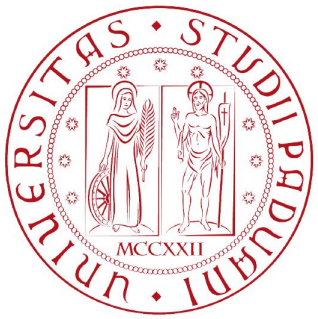


UNIVERSITY OF PADOVA
Bachelor Degree in Information Engineering

# Analysis and comparison of models for HIV-1 pathogenesis and transmission

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February 21$^{st}$, 2013
A.Y. 2012/2013

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# Chapter 1

# Introduction

Since his development, mathematical modeling has always had an important role in the study of epidemics. The ability to predict the trend of a transmission or a pathogenesis helps biologists, doctors and sociologists involved in the search of a solution for the main diseases. Thanks to the models, it is possible to test the actual efficacy of a drug or to understand if population put preventative measures into practice. Models can also be useful in the control of transmissions allowing the estimation of the level of vaccination to be used.

Unfortunately, in most cases the a priori estimate of parameters used in the models is impossible, so it is needed to resort to data fitting and regression analysis. Moreover, there is a lack of knowledge of the transmission process and the viral, bacterial, parasitical, fungal evolution in the first approach to a new kind of infection (e.g. HIV/AIDS). Although planned experiments can be used to obtain information in many sciences, experiments with infectious diseases in human populations are generally not possible for ethical and practical reasons. The only available data is from naturally occurring epidemics and infections, but, as we will see later, these data are not complete since many cases are not reported due to social stigma or medical system inefficiency. All these drawbacks make models difficult to validate and to be used in clinical practice.

Sexually transmitted diseases (STDs) need other remarks with regards to characteristics, which are different from other infections. STDs are restricted to sexually active population and transmission take place between males and females in heterosexual community, so the assumption of uniform mixing is wrong. This problems are handled, for example, in [1] by H.W. Hethcote and J.A. Yorke, who divided population into eight groups depending on gender and sexual activity level. The carrier is often asymptomatic in first stages of infection. The infection, finally, does not induce acquired immunity so the removed class (i.e. who have had the disease) need to be considered susceptible.

In this script, after a general discussion of transmission models used in the following chapters, we will study transmission and pathogenesis of HIV-1 virus through the analysis of different models that take into account specific characteristics of the virus and for its spread control. Now, we will try to understand how HIV acts in human body in order to be able to model systems that will be discussed next.

## 1.1 Brief exposition about HIV-1 virus

HIV is the virus that leads to acquired immune deficiency syndrome, AIDS. HIV is a member of the genus Lentivirus, part of the family of Retroviridae. Lentiviruses have many morphologies and biological properties in common. Two types of HIV have been characterized: HIV-1 and HIV-2. HIV-1 is the virus that was initially discovered and termed both LAV and HTLV-III. It is more virulent, more infective, and is the cause of the majority of HIV infections globally. In this dissertation, we consider HIV-1 due to its spread and importance. Three groups of HIV-1 have been identified on the basis of differences in the envelope region: M, N, and O. Group M is the most prevalent and is subdivided into eight subtypes (or clades), based on the whole genome, which are geographically distinct. The most prevalent are subtypes B (found mainly in North America and Europe), A and D (found mainly in Africa), and C (found mainly in Africa and Asia). Most HIV-1 research is focused on subtype B; few laboratories focus on the other subtypes.

HIV is composed of two copies of positive single-stranded RNA that codes for the virus's nine genes enclosed by a conical capsid composed of 2,000 copies of a viral protein. The single-stranded RNA is tightly bound to nucleocapsid proteins and enzymes needed for the development of the virion such as reverse transcriptase, proteases, ribonuclease and integrase. A matrix composed of viral protein surrounds the capsid ensuring the integrity of the virion particle. This is, in turn, surrounded by the viral envelope that is composed of two layers of fatty molecules called phospholipids taken from the membrane of a human cell when a newly formed virus particle buds from the cell. Embedded in the viral envelope are proteins from the host cell and about 70 copies of a complex HIV protein that protrudes through the surface of the virus particle.

Sexual intercourse is the major mode of HIV transmission. HIV is present in the seminal fluid, which is passed from a male to his sexual partner. The virions can then infect numerous cellular targets and disseminate into the whole organism. Other transmission ways are contaminated blood transfusions, hypodermic needles, and from mother to child during pregnancy, delivery, or breastfeeding.

Many species are infected by lentiviruses, which are characteristically

responsible for long-duration illnesses with a long incubation period. Lentiviruses are transmitted as single-stranded, positive-sense, enveloped RNA viruses. Upon entry into the target cell, the viral RNA genome is converted (reverse transcribed) into double-stranded DNA by a virally encoded reverse transcriptase that is transported along with the viral genome in the virus particle. The resulting viral DNA is then imported into the cell nucleus and integrated into the cellular DNA by a virally encoded integrase and host co-factors.

The primary infection starts when HIV enters $CD4^+$ T and macrophages cells (the first cells infected by HIV and perhaps the source of HIV production when $CD4^+$ T-cells become depleted in the patient) by the adsorption of glycoproteins on its surface to receptors on the target cell followed by fusion of the viral envelope with the cell membrane and the release of the HIV capsid into the cell. Shortly after the viral capsid enters the cell, an enzyme called reverse transcriptase liberates the single-stranded RNA genome from the attached viral proteins and copies it into a complementary DNA (cDNA) molecule. During this period there is a rapid increase in the number of viral particles in the plasma which can reach well over 10 million copies per ml. The replication cycle of the virus is very fast, with the generation of about $10^{10}$ virions every day. The process of reverse transcription is extremely error-prone, with a high mutation rate of approximately $3 \times 10^5$ per nucleotide base per cycle of replication and recombinogenic properties of reverse transcriptase. The resulting mutations may cause drug resistance or allow the virus to evade the body's immune system. The best current therapy for HIV involves the simultaneous administration of two or more anti-viral drugs, potential inhibitors of HIV replication in vivo. These drug cocktails generally consist of reverse transcriptase inhibitors (RTIs) that block the infection of target T-cells by infection virus and protease inhibitors (PIs) that prevent HIV protease from cleaving HIV polyprotein into functional units, causing infected cells to produce virus particles that are noninfectious. The introduction of these potent antiviral agents has, also, opened the door to defining kinetic parameters associated with HIV-1 dynamics in infected individuals. While in primary infection the infectious HIV-1 particles seek out target cells, mostly $CD4^+$ T-cells, and infect them until a peak in viral concentration is reached. After which, due to limitations of target cells and/or the emergence of cytotoxic (or effector) T-cells that target HIV-1 infected cells, the viral load begins to decline.

Primary infection ends when the viral loads reach a set point which defines the beginning of latency. Viral load at set point is a good indicator of the future of the disease. At this point, the virus and its host cell avoid detection by the immune system. During latency, there can be numerous changes in the viral load totals but not to the extent seen in primary infection. In many patients the behavior is characteristic of a damped oscillating system in which there are substantial oscillations in viral loads until a quasi-

steady state level is reached. This state can last for many years until the virus becomes more active, i.e., the patient receives an anti-viral therapy which causes viral totals to greatly diminish , or the patient develops AIDS and the $CD4^+$ T-cell count, normally around $1000/\mu L$, decreases to $200/\mu L$ or below. In this case, the virus is transcribed, producing new RNA genomes and viral proteins that are packaged and released from the cell as new virus particles that begin the replication cycle anew. During viral replication, the integrated DNA provirus is transcribed into mRNA, which is then spliced into smaller pieces. These small pieces are exported from the nucleus into the cytoplasm, where they are translated into the regulatory proteins. As the newly produced proteins accumulates in the nucleus, it binds to viral mRNAs and allows unspliced RNAs to leave the nucleus, where they are otherwise retained until spliced. At this stage, structural proteins are produced from the full-length mRNA. The full-length RNA is actually the virus genome, that is packaged into new virus particles.

The final step of the viral cycle, assembly of new HIV-1 virions, begins at the plasma membrane of the host cell. A polyprotein goes through the endoplasmic reticulum and is transported to the Golgi complex where it is cleaved in envelope glycoproteins. These are transported to the plasma membrane of the host cell where the forming virion begins to bud from the host cell. Maturation occurs either in the forming bud or in the immature virion after it buds from the host cell. During maturation, HIV proteases cleave the polyproteins into individual functional HIV proteins. This cleavage step can be inhibited by protease inhibitors. The various structural components then assemble to produce a mature HIV virion. The mature virion is then able to infect another cell.

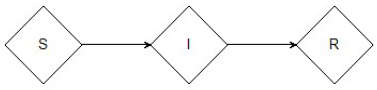
# Chapter 2

# General transmission models

## 2.1 Infectious diseases

In the classical (but still highly relevant) models we consider here the total population is taken to be constant. If a small group of infected individuals is introduced into a large population, a basic problem is to describe the spread of the infection within the population as a function of time. Of course this depends on a variety of circumstances, including the actual disease involved, but as a first attempt at modelling directly transmitted diseases we make some not unreasonable general assumptions.

Consider a disease which, after recovery, confers immunity which, if lethal, includes deaths: dead individuals are still counted. Suppose the disease is such that the population can be divided into three distinct classes: the susceptibles, $S$, who can catch the disease; the infectives, $I$ , who have the disease and can transmit it; and the removed class, $R$, namely, those who have either had the disease, or are recovered, immune or isolated until recovered. The progress of individuals is schematically represented by




Such models are often called SIR models. The number of classes depends on the disease. SI models, for example, have only susceptible and infected classes while SEIR models have a suceptible class, $S$, a class in which the disease is latent, $E$, an infectious class, $I$, and a recovered or dead class, $R$. The assumptions made about the transmission of the infection and incubation period are crucial in any model; these are reflected in the terms in the equations and the parameters. With $S(t)$, $I(t)$ and $R(t)$ as the number of individuals in each class we assume here that:

- The gain in the infective class is at a rate proportional to the number

of infectives and susceptibles, that is, $rSI$, where $r > 0$ is a constant parameter. The susceptibles are lost at the same rate;

- The rate of removal of infectives to the removed class is proportional to the number of infectives, that is, $aI$ where $a > 0$ is a constant; $1/a$ is a measure of the time spent in the infectious state;
- The incubation period is short enough to be negligible; that is, a susceptible who contracts the disease is infective right away.

We now consider the various classes as uniformly mixed; that is, every pair of individuals has equal probability of coming into contact with one another. This is a major assumption and in many situations does not hold as in most sexually transmitted diseases (STD's). The model mechanism based on the above assumptions is then

$$\begin{aligned} \frac{dS}{dt} &= -rSI, \\ \frac{dI}{dt} &= rsI - aI, \\ \frac{dR}{dt} &= aI. \end{aligned} \tag{2.1}$$

where $r > 0$ is the infection rate and $a > 0$ the removal rate of infectives. This is the classic KermackMcKendrick [9] model. We are, of course, only interested in nonnegative solutions for $S$, $I$ and $R$. This is a basic model but, even so, we can make some highly relevant general comments about epidemics and, in fact, adequately describe some specific epidemics with such a model. The constant population size is built into the system (2.1) since, on adding the equations,

$$\frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = 0 \quad \Rightarrow \quad S(t) + I(t) + R(t) = N. \tag{2.2}$$

where $N$ is the total size of the population. Thus, $S$, $I$ and $R$ are all bounded above by $N$. The mathematical formulation of the epidemic problem is completed given initial conditions such as

$$S(0) > 0, \quad I(0) > 0, \quad R(0) = 0. \tag{2.3}$$

A key question in any epidemic situation is, given $r$ , $a$, $S(0)$ and the initial number of infectives $I(0)$, whether the infection will spread or not, and if it does how it develops with time, and crucially when it will start to decline. From (2.2),

$$\left[\frac{dI}{dt}\right]_{t=0} = I(0)[rS(0) - a], \left[\frac{dI}{dt}\right]_{t=0} > 0 \,\text{if}\, S(0) > \rho, \left[\frac{dI}{dt}\right]_{t=0} < 0 \,\text{if}\, S(0) < \rho. \tag{2.4}$$

Since, from (2.1), $dS/dt \leq 0$, $S \leq S(0)$ we have, if $S(0) < a/r$ ,

$$\frac{dI}{dt} = I(rS - a) \leq 0 \quad \text{for all} \quad t \geq 0. \tag{2.5}$$

in which case $I(0) > I(t) \to 0$ as $t \to \infty$ and so the infection dies out; that is, no epidemic can occur. On the other hand if $S(0) > a/r$ then $I(t)$ initially increases and we have an epidemic. The term 'epidemic' means that $I(t) > I(0)$ for some $t > 0$. We thus have a threshold phenomenon. If $S(0) > S_c = a/r$ there is an epidemic while if $S(0) < S_c$ there is not. The critical parameter $\rho = a/r$ is sometimes called the relative removal rate and its reciprocal $\sigma(= r/a)$ the infections contact rate. We write

$$\mathscr{R}_0 = \frac{rS(0)}{a}. \tag{2.6}$$

where $\mathscr{R}_0$ is the basic reproduction rate of the infection, that is, the number of secondary infections produced by one primary infection in a wholly susceptible population. Here $1/a$ is the average infectious period. If more than one secondary infection is produced from one primary infection, that is, $\mathscr{R}_0 > 1$, clearly an epidemic ensues. The whole question of thresholds in epidemics is obviously important. The definition and derivation or computation of the basic reproduction rate is crucial and can be quite complicated.

