Modelling the Spread of HIV/AIDS amongst Injecting Drug Users

Gordon Hay BSc

Department of Statistics and Modelling Science
University of Strathclyde

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Contents

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Abstract

The sharing of injecting equipment by injecting drug users (IDUs) is one of the primary causes of the spread of HIV in Scotland. Mathematical models of disease spread can explore the transmission dynamics and can assist in evaluating control strategies such as needle exchanges.

A simple deterministic model is examined and local and global stability results are presented. A deterministic model in which infected IDUs are considered separately from uninfected IDUs is created. The infectivity of a needle is then examined. It is first assumed that the infectivity of a needle depends on the amount of infectious material within it, then models in which this infectivity varies over time from injection are explored. Models in which the initial infectiousness of a needle depend on the length of time the person who infected it had been infected with HIV are also presented. A stochastic model is developed and explored in a threefold manner; analytically, numerically and using Monte-Carlo simulation methods. In particular, the probability that the disease dies out is examined.

Although these simple models use only a small number of parameters, little is known about the values that these parameters may take. Seroprevalence and behavioural data from Glasgow are used to inform these models, and also to provide an estimate for the probability than an IDU becomes infected after injecting with an infected needle. The effect that the variability in the parameter values may have on the spread of the disease is examined by performing both an uncertainty analysis and a sensitivity analysis. These show that the two behavioural parameters that can be altered by control strategies have a greater influence on the spread of the disease than some other parameters.

—Ye cookin? An need a shot Mark. Ah really need a shot. C'moan Marky, cook us up a shot...

At last ah could be ay some practical help. There were syringes and needles lying aw ower the place. Ah tried tae remember which works wir mine. Sick Boy says that he'd never, ever share... Whin yir feeling like ah am, the truth is thit ye dinnae care too much. Ah take the nearest, which at least isnae Spud's, as he's been sittin ower the other side ay the room. If Spud isnae HIV postitive by now, then the Government should send a deputation ay statisticians doon tae Leith, because the laws ay probability urnae operatin properly here.

Adapted from Trainspotting, by Irvine Welsh.

Chapter 1

Introduction and Literature Review

1.1 Motivation

The catalogue of destruction caused by epidemics throughout history seems like fiction in today's world of sanitation, hygiene and modern medicine. In the fourteenth century there were some twenty five million deaths from the Black Death and in 1919 the world pandemic of influenza claimed twenty million. But today millions of people live in areas where diseases such as malaria and schistosomiasis are endemic. In areas where people depend on their livestock, diseases such as East Coast Fever and Bovine Trypanosomiasis cause high mortality in domesticated cattle. More recently the disease AIDS has appeared; the full effect of which can only be guessed at. Predicting the effect of old and new diseases and trying to understand and control them has been the motivation of epidemiologists and researchers creating mathematical models of disease spread for decades.

The disease AIDS (Acquired Immune Deficiency Syndrome) and the associated virus HIV (Human Immunodeficiency Virus) appeared in the early 1980s and mirroring the explosion in the number of people infected with the virus has been the explosion of research into the disease. With the scientific literature growing so rapidly it is now impossible to read more than a fraction of it. However this

literature is very varied and when a particular area is singled out for research the available literature may be found to be limited. This appears to be the case when considering the spread of the disease via shared injecting equipment, which accounts for 48% of the recorded cases in Scotland (ANSWER, 1995). While many researchers are concentrating on producing mathematical models of the sexual spread of the disease entirely excluding spread amongst those that share needles, there also appear to be many researchers looking into the epidemiology of the disease spread through injecting equipment without producing mathematical models.

This Thesis attempts to fill this gap, that is to create mathematical models which encompass the findings of the medical sociologists, psychologists and epidemiologists studying people that inject drugs. The object of these models is to help us understand the basic dynamical epidemiological processes underlying the spread of HIV and AIDS amongst injecting drug users (IDUs). They can then help us evaluate control strategies such as needle exchange schemes, better health education and the distribution of bleach with which to clean needles. Indeed similar deterministic models have been used for this purpose in the USA (Kaplan, 1989; Kaplan and O'Keefe, 1993). Such models cannot however at present be used to predict accurately exactly how many new cases of AIDS there will be in the future as any modelling done relies on parameters which at present cannot be estimated with any precision.

There are two basic types of mathematical model, the deterministic model and the stochastic model. Stochastic models can more accurately describe the randomness inherent in real life. On the other hand deterministic models are much easier to analyse, enabling them to include more factors important to the spread of the disease and also to rapidly explore varying aspects of the model. The approach in this Thesis is hopefully to recognise the benefits of both types of

models and to use both deterministic and stochastic theory to model the spread of HIV via shared injecting equipment.

In this Thesis we explore mathematical models for the spread of HIV amongst IDUs. We begin in this chapter by discussing the virus and the disease AIDS which follows on almost inevitably after infection with the virus and we explore drug abuse and needle sharing, with particular respect to Glasgow. We then look at some of the general theory behind the use of mathematics in describing spread of disease and explore developments in this theory relevant to host / vector and sexually transmitted disease models. We briefly review the vast literature on the sexual spread of HIV and close this chapter by looking at models for the spread of the virus through needle sharing.

In Chapter 2 we present a deterministic model for the spread of HIV amongst IDUs who visit shooting galleries. We show that there exists a non-zero equilibrium value for the proportions of the IDU population and needles that are infected. This equilibrium value is shown to be both locally and globally stable. In Chapter 3 we develop a comparable stochastic simulation model and look at analytical stochastic models. In the absence of a tractable solution to the analytical model, we examine a numerical approximation to the stochastic model. In Chapter 4 we attempt to improve on the deterministic and stochastic models previously presented by including more realistic assumptions. In particular we examine the effect of a non-constant probability of infection in both an IDU and a needle. In Chapter 5 we examine the values which the parameters included in the models may take, leaving the discussion of the infectivity parameter until Chapter 6. We also derive a value for this parameter using data collected from Glasgow. In Chapter 7 we unite the preceding chapters by performing uncertainty and sensitivity analyses. We make suggestions for future work by introducing heterogeneity in Chapter 8. We do this by relaxing the assumption that IDUs select

needles at random from shooting galleries and we conclude in Chapter 9 with a discussion of the work presented.

1.2 HIV and AIDS

1.2.1 Introduction

AIDS was first discovered in 1981 when young men in the USA sought medical attention with similar symptoms including *pneumocystis carinii*, a form of pneumonia and the skin tumour, Kaposi's sarcoma (CDC, 1981*a*). Initial research into the syndrome concentrated on the fact that these men were all homosexuals (CDC, 1981*b*). When it emerged in 1982 that blood transfusion could transmit AIDS, speculation about the homosexual connection was dismissed and with the discovery of the syndrome in haemophiliacs who had received plasma-derived clotting factors and that the disease can also be transmitted from an infected mother to her new-born child, it was suspected that only a virus could be responsible.

Researchers exploring retroviruses, such as the Feline Leukaemia Virus, isolated a human retrovirus from a rare T-cell leukaemia (Barre-Sinoussi *et al.*, 1983). Soon after, Gallo identified a virus which is now called HIV-1 (Gallo *et al.*, 1984). Later a second virus was discovered which was slightly different to HIV-1, this was termed HIV-2. As both viruses cause AIDS, and in the context of AIDS and needle sharing there appears to be no difference in their transmission, the viruses will both be referred to in this Thesis as HIV.

HIV can be isolated in most body fluids, including saliva, but only in blood, semen and cervical secretions is the virus thought to be infectious. Once infected with the virus, it may be at least six weeks, occasionally longer, before antibodies can be detected, resulting in a window period where a person may be infected and infectious but this infectivity cannot be detected. The popular notion of an

AIDS test is therefore a misnomer as it is usually an HIV antibody test that is performed. This test can only detect the presence of antibodies to HIV, not the presence or absence of HIV itself, although tests which detect the virus may soon be commercially available. Once infected with the virus, a person will remain infected for life, although the symptoms related to the infection will vary over the course of the infection. After an initial acute viral illness, individuals may be completely asymptomatic, and remain in this state for several, possibly many, years. Many varying conditions which may occur after this stage cause the individual to be classified as having AIDS Related Complex (ARC). These symptoms, such as swollen lymphatic glands, confirm that AIDS is a syndrome which affects the immune system. The disease will then progress to full blown AIDS. The average incubation time, that is the time from initial HIV infection to the onset of AIDS is very variable but usually between 8 and 12 years (Sietz and Müller, 1994). The infectivity of a person varies throughout this period. There is a short initial period when individuals are very infectious followed by a relatively long period of low infectiousness. Just before an individual starts to develop clinical symptoms of AIDS the infectiousness starts to rise again.

The World Health Organization has produced a classification schema for describing the spread of HIV in different countries. Countries are classified as Type I and Type II countries. Type I countries include North America and Western Europe where the majority of cases are in homosexual men and IDUs. In Type II countries, such as those in sub-Saharan Africa, the spread is mostly through heterosexual intercourse.

1.2.2 The Homosexual Epidemic

AIDS was first discovered in North America in homosexuals, leading to a 'gay plague' image. At that time new sexual freedom had occurred within the ho-

mosexual community, leading to high levels of promiscuity. While the term homosexual intercourse covers a wide variety of activities, the highest risk is from men who practise unprotected anal penetration. This can lead to rectal trauma, which can result in the virus passing from infected semen into the blood stream. Oral intercourse may also result in the virus being transmitted, although this is not thought to be a high risk activity. The homosexual community was quick to react to this new disease, setting up AIDS charities and help groups. Epidemiological studies were started, including the San Fransisco Gay Mens' Health Study, from which many parameters in subsequent prediction models were taken (McKusick *et al.*, 1985*a*; 1985*b*). Health campaigns both within and outwith the homosexual community are increasingly becoming seen as successful in reducing the spread of the disease, particularly through safe sex campaigns promoting the use of condoms. The epidemiology of AIDS amongst homosexuals varies widely from country to country and city to city. In Scotland over the last ten years 29% of infections were in homosexual or bisexual men (ANSWER, 1995). Despite prevention initiatives, some people in this category are still engaging in unprotected sexual intercourse.

1.2.3 The Heterosexual Epidemic

While the majority of cases of AIDS in Europe and North America are due to homosexual transmission, the spread of the disease in many parts of the world including sub-Saharan Africa and the Caribbean is almost completely through heterosexual intercourse. There are many parts of Africa where the disease is at a level of prevalence which is resulting in substantial demographic changes in populations, leading to major public health problems in countries where medical resources are limited. Families are being destroyed where both parents have AIDS. Inaccuracies in data collection in these countries are also common. Seroprevalence levels in various countries have been reported, for example 14% in a

sample of 1,011 pregnant women in Kampala, Uganda, and 61% in a sample of 286 female prostitutes in Nairobi, Kenya (Piot and Carael, 1988). Certain conditions may increase the probability of transmission, including the presence of genital ulcers caused by other sexually transmitted diseases. As the probability of transmission from male to female is thought to be greater than the probability of transmission from female to male (Padian *et al.*, 1987), the majority of infected individuals are female. The high seroprevalence rates of pregnant women in Type II countries, between 5 and 25%, has led to estimates of between 1 and 15% of new born children being HIV positive in these areas. In Type I countries there is not a similar paediatric AIDS problem, although in some areas such as New York where the predominant mode of transmission is through sharing injecting equipment, both female needle sharers and the heterosexual partners of male needle sharers are becoming infected resulting in significant amounts of paediatric cases (Blower *et al.*, 1991).

1.2.4 The Needle Sharing Epidemic

The first signs of the needle sharing epidemic were in New York in the early 1980s, where the world wide AIDS epidemic began. HIV attributable to IDUs has been reported in many countries, including most of Europe, North America, South America, Australia and Asia. In some parts of the world, such as New Jersey and Connecticut in the USA, Edinburgh in the UK, Italy and Thailand, drug injecting accounts for the majority of AIDS cases (Des Jarlais *et al.*, 1992). Drug injecting was present in Edinburgh before the introduction of HIV (Ditton and Speirits, 1982), indeed there was a rapid increase in the number of IDUs in the early 1980s. With few treatment facilities and the apparent ease of transition into injecting heroin, due in part to the influx of inexpensive, high quality heroin, Edinburgh, in common with Glasgow and other cities in the U.K., began to react to the drug problem. Prior to 1982, it was comparatively easy to obtain

clean injecting equipment, but as the drug problem escalated, the police cracked down on the availability of injecting equipment leading to individuals sharing bloodstained needles and syringes. The most immediate result of this policy was the rapid spread of hepatitis B, a recognised disease transmitted via shared injecting equipment. This epidemic masked the more alarming HIV epidemic. However when HIV became recognisable, blood samples stored for hepatitis testing revealed the true extent of the epidemic in Edinburgh, with reports of a 40% prevalence among IDUs (Robertson *et al.*, 1986; Peutherer *et al.*, 1985). It should be noted that this figure came from what could possibly be an extremely biased survey as those in the sample were IDUs infected with a disease which is also transmitted via injecting equipment. At that time in Glasgow, just 70km west of Edinburgh, Follet (1986) reported a 4.5% seroprevalence in a sample of 606 IDUs, and noted that 74% of those infected had identifiable links with Edinburgh. The Edinburgh figure was similar to those found in large groups of IDUs in large cities world-wide such as 50% in New York (Des Jarlais and Friedman, 1987) and Bangkok where prevalence rates rose from 15.6% in 1988 to 42.7% in 1989 (Vanichseni *et al.*, 1992).

More recently the monitoring of HIV infection and AIDS became more systematic, with several monitoring systems in Scotland coming within the remit of the Scottish Centre for Infection and Environmental Health. This unit, based in Glasgow, has responsibility for monitoring infectious diseases in Scotland. Routine testing of blood donations for HIV commenced in 1985, as did the blood tests of those worried about infection. In 1988 a surveillance scheme was introduced which collated epidemiological data on everybody in Scotland who had a named HIV test. This concentrated on the homosexual and IDU sections of the community, although there were concerns that HIV may have started to spread in the heterosexual population. In response to these concerns voluntary testing of pregnant women began. In 1990 a system of anonymous testing of blood or

urine samples began, as these were anonymous and blood taken specifically for HIV testing was excluded, this soon became an important epidemiological tool in examining HIV infection in the general population. Figure 1.1, which is extracted from the register of HIV infected persons (ANSWER, 1995), can be thought of as giving a short description of the first ten years since HIV was introduced into IDU population in Scotland. This figure charts the number of infected people

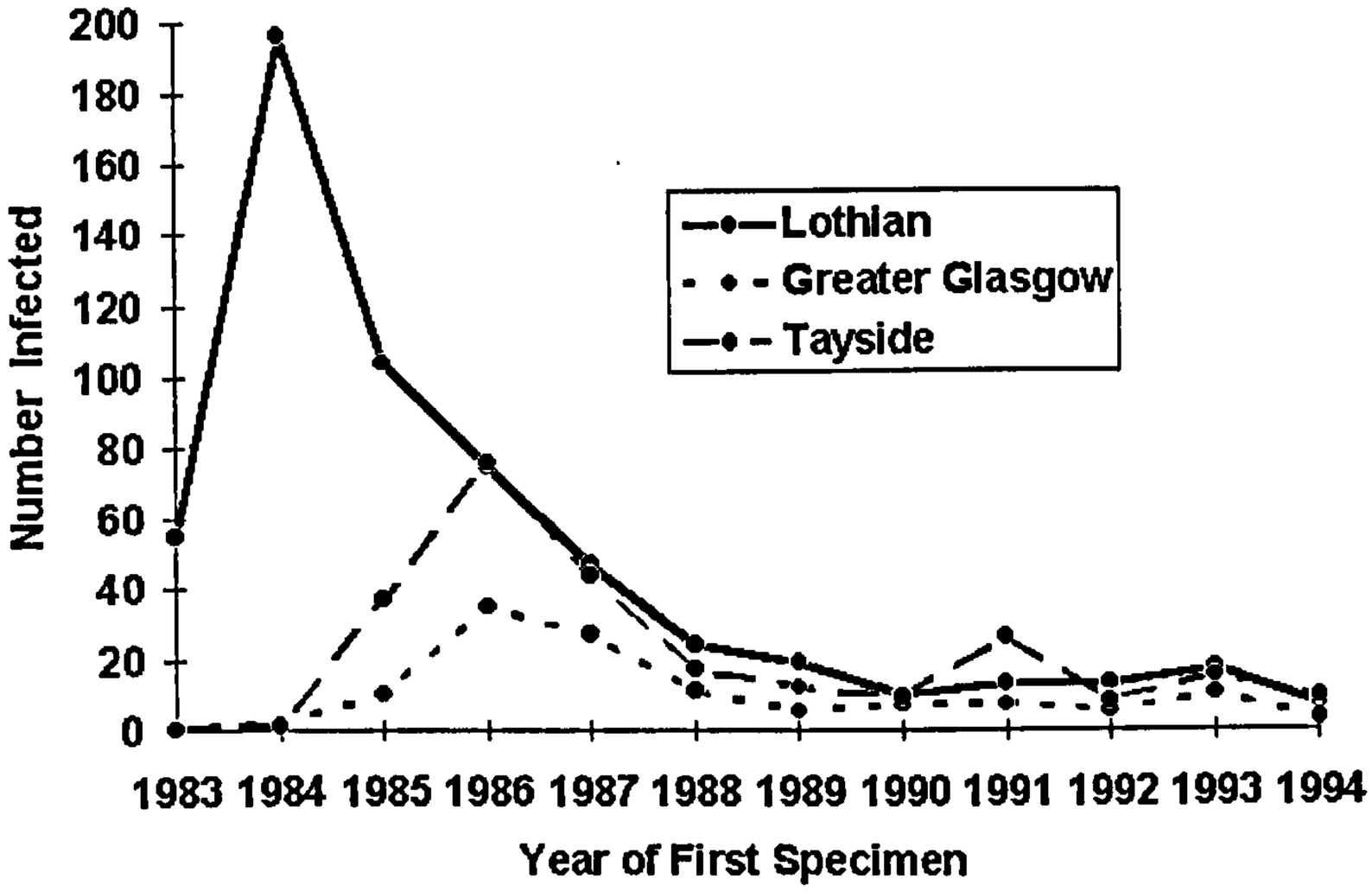

Figure 1.1: The number of newly infected IDUs in Lothian, Greater Glasgow and Tayside.

claiming drug injecting as a risk factor by the first year a positive specimen was found. The data is presented by Health Board area, however the majority of cases in Lothian, Tayside and Greater Glasgow would occur in the cities of Edinburgh, Dundee and Glasgow respectively. It is clear from this that HIV was present in Edinburgh in 1983, but there were no cases uncovered elsewhere in Scotland that year. The Edinburgh data reached a peak in 1984, whereas the Glasgow and Dundee data both peaked two years later, confirming the 'Edinburgh Connection' proposed by Follet (1986). Over the last decade, there were 1,057 HIV cases attributable to drug injecting in Scotland. When the progression to AIDS is considered, by the end of 1994 there were 64 AIDS and a further 155 deaths

attributable to drug injecting.

