters in the area of mathematical modeling of gene regulatory networks is existed in a process of development of model that is instituted on empirical facts, since it is so much hard to define goodness of obtainable data. However, several ways to definite gene regulatory networks identification; in a lot of time the common way we can postpone structured and unstructured ways. In unstructured modeling way there is a supposition indicating that each gene regulating every other gene. Through adopting additional field of knowledge, it would possible to further develop the structured model.

3.1 Hybrid System

Many heterogeneous dynamics that interact with each other and define their attitudes across duration can be found in hybrid dynamical systems. What are meant by heterogeneity are the systems that include two various kinds of dynamics event-driven discrete variable dynamics, and Time-driven continuous variable dynamics, the development that are depending on if then-else kind of basics, which is sometimes described by automata or even petri networks. The different types of dynamics interacting each other generating complicate dynamical conducts, like convert the value of a continuous variable overrides during a threshold, or state hop one limited discrete event occurring to recall just little matters. For instance [28], we

assume there is a regular place with temperature monitoring system used in winter supposing that the collection dot of the existed thermostat is a 70 degrees Fahrenheit. In this case, the furnace is going to turn "ON" in the case if the temperature of the room is below the set point, and will turn "OFF " on the other hand. Here, a model hybrid system is the place temperature control system, such as in the case of the oven, and the heat flow properties of the place, take shape the continued variable dynamics, while the turn on- turn off thermostat may be modeled as an unattached accident system with those situations "turn-on" and "turn-off" [28]. Furthermore, the transition occurred between the discrete states is made by the temperature fixed in the place, whereas the development of the temperature be based on if the oven is put turn-on or turn-off, for example the unattached case of the thermostat. Hence, the temperature control system includes the interaction of discrete and continuous dynamics that may be modeled and considered as a hybrid system. In fact, hybrid systems are used in many purposes, like manufacturing systems, air traffic administration, and vehicles engine control. Hybrid systems used in the hierarchical arrangements of complicated systems, in the interaction of discrete delineation algorithms and continuous control algorithms in vehicle, intelligent systems [28,29] Furthermore, hybrid systems may also be used in networked embedded control systems interacting with the physical universe, through the role played in the evolution of systems having acquaintances and networking essence interacting with the physical world and human workers as well; same as these systems that are as well named as Cyber-Physical Systems (CPS). Therefore, computer experts have tendency to consider hybrid systems namely as discrete (computer) programs that interact with the physical milieu. Also they have devolved the computational models, like bounded state machine, automata and petri networks, by using discrete systems to hybrid systems through entrench the continuous variable dynamics into the discrete models.

3.2 Features of hybrid dynamics

The paths of a hybrid automaton that showing many characteristics is noticeable now. Beginning with a specific place, the continued part of the case appears in accordance with the continuous dynamics connected with this place, remaining in the invariant location [30]. Then, at limited time moment in R, named a case duration, and the discrete area of the case (the place) is switched to other place. That is considered an immediate switch and has been prudent, that is very essential stipulation for the transmission to happen because guarding this transition is totally convinced. Furthermore, the transition makes a huge rebound the continuous portion of the state. Then, and after the instant movement is being happen, the continuous part of the state, beginning with the new continuous state, will principally appear in accordance to the continuous dynamics of a new place. Hence, two phenomenon are connected to any juvenile appeared, the first is switch and the second is jump, depicting the immediate transmission of serially, the discrete and the continuous portion of the state in such a happening time. However, the events and events time's issues is the most important features of the hybrid system. Firstly, the events might be outwardly; induced through the labels (symbols) leading to controlled switching and jumps. Secondly, the events probably inwardly induced; leading to what is so named "independent switching and jumps". The appearance of inwardly induced events is limited by the guards and the invariants place. However, whenever the infringement of the place constants be imminent, the hybrid switches to a newly place, with possible a reconstruct of the continuous state. The automation involves event duration, the guards will define to what place the transmission is probable. (There might be additional than one; moreover, it is potential to mutation to the similarity place). However, if infringement of the place invariants is not imminent, then there are still discrete transmissions that may happen if the conformable guards are being contented therefore, if it is fixed at a limited time moment, the guard of a discrete transmission has been contented and this might result in an event to take place. Consequently, one might get a large number of trajectories of the hybrid automaton, and a tighter speciation of the conduct of the hybrid automaton is crucially dependent on an extra restricted description of the guards. Intuitively, the

place in variants provides enforcing situations, while the guards provide ability conditions.

3.3 Hybrid Automata

Finite automata studying the model discrete event systems because it has been applied in a good way of modeling, like connection protocols and computer programing, in which the logic correctness is, consider the basic concern. However, finite automata are incapable of modeling, for instance the electronic physical systems, while together discrete event dynamics and continuous physical dynamics getting along and interacting with another. Hybrid automata produces official models for electronic-physical systems, which may be considered like a prolongation of finite automata through gathering continuous dynamics into each of its discrete cases (which also named modes). Each of the modes is connected with constraints. Edges existed between modes are suspended with guards specifying the conditions where the mode transmission could be aroused; every point is being connected to a reconstruct map showing the way how the continuous variables are being updated after the discrete transmission taking place. Hybrid automata are given a definition below [28].

Definition: H is a collection of a hybrid automaton H = {Q, X, f, Init, Inv, E, G, R},

Wherever

- Q = $\{q_1, q_2, \cdots\}$ is a finite group of discrete states;
- X $\subseteq R^n$ represent the state area in which the continuous state variables get values;
- f: Q × X →R^n assigns to every discrete state q ∈ Q an Analytical Transporter field f (q, ·);
- Init $\subseteq$ Q × X is the group of initial states;
- Inv: Q → 2^x refers to every discrete state q ∈ Q a collection Inv (q) $\subseteq$ X named the fixed collection;
- E $\subseteq$ Q × Q is the group of discrete transmission;
- G: E → 2^x refers to every discrete transition (q,$\acute{q}$) ∈ E a guard group G (q,$\acute{q}$) $\subset$ X;
- R: E × X → 2^x is a reset map.

