Pair Formation and Disease Dynamics:
Modeling HIV and HCV Among Injection Drug Users in Victoria, BC

by

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B.Sc., University of Victoria, 2007
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ABSTRACT

New survey data indicate that injection drug users (IDU) in Victoria, BC who share syringes do so with a single person. These partnerships pose an obvious health risk to IDU, as blood borne illnesses are transmitted through the sharing of injection equipment. Here we formulate an ordinary differential equation (ODE) model of pair formation and separation. Susceptible-infectious (SI) disease dynamics are built into this model so as to describe the syringe-mediated transmission of human immune deficiency virus (HIV) and hepatitis C virus (HCV) among IDU. We utilize a novel parameter estimation approach, and fit the distribution of partnership durations observed in Victoria. The basic reproduction number is derived, and its qualitative behavior explored with both analytical and numerical techniques.

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Chapter 1

Introduction

The goal of this thesis is to explore newly collected syringe-sharing data, and to develop pertinent mathematical models to describe the injection-mediated transmission of human immune deficiency virus (HIV) and hepatitis C virus (HCV) among injection drug users (IDU) who share syringes in Victoria, BC. These types of models can be used by public health authorities to evaluate potential public health actions, inform efficient allocation of resources, and reduce the harm to persons at risk of HIV and HCV infection.

Recent Canadian public health reports indicate that the prevalence of both HIV and HCV among IDU are higher in Victoria, BC than national averages. In 2004 the HIV prevalence among Victoria IDU was estimated to be 16.0%, much higher than the national (averaged across Victoria, Regina, Toronto, and Sudbury) estimated prevalence of 8.1% [2]. Similarly, the HCV prevalence among Victoria IDU at that time was estimated to be 79.3%, whereas the national level was estimated as 63.8%. In 2006 HIV and HCV levels (15.4% and 68.5%, respectively) observed among Victoria IDU were above the corresponding national (averaged across Victoria, Edmonton, Quebec City (including Ottawa), Regina, Toronto, Sudbury, and Winnipeg) levels of

13.2% (HIV) and 65.7% (HIV).

In an effort to identify risk factors particular to Victoria IDU that could be contributing to increased HIV/HCV transmission and prevalence, a survey of IDU, involving interviews and questionnaires, was conducted at Victoria's AIDS Vancouver Island Street Outreach Services (AVI-SOS) needle exchange in May and June of 2008.

A transdisciplinary research team involving public health service providers, mathematicians, statisticians and anthropologists designed the questionnaire and administered the interviews. The goal of the survey was to begin a dialogue about reducing harm to IDU, and to identify what risk factors are present specifically for Victoria IDU that may be contributing to increased rates of HIV and HCV .

A large percentage of people interviewed live in poverty and face marginalization on multiple other fronts, such as access to health resources. Prevention of transmission can improve their wellness and safety. Reducing the HIV and HCV transmission risk of IDU in Victoria is crucial to maintaining public health and reducing harm to vulnerable individuals.

Both HIV and HCV are blood-borne infections: they are easily transmitted via syringe-sharing. To address this, portions of the questionnaire focused on equipment sharing practices. Did the interviewee share syringes? With whom? How long had that relationship been going on? The data indicate that Victoria IDU who share syringes do so in pairs, not groups, and the partners are trusted individuals rather than strangers or acquaintances.

The partnership and disease dynamics of syringe-sharing pairs of individuals are the focus of the mathematical models developed in this thesis. How do these pairs form? When do they separate? What is the disease history of HIV or HCV under this epidemic framework? Existing work in partnership and disease modeling tends to focus on sexual transmission and heteronormative pair dynamics (female-male pairs

only). Our new survey data indicate that this is not a detailed enough arena in which to approach the modeling of pair formation and disease dynamics among Victoria IDU. There is a need to investigate sex and pair-type specific population models.

We use differential equations to model the evolution of population categories such as infectious single females, susceptible males paired with males, and susceptible males paired with females. The per-person pair formation rate, the per-pair separation rate, and the disease transmission parameter are the focus of public health strategies suggested by this thesis. These parameters are reasonably accessible through public health actions such as education campaigns and syringe distribution, and it would seem that each should have a role in determining the risk of infection.

A new statistical method is developed and employed to estimate the pairing dynamics model parameters from the available categorical syringe-sharing pair data. The possible ranges of these parameters were unknown prior to this work. Analysis of the disease dynamics within these novel bounds indicate that the pair formation and separation rates, and the disease transmission parameter significantly affect the disease progression.

Thesis Overview

Chapter 2 presents the objectives, design, results, and analysis of the IDU survey at AVI-SOS. Existing mathematical models of partnership and disease dynamics are introduced and discussed.

Chapter 3 presents the pairing model and related parameter estimates. It includes the methods and results of a likelihood approach to model fitting.

Chapter 4 presents the pairing and disease model and its analysis. The next generation matrix and basic reproduction number are derived; the parameter dependence of the basic reproduction number is explored.

Chapter 5 summarizes the results and contributions of the thesis; potential applications and future research avenues are listed.

Chapter 2

Preliminary Data and Existing Models

In this chapter we present the objectives and outcomes of the surveys administered at AVI-SOS. We introduce existing mathematical models of syringe-sharing and disease transmission, and discuss why a novel model is needed to address HIV and HCV transmission among IDU in Victoria, BC.

2.1 Syringe Sharing in Victoria, British Columbia

2.1.1 IDU Interviews and Questionnaire

Objectives

The survey was designed to identify and explore the HIV/HCV transmission risk factors experienced by each interviewee. Data were collected during the interview to allow researchers the opportunity to address the question of why Victoria features relatively high rates of HIV and HCV among IDU, and to identify avenues to reduce transmission of these viruses in this population.

Design

Interviews were structured according to a questionnaire; ethics approval was granted by the University of Victoria Human Research Ethics Board. The questionnaire was designed in collaboration with members of the transdisciplinary injection drug risk research group, and clients of AVI-SOS. The format was edited in consultation with the interviewers and a small group of interviewees. The final questionnaire structure covered basic demographics including sex and age, as well as HIV/HCV risk factors such as housing stability, substance use and history, and personal transmission-risk networks (acquaintances with a sexual or drug-related basis). Syringe-sharing variables were a part of the individual's personal risk network: participants were asked to construct an egocentric network of drug-using contacts with an interview script such as the following

> ... think of up to five individuals with whom you have used drugs in the last six months. We do not want to know their names. What is the sex of the first individual? How long have you known this person? What is their relationship to you? In the last six months, have you had sex with this person? Shared syringes with this person? Do you ever inject them, or ask them to inject you? Do you share other drug paraphenalia with this person? If yes, what types?

Recruitment and Sampling

Participants were recruited by needle exchange personnel through posters and word of mouth; eligibility requirements stated that an individual had injected drugs in the six months prior to the survey date, and that they were 18 years of age or older. Interviewers were members of the transdisciplinary research team. Completion of the interview and questionnaire was voluntary - participants were able to leave at any

time or to omit sections of the survey as they wished - and all individuals were given twenty dollars and a snack as compensation for their time.

2.1.2 Statistical Methods

All analyses were performed with R 2.9.0 (R Foundation for Statistical Computing, 2009).

The simple logistic regression (SLR) model $Y \sim X$ describes the predicted odds of an event Y, dependent on the variable X as

$$\log(\text{odds } y) = \beta_0 + \beta_1 x.$$

In practice, this is utilized to estimate the rate e^{β_1} at which the odds of outcome Y change when a binary condition X is present. For example, let Y denote the event that person B is a sex partner of person A, and let X denote the event person B shares syringes with person A; suppose SLR analysis produces a statistically significant coefficient $\beta_1 = 2$. From this, we infer that if person B does share syringes with person A, it is $e^2 \approx 7$ times more likely than not that they are also sex partners.

2.1.3 Results

A total of 105 IDU participated in the survey; $N = 90$ questionnaires were deemed reliable and usable. Table 2.1 summarizes the descriptive statistics obtained from these questionnaires. Table 2.2 lists the results of statistical analyses.

Descriptive Statistics

The majority of persons interviewed were male (70%), and had engaged in nonspecific equipment (syringes, pipes, cooking spoons, etc.) sharing in the six months prior to

Table 2.1: Summary results of IDU survey ($N = 90$) completed at AVI-SOS needle exchange, Victoria, BC, May-June 2008. Nonspecific sharing includes sharing of syringes, pipes, cooking spoons, and other drug paraphernalia. In rows 2-7, percentages are given with respect to the number of observations in row 1 (e.g. 8/27=30% of women had shared syringes).

Characteristic	Overall Freq. (%)	Female (%)	Males (%)
Gender	90	27	63
Nonspecific equipment sharing	66 (73)	21 (77)	45 (68)
Shared syringes	19 (21)	8 (30)	11 (24)
Injector	40 (44)	16 (59)	24 (53)
Shared syringes as Injector	17 (19)	7 (26)	10 (16)
Injectee	30 (30)	11 (41)	16 (36)
Shared syringes as Injectee	10 (11)	6 (22)	4 (6)

being surveyed (73%). Syringe sharing was less frequently reported (21%). Forty-four percent of persons reported acting as an injector (assisted someone else with injection), and 30% had been an injectee (obtained help injecting from another person). The raw data indicate that 52% of people reported acting as an injector or injectee with a personal risk-network member, however only 38% of these individuals also shared syringes with that network member.

Chi-square Analyses and Logistic Regression

Table 2.2: Simple logistic regression (SLR) results. $Y \sim X$ corresponds to $\log(\text{odds } y) = \beta_0 + \beta_1 x$. Let P denote a reported member of an IDU personal risk network.

Model	β_1	s.e.(β_1)	p-value	e^{β_1}
P is injector or injectee $\sim$ share syringes with P	3.04	1.40	0.00356	20.9
P is sex partner $\sim$ share syringes with P	2.63	0.56	<0.0001	13.9
female $\sim$ share syringes with a sex partner	1.68	0.65	0.01	5.4

Sharing syringes with an individual is not independent of the existence of an injector/injectee relationship ($\chi^2_{138,1}$=13.5934, p=0.00027). All eight women who reported sharing syringes did so as an injectee (6/8) or injector (7/8); most (10/11) of the eleven men who shared syringes did so as an injectee (4/11) or injector (10/11). Sim-

ple logistic regression indicates that if syringes were shared, it is 21 times more likely to have been as an injector or injectee (SLR coeff.=3.0419, p=0.00356).

Sexual relationships are also not independent of syringe sharing ($\chi^2_{138,1}$=26.2297, p<0.0001). Where syringes were shared, it was 14 times more likely to have been with a sex partner (SLR coeff.=2.6301, p<0.0001). In cases where syringes were shared with a sex partner, it is five times more likely to have been as a female (SLR coeff.=1.6788, p=0.0109). Of the women who shared syringes, most (88%) did so with a sex partner.

The size of personal risk network reported (mean=1.567, var=1.256) differed significantly from the number of syringe sharing partners within that network (mean=1.000, var=0.000). Although people who shared nonspecific equipment did so with a number of individuals (mean=1.636, var=0.685), syringes in particular were shared with only one member of an IDU personal risk network.

Summary

The results of the IDU survey conducted in Victoria indicate that syringe-sharing is a behavior undertaken with a single trusted partner: persons who share syringes do so in pairs, not groups. Furthermore, men and women have different pairing patterns. Women who share syringes are likely to do so with a male sex partner. Men, however, may have either a female or a male syringe sharing partner, and the existence of a sharing relationship is not a significant predictor of a sexual relationship.

Mathematical modeling can be used to further explore the dynamics of syringe sharing relationships in Victoria, and their interaction with the transmission of HIV and HCV among IDU. By creating a model which reflects population-specific behaviors such as male-male and male-female pairing we may investigate potential public health routes for reducing risk among Victoria IDU.

2.2 Mathematical Epidemiology

Mathematical descriptions of disease may model incidence (new cases), prevalence (current cases), or final size (total cases) of an epidemic. A realistic model has some predictive value, but the best use of mathematical disease models is as an experimental ground for proposed or possible public health actions. Where a real-life experiment with syringe sharing, for example, would be unethical, mathematics can be used to compare the qualitative behavior of a disease under various sharing scenarios.

2.2.1 Compartmental HIV/HCV Disease Modeling

Infection of individuals and the resulting population disease dynamics are often modeled by dividing the population into compartments, specified in relation to infection status, and describing these with a system of ordinary differential equations (ODEs). The susceptible-infectious-recovered (SIR) model is the basis for this class of models.

Formulated by Kermack and McKendrick in 1927 [13], the SIR model describes a disease history which sees susceptible individuals become infectious through interactions with the existing infectious class, and infectious individuals being removed (through death, or recovery and subsequent immunity) from the population. This acurately represents the progression of illnesses such as chickenpox or measles, which impart lifelong immunity upon recovered individuals. Figure 2.1 shows the flow of a normalized simple SIR model in which infectious individuals recover at constant rate γ, and there is no death.

The rate of transmission - the rate that susceptibles move into the infectious class - was originally described by a mass action term of the form βSI, where β is a positive transmission parameter, and S and I denote the population proportions of susceptible and infectious individuals, respectively. Mass action is a chemistry law

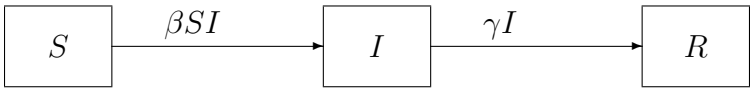

Figure 2.1: Compartmental flow of a simple SIR model. S, I, and R are the population proportions of susceptible, infectious, and recovered or removed individuals, respectively.

that states the rate of interactions between two well-mixed populations of randomly interacting particles is proportional to the product of the sizes of the populations. If we assume that susceptible and infectious persons are well-mixed and meet one another randomly, the rate that they contact one another is proportional to SI. The transmission parameter β is then related to the "success" of this contact: is the susceptible person infected as a result of meeting the infectious person? The dynamics of the SIR disease model in this basic case are given by the system of ODEs

$$\begin{aligned} S'(t) &= -\beta SI \\ I'(t) &= \beta SI - \gamma I \\ R'(t) &= \gamma I, \end{aligned}$$

with nonnegative initial conditions $S(0), I(0)$, and $R(0)$.

Once infected, some individuals with HIV or HCV will experience a drop in viral load to undetectable levels; effectively, this represents recovery from illness (*i.e.*, movement into the recovered class of the population). Usually, however, these diseases are considered lifelong (without recovery), hence a susceptible-infectious (SI) type compartmental model is more often employed to describe their dynamics. So-called stage models, involving multiple infectious classes (e.g. I_1, I_2) that differ from each other

in transmission or risk of death are often used in the modeling of HIV or HCV. Other context-specific details, such as syringe sharing risk categories, can also be woven into the basic model framework through the use of additional compartments.

2.2.2 Syringe-sharing Models

Vector Models

The first mathematical model to explicitly describe syringe sharing and SI infection dynamics [11] considered needles as transmission vectors, a role similar to that of mosquitos in the progression of malaria. This model and related works [19, 6] give needles their own life dynamics, essentially allowing them to interact randomly with human users.

It is assumed that all IDU use shooting galleries (places where drugs are bought and consumed, and syringes are shared); every injection act is thus assumed to involve a shared syringe. The rate that individuals share syringes is determined by the average rate of visitation to shooting galleries, the number of shooting galleries, and the number of syringes available in a particular gallery. Susceptible individuals using an infectious syringe become infectious themselves with probability α; a syringe is assumed infectious after use by an infectious individual.

Differential equations model the evolution of both the population proportion of infected IDU (I), and the probability that a syringe being used at time t by an IDU is infectious (β); $S = 1 - I$ represents the susceptible proportion of IDU.

The per-IDU rate of injecting (*i.e.*, sharing) is λ; the total rate of injecting by all IDU is γ. The term $\lambda\alpha\beta$ describes the rate that infectious syringes transmit to the individual using them. Assuming infectious persons are removed at the constant rate σ, we have

$$I'(t) = \lambda\alpha\beta S - \sigma I.$$

Syringes are assumed to remain infectious unless they are "flushed" by the blood of a susceptible user; this flushing occurs with probability θ each time a susceptible uses an infectious syringe. The term $[1-S(1-\theta)]$ is the probability that an infectious syringe being used (which occurs at overall rate $\gamma\beta$) is not flushed by the blood of a susceptible IDU. The dynamics of β, the probability that a syringe being used at time t is infectious, are given by

$$\beta'(t) = \gamma I - \gamma\beta[1 - S(1-\theta)].$$

The major problem with this "needles as vectors" view, however, is that needles don't have their own lives - they are attached to, or exchanged among owners. While humans can indeed seek out injecting equipment, the reverse is not true.

Compartmental Syringe-sharing Models

Models of syringe sharing based on traditional SI- or SIR-type compartmental models [3, 10, 17] do not consider needles explicitly, but typically use parameters to describe the per person rate of sharing, and the per sharing act probability of an individual becoming infected.

To illustrate this type of model, let S and I denote the population proportions of susceptible and infectious individuals, respectively, and denote the per-person rate of sharing with infectious partners by $\lambda = \lambda(S, I)$. The dynamics of I are then given by

$$I'(t) = \lambda\beta S$$

where β is the per-act probability of transmission via syringe-sharing.

Such models can incorporate a great deal of heterogeneity; for example, Blower et al. [3] model sexual, vertical (mother to child), and injection-mediated transmis-

sion of HIV in a population categorized into gender-, sexual-, and drug-specific risk groups. The resulting 34 differential equations are capable of capturing many important aspects of HIV dynamics in this population, but, as the authors conclude, a number of parameters are not well understood or estimated. The per-partnership probability of transmission, for example, is simply not an accessible quantity.

Sharing Group Models

Another problematic feature of compartmental models of syringe sharing is their implicit assumption of random mixing, either within or between categories. Sharing of injection equipment is not often random, it usually occurs within small and familiar groups - sharing with strangers is rare [8]. Several models [20, 25, 18] represent the size of such groups, and the frequency with which individuals participate in them, and calculate resulting probabilities of infection for given individual IDUs.

Consider the general case that the rate of participating in a syringe-sharing group is λ. Let n be the expected size of such a sharing group; n may depend on social norms, availability of equipment, and other context-specific variables. The dynamics of the infectious proportion of the population are given by

$$I'(t) = \lambda \beta I$$

where $\beta = \beta(n, I)$ is the per-act probability of transmission to a particular IDU during an episode of group sharing.

Each episode of sharing is explicitly modeled, rather than the average rate of sharing an individual experiences, eliminating the need for several awkward parameters found in compartmental models. These formulations utilize random group composition, however, so sharing still effectively occurs with random strangers.

Computer Simulation Models

Stochastic simulations of individual based syringe sharing models [17, 21, 16, 9] are used to explore scenarios that may be difficult to describe analytically. These can also be used as an experiment to identify possible outcomes of proposed public health actions, such as a reduction in sharing with strangers [16, 9]. Blower and coauthers' compartmental model of New York City IDU [3] differentiates between buddy-users (familiar and stable sharing partners) and stranger-users (one-time and random sharing partners). Reducing the number of buddy-users (*i.e.*, sharing group size) has been shown to be an effective prevalence reducing intervention, both through simulations [9] and mathematical analysis [25]. Reducing the number of stranger-users (*i.e.*, random sharing behavior) is also an effective harm reduction measure [25, 16].

Among Victoria IDU, the importance of nonrandom sharing behavior is clear: the average reported number of sharing partners is exactly one. How to realistically model lasting buddy-user relationships with an analytically tractable model is not a trivial problem. Compartmental models with mass action or proportional mixing terms can only describe instantaneous contacts with sharing partners. To incorporate the reality of lasting partnerships between two individuals, the pairing process itself must be explicitly modeled.

2.2.3 Partnership Models

The first mathematical model of partnerships was published by Kendall in 1949 [12]. The purpose of this research was to identify optimal marrying ages, likely in keeping with the Western post-war focus on rebuilding and recovering from war-induced population loss and upheaval. Also in keeping with the times however, no pair separation was built into this model! Divorce was socially unacceptable, thus only pair formation was considered as a partnership dynamic.

