MODELING STOCHASTIC HYBRID SYSTEMS WITH MEMORY WITH AN APPLICATION TO IMMUNE RESPONSE OF CANCER DYNAMICS

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ABSTRACT

MODELING STOCHASTIC HYBRID SYSTEMS WITH MEMORY WITH AN APPLICATION TO IMMUNE RESPONSE OF CANCER DYNAMICS

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Dynamics of cancer involve some complex interactions like immune system responses. Many different models of immune response to tumor growth exist in the literature. Most of the available models are first principles models which have problems in determining the model parameters. For potential use in treatment planning, a model should be able to adopt to subject by subject variability and unknown factors. However, such an approach for a complicated problem like cancer dynamics has some drawbacks. First of all, there exist some unknown factors. Secondly, models with fixed parameters do not allow considering subject-by-subject variability. An alternative approach to this problem is inferring the parameters and determining system behaviour from empirical observation. In inferential modeling case, we first select a model class and infer the parameters from the observations. For this purpose, we used hybrid systems that are suitable for inferential modeling due to their analytical and computational advances. For many biological and physiological systems, the behaviour of system and its responses depend on whole history rather than a combination of historical events. We utilize and further develop hybrid systems with memory to have a more realistic representation. Finally, we also incorporate stochastic calculus in our model to include uncertainities and random perturbation.

Keywords : stochastic hybrid systems, hybrid systems with memory, memory hybrid automata, tumor-immune dynamics, mathematical modeling

ÖZ

HAFIZALI STOKASTİK HİBRİT SİSTEMLERİN MODELLENMESİ VE BAĞIŞIKLIK SİSTEMİNİN KANSER DİNAMİKLERİNE TEPKİSİNE UYGULAMASI

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Bulaşıcı hastalıklarda hastalığın yayılmasını kontrol etmek için kullanılan eşik değer dinamiği matematiksel epidemiolojide büyük bir öneme ve ilgiye sahiptir. En bilinen eşik değerlerinden biri, esas çoğalma oranı olan R_0'dır. Bulaşı hastalıkların temel sorunlarından biri de onun formüllenmesi ve hesaplanmasıdır. Kanser dinamikleri bağışıklık sistemi tepkileri gibi bazı karışık etkileşimler içerir. Literatürde tümör büyümesine bağışıklık tepkisinin pek çok değişik modeli bulunmaktadır. Kullanılabilir modellerin pek çoğu, model parametrelerinin karar verilmesinde problemleri olan ilk ilkeler modelleridir. Tedavi planlamasının potensiyel kullanımı için bir model, bireyden bireye değiş- kenliği ve bilinmeyen faktörleri benimsemelidir. Fakat, kanser dinamikleri gibi karmaşık bir problem için böylesi bir yaklaşımın bazı sakıncalara sahiptir. Öncelikle, bazı bilinmeyen faktörler bulunmaktadır. İkinci olarak, sabit parametreli modeller süje-süje çeşitliliğini göz önünde bulundurmaya izin vermez. Bu probleme alternatif bir çözüm deneysel gözlemlerden parametreleri çıkarmak ve sistem davranışına karar vermektir. Çıkarımsal modelleme durumunda, ilk önce bir model sınıfı seçeriz ve parametreleri gözlemlerden çıkarırız. Bu amaçla, analitik ve hesaplama avantajları olan hibrit sistemleri kullandık. Çoğu biyolojik ve fizyolojik sistem için, sistemin davranışı ve tepkisi geçmiş olayların kombinasyonundan ziyade tüm geçmişe dayanır. Daha gerçekçi bir gösterim elde ede bilmek için, hafızlı hibrit sistemden faydalandık ve daha da geliştirdik. Son olarak, belirsizlikleri ve rastgele pertürbasyonları dahil edebilmek için, stokastik kalkülüsü de modelimizle birleştirdik.

Anahtar Kelimeler: stokastik hibrit sistemler, hafızalı hibrit sistemler, hafızalı hibrit otomata, tümör-bağışıklık dinamikleri, matematiksel modelleme

To My Family

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CHAPTER 1

INTRODUCTION

1.1 Introduction of the Work

Modeling a dynamical system mathematically is crucial for understanding and controlling many scientific and engineering problems. If a mathematical model is developed for a dynamical system, the observation of the dynamical system under various conditions can be done and the dynamical system's future behavior with different initial conditions can be analyzed. This information can be used to come up with strategies which can carry the system to a desired state.

The developments in different areas of science and technology have increased the importance of mathematical modeling of dynamical systems. Hybrid systems provide a promising area in mathematical modeling of many biological and physiological systems by combining Boolean and continuous variables and allowing them to regulate each other [48], [57], [78], [65]. This property provides various advantages in modeling complex processes and designing control systems. A control application can be thought as the first use of hybrid systems. By the study of engineering systems which contain relays and/or hysteresis, 1950's can be thought of the years of the start of hybrid system research [64]. Later in 1990's, hybrid systems started to take attention people's attention due to the vast development and implementation of digital micro controllers and embedded devices [64]. Their use increased with the developments of control applications like robotics, air traffic control, etc.. During the last decade, many researchers from various disciplines such as computer science, control systems engineering, and mathematics [6], [85] have performed considerable research activities on hybrid systems. Modeling [4], [11], [12], [92], reachability analysis [4], [5] ,[10], stability and stabilization [32], [51], [54], [62], [63], [95], observability and controllability [14], [92], [96] and optimal control [13], [104] are the mostly studied issues [64] of this phenomena. Today, hybrid systems serve as an important device for investigating various modeling [38], [40], [78], [65] and theoretical problems [39], [78], [65] in nature and science. Moreover, some dynamical systems that have threshold phenomena can be best formalized by hybrid systems.

Multi-stationarity is the existence of multiple stationary steady states in a dynamical system. Since Delbrück's [33] suggestion stating "Epigenetic differentiation reflects multi-stationary", it is widely considered in modeling of complex systems. Hybrid systems are essentially useful in modeling multi-stationary processes.

By piecewise linear systems, a subclass of hybrid systems, complex nonlinear dynamical systems can be approximated as a combination of piecewise analytically solvable systems, except the ones that are chaotic. Many different formalizations of hybrid systems are used in various fields. In this work, we focus on the state space representation and hybrid automata representation.

Since many dynamical systems depend on history [27], [58], mathematical models with memory has taken attention to mimic this property. Hybrid systems with memory are investigated in this work, because of the profits and advanced features of hybrid systems. The future behavior of the system depends on both the state transition and the memory which is updated at the state transitions. In this work, we propose that, memory can be thought as a "functional memory" not an "initial condition memory". The history dependent behavior appears in many biological systems. One of the obvious one is immune response which is also investigated in this work.

1.2 Aim and Importance of the Work

The dynamics of cancer involve some complex interactions like immune system responses. Many different approaches to model immune response to tumor growth exist in the literature. Most of the available models are first principles models which have problems in determining the model parameters. For potential use in treatment planning, a model with capability of adopting to subject by subject variability and unknown factors has an advantage of suggesting the best choice for each case. A common solution to this problem is inferring the parameters and determining the system behavior from empirical observation. In inferential modeling case we first select a model class and infer the parameters from the observations. In this case, hybrid systems are suitable for use in inferential modeling due to their analytical and computational advances. By hybrid systems with memory phenomena, the representation of factors which may depend on the whole history, rather than a combination of historical events, can be efficiently modeled. Including stochastic calculus in the model, more accurate results can be obtained.

In this work, we build a hybrid system with memory to use in an inferential model. We propose Stochastic Hybrid Systems with Memory (SHSM), and apply this formalization to tumor-immune dynamics with two different approaches. One model is piecewise linear and the other model is nonlinear. For the one which is nonlinear, we choose Kuznetsov's very well known model and improve it. Such a model can be trained with the initial data from each case and then it can be used in a personalized planning. The memory has been used according to the different stopping times since the model has acted with different dynamics due to the nature of cancer. That has led us to the conclusion that the model has memorized some aspects of immune dynamics.

In order to find the parameters of the piecewise linear model, we use SDE Toolbox and simulated the model. We find parameter values for every state of the piecewise model. To obtain more realistic values, we use the data from the literature. It is very important how we choose the data. According to the data we work on, mainly two different group of mice are investigated under IL1-α effect. One group is able to defend the host against tumor growth with immune system variables , and the other group fails in this process. Their defense mechanism and cancer growth differs widely. This shows us that memorization capability of immune system is very important for the organism. We investigate Memory Hybrid Automata in the logic sense and by doing this we provide a research area if Hybrid Systems with Memory formalization is reachable and decidable.

1.3 Explanation of the Work

Outline of the thesis is as follows: In Chapter 2, we give a brief description of the related mathematical tools. In Chapter 3, we give tumor-immune dynamics, especially the ones we used in the application part, and we mention some important mathematical models which are used to model tumor-immune system dynamics. In Chapter 4, an introduction to deterministic and stochastic hybrid systems with memory, or shortly DHSM and SHSM respectively, is given. In Chapter 5, a brief mathematical description of stochastic hybrid systems is given, two applications on tumor-immune dynamics is done. One model is piecewise linear and the other one is a developed version of Kuznetsov's model. In Chapter 6, Memory Hybrid Automata is introduced, some basic definitions on Memory Hybrid Automata are given and a few theorems are represented and proved. Finally in Chapter 7, we will sum up the work and mention some future progress.

CHAPTER 2

HYBRID SYSTEMS

In this chapter, some basic information about dynamical systems, hybrid dynamical systems, hybrid automata, graph theory, stochastic hybrid systems and stochastic hybrid automata will be given.

As we start, the concepts of dynamics must be carefully explained. The theory of dynamics is the subjectthat deal with change, with systems that evolve in time [94]. The solutions of such a system may settle down to an equilibrium, keep repeating in cycles, or do something more complicated. This is how the dynamical systems keeps dealing with the analysis.

2.1 Examples of Dynamical Systems

We, now give some classical examples of dynamical systems. For a detailed discussion of these examples please see [19], [94], [102]. The exponential growth of a population of organisms is one of the typical examples of dynamical systems. This system is given by the first-order equation

$$\dot{x} = rx, \tag{2.1}$$

where x is the population at time t and r is the growth rate. This system is described by only one variable, at the initial value of the population x is enough to determine the population at any later time. Moreover, this is a linear system because the differential equation (2.1) is linear in x.

Another example can be thought as the Lotka-Volterra equations, also known as the predator-prey equations which are mostly used to explain the dynamics of biological systems. Two species interact each other where one is prey and the other is predator. Their population change in time according to the pair of equations [61], [94], [101]:

$$\frac{dx}{dt} = x(\alpha - \beta y), \tag{2.2}$$

$$\frac{dy}{dt} = -y(\gamma - \delta x), \tag{2.3}$$

where x is the population of prey, y is the population of some predator, $\frac{dx}{dt}$, $\frac{dy}{dt}$ are the growth rates of the two populations over time. The values α, β, γ and δ are parameters describing the interaction of the two species.

First equation refers to the prey population. Assuming that the prey have an unlimited food supply, the exponential growth of the prey is given by the term αx. The rate of predation of the prey which is assumed to be proportional to the rate of the meeting of the predator and theprey is represented above by βxy.

Second equation in the system refers to the predator population. In this equation, δxy represents the growth of the predator population. The term, γy describes the loss rate of the predators because of their natural death or emigration. Therefore, the equation gives the change of predator population by the growth causing from the food supply and the loss from natural death [61], [94], [101].

2.1.1 An example

An illustration of the predator-prey model can be given by two species of animals, a rabbit (prey) and a fox (predator). If the initial conditions are 80 rabbits and 40 foxes, one can plot the progression of the two species over time. The choice of time interval is arbitrary. you may see the Figure 2.1

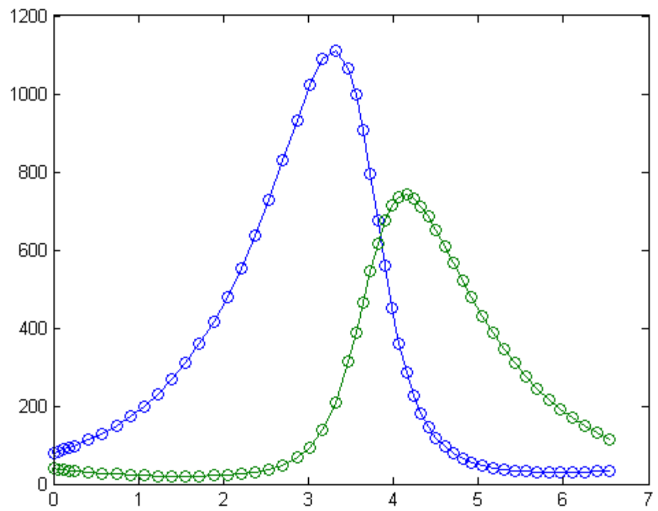

Figure 2.1: An example of population dynamics of prey and predators. Initial conditions were set to prey=80 and predator=40.

2.2 Hybrid Systems

A hybrid system is a special kind of dynamical systems that is formed by both continuous and Boolean variables regulating each other [48], [57], [65], [78]. In hybrid system formulation, the governing differential equations of continuous variables and Boolean state of a discrete variable can regulate each other.

One may find the typical examples of hybrid systems in nature and technology. Two main examples are those including real physical switches and those referring dynamical systems with threshold phenomena. The continuous traffic flow regulated by traffic lights, which is discrete, and an electrical circuit protected by a fuse and the temperature controlled by a thermostat can be given as examples for the first group. For the second group of hybrid systems, the dynamical systems which are switching whenever a threshold surpassed is considered. The bouncing ball and also the activation or the inhibition of a gene when a corresponding protein surpass a threshold are famous examples for this group.

The representation of hybrid systems differs because of its use in different fields such as control engineering, computer engineering, logistics, automation and dynamical systems theory. Hybrid automata can be considered as a general representation for hybrid systems. We will give some detailed information about hybrid automata later but as a start we may give a representation of a hybrid system basically as follows;

$$\begin{aligned} \frac{dy}{dt} &= f_s(y(t), x_e(t)), \\ s(t) &= (s_k, s_x) \text{ if } y(t) \in U_k, \end{aligned}$$

where $U_1, U_2, \ldots, U_n$ are subspaces of the state space Y of y and s_x is an external state input.

A relatively simpler hybrid system model suitable for gene networks and similar processes is obtained by partitioning the state space by a single threshold intersecting each axis(variable). This limitation of threshold conditions is sufficiently realistic for problems investigated and it simplifies handling effects of delays which are very important in biological regulatory systems. The delay between the interaction of variables introduces difficulties in analysis and simulations but supplies the system by the capability to memorize functions rather than values. In other words, states are functions instead of initial values. Therefore, an adaptation of the above system for delayed case can be given as follows;

$$\begin{aligned} \frac{dy}{dt} &= f_s(y(t), x_e(t)), \\ s(t) &= F_B(Q(y(t)), s(t-\tau), s_x(t)), \end{aligned}$$

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

where

- $f_s : Y \times X_e \to \mathbf{R}^n$ is a switching function determined by the state vector $s(t)$,
- y is an n dimensional vector of continuous variables,
- x_e is a vector representing the continuous external inputs,
- $s(t) : \mathbf{R} \to [0, 1]^m$ is the state vector,
- $F_B : [0, 1]^{n+m+k} \to [0, 1]^m$ is a Boolean function,
- $s_x(t)$ is a vector representing the Boolean external inputs,
- $Q(.)$ is the quantization operation, and
- τ is the delay.

By this representation the delay is covered by the piecewise constant part.

2.2.1 Example (Bouncing Ball)

We now consider a classical example of hybrid systems in order to illustrate the formulation above. Think of a ball which is released from its center with height $x(t_0) = x_0$ at time $t = t_0$ without any initial velocity i.e. $v(t_0) = 0$. The ball will accelerate downwards until the time when it hits to the ground with velocity

$$v(t) = v(t_0) - gt$$

and position

$$x(t) = x(t_0) - \frac{1}{2}gt^2.$$

Here g is the acceleration due to gravity. For simplicity, nonelastic collision is considered and mechanical properties of the ball are ignored. Let r be the radius of the ball. The ball hits to the ground when $x(t) = r$. After the hit, the ball compresses and all the kinetic energy will turn into compression until the ball stops, i.e. $v(t) = 0$ where it will decelerates by

$$\frac{dv}{dt} = k.$$

After the compression the ball will start to accelerate upwards with

$$\frac{dv}{dt} = \rho k,$$

where $0 < \rho < k$.

In this example, different states of the system can be given as;

$$\begin{aligned} s_1 &= x(t) > r, \\ s_2 &= (x(t) \leq r) \wedge (v(t) \leq 0), \\ s_3 &= (x(t) \leq r) \wedge (v(t) > 0), \end{aligned}$$

where $\wedge$ is the logical AND conjunction. Here, the state is 1 if the binary relation between the terms is true and 0 otherwise. The state representation of the bouncing ball is given by

$$
\begin{aligned}
\frac{dx}{dt} &= v, \\
\frac{dv}{dt} &= -(s(t) = s_1)g + (s(t) = s_2)k + (s(t) = s_3)\rho k, \\
s_1 &= x(t) > r, \\
s_2 &= (x(t) \leq r) \wedge (v(t) \leq 0), \\
s_3 &= (x(t) \leq r) \wedge (v(t) > 0),
\end{aligned}
$$

For a detailed discussion of this example see [78], and [65] and for different examples of dynamical systems with state space representation see [81].

2.3 An Overview of The Graph Theory

A hybrid system can also be represented by a graph. In such a representation, the nodes correspond to different states of the system and the edges correspond to possible state transitions of the system. We now give basic definitions of the graph theory that will be useful to explain our work in the following chapters.

Definition 2.1. A graph G is a finite nonempty set $V(G)$ of vertices (also called points or nodes) and a set $E(G)$ of edges also called or lines. The set $V(G)$ is called the vertex set and $E(G)$ its edge set [26].

Let u and v be two vertices of a graph G. If $e = uv$ is an edge of G, then we say that u and v are adjacent in G, and that e joins u and v. For example, a graph G is defined by the sets

$$V(G) = \{u, v, w, x, y, z\}$$

and

$$E(G) = \{uv, uw, wx, xy, xz\}\,.$$

If more than one edge join a pair of vertices in a graph, then this graph is called $multigraph$. Two or more edges that join the same pair of vertices are called $paralleledges$. An edge that join itself is a $loop$ [26].

Definition 2.2. A network $G = (V, E)$ is a directed graph in which every edge e is assigned an initial vertex and a terminal vertex [78], [65].

Graphs or networks have lots of benefits in the sense of formalizing the systems that have interconnected elements such as dynamical systems, artificial intelligence tools, traffic, fluid flow, social interactions, networks of computers, chemical bonds and linguistics. Practical and useful information can be obtained in the case of complex networks, by the analysis of the network of the system.

There are two main ways of describing a dynamical system by a graph representation. First way is the state space representation [81] as illustrated in the previous section. Second way is to display the cause-effect relation [65], [78], [88], [98], [99]. A plus sign on the edge corresponds to the activation and a minus sign corresponds to the repression. For flows, weighted graphs can be introduced.

Gene regulatory systems have various models in mathematical biology and bioinformatics. Genes regulate the metabolism by activating or repressing protein synthesis. The mechanism in a cellular system can be well understood by the regulatory relations in a gene network. When illustrating gene networks in graph representation, nodes correspond to the genes and directed edges to their relations such that a positive directed edge from a gene to the other means the activation, whereas a negative directed edge means the repression [93], [88]. The knowledge on the relations in gene networks are limited because of the complexity of these networks [40].

Boolean approach is the generally used modeling technique in gene networks. Depending on the activity level of the gene there exist two different states: active or inactive respectively, 1 or 0 [98], [99]. There are some different approaches such that NK model which can be used for modeling gene regulatory networks as Kauffman used [88]. In this system, connectivity can be thought as K and the nodes can be thought as N.

2.4 Discrete Event Systems

In this section, we give some basic information on discrete event systems and some related material that will be useful in the following chapters.

2.4.1 Automaton (State Machine)

Definition 2.3. A state machine or an automaton $M = (Q, q_0, V, I, E)$ is a tuple with 5 components which consist of [78],[65]

- a finite set of locations Q,
- an initial location $q_0 \in Q$,
- a finite set of variable V, which defines the set T_V of all possible values of V,
- an initial set of values to the variables $I \subseteq T_V$, and
- a set of edges E, where an edge $e = (q_1, q_2, g, a) \in E$ consists of
  - the source location $q_1 \in Q$,
  - the destination location $q_2 \in Q$,
  - the guard $g \subset T_V$ of an edge

– the action part of the edge $a : T_V \rightarrow T_V$, where the action a can happen when $V \in g$

The state space of M is $\sum = Q \times T_V$. An automaton M is a $hybrid\ \ automaton$ if V includes continuous variables.

The automatons (state machines) can be represented by directed graphs. In such a representation, the vertices (nodes) correspond to the states and the edges correspond to the possible transitions from one state to another.

2.4.2 Regular Languages

The following definitions are collected from [65] and [78].

Definition 2.4. A regular language is the set of all orderings of events which can happen in a system. An alphabet A is a finite nonempty set of events. A trace (string, word) is a finite sequence of events from an alphabet.

Assuming A^* denotes the set of all finite traces of A including the empty string a language L over A is defined as

$$L \subseteq A^*.$$

A $formal\ \ language$ is a language marked by an automaton.

