The Effect of Incidence Rates on the Dynamics of a Model for HIV Epidemiology

BY

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A Thesis Submitted to the Faculty of Graduate Studies
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Of

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Contents

Chapter 1

Mathematical Epidemiology

1.1 Infectious Diseases

Improvements in sanitation and healthcare programs in the 1950s and 1960s resulted in the common belief that infectious diseases would soon be eliminated [32]. We have all seen the effects of antibiotics and immunization on human morbidity and mortality worldwide. Indeed, the eradication of smallpox through a worldwide vaccination program is deemed to be one of man's great triumphs over infectious diseases. Such successes have created an aura of dominance over infectious diseases. In the developed nations this has been partially true, and consequently, attention has shifted to other chronic diseases such as cardiovascular disease and cancer. However, in the developing nations, infectious diseases have continued to be a major cause of mortality and economic devastation. Moreover, the microbes (bacteria, viruses, fungi, and parasites) that cause infectious diseases have shown an ability to adapt to their environments, allowing new variants to emerge and

necessitating new control strategies. The HIV/AIDS epidemic and outbreaks of diseases such as ebola, west nile, influenza, and SARS are events of continued concern and interest to many people and remind us that communicable diseases are a part of modern life as well.

The emergence and detection of new diseases has been discussed in recent books such as [65], [10]. Changes caused by human or animal invasions of new ecosystems, global warming, environmental degradation, increased international travel, and new economic patterns will continue to provide opportunities for the spread of both new and existing disease-causing microbes. For example, hantavirus was discovered in the southwestern United States following an outbreak in May of 1993. Hantavirus is thought to have existed in this region previously but at low levels which were likely undetected. The virus is known to be maintained and transmitted primarily within the deer mouse populations without producing obvious disease. Hantavirus may be transmitted to humans through contact with infected deer mouse secretions and causes hantavirus pulmonary syndrome (HPS) with a high mortality rate of 40% [9], [23]. The 1993 HPS outbreak is believed to be attributed to environmental conditions and a subsequent increased deer mice population caused by unusual weather in 1991-92 [23], [61]. Specifically, it is believed that the increased rainfall in 1991-92 and a mild winter in 1992 produced conditions favorable for the large observed increase in the deer mouse population of 1993 and thus led to increased rates of contact between humans and deer mice.

In spite of the advances in the healthcare systems, the global curse of infectious diseases continues; not only do these diseases continue to cause morbidity and mortality in a

large number of humans, particularly in developing countries, but also the emergence and spread of new antimicrobial-resistant microbes is now threatening to undermine our ability to treat infections and save lives. The leading killers have been respiratory infections, malaria, HIV/AIDS, diarrhoeal diseases, and tuberculosis [32]. In each case, resistance to the first-line drugs has been observed. In some cases, the level of resistance has forced a change to more expensive second- or third-line drugs. The possible development of resistance against multiple drugs is a major public health challenge to humans worldwide.

Infectious diseases are responsible for almost half of the mortality in developing countries, where the population has limited access to the drugs and healthcare facilities necessary for prevention. In July 2000, the World Health Organization (WHO) identified *three major infectious disease threats to be HIV, TB, and malaria* [76], which happen to be caused by a virus, bacteria, and parasite, respectively. None of these possesses an effective vaccine. Of all the mortality caused by infectious disease, approximately half can be attributed just to HIV, TB, and malaria, which cause over 300 million illnesses and more than 5 million deaths each year [32].

The social and economic burden imposed by these diseases is staggering. These diseases penalize poor communities, as they perpetuate poverty through loss of work, school drop-out, decreased financial investment and increased social and political instabilities. Sustainable development is feasible if countries can tame the infectious diseases that disempower their people. If these diseases continue unchecked, they damage the social fabric, diminish agricultural and industrial production, undermine political, social and economic stability, and contribute to regional and global insecurity. Some of the examples include:

(i) Africa's Gross Domestic Product would be up to $100 billion (US) greater if malaria had been eliminated years ago [76].

(ii) A nation can expect a decline in Gross Domestic Product of 1% per year when more than 20% of an adult population is infected with HIV [76].

(iii) Increasingly, infectious diseases are moving across borders. Over half of the TB cases in some wealthy countries are among foreign-born populations [76]. Over 12,000 cases of malaria were reported among European travellers last year [76].

Infectious diseases are a matter of national security due to the potential misuse of microbial pathogen in bioterrorism. Some accounts of infectious diseases, such as bubonic plague and smallpox, have impacted the growth of nations and historically contributed to the rise and fall of empires [10], [65]. More recently, we have seen other diseases such as mad-cow, hoof-and-mouth, SARS, and avian influenza affecting the economies of various countries across North America, Asia, and Europe.

Due to recent advances in medicine, there are some improvements in the control of HIV, TB, and malaria [60], [76]; but these are apparently inadequate in reversing the patterns of these diseases worldwide. Many countries have shown that, by using available tools both widely and wisely, TB deaths can be reduced five-fold, HIV infection rates can also be reduced by 80% and malaria death rates can be halved [76]. However, many countries have an annual healthcare budget of less than $50 per capita. The cost of the tools needed to fight HIV, TB, and malaria in such countries is prohibitive [76]. In such countries, life threatening diseases such as measles, respiratory infections, and diarrhoeas

are often not treated. Consequently, in parts of the world, diseases such as measles, malaria, typhus, cholera, schistosomiasis, and sleeping sickness are still endemic (disease persistent) [32].

The advantages of the well-funded effective healthcare on the control of infectious diseases are documented and obvious. The prevalence and effect of many diseases in less developed countries is probably less well known but may be even more important. The application of mathematical modelling to optimize utilization of health care resources is an important area in need of development.

1.2 HIV Epidemiology

Of the many infectious diseases, HIV/AIDS is the fastest growing threat to economic and social development today and a potential risk for national and regional security, as recognized by the United Nations Security Council in January 2000 [71]. What sets this disease apart from other epidemics is the speed of its spread and the extent of its devastation.

In December 2002, WHO, in collaboration with UNAIDS (the United Nations AIDS Division), released their AIDS Epidemic Update with estimates based on the most recent available data on the spread of HIV in countries around the world. There were 42 million people living with HIV/AIDS world-wide. 38.6 million of these were adults, 19.2 million were women and 3.2 million were children under the age of 15. Five million new infections with HIV occurred in 2002, of which 4.2 million were adults and 2 million of them were

women. A total of 3.1 million people died of HIV/AIDS related causes in 2002. Sub-Saharan Africa had the highest number of HIV positive individuals (29.4 million people were living with HIV/AIDS) followed by South and South-East Asia (6 million). In North America there were 980,000 people living with HIV/AIDS, 570,000 in Western Europe and 1.2 million in Eastern Europe and Central Asia. The number of HIV positive individuals in Australia and New Zealand has remained constant since 2001 (15,000 people). In Latin America and the Caribbean the figures were 1.5 million and 440,000 respectively. Asia had 1.2 million people living with HIV/AIDS. North Africa and the Middle East have 550,000 people living with HIV/AIDS [71].

On 14 March 2003 in Geneva, an expert group set up by WHO stressed that *unsafe sex is the primary mode of transmission of HIV* in Africa. This group reaffirmed that unsafe sexual practices are responsible for the vast majority of HIV infections in sub-Saharan Africa, and that safer sex promotion must remain the primary feature of prevention programs in the region [70].

Recently WHO and UNAIDS hosted a meeting of experts which addressed issues related to unsafe injection practices and HIV in healthcare contexts and evaluated the relative contribution of these practices in HIV transmission in sub-Saharan Africa. Following a review of the evidence, which included recent articles suggesting that a majority of HIV infections in sub-Saharan Africa are due to unsafe medical practices, particularly relating to injections, the experts concluded that such suggestions are not supported by the vast majority of evidence and that *unsafe sexual practices continue to be responsible for the overwhelming majority of infections* [70]. While a combination of prevention mea-

sures is required to tackle all modes of HIV transmission, the promotion of safer sexual practices must remain the primary feature of prevention programs in the region. This position is strongly supported by epidemiological and biomedical data [70]. For example, children between 5-14 years, who are generally not yet sexually active, have very low infection rates; age-specific infection rates among young women and men strongly follow patterns of sexual behavior and those of other sexually transmitted infections (such as herpes simplex virus-2); in sexually active couples both partners are often infected; and, there is no consistent association between higher HIV rates and lower injection safety standards.

Modelling of the epidemic with the best available information also shows that the overwhelming majority of infections are due to unsafe sex [70]. WHO has previously estimated that unsafe injection practices account for about 2.5% of HIV infections in sub-Saharan Africa. Although there is a margin of uncertainty around this estimate, the conclusion remains that unsafe sex is by far the predominant mode of transmission in sub-Saharan Africa [70].

With approximately 3.5 million Africans becoming infected in 2002 alone, and a total of 29.4 million adults and children living with HIV/AIDS in the region, the prevention of HIV through the practice of safer sex should be the mainstay of the response to AIDS in the region. Discussions about the importance of other modes of transmission should at no time weaken this central part of the response.

In the context of the HIV/AIDS epidemic, WHO and UNAIDS continue to strive to understand the global and local epidemiology of HIV.

1.3 Mathematical Modelling

Mathematical modelling of epidemiology has been one of the first successes of Mathematical Biology. Many of the early developments in such modelling are due to public health physicians. The first model appearing in the literature was for the evaluation of vaccination with the smallpox virus in 1760 by Daniel Bernoulli. Bernoulli was a mathematician who had training as a physician. Modern mathematical epidemiology seems to have started around 1870 with contributions by P.D. En'ko and later by public heath physicians such as Sir R.A. Ross, W.H. Hamer, A.G. McKendrick, W.O. Kermack, and from statistician J. Brownlee. Of particular interest is Dr. Ross receiving his second Noble Prize in medicine for demonstrating the transmission dynamics of malaria from mosquitoes to humans. His work predicted that malaria could be avoided if the mosquito population could be reduced below a critical threshold level. His predictions were supported by field trials and led to brilliant advances in malaria control [32], [10]

With the revived emphasis on infectious diseases, mathematical models become important tools in analyzing the spread and control of infectious diseases. The use of mathematical models has substantially contributed to the understanding of the mechanism of disease transmission and to the evaluation of proper control strategies. Both aspects, however, depend greatly on the assumptions made in the model formulation. Often there exists a trade off between model assumptions and reliable data to support them. This model formulation process helps to clarify assumptions, variables, and parameters; moreover, models often give rise to qualitative and quantitative concepts such as epidemic

threshold, basic reproduction number, contact number, replacement number, and endemic equilibrium number. Mathematical models and computer simulations are useful experimental tools for building and testing theories, assessing qualitative conjectures, determining sensitivities to changes in parameter values and estimating key parameters from data. Understanding the transmission characteristics of infectious diseases in communities, regions, and countries can lead to better approaches to decreasing the transmission of these diseases. Mathematical models are used in comparing, planning, implementing, evaluating, and optimizing various detection, prevention, therapy, and control programs. Epidemiology modelling can contribute to the design and analysis of epidemiological surveys, suggest crucial data that should be collected, identify trends, make general forecasts, and estimate the uncertainty in these forecasts [32].

The goal of this thesis is to better understand how HIV epidemiology models with nonlinear incident rates differ in terms of their disease transmission dynamics. In studying these models the goal is two fold: one is to examine the epidemic models to gain insight into the biology of the disease; the other is to gain a deeper understanding of the theory of nonlinear dynamical systems and differential equations.

For this purpose, the thesis is organized into a review of dynamical systems in Chapter 2, a formulation of an HIV epidemiology model in Chapter 3, the analysis of this model with three choices of incidence function in Chapter 4, and a discussion and comparison of these analyses in Chapter 5.

Chapter 2

Dynamical Systems Theory

Although the application of dynamical systems theory is widespread in the literature, it is still growing in the field of mathematical biology. Many of the current topics of mathematical biology consist of the formulation and analysis of mathematical models; these models often take the form of differential or difference equations, partial differential equations, or stochastic differential equations with or without time delay. The analysis of such models generally involves the local and global stability of their steady-states (equilibrium points), and bifurcation behaviors. Global analysis, which is a major focus in this thesis, is not generally easy to perform. It is often conjectured that when a system has a unique stable equilibrium, it is globally asymptotically stable. However, the existence of periodic solutions (limit cycles) contradicts such a conjecture. In the absence of any periodic solutions, it is still a challenging task to investigate the global analysis of the system.

In dynamical systems theory, there are several techniques which might be employed to

study the global behavior of an equilibrium point, such as the Dulac criterion, the use of the Poincaré index, and the construction of Lyapunov functions. In this thesis, we apply the Poincaré-Bendixson theorem and Dulac criterion to several models for the dynamics of HIV epidemiology to examine their global behavior.

In the present chapter, we provide a review of some of the fundamental concepts and theorems of dynamical systems which are used in the analysis of the models discussed in Chapters 3 and 4. The references used throughout this chapter are primarily [63], [31], [75]; examples of applications to the HIV epidemiology models can been seen in Chapter 4.

2.1 Nonlinear Systems

Consider an autonomous system of ordinary differential equations:

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x}), \quad \mathbf{x} = (x_1, ..., x_n) \in \mathbb{R}^n, \quad t \in \mathbb{R} \tag{2.1.1}$$

where $\mathbf{f} = (f_1, ..., f_n)$ with each $f_i : \mathbb{R}^n \to \mathbb{R}$ being a real-valued function for $i = 1, ..., n$.