1.2.5 A Hidden Epidemic

It is widely recognised that needle sharing is a very high risk activity, therefore public health authorities in both Western Europe and North America have targeted IDUs with information about risk reduction techniques such as needle exchanges and bleaching needles to sterilise them. However there are many parts of the world where basic hygiene within the health services with respect to sterilising needles is not possible due to the lack of resources, in particular Romania (Hersh *et al.*, 1993), as well as other parts of Eastern Europe or Africa (Hoelscher *et al.*, 1994). Due to the lack of clean needles, it was not uncommon for several people to be injected with the same needle, which may transmit HIV and other viruses.

1.3 The Social Context

1.3.1 Drug Misuse

Up until 1868, opium was available over the counter without any form of restriction. The only conceived problems were poisoning, including 'infant doping', where child minders would drug their charges. The Dangerous Drugs Act of 1920 was the first legislative act in the style of present day law, which led to opiates only being available by prescription. In the period leading up to the 1960s, Britain's drug problem was small, but between 1964 and 1968 the number of opiate addicts known to the Home Office rose from 342 to 2,782 (Ghodse, 1989). For the first time in Britain, injectable heroin instead of morphine was the opiate of choice and an active black market of pure heroin and cocaine appeared. In Glasgow, in the early 1980s there was an epidemic of heroin use, as there was in other British

cities (Parker *et al.*, 1989). In more recent times, the number of addicts in the United Kingdom notified to the Home Office has risen to just under 34,000 in 1994, whereas data from the Regional Drug Misuse Databases, which record the number of new contacts at a range of drug agencies, show that there were over 21,000 individuals starting agency contact between 1 October 1993 and 31 March 1994 and that 8,746 individuals were injecting their main drug. The data from the Regional Drug Misuse Databases refer to Great Britain as Northern Ireland does not, as yet, have a database.

It has been shown that the above 'official' statistics vastly underestimate the true extent of drug misuse and drug injecting in the UK (Sutton and Maynard, 1993). While it is difficult to estimate the size of this covert population, Frischer *et al.* (1993*a*) have used log-linear analysis to model the relationship between four data sources in order to estimate the number of IDUs in Glasgow, obtaining a figure of 8,400, which represents 13 per 1,000 of the population aged 15-55. This is an increase from the 5,000 estimated in 1983 (Haw, 1985). Elsewhere Squires *et al.* (1995) estimate the number of opiate or cocaine misusers to be 2,344 in Liverpool and Hay and McKeganey (1996) estimate that there are 2,557 opiate or benzodiazepine users in Dundee. In broader terms, it is estimated that there are 20,000 current IDUs in Scotland (ANSWER, 1995), and a further 100,000 in England and Wales (Giesecke *et al.*, 1994).

While there are many prejudices and misconceptions about IDUs, there are some characteristics of drug users which can be described. Many drug users living in Glasgow reside in the large housing schemes on the peripheral areas, where other socio-economic problems include high unemployment, low income and social deprivation. There is an identifiable sense of loyalty within these communities where outsiders are treated with suspicion and this often hampers research. McKeganey and Barnard have studied drug users, in particular IDUs, within the

community from a sociological perspective, providing an insight into why IDUs share needles and the perceived risks in doing so (McKeganey and Barnard, 1992). They also explore the links between drug injecting and prostitution (McKeganey and Barnard, 1996).

With the epidemic of heroin use at the start of the last decade, different areas developed differing strategies to deal with this problem. For example, in Edinburgh one attempt to reduce the amount of drug injecting was to stop the supply of needles from pharmacies. This supply was illegal in other countries, but quite legal in the U.K. (Robertson, 1990). This had the effect of increasing the amount of sharing of needles. At that time the only apparent risks were hepatitis and other injecting related problems such as septicaemia, abscesses and endocarditis.

The prevalence and patterns of drug use within the penal system is seen to be of concern (Shewan *et al.*, 1995). It is the policy of the United Kingdom's prison service to refuse to issue condoms and injecting equipment to inmates, something which the World Health Organization (1987) advocates should be considered.

1.3.2 Drug Injecting

In order to inject a drug such as heroin it must first be dissolved in water. This can be done in small vessels such as bottle caps known as 'cookers', which are heated (Koester *et al.*, 1989). Some users will place cotton in this vessel with which to filter the dissolved drug. This filter may be used several times, and in the absence of drugs with which to inject, this residue may be injected. If any of the needles which have used this filter have been infected there is a possibility that the filter may be a source of HIV transmission. When IDUs are wanting to share drugs that have been jointly purchased, instead of dividing up the raw drug it may be easier to divide up the dissolved liquid. One method known as front-loading is to draw all of the solution into one syringe, from which half would

then be injected into another (Grund *et al.*, 1991). This has also been described in Glasgow (Green *et al.*, 1993). This liquid could then be injected into the blood stream. If the first needle or syringe was infected, this could pass on the virus into the second syringe. Most injections are intraveneous, that is the drug is injected directly into a vein. Intramuscular injection refers to the practise of injecting the liquid directly into the muscles, something which may occur when an IDU has difficulty finding a vein to inject into. Once the drug has been injected into the blood stream some users will draw back some of their own blood into the syringe and re-inject this in order to get the full benefit of the drug. This could leave more contaminated blood in the syringe than normal injection procedures due to the amount of blood in contact with the syringe (Samuels *et al.*, 1992).

1.3.3 Needle Sharing

It is not clear why people share needles although several theories have been explored. In several parts of the world such as many states in the USA, it is illegal to be in possession of injecting equipment, or in other places the police will confiscate injecting equipment and not allow pharmacies to sell it. This was the situation in Edinburgh in the early 1980s. In other parts of the world however needles can be purchased quite freely, as in Italy, and there are pharmacies in Glasgow which legally sell injecting equipment. One result of restrictions on obtaining injecting equipment is that many individuals can use the same set of equipment. This sharing can occur in different forms, one example is the friendship networks which are common in Glasgow, where people will share with their close friends or partners. They do not perceive any risk of infection and they do not classify this as sharing (McKeganey and Barnard, 1992). There are also sharing structures such as shooting galleries. Samuels *et al.* (1992) describe differing forms of shooting gallery, such as the residential shooting gallery, where long and short term residents and non residents share injection equipment, and non-residential

shooting galleries where IDUs usually pay money or drugs to use the facilities, where they can also purchase drugs. This results in relatively large groups of IDUs sharing equipment. The non-residential shooting gallery was thought to be common in Edinburgh in the early 1980s, as visiting such shooting galleries eliminated the risk of being caught by the police in possession of either drugs or the related paraphernalia.

1.3.4 Seroprevalence and Behavioural Studies of IDUs

In 1990 a World Health Organisation study involving twelve centres began to study risk behaviours of IDUs. Glasgow was one such centre, the others were Athens, Bangkok, Berlin, London, Madrid, New York, Rio de Janeiro, Rome, Santos, Sydney and Toronto. A description of the methodology and the main results from these studies can be found in Stimson *et al.* (1997). Approximately 500 IDUs were recruited each year in Glasgow from 1990 to 1994, and this resulted in the collection of demographic and behavioural data, along with saliva specimens in order to test for HIV. Similar studies using the same protocol were also carried out in Edinburgh during 1992 - 1994, Dundee in 1994, and have more recently been carried out in other health board areas.

The saliva testing confirmed the continuing low prevalence of HIV due to drug injecting in Glasgow. From these samples the estimated prevalence of HIV infection fell from 1.8% in 1990 to 1.0% in 1994 (Taylor *et al.*, 1994). This contrasts with the corresponding data from Edinburgh and Dundee where the estimated prevalence figures for 1994 were 19.7% and 27% respectively (Davies *et al.*, 1995; Haw *et al.*, 1996). The vast majority of IDUs in the Glasgow samples injected daily, however the proportion injecting with used needles dropped over the five year period. Valuable data on sharing frequency and the needle cleaning practices has also been collected from this study.

Although there has been no attempt as yet to utilise this epidemiological data in mathematical models, other quantitative research resulting from this original research has been reported in the literature. In combination with the log-linear analysis which gave rise to an estimate of the number of IDUs Frischer *et al.* (1993*a*) estimated that there were ninety three HIV infected current IDUs in Glasgow in 1990. Following on from a statistical description of the HIV prevalence and incidence in Glasgow by Frischer *et al.* (1992*a*), Bloor *et al.* (1994) proposed reasons why the prevalence of HIV was so low, especially considering the high HIV prevalence in Edinburgh. Frischer *et al.* (1992*b*) described the reduction in needle sharing through the sucessive samples of IDUs, but noted that a third of the sample in 1990 still injected with used equipiment. Linear structural modelling techniques were used to identify HIV risk practices in the Glasgow sample (Frischer *et al.*, 1993*b*). Travel, sexual activity, prostitution and the sharing injecting equipment were positively associated with increased risk of HIV infection. This quantitative approach was combined with a qualitative study by Barnard and Frischer (1995) in which the relationships identified in the structural models were explained using ethnographic data.

As the behavioural and seroprevalence study questionnaire also asked about sexual practices, including those of prostitutes, the link between drug use, prostitution and HIV spread could be examined. Taylor *et al.* (1993) studied a sample of fifty one female streetworking prostitutes who had been included in the larger IDU study. Although condoms were almost always used during commercial sexual contacts, they were rarely used by partners of prostitutes within private relationships. Coupled with the higher than average HIV prevalence in this group, this research highlighted concerns about the heterosexual spread of HIV from drug injecting prostitutes, given that 71% of Glasgow's estimated 1,100 streetworking prostitutes are thought to be IDUs (McKeganey *et al.*, 1992). In contrast with the concerns about drug injecting prostitutes spreading HIV to the

heterosexual population, there are also concerns about the additional risk of female IDUs becoming infected, through having to resort to prostitution to finance a drug habit, from often having to share their drug injecting partner's injecting equipment and due to the added risk of becoming infected through sexual contact with an infected partner. These risks are detailed in Barnard (1992).

The mobility of IDUs was studied by Goldberg *et al.* (1994). As Glasgow IDUs are highly mobile, there are still concerns that HIV infection may be imported from outwith the city. The prison experience of IDUs was also explored using the combined data from the behavioural and seroprevalence studies. Covell *et al.* (1993) noted that 52% of IDUs had been in prison. Drug injecting often continues when an IDU is detained in prison. This was highlighted from a well documented outbreak in Glenochil Prison (Taylor *et al.*, 1995; Gore *et al.*, 1995). There is additional concern relating to injecting in prison as IDUs from different areas of Scotland are often in the same prison thus HIV may be spread from one area to another. Other studies have examined drug injecting and HIV risk in prison (Shewan *et al.*, 1995), again confirming that IDUs continue to share within prison. Power *et al.* (1992) described a study of 559 inmates throughout the Scottish prison system. From this sample 154 (27.5%) had injected drugs before imprisonment, 43 (7.7%) had used drugs within prison and 32 (5.7%) reported sharing within prison.

The data from Glasgow has also been compared and contrasted with other areas. Des Jarlais *et al.* (1995) included Glasgow in a study of cities where HIV prevalence has continued at a low level. This research examined possible reasons why there is a low prevalence, and although there were no firm conclusions, the presence of needle exchanges and other harm reduction strategies can perhaps be seen as preventative of a high prevalence of HIV.

Although Glasgow was part of the multi-centre behavioural and seropreva-

lence study, research into HIV and drug injecting has also been carried out in Edinburgh, a city which bore the brunt of the HIV epidemic in the last decade. Robertson first noted the presence of HIV within a sample of IDUs attending a surgery in North West Edinburgh in 1985 (Robertson, 1986). This cohort has been extensively followed, for example by Robertson *et al.* (1994) who describe this cohort over ten years and by Ronald *et al.* (1992) who noted the reduction of risk related behaviours. Ronald *et al.* (1994) considered drug injecting as a cofactor in the progression from HIV to AIDS showing that heroin injecting increased the risk of progression. Many of these IDUs are also included in a larger group which included those infected through sexual contact, known as the Edinburgh City Hospital Cohort. This group has again been extensively studied (Brettle *et al.*, 1996*a*).

The epidemiology of diseases spread through injecting equipment in Edinburgh was studied by Burns *et al.* (1996). The epidemic of injecting drugs was associated with four overlapping epidemics of bloodborne viruses; HIV, hepatitis B, C and D. Initially only hepatitis B was recognised. The paper speculates that the explosive drug-related Edinburgh HIV epidemic may have been self-terminating and that the epidemic in female IDUs came three months after that in male IDUs.

The spread of HIV has also been studied at a national level in Scotland. Raab *et al.* (1994*a*) used HIV test data in forecasting the AIDS epidemic in Scotland. It is noted in this study that more concise information about the incubation period is perhaps needed. This is explored in Raab *et al.* (1994*b*), where forecasts were produced using Bayesian techniques which used the available knowledge about the incubation period. In both these studies the estimates were show to closely fit the initial stages of the epidemic. Mok (1994) explored the vertical transmission of HIV from mother to child and other studies have also examined drug use and pregnancy (Johnstone *et al.*, 1994). Brettle *et al.* (1996*b*) also explored the

progression of HIV in pregnant women through CD4 count modelling; this is one of several studies which used data on CD4 counts when modelling HIV in IDUs (McNeil *et al.*, 1996; Allardice *et al.*, 1992.)

1.4 Mathematical Modelling of the Spread of Infectious Diseases

1.4.1 Origins

Despite Fracasterius in 1546 postulating a living principle of contagion, it was not until the rise of the science of bacteriology in the latter part of the nineteenth century, due mainly to the work of Pasteur and Koch, that an understanding of the infectiousness of certain diseases came about. The first recorded combination of mathematics and medicine appears to be the work of Bernoulli (1760) in which he investigated the benefits of variolation against smallpox. The idea of a living organism invading the human body must originally have been received with much scepticism, but with the ability of early microscopes to show these organisms in the blood the foundations of the study of infectious diseases had been laid.

1.4.2 Development of Mathematical Models

In describing the early history of the mathematical modelling of infectious disease, two diseases will be described in detail; measles and malaria. Models for measles serve as a prototype for many other diseases which are spread in a similar manner such as chickenpox, mumps and whooping cough. Measles is more commonly used as an example of a disease which can be modelled because the data are better. The modelling of malaria differs from these basic models in that even the simplest models need to include two populations; man and mosquito. These models are a good introduction to two-sex models which are needed in modelling the spread

of sexually transmitted diseases and, as will be shown later are relevant to the spread of HIV within a population of IDUs.

There have been many studies into the spread of measles and the disease is one of the best documented. Although it is not fatal in developed countries, it is still a major killer of children in many parts of the world including India. The virus is highly contagious because it is airborne and easily transmitted, unlike a virus such as that which causes glandular fever which requires physical contact. For measles, after an individual becomes infected there is an incubation period of between nine and eleven days before the illness becomes apparent. During this incubation period the individual is not infectious. There follows a short infectious period of seven to fourteen days (Benenson, 1990). Once an individual has recovered from the illness he or she will become permanently immune to the disease, so from the infected state an individual will pass to a recovered or removed state from which they cannot return to the susceptible or infected state. This well documented progression of events can be easily modelled using a compartmental model. A compartmental model is a mathematical model which divides the population amongst whom a disease is spreading into disjoint compartments such as susceptible, incubating, infectious and immune individuals.

Hamer (1906) considered that the course of an epidemic must depend on the number of susceptibles and the contact rate between susceptibles and an infective individual. This idea, Hamer's 'mass-action principle', which is fundamental to most deterministic theory, can be seen in the Hamer-Soper model; a type of compartmental model. We shall now describe the Hamer-Soper model.

The population of interest is split into three groups, susceptibles $S(t)$, infectives $I(t)$ and a removed group $R(t)$, the number of people in each of the groups being a function of t, time. The removed group consists not only of the deaths from the disease but also removal due to isolation or recovery. The transitions between

these three states can be described as follows:

1) A susceptible becomes infected by contact with an infective.

2) An infective is removed.

3) A susceptible enters the population, either through migration or birth.

4) An infective enters the population by migration.

5) A susceptible or infective leaves the population either by death or migration.

In this deterministic theory each of these transitions has an associated rate giving rise to a set of differential equations. As an example the simpler situation where the population is fixed, so that transitions 3, 4 and 5 do not occur, is presented.