2.4.3 Hybrid Automata

A hybrid automata is a formal representation of hybrid systems. A hybrid automaton is an automaton that includes continuous variables in V as mentioned in the state machine. Hybrid automata have been used to model and analyze a variety of systems including embedded systems, systems biology, air traffic control systems.

Definition 2.5. A hybrid automaton is defined as $H = \{Q, Y, Init, f, Inv, E, G, R\}$ consisting of [17], [58], [66], [83]

- a set of discrete states $Q = \{q_1, q_2, \ldots, q_m\}$ also called locations,
- a space of continuous variables $Y = \mathbf{R}^n$,
- a set of initial conditions $Init \subseteq Q \times Y$,
- a vector field $f : Q \times Y \rightarrow Y$ governing the continuous evolution,
- an invariant set (domain, subspace) for each $q \in Q$, $Inv : Q \rightarrow P(Y)$ where $P(.)$ denotes the power set. Each state's governing dynamics is valid within its invariant set.
- A set of edges (state transitions) $E \subset Q \times Q$,

- guard conditions for each edge $G : E \to P(Y)$,
- a reset map for each combination of edges and continuous states $R : E \times Y \to P(Y)$. A reset map represents possible jumps in the values of the continuous variables which takes place with a state transition.

2.4.3.1 Hybrid Time Sets

Definition 2.6. A hybrid time set is a finite or infinite sequence of intervals $\tau = I_{ii=0}^{N}$ such that

- $I_i = [\tau_i, \tau_i^{'}]$ for all $i < N$;
- if $N < \infty$ then either $I_N = [\tau_N, \tau_N^{'}]$ or $I_N = [\tau_N, \tau_N^{'})$; and
- $\tau_i \leq \tau_i^{'} = \tau_{i+1}^{'}$ for all i.

2.4.3.2 Hybrid Trajectory

The solutions of the state variables of hybrid systems are defined by hybrid trajectories.

Definition 2.7. A hybrid trajectory is a triple (τ, q, y) which consists of $\tau = \{T_0, T_1, \ldots, T_N\}$, $q = \{q_0, \ldots, q_N\}$, $y = \{y_0, \ldots, y_N\}$, where $q_i : T_i \to Q$ and $y_i : T_i \to \mathbf{R}^n$ [65],[78].

2.4.3.3 Executions

Definition 2.8. A hybrid trajectory (τ, q, y) is an execution of a hybrid automaton H if the following conditions hold [78],[65]:

- Initial condition: $(q_0(0), y_0(0)) \in Init$.
- Discrete evolution:
  - $\left(q_i(\tau_i^{'}), q_{i+1}(\tau_{i+1})\right) \in E$
  - $y_i(\tau_i^{'}) \in G\left(q_i(\tau_i^{'}), q_{i+1}(\tau_{i+1})\right)$
  - $y_{i+1}(\tau_{i+1}) \in R\left(q_i(\tau_i^{'}), q_{i+1}(\tau_{i+1}), y_i(\tau_i^{'})\right)$.
- Continuous evolution: $q_i : T_i \to Q$ is constant over $t \in T_i$, $y_i : T_i \to \mathbf{R}^n$ is the solution of the differential equation
  - $\frac{dy_i}{dt}(t) = f_{q_{i(t)}}(y_i(t))$

  and for all $t \in \left[\tau_i, \tau_i^{'}\right)$, $y_i \in Inv(q_i)$.

If τ is a finite sequence and the last interval in τ is closed, then the execution is *finite*. If τ is an infinite sequence, or the sum of the time intervals is infinite then it's *infinite*. If it is infinite where the sum of time intervals $\tau_N - \tau_0 < \infty$, then it is called *zeno*.

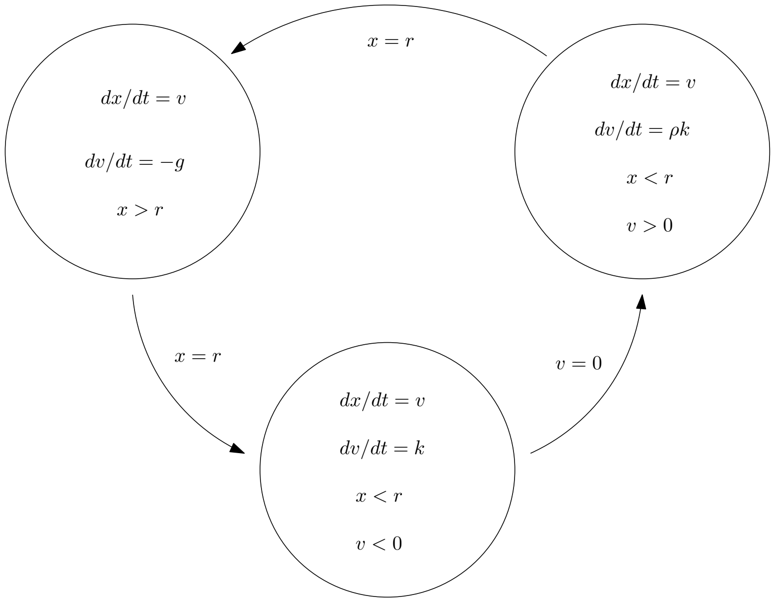

Figure 2.2: Hybrid automaton representation of bouncing ball example [78], [65].

2.4.4 An Example: Bouncing Ball

If the bouncing ball example considered, there exist three locations depending on the states. $x = r$, $v = 0$ and $x = r$ are the guard conditions for the states from first to second, from second to third and from third to one, respectively (see Figure 2.2). Assuming $k >> g$, only one state is obtained. The guard condition makes the system show a jump behavior (see Figure 2.3). For a detailed discussion see [65] and [78].

2.5 Piecewise Linear Dynamical Systems

Let F be a functional which maps the input variable $x(t)$ to the output function of the variable $y(t)$ and let x_1, x_2 be two input variables of F with output function of variables y_1, y_2 respectively. More precisely, we have

$$y_1(t) = F(x_1),$$

$$y_2(t) = F(x_2).$$

The system above F is called linear if the following condition holds [72], [75]:

$$\alpha_1 y_1(t) + \alpha_2 y_2(t) = F(\alpha_1 x_1(t) + \alpha_2 x_2(t)).$$

Linear systems have many advantages in mathematical modeling [78], [88]. For example, the linear system,

$$\frac{dy}{dt} = My,$$

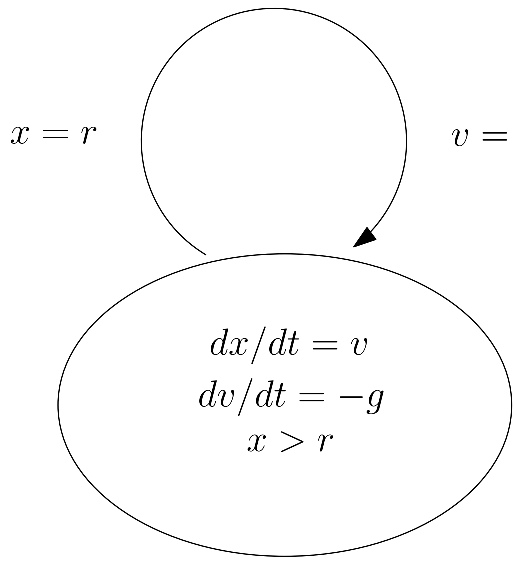

Figure 2.3: Bouncing ball representation where $k >> g$ [78], [65].

has the solution

$$y(t) = y_0(t)exp(t - t_0)M,$$

where y_0, t_0 are the initial values. For nonlinear systems, piecewise linear models can be considered for suitable approximations because of their simplicity.

Suppose that the state space of a dynamical system be formed by k disjoint subspaces. More precisely [78]

$$U = U_1 \cup U_2 \cup \ldots \cup U_k$$

and

$$U_i \cap U_j = \emptyset \text{ where } i \neq j.$$

Let $y_0, y_1, y_2 \in U_i$, where

$$y_2 - y_0 = r\left(y_1 - y_0\right).$$

Assume that $y_0(t), y_1(t), y_2(t)$ respectively indicates that if the system starts with the initial state $y(t_0) = y_0$, then the function representing its temporal evolution for $t > t_0$ is denoted by $y_0(t)$. The system is called piecewise linear in U_i if for all $t_0 < t < t_i$,

$$y_2\left[t_0, t_i\right] - y\left[t_0, t_i\right] = M\left(y_1\left[t_0, t_i\right] - y\left[t_0, t_i\right]\right),$$

where

$$y_0(t), y_1(t), y_2(t) \in U_i$$

and M is a constant matrix.

The system is called *piecewise linear* if it is piecewise linear in all subspaces of its state space. To represent a piecewise linear system, as the switching differential equations the following representation is used [78]

$$\frac{dy}{dt} = M_{s(t)}y(t) + N_{s(t)}x_e(t) + k_{s(t)},$$

$$s(t) = s_i \text{ if } y(t) \in U_i,$$

where

- $y(t) \in \mathbf{R}^n$ is a column vector denoting the continuous variables,
- $s(t) \in \{1, 2, \ldots, p\}$ is a variable denoting the state of the system,
- $M : s \to \mathbf{R}^{n \times n}$ is a switching matrix and the elements are determined by the state of the system,
- $k : s \to \mathbf{R}^n$ is a switching vector and the elements are determined by the state of the system,
- $U \subset \mathbf{R}^n$ is a subspace of the system's state space.

In this representation, subscript i denotes the i^{th} element of the corresponding vector.

Systems that exhibit nonlinear behavior can be approximated by piecewise linear systems including threshold phenomena. Critical measures, approximation accuracy and physical interpretation make piecewise linear systems useful.

2.6 Stochastic Hybrid Systems and Stochastic Automata

Deterministic and non-deterministic hybrid systems have taken attention the interest of researchers in the recent years. They both have some limitations and to observe random failures because of unexpected transitions from one state to another, or random task execution times which decide the time of the system in different modes, studies have been trended towards a wider area of hybrid systems. To overcome these difficulties and to model these randomness more realistically, Stochastic Hybrid Systems (SHS) have been studied, developed and applied to several areas, such as power industry [30], flexible manufacturing, and fault tolerant control [43].

According to different application areas, different types of Stochastic Hybrid Models have been developed. Models have differences mainly at the entrance of the stochasticity the process [89]. For example, continuous evolution described as stochastic hybrid systems, transitions may happen randomly, the destinations of discrete transitions may be handled by probability kernels on the state space, etc.

Various classes of stochastic hybrid processes have been developed for different kinds of problems, e.g. e.g., counting processes with diffusion intensity [69, 89], diffusion processes with Markovian switching parameters [70, 103], Markov decision drift processes [89], piecewise deterministic Markov processes [28, 29, 53], controlled switching diffusions [15, 42, 43], and more recent stochastic hybrid systems of [52, 84]. Subject to different kinds of problems they have been developed for, they have various degrees of modeling power.

Now, we give the definition of Stochastic Hybrid Systems (SHS) from Hespana [22], [50].

Definition 2.9. The following differential equation defines Stochastic Hybrid Systems

$$x = f(q, x, t)$$

, a family of m discrete transition (reset) maps

$$(q, x) = \phi_\ell(q^-, x^-, t), \ell \in \{1, ..., m\},$$

and a family of m transition intensities

$$\lambda_\ell(q, x, t), \ell \in \{1, ..., m\},$$

where $\mathbf{Q}$ denotes a (typically finite) set and $f : \mathbf{Q} \times \mathbf{R}^n \times [0, \infty) \to \mathbf{R}^n$, $\phi_\ell : \mathbf{Q} \times \mathbf{R}^n \times [0, \infty) \to \mathbf{Q} \times \mathbf{R}^n$ $\lambda_\ell : \mathbf{Q} \times \mathbf{R}^n \times [0, \infty) \to [0, \infty)$ $\forall \ell \in 1, ..., m.$ A SHS represents a jump process $q : \Omega \times [0, \infty] \to \mathbf{Q}$ called the *discrete state*; a stochastic process $x : \Omega \times [0, \infty) \to \mathbf{R}^n$ with piecewise continuous sample paths called the *continuous state*; and *m* stochastic counters $N_\ell : \Omega \times [0, \infty) \to N_{>0}$ called the *transition counters*.

2.6.1 Example of Stochastic Hybrid Model

A stochastic hybrid system can be shown by a directed graph as in Figure 2.4 [50], [22]. Within this representation scheme each node corresponds to a discrete mode and each edge to a transition between discrete modes. The nodes represents both the corresponding discrete mode and the vector fields that determines the evolution of the continuous state in the mode they belong to. The start of each edge is represented by the corresponding transition intensity and the end is represented by the reset map.

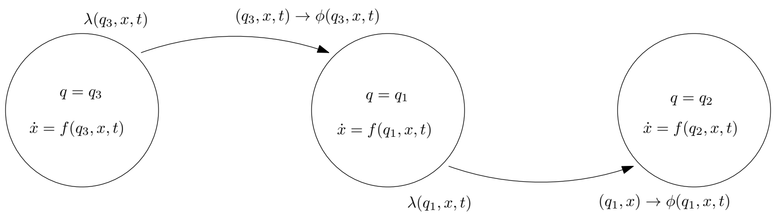

Figure 2.4: Graphical representation of a Stochastic hybrid system [22], [50]

For a mathematically precise characterization of Stochastic Hybrid Systems, Hespana assumes that for every $(q_0, x_0, t_0) \in Q \times \mathbf{R}^n \times [0, \infty)$ there exists a unique global solution $\varphi(.; t_0, q_0, x_0) \to \mathbf{R}^n$ to $x = f(q, x, t)$ with initial condition $x(t_0) = x_0$ and $q(t_0) = q_0$. The $\mu_k^\ell, \ell \in \{1, ..., m\}, k \in N$ denote independent random variables all uniformly distributed in the interval $[0, 1]$. Those are *transition triggers*. By assuming an initial condition $(q_0, x_0, t_0) \in Q \times \mathbf{R}^n \times [0, \infty)$ and for a given $\omega \in \Omega$, the sample paths of $q(\omega, .) : [t_0, \infty) \to Q$, $x(\omega, .) : [t_0, \infty) \to \mathbf{R}^n$ and all the $N_\ell(\omega, .) : [t_0, \infty) \to N$ is constructed as follows [22]:

1. Set $t_0(\omega) = t_0$, $q(\omega, 0) = 0,$, $x(\omega, 0) = 0$, $N_\ell(\omega, 0) = 0$, $\forall \ell$.

2. Let $t_1(\omega)$ be the largest time on $(t_0(\omega), \infty]$ for which

$$\exp\{-\int_{t_0(\omega)}^{t} \lambda_\ell(q(\omega, t_0(\omega)), \varphi(s; t_0(\omega)), q(\omega, t_0(\omega)), x(\omega, t_0(\omega)), s)ds\} > \mu_0^\ell(\omega)$$

$\forall t \in [t_0(\omega), t_1(\omega)), \ell \in 1, ..., m$

3. On the interval $[t_0(\omega), t_1(\omega))$, the sample paths of $q(\omega, .)$ and all the counters $N_\ell(\omega, .)$ remain constant, whereas the sample path of $x(\omega, .)$ equals $\varphi(.; t_0(\omega), q(\omega, t_0(\omega)), x(\omega, t_0(\omega)))$.

4. Denoting by $\ell_\omega \in 1, 2, , , , , m$ the index for which (4) is violated at time $t = t_1(\omega)$, the counter $N_{\ell_1(\omega)}(\omega)$ is incremented by one and

$$(q(\omega, t_1(\omega)), x(\omega, t_1(\omega))) = \phi_{\ell_1(\omega)}(q^-(\omega, t_1(\omega)), x^-(\omega, t_1(\omega))).$$

5. In case $t_1(\omega) < \infty$, repeat the construction from the step 2 above with $t_0(\omega)$, $\mu_0^\ell(\omega)$, $t_1(\omega)$, $\ell_1(\omega)$ replaced by $t_k(\omega)$, $\mu_k^\ell(\omega)$, $t_{k+1}(\omega)$, $\ell_{k+1}(\omega)$.

2.6.2 Stopping Time, Hitting Time and Number of Visits

In this subsection, we give some basic information and definitions on stopping time, hitting time and number of visits. Following material can be found in [9], [18], [55].

Definition 2.10. Let $X = \{X_n : n \geq 0\}$ be a stochastic process. A stopping time with respect to X is a random time such that for each $n \geq 0$, the event $\tau = n$ is completely determined by (at most) the total information known up to time n, $\{X_0, ..., X_n\}$.

Definition 2.11. Suppose X_t is a stochastic process and S is a set. The hitting time is the first time X_t hits S.

$$\tau = min\{t|X_t \in S\}$$

A hitting time can be thought as a stopping time due to the fact that at time t, for $s \leq t$ one knows all the values X_s, therefore one can decide whether $X_s \in S$ for some $s \leq t$. In the case of modeling optimal decision problems related to stochastic process X_t, stopping times may serve an option.

Consider that $X_0, X_1, ...$ is a Markov chain with state space S where the initial probability distribution is ϕ, and transition probabilities matrix is P. Define the first passage time from state i to state j as the number T_{ij} of steps taken by the chain until it arrives for the first time at state j given that $X_0 = i$. Probability distribution function can be given by;

$$h_{ij}^{(n)} = P(T_{ij} = n) = P(X_n = j, X_{n-1} \neq j, ..., X_1 \neq j)|X_0 = i$$

The first passage times can be found as the following: $h_{ij}^{(n)} = p_{ij}$ and, for $n \geq 2$,

$$h_{ij}^{(n)} = \sum_{k \in S-j} p_{ik} h_{kj}^{(n-1)}.$$

Let H^n denote the matrix with entries $h_{ij}^{(n)}$ and $H_0^{(n)}$ the same matrix except that the diagonal entries are set equal to 0. Then $H^{(1)} = P$ and one can calculate;

$$H^{(n)} = PH_0^{(n-1)}.$$

Assume that h_{ij} is the reaching probability from state i to j, in other words the probability if the state j is ever reached from the state i. Then

$$h_{ij} = P(T_{ij} < \infty) = \sum_{n=1}^{\infty} P(T_{ij} = n) = \sum_{n=1}^{\infty} h_{ij}^n.$$

Moreover, one define the hitting time, T_A, of a subset $A \subseteq S$ as the first time(possibly infinite) that $X_n \in A$. The probability starting from i that X_n ever hits A is then

$$h_{iA} = P(T_A < \infty | X_0 = i) = P(T_{iA}).$$

Number of Visits

Given $X_0 = i$, one can count the number of visits to state j over a period of time as the following. Let the function $I_{ij}(n)$ to be 1 if $X_n = j$ given that $X_0 = i$, and 0 otherwise. The number of visits to state j, starting at state i, by time n can be represented as

$$N_{ij}(n) = \sum_{k=1}^{n} I_{ij}(k).$$

The initial passage time from i to j is distributed according to $h_{ij}^{(n)}$ and all the subsequent return times to j follow the distribution $h_{jj}^{(n)}$. If the chain is presently in a given state, the first time it will visit state j is a stopping time.

A counting process is a random process $N(t), t \geq 0$, such that

1. $N(t)$ is nonnegative integer for each t;
2. $N(t)$ is nondecreasing in t; and
3. $N(t)$ is right-continuous.

One can say that, $N(t) - N(s)$ represents the number of events in $(s, t]$.

CHAPTER 3

TUMOR-IMMUNE DYNAMICS AND MODELS FROM LITERATURE

In the modern world, cancer is a leading cause of death. Thus, improving treatment of cancer is an important objective. Surgery, chemotherapy and radiotherapy are the most developed and clinically used methods in cancer treatment. However, there are many cases where these methods do not develop a cure. Even though it is not clinically verified, immunotherapy is a promising alternative or complementary approach for the moment. It is obvious that understanding of tumor-immune dynamics and modeling this dynamic realistically is a crucial requirement for development of immunotherapatic methods. but in some cases they do not develop a cure. Although tumor regression can be observed for a period of time, a tumor growth can be observed later. Immunotherapy is an attracting and important treatment method and in that sense, the understanding of tumor-immune dynamics and modeling these dynamics realistically plays a crucial role. In this chapter, we will give necessary information about the tumor-immune dynamics and we provide several variables immune variables that affect tumor growth and we will mention important mathematical models of tumor-immune dynamics.

3.1 Tumor-Immune Interaction

Tumor growth and immune response dynamics are complex and are not very well understood. Spontaneously growing tumors have low immunogenicity. In other words, tumors provoke an immune response at a very low level. As a result they diffuse uncontrollably in a host. In a process called cancer immunosurveillance, the immune system can identify and destroy emerging tumor cells and this process operates an important defense against cancer. Tumor growth exhibits different strategies for escaping from immune surveillance. Some are listed as follows [60]:

- the selection of tumor clones resistant to cytolytic mechanisms, the loss or masking of tumor antigens,
- the loss of major histocompatibility complex class I molecules,
- tumor induced disorders in immunoregulation [20, 73, 97].

However, immune system is able to attack and kill cancer cells, and immune response of tumor growth is crucial and powerful to inhibit tumor in the host [47, 49].

There are three main roles of immune system for cancer prevention [100].Firstly, the host may be guarded by the immune system from virus-induced tumors by defating the viral infections. Secondly, there are two major factors which can prevent the establishment of an inflammatory environment causing tumorigenesis. One factor is the timely elimination of pathogens and the other one is its prompt resolution. Finally, tumor cells can be detected and destroyed in some specific tissues by immune system which express tumor-specific antigens. The third role is also named as immunosurveillance and in this case immune system realizes transformed cancer cells and defeats them before they become malignant. For a detailed description of the tumor- immune dynamics, you may see Figure 3.1 and for a detailed explanation of natural innate and adaptive immunity of cancer, one may see [100].