The vector function $\mathbf{f}$ is said to be differentiable on an open subset $E \subseteq \mathbb{R}^n$ if each of its components f_i possesses continuous first order partial derivatives $\frac{\partial f_i}{\partial x_j}$ $(i = 1, 2, ..., n; j = 1, 2, ..., n)$ on E. In this case, $\mathbf{f}$ is said to belong to the *class of differentiable functions on* E, written as $\mathbf{f} \in C^1(E)$. More generally, we say that $\mathbf{f}$ is *differentiable of order* m *on* E, written as $\mathbf{f} \in C^m(E)$, if each f_i possesses partial derivatives to order m which are continuous on E. Finally $\mathbf{f}$ is said to be *smooth on* E, written as $\mathbf{f} \in C^\infty(E)$, if all partial

derivatives of its components to arbitrary order are continuous on E.

A solution of (2.1.1) is a real-valued differentiable function $\mathbf{x}(t) = (x_1(t), x_2(t), ..., x_n(t))$ defined on some open interval $I \subseteq \mathbb{R}$ (of the independent variable t) which together with its derivative $\frac{d\mathbf{x}(t)}{dt}$ satisfies (2.1.1) identically on I, that is, $\frac{d\mathbf{x}(\mathbf{t})}{dt} = \mathbf{f}(\mathbf{x}(t))$ for all $t \in I$.

Typically we are interested in a solution $\mathbf{x}(t)$ on I satisfying some prescribed initial condition $\mathbf{x}(t_0) = \mathbf{x}_0$ where t_0 is a prescribed point in I. Without loss of generality, we may assume t_0 is chosen to be the origin ($t_0 = 0$).

A solution of the initial-value problem consisting of the system (2.1.1) together with the initial condition $\mathbf{x}(0) = \mathbf{x}_0$ is uniquely determined on an open interval containing $t = 0$ if $\mathbf{f} \in C^1(E)$, as indicated in the following theorem [[63], pp.74].

Theorem 2.1.1 *(Picard): Let E be an open subset of $\mathbb{R}^n$ containing $\mathbf{x}_0$. If $\mathbf{f} \in C^1(E)$, then there exists a real number $a > 0$ such that the system of differential equations (2.1.1) with the initial condition $\mathbf{x}(0) = \mathbf{x}_0$ has a unique solution $\mathbf{x}(t)$ on the interval $(-a, a)$.*

The above theorem simply states that for a given initial condition, $\mathbf{x}_0$, there is a unique solution curve of (2.1.1), defined on some sufficiently small interval on the t-axis containing $t = 0$, that passes through the point $\mathbf{x}_0$ when $t = 0$. Comment: Although Picard's theorem guarantees only the local existence and uniqueness of this solution curve (on some sufficiently small interval containing $t = 0$), we shall assume that this interval may be extended to include all real values of t. As an immediate consequence of this theorem, and our assumption, the solutions of (2.1.1) in E with different initial conditions in E *have no point of intersection* in E.

Let the mapping $\mathbf{x} = \phi(t, \mathbf{x}_0)$, with $\phi(t, \mathbf{x}_0) : \mathbb{R} \to E$ for E an open subset of $\mathbb{R}^n$, represent that *unique solution curve (trajectory)* of the system (2.1.1) satisfying the initial condition $\phi(0, \mathbf{x}_0) = \mathbf{x}_0$. This solution represents a curve in E, defined by

$$\Gamma_{\mathbf{x}_0} = \{\mathbf{x} \in E : \ \mathbf{x} = \phi(t, \mathbf{x}_0), \ t \in \mathbb{R}\}. \tag{2.1.2}$$

The *positive half-trajectory* through the point $\mathbf{x}_0 \in E$ is defined by

$$\Gamma^+_{\mathbf{x}_0} = \{\mathbf{x} \in E : \ \mathbf{x} = \phi(t, \mathbf{x}_0), \ t \geq 0\}. \tag{2.1.3}$$

The *negative half-trajectory* through the point $\mathbf{x}_0 \in E$ is defined by

$$\Gamma^-_{\mathbf{x}_0} = \{\mathbf{x} \in E : \ \mathbf{x} = \phi(t, \mathbf{x}_0), \ t \leq 0\}. \tag{2.1.4}$$

Comment: For the purpose of notation, we will denote the trajectory $\Gamma_{\mathbf{x}_0}$ as simply Γ when $\mathbf{x}_0$ plays no role in the discussion.

2.2 Local Stability

One of the main objectives in this thesis will be the study of the behavior of solutions for large values of time, that is the asymptotic behavior of the solutions, and the concepts of limit points and sets are defined for this purpose.

Definition 2.2.1 *A point $\mathbf{P} \in E$ is called an $\omega-$limit point of the trajectory $\mathbf{x} = \phi(t, \mathbf{x}_0)$ of the system (2.1.1) if there is an increasing sequence $\{t_n\}$ with $t_n \to \infty$ as $n \to \infty$ such that*

$$\lim_{n \to \infty} \phi(t_n, \mathbf{x}_0) = \mathbf{P}. \tag{2.2.1}$$

The collection of all $\omega-$limit points of a trajectory of (2.1.1) is called the $\omega-$limit set and denoted by $\omega(\Gamma_{\mathbf{x}_0})$.

Definition 2.2.2 *A point $\mathbf{Q} \in E$ is called an $\alpha-$limit point of the trajectory $\mathbf{x}=\phi(t,\mathbf{x}_0)$ of the system (2.1.1) if there is a decreasing sequence $\{t_n\}$ with $t_n \to -\infty$ as $n \to \infty$ such that*

$$\lim_{n\to\infty} \phi(t_n, \mathbf{x}_0) = \mathbf{Q}. \tag{2.2.2}$$

The collection of all $\alpha-$limit points of a trajectory of (2.1.1) is called the $\alpha-$limit set and denoted by $\alpha(\Gamma_{\mathbf{x}_0})$.

The set of all limit points for $\Gamma_{\mathbf{x}_0}$ is $\alpha(\Gamma_{\mathbf{x}_0}) \cup \omega(\Gamma_{\mathbf{x}_0})$ and is called the *limit set* of $\Gamma_{\mathbf{x}_0}$. A *complete trajectory* is the trajectory together with its limit set, namely, $\Gamma_{\mathbf{x}_0} \cup \alpha(\Gamma_{\mathbf{x}_0}) \cup \omega(\Gamma_{\mathbf{x}_0})$.

Let K be an open subset of E. The set of all trajectories $\mathbf{x}=\phi(t,\mathbf{x}_0)$ for $\mathbf{x}_0 \in K$ is called the *flow* of the system (2.1.1) in K. In other words, the flow of (2.1.1) in K is the complete family of trajectories with initial conditions in K. The flow of (2.1.1) is also called the flow defined by (2.1.1) or the flow of the vector field $\mathbf{f}(\mathbf{x})$.

An important part of dynamical systems theory is the concept of invariant sets with respect to the system (2.1.1). A subset K is an *invariant set* with respect to (2.1.1), if $\Gamma_{\mathbf{x}_0} \subset K$ for any $\mathbf{x}_0 \in K$. A subset K is called *positively invariant* if $\Gamma^+_{\mathbf{x}_0} \subset K$ for any $\mathbf{x}_0 \in K$. A subset K is called *negatively invariant* if $\Gamma^-_{\mathbf{x}_0} \subset K$ for any $\mathbf{x}_0 \in K$. In other words, K is positively (negatively) invariant if every trajectory starting in K remains in K for all $t \geq 0$ ($t \leq 0$).

With the above discussion, we can show that the $\alpha-$ and $\omega-$limit sets are examples of invariant sets with respect to the flow of (2.1.1). It is also clear that the trajectories of solutions that exist for all time are themselves invariant sets with respect to (2.1.1).

The existence of bounded positively invariant region containing all of the $\omega-$limit sets of a system such as (2.1.1) is useful because it allows us to examine the dynamics of the system inside this bounded region. In some applications, the analysis of the flow inside and outside a positively invariant region may be connected to provide global statements about the flow of (2.1.1). The following definition discusses how the flow of (2.1.1) might behave outside a positively invariant region.

Definition 2.2.3 *A closed invariant set $\Omega \subset E$ is called an attracting set of (2.1.1), if there is some neighborhood N of Ω, such that, for all $\mathbf{x} \in N$, the flow $\phi(t, \mathbf{x})$ of (2.1.1) remains in N for all $t \geq 0$, and $\phi(t, \mathbf{x}) \to \Omega$ as $t \to \infty$.*

Comment: This definition does not require the flow of (2.1.1) to enter Ω as $t \to \infty$.

In Figure 2.1, we illustrate a positively invariant set, Ω, as the flow of the system, denoted by the arrows starting in Ω, remains in Ω. Also Figure 2.1 illustrates an attracting set, Ω, since the flow of the system, in a neighborhood of Ω, approaches Ω eventually (and, in this illustration, enters Ω).

In the class of solutions of (2.1.1), there may be solutions that do not move with time, that is, they are fixed for all $t \in \mathbb{R}$.

Definition 2.2.4 *(equilibrium point) A point $\bar{\mathbf{x}} \in R^n$ is called an equilibrium point (equilibrium solution, or critical point) of (2.1.1) if it satisfies the condition $\mathbf{f}(\bar{\mathbf{x}}) = \mathbf{0}$.*

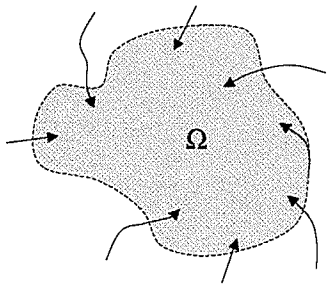

Figure 2.1: Positively invariant region Ω attracting solutions

It is noted that an equilibrium solution of (2.1.1) is always an invariant set with respect to (2.1.1); and if the $\omega - limit$ $(\alpha - limit)$ set of a trajectory of (2.1.1) is a single point in E, then this point must be an equilibrium point.

In the following we discus equilibrium points and their properties. Although equilibria can be classified as *hyperbolic* or *non-hyperbolic,* subsequent analysis of the models presented in this thesis involves only hyperbolic equilibria.

Characterization of equilibrium points may be based on properties of the Jacobian of (2.1.1). The Jacobian of (2.1.1) at an arbitrary point $\mathbf{x} \in E$ is defined by the matrix:

$$J(\mathbf{f}(\mathbf{x})) = \begin{pmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \cdots & \frac{\partial f_1}{\partial x_n} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \cdots & \frac{\partial f_2}{\partial x_n} \\ \vdots & \vdots & \cdots & \vdots \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \cdots & \frac{\partial f_n}{\partial x_n} \end{pmatrix},$$

where $\frac{\partial f_i}{\partial x_j}$ denotes the partial derivative of the function f_i with respect to the jth component of $\mathbf{x}$. This Jacobian is also denoted by $J(\mathbf{x})$, and is sometimes referred to as the linearization of the vector field $\mathbf{f}(\mathbf{x})$, because when $\bar{\mathbf{x}}$ is an equilibrium point, $J(\bar{\mathbf{x}})$ is the coefficient of the first-order term (linear approximation) of the Taylor expansion of $\mathbf{f}(\mathbf{x})$ about $\bar{\mathbf{x}}$. An equilibrium point $\bar{\mathbf{x}}$ is called *hyperbolic* if all the eigenvalues of the Jacobian evaluated at this equilibrium point, $J(\bar{\mathbf{x}})$, have non-zero real parts. Otherwise, $\bar{\mathbf{x}}$ is called *non-hyperbolic.*

Hyperbolic equilibrium points of the system (2.1.1) may be further classified by their local asymptotic behavior as attractors, repellers, or saddles.

Definition 2.2.5 *An (hyperbolic) equilibrium point $\bar{\mathbf{x}}$ of (2.1.1) is called an "attractor" if there exists a neighborhood $\Omega \subset E$ containing $\bar{\mathbf{x}}$ such that Ω is positively invariant and $\bar{\mathbf{x}}$ is the $\omega-$limit set of any trajectory in Ω.*

Definition 2.2.6 *An (hyperbolic) equilibrium point $\bar{\mathbf{x}}$ of (2.1.1) is called a "repeller" if there exists a neighborhood $\Omega \subset E$ containing $\bar{\mathbf{x}}$ such that Ω is negatively invariant and $\bar{\mathbf{x}}$ is the $\alpha-$limit set of any trajectory in Ω.*

Definition 2.2.7 *An (hyperbolic) equilibrium point $\bar{\mathbf{x}}$ of (2.1.1) is called a "saddle" if there exists a neighborhood $\Omega \subset E$ containing $\bar{\mathbf{x}}$ such that Ω contains some trajectory with $\bar{\mathbf{x}}$ as the $\alpha-$limit set and some trajectory with $\bar{\mathbf{x}}$ as the $\omega-$limit set in Ω. Thus, Ω is neither positively nor negatively invariant.*

Figure 2.2 illustrates the behavior of trajectories near these types of equilibria in a planar system (in $\mathbb{R}^2$).

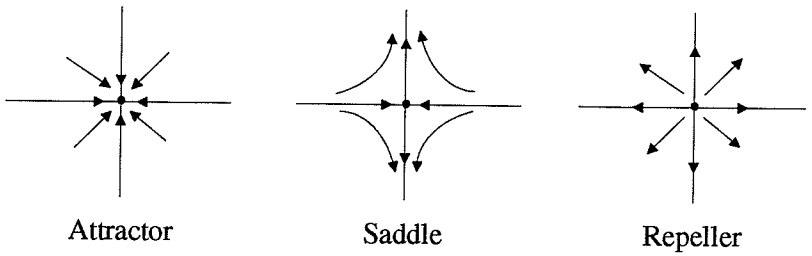

Figure 2.2: Hyperbolic equilibria and their types stability

The stability type of a hyperbolic equilibrium point is unaffected by small perturbations; near the equilibrium point, the linear term in the Taylor expansion of the vector field, $J(\bar{\mathbf{x}})$, can be used to describe the behavior of the flow near $\bar{\mathbf{x}}$. In contrast, the stability of non-hyperbolic equilibria may depend on higher order terms in the Taylor expansion of the vector field, and thus the Jacobian might not be informative [[31], pp 274-75].