It wasn't until 1974 that pair separation was explicitly modeled along with partnership formation [26]. Yellin and Samuelson modeled the numbers of single males (Y), single females (X), and married pairs (P) with the general system

$$\begin{aligned} X'(t) &= -\lambda_1 X + f_1 P - M(X,Y) \\ Y'(t) &= -\lambda_2 Y + f_2 P - M(X,Y) \\ P'(t) &= -\lambda_3 P + M(X,Y), \end{aligned}$$

where λ_1 and λ_2 and are mortality rates of females and males, respectively; f_1 and f_2 are per-pair rates of female production (through birth or marriage dissolution) and male production, respectively; λ_3 is the rate of marriage breakup due to death of a partner or divorce; $M(X,Y)$ is the marriage function. The phrase "marriage function" came into use as a result of the focus of early pair models on marriage, and it represents the mathematical term describing how pairs are formed.

Kendall, and Yellin and Samuelson note that a realistic marriage function must satisfy three properties:

1. First degree homogeneity: $M(qX, qY) = qM(X,Y)$, where $q > 0$
2. Positivity: $M(X,Y) \geq 0$ and $M(X,0) = M(0,Y) = 0$
3. Monotonicity: $M(X+\epsilon, Y) \geq M(X,Y)$ and $M(X, Y+\epsilon) \geq M(X,Y)$, $\epsilon > 0$

Taken together, these conditions ensure that the pairing rate increases in a linear fashion with population size, and that only female-male pairings are allowed. The minimum function and the harmonic mean are two functions satisfying the three conditions listed. A more common marriage or mixing function in current use is proportional mixing:

$$M(X,Y) \propto X \cdot \frac{Y}{X+Y}.$$

Proportional mixing attempts to describe the idea that a fraction $\frac{Y}{X+Y}$ of the contacts made by individuals of type X will be with individuals of type Y.

The bisexual model of Yellin and Samuelson was further generalized by Hadeler *et al.* in 1988 [7]. As with the marriage model of Kendall, current events had an effect on the research directions chosen. HIV/AIDS was the new epidemic (the names HIV and AIDS came into use in 1986 and 1982, respectively) and required new epidemic models.

2.2.4 Partnership and Disease Models

The focus on homosexual males in the years following the identification of HIV and AIDS was clearly realized in Dietz's model of disease transmission and pair dynamics [4]. Building on the model [7], interactions between homosexual males and sex trade workers, and between heterosexual males and sex trade workers were added as potential transmission routes. The lone class of pairs included only female-male pairs, giving a total of five categories to be modeled: single males, single females, homosexual males, sex trade workers, and female-male pairs.

The basic bisexual pairing model [7] is also the basis of Dietz and Hadeler's SIS partnership model formulation [5]. This is the first epidemic model in which pairing length is explicity considered; traditional epidemic models allow for only instantaneous pair durations. Heterogeneous contact and pair rates are examined, similarly to the heterogenous rates seen in Kermack and McKendrick's general SIR formulation.

The growing complexity of pair and disease models decreases analytic tractability. By considering a homosexual population, Kretzschmar and colleagues were able to examine short and long pair durations [15], and heterogeneous transmission and staged infection [14]. Pairs are classified as having both partners susceptible (P_{00}),

both partners infectious (P_{11}), or one susceptible and one infectious partner (P_{01}). Transmission may occur between infectious and susceptible partners, moving pairs between classes. Unpaired individuals are classified as susceptible (X_0) or infectious (X_1); they form pairs at rate α_F, a fraction $\frac{X_0}{X_0+X_1}$ of which will be with susceptible persons, and the remaining fraction will be with infectious persons. Every infectious person, paired or unpaired, recovers at a constant rate γ; every pair breaks at rate α_B. Figure 2.2 shows the flow of this type of model.

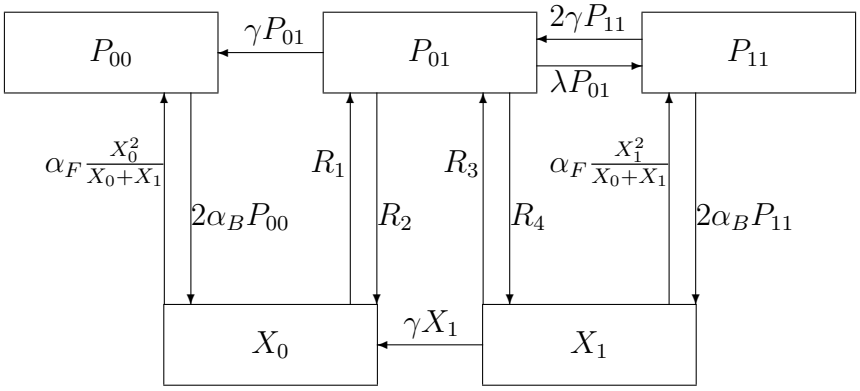

Figure 2.2: Compartmental flow of a generalized homosexual pair infection model; transmission is explicitly modelled as occuring within pairs such that only pairs may change infection status, not individuals. Single individuals are susceptible (X_0) or infectious (X_1); pairs are composed of two susceptible persons (P_{00}), two infectious individuals (P_{11}), or one susceptible person plus one infectious person (P_{01}). Infection is transmitted from infectious partners to susceptible partners at rate λ; infectives recover with rate γ; pairs break at rate α_B and form (via proportional mixing) at rate α_F. $R_1 = \alpha_F \frac{X_0 X_1}{X_0+X_1}$; $R_2 = \alpha_B P_{01}$; $R_3 = \alpha_F \frac{X_1 X_0}{X_0+X_1}$; $R_4 = \alpha_B P_{01}$. See, for example, Kretzschmar *et al.* 1994 [15].

Pairing models that describe only female-male partnerships do not have enough detail to allow for male-male pairs as needed to describe syringe-sharing in Victoria IDU. Homosexual pairing and disease models cannot capture the gender-specific heterogeneities observed in this population.

In summary, much has been done within the areas of compartmental disease modeling, syringe-sharing modeling, partnership modeling, and partnership/disease modeling. No framework exists, however, that encompasses the pairing dynamics visible through Victoria IDU interviews. This type of reference requires explicit modeling of the population dynamics of females, males, female-male pairs, and male-male pairs, all within a SI-type disease progression scheme.

Chapter 3

Pairing Model

This chapter presents the model of pairing dynamics, and the results of applying a simplified version of this model to data collected May-June 2008 at Victoria, Canada.

We develop a model that explicitly accounts for the formation and separation of both females-male pairs and male-male pairs; differential equations describe the evolution of the population proportions of single and paired individuals, with respect to both sex and pair type. This is necessary to adequately describe the observed partnership dynamics of IDU who share syringes in Victoria. The inclusion of gender-specific pairing dynamics allows us to capture the 30:70 female to male sex ratio, and the two types of pairs specific to syringe-sharing in this group of people.

The notation of the pairing model will be used throughout this thesis, and is summarized in Table 3.1.

Population Categories

Consider a population of n persons who mix randomly and form female-male pairs and male-male pairs; pairs separate at a constant rate α_B. Assume that the population is mixing homogeneously, and that concurrent pairings do not occur (the average

Table 3.1: Notation of pairing model.

n	population size (persons)
n_f	number of unpaired females
n_{FM}	number of females in a pairing with a male
n_M	number of unpaired males
n_{MF}	number of males in a pairing with a female
n_{MM}	number of males in a pairing with a male
N_F	population proportion composed of unpaired females
N_{FM}	population proportion composed of females in a pairing with a male
N_M	population proportion composed of unpaired males
N_{MF}	population proportion composed of males in a pairing with a female
N_{MM}	population proportion composed of males in a pairing with a male
α_F	per person rate of pair formation
α_B	per pair rate of separation
P	population proportion composed of females, both paired and unpaired

number of syringe-sharing partners reported by Victoria IDU was exactly one). We do not consider female-female pairings here, as none were observed during data collection, but the model given could be extended to include this category of persons. Let n be composed of n_F single females, n_{FM} females who are in a pairing with a male, n_M single males, n_{MF} males who are in a pairing with a female, and n_{MM} males who are in a pairing with another male. Notice that $n_{FM} = n_{MF}$, and that model compartments refer to numbers of individuals, not to numbers of pairs.

Rates of Flow

To describe intercompartmental movements we let α_F be the per person rate of pair formation. Pair formation is modeled by proportional mixing (see Section 2.2.3). When a pair forms, two single individuals move to paired classes, and when a pair breaks both members move back to singles' classes; persons do not move from one pairing directly to another.

The rate of pair formation initiated by a male is then $\alpha_F n_M$; a fraction n_F/n of these will be pairs formed with a female, thus the rate of movement from the n_M to

the n_{MF} class if $\alpha_F n_M n_F/n$. The remaining fraction, n_M/n, of pairs formed by a male will be with another male, moving individuals from the n_M to the n_{MM} category. The rate $\alpha_F n_M n_M/n$ is doubled to reflect the fact that both members of a male-male pair come from the same (n_M) class. The term $\alpha_F n_F$ describes the rate of pair formation by females, however, only the fraction n_M/n of these will be with a male and thus successful (no female-female pairing occurs under our model).

Let α_B denote the per pair rate of separation; each person in a paired class is a member of one pair, and thus experiences the per-pair rate of separation. Figure 3.1 shows the flow between pairing model compartments.

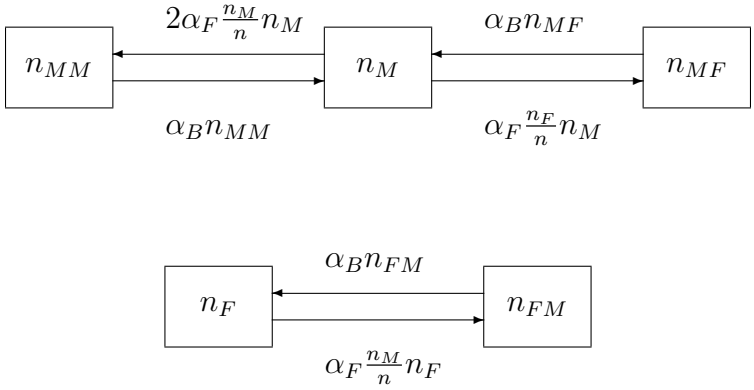

Figure 3.1: Compartmental flow of the pairing model.

3.1 Model

The differential equations describing the pairing dynamics of the population described above are

$$\begin{aligned}
n_F' &= \alpha_B n_{FM} - \alpha_F \frac{n_M}{n} n_F \\
n_{FM}' &= \alpha_F \frac{n_M}{n} n_F - \alpha_B n_{FM} \\
n_M' &= \alpha_B n_{MF} + \alpha_B n_{MM} - 2\alpha_F \frac{n_M}{n} n_M - \alpha_F \frac{n_F}{n} n_M \\
n_{MF}' &= \alpha_F \frac{n_F}{n} n_M - \alpha_B n_{MF} \\
n_{MM}' &= 2\alpha_F \frac{n_M}{n} n_M - \alpha_B n_{MM},
\end{aligned}$$

with nonnegative initial conditions $n_F(0), n_{FM}(0), n_M(0), n_{MF}(0), n_{MM}(0)$. Let $N_F = n_F/n$, $N_M = n_M/n$, $N_{FM} = n_{FM}/n$, $N_{MF} = n_{MF}/n$, and $N_{MM} = n_{MM}/n$ be the population proportions of single females, single males, females paired with males, males paired with females, and males paired with males, respectively. Because $N_{FM} = N_{MF}$, we may easily reduce the dimensions by one. The normalized and reduced pairing model is then

$$N_F' = \alpha_B N_{FM} - \alpha_F N_M N_F \tag{3.1}$$

$$N_{FM}' = \alpha_F N_M N_F - \alpha_B N_{FM} \tag{3.2}$$

$$N_M' = \alpha_B N_{FM} + \alpha_B N_{MM} - 2\alpha_F N_M^2 - \alpha_F N_F N_M \tag{3.3}$$

$$N_{MM}' = 2\alpha_F N_M^2 - \alpha_B N_{MM}, \tag{3.4}$$

with nonnegative initial conditions $N_F(0), N_{FM}(0), N_{MF}(0), N_M(0), N_{MM}(0)$, and satisfying

$$N_F + N_M + 2N_{FM} + N_{MM} = 1. \tag{3.5}$$

Define the fraction of the population that is female to be

$$P = N_F + N_{FM}.$$

Note that P is a constant (as is $(1-P)$, the population proportion of males) because

$$\begin{aligned} P'(t) &= N_F' + N_{FM}' \\ &= \alpha_B N_{FM} - \alpha_F N_M N_F + \alpha_F N_M N_F - \alpha_B N_{FM} \\ &= 0. \end{aligned}$$

Then

$$N_{FM}^* = P - N_F^*. \tag{3.6}$$

3.1.1 Existence and Uniqueness of Positive Equilibrium

We now focus on the realistic case that there are both females and males, *i.e.*, $0 < P < 1$, and prove (for a given value of P) the existence and uniqueness of the positive equilibrium solution of the pairing model.

Cubic Condition $\mathbf{F}(\mathbf{N_F^*})$

Assume that $0 < P < 1$. Let $x_0 = (N_F^*, N_{FM}^*, N_M^*, N_{MM}^*)$ be a positive equilibrium solution of (3.1)-(3.4). From (3.2)

$$N_M^* = \frac{\alpha_B}{\alpha_F}\frac{N_{FM}^*}{N_F^*} \quad (N_F^* \neq 0). \tag{3.7}$$

From (3.4)

$$N^*_{MM} \;=\; 2\frac{\alpha_F}{\alpha_B}{N^*_M}^2. \tag{3.8}$$

For simplicity of notation, let

$$r \;=\; \frac{\alpha_B}{\alpha_F}. \tag{3.9}$$

Substituting (3.7)-(3.9) into (3.5) we have that

$$1 = N^*_F + r\frac{P-N^*_F}{N^*_F} + 2(P-N^*_F) + 2\frac{1}{r}\left(r\frac{P-N^*_F}{N^*_F}\right)^2,$$

which implies

$${N^*_F}^2 = {N^*_F}^3 + r\left(P-N^*_F\right)N^*_F + 2(P-N^*_F){N^*_F}^2 + 2{N^*_F}^2 r\left(\frac{P-N^*_F}{N^*_F}\right)^2,$$

hence

$$0 \;=\; {N^*_F}^3 + \left(1-r-2P\right){N^*_F}^2 + 3rPN^*_F - 2rP^2. \tag{3.10}$$

This cubic equation is satisfied by an equilibrium solution N^*_F of (3.1).

To determine the number of possible steady state solutions N^*_F, we analyze the right hand side of (3.10) as a function in N^*_F:

$$F(N^*_F) \;=\; {N^*_F}^3 + \left(1-r-2P\right){N^*_F}^2 + 3rPN^*_F - 2rP^2 \tag{3.11}$$

$$F'(N^*_F) \;=\; 3{N^*_F}^2 + 2(1-r-2P)N^*_F + 3rP. \tag{3.12}$$

The zeros of the cubic polynomial $F(N^*_F)$ are the steady state solutions of (3.1); we

use these to infer the equilibrium behavior of the entire system (3.1)-(3.4). To prove the existence and uniqueness of the equilibrium solution N_F^*, we need to show that (3.11) has a zero in the interval $(0, P)$ and that it is unique.

Multiplicity of $\mathbf{F}(\mathbf{N_F^*})$ Zeros (Descartes' Rule of Signs)

In order to determine the number of positive zeros of (3.11), we write (3.10) as

$$0 = A{N_F^*}^3 + B{N_F^*}^2 + CN_F^* + D.$$

Descartes' Rule of Signs tells us that the number of positive roots of this equation is either equal to the number of sign changes in the ordered set A, B, C, D, or less than it by a multiple of two. When $1 - r - 2P > 0$, we have $A, B, C > 0$ and $D < 0$, corresponding to a single sign change. Thus (3.10) has one positive root.

When $1 - r - 2P < 0$, we have $A > 0$, $B < 0$, $C > 0$, and $D < 0$, corresponding to three sign changes (positive A to negative B, negative B to positive C, and positive C to negative D). Thus (3.10) has one or three positive roots.

We conclude that (3.11) has one or three positive zeros when $1 - r < 2P$, and a single positive zero when $1 - r > 2P$. To consider the latter situation, we examine the graphical properties of $F(N_F^*)$.

Graphical Interpretation of $\mathbf{F}(\mathbf{N_F^*})$

We know that (3.11) has either one or three positive zeros. To determine the orientation of $F(N_F^*)$ in relation to these, we consider the graphical properties of the function at the boundaries zero and P.

When $N_F^* = 0$

$$\begin{aligned} F(0) &= -2rP^2 < 0 \\ F'(0) &= 3rP > 0. \end{aligned}$$

Thus F is negative and increasing when N_F^* is zero.

At the boundary $N_F^* = P$ we see

$$\begin{aligned} F(P) &= P^3 + (1 - r - 2P)P^2 + 3rP^2 - 2rP^2 \\ &= P^2 - P^3 \\ &= P^2(1 - P) \\ &> 0 \end{aligned}$$

$$\begin{aligned} F'(P) &= 3P^2 + 2(1 - r - 2P)P + 3rP \\ &= P(r + 2 - P) \\ &> P(1 - P) \\ &> 0 \end{aligned}$$

Because $P < 1$ by definition, it is always true that $F(N_F^*)$ is positive and increasing near the boundary $N_F^* = P$.

There are four possible scenarios in which a cubic function has either three or one positive real zeros, is negative and increasing near zero, and is positive and increasing near $P > 0$. Figure 3.1.1 (a) shows the case that $F(N_F^*)$ has three positive real zeros. Figures 3.1.1 (b)-(d) show the possible orientations of $F(N_F^*)$ in the case that there is a single positive real zero. To prove the uniqueness of the pairing model equilibrium

when $2P > 1 - r$, we show that only the cases depicted in Figure 3.1.1 (b) and (c) are possible.

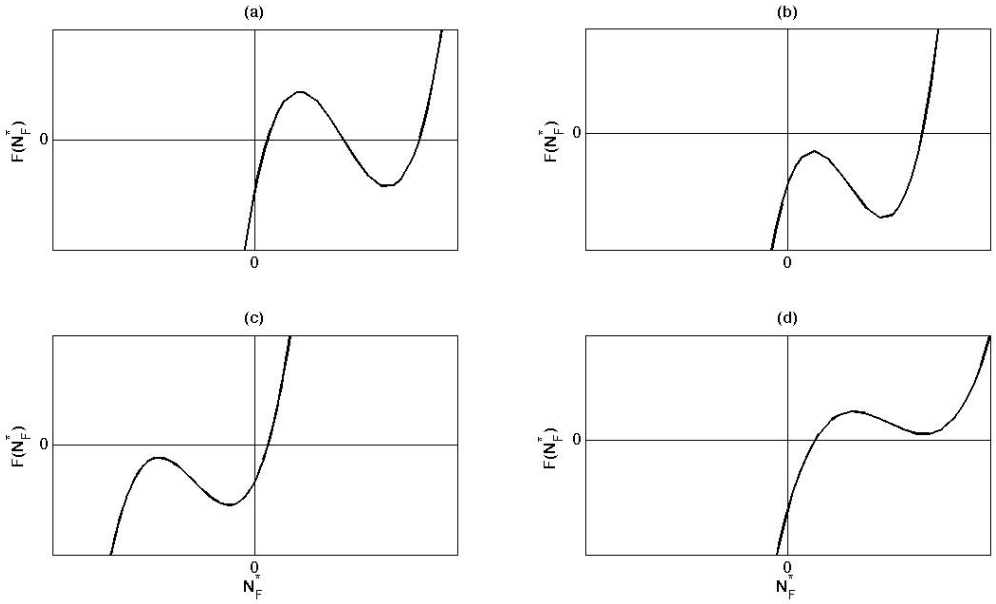

Figure 3.2: The four possible configurations of $F(N_F^*)$, given that the function has one (a) or three (b-d) positive zeros, and that the function is negative and increasing near zero, and positive and increasing near some $P > 0$.