Suppose that at time t we have $x(t)$ susceptibles, $y(t)$ infectives and $z(t)$ removed individuals. We can abbreviate these time-dependent values as x, y and z. With an infection rate of β between a single susceptible and a single infected individual, so that the number of new infections occurring in a small time interval of length $\mathrm{d}t$ is $\beta xy\mathrm{d}t$, and a removal rate of γ per infected individual the differential equations can be shown to be

$$\frac{\mathrm{d}x}{\mathrm{d}t} = -\beta xy,$$

$$\frac{\mathrm{d}y}{\mathrm{d}t} = \beta xy - \gamma y,$$

and

$$\frac{\mathrm{d}z}{\mathrm{d}t} = \gamma y. \tag{1.1}$$

We can define $\rho = \gamma/\beta$ to be the relative removal rate and at time $t = 0$ we have $x(0) = x_0$, $y(0) = y_0$ and $z(0) = z_0$. From Equation 1.1 we have

$$\frac{\mathrm{d}y}{\mathrm{d}t} = \beta y_0(x_0 - \rho)$$

so an epidemic can only develop if $x_0 > \rho$.

We can re-express part of Equation 1.1 as

$$\frac{\mathrm{d}y}{\mathrm{d}t} = \beta y_0 \rho \left(\frac{x_0}{\rho} - 1 \right)$$

from which an epidemic will occur if

$$x_0/\rho > 1.$$

Thus R_0, the basic reproductive number, is x_0/ρ. R_0 is defined as the number of secondary infections produced when one infected individual is introduced into a host population at equilibrium where everyone is susceptible (MacDonald, 1952; Anderson and May, 1991). We expect an epidemic to occur if and only if R_0 exceeds one.

This general type of model was extended by Kermack and McKendrick (1927). Their more elaborate models resulted in the famous threshold theorem which stated that the introduction of a small number of infectious cases into a population of susceptibles would not give rise to an epidemic outbreak if the density of susceptibles was below a certain limit. If the initial density of susceptibles exceeded this limit or threshold, then the resulting epidemic would reduce the density to as far below the threshold as it was originally above. This threshold value is intrinsically linked to R_0; for estimates of threshold values and R_0 in various communities and for various infections see Anderson and May (1991).

Further work on this model related to measles was undertaken by Soper (1929), who examined recurrent epidemics. This can be achieved by introducing susceptibles into the population at rate α. This corresponds to immigration of susceptibles into the population. If we simplify this model by only looking only at susceptibles and infectives and ignoring births and deaths into and out of the population we have:

$$\frac{dx}{dt} = -\beta xy + \alpha$$

and

$$\frac{dy}{dt} = \beta xy - \gamma y,$$

the solution of which resulted in damped oscillations in the number of infectives Soper (1929), which published data on measles does not display.

Deterministic models can predict the undamped oscillation observed in the data, but to take account of this we need to include seasonal variation in the contact rate (Bolker, 1993). Another method of modelling undamped oscillations is to use stochastic models such as McKendrick (1926) or Bartlett (1960). As an example, let $X(t)$ and $Y(t)$ denote the number of susceptibles and infectives at time t. Then in the small time interval $[t, t + \mathrm{d}t]$ we have the transition probabilities

$$\Pr\{(X, Y) \to (X - 1, Y + 1)\} = \beta XY\mathrm{d}t$$

and

$$\Pr\{(X, Y) \to (X, Y - 1)\} = \gamma Y\mathrm{d}t. \tag{1.2}$$

The latter part of Equation 1.2 refers to the removal of infectives. This type of model, which is difficult to solve, is the stochastic 'continuous-infection' model which did not attract much attention initially.

An alternative form of stochastic model, the Chain Binomial Model, was developed independently by Greenwood (1931) and Reed and Frost in 1928; see Abbey (1952). These are discrete time models as the spread of the disease is modelled in discrete generations. This model assumes a relatively short infectious period and constant latent and incubation periods, allowing the number of new cases occurring from adequate contact with a single infective to be modelled by a binomial distribution. Each new infective would then go on at the next 'generation' of the disease to infect other susceptibles with the same binomial distribution, leading to a chain of binomials, hence the name. This model could be used to describe the spread of a disease such as chickenpox, where the spread of the disease can be well documented between families and between family members. Greenwood's model assumes that the probability that a susceptible becomes infected depends

only on the presence of an infective. This can be thought of as a simplification of the Reed-Frost model in which the probability of infection depends on the number of infectives present, and each infective infects susceptibles independently

The mathematical modelling of epidemics after the second world war continued with more work done on both deterministic and the Chain Binomial Models. Work was being done on the mathematical theory of stochastic processes, such as Bartlett (1949), who developed a partial differential equation for the probability generating function of two variables. This gave rise to renewed interest in the continuous infection model. This model was also explored by Bailey (1953) giving rise to Whittle's famous (1955) paper, directly following Bailey, in which he derives a stochastic threshold theorem corresponding to Kermack and McKendrick's deterministic result. In a more basic sense, at the start of the epidemic when the number of susceptibles can be reasonably approximated as n, the population size, Equation 1.2 can be compared to a simple birth-death process with constant birth rate $n\beta$ and constant death rate γ. Again denoting $\rho = \gamma/\beta$, a threshold theorem can be obtained which states that if $n \leq \rho$ then a major outbreak cannot occur, but if $n > \rho$ then a minor or major epidemic occurs with probability ρ/n and $1 - \rho/n$ respectively. Whittle (1955) presents the proof, extending it by determining the probability that an epidemic of not more than a given intensity takes place.

1.4.3 Modelling the Spread of Malaria

While Hamer, and later Soper, were developing the theory for measles, Ross (1911), was developing similar theory for the spread of malaria. Malaria in man is due to infection by one of four parasites of the family *Plasmodium*. Parasites are different from viruses in that they can reproduce sexually and can therefore be categorised as being at certain stages of their lives. Some parasites such as

those that cause malaria need to spend part of their life in humans and another part in an intermediate host. For more detailed explanation of the differences between viruses, parasites and bacteria see Anderson and May (1991). An individual becomes infected by sporozoite forms of the parasite after they have been bitten by a female mosquito taking a blood meal which is necessary for the development of her eggs. The parasites reproduce asexually within the human host changing from sporozoites to trophozoites and eventually into gametocytes, which are sexual forms of the parasite. Although there may be parasites at different stages of their life cycle within the human host, it may be convenient to only examine the gametocyte rate, which is not strictly a rate as it is the number of gametocytes in the blood (MacDonald, 1957), as it is gametocytes which then infect the female mosquito. The sexual forms of the parasite then multiply within the female, completing the circle by liberating sporozoites into the salivary glands. We therefore have two indicators of infectiousness, the gametocyte rate in humans and the sporozoite rate in the mosquito.

A basic deterministic formulation of the essentials of the population dynamics of malaria was given by Ross (1911). We define the following parameters for the human population:

n: total population size;

y: total number of infected individuals;

f: proportion of infected individuals who are also infectious;

γ: recovery rate;

μ: birth rate;

ν: death rate.

Again we have abbreviated the notation for the time-dependent values, such as

the total number of infected indivuals. A set of definitions, employing the same symbols but with primes can be applied to the mosquito population. We adopt the concept of homogeneous mixing, based on the assumption that the mosquitoes have a man biting rate b'. So in a time interval $(t, t+\mathrm{d}t)$ we see that y' infected mosquitoes make $b'f'y'\mathrm{d}t$ infectious bites, of which a proportion $(n-y)/n$ are on susceptible humans. Thus, the number of new human infections in $(t, t+\mathrm{d}t)$ is $b'f'y'(n-y)\mathrm{d}t/n$.

Taking into account the recovery and death rates, it follows immediately that the differential equation describing the rate of growth of the human infected population is

$$\frac{\mathrm{d}y}{\mathrm{d}t} = \frac{b'f'y'(n-y)}{n} - (\gamma+\nu)y.$$

An analogous argument leads to

$$\frac{\mathrm{d}y'}{\mathrm{d}t} = \frac{b'fy(n'-y')}{n} - (\gamma'+\nu')y'$$

for the infected mosquito population. These two equations are not exactly symmetrical with the regard to y and y'. The transmission of disease from a mosquito to man, or vice versa, is in each case controlled by the man biting rate of the mosquitoes. Thus only b' exists; there is no corresponding quantity b, since man does not bite mosquitoes.

Setting $m = y/n$ and $u = y'/n$ leads to

$$\frac{\mathrm{d}m}{\mathrm{d}t} = b'f'u(1-m) - (\gamma+\nu)m$$

and

$$\frac{\mathrm{d}u}{\mathrm{d}t} = b'fm(a-u) - (\gamma'+\nu')u,$$

where $a = n'/n$. From these equations information about equilibrium values and the basic reproductive number, R_0, defined as the number of new cases resulting from the introduction of a single infective into a population of susceptibles at equilibrium, can be explored. From this differing control strategies can be stud-

ied. For example we can study the effect of reducing the size of the mosquito population by looking at its effect on R_0.

1.4.4 Modelling the Spread of Sexually Transmitted Diseases

It was noted by Ross that his models for malaria transmission could also be applied to sexually transmitted diseases, with similarities between the prevalence of disease in the human and vector host and prevalence in males and females. Before the discovery of the HIV virus, most mathematical models of the spread of sexually transmitted disease concentrated on the spread of gonorrhoea (Hethcote and Yorke, 1984). While the disease is not fatal, in the USA roughly one million cases per year are reported. This suggests that between two or three million cases may actually arise annually. It has been estimated that 10-17 percent of women with gonorrhoea develop pelvic inflammatory diseases, which can lead to sterility. The disease is also virtually asymptomatic in many people, especially women. In contrast to diseases such as measles, recovery from the disease does not confer life long immunity, therefore Whittle's and Kermack and McKendrick's threshold theorems cannot be applied directly. If a removed compartment was valid, a basic deterministic model can presented which is relevant to both host/vector and venereal diseases. For a human population, consider a model with the numbers of susceptibles, infectives and removed individuals denoted by x, y and z respectively, with $x+y+z=n$. Corresponding numbers in the intermediate vector are denoted as (x', y', z'). We assume that the numbers of new infections in a small time interval time $[t, t+\mathrm{d}t]$ are $\beta x y' \mathrm{d}t + \mathrm{o}(\mathrm{d}t)$ for humans and $\beta' x' y \mathrm{d}t + \mathrm{o}(\mathrm{d}t)$ for vectors. The corresponding quantities for removals are simply $\gamma y \mathrm{d}t + \mathrm{o}(\mathrm{d}t)$ and $\gamma' y' \mathrm{d}t + \mathrm{o}(\mathrm{d}t)$, resulting in the two sets of equations:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = -\beta x y',$$

$$\frac{dy}{dt} = \beta x y' - \gamma y,$$

$$\frac{dz}{dt} = \gamma y,$$

and

$$\frac{dx'}{dt} = -\beta' x' y,$$

$$\frac{dy'}{dt} = \beta' x' y - \gamma' y,'$$

$$\frac{dz'}{dt} = \gamma' y',$$

from which a threshold theorem similar to that obtained by Kermack and McKendrick can be obtained. We should stress that in the case of many such diseases there is no immunity after infection, hence such a model may not be valid. We can also model the sexual spread of disease using stochastic theory, by representing the respective number of susceptible and infective males by $X_1(t)$ and $Y_1(t)$ and similarly $X_2(t)$ and $Y_2(t)$ for the susceptible and infective females. By considering the transition probabilities, we can develop a partial differential equation satisfied by the probability generating function. Exact analysis may not be possible, but as in the single population case, an approximate threshold theorem can be obtained by considering the model as a continuous time branching process and using relevant results (Bailey, 1975).

Other works on the mathematical modelling of sexually transmitted diseases develop the theory, combining it with epidemiological data, particularly Hethcote and Yorke (1984). Bailey (1979) provides a good introduction and reference list relevant to sexually transmitted diseases. More recent work on the sexual spread of HIV is also relevant to other sexually transmitted diseases.

1.4.5 Modelling the Sexual Spread of HIV and AIDS

Early attempts at modelling the spread of HIV concentrated on the transmission among homosexuals, which was the population initially thought to be at most risk

from the disease. An initial model is not unlike that for the spread of measles, but with no removals in the model as people do not develop immunity from the disease and the parameter β which corresponded in the measles model to the rate at which infection occurs between a single infected and a single susceptible individual will be replaced by $\beta\kappa$, where κ is the rate at which a susceptible acquires new sexual partners and β is now interpreted as the probability infection occurs during such a partnership (Isham, 1988). The theory behind this model will therefore be similar to the theory already discussed. Such a model does not include any significant biological factors about HIV and AIDS therefore it can only serve as an introduction to more realistic models. Anderson and May (1991) presented a model which did incorporate more realistic features, such as the uncertainty about whether everybody infected with the virus will go on to develop the disease and people effectively becoming removed when full blown AIDS develops. They split the population into five compartments: susceptibles, $X(t)$; infectious individuals of types 1 and 2; $Y_1(t)$ and $Y_2(t)$ respectively; those with clinical AIDS; $A(t)$ and non-infectious individuals of type 2; $Z(t)$, where type 1 infectives are assumed to progress into the AIDS compartment but type 2 infectives will progress into a non-infectious state. They assumed that a proportion f of the population are type 1, hence $1-f$ will be type 2. Setting $f=1$ would give a model in which all individuals with HIV will go on to develop AIDS and this is now the course of events in accepted by today's scientific community.

We have

$$\frac{\mathrm{d}X}{\mathrm{d}t} = B - (\mu+\lambda)X,$$

$$\frac{\mathrm{d}Y_1}{\mathrm{d}t} = f\lambda X - (\mu+\upsilon_1)Y_1,$$

$$\frac{\mathrm{d}Y_2}{\mathrm{d}t} = (1-f)\lambda X - (\mu+\upsilon_2)Y_2,$$

$$\frac{\mathrm{d}A}{\mathrm{d}t} = \upsilon_1 Y_1 - (\mu+\alpha)A,$$

and
$$\frac{\mathrm{d}Z}{\mathrm{d}t} = \upsilon_2 Y_2 - \mu Z, \tag{1.3}$$

where B is the rate at which susceptibles join the sexually active population, μ is the *per capita* death rate of the community, (neglecting the disease) υ_1 is the rate at which type 1 infected individuals develop AIDS, and υ_2 is the rate at which type 2 individuals become non-infectious. α is the additional death rate due to AIDS, λ is the *per capita* rate at which susceptibles become infected, or the force of infection, which is given as

$$\lambda = c(\beta_1 Y_1 + \beta_2 Y_2)/N.$$

Here c is the average number of sexual partners per unit time, for $k = 1, 2$, β_k is the probability that infection will be acquired from an infected sexual partner of type k and Y_k/N is the probability that a partner chosen at random will be an infective of type k. N is the total size of the sexually active population.

As an approximation to the start of the epidemic, we can make some simplifying assumptions, such as ignoring death from AIDS and treating the population size as being fixed, which will lead to the number of infectives increasing exponentially, such that

$$Y(t) \simeq Y(0)\exp(\Lambda t)$$

where $\Lambda = \beta c - \upsilon$ and $Y(t) = Y_1(t) = Y_2(t)$. From this approximation the initial doubling time can be evaluated and we can also obtain an expression for the number of individuals with AIDS in the early stages of the epidemic. Equation 1.3 can be solved numerically to show an exponential increase towards the start of the epidemic, levelling off when AIDS related deaths begin to remove seropositives. This levelling off is also to be found in the data from America, such as the San Fransisco Gay Men's Health Study (McKusick *et al.*, 1985*a*, 1985*b*), but this may also be attributable to changes in sexual practices.

The previous model assumed, for mathematical simplicity, that the rate of

acquiring sexual partners is the same for all individuals and also that the choice of sexual partner is random. As in the models for the spread of gonorrhoea, this may not be realistic and, as May and Anderson (1988) argue, heterogeneity in the rate of acquisition of sexual partners cannot be ignored. This can be introduced by dividing the population at risk into groups, characterised by the average number of sexual partners per unit time. Using the notation X_i to denote the number of susceptibles who have on average i sexual partners per unit time, with similar notation for the other compartments, we have

$$\frac{\mathrm{d}X_i}{\mathrm{d}t} = B_i - (\mu + \lambda_i)X_i,$$

$$\frac{\mathrm{d}Y_{1i}}{\mathrm{d}t} = f\lambda_i X_i - (\mu + \upsilon_1)Y_{1i},$$

$$\frac{\mathrm{d}Y_{2i}}{\mathrm{d}t} = (1-f)\lambda_i X_i - (\mu + \upsilon_2)Y_{2i},$$

$$\frac{\mathrm{d}A_i}{\mathrm{d}t} = \upsilon_1 Y_{1i} - (\mu + \alpha)A_i$$

and

$$\frac{\mathrm{d}Z_i}{\mathrm{d}t} = \upsilon_2 Y_{2i} - \mu Z_i.$$

Here

$$\frac{\mathrm{d}N_i}{\mathrm{d}t} = B_i - \mu N_i - \alpha A_i,$$

where $N_i(t)$ is the number of individuals in the ith group at time t. They assume that the force of infection for an individual in the ith group is $\lambda_i = i\lambda$, where λ is the force of infection per partner, which will depend on the probability that partner is infectious and transmission parameters β_k. For $k = 1, 2$, β_k is the probability that a single contact between a susceptible and an infected individual in class k will result in the susceptible becoming infected. π, the probability that a randomly chosen partner is infectious, can be obtained by weighting potential partners by their sexual activity rate hence

$$\lambda = \sum_j j(\beta_1 Y_{1j} + \beta_2 Y_{2j})\Big(\sum_j jN_j\Big)^{-1}.$$

This model can also be evaluated numerically, although a probability distribution describing the proportions in each sexual activity group is required. The model

can be explored for differing amounts of variation in the sexual activity rates, measured by the coefficient of variation, CV= σ/m, where m is the mean of the distribution describing sexual activity rates and σ^2 is its variance.

