Deterministic Compartmental Models for HIV and TB

Eric Okyere (eric@aims.ac.za)
African Institute for Mathematical Sciences (AIMS)

Supervised by John Hargrove
South African Centre for Epidemiological Modelling and Analysis (SACEMA)

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Abstract

This research provides a detailed review of a deterministic compartmental model for Human Immunodeficiency Virus (HIV) and tuberculosis (TB) to understand better the dynamics of the twin epidemics in a South African township. This model is built on SIR and population models. The HIV epidemic in Southern Africa constitutes the most serious health problem in the region. What makes the study and control of the disease even more complex is its interaction with the parallel tuberculosis (TB) epidemic. Evaluation of the basic reproduction number, R_0, was carried out using the method of linearisation near the disease-free equilibrium. The population is divided into compartments, in and out flows from compartments leading to a corresponding differential equation. A numerical solver in octave is then used to compute the solutions. Our results demonstrated that the prevalence of *Mycobacterium tuberculosis* would be very high in the township, as compared to that at the national level.

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1. Introduction

The Human Immunodeficiency Virus (HIV) epidemic in Southern Africa constitutes the most serious health problem in the region and one that we do not fully understand. What makes the matter even more complex is the interaction with the parallel tuberculosis (TB) epidemic which affects both HIV-positive and HIV-negative people. TB and HIV are the leading causes of death from infectious diseases among adults globally and the number of TB cases has risen significantly since the start of the HIV epidemic, particularly in Sub-Saharan Africa where the HIV epidemic is most severe [2]. The World Health Organization (WHO) TB-control strategy, which is based on the directly observed treatment, short course (DOTS) strategy, has failed to contain the TB epidemic in Africa, largely due to the effects of the HIV epidemic in the region [2]. Recent approaches aiming to understand the situation have attempted to model the twin epidemics using deterministic compartmental models. This project reviews the formal mathematical work on deterministic models of this nature and considers the relevance of the modeling approach to the HIV and TB epidemics in Southern Africa.

The first chapter provides some basic background information on TB and HIV. Our main goal here is to understand the basic epidemiology of these two deadly diseases and gain insight into how they affect each other. In Chapter 2, we will review the basic reproduction number (threshold parameter) which is crucial in disease modeling, the classical SIR model, and linear models for age-dependent population dynamics. In Chapter 3, we will present a deterministic compartmental model for the interaction between HIV and TB epidemics. This model will be presented as system of coupled first order linear partial differential equations (age-structured population model). In Chapter 4, we will discuss parameters related to HIV and TB. We will further perform numerical simulations to estimate some HIV and TB parameters.

1.1 What Is TB ?

Tuberculosis (TB), is a bacterial infection that causes more deaths in the world than any other infectious disease. The bacteria is called *Mycobacterium tuberculosis* and it usually affects the lungs (pulmonary tuberculosis). It can also affect the central nervous system, the lymphatic system, the brain, spine and the kidneys. Only people who have pulmonary TB are infectious. One-third of the world's population is currently infected with the TB bacillus and new infections are occurring at a rate of one per second [3].

1.1.1 Exposure To Tubercle Bacilli

Exposure is defined as a contact between two individuals in sufficient proximity to allow conversation between them, or, within confined spaces, where the air exchange (ventilation) of the space has been incomplete between the visits of the two people [4].

There are three major factors that determine the risk of becoming exposed to tubercle bacilli, they

include the number of incident infectious cases in the community, the duration of infectiousness, and the number and nature of interactions between a case and a susceptible contact per unit of time of infectiousness [4].

TB spreads from person to person through the air as a person with active tuberculosis coughs, sneezes, speak, spits, kisses. Note that not everyone infected with *Mycobacterium tuberculosis* becomes sick. After a person becomes infected, the tuberculosis bacteria are controlled by the person's immune system. When the bacteria spreads out of control, the infection becomes active. A person can have active or latent (inactive) TB. Both active and latent TB are treatable and curable. Active TB means the bacteria are active in the body and they weaken the immune system, making it impossible to stop them from causing illness. Only people with active TB can spread the disease. People with latent TB do not feel sick and do not have any symptoms. In some people, *Mycobacterium tuberculosis* remains inactive for a lifetime without becoming active while others are likely to develop active TB if their immune system is compromised by some deadly disease such as HIV. The early symptoms of active tuberculosis include: coughing up blood, weight loss, fever, loss of appetite, and also shortness of breath indicates an advanced stage of active tuberculosis.

1.1.2 TB Progression

TB progression from latent infection to active disease varies greatly. For instance, people with AIDS are more likely to develop to active TB after infection. A patient with AIDS who becomes infected with *Mycobacterium tuberculosis* has a 50% chance of developing active tuberculosis within 2 months and a 5 to 10% chance of developing active disease each year thereafter. According to the World Health Organization (WHO), infants and young children infected with *Mycobacterium tuberculosis* are also more likely to develop active TB than older people since their immune system are not yet well developed.

1.1.3 MDR-TB and XDR-TB

Multidrug-resistant tuberculosis (MDR-TB) is a form of tuberculosis that is resistant to at least *isoniazid* and *rifampicin*, the two most powerful first-line anti-TB drugs. The World Health Organization (WHO), defines extensively drug resistant TB (XDR-TB) as MDR-TB plus resistance to any fluoroquinolone and at least 1 of 3 injectable second-line drugs capreomycin, kanamycin, amikacin. People who have active TB usually develop MDR-TB or XDR-TB when they fail to fulfil their prescription of TB medicine as ordered by the doctor. MDR-TB is dangerous and very difficult to treat. The most important factor in preventing Resistant drug TB is to ensure full compliance with anti-TB treatment. As recommended by the WHO, directly observed therapy (DOT) is an effective treatment measure. In 2006, 53 people in the province of KwaZulu Natal in South Africa were identified as having XDR-TB, 52 of the patients died on average within 25 days, including those on antiretroviral therapy. Anyone can get TB, but some people are highly susceptible. Those that are at high risk include: people with HIV, people in close contact with infectious individuals, people who are malnourished, health care workers, prison guards, alcoholics,

intravenous drug users and the homeless [5].

1.1.4 TB Skin Test and Treatment

The tuberculin skin testing is the major method of diagnosing the tuberculosis infection. When the test result is positive it implies there is tubercle bacilli. It is normally used to distinguish between infected individual from the exposed individual without infection. The infected individuals will then be put on the DOT strategy in other to reduce infections and also treat the disease. An active TB patient can be treated by a combination of anti-tuberculosis therapies such as the ones mentioned in subsection 1.1.3. Latent TB can be treated with isoniazid. The treatment is very effective provided the patients takes it for at least six months as prescribed.

1.2 HIV/AIDS

AIDS stands for Acquired Immune Deficiency Syndrome. It is a life threatening disease caused by HIV which is a sexually transmitted disease. One can become infected with the virus through unprotected sex and sharing of hypodermic needles. The virus is not transmitted through saliva, spit, sweat, tears, air or insects. HIV in humans is now pandemic. As of January 2006, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) estimate that AIDS had killed more than 25 million people since it was first recognized on December 1, 1981, making it one of the most destructive pandemics in recorded history. In 2005 alone, AIDS claimed an estimated 2.4-3.3 million lives, of which more than 570,000 were children. It is estimated that about 0.6% of the world's living population is infected with HIV. A third of these deaths are occurring in sub-Saharan Africa, retarding economic growth and increasing poverty.

1.2.1 Stages of HIV Infection

Generally there are four stages of HIV infection. They are briefly described as follows;

- stage 1: *Primary HIV infection: The first stage of infection is extremely infectious. It normally lasts for a few weeks and is often accompanied by a short flu-like illness*
- stage 2: *Asymptomatic stage: This stage lasts for an average of ten years and the infected person does not show any symptoms of the disease*
- stage 3: *Symptomatic HIV infection: This is the stage where a lot of symptoms (diarrhoea, heavy weight loss, fever, cough and shortness of breath) begin to manifest because the immune system is severely damaged by the virus.*
- stage 4: *Progression from HIV to AIDS : The final stage occurs when the immune system is extremely weakened. As a result, certain infections called "opportunistic" (infections*

which cannot attack people with healthy immune system) take the opportunity to infect the HIV-patients. This is where the patients develop full blown AIDS.