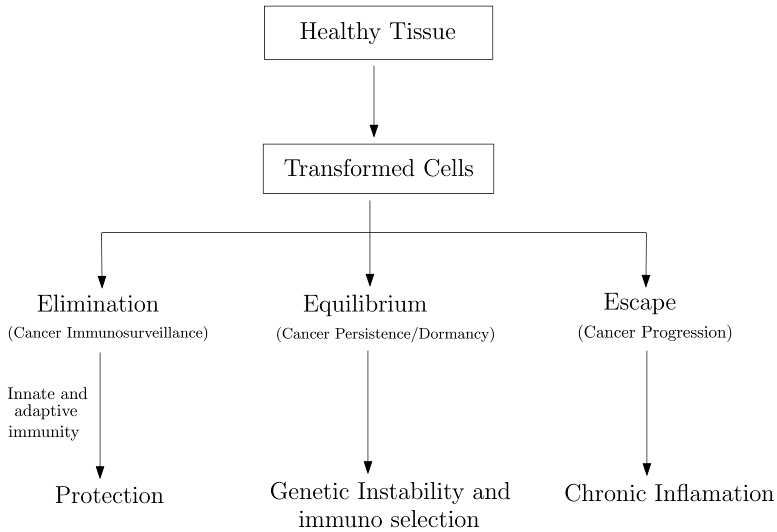

Figure 3.1: Tumor-immune system dynamics. For a detailed version see [100].

3.1.1 Immune System Variables

The adaptive immune system which is a powerful immune response as much as immunological memory, is antigen specific and requires the recognition of specific ”non-self” antigens during a process called antigen presentation [80]. A signature antigen identifies and remembers each pathogen [80].

Antigen specificity allows for the creation of responses and these responses is provided by ”memory cells” in the host. The ability to assemble these responses is maintained in the body by ”memory cells”. Once the host is infected by a pathogen, these specific memory cells identify and destroy it.

Long-term active memory is obtained by activation of B and T cells. By immunization which is to introduce an antigen from a pathogen in order to stimulate the immune system and develop specific immunity against that particular particular pathogen without causing disease associated with that organism , active immunity can be obtained artificially [2]. Immunization is successful because it exploits the natural specificity of the immune system.

3.1.1.1 IL-1α

Interleukin-1 alpha ($IL-1\alpha$) is a protein of the interleukin-1 family where in humans is encoded by the IL1A gene [68, 74]. In general, Interleukin 1 is responsible for the production of inflammation, as well as the promotion of fever and sepsis. $IL-1\alpha$ is a cytokine of the interleukin-1 family. Cytokine is a group of soluble proteins, peptides, or glycoproteins which acts as hormonal regulators or signaling molecules and help in cell signaling. $IL-1\alpha$ inhibitors are being produced to prevent inflammation, as well as the promotion of fever and sepsis, so that they treat diseases. It possesses metabolic, physiological, haematopoietic activities, and plays one of the central roles in the regulation of the immune responses. For detailed information on $IL-1\alpha$, one may see the following works [7, 8, 16, 34, 67, 71, 90]

3.1.1.2 Effector Cells and Their Role In Immune System

Effector cell is basically a lymphocyte (as a T cell) that has been induced to differentiate into a form (as a cytotoxic T cell) capable of mounting a specific immune response-called also effector lymphocyte [100]. Tumor escape can result from changes that occur at the level of the tumor by directly inhibiting tumor recognition or cytolysis by immune effector cells. Effector immune cells employ extremely diverse mechanisms to control tumor targets including the induction of tumor cell death by mitochondrial and cell death receptor pathways, and thus evasion of immunosurveillance is often referred to as the seventh hallmark of cancer [36, 105]. In combination, these diverse intrinsic and extrinsic tumor-suppressor mechanisms, which are related to each other, are remarkably effective and specific.

3.1.1.3 Tumor-Immune System Experiments Observing IL1-α And Effector Cell Effect

This part includes a summary of the work [37] which is used in the application of the model in Chapter 5.

As mentioned before, IL1-α is essential for the immune system and effective on the growth of tumor size. In the work of Dvorkin et al. [37], this effect has been investigated by some experiments on different mice groups. They have investigated where anti-tumor immune responses were assessed in comparative studies using spleen cells from mice injected with an IL1-α -positive (Clone 2) cell line or a non-IL1-α -expressing (Clone 5) fibrosarcoma cell line. All IL1-α-positive fibrosarcoma clones induced regressing tumors when injected mice; initially, cells started to grow for 10-15 days and subsequently regressed within 20-40 days (see Figure 5.2). On the contrary, cells of non-IL1-α-expressing clones grew progressively and resulted in the death of tumor-bearing mice [37]. Both types of cell lines (IL1-α-positive and -negative) show similar growth patterns. In these experiments, two clones-the IL1-α-positive Clone 2 and the non-IL1-α-expressing Clone 5-were assessed in a comparative manner in studies on the immune mechanisms, which are activated by tumor cell-associated IL1-α, which subsequently leads to tumor regression. Violent cells of Clone 5 induce early and transient anti-tumor T cell-mediated responses, which are insufficient to induce tumor regression. This work states the role of tumor cell-associated IL1-α in the induction of specific immune responses against epitopes on the malignant cells, ultimately leading to tumor regression and the development of an immune memory, which protects the mice from a challenge with the violent tumor cells. The data, different levels of tumor size according to different Clones and S.I. values can be seen from Figures 5.2, 5.3 and 5.4.

In Dvorkin's work, Stimulator Index(S.I.) has been formulated as S.I.=optical density (OD; effector cells+stimulator cells)/OD (effector cells).

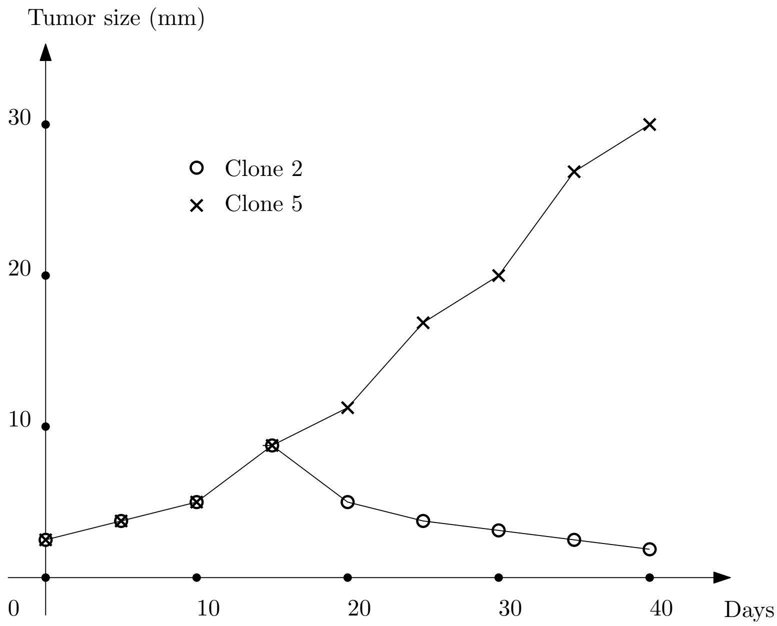

Figure 3.2: Clone 2 and Clone 5 tumor growth according to days [37].

3.2 Tumor-Immune Mathematical Models

Advances in cancer immunology and developments in immunotherapy propose that the immune system has an important role to defense the host against tumor, and they could be benefited for preventing or curing tumor growth. Although theoretical and experimental studies of tumor-immune system dynamics have a long history, there are still many unanswered questions about the complex interaction mechanisms between the immune system and a growing tumor. Indeed, the multidimensional nature of these complex interactions requires cross-disciplinary approaches to capture more realistic

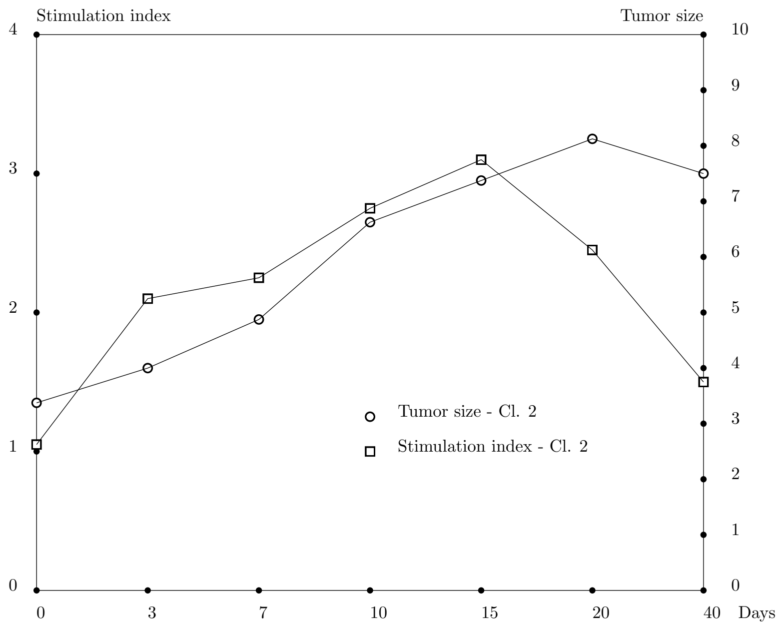

Figure 3.3: Clone 2 S.I. and tumor growth according to days [37].

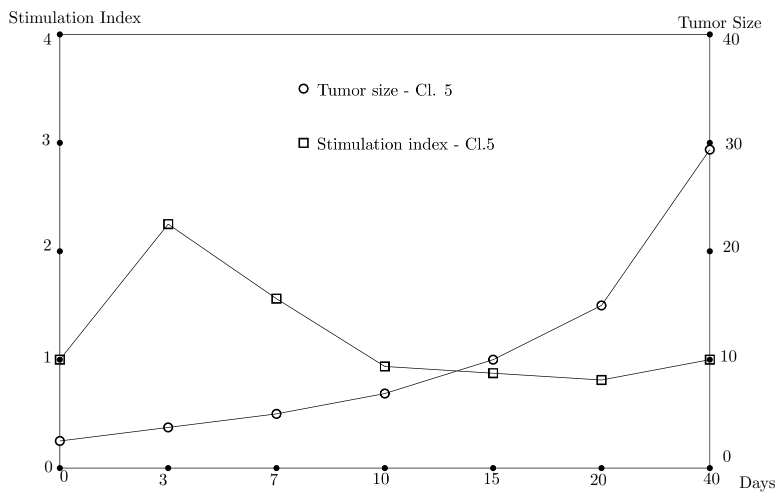

Figure 3.4: Clone 5 S.I. and tumor growth data according to days [37].

dynamics of the essential biology. Such approaches include combining cancer immunology with mathematics. There exist different approaches to model tumor-immune dynamics. To mention some of them, we can list kinematic approaches, diffusion processes, predator-prey approach [1]. A variety of mathematical models including the dynamics of the immune system and growing tumor have been researched [60], [1]. Thorough these models, important parameters have been obtained and some predictions have been done [60]. One of the most effective models has been introduced by Kuznetsov [60] An interesting source of complexity of the competitive interaction is the ability of living systems to hide themselves when chased and to learn from the surrounding environment, where they operate. The learning is an intrinsic characteristic of some system and contributes to refine the expression of its individual strategy.

Cattani& Ciancio have modeled hiding-learning dynamics in a Hybrid two scales mathematical tools for active particles modeling complex systems with learning hiding dynamics in 2007 [24].

In 2008 D'Onofrio proposed meta-modeling tumor-immune system interaction, tumor evasion and immunotherapy [35] Bellomo introduced hiding-learning dynamics with respect to stochastic game theory in 2010 [25]. In 2010 Cattani, Ciancio and d'Onofrio proposed meta-modeling of the learning-hiding competition between tumors and the immune system [25]. For more detailed analysis of the models in the literature, you may see [1].

In the following section, you may find his model and a brief description of the developments of his model.

3.2.1 Kuznetsov's Model

Kuznetsov's model can be formulated as the following[60];

$$\frac{dE}{dt} = s + F(C,T) - d_1E - k_1ET + (k_{-1} + k_2)C, \tag{3.1}$$

$$\frac{dT}{dt} = aT(1 - bT_{tot}) - k_1ET + (k_{-1} + k_3)C, \tag{3.2}$$

$$\frac{dC}{dt} = k_1ET - (k_{-1} + k_2 + k_3)C, \tag{3.3}$$

$$\frac{dE^*}{dt} = k_3C - d_2E^*, \tag{3.4}$$

$$\frac{dT^*}{dt} = k_3C - d_3T^*, \tag{3.5}$$

where E, T, C are the local concentrations of effector cells, tumor cells, effector cell-tumor cell conjugates, and E^*,T^* are inactivated effector cells, and lethally hit TC cells, respectively as described in [60].

The complexity and competitive structure of tumor-immune system dynamics can be modeled by a nonlinear system in a way that to consider the immune system cells and tumor cells as interacting populations would be the simplest way of modeling. The dynamical system of tumor-immune dynamics, proposed by D'Onofrio, considers the following assumptions

- is a Lotka-Volterra like model,
- there exist a tumor free equilibrium,
- the number of tumor cells may tend asymptotically to either infinity or to a finite value,
- there exist an equilibrium state compatible with a finite small value of the tumor cells,
- for any time t, none of the variables take negative values,
- the influx of lymphocytes is a function of the tumor cells.

The following model, which is proposed by D'Onofrio [23], considers the evolution of the number of cells belonging to the two competing populations:

$$\frac{dn_1}{dt} = c_1 n_1 F(n_1) - c_2 \phi(n_1) n_1 n_2, \tag{3.6}$$

$$\frac{dn_2}{dt} = c_3 n_1 \varphi(n_1) n_2 + c_4 \beta(t) q(n_1) + \Omega(t), \tag{3.7}$$

where n_1 is the numerical density of tumor cells, n_2 the numerical density of lympho cyte population, under conditions $n_1 \geq 0$ and $n_2 \geq 0$, while $F(n1); \phi(n_1); \varphi(n_1)$ and $q(n_1)$ are deterministic functions of n_1.

By combining the previous ideas Cattani et al. [25] proposed the following model of tumor-immune dynamics:

$$x' = x(F(x) - \phi(x; a(t))y),$$
$$y' = P(x, y; b(t))y - \mu(x)y + q(x; c(t)),$$

where $a(t)$, $b(t)$ and $c(t)$ are three positive time-varying continuous parameters through which the t the process of increase of the parameters is far faster learning-hiding processes express themselves; the rates $\phi(x; a(t))$, $P(x, y; b(t))$ and $q(x; c(t))$ are monotone increasing functions of $a(t)$, $b(t)$ and $c(t)$, respectively. By the following assumptions, Cattani and Ciancio improved the previous model by including learning, hiding parameters:

- The learning of immune system of the presence of tumor cells, which is a fast process;
- The learning of tumor cells in evading from the immune control which is very slow.

CHAPTER 4

DETERMINISTIC AND STOCHASTIC HYBRID SYSTEMS WITH MEMORY

In this chapter, hybrid systems with memory are introduced and illustrated by several examples. In order to observe the dependence of behavior on history, we include a memory set in the definition. For a wide range of switching systems in nature and technology, the system's behavior and response to external inputs are determined not only by the initial values but by the whole history [76], [79]. Especially, for systems requiring history memorization capabilities like many biological systems, this is a requirement [76], [79].

4.1 Definition

The state of a hybrid system is defined by the values of the continuous variables and a discrete control mode. More precisely, we have the following definition for hybrid systems with memory.

Definition 4.1. A Hybrid system with memory H is a collection

$$H = \{Q,\ X,\ U,\ T,\ Init,\ M,\ f,\ Inv,\ E,\ G,\ R\}$$

consisting of [76]

- a set of discrete states $Q = \{q_1, \dots, q_m\}$ also called locations,
- a space of continuous variables $X = \mathbf{R}^n$,
- a set of initial conditions $Init \subseteq Q \times X \times M$,
- a space of inputs $U = \mathbf{R}^z$ (control, disturbance or both),
- a space of independent variables $T = \mathbf{R}^k$, typically the time $T = [t_0, \infty)$,
- a vector field $f : Q \times X \times U \times M \longrightarrow X$, governing the continuous evolution,
- an invariant set (domain, subspace) for each $q \in Q$, $\quad Inv : Q \longrightarrow P(Y)$ where $P(.)$ denotes the power set. Each state's governing dynamics is valid within its invariant set.

- A set of edges (state transitions) $E \subset Q \times Q$,
- guard conditions for each edge $G: \; E \times M \longrightarrow P(X)$,
- a reset map for each edge $R: \; E \times X \times U \longrightarrow P(X)$,
  - For verifiability analysis $R: \; E \times G \longrightarrow X$, can be considered.
- $M(t) \in M$ is a growing memory of past state transitions such that
  - $M(0) = \{M_0\} = \{(t_0, x_0, q_0)\}$,
  - if $M(t; -) = \{M_0, M_1, \ldots, M_i\}$ and $x(t_j) \in g\{q(t), \, q \in Q\}$ then $M(t; +) = \{M(t; -), M_{i+1}\}$,
  - $M_{i+1} = \{t_j, \, x(t_{j-}), \, q(t_{j-})\}$

With this definition the prior evolution of the system is sampled at state transitions containing the time and the values of variables before and after the state transition. In this definition, $M(t)$ is piecewise constant between state transitions.

A typical subclass is the piecewise linear hybrid system with memory with a state space description as follows [76]:

$$\begin{aligned} \frac{dx}{dt} &= A_{q(t),M(t)} \, x(t) + B_{q(t),M(t)} \, u(t) + k_{q(t),M(t)}, \\ x(0) &= x_0, \quad q(0) = q_0, i = 1, \, 2, \ldots, n, \\ q(t) &= q_j \; \text{ if } \; x(t) \in X_j. \end{aligned}$$

If $x(t_{0_-}) \in X_j$, $x(t_{0_+}) \notin X_j$ and $M(t_{0_-}) = \{M_1, \ldots, M_k\}$ then,

$$\begin{aligned} M(t_{0_+}) &= \{M(t_{0_-}), M_{k+1}\}, \\ M_{k+1} &= \{t_0, x(t_{0_-}), x(t_{0_+})\}. \end{aligned}$$

4.2 Examples

In order to illustrate the use of hybrid systems with memory, we now give the following examples. The first example has different trajectories according to the subspace in which the initial value appears. The second example illustrates an example in which the initial value affects the speed by which the trajectory is traversed. Following examples can be found also in [46].

4.2.1 Example 1

Let us consider $Q = \{q_1, q_2, q_3, q_4\}$, a set of discrete states. We choose a space of continuous variables $Y = \mathbf{R}^2$ with the following subspaces:

$$\begin{aligned} Inv(q_1) &= \{y_1 \leq 1, y_2 \leq 1\}, \\ Inv(q_2) &= \{y_1 > 1, y_2 \leq 1\}, \\ Inv(q_3) &= \{y_1 \leq 1, y_2 > 1\}, \\ Inv(q_4) &= \{y_1 > 1, y_2 > 1\}. \end{aligned}$$

For simplicity let us denote these by $I_i = Inv(q_i)$ for each $1 \leq i \leq 4$. A simple hybrid system with memory model can be obtained by the following governing equations

$$\begin{aligned} \frac{dy}{dt} &= A_{q(t),\,M(t)}\, y(t) + k_{q(t),M(t)}, \\ A_{(0,0),0} &= A_{(0,1),0} = A_{(1,0),0} = A_{(1,1),0} = \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix}, \\ k_{(1,1),0} &= \begin{pmatrix} 5 \\ 4 \end{pmatrix}, \\ y_1 &= y_2 = 1. \end{aligned}$$

From this we obtain the following system of linear ordinary differential equations:

$$\begin{aligned} \frac{dy_1}{dt} &= -y_1 + 5, \\ \frac{dy_2}{dt} &= -y_2 + 4. \end{aligned}$$

This has the solution

$$\begin{aligned} y_1(t) &= 5 - (5 - y_1(0))\, e^{-t}, \\ y_2(t) &= 4 - (4 - y_2(0))\, e^{-t}. \end{aligned}$$

As time varies, this solution produces points on the line $\ell : 4y_1(t) - 5y_2(t) = 0$. In particular as time goes to infinity, we approach to the point $(5, 4)$.

Recall that the space Y is partitioned into four subspaces by the threshold values. Let us start with an initial point in the subspace I_1. In other words $y_1(t) \leq 1$ and $y_2(t) \leq 1$. (See Figure 4.1.)

