DEVELOPMENT OF TOOLS FOR MODELING HYBRID SYSTEMS WITH MEMORY

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AUGUST 2008

DEVELOPMENT OF TOOLS FOR MODELING HYBRID SYSTEMS WITH MEMORY

A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF APPLIED MATHEMATICS
OF
THE MIDDLE EAST TECHNICAL UNIVERSITY

BY

NURGÜL GÖKGÖZ

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE
DEGREE OF
MASTER OF SCIENCE
IN
THE DEPARTMENT OF SCIENTIFIC COMPUTING

AUGUST 2008

Approval of the Graduate School of Applied Mathematics

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ABSTRACT

DEVELOPMENT OF TOOLS FOR MODELING HYBRID SYSTEMS WITH MEMORY

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August 2008, 114 pages

Regulatory processes and history dependent behavior appear in many dynamical systems in nature and technology. For modeling regulatory processes, hybrid systems offer several advances. From this point of view, to observe the capability of hybrid systems in a history dependent system is a strong motivation. In this thesis, we developed functional hybrid systems which exhibit memory dependent behavior such that the dynamics of the system is determined by both the location of the state vector and the memory. This property was explained by various examples. We used the hybrid system with memory in modeling the gene regulatory network of human immune response to *Influenza A* virus infection. We investigated the sensitivity of the piecewise linear model with memory. We introduced how the model can be developed in future.

Keywords: piecewise linear systems, hybrid systems, memory, regulatory gene

networks, *Influenza A* virus infection.

ÖZ

HAFIZALI HİBRİT SİSTEMLERİN MODELLENMESİ İÇİN YÖNTEMLERİN GELİŞTİRİLMESİ

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Ağustos 2008, 114 sayfa

Düzenleyici süreçler ve geçmişe dayalı davranış doğadaki ve teknolojideki pek çok dinamik sistemde ortaya çıkar. Düzenleyici süreçleri düzenlemede, hibrit sistemler çeşitli ilerlemeler sunar. Bu bakımdan, hibrit sistemlerin geçmişe dayalı bir sistemde yeteneğini gözlemlemek güçlü bir motivasyondur. Bu tezde, hafızaya dayalı davranış sergileyen hibrit sistemler geliştirdik; öyle ki sistemin dinamikleri hem durum vektörünün konumu, hem de hafıza tarafndan belirlenir. Bu özellik, çeşitli örneklerle açıklandı. Bu hafızalı hibrit sistemi, *İnfluenza A* virüsü enfeksiyonuna karşı insan bağışıklık tepkisinin düzenleyici gen ağının modellenmesinde kullandık. Hafızalı parçalı doğrusal modelin duyarlılığını inceledik. İlerde modelin nasıl geliştirilebileceğini ortaya koyduk.

Anahtar Kelimeler: parçalı doğrusal sistemler, hibrit sistemler, hafıza, düzenleyici gen ağları, *İnfluenza A* virüsü enfeksiyonu.

To my family

Acknowledgments

First I would like to thank my supervisor Assist. Prof. Dr. Hakan Öktem, who has always supported me in my graduate study, for his invaluable guidance, suggestions, comments, encouragements, patience and motivation throughout this study.

I am also grateful to my co-advisor Prof. Dr. Gerhard Wilhelm Weber for his kindness and encouragement in the completion of this thesis.

I am indebted to Nilüfer, Ethem, Sedat, Ayşegül, Müşerref and Hatice for their endless support, kindness and much else.

I would especially like to thank Derya and Mustafa for their kindly assistance, valuable encouragements and infinite patience and support.

Also, the environment of IAM (Institute of Applied Mathematics) has an important place in this study.

Finally, I would like to express my deepest gratitude to my family: to my admirable father, to my lovely mother and to my dear brother for their love, unfailing support and patience.

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CHAPTER 1

INTRODUCTION

1.1 Introduction to the Work

Mathematical modeling of a dynamical system is an essential method for understanding or controlling many science and engineering problems. By constructing a mathematical model for a dynamical system, one can investigate the dynamical system with different conditions, determine the dynamical system's future development under different initial conditions or construct some control strategies so that the system can be brought to a desired state.

Because of the developments in many different areas of science, mathematical modeling of dynamical systems become much more important. From this point of view, hybrid systems are very useful, since hybrid systems are the systems constructed by both continuous and Boolean variables regulating each other [25], [28], [43]. This property allows various advantages in modeling complex processes and designing control systems. Hybrid system formalization firstly used in control application. By the study of engineering systems which contain relays and/or hysteresis, 1950's can be thought of a start of hybrid system research [37]. Due to the vast development and implementation of digital micro controllers and embedded devices, 1990's were the years that started to take people's attention [37]. With the developments of control applications like robotics, air traffic control, etc.

their use increased. During last decade, many researchers from various disciplines such as computer science, control systems engineering, and mathematics [5], [51] have performed considerable research activities on hybrid systems. Modeling [3], [7], [8], [54], reachability analysis [3], [4] ,[6] , stability and stabilization [17], [26], [29], [34], [35], [58], observability and controllability [10], [54], [59] and optimal control [9], [68] are the primarily studied issues [37]. Today, hybrid systems serve important advances for various modeling [19], [21], [43] and theoretical problems [20], [43] in nature and science. Moreover, some dynamical systems that have threshold phenomena can best be formalized by hybrid systems. By piecewise linear systems which is a subclass of hybrid systems, complex nonlinear dynamical systems can best 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 thesis, state space representation and hybrid automata representation are used.

Since many dynamical systems are history dependent [16], [30] constructing a mathematical model with memory has taken attention. Because of the usefulness and advanced features of hybrid systems, hybrid systems with memory are investigated in this thesis. The future behavior of the system depends on the state transition and the memory. The issue of this work, in the sense of memory, can be thought as "functional memory" not "initial condition memory". History dependent behavior appears in many biological systems. One of the obvious one is immune response which is also investigated in this thesis.

1.2 Explanation of the Work

In this thesis, development of tools for hybrid systems is considered. In Chapter 2, a background of the study is given. In Chapter 3, the definition of hybrid systems with memory is given and explained with two illustrative examples. In Chapter 4, a dynamical model of the human response of immune system to influenza A virus infection is explained in detail in order to compare the results with the hybrid model. In Chapter 5, an application of hybrid systems with memory to the dynamical model of human immune response to influenza A virus infection is done. In Chapter 6, sensitivity analysis of the hybrid model is investigated. In Chapter 7, future work of the model is considered and Chapter 8 is the conclusion chapter.

1.3 Aim and Importance of the Work

This thesis consists of modeling hybrid systems with memory. In this work, the use of piecewise linear systems depending on memory is investigated. Since gene networks are multi stationary and history dependent, modeling these systems by an appropriate piecewise linearity is important. By using the idea of piecewise linearity, reduced complexity is obtained. Also a more realistic model can be constructed.

This work has some important features. Firstly, complex dynamical systems which are history dependent can be modeled by hybrid systems with memory. By using hybrid system formulation complex dynamics can be reconstructed and investigated easily. Secondly, since regulatory gene networks are multi stationary, they can be divided into subsystems by the idea of state space representation and

each state transition can decide the new state's dynamics. Moreover, by analyzing the sensitivity of the hybrid model, a confident way of determining the parameter values is investigated. By applying this tool, understanding the model's behavior in response to changes in its inputs and ensuring the correct use of the model is studied.

CHAPTER 2

BACKGROUND

2.1 Dynamical Systems

Before starting, the concepts of dynamics must be well determined. Dynamics is the subject that deals with change, with systems that evolve in time [57]. The system can settle down to equilibrium, keep repeating in cycles, or do something more complicated, this is the dynamics that is to be analyzed in terms of dynamical systems. Differential equations, classical mechanics, chemical kinetics, population biology, etc., are the most probable areas to face with dynamical ideas.

2.1.1 Examples of Dynamical Systems

For detailed discussion of the examples see [14], [57], [66]. One typical example of dynamical systems is the exponential growth of a population of organisms. This system is given by the first order equation

$$\dot{x} = rx, \tag{2.1.1}$$

where x is the population at time t and r is the growth rate. This system is given by one variable, x, i.e., $n = 1$ because the current value of the population x is

enough to determine the population at any later time. Moreover, this system is linear because the differential equation (2.1.1) is linear in x.

Another typical example of dynamical systems is the swinging of a pendulum represented by the equation

$$\ddot{y} + \frac{\rho}{L} \sin y = 0, \tag{2.1.2}$$

where y is the angle of the pendulum from vertical, ρ is the acceleration due to gravity, and L is the length of the pendulum. This system's state is given by two variables: its current angle y and the angular velocity $\dot{y}$ at time t. In other words, to determine the solution uniquely the initial values of both y and $\dot{y}$ are needed. The system (2.1.2) is equivalent to the following one:

$$\begin{aligned} \dot{y}_1 &= y_2, \\ \dot{y}_2 &= -\frac{\rho}{L} \sin y_1, \end{aligned}$$

which is nonlinear.

Suppose the solution to this pendulum system is known for some particular initial conditions. Then a pair of function $y_1(t)$ and $y_2(t)$ will be obtained, representing the position and velocity of the pendulum, respectively. In an abstract space where coordinates are y_1 and y_2, the solution

$$(y_1(t), y_2(t))$$

corresponds to a point moving along a curve in this space which can be seen by the Figure (2.1).

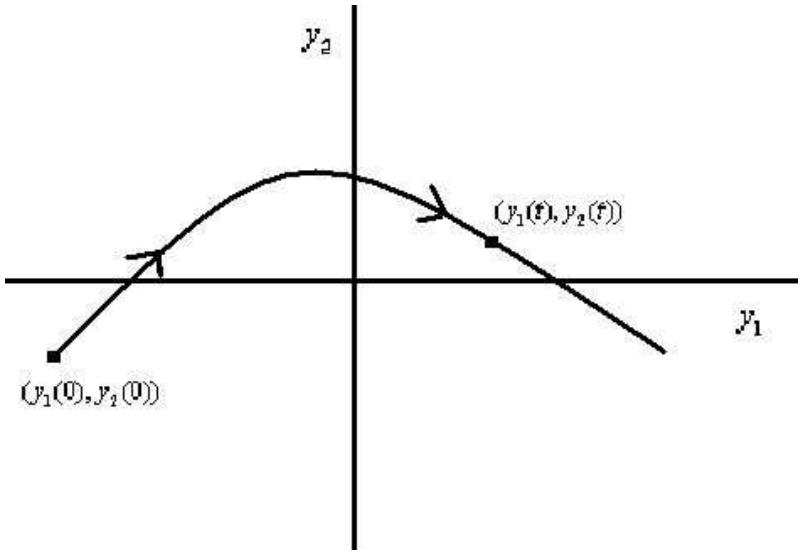

Figure 2.1: A trajectory in the phase space of the pendulum system [57].

In Figure 2.1, the curve is called as trajectory and the space is called the phase space of the system.

2.2 Hybrid Systems

Hybrid systems are some kind of dynamical systems that are formed by both continuous and Boolean variables regulating each other [25], [28], [43]. Therefore, in hybrid systems the ranges of some continuous variables can determine the Boolean state of a discrete variable where the Boolean state of a discrete variable can determine the governing differential equation of a continuous variable.

There are typical examples of hybrid systems in nature and technology. The first group includes real physical switches. Traffic flow, which is continuous, regulated by traffic lights, which is discrete, an electrical circuit protected by a

fuse and temperature controlled by a thermostat are the examples of the first group.

The second group of hybrid systems are the dynamical systems subject to threshold phenomena. In this case the dynamical system switches when a threshold exceeded. Bouncing ball and the activation or the inhibition of a gene when a corresponding protein or protein complex exceed a threshold are some examples of the second group. Hybrid systems can be represented in different ways since it is considered in various fields such as control engineering, computer engineering, logistics, automation, dynamical systems theory.

A general representation is hybrid automata. Hybrid automata will be given later in this thesis, but before, a state space representation will be given. The following equations represent a hybrid system:

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

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. An another representation can be the one that the state space is partitioned by single threshold crossings at each axis (variable). So that the above equation can be generalized as the following one:

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

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

where

- $f_s : Y \times X_e \rightarrow \mathbf{R}^n$ 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,
- $s(t) : \mathbf{R} \rightarrow [0,1]^m$ is the state vector,
- $F_B : [0,1]^{n+m+k} \rightarrow [0,1]^m$ 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.

2.2.1 Example (Bouncing Ball)

Consider a ball which is released from its center with height $x(t_0) = x_0$ at time $t = t_0$ without an initial velocity $v(t_0) = 0$. The ball will accelerate downwards until the time when it hits to the ground with

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

and

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

where g is the acceleration due to gravity. As a simple case, nonelastic collision and no mechanical properties of the ball are considered. 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 decelerate 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 considered 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. Here, the state is 1 if the binary relation between the terms is true and 0 otherwise. The state representation of the bouncing ball

example 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 different examples of dynamical systems with state space representation see [46] and for detailed discussion of this example see [43] and [38].

2.3 An Overview of The Graph Theory

A hybrid system can also be represented as a graph. In this representation, the nodes corresponds to different states of the system and the edges corresponds to possible state transitions of the system. So, to give basic definitions of the graph theory will be useful.

Definition 2.3.1. A graph G is a finite nonempty set $V(G)$ of objects called vertices (also called points or nodes) and a (possibly nonempty) set $E(G)$ of $2-$element subsets of $V(G)$ called edges (or lines). The set $V(G)$ is called the vertex set of G and $E(G)$ its edge set [15].

If $e = uv$ is an edge of a graph G, then we say that u and v are adjacent in G, and that e joins u and v (It is also possible to say that each of u and v is adjacent

to or with the other). 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 *parallel edges*. An edge that join itself is a *loop* [15].

Definition 2.3.2. A network $G = (V, E)$ is a directed graph where every edge e is assigned an initial vertex and a terminal vertex [43].

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

There are two main ways of defining a dynamical system by graph representation. First way is state space representation [46] as illustrated in the previous section. Second way is to display the cause-effect relation [43], [52], [62], [63]. A plus sign on the edge corresponds to the activation and a minus sign corresponds to the repression. For flows, capacities of arcs can be introduced.

Gene regulatory systems have various models in mathematical biology and bioinformatics with the developments in technological developments. Genes regulate the metabolism functions by activating or repressing protein synthesis. The

mechanism in a cellular system can well be 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 [55], [52]. The knowledge on the relations in gene networks are limited because of the complexity of these networks [21].

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. Boolean functions can be used with this approach [62], [63]. There are some different approaches such that NK model can be used for modeling gene regulatory networks as Kauffman used this representation [52]. In this system, connectivity can be thought as K and the nodes can be thought as N.

2.4 Discrete Event Systems

2.4.1 Automaton (State Machine)

Definition 2.4.1. A state machine or an automaton M is a $5-$tuple $M = (Q, q_0, V, I, E)$ consisting of [43]

- 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 this representation, the vertices (nodes) corresponds to the states and the edges corresponds to the possible transitions from one state to another.

2.4.2 Regular Languages

Following definitions are collected from [38] and [43].

Definition 2.4.2. A regular language is the set of all orderings of events which can happen in a system.

Definition 2.4.3. An alphabet A is a finite nonempty set of events.

Definition 2.4.4. 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

Hybrid automata is a well-defined formal representation of hybrid systems. A hybrid automaton is an automaton that includes continuous variables in V as mentioned in state machine.

Definition 2.4.5. A hybrid automaton is defined as $H = \{Q, Y, Init, f, Inv, E, G, R\}$ consisting of [12], [30], [39], [47]

- 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 $f : Q \times Y \to Y$ governing the continuous evolution,
- an invariant set (domain,subspace) for each $q \in Q$, $Inv : Q \to P(Y)$ 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 $R : E \times Y \rightarrow P(Y)$. A reset map represents possible jumps in the values of the continuous variables which takes place with a state transition.

Hybrid Time Sets

A *hybrid time set* is defined as a sequence of intervals $\tau = \{T_0, T_1, \ldots, T_N\}$ where N can be finite or infinite, such that

$$T_i = \left[\tau_i, \tau_i^{'}\right]$$

if

$$N < \infty$$

then either

$$T_N = \left[\tau_N, \tau_N^{'}\right]$$

or

$$T_N = \left[\tau_N, \tau_N^{'}\right)$$

where

$$\tau_i \leq \tau_i^{'} = \tau_{i+1}$$

for all i [43].

Hybrid Trajectory

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

Definition 2.4.6. 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 $q_i : T_i \rightarrow Q$ and $y_i : T_i \rightarrow \mathbf{R}^n$ [43].

Executions

Definition 2.4.7. A hybrid trajectory (τ, q, y) is an execution of a hybrid automaton H if the following conditions hold [43]:

- 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: $q_i : T_i \rightarrow Q$ is constant over $t \in T_i$, $y_i : T_i \rightarrow \mathbf{R}^n$ is the solution of the differential equation
  - $\frac{dy_i}{dt} = f_{q_{i(t)}}(y_i(t))$

  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*.

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 detailed discussion see [43] and [38].

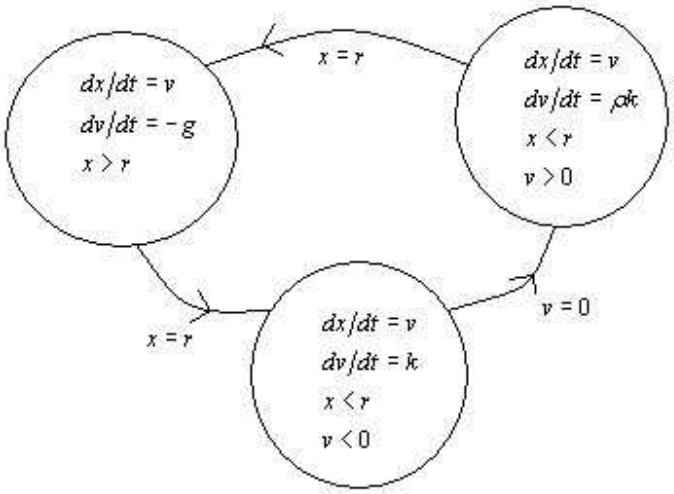

Figure 2.2: Hybrid automaton representation of bouncing ball example [38], [43].

2.5 Piecewise Linear Dynamical Systems

Let F be a functional which maps the input variable $x(t)$ to output variable $y(t)$ and let x_1, x_2 are two input variables of F with output variables y_1, y_2 respectively such that

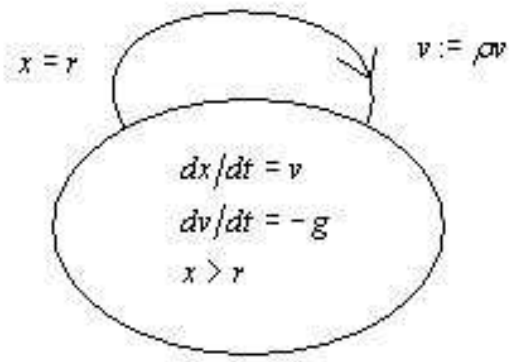

Figure 2.3: Hybrid automata representation of bouncing ball when $k >> g$ [38], [43].

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

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

The system F is linear if and only if the following condition holds [41], [42]:

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

Linear systems have many advantages in mathematical modeling [43], [52]. A linear system,

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

has analytical solution

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

and y_0, t_0 are the initial values. For some nonlinear systems piecewise linear models can be considered because of their simplicity.

Let the state space of a dynamical system be formed by k disjoint subspaces such that [43]

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

and

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

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

$$y_2 - y_0 = r\,(y_1 - y_0)\,.$$

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 piecewise linear in U_i if

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

where

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

and M is a constant matrix,

$$\text{for all } t_0 < t < t_i.$$

The system is 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 [43]

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

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

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,
- $M : s \rightarrow \mathbf{R}^{n \times n}$ is a switching matrix and the elements are determined by the state of the system,
- $k : s \rightarrow \mathbf{R}^n$ 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 well be approximated by piecewise linear systems including threshold phenomena. Critical measures, approximation accuracy and physical interpretation make piecewise linear systems suitable for use.

CHAPTER 3

HYBRID SYSTEMS WITH MEMORY

In this chapter, hybrid systems with memory is introduced and explained by two illustrative examples. Hybrid systems is explained in the previous chapter. By including a memory set in the definition, to observe the history dependent behavior in detail is aimed. 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 value but by the whole history [45]. Especially, for systems requiring history memorization capabilities like many biological systems, this is a requirement [45]. With this approach, initial state of the system can be determined by the output or, conversely, the output can be determined by investigating the initial state.

3.1 Definition

Definition 3.1.1. A Hybrid system with memory H is a collection

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

consisting of [45]

- a set of discrete states $Q = \{q_1, \ldots, q_m\}$ 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 $q \in Q$, $Inv : Q \longrightarrow P(Y)$ 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 past 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 [45]:

$$
\begin{aligned}
\frac{dx}{dt} &= A_{q(t),M(t)}\, x(t) + B_{q(t),M(t)}\, u(t) + k_{q(t),M(t)} \\
x(0) &= x_0, \quad q(0) = q_0, i = 1,\, 2, \ldots, n, \\
q(t) &= q_j \text{ if } x(t) \in X_j, \\
if \quad x(t_{0_-}) &\in X_j \text{ and } x(t_{0_-}) \notin X_j and, \\
M(t_{0_-}) &= \{M_1, \ldots, M_k\}, \quad k = 1,\, 2, \ldots, \\
\text{then} & \\
M(t_{0_+}) &= \{M(t_{0_-}), M_{k+1}\}, \\
M_{k+1} &= \{t_0, x(t_{0_-}), x(t_{0_+})\}.
\end{aligned}
$$

After introducing hybrid systems with memory, some illustrative examples will be introduced.

3.2 Examples

3.2.1 Illustrative Example 1

For illustration the following example is presented;

$Q = \{q_1, q_2, q_3, q_4\}$,

$Y = \mathbf{R}^2$,

$Inv(q_1) = \{y_1 \leq 1, y_2 \leq 1\}$,

$Inv(q_2) = \{y_1 > 1, y_2 \leq 1\}$,

$Inv(q_3) = \{y_1 \leq 1, y_2 > 1\}$,

$Inv(q_4) = \{y_1 > 1, y_2 > 1\}$.

A simplified model is used such that

$$\begin{aligned} \frac{dy}{dt} &= A_{q(t),\,M(t)}\, y(t) + k_{q(t),M(t)}, \\ A_{((0,0),0)} &= A_{((0,1),0)} = A_{(1,0),0} = A_{((1,1),0)} = \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix}, \\ k_{((1,1),0)} &= \begin{pmatrix} 5 \\ 4 \end{pmatrix}, \\ h_1 &= h_2 = 1. \end{aligned}$$

The threshold values partitions the space into four subspaces. Initial points are in subspace I. In other words $y_1(t) \leq 1$ and $y_2(t) \leq 1$. (See 3.1)

In this representation, the initial subspace of the point which is subspace I is divided into two half spaces by the line which is constructed by the initial focal point and the intersection point of the threshold which is $(1, 1)$.

