

**Mathematical models linking
within-host and between-host HIV dynamics
Report submitted to REU program**

Aidan Backus

University of California, Berkeley

Angelica Bloomquist

San Diego State University

J Montgomery Maxwell

DePaul University

Elyssa Sliheet

Southwestern University

Yuanming Tang

MiraCosta College

University of California, Berkeley

Carlos Villanueva-Chavez

University of Oklahoma

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Chapter 1

Introduction

The HIV epidemic remains one of the most devastating problems worldwide with 36.7 million people living with HIV/AIDS and an estimate of 1.8 million annual new infections. Given the persistence of new infections and the lack of prevention strategy, it is of paramount importance to better understand HIV transmission dynamics, and especially quantify the risk of HIV infection, in order to better control and prevent HIV endemics. Substantial work has been done to understand HIV dynamics, although previous mathematical models have exclusively focused on either within-host or between-host dynamics separately. Here we attempt to link both dynamics by considering how within-host patterns play a role in the between-host transmission of HIV within communities.

Risk of HIV infection is defined as the probability that a susceptible, HIV-negative individual (recipient) is infected by HIV by means of contact of bodily fluids from an HIV-positive individual (donor). It has been established that the risk of infection is dependent on the mode of contact and status of the host, i.e. the stage of infection of the donor. Wawer et al. [9] has studied 235 HIV-discordant couples in Uganda and found that the rate of HIV transmission per coital act was highest (1 in 120) during acute-stage infection, but much lower (1 in 670) during chronic-stage. This is supported by Tuckwell et al. [11], who has modeled the connection between risk of infection, mode of contact, and number of virus transferred to find that acute-stage donors have the highest probability of transmission and transfer by needlestick is generally riskier than sexual transmission, *ceteris paribus*.

Along with risk of infection, another measure of the danger of an infection is its associated risk of death, and it is well known that HIV infection shortens an individual's lifespan by destroying CD4⁺T cells and thus weakening the immune system. For this reason, CD4⁺T cell levels are used as the standard to evaluate HIV patient's conditions.

Both risk of infection and risk of death are also influenced by the antibody profile of the patient. Although the effects of antibodies in HIV patients are not completely understood, Ciupe et al. has found out antibodies in SIV-positive rhesus macaques reduce SIV infectivity [16], and Tomaras et al. [10] have speculated that HIV antibodies may reduce infectivity of HIV in a similar fashion. Furthermore, Vaidya et al. [17] has found significant correlation between rate of viral infectivity decay and rate of increase of plasma antibodies during HIV infection. Hence, antibodies play an important role in determining the risk of infection.

In this study, we develop mathematical models linking within-host and between-host dynamics. Our within-host models incorporate both viral load and antibody count to quantify the risk of HIV infection and life expectancy of an infected individual at each time since infection. Both within-host models demonstrate that risk of infection and life expectancy change with antibody level thus establishing a connection among within-host and between-host dynamics. We incorporate the results from within-host dynamics to our two between host models to study how HIV is transmitted throughout a community.

1.1 Force of infection

Following [15], we assume that the spread of HIV in a population is *frequency-dependent*: that is, the force of infection is dependent on the prevalence of the infection in the population, rather than simply the number of infected individuals. This assumption can be interpreted as the claim that the amount of sexual or otherwise

risky behavior is limited and saturated in a large population, as an individual can only have sexual contact with a limited number of individuals per unit time.

The *force of infection*, written λ , is defined to be the per capita rate at which susceptible individuals are infected with HIV. We will use λ in our between-host models.

We assume further that the probability of spreading the virus through sexual contact is purely a function of time since the donor has been infected, which we call their *age of infection*, a .

Under these assumptions, we have

$$\lambda = \frac{\kappa}{S(t) + \int_0^\infty I(t, a) da} \int_0^\infty \beta(a) I(t, a) da,$$

where κ is the average number of sexual contacts per unit time, $S(t)$ is the number of susceptible individuals in the population at time t , $I(t, a)$ is the number of infected individuals in the population at time t with age of infection a , and $\beta(a)$ is the probability of transmission. Under these assumptions, $\int_0^\infty I(t, a) da$ is the total number of infected individuals and so $S(t) + \int_0^\infty I(t, a) da$ is the total population at time t .

Alternatively, we can consider J infected compartments, so that $I(t, \cdot)$ is constant on

$$[0, a_1), [a_1, a_2), \dots, [a_{J-1}, a_J].$$

then

$$\lambda = \frac{\kappa}{S + \sum_{j=1}^J I_j} \sum_{j=1}^J \beta_j I_j.$$

The definition of λ indicates that before we can develop our between-host model, we need β , which in turn will be determined by the viral load and antibody profile of the donor. We also require the death rate of the infected individuals, which is a function of their $CD4^+$ T cell count, also determined by the within-host dynamics.

Chapter 2

Within-host modeling

2.1 Model description

2.1.1 Classical viral dynamics model

We consider the following standard viral dynamics model for HIV, as derived in [14]:

$$\begin{cases} \dot{T} = \theta - dT - kTV, & T(0) = T_0 \\ \dot{I} = kTV - \delta I, & I(0) = I_0 \\ \dot{V} = pI - cV, & V(0) = V_0 \end{cases} \quad (2.1)$$

T, I , and V represent the number of target cells, infected cells, and virions, respectively. CD4⁺T cells are produced at a rate θ and die at rate d . Uninfected cells become infected with an infection rate proportional to target cell and viral particles at rate k and die at rate δ . Viruses are produced by infected cells at rate p per infected cell and are cleared at rate c . Table 2.1 summarizes the parameters of the model. A schematic diagram of the model is shown in Figure 2.1.

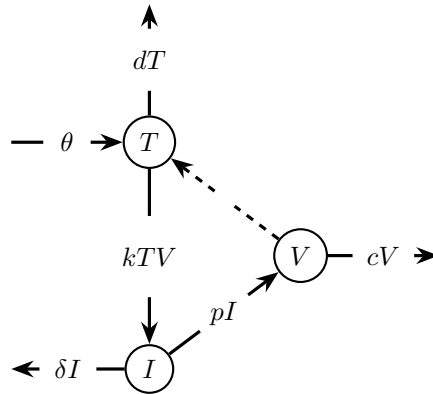


Figure 2.1: Diagram for viral dynamics

2.1.2 Modeling Antibodies: Approach I

Approach I in this study expands upon the viral dynamics model described in (2.1) used to describe the early stages of HIV infection. As in [18] we extend the previous HIV dynamics by incorporating two possible effects of virus-specific antibodies: virus neutralization i.e. the reduction of virus infectivity with efficacy ϵ_A , and enhanced viral clearance as a result of an antibody binding to a cell-free virus with per capita rate

of $\sigma A(t)$. Throughout the paper, $A(t)$ represents the time course of virus-specific antibodies. The efficacy of virus neutralization due to antibodies is modeled with the formula $\epsilon_A = \frac{\eta A(t)}{1 + \eta A(t)} \in [0, 1]$. That is, $\epsilon_A = 0$ in the absence of antibodies ($A(t) = 0$) and $\epsilon_A = 1$ in the event of extremely high antibody levels ($A(t) \rightarrow \infty$). Constants η and σ are introduced in order to scale the net effect of viral neutralization, and viral clearance by antibodies on viral-dynamics. Note that $\eta = \sigma = 0$ corresponds to the absence of antibodies. From the data, the trend of virus-specific antibodies is that the level remains low for some time following infection, then steadily increases and saturates at a maximum level. We model the antibody behavior as $A(t) = \frac{Mt^n}{B^n + t^n}$, where M represents the maximum antibody level, B represents the time post infection when half the antibody level is achieved, and n is a Hill coefficient. Numerical values for σ, η, M, B , and n are estimated using data-fitting and are summarized in Table 2.1, and the model is drawn schematically in Figure 2.2. Approach I is described by the following equations:

$$\begin{cases} \dot{T} = \theta - dT - (1 - \epsilon_A)kTV, & T(0) = T_0 \\ \dot{I} = (1 - \epsilon_A)kTV - \delta I, & I(0) = I_0 \\ \dot{V} = pI - cV - \sigma A(t)V, & V(0) = V_0 \end{cases} \quad (2.2)$$

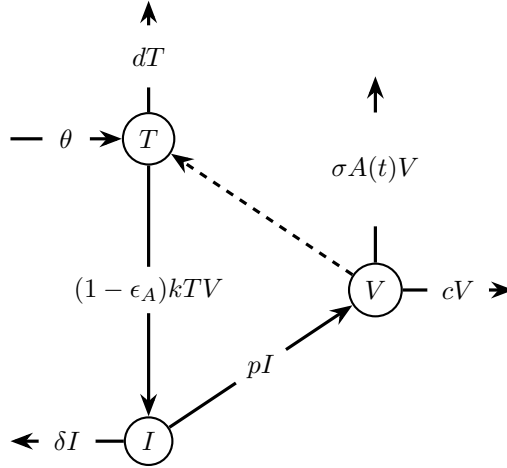


Figure 2.2: Diagram for Approach I

Parameter	Meaning	Value	Source
T_0	Initial CD4 ⁺ T cell count	1000 ml ⁻¹	[17]
I_0	Initial infected cells	0 ml ⁻¹	data-fitted
V_0	Initial virus load	1/300 vRNA ml ⁻¹	[12]
d	CD4 ⁺ T cell death rate	0.01 day ⁻¹	[15]
θ	CD4 ⁺ T cell production	dT_0 ml ⁻¹ day ⁻¹	[17]
k	CD4 ⁺ T cell infection rate	$0.65 \cdot 10^{-6}$ ml RNA ⁻¹ day ⁻¹	[4]
δ	Death rate of infected cells	0.39 day ⁻¹	[4]
p	Production rate of virus	5000 day ⁻¹	[12]
c	Death rate of virus	23 day ⁻¹	[17]
M	Maximum antibody load	2.5 O.D	data-fitted
B	Time at which $A(t) = M/2$	21.69 day	data-fitted
n	Hill's coefficient	20.96 O.D. day ⁻¹	data-fitted
η	Scaling factor in ϵ_A	0.4	data-fitted
σ_I	Clearance rate of virus by antibodies (Approach I)	0.35 ml ng ⁻¹ day ⁻¹	data-fitted
α	Proportion of virus being infectious	0.9	data-fitted
ℓ	Production rate of antibodies	.039 day ⁻¹	data-fitted
w	Death rate of antibodies	0.065 day ⁻¹	data-fitted
σ_{II}	Infectivity reduction of virus by antibodies (Approach II)	$6.63 \cdot 10^{-6} \text{ml ng}^{-1} \text{day}^{-1}$	data-fitted
ζ	Clearance rate of virus by antibodies (Approach II)	1/4000 ml ng ⁻¹ day ⁻¹	data-fitted

Table 2.1: Within-host parameters

2.1.3 Approach II

The main ideas behind this approach are to incorporate antibodies, A , into the within-host model as a separate compartment and to divide the total viral load V into two: infectious virus V_I and noninfectious virus V_N .

Since some virus produced by the infected cells I can be non-infectious, we assume a fraction $\alpha \in [0, 1]$ of newly produced virus becomes infectious and the remaining $(1 - \alpha)$ are non-infectious. Following this assumption, we have infected cells producing infectious virus V_I at a rate $\alpha p I$ and non-infectious virus V_N being created at a rate of $(1 - \alpha)p I$. Infectious virus and non infectious are both cleared by the body at a rate of c .

Since both infectious and non-infectious virus trigger production of antibodies, antibodies are produced at rate ℓ per virus and get cleared at a rate of w . We assume that antibodies neutralize infectious virus, i.e. convert V_I into V_N , at rate $\sigma V_I A$. Antibodies also clear out virions at a rate $\zeta A(V_I + V_N)$.

A schematic diagram of Approach II is given in Figure 2.3. A summary of the parameters are given in Table 2.1.

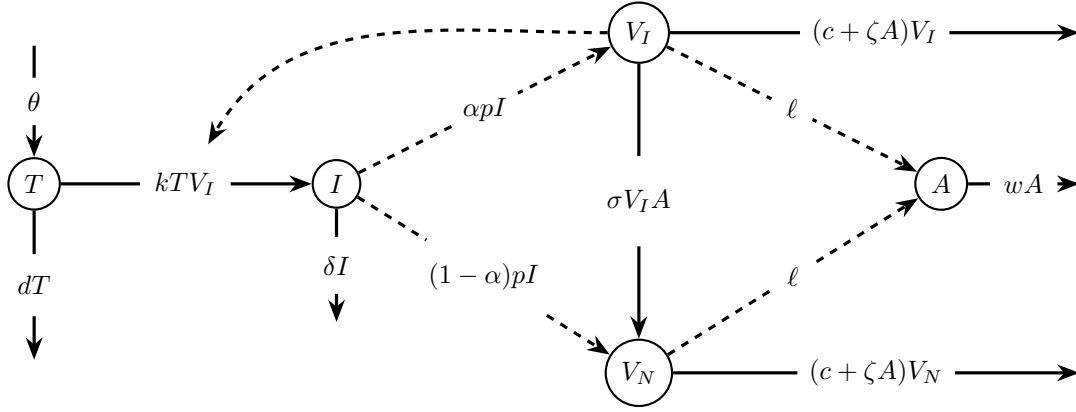


Figure 2.3: Diagram for Approach II

The model we have is as follows:

$$\begin{cases} \dot{T} = \theta - dT - kTV_I, T(0) = T_0 \\ \dot{I} = kTV_I - \delta I, I(0) = I_0 \\ \dot{V}_I = \alpha pI - cV_I - \sigma V_I A - \zeta V_I A, V_I(0) = V_{I0} \\ \dot{V}_N = (1 - \alpha)pI + \sigma V_I A - cV_N - \zeta V_N A, V_N(0) = V_{N0} \\ \dot{A} = \ell(V_I + V_N) - wA, A(0) = A_0 \end{cases} \quad (2.3)$$

2.2 Model analysis and probability of infection

2.2.1 Risk of infection

For a susceptible individual (recipient) to be infected by HIV through a single contact with an HIV-infected individual (donor), the following conditions have to be satisfied: first, the virus has to reach the target cells (transmission); second, at least one target cell has to be infected by the virus (infection); and third, the infected target cells have to establish a persistent infection (persistence).