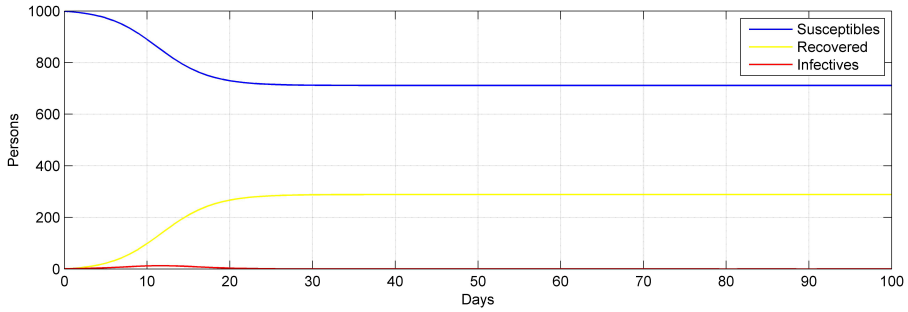



Figure 2.1: Threshold fenomenon. For $S_c \to S(0)$ the number of infectives decreases.

We can derive some other useful analytical results from this simple model. From (2.1) and (2.2)

$$\frac{dI}{dt} = \frac{(rS - a)I}{rSI} = -1 + \frac{\rho}{S}, \quad \rho = \frac{a}{r}, \quad (I \neq 0). \tag{2.7}$$

The singularities all lie on the $I = 0$ axis. Integrating the last equation gives the $(I, S)$ phase plane trajectories as

$$I + S\rho \ln S = constant = I(0) + S(0)\rho \ln S(0) \tag{2.8}$$

where we have used the initial conditions. Note that with (2.3), all initial values $S(0)$ and $I(0)$ satisfy $I(0) + S(0) = N$ since $R(0) = 0$ and so for $t > 0$, $0 \leq S + I < N$. If an epidemic exists we would like to know how severe it will be. From (2.5) the maximum $I$ , $I_{max}$ , occurs at $S = \rho$ where $dI/dt = 0$. From (2.8) , with $S = \rho$,

$$\begin{aligned} I_{max} &= \rho \ln \rho - \rho + I(0) + S(0) - \rho \ln S(0) \\ &= I(0) + [S(0) - \rho] + \rho \ln \frac{\rho}{S(0)} \\ &= N - \rho + \rho \ln \frac{\rho}{S(0)} \end{aligned} \tag{2.9}$$

For any initial values $I(0)$ and $S(0) > \rho$, the phase trajectory starts with $S > \rho$ and we see that $I$ increases from $I(0)$ and hence an epidemic ensues. It may not necessarily be a severe epidemic as is the case if $I(0)$ is close to $I_{max}$. If $S(0) < \rho$ then $I$ decreases from $I(0)$ and no epidemic occurs. Since the axis $I = 0$ is a line of singularities, on all trajectories $I \to 0$ as $t \to \infty$. From 2.1, $S$ decreases since $dS/dt < 0$ for $S = 0$, $I = 0$. From (2.1),

$$\begin{aligned} \frac{dS}{dR} &= -\frac{S}{\rho} \\ \Rightarrow \quad S = S(0)e^{-R/\rho} &\geq S(0)e^{-N/\rho} > 0 \\ \Rightarrow \quad 0 < S(\infty) &\leq N. \end{aligned} \tag{2.10}$$

In fact, $0 < S(\infty) < \rho$. Since $I(\infty) = 0$, (2.2) implies that $R(\infty) = NS(\infty)$. Thus, from (2.10),

$$S(\infty) = S(0)e^{\frac{R(\infty)}{\rho}} = S(0)e^{-\frac{N-S(\infty)}{\rho}} \tag{2.11}$$

and so $S(\infty)$ is the positive root $0 < z < \rho$ of the transcendental equation

$$S(0)e^{-\frac{Nz}{\rho}} = z. \tag{2.12}$$

We then get the total number of susceptibles who catch the disease in the course of the epidemic as

$$I_{total} = I(0) + S(0) - S(\infty), \tag{2.13}$$

where $S(\infty)$ is the positive solution $z$ of (2.12). An important implication of this analysis, namely, that $I(t) \to 0$ and $S(t) \to S(\infty) > 0$, is that the disease dies out from a lack of infectives and not from a lack of susceptibles. The threshold result for an epidemic is directly related to the relative removal rate, $\rho$: if $S(0) > \rho$ an epidemic ensues whereas it does not if $S(0) < \rho$. For a given disease, the relative removal rate varies with the community and hence determines whether an epidemic may occur in one community and not in

another. The number of susceptibles $S(0)$ also plays a major role, of course. For example, if the density of susceptibles is high and the removal rate, a, of infectives is low (through ignorance, lack of medical care, inadequate isolation and so on) then an epidemic is likely to occur. Expression (2.9) gives the maximum number of infectives while (2.13) gives the total number who get the infection in terms of $\rho(= a/r)$, $I(0)$, $S(0)$ and $N$. In most epidemics it is difficult to determine how many new infectives there are each day since only those that are removed, for medical aid or whatever, can be counted. Public Health records generally give the number of infectives per day, week or month. So, to apply the model to actual epidemic situations, in general we need to know the number removed per unit time, namely, $dR/dt$, as a function of time. From (2.10), (2.2) and (2.1) we get an equation for $R$ alone; namely,

$$\frac{dR}{dt} = aI = a(N - R - S) = a[N - R - S(0)e^{-R/\rho}], \quad R(0) = 0, \quad (2.14)$$

which can only be solved analytically in a parametric way: the solution in this form however is not particularly convenient. Of course, if we know $a$, $r$, $S(0)$ and $N$ it is a simple matter to compute the solution numerically. Usually we do not know all the parameters and so we have to carry out a best fit procedure assuming, of course, the epidemic is reasonably described by such a model. In practice, however, it is often the case that if the epidemic is not large, $R/\rho$ is small, at least $R/\rho < 1$. Following Kermack and McKendrick [9] we can then approximate (2.14) by

$$\frac{dR}{dt} = a\left\{N - S(0) + \left[\frac{S(0)}{\rho} - 1\right]R - \frac{S(0)R^2}{2\rho^2}\right\}. \quad (2.15)$$

Factoring the right-hand side quadratic in $R$, we can integrate this equation to get, after some elementary but tedious algebra, the solution

$$\begin{aligned} R(t) &= \frac{r^2}{S(0)}\left\{\left[\frac{S(0)}{\rho} - 1\right] + \alpha \tanh\left(\frac{\alpha a t}{2} - \phi\right)\right\} \\ \alpha &= \sqrt{\left[\frac{S(0)}{\rho} - 1\right]^2 + \frac{2S(0)[N - S(0)]}{\rho^2}}, \\ \phi &= \frac{\tanh^{-1}\left(\frac{S(0)}{\rho}\right)}{\alpha}. \end{aligned} \quad (2.16)$$

The removal rate is then given by

$$\frac{dR}{dt} = \frac{a\alpha^2\rho^2}{2S(0)} \operatorname{sech}^2\left(\frac{\alpha a t}{2} - \phi\right), \quad (2.17)$$

which involves only 3 parameters, namely, $a\alpha^2\rho^2/2S(0)$, $\alpha a$ and $\phi$. With epidemics which are not large, it is this function of time which we should fit

to the public health records. On the other hand, if the disease is such that we know the actual number of the removed class then it is $R(t)$ in (2.16) we should use. If $R/\rho$ is not small, however, we must use the differential equation (2.14) to determine $R(t)$.

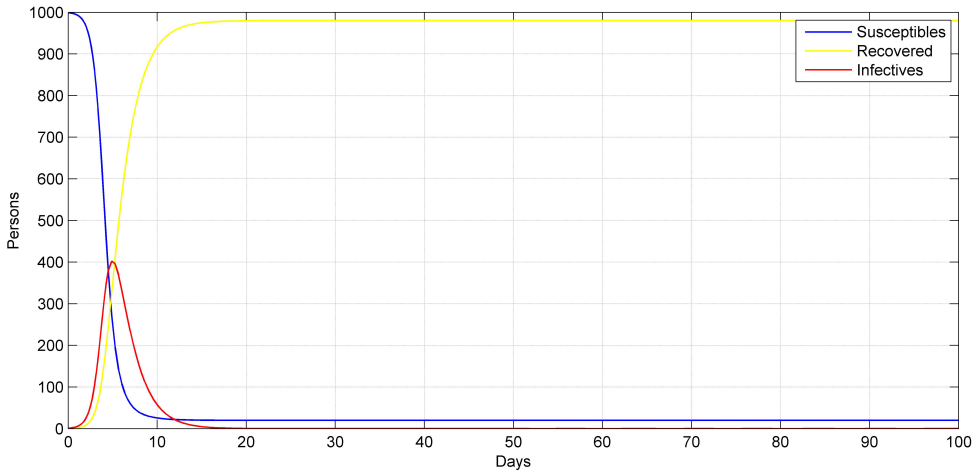



Figure 2.2: Typical situation of infective disease dynamics. Parameter values are: $r = 2.18 * 10^{-3}$, $N = 1000$, $\rho = 202$, $S(0) = 999$, $I(0) = 1$.

## 2.2 Sexually transmitted diseases

In this section we present a simple classical epidemic model which incorporates some of the basic elements in the heterosexual spread of venereal diseases. We have in mind such diseases as gonorrhea and AIDS. The monograph by Hethcote and Yorke [1] is still a good survey of models used for the spread and control of gonorrhea. They show how models and data can be used to advantage, the conclusions they arrived at are specifically aimed at public health workers. For the model here we assume there is uniformly promiscuous behaviour in the population we are considering. As a simplification we consider only heterosexual encounters. The population consists of two interacting classes, males and females, and infection is passed from a member of one class to the other. It is a criss-cross type of disease in which each class is the disease host for the other. In all of the models we have assumed homogeneous mixing between certain population subgroups. Dietz and Hadeler [7], for example, considered epidemic models for STDs in which there is heterogeneous mixing. More complex models can include the pairing of two susceptibles, which confers temporary immunity, several subgroups and so on. We discuss a multi-group example later in this section.

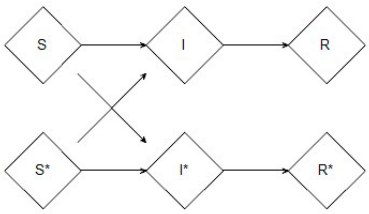



Figure 2.3

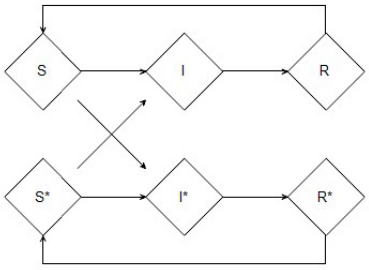



Figure 2.4

Criss-cross infection is similar in many ways to what goes on in malaria and bilharzia, for example, where two criss-cross infections occur. Since the incubation period for venereal diseases is usually quite shortin gonorrhea, for example, it is three to seven dayswhen compared to the infectious period, we use an extension of the simple epidemic model in 2.1. We divide the promiscuous male population into susceptibles, $S$, infectives, $I$, and a removed class, $R$; the similar female groups we denote by $S^*$, $I^*$ and $R^*$. If we do not include any transition from the removed class to the susceptible group, the infection dynamics is schematically described in figure 2.3. Here $I^*$ infects $S$ and $I$ infects $S^*$. As we noted above, the contraction of gonorrhea does not confer immunity and so an individual removed for treatment becomes susceptible again after recovery. In this case a better dynamics flow diagram for gonorrhea is represented in figure 2.4.

