# ANALYSIS AND IMPLEMENTATION OF A POSITIVITY PRESERVING NUMERICAL METHOD FOR AN HIV MODEL

by

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the degree of
Magister Scientiae
in the
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# Abstract

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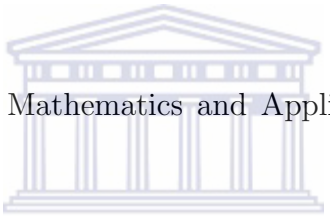


This thesis deals with analysis and implementation of a positivity preserving numerical method for a vaccination model for the transmission dynamics of two HIV-subtypes in a given community. The continuous model is analyzed for stability and equilibria. The qualitative information thus obtained is used while designing numerical method(s). Three numerical methods, namely, Implicit Finite Difference Method (IFDM), Non-standard Finite Difference Method (NSFDM) and the Runge-Kutta method of order four (RK4), are designed and implemented. Extensive numerical simulation are carried out to justify theoretical outcomes.

**Keywords:** HIV model(s), stability, reproduction number, equilibria, Implicit finite difference method, Non-standard finite difference method, Runge-Kutta method, preservation of positivity, analysis of the numerical methods.

November 2007

# Declaration

I declare that *Analysis and Implementation of a Positivity Preserving Numerical Method for an HIV model* is my own work, that it has not been submitted before for any degree or assessment in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by means of complete references.


Jo-Anne Wyngaardt November 2007

Signed:.....

# Acknowledgement

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**Jo-anne Wyngaardt**

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**Publications**: A part of this thesis has been submitted in the form of following research reports whose modified versions might be submitted as research paper(s) to some international journals for publication:

1. **K.C. Patidar and J. Wyngaardt**, Some HIV models and methods for their solutions, Report Nr. UWC-MRR 2006/05, University of the Western Cape, December 2006.

2. **K.C. Patidar and J. Wyngaardt**, On the validity of a numerical method for mathematical model(s) in population biology, Report Nr. UWC-MRR 2007/06, University of the Western Cape, November 2007.

# Chapter 1

# Introduction

This thesis deals with the analysis and implementation of a positivity preserving numerical method for a typical HIV model. The main goals achieved in this thesis are necessary descriptions of some theoretical and numerical tools to handle such a model for HIV. These techniques can be used/extended in an analogous way for other modified models (as can be seen shortly in forthcoming sections) where other factors are incorporated which may eventually lead to some more complex terms and/or equations in the system. In order for one to be able to understand the relevence of the problem, we introduce below what is known as HIV.



## 1.1 What is HIV?

HIV is an acronym for the phrase "Human Immunodeficiency virus". This virus causes AIDS (Acquired Immuno-deficiency Syndrome). The people infected with HIV are eventually killed through AIDS. Infections by the virus HIV-1 (one of the most common type of HIV for which there exist several subtypes as described in section 1.4) has many highly complex characteristics, most of which are still not understood [62]. The fact that the disease progression can last more than 10 years from the first day of infection is just one of them. Another is that while most viral infections can

be eliminated by an immune response, HIV can be controlled only partly by it.

HIV primarily infects a class of white blood cells or lymphocytes, called CD4 T-cells. The virus has a high affinity for a receptor present on the cell surface of each of these cells which guides the virus to their location in *vivo*. When the CD4 T-cell count, normally around $1000/\mu L$, decreases to $200/\mu L$ or below, a patient is characterized as having AIDS.

One would think that these CD4 T-cells can fight against the HIV virus. Unfortunately, these cells are the hosts for the HIV virus once a person is infected. The HIV virus turns these cells into virus producing factories, making many copies of the virus. The virus then weakens the immune system and may even kill more of these CD4 T-cells. Because of the central role of the CD4 T-cells in immune regulation, their depletion has widespread deleterious effects of the functioning of the immune system as a whole and this is what leads to AIDS.



## 1.2 HIV vs AIDS

The first reports of AIDS was in April 1981, when five men appeared in different hospitals around the Los Angeles district [29]. They were all very ill with unusual symptoms. The most common factor about these five patients, was that they were all homosexual. It was then thought that the disease only affected homosexual men and heroin addicts. During the early days of AIDS the disease was called *GRID* (Gay-Related Immune Deficiency). Before the end of 1981, similar cases were found in non-homosexual groups. Some drug users aquired it via bloodstream. When they found that the disease can infect both men and women, the name *GRID* was no longer appropriate and it changed to *AIDS* (Acquired Immuno-deficiency Syndrome).

**Acquired** indicates that the unknown causative agent is transmitted to human beings exogenously, from external sources in the course of their natural life span, rather

than passed endogenously, in the germ line.

**Immune-deficiency** indicates that symptoms result from a fault in the immune system (the very bodily mechanism that has evolved to combat disease).

**Syndrome** indicates that there are a range of symptoms associated with the infection, rather than a single disease.

During the early days of AIDS, there was a mystery around it. People were asking many questions like, what is AIDS, where does it come from, why is this happening now, how does it spread, etc. AIDS was also considered forbidden territory. People did not talk openly about it, as we do today. It was then thought that HIV causes AIDS.

Virologists Luc Montagnier, Jay Levy, Robert Gallo and their teams [41] isolated the same retrovirus, but only Montagnier and Levy had correctly diagnosed the virus. According to them, the virus is not an oncovirus (a virus associated with cancer) as Gallo thought, but is a lentivirus, because of its slow pathogenic course within the body (Note that the lentivirus is a genus of slow viruses of the Retroviridae family, characterized by a long incubation period. It can deliver a significant amount of genetic information into the DNA of the host cell). Gallo and Montagnier struggled for several years about primacy. In March 1987 Ronald Reagan (the then President of USA) and Jacques Chirac (French Prime minister) called a press conference to announce the renaming of this retrovirus which is known today as Human Immunodeficiency Virus (HIV).

Nowadays, we hear a lot about HIV from the media. Many educational and medical institutions started educating people publically about AIDS and HIV. Moreover, effective antiretrovirol drugs (ARVs) are being developed to treat HIV infected individuals.

## 1.3 History and status of HIV in South Africa

South Africa is currently experiencing one of the most severe HIV epidemics in the world. By the end of 2005, there were five and a half million people living with HIV in South Africa [6], and almost 1000 AIDS deaths occurring every day around the globe, according to UNAIDS estimates [77]. A survey published in 2004 found that South Africans spent more time at funerals than they did having their hair cut, shopping or having barbecues. It also found that more than twice as many people had been to a funeral in the past month than to a wedding [73].

South Africa has had a turbulent past, and this history is relevant to the explosive spread of HIV in the country. Below we describe (chronologically) the different stages and measures taken regarding this epidemic in South Africa [6] which indicates that how the disease was evolving despite the various initiatives taken by the government:



**1980s:** In 1985, a State of Emergency was declared in South Africa that would last for five years. This was a result of riots and unrest that had arose in response to Apartheid (the system of racial segregation that had been in place since the 1950s). Apartheid prohibited mixed-race marriages and sex between different ethnic groups, and categorised separate areas in which different races lived. In the same year, the government set up the country's first AIDS advisory group in response to the increasingly apparent presence of HIV amongst South Africans. The first recorded case of AIDS in South Africa was diagnosed in 1982, and although initially HIV infections seemed mainly to be occurring amongst gay men, by 1985 it was clear that other sectors of society were also affected. Towards the end of the decade, as the abolition of Apartheid began, an increasing amount of attention was paid to the AIDS crisis.

**1990:** The first national antenatal survey to test for HIV found that 0.8% of pregnant women were HIV-positive [81]. It was estimated that there were between 74,000 and 120,000 people in South Africa living with HIV. Antenatal surveys have subsequently

been carried out annually.

**1991:** The number of diagnosed heterosexually transmitted HIV infections equalled the number transmitted through sex between men. Since this point, heterosexually acquired infections have dominated the epidemic. Several AIDS information, training and counselling centres were established during the year.

**1992:** The government's first significant response to AIDS came when Nelson Mandela addressed the newly formed National AIDS Convention of South Africa (NACOSA). The purpose of NACOSA was to begin developing a national strategy to cope with AIDS. The free National AIDS helpline was founded.

**1993:** The National Health Department reported that the number of recorded HIV infections had increased by 60% in the previous two years and the number was expected to double in 1993. The HIV prevalence rate among pregnant women was 4.3%.



**1994:** The Minister for Health accepted the basis of the NACOSA strategy as the foundation of the government's AIDS plan. There was criticism that the plan, however well intended, was poorly thought and disorganised. The South African organisation Soul City was formed, with the aim of developing media productions to educate people about health issues, including HIV/AIDS.

**1995:** The International Conference for people living with HIV and AIDS was held in South Africa. The then Deputy President Thabo Mbeki, acknowledged the seriousness of the epidemic, and the South African Ministry of Health announced that around 850,000 people (2.1% of the then total population) were suspected to be HIV-positive [66].

**1996:** The HIV prevalence rate among pregnant women was 12.2%.

**1997:** The HIV prevalence rate among pregnant women was 17.0%. A national review of South Africa's AIDS response to the epidemic found that there was a lack of political leadership.

**1998:** The pressure group Treatment Action Campaign (TAC) was founded, to campaign for the rights of people living with HIV, and to demand access to HIV treatment in South Africa for all those who were in need of it.

**1999:** The HIV prevalence rate among pregnant women was 22.4%.

**2000:** The Department of Health outlined a five-year plan to combat AIDS, HIV and STIs [22]. A National AIDS Council was set up to oversee these developments. At the International AIDS Conference in Durban, the new South African President Thabo Mbeki made a speech in which he mentioned that the main cause of AIDS is the problem of poverty and not the HIV. President Mbeki then consulted a number of dissident scientists who rejected the link between HIV and AIDS.

**2001:** The HIV prevalence rate among pregnant women was 24.8%.

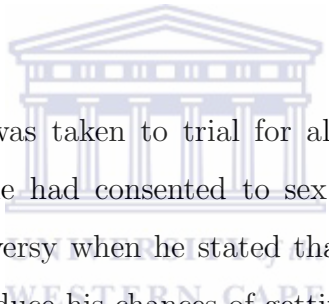
**2002:** The honourable High Court of South Africa ordered the government to make the drug 'Nevirapine' available to pregnant women to help prevent mother to child transmission of HIV. Despite international drug companies offering free or cheap antiretroviral drugs, [71] the Health Ministry remained hesitant about providing treatment for people living with HIV.

**2003:** The government approved a plan to make antiretroviral treatment publicly

available. The HIV prevalence rate among pregnant women by the end of this year was 27.9%.

**2004:** The South African government's treatment program began to take effect in Gauteng (one of the nine provinces in South Africa), followed by other provinces.

**2005:** At least one service point for AIDS related care and treatment had been established in all of the 53 districts in the country, meeting the government's 2003 target. However, it was clear that the number of people receiving antiretroviral drugs was well behind initial targets. The HIV prevalence rate among pregnant women was 30.2%.



**2006:** A senior politician was taken to trial for allegedly raping an HIV-positive woman. He argued that she had consented to sex and was eventually found not guilty, but attracted controversy when he stated that he had showered after sex in the belief that this would reduce his chances of getting infected with HIV. Criticism of the government's response to AIDS heightened, with UN special envoy Stephen Lewis attacking the government as 'obtuse and negligent' at the International AIDS Conference in Toronto. At the end of the year, the government announced a draft framework to tackle AIDS and pledged to improve antiretroviral drug access. Civil society groups claimed that this marked a turning point in the government's response.

Further upcoming informations regarding various issues associated with HIV and AIDS can be found in [6].

### 1.3.1 The South African Department of Health Study, 2005

Based on its sample of more than 16,510 women attending antenatal clinics across all nine provinces, the South African Department of Health Study estimates that 30.2% of pregnant women were living with HIV in 2005. The provinces that recorded the

highest HIV rates were KwaZulu-Natal, Mpumalanga and Gauteng.

Until 1998 South Africa had one of the fastest expanding epidemics in the world, but HIV prevalence is now growing more slowly. Among teenage girls, the rate declined from 1998 to 2002, and has since risen only slightly, indicating that the rate of new infections may have peaked. Historical prevalence figures can be found in our South Africa as indicated in the Tables 1.1 and 1.2.

Because infection rates vary between different groups of people, the findings from antenatal clinics cannot be applied directly to men, newborn babies and children. However, some simple calculations can yield an approximate estimate of the total number of people living with HIV in South Africa.

Based on the antenatal data, the study estimates that 6.29 million South Africans were living with HIV at the end of 2004, including 3.3 million women and 104,863 babies. In producing these data, it is assumed that pregnant women accurately represented all women aged 15 - 49 years, that men are 85% as likely to be infected as women, and that 30% of babies born to infected mothers will themselves have HIV (ignoring any reductions due to preventive action).



### 1.3.2 The South African National HIV Survey, 2005

The National HIV Survey is a "household" survey. This involves sampling a proportional cross-section of society, including a large number of people from each geographical, racial and other social groups. The researchers took great pains to try to make the sample as generalized as possible, and the findings are later adjusted to correct for likely over- or under-representation of individual groups (according to census data).

The surveyers visited 12,581 households across South Africa, of which 10,584 (84%) took part in the survey. Of the 24,236 people within these households who were eligible to take part, 23,275 (96%) agreed to be interviewed and 15,851 (65%) agreed to take an HIV test. This means that only 55% of eligible people were tested.

Table 1.1: Province-wise estimated HIV prevalence percentage among antenatal clinic attendees [6]

| Province | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 |
|---|---|---|---|---|---|---|
| KwaZulu-Natal | 36.2 | 33.5 | 36.5 | 37.5 | 40.7 | 39.1 |
| Mpumalanga | 29.7 | 29.2 | 28.6 | 32.6 | 30.8 | 34.8 |
| Gauteng | 29.4 | 29.8 | 31.6 | 29.6 | 33.1 | 32.4 |
| North West | 22.9 | 25.2 | 26.2 | 29.9 | 26.7 | 31.8 |
| Free State | 27.9 | 30.1 | 28.8 | 30.1 | 29.5 | 30.3 |
| Eastern Cape | 20.2 | 21.7 | 23.6 | 27.1 | 28.0 | 29.5 |
| Limpopo | 13.2 | 14.5 | 15.6 | 17.5 | 19.3 | 21.5 |
| Northern Cape | 11.2 | 15.9 | 15.1 | 16.7 | 17.6 | 18.5 |
| Western Cape | 8.7 | 8.6 | 12.4 | 13.1 | 15.4 | 15.7 |
| National | 24.5 | 24.8 | 26.5 | 27.9 | 29.5 | 30.2 |

Table 1.2: Age-wise estimated HIV prevalence percentage among antenatal clinic attendees [6]



| Age group (yrs) | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 |
|---|---|---|---|---|---|---|
| <20 | 16.1 | 15.4 | 14.8 | 15.8 | 16.1 | 15.9 |
| 20-24 | 29.1 | 28.4 | 29.1 | 30.3 | 30.8 | 30.6 |
| 25-29 | 30.6 | 31.4 | 34.5 | 35.4 | 38.5 | 39.5 |
| 30-34 | 23.3 | 25.6 | 29.5 | 30.9 | 34.4 | 36.4 |
| 35-39 | 15.8 | 19.3 | 19.8 | 23.4 | 24.5 | 28.0 |
| 40+ | 11.0 | 9.8 | 17.2 | 15.8 | 17.5 | 19.8 |

The main reasons given for refusing HIV testing were fear of having a blood sample taken (58%); religious objections to having a blood sample taken (16%) and not wanting to learn HIV status (7%). A further 13% of people who refused were, for various reasons, afraid or mistrustful of the survey. The report of the survey claims that people at high risk for HIV infection were more likely to take part, and

the results were adjusted to compensate for this perceived bias. The response rate is considered "good" by the standards of this type of survey, but is considerably lower than that found in other parts of sub-Saharan Africa [70].

Based on this survey, the researchers estimated that 10.8% of the South Africans over previous two years were living with HIV in 2005.

## 1.4 HIV types, groups and subtypes

HIV is a highly variable virus which mutates very readily. This means there are many different strains of HIV, even within the body of a single infected person. Based on genetic similarities, the numerous virus strains may be classified [6] into types, groups and subtypes.

There are two types of HIV: HIV-1 and HIV-2. Both types are transmitted either by sexual contacts or through blood, and also from mother to child. These subtypes appear to cause clinically indistinguishable AIDS. However, it seems that HIV-2 is not easily transmitted, and the period between initial infection and illness is longer in this case. This type of HIV is concentrated in West Africa and is rarely found elsewhere. Therefore, the predominant virus (worldwide) is HIV-1, and generally when people refer to HIV without specifying the type of virus they mean it as HIV-1.

As is mentioned in Figure 1.1 (page 11), the strains of HIV-1 can be classified into three Groups : the "major" Group M, the "outlier" Group O and the "new" Group N. These three groups may represent three separate introductions of simian immunodeficiency virus into humans.

While more than 90% of HIV-1 infections belong to HIV-1 Group M, Group O appears to be restricted only to the West-Central Africa whereas the Group N - discovered in Cameroon (in 1998) - is extremely rare.

Within Group M there are known to be at least nine genetically distinct subtypes (or classes) of HIV-1, namely, subtypes A, B, C, D, F, G, H, J and K.

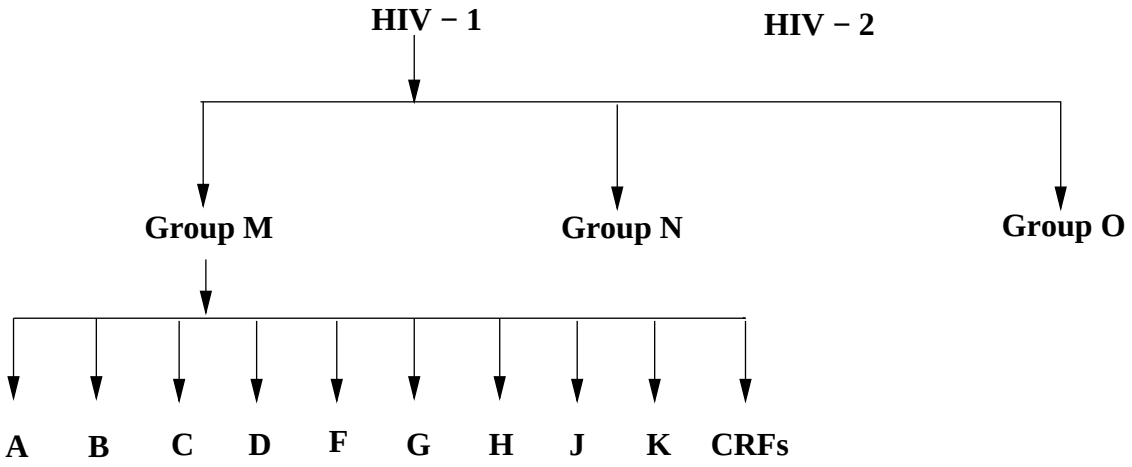



Figure 1.1: Classification of HIV into Various Groups

Occasionally, two viruses of different subtypes can meet in the cell of an infected person and mix together their genetic material to create a new hybrid virus (a process similar to sexual reproduction, and sometimes called "viral sex") [16]. Many of these new strains do not survive for long, but those that infect more than one person are known as "circulating recombinant forms" or CRFs. For example, the CRF A/B is a mixture of subtypes A and B.