First, depending on the mode of transmission, we assume some small fraction, $m = m_1 m_2$, of the HIV and antibodies in the bloodstream of the donor actually survive the transmission process, where m_1 is the scaling factor between donor blood and released bodily fluid (e.g. semen), and m_2 is the proportion of released virus that reaches the target cell in the recipient. Hence, $mV_{\text{donor}}(a)$ HIV particles and $mA_{\text{donor}}(a)$ free antibodies are transmitted and reach target cells of recipients.

After $mV_{\text{donor}}(a)$ virus have reached the target cells of the recipient, the probability of infection, P_{inf} , can be expressed as $P_{\text{inf}} = P_{\text{cell}} P_{\text{persist}}$, where P_{cell} denotes the probability that at least one target cell gets infected by the transmitted viruses, and P_{persist} denotes the probability that an infected cell infection will establish a persistent infection.

The process, and the probability, of a successful infection through a single contact is depicted schematically in Figure 2.4.

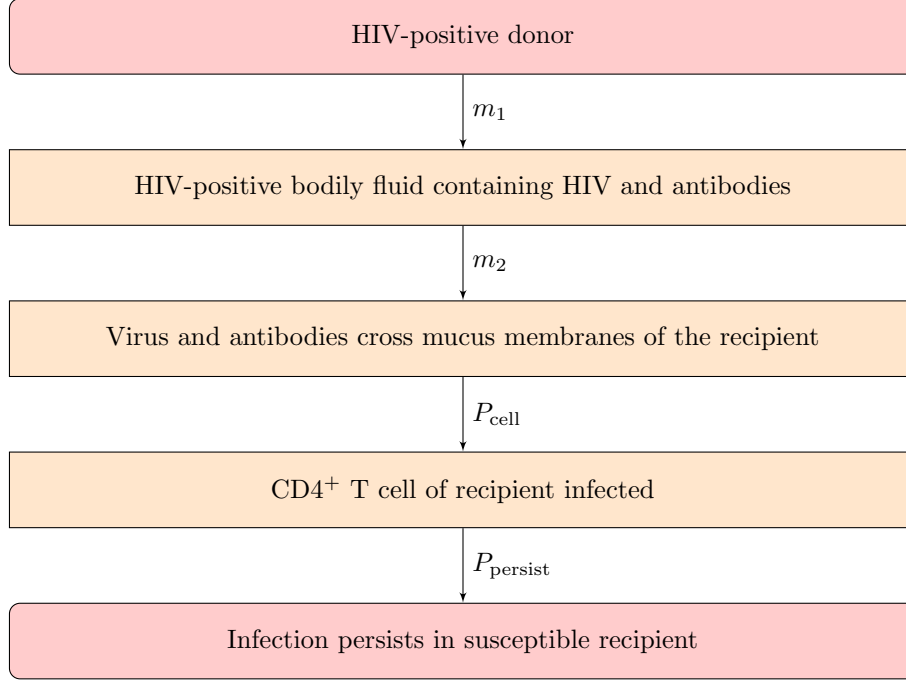


Figure 2.4: Diagram of transmission stages

We first compute P_{cell} .

Suppose that virus particles infect target cells at a rate ρ per virus, and let

$$\gamma(t) = \rho \int_0^t V(s) ds \quad (2.4)$$

be the expected number of infections in target cells in the new host before time t . We will assume that new infections are an inhomogeneous Poisson process; then the probability of n target cells being infected is $\gamma^n e^{-\gamma} (n!)^{-1}$. In particular, the probability that no cells are infected at all before time t is $e^{-\gamma(t)}$. It follows that the probability that at least one cell is infected before time t is $1 - e^{-\gamma(t)}$. The probability that at least one cell is ultimately infected is

$$P_{\text{cell}} = \lim_{t \rightarrow \infty} 1 - e^{-\gamma(t)}. \quad (2.5)$$

We will now derive ρ and V under the assumptions of each model.

Per our model as well as empirical evidence, the host will not produce a significant number of antibodies for the first few weeks, so we make the approximating assumption that all free antibodies are those transmitted by the donor, and not produced by the host. Therefore, $\dot{A} + wA = 0$, and in particular $A(t) = A_{\text{donor}}(a)e^{-wt}$. We also assume $I = 0$ because no cells have been infected yet.

For Approach I, cells are infected at a rate of $\rho = (1 - \epsilon(A(a)))kT_0$ per virus, $V(0) = mV_{\text{donor}}(a)$, and the logarithmic derivative

$$-\frac{\dot{V}}{V} = c + \sigma A.$$

Integrating both sides we have

$$\ln \left(\frac{mV_{\text{donor}}(a)}{V(t)} \right) = ct + \sigma \int_0^t A(s) ds = ct + m\sigma A_{\text{donor}}(a) \int_0^t e^{-ws} ds = ct + \frac{m\sigma A_{\text{donor}}(a)}{w} (1 - e^{-ws}).$$

Hence

$$V(t) = mV_{\text{donor}}(a) \exp \left[-cs - \frac{m\sigma A_{\text{donor}}(a)}{w} (1 - e^{-ws}) \right] ds.$$

Then from (2.4) and (2.5),

$$P_{\text{cell}}^I(a) = 1 - \exp \left\{ -(1 - \epsilon_{mA_{\text{donor}}(a)})kT_0mV_{\text{donor}}(a) \int_0^\infty \exp \left[-cs - \frac{m\sigma A_{\text{donor}}(a)}{w}(1 - e^{-ws}) \right] ds \right\}.$$

For Approach II, while $mV_{\text{donor}}(a)$ viruses are transmitted, only a proportion of them, $\nu = \frac{V_I}{V_I + V_N}$, are actually infectious. Cells are infected at a rate of $\rho = kT_0$ per infectious virus, $V_I(0) = mV_{\text{donor}}(a)\nu(a)$, and the logarithmic derivative

$$-\frac{\dot{V}_I}{V_I} = c + \sigma A$$

Similarly to Approach I,

$$\ln \left(\frac{m\nu(a)V_{\text{donor}}(a)}{V_I(t)} \right) = ct + \frac{m\sigma A_{\text{donor}}(a)}{w}(1 - e^{-wt}).$$

It follows that

$$V_I(t) = m\nu(a)V_{\text{donor}}(a) \exp \left[-ct - \frac{m\sigma A_{\text{donor}}(a)}{w}(1 - e^{-wt}) \right]$$

and so

$$P_{\text{cell}}^{II}(a) = 1 - \exp \left\{ -kT_0mV_{\text{donor}}(a)\nu(a) \int_0^\infty \exp \left[-cs - \frac{m\sigma A_{\text{donor}}(a)}{w}(1 - e^{-ws}) \right] ds \right\}.$$

2.2.2 Viral persistence

We will compute the basic reproduction number \mathcal{R}_0 , the expected number of new infected cells if a single infected cell is introduced to a population of entirely uninfected cells. \mathcal{R}_0 is computed using the next-generation matrix method [1]. We shall prove stability of the infection-free equilibria when $\mathcal{R}_0 < 1$ and persistence of the virus when $\mathcal{R}_0 > 1$.

First we compute the basic reproduction number \mathcal{R}_0 of the model. We find F , the new-infection matrix linearized about the infection free equilibrium, IFE = $(\theta/d, 0, 0)$, as

$$F = \begin{bmatrix} 0 & \frac{k\theta}{d} \\ p & 0 \end{bmatrix}$$

and the transfer matrix V , the linearization of all of the other terms in the Jacobian of the system (so that $F - V$ is the Jacobian),

$$V = \begin{bmatrix} \delta & 0 \\ 0 & c \end{bmatrix}.$$

Computing the spectral radius of FV^{-1} , we find $\mathcal{R}_0 = \frac{k\theta p}{cd\delta}$.

We follow a similar method for this model. The infection-free equilibrium is given by IFE = $(\theta/d, 0, 0, 0, 0)$,

$$F = \begin{bmatrix} 0 & \frac{k\theta}{d} & 0 \\ \alpha p & 0 & 0 \\ (1 - \alpha)p & 0 & 0 \end{bmatrix},$$

and

$$V = \begin{bmatrix} \delta & 0 & 0 \\ 0 & c & 0 \\ 0 & 0 & c \end{bmatrix}$$

Computing the spectral radius of FV^{-1} , we find $\mathcal{R}_0 = \frac{k\theta\alpha p}{cd\delta}$.

In a deterministic model, one expects the virus to persist and tend to its set-point, or infected equilibrium, if $\mathcal{R}_0 > 1$. We write $(T^*, I^*, V_I^*, V_N^*, A^*)$ for the components of the endemic equilibrium. We can think of as the values of the infection compartments during the chronic stage, once the infection has stabilized but AIDS has not yet onset.

By setting each of the time derivatives $\dot{T} = \dot{I} = \dot{V}_I = \dot{V}_N = \dot{A} = 0$ and assuming $V > 0$, a symbolic computation gives

$$\begin{aligned} T^* &= \frac{w\delta c^2 + \ell\theta p\sigma}{p(\ell d\sigma + \alpha wck)} \\ I^* &= \frac{wc^2 d}{\delta} \frac{\mathcal{R}_0 - 1}{\ell d\sigma + \alpha wck} \\ V_I^* &= wc^2 d\delta \frac{\mathcal{R}_0 - 1}{w\delta kc^2 + \ell k\theta p\sigma} \\ A^* &= \ell cd \frac{\mathcal{R}_0 - 1}{\ell d\sigma + \alpha wck} \\ V_N^* &= \frac{w}{\ell} A^* - V_I^*. \end{aligned}$$

However, in considering the probability of transmission we use a stochastic model, because during this time period there are very few infected cells and virions $((V_I, I) \approx 0)$ and so it is possible, due to its stochasticity that the virus may go extinct even if $\mathcal{R}_0 > 1$. The probability P_{persist} that the virus persists in a new host after it infects a single cell is given by $P_{\text{persist}} = 1 - e^{-\mathcal{R}_0}$ [6].

2.2.3 Viral extinction

For both models, the infection-free equilibrium is locally and globally stable iff $\mathcal{R}_0 < 1$, and so in this case the virus will go extinct. The argument for Approach II follows [13].

Theorem 2.1 (global stability of IFE, Approach I). *Suppose $\mathcal{R}_0 < 1$. Then IFE is globally asymptotically stable for Approach I.*

Proof. Suppose that $M > 0$ and $\beth > 0$ is arbitrary. Then there is a $t_0 > 0$ such that if $t > t_0$ then $|A(t) - M| < \beth$. So we can approximate (2.2) arbitrarily well by the classical model (2.1) with k replaced by $(1 - \epsilon_M)k$ and c replaced by $c + \sigma M$ by simply choosing t_0 large enough. This approximation has a basic reproduction number

$$\mathcal{R}_0^{\text{approx}} = \frac{(1 - \epsilon_M)kp\theta}{(c + \sigma M)d\delta} < \frac{kp\theta}{cd\delta} = \mathcal{R}_0 < 1.$$

The classical model is known to have a globally asymptotically stable IFE if its basic reproduction number is < 1 . Therefore, any approximate solution curve $(\tilde{T}, \tilde{I}, \tilde{V}) \rightarrow \text{IFE}$. However, assuming no bifurcations, the actual solution curves depend continuously on the parameters – and indeed the Jacobian matrix is negative definite in a neighborhood of $((1 - \epsilon_M)k, p, \theta, \sigma M, d, \delta)$, assuming $\mathcal{R}_0 < 1$, so there can be no bifurcations there. \square

Theorem 2.2 (global stability of IFE, Approach II). *Suppose $\mathcal{R}_0 < 1$. Then IFE is globally asymptotically stable for Approach II.*

Proof. Let $T_0 = \theta/d$ be the initial condition on the target cells and

$$\bar{U} = \{(T, I, V_I, V_N, A) \in \mathbb{R}_+^5 : T \leq T_0\}$$

be the biologically feasible region. Then

$$kT_0 = \frac{c\delta}{\alpha p} \mathcal{R}_0.$$

Consider the smooth function

$$L(T, I, V_I, V_N, A) = T - T_0 \left(1 + \ln \frac{T}{T_0}\right) + I + \frac{\delta}{\alpha p} V_I.$$

Then $L(\text{IFE}) = 0$ and

$$\nabla L = \left(1 - \frac{T_0}{T}, 1, \frac{\delta}{\alpha p}, 0, 0\right)$$

Hence the only critical points are the line $T = T_0$ (on which $L \leq 0$), and $\lim_{T \rightarrow 0} L = +\infty$ it follows that $L \leq 0$. Moreover,

$$\begin{aligned}\dot{L} &= \left(1 - \frac{T_0}{T}\right) (\theta - dT - kTV_I) + kTV_I - \delta I + \frac{\delta}{\alpha p} (\alpha p I - cV_I - \sigma AV_I) \\ &\leq kT_0 V_I + dT_0 - \theta \frac{T_0}{T} - kTV_I - dT + \theta + kTV_I - \delta I + \delta I - \frac{\delta c}{\alpha p} V_I \\ &\leq d(T_0 - T) + kT_0 V_I - \frac{\delta c}{\alpha p} V_I \leq d \left(\frac{T_0}{T} - 1 \right) (T - T_0) + \left(kT_0 - \frac{c\delta}{\alpha p} \right) V_I \\ &= d \left(\frac{T_0}{T} - 1 \right) (T - T_0) - V_I \frac{c\delta}{\alpha p} (\mathcal{R}_0 - 1) \leq 0\end{aligned}$$

with equality iff $T = T_0$ and $V_I = 0$. Thus, L is strictly Lyapunov on the interior

$$\{(T, I, V_I, V_N, A) \in \bar{U} : T < T_0 \text{ or } V_I > 0\},$$

where IFE is asymptotically stable by Lyapunov's theorem.