In order to determine the behavior of solutions near a hyperbolic equilibrium $\bar{\mathbf{x}}$, the system (2.1.1) is first linearized around $\bar{\mathbf{x}}$; the linearized system of (2.1.1) around $\bar{\mathbf{x}}$ is given by the following linear differential equation system

$$\frac{d\mathbf{x}}{dt} = A\mathbf{x}, \tag{2.2.3}$$

where $A = J(\mathbf{f}(\bar{\mathbf{x}}))$.

Theorem 2.2.8 *(Hartman-Grobman) Let K be an open subset of $\mathbb{R}^n$, let $\phi(t, \mathbf{x}_0)$ denote the flow of (2.1.1) for $\mathbf{x}_0 \in K$, and let $\bar{\mathbf{x}} \in K$ be a hyperbolic equilibrium point of (2.1.1). The flow $\phi(t, \mathbf{x}_0)$ of the nonlinear system (2.1.1) in K is topologically equivalent to the*

flow of the linearized system (2.2.3) in a neighborhood of $\bar{\mathbf{x}}$.

Remark 2.2.9 *The topologically equivalence of (2.1.1) and (2.2.3) near* $\bar{\mathbf{x}}$ *means that a homeomorphism exists between (2.1.1) and (2.2.3) near* $\bar{\mathbf{x}}$, *which maps trajectories of (2.1.1) in some open set* U *near* $\bar{\mathbf{x}}$ *onto trajectories of (2.2.3) in some open set* V *near* $\bar{\mathbf{x}}$, *and preserves the parametrization by time. Thus, near* $\bar{\mathbf{x}}$, *the flow of (2.1.1) and (2.2.3) are qualitatively the same, and the linearization of a system (2.1.1) enables us to characterize the behavior of solutions near an equlibrium point.*

It is easy to see that, for distinct eigenvalues, the solutions of (2.2.3) are linear combinations of the terms of the form $ve^{\lambda t}$, where λ represents an eigenvalue of A (with non-zero real part), and that the nature of the solution near the equilibrium point $\bar{\mathbf{x}}$ can be determined by the signs of the real parts of these eigenvalues of A. Thus, we have the following conclusions:

Corollary 2.2.10 *Under the conditions of the Hartman-Grobman Theorem, the following are true:*

(i) *The (hyperbolic) equilibrium* $\bar{\mathbf{x}}$ *is an attractor if all eigenvalues* λ *of* A *have negative real parts* $(Re(\lambda) < 0)$;

(ii) *The (hyperbolic) equilibrium* $\bar{\mathbf{x}}$ *is a repeller if all eigenvalues* λ *of* A *have positive real parts* $(Re(\lambda) > 0)$;

(iii) *The (hyperbolic) equilibrium* $\bar{\mathbf{x}}$ *is a saddle if there is at least one eigenvalue* λ *of* A *with negative real part and at least one with positive real part.*

Local stability is a property which is related to the equilibria of a system. Roughly speaking, an equilibrium point $\bar{\mathbf{x}}$ is locally stable if all solutions near $\bar{\mathbf{x}}$ stay close to $\bar{\mathbf{x}}$. In dynamical systems theory, an equilibrium point of a system is said to be *locally asymptotically stable*, if it is an attractor as in Corollary 2.2.10. If a hyperbolic equilibrium point is not an attractor, it is said to be unstable. If the equilibrium solution is locally asymptotically stable, then there exists a neighborhood of the equilibrium point in which every solution of (2.1.1) starting in this neighborhood approaches the equilibrium point as $t \to \infty$. In other words, the equilibrium point is the $\omega-$limit set of every solution with an initial condition in this neighborhood.

2.3 Global Stability

An equilibrium point is *globally asymptotically stable*, if every solution with an arbitrary initial condition in E (the domain of the system (2.1.1)) approaches the equilibrium point as $t \to \infty$. Thus, if the equilibrium point is globally asymptotically stable, then it is also locally asymptotically stable. However, the converse is not always true.

In the following we discuss a class of solutions that are periodic, important since the existence of a period solution may be used to show that an equilibrium point is not asymptotically stable.

Definition 2.3.1 *A cycle or periodic orbit of (2.1.1) is any closed solution curve which is not an equilibrium point.*

Definition 2.3.2 *A limit cycle, Γ, of a planar system is a cycle (periodic orbit) of (2.1.1)*

which is the $\alpha-$ or $\omega-$limit set of some trajectory of (2.1.1) other than Γ itself. In addition:

(i) *if Γ is the $\omega-$limit set of every trajectory in some region containing Γ, then Γ is called an $\omega-$limit cycle or a stable limit cycle*;

(ii) *if Γ is the $\alpha-$limit set of every trajectory in some region containing Γ, then Γ is called an $\alpha-$limit cycle or an unstable limit cycle*;

(iii) *if Γ is the $\omega-$ and the $\alpha-$limit set of some trajectory other than Γ in some region, then Γ is called a semi-stable limit cycle.*

We emphasize that all limit cycles are periodic orbits, and that not all periodic orbits are limit cycles.

A trajectory may form a closed curve (cycle) by beginning and ending at limit sets and thus is "bounded" by these limit sets. A trajectory whose $\alpha-$limit set is an equilibrium point and $\omega-$limit set is another equilibrium point is called a *hetroclinic trajectory* (also called sepatrice or graphic trajectory). The union of connected hetroclinic trajectories forming a closed curve is called a *hetroclinic cycle* (also called polygon, separtrix cycle, or graphix cycle). A trajectory whose $\alpha-$ and $\omega-$limit sets are both the same equilibrium point is called a *homoclinic cycle*. Homoclinic cycles are special cases of a hetroclinic cycle containing only one equilibrium point. For this reason, a homoclinic cycle can not contain an equilibrium point which is either an attractor or repeller. The cycle both leaves and returns to a small neighborhood of the equilibrium point, which violates definitions 2.2.6 (attractor) and 2.2.7 (repeller). Illustrations of limit cycles and their stability can be seen

in Figure 2.3, while illustrations of homoclinic and hetroclinic cycles can be seen in Figure 2.4.

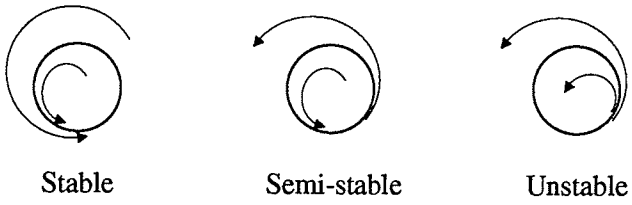

Figure 2.3: Limits cycles and their types of stability

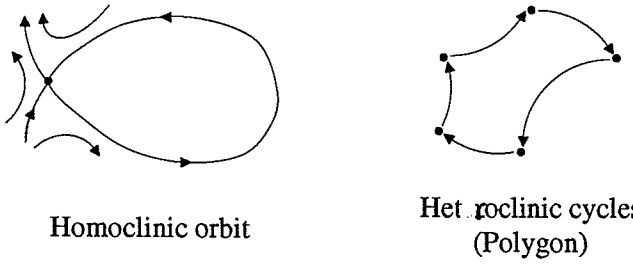

Figure 2.4

Suppose now that $E \subset \mathbb{R}^2$, where E is a simply-connected region. The following criterion can be used to show the non-existence of periodic solutions (limit cycles), hetroclinic or homoclinic cycles in E.

Theorem 2.3.3 *(Bendixson's Criterion) Given the system (2.1.1), with* $\mathbf{f} \in C^1(E)$ *and* E *a, simply-connected region in* $\mathbb{R}^2$. *If the divergence of the vector field* $\mathbf{f}$, *defined by*

$$\nabla \cdot \mathbf{f} = \left(\frac{\partial}{\partial x_1}, \frac{\partial}{\partial x_2} \right) \cdot (f_1, f_2) = \frac{\partial f_1}{\partial x_1} + \frac{\partial f_2}{\partial x_2},$$

is not identically zero and does not change sign in E, then (2.1.1) has no closed solution lying entirely in E.

This follows from Green's Theorem and its proof can be found in [[63], [31], [75]]. In addition, it can be shown that under the hypothesis of Bendixson's Criterion, there are no hetroclinic or homoclinic cycles in E whenever $\nabla \cdot \mathbf{f}$ is not identically zero and does not change sign in E.

The following theorem generalizes the Bendixson criterion by using a real-valued function known as a Dulac function.

Theorem 2.3.4 *(Dulac's Criterion) Consider the system (2.1.1), with $\mathbf{f} \in C^1(E)$ and E a simply-connected region in $\mathbb{R}^2$. If there exists a real-valued function $D \in C^1(E)$ such that $\nabla \cdot (D\mathbf{f})$ is not identically zero and does not change sign in E, then (2.1.1) has no closed solution lying entirely in E.*

The function D is called a *Dulac function.* This theorem reduces to Bendixson's Criterion in the special case when the Dulac function D is simply equal to 1. There is no general method for determining an appropriate Dulac function for a given system of planar autonomous differential equations. Similarly to theorem 2.3.3, it can be shown that under the hypothesis of Dulac's Criterion, there are no hetroclinic or homoclinic cycles in E whenever $\nabla \cdot \mathbf{f}$ is not identically zero and does not change sign in E [[63], pp 262].

Theorem 2.3.4 is often applied in conjunction with the following theorem by Poincaré and Bendixson.

Theorem 2.3.5 *(Poincaré-Bendixson) Consider the system (2.1.1), with* $\mathbf{f} \in C^1(E)$ *and* E *an open subset of* $\mathbb{R}^2$. *Suppose that* Ω *is a positively invariant compact subset of* E *for the system (2.1.1) and that* Γ *is a trajectory with an initial condition in* Ω. *If the* $\omega-$*limit set of* Γ *contains no equilibrium point of (2.1.1), then it must be a periodic solution of (2.1.1).*

As an immediate consequence of the above theorem, one may conclude that if Ω contains a unique equilibrium point of (2.1.1), but no periodic solutions, then this equilibrium point is globally asymptotically stable in Ω.

This completes the review of dynamical systems theory necessary for the purpose of this thesis. For more information please consult [63], [31], [75]. The applications of this review will be seen in the following chapters.

Chapter 3

Model Formulation

The HIV virus differs from other diseases in that it has a longer incubation period (6 years or more) and there is presently no cure for this disease [60], [17]. These two features of the disease's epidemiology help us to identify essential features of the model. Since the incubation period of HIV is longer than for most diseases, the population size is affected by immigration, and by mortality from both the disease and natural causes. This makes it necessary to include what is called the model's *vital dynamics,* i.e., changes in the sexually active population defined as a result of immigration and emigration (the former is often called recruitment; the latter being called removal). Since sexual transmission is the primary mode of HIV transmission [70], [17],[60], the vital dynamics for our model involve specifically persons entering and leaving the sexually active population. Since there is currently no cure for HIV, it is not necessary to introduce replacement of susceptible persons from the infected persons subpopulation; nor is there removal of infected persons, who have developed immunity to the disease, and replacement back into a sexually active

population. This precludes this use of a susceptible-infected-susceptible model (SIS), or a susceptible-infected-recovered model (SIR).

The model we present is a variant of a classical deterministic epidemic model which has appeared in [73],[18],[34]. This model, involving the two classes of *susceptible* persons and *infected* persons only, allows us to readily examine and compare various choices for the so-called *incidence function*, which represents the rate of disease transmission (incidence) between susceptible and infected persons. The choice of incidence function is discussed later in section 3.3.

More detailed models have been suggested in the literature [18],[28],[34]; however, analysis of these models is considerably more difficult and will not be discussed in this thesis.

There are numerous modes of HIV transmission (such as sexual contact, needle-sharing, and blood transfusions), all of which have particular characteristics which must be incorporated through the model parameters. Our model focuses solely on HIV transmission via sexual means as this is recognized as the primary mode of transmission [70],[60]. When considering various models which have appeared in the literature [32],[3],[34],[53],[28],[52],[57], one should be careful to recognize the significance of the assumptions incorporated in each model and their importance in relation to the estimation of the model parameters.

3.1 Sexually Active Population

The model we discuss in this thesis monitors the temporal dynamics of two sexually active sub-populations, namely, the susceptible population whose size at time t is denoted by S, and the population of HIV-infected individuals whose size at time t is denoted by I. Since the model under consideration monitors population sizes, it is realistic to assume that all the associated model variables and parameters are non-negative. Due to the long time associated with the development of the disease, the *unit of time will be assumed to be years*, unless explicitly stated otherwise. The total size of the sexually active population is denoted

$$N = N(t) = S(t) + I(t), \tag{3.1.1}$$

which, by virtue of the time scale used in the model, is *not assumed to be constant* over the time interval under consideration. Thus, our model includes the effects of the vital dynamics of the population, as well as the effects of disease transmission within the population. As noted above, it is assumed throughout the following that $S(t) \geq 0$ and $I(t) \geq 0$.

3.1.1 Susceptible Subpopulation

The model assumes that all new individuals recruited into the sexually active community, at a rate π *persons per year*, are susceptible. It is assumed that the size of this subpopulation decreases through the natural cessation of sexual activity at a constant relative rate μ *per year,* called the natural removal rate. It is further assumed to be reduced at a

rate of $f(S,I)$ *persons per year* by infection of susceptible persons with HIV, which may be acquired following contact with the infectious population I. The function $f(S,I)$ is known as the incidence function and represents the nature of the interaction of the two subpopulations. In addition, in most instances, $f(S,I)$ contains a parameter β which represents the probability of HIV transmission *per sexual contact per year,* and is called the transmission coefficient. We emphasize that only one transmission parameter β appears in the model, because sexual transmission of HIV has been identifed as the primary mode of disease transmission [60],[70],[17]. Specific interpretations will be given in relation to the specific choices of this incidence function in subsequent work. Thus, the size of the susceptible population $S(t) \geq 0$ is modelled through the (nonlinear) differential equation:

$$\frac{dS}{dt} = \pi - \mu S - f(S,I);\ t > t_0, \tag{3.1.2}$$

with the initial condition $S(t_0) = S_0$.