Observe that the line $\ell : 4y_1 - 5y_2 = 0$ divide I_1 into two subspaces. Trajectories will approach to the point $(5, 4)$. If the initial point is below (respectively above) this

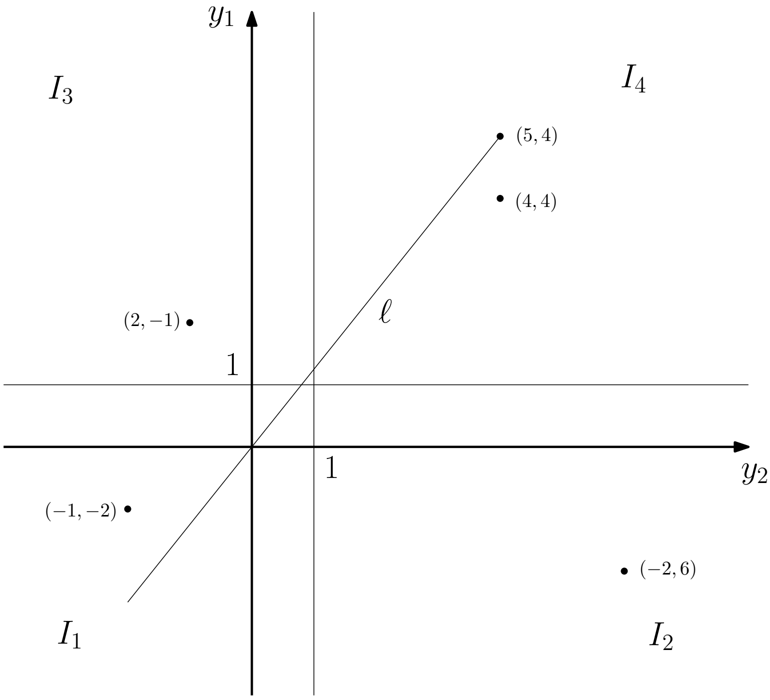

Figure 4.1: State space representation of Example 1.

line, then the trajectory will cross $y_2 = 1$ (respectively $y_1 = 1$). According to these two possibilities, two different rounding trajectories occur. Initially, the memory set is equal to $M(t) = m_0$. As the trajectory crosses threshold, the memory determines the direction of the trajectory.

Case A: (Below the line)

When a trajectory crosses $y_2 = 1$, the memory set will be equal to $m_1 \in M(t)$. The conditions $m_1 \in M(t)$ and $y_2(t_{1_+}) = y_2(t_{1_-}) = 1$ identify this case. The governing system of differential equations according to state space partitions is given as:

$$
\begin{aligned}
\frac{dy}{dt} &= A_{q(t),\,M(t)}\, y(t) + k_{q(t),M(t)}, \\
A_{(0,0),1} &= A_{(0,1),1} = A_{(1,0),1} = A_{(1,1),1} = \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix}, \\
k_{((0,0),1)} &= \begin{pmatrix} -2 \\ 6 \end{pmatrix}, \; k_{((0,1),1)} = \begin{pmatrix} 4 \\ 4 \end{pmatrix}, \; k_{((1,0),1)} = \begin{pmatrix} -1 \\ -2 \end{pmatrix}, \\
k_{((1,1),1)} &= \begin{pmatrix} 2 \\ -1 \end{pmatrix}.
\end{aligned}
$$

Suppose that the initial point is $(0.1, 0.5)$. As the trajectory starts to move, it will cross threshold $y_2(t) = 1$ and initial focal point will change as it enters subspace I_2. The governing differential equation of this subspace is

$$\begin{aligned}\frac{dy}{dt} &= A_{(0,1),1}\,y(t) + k_{(0,1),1},\\ \begin{pmatrix}\frac{dy_1}{dt}\\ \frac{dy_2}{dt}\end{pmatrix} &= \begin{pmatrix}-1 & 0\\ 0 & -1\end{pmatrix}\begin{pmatrix}y_1\\ y_2\end{pmatrix} + \begin{pmatrix}4\\ 4\end{pmatrix},\end{aligned}$$

with solution

$$\begin{pmatrix}y_1\\ y_2\end{pmatrix} = \begin{pmatrix}4-(4-y_1(0))\,e^{-t}\\ 4-(4-y_2(0))\,e^{-t}\end{pmatrix}.$$

As the trajectory passes from I_1 to I_2, the focal point changes from $(5,4)$ to $(4,4)$. During this movement, the trajectory will cross the threshold $y_1 = 1$ and enters subspace I_4 eventually. The governing differential equation of subspace I_4 is

$$\begin{aligned}\frac{dy}{dt} &= A_{(1,1),1}\,y(t) + k_{(1,1),1},\\ \begin{pmatrix}\frac{dy_1}{dt}\\ \frac{dy_2}{dt}\end{pmatrix} &= \begin{pmatrix}-1 & 0\\ 0 & -1\end{pmatrix}\begin{pmatrix}y_1\\ y_2\end{pmatrix} + \begin{pmatrix}2\\ -1\end{pmatrix},\end{aligned}$$

with solution

$$\begin{pmatrix}y_1\\ y_2\end{pmatrix} = \begin{pmatrix}2-(2-y_1(0))\,e^{-t}\\ -1-((-1)-y_2(0))\,e^{-t}\end{pmatrix}.$$

When the trajectory passes through the subspace I_4, it moves towards $(2,-1)$ and crosses the threshold $y_2 = 1$. Thus it enters the subspace I_3 for which the governing equations are as follows:

$$\begin{aligned}\frac{dy}{dt} &= A_{(1,0),1}\,y(t) + k_{(1,0),1},\\ \begin{pmatrix}\frac{dy_1}{dt}\\ \frac{dy_2}{dt}\end{pmatrix} &= \begin{pmatrix}-1 & 0\\ 0 & -1\end{pmatrix}\begin{pmatrix}y_1\\ y_2\end{pmatrix} + \begin{pmatrix}-1\\ -2\end{pmatrix},\end{aligned}$$

with solution

$$\begin{pmatrix}y_1\\ y_2\end{pmatrix} = \begin{pmatrix}-1-((-1)-y_1(0))\,e^{-t}\\ -2-((-2)-y_2(0))\,e^{-t}\end{pmatrix}.$$

The trajectory moves toward $(-1,-2)$ when it is in subspace I_3 and crosses $y_1 = 1$. Then it enters the subspace I_1. The governing differential equation of subspace I is

$$\begin{aligned}\frac{dy}{dt} &= A_{(1,0),1}\,y(t) + k_{(1,0),1},\\ \begin{pmatrix}\frac{dy_1}{dt}\\ \frac{dy_2}{dt}\end{pmatrix} &= \begin{pmatrix}-1 & 0\\ 0 & -1\end{pmatrix}\begin{pmatrix}y_1\\ y_2\end{pmatrix} + \begin{pmatrix}-2\\ 6\end{pmatrix},\end{aligned}$$

with

$$\begin{pmatrix}y_1\\ y_2\end{pmatrix} = \begin{pmatrix}-2-((-2)-y_1(0))\,e^{-t}\\ 6-(6-y_2(0))\,e^{-t}\end{pmatrix}.$$

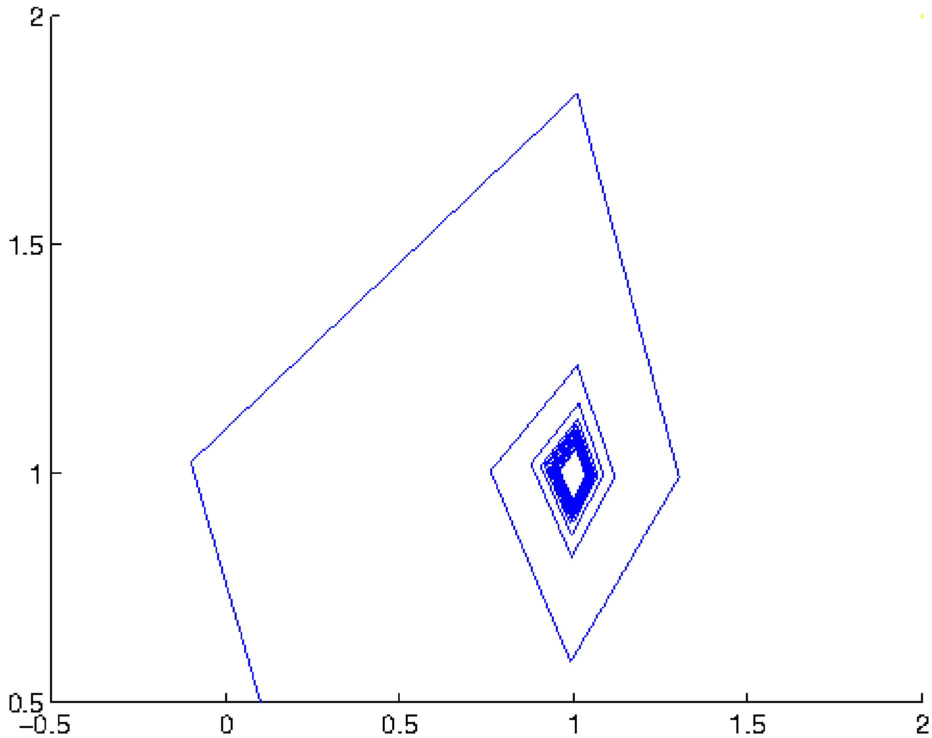

Figure 4.2: Rounding trajectories with initial values $(0.1, 0.5)$.

The representation of Case A according to initial point $(0.1, 0.5)$ is shown by the Figure 4.2. In this case the rounding trajectories are counter clockwise.

Case B Above the line:

Suppose that the initial point is chosen as $(0.5, 0.5)$. Note that this is a point above the line $\ell : 4y_1 - 5y_2 = 0$. When the trajectory crosses $y_1 = 1$, the memory set will be equal to $m_1 \in M(t)$. Conditions $m_1 \in M(t)$ and $y_1(t_{1_+}) = y_1(t_{1_-}) = 1$ identify this case. The governing differential equations according to state space partitions are given as

$$\begin{aligned}
\frac{dy}{dt} &= A_{q(t),\,M(t)}\, y(t) + k_{q(t),M(t)}, \\
A_{((0,0),1)} &= A_{((0,1),1)} = A_{(1,0),1} = A_{((1,1),1)} = \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix}, \\
k_{((0,0),1)} &= \begin{pmatrix} 2 \\ -1 \end{pmatrix}, \quad k_{((0,1),1)} = \begin{pmatrix} -1 \\ -2 \end{pmatrix}, \quad k_{((1,0),1)} = \begin{pmatrix} 4 \\ 4 \end{pmatrix}, \\
k_{((1,1),1)} &= \begin{pmatrix} -2 \\ 6 \end{pmatrix}.
\end{aligned}$$

The focal points are different in each transition state; in other words because of the memory. As the trajectory starts to move, it will cross the threshold $y_1(t) = 1$ and the initial focal point will change, and according to the partitioning of the space it will enter subspace I_3.

The governing differential equation of subspace I_3 is

$$\begin{aligned}
\frac{dy}{dt} &= A_{(1,0),1}\, y(t) + k_{(1,0),1}, \\
\begin{pmatrix} \frac{dy_1}{dt} \\ \frac{dy_2}{dt} \end{pmatrix} &= \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix} + \begin{pmatrix} 4 \\ 4 \end{pmatrix},
\end{aligned}$$

with solution

$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} 4 - (4 - y_1(0))\, e^{-t} \\ 4 - (4 - y_2(0))\, e^{-t} \end{pmatrix}.$$

All trajectories in space I_2 will converge to the corresponding focal point $(4, 4)$. During this movement, the point will cross threshold $y_2 = 1$ and will enter subspace $_4$. The governing differential equation of subspace I_4 is

$$\begin{aligned}
\frac{dy}{dt} &= A_{(1,1),1}\, y(t) + k_{(1,1),1}, \\
\begin{pmatrix} \frac{dy_1}{dt} \\ \frac{dy_2}{dt} \end{pmatrix} &= \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix} + \begin{pmatrix} -2 \\ 6 \end{pmatrix},
\end{aligned}$$

with solution

$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} -2 - ((-2) - y_1(0))\, e^{-t} \\ 6 - (6 - y_2(0))\, e^{-t} \end{pmatrix}.$$

All trajectories in subspace I_4 will converge to $(-2, 6)$. Then the trajectory will cross $y_1 = 1$ and enter subspace I_2. The governing differential equation of subspace I_2 is

$$\begin{aligned} \frac{dy}{dt} &= A_{(0,1),1}\, y(t) + k_{(0,1),1}, \\ \begin{pmatrix} \frac{dy_1}{dt} \\ \frac{dy_2}{dt} \end{pmatrix} &= \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix} + \begin{pmatrix} -1 \\ -2 \end{pmatrix}, \end{aligned}$$

with solution

$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} -1 - ((-1) - y_1(0))\, e^{-t} \\ -2 - ((-2) - y_2(0))\, e^{-t} \end{pmatrix}.$$

All points in subspace I_2 will converge to $(-1, -2)$. Then the trajectory will cross $y_2 = 1$ and enter the subspace I_1. The governing differential equation of subspace I_1 is

$$\begin{aligned} \frac{dy}{dt} &= A_{(0,0),1}\, y(t) + k_{(0,0),1}, \\ \begin{pmatrix} \frac{dy_1}{dt} \\ \frac{dy_2}{dt} \end{pmatrix} &= \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix} + \begin{pmatrix} 2 \\ -1 \end{pmatrix}, \end{aligned}$$

with solution

$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} 2 - (2 - y_1(0))\, e^{-t} \\ -1 - ((-1) - y_2(0))\, e^{-t} \end{pmatrix}.$$

The representation of Case B according to initial point $(0.5, 0.5)$ is shown by the Figure 4.3. In this case the rounding trajectories will be clockwise.

4.2.2 Example 2

In this example, we illustrate how the state transitions of a piecewise linear model can get slower because of its dependence on the memory. For simplicity, we again consider the following equation:

$$\frac{dy}{dt} = A_{q(t),\,M(t)}\, y(t) + k_{q(t),M(t)}.$$

The solution of this system is given by

$$y^m(t) = y_0^m(t)\, e^{(t-t_0)\,A^m} + (e^{(t-t_0)\,A^m} - 1)\,(A^m)^{-1}\, k^m,$$

where m is the m^{th} component of the corresponding variable and A^m yields the m^{th} eigenvalue of matrix A. This equation can be rewritten as

$$y_{n+1}^m = h = e^{T_n A^m}(y_n^m + (A^m)^{-1}\, k^m) - (A^m)^{-1}\, k^m,$$

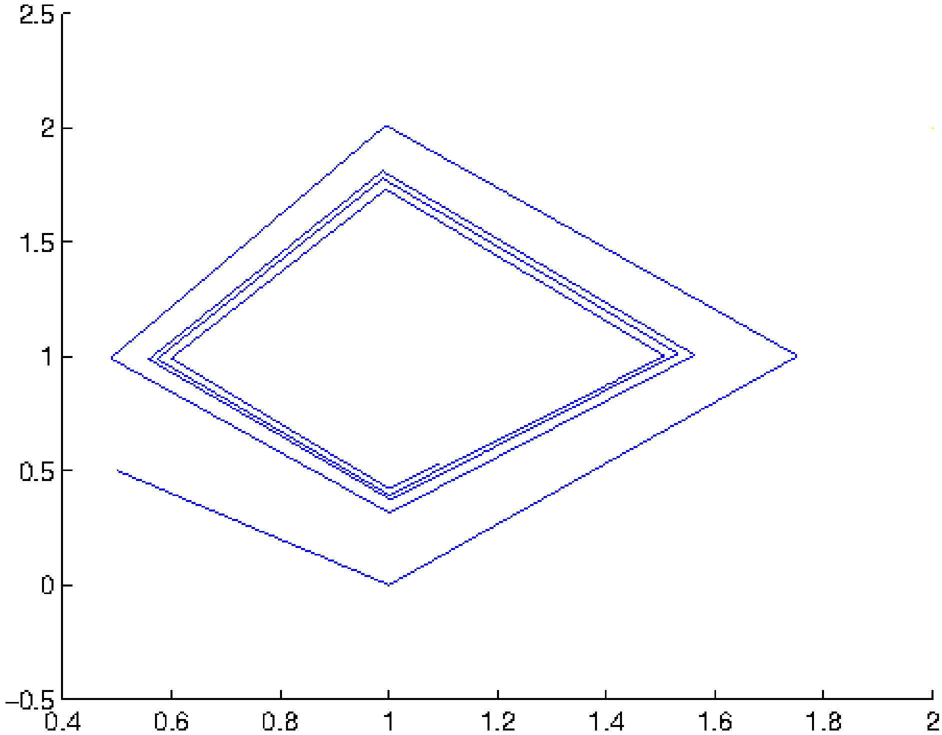

Figure 4.3: Rounding trajectories with initial values $(0.5, 0.5)$.

where n indicates the n^{th} state transition and h is the corresponding threshold value. By rearranging, we obtain

$$e^{T_n A^m} = \frac{h + (A^m)^{-1} k^m}{y_n^m + (A^m)^{-1} k^m},$$

so that the state transition time of the n^{th} state can be calculated from this equation:

$$T_n = \left[\ln \frac{h + (A^m)^{-1} k^m}{y_n^m + (A^m)^{-1} k^m} \right] / A^m.$$

In this example, the focal points do not change but according to the subspace of the initial values the trajectories behave faster or slower. In order to satisfy these conditions, we can consider the following governing differential equations:

$$\frac{dy}{dt} = bA_{q(t),\, M(t)}\, y(t) + \frac{1}{b}\, k_{q(t),M(t)},$$

where $0 < b < 1$.

Then this system has solutions

$$y^m(t) = y_0^m(t)\, e^{(t-t_0)\, b\, A^m} + (e^{(t-t_0)\, b\, A^m} - 1)\, (A^m)^{-1}\, k^m,$$

with state transition time of the n^{th} state;

$$T_n^* = \left[\ln \frac{h + (A^m)^{-1} k^m}{y_n^m + (A^m)^{-1} k^m} \right] / b(A^m).$$

Obviously, $T_n < T_n^*$, since $0 < b < 1$ and $1 < \frac{1}{b} < \infty$. Again, assume a system that has a periodic solution

$$A_{(0,0),0} = A_{(0,1),0} = A_{(1,0),0} = A_{((1,1),0)} = \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix},$$

with threshold values

$$y_1 = y_2 = 1$$

and focal points

$$k_{((0,0),0)} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \quad k_{((0,1),0)} = \begin{pmatrix} 2 \\ 0 \end{pmatrix}, \quad k_{((1,0),0)} = \begin{pmatrix} 0 \\ 2 \end{pmatrix}, \quad k_{((1,1),0)} = \begin{pmatrix} 2 \\ 2 \end{pmatrix}.$$

Let us choose $b = \frac{1}{2}$ and let us consider $Q = \{q_1, q_2, q_3, q_4\}$, a set of discrete states. We choose a space of continuous variables $Y = \mathbf{R}^2$ with the following subspaces:

$$\begin{aligned} Inv(q_1) &= \{y_1 \leq 1, y_2 > 1\}, \\ Inv(q_2) &= \{y_1 > 1, y_2 > 1\}, \\ Inv(q_3) &= \{y_1 \leq 1, y_2 \leq 1\}, \\ Inv(q_4) &= \{y_1 > 1, y_2 \leq 1\}. \end{aligned}$$

For simplicity let us denote these by $I_i = Inv(q_i)$ for each $1 \leq i \leq 4$. Our initial set is $Init = \{q = q_1, y_1, y_2 \in \mathbf{R}\}$. If $M(t) = m_0$, then the governing differential equations for the subspace I_4 are:

$$\begin{aligned}\frac{dy}{dt} &= A_{(1,0),0}\, y(t) + k_{(1,0),0}, \\ \begin{pmatrix} \frac{dy_1}{dt} \\ \frac{dy_2}{dt} \end{pmatrix} &= \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \end{pmatrix},\end{aligned}$$

with solution

$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} y_1(0)\, e^{-t} \\ y_2(0)\, e^{-t} \end{pmatrix}.$$

All trajectories in that region approach to $(0, 0)$. Then the trajectory will cross $y_1 = 1$ and enter subspace I_3 for which the governing differential equations are

$$\begin{aligned}\frac{dy}{dt} &= A_{(0,0),0}\, y(t) + k_{(0,0),0}, \\ \begin{pmatrix} \frac{dy_1}{dt} \\ \frac{dy_2}{dt} \end{pmatrix} &= \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix} + \begin{pmatrix} 0 \\ 2 \end{pmatrix},\end{aligned}$$

with solution

$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} y_1(0)\, e^{-t} \\ 2 - (2 - y_2(0))\, e^{-t} \end{pmatrix}.$$

All trajectories in that region will approach to $(0, 2)$. Then the point will cross $y_2 = 1$ and enter subspace I_1. The governing differential equations of subspace I_1 are

$$\begin{aligned}\frac{dy}{dt} &= A_{(1,1),0}\, y(t) + k_{(1,1),0}, \\ \begin{pmatrix} \frac{dy_1}{dt} \\ \frac{dy_2}{dt} \end{pmatrix} &= \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix} + \begin{pmatrix} 2 \\ 2 \end{pmatrix},\end{aligned}$$

with solution

$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} 2 - (2 - y_1(0))\, e^{-t} \\ 2 - (2 - y_2(0))\, e^{-t} \end{pmatrix}.$$

All trajectories in that region will approach to $(2, 2)$. Then the trajectory will cross $y_1 = 1$ and enter subspace I_2. The governing differential equations of subspace I_2 are

$$\begin{aligned}\frac{dy}{dt} &= A_{(0,1),0}\, y(t) + k_{(0,1),0}, \\ \begin{pmatrix} \frac{dy_1}{dt} \\ \frac{dy_2}{dt} \end{pmatrix} &= \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix} + \begin{pmatrix} 2 \\ 0 \end{pmatrix},\end{aligned}$$

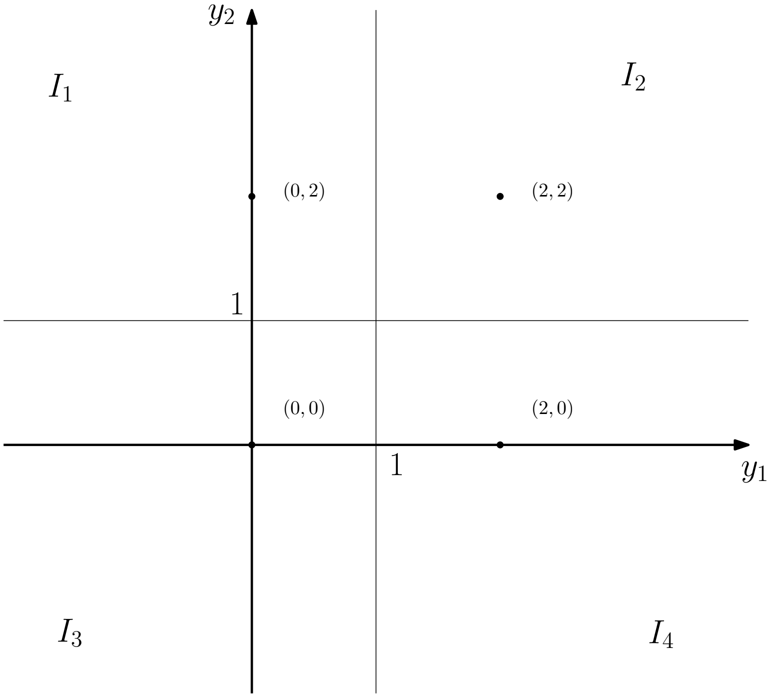

Figure 4.4: State space representation of Example 2

with solution

$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} 2 - (2 - y_1(0))\, e^{-t} \\ y_2(0)\, e^{-t} \end{pmatrix}.$$

All trajectories in that region will approach to $(2,0)$.