Feasibility and Uniqueness of Equilibrium

We now need to show that at least one pairing equilibrium is feasible *i.e.*, there is a positive zero of $F(N_F^*)$ in the interval $(0, P)$. This will give us the biologically meaningful situation, $0 < N_F^* < P$.

First notice that $F(N_F^*)$ is negative near zero, and positive near P. It follows that $F(N_F^*)$ must have at least one zero in the interval $(0, P)$. To show the uniqueness of this zero, we must consider the two cases $2P < 1 - r$ and $2P > 1 - r$. When $2P < 1 - r$, Descartes' Rule of Signs tells us that (3.11) has a single positive zero.

To prove that $F(N_F^*)$ has a single positive zero, rather than three, when $2P > 1-r$,

let N^*_{Fcrit} be a critical point of (3.11). By (3.11) and (3.12)

$$\begin{aligned} F(N^*_F) &= \frac{1}{3}N^*_F F'(N^*_F) + \frac{1}{3}(1-r-2P){N^*_F}^2 + 2rPN^*_F - 2rP^2 \\ &= \frac{1}{3}N^*_F F'(N^*_F) + \frac{1}{3}(1-r-2P){N^*_F}^2 + 2rP\left(N^*_F - P\right), \end{aligned}$$

which evaluated at N^*_{Fcrit} yields

$$F(N^*_{Fcrit}) = \frac{1}{3}(1-r-2P)N^{*2}_{Fcrit} + 2rP\left(N^*_{Fcrit} - P\right). \tag{3.13}$$

Now we know that there is a root N^*_F of (3.11) such that $N^*_F < P$, hence

$$N^*_{Fcrit} - P < 0.$$

We also have that $P > (1-r)/2$, which implies that

$$1 - r - 2P < 0.$$

It follows that

$$F(N^*_{Fcrit}) < 0 \;\forall\; N^*_{Fcrit}.$$

This implies that there is a single zero of the cubic function $F(N^*_F)$ when $2p < r - 1$ (see Figure 3.1.1 (b)-(c) for the cases where $F(N^*_{Fcrit}) < 0 \;\forall\; N^*_{Fcrit}$).

In summary, there is a unique positive zero $0 < N^*_F < P$ of the polynomial (3.11) for all cases when $0 < P < 1$. Using this we infer the exitence and feasibility of the equilibrium solution of (3.1)-(3.4).

From (3.6) $N^*_{FM} = P - N^*_F > 0$, thus N^*_{FM} is feasible, *i.e.*, $N^*_{FM} \in (0, P)$. Next, note that (3.5) implies that $N^*_M < 1 - P$ and $N^*_{MM} < 1 - P$; to show that N^*_M and N^*_{MM} are feasible, we need to prove that they are each positive. From (3.5),

not all of $N_F^*, N_{FM}^*, N_M^*, N_{MM}^*$ can be zero. If we consider the case the $N_M^* = 0$, then, (**??**) implies that the derivative of N_M is non-negative (N_M^* will not become negative). Similarly, if $N_{MM}^* = 0$, (3.4) indicates that $N'_{MM}(t) \geq 0$, thus N_{MM}^* is also non-negative. We therefore conclude that there is a unique positive equilibrium, $x_0 = (N_F^*, N_{FM}^*, N_M^*, N_{MM}^*)$, of the pairing model (3.1)-(3.4).

3.1.2 Stability of Positive Equilibrium

To prove stability of the pairing model's positive equilibrium, we reduce the four dimensional model (3.1)-(3.4) to two dimensions. Substitute

$$N_{FM} = P - N_F$$

and

$$\begin{aligned} N_{MM} &= 1 - (N_F + N_{FM}) - N_{MF} - N_M \\ &= 1 - P - (P - N_F) - N_M \end{aligned}$$

into (3.1)-(3.4), to obtain the system

$$\begin{aligned} N'_F &= \alpha_B(P - N_F) - \alpha_F N_M N_F \qquad (3.14) \\ N'_M &= \alpha_B(P - N_F) + \alpha_B(1 - 2P + N_F - N_M) - 2\alpha_F {N_M}^2 - \alpha_F N_M N_F \\ &= \alpha_B(1 - P - N_M) - 2\alpha_F N_M^2 - \alpha_F N_M S_F \end{aligned}$$

Jacobian of Reduced Pairing Model

The Jacobian of (3.14), with respect to $x = (N_F, N_M)^T$, is

$$J = \begin{pmatrix} -\alpha_B - \alpha_F N_M & -\alpha_F N_F \\ -\alpha_F N_M & -\alpha_B - 4\alpha_F N_M - \alpha_F N_F \end{pmatrix}.$$

The trace of J is negative:

$$Tr(J) = -(2\alpha_B + 5\alpha_F N_M + \alpha_F N_F) < 0.$$

The determinant of J is positive:

$$\begin{aligned} |J| &= (\alpha_B + \alpha_F N_M)(\alpha_B + 4\alpha_F N_M + \alpha_F N_F) + \alpha_F N_F(-\alpha_F N_M) \\ &= \alpha_B^2 + 5\alpha_F \alpha_B N_M + \alpha_F \alpha_B N_F + 4\alpha_F^2 {N_M}^2 > 0. \end{aligned}$$

Thus every eigenvalue of J has strictly negative real part (for $\alpha_B, \alpha_F > 0$), and the steady state of the linearized system is stable. This implies that the equilibrium solution of the reduced nonlinear system (3.14) is locally stable, and hence the equilibrium solution of the full nonlinear pairing model (3.1)-(3.4) is also locally stable.

3.2 Parameter Estimation

To estimate the pairing parameter α_F, and fit parameters of the pairing length distribution to available data, we now consider a simplified homosexual pairing model. The data is given in Appendix B; Table 3.2 summarizes the notation used.

3.2.1 Observed Pairing Lengths

Ninety IDU were asked whether they were currently in a syringe-sharing relationship (see Section 2.1). Persons who reported being in a pair were asked how long they had known their partner; this duration (years) was recorded as the pairing length. Seventy one persons reported having no syringe-sharing partner; pairing lengths (minimum=0.5, maximum=28) were recorded for the remaining 19 individuals interviewed.

Simplified Pairing Model

We considered a simplified and discrete-time pairing model in which single individuals mix randomly and form pairs with rate α_F. Pairs separate at the constant per-pair rate α_B. The lengths of these pairings are assumed independent and identically distributed random variables (i.i.d.). We ignore sex, and categorize persons according to pairing status and length.

Table 3.2: Notation of simplified pairing model.

$N_0^{(t)}$	number of single individuals, at time t
$N_i^{(t)}$	number of individuals in i^{th} year of pairing, at time t
$P_{0,1}$	probability that a single individual enters a pair in Δt
$P_{i,i+1}$	probability that a paired individual moves from class N_i to N_{i+1} in Δt
p_i	fraction of population in class N_i
M	number of pair classes

Let N_0 denote the class of single individuals and N_i denote the class of individuals currently in the i^{th} year of a pairing ($1 \leq i \leq M$); $N_j^{(t)}$ is the number of individuals in the j^{th} class at time t. Let $N^{(t)}$ denote the total population size at time t; $N^{(t)}$ is a constant in our model. At time $t + \Delta t$, individuals enter a pair, remain in a pair, or leave a pair with the transition probability $P_{0,1}$, $P_{j,j+1}$, or $P_{j,0} = 1 - P_{j,j+1}$, respectively. For tractability, we define M as the number of pairing classes: individuals in the N_M class who do not break up at time $t + \Delta t$ remain in this class, rather than move to a

N_{M+1} class. Figure 3.3 shows the flow of this model.

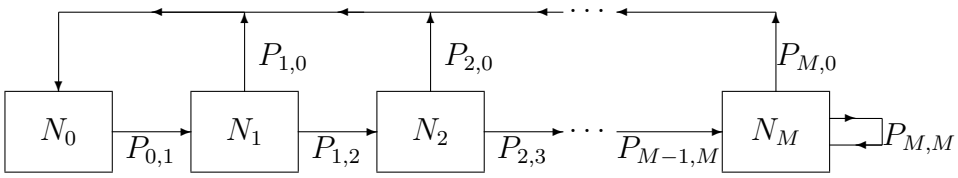

Figure 3.3: Compartmental flow chart of the simplified pairing model.

The $M+1$ equations of the simplifed pairing model are

$$N_0^{(t+1)} = \sum_{i=0}^{M-1}(1-P_{i,i+1})N_i^{(t)} + (1-P_{M,M})N_M^{(t)} \tag{3.15}$$

$$N_i^{(t+1)} = P_{i-1,i}N_{i-1}^{(t)} \quad 2 \le i \le M-1 \tag{3.16}$$

$$N_M^{(t+1)} = P_{M-1,M}N_{M-1}^{(t)} + P_{M,M}N_M^{(t)}, \tag{3.17}$$

where

$$N^{(t)} = \sum_{i=0}^{M} N_i^{(t)}. \tag{3.18}$$

Pairing Length Distribution f(y)

Once an individual has entered a pair, the duration or lifetime of that partnership is assumed to follow some probability distribution $f(y)$, with cumulative distribution $F(y)$. For example, this means that the probability a person is in the N_2 class at time $t+\Delta t$, given that they are in the N_1 class at time t, is

$$P_{1,2} = 1 - F(\Delta t) = 1 - F(1),$$

because $F(1)$ is the probability that the pairing lasts no more that one year.

Transition Probabilities $\mathbf{P_{i,i+1}}$ for Unimodal $\mathbf{f(y)}$

The general form of transition probabilities for individuals already in a pair are written

$$\begin{aligned} \text{Prob(breakup in } i^{th} \text{ class)} &= \frac{F(i) - F(i-1)}{1 - F(i-1)} \quad 1 \leq i < M \\ \text{Prob(breakup in } M^{th} \text{ class)} &= \frac{F(M + \Delta t) - F(M)}{1 - F(M)}. \end{aligned}$$

It follows that

$$\begin{aligned} P_{i,i+1} &= 1 - \frac{F(i) - F(i-1)}{1 - F(i-1)} \\ &= \frac{1 - F(i)}{1 - F(i-1)} \qquad 1 \leq i < M, \end{aligned} \tag{3.19}$$

and

$$P_{M,M} = \frac{1 - F(M + \Delta t)}{1 - F(M)}, \tag{3.20}$$

where $P_{i,i+1}$ is the probability of transitioning to the next pairing length class, and $P_{M,M}$ is the probability of remaining in class N_M.

Because of the assumption of proportional mixing, persons leave the N_0 class at rate $-\alpha_F N_0^{(t)}/N^{(t)}$, thus the time an individual spends single is exponentially distributed with parameter $-\alpha_F N_0^{(t)}/N^{(t)}$. From this, it follows that the probability of forming a pair and leaving the N_0 class is

$$P_{0,1} = 1 - \exp(-\alpha_F N_0^{(t)}/N^{(t)}).$$

Transition Probabilities $\mathbf{P_{i,i+1}}$ for Bimodal $\mathbf{f(y)}$

The pairing length data are bimodal: most paired IDU reported a pairing length of less than five or greater than 20 years. To model a bimodal pairing distribution, we assume $f(y)$ to be composed of two density functions f_1 and f_2. That is,

$$f(y) = \rho f_1(y) + (1-\rho) f_2(x),$$

where ρ is the probability that y falls within f_1. The cumulative density of the bimodal distribution is thus

$$F(y) \;=\; \rho F_1(y) + (1-\rho) F_2(y) \tag{3.21}$$

Substituting (3.21) into (3.19) and (3.20)

$$P_{i,i+1} \;=\; \frac{1-\rho F_1(i) - (1-\rho) F_2(i)}{1-\rho F_1(i-1) - (1-\rho) F_2(i-1)} \quad 1 \le i \le M-1 \tag{3.22}$$

and

$$P_{M,M} \;=\; \frac{1-\rho F_1(M+\Delta t) - (1-\rho) F_2(M+\Delta t)}{1-\rho F_1(M) - (1-\rho) F_2(M)}. \tag{3.23}$$

are the transition probabilities corresponding to a bimodal pairing length distribution.

Class Probabilities $\mathbf{p_i}$

Let $p_i = N_i^{(t)}/N^{(t)}$ denote the probability that a randomly chosen individual is a member of the N_i class. Here we derive analytical forms of $p_0, p_1, \ldots, p_M$ as functions of the parameters of $f(y)$, the pairing length distribution.

Let $X^{(t)}$ be the state vector $(N_0^{(t)}, N_1^{(t)}, \ldots N_M^{(t)})$, then the simplified pairing model

may be written

$$X^{(t+\Delta t)} = TX^{(t)}$$

where

$$T = \begin{pmatrix} (1-P_{0,1}) & (1-P_{1,2}) & \dots & (1-P_{M-1,M}) & (1-P_{M,M}) \\ P_{0,1} & 0 & \dots & 0 & 0 \\ 0 & P_{1,2} & \dots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \dots & P_{M-1,M} & P_{M,M} \end{pmatrix}.$$

Consider the equilibrium vector, $x_0 = (N_0^*, N_1^*, \dots, N_M^*)$, of the matrix T. Solving the difference equations (3.15)-(3.17) for N_1 through N_M at equilibrium,

$$\begin{aligned} N_1^* &= P_{0,1}N_0^* && (3.24) \\ N_2^* &= P_{0,1}P_{1,2}N_0^* \\ &\vdots \\ N_{M-1}^* &= \prod_{i=1}^{M-1} P_{i-1,i}N_0^* && (3.25) \\ N_M^* &= (1-P_{M,M})^{-1}\prod_{i=1}^{M} P_{i-1,i}N_0^*. && (3.26) \end{aligned}$$

Thus the equilibrium proportions of individuals in each paired class $\left(p_i = \frac{N_i^*}{N^*}\right)$ are

$$\begin{aligned} p_1 &= P_{0,1}\frac{N_0^*}{N^*} && (3.27)\\ &\vdots \\ p_{M-1} &= \prod_{i=1}^{M-1} P_{i-1,i}\frac{N_0^*}{N^*} && (3.28)\\ p_M &= (1-P_{M,M})^{-1}\prod_{i=1}^{M} P_{i-1,i}\frac{N_0^*}{N^*}. && (3.29) \end{aligned}$$

From (3.18) we have that

$$N_0^* = N^* - \sum_{i=1}^{M} N_i^*$$

Substituting (3.24)-(3.26) into this expression yields

$$\begin{aligned} N_0^* &= N^* - N_0^*\sum_{i=1}^{M-1}\prod_{j=1}^{i} P_{j-1,j} - N_0^*(1-P_{M,M})^{-1}\prod_{i=1}^{M} P_{i-1,i} \\ &= N^* - N_0^*\left[\sum_{i=1}^{M-1}\prod_{j=1}^{i} P_{j-1,j} + (1-P_{M,M})^{-1}\prod_{i=1}^{M} P_{i-1,i}\right]. \qquad (3.30) \end{aligned}$$

Then

$$\begin{aligned} p_0 &= \frac{N_0^*}{N^*} \\ &= \left(1 + \sum_{i=1}^{M-1}\prod_{j=1}^{i} P_{j-1,j} + (1-P_{M,M})^{-1}\prod_{i=1}^{M} P_{i-1,i}\right)^{-1}, \qquad (3.31) \end{aligned}$$

and substituting (3.31) back into (3.27)-(3.29)

$$p_1 = \frac{P_{0,1}}{1+\sum_{k=1}^{M-1}\prod_{j=1}^{k}P_{j-1,j}+(1-P_{M,M})^{-1}\prod_{j=1}^{M}P_{j-1,j}} \tag{3.32}$$

$$\vdots$$

$$p_i = \frac{\prod_{j=1}^{i}P_{j-1,j}}{1+\sum_{k=1}^{M-1}\prod_{j=1}^{k}P_{j-1,j}+(1-P_{M,M})^{-1}\prod_{j=1}^{M}P_{j-1,j}},\ i<M \tag{3.33}$$

$$p_M = \frac{(1-P_{M,M})^{-1}\prod_{j=1}^{M}P_{j-1,j}}{\left(1+\sum_{k=1}^{M-1}\prod_{j=1}^{k}P_{j-1,j}+(1-P_{M,M})^{-1}\prod_{j=1}^{M}P_{j-1,j}\right)}. \tag{3.34}$$

Likelihood Derivation

For our purposes, the likelihood function $L(\cdot)$ is the conditional probability statement

$$L(X|\xi) \propto \text{Prob}(X|\xi),$$

where $X \in \mathbb{R}^n$ is a set of n data points, and $\xi \in \mathbb{R}^m$ is a vector of parameters.

The likelihood function is not a a probability density function because $\int_{-\infty}^{\infty} L(x)dx$ need not equal unity. It is an easier function to work with than the conditional probability density function $\text{Prob}(X|\xi)$ because there is no normalizing constant (in the current case, probability density normalizing constants are inverses of $|\xi|$-dimensional integrals).

The most common use of likelihood functions is in parameter estimation. Given a particular ξ, $L(\cdot)$ increases with the probability of observing a particular X. By maximizing the likelihood function, we may determine ξ such that the probability of observing the data is maximized. This is a data-informed method of model selection. The parameter set ξ associated with the maximum likelihood is referred to as the maximum likelihood estimate (MLE) of the parameters. In many cases, the log

likelihood

$$l(X) = \log(L(X))$$

is maximized for ease of computation.

In the case of the simplified pairing model, X corresponds to $X^{(t)}$, the set of observed pairing class frequencies at a time t. The parameters involved in the likelihood, ξ, are the set of pairing length distribution parameters plus the pair formation rate α_F; these parameters are contained in the p_i terms of the likelihood and log likelihood. Because pairing lengths are assumed to be independent, $X^{(t)}$ follows a multinomial distribution with likelihood

$$L(X^{(t)}) \propto \frac{N^{(t)}!}{N_0^{(t)}!N_1^{(t)}!\ldots N_M^{(t)}!} p_0^{N_0^{(t)}} p_1^{N_1^{(t)}} \ldots p_M^{N_M^{(t)}} \tag{3.35}$$

where p_0 is the probability that an individual is single, and p_i is the long-run probability that an individual is in the i^{th} year of a pairing (*i.e.*, the fraction of the population in the N_i^* class). The log-likelihood is

$$l(X^{(t)}) = C + \log(N^{(t)}!) - \sum_{i=0}^{M} \log(N_i^{(t)}) + \sum_{i=0}^{M} N_i^{(t)} \log(p_i), \tag{3.36}$$

where C is a constant. To maximize $L(X^{(t)})$, we minimize the negative log likelihood $l(X^{(t)})$.

MLE Methods

Parameters were estimated by numerical analysis. All computations were performed using MATLAB & Simulink Student Version 7.4.0.287 R2007a (The Math Works, Inc., 2007); the negative log likelihood was minimized with the simulated annealing algorithm `anneal` [24]. Twenty runs were performed for each of the six sets of model

assumptions. The estimate corresponding to the mimimum negative log likelihood was retained as the MLE.

We assumed the pairing population to be at equilibrium; this allows analytical forms of p_i to be derived so that the likelihood may be evaluated. The vector of observed pairing length frequencies was fit to the expected equilibrium vector, $x_0 = (N_0^*, N_1^*, \ldots, N_M^*)$ under various combinations of pairing length assumptions and data classification schemes.

Three pairing length distributions, $f(y)$, were considered:

a) Exponential distribution with mean λ: $f(y) = \lambda^{-1} e^{-\lambda y}$.

b) Gamma distibution with shape parameter k and scale parameter θ: $f(y) = y^{k-1} \frac{e^{-y/\theta}}{\theta^k \Gamma(k)}$, where $\Gamma(\cdot)$ is the gamma function $\Gamma(z) = \int_0^\infty t^{z-1} e^{-t} dt$.

c) Bimodal distribution composed of one exponentially distributed peak followed by one gamma-distributed peak: $f(y) = \rho \lambda^{-1} e^{-\lambda y} + (1-\rho) y^{k-1} \frac{e^{-y/\theta}}{\theta^k \Gamma(k)}$, where ρ is the probability that an observation falls under the left-handmost peak.