The classification of HIV strains into subtypes and CRFs is a complex issue and the definitions are subject to change as new discoveries are made. Some scientists talk about subtypes A1, A2, A3, F1 and F2 instead of A and F, though others regard the former as sub-subtypes. One of the CRFs is called A/E because it is thought to have resulted from hybridization between subtype A and some other "parent" subtype E. However, no one has ever found a pure form of subtype E. Confusingly, many people still refer to the CRF A/E as "subtype E" (in fact it is most correctly called CRF01_AE).

A virus isolated in Cyprus was originally placed in a new subtype I, before being reclassified as a recombinant form A/G/I. It is now thought that this virus represents an even more complex CRF comprised of subtypes A, G, H, K and unclassified regions. The designation "I" is no longer used [31, 75].

The HIV-1 subtypes and CRFs are very oddly distributed throughout the world, with the most widespread being subtypes B and C. Subtype C is largely predominant in southern and eastern Africa, India and Nepal. It has caused the world's worst HIV epidemics and is responsible for around half of all infections. Historically, subtype B has been the most common subtype in Europe, the Americas, Japan and Australia. Although this remains the case, other subtypes are becoming more frequent and now account for at least 25% of new infections in Europe. Subtype A and CRF A/G predominate in west and central Africa, with subtype A possibly also causing much of the Russian epidemic [12]. Subtype D is generally limited to east and central Africa; A/E is prevalent in south-east Asia, but originated in central Africa; F has been found in central Africa, south America and eastern Europe; G and A/G have been observed in western and eastern Africa and central Europe. Subtype H has only been found in central Africa; J only in central America; and K only in the Democratic Republic of Congo and Cameroon.

In the section below, we provide some models which are focused mainly on subtypes of HIV-1 type described as above.



## 1.5 Some HIV Models

Ever since the pioneer works of Kermack and McKendrick [48] in 1927, many epidemics have been modelled and extensive mathematical analysis has been carried out for them. The development of mathematical models for HIV models and their analysis received much attention only in the past two-three decades. In this section we present some of these HIV models (starting from the simplest one and then their subsequent modifications) as they have evolved and the available methods for their solutions.

### 1.5.1 *Model-I* (A single subtype circulating in a community (with a vaccine))

McLean and Blower [58] described a model that reflects the observed epidemiology of HIV in San Francisco. The population they considered was an imaginary homosexual population. This model basically investigates a single subtype circulating in a community.

The total population in this model is divided into four classes:

- susceptibles ($X$),
- vaccinated ($V$),
- infectious ($Y$), and
- AIDS patients ($A$).



The size of sexually active community is denoted by $N = X + Y + V$ which means that they assumed that AIDS patients are not included. (Note in the above that $N$ denote the size of sexually active community and not the total population).

The biological assumptions and governing equations of the model are

- Individuals recruited into the sexually active community at a constant rate $\Pi$.
- They leave the community at a constant rate $\mu$.
- A fraction $\rho$ of new recruits are vaccinated and it takes a fraction $\varepsilon$ on them.
- The risk of being infected depends on per partnership infection probability $\beta$, the average number of new partners per unit time $c$, and fraction of the community that are infectious $\frac{Y}{N}$.
- Some vaccinated individuals loose their vaccine-induced immunity due to a finite duration of the vaccine's effects. The vaccinated individual then joins the susceptible class at a rate $wV$.

Taking the above into account, the rate of change in the number of susceptibles is

$$\frac{dX}{dt} = (1-\varepsilon\rho)\Pi - \mu X - \frac{\beta c XY}{N} + wV. \tag{1.1}$$

The rate of change in the number of vaccinated individuals is given by

$$\frac{dV}{dt} = \varepsilon\rho\Pi - \mu V - wV - \frac{(1-\psi)\beta c VY}{N}, \tag{1.2}$$

where $\psi$ is the degree of protection afforded by the vaccine.

The size of the infectious population is given by

$$\frac{dY}{dt} = \frac{\beta c\left[X + (1-\psi)V\right]Y}{N} - (\mu+\gamma)Y \tag{1.3}$$

and finally the rate of change in the number of AIDS patients is given by

$$\frac{dA}{dt} = \gamma Y - (\mu+\alpha)A, \tag{1.4}$$

where $\alpha$ is the average death rate.

We refer the model constituted by above four equations (1.1-1.4) as the *Model-I*.



### 1.5.2 *Model-II* (The transmission model of two HIV subtypes without vaccination)

To assess vaccine programs for the control of two HIV subtypes, Porco and Blower [68] developed mathematical models described below.

Firstly they formulated a model of the intrinsic transmission dynamics of two HIV subtypes in a homosexual community. The individuals that are in the model are part of the sexually active community. Out of the various subtypes found through investigations, they considered any two of these and refered to them as subtype-1 and subtype-2.

The total population in their model is divided into the following five classes:

(i) susceptibles, $X$,

(ii) individuals who are infected with subtype-1 but have not developed AIDS, $Y_1$,

(iii) individuals who are infected with subtype-2 but have not developed AIDS, $Y_2$,

(iv) individuals who have developed AIDS, $A_1$,

(v) individuals who have developed AIDS, $A_2$.

Like the previous model, again the total size of the sexually active community is given by $N = X + Y_1 + Y_2$.

After incorporating necessary assumptions, the model that Porco and Blower developed is given by the following set of equations

$$\left.\begin{aligned}
\frac{dX}{dt} &= \Pi - \mu X - \frac{\beta_1 c X Y_1}{N} - \frac{\beta_2 c X Y_2}{N} \\
\frac{dY_1}{dt} &= \frac{\beta_1 c X Y_1}{N} - \mu Y_1 - \gamma_1 Y_1 \\
\frac{dY_2}{dt} &= \frac{\beta_2 c X Y_2}{N} - \mu Y_2 - \gamma_2 Y_2 \\
\frac{dA_1}{dt} &= \gamma_1 Y_1 - (\mu + \alpha) A_1 \\
\frac{dA_2}{dt} &= \gamma_2 Y_2 - (\mu + \alpha) A_2,
\end{aligned}\right\} \tag{1.5}$$

where $\alpha$ is the average death rate.

We refer the above model as the *Model-II*.

### 1.5.3 *Model-III* (The transmission model of two HIV-subtypes with vaccination)

This model is an extention of *Model-II* in which the authors (Porco and Blower [68]) included the effects of vaccination with a prophylactic vaccine.

The fraction of the individuals entering the sexually active community and who enter the vaccinated community is denoted by $\rho$. Then a fraction of those individuals,

who have a protective immune response is denoted by $e$ and hence the fraction of individuals who are effectively vaccinated is $\rho e$.

The model assumes that the individuals that have been effectively vaccinated are less likely to be infected. The degree of protection against the infection for an effectively vaccinated individual is between 0 and 1. Where 0 is for no protection and 1 is for complete prevention of infection for those exposed to a given subtype.

Again the total sexually active community is $N = X + V + Y_1 + Y_2$.

Noting that $V(t)$ denotes vaccinated susceptible individuals, the model (taking into account the above specifications where $X$, $Y_1$ and $Y_2$ has the same meaning as mentioned in the previous model) is therefore given by the following set of equations, altogether, referred to as *Model-III*:

$$\left.\begin{aligned}
\frac{dX}{dt} &= \Pi(1-\rho e) - \mu X - \frac{\beta_1 cXY_1}{N} - \frac{\beta_2 cXY_2}{N} \\
\frac{dV}{dt} &= \Pi\rho e - \mu V - \frac{\beta_1 c(1-\zeta_1)VY_1}{N} - \frac{\beta_2 c(1-\zeta_2)VY_2}{N} \\
\frac{dY_1}{dt} &= \frac{\beta_1 cXY_1}{N} + \frac{\beta_1(1-\zeta_1)cVY_1}{N} - \mu Y_1 - \gamma_1 Y_1 \\
\frac{dY_2}{dt} &= \frac{\beta_2 cXY_2}{N} + \frac{\beta_2(1-\zeta_2)cVY_2}{N} - \mu Y_2 - \gamma_2 Y_2 \\
\frac{dA_1}{dt} &= \gamma_1 Y_1 - (\mu+\alpha)A_1 \\
\frac{dA_2}{dt} &= \gamma_2 Y_2 - (\mu+\alpha)A_2,
\end{aligned}\right\} \tag{1.6}$$

where $\zeta_1$ and $\zeta_2$ denote the degree of protection that the vaccine confers against infection by the two subtypes in the individuals who are effectively vaccinated and $\alpha$ denotes the average death rate.

### 1.5.4 *Model-IV* (The transmission dynamics of two HIV subtypes: modification of *Model-III*)

The model considered by Gumel [37] is a modification of *Model-III*. He included per capita rate ($\tau$) of treatment coverage and excluded the individuals who developed AIDS from subtype-1 and subtype-2 infection. He also included a recovery rate for individual in subtype-i, denoted by $\gamma_i$, where $i = 1, 2$. His model consists of the following equations:

$$\frac{dX}{dt} = \Pi(1-\rho) - \mu X - \frac{1}{N}\beta_1 cXY_1 - \frac{1}{N}\beta_2 cXY_2,\ t > t_0,\ X(t_0) = X^0, \tag{1.7}$$

$$\frac{dV}{dt} = \Pi\rho - \mu V - \frac{1}{N}(1-\xi_1)\beta_1 cVY_1 - \frac{1}{N}(1-\xi_2)\beta_2 cVY_2,\ t > t_0,\ V(t_0) = V^0, \tag{1.8}$$

$$\frac{dY_1}{dt} = \frac{1}{N}\beta_1 cXY_1 + \frac{1}{N}(1-\xi_1)\beta_1 cVY_1 - (\mu+\gamma_1+\tau)Y_1,\ t > t_0,\ Y_1(t_0) = Y_1^0, \tag{1.9}$$

$$\frac{dY_2}{dt} = \frac{1}{N}\beta_2 cXY_2 + \frac{1}{N}(1-\xi_2)\beta_2 cVY_2 - (\mu+\gamma_2+\tau)Y_2,\ t > t_0,\ Y_2(t_0) = Y_2^0, \tag{1.10}$$



where $N(t) = X(t) + V(t) + Y_1(t) + Y_2(t)$ with

(i) $X(t)$: susceptible individuals,

(ii) $V(t)$: vaccinated susceptible individuals,

(iii) $Y_1(t)$: individuals infected with an endemic HIV-subtype 1,

(iv) $Y_2(t)$: individuals infected with an invading HIV-subtype 2

and the associated parameters are

- $\Pi$: annual recruitment rate of individuals into the sexually active community,
- $\rho$: fraction of susceptible individuals vaccinated,
- $\mu$: rate of stopping sexual activity,

- $c$: number of sexual partners,

whereas for $i = 1, 2$,

- $\beta_i$: probability of per partnership transmission,
- $\xi_i$: vaccine induced immunity against subtype - $i$,
- $\tau$: per capita rate of treatment coverage,
- $\gamma_i$: recovery rate of subtype - $i$.

We refer to this model as *Model-IV*.

Models presented above are some of the popularly studied models. Other models can be found in the list of references in the articles cited along with these works.



## 1.6 Literature Survey

In this section, we briefly mentioned few of the methods developed to solve the models described in previous section. The works presented in this section are in the chronological order and is not classified based on any specific model due to the fact that some of the articles deal with more than one model described earlier. We include both analytical and numerical approaches to solve such models. We apologise if there are any omitions which might occured due to unavailability of the literature but are (of course) totally unintentional.

Anderson et al. [3] described some preliminary attempts to formulate simple mathematical models of the transmission dynamics of HIV infection in homosexual communities. In conjunction with a survey of the available epidemiological data on HIV infection and the incidence of AIDS, the models are used to assess how various processes influence the course of the initial epidemic following the introduction of the virus. They mentioned that the models of the early stages of viral spread

provide crude methods for estimating the basic reproductive rate of the virus, given a knowledge of the incubation period of the disease (AIDS) and the initial doubling time of the epidemic. To assess the influence of variation in the incubation period and heterogeneity in sexual activity, they formulated more complex models.

In [11], Blythe and Anderson studied a proportionate mixing one-sex model of sexual transmission of HIV and described it in which sexual activity (new partners per unit time) is defined as a continuous variable in a set of integro-partial-differential equations. They developed a discrete activity-class approximation by matching equilibrium state and rate variables as closely as possible with the continuous-variable model and consists only of ordinary differential equations. Activity-class boundaries are arbitrary, and each class is characterized by a single level of activity. If there are $N$ classes, the level of activity in $N-1$ of them is such that the steady-state susceptible class sub-population is equal to the population in the equivalent section of the continuous model. They chose the activity level for the remaining class in such a way that the condition for endemicity of the infection in the approximation is equal to that for the equivalent continuous-variable model and this minimizes errors in the steady-state population. The relationship between the discrete and continuous-variable models is explored, via numerical and analytical studies, in order to evaluate the accuracy of the approximation.

Blythe and Anderson [9] derived distributions describing variation in the incubation and infections periods of the HIV from a series of risk or hazard functions. Four possible forms of the probability density function are considered, namely, exponential, Weibull, Erlang/gamma, and rectangular, and the properties and underlying risk functions are compared and contrasted. They also analyzed (both theoretically and numerically) the models of the transmission dynamics of the virus, encapsulating different assumptions concerning the distributed incubation and infectious periods.

In [10], Blythe et al. considered two different approaches to the encapsulation of temporal variation in the infectiousness of HIV-infected persons, and variability in

the incubation period of AIDS, in simple homogeneous mixing models of viral transmission in male homosexual communities are described. The first approach is based on the division of the infected population into a series of subclasses with differing levels of infectivity and different durations of occupancy. The second approach is more mechanistic in character and is based on an attempt to relate changes in viral abundance within an infected person to the likelihood that the disease AIDS develops. Variable incubation is induced by variation in the rate of change of viral abundance in the infected population. They compared the numerical projections of changes in the incidence of AIDS through time, generated from both types of model, with projections based on the assumption of constant infectivity throughout the incubation period of AIDS. Their model formulation also highlights areas in which more detailed quantitative epidemiological studies are required. Finally they discuss the methods of parameter estimation.

Kakeshashi [47] studied the spread of HIV/AIDS in Japan which was analyzed using a mathematical model incorporating pair formations between adults and sexual contacts with commercial sex workers. The parameters involved in the model were carefully specified as realistically as possible to the actual situation in Japan. Plausible ranges were assigned to those parameters for which values are not known precisely. The model was used to simulate the effect of HIV infected commercial sex workers introduced into a population without HIV. It was shown that the model could generate different scenarios, an explosive infection or a temporal spread, according to different settings of the parameters.

Then the condition for occasional introduction of HIV infected commercial sex workers to be able to cause an explosive spread of HIV infection was analyzed. This condition was summarized in terms of the critical transmission probability so that we could easily evaluate the degree of the risk. For some unclear parameters, sensitivity to the critical transmission probability was calculated. A plausible range of the critical transmission probability was also calculated using the Latin hypercube sampling

method where the parameters were distributed on the plausible ranges. According to the analyses of the model it was concluded that the actual situation of HIV spread in Japan should lie very near the critical point that determines whether the explosive HIV spread actually takes place. This study also suggested that effective action taken immediately could be useful to prevent explosive HIV infection in Japan.

In [57], May and Anderson reviewed data on HIV infections and AIDS disease among homosexual men, heterosexuals, intravenous (IV) drug abusers and children born to infected mothers, in both developed and developing countries. They derived the estimates of the model's parameters from the epidemiology data, and predictions are compared with observed trends. They also combine these epidemiological models with demographic considerations to assess the effects that heterosexually-transmitted HIV/AIDS may eventually have on rates of population growth, on age profiles and on associated economic and social indicators, in African and other countries. They also discussed about the degree to which sexual or other habits must change to bring the 'basic reproductive rate', $R_0$ of HIV infections below unity.

Boily and Anderson [13] developed a simple model of the transmission of HIV-1 by heterosexual contact and from mother to unborn infant to assess the influence of patterns of mixing between low and high sexual activity classes of the two sexes on the pattern of spread of the virus and the demographic impact of AIDS. Their numerical studies of the model behaviour are based, wherever possible, on parameter estimates derived from epidemiological studies of HIV-1 spread in Africa. Their analyses reveal that the assumed pattern of mixing, ranging from assortative (like with like) through random (proportional) to disassortative (like with unlike), has a very major impact on the predicted spread of the virus and the concomitant demographic impact of AIDS. They predicted patterns of strong assortative mixing to generate the least spread and demographic impact, by comparison with proportional or disassortative mixing. They also conclude via the analyses that the rules governing behaviour changes, once AIDS-induced mortality changes the structure of the population (i.e. the numbers

in the low and high sexual activity classes of the two sexes), have a very significant influence on the course of the epidemic. They compared the predicted patterns with observed trends in Africa.

John [45] considered a model of the transmission dynamics of HIV-1 appropriate to urban areas of Africa and discussed its behaviour explored through numerical studies. The model is a two-sex model with age-dependent demographic and behavioural parameters. Adults are classified by age, sex, risk group, and epidemiological status. He explored sex and age patterns of infection as is the potential economic impact of changes in the sex and age composition of the population.

Genetic variation is the hallmark of infections with lentiviruses in general and the viruses (HIV-1, HIV-2) in particular. In [63] Nowak reviewed both experimental evidence for the variability of the previous HIV genome during the course of an individual infection and mathematical models that outline the potential importance of antigenic variation as a major factor to drive disease progression. The essential idea is that the virus evades immune pressure by the continuous production of new mutants resistant to current immunological attack. This results in the accumulation of antigenic diversity during the asymptomatic period.

The existence of an antigenic diversity threshold is derived from the asymmetric interaction between the virus quasi-species and the CD4 T-cell population: CD4 T-cells mount immune responses some of which are directed against specific HIV variants, but each virus strain can induce depletion of all CD4 T-cells and therefore impair immune responses regardless of their specificity. Therefore, increasing HIV diversity enables the virus population to escape from control by the immune system. In this context the observed genetic variability is responsible for the fact that the virus establishes a persistent infection without being cleared by the immune response and induces immunodeficiency disease after a long and variable incubation period.

Gani and Yakowitz [32] considered a random allocation model for the transmission of HIV by needle sharing among a group of intravenous drug users who are friends

or relatives (buddy-users). A Markov chain approach is used to track the increase in infectives in a stable group of such intravenous drug users, some of whom are HIV positive. The model is modified to allow for the replacement of infectives in the group, with the group size remaining constant.