They are referring to (q, x), where q ∈ Q and x ∈ X, as the state of H. We consider a given temperature control system sample [28]. This system consists of two discrete modes that are compatible to the turn-on, turn-off operation of the thermostat. The temperature is subjected to various continuous dynamics depending on whether the kiln is put on or off. It is also presumed also that the oven is already off and the temperature is put less than 60 degree. At the time we set the temperature control process, the oven will be work and the room temperature stays below 70 degree. As soon as the room temperature reaches to 70 degree, the furnace will be turned-off. Owing to latency, the furnace will be turned-off before the temperature gets to 71 degree. At the time when the furnace becomes off, the place temperature starts dropping because of the temperature losses. As soon as the temperature decreases below 70 degree, the oven will immediately become ordered to be on; for virtually purpose it turns-on before the temperature is dropping to 69 degree. Therefore, the temperature control system could be modeled like being a hybrid automaton with factors in the model identified as follows, see Figure 8.

- $Q = \{ON, OFF\}$;
- $X = R$ represents the domain of the room temperature;
- $F(ON, x) = -x + 100$ and $f(OFF, x) = -x$;
- $Init = \{OFF\} \times \{x \leq 60\}$;
- $Inv(ON) = \{x \in R: x \leq 71\}$, and $Inv(OFF) = \{x \in R: x \geq 69\}$;
- $E = \{(ON, OFF), (OFF, ON)\}$;
- $G(ON, OFF) = \{x \in R: x \leq 70\}$, and $G(OFF, ON) = \{x \in R: x \geq 70\}$;
- $R((ON, OFF), x) = \{x\}$, and $R((OFF, ON), x) = \{x\}$.

A directed graph could be considered as a hybrid automaton. To graphically act a hybrid automaton, a directed graph is drawn first (V, E) with single to single charting between the vertices V and the discrete state Q, whereas E is considered as the similar as in the defining of a hybrid automaton.
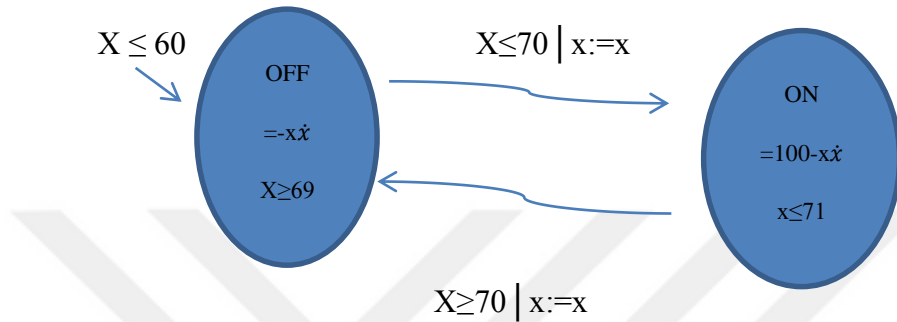

Figure 8: Temperature control hybrid automaton model [28].

It is consider a bouncing ball the perpendicular locus of the ball is represented by x_1 and the speed by x_2. As soon as the ball is on the ground ($x_1 > 0$), the continuous dynamics can be denoted as, $\dot{x}_1 = x_2$; $\dot{x}_2 = -g$, whereas g is the gravity constant. When the ball is hitting the ground ($x_1 = 0$), a discrete jump happens. The velocity x_2 is reset in accordance with $x_2 := -cy_2$, where c ∈ (0, 1) is a coefficient of indemnity. It is important to explain a hybrid automaton, in order to portray this operation, see Figure 9. Where,

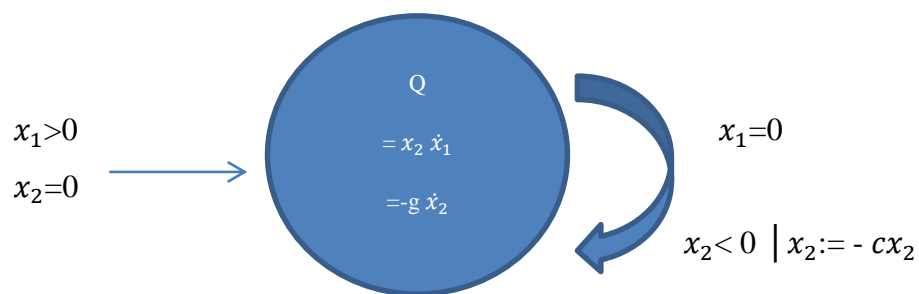Figure 9: model for the bouncing ball by using Hybrid automata [28]

- Q = {q};
- X $= R^2$;
- F (q, x) $= \begin{bmatrix} x_2 \\ g \end{bmatrix}$;
- Init = {q} $\times \{x \in R^2 \mid x_1 > 0, x_2 = 0\}$;
- Inv (q) = $\{x \in R^2 \mid x_1 \geq 0\}$;
- E = {(q, q)};
- G (q, q) = $\{x \in R^2 \mid x_1 = 0, x_2 < 0\}$;
- R ((q, q), x) = $\{x_1 = x_1, x_2 = -cx_2\}$.

CHAPTER 4

BIOLOGICAL BACKGROUND

Tumor dormancy can be defined as a balance condition by which confirmed cancer cell population stays active for a long while once being subjected to anti-tumor healing [31]. During these dormant periods, the number of cells may be changed slightly while they stay totally stable until being suddenly grown next plentiful years subsequent. Such recumbent states are repeatedly grown next many anti-tumors therapeutic protocols. One of such recumbent states is experimentally make in a murine B-cell lymphoma [32], BCL1 lymphoma. Tumor cells are resulted from a monocular cell that carries a flatten immunoglobulin (IgM) containing an unparalleled idiotype. The antibody to this idiotype, after an effective or an inefficient fortification, able in an accurate way, distinguishes between tumor and non-tumor B-cells. It can also be decisive factor to capture the growth of the tumor [33]. Although many cellular impenetrable techniques have been used in this process, there still powerful evidences that the signaling abilities of the antibodies has a key function in the process of the incitement of inertness throughout the induction of calmness or apoptosis [34]. researches done in this regard points toward the reaction of human B tumor cells (Daudi) to anti-IgM is that the same of BCL1cells to anti-idiotypic antibody [35].Cellular inhabitance levels of the interaction between the tumor B-cells and curative antibody experimented inside mice BCL1 lymphoma showed that the result of anti-idiotype fortification is crucially affected by the ratio of stirrer calmness and apoptosis of tumor cells. Hence, it would be tough to measure these ratios experimentally. To make balance between inhabitance level samples and empirical datum and to lead future immune therapeutic interventions at the gene/protein level, the resolution within an individual cell is modeled in order to endure apoptosis or to be calmness to respond to signaling through the antibody fastening to the B cell receptor. However, the mammalian cell might pass through two inevitable transition phases during cell-cycle advancement. Headmost one happens at the terminus of G1. During G1, the milieu and bulk is being monitored by the cell. At the time the outer elements and the bulk of the cell are convenient, the

