Epidemiological modeling of HIV in populations with different sexual structures

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Introduction

The subject of this thesis is investigating populations with individuals who are infected with HIV. We can distinguish different kinds of groups, like men and women, young and old, heterosexual, homosexual and bisexual or other subdivisions. We have studied several articles on modeling HIV in a population to get an impression of the research that has already been done in this field. We noticed that in these articles populations consisting of heterosexuals, heterosexuals with homosexuals, or homosexuals with bisexuals were considered, but not populations consisting of heterosexuals, bisexuals and homosexuals. Therefore, we like to investigate the influence of the sexual intercourse between these groups on the transmission of HIV.
We divide a population in the groups of the susceptible and infected heterosexuals (S_1, I_1), bisexuals (S_2, I_2) and homosexuals (S_3, I_3). We would like to know what the differences are between models in which the group of bisexuals is ignored and models where it is included, and whether it is really necessary to consider this group separately.
The dynamics of these models are best studied in terms of their equilibria and their stability. The most important question in much of epidemiology is whether a disease will spread if it is introduced in a virgin population. Mathematically, this corresponds to finding the Disease Free Equilibrium (DFE). This is the steady state in which the disease has gone extinct.
We have three chapters in this report. Chapter 1 consists of four sections. We explain what HIV and AIDS are in the first section. In the second section we will give the Kermack and McKendrick model, or the *SIR* model, on which our models will be based. We extend this model with a birth and a death rate in the third section. In the last section we summarize some articles in which the authors investigated the influence of HIV on the population size. This thesis discusses the effect of the disease on a population's size, so we will review literature dealing with this aspect.
In the second chapter we adapt the *SIR* models of chapter one. We develop a model for the heterosexuals and the homosexuals in the first section and in the second section we add the bisexuals. In the third section we introduce behavioural difference for the bisexuals. The differences and similarities of these models are studied in the fourth section.
The third chapter contains three sections. In the first section we assume that there exists a vaccine for the disease and in the second section we assume that there is a cure. We investigate under which circumstances it is better to look for a vaccine or for a cure by comparing their equilibria.

Chapter 1

Preliminaries

This chapter consists of four sections. The first section is a general introduction to HIV and AIDS. In the second section we will introduce the Kermack and McKendrick model [7, 10, 21]. This is the most basic model which describes how an infection affects a population's size. In the third section we will try to make this model more realistic by adding a birth and a death rate. We will adapt these models in the chapters two and three. In the last section we will give some examples of modeling the influence of HIV on population sizes. This is carried out by summarizing previous articles in which the focus laid on different aspects, like medicine and sexual activity.

1.1 What are HIV and AIDS?

In the early eighties of the last decade some men in San Francisco (and simultaneously in New York) were diagnosed with the rare diseases *Candidiasis* (a type of fungal infection) and *Kaposi's sarcoma* (a kind of tumor). The individuals who got these diseases were young homosexual men. In 1984 the Frenchman dr. Luc Montagnier and his team discovered that a virus was the underlying cause of these diseases, which they named the Human Immunodeficiency Virus (HIV).
HIV is the virus that causes Acquired Immunodeficiency Syndrome (AIDS). The virus attaches itself to the $CD4^+$ T-lymphocytes, or T-cells, which are a part of the human immune system. Normally, these lymphocytes recognize infected cells and kill them. The HI-virus attaches itself to the T-lymphocytes and automatically reproduces through these new cells, because the T-cells do not recognize the HI-virus. As a result the number of $CD4^+$ T-lymphocytes, which are able to recognize infected cells, declines and this decrease causes permanent damage to the immune system. Eventually this number is so small, that the immune system loses its ability to fight infections. When someone reaches this stadium, this person is said to have AIDS. The time between getting infected with HIV and contracting AIDS is, in general, five years but it can vary.
One serious problem with HIV is that most of the time there are no symptoms. Someone may experience the same symptoms as other viral infections like fever, headache or rash, but for the majority of infected individuals, there may be no symptoms at all. A person with AIDS can have a combination of symptoms, such as extreme weakness, a rapid weight loss, frequent fevers that last for several weeks with no explanation, heavy sweating at night, swollen lymph glands, minor infections that cause skin rashes and mouth, genital, and anal

sores, white spots in the mouth or throat, chronic diarrhea, a cough that will not disappear and having trouble remembering things [14]. These symptoms do not have to occur, so the virus can be transmitted because someone can be infected without knowing this. Transmission can happen through breast feeding, unprotected sexual intercourse (no condom), sharing (not sterilized) needles, and blood transfusions. However, for simplicity, we will assume in all models presented in this thesis, that the only way to transmit HIV from one person to another is through sexual intercourse.
Since the discovery of the virus, many researchers have investigated HIV from different points of view. For instance, they have tried to find a medicine against the disease. Nowadays, there is still no cure for HIV, but there has been a breakthrough. It has been discovered that when someone is infected with HIV, the virus uses the integrase enzym of someone to paste a copy of its genetic information into the DNA of this person. The breakthrough is that scientists say they have grown a crystal that enables them to see the structure of the integrase enzym[1]. This helps them to find a cure for HIV, but it has not been found yet.
For now there is a combination of medicines, which can suppress the decline of the number of $CD4^+$ T cells. This combination is called *(highly active) antiretroviral therapy* ((HA)ART). Unfortunately, these medicines have a lot of side effects and they do not work with every patient. Moreover, they are expensive to produce. A cheaper remedy would be a vaccine, but it is proving hard to find one. In 2009 Ferstandi Arnold et al. [11] published an article in which it was explained which components a vaccine for AIDS needs. Also a vaccine has already been tested in Thailand[2] and in North America[3]. The vaccine tested in Thailand seems to reduce the risk of becoming infected with HIV by 31%, but researchers think it will still take many years before a vaccine might be available.
HIV was also investigated by developing models in which the viral dynamics of the disease were studied. In these models, one can predict what the influence of the disease is within a human body or what its effects are on a population. This thesis is about the latter, so we will develop models in which the dynamics of the virus within a population is investigated.

1.2 The *SIR* model

One of the most basic models which describes how an infection affects a population's size is the *SIR* model. This model was developed by Kermack and McKendrick [7, 10, 21]. We will use this model as a basis for our research, because it is the most common model used to investigate the influence of a disease on the population size. Other mathematical models for infectious diseases or variations of the *SIR* model can be found amongst others in the books written by Anderson et al. [1], Dieckmann and Heesterbeek [8], Hethcote [12] and Murray [21].
The *SIR* model consists of three groups of persons, namely S, I, and R. The group of susceptible people is denoted with S, I is the group of infected individuals and R is the group of people who got infected and have recovered from the infection or are dead. In this model it is assumed that if someone is recovered, this person has become immune for this certain infection. As a result, there is no transmission from R to S. The transmission model that belongs to this model is given in Figure 1.1 and its differential equations are

[1]See amongst others www.reuters.com and www.observer.org
[2]See http://news.aol.com/health/
[3]See http://abcnews.go.com

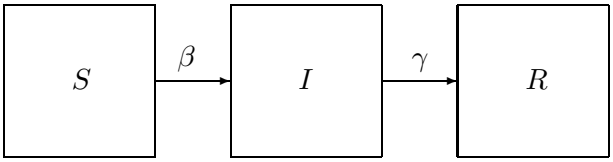

Figure 1.1: The transmission model belonging to the equations of (1.1), where S stands for the susceptibles, I for the infected and R for the individuals who are recovered from the infection or are dead. Furthermore, β is the transmission rate from S to I and γ is the transmission and death rate for I.

$$\begin{aligned} \tfrac{dS}{dT} &= -\beta SI, \\ \tfrac{dI}{dT} &= \beta SI - \gamma I = I(\beta S - \gamma), \\ \tfrac{dR}{dT} &= \gamma I. \end{aligned} \tag{1.1}$$

The constant β in the first equation stands for b/N, where b is the number of susceptibles that each infected person transmits the pathogen to in a (small) time interval, and N is the size of the population that is investigated. Thus β is the rate in which susceptibles get infected. We often call βI the force of infection. In the equations the term T stands for time. Furthermore, someone who is infected recovers or dies with a certain rate, say γ. Note that the sum $\frac{dS}{dT} + \frac{dI}{dT} + \frac{dR}{dT}$ is zero, so it is assumed that the population size is constant. The equations are nondimensionalized by substituting $s := S/N$, $i := I/N$, $r := R/N$ and $t := \frac{1}{\gamma}T$. The model then becomes

$$\begin{aligned} \tfrac{ds}{dt} &= -R_0 si, \\ \tfrac{di}{dt} &= i(R_0 s - 1), \\ \tfrac{dr}{dt} &= i, \end{aligned} \tag{1.2}$$

where $R_0 := \frac{\beta N}{\gamma}$. This term is known as the *reproductive ratio* and stands for the rate that an infected person can transmit the disease to someone else first hand. It is the most important parameter in all of mathematical epidemiology, because the stability of an equilibrium often depends on whether or not R_0 is greater than a constant, say c. Usually, if R_0 is greater than c, then the equilibrium is stable, it is unstable if R_0 is smaller than c, and it is neutrally stable if it is equal to c. Model (1.2) will be referred to with *SIR*.
The equilibria of this system are found by solving the differential equations of model SIR at steady state. The term $\frac{dr}{dt}$ can be ignored, because r has no influence on s, i and their differential equations. The equations are equal to zero when $(s, i) = (x, 0)$ for $x \in [0, 1]$. This means that there is a family of Disease Free Equilibria (DFEs). The Jacobian matrix for model SIR in $(x, 0)$ for a certain $x \in [0, 1]$ is

$$J = \begin{pmatrix} 0 & -R_0 x \\ 0 & R_0 x - 1 \end{pmatrix}.$$

An equilibrium is stable if and only if every real part of the eigenvalues of its Jacobian is less than zero. Equilibrium $(x, 0)$ for $x \in [0, 1]$ has 0 and $R_0 x - 1$ as eigenvalues, so if $R_0 x - 1 > 0$, then the equilibrium is unstable and if $R_0 x - 1 \leq 0$, then it is neutrally stable. We perform numerical simulations to show the differences between these two kinds of stability of the steady states.

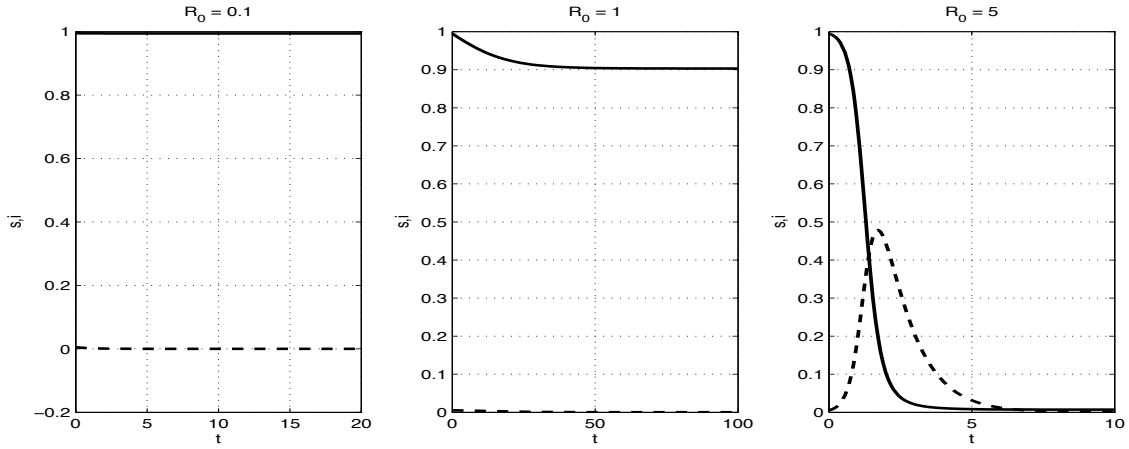

Figure 1.2: In these graphs we have plotted the dimensionless vectors s against t of model SIR. The parameters s and t were respectively defined as $\frac{S}{N}$, and $\frac{1}{\gamma}T$, where N is the total population size, c is the death rate of the infected, and T is the time unit in which we have measured the rates. Note that if we would like to translate s back to S, we have to compute $S = Ns$ due to the substitution. Our initial vector is $(s(0), i(0)) = (0.995, 0.005)$ and we varied the value of R_0. In the left picture we have $R_0 = 0.1$, in the middle $R_0 = 1$, and in the right graphs we have $R_0 = 5$. The solid line represents the dimensionless susceptibles (s) and the dashed line the dimensionless infected individuals (i). With these constants it is clear that in the left and middle picture we have a nonzero equilibrium, and in the right graph we have the zero steady state.

We assume that the population size N is constant, say $N = 1000$. Furthermore, we assume that the group of susceptibles consists of 995 individuals and 5 people are already infected with a certain disease, say the flu, so the initial values are $(s(0), i(0)) = (0.995, 0.005)$. We have plotted the graph with these initial values and with $R_0 = 0.1$, $R_0 = 1$, and $R_0 = 5$ in the time interval $[0, 100]$ in Figure 1.2. The value $R_0 = 5$ means that the number of susceptibles that each infected person transmit the flu to, is five times the rate in which someone recovers from the flu or dies. This follows from $\beta = \frac{b}{N}$ and $R_0 = \frac{\beta N}{\gamma}$. In the case of the flu, an infected individual can transmit the virus to every person within a certain radius, while it takes about four to six weeks to recover from it. Furthermore, R_0 also depends on how densely populated the area is. We assume that $R_0 = 5$ could be realistic.
We notice in Figure 1.2 that i is eventually zero, but this does not hold for s. This is because if every infected person has recovered or died before every susceptible has been infected with the virus, nobody can get infected anymore. As soon as we add a (small) group of infected, while not everyone is immune for the virus, the population size converges to another equilibrium, so every nonzero DFE is unstable.

1.3 The *SIR* model with a birth and death rate

Let us use the *SIR* model to investigate how the flu affects a population's size. We assume that each newborn is susceptible to the flu. The most basic *SIR* model has no term for the birth and death rate of the susceptible population. We include these terms for the susceptible population to get a somewhat more realistic model. The new transmission model is given in

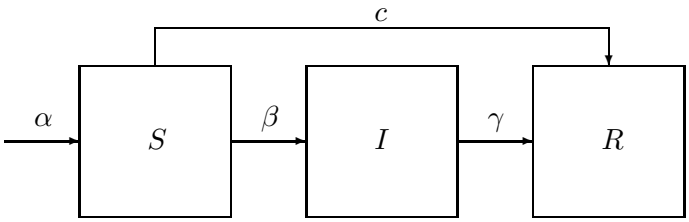

Figure 1.3: This is the transmission model belonging to the equations of (1.3), where S still stands for the group of susceptibles, I for the infected and R is defined as the individuals who are immune to the disease or are dead. Furthermore, β is the transmission rate from S to I, c is the death rate for S, and γ is the transmission rate plus the death rate of I.

Figure 1.3, and our system of equations is

$$\begin{aligned} \tfrac{dS}{dT} &= \alpha(S+I) - \beta SI - cS, \\ \tfrac{dI}{dT} &= \beta SI - \gamma I, \\ \tfrac{dR}{dT} &= \gamma I + cS. \end{aligned} \tag{1.3}$$

The constants α and c are respectively the birth and the death rate of the susceptible population. We assume that migration can be neglected. Our model has two steady states, namely $(s,i) = (0,0)$ (the DFE) and $(s,i) = (\frac{\gamma}{\beta}, \frac{\gamma(\alpha-c)}{\beta(\gamma-\alpha)})$. The DFE is stable if and only if $c > \alpha$. We notice that, if $c > \alpha$, the value of i in the other steady state is less than zero, so this other equilibrium is disregarded when c exceeds α. This is logical, because if the death rate exceeds the birth rate, the population will eventually become extinct.
With the same substitutions as before the nondimensional form of (1.3) is

$$\begin{aligned} \tfrac{ds}{dt} &= a(s+i) - R_0 si - c_1 s, \\ \tfrac{di}{dt} &= i(R_0 s - 1), \\ \tfrac{dr}{dt} &= i + c_1 s. \end{aligned} \tag{1.4}$$

with $a = \frac{\alpha}{\gamma}$, $R_0 = \frac{\beta N}{\gamma}$, $c_1 = \frac{c}{\gamma}$, and $t = \frac{1}{\gamma}$s. We can distinguish two cases, namely $a = c_1$ and $a \neq c_1$. If $a = c_1$, then the equilibrium is $(s,i) = (x,0)$, for any $x \in [0,1]$, and if $a \neq c_1$, then our steady states are $(s,i) = (0,0)$ and $(s,i) = (\frac{1}{R_0}, \frac{a-c_1}{R_0(a-1)})$. It is unlikely for a and c_1 to be equal, because usually the birth and death rate of a population are almost the same, and $c_1 \neq c$.
The chosen constants in our following illustration are not based on known data, but we only use them as an example. We have chosen $a = 0.2$, $R_0 = 2$, $(s(0), i(0)) = (0.995, 0.005)$, and $c_1 = 0.2$ (the special case) or $c_1 = 0.5$. The plots are given in Figure 1.4. We notice that we have a nonzero DFE if $a = c_1$, but we already mentioned that this equality is not likely to occur.
The birth and death rate in model (1.4) are not convenient, because its only DFE is $(s,i) = (0,0)$, except in the unlikely case that $a = c_1$. Since we would like to investigate how a small group of infected could affect a population with only susceptibles or when the disease has disappeared before the population has gone extinct, we will further modify the *SIR* by taking the birth rate to be constant instead of a constant times the population size. Model (1.4)

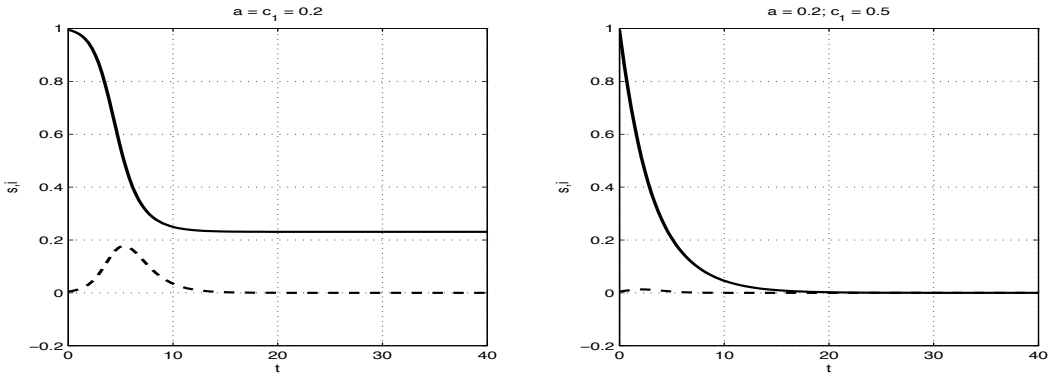

Figure 1.4: These are graphs for model (1.4) were we have plotted s, the dimensionless vector for the susceptible population, on the y-axis, and t, the vector for the time unit on the x-axis . We have chosen the constants $a = 0.2$, $(s(0), i(0)) = (0.995, 0.005)$, $c_1 = 0.2$ (left), and $c_1 = 0.5$ (right). The solid line represents the susceptibles and the dotted line the infected individuals. We notice that with our chosen constants (s, i) converges to approximately $(0.22, 0)$ in the left graph, and in the right graph the vector (s, i) converges to $(0, 0)$.

then becomes

$$\begin{aligned} \frac{ds}{dt} &= a - R_0 si - c_1 s, \\ \frac{di}{dt} &= i(R_0 s - 1), \\ \frac{dr}{dt} &= i. \end{aligned} \tag{1.5}$$

We refer to this model with SIR_{bd}, because this is a SIR model with a birth and a death rate. The term a is redefined as $a := \frac{\alpha}{N\gamma}$. This model has $(s, i) = (\frac{a}{c_1}, 0)$ as nonzero DFE. The eigenvalues of its Jacobian matrix $-c_1$ and $\frac{aR_0 - c_1}{c_1}$, so the DFE is stable if and only if

$$aR_0 < c_1 \Leftrightarrow R_0 < \frac{c_1}{a}. \tag{1.6}$$

Hence, we find that the stability of the DFE of model SIR_{bd} depends on the *reproductive ratio*. In Chapter 2 we introduce variations of the *SIR* models.

