CoMPLEX
University College London

Mini Project 3

Understanding The Mathematics of HIV Transmission In Concentrated Settings

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Abstract

In this project we will look at how mathematical modeling can enhance our understanding of the HIV transmission between FSWs and clients in concentrated settings. Initially we present a review of the various available modeling approaches to date and then develop and study a theoretical framework in which to explore the key aspects that drive the HIV transmission between female sex workers (FSWs) and their clients. Using analytical tools (steady-state analysis, complicated algebraic manipulations) and numerical analysis we explore the effect of model key parameters (sexual activity rates and retirement rates) on HIV prevalence and R_0. Our results point towards the key drivers of HIV transmission between these two groups how they can be used to fight HIV transmission.

Contents

Chapter 1

Introduction

HIV infection remains a global issue with over 34 million people living with HIV worldwide [41]. HIV disease progresses in three stages: the acute infection stage, the clinical latency stage and the AIDS stage [4]. During the early period of infection (acute infection stage) large amounts of the HIV virus are being produced in your body. The virus uses CD4 cells to replicate and destroys them in the process. CD4 cells are a type of helper T cells responsible for signaling when invaders enter and hence vital for the adaptive immune system of the organism. Because of their destruction by the HIV virus the CD4 count can fall rapidly in the initial stage of HIV progression until eventually hosts immune response begins to bring the level of virus back down to a level called a viral set point, which is a relatively stable level of virus in your body. At this point, your CD4 count begins to increase, but it may not return to pre-infection levels. Following this initial stage is a much longer one called latent period, where the virus produces no symptoms, but the HIV virus remains active and can reproduce albeit at slower pace [4]. The person remains infectious but less than in the initial stage. The second clinical latency stage can last a long time. If treatment with anti-retroviral drugs (ART) is taken the infected person may remain in this stage, is less infectious and may never progress to the last AIDS stage. ART is normally available when CD4 count falls below 350 cells/mm3. The third and final stage is AIDS occurs when the CD4 count drops further and remains below 200 cells/mm3. This stage is characterized with a severely damaged immune system and hence the body becomes vulnerable to opportunist infections. Most of HIV diagnosis occurs after the initial infectious stage and when the person enters the second clinical latency stage of progression. The asymptotic nature of the initial stage makes the early capture of HIV difficult and this in turn makes the disease difficult to control.

In different settings across the world the transmission of the HIV virus occurs amongst different population groups. In concentrated settings the transmission of HIV is generally between different high-risk groups (female sex workers and their clients, men who have sex with men or injection drug users) with the HIV prevalence amongst the general population remaining low and below 1% [5]. In generalized settings the HIV prevalence in the general population is greater than 1% and transmission can occur among all population groups [5].

There have been many worldwide studies that looked at the behavioral, epidemiological, social and cost aspects of HIV transmission and hence potential intervention. Avahan, funded by Bill and Melinda Gates Foundation from 2003, represents the largest HIV prevention intervention targeting FSWs, MSM and IDUs in 63 districts in India and aiming to reduce the HIV transmission and prevalence among these high-risk groups [19]. Specifically Avahans aim in targeting female sex workers (FSWs) was to increase their consistency of condom use, and as a consequence reduce HIV transmission between FSWs and clients, and subsequently the general population. To achieve this, the Avahan programme provides community support and funds large-scale surveys to access its impact and cost. Avahan funding included a large-scale programme evaluation. Specifically, a series of district level cross-sectional integrated behavioral and biological surveys (IBBAs) were conducted [2][3]. These datasets have been previously combined with extensive mathematical modeling to assess Avahans impact [27][33]. We note that even though the collected data from studies such as Avahan are crucial in understanding the nature of HIV transmission based on behavioral, epidemiological and cost data, the impact of different interventions requires analytical studies such as to understand the cost-effectiveness of different interventions and how to optimally design them (e.g. which components are crucial etc) [27].

Therefore, mathematical and computational modeling is essential in the study and fight against HIV transmission. One of the prime uses of modeling is to gain better understanding of the transmission dynamics of the infection both in within-host and population scenarios. Using a modeling framework defined by theoretical mathematical equations we can design a unique framework for comparing the effect and significance of various model parameters, testing possible hypothesis, evaluating the efficiency of interventions for prevention of HIV transmission, aid the design of controlled programs in different settings as well as quantifying the socioeconomic effects of the infection. These aspects cannot be conducted in as part of epidemiological or behavioral studies or tested with any other means.

Mathematical modeling of HIV is mainly conducted in two different levels, within-host and population level. A review of previous models in both of these categories is outlined in Chapter 2. The former modeling approach allows the study of the disease progression and behavior of the infection within the human body, with a potential to explore its dynamics, temporal evolution and stages and response to drug and therapy in general. This type of modeling is essential in order to understand the disease itself in a molecular level and aids towards the goal of finding a cure. The latter models focus on the HIV transmission between and within different population groups and explore the various risk factors and how to potentially reduce these and hence reduce the risk of HIV transmission and increased HIV prevalence or incidence. This category of mathematical models is vital for research regarding prevention mechanisms as well as monitoring the outbreak of an epidemic.

One of the most important factors concerning a disease is its ability to spread within a population. If the spread can be controlled then the infection will not reach pandemic state and can be constraint. One of the key things in halting the spread of infections

such as HIV, is the rate at which additional (secondary) infections can originate from the primary infection. If no secondary infections can occur, or they occur and are controlled then the spread of the infection can also be controlled. A parameter that can capture this analytically is the reproduction number R_0 defined as the number of secondary infections produced due to an individual entering a disease free population. Within the mathematical models for HIV transmission (as well as other infectious diseases) the value of R_0 controls the fate of the epidemic [11], with R_0 value less than 1 yielding a disease-free steady state and controlled epidemic whereas a value of R_0 greater than 1 allows for a secondary spread of the infections and the HIV reaching an endemic steady state. Due to the importance of this parameter vast amount of research has focused this parameter both for within-host and population models.

Within this project we will look at how mathematical modeling can aid our understanding of the HIV transmission between FSWs and clients in concentrated settings. We will first review, in Chapter 2, the various available modeling approaches available to date and then use the gained knowledge, in Chapter 3, to develop and study a theoretical framework in which to explore the key aspects that drive the HIV transmission between female sex workers (FSWs) and their clients. Specifically we will use analytical tools (steady-state analysis, complicated algebraic manipulations) and numerical analysis to explore the effect of model key parameters (sexual activity rates and retirement rates) on HIV prevalence and R_0. Our results will be used to interpret the key drivers of HIV transmission between these two groups and we will discuss how this is important in the quest against HIV.

Chapter 2

Review of HIV Models

Mathematical and computational modeling plays an important role in the quest to gain a better understanding of the complex processes that control the progression of HIV and affect the transmission of HIV in different setting and between populations. Constructing mathematical models allows for theoretical framework to be developed in which the transmission dynamics of the infection both in within-host and between different populations can be studied.

Mathematical modeling of HIV is mainly conducted in two different levels: the cellular level i.e. within a human host or on population level i.e. between different society subpopulations. In the remainder of this chapter we outline the characteristics of these two modeling levels, present different mathematical and computational approaches used as well as highlight the difference between them.