Around 1991-92, a number of prophylactic vaccines against HIV have passed through phase I of the clinical trials, and phase II clinical trials were being planned. McLean and Blower [58] mentioned that these vaccines are not expected to be perfect and might fail in a number of different ways. They showed how to equate different aspects of imperfection in a prophylactic vaccine in terms of impact upon levels of herd immunity, and hence upon the vaccine coverage required for eradication. Such comparisons reveal that an otherwise perfect vaccine that gives protection which wanes with a half-life of 10 years is only as good as a vaccine that works in 30% of people giving them complete, lifelong protection. Furthermore, they compare predicted patterns of seroconversion that would be observed in clinical trials and in community-wide vaccination campaigns for vaccines that confer the same levels of herd immunity but are imperfect in different ways.



Theory is linked with data to assess the probability of eradicating HIV in San Francisco through the use of prophylactic vaccines. In [7] Blower and McLean quantified the necessary vaccine efficacy levels and population coverage levels for eradication. They assessed the likely impact of risk behaviour changes on vaccination campaigns. Their results show that it is unlikely that vaccines will be able to eradicate HIV in San Francisco unless they are combined with considerable reductions in risk behaviour. Furthermore, if risk behaviour increases as the result of a vaccination campaign, then vaccination could result in a perverse outcome by increasing the severity of the epidemic.

Mollison et al. [61] discussed that the problems of understanding and controlling disease has raised a range of challenging mathematical and statistical research topics, from broad theoretical issues to specific practical ones. They indicated that

in particular, the interest in acquired immune deficiency syndrome has stimulated much progress in diverse areas of epidemic modelling, particularly with regard to the treatment of heterogeneity, both between individuals and in mixing of subgroups of the population.

At the same time better data and data analysis techniques have become available, and there have been exciting developments in relevant theory, ranging from random graphs and spatial stochastic processes to the structural stability of difference and differential equations. This progress in specific areas is now being matched by interdisciplinary cooperation aimed at elucidating relationships between the widely varying types of model that have been found useful, to determine their strengths and limitations in relation to basic aims such as understanding, prediction, and evaluation and implementation of control strategies. Such interdisciplinary work can be expected to make major contributions to the modelling of a wide range of human, animal and plant diseases, as well as to general statistical and biomathematical theory.

Garnett and Anderson [33] presented a mathematical model of the transmission dynamics of HIV-1 in a heterosexual population stratified by age, sex, and sexual activity (defined by rates of sexual partner acquisition). The model represents an extension of previous studies with a special focus on patterns of mixing or contact between sexual activity and different age classes of the two sexes. A range of mixing patterns between these groups is specified for both sexes. Mixing is described on two scales from fully assortative to fully disassortative, with random defined either according to numbers of sexual partnerships or numbers of people.

Above authors mentioned that the sexual partnerships in the model are balanced by changes in the rates of sexual partner acquisition between particular groups and a range of changes, from only women changing behaviour to only men changing behaviour, are analyzed. The pattern of mixing is most influential in determining the shape and magnitude of the epidemic, but the manner in which people choose partners (i.e., dependent on numbers or proportions in the population) is also important.

They also illustrated relative importance of variation in transmission probabilities and mean rates of partner change on the course of the HIV epidemic. They indicated furthermore that the analysis of the sensitivity of predictions to changing parameters in the force of infection term of the model provides a theoretical basis from which the influence of control strategies and the demographic effects of HIV can be analyzed.

In [35] Greenhalgh and Hay developed and analyzed a model for the spread of HIV/AIDS amongst a population of injecting drug users. Their work is based on a model originally due to Kaplan (1989, Rev. Inf. Diseases 11, 289-98). They start off with a brief literature survey and review; this is followed up by a detailed description of Kaplan's model. They then outline a more realistic extension of Kaplan's model. Then they perform an equilibrium and stability analysis on this model. They found that there is a critical threshold parameter $R_0$ which determines the behaviour of the model. If $R_0 \leq 1$ there is a unique disease-free equilibrium, and if $R_0 < 1$ the disease dies out. If $R_0 > 1$ this disease-free equilibrium is unstable, and in addition there is a unique endemic equilibrium which is locally stable. If a certain condition is satisfied (and for Kaplan's model this condition is always satisfied), additional complete global-stability results are shown. They confirmed these results and explored them further via simulations.

Williams and Anderson [80] considered a mathematical model of the transmission dynamics of the HIV-1 in England and Wales. The model mimics transmission within and between different sexual activity classes (or needle sharing classes in the case of intravenous drug users) and within and between different risk groups such as male homosexuals, intravenous drug users and heterosexuals. They described the patterns of mixing and sexual contact by mixing matrices whose elements define the degree of assortative or disassortative contact between different stratifications of the sexually active population.

The parameters that the above authors used were based on published data but likely patterns of mixing are crudely estimated by fitting model projections to past

temporal trends in the incidence of AIDS in the different at-risk groups in England and Wales. They shown many different parameter combinations fitting past trends and explained that each has different implications for projections into the future. The also highlighted the importance of mixing patterns to future trends. They concluded that future trends are uncertain (on the basis of current information) particularly within the heterosexual population. Small changes in the values of key parameters induce significant changes in projected trends. They also indicated that the transmission models are of greatest value as tools to highlight needs for data for accurate projection and as a template for assessing the relative contribution of various factors to future trends in the incidence of AIDS.

Porco and Blower [68] developed and used mathematical models to assess vaccine programs for controlling two subtypes of HIV, both for developing countries where more than one subtype is present and for countries where only one subtype is present but other subtypes may invade. They began by formulating a model of the intrinsic transmission dynamics of the two HIV subtypes and then extended this model to include the effects of a prophylactic vaccine that provides a degree of protection against infection by one subtype and vaccine-induced cross-immunity against infection by the second subtype. Using these models, they assessed the potential impact of using a prophylactic vaccine when one subtype of HIV is endemic and a second subtype is introduced into the community. In each case, mass vaccination could result in one of four possible outcomes: (1) both subtypes are eradicated, (2) the endemic subtype persists and the invading subtype is eradicated, (3) the endemic subtype is eradicated and the invading subtype persists, or (4) both subtypes coexist.

In [69], Raab et al. described the methodology developed to carry out predictions of the AIDS epidemic in Scotland. Information on the HIV epidemic comes from formal case reports of AIDS cases and HIV positive tests, reports from surveillance schemes and from special studies. They reviewed these sources of information, upto the end of 1994. Prior information on aspects of HIV disease is available from various

published and unpublished sources. They proposed a simple model of the HIV epidemic in Scotland and the information is summarized in terms of this model. Using the Monte Carlo methods, the Bayesian methodology is described and used to predict future cases of AIDS in Scotland.

Tuckwella and Le Corfecb [76] developed a simple stochastic mathematical model and investigated for early HIV-1 population dynamics. Their model, which is a multidimensional diffusion process, includes activated uninfected CD4 T-cells, latently and actively infected CD4 T-cells and free virions occurring in plasma. They assumed that the stochastic effects will arise in the process of infection of CD4 T-cells and transitions may occur from uninfected to latently or actively infected cells by chance mechanisms. Using the then available parameter values, they examined the intrinsic variability in response to a given initial infection by solving the stochastic system numerically. They estimated the statistical distributions of the time of occurrence and the magnitude of the early peak in viral concentration.

For many years compartmental models have provided useful insights into the spread of epidemics. Such models are usually fairly easy to set up, but even the simpler models have the disadvantage that they are intractable to analytic solution. In [36] Griffiths et al. examined models of the HIV/AIDS epidemic, and showed that the equations may be linearized in a piecewise manner over time, thus allowing analytic solutions to be obtained. Indications of the usefulness of this approach are provided. In particular, an analytic solution gives insight into the mechanism of the epidemic, together with a clearer picture of the sensitivity of results to changes in parametervalues. Further, the processes of parameter estimation and the methodology of back-calculation also benefit from the provision of functional forms for the state variables.

In the paper by Lenbury et al. [52], geometric singular perturbation arguments are utilized to develop a separation condition for the identification of limit cycles in higher-dimensional ($n \geq 4$) dynamical systems characterized by highly diversified

time responses, in which there exists a three-dimensional subsystem which quickly reaches a quasi-steady state. The condition, which has been used until then to analyze relaxation oscillation in slow-fast systems, was extended to accommodate dynamical systems in which more state variables are involved in a special manner that still allows for the use of singular perturbation techniques. Application is then made to a model of HIV infection in T helper (TH) cell clones with limiting resting TH cell supply.

Porco and Blower [67] analyzed a mathematical model of the simultaneous transmission of two HIV subtypes and their control by vaccines. Two vaccines are analyzed which utilize different mechanisms, one in which the vaccine take differs for each subtype, and the other in which a different level of reduced infectivity results after infection by each subtype. The equilibrium outcome is different for each case; equilibrium coexistence of the two subtypes is possible in the differential take model, but not in the differential reduced infectivity model. This was the first step in understanding the interaction of HIV subtypes and differentially effective vaccines with different modes of action.



In [19] Coutinho et al. considered the variation of viraemia in the natural course of HIV infection which is expected to have major influence on the probability of transmission and, consequently, on the epidemiology of HIV/AIDS. In this paper they proposed a model which takes into account the time evolution of HIV viraemia (measured as HIV-RNA copies per ml of blood) in an infected individual and its impact on the threshold for the establishment of an endemic level, and mainly on the relative contribution of each of the clinical phases of the infection to the total transmission of HIV per infected individual.

Coutinho et al. [19] considered that an infected individual passes through three phases of viraemia. The first phase, which lasts for 6-7 weeks, is characterized by very high viraemia. In the second phase, which lasts about 10 years, the viraemia is much lower, increasing again in the last phase, which lasts up to two years, and ends in full-blown AIDS. They showed that the relative contribution of each phase to the

total transmission of HIV is very sensitive to the model they assumed for the dependence of the transmissibility of HIV on the viral load. For instance, if they assume that transmissibility is proportional to the decimal logarithm of viraemia, then the second phase predominates always. They indicated that due to the epidemiological importance of this fact, further improvement on virological research to better understand the dependence of HIV transmissibility on the viral concentration in biological fluids is necessary.

Callaway and Perelson [18] showed that HAART (highly active antiretroviral therapy) reduces the viral burden in HIV-1 infected patients below the threshold of detectability. However, substantial evidence indicates that viral replication persists in these individuals. In this paper they examined the ability of several biologically motivated models of HIV-1 dynamics to explain sustained low viral loads. At or near drug efficacies that result in steady state viral loads below detectability, most models are extremely sensitive to small changes in drug efficacy. They argued that if these models reflect reality many patients should have cleared the virus, contrary to observation. They found that a model in which the infected cell death rate is dependent on the infected cell density does not suffer this shortcoming. The shortcoming was also overcomed in two more conventional models that include small populations of cells in which the drug is less effective than in the main population, suggesting that difficulties with drug penetrance and maintenance of effective intracellular drug concentrations in all cells susceptible to HIV infection may underlie ongoing viral replication.

Ribeiro et al. [72] showed that HIV-1 infects cells of the immune system and leads to depletion of CD4+ T-cells, and to an increase of CD8+ T-lymphocytes. They mentioned that not much is known about the dynamics of turnover (proliferation and death) of the CD4+ and CD8+ T-cell populations in HIV-infected and healthy individuals. Using deuterated-glucose labeling, they developed a new experimental technique that provides information on cell turnover in *vivo*. However, the quantitative interpretation of the data requires the development of specific dynamic

models. In this paper they derive two models, a simple one-compartment model and a more complex two-compartment model. These models allow for robust quantification of death and proliferation rates. They demonstrated that more realistic models can account not only for differences in the turnover rates between HIV-infected and healthy individuals, but also take into consideration the elevated state of activation in HIV infection. The use of these models in the interpretation of the experimental data certainly increases one's knowledge of T-cell dynamics in the context of HIV infection.

Diaz et al. [23] designed anti-HIV compounds which has now become a crucial area for scientists working in numerous interrelated fields of science such as molecular biology, medicinal chemistry, mathematical biology, molecular modelling and bioinformatics. In this context, the development of simple but physically meaningful mathematical models to represent the interaction between anti-HIV drugs and their biological targets is of major interest.

Above authors applied Markov chain theory in an attempt to describe the interaction between the antibiotic paromomycin and the packaging region of the RNA in Type-1 HIV. In this model, they used a nucleicacid squeezed graph. The vertices of the graph represent the nucleotides while the edges are the phosphodiester bonds. A stochastic (Markovian) matrix was subsequently defined on this graph, an operation that codifies the probabilities of interaction between specific nucleotides of HIV-RNA and the antibiotic. The strength of these local interactions can be calculated through an inelastic vibrational model. The successive power of this matrix codifies the probabilities with which the vibrations after drug-RNA interactions vanish along the polynucleotide main chain. The sums of self-return probabilities in the k-vicinity of each nucleotide represent physically meaningful descriptors. A linear discriminant function was developed and gave rise to excellent discrimination in 80.8 % of interacting and footprinted nucleotides. They employed the Jack-knife method to assess the stability and predictability of the model. On the other hand, a linear

regression model predicted the local binding affinity constants between a specific nucleotide and the antibiotic ($R(2) = 0.91$, $Q(2) = 0.86$). These kinds of models could play an important role either in the discovery of new anti-HIV compounds or the study of their mode of action.

Percus et al. [65] mentioned that in HIV-1 infected patients, the treatment with combination antiretroviral therapy frequently have the level of HIV-1 RNA detectable in plasma driven below the lower limit of detection of current, 50 copies ml(-1). Patients may continue to exhibit viral loads (VLs) below the assay limit for years, yet on some occasions the VL may be above the limit of detection. Whether these 'blips' in VL are simply assay errors or are indicative of intermittent episodes of increased viral replication is of great clinical concern. By analyzing the occurrence of viral blips in 123 treated HIV-infected patients, they showed that patients do not share a common probability distribution of blip amplitude and thus reject the hypothesis that blips are solely due to assay variation.

In [14] Bortz and Nelson performed a formal sensitivity analysis on a delay differential equation model for the viral dynamics of an in vivo HIV infection during protease inhibitor therapy. They presented results of both a differential analysis as well as a principle component based analysis and provided evidence that suggests the exact times at which specific parameters have the most influence over the solution. They offer insight into the pairwise mathematical relationships between the productively infected T-cell death rate delta, the viral plasma clearance rate $c$, and the time delay $\tau$ between infection and viral production as they relate to the viral dynamics. The results support the claim that the presence of a nonzero delay has a major impact on the model dynamics. Lastly, they comment upon the inadequacies of an alternative principle component based analysis.

A theoretical model was proposed by Hsien and Chen [42] for a community which has the structure of two classes (direct and indirect) of commercial sex workers (CSW), and two classes of sexually active male customers with different levels of sexual ac-

tivity. The direct CSW's work in brothels while the indirect CSW's are based in commercial establishments such as bars, cafes, and massage parlours where sex can be bought on request and conducted elsewhere. Behaviour change and the resulting change of activity class occurs between the two classes of CSW's and two classes of males under the setting of the proliferation of HIV/AIDS epidemic and the subsequent intervention programmes.

In recent years, this phenomenon has been observed in several countries in Asia. Given the lowerlevels of condom use and higher HIV prevalence of the indirect CSW's, ascertaining the impact of this change in the structure of the sex industry on the spread of HIV is the main focus of their paper. They gave the complete analysis of the disease-free model. For the full model, local analysis was performed for the case of preferred mixing without activity class change, as well as the case with activity class change and restricted mixing. The basic reproduction number for the spread of epidemic was derived for each case. Results of biological significance include: (i). the change of behaviour by the CSW's has a more direct effect on the spread of HIV than that of the male customers; (ii). the basic reproduction number is obtained by considering all possible infection cycles of the heterosexual transmission of HIV which indicates the importance of understanding the sexual networking in heterosexual transmission of HIV; (iii). the social dynamics of the sex industries.

In [44] Jafelice et al. paper introduced a model for the evolution of positive HIV population and manifestation of AIDS. The focus was on the nature of the transference rate of HIV to AIDS. Expert knowledge indicates that the transference rate is uncertain and depends strongly on the viral load and the CD4+ level of the infected individuals. Here, they suggest to view the transference rate as a fuzzy set of the viral load and CD4+ level values. In this case the dynamic model results in a fuzzy model that preserves the biological meaning and nature of the transference rate. Its behavior fits the natural history of HIV infection reported in the medical science domain. The paper also includes a comparison between the fuzzy model and

a classic Anderson's model using data reported in the literature.

Gumel et al. [38] investigated a class of finite-difference methods, designed via the non-standard framework of Mickens, for solving *Model-IV* described in previous subsection. They shown that this class of methods can often give numerical results that are asymptotically consistent with those of the corresponding continuous model.

Hewer and Meyer [40] presented a major problem impeding the development of an effective HIV-1 vaccine is the rapid antigenic variability that occurred throughout the viral genome. They indicated that the high number of errors made by the reverse transcriptase (RT) enzyme and the absence of an RT proofreading mechanism during HIV-1 replication leads to new antigenic variants that escape current immunological attack. In turn, accumulation of escape mutants leads to a persistent infection. It has been hypothesized through many means including mathematical modeling that preventing HIV persistence necessitates a vaccine that enhances immunity against a sufficiently large fraction of mutant stains. To this extent they have developed a 4 branched and an 8 branched multiple epitope immunogen (MEI) that in theory represent 6.7107 and 1.81016 envelope V3 loop sequences respectively. Both MEI constructs were recognized by antibodies in sera from AIDS and/or HIV-1 positive patients from South Africa and Puerto Rico. The immunogens also induced immune responses in MF1 mice and New Zealand White rabbits with the octameric MEI proving to be a more effective antigen. This data supports our hypothesis that synthetic peptides designed to represent the variable regions of HIV-1 envelope should induce immunity against a large quantity of mutant strains.

In [46] Jonesa and Perelson explained that when highly active antiretroviral therapy is administered for long periods of time to HIV-1 infected patients, most patients achieve viral loads that are "undetectable" by standard assay (i.e., HIV-1 RNA $< 50$ copies/$ml$). Yet despite exhibiting sustained viral loads below the level of detection, a number of these patients experience unexplained episodes of transient viremia orvi-ral "blips". They proposed here that transient activation of the immune system by

opportunistic infection may explain these episodes of viremia. Indeed, immune activation by opportunistic infection may spur HIV replication, replenish viral reservoirs and contribute to accelerated disease progression.

In order to investigate the effects of intercurrent infection on chronically infected HIV patients under treatment with highly active antiretroviraltherapy, the above two authors extended a simple dynamic model of the effects of vaccination on HIV infection *(Jones, L.E., Perelson, A.S., 2002. Modeling the effects of vaccination on chronically infected HIV-positive patients. JAIDS 31, 369-377)* to include growing pathogens. Then they proposed a more realistic model for immune cell expansion in the presence of pathogen, and included this in a set of competing models that allow low baseline viral loads in the presence of drug treatment. They also mentioned that programmed expansion of immune cells upon exposure to antigen is a feature not previously included in HIV models, and one that is especially important to consider when simulating an immune response to opportunistic infection. Using these models they showed that viral blips with realistic duration and amplitude can be generated by intercurrent infections in HAART treated patients.