Now we shall consider a solution curve X satisfying the initial conditions $T(0) = T_0$ and $V_I(0) = 0$. If $I(0) = 0$ also then it is easy to see that $(V_N, A) \rightarrow (0, 0)$, whence $X \rightarrow \text{IFE}$. Otherwise, $I(0) > 0$, so $\dot{V}_I(0) = pI(0) > 0$. Thus there is a $\mathfrak{J} > 0$ such that $V_I(\mathfrak{J}) > 0$. Translating back in time by \mathfrak{J} we arrive at a solution curve \tilde{X} for which $V_I(0) > 0$, so \tilde{X} tends to IFE. Thus $X \rightarrow \text{IFE}$ also. This completes the proof. \square

2.3 Numerical results

2.3.1 Parameter estimation

Approach I M , B , and n in $A(t)$ were obtained by fitting the curve to antibody data (recorded in optical density) using MATLAB's "Curve Fitting" tool. In Figure 2.5 we show the results of curve fitting for the antibody count. Furthermore, it has been estimated [by a reference] that antibodies reduced the viral load of the steady state

$$V_s = \frac{p\theta}{\delta c} - \frac{d}{k}$$

by two orders of magnitude. Hence, we obtain the following expression for the steady state of the total viral load with antibodies:

$$\bar{V} = \frac{1}{100} V_s = \frac{p\theta}{\delta(c + \frac{\sigma a}{f})} - \frac{d}{(1 - \epsilon_s)k} \quad (2.6)$$

Solving for σ obtains:

$$\sigma = \frac{f}{a} \left(\left[\frac{\delta}{p\theta} \left(\frac{1}{100} V_s + \frac{d}{(1 - \epsilon_s)k} \right) \right]^{-1} - c \right) \quad (2.7)$$

Note that $\epsilon_s = \frac{\eta a}{1 + \eta a}$ because $A(t) = a$ at the steady state. In order to maintain $\bar{V} = \frac{1}{100} V_s$, from (2.7) we obtain that $\sigma \in [0, 1.1]$ and $\eta \in [0, 1]$. Otherwise, we get negative values for σ or η . Therefore, we take the average values of σ and η to get $\eta = 0.4$ and $\sigma = 0.35$.

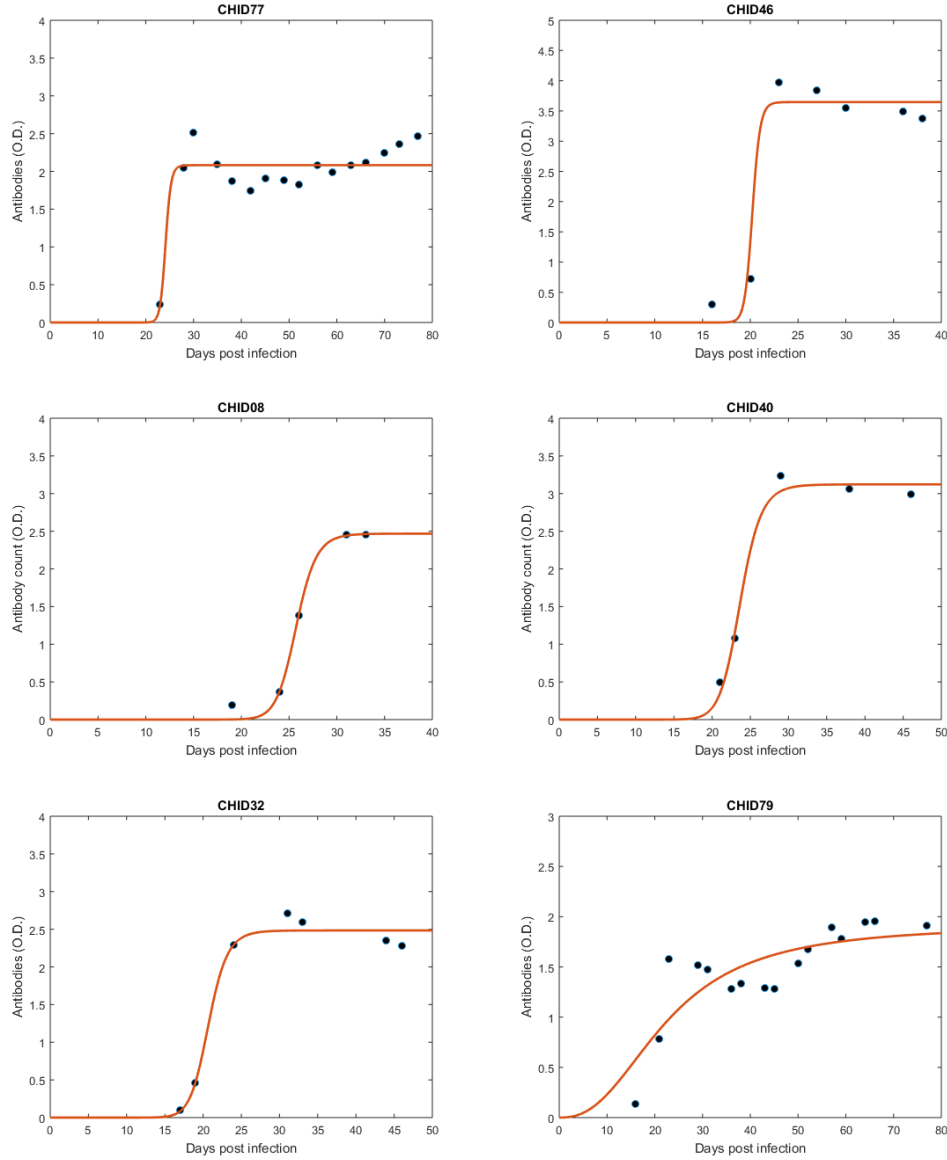


Figure 2.5: Antibody curve fitting

Approach II We take initial number of target cells, T_0 , to be 10^4 per ml or 1% of 10^6 per ml total $CD4^+$ cell count. We assume this is the start of infection, thus there are no infected cells yet, $I_0 = 0$. The initial virus concentration is often unknown, but here we took $V_{I0} = 1/300$ initial virus RNA copies per ml. Antibody production is triggered by the creation of virus, so we can take $A_0 = 0$, thus we have the initial condition for non infectious virus is $V_{N0} = 0$. To find ℓ and w , we fit the antibody and viral load data from the six patients' data with our fifth differential equation giving us $\ell = 0.03866$ and $w = 0.065382969$.

Using the set point of this system from above, we were able to find the proportion of infectious virus,

$$\frac{V_I^*}{V_I^* + V_N^*} = \frac{c\delta(ad\sigma + abck)}{b\delta kc^2 + ak\theta p\sigma}.$$

From [17], we can set this proportion equal to the ratio of infection rate at the set point, β_∞ to their initial infection rate, β_0 . Plugging each patient's individual ℓ and w values into the above proportion and setting that equal to their respective ratio, $\frac{\beta_\infty}{\beta_0}$, we solved for σ .

$$\dot{T} = \theta - dT - kTV_I \frac{V}{V_I + V_N}$$

$$k \frac{V_I^*}{V_I^* + V_N^*} = k \frac{\beta_\infty}{\beta_0}$$

Thus we have

$$\frac{c\delta(ad\sigma + \alpha bck)}{b\delta kc^2 + ak\theta p\sigma} = \frac{\beta_\infty}{\beta_0}.$$

Solving for σ , we obtained a value of $6.63 \cdot 10^{-4}$.

2.4 Results

Solutions to the two systems of differential equations, from Approach I and Approach II, are functions with respect to the age of infection for the viral load, CD4⁺T cell count, and infected cells. Additionally, Approach II offers solutions for the antibodies and neutralized infected cells as functions of the age of infection. From these solutions we calculate P_{cell} and the rate of viral host death for Approach I and Approach II.

Approach II has $\mathcal{R}_0^{II} \approx 3.261$ and Approach I has $\mathcal{R}_0^I = \alpha^{-1}\mathcal{R}_0^{II} = 3.623$. Since $P_{\text{persist}} = 1 - e^{-\mathcal{R}_0}$, then both Approach I and Approach II $P_{\text{persist}} \approx 0.96$.

2.4.1 Probability of transmission, Approach I

Figure 2.6 of the probability of transmission over the age of the donors infection incorporates the presence of antibodies by using the Hill function $A(t)$.

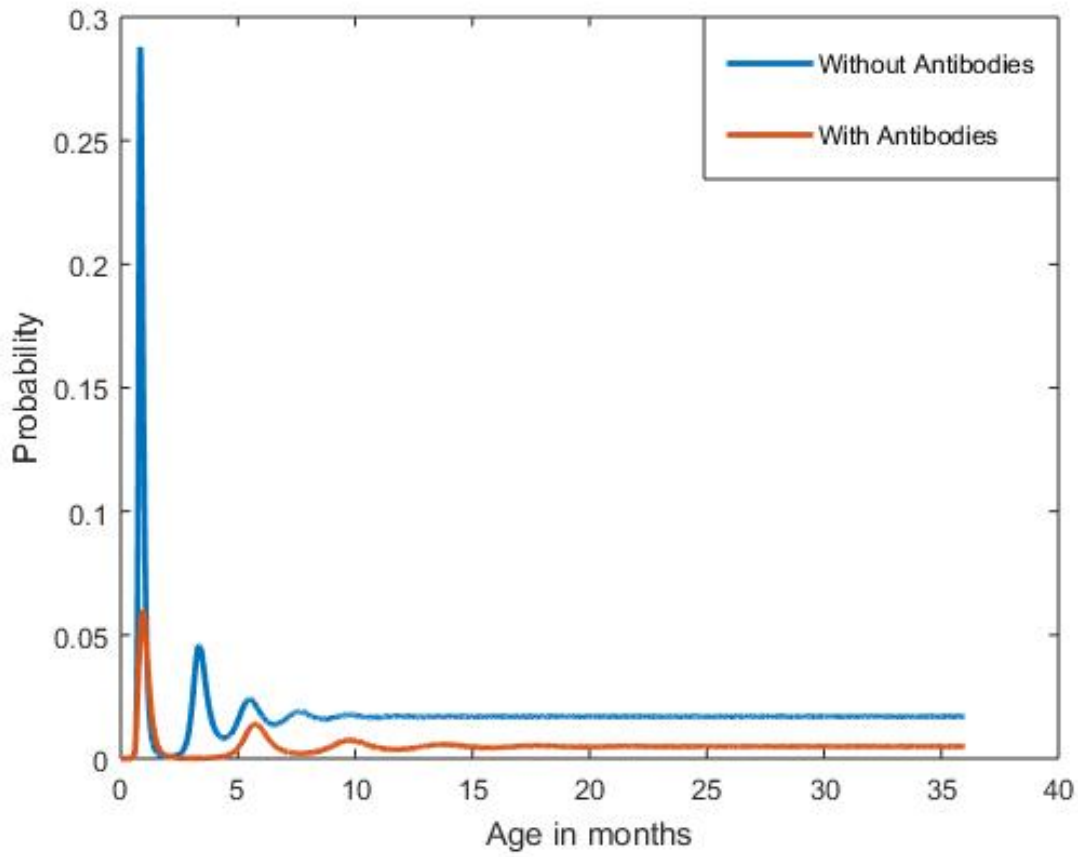


Figure 2.6: Probability of transmission, Approach I

The probability of transmission rises to ≈ 0.06 before leveling off at ≈ 0.0045 .

Note from the graph that the inclusion of antibodies in the model significantly decreases the probability of transmission by nearly half the value in the chronic stage of the infection (months 10-36). Furthermore, the initial spike in transmission probability at approximately one month into the donor's infection occurs because the antibodies in the donor's blood have not yet begun to fully propagate. In this model, the probability of transmission remains steady for months until the donor's infection develops into AIDS.