An even simpler version involving only susceptibles and infectives is shown in figure 2.5 which, by way of illustration, we now analyse. It is a criss-cross SI model. We take the total number of males and females to be constant and equal to $N$ and $N^*$ respectively. Then,

$$S(t) + I(t) = N, \quad S^*(t) + I^*(t) = N^* \tag{2.18}$$

As before we now take the rate of decrease of male susceptibles to be proportional to the male susceptibles times the infectious female population with a similar form for the female rate. We assume that once infectives have

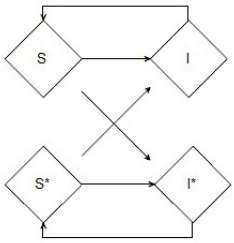



Figure 2.5

recovered they rejoin the susceptible class. A model for criss-cross SI is then (2.18) together with

$$\begin{aligned} \frac{dS}{dt} &= -rSI^* + aI, \quad \frac{dS^*}{dt} = -r^*S^*I + a^*I^* \\ \frac{dI}{dt} &= rSI^* - aI, \quad \frac{dI^*}{dt} = r^*S^*I - a^*I^*, \end{aligned} \tag{2.19}$$

where $r$,$a$, $r^*$ and $a^*$ are positive parameters. We are interested in the progress of then disease given initial conditions $S(0)$, $I(0)$, $S^*(0)$, $I^*(0)$. Although (2.19) is a 4th-order system, with (2.18) it reduces to a 2nd-order system in either $S$ and $S^*$ or $I$ and $I^*$. In the latter case we get

$$\frac{dI}{dt} = rI^*(N-I) - aI, \quad \frac{dI^*}{dt} = r^*I(N^* - I^*) - a^*I^*, \tag{2.20}$$

which can be analysed in the $(I, I^*)$ phase plane in the standard way. The equilibrium points, that is, the steady states of (2.20), are $I = 0 = I^*$ and

$$I_s = \frac{NN^* - \rho\rho^*}{\rho + N^*}, \quad I_s^* = \frac{NN^* - \rho\rho^*}{\rho^* + N}, \quad \rho = \frac{a}{r}, \quad \rho^* = \frac{a^*}{r^*}. \tag{2.21}$$

Thus nonzero positive steady state levels of the infective populations exist only if $NN^*/\rho\rho^* > 1$: this is the threshold condition somewhat analogous to that found in 2.1. We now expect that, if the positive steady state exists then the zero steady state is unstable. This is indeed the case. The eigenvalues $\lambda$ for the linearisation of (2.20) about $I = 0 = I^*$ are given by

$$\begin{aligned} \begin{vmatrix} -a-\lambda & rN \\ r^*N^* & -a^*-\lambda \end{vmatrix} &= 0 \\ \Rightarrow 2\lambda = -(a+a^*) \pm \sqrt{(a+a^*)^2 + 4aa^*\left(\frac{NN^*}{\rho\rho*} - 1\right)}&. \end{aligned} \tag{2.22}$$

So, if the threshold condition $NN^*/\rho\rho^* > 1$ holds, $\lambda_1 < 0 < \lambda_2$ and the origin is a saddle point in the $(I, I^*)$ phase plane. If the threshold condition

is not satisfied, that is, $(0 <)NN^*/\rho\rho^* < 1$, then the origin is stable since both $\lambda < 0$. In this case positive $I_s$ and $I_s^*$ do not exist. If $I_s$ and $I_s^*$ exist, meaning in the context here that they are positive, then linearising (2.20) about it, the eigenvalues $\lambda$ satisfy

$$\begin{vmatrix} -a - rI_s^* - \lambda & rN - rI \\ r^*N^* - r^*I^* & -a^* - r^*I_s^* - \lambda \end{vmatrix} = 0; \tag{2.23}$$

that is,

$$\lambda^2 + \lambda[a + a^* + rI_s^* + r^*I_s] + [a^*rI_s^* + ar^*I_s + rr^*(I^*N + IN^*) + aa^* - rr^*NN^*] = 0, \tag{2.24}$$

the solutions of which have $\Re[\lambda] < 0$ and so the positive steady state $(I_s, I^*s)$ in (2.21) is stable. The threshold condition for a nonzero steady state infected population is $NN^*/\rho\rho^* = (rN/a)(r^*N^*/a^*) > 1$. We can interpret each term as follows. If every male is susceptible then $rN/a$ is the average number of males contacted by a female infective during her infectious period; a reciprocal interpretation holds for $r^*N^*/a^*$. These quantities, $rN/a$ and $r^*N^*/a^*$, are the maximal male and female contact rates respectively.

### 2.2.1 Multi-Group Model for Gonorrhea and Its Control

Although the SI model in the last section is a particularly simple one, it is not too unrealistic. In the case of gonorrheal infections, however, it neglects many relevant factors. For example, as already mentioned a large proportion of females, although infected and infectious, show no obvious symptoms; that is, they form an asymptomatic group. There are, in fact, various population subgroups. For example, we could reasonably have susceptible, symptomatic, treated infective and untreated infective groups. Hethcote and Yorke [1] proposed and analysed an 8-group model for gonococcal infections consisting of

**1 - (2)** sexually very active women (men) who are asymptomatic when infectious,

**3 - (4)** sexually active women (men) who are asymptomatic when infectious,

**5 - (6)** sexually very active women (men) who are symptomatic when infectious,

**7 - (8)** sexually active women (men) who are symptomatic when infectious.

If the total populations of active male and female are $N$ and $N^*$, assumed constant, we can normalise the various group populations as fractions of $N$

and $N^*$. Denote the groups of women with indices 1, 3, 5, 7 and the men with indices 2, 4, 6, 8. Then if $N_i$, $i = 1, 2, \ldots, 8$ denote the normalised populations

$$N_1 + N_3 + N_5 + N_7 = 1, \quad N_2 + N_4 + N_6 + N_8 = 1. \tag{2.25}$$

Since neither immunity nor resistance is acquired in gonococcal infections we consider only two classes, susceptibles and infectives. If $I_i(t), i = 1, 2, \ldots, 8$ denote the fractions infectious at any time $t$, the fractional numbers of susceptibles at that time are then $1 - I_i(t), i = 1, 2, \ldots, 8$. We again assume homogeneous mixing. For each group let $D_i$ be the mean length of time (in months) of the infection in group $i$. Then, there is a $1/D_i$ chance of an infective recovering each month. This implies that the removal rate per month is $I_i/D_i$. Let $L_{ij}$ be the number of effective contacts per month of an infective in group $j$ with an individual in group $i$. Since the model here considers only heterosexual (as opposed to homosexual) contacts we have $L_{ij} = 0$ if $i + j$ even. The matrix $[L_{ij}]$ is called the contact matrix. Although there are seasonable variations in the $L_{ij}$ we take them to be constant here. Then the average number of susceptibles infected per unit time (month) in group $i$ by group $j$ is $L_{ij}(1 - I_i)$. Thus the model differential equation system is

$$\frac{d(N_i I_i)}{dt} = \sum_{j=1}^{8} L_{ij}(1 - I_i)N_j I_j - \frac{N_i I_i}{Di} \tag{2.26}$$

with given initial conditions $I_i(0)$. Here the first term is the rate of new infectives, the second is the incidence rate of new infectives, the third is the recovery rate of infectives. By considering the linearisation about the nonzero steady state the effect of varying the parameters can be assessed and hence the effects of various control strategies. This model is analysed in detail by [26]. Major aims in control include of course the reduction in incidence and an increase in detection, each of which affects the long term progress of the spread of the disease. So, screening, detection and treatment of infectives is the major first step in control. The research [1] compares various control methods for gonorrhea; it also has references to other models which have been proposed. As an example, suppose $C$ is a parameter proportional to the number of women screened and $CR_i$ is the rate at which infected women are detected in group $i$. Let $EP_i$ be the general supplementary detection rate where $E$ is a measure of the effort put in and $P_i$ is the population of a group $i$: $E$ depends on the control strategy. Then, in place of (2.26) we have the control model

$$\frac{d(N_i I_i)}{dt} = \sum_{j=1}^{8} L_{ij}(1 - I_i)N_j I_j - \frac{N_i I_i}{Di} - CR_i - EP_i \tag{2.27}$$

Different control methods imply different $R_i$ and $P_i$. Suppose there is general screening of women. On the basis that the number of infected women

detected is directly proportional to the number infected and the supplementary programme is general screening of the women population, we have

$$P_i = R_i = I_i N_i,\ i = 1, 3, 5, 7; \quad P_i = R_i = 0,\ i = 2, 4, 6, 8. \tag{2.28}$$

If the programme is for men, the odd and even number range is interchanged. The cost and social range of screening are not negligible factors in the practical implementation of such programmes. The political and sociological considerations can also be rather sensitive. It should be emphasised again, that venereal disease models, which are to be used in control programmes, must have a realistic validation, which can only come from a comparison of their solutions and predictions with actual data. This should, of course, apply to all disease control models.

# Chapter 3

# HIV transmission models

## 3.1 Simple model for HIV Infection in a Homosexual Population

Here we are interested in the development of an AIDS epidemic in a homosexual population. Let us assume there is a constant immigration rate B of susceptible males into a population of size $N(t)$. Let $X(t)$, $Y(t)$, $A(t)$ and $Z(t)$ denote respectively the number of susceptibles, infectious males, AIDS patients and the number of HIV-positive or seropositive men who are noninfectious. We assume susceptibles die naturally at a rate $\mu$; if there were no AIDS, the steady state population would then be $N^* = B/\mu$. We assume AIDS patients die at a rate $d$: $1/d$ is of the order of months to years, more often the latter. Figure 3.1 is a flow diagram of the disease on which we base our model. As in previous models we consider uniform mixing. A reasonable first model system, based on the flow diagram in figure 3.1, is then

$$\begin{aligned}
\frac{dX}{dt} &= B - \mu X - \lambda c X, \quad \lambda = \frac{\beta Y}{N}, \\
\frac{dY}{dt} &= \lambda c X - (\nu + \mu) Y, \\
\frac{dA}{dt} &= p\nu Y - (d + \mu) A, \\
\frac{dZ}{dt} &= (1 - p)\nu Y - \mu Z, \\
N(t) &= X(t) + Y(t) + Z(t) + A(t).
\end{aligned} \tag{3.1}$$

Here $B$ is the recruitment rate of susceptibles, $\mu$ is the natural (non-AIDS-related) death rate, $\lambda$ is the probability of acquiring infection from a randomly chosen partner ($\lambda = \beta Y/N$, where $\beta$ is the transmission probability), $c$ is the number of sexual partners, $d$ is the AIDS-related death rate, $p$ is the proportion of HIV-positives who are infectious and $\nu$ is the rate of conversion from infection to AIDS here taken to be constant. 1/v, equal to D say,

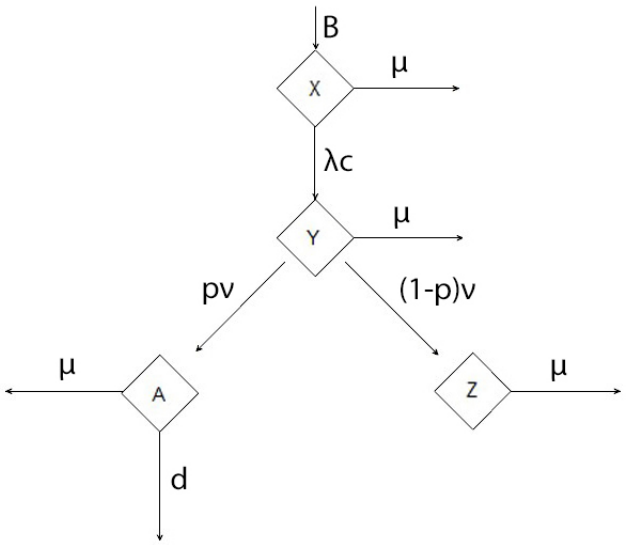



Figure 3.1

is then the average incubation time of the disease. (Actually $\lambda$ here is more appropriately $\beta Y/(X+Y+Z)$ but $A$ is considered small in comparison with $N$). Note that in this model the total population $N(t)$ is not constant, as was the case in the epidemic models in 2.1. If we add equations (3.1) we get

$$\frac{dN}{dt} = B - \mu N - dA. \tag{3.2}$$

An epidemic ensues if the basic reproductive rate $R_0 > 1$: that is, the number of secondary infections which arise from a primary infection is greater than 1. If, at $t = 0$, an infected individual is introduced into an otherwise infection-free population of susceptibles, we have initially $X \approx N$ and so near $t = 0$,

$$\frac{dY}{dt} \approx (\beta c - \nu - \mu)Y \approx \nu(R_0 - 1)Y \tag{3.3}$$

since the average incubation time, $1/\nu$, from infection to development of the disease, is very much shorter than the average life expectancy, $1/\mu$, of a susceptible; that is, $\nu \gg \mu$. Thus the approximate threshold condition for an epidemic to start is, from the last equation,

$$R_0 \approx \frac{\beta c}{\nu} > 1. \tag{3.4}$$

Here the basic reproductive rate $R_0$ is given in terms of the number of sexual partners $c$, the transmission probability $\beta$ and the average incubation time

of the disease $1\nu$. When an epidemic starts, the system (3.1) evolves to a steady state given by

$$\begin{aligned} X^* &= \frac{(\nu+\mu)N^*}{c\beta}, \\ Y^* &= \frac{(d+\mu)(B-\mu N^*)}{p\nu d}, \\ Z^* &= \frac{(1-p)(d+\mu)(B-\mu N^*)}{pd\mu}, \\ A^* &= \frac{B-\mu N^*}{d}, \\ N^* &= \frac{B\beta[\mu(\nu+d+\mu)+\nu d(1-p)]}{(v+\mu)[b(d+\mu)-p\nu]}. \end{aligned} \tag{3.5}$$