cell goes through DNA installation and partition. While the other one take place when DNA replication is totally finished. As soon as the cell examined showing that DNA and chromatid bias existed, mitosis is started and the cell is immediately separated into two Girondins cells. Cells might also be put in the so-called G0case, in which cells quit plain progression throughout the cell-period and become tranquil. However, the processes taking place during the cell-period are checked and monitored by a set of molecular indication. The essential ingredients of the system are the so-called cyclin-dependent kinases (CDKs) with activating their companion proteins, the cyclins [36]. During G1, CDK effectiveness is esteemed down owing to the pertinent cyclin partners missing their output is prevented and they are being quickly increasing. Late in G1, cyclin installation is confirmed, and consequently the CDKs are activated. CDK an effectiveness residue in a high way during S, G2, and M, since it is indispensable for DNA reproduction and other operations happening through the last Phases of the cycle. Late in G2, the anaphase reinforcing congregation (APC) is invigorate and marks limited target proteins (such as cyclins) for degeneration. Cdh1 is an ingredient of APC and is itself prevented by cyclin/CDK complexes. Cyclin/CDK complexes that enable deactivated via linking of CDK inhibitors such as p21 and p27. Whenever concentricity of CDK inhibitors are enough topmost, cyclin/CDK congregation are forbid from linking and subsequently phosphorylating target effector substrates and advancement during the cell-cycle is moreover blocked or even postponed .However, Marches et al (1998) made a very interesting observation suggesting that the technique by which anti-IgM antibody induces cell calmness is created by increasing in the standard of terms of p21[37].Other tests done by Marches et al. (1999) indicating that the fate (whether they become quiescent or apoptotic) of (human) B lymphoma cells catalyzed with an antibody to the B cell recipients is highly dependent on the level of inducible p21. Affected by the antibody (anti-IgM), p21 levels are increasing and subsequently quiescence does. Yet, in cells where the level of inducible p21 is reduced by transfer with a vector include Drugs p21, anti-IgM stimulation outcome is increasing the apoptosis, see Figure.10.These findings, that might look intuitive to some extent, indicated that the complication of the cellular network connecting breed, quietness and apoptosis.
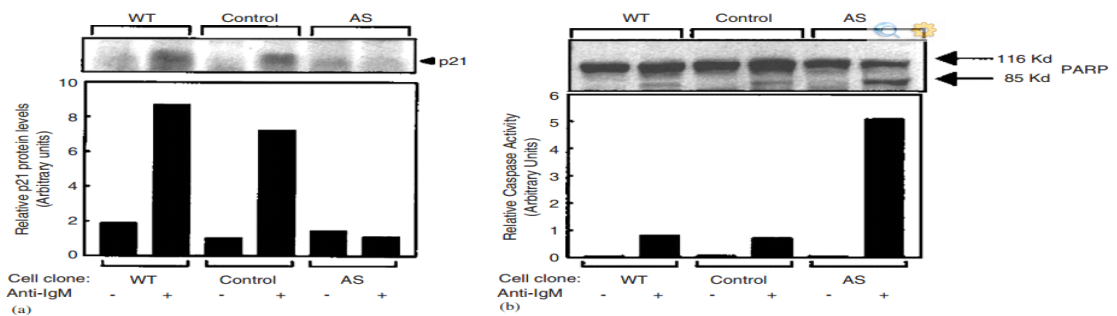
Figure.10 Experimental observations by Marches et al.(1999) [32].

This shape displays how (a) p21 and (b) action varied in reaction to an antibody to cell flatten IgM. WT: wild kind Daudi cells. Monitoring: Daudi cells transfer with a vector with no cDNA drawers. As: Daudi cells transferred with a vector containing antisense p21 [32]. Following, cells transferred with drugs p21 is described as antisense cells and cells that are not transferred are described to as wild type cells. Marches et al. (1999) hints to a possible cause for their results considering cell destiny is dependent on p21 inducibility: p21 is not only a regulator of the cell-cycle but it also contains an anti-apoptotic impact. As a matter of fact, the mutual point of several controller of reproduction having a double meaning. On one hand, if they are inhibitors of reproduction (like p21), they also will act as anti-apoptotic signals. The first one, if they trigger cloning (such as the transcription factor Myc), they also will represent as pro-apoptotic factors. However, it seems there is a tough cross-speak among cell-cycle regulatory technique and apoptosis. Even though the actual mechanisms are not totally obvious, Disruptions of CDK inhibitors by caspase-mediated cleavage and a CDK-mediated activation of apoptosis might also be concerned [38]. Nishioka and Welsh (1994) made another important observation suggesting that cells in G0 (i.e. quiescent cells) are less liable to apoptosis than cells in G1 (i.e. cells moving ahead through the cell-cycle). Hence, caspases are a family of protein representing as initiators of and assassin of the main steps in the apoptotic pathway. Both meanings are done by cleavage of specific substrates .The steps in caspase activation and in the apoptotic process are highly commanded by caspases

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mainly organize in cooperation between anti- and pro-apoptotic members of the Bcl-2 family. Particularly, the Bcl-2 protein prevents the motion of executioner caspases. However, the main focus of this work is on the association between Bcl-2 and cell-cycle regulation by the contact between Myc and Bcl-2. Myc arranges reproduction of a little cyclins and subsequently acts as a promoter of cell-cycle development .It may also symbolizes as a pro-apoptotic factor through inhibiting Bcl-2. On the other hand, Bcl-2 is characterized by having an inhibitory influence on cell-cycle development, while stimulating the action of CDK inhibitors. It is widely identified that Bcl-2 has the ability to inhibit cell-cycle advancement cross the regulation of p27.

