Project Report

On

A MATHEMATICAL MODEL OF HEPATITIS C VIRUS INFECTION

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by

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CERTIFICATE

This is to certify that the dissertation entitled, **A MATHEMATICAL MODEL OF HEPATITIS C VIRUS INFECTION** is a bonafide record of the work done by Ms. **GINU GEORGE** under my guidance as partial fulfillment of the award of the degree of **Master of Science in Mathematics** at St. Teresa's College (Autonomous), Ernakulam affiliated to Mahatma Gandhi University, Kottayam. No part of this work has been submitted for any other degree elsewhere.

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DECLARATION

I hereby declare that the work presented in this project is based on the original work done by me under the guidance of **Smt.VEENA V S**, Assistant Professor, Department of Mathematics, St.Teresa's College(Autonomous), Ernakulam and has not been included in any other project submitted previously for the award of any degree.

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Contents

Chapter 1

INTRODUCTION

Mathematical modeling is a scientific attempt to describe real life phenomena using mathematical tools. Each model consists of a set of variable parameters and rules of evolution for these parameters. By applying these rules to the model's parameters, one can learn a lot about the phenomenon in question, and, based on the results, make informed decisions, predict the future, or make the optimal choice between different options. Many mathematical models are implemented on computers; their simulations can run in a matter of minutes, or even seconds, often replacing real life experiments that consume vast amounts of time and resources.

1.1 Mathematical model

Mathematical modelling is the process of describing a real world problem in mathematical terms, usually in the form of equations, and then using these equations both to help understand the original problem, and also to discover new features about the problem. Modelling both lies at the heart of much of our understanding of the world, and it allows engineers to design the technology of the future.

In mathematical modelling, we take a real-world problem and write it as an equivalent mathematical problem. We then solve the mathematical problem, and interpret its solution in terms of the real-world problem. After this we see to what extent the solution is valid in the

context of the real-world problem. So, the stages involved in mathematical modelling are formulation, solution, interpretation and validation.

Mathematical models are used to solve many real-life situations like:

- **launching a satellite.**
- **predicting the arrival of the monsoon.**
- **controlling pollution due to vehicles.**
- **reducing traffic jams in big cities.**
- **estimating treatment prolongation for persistent infections**

Mathematical models can take many forms, including dynamical systems, statistical models, differential equations, or game theoretic models. These and other types of models can overlap, with a given model involving a variety of abstract structures. In general, mathematical models may include logical models.

1.2 HCV infection

Hepatitis C is a liver disease caused by the hepatitis C virus (HCV): the virus can cause both acute and chronic hepatitis, ranging in severity from a mild illness lasting a few weeks to a serious, lifelong illness. Hepatitis C is a major cause of liver cancer. The hepatitis C virus is a bloodborne virus: the most common modes of infection are through exposure to small quantities of blood. This may happen through injection drug use, unsafe injection practices and unsafe health care.

The liver is the biggest organ in the body, and it plays an vital role in all metabolic processes in the body. The main job of the liver is to filter the blood, fight infections among other functions. Once the liver is infected, its functions are affected too. However, viruses, which are tiny infectious agents, can to replicate inside the living cells of an organism; they are the most popular cause for hepatitis, that is why it is often called 'viral hepatitis' There are numerous kinds of viral hepatitis such as A, B, C, D, and E. The most well-known sorts of viral hepatitis are hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C

virus (HCV).

Globally, an estimated 71 million people have chronic hepatitis C virus infection. HCV infection, the vaccine does not exist yet, but the active research is ongoing. Scientists are working on a vaccine, but challenges specific to hepatitis C have historically made developing the vaccine difficult.

Hepatitis C virus infection emerged after most blood transfusion infections were associated with either hepatitis A (HAV) or hepatitis B (HBV) virus. It was first identified in 1989 when a team of Choo isolated this single stranded RNA from the serum of infected chimpanzees. They re-named the Non-A, Non-B hepatitis as hepatitis C.

After exposure to HCV, a strong host immune response is launched. Thus, some patients with hepatitis C virus infection will naturally clear the virus during the early phase of infection without medical intervention. Antiviral therapy has been used to cure chronically HCV infected patients. It is currently the only available treatment because of the lack of an HCV vaccine. Newly, direct-acting antivirals (DAAs) is the most common way that is used to give treatments that target certain steps of the life cycle of the HCV. However, antiviral therapy is expensive, associated with side effects, and not effective in all patients.

1.3 Immune Responses

An immune response is a reaction that occurs within an organism for the purpose of defending against foreign invaders. These invaders include a wide variety of different microorganisms including viruses, bacteria, parasites, and fungi which could cause serious problems to the health of the host organism if not cleared from the body. There are two distinct aspects of the immune response, the innate and the adaptive, which work together to protect against pathogens.

The innate immune system cells such as natural killer (NK) and macrophages are always ready to fight microbes and all other pathogens in a non-specific way, no matter what kind of pathogen they are fighting.However, this kind of response cannot recognize some pathogens and then eliminate infectious organisms.