Case A: If $m_1 \in M(t)$ and $y_1(m_1) = y_1(t_{1_+}) = y_1(t_{1_-}) = 1$ and $y_2(t_{1_+}) = y_2(t_{1_-}) < 1$ or if $m_2 \in M(t)$ and $y_1(m_2) = y_1(t_{2_+}) = y_1(t_{2_-}) = 1$ and $y_2(t_{2_+}) = y_2(t_{2_-}) < 1$, the governing dynamics of the system do not change.

Case B: If $m_1 \in M(t)$ and $y_1(m_1) = y_1(t_{1_+}) = y_1(t_{1_-}) = 1$ and $y_2(t_{1_+}) = y_2(t_{1_-}) \geq 1$ or if $m_2 \in M(t)$ and $y_1(m_2) = y_1(t_{2_+}) = y_1(t_{2_-}) = 1$ and $y_2(t_{2_+}) = y_2(t_{2_-}) \geq 1$, the differential equations for the subspace I_3 that govern the system look as follows:

$$\begin{aligned} \frac{dy}{dt} &= b\, A_{(0,0),0}\, y(t) + \frac{1}{b}\, k_{(0,0),0}, \\ \begin{pmatrix} \frac{dy_1}{dt} \\ \frac{dy_2}{dt} \end{pmatrix} &= \frac{1}{2} \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix} + 2 \begin{pmatrix} 0 \\ 2 \end{pmatrix}, \end{aligned}$$

with solution

$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} y_1(0)\, e^{-\frac{1}{2}t} \\ 2 - (2 - y_2(0))\, e^{-\frac{1}{2}t} \end{pmatrix}.$$

As time goes to infinity, all trajectories in region I_3 will approach to $(0,2)$. Then, the trajectory will cross $y_1 = 1$ and enter the subspace I_1. The governing system of differential equations of subspace I_1 are

$$\begin{aligned}\frac{dy}{dt} &= b\,A_{(0,1),1}\,y(t) + \frac{1}{b}\,k_{(1,1),1},\\ \begin{pmatrix}\frac{dy_1}{dt}\\ \frac{dy_2}{dt}\end{pmatrix} &= \frac{1}{2}\begin{pmatrix}-1 & 0\\ 0 & -1\end{pmatrix}\begin{pmatrix}y_1\\ y_2\end{pmatrix} + 2\begin{pmatrix}2\\ 2\end{pmatrix},\end{aligned}$$

with solution

$$\begin{pmatrix}y_1\\ y_2\end{pmatrix} = \begin{pmatrix}2-(2-y_1(0))\,e^{-\frac{1}{2}t}\\ 2-(2-y_1(0))\,e^{-\frac{1}{2}t}\end{pmatrix}.$$

All trajectories in that region will approach to $(2,2)$. Then, the trajectory will cross $y_2 = 1$ and enter subspace I_2. The governing differential equations of subspace I_4 are

$$\begin{aligned}\frac{dy}{dt} &= b\,A_{(1,1),1}\,y(t) + \frac{1}{b}\,k_{(1,1),1},\\ \begin{pmatrix}\frac{dy_1}{dt}\\ \frac{dy_2}{dt}\end{pmatrix} &= \frac{1}{2}\begin{pmatrix}-1 & 0\\ 0 & -1\end{pmatrix}\begin{pmatrix}y_1\\ y_2\end{pmatrix} + 2\begin{pmatrix}2\\ 0\end{pmatrix},\end{aligned}$$

with solution

$$\begin{pmatrix}y_1\\ y_2\end{pmatrix} = \begin{pmatrix}2-(2-y_1(0))\,e^{-\frac{1}{2}t}\\ y_2(0)\,e^{-\frac{1}{2}t}\end{pmatrix}.$$

All trajectories in that region exponentially approach to $(2,0)$. Then the trajectory will cross $y_1 = 1$ and enter subspace I_4. The governing differential equations of subspace I_4 are

$$\begin{aligned}\frac{dy}{dt} &= b\,A_{(1,0),0}\,y(t) + \frac{1}{b}\,k_{(1,0),0},\\ \begin{pmatrix}\frac{dy_1}{dt}\\ \frac{dy_2}{dt}\end{pmatrix} &= \frac{1}{2}\begin{pmatrix}-1 & 0\\ 0 & -1\end{pmatrix}\begin{pmatrix}y_1\\ y_2\end{pmatrix} + 2\begin{pmatrix}0\\ 0\end{pmatrix},\end{aligned}$$

with solution

$$\begin{pmatrix}y_1\\ y_2\end{pmatrix} = \begin{pmatrix}y_1(0)\,e^{-\frac{1}{2}t}\\ y_2(0)\,e^{-\frac{1}{2}t}\end{pmatrix}.$$

In this case the focal points don't change but the state transition times are slower in the second case, since

$$\left[ln\frac{1+(-1)^{-1}\,k^m}{y_n^m+(A^m)^{-1}\,k^m}\right]/(-1) < \left[ln\frac{1+(-1)^{-1}\,k^m}{y_n^m+(A^m)^{-1}\,k^m}\right]/(-1/2).$$

4.3 Stochastic Hybrid Systems with Memory

Previously, the deterministic case of hybrid systems with memory is explained and applied. In deterministic case, the first transitions are determined by a partition of the initial set of variables and the future behavior of these variables are determined accordingly. However, in nature and science, there exists random behaviors. With a deterministic approach, this randomness cannot be investigated properly. For a more realistic model, stochastic hybrid systems with memory [76] should be developed. In such a model, the first behavior of variable or variables, can be thought as random until the boundary is hit or until the state transition occurs. After hitting one of the boundaries, the system exhibits a differentiation depending on which boundary is hit or which state transition is occurred. This property characterizes the effect of the memory on the system. Depending on the memory, the system may have different solutions with different distributions, mean and variance values.

If such a model, in which memory is contained, can be constructed then the history of the system can be investigated by analyzing the distributional behavior, mean or variance values of the system. The future behavior of the system can be arranged by the control variables, so that the system can exhibit the desired behavior. To illustrate this, we consider the system with dimension $n = 1$ and the initial set $Y(t_0) \in Inv(q(t_0), m(t_0))$ where $(q(t_0), m(t_0))$ is the initial state of the system, the governing dynamics of the system until it hits one of the boundaries can be expressed by [76]

$$dY_t = \sigma_0 Y_t dW_t, \tag{4.1}$$

$$Y_0 = y_0, \forall y_0 \in (b_1, b_2), \tag{4.2}$$

where b_1, b_2 are the boundaries of the initial set. According to the boundary it hits the system exhibits different behaviors such that

$$dY_t = \begin{cases} -a_2[Y_t - c_2]dt + \sigma_2 dW_t, & \text{if } \tau^* = \tau_2, \\ -a_1[Y_t - c_1]dt + \sigma_1 dW_t, & \text{if } \tau^* = \tau_1, \end{cases}$$

This type of modeling allows us to construct models for the systems which shows random behavior in the memory. Moreover, if the model is constructed properly, then the possible effects of different conditions on the behavior of system can be measured by computer simulations without any need of real experiments.

In addition, the control mechanism of the system can be investigated by the external input variables. For example, in biological systems, drug effect can be investigated.

4.3.1 An Example of SHSM

For an illustration of stochastic hybrid systems with memory, we can start with investigating the stochastic predator-prey type equation. We have chosen this type of equation as an example because of its wide usage in several areas of science. In this type of equation, two species interact each other where one is prey and the other is predator. Since these type of equations describe the general win-loss relations, they can be used in the tumor cell-immune system interactions. The predator-prey type equation can be given as the follows [3]:

$$dX = X(a_{10} - a_{12}Y)dt + \sqrt{a_{10}X}dW_1 - \sqrt{a_{12}Y}dW_2, \tag{4.3}$$
$$dY = Y(a_{21}X - a_{20})dt + \sqrt{a_{21}XY}dW_3 - \sqrt{a_{20}Y}dW_4, \tag{4.4}$$

where $Y(t_0), X(t_0) \in Inv(q(t_0), m(t_0))$ and $(q(t_0), m(t_0))$ is the initial state of the system, the governing dynamics of the system until the trajectory hits one of the boundaries.

When we add the memory phenomena, we enable the system to behave differently depending on the boundary which is hit. More precisely we have the following:

$$\begin{array}{ll} dX = X(b_{10} - b_{12}Y)dt + \sqrt{b_{10}X}dW_1 - \sqrt{b_{12}Y}dW_2, & \\ dY = Y(b_{21}X - b_{20})dt + \sqrt{b_{21}XY}dW_3 - \sqrt{b_{20}Y}dW_4, & \\ & \text{if } \tau^* = \tau_1 \\ dX_t = X(c_{10} - c_{12}Y)dt + \sqrt{c_{10}X}dW_1 - \sqrt{c_{12}Y}dW_2, & \\ dY_t = Y(c_{21}X - c_{20})dt + \sqrt{c_{21}XY}dW_3 - \sqrt{c_{20}Y}dW_4, & \\ & \text{if } \tau^* = \tau_2 \end{array}$$

The boundaries will be determined by the hitting time probabilities. The probabilities have been given in the table [3]. Let $Z = (X, Y)$ be the random variable. According to these hitting times, we can determine the hitting time probabilities. We choose the threshold according to the hitting time probability.

i	Change,$(\Delta Z)_i$	Probability, p_i
1	(1,0)	$a_{10}X\Delta t$
2	(-1,0)	$a_{12}XY\Delta t$
3	(0,1)	$a_{21}XY\Delta t$
4	(0,-1)	$a_{20}Y\Delta t$

Table 4.1: Probabilities according to changes.

4.3.2 Another example of SHSM

Another example of stochastic hybrid systems with memory can be given as follows [76]. Let $Q = \{q_0, q_1, q_2\}$, $Y = \mathbf{R}$, $Init = \{q = q_0, y_0 \in (b_1, b_2)\}$, $Inv(q_0) = y_0 \in (b_1, b_2)$.

The system evolution at initial state $q = q_0$ is

$$dy_t = \sigma_0 Y_t dW_t$$

until it hits one of the boundaries of the initial set b_1 or b_2.

The system above is a classical example of a stochastic system known as Geometric Brownian Motion without drift and its solution is given by

$$y_t = y_0 \exp\{\sigma_0 W_t - \frac{1}{2}\sigma^2 t\}.$$

The hitting time of each barriers is defined by stopping times:

$$\begin{aligned} \tau_1 &= inf\{t \in \mathbf{R}^+ : Y_t \geq b_2\}, && (4.5) \\ \tau_2 &= inf\{t \in \mathbf{R}^+ : Y_t \leq b_1\}. && (4.6) \end{aligned}$$

Here, τ_1 and τ_2 are random variables. Thus, in each run, the first transition occur by hitting b_1 or b_2 is totally random. We take $\tau^* = min\{\tau_1, \tau_2\}$ as the first transition time and therefore the memory set will be

$$M = \{m_0, (\tau^*, b)\} = \begin{cases} (\tau^*, b_1), & \text{if} \quad y_{\tau^*} = b_1, \\ (\tau^*, b_2), & \text{if} \quad y_{\tau^*} = b_2, \end{cases}$$

After hitting one of the boundaries, the system experiences a different behavior depending on the barrier which is hit.

$$q(t) = \begin{cases} q_1, & \text{if} \quad b = b_1, \\ q_2, & \text{if} \quad b = b_2, \end{cases} \tag{4.7}$$

$$dY_t = \begin{cases} -a_1 \left[Y_t - c_1\right] dt + \sigma_1 dW_t, & \text{if} \quad q(t) = q_1, \\ -a_2 \left[Y_t - c_2\right] dt + \sigma_2 dW_t, & \text{if} \quad q(t) = q_2, \end{cases} \tag{4.8}$$

Thus, our system can adopt two different behaviors and as a result it has two different asymptotic distributions depending on its memory set. Such, stochastic systems are known as the Ornstein-Uhlenbeck process and widely used because of its mean reversion property. Additionally, unlike the Brownian Motions, it has a stationary probability distribution. Thus, our system can evolve according to two different stationary probability distributions and revert to two different means. The solution of the model is

$$Y_t = \begin{cases} y_0 e^{-a_1 t} + c_1 \left(1 - e^{-a_1 t}\right) + \int_0^t \sigma_1 e^{a_1(s-t)} dW_s, & \text{if} \quad q(t) = q_1, \\ y_0 e^{-a_2 t} + c_2 \left(1 - e^{-a_2 t}\right) + \int_0^t \sigma_2 e^{a_2(s-t)} dW_s, & \text{if} \quad q(t) = q_2, \end{cases}$$

where y_0 is assumed to be a constant from the initial set. Thus the distribution of the system after differentiation is apparently a Gaussian distribution with possibly two distinct mean and variance values. The systems behavior will be

$$\begin{aligned} \mathbf{E}(Y_t) &= y_0 e^{-a_i t} + c_i \left(1 - e^{-a_i t}\right), \\ \mathbf{V}(Y_t) &= \frac{\sigma_i^2}{2a_i}\left(1 - e^{-2a_i, t}\right) \end{aligned}$$

where $i = 1$ if b_1 is reached first and $i = 2$ else.

CHAPTER 5

THE STOCHASTIC HYBRID SYSTEMS WITH MEMORY MODEL AND THE APPLICATION ON TUMOR GROWTH

The dynamical system of IL1-α response to tumor growth is deeply explained in Chapter 3. According to the work of Dvorkin et al. [37], this system demonstrates different levels of tumor growth and includes immune system variables according to different levels of IL1-α injection.

This chapter includes the precise description of stochastic hybrid systems with memory, an application of SHSM to the dynamical model of IL1-α response to tumor growth, simulation results and a discussion on Kuznetsov's model with Stochastic calculus.

In this chapter, we will explain the stochastic hybrid system with memory model briefly, and modify the model according to the specific problem of IL1-α response to tumor growth.

5.1 The Stochastic Hybrid Systems with Memory Model

We have mentioned about stochastic hybrid systems with memory in the previous chapter. Now we will give a precise description. There are two stochastic models in the literature which have taken attention; stochastic hybrid models due to Ghosh [44], and Bensoussan [15]. We combine these two ideas and add memory to the system by describing it as a stochastic process where the memory changes the system dynamics as it accumulates information. We use a similar notation as Bensoussan and Ghosh did as follows. Construct a Markov process (X(t),M(t)). On some set D, we have

$$x(t_i) = X(x(t_i^-), m(t_i^-), q(t_i^-), t_i), \tag{5.1}$$

$$m(t_i) = M(x(t_i^-), m(t_i^-), q(t_i^-), t_i). \tag{5.2}$$

We also have a sequence of stopping times

$$\tau_1 < \tau_2 < ... < \tau_n < ...,$$

where the values $\tau_n \uparrow \infty$ are successive stopping times. We propose, $x(t_i^-)$ is the continuous variables, $m(t_i^-)$ is the memory, $q(t_i^-)$ is the state and t_i is the time. For

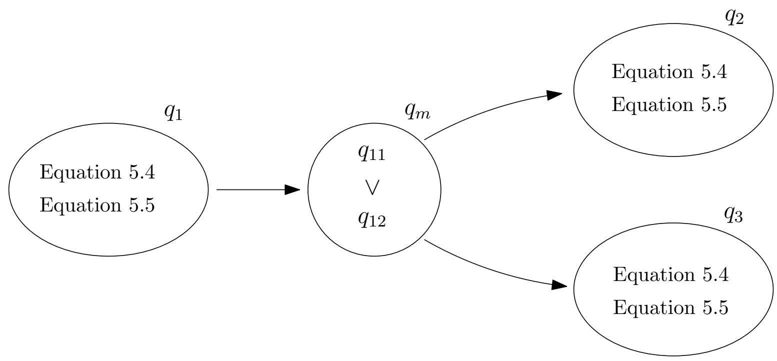

Figure 5.1: Representation of the states.

$\tau_n < t \leq \tau_{n+1}$, we have

$$\begin{aligned} dX(t) &= g_{m_i}(x(t), m(t), q(t))dt + \sigma_{m_i}(x(t), m(t), q(t))dW(t), \quad (5.3) \\ P(m(t+\delta t = j), m(t) = i, X(s), m(s), s \leq t) &= \lambda_{ij}(X(t))\delta t + 0(\delta t), i \neq j, \\ X(0) &= X_0, m(0) = 0, \\ m(t) &= \sum_{i=0}^{\infty}(M(x(t_i), m(t_i)) - m(t_i))1_{t_i \leq t}, \end{aligned}$$

where g_{m_i}, σ_{m_i} and λ_{ij} are suitable functions.

5.2 Application on the Data with SHSM, Parameter Estimation, Simulation Results

In our work, we will use the data of Dvorkin et al. [37] in order to apply our model. For instance, we have used the values of data which include Clone 2 and Clone 5 tumor diameters according to days. Clone 2 has been injected with IL1-α, whereas Clone 5 has not been. As previously mentioned according to different levels of IL1-α, different levels of tumor growth and effector cells have been observed. These effects can be seen from the Figures 5.2, 5.3 and 5.4. Moreover the precise values can be seen from the Table 5.1. In this table S.I. refers the Stimulator Index which is the ratio for immune cells (the effector cell and stimulator cells) and the tumor size has been measured in millimeters (mm). By observing the data, one can see that Clone 2 and Clone 5 is behaving similarly until Day 3. After Day 3, Stimulation Index is decreasing in Clone 5 and after Day 15 tumor size is increasing in Clone 5. For this purpose, we have designed the system by partitioning the model into 4 main states such as; first state, namely q_1, includes the behavior of both Clone 2 and Clone 5 until day 3, second state, namely q_m, include different behaviors of Clone 2 and Clone 5 until day 15, third and fourth states, q_2 and q_3, include complete different behaviors on tumor growth and S.I. values. You may see the hybrid automata representation of the model in Figure 5.1

For SHSM simulation, we have chosen Ornstein-Uhlenbeck type stochastic differential

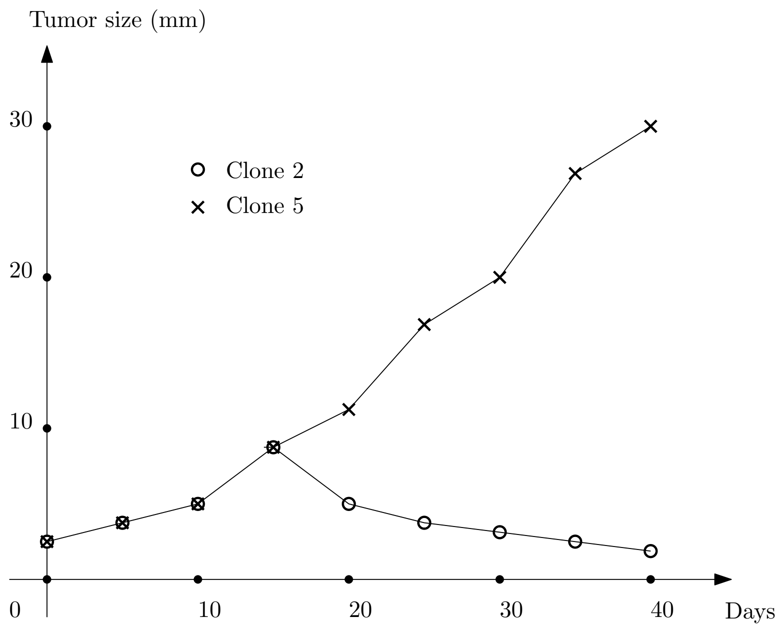

Figure 5.2: Clone 2 and Clone 5 tumor growth according to days [37].