4.1. Nonlinear Dynamics of Immunogenic Tumor Parameter Estimation

There have been many studies confirming that the outgrowth of tumor Cell inhabitance is exponential for small amount of tumor cells, whereas this outgrowth is becoming slow at large inhabitance bulk. The curb of development might be happen because the rivalry of cells for metabolite sand/or growth elements, or even by outgrowth rein elements created by the tumor cells. In most situations of no exponential tumor growth, the kineticsisis well mentioned by the logistic or Gompertz equation. To be more obvious, consider a tumor with cells that are "immunogenic", and eventually are vulnerable to immune attack by cytotoxic effecter cells, e.g., CTL or NK cells. However, the interaction between effecter cells (EC) and neoplasm cells (TC) in vitro can be the following kinetic scheme.

$$E+T \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \overset{k_2}{\longrightarrow} E+T^* $$
$$C \overset{k_3}{\longrightarrow} E^*+T$$
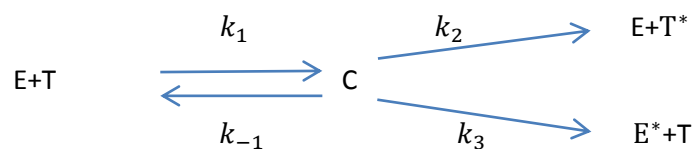
As seen from the scheme E, T, C, E*, T* those symbols are collections of native concentricity of effecter cells, disease cells, effecter cell-neoplasm or cell Compare,

inactivated effector cells, and "lethally beats" TC cells, one by one. The effective tumor cells are prepared for death. At times called "cells designed to die". The containment of inactivated effected cells is a strange property of this system. NK cells, also to a less extent CTL, in the past decades it seems that medicine have limited skill to resist or kill goal cells [39]. The reason might be because of the attrition of molecules that are in charge for the cytotoxic effecter other regulatory effects; probably owing to liberation of molecules out of tumor cell in time the TC and EC are both combined. The parameters (k_1, k_{-1}, k_2 and k3) are non-negative kinetic invariables: k_1 and k_{-1} express the ratios of linking EC to TC and division of EC from TC with not destroying cells; k2 is considered as the rate which EC-TC associations irreversibly program TC for lysis; and k3 is ratio at which EC-TC connections inactivate EC The subsequent system of differential equations as a basic model for the interactions among EC and a rising immunogenic tumor in vivo.

$$\frac{dE}{dt} = s + F(C, T) - d_1 E - k_1 ET + (k_{-1} + k_2) C \tag{4}$$

$$\frac{dT}{dt} = aT (1 - bT_{tot}) - k_1 ET + (k_{-1} + k_3) C \tag{5}$$

$$\frac{dC}{dt} = k_1 ET - (k_{-1} + k_2 + k_3) C \tag{6}$$

$$\frac{dE^*}{dt} = k_3 C - d_2 E^* \tag{7}$$

$$\frac{dT^*}{dt} = k_2 C - d_3 T^* \tag{8}$$

It seems that E, T, C can be considered as number of unrestrained EC, unbound TC, and EC-TC complexes in series, located at the place of the tumor, by a move from the spleen, and E* and T* stand for inactivated EC and mortally beats TC at the tumor place. For the gross amount of un hit TC cells that lies in the spleen are T_{tot} =T+C These parameters are " natural" (non-promoted by TC existence) the flow ratio

of overripe EC across the section of TC position; and d_1, d_2 and d_3 are favorable invariables instead of the ratio of removal of E, E*and T* cells respectively, come from their demolition or decampment from the TC localization region. It suppose that tumor is not metastasize therefore, no migration of T Cor EC-TC complexes. The better growth rate of the TC amount can be expressed as a. But this parameter fit in case of multiplication and death of TC. Ultimate transportation amplitude of biological environment for TC, the greatest limit of cells due, in addition, to contest for sources like (glucose, oxygen etc.) is b^{-1}.The meaning F(C, T) describes the rate of cytotoxic effecter cells collect in the position of TC localization according to the existence of disease. In cooperation EC Multiplication due to prompting by TC and superior EC decampment into this area from close tissues (near the lymph nodes) possibly will donate the procedure of EC and piling up [39]. Analysis of Kuznetsov (1979) proposes the following candid form for the gathering of effecter cells:

$$F(C, T) = \frac{FC}{g+T} \tag{9}$$

As can be understood (f and g) are constants and positive. Remind that this equation depends on C, and focusing on EC-TC combination however it does not depend on E. Result of multiplication and flux of effecter cells across the spleen happens during a small period of time. Scale, possibly tens of hours. So that this will stimulate the function of a quasi-Steady-state parataxis OF $(\frac{dc}{dt} \sim 0)$which gives us

$$C \sim KET \tag{10}$$

In the above description $K=k_1 / (k_2 + k_3 + k_{-1})$ system component. EC-TC conjugates commonly involves a small section of effecters number or tumor cells (reach to 1-10%).This criteria will motivate the approximation $T_{tot} \sim T$ That lies, along with Eqs.9 and 10, Facilitates Eqs.4 and 5 to:

$$\frac{dE}{dt} = s + \frac{PET}{g+T} - mET - dE \tag{11}$$

$$\frac{dT}{dt} = aT (1-bT) - nET \tag{12}$$

From equations (11), (12) It is shown that p=fK, m=Kk_3, n=Kk_2, and d=d_1.

4.2. Parameter Estimates

As observe the rest parameters of the system evaluated as follows. First suppose s, the usual value flow rate of effecter cells through the area that cancer was settled. Hence the spleen of a BALB/ c mouse has 10^8 splenocytes nearly. CTL precursor's indecision gives a reaction to alloantigen shapes many tenths of a percent of the whole lymphocytes number. Thus we presume that number of CTL precursors reacts to cancer, E_p = 3.3 x 10^5 cells. So it is obvious that life time of lymphocytes starting from the blood and the spleen is not recognized accurately but might be concluded to be nearly (thirty days) much extra perhaps. Therefore it will be suppose that if the tumor is not appear in this case the CTL initial number, E (0) ~E_p . So it will be considered that a steady state is discovered and constructed, from the written Eq. (4), s ~E_pd= 1.3x10^4 cells day^{-1} Also the additional parameters, p, g, m, n and d, was already predestined from the experienced facts methods , see Figure 11.

With a = 0.18 day^{-1}, b = 2.0×10^{-9} $cell^{-1}$, and s = 1.3×10^4 $cell^{-1}$ day^{-1} it estimate as:

p=0.1245 day^{-1},   d=0.0412 day^{-1},   m=3.422×10^{-10} $day^{-1}cell^{-1}$,
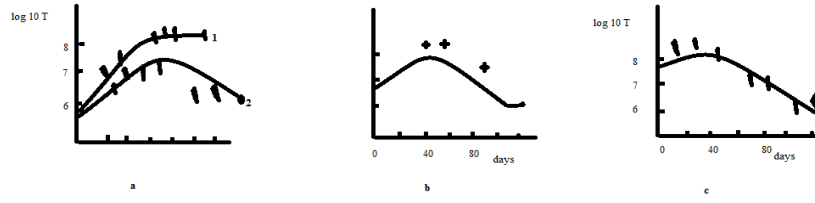g=2.019×10^7 cells,   n =1.101×$10^{-7}day^{-1}cell^{-1}$

Figure11: Growth of BCL1 tumor in the spleens of chimeric mice [39].