The above models assumed that infected individuals move out of the incubating class at a constant *per capita* rate (Medley *et al.*, 1988). One method of incorporating this is to assume that the probability of getting AIDS at time τ since becoming infected with HIV is $\upsilon_0\tau^\nu$ where υ_0 and ν are parameters which can be estimated from data. This would result in the incubation time having a Weibull distribution, the average incubation period D being

$$D = \Gamma\left(\frac{\nu+2}{\nu+1}\right)\left(\frac{\nu+1}{\upsilon_0}\right)^{1/(\nu+1)}.$$

The above models also assumed a constant level of infectiousness throughout this infectious period. There is evidence however that this may not be the case, as shown by Anderson and May (1988). A time dependent transmission probability can be created which would correspond to people being more infectious when initially infected with the virus and just before developing AIDS;

$$\beta(\tau) = \beta_0 \exp(-\tau/T_0) + \beta_1 \exp[-(t-\tau)/T_1].$$

These two approaches add to the complexity of the subsequent models as an extra variable τ, corresponding to time since infection has been introduced and we need partial differential equations to describe the progress of the disease. Another possible approach to include the time dependent transmission probability would to add extra compartments to the model (Anderson and May, 1991). Parts of Equation 1.3 could be replaced by

$$\frac{\mathrm{d}Y_1}{\mathrm{d}t} = \lambda X - \upsilon_0 Y_1,$$

$$\frac{\mathrm{d}Y_2}{\mathrm{d}t} = \upsilon_0 Y_1 - sY_2,$$

$$\frac{\mathrm{d}Y_3}{\mathrm{d}t} = sY_2 - \upsilon_1 Y_3,$$

and $$\frac{dA}{dt} = v_1 Y_3 - \alpha A.$$

In this model it is assumed that everyone who is infected with HIV will go on to develop AIDS, as is currently thought to be the case. The classes Y_1, Y_2 and Y_3 have different meanings to previously. Each infected individual moves through three phases corresponding to the three infected classes. Susceptibles move into the first period of infectiousness corresponding to Y_1 at *per capita* rate λ, where λ is the force of infection per susceptible individual per unit time, in which the probability of infecting a susceptible partner during the course of the partnership will be some constant value β_0, they then move into a second infected compartment, within which they are not infectious, at rate $v_0 = 1/T_0$, and then move into a third infected and infectious compartment at rate $s = 1/D$, where the associated probability of infecting a susceptible partner will be β_1. From this third compartment they will then move into the AIDS class at rate $v_1 = 1/T_1$. The individuals who have AIDS die at *per capita rate* α and do not mix with the other individuals. Hence the total period with HIV is $T_0 + D + T_1$ where T_0, D and T_1 are the times spent in the three classes. The force of infection per unit time is $\lambda = c(\beta_0 Y_1 + \beta_1 Y_3)/(X + Y_1 + Y_2 + Y_3)$ where c is the rate of acquiring new sexual partners.

The above models considered a population of homosexuals, however in many parts of the world, such as sub-Saharan Africa, the spread of HIV and AIDS has been mostly due to heterosexual transmission. The theory behind the two sex models of the spread of gonorrhoea can be extended to model the heterosexual spread of HIV, where there will be separate transmission probabilities for male to female and female to male per sexual act. It has been suggested that $\beta_f < \beta_m < \beta$ where β_m is the probability of transmission per sexual act from infected male to susceptible female; β_f is the transmission probability per sexual act from infected female to infected male and β is the corresponding probability for two homosexual

males. Compartmental models can also be extended to include groups such as female prostitutes and male bisexuals, and split the male and female populations into promiscuous and non-promiscuous individuals (Knox *et al.*, 1986).

Models relating to the sexual spread in Africa must also re-examine the assumptions used in previous models such as the population size remaining constant. The demographic consequences of such spread are discussed by Anderson *et al.* (1988). Such demographic models also include the high prevalence of paediatric AIDS and the effect on future population sizes.

The mixing patterns used in the above models all assume that the duration of sexual partnership is negligible and if transmission occurs within a partnership it must occur instantaneously, this however is a simplification about which Dietz and Hadeler (1988) note 'the formation of a pair of susceptibles renders them in a sense temporarily immune to infection as long as the partners do not separate and have no other contacts with other partners'. This pair formation should be included in both homosexual and heterosexual models. Such models have been studied by Dietz (1987).

Using a heterosexual population as an illustration we can divide the population in to three compartments; males, females and pairs, denoting the number of individuals in the first two compartments at time t as $m(t)$ and $f(t)$ respectively and the number of pairs at time t as $p(t)$. Suppose that the rate at which these pairs form is $\phi(m, f)$ which depends on the number of males and females, and the pairs separate at rate σ. There is a natural mortality rate μ in the population and new individuals arrive in the population at influx rate λ. A model for the pair formation will be

$$\frac{\mathrm{d}m(t)}{\mathrm{d}t} = \lambda + (\sigma + \mu)p(t) - \mu m(t) - \phi(m, f),$$

$$\frac{\mathrm{d}f(t)}{\mathrm{d}t} = \lambda + (\sigma + \mu)p(t) - \mu f(t) - \phi(m, f),$$

and $$\frac{\mathrm{d}p(t)}{\mathrm{d}t} = -(\sigma + 2\mu)p(t) + \phi(m, f).$$

This model has to be extended to include the presence or absence of infection, denoting for example in the males m_0 as the number of susceptible males and m_1 as the number of infective males, f_0, f_1 respectively for susceptible and infective females and p_{01} as the number of pairs with a susceptible male but infective female, and $\phi_{01}(t)$ is the rate at which pairs with a susceptible male and infective female form. We define p_{00}, p_{10}, p_{11}, ϕ_{00}, ϕ_{10} and ϕ_{11} in the analogous fashion. We then have

$$\frac{\mathrm{d}m_0(t)}{\mathrm{d}t} = \lambda + (\sigma_{00} + \mu)p_{00}(t) + (\sigma_{01} + \mu)p_{01}(t) - \mu m_0(t) - \phi_{00}(t) - \phi_{01}(t),$$

$$\frac{\mathrm{d}m_1(t)}{\mathrm{d}t} = (\sigma_{10} + \mu)p_{10}(t) + (\sigma_{11} + \mu)p_{11}(t) - \mu m_1(t) - \phi_{10}(t) - \phi_{11}(t),$$

$$\frac{\mathrm{d}f_0(t)}{\mathrm{d}t} = \lambda + (\sigma_{00} + \mu)p_{00}(t) + (\sigma_{10} + \mu)p_{10}(t) - \mu f_0(t) - \phi_{00}(t) - \phi_{10}(t),$$

$$\frac{\mathrm{d}f_1(t)}{\mathrm{d}t} = (\sigma_{01} + \mu)p_{01}(t) + (\sigma_{11} + \mu)p_{11}(t) - \mu f_1(t) - \phi_{01}(t) - \phi_{11}(t),$$

$$\frac{\mathrm{d}p_{00}(t)}{\mathrm{d}t} = -(\sigma_{00} + 2\mu)p_{00}(t) + \phi_{00}(t),$$

$$\frac{\mathrm{d}p_{01}(t)}{\mathrm{d}t} = -(\sigma_{01} + 2\mu)p_{01}(t) + \phi_{01}(t),$$

$$\frac{\mathrm{d}p_{10}(t)}{\mathrm{d}t} = -(\sigma_{10} + 2\mu)p_{10}(t) + \phi_{10}(t),$$

and $$\frac{\mathrm{d}p_{11}(t)}{\mathrm{d}t} = -(\sigma_{11} + 2\mu)p_{11}(t) + \phi_{11}(t). \tag{1.4}$$

We also have to alter Equation 1.4 to include within partnership infections. To do this we assume that a partnership begins with a sexual act, then subsequent acts occur as a Poisson process of rate ρ until terminated by separation. We also assume that sexual contact only occurs within a pair. Assuming that the male to female transmission probability is ε_m and the female to male transmission is ε_f we then have

$$\frac{\mathrm{d}p_{00}(t)}{\mathrm{d}t} = -(\sigma_{00} + 2\mu)p_{00}(t) + \phi_{00}(t),$$

$$\frac{\mathrm{d}p_{01}(t)}{\mathrm{d}t} = -(\sigma_{01} + 2\mu + \varepsilon_f)p_{01}(t) + (1 - \varepsilon_f)\phi_{01}(t),$$

$$\frac{\mathrm{d}p_{10}(t)}{\mathrm{d}t} = -(\sigma_{10} + 2\mu + \varepsilon_m)p_{10}(t) + (1 - \varepsilon_m)\phi_{10}(t),$$

and

$$\frac{\mathrm{d}p_{11}(t)}{\mathrm{d}t} = -(\sigma_{11} + 2\mu)p_{11}(t) + \phi_{11}(t) + \varepsilon_f\phi_{01}(t) + \varepsilon_m\phi_{10}(t) + \varepsilon_f\rho p_{01}(t) + \varepsilon_m\rho p_{10}(t).$$

Dietz and Hadeler (1988) discuss the properties of this model and Dietz goes on to extend the model, to include homosexual males and bisexuals, having in Dietz (1987) twenty nine variables in his models, with forty two parameters. This model demonstrates the problem that with so many parameters, it may be difficult to obtain reliable estimates, although Dietz uses data relevant to Germany for estimation.

Other research has explored and evaluated differing mixing frameworks; such as *assortative mixing* where all sexual activity occurs within the groups, *proportional mixing* where the fraction of sexual contacts of people in activity class i that are made with people in class j is equal to the fraction of total contacts made by the population that are due to people in class j or *preferred mixing* which is a linear combination of assortative and proportional mixing. Blythe *et al.* (1991) present a unified theory of sexual mixing which also includes pair formation.

Sattenspiel (1989) examined the structure and social context of social interactions relevant to the spread of HIV, in which she first described previous models which stratified the population of interest into subgroups, which she noted can either correspond to sexual activity or to geographic location. This is achieved by looking at n subgroups, with a $n \times n$ matrix with n^2 terms in it describing the interactions between groups. Consider two infection rates in the population, α_i, the within group infection rate from an infected individual to a susceptible individual in subgroup i and β_{ij}, the rate of infection from an infected person in group i to a susceptible in group j. This only includes varying probabili-

ties of infection between groups, not varying probabilities of mixing. Sattenspiel (1987) developed models for the spread of hepatitis A which included migration matrices to describe the probability of two individuals from different subgroups coming into contact with each other and explores the effect of heterogeneity in these models by varying the migration matrix. This approach is similar to that of Abramson and Rothschild (1988), which also includes both physiological and behavioural co-factors in the matrix models.

Another form of matrix model which has been used not only to examine the spread of HIV, but other diseases such as measles and rabies, is the spatial model of disease spread (Mollison, 1977; Cliff *et al.*, 1981 and Gani, 1990). In this the mass action assumption of Hamer, in which contact between susceptibles and infectives occurrs by homogeneous mixing throughout the population, is re-examined. A simple model of this type would model the disease spread on a two dimensional lattice where, at the point (i, j) at time t, there could be a susceptible S, an infective I, or an immune R individual. Assuming that time is discrete, at time $t + 1$ the infectivity status of the individual at that point would be dependent on the infectivity status of the eight neighbouring points on the lattice at time t, those at $(i \pm 1, j \pm 1)$. This model can be developed using the theory behind Markov fields, or alternatively by computer simulation. Other research uses matrix models such as random graphs and random cellular automata (Yakowitz *et al.*, 1990). Other models which use a similar lattice structure can be used to evaluate differing vaccination programs, although this is more relevant to diseases such as measles (Greenhalgh, 1986). Spatial models have also been developed to describe the spread of rabies within foxes, where the mass-action assumption of homogeneous mixing is also unrealistic. Such models have been used to explore the geographical spread of the disease throughout Europe and to consider the possible options for the control of the disease if it ever entered the United Kingdom (Murray, 1993).

1.4.6 Modelling the Spread of HIV via Needle Sharing

The first paper which concentrated on the spread of HIV via needle sharing was presented by Kaplan (1989). We shall only briefly mention this paper in this literature review as the next chapter is concerned with extending and adapting this model. This paper modelled the prevalence of HIV in a population of IDUs who share needles within shooting galleries. Two proportions are examined, the proportion of IDUs who are infected and the proportion of needles that are infected. The model is deterministic in nature and employs quite restrictive assumptions.

Allard (1990) presents a mathematical model which describes the risk of infection from sharing injection equipment. He examines the probability that a syringe becomes infected when used once by an infected person, and then extends this to obtain the probability that the needle becomes infected after being used C^* times. He similarly describes the probability that a person becomes infected after using an infected needle C times. Using these probabilities, different sharing scenarios are described such as random sharing and sharing between partners. Although it is recognised that the the probability of a person becoming infected after using an infected needle is unknown, Allard demonstrates that random sharing, such as that which happens in shooting galleries, is more risky for a wide range of parameter values. This paper, however, was only concerned with the probability of becoming infected and as such did not include any of the population dynamics of the IDU population. Aylward *et al.* (1995) describe in a similar fashion the related problem of contaminated medical equipment being reused in vaccination campaigns in developing countries.

Peterson *et al.* (1990) present a Monte Carlo simulation of HIV infection in a population of IDUs. The stochastic nature of this paper contrasts with Kaplan's deterministic approach and this is commented on by the authors. As this paper uses computer intensive techniques, many compartments can be employed,

describing both HIV infection progression and the drug-using dynamics including monthly, weekly and daily injecting. A disease progression model is created which includes acute infection, asymptomatic and pre-AIDS symptoms compartments, as well as an AIDS compartment. In parallel to this disease progression model, a model which also describes the progression between monthly use, weekly use and daily use is also described. Two other states are possible within this drug use dynamic system; using 'jail not using' and 'community not using'. Both of these states allow IDUs to remain in the system without returning into the general population or dying from reasons other than AIDS. They do not, however, account for the possibility of needle sharing within prison. A third model describes the social networks in which sharing occurs. They categorise the various sharing mechanisms into pooled sharing within shooting galleries, sharing within small groups, and sharing with a stranger.

The three interacting models are then combined. Having noted that an important benefit of stochastic modelling is its capacity to join disparate sociological, behavioural and clinical information into one model, they describe various scenarios, and show that random sharing results in higher numbers of infected IDUs than structured sharing. They demonstrate the effect of various intervention programs and suggest that the model's ability to mimic complex social networks and to incorporate a sufficiently realistic structure of HIV progression makes it readily adaptable for use in other localities. They suggest that this justifies the expense of acquiring local drug and behavioural data.

Blower *et al.* (1991) present a deterministic model which they used to assess the epidemiological consequences of heterosexual, IDU and perinatal transmission in New York City. They demonstrate the significance of the dynamic interaction of heterosexual and IDU transmission. The model consists of thirty four ordinary differential equations and employs twenty biological-behavioural transmission pa-

rameters. When it is used to predict the future number of adult or paediatric AIDS cases, there was considerable uncertainty as demonstrated by extremely wide confidence intervals of the prediction estimates. An in-depth sensitivity analysis is undertaken. It was found that only a few key parameters are important in predicting the spread of the disease, however the biological parameters describing the probability of transmission both through sexual contact and by needle sharing are important. They conclude that their results suggest that long term precise estimates of the future number of AIDS cases will only be possible once values of these key variables have been evaluated accurately.

Within their model, IDUs are classified as either stranger-users or buddy-users; the former being comparable to the shooting galleries that Kaplan models and the latter described as the sharing with close friends or relatives in social environments. As they do not specifically include injecting equipment as a vector for HIV transmission in the same way that Kaplan (1989) does, they note that the risk of infection in stranger-users depends only on the rate of sharing needles, the HIV transmission efficiency per injection and the seroprevalence in that sub-group of users. In addition, the risk of infection in buddy users also depends on the stability of the buddy affiliations over time. Different sexual mixing matrices are also described.

Atkinson (1996) used simulation techniques in examining HIV transmission among IDUs. In a similar fashion to Peterson, he opted for using a mathematical simulation language in describing the transmission dynamics, in this case the General Purpose Simulation System, citing Leslie and Brunham (1990) as a good example of the techniques in modelling the homosexual spread of HIV. The shooting gallery is again focused on, and as the simulation package modelled individual IDUs within a hypothetical cohort, heterogeneity of sharing needles could be included. Atkinson notes that in contrast to the spread of a disease such

as measles, the spread of HIV results from an exchange of body fluids after a conscious partnership selection, the spread of HIV among IDUs involving needles as an intermediate vector.

Simulation languages are also useful in that the stochastic variability can be directly included and common distributions such as the Weibull distribution can be assumed for parts of the disease spread dynamics. The modelling concentrated on a single shooting gallery which consisted of one hundred IDUs. These IDUs could either share with one other person, or share with up to four others, sharing either daily or weekly. An IDU would either always clean the needle before injection, or never clean the needle before injection. Initially all needles are clean and the disease spread is sparked by the introduction of one infected individual. A seniority between IDUs in sharing is modelled, as is a rotation of needles resulting in each needle being discarded after it has been used fifty times. The disease progression is modelled including an incubation period, and all infected IDUs die a fixed length of time after becoming infected.