Initially, the memory set is equal to $M(t) = m_0$.

The equation of the line that partitions the initial subspace, I, into half spaces can be found by solving;

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

Then, the solution is

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

As time goes to infinity, the line which also includes the origin, $(0, 0)$, is

$$4y_1(t) - 5y_2(t) = 0.$$

If the point is in subspace I and above this line, as it moves toward the initial focal point, it will cross $h_1 = 1$. Conversely, if the point is in subspace I and below this line, as it moves toward the initial focal point, it will cross $h_2 = 1$. According to these two possibilities, two systems and different rounding trajectories occur. When it crosses one of these two thresholds, according to the memory of the system the trajectories will be clockwise or counterclockwise.

Case I Below the line:

When the trajectories crosses $h_2 = 1$, the memory set will be equal to $m_1 \in M(t)$.

$m_1 \in M(t)$ and $y_2(t_{1_+}) = y_2(t_{1_-}) = 1$ conditions identify this case. The governing system of differential equations according to state space partitions is given as:

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

The initial point is $(0.1, 0.5)$. As it starts to move, it will cross threshold $y_2(t) = 1$ and initial focal point will disappear, and according to the new partitions it will enter subspace II.

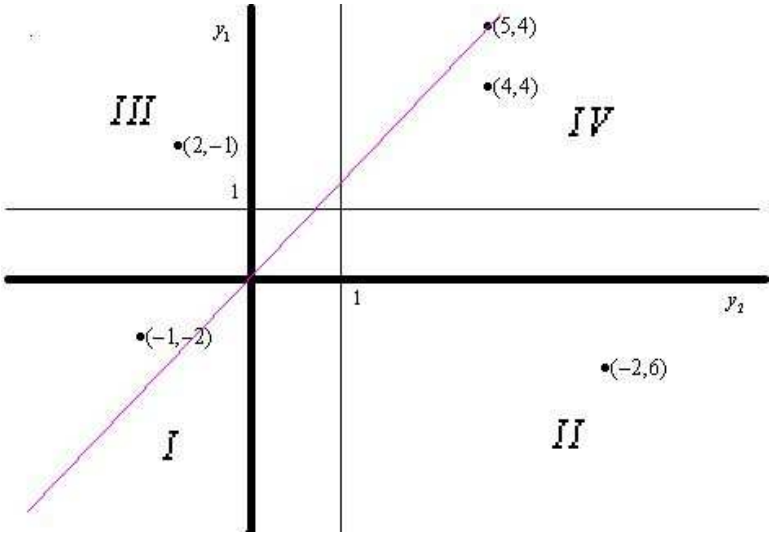

Figure 3.1: State space representation of Example 1.

The governing differential equation is

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

that has a 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 points of which has the properties of case I will converge to $(4, 4)$. During this movement, the point will cross threshold $h_1 = 1$ and will enter subspace IV. The governing differential equation of subspace IV is

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

that has a solution

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

All points in subspace IV will converge to $(2, -1)$. Then, the point will cross

$h_2 = 1$ and enter the subspace III. The governing equation of subspace III is

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

that has a 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 III will converge to $(-1, -2)$. Then the point will cross $h_1 = 1$ and enter subspace I. The governing differential equation of subspace I is

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

that has a solution

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

The representation of case I according to initial point $(0, 1, 0.5)$ is shown by the figure. In this case the rounding trajectories are clockwise.

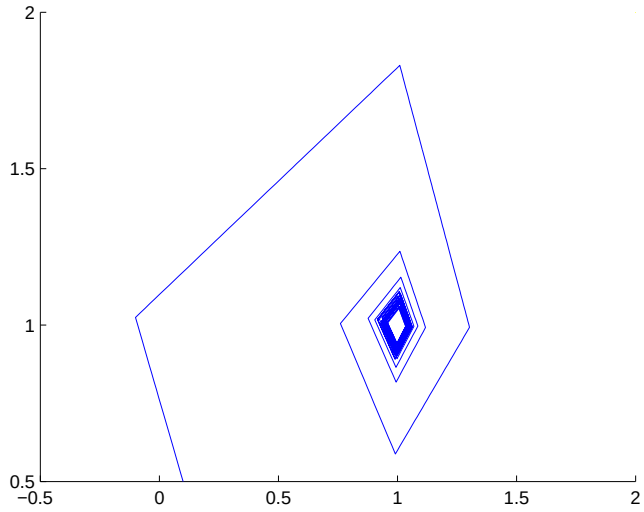

Figure 3.2: Rounding trajectories with initial values $(0.1, 0.5)$.

Case II Above the line:

When the trajectory crosses $h_1 = 1$ the memory set will be equal to $m_1 \in M(t)$. $m_1 \in M(t)$ and $y_1(t_{1_+}) = y_1(t_{1_-}) = 1$ conditions 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 because of the transition state; in other words because of memory.

The initial point is chosen as $(0.5, 0, 5)$. As it starts to move it will cross the threshold $y_1(t) = 1$ and the initial focal point will disappear, and according to the partitioning of the space it will enter subspace III.

The governing differential equation of subspace III is

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

that has a 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 points which has the properties of case II will converge to $(4, 4)$. During this movement, the point will cross threshold $h_2 = 1$ and will enter subspace IV. The governing differential equation of subspace IV is

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

that has a 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 points in subspace IV will converge to $(-2, 6)$. Then the point will cross $h_1 = 1$ and enter subspace II. The governing differential equation of subspace II is

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

that has a 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 II will converge to $(-1, -2)$ than the point will cross $h_2 = 1$ and enter the subspace I. The governing differential equation of subspace I is

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

that has a 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 II according to initial point $(0.5, 0.5)$ is shown by the figure. In this case the rounding trajectories will be counter clockwise.

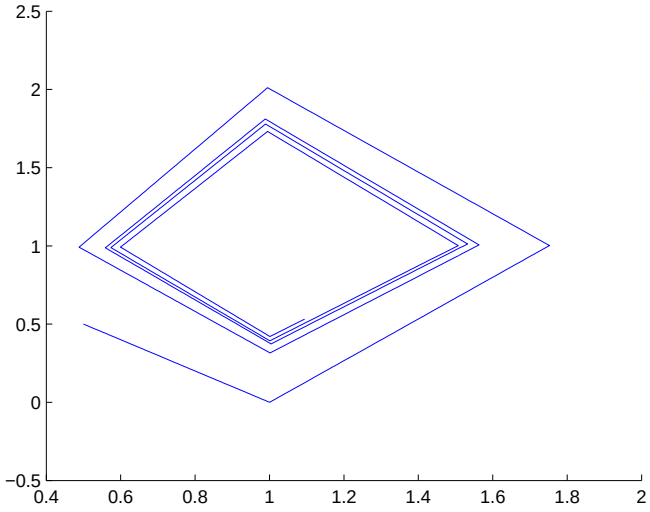

Figure 3.3: Rounding trajectories with initial values $(0.5, 0.5)$.

3.2.2 Illustrative Example 2

In this illustrative example, we tried to illustrate how the state transitions of a piecewise linear model can get slower by depending on the memory.

Again a simplified model is used:

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

the solutions of this system are given as

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

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

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

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:

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

In this example, we want that the transitions are slower but the focal points do not change. In order to satisfy these conditions, a model can be constructed such that

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

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;

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

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

$$h_1 = h_2 = 1$$

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 $b = \frac{1}{2}$.

$Q = \{q_1, q_2, q_3, q_4\}$,

$Y = \mathbf{R}^2$,

$Init = \{q = q_1, y_1, y_2 \in \mathbf{R}\}$,

$Inv(q_1) = \{y_1 \leq 1, y_2 > 1\}$,

$Inv(q_2) = \{y_1 > 1, y_2 > 1\}$,

$Inv(q_3) = \{y_1 \leq 1, y_2 \leq 1\}$,

$Inv(q_4) = \{y_1 > 1, y_2 \leq 1\}$,

If $M(t) = m_0$, then the governing differential equations are:

For subspace IV;

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

where the solution is

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

All points in that region exponentially approach to $(0, 0)$. Then the point will cross $h_1 = 1$ and enter subspace III. The governing differential equation of subspace III is

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

where the solution is

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

All points in that region exponentially approach to $(0, 2)$. Then the point will cross

$h_2 = 1$ and enter subspace I. The governing differential equation of subspace I is

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

where the solution is

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

All points in that region exponentially approach to $(2, 2)$. Then the point will cross $h_1 = 1$ and enter subspace II. The governing differential equation of subspace II is

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

where the solution is

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

All points in that region exponentially approach to $(2, 0)$.

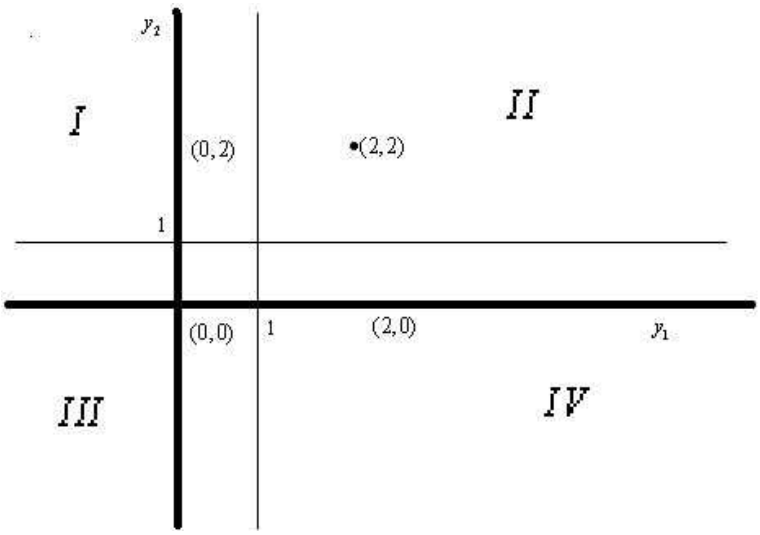

Figure 3.4: State space representation of Example 2

Case I

- 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 II

- 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 that govern the system look as follows:

For subspace III :

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

where the solution is

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

as time goes to infinity, all points in region III will exponentially approach to $(0,2)$. Then, the point will cross $h_1 = 1$ and enter subspace I. The governing system of differential equations of subspace I is

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

where the solution is

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

All points in that region exponentially approach to $(2,2)$. Then, the point will cross $h_2 = 1$ and enter subspace II. The governing differential equation of subspace IV is

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

where the solution is

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

All points in that region exponentially approach to $(2, 0)$. Then the point will cross $h_1 = 1$ and enter subspace IV. The governing differential equations of subspace IV are

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

where the solution is

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

In that case the focal points don't change but the state transition times are

slower in the second case, since

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

CHAPTER 4

DYNAMICAL MODEL OF HUMAN IMMUNE RESPONSE TO INFLUENZA A VIRUS INFECTION

In this chapter, a dynamical model of human immune response to influenza A virus infection is introduced and this chapter includes a summary of the work of Baris Hancioglu, David Swigon and Gilles Clermont [22].

4.1 Biology of Influenza

Influenza A virus (IAV) interacts with the host respiratory tract, then attacks healthy cells, binds to cell surface receptors via one of the major surface glycoproteins, HA, and converts the healthy cells to infected cells [60]. In these infected cells, the virus multiply and NA's, another glycoprotein, action causes the release of the newly synthesized virus particles [61]. Effector cells and molecules reply to the attack of IAV infection [1], [60]. The host can neutralize the free virus, kill infected cells and limit the spread of viral particles by increasing healthy cell

resistance to infection [22]. A general decline in cellular protein synthesis occurs in host because of the inhibition of the polyadenylation-site cleavage of host pre-mRNAs that is caused by the $NS1$ protein of influenza virus which shuts off host gene expression [53]. However, an activation of various host genes due to host antiviral defense, like interferon- alpha/beta, MxA, $2', 5'$-oligoadenylate synthetase, and Fas happens upon infection [53].

Antigen presenting cells (APC) are important since the human immune response can induct and amplify by them [2]. APC alerts both innate and adaptive immunity [22].

As the first response of the human immune system, the innate immunity is alerted with secreting interferon α and β (IFN) molecules by APC and infected cells [27],[32], [49], [50], [56]. MxA protein significantly contributes to IFN-mediated host defense mechanisms against influenza A virus [49]. IFN contacts with healthy cells and forms an infection resistant state from healthy cells, so that the adaptive immune system gains time to response and eliminates virus since the infection resistant state prevents the efficient spread of the virus [48].

As the second response of the human immune system the cellular component of innate immunity, effector cells (cyhotoxic T cells (CTL), or natural killer (NK)) is alerted by APC, so that the cellular component of innate immunity prevents infected cells release a mature virus by destroying them [22].

Finally, adaptive immunity is alerted by APC which activates the proliferation of virus-specific plasma cells, so that they start the production of antibodies (Abs) which binds with IAV and inactivities it [22].

4.2 The ODE Model

In the dynamical model of Hancioglu, Swigon and Clermont, three important components of the immune response are observed, namely, the interferon and cellular components of innate immunity and the adaptive immunity. These three components limits the concentration of the virus and prevents the damage to the system. Interferon immunity removes the "substrate" that virus needs for reproduction, cellular immunity removes the source of new viruses and adaptive immunity lowers the effective concentration of the virus [22].

A simplified model of population dynamics is used while modeling the human immune response against IAV infection by Hancioglu, Swigon and Clermont see Figure 4.1.

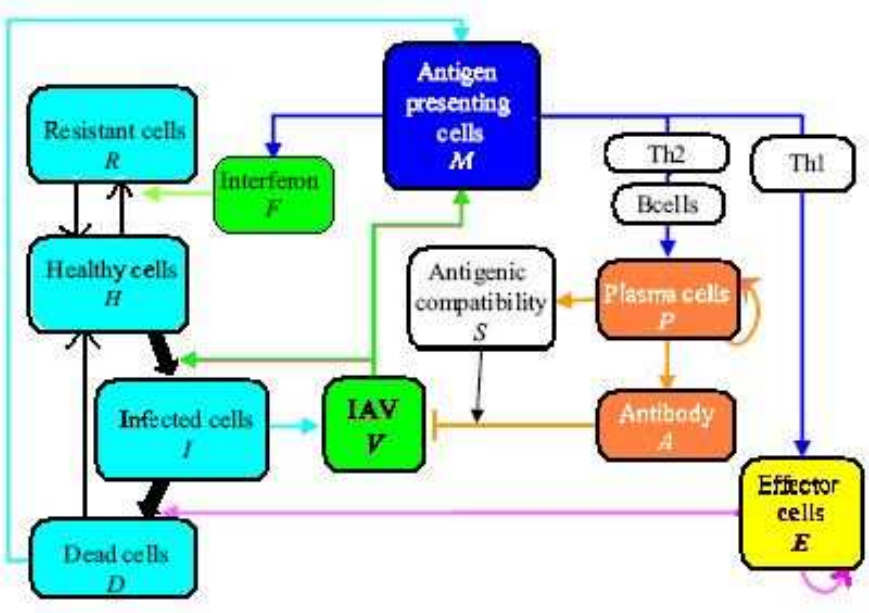

Figure 4.1: The interactions that the ODE model depends on [22].

Four states for the epithelial cells of the respiratory tract are considered: healthy (H), infected (I), dead (D) or resistant (R). It is noted that $H+I+D+R=1$, in other words; the number of elliptical cells are considered as constants.

Firstly, the healthy cells interface with the virus particles (V) and are converted to infected cells which causes the release of new virus particles till death. The activation of APC (M) is alerted by the dead cells. The reproduction of interferon α and β (F) is due to the stimulation by APC. They form a resistant state by interacting with the healthy cells. Effector cells (E) destroy infected cells and also are alerted by APC. Effector cells causes the production of plasma cells (P) and this effects the production of antibodies (A). Antibodies neutralize virus. The antigenic compatibility (S) infers the affinity between virus and antibodies. These interactions are shown with 10 differential equations and 1 algebraic equation by Hancioglu, Swigon and Clermont:

$$\frac{dV}{dt} = \gamma_V I - \gamma_{VA} SAV - \gamma_{VH} HV - \alpha_V V - \frac{\alpha_{v_1} V}{1+\alpha_{v_2} V}, \tag{4.2.1}$$

$$\frac{dH}{dt} = b_{HD} D(H+R) + a_R R - \gamma_{HV} VH - b_{HF} FH, \tag{4.2.2}$$

$$\frac{dI}{dt} = \gamma_{HV} VH - b_{IE} EI - a_I I, \tag{4.2.3}$$

$$\frac{dM}{dt} = (b_{MD} D + b_{MV} V)(1-M) - a_M M, \tag{4.2.4}$$

$$\frac{dF}{dt} = b_F M + c_F I - b_{FH} HF - a_F F, \tag{4.2.5}$$

$$\frac{dR}{dt} = b_{HF} FH - a_R R, \tag{4.2.6}$$

$$\frac{dE}{dt} = b_{EM} ME - b_{EI} IE + a_E(1-E), \tag{4.2.7}$$

$$\frac{dP}{dt} = b_{PM} MP + a_P(1-P), \tag{4.2.8}$$

$$\frac{dA}{dt} = b_A P - \gamma_{AV} SAV - a_A A, \tag{4.2.9}$$

$$\frac{dS}{dt} = rP(1-S), \tag{4.2.10}$$

$$D = 1 - H - R - I. \tag{4.2.11}$$

Equation (4.2.1) of the system infers the rate of change of virus concentration V. It indicates the production rate of the viral particle by infected cells, rate of neutralization of IAV by specific antibodies, the rate of adsorption of viral particles. The term $(\alpha_{v_1}V)/(1+\alpha_{v_2}V)$ describes the nonspecific mucociliary removal of virions which is caused by cough and other mechanism.

Equation (4.2.2) of the system describes the rate of change of healthy cells H.

Equation (4.2.3) of the system defines the time rate of change of infected cells I.

Equation (4.2.4) of the system infers that the time rate of increase of activated APC (M) is proportional to the amount of dead cells.

Equation (4.2.5) of system determines the time rate of change of interferons α and $\beta\,(F)$. APC and infected cells effects the production rate of F.

Equation (4.2.6) of the system indicates that healthy cells form resistant cells ($b_{HF}FH$) and resistant cells convert back to healthy cells ($a_R R$).

Equation (4.2.7) of the system defines the rate of change of effector cells E concentration.

Equation (4.2.8) of the system determines the activation process of plasma cells alerted by APC.

Equation (4.2.9) of the system defines the time rate of change of the concentration of antibodies A.

The variable S in the model quantifies the affinity between antibodies and virus strain in an individual. It can take value from 0 (no compatibility) to 1

(maximal compatibility). The initial value $S(0)$ of S infers the immune memory of host.

The variable D, dead cell proportion, stands for tissue damage [23] and is used to understand the severity of the disease and $D_{max} = 0.36$.

In the Figures 4.2, 4.3 and 4.4 time-courses of the viral load, proportion of respiratory epithelial cells, and the three arms of the immune response for a standard course of the disease can be found according to the initial values

$$(V, H, I, M, F, R, E, P, A, S, D) = (0.01, 1, 0, 0, 0, 0, 1, 1, 1, 0.1, 0).$$

The disease can have three different regimes: asymptomatic, typical and severe cases [22]. Figures 4.2, 4.3, 4.4 belong to the typical state with initial values

$$(V, H, I, M, F, R, E, P, A, S, D) = (0.01, 1, 0, 0, 0, 0, 1, 1, 1, 0.1, 0).$$

For asymptomatic case of the ODE model please see the Figures 4.5, 4.6 and 4.7 where the initial values are

$$(V, H, I, M, F, R, E, P, A, S, D) = (0.01, 1, 0, 0, 0, 0, 1, 1, 1, 0.3, 0).$$

The figures are obtained by our matlab m-files which are contained in the appendix part.

Table 4.1: Model parameters used for the baseline case [22].

Parameter	Value	Description	Sources
γ_V	510	Rate constant of influenza A virus (IAV) particles secretion per infected epithelial cells	[71]
γ_{VA}	619.2	Rate constant of neutralization of IAV by antibodies	[11]
γ_{VH}	1.02	Rate constant of adsorption of IAV by infected epithelial cells	[11]
α_V	1.7	Rate constant of nonspecific IAV removal	[11]
a_{V1}	100	Rate constant of nonspecific IAV removal	
a_{V2}	2300	Rate constant of nonspecific IAV removal	
b_{HD}	4	Rate constant of regeneration of epithelial cells	[31]
a_R	1	Rate constant of epithelial cells' virus resistance state decay	[40]
γ_{HV}	0.34	Rate constant of epithelial cells infected by IAV	[40]
b_{HF}	0.01	Rate constant of epithelial cells' virus resistance state induction	[11]
b_{IE}	0.066	Rate constant of epithelial cells that CTL damage	[11]
a_I	1.5	Rate constant of epithelial cells damage by cytopathicity of IAV	[71]
b_{MD}	1	Rate constant of simulation of antigen presenting cells by dead cells	[40]
b_{MV}	0.0037	Rate constant of simulation of antigen presenting cells by virus particles	[40]
a_M	1	Rate constant of stimulated state loss of antigen presenting cells	[40]
b_F	250.000	Interferon (IFN) production rate per APC	[11]
c_F	2000	Interferon (IFN) production rate per infected cell	Estimated
b_{FH}	17	Rate constant of epithelial cells that IFN binds	[11]
a_F	8	Rate constant of IFN's naturally decay	[11]
b_{EM}	8.3	Rate constant of stimulation of effector cells	[40]
b_{EI}	2.72	Rate constant of death of effector by lytic interactions with infected epithelial cells	[11]
a_E	0.4	Rate constant of death of effector cells	[40]
b_{PM}	11.5	Rate constant of plasma cells production	[40]
a_P	0.4	Rate constant of naturally death of plasma cells	[40]
b_A	0.043	Antibody production rate per plasma cells	[40]
γ_{AV}	146.2	Rate constant of antibodies which binds to IAV	[11]
a_A	0.043	Rate constant of natural death of antibodies	[40]
r	$3e-5$	Rate constant for S variable	Estimated

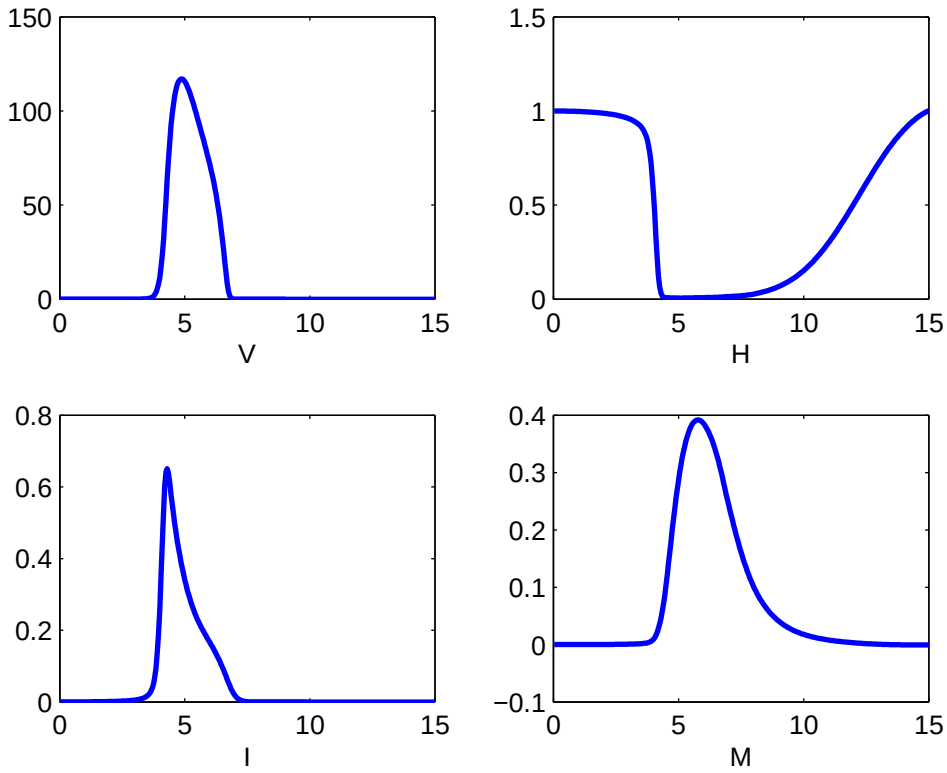

Figure 4.2: ODE model graphics of V, H, I and M variables with initial values $(V, H, I, M, F, R, E, P, A, S, D) = (0.01, 1, 0, 0, 0, 0, 1, 1, 1, 0.1, 0)$.