3.1.2 HIV-infected Subpopulation

This subpopulation generally increases in size following the HIV infection of susceptible individuals as a result of the interaction described above. It is assumed to increase at a rate of $f(S,I)$ *persons per year* as a direct result of the transition of members of S to I. Moreover, it is assumed to diminish through the natural cessation of sexual activity at a relative rate μ *per year* and through the disease-induced cessation of sexual activity at a relative rate d *per year*, called the disease-induced removal rate. The latter effect is included in an effort to describe the fact that a portion of the infected population

reduces its sexual activity as a result of its infection. This assumption is reasonable since HIV/AIDS is known to cause behavioral changes in some members of the infected population I [60],[3],[37]. Thus, the infected population $I(t) \geq 0$ is modelled through the (nonlinear) differential equation:

$$\frac{dI}{dt} = f(S, I) - \mu I - dI; \; t > t_0, \tag{3.1.3}$$

with the initial condition $I(t_0) = I_0$.

3.2 The Model Equations

Based on the formulation given above, the general model to be studied in subsequent work consists of the (nonlinear) initial-value problem (IVP):

$$\begin{aligned} \frac{dS}{dt} &= \pi - \mu S - f(S, I); \quad t > t_0, \; S(t) \geq 0, \; S(t_0) = S_0, \\ \frac{dI}{dt} &= f(S, I) - \mu I - dI; \quad t > t_0, \; I(t) \geq 0, \; I(t_0) = I_0. \end{aligned} \tag{3.2.1}$$

Our model contains a general (nonlinear) incidence function $f(S, I)$. We will make various choices for the specific incidence function to generate different models and compare the effects of these choices on the dynamics of the model.

3.3 Nonlinear Incidence Functions Used

In the formulation of a set of model equations, an important question to ask is what incidence function should be chosen to represent the nature of the interaction between the subpopulations. Many of the classical models of disease transmission employ a nonlinear mass action (also called bilinear) incidence rate given by $f(S,I) = \beta SI$ where β is a constant representing the *probability of transmission per contact per year* and S and I are respectively the sizes of the susceptible and infected populations [3]. The motivation for this mass action rate is simple homogeneous mixing of the subpopulations. However, a number of authors have suggested that the incidence rate for disease transmission involves a more complex process and that the incidence function chosen should reflect this [10],[14],[32]. For example, to incorporate behavioral change in the infected subpopulation and to prevent the unboundedness which occurs with the mass action rate, Lui et al. [46] proposed a nonlinear incidence function with a saturated incidence (also called a Holling-type function) given by $f(S,I) = \kappa I^l S/(1+\alpha I^h)$ where $\kappa, h, l, \alpha > 0$. Capasso and Serio [10] use a similar saturated incidence (Holling-type II) function to model cholera epidemics, which is another infectious disease. Holling-type functions together with the class of Ivlev functional responses, given by $f(S,I) = 1 - e^{-aI}$ where $a > 0$, are widely used in population models representing predator-prey systems [3],[10],[73], which often exhibit periodic solutions. Many diseases such as measles and pertussis also exhibit periodicity [22],[2],[73] and in some sense infectious diseases can be seen as predators and their hosts can be seen as prey. A nonlinear incidence function representing proportional

mixing, given by $f(S,I) = \beta SI/(S+I)$ has been used by [18],[3],[32] and its formulation from basic principles is discussed in [32]. In the case of HIV, it is known that the probability of transmission is a function of the viral load inside the body of the HIV infected person [60] and it has been suggested that an appropriate function should model this fact. A better, if not complete, understanding of the disease's progression and the body's associated immune response is desirable in choosing an incidence function that effectively represents the disease's dynamics.

We will investigate three choices for the incidence functions, $f(S,I)$:

(i) the mass action incidence, $f(S,I) = \beta SI$, which has appeared in [3],[32],

(ii) the saturated incidence, $f(S,I) = \beta SI/(1+\alpha I)$, which has appeared in [28],[32],

(iii) the proportional mixing, $f(S,I) = \beta SI/(\alpha S+\alpha I)$, which has appeared in [18],[32].

Comment: the parameter α has units of *per person* and has been added for purposes of dimensional consistency. In the following chapter, α will have a value unity and hence will not appear explicitly in the subsequent analysis.

In Chapter 4, the model (3.2.1), with the above choices of incidence function, is analyzed and the local and global stability properties of each model equilibrium solutions are determined.

Chapter 4

Stability Analysis for Models of HIV

One of the most important concerns in the analysis of epidemiological models is the determination of the asymptotic behavior of their solutions, which is usually based on the stability of their associated equilibria. These models typically possess a disease-free equilibrium and at least one endemic equilibrium. The stability of the disease-free equilibrium is dependent on a threshold parameter, R_0, which is called the *basic reproduction number.* Biologically, this quantity is defined to be *the average number of new infectious cases produced by one infected case introduced into a population that is wholly susceptible* [13],[3]. Mathematically, R_0 determines the condition under which the disease-free equilibrium is locally asymptotically stable.

As is normal, if $R_0 > 1$, then the disease-free equilibrium is unstable and there is a unique endemic equilibrium (which is in most cases locally asymptotically stable [3]). While this dynamical behavior is normal in most disease transmission models, other dy-

namic behavior has been observed in epidemiological models through the existence of periodic solutions or even multiple endemic equilibria existing simultaneously, in which the disease-free equilibrium and an endemic equilibrium may coexist as locally asymptotically stable equilibria [52],[2],[18],[73]. This unusual behavior emphasizes the importance of the analysis of such models, as this has important implications in predicting and controlling the spread of the disease.

In addition to the local stability and global stability of the endemic equilibria, the number of equilibrium points present for various parameter conditions is critically important in the analysis of the model. It is also important to locate the endemic equilibria as they determine the severity of the *disease prevalence* in the population and may yield possible estimates of the *disease incidence* of infection in the population.

Our goal in this chapter is to examine a method for determining the global asymptotic behavior of the solutions of three models representing HIV epidemiology and to determine their local and global dynamics. Each of the following sections is intended to stand alone and may be read independent of section order. Thus, there is a significant repetition of text in these three sections.

4.1 Analysis for Model with Mass Action Incidence

In this section the model equations (3.2.1) are analyzed to determine the global stability of associated equilibria. We use a specific incidence function called mass action (or bilinear) incidence to represent the transmission dynamics of HIV in a sexually active community

by letting $f(S,I) = \beta SI$. Here the general system (3.2.1) becomes

$$\begin{aligned} \frac{dS}{dt} &= \pi - \mu S - \beta SI; \qquad t > t_0,\ S(t) \geq 0,\ S(t_0) = S_0, \\ \frac{dI}{dt} &= \beta SI - \mu I - dI; \quad t > t_0,\ I(t) \geq 0,\ I(t_0) = I_0. \end{aligned} \tag{4.1.1}$$

We are modelling populations, and therefore the variables S and I must be non-negative quantities. The parameters of the equations are all assumed to be positive.

4.1.1 Equilibria and Local Stability Analysis

Disease-free equilibrium: From the definition of equilibria (2.2.4), the equilibrium points of (4.1.1) must satisfy the following equations

$$\begin{aligned} 0 &= \pi - \mu S - \beta IS \\ 0 &= \beta IS - (\mu + d)I. \end{aligned} \tag{4.1.2}$$

In the absence of HIV infection in the population, no persons are infected with HIV and therefore $I = 0$. Solving (4.1.2) for S, with the additional constraint of $I = 0$, gives the *disease-free* equilibrium solution

$$E_0 = \Big(S, I\Big) = \Big(\frac{\pi}{\mu}, 0\Big). \tag{4.1.3}$$

It is important to emphasize that E_0 is biologically meaningful for all combinations of parameters, i.e., throughout the model's parameter space. In addition, E_0 always lies on the positive S-axis.

To investigate the local stability of the disease-free equilibrium, the Jacobian of (4.1.1)

$$J = \begin{bmatrix} -\mu - \beta I & -\beta S \\ \beta I & \beta S - \mu - d \end{bmatrix}, \tag{4.1.4}$$

must be evaluated at the equilibrium point E_0, which becomes

$$J(E_0) = \begin{bmatrix} -\mu & \frac{-\beta\pi}{\mu} \\ 0 & \frac{\beta\pi}{\mu} - \mu - d \end{bmatrix}. \tag{4.1.5}$$

The eigenvalues λ_i, $(i = 1, 2)$ of $J(E_0)$ are found by solving the characteristic equation

$$p(\lambda) = \det(J(E_0) - \lambda I) = 0. \tag{4.1.6}$$

Since $J(E_0)$ in (4.1.5) is an upper triangular matrix, its eigenvalues are

$$\lambda_1 = -\mu \tag{4.1.7}$$

and

$$\lambda_2 = \frac{\pi\beta}{\mu} - \mu - d. \tag{4.1.8}$$

These eigenvalues determine the local stability of the equilibrium point E_0, and whenever this point is hyperbolic, we can apply the Hartman-Grobman theorem and Collorory 2.2.10.

The disease-free equilibrium is an attractor and is therefore locally asymptotically stable whenever both eigenvalues in (4.1.7) and (4.1.8) have negative real parts, that is, whenever $Re(\lambda_1) < 0$ and $Re(\lambda_2) < 0$. Since λ_1 and λ_2 are both real, this situation occurs

when $\mu > 0$ (which has previously been assumed) and when

$$\frac{\pi\beta}{\mu} - \mu - d < 0,$$

which is equivalent (under the assumption that all parameters are positive) to

$$\frac{\pi\beta}{\mu\ (\mu + d)} < 1.$$

Thus, E_0 is locally asymptotically stable whenever $R_0 < 1$, in which we define the so-called *basic reproduction number*

$$R_0 = \frac{\pi\beta}{\mu\ (\mu + d)}. \tag{4.1.9}$$

We may then draw the following conclusion.

Theorem 4.1.1 *The disease-free equilibrium, E_0, is local asymptotic stablility if $R_0 < 1$, and is unstable if $R_0 > 1$.*

Remark 4.1.2 *For $R_0 = 1$, we cannot determine the local asymptotic stability of E_0, using the above theorem.*

Endemic equilibrium: In the presence of HIV infection in the population, the *endemic equilibrium* must satisfy (4.1.2) and the constraint of $I \neq 0$. Solving (4.1.2) for S, I, with the constraint $I \neq 0$, gives the unique endemic equilibrium

$$E^* = \left(\frac{\mu + d}{\beta}, \frac{\pi\beta - \mu(\mu + d)}{\beta(\mu + d)}\right) \tag{4.1.10}$$

$$= \left(\frac{\mu + d}{\beta}, \frac{\mu(R_0 - 1)}{\beta}\right) \tag{4.1.11}$$

It is necessary to determine the conditions for which the endemic equilibrium point E^* lies in the region $S \geq 0, I > 0$. In this region only is E^* biologically meaningful. We emphasize that the endemic equilibrium point E^* represents disease persistence, and so E^* cannot occur at $I = 0$. Hence we demand that E^* must lie only in the region $S \geq 0, I > 0$ to make E^* biologically meaningful. As an immediate consequence of the above we state

Theorem 4.1.3 *There exists a unique endemic equilibrium point, E^*, located in the region $S(t) \geq 0$, $I(t) > 0$, if and only if $R_0 > 1$.*

To investigate the local stability of the endemic equilibrium point we evaluate the Jacobian (4.1.4) at E^*:

$$J(E^*) = \begin{bmatrix} \dfrac{-\pi\beta}{\mu+d} & -\mu-d \\ \dfrac{\pi\beta-\mu^2-\mu d}{\mu+d} & 0 \end{bmatrix} \tag{4.1.12}$$

The eigenvalues λ_i $(i = 1, 2)$ of $J(E^*)$ are found by solving the characteristic equation

$$p(\lambda) = \det(J(E^*) - \lambda I) = 0. \tag{4.1.13}$$

The characteristic polynomial $p(\lambda)$ in (4.1.13) is

$$p(\lambda) = \lambda^2 + p_1\lambda + p_0, \tag{4.1.14}$$

where

$$p_0 = \det(J(E^*)) = \frac{(\pi\beta-\mu^2-\mu d)(\mu+d)}{\mu+d} = \mu(\mu+d)(R_0-1), \tag{4.1.15}$$

$$p_1 = -trace(J(E^*)) = \frac{\pi\beta}{\mu + d} = \mu R_0. \tag{4.1.16}$$

To determine the local stability of the endemic equilibrium, we need only find the sign of the real parts of the eigenvalues of (4.1.12). The endemic critical point is stable, and attracts solution curves for the system [59], provided that

$$p_0 > 0 \text{ and } p_1 > 0. \tag{4.1.17}$$

We can see that $R_0 > 1$ implies both $p_0 > 0$ and $p_1 > 0$, and this leads to the local stability condition for the unique endemic equilibrium in terms of the basic reproductive number.

Theorem 4.1.4 *The endemic equilibrium point, E^*, is locally asymptotically stable if $R_0 > 1$.*

4.1.2 Global Stability Analysis

Dulac function: In this section, we show that certain types of solutions such as periodic orbits, homoclinic or hetroclinic cycles cannot exist for the model with mass action incidence.