Snedecor [74] considered some recent advances in the chemotherapy of HIV infection that have been successful in delaying the progression of disease in many patients and are responsible for the decline in HIV-related deaths in the United States. It is mentioned in this article that there are many patients who fail to maintain suppressed viral loads on treatment. Means to extend the utility of currently available drugs include developing improved ways to assess the therapeutic impact of drug-resistant variants.

A mathematical model to incorporate the presence of resistance mutations with either primary or secondary classifications was created as a means to explore the association between phenotypic resistance and duration of viral response to therapy. The model, which includes phenotypic and genotypic resistance information for each viral mutant, was presented with a simplified five-codon genome. The analysis in

this paper suggests that, in the model, the resistance phenotypes of the strains with an intermediate number of mutations are the primary determinants of both the total duration of viral suppression with a single treatment and the difference between the durations of suppression of the forward and reverse sequential administrations of two treatments. These findings implied that a model including the resistance phenotype and in vivo response of genotypically-resistant viral strains may lead to a priori prediction of successful anti-HIV drug selection for an individual harboring drug-resistant virus.

Hsieh and Wang [43] noticed that the basic reproduction number is obtained for an HIV epidemic model incorporating direct and indirect commercial sex as well as behavior change by the female commercial sex workers (CSWs) and their male customers in response to the proliferation of the disease in the community. Using the work of van den Driessche P., and Watmough J. (Math. Biosci. 180:29-48, 2002), they computed the threshold parameters for the local asymptotic stability of the Disease-Free Equilibrium (DFE), by considering the transfers in and out of the infective classes.



Hsieh and Wang in the above work used numerical examples to describe the uniqueness and global properties of the endemic equilibrium when DFE is unstable and discussed the implications of the results for the design of public health policies such as targeting strategy to target intervention and control measures toward specific high-risk population groups in order to reduce infections. They showed that targeting any one sector of the commercial sex alone for prevention will be difficult to have a decided effect on eradicating the epidemic. However, if the aim of the targeted intervention policy is not eradication of the epidemic but decrease in HIV incidence of a particular high-risk group, then concentrated targeting strategy could be sufficient, if properly implemented. They also demonstrated the usefulness of the theorem of van den Driessche and Watmough in obtaining threshold parameters for complicated infectious diseases models.

In [78] Laera et al. presented previous clinical trials in previous HIV-infected patients involving infusion of T-cells protected by an antiviral gene that failed to show any therapeutic benefit. They mentioned that the value of such a treatment approach is still highly controversial. In this study, they analyzed the anticipated effects of gene-modifiedcells on virus and T-cell kinetics. Because technically only a small fraction of all T-cells in a patient can be manipulated ex vivo, therapeutic success will depend on the accumulation of gene-modified cells after infusion into the patient by in vivo selection. Their simulations predicted that a significant therapeutic benefit is conferred only by antiviral genes that inhibit previous HIV replication before virus integration (class I genes). Genes that inhibit viral protein expression (class II, used in previous clinical trials), require a much higher inhibitory activity than class I genes to promote the regeneration of T-cells and reduce the viral load. They further indicated that in determining the clinical outcome the regenerative capacity of the gene-modified cells and the level of previous HIV replication in the patient are crucial. These results can be important for guiding future strategies in the field of gene therapy for previous HIV infection.



Besides the above mentioned works, the readers may find the articles [15, 21, 34, 39, 51] further relevant to the subject.

Based on the above descriptions and survey, we decided to work on the model that has two HIV subtypes. Such a model is analyzed in Chapter 2 and some numerical methods are developed and analyzed for this model in Chapter 3. Chapter 4 contains the comparative numerical results obtained with various methods presented in Chapter 3. Summery of the thesis and some concluding remarks indicating our future research plans are given in Chapter 5.

# Chapter 2

# Analysis of the model governing the transmission dynamics of two HIV-subtypes



Our aim is to construct some reliable numerical methods for relevant HIV model(s). In order for us to be able to design these numerical methods, it is essential that we look at the qualitative properties of the model(s). To this end, in this chapter we analyse the following model (referred to as *Model IV* in Chapter 1) given by the set of differential equations (1.7)-(1.10) which deals with the "Transmission Dynamics of two HIV subtypes" [37] in a given community.

## 2.1 Disease Free Equilibrium

The Disease Free Equilibrium (DFE) ($X^* \neq 0, V^* \neq 0, Y_1^* = 0, Y_2^* = 0$) corresponding to this model is obtained by solving

$$\Pi(1-\rho) - \mu X^* = 0, \tag{2.1}$$

$$\Pi\rho - \mu V^* = 0 \tag{2.2}$$

which gives

$$(X^*, V^*, Y_1^*, Y_2^*) = \left(\frac{\Pi(1-\rho)}{\mu}, \frac{\Pi\rho}{\mu}, 0, 0\right). \tag{2.3}$$

## 2.2 Stability of the Disease Free Equilibrium

The Jacobian corresponding to (1.7)-(1.10) is given by

$$J(X,V,Y_1,Y_2) = \begin{bmatrix} -\mu - \frac{\beta_1 cY_1}{N} - \frac{\beta_2 cY_2}{N} & 0 & -\frac{\beta_1 cX}{N} & -\frac{\beta_2 cX}{N} \\ 0 & -\mu - \frac{(1-\xi_1)\beta_1 cY_1}{N} - \frac{(1-\xi_2)\beta_2 cY_2}{N} & -\frac{(1-\xi_1)\beta_1 cV}{N} & -\frac{(1-\xi_2)\beta_2 cV}{N} \\ \frac{\beta_1 cY_1}{N} & \frac{(1-\xi_1)\beta_1 cY_1}{N} & J_{33} & 0 \\ \frac{\beta_2 cY_2}{N} & \frac{(1-\xi_2)\beta_2 cY_2}{N} & 0 & J_{44} \end{bmatrix} \tag{2.4}$$



where

$$J_{33} = \frac{\beta_1 cX}{N} + \frac{(1-\xi_1)\beta_1 cV}{N} - (\mu+\gamma_1+\tau) \text{ and } J_{44} = \frac{\beta_2 cX}{N} + \frac{(1-\xi_2)\beta_2 cV}{N} - (\mu+\gamma_2+\tau).$$

Evaluating the above Jacobian at the DFE, we obtain

$$J_{DFE} \equiv J(X^*, V^*, Y_1^*, Y_2^*) = \begin{bmatrix} -\mu & 0 & -\frac{\beta_1 cX^*}{N} & -\frac{\beta_2 cX^*}{N} \\ 0 & -\mu & -\frac{(1-\xi_1)\beta_1 cV^*}{N} & -\frac{(1-\xi_2)\beta_2 cV^*}{N} \\ 0 & 0 & J_{33}^* & 0 \\ 0 & 0 & 0 & J_{44}^* \end{bmatrix}, \tag{2.5}$$

where

$$J_{33}^* = \frac{\beta_1 cX^*}{N} + \frac{(1-\xi_1)\beta_1 cV^*}{N} - (\mu+\gamma_1+\tau) \text{ and } J_{44}^* = \frac{\beta_2 cX^*}{N} + \frac{(1-\xi_2)\beta_2 cV^*}{N} - (\mu+\gamma_2+\tau).$$

Using (2.3) along with (2.5) and the fact that the matrix in (2.5) is triangular, the eigenvalues (denoted by $\lambda_i,\ i = 1,\ 2,\ 3, 4$) are precisely the diagonal entries. Thus

$$\left.\begin{aligned} \lambda_1 &= -\mu, \\ \lambda_2 &= -\mu, \\ \lambda_3 &= \beta_1 c(1-\rho\xi_1) - (\mu+\gamma_1+\tau), \\ \lambda_4 &= \beta_2 c(1-\rho\xi_2) - (\mu+\gamma_2+\tau). \end{aligned}\right\} \tag{2.6}$$

(Note in the above that as $t \to \infty$, $dN/dt \to 0$ which means that $N \to \Pi/\mu$.)

Since $\mu$ is positive, it is evident now from the above equation that both $\lambda_1$ and $\lambda_2$ are negative whereas

$$\lambda_3 < 0 \ \text{ if } \ \beta_1 c(1-\rho\xi_1) < (\mu+\gamma_1+\tau), \ \text{ i.e. } \ \frac{\beta_1 c(1-\rho\xi_1)}{(\mu+\gamma_1+\tau)} < 1.$$

Similarly,

$$\frac{\beta_1 c(1-\rho\xi_1)}{(\mu+\gamma_1+\tau)} \text{ and } \frac{\beta_2 c(1-\rho\xi_2)}{(\mu+\gamma_2+\tau)}$$

are respectively, denoted by, $R_\rho^{(1)}$ and $R_\rho^{(2)}$, and are called the reproduction numbers.

We therefore have the following result about the local asymptotic stability of the disease-free equilibrium.

**Lemma 2.1.** *The disease-free equilibrium of the HIV model is locally asymptotically stable if* $R_0 = \max\left\{R_\rho^{(1)}, R_\rho^{(2)}\right\} < 1$.

**Remark 2.2.** This lemma shows that a small flow of HIV infected individuals into the community would not result in a major epidemic provided $R_0 < 1$. Furthermore, We found that the disease-free equilibrium of HIV model under consideration is locally asymptotically stable if the reproduction number for both of the subtypes is less than unity. This means that a small influx of HIV-infected individuals into the community would not result in a major epidemic provided that the maximum of the two reproduction numbers is less than unity.

- When both reproduction numbers exceeds unity, the subtype with the higher reproduction number eventually overcomes the other and becomes the only existing HIV subtype at steady state.

- The two subtypes co-exist if the two reproduction numbers are equal and greater than unity.

This information provided in the above remark will be useful in designing suitable numerical methods.

We have shown that HIV will persist (or be established in the community) if and only if at least one of the two eigenvalues of the associated Jacobian matrix has a positive real part (so that the maximum of the two reproduction number will be greater than unity). For a general discussion on the stability analysis, the readers are referred to Appendix C.



**Remark 2.3.** Adding the four equations (1.7-1.10), we obtain

$$\frac{dN}{dt} = \Pi - \mu(X+V) - (\mu+\gamma_1+\tau)Y_1 - (\mu+\gamma_2+\tau)Y_2.$$

Therefore, if there are no sub-types, then the total population will be $N = X + V$ meaning that

$$N \to \Pi - \mu(X+V) \text{ as } t \to \infty.$$

Hence the following feasible region:

$$\mathcal{D} = \left\{(X, V, Y_1, Y_2) \in \mathbb{R}^4_+ : X + V + Y_1 + Y_2 \leq \Pi/\mu\right\},$$

is positively invariant. It is therefore sufficient to consider the solution of (1.7-1.10) in $\mathcal{D}$.

**Theorem 2.4.** *The disease-free equilibrium of the HIV model is globally asymptotically stable if* $R_0 = \max\left\{R_\rho^{(1)}, R_\rho^{(2)}\right\} < 1$.

**Proof.** We consider the Lyapunov functions $V_1 = Y_1$ and $V_2 = Y_2$ which have the following Lyapunov derivatives

$$\begin{aligned}
\dot{V}_1 &= \left[\frac{\beta_1 cX}{N} + \frac{(1-\xi_1)\beta_1 cV}{N} - (\mu+\gamma_1+\tau)\right] Y_1 \\
&= \left[\frac{\beta_1 c}{N}\frac{(1-\rho)\Pi}{\mu} + \frac{(1-\xi_1)\beta_1 c}{N} - (\mu+\gamma_1+\tau)\right] Y_1 \\
&= (\mu+\gamma_1+\tau)\left(R_\rho^{(1)} - 1\right) Y_1 \\
&\leq 0 \text{ for } R_\rho^{(1)} \leq 1. \qquad (2.7)
\end{aligned}$$

Similarly,

$$\dot{V}_2 \leq 0 \text{ for } R_\rho^{(2)} \leq 1. \qquad (2.8)$$

Therefore, using the Lyapunov stability theorem (see Appendix C), the DFE is globally asymptotically stable under the condition $R_0 = \max\left\{R_\rho^{(1)}, R_\rho^{(2)}\right\} < 1$.



## 2.3 Other Equilibria

The procedure for finding the other equilibria, viz.,

- subtype-1 only equilibrium
- subtype-2 only equilibrium
- co-existing equilibrium

is similar to the one we described above and the Jacobian matrix given in (2.4) can be evaluated on these equilibria. The resulting eigenvalues can then provide relevent constraints. However, the closed form solutions (from the equations providing these three equilibria) are not easily obtainable due to the presense of nonlinearities and the other sophesticated tools to do so are beyond the scope of this thesis. However, the interested readers may wish to find some clues via the theory of Gröbner basis [20].

# Chapter 3

# Numerical Methods for *Model-IV*

In this chapter we present some numerical methods for *Model-IV* described by the equations (1.7)-(1.10) in Chapter 1. We then give analysis for some of these methods. The comparative numerical results for all these methods will be provided in the next chapter.



It is known that the standard methods do not perform well due to unstable solution profiles for the type of problems we are dealing with and the usual option initially is left on choosing an implicit method which can stablize the procedure. Taking this fact into account, there is no point in considering any explicit finite difference method. We rather consider an Implicit Finite Difference Method (IFDM). We do fixed-point analysis of this method and found the conditions for stability. Later in next chapter, we see through numerical illustrations that this method does not preserve positivity property (a very important and essential property that is expected for many models in population biology). To overcome this drawback, a novel numerical method (initially presented in Gumel et al. [38]) referred to as non-standard finite difference method (NSFDM) is discussed in details. The aspects associated with order of convergence are also addressed. It is shown that this in transient dynamics, the NSFDM does not have extraneous solutions unlike IFDM and therefore it is dynamically consistent in the sense of [59, 30].

To start with, we fix some notations. The time interval $t \geq 0$ is discretized in a standard way by means of points $t_n = n\ell$, where $n = 0, 1, 2, ...$, and $\ell$ denote the time step-size. The solution of this model (i.e., (1.7)-(1.10)) at $t_n$ is denoted by $X(t_n)$, $V(t_n)$, $Y_1(t_n)$, $Y_2(t_n)$.

## 3.1 Implicit Finite Difference Method

Using the forward difference approximations for the first derivative terms, we obtain the following Implicit Finite Difference Method (IFDM) for each of the equations (1.7)-(1.10)

$$\frac{X^{n+1} - X^n}{\ell} = \Pi(1-\rho) - \mu X^{n+1} - \frac{\beta_1 c Y_1^n X^{n+1} + \beta_2 c Y_2^n X^{n+1}}{X^n + V^n + Y_1^n + Y_2^n}, \tag{3.1}$$

$$\frac{V^{n+1} - V^n}{\ell} = \Pi\rho - \mu V^{n+1} - \frac{(1-\xi_1)\beta_1 c Y_1^n V^{n+1} + (1-\xi_2)\beta_2 c Y_2^n V^{n+1}}{X^{n+1} + V^n + Y_1^n + Y_2^n}, \tag{3.2}$$

$$\frac{Y_1^{n+1} - Y_1^n}{\ell} = \frac{\beta_1 c Y_1^{n+1} X^{n+1} + (1-\xi_1)\beta_1 c Y_1^{n+1} V^{n+1}}{X^{n+1} + V^{n+1} + Y_1^n + Y_2^n} - (\mu + \gamma_1 + \tau) Y_1^{n+1}, \tag{3.3}$$

$$\frac{Y_2^{n+1} - Y_2^n}{\ell} = \frac{\beta_2 c Y_2^{n+1} X^{n+1} + (1-\xi_2)\beta_2 c Y_2^{n+1} V^{n+1}}{X^{n+1} + V^{n+1} + Y_1^{n+1} + Y_2^n} - (\mu + \gamma_2 + \tau) Y_2^{n+1}. \tag{3.4}$$

The method consisting of (3.1)-(3.4) is referred to as the Implicit Finite Difference Method (IFDM). The method is first order accurate (as is evident from the numerical results provided in the next Chapter).

**Remark 3.1.** The IFDM is implicit by construction, but the terms can be re-arranged in order to have explicit expressions (fortunately in this case) so as to solve it via an iterative procedure, i.e.,

$$X^{n+1} = \frac{X^n + \Pi\ell(1-\rho)}{1 + \ell\left[\mu + \frac{c\left(\beta_1 Y_1^n + \beta_2 Y_2^n\right)}{X^n + V^n + Y_1^n + Y_2^n}\right]}, \tag{3.5}$$

$$V^{n+1} = \frac{V^n + \Pi\ell\rho}{1+\ell\left\{\mu + \frac{c\left[(1-\xi_1)\beta_1 Y_1^n + (1-\xi_2)\beta_2 Y_2^n\right]}{X^{n+1}+V^n+Y_1^n+Y_2^n}\right\}}, \tag{3.6}$$

$$Y_1^{n+1} = \frac{Y_1^n}{1+\ell\left\{\mu+\gamma_1+\tau - \frac{\beta_1 c[X^{n+1}+(1-\xi_1)V^{n+1}]}{X^{n+1}+V^{n+1}+Y_1^n+Y_2^n}\right\}}, \tag{3.7}$$

$$Y_2^{n+1} = \frac{Y_2^n}{1+\ell\left\{\mu+\gamma_2+\tau - \frac{\beta_2 c[X^{n+1}+(1-\xi_2)V^{n+1}]}{X^{n+1}+V^{n+1}+Y_1^{n+1}+Y_2^n}\right\}}. \tag{3.8}$$

### 3.1.1 Analysis of the Implicit Finite Difference Method

Denoting the right hand sides of equations (3.5)-(3.8) by $f_i(X^n, V^n, Y_1^n, Y_2^n)$, $(i = 1, 2, 3, 4)$, we have the relations

$$X^{n+1} = f_1(X^n, V^n, Y_1^n, Y_2^n), \tag{3.9}$$

$$V^{n+1} = f_2(X^n, V^n, Y_1^n, Y_2^n), \tag{3.10}$$

$$Y_1^{n+1} = f_3(X^n, V^n, Y_1^n, Y_2^n), \tag{3.11}$$

$$Y_2^{n+1} = f_4(X^n, V^n, Y_1^n, Y_2^n). \tag{3.12}$$

Furthermore, we denote the equilibrium solution profile by $(X^*, V^*, Y_1^*, Y_2^*)$.

#### 3.1.1.1 The Disease Free Equilibrium of Implicit Finite Difference Method

The DFE is obtained by solving the fixed-point problem as follows.