2.1 Within-Host Models

The within-host modeling is generally associated with the immunological properties of the HIV disease progression and focus on understanding the response of the organism to the virus. Different analytical approaches have been used to undertake such cellular level modeling including applications of ordinary differential equations (ODEs), stochastic differential equations (SDEs), delay differential equations (DDEs) as well as partial differential equations (PDEs). In each of these systems a simplified network of differential equation are used to describe the temporal (ODEs) or spatio-temporal (PDEs) evolution of the HIV virus in absence or presence of noise (SDEs) and sometimes considering the effect of temporal delay in progression (DDEs)

The most basic model formulated is a simple system of ordinary differential equations describing the dynamical evolution of the virus population and the (infected and uninfected) CD 4+ cell population. The main characteristics of these equations are the rate of influx of new (uninfected) cells, the natural and the infection-related death rate, the infection rate as well as the virus clearance rate. All these terms constitute the basic formulation which has two steady states, the infection-free and the infected steady state.$R_0 < 1$ yields that the systems will reach the infection-free steady state and $R_0 > 1$ the opposite. Many variations-additions have been made to this simple model, in the con-

text of ODEs. One of the basic added features was the return of cells to the uninfected state due to the observation that there are infected cells that are not yet producing virus [29]. This was approached in different ways. Rong et al. [32] added an eclipse class, where the cell are not producing any virus and return to the uninfected class at a constant rate, whereas Chandra and Srivastava simulated the return of cells from the infected class itself (without introducing a new class) [35]. Furthermore, a different variation was the introduction of non-linear interaction between uninfected cells and virus by Wang and Song [38], in contrast to the vast majority of mathematical models use a linear interaction term proportional to the concentration of virus and uninfected cells. Their non-linear terms would account for saturation in high virus concentrations and enhanced interaction in the case of small viral load or multiple exposures. Using numerical analysis they confirmed the stability of the two steady states for $R_0 < 1$ or $R_0 > 1$. Despite the simplicity of ODE models useful insights were provided by their analysis and data were successfully fitted.

In addition to ODEs there are two more approaches used extensively in infectious diseases modeling that are still part of the deterministic regime. These are delay differential equations (DDEs) and partial differential equations (PDEs). As discussed previously there is the period where the cells are infected but not yet infectious (do not produce virus)[4]. This means that there is an intrinsic delay that needs to be taken into account when modeling HIV. As a result a number of researchers focused on DDEs to model the dynamics of the infections. Initially, this delay was modeled by Perelson et al. [29] with the addition of a fourth class of cells, the latently infected cells. Culshaw and Ruan [9] simplified the model by including three classes and using discrete delay to model the non-infectious stage. They found that the system can exhibit reach dynamics depending on the parameter assumptions and that despite the fact that some parameters can give the appropriate stability, independently of the delay, in certain cases delay-dependent oscillations can occur. Finally, to account for the different rates of virion production by the cells and the different death rate, Nelson et al. [26] used PDEs to create an age-structured model for HIV where the above are time-dependent. They showed that this model is a generalization of the standard ODE models used before and found two steady states (uninfected and infected).

In order to account for fluctuations in the system and explicitly include noise, stochastic models are also extensively used to simulate HIV dynamics. Since the majority of biological phenomena have a degree of randomness this type of modeling seems appropriate. The randomness stems from the complexity of biological phenomena and hence from the fact that the same setting can often produce different results (same number of cells and virions interacting yields different end-situations). These models are particularly important for the early stages of HIV dynamics and the calculation of extinction probabilities. Tuckwell and Le Corfec incorporated noise in the standard equations and added stochasticity to the mechanisms that control infection as well as movement across the different classes of cells, to model the early dynamics of HIV [36]. Additionally they examined the effect of different parameters using perturbation. Another example of stochastic models used in early stages is the model by Pearson et al. [28]. They tested two different ways of viral production, continuous and in bursts. This separation is impossible

using deterministic models since for a certain set of parameter values there exists a single realization and so continuous versus in burst would give the exact same results. What was show is that these two types not only have different early dynamics but also different extinction probabilities. Finally, Dalal et al. [10] posed a deterministic ODE model of HIV dynamics including the effect of Highly Active Antiretroviral Treatment (HAART). HAART inhibits the process of virus particle formation [10] and as a results keeps the viral load low and the CD4+ levels high. Stochastic death rates were then added to both CD4+ cells and virions due to the randomness introduced by various biological phenomena that drive their death. They proved that the model possesses non-negative solutions and that in certain cases it approaches asymptotically the disease-free equilibrium.

2.2 Population Models

The population models of HIV transmission focus on exploring the key drivers of HIV infection among different population groups. These models are compartmentalized with different compartments representing different society population groups. And a number of different mathematical tools can be used to study the transmission among different compartments.

The vast majority of population (transmission) models are based on the basic SIR (susceptible-infected-recovered or dead) model introduced by Kermack and McKendrick [20]. This is a system of three ODEs describing the evolution of the three populations and was used to model, among many other infectious diseases, HIV transmission. One of the first deterministic ODE models for HIV was proposed and explored by May et al. [22]. They introduced two simple models of homosexual men, one with a closed (constant) population and the other with a varying population by including constant immigration and death rates. Another very important aspect of their work was incorporating the effect of non-homogeneous mixing by dividing the population is subpopulation with different mixing. They derived analytical expression for the simplest model but numerical simulation was needed for the more complicated models (varying population, non-homogeneous mixing). A similar model was studied by Hyman and Stanley [18] focusing mainly on the initial stages of the epidemic and the effect of random or like prefers like mixing, concluding that different mixing was a very strong effect on the dynamics of the epidemic. Later models studied heterogeneous populations and particularly high risk groups, which drive the infections, such as that of female sex worker and male clients [24],[31].

Moreover, as with within-host modeling, PDE and SDE models are used for deterministic population models as well. A good example for this kind of modeling is the paper by Garnett and Anderson [15]. They extended previous literature and proposed a two-sex PDE model stratified by age and sex activity. They concluded that the mixing patterns among age and sex activity classes play a crucial role on the demographic impact of the disease and can substantially affect its course. Regarding DDEs, a very interesting paper by Mukandavire et al. [25] proposed the use of discrete delay differential equations to model the incubation period explicitly, in contrast to previous papers. The model was then solved numerically to identify the effect of the incubation period on the dynamics of

HIV epidemic and what was found is that long incubation period comes with increased HIV/AIDS prevalence ratio.

Alongside deterministic models (ODEs, PDEs, DDEs) stochastic methods are used to model HIV epidemiology. This type of methodology is particularly interesting when trying to include environmental randomness (noise) or simulate complex interactions. For the latter, a very interesting and promising approach is the use networks (graph theory) to represent the interactions/relations of the population. Dala et al. [10] introduced noise (stochasticity) to a system of equations describing AIDs and condom use by the means of parameter perturbation, hence creating a system of SDEs. Their results indicated that the system processed biologically relevant solution and that noise helped stabilize the system. Furthermore, they concluded that noise did not affect the importance of critical parameter such as condom use. In a more computational rather than mathematical approach, Gray et al. [16] performed a stochastic stimulation to study the effect of antiretroviral therapy and vaccines on HIV dynamics. What they found is that over a period of 20 years there can be a substantial decrease in HIV infection by combining ART and low efficiency vaccines, but this is highly dependent on the behavior of both HIV-positive and HIV negative individuals. Behavioral disinhibition due to treatment (vaccines, ART) could substantially decrease its effectiveness. Regarding stochastic simulations using networks, one of the first papers using this approach was proposed by Morris and Kretzschmar [23], to explore the effect of concurrent relationships and the different with sequential monogamy in HIV transmission. Concurrent relationships admitted dramatic changes in the early stages of the epidemic and rapid increase in the number of infected and the speed of infection. A more complicated stochastic network simulation was conducted by Sloot et al. [34]. Using complex networks they included all the different types of HIV spreading (homosexual, heterosexual, drug users) and their results were in agreement to real data.

Mathematical and computational modeling of infectious diseases and more specifically of HIV is a very promising field. Although such research has been conducted for several decades there are still large unexplored or underexplored areas. It is clear that mathematics and informatics offer more and more useful tools and methods to answer important questions in both internal and external level each with its benefits and drawbacks. In the following chapter a model for the HIV transmission between female sex worker FSW and their clients is presented and analyzed with the main focus placed on the importance of relative populations or sexual activity rates and retirement rates.

Motivated by the modeling reviewed here, in this project we have focused on using deterministic system of ODEs to describe the HIV transmission between female sex worker FSW and their clients. This framework is motivated by the core group theory analyzed in [29] and which explores whether a core group can be responsible for HIV transmission or is it the interplay between different interactions and key processes that drives the infection. In the following chapter a simple model is presented and analyzed using steady-state analytical and numerical solutions with the main focus placed on the importance of relative populations or sexual activity rates and retirement rates. The data for the models parameters are drawn from the Avahan dataset and our results are discussed in

Chapter 3.