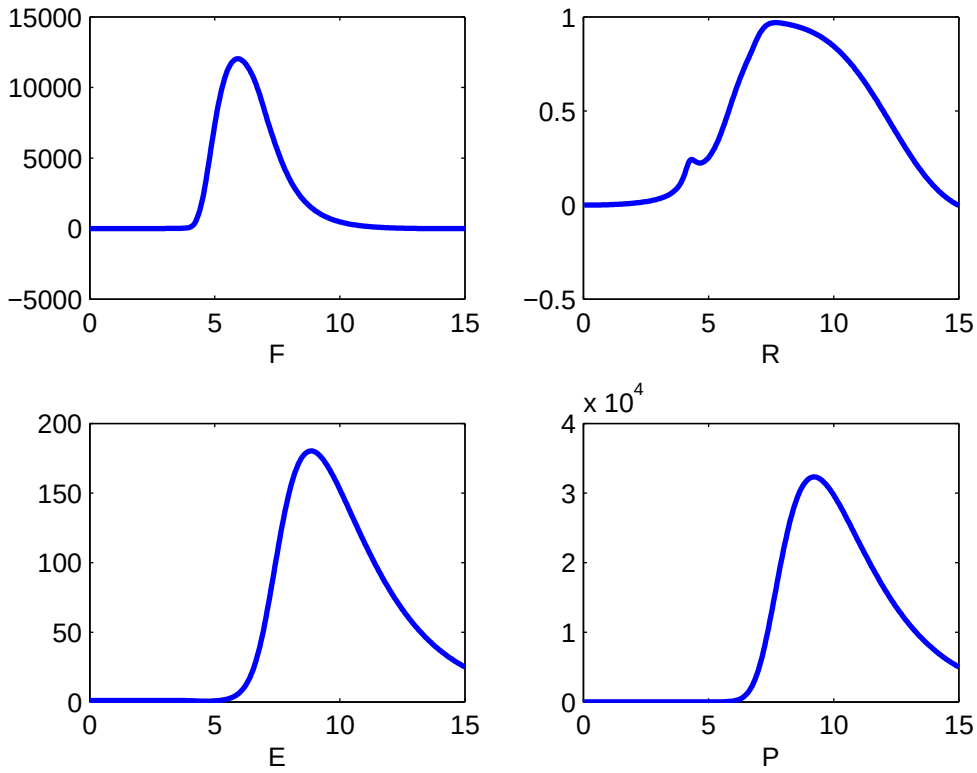

Figure 4.3: ODE model graphics of F, R, E and P variables with initial values $(V, H, I, M, F, R, E, P, A, S, D) = (0.01, 1, 0, 0, 0, 0, 1, 1, 1, 0.1, 0)$.

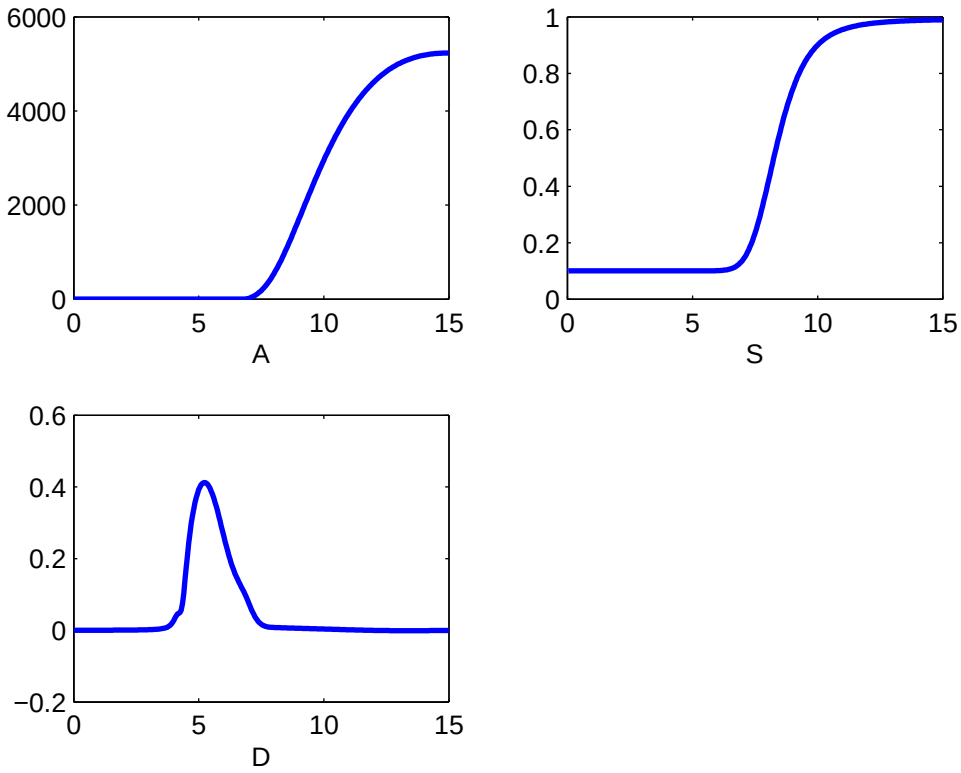

Figure 4.4: ODE model graphics of A, S and D variables with initial values $(V, H, I, M, F, R, E, P, A, S, D) = (0.01, 1, 0, 0, 0, 0, 1, 1, 1, 0.1, 0)$.

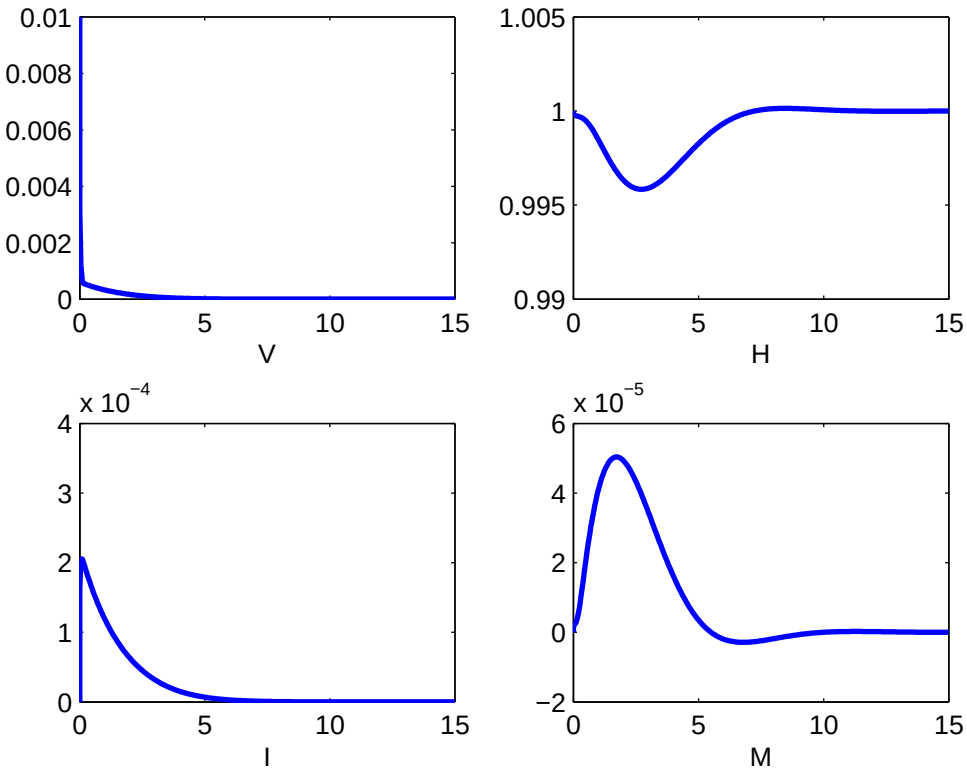

Figure 4.5: ODE model graphics of V, H, I and M variables with initial values $(V, H, I, M, F, R, E, P, A, S, D) = (0.01, 1, 0, 0, 0, 0, 1, 1, 1, 0.3, 0)$.

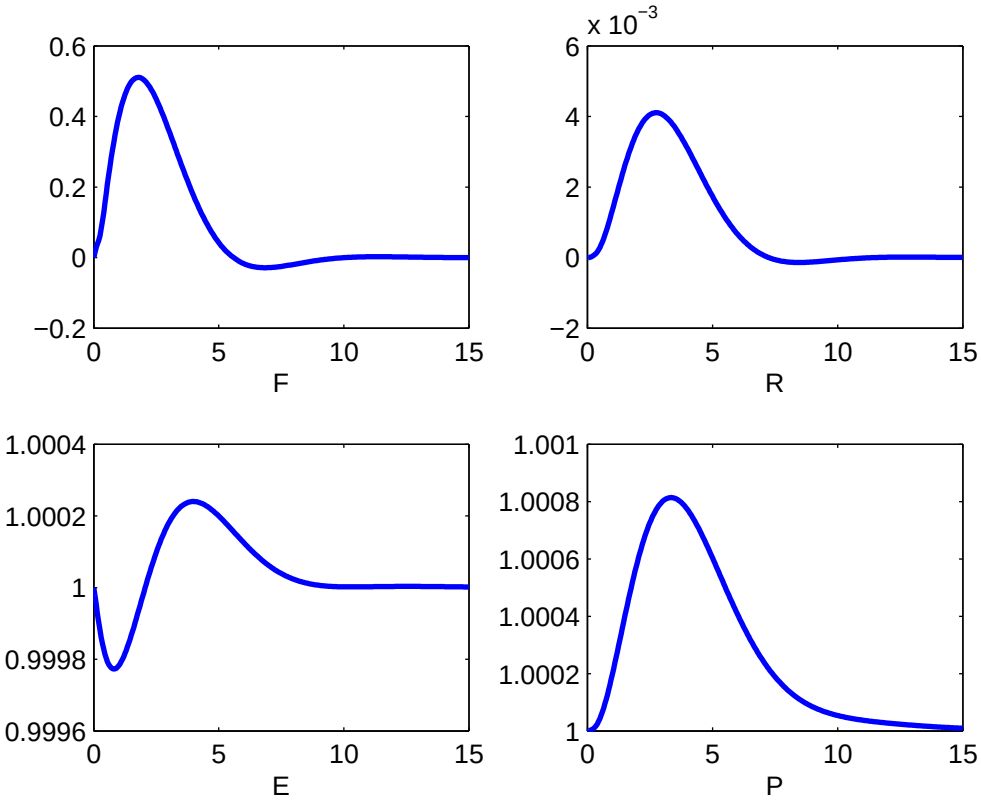

Figure 4.6: ODE model graphics of F, R, E and P variables with initial values $(V, H, I, M, F, R, E, P, A, S, D) = (0.01, 1, 0, 0, 0, 0, 1, 1, 1, 0.3, 0)$.

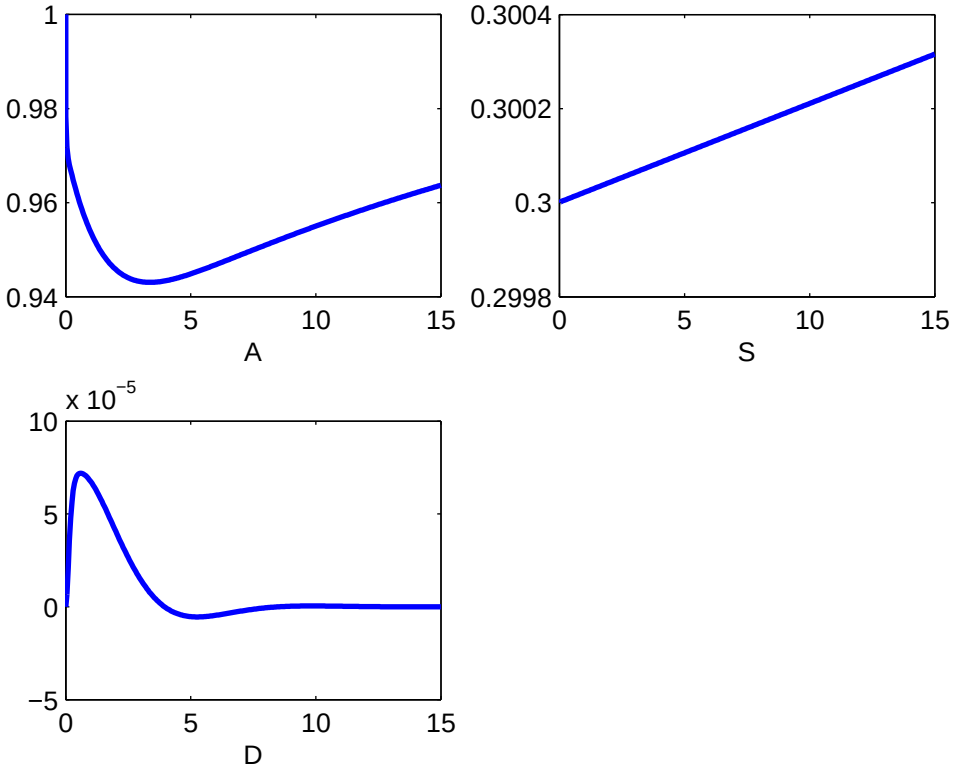

Figure 4.7: ODE model graphics of A, S and D variables with initial values $(V, H, I, M, F, R, E, P, A, S, D) = (0.01, 1, 0, 0, 0, 0, 1, 1, 1, 0.3, 0)$.

4.3 Sensitivity Analysis

In the work of Hancioglu, Swigon and Clermont, sensitivity analysis with respect to random perturbations of the model parameters is done in order to determine the robustness of the simplified uncomplicated influenza model against the perturbed parameter values and investigate which parameters effect the system more than the others. In this way, key processes and immune system mechanisms can be understood. To understand the sensitivity effect on the system, the baseline value is increased and decreased threefold for every parameter.

4.3.1 Sensitivity to Pathogen Virulence

The parameters γ_{HV} and γ_V infer the virulence and stand for the rate of infection of epithelial cells by IAV and the rate of IAV particles secretion per infected epithelial cell, respectively. The healthy cells are infected faster in the case of high virulence. Only for one parameter, namely, γ_{HV}, different disease regimes occur. For a three times higher baseline value of γ_{HV}, disease always develops independently from the initial viral load $V(0)$. For a three times less baseline value of γ_{HV}, disease can be asymptomatic, typical or severe depending on the initial viral load $V(0)$. For lower values, the disease is asymptomatic.

4.3.2 Sensitivity to Interferon Response

The interferon production rate constant and the rate constant of induction of resistant state are symbolized by b_F and b_{HF}, respectively. Disease always develops for standard values of $V(0)$ and $S(0)$ in the case of any change in the standard value of b_F. On the other hand, the high values of b_{HF} cause asymp-

tomatic disease regime. In the case of higher values of b_F or b_{HF}, the duration of disease becomes shorter. However, lower values of b_F or b_{HF} cause the increase of damage. When either of these constant is higher, less virus shedding with a longer contagious period occurs in disease. For a two times higher baseline value b_F, i.e. $b_F = 500.000$, the contagious period is about 3.5 days where for a two times smaller baseline value of b_F, i.e. $b_F = 125.000$, the contagious period is about 2.5 days.

Therefore, the difference in the length of the infectious period is important for different levels of innate immune response. When $b_F = 0$ and $b_{HF} = 0$, the disease is cleared by the adaptive immune response and the host goes into the healthy state.

4.3.3 Sensitivity to Cellular Component of Innate Immunity

The parameters b_{EM} and b_{IE} characterize the rate constant of production of effector cells and the rate constants of removal of infected cells by effectors, respectively. In the case of sufficiently large b_{EM} and b_{IE}, typical disease conditions occur and the disease is cleared without symptoms with given standard initial immunity and standard initial amount of virus. For low values of b_{EM} and b_{IE}, the symptoms last longer. When b_{EM} has high values, the maximum damage D_{max} is high and also can cause death. However, high values of b_{IE} results in lower damage of epithelial cells.

When $b_{EM} = 0$, the innate and adaptive immune responses clear the disease and the host goes into the healthy state.

4.3.4 Sensitivity to Adaptive Response

Activation of cellular and interferon components of innate immunity is faster than activation of adaptive immune response. The plasma cell production rate constant, antibody production rate constant and the rate constant of neutralization of IAV by antibodies are symbolized by the parameters b_{PM}, b_A and γ_{VA}, respectively. At sufficiently large values of these parameters, the infection is cleared with symptoms after administration of a standard inoculum. If b_A is high, the resulting maximum damage, D_{max}, is lower while the other two parameters have no effect on damage. Moreover, if b_A has high values, the contagious period becomes shorter.

The parameter γ_{VA} is only effective on the onset of the disease. On the other hand, b_{MP} is only effective on virus shedding at the peak. The system is much more sensitive to the parameter b_A.

4.4 Impact of Antigenic Distance

The impact variable S determines how much efficient the existing antibodies of the host are against the virus of the strain causing the illness. The probability of match between the existing antibodies and the antigenic structure of the viral strain is characterized by this parameter. Figure 4.8 shows that damage changes with different values of $S(0)$, the initial value of S.

In the work of Hancioglu, Swigon and Clermont $S(0)$ is chosen as 0.1 in the simulations of disease. The value S indicates the partial match of antibodies because of the organism's history of previous contacts with the virus. In the case of $S(0) = 0$, the damage is higher [69]. As $S(0)$ takes higher values, the disease

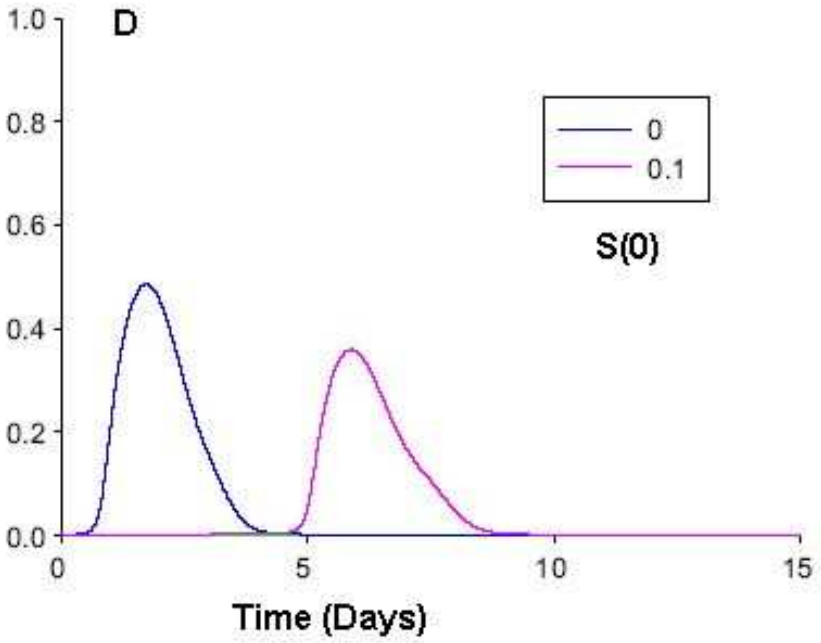

Figure 4.8: Damage for different values of $S(0)$ [22].

becomes asymptomatic [36], [70]. When $S(0)$ is chosen as equal to 0, the disease always develops no matter what the initial viral load is. In other words, the threshold for typical regime of the disease is equal to $-\infty$. If $S(0) = 0.0124$, this value becomes finite. As $S(0)$ takes higher values, the threshold for the severe regime of the disease increases. If $S(0) > 0.2$, the disease becomes asymptomatic unless $V(0) > 1$. As $S(0)$ takes higher values, the onset of the disease delays. For all values of $S(0)$, the duration of the disease does not change. On the other hand, for higher values of $S(0)$, the damage is lower and the contagious period is shorter [69].

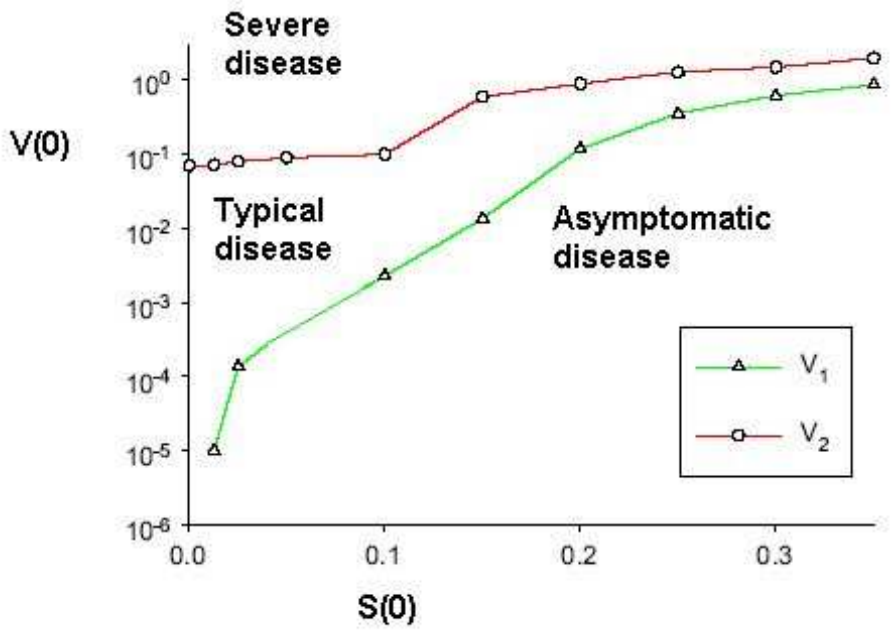

Figure 4.9: Different types of disease depending on the values of $S(0)$ and $V(0)$ [22].