Substituting $Y_1^* = 0$ and $Y_2^* = 0$ in the equations obtained from (3.9)-(3.12) after substituting $Z^*$ both for $Z^{n+1}$ and $Z^n$ (where $Z$ is $X$, $V$, $Y_1$ and $Y_2$). Thus we obtain the DFE as

$$(X^*,\, V^*,\, Y_1^*,\, Y_2^*) = \left(\frac{\Pi(1-\rho)}{\mu},\, \frac{\Pi\rho}{\mu},\, 0,\, 0\right). \tag{3.13}$$

#### 3.1.1.2 Subtype-1, Subtype-2 and Co-existing Equilibria for the Implicit Finite Difference Method

The fixed points of subtype-1 only equilibrium, subtype-2 only equilibrium and the coexisting equilibrium are more complicated than that of the disease free equilibrium. This is because all three cases involves nonlinear equations. One option that one could consider here is to focus on the nonlinear root finding problems.

**Remark 3.2.** When one deals with the numerical methods, (s)he, at first, checks whether the "fixed-points" of the numerical methods coincide with the "critical points" of the continuous problem. The ultimate aim that one has is to check whether the method provides converging solution profiles and if such a convergence takes place then under what conditions? The role of this fixed-points is merely to provide the critical step-sizes that one requires to ensure the stability of the scheme. Unlike the case of DFE, in this case therefore, not much can be learnt analytically about these fixed-points and therefore the convergence of the method can be judged through "Double Mesh Principle".



#### 3.1.1.3 Convergence of the Implicit Finite Difference Method

Consider equation (3.1).

The Taylor series expansion of $X^{n+1}$ about $t = t_n$ gives,

$$X^{n+1} = X^n + \ell \dot{X}^n + \frac{\ell^2}{2!}\ddot{X}^n + ... \tag{3.14}$$

Also, from (1.7), we obtain at $t_n$

$$\dot{X}^n = \Pi(1-\rho) - \mu X^n - \frac{1}{N}\beta_1 c Y_1^n X^n - \frac{1}{N}\beta_2 c Y_2^n X^n. \tag{3.15}$$

Using (3.14) and (3.15) into (3.1), we get the truncation error of the method (3.1) to approximate $X$ as

$$\tau(X) = \left(\frac{\ddot{X}}{2} + \left(\mu + \frac{\beta_1 c Y_1 + \beta_2 c Y_2}{N}\right)\dot{X}\right)\ell^2 + O(\ell^3). \tag{3.16}$$

Hence the method (3.1) is of order one.

A similar approach applied to the methods (3.2), (3.3) and (3.4) (the methods for $V$, $Y_1$, $Y_2$), respectively, yields

$$\begin{aligned}\tau(V) &= \left[\frac{\ddot{V}}{2} + \mu\dot{V} - \left(\frac{c\left[(1-\xi_1)\beta_1 Y_1 + (1-\xi_2)\beta_2 Y_2\right]\dot{X}}{N}\right)V\right]\ell^2 \\ &\quad + O(\ell^3),\end{aligned} \tag{3.17}$$

$$\begin{aligned}\tau(Y_1) &= \left[\frac{\ddot{Y}_1}{2} + \left((\mu+\gamma_1+\tau) - \frac{\{\beta_1 c(X+(1-\xi_1))V\}}{N}\right)\dot{Y}_1\right. \\ &\quad \left. + \left(\{(X+(1-\xi_1)V)\}\left(\dot{X}+\dot{V}\right) - \{\dot{X}+(1-\xi_1)\dot{V}\}\right)\frac{\beta_1 c}{N}Y_1\right]\ell^2 \\ &\quad + O(\ell^3)\end{aligned} \tag{3.18}$$



and

$$\begin{aligned}\tau(Y_2) &= \left[\frac{\ddot{Y}_2}{2} + \left((\mu+\gamma_2+\tau) - \frac{\{\beta_2 c(X+(1-\xi_2))V\}}{N}\right)\dot{Y}_2\right. \\ &\quad \left. + \left(\{(X+(1-\xi_2)V)\}\left(\dot{X}+\dot{V}+\dot{Y}_1\right) - \{\dot{X}+(1-\xi_2)\dot{V}\}\right)\frac{\beta_2 c}{N}Y_2\right]\ell^2 \\ &\quad + O(\ell^3)\end{aligned} \tag{3.19}$$

which means that these are also first order accurate.

As can be seen from the convergence estimates (3.16)-(3.19), the IFDM is only first-order accurate and that too under severe restrictions on step-size (such a restriction can be found by a more detailed analysis). This means that one requires a large number of iterations to generate the accurate solution profile. Hence, it is a good idea to consider higher order methods. To this end, we consider below the fourth-order Runge-Kutta Method.

## 3.2 Runge-Kutta Method of Order Four

The Runge-Kutta method of order four (RK4) for the system of equations (1.7)-(1.10) can be described as follows:

Given the initial conditions

$$X(t_0) = X^0,\ V(t_0) = V^0,\ Y_1(t_0) = Y_1^0,\ \text{ and }\ Y_2(t_0) = Y_2^0,$$

we assume that the values $X^{1,j},\ V^{1,j},\ Y_1^{1,j},\ Y_2^{1,j}$ have been computed, where $j = 0(1)n$. We then obtain $X^{1,j+1},\ V^{1,j+1},\ Y_1^{1,j+1},\ Y_2^{1,j+1}$ in the following manner: For each $i = 1(1)4$, we calculate

$$k_{1,i} = \ell f_i\left(t_j,\ X^{1,j},\ V^{1,j},\ Y_1^{1,j},\ Y_2^{1,j}\right), \tag{3.20}$$

$$k_{2,i} = \ell f_i\left(t_j + \frac{\ell}{2},\ X^{1,j} + \frac{k_{1,1}}{2},\ V^{1,j} + \frac{k_{1,2}}{2},\ Y_1^{1,j} + \frac{k_{1,3}}{2},\ Y_2^{1,j} + \frac{k_{1,4}}{2}\right), \tag{3.21}$$

$$k_{3,i} = \ell f_i\left(t_j + \frac{\ell}{2},\ X^{1,j} + \frac{k_{2,1}}{2},\ V^{1,j} + \frac{k_{2,2}}{2},\ Y_1^{1,j} + \frac{k_{2,3}}{2},\ Y_2^{1,j} + \frac{k_{2,4}}{2}\right), \tag{3.22}$$

$$k_{4,i} = \ell f_i\left(t_j + \ell,\ X^{1,j} + k_{3,1},\ V^{1,j} + k_{3,2},\ Y_1^{1,j} + k_{3,3},\ Y_2^{1,j} + k_{3,4}\right), \tag{3.23}$$

where $f_1 = X$, $f_2 = V$, $f_3 = Y_1$ and $f_4 = Y_2$ in the above.

Then we compute

$$w_{i,j+1} = w_{i,j} + \frac{1}{6}\left(k_{1,i} + 2k_{2,i} + 2k_{3,i} + k_{4,i}\right), \tag{3.24}$$

where $w_{i,j}$ stands for $X^j$, $V^j$, $Y_1^j$ and $Y_2^j$ when $i$ is respectively, 1, 2, 3 and 4.

Though tedius, but one can check that like the IFDM, the above method (RK4) is also not free of step-size restrictions. Since in the population biology, one might require the information at various time levels, one need to have flexibilities in choosing the step-sizes. To this end, we consider below another class of finite difference methods, termed as Non standard Finite Difference Method (NSFDM). Even though this NSFDM is only first order accurate, it is free of step-size restrictions. Moreover, unlike IFDM and RK4, this method always provides positive solutions and hence it is dynamically consistent.

## 3.3 Non-Standard Finite Difference Method

One can see that $Y_1^{n+1}$ and $Y_2^{n+1}$ (respectively, in (3.7) and (3.8) has negative denominators, because of the approximation of the terms in equations (1.9) and (1.10) which might cause problems as they will contribute towards negative profile of the solution. This has occured due to the following:

The terms

$$\frac{\beta_1 cXY_1}{N}$$

and

$$\frac{(1-\xi_1)\beta_1 cVY_1}{N}$$

in (1.9) are approximated by

$$\frac{\beta_1 cX^{n+1}Y_1^{n+1}}{X^{n+1}+V^{n+1}+Y_1^n+Y_2^n} \tag{3.25}$$

and

$$\frac{(1-\xi_1)\beta_1 cV^{n+1}Y_1^{n+1}}{X^{n+1}+V^{n+1}+Y_1^n+Y_2^n}. \tag{3.26}$$

respectively. A similar approach was used for the terms

$$\frac{\beta_2 cXY_2}{N}$$

and

$$\frac{(1-\xi_2)\beta_2 cVY_2}{N}$$

in (1.10).

To overcome this drawback, we use the non-local approximation for those terms as follows.

We construct the two methods for $Y_1$ and $Y_2$, which must preserve the positivity property of the model. The variables $Y_1$ and $Y_2$ in the first two terms of the equations

$\frac{dY_1}{dt}$ and $\frac{dY_2}{dt}$ of the HIV *Model IV*, are respectively, approximated using their non-local representations given below

$$Y_1 \to 2Y_1^n - Y_1^{n+1} \text{ and } Y_2 \to 2Y_2^n - Y_2^{n+1}. \tag{3.27}$$

(It should be noted that the methods of $X$ and $V$ do not have negative solutions for $0 < \xi_1,\ \xi_2 < 1$ in (3.1)-(3.2), we need only to ensure that the methods $Y_1$ and $Y_2$ preserve positivity.)

Thus we have the following methods for $Y_1$ and $Y_2$

$$\begin{aligned} \frac{Y_1^{n+1} - Y_1^n}{\ell} &= \frac{\beta_1 c X^{n+1}(2Y_1^n - Y_1^{n+1}) + (1-\xi_1)\beta_1 c V^{n+1}(2Y_1^n - Y_1^{n+1})}{X^{n+1} + V^{n+1} + Y_1^n + Y_2^n} \\ &- (\mu + \gamma_1 + \tau)\, Y_1^{n+1} \end{aligned} \tag{3.28}$$

and

$$\begin{aligned} \frac{Y_2^{n+1} - Y_2^n}{\ell} &= \frac{\beta_2 c X^{n+1}(2Y_2^n - Y_2^{n+1}) + (1-\xi_2)\beta_2 c V^{n+1}(2Y_2^n - Y_2^{n+1})}{X^{n+1} + V^{n+1} + Y_1^{n+1} + Y_2^n} \\ &- (\mu + \gamma_2 + \tau)\, Y_2^{n+1}. \end{aligned} \tag{3.29}$$



Rearranging $Y_1^{n+1}$ and $Y_2^{n+1}$, the non-standard method, referred to as NSFDM, for solving the HIV-model consists of the equations:

$$X^{n+1} = \frac{X^n + \Pi\ell(1-\rho)}{1 + \ell\left[\mu + \frac{c\left(\beta_1 Y_1^n + \beta_2 Y_2^n\right)}{X^n + V^n + Y_1^n + Y_2^n}\right]}, \tag{3.30}$$

$$V^{n+1} = \frac{V^n + \Pi\ell\rho}{1 + \ell\left\{\mu + \frac{c\left((1-\xi_1)\beta_1 Y_1^n + (1-\xi_2)\beta_2 Y_2^n\right)}{X^{n+1} + V^n + Y_1^n + Y_2^n}\right\}}, \tag{3.31}$$

$$Y_1^{n+1} = \frac{\left\{1 + \frac{2\ell\beta_1 c\left[X^{n+1} + (1-\xi_1)V^{n+1}\right]}{X^{n+1} + V^{n+1} + Y_1^n + Y_2^n}\right\} Y_1^n}{1 + \ell\left\{\frac{\beta_1 c[X^{n+1} + (1-\xi_1)V^{n+1}]}{X^{n+1} + V^{n+1} + Y_1^n + Y_2^n} + \mu + \gamma_1 + \tau\right\}}, \tag{3.32}$$

$$Y_2^{n+1} = \frac{\left\{1 + \frac{2\ell\beta_2 c\left[X^{n+1} + (1-\xi_2)V^{n+1}\right]}{X^{n+1} + V^{n+1} + Y_1^{n+1} + Y_2^n}\right\} Y_2^n}{1 + \ell\left\{\frac{\beta_2 c[X^{n+1} + (1-\xi_2)V^{n+1}]}{X^{n+1} + V^{n+1} + Y_1^{n+1} + Y_2^n} + \mu + \gamma_2 + \tau\right\}}. \tag{3.33}$$

**Remark 3.3.** According to Mickens terminology, these methods are 'non-standard' because non-local discretization have been used. The specific rule used above is one of the few modelling rules set by Mickens [59] and subsequently addressed in several articles as is mentioned in [64]. For the sake of completeness, we provide these rules in Appendix B.

### 3.3.1 Analysis of the Non-Standard Finite Difference Method

#### 3.3.1.1 The Disease Free Equilibrium of the Non-Standard Finite Difference Method

To find the disease free equilibrium for NSFDM, is the same process as to find disease free equilibrium for IFDM due to the fact that the equations for $X^{n+1}$ and $V^{n+1}$ are the same for both methods.



#### 3.3.1.2 Subtype-1, Subtype-2 and Co-existing Equilibria for the Non-Standard Finite Difference Method

The similar discussion as in the sub-section 3.1.1.2 explains the complexity issues in calculating these fixed points. Furthermore, generally the aim is to look for the ways to eradicate/control the disease and for that, the DFE is mostly sufficient.

#### 3.3.1.3 Convergence of the Non-Standard Finite Difference Method

Like the IFDM, the NSFDM is also first order accurate. The procedure for studying the convergence is analogous to that of the IFDM.

The three methods (IFDM, NSFDM and RK4) described in this chapter are simulated and compared using the same set of parameter values and initial condition. The comparative results are provided in next chapter.

# Chapter 4

# Comparative Numerical Results

In this chapter we will provide extensive numerical results obtained via various methods developed for *Model IV*.

The parameters used in the simulations are $\mu = \frac{1}{32}$, $\Pi = 2000$, $c = 4$, $\gamma_1 = 0.1$, $\gamma_2 = 0.1$, $\xi_1 = 0.3$, $\xi_2 = 0.4$, $\rho = 0.5$, $\tau = 0.4$, $X(0) = 8000$, $V(0) = 800$, $Y_1(0) = 200$, and $Y_2(0) = 300$ (see [38]).



The two parameters $\beta_1$ and $\beta_2$ are chosen in such a way that they give different reproduction numbers mentioned as per below

(i) $\beta_1 = 0.03,\ \beta_2 = 0.035 \Rightarrow R_\rho^{(1)} = 0.1920,\ R_\rho^{(2)} = 0.21082$. Expected output: both Subtypes should be eliminated.

(ii) $\beta_1 = 0.03,\ \beta_2 = 0.35 \Rightarrow R_\rho^{(1)} = 0.1920,\ R_\rho^{(2)} = 2.1082$. Expected output: Subtype-2 should persist.

(iii) $\beta_1 = 0.3,\ \beta_2 = 0.035 \Rightarrow R_\rho^{(1)} = 1.920,\ R_\rho^{(2)} = 0.21082$. Expected output: Subtype-1 should persist.

(iv) $\beta_1 = 0.3,\ \beta_2 = 0.35 \Rightarrow R_\rho^{(1)} = 1.920,\ R_\rho^{(2)} = 2.1082$. Expected output: Subtype-2 should invade Subtype-1 meaning that Subtype-2 should persist.

(v) $\beta_1 = 0.35,\ \beta_2 = 0.3 \Rightarrow R_\rho^{(1)} = 2.240,\ R_\rho^{(2)} = 1.8071$. Expected output: Subtype-1 should invade Subtype-2 meaning that Subtype-1 should persist.

The above theoretical observation is confirmed with the two numerical methods (IFDM and NSFDM) and the results obtained by both of them are similar. (In the table below, note that $X^*$, $V^*$, $Y_1^*$, $Y_2^*$ denote the equilibrium solutions of different solution profiles).

Table 4.1: Effect of reproduction numbers, using IFDM/NSFDM/RK-4, $\ell = 0.001$

| $R_\rho^{(1)}$ | $R_\rho^{(2)}$ | $X^*$ | $V^*$ | $Y_1^*$ | $Y_2^*$ |
|---|---|---|---|---|---|
| 0.1920 | 0.21082 | 32000 | 32000 | 0 | 0 |
| 0.1920 | 2.1082 | 1379 | 2233 | 0 | 3552 |
| 1.9200 | 0.21082 | 1702 | 2378 | 3525 | 0 |
| 1.920 | 2.1082 | 1379 | 2233 | 0 | 3552 |
| 2.240 | 1.8071 | 1270 | 1785 | 3585 | 0 |



The letters $E$ and $C$ with $EX$, $EV$, $EY_1$, $EY_2$ and $RX$, $RV$, $RY_1$, $RY_2$ in the table captions, indicate, respectively, "Error" and "Rate of Convergence" for the particular compartment. (It should be noted that the errors and the rates of convergence are obtained by using the well-known double mesh principle [28] as the exact solution is not available for this model.)

We expect the error to be less for the cases where the particular subtype is expected to be eliminated.

For figures, the parameters used in the simulations are $\mu = \frac{1}{32}$, $\Pi = 2000$, $c = 4$, $\gamma_1 = 0.1$, $\gamma_2 = 0.1$, $\xi_1 = 0.3$, $\xi_2 = 0.4$, $\rho = 0.5$, $\tau = 0.4$, $X(0) = 8000$, $V(0) = 800$, $Y_1(0) = 200$, and $Y_2(0) = 300$ as above and $\beta_1 = 0.3$, $\beta_2 = 0.35$.