2.4.2 Probability of transmission, Approach II

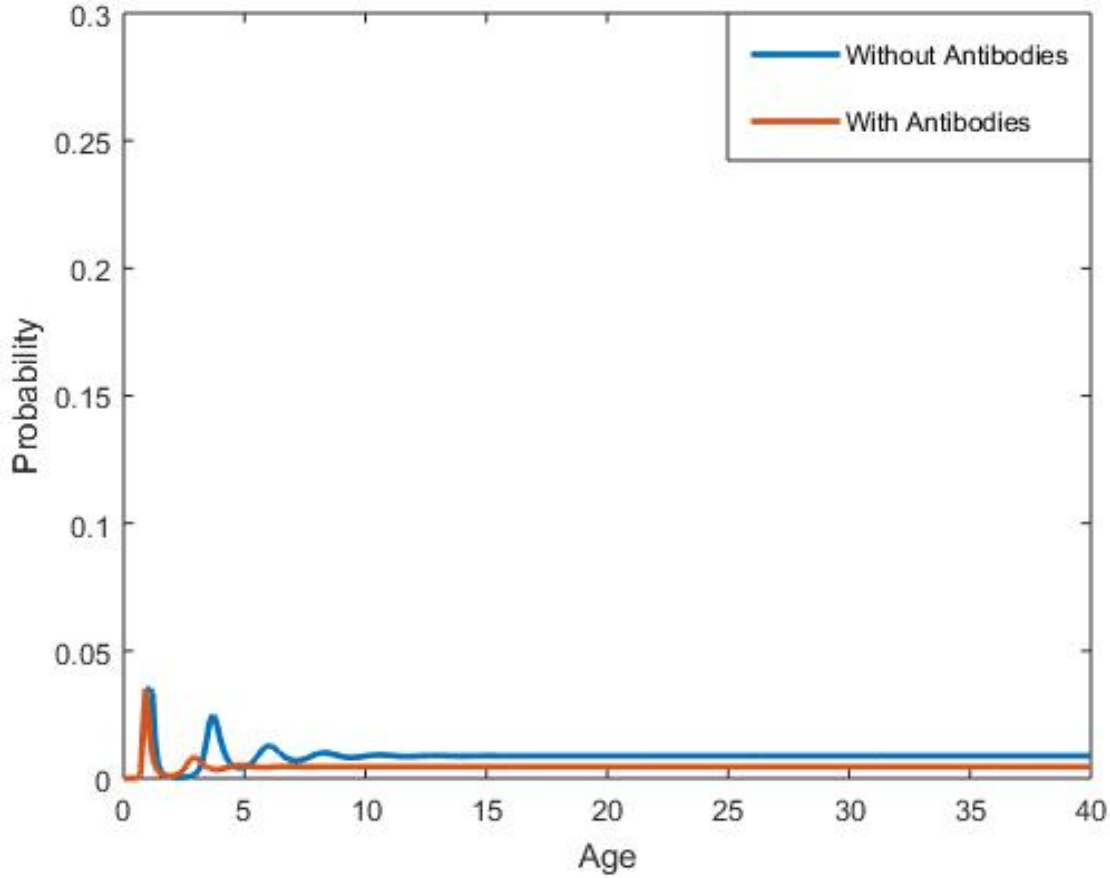


Figure 2.7: Probability of transmission, Approach II

Figure 2.7 similarly depicts probability of transmission in Approach II. The inclusion of antibodies decreases the probability of transmission.

As with the first approach, there is an initial rise in the probability of transmission to ≈ 0.04 before leveling off at ≈ 0.0045 . Additionally, like with the first approach, the brief spike in the probability of transmission may be explained by a slow growth in the level of active antibodies present in the donor.

2.4.3 Sensitivity of probability of transmission to m

The proportion of the donor's viral load that is transmitted to the recipient of the virus is extremely important towards establishing the probability that the recipient of the virus will become infected. Therefore, the sensitivity of the probability of infection to different values of m was examined in order to perceive how different methods of viral load transmission will affect the probability of transmission. A higher value of m may be associated with a more direct method of viral load transmission, such as transmission through needle-stick injection drug use or blood transfusion. A lower value of m is for viral load transmissions through unprotected sex.

Figure 2.8 shows the probability of transmission as a function of the age of the donor's infection and m . Figure 2.9 shows the probability of transmission for viral ages of fifteen days, one year, and five years. From these images it is seen that the probability of transmission is very sensitive at later ages of infection, as it was expected to be. However, in the early ages of infection, the probability of transmission is not sensitive

to changes in m . The most likely explanation for this behavior in the early ages of infection is that the viral load within the donor is too low, for the probability of transmission to be affected by different types of viral load transmission.

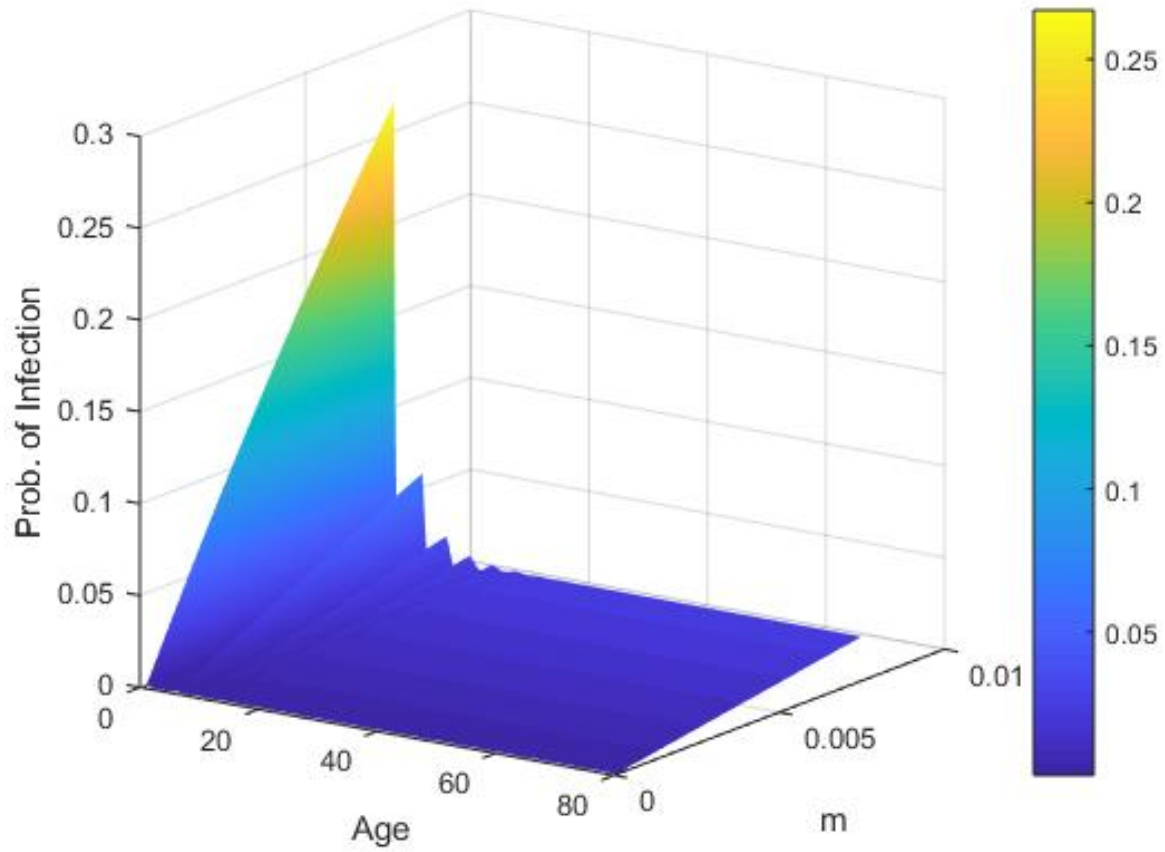


Figure 2.8: Sensitivity of P_{inf} to m

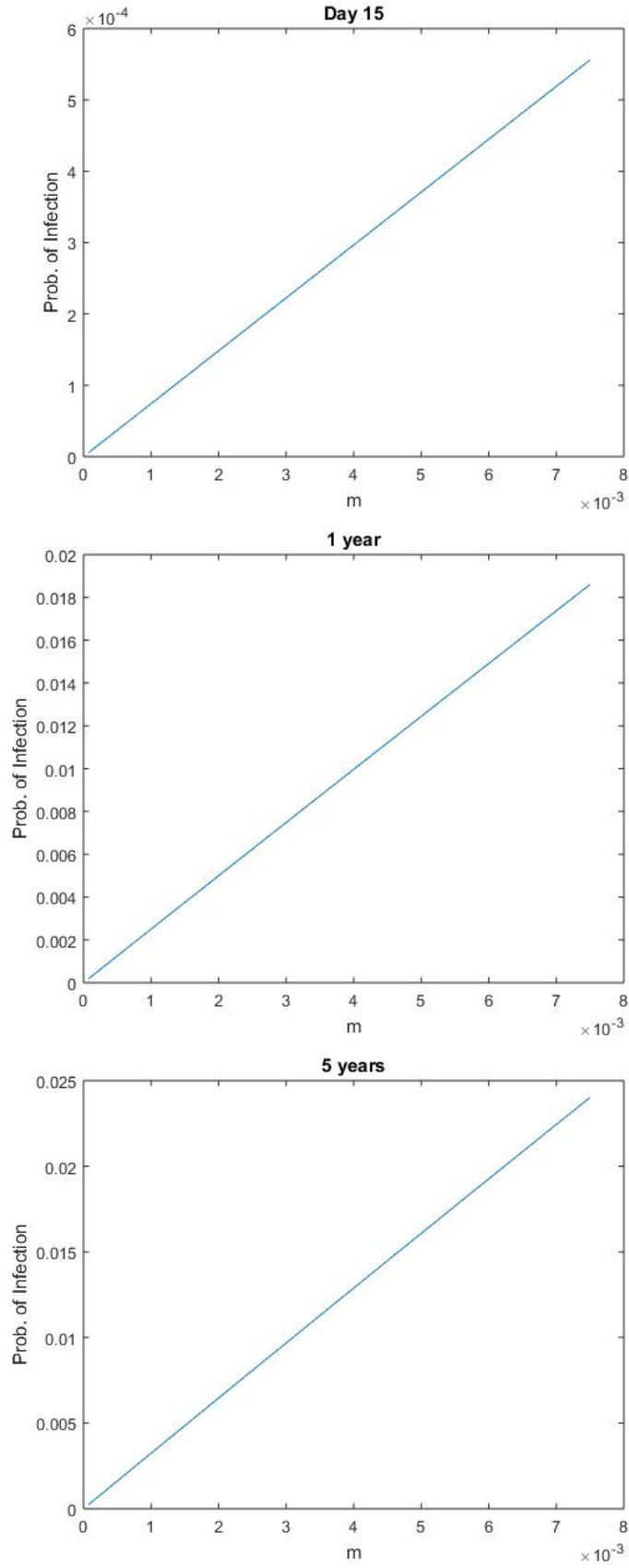


Figure 2.9: Sensitivity of P_{inf} to m at fixed times

2.4.4 Rate of death, Approach I

The following are graphs for the death rate and CD4+T cell count of infected patients as a function of the age of infection. The behavior of the death rate over the age of infection is inversely correlated to the behavior of the CD4+T cell count. This is because the viral hosts do not die directly from HIV, viral hosts die from other diseases, which they are too weak to fight against due to a low CD4+T cell count. Therefore, as the CD4+T cell count of a viral host diminishes, the viral host's life expectancy also decreases and so the viral host's rate of death increases.

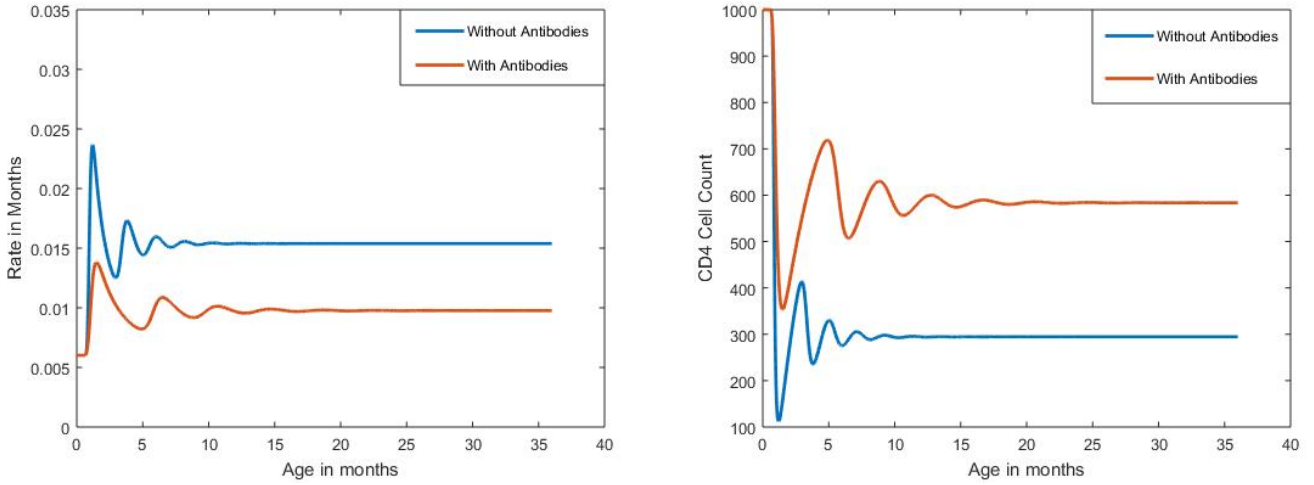


Figure 2.10: Approach I death rate

While infection first begins to grow within the host of the virus, the rate of death initial rises as the CD4+T cell count of the viral host decreases. Once the number of antibodies begin to increase and the viral load begins to decrease in the viral host, then the rate of death decreases as well. The rate of death reaches a steady state of ≈ 0.01 or a life expectancy of ≈ 8.3 years.