Oppositely, the adaptive immune responses are more complex than the innate immune responses. They are responsible for recognizing the physical structure of a pathogen. Once an antigen has been recognized, the adaptive immune system is able to create an army of immune cells for neutralizing or eliminating the antigen.The adaptive responses can perceive proteins that are shaped by the pathogen. When the adaptive responses are activated, they begin to divide in numbers. The lymphocytes, which are white blood cells, are the most paramount factor of the adaptive immune system. They can be grouped into two important kinds of cells; B-lymphocytes, which is called B-cells, and T-lymphocytes, which is called T-cells.B-cells and T-cells are the fundamental players in the host immune response. B-cells produce antibodies. They are named as B-cells because they are produced in the human bone marrow. B-cells begin to divide into memory and effector cells once they are activated.

These new B-cells are repetitions with the same certain receptors that can recognize HCV. The memory B-cells will stay in the system in case HCV enters the host in the future, but they take no action. On the other hand, the effector B-cells, which are called plasma cells, are responsible for the release of new antibodies. T-cells come into two different types of cells, T-helper cells and T-killer cells (cytotoxic T-lymphocytes (CTLs)). T-helper cells are considered an essential part in the activation of the B-cells and, in this way, in the release of antibodies.

The interactions between pathogens and immune responses can be viewed as a predator-prey system. The predator is the immune cells like the B-cells and T-cells and the prey is the virus.The predator types

can minimize the sustenance resource to levels that are too low for other predator types to survive.

Chapter 2

MODEL OF VIRAL DYNAMICS

Mathematical modeling is a useful tool in studying of virus dynamics because it helps to understand the biological mechanisms involved and interpret the experimental results. In this section, first, consider the early basic ordinary differential equation (ODE) model that has been applied to virus dynamics. Then, show the original mathematical model of viral dynamics under antiviral therapy. This model had proved very successful in understanding the pathogenesis and guiding therapy for hepatitis C virus (HCV) infection. After that, introduce the extended model of the original model that considers the proliferation of liver cells. Finally, we proceed to introduce the model that shows the interaction between the immune response and hepatitis C virus (HCV).

The early mathematical model for the basic dynamics of the virus was developed and analysed in to understand the dynamics of HIV, hepatitis B (HBV) and some other viruses infection. The basic principles of the early virus dynamics model are shown in Figure 2.1. The model design is based on three variables: the number of uninfected or target cells T, that infected when they meet free viruses V, the number of infected cells I, which produce new virus particles that leave the cell and find other uninfected cells.

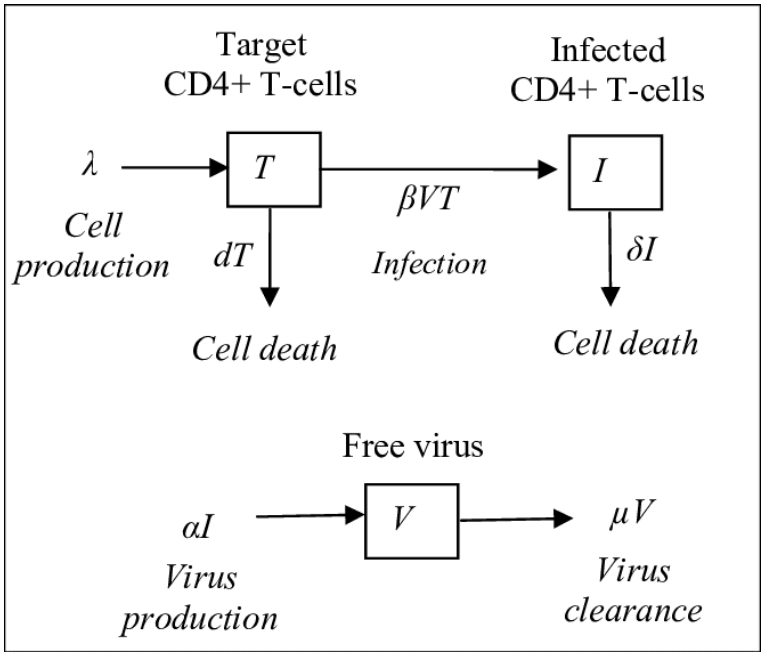


Figure 2.1: A schematic diagram of the basic model of viral infection.

The basic model of virus dynamics can be written in the chemical reaction notation:

$$\mathbf{T + V \rightarrow I \rightarrow kV}$$

The equations that describe the interaction between these cells and virus particles are given by ordinary differential equations:

$$\frac{dT}{dt} = \lambda - dT - \beta VT \tag{2.1}$$

$$\frac{dI}{dt} = \beta VT - \delta I \tag{2.2}$$

$$\frac{dV}{dt} = \alpha I - \mu V \tag{2.3}$$

This model assumes that uninfected cells T, are produced at a rate s,and they are subject to natural death at a rate dT, and become infected by the interaction with virus at a rate βVT. Infected cells I, are naturally die at a rate δI, Free virus is produced by infected cells at a rate αI and clearance at a rate μV. Thus, the average lifetime of an infected cell is $\frac{1}{\delta}$,the average lifetime of a free virus particle is $\frac{1}{\mu}$, the total number of virus particles produced from one infected cell is $\frac{\alpha}{\delta}$.