Chapter 3

Mathematical Model for HIV Transmission Between FSWs and Their Clients

3.1 Overview

In this chapter we develop and study two simple deterministic ODE models for HIV transmission between FSWs and their clients. The first model accounts for keeping the population of FSWs and their clients constant in time, whereas in the second model we allow for influx of new individuals in each population group and hence the second model is a variable population model. In the literature the difference between these two models is often discussed with the former model chosen for ultimately due to simplicity. Our aims in developing both models is to explore how different are the results on the two models.

Each model is comprised of four compartments: susceptible and infected populations of FSWs and susceptible and infected clients. We assume a movement from susceptible to infected compartments with HIV infection and once and individual is infected becomes infectious. Hence for simplicity we do not account for the latent period of infection. The steady state solutions of both models are used for our analysis. For the first model (constant populations) an analytical solution for the steady state prevalence is possible due to the simplicity of the equations in contrast to the variable population models where numerical solutions are necessary. Parameter values for both models are drawn from the Avahan data set as used in [27].

The goal of our modeling is to explore the importance of two key parameters, the retirement rate and the sexual activity rate on HIV transmission between these two populations. As measures of the level of transmission we will use HIV prevalence in FSWs and clients and their respective R_0. Hence, we will focus on exploring how the number of sexual partners and the retirement rate affect the prevalence ratios and the partial reproduction number ratios. Simultaneously, we want to investigate if these effects are different in the fixed and the variable model.

3.2 Description of Mathematical Model

The general system of differential equations describing the HIV transmission is given below.

$$\frac{dS_c}{dt} = K_c N_c - \lambda_c S_c + (\mu + \delta_c) S_c \tag{3.1}$$

$$\frac{dI_c}{dt} = \lambda_c S_c - (\mu + \gamma + \delta_c) I_c \tag{3.2}$$

$$\frac{dS_{sw}}{dt} = K_{sw} N_{sw} - \lambda_{sw} S_{sw} + (\mu + \delta_{sw}) S_{sw} \tag{3.3}$$

$$\frac{dI_{sw}}{dt} = \lambda_{sw} S_{sw} - (\mu + \gamma + \delta_{sw}) I_{sw} \tag{3.4}$$

The first term of the susceptible compartments, $K_i N_i$, is the influx of individuals which is given by a constant rate, K_i, times the total population for each group N_i, to represent in the case of the variable population model the decrease or increase of incoming individuals due to the increase or decrease of the total population. The second term, $\lambda_i S_i$ is the number of individuals leaving the susceptible compartment due to infection and become infected, hence the negative sign, and is proportional to the total susceptible population. This is the same as the first term in (3.2,3.4), the number of people entering the infected population, from the susceptible population, due to the infection. This term is comprised of the infection rate λ_i times the total susceptible population S_i. The third term in equations (3.1,3.3) is the individuals leaving the susceptible population for reason other than infection, specifically due to retirement or death. A similar term is the second term of the infected population (3.2,3.4) but with the addition of HIV-related mortality rate.

The force of infection for clients and FSW are given by λ_c, λ_{sw}. We account for the force of infection to be proportional to the transmission probability (β_{fm}, β_{fm}) and the rate of sexual activity (C_c, C_{sw}) with respective partners $(I_{sw}/N_{sw}$ for the clients and I_c/N_c for the FSWs).

$$\lambda_c = \beta_{fm} C_c \frac{I_{sw}}{N_{sw}}$$

$$\lambda_{sw} = \beta_{mf} C_{sw} \frac{I_c}{N_c}$$

Additionally let us define for both model $N_c = S_c + I_c$ and $N_{sw} = S_{sw} + I_{sw}$ as the total population of clients and FSWs respectively, equal to the susceptible plus the infected population for each group. Assuming that sexual activity has 1-1 correspondence we have:

$$C_c N_c = C_{sw} N_{sw} \tag{3.5}$$

This equation means that the total number of sexual encounters for clients is equal to the total number of sexual encounters for FSW. From (3.1) let us further define:

$$\rho_c = \frac{C_c}{C_s w} = \frac{N_{sw}}{N_c} \tag{3.6}$$

3.3 Parameter definition and values

Parameter Description	**Symbol**	**Model Value**	**References**
natural death rate	μ	0.02 (50 years)	[1]
HIV related death rate	γ	0.1 (10 years)	[21]
retirement rate for clients	δ_c	0.14 (7.063 years)	[2][30]
retirement rate for FSWs	δ_{sw}	0.17 (5.762 years)	[2][30]
clients sexual activity rate	C_c	24.8 (FSWs per client per year)	[2][30]
FSWs sexual activity rate	C_{sw}	438.48 (clients per FSW per year)	[2][30]
rate of individual entering client susceptible population	K_c	0.16	current paper
rate of individual entering FSW susceptible population	K_{sw}	0.19	current paper
risk of infection from female to male	β_{fm}	0.006	[7][8]
risk of infection from male to female	β_{mf}	0.006	[7][8]

Here, the life expectancy in India has been taken to be 50 year. Furthermore, the influx rates, K_i, in our model are functions of other model parameters so their value is not found in a specific reference.

3.4 Constant Population Model w/ $\gamma << 1$

For the constant population model we take N_i to be time-independent (constant) and we also make a further simplification by assuming that due to treatment the HIV-related mortality rate is negligible and hence part of the natural death rate. The reason is that keeping the HIV mortality rate will introduce and I_i term in the S_i equation changing the nature of the model from an SI(R) to an SIS, since individuals will be entering the susceptible population from the infected population. The ODE system describing our model is as follows:

$$\frac{dS_c}{dt} = K_c N_c - \lambda_c S_c - (\mu + \delta_c) S_c \tag{3.7}$$

$$\frac{dI_c}{dt} = \lambda_c S_c - (\mu + \delta_c) I_c \tag{3.8}$$

$$\frac{dS_{sw}}{dt} = K_{sw} N_{sw} - \lambda_{sw} S_{sw} - (\mu + \delta_{sw}) S_{sw} \tag{3.9}$$

$$\frac{dI_{sw}}{dt} = \lambda_{sw} S_{sw} - (\mu + \delta_{sw}) I_{sw} \tag{3.10}$$

By taking $\frac{dS_i}{dt} + \frac{dI_i}{dt} = 0$ (N_c, N_{sw}) we arrive at $K_i = \mu + \delta_i$.

3.4.1 Non-Dimensionalization of The Model

Non-dimensionalizing the model (3.6)-(3.9) with respect to the population sizes (N_i) admits the prevalence mode. Let us define $X_i = \frac{S_i}{N_i}$ and $Y_i = \frac{I_i}{N_i}$. Then, by dividing the equation for the client and FSW populations by N_c, N_{sw} respectively, we arrive at the system of ODEs, that describes the HIV prevalence in susceptible and infected clients (X_c, Y_c) and susceptible and infected FSWs (X_{sw}, Y_{sw}):

$$\frac{dX_c}{dt} = (\mu + \delta_c) - \beta_{fm} C_c Y_{sw} X_c - (\mu + \delta_c) X_c \tag{3.11}$$

$$\frac{dY_c}{dt} = \beta_{fm} C_c Y_{sw} X_c - (\mu + \delta_c) Y_c \tag{3.12}$$

$$\frac{dX_{sw}}{dt} = (\mu + \delta_{sw}) - \beta_{mf} C_{sw} Y_c X_{sw} - (\mu + \delta_{sw}) X_{sw} \tag{3.13}$$

$$\frac{dY_{sw}}{dt} = \beta_{mf} C_{sw} Y_c X_{sw} - (\mu + \delta_{sw}) Y_{sw} \tag{3.14}$$

Next we analyse this system using steady-state analysis.