If we linearise about this steady state it can be shown that $(X, Y, Z, A)$ tends to $(X^*, Y^*, Z^*, A^*)$ in a damped oscillatory manner with a period of oscillation given in terms of the model parameters. With typical values for the parameters at the time [4] the period of epidemic outbreaks was of the order of 30 to 40 years. It is unrealistic to think that the parameters characterising social behaviour associated with the disease would remain unchanged over that time span. The life expectancy of people with HIV has dramatically increased since then, due mainly of course, to new medicines such as AZT and protease inhibitors. We can get some interesting information from an analysis of the system during the early stages of an epidemic. Here the population consists of almost all susceptibles and so $X \approx N$ and the equation for the growth of the infectious, that is, HIV-positive, Y -class is approximated by (3.3), the solution of which is

$$Y(t) = Y(0)e^{\nu(R_0-1)t} = Y(0)e^{rt}, \tag{3.6}$$

where $R_0$ is the basic reproductive rate, $1/\nu$ is the average infectious period and $Y(0)$ is the initial number of infectious people introduced into the susceptible population. The intrinsic growth rate, $r = \nu(R_0 - 1)$, is positive only if an epidemic exists ($R_0 > 1$). From (3.6) we can obtain the doubling time for the epidemic, that is, the time $t_d$ when $Y(t_d) = 2Y(0)$, as

$$t_d = r^{-1}\ln 2 = \frac{\ln 2}{\nu(R_0-1)}. \tag{3.7}$$

We thus see that the larger the basic reproductive rate $R_0$ the shorter the doubling time. If we substitute (3.6) into equation (3.1) for the AIDS patients, we get

$$\frac{dA}{dt} = p\nu Y(0)e^{rt} - (d+\mu)A. \tag{3.8}$$

Early on in the epidemic there are no AIDS patients, that is, $A(0) = 0$, and so the solution is given by

$$A(t) = p\nu Y(0)\frac{e^{rt} - e^{-(d+\mu)t}}{r + d + \mu}. \tag{3.9}$$

In the following table there are estimates for the model parameters that are used next in our simulations.

| $r$ | $d$ | $\mu$ | $B$ | $\nu$ | $p$ | $c$ |
|---|---|---|---|---|---|---|
| $0.88yr^{-1}$ | $1yr^{-1}$ | $1/32yr^{-1}$ | $13333.3yr^{-1}$ | $0.2yr^{-1}$ | 0.3 | $24yr^{-1}$ |

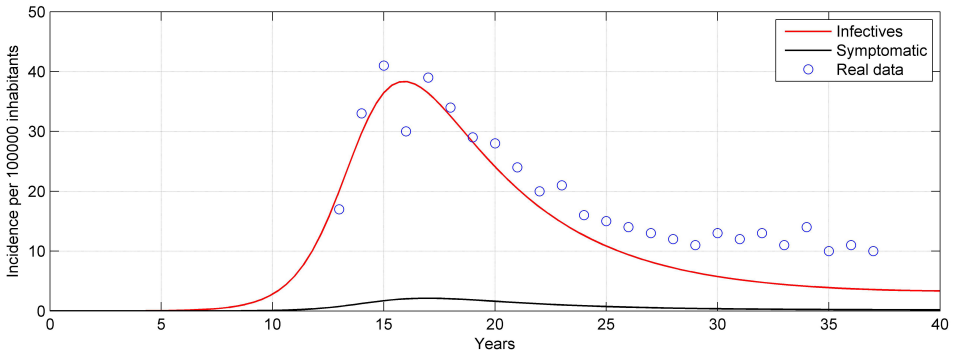



Figure 3.2: Data fits of model (3.1) using data from ISS [27].

With these estimates we then get an approximate doubling time for the HIV-positive class as roughly 9 months. Numerical simulations of the model system of equations (3.1) give a clear picture of the epidemic development after the introduction of HIV into a susceptible homosexual population. Figure 3.2 shows one such simulation: the model predicts that HIV incidence reaches a maximum around 12 to 15 years after the introduction of the virus into the population. It should be kept in mind that this is an early (and now more a pedagogical) model. It is interesting to compare these predictions of the mid-1980s with the situation in 2000. In spite of the simplicity of the models, the results were in line with observation in homosexual communities. More realistic, and not always more complex models, have been proposed such as those discussed below. With the accumulation of more data and information of the epidemic, even more sophisticated models will no doubt be required in the normal progression of realistic modelling. A practical use of good models at any stage is that, among other things, it poses questions which can guide data collection and focus on what useful information can be obtained from sparse or less than complete data. Estimates of epidemic

severity doubling time, and so on, are in themselves of considerable interest and use. The model here is for a homosexual population. Now that the epidemic is very much heterosexual other models are required. The approach described here is a reasonable starting point.

## 3.2 Model for public health educational campaigns

The population of interest is with high HIV/AIDS prevalence due to heterosexual transmission (Sub-Saharan Africa). We classify the sexually active population into four classes: susceptibles $S(t)$, educated $E(t)$, infected $I(t)$, and AIDS cases who are ill or showing AIDS symptoms $A(t)$ at time $t$. It is assumed that, at any moment in time, new recruits enter the sexually active population at a rate $b$. A proportion $\pi$ of these individuals are assumed to be educated (categorized in the $E$ class) and the complementary proportion $(1-\pi)$, are susceptibles (and move to the susceptible class $S$). Sexually mature susceptibles $S$ are also educated at a constant rate $\epsilon$ into the $E$ class of educated individuals. Susceptible individuals acquire infection at a time dependent rate $\lambda_0$. Upon effective contact with an infective individual, a susceptible individual move into the $I$ class of infected individuals. Educated individuals are infected at a rate $(1-\sigma)\lambda_0$, where $\sigma$ is the overall effectiveness of the public health educational campaigns, that is the factor by which the average infection rate of educated individuals is reduced relatively to the infection rate of non-educated individuals. In this context, $0 < \sigma < 1$, the range does not include 0 and 1 because 0 implies that education is useless and 1 implies that education is completely effective. Upon becoming infected with HIV, educated individuals enter the class I of infected individuals. The model assumes a constant incubation period ($\tau > 0$) for both infected susceptible and educated individuals from the time of being infected to the development of AIDS symptoms. In reality $\tau$ varies due to a number of factors (e.g., genetic heterogeneity) and other studies [22] have considered variable incubation period from the time of HIV infection to the development of AIDS. We assume no latent period for HIV since the latent period is negligible compared to the period of infectivity. The natural death rate is assumed to be proportional to the number in each class, $\mu > 0$. AIDS patients have an additional disease-induced mortality rate, $\nu > 0$. The probability that an infected individual remains in the incubation period time $t$ units before developing AIDS is given by a step function with value 1 for $0 \leq t < \tau$ and value zero for $t > \tau$. There is a constant emigration rate $m > 0$ of individuals to other countries except for the AIDS patients. This assumption makes the model more appropriate to

developing countries where a significant proportion of the population emigrate to developed countries for better educational facilities and in search of employment. The probability that an infected individual in the incubation period time $t$ units has survived to develop AIDS is $k = e^{-(m+\mu)\tau}$ for susceptible and educated. Infected individuals progress to AIDS stage at a rate $k\lambda_\tau$ for the susceptibles and $(1-\sigma)k\lambda_\tau$ for the educated individuals, where $\lambda_\tau$ is the average per capita risk of infection. The infection rate $\lambda_i$ for $i = 0$; $\tau$ depends on the probability of transmission per partnership $\beta$, the rate at which an individual acquires new sexual partners $c$ and the proportion of infected individuals in each category. The probability of transmission from an individual in category $I$ to susceptible individuals in category $S$ or $E$ is $\beta$. Assuming homogeneous mixing we have

$$\lambda_i = \frac{\beta c I(t-i)}{N(t-i)}, \quad N(t-i) = S(t-i) + E(t-i) + I(t-i), \quad i = 0, \tau, \tag{3.10}$$

where $N(t-i)$ for $i = 0$; s is the total sexually active population (excluding AIDS patients). A total variable population size is

$$N_T(t) = S(t) + E(t) + I(t) + A(t). \tag{3.11}$$

Educational campaign is intended to reduce the product $\beta c$ to $(1-\sigma)\beta c$, which then reduces the infection rate $\lambda_0$ to $(1-\sigma)\lambda_0$. The model structure is shown in figure 3.3. HIV/AIDS is assumed to have been in the population for at least a time $\tau > 0$, such that initial perturbations or transients have died out. The model equations take the following form for $t > \tau$:

$$\begin{aligned}
\frac{dS(t)}{dt} &= (1-\pi)b - \lambda_0 S(t) - (\epsilon + \mu + m)S(t), \\
\frac{dE(t)}{dt} &= \pi b + \epsilon S(t) - (1-\sigma)\lambda_0 E(t) - (\mu + m)E(t), \\
I(t) &= \int_{t-\tau}^{t} \lambda_0 [S(u) + (1-\sigma)E(u)] e^{(\mu+m)(t-u)}\, du, \\
\frac{dA(t)}{dt} &= k\lambda_\tau [S(t-\tau) + (1-\sigma)E(t-\tau)] - (\mu + \nu)A(t).
\end{aligned} \tag{3.12}$$

It is convenient to shift time by $\tau$, so that system (3.12) holds for a new $t > 0$, with the initial condition for system (3.12) given as

$$S(\theta) = \phi_1(\theta),\ E(\theta) = \phi_2(\theta),\ I(\theta) = \phi_3(\theta),\ A(\theta) = \phi_4(\theta),\ \phi \in [-\tau, 0]. \tag{3.13}$$

The integral in system (3.12) represents the summation over the interval $[t-\tau, t]$ of those individuals who become infectives at time $u \geq 0$ and have neither developed AIDS nor died. For the model to be analyzed, an equivalent delay differential equation should be obtained for standard theorems