In order to simulate the disease spread, a heterogeneous structure was assigned to this cohort. The parameters used in the simulation were gathered from the available literature, in particular, the probability of infection per injection with an infectious needle was assumed to be 0.005. This probability was then used indirectly in sampling from a geometric distribution the number of injections with an infected needle that were required to infect an IDU. It was assumed that seroconversion occurred after fifty days after initial infection. Incubation times and survival rates are again drawn from the available literature. Different scenarios are modelled in which the sharing rates and the probability of an IDU cleaning the needle are varied, and the results are presented over a period of five years following the introduction of the infected IDU.

Within the discussion, it is noted that the highest risk combination of sharing

and cleaning resulted in the highest infection rates, resulting in over half of the cohort of IDUs becoming infected after five years. A comparison to herd immunity is discussed such that the effect of some IDUs cleaning needles may offer some protection to those that do not clean needles. Goforth and Berleant (1994) also describe the use of simulation models when examining HIV spread, however their paper describes the qualities of the simulation program 'The Interactive Model for AIDS prediction' (IMAP2) rather than the theoretical aspects of the models.

Capasso *et al.* (1995) combine some of the more basic ideas from Kaplan's (1989) model with a mathematical model for the basic single population SIR model with vital dynamics for AIDS as analysed by Jacquez *et al.* (1988). They mimic the assumptions of Kaplan in that they include the flushing of infected blood from a needle by the blood of an uninfected IDU in their models and they assume that an addict becomes infected after exposure to HIV with probability α. They also provide an explicit expression of the force of infection based on the kinetics of HIV transmission due to sharing of drug injection equipment within a friendship group of IDUs. Within this mainly mathematical paper, in which they examine the stability of the equilibria, they go on to extend the one-group model into a multiple-group model.

Iannelli *et al.* (1997) study several hypotheses about the dynamics of HIV epidemics among IDUs. The paper is described as 'A study of contact structure through a mathematical model' and examines the spread of the disease as described by a system of deterministic equations, following on from Blythe and Anderson (1988) and Thieme and Castillo-Chavez (1989). Data from the Latium region of Italy is compared to the numerical results from the model, and a best-fit estimate of the parameters is obtained. They show that heterogeneous models provide a better fit to the observed data, as does assuming that there exists a peak in infectivity soon after infection. They note some of the difficulties in aim-

ing for models that accurately reflect the course of the epidemic, such as data usually only being available on AIDS incidence rather than HIV prevalence. The authors chose to ignore the role of needles as disease vectors, opting instead to model HIV transmission through needle sharing by using the 'mass-action law' as described previously in this chapter in the context of modelling the spread of measles. They also combine sexual and needle sharing transmission.

They seek to answer some key questions about modelling HIV transmission, including how relevant is the hypothesis of variable infectiousness during the incubation period and whether it is possible to assume that IDUs form a homogeneous group with respect to the disease transmission. The system of differential equations used includes ordinary and partial derivatives, and although we do not reproduce them here, a discussion of the parameters, and their distributional form is warranted. In particular the infectiousness is modelled as an initial peak followed by a low, almost zero, level of infectiousness, which is then followed by an increasing level of infectiousness as the IDU progresses to AIDS. This presented problems in estimating the infectiousness distribution from epidemiological data as this was intrinsically linked to the distribution describing the length of time the IDU had been infected, therefore they normalise the infectiousness curve by assuming the value 1 at the first peak and exploring the infectiousness of an individual over time relative to the infectiousness of an individual at the first peak of infectivity.

Arcà, Perucci and Spadea (1992) also employ data from an Italian region when they model the interaction between the heterosexual and IDU populations. They split the population into eight groups by gender, sexual activity and whether or not they inject. To model the varying infectivity of HIV, they spilt the infected compartment into three, and these assumptions result in a system of forty differential equations. In contrast to Kaplan's model, the infection process is described

by the force of infection per needle sharing partnership rather than by a probability related to infection following one random sharing act. This enables different mixing patterns to be examined. They then obtained data from behavioral and epidemiological research to construct the parameters for this model, concluding that the model solutions appear to fit with the observed surveillance data.

A stochastic model of the HIV epidemic involving both sexual contact and intraveneous drug use was created by Tan and Tang (1993). Three interacting populations are examined; IDUs, homosexual men and homosexual men who are also IDUs. They assume a latent stage in the disease progression, and partition the infective stage into five substages. In their list of basic assumptions, they create the framework for describing the transmission dynamics, including variable levels of sexual activity or needle sharing, variable infectivity throughout the disease progression, immigration, emigration and mixing patterns. Using a variety of probabilistic techniques and after some eloquent mathematics, they model the process as a chain multinomial distribution. They also derive the expected numbers of this distribution and extend the model into a continuous time model. This is again highly theoretical, however they illustrate the application of the model using some Monte Carlo studies. In this they assume three levels of sexual activity and three levels of sharing. The parameters used in these simulations and the initial values are derived from the literature. They assume that since the probabilities of HIV transmission from sexual or needle sharing contacts are proportional to the amount of free HIV in blood or body fluid (Redfield and Burke, 1988) they chose probabilities of HIV transmission in both the sexual and drug use spread to comply with these amounts of HIV. For example, during the infection period, the probability of HIV transmission is chosen as a monotonically increasing function of the infection duration. They examine four scenarios to contrast a deterministic model with stochastic models in which mixing patterns have a recognised distribution or randomness. They show that although the random-

ness in the number of different partners per unit time seemed to have little effect on the spread of the disease, the deterministic model was a poor approximation to the corresponding expected numbers of the stochastic model.

Gani and Yakowitz (1993) use a Markov Chain approach to modelling the spread of HIV among IDUs. In contrast to Kaplan's model, they assume a stable group of buddy-users, some of which are infected. They extend the model to include immigration and emigration. Recursive techniques were used to derive the various probabilities associated with the model from the probability of needle sharing and the probability of transmitting HIV through an infected needle. The latter probability is taken to be either 0.175 or 0.35. They compare the form of the matrix that they had derived to a chain binomial infection model previously outlined by Gani and Jerwood (1971). In conclusion, they note that although data on IDUs are difficult to obtain, the model can be used to examine the effect of changes of the above probabilities. However this model examines the disease transmission almost at a micro level which they regard as a necessary foundation for the macroscopic effects on a large population of IDUs. Gani and Yakowitz (1993) also model the spread of HIV among IDUs using a random allocation method in conjunction with the Markov chain aproach, further adapting the methodology to include the replacement of infectives.

Kretzschmar and Wiessing (1998) explore the risk of a future rise in the prevalence of HIV in an IDU population with low HIV prevalence but continuing risk behaviour. They create a stochastic simulation model to describe a network of buddy relationships (sharing in small groups of friends in a setting like the home of one of the participants) in an IDU population, modelling both the transmission of the disease between buddies and between strangers. They combine results from two surveys of IDUs in the Netherlands to obtain estimates for the behavioural parameters, while assuming that the infectivity of a needle, as expressed as the

probability of transmission in one sharing event, depends on how long the IDU has been infected with the virus. After demonstrating the typical spread of the disease using the parameters derived from surveys they go on to investigate different prevention strategies. They note that there exists a threshold sharing frequency, below which the epidemic never takes off. Above this threshold there are a range of sharing frequencies for which a large stochastic variation between single epidemics can be observed, hence they suggest that making predictions about the future course of the epidemic is virtually impossible. Although they find that introducing risk reduction behaviours into the population will not completely eliminate the disease (in some cases the prevalence decreases very slowly), they conclude that prevention measures specifically focussed on new IDUs can have a large impact on the incidence of HIV.

The basic reproductive number R_0 for HIV within an IDU population is estimated by Massad *et al.* (1994). They adapt the malaria models of Ross (1911) and Macdonald (1957), noting that in an outbreak of malaria among IDUs in Brazil which was attributed to needle sharing, the insect vector may have been replaced by needles. They therefore adapt the notation and parameters in Macdonald's model to make them relevant to HIV spread. After deriving an equation for R_0 using this analogy, they then create a mathematical model similar to Kaplan's and, by analysing the stability of their system of equations around the trivial solution (that is when the disease dies out), they obtain a similar expression for R_0. They again seek to draw an analogy with Macdonald by introducing heterogeneity, both in the probability that a needle becomes infected after an infected IDU has used it, and in the rate at which the IDU injects. They use data from a behavioural study to obtain parameters used in calculating R_0 and show that their results are consistent with Kaplan's. They also show that their results suggest that the prevalence of HIV in the drug injecting community in Santos, Brazil is, at 61.5%, close to their estimated equilibrium value of 67%.

1.5 Conclusion

In conclusion it is worth discussing a paper by Blower and Medley (1992) which proposes the utility of mathematical models in understanding the dynamics of HIV transmission among IDUs. After defining epidemiological mathematical models for a non-specialist audience, they discuss at length the data requirements for such models. They split the required data into three groups, demographic, behavioural and biological. Behavioural studies as described in Section 1.2.4, can be used to estimate some parameters, but questionnaires which code responses into categories are not always the best tool to detect behavioural changes. For example a IDU changing their average number of sharing partners per week from five to two would still be coded into a category like 0-5. They note the difficulty in estimating the biological parameters, in particular the probability of becoming infected after using an infected needle. They conclude that when examining the interaction between the IDU population and the heterosexual population there is a greater need for demographic data, particularly the size and the sex ratio of IDU population and the bridge population by which the disease can pass between the two populations. In conclusion they note the uses of mathematical models in this field, however they stress the importance of obtaining more direct data that can be used in models. They hoped that their paper would generate a closer collaboration between modellers and drug use researchers, something that this Thesis also hopes to achieve.

Chapter 2

Deterministic Models

2.1 Kaplan's Deterministic Models

Kaplan (1989) presents a deterministic model for the spread of HIV among injecting drug users (IDUs) who visit shooting galleries. This was the first paper which explored the modelling of disease spread via shared injecting equipment. The model is deterministic and initially assumes a homogeneously mixing population of IDUs. To provide a tractable model there are many assumptions which render it practically invalid for determining the future nature and extent of the epidemic but, as Kaplan notes, it is useful in evaluating control strategies. In particular it assumes that all sharing occurs in shooting galleries, that needles are selected at random and needles that have been infected remain infected until cleaned or flushed. This last assumption excludes the very real possibility that needles will lose their infectivity over time. Kaplan however does explore this possibility later in the paper. The assumptions used by Kaplan are as follows:

1) The population that is of interest is large.

2) All sharing occurs in shooting galleries.

3) Each IDU visits shooting galleries according to a Poisson process independently of other IDUs.

4) Injection equipment becomes infectious if it is used by an infected IDU.

5) When infectious equipment is used by an uninfected IDU, the act of injecting will flush the needle with a fixed probability. Flushing is defined as the needle unintentionally getting cleaned by the uninfected blood of the IDU.

6) Any uninfected IDU who uses infectious injection equipment is considered to have been exposed to HIV.

7) Given exposure to HIV an IDU becomes infected with a fixed probability.

8) The needle sharing IDU population remains constant. Infected and susceptible IDUs who leave the population are immediately replaced by susceptibles.

The spread of HIV through sexual contact and through sharing injecting equipment outwith shooting galleries is ignored.

The model which Kaplan presents comprises two differential equations, one which describes the rate of change over time of the proportion of the population that is infected, the other describing the probability of an IDU encountering infectious equipment. These differential equations are

$$\frac{\mathrm{d}\beta(t)}{\mathrm{d}t} = \lambda\gamma\pi(t) - \lambda\gamma\beta(t)[1 - (1 - \pi(t))(1 - \theta)] \tag{2.1}$$

and

$$\frac{\mathrm{d}\pi(t)}{\mathrm{d}t} = (1 - \pi(t))\lambda\beta(t)\alpha - \pi(t)\mu. \tag{2.2}$$

Here $\pi(t)$ is the proportion of the IDU population that is infected at time t, $\beta(t)$ is the proportion of needles infected at time t, λ is the rate per individual of visiting shooting galleries, γ is defined as the gallery ratio such that if there are N IDUs and n needles within the various shooting galleries then $\gamma = N/n$. θ is defined to be the probability that an uninfected IDU flushes an infected needle with a single injection, α is the probability that, given exposure to HIV an IDU will become infected and μ is the total rate at which infected IDUs leave the sharing injecting population. This includes IDUs who cease sharing because

they develop AIDS, IDUs who die from AIDS and IDUs who cease sharing for other reasons. Kaplan does not solve these equations explicitly, instead he looks at the steady state situation and analyses R_0, the basic reproductive ratio of infection. R_0 can be interpreted as the number of new infections amongst IDUs that occur on introducing a single infected IDU into a population of susceptibles at equilibrium directly caused by the original infected IDU. In a deterministic model, the epidemic will only develop if R_0 is greater than 1. Looking at β and π, the steady state values of $\beta(t)$ and $\pi(t)$ are obtained by setting the derivatives both to zero. This gives $\beta = 0, \pi = 0$ or $\beta = \beta^*$, $\pi = \pi^*$, where the non zero equilibrium values β^* and π^* are given by

$$\beta^* = \frac{\lambda\alpha - \mu\theta}{\lambda\alpha} \tag{2.3}$$

and

$$\pi^* = \frac{\lambda\alpha - \mu\theta}{\lambda\alpha + \mu(1-\theta)}. \tag{2.4}$$

Equations 2.3 and 2.4 are not valid when $\lambda\alpha \leq \mu\theta$, in which case the only equilibrium is $\pi = 0$ and $\beta = 0$. This suggests that

$$R_0 = \frac{\lambda\alpha}{\mu\theta}. \tag{2.5}$$

Kaplan proves Equation 2.5 for R_0 directly. Clearly we expect an epidemic to result only if the initially infected IDU can generate more than one secondary infection, that is if $R_0 > 1$.

We can explore this model by numerically integrating Equations 2.1 and 2.2 using the program SOLVER. Kaplan suggests values for the parameters used in the model, however in 1989 when this paper was published, little was known about the transmission dynamics and the associated parameter values. In particular, the value of the parameter α could not, at that time, be estimated with any precision. Indeed later papers by Kaplan, such as Kaplan and O'Keefe (1993) suggest that the value used in this original paper may be a gross overestimate of the true probability of infection. We shall discuss parameter value estimation

in Chapters 5 and 6, however in developing the modelling techniques initially presented in this chapter, we shall employ the suggested values from the original paper. In particular we shall define a set of standard parameters and initial values which will enable us to explore individual parameters with reference to a standard set of remaining parameters.

λ is set at 5.952×10^{-3} visits per hour, which corresponds to IDUs visiting shooting galleries once a week, $\mu = 1.43 \times 10^{-5}$ deaths per hour, which corresponds to the life expectancy of an infected IDU of eight years, $\alpha = 0.075$, $\theta = 0.25$ and a gallery ratio $\gamma = 10$. Although in this deterministic model the size of the IDU population and the number of shooting galleries are only expressed relative to each other in the parameter γ, we wish to model the spread of HIV within a population consisting of 10,000 IDUs. This is approximately the number of drug injectors in Glasgow (Frischer *et al.*, 1993*a*). As we require $\gamma = 10$, we assume that there are 1,000 needles within shooting galleries. We assume that HIV is introduced into a susceptible population when one IDU becomes infected from an external source at time $t = 0$ thus initially one IDU and no needles are infected. Hence the initial proportions of infected IDUs and needles are $\pi(0) = 0.0001$ and $\beta(0) = 0$ respectively. The differential equations are strictly valid only when the number of infected needles and IDUs are large. For smaller numbers a stochastic model is strictly needed. We shall return to this point later in the thesis.