3.4.2 Steady-State Solutions

Taking the left hand side of the equations to zero admits the steady state solution for the system and hence the long-time behaviour. When the time derivative is zero we are left we a system of four algebraic equations for four unknowns $(X_c, Y_c, X_{sw}, Y_{sw})$. There are two solutions that can be found analytically. The first is the disease free equilibrium

where $X_c = X_{sw} = 1$ and $Y_c = Y_{sw} = 0$. The second is the endemic equilibrium where the infection has not died out but persists. The endemic steady-state solution is:

$$X_c{}^* = \frac{(\mu + \delta_c)(c_{sw}\beta_{mf} + \mu + \delta_{sw})}{c_{sw}\beta_{mf}(c_c\beta_{fm} + \mu + \delta_c)} \tag{3.15}$$

$$X_{sw}{}^* = \frac{(\mu + \delta_s w)(c_c\beta_{fm} + \mu + \delta_c)}{c_c\beta_{fm}(c_{sw}\beta_{mf} + \mu + \delta_{sw})} \tag{3.16}$$

$$Y_c{}^* = \frac{c_c c_{sw}\beta_{mf}\beta_{fm} - (\mu + \delta_c)(\mu + \delta_{sw})}{c_{sw}\beta_{mf}(c_c\beta_{fm} + \mu + \delta_c)} \tag{3.17}$$

$$Y_{sw}{}^* = \frac{c_c c_{sw}\beta_{mf}\beta_{fm} - (\mu + \delta_c)(\mu + \delta_{sw})}{c_c\beta_{fm}(c_{sw}\beta_{mf} + \mu + \delta_{sw})} \tag{3.18}$$

3.4.3 Prevalence Ratio

Using the endemic steady-state solutions for the infected population prevalence (3.17)-(3.18) and simplifying by taking the transmission probabiliy from males to females, β_{mf}, to be equal to the transmission probability from females to males,β_{fm}, ($\beta_{fm} = \beta_{mf} = \beta$) we can define the ratio of FSWs and clients prevalence:

$$\frac{Y_{sw}}{Y_c} = \frac{C_{sw}(C_c\beta + \mu + \delta_c)}{C_c(C_{sw}\beta + \mu + \delta_{sw})} \tag{3.19}$$

3.4.4 Reproduction and Partial Reproduction Numbers

Applying the methodology used in [37] found in Appendix A, we can define the reproduction number of our compartmental constant population model as:

$$R_0 = \sqrt{\frac{\beta_{mf}\beta_{fm}C_c C_{sw}}{(\mu + \delta_c)(\mu + \delta_{sw})}} \tag{3.20}$$

The reproduction number can also be defined as the square root of the multiplied partial reproduction numbers. The partial reproduction numbers are defined as the number of secondary infections produced in a disease-free compartment when a single infected individual is introduced in different compartment. From (3.20), the partial reproduction numbers are given by:

$$R_0^c = \frac{\beta_{mf}C_c}{\mu + \delta_c} \tag{3.21}$$

$$R_0^{sw} = \frac{\beta_{fm}C_{sw}}{\mu + \delta_{sw}} \tag{3.22}$$

From the above equations for the partial reproduction numbers their ratio is given by:

$$\frac{R_0^{sw}}{R_0^c} = \frac{C_{sw}}{C_c}\frac{\mu+\delta_c}{\mu+\delta_{sw}} \tag{3.23}$$

3.4.5 Description of HIV Prevalence and R_0 In Terms of Sexual Activity and Retirement Rate

Rewritting the infected prevalence with respect to the reproduction numbers we can show that there is a one to one correspondence in the prevalence and partial reproduction number ratios.

$$\begin{aligned} Y_c^* =& \frac{c_c c_{sw}\beta_{mf}\beta_{fm} - (\mu+\delta_c)(\mu+\delta_{sw})}{c_{sw}\beta_{mf}(c_c\beta_{fm}+\mu+\delta_c)} \\ =& \frac{\frac{c_c c_{sw}\beta_{mf}\beta_{fm}}{(\mu+\delta_c)(\mu+\delta_{sw})} - 1}{\frac{c_{sw}\beta_{mf}}{(\mu+\delta_c)(\mu+\delta_{sw})}(c_c\beta_{fm}+\mu+\delta_c)} \\ =& \frac{R_0^2-1}{R_0^{sw}(R_0^c+1)} \end{aligned}$$

Following the same procedure we get an equation for the FSW prevalence wrt to reproduction numbers:

$$Y_{sw}^* = \frac{R_0^2-1}{R_0^c(R_0^{sw}+1)}$$

Hence. the prevalence ratio is equal to:

$$\frac{Y_{sw}}{Y_c} = \frac{R_0^2+R_0^{sw}}{R_0^2+R_0^c} \tag{3.24}$$

This means that $Y_{sw} > Y_c$ or $Y_c > Y_{sw} \iff R_0^{sw} > R_0^c$ or $R_0^c > R_0^{sw}$.

To explore the effect of the key parameters we are investigating (retirement and sexual activity rate) we wanted to know what is the dependence of these ratios on $\rho_c = \frac{C_c}{C_{sw}}$ and $\rho_\delta = \frac{\delta_c}{\delta_{sw}}$. There is no way to write the ratios as functions of ρ_c, ρ_δ so in order to have an indication of what the dependence was we further simplified equations (3.19) and (3.23) by neglecting μ due to the fact that it is an order of magnitude less than the retirement rates (δ) and explored the conditions on these key parameters in order to have the FSW prevalence greater than the client prevalence. Let us first start with the prevalence ratio.

$$\frac{Y_{sw}{}^*}{Y_c{}^*} > 1 \iff \frac{C_{sw}(C_c\beta + \mu + \delta_c)}{C_c(C_{sw}\beta + \mu + \delta_{sw})} > 1$$

$$C_{sw}(C_c\beta + \mu + \delta_c) > C_c(C_{sw}\beta + \mu + \delta_{sw}) \iff$$

$$C_{sw}(\mu + \delta_c) > C_c(\mu + \delta_{sw}) \iff \frac{C_{sw}}{C_c} > \frac{\mu + \delta_{sw}}{\mu + \delta_c}$$

Retirement rates in the current setting are in the order of one over 5-7 years, O(1), in contrast to the natural death rate which is in the order of one over 50 years. Consequently we can ignore it and rewritte the above inequality, using the definition of ρ_c, ρ_δ, as:

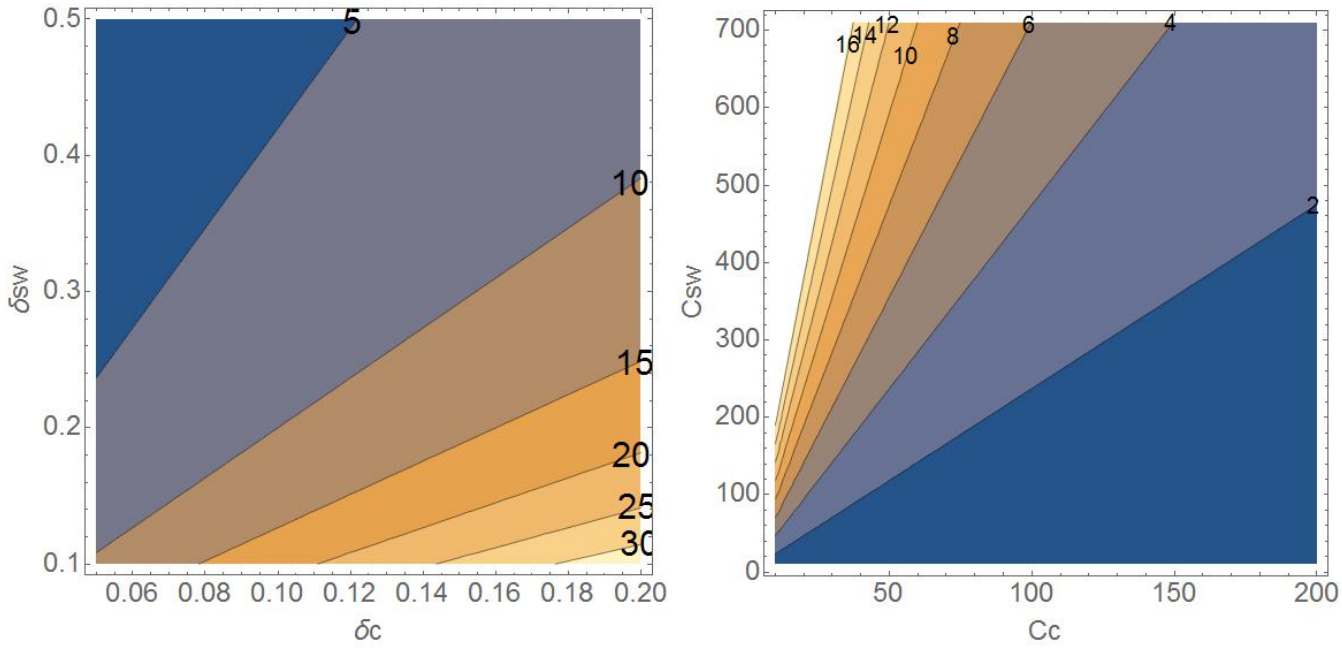
$$Y_{sw}{}^* > Y_c{}^* \tag{3.25}$$
$$\rho_c < \rho_\delta \tag{3.26}$$