1.4 Review literature dealing with the effect of HIV on a population's size

In this section we will review some articles, to get a better impression of what already has been done in epidemiological modeling on HIV in populations.

Approach with statistics

Much research centers on estimating the rate constants in differential equations (DE) using elaborate statistics. The investigation is focussed on how these constants could be approximated and how they could be affected by, for example, riskier behavior of infected individuals. See also [2, 3, 4, 16, 22, 27, 28].

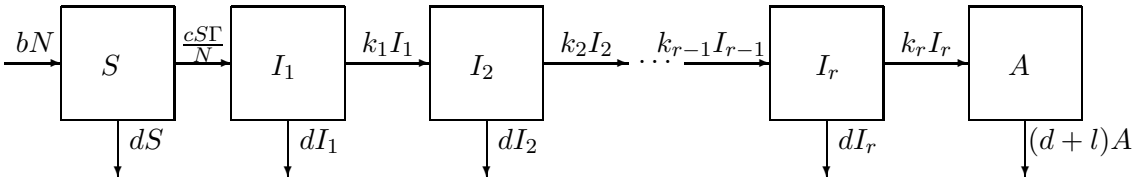

Figure 1.5: This is the transmission model belonging to the system of equations in model (1.7) used by Lin et al. [18]. It consists of the susceptibles (S), the infected who already are said to have AIDS (A) and the other infected (I_j). The transmission rates are $\frac{cS\Gamma}{N}$ for transmissions from S to I_1, k_jI_j for $j = 1, \ldots, r-1$ for transmissions from I_{j-1} to I_j, and k_rI_r denotes the transmissions from I_j to A. Furthermore, the constants d and $d + l$ are the death rates, and the birth rate for S is a fraction of the total population size (bN).

Approach with Graph Theory

Graph theory has also been used in the investigation of the effects of HIV on populations. Kretzschmar et al. [15] and Morris and Kretzschmar [20] have used nodes and vertices to describe the relationships between (two) human beings. The nodes portray the people who are sexually active and the vertices the interactions between these individuals. This approach lends itself particularly well to study situations where the individuals differ in the number of sexual contacts.

Approach with (applied) Analysis

We develop systems in this thesis, which are based on the *SIR* model from Section 1.2. Therefore, we review some articles in which the systems are also based on this model. We will use the assumptions and the systems in these articles to develop our own models.

Gender: research based on homosexuals or heterosexuals

At first it was thought that only homosexuals could get infected with HIV, since most of the individuals infected with HIV were found in the homosexual community. Therefore, a lot more data has been collected on infected homosexuals, than on infected heterosexuals.
Lin et al. made a model for the groups of homosexuals [18]. A population was divided into $r + 2$ groups, namely the susceptibles (S), the individuals who have AIDS (A) and r groups of infected individuals ($\{I_q\}_{q=1}^r$). The group of infected was divided in r subgroups, because it was thought that the transmission rate would change the longer someone was infected. The sum of all the subgroups of infected is denoted with I, so $I = \sum_{q=1}^r I_q$. The population size was a variable N and an infected person could only reach the stage of having AIDS by going through every stage of the infected. Their transmission model is given in Figure 1.5. and the system of equations was

$$\begin{aligned} \tfrac{dI_1}{dt} &= cS\Gamma/N - (k_1 + d)I_1, \\ \tfrac{dI_q}{dt} &= k_{q-1}I_{q-1} - (k_q + d)I_q, \quad q = 2, 3, \ldots, r, \\ \tfrac{dN}{dt} &= (b - d)N - k_rI_r, \end{aligned} \tag{1.7}$$

where c is the average number of contacts of an individual per unit time, Γ denotes the force of infection $\sum_{q=1}^r \beta_q I_q$ where β_q is the probability of transmitting the disease during one contact by an infected from group I_q d is the death rate and b is the birth rate for the susceptibles. It

is assumed that someone who has become sexually active is a susceptible and that someone who has AIDS is too weak to be sexually active. Therefore, $\beta_{q+1}A$ is not included in Γ, and A is not included in N. As a result S is defined as $N-\sum_{q=1}^{r} I_q$, so if all the I_q for $q=1,\ldots,r$ are known, S' can be computed. The susceptibles (S) and the individuals who have AIDS (A) are left out of the system, because both can be calculated from the infected (I_q). The definition of A' is $k_r I_r-(d+l)A$. The parameter l is the disease related death rate for the individuals who have AIDS.
For algebraic convenience Lin et. al. decided to set $k_q = k$ for all q. In this model the reproductive ratio R_0 was then defined as $\sum_{q=1}^{r}\left(\frac{k}{b+k}\right)^{q-1}\frac{c\beta_q}{b+k}$. It was found that if $R_0<1$, then the DFE is the only equilibrium, and it is locally stable. If $R_0>1$, then the DFE is unstable and there exists a unique endemic equilibrium. Endemic equilibrium points are steady state solutions where the disease persists in the population [25].
This one-sex model (for homosexuals) was extended to a two-sex model (for heterosexuals), namely

$$\begin{aligned}
&\tfrac{dI_{1,m}}{dt} = c_m S_m \Gamma_f/N_f-(k_1+d)I_{1,m},\\
&\tfrac{dI_{q,m}}{dt} = k_{q-1}I_{q-1,m}-(k_q+d)I_{q,m},\quad q=2,3,\ldots,r,\\
&\tfrac{dN_m}{dt} = (b-d)N_m-k_rI_{q,m},\\
&S_m = N_m-\textstyle\sum_{q=1}^{r} I_{q,m},\\
&\tfrac{dI_{1,f}}{dt} = c_f S_f \Gamma_m/N_m-(k_1+d)I_{1,f},\\
&\tfrac{dI_{q,f}}{dt} = k_{q-1}I_{q-1,f}-(k_q+d)I_{q,f},\quad q=2,3,\ldots,r,\\
&\tfrac{dN_f}{dt} = (b-d)N_f-k_rI_{q,f},\\
&S_f = N_f-\textstyle\sum_{q=1}^{r} I_{q,f}.
\end{aligned} \tag{1.8}$$

The first four equations are for the male population and the last four equations are for the female population. When it was assumed that $c_m N_m(t) = c_f N_f(t)$, it could be proven that (1.8) is actually the same as (1.7). Therefore, under the assumption $c_m N_m(t) = c_f N_f(t)$, there was no need to make the distinction between a homosexual and a heterosexual, see also [6, 13, 26].

Medicines: ART, cure or vaccine

Another topic of research is how ART can suppress the spread of HIV, for instance see Blower et al. [5] had a transmission model with one group of susceptibles (X) and four groups of infected (Y_R^U, Y_R^T, Y_S^T and Y_S^U). The group of infected was denoted by Y, the U stands for people who do not use ART (Untreated), the T stands for someone who uses ART (Treated), the R stands for a *drug-resistant* strain of the virus and S means that the person is infected with a *drug-sensitive* strain. See Figure 1.6 for the transmission model [4]. The system of equations was

$$\begin{aligned}
\tfrac{dX}{dt} &= \pi - X[c(\tfrac{\beta_S^U Y_S^U+\beta_S^T Y_S^T+p_S^U\beta_S^U Y_R^U+p_S^T\beta_S^T Y_R^T+\beta_R^U Y_R^U+\beta_R^T Y_R^T}{N})+\mu],\\
\tfrac{dY_S^U}{dt} &= Xc\big[\tfrac{\beta_S^U Y_S^U+\beta_S^T Y_S^T+p_S^U\beta_S^U Y_R^U+p_S^T\beta_S^T Y_R^T}{N}\big]+Y_R^U q+Y_S^T g_S-Y_S^U(\sigma_S+v_S^U+\mu),\\
\tfrac{dY_S^T}{dt} &= Y_S^U\sigma_S-Y_S^T(g_S+r+v_S^T+\mu),\\
\tfrac{dY_R^U}{dt} &= Xc\big(\tfrac{\beta_R^U Y_R^U+\beta_R^T Y_R^T}{N}\big)-Y_R^T g_R-Y_R^U(q+e\sigma_R+v_R^U+\mu),\\
\tfrac{dY_R^T}{dt} &= Y_R^U e\sigma_R+Y_S^T r-Y_R^T(g_R+v_R^T+\mu).
\end{aligned} \tag{1.9}$$

[4] This transmission model can also be found in [10].

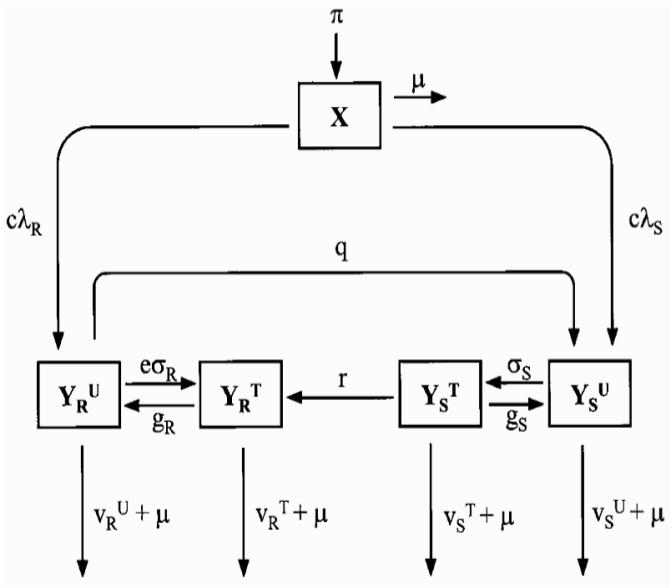

Figure 1.6: This transmission model belongs to the equations in model (1.9) from Blower et al. [5] and it consists of five groups, namely the susceptibles (X) and four groups of infected (Y_R^U, Y_R^T, Y_S^T and Y_S^U). The superscripts U stands for *untreated* and T stands for *treated*. The subscripts R (*drug-resistant*) and S (*drug-sensitive*) are for the type of strain the individual is infected with. The terms μ, v_R^U, v_R^T,v_S^U and v_S^T are the death rates, π is the birth rate, $c\lambda_R$ and $c\lambda_S$ are the forces of infection, g_R and g_S are the rates at which the infected give up using ART, $e\sigma_R$ and σ_S are the effective treatment rates and $1/q$ is the average time for an untreated drug-resistant infection to revert to a drug-sensitive infection.

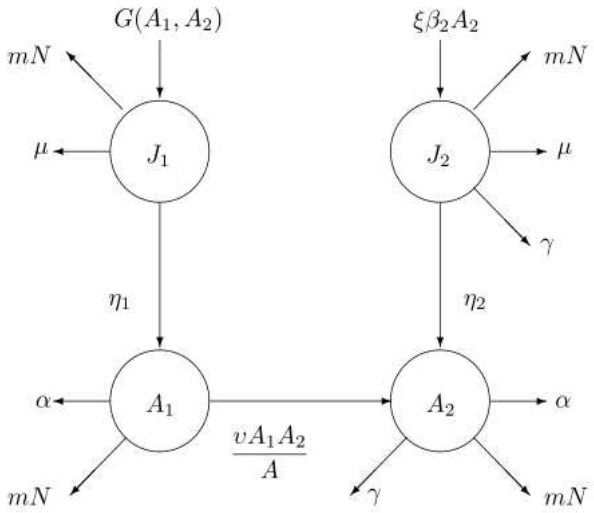

Figure 1.7: This is the transmission model of the equations in (1.10) from Lopez [19]. It consists of the susceptible and infected juveniles (J_1 and J_2) and the susceptible and infected adults (A_1 and A_2). The terms η_1 and η_2 are the rate at which the juveniles become adults, $G(A_1, A_2)$ and $\xi\beta_2 A_2$ are the birth rates, α and μ the natural death rates for respectively the adults and the juveniles, γ is the extra death rate for the infected, mN is the death rate due to overpopulation and $\frac{\upsilon A_1 A_2}{A}$ is the force of infection.

The focus of this article was on how ART could affect the risk behavior and how the rate of emergence of resistance would change. This was done with uncertainty analysis, were each uncertain parameter was assigned to a probability density function. This reflected either the uncertainty in the value of the parameter, or the degree to which the parameter could vary if it was being used as an experimental variable. In their analysis they used Latin Hypercube Sampling, which is a type of Monte Carlo sampling, and model (1.9). The result found was that the higher the usage of ART, the greater the number of prevented infections, and the higher the usage of ART, the more the effect of increased risky behavior would be neutralized. More recently, Lopez [19] investigated whether or not everyone who is infected with the virus should be treated with medicines which will extend the life expectancy of the infected. The population was divided into a group of juveniles (J) and a group of adults (A). Both of these groups were split into a group of infected (J_2, A_2) and into a group of susceptibles (J_1, A_1). It was assumed that juveniles are not sexually active yet and that infected adults can get newborns who are susceptible or are infected. With these definitions the transmission model of Figure 1.7 was developed. In this model the constants $\eta_i,\ i = 1, 2$, are the rates at which juveniles become adults in the respective groups. Furthermore, the natural death rates for the juveniles is μ, the natural death rate for the adults is α, and the death rate for the infected is γ. There is an extra constant mN for the death rate due to overpopulation. The total birth rate of the juveniles depends on the rate at which the susceptible and the infected adults reproduce, $\beta_1 A_1 + \beta_2 A_2$. It is assumed that the newborns of the susceptible adults are also susceptible and that $(1 - \xi)\beta_2 A_2$ are the susceptible newborns of the infected adults. This gives $G(A_1, A_2) = \beta_1 A_1 + (1 - \xi)\beta_2 A_2$ as birth rate for the susceptible juveniles and $\xi\beta_2 A_2$ as birth rate for the infected juveniles. Furthermore, it was assumed that the juveniles do not have sexual interaction, so there is no transmission from J_1 to J_2 and the transmission from

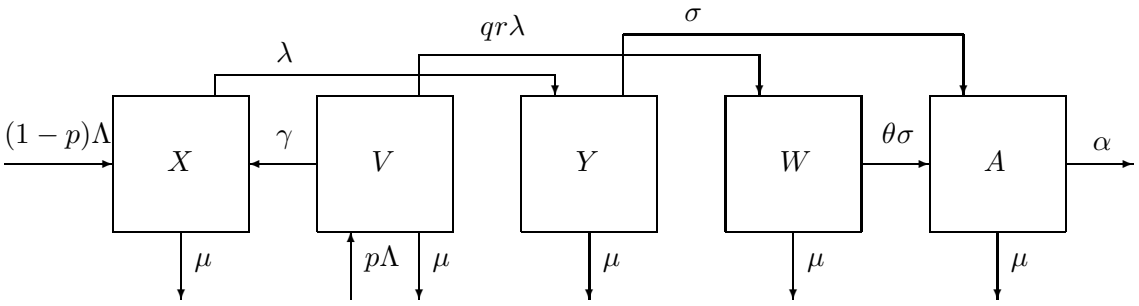

Figure 1.8: This is the model for the equations of (1.11), used by Elbasha and Gumel [9]. We have the groups of the unvaccinated (X) and vaccinated susceptibles (V), the unvaccinated (Y) and vaccinated (W) infected and the individuals who have AIDS. The birth rates are $(1-p)\Lambda$ and $p\Lambda$, μ is the death rate for each group, with α as an extra constant for the death rate of the individuals who have AIDS, λ is the force of infection, γ is the rate of waning immunity, σ is progression rate, $1-q$ is the degree protection, θ is the modification parameter and r is the rate for the risk behavior.