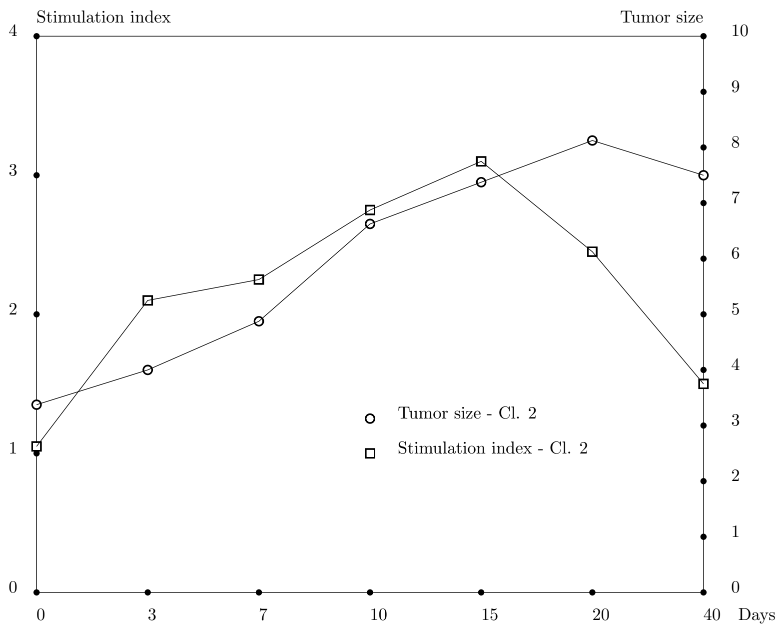

Figure 5.3: Clone 2 S.I. and tumor growth according to days [37].

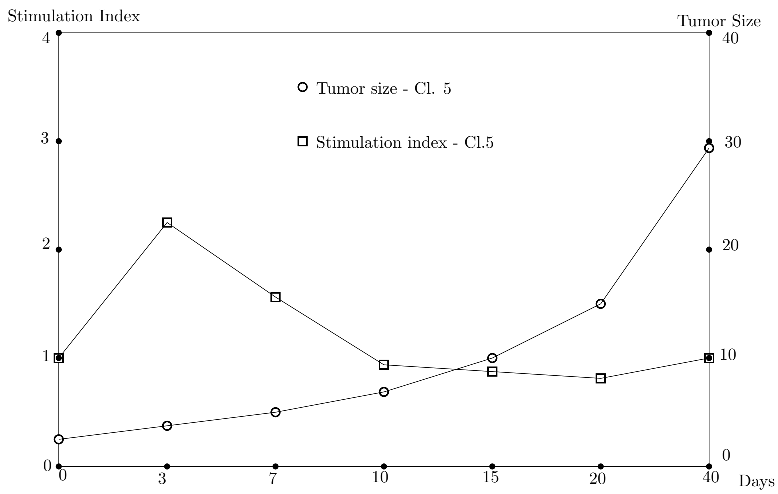

Figure 5.4: Clone 5 S.I. and tumor growth data according to days [37].

Days	Clone 2		Clone 5	
	S.I.	Tumor Size(mm)	S.I.	Tumor Size(mm)
0	1	3.05	1	3.125
3	1.988	3.7	2.129	3.75
7	2.344	4.35	1.443	4
10	2.822	6.35	0.914	5.5
15	3.011	7.345	0.914	8.5
20	3.411	6	0.886	15.125
40	3.266	3.7	0.943	29.125

Table 5.1: S.I. and Tumor Growth data of Clone 2 and Clone 5

equation and partitioned the system according to our data sets as the following;

$$dX^1(t) = [\beta_{11}^{q_k,m_i}\alpha_1^{q_k,m_i} + \beta_{12}^{q_k,m_i}\alpha_2^{q_k,m_i} - \beta_{11}^{q_k,m_i}X_t^1 - \beta_{12}^{q_k,m_i}{X_t}^2]dt + \sigma_1^{q_k,m_i}dW_t^1, \tag{5.4}$$

$$dX^2(t) = [\beta_{21}^{q_k,m_i}\alpha_2^{q_k,m_i} + \beta_{22}^{q_k,m_i}\alpha_2^{q_k,m_i} - \beta_{21}^{q_k,m_i}X_t^1 - \beta_{22}^{q_k,m_i}{X_t}^2]dt + \sigma_1^{q_k,m_i}dW_t^2. \tag{5.5}$$

Due to different memory values and different states, we have different parameter values; $\beta_{11}^{q_k,m_i}$, $\beta_{12}^{q_k,m_i}$, $\beta_{21}^{q_k,m_i}$, $\beta_{22}^{q_k,m_i}$, $\alpha_1^{q_k,m_i}$, $\alpha_2^{q_k,m_i}$, $\sigma_1^{q_k,m_i}$, $\sigma_2^{q_k,m_i}$ where $q_k \in \{q_1, q_{11}, q_{12}, q_2, q_3\}$ and $i = 1, 2, ...$ Now, let us consider a linear SDE;

$$dX_t = \alpha(t, X_t)dt + \beta(t, X_t)dW_t, \tag{5.6}$$

where

$$\alpha(t, X_t) = a_1(t)X_t + a_2(t),$$
$$\beta(t, X_t) = b_1(t)X_t + b_2(t).$$

For a general piecewise linear form, we will have a similar form, similar to the work of Gebert [41] and as described in the work of Öktem [77];

$$\alpha(t+1, X_{t+1}) = M_1^{q_k,m_i}X_t + k_1^{q_k,m_i}(t),$$
$$\beta(t+1, X_{t+1}) = M_2^{q_k,m_i}X_t + k_2^{q_k,m_i}(t),$$

where $M_1^{s(t)}$ and $M_2^{s(t)}$ are matrices and k_1 and k_2 are vectors. Then the above linear SDE can be written as;

$$dX_{t+1} = (M_1^{q_k,m_i}X_t + k_1^{q_k,m_i}(t))X_t + (M_2^{q_k,m_i}X_t + k_2^{q_k,m_i}(t))dW_t. \tag{5.7}$$

In this representation parameter values are focal points and thresholds. To find these parameters, there are works in the literature [87],[77]. For the Ornstein-Uhlenberg process with memory, we use a similar form done above. By replacing above equations in the two dimensional Ornstein-Uhlenberg process we obtain;

$$\begin{bmatrix} dX_1 \\ dX_2 \end{bmatrix} = \left[\begin{bmatrix} \beta_{11}^{q_k,m_i} & \beta_{12}^{q_k,m_i} \\ \beta_{21}^{q_k,m_i} & \beta_{22}^{q_k,m_i} \end{bmatrix}\begin{bmatrix} \alpha_1^{q_k,m_i} \\ \alpha_2^{q_k,m_i} \end{bmatrix} - \begin{bmatrix} \beta_{11}^{q_k,m_i} & \beta_{12}^{q_k,m_i} \\ \beta_{21}^{q_k,m_i} & \beta_{22}^{q_k,m_i} \end{bmatrix}\begin{bmatrix} X_1 \\ X_2 \end{bmatrix}\right]dt + \begin{bmatrix} \sigma_1 dW_1 \\ \sigma_2 dW_2 \end{bmatrix}, \tag{5.8}$$

or we can write;

$$dX = (N^{q_k,m_i} - M^{q_k,m_i}X)dt + \sigma dW. \tag{5.9}$$

In the Equation 5.9, the term N^{q_k,m_i} is the focal point vector and M^{q_k,m_i} is matrix.

Moreover the memory set will include the first transition in the first state, existence of IL1-α, time and state conditions. It will include and act according to q_{11} or q_{12}. The memory set can be given as;

$$m = \{((X_1 < 2.344 \wedge X_2 < 4) \vee (X_1 \geq 2.344 \wedge X_2 \geq 4)), q_m, m(i), \theta_{IL1-\alpha}, t(i)\},$$

where $i = 1, 2$ and $\theta_{IL1-\alpha}$ indicates the existence of IL1-α variable. For our example, we have added $\theta_{IL1-\alpha}$ to the memory set.

For a stochastic process to reach states, let's say A or B, has been given by the following procedure according to Allen [3]. If $X(t)$ is a stochastic process, and a solution of the

$$dX(t) = a(X(t))dt + b(X(t))dW(t), \;\; X(0) = x,$$

and $A < x < B$. then the transition probability density function for a linear stochastic process, defined above, is a solution of the backward Kolmogorov differential equation

$$\frac{\partial p(y, x, t)}{\partial t} = a(x)\frac{\partial p(y, x, t)}{\partial x} + \frac{b^2(x)}{2}\frac{\partial^2 p(y, x, t)}{\partial x^2}. \tag{5.10}$$

If $Q(x, t)$ is the probability that the process does not reach states, let's say, A or B in time $[0, t]$, then we have [3]

$$Q(x, t) = \int_A^B p(y, x, t)dy.$$

Let $T(x)$ be the random variable referring the time for the stochastic process to reach states A or B and let $p_t(x, t)$ be the probability density function of it. The expected time can be foundnd by the following integral [3]:

$$E(T(x)) = \int_0^\infty Q(x, t)dt. \tag{5.11}$$

5.3 Simulation

For simulation and parameter estimation we have used SDE toolbox for MATLAB [86]. Besides parameter values, we are able to find Monte-Carlo statistics results including process mean, process variance, process median, confidence interval for the trajectories, process skewness, process kurtosis, process moments by using this toolbox. All of these results exist in the appendix.

Since we find parameter values, the equations for each state can be given. To test the model we have kept some data values and modeled according to these data values. You may see the Figures 5.10 and 5.11.

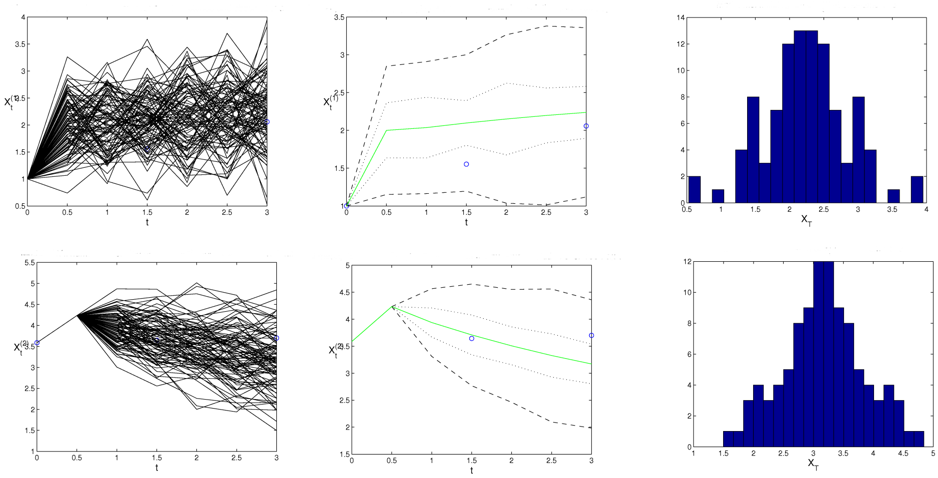

Figure 5.5: State q_1 simulation results for Ornstein-Uhlenberg process. First row gives the numerical solution over 100 trajectories and observations, empirical mean, 95 percent CI, q1, q3 quartiles of the numerical solution over 100 trajectories from left to right for X_1 and the second row gives the same for X_2

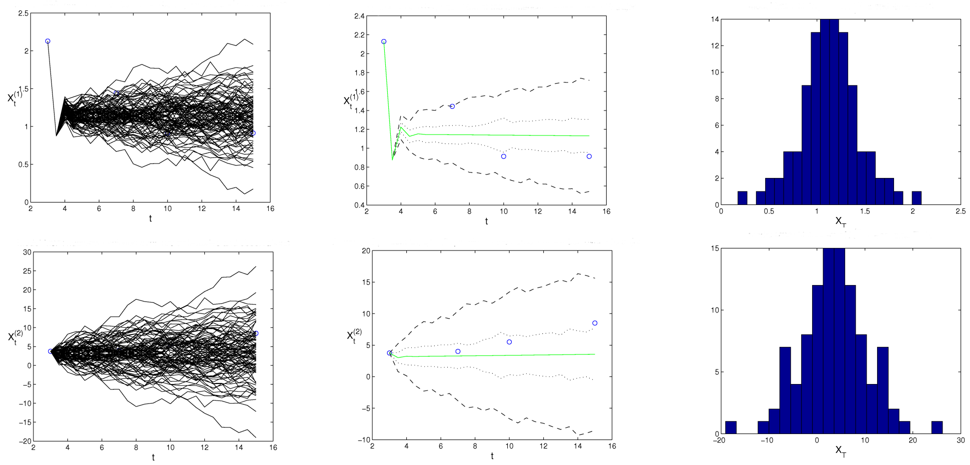

Figure 5.6: State q_{11} simulation results for Ornstein-Uhlenberg process. First row gives the numerical solution over 100 trajectories and observations, empirical mean, 95 percent CI, q1, q3 quartiles of the numerical solution over 100 trajectories from left to right for X_1 and the second row gives the same for X_2

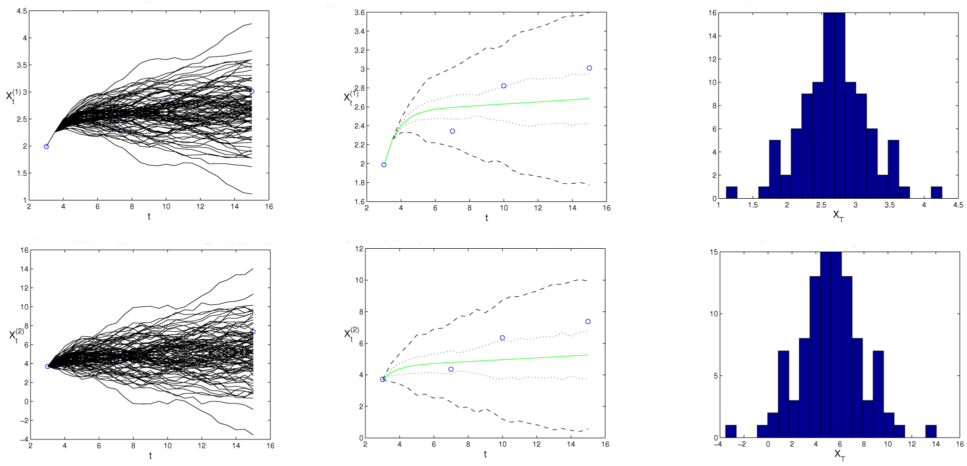

Figure 5.7: State q_{12} simulation results for Ornstein-Uhlenberg process. First row gives the numerical solution over 100 trajectories and observations, empirical mean, 95 percent CI, q1, q3 quartiles of the numerical solution over 100 trajectories from left to right for X_1 and the second row gives the same for X_2

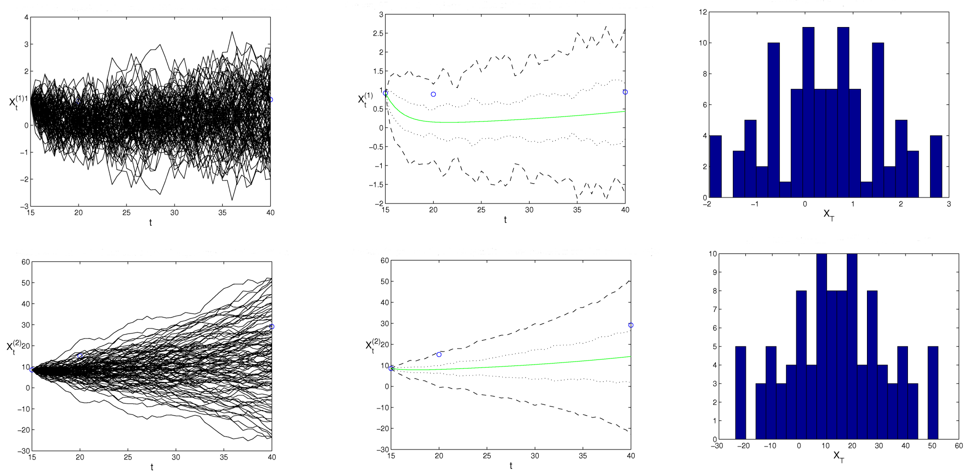

Figure 5.8: State q_2 simulation results for Ornstein-Uhlenberg process. First row gives the numerical solution over 100 trajectories and observations, empirical mean, 95 percent CI, q1, q3 quartiles of the numerical solution over 100 trajectories from left to right for X_1 and the second row gives the same for X_2

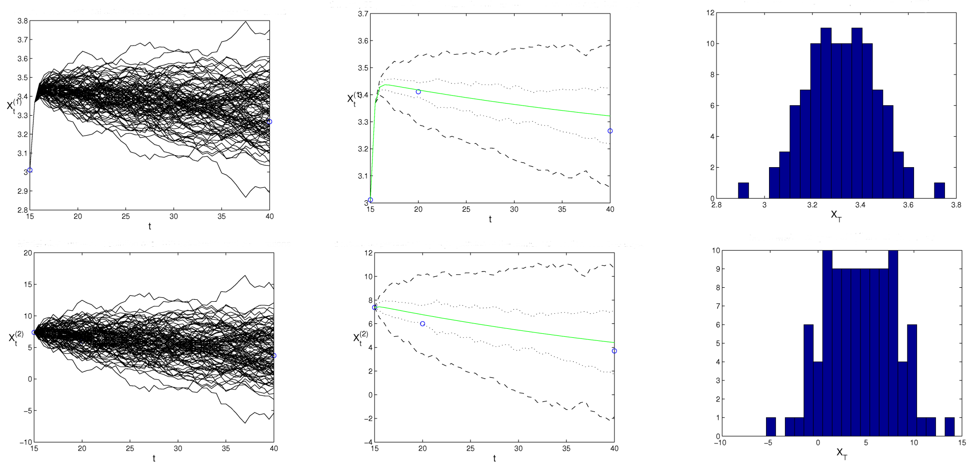

Figure 5.9: State q_3 simulation results for Ornstein-Uhlenberg process. First row gives the numerical solution over 100 trajectories and observations, empirical mean, 95 percent CI, q1, q3 quartiles of the numerical solution over 100 trajectories from left to right for X_1 and the second row gives the same for X_2

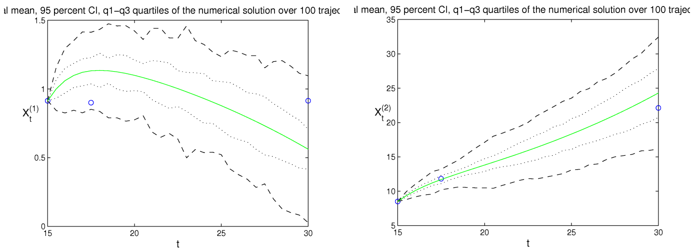

Figure 5.10: State q_2 test data values. In that state we wait the system t where we wait the system to behave like Clone 5. Simulation on the left refers to variable X_1 and simulation on the right refers variable X_2.

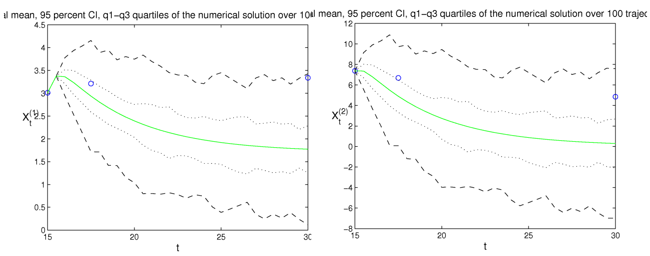

Figure 5.11: State q_3 test data values. In that state we wait the system t where we wait the system to behave like Clone 2. Simulation on the left refers to variable X_1 and simulation on the right refers variable X_2.

5.4 Kuznetsov's Model and Some Discussions

We continue with the Kuznetsov's model. His model has been investigated deeply in the previous chapter. As mentioned before his model is one of the mostly studied model in literature. Moreover, his model is used to describe the kinetics of growth and regression of the B-Lymphoma BCL_l in the spleen of mice [60]. By comparing his model with experimental data, numerical estimates of parameters describing processes that cannot be measured in vivo are derived [60]. We start with his model's normalized version [60]:

$$\frac{dx}{\tau} = \sigma + \frac{\rho xy}{\eta + y} - \mu xy - \delta x, \tag{5.12}$$

$$\frac{dy}{\tau} = \alpha y(1 - \beta y) - xy. \tag{5.13}$$

In the paper [60] parameter values are given as the following;

$$\begin{aligned} &\sigma = 0.1181,\ \rho = 1.131,\ \eta = 20.19,\ \mu = 0.00311,\ \delta = 0.3743, \\ &\alpha = 1.636,\ \beta = 2.0x10^{-3}. \end{aligned} \tag{5.14}$$

The normalized Kuznetsov model shall be turned into a stochastic differential equation system, firstly:

$$\begin{aligned} dX(t) =& \sigma + \frac{\rho X(t)Y(t)}{\eta + Y} - \mu X(t)Y(t) - \delta X(t) + \sqrt{\sigma} dW_1(t) \\ &+ \sqrt{\frac{\rho X(t)Y(t)}{\eta + Y(t)}} dW_2(t) - \sqrt{\mu X(t)Y(t)} dW_3(t) - \sqrt{\delta X} dW_4(t), \\ dY(t) =& \alpha Y(t)(1 - \beta Y(t)) - X(t)Y(t) + \sqrt{\alpha Y(t)(1 - \beta Y(t))} dW_5(t) \\ &- \sqrt{X(t)Y(t)} dW_6(t), \end{aligned} \tag{5.15}$$

where $dW_1, dW_2, dW_3, dW_4, dW_5$ and dW_6 are different Wiener processes.