The exact same holds for the partial reproduction number ratio, from (3.23), if we neglect the natural death rate. Hence, the FSW prevalence and partial reproduction number is greater than that of the clients if the sexual activity ratio is less than the retirement rate ratio.

$$R_0^{sw} > R_0^c \tag{3.27}$$
$$\rho_c < \rho_\delta \tag{3.28}$$

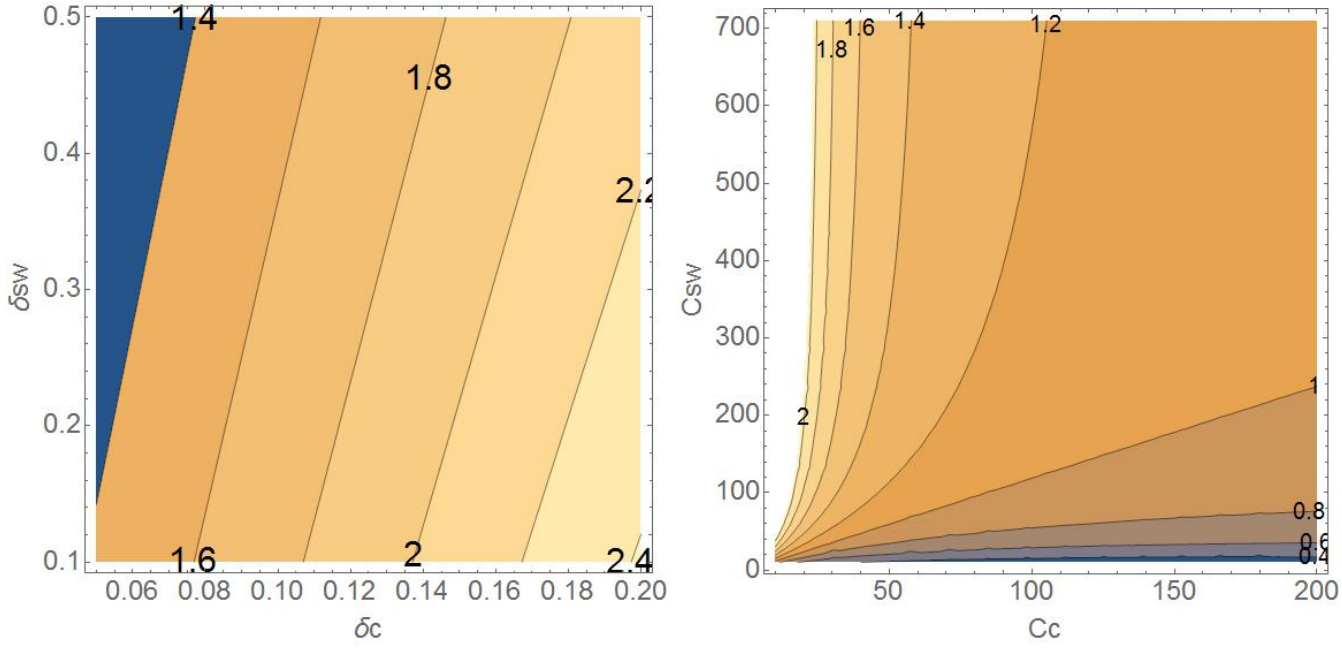
3.4.6 Contour Plots

The results of section 3.4.5 are also supported by the following contour plots in Figure 3.1 and 3.2. Here, we created contour plot of the two ratios for varying sex act rate and constant retirement rate and for varying retirement rate and constant sex act rate. Additionally what they reveal is the type of dependence on the key parameter ratios (ρ_c, ρ_δ)



(a) (b)

Figure 3.1: (a)Contour plot of partial reproduction numbers ratio with respect to δ_c, δ_{sw}, for $\mu = 0.02, \beta = 0.006, C_c = 25, C_{sw} = 438$. (b)Contour plot of partial reproduction numbers ratio with respect to C_c, C_{sw}, for $\mu = 0.02, \beta = 0.006, \delta_c = 0.14, \delta_{sw} = 0.17$.



(a) (b)

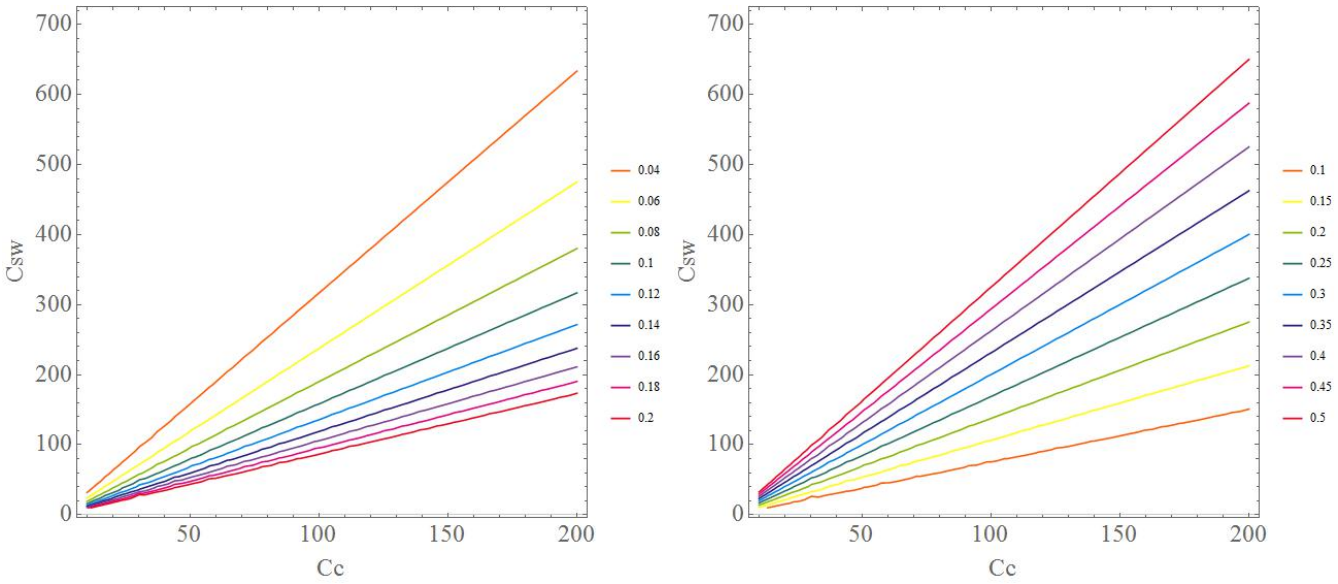
Figure 3.2: (A)Contour plot of prevalence ratio with respect to δ_c, δ_{sw}, for $\mu = 0.02, \beta = 0.006, C_c = 24, C_{sw} = 438$. (B)Contour plot of prevalence ratio with respect to δ_c, δ_{sw}, for $\mu = 0.02, \beta = 0.006, \delta_c = 0.14, \delta_{sw} = 0.17$.