We shall next look at the result of some numerical simulations to examine the effect of individually altering λ, the rate at which an IDU visits shooting galleries, α, the probability of infection from an infected needle, θ, the flushing probability and γ, the gallery ratio. The remaining parameter values are kept fixed. Looking at $\pi(t)$, the proportion of the population that is infected at time t, we can see in Figure 2.1 that $\pi(t)$ follows a logistic type curve. This type of logistic curve is found in many types of modelling, particularly population

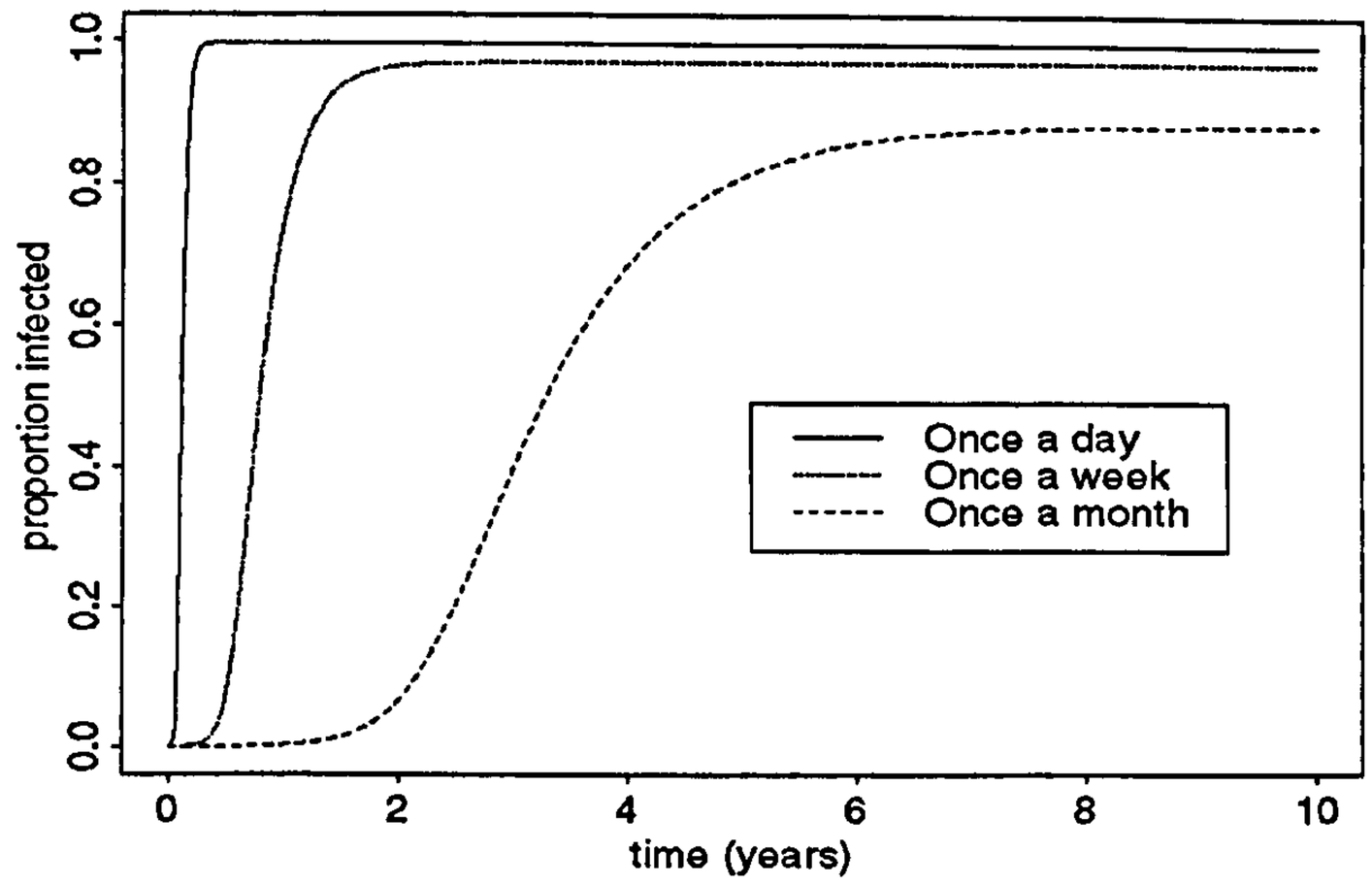

Figure 2.1: The effect of varying λ, in the model described in Equations 2.1 and 2.2. The value of λ in the three curves corresponds to once per day, once per week and once per month. Remaining parameters as indicated in text.

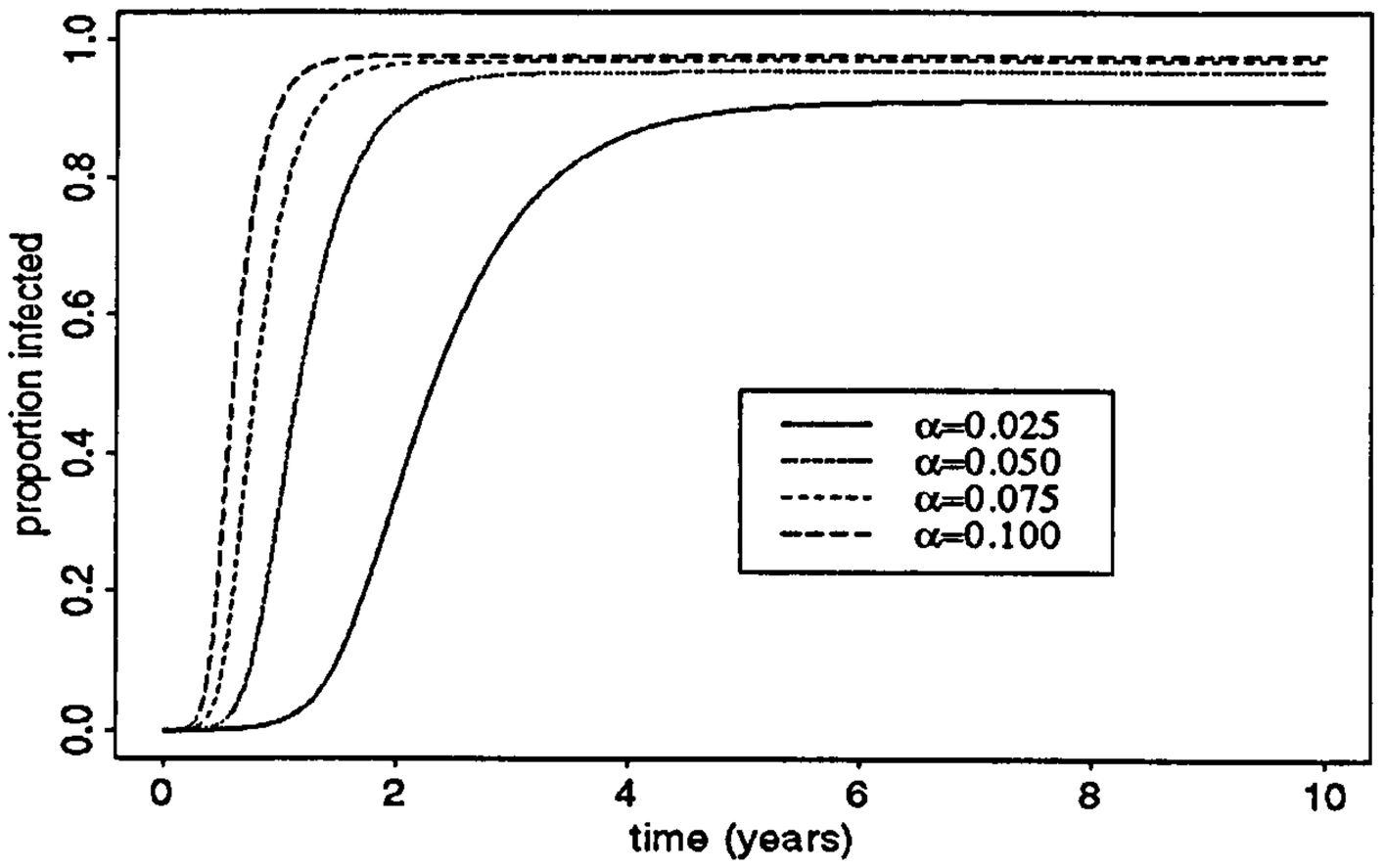

Figure 2.2: The effect of varying α, in the model described in Equations 2.1 and 2.2. Remaining parameters as indicated in text.

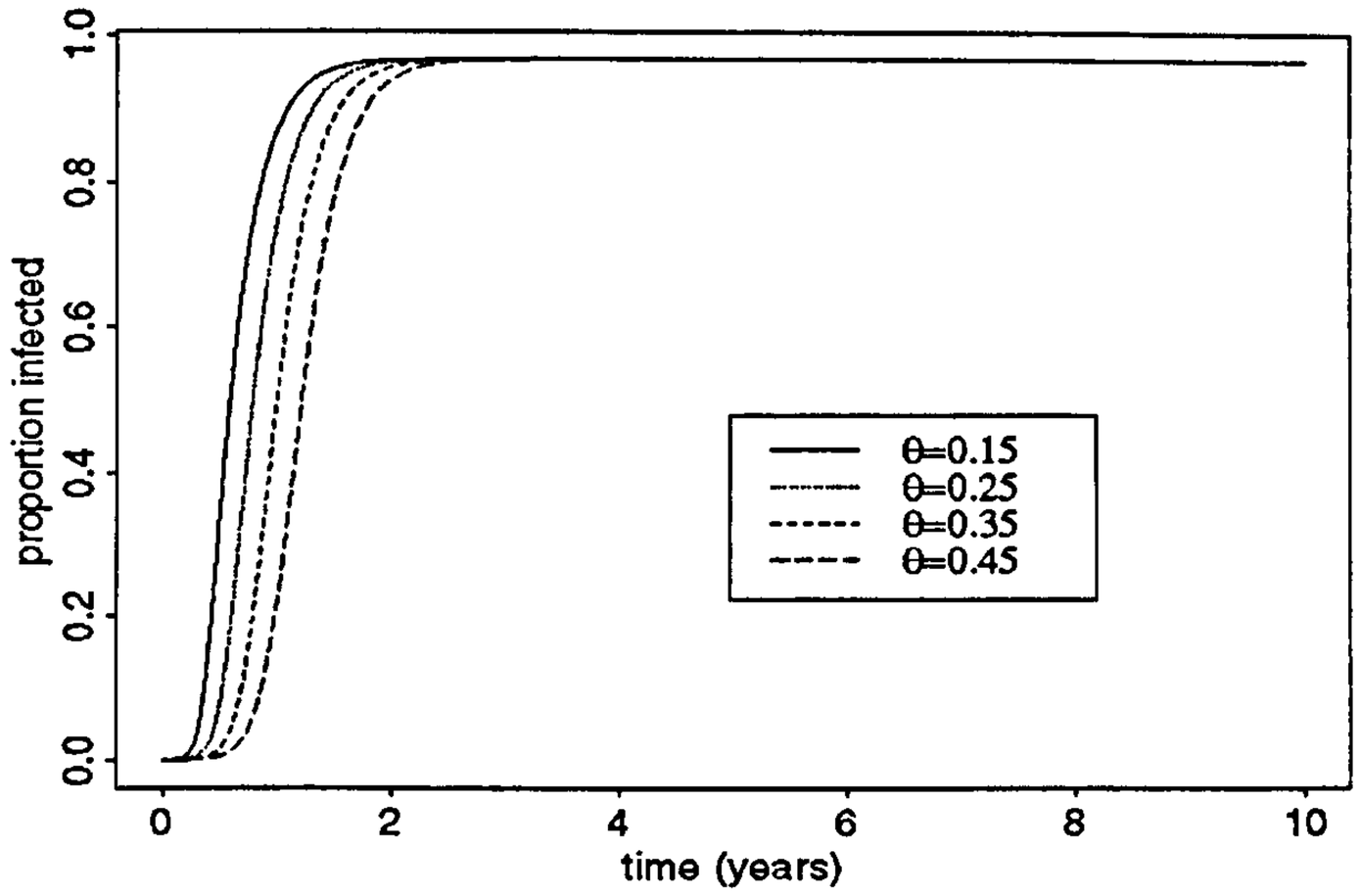

Figure 2.3: The effect of varying θ, in the model described in Equations 2.1 and 2.2. Remaining parameters as indicated in text.

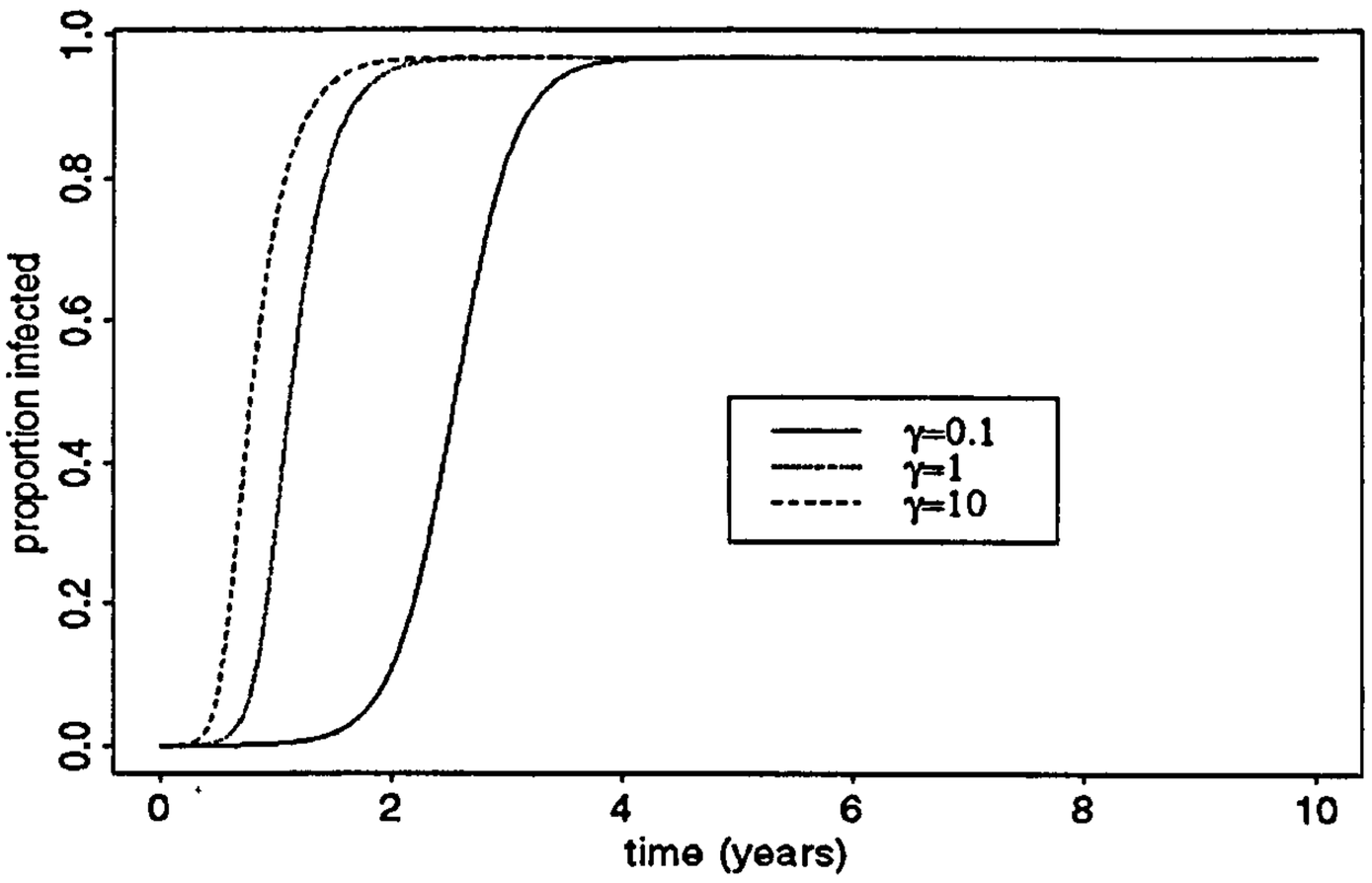

Figure 2.4: The effect of varying γ, in the model described in Equations 2.1 and 2.2. Remaining parameters as indicated in text.

growth modelling when there is a carrying capacity as described by Nisbet and Gurney (1982). This confirms that the proportion infected increases slowly to begin with, this rate of increase will increase, then the rate of increase slows down as the proportion of the population that is infected increases slowly towards its maximum value. From Figure 2.1 we can see the effect of varying the rate at which IDUs visit shooting galleries. When λ corresponds to IDUs visiting once a day, the disease spreads rapidly. The disease spreads less rapidly when it is assumed that IDUs visit shooting galleries less often and $\pi(t)$ reaches lower equilibrium values. Figure 2.2 shows the effect of varying α, the probability of becoming infected on exposure to HIV. We can see that as α increases, the speed at which the epidemic develops increases and $\pi(t)$ reaches a higher equilibrium value.

We can see from Figure 2.3 the effect of varying θ, the probability that an infected needle is flushed by an uninfected IDU. The epidemic takes off quicker for lower values of θ, although over the parameter values illustrated by the simulations in Figure 2.3 the equilibrium values appear less varied than those obtained by varying α and λ. Indeed on keeping the other parameters constant, π^* ranges from 0.968 when $\theta = 0.15$ to 0.969 when $\theta = 0.45$. Decreasing either α or λ or both has the effect of lowering R_0, which suggests that control strategies which decrease the rate at which IDUs share may be useful in reducing the proportion of the population that becomes infected. We can also see from Figure 2.4 that varying γ does not have any effect on the equilibrium value of π, which reflects the absence of γ from Equation 2.4. Lowering γ, or increasing the amount of injecting equipment available whilst keeping the number of IDUs fixed will have the effect of slowing down the spread of the disease.

It is worth noting that the terms which represent the death of IDUs or other removals may be very artificial. It is assumed that when an infected IDU dies,

they are immediately replaced by a susceptible IDU, keeping the population size constant. This implies that the rate at which people enter the IDU population is dependent on the rate at which infected IDUs cease sharing injection equipment, which is questionable. This birth/death process results in most of the population becoming infected, other more realistic forms of representing death or removal will result in different types of curve. Kaplan concludes by showing that his model demonstrates that policies such as the distribution of cleansing solutions and/or injecting equipment amongst IDUs could slow down or stop the intravenous transmission of HIV in shooting galleries.

2.2 Analytical Results for Kaplan's Deterministic Model

We will now explore some of the quanitites of the deterministic model, in paticular the stability of the equilibrium values β^* and π^*.

2.2.1 Existence of Equilibria

We shall first prove the existance of the equilibrium values. Consider the differential Equations 2.1 and 2.2 which describe the spread of the disease. These can be re-expressed as

$$\frac{\mathrm{d}\beta(t)}{\mathrm{d}t} = \lambda\gamma[(1-\beta(t))\pi(t) - \theta\beta(t)(1-\pi(t))] \tag{2.6}$$

and

$$\frac{\mathrm{d}\pi(t)}{\mathrm{d}t} = (1-\pi(t))\lambda\beta(t)\alpha - \pi(t)\mu. \tag{2.7}$$

Lemma 2.1

(a) Suppose that $R_0 \leq 1$. Then the equilibrium where the disease has died out $\beta^* = \pi^* = 0$ is the only equilibrium.