For the system (4.1.1), let

$$\begin{aligned} U &= \pi - \mu S - \beta IS, \\ V &= -\mu I - dI + \beta IS. \end{aligned}$$

We now show that the real-valued scalar function, $D = \frac{1}{I} > 0$, defined for all $I > 0$, satisfies

$$\begin{aligned} \frac{\partial(DU)}{\partial S} + \frac{\partial(DV)}{\partial I} &= \frac{-\mu}{I} - \beta \\ &= -(\frac{\mu}{I} + \beta) \\ &< 0, \text{ for } S \geqslant 0,\ I > 0. \end{aligned} \tag{4.1.18}$$

Since the parameters and the variables are all positive, the expression does not change sign in the region $S \geqslant 0$, $I > 0$, nor is it exactly zero. Thus, the function D represents an acceptable Dulac function for (4.1.1) in the region. It follows, from Theorem 2.3.4, that the model contains no periodic orbits, homoclinic or hetroclinic cycles in the region $S \geqslant 0$, $I > 0$.

We can now investigate the conditions for the global asymptotic stability of the model.

Positively invariant regions: Here we construct a bounded region containing all the equilibrium points for the model, and we show that the region is positively invariant with respect to the flow of (4.1.1). We also consider two bounded sub-regions, because the Dulac function $D = \frac{1}{I}$ is not defined for $I = 0$ (the disease-free axis), while E_0 occurs on this portion of the boundary.

Let Ω be the region defined by

$$\Omega = \{(S, I) : S \geq 0, I \geq 0,\ \ S + I \leq \frac{\pi}{\mu}\}; \tag{4.1.19}$$

and let Ω_0 be the sub-region

$$\Omega_0 = \{(S, I) : S \geq 0, I = 0, \quad S \leq \frac{\pi}{\mu}\}; \tag{4.1.20}$$

and let Ω^* be the sub-region

$$\Omega^* = \{(S, I) : S \geq 0, I > 0, \quad S + I \leq \frac{\pi}{\mu}\}. \tag{4.1.21}$$

For future reference we note that it is easily shown that the endemic equilibrium E^* lies in Ω^* and hence Ω, whenever $R_0 > 1$.

The following discussion shows that Ω, Ω_0, and Ω^* are positively invariant regions with respect to (4.1.1), and that Ω attracts all solutions of (4.1.1) in $S \geq 0, I \geq 0$.

To show that Ω_0 is a positively invariant region, we examine the flow of (4.1.1) along the S-axis ($I = 0$). For $S \geq 0, I = 0$, (4.1.1) becomes

$$\begin{aligned} \frac{dS}{dt} &= \pi - \mu S, \\ \\ \frac{dI}{dt} &= 0. \end{aligned} \tag{4.1.22}$$

The flow of (4.1.1) along this axis is restricted to this axis since $\frac{dI}{dt} = 0$. In addition, the flow along this axis is directed towards E_0, since in the region $S \geq 0, I = 0$, we have only three cases in which the initial conditions $\mathbf{x}_0$ for which solutions $\Gamma_{\mathbf{x}_0}$ of (4.1.22) may occur:

i) $\mathbf{x}_0 \in \{(S, I) : 0 \leq S < \frac{\pi}{\mu}, I = 0\}$, then $\frac{dS}{dt} > 0$, and all $\Gamma_{\mathbf{x}_0}$ of (4.1.22) are attracted to E_0;

ii) $\mathbf{x}_0 = E_0$, then $\frac{dS}{dt} = 0$, and all $\Gamma_{\mathbf{x}_0}$ of (4.1.22) remain at E_0;

iii) $\mathbf{x}_0 \in \{(S, I) : S > \frac{\pi}{\mu}, I = 0\}$, then $\frac{dS}{dt} < 0$, and all $\Gamma_{\mathbf{x}_0}$ of (4.1.22) are attracted to E_0.

From i) and ii) we see that Ω_0 *is a positively invariant region*, since all solutions having initial conditions starting in Ω_0 remain in Ω_0.

In addition, we may conclude from i), ii), and iii), that E_0 *attracts solutions* with initial conditions in $S \geq 0, I = 0$.

To show Ω is a positively invariant region, we examine the flow of (4.1.1) along the boundary of Ω, consisting of the three components: i) $I = 0$, ii) $S = 0$, iii) $S + I = \frac{\pi}{\mu}$.

i) Along the S-axis ($I = 0$), we have Ω_0 which is a positively invariant region (as shown above) and the flow of (4.1.1) is restricted to the $I = 0$ axis.

ii) Along the I-axis, ($S = 0$), for $I > 0$, (4.1.1) becomes

$$\begin{aligned} \frac{dS}{dt} &= \pi, \\ \\ \frac{dI}{dt} &= -\mu I - dI. \end{aligned} \tag{4.1.23}$$

We can see that the flow of (4.1.1) along the positive I axis is directed into $S > 0, I > 0$, since $\frac{dS}{dt} > 0$ and $\frac{dI}{dt} < 0$. Thus, solution curves beginning on the positive I-axis are directed into the first quadrant.

iii) We now investigate the flow of (4.1.1) in the first quadrant ($S > 0, I > 0$), and in particular along that portion of the boundary curve $S + I = \frac{\pi}{\mu}$ within it. For $S > 0$ and

$I > 0$, we consider the total population size $N = S + I$. From (4.1.1), we calculate

$$\begin{aligned} \frac{dN}{dt} &= \frac{dS}{dt} + \frac{dI}{dt} \\ &= \pi - \mu(S + I) - dI \\ &= \pi - \mu N - dI. \end{aligned} \tag{4.1.24}$$

In particular, for $S + I \geq \frac{\pi}{\mu}$,

$$\frac{dN}{dt} \leq \pi - \mu(\frac{\pi}{\mu}) - dI \leq -dI < 0 \tag{4.1.25}$$

which confirms that as t increases, $N = S + I$ decreases, so that the flow of (4.1.1) for $S + I \geq \frac{\pi}{\mu}$ is directed toward Ω. Thus, the flow along the boundary curve $S + I = \frac{\pi}{\mu}$ is directed into Ω. It follows that Ω *is a positively invariant region* for (4.1.1).

In addition, from the above discussion, we may conclude that Ω *attracts all solutions* for the region $S \geq 0, I \geq 0$.

Finally we consider the subregion Ω^* of Ω. We have shown that Ω and Ω_0 are both positively invariant. Moreover, since solutions which intersect Ω_0 must actually have started at some initial point in Ω_0, and since Ω^* is the complement of Ω_0 in Ω, it is immediately evident that Ω^* *is also a positively invariant region* of (4.1.1).

Similarly, we may conclude that Ω^* *attracts solutions* for the region outside Ω^* (not including $S \geq 0, I = 0$).

Thus, we are lead to.

Theorem 4.1.5 *For the system (4.1.1) with the positively invariant region Ω (4.1.19):*

(a) If $R_0 \leq 1$, then the disease-free equilibrium E_0 is globally asymptotically stable in $S \geq 0, I \geq 0$.

(b) If $R_0 > 1$, then the endemic equilibrium E^* is globally asymptotically stable in $S \geq 0, I > 0$ and E_0 attracts in $S \geq 0, I = 0$.

Proof:

Since Ω is a positively invariant compact set, and attracts all solutions for (4.1.1), we can restrict our attention to the dynamics analysis in Ω.

(a) For $R_0 \leq 1$: E_0 is a unique equilibrium point lying on the boundary of Ω. Since E_0 is unique in Ω, it follows from the Poincaré-Bendixson theorem that no limit cycle can occur in Ω unless it surrounds E_0. But E_0 is a boundary point of Ω and hence no limit cycle can occur lying entirely in Ω surrounding E_0. Also, since E_0 is locally asymptotically stable, no homoclinic or hetroclinic cycles can occur in Ω. Therefore no limit cycles, homoclinic or hetroclinic cycles can exist entirely in Ω. Since Ω contains a nonempty ω-limit set, and E_0 is the only equilibrium in Ω, it follows that E_0 is an ω-limit set in Ω attracting every solution in Ω. Since Ω attracts all solutions of (4.1.1), and E_0 attracts all solutions in Ω, it follows that E_0 attracts all solutions in the region $S \geq 0, I \geq 0$. Therefore E_0 is globally asymptotically stable for the region $S \geq 0, I \geq 0$.

(b) For $R_0 > 1$, we divide Ω into the positively invariant regions Ω_0 (4.1.20) and Ω^* (4.1.21) as discussed above.

In Ω_0, E_0 attracts all solutions with initial conditions starting in Ω_0 ($S \geq 0, I = 0$).

In Ω^*, a unique endemic equilibrium E^* exists. Since Ω is a positively invariant compact region, the ω-limit set of every solution with initial condition in Ω must be in

Ω. By the Poincaré-Bendixson theorem, the ω-limit set must be an equilibrium point or a limit cycle or a hetroclinic cycle. By Dulac's criteria, there are no periodic solutions, homoclinic or hetroclinic cycles in Ω or Ω^*, and hence the ω-limit set for solutions having initial conditions in Ω^* must consist of an equilibrium point. Since E_0 is locally unstable for $R_0 > 1$, E_0 cannot be the ω-limit set for Ω^*. It follows that the unique endemic equilibrium is the ω-limit set of every solution with initial condition in Ω^*. Therefore E^* attracts all solutions with initial conditions in Ω^* and is a globally asymptotically stable equilibrium in Ω^*. Since E^* attracts all solutions in Ω^*, and Ω^* attracts all solutions of (4.1.1) for $S \geq 0, I > 0$, it follows that E^* attracts all solutions in the region $S \geq 0, I > 0$. Therefore E^* is globally asymptotically stable for the region $S \geq 0, I > 0$.

This completes the proof of Theorem 4.1.5, and thus, the global asymptotic stability for the model's equilibria.

The global stability analysis confirms the results found in the local stability analysis, and shows the disease-free equilibrium is stable at $R_0 = 1$.

We proceed to the next section for the analysis of the model containing the saturated incidence rate function.

4.2 Analysis for Model with Saturated Incidence

In this section we analyze a model which uses saturated incidence (Holling type I) to represent the transmission of HIV in a sexually active community. We let $f(S, I) = \frac{\beta IS}{1+I}$, in which case system (3.2.1) becomes

$$\frac{dS}{dt} = \pi - \mu S - \frac{\beta IS}{1+I}; \qquad t > t_0,\ S(t) \geq 0,\ S(t_0) = S_0,$$

$$\frac{dI}{dt} = \frac{\beta IS}{1+I} - \mu I - dI; \quad t > t_0,\ I(t) \geq 0,\ I(t_0) = I_0. \tag{4.2.1}$$

As in section 4.1, we are modelling populations and therefore the variables S and I must be non-negative quantities. The parameters of our equations are, once again, all assumed to be positive.

4.2.1 Equilibria and Local Stability Analysis

Disease-free equilibrium: From the definition of equilibria (2.2.4), the equilibrium points of () must satisfy the following equations

$$0 = \pi - \mu S - \frac{\beta IS}{1+I};$$

$$0 = \frac{\beta IS}{1+I} - (\mu + d)I. \tag{4.2.2}$$

In the absence of HIV infection in the population, no persons are infected with HIV and therefore $I = 0$. Solving (4.2.2) for S, with the additional constraint of $I = 0$, gives the *disease-free* equilibrium solution

$$E_0 = \Big(S, I\Big) = \Big(\frac{\pi}{\mu}, 0\Big). \tag{4.2.3}$$

It is important to emphasize that E_0 is biologically meaningful for all combinations of parameters, i.e., throughout the model's parameter space. In addition, E_0 always lies on the positive S-axis.

To investigate the local stability of the disease-free equilibrium, the Jacobian of (4.2.1)

$$J = \begin{bmatrix} -\mu - \dfrac{\beta I}{1+I} & -\dfrac{\beta S}{1+I} + \dfrac{\beta I S}{(1+I)^2} \\ \dfrac{\beta I}{1+I} & \dfrac{\beta S}{1+I} - \dfrac{\beta I S}{(1+I)^2} - \mu - d \end{bmatrix}, \tag{4.2.4}$$

must be evaluated at the equilibrium point E_0, i.e.,

$$J(E_0) = \begin{bmatrix} -\mu & -\dfrac{\pi\beta}{\mu} \\ 0 & -\mu - d + \dfrac{\pi\beta}{\mu} \end{bmatrix}. \tag{4.2.5}$$

The eigenvalues λ_i $(i = 1, 2)$ of $J(E_0)$ are found by solving the characteristic equation

$$p(\lambda) = \det(J(E_0) - \lambda I) = 0. \tag{4.2.6}$$

Since $J(E_0)$ in (4.2.5) is an upper triangular matrix, its eigenvalues are

$$\lambda_1 = -\mu \tag{4.2.7}$$

and

$$\lambda_2 = \frac{\pi\beta}{\mu} - \mu - d. \tag{4.2.8}$$

These eigenvalues determine the local stability of the equilibrium point E_0; and whenever this point is hyperbolic, we can apply the Hartman-Grobman theorem and Collorory 2.2.10.

The disease-free equilibrium is an attractor and is therefore locally asymptotically stable whenever both eigenvalues in (4.2.7) and (4.2.8) have negative real parts, i.e., whenever $Re(\lambda_1) < 0$ and $Re(\lambda_2) < 0$. Since λ_1 and λ_2 are both real, this situation occurs when $\mu > 0$ (which has previously been assumed) and when

$$\frac{\pi\beta}{\mu} - \mu - d < 0, \tag{4.2.9}$$

which is equivalent (under the assumption that all parameters are positive) to

$$\frac{\pi\beta}{\mu\,(\mu+d)} < 1. \tag{4.2.10}$$

Thus, E_0 is locally asymptotically stable whenever $R_0 < 1$, in which we define the so-called *basic reproduction number*

$$R_0 = \frac{\pi\beta}{\mu\,(\mu+d)}. \tag{4.2.11}$$

We may then draw the following conclusion.