Table 4.2: Maximum Errors via IFDM for $\beta_1 = 0.03$, $\beta_2 = 0.035$

| $\ell$ | $EX$ | $EV$ | $EY_1$ | $EY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 4.11e+00 | 4.63e+00 | 3.75e-01 | 5.40e-01 |
| 2.50e-02 | 2.05e+00 | 2.32e+00 | 1.89e-01 | 2.72e-01 |
| 1.25e-02 | 1.03e+00 | 1.16e+00 | 9.46e-02 | 1.36e-01 |
| 6.25e-03 | 5.14e-01 | 5.79e-01 | 4.74e-02 | 6.82e-02 |
| 3.13e-03 | 2.57e-01 | 2.90e-01 | 2.37e-02 | 3.41e-02 |
| 1.56e-03 | 1.28e-01 | 1.45e-01 | 1.19e-02 | 1.71e-02 |
| 7.81e-04 | 6.42e-02 | 7.24e-02 | 5.93e-03 | 8.54e-03 |
| 3.91e-04 | 3.21e-02 | 3.62e-02 | 2.97e-03 | 4.27e-03 |

Table 4.3: Maximum Errors via NSFDM for $\beta_1 = 0.03$, $\beta_2 = 0.035$

| $\ell$ | $EX$ | $EV$ | $EY_1$ | $EY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 4.46e+00 | 4.71e+00 | 7.69e-01 | 1.22e+00 |
| 2.50e-02 | 2.23e+00 | 2.36e+00 | 3.88e-01 | 6.14e-01 |
| 1.25e-02 | 1.11e+00 | 1.18e+00 | 1.95e-01 | 3.09e-01 |
| 6.25e-03 | 5.57e-01 | 5.89e-01 | 9.78e-02 | 1.55e-01 |
| 3.13e-03 | 2.78e-01 | 2.94e-01 | 4.89e-02 | 7.75e-02 |
| 1.56e-03 | 1.39e-01 | 1.47e-01 | 2.45e-02 | 3.88e-02 |
| 7.81e-04 | 6.96e-02 | 7.36e-02 | 1.22e-02 | 1.94e-02 |
| 3.91e-04 | 3.48e-02 | 3.68e-02 | 6.12e-03 | 9.69e-03 |



Table 4.4: Maximum Errors via RK4 for $\beta_1 = 0.03$, $\beta_2 = 0.035$

| $\ell$ | $EX$ | $EV$ | $EY_1$ | $EY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 1.96e-01 | 3.35e-02 | 3.32e-02 | 5.90e-02 |
| 2.50e-02 | 9.78e-02 | 1.67e-02 | 1.65e-02 | 2.94e-02 |
| 1.25e-02 | 4.89e-02 | 8.36e-03 | 8.26e-03 | 1.47e-02 |
| 6.25e-03 | 2.44e-02 | 4.18e-03 | 4.13e-03 | 7.34e-03 |
| 3.13e-03 | 1.22e-02 | 2.09e-03 | 2.06e-03 | 3.67e-03 |
| 1.56e-03 | 6.11e-03 | 1.04e-03 | 1.03e-03 | 1.83e-03 |
| 7.81e-04 | 3.06e-03 | 5.22e-04 | 5.16e-04 | 9.17e-04 |
| 3.91e-04 | 1.53e-03 | 2.61e-04 | 2.58e-04 | 4.59e-04 |

Table 4.5: Maximum Errors via IFDM for $\beta_1 = 0.03$, $\beta_2 = 0.35$

| $\ell$ | $EX$ | $EV$ | $EY_1$ | $EY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 1.47e+01 | 1.68e+01 | 3.82e-01 | 5.04e+01 |
| 2.50e-02 | 7.20e+00 | 8.37e+00 | 1.92e-01 | 2.49e+01 |
| 1.25e-02 | 3.56e+00 | 4.18e+00 | 9.65e-02 | 1.24e+01 |
| 6.25e-03 | 1.77e+00 | 2.08e+00 | 4.84e-02 | 6.16e+00 |
| 3.13e-03 | 8.84e-01 | 1.04e+00 | 2.42e-02 | 3.08e+00 |
| 1.56e-03 | 4.41e-01 | 5.21e-01 | 1.21e-02 | 1.54e+00 |
| 7.81e-04 | 2.20e-01 | 2.60e-01 | 6.05e-03 | 7.68e-01 |
| 3.91e-04 | 1.10e-01 | 1.30e-01 | 3.03e-03 | 3.84e-01 |

Table 4.6: Maximum Errors via NSFDM for $\beta_1 = 0.03$, $\beta_2 = 0.35$

| $\ell$ | $EX$ | $EV$ | $EY_1$ | $EY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 3.08e+02 | 1.39e+02 | 8.23e-01 | 2.37e+02 |
| 2.50e-02 | 1.57e+02 | 6.90e+01 | 4.17e-01 | 1.22e+02 |
| 1.25e-02 | 7.92e+01 | 3.43e+01 | 2.10e-01 | 6.19e+01 |
| 6.25e-03 | 3.98e+01 | 1.71e+01 | 1.06e-01 | 3.12e+01 |
| 3.13e-03 | 1.99e+01 | 8.55e+00 | 5.29e-02 | 1.56e+01 |
| 1.56e-03 | 9.98e+00 | 4.27e+00 | 2.65e-02 | 7.83e+00 |
| 7.81e-04 | 4.99e+00 | 2.14e+00 | 1.32e-02 | 3.92e+00 |
| 3.91e-04 | 2.50e+00 | 1.07e+00 | 6.62e-03 | 1.96e+00 |

Table 4.7: Maximum Errors via RK4 for $\beta_1 = 0.03$, $\beta_2 = 0.35$

| $\ell$ | $EX$ | $EV$ | $EY_1$ | $EY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 1.41e+01 | 4.71e+00 | 2.61e-02 | 8.94e+00 |
| 2.50e-02 | 7.07e+00 | 2.35e+00 | 1.30e-02 | 4.46e+00 |
| 1.25e-02 | 3.53e+00 | 1.18e+00 | 6.49e-03 | 2.23e+00 |
| 6.25e-03 | 1.77e+00 | 5.87e-01 | 3.24e-03 | 1.11e+00 |
| 3.13e-03 | 8.83e-01 | 2.94e-01 | 1.62e-03 | 5.57e-01 |
| 1.56e-03 | 4.41e-01 | 1.47e-01 | 8.11e-04 | 2.78e-01 |
| 7.81e-04 | 2.21e-01 | 7.34e-02 | 4.05e-04 | 1.39e-01 |
| 3.91e-04 | 1.10e-01 | 3.67e-02 | 2.03e-04 | 6.96e-02 |

Table 4.8: Maximum Errors via IFDM for $\beta_1 = 0.3$, $\beta_2 = 0.035$

| $\ell$ | $EX$ | $EV$ | $EY_1$ | $EY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 2.17e+01 | 2.04e+01 | 4.30e+01 | 5.29e-01 |
| 2.50e-02 | 1.08e+01 | 1.02e+01 | 2.13e+01 | 2.67e-01 |
| 1.25e-02 | 5.36e+00 | 5.07e+00 | 1.06e+01 | 1.34e-01 |
| 6.25e-03 | 2.67e+00 | 2.53e+00 | 5.29e+00 | 6.70e-02 |
| 3.13e-03 | 1.34e+00 | 1.27e+00 | 2.64e+00 | 3.35e-02 |
| 1.56e-03 | 6.67e-01 | 6.33e-01 | 1.32e+00 | 1.68e-02 |
| 7.81e-04 | 3.34e-01 | 3.16e-01 | 6.59e-01 | 8.38e-03 |
| 3.91e-04 | 1.67e-01 | 1.58e-01 | 3.30e-01 | 4.19e-03 |

Table 4.9: Maximum Errors via NSFDM for $\beta_1 = 0.3$, $\beta_2 = 0.035$

| $\ell$ | $EX$ | $EV$ | $EY_1$ | $EY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 3.71e+02 | 2.06e+02 | 2.51e+02 | 1.24e+00 |
| 2.50e-02 | 1.88e+02 | 1.02e+02 | 1.28e+02 | 6.26e-01 |
| 1.25e-02 | 9.46e+01 | 5.07e+01 | 6.49e+01 | 3.15e-01 |
| 6.25e-03 | 4.74e+01 | 2.53e+01 | 3.26e+01 | 1.58e-01 |
| 3.13e-03 | 2.38e+01 | 1.26e+01 | 1.64e+01 | 7.91e-02 |
| 1.56e-03 | 1.19e+01 | 6.32e+00 | 8.19e+00 | 3.96e-02 |
| 7.81e-04 | 5.95e+00 | 3.16e+00 | 4.10e+00 | 1.98e-02 |
| 3.91e-04 | 2.97e+00 | 1.58e+00 | 2.05e+00 | 9.90e-03 |



Table 4.10: Maximum Errors via RK4 for $\beta_1 = 0.3$, $\beta_2 = 0.035$

| $\ell$ | $EX$ | $EV$ | $EY_1$ | $EY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 1.91e+01 | 8.41e+00 | 1.10e+01 | 5.15e-02 |
| 2.50e-02 | 9.54e+00 | 4.21e+00 | 5.48e+00 | 2.57e-02 |
| 1.25e-02 | 4.77e+00 | 2.11e+00 | 2.74e+00 | 1.28e-02 |
| 6.25e-03 | 2.39e+00 | 1.05e+00 | 1.37e+00 | 6.40e-03 |
| 3.13e-03 | 1.19e+00 | 5.26e-01 | 6.85e-01 | 3.20e-03 |
| 1.56e-03 | 5.96e-01 | 2.63e-01 | 3.42e-01 | 1.60e-03 |
| 7.81e-04 | 2.98e-01 | 1.32e-01 | 1.71e-01 | 8.00e-04 |
| 3.91e-04 | 1.49e-01 | 6.58e-02 | 8.56e-02 | 4.00e-04 |

Table 4.11: Maximum Errors via IFDM for $\beta_1 = 0.3$, $\beta_2 = 0.35$

| $\ell$ | $EX$ | $EV$ | $EY_1$ | $EY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 4.29e+00 | 1.05e+01 | 6.95e+00 | 2.94e+01 |
| 2.50e-02 | 2.22e+00 | 5.25e+00 | 3.44e+00 | 1.45e+01 |
| 1.25e-02 | 1.13e+00 | 2.62e+00 | 1.71e+00 | 7.22e+00 |
| 6.25e-03 | 5.69e-01 | 1.31e+00 | 8.54e-01 | 3.60e+00 |
| 3.13e-03 | 2.86e-01 | 6.53e-01 | 4.27e-01 | 1.80e+00 |
| 1.56e-03 | 1.43e-01 | 3.26e-01 | 2.13e-01 | 8.98e-01 |
| 7.81e-04 | 7.16e-02 | 1.63e-01 | 1.07e-01 | 4.49e-01 |
| 3.91e-04 | 3.58e-02 | 8.16e-02 | 5.33e-02 | 2.24e-01 |

Table 4.12: Maximum Errors via NSFDM for $\beta_1 = 0.3$, $\beta_2 = 0.35$

| $\ell$ | $EX$ | $EV$ | $EY_1$ | $EY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 2.35e+02 | 1.01e+02 | 4.09e+01 | 1.55e+02 |
| 2.50e-02 | 1.20e+02 | 5.05e+01 | 2.10e+01 | 8.05e+01 |
| 1.25e-02 | 6.06e+01 | 2.52e+01 | 1.06e+01 | 4.10e+01 |
| 6.25e-03 | 3.05e+01 | 1.26e+01 | 5.36e+00 | 2.07e+01 |
| 3.13e-03 | 1.53e+01 | 6.28e+00 | 2.69e+00 | 1.04e+01 |
| 1.56e-03 | 7.65e+00 | 3.14e+00 | 1.35e+00 | 5.21e+00 |
| 7.81e-04 | 3.83e+00 | 1.57e+00 | 6.74e-01 | 2.61e+00 |
| 3.91e-04 | 1.92e+00 | 7.85e-01 | 3.37e-01 | 1.30e+00 |



Table 4.13: Maximum Errors via RK4 for $\beta_1 = 0.3$, $\beta_2 = 0.35$

| $\ell$ | $EX$ | $EV$ | $EY_1$ | $EY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 1.15e+01 | 3.58e+00 | 1.97e+00 | 5.34e+00 |
| 2.50e-02 | 5.73e+00 | 1.79e+00 | 9.85e-01 | 2.66e+00 |
| 1.25e-02 | 2.86e+00 | 8.94e-01 | 4.92e-01 | 1.33e+00 |
| 6.25e-03 | 1.43e+00 | 4.47e-01 | 2.46e-01 | 6.65e-01 |
| 3.13e-03 | 7.16e-01 | 2.23e-01 | 1.23e-01 | 3.32e-01 |
| 1.56e-03 | 3.58e-01 | 1.12e-01 | 6.14e-02 | 1.66e-01 |
| 7.81e-04 | 1.79e-01 | 5.58e-02 | 3.07e-02 | 8.30e-02 |
| 3.91e-04 | 8.94e-02 | 2.79e-02 | 1.53e-02 | 4.15e-02 |

Table 4.14: Maximum Errors via IFDM for $\beta_1 = 0.35$, $\beta_2 = 0.3$

| $\ell$ | $EX$ | $EV$ | $EY_1$ | $EY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 3.25e+00 | 1.26e+01 | 3.85e+01 | 1.15e+01 |
| 2.50e-02 | 1.51e+00 | 6.26e+00 | 1.89e+01 | 5.64e+00 |
| 1.25e-02 | 7.26e-01 | 3.12e+00 | 9.39e+00 | 2.79e+00 |
| 6.25e-03 | 3.56e-01 | 1.55e+00 | 4.67e+00 | 1.39e+00 |
| 3.13e-03 | 1.78e-01 | 7.77e-01 | 2.33e+00 | 6.92e-01 |
| 1.56e-03 | 8.92e-02 | 3.88e-01 | 1.16e+00 | 3.46e-01 |
| 7.81e-04 | 4.47e-02 | 1.94e-01 | 5.82e-01 | 1.73e-01 |
| 3.91e-04 | 2.24e-02 | 9.70e-02 | 2.91e-01 | 8.63e-02 |

Table 4.15: Maximum Errors via NSFDM for $\beta_1 = 0.35$, $\beta_2 = 0.3$

| $\ell$ | $EX$ | $EV$ | $EY_1$ | $EY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 2.43e+02 | 1.15e+02 | 1.50e+02 | 5.75e+01 |
| 2.50e-02 | 1.24e+02 | 5.72e+01 | 7.75e+01 | 2.94e+01 |
| 1.25e-02 | 6.26e+01 | 2.85e+01 | 3.94e+01 | 1.48e+01 |
| 6.25e-03 | 3.15e+01 | 1.43e+01 | 1.99e+01 | 7.46e+00 |
| 3.13e-03 | 1.58e+01 | 7.12e+00 | 9.97e+00 | 3.74e+00 |
| 1.56e-03 | 7.90e+00 | 3.56e+00 | 4.99e+00 | 1.87e+00 |
| 7.81e-04 | 3.96e+00 | 1.78e+00 | 2.50e+00 | 9.37e-01 |
| 3.91e-04 | 1.98e+00 | 8.90e-01 | 1.25e+00 | 4.69e-01 |



Table 4.16: Maximum Errors via RK4 for $\beta_1 = 0.35$, $\beta_2 = 0.3$

| $\ell$ | $EX$ | $EV$ | $EY_1$ | $EY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 1.18e+01 | 3.88e+00 | 5.23e+00 | 2.97e+00 |
| 2.50e-02 | 5.89e+00 | 1.94e+00 | 2.61e+00 | 1.48e+00 |
| 1.25e-02 | 2.94e+00 | 9.69e-01 | 1.31e+00 | 7.39e-01 |
| 6.25e-03 | 1.47e+00 | 4.84e-01 | 6.53e-01 | 3.69e-01 |
| 3.13e-03 | 7.35e-01 | 2.42e-01 | 3.27e-01 | 1.85e-01 |
| 1.56e-03 | 3.68e-01 | 1.21e-01 | 1.63e-01 | 9.22e-02 |
| 7.81e-04 | 1.84e-01 | 6.05e-02 | 8.17e-02 | 4.61e-02 |
| 3.91e-04 | 9.19e-02 | 3.03e-02 | 4.08e-02 | 2.31e-02 |

Table 4.17: Order of Convergence of the IFDM for $\beta_1 = 0.03$, $\beta_2 = 0.035$

| $\ell$ | $RX$ | $RV$ | $RY_1$ | $RY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 1.00 | 1.00 | 0.99 | 0.99 |
| 2.50e-02 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1.25e-02 | 1.00 | 1.00 | 1.00 | 1.00 |
| 6.25e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 3.13e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1.56e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 7.81e-04 | 1.00 | 1.00 | 1.00 | 1.00 |

Table 4.18: Order of Convergence of the NSFDM for $\beta_1 = 0.03$, $\beta_2 = 0.035$

| $\ell$ | $RX$ | $RV$ | $RY_1$ | $RY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 1.00 | 1.00 | 0.99 | 0.99 |
| 2.50e-02 | 1.00 | 1.00 | 0.99 | 0.99 |
| 1.25e-02 | 1.00 | 1.00 | 1.00 | 1.00 |
| 6.25e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 3.13e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1.56e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 7.81e-04 | 1.00 | 1.00 | 1.00 | 1.00 |



Table 4.19: Order of Convergence of the RK4 for $\beta_1 = 0.03$, $\beta_2 = 0.035$

| $\ell$ | $RX$ | $RV$ | $RY_1$ | $RY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 1.00 | 1.00 | 1.00 | 1.00 |
| 2.50e-02 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1.25e-02 | 1.00 | 1.00 | 1.00 | 1.00 |
| 6.25e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 3.13e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1.56e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 7.81e-04 | 1.00 | 1.00 | 1.00 | 1.00 |

Table 4.20: Order of Convergence of the IFDM for $\beta_1 = 0.03$, $\beta_2 = 0.35$

| $\ell$ | $RX$ | $RV$ | $RY_1$ | $RY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 1.03 | 1.01 | 0.99 | 1.02 |
| 2.50e-02 | 1.01 | 1.00 | 1.00 | 1.01 |
| 1.25e-02 | 1.01 | 1.00 | 1.00 | 1.00 |
| 6.25e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 3.13e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1.56e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 7.81e-04 | 1.00 | 1.00 | 1.00 | 1.00 |

Table 4.21: Order of Convergence of the NSFDM for $\beta_1 = 0.03$, $\beta_2 = 0.35$

| $\ell$ | $RX$ | $RV$ | $RY_1$ | $RY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 0.97 | 1.01 | 0.98 | 0.96 |
| 2.50e-02 | 0.99 | 1.01 | 0.99 | 0.98 |
| 1.25e-02 | 0.99 | 1.00 | 0.99 | 0.99 |
| 6.25e-03 | 1.00 | 1.00 | 1.00 | 0.99 |
| 3.13e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1.56e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 7.81e-04 | 1.00 | 1.00 | 1.00 | 1.00 |



Table 4.22: Order of Convergence of the RK4 for $\beta_1 = 0.03$, $\beta_2 = 0.35$

| $\ell$ | $RX$ | $RV$ | $RY_1$ | $RY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 1.00 | 1.00 | 1.00 | 1.00 |
| 2.50e-02 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1.25e-02 | 1.00 | 1.00 | 1.00 | 1.00 |
| 6.25e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 3.13e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1.56e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 7.81e-04 | 1.00 | 1.00 | 1.00 | 1.00 |

Table 4.23: Order of Convergence of the IFDM for $\beta_1 = 0.3$, $\beta_2 = 0.035$

| $\ell$ | $RX$ | $RV$ | $RY_1$ | $RY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 1.01 | 1.01 | 1.01 | 0.99 |
| 2.50e-02 | 1.01 | 1.00 | 1.01 | 1.00 |
| 1.25e-02 | 1.00 | 1.00 | 1.00 | 1.00 |
| 6.25e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 3.13e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1.56e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 7.81e-04 | 1.00 | 1.00 | 1.00 | 1.00 |

Table 4.24: Order of Convergence of the NSFDM for $\beta_1 = 0.3$, $\beta_2 = 0.035$

| $\ell$ | $RX$ | $RV$ | $RY_1$ | $RY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 0.98 | 1.01 | 0.97 | 0.98 |
| 2.50e-02 | 0.99 | 1.01 | 0.98 | 0.99 |
| 1.25e-02 | 1.00 | 1.00 | 0.99 | 1.00 |
| 6.25e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 3.13e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1.56e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 7.81e-04 | 1.00 | 1.00 | 1.00 | 1.00 |