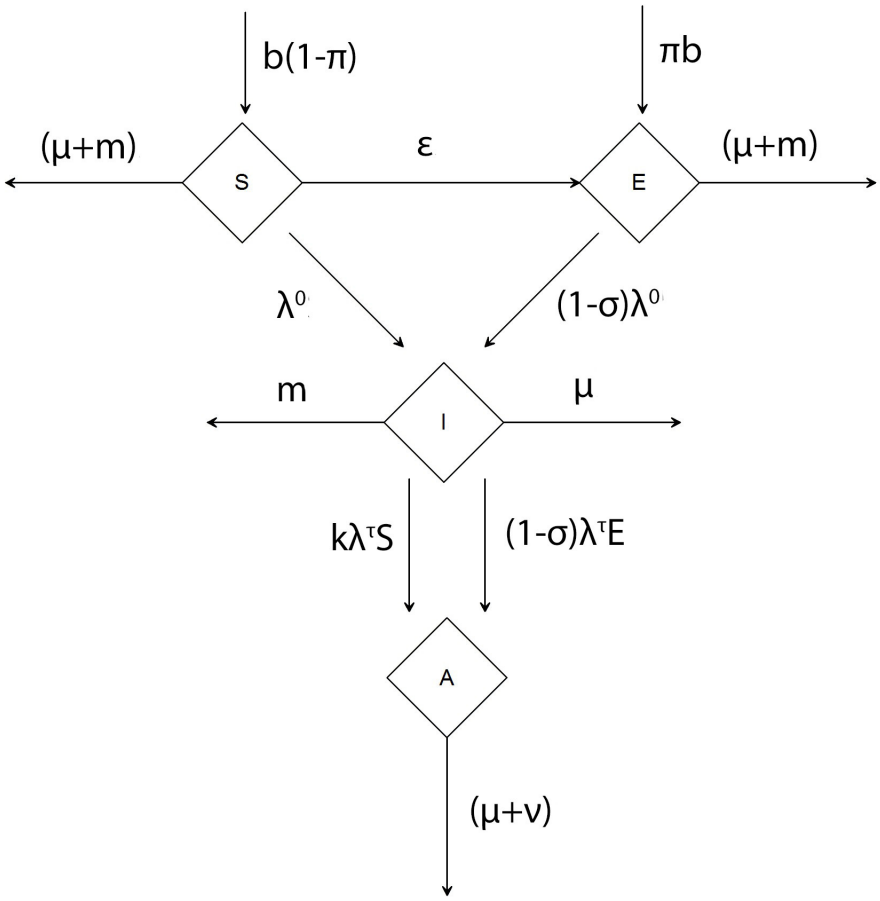



Figure 3.3

to be applied. System (3.12) as a delay differential equation becomes

$$\begin{aligned}
\frac{dS(t)}{dt} &= (1-\pi)b - \lambda_0 S(t) - (\epsilon+\mu+m)S(t),\\
\frac{dE(t)}{dt} &= \pi b + \epsilon S(t) - (1-\sigma)\lambda_0 E(t) - (\mu+m)E(t),\\
\frac{dI(t)}{dt} &= \lambda_0[S(t)+(1-\sigma)E(t)] - k\lambda_\tau[S(t-\tau)+(1-\sigma)E(t-\tau)] - (\mu+m)I(t),\\
\frac{dA(t)}{dt} &= k\lambda_\tau[S(t-\tau)+(1-\sigma)E(t-\tau)] - (\mu+\nu)A(t).
\end{aligned} \tag{3.14}$$

where $k = e^{-(\mu+m)\tau}$ and parameters $\phi, b, \epsilon, m, \mu, \nu, \sigma, \tau, \beta$ and $c \in \mathbb{R}_+$. We state the following theorem whose proof follows from [23].

**Theorem 3.2.1.** *Every solution of the integro-differential system* (3.12)

*satisfies the system* (3.14) *and an additional equation. Conversely, let* $S(t)$, $E(t)$, $I(t)$ *and* $A(t)$ *be a solution of the differential-difference equation system* (3.14), *with* $N_T(t)$ *given by* (3.11), *and initial conditions given on* $[-\tau, 0]$ *stated above. If in addition,*

$$I(0) = \int_{-\tau}^{0} \lambda_0[S(u) + (1-\sigma)E(u)]e^{(\mu+m)(t-u)}\, du, \tag{3.15}$$

*then this solution satisfies the integro-differential equation system* (3.12).

**Lemma 3.2.1.** *System* (3.14) *is dissipative and preserves positively.*

Model system (3.14) describes human population therefore it is very important to prove that all state variables are non-negative for all time. We state theorem 3.2.2 for positivity.

**Theorem 3.2.2.** *Let the initial data be* $S(t) \geq 0$ *on* $[-\tau, 0]$, $E(t) \geq 0$ *on* $[-\tau, 0]$, $I(t) \geq 0$ *on* $[-\tau, 0]$, $A(t) \geq 0$. *Then, solutions of* $S(t)$, $E(t)$, $I(t)$ *and* $A(t)$ *of system* (3.14) *are positive for all* $t > 0$ *(with the compatibility condition* (3.15)*).*

We begin our analysis from model system (3.14) without public health educational campaigns $\epsilon = \pi = \sigma = E = 0$ and this reduces to the following system of equations:

$$\begin{aligned}
\frac{dS(t)}{dt} &= b - \beta\frac{S(t)I(t)}{N(t)} - (\mu+m)S(t),\\
\frac{dI(t)}{dt} &= \beta\frac{S(t)I(t)}{N(t)} - \beta ck\frac{S(t-\tau)I(t-\tau)}{N(t-\tau)} - (\mu+m)I(t),\\
\frac{dA(t)}{dt} &= \beta ck\frac{S(t-\tau)I(t-\tau)}{N(t-\tau)} - (\mu+\nu)A(t).
\end{aligned} \tag{3.16}$$

where $N(t) = S(t) + I(t)$ and $k = e^{-(\mu+m)\tau}$. All parameters for the model system (3.16) are assumed to be non-negative for all time $t > 0$. The model has a disease-free equilibrium

$$\mathscr{E}_0 = (\frac{b}{m+\mu}, 0, 0). \tag{3.17}$$

The basic reproductive number $R_0$ for system (23) is

$$\int_0^{\tau} \beta c e^{-(m+\mu)t} = \frac{\beta c(1-k)}{m+\mu}\, dt, \tag{3.18}$$

and this defines the number of new infections generated by a single infected individual in a completely susceptible population [22]. Mathematically, $R_0$ is defined as the spectral radius. The basic reproductive number $R_0$ measures the power of a disease to invade a population under conditions that

facilitate maximal growth. Since 1911, control and intervention efforts have been based on the concept of the basic reproductive number, introduced by Kermack and McKendrick [9]. Next, we consider the model with public health educational campaigns.

Model system (3.14) with public health educational campaigns has a disease-free equilibrium given by

$$\mathscr{E}_0 = (\bar{S}, \bar{E}, \bar{I}, \bar{A}) = (\frac{(1-\pi)b}{m+\epsilon+\mu}, \frac{b\epsilon + b\pi(m+\mu)}{(m+\mu)(m+\epsilon+\mu)}, 0, 0). \tag{3.19}$$

The education-induced basic reproductive number for model system (3.14), denoted by $\mathscr{R}_E$ with the subscript $E$ indicating education, is

$$\mathscr{R}_E = \int_0^\tau \beta c \frac{\bar{S} + (1-\sigma)\bar{E}}{\bar{S}+\bar{E}} e^{-(m+\mu)t}\, dt = \mathscr{R}_0 \frac{(1-\pi\sigma)(m+\mu) + (1-\sigma)\epsilon}{m+\mu+\epsilon} \tag{3.20}$$

where

$$\mathscr{R}_0 = \frac{\beta c(1-k)}{m+\mu}, \tag{3.21}$$

is the basic reproductive number of model system (3.14) when there are no public health educational campaigns, that is $\epsilon = \pi = \sigma = E = 0$, in which case $\mathscr{R}_E$ reduces to $\mathscr{R}_0$. Note that $\mathscr{R}_0 < 1$, therefore $\mathscr{R}_E < 1$ irrespective of the values of $\pi$, $\sigma$ and $\epsilon$. Biologically speaking, this measures the number of new secondary infections generated by a single HIV-infected individual in a community with no public health educational campaigns as a control strategy for HIV/AIDS. We state theorem 3.2.3 for the stability of system (3.14) at $\mathscr{E}_0$.

**Theorem 3.2.3.** *The model system* (3.14) *always has the disease-free equilibrium* $\mathscr{E}_0$. *If* $\mathscr{R}_E < 1$, *the disease-free equilibrium is locally asymptotically stable in* $\Phi$.

In order to study the effects of public health educational campaigns in slowing the development of HIV/AIDS epidemic in a community, we investigate the basic reproductive number which is a measure of the power of a disease to invade a population under conditions that facilitate maximal growth. We rewrite the education-induced reproductive number as

$$\mathscr{R}_E = \mathscr{R}_0 H_1, \tag{3.22}$$

where

$$H_1 = \frac{(1-\pi\sigma)(m+\mu) + (1-\sigma)\epsilon}{m+\mu+\epsilon} \tag{3.23}$$

Note that $H_1$ is the factor by which public health educational campaigns reduce the number of secondary HIV infectives if adopted in a community.

If $\mathscr{R}_0 < 1$, HIV/AIDS cannot develop into an epidemic and public health educational campaigns may not be necessary. For $\mathscr{R}_0 > 1$ we want to determine the necessary condition for slowing the development of HIV/AIDS. We have

$$\Delta_E := \mathscr{R}_0 - \mathscr{R}_E = \mathscr{R}_0\left[1 - \frac{(1-\pi\sigma)(m+\mu)+(1-\sigma)\epsilon}{m+\mu+\epsilon}\right] = \mathscr{R}_0(1-H_1) \tag{3.24}$$

for which $\Delta_E > 0$ is expected for slowing down the spread of the HIV/AIDS in a community and is satisfied for all $0 < \epsilon, \pi, \sigma < 1$. We note that under this condition the factor $H_1$ multiplying $\mathscr{R}_0$ is less than unity ($H_1 < 1$), indicating that public health educational campaigns have the capability of slowing down HIV/AIDS if adopted in a community. Differentiating $\mathscr{R}_E$ partially with respect to $\pi, \epsilon$ and $\sigma$ we obtain

$$\begin{aligned}
\frac{\partial \mathscr{R}_E}{\partial \pi} &= -\frac{\sigma(m+\mu)}{m+\epsilon+\mu}\mathscr{R}_0, \\
\frac{\partial \mathscr{R}_E}{\partial \epsilon} &= -\frac{\sigma(1-\pi)(m+\mu)}{(m+\epsilon+\mu)^2}\mathscr{R}_0, \\
\frac{\partial \mathscr{R}_E}{\partial \sigma} &= -\frac{\pi(m+\mu)+\epsilon}{m+\epsilon+\mu}\mathscr{R}_0.
\end{aligned} \tag{3.25}$$

From (3.25) we see that a necessary condition for slowing down the development of HIV/AIDS epidemic are $\sigma > 0$ and $\pi < 1$. The conditions

$$\Delta_E > 0, \quad \frac{\partial \mathscr{R}_E}{\partial \pi} < 0, \quad \frac{\partial \mathscr{R}_E}{\partial \epsilon} < 0, \quad \frac{\partial \mathscr{R}_E}{\partial \sigma} < 0 \tag{3.26}$$

for slowing down the epidemic are satisfied for all $0 < \epsilon, \pi, \sigma < 1$. Setting the education-induced reproductive number $\mathscr{R}_E = 1$ and solving for $\pi, \sigma$ and $\epsilon$ gives the threshold proportion of educated adolescence, education rate for susceptible individuals and education efficacy respectively as follows:

$$\begin{aligned}
\pi_c &= \frac{1}{\sigma}\left[1 - \frac{(m+\mu)+\sigma\epsilon}{\mathscr{R}_0(m+\mu)}\right], \\
\epsilon_c &= \frac{m+\mu}{\sigma}[\mathscr{R}_0(1-\pi\sigma)-1], \\
\sigma_c &= \frac{(m+\mu)(\mathscr{R}_0-1)}{\mathscr{R}_0\pi(m+\mu)+\epsilon}.
\end{aligned} \tag{3.27}$$

Public health educational campaigns on HIV/AIDS would succeed in controlling the epidemic $\mathscr{R}_E < 1$ if $\pi > \pi_c, \epsilon > \epsilon_c$ and $\sigma > \sigma_c$. The threshold values, $\pi_c$ exist when $\sigma > 0$ and

$$\frac{m+\mu+\sigma\epsilon}{\mathscr{R}_0(m+\mu)} < 1 \tag{3.28}$$

$\epsilon_c$ exist when $\sigma > 0$ and $\mathscr{R}_0(1 - \pi\sigma) > 1$ and $\sigma_c$ exist when $\mathscr{R}_0 > 1$ and $\mathscr{R}_0\pi(m + \mu) + \epsilon > 0$. We note that $\pi_c$ and $\epsilon_c$ are decreasing functions of $\sigma$ (effectiveness of education). Thus, if education is not very effective (small $\sigma$), high values of $\pi_c$ and $\epsilon_c$ are required. We also note that $\pi_c$ and $\epsilon_c$ are increasing functions of $\mathscr{R}_0$, thus for populations where $\mathscr{R}_0$ is large, high values of $\pi_c$ and $\epsilon_c$ are required to control HIV/AIDS using public health educational campaigns. We conclude that in population where education is not effective or $\mathscr{R}_0$ is large, HIV/AIDS may not be controlled using public health educational campaigns alone because the corresponding values of $\pi_c$ and $\epsilon_c$ required are high and perhaps unattainable for such populations. The education-induced basic reproductive number ($\mathscr{R}_E$) can be written as $\mathscr{R}_E(\pi, \epsilon)$ to emphasize the role of educating sexually immature and sexually mature individuals in controlling HIV/AIDS. We note that $\mathscr{R}_E(\pi, \epsilon) < \mathscr{R}_E(0, \epsilon)$ and $\mathscr{R}_E(\pi, \epsilon) < \mathscr{R}_E(\pi, 0)$ suggest that educating sexually immature and sexually mature individuals concurrently is more effective in slowing down HIV/AIDS than concentrating on a cohort public health educational campaign of either the sexually immature or sexually mature individuals only.