5.1 The model

Building complete kinetic model of genetic regulatory system requires details knowledge on reaction mechanisms. In many situations, this information is not available and ones need to take resource to more approximate models. One such class of model will be considered, a class of piecewise-linear differential equations. The piecewise-linear have favorable mathematical properties that facilitate their analysis. In order to simulate the tumor-immune dynamics with the hybrid system formalism, firstly we have simulated Kuznetsov modified model, see Figure 12. The MATLAB function we have used can be found in appendices. Five genes regulate each other and regulate itself; E represent effector cell, T represent tumor cell, C represent effector cell–tumor cell conjugates, E^* represent inactivated cell and T^* represent lethally hit tumor cell.
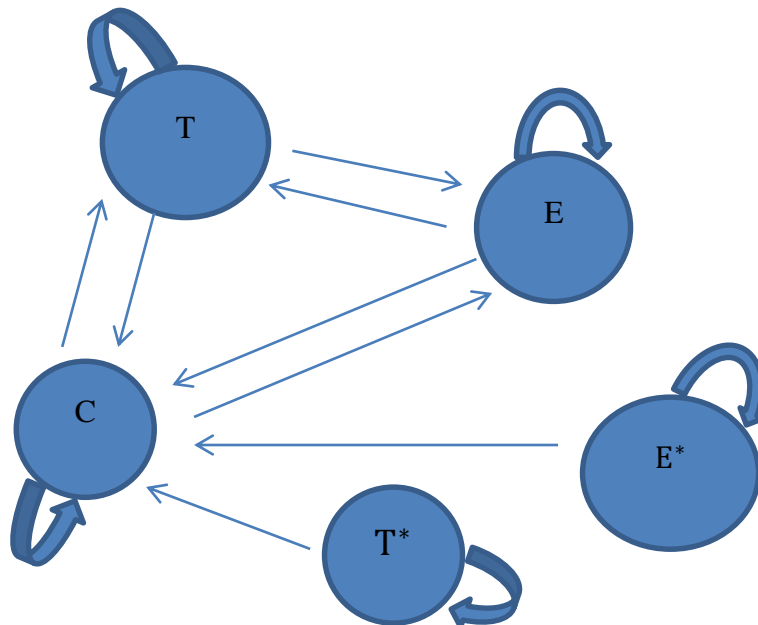

Figure 12: The model derived from PLDE for five genes network

$$\frac{dE}{dt} = \mu_{q(t)}^{E}E + 0[c] + 0[T] + k_{q(t)}^{T} \tag{13}$$

$$\frac{dT}{dt} = \mu_{q(t)}^{T}T + 0[E] + 0[c] + k_{q(t)}^{T} \tag{14}$$

$$\frac{dc}{dt} = \mu_{q(t)}^{c}c + 0[E] + 0[T] + k_{q(t)}^{c} \tag{15}$$

$$\frac{dE^{*}}{dt} = \mu_{q(t)}^{E^{*}}E^{*} + 0[c] + k_{q(t)}^{E^{*}} \tag{16}$$

$$\frac{dT^{*}}{dt} = \mu_{q(t)}^{T^{*}}T^{*} + 0[c] + k_{q(t)}^{T^{*}} \tag{17}$$

As we mentioned the tumor-immune interaction is approximated by piecewise linear system state. Each state approximates the change of the concentration of a cell. The state transitions occur when a threshold is exceeded by an external variable. One of the essential assumptions to obtain piecewise linear model is that every subsystem can be approximated by such actions: when one variable goes up, another one goes down. For illustration, If E, T are variables and evolution of variable E dependent on the state T, see Figure 13. A state E could be as

$$\frac{dE}{dt} = \mu_{s(t)}^{E}[E] + 0[T] + k_{s(t)}^{E}$$
$$S(t) = F(Q_{T}([T](t))$$
$$Q_{T}([T](t)) = i \text{ if } h_{i}^{T} < [T](t) \le h_{i+1}^{T} \text{ For } i=1, 2, ...n \tag{18}$$

$$\frac{dT}{dt} = \mu_{s(t)}^{T}[T] + 0[E] + k_{s(t)}^{T}$$
$$S(t) = F(Q_{E}([E](t))$$
$$Q_{E}([E](t)) = i \text{ if } h_{i}^{E} < [E](t) \le h_{i+1}^{E} \text{ For } i=1, 2, ...n \tag{19}$$

If a variable E or T has n discreet states then the state E have n^2 states. In general number of states $2^{(n2)} 3^{(n3)} \ldots m^{(nm)}$, where n_i is the number of variables having I states (i=2, 3,…m). In this work $\mu_{s(t)}$ for all states is taken to be -1, at each state the k are obtained according to numerical simulations of the model presented.
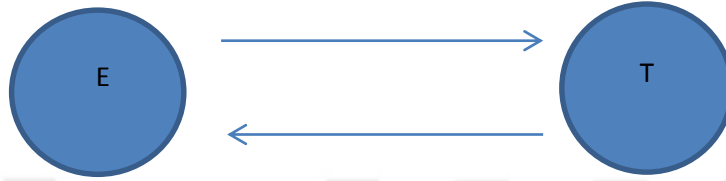

Figure 13: The model derived from PLDE for two genes network

The hybrid dynamical system model assumes several threshold, ratio and derivative dependent effects of regulatory factors. The parameters of the hybrid dynamical system are found according to numerical simulations of the computational model. According to these assumptions the following modules are constructed:

$$\frac{dE}{dt} = \mu_{s(t)}^{E} + 0[T] + k_{s(t)}^{E}, \tag{20}$$

$$S(t) = \begin{cases} s_1 & if(T \geq t_1) \\ s_2 & if(T < t_1) \end{cases}, \text{and}$$

$$k_{s1}^{E} = 3 , k_{s2}^{E} = 40 , t_1 = 200 , \mu_{s1,s2}^{E} = -1$$

See first diagram result Figure 14.

$$\frac{dT}{dt} = \mu_{s(t)}^{T} + 0[E] + k_{s(t)}^{T}, \tag{21}$$

$$S(t) = \begin{cases} s_1 & if(E \geq e) \\ s_2 & if(E < e) \end{cases}, \text{and}$$

$$k_{s1}^{T} = 400 , k_{s2}^{T} = 0 , e = 3 , \mu_{s1,s2}^{T} = -1$$

See second diagram result Figure 15.