For each distribution examined, two separate data classification schemes were considered. The first involves one-year data bins: observed pairing lengths are categorized as length zero, one, two, and so forth. The second defines pairing length according to five-year bins; observations are designated as length zero, one to five, six to ten, and the like. To illustrate, consider a hypothetical dataset set of six observations: two single persons, two persons in a one year pair, and two persons in a four year pairing. Under the 1-year bin scenario, N_0, N_1, and N_4 all have two members. Under the 5-year bin model, however, there are two observations in the singles' class N_0, and four observations in the 1-5 year class. The data categories were applied after all transition probabilities were calculated (i.e., $\Delta t = 1$ year for every case considered).

The per-person pair formation rate, α_F, was estimated under each of the six possible combinations of pairing distribution and data classification. In the two cases involving the bimodal distribution (c), ρ, defined to be the probability of an observation falling in the lefthand-most peak, was also estimated.

3.2.2 Results

Table 3.3 lists the MLE parameter values and corresponding likelihood $L(X)$. Six sets of parameter estimates are given, corresponding to each of the three pairing length distribution assumptions modeled under each of two data classification schemes considered. Figure 3.4 compares MLE predictions of the three distribution models using 1-year data bins; Figure 3.5 compares predicted densities in the case of 5-year data bins.

Table 3.3: Estimated parameters of simplified pairing model. Values correspond to numerically minimized negative log-likelihood; the associated likelihood value is given as $L(X)$. Three pairing length distribution assumptions and two data classification schemes (*i.e.*, six scenarios total) are considered.

Distribution	Parameter	Estimate 1 (1-year data bins)	Estimate 2 (5-year data bins)
Exponential	α_F	0.0231	0.0206
	λ	14.3264	16.1195
	$L(X)$	112.3112	81.1832
Gamma	α_F	0.0120	0.0115
	k	61.9257	75.4545
	θ	0.4459	0.3779
	$L(X)$	110.4892	80.4512
Bimodal	α_F	0.0255	0.0278
	ρ	0.5473	0.6501
	λ	3.0136	1.9587
	k	76.9248	71.5443
	θ	0.3674	0.472
	$L(X)$	110.0236	79.8846

In general, 1-year data bins produce higher likelihood values than do 5-year data

bins. The MLE exponential, gamma, and bimodal models returned likelihoods of 112.3112, 110.4892, and 110.0236, respectively, under the 1-year data classification, whereas the same models under the 5-year data scheme produced the lower likelihoood values 81.1832, 80.4512, and 79.8846.

The MLE bimodal function obtained using 1-year data bins is a better fit to the sample pairing length data than the MLE pure exponential or pure gamma distribution. The sample mean pairing length was $\bar{y} = 13.184$ years. Let $\bar{y_1}$ and $\bar{y_5}$ denote the estimates of $\bar{y}$ using 1-year data bin and 5-year data bins, respectively. The estimated mean under the bimodal distribution using 1-year data bins was $\bar{y_1} = 14.4436$; the estimated mean under the bimodal distribution using 5-year data bins was $\bar{y_5} = 13.0890$. The MLE pure exponential distribution captures the mean ($\bar{y_1} = 14.3246,\ \bar{y_5} = 16.1195$), but fails to recognize the multimodal nature of the data. The MLE pure gamma distribution both fails to capture all shorter pairings, and seriously overestimates the mean length of pairing ($\bar{y_1} = 27.6127, \bar{y_5} = 28.5142$).

In the two cases involving exponentially distributed pairing lengths, the per-pair breakage rate α_B is estimated by λ^{-1}. This is because as the time step Δt becomes very small, the discrete simplified pairing model acts like a differential equation model of pairing. Compartmental pairing models such as this implicitly assume an exponentially distributed pairing length. It follows that the inverse of the mean time spent in a paired class is equal to the [exponential] rate that individuals leave that class *i.e.*, $\lambda^{-1} = \alpha_B$. Using 1-year data categories, the MLE point estimate of α_B is $(14.3264)^{-1} = 0.06980$; using 5-year data bins, the point estimate of α_B is $(16.1195)^{-1} = 0.06203$. This suggests that pair breakage is more frequent than pair formation. The quantity α_B cannot be estimated directly from the parameters of the gamma and bimodal distributions.

The fitting of observed pairing lengths to a homosexual pairing model, rather than

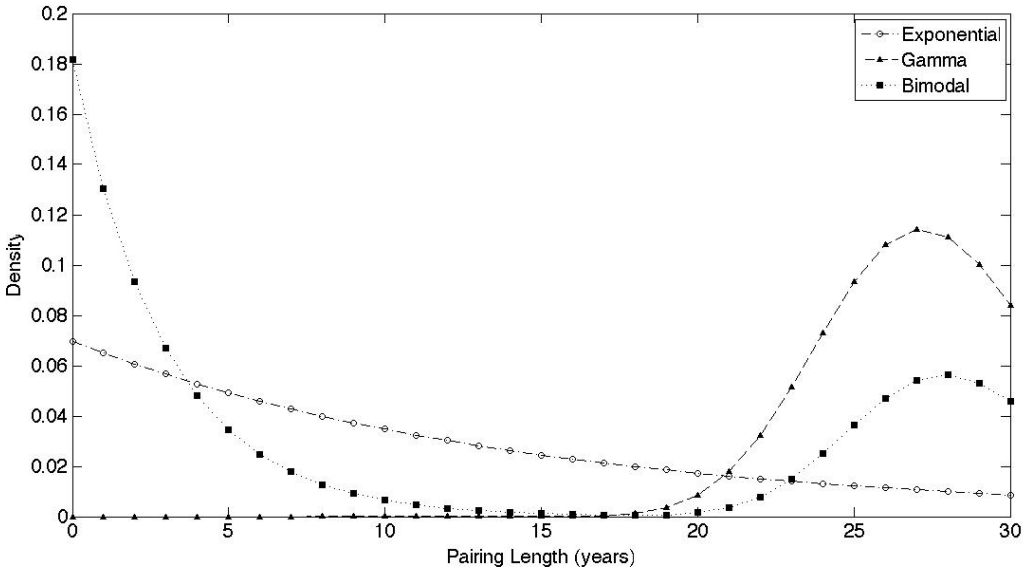

Figure 3.4: Expected pairing length distributions under 1-year data categories. Exponential distribution mean $\lambda = 14.3264$; gamma distribution with shape $k = 61.9257$, scale $\theta = 0.4459$; bimodal probability density function $f(x) = \rho f_1(x) + (1-\rho)f_2(x)$ where f_1 is exponential distribution ($\lambda = 3.0136$), f_2 is gamma distribution ($k = 76.9248, \theta = 0.3674$), and $\rho = 0.5473$.

the full model (3.1)-(3.4) was necessitated by the lack of detailed data, and a scarcity of observations in general. Ideally, many individuals of each sex would be interviewed regarding current and past sharing partnerships. With the additional information of how long pairings last (currently we only know the length distribution of those pairings in progress), the full pairing model could be used to estimate α_B for pairing length distributions other than a pure exponential.

The homosexual pairing model differs from the full pairing model in that the pairing rate α_F is likely overrestimated. Single females effectively pair at rate $\alpha_F N_M N_F < \alpha_F(N_M+N_F)^2$; similarly, single males pair at rate $\alpha_F(N_M+N_F)N_M < \alpha_F(N_M+N_F)^2$. In the simplified pairing model, however, every individual is assumed to pair at the higher rate $\alpha_F(N_M + N_F)^2$. In a population such as Victoria's IDU, where there is a sex ratio much different than 50%, the collection of a larger dataset such that the

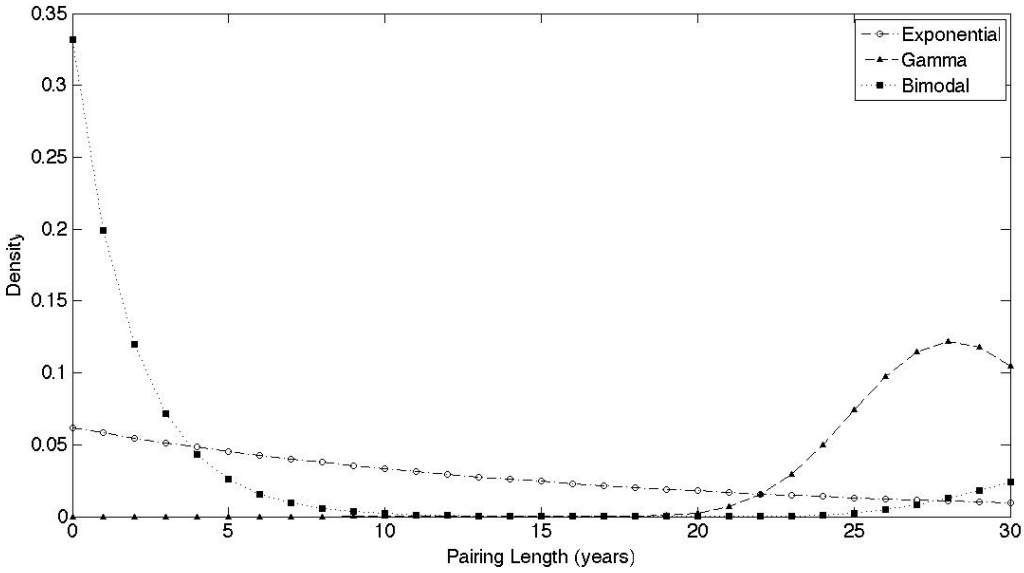

Figure 3.5: Expected pairing length distributions under 5-year data categories. Exponential distribution mean $\lambda = 16.1195$; gamma distribution with shape $k = 75.4545$, scale $\theta = 0.3779$; bimodal probability density function $f(x) = \rho f_1(x) + (1-\rho)f_2(x)$ where f_1 is exponential distribution ($\lambda = 1.9587$), f_2 is gamma distribution ($k = 71.5443, \theta = 0.4720$), and $\rho = 0.6501$.

full pairing model can be fit and compared to the simplified model's predictions, is desireable.

In summary, we have modeled male-male and female-male pairing in a population of male and female individuals. A simplified (homosexual) version of this model is used to estimate parameters from observed pairing lengths and pairing class frequencies. The interval $(0, 0.5]$ is a reasonable neighborhood for preliminary investigations regarding both the per-person pairing rate α_F and the per-pair separation rate α_B. To address our original goal of using mathematical modeling to investigate HIV and HCV transmission factors among Victoria IDU, we now require SI disease dynamics to be considered and to be built into the bisexual pairing model.

Chapter 4

Pairing and Disease Model

This chapter presents the model of susceptible-infective (SI) disease spread within a population of female-male and male-male pair forming individuals. A second pairing and disease model that includes vital dynamics is derived. This model is analyzed and the basic reproduction number $\mathcal{R}_0$ is determined; the behavior of $\mathcal{R}_0$ is investigated analytically and numerically with reference to parameter values suitable for Victoria IDU. The notation of Chapter 3 (see Table 3.1) is retained, and additional notation is summarized in Table 4.1.

Table 4.1: Notation of pairing and disease model.

S_F	population proportion composed of susceptible single females
S_{FM}	population proportion composed of susceptible females paired with a male
I_F	population proportion composed of infectious single females
I_{FM}	population proportion composed of infectious females paired with a male
S_M	population proportion composed of susceptible single males
S_{MM}	population proportion composed of susceptible males paired with a male
S_{MF}	population proportion composed of susceptible males paired with a female
I_M	population proportion composed of single infectious males
I_{MM}	population proportion composed of infectious males paired with a male
I_{MF}	population proportion composed of infectious males paired with a female
β	transmission parameter
b	rate of migration into population
d	death rate of susceptible individuals
γ	death rate of infectious individuals

Population Categories

To model disease dynamics within the N members of the population described in Chapter 3, we consider the infection status (susceptible or infected), relationship status (single or paired), and the gender (female or male) of the N members of the population. Let s_F, s_{FM}, s_M, s_{MF}, and s_{MM} denote the susceptible population classes composed of single females, females paired with males, single males, males paired with females, and males paired with males, respectively. Let i_F, i_{FM}, i_M, i_{MF}, and i_{MM} refer to the corresponding categories of infectious persons. Finally, label the fractions of the population in each of these classes as $S_F, S_{FM}, S_M, S_{MF}, S_{MM}, I_F, I_{FM}, I_M, I_{MF}$, and I_{MM}. Using the notation of Chapter 3, we see that each pairing category is composed of two subcategories with respect to infection status; for example, $N_F = S_F + I_F$, and $N_{FM} = S_{FM} + I_{FM}$.

Rates of Flow

We assume that disease is transmitted between partners only (for the purposes of investigating transmission via syringe sharing), that partnerships are exclusive (the average number of partners reported by IDUs who shared was exactly one), and that infections progress according to a susceptible-infectious (SI) model (HIV and HCV are lifelong illnesses). As a result of the latter, there is no movement from infectious classes into susceptible classes. Because there are no concurrent pairings, an individual is effectively contagious within the larger population only when she or he leaves a relationship. New infections are thus reflected with flow from the paired susceptible fractions (S_{FM}, S_{MF}, S_{MM}) to the unpaired infectious portions of the population (I_F, I_M).

The total rate of movement out of a paired susceptible compartment S_{XY} is $\alpha_B S_{XY}$; each paired susceptible is a member of one pair, and experiences the per-pair

separation rate α_B. The probability that a susceptible in this class is paired with an infectious is $\frac{I_{YX}}{NYX}$, and a fraction $\frac{\beta}{\alpha_B+\beta}$ of those leaving will be infectious before the pair separates. Thus $\alpha_B \frac{\beta}{\alpha_B+\beta} \frac{I_{YX}}{N_{YX}} S_{YX}$ is the rate of movement from the S_{XY} class into the I_X class of infectious singles. The complementary term, $\alpha_B \frac{\alpha_B}{\alpha_B+\beta} \frac{I_{YX}}{N_{YX}} S_{XY}$, gives the rate at which susceptible individuals of sex X leave a pairing with an infectious individual of sex Y and enter the susceptible singles' class S_X. Every susceptible in a pair with another susceptible returns to a susceptible singles' class upon separation of the pair.

Pairing dynamics proceed as in Chapter 3. Male-male and male-female pairs form due to random and proportional mixing at the per-person rate of pair formation α_F. Each pair breaks at rate α_B; the pair members move into susceptible or infectious singles' classes according to the disease process described above.

Figure 4.1 shows the flow of the pairing and disease model. For clarity, we derive each equation separately.

4.1 Model

Here we derive the ten differential equations of the pairing and disease model.

Single Infectious Females $\mathbf{I_F}$

Single infectious females form pairs with single males, and the infection status of the males does not affect this process. According to the proportional mixing model, the rate of pair formation among infectious single females (*i.e.,* movement from I_F to I_{FM}) is then $\alpha_F N_M I_F$. Every infectious female leaving a pair returns to the single infectious female class, and this occurs at rate $\alpha_B I_{FM}$. Furthermore, a fraction $\frac{\beta}{\alpha_B+\beta}$ of those susceptible females paired with infectious males will be infected during their

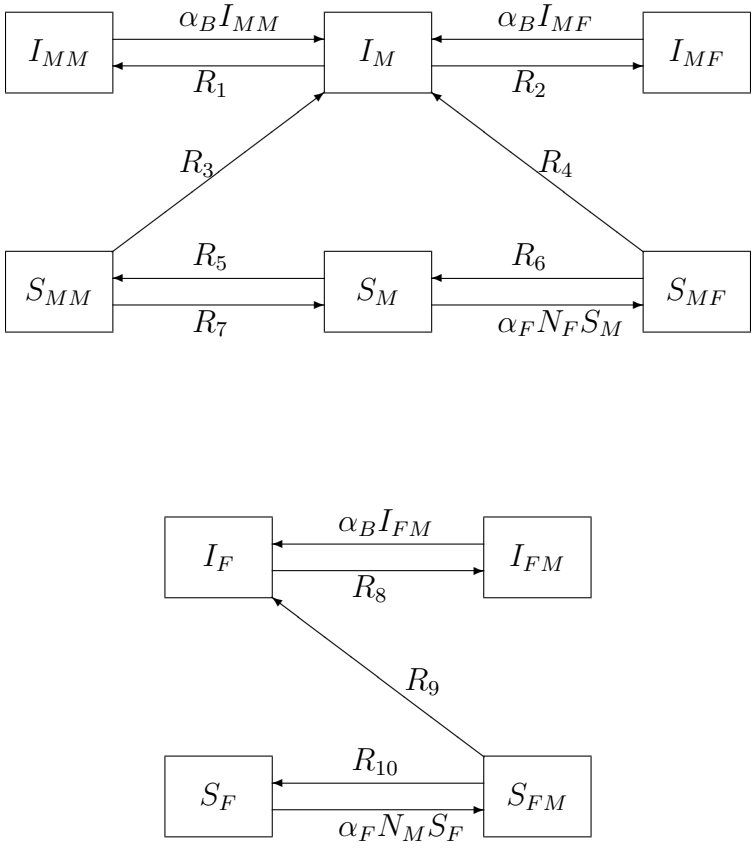

Figure 4.1: Compartmental flow of the pairing and disease model.

$$
\begin{aligned}
R_1 &= 2\alpha_F N_M I_M & R_6 &= \alpha_B \left(\tfrac{S_{FM}}{N_{FM}} + \tfrac{\alpha_B}{\alpha_B+\beta} \tfrac{I_{FM}}{N_{FM}} \right) S_{MF} \\
R_2 &= \alpha_F N_F I_M & R_7 &= \alpha_B \left(\tfrac{S_{MM}}{N_{MM}} + \tfrac{\alpha_B}{\alpha_B+\beta} \tfrac{I_{MM}}{N_{MM}} \right) S_{MM} \\
R_3 &= \alpha_B \tfrac{\beta}{\alpha_B+\beta} \tfrac{I_{MM}}{N_{MM}} S_{MM} & R_8 &= \alpha_F N_M I_F \\
R_4 &= \alpha_B \tfrac{\beta}{\alpha_B+\beta} \tfrac{I_{FM}}{N_{FM}} S_{MF} & R_9 &= \alpha_B \tfrac{\beta}{\alpha_B+\beta} \tfrac{I_{MF}}{N_{MF}} S_{FM} \\
R_5 &= 2\alpha_F N_M S_M & R_{10} &= \alpha_B \left(\tfrac{S_{MF}}{N_{MF}} + \tfrac{\alpha_B}{\alpha_B+\beta} \tfrac{I_{MF}}{N_{MF}} \right) S_{FM}
\end{aligned}
$$

partnership, and upon pair separation will move to the single infectious female class. The probability that a susceptible paired female has an infectious partner is $\frac{I_{MF}}{N_{MF}}$, thus the rate of movement from the S_{FM} class into the I_F class due to break up of partnerships during which transmission occurred is $\alpha_B \frac{\beta}{\alpha_B+\beta} \frac{I_{MF}}{N_{MF}} S_{FM}$. The totality of these flows yields

$$I'_F(t) = -\alpha_F N_M I_F + \alpha_B I_{FM} + \alpha_B \frac{\beta}{\alpha_B+\beta} \frac{I_{MF}}{N_{MF}} S_{FM}. \tag{4.1}$$