2.4.5 Rate of death, Approach II

In Approach II, as with Approach I, the rate of death has an inverse relation to the CD4+T cell count.

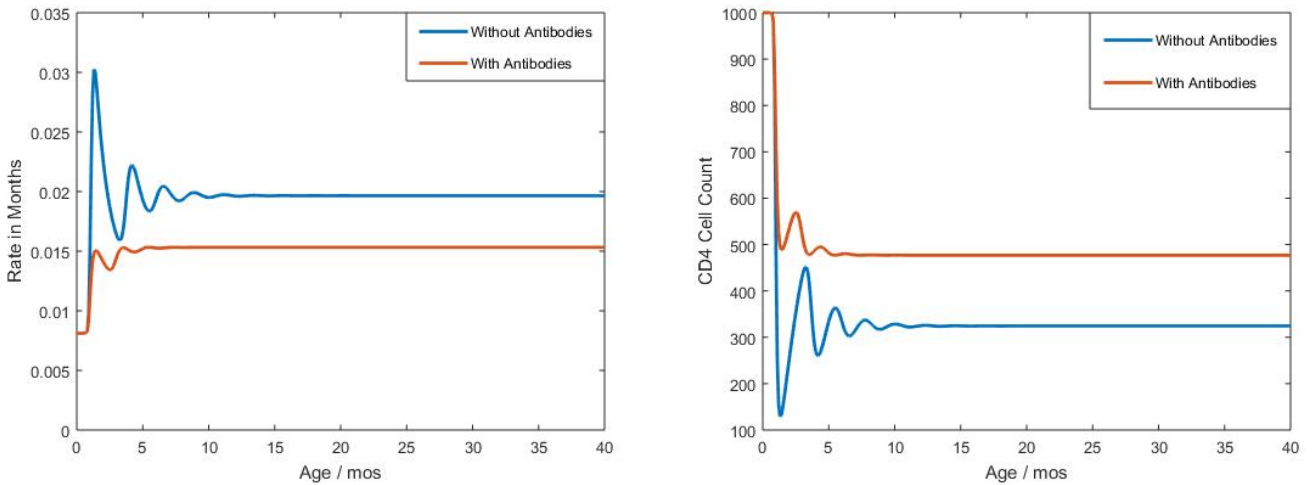


Figure 2.11: Approach II death rate

An initial spike occurs in the rate of death as the CD4+T cell count decreases. The rate of death then decreases to its steady state value of ≈ 0.015 or a life expectancy of ≈ 5.6 years.

Chapter 3

AIDS

3.1 Extension of within-host models

AIDS is the final and most severe stage of HIV infection when high viral load and low CD4+ T cell count cause immunodeficiency and increased risk of developing common infections in the victim. An untreated HIV-positive individual will generally enter into the AIDS stage after eight to ten years post-infection.

The within-host models described in Chapter 2 are insufficient at simulating risk of infection of the AIDS stage because they do not account for the spike of viral load, fall of CD4+ T cell count, and drop of antibody level of AIDS stage. In the aforementioned models, the susceptible T cell count, infected cell count and viral load reach a stable equilibrium after a few months and stay there. This steady state has been estimated to fit actual steady states of HIV-positive patients.

It is important to take AIDS stage into consideration so that between-host dynamics will be more accurate. More specifically, the viral load and CD4+ T cell count of AIDS stage are taken into consideration, since risk of infection is dependent on viral load and lifespan of AIDS patients is dependent on CD4+ T cell count.

To this end, we extend our existing models by mimicking the behavior of CD4+ T cells and viral load of the AIDS stage.

3.2 AIDS simulation methods

We do not have data of *how* CD4+T cell count, viral load, and antibody levels change from chronic stage to AIDS stage. It is known that CD4+T cell count and antibody levels drops and viral load increases in AIDS stage. We assume that an untreated individual enters AIDS stage at 3000 days post infection and that AIDS stage individual's CD4+ T cell count and antibody level follows an exponential decay function, bounded below at 0. We also assume that there is an increase of the viral load in AIDS stage and that it is bounded above at 10^6 . We used a Hill's function to control the upper bound of the viral load, as well as the rate at which the viral load increases and the time at which the viral load is half way to its upper bound.

$$Virus_1(a) = \begin{cases} V(a) & a \leq 3000 \\ V(3000) + \frac{10^6(a-3000)^7}{700^7+(a-3000)^7} & a > 3000 \end{cases} \quad \text{AIDS stage}$$

To mimic actual CD4+ cell count of AIDS stage, we introduce an exponential decay for CD4+ T cell count beginning at $a = 3000$ as follows:

$$CD4_1(a) = \begin{cases} \frac{1}{10}[T(a) + I(a)] & a < 3000 \\ \frac{1}{10}[T(a) + I(a)] \exp \{-0.01(a - 3000)\} & a \geq 3000 \end{cases} \quad \text{AIDS stage}$$

Antibodies also decay quickly because in the absence of CD4+ T cells, the suppressed immune system of the infected person can no longer produce HIV-specific antibodies. Hence

$$Ab_1(a) = \begin{cases} \frac{Ma^n}{B^n+a^n} & a < 3000 \\ M \exp(-0.003(a - 3000)) & a \geq 3000 \end{cases} \quad \text{AIDS stage}$$

3.3 Risk of infection including AIDS stage

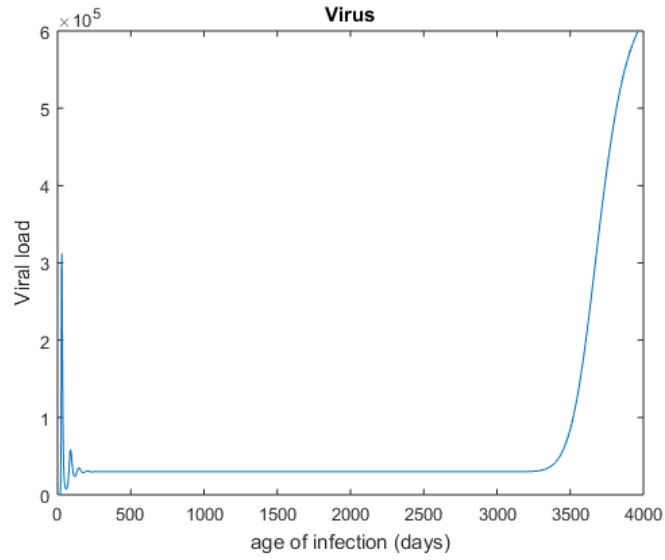


Figure 3.1: Viral load with AIDS modifier

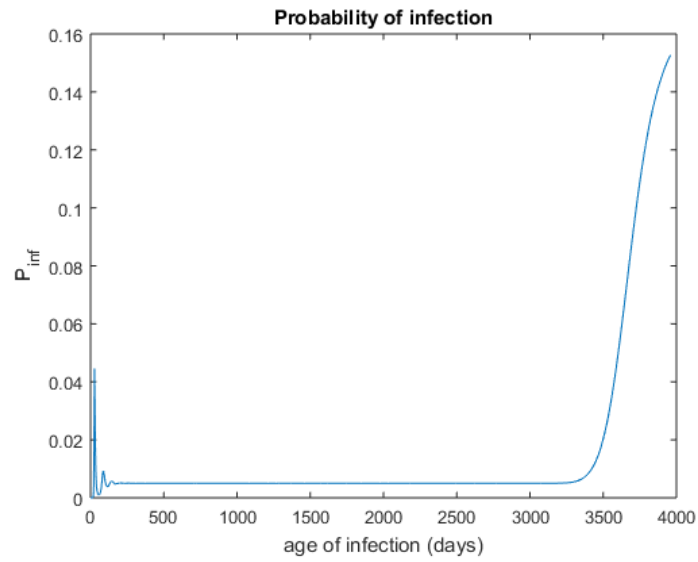


Figure 3.2: P_{inf} with AIDS modifier

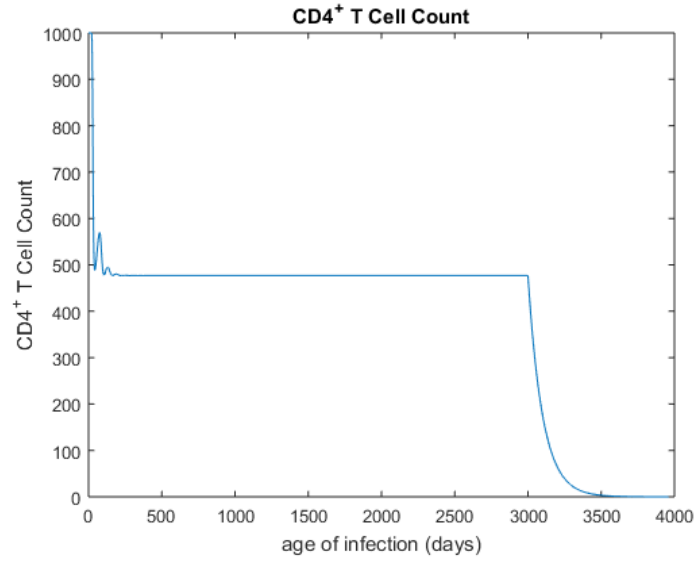


Figure 3.3: CD4⁺ T cell count with AIDS modifier

When an HIV infected person enters the AIDS stage their viral load increases. Consequently, the HIV infected person's probability of transmission increases and their CD4⁺ T cell count decreases. The CD4⁺ T cell decreases in the AIDS stage until it reaches a negligible level. Someone who is infected with HIV is considered to have developed AIDS when their CD4⁺ T count goes below 200 per milliliter. When the CD4⁺ T cell count of an infected person decreases, their life expectancy decreases as well and so their rate of death increases.

Chapter 4

Between-host modeling

4.1 Model description

Clinically, when an individual is infected with HIV, their condition is primarily associated with CD4⁺T cell count. We showed in the previous chapters that the death rate of an HIV-positive individual largely depends on their CD4⁺T cell count as HIV weakens an individual's immune system and decreases their life expectancy by destroying their CD4⁺T cells and facilitating their exposure to new diseases. As a result, CD4⁺T cell count has become the primary indicator of the strength of an HIV-infected individual's immune system. Based on immune levels, the HIV infected population has been divided into four stages of infection: eclipse, acute, chronic, and AIDS. Furthermore, we also showed that the probability of HIV infection P_{inf} largely depends upon an infected individual's viral load which in turn affects CD4⁺T cell count. Hence, there is a close relationship between CD4⁺T cell count and probability of infection P_{inf} .

We again use a "two-model" approach, one a transport equation PDE in the number of infected individuals I and another an ODE.

4.1.1 ODE model

Our model is largely based on that given by Rahman et al. [15] with the major difference being we don't consider treatment. In our model, we consider a homogeneous sexually active population between the ages of 15-49 years, and divide them into five groups: a susceptible group S and four infected groups I_1, I_2, I_3 , and I_4 (corresponding to the eclipse, acute, chronic, and AIDS stages respectively) categorized based on probability of infection P_{inf} . The transmission dynamic of our model is as follows: people become sexually active and are recruited into the susceptible population S at rate Λ . A susceptible individual moves to the compartment I_1 at rate λ if he/she is infected by an individual from any of the four infected compartments. If a susceptible individual is never infected then he/she dies or leaves the sexually active population at rate μ_0 . The individuals in I_1 either die at a rate μ_1 or move to I_2 at rate δ_1 due to changes in their CD4⁺T cell count and P_{inf} . Similarly, people in I_2 die at a rate μ_2 or move into I_3 at rate δ_2 , and people in I_3 die at a rate μ_3 or move into I_4 at rate δ_3 where they die at rate μ_4 .

We use HIV prevalence data in South Africa from 1990 to parameterize our model. We divide our population as follows: N is the total population of South Africa. It was estimated that 0.3% of the population was infected with HIV/AIDS. However, we cannot uniformly distribute infected individuals into different stages of infection due to the different time span of each stage. From the previous model we approximate the eclipse phase to last from days 0-16 post infection, acute phase to last from days 16-80, chronic phase last the remaining 8 years, and AIDS from years 8-10 post infection. Hence $I_j(0) = 0.003N \frac{\text{length of stage } j}{10 \text{ years}}$ where $j = \{1, 2, 3, 4\}$

The between-host ODE model is described by the following equations:

$$\begin{cases} \dot{S} = \Lambda - (\lambda + \mu_0)S, \\ \dot{I}_1 = \lambda S - \mu_1 I_1 - \delta_1 I_1, \\ \dot{I}_2 = \delta I_1 - \mu_2 I_2 - \delta_2 I_2, \\ \dot{I}_3 = \delta I_2 - \mu_3 I_3 - \delta_3 I_3, \\ \dot{I}_4 = \delta I_3 - \mu_4 I_4, \end{cases} \quad (4.1)$$

where

$$\lambda = \kappa \sum_{j=1}^4 \beta_j \frac{I_j}{S + \sum_{k=1}^4 I_k}$$

is the force of infection, as derived in Chapter 1.