1.3 How TB and HIV Affect Each Other

Each disease acts as a catalyst in the progression of the other. TB significantly reduces the survival time for people with HIV/AIDS. HIV infection is the the largest risk factor for the progression of inactive TB to active TB, and *Mycobacterium tuberculosis* can speed up the progression of HIV. It is important to note that people who are HIV positive together with active TB are less infectious in terms of TB disease than those with only active TB.

1.4 Motivation

We are motivated to model this pair of diseases due to the facts issued by the World Health Organization. They include the following:

- *TB is the most common opportunistic infection in people with AIDS*
- *TB is the first manifestation of AIDS in over 50% of the cases in developing countries*
- *TB is the leading killer of people with AIDS.*

2. Epidemiological And Population Models

In this chapter, we will discuss the meaning and the importance of the reproduction number in infectious disease modelling and investigate the qualitative dynamics of the classical SIR model with solution paths and phase portraits. In the last section of this chapter, we will discuss linear population models with age-structure.

2.1 The Basic Reproduction Number

This is sometimes referred to as a rate or ratio. It is one of the most useful threshold parameters, which characterize mathematical problems concerning infectious diseases. It is widely used in mathematical epidemiology models. The basic reproduction number denoted R_0, is the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual [1, 6]. If $R_0 < 1$, then on average an infected individual produces less than one new infected individual over the course of its infectious period, and the infection cannot grow. Conversely, if $R_0 > 1$, then each infected individual produces, on average, more than one new infection, and the disease can spread in the population. For the case of a single infected compartment, R_0 is simply the product of the infection rate and the mean duration of the infection. However, for more complicated models with several infected compartments this simple definition of R_0 is insufficient. For a more general situation we can establish this parameter by investigating the stability of the infection-free equilibrium. This parameter identifies critical conditions for an epidemic to grow or die out. Furthermore, it can provide significant insight into the transmission dynamics of a disease and can guide strategies to control its spread

2.2 The Classic Epidemic Model SIR

The population is partitioned into compartments of Susceptible Individuals, Infective Individuals and Recovered Individuals, with population size $S(t)$, $I(t)$, and $R(t)$ respectively. The total population is denoted by $N = S(t) + I(t) + R(t)$, where $S, I, R \geq 0$, because they represent the numbers of people. This model does not include vital dynamics (birth rate and death rate) [1]. For simplicity, it is assumed that the total population N is constant with time.

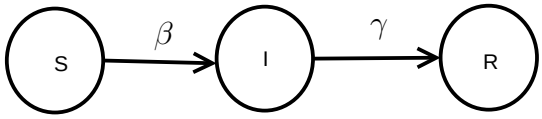


Figure 2.1: A schematic of system (2.1), where s is the susceptibles, I is the infectives and R is the removeds, β is the infection rate, γ is the removal rate.

A system of three differential equations describes this model

$$\begin{aligned} \frac{dS}{dt} &= -\frac{\beta\, SI}{N}; & S(0) = S_0 \geq 0, \\ \frac{dI}{dt} &= \frac{\beta\, SI}{N} - \gamma I; & I(0) = I_0 \geq 0, \\ \frac{dR}{dt} &= \gamma\, I; & R(0) = R_0 \geq 0, \end{aligned} \tag{2.1}$$

Removal from compartment I to R could be due to successful treatment or the immune system has being able to fight against the disease to lessen infectiousness such that the patients becomes uninfectious. For example, when an HIV-positive person reaches the late stage of the disease (full blown AIDS), the person becomes very weak and hence cannot infect others. Removal rate rate is therefore the rate at which infected individuals are removed from the infected population (ie they can no longer infect susceptibles).

The SI expression in the dynamical system is known as an interaction term. This occurs when there is a contact between a susceptible and an infected individuals, that is why it is a product of S and I in (2.1) For instance, sexual contact, between HIV-negative person and HIV-positive person. When this happens, the infected individuals increase their population by reducing the susceptible population. That is why there is minus sign against the expression with SI in the S-rate equation and positive sign in the I-rate equation.

From $N = S + I + R$, dividing through by N we obtain $s + i + r = 1$ where

- $s \equiv \frac{S}{N}$ is called susceptible fraction,
- $i \equiv \frac{I}{N}$ is called infection fraction,
- $r \equiv \frac{R}{N}$ is called removal fraction,

Also we let these fractions at time t_0 be

- $s_0 \equiv \frac{S_0}{N}$ is called initial susceptible fraction,
- $i_0 \equiv \frac{I_0}{N}$ is called initial infection fraction,

- $r_0 \equiv \frac{R_0}{N}$ is called initial removal fraction,

Since all the fractional variables sum up to 1 one of the variables can be eliminated and hence the dimension of the system is reduced.

Since the total population N is constant, dividing through system (2.1) by N and re-arranging we obtain

$$\begin{aligned} \frac{d}{dt}\left[\frac{S}{N}\right] &= -\beta\frac{S}{N}\cdot\frac{I}{N} \\ \frac{d}{dt}\left[\frac{I}{N}\right] &= \beta\frac{S}{N}\cdot\frac{I}{N} - \gamma\frac{I}{N} \\ \frac{dR}{dt}\left[\frac{R}{N}\right] &= \gamma\tfrac{I}{N} \end{aligned} \tag{2.2}$$

Hence substituting the fractional variables s ,i and r into (2.2) and knowing that $r = 1 - s - i$, we can ignore the equation in R and obtain an equivalent reduced system of differential equations as

$$\begin{aligned} \frac{ds}{dt} &= -\beta si; \qquad s(0) = i_0 \geq 0, \\ \frac{di}{dt} &= \beta si - \gamma i; \quad i(0) = i_0 \geq 0, \end{aligned} \tag{2.3}$$

We can simply combine the equations in system (2.3) to obtain a single equation which relates s and i as

$$\frac{di}{ds} = \frac{\beta\ si - \gamma\ i}{-\beta\ si}. \tag{2.4}$$

But by definition, the reproduction number is

$$\sigma = \frac{\beta}{\gamma} \tag{2.5}$$

where σ is the reproduction number. Hence the simplified equation becomes

$$\frac{di}{ds} = -1 + \frac{1}{\sigma\ s}. \tag{2.6}$$

This equation (2.6) is separable, therefore solving together with the initial conditions yields

$$i(t) + s(t) = i_0 + s_0 + \frac{\ln s(t)}{\sigma} - \frac{\ln s_0}{\sigma} \tag{2.7}$$

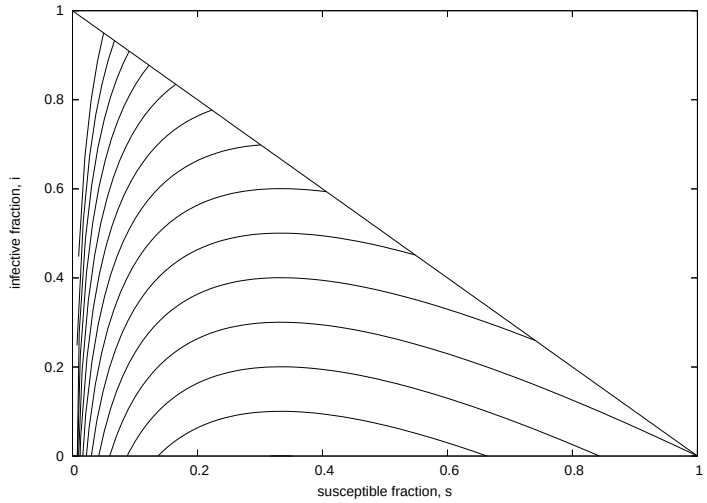


Figure 2.2: Phase portrait for an SIR epidemic model with reproduction number, $\sigma = 3$