Paired Infectious Females $\mathbf{I_{FM}}$

Flow into the I_{FM} class is due to the pairing of single infectious females (see above), and flow out of this compartment is a result of pair separation, thus

$$I'_{FM}(t) = \alpha_F N_M I_F - \alpha_B I_{FM}. \tag{4.2}$$

Single Infectious Males $\mathbf{I_M}$

When an infectious male pairs with another infectious male, two individuals are removed from the class of single infectious males; the rate out of I_M due to pairing of infectious males is then $2\alpha_F I_M^2$. Members of the infectious single male class also pair with single susceptible males (at rate $\alpha_F S_M I_M$), and single susceptible males meet and pair with single infectious males at rate $\alpha_F I_M S_M$. Male-female pairs involving an infectious male form at the rate $\alpha_F N_F I_M$. Movement into the I_M compartment reflects previously infected males leaving either a male-male or female-male pair. The terms $\alpha_B I_{MM}$ and $\alpha_B I_{MF}$ are the rates of pair separation of previously infected males paired with males and females, respectively. Of those susceptible males paired with other males (S_{MM}), a fraction $\frac{I_{MM}}{N_{MM}}$ will have infectious partners, and they will be infected during the partnership with probability $\frac{\beta}{\alpha_B+\beta}$; the term $\alpha_B \frac{\beta}{\alpha_B+\beta} \frac{I_{MM}}{N_{MM}} S_{MM}$ is

thus the rate at which males infected in their most recent partnership leave that pairing and enter the single infectious male class. Similarly, the term $\alpha_B \frac{\beta}{\alpha_B+\beta}\frac{I_{FM}}{N_{FM}}S_{MF}$ represents influx from the susceptible paired male class due to transmission in and subsequent separation of a partnership with an infectious female. These movements give us

$$\begin{aligned} I'_M(t) &= -2\alpha_F I_M^2 - \alpha_F S_M I_M - \alpha_F I_M S_M - \alpha_F N_F I_M + \alpha_B \frac{\beta}{\alpha_B+\beta}\frac{I_{MM}}{N_{MM}}S_{MM} \\ &\quad +\alpha_B I_{MM} + \alpha_B I_{MF} + \alpha_B \frac{\beta}{\alpha_B+\beta}\frac{I_{FM}}{N_{FM}}S_{MF} \\ &= -2\alpha_F N_M I_M - \alpha_F N_F I_M + \alpha_B I_{MM} + \alpha_B I_{MF} \\ &\quad +\alpha_B \frac{\beta}{\alpha_B+\beta}\left(\frac{I_{MM}}{N_{MM}}S_{MM} + \frac{I_{FM}}{N_{FM}}S_{MF}\right). \end{aligned} \tag{4.3}$$

Infected Males Paired with Females $\mathbf{I_{MF}}$

Movement into I_{MF} is due solely to pairing of single infectious males with the opposite sex, and flow out of I_{MF} is due to pair separation.

$$I'_{MF}(t) = \alpha_F N_F I_M - \alpha_B I_{MF} \tag{4.4}$$

Infectious Males Paired with Males $\mathbf{I_{MM}}$

Movement into I_{MM} is due to pairings of either two infectious males or one infectious male with one susceptible male; $\alpha_F I_M S_M$ represents those pairings initiated by susceptible males, while $\alpha_F S_M I_M$ describes the rate of pairing with susceptible males initiated by infectious males. All infectious paired males experience pair separation at the per-pair rate α_B. The sum of these dynamics is

$$\begin{aligned} I'_{MM}(t) &= 2\alpha_F I_M^2 + \alpha_F I_M S_M + \alpha_F S_M I_M - \alpha_B I_{MM} \\ &= 2\alpha_F N_M I_M - \alpha_B I_{MM}. \end{aligned} \tag{4.5}$$

Single Susceptible Females $\mathbf{S_F}$

Single susceptible females are moved out of this category when they form pairs with single males (at rate $\alpha_F N_M S_F$). Of those susceptible females paired with males, the fraction $\frac{S_{MF}}{N_{MF}}$ have susceptible partners, and thus cannot be infected during their partnership. When the pair separates, these susceptible women return to the single susceptible female class. Susceptible women with infectious male partners escape infection with probability $\frac{\alpha_B}{\alpha_B+\beta}$, thus the term $\alpha_B \frac{\alpha_B}{\alpha_B+\beta} \frac{I_{MF}}{N_{MF}} S_{FM}$ describes the rate of pair separation involving susceptible women who are not infected by their infectious male partners. The dynamics are described by

$$S'_F(t) = \alpha_B \left(\frac{S_{MF}}{N_{MF}} S_{FM} + \frac{\alpha_B}{\alpha_B + \beta} \frac{I_{MF}}{N_{MF}} S_{FM} \right) - \alpha_F N_M S_F. \tag{4.6}$$

Susceptible Females Paired with Males $\mathbf{S_{FM}}$

As with I_{FM}, the dynamics of S_{FM} are determined solely by pair formation and separation:

$$S'_{FM}(t) = \alpha_F N_M S_F - \alpha_B S_{FM}. \tag{4.7}$$

Single Suceptible Males $\mathbf{S_M}$

Single susceptible males leave this class when they enter pairs initiated by another susceptible male, an infectious male, or a single female. These pairings occur at the rates $\alpha_F S_M^2$, $\alpha_F S_M I_M$, and $\alpha_F N_F$, respectively. Single susceptible males also enter a new class when they initiate a pair with an infectious male (this occurs at rate $\alpha_F I_M S_M$). Paired susceptible males whose partners are also susceptible (the fractions $\frac{S_{FM}}{N_{FM}}$ and $\frac{S_{MM}}{N_{MM}}$ of female-male pairs and male-male pairs, respectively) separate from their partner at rate α_B and enter the single suceptible male class. Paired susceptible

males whose partners are infectious will remain uninfected throughout that pairing with probability $\frac{\alpha_B}{\alpha_B+\beta}$; the terms $\alpha_B\frac{\alpha_B}{\alpha_B+\beta}\frac{I_{FM}}{N_{FM}}S_{MF}$ and $\alpha_B\frac{\alpha_B}{\alpha_B+\beta}\frac{I_{MM}}{N_{MM}}S_{MM}$ describe the rate of influx into the single susceptible male class of males leaving a pairing who have not been infected by their infectious female or infectious male partner, respectively. The total dynamics of the single and susceptible male compartment are

$$\begin{aligned} S'_M(t) &= -2\alpha_F S_M^2 - 2\alpha_F I_M S_M + \alpha_B \frac{S_{MM}}{N_{MM}} S_{MM} + \alpha_B \frac{\alpha_B}{\alpha_B+\beta}\frac{I_{MM}}{N_{MM}} S_{MM} \\ &\quad -\alpha_F N_F S_M + \alpha_B \frac{S_{FM}}{N_{FM}} S_{MF} + \alpha_B \frac{\alpha_B}{\alpha_B+\beta}\frac{I_{FM}}{N_{FM}} S_{MF} \\ &= -2\alpha_F N_M S_M - \alpha_F N_F S_M + \alpha_B \left(\frac{S_{MM}}{N_{MM}} S_{MM} + \frac{S_{FM}}{N_{FM}} S_{MF}\right) \\ &\quad +\alpha_B \frac{\alpha_B}{\alpha_B+\beta}\left(\frac{I_{MM}}{N_{MM}} S_{MM} + \frac{I_{FM}}{N_{FM}} S_{MF}\right). \end{aligned} \tag{4.8}$$

Susceptible Males Paired with Females $\mathbf{S_{MF}}$

The dynamics of S_{MF} closely resemble thos of I_{FM}, S_{FM}, and I_{MF}. Influx is due to pairing with single females ($\alpha_F N_F S_M$), and outflow is due to pair separation ($\alpha_F S_{MF}$). These give us

$$S'_{MF}(t) = \alpha_F N_F S_M - \alpha_B S_{MF}. \tag{4.9}$$

Susceptible Males Paired with Males $\mathbf{S_{MM}}$

Pairings involving two susceptible males occur at rate $\alpha_F S_M$, and remove two individuals from the single susceptible male category. Pairings with infectious males may be initiated by the suceptible ($\alpha_F I_M S_M$) partner or the infectious partner ($\alpha_F S_M I_M$). All susceptible males in a male-male pair experience pair separation at the rate α_B,

hence

$$\begin{aligned} S'_{MM}(t) &= 2\alpha_F S_M^2 + \alpha_F S_M I_M + \alpha_F I_M S_M - \alpha_B S_{MM} \\ &= 2\alpha_F N_M S_M - \alpha_B S_{MM}. \end{aligned} \tag{4.10}$$

The nonnegative initial conditions are $I_F(0), I_{FM}(0), I_M(0), I_{MF}(0), I_{MM}(0), S_F(0)$, $S_{FM}(0), S_M(0), S_{MF}(0)$, and $S_{MM}(0)$. These satify

$$I(0) = I_F(0) + I_{FM}(0) + I_M(0) + I_{MF}(0) + I_{MM}(0) > 0,$$

and

$$S_F(0), S_{FM}(0), S_M(0), S_{MF}(0), S_{MM}(0) > 0.$$

It is also true that

$$N_M = S_M + I_M,$$

$$N_F = S_F + I_F,$$

$$N_{FM} = S_{FM} + I_{FM},$$

$$N_{MF} = S_{MF} + I_{MF},$$

$$N_{MM} = S_{MM} + I_{MM},$$

and

$$1 = S_F + I_F + S_{FM} + I_{FM} + S_M + I_M + S_{MM} + I_{MM} + S_{MF} + I_{MF}.$$

Note that as with the basic pairing model (3.1)-(3.4), $N_{FM} = N_{MF}$; it is not necessarily true, however, that $S_{FM} = S_{MF}$, or that $I_{FM} = I_{MF}$. This is because the

distribution of infectious and susceptible persons need not be the same between pairing classes: paired persons do not necessarily have a partner of like infection status.

4.1.1 Basic Reproduction Number and Next Generation Matrix Method

The basic reproduction number ($\mathcal{R}_0$) is the expected number of secondary infections produced by a single infectious individual introduced into a disease-free population. The characterization of $\mathcal{R}_0$ for a particular disease model is an important aspect of mathematical epidemiology.

The magnitude of $\mathcal{R}_0$ is disease- and context-dependent, with larger $\mathcal{R}_0$ values associated with increased disease transmission. It is also a threshold condition for the disease circumstances being modeled: if $\mathcal{R}_0$ is greater than one, then the disease may invade the population and cause a significant outbreak of infection. If $\mathcal{R}_0$ is less than one, the disease does not invade if introduced at a low level.

A mathematical expression for $\mathcal{R}_0$ indicates what effect particular parameters and, by extension, public health actions can and do have on the spread of the infectious disease.

Next Generation Matrix Method

Given a compartmental disease model such as (4.1)-(4.10), the next generation matrix method of Watmough and van den Driessche [23] may be used to determine the analytical form of the basic reproduction number and the stability of the disease free equilibrium (DFE).

To begin, the disease model is written

$$x'(t) = f(x),$$

where $x \in \mathbb{R}^n$, and the first k elements of x correspond to the infectious classes, followed by $n-k$ non-infectious classes. For the pairing and disease model, $x = (I_F, I_{FM}, I_M, I_{MF}, I_{MM}, S_F, S_{FM}, S_M, S_{MF}, S_{MM})$.

The first k equations of $f(x)$, corresponding to the infectious class' dynamics, are then partitioned into two $k \times 1$ vectors,

$$f_k(x) = \mathcal{F} - \mathcal{V},$$

with $\mathcal{F}$ describing new infections, and $\mathcal{V}$ containing information on all other inter-compartmental flows. The Jacobian matrices, with respect to $(x_1, \ldots, x_k)$, of $\mathcal{F}$ and $\mathcal{V}$ are calculated as F and V, respectively. The next generation matrix is FV^{-1}, evaluated at the DFE.

The full model $x'(t) = f(x)$ must satisfy five assumptions:

A1 The rates of transfer into, transfer out of, and appearance of new infectious individuals in each compartment are nonegative.

A2 The rates of transfer out of and appearance of new infectious individuals in an empty compartment is zero.

A3 No new infections arise in disease-free compartments (e.g. infectious persons leave susceptible class).

A4 There is no immigration of infectious individuals.

A5 The equilibria of the disease-free system, *i.e.*, the $n-k$ equations corresponding to the susceptible classes $x_{k+1} \ldots x_n$, is linearly stable.

Conditions A1-A4 ensure that the eigenvalues of $F - V$ have negative real part if and only if the spectral radius, ρ, of the next generation matrix is less than one.

Thus when condition A5 is also met, the local stability of the entire system at the DFE is competely determined by the matrix FV^{-1}.

The basic reproduction number is defined to be $\rho(FV^{-1})$. When A1-A5 are satisfied and $\mathcal{R}_0 < 1$, the DFE is locally stable.

Application of Method

In the case of the pairing and model (4.1)-(4.10), the DFE is
$x_0 = (0, 0, 0, 0, 0, S_F = N_F^*, S_{FM} = N_{FM}^*, S_M = N_M^*, S_{MF} = N_{MF}^*, S_{MM} = N_{MM}^*)$, where $N_F^*, \ldots, N_{MM}^*$ are the equilibrium solution of the basic pairing model (3.1)-(3.4). Assumptions A1-A4 are satisfied by construction of the model. The disease-free system is the set of susceptibles' equations, (4.6)-(4.10), with $I_F = I_{FM} = I_M = I_{MF} = I_{MM} = 0$; this is equivalent to the pairing model of Chapter 3. The linear stability of this system, *i.e.*, the satisfaction of A5, is shown in Section 3.1.2. Therefore, we may use the method of [23] to determine $\mathcal{R}_0$ and the stability of the pairing model with disease at the DFE.

The vector describing new infections is

$$\mathcal{F} = \begin{pmatrix} \alpha_B \frac{\beta}{\alpha_B+\beta} \frac{I_{MF}}{N_{MF}} S_{FM} \\ 0 \\ \alpha_B \frac{\beta}{\alpha_B+\beta} \left(\frac{I_{FM}}{N_{FM}} S_{MF} + \frac{I_{MM}}{N_{MM}} S_{MM} \right) \\ 0 \\ 0 \end{pmatrix}.$$

The vector describing all other compartmental flows is

$$\mathcal{V} = \begin{pmatrix} \alpha_F N_M I_F - \alpha_B I_{FM} \\ \alpha_B I_{FM} - \alpha_F N_M I_F \\ (\alpha_F(2N_M+N_F) I_M - \alpha_B(I_{MF}+I_{MM}) \\ \alpha_B I_{MF} - \alpha_F N_F I_M \\ \alpha_B I_{MM} - 2\alpha_F N_M I_M \end{pmatrix}.$$

Differentiating $\mathcal{F}$ and $\mathcal{V}$ with respect to $(I_F, I_{FM}, I_M, I_{MF}, I_{MM})$, and evaluating each at the DFE,

$$F(x_0) = \begin{pmatrix} 0 & 0 & 0 & \alpha_B \frac{\beta}{\alpha_B+\beta} & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & \alpha_B \frac{\beta}{\alpha_B+\beta} & 0 & 0 & \alpha_B \frac{\beta}{\alpha_B+\beta} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$V(x_0) = \begin{pmatrix} \alpha_F N_M^* & -\alpha_B & 0 & 0 & 0 \\ -\alpha_F N_M^* & \alpha_B & 0 & 0 & 0 \\ 0 & 0 & \alpha_F(2N_M^* + N_F^*) & -\alpha_B & -\alpha_B \\ 0 & 0 & -\alpha_F N_F^* & \alpha_B & 0 \\ 0 & 0 & -\alpha_F N_M^* & 0 & \alpha_B \end{pmatrix}.$$

The first row of $V(x_0)$ is a multiple of the second row of $V(x_0)$, thus V is singular when evaluated at the DFE. It follows that FV^{-1} does not exist, and the basic reproduction number is undefined (the eigenvalues and spectral radius of FV^{-1} approach infinity). Essentially, this occurs because there is no supply of "fresh" susceptibles. A more realistic model incorporates the vital dynamics of a population: birth, migration and death.

4.2 Model with Vital Dynamics

In this section we add population influx and outflow to the pairing and disease model of Section 4.1. The next generation method of [23] is employed to find an analytic expression for the basic reproduction number, $\mathcal{R}_0$.

Define d to be the percent death rate of susceptible individuals; define γ to be the percent death rate of infectious individuals ($\gamma \geq d$). Let $P = N_F + N_{FM}$ be

the proportion of the population that is female (as in Chapter 3). Note that at the DFE, $N_F = S_F$ and $N_{FM} = S_{FM}$. Let the rate of influx into the population (e.g. maturation or migration into the injecting community) be b, and assume that persons entering the population are susceptible. Figure 4.2 shows the flow of the disease and pairing model with vital dynamics.

Rates of Flow

The rates of flow due to pairing and infection dynamics in the pairing and disease model with vital dynamics are the same as those derived in Section 4.1 for the pairing and disease model without vital dynamics. The additional terms needed to describe birth or migration into the population are the rate of influx of new females (bP) and the rate of influx of new males ($b(1-P)$). All newly introduced individuals are assumed to enter a susceptible singles' class (S_F or S_M).

Each susceptible compartment S is reduced at the death rate dS, and each infectious compartment I is reduced at the death γI, where $d \geq 0, \gamma > 0$ are percent death rates.

Paired persons also change class following the death of their partner; they enter a singles' class. Consider those pairs involving a female and an infectious male. Each female is infectious with probability $\frac{I_{FM}}{N_{FM}}$, and the death rate of such individuals is γ; the term $\frac{I_{FM}}{N_{FM}}\gamma I_{MF}$ is thus the rate of influx from I_{MF} into I_M due to death of infectious female partners. Similarly, $\frac{S_{FM}}{N_{FM}}dI_{MF}$ is the rate of influx into I_M from I_{MF} due to death of susceptible female partners. A pair of rate terms such as these describe the movement out of each paired infectious class into the appropriate singles' class corresponding to death of infectious partners and death of a susceptible partners.

Now consider those pairs involving susceptible males with female partners: each woman is susceptible with probability S_{FM}/N_{FM} and infectious with probability

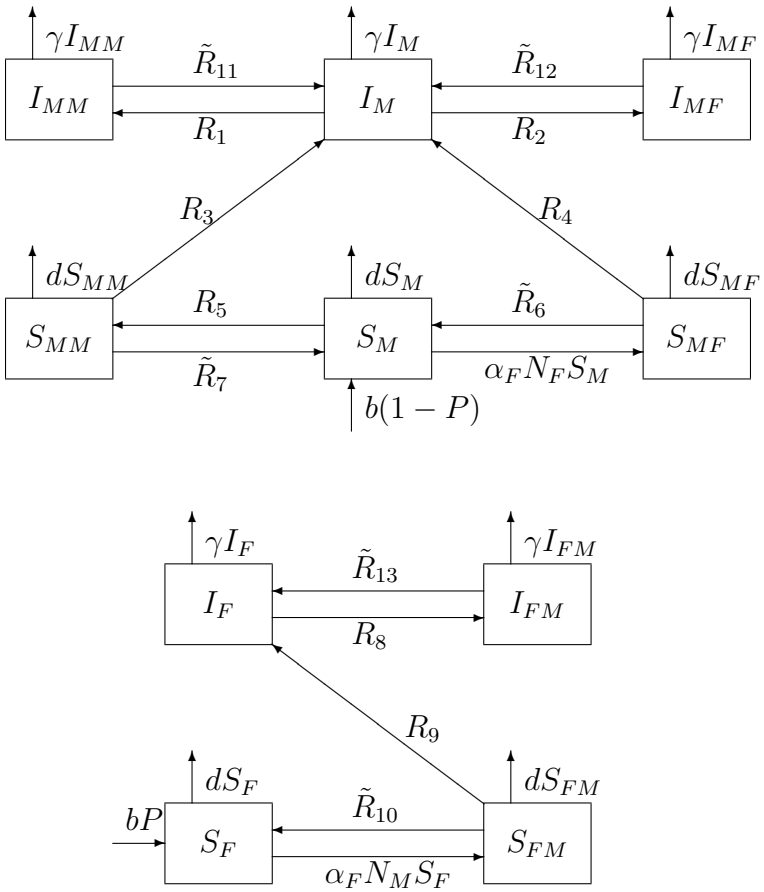

Figure 4.2: Compartmental flow of the pairing and disease model with vital dynamics. $R_1 - R_{10}$ are as given for the model without vital dynamics in Figure 4.1.

$$\tilde{R}_6 = R_6 + d\tfrac{S_{MF}}{N_{MF}} S_{FM} + \gamma \tfrac{S_{MF}}{N_{MF}} I_{FM} \qquad \tilde{R}_7 = R_7 + d\tfrac{S_{MM}}{N_{MM}} S_{MM} + \gamma \tfrac{S_{MM}}{N_{MM}} I_{MM}$$
$$\tilde{R}_{10} = R_{10} + d\tfrac{S_{FM}}{N_{FM}} S_{MF} + \gamma \tfrac{S_{FM}}{N_{FM}} I_{MF} \qquad \tilde{R}_{11} = \alpha_B I_{MM} + d\tfrac{I_{MM}}{N_{MM}} S_{MM} + \gamma \tfrac{I_{MM}}{N_{MM}} I_{MM}$$
$$\tilde{R}_{12} = \alpha_B I_{MF} + d\tfrac{I_{MF}}{N_{MF}} S_{FM} + \gamma \tfrac{I_{MF}}{N_{MF}} I_{FM} \qquad \tilde{R}_{13} = \alpha_B I_{FM} + d\tfrac{I_{FM}}{N_{FM}} S_{MF} + \gamma \tfrac{I_{FM}}{N_{FM}} I_{MF}$$

I_{FM}/N_{FM}. The total rate out of the paired susceptible compartment S_{MF} due to partner death is thus $\left(\frac{S_{FM}}{N_{FM}}d + \frac{I_{FM}}{N_{FM}}\gamma\right) S_{MF}$. Similar terms are seen in the equations decribing the evolution of S_{FM} and S_{MM}.