(b) If $R_0 > 1$ then the equilibrium values are given by

$$\beta^* = 1 - \frac{\mu\theta}{\lambda\alpha} \quad \text{and} \quad \pi^* = \frac{\lambda\alpha - \mu\theta}{\lambda\alpha + \mu(1-\theta)}.$$

Whatever the initial proportions of infected needles and infected IDUs, provided $\beta(0) > 0$ or $\pi(0) > 0$ such that the disease is initially present $\beta(t) \to \beta^*$ and $\pi(t) \to \pi^*$ as $t \to \infty$. If $\beta(0) = \pi(0) = 0$, that is the disease is not initially present then $\beta(t) = \pi(t) = 0$ for all times $t > 0$.

Proof

Let π^* and β^* denote the respective equilibrium proportions of infected IDUs and needles. From Equations 2.1 and 2.2

$$\frac{\pi^*}{1-\pi^*} = \frac{\theta\beta^*}{1-\beta^*} = \frac{\lambda\alpha\beta^*}{\mu}. \tag{2.8}$$

From the last equality we deduce that $\beta^* = 0$ or $\beta^* = 1 - \frac{\mu\theta}{\lambda\alpha}$. So if $R_0 \leq 1$ ($\lambda\alpha \leq \mu\theta$) the only feasible solution is $\beta^* = \pi^* = 0$. If $R_0 > 1$ ($\lambda\alpha > \mu\theta$) then this solution is possible but there is a unique other solution where

$$\beta^* = 1 - \frac{\mu\theta}{\lambda\alpha}$$

and

$$\pi^* = \frac{\lambda\alpha}{\mu}\left(1 - \frac{\mu\theta}{\lambda\alpha}\right)(1-\pi^*)$$

which implies that $\pi^* = \frac{\lambda\alpha - \mu\theta}{\lambda\alpha + \mu(1-\theta)}$. Hence we have proven the statements concerning the existence and uniqueness of the equilibria in Theorem 2.1.

We can also graphically demonstrate the existance of the endemic equilibrium as follows. Equating these derivatives in Equations 2.6 and 2.7 to zero, we can obtain the isoclines

$$\beta = \frac{\pi}{\theta + (1-\theta)\pi} \tag{2.9}$$

and

$$\beta = \frac{\mu\pi}{\lambda\alpha(1-\pi)}. \tag{2.10}$$

These can be shown graphically in Figures 2.5 and 2.6. Two figures are shown,

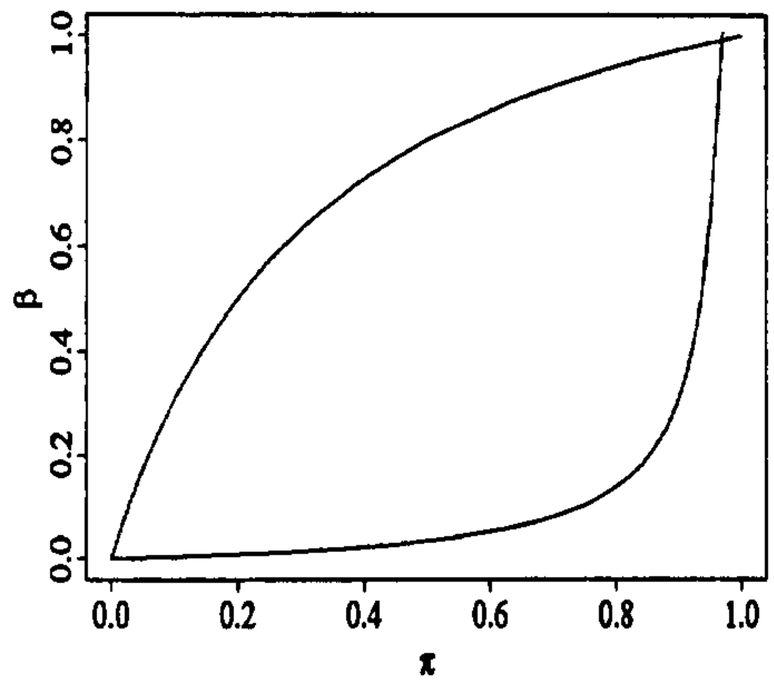

Figure 2.5: Isoclines using values from Kaplan (1989).

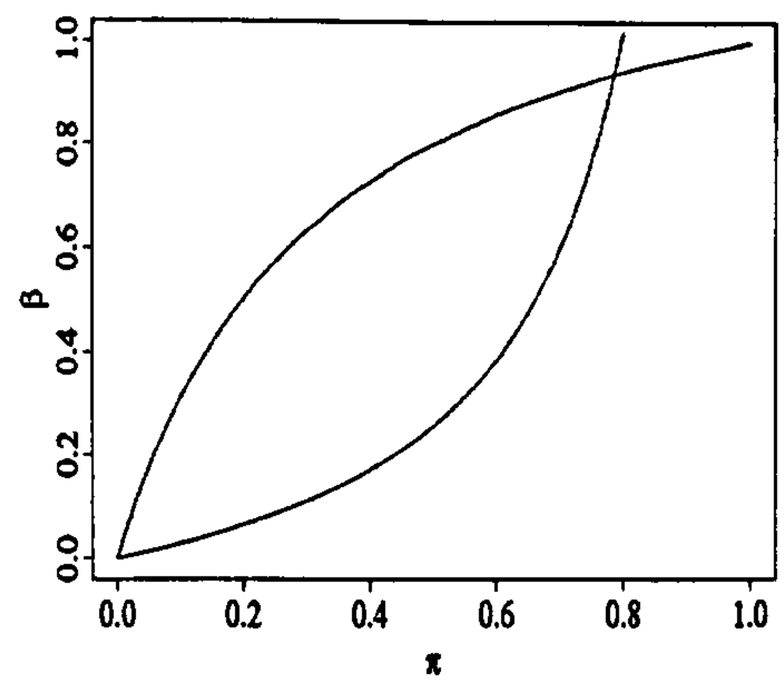

Figure 2.6: Isoclines as before with $\alpha = 0.01$.

one with the parameter values as described in Kaplan (1989), the other with a far lower value for α from which the point at which the isoclines cross may be more easily seen. These figures again illustrate that π^* decreases as α decreases.

Information about the equilibrium points can be gathered graphically from these plots. The intersection of these isoclines denotes the equilibrium point, (π^*, β^*). The position of this equilibrium point is dependent on the two isoclines, and in particular the gradient of them. These will be

$$\frac{\mathrm{d}\beta}{\mathrm{d}\pi} = \frac{\theta}{[\theta + (1-\theta)\pi]^2} \tag{2.11}$$

and

$$\frac{\mathrm{d}\beta}{\mathrm{d}\pi} = \frac{\mu}{\lambda\alpha(1-\pi)^2}, \tag{2.12}$$

which will give the initial gradients to be $\frac{1}{\theta}$, $\frac{\mu}{\lambda\alpha}$. For the isoclines to intersect we must have $\frac{1}{\theta} > \frac{\mu}{\lambda\alpha}$, or equivalently $R_0 > 1$ (using Equation 2.5).

2.2.2 Local Stability of Equilibria

We can also explore the local stability of the equilibrium value by considering whether if the proportions β, π are slightly displaced from this point (π^*, β^*), will they return to it or move away. We can write

$$\beta(t) = \beta^* + b(t) \tag{2.13}$$

and
$$\pi(t) = \pi^* + p(t), \tag{2.14}$$

where $p(t)$ and $b(t)$ are assumed to be small. Then we can re-express Equations 2.1 and 2.2 as

$$\frac{\mathrm{d}(\beta^* + b(t))}{\mathrm{d}t} = \lambda\gamma[(1 - (\beta^* + b(t)))(\pi^* + p(t)) - \theta(\beta^* + b(t))(1 - (\pi^* + p(t)))] \tag{2.15}$$

and
$$\frac{\mathrm{d}(\pi^* + p(t))}{\mathrm{d}t} = (1 - (\pi^* + p(t)))\lambda(\beta^* + b(t))\alpha - (\pi^* + p(t))\mu. \tag{2.16}$$

which working to the first order in small quantities and using the equilibrium equations will reduce to

$$\frac{\mathrm{d}p(t)}{\mathrm{d}t} = [-\lambda\alpha\beta^* - \mu]p(t) + [\lambda\alpha - \lambda\alpha\pi^*]b(t) \tag{2.17}$$

and
$$\frac{\mathrm{d}b(t)}{\mathrm{d}t} = \lambda\gamma[1 - \beta^* + \theta\beta^*]p(t) + \lambda\gamma[\theta\pi^* - \theta - \pi^*]b(t). \tag{2.18}$$

We can simplify this by rewriting the equations as

$$\frac{\mathrm{d}p(t)}{\mathrm{d}t} = k_{11}p(t) + k_{12}b(t) \tag{2.19}$$

and
$$\frac{\mathrm{d}b(t)}{\mathrm{d}t} = k_{21}p(t) + k_{22}b(t), \tag{2.20}$$

where $k_{11} = -\lambda\alpha\beta^* - \mu$, $k_{12} = \lambda\alpha - \lambda\alpha\pi^*$, $k_{21} = \lambda\gamma[1 - \beta^* + \theta\beta^*]$ and $k_{22} = \lambda\gamma[\theta\pi^* - \theta - \pi^*]$. Noting that from Equations 2.19 and 2.20

$$\frac{\mathrm{d}^2p(t)}{\mathrm{d}t^2} - (k_{11} + k_{22})\frac{\mathrm{d}p(t)}{\mathrm{d}t} + (k_{11}k_{22} - k_{12}k_{21})p = 0,$$

the solution $p(t)$ can be expressed as

$$A_1 \exp(\lambda_1 t) + A_2 \exp(\lambda_2 t) \tag{2.21}$$

for some constants A_1, A_2 which can be found from the initial conditions, where λ_1, λ_2 are the roots of the auxiliary equation

$$\lambda^2 - (k_{11} + k_{22})\lambda + (k_{11}k_{22} - k_{12}k_{21}) = 0. \tag{2.22}$$

The behavioural characteristics of this local deterministic system will be determined from the values of λ_1, λ_2. The roots will be

$$\lambda_1 = \frac{1}{2}[(k_{11} + k_{22}) + \sqrt{\{(k_{11} - k_{22})^2 + 4k_{12}k_{21}\}}] \tag{2.23}$$

$$\lambda_2 = \frac{1}{2}[(k_{11} + k_{22}) - \sqrt{\{(k_{11} - k_{22})^2 + 4k_{12}k_{21}\}}] \tag{2.24}$$

and defining

$$\Delta = (k_{11} - k_{22})^2 + 4k_{12}k_{21} \tag{2.25}$$

we can see that if $\Delta < 0$ then λ_1 and λ_2 will be complex numbers, which will give rise to exponentially damped sinusoidal solutions if $(k_{11} + k_{22}) < 0$ and exponentially increasing sinusoidal solutions if $(k_{11} + k_{22}) > 0$. If $\Delta > 0$ then both λ_1 and λ_2 will be real numbers. In that case returning to Equation 2.21 we can see that $p(t)$ will increase exponentially as t increases if either λ_1 or $\lambda_2 > 0$ and decrease if both are negative.

Returning to our example and substituting our parameters for k_{11}, k_{12}, k_{21} and k_{22} , we can see that

$$\Delta = ([-\lambda\alpha\beta^* - \mu] - \lambda\gamma[\theta\pi^* - \theta - \pi^*])^2 + 4\lambda\gamma[\lambda\alpha - \lambda\alpha\pi^*][1 - \beta^* + \theta\beta^*] \tag{2.26}$$

will always be non-negative as λ, γ, α and θ are defined to be non-negative and each of the quantities π^* and β^* lie between zero and one.

To examine $p(t)$, reformulating the equation for the roots gives

$$\lambda_1 = \frac{1}{2}\Big[([-\lambda\alpha\beta^* - \mu] + \lambda\gamma[\theta\pi^* - \theta - \pi^*]) + \sqrt{\Delta}\Big] \tag{2.27}$$

and

$$\lambda_2 = \frac{1}{2}\Big[([-\lambda\alpha\beta^* - \mu] + \lambda\gamma[\theta\pi^* - \theta - \pi^*]) - \sqrt{\Delta}\Big]. \tag{2.28}$$

λ_1, λ_2 can be shown to be both negative as follows.

λ_2 will be negative as $k_{11} + k_{22} < 0$ as both k_{11} and k_{22} are negative. λ_1 will be negative if $\sqrt{((k_{11} + k_{22})^2 + 4(k_{12}k_{21} - k_{11}k_{22}))} < k_{11} + k_{22}$. However this is true as

$$k_{12}k_{21} - k_{11}k_{22} = [\lambda\alpha - \lambda\alpha\pi^*]\lambda\gamma[1 - \beta^* + \theta\beta^*] \tag{2.29}$$

$$+ [\lambda\alpha\beta^* + \mu]\lambda\gamma[\theta\pi^* - \theta - \pi^*],$$

$$= \lambda\gamma\Big[[\lambda\alpha - \lambda\alpha\pi^*][1 - \beta^* + \theta\beta^*] + [\lambda\alpha\beta^* + \mu][\theta\pi^* - \theta - \pi^*]\Big].$$

From the equilibrium versions of Equations 2.1 and 2.2,

$$\lambda\alpha(1 - \pi^*) = \frac{\mu\pi^*}{\beta^*} \quad \text{and} \quad \theta\pi^* - \theta - \pi^* = -\frac{\pi^*}{\beta^*}$$

so $$[\lambda\alpha - \lambda\alpha\pi^*][1 - \beta^* + \theta\beta^*] + [\lambda\alpha\beta^* + \mu][\theta\pi^* - \theta - \pi^*] \tag{2.30}$$

$$= \frac{\mu\pi^*}{\beta^*}[1 - \beta^* + \theta\beta^*] - [\lambda\alpha\beta^* + \mu]\frac{\pi^*}{\beta^*},$$

$$= \frac{\mu\pi^*}{\beta^*} - \mu\pi^* + \mu\pi^*\theta - \lambda\alpha\pi^* - \frac{\mu\pi^*}{\beta^*},$$

$$= \mu\pi^*(\theta - 1) - \lambda\alpha\pi^* < 0.$$

Hence λ_1 is also negative. Hence $p(t)$ will decrease exponentially, which tells us that the endemic equilibrium point is locally stable to small perturbations whenever it exists. We could similarly perform a local stability analysis of the equilibrium where the proportion of infected needle and the proportion of infected IDUs are zero $\beta^* = \pi^* = 0$. This equilibrium is locally stable if $R_0 < 1$ and locally unstable if $R_0 > 1$. However in the next section we shall show that these results are global stability results.

2.2.3 Global Stability of Equilibria

Having proved the existance and uniqueness of the endemic equilibria and proved that thes equilibria is locally stable, we shall now prove the global stability results.

Theorem 2.1

(a) From Lemma 2.1 we have shown that if $R_0 \leq 1$ the equilibrium where the disease dies out is the only equilibrium. This equilibrium is globally stable. Whatever the initial proportions of infected IDUs and infected needles the disease will

die out and both $\beta(t)$ and $\pi(t)$ will tend to zero.

(b) If $R_0 > 1$ then there are two possible equilibria, one where the disease has died out and a unique endemic equilibrium. The equilibrium where the disease has died out is locally unstable. The endemic equilibrium where the disease is present is globally stable. Whatever the initial proportions of infected needles and infected IDUs, provided $\beta(0) > 0$ or $\pi(0) > 0$ so disease is present $\beta(t) \to \beta^*$ and $\pi(t) \to \pi^*$ as $t \to \infty$. If $\beta(0) = \pi(0) = 0$, such that no disease is present initially then $\beta(t) = \pi(t) = 0$ for all times $t > 0$.

Proof

Suppose first that $R_0 < 1$. We shall show that $\pi \to 0$, $\beta \to 0$ as $t \to \infty$.

Let $u = \beta + k\pi$ for $k \geq 0$. Then

$$\frac{\mathrm{d}\beta}{\mathrm{d}t} = \lambda\gamma[\pi - \theta\beta - \beta\pi(1-\theta)] \leq \lambda\gamma\pi - \lambda\gamma\theta\beta \tag{2.31}$$

and

$$\frac{\mathrm{d}\pi}{\mathrm{d}t} = \lambda\alpha\beta - \mu\pi - \lambda\alpha\beta\pi \leq \lambda\alpha\beta - \mu\pi. \tag{2.32}$$

Hence

$$\frac{\mathrm{d}u}{\mathrm{d}t} \leq (\lambda\gamma - k\mu)\pi + \beta(\lambda\alpha k - \lambda\gamma\theta) < 0, \tag{2.33}$$

if $\frac{\gamma\theta}{\alpha} > k > \frac{\lambda\gamma}{\mu}$. As $R_0 < 1$ we can choose such a k. Then $\frac{\mathrm{d}u}{\mathrm{d}t} \leq -\epsilon u$ for some $\epsilon > 0$ as both terms in Equation 2.33 are negative. Hence $0 \leq u \leq u_0 e^{-\epsilon t}$. Therefore $u \to 0$ as $t \to \infty$. We deduce that $\pi \to 0$ and $\beta \to 0$ as $t \to \infty$.

This proof breaks down if $R_0 = 1$ and this case will be discussed later. We shall now prove the assertions about stability in Theorem 2.1 in the situation where $R_0 > 1$ namely:

a) $\pi(0) = 0, \beta(0) = 0$ implies that $\pi(t) = 0, \beta(t) = 0,$ for all $t,$

and

b) $\pi(0) > 0$ or $\beta(0) > 0$ implies that $\pi(t) \to \pi^*, \beta(t) \to \beta^*$ as $t \to \infty$.

The proof of a) is trivial but b) is more difficult. Write $\tilde{\beta} = \beta - \beta^*$, $\tilde{\pi} = \pi - \pi^*$.