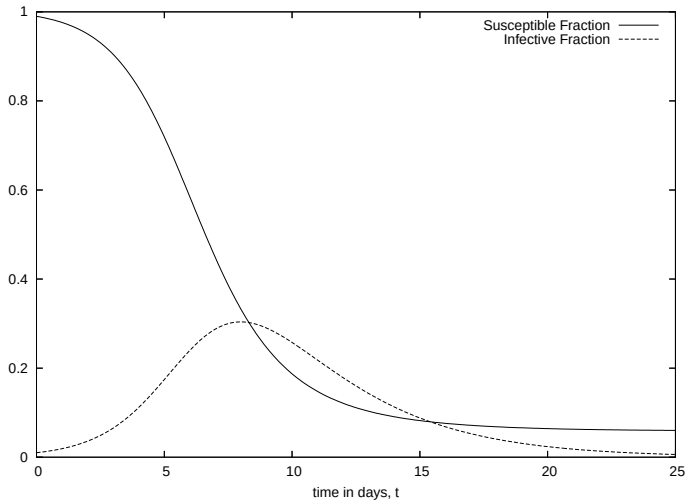


Figure 2.3: Solution of an SIR epidemic for $\sigma = 3$ with initial conditions $(s_0, i_0) = (0.99, 0.01)$

2.3 The classic Endemic Model SIR

We now add vital dynamics (birth and death rate) to the model. The basic assumption for this model is that the birth and death rate are equal, so that the total size N of the whole population remains constant. In this model, the total population is divided into three epidemiological classes; susceptible individuals S, infected individuals I and recovered individuals R

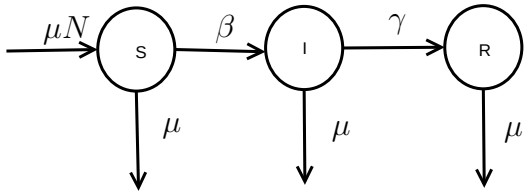


Figure 2.4: A schematic of system (2.8), where s is the susceptibles, I is the infectives and R is the removeds, β is the infection rate, γ is the removal rate. Here β and γ have the same meaning as in the epidemic SIR model discussed in the previous section. The new parameter here is μ which is the death rate.

From Fig 2.4 we deduce the following systems of differential equations.

$$\begin{aligned} \frac{dS}{dt} &= -\mu N - \mu S - \frac{\beta\ SI}{N}; & S(0) = S_0 \geq 0, \\ \frac{dI}{dt} &= \frac{\beta\ SI}{N} - \gamma I - \mu I; & I(0) = I_0 \geq 0, \\ \frac{dR}{dt} &= \gamma\ I - \mu R; & I(0) = I_0 \geq 0, \end{aligned} \tag{2.8}$$

Where $N = S(t) + I(t) + R(t)$ [1]

A similar derivation as in section 2.2 gives us the equivalent system of ODE's as

$$\begin{aligned} \frac{ds}{dt} &= \mu - \mu s - \beta si; & s(0) = s_0 \geq 0, \\ \frac{di}{dt} &= \beta si - (\gamma + \mu)i; & i(0) = i_0, \geq 0. \end{aligned} \tag{2.9}$$

With $r(t) = 1 - s(t) - i(t)$. The reproduction number for the model is

$$\sigma = \frac{\beta}{\gamma + \mu},$$

where $\dfrac{1}{\gamma + \mu}$ is the *average death-adjusted infectious period* [1].

2.3.1 Equilibrium Points

To the determine the stability of this model we must first evaluate the equilibrium or steady state points of the reduced systems of the ODE's (2.9). The points to be found are disease-free (where $i = 0$), and endemic (where $i \neq 0$). We set the right-hand side of the equations in system (2.9) to zero and then solve for the various values of s and i as

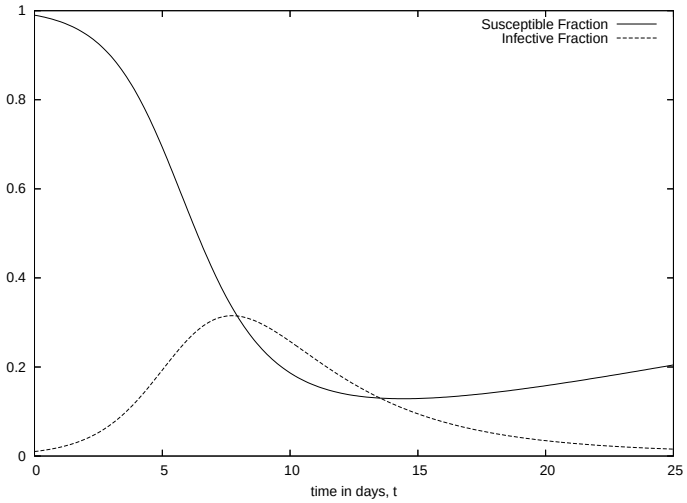


Figure 2.5: Solution of an SIR epidemic model for $\sigma = 3$ with initial conditions $(s_0, i_0) = (0.99, 0.01)$, and . Parameter values were adapted from [1]

$$\begin{aligned} \mu - \mu s - \beta si &= 0 \quad (2.10) \\ \beta si - (\gamma + \mu) i &= 0 \quad (2.11) \end{aligned}$$

From equation (2.11), we have $[\beta s - (\gamma + \mu)]i = 0$, which has solutions
$i = 0$ and $\beta s - (\gamma + \mu) = 0, \quad s = \dfrac{\gamma + \mu}{\beta}$, but from the model σ is defined as $\sigma = \dfrac{\beta}{\gamma + \mu}$.
Hence equation (2.11) has solutions; $i = 0, s = \dfrac{1}{\sigma}$. We then substitute i and s into equation (2.10) to get the following equilibrium points $(s, i) = (1, 0)$ and $(s, i) = \left(\dfrac{1}{\sigma}, \dfrac{\mu(\sigma - 1)}{\beta}\right)$. It is clear that the point $(s, i) = (1, 0)$ is the disease-free equilibrium since the infected fraction $i = 0$

2.3.2 Stability Analysis of Disease-Free Equilibrium

To determine the stability of the system at the disease-free equilibrium $(s, i) = (1, 0)$, we will linearise the reduced system (2.9) about the equilibrium point by the taking the Jacobian. We will then re-define the system as

$$\begin{aligned} f(s, i) &= \mu - \mu s - \beta si \\ g(s, i) &= \beta si - (\gamma + \mu) i \quad . \end{aligned} \quad (2.12)$$

Hence the Jacobian of f and g with rspect to s and i is given by

$$J = \begin{bmatrix} \frac{\partial f}{\partial s} & \frac{\partial f}{\partial i} \\ \frac{\partial g}{\partial s} & \frac{\partial g}{\partial i} \end{bmatrix} = \begin{bmatrix} -\beta i - \mu & -\beta s \\ \beta i & \beta s - (\gamma + \mu) \end{bmatrix}.$$

Therefore, the Jacobian J_0 at the disease-free equilibrium, D_0 (ie when $s = 1$ and $i = 0$) is evaluated as

$$J_0 = \begin{bmatrix} -\mu & -\beta \\ 0 & \beta - (\gamma + \mu) \end{bmatrix}.$$

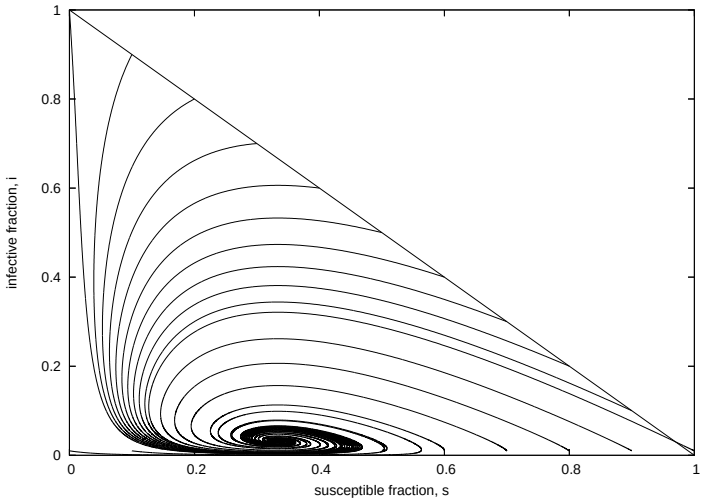
For D_0 to be a asymptotically stable, both eigenvalues $\lambda_j < 0, \quad (j = 1, 2)$ of J_0 must be negative. From J_0, it is clear that $\lambda_1 = -\mu$ is negative and therefore if $\lambda_2 = \beta - (\gamma + \mu) < 0$ then both eigenvalues are negative. $\lambda_2 < 0$ implies that $\beta < \gamma + \mu$, therefore $\frac{\beta}{\gamma+\mu} < 1$. Hence the disease-free equilibrium is asymptotically stable if the basic reproduction number, $\sigma = \frac{\beta}{\gamma+\mu} < 1$. On the other hand, if $\lambda_2 = \beta - (\gamma + \mu) > 0$, then D_0 is unstable.