Theorem 4.2.1 *The disease-free equilibrium, E_0, is locally asymptotically stable if $R_0 < 1$, and is unstable if $R_0 > 1$.*

Remark 4.2.2 *For $R_0 = 1$, we cannot determine the local asymptotic stability of E_0 using this theorem.*

Endemic equilibrium: In the presence of HIV infection in the population, the *endemic equilibrium* must satisfy (4.2.2) and the constraint $I \neq 0$. Solving (4.2.2) for S, I with

this constraint $I \neq 0$, gives the unique endemic equilibrium

$$E^* = \left(\frac{\mu+d+\pi}{\beta+\mu}, \frac{\pi\beta-\mu(\mu+d)}{(\mu+\beta)(\mu+d)}\right) \tag{4.2.12}$$

$$= \left(\frac{\mu+d+\pi}{\beta+\mu}, \frac{\mu(R_0-1)}{\mu+\beta}\right) \tag{4.2.13}$$

It is necessary to determine the conditions for which the endemic equilibrium point E^* lies in the region $S \geq 0, I > 0$. In this region only is E^* biologically meaniful. We emphasize that the endemic equilibrium point E^* represents disease persistence, and so E^* cannot occur at $I = 0$. Hence we demand that E^* must lie only in the region $S \geq 0, I > 0$ to make E^* biologically meaningful. Thus, we state

Theorem 4.2.3 *There exists a unique endemic equilibrium point, E^*, located in the region $S(t) \geq 0,\ I(t) > 0$, if and only if $R_0 > 1$.*

To investigate the local stability of the endemic equilibrium, we evaluate the Jacobian (4.2.4) at E^* :

$$J(E^*) = \begin{bmatrix} J_{11} & J_{12} \\ J_{21} & J_{22} \end{bmatrix} \tag{4.2.14}$$

where

$$J_{11} = -\mu - \frac{\beta\,(\pi\,\beta - \mu^2 - \mu\,d)}{(\mu\,d + \beta\,\mu + \mu^2 + \beta\,d)\,(W)},$$

$$J_{12} = \frac{-\beta\,(\mu+d+\pi)}{(\mu+\beta)\,(W)} + \frac{\beta\,(\pi\,\beta - \mu^2 - \mu\,d)\,(\mu+d+\pi)}{(\mu+\beta)\,(\mu\,d+\beta\,\mu+\mu^2+\beta\,d)\,(W)^2},$$

$$J_{21} = \frac{\beta\,(\pi\,\beta - \mu^2 - \mu\,d)}{(\mu\,d + \beta\,\mu + \mu^2 + \beta\,d)\,(W)},$$

$$J_{22} = \frac{\beta\,(\mu+d+\pi)}{(\mu+\beta)\,(W)} - \frac{\beta\,(\pi\,\beta-\mu^2-\mu\,d)\,(\mu+d+\pi)}{(\mu\,d+\beta\,\mu+\mu^2+\beta\,d)\,(\mu+\beta)\,(W)^2} - \mu - d,$$

and where $W = \left(1 + \frac{\pi\,\beta-\mu^2-\mu\,d}{\mu\,d+\beta\,\mu+\mu^2+\beta\,d}\right)$.

The eigenvalues λ_i, $(i = 1, 2)$ of $J(E^*)$ are found by solving the characteristic equation

$$p(\lambda) = \det(J(E^*) - \lambda I) = 0, \tag{4.2.15}$$

i.e.,

$$\lambda^2 + p_1\lambda + p_0 = 0, \tag{4.2.16}$$

where

$$\begin{aligned} p_0 &= \det(J(E^*)), \qquad (4.2.17)\\ &= \frac{\pi\,\beta\,\mu\,d+\pi\,\beta^2\mu+\pi\,\beta\,\mu^2+\pi\,\beta^2 d-2\,\mu^3 d-\mu^3\beta-\mu^4-2\,\mu^2\beta\,d-\mu^2 d^2-\mu\,d^2\beta}{\beta\,(\mu+d+\pi)},\\ &= \frac{(R_0-1)\mu(\mu+d)^2(\mu+\beta)}{\beta\,(\mu+d+\pi)} \end{aligned}$$

and

$$\begin{aligned} p_1 &= -trace(J(E^*)), \qquad (4.2.18)\\ &= \frac{(2\,\pi\,\beta\,\mu-2\,\mu^2 d-\mu\,d^2-\mu^3+\beta\,\pi\,d+\pi\,\beta^2)}{\beta\,(\mu+d+\pi)},\\ &= \left(R_0\frac{(\beta\,+2\mu+d)}{(\mu+d)}-1\right)\left(\frac{\mu(\mu+d)^2}{\beta(\,\mu+d+\,\pi)}\right) \end{aligned}$$

To determine the local stability of the endemic equilibrium, we need only find the sign of the real parts of the eigenvalues of (4.2.14). The endemic equilibrium point is stable, and attracts solution curves for the system [59], provided that

$$p_0 > 0, \text{ and } p_1 > 0. \tag{4.2.19}$$

Clearly $p_0 > 0$ whenever $R_0 > 1$, and

$$p_1 > 0 \text{ whenever } \left(R_0 \frac{(\beta + 2\mu + d)}{(\mu + d)} - 1\right) > 0. \tag{4.2.20}$$

We can see that $R_0 > 1$ implies both $p_0 > 0$ and $p_1 > 0$, and this leads to the local stability condition for the unique endemic equilibrium, E^*.

Theorem 4.2.4 *The endemic equilibrium point, E^*, is locally asymptotically stable if $R_0 > 1$.*

4.2.2 Global Stability Analysis

Dulac function: As in the previous case, we show that certain types of solutions such as periodic orbits, homoclinic or hetroclinic cycles cannot occur for the model with saturated incidence.

For the system (4.2.1), we let

$$\begin{aligned} U &= \pi - \mu S - \frac{\beta IS}{1+I}, \\ V &= -\mu I - dI + \frac{\beta IS}{1+I}. \end{aligned}$$

The real-valued scalar function, $D = \frac{1}{I} > 0$, defined for all $I > 0$, satisfies

$$\begin{aligned} \frac{\partial(DU)}{\partial S} + \frac{\partial(DV)}{\partial I} &= \frac{-\mu}{I} - \frac{\beta}{(1+I)} - \frac{\beta S}{(1+I)^2} \\ &= -\Big(\frac{\mu}{I} + \frac{\beta}{(1+I)} + \frac{\beta S}{(1+I)^2}\Big) \\ &< 0, \text{ for } S \geqslant 0,\ I > 0. \end{aligned} \tag{4.2.21}$$

Since the parameters and the variables are all positive, the expression does not change sign in the region $S \geqslant 0$, $I > 0$, nor is it exactly zero. Thus, the function D represents a Dulac function for (4.2.1) in this region. It follows, from Thereom 2.3.4, that the model contains no periodic orbits, homoclinic or hetroclinic cycles in the region $S \geqslant 0$, $I > 0$.

We now determine the conditions for the global asymptotic stability of the model.

Positively invariant regions: Here we construct a bounded region containing all the equilibrium points for the model, and show that the region is positively invariant with respect to the flow of (4.2.1). We also consider two bounded sub-regions, because the Dulac function $D = \frac{1}{I}$ is not defined for $I = 0$ (the disease-free axis), and while E_0 occurs on this portion of the boundary.

Let Ω be the region of the model such that

$$\Omega = \{(S, I) : S \geq 0, I \geq 0, \ \ S + I \leq \frac{\pi}{\mu}\}; \tag{4.2.22}$$

and let Ω_0 be the sub-region

$$\Omega_0 = \{(S, I) : S \geq 0, I = 0, \ \ S \leq \frac{\pi}{\mu}\}; \tag{4.2.23}$$

and let Ω^* be the sub-region

$$\Omega^* = \{(S, I) : S \geq 0, I > 0, \quad S + I \leq \frac{\pi}{\mu}\}. \tag{4.2.24}$$

For future reference we note that it is easily shown that the endemic equilibrium E^* lies in Ω^*, and hence Ω, whenever $R_0 > 1$.

The following discussion shows that Ω, Ω_0, and Ω^* are positively invariant regions with respect to (4.2.1), and that Ω attracts all solutions of (4.2.1) in $S \geq 0, I \geq 0$.

To show that Ω_0 is a positively invariant region, we examine the flow of (4.2.1) along the S-axis ($I = 0$). For $S \geq 0, I = 0$, (4.2.1) becomes

$$\begin{aligned} \frac{dS}{dt} &= \pi - \mu S, \\ \\ \frac{dI}{dt} &= 0. \end{aligned} \tag{4.2.25}$$

The flow of (4.2.1) along this axis is restricted to this axis since $\frac{dI}{dt} = 0$. In addition, the flow along this axis is directed towards E_0, since in the region $S \geq 0, I = 0$, we have only three cases in which the initial conditions $\mathbf{x}_0$ for which solutions $\Gamma_{\mathbf{x}_0}$ of (4.2.25) may occur:

i) $\mathbf{x}_0 \in \{(S, I) : 0 \leq S < \frac{\pi}{\mu}, I = 0\}$, then $\frac{dS}{dt} > 0$, and all $\Gamma_{\mathbf{x}_0}$ of (4.2.25) are attracted to E_0;

ii) $\mathbf{x}_0 = E_0$, then $\frac{dS}{dt} = 0$, and all $\Gamma_{\mathbf{x}_0}$ of (4.2.25) remain at E_0;

iii) $\mathbf{x}_0 \in \{(S,I) : S > \frac{\pi}{\mu}, I = 0\}$, then $\frac{dS}{dt} < 0$, and all $\Gamma_{\mathbf{x}_0}$ of (4.2.25) are attracted to E_0.

From i) and ii) we see that Ω_0 *is a positively invariant region*, since all solutions having initial conditions starting in Ω_0 remain in Ω_0.

In addition, we can conclude from i), ii), and iii), that E_0 *attracts all solutions* with initial conditions in $S \geq 0, I = 0$.

In order to show Ω is a positively invariant region, we examine the flow of (4.2.1) along the boundary of Ω, consisting of the three components: i) $I = 0$, ii) $S = 0$, iii) $S + I = \frac{\pi}{\mu}$.

i) Along the S-axis ($I = 0$), we have Ω_0 which is a positively invariant region (as shown above) and the flow of (4.2.1) is restricted to the $I = 0$ axis.

ii) Along the I-axis, ($S = 0$), for $I > 0$, (4.2.1) becomes

$$\begin{aligned} \frac{dS}{dt} &= \pi, \\ \\ \frac{dI}{dt} &= -\mu I - dI. \end{aligned} \tag{4.2.26}$$

We can see that the flow of (4.2.1) along the positive I axis is directed into $S > 0, I > 0$, since $\frac{dS}{dt} > 0$ and $\frac{dI}{dt} < 0$. Thus, solution curves beginning on the positive I-axis are directed into the first quadrant.

iii) We now investigate the flow of (4.2.1) in the first quadrant ($S > 0, I > 0$), and in particular along that portion of the boundary curve $S + I = \frac{\pi}{\mu}$ within it. For $S > 0$ and $I > 0$, we consider the total population size $N = S + I$. From (4.2.1), we calculate

$$\begin{aligned} \frac{dN}{dt} &= \frac{dS}{dt} + \frac{dI}{dt} \\ &= \pi - \mu(S+I) - dI \\ &= \pi - \mu N - dI. \end{aligned} \tag{4.2.27}$$

In particular, for $S + I \geq \frac{\pi}{\mu}$,

$$\frac{dN}{dt} \leq \pi - \mu(\frac{\pi}{\mu}) - dI \leq -dI < 0 \tag{4.2.28}$$

which confirms that as t increases, $N = S + I$ decreases, so that the flow of (4.2.1) for $S + I \geq \frac{\pi}{\mu}$ is directed toward Ω. Thus, the flow along the boundary curve $S + I = \frac{\pi}{\mu}$ is directed into Ω. It follows that Ω *is a positively invariant region* for (4.2.1).

In addition, from the above discussion, we may conclude that Ω *attracts all solutions* for the region $S \geq 0, I \geq 0$.

Finally we consider the subregion Ω^* of Ω. We have shown that Ω and Ω_0 are both positively invariant. Moreover, since solutions which intersect Ω_0 must actually have started at some initial point in Ω_0, and since Ω^* is the complement of Ω_0 in Ω, it is immediately evident that Ω^* *is also a positively invariant region* of (4.2.1).

Similarly, we may conclude that Ω^* *attracts solutions* for the region outside Ω^* (not including $S \geq 0, I = 0$).

Thus we are lead to

Theorem 4.2.5 *For the system (4.2.1) with the positively invariant region Ω (4.2.22):*

(a) If $R_0 \leq 1$, then the disease-free equilibrium E_0 is globally asymptotically stable in $S \geq 0, I \geq 0$.

(b) If $R_0 > 1$, then the endemic equilibrium E^* is globally asymptotically stable in $S \geq 0, I > 0$ and E_0 attracts in $S \geq 0, I = 0$.

Proof:

Since Ω is a positively invariant compact set, and attracts all solutions for (4.2.1), we can restrict our attention to the dynamics analysis in Ω.

(a) For $R_0 \leq 1$: E_0 is a unique equilibrium point lying on the boundary of Ω. Since E_0 is unique in Ω, it follows from the Poincaré-Bendixson theorem that no limit cycle can occur in Ω unless it surrounds E_0. But E_0 is a boundary point of Ω and hence no limit cycle can occur lying entirely in Ω surrounding E_0. Also, since E_0 is locally asymptotically stable, no homoclinic or hetroclinic cycles can occur in Ω. Therefore no limit cycles, homoclinic or hetroclinic cycles can exist entirely in Ω. Since Ω contains a nonempty ω-limit set, and E_0 is the only equilibrium in Ω, it follows that E_0 is an ω-limit set in Ω attracting every solution in Ω. Since Ω attracts all solutions of (4.2.1), and E_0 attracts all solutions in Ω, it follows that E_0 attracts all solutions in the region $S \geq 0, I \geq 0$. Therefore E_0 is globally asymptotically stable for the region $S \geq 0, I \geq 0$.