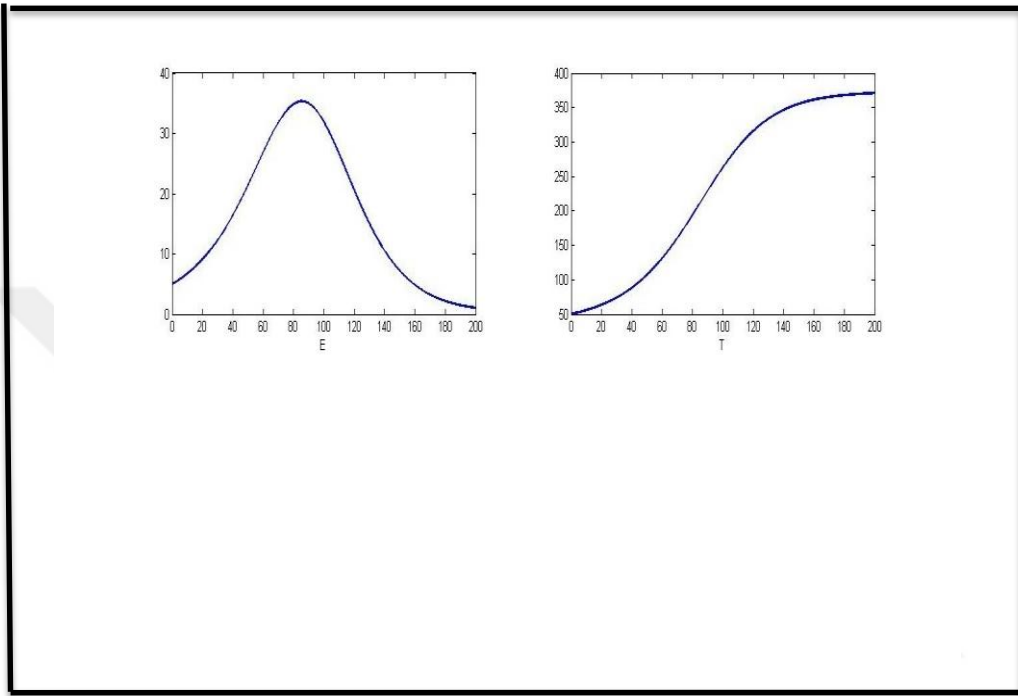With different initial values see third diagram result Figure 16, E=0.5, T=150.

Figure 14: Simulation result of the model that derived from PLDE for five genes networks with using initial values E=5, T=150.
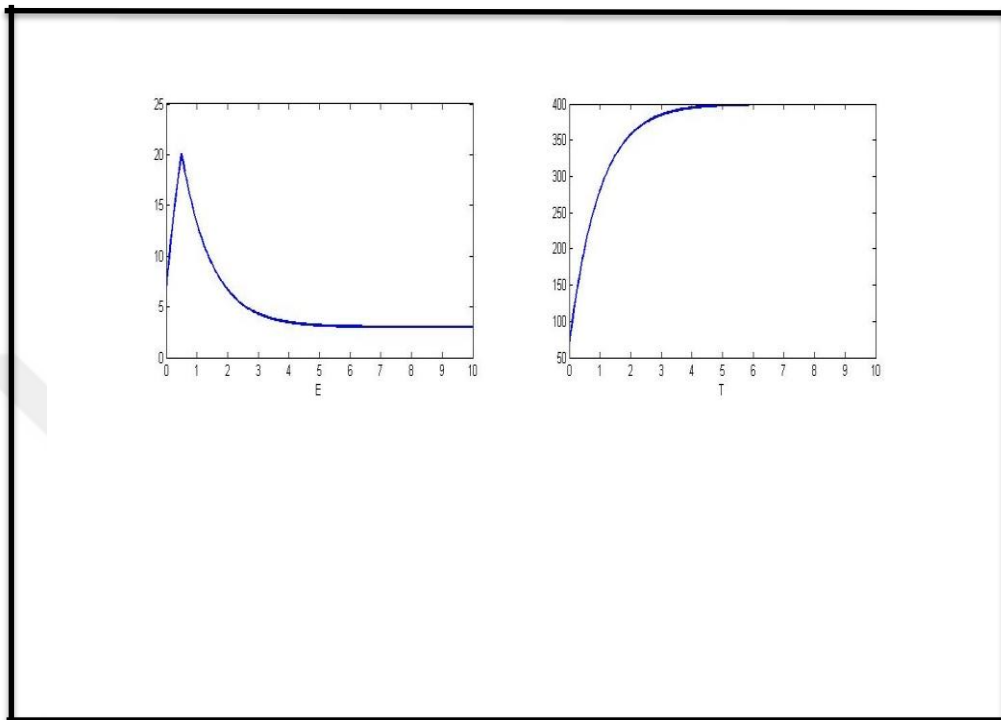
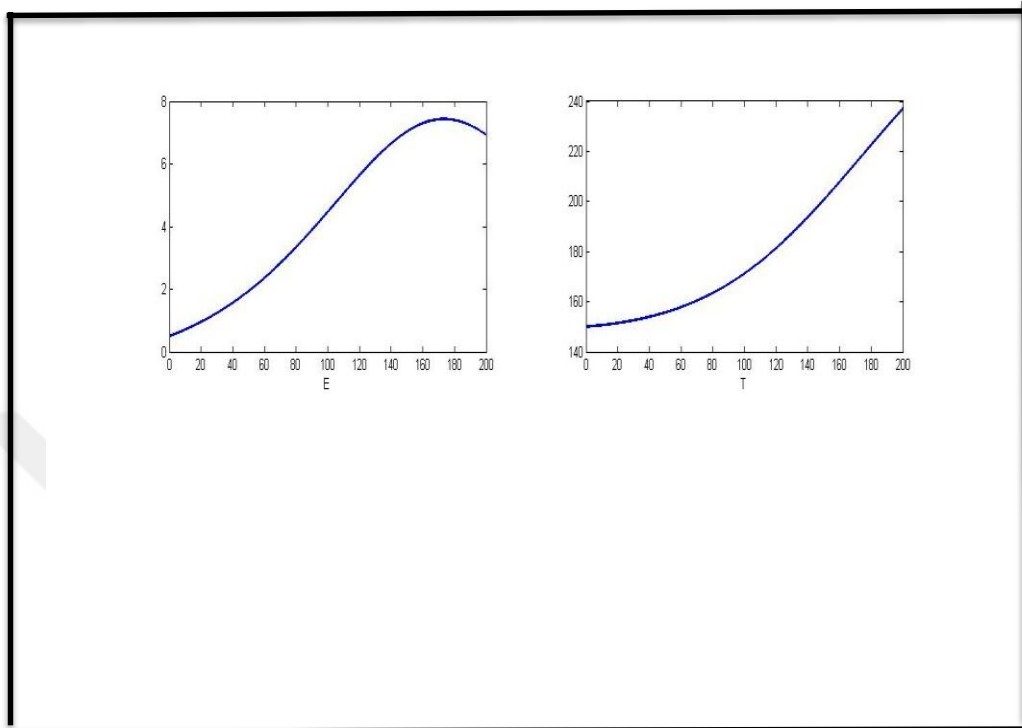Figure15: Simulation result of hybrid dynamical system with initial values E=5, T=150.