The parameter r stands for the rate of improvement of antigenic distance. When $r = 0$, the antibodies are not able to match antigens. When $S(0) = 0$ and $r(0) = 0$, the organism completely fails to develop antibodies and this situation leads to the recurrence of the disease and causes a chronic state. The following values stands for the chronic state [22];

$$(V, H, I, M, F, R, E, P, A) = (5.26, 0.06, 0.018, 0.05, 1484, 0.89, 67.0).$$

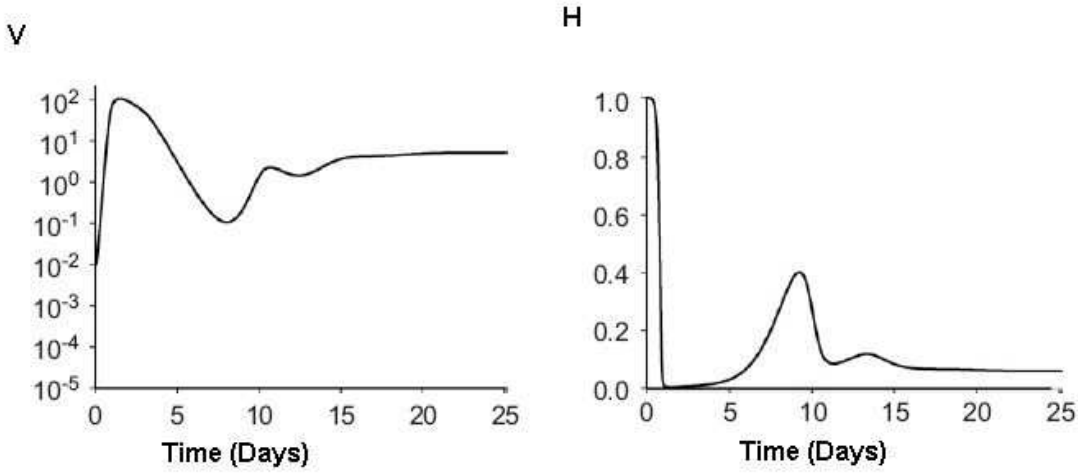

Figure 4.10: Virus load (on the left) and healthy cell proportion (on the right) of an individual without adaptive response, i.e., $S(0) = 0$ and $r = 0$ [22].

The organism can clear the virus and the disease although r takes very low values, such as $r = 10^{-5}$. This is shown by Figure 4.11. If $S(0) > 0$ and $r = 0$, the organism partially fails to develop antibodies. This situation leads to a chronic state whenever $S(0)$ is sufficiently small actually less than 10^{-7}.

Table 4.2: One-way sensitivity analysis on model parameters [22].

Parameter	*Baseline* (*range*)	*Model behavior*
γ_{HV}	$0.34\,(0.1-1)$	At high virulence, disease always develops. At less virulence, damage is higher. So, high virulence may cause death
γ_V	$510\,(150-1500)$	At less virulence, the longer contagious period occurs. The model behaves the same as in case for γ_{HV}.
γ_{VA}	$619.2\,(200-1800)$	For low γ_{VA}, disease always develops. For high values, the duration and the onset of disease are about the same.
b_{MD}	$2\,(0.6-6)$	The higher b_{MD},the shorter the duration of disease and the lesser damage. Very low values may cause death.
b_{IE}	$0.066\,(0.02-0.1)$	At high b_{IE}, asymptomatic disease is observed for standard $V(0)$ and $S(0)$. At high values damage is lower and the duration of disease is shorter.
a_I	$1.5\,(0.5-4.5)$	At high a_I, asymptomatic disease is observed for standard $V(0)$ and $S(0)$. At high values damage is lower and the duration of disease is shorter.
b_{HD}	$4\,(2-8)$	At high values damage is lower and the duration of disease is shorter.
b_F	$25.000\,(125.000-500.000)$	At high values damage is lower and the duration of disease is shorter.
b_A	$0.043\,(0.01-0.12)$	At high values damage is lower.
b_{HF}	$0.02\,(0.005-0.03)$	At high b_{HF}, asymptomatic disease is observed for standard $V(0)$ and $S(0)$. At high values damage is lower and the duration of disease is shorter.
b_{EM}	$8.3\,(2.5-25)$	At high b_{EM}, asymptomatic disease is observed for standard $V(0)$ and $S(0)$. At low values damage is lower.
b_{PM}	$11.3\,(3-30)$	Onset, damage and duration of disease is about the same for various values of b_{PM}
$S(0)$	$0-1$	For $S(0)=0$, disease always develops. At high values, damage is lower and the onset of disease is later.

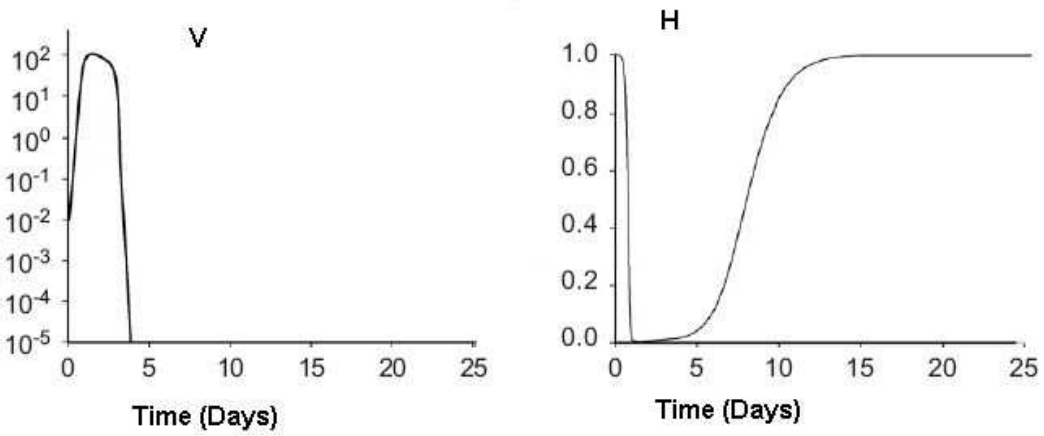

Figure 4.11: Virus load (on the left) and healthy cell proportion (on the right) with $S(0) = 0$ and $r = 10^{-5}$ [22].

CHAPTER 5

APPLICATION OF HYBRID SYSTEM WITH MEMORY

This chapter includes an application of hybrid system with memory to the dynamical model of human immune response to influenza A virus infection which is explained in Chapter 4. The dynamical system of human immune response to influenza A virus is explained in Chapter 4. According to the work of Hancioglu, Swigon and Clermont, the system demonstrates different disease regimes according to the different values of S and V variables: severe, typical and asymptomatic regimes and moreover, with some values of V, H, I, M, F, R, E, P, A, S, D the disease can stay chronic, i.e., V, virus load values, never decrease and H, healthy cell proportion, never increase as shown in Figure 4.10.

In this chapter, an application of human immune response to influenza A virus infection with piecewise linear system with memory which is a subclass of hybrid systems is illustrated. The change of variables is approximated modularly. Every variable is effected from other variable or variables and this idea infers that the value of a variable is the external input of one to another. The variables which are external inputs of an another variable are determined with the ODE model in Chapter 4. The model is approximated by using the idea of when a goes up, b goes down. The variable μ is taken as -1 at each state. Numerical simulations

of the ODE model are investigated and the corresponding k and h values are obtained.

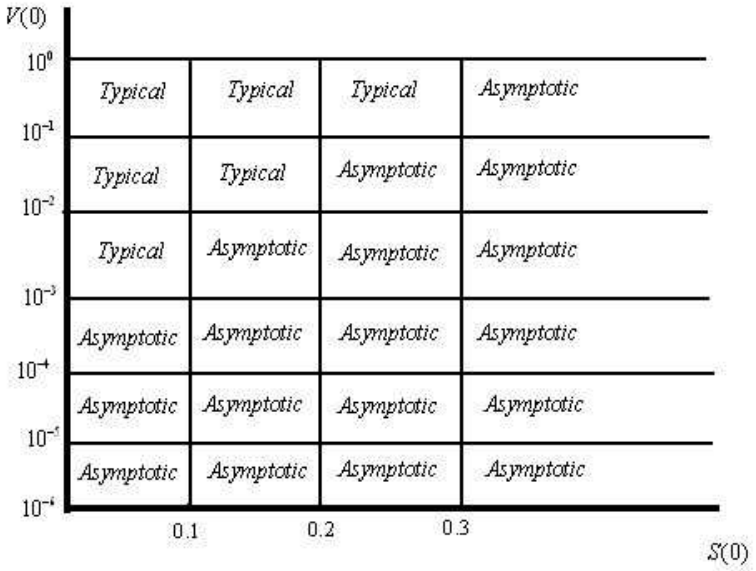

Figure 5.1: Approximated disease regimes according to initial values of $S(0)$ and $V(0)$.

The variables S, V and the memory set determines the new dynamics of the system. The initial set of S and V variables and the corresponding disease regimes are given by the Figure 4.9. Here V stands for the virus load and the regime of the disease changes due to the virus load. The guard conditions in our model are shown by the Figure 5.2 and invariant sets of our model are illustrated by the Figure 5.3. There are two possibilities that can be distinguished by the memory set and the guard conditions. Firstly, if the host is not faced with the virus before, (m_0), then three of the different types can occur according to the guard conditions. Secondly, if the host is faced with the virus before, (m_i where

$i \in \{1, \ldots, n\}$), then an asymptomatic regime occurs only. In this application $m_{i+1} = \{(t_i, V_{t_i}, q_{t_i})\}$ and $V(t_{i-}) > 0$ is assumed. When $V(t_{i-}) > 0$, i increases by 1, in other words, every time the host faces with the virus memory set increases by 1. The initial values of Figure 4.9 is approximated by partitioning the set discretely. If in these subsets most of the region behaves asymptomatic the subset is assumed as asymptomastic. Since typical and severe regimes exhibit similar behaviors, severe regime is also regarded as typical. The vector fields, governing the continuous evolution, is obtained in the following Sections 5.1, 5.2 and 5.3. By giving initial values, a governing differential equation is acquired for every state. The state space representation of the regimes according to the corresponding S and V values can be seen from the Figure 5.1. According to these assumptions the model can be approximated as

- $Q = \{q_1, q_2, q_3, q_4\}$,
- $S \in [0,1], H \in [0,1], R \in [0,1], I \in [0,1], D \in [0,1]$ and $V = M = F = E = P = A = \mathbf{R}$,
- $Init = \{q_1\} \times \{V, H, I, M, F, R, E, P, A, S, D\} \times \{m_{i-1}\}$,
- $V = \mathbf{R}$,
- $T = [t_0, \infty)$,
-
  - $f_{q_1} : \frac{dS}{dt} = \mu_{q^1}[S] + \eta[V]$, where $\mu_{q^1} = 0$ and $\eta = 0$,
  - $f_{q_2} : \frac{dy}{dt} = A_{q_2(t),M(t)}y(t) + B_{q_2(t),M(t)}y(t) + k_{q_2(t),M(t)}$,
  - $f_{q_3} : \frac{dy}{dt} = A_{q_3(t),M(t)}y(t) + B_{q_3(t),M(t)}y(t) + k_{q_3(t),M(t)}$,
  - $f_{q_4} : \frac{dy}{dt} = A_{q_4(t),M(t)}y(t) + B_{q_4(t),M(t)}y(t) + k_{q_4(t),M(t)}$,

- – $Inv(q_1) = \{V = 0, H = 1\}$,
  – $Inv(q_2) = \{V > 0, D > 0\}$,
  – $Inv(q_3) = \{V > 0, D > 0\}$,
  – $Inv(q_4) = \{(V, H, I, M, F, R, E, P, A, S, D)$
  $= (5.26, 0.06, 0.018, 0.05, 1484, 0.89, 67.0, 1, 1, 0, 0)\}$,
- $E = \{(q_1, q_2), (q_1, q_3), (q_1, q_4), (q_2, q_1), (q_3, q_1)\}$,
- – $G(q_1, q_2) = \{(S \in [0, 0.1) \times V \in [10^{-3}, \infty))$
  $\vee (S \in [0.1, 0.2) \times V \in [10^{-2}, \infty))$
  $\vee (S \in [0.2, 0.3) \times V \in [10^{-1}, \infty))\}$
  $\times \{m_1\}$
  – $G(q_1, q_3) = \{(S \in [0, 0.1) \times V \in (0, 10^{-3}))$
  $\vee (S \in [0.1, 0.2) \times V \in (0, 10^{-2}))$
  $\vee (S \in [0.2, 0.3) \times V \in (0, 10^{-1}))$
  $\vee (S \in [0.3, 1) \times V \in (0, \infty))\}$
  $\times \{m_i\}$, where $i \in \{1, \ldots, n\}$,
  – $G(q_1, q_4) = \{(V, H, I, M, F, R, E, P, A, S, D)$
  $= (0.01, 1, 0, 0, 0, 0, 1, 1, 1, 0, 0)\}$
  $\times \{m_1\}$,
  – $G(q_3, q_1) = \{V = 0\} \times \{m_i\}$,
  – $G(q_2, q_1) = \{V = 0, S = 1\} \times \{m_i\}$,
- $M = \{m_0, \ldots, m_n\}$.

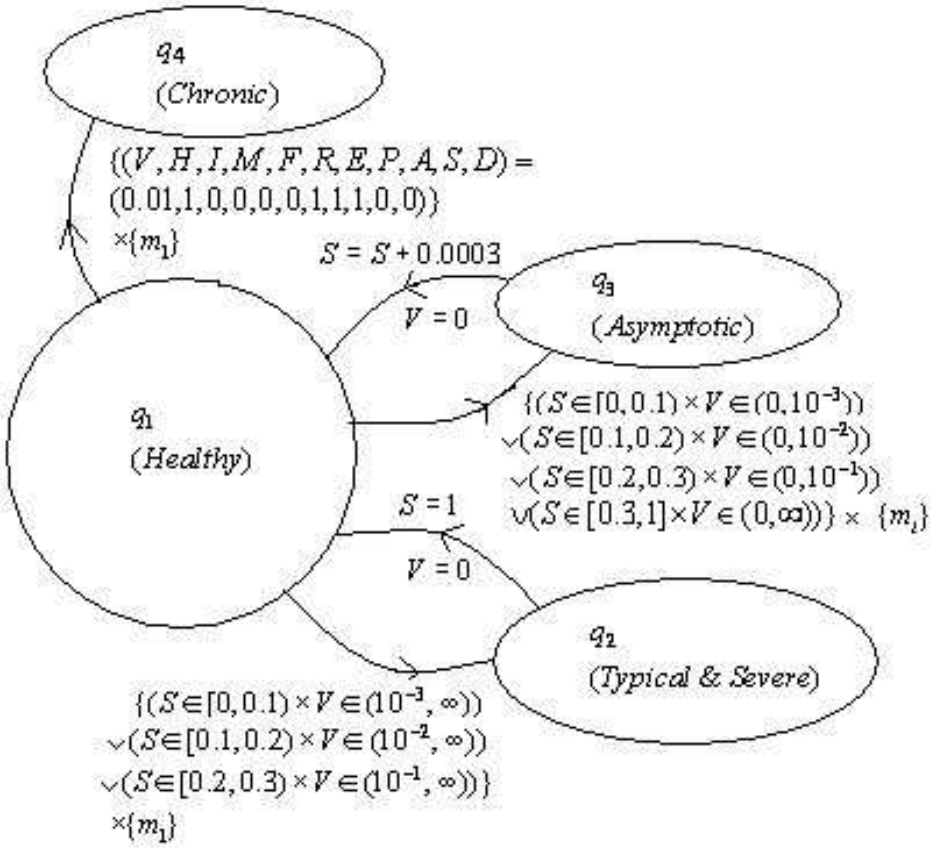

Figure 5.2: Guard conditions of the corresponding states.

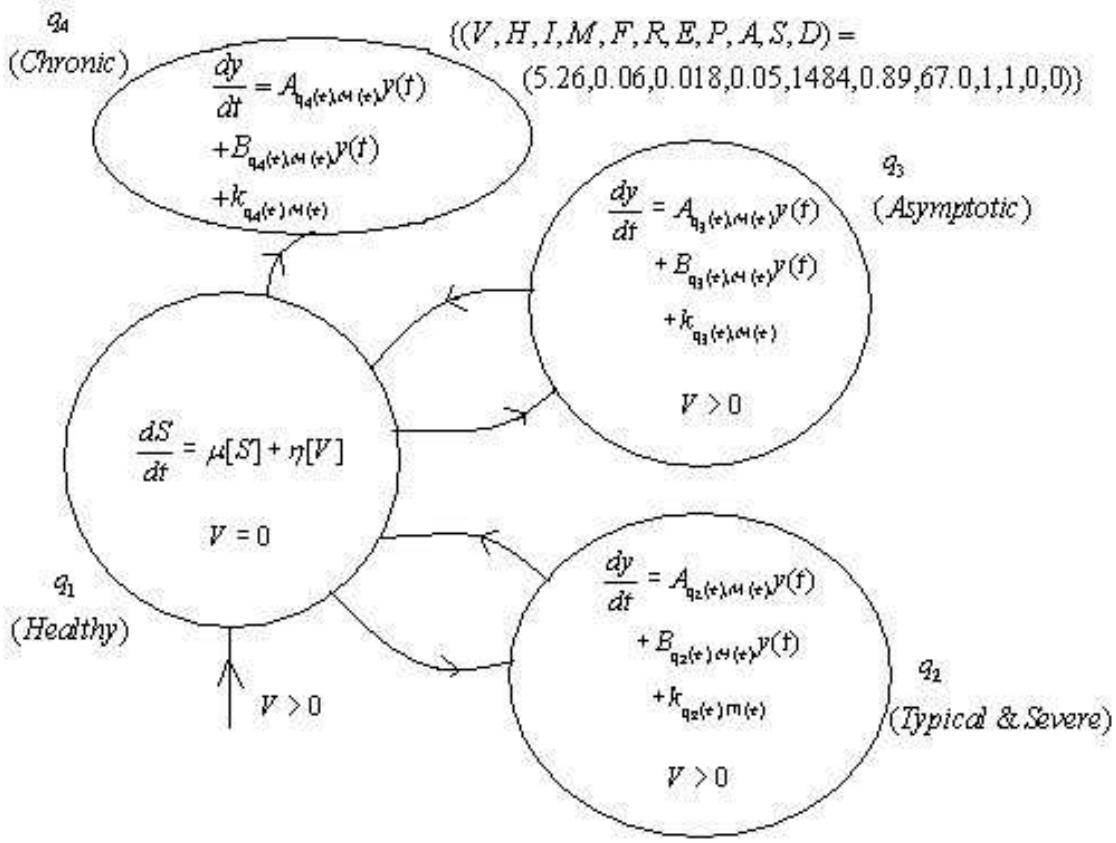

Figure 5.3: Invariant sets and the governing dynamics of the states.

5.1 Typical Regime

The characteristic behavior of the typical case is that V, virus load, exhibits an increase and by the effect of other variables it decreases. The antigenic compatibility variable, S, increases to 1 and never decreases. The general dynamics of the typical case are approximated by the following equations with the initial values $(V, H, I, M, F, R, E, P, A, S, D) = (0.01, 1, 0, 0, 0, 0, 1, 1, 1, 0.1, 0)$ so that a comparison with the ODE model can be done. In this model, since the value of S is taken as 0.1, the related focal points and threshold values must be considered with this in mind. For example, in S module the focal points are taken as 0.1 and 1. For a different value of S, let us say that S^*, the corresponding focal points should be taken as S^* and 1 because of the fact that after every state transition, from healthy state to typical state, the value of S increases to 1 as a result of the governing dynamics of the typical state. Similarly, the threshold values related to S, existing in the modules V and A with threshold values $S = 0.1$ and $S = 0.15$, respectively, should be considered as S^* and $S^* + 0.05$. The same approach should be considered for the variable V. There is no need to do the same approach for other variables, since the initial state is healthy state, q_1, and the values of other variables are assumed to be at their equilibrium values.

The variable V is effected by the values of I, infected cell proportion, S, A, concentration of antibodies and H, healthy cell proportion. The approximation of variable V can be illustrated as

$$\frac{dV}{dt} = \mu^V_{q(t),M(t)} V + 0[I] + 0[S] + 0[A] + 0[H] + k^V_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } I \geq 0.0000001 \wedge S \geq 0.1 \wedge A \geq 1 \wedge H \geq 0.99999, \\ q_2 & \text{if } I \geq 0.0000001 \wedge S \geq 0.1 \wedge A \geq 1 \wedge H < 0.99999, \\ q_3 & \text{if } I \geq 0.0000001 \wedge S \geq 0.1 \wedge A < 1 \wedge H \geq 0.99999, \\ q_4 & \text{if } I \geq 0.0000001 \wedge S \geq 0.1 \wedge A < 1 \wedge H < 0.99999, \\ q_5 & \text{if } I \geq 0.0000001 \wedge S < 0.1 \wedge A \geq 1 \wedge H \geq 0.99999, \\ q_6 & \text{if } I \geq 0.0000001 \wedge S < 0.1 \wedge A \geq 1 \wedge H < 0.99999, \\ q_7 & \text{if } I \geq 0.0000001 \wedge S < 0.1 \wedge A < 1 \wedge H \geq 0.99999, \\ q_8 & \text{if } I \geq 0.0000001 \wedge S < 0.1 \wedge A < 1 \wedge H < 0.99999, \\ q_9 & \text{if } I < 0.0000001 \wedge S \geq 0.1 \wedge A \geq 1 \wedge H \geq 0.99999, \\ q_{10} & \text{if } I < 0.0000001 \wedge S \geq 0.1 \wedge A \geq 1 \wedge H < 0.99999, \\ q_{11} & \text{if } I < 0.0000001 \wedge S \geq 0.1 \wedge A < 1 \wedge H \geq 0.99999, \\ q_{12} & \text{if } I < 0.0000001 \wedge S \geq 0.1 \wedge A < 1 \wedge H < 0.99999, \\ q_{13} & \text{if } I < 0.0000001 \wedge S < 0.1 \wedge A \geq 1 \wedge H \geq 0.99999, \\ q_{14} & \text{if } I < 0.0000001 \wedge S < 0.1 \wedge A \geq 1 \wedge H < 0.99999, \\ q_{15} & \text{if } I < 0.0000001 \wedge S < 0.1 \wedge A < 1 \wedge H \geq 0.99999, \\ q_{16} & \text{if } I < 0.0000001 \wedge S < 0.1 \wedge A < 1 \wedge H < 0.99999, \end{cases}$$

$$\begin{aligned} k^V_{q_1} = 0,\ k^V_{q_5} = 0,\ k^V_{q_9} = 0,\ k^V_{q_{13}} = 0, \\ k^V_{q_2} = 0,\ k^V_{q_6} = 0,\ k^V_{q_{10}} = 2500,\ k^V_{q_{14}} = 0, \\ k^V_{q_3} = 0,\ k^V_{q_7} = 0,\ k^V_{q_{11}} = 0,\ k^V_{q_{15}} = 0, \\ k^V_{q_4} = 0,\ k^V_{q_8} = 0,\ k^V_{q_{12}} = 0,\ k^V_{q_{16}} = 0, \end{aligned}$$

where $\mu^V_{q_1,q_2,q_3,q_4,q_5,q_6,q_7,q_8,q_9,q_{10},q_{11},q_{12},q_{13},q_{14},q_{15},q_{16}} = -1$.