(b) For $R_0 > 1$, we divide Ω into the positively invariant regions Ω_0 (4.2.23) and Ω^* (4.2.23) as discussed above.

In Ω_0, E_0 attracts all solutions with initial conditions starting in Ω_0 ($S \geq 0, I = 0$).

In Ω^*, a unique endemic equilibrium E^* exists. Since Ω is a positively invariant compact region, the ω-limit set of every solution with initial condition in Ω must be in

Ω. By the Poincaré-Bendixson theorem, the ω-limit set must be an equilibrium point or a limit cycle or a hetroclinic cycle. By Dulac's criteria, there are no periodic solutions, homoclinic or hetroclinic cycles in Ω or Ω^*, and hence the ω-limit set for solutions having initial conditions in Ω^* must consist of an equilibrium point. Since E_0 is locally unstable for $R_0 > 1$, E_0 cannot be the ω-limit set for Ω^*. It follows that the unique endemic equilibrium is the ω-limit set of every solution with initial condition in Ω^*. Therefore E^* attracts all solutions with initial conditions in Ω^* and is a globally asymptotically stable equilibrium in Ω^*. Since E^* attracts all solutions in Ω^*, and Ω^* attracts all solutions of (4.2.1) for $S \geq 0, I > 0$, it follows that E^* attracts all solutions in the region $S \geq 0, I > 0$. Therefore E^* is globally asymptotically stable for the region $S \geq 0, I > 0$.

This completes the proof of Theorem 4.2.5, and thus, the global asymptotic stability for the model's equilibria.

The global stability analysis confirms the results found in the local stability analysis, and shows the disease-free equilibrium is stable at $R_0 = 1$. By comparison with the previous section, we can see that the basic reproduction numbers for saturated and mass action incidence are identical, but that the mass action incidence produces a greater severity of the endemic infection than that of the saturated incidence. This can been seen by comparing the infected individuals at the two endemic equlibrium points for each incidence.

In the next section we examine the model containing proportional mixing incidence.

4.3 Analysis for Model with Proportional Mixing Incidence

In this section we analyze a model which uses proportional mixing incidence to represent the transmission of HIV in the population. By letting $f(S,I) = \frac{\beta IS}{S+I}$, system (3.2.1) becomes

$$\begin{aligned} \frac{dS}{dt} &= \pi - \mu S - \frac{\beta IS}{S+I}; \qquad t > t_0,\ S(t) \geq 0,\ S(t_0) = S_0, \\ \frac{dI}{dt} &= \frac{\beta IS}{S+I} - \mu I - dI; \quad t > t_0,\ I(t) \geq 0,\ I(t_0) = I_0, \end{aligned} \tag{4.3.1}$$

and with $(S(t), I(t)) \neq (0,0)$.

We are modelling populations, and therefore the variables S and I must be non-negative quantities. The parameters of our equations are assumed to be positive as well.

We note that the proportional mixing incidence function is undefined at the origin and so this point is excluded from the feasibility region of the model. This does not change the analysis of this section as compared to the previous two sections. It simply means that we have one less initial condition to choose from as compared to the previous two sections. There is no loss of generality here, and we can determine the solution starting at the origin $\mathbf{x}_0 = (0,0)$ as simply being the solution trajectory $\Gamma_{\mathbf{x}_0} \in \{(S,I) : 0 \leq S \leq \frac{\pi}{\mu}, I = 0\}$. Although parts of this section may discuss the feasibility region to be the same as sections 4.1 and 4.2. (for convenience of notation), it is clear that the origin is not included in the

system's feasibility region as defined by 4.3.1.

4.3.1 Equilibria and Local Stability Analysis

Disease-free equilibrium: From the definition of equilibria (2.2.4), the equilibrium of (4.3.1) must satisfy the following equations

$$\begin{aligned} 0 &= \pi - \mu S - \frac{\beta I S}{S+I}; \\ 0 &= \frac{\beta I S}{S+I} - (\mu + d)I. \end{aligned} \tag{4.3.2}$$

In the absence of HIV infection in the population, no persons are infected with HIV and therefore $I = 0$. Solving (4.3.2) for S with the additional constraint of $I = 0$, gives the *disease-free* equilibrium solution

$$E_0 = \Big(S, I\Big) = \Big(\frac{\pi}{\mu}, 0\Big). \tag{4.3.3}$$

As in the previous sections, we emphasize that E_0 is biologically meaningful for all combinations of parameters, i.e., for all of the model's parameter space. In addition, E_0 always lies on the positive S- axis.

To investigate the local stability of the disease-free equilibrium, the Jacobian of (4.3.1)

$$J = \begin{bmatrix} -\mu - \dfrac{\beta I}{S+I} + \dfrac{\beta I S}{(S+I)^2} & -\dfrac{\beta S}{S+I} + \dfrac{\beta I S}{(S+I)^2} \\ \dfrac{\beta I}{S+I} - \dfrac{\beta I S}{(S+I)^2} & \dfrac{\beta S}{S+I} - \dfrac{\beta I S}{(S+I)^2} - \mu - d \end{bmatrix}, \tag{4.3.4}$$

must be evaluated at the equilibrium point E_0.

Evaluating the Jacobian (4.3.4) at the disease-free point E_0, gives

$$J(E_0) = \begin{bmatrix} -\mu & -\beta \\ 0 & -\mu - d + \beta \end{bmatrix}. \tag{4.3.5}$$

The eigenvalues λ_i, $(i = 1, 2)$ of $J(E_0)$ are found by solving the characteristic equation

$$p(\lambda) = \det(J(E_0) - \lambda I) = 0. \tag{4.3.6}$$

Since $J(E_0)$ in (4.3.5) is an upper triangular matrix, its eigenvalues are

$$\lambda_1 = -\mu \tag{4.3.7}$$

and

$$\lambda_2 = \beta - \mu - d. \tag{4.3.8}$$

These eigenvalues determine the local stability of the equilibrium point E_0 and since this point is hyperbolic; we can apply Hartman-Grobman theorem and Collorary 2.2.10.

The disease-free equilibrium is an attractor and is therefore locally asymptotically stable whenever both eigenvalues in (4.3.7) and (4.3.8) have negative real parts, i.e., whenever $Re(\lambda_1) < 0$ and $Re(\lambda_2) < 0$. Since λ_1 and λ_2 are both real, this situation occurs when $\mu > 0$ (which has previously been assumed) and when

$$\beta - \mu - d < 0,$$

which is equivalent (under the assumption that all parameters are positive) to

$$\frac{\beta}{\mu + d} < 1.$$

Thus, E_0 is locally asymptotically stable whenever $R_0 < 1$, in which we define the so-called *basic reproduction number*

$$R_0 = \frac{\beta}{\mu + d}. \tag{4.3.9}$$

We may then draw the following conclusion.

Theorem 4.3.1 *The disease-free equilibrium, E_0, is locally asymptotically stable if $R_0 < 1$, and is unstable if $R_0 > 1$.*

Remark 4.3.2 *For $R_0 = 1$, we cannot determine the local asymptotic stability of E_0 using this theorem.*

Endemic equilibrium: In the presence of HIV infection in the population, the *endemic equilibrium* must satisfy (4.3.2) and the constraint of $I \neq 0$. Solving (4.3.2) for S, I with this constraint $I \neq 0$, gives the endemic equilibrium

$$E^* = \left(\frac{\pi}{\beta - d}, \frac{\pi(\beta - \mu - d)}{(\beta - d)(\mu + d)}\right), \tag{4.3.10}$$

$$= \left(\frac{\pi}{\beta - d}, \frac{\pi(R_0 - 1)}{(\beta - d)}\right) \tag{4.3.11}$$

It is necessary to determine the conditions for which the endemic equilibrium point E^* lies in the region $S \geq 0, I > 0$. In this region only is E^* biologically meaningful. We emphasize that the endemic equilibrium point E^* represents disease persistence, and so E^* can not occur at $I = 0$. Hence we demand that E^* must lie only in the region $S \geq 0, I > 0$ to make E^* biologically meaningful.

Theorem 4.3.3 *There exists a unique endemic equilibrium point, E^*, located in the region $S(t) \geq 0$, $I(t) > 0$, if and only if $R_0 > 1$.*

To investigate the local stability of the endemic equilibrium we evaluate Jacobian (4.3.4) at E^* :

$$J(E^*) = \begin{bmatrix} J_{11} & J_{12} \\ J_{21} & J_{22} \end{bmatrix} \tag{4.3.12}$$

where

$$J_{11} = -\mu - \frac{\beta\pi\left(-\mu - d + \beta\right)}{\left(-d+\beta\right)\left(d+\mu\right)W} + \frac{\beta\pi^2\left(-\mu - d + \beta\right)}{\left(-d+\beta\right)^2\left(d+\mu\right)\left(W\right)^2},$$

$$J_{12} = \frac{-\beta\pi}{\left(-d+\beta\right)W} + \frac{\beta\pi^2\left(-\mu - d + \beta\right)}{\left(-d+\beta\right)^2\left(d+\mu\right)\left(W\right)^2},$$

$$J_{21} = \frac{\beta\pi\left(-\mu - d + \beta\right)}{\left(-d+\beta\right)\left(d+\mu\right)W} - \frac{\beta\pi^2\left(-\mu - d + \beta\right)}{\left(-d+\beta\right)^2\left(d+\mu\right)\left(W\right)^2},$$

$$J_{22} = \frac{\beta\pi}{\left(-d+\beta\right)W} - \frac{\beta\pi^2\left(-\mu - d + \beta\right)}{\left(-d+\beta\right)^2\left(d+\mu\right)\left(W\right)^2} - \mu - d,$$

and where $W = \left(\frac{\pi}{-d+\beta} + \frac{\pi\left(-\mu - d + \beta\right)}{\left(-d+\beta\right)\left(d+\mu\right)}\right)$.

The eigenvalues λ_i $(i = 1, 2)$ of $J(E^*)$ are found by solving the characteristic equation

$$p(\lambda) = \det(J(E^*) - \lambda I) = 0. \tag{4.3.13}$$

The characteristic polynomial $p(\lambda)$ from (4.3.13) is obtained as

$$p(\lambda) = \lambda^2 + p_1\lambda + p_0, \tag{4.3.14}$$

where

$$p_0 = \det(J(E^*)) = \frac{-2\beta d^2 + \mu\ \beta^2 + 2\mu d^2 + d^3 + \beta^2 d - \mu^2\beta + \mu^2 d - 3\mu d\beta}{\beta},$$
$$= \frac{(\beta - d)(\mu + d)(\beta - \mu - d)}{\beta}, \tag{4.3.15}$$
$$p_1 = -trace(J(E^*)) = \frac{-\beta d + \beta^2}{\beta} = \beta - d. \tag{4.3.16}$$

To determine the local stability of the endemic equilibrium, we need only find the sign of the real parts of the eigenvalues of (4.3.12). The endemic critical point is stable, and attracts solution curves for the system [59], provided that

$$p_0 > 0 \text{ and } p_1 > 0. \tag{4.3.17}$$

For our system,

$$p_1 > 0 \text{ whenever } \beta - d > 0, \tag{4.3.18}$$

and similarly

$$p_0 > 0 \text{ whenever } \frac{(\beta - d)(\mu + d)(\beta - \mu - d)}{\beta} > 0.$$

We can see that $\beta - d > 0$ whenever $\beta - \mu - d > 0$, and so

$$p_0 > 0 \text{ and } p_1 > 0 \text{ whenever } \beta - \mu - d > 0. \tag{4.3.19}$$

We can see that $R_0 > 1$ implies both $p_0 > 0$ and $p_1 > 0$, since $\beta - \mu - d = (R_0 - 1)(\mu + d)$. The above discussion leads us to the local stability condition for E^*.

Theorem 4.3.4 *The endemic equilibrium point, E^*, is locally asymptotically stable if $R_0 > 1$.*

4.3.2 Global Stability Analysis

Dulac function: In the section, we show that certain types of solutions such as periodic orbits, homoclinic or hetroclinic cycles cannot exist for the model with proportional mixing incidence.

For the system (4.3.1), let

$$\begin{aligned} U &= \pi - \mu S - \frac{\beta IS}{S+I}, \\ V &= -\mu I - dI + \frac{\beta IS}{S+I}. \end{aligned} \tag{4.3.20}$$

The real-valued scalar function, $D = \frac{1}{I} > 0$, defined for all $I > 0$, satisfies

$$\begin{aligned} \frac{\partial(DU)}{\partial S} + \frac{\partial(DV)}{\partial I} &= \frac{-\mu}{I} - \frac{\beta I}{(S+I)^2} - \frac{\beta S}{(S+I)^2} \\ &= -\Big(\frac{\mu}{I} + \frac{\beta}{(S+I)}\Big) \\ &< 0, \text{ for } S \geqslant 0,\ I > 0. \end{aligned} \tag{4.3.21}$$

Since the parameters and the variables are all positive, the expression does not change sign in the region $S \geqslant 0$, $I > 0$, nor is it exactly zero. Thus, the function D represents an acceptable Dulac function for (4.3.1) in the region. It follows, from thereom 2.3.4, that the model contains no periodic orbits, homoclinic or hetroclinic cycles in the region $S \geqslant 0$, $I > 0$.

We can investigate the conditions for the global asymptotic stability of the model.