2.3.3 Stability Analysis of Endemic Equilibrium

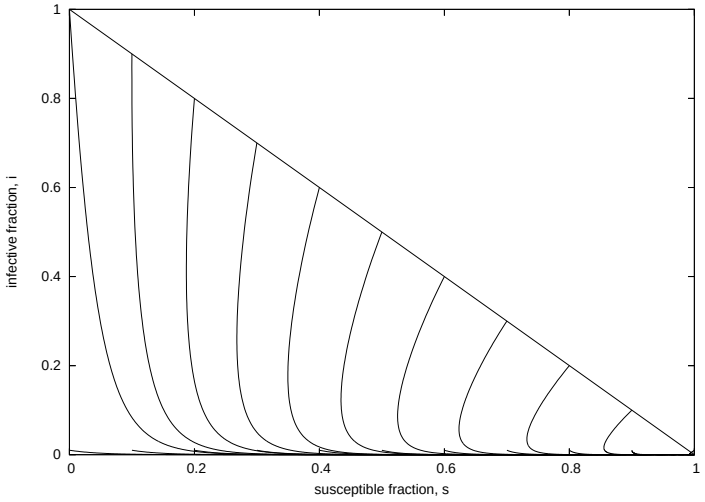
The Jacobian J_e at $(s, i) = (\frac{1}{\sigma}, \frac{\mu(\sigma-1)}{\beta})$ is given by

$$J_e = \begin{bmatrix} -\mu\sigma & -\frac{\beta}{\sigma} \\ \mu(\sigma - 1) & 0 \end{bmatrix}.$$

The characteristic equation of J_e is given by $\lambda^2 - (-\sigma\mu)\lambda + \frac{\beta\mu(\sigma-1)}{\sigma} = 0$. Since the trace of J_e is less than zero $(-\sigma\mu < 0)$ and its determinant, $\frac{\beta\mu(\sigma-1)}{\sigma} > 0$ is positive, the endemic equilibrium is asymptotically stable. This conclusion is true since $\sigma > 1$ in the endemic situation. Conversely, it becomes unstable when $\sigma < 1$.



Phase plane portrait for SIR endemic model with $\sigma = 3$. Parameter values adapted from [1]



Phase plane portrait for SIR endemic model with $\sigma = 0.5$. Parameter values adapted from [1]

2.4 Population Models

This section presents population models with age structure. We will focus our attention on population models with age structure either on time independent or time dependent.

Structured population models generally describe how the distribution of a population changes over time, with respect to structure variables.These variables may include age, mass, size and others that are correlated with individual development. In a model with age-structure, the birth (fertility) and death (mortality) rates depend on the age-structure, i.e if the population is subjected to constant environmental conditions. On the other hand, these rates will also depend on time if there is time variation in the environmental conditions. In this study, we will consider structured population models with birth and death rates which depends on age-structure. But for simplicity, we will assume a constant birth rate.

2.4.1 Population Model With Age Structure, Time Independent

In a model with age structure, the death and the birth rate depends on the age structure of the population. This subsection presents a population model where the birth and rate are time independent. The model is often called Mackendrick-Von Foster equation. It is a first order partial differential given by

$$\frac{\partial n(a,t)}{\partial t} = -\frac{\partial n(a,t)}{\partial a} - \mu(a)n(a,t) \qquad a,t \geq 0. \tag{2.13}$$

The initial condition

$$n(a,0) = n_0(a) = f(a) \tag{2.14}$$

implies that at $t = 0$, we have a start population with age distribution $f(a)$. This is a boundary condition for t. The boundary condition on a is given by

$$n(0,t) = \int_0^\infty b(a)n(a,t)\mathrm{d}a \tag{2.15}$$

where, $\mu(a)$ is the death rate and $b(a)$ represent birth rate [7]. The range of integration is determined by the earliest and latest age at which an individual can be productive. For simplicity it is taken to be 0 and ∞

The general solution to this sysems is given by

$$n(a,t) = n(a-t,0)\exp\left[-\int_{a-t}^{a}\mu(s)\mathrm{d}s\right] \qquad a \geq t \tag{2.16}$$

$$n(a,t) = n(0,t-a)\exp\left[-\int_{0}^{a}\mu(s)\mathrm{d}s\right] \qquad a < t. \tag{2.17}$$

This can be obtained by using the method of characteristics. It can be found in many mathematical biology text books (see for example, book by J.D Murray, [7]). Our main goal for this section is that, in our next chapter we shall apply this model equation in our model formulation for HIV and Tuberculosis which will basically be systems of coupled age-structured models. We will perform numerical simulations instead of qualitative analysis.

The solution has a natural interpretation in terms of survivorship. The probability $l(a_1, a_2)$ of surviving the time interval between age a_1 and a_2 with $a_1, a_2 \geqslant 0$ is defined as

$$l(a_1,a_2) = \frac{l(0,a_2)}{l(0,a_1)} = \exp\left[-\int_{a_1}^{a_2}\mu(s)\,ds\right]. \tag{2.18}$$

With this definition (2.18) we can re-write the general solution in a reduced form as

$$n(a,t) = n(a-t,0)l(a-t,a) \qquad a \geq t \tag{2.19}$$

$$n(a,t) = n(0,t-a)l(0,a) \qquad a < t \tag{2.20}$$

Where equation (2.20) represent individuals aged $a - t$ at time t=0, who survived to age a and equation (2.19) represent those members born $t - a$ time units ago who survived to age a.

2.4.2 Population Model With Age Structure, Time Dependent

This is the type of structured population model whereby the birth and death rate depend on both age and time. This occurs, when the environment changes over time. The model equation is given by

$$\frac{\partial n(a,t)}{\partial t} = -\frac{\partial n(a,t)}{\partial a} - \mu(a,t)n(a,t) \qquad a,t \geq 0 \tag{2.21}$$

Similarly, the boundary conditions for $t = 0$ and $a = 0$ are respectively given by

$$\begin{aligned} n(a,0) &= f(a) && a \geq 0 \\ n(0,t) &= \int_0^\infty b(a,t)n(a,t)\mathrm{d}a && t \geq 0 \end{aligned} \tag{2.22}$$

3. Age-structured model for HIV and TB

In this chapter, we present a deterministic compartmental age-structured population model of the interaction between HIV and TB epidemics. Deterministic compartmental models are when the population is divided into different epidemiological states and the movements between the states are represented by a system of differential equations. The model will be fitted to a data from a South African township to estimate some parameters of these deadly diseases.

According to [8], TB notification rate has increased from 200 to 600 per 100,000 population per year between 1995 and 2004 due to the simultaneous HIV epidemic. It was also found that in 2004, 60% of TB patients aged between 15 and 49 were HIV-positive. Detailed information on these changes in the township can be found in [2, 8].

In 2005, a sample of 762 adults aged over 15 were selected from population and studied to find out how many had undiagnosed TB (table 3.1,[8]): The result was 12/762. At the same year, the number of TB notification was 259, of which 201 were pulmonary TB cases. An estimated 66% of notified people were HIV-positive.

	HIV-	HIV+	Total
Undiagnosed TB	3	9	12
Treated TB	4	7	11
Total	588	174	762

Table 3.1: Results of sample survey in 2005 [8]

3.1 The Model

The model consist of sixteen compartments with each being structured by age. We assume that only people with active TB can transmit the disease to others [9].