A_1 to A_2 is given by $\frac{vA_1A_2}{A_1+A_2} =: \frac{vA_1A_2}{A}$.
Then the system of equations belonging to the transmission model in Figure 1.7 is

$$\begin{aligned}
\tfrac{dJ_1}{dt} &= \beta_1 A_1 + (1-\xi)\beta_2 A_2 - \eta_1 J_1 - \mu J_1 - m J_1 N,\\
\tfrac{dA_1}{dt} &= \eta_1 J_1 - \tfrac{vA_1A_2}{A} - \alpha A_1 - m A_1 N,\\
\tfrac{dJ_2}{dt} &= \xi\beta_2 A_2 - \eta_2 J_2 - \mu J_2 - \gamma J_2 - m J_2 N,\\
\tfrac{dA_2}{dt} &= \eta_2 J_2 + \tfrac{vA_1A_2}{A} - \alpha A_2 - \gamma A_2 - m A_2 N.
\end{aligned} \tag{1.10}$$

If the parameters prove to remain constant over time, it was determined that the HI-virus would die out naturally in the US. It was also discovered that if a cure would be found, the number of infected people would increase. Therefore the question was posed whether it would be wise to treat every infected person or not.
Another way to stop the spread of HIV is by introducing a vaccine. No vaccine has been invented yet, but there are articles in which the writers investigated the influence of a vaccine on the spread of HIV. For instance, Elbasha and Gumel [9] and Sharomi et al. [24] assumed that there would be an imperfect vaccine and investigated what its potential impact would be. These articles are a lot alike. The same questions are posed and their basic models are almost equal. This is because some co-authors have worked on both articles. The model consists of the unvaccinated susceptibles (X) and infected (Y), the vaccinated susceptibles (V) and infected (W), and the infected who have AIDS (A). The basic model of Elbasha and Gumel is given in Figure 1.8. The system of equations belonging to the transmission model is

$$\begin{aligned}
\tfrac{dX}{dt} &= (1-p)\Lambda - \mu X - \lambda X + \gamma V,\\
\tfrac{dV}{dt} &= p\Lambda - \mu V - qr\lambda V - \gamma V,\\
\tfrac{dY}{dt} &= \lambda X - (\mu+\sigma)Y,\\
\tfrac{dW}{dt} &= qr\lambda V - (\mu+\theta\sigma)W,\\
\tfrac{dA}{dt} &= \sigma Y + \theta\sigma W - (\mu+\alpha)A.
\end{aligned} \tag{1.11}$$

where $\lambda = \frac{\beta Y + s\beta W}{N}$. The model of Sharomi et al. is the same except it did not have the term r, which stands for the increase of risk behavior. Note that this term is not necessary, because it only appears in combination with q. Therefore, it is sufficient to change the value of q. This constant denotes the amount of risky behavior. The terms $(1-p)\Lambda$ and $p\Lambda$ are the

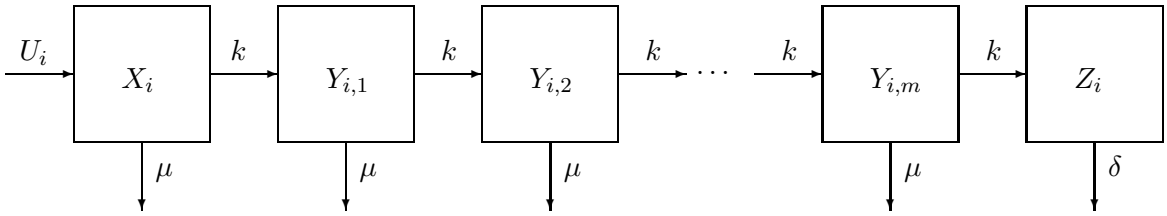

Figure 1.9: This is the transmission model for the i-th group of model (1.12), used by Jacquez et al. [13]. It consists of the susceptibles (X_i), the infected individuals (Y_i) and the people who already have AIDS. The parameter μ is the death rate for the susceptibles and infected, δ is the death rate for the people with AIDS, U_i is the birth rate and k is the rate at which someone from group $Y_{i,r}$ goes to group $Y_{i,r-1}$.

birth rates for individuals who have become sexually active and are respectively vaccinated (p) and unvaccinated ($1-p$), μ is the death rate, λ is the force of the infection, γ is the rate in which the vaccine becomes weaker (*waning immunity*) and β is the transmission coefficient. The full explanation of the parameters can be found in [24].
Both articles were about so-called backward bifurcation in disease models, in which the *reproduction number* R_0 is the backward bifurcation parameter. Often it holds that an equilibrium will be stable if $R_0 < 1$ and unstable when $R_0 > 1$. Backward bifurcation is the phenomenon that if $R_0 < 1$, a stable DFE co-exists with a stable endemic equilibrium (bistability). It was found that if $q = 0$, there would be no bistability. This is the case when the vaccine is perfect.

Sexual activity

The influence of the sexual activity on the spread of HIV has been investigated by, for instance, Jacquez et al. [13]. They have investigated what the effect is of a group of people with high sexual activity on a group which does not have much sexual intercourse. For this investigation a model with three groups was constructed, namely the susceptibles (X_i), the infected individuals (Y_i) and the individuals who have AIDS (Z_i). These groups were subdivided into n groups, where the people in a subgroup share the same sexual activity. The transmission model for the i-th group is given in Figure 1.9. Here U_1 is the expected number of new susceptibles, $Y_{i,j}$, for $j = 1, \ldots, m$, is the number of individuals who are in the j-stage of the infection and are part of the i-th group in sexual activity, k is the the fractional rate from group $Y_{i,r}$ to $Y_{i,r-1}$, μ is the competing mortality rate, which is the fractional rate at which members transfer out of the groups for nondisease related reasons, and δ is the mortality rate for group Z_i. In the model it was assumed that these parameters are constants. The model used was

$$\begin{array}{lcl} \frac{dX_i}{dt} & = & -c_i X_i \sum_{j=1}^{n} \Big\{ \rho_{i,j} \sum_{r=1}^{m} \big(\beta_{i,j,r} \frac{X_{j,r}}{X_j + Y_j} \big) \Big\} - \mu X_i + U_i, \\ \frac{dY_{i,1}}{dt} & = & c_i X_i \sum_{j=1}^{n} \Big\{ \rho_{i,j} \sum_{r=1}^{m} \big(\beta_{i,j,r} \frac{X_{j,r}}{X_j + Y_j} \big) \Big\} - (k+\mu) Y_{i,1}, \\ \frac{dY_{i,r}}{dt} & = & k Y_{i,r-1} - (k+\mu) Y_{i,r}, \ r = 2, 3, \ldots, m, \\ \frac{dZ}{dt} & = & k Y_{i,m} - \delta Z_i, \end{array} \tag{1.12}$$

where t is the time unit, c_i is the number of individuals one person has sexual contact with in one time unit, $\beta_{i,j,r}$ is the fraction of contacts between a susceptible person in group i and

someone from group $Y_{j,r}$, that transmits the virus and $\rho_{i,j}$ is the proportion of the contacts between individuals of groups i and j. The sum $\sum_j \rho_{i,j}$ must be equal to one and it is assumed that $c_i(X_i + Y_i)\rho_{i,j} = c_j(X_j + Y_j)\rho_{j,i}$.
The first part of the equation for the rate of change of X_i is given by $-c_i X_i \sum_{j=1}^{n} \Big\{ \rho_{i,j} \sum_{r=1}^{m} \big(\beta_{i,j,r} \frac{X_{j,r}}{X_j+Y_j}\big) \Big\}$, because $c_i X_i$ is the total number of contacts of X_i per time unit, $\rho_{i,j}$ denotes the fraction of these contacts that are with group j, $\frac{X_{j,r}}{X_j+Y_j}$ is the probability that the contact with group j is with a person in the r-th infectious subgroup, and $\beta_{i,j}$, is the fraction of those contacts that results in transmission. The second part $-\mu X_i$ is the death rate and U_i is the birth rate. In an analogous way the terms of the other equations can be explained.
With this model two values of μ ($\mu = 0$ and $\mu > 0$) were considered and three types of contact rates (mixing). This means that the values of $\rho_{i,j}$ were varied. The three types of mixing were restricted mixing ($\rho_{i,i} = 1$), proportional mixing ($\rho_{i,j} = c_j \frac{X_j+Y_j}{c}$) and preferred mixing ($\rho_{i,i} = \rho_i + (1-\rho_i)\frac{c_i(1-\rho_i)(X_i+Y_i)}{\sum_k c_k(1-\rho_k)(X_k+Y_k)}$ and $\rho_{i,j} = (1-\rho_i)\frac{c_j(1-\rho_i)((X_j+Y_j)}{\sum_k c_k(1-\rho_k)(X_k+Y_k)}$ if $i \neq j$).
After the steady states of the model were determined, the values of the parameters were varied. The focus was on the rate of the sexual activity and the transmission probability. The conclusion was that the mixing of the high (sexual) activity groups did have much effect on the spread of the virus in the groups of low activity. It was also found that the higher the sexual activity, the more likely the system would reach its endemic equilibrium. This would also happen if the transmission probability would increase. For further research more and better data would be needed about for example sexual preference (bisexuality) and needle sharing. It was assumed that with accurate data better education or medicine could be given to the groups which would affect the spread of the virus negatively. Lin had used the same model in [17] except the term μ_i was replaced by $\mu_i U$.

Chapter 2

Influence of bisexuals on population dynamics with HIV

In the models of the articles in Chapter 1 we noticed that the heterosexuals and the homosexuals were considered (not necessarily at the same time), but the group of bisexuals was not or barely mentioned. It is unlikely that a heterosexual transmits HIV to a homosexual, and vice versa, because we can assume that there is no sexual interaction between these two groups. Therefore, we would like to investigate the influence of the group of bisexuals on the heterosexuals and homosexuals in the spread of HIV. Can the total population be split into heterosexuals and homosexuals and thus can the group of bisexuals be ignored?
To investigate this influence, we develop two extensions of the *SIR* model in Section 1.2, which we will compare to each other. In our first extension we divide the groups of susceptibles and infected into a group of heterosexuals and a group of homosexuals. In the second extension we include the bisexual population. Like we already mentioned in our introduction, we will assume that in all models in this thesis, the only way to transmit HIV from one person to another is through sexual intercourse. A group of susceptibles will be referred to as S_j and a group of infected individuals will be denoted by I_j. A person of S_1 or I_1 is heterosexual, a person of S_2 or I_2 is bisexual and someone from S_3 or I_3 is homosexual. We assume that someone can only leave the group of infected by dying or by getting too ill to have sexual intercourse. In these cases they transmit to group R, the "resistant" group. Unless specified we assume in this chapter that there is no cure or vaccine for HIV.
Contrary to Lin et al. [18] and Lopez [19] we will not consider the female, juvenile or adult population; we assume that the transmission of HIV does not depend on the sex or the age of the persons. We also do not make any the distinction in the different kinds of mixing and we do not have as many groups as Jacquez et al. [13].

2.1 Model with heterosexuals and homosexuals

In this section we have the groups S_1, S_3, I_1 and I_3. We mentioned that it is unlikely to have sexual interaction between the heterosexuals and the homosexuals. We distinguish the group of infected by the sexual preferences of the individuals, so it does not matter by whom someone gets infected. A susceptible heterosexual who is infected by a homosexual is an infected heterosexual, which means that this person has become a member of group I_1.
We define $b_{j,k}/N$ as $\beta_{j,k}$, where $b_{j,k}$ is the number of susceptibles of group S_j that each infected

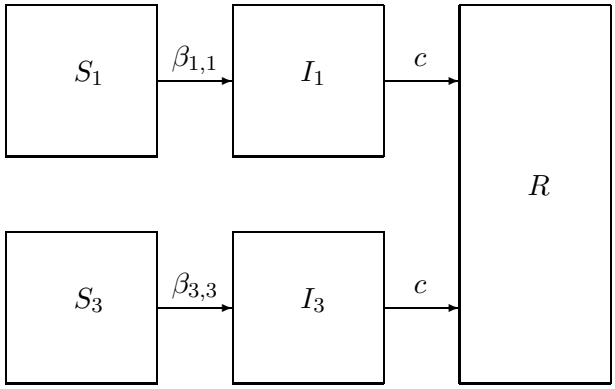

Figure 2.1: This is the transmission model belonging to the system of equations in (2.1). It consists of the susceptible and infected heterosexuals (S_1 and I_1), and the susceptible and infected homosexuals (S_3 and I_3). The term c is the rate at which infected people die or become sexually inactive. We will refer to it as the death rate of the infected. The rate at which someone from S_j gets infected by someone from I_j is denoted with $\beta_{j,j}$ for $j = 1, 3$.

person from I_k transmits the virus to in a certain time interval, and N is the population size. Thus $\beta_{j,k}$ is the rate at which a susceptible from S_j gets infected by someone from I_k. In this section we only have $\beta_{1,1}$ and $\beta_{3,3}$, because we assume that there is no interaction between the heterosexuals and homosexuals. With this information the transmission model of Figure 2.1 is obtained. An arrow between two groups means that someone from one group can become a member of the other group. All rates are nonnegative constants. With these assumptions, the extension of model (1.1) is

$$\begin{aligned} \tfrac{dS_1}{dT} &= -\beta_{1,1} S_1 I_1, \\ \tfrac{dS_3}{dT} &= -\beta_{3,3} S_3 I_3, \\ \tfrac{dI_1}{dT} &= \beta_{1,1} S_1 I_1 - c I_1, \\ \tfrac{dI_3}{dT} &= \beta_{3,3} S_3 I_3 - c I_3, \\ \tfrac{dR}{dt} &= c(I_1 + I_3). \end{aligned} \tag{2.1}$$

In this chapter we can ignore the equation for $\frac{dR}{dt}$, because R has no influence on the other classes and their differential equations. This follows from the assumption that there exists no cure for HIV and AIDS. Note that we have assumed that all infected individuals are infectious and that the latent period is of limited significance, and therefore neglected.
The term c is the rate at which an infected has become sexually inactive. We will refer to it as the "death rate". The steady states of (2.1) are $(S_1, S_3, I_1, I_3) = (x, y, 0, 0)$, with $x, y \geq 0$ and its Jacobian matrix is

$$J_{(x,y,0,0)} := \begin{pmatrix} 0 & 0 & -\beta_{1,1} x & 0 \\ 0 & 0 & 0 & -\beta_{3,3} y \\ 0 & 0 & \beta_{1,1} x - 1 & 0 \\ 0 & 0 & 0 & \beta_{3,3} x - 1 \end{pmatrix}.$$

It is clear that an equilibrium $(x, y, 0, 0)$, $x, y \geq 0$, is neutrally stable or unstable, because $J_{(x,y,0,0)}$ always has two eigenvalues equal to zero. If we assume that every transmission rate

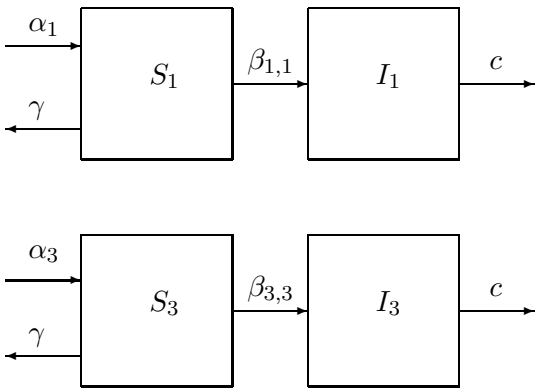

Figure 2.2: This is the transmission model belonging to the equations in (2.2). It consists of the susceptible and infected heterosexuals (S_1 and I_1) and the susceptible and infected homosexuals (S_3 and I_3). The birth rates are α_1 for the heterosexuals and α_3 for the homosexuals, the death rates are γ for the susceptibles and c for the infected, and $\beta_{1,1}$ and $\beta_{3,3}$ are the transmission rates.

has the same value, then with the substitutions $S := S_1 + S_3$ and $I := I_1 + I_3$ model (2.1) is equal to model (1.1).
We add a birth and a death rate to make this model somewhat more realistic. The rates depend on the size of the population. Therefore, we choose these rates equal to a constant times the size of the population. Our new transmission model can be found in Figure 2.2, and the system of equations belonging to this model is

$$\begin{aligned}
\tfrac{dS_1}{dT} &= \alpha_1(S_1 + S_3 + I_1 + I_3) - \gamma S_1 - \beta_{1,1} S_1 I_1, \\
\tfrac{dS_3}{dT} &= \alpha_3(S_1 + S_3 + I_1 + I_3) - \gamma S_3 - \beta_{3,3} S_3 I_3, \\
\tfrac{dI_1}{dT} &= \beta_{1,1} S_1 I_1 - c I_1, \\
\tfrac{dI_3}{dT} &= \beta_{3,3} S_3 I_3 - c I_3.
\end{aligned} \tag{2.2}$$

Note that this is twice the *SIR* model. The terms α_1 and α_3 are the birth rates for respectively S_1 and S_3, and represent the new individuals who have become sexually active. We assume that everyone who has become sexually active is susceptible for HIV. The term γ is the death rate of the susceptibles and we assume that this rate is smaller than the rate at which the infected die or have become sexually inactive. This is because someone who is infected with HIV is more vulnerable to other diseases than someone who is not HIV-infected. This system only has the zero vector as DFE. We would like to know what the influence of the infected is on the population size of the susceptibles. It is not interesting to have the zero vector as the only disease free steady state, because if a population has gone extinct, then no other equilibrium can be obtained.
We try to find an extension with birth rates such that we do have a nonzero DFE. In mathematical biology it is common to choose the birth rates as constants, while the death rates are defined as the rate at which someone dies multiplied with the population size, see for instance [7]. Therefore, we assume that the birth rates are constants and that the death rates are a

constant times the population size. The system of equations then becomes

$$\begin{aligned} \tfrac{dS_1}{dT} &= \alpha_1 - \beta_{1,1} S_1 I_1 - \gamma S_1, \\ \tfrac{dS_3}{dT} &= \alpha_3 - \beta_{3,3} S_3 I_3 - \gamma S_3, \\ \tfrac{dI_1}{dT} &= \beta_{1,1} S_1 I_1 - c I_1, \\ \tfrac{dI_3}{dT} &= \beta_{3,3} S_3 I_3 - c I_3. \end{aligned} \tag{2.3}$$