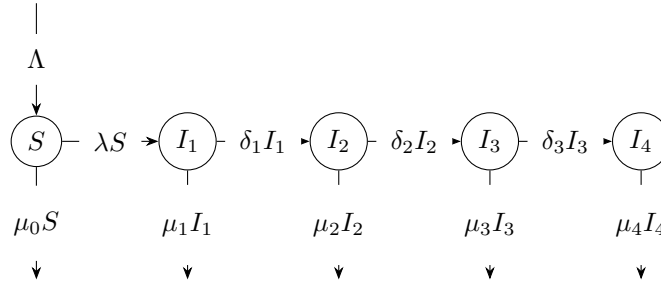


Figure 4.1: Diagram for between-host ODE model

Parameter	Meaning	Value
N	Total population	$2 \cdot 10^7$ people
κ	Average unprotected sexual contacts	$\text{month}^{-1} \text{ person}^{-1}$
Λ	Recruitment rate into S_0	$\mu_0 S_0$ people month^{-1}
λ	Force of infection	
δ_1	Transfer rate from I_1 to I_2	month^{-1}
δ_2	Transfer rate from I_2 to I_3	month^{-1}
δ_3	Transfer rate from I_3 to I_4	month^{-1}
μ_0	Death rate of susceptible population	month^{-1}
μ_1	Death rate of eclipse population	month^{-1}
μ_2	Death rate of acute population	month^{-1}
μ_3	Death rate of chronic population	month^{-1}
μ_4	Death rate of AIDS population	0.01 month^{-1}
S_0	Initial susceptible population	$N(1 - 4 * 0.003)$
I_{1_0}	Initial population in eclipse phase	$0.003N \frac{16}{10*365}$
I_{2_0}	Initial population in acute phase	$0.003N \frac{64}{10*365}$
I_{3_0}	Initial population in chronic phase	$0.003N \frac{365*8-80}{10*365}$
I_{4_0}	Initial population in AIDS phase	$0.003N \frac{2*365}{10*365}$

Table 4.1: Parameters for ODE model

4.1.2 PDE model

As opposed to dividing the infected population into 4 compartments based on CD4⁺T cell count, we can use an age structure partial differential equation model. Using this approach we can consider infinitely many ages of infection in our between host model. Similarly to the ODE model, individuals enter the susceptible population at a rate Λ , and grows out of the sexually active age or dies naturally at a rate d .

Thus the force of infection is given by

$$\lambda = \kappa \frac{\int_0^\infty \beta(a) I(t, a) da}{S + \int_0^\infty I(t, a) da}.$$

The model is an age-structure model similar to that given by Hakansson [7], and is given as follows:

$$\begin{cases} S' &= \Lambda - dS - \lambda S \\ \frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} &= -\mu(a)I(t, a) - dI(t, a) \\ I(t, 0) &= \lambda S, \end{cases} \quad (4.2)$$

where $\beta(a)$ is the probability of infection as a function of age from the infected host and $\mu(a)$ is the death rate due to age, both of these parameters come from the within host model.

4.2 Model justification

We now will show the significance of giving probabilities and death rates that vary over time, as opposed to assuming that they are constant.

First we suppose that the probability is constant (taken at its steady state) but allow the death rate to vary, and observe that the rate of change of the prevalence varies significantly.

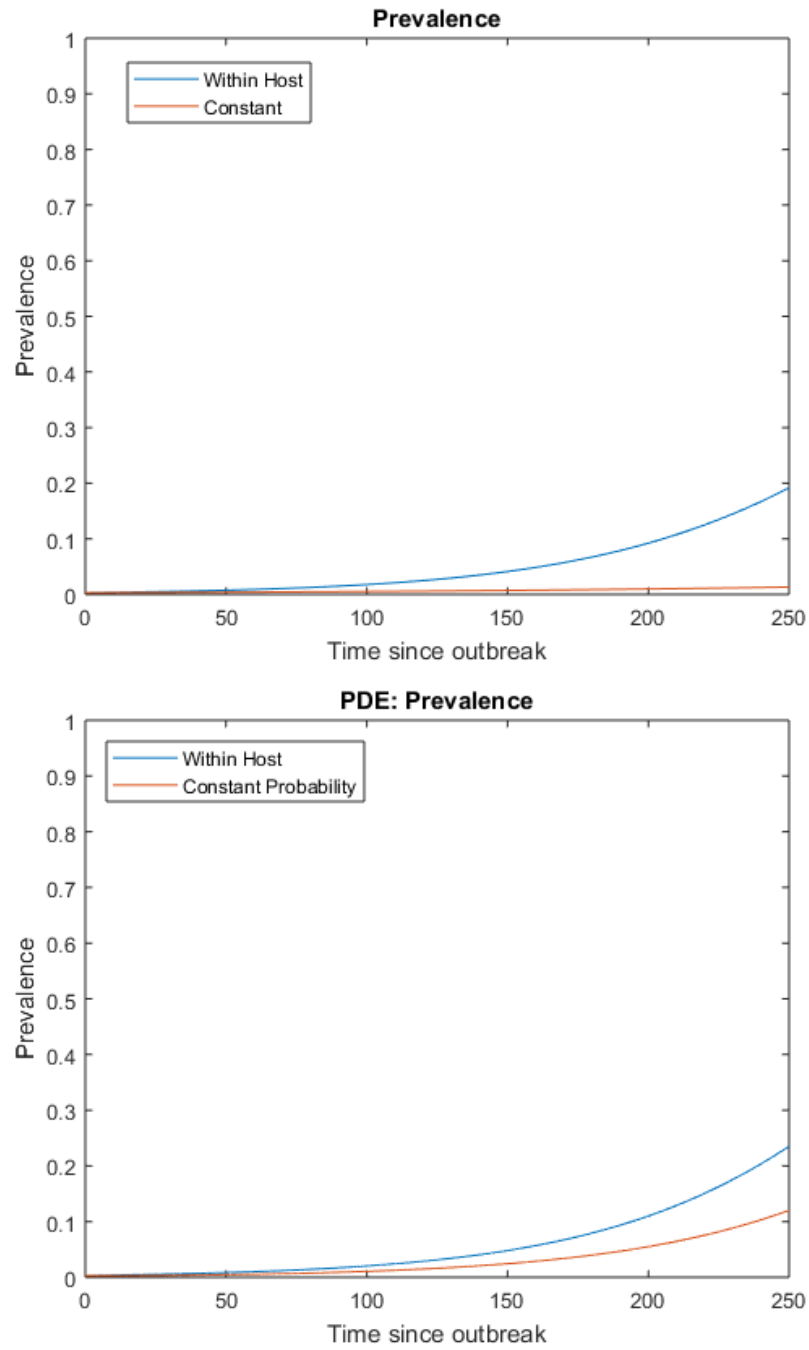


Figure 4.2: Prevalence: within host vs constant probability

Similarly for the death rate. If it is taken at its steady state (or even slightly above its steady state) not enough AIDS patients die and the prevalence is overestimated.

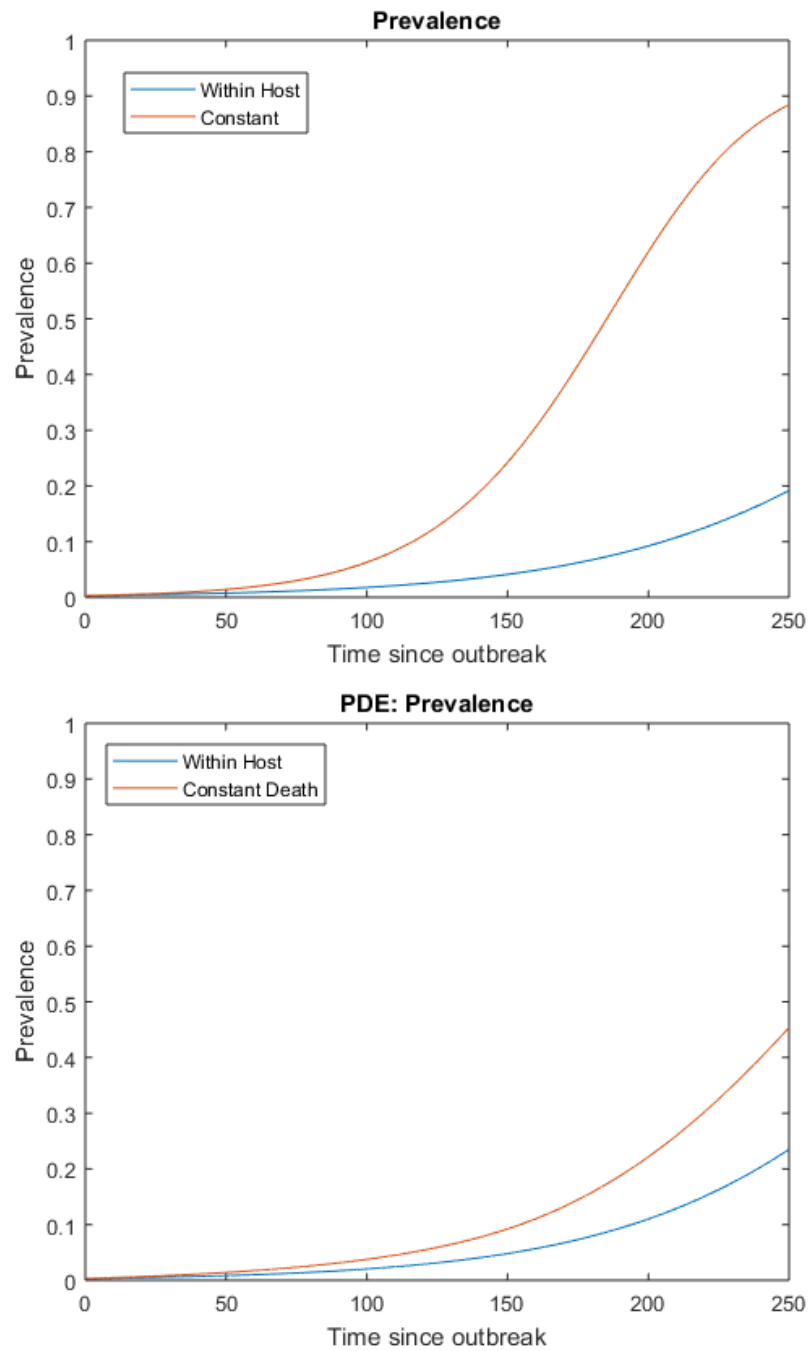


Figure 4.3: Prevalence: death vs constant death rate

4.3 Model analysis

We shall now present stability results for a generalized form of the ODE (4.1) where we assume that there are J infected compartments, so that the force of infection

$$\lambda = \kappa \frac{\sum_{j=1}^J \beta_j I_j}{S + \sum_{k=1}^J I_k}.$$

Of course, this reduces to the model when $J = 4$, but for the sake of future work (possibly including compartments for treatment) we do not make this assumption.

One can also interpret these results as being significant even for *approximations* of the PDE. The relative difficulty of model analysis in infinite dimensions, gives us a practical use for our ODE model.

Let $\alpha = \delta + \mu$, $\delta_J = 0$, and allow j to range over $\{2, 3, \dots, J\}$. Then our generalized system is

$$\begin{cases} \dot{S} &= \Lambda - (\lambda + \mu_0)S \\ \dot{I}_1 &= \lambda S - \alpha_1 I_1 \\ \dot{I}_j &= \delta_{j-1} I_{j-1} - \alpha_j I_j \quad \text{where } j = 2, \dots, J \end{cases}. \quad (4.3)$$

4.3.1 Basic reproduction number

We begin by deriving the basic reproduction number \mathcal{B}_0 , which can be interpreted as the expected number of new infections if an eclipse-stage individual is introduced to a perfectly susceptible but healthy population, to show that $\mathcal{B}_0 = 1$ is a bifurcation point of the model (4.3).

In the argument that follows, if A is a matrix, then we will write $(A)_{i,j}$ for the i, j th entry of A . Moreover, we will write solution curves as

$$(S, \vec{I}) \in \mathbb{R} \times \mathbb{R}^J$$

where $\vec{I} = (I_1, I_2, \dots, I_J)$ is the vector of infected compartments.

Let $S_0 = \Lambda/\mu_0$ be the initial condition on susceptible individuals. Then, the disease-free equilibrium of (4.3) is given by DFE $= (S_0, \vec{0})$. This follows by considering the system of equations

$$\begin{cases} \Lambda &= (\lambda + \mu_0)S^* \\ \lambda S^* &= \alpha_1 I_1^* \\ \delta_{j-1} I_{j-1}^* &= \alpha_j I_j^* \end{cases} \quad (4.4)$$

and letting $\vec{I} = \vec{0}$. In this case, the force of infection $\lambda = 0$, and so both sides of each equation vanish, except $\Lambda = \mu_0 S$, which of course converges to $S = S_0$.

Recall that the linearization of the infected components about the disease-free equilibrium DFE can be written $F - V$, where F is the new-infection matrix and V is the transfer matrix. From there, the next-generation matrix will be given by FV^{-1} as usual.

It follows from (4.3) that at DFE, the total population $S + \sum_{k=1}^J I_k = S$, so

$$\dot{S} = \kappa \sum_{j=1}^J \beta_j I_j.$$

Therefore, for each j , $(F)_{1,j} = \kappa \beta_j$ and $(F)_{k,j} = 0$ for each $k \geq 2$.