	No TB	Latent TB (fast rate)	Latent TB (slow rate)	Active TB
Not at risk for HIV	$S_0(t,a)$	$E_0(t,a)$	$F_0(t,a)$	$I_0(t,a)$
At risk but HIV−	$S_1(t,a)$	$E_1(t,a)$	$F_1(t,a)$	$I_1(t,a)$
HIV+ early stage	$S_2(t,a)$	$E_2(t,a)$	$F_2(t,a)$	$I_2(t,a)$
HIV+ late stage	$S_3(t,a)$	$E_3(t,a)$	$F_3(t,a)$	$I_3(t,a)$

Table 3.2: The variables t and a represent time and age respectively.

We let $P(t)$ denote the total population with $\phi(t)$ representing the fraction of the total population that transmit TB

$$\phi(t) = \sum_{n=0}^{3} \int_0^\infty I_n(t,a)da/P(t)$$

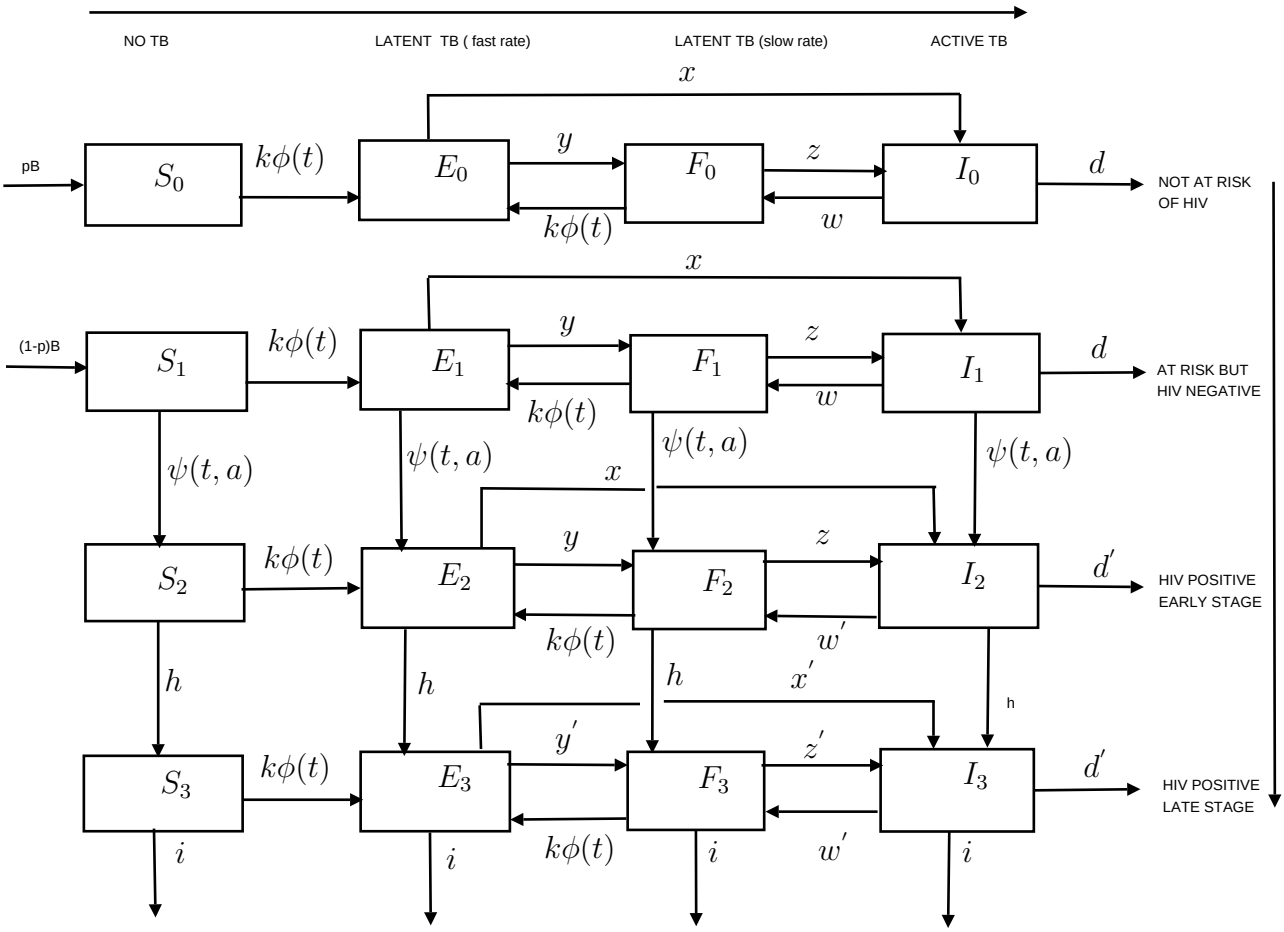


Figure 3.1: Compartmental age-structured model for HIV and TB with natural mortality $m(a)$ in every compartment. The absence of birth inflows into the S_2 and S_3 compartmentall is due to our assumption that mother-to-child transmission of HIV are neglected. People who get infected by M.tuberculosis move from an S-compartment to an E-compartment where they have a relatively high risk of progressing to active TB (disease stage). If After a few years they haven't developed the disease, then they move to compartment F where progression to the disease is still possible but at a slow rate. But a reinfection may bring them back to the E-compartment. successfully treated or naturally recovered people return from compartment I to the low risk compartment F. People who get infected by HIV move from a compartment with subscript 1 to the corresponding compartment with subscript 2 (early HIV stage). After several years, they move to the compartment with subscript 3 which corresponding to the HIV late stage.

. Where $P_n = S_n + E_n + F_n + I_n$ with $0 \leq n \leq 3$

3.2 Force of Infection

Force of infection is the rate at which susceptible individuals become infected by an infectious disease. We assume that, the force of infection by HIV for people aged a at time t is given by;

$$\psi(t,a) = \rho(a)\frac{\int_0^\infty f(a,b)\rho(b)[P_2(t,b)+P_3(t,b)]db}{\int_0^\infty f(a,b)\rho(b)[P_1(t,b)+P_2(t,b)+P_3(t,b)]db}$$

.

where $\rho(a)$ measures the risk of getting HIV at age a and $b \longmapsto f(a,b)$ is the age-distribution of partners of person of aged a

Natural mortality	$m(a)$	$\sigma(a)'/\sigma(a)$
Births	B	1000/year
Proportion not at risk of HIV	p	0.55
Progression rate to late stage HIV	h	0.25/year
Death rate for late stage HIV	i	0.125/year
Start of the HIV epidemic	to	1982/year
TB transmission	k	21/year
duration of treatment	τ	6 months
If HIV-negative or early stage HIV		
Fast progression rate to TB	x	0.033/year
Fast to slow progression rate	y	0.2/year
Slow progression to TB	z	0.001/year
If late stage HIV		
Fast progression rate to TB	x'	0.41/year
Fast to slow progression rate	y'	0.2/year
Slow progression rate to TB	z'	0.1/year
If HIV-negative		
Recovery rate if untreated	r	0.29/year
Detection rate	q	2.2/year
Successful treatment	s	80%
Total recovery rate	w	$r+sq$
TB death rate	d	0.22/year
If HIV-positive		
Recovery rate	r'	0.44/year
Detection rate	q'	1.4/year
Successful treatment	s	80%
Total recovery rate	w'	$r'+sq'$
TB death rate	d'	1.6/year

Table 3.3: Parameter values

The model's equations for people who are not risk of being infected by HIV are:

$$\begin{aligned}
\frac{\partial S_0}{\partial t}+\frac{\partial S_0}{\partial a} &= -\left[m(a)+k\phi(t)\right]S_0(t,a)\\
\frac{\partial E_0}{\partial t}+\frac{\partial E_0}{\partial a} &= -\left[m(a)+x+y\right]E_0(t,a)+k\phi(t)\left[S_0(t,a)+F_0(t,a)\right]\\
\frac{\partial F_0}{\partial t}+\frac{\partial F_0}{\partial a} &= -\left[m(a)+z+k\phi(t)\right]F_0(t,a)+yE_0(t,a)+wI_0(t,a)\\
\frac{\partial I_0}{\partial t}+\frac{\partial I_0}{\partial a} &= -\left[m(a)+w+d\right]I_0(t,a)+xE_0(t,a)+zF_0(t,a)
\end{aligned} \tag{3.1}$$