Table 4.25: Order of Convergence of the RK4 for $\beta_1 = 0.3$, $\beta_2 = 0.035$

| $\ell$ | $RX$ | $RV$ | $RY_1$ | $RY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 1.00 | 1.00 | 1.00 | 1.00 |
| 2.50e-02 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1.25e-02 | 1.00 | 1.00 | 1.00 | 1.00 |
| 6.25e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 3.13e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1.56e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 7.81e-04 | 1.00 | 1.00 | 1.00 | 1.00 |

Table 4.26: Order of Convergence of the IFDM for $\beta_1 = 0.3$, $\beta_2 = 0.35$

| $\ell$ | $RX$ | $RV$ | $RY_1$ | $RY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 0.95 | 1.01 | 1.01 | 1.02 |
| 2.50e-02 | 0.98 | 1.00 | 1.01 | 1.01 |
| 1.25e-02 | 0.99 | 1.00 | 1.00 | 1.00 |
| 6.25e-03 | 0.99 | 1.00 | 1.00 | 1.00 |
| 3.13e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1.56e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 7.81e-04 | 1.00 | 1.00 | 1.00 | 1.00 |

Table 4.27: Order of Convergence of the NSFDM for $\beta_1 = 0.3$, $\beta_2 = 0.35$

| $\ell$ | $RX$ | $RV$ | $RY_1$ | $RY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 0.97 | 1.01 | 0.96 | 0.95 |
| 2.50e-02 | 0.98 | 1.00 | 0.98 | 0.97 |
| 1.25e-02 | 0.99 | 1.00 | 0.99 | 0.99 |
| 6.25e-03 | 1.00 | 1.00 | 0.99 | 0.99 |
| 3.13e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1.56e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 7.81e-04 | 1.00 | 1.00 | 1.00 | 1.00 |



Table 4.28: Order of Convergence of the RK4 for $\beta_1 = 0.3$, $\beta_2 = 0.35$

| $\ell$ | $RX$ | $RV$ | $RY_1$ | $RY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 1.00 | 1.00 | 1.00 | 1.00 |
| 2.50e-02 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1.25e-02 | 1.00 | 1.00 | 1.00 | 1.00 |
| 6.25e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 3.13e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1.56e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 7.81e-04 | 1.00 | 1.00 | 1.00 | 1.00 |

Table 4.29: Order of Convergence of the IFDM for $\beta_1 = 0.35$, $\beta_2 = 0.3$

| $\ell$ | $RX$ | $RV$ | $RY_1$ | $RY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 1.11 | 1.01 | 1.02 | 1.03 |
| 2.50e-02 | 1.06 | 1.01 | 1.01 | 1.02 |
| 1.25e-02 | 1.03 | 1.00 | 1.01 | 1.01 |
| 6.25e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 3.13e-03 | 0.99 | 1.00 | 1.00 | 1.00 |
| 1.56e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 7.81e-04 | 1.00 | 1.00 | 1.00 | 1.00 |

Table 4.30: Order of Convergence of the NSFDM for $\beta_1 = 0.35$, $\beta_2 = 0.3$

| $\ell$ | $RX$ | $RV$ | $RY_1$ | $RY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 0.97 | 1.00 | 0.95 | 0.97 |
| 2.50e-02 | 0.98 | 1.00 | 0.98 | 0.98 |
| 1.25e-02 | 0.99 | 1.00 | 0.99 | 0.99 |
| 6.25e-03 | 1.00 | 1.00 | 0.99 | 1.00 |
| 3.13e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1.56e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 7.81e-04 | 1.00 | 1.00 | 1.00 | 1.00 |



Table 4.31: Order of Convergence of the RK4 for $\beta_1 = 0.35$, $\beta_2 = 0.3$

| $\ell$ | $RX$ | $RV$ | $RY_1$ | $RY_2$ |
|---|---|---|---|---|
| 5.00e-02 | 1.00 | 1.00 | 1.00 | 1.00 |
| 2.50e-02 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1.25e-02 | 1.00 | 1.00 | 1.00 | 1.00 |
| 6.25e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 3.13e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1.56e-03 | 1.00 | 1.00 | 1.00 | 1.00 |
| 7.81e-04 | 1.00 | 1.00 | 1.00 | 1.00 |