Model (2.3) is made dimensionless by substituting $s_k := \frac{S_k}{N}$, $i_k := \frac{I_k}{N}$, for $k = 1, 3$, $t := \frac{1}{c}T$, $a_j := \frac{\alpha_j}{cN}$, for $j = 1, 3$, $p_{j,j} := \frac{\beta_{j,j}N}{c}$ for $j = 1, 3$, and $c_1 := \frac{\gamma}{c}$. Then we find

$$\begin{aligned} \tfrac{ds_1}{dt} &= a_1 - p_{1,1} s_1 i_1 - c_1 s_1, \\ \tfrac{ds_3}{dt} &= a_3 - p_{3,3} s_3 i_3 - c_1 s_3, \\ \tfrac{di_1}{dt} &= p_{1,1} s_1 i_1 - i_1, \\ \tfrac{di_3}{dt} &= p_{3,3} s_3 i_3 - i_3. \end{aligned} \tag{2.4}$$

We will denote this model by HH_{bd}, because it consists of the heterosexuals (H) and the homosexuals (H) and we have included a birth (b) and death (d) rate. Our DFE is $(s, i) = (\frac{a_1}{c_1}, \frac{a_3}{c_1}, 0, 0)$. The Jacobian matrix in the DFE is

$$J = \begin{pmatrix} -c_1 & 0 & -\frac{p_{1,1}a_1}{c_1} & 0 \\ 0 & -c_1 & 0 & -\frac{p_{3,3}a_3}{c_1} \\ 0 & 0 & \frac{p_{1,1}a_1}{c_1} - 1 & 0 \\ 0 & 0 & 0 & \frac{p_{3,3}a_3}{c_1} - 1 \end{pmatrix},$$

and its eigenvalues are twice $-c_1$, $\frac{a_1 p_{1,1} - c_1}{c_1}$, and $\frac{a_3 p_{3,3} - c_1}{c_1}$. Without loss of generality we assume that $a_3 p_{3,3} < a_1 p_{1,1}$. We then have a stable DFE if and only if

$$a_1 p_{1,1} < c_1.$$

This inequality is, in our original model (2.3), the same as

$$\frac{\alpha_1 b_{1,1}}{cN} < \gamma. \tag{2.5}$$

If we assume that the birth rate is approximately the same as the death rate, so $\alpha \approx \gamma N$, and we also assume that the death rate of the infected is greater than the death rate of the susceptibles, so $\gamma < c$, then $\alpha_1 < \alpha \approx \gamma N < cN$. As a result, inequality (2.5) holds if and only $b_{1,1} < \gamma$. This is realistic, because the number of people an infected individual transmits HIV to is very small compared to the death rate of the infected. We conclude that we have a stable and nonzero DFE.

2.2 Model with heterosexuals, homosexuals and bisexuals

In this section we will adapt model (2.3), because we also would like to consider the group of bisexuals. We do not adapt the other models from Section 2.1, because we are still interested in finding a model which has a nonzero DFE. In Section 2.2.1 we consider the homosexuals and the bisexuals as one group, while in Section 2.2.2 we will separate these two groups.

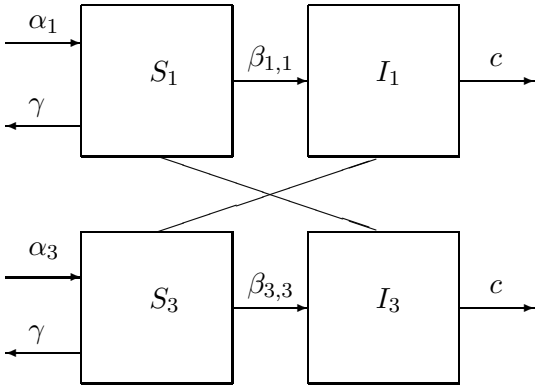

Figure 2.3: This is the transmission model belonging to the equations in (2.6). It consists of the susceptible and infected heterosexuals (S_1 and I_1) and the susceptible and infected homosexuals and bisexuals (S_3 and I_3). The birth rates are α_1 for the heterosexuals and α_3 for the homosexuals, the death rates are γ for the susceptibles and c for the infected, and $\beta_{1,1}$, $\beta_{1,3}$ and $\beta_{3,3}$ are the transmission rates.

2.2.1 Model with a hidden group of bisexuals

We still have the same definitions as in Section 2.1. Now we consider S_3 and I_3 to consist of both homosexuals and bisexuals. In this case it is possible to have interaction between the four groups. So in a sense, the group of bisexuals is "hidden" among the group of homosexuals. For simplicity, we assume that the transmission rate constants are symmetric, so $\beta_{j,k} = \beta_{k,j}$ for $j, k = 1, 3$. With this information we obtain the transmission model of Figure 2.3. A line between two groups means that there is interaction between these two groups, and an arrow still means that someone from one group can become a member of the other group. To make the figure more legible, $\beta_{1,3}$ is not included in the transmission model.
The system of equations then becomes

$$\begin{aligned}
\tfrac{dS_1}{dT} &= \alpha_1 - \beta_{1,1}S_1I_1 - \beta_{1,3}S_1I_3 - \gamma S_1,\\
\tfrac{dS_3}{dT} &= \alpha_3 - \beta_{3,3}S_3I_3 - \beta_{1,3}S_3I_1 - \gamma S_3,\\
\tfrac{dI_1}{dT} &= \beta_{1,1}S_1I_1 + \beta_{1,3}S_1I_3 - cI_1,\\
\tfrac{dI_3}{dT} &= \beta_{3,3}S_3I_3 + \beta_{1,3}S_3I_1 - cI_3.
\end{aligned} \tag{2.6}$$

This model is made dimensionless by substituting $s_k := \frac{S_k}{N}$, $i_k := \frac{I_k}{N}$, for $k = 1, 3$, $t := \frac{1}{c}T$, $a_j := \frac{\alpha_j}{cN}$, for $j = 1, 3$, $p_{j,k} := \frac{\beta_{j,k}N}{c}$ for $j, k = 1, 3$, and $c_1 := \frac{\gamma}{c}$. Then we find

$$\begin{aligned}
\tfrac{ds_1}{dt} &= a_1 - p_{1,1}s_1i_1 - p_{1,3}s_1i_3 - c_1s_1,\\
\tfrac{ds_3}{dt} &= a_3 - p_{1,3}s_3i_1 - p_{3,3}s_3i_3 - c_1s_3,\\
\tfrac{di_1}{dt} &= p_{1,1}s_1i_1 + p_{1,3}s_1i_3 - i_1,\\
\tfrac{di_3}{dt} &= p_{1,3}s_3i_1 + p_{3,3}s_3i_3 - i_3.
\end{aligned} \tag{2.7}$$

We refer to this model with $HH_{B,bd}$, because it consists of the hetero- and homosexuals with a birth and a death rate, and the bisexuals are hidden in the group of homosexuals. This system has $(s_1, s_3, i_1, i_3) = (\frac{a_1}{c_1}, \frac{a_3}{c_1}, 0, 0)$ as DFE. Note that the zero vector is not a steady state. The only differences in the equations of model $HH_{B,bd}$ and HH_{bd} are the terms $p_{1,3}s_1i_3$

and $p_{1,3}s_3i_1$, so apparently these terms have no effect on what the DFE of the model is. The eigenvalues of the Jacobian matrix at the DFE are twice $-c_1$ and

$$\frac{\frac{1}{2}(a_1p_{1,1}+a_3p_{3,3})-c_1 \pm \frac{1}{2}\sqrt{a_1^2p_{1,1}^2-2a_1a_3p_{1,1}p_{3,3}+a_3^2p_{3,3}^2+4a_1a_3p_{1,3}^2}}{c_1},$$

so the DFE is stable if and only if

$$a_1p_{1,1}+a_3p_{3,3}+\sqrt{(a_1p_{1,1}-a_3p_{3,3})^2+4a_1a_3p_{1,3}^2}<2c_1. \tag{2.8}$$

We have a stable and nonzero DFE if c_1 is greater than a combination of the scaled birth rates multiplied with the scaled transmission rates. We can not really determine what the relation between the magnitude of the constants in (2.8) is, but we notice that the left hand side only consists of the terms $a_jp_{m,n}$ for $j,m,n=1,3$. In Section 2.1 we rewrote inequality (2.5) and we concluded that $a_1p_{1,1}$ is smaller than c_1, under the assumption that the total birth rate is almost equal to the death rate. Inequality (2.8) is not very different from inequality (2.5), so the DFE of model $HH_{B,bd}$ is probably also stable.
We could not find out whether there are other equilibria, but by simplifying we can make some progress. We assume that every transmission rate is the same for sexual interaction between each group, say $p := \frac{\beta N}{c}$. With this assumption we find that there is only one other steady state, namely

$$(s_1,s_3,i_1,i_3)=\Big(\frac{a_1}{p(a_1+a_3)},\frac{a_3}{p(a_1+a_3)},\frac{(a_1^2+a_1a_3)p-a_1c_1}{p(a_1+a_3)},\frac{(a_3^2+a_1a_3)p-a_3c_1}{p(a_1+a_3)}\Big).$$

We can reduce $HH_{B,bd}$ to model SIR_{bd} by substituting $s := s_1+s_3$, $i := i_1+i_3$, $R_0 := p$, and $a := a_1+a_3$. It is clear that inequality (1.6) still holds, with $R_0 = p$, so we have

$$0 \le \frac{p}{c_1} < \frac{1}{a} =: A_1. \tag{2.9}$$

With its original parameters this is equal to

$$0 \le \frac{b\alpha}{cN} < \gamma.$$

This is almost the same as inequality (2.5) in Section 2.1, except we now have $b\alpha$ instead of $b_{1,1}\alpha_1$. The rate α_1 is smaller than α, because α is the total birth rate, while α_1 is only the birth rate of the susceptible population. We do not know what the difference between b and $b_{1,1}$ is, but since they both are probably very small, we assume that they have the same value. In Section 2.1 we concluded that the DFE is probably stable, under the assumption that $\alpha \approx \gamma N$. If we again assume this, then the DFE of model $HH_{B,bd}$ is probably also stable, because it is still likely that $b < \gamma$.
If the DFE is not stable, then (s,i) converges to the other equilibrium of model $HH_{B,bd}$, $\Big(\frac{a_1}{p(a_1+a_3)},\frac{a_3}{p(a_1+a_3)},\frac{(a_1^2+a_1a_3)p-a_1c_1}{p(a_1+a_3)},\frac{(a_3^2+a_1a_3)p-a_3c_1}{p(a_1+a_3)}\Big)$. In model SIR_{bd} this is equilibrium $(s,i)=(\frac{1}{p},\frac{ap-c_1}{p})$. Note that this equilibrium is only positive if and only if $ap > c_1$, which holds if the DFE is unstable. The population size in the steady states is found by multiplying (s,i) with N.
In short, we find that if each group has the same transmission rate and if this is less than

the death rate of the susceptible population, then the infected population will go extinct.

Estimating the parameters of the model with known data

We assume that every transmission rate is the same, because we do not know how to approximate them individually. We will explain how we estimate the rates of model SIR_{bd}, with $R_0 = p$. We use the data of the Dutch population in 2007-2008 found at the site of *Statistics Netherlands* or in Dutch *Centraal Bureau voor de Statistiek* (CBS)[1]. The constants of the equations will be approximated by looking at how the individuals are distributed by age. The sizes are given in the following table

population size (distinguished by age)	2007	2008
< 20	$4.0 \cdot 10^6$	$3.9 \cdot 10^6$
$20 - 40$	$4.3 \cdot 10^6$	$4.3 \cdot 10^6$
$40 - 65$	$5.7 \cdot 10^6$	$5.8 \cdot 10^6$
$65 - 80$	$1.8 \cdot 10^6$	$1.8 \cdot 10^6$
> 80	$0.6 \cdot 10^6$	$0.6 \cdot 10^6$

We assume that individuals who are older than 65, or younger than 16 are not sexually active. Because no further distinction is made in the group of people younger than twenty years old, the number of individuals between sixteen and twenty is estimated. Let us assume that the individuals between zero and twenty years old are uniformly distributed over the years. This assumption is based on the age-pyramid from the CBS. The ages are divided in ten groups, namely 0-10, 10-20, ..., 80-90 and 90-100.
Furthermore, according to the CBS in the next fifty years the number of individuals between zero and twenty years old, will approximately remain the same. This means that we assume that $1/5 \cdot 3.9 \cdot 10^6 = 0.8 \cdot 10^6$ is the number of individuals between 16 and 20 in 2007. In an analoguous way $0.8 \cdot 10^6$ is estimated as the number of individuals between the 16 and 20 in 2008. Our population size, the size of individuals who are sexually active, was $1.1 \cdot 10^7$, so $N = 11000000$. We still need to compute the birth and death rates. We define the birth rate as the number of fifteen year-olds in 2007, which is $2.0 \cdot 10^5$, so $\alpha = 20000$. This number is obtained by looking at the age-pyramid of the CBS and the assumption that the individuals between zero and twenty years old are uniformly distributed over the years. Since we assumed that only individuals between 16 and 65 are sexually active, we also need to find the number of deaths in this category. At the website of the CBS we also found an age-pyramid for the deaths. We find that 24148 persons between the 16 and 65 died in 2007, and this amount was 24672 in 2008. We estimated that yearly 124000 persons turn 66, so the number of deaths is approximately 145000. Data about HIV is found at the website of *SOA AIDS*[2]. We found that at the end of 2007 about 14000 persons were infected with HIV and in 2008 this was about 14500. Furthermore, it is estimated that in 2009 each week two people died because of HIV/AIDS. This is about a hundred people per year. We assume that this is also an approximation for 2008.
Together this gives us the constants $\gamma = 0.013$ ($\approx \frac{145000}{11000000}$), $c = 0.007$ ($\approx \frac{100}{14000}$), thus $c_1 = \frac{\gamma}{c} = 1.86$, and $a = 0.3$ ($\approx \frac{\alpha}{Nc}$).
We have performed numerical simulations with the initial conditions $(s(0), i(0)) = (\frac{a}{c_1} - \epsilon, \epsilon)$,

[1]The name of the site is www.cbs.nl
[2]Their website is www.soaaids.nl

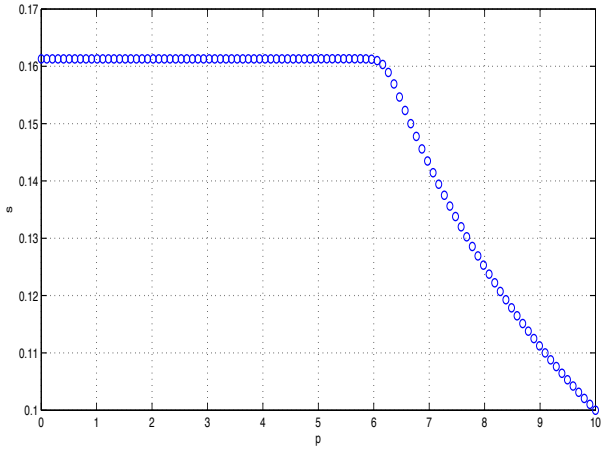

Figure 2.4: We have plotted the vector s in the steady states of model SIR_{bd}, with $R_0 = p$, and the birth and death rates are $a = 0.3$, $c_1 = 1.86$. On the y-axis we have put s and on the x-axis we have p. If the value of p varies, then the value of s in the equilibria also changes. We have chosen $(s(0), i(0)) = (\frac{a}{c_1} - \epsilon, \epsilon)$, with $\epsilon = 10^{-3}$, as initial conditions. We notice that if p is between 0 and 6.1 we have our DFE and if $p > 6.1$, the size of s converges to the nontrivial steady state.

with $\epsilon = 10^{-3}$. The number of susceptible individuals in the DFE can be computed via the value of s in the DFE. This was $s = \frac{a}{c_1}$, so S is equal to $\frac{a}{c_1} \cdot N$. In Figure 2.4 we see that this is indeed true for $p < 6.1$. Furthermore, the DFE is unstable if p becomes greater than 6.1. When $p > 6.1$, s converges to $(\frac{1}{p}, \frac{ap - c_1}{p})$. This is exactly the function of s in Figure 2.4 if $p \in (6.1, 10)$. Note that this nontrivial is positive, if $c_1 < ap$, which is exactly when the DFE becomes unstable.
The transmission rate is small compared with the birth and death rates. A value of $p = 6.1$ is very unlikely, because it means that an infected will transmit the virus to 6.1 times the death rate of the infected people each time this individual has sexual intercourse with a susceptible. According to our model the Dutch population will become disease free, if the birth and death rates remain constant over time. Then eventually no one will be infected with the HI-virus anymore.