After the discovery of hepatitis virus type C, it became significant to study the dynamics of the virus.

Extended the previous model in by including a separate differential equation for healthy hepatocytes. This model, which is called original model, also describes the viral kinetics in HCV patients during IFN-α treatment. The original model during treatment is given by the following system of ordinary differential equations:

$$\frac{dT}{dt} = s - dT - (1-\eta)\beta VT \tag{2.4}$$

$$\frac{dI}{dt} = (1-\eta)\beta VT - \delta I \tag{2.5}$$

$$\frac{dV}{dt} = (1-\epsilon)\alpha I - \mu V \tag{2.6}$$

ϵ is the efficiency of the drug in blocking production of the virus from infected cells and η is the efficiency of the drug in stopping infection. The remaining parameters are defined similarly to the basic model (1). Treatment of patients with chronic hepatitis C with recombinant interferon alfa (rIFN-alpha) can cause a decrease of serum transaminases and hepatitis C virus (HCV) RNA. Recent trials evaluating combination therapy of IFN-alpha and ribavirin suggested a potential synergistic effect. They concluded that it is important to control the dynamic of HCV virus in the early phase of their stage to help to guide treatment because it has a very high dynamic. After that, several articles were published to use this model to better understand HCV infection.

The previous model ignores the proliferation of both infected I and uninfected Tcells .Therefore, extended the original model by adding a proliferation terms r for both infected and uninfected hepatocytes (Figure 2.2) that allow the total number $(T+I)$ of liver cells to reach a maximum size T_{max}.

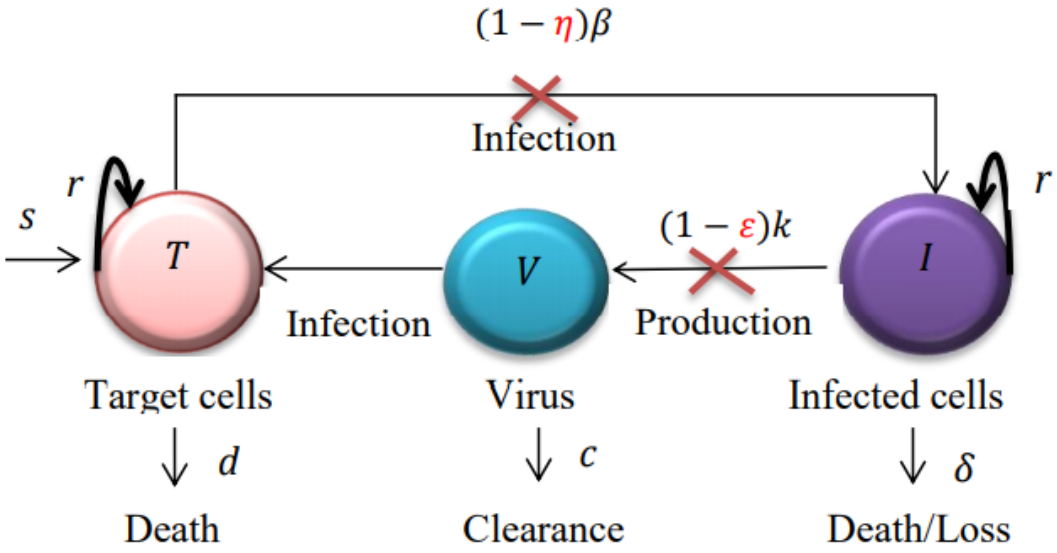


Figure 2.2:

The corresponding differential equations of the extended mathematical model are given by:

$$\frac{dT}{dt} = s + rT - (1 - \frac{(T+I)}{T_{max}}) - dT - (1-\eta)\beta VT \tag{2.7}$$

$$\frac{dI}{dt} = (1-\eta)\beta VT + rI(1 - \frac{(T+I)}{T_{max}}) - \delta I \tag{2.8}$$

$$\frac{dV}{dt} = (1-\epsilon)\alpha I - \mu V \tag{2.9}$$

In this model, r represents the maximum proliferation rate of the uninfected T and infected I, hepatocytes, which means that T and I hepatocytes can proliferate under a blind homeostasis process, in which there is no distinction between infected and uninfected cells in the density-dependent term. The number $(T + I)$ represents the total hepatocyte population which can increase up to a maximum of T_{max}. The remaining parameters are defined similarly to the original model. The presentation of the hepatocytes proliferation in this model is the new advantage that has demonstrated an important role in understand-

ing the viral dynamics later on.

The immune response of the CTL is responsible to ban the reproduction of the virus, and the immune response of the antibody is responsible to neutralize the virus. Therefore, Wodarz (2003) proposed a model that deals with the interaction between HCV and immune responses in a host. This model extended to model given by adding two differential equations, one represents the number of CTLs and is denoted by Z, and the other one represents the number of the antibody response and is denoted by W.