Model's equations for those at are risk of being infected by HIV include:

$$\begin{aligned}
\frac{\partial S_1}{\partial t}+\frac{\partial S_1}{\partial a} &= -\left[m(a)+k\phi(t)+\psi(t,a)\right]S_1(t,a)\\
\frac{\partial E_1}{\partial t}+\frac{\partial E_1}{\partial a} &= -\left[m(a)+x+y+\psi(t,a)\right]E_1(t,a)+k\phi(t)\left[S_1(t,a)+F_1(t,a)\right]\\
\frac{\partial F_1}{\partial t}+\frac{\partial F_1}{\partial a} &= -\left[m(a)+z+k\phi(t)+\psi(t,a)\right]F_1(t,a)+yE_1(t,a)+wI_1(t,a)\\
\frac{\partial I_1}{\partial t}+\frac{\partial I_1}{\partial a} &= -\left[m(a)+w+d+\psi(t,a)\right]I_1+xE_1(t,a)+zF_1(t,a)
\end{aligned} \tag{3.2}$$

The equations for those at early stage of HIV (HIV positive):

$$\begin{aligned}
\frac{\partial S_2}{\partial t}+\frac{\partial S_2}{\partial a} &= -\left[m(a)+k\phi(t)+h\right]S_2(t,a)+\psi(t,a)S_1(t,a)\\
\frac{\partial E_2}{\partial t}+\frac{\partial E_2}{\partial a} &= -\left[m(a)+x+y+h\right]E_2(t,a)+k\phi(t)\left[S_2(t,a)+F_2(t,a)\right]+\psi(t,a)E_1(t,a)\\
\frac{\partial F_2}{\partial t}+\frac{\partial F_2}{\partial a} &= -\left[m(a)+z+k\phi(t)+h\right]F_2(t,a)+yE_2(t,a)+w^{'}I_2(t,a)+\psi(t,a)F_1(t,a)\\
\frac{\partial I_2}{\partial t}+\frac{\partial I_2}{\partial a} &= -\left[m(a)+w^{'}+d^{'}+h\right]I_2(t,a)+xE_2(t,a)+zF_2(t,a)+\psi(t,a)I_1(t,a)
\end{aligned} \tag{3.3}$$

Model's equations for those at late stage of HIV infection are:

$$\begin{aligned}
\frac{\partial S_3}{\partial t}+\frac{\partial 3_2}{\partial a} &= -\left[m(a)+k\phi(t)+i\right]S_3(t,a)+hS_1(t,a)\\
\frac{\partial E_3}{\partial t}+\frac{\partial E_3}{\partial a} &= -\left[m(a)+x^{'}+y^{'}+i\right]E_3(t,a)+K\phi(t)\left[S_3(t,a)+F_3(t,a)\right]+hE_2(t,a)\\
\frac{\partial F_3}{\partial t}+\frac{\partial F_3}{\partial a} &= -\left[m(a)+z^{'}+k\phi(t)+i\right]F_3(t,a)+y^{'}E_3(t,a)+w^{'}I_3(t,a)+hF_2(t,a)\\
\frac{\partial I_3}{\partial t}+\frac{\partial I_3}{\partial a} &= -\left[m(a)+w^{'}+d^{'}+i\right]I_3(t,a)+x^{'}E_3(t,a)+z^{'}F_3(t,a)+hI_2(t,a)
\end{aligned} \tag{3.4}$$

We are neglecting here both mother-to-child transmission of HIV and the impact of HIV/TB on the number of births. The boundary conditions therefore becomes;

$$\begin{array}{llll} S_0(t,0) = pB & E_0(t,0) = 0 & F_0(t,0) = 0 & I_0(t,0) = 0 \\ S_1(t,0) = p^{'}B & E_1(t,0) = 0 & F_1(t,0) = 0 & I_1(t,0) = 0 \\ S_2(t,0) = 0 & E_2(t,0) = 0 & F_2(t,0) = 0 & I_2(t,0) = 0 \\ S_3(t,0) = 0 & E_3(t,0) = 0 & F_3(t,0) = 0 & I_3(t,0) = 0 \end{array}$$

Where $p + p' = 1$. Initial age distributions at time 0 complete the initial boundary value problem for the model. We take the endemic TB steady state plus a twenty year old year HIV infected person. To obtain the TB endemic state age distributions, we set the time derivates of the first four model equations (3.1) to zero. Hence we obtain the following four differential equations with age a as independent variable.

$$\begin{aligned} \frac{dS_0}{da} &= -\left[m(a) + k\phi(t)\right] S_0(a) \\ \frac{dE_0}{da} &= -\left[m(a) + x + y\right] E_0(a) + k\phi(t)\left[S_0(a) + F_0(a)\right] \\ \frac{dF_0}{da} &= -\left[m(a) + z + k\phi(t)\right] F_0(a) + yE_0(a) + wI_0(a) \\ \frac{dI_0}{da} &= -\left[m(a) + w + d\right] I_0(a) + xE_0(a) + zF_0(a) \end{aligned} \tag{3.5}$$

That is the time dependence is dropped out. The solution to these systems of differential equations (3.5) becomes the endemic TB steady state age-distributions.

Prevalence of MTB	$\sum_{n=0}^{3}(E_n + F_n + I_n)/\mathrm{P}$
TB incidence rate	$x(E_0 + E_1 + E_2) + x'E_3 + z(F_0 + F_0 + F_2) + Z'F_3$
TB notification rate	$q(I_0 + I_1 + I_2) + q'I_3$
Undiagnosed TB	$I_0 + I_1 + I_2 + I_3$
Treated TB	$\tau\times$ notification rate
TB prevalence	Treated TB + Undiagnosed TB
HIV prevalence	$\sum_{n=1}^{3} P_n/P$

Table 3.4: Relationship between medical terms and model

3.3 Model Equations Description

We briefly discuss an intuitive interpretation of the first-four model equations (3.1). Since they are all age-structured models, the descriptions will be similar for the other equations [(3.2) (3.3), (3.4)]. The first equation implies that, $S_0(t,a)$ (which represents the number of susceptible individuals, of age a, at time t) at a given point in time may change with age $\left(\frac{\partial S_0}{\partial a}\right)$ and likewise the number at a given age may change over time $\left(\frac{\partial S_0}{\partial t}\right)$, as susceptibles are lost by natural death at a rate $m(a)$ or as they transferred to the latent TB class, $E_0(t,a)$ at a rate $k\phi(t)$.

The left-hand side of the other three equations will follow the same explanation as the first, so we will rather explain the right-hand side. The second equation means that the $E_0(t,a)$ population are lost by natural mortality of rate $m(a)$ or as they are transferred to the $F_0(t,a)$ and $I_0(t,a)$ classes at the rates y and x respectively. $E_0(t,a)$ increases their population through the outflows from the $S_0(t,a)$ and $F_0(t,a)$ compartments with the equal rates as $k\phi(t)$ as shown in the model diagram. The third and fourth model equations will also follow similar explanations as above.

3.4 Basic Reproduction Number For TB

We compute the basic reproduction number for TB Only. We assume here a constant mortality (we ignore age-dependence) and that there is no HIV. To do this, we use only the first-four equations (3.1) in the model's equations. But we further ignore the S_0 compartment since we require only the infected compartments (E_0, F_0 and I_0). Therefore the basic reproduction number R_0 for TB is given by the spectral radius of the matrix

$$\begin{pmatrix} 0 & 0 & k \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} x+y+m & 0 & 0 \\ -y & z+m & -w \\ -x & -z & w+m+d \end{pmatrix}^{-1}$$

[9]

Hence using XMAXIMA, we get the spectral radius of the above matrix to be

$$R_0 = \frac{k(mx+xz+yz)}{[m(m+d+w)+z(m+d)](m+x+y)}$$

Using the parameter values in table 3.3, we obtain $R_0 = 1.6$

4. Parameter Values And Simulations

In this chapter, we discuss parameter values related to TB and HIV in our model and also demographic parameters. We will then perform numerical simulations to generate some important results.