2.2.2 Model with three separate groups

We now extend model HH_{bd} of Section 2.1 with the group of bisexuals. The system of equations is given below and its transmission model can be found in Figure 2.5.

$$\begin{aligned}
\tfrac{dS_1}{dT} &= \alpha_1 - \beta_{1,1} S_1 I_1 - \beta_{1,2} S_1 I_2 - \beta_{1,3} S_1 I_3 - \gamma S_1, \\
\tfrac{dS_2}{dT} &= \alpha_2 - \beta_{2,2} S_2 I_2 - \beta_{1,2} S_2 I_1 - \beta_{2,3} S_2 I_3 - \gamma S_2, \\
\tfrac{dS_3}{dT} &= \alpha_3 - \beta_{3,3} S_3 I_3 - \beta_{2,3} S_3 I_2 - \beta_{1,3} S_3 I_1 - \gamma S_3, \\
\tfrac{dI_1}{dT} &= \beta_{1,1} S_1 I_1 + \beta_{1,2} S_1 I_2 + \beta_{1,3} S_1 I_3 - c I_1, \\
\tfrac{dI_2}{dT} &= \beta_{2,2} S_2 I_2 + \beta_{1,2} S_2 I_1 + \beta_{2,3} S_2 I_3 - c I_2, \\
\tfrac{dI_3}{dT} &= \beta_{3,3} S_3 I_3 + \beta_{2,3} S_3 I_2 + \beta_{1,3} S_3 I_1 - c I_3.
\end{aligned} \tag{2.10}$$

If we assume that $\beta_{1,2} = \beta_{1,3}$, and $\beta_{2,2} = \beta_{2,3} = \beta_{3,3}$, then with the substitutions $S_3 := S_2 + S_3$, $I_3 := I_2 + I_3$, and $\alpha_3 := \alpha_2 + \alpha_3$ model (2.10) is equal to models $HH_{B,bd}$, before it was

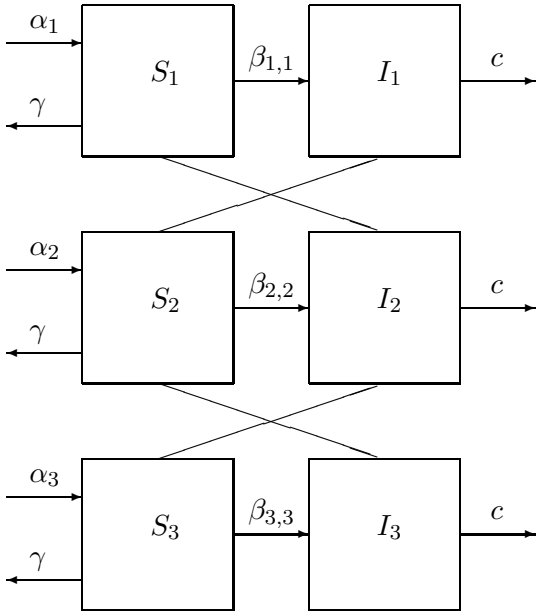

Figure 2.5: This is the transmission model for model (2.10). There are six groups in this model, namely the heterosexual (S_1), homosexual (S_3) and bisexual (S_2) susceptibles, and the infected heterosexuals (I_1), homosexuals (I_3) and bisexuals (I_2). The birth rates are α_1 for S_1, α_2 for S_2, and α_3 for S_3. The death rates are γ for the susceptibles and c for infected individuals. The transmission rates are $\beta_{1,1}$, $\beta_{2,2}$, and $\beta_{3,3}$. The transmission rates $\beta_{1,2}$ and $\beta_{2,3}$ are not given to make the model more legible, and we assume that $\beta_{1,3}$ is zero.

nondimensionalised, and SIR_{bd}. To avoid this equality, we still assume that there is no direct interaction between heterosexuals and homosexuals. So we assume that the transmission of HIV from the heterosexuals to the homosexuals goes through the bisexuals.
From now on we also assume that every transmission rate is the same, say β. Every interaction between the heterosexuals and the homosexuals goes through the bisexual group. Again we substitute $s_j := \frac{S_j}{N}$, $i_j := \frac{I_j}{N}$, $a_j := \frac{\alpha_j}{cN}$, for $j = 1, 2, 3$, $p := \frac{\beta N}{c}$, and $c_1 := \frac{\gamma}{c}$ to make the model dimensionless. Then (2.10) becomes

$$\begin{aligned}
\tfrac{ds_1}{dt} &= a_1 - ps_1i_1 - ps_1i_2 - c_1s_1,\\
\tfrac{ds_2}{dt} &= a_2 - ps_2i_2 - ps_2i_1 - ps_2i_3 - c_1s_2,\\
\tfrac{ds_3}{dt} &= a_3 - ps_3i_3 - ps_3i_2 - c_1s_3,\\
\tfrac{di_1}{dt} &= ps_1i_1 + ps_1i_2 - i_1,\\
\tfrac{di_2}{dt} &= ps_2i_2 + ps_2i_1 + ps_2i_3 - i_2,\\
\tfrac{di_3}{dt} &= ps_3i_3 + ps_3i_2 - i_3.
\end{aligned} \tag{2.11}$$

We refer to model (2.11) with HBH_{bd}, which stands for the heterosexual (H), bisexual (B), and homosexual (H) population with a birth (b) and death (d) rate.

Mathematical analysis of our model

The DFE of model $HH_{B,bd}$ is $(s_1, s_2, s_3, i_1, i_2, i_3) = (\frac{a_1}{c_1}, \frac{a_2}{c_1}, \frac{a_3}{c_1}, 0, 0, 0)$. The Jacobian in this point, say J_{DFE}, has three eigenvalues equal to $-c_1$. The other three eigenvalues

might be determined, but that is not necessary. Rather than investigating the eigenvalues themselves, we use a well-known criterion with which we can ensure that the DFE is stable, the *Routh-Hurwitz Conditions* [21]. An elementary proof of this condition is among others given by P.C. Parks [23].

Theorem 2.2.1 *(Routh-Hurwitz Conditions) If A is a square matrix of $n \times n$, I is the $n \times n$ identity matrix, the λ_i's for $i = 1, \ldots, n$ are its eigenvalues, and*

$$\det(\lambda I - A) = |\lambda I - A| = \lambda^n + a_1\lambda^{n-1} + \ldots + a_{n-1}\lambda + a_n = 0.$$

Then all eigenvalues of A have negative real parts if a_n is greater than zero and if $D_1 > 0,\ D_2 > 0, \ldots, D_n > 0$, where $D_k,\ k = 1, \ldots, n$ is defined as

$$D_k = \begin{vmatrix} a_1 & a_3 & a_5 & \ldots \\ 1 & a_2 & a_4 & \ldots \\ 0 & a_1 & a_3 & \ldots \\ 0 & 1 & a_2 & \ldots \\ \vdots & \vdots & \ddots & \\ 0 & 0 & \ldots & a_k \end{vmatrix}$$

□

It is not necessary to apply the Routh-Hurwitz Conditions on J_{DFE} itself, because three eigenvalues are already known. We define $D := |J_{DFE} - \lambda I|$ as the characteristic polynomial. D is divided by $(\lambda + c_1)^3$, because it is already known that $-c_1$ is three times an eigenvalue of J_{DFE}.
Then the polynomial becomes $\frac{D}{(\lambda+c_1)^3} = P(\lambda) = \lambda^3 + C_1\lambda^2 + C_2\lambda + C_3$ with

$$\begin{aligned} C_1 &= 3 - \tfrac{(a_1+a_2+a_3)p}{c_1}; \\ C_2 &= 3 + \tfrac{a_1a_3p^2}{c_1^2} - \tfrac{2(a_1+a_2+a_3)p}{c_1}; \\ C_3 &= 1 + \tfrac{a_1a_2a_3p^3}{c_1^3} + \tfrac{a_1a_3p^2}{c_1^2} - \tfrac{(a_1+a_2+a_3)p}{c_1}. \end{aligned} \tag{2.12}$$

According to Theorem 2.2.1 we find that the following conditions should hold in order to have negative eigenvalues.

$$\begin{aligned} &D_1 := C_1 > 0, \\ &D_2 := C_1C_2 - C_3 > 0, \text{ and} \\ &D_3 := C_3D_2 - a_1 \cdot 0 = C_3D_2 > 0. \end{aligned} \tag{2.13}$$

It is sufficient to find when $C_3 > 0$, because from $D_1 > 0$, $D_2 > 0$, and $C_3 > 0$ it follows that $D_3 > 0$.
To make calculations easier, we assume that 5% of the people who have become sexually active is homosexual and 1% is bisexual. Let us say that $a = 0.3$ (like in the application of model $HH_{B,bd}$) is the total "birth" rate, so $a_1 = 0.28$, $a_2 = 0.005$ and $a_3 = 0.015$. We define A_2 as the upper bound for $x = \frac{p}{c_1}$ for when the DFE of model HBH_{bd} is stable. Then we find

$$0 \leq \frac{p}{c_1} < 3.5 =: A_2. \tag{2.14}$$

The upper bound A_1 in (2.9) was defined as $\frac{1}{a}$, so $A_1 \approx 3.3$. The difference between these upper bounds A_1 and A_2 with $a_1 = 0.28$, $a_2 = 0.005$, and $a_3 = 0.015$, is $A_2 - A_1 \approx 0.2$, so

A_2 is about 1.06 times A_1. In Section 2.2.1 we concluded that, under certain conditions, it is likely that the DFE of model $HH_{B,bd}$ is stable. The value of upper bound A_2 in (2.14) is greater than A_1, so the DFE of model HBH_{bd} is probably also stable, if $a_1 = 0.28$, $a_2 = 0.005$, and $a_3 = 0.015$.
We assume that the total (scaled) birth rate is always 0.3, so A_1 is 3.3. For instance, let us assume that about 70% of the population is heterosexual, 5% is bisexual, and 25% is homosexual. This is an extreme example, because the percentage of homosexuals is probably not really this large. In this particular case $a_1 = 0.21$, $a_2 = 0.015$, and $a_3 = 0.075$, and we then find that A_2 is 4.4. This is about 1.3 times A_1 in (2.9), so the DFE of model HBH_{bd} is probably also stable if $a_1 = 0.28$, $a_2 = 0.005$, and $a_3 = 0.015$, and if the other rates do not change. What does a factor 1.06 or 1.3 mean for $\frac{p}{c_1}$?
The term p was defined as $\frac{\beta N}{c}$, β was equal to $\frac{b}{N}$, and c was $\frac{\gamma}{c}$. Thus $\frac{p}{c_1}$ is equal to $\frac{b}{\gamma}$, with b the number of individuals that each infected person transmits the virus to, and γ the death rate of the infected. We already mentioned that the value of b is (very) small compared with the birth and death rates, so a factor 1.06 or 1.3 does not have much effect on the stability of the DFE.
We use the same data as before for estimating the parameters of model $HH_{B,bd}$. There are no specific data about how many homosexuals are living in the Netherlands. In 2005 there were $5.3 \cdot 10^4$ cases of registered partnership/weddings between homosexuals[3]. This is about 1% of the total population, but not every person who is homosexual is registered. We assume that 5% of the population is homosexual, 1% is bisexual and 94% is heterosexual. This means that we assume that the susceptible population consists of 10.34 million heterosexuals, 0.11 million bisexuals, and 0.55 million homosexuals, so divided by 11 gives $s_1 = 0.945$, $s_2 = 0.005$ and $s_3 = 0.05$.
In 2008 $1.7 \cdot 10^3$ individuals got infected with the HI-virus. This made the total number of infected individuals $1.5 \cdot 10^4$. According to data from 2006[4], 59% of the new cases of HIV infection were transmitted through sexual intercourse between homosexuals and bisexuals. Furthermore, 33% of the new cases were through heterosexual intercourse. The rest of the new cases did not know how they got the infection. Let us assume that 6% of the new cases were transmitted by the bisexuals and 53% through homosexual intercourse.
We consider the 92% (33% + 6% + 53%) as the total amount of new cases. So we assume that 36% of the new cases were caused by heterosexual intercourse, 7% by bisexual intercourse and 57% by homosexual intercourse. With this assumption the number of infected heterosexuals is $4.7 \cdot 10^3$, the number of infected bisexuals is $0.9 \cdot 10^2$ and the number of infected homosexuals is $8.5 \cdot 10^3$. These numbers are also divided by N. Then the initial vector for the Dutch population in 2008 is $(s_1, s_2, s_3, i_1, i_2, i_3) = (0.94, 0.01, 0.05, 4.3 \cdot 10^{-4}, 8.4 \cdot 10^{-5}, 7.8 \cdot 10^{-4})$.
The death rates are the same as in the example for two groups in Section 2.1 and the birth rates are as we have assumed before. So the constants for model $HH_{B,bd}$ are $a_1 = 0.28$, $a_2 = 0.005$, $a_3 = 0.015$, $\gamma = 0.013$, $c = 0.007$ and $c_1 = 1.86$. The DFE is stable if and only if (2.14) holds. This means that p should be less than 1, which is shown in Figure 2.6.

Other equilibria

In model $HH_{B,bd}$ we found that the sum of the susceptibles in the nontrivial steady state was $\frac{1}{p}$. If $p > 6.5$, then $s := s_1 + s_2 + s_3$ has a similar shape as $\frac{1}{p}$, but it is not exactly the same.

[3] www.coc.nl
[4] Data was found at www.rivm.nl

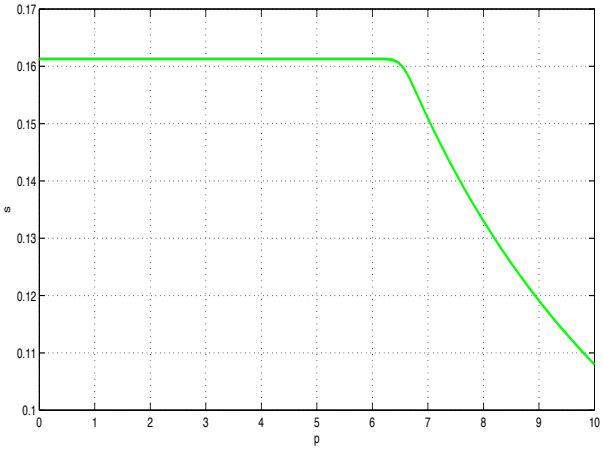

Figure 2.6: We have plotted the dimensionless vector for the susceptible population at the steady state of model $HH_{B,bd}$ against the scaled transmission rate, with $a_1 = 0.28$, $a_2 = 0.005$, $a_3 = 0.015$, $\gamma = 0.013$, $c = 0.007$ and $c_1 = 1.86$. The initial vector is $(s_1(0), s_2(0), s_3(0), i_1(0), i_2(0), i_3(0)) = (0.94, 0.01, 0.05, 4.3 \cdot 10^{-4}, 8.4 \cdot 10^{-5}, 7.8 \cdot 10^{-4})$. If $p > 6.5$, then the DFE is unstable.

Therefore, we think that $s := s_1 + s_2 + s_3$ is a function of the form $\frac{m(a_1,a_2,a_3,p,c_1)}{p}$, with m a constant depending on a_1, a_2, a_3, p, and c_1, because the graph looks like Figure 2.4. We try to compute the nontrivial equilibrium ourselves, because Maple was apparently not able to do this. We assume that

$$s := s_1 + s_2 + s_3 = \frac{f(a_1, a_2, a_3, p, c_1)}{g(a_1, a_2, a_3, p, c_1)p},$$

and

$$i := i_1 + i_2 + i_3 = \frac{F(a_1, a_2, a_3, p, c_1)}{G(a_1, a_2, a_3, p, c_1)p},$$

with f, g, F, G nonzero continuous functions, because the shape of s in the nontrivial steady state looks like $\frac{1}{p}$ times a constant. Then our s_j's are of the form $\frac{k_j f(a_1,a_2,a_3,p,c_1)}{g(a_1,a_2,a_3,p,c_1)p}$ and our i_j's are of the form $\frac{l_j F(a_1,a_2,a_3,p,c_1)}{G(a_1,a_2,a_3,p,c_1)p}$, with $k_j, l_j \in [0, 1]$, for $j = 1, 2, 3$, $k_1 + k_2 + k_3 = 1$, and $l_1 + l_2 + l_3 = 1$. The constants k_j and l_j can still depend on a_1, a_2, a_3, c_1, and p. Eventually we find that the equilibrium is of the form

$$\Big(\frac{l_1}{p(l_1 + l_2)}, \frac{l_2}{p}, \frac{l_3}{p(l_2 + l_3)}, \frac{a_1 p(l_1 + l_2) - c_1 l_1}{p(l_1 + l_2)}, \frac{a_2 p - c_1 l_2}{p}, \frac{a_3 p(l_2 + l_3) - c_1 l_3}{p(l_2 + l_3)}\Big).$$

If we substitute these values in Maple, we find

$$l_1 = \frac{a_1 a_a p^2}{c_1(c_1 - a_1 p)};\ l_2 = \frac{a_2 p}{c_1} \quad \text{and} \quad l_3 = \frac{a_2 a_3 p^2}{c_1(c_1 - a_3 p)}.$$

Strangely enough, these values give the DFE instead of the nontrivial equilibrium. So apparently the sum of the susceptible population size in the nontrivial steady state is not of the form $\frac{1}{p} m(a_1, a_2, a_3, p, c_1)$.

We were able to give a substitution for model $HH_{B,bd}$ such that it was reduced to model SIR_{bd}. We assumed that there is no interaction between the heterosexuals and homosexuals

such that it would not be possible to reduce our model to a less complicated model. If we substitute $s := s_1 + s_2 + s_3$, $i := i_1 + i_2 + i_3$, and $a := a_1 + a_2 + a_3$ in model $HH_{B,bd}$, we find

$$\begin{aligned}\frac{ds}{dt} &= a - p(si - s_1 i_3 - s_3 i_1) - c_1 s,\\ \frac{di}{dt} &= p(si - s_1 i_3 - s_3 i_1) - i.\end{aligned}$$

Note that the single group terms s_1,, s_3, i_1, and i_3 still feature in the equations. We are not able to find a substitution such that we only have the s and i left, so we can not simplify model $HH_{B,bd}$.
As a result, the sum of the population in the nontrivial steady state is probably a term similar to, but not equal to $\frac{1}{p}$ times a function $m(a_1, a_2, a_3, c_1, p)$.