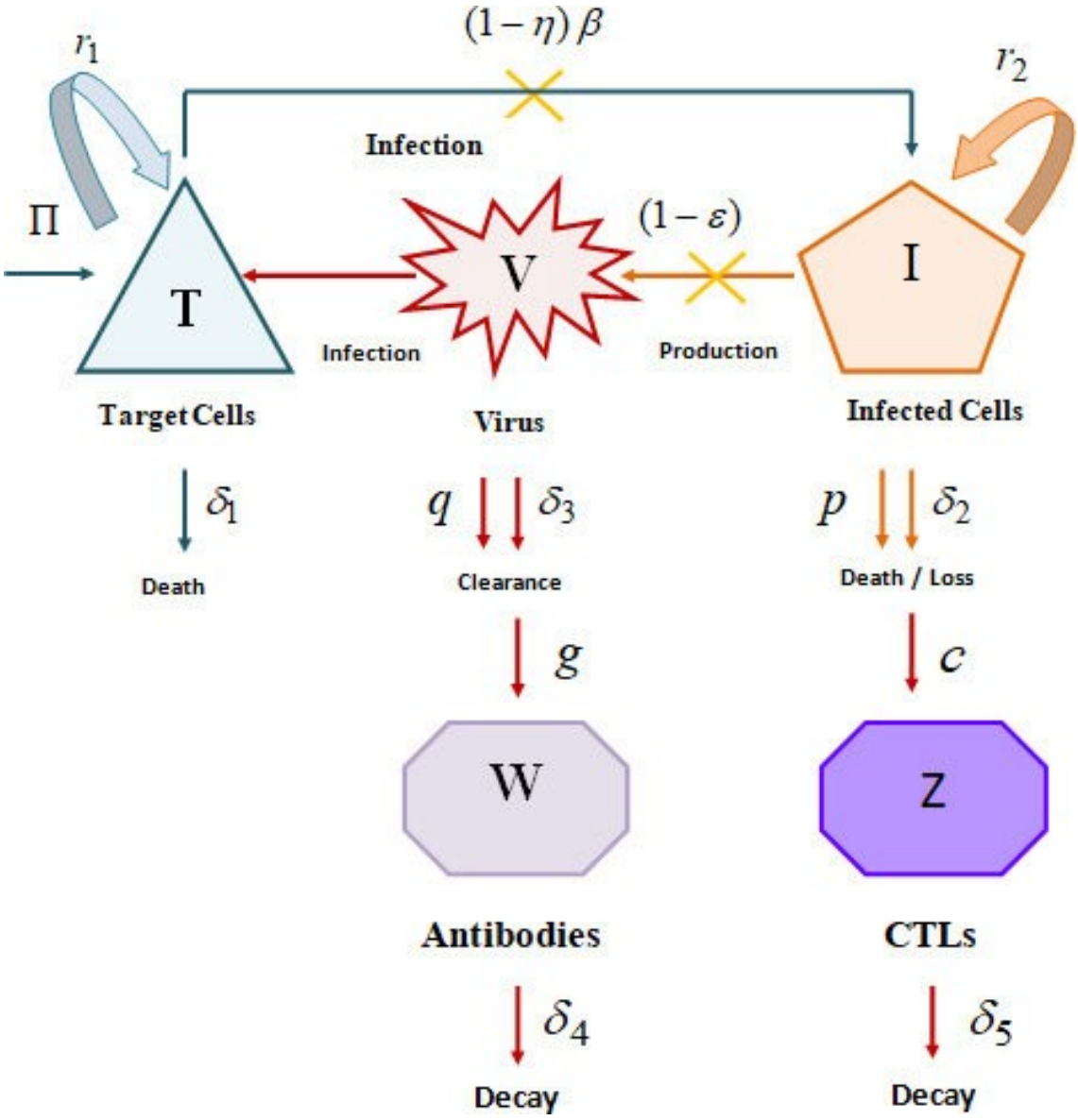


Figure 2.3:

Consider the extension of given by the system of ordinary differential equations:

$$\frac{dT}{dt} = s - dT - \beta VT \tag{2.10}$$

$$\frac{dI}{dt} = \beta VT - \delta I - pIZ \tag{2.11}$$

$$\frac{dV}{dt} = \alpha I - \mu V - qVW \tag{2.12}$$

$$\frac{dZ}{dt} = cIZ - \delta_5 Z \tag{2.13}$$

$$\frac{dW}{dt} = gVW - \delta_4 W \tag{2.14}$$

Here, pIZ represents the rate of killing the infected cells by the CTL response, and the qVW represents the rate of neutralized virus particles by the antibody. In response to virus antigen that is produced from infected cells, I, at a rate cIZ, CTLs increase. Also, CTLs decay at rate $\delta_5 Z$ in the lack of antigenic stimulation. In response to virus particles, antibodies progress at a rate gVW. In addition, antibody decay at a rate $\delta_4 W$. Thus, it was concluded that the immune response balance plays a crucial role in controlling the virus as it develops over time.