The variable H is effected by the values of D, dead cell proportion, R, resistant cell proportion, V and F, amount of interferon. The approximation of variable H can be shown as

$$\frac{dH}{dt} = \mu^H_{q(t),M(t)} H + 0[D] + 0[R] + 0[V] + 0[F] + k^H_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } D \geq 0.00001 \wedge R \geq 0.00001 \wedge V \geq 0 \wedge F \geq 0.00001, \\ q_2 & \text{if } D \geq 0.00001 \wedge R \geq 0.00001 \wedge V \geq 0 \wedge F < 0.00001, \\ q_3 & \text{if } D \geq 0.00001 \wedge R \geq 0.00001 \wedge V < 0 \wedge F \geq 0.00001, \\ q_4 & \text{if } D \geq 0.00001 \wedge R \geq 0.00001 \wedge V < 0 \wedge F < 0.00001, \\ q_5 & \text{if } D \geq 0.00001 \wedge R < 0.00001 \wedge V \geq 0 \wedge F \geq 0.00001, \\ q_6 & \text{if } D \geq 0.00001 \wedge R < 0.00001 \wedge V \geq 0 \wedge F < 0.00001, \\ q_7 & \text{if } D \geq 0.00001 \wedge R < 0.00001 \wedge V < 0 \wedge F \geq 0.00001, \\ q_8 & \text{if } D \geq 0.00001 \wedge R < 0.00001 \wedge V < 0 \wedge F < 0.00001, \\ q_9 & \text{if } D < 0.00001 \wedge R \geq 0.00001 \wedge V \geq 0 \wedge F \geq 0.00001, \\ q_{10} & \text{if } D < 0.00001 \wedge R \geq 0.00001 \wedge V \geq 0 \wedge F < 0.00001, \\ q_{11} & \text{if } D < 0.00001 \wedge R \geq 0.00001 \wedge V < 0 \wedge F \geq 0.00001, \\ q_{12} & \text{if } D < 0.00001 \wedge R \geq 0.00001 \wedge V < 0 \wedge F < 0.00001, \\ q_{13} & \text{if } D < 0.00001 \wedge R < 0.00001 \wedge V \geq 0 \wedge F \geq 0.00001, \\ q_{14} & \text{if } D < 0.00001 \wedge R < 0.00001 \wedge V \geq 0 \wedge F < 0.00001, \\ q_{15} & \text{if } D < 0.00001 \wedge R < 0.00001 \wedge V < 0 \wedge F \geq 0.00001, \\ q_{16} & \text{if } D < 0.00001 \wedge R < 0.00001 \wedge V < 0 \wedge F < 0.00001, \end{cases}$$

$$k^H_{q_1} = 1,\ k^H_{q_5} = 1,\ k^H_{q_9} = 1,\ k^H_{q_{13}} = 1,$$
$$k^H_{q_2} = 0,\ k^H_{q_6} = 1,\ k^H_{q_{10}} = 1,\ k^H_{q_{14}} = 1,$$
$$k^H_{q_3} = 1,\ k^H_{q_7} = 1,\ k^H_{q_{11}} = 1,\ k^H_{q_{15}} = 1,$$
$$k^H_{q_4} = 1,\ k^H_{q_8} = 1,\ k^H_{q_{12}} = 1,\ k^H_{q_{16}} = 1,$$

where $\mu^H_{q_1,q_2,q_3,q_4,q_5,q_6,q_7,q_8,q_9,q_{10},q_{11},q_{12},q_{13},q_{14},q_{15},q_{16}} = -1$.

The variable I is influenced by the values of H, V and E, effector cell concentration. The approximation of variable I can be given as

$$\frac{dI}{dt} = \mu^I_{q(t),M(t)} I + 0[H] + 0[V] + 0[E] + k^I_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } H \geq 0.99999 \ \wedge \ V \geq 1 \ \wedge \ E \geq 1.000001, \\ q_2 & \text{if } H \geq 0.99999 \ \wedge \ V \geq 1 \ \wedge \ E < 1.000001, \\ q_3 & \text{if } H \geq 0.99999 \ \wedge \ V < 1 \ \wedge \ E \geq 1.000001, \\ q_4 & \text{if } H \geq 0.99999 \ \wedge \ V < 1 \ \wedge \ E < 1.000001, \\ q_5 & \text{if } H < 0.99999 \ \wedge \ V \geq 1 \ \wedge \ E \geq 1.000001, \\ q_6 & \text{if } H < 0.99999 \ \wedge \ V \geq 1 \ \wedge \ E < 1.000001, \\ q_7 & \text{if } H < 0.99999 \ \wedge \ V < 1 \ \wedge \ E \geq 1.000001, \\ q_8 & \text{if } H < 0.99999 \ \wedge \ V < 1 \ \wedge \ E < 1.000001, \end{cases}$$

$$k^I_{q_1} = 0, \ \ k^I_{q_5} = 0,$$
$$k^I_{q_2} = 0, \ \ k^I_{q_6} = 15,$$
$$k^I_{q_3} = 0, \ \ k^I_{q_7} = 0,$$
$$k^I_{q_4} = 0, \ \ k^I_{q_8} = 0,$$

where $\mu^I_{q_1,q_2,q_3,q_4,q_5,q_6,q_7,q_8} = -1$.

The variable M, activated APC proportion, is influenced by the values of D and V. The approximation of variable M can be illustrated as

$$\frac{dM}{dt} = \mu^M_{q(t),M(t)} M + 0[D] + 0[V] + k^M_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } D \geq 0.2 \ \wedge \ V \geq 5, \\ q_2 & \text{if } D \geq 0.2 \ \wedge \ V < 5, \\ q_3 & \text{if } D < 0.2 \ \wedge \ V \geq 5, \\ q_4 & \text{if } D < 0.2 \ \wedge \ V < 5, \end{cases}$$

$$k_{q_1}^M = 0.5,$$
$$k_{q_2}^M = 0.5,$$
$$k_{q_3}^M = 0,$$
$$k_{q_4}^M = 0,$$

where $\mu_{q_1,q_2,q_3,q_4}^M = -1$

The values of M, I and H effects the amount of interferons, F. The approximation of variable F can be given as

$$\frac{dF}{dt} = \mu_{q(t),M(t)}^F F + 0[M] + 0[I] + 0[H] + k_{q(t),M(t)}^F,$$

$$q(t) = \begin{cases} q_1 & \text{if } M \geq 0.2 \ \wedge \ I \geq 0.0000001 \ \wedge \ H \geq 0.9999999, \\ q_2 & \text{if } M \geq 0.2 \ \wedge \ I \geq 0.0000001 \ \wedge \ H < 0.9999999, \\ q_3 & \text{if } M \geq 0.2 \ \wedge \ I < 0.0000001 \ \wedge \ H \geq 0,9999999, \\ q_4 & \text{if } M \geq 0.2 \ \wedge \ I < 0.0000001 \ \wedge \ H < 0.9999999, \\ q_5 & \text{if } M < 0.2 \ \wedge \ I \geq 0.0000001 \ \wedge \ H \geq 0.9999999, \\ q_6 & \text{if } M < 0.2 \ \wedge \ I \geq 0.0000001 \ \wedge \ H < 0.9999999, \\ q_7 & \text{if } M < 0.2 \ \wedge \ I < 0.0000001 \ \wedge \ H \geq 0.9999999, \\ q_8 & \text{if } M < 0.2 \ \wedge \ I < 0.0000001 \ \wedge \ H < 0.9999999, \end{cases}$$

$$k_{q_1}^F = 0, \ \ k_{q_5}^F = 0,$$
$$k_{q_2}^F = 12000, \ \ k_{q_6}^F = 0,$$
$$k_{q_3}^F = 0, \ \ k_{q_7}^F = 0,$$
$$k_{q_4}^F = 0, \ \ k_{q_8}^F = 0,$$

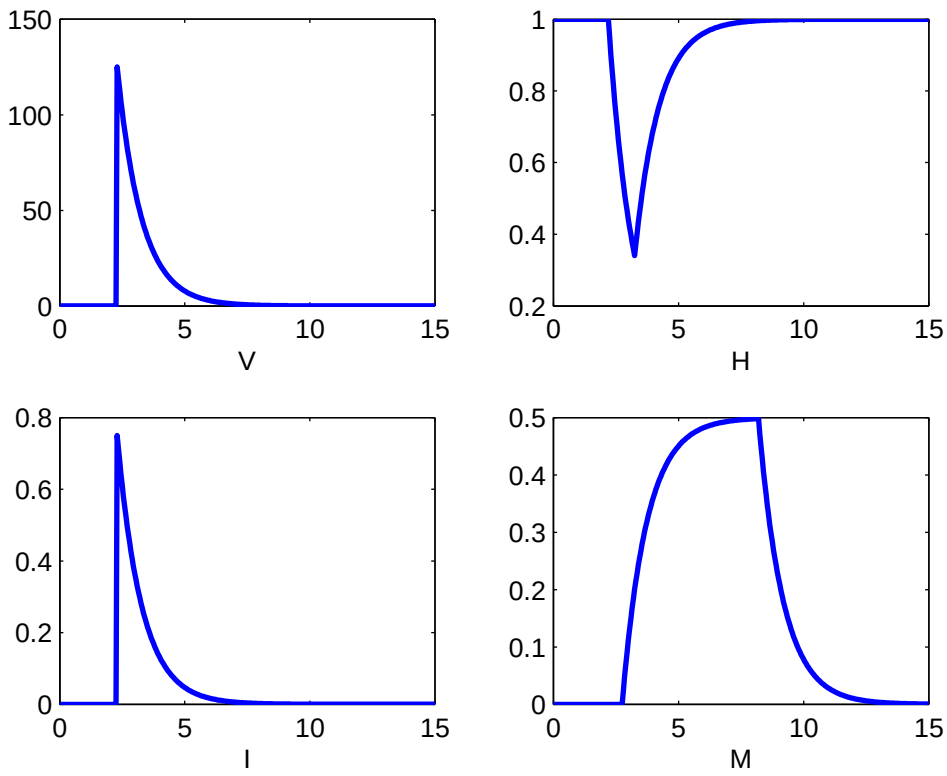

Figure 5.4: Numerical simulations of V, I, H and M variables with initial values $(V, H, I, M, F, R, E, P, A, S, D) = (0.01, 1, 0, 0, 0, 0, 1, 1, 1, 0.1, 0)$.

where $\mu^{F}_{q_1,q_2,q_3,q_4,q_5,q_6,q_7,q_8} = -1$.

The variable R, resistant cell proportion, is influenced from the values of F and H. The approximation of variable R can be shown as

$$\frac{dR}{dt} = \mu^{R}_{q(t),M(t)}R + 0[F] + 0[H] + k^{R}_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } F \geq 10 \ \wedge \ H \geq 0.9999999, \\ q_2 & \text{if } F \geq 10 \ \wedge \ H < 0.9999999, \\ q_3 & \text{if } F < 10 \ \wedge \ H \geq 0.9999999, \\ q_4 & \text{if } F < 10 \ \wedge \ H < 0.9999999, \end{cases}$$

$$k^{R}_{q_1} = 0,$$
$$k^{R}_{q_2} = 0,$$
$$k^{R}_{q_3} = 1,$$
$$k^{R}_{q_4} = 0,$$

where $\mu^{R}_{q_1,q_2,q_3,q_4} = -1$.

The values of M and I effects the effector cell amount, E. The approximation of variable E is illustrated as

$$\frac{dE}{dt} = \mu^{E}_{q(t),M(t)}E + 0[M] + 0[I] + k^{E}_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } M \geq 0.3 \ \wedge \ I \geq 0.00001, \\ q_2 & \text{if } M \geq 0.3 \ \wedge \ I < 0.00001, \\ q_3 & \text{if } M < 0.3 \ \wedge \ I \geq 0.00001, \\ q_4 & \text{if } M < 0.3 \ \wedge \ I < 0.00001, \end{cases}$$

$$k^E_{q_1} = 180,$$
$$k^E_{q_2} = 180,$$
$$k^E_{q_3} = 25,$$
$$k^E_{q_4} = 0,$$

where $\mu^E_{q_1,q_2,q_3,q_4} = -1$

Activated plasma cell amount, P, is influenced by the values of M, amount of activated APC. The approximation of variable P is given as

$$\frac{dP}{dt} = \mu^P_{q(t),M(t)} P + 0[M] + k^P_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } M \geq 0.000001 \ \wedge \ M \geq 0.3, \\ q_2 & \text{if } M \geq 0.000001 \ \wedge \ M < 0.3, \\ q_3 & \text{if } M < 0.000001 \ \wedge \ M < 0.3, \end{cases}$$

$$k^P_{q_1} = 33000,$$
$$k^P_{q_2} = 5000,$$
$$k^P_{q_3} = 0,$$

where $\mu^P_{q_1,q_2,q_3} = -1$.

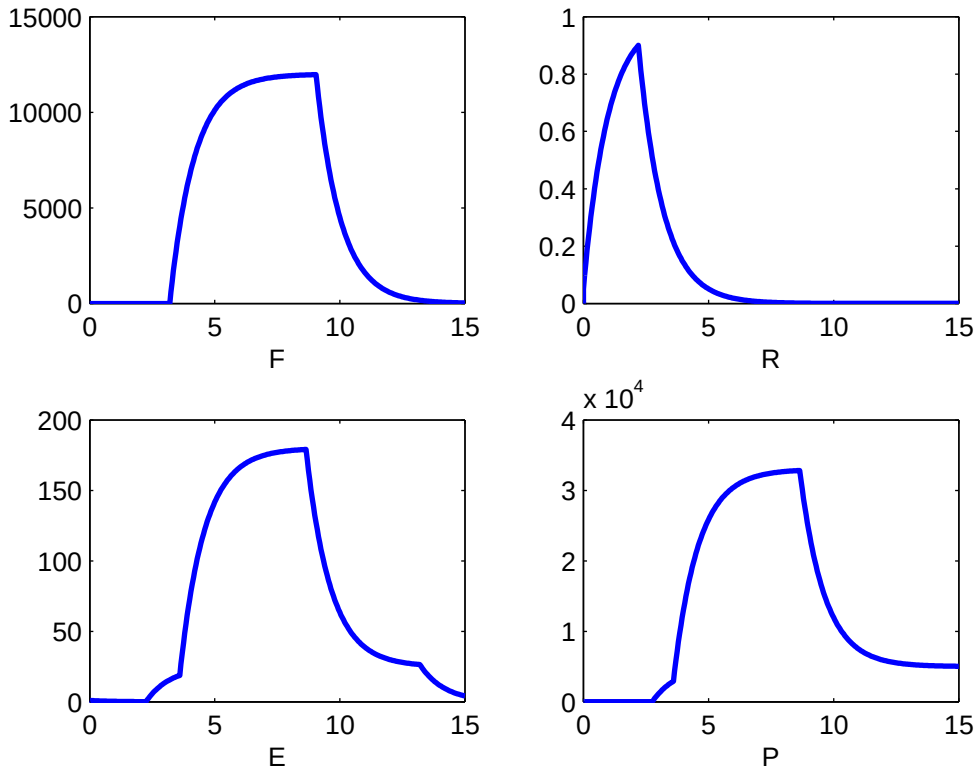

Figure 5.5: Numerical simulations of F, R, E and P variables with initial values $(V, H, I, M, F, R, E, P, A, S, D)$ =$(0.01, 1, 0, 0, 0, 0, 1, 1, 1, 0.1, 0)$.

A, concentration of antibodies, is effected from the values of S, P and V. The approximation of variable A is shown as

$$\frac{dA}{dt} = \mu^{A}_{q(t),M(t)}A + 0[S] + 0[P] + 0[V] + k^{F}_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } S \geq 0.15 \ \wedge \ P \geq 5000 \ \wedge \ V \geq 0, \\ q_2 & \text{if } S \geq 0.15 \ \wedge \ P \geq 5000 \ \wedge \ V < 0, \\ q_3 & \text{if } S \geq 0.15 \ \wedge \ P < 5000 \ \wedge \ V \geq 0, \\ q_4 & \text{if } S \geq 0.15 \ \wedge \ P < 5000 \ \wedge \ V < 0, \\ q_5 & \text{if } S < 0.15 \ \wedge \ P \geq 5000 \ \wedge \ V \geq 0, \\ q_6 & \text{if } S < 0.15 \ \wedge \ P \geq 5000 \ \wedge \ V < 0, \\ q_7 & \text{if } S < 0.15 \ \wedge \ P < 5000 \ \wedge \ V \geq 0, \\ q_8 & \text{if } S < 0.15 \ \wedge \ P < 5000 \ \wedge \ V < 0, \end{cases}$$

$$k^{A}_{q_1} = 5000, \ \ k^{A}_{q_5} = 1,$$
$$k^{A}_{q_2} = 5000, \ \ k^{A}_{q_6} = 1,$$
$$k^{A}_{q_3} = 5000, \ \ k^{A}_{q_7} = 1,$$
$$k^{A}_{q_4} = 5000, \ \ k^{A}_{q_8} = 1,$$

where $\mu^{A}_{q_1,q_2,q_3,q_4,q_5,q_6,q_7,q_8} = -1$.

Plasma cell proportion, P, effects S. The approximation of variable S, antigenic compatibility, is given as

$$\frac{dS}{dt} = \mu^{S}_{q(t),M(t)}S + 0[P] + k^{S}_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } P \geq 5000, \\ q_2 & \text{if } P < 5000, \end{cases}$$

$$k^S_{q_1} = 1,$$
$$k^S_{q_2} = 0.1,$$

where $\mu^S_{q_1,q_2} = -1$.

The variable D, dead cell proportion, is influenced by the values of H, R and I. The approximation of variable D can be illustrated as

$$\frac{dD}{dt} = \mu^D_{q(t),M(t)} D + 0[H] + 0[R] + 0[I] + k^D_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } H \geq 0.99 \ \wedge \ R \geq 0.9 \ \wedge \ I \geq 0.001, \\ q_2 & \text{if } H \geq 0.99 \ \wedge \ R \geq 0.9 \ \wedge \ I < 0.001, \\ q_3 & \text{if } H \geq 0.99 \ \wedge \ R < 0.9 \ \wedge \ I \geq 0.001, \\ q_4 & \text{if } H \geq 0.99 \ \wedge \ R < 0.9 \ \wedge \ I < 0.001, \\ q_5 & \text{if } H < 0.99 \ \wedge \ R \geq 0.9 \ \wedge \ I \geq 0.001, \\ q_6 & \text{if } H < 0.99 \ \wedge \ R \geq 0.9 \ \wedge \ I < 0.001, \\ q_7 & \text{if } H < 0.99 \ \wedge \ R < 0.9 \ \wedge \ I \geq 0.001, \\ q_8 & \text{if } H < 0.99 \ \wedge \ R < 0.9 \ \wedge \ I < 0.001, \end{cases}$$

$$k_{q_1}^D = 0, \;\; k_{q_5}^D = 0.5,$$
$$k_{q_2}^D = 0.5, \;\; k_{q_6}^D = 0,$$
$$k_{q_3}^D = 0, \;\; k_{q_7}^D = 0.5,$$
$$k_{q_4}^D = 0, \;\; k_{q_8}^D = 0,$$

where $\mu^D_{q_1,q_2,q_3,q_4,q_5,q_6,q_7,q_8} = -1$.

The whole system can be demonstrated as;

$$\frac{dy}{dt} = A_{q^2(t),M(t)}y(t) + B_{q^2(t),M(t)}y(t) + k_{q^2(t),M(t)},$$

where $q^2(t) = \left\{q^V(t) \cup q^H(t) \cup q^I(t) \cup q^M(t) \cup q^F(t) \cup q^R(t) \cup q^E(t) \cup q^P(t) \cup q^A(t) \cup q^S(t) \cup q^D(t)\right\}$ and $y = [V \; H \; I \; M \; F \; R \; E \; P \; A \; S \; D]'$ and

$$\mathbf{A_{q^2(t),M(t)}} = \begin{pmatrix} -1 & 0 & \dots & \dots & 0 \\ 0 & -1 & 0 & \dots & 0 \\ \vdots & & \ddots & & \vdots \\ \vdots & & 0 & -1 & 0 \\ 0 & \dots & \dots & 0 & -1 \end{pmatrix}_{(11\times 11)},$$

$$\mathbf{B_{q^2(t),M(t)}} = \begin{pmatrix} 0 & \dots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \dots & 0 \end{pmatrix}_{(11\times 11)}.$$

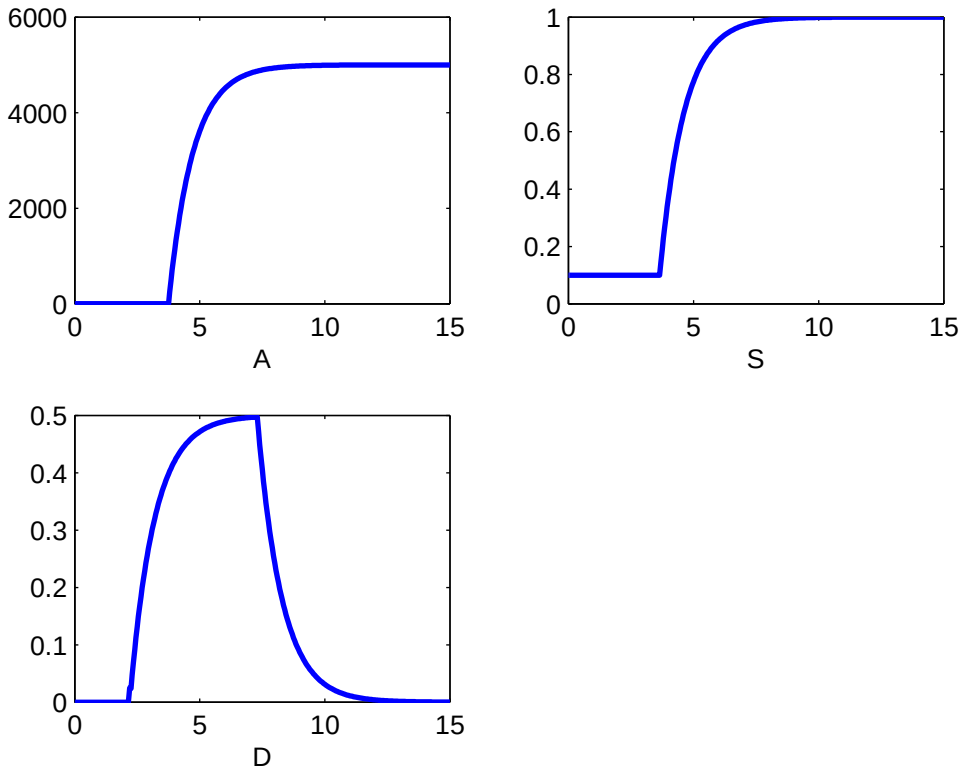

Figure 5.6: Numerical simulations of A, S and D variables with initial values $(V, H, I, M, F, R, E, P, A, S, D)$ =$(0.01, 1, 0, 0, 0, 0, 1, 1, 1, 0.1, 0)$.