4.1 Demographic Parameters

With this, we are interested in survival curve and natural mortality. We assume a survival curve without HIV and TB. This is given by $\sigma(a) = \exp(-\lambda a^{\nu})$ with $\lambda = 10^{-7}$ and $\nu = 4$. The natural mortality is therefore given by $m(a) = -\sigma'(a)/\sigma(a)$ with a as age in years.

4.2 HIV Parameters

For the purpose of our model formulation, we have taken the age-dependent risk $\rho(a)$ of getting HIV as

$$\rho(a) = \begin{cases} 0 & if \quad a < 15 \\ 5 \times 10^{-5} \times 12^2 \times (a-15)^2 exp(-0.24(a-b)^2) & if \quad a \geq 15 \end{cases} \tag{4.1}$$

where a is age in years (Fig 4.1(c)). We have also taken the age distribution of partners $f(a, b)$ to be proportional to $\exp(-0.05(a-b)^2)$ [Fig 4.1(b)]

4.3 TB Parameters

In this subsection, we shall discuss parameters related to TB progression, active TB without Treatment and we will finally talk about parameters associated with treatment. These parameters will be derived from information obtained from [8, 10, 11]

4.3.1 Pregression From Latent To Active TB

It has been establised in [10] that progression to active TB is said to be rapid if it occurs within 5 years after infection. According to the same paper, 14% of HIV-negative people or early HIV-positive people develop active TB within these five years. After that the progression is slow which is 0.001/year. Also 67% people who are in their late stage of HIV develop TB within 5 year, after that the progression rate is slow, 0.1/year. As indicated in table (3.3), we assume that $y = y'$ to be 0.2/year

With this information, we evaluate the following parameters x, x', z and z' as follows. We translate this information within the model by equations;

$$\frac{x}{x+y} = \frac{14}{100} \tag{4.2}$$

$$\frac{x'}{x'+y'} = \frac{67}{100} \tag{4.3}$$

$z = 0.001$/year and $z' = 0.1$/year. From 4.2 and 4.3, we obtain x=0.033/year and x'=0.41/year. The reason why $x' > x$ is due to the fact that, people who are in their late stage of HIV develop TB at a faster rate than those who are HIV-negative or early HIV-positive

4.3.2 Active TB Without Treatment

According to [11], the duration of illness for untreated TB is 2.0 years if HIV-negative and 0.5 years if HIV-positive. The average case fatality rate for HIV-negative and HIV-positive people are 43% and 78% respectively. We translate this information within the model to obtain the equations:

$\frac{1}{r+d} = 2.0$ years, $\frac{d}{r+d} = \frac{43}{100}$, $\frac{1}{r'+d'} = 0.5$ years, $\frac{d'}{r'+d'} = \frac{78}{100}$

Solving we obtain $r = 0.29$/year , $d = 0.22$/year, $r' = 0.44$/year and $d' = 1.6$/year

4.3.3 Treatment

To estimate the detection rates q and q', we consider the situation in 2005 of the township of South Africa. According to [8], adult population was estimated to be 10,408. The estimate for the prevalence of HIV-negative people with undiagnosed was 3/762 and that of HIV-positive people with undiagnosed TB was 9/762.

Now let;

- $I_0 + I_1 =$ Number of HIV-negative people who have TB
- $I_2 + I_3 =$ Number of HIV-positive people who have TB

Therefore from the information given above we obtain;

- $I_0 + I_1 \simeq 10,408 \times 3/762 \simeq 41$
- $I_2 + I_3 \simeq 10,408 \times 9/762 \simeq 123$

This reference also indicates that, the number of TB notifications was 259 in 2005, of these 88 (34%) were HIV-negative and 171 (66%) were HIV-positive. We finally evaluate the detection rates from the following equations as ;

$$q(I_0 + I_1) \simeq 88, \quad q'(I_2 + I_3) \simeq 171$$

Hence $q \simeq 2.2$/year and $q' \simeq 1.4$/year.

4.4 Simulated Results

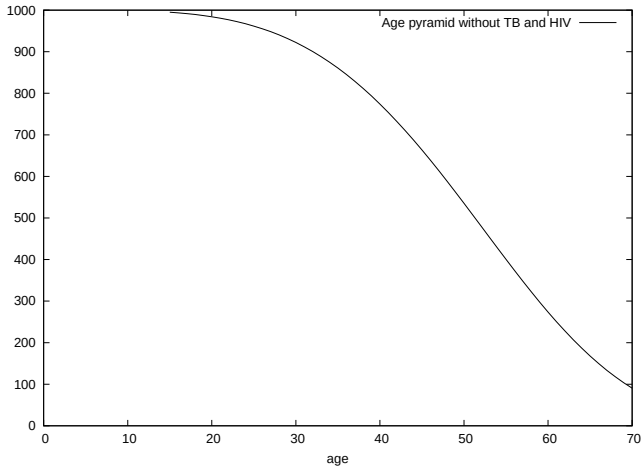
The model was discretized with a time and age step of one month. The simulation was performed with a population having a normal age pyramid as shown in Fig 4.1 a. Number of people with HIV and Number of TB notifications as function of age in 1996, 1998,...2004 are shown in Fig. 4.2(a) and Fig. 4.3(a) respectively. HIV prevalence as function of age in 1996 and 2004 (Fig 4.2(b)), TB notification rate as function of age in 1996 and 2004 (Fig. 4.3(b)). HIV prevalence as function of time ((Fig. 4.2(c)) and TB notification rate a function of time (Fig. 4.3(c))

The results in table 4.1 was obtained from the simulated population at time t=2005. The prevalence of *Mycobacterium tuberculosis* among adults was 97% for the year 2005.

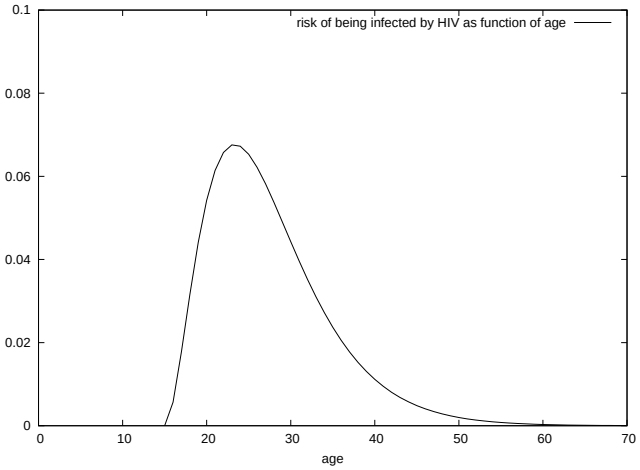
	HIV-	HIV+	Total
Undiagnosed TB	3	5	8
Treated TB	4	4	8
Total	587	175	762

Table 4.1: Simulated values

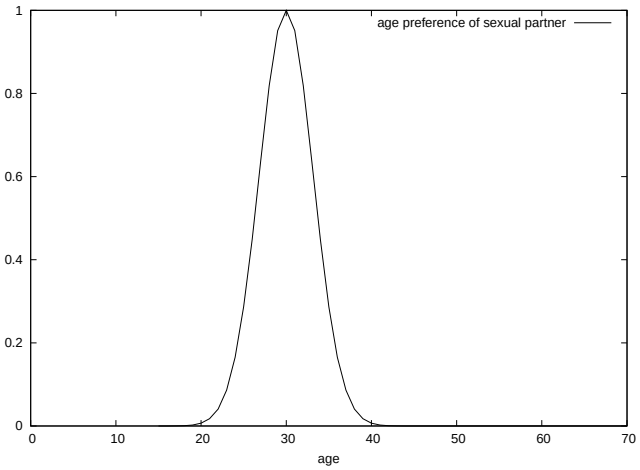
HIV prevalence among TB notifications was 54% instead of 66% at time t=2005. From the simulation we found out that if the the parameter w is high (i.e high values of detection rate r and successfully treatment s), then R_0 can be less than 1.