From the contour plots we can see that for both ratios there seems to be a proportional dependence on ρ_δ and an inverse proportionality to ρ_c, since for increasing δ_c or decreasing δ_{sw} the contours get bigger whereas for increasing C_c or decreasing C_{sw} the contours get smaller. This observation can be summarized mathematically as:

$$\frac{d\frac{R_0^{sw}}{R_0^c}}{d\rho_\delta} > 0 \qquad \frac{d\frac{R_0^{sw}}{R_0^c}}{d\rho_c} < 0 \tag{3.29}$$

$$\frac{d\frac{Y_{sw}}{Y_c}}{d\rho_\delta} > 0 \qquad \frac{d\frac{Y_{sw}}{Y_c}}{d\rho_c} < 0 \tag{3.30}$$

Regarding the balance of these ratios, what we usually expect is that the prevalence of FSW is greater than the client prevalence and hence the ratio greater than one and the same holds for the partial reproduction numbers. It is interesting to see if there are realistic parameter values where this balance reverts and how it is affected by the parameters we investigate. To this end we made a contour plot where the ratios are equal to unity with respect to the sexual activity rate and investigated the effect of varying the retirement rate. In the following figures the contour line divides the plot into two parts. The part below the line (right hand corner) represents the region where the ratio is less than 1 whereas the part above the line (left hand corner) represents the parameter region where the ratio is greater than 1. Each line is for a different value of δ_c, δ_{sw} in each plot respectively. What we can see from the plots is that for some values of δ_s the region where $Y_c{}^*$ is greater than $Y_{sw}{}^*$ is unrealistic since the values of the sex act rate, for the two groups, are very close. But with decreasing δ_c or increasing δ_{sw} we enter parameter regions, less than 1, which are more realistic. In addition to these plots in Figure 3.4 we can see clearly the effect of lowering the client retirement rate and increasing the FSW rate. So what we notice is that clients who stay in commercial sex for long periods and FSWs that stay for very short can turn the balance of the ratio.



(a) (b)

Figure 3.3: (A)Contour plot of prevalance ratio equal to 1 with respect to C_c, C_{sw}, for $\mu = 0.02, \beta = 0.006, \delta_{sw} = 0.17$ and different values of δ_c. (B)Contour plot of partial reproduction numbers ratio equal to 1 with respect to C_c, C_{sw}, for $\mu = 0.02, \beta = 0.006, \delta_c = 0.14$ and different values of δ_{sw}

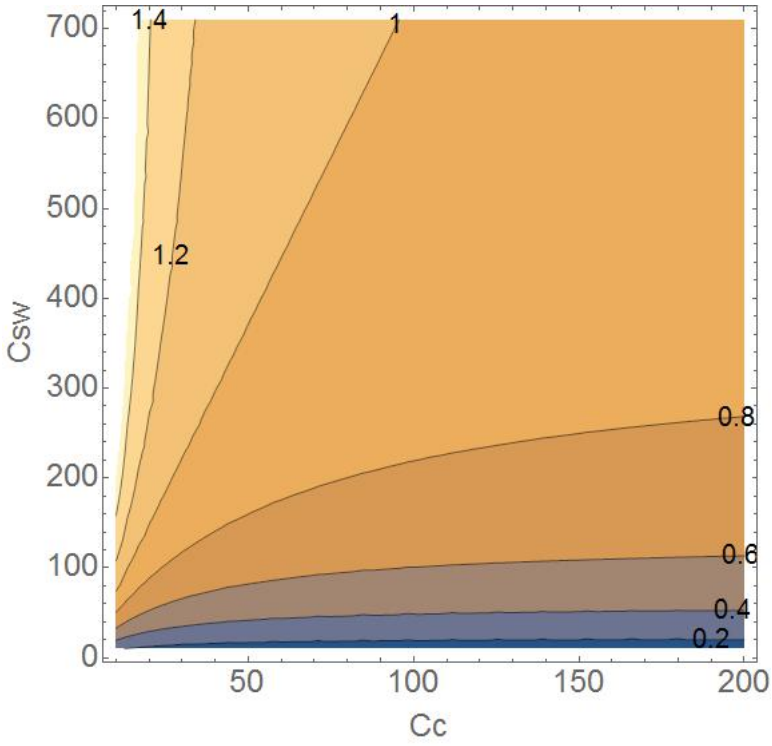


Figure 3.4: Contour plot of prevalence ratio with respect to δ_c, δ_{sw}, for $\mu = 0.02, \beta = 0.006, \delta_c = 0.05, \delta_{sw} = 0.5$.

The graphs for the partial reproduction numbers ratio are exactly the same due to

the correspondence found in sub-section 3.4.5.

In conclusion, we found that the control of the endemic equilibrium prevalence and reproduction numbers lies in the balance of the sexual activities ratio and the retirement rates ratio. Both seem to play a vital role in interchaning the balance between these ratios. It is interesting to see how this result are affected by a variable population model with the inclusion of HIV mortality and that is what we investigate in the next section.

3.5 Variable Population Model

In order to add complexity to our previous model constant population model we conducted the same analysis for a variable population.To make the model more realistic, HIV mortality rate was included in the equations and the ODE system describing it is given by (3.1-3.4).

Let us define X_i, Y_i as before. For the case of the variable population, $N_i = N_i(t)$ and hence $S'(t) = X'(t)N(t) + X(t)N'(t)$. Something similar holds for I(t). Furthermore, $\frac{d(S+I)}{dt} = \frac{dN}{dt}$. From these two equations, we derive the non-dimensionalized model.

$$\frac{dX_c}{dt} = K_c - \lambda_c X_c - K_c X_c + \gamma Y_c X_c \tag{3.31}$$

$$\frac{dY_c}{dt} = \lambda_c X_c + \gamma Y_c^2 - (\gamma + K_c) Y_c \tag{3.32}$$

$$\frac{dX_{sw}}{dt} = K_{sw} - \lambda_{sw} X_{sw} - K_{sw} X_{sw} + \gamma Y_{sw} X_{sw} \tag{3.33}$$

$$\frac{dY_{sw}}{dt} = \lambda_{sw} X_{sw} + \gamma Y_{sw}^2 - (\gamma + K_{sw}) Y_{sw} \tag{3.34}$$

The reproduction number for the variable model is calculated in the Appendix A and is given by:

$$R_0 = \sqrt{\frac{\beta^2 C_c C_{sw}}{(\gamma + \mu + \delta_c)(\gamma + \mu + \delta_{sw})}} \tag{3.35}$$

The partial reproduction numbers are $R_0^c = \frac{\beta C_c}{\gamma+\mu+\delta_c}, R_0^{sw} = \frac{\beta C_{sw}}{\gamma+\mu+\delta_{sw}}$, with their ratio being:

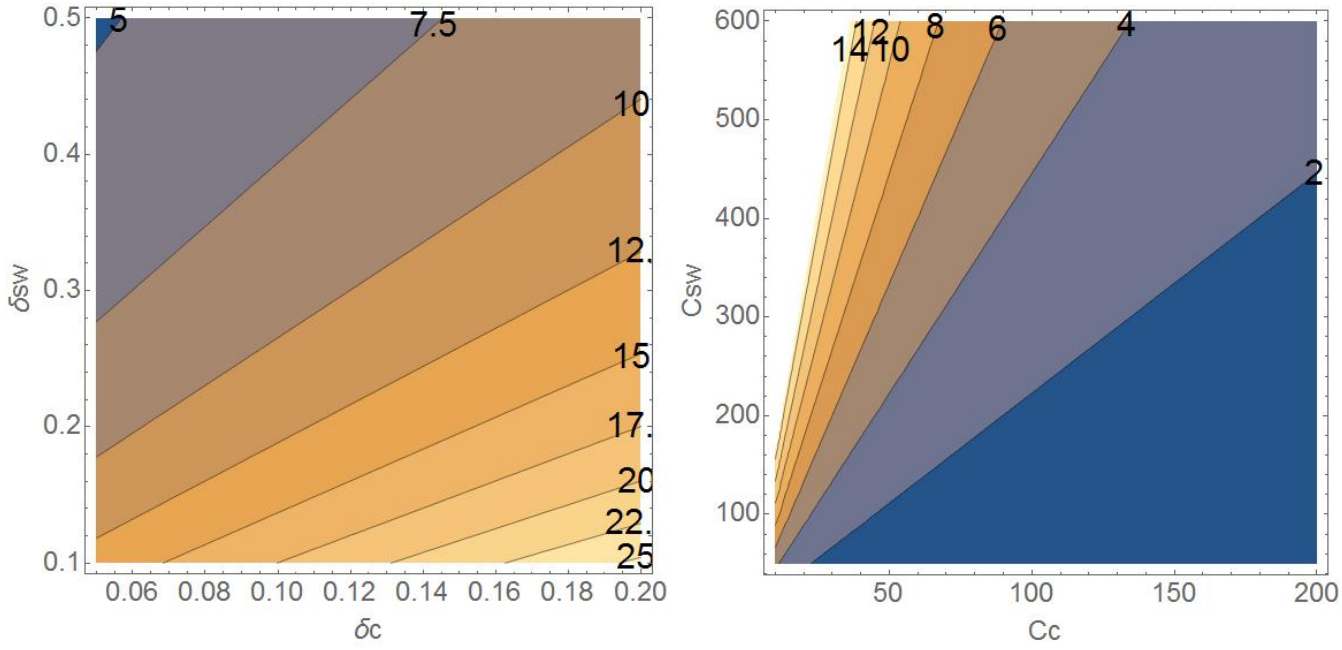
$$\frac{R_0^{sw}}{R_0^c} = \frac{1}{\rho_c} \frac{\gamma + \mu + \delta_c}{\gamma + \mu + \delta_{sw}} \tag{3.36}$$