Similarly, $(V)_{j,j} = \alpha_j$ for each $j \leq J$ and $(V)_{j+1,j} = -\delta_j$ for each $j < J$, with zeroes elsewhere in V . Then V^{-1} is lower-triangular, and for each $k \geq j$,

$$(V^{-1})_{k,j} = \frac{\prod_{i=j+1}^k \delta_i}{\prod_{i=j}^k \alpha_i}.$$

It follows that $(FV^{-1})_{k,j} = 0$ for each $k \geq 2$ and

$$(FV^{-1})_{1,j} = \kappa \sum_{i=j}^J \beta_i \frac{\prod_{m=j+1}^i \delta_m}{\prod_{m=j}^i \alpha_m} = \frac{\kappa}{\prod_{i=1}^J \alpha_i} \sum_{i=j}^J \left(\beta_i \prod_{m=j}^i \delta_m \prod_{m=i}^J \alpha_m \right).$$

Clearly now FV^{-1} is a rank-1 linear map, so all but one of its eigenvalues is 0. But the vector $v = (1, 0, 0, \dots, 0) \in \mathbb{R}^J$ is mapped to $(FV^{-1})_{1,1}v$, so it is an eigenvector. Thus the last eigenvalue, and in particular the spectral radius, is given by $(FV^{-1})_{1,1}$. So we have $\mathcal{B}_0 = (FV^{-1})_{1,1}$. In particular,

$$\mathcal{B}_0 = \frac{\kappa}{\prod_{j=1}^J \alpha_i} \sum_{j=1}^J \left(\beta_j \prod_{k=1}^j \delta_k \prod_{k=j}^J \alpha_k \right). \quad (4.5)$$

It is of theoretical and practical interest that \mathcal{B}_0 is *linear* in κ : it confirms the insight that the rate of sexual contact in a society is one of the main deciding factors in the spread of HIV.

4.3.2 Epidemic resolution and persistence

When $\mathcal{B}_0 < 1$, we will show that the epidemic is self-resolving by way of showing global stability of the disease-free equilibrium. $\mathcal{B}_0 = 1$ is a bifurcation point of the model, and we show that the disease-free equilibrium is unstable when $\mathcal{B}_0 > 1$.

We begin by restricting ourselves to the *biologically feasible* region $\bar{U} \subset \mathbb{R} \times \mathbb{R}^J$ consisting of the images of all solution curves (S, \vec{I}) for which $S \in [0, S_0]$ and each $I_j \geq 0$. Since $S \leq S_0$ for all time provided that S_0 is an initial condition, this is no loss.

Define the *infectious region* of \bar{U} , written U , to be its interior. Then

$$U = \bar{U} \cap \mathbb{R}_+ \times \mathbb{R}_+^J.$$

To show the existence of an endemic equilibrium, we again solve the system (4.4) using a computer algebra system. We find that for each j ,

$$I_j^* = \frac{S_0}{\delta_1 - \mu_1} \prod_{i=2}^j \frac{\delta_{i-1}}{\delta_i + \mu_i}$$

and that S^* is the solution to the quadratic equation

$$0 = \Lambda - \left(\mu_0 + \frac{\sum_{j=1}^J \beta_j I_j^*}{S^* + \sum_{j=1}^J I_j^*} \right) S^*.$$

However, proving stability of the endemic equilibrium is quite difficult because the model is high-dimensional and nonlinear.

We instead compromise and show that the epidemic will not resolve itself if $\mathcal{B}_0 > 1$; one must instead introduce treatment to lower \mathcal{B}_0 to below 1 in order for the epidemic to resolve.

Recall the definition of uniform persistence [2].

Definition 4.1. An epidemic is said to be *uniformly persistent* if there exists a $\beth > 0$ such that for each solution curve $(S, \vec{I}) \in \bar{U}$ of the epidemic,

$$\liminf_{t \rightarrow \infty} \min_{1 \leq j \leq J} I_j(t) > \beth.$$

We interpret uniform persistence as meaning that the epidemic will not resolve.

Theorem 4.2. *If $\mathcal{B}_0 < 1$, then DFE is globally asymptotically stable. But if $\mathcal{B}_0 > 1$, then the epidemic is uniformly persistent.*

Proof. For convenience, let $N = S + \sum_{j=1}^J I_j$ be the total population.

Suppose that $\mathcal{B}_0 < 1$. Let $c \in \mathbb{R}_+^J$ be defined by

$$c_i = \frac{1}{\prod_{j=i}^J \alpha_j} \sum_{j=i}^J \left(\beta_j \prod_{k=i}^j \delta_k \prod_{k=j}^J \alpha_k \right).$$

In particular, $\mathcal{B}_0 = c_1$.

Let $L(S, \vec{I}) = \langle c, \vec{I} \rangle$. Then $L \in (\mathbb{R} \times \mathbb{R}^J)^*$ is positive and smooth, and $L(\text{DFE}) = 0$, so L could be Lyapunov on \bar{U} if $\dot{L} \leq 0$ and $\dot{L} = 0$ precisely at DFE.

We claim that L is, in fact, Lyapunov. This will follow because

$$\dot{L} = \langle c, \dot{I} \rangle = c_1(\lambda S - \alpha_1 I_1) + \sum_{j=2}^J c_j(\delta_{j-1} I_{j-1} - \alpha_j I_j).$$

Now $S \leq N$ and $\lambda = \langle \beta, I \rangle$, so $\lambda S \leq \langle \beta, I \rangle$. Moreover,

$$I_1(c_2 \delta_1 - c_1 \alpha_1) = \frac{I_1}{\prod_{j=2}^J \alpha_j} (\beta_1 \prod_{j=2}^J \alpha_j) = \beta_1 I_1$$

and similarly one can check $I_j(c_{j+1} \delta_j - c_j \alpha_j) = \beta_j I_j$ for each $j \in [1, J] \cap \mathbb{N}$. Grouping like terms,

$$\dot{L} \leq c_1 \langle \beta, \vec{I} \rangle - \sum_{j=1}^J I_j(c_{j+1} \delta_j - c_j \alpha_j) = (\mathcal{R}_0 - 1) \langle \beta, \vec{I} \rangle.$$

Since $\beta \in \mathbb{R}_+^J$, it follows that $\dot{L} \leq 0$ with equality iff $\vec{I} = \vec{0}$. An application of Lyapunov's theorem completes the proof of global stability.

Now suppose instead $\mathcal{B}_0 > 1$. Let

$$\tilde{S}(\varepsilon) = \frac{S_0 - \varepsilon}{S_0 + (J+1)\varepsilon} \leq 1.$$

By Theorem 4.6 in [3], it will suffice to prove that if W is the stable manifold of DFE, then $W \cap U$ is empty. Then, any positive solution of the system is uniformly persistent.

Thus, suppose that there is a solution curve $(S, \vec{I}) \in W \cap U$. Then by stability of DFE, for each $\varepsilon > 0$, if t is large enough,

$$|\vec{I}(t)| < \varepsilon. \tag{4.6}$$

Introduce the “weighted linearization” $D = \tilde{S}F - V$, so that given ε ,

$$\dot{I} = (F - V)\vec{I} \geq D(\varepsilon)\vec{I} \tag{4.7}$$

where the inequality is taken componentwise. Clearly $D(0) = F - V$ is the linearization at DFE.

Let $\sigma(\varepsilon) = \text{Spec } D(\varepsilon)$ be the spectrum of $D(\varepsilon)$. Then, because $\mathcal{B}_0 > 1$, $\sigma(0)$ has a positive element by Theorem 2 in [5].

By continuity of Spec , we can choose ε small enough that $\sigma(\varepsilon)$ has a positive element. So there is a solution to the ODE $\dot{X} = D(\varepsilon)X$ which grows exponentially. It follows from (4.7) that I blows up, in contradiction to (4.6). Thus $W \cap U = \emptyset$, which completes the proof. \square

The proof of Theorem 4.2 does not appear to use finite-dimensionality in an absolutely essential way; thus we can conjecture that the basic reproduction number of the PDE can be recovered by a limiting argument on (4.5), similar to the ones used in the definition of an integral, and that one expects to recover the same results of global stability, bifurcation, and uniform persistence. Arguments similar to those given by Harkansson [7] may suffice to accomplish this, but we do not pursue this “functional-analytic” approach here.

However, we can show that the PDE has a disease-free equilibrium $(S_0, 0)$. Indeed, in this case one has

$$\begin{aligned} S' &= 0 \\ \partial_t I + \partial_a I &= 0 \\ I &= 0 \end{aligned}$$

which is clearly an equilibrium, though we do not claim that it is stable.

4.4 Results

Public health officials are primarily concerned with the prevalence of HIV, number of new infections generated by HIV, and the death rate due to HIV in a population.

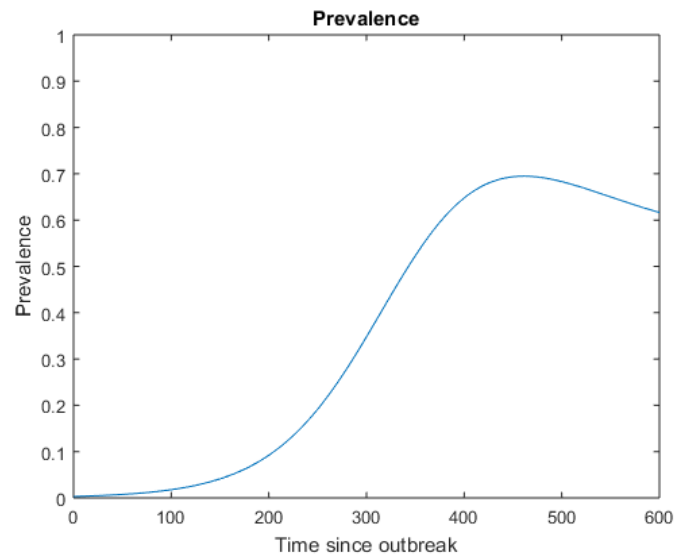
4.4.1 Prevalence

One of the major concerns in the epidemiology of HIV is the prevalence of the disease, or what percent of the total population is infected. From the South African data given by Rahman et al. [15], we wanted to remain consistent with approximately 20% prevalence after 20 years post infection.

We were able to achieve results consistent with the data from South Africa by adjusting the value of κ , the number of contacts, to agree with the data.

We first show the prevalence over time predicted by the ODE model. Both yield results that are consistent with the data from South Africa. We found the value of κ to be 4.4 and 5.5 in the ODE and PDE models, respectively.

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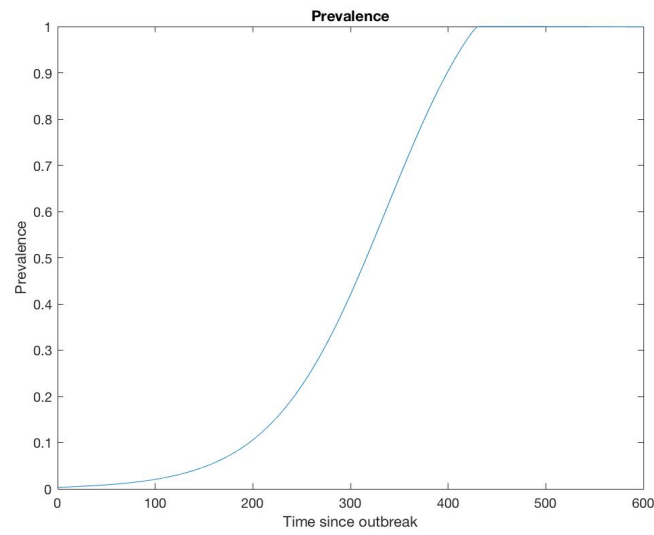


Figure 4.5: Prevalence over 50 years as given by PDE model

We also compare the prevalence over time of the ODE and PDE over the first 25 years.

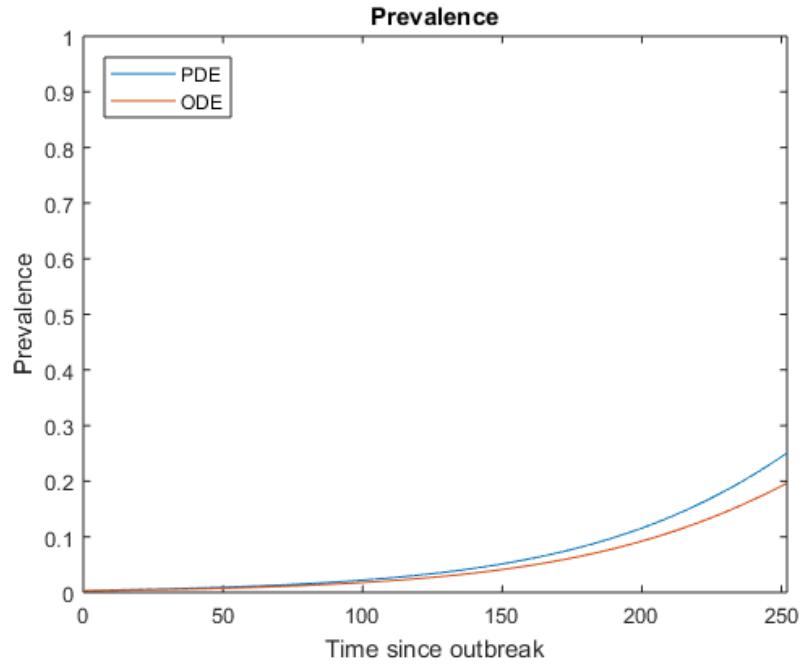


Figure 4.6: Comparison of prevalence of models

4.4.2 New infections

It is also important to know the number of new infections generated by the disease in a specific period of time. Using the ODE model, we find the number of new infections generated over time.