For numerical solutions, Euler-Maruyama method has been applied to Equations 5.15. The following gives us the numerical representation;

$$\begin{aligned} dX_{n+1} =& X_n + \sigma + \frac{\rho X_n Y_n}{\eta + Y_n} - \mu X_n Y_n - \delta X_n + \sqrt{\sigma}\Delta W_1 + \\ &\sqrt{\frac{\rho X_n Y_n}{\eta + Y_n}} \Delta W_2 - \sqrt{\mu X_n Y_n} \Delta W_3 - \sqrt{\delta X_n} \Delta W_4, \end{aligned} \tag{5.16}$$

$$dY_{n+1} = Y_n + \alpha Y_n(1 - \beta Y_n) - X_n Y_n + \sqrt{\alpha Y_n(1 - \beta Y_n)} \Delta W_5 - \sqrt{X_n Y_n} \Delta W_6. \tag{5.17}$$

As we have simulated the model with Euler-Maruyama method, it is essential to question if Euler-Maruyama method is stable for the above equations. One can check this by considering a nonlinear test equation for SDEs of, e.g., the form

$$dX_t = f(X_t)dt + \sigma dW_t,$$

where f satisfies a one-sided dissipative Lipschitz condition. For the rest of the steps one can see [21]

As described in the Chapter 4, we can find the transition probabilities as in the following;

$$
\begin{aligned}
&Prob\{\Delta X(t) = i, \Delta Y(t) = j | (X(t), Y(t))\} = \\
&= \begin{cases}
\frac{\rho X(t)Y(t)\Delta t}{\eta + Y(t)\Delta t} + o(\Delta t) & (i,j) = (1,0), \\
\mu X(t)Y(t)\Delta t + \delta X(t)\Delta t + o(\Delta t) & (i,j) = (-1,0), \\
\alpha Y(t)\Delta t + o(\Delta t) & (i,j) = (0,1), \\
\alpha Y(t)\Delta t(1 - \beta Y(t)\Delta t) + X(t)Y(t)\Delta t + o(\Delta t) & (i,j) = (0,-1), \\
o(\Delta t) & (i,j) = (0,0).
\end{cases}
\end{aligned} \tag{5.18}
$$

Also the transition probabilities have been given in the table. Let $Z = (X, Y)$ is the random variable.

i	Change,$(\Delta Z)_i$	Probability, p_i
1	(1,0)	$\frac{\rho xy}{\eta + y}$
2	(-1,0)	$\mu xy + \delta x$
3	(0,1)	αy
4	(0,-1)	$\alpha y(1 - \beta y) + xy$

Table 5.2: Probabilities according to changes

These transition probabilities give us the probabilities of change in states. When it comes to the hitting time we propose that some of the transitions will not occur. According to the hitting time probabilities we will have the following stochastic hybrid system;

If $\tau^* = \tau_1$, then

$$
\begin{aligned}
dX(t) =& \sigma_1 + \frac{\rho_1 X(t)Y(t)}{\eta_1 + Y} - \mu_1 X(t)Y(t) - \delta_1 X(t) + \sqrt{\sigma_1} dW_1(t) \\
&+ \sqrt{\frac{\rho_1 X(t)Y(t)}{\eta_1 + Y(t)}} dW_2(t) - \sqrt{\mu_1 X(t)Y(t)} dW_3(t) - \sqrt{\delta_1 X} dW_4(t), \\
dY(t) =& \alpha_1 Y(t)(1 - \beta_1 Y(t)) - X(t)Y(t) + \sqrt{\alpha_1 Y(t)(1 - \beta_1 Y(t))} dW_5(t) \\
&- \sqrt{X(t)Y(t)} dW_6(t).
\end{aligned} \tag{5.19}
$$

If $\tau^* = \tau_2$, then

$$
\begin{aligned}
dX(t) =& \sigma_2 + \frac{\rho_2 X(t)Y(t)}{\eta_2 + Y} - \mu_2 X(t)Y(t) - \delta_2 X(t) + \sqrt{\sigma_2} dW_1(t) \\
&+ \sqrt{\frac{\rho_2 X(t)Y(t)}{\eta_2 + Y(t)}} dW_2(t) - \sqrt{\mu_2 X(t)Y(t)} dW_3(t) - \sqrt{\delta_2 X} dW_4(t), \\
dY(t) =& \alpha_2 Y(t)(1 - \beta_2 Y(t)) - X(t)Y(t) + \sqrt{\alpha_2 Y(t)(1 - \beta_2 Y(t))} dW_5(t) \\
&- \sqrt{X(t)Y(t)} dW_6(t),
\end{aligned} \tag{5.20}
$$

where $dW_1, dW_2, dW_3, dW_4, dW_5$ and dW_6 are different Wiener processes.

In our tumor-immune problem we have two different behaviors according to different hitting times in Kuznetsov's modified model. For instance, if $\tau^* = \tau_1$, we guess the system to behave like Clone 2 and then the equations will be;

$$\begin{aligned} dX(t) =& \sigma_1 - \mu_1 X(t)Y(t) - \delta_1 X(t) + \sqrt{\sigma_1} dW_1(t) - \sqrt{\mu_1 X(t)Y(t)} dW_3(t) - \sqrt{\delta_1 X} dW_4(t), \\ dY(t) =& - X(t)Y(t) - \sqrt{X(t)Y(t)} dW_6(t). \end{aligned} \tag{5.21}$$

If $\tau^* = \tau_2$, we guess the system to behave like Clone 5 and then the equations will be;

$$\begin{aligned} dX(t) =& \sigma_2 + \frac{\rho_2 X(t)Y(t)}{\eta_2 + Y} + \sqrt{\sigma_2} dW_1(t) + \sqrt{\frac{\rho_2 X(t)Y(t)}{\eta_2 + Y(t)}} dW_2(t), \\ dY(t) =& \alpha_2 Y(t)(1 - \beta_2 Y(t)) + \sqrt{\alpha_2 Y(t)(1 - \beta_2 Y(t))} dW_5(t). \end{aligned} \tag{5.22}$$

You may see the graph representation of the states in Figure 5.12. In this model, we

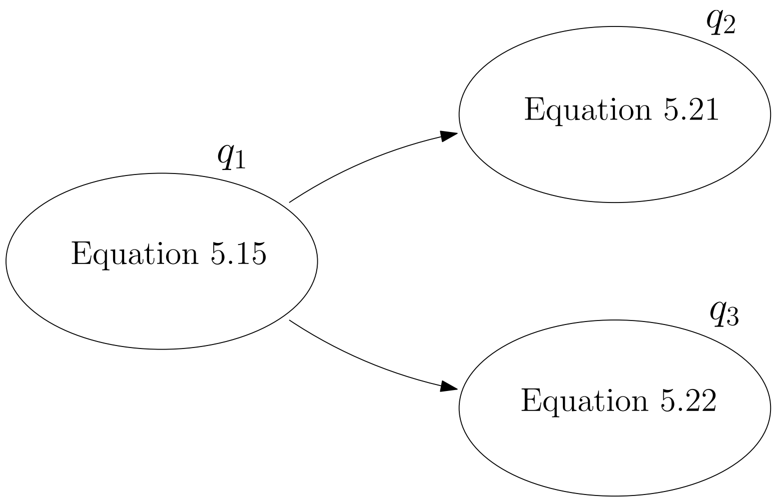

Figure 5.12: Representation of the states for Kuznetsov's modified model.

will have the memory set as in the following;

$$m_= \{((X_1 < 2.344 \wedge X_2 < 4) \vee (X_1 \geq 2.344 \wedge X_2 \geq 4)), q_1, m(i), \theta_{IL1-\alpha}, \tau\},$$

where $\tau \in \{\tau_1, \tau_2\}$ and $\theta_{IL1-\alpha}$ is again a variable controlling the existence of $IL1 - \alpha$

We have also simulated Kuznetsov's stochastic model. You may see the Figures 5.13 and 5.14.

By the same way as we do in the previous model, we can find the expected hitting times. If $Q(x, t)$ is the probability that the process does not reach states, let us say, A or B in time $[0, t]$, then we have [3]

$$Q(x, t) = \int_A^B p(y, x, t) dy$$

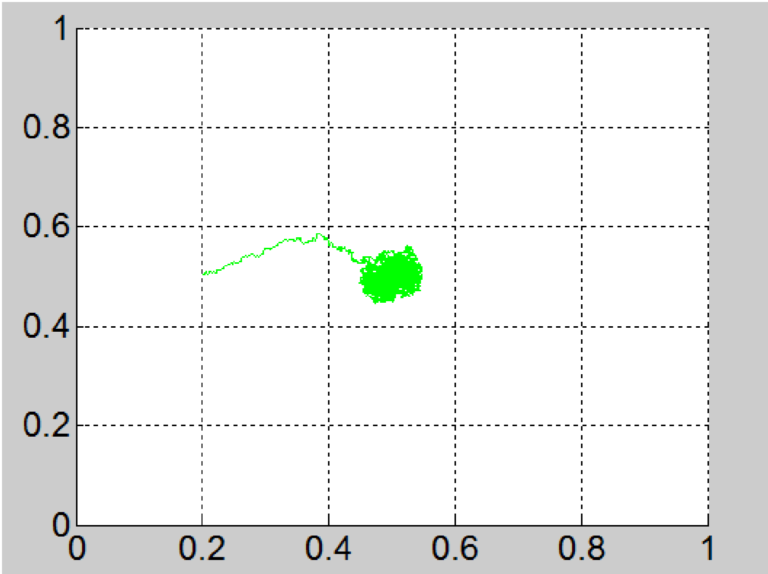

Figure 5.13: Kuznetsov's Model with Stochastic Calculus (phase plane)

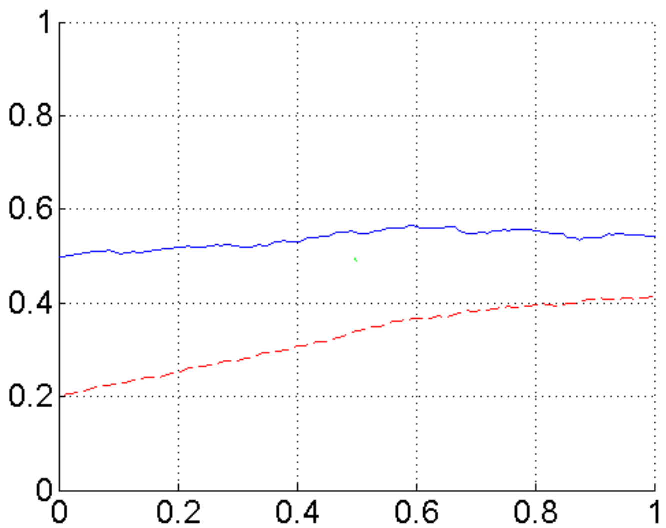

Figure 5.14: Kuznetsov's Model with Stochastic Calculus (x and y variables)

Let $T(x)$ be the random variable referring the time for the stochastic process to reach states A or B and $p_t(x,t)$ is the probability density function of it. Expected time can be find as follows [3]:

$$E(T(x)) = \int_0^\infty Q(x,t)dt. \tag{5.23}$$

We have two models with memory. One is piecewise linear and the other one is a modified model of Kuznetsov. They both model the same tumor-immune dynamics described in Dvorkin's paper.

CHAPTER 6

MEMORY HYBRID AUTOMATA

In this chapter, we will give some basic information about automata theory and observe memory hybrid automata in the sense of reachability and decidability. This Chapter of the thesis, is a joint work with Carla Piazza and Alberto Cassagrande.

6.1 Definitions

Given a set S, we write $\mathcal{P}(S)$ and $\mathcal{P}_f(S)$ to denote the *power set* of S (i.e., the set of all subsets of S) and the set of the finite cardinality subsets of S (i.e., $\mathcal{P}_f(S) \stackrel{\text{def}}{=} \{s | s \in \mathcal{P}(s) \wedge |s| \in \mathbb{N}\}$), respectively. By using the expression *finite power set* of S, we mean the set $\mathcal{P}_f(S)$.

We use the notation X and $\mathbf{X}$, respectively, to denote continuous variables and tuples of continuous variables.

6.1.1 Hybrid Automata

Definition 6.1 (Hybrid Automaton - Syntax)**.** A *hybrid automaton* of dimension $\mathrm{dims}(H)$ is a tuple $H = \langle \mathcal{Q}, \mathcal{E}, \mathbf{X}, T, M, \mathcal{F}, Inv, Act, Res \rangle$ where:

$\mathcal{Q}$ is a finite set of *locations*

$\mathcal{E} \subseteq \mathcal{Q} \times \mathcal{Q}$ is a set of *edges*

$\mathbf{X}$ is a vector of continuous *variables* whose domain is $\mathbb{X} = \mathbb{R}^{\mathrm{dims}(H)}$

T is the *time variable*. It contains the elapsed time from the begin of the computation and its domain is $\mathbb{T} = \mathbb{R}_{\geq 0}$

M is the automaton *memory* and takes values in $\mathbb{M} \subseteq \mathcal{P}_f(\mathbb{T} \times \mathbb{X} \times \mathcal{Q})$

$\mathcal{F} : (\mathcal{Q} \times \mathbb{M}) \mapsto (\mathbb{X} \mapsto \mathbb{X})$ is the *dynamics* and associates a vector field to each possible location and memory value

$Inv : (\mathcal{Q} \times \mathbb{M}) \mapsto \mathcal{P}(\mathbb{X})$ is the *invariant* which rules the valid values for the continuous variables in each locations

$Act : (\mathcal{E} \times \mathbb{M}) \mapsto \mathcal{P}(\mathbb{X})$ is the *activation*. The automaton are enabled to cross an edges in a particular memory condition only if the values of continuous variable are included into the region indicated by the activation itself

$Res : (\mathcal{E} \times \mathbb{M}) \mapsto (\mathbb{X} \mapsto \mathcal{P}(\mathbb{X}))$ is the *reset*. By crossing an edge, the continuous variable values are updated according it.

Let m be the memory value $\{\langle t_0, x_0, q_0\rangle, \ldots, \langle t_l, x_l, q_l\rangle\}$ where $t_{i-1} \leq t_i$ for all $i \in [1, l]$, we write $\overline{m_i}$ and m_i, with $i \leq l$, to mean the tuple $\langle t_i, x_i, q_i\rangle$ and the set $\{\langle t_0, x_0, q_0\rangle, \ldots, \langle t_i, x_i, q_i\rangle\}$, respectively.

Definition 6.2 (Hybrid Automaton State)**.** A *state* of H is a point of the state space $\mathbb{S} \subseteq \mathcal{Q} \times \mathbb{M} \times \mathbb{X} \times \mathbb{T}$.

A state $\langle q, m, x, t\rangle$, where $m = \{\langle t_0, x_0, q_0\rangle, \ldots, \langle t_l, x_l, q_l\rangle\}$ and $t_{i-1} \leq t_i$ for all $i \in [1, l]$, is said to be *admissible* if

- $t_i \leq t$ for all $i \in [0, l]$,
- $x_l \in Act(\langle q_l, q\rangle, m)$ and $x_i \in Act(\langle q_i, q_{i+1}\rangle, m_i)$ for all $i \in [0, l-1]$,
- $x \in Inv(q, m)$ and $x_i \in Inv(q_i, m_i)$ for all $i \in [0, l]$.

Since hybrid automata have a double nature, the transition systems defining their semantics contains two different transition relations: the *continuous reachability transition relation* and the *discrete reachability transition relation*.

Definition 6.3 (Hybrid Automaton - Semantics)**.** The *continuous reachability transition relation* $\xrightarrow{t}_C$ between states, with $t \geq 0$ denoting the transition elapsed time, is defined as follows:

$\langle q, m, x, t\rangle \xrightarrow{\delta}_C \langle q', m', x', t'\rangle \iff$ $q = q'$, $m = m'$, $t' = t + \delta$, and there exists a continuos $f : [0, \delta] \mapsto \mathbb{X}$ such that $f(0) = x$, $f(\delta) = x'$, $\frac{\partial f}{\partial t}(s) = \mathcal{F}(q, m)(f(s))$, and $f(s) \in Inv(q, m)$ for all $s \in \mathrm{dom}(f)$. In such a case, f is called *flow function*.

The *discrete reachability transition relation* $\xrightarrow{e}_D$ is defined as follows:

$\langle q, m, x, t\rangle \xrightarrow{e}_D \langle q', m', x', t'\rangle \iff$ $t = t'$, $e = \langle q, q'\rangle \in \mathcal{E}$, $x \in Act(e, m)$, $x' \in$ e,m(x), and $m' = m \cup \{\langle t, x, q\rangle\}$

We write $\ell \rightarrow_C \ell'$ and $\ell \rightarrow_D \ell'$ meaning respectively that there exists a $t \in \mathbb{T}$ such that $\ell \xrightarrow{t}_C \ell'$ and that there exists an $e \in \mathcal{E}$ such that $\ell \xrightarrow{e}_D \ell'$.

Definition 6.4 (Memoryless Hybrid Automaton)**.** A *memoryless hybrid automaton* is a hybrid automaton such that $\mathcal{F}$, Act, and Res do not depend on the memory value i.e., $\mathcal{F}(q,m) = \mathcal{F}(q,m')$, $Act(e,m) = Act(e,m')$, and e,m $=$ e,m' for all $m, m' \in \mathbb{M}$.

Since memory is not used during the computation of memoryless hybrid automata, we may define both syntax and semantics of any of them by avoiding the use of memory in Definitions 6.1, 6.2, and 6.3.

Building upon a combination of both continuous and discrete transitions, we can formulate the notion of *reachability*.

Definition 6.5 (Hybrid Automata - Reachability)**.** The hybrid automaton H *reaches* a state ℓ from a state ℓ' if there exists a sequence of admissible states $\ell_0, \dots, \ell_n$, with $\ell = \ell_0$ and $\ell' = \ell_n$, such that $\ell_{i-1} \to \ell_i$ holds for each $i \in [1, n]$. In such a case, we also say that ℓ' is *reachable* from ℓ in H.

The problem of deciding whether a hybrid automaton H reaches a set of states T from a second set of states S is known as the *reachability problem* of T from S over H. There exists (memoryless) hybrid automata over which the reachability problem is not decidable [4].

6.2 Decidability

Theorem 6.1. *Any hybrid automaton H with memory can be encoded into a memoryless hybrid automaton H_M which has the same reachability property.*

Proof. Sketch. The memory domain $\mathbb{M}$ has the same cardinality of $\mathbb{R}$ and there should exist a bijective function $f_e : \mathbb{M} \mapsto \mathbb{R}$. Hence, we can encode the whole memory into a single continuous variable. Let us call such a variable X_M and let X_T be a variable which stores the time elapsed during the continuous evolutions. Let H be the tuple $\langle \mathcal{Q}, \mathcal{E}, \mathbf{X}, T, M, \mathcal{F}, Inv, Act, Res \rangle$ where $\mathbf{X} = \langle X_1, \dots, X_n \rangle$. The automaton H_M is the tuple $\langle \mathcal{Q}, \mathcal{E}, \mathbf{X}', T, \mathcal{F}', Inv', Act', Res' \rangle$, where:

- $\mathbf{X}' = \langle X_M, X_T X_1, \dots, X_{\text{dims}(H)} \rangle$ and $\mathbb{X}' = \mathbb{R} \times \mathbb{R}^{\text{dims}(H)}$,
- $\mathcal{F}'(q)(x') \stackrel{\text{def}}{=} \langle 0, 1, f_1(x_M)(x), \dots, f_n(x_M))(x) \rangle$ where the two vectors x and x' are respectively $\langle x_1, \dots, x_n \rangle$ and $x' = \langle x_M, x_T, x_1, \dots, x_n \rangle$ and the f_i functions are such that $\mathcal{F}(q, f_e^{-1}(x_M)) = \langle f_1(x_M), \dots, f_n(x_M) \rangle$,
- $Inv'(q) \stackrel{\text{def}}{=} \bigcup_{m \in \mathbb{M}} (\{f_e(m)\} \times \mathbb{T} \times Inv(q,m))$,
- $Act'(e) \stackrel{\text{def}}{=} \{\langle x_M, x_T, x_1, \dots, x_n \rangle | \langle x_1, \dots, x_n \rangle \in Act(e, f_e^{-1}(x_M))\}$
- $Res'(e)(\langle x_M, x_T, x_1, \dots, x_n \rangle) \stackrel{\text{def}}{=} \langle x'_M, x_T, f_1(x_M)(x_1), \dots, f_n(x_M)(x_n) \rangle$ with $x = \langle x_1, \dots, x_n \rangle$, $e = \langle q, q' \rangle$, e,$\text{f}_e^{-1}(x_M) = \langle f_1(x_M), \dots, f_n(x_M) \rangle$, and $x'_M \stackrel{\text{def}}{=} f_e(f_e^{-1}(x_M) \cup \{\langle x_T, x, q \rangle\})$.

The proof can be finished by showing $\langle q, m, x, t\rangle \xrightarrow{\delta}_C \langle q', m', x', t'\rangle$ in H if and only if $\langle q, \bar{x}, t\rangle \xrightarrow{\delta}_C \langle q', \bar{x}', t'\rangle$ in H_M and $\langle q, m, x, t\rangle \xrightarrow{e}_D \langle q', m', x', t'\rangle$ in H if and only if $\langle q, \bar{x}, t\rangle \xrightarrow{e}_D \langle q', \bar{x}', t'\rangle$ in H_M with $x = \langle x_1, \dots, x_n\rangle$, $x' = \langle x'_1, \dots, x'_n\rangle$, $\bar{x} = \langle f_e(m), t, x_1, \dots, x_n\rangle$, and $\bar{x}' = \langle f_e(m'), t', x'_1, \dots, x'_n\rangle$. $\square$

We call *memoryless encoding* any function which encodes hybrid automata into memoryless hybrid automata preserving original reachability properties.