From theorem 3.2.3, we note that if the disease-free equilibrium exists, it is locally asymptotically stable if and only if $\mathscr{R}_E < 1$. However, the disease-free equilibrium may not be globally asymptotically stable even if $\mathscr{R}_E < 1$. In the presence of public health educational campaigns the basic reproductive number ($\mathscr{R}_E$ in this case) does not completely describe the equilibrium behaviour of the model. There is the possibility of backward bifurcation (bistability), where a stable endemic state co-exist with the disease-free equilibrium when $\mathscr{R}_E < 1$. The public health implication of backward bifurcation is that the classical requirement of having the basic reproductive number less than unity, although necessary, is no longer sufficient for disease control.

| $b$ | $\mu$ | $\nu$ | $m$ | $\tau$ | $\pi$ | $\epsilon$ | $c$ | $\sigma$ |
|---|---|---|---|---|---|---|---|---|
| $0.029yr^{-1}$ | $0.02yr^{-1}$ | $0.333yr^{-1}$ | $0.01yr^{-1}$ | $8yr$ | 0.2 | $0.15yr^{-1}$ | $3yr^{-1}$ | 0.6 |
| $0.029yr^{-1}$ | $0.02yr^{-1}$ | $0.333yr^{-1}$ | $0.01yr^{-1}$ | $8yr$ | 0.4 | $0.3yr^{-1}$ | $3yr^{-1}$ | 0.7 |

Table 3.1

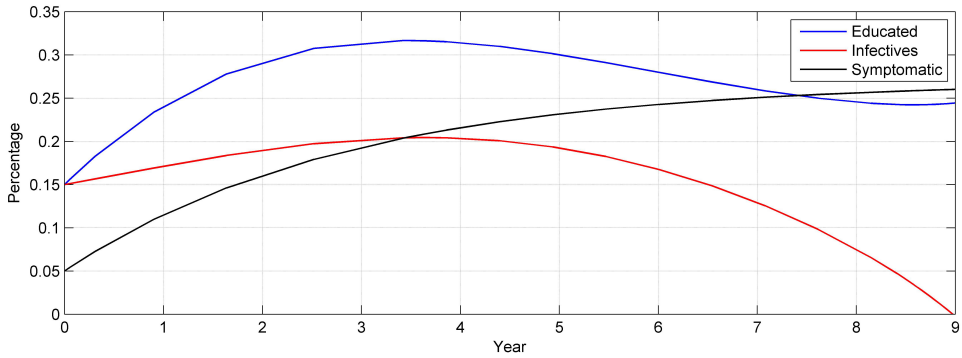



Figure 3.4: Simulation for model (3.14) using parameter values in table 3.1

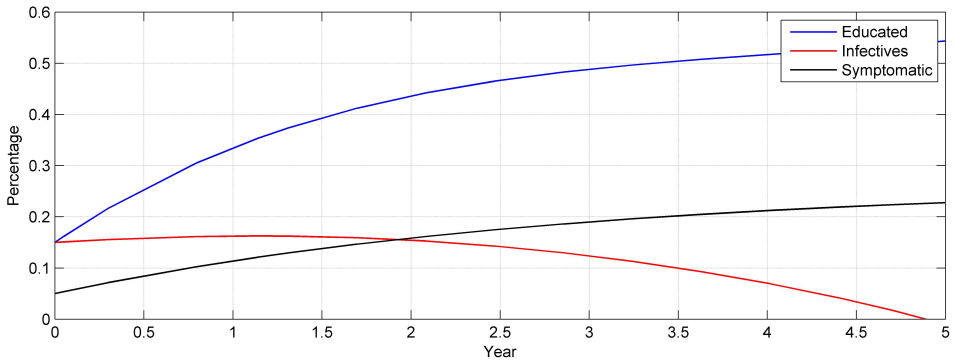



Figure 3.5: Increasing rate of educating adults, efficiency of education, and proportion of individual educated, number of infected dramatically decreases after five years.

# Chapter 4

# HIV pathogenesis models

In this chapter we will consider deterministic and stochastic models for the analysis of pathogenesis of HIV-1 virus. Deterministic models can include time delay and we will see how this influences final results of simulations. Stochastic model that will be studied allows for the possibility of viral extinction under a given threshold of viral volumes at the beginning of infection. We show for each model a Matlab® simulation.

## 4.1 Deterministic models

### 4.1.1 Effector model

With this in mind we have the following set of equations as our basic model,

$$\begin{aligned} \frac{dT}{dt} &= s - dT - kVT, \\ \frac{dT^*}{dt} &= kVT - \delta T^* - d_x E T^*, \\ \frac{dV}{dt} &= N\delta T^* - cV, \\ \frac{dE}{dt} &= pT^* - d_E E. \end{aligned} \tag{4.1}$$

The initial conditions are $T(0), T^*(0), V(0), E(0) = 0$. Here $T, T^*, V$ and $E \in \mathbb{R}_+$ and all parameters are in $\mathbb{R}_+$. The constant $s$ represents a source of healthy cells and $d$ is their death rate. $k$ is the infectivity rate, $\delta$ is the death rate of the infected cells and $d_x$ represents the effectiveness of the immune response. $N$ is the number of virus particles produced per infected cell and $c$ is the viral clearance rate. The inclusion of the term $d_x E T^*$, allows for the removal of productively infected T cells due to a cell mediated immune response. Model (4.1) has two steady states: the infection-free steady state $\mathscr{E}_0 = (\bar{T}, 0, 0, 0)$ with $\bar{T} = s/d$ and the infected steady state

$\mathscr{E}_1 = (\bar{T}, \bar{T}^*, \bar{V}, \bar{E})$ where

$$\begin{aligned}
\bar{T} &= \frac{c^2 d_x p}{2k^2 N^2 \delta^* d_E}\left[\frac{kN\delta^2 d_E}{cd_x p} - d + \sqrt{\left(\frac{kN\delta^2 d_E}{cd_x p} - d\right)^2 + 4s\frac{k^2N^2\delta^2 d_E}{c^2 d_x p}}\right],\\
\bar{T}^* &= \frac{d_E}{d_x p}\left(\frac{kN\delta\bar{T}}{c} - \delta\right),\\
\bar{V} &= \frac{N\delta}{c}\bar{T}^*,\\
\bar{E} &= \frac{p}{d_E}\bar{T}^*.
\end{aligned} \tag{4.2}$$

From $\bar{T}^* > 0$, we have that the infected steady state exists if and only if $k_1 N\bar{T}/c > 1$, which is equivalent to $kNs/(dc) > 1$, i.e., $kN\bar{T}/c > 1$. Note that $\mathscr{R}_0 = kNs/(dc)$ is the basic reproductive ratio of the basic model (without the immune response). We will study the mathematical properties of the solutions of model (4.1). To study the local stability of the steady states of model (4.1), we linearized the system about a given steady state to get

$$\begin{vmatrix} -d - k\bar{V} - \lambda & 0 & -k\bar{T} & 0\\ k\bar{V} & -\delta - d_x\bar{E} - \lambda & k\bar{T} & -d_x\bar{T}^*\\ 0 & N\delta & -c - \lambda & 0\\ 0 & p & 0 & -d_E - \lambda \end{vmatrix} = 0, \tag{4.3}$$

where $\lambda$ is an eigenvalue. We have the following result for the infection-free steady state. The characteristic equation for the linearized system is

$$\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0, \tag{4.4}$$

where

$$\begin{aligned}
a_1 &= c + \delta + d_x\bar{E} + d_E + d + k\bar{V},\\
a_2 &= k(d_E + c + \delta + d_x\bar{E})\bar{V} + dd_E + \delta d_E + d\delta + dc + cd_E + d_x\bar{E}c\\
&\quad + \bar{T}^* p d_x + dd_x\bar{E} + \delta c - \delta k\bar{T}N + d_x\bar{E}d_E,\\
a_3 &= d_x[k(c + d_E)\bar{V} + dc + cd_E + dd_E]\bar{E} - \delta kN(d_E + d)\bar{T}\\
&\quad + k(\delta d_E + d_E c + pd_x\bar{T}^* + \delta c)\bar{V} + \delta cd_e + pd_x(d + c)\bar{T}^* + \delta d_E d\\
&\quad + \delta dc + cd_E d,\\
a_4 &= kc(d_E d_x\bar{E} + \delta d_E + \bar{T}^* d_x p)\bar{V} + dcd_E d_x\bar{E} + cd_E\delta d - \delta dk\bar{T}Nd_E\\
&\quad + \bar{T}^* p d_x cd.
\end{aligned} \tag{4.5}$$

By the Routh-Hurwitz conditions, all eigenvalues of (4.4) have negative real part if and only if

$$a_1 > 0, \quad a_4 > 0, \quad B_1 := a_1a_2 - a_3 > 0, \quad B_1a_3 - a_1a_4 > 0. \tag{4.6}$$

**Theorem 4.1.1.** *The infection-free steady state of model* (4.1) *is locally asymptotically stable when* $\mathscr{R}_0 < 1$ *and unstable when* $\mathscr{R}_0 > 1$.

*Proof.* The Jacobian matrix at the non-infected steady state is

$$\begin{pmatrix} -d & 0 & -\frac{ks}{d} & 0 \\ 0 & -\delta & \frac{ks}{d} & 0 \\ 0 & N\delta & -c & 0 \\ 0 & p & 0 & -d_E \end{pmatrix}, \tag{4.7}$$

which produces the eigenvalues

$$\lambda_1 = -d, \quad \lambda_2 = -d_E, \quad \lambda_{3,4} = \frac{-(c+\delta) \pm \sqrt{(c-\delta)^2 + \frac{4ksN\delta}{d}}}{2}. \tag{4.8}$$

Hence it is easily seen that all eigenvalues are real and negative given 4.1.1 is satisfied. Under this assumption the non-infected steady-state is locally stable. □

**Theorem 4.1.2.** *The infected steady state* (4.2) *is stable if and only if the Routh-Hurwitz inequalities* (4.6) *evaluated at this steady state are satisfied.*

Pawelek et al. [16] collected data from 10 patients to provide an evaluation for model discussed above. We used data from 4 patients in our simulations. Figure 4.1 shows data fit for patient 3 with a RMS (root mean square) of 0.172, a good result if compared to data fit for patient 2 in figure 4.6, whose RMS is 0.647 for model (4.1) and 0.506 for model (4.13). Parameter values are in table 4.1 and 4.3.

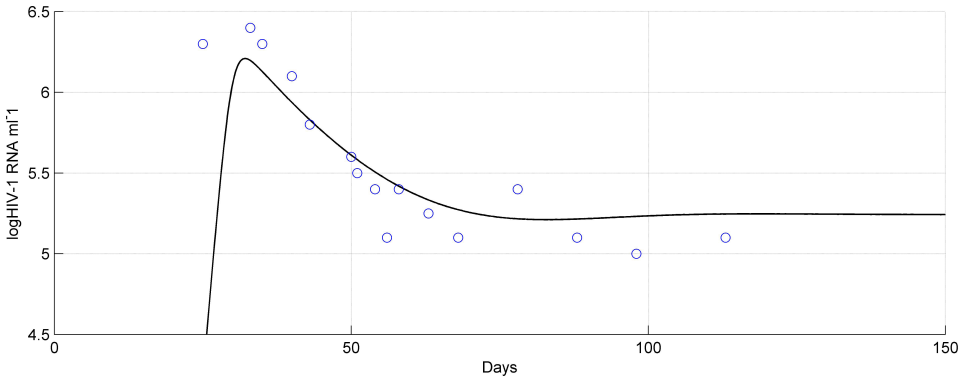



Figure 4.1: Data fits of model (4.1) for patient 3

### 4.1.2 Model with response activation time delay

In this section we introduce a time delay in the model (4.1) by assuming that the immune response at time $t$ is generated by the infection of a cell $T^*$ at time $t-\tau$, where $\tau$ is constant. The model then becomes

$$\begin{aligned}
\frac{dT(t)}{dt} &= s - dT - kVT,\\
\frac{dT^*(t)}{dt} &= kVT - \delta T^* - d_x E T^*,\\
\frac{dV(t)}{dt} &= N\delta T^* - cV,\\
\frac{dE(t)}{dt} &= pT^*(t-\tau) - d_E E,
\end{aligned} \tag{4.9}$$

where the term $T^*(t-\tau)$ allows for a time delay between the moment of infection and the recognition of the infected cells by the cytotoxic $CD8^+$ T cells. The initial values are

$$T(0), \quad T^*(\theta) = 0, \quad V(0), \quad E(0) = 0, \quad \theta \in [-\tau, 0]. \tag{4.10}$$

From (4.9) we obtain the following determinant:

$$\begin{vmatrix}
-d - k\bar{V} - \lambda & 0 & -k\bar{T} & 0\\
k\bar{V} & -\delta - d_x\bar{E} - \lambda & k\bar{T} & -d_x\bar{T}^*\\
0 & N\delta & -c-\lambda & 0\\
0 & pe^{-\lambda\tau} & 0 & -d_E - \lambda
\end{vmatrix} = 0, \tag{4.11}$$

The analysis of free-infection steady state lead to the same results of 4.1.1. The following theorem shows the conditions for stability of the infected steady state.