Chapter 3

MODEL OF HEPATITIS C VIRUS INFECTION

3.1 Mathematical Model

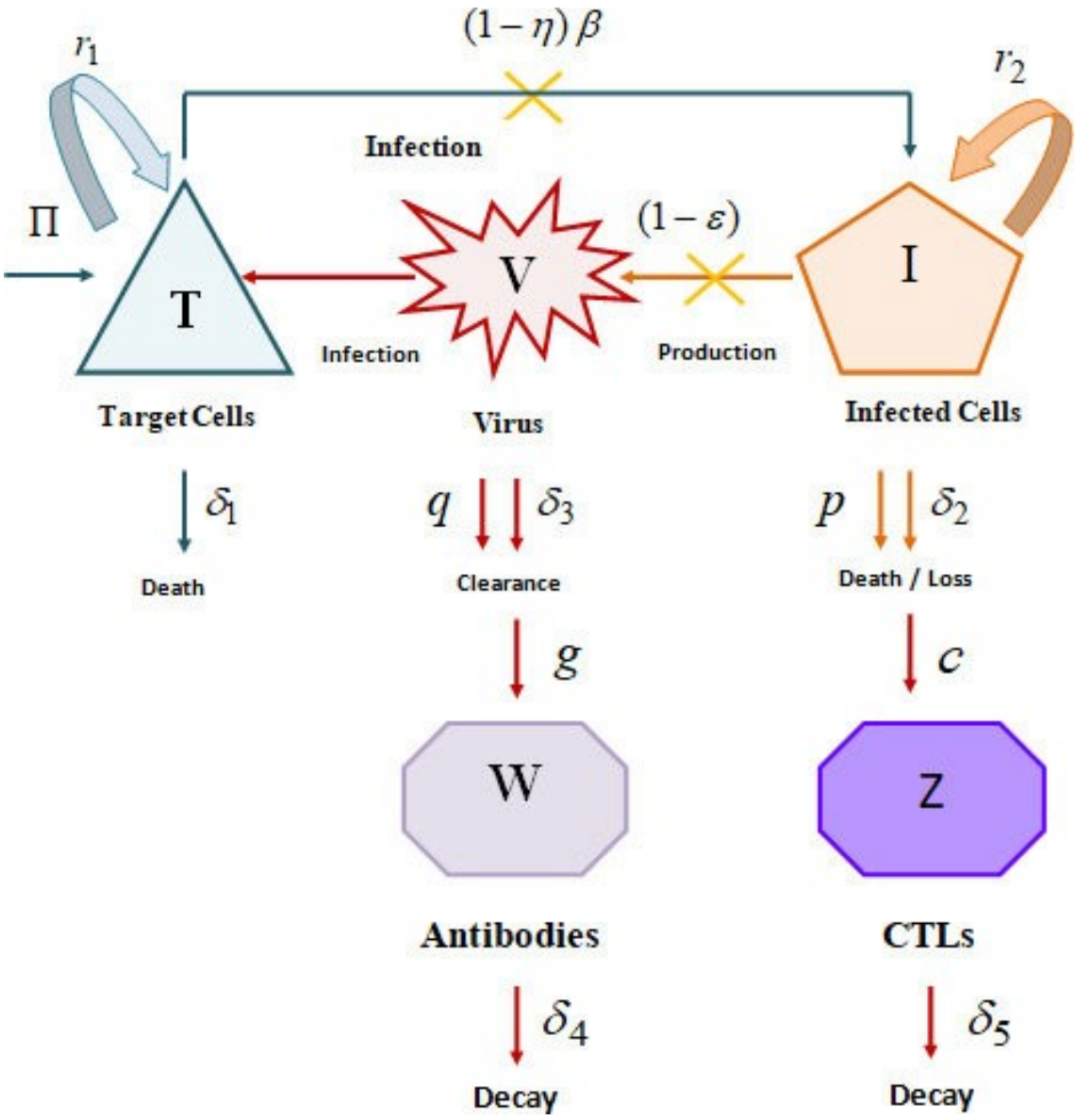
Although hepatitis C virus kinetics and immune determinants during primary infection have been described, the virus-host interplay is not fully understood. Each model consists of a set of variable parameters and rules of evolution for these parameters.

We used mathematical modeling to specify and measure virus-host dynamics. In this section, interested in understanding the interactions between the hepatitis C virus and the immune system under treatment, taking into consideration the proliferation for both infected and uninfected hepatocytes.

Combine model (2) and model (3) to obtain a new mathematical model of HCV that incorporates the immune system and cell proliferation.

$$\frac{dT}{dt} = s + rT(1 - \frac{T+1}{T_{max}}) - dT - (1-\eta)\beta VT \tag{3.1}$$

$$\frac{dI}{dt} = (1-\eta)\beta VT + rI(1 - \frac{T+1}{T_{max}}) - \delta I - pIZ \tag{3.2}$$



$$\frac{dV}{dt} = (1-\epsilon)\alpha I - \mu V - qVW \tag{3.3}$$

$$\frac{dZ}{dt} = cIZ - \delta_5 Z \tag{3.4}$$

$$\frac{dW}{dt} = gVW - \delta_4 W \tag{3.5}$$

Table 3.1: The parameters that are used in the model are listed with their units in Table:

Parameters	Interpretation	Units
η	The efficacy of the drug in stopping new infection	Unitless
ϵ	The efficacy of the drug in blocking virus production from infected cells (I)	Unitless
α	Production rate of the virus particles (V) from infected cells (I)	$virionscells^{-}1day^{-}1$
β	The rate at which virus (V) infects healthy cells (T)	$mlday^{-}1virions^{-}1$
δ_5	Natural decay rate of CTLs (Z) in the absence of antigenic stimulation	$day^{-}1$
δ_4	Natural decay rate of antibody (W)	$day^{-}1$
μ	Natural clearance rate of virus particles (V)	$day^{-}1$
g	Development rate of antibody (W) in response to virus particles (V)	$day^{-}1$
δ_2	The rate at which CTLs (Z) kills infected cells (I)	$day^{-}1$
p	Natural death rate of infected cells (I)	$day^{-}1$
δ_3	The rate at which antibody (W) neutralized the virus particles (V)	$day^{-}1$
q	Natural clearance rate of virus particles (V)	$day^{-}1$
δ_1	Natural death rate of healthy cells (T)	$day^{-}1$
r	The maximum proliferation rate of the uninfected (T) and infected (I) cells	$day^{-}1$
s	Natural production rate of healthy cells (T)	$cellml^{-}1day^{-}1$
T_{max}	Maximum size of growth of the liver	$cellml^{-}1$
c	Expand rate of CTLs (Z) in response to virus antigen derived from infected cells (I)	$day^{-}1$

3.2 Successful Drug Therapy

Hepatitis C is the number one cause of liver cancer and liver transplants. Its brought on by a virus you can catch if you come into contact with contaminated blood. You could get it from an unclean tattoo needle.Its curable. But curing it has not always been easy or comfortable. For decades, you needed painful shots of a medicine called interferon and a pill called ribavirin. These drugs didn't target the virus that made you sick. Instead, they amped up your immune system so you'd fight it the way you do when you get the flu. But the treatment didn't always get the virus out of your body. Cure rates hovered around 50 persentage. And people who stuck with the yearlong treatment not all did had to live with chemo-like side effects.These days, more and more

people can get rid of the virus by simply taking a pill, at home, for just a few weeks. There are several ways to do it without having to get shots.Here's a closer look at some of the drugs and a peek at those on the horizon.

The definition of the critical drug efficiency was observed. Thus, if the efficiency of a drug, ϵ which acts to block the production of the virus from infected cells. It was greater than the value of the critical drug efficiency, viral levels persistently decay on treatment eventually prompting eradication. If the efficacy of a drug η, which acts to block the new infection. It was less than the value of the critical drug efficiency. Viral levels in any case would decay, but in the end they would balance at a nonzero steady state in spite of proceeding with treatment. This discovery demonstrated that the idea of ϵ_c applies to HCV dynamic models in which healthy cells (target cells)T levels are permitted to vary.

Chapter 4

CASE STUDY : HEPATITIS C VIRUS INFECTION

Hepatitis C is a liver disease caused by the hepatitis C virus (HCV). Hepatitis C is a major cause of liver cancer. The three most common of these types are Hepatitis A, Hepatitis B, and Hepatitis C. Hepatitis A virus survives in fecal matter and is primarily transmitted through sexual contact. The Hepatitis A virus causes only a short span of infection and, therefore, does not become chronic. People with Hepatitis A improve without treatment.

The Hepatitis B virus is spread similarly to HIV, but is 100 times more infectious because the virus can survive outside the host for many days. Hepatitis B can become chronic in approximately 6 percent of infected individuals and causes extensive damage to the liver. Hepatitis C is a bloodborne pathogen and is trans mitted primarily by exposure to blood through the skin, such as through Intravenous Drug Use (IDU), by long-term hemodialysis , or by healthcare workers after possible exposure to Hepatitis C positive blood.

There is no vaccine for Hepatitis C. However, a combination of harm reduction strategies such as the provision of new needles and syringes, the treatment of substance abuse, and the following of infection control guidelines in healthcare are becoming a successful prevention campaign due to the growth of community planning groups.

4.1 Hepatitis C Background

4.1.1 Genotype

The major HCV genotype worldwide is genotype 1, which accounts for 40 percentage-80percentage of all isolates. Genotype 1 also may be associated with more severe liver disease and a higher risk of hepatocellular carcinoma. Genotypes 1a and 1b are prevalent in the United States, whereas in other countries, genotype 1a is less frequent.

After the virus enters the body, there is an incubation period lasting 1.5 to 6 months (average 4 months) until illness begins. During the acute phase (first 6 months after infection) most persons have no symptoms or might experience a mild illness. The initial test is the Hepatitis antibody enzyme immunoassay test which indicates either past or present infection. If the Hepatitis antibody enzyme test is positive, a Polymerase Chain Reaction (PCR) test is given. This test detects the presence of the Hepatitis C virus in the blood and, thus, is used to diagnose chronic Hepatitis C infection.

4.1.2 Hepatitis C Virus Progression

Progression begins with inflammation of the liver, followed by death of liver cells. This causes scarring and hardening of liver tissue. About 20 percent of people with chronic hepatitis C go on to develop cirrhosis of the liver in 15 to 20 years. About 75 to 85 percent of people with hepatitis C progress to the chronic phase. However, even in the chronic phase, it may take years for symptoms to show. Progression begins with inflammation of the liver, followed by death of liver cells.