5.2 Asymptomatic Regime

The characteristic behavior of the asymptomatic case is that V, virus load, decreases immediately and antigenic compatibility variable, S, increases by 0.0003 and never decreases. The general dynamics of the typical case are approximated by the following equations with the initial values $(V, H, I, M, F, R, E, P, A, S, D) = (0.01, 1, 0, 0, 0, 0, 1, 1, 1, 0.3, 0)$ so that a comparison with the ODE model can be done. In this model, since the value of S is taken as 0.3, the related focal points and threshold values must be considered with this in mind. For example, in module S the focal points are taken as 0.3 and 0.3003. For different value of S, let us say S^*, the corresponding focal points should be taken as S^* and $S^* + 0.0003$ because of the fact that after every state transition, from healthy state to asymptomatic state, the value of S increases by 0.0003 as a result of the governing dynamics of the asymptomatic state. Similarly, the threshold values related to S, existing in the modules V and A with threshold values $S = 0.3001$ should be considered as $S^* + 0.0001$. The same approach should be considered for the variable V. Moreover $S = 1$ is a special case such that, S value does not increase by 0.0003 since the maximum value for S is 1 but still asymptomatic regime occurs, i.e., virus load, V, decreases immediately.

The variable V is effected from the values of I, infected cell proportion, S, A, concentration of antibodies and H, healthy cell proportion. The approximation of variable V can be illustrated as

$$\frac{dV}{dt} = \mu^V_{q(t),M(t)} V + 0[I] + 0[S] + 0[A] + 0[H] + k^V_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } I \geq 5 \times 10^{-6} \wedge S \geq 0.3001 \wedge A \geq 0.965 \wedge H \geq 0.9998, \\ q_2 & \text{if } I \geq 5 \times 10^{-6} \wedge S \geq 0.3001 \wedge A \geq 0.965 \wedge H < 0.9998, \\ q_3 & \text{if } I \geq 5 \times 10^{-6} \wedge S \geq 0.3001 \wedge A < 0.965 \wedge H \geq 0.9998, \\ q_4 & \text{if } I \geq 5 \times 10^{-6} \wedge S \geq 0.3001 \wedge A < 0.965 \wedge H < 0.9998, \\ q_5 & \text{if } I \geq 5 \times 10^{-6} \wedge S < 0.3001 \wedge A \geq 0.965 \wedge H \geq 0.9998, \\ q_6 & \text{if } I \geq 5 \times 10^{-6} \wedge S < 0.3001 \wedge A \geq 0.965 \wedge H < 0.9998, \\ q_7 & \text{if } I \geq 5 \times 10^{-6} \wedge S < 0.3001 \wedge A < 0.965 \wedge H \geq 0.9998, \\ q_8 & \text{if } I \geq 5 \times 10^{-6} \wedge S < 0.3001 \wedge A < 0.965 \wedge H < 0.9998, \\ q_9 & \text{if } I < 5 \times 10^{-6} \wedge S \geq 0.3001 \wedge A \geq 0.965 \wedge H \geq 0.9998, \\ q_{10} & \text{if } I < 5 \times 10^{-6} \wedge S \geq 0.3001 \wedge A \geq 0.965 \wedge H < 0.9998, \\ q_{11} & \text{if } I < 5 \times 10^{-6} \wedge S \geq 0.3001 \wedge A < 0.965 \wedge H \geq 0.9998, \\ q_{12} & \text{if } I < 5 \times 10^{-6} \wedge S \geq 0.3001 \wedge A < 0.965 \wedge H < 0.9998, \\ q_{13} & \text{if } I < 5 \times 10^{-6} \wedge S < 0.3001 \wedge A \geq 0.965 \wedge H \geq 0.9998, \\ q_{14} & \text{if } I < 5 \times 10^{-6} \wedge S < 0.3001 \wedge A \geq 0.965 \wedge H < 0.9998, \\ q_{15} & \text{if } I < 5 \times 10^{-6} \wedge S < 0.3001 \wedge A < 0.965 \wedge H \geq 0.9998, \\ q_{16} & \text{if } I < 5 \times 10^{-6} \wedge S < 0.3001 \wedge A < 0.965 \wedge H < 0.9998, \end{cases}$$

$$\begin{aligned} k^V_{q_1} = 0,\ k^V_{q_5} = 0,\ k^V_{q_9} = 0,\ k^V_{q_{13}} = 0.1, \\ k^V_{q_2} = 0,\ k^V_{q_6} = 0,\ k^V_{q_{10}} = 0,\ k^V_{q_{14}} = 0, \\ k^V_{q_3} = 0,\ k^V_{q_7} = 0,\ k^V_{q_{11}} = 0,\ k^V_{q_{15}} = 0, \\ k^V_{q_4} = 0,\ k^V_{q_8} = 0,\ k^V_{q_{12}} = 0,\ k^V_{q_{16}} = 0, \end{aligned}$$

where $\mu^V_{q_1,q_2,q_3,q_4,q_5,q_6,q_7,q_8,q_9,q_{10},q_{11},q_{12},q_{13},q_{14},q_{15},q_{16}} = -1$.

The variable H is effected from the values of D, dead cell proportion, R, resistant cell proportion, V and F, amount of interferon. The approximation of variable H can be represented as

$$\frac{dH}{dt} = \mu^H_{q(t),M(t)} H + 0[D] + 0[R] + 0[V] + 0[F] + k^H_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } D \geq 1\times10^{-6} \wedge R \geq 1\times10^{-4} \wedge V \geq 1\times10^{-6} \wedge F \geq 0.02, \\ q_2 & \text{if } D \geq 1\times10^{-6} \wedge R \geq 1\times10^{-4} \wedge V \geq 1\times10^{-6} \wedge F < 0.02, \\ q_3 & \text{if } D \geq 1\times10^{-6} \wedge R \geq 1\times10^{-4} \wedge V < 1\times10^{-6} \wedge F \geq 0.02, \\ q_4 & \text{if } D \geq 1\times10^{-6} \wedge R \geq 1\times10^{-4} \wedge V < 1\times10^{-6} \wedge F < 0.02, \\ q_5 & \text{if } D \geq 1\times10^{-6} \wedge R < 1\times10^{-4} \wedge V \geq 1\times10^{-6} \wedge F \geq 0.02, \\ q_6 & \text{if } D \geq 1\times10^{-6} \wedge R < 1\times10^{-4} \wedge V \geq 1\times10^{-6} \wedge F < 0.02, \\ q_7 & \text{if } D \geq 1\times10^{-6} \wedge R < 1\times10^{-4} \wedge V < 1\times10^{-6} \wedge F \geq 0.02, \\ q_8 & \text{if } D \geq 1\times10^{-6} \wedge R < 1\times10^{-4} \wedge V < 1\times10^{-6} \wedge F < 0.02, \\ q_9 & \text{if } D < 1\times10^{-6} \wedge R \geq 1\times10^{-4} \wedge V \geq 1\times10^{-6} \wedge F \geq 0.02, \\ q_{10} & \text{if } D < 1\times10^{-6} \wedge R \geq 1\times10^{-4} \wedge V \geq 1\times10^{-6} \wedge F < 0.02, \\ q_{11} & \text{if } D < 1\times10^{-6} \wedge R \geq 1\times10^{-4} \wedge V < 1\times10^{-6} \wedge F \geq 0.02, \\ q_{12} & \text{if } D < 1\times10^{-6} \wedge R \geq 1\times10^{-4} \wedge V < 1\times10^{-6} \wedge F < 0.02, \\ q_{13} & \text{if } D < 1\times10^{-6} \wedge R < 1\times10^{-4} \wedge V \geq 1\times10^{-6} \wedge F \geq 0.02, \\ q_{14} & \text{if } D < 1\times10^{-6} \wedge R < 1\times10^{-4} \wedge V \geq 1\times10^{-6} \wedge F < 0.02, \\ q_{15} & \text{if } D < 1\times10^{-6} \wedge R < 1\times10^{-4} \wedge V < 1\times10^{-6} \wedge F \geq 0.02, \\ q_{16} & \text{if } D < 1\times10^{-6} \wedge R < 1\times10^{-4} \wedge V < 1\times10^{-6} \wedge F < 0.02, \end{cases}$$

$$\begin{aligned} k^H_{q_1} = 1,\ k^H_{q_5} = 0.995,\ k^H_{q_9} = 0.995,\ k^H_{q_{13}} = 1, \\ k^H_{q_2} = 1,\ k^H_{q_6} = 1,\quad k^H_{q_{10}} = 1,\quad k^H_{q_{14}} = 1, \\ k^H_{q_3} = 1,\ k^H_{q_7} = 1,\quad k^H_{q_{11}} = 1,\quad k^H_{q_{15}} = 1, \\ k^H_{q_4} = 1,\ k^H_{q_8} = 1,\quad k^H_{q_{12}} = 1,\quad k^H_{q_{16}} = 1, \end{aligned}$$

where $\mu^H_{q_1,q_2,q_3,q_4,q_5,q_6,q_7,q_8,q_9,q_{10},q_{11},q_{12},q_{13},q_{14},q_{15},q_{16}} = -1$.

The variable I is influenced by the values of H, V and E, effector cell concentration. The approximation of variable I can be given as;

$$\frac{dI}{dt} = \mu^I_{q(t),M(t)} I + 0[H] + 0[V] + 0[E] + k^I_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } H \geq 1 \ \wedge \ V \geq 0.01 \ \wedge \ E \geq 1, \\ q_2 & \text{if } H \geq 1 \ \wedge \ V \geq 0.01 \ \wedge \ E < 1, \\ q_3 & \text{if } H \geq 1 \ \wedge \ V < 0.01 \ \wedge \ E \geq 1, \\ q_4 & \text{if } H \geq 1 \ \wedge \ V < 0.01 \ \wedge \ E < 1, \\ q_5 & \text{if } H < 1 \ \wedge \ V \geq 0.01 \ \wedge \ E \geq 1, \\ q_6 & \text{if } H < 1 \ \wedge \ V \geq 0.01 \ \wedge \ E < 1, \\ q_7 & \text{if } H < 1 \ \wedge \ V < 0.01 \ \wedge \ E \geq 1, \\ q_8 & \text{if } H < 1 \ \wedge \ V < 0.01 \ \wedge \ E < 1, \end{cases}$$

$$\begin{aligned} k^I_{q_1} = 0, \ \ k^I_{q_5} = 0, \\ k^I_{q_2} = 0, \ \ k^I_{q_6} = 0, \\ k^I_{q_3} = 0, \ \ k^I_{q_7} = 0, \\ k^I_{q_4} = 0, \ \ k^I_{q_8} = 0.0002, \end{aligned}$$

where $\mu^I_{q_1,q_2,q_3,q_4,q_5,q_6,q_7,q_8} = -1$.

The variable M, activated APC proportion, is influenced by the values of D and V. The approximation of variable M can be illustrated as

$$\frac{dM}{dt} = \mu^M_{q(t),M(t)} M + 0[D] + 0[V] + k^M_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } D \geq 1 \times 10^{-5} \ \wedge \ V \geq 0.0005, \\ q_2 & \text{if } D \geq 1 \times 10^{-5} \ \wedge \ V < 0.0005, \\ q_3 & \text{if } D < 1 \times 10^{-5} \ \wedge \ V \geq 0.0005, \\ q_4 & \text{if } D < 1 \times 10^{-5} \ \wedge \ V < 0.0005, \end{cases}$$

$$k^M_{q_1} = 0.00005,$$
$$k^M_{q_2} = 0,$$
$$k^M_{q_3} = 0.00005,$$
$$k^M_{q_4} = 0,$$

where $\mu^M_{q_1,q_2,q_3,q_4} = -1$.

The values of M, I and H effects the amount of interferons, F. The approximation of variable F can be given as

$$\frac{dF}{dt} = \mu^F_{q(t),M(t)}F + 0[M] + 0[I] + 0[H] + k^F_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } M \geq 1 \times 10^{-6} \ \wedge \ I \geq 1 \times 10^{-7} \ \wedge \ H \geq 0.99999, \\ q_2 & \text{if } M \geq 1 \times 10^{-6} \ \wedge \ I \geq 1 \times 10^{-7} \ \wedge \ H < 0.99999, \\ q_3 & \text{if } M \geq 1 \times 10^{-6} \ \wedge \ I < 1 \times 10^{-7} \ \wedge \ H \geq 0.9999, \\ q_4 & \text{if } M \geq 1 \times 10^{-6} \ \wedge \ I < 1 \times 10^{-7} \ \wedge \ H < 0.99999, \\ q_5 & \text{if } M < 1 \times 10^{-6} \ \wedge \ I \geq 1 \times 10^{-7} \ \wedge \ H \geq 0.9999, \\ q_6 & \text{if } M < 1 \times 10^{-6} \ \wedge \ I \geq 1 \times 10^{-7} \ \wedge \ H < 0.99999, \\ q_7 & \text{if } M < 1 \times 10^{-6} \ \wedge \ I < 1 \times 10^{-7} \ \wedge \ H \geq 0.99999, \\ q_8 & \text{if } M < 1 \times 10^{-6} \ \wedge \ I < 1 \times 10^{-7} \ \wedge \ H < 0.99999, \end{cases}$$

$$k^F_{q_1} = 0, \ \ k^F_{q_5} = 0,$$
$$k^F_{q_2} = 0.5, \ \ k^F_{q_6} = 0,$$
$$k^F_{q_3} = 0.5, \ \ k^F_{q_7} = 0,$$
$$k^F_{q_4} = 0, \ \ k^F_{q_8} = 0,$$

where $\mu^{F}_{q_1,q_2,q_3,q_4,q_5,q_6,q_7,q_8} = -1$.

The variable R, resistant cell proportion, is influenced from the values of F and H. The approximation of variable R can be shown as

$$\frac{dR}{dt} = \mu^{R}_{q(t),M(t)}R + 0[F] + 0[H] + k^{R}_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } F \geq 0.02 \ \wedge \ H \geq 0.997, \\ q_2 & \text{if } F \geq 0.02 \ \wedge \ H < 0.997, \\ q_3 & \text{if } F < 0.02 \ \wedge \ H \geq 0.997, \\ q_4 & \text{if } F < 0.02 \ \wedge \ H < 0.997, \end{cases}$$

$$k^{R}_{q_1} = 0,$$
$$k^{R}_{q_2} = 0.00041,$$
$$k^{R}_{q_3} = 0,$$
$$k^{R}_{q_4} = 0,$$

where $\mu^{R}_{q_1,q_2,q_3,q_4} = -1$.

The values of M and I effects the effector cell amount, E. The approximation of variable E is illustrated as

$$\frac{dE}{dt} = \mu^{E}_{q(t),M(t)}E + 0[M] + 0[I] + k^{E}_{q(t),M(t)},$$

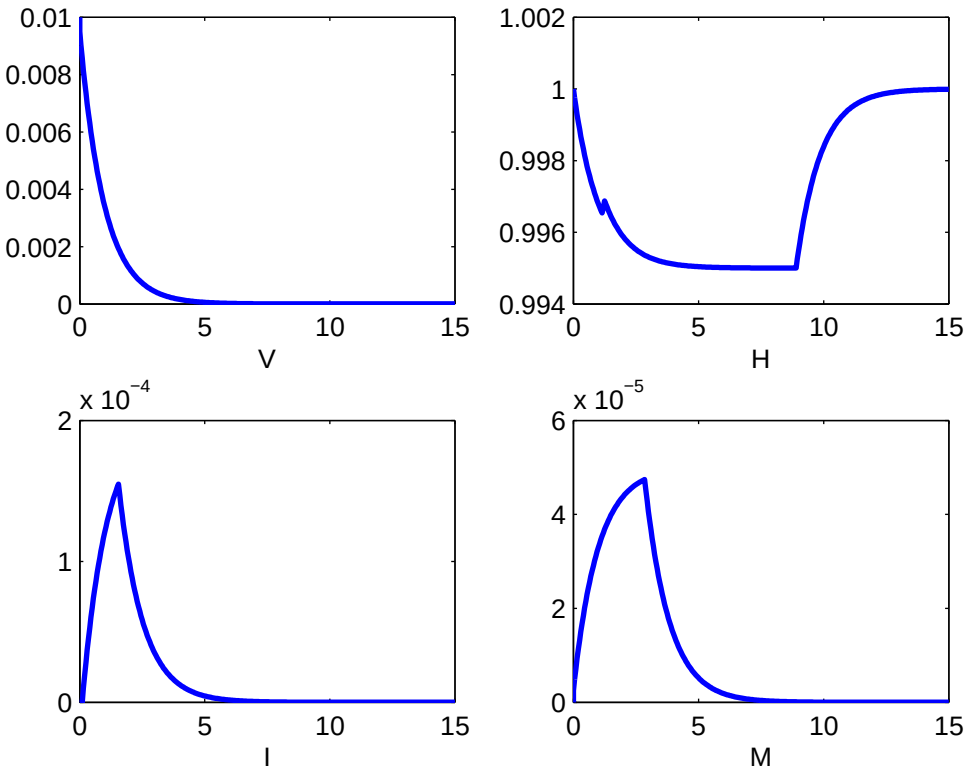

Figure 5.7: Numerical simulations of V, H, I and M variables with initial values $(V, H, I, M, F, R, E, P, A, S, D)$ =$(0.01, 1, 0, 0, 0, 0, 1, 1, 1, 0.3, 0)$.

$$q(t) = \begin{cases} q_1 & \text{if } M \geq 0.5 \times 10^{-5} \ \wedge \ M \geq 4 \times 10^{-5} \ \wedge \ I \geq 1 \times 10^{-6}, \\ q_2 & \text{if } M \geq 0.5 \times 10^{-5} \ \wedge \ M \geq 4 \times 10^{-5} \ \wedge \ I < 1 \times 10^{-6}, \\ q_3 & \text{if } M \geq 0.5 \times 10^{-5} \ \wedge \ M < 4 \times 10^{-5} \ \wedge \ I \geq 1 \times 10^{-6}, \\ q_4 & \text{if } M \geq 0.5 \times 10^{-5} \ \wedge \ M < 4 \times 10^{-5} \ \wedge \ I < 1 \times 10^{-6}, \\ q_5 & \text{if } M < 0.5 \times 10^{-5} \ \wedge \ M < 4 \times 10^{-5} \ \wedge \ I \geq 1 \times 10^{-6}, \\ q_6 & \text{if } M < 0.5 \times 10^{-5} \ \wedge \ M < 4 \times 10^{-5} \ \wedge \ I < 1 \times 10^{-6}, \end{cases}$$

$$k^E_{q_1} = 1.0002, \ \ k^E_{q_4} = 0.9997,$$
$$k^E_{q_2} = 1.0002, \ \ k^E_{q_5} = 1,$$
$$k^E_{q_3} = 1, \ \ k^E_{q_6} = 1,$$

where $\mu^E_{q_1,q_2,q_3,q_4,q_5,q_6} = -1$.

Activated plasma cell amount, P, is influenced by the values of M, amount of activated APC. The approximation of variable P is given as

$$\frac{dP}{dt} = \mu^P_{q(t),M(t)} P + 0[M] + k^P_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } M \geq 0.5 \times 10^{-5}, \\ q_2 & \text{if } M < 0.5 \times 10^{-5}, \end{cases}$$

$$k^P_{q_1} = 1.0008,$$
$$k^P_{q_2} = 1,$$

where $\mu^P_{q_1,q_2} = -1$.

The variable A, concentration of antibodies, is effected from the values of S, P

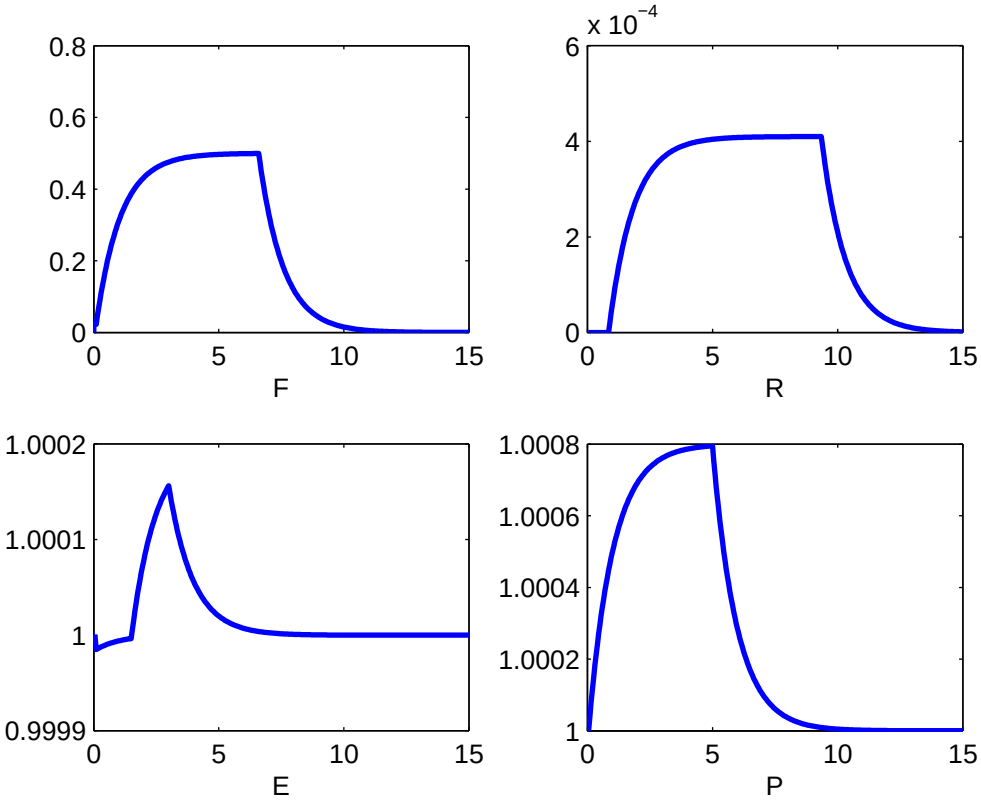

Figure 5.8: Numerical simulations of F, R, E and P variables with initial values $(V, H, I, M, F, R, E, P, A, S, D)$ =$(0.01, 1, 0, 0, 0, 0, 1, 1, 1, 0.3, 0)$.

and V. The approximation of variable A is shown as

$$\frac{dA}{dt} = \mu^{A}_{q(t),M(t)}A + 0[S] + 0[P] + 0[V] + k^{F}_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } S \geq 0.3001 \ \wedge \ P \geq 1.00001 \ \wedge \ V \geq 0.0005, \\ q_2 & \text{if } S \geq 0.3001 \ \wedge \ P \geq 1.00001 \ \wedge \ V < 0.0005, \\ q_3 & \text{if } S \geq 0.3001 \ \wedge \ P < 1.00001 \ \wedge \ V \geq 0.0005, \\ q_4 & \text{if } S \geq 0.3001 \ \wedge \ P < 1.00001 \ \wedge \ V < 0.0005, \\ q_5 & \text{if } S < 0.3001 \ \wedge \ P \geq 1.00001 \ \wedge \ V \geq 0.0005, \\ q_6 & \text{if } S < 0.3001 \ \wedge \ P \geq 1.00001 \ \wedge \ V < 0.0005, \\ q_7 & \text{if } S < 0.3001 \ \wedge \ P < 1.00001 \ \wedge \ V \geq 0.0005, \\ q_8 & \text{if } S < 0.3001 \ \wedge \ P < 1.00001 \ \wedge \ V < 0.0005, \end{cases}$$

$$k^{A}_{q_1} = 0.96, \ \ k^{A}_{q_5} = 0.94,$$
$$k^{A}_{q_2} = 0.96, \ \ k^{A}_{q_6} = 0.94,$$
$$k^{A}_{q_3} = 0.94, \ \ k^{A}_{q_7} = 0.94,$$
$$k^{A}_{q_4} = 0.96, \ \ k^{A}_{q_8} = 0.94,$$

Plasma cell proportion, P, effects S. The approximation of variable S, antigenic compatibility, is given as

$$\frac{dS}{dt} = \mu^{S}_{q(t),M(t)}S + 0[P] + k^{S}_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } P \geq 1, \\ q_2 & \text{if } P < 1, \end{cases}$$

$$k^S_{q_1} = 0.3003,$$
$$k^S_{q_2} = 0.3,$$

where $\mu^S_{q_1,q_2} = -1$.