**Theorem 4.1.3.** *In the case of $\tau > 0$, the infected steady state is locally asymptotically stable when $\tau < \tau^*$, where $\tau^* = \min_{j\in\mathbb{N}}(\tau_1^j, \tau_2^j)$ with*

$$\begin{aligned}
\tau_1^j &= \frac{1}{\omega}\left[\arccos\left(\frac{\alpha_1 c\omega^2 + \omega^2(\omega^2 - \alpha_2)}{\alpha_3(c^2+\omega^2)}\right) + 2j\pi\right],\\
\tau_2^j &= \frac{1}{\omega}\left[2\pi - \arccos\left(\frac{\alpha_1 c\omega^2 + \omega^2(\omega^2 - \alpha_2)}{\alpha_3(c^2+\omega^2)}\right) + 2j\pi\right].
\end{aligned} \tag{4.12}$$

*Here $\alpha_1 = d_E + c + \mathscr{R}_0\delta$, $\alpha_2 = d_E(c + \mathscr{R}_0\delta)$, $\alpha_3 = (\mathscr{R}_0 - 1)d_E\delta$ and $\omega$ is $\Im[\lambda]$. Moreover, a Hopf bifurcation[1] occurs at the infected steady state when $\tau = \tau^*$.*

[1] A Hopf bifurcation is a local bifurcation in which a fixed point of a dynamical system loses stability as a pair of complex conjugate eigenvalues of the linearization around the fixed point cross the imaginary axis of the complex plane. Under reasonably generic assumptions about the dynamical system, we can expect to see a small-amplitude limit cycle branching from the fixed point.

The proof is based on the analysis of threshold values of $\tau_2$ for the cross of imaginary axis, substituting $\lambda = i\omega$.

In figure 4.2 and 4.3 we show two possible behaviors of model (4.9).

### 4.1.3 Model with response activation and intracellular time delay

Ciupe et al. [12] incorporated one time delay into an HIV-1 model to account for the time needed to activate the $CD8^+$ T cell response, i.e., the immune cells at time t were activated by infected cells at time $t - \tau_2$, where $\tau_2$ is a constant. Pawelek et al. [16] include this immune delay as well as an intracellular delay, $\tau_1$, between viral entry and viral production (this phase is referred to as the eclipse phase). The model is described by a system of differential equations (4.1). Schematic diagram at the model is given in figure 4.4. It includes four variables: uninfected target cells $T(t)$, productively infected cells $T^*(t)$, free virus $V(t)$, and effector cells $E(t)$. The parameter $s$ represents the rate at which target cells are created, $d$ is the death rate of target cells, $k$ is the infection rate, and $\delta$ is the death rate of productively infected cells. As described in [13], we assume $k_1 = ke^{-a\tau_1}$, where $\alpha(d < \alpha < \delta)$ is the death rate of infected cells before viral production commences. Thus, $e^{-a\tau_1}$ is the probability that an infected cell survives the eclipse phase to produce virions. The constant $d_x$ represents the killing rate of infected cells by effector cells. $N$ is the number of virions produced by an infected cell during its lifespan, and c is the viral clearance rate constant. Effector cells are assumed to be generated at a rate proportional to the level of productively infected cells, and die at a rate $d_E$. Note that the generation of effector cells was described using a mass action term $pET^*$ in other studies. However, it generates a steady state of infected cells, $T^* = d_E/p$, which is independent of any viral parameters. Here, we assumed the same generation rate for effector cells as in [12]. The model including the two delays is given by

$$\begin{aligned}
\frac{dT(t)}{dt} &= s - dT - kVT, \\
\frac{dT^*(t)}{dt} &= k_1 V(t-\tau_1)T(t-\tau_1) - \delta T^* - d_x E T^*, \\
\frac{dV(t)}{dt} &= N\delta T^* - cV, \\
\frac{dE(t)}{dt} &= pT^*(t-\tau_2) - d_E E.
\end{aligned} \tag{4.13}$$

$\mathscr{R}_0$ is intracellular delay-dependent, because $k_1 = ke^{-\alpha\tau_1}$ can be good approximated to $k$. Both $\alpha$ and $\tau_1$, in fact, are very small. The determinant

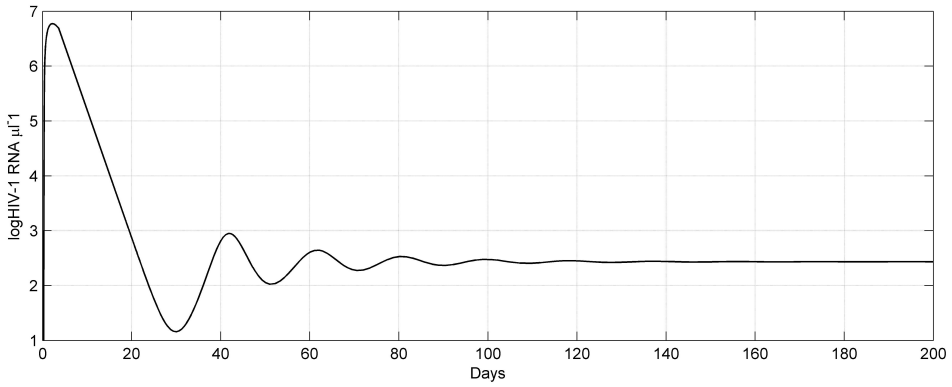



Figure 4.2: Simulation of model (4.9) that exhibits damped oscillations. Parameter values in first line of table 4.2

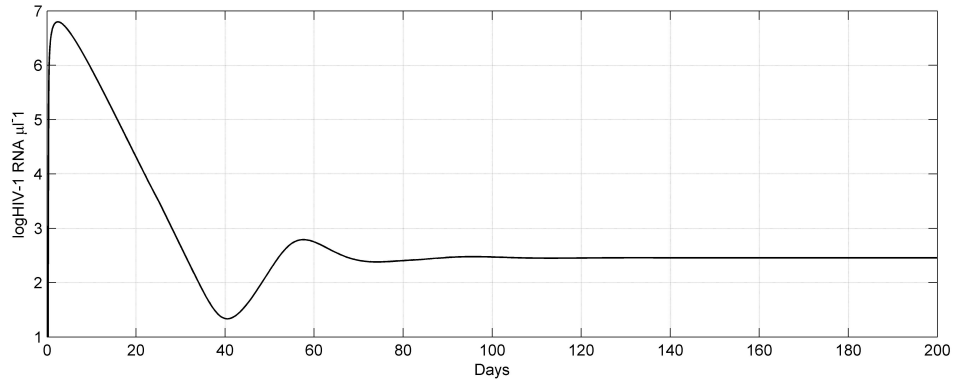



Figure 4.3: Simulation of model (4.9). After an initial peak, viral load settle to a costant value. . Parameter values in second line of table 4.2

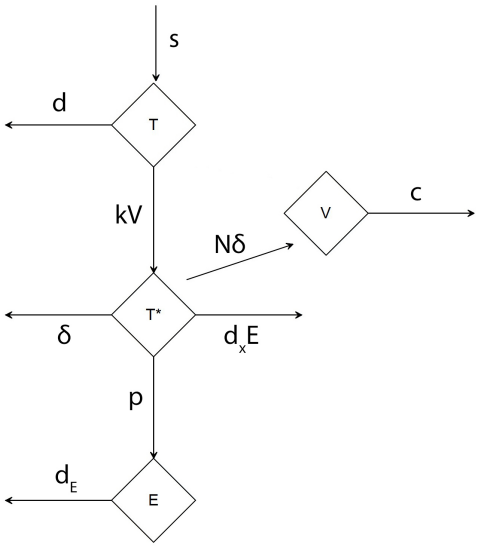



Figure 4.4

is given by:

$$\begin{vmatrix} -d-k\bar{V}-\lambda & 0 & -k\bar{T} & 0 \\ k\bar{V}e^{-\lambda\tau_1} & -\delta-d_x\bar{E}-\lambda & k\bar{T}e^{-\lambda\tau_1} & -d_x\bar{T}^* \\ 0 & N\delta & -c-\lambda & 0 \\ 0 & pe^{-\lambda\tau_2} & 0 & -d_E-\lambda. \end{vmatrix} = 0, \tag{4.14}$$

Again, there is no need to analyze the free-infection steady state. At the infected steady state, the characteristic Eq. given by (4.14) can be simplified to

$$(\lambda+d+k\bar{V})(\lambda+c)[(\lambda+\mathscr{R}_0\delta)(\lambda+d_E)+(\mathscr{R}_0-1)d_E\delta e^{-\lambda\tau_2}] = (\lambda+d)(\lambda+d_E)\mathscr{R}_0 c\delta e^{-\lambda\tau_1}. \tag{4.15}$$

For a special case of $\tau_2 = 0$, we have the following theorem for the stability of the infected steady state.

**Theorem 4.1.4.** *The infected steady state of model* (4.13) *is locally asymptotically stable when* $\mathscr{R}_0 > 1$ *in the case of* $\tau_2 = 0$.

*Proof.* In the case of $\tau_2 = 0$, the characteristic equation is

$$(\lambda+d+k\bar{V})(\lambda+c)[(\lambda+\mathscr{R}_0\delta)(\lambda+d_E)+(\mathscr{R}_0-1)d_E\delta] = (\lambda+d)(\lambda+d_E)\mathscr{R}_0 c\delta e^{-\lambda\tau_1}. \tag{4.16}$$

Obviously, Eq. (4.16) does not have a nonnegative real solution. Now we prove that (4.16) does not have any complex root $k$ with a nonnegative real part. Suppose, by contradiction, that $k = x + iy$ with $x \geq 0$ is a root of (4.16). Because its complex conjugate $k = x - iy$ is also a root of (4.16), we can assume that $y > 0$. When $\mathscr{R}_0 \to 1$, we have $\bar{V} \to 0$. Thus, Eq. (4.16) reduces to $(\lambda + c)[(\lambda + \delta) = c\delta e^{-\lambda\tau_1}$. Using the same arguments as above, we can show that it does not have any root with a nonnegative real part. By the continuous dependence of roots of the characteristic equation on $\mathscr{R}_0$, we know that the curve of the roots must cross the imaginary axis as $\mathscr{R}_0$ decreases sufficiently close to 1. That is, the characteristic Eq. (4.16) has a pure imaginary root, say, $iy_0$, where $y_0 > 0$. From (4.16), we have

$$(iy_0 + d + k\bar{V})(iy_0 + c)[(iy_0 + \mathscr{R}_0\delta)(iy_0 + d_E) + (\mathscr{R}_0 - 1)d_E\delta] = (iy_0 + d)(iy_0 + d_E)\mathscr{R}_0 c\delta e^{-iy_0\tau_1}. \quad (4.17)$$

We claim that the following inequality holds:

$$|(iy_0 + \mathscr{R}_0\delta)(iy_0 + d_E) + (\mathscr{R}_0 - 1)d_E\delta| > |iy_0 + d_E|\mathscr{R}_0\delta. \quad (4.18)$$

In fact, after straightforward computations, we have

$$|(iy_0 + \mathscr{R}_0\delta)(iy_0 + d_E) + (\mathscr{R}_0 - 1)d_E\delta|^2 - |iy_0 + d_E|^2(\mathscr{R}_0\delta)^2 = [y_0^2 - (\mathscr{R}_0 - 1)d_E\delta]^2 + 2\mathscr{R}_0(\mathscr{R}_0 - 1)(d_E\delta)^2 + (d_E y_0)^2 > 0. \quad (4.19)$$

Thus, (4.18) holds. It follows from $|iy_0 + d + k\bar{V}| \geq |d + iy_0|$, $|c + iy_0| > c$, and the inequality (4.18) that the modulus of the left-hand side of (4.17) is greater than the modulus of the right-hand side. This leads to the contradiction. Therefore, we conclude that the characteristic Eq.(4.16) does not have any root with a nonnegative real part. Thus, the infected steady state is locally asymptotically stable when $\mathscr{R}_0 > 1$ in the case of $\tau_2 = 0$. □

Figure 4.5 displays the best fit for model (4.13) with a RMS error of 0.048. Although data fits of model (4.13) are usually better than model (4.1), in figure 4.7 results are similare in both models. This highlights that more data are needed for models validation.