Figure 16: Simulation result of hybrid system with using initial values E=0.5, T=150.

For further applications of hybrid systems on biological systems, one may check (Kahraman M., (2007), "Modeling functional dynamical system by piecewise linear system with delay", METU.) and (Gökgöz N., (2008), "Development of tools for modeling hybrid system with memory", Middle East Technical University.).

5.2 Sensitivity Analysis

A sensitivity analysis is a technique used to determine how different values of an independent variable impact a particular dependent variable under a given set of assumptions. This technique is used within specific boundaries that depend on one or more input variables, such as the sensitivity analysis we will do it for our model. Sensitivity analysis also referred to as what-if or simulation analysis is a way to predict the outcome of a decision given a certain range of variables. By creating a given set of variables, the analyst can determine how changes in one variable impact the outcome. Sensitivity analysis have some advantages, one of those advantages is simplicity that is mean there is no complicated theory to understand, also it have directing managements effort and source of planning information; but It still have disadvantages like it is not relative in nature it considers the extent of variables change. It does not take into account the probability of such changes taking place.

Id	State	Threshold	Range	Model behavior
A	E	t_1	(0-160)	The host is able to clear the tumor
B	E	t_1	(160-399]	The host is able to clear the tumor
C	E	t_1	[400-∞)	The host is not able to clear the tumor

Table 1: Sensitivity analysis of E state

Id	State	Threshold	Range	Model behavior
A	T	E	(0-3]	The host is not able to clear tumor
B	T	E	[3.1- 13.9)	The host is able to clear the tumor
C	T	E	(13.9-∞)	The host is able to clear the tumor

Table 2: Sensitivity analysis of T state

We have tried sensitivity analysis for the two states (E, T), for the first state E, we used threshold t_1 in different ranges with different values as we used in Table 1. Each one gave different result behavior simulation as it can be seen in Figure 17.
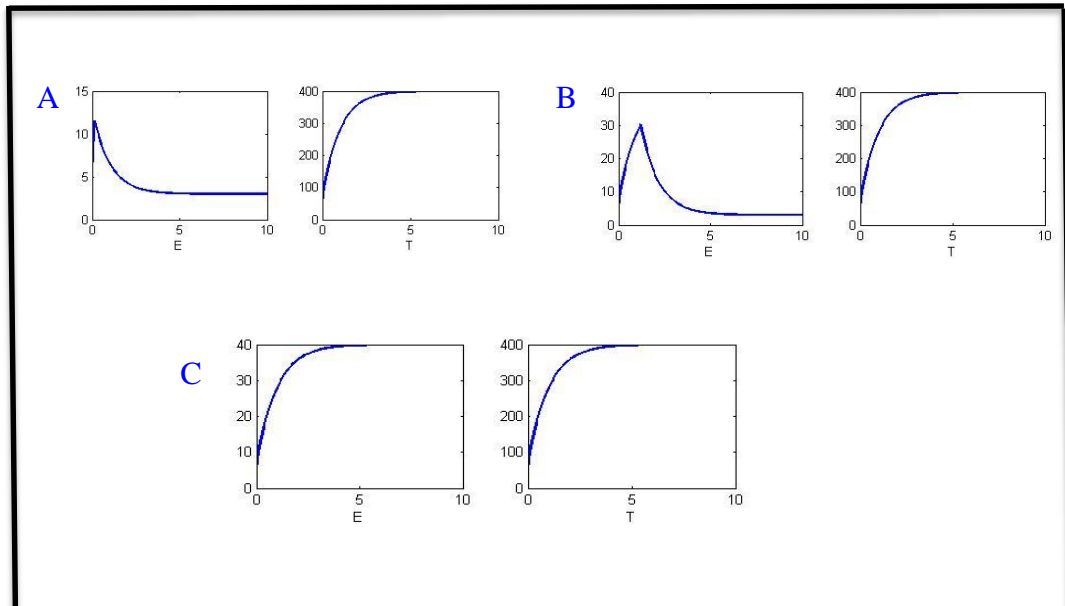

Figure 17: Simulation of hybrid system with different values. For part A, we used threshold t_1=100, for part B, we used threshold t_1=300 and for part C, we used threshold t_1=450.

For the second state T, we used threshold E also in different ranges with different values as it can be seen in Table 2. Each one gave different behavior result as it can be seen in Figure 18, because of the change in the parameters; it starts to behave like in the thermostat example. In other words, it starts to oscillate between two values. That leads us to conclusion that, within these ranges of parameter values, the model does not behave as the original one.
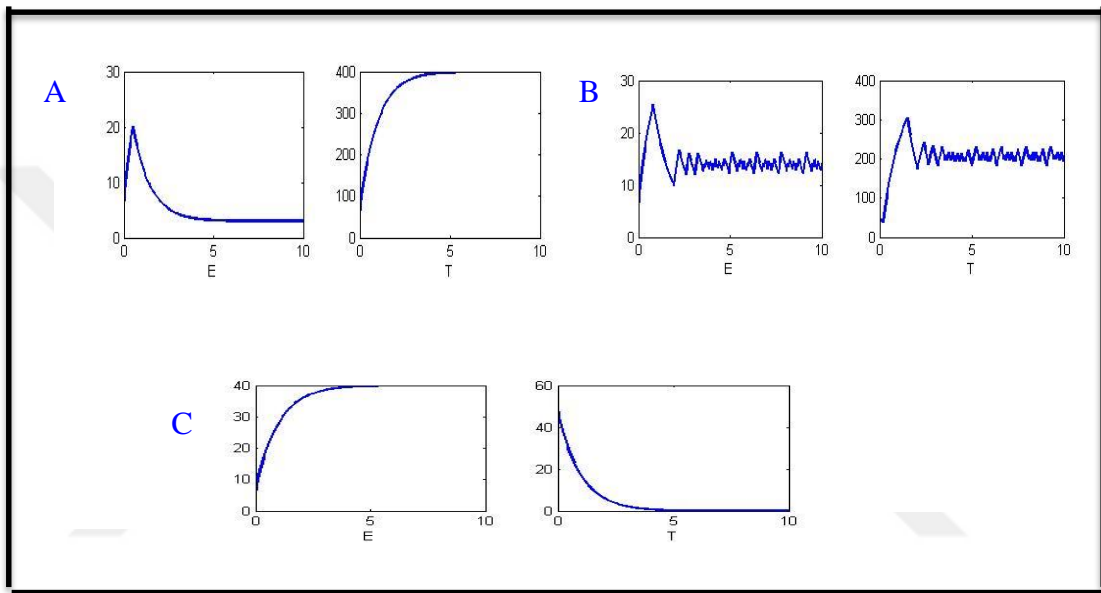