The variable D, dead cell proportion, is influenced by the values of H, R and I. The approximation of variable D can be illustrated as

$$\frac{dD}{dt} = \mu^D_{q(t),M(t)} D + 0[H] + 0[R] + 0[I] + k^D_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } H \geq 0.999999 \ \wedge \ R \geq 2 \times 10^{-3} \ \wedge \ I \geq 1 \times 10^{-7}, \\ q_2 & \text{if } H \geq 0.999999 \ \wedge \ R \geq 2 \times 10^{-3} \ \wedge \ I < 1 \times 10^{-7}, \\ q_3 & \text{if } H \geq 0.999999 \ \wedge \ R < 2 \times 10^{-3} \ \wedge \ I \geq 1 \times 10^{-7}, \\ q_4 & \text{if } H \geq 0.999999 \ \wedge \ R < 2 \times 10^{-3} \ \wedge \ I < 1 \times 10^{-7}, \\ q_5 & \text{if } H < 0.999999 \ \wedge \ R \geq 2 \times 10^{-3} \ \wedge \ I \geq 1 \times 10^{-7}, \\ q_6 & \text{if } H < 0.999999 \ \wedge \ R \geq 2 \times 10^{-3} \ \wedge \ I < 1 \times 10^{-7}, \\ q_7 & \text{if } H < 0.999999 \ \wedge \ R < 2 \times 10^{-3} \ \wedge \ I \geq 1 \times 10^{-7}, \\ q_8 & \text{if } H < 0.999999 \ \wedge \ R < 2 \times 10^{-3} \ \wedge \ I < 1 \times 10^{-7}, \end{cases}$$

$$k_{q_1}^D = 0,\ \ k_{q_5}^D = 0,$$
$$k_{q_2}^D = 0,\ \ k_{q_6}^D = 0,$$
$$k_{q_3}^D = 0,\ \ k_{q_7}^D = 0,$$
$$k_{q_4}^D = 0.000071,\ \ k_{q_8}^D = 0,$$

where $\mu^D_{q_1,q_2,q_3,q_4,q_5,q_6,q_7,q_8} = -1$.

The whole system can be demonstrated as;

$$\frac{dy}{dt} = A_{q^3(t),M(t)}y(t) + B_{q^3(t),M(t)}y(t) + k_{q^3(t),M(t)},$$

where $q^3(t) = \left\{q^V(t) \cup q^H(t) \cup q^I(t) \cup q^M(t) \cup q^F(t) \cup q^R(t) \cup q^E(t) \cup q^P(t) \cup q^A(t) \cup q^S(t) \cup q^D(t)\right\}$ and $y = [V\ H\ I\ M\ F\ R\ E\ P\ A\ S\ D]'$ and

$$\mathbf{A_{q^3(t),M(t)}} = \begin{pmatrix} -1 & 0 & \dots & \dots & 0 \\ 0 & -1 & 0 & \dots & 0 \\ \vdots & & \ddots & & \vdots \\ \vdots & & 0 & -1 & 0 \\ 0 & \dots & \dots & 0 & -1 \end{pmatrix}_{(11\times 11)},$$

$$\mathbf{B_{q^3(t),M(t)}} = \begin{pmatrix} 0 & \dots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \dots & 0 \end{pmatrix}_{(11\times 11)}.$$

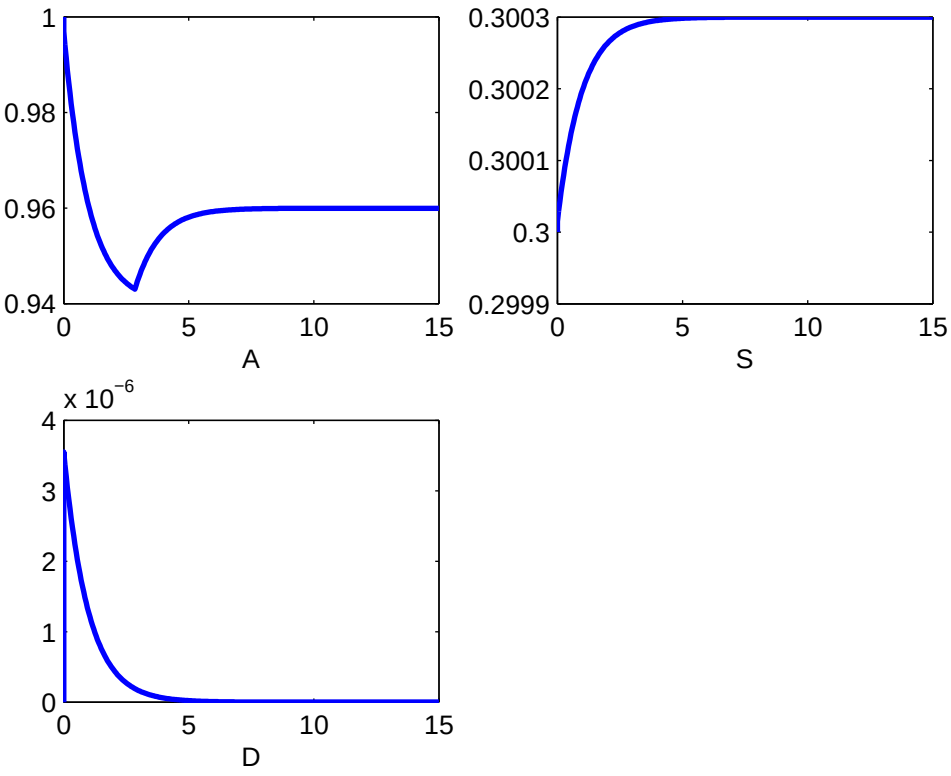

Figure 5.9: Numerical simulations of A, S and D variables with initial values $(V, H, I, M, F, R, E, P, A, S, D)$ =$(0.01, 1, 0, 0, 0, 0, 1, 1, 1, 0.3, 0)$.

5.3 Chronic Regime

As mentioned in Chapter 4, the disease can exhibit chronic behavior. The characteristic behavior of this regime is that virus load, V, can not be decreased by the organism and the healthy cell proportion, H, can not increase as illustrated by the Figure 4.10. Moreover, following values characterizes the chronic regime [22];

$$(V, H, I, M, F, R, E, P, A) = (5.26, 0.06, 0.018, 0.05, 1484, 0.89, 67.0).$$

A hybrid model of two variables constructed in this case since this is a special case because antigenic compatibility variable S does not change, its value stays at 0, V does not decrease and H can not reach 1. So, a model of two variables which characterizes this regime is constructed.

$$\frac{dV}{dt} = \mu^V_{q(t),M(t)} V + 0[H] + k^V_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } H \geq 0.1, \\ q_2 & \text{if } H < 0.1, \end{cases}$$

$$k^V_{q_1} = 100,$$
$$k^V_{q_2} = 5,$$

where $\mu^V_{q_1,q_2} = -1$.

$$\frac{dH}{dt} = \mu^H_{q(t),M(t)} M + 0[V] + k^H_{q(t),M(t)},$$

$$q(t) = \begin{cases} q_1 & \text{if } V \geq 1 \times 10^{-6} \ \wedge \ V \geq 70, \\ q_2 & \text{if } V \geq 1 \times 10^{-6} \ \wedge \ V < 70, \\ q_3 & \text{if } V < 1 \times 10^{-6} \ \wedge \ V < 70, \end{cases}$$

$$k_{q_1}^H = 0,$$
$$k_{q_2}^H = 0.06,$$
$$k_{q_3}^H = 0,$$

where $\mu_{q_1,q_2,q_3}^H = -1$.

The whole system can be demonstrated as;

$$\frac{dy}{dt} = A_{q^4(t),M(t)}y(t) + B_{q^4(t),M(t)}y(t) + k_{q^4(t),M(t)},$$

where $q^4(t) = \left\{q^V(t) \cup q^H(t)\right\}$ and $y = [V \ H]'$ and

$$\mathbf{A_{q^4(t),M(t)}} = \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix},$$

$$\mathbf{B_{q^4(t),M(t)}} = \begin{pmatrix} 0 & 0 \\ 0 & 0 \end{pmatrix}.$$

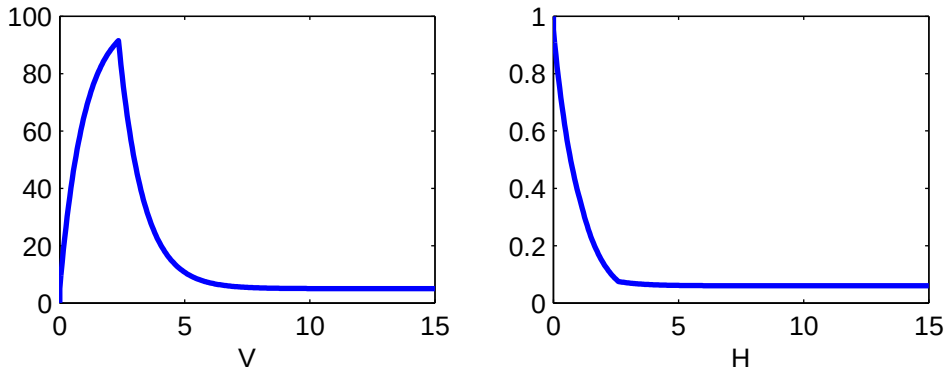

Figure 5.10: Hybrid model simulation of the chronic state

CHAPTER 6

SENSITIVITY ANALYSIS OF THE MODEL

6.1 Introduction

To determine if a model is sensitive to changes in the value of the model or to changes in the structure of the model, sensitivity analysis is used. Parameter sensitivity is useful to explain if a change in the parameter causes a change in the dynamic behavior of the system. Since sensitivity analysis helps to understand how the model responds to changes in parameter values, it is useful in both model building and model evaluation.

Sensitivity analysis represents a confident way of determining the parameter values, since to measure them with a great accuracy in the real world is very difficult, or sometimes impossible. Thus, most of the time parameter values are estimated when modeling a dynamical system. Sensitivity analysis helps to decide on the accuracy of the parameter which makes the model sufficiently valid. It also demonstrates if using a parameter in the model is reasonable or not.

By performing sensitivity tests, to understand the dynamics of a system is also possible. A leverage point, a parameter whose specific value can significantly effect the behavior of the system, can be observed by experimenting with

a wide range of values. There are some different approaches to analyze sensitivity like constructing a sensitivity equation [64] and analyzing the system's dynamics according to this equation or solving an inverse problem [13].

6.2 Sensitivity Analysis of The Hybrid Model

In the hybrid model with memory, there are two parameters: thresholds and focal points. In this chapter, we investigated the different values of thresholds in order to determine the effect of varying the inputs of our model on the output of the model itself. This tool is important in the sense of understanding the model's behavior in response to changes in its inputs and ensuring the correct use of the model.

In order to study sensitivity, the baseline values for every threshold are increased and decreased and the effects of changes in the model are investigated. For this purpose, the m-file which is also used in order to obtain the simulations of Chapter 5 and represented in the Appendix is used. The resulting simulations of the m-file are investigated with different threshold values. Depending on the varying values, some changes in the regime, the severity or the duration of disease are observed (see Tables 6.1 and 6.2). If the virus load does not increase and starts to decrease immediately in typical case, this is considered as a change in the disease regime, actually towards an asymptomatic state. If dead cell proportion, D, increases, this is commented as the severity of disease increases like Hancioglu, et al. [22] considered in their work. If healthy cell proportion, H, cannot reach 1 and the virus load cannot reach 0, then this is considered as the chronic regime. In order to decide the duration of disease, the times when D

exceeds and drops below 0.1 is measured. In the tables, the threshold values named as h_V, h_H, h_I, h_M, h_F, h_R, h_E, h_P, h_A, h_S and h_D are the threshold values that are used to construct the hybrid model in every module for typical and asymptomatic regimes in Chapter 5. For example, the variable h_I of module V in the Table 6.1 corresponds to the I value of module V of Chapter 5, i.e. 10^{-7}.

Table 6.1: Sensitivity analysis of typical regime

Module	Threshold	Baseline(range)	Model behavior
V	h_I	$10^{-7}[10^{-7} - 10^{-6}]$	• as gets higher values the organism is not able to clear the virus in 15 days. • for lower values asymptomatic regime occurs.
	h_S	$0.1[0 - 0.1]$	• for higher values the disease is asymptomatic.
	h_A	$0.1[0 - 1]$	• for higher values the disease is asymptomatic.
	h_H	$0.99999[0 - 1]$	• does not effect.
H	h_D	$10^{-5}[10^{-5} - 0.36]$	• for $h_D = 0$ the organism is able to clear the virus in 5 days. • for higher values the duration of disease extends.
	h_R	$10^{-5}[0 - 0.99]$	• for higher values asymptomatic regime occurs and duration and severity of disease increase.
	h_V	$0[0 - 0.01]$	• for higher values the disease is asymptomatic and duration and severity of disease increase.
	h_F	$0.99999[0 - 1]$	• for $h_F = 0$ the disease is asymptomatic and duration and severity of disease increase.
I	h_H	$0.99999(0 - 1)$	• for $h_H = 0$ the disease approaches to chronic regime (can not clear the virus in 15 days).
	h_V	$1[0.001 - 120]$	• for lower values the disease is asymptomatic. • for higher values, virus load gets higher values till the virus is cleaned.
	h_E	$1.000001(0.09 - \infty)$	• for lower values the disease approaches to chronic state.
M	h_D	$0.99999(0 - 1]$	• for $h_D = 0$ disease approaches to chronic.
	h_V	5	• does not effect.
F	h_M	$0.2(0 - \infty)$	• does not effect.
	h_I	$10^{-7}[0 - 1]$	• does not effect.
	h_H	$0.9999999[0 - 1]$	• does not effect.
R	h_F	$10(0 - \infty)$	• for $h_F = 0$ disease is asymptomatic.
	h_H	$0.9999999[0 - 1]$	• does not effect.
E	h_M	$0.3[0.1 - \infty)$	• out of the range, the disease approaches to chronic.
	h_I	$1[0.001 - 120]$	•$h_I = 0$ the disease approaches to chronic.
P	h_{M_1}	10^{-6}	• does not effect.
	h_{M_2}	0.3	• does not effect.
A	h_S	$0.15[0 - 1]$	• does not effect.
	h_P	$5000(0 - \infty)$	• does not effect.
	h_V	$0(0 - \infty)$	• does not effect.
S	h_P	$5000(0 - \infty)$	• does not effect.
D	h_H	$0.99[0 - 1]$	• does not effect.
	h_R	$0.9[0 - 1]$	• as approaches to 0 the organism's reply is late. • when $h_R = 0$, severity of disease increase.
	h_I	$0.001(0 - 1)$	• $h_I = 0$ the disease is asymptomatic.

Table 6.2: Sensitivity analysis of asymptomatic regime

Module	Threshold	Baseline(range)	Model behavior
V	h_I	$5 \times 10^{-6}[0-1]$	• does not effect.
	h_S	$0.1[0-0.1]$	• does not effect.
	h_A	$0.1[0-1]$	• does not effect.
	h_H	$0.9998[0-1]$	• does not effect.
H	h_D	$10^{-6}[9 \times 10^{-7} - 1.2 \times 10^{-6}]$	• for higher values severity increases.
	h_R	$10^{-4}[3 \times 10^{-5} - 1.7 \times 10^{-4}]$	• for higher and lower values severity increases.
	h_V	$10^{-6}[0-10^{-5}]$	• for higher values severity increases.
	h_F	$0.02[0-0.025]$	• for higher values severity increases.
I	h_H	$1[0.9989-1]$	• for lower values duration of severity increases
	h_V	$0.001[0.0075-0.01]$	• for lower values duration of severity increases
	h_E	$1[1-\infty)$	• for lower values severity increases.
M	h_D	$0.00001[0-1]$	• does not effect.
	h_V	$0.0005[0-0.0095]$	• for higher values severity increases.
F	h_M	$0.000001[0-2.5 \times 10^{-6}]$	• for higher values severity increases.
	h_I	$10^{-7}(0-0.00002)$	• for higher values duration of severity increases. • for $h_I = 0$ severity increases.
	h_H	$0.99999[0.9966-1]$	• for lower values severity increases.
R	h_F	$0.02[0-0.049]$	•for higher values severity increases.
	h_H	$0.997[0.9968-1]$	• for lower values severity increases.
E	h_{M_1}	0.000005	• does not effect.
	h_{M_2}	0.00004	• does not effect.
	h_I	0.000001	• does not effect.
P	h_M	0.000005	• does not effect.
A	h_S	$0.3001[0-1]$	• does not effect.
	h_P	1.00001	• does not effect.
	h_V	0.0005	• does not effect.
S	h_P	1	• does not effect.
D	h_H	$0.999999[0.99999-1]$	• for lower values severity increases.
	h_R	0.002	• for higher and lower values stays asymptomatic.
	h_I	10^{-7}	• for higher and lower values stays asymptomatic.

CHAPTER 7

FUTURE WORK

In this work, the deterministic case of hybrid systems with memory is explained and applied. In this case, the first transitions are determined by partitioning the initial set of variables and the future behavior of these variables are determined according to these partitionings. However, in nature and science, there exist random behaviors. With our deterministic approach, this randomness cannot be investigated properly. For a more realistic model, stochastic hybrid systems with memory [45] should be developed. In that case, the first behavior of variable or variables can be thought as random until the event of hitting to the boundaries or until the state transition. After hitting one of the boundaries, the system exhibits a differentiation depending on which boundary is hitted or which state transition is occurred. This property characterizes the effect of the memory on the system. Depending on the memory, the system can have different solutions with different distributions, mean and variance values.

If such a model can be constructed, in which memory is contained, then the history of the system can be investigated by analyzing the distributional behavior, mean or variance values of the system. By this way, the future behavior of the system can be arranged by control variables, so that the system can exhibit the desired behavior. As an illustration, if the dimension is assumed as $n = 1$ and the initial set $Y(t_0) \in Inv(q(t_0), m(t_0))$ where $(q(t_0), m(t_0))$ is the zero state of the

system, the governing dynamics of the system until it hits one of the boundaries can be denoted by [45]

$$dY_t = \sigma_0 Y_t dW_t, \tag{7.0.1}$$

$$Y_0 = y_0, \forall y_0 \in (b_1, b_2), \tag{7.0.2}$$

where b_1, b_2 is 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 constructing models for the systems which shows random behavior in the memory. Moreover, if the model is constructed properly, then the possible effects of changes in conditions on system behaviors 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.

CHAPTER 8

CONCLUSION

In this thesis, hybrid systems with memory are introduced, applied and investigated. Firstly, a background of the system is explained in detail by giving examples. Then, the system is introduced with two illustrative examples. An ODE model of human immune response to *Influenza A* virus, chosen from literature, is explained and the application of a hybrid model with memory to this ODE model is performed piecewise linearly. 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. The sensitivity analysis of the hybrid model is observed in order to find the baseline values of thresholds, so that an uncertainty analysis of the model can be done in the future.

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.

In this work, a deterministic case of the proposed model is observed. However, a stochastic case will give more realistic results as discussed in the future work part. To model the memory dependent behavior with stochastic hybrid systems with memory is a promising challenge.