2.3 Introducing behavioural difference for bisexuals

The main question in this thesis was whether or not the influence of the group of bisexuals could be ignored. Therefore, we make a distinction between the transmission rates of the heterosexuals, homosexuals and the bisexuals. We assume that the rate between a bisexual and a heterosexual or homosexual is d times β. This d is a constant greater than zero. If it is less than one, this means that the bisexuals have more often safe sex compared with the other two groups. If d is greater than one, it means the opposite. The dimensionless system of equations is

$$\begin{aligned}\frac{ds_1}{dt} &= a_1 - ps_1 i_1 - pds_1 i_2 - c_1 s_1,\\ \frac{ds_2}{dt} &= a_2 - pds_2 i_1 - pd^2 s_2 i_2 - pds_2 i_3 - c_1 s_2,\\ \frac{ds_3}{dt} &= a_3 - pds_3 i_2 - ps_3 i_3 - c_1 s_3,\\ \frac{di_1}{dt} &= ps_1 i_1 + pds_1 i_2 - i_1,\\ \frac{di_2}{dt} &= pds_2 i_1 + pd^2 s_2 i_2 + pds_2 i_3 - i_2,\\ \frac{di_3}{dt} &= pds_3 i_2 + ps_3 i_3 - i_3.\end{aligned} \tag{2.15}$$

Its transmission model is given in Figure 2.7. We will refer to model (2.15) with HB_dH_{bd}, where the the capital letters still refer to the hetero-, bi, and homosexuals, the underscore bd denotes the birth and death rate, and the underscore d refers to the extra term d for the transmissions where a bisexual is involved. This model only has one steady state which is $(s_1, s_2, s_3, i_1, i_2, i_3) = (\frac{a_1}{c_1}, \frac{a_2}{c_1}, \frac{a_3}{c_1}, 0, 0, 0)$. The Jacobian of this DFE has three times the eigenvalue $-c_1$. We will apply the Routh-Hurwitz Condition again to determine whether we have a stable or unstable equilibrium. The constants of the characteristic polynomial after dividing by $(\lambda + c_1)^3$ and substituting $x := \frac{p}{c_1}$ are

$$\begin{aligned}C_1 &:= 3 - (a_1 + a_2 d^2 + a_3)x;\\ C_2 &:= 3 + a_1 a_3 x^2 - 2(a_1 + a_2 d^2 + a_3)x;\\ C_3 &:= 1 + a_1 a_2 a_3 d^2 x^3 + a_1 a_3 x^2 - (a_1 + a_2 d^2 + a_3)x.\end{aligned}$$

Again we find that the stability of the DFE depends on an inequality of the form $\frac{p}{c_1} < A_3$, with $A_3 \in \mathbb{R}$. We define A_3 as the upper bound for $\frac{p}{c_1}$ in model HB_dH_{bd}. If $d = 1$ or if $a_2 = 0$, then we have $A_3 = A_2$, which was the upper bound for $\frac{p}{c_1}$ in model $HH_{B,bd}$.
We vary the value of d, so we can compare A_1, A_2 and A_3. For instance, in the case of the Dutch population in 2008, we again have $a_1 = 0.28$, $a_2 = 0.005$ and $a_3 = 0.015$. Then A_3

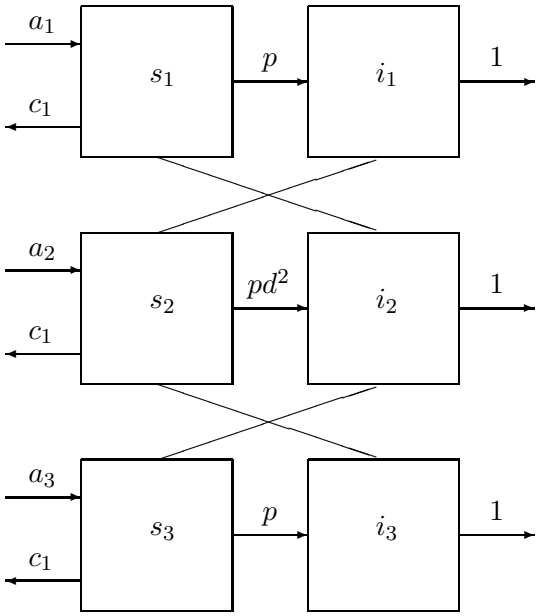

Figure 2.7: This is the transmission model of HB_dH_{bd}. In HB_dH_{bd} the parameters were already nondimensionalised, so the names differ from the last transmission model in Figure 2.5. We have six groups, namely the heterosexual (s_1), bisexual (s_2) and homosexual (s_3) susceptibles, and the infected heterosexuals (i_1), bisexuals (i_2) and homosexuals (i_3). The scaled birth rates are a_1, a_2, and a_3 for respectively the heterosexuals, the bisexuals, and the homosexuals. The death rates are γ for the susceptibles and c for infected individuals. After nondimensionalising we find c_1 and 1. The scaled transmission rates are p for the sexual interactions between individuals who are not bisexual, pd for interactions in which one of the two is bisexual and pd^2 for sexual intercourse between two bisexuals. We still assume that there is no interaction between heterosexuals and homosexuals.

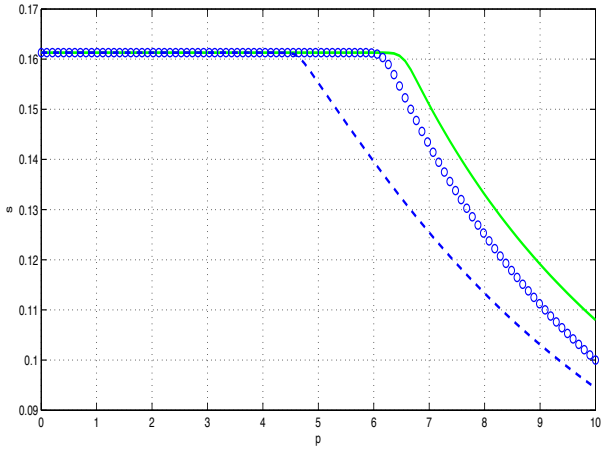

Figure 2.8: These are the three graphs of the models HH_{bd} (line of circles), $HH_{B,bd}$(solid line), and HB_dH_{bd} (dashed line), with the vector s on the y-axis and p on the x-axis. If s is multiplied with N, then we find the values of the susceptible population at steady state. The constants were $a_1 = 0.28$, $a_2 = 0.005$, $a_3 = 0.015$, $\gamma = 0.013$, $c = 0.007$ and $c_1 = 1.86$. The initial conditions were $(s_1(0), s_2(0), s_3(0), i_1(0), i_2(0), i_3(0)) = (0.94, 0.01, 0.05, 4.3\cdot10^{-4}, 8.4\cdot10^{-5}, 7.8\cdot10^{-4})$. We have chosen for $d = 5$ in model HB_dH_{bd}. For p between zero and a certain constant, each model has a stable DFE. If p becomes greater than this constant, the DFE is unstable and the population sizes converge to another equilibrium. In model (2.7), it converges to $\frac{1}{p}$. In the other two models it looks like they also converge to some constant times $\frac{1}{p}$, but we were not able to determine these constants.

is approximately 3.5 when $d = 0.9$ or 1.1, which is equal to A_2, under the same conditions. If d is about 2, then $A_1 = A_3$, and if $d = 5$, then A_3 is about 2.5. In the latter case we have A_1 is approximately 1.3 times A_3. Our another example of Section 2.2.2 was $a_1 = 0.21$, $a_2 = 0.015$ and $a_3 = 0.075$. In this case $d = 2.4$ gives $A_1 \approx A_3$. We already mentioned in Section 2.2.2 that a factor 1.06 or 1.3 does not have much effect on $\frac{p}{c_1}$, so we conclude that the DFE of model HB_dH_{bd} is probably also stable. The p, s-graph of model HB_dH_{bd} looks like the p, s-graphs of $HH_{B,bd}$ and $HH_{B,bd}$, so we have plotted these graphs together in Figure 2.8.

2.4 Differences and similarities between the models

We compare models $HH_{B,bd}$, HBH_{bd}, and HB_dH_{bd} with each other. This is done by looking at what the DFE is of each model and whether this DFE is stable or not.

The DFE

The *SIR* models in Sections 1.2 and 1.3 have the zero vector as DFE. To avoid this, we have chosen the birth rates to be constant. We then found that each model has the scaled birth rates divided by c_1 as total "population size" in the DFE. Since HH_{bd}, $HH_{B,bd}$, HBH_{bd}, and HB_dH_{bd} refer to dimensionless models, we do not find the population size in the DFE. We can compute the actual population size of the susceptibles in the DFE by multiplying by N, the total population size. Note that this value changes, because we have a birth and death which are not equal.
Lin et al. [18] had found that, with some assumptions, the extension of their model (1.8)

would be the same as model (1.7). We also found that model $HH_{B,bd}$ is equal to model SIR_{bd}, if we assume that the transmission rates are the same for each group. For models HBH_{bd} and $HH_{B,bd}$ we were not able to find similar conditions such that it could be reduced to a more simple system of equations.

Stability of the DFE

We found that the DFEs of the models HH_{bd}, $HH_{B,bd}$, HBH_{bd}, and HB_dH_{bd} were of the same form. By choosing the birth rates to be constant, we also found that the DFEs were stable if and only if $\frac{p}{c_1} < A_j$, with A_j for $j = 1, 2$ or 3 a constant depending on the birth rates. We saw that the difference $A_1 - A_2$ was 0.2 if we assumed that 94% of the population is heterosexual, 1% is bisexual, and 5% is homosexual. This result was found under the assumption that every transmission rate would be the same. We were not able to solve the system of equations without this assumption. In model HB_dH_{bd} we have added the term d, so we would be able to make a distinction between the transmission rates. If d is less than one, this means that the bisexuals have more often safe sex compared with the other two groups, while if d is greater than one, it means the opposite. If $d = 1$, then we have model $HH_{B,bd}$.
In the case of the Dutch population in 2008, we have chosen $d = 5$, and we have plotted the p, s-graphs of the models $HH_{B,bd}$, HBH_{bd}, and HB_dH_{bd} together. These graphs are given in Figure 2.8. We notice that the graphs have the same shape. At first the population sizes converge to the DFE, but when p is larger than a certain constant, the sizes converge to another equilibrium. With these constants, the DFE of model HB_dH_{bd} only becomes unstable for a smaller value of p compared to the DFEs of the other two models. This is due to the value of d. If d decreases, then the interval in which the DFE is stable becomes larger. So the larger the value of d, the more likely the DFE of HB_dH_{bd} is unstable. This only holds if the other constants remain the same.
The inequality $\frac{p}{c_1} < A_j$ only hold if and only if the number of people someone transmits the virus to is small. As a result there is a small probability that our DFE could be unstable and hence we looked for other equilibria.
For model $HH_{B,bd}$ we were able to determine that m is the constant function equal to one, and the only other equilibrium is $\left(\frac{1}{p}, \frac{ap-c_1}{p}\right)$. The ratio $s : i$ in this steady state is then $1 : ap - c_1$. The DFE is unstable if and only if $\frac{p}{c_1} < A_1 := \frac{1}{a}$, so the value of p should be large compared to our birth and death rates. As a result, the number of infected could be larger than the number of susceptibles in the nontrivial steady state.
For models $HH_{B,bd}$ and HB_dH_{bd} we were only able to prove that the shape of Figure (2.6) is not of the form $\frac{1}{p} \cdot m(a_1, a_2, a_3, c_1, p)$. This is because we have assumed that there is no sexual interaction between the heterosexuals and the homosexuals. As a result, we do not have the transmission rate $\beta_{1,3}$ and we are not able to make substitutions such that HBH_{bd} becomes model $HH_{B,bd}$.

Conclusion

Since the DFEs of the four models are of the same form, the sum of the susceptible population in the DFE is always the same. As a result, there is no difference in the population size in the DFEs of the models.
There were some differences between the values of the upper bounds A_j for $j = 1, 2, 3$. In

the case of the Dutch population in 2008, we found that the difference between A_2 and A_3 was (almost) zero, if $d = 0.9$ or $d = 1.1$. The values of A_1 and A_2 for models HH_{bd} and $HH_{B,bd}$ differed. This is due to the assumption that the heterosexuals and homosexuals have no contact with each other. If we assume that 70% of the population is heterosexual, then A_2 was about 1.3 times A_1. In reality, the percentage of homosexuals is smaller, so the value of A_2 is also probably smaller.
The differences between model HH_{bd} and HB_dH_{bd} were greater, but in the case of the Dutch population, with $d = 5$, A_3 was only about 1.3 times A_1. We do not know whether bisexuals have safe sex more often, so we can not conclude whether we should choose $d = 0.9$ or $d = 1.1$ or even $d = 5$. We might as well choose $d = 1$. There is a difference between the values of A_1, A_2 and A_3, but with each model we concluded that the DFE of its particular model is stable regardless of the value of A_j for $j = 1, 2, 3$. Therefore, we conclude that if the transmission rates are the same, we can assume that the group of bisexuals does not have to be separated from the group of homosexuals.

Chapter 3

Extensions of our model with medicine

In Chapter 2 we concluded that the group of bisexuals essentially could be ignored. We drew this conclusion under the condition that the transmission rates between the bisexuals and the heterosexuals, and between the bisexuals and the homosexuals are the same. As a result we continue using model $HH_{B,bd}$, which consists of the groups S_1, I_1, S_3 and I_3. We redefine S_3 as the susceptibles who are homosexual or bisexual, and I_3 is the group of homosexuals and bisexuals who are infected with the HI-virus. From now on we rename S_3 and I_3 as S_2 and I_2. The same assumptions as before still hold. In Chapter 1 we mentioned that there has been a breakthrough in finding a cure and a vaccine against HIV. Therefore, we investigate the influence of a vaccine or a cure on the spread of HIV and on the size of the (susceptible) population size in the equilibria. So our question is: does a vaccine or a cure have much effect on the spread of HIV?
In the first section we assume that there is a vaccine for HIV, in the second section it is assumed that there is a cure for HIV/AIDS. In the last section we compare the results of these models with each other.

3.1 Model with a vaccine

We assume that a vaccine for HIV is found and we assume that there is no cure in this model, so the death rates are the same as in model $HH_{B,bd}$. There is a possibility that a person is not vaccinated. This is because someone can decide not to get the vaccine, someone can live in a place where they do not have the vaccine, or for other reasons. It is not known whether the vaccine works perfectly or not. However, if someone is vaccinated, but the vaccine does not work, then we consider this person as someone who is not vaccinated. We have two kinds of susceptibles, namely the susceptibles who were vaccinated and the susceptibles who were unvaccinated. We assume that there are two transmission rates, one for the vaccinated and one for the unvaccinated individuals. If these rates are the same, then we have model $HH_{B,bd}$. Normally the rate at which vaccinated people get infected and transmit the virus to someone else is (much) smaller than the rate at which unvaccinated people do. Therefore, we can assume that the transmission rate of the vaccinated is smaller than the transmission rate of the unvaccinated. The death rates are still γ for the susceptible population and c for

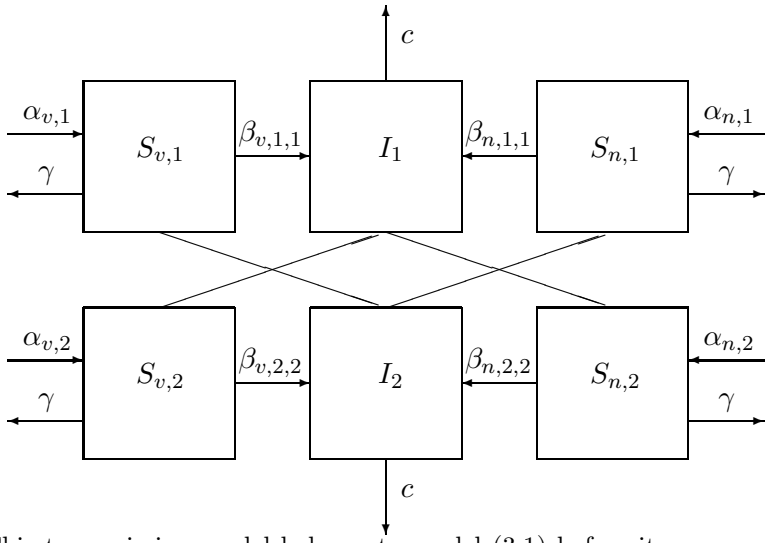

Figure 3.1: This transmission model belongs to model (3.1) before it was nondimensionalised. We have the vaccinated ($S_{v,1}$, $S_{v,2}$) and unvaccinated ($S_{n,1}$, $S_{n,2}$) susceptibles, and the infected (I_1, I_2). The birth rates are $\alpha_{v,1}$, $\alpha_{v,2}$ for the vaccinated and $\alpha_{n,1}$, $\alpha_{n,2}$ for the unvaccinated susceptibles. The death rates are γ for the susceptibles and c for the infected. We have the transmission rates $\beta_{v,1}$ and $\beta_{v,2}$ for the transmission between vaccinated susceptibles and infected people, and $\beta_{n,1}$ and $\beta_{n,2}$ for the transmission between unvaccinated susceptibles and the infected.

the infected and we assume that the vaccine does not influence these rates. Furthermore, we have two different birth rates, because everyone who has become sexually active can decide whether to be vaccinated or not.
Our model consists of six groups and the dimensionless system of equations is

$$\begin{aligned}
\tfrac{ds_{v,1}}{dt} &= a_{v,1} - p_{v,1,1}s_{v,1}i_1 - p_{v,1,2}s_{v,1}i_2 - c_1 s_{v,1},\\
\tfrac{ds_{n,1}}{dt} &= a_{n,1} - p_{n,1,1}s_{n,1}i_1 - p_{n,1,2}s_{n,1}i_2 - c_1 s_{n,1},\\
\tfrac{ds_{v,2}}{dt} &= a_{v,2} - p_{v,1,2}s_{v,2}i_1 - p_{v,2,2}s_{v,2}i_2 - c_1 s_{v,2},\\
\tfrac{ds_{n,2}}{dt} &= a_{n,2} - p_{n,1,2}s_{n,2}i_1 - p_{n,2,2}s_{n,2}i_2 - c_1 s_{n,2},\\
\tfrac{di_1}{dt} &= p_{v,1,1}s_{v,1}i_1 + p_{v,1,2}s_{v,1}i_2 + p_{n,1,1}s_{n,1}i_1 + p_{n,1,2}s_{n,1}i_2 - i_1,\\
\tfrac{di_2}{dt} &= p_{v,1,2}s_{v,2}i_1 + p_{v,2,2}s_{v,2}i_2 + p_{n,1,2}s_{n,2}i_1 + p_{n,2,2}s_{n,2}i_2 - i_2.
\end{aligned} \tag{3.1}$$

In this system $a_{v,1}$, $a_{n,1}$, $a_{v,2}$, and $a_{n,2}$ are the scaled birth rates, $p_{v,i,j}$ and $p_{n,i,j}$ for $i,j = 1,2$ are the scaled transmission rates for the interaction between people from $S_{n,i}$ or $S_{v,i}$ with I_j, and c_1 is still defined as $\frac{\gamma}{c}$. The difference between these two rates can be seen as a measure of how good the vaccine is. This only holds if the vaccine does not change the risk behavior of the susceptibles. If the transmission rates are zero, then we have a perfect vaccine. Note that we do not have an extra term or factor for the waning immunity. This waning immunity means that if someone is vaccinated, that over time this vaccine becomes weaker. The transmission model is given in Figure 3.1. It is clear that the DFE of this model is $(s_{v,1}, s_{n,1}, s_{v,2,}, s_{n,2}, i_1, i_2) = (\frac{a_{v,1}}{c_1}, \frac{a_{n,1}}{c_1}, \frac{a_{v,2}}{c_1}, \frac{a_{n,2}}{c_1}, 0, 0)$. Its Jacobian has four times $-c_1$ as eigenvalue and the other two eigenvalues are of the form $\frac{1}{c_1}h \pm \sqrt{q}$, with h and q functions depending on the birth, death, and transmission rates. We do not give the formulas for these functions, because they are (very) complicated.