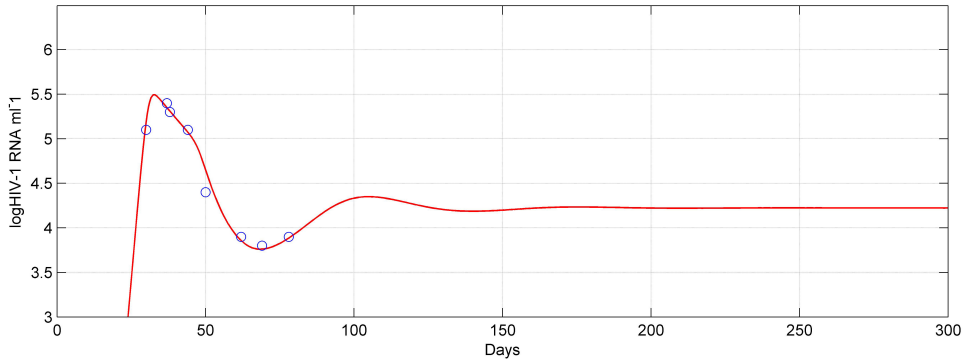



Figure 4.5: Data fits of model (4.13) for patient 4

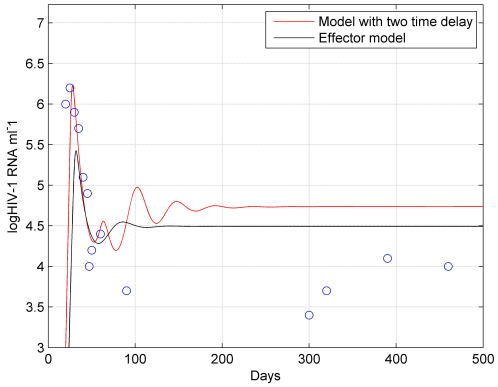



Figure 4.6: Data fits of model (4.13) and (4.9) for patient 2

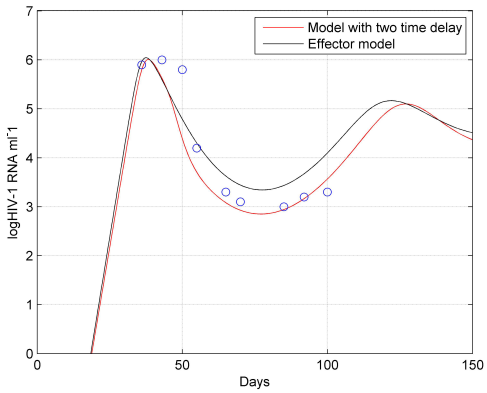



Figure 4.7: Data fits of model (4.13) and (4.9) for patient 1

| Patient | $d_x \times 10^{-4}$ ml cells day$^{-1}$ | $p$ day$^{-1}$ | $d_E$ day$^{-1}$ | $N$ viron cells$^{-1}$ | $d$ day$^{-1}$ | $k \times 10^{-7}$ ml viron day$^{-1}$ | $s$ cells ml day$^{-1}$ | $\delta$ day$^{-1}$ |
|---|---|---|---|---|---|---|---|---|
| 1 | 5.4 | 0.01 | 0.02 | 5617 | 0.0065 | 6.4 | 65 | 0.1 |
| 2 | 7.2 | 2 | 2.13 | 1341 | 0.012 | 7.5 | 120 | 0.59 |
| 3 | 1 | 0.01 | 0.97 | 6689 | 0.0085 | 6.6 | 85 | 0.1 |

Table 4.1: Table for effector model

| $d_x$ $\mu$l cells day$^{-1}$ | $c$ day$^{-1}$ | $p$ day$^{-1}$ | $d_E$ day$^{-1}$ | $\tau$ days | $N$ viron cells$^{-1}$ | $d$ day$^{-1}$ | $k$ $\mu$l viron day$^{-1}$ | $s$ cells $\mu$l day$^{-1}$ | $\delta$ day$^{-1}$ |
|---|---|---|---|---|---|---|---|---|---|
| 0.623 | 0.537 | 1.768 | 0.403 | 3.3 | 1606.99 | 0.017 | 0.00063 | 0.17 | 0.541 |
| 0.388 | 0.387 | 1.258 | 3.059 | 24.96 | 1410.59 | 0.0085 | 0.00066 | 0.085 | 0.588 |

Table 4.2: Table for model with one time delay

| Patient | $d_x \times 10^{-4}$ ml cells day$^{-1}$ | $p$ day$^{-1}$ | $d_E$ day$^{-1}$ | $\tau_1$ days | $\tau_2$ days | $N$ viron cells$^{-1}$ | $d$ day$^{-1}$ | $k \times 10^{-7}$ ml viron day$^{-1}$ | $s$ cells ml day$^{-1}$ | $\delta$ day$^{-1}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3.7 | 0.3 | 1.81 | 0.1 | 9.2 | 2374 | 0.0065 | 6.4 | 65 | 0.3 |
| 2 | 9.9 | 0.01 | 0.01 | 0.1 | 35 | 2244 | 0.012 | 7.5 | 120 | 0.35 |
| 4 | 9.4 | 0.02 | 0.81 | 0.5 | 16.1 | 1261 | 0.0046 | 48 | 46 | 0.1 |

Table 4.3: Table for model with two time delays

## 4.2 Stochastic model

Tan and Wu introduced a stochastic model on the basis of Perelsons deterministic model [20]. Although [20] and [18] models are similar, their solutions differ because different parameter values are used and different time periods of infection are studied. Therefore, direct comparison of the two stochastic approaches is not possible. In this section we develop a new model by applying Tan and Wus stochastic approach [19] to Phillipss deterministic model [18] used by Tuckwell and Le Corfecs multi-dimensional diffusion process [17]. Numerical solutions are obtained in the same manner as that used in the previous model except that we no longer use a multi-dimensional diffusion process method. The new model enables us to compare the two stochastic approaches directly. The four variables used in this model are the same as described in the previous section. By applying Tan and Wus stochastic approach, a four-dimensional stochastic process $X = \{T(t), L(t), I(t), V(t)\}$ is described based on the following set of assumptions:

- New normal CD4$^+$ T-cells are generated stochastically from precursor cells. This is modeled by a Poisson process with rate $\lambda\delta t$.
- Susceptible CD4$^+$ T-cells can be infected by HIV-1 to become latently or actively infected cells. The conditional probability that an HIV-1 infects a CD4$^+$ T-cell during $[t, t+\delta t)$ is $k_1 T(t)\delta t + o(\delta t)$. A CD4$^+$ T-cell infected by HIV-1 during $[t, t+\delta t)$ becomes latent with probability $p$.
- Activation of an $L(t)$ cell during $[t, t+\delta t)$ takes place with probability $\alpha\delta t + o(\delta t)$.
- The probability of death of a $T(t)$ cell and an $L(t)$ cell is $\mu\delta t + o(\delta t)$. Similarly the probability of death of an $I(t)$ cell and a $V(t)$ during $[t, t+\delta t)$ are $a\delta t + o(\delta t)$ and $\gamma\delta t + o(\delta t)$, respectively.
- An $I(t)$ cell releases $c$ HIV-l particles during $[t, t+\delta t)$. This process is modeled deterministically and the random variation of this quantity is ignored.

Given the above assumptions, the numerical solutions for the $(n+1)$th step of the four variables are given by the following algorithm:

$$\begin{aligned} T_{n+1} &= T_n + S_n - F_n - D_{Tn}, \\ L_{n+1} &= L_n + X_n - F'_n - D_{Ln}, \\ I_{n+1} &= I_n + F_n - X_n + F'_n - D_{In}, \\ V_{n+1} &= V_n + cI_n\delta t - F_n - D_{Vn}, \end{aligned} \tag{4.20}$$

where

$$\begin{aligned} S_n &\sim \text{Poisson with a mean of } \lambda\delta t, \\ F_n, D_{Vn}|[T_n, V_n] &\sim \text{Multinomial}[V_n; k_1 T_n \delta t, \gamma\delta t], \\ F'_n, D_{Ln}|L_n &\sim \text{Multinomial}[L_n, \alpha\delta t, \gamma\delta t], \\ X_n|F_n &\sim \text{Binomial}[F_n, p], \\ D_{Tn}|T_n &\sim \text{Binomial}[T_n, \mu\delta t], \\ D_{In}|I_n &\sim \text{Binomial}[I_n, a\delta t]. \end{aligned}$$

The conditional distribution method is used to generate the multinomial random variables. The deterministic solutions are computed by replacing all terms in Eqs. (4.20) with expected values of the corresponding distributions.

Using the model described above, Kamina et al. generated 1000 Monte-Carlo samples for 60 post-primary infection days with time step of 0.01 days. They repeatedly generated sample paths for the six different initial viral volumes, $V(0) = 2, 5, 10, 50, 100$, and 300. Parameter values are

| $\lambda\,(\text{mm}^{-3}\ \text{day})^{-1}$ | $\mu\,\text{day}^{-1}$ | $k_1\,(\text{mm}^{-3}\ \text{day})^{-1}$ | $k_2\,(\text{mm}^{-3}\ \text{day})^{-1}$ | $p$ | $\alpha\,\text{day}^{-1}$ | $a\,\text{day}^{-1}$ | $c\,\text{day}^{-1}$ | $\gamma\,\text{day}^{-1}$ |
|---|---|---|---|---|---|---|---|---|
| 0.272 | 0.00136 | 0.00027 | 0.00027 | 0.1 | 0.036 | 0.33 | 100 | 2 |

In figure 4.8 we note that model (4.20) is able to predict viral extinction in an early period of HIV-1 infection.

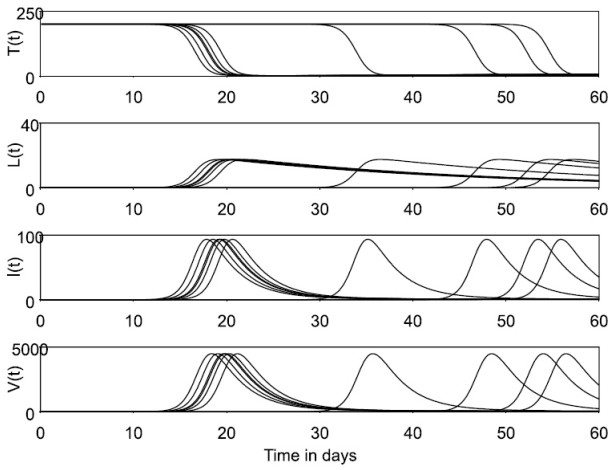



Figure 4.8: Ten sample paths of infected steady state from the Monte-Carlo simulation of (4.20) generated in [21]

# Chapter 5

# Conclusion

In this thesis, we showed how model theory takes on an important role in epidemiology and virology since its regular application to real study cases.

Although model development is relatively simple if spread dynamics or viral evolution is known, model verification and validation need more data that are not always available. Collection of data requires ongoing commitment that health workers cannot honor. Studies, that are involved in serious epidemics such as HIV, would need specific departments in hospitals and clinics to assign this role. Since nineties Departments of Health of developed countries have seriously activated qualified systems to analyze data. In Italy the task has been assigned to Istituto Superiore della Sanit that every year publishes a paper with current data organized in regions, gender and transmission medium.

We focused on HIV-1 virus that leaded to the worst outbreak of ninth century in terms of number of infected people and social implications. We analyzed epidemic and pathogenesis models to give a complete evaluation of the problem. The former gave us the opportunity to understand how we can model different characteristics of the spread dynamics such as educational campaigns. The latter explain the problem of data collection seen above, through Matlab® simulations and data fits. The use of data collected from few patients does not allow for a statistical approach required to model validation. With a stochastic model, we could also consider the possibility of viral extinction in the case of low viral load during the first stages of infection.

In the perspective of an increase in efficiency of public health facilities involved in HIV/AIDS disease, we expect an improvement of models in the near future, although the still partial knowledge of some inner workings.

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