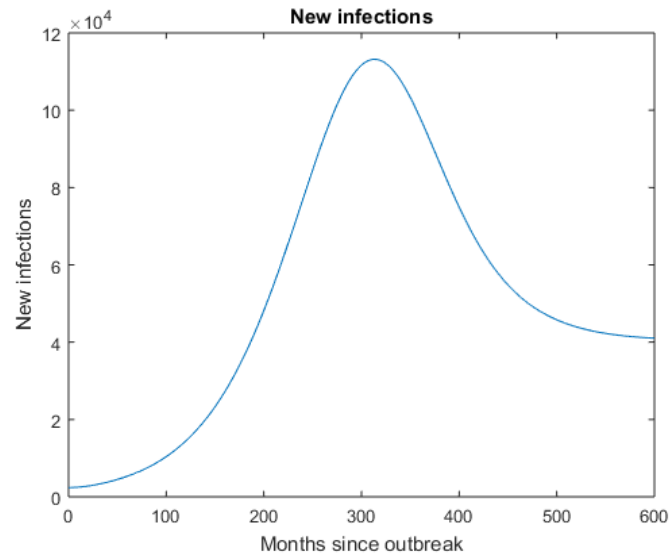


Figure 4.7: New infections as given by ODE model

We can also see this term distributed over ages of infected:

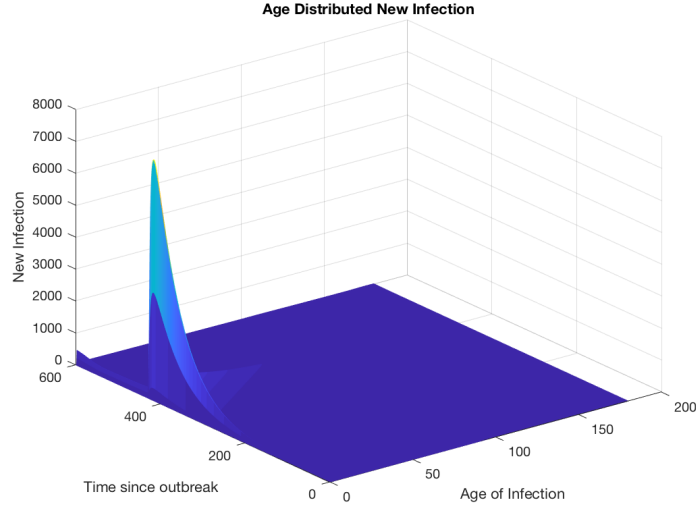


Figure 4.8: New infections as given by PDE model

In figure 4.8, it is evident that the most transmissible age of infection is in the acute stage, this is approximately 3 weeks post infection. This is valuable information to target treatment for these people at this infectious time to lower prevalence in the population.

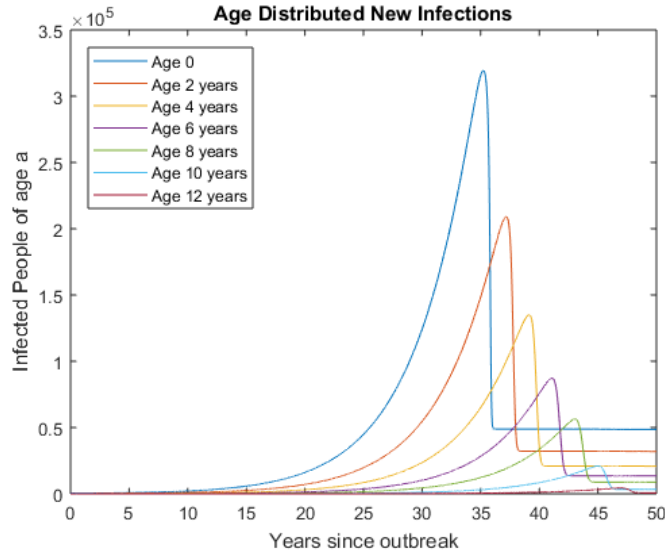


Figure 4.9: New infections as given by PDE model

Figure 4.9 shows that the highest number of new infections come from individuals who have had HIV for approximately three weeks. These newly infected individuals have much higher viral loads and in turn higher probabilities of transmissions, so of course infect the most people. As an individual's age of infection increases, they are causing less infections, and when someone has had HIV for 12 years, they are infecting almost no people. An individual will most likely not live 12 years because of the extremely low $CD4^+$ count and in turn cannot infect others. .

Infected population over time

We can see the number of infected people at different stages of infection at any time t in the between host model, scaled by the length of time spent in the stage.. (Notice that because the ecliptic and acute populations are so similar, the two curves are superimposed.)

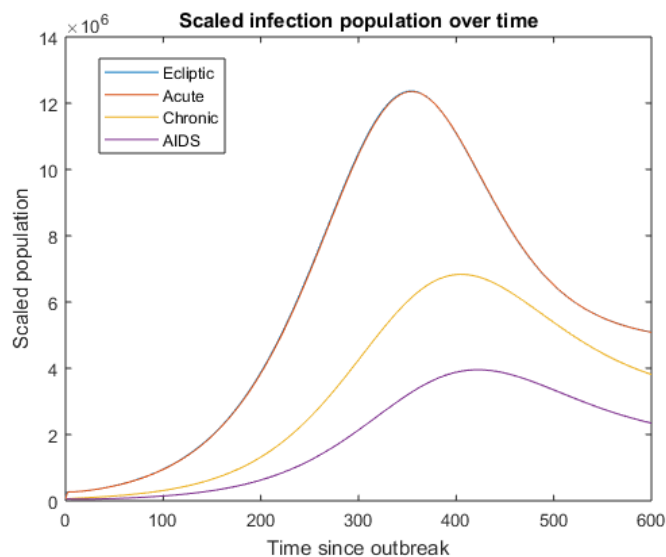


Figure 4.10: Scaled infected populations as given by ODE model

Similarly, we can see the infected population of different ages using the PDE model.

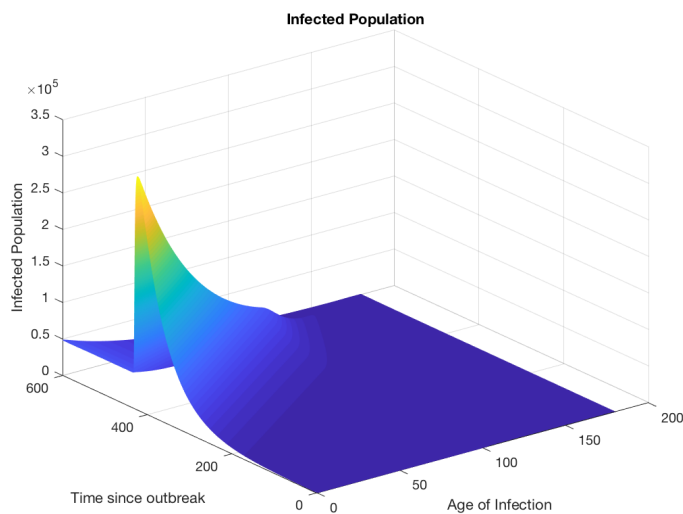


Figure 4.11: Infected population as given by PDE model

We see that it takes approximately 200 months for the infected population to rise. It is clear that this initial infection is from individuals with age in the acute phase. As time and age progress, we also see that individuals start to die, the number of infected people living with an age greater than approximately 125

months is zero. This is due to the fact that This is past the AIDS stage and the individual has a very high viral load and low $CD4^+$ cell count, so a very high death rate.

4.4.3 Death rate

We first show the death rate of the population as a whole, as depicted by the ODE.

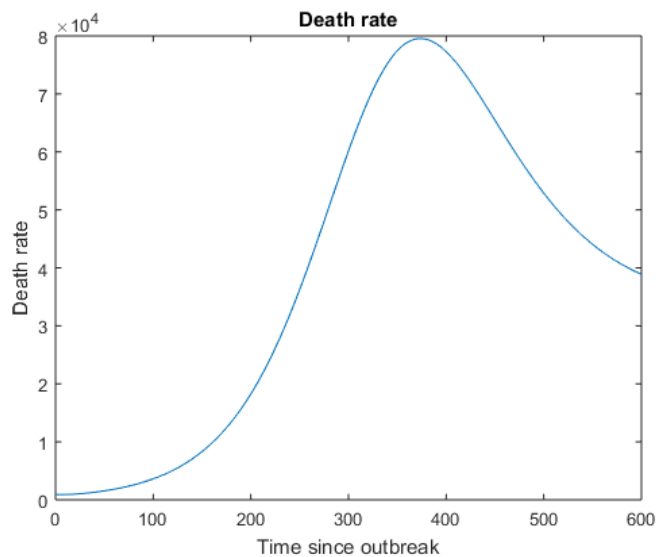


Figure 4.12: Death rate as given by ODE model

Now we show the age distributed death rate, as given by the PDE model. There are two main peaks in the death rate, where age is 0 and where age is around 8 years. When individuals are newly infected they experience a sudden drop in $CD4^+$ cell count, which leads to an increased rate of death. The second peak represents when an individual has had HIV for approximately 8 years which represents AIDS.

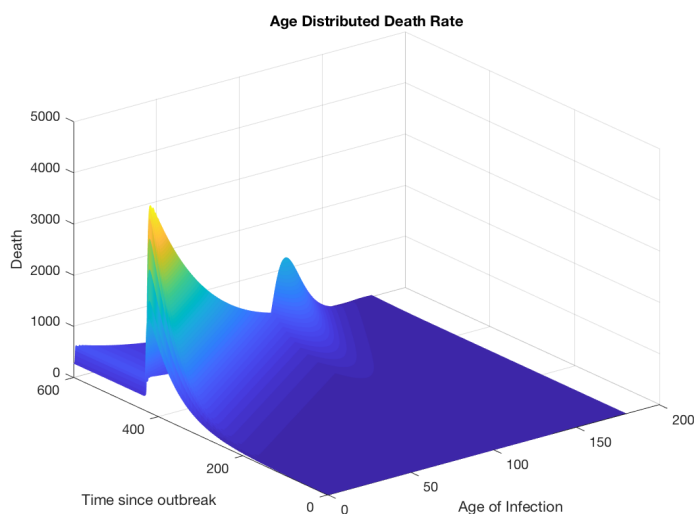


Figure 4.13: Death rate as given by PDE model

Chapter 5

Conclusion

5.1 Discussion

Mathematical modeling of both between-host and within-host HIV dynamics has, over the past few decades, revealed many features of the disease [14]. However, previous between-host models have not used within-host HIV dynamics to generate the parameters, such as the transmission rate and the rate of death, for a between-host model. We successfully created a model that links within-host and between-host viral dynamics, and showed that the previously ignored shortcomings, which arise from assuming a constant death rate and transmission rate and in neglecting the effect of antibodies, actually have a significant effect on the long-term behavior of the between-host model.

In order to link within-host and between-host dynamics, we first developed a within-host model that accounted for the effect of antibodies on the viral load and infected $CD4^+$ T cells. Two approaches were used to model the antibody profile of a donor, one through fitting a function of antibodies with respect to the available data, the second by modeling the dynamics themselves. Both approaches were used to generate the probability of transmission and death rates of individuals in the population who are infected. The two within-host models' probability of transmission and death rates largely agree in their qualitative and quantitative trends. Additionally, it was found that the probability of infection is very sensitive during the chronic stage of infection to the proportion of the viral load that is transferred to the recipient; this finding is supported by higher infection transmission rates among needle-stick transmitted HIV infections, which are associated with a higher viral load transmission, then the infection transmission rates of sexually transmitted HIV infections.

We then used the results of the within-host model, modified using a piece-wise model to represent the onset of AIDS, as an input for a pair of frequency-based models, one an ODE model designed for theoretical work and the other a transport equation-based model designed to recover numerical results. Again, the two models largely agreed, and a generalization of the ODE model approximates the PDE model arbitrarily well, as shown by the method of lines.

Numerically, we observe that the infection is most likely to be transmitted between weeks 2 and 4, what we define as the *acute* stage of the infection. In contrast, the transmission of the infection is less probable in the eclipse stage prior to the acute phase. Regarding policy implementation, it is during the acute phase when it would be most effective, even if a majority of new infections emerge from the chronic and AIDS phases, because so many more individuals are in the chronic or AIDS phases than the acute phase, and so targeting the acute patients would have the greatest effect per person.

We also observe that the between-host epidemic eventually reaches a “critical mass” at around 30 years, at which point the population of susceptible individuals becomes small enough that the prevalence cannot go any higher. This suggests that if the epidemic was allowed to spread without treatment, it would eventually level off.

5.2 Future work

Our model has several limitations that could be addressed. We had limited data on the antibody profile in the acute phase and the viral load and $CD4^+$ T cell count in AIDS phase, limiting the numerical usefulness of the model. Most unrealistically, the between-host model does not have treatment compartments, but if the within-host model could be extended to account for treatment then it would not be difficult to extend the between-host model, either by adding more compartments as done by Rahman et al. [15] or by adding a third temporal variable denoting time since the beginning of treatment.

We further assumed that sexual contact happens with a randomly selected individual in the population, and did not distinguish between gender and sexuality. While these are standard assumptions to make in a frequency-based epidemic model, it is possible that a more realistic model would be a network model as done by Keeling et al. [8], rather than a differential model; but we do not pursue this possibility.

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