Theorem 6.2. *Let* $\mathbb{D}$ *be* $\{-1, 0, 1\}$. *For the class of hybrid automata with the following properties:*

- $\mathcal{F}(q, m)(x) = \langle 0, \dots, 0\rangle = \vec{0}$,
- $Inv(q, m) = \mathbb{D}^n$,
- $Act(e, m)$ *has either the form* $\mathbf{X} = \mathbb{D}^n$ *or* $\sum_{j=0}^{|m|} x_{i,j} = 0$ *where* $x_{i,j}$ *is the value of the* i*-th component of* x_i *and* x_i *is the continuous part of* $\overline{m_j}$,
- *e,m*$(\langle x_1, \dots, x_n\rangle) \in \mathbb{D}^n$.

The reachability problem is undecidable.

Proof. Sketch. Reduce halting problem for two counters Turing machines to reachability problem for above class. Let C_1 and C_2 be the two counters that we want to encode and val(C_i) be the value stored into the counter C_i. Each counter C_i can be encoded by the memory projection on the one continuous variables X_i. The value val(C_i) is the sum of all the $x_{i,j}$'s i.e., val$(C_i) = \sum_{j=0}^{|m|} x_{i,j}$. Let the tuple of continuous variables $\mathbf{X}$ be equal to $\langle X_1, X_2\rangle$. The computation always begins with the continuous assignment $\mathbf{X} = \langle 0, 0\rangle$. Figures 6.1, 6.2, 6.3, and 6.4 depict the sets of nodes and edges which can be used to encode the steps of a 2-counter machine. The wanted 2-counter machine configuration is reached after crossing a dashed edge. Two blocks, A and B, can be composed by joining a dashed edge of A with the not-dashed edge of B. The obtained edge has, as reset, the reset of former and, as activation, the activation of the latter. The location **Halt** corresponds to the halt state of the 2-counter machine. $\square$

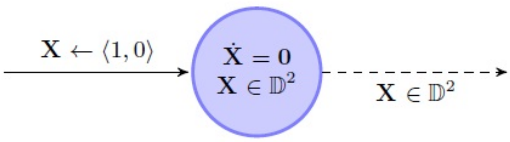

Figure 6.1: The automata component which increments the value of C_1.

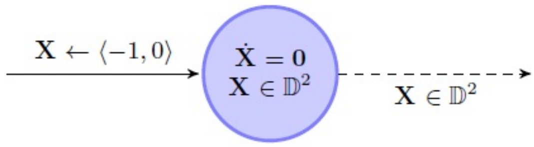

Figure 6.2: The automata component which decreases the value of C_1.

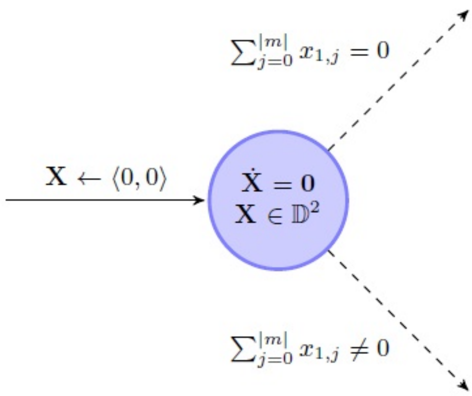

Figure 6.3: The automata component which tests whether C_1 is equal to 0.

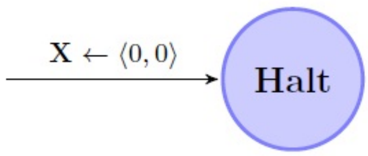

Figure 6.4: The automata component which decreases the value of C_1.

CHAPTER 7

CONCLUSION

In this work, the theory of hybrid systems with memory is explained and applied. Moreover, by investigating memory hybrid automata, we research hybrid systems with memory in the sense of logic. Firstly, a background of the system is explained and detailed by giving examples. Then, we give some preliminary material for tumor-immune dynamics and mathematical models. Hybrid Systems with memory is explained with examples both in deterministic and stochastic cases. We applied this formalization with two different approaches on data found from the literature. Hybrid systems with memory can be used in modeling dynamical systems which have regulatory processes and exhibit history dependent behaviors. Modeling gene regulatory networks by investigating their skill on memory is investigated by the application.

Complex networks, which involve memory can be modeled in a simpler way by using hybrid system with memory where the dynamics of the system is determined by the location of the state vector and the memory. The memorization capability of gene regulatory networks can be mimicked by this approach. Designing the system including memory and changing the dynamics of the system according to that phenomena, gives us a simpler analyzing approach.

In the automata sense, hybrid systems with memory are able to provide solutions, also.

This work, gives us a lot of open questions in tumor-immune dynamics, automata applications, and in the mathematical aspect which are worth to investigate. Also, it gives an idea about how one can include memory to the dynamics in a simpler way.

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APPENDIX A

APPENDIX HEADING

A.1 State q_1 Monte Carlo Simulation Results

```
ESTIMATED PARAMETER VALUES AND 95 pct. CONFIDENCE INTERVALS
------------------------------------------------------
free parameter #1): 3.848369e-01 [       NaN,        NaN]
free parameter #2): 1.076445e-01 [       NaN,        NaN]
free parameter #3): 7.519055e-02 [       NaN,        NaN]
free parameter #4): -1.220812e-01 [       NaN,        NaN]
free parameter #5): 1.239746e-01 [       NaN,        NaN]
free parameter #6): -2.870906e-02 [       NaN,        NaN]
free parameter #7): -4.440892e-16 [       NaN,        NaN]
free parameter #8): 9.816838e-02 [       NaN,        NaN]


CONSTANT PARAMETER VALUES
------------------------------------------------------
constant parameter #1): 1
constant parameter #2): 3.587500e+00

-------------------------------------------------------------------------------------------------
-------------------------- MONTE-CARLO STATISTICS FOR X_T (VARIABLE 1) ---------------------------
-------------------------------------------------------------------------------------------------

Process mean at time 3:                                         2.030960e+00
Process variance at time 3:                                     8.687306e-04
Process median at time 3:                                       2.030960e+00
95 percent confidence interval for the trajectories at time 3:  [1.973740e+00, 2.088179e+00]
Process first and third quartiles at time 3:                    [2.011870e+00, 2.050049e+00]
Process skewness at time 3:                                     -1.556519e-13
Process kurtosis at time 3:                                     3.014282e+00
Process moment of order 2 at time 3:                            8.669931e-04
Process moment of order 3 at time 3:                            -3.985494e-18
Process moment of order 4 at time 3:                            2.274857e-06
Process moment of order 5 at time 3:                            -1.762772e-20
Process moment of order 6 at time 3:                            9.492631e-09
Process moment of order 7 at time 3:                            -1.037525e-22

-------------------------------------------------------------------------------------------------
-------------------------- MONTE-CARLO STATISTICS FOR X_T (VARIABLE 2) ---------------------------
-------------------------------------------------------------------------------------------------

Process mean at time 3:                                         3.490043e+00
Process variance at time 3:                                     3.163216e-02
Process median at time 3:                                       3.490043e+00
95 percent confidence interval for the trajectories at time 3:  [3.143044e+00, 3.837043e+00]
Process first and third quartiles at time 3:                    [3.365109e+00, 3.614978e+00]
Process skewness at time 3:                                     1.179298e-14
Process kurtosis at time 3:                                     2.783211e+00
Process moment of order 2 at time 3:                            3.156890e-02
Process moment of order 3 at time 3:                            6.634634e-17
Process moment of order 4 at time 3:                            2.784863e-03
Process moment of order 5 at time 3:                            9.946984e-18
Process moment of order 6 at time 3:                            3.724400e-04
Process moment of order 7 at time 3:                            1.903168e-18
```

A.2 State q_{11} Monte Carlo Simulation Results

```
ESTIMATED PARAMETER VALUES AND 95 pct. CONFIDENCE INTERVALS
```

```
-------------------------------------------------------
free parameter #1): 7.606058e-01 [   0.76061,    0.76061]
free parameter #2): 3.443907e+00 [    3.4439,     3.4439]
free parameter #3): 4.863642e-01 [   0.48636,    0.48636]
free parameter #4): -6.936335e-01 [  -0.69363,   -0.69363]
free parameter #5): 2.667027e+00 [     2.667,      2.667]
free parameter #6): -3.069335e-01 [  -0.53151,  -0.082359]
free parameter #7): 1.652102e-01 [   0.16521,    0.16521]
free parameter #8): 7.763909e-01 [   0.77639,    0.77639]

CONSTANT PARAMETER VALUES
-------------------------------------------------------
constant parameter #1): 2.129000e+00
constant parameter #2): 3.750000e+00

----------------------------------------------------------------------------------------------------
-------------------------- MONTE-CARLO STATISTICS FOR X_T (VARIABLE 1) ---------------------------
----------------------------------------------------------------------------------------------------

Process mean at time 15:                                          -1.414615e+00
Process variance at time 15:                                      1.491077e+00
Process median at time 15:                                        -1.414615e+00
95 percent confidence interval for the trajectories at time 15:  [-3.718877e+00, 8.896466e-01]
Process first and third quartiles at time 15:                     [-2.189481e+00, -6.397495e-01]
Process skewness at time 15:                                      1.242962e-16
Process kurtosis at time 15:                                      2.767709e+00
Process moment of order 2 at time 15:                             1.476166e+00
Process moment of order 3 at time 15:                             2.263120e-16
Process moment of order 4 at time 15:                             6.153472e+00
Process moment of order 5 at time 15:                             6.749783e-15
Process moment of order 6 at time 15:                             3.639590e+01
Process moment of order 7 at time 15:                             1.189753e-13

----------------------------------------------------------------------------------------------------
-------------------------- MONTE-CARLO STATISTICS FOR X_T (VARIABLE 2) ---------------------------
----------------------------------------------------------------------------------------------------

Process mean at time 15:                                          2.604727e+00
Process variance at time 15:                                      6.024406e+00
Process median at time 15:                                        2.604727e+00
95 percent confidence interval for the trajectories at time 15:  [-2.146572e+00, 7.356027e+00]
Process first and third quartiles at time 15:                     [1.020924e+00, 4.188530e+00]
Process skewness at time 15:                                      -1.049841e-15
Process kurtosis at time 15:                                      2.987087e+00
Process moment of order 2 at time 15:                             5.964162e+00
Process moment of order 3 at time 15:                             -1.552369e-14
Process moment of order 4 at time 15:                             1.084118e+02
Process moment of order 5 at time 15:                             -1.200289e-12
Process moment of order 6 at time 15:                             3.004315e+03
Process moment of order 7 at time 15:                             -7.000996e-11
```

A.3 State q_{12} Monte Carlo Simulation Results

```
ESTIMATED PARAMETER VALUES AND 95 pct. CONFIDENCE INTERVALS
-------------------------------------------------------
free parameter #1): 8.584284e-01 [       NaN,        NaN]
free parameter #2): -2.027032e+00 [       NaN,        NaN]
free parameter #3): 3.187010e+00 [       NaN,        NaN]
free parameter #4): -7.508870e-01 [       NaN,        NaN]
free parameter #5): 3.803386e+00 [       NaN,        NaN]
free parameter #6): -8.999565e-01 [       NaN,        NaN]
free parameter #7): 7.105427e-14 [       NaN,        NaN]
free parameter #8): 3.083643e-01 [       NaN,        NaN]

CONSTANT PARAMETER VALUES
-------------------------------------------------------
constant parameter #1): 1.988000e+00
constant parameter #2): 3.700000e+00

----------------------------------------------------------------------------------------------------
-------------------------- MONTE-CARLO STATISTICS FOR X_T (VARIABLE 1) ---------------------------
----------------------------------------------------------------------------------------------------

Process mean at time 15:                                          2.385032e+00
Process variance at time 15:                                      1.244122e-01
Process median at time 15:                                        2.385032e+00
95 percent confidence interval for the trajectories at time 15:  [1.707513e+00, 3.062552e+00]
Process first and third quartiles at time 15:                     [2.119646e+00, 2.650418e+00]
Process skewness at time 15:                                      -2.134269e-15
Process kurtosis at time 15:                                      2.129957e+00
Process moment of order 2 at time 15:                             1.231681e-01
Process moment of order 3 at time 15:                             -9.365772e-17
```

```
Process moment of order 4 at time 15:                          3.296832e-02
Process moment of order 5 at time 15:                          -3.993984e-17
Process moment of order 6 at time 15:                          1.184751e-02
Process moment of order 7 at time 15:                          -1.997568e-17

-----------------------------------------------------------------------------------------------
------------------------- MONTE-CARLO STATISTICS FOR X_T (VARIABLE 2) --------------------------
-----------------------------------------------------------------------------------------------

Process mean at time 15:                                       4.463245e+00
Process variance at time 15:                                   2.252225e+00
Process median at time 15:                                     4.463245e+00
95 percent confidence interval for the trajectories at time 15: [1.551817e+00, 7.374673e+00]
Process first and third quartiles at time 15:                  [3.305425e+00, 5.621065e+00]
Process skewness at time 15:                                   -1.051096e-15
Process kurtosis at time 15:                                   2.130050e+00
Process moment of order 2 at time 15:                          2.229703e+00
Process moment of order 3 at time 15:                          -3.552714e-15
Process moment of order 4 at time 15:                          1.080472e+01
Process moment of order 5 at time 15:                          -2.179257e-14
Process moment of order 6 at time 15:                          7.062191e+01
Process moment of order 7 at time 15:                          -9.436271e-14
```

A.4 State q_2 Monte Carlo Simulation Results

```
ESTIMATED PARAMETER VALUES AND 95 pct. CONFIDENCE INTERVALS
-----------------------------------------------------
free parameter #1): -1.285206e+00 [   -1.2852,    -1.2852]
free parameter #2): 4.722008e-01 [   -4.3773,     5.3217]
free parameter #3): 1.091098e+00 [    1.0911,     1.0911]
free parameter #4): 1.119245e-01 [   0.11192,    0.11192]
free parameter #5): -8.980802e-01 [   -2.3447,    0.54854]
free parameter #6): 1.896609e+00 [    1.8966,     1.8966]
free parameter #7): 4.863881e-01 [   0.48639,    0.48639]
free parameter #8): 4.882580e+00 [    2.1658,     7.5994]

CONSTANT PARAMETER VALUES
-----------------------------------------------------
constant parameter #1): 9.140000e-01
constant parameter #2): 8.500000e+00

-----------------------------------------------------------------------------------------------
------------------------- MONTE-CARLO STATISTICS FOR X_T (VARIABLE 1) --------------------------
-----------------------------------------------------------------------------------------------

Process mean at time 40:                                       -1.285859e+00
Process variance at time 40:                                   9.328914e-01
Process median at time 40:                                     -1.285859e+00
95 percent confidence interval for the trajectories at time 40: [-3.009734e+00, 4.380165e-01]
Process first and third quartiles at time 40:                  [-1.945348e+00, -6.263687e-01]
Process skewness at time 40:                                   -5.199673e-16
Process kurtosis at time 40:                                   2.291463e+00
Process moment of order 2 at time 40:                          9.235625e-01
Process moment of order 3 at time 40:                          -4.685141e-16
Process moment of order 4 at time 40:                          1.994229e+00
Process moment of order 5 at time 40:                          -1.652567e-15
Process moment of order 6 at time 40:                          5.869143e+00
Process moment of order 7 at time 40:                          -4.516942e-15

-----------------------------------------------------------------------------------------------
------------------------- MONTE-CARLO STATISTICS FOR X_T (VARIABLE 2) --------------------------
-----------------------------------------------------------------------------------------------

Process mean at time 40:                                       4.684024e-01
Process variance at time 40:                                   6.600899e+01
Process median at time 40:                                     4.684024e-01
95 percent confidence interval for the trajectories at time 40: [-1.414650e+01, 1.508331e+01]
Process first and third quartiles at time 40:                  [-4.968686e+00, 5.905490e+00]
Process skewness at time 40:                                   -1.907867e-17
Process kurtosis at time 40:                                   2.892773e+00
Process moment of order 2 at time 40:                          6.534890e+01
Process moment of order 3 at time 40:                          -1.023182e-14
Process moment of order 4 at time 40:                          1.260435e+04
Process moment of order 5 at time 40:                          -6.977643e-11
Process moment of order 6 at time 40:                          4.274414e+06
Process moment of order 7 at time 40:                          -6.053131e-08
```

A.5 State q_3 Monte Carlo Simulation Results

```
ESTIMATED PARAMETER VALUES AND 95 pct. CONFIDENCE INTERVALS
------------------------------------------------------
free parameter #1): 1.724526e+00 [       NaN,        NaN]
free parameter #2): 1.853089e+00 [       NaN,        NaN]
free parameter #3): 7.469868e-01 [       NaN,        NaN]
free parameter #4): 7.085931e-01 [       NaN,        NaN]
free parameter #5): 7.309582e-01 [       NaN,        NaN]
free parameter #6): 9.813817e-01 [       NaN,        NaN]
free parameter #7): 7.105427e-15 [       NaN,        NaN]
free parameter #8): 1.119457e+00 [       NaN,        NaN]

CONSTANT PARAMETER VALUES
------------------------------------------------------
constant parameter #1): 3.011000e+00
constant parameter #2): 7.375000e+00

--------------------------------------------------------------------------------------------------
------------------------- MONTE-CARLO STATISTICS FOR X_T (VARIABLE 1) ---------------------------
--------------------------------------------------------------------------------------------------

Process mean at time 40:                                        1.672971e+00
Process variance at time 40:                                    1.624704e+00
Process median at time 40:                                      1.672971e+00
95 percent confidence interval for the trajectories at time 40:  [-6.072571e-01, 3.953200e+00]
Process first and third quartiles at time 40:                   [6.777698e-01, 2.668173e+00]
Process skewness at time 40:                                    -1.356342e-16
Process kurtosis at time 40:                                    2.676510e+00
Process moment of order 2 at time 40:                           1.608457e+00
Process moment of order 3 at time 40:                           -2.808864e-16
Process moment of order 4 at time 40:                           7.065088e+00
Process moment of order 5 at time 40:                           -7.277512e-15
Process moment of order 6 at time 40:                           4.890849e+01
Process moment of order 7 at time 40:                           -1.303935e-13

--------------------------------------------------------------------------------------------------
------------------------- MONTE-CARLO STATISTICS FOR X_T (VARIABLE 2) ---------------------------
--------------------------------------------------------------------------------------------------

Process mean at time 40:                                        1.897599e+00
Process variance at time 40:                                    1.724602e+00
Process median at time 40:                                      1.897599e+00
95 percent confidence interval for the trajectories at time 40:  [-5.681222e-01, 4.363321e+00]
Process first and third quartiles at time 40:                   [1.006893e+00, 2.788305e+00]
Process skewness at time 40:                                    -1.300512e-15
Process kurtosis at time 40:                                    2.555462e+00
Process moment of order 2 at time 40:                           1.707356e+00
Process moment of order 3 at time 40:                           -2.945422e-15
Process moment of order 4 at time 40:                           7.600586e+00
Process moment of order 5 at time 40:                           -1.964762e-14
Process moment of order 6 at time 40:                           4.831541e+01
Process moment of order 7 at time 40:                           -1.743400e-13
```

CURRICULUM VITAE

PERSONAL INFORMATION

Surname, Name: Gökgöz, Nurgül
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EDUCATION

Degree	Institution	Year of Graduation
Ph.D.	Scientific Computing Institute of Applied Mathematics, METU	February 2014
M.S.	Scientific Computing Institute of Applied Mathematics, METU	August 2008
B.S.	Mathematics, METU	January 2005

PROFESSIONAL EXPERIENCE

Year	Place	Enrollment
May 2010 - Present	Grup Ortadoğu	Instructor
February 2007 - May 2010	TÜBITAK Project No : 104T133	Research Project Assistant
February 2005 - July 2006	Özel Bilisim Dersaneleri, Ankara	Instructor

FOREIGN LNAGUAGES

Turkish (native), English (fluently), French (elementary)

PUBLICATIONS

Conference Presentations

H. Öktem, A. Hayfavi, N. Çalıskan, N. Gökgöz. An Introduction of Hybrid Systems with Memory, International Workshop on Hybrid Systems Modeling, Simulation and Optimization, Koç University, Istanbul, May 14-16 2008.

N. Gökgöz. Hafızalı Hibrit Sistem Modelinin İnfluenza A Virüsü-Bağışıklık Sistemi Üzerine Uygulaması. XXIV. Ulusal Matematik Sempozyumu, Uludağ Üniversitesi, Bursa, 7 – 10 Eylül 2011.

N. Gökgöz, H. Öktem. A Case Study: An Application of Hybrid Systems with Memory on Tumor System. International Science and Technology Conference, İstanbul 2011.

Papers in the submission progress

H. Öktem, A. Hayfavi, N. Çalıskan, N. Gökgöz. An Introduction of Hybrid Systems with Memory.

N. Gökgöz, H. Öktem. Piecewise Linear Modeling of Tumor-Immune Dynamics by Stochastic Hybrid Systems with Memory.

N. Gökgöz, H. Öktem. Nonlinear Dynamics of Tumor-Immune Interactions by Stochastic Hybrid Systems with Memory Approach.

A. Cassagrande, N. Gökgöz, C. Piazza. Logics of Memory Hybrid Automata.