Appending birth and death terms to the pairing and disease model (4.1)-(4.10), the pairing and disease model with vital dynamics is

$$
\begin{aligned}
I'_F &= -\alpha_F N_M I_F + \alpha_B I_{FM} + \alpha_B \frac{\beta}{\alpha_B+\beta}\frac{I_{MF}}{N_{MF}} S_{FM} + \gamma \frac{I_{FM}}{N_{FM}} I_{MF} && (4.11)\\
&\quad + d\frac{I_{FM}}{N_{FM}} S_{MF} - \gamma I_F && (4.12)\\
I'_{FM} &= \alpha_F N_M I_F - \alpha_B I_{FM} - \gamma \frac{I_{FM}}{N_{FM}} I_{MF} - d\frac{I_{FM}}{N_{FM}} S_{MF} - \gamma I_{FM} && (4.13)\\
I'_M &= -2\alpha_F N_M I_M - \alpha_F N_F I_M + \alpha_B I_{MM} + \alpha_B I_{MF}\\
&\quad + \alpha_B \frac{\beta}{\alpha_B+\beta}\left(\frac{I_{MM}}{N_{MM}} S_{MM} + \frac{I_{FM}}{N_{FM}} S_{MF}\right) + \gamma\left(\frac{I_{MF}}{N_{MF}} I_{FM} + \frac{I_{MM}}{N_{MM}} I_{MM}\right)\\
&\quad + d\left(\frac{I_{MF}}{N_{MF}} S_{FM} + \frac{I_{MM}}{N_{MM}} S_{MM}\right) - \gamma I_M && (4.14)\\
I'_{MF} &= \alpha_F N_F I_M - \alpha_B I_{MF} - \gamma \frac{I_{MF}}{N_{MF}} I_{FM} - d\frac{I_{MF}}{N_{MF}} S_{FM} - \gamma I_{MF} && (4.15)\\
I'_{MM} &= 2\alpha_F N_M I_M - \alpha_B I_{MM} - \gamma \frac{I_{MM}}{N_{MM}} I_{MM} - d\frac{I_{MM}}{N_{MM}} S_{MM} - \gamma I_{MM} && (4.16)\\
S'_F &= bP + \alpha_B\left(\frac{S_{MF}}{N_{MF}} S_{FM} + \frac{\alpha_B}{\alpha_B+\beta}\frac{I_{MF}}{N_{MF}} S_{FM}\right) - \alpha_F N_M S_F\\
&\quad + \gamma \frac{S_{FM}}{N_{FM}} I_{MF} + d\frac{S_{FM}}{N_{FM}} S_{MF} - dS_F && (4.17)\\
S'_{FM} &= \alpha_F N_M S_F - \alpha_B S_{FM} - \gamma \frac{S_{FM}}{N_{FM}} I_{MF} - d\frac{S_{FM}}{N_{FM}} S_{MF} - dS_{FM} && (4.18)
\end{aligned}
$$

$$
\begin{aligned}
S'_M &= -2\alpha_F N_M S_M - \alpha_F N_F S_M + \alpha_B \left(\frac{S_{MM}}{N_{MM}} S_{MM} + \frac{S_{FM}}{N_{FM}} S_{MF} \right) \\
&\quad + \alpha_B \frac{\alpha_B}{\alpha_B + \beta} \left(\frac{I_{MM}}{N_{MM}} S_{MM} + \frac{I_{FM}}{N_{FM}} S_{MF} \right) \\
&\quad + b(1-P) + \gamma \left(\frac{S_{MF}}{N_{MF}} I_{FM} + \frac{S_{MM}}{N_{MM}} I_{MM} \right) \\
&\quad + d \left(\frac{S_{MF}}{N_{MF}} S_{FM} + \frac{S_{MM}}{N_{MM}} S_{MM} \right) - dS_M \qquad (4.19) \\
S'_{MF} &= \alpha_F N_F S_M - \alpha_B S_{MF} - \gamma \frac{S_{MF}}{N_{MF}} I_{FM} - d \frac{S_{MF}}{N_{MF}} S_{FM} - dS_{MF} \qquad (4.20) \\
S'_{MM} &= 2\alpha_F N_M S_M - \alpha_B S_{MM} - \gamma \frac{S_{MM}}{N_{MM}} I_{MM} - d \frac{S_{MM}}{N_{MM}} S_{MM} - dS_{MM} \qquad (4.21)
\end{aligned}
$$

with nonnegative initial conditions $I_F(0), I_{FM}(0), I_M(0), I_{MF}(0), I_{MM}(0), S_F(0)$, $S_{FM}(0), S_M(0), S_{MF}(0)$, and $S_{MM}(0)$. The initial conditions satisfy

$$
I(0) = I_F(0) + I_{FM}(0) + I_M(0) + I_{MF}(0) + I_{MM}(0) > 0,
$$

and

$$
S_F(0), S_{FM}(0), S_M(0), S_{MF}(0), S_{MM}(0) > 0.
$$

4.2.1 Basic Reproduction Number $\mathcal{R}_0$

Now we follow the notation and method of [23], as outlined in Section 4.1.1, to calculate the next generation matrix FV^{-1} and the basic reproduction number, $\mathcal{R}_0$, of the pairing and disease model with vital dynamics (4.11)-(4.21).

New infections are only seen in the I_F and I_M classes, thus the vector of new

infections is

$$\mathcal{F} = \begin{pmatrix} \alpha_B \frac{\beta}{\alpha_B+\beta} \frac{I_{MF}}{N_{MF}} S_{FM} \\ 0 \\ \alpha_B \frac{\beta}{\alpha_B+\beta} \left(\frac{I_{FM}}{N_{FM}} S_{MF} + \frac{I_{MM}}{N_{MM}} S_{MM} \right) \\ 0 \\ 0 \end{pmatrix}.$$

The nonzero terms of $\mathcal{F}$ correspond to persons who became infectious during the course of a relationship, and are now leaving the pairing in which they became infectious to enter an infectious singles' class. All other population dynamics are then captured by

$$\mathcal{V} = \begin{pmatrix} \alpha_F N_M I_F + \gamma I_F - \alpha_B I_{FM} - \gamma \frac{I_{FM}}{N_{FM}} I_{MF} - d \frac{I_{FM}}{N_{FM}} S_{MF} \\ \alpha_B I_{FM} + \gamma I_{FM} + \gamma \frac{I_{FM}}{N_{FM}} I_{MF} + d \frac{I_{FM}}{N_{FM}} S_{MF} - \alpha_F N_M I_F \\ (\alpha_F(2N_M+N_F)+\gamma) I_M - \gamma \left(\frac{I_{MF}}{N_{MF}} I_{FM} + \frac{I_{MM}}{N_{MM}} I_{MM} \right) - d \left(\frac{I_{MF}}{N_{MF}} S_{FM} + \frac{I_{MM}}{N_{MM}} S_{MM} \right) - \alpha_B (I_{MF} + I_{MM}) \\ \alpha_B I_{MF} + \gamma I_{MF} + \gamma \frac{I_{MF}}{N_{MF}} I_{FM} + d \frac{I_{MF}}{N_{MF}} S_{FM} - \alpha_F N_F I_M \\ \alpha_B I_{MM} + \gamma I_{MM} + \gamma \frac{I_{MM}}{N_{MM}} I_{MM} + d \frac{I_{MM}}{N_{MM}} S_{MM} - 2\alpha_F N_M I_M \end{pmatrix}.$$

By construction, A1-A4 are satisfied by the pairing and disease model with vital dynamics. The proof of A5, including the existence and uniqueness of the positive equilibrium solution of the disease free system, is given in Appendix A.

The Matrices F and V

Let $(\tilde{N}_F, \tilde{N}_{FM}, \tilde{N}_M, \tilde{N}_{MM})$ be the unique positive equilibrium of the disease-free pairing system with vital dynamics (see Appendix A). Differentiating $\mathcal{F}$ and $\mathcal{V}$ with respect to $(I_F, I_{FM}, I_M, I_{MF}, I_{MM})$, and evaluating at the DFE

$$x_0 = (0, 0, 0, 0, 0, S_F = \tilde{N}_F, S_{FM} = \tilde{N}_{FM}, S_M = \tilde{N}_M, S_{MF} = \tilde{N}_{MF}, S_{MM} = \tilde{N}_{MM}),$$

$$F(x_0) = \begin{pmatrix} 0 & 0 & 0 & \frac{\alpha_B\beta}{\alpha_B+\beta} & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{\alpha_B\beta}{\alpha_B+\beta} & 0 & 0 & \frac{\alpha_B\beta}{\alpha_B+\beta} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$V(x_0) = \begin{pmatrix} \alpha_F\tilde{N}_M + \gamma & -\alpha_B - d & 0 & 0 & 0 \\ -\alpha_F\tilde{N}_M & \alpha_B + \gamma + d & 0 & 0 & 0 \\ 0 & 0 & \gamma + \alpha_F(2\tilde{N}_M + \tilde{N}_F) & -\alpha_B - d & -\alpha_B - d \\ 0 & 0 & -\alpha_F\tilde{N}_F & \alpha_B + \gamma + d & 0 \\ 0 & 0 & -2\alpha_F\tilde{N}_M & 0 & \alpha_B + \gamma + d \end{pmatrix}.$$

Notice that this is the V matrix of the disease model without vital dynamics, with the α_B terms replaced by $\alpha_B + d$, and with the addition of γ terms on the diagonal. This represents the increased rate of removal from paired classes due to the vital dynamics: because the system is near the DFE, any paired infectious individuals have susceptible partners. The death of a susceptible partner (occurs with rate d) moves the infectious partner from the paired class to the singles' class, effectively increasing the pair separation rate, α_B, by a factor d. The gamma terms are the removal from an infectious class due to the death of the infectious individual.

For ease of notation, we drop the tilde, and let

$$x_0 = (0, 0, 0, 0, 0, N_F, N_{FM}, N_M, N_{MF}, N_{MM})$$

denote the DFE of (4.1)-(4.10).

Next Generation Matrix $\mathbf{FV^{-1}}$

Now we use a block approach to find FV^{-1}. Let

$$V(x_0) = \begin{pmatrix} A & 0 \\ 0 & B \end{pmatrix}$$

where

$$A = \begin{pmatrix} \alpha_F N_M + \gamma & -\alpha_B - d \\ -\alpha_F N_M & \alpha_B + \gamma + d \end{pmatrix}$$

and

$$B = \begin{pmatrix} \gamma + \alpha_F(2N_M + N_F) & -\alpha_B - d & -\alpha_B - d \\ -\alpha_F N_F & \alpha_B + \gamma + d & 0 \\ -2\alpha_F N_M & 0 & \alpha_B + \gamma + d \end{pmatrix}.$$

Then

$$V^{-1}(x_0) = \begin{pmatrix} A^{-1} & 0 \\ 0 & B^{-1} \end{pmatrix},$$

and

$$FV^{-1} = \tilde{\beta} \begin{pmatrix} 0 & 0 & \bar{b}_{21} & \bar{b}_{22} & \bar{b}_{23} \\ 0 & 0 & 0 & 0 & 0 \\ \bar{a}_{21} & \bar{a}_{22} & \bar{b}_{31} & \bar{b}_{32} & \bar{b}_{33} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

where $\tilde{\beta} = \frac{\alpha_B \beta}{\alpha_B + \beta}$, and $\bar{a}_{ij}$ and $\bar{b}_{ij}$ are the ij entries of A^{-1} and B^{-1}, respectively.

Spectral Radius $\rho(\mathbf{FV^{-1}})$

The eigenvalues of FV^{-1} are zero (with multiplicity three) and
$\tilde{\beta}\left(\frac{1}{2}\bar{b}_{31} \pm \frac{1}{2}\sqrt{\bar{b}_{31}^2 + 4\bar{a}_{21}\bar{b}_{21}}\right)$, thus the spectral radius (and basic reproduction number)

is

$$\mathcal{R}_0 \;=\; \rho\left(FV^{-1}\right) \;=\; \tilde{\beta}\left(\frac{\bar{b}_{31}}{2}+\sqrt{\left(\frac{\bar{b}_{31}}{2}\right)^2+\bar{a}_{21}\bar{b}_{21}}\right). \tag{4.22}$$

Notice that

$$|A| = (\alpha_F N_M+\gamma)(\alpha_B+\gamma+d)-\alpha_F N_M(\alpha_B+d),$$

and

$$\begin{aligned} |B| \;=\; & -2\alpha_F N_M(\alpha_B+d)(\alpha_B+\gamma+d) \\ & +(\alpha_B+\gamma+d)[(\alpha_B+\gamma+d)(\gamma+\alpha_F(2N_M+N_M))-\alpha_F N_F(\alpha_B+d)]. \end{aligned}$$

Let a_{ij} and b_{ij} denote entries of A and B, respectively. Next we determine the form of $\bar{a}_{21}, \bar{b}_{21}$, and $\bar{b}_{31}$:

$$\begin{aligned} \bar{a}_{21} \;&=\; \frac{-a_{21}}{|A|} \\ &=\; \frac{\alpha_F N_M}{(\alpha_F N_M+\gamma)(\alpha_B+\gamma+d)-\alpha_F N_M(\alpha_B+d)} \\ &=\; \frac{\alpha_F N_M}{\gamma(\alpha_F N_M+\alpha_B+\gamma+d)} \\ &=\; \frac{1}{\gamma}\cdot\frac{(\alpha_B+\gamma+d)^{-1}}{[(\alpha_B+\gamma+d)^{-1}+(\alpha_F N_M)^{-1}]} \end{aligned} \tag{4.23}$$

$$
\begin{aligned}
\bar{b}_{21} &= \frac{1}{|B|}\begin{vmatrix} b_{23} & b_{21} \\ b_{33} & b_{31} \end{vmatrix} \\
&= \frac{1}{|B|}\begin{vmatrix} 0 & -\alpha_F N_F \\ \alpha_B+\gamma+d & -2\alpha_F N_M \end{vmatrix} \\
&= \frac{\alpha_F N_F(\alpha_B+\gamma+d)}{|B|} \\
&= \frac{\alpha_F N_F}{-2\alpha_F N_M(\alpha_B+d)+[(\alpha_B+\gamma+d)(\gamma+\alpha_F(2N_M+N_F))-\alpha_F N_F(\alpha_B+d)]} \\
&= \frac{\alpha_F N_F}{\gamma(2\alpha_F N_M+\alpha_F N_F+\alpha_B+\gamma+d)} \\
&= \frac{1}{\gamma}\cdot\frac{\alpha_F N_F}{(\alpha_F N_F+2\alpha_F N_M)}\cdot\frac{(\alpha_B+\gamma+d)^{-1}}{[(\alpha_B+\gamma+d)^{-1}+(\alpha_F N_F+2\alpha_F N_M)^{-1}]}
\end{aligned} \tag{4.24}
$$

$$
\begin{aligned}
\bar{b}_{31} &= \frac{1}{|B|}\begin{vmatrix} b_{21} & b_{22} \\ b_{31} & b_{32} \end{vmatrix} \\
&= \frac{1}{|B|}\begin{vmatrix} -\alpha_F N_F & \alpha_B+\gamma+d \\ -2\alpha_F N_M & 0 \end{vmatrix} \\
&= \frac{2\alpha_F N_M(\alpha_B+\gamma+d)}{|B|} \\
&= \frac{2\alpha_F N_M}{-2\alpha_F N_M(\alpha_B+d)+[(\alpha_B+\gamma+d)(\gamma+\alpha_F(2N_M+N_F))-\alpha_F N_F(\alpha_B+d)]} \\
&= \frac{2\alpha_F N_M}{\gamma(2\alpha_F N_M+\alpha_F N_F+\alpha_B+\gamma+d)} \\
&= \frac{1}{\gamma}\cdot\frac{2\alpha_F N_M}{(2\alpha_F N_M+\alpha_F N_F)}\cdot\frac{(\alpha_B+\gamma+d)^{-1}}{[(\alpha_B+\gamma+d)^{-1}+(\alpha_F N_F+2\alpha_F N_M)^{-1}]}
\end{aligned} \tag{4.25}
$$

Analytic Form of $\mathcal{R}_0$

Substituting (4.23), (4.24), and (4.25) into (4.22) and simplifying, we have

$$
\mathcal{R}_0 = \frac{\tilde{\beta}}{\gamma}\left(\mathcal{R}_1+\sqrt{\mathcal{R}_1^2+\mathcal{R}_2}\right) \tag{4.26}
$$

where

$$\mathcal{R}_1 = \frac{\alpha_F N_M (\alpha_B + \gamma + d)^{-1}}{(\alpha_F N_F + 2\alpha_F N_M)[(\alpha_F N_F + 2\alpha_F N_M)^{-1} + (\alpha_B + \gamma + d)^{-1}]} \quad (4.27)$$

$$\mathcal{R}_2 = \frac{\alpha_F N_F (\alpha_B + \gamma + d)^{-2}[(\alpha_F N_F + 2\alpha_F N_M)^{-1} + (\alpha_B + \gamma + d)^{-1}]^{-1}}{(\alpha_F N_F + 2\alpha_F N_M)[(\alpha_F N_M)^{-1} + (\alpha_B + \gamma + d)^{-1}]} \quad (4.28)$$

To understand the relationships between $\mathcal{R}_0$ and the parameters and variables of the pairing and disease model with vital dynamics, we need to analytically and numerically investigate the behavior of $\mathcal{R}_0$.

4.3 Interpretation of $\mathcal{R}_0$

The expression (4.22) given for $\mathcal{R}_0$ contains four terms: $\bar{a}_{21}, \bar{b}_{21}, \frac{1}{2}\bar{b}_{31}$, and $\tilde{\beta}$. The first three are expected times certain infectious individuals spend paired, and the last is the effective overall transmission rate.

The Terms $\bar{a}_{21}$, $\bar{b}_{21}$, and $\bar{b}_{31}$

The v_{ij} term of V^{-1} is the average time an infectious individual introduced into the x_j class at the DFE will spend in the x_i class during its lifetime [23]. The term $\bar{a}_{21}$ is thus the time an individual introduced into the x_1 class (*i.e.*, single infectious female) will spend in the x_2 class (*i.e.*, infectious female paired with a male) during their lifetime. We can see this is indeed the meaning of (4.23) through the following reasoning.