Positively invariant regions: Here we construct a bounded region containing all the equilibrium points for the model and we show that the region is positively invariant with

respect to the flow of (4.3.1). We also consider two bounded sub-regions, because the Dulac function $D = \frac{1}{I}$ is not defined for $I = 0$ (the disease-free axis), and while E_0 occurs on this portion of boundary.

Let Ω be the region defined by

$$\Omega = \{(S, I) : S, I \geq 0, \quad S + I \leq \frac{\pi}{\mu}\}; \tag{4.3.22}$$

and let Ω_0 be the sub-region

$$\Omega_0 = \{(S, I) : S \geq 0, I = 0, \quad S \leq \frac{\pi}{\mu}\}; \tag{4.3.23}$$

and let Ω^* be the sub-region

$$\Omega^* = \{(S, I) : S \geq 0, I > 0, \quad S + I \leq \frac{\pi}{\mu}\}. \tag{4.3.24}$$

For future reference we note that it is easily shown that the endemic equilibrium E^* lies in Ω^* and hence Ω whenever $R_0 > 1$.

The following discussion shows that Ω, Ω_0, and Ω^* are positively invariant regions with respect to (4.3.1), and that Ω attracts all solutions of (4.3.1) in $S \geq 0, I \geq 0$.

To show that Ω_0 is a positively invariant region, we examine the flow of (4.3.1) along the S-axis ($I = 0$). For $S \geq 0, I = 0$, (4.3.1) becomes

$$\frac{dS}{dt} = \pi - \mu S,$$

$$\frac{dI}{dt} = 0. \tag{4.3.25}$$

The flow of (4.3.1) along this axis is restricted to this axis since $\frac{dI}{dt} = 0$. In addition, the flow along this axis is directed towards E_0, since in the region $S \geq 0, I = 0$, we have only three cases in which the initial conditions $\mathbf{x}_0$ for which solutions $\Gamma_{\mathbf{x}_0}$ of (4.3.25) may occur:

i) $\mathbf{x}_0 \in \{(S, I) : 0 \leq S < \frac{\pi}{\mu}, I = 0\}$, then $\frac{dS}{dt} > 0$, and all $\Gamma_{\mathbf{x}_0}$ of (4.3.25) are attracted to E_0;

ii) $\mathbf{x}_0 = E_0$, then $\frac{dS}{dt} = 0$, and all $\Gamma_{\mathbf{x}_0}$ of (4.3.25) remain at E_0;

iii) $\mathbf{x}_0 \in \{(S, I) : S > \frac{\pi}{\mu}, I = 0\}$, then $\frac{dS}{dt} < 0$, and all $\Gamma_{\mathbf{x}_0}$ of (4.3.25) are attracted to E_0.

From i) and ii) we see that Ω_0 *is a positively invariant region*, since all solutions having initial conditions starting in Ω_0 remain in Ω_0.

In addition, we can conclude from i), ii), and iii), that E_0 *attracts all solutions* with initial conditions in $S \geq 0, I = 0$.

In order to show Ω is a positively invariant region, we examine the flow of (4.3.1) along the boundary of Ω, consisting of the three components: i) $I = 0$, ii) $S = 0$, iii) $S + I = \frac{\pi}{\mu}$.

i) Along the S-axis ($I = 0$), we have Ω_0 which is a positively invariant region (as shown above) and the flow of (4.3.1) is restricted to the $I = 0$ axis.

ii) Along the I-axis, $(S = 0)$, for $I > 0$, (4.3.1) becomes

$$\begin{aligned} \frac{dS}{dt} &= \pi, \\ \\ \frac{dI}{dt} &= -\mu I - dI. \end{aligned} \tag{4.3.26}$$

We can see that the flow of (4.3.1) along the positive I axis is directed into $S > 0, I > 0$, since $\frac{dS}{dt} > 0$ and $\frac{dI}{dt} < 0$. Thus, solution curves beginning on the positive I-axis are directed into the first quadrant.

iii) We now investigate the flow of (4.3.1) in the first quadrant $(S > 0, I > 0)$, and in particular along that portion of the boundary curve $S + I = \frac{\pi}{\mu}$ within it. For $S > 0$ and $I > 0$, we consider the total population size $N = S + I$. From (4.3.1), we calculate

$$\begin{aligned} \frac{dN}{dt} &= \frac{dS}{dt} + \frac{dI}{dt} \\ &= \pi - \mu(S + I) - dI \\ &= \pi - \mu N - dI. \end{aligned} \tag{4.3.27}$$

In particular, for $S + I \geq \frac{\pi}{\mu}$,

$$\frac{dN}{dt} \leq \pi - \mu(\frac{\pi}{\mu}) - dI \leq -dI < 0 \tag{4.3.28}$$

which confirms that as t increases, $N = S + I$ decreases, so that the flow of (4.3.1) for $S + I \geq \frac{\pi}{\mu}$ is directed toward Ω. Thus, the flow along the boundary curve $S + I = \frac{\pi}{\mu}$ is directed into Ω. It follows that Ω *is a positively invariant region* for (4.3.1).

In addition, from the above discussion, we may conclude that Ω *attracts all solutions* for the region $S \geq 0, I \geq 0$.

Finally we consider the subregion Ω^* of Ω. We have shown that Ω and Ω_0 are both positively invariant. Moreover, since solutions which intersect Ω_0 must actually have started at some initial point in Ω_0, and since Ω^* is the complement of Ω_0 in Ω, it is immediately evident that Ω^* *is also a positively invariant region* of (4.3.1).

Similarly, we may conclude that Ω^* *attracts solutions* for the region outside Ω^* (not including $S \geq 0, I = 0$).

Thus, we are lead to

Theorem 4.3.5 *For the system (4.3.1) with the positively invariant region Ω (4.3.22): (a) If $R_0 \leq 1$, then the disease-free equilibrium E_0 is globally asymptotically stable in $S \geq 0, I \geq 0$.*

(b) If $R_0 > 1$, then the endemic equilibrium E^* is globally asymptotically stable in $S \geq 0, I > 0$ and E_0 attracts in $S \geq 0, I = 0$.

Proof:

Since Ω is a positively invariant compact set, and attracts all solutions for (4.3.1), we can restrict our attention to the dynamics analysis in Ω.

(a) For $R_0 \leq 1$: E_0 is a unique equilibrium point lying on the boundary of Ω. Since E_0 is unique in Ω, it follows from the Poincaré-Bendixson theorem that no limit cycle can occur in Ω unless it surrounds E_0. But E_0 is a boundary point of Ω and hence no limit cycle can occur lying entirely in Ω surrounding E_0. Also, since E_0 is locally

asymptotically stable, no homoclinic or hetroclinic cycles can occur in Ω. Therefore no limit cycles, homoclinic or hetroclinic cycles can exist entirely in Ω. Since Ω contains a nonempty ω-limit set, and E_0 is the only equilibrium in Ω, it follows that E_0 is an ω-limit set in Ω attracting every solution in Ω. Since Ω attracts all solutions of (4.3.1), and E_0 attracts all solutions in Ω, it follows that E_0 attracts all solutions in the region $S \geq 0, I \geq 0$. Therefore E_0 is globally asymptotically stable for the region $S \geq 0, I \geq 0$.

(b) For $R_0 > 1$, we divide Ω into the positively invariant regions Ω_0 (4.1.20) and Ω^* (4.3.24) as discussed above.

In Ω_0, E_0 attracts all solutions with initial conditions starting in Ω_0 ($S \geq 0, I = 0$).

In Ω^*, a unique endemic equilibrium E^* exists. Since Ω is a positively invariant compact region, the ω-limit set of every solution with initial condition in Ω must be in Ω. By the Poincaré-Bendixson theorem, the ω-limit set must be an equilibrium point or a limit cycle or a hetroclinic cycle. By Dulac's criteria, there are no periodic solutions, homoclinic or hetroclinic cycles in Ω or Ω^*, and hence the ω-limit set for solutions having initial conditions in Ω^* must consist of an equilibrium point. Since E_0 is locally unstable for $R_0 > 1$, E_0 cannot be the ω-limit set for Ω^*. It follows that the unique endemic equilibrium is the ω-limit set of every solution with initial condition in Ω^*. Therefore E^* attracts all solutions with initial conditions in Ω^* and is a globally asymptotically stable equilibrium in Ω^*. Since E^* attracts all solutions in Ω^*, and Ω^* attracts all solutions of (4.3.1) for $S \geq 0, I > 0$, it follows that E^* attracts all solutions in the region $S \geq 0, I > 0$. Therefore E^* is globally asymptotically stable for the region $S \geq 0, I > 0$.

This completes the proof of Theorem 4.3.5, and thus, the global asymptotic stability

for the model's equilibria.

The results of this section were used in [18] (without proof) to explore the appearance of multiple stable equilibria (bistability) appearing in their model.

The global stability analysis confirms the results found in the local stability analysis, and shows the disease-free equilibrium is stable at $R_0 = 1$. By comparing with the two previous sections, we can see that the parameter values for basic reproduction numbers for proportional mixing $R_{0(3)}$, given by (4.3.9), differs from those of saturated and mass action incidence $R_{0(2)}$, given by (4.2.11), or equivallently $R_{0(1)}$, given by (4.1.9). However, the difference is simply a factor of $\frac{\pi}{\mu}$, and we can effectively scale $R_{0(3)}$ in terms of $R_{0(1)}$, i.e., $R_{0(3)} = \frac{\mu}{\pi} R_{0,(1)}$.

In the next chapter we will discuss and compare the analysis of the models in this chapter.

Chapter 5

Conclusion, Discussion, and Directions for Future Work

5.1 Conclusion

In this thesis, we have made a systematic effort towards analyzing three mathematical models of HIV epidemiology, using three different choices for the incidence of infection. Whether these choices of incidence function are realistic may not be evaluated by the analysis of the associated equations, but there is opportunity for future work between the mathematical and medical communities.

As shown in the literature [54], [2], the basic reproduction number may be independent of the functional form of incidence of infection. Here we have confirmed this fact for two different types of incidence of infection with the third being similiar in structure. However, the disease dynamics such as transient and asymptotic behaviors of the model solutions

for the population profiles, and more importantly the level of epidemicity depend greatly on the functional form of such incidence. Therefore, the factors affecting the incidence of infection are crucial in understanding the disease dynamics and evaluating appropriate control strategies.

The basic reproduction number (R_0) is a critical factor that governs the disease dynamics. In other words, the disease can be controlled if $R_0 \leq 1$, but spreads otherwise.

It is important to emphasize that parameters play a major role in the estimation of the basic reproduction number, and therefore the number of newly infected cases. Since these parameters are estimated from data collected in clinical investigations, their values are subject to different kinds of uncertainties. Therefore, for quality assurance of the model predictions, sensitivity and uncertainty analyses may need to be carried out. Such analyses have frequently been done in modelling infectious diseases such as HIV/AIDS and TB, and we refer to [5], [64], [39] for more details.

5.2 Discussion

Mathematical models have been recognized as fundamental instruments in understanding the mechanism of disease transmission and pathogenesis, and assist in developing feasible control strategies [3], [13]. The development of these strategies depends greatly on the formulation of sound mathematical models and on the assumptions adopted in the modelling process. In recent years, there has been a surge of interest in the extension of models to incorporate as much biological information as possible. In this extension, the

incidence rate has been shown to be a major factor that substantially affects the dynamics of the disease. Although classical models of epidemics (SIR with mass action incidence) lead to general conclusions concerning the long term disease dynamics, they may not provide details of the complexities in the population behavior. This has been a major reason for developing models with nonlinear incidence such as saturated and proportional mixing, which seem to be more realistic with large populations in the presence of control strategies. Mass action incidence has been shown to work well for modelling of childhood diseases in small populations of students during the school term [13].

In this thesis, we considered three models of HIV with mass action, saturated, and proportional mixing incidence rates and compared their global dynamics. Although there is no general method of finding Dulac functions, we found that we could use the same Dulac function in all three cases to eliminate the possible existence of periodic orbits, homoclinic or hetroclinic cycles. The positively invariant regions used in the analysis of all three models were found be the same as well.

The disease-free equilibrium was found to be identical for all three models and independent of the chosen incidence rate. We note that the location of E_0 is solely a function of the parameters for immigration rate π and natural removal rate μ.

The endemic equilibrium of the three models corresponds to the case where HIV infection persists ($I \neq 0$), and unlike the disease-free equilibrium, it was found to be dependent on the choice of incidence function. The location of endemic equilibrium point is a measure of the severity of the epidemic in the long term. By comparing each endemic equilibria, it can be seen that mass action incidence produces a greater severity of the

epidemic infection than that for saturated incidence.

In each model, the most important parameters for the epidemic control were shown to be β and d. As we already mentioned, even if R_0 is independent of the choice of incidence, the dynamics of the disease will depend on the functional form of the incidence, which has important epidemiological implications for epidemic control. Thus, in addition to estimating the parameters of the model, the choice of incidence function plays a significant role in public health decision making.

5.3 Directions for Future Work

This thesis can be viewed as an initiating point for future work in the field of mathematical epidemiology. Possible enhancements of this thesis include further work in extensions of the models, their numerical studies, and parameter estimation.

There are several ways to extend the model by incorporating the effect of control strategies (e.g., treatment, vaccination, quarantine) or by generalizing nonlinear incidence rates. The analysis of these models often requires the innovation of new mathematical techniques in the area of dynamical systems theory and differential equations.

Numerical studies should include two main directions:. to design new numerical techniques to reproduce the real dynamics of models analyzed by the theoretical studies, and to illustrate the dynamical behavior of the models through extensive numerical simulations.

Parameter estimation may include both collection of accurate and most recent data

through clinical studies, and their statistical analysis for uncertainty analysis and quality assurance.

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