(a)

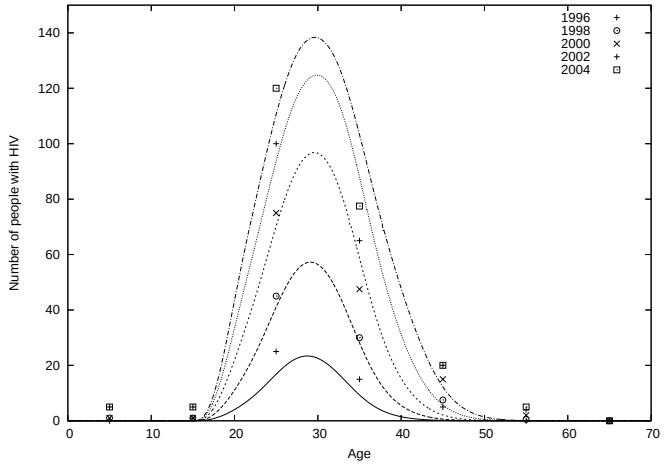


(b)

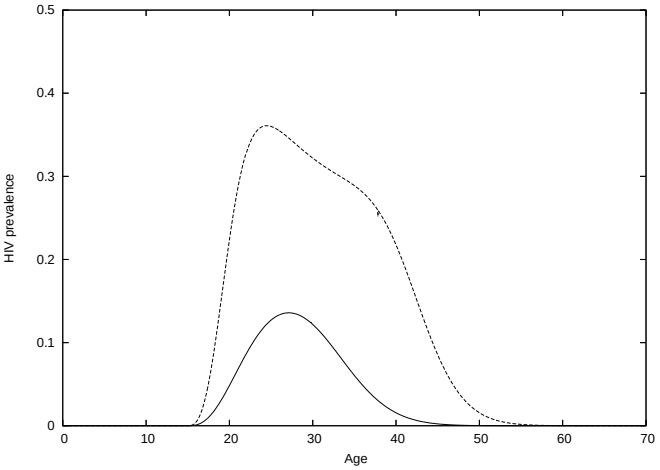


(c)

Figure 4.1: Subfig (a) represent age pyramid without TB and HIV, (b) represent risk of being infected by HIV and (c) depicts age preference of sexual partner.



(a)



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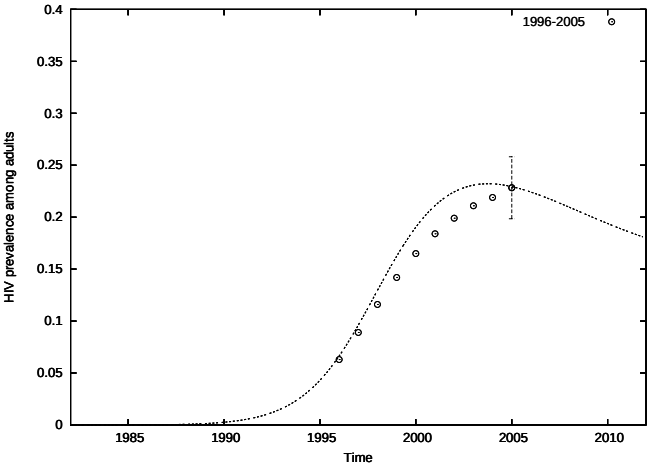
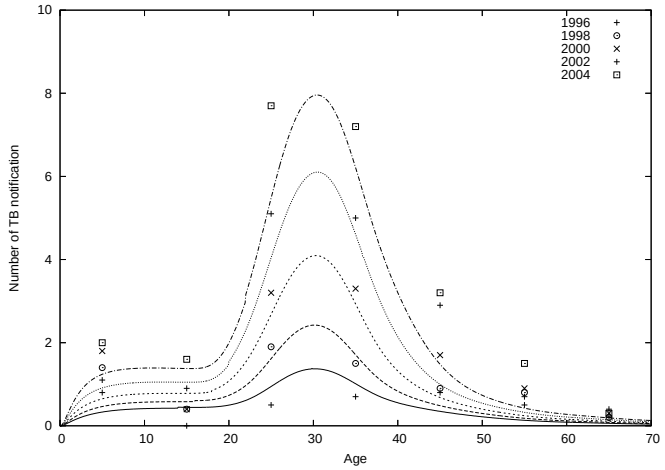
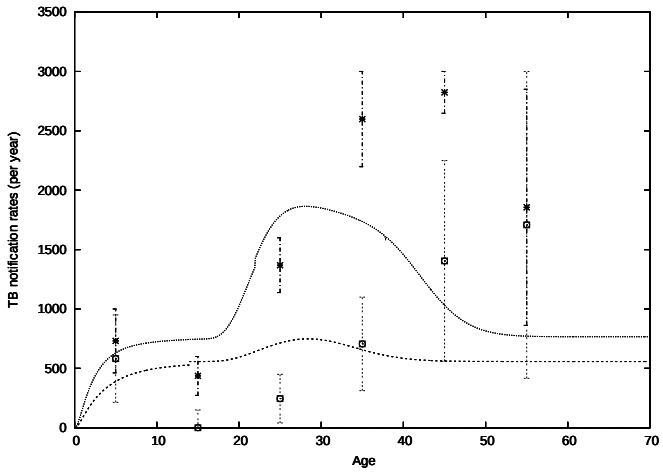


(c)

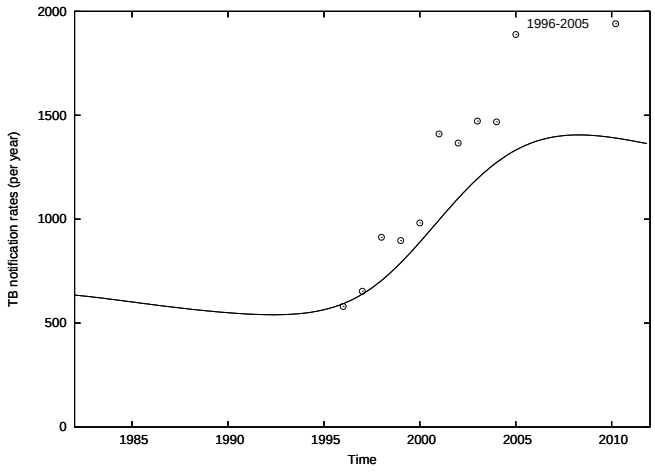
Figure 4.2: Subfig (a) represent number of people with HIV as function of age in 1996,1998,...2004, (b) HIV prevalence as function of age in 1996 and 2004, (c) represent HIV prevalence as function of time. Data from [2].



(a)



(b)



(c)

Figure 4.3: Subfig (a) shows the number of TB notifications a function of age in 1996,1998,...2004, (b) represent TB notification (per year) as function of age and (c) represent TB notification rates (per year) as function of time. Data from [2].

5. Conclusion

In this essay we have reviewed age-structured population models for HIV and TB interaction in a South African township. The choice to investigate these two methods in conjunction is motivated by their close relationship.

In chapter 1, we investigated the basic epidemiology of Tuberculosis (TB) and HIV, introducing relatively simple compartmental models.

In chapter 2, we went on to study age-structured population models. We then merged the ideas from these models into a more sophisticated description of the interactions of the two diseases, and how they affect each other.

The interactions between HIV and TB lead to drastic problems since the immunodeficiency caused by AIDS leads people to contract TB. To reflect this, the model presented in chapter 3 takes both diseases into account and considers all possible interactions by dividing the population into relevant categories.

Further, we reviewed different epidemiological techniques to estimate parameters in the model. The estimation of these parameters relied on the extraction of relevant information from data available in the literature. Finally, we were able to present computed solutions of the model numerically, using octave.

It was found that where the level of successful treatment was high, the basic reproduction number, R_0 can take values less than 1. This would lead to a decline in the TB epidemic, the disease for which treatment exists being our focus.

Our model does have certain drawbacks. It does not take into account some important factors. For example, the random mixing assumption used in our model excludes children, which is clearly not realistic. Secondly, the absence of a recovery compartment in the model is a serious disadvantage. The addition of a recovery category would substantially improve our model, though the limited time frame for this project required us to omit the consideration of this extension.

The most obvious extension of this project would be to incorporate the above mentioned factors, and to include the vertical transmission of HIV/AIDS, from mother to child. Investigating local and global stability analysis for this model would also be an interesting avenue of exploration.

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