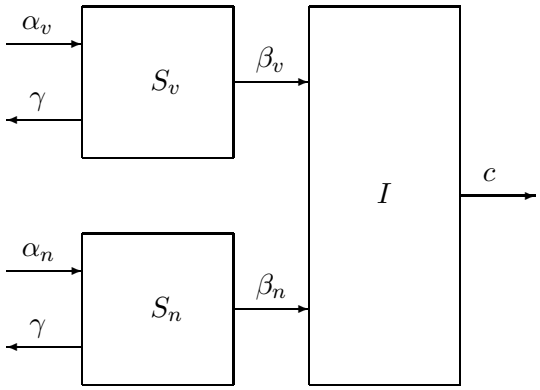

Figure 3.2: This transmission model belongs to model V_{bd}, before it was nondimensionalised. We have the vaccinated (S_v) and unvaccinated (S_n) susceptibles, and the infected (I). The birth rates are α_v and α_n for respectively the vaccinated and the unvaccinated susceptibles. The death rates are still γ for the susceptibles and c for the infected. There are two kinds of transmission rates, namely β_v for the transmissions between vaccinated susceptibles and infected people, and β_n for the transmissions between unvaccinated susceptibles and the infected.

We assume that the transmission rates for sexual intercourse where vaccinated susceptibles are involved are the same, and we assume that the transmission rates at which the unvaccinated susceptibles get infected are also equal. So we assume that all the $p_{v,j,k}$'s for $j,k = 1,2$ have the same value and that all the $p_{n,j,k}$'s for $j,k = 1,2$ are the same. Then model (3.1) is the extension of model SIR_{bd}, before it was nondimensionalised and with the substitutions $S_v := S_{v,1} + S_{v,2}$, $S_n := S_{n,1} + S_{n,2}$ and $I := I_1 + I_2$. The birth rate for the vaccinated individuals is defined as $\alpha_v := \alpha_{v,1} + \alpha_{v,2}$ and the birth rates for the unvaccinated is $\alpha_n := \alpha_{n,1} + \alpha_{n,2}$. We define β_v as transmission rate for sexual interactions between individuals from group S_v and I_k, and β_n for interactions between members of S_n and I_k for $k = 1,2$.
With the substitutions $a_v := \frac{\alpha_v}{cN}$, $a_n := \frac{\alpha_n}{cN}$, $p_v := \frac{\beta_v N}{c}$, $p_n := \frac{\beta_n N}{c}$, $s_v := \frac{S_v}{cN}$, $s_n := \frac{S_n}{cN}$, $i := \frac{I}{cN}$, where N is the total population size, and $t := cT$, where T is the time, we define the dimensionless system of equations given in (3.2). The transmission model belonging to this system is given in Figure 3.2.

$$\begin{aligned} \tfrac{ds_v}{dt} &= a_v - p_v s_v i - c_1 s_v, \\ \tfrac{ds_n}{dt} &= a_n - p_n s_n i - c_1 s_n, \\ \tfrac{di}{dt} &= p_v s_v i + p_n s_n i - i. \end{aligned} \tag{3.2}$$

We refer to this model with V_{bd}, where V stands for vaccine and bd still denotes the birth and death rate. Note that if $p_v = p_n = p$ for $p \in \mathbb{R}$, this model is the same as model SIR_{bd} with the substitutions $s := s_v + s_n$ and $a = a_v + a_n$. Then the DFE is $(s,i) = (\frac{a}{c_1}, 0)$ and this is stable if and only if $\frac{p}{c_1} < \frac{1}{a}$.
Since the vaccinated and the unvaccinated people together form the whole susceptible population, we can define this population as $s := s_v + s_n$. Note that this is already a dimensionless variable. The terms a_v and a_n together are the total (scaled) birth rate, which we define as

$a := a_v + a_n$. As a result, we know there exist $q, u \in [0,1]$ such that $s_v = qs$, $s_n = (1-q)s$, $a_v := ua$, and $a_n := (1-u)a$. Model V_{bd} then becomes

$$\begin{array}{ll} \frac{ds}{dt} & = a - (p_v q + p_n(1-q))si - c_1 s, \\ \frac{di}{dt} & = (p_v q + p_n(1-q))si - i. \end{array} \tag{3.3}$$

This model only has two steady states, namely the DFE $(s,i) = (\frac{a}{c_1}, 0)$, and $(s,i) = (\frac{1}{p_v q + p_n - p_n q}, \frac{ap_n q + c_1 - ap_v q - ap_n}{p_n q - p_v q - p_n})$. The eigenvalues of the Jacobian matrix in the DFE are $-c_1$ and $\frac{ap_n q + c_1 - ap_v q - ap_n}{c_1}$, so the DFE is stable if and only if

$$a(1-q)p_n + aqp_v < c_1 \Longleftrightarrow \frac{p_n - \frac{c_1}{a}}{p_n - p_v} < q. \tag{3.4}$$

We assume that the vaccine will be given to as many people as possible. If from a certain point in time every new sexually active person is vaccinated, then $q = 1$, $a_n = 0$, $a_v = a$, and the DFE becomes $(s_v, s_n, i) = (\frac{a}{c_1}, 0, 0)$. By (3.4) we then find

$$p_v < \frac{c_1}{a}.$$

This looks like inequality (2.9) for model $HH_{B,bd}$ in Chapter 2. We concluded that the DFE of $HH_{B,bd}$ is probably stable. We assume that the invention of a vaccine does not change the birth or death rates drastically, so it is assumed that c_1 stays the same and $a = a_v + a_n$ is the total (scaled) birth rate, which also has the same value as before. The vaccine should prevent someone from contracting HIV, which means that p_v should be (much) smaller than p. So if everyone gets vaccinated, then it becomes more likely that the DFE of model V_{bd} is stable.
We look at the left inequality of (3.4). Under the condition that the vaccine does not change the birth and death rates, $\frac{c_1}{a}$ stays the same. We assume that the virus is transmitted to the unvaccinated persons at the same rate as if the vaccine does not exist at all, so we assume that p_n in model V_{bd} has the same value as p in model $HH_{B,bd}$. Furthermore, we reasoned that p_v should be smaller than p, and thus with our assumption also smaller than p_n. Together this and (3.4) gives us

$$p_v q + p_n - q p_n < p.$$

As a result, even if not everyone is vaccinated, we still conclude that with a vaccine the DFE becomes more stable.
We use the same data of the Dutch population again for our numerical simulation. We are only interested in the DFE, so we take as initial vector $(s_v(0), s_n(0), i(0)) = (\frac{ma}{c_1} - \epsilon, \frac{(1-m)a}{c_1} - \epsilon, 2\epsilon)$, with $a = 0.3$, $c_1 = 1.86$, and $o = 0.1, 0.2, \ldots, 0.9$. The constant o indicates the percentage of successfully vaccinated individuals. We have chosen $p_v = 10^{-3}$, $\gamma = 0.013$, and $c = 0.007$. When 90% of the sexual active people is vaccinated, the DFE is unstable if p_n is greater than (approximately) 32. We have varied p_n from zero to fifty in our plots in Figure 3.3, because otherwise the graph would be unclear. Note that it is very unrealistic to have a scaled transmission rate of 32, because it means that each infected person transmits the virus to 32 times the death rate of the infected persons in one time unit.
We notice that the smaller the number of vaccinated people, the greater the bound of p_n for a stable DFE. In Figure 3.3 we also see that the sum of the susceptible population in the nontrivial equilibrium becomes smaller if more people are vaccinated. When 90% of the population is vaccinated, the size of the susceptible population in the nontrivial steady state

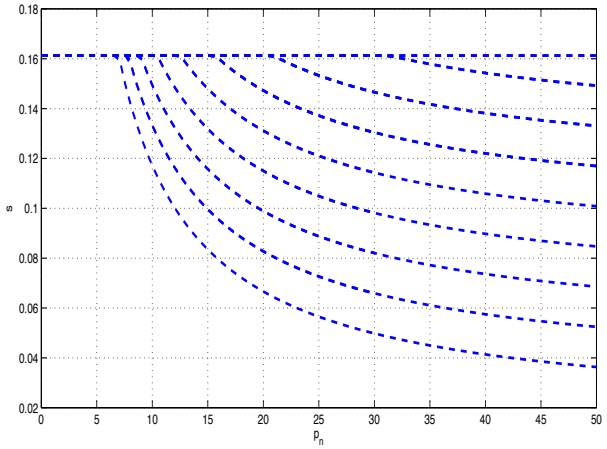

Figure 3.3: We have plotted graphs of the model V_{bd}, which has the dimensionless vector s for the susceptible population on the y-axis and the vector p_n on the x-axis. The size of the susceptible population at steady state is found by multiplying the vector s with N, and if p_n is multiplied with $\frac{c}{\beta N}$, then we find the original transmission rate. We have chosen the values $p_v = 10^{-3}$, $a = 0.3$, $c_1 = 1.86$, $\gamma = 0.013$, $c = 0.007$, and $p_n = 0, \ldots, 50$, and we have varied the percentage of people who are vaccinated. The lowest graph belongs to the case when 10% of the population is vaccinated. When the percentage of vaccinated individuals grows, the size of the susceptible population in the equilibria becomes greater. We have chosen as percentages 10%, 20%, ..., 90%, so $a_v = ma$, with $o = 0.1, 0.2, \ldots, 0.9$, and $a_n = a - a_v$. The initial conditions were $(s_1(0), s_2(0), s_3(0), i_1(0), i_2(0), i_3(0)) = (0.94, 0.01, 0.05, 4.3 \cdot 10^{-4}, 8.4 \cdot 10^{-5}, 7.8 \cdot 10^{-4})$.

decreases slowly. If we compare Figure 3.3 to Figure 2.8, then we conclude that, with our assumptions, it is indeed more likely to have a stable DFE if there is a vaccine and if the sexual behavior does not change drastically. In our model a vaccine does not change the total amount of susceptibles in the DFE; this is still $\frac{a}{c_1}$.

3.2 Model with a cure

In this section we assume that a cure for HIV/AIDS exists. Model $HH_{B,bd}$ is extended with a group R, which is the group of infected who get the medicine against the virus. We assume that individuals who have recovered will become susceptible again with a constant rate w, because the virus changes so quickly. Until this happens, we assume they are immune to the disease. The birth and the death rate for the susceptibles are the same for this system of equations as in model $HH_{B,bd}$, but the death rate for the infected changes. This is because a cure should decrease the number of deaths due to the virus. We denote the death rate for the infected with c'. The death rate for the individuals who have recovered from the virus is γ, because these people are not infected. The system of equations belonging to this model is

$$\begin{aligned}
\tfrac{dS_1}{dT} &= \alpha_1 + u_1 wR - \beta_{1,1} S_1 I_1 - \beta_{1,2} S_1 I_2 - \gamma S_1, \\
\tfrac{dS_2}{dT} &= \alpha_2 + u_2 wR - \beta_{2,2} S_2 I_2 - \beta_{1,2} S_2 I_1 - \gamma S_2, \\
\tfrac{dI_1}{dT} &= \beta_{1,1} S_1 I_1 + \beta_{1,2} S_1 I_2 - (c' + \delta) I_1, \\
\tfrac{dI_2}{dT} &= \beta_{2,2} S_2 I_2 + \beta_{1,2} S_2 I_1 - (c' + \delta) I_2, \\
\tfrac{dR}{dT} &= \delta(I_1 + I_2) - wR - \gamma R.
\end{aligned} \tag{3.5}$$

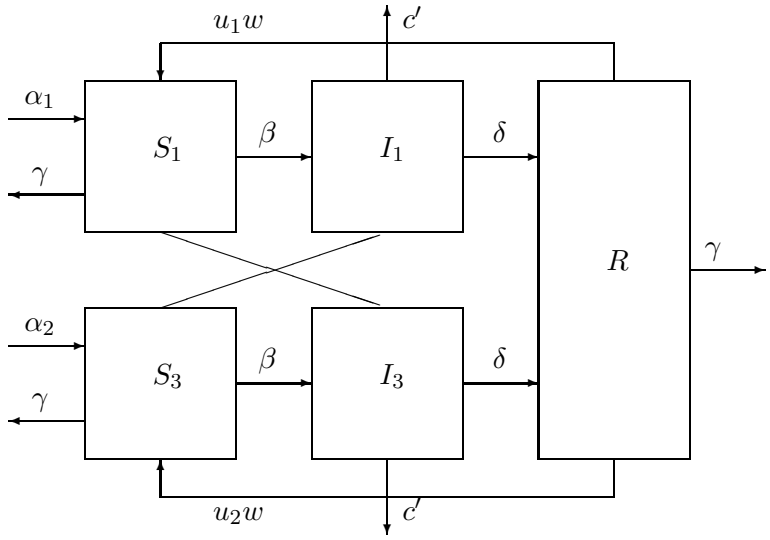

Figure 3.4: This is the transmission model of (3.5). It consists of the susceptible (S_1, S_2), the infected (I_1, I_2) and the recovered (R) population. The birth rates are α_1 and α_2 for the susceptibles, the death rates are γ for the susceptibles and the individuals who have recovered of HIV/AIDS, and c' is the death rate for the infected. The transmission rates are $\beta_{j,k}$ for $j,k = 1,2$ and the term δ is the rate at which someone recovers from HIV/AIDS. Someone who is recovered, can become susceptible again at rate u_kw, for $k = 1,2$, with $u_1 + u_2 = 1$.

The transmission model is given in Figure 3.4. The extra term w is the rate at which an individual who has recovered from HIV becomes susceptible again and δ is the rate at which someone who uses the cure recovers from HIV. The constants u_1 and u_2 are the ratios of the susceptible population that belongs to the group of heterosexuals, and to the group of homo- and bisexuals. Obviously, $u_1 + u_2 = 1$.
Note that we do not consider the drug-resistancy and the drug-sensitivity in these models. We neglect these factors because current research, which focusses on finding a cure for HIV, seems to indicate that a possible cure would differ significantly from known drugs and cures for other diseases. Therefore, at this point, it is not possible to incorporate the drug-resistancy and the drug-sensitivity realistically into our model.
We substitute $s_j := \frac{S_j}{N}$, $i := \frac{I_j}{N}$, $a'_j := \frac{\alpha_j}{N(c'+\delta)}$ for $j = 1,2$, $p = \frac{\beta N}{c'+\delta}$, $c'_1 := \frac{\gamma}{c'+\delta}$, $\delta_c := \frac{\delta}{c'+\delta}$, $w_c := \frac{w}{c'+\delta}$, and $t := \frac{1}{c'+\delta}T$. Then model (3.5) becomes

$$\begin{aligned}
\tfrac{ds_1}{dt} &= a'_1 + u_1w_cr - p_{1,1}s_1i_1 - p_{1,2}s_1i_2 - c'_1s_1,\\
\tfrac{ds_2}{dt} &= a'_2 + u_2w_cr - p_{1,2}s_2i_1 - p_{2,2}s_2i_2 - c'_1s_2,\\
\tfrac{di_1}{dt} &= p_{1,1}s_1i_1 + p_{1,2}s_1i_2 - i_1,\\
\tfrac{di_2}{dt} &= p_{1,2}s_2i_1 + p_{2,2}s_2i_2 - i_2,\\
\tfrac{dr}{dt} &= \delta_ci - w_cr.
\end{aligned} \tag{3.6}$$

The DFE of model (3.6) is $(s_1, s_2, i_1, i_2, r) = (\frac{a'_1}{c'_1}, \frac{a'_2}{c'_1}, 0, 0, 0)$ and the eigenvalues of its Jacobian are twice $-c'_1$, $-w$, and

$$\frac{1}{2c'_1}(a'_1p_{1,1} + a'_2p_{2,2} - 2c'_1) \pm \sqrt{a'^2_1p^2_{1,1} + a'^2_2p^2_{2,2} + 4a'_1a'_2p^2_{1,2} - 2a'_1a'_2p_{1,1}p_{2,2}}.$$

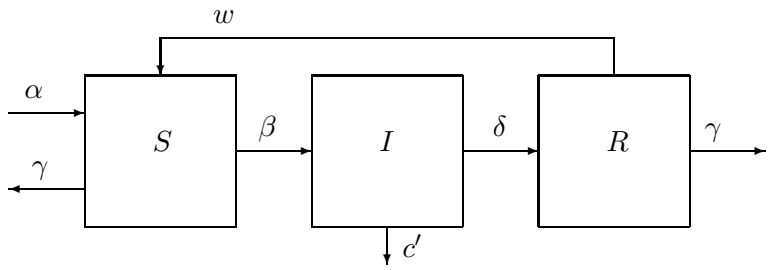

Figure 3.5: This is the transmission model of C_{bd} before it was nondimensionalised. It consists of the susceptible (S), the infected (I) and the recovered (R) population. The birth rate is α for the susceptibles, the death rates are γ for the susceptibles and the individuals who have recovered of HIV/AIDS, and c' is the death rate for the infected. The transmission rate is β and the term δ is the rate at which someone recovers from HIV/AIDS. Someone who has recovered, can become susceptible again at rate w.