Comparing (3.36) with (3.23) we can see that the only difference is the HIV-mortality rate γ. If we assume small HIV mortality rate, due to treatment, and again neglect the natural death rate, μ, being an order of magnitute smaller than the retirement rate we

arrive at the same dependency of the partial reproduction number ratio on ρ_c, ρ_δ, as for the constant population model. This cannot be done for the prevalence ratio but we can infer from the constant population model results that there might be an one to one correspondence between the two ratios in the variable model as well as and so something similar to (3.25)-(3.26).

Due to the complexity of the problem the steady-state analysis yields 16 different solutions. One of these is the disease-free equilibrium and the rest correspond to the endemic. Only one of the solutions gives realistic values since most of them give either negative solution or larger than one. A numerical simulation was also conducted for the full system (ODEs) showing that there is indeed a single endemic equilibrium independent of initial conditions. An analytical solution for the steady state was impossible due to the fact that the algebraic equations had strong non-linearities. Consequently, the steady-state solution was found numerically.

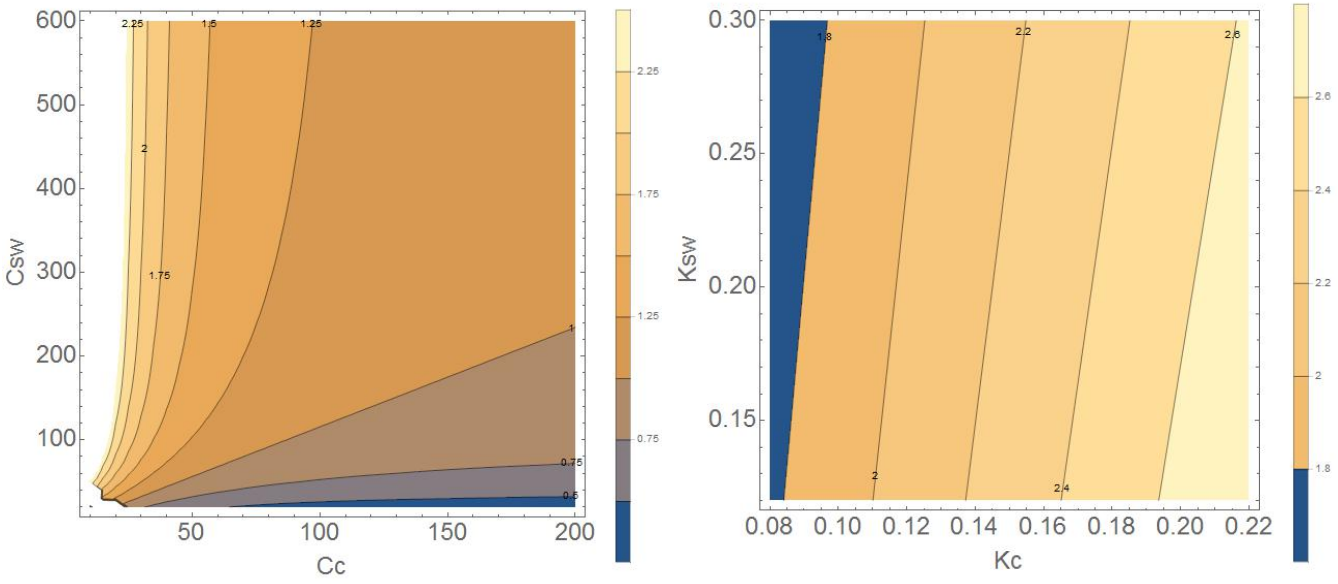
To compare this model with the previous, constant population, one we created the same contour plots to check the dependence of this model on the key parameters being investigated. In Figure 3.5 we see the contour plots of the partial reproduction numbers ratio with respect to the sexual act rates and the retirement rates the two plots respectively. The similarity with the constant population model, on the dependence in these parameters, is evident. Again, here there seems to be an inverse proportionality to ρ_c and a proportional dependence on ρ_δ.



(a) (b)

Figure 3.5: (A)Contour plot of partial reproduction numbers ratio with respect to C_c, C_{sw}, for $\mu = 0.02, \beta = 0.006, \delta_c = 0.14, \delta_{sw} = 0.17$. (B)Contour plot ofpartial reproduction numbers ratio with respect to δ_c, δ_{sw}, for $\mu = 0.02, \beta = 0.006, C_c = 24.8, C_{sw} = 438$.

Using numerical simulation we also created the contour plots for the endemic steady-state prevalence ratio, $\frac{Y_{sw}{}^*}{Y_c{}^*}$. As with the partial reproduction numbers ratio we see the similarity with the constant population model and the same dependencies. The difference is that the non-dimensionalized model for the variable population has no explicit dependence on the retirement rates and hence the prevalence also has no dependence. The only dependence can come from K_i if we assume that it is a function of δ_i. For the following plot we have assumed that $K_i = \mu + \delta_i$.



(a) (b)

Figure 3.6: (A)Contour plot of prevalence ratio with respect to c_c, c_{sw}, for $\mu = 0.02, \beta = 0.006, K_c = 0.16, K_{sw} = 0.19$. (B)Contour plot of prevalence ratio with respect to K_c, K_{sw}, for $\mu = 0.02, \beta = 0.006, C_c = 24.8, C_{sw} = 438$.

To conclude, comparing these plots with the constant population models we see that there is a clear similarity in the effect of the sexual activity and retirement rates on the two ratios. So assuming that the influx of individuals and variable population sizes seem not to affect the results, it is the balance between retirement rate and number of sexual partners that drive the HIV prevalence and whether the endemic HIV infection occurs.

3.6 Results

We examined the effect of sexual act rate and retirement rate (motility) of clients and FSWs on the HIV prevalence and Ro in commercial sex settings. Our results indicate that both parameters play an important role in the balance between the prevalence of both groups and as a result in identifying the group with the higher risk.

What is normally expected is that FSW are the main risk group and hence interventions tend to target that particular group, but this can turn out to be ineffective if

there is a low retirement rata for clients and in addition a high for FSW. The shorter FSW stay in that setting the lower the risk of getting infected is despite having a larger number of sexual acts per year and the longer clients stay the higher are the chances of infection. This effect is enhanced when the difference in the sex act rate or alternatively the difference in the relative populations (balance equation) is not large. In our current setting (South India) the difference is large since Cc= 24.8 whereas Csw= 438.48, but for different setting it might not be the case. To conclude, our modeling points towards the fact that the retirement and sexual activity rates play a vital role since they affect steady-state prevalence and highlight different groups as the main target of interventions and consequently they are key for understanding and preventing HIV transmission.