The effective pairing rate of infectious females is $\alpha_F S_M$; $1/(\alpha_F S_M)$ is thus the expected time an infectious female will spend unpaired. The term $(\alpha_B + \gamma + d)$ is the rate that paired infectious females become single - through pair separation, death of an infectious partner, or death of a susceptible partner - thus $1/(\alpha_B + \gamma + d)$

gives the average time an initial infectious female will spend paired. The fraction $(\alpha_B + \gamma + d)^{-1})/((\alpha_B + \gamma + d)^{-1}) + (\alpha_F S_M)^{-1}))$ is the proportion of time that an average infectious female spends in a pair. Then $\bar{a}_{21}$ is the expected lifetime of an infectious individual $(1/\gamma)$, multiplied by the fraction of time spent paired. This yields the total time an average infectious female will spend paired with a male, as expected.

Following similar logic, we deconstruct $\bar{b}_{21} = v_{43}$. As with all newly infectious persons, $1/\gamma$ is the expected lifetime following infection of that individual. In the case of infectious males pairing with susceptible females, the effective pairing rate is $\alpha_F S_F$. The total pairing rate, including partnership formation with both males and females, is $\alpha_F S_F + 2\alpha_F S_M$. The inverse quantity, $(\alpha_F S_F + 2\alpha_F S_M)^{-1}$ is thus the expected time an infectious male will spend paired. As with the prior case of infectious paired females, the term $(\alpha_B + \gamma + d)^{-1}$ gives the expected time an initially infected male will spend paired. The fraction $(\alpha_B+\gamma+d)^{-1}/((\alpha_F S_F+2\alpha_F S_M)^{-1}+(\alpha_B+\gamma+d)^{-1})$ is therefore the expected proportion of time an infectious male spends paired. The term $\bar{b}_{21}$ is then the expected infectious lifetime of a male, multipled by the fraction of time spent paired, and then multiplied again by the fraction of paired time spent with a female; this gives the expected time an infectious male spends paired with a female, *i.e.*, in the I_{MF} portion of the population.

Finally, $\bar{b}_{31}$ contains the terms $1/\gamma$ and $(\alpha_B+\gamma+d)^{-1}/((\alpha_F S_F+2\alpha_F S_M)^{-1}+(\alpha_B+\gamma+d)^{-1})$, which are interpreted following the reasoning of the previous paragraphs. The third term of $\bar{b}_{31}$ is $2\alpha_F S_M/((\alpha_F S_F+2\alpha_F S_M)^{-1}+(\alpha_B+\gamma+d)^{-1})$; this represents the expected proportion of time spent paired that an infectious male has a male partner. The product of the three terms in $\bar{b}_{31}$ gives us the expected time an infectious male spends paired with another male.

The Term $\tilde{\beta}$

The lefthand-most term of (4.22) is

$$\tilde{\beta} = \alpha_B \cdot \frac{\beta}{\alpha_B + \beta},$$

where $\beta/(\alpha_B + \beta)$ is the probability that transmission occurs before separation of a pair involving one susceptible and one infectious individual. Recall that α_B is the rate that each pair separates. Thus $\tilde{\beta}$ is the rate at which new infections appear in the population (recall that "newly" infectious individuals' disease status is only apparent upon pair separation).

Special Cases

The formulation (4.22) for $\mathcal{R}_0$ can be interpreted in relation to simpler compartmental disease models by considering two special cases: $\bar{b}_{31} = 0$, and $\bar{a}_{21} = 0$ or $\bar{b}_{21} = 0$.

When $\bar{a}_{21} = 0$ or $\bar{b}_{21} = 0$ we have the situation that no female-male pairs form; effectively, the disease is transmited only within a homosexual pairing population. The basic reproduction number is given by

$$\mathcal{R}_0 = \tilde{\beta}\bar{b}_{31}.$$

This is equivalent to the expression for $\mathcal{R}_0$ that is recovered from the basic homosexual SI compartmental epidemic model; see, for example [22].

In the case that $\bar{b}_{31} = 0$, no male-male pairing occurs, and the basic reproduction number is

$$\mathcal{R}_0 = \tilde{\beta}\sqrt{\bar{a}_{21}\bar{b}_{21}}.$$

This is the $\mathcal{R}_0$ given by the classic two-sex epidemic model; see, for example, [22].

$\mathcal{R}_0$ is Bounded

Here we show that the term $\left(1+\sqrt{\mathcal{R}_1^2+\mathcal{R}_2}\right)$ of (4.26) is bounded above, hence $\mathcal{R}_0$ is also bounded above.

First we have that

$$\begin{aligned}
2\mathcal{R}_1+\mathcal{R}_2 &= \frac{2\alpha_F N_M(\alpha_B+\gamma+d)^{-1}}{(\alpha_F N_F+2\alpha_F N_M)[(\alpha_F N_F+2\alpha_F N_M)^{-1}+(\alpha_B+\gamma+d)^{-1}]} \\
&\quad + \frac{\alpha_F N_F(\alpha_B+\gamma+d)^{-2}[(\alpha_F N_F+2\alpha_F N_M)^{-1}+(\alpha_B+\gamma+d)^{-1}]^{-1}}{(\alpha_F N_F+2\alpha_F N_M)[(\alpha_F N_M)^{-1}+(\alpha_B+\gamma+d)^{-1}]} \\
&= \frac{1}{\frac{\alpha_B+\gamma+d}{\alpha_F N_F+2\alpha_F N_M}+1}\cdot\frac{2\alpha_F N_M+(\frac{\alpha_B+\gamma+d}{\alpha_F N_M}+1)^{-1}\alpha_F N_F}{\alpha_F N_F+2\alpha_F N_M} \\
&< 1.
\end{aligned}$$

Now

$$\begin{aligned}
2\mathcal{R}_1+\mathcal{R}_2 &\leq 1 \\
\Rightarrow \mathcal{R}_1^2+\mathcal{R}_2 &\leq 1-2\mathcal{R}_1+\mathcal{R}_1^2 \\
\Rightarrow \sqrt{\mathcal{R}_1^2+\mathcal{R}_2} &\leq 1-\mathcal{R}_1 \\
\Rightarrow \mathcal{R}_1+\sqrt{\mathcal{R}_1^2+\mathcal{R}_2} &\leq 1.
\end{aligned}$$

We conclude that

$$\begin{aligned}
\mathcal{R}_0 &= \frac{\tilde{\beta}}{\gamma}\cdot\left(\mathcal{R}_1+\sqrt{\mathcal{R}_1^2+\mathcal{R}_2}\right) \\
&\leq \frac{\tilde{\beta}}{\gamma} \\
&\leq \frac{\beta}{\gamma}.
\end{aligned}$$

To understand how the basic reproduction number depends on specific model parameters $(\alpha_B, \alpha_F, \beta, d, \gamma)$, we need reasonable parameter ranges with which to inform

numerical investigations.

4.4 Parameter Exploration

In this section we explore the dependence of $\mathcal{R}_0$ on $\alpha_F, \alpha_B, \beta, d$, and γ. We use survey data (see Section 2.1) and 2006 reports of Victoria IDU HIV and HCV prevalence to estimate the parameter P,the pairing class densities and the corresponding distribution of susceptibles and infectious individuals among pairing classes. These estimates are used in numerical analysis of the qualitative behavior of $\mathcal{R}_0$. The pairing frequency data used is given in Appendix B.

4.4.1 Parameter and Variable Estimates

Population Proportion of Females P

Sex, syringe-sharing status (*i.e.*, pairing status), and where applicable, the sex of a person's syringe-sharing partner, were recorded for $N = 90$ individuals as part of the IDU interviews conducted in May-June 2008 (see Section 2.1). The resulting point estimate of the female fraction of the population (P) is

$$\hat{P} = \frac{27}{90} = 0.3$$

Death Rates d and γ

The expected life span of Canadian females and males born between 1960 and 1990 is in the neighborhood of 75 years (Statistics Canada website www.statcan.gc.ca, November 12, 2009). Thus, the point estimate $\hat{d} = 1/75 = 0.0133$ is an appropriate approximation of the death rate of susceptible individuals as described by the ODE system (4.11)-(4.21).

Pairing Class Densities

Estimates of the percentages of persons in each of the pairing classes (*i.e.*, $\hat{N}_F, \hat{N}_{FM}, \hat{N}_M, \hat{N}_{MF}, \hat{N}_{MM}$) are calculated as the number of individuals who reported being in a given category, divided by the total number of individuals (90). These are listed in Appendix B. The variables dependent on infection status were not directly observable due to ethical restrictions on questioning interviewees regarding their own HIV/HCV status and that of their partner(s). We indirectly estimate these variables by combining the pairing class estimates with existing HIV and HCV prevalence estimates.

Infection Class Densities

In 2006 the HIV prevalence of this population was estimated to be 15.4%, and HCV prevalence estimated to be 68.5% [1]. We use these values as an estimate of the current HIV and HCV prevalence among Victoria IDU.

If we assume pairing to be independent of infection status, the infectious fractions of the pairing population ($I_F, I_{FM}, I_M, I_{MF}, I_{MM}$) may be estimated as the prevalence multiplied by the corresponding pairing (with respect to syringe sharing) fraction estimates ($\hat{N}_F, \hat{N}_{FM}, \hat{N}_M, \hat{N}_{MF}, \hat{N}_{MM}$) given in Appendix B. For example, the estimated fraction of single females infected with HIV is

$$\begin{aligned} \hat{I}_F &= 15.4\% \times \hat{N}_F \\ &= 15.4\% \times \frac{20}{90} \\ &\approx 0.034 \end{aligned}$$

The population proportion of single and susceptible females, S_F, is then estimated by subtracting the estimated infectious single females from the estimated total single females: $\hat{S}_F = \hat{N}_F - \hat{I}_F$. Table 4.2 summarizes the pairing and prevalence estimates

calculated using these methods.

Table 4.2: Estimated susceptible and infectious pairing class fractions of Victoria IDU with respect to (w.r.t.) HIV and HCV. HIV population prevalence is assumed to be 15.4%, HCV population prevalence is 68.5%, both as estimated by a 2006 public health study of Victoria IDU [1].

Population Fraction	w.r.t HIV	w.r.t HCV
I_F	0.03388	0.1507
I_{FM}	0.01232	0.0548
I_M	0.08932	0.3973
I_{MF}	0.00616	0.0274
I_{MM}	0.01232	0.0548
S_F	0.18612	0.0693
S_{FM}	0.06768	0.0252
S_M	0.49068	0.1827
S_{MF}	0.03384	0.0126
S_{MM}	0.06768	0.0252

In the next section we utilize these parameter and variable estimates and explore the behavior of $\mathcal{R}_0$ (4.22) with respect to $\beta, \alpha_B, \alpha_F, d$, and γ.

4.4.2 Parameter Dependence of $\mathcal{R}_0$

We determine the qualitative behavior of $\mathcal{R}_0$ with respect to β via analysis of the partial derivative. The relationship between $\mathcal{R}_0$ and each of the parameters α_B, α_F, d, and γ is explored numerically.

Dependence of $\mathcal{R}_0$ on β

From (4.26), the partial derivative of $\mathcal{R}_0$ with respect to the transmission parameter β is

$$\begin{aligned} \frac{\partial \mathcal{R}_0}{\partial \beta} &= \frac{1}{\gamma} \cdot \frac{\alpha_B^2}{(\alpha_B + \beta)^2} \cdot \left(\mathcal{R}_1 + \sqrt{\mathcal{R}_1^2 + \mathcal{R}_2} \right) \\ &> 0, \end{aligned}$$

where $\mathcal{R}_1, \mathcal{R}_2 > 0$. Thus $\mathcal{R}_0$ is increasing in β. Any public health action reducing the chance of transmission via syringe sharing (e.g. increasing supply of clean syringes or decreasing injection rates) will aid in reducing secondary infections and the spread of disease.

As β grows, $\mathcal{R}_0$ becomes bounded by $\frac{\alpha_B}{\gamma}$. Notice that

$$\lim_{\beta\to\infty} \tilde{\beta} = \lim_{\beta\to\infty} \frac{\alpha_B \beta}{\alpha_B + \beta} = \alpha_B.$$

If we consider the boundedness of $\mathcal{R}_0$ as shown previously, it is clear that in the limit of a large transmission parameter β, the basic reproduction number is controlled by the pair separation rate, α_B, and the average infectious period, $\frac{1}{\gamma}$, that is

$$\begin{aligned} \mathcal{R}_0 &\leq \\ \Rightarrow \mathcal{R}_0 &\leq \frac{\alpha_B}{\gamma} \end{aligned}$$

when β is large.

Using similar logic, when the pair separation rate, α_B, is large, the basic reproduction number is controlled by β and $\frac{1}{\gamma}$. The situation where α_B is large corresponds to the basic homogeneous mixing model: individuals do not have finite partnerships, and each contact is instantaneous.

We numerically investigate the dependence of $\mathcal{R}_0$ on the remaining parameters of the model. In all cases, we set $N_F = 0.20$ and $N_M = 0.50$ (based on the estimates given in Appendix B). The parameters α_B and α_F are more likely to be targets of public health actions (for example, education campaigns regarding safe syringe-sharing and optimal partnership practices) than the death rate, due to greater ease of manipulation. For this reason, we plot $\mathcal{R}_0$ contours with respect to α_B and α_F, and vary the value(s) of β, d, and γ.

Dependence of $\mathcal{R}_0$ on $\alpha_\mathbf{B}$ and $\alpha_\mathbf{F}$

Figure 4.3 shows the relationship between $\mathcal{R}_0$ and the pair formation and separation rates α_F and α_B ($\beta = 0.1, d = \gamma = 0.0133$).

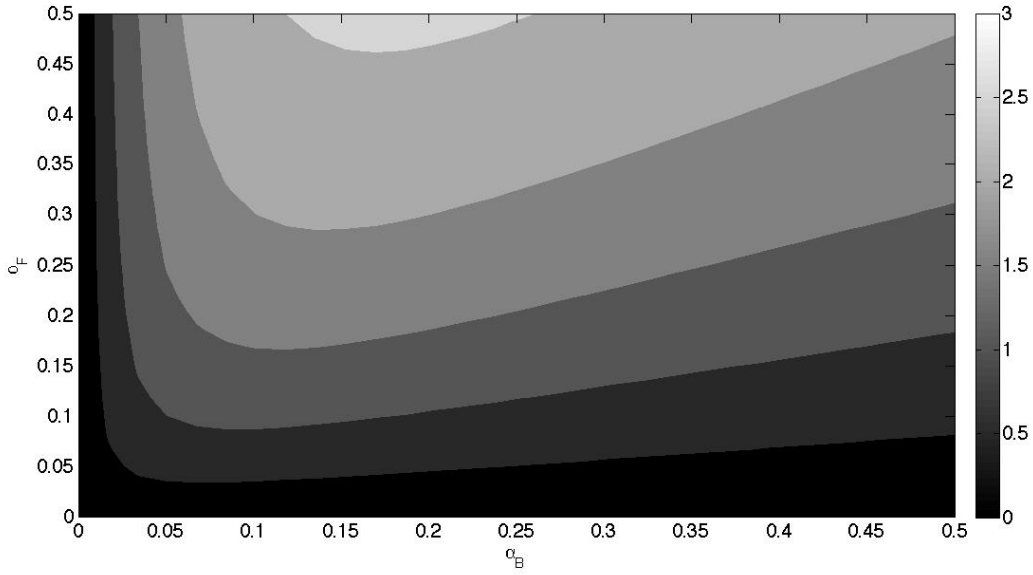

Figure 4.3: Basic reproduction number, $\mathcal{R}_0$, of pairing and disease model with vital dynamics; contours plotted as function of per-person pair formation rate, α_F, and per-pair separation rate, α_B. Darker shades correspond to decreasing $\mathcal{R}_0$; values of $\mathcal{R}_0$ are given on right-hand side shading legend (min=0, max=3). Transmission parameter $\beta = 0.1$; death rate of susceptible individuals $d = 0.0133$; death rate of infectious individuals $\gamma = 0.0133$. Population proportion of susceptible and single females $N_F = 0.20$; population proportion of susceptible and single males $N_M = 0.50$.

When α_B or α_F is small, infectious persons have very long or very few partnerships, repectively. Both of these situations physically limit the secondary infections such an individual may produce, thus $\mathcal{R}_0$ is small.

There is an interval of small α_B values within which $\mathcal{R}_0$ initially increases with α_B. When pairs break more frequently, partnerships are shorter and it is possible for an infectious individual to enter a larger number of pairs. It follows that more secondary infections can occur. Outside of this range (e.g. $0.1 < \alpha_B$ in Figure 4.3),

however, the pair separation rate actually has a negative effect on $\mathcal{R}_0$. This is because the probability of transmission decreases with shorter pair duration.

Increased pair formation generally has a positive effect on $\mathcal{R}_0$. An infectious individual who has a greater number of partners may cause a greater number of secondary infections. The only exception to this is the case where α_B is very small, as the number of lengthy partnerships a person can have is physically limited by the expected life span.

These patterns of dependence on α_B and α_F are preserved when β, d, and γ are varied within a reasonable set of values (e.g. $\beta, d, \gamma \in (0, 0.5)$). The values of $\mathcal{R}_0$ produced increase with β (e.g. in Figure 4.3, $\beta = 0.1$ and $0 \leq \mathcal{R}_0 \leq 3$, whereas when $\beta = 1$ we see the range $2 \leq \mathcal{R}_0 \leq 12$), as expected from the partial derivative analysis. $\mathcal{R}_0$ decreases with both d and γ (see Figure 4.4).

Dependence of $\mathcal{R}_0$ on d and γ

Figure 4.4 shows the behavior of $\mathcal{R}_0$ under three sets of conditions for d and γ ($\beta = 0.1, N_F = 0.2, N_M = 0.5$ in all cases). The qualitative behavior of $\mathcal{R}_0$ is independent of d and γ (Figure 4.4a-c). The magnitude of $\mathcal{R}_0$, however, decreases with γ (e.g. in Figure 4.4(a) $\mathcal{R}_0 \in [0, 4]$, whereas for increased γ in Figure 4.4(b), $\mathcal{R}_0 \in [0, 2]$). The death rate of susceptibles, d, has a small and negative effect on the magnitude of $\mathcal{R}_0$ (compare Figure 4.4(b) with 4.4(c)).