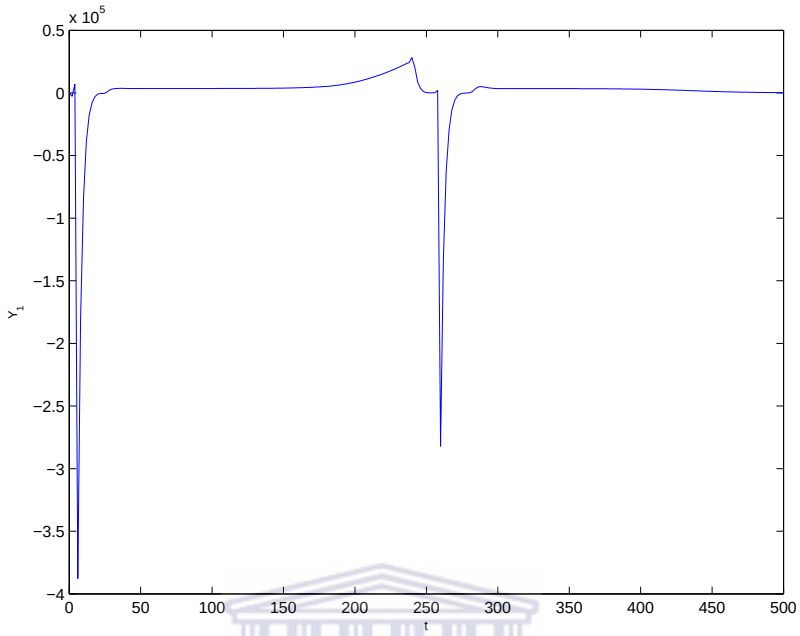



Figure 4.1: Profile of $Y_1(t)$ generated by IFDM with $\ell = 2$



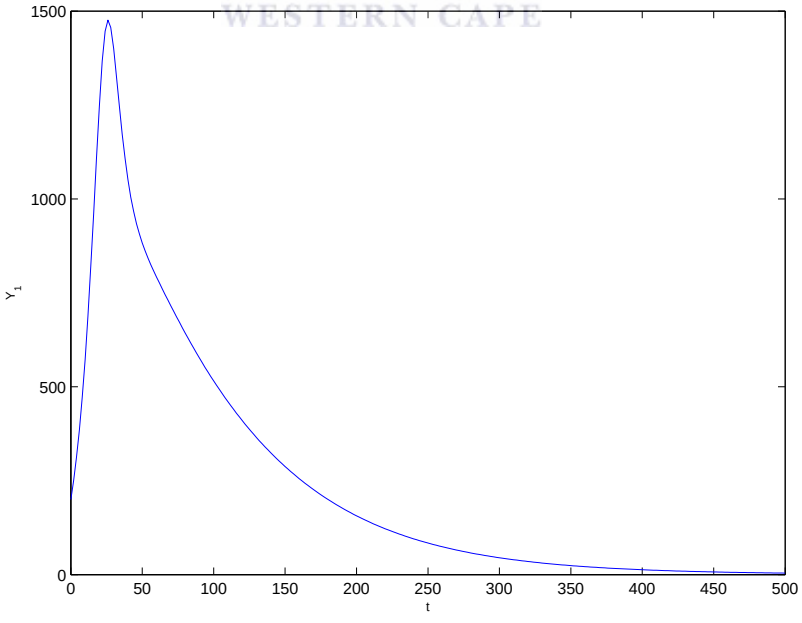



Figure 4.2: Profile of $Y_1(t)$ generated by NSFDM with $\ell = 2$

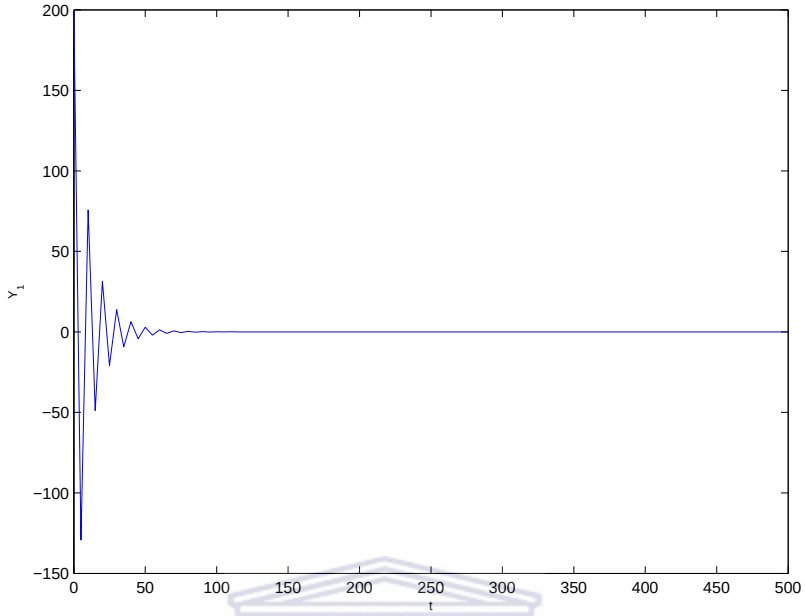



Figure 4.3: Profile of $Y_1(t)$ generated by IFDM with $\ell = 5$



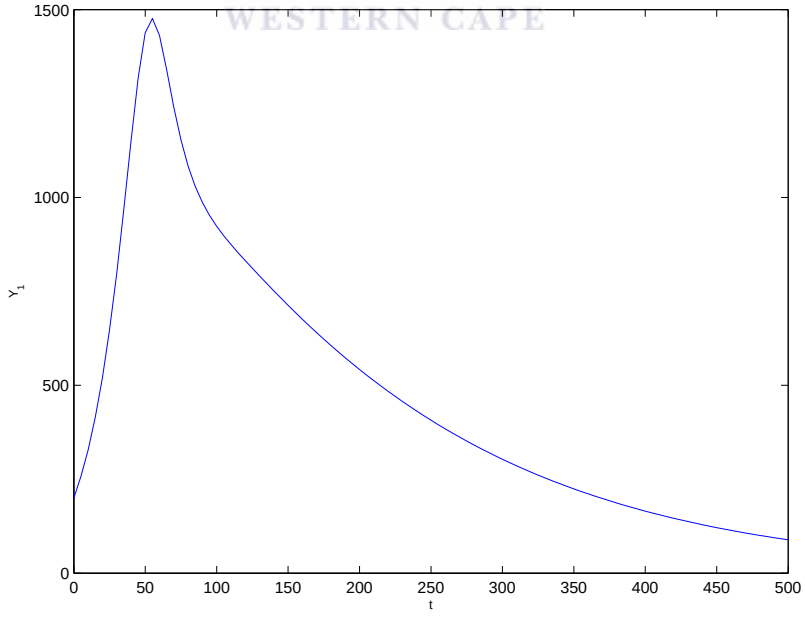



Figure 4.4: Profile of $Y_1(t)$ generated by NSFDM with $\ell = 5$

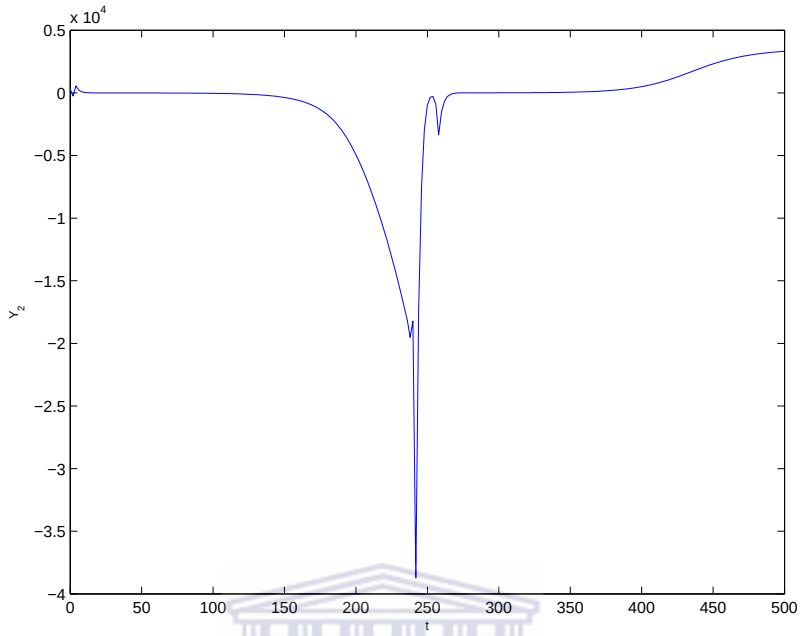



Figure 4.5: Profile of $Y_2(t)$ generated by IFDM with $\ell = 2$



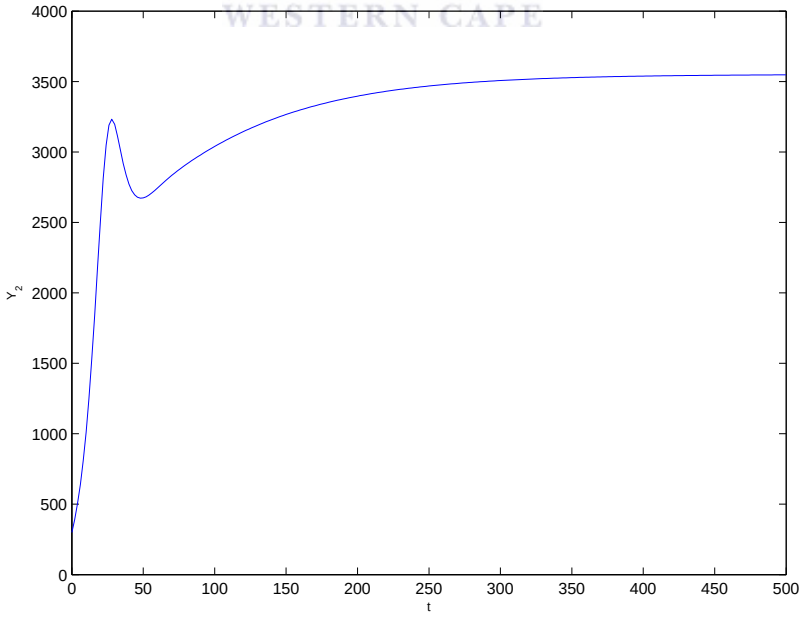



Figure 4.6: Profile of $Y_2(t)$ generated by NSFDM with $\ell = 2$

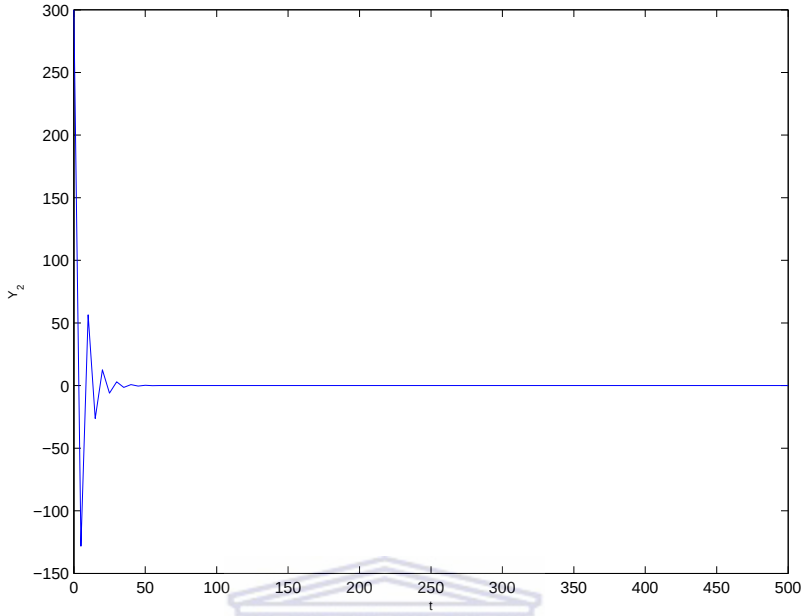



Figure 4.7: Profile of $Y_2(t)$ generated by IFDM with $\ell = 5$



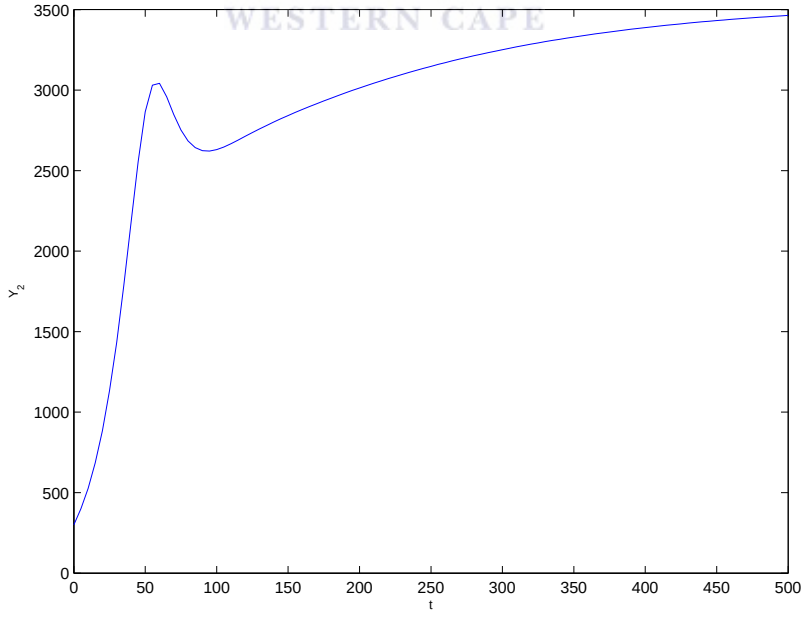



Figure 4.8: Profile of $Y_2(t)$ generated by NSFDM with $\ell = 5$

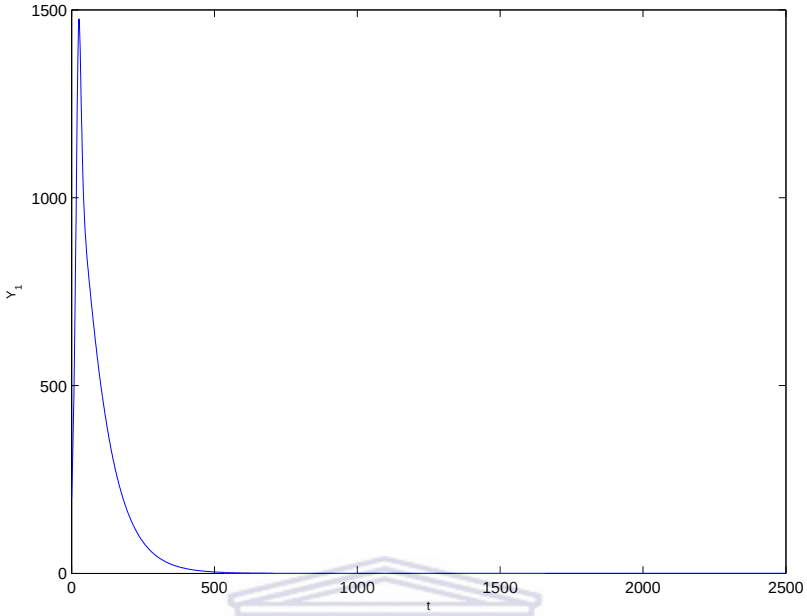



Figure 4.9: Extended Profile of $Y_1(t)$ generated by NSFDM with $\ell = 2$



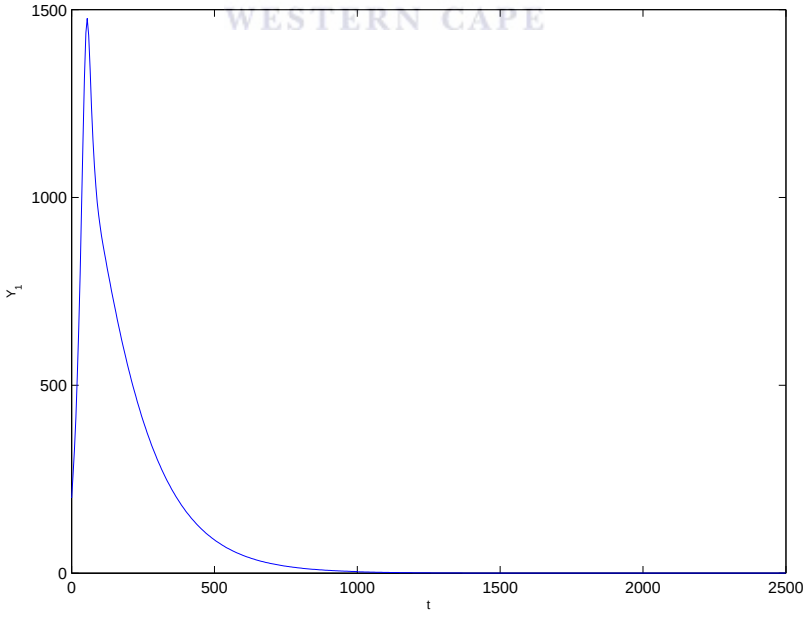



Figure 4.10: Extended Profile of $Y_1(t)$ generated by NSFDM with $\ell = 5$

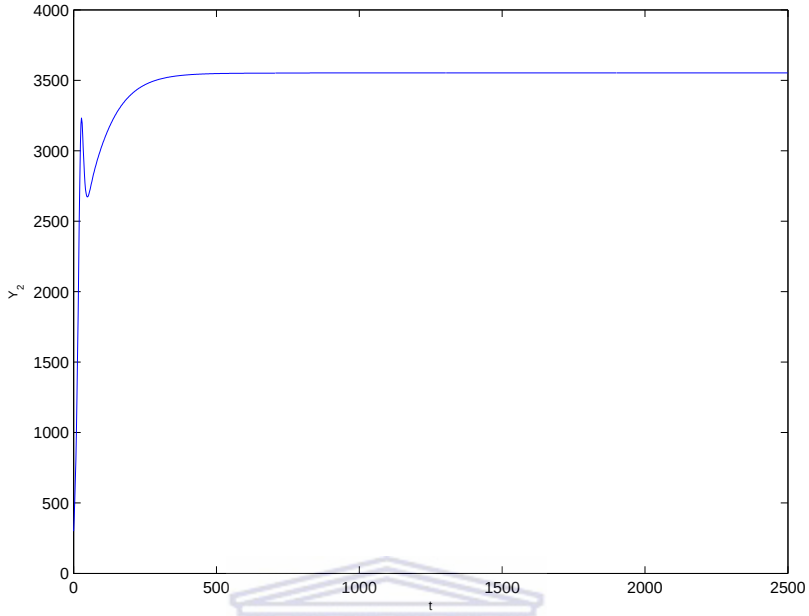



Figure 4.11: Extended Profile of $Y_2(t)$ generated by NSFDM with $\ell = 2$



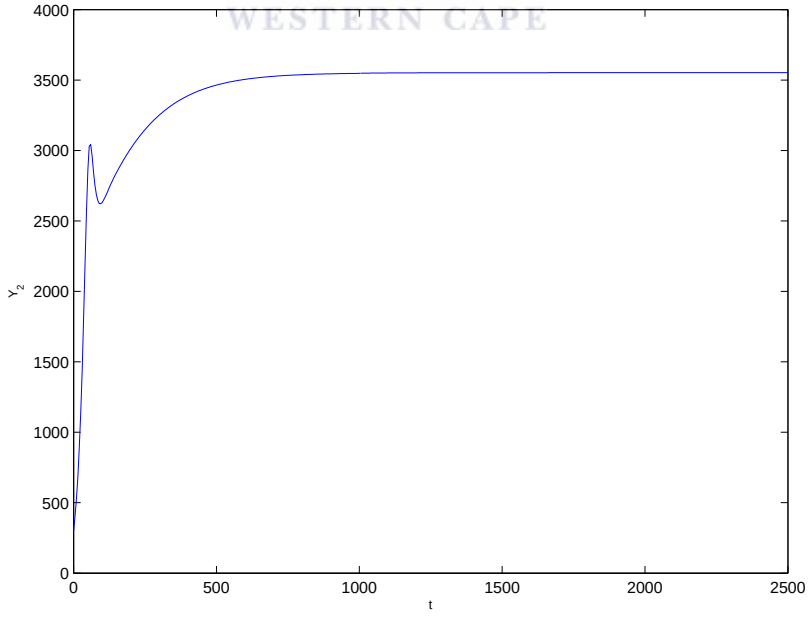



Figure 4.12: Extended Profile of $Y_2(t)$ generated by NSFDM with $\ell = 5$

Our initial aim was to check the performance of the NSFDM as compared to an IFDM. We did so in a variety of ways. We calculated the errors and looked at the order of convergence and found that both the approaches have similar results. We also calculated the reproduction numbers for the various choices of the associated parameters and found that both of these methods as well as RK4 give the same answer.

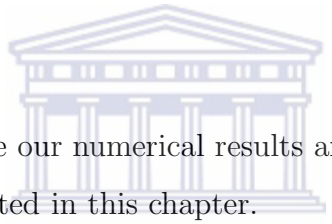
As is seen in the literature that one develops some methods and convinced that it satisfies a number of properties. However, there are a number of issues through which one can distinguish between various associated methods. One such method that we can consider here is the positivity property that we expect the solution to satisfy. It can be seen from figures 4.1, 4.3, 4.5, 4.7 that the IFDM performs very poorly in the transient state whereas there is no problem with NSFDM (see, figures 4.2, 4.4, 4.6, 4.8). It preserves the positivity of the solution as needed. In order to see the extended profile of $Y_1$ and $Y_2$ using NSFDM, we plot some more graphs. See figures 4.9-4.12.



It is evident from the numerical results that the error is much smaller in the case of RK4 as compared to other two methods. However, one should note that the order of the method does not remain four as is expected classically. This unusual but well-known phenomenon is termed in the literature as "order reduction" (see, e.g., [17, 27]) and is due to the fact being solved over the large intervals, the problem resembles to the stiff problem.

# Chapter 5

# Summary, Conclusions and Future Plans



In this chapter we summerise our numerical results and discuss main pitfalls. Future directions will also be indicated in this chapter.



This thesis dealt with design, analysis and implementation of a positivity preserving numerical method for an HIV model describing the transmission dynamics of two HIV subtypes in a given community. The area of HIV is introduced with appropriate details in Chapter 1 where some relevant models and associated literature is also provided. Then the qualitative analysis for a particular model is carried out in Chapter 2. Some numerical methods are developed in Chapter 3. Extensive numerical simulation are carried out and comparative numerical results were presented in Chapter 4. The methods developed in this thesis can also be extended for some other models given in Chapter 1.

As is known, the immune system of the body defends the body against bacteria and viruses. It reduces the basic reproduction number $R_0$ of a disease and may clear it if $R_0$ becomes less than 1. The AIDS virus attacks the immune system itself, eventually destroying its ability to reduce $R_0$ below 1 and persists in the body before this happens by hiding in cells that are not recognized as infected by the immune

system. Any control policy, in general, aims at reducing $R_0$ below 1. In the case of the HIV model that we have considered, this $R_0$ is the maximum of the two reproduction numbers $R_\rho^{(1)}$ and $R_\rho^{(2)}$, which are defined as

$$R_\rho^{(1)} = \frac{\beta_1 c(1-\rho\xi_1)}{(\mu+\gamma_1+\tau)}$$

and

$$R_\rho^{(2)} = \frac{\beta_2 c(1-\rho\xi_2)}{(\mu+\gamma_2+\tau)}.$$

In order to keep these two reproduction numbers less than 1, it is suggested that one should try to increase the parameters $\mu$ and $\tau$ and decrease the parameters $\beta_1$, $\beta_2$, and implement various other strategies so that the other parameters $\rho$, $\xi_1$, $\xi_2$, $\gamma_1$ and $\gamma_2$ increases. This is what exactly the health practitioners should take into account. Various vaccination strategies could be designed accordingly.

As is pointed out in previous chapter, the model problem that we have solved is defined over a large interval and that is where stiffness arises. To this end, currently, we are investigating whether some novel techniques which are well-known for singular perturbation problems, can be used to resolve such issues.

# Appendix A

# On the Reproduction Number $R_0$

The threshold for many epidemiology models is the basic reproduction number $R_0$, which is defined as the average number of secondary infections produced when one infected individual is introduced into a host population where everyone is susceptible [25]. For many deterministic epidemiology models, an infection can get started in a fully susceptible population if and only if $R_0 > 1$. Thus the basic reproduction number $R_0$ is often considered as the threshold quantity that determines when an infection can invade and persist in a new host population.

Note that $R_0$ is also called the basic reproduction ratio [24] or basic reproductive rate [4].

For the basic endemic models without age structure, the expressions for the basic reproduction number $R_0$ are intuitively obvious as the product of the contact rate, the average infectious period, and the fraction surviving the latent period (provided there is an exposed class in the model). But for more complicated models, expressions for $R_0$ must be derived from threshold conditions for the stability of the disease-free equilibrium or the existence of an endemic equilibrium in the feasible region.

The basic reproductive rate, $R_0$, is essentially the average number of successful offspring that a parasite is intrinsically capable of producing ([1, 2, 25, 26, 55, 56, 82]). It is, in effect, Fisher's (1930) 'net reproductive value' for the parasite. This concept is central to any discussion of the overall population biology of an organism. Clearly a parasitic species must have $R_0 > 1$ if it is to be capable of invading, and establishing itself within, a host population. For a microparasite (represented by a compartmental model), $R_0$ is more precisely defined as the average number of secondary infectious produced when one infected individual is introduced into a host population where everyone is susceptible. (Note that, a parasite is an organism which obtain food only by living in or on another organism. Parasites can be categorized into two,

namely, microparasites and macroparasites. Microparasites may be thought of as those parasites which have direct reproduction - usually at very high rates within the host. Macroparasites may be thought of as those having no direct reproduction within the definitive host. For a macroparasite (represented by a distributional model), $R_0$ is the average number of female offspring produced throughout the lifetime of a mature female parasite, which themselves achieve reproductive maturity in the absence of density-dependent constraints.)

When such a microparasitic infection becomes established in a host population, the fraction remaining susceptible decreases. Eventually an equilibrium may be attained, with the rate at which susceptible individuals are infected being balanced against a rate at which newly susceptible individuals appear (usually by birth, but possibly also by immigration or by loss of immunity). At equilibrium, each infection will on average produce exactly one secondary infection; that is, at equilibrium the effective reproductive rate of the parasite is $R = 1$. If we assume the host population is homogeneously mixed, in the sense that, on average, all hosts have intrinsically similar epidemiological properties ( independent of age, genetic make-up, social habits, geographical location, etc.), then the number of secondary infections produced by an infected individual will be linearly proportional to the probability that any one random contact is with a susceptible individual. In this event, the effective reproductive rate, $R$, is equal to the basic rate, $R_0$, discounted by $x$, the fraction of the host population that is susceptible: $R = R_0 x$. Thus, under the rough approximation of treating the host population as homogeneously mixed, for a microparasite the equilibrium condition $R = 1$ leads to an important relation between $R_0$ and the fraction, $x^*$, of the host population that is susceptible at equilibrium:

$$R_0 \; x^* \;\; = \;\; 1 \tag{1}$$

Equation (1) has applications which will be discussed later. Beyond this, it has general interest for ecologists. For one thing, it is notoriously difficult to assess the intrinsic reproductive capacity, $R_0$, of any species of organism (even humans). It is

also a problem for ecologists to detemine exactly what density-dependent mechanisms operate to hold the reproductive rate of natural populations below their intrinsic capacities - capacities which could, if realized, blanket the world with that species. Equation (1) resolves both these problems for microparasites: because $x^*$ can be found from serological or other data on age-specific susceptibility, the elusive quatity $R_0$ can be calculated; and the density-dependent process holding $R$ below $R_0$ is simply the removal of susceptibles by immunity, following infection (which corresponds, in essence, to a very simple form of predation upon hosts by the parasite). Thus equation (1) and the surrounding discussion illustrate the concepts of basic reproductive rates and density-dependent regulation of populations more clearly and quanititatively than the examples conventionally used in introductory biology textbooks and courses.

# Appendix B

One or more of the following rules [59] can be helpful in designing the non-standard finite difference methods:

**Rule 1.** The orders of the discrete derivatives should be equal to the orders of the corresponding derivatives of the differential equation. (When the orders of the discrete derivatives are larger than the corresponding orders that appear in the differential equation, numerical instabilities in the form of oscillations often appear. Depending on the particular differential equation, these oscillations may be bounded or unbounded. The mathematical reason for their occurrence is that the discrete equations have a larger class of solutions than the differential equation).

**Rule 2.** Denominator functions for the discrete derivatives must, in general, be expressed in terms of more complicated functions of the step-sizes than those conventionally used. (These denominator functions, generally, are functions, that are related to particular solutions or properties of the general solution to the differential equation).

**Rule 3.** Nonlinear terms should, in general, be replaced by nonlocal discrete representations.

**Rule 4.** Special conditions that hold for the solutions of the differential equations should also hold for the solutions of the finite difference scheme.

**Rule 5.** The scheme should not introduce extraneous or spurious solutions.

**Rule 6.** For differential equations having $N(\geq 3)$ terms, it is generally useful to construct finite difference schemes for various sub-equations composed of $M$ terms,

where $M < N$, and then combine all the schemes together in an overall consistent finite difference model.

The first five rules above had originally appeared in [59] and later modified (and/or interpreted differently but having the similar meanings) as per the individual requirements, see, e.g., [5], [53]. For the detailed explanations of these rules, we refer the readers to [59, 60]. Furthermore, a systematic definition of these nonstandard finite difference methods is currently being designed in [54].

By the nonstandard finite difference methods, we mean those in which at least one of the nonstandard modeling rules, proposed by Mickens above, is used.

# Appendix C

# Stability Analysis in General

Linear stability of the systems of ordinary differential equations such as arise in interacting population models and reaction kinetics systems (cf. Chapter 3 and 6) is determined by the roots of a polynomial. The stability analysis we are concerned with involves linear systems of the vector form

$$\frac{d\mathbf{x}}{dt} = A\mathbf{x},$$

where $A$ is the matrix of the linearised nonlinear interaction/reaction terms: it is the Jacobian matrix about the steady state—the community matrix in ecological terms. Solutions are obtained by setting

$$\mathbf{x} = \mathbf{x}_0 e^{\lambda t},$$



in the above equation where $\mathbf{x}_0$ is a constant vector and the eigenvalues $\lambda$ are the roots of the *characteristic polynomial*

$$|A - \lambda I| = 0,$$

where $I$ is the identity matrix. The solution $\mathbf{x} = 0$ is stable if all the roots $\lambda$ of the characteristic polynomial lie in the left-hand complex plane; that is $Re\,\lambda < 0$ for all roots $\lambda$. If this holds then $\mathbf{x} \to 0$ exponentially as $t \to \infty$ and hence $\mathbf{x} = 0$ is stable to small (linear) perturbations. If the system is of $n$th order, the characteristic polynomial can be taken in the general form

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + ... + a_n = 0,$$

where the coefficient $a_i, i = 0, 1, ..., n$ are all real. We tacitly assume $a_n \neq 0$ since otherwise $\lambda = 0$ is a solution, and the polynomial is then of order $n - 1$ with the equivalent $a_n \neq 0$. We require conditions on the $a_i, i = 0, 1, ..., n$ such that the zeros

of $P(\lambda)$ have $Re\,\lambda < 0$. The necessary and sufficient conditions for this hold are the *Routh-Hurwitz* conditions. There are various equilvalent forms of these, one of which is, together with $a_n > 0$,

$$D_1 = a_1 > 0,$$

$$D_2 = \begin{vmatrix} a_1 & a_3 \\ 1 & a_2 \end{vmatrix} > 0,$$

$$D_3 = \begin{vmatrix} a_1 & a_3 & a_5 \\ 1 & a_2 & a_4 \\ 0 & a_1 & a_3 \end{vmatrix} > 0,$$

$$D_4 = \begin{vmatrix} a_1 & a_3 & . & . & . & . \\ 1 & a_2 & a_4 & . & . & . \\ 0 & a_1 & a_3 & . & . & . \\ 0 & 1 & a_2 & . & . & . \\ . & . & . & . & . & . \\ 0 & 0 & . & . & . & a_k \end{vmatrix} > 0, k = 1, 2, ..., n.$$



These conditions are derived, using complex variable methods, in standard texts on the theory of dynamical systems [79].

Finally, the following theorem, known as the Lyapunov Stability Theorem, is useful in determining stability of the equilibria.

**Theorem.** Let $x = 0$ be an equilibrium point for a system described by

$$\dot{x} = f(x)$$

where $f : U \to \mathbb{R}^n$ is locally Lipschitz and $U \subset \mathbb{R}^n$ is a domain that contains the origin. Let $V : U \to \mathbb{R}$ be continuously differentiable, positive definite function in $U$.

Then,

Case 1. If $\dot{V}(x) = \left(\frac{\partial V}{\partial x}\right) f$ is negative semidefinite, then $x = 0$ is a stable equilibrium point,

Case 2. If $\dot{V}(x)$ is negative definite, then $x = 0$ is an asymptotically stable equilibrium point,

where $V$ is called a Lyapunov function. Moreover, if the above conditions holds for all $x \in \mathbb{R}^n$ and $\|x\| \to \infty$ implies that $V(x) \to \infty$, then $x = 0$ is globally stable in Case 1 and globally asymptotically stable in Case 2.

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