This causes scarring and hardening of liver tissue. The virus can cause both acute and chronic hepatitis, ranging in severity from a mild illness lasting a few weeks to a serious, lifelong illness. Hepatitis C is a major cause of liver cancer. In approximately 15 percent of these cases, a person develops cirrhosis, necrosis, and, then, cancer. Five percent die.

This stage of the Hepatitis C progression is known as Chronic Hepatitis C and is defined as infection with the Hepatitis C virus recurring for more than six months based on the presence of the Hepatitis C single-stranded RNA in the blood. There is no cure for Hepatitis C, but a proper medication regime can stop the virus from replicating itself.

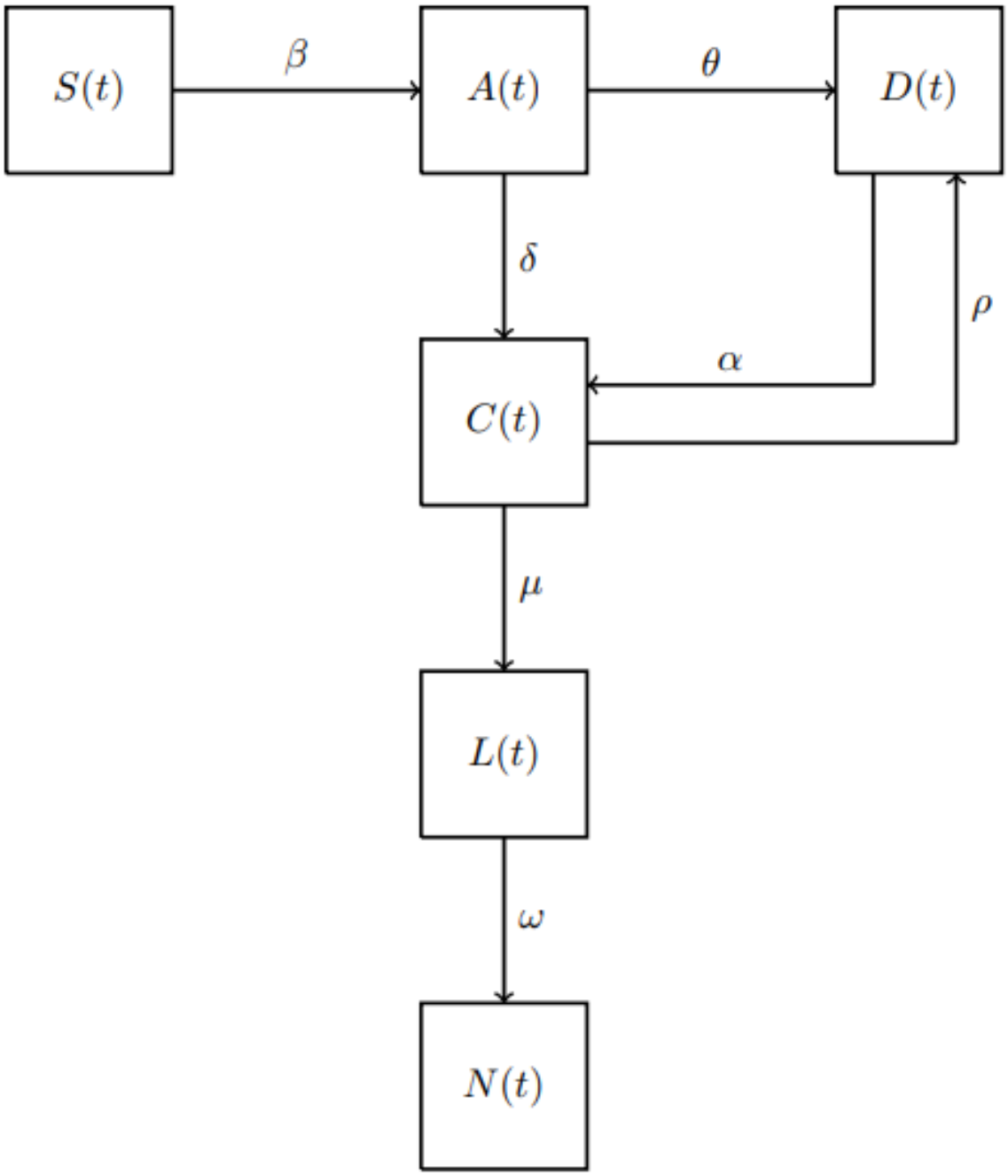
4.1.3 Treatment

Currently, the most effective therapy for hepatitis C is a drug combination consisting of pegylated interferon and ribavirin. Pegylated interferon is taken weekly as an injection and ribavirin is a twice daily tablet. Globally, around 150 million people are infected with hepatitis C virus (HCV). India contributes a large proportion of this HCV burden. The prevalence of HCV infection in India is estimated at between 0.5 percentage and 1.5 percentage. It is higher in the northeastern part, tribal populations and Punjab, areas which may represent HCV hotspots, and is lower in western and eastern parts of the country. The predominant modes of HCV transmission in India are blood transfusion and unsafe therapeutic injections. There is a need for large field studies to better understand HCV epidemiology and identify high-prevalence areas, and to identify and spread awareness about the modes of transmission of this infection in an attempt to prevent disease transmission.