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appendix A

Matlab m-file for Chapter 4

The following m-file is written by inspiring from the m-files of M. Kahraman [30]. In order to obtain the ODE simulations of Chapter 4 the following matlab m-file is used. Initial values of the typical case is given in "initial values of global variables" which are used in the simulations for the typical regime of ODE model. For the asymptomatic type simulations of Chapter 4, $S = 0.3$ is used.

```
function result=influenza_1
global V;
global H;
global I;
global M;
global F;
global R;
global E;
global P;
global A;
global S;
global D;
% initial values of global variables************
```

```
V=0.01;

H=1;

I=0;

M=0;

F=0;

R=0;

E=1;

P=1;

A=1;

S=0.1;

D=0;

%initial values of iteration**************

V_i=V;

H_i=H;

I_i=I;

M_i=M;

F_i=F;

R_i=R;

E_i=E;

P_i=P;

A_i=A;

S_i=S;

D_i=D;

%time

t_initial=0;
```

```
t=t_initial;
t_step=0.05;
t_final=15;
%Arrays of variables and time
V_array=[0 V];
H_array=[0 H];
I_array=[0 I];
M_array=[0 M];
F_array=[0 F];
R_array=[0 R];
E_array=[0 E];
P_array=[0 P];
A_array=[0 A];
S_array=[0 S];
D_array=[0 D];
t_array=t_initial;
options = odeset('RelTol',1e-4,'AbsTol',[1e-4 1e-4 1e-5]);
for t=t_initial:t_step:t_final
%V*******************************************************
    aa= ode23t(@dV_dt,[t t+t_step],V);
    V_i=aa.y(11);
    V_array=[V_array;[t V_i]];
%H*******************************************************
    aa = ode23t(@dH_dt,[t t+t_step],H);
    H_i=aa.y(11);
```

```
    H_array=[H_array;[t H_i]];
%I*******************************************************
    aa = ode23t(@dI_dt,[t t+t_step],I);
    I_i=aa.y(11);
    I_array=[I_array;[t I_i]];
%M*******************************************************
    aa = ode23t(@dM_dt,[t t+t_step],M);
    M_i=aa.y(11);
    M_array=[M_array;[t M_i]];
%F*******************************************************
    aa = ode23t(@dF_dt,[t t+t_step],F);
    F_i=aa.y(11);
    F_array=[F_array;[t F_i]];
%R*******************************************************
    aa = ode23t(@dR_dt,[t t+t_step],R);
    R_i=aa.y(11);
    R_array=[R_array;[t R_i]];
%E*******************************************************
    aa = ode23t(@dE_dt,[t t+t_step],E);
    E_i=aa.y(11);
    E_array=[E_array;[t E_i]];
%P*******************************************************
    aa = ode23t(@dP_dt,[t t+t_step],P);
    P_i=aa.y(11);
    P_array=[P_array;[t P_i]];
```

```
 %A*******************************************************
    aa = ode23t(@dA_dt,[t t+t_step],A);
    A_i=aa.y(11);
    A_array=[A_array;[t A_i]];
 %S*******************************************************
    aa = ode23t(@dS_dt,[t t+t_step],S);
    S_i=aa.y(11);
    S_array=[S_array;[t S_i]];
  %D*******************************************************
     D_i=D_equation(H,R,I);
     D_array=[D_array;[t D_i]];
 %Change global variables
 V=V_i;
 H=H_i;
 I=I_i;
 M=M_i;
 F=F_i;
 R=R_i;
 E=E_i;
 P=P_i;
 A=A_i;
 S=S_i;
 D=D_i;
end
subplot(2,2,1)
```

```
plot(V_array(:,1),V_array(:,2),'LineWidth',2);
xlabel('V')
subplot(2,2,2)
plot(H_array(:,1),H_array(:,2),'LineWidth',2);
xlabel('H')
subplot(2,2,3)
plot(I_array(:,1),I_array(:,2),'LineWidth',2);
xlabel('I')
subplot(2,2,4)
plot(M_array(:,1),M_array(:,2),'LineWidth',2);
xlabel('M')
figure;
subplot(2,2,1)
plot(F_array(:,1),F_array(:,2),'LineWidth',2);
xlabel('F')
subplot(2,2,2)
plot(R_array(:,1),R_array(:,2),'LineWidth',2);
xlabel('R')
subplot(2,2,3)
plot(E_array(:,1),E_array(:,2),'LineWidth',2);
xlabel('E')
subplot(2,2,4)
plot(P_array(:,1),P_array(:,2),'LineWidth',2);
xlabel('P')
figure;
```

```
subplot(2,2,1)
plot(A_array(:,1),A_array(:,2),'LineWidth',2);
xlabel('A')
subplot(2,2,2)
plot(S_array(:,1),S_array(:,2),'LineWidth',2);
xlabel('S')
subplot(2,2,3)
plot(D_array(:,1),D_array(:,2),'LineWidth',2);
xlabel('D')
end
%Differential equation of V
function result = dV_dt(t,param_V)
    global I;
    global S;
    global A;
    global H;
    gama_V=510;
    gama_VA=619.2;
    gama_VH=1.02;
    alfa_V=1.7;
    a_V1=100;
    a_V2=23000;
    result=gama_V*I-gama_VA*S*A*param_V-gama_VH*H*param_V
    -alfa_V*param_V-((a_V1*param_V)/(1+a_V2*param_V));
end
```

```
%Differential equation of H
function result=dH_dt(t,param_H)
     global D;
     global R;
     global V;
     global F;
     b_HD=4;
     a_R=1;
     gama_HV=0.34;
     b_HF=0.01;
result=b_HD*D*(param_H+R)+a_R*R-gama_HV*V*param_H-b_HF*F*param_H;
end
%Differential equation of I
function result = dI_dt(t,param_I)
    global V;
    global H;
    global E;
    gama_HV=0.34;
    b_IE=0.066;
    a_I=1.5;
    result=gama_HV*V*H-b_IE*E*param_I-a_I*param_I;
end
%Differential equation of M
function result = dM_dt(t,param_M)
    global D;
```

```
    global V;
    b_MD=1;
    b_MV=0.0037;
    a_M=1;
    result=(b_MD*D+b_MV*V)*(1-param_M)-a_M*param_M;
end
%Differential equation of F
function result = dF_dt(t,param_F)
    global M;
    global I;
    global H;
    b_F=250000;
    c_F=2000;
    b_FH=17;
    a_F=8;
    result=b_F*M+c_F*I-b_FH*H*param_F-a_F*param_F;
end
%Differential equation of R
function result = dR_dt(t,param_R)
    global F;
    global H;
    b_HF=0.01;
    a_R=1;
    result= b_HF*F*H-a_R*param_R;
end
```

```
%Differential equation of E
function result = dE_dt(t,param_E)
    global M;
    global I;
    b_EM=8.3;
    b_EI=2.72;
    a_E=0.4;
    result=b_EM*M*param_E-b_EI*I*param_E+a_E*(1-param_E);
end
 %Differential equation of P
 function result = dP_dt(t,param_P)
     global M;
     b_PM=11.5;
     a_P=0.4;
     result=b_PM*M*param_P+a_P*(1-param_P);
 end
  %Differential equation of A
  function result = dA_dt(t,param_A)
    global P;
    global S;
    global V;
    b_A=0.043;
    gama_AV=146.2;
    a_A=0.043;
    result=b_A*P-gama_AV*S*param_A*V-a_A*param_A;
```

```
  end
  %Differential equation of S
  function result = dS_dt(t,param_S)
      global P;
      r=0.00003;
      result=r*P*(1-param_S);
  end
%Algebraic equation of D
function result=D_equation(param_H,param_R,param_I)
    result=1-param_H-param_R-param_I;
end
```

APPENDIX B

MATLAB M-FILE FOR CHAPTER 5

The following m-file is written by inspiring from the m-files of M. Kahraman [30]. For Chapter 5 the following m-file is used. Only the m-file which is used for the typical regime is given. For asymptomatic and chronic types m-files can be written by using the corresponding threshold and focal point values.

```
function infuenza_hybrid_new
%V
V=0.01;
global V_array;
V_array=[0 V];
%H
H=1;
global H_array;
H_array=[0 H];
%I
I=0;
global I_array;
I_array=[0 I];
%M
```

```
M=0;
global M_array;
M_array=[0 M];
%F
F=0;
global F_array;
F_array=[0 F];
%R
R=0;
global R_array;
R_array=[0 R];
%E
E=1;
global E_array;
E_array=[0 E];
%P
P=1;
global P_array;
P_array=[0 P];
%A
A=1;
global A_array;
A_array=[0 A];
%S
S=0.1;
```

```
global S_array;
S_array=[0 S];
%D
D=0;
global D_array;
D_array=[0 D];
%time
t_step=0.05;
t_initial=0;
t_final=15;
global t;
for t=t_initial:t_step:t_final
    V=V_module(V,I,S,A,H,t_step);
    V_array=[V_array;[t V]];
    H=H_module(H,D,R,V,F,t_step);
    H_array=[H_array;[t H]];
    I=I_module(I,H,V,E,t_step);
    I_array=[I_array;[t I]];
    M=M_module(M,D,V,t_step);
    M_array=[M_array;[t M]];
    F=F_module(F,M,I,H,t_step);
    F_array=[F_array;[t F]];
    R=R_module(R,F,H,t_step);
    R_array=[R_array;[t R]];
    E=E_module(E,M,I,t_step);
```

```
    E_array=[E_array;[t E]];
    P=P_module(P,M,t_step);
    P_array=[P_array;[t P]];
    A=A_module(A,S,P,V,t_step);
    A_array=[A_array;[t A]];
    S=S_module(S,P,t_step);
    S_array=[S_array;[t S]];
    D=D_module(D,H,R,I,t_step);
    D_array=[D_array;[t D]];
end
subplot(2,2,1)
plot(V_array(:,1),V_array(:,2),'LineWidth',2);
xlabel('V')
subplot(2,2,2)
plot(H_array(:,1),H_array(:,2),'LineWidth',2);
xlabel('H')
subplot(2,2,3)
plot(I_array(:,1),I_array(:,2),'LineWidth',2);
xlabel('I')
subplot(2,2,4)
plot(M_array(:,1),M_array(:,2),'LineWidth',2);
xlabel('M')
figure;
subplot(2,2,1)
plot(F_array(:,1),F_array(:,2),'LineWidth',2);
```

```
xlabel('F')
subplot(2,2,2)
plot(R_array(:,1),R_array(:,2),'LineWidth',2);
xlabel('R')
subplot(2,2,3)
plot(E_array(:,1),E_array(:,2),'LineWidth',2);
xlabel('E')
subplot(2,2,4)
plot(P_array(:,1),P_array(:,2),'LineWidth',2);
xlabel('P')
figure;
subplot(2,2,1)
plot(A_array(:,1),A_array(:,2),'LineWidth',2);
xlabel('A')
subplot(2,2,2)
plot(S_array(:,1),S_array(:,2),'LineWidth',2);
xlabel('S')
subplot(2,2,3)
plot(D_array(:,1),D_array(:,2),'LineWidth',2);
xlabel('D')
%V module
function result_V=V_module(V,I,S,A,H,t_step)
i=0.0000001;
s=0.1;
a=1;
```

```
h=0.99999;
k1=0;
k2=0;
k3=0;
k4=0;
k5=0;
k6=0;
k7=0;
k8=0;
k9=0;
k10=2500;
k11=0;
k12=0;
k13=0;
k14=0;
k15=0;
k16=0;
if I>=i & S>=s & A>=a & H>=h
    f=@(x)(-1)*x+k1;
    result_V=Euler_Method(V,f,t_step);
elseif I>=i & S>=s & A>=a & H<h
    f=@(x)(-1)*x+k2;
    result_V=Euler_Method(V,f,t_step);
elseif I>=i & S>=s & A<a & H>=h
    f=@(x)(-1)*x+k3;
```

```
    result_V=Euler_Method(V,f,t_step);
elseif I>=i & S>=s & A<a & H<h
    f=@(x)(-1)*x+k4;
    result_V=Euler_Method(V,f,t_step);
elseif I>=i & S<s & A>=a & H>=h
    f=@(x)(-1)*x+k5;
    result_V=Euler_Method(V,f,t_step);
elseif I>=i & S<s & A>=a & H<h
    f=@(x)(-1)*x+k6;
    result_V=Euler_Method(V,f,t_step);
elseif I>=i & S<s & A<a & H>=h
    f=@(x)(-1)*x+k7;
    result_V=Euler_Method(V,f,t_step);
elseif I>=i & S<s & A<a & H<h
    f=@(x)(-1)*x+k8;
    result_V=Euler_Method(V,f,t_step);
elseif I<i & S>=s & A>=a & H>=h
    f=@(x)(-1)*x+k9;
    result_V=Euler_Method(V,f,t_step);
elseif I<i & S>=s & A>=a & H<h
    f=@(x)(-1)*x+k10;
    result_V=Euler_Method(V,f,t_step);
elseif I<i & S>=s & A<a & H>=h
    f=@(x)(-1)*x+k11;
    result_V=Euler_Method(V,f,t_step);
```

```
elseif I<i & S>=s & A<a & H<h
    f=@(x)(-1)*x+k12;
    result_V=Euler_Method(V,f,t_step);
elseif I<i & S<s & A>=a & H>=h
    f=@(x)(-1)*x+k13;
    result_V=Euler_Method(V,f,t_step);
elseif I<i & S<s & A>=a & H<h
    f=@(x)(-1)*x+k14;
    result_V=Euler_Method(V,f,t_step);
elseif I<i & S<s & A<a & H>=h
    f=@(x)(-1)*x+k15;
    result_V=Euler_Method(V,f,t_step);
elseif I<i & S<s & A<a & H<h
    f=@(x)(-1)*x+k16;
    result_V=Euler_Method(V,f,t_step);
end
%H module
function result_H=H_module(H,D,R,V,F,t_step)
d=0.00001;
r=0.00001;
v=0;
f=0.00001;
k1=1;
k2=0;
k3=1;
```

```
k4=1;
k5=1;
k6=1;
k7=1;
k8=1;
k9=1;
k10=1;
k11=1;
k12=1;
k13=1;
k14=1;
k15=1;
k16=1;
 if D>=d & R>=r & V>=v & F>=f
    f=@(x)(-1)*x+k1;
    result_H=Euler_Method(H,f,t_step);
 elseif D>=d & R>=r & V>=v & F<f
    f=@(x)(-1)*x+k2;
    result_H=Euler_Method(H,f,t_step);
 elseif D>=d & R>=r & V<v & F>=f
    f=@(x)(-1)*x+k3;
    result_H=Euler_Method(H,f,t_step);
 elseif D>=d & R>=r & V<v & F<f
    f=@(x)(-1)*x+k4;
    result_H=Euler_Method(H,f,t_step);
```

```
elseif D>=d & R<r & V>=v & F>=f
   f=@(x)(-1)*x+k5;
   result_H=Euler_Method(H,f,t_step);
elseif D>=d & R<r & V>=v & F<f
   f=@(x)(-1)*x+k6;
   result_H=Euler_Method(H,f,t_step);
elseif D>=d & R<r & V<v & F>=f
   f=@(x)(-1)*x+k7;
   result_H=Euler_Method(H,f,t_step);
elseif D>=d & R<r & V<v & F<f
   f=@(x)(-1)*x+k8;
   result_H=Euler_Method(H,f,t_step);
elseif D<d & R>=r & V>=v & F>=f
   f=@(x)(-1)*x+k9;
   result_H=Euler_Method(H,f,t_step);
elseif D<d & R>=r & V>=v & F<f
   f=@(x)(-1)*x+k10;
   result_H=Euler_Method(H,f,t_step);
elseif D<d & R>=r & V<v & F>=f
   f=@(x)(-1)*x+k11;
   result_H=Euler_Method(H,f,t_step);
elseif D<d & R>=r & V<v & F<f
   f=@(x)(-1)*x+k12;
   result_H=Euler_Method(H,f,t_step);
elseif D<d & R<r & V>=v & F>=f
```

```
    f=@(x)(-1)*x+k13;
    result_H=Euler_Method(H,f,t_step);
 elseif D<d & R<r & V>=v & F<f
    f=@(x)(-1)*x+k14;
    result_H=Euler_Method(H,f,t_step);
 elseif D<d & R<r & V<v & F>=f
    f=@(x)(-1)*x+k15;
    result_H=Euler_Method(H,f,t_step);
 elseif D<d & R<r & V<v & F<f
    f=@(x)(-1)*x+k16;
    result_H=Euler_Method(H,f,t_step);
 end
%I module
function result_I=I_module(I,H,V,E,t_step)
h=0.99999;
v=1;
e=1.000001;
k1=0;
k2=0;
k3=0;
k4=0;
k5=0;
k6=15;
k7=0;
k8=0;
```

```
if H>=h & V>=v & E>=e
   f=@(x)(-1)*x+k1;
   result_I=Euler_Method(I,f,t_step);
elseif H>=h & V>=v & E<e
   f=@(x)(-1)*x+k2;
   result_I=Euler_Method(I,f,t_step);
elseif H>=h & V<v & E>=e
   f=@(x)(-1)*x+k3;
   result_I=Euler_Method(I,f,t_step);
elseif H>=h & V<v & E<e
   f=@(x)(-1)*x+k4;
   result_I=Euler_Method(I,f,t_step);
elseif H<h & V>=v & E>=e
   f=@(x)(-1)*x+k5;
   result_I=Euler_Method(I,f,t_step);
elseif H<h & V>=v & E<e
   f=@(x)(-1)*x+k6;
   result_I=Euler_Method(I,f,t_step);
elseif H<h & V<v & E>=e
   f=@(x)(-1)*x+k7;
   result_I=Euler_Method(I,f,t_step);
elseif H<h & V<v & E<e
   f=@(x)(-1)*x+k8;
   result_I=Euler_Method(I,f,t_step);
end
```

```
%M module
function result_M=M_module(M,D,V,t_step)
d=0.2;
v=5;
k1=0.5;
k2=0.5;
k3=0;
k4=0;
if D>=d & V>=v
    f=@(x)(-1)*x+k1;
    result_M=Euler_Method(M,f,t_step);
elseif D>=d & V<v
    f=@(x)(-1)*x+k2;
    result_M=Euler_Method(M,f,t_step);
elseif D<d & V>=v
    f=@(x)(-1)*x+k3;
    result_M=Euler_Method(M,f,t_step);
elseif D<d & V<v
    f=@(x)(-1)*x+k4;
    result_M=Euler_Method(M,f,t_step);
end
%F module
function result_F=F_module(F,M,I,H,t_step)
m=0.2;
i=0.0000001;
```

```
h=0.9999999;
k1=0;
k2=12000;
k3=000;
k4=000;
k5=0;
k6=0;
k7=0;
k8=0;
  if M>=m & I>=i & H>=h
    f=@(x)(-1)*x+k1;
    result_F=Euler_Method(F,f,t_step);
 elseif M>=m & I>=i & H<h
    f=@(x)(-1)*x+k2;
    result_F=Euler_Method(F,f,t_step);
 elseif M>=m & I<i & H>=h
    f=@(x)(-1)*x+k3;
    result_F=Euler_Method(F,f,t_step);
 elseif M>=m & I<i & H<h
    f=@(x)(-1)*x+k4;
    result_F=Euler_Method(F,f,t_step);
 elseif M<m & I>=i & H>=h
    f=@(x)(-1)*x+k5;
    result_F=Euler_Method(F,f,t_step);
 elseif M<m & I>=i & H<h
```

```
    f=@(x)(-1)*x+k6;
    result_F=Euler_Method(F,f,t_step);
 elseif M<m & I<i & H>=h
    f=@(x)(-1)*x+k7;
    result_F=Euler_Method(F,f,t_step);
 elseif M<m & I<i & H<h
    f=@(x)(-1)*x+k8;
    result_F=Euler_Method(F,f,t_step);
 end
%R module
function result_R=R_module(R,F,H,t_step)
f=10;
h=0.9999999;
k1=0;
k2=0;
k3=1;
k4=0;
if F>=f & H>=h
    f=@(x)(-1)*x+k1;
    result_R=Euler_Method(R,f,t_step);
elseif F>=f & H<h
    f=@(x)(-1)*x+k2;
    result_R=Euler_Method(R,f,t_step);
elseif F<f & H>=h
    f=@(x)(-1)*x+k3;
```

```
    result_R=Euler_Method(R,f,t_step);
elseif F<f & H<h
    f=@(x)(-1)*x+k4;
    result_R=Euler_Method(R,f,t_step);
end
%E module
function result_E=E_module(E,M,I,t_step)
m=0.3;
i=0.00001;
k1=180;
k2=180;
k3=25;
k4=0;
if M>=m & I>=i
    f=@(x)(-1)*x+k1;
    result_E=Euler_Method(E,f,t_step);
elseif M>=m & I<i
    f=@(x)(-1)*x+k2;
    result_E=Euler_Method(E,f,t_step);
elseif M<m & I>=i
    f=@(x)(-1)*x+k3;
    result_E=Euler_Method(E,f,t_step);
elseif M<m & I<i
    f=@(x)(-1)*x+k4;
    result_E=Euler_Method(E,f,t_step);
```

```
end

%P module
function result_P=P_module(P,M,t_step)
m1=0.000001;
m2=0.3;

k1=33000;
k2=5000;
k3=5000;
k4=000;

if M>=m1 & M>=m2
    f=@(x)(-1)*x+k1;
    result_P=Euler_Method(P,f,t_step);
elseif M>=m1 & M<m2
    f=@(x)(-1)*x+k2;
    result_P=Euler_Method(P,f,t_step);
 elseif M<m1 & M>=m2
    f=@(x)(-1)*x+k3;
    result_P=Euler_Method(P,f,t_step)
elseif M<m1 & M<m2
    f=@(x)(-1)*x+k4;
    result_P=Euler_Method(P,f,t_step);
end
```

```
%A module
function result_A=A_module(A,S,P,V,t_step)
s=0.15;
p=5000;
v=0;
k1=5000;
k2=5000;
k3=5000;
k4=5000;
k5=1;
k6=1;
k7=1;
k8=1;
if S>=s & P>=p & V>=v
    f=@(x)(-1)*x+k1;
    result_A=Euler_Method(A,f,t_step);
 elseif S>=s & P>=p & V<v
    f=@(x)(-1)*x+k2;
    result_A=Euler_Method(A,f,t_step);
 elseif S>=s & P<p & V>=v
    f=@(x)(-1)*x+k3;
    result_A=Euler_Method(A,f,t_step);
 elseif S>=s & P<p & V<v
    f=@(x)(-1)*x+k4;
    result_A=Euler_Method(A,f,t_step);
```

```
 elseif S<s & P>=p & V>=v
    f=@(x)(-1)*x+k5;
    result_A=Euler_Method(A,f,t_step);
 elseif S<s & P>=p & V<v
    f=@(x)(-1)*x+k6;
    result_A=Euler_Method(A,f,t_step);
 elseif S<s & P<p & V>=v
    f=@(x)(-1)*x+k7;
    result_A=Euler_Method(A,f,t_step);
 elseif S<s & P<p & V<v
    f=@(x)(-1)*x+k8;
    result_A=Euler_Method(A,f,t_step);
 end
%S module
function result_S=S_module(S,P,t_step)
if P<5000
    f=@(x)(-1)*x+0.1;
    result_S=Euler_Method(S,f,t_step);
elseif P>=5000
    f=@(x)(-1)*x+1;
    result_S=Euler_Method(S,f,t_step);
end
%D module
function result_D=D_module(D,H,R,I,t_step)
h=0.99;
```

```
r=0.9;
i=0.001;
k1=0;
k2=0.5;
k3=0;
k4=0;
k5=0.5;
k6=0;
k7=0.5;
k8=0;
if H>=h & R>=r & I >=i
    f=@(x)(-1)*x+k1;
    result_D=Euler_Method(D,f,t_step);
elseif H>=h & R>=r & I <i
    f=@(x)(-1)*x+k2;
    result_D=Euler_Method(D,f,t_step);
elseif H>=h & R<r & I >=i
    f=@(x)(-1)*x+k3;
    result_D=Euler_Method(D,f,t_step);
elseif H>=h & R<r & I <i
    f=@(x)(-1)*x+k4;
    result_D=Euler_Method(D,f,t_step);
elseif H<h & R>=r & I >=i
    f=@(x)(-1)*x+k5;
    result_D=Euler_Method(D,f,t_step);
```

```
elseif H<h & R>=r & I <i
    f=@(x)(-1)*x+k6;
    result_D=Euler_Method(D,f,t_step);
elseif H<h & R<r & I >=i
    f=@(x)(-1)*x+k7;
    result_D=Euler_Method(D,f,t_step);
elseif H<h & R<r & I <i
    f=@(x)(-1)*x+k8;
    result_D=Euler_Method(D,f,t_step);
end
```