3.7 Discussion

In this project we have focused on using mathematical modeling and analytical studies to explore the key factors that drive the changes in HIV prevalence and basic reproduction number R_0 in settings where HIV epidemics is concentrated. In such settings most HIV transmission occurs amongst high-risk population groups such as FSWs and their clients, MSM or IDUs whereas the general population has HIV prevalence less than 1%. India has one of the worlds most concentrated HIV epidemics and here the Avahan HIV prevention intervention has been ongoing since 2003 funded by the Bill and Melinda Gates Foundation.

Our focus in this project has been the HIV transmission between FSWs and their clients. With the collated knowledge of previous modeling reviewed in Chapter 2, we formulated a new deterministic model as a system of ODEs to describe the key components of this HIV transmission. Two variations of the model were explored: one when the FSWs and clients population remains constant and one which accounts for influx of new individual in these populations groups (variable population model). The decision of whether a constant or variable model is to be used in modeling HIV transmission is a complex one and each model has its own advantages.

The constant model is obviously simpler and as evident from our analysis can be solved analytically to capture the long-time steady state solutions. In the case of the variable model this is not plausible, and instead the stead-state solutions need to be derived numerically. The reason why we looked at these two models in parallel was to see if the overall conclusions are different. Our conclusions in Chapter 3 suggest that indeed the results remain the same for the two models. We note that this is in line with the conclusions of the work by Panovska-Griffiths et al [27], where incorporating a variable population instead of constant did not affect the overall results of the modeling study. We note however that our analysis is limited in its simplicity and therefore further analytically and numerical studies are needed to fully discuss the difference between constant and variable population models. This was not within the scope of this project and therefore was not discussed here.

The aim of our project was instead to use steady state analysis of the model to ex-

plicitly study the importance of two key transmission parameters: the retirement rates and the sexual activity rates of FSWs and clients on HIV transmission between these two populations. As measures of the level of transmission we used HIV prevalence in FSWs and clients and their respective R_0. Simultaneously, we explored if these effects are different in the fixed and the variable model.

Our results (3.25-3.28) suggest that it is the balance between the number of sexual partners and their retirement rates that drives the increase in HIV prevalence and reproduction number. For example, using the (3.25-3.27) we can see for the FSW prevalence and partial reproduction number to be greater than that of the clients their sexual activity ratio has to be less than the retirement rate ratio. This is also supported by contour plots in Figure 3.1 and 3.2. Furthermore from these expressions we notice that clients who stay in commercial sex for long periods and FSWs that stay for very short can turn the balance of the ratio of reproduction numbers and prevalence and hence drive the HIV transmission.

In summary the work presented here represents a step towards better understanding of the key drivers of HIV transmission between FSWs and their clients. Specifically our results show that the effect from sexual activity and retirement rates are analogous on HIV prevalence and reproduction number in FSWs and clients: if the former increases so will the latter. Furthermore it is the balance between sexual activity and retirement rate seems to drive the increase in these two variables. Numerical simulations of the model equations were beyond the scope of this project and hence were not included. The next natural step in this work would be to numerically solve the two systems of equations and explore how the dynamical behavior changes and if the influence from sexual activity and retirement rates on HIV prevalence remains the same.

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Appendix A

Reproduction Number For Compartmental Models

R_0 as mentioned in the introduction is defined as the average number of secondary infection produced from an infected individual when entering a disease-free environment. This definition is clear for single population models and R_0 is generally given by the contact rate times the infectious period or death-adjusted infectious period, depending on the model [17]. Hence, it is usually given by the simple formula:

$$R_0 = \frac{\beta c}{\gamma + \mu} \tag{A.1}$$

Here, βc is infection probability times sexual activity rate so effectively an average number of infective contacts and $\gamma+\mu$ is the mortality rate plus the HIV related mortality rate.

The situation is more complicated for models where there is more than one compartments. For these models a more general definition is appropriate where R_0 is defined as the number of new infections produced by a typical infective individual in a population at a disease free equilibrium [37].Van den Driessche and Watmough [37] addressed this problem and proposed a general method for calculating R_0 for compartmental models. Their method was used to derive the reproduction number for our models (constant and variable). Here we derive R_0 for the variable population model. The same method is used to derive it for the constant population model as well.

First let us define $\mathcal{F}_i$ as the rate of new infections for compartment i and $\mathcal{V}_i$ the transfer of individuals from compartment i by means other than infection. For our variable population model there are four compartments, the susceptible client and female sex workers and the infected.

$$
\begin{aligned}
\frac{dS_c}{dt} =& K_c N_c - \beta_{fm} C_c \frac{I_{sw}}{N_{sw}} S_c + (\mu + \delta_c) S_c \\
\frac{dI_c}{dt} =& \beta_{fm} C_c \frac{I_{sw}}{N_{sw}} S_c - (\mu + \gamma + \delta_c) I_c \\
\frac{dS_{sw}}{dt} =& K_{sw} N_{sw} - \beta_{mf} C_{sw} \frac{I_c}{N_c} S_{sw} + (\mu + \delta_{sw}) S_{sw} \\
\frac{dI_{sw}}{dt} =& \beta_{mf} C_{sw} \frac{I_c}{N_c} S_{sw} - (\mu + \gamma + \delta_{sw}) I_{sw}
\end{aligned}
$$

From the above definitions we have:

$$
\mathcal{F} = \begin{pmatrix} 0 \\ \beta_{fm} C_c \frac{I_{sw}}{N_{sw}} S_c \\ 0 \\ \beta_{mf} C_{sw} \frac{I_c}{N_c} S_{sw} \end{pmatrix}
$$

$$
\mathcal{V} = \begin{pmatrix} -K_c N_c + \beta_{fm} C_c \frac{I_{sw}}{N_{sw}} S_c - (\mu + \delta_c) S_c \\ (\mu + \gamma + \delta_c) I_c \\ -K_{sw} N_{sw} + \beta_{mf} C_{sw} \frac{I_c}{N_c} S_{sw} - (\mu + \delta_{sw}) S_{sw} \\ (\mu + \gamma + \delta_{sw}) I_{sw} \end{pmatrix}
$$

To proceed let us also define F and V, where $F = \frac{\partial \mathcal{F}_i}{\partial x_j}(x_0)$ and $F = \frac{\partial \mathcal{V}_i}{\partial x_j}(x_0)$. Only the infected compartments are taken into account for this calculation, so {i,j,k}=I_c, I_{sw}. x_0 is the value of the population in each compartment at the disease free equilibrium, so in this case $x_0 = (1, 0, 1, 0)$. From these formulas we can see that the {i,j} component of F gives the rate at which infected individuals from compartment j produce new infections in compartment i and the {j,k} component of V^{-1} gives the time an individual from compartment k spends at compartment j. Hence, FV^{-1} admits the average number of new infections in compartment i produced by an individual introduced in compartment k. This is called the next generation matrix [37] and its spectral radius gives R_0 for the system. In our particular model F and V are:

$$
F = \begin{pmatrix} 0 & \beta_{fm} C_c \\ \beta_{mf} C_{sw} & 0 \end{pmatrix}
$$

$$
V = \begin{pmatrix} (\mu + \gamma + \delta_c) & 0 \\ 0 & (\mu + \gamma + \delta_{sw}) \end{pmatrix}
$$

FV^{-1} is then given by:

$$FV^{-1} = \begin{pmatrix} 0 & \frac{\beta_{fm} C_c}{(\mu+\gamma+\delta_{sw})} & 0 \\ \frac{\beta_{mf} C_{sw}}{(\mu+\gamma+\delta_c)} & 0 & \end{pmatrix}$$

This matrix admits a double eigenvalue and its square root gives the spectral radius and hence the reproduction number:

$$R_0 = \sqrt{\frac{\beta_{mf}\beta_{fm} C_c C_{sw}}{(\gamma+\mu+\delta_c)(\gamma+\mu+\delta_{sw})}}$$

Following the exact same procedure we can find the reproduction number for the constant population model defined as:

$$R_0 = \sqrt{\frac{\beta_{mf}\beta_{fm} C_c C_{sw}}{(\mu+\delta_c)(\mu+\delta_{sw})}}$$