The negative dependence of $\mathcal{R}_0$ on γ and d is proved by examining the partial derivatives of $\mathcal{R}_0$ with respect to both d and γ. From (4.26),

$$\frac{\partial \mathcal{R}_0}{\partial \gamma} = -\frac{\tilde{\beta}}{\gamma^2}\left(\mathcal{R}_1 + \sqrt{\mathcal{R}_1^2 + \mathcal{R}_2}\right) + \frac{\tilde{\beta}}{\gamma}\left(\frac{\partial \mathcal{R}_1}{\partial \gamma} + \frac{1}{2} \cdot \frac{2\mathcal{R}_1 \frac{\partial \mathcal{R}_1}{\partial \gamma} + \frac{\partial \mathcal{R}_2}{\partial \gamma}}{\sqrt{\mathcal{R}_1^2 + \mathcal{R}_2}}\right)$$

where $\tilde{\beta}, \gamma, \mathcal{R}_1, \mathcal{R}_2 > 0$. Thus, to show that $\frac{\partial \mathcal{R}_0}{\partial \gamma} < 0$, it is sufficient to show that $\frac{\partial \mathcal{R}_1}{\partial \gamma}$

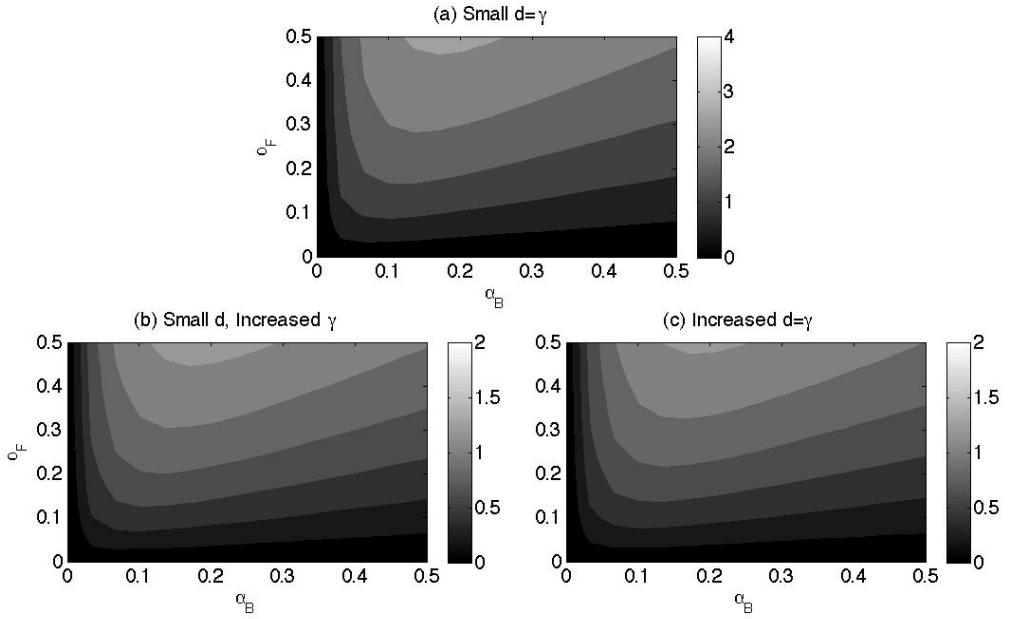

Figure 4.4: Basic reproduction number, $\mathcal{R}_0$, of pairing and disease model with vital dynamics. $\mathcal{R}_0$ decreases with both the death rate of susceptible individuals (d), and the death rate of infectious individuals (γ). (a) $d = \gamma = 0.0133$; (b) $d = 0.0133 < \gamma = 0.0266$; (c) $d = \gamma = 0.0266$. Contours plotted as function of per-person pair formation rate, α_F, and per-pair separation rate, α_B. Darker shades correspond to decreasing $\mathcal{R}_0$; values of $\mathcal{R}_0$ are given on right-hand side of each subplot. Transmission parameter $\beta = 0.1$; population proportion of susceptible and single females $S_F = 0.20$; population proportion of susceptible and single males $S_M = 0.50$.

and $\frac{\partial \mathcal{R}_2}{\partial \gamma}$ are both negative. Consider $\mathcal{R}_1$. From (4.27),

$$\begin{aligned}
\mathcal{R}_1 &= \frac{\alpha_F N_M (\alpha_B + \gamma + d)^{-1}}{(\alpha_F N_F + 2\alpha_F N_M)[(\alpha_F N_F + 2\alpha_F N_M)^{-1} + (\alpha_B + \gamma + d)^{-1}]} \\
&= \frac{\alpha_F N_M}{\alpha_F N_F + 2\alpha_F N_M} \cdot \frac{1}{\left(\frac{\alpha_B + \gamma + d}{\alpha_F N_F + 2\alpha_F N_M} + 1\right)}.
\end{aligned}$$

Differentiating with respect to γ,

$$\begin{aligned}
\frac{\partial \mathcal{R}_1}{\partial \gamma} &= -\frac{\alpha_F N_M}{\alpha_F N_F + 2\alpha_F N_M} \cdot \frac{1}{\left(\frac{\alpha_B + \gamma + d}{\alpha_F N_F + 2\alpha_F N_M} + 1\right)^2} \cdot \frac{1}{\alpha_F N_F + 2\alpha_F N_M} \\
&< 0.
\end{aligned}$$

From (4.28),

$$\begin{aligned}\mathcal{R}_2 &= \frac{\alpha_F N_F(\alpha_B+\gamma+d)^{-2}[(\alpha_F N_F+2\alpha_F N_M)^{-1}+(\alpha_B+\gamma+d)^{-1}]^{-1}}{(\alpha_F N_F+2\alpha_F N_M)[(\alpha_F N_M)^{-1}+(\alpha_B+\gamma+d)^{-1}]} \\ &= \frac{\alpha_F N_F}{\alpha_F N_F+2\alpha_F N_M}\cdot\frac{1}{\left(\frac{\alpha_B+\gamma+d}{\alpha_F N_F+2\alpha_F N_M}+1\right)}\cdot\frac{1}{\left(\frac{\alpha_B+\gamma+d}{\alpha_F N_M}+1\right)}.\end{aligned}$$

This gives that partial derivative

$$\begin{aligned}\frac{\partial\mathcal{R}_2}{\partial\gamma} &= -\frac{\alpha_F N_M}{\alpha_F N_F+2\alpha_F N_M}\cdot\frac{1}{(\frac{\alpha_B+\gamma+d}{\alpha_F N_F+2\alpha_F N_M}+1)^2}\cdot\frac{1}{\alpha_F N_F+2\alpha_F N_M}\cdot\frac{1}{\left(\frac{\alpha_B+\gamma+d}{\alpha_F N_M}+1\right)} \\ &\quad -\frac{\alpha_F N_M}{\alpha_F N_F+2\alpha_F N_M}\cdot\frac{1}{\left(\frac{\alpha_B+\gamma+d}{\alpha_F N_F+2\alpha_F N_M}+1\right)}\cdot\frac{1}{\left(\frac{\alpha_B+\gamma+d}{\alpha_F N_M}+1\right)^2}\cdot\frac{1}{\alpha_F N_M} \\ &< 0.\end{aligned}$$

Both $\frac{\partial\mathcal{R}_1}{\partial\gamma}<0$ and $\frac{\partial\mathcal{R}_2}{\partial\gamma}<0$, therefore $\frac{\partial\mathcal{R}_0}{\partial\gamma}<0$.

Next we consider the partial derivative of $\mathcal{R}_0$ with respect to d. From (4.26)

$$\frac{\partial\mathcal{R}_0}{\partial d} = \frac{\tilde{\beta}}{\gamma}\cdot\left(\frac{\partial\mathcal{R}_1}{\partial d}+\frac{1}{2}\cdot\frac{2\mathcal{R}_1\frac{\partial\mathcal{R}_1}{\partial d}+\frac{\partial\mathcal{R}_2}{\partial d}}{\sqrt{\mathcal{R}_1^2+\mathcal{R}_2}}\right).$$

Again, we need only show that $\frac{\partial\mathcal{R}_1}{\partial d}$ and $\frac{\partial\mathcal{R}_1}{\partial d}$ are both negative to prove that $\frac{\partial\mathcal{R}_0}{\partial d}<0$. Because d and γ only appear in the $(\alpha_B+\gamma+d)$ term of both $\mathcal{R}_1$ and $\mathcal{R}_2$, we have that

$$\frac{\partial\mathcal{R}_1}{\partial d}=\frac{\partial\mathcal{R}_1}{\partial\gamma}<0$$

and

$$\frac{\partial\mathcal{R}_2}{\partial d}=\frac{\partial\mathcal{R}_1}{\partial\gamma}<0.$$

Therefore, $\mathcal{R}_0$ decreases with d.

In summary, we have modeled SI disease spread in a population of males and females who form male-male and female-male pairs. The vital dynamics model is

derived, and the basic reproduction number, $\mathcal{R}_0$ formulated. The transmission parameter β has a positive effect on $\mathcal{R}_0$, and the percent death rates of susceptible (d) and infectious (γ) individuals have negative effects on $\mathcal{R}_0$, as expected. The rate of pair formation has a positive effect on $\mathcal{R}_0$, provided pairs do not last so long that the number of physically possible partnerships one individual may engage in is not physically limited by the finite human lifetime. As pair duration decreases, $\mathcal{R}_0$ slightly decreases, due to the resulting decrease in transmission probability for a given partnership.

Chapter 5

Discussion and Conclusions

In this chapter we summarize the results and contributions of this thesis. Public health applications and future research avenues are presented.

5.1 Summary of Results

The major outcomes of this thesis are the characterization of Victoria IDU syringe-sharing data, the development of a novel pairing model and parameter estimation method specific to this data, and the formulation, analysis, and parameter exploration of the pairing model with SI disease dynamics.

Victoria IDU Data

The interviews designed and undertaken by the transdisciplinary injection drug risk group at the AIDS Vancouver Island Street Outreach Services needle exchange provided new insight into syringe-sharing patterns among Victoria IDU, and identified pairing as a population-specific risk behavior. Statistical analyses indicate that syringe-sharing partnerships are strong predictors of sexual partnerships between women and men, and that non-sexual syringe-sharing pairs of men are also common.

All syringe-sharing pairs are strongly correlated with injector/injectee relationships; the trusting and exclusive nature of these pairs is more identifiable than a sexual component.

The differences observed between males and females with regards to injector/injectee partnerships indicate that sex-specific education campaigns on safer injecting methods would be valuable in Victoria. Women are likely to share syringes with a sex partner, and individuals who share are likely to do so as an injector/injectee. Giving women the tools and knowledge necessary to engage in safe self injection may reduce syringe sharing and IDU risk.

Pairing Model

The pairing model developed in this thesis is novel because it considers male-male pairings as well as female-male pairings, and because newly infectious individuals are recognized as a risk to the larger poulation only when they leave the pair within which transmission occurred. Existing partnership models identify only female-male relationships; a pairing model with explicit descriptions of sex, pair types, and pairing length is necessary to encompass the syringe-sharing patterns observed among Victoria IDU. The single positive equilibrium of the pairing model is locally stable.

Parameter Estimation Methods

The MLE approach developed in Chapter 3 is, to our knowledge, a new method for fitting categorical (non-time series) data to a dynamical model. A bimodal function ($E(X) = 14.4436, V(X) = 4.8483$) best fit the pairing length data obtained from the Victoria IDU survey. The point estimates $\hat{\alpha_B} = 0.07$ and $\hat{\alpha_F} = 0.02$ indicate that the exploration of $\mathcal{R}_0$ within the parameter space $\alpha_B, \alpha_F \in (0, 0.5)$ of Section 4.4.2 is reasonable. The estimated values of the per-person pair formation rate (α_F) and

per-pair separation rate (α_B) provide a cardinal characterization of these parameters.

Pairing and Disease Model

The pairing and disease model is specifically tailored to examining syringe-mediated HIV or HCV spread within Victoria IDU. By considering transmission within explicitly modeled pairs of individuals, we have captured what survey data identify as a significant potential transmission route. The basic reproduction number, $\mathcal{R}_0$, increases with the transmission of infection, and decreases with the death of infectious individuals. Furthermore, $\mathcal{R}_0$ saturates with each of the transmission parameter β and the pair separation rate, α_B. The minimum values of $\mathcal{R}_0$ are associated with a long average pair duration or a low frequency of pair formation. $\mathcal{R}_0$ is bounded above by $\frac{\beta}{\gamma}$, *i.e.*, the expression for $\mathcal{R}_0$ recovered from the basic one sex model.

This model provides a framework for identifying high risk pairing classes within a population. The pairing and disease models of Chapter 4 assume homogeneous pair and transmission risk behaviors between poulation categories. If the model identifies the predicted equilibrium prevalence within a particular group to be larger than the observed population prevalence, that subpopulation of persons is likely living with higher than average risk factors. Reducing risk and transmission within such groups should be a priority of health officials.

5.2 Limitations

The original purpose of the IDU interviews conducted in May-June 2008 was to quantify the composition of an IDUs personal sharing network: how many people does one share equipment with? What is their relationship to the IDU in question? How long have they known this person? What types of equipment do they share?

Small Sample Size

This data informed the development of the models of this thesis. The inclusion of sharing partners, rather than sharing groups is a direct of consequence data analysis. In turn, these models illuminate how to better conduct surveys and collect data in the future. The 90 interviews conducted provide a great amount of detail on the types and frequencies of equipment sharing within the Victoria IDU population, but the actual number of syringe-sharing participants was quite small. A larger number of observations would allow for better parameter estimation (e.g. α_B and α_F) with respect to syringe sharing pairs and transmission of infection.

Data Simplicity

The simplified homosexual pairing model used to estimate the pairing model parameters was necessitated by the lack of information on pairing length distributions. Because data was collected only on in-progress pairings, we have no information on how long these pairings might last into the future. The highly skewed sex ratio (30:70 female to male) of this population, plus the two types of syringe-sharing pairs observed, were details we could not account for with the homosexual model used to estimate pairing parameters.

The per-pair separation rate, α_B is not explicitly accounted for by the homosexual pairing model. To better estimate the parameter α_B, we require more detailed data (including information on past and completed pairings) so that the full pairing model (3.1)-(3.4) may be fit.

Syringe-sharing as the Lone Transmission Route

Sexual transmission is an important route of transmission for blood borne illnesses such as HIV and HCV. In the case of HCV, there is evidence that drug equipment

other than syringes (e.g. cooking spoons, tourniquets) can play a role in transmission.

Sexual transmission, in addition to transmission via syringe-sharing, could be added to the pairing and disease model. For example, assigning a higher transmission value to female-male pairs than to male-male partners is one method of accounting for the increased infection potential provided by a sexual relationship. Among Victoria IDU, not all sexual partnerships are complemented by a syringe-sharing partnership, and vice-versa; it is not clear whether this is a population-specific detail, but in a model applied to Victoria data, it should certainly be addressed.

The inclusion of female-female pairs is one model extension that we briefly investigated in the course of developing this thesis. The modeling of female-female, female-male, and male-male pairs is one basis for building other types of equipment sharing into a partnership and disease model.

Appendix A

Disease-free System with Vital Dynamics

Following the notation of Chapter 3, let $N_F, N_{FM}, N_M, N_{MF}, N_{MM}$ denote the population proportions of single female, females paired with males, single males, maes paired with females, and males paired with males, respectively. Assume pairing dynamics to occur as described by (3.1)-(3.4). Let b be the rate of immigration or maturation into the population; let d be the percent death rate. The disease-free pairing model with vital dynamics is

$$\begin{aligned}
N_F'(t) &= \alpha_B N_{FM} - \alpha_F N_M N_F + bP + dN_{MF} - dN_F \\
N_{FM}'(t) &= -\alpha_B N_{FM} + \alpha_F N_M N_F - dN_{FM} - dN_{MF} \\
N_M'(t) &= \alpha_B N_{MF} + \alpha_B N_{MM} - 2\alpha_F N_M^2 - \alpha_F N_F N_M \\
&\quad + dN_{MM} + dN_{FM} - dN_M + b(N_M + N_{MF} + N_{MM}) \\
N_{MF}'(t) &= -\alpha_B N_{MF} + \alpha_F N_M N_F - dN_{MF} - dN_{FM} \\
N_{MM}'(t) &= 2\alpha_F N_M^2 - \alpha_B N_{MM} - 2dN_{MM}.
\end{aligned}$$

Assume that the population size is constant ($b = d$). Note that the population proportion of females ($P = N_F + N_{FM}$) is also constant, *i.e.* $P'(t) = N'_F(t) + N'_{FM}(t) = 0$. Substituting $P - N_F = N_{MF} = N_{FM}$, $1 - 2P - N_M + N_F = N_{MM}$, and $b = d$ into these equations and simplifying, we obtain the 2-dimensional system

$$N'_F(t) = -\alpha_F N_M N_F + (\alpha_B + 2d)(P - N_F) \quad \text{(A.1)}$$

$$N'_M(t) = -2\alpha_F N_M^2 - \alpha_F N_F N_M + (\alpha_B + 2d)(1 - P - N_M). \quad \text{(A.2)}$$

A.1 Existence and Uniqueness of Positive Equilibrium

Let $x_0 = (N_F = \tilde{N}_F, N_M = \tilde{N}_M)$ denote an equilibrium solution of (A.1)-(A.2). From (A.1)-(A.2), we have that

$$0 = -\alpha_F \tilde{N}_M \tilde{N}_F + (\alpha_B + 2d)(P - \tilde{N}_F) \quad \text{(A.3)}$$

$$0 = -2\alpha_F \tilde{N}_M^2 - \alpha_F \tilde{N}_F \tilde{N}_M + (\alpha_B + 2d)(1 - P - \tilde{N}_M). \quad \text{(A.4)}$$

Solving (A.3) gives

$$\tilde{N}_M = \frac{(\alpha_B + 2d)(P - \tilde{N}_F)}{\alpha_F \tilde{N}_F}.$$

Substituting this into (A.4) and simplifying,

$$0 = \tilde{N}_F^3 + (1 - 2P - \tilde{r})\tilde{N}_F^2 + 3\tilde{r}P\tilde{N}_F - 2\tilde{r}P^2,$$

where $\tilde{r} = \frac{\alpha_B + 2d}{\alpha_F}$. This equation has the same form as (3.10) and therefore has a single positive root, $0 < \tilde{N}_F < P$ (see Section 3.1.1). Following the logic of Section 3.1.1, we conclude that there is a single positive equilibrium of the disease-free pairing

system with vital dynamics(A.1)-(A.2).

A.2 Linear Stability of Equilibrium

The Jacobian of (A.1)-(A.2), with respect to $x = (N_F, N_M)$ is

$$J = \begin{pmatrix} -\alpha_F N_M - \alpha_B - 2d & -\alpha_F N_F \\ -\alpha_F N_M & -4\alpha_F N_M - \alpha_F N_F - \alpha_B - 2d \end{pmatrix}.$$

The trace of J is negative:

$$Tr(J) = -\alpha_F N_M - 4\alpha_F N_M - \alpha_F N_F - \alpha_B - 2d < 0.$$

The determinant of J is positive:

$$\begin{aligned} |J| &= (\alpha_F N_M + \alpha_B + 2d)(4\alpha_F N_M + \alpha_F N_F + \alpha_B + 2d) - \alpha_F^2 N_M N_F \\ &= 4\alpha_F^2 N_M^2 + 4\alpha_F N_M(\alpha_B + 2d) + \alpha_F N_F(\alpha_B + 2d) + (\alpha_B + 2d)^2 \\ &> 0. \end{aligned}$$

Therefore, all eigenvalues of J have negative real part. In particular, the linearized system evaluated at the DFE $x_0 = (0, 0, 0, 0, 0, S_F = \tilde{N}_F, N_{FM} = \tilde{N}_{FM}, N_M = \tilde{N}_M, N_{MF} = \tilde{N}_{MF}, N_{MM} = \tilde{N}_{MM})$ is stable. Thus the positive equilibrium of the disease-free pairing model with vital dynamics is linearly stable.

Appendix B

Data

Table B.1: Observed pairing length frequencies. $N = 19$ IDU currently in syringe-sharing relationships were interviewed at AIDS Vancouver Island, Victoria, May-June 1008.

Length (years)	0.5	1	2	3	6	9	13	14	15	20	21	26	27	28
Frequency	1	1	1	2	2	1	1	1	2	2	2	1	1	1

Table B.2: Observed pairing type frequencies. $N = 90$ IDU were interviewed at AIDS Vancouver Island, Victoria, May-June 2008. Males paired with males are those men who are in trusting relationships with other men, characterized by the sharing of syringes. Female-male (F-M) pairs may be with respect to (w.r.t.) either sexual or syringe-sharing partnerships. Overall pairing frequencies are w.r.t. sex partners, syringe-sharing partners, or both; syringe-sharing pairing class frequencies are w.r.t. only syringe-sharing, irrespective of any concurrent sexual relationship.

Category	Overall (%)	w.r.t. Syringe-sharing (%)
Single Females (N_F)	18 (0.20)	20 (0.22)
Females Paired with Males (N_{FM})	9 (0.10)	8 (0.08)
Single Males (N_M)	45 (0.50)	52 (0.58)
Males Paired with Females (N_{MF})	11 (0.12)	4 (0.04)
Males Paired with Males (N_{MM})	7 (0.08)	7 (0.08)
Total	90 (1.00)	90 (1.00)

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