Figure 18: Simulation of hybrid system with different values. For part A, we used threshold E=2, for part B, we used threshold E=13.8 and for part C, we used threshold E=400.

CHAPTER 6

CONCLUSIONS

There exist ways for modeling gene regulatory networks, which means gene involved in controlling the expression of one or more other genes, Such as modeling by graph, Bayesian network, Boolean network, piecewise linear differential equation, ordinary differential equation and hybrid dynamical system. The main structure of the model generally depends on the theory that the organization among genes could be described with a piecewise linear differential equation. The most attractive feature of piecewise linear systems is their capability of substituting more complex systems into locally solvable systems. This is essentially important when simulation, solution or analysis of a first principle model of a dynamical process is not possible with reasonable computational resources. In these cases, approximations and abstractions of an exact model are much more useful and hybrid dynamical systems form a significant tool for this purpose. Piecewise linear differential equations can be used to approximate nonlinear models. And this method is convenient with biological applications in the sense of computer simulations which we investigated in this work. We have simulated the Kuznetsov model in order to use the data obtained from simulation in our hybrid system model. Then, in order to make a clear approximation to the model of Kuznetsov, we have used states (E, T), which refers to effector cells and tumor cells, we have done the simulations of both models, Kuznetsov and piecewise linear differential equations. We have seen that piecewise linear differential equations gives good approximations. In order to test our models sensitivity to the parameters, threshold and focal point, we have carried out a sensitivity analysis for two states by changing the threshold values, which means it starts to oscillate between two values. That leads us to conclude that, except the parameter values which makes the model oscillate or changes the behavior, the model we discussed is robust.

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```
function result =lymphoma_1
global E;
global T;
% initial values of global variables*****
E=5;
T=50;
%initial values of iteration*****
E_i=E;
T_i=T;
%time
t_initial=0;
t=t_initial;
t_step=0.05;
t_final=15;
%Arrays of variables and time
E_array=[0 E];
T_array=[0 T];
t_array=t_initial;
options = odeset('RelTol',1e-4,'AbsTol',[1e-4 1e-4 1e-5]);
for t=t_initial:t_step:t_final
%E*****
aa= ode23t(@dE_dt,[t t+t_step],E);
E_i=aa.y(2);
E_array=[E_array;[t E_i]];
%T*****
aa = ode23t(@dT_dt,[t t+t_step],T);
T_i=aa.y(2);
T_array=[T_array;[t T_i]];
%Change global variables
E=E_i;
```

```matlab
    T=T_i;
end
subplot(2,2,1)
plot(E_array(:,1),E_array(:,2),'LineWidth',2);
xlabel('E')
subplot(2,2,2)
plot(T_array(:,1),T_array(:,2),'LineWidth',2);
xlabel('T')
end
%Differential equation of E
function result = dE_dt(t,param_E)
global T;
s=0.1181;
p=1.131;
m=20.19;
d=0.00311;
g=0.3743;
result=s+(p*param_E*T/(g+T))-m*param_E*T-d*param_E;
end
%Differential equation of E
function result = dT_dt(t,param_T)
global E;
a=0.18;
b=2.0;
n=1.1;
result=a*param_T*(1-b*param_T)-n*E*param_T;
result=E;
end
```

```matlab
functionlymp_hybrid
%E
E=5;
global E_array;
E_array=[0 E];
%T
T=50;
global T_array;
T_array=[0 T];
%time
t_step=0.05;
t_initial=0;
t_final=10;
for t=t_initial:t_step:t_final
E=E_module(E,T,t_step);
E_array=[E_array;[t E]];
T=T_module(T,E,t_step);
T_array=[T_array;[t T]];
end
subplot(2,2,1)
plot(E_array(:,1),E_array(:,2),'LineWidth',2);
xlabel('E')
subplot(2,2,2)
plot(T_array(:,1),T_array(:,2),'LineWidth',2);
xlabel('T')
%E module
function result_E=E_module(E,T,t_step)
t1=200;
k1=3;
k2=40;
if T>=t1
f=@(x)(-1)*x+k1;
```

```matlab
result_E=Euler_Method(E,f,t_step);
elseif T<t1
f=@(x)(-1)*x+k2;
result_E=Euler_Method(E,f,t_step);
end
%T module
function result_T=T_module(T,E,t_step)
e=3;
k1=400;
k2=0;
if E>=e
f=@(x)(-1)*x+k1;
result_T=Euler_Method(T,f,t_step);
elseif E<e
f=@(x)(-1)*x+k2;
result_T=Euler_Method(T,f,t_step);
end
```

Curriculum Vitae

PERSONAL INFORMATION:

Full Name: Hannadi Nowzad Mohammed Al-Windawy

Date of Birth: August^{14th} 1990

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CERTIFICATION:

B.sc in Computer Science, Cihan University, 2012

M.sc in mathematics and computer science, Çankaya University, 2016

LANGUAGES:

Arabic: native

English

Kurdish

Little Turkish

COMPUTER SOFTWARE PROGRAMS:

General.

Experience in the use of the Internet.

Microsoft Word, Excel, Access, PowerPoint.

Matlab.

C++.

Maintenance of computer and format.

Computer networks.

1- Shaqlawa technical institute (lecturer for two years (computer lectures)).

2- Shaqlawa high school for girls (lecturer for 6 months (mathematics lessons)).