So the DFE is stable if and only if

$$\frac{1}{2c_1'}(a_1'p_{1,1} + a_2'p_{2,2}) + \sqrt{a_1'^2p_{1,1}^2 + a_2'^2p_{2,2}^2 + 4a_1'a_2'p_{1,2}^2 - 2a_1'a_2'p_{1,1}p_{2,2}} < 1. \tag{3.7}$$

It is hard to draw conclusions from this inequality, because we do not know what the values of the birth and transmission rates are. It consists of terms $a_j'p_{m,n}$ for $j,m,n = 1,2$, and in Chapter 2 we concluded that the scaled birth rate multiplied with the transmission rate is probably (very) small. Since the scaled birth rate differ, we can not draw this conclusion. We make more progress by assuming that the transmission rates are the same.
With this assumption, we have an extension of model SIR_{bd}. The dimensionless system is given below.

$$\begin{aligned} \tfrac{ds}{dt} &= a' + w_c r - psi - c_1' s, \\ \tfrac{di}{dt} &= psi - i, \\ \tfrac{dr}{dt} &= \delta_c i - w_c r. \end{aligned} \tag{3.8}$$

The transmission model before it was nondimensionalised is given in Figure 3.5. We will refer to this model with C_{bd}, because C denotes the cure and bd stands for the birth and death rates. This model has two steady states, namely the DFE $(s,i,r) = (\frac{a'}{c_1'}, 0, 0)$ and $(s,i,r) = \left(\frac{1}{p}, \frac{a'p - c_1'}{p(1-\delta_c)}, \frac{\delta_c(a'p-c_1')}{p(1-\delta_c)w_c}\right)$. The eigenvalues of the Jacobian in the DFE are $-c_1'$, $-w$, and $\frac{a'p-c_1'}{c_1}$, so the DFE is stable if and only if

$$\frac{p}{c_1'} < \frac{1}{a'} \Leftrightarrow a'p < c_1'. \tag{3.9}$$

This looks like the same bound as in Chapter 2, but we have $c_1' = \frac{\gamma}{c'+\delta}$ instead of $c_1 = \frac{\gamma}{c}$ and $a' = \frac{\alpha}{(c'+\delta)N}$ instead of $a = \frac{\alpha}{cN}$. Let us assume that the invention of a cure only has effect on the death rate of the infected (and of course on the rate at which infected recover). Then the difference between the inequalities (2.9) and (3.9) only depends on c and c'. The inequalities (2.9) and (3.9) are the same if and only if

$$c_1 = c_1' \Leftrightarrow c = c' + \delta.$$

The constant c was defined as the death rate of the infected without any medicine. If we assume that a cure does not change anything about the behavior of the population and the virus, then the rate at which someone gets infected stays the same. In our model with the cure the rate at which someone leaves the group of infected is exactly $c' + \delta$. The rate at which someone recovers does not have to be same as the rate at which an infected dies. Therefore, it is not necessary to have the equality $c = c' + \delta$. We can distinguish three cases, namely

$$\begin{array}{lllll} 1) & c < c' + \delta & \iff & c - c' < \delta & (\Leftrightarrow c_1 > c_1'), \\ 2) & c = c' + \delta & \iff & c - c' = \delta & (\Leftrightarrow c_1 = c_1'), \text{ and} \\ 3) & c > c' + \delta & \iff & c - c' > \delta & (\Leftrightarrow c_1 < c_1'). \end{array}$$

A cure should decrease the number of deaths due to the HI-virus per time unit. It is logical to assume that $c' < c$ and $\delta > c'$, because otherwise we do not have a good cure. Unfortunately, the greater the value of δ, the more likely we have inequality $c < c' + \delta$. Thus the greater the rate at which infected people recover, the more unstable our DFE becomes. Also the size of $\frac{a}{c_1'}$ in the DFE would change. If the difference $c - c'$ is greater than the recovery rate, then the size of $\frac{a}{c_1'}$ decreases compared with $\frac{a}{c_1}$, and vice versa.
Again we use the data of the Dutch population in 2007-2008. A cure has no effect on the death rate of the susceptible population, so γ is still equal to 0.013. Although this also holds for the birth rate, the scaled birth rate does change, because we divide by $c' + \delta$. Since we do not know how much the death rate for the infected will decrease, and we do not have any clue what the value of δ should be, we just assume that c' is 0.005 and we choose $\delta = 0.1$. The value of s in the DFE is $\frac{a'}{c_1'} = \frac{a}{c_1}$, because a' and c_1' have the same denominator. As a result, the value of s in the DFE does not change, if δ changes. Changing the value of w also has no influence on the size of s in the DFE. We have plotted the p, s-graph in Figure 3.6.
If the DFE is unstable, then (s, i) converge to the other equilibrium, in which the value of s is (again) $\frac{1}{p}$. In the nontrivial steady state the value of the total size of the non-infected $(s + r)$ depends on the sizes of δ and w. With the same data as before we have plotted several $p, s + r$-graphs in Figure 3.7. The values of s and r in the nontrivial state are respectively $\frac{1}{p}$ and $\frac{\delta_c(ap - c_1)}{p(1-\delta_c)w_c}$. We define the sum as

$$l(p) := s + r = \frac{1}{p} + \frac{\delta_c(ap - c_1')}{p(1 - \delta_c)w_c}.$$

The derivative is greater than zero if and only if

$$w_c < \frac{\delta_c c_1'}{1 - \delta_c}. \tag{3.10}$$

So if $w_c < \frac{\delta_c c_1'}{1-\delta_c}$, then the size of the non-infected population in the nontrivial steady state will be greater than the susceptible population in the DFE.

3.3 Differences and similarities between the models

We will compare the models SIR_{bd}, V_{bd}, and C_{bd} with each other. This is done by comparing the DFEs and whether they are stable or not.

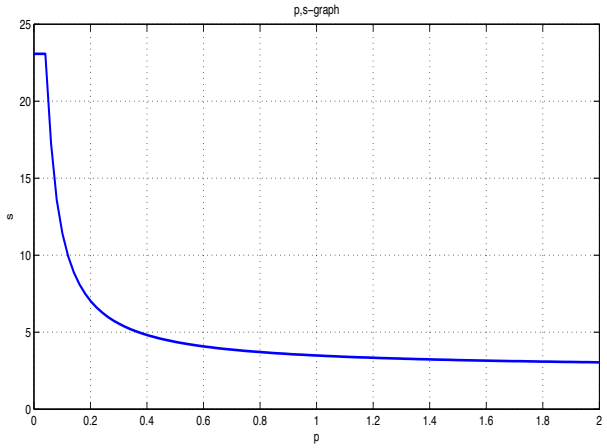

Figure 3.6: This is a graphs of model C_{bd}, with the dimensionless s for the susceptible population on the y-axis and the scaled transmission rate p on the x-axis. The constants were $\gamma = 0.013$, $c' = 0.005$, and $a = \frac{0.3}{c'+\delta}$, with $\delta = 0.1$ and $w = 0.05$. We have a stable DFE when p is between zero and 0.005. We do not vary the values of δ and w, because changing them has no effect on the size of the dimensionless susceptible population in the steady states. We notice that the dimensionless size of the susceptible population in the DFE becomes greater, but it is unstable with a much smaller value of p compared to the models in Chapter 2 and in Section 3.1.

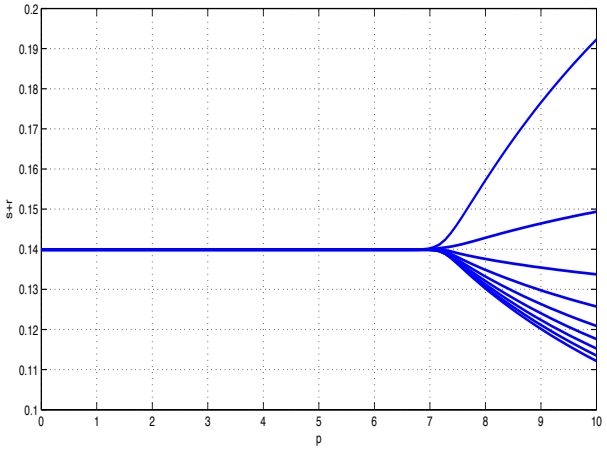

Figure 3.7: These are graphs of model C_{bd}, with the dimensionless $s+r$ for the non-infected population on the y-axis and the scaled transmission rate p on the x-axis, and with $a = 0.3/(c' + \delta)$, $\gamma = 0.013$, and $c' = 0.008$. We have varied the values of w. We have taken $\delta = 0.1$ and $w = 0.1, 0.2, \ldots, 0.9$. Changing w has no affect on the size of the susceptible population in the steady states, but it does have effect on the size of the the recovered individuals.

The DFE

The population size of the susceptibles in the DFE of model SIR_{bd} is $\frac{a}{c_1}$, with $c_1 = \frac{\gamma}{c}$. In model V_{bd} the total population size in the DFE is $\frac{a_v}{c_1} + \frac{a_n}{c_1}$. We assumed that a vaccine would not affect the birth and death rate of the population. Since $a_v + a_n$ is the total (scaled) birth rate, a in SIR_{bd} is equal to $a_v + a_n$ in V_{bd}.
We have explained that the size of the susceptible population in the DFE of model C_{bd} is not the same if the cure only affects the death rate of the infected (and the recovery rate). We found that the population size in the nontrivial steady state of model C_{bd} depended on the equation $w_c < \frac{\delta_c c_1}{1-\delta_c}$. If this inequality holds, then the dimensionless non-infected population in the DFE will be smaller than its size in the nontrivial steady state.

Stability of the DFE

The stability of model SIR_{bd} holds when $\frac{p}{c_1} < \frac{1}{a}$ and in C_{bd} this inequality was $\frac{p}{c_1'} < \frac{1}{a'}$. The bound for the stability of the DFE of model V_{bd} was $p_n a_n + p_v a_v < c_1$.
If many people are vaccinated, then the DFE in model V_{bd} becomes more stable. If many people in model C_{bd} recover from HIV, then the susceptible population in the DFE becomes greater. So according to our models, if a vaccine does not affect the transmission, birth or death rates, then a vaccine will make it (even) more likely that the DFE is stable.
If a cure does not affect the death rate of the infected, then the population size will increase. This is very unlikely, so we looked at what would happen if the death rate of the infected would change. We found that if the difference between the death rates of the infected before and after a cure was found, was greater than the rate at which an infected recovers from HIV, then the size of the population in the DFE would become greater. If this difference is smaller, then the population size would decrease. Also the interval in which we would have a stable DFE changes. In our example of the Dutch population, the interval in which the DFE is stable becomes smaller, and vice versa.

Conclusion

How a vaccine or a cure affects the population size depends on several factors, like

- how many people will be vaccinated?
- how quickly does the virus change such that a recovered or vaccinated person will become a susceptible again?
- does the sexual behavior of the individuals change?

In this chapter we assumed that the vaccine and the cure do not affect the birth and death rates. Furthermore, we assumed that the sexual behavior of the population would not change. Then we found that if a vaccine would be introduced, then the DFE of model V_{bd} would be the same as the DFE of model $HH_{B,bd}$. Since a vaccine should prevent someone from contracting a disease, we concluded that the DFE of model V_{bd} is more stable than the DFE of model $HH_{B,bd}$.
A cure will make the death rate of the infected become smaller. If citizens of a population do not change their sexual behavior and the birth and death rates of the susceptibles do not change, then the stability of the DFE and the the size of the population in the steady states change. This depends on whether the difference between the death rates before and after a

cure was introduced is greater or smaller than the rate at which someone would recover from HIV. If this difference is greater, than the size of the population in the DFE will become greater and the interval in which this DFE is stable will become smaller. If the difference was smaller, then it is the other way around.

Summary and discussion

In Chapter 1 we explained what HIV/AIDS is and we introduced the most basic model used in epidemiological modeling in populations. Furthermore, we gave a review of literature to get an impression of the research that has been done in this area.
In Chapter 2 we investigated the influence of the bisexuals on the spread of HIV in a population. The investigation was done by developing a model where we only have heterosexuals and homosexuals. Then we extended this model with the group of bisexuals. Our assumptions for these models were

1. The latent period of HIV is not considered in our models;
2. The virus is only transmitted via sexual intercourse;
3. Each person who has become sexually active is not infected with the virus;
4. The number of individuals who become sexually active is constant;
5. The death rate of the susceptible population and the death rate of the infected are a constant times the size of respectively the susceptible or infected population;
6. In the model with the bisexuals we have assumed that the sexual interaction between the homosexuals and heterosexuals is insignificant;
7. The transmission rate is the same for interaction between each considered group;
8. There is no vaccine or cure for the HI-virus.

In model HB_dH_{bd} we assumed that the transmission rate of the bisexuals is a constant times the transmission rate of the heterosexuals and homosexuals.
With our models we investigated when the HI-virus would become extinct and what the size of the population in that case would be. We also computed whether it is likely for the virus to die out naturally. We found in each model that it is very likely that the virus will die out naturally in the Dutch population. We concluded this because the transmission rate is much smaller than the birth and death rates.
In models $HH_{B,bd}$, HBH_{bd}, and HB_dH_{bd} we found that the total population size would eventually become the same constant and in each model it was very likely that nobody would be HI-infected anymore. As a result, we concluded that it was not necessary to make the distinction between a homosexual or bisexual.
In the last chapter we tried to simulate what the difference would be if a population would have a vaccine or a cure for HIV. We started of with the assumptions of Chapter 2. We then developed a model where we incorporated a vaccine for HIV and a model in which we

assumed that found a cure. For simplicity, we assumed that we would only have one medicine at a time, so if we have a vaccine, then we do not have a cure and vice versa. Furthermore, a vaccine or a cure has no influence on the number of people who become sexually active and on the death rate of the susceptible population. This means that we assumed that the transmission rate, the birth rates, and the death rate of the susceptibles would not change.
We compared our findings with the results we obtained from model $HH_{B,bd}$. With our assumptions we found that with the existence of a vaccine, it is more likely that the infected population become extinct. On the other hand, if we have a cure for HIV, then it is important to know how good this cure actually is. We found that if the recovery rate is great, then it becomes more likely that the DFE is unstable.
Our models can be interpreted in different ways. We had the groups heterosexual, bisexual, and homosexual susceptibles or infected. For instance, the model with only the heterosexuals and homosexuals could also be interpreted as a model which makes the distinction between male and female or adolescents and adults. Note that if we make the distinction between juvenile and adults, then it is also reasonable to drop the assumption that transmission can only occur through sexual intercourse. It is also possible to use these models for other diseases, which can be transmitted to other people, like the flu, the small pox, or other sexually transmitted diseases.
We made a lot of assumptions during our investigation. The most important one was that we assumed that the birth rate was a constant, while the death rates were a constant times its population size. This is not realistic, because the birth rate of a population normally (always) depends on it. However, mathematically this assumption had to be made in order to have a nonzero steady state. This is necessary, because we would like to predict what the influence of the virus is on a virgin population.
Let us have a look at the list of our assumptions. The latent period of HIV was neglected. Someone might be infected for years, before finding it out. To improve our investigation we could try to model this.
The second and the third assumption are related, because if the virus could only be transmitted via sexual intercourse, than it is logical to assume that each person who has become sexually active, is not infected yet. Of course, transmission also occurs through, for instance, sharing needles or breast feeding. Therefore, we could drop these two assumptions. As a result, it might be more useful to adapt our models, because the interpretation of our models changes as soon as other possibilities of transmitting HIV are considered.
By definition it is reasonable to assume that the sexual interaction between hetero-, and homosexuals can be ignored. People who are attracted to persons of their own sex, will probably not have much sexual intercourse with persons from the other sex.
Furthermore, we assumed that the transmission rates for each group would be the same. With this assumption we were able to determine what the ratio of the transmission, birth, and death rates was at the disease free equilibrium. This assumption makes sense, because the risk behavior of someone does not only depend on his or her sexual preference. We also did not know how to approximate these rates.
The assumption about a cure or a vaccine is realistic, because they do not exist yet. However, in the future there might be one. Therefore, it is not a waste of time to develop realistic models in which a cure or a vaccine is considered.

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