4.2 Equations and Analysis

To simplify the model into a set of ordinary differential equations that we have discussed so far, we will consider only the relationship between the Dormant infected individuals and the Chronic infected individuals.

Again, once an individual is infected with the Hepatitis C virus, the virus will always be present. Therefore, the infected population, $I(t)$, will either have chronic Hepatitis C infections, $C(t)$, for the next couple of decades or they will be considered "cured" (virus is dormant) by a Sustained Viral Response (SVR).



We define:

$S(t)$ = **the number of Susceptible people**

$A(t)$ = **the number of Acute infected people**

$C(t)$ = **the number of Chronic infected people**

$D(t)$ = **the number of Dormant infected people**

$L(t)$ = **the number of infected people with Liver disease**

$N(t)$ = **the number of infected people with Necrosis of the Liver**

β =**the rate increase of infected people due to IVDA (intravenous drug abuse)**

δ = **the rate increase of chronic infected people due the bodies inability to kill the active hepatitis C cells**

θ = **the rate increase of acute infected people with sustained viral response (6months)**

ρ = **the rate increase of hepatitis C dormant people due to medication, diet, and alcohol abstinence**

α = **the rate increase of people with unsustained response (6 months)**

μ = **the rate increase of extended chronic hepatitis C infected people**

ω = **the rate increase of people with extended liver disease**

$$\frac{dC}{dt} = \alpha D - \rho C \tag{4.1}$$

$$\frac{dD}{dt} = \rho C - \alpha D \tag{4.2}$$

with I(t) = D(t) + C(t) thus,

$$\frac{dI}{dt} = \frac{dD}{dt} + \frac{dC}{dt} = \rho C - \alpha D + \alpha D - \rho C = 0 \tag{4.3}$$

Where I is constant.

$\frac{dC}{dt}$ and $\frac{dD}{dt}$ have dimensions of (number of people) / (time) and have units of $1/(time)(day^{-}1)$

Defining $x^*(t)$as the fraction of the number of infected in the Chronic stage and $y^*(t)$as the fraction of the number of infected in the Dormant stage. We define dimensionless variables.

$$x^* = \frac{C}{I} \tag{4.4}$$

$$y^* = \frac{D}{I} \tag{4.5}$$

$$t^* = \frac{t}{\frac{1}{\rho}} = \rho t \tag{4.6}$$

Thus, if $x = \alpha/(\alpha + \rho)$ is reached, the virus returns to an active state and the patient becomes chronic. Notice, this steady state is feasible only if x > 0 which means that $\alpha\rho > 0$. Therefore, $\alpha\rho$ must be positive for the virus to progress to the chronic state.

4.2.1 Future Studies-The Next Step

The next step would be to apply one more variable to the model and increase the complexity to a system of two first-order differential equations. solutions to these differential equations are found by graphing an xy plane (phase plane) which shows all trajectories of the solutions through every point. Steady-states are then found by finding the intersection of the x and y nullcline curves of $\frac{d(x)}{d(t)} = 0$ and $\frac{d(y)}{d(t)} = 0$.

A preventive vaccine is needed to stop HCV transmission to uninfected individuals, and to those who are cured with DAA but remain at risk for re-exposure to the virus. However, vaccine development is complicated by our poor understanding of the adaptive immune responses to the virus.

Chapter 5

CONCLUSION

Hepatitis C is a liver disease caused by the hepatitis C virus (HCV): the virus can cause both acute and chronic hepatitis, ranging in severity from a mild illness lasting a few weeks to a serious, lifelong illness. Hepatitis C is a major cause of liver cancer. This model is a combination of proliferation model and immune responses model. Our model is considering the immune response to the HCV infection and accounts of the proliferation for the uninfected and infected hepatocytes. Also, it considers the mechanisms of cell death and killing by CTLs and antibody. To determine the stability of the model, we evaluated the equilibrium points or steady states.

we illustrated the dominant CTL response and the dominant antibody response. We changed the parameters of the neutralized rate of virus particles to be bigger than the killing rate of the infected cells. This showed that the proliferation rate of CTLs is much stronger than the natural production rate of antibody. Hence, the CTLs response increases and the antibody response become ineffective.Likewise, we changed the parameters of the neutralized rate of virus particles to be less than the killing rate of the infected cells. This showed the proliferation rate of antibody is stronger than the natural production rate of CTLs. Thus, the antibody response increases and the CTLs response become ineffective. Then, we made the parameters of the neutralized rate of virus particles and the killing rate of the infected cells to be equal. This showed that both CTL and antibody responses are equally

determined. The two immune responses CTLs and antibody contend with each other to clearance of the infection.

The proposed model here represents HCV RNA decay under variety of treatment and takes into consideration both the immune system and cell proliferation. The study provides useful tools not only for fitting HCV infections but also for modeling other similar infections with hepatocytes viruses, such as hepatitis A and B virus. This model allows predicting the viral decay and can help in understanding the kinetics of the HCV under different treatment. It can be used for better understanding the viral kinetics in patients.

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