Then

$$\frac{\mathrm{d}\tilde{\beta}}{\mathrm{d}t} = -\lambda\gamma\theta\tilde{\beta} - \lambda\gamma\tilde{\beta}\pi(1-\theta) + \lambda\gamma\tilde{\pi} - \lambda\gamma\beta^*\tilde{\pi}(1-\theta) \tag{2.35}$$

and

$$\frac{\mathrm{d}\tilde{\pi}}{\mathrm{d}t} = \lambda\alpha\tilde{\beta} - \mu\tilde{\pi} - \lambda\alpha(\tilde{\beta}\pi^* + \beta\tilde{\pi}). \tag{2.36}$$

If $x = \begin{pmatrix} \tilde{\beta} \\ \tilde{\pi} \end{pmatrix}$, we can express these equations as

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \mathbf{V}_x x,$$

where

$$\mathbf{V}_x = \begin{pmatrix} -\lambda\gamma[\theta + (1-\theta)\pi] & \lambda\gamma[1-(1-\theta)\beta^*] \\ \lambda\alpha(1-\pi^*) & -[\mu + \lambda\alpha\beta] \end{pmatrix}. \tag{2.37}$$

Define

$$\mathbf{V}_0 = \begin{pmatrix} -\lambda\gamma\theta & \lambda\gamma[1-(1-\theta)\beta^*] \\ \lambda\alpha(1-\pi^*) & -\mu \end{pmatrix}. \tag{2.38}$$

We assert that there exists a matrix

$$\mathbf{W} = \begin{pmatrix} w_1 & 0 \\ 0 & w_2 \end{pmatrix} \quad \text{with} \quad w_1, w_2 > 0$$

such that $\mathbf{W}\mathbf{V}_0 + \mathbf{V}_0^T\mathbf{W}$ is negative semidefinite. In other words for all $y = (y_1, y_2)$, $y^T(\mathbf{W}\mathbf{V}_0 + \mathbf{V}_0^T\mathbf{W})y \leq 0$. We can write $\mathbf{V}_0 = \begin{pmatrix} -A & B \\ C & -D \end{pmatrix}$.

Then

$$AD - BC = \lambda\gamma\theta\mu - \lambda^2\alpha\gamma(1-\pi^*)[1-(1-\theta)\beta^*] \tag{2.39}$$

$$= \lambda\gamma\theta\mu - \lambda\gamma\mu\frac{\pi^*}{\beta^*}[1-(1-\theta)\beta^*]$$

using $\lambda\alpha(1-\pi^*) = \dfrac{\pi^*}{\beta^*}$ from the equilibrium equations

$$= \lambda\gamma\left[\mu\theta - \mu\frac{\pi^*}{\beta^*} + \mu(1-\theta)\pi^*\right]$$

$$= \frac{\lambda\gamma\mu}{\beta^*}[-\pi^* + \theta\beta^* + \beta^*\pi^*(1-\theta)]$$

$$= 0, \qquad \text{again using the equilibrium equations.}$$

Now

$$\mathbf{W}\mathbf{V}_0 + \mathbf{V}_0^T\mathbf{W} = \begin{pmatrix} -Aw_1 & Bw_1 \\ Cw_2 & -Dw_2 \end{pmatrix} + \begin{pmatrix} -Aw_1 & Cw_2 \\ Bw_1 & -Dw_2 \end{pmatrix}, \tag{2.40}$$

or

$$y^T(\mathbf{W}\mathbf{V}_0 + \mathbf{V}_0^T\mathbf{W})y = -2Aw_1y_1^2 + 2(Bw_1 + Cw_2)y_1y_2 - 2Dw_2y_2^2. \tag{2.41}$$

For this quadratic form in y_1 and y_2 to be negative semi-definite we need

$4ADw_1w_2 \geq (Bw_1 + Cw_2)^2$ or equivalently $0 \geq (Bw_1 - Cw_2)^2$. Hence we choose $w_1 = C, w_2 = B$, both positive. Then

$$y^T(\mathbf{W}\mathbf{V}_0 + \mathbf{V}_0^T\mathbf{W})y = -2(\sqrt{AC}y_1 - \sqrt{BD}y_2)^2 \leq 0. \tag{2.42}$$

$\mathbf{W}\mathbf{V}_0$ is symmetric (hence has real eigenvalues). Define

$$h = x^T\mathbf{W}x = w_1x_1^2 + w_2x_2^2. \tag{2.43}$$

Write $\dot{x}_1 = \dfrac{\mathrm{d}x_1}{\mathrm{d}t}$, $\dot{x}_2 = \dfrac{\mathrm{d}x_2}{\mathrm{d}t}$ and $\dot{x} = \dfrac{\mathrm{d}x}{\mathrm{d}t}$

$$\text{then} \qquad \frac{\mathrm{d}h}{\mathrm{d}t} = 2w_1x_1\dot{x}_1 + 2w_2x_2\dot{x}_2, \tag{2.44}$$

$$= (x_1, x_2)\begin{pmatrix} w_1 & \cdot \\ \cdot & w_2 \end{pmatrix}\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \end{pmatrix} + (\dot{x}_1, \dot{x}_2)\begin{pmatrix} w_1 & \cdot \\ \cdot & w_2 \end{pmatrix}\begin{pmatrix} x_1 \\ x_2 \end{pmatrix}$$

$$= x^T\mathbf{W}\dot{x} + \dot{x}^T\mathbf{W}x.$$

But $\dot{x} = \mathbf{V}x$. Hence

$$\frac{\mathrm{d}h}{\mathrm{d}t} = x^T\mathbf{W}\mathbf{V}x + x^T\mathbf{V}^T\mathbf{W}x, \tag{2.45}$$

$$= x^T(\mathbf{W}\mathbf{V} + \mathbf{V}^T\mathbf{W})x.$$

$$\text{If} \qquad \mathbf{V} = \begin{pmatrix} v_{11} & v_{12} \\ v_{21} & v_{22} \end{pmatrix}, \tag{2.46}$$

$$\mathbf{W}\mathbf{V} = \begin{pmatrix} v_{11}w_1 & v_{12}w_1 \\ v_{21}w_2 & v_{22}w_2 \end{pmatrix} \tag{2.47}$$

$$\text{and} \qquad \mathbf{W}\mathbf{V} + \mathbf{V}^T\mathbf{W} = \begin{pmatrix} 2v_{11}w_1 & v_{12}w_1 + v_{21}w_2 \\ v_{12}w_1 + v_{21}w_2 & 2v_{22}w_2 \end{pmatrix}. \tag{2.48}$$

$$\text{Writing } \mathbf{V}_0 = \begin{pmatrix} v_{11}^0 & v_{12}^0 \\ v_{21}^0 & v_{22}^0 \end{pmatrix}, \tag{2.49}$$

we note that $v_{11} \leq v_{11}^0$, $v_{22} \leq v_{22}^0$, $v_{12} = v_{12}^0$ and $v_{21} = v_{21}^0$. Hence

$$x^T(\mathbf{W}\mathbf{V} + \mathbf{V}^T\mathbf{W})x = 2v_{11}w_1x_1^2 + 2(v_{12}w_1 + v_{21}w_2)x_1x_2 + 2v_{22}w_2x_2^2, \tag{2.50}$$

$$\leq 2v_{11}^0w_1x_1^2 + 2(v_{12}^0w_1 + v_{21}w_2)x_1x_2 + 2v_{22}^0w_2x_2^2$$

$$= x^T(\mathbf{W}\mathbf{V}_0 + \mathbf{V}_0^T\mathbf{W})x.$$

Note that

$$\frac{dh}{dt} = x^T(\mathbf{WV} + \mathbf{V}^T\mathbf{W})x, \tag{2.51}$$

$$\leq x^T(\mathbf{WV}_0 + \mathbf{V}_0^T\mathbf{W})x,$$

$$\leq 0. \qquad \text{using Equation 2.42}$$

Therefore $h = x^T\mathbf{W}x$ is monotone decreasing over time.

If k is a constant the curves $h = k = w_1x_1^2 + w_2x_2^2$ are ellipses centre (β^*, π^*) and axes proportional to w_1, w_2. We assert that there exists $\epsilon > 0$ such that motion never enters $|\beta^2 + \pi^2| < \epsilon^2$. Write $\beta_0 = \beta(0)$ and $\pi_0 = \pi(0)$.

a) If we start with $0 \leq \beta_0 \leq \beta^*, 0 \leq \pi_0 \leq \pi^*$ then the trajectory stays in the ellipse passing through (β_0, π_0), centre (β^*, π^*) for $h \leq w_1(\beta_0 - \beta^*)^2 + w_2(\pi_0 - \pi^*)^2 < w_1\beta^{*2} + w_2\pi^{*2}$, with strict inequality as either $\beta_0 > 0$ or $\pi_0 > 0$.

By continuity of h in a small circle centre the origin

$$h > w_1(\beta^* - \beta_0)^2 + w_2(\pi^* - \pi_0)^2 \tag{2.52}$$

and the result follows.

b) If we start with $\beta_0 > \beta^*$ or $\pi_0 > \pi^*$. Draw a circle centre the origin radius $\min((\beta^*/2), (\pi^*/2))$. If the trajectory never enters this circle the result follows. If the trajectory enters this circle it must cross the boundary of the circle for the first time at (β_1, π_1) say where $0 \leq \beta_1 \leq \beta^*$ and $0 \leq \pi_1 \leq \pi^*$. Either $\beta_1 > 0$ or $\pi_1 > 0$. Hence the trajectory will stay in the ellipse passing through (β_1, π_1), centre (β^*, π^*). This result follows by arguing as previously.

Hence there is an $\epsilon > 0$ such that $|\beta^2 + \pi^2| \geq \epsilon$ for all t. By choosing $\epsilon_1 = \frac{\epsilon}{\sqrt{2}}$ we deduce that there exists $\epsilon_1 > 0$ such that $\beta \geq \epsilon_1$ or $\pi \geq \epsilon_1$ for all t.

Now
$$\frac{dh}{dt} = \frac{1}{2}(x^T(\mathbf{WV} + \mathbf{V}^T\mathbf{W})x) \tag{2.53}$$

$$= -\lambda\gamma(\theta + (1-\theta)\pi)x_1^2w_1$$

$$+ [\lambda\gamma(1-(1-\theta)\beta^*)w_1 + \lambda\alpha(1-\pi^*)w_2]x_1x_2 - (\mu+\lambda\alpha\beta)x_2^2w_2$$

$$= (x^T(\mathbf{W}\mathbf{V}_0 + \mathbf{V}_0^T\mathbf{W})x) - \lambda\gamma(1-\theta)\pi x_1^2w_1 - \lambda\alpha\beta x_2^2w_2$$

$$\leq -\lambda\gamma(1-\theta)\pi x_1^2w_1 - \lambda\alpha\beta x_2^2w_2. \qquad \text{using Equation 2.42}$$

Now for all (π, β) either $\pi \geq \epsilon_1$ or $\beta \geq \epsilon_1$.

a) If $\pi \geq \epsilon_1$ then either (i) $\beta \geq \epsilon_1$ or (ii) $x_1 = \tilde{\beta} < -(\beta^* - \epsilon_1)$.

Without loss of generality $\epsilon_1 < \frac{1}{2}\beta^*$.

(i) If $\pi \geq \epsilon_1$ and $\beta \geq \epsilon_1$ then

$$\frac{\mathrm{d}h}{\mathrm{d}t} \leq -\phi h, \quad \text{where} \quad \phi = \epsilon_1 \min\{\lambda\gamma(1-\theta), \lambda\alpha\beta\} > 0. \tag{2.54}$$

(ii) If $\pi \geq \epsilon_1$ and $x_1 < -(\beta^* - \epsilon_1) < -\frac{1}{2}\beta^*$ then (2.55)

$$\frac{\mathrm{d}h}{\mathrm{d}t} \leq -w_1\lambda\gamma(1-\theta)\epsilon_1\frac{\beta^{*2}}{4} = -\phi_1, \quad \text{where} \quad \phi_1 > 0. \tag{2.56}$$

b) Similarly if $\beta \geq \epsilon_1$ either $\frac{\mathrm{d}h}{\mathrm{d}t} \leq -\phi h$ or $\frac{\mathrm{d}h}{\mathrm{d}t} \leq -\phi_2$, where $\phi_2 > 0$.

As h is monotone decreasing $0 \leq h \leq h(0)$ for all t therefore $\frac{\mathrm{d}h}{\mathrm{d}t} \leq -\phi h$ or

$$\frac{\mathrm{d}h}{\mathrm{d}t} \leq -\min(\phi_1, \phi_2)\frac{h}{h(0)}. \tag{2.57}$$

So
$$\frac{\mathrm{d}h}{\mathrm{d}t} \leq -\psi h \text{ where } \psi = \min\left\{\phi, \frac{\phi_1}{h(0)}, \frac{\phi_2}{h(0)}\right\} > 0. \tag{2.58}$$

Integrating we deduce that $0 \leq h \leq h(0)e^{-\psi t}$ which implies that $h \to 0$ as $t \to \infty$. Therefore $\pi \to \pi^*$, $\beta \to \beta^*$ as $t \to \infty$.

We can modify this proof to show that the disease free equilibrium is globally stable when $R_0 = 1$. As before

$$h = w_1\beta^2 + w_2\pi^2$$

as β^* and π^* are both zero, and h is still monotone decreasing in t. We now have that (β, π) is a two-dimensional flow in the compact set

$$D = \{(\beta, \pi) : \beta \geq 0, \pi \geq 0, h \leq w_1\beta_0^2 + w_2\pi_0^2\}.$$

We also have the following Lemma.

Lemma 2.2

The system has no closed orbits inside the region D.

Proof

As h is monotone decreasing it must be constant on a closed orbit. But in D the curves where h are constant are incomplete arcs of ellipses and therefore D cannot contain any closed orbits. Thus we have proved Lemma 2.2.

Therefore by using the Poincaré-Bendixson Theorem (Jordan and Smith, 1977) all solutions starting in D tend to the unique disease free equilibrium.

This completes the proof of Theorem 2.1. We have therefore shown that the two possible equilibrium values exist and we have established that the first equilibrium is globally stable when $R_0 \leq 1$ and that when $R_0 > 1$ and $\beta_0 > 0$ or $\pi_0 > 0$ then $\beta(t) \to \beta^*$ and $\pi(t) \to \pi^*$ as $t \to \infty$ where (β^*, π^*) is the unique endemic equilibrium.

2.2.4 Stochastic Variation around the Deterministic Trajectory

The above analysis has been purely deterministic. We are also interested in whether or not a stochastic trajectory will hit the axes. In our example this will not automatically result in an equilibrium as in a predator-prey system (Renshaw, 1991), but it will still be of interest. If the equilibrium point is far enough from the axes relative to the likely variation in stochastic values then the trajectory should avoid them. To explore this we can evaluate the variances associated with the trajectories.

We first have to convert Equations 2.1 and 2.2 into differential equations for

the absolute numbers of infected IDUs and needles. These will be

$$\frac{\mathrm{d}i(t)}{\mathrm{d}t} = \lambda I(t)\left(1 - \frac{i(t)}{n}\right) - \frac{\lambda\theta}{n} i(t)(N - I(t)) \tag{2.59}$$

and

$$\frac{\mathrm{d}I(t)}{\mathrm{d}t} = \frac{\lambda\alpha}{n} i(t)(N - I(t)) - \mu I(t). \tag{2.60}$$

where $i(t)$ is the absolute number of infected needles at time t and $I(t)$ is the absolute number of infected IDUs at time t. The IDU population will be of constant size N and the number of needles will be n, also a constant. We denote the endemic equilibrium values for IDUs and needles as I^* and i^* respectively. For $R_0 > 1$ these are given by

$$i^* = n\frac{\lambda\alpha - \mu\theta}{\lambda\alpha} \tag{2.61}$$

and

$$I^* = N\frac{\lambda\alpha - \mu\theta}{\lambda\alpha + \mu(1-\theta)}. \tag{2.62}$$

Let δt denote a small time increment, Equations 2.59 and 2.60 can be rewritten as

$$i(t+\delta t) - i(t) \simeq \left[\lambda I(t)\left(1 - \frac{i(t)}{n}\right) - \frac{\lambda\theta}{n} i(t)(N - I(t))\right]\delta t \tag{2.63}$$

and

$$I(t+\delta t) - I(t) \simeq \left[\frac{\lambda\alpha}{n} i(t)(N - I(t)) - \mu I(t)\right]\delta t. \tag{2.64}$$

We can convert these into stochastic equations in a similar manner to that of Renshaw (1991, p 182) by adding on noise components δZ_1 and δZ_2 to produce

$$i(t+\delta t) - i(t) \simeq \left[\lambda I(t)\left(1 - \frac{i(t)}{n}\right) - \frac{\lambda\theta}{n} i(t)(N - I(t))\right]\delta t + \delta Z_1(t) \tag{2.65}$$

and

$$I(t+\delta t) - I(t) \simeq \left[\frac{\lambda\alpha}{n} i(t)(N - I(t)) - \mu I(t)\right]\delta t + \delta Z_2(t). \tag{2.66}$$

Here $\delta Z_1(t)$ and $\delta Z_2(t)$ are independent of $\delta Z_1(s)$ and $\delta Z_2(s)$ for all times $s \neq t$. We can express $i(t), I(t)$ as

$$i(t) = i^*[1 + u_1(t)] \tag{2.67}$$

and

$$I(t) = I^*[1 + u_2(t)]. \tag{2.68}$$

This gives us

$$i^*[u_1(t+\delta t)-u_1(t)] = \Big[\lambda I^*[1+u_2(t)]\Big(1-\frac{i^*[1+u_1(t)]}{n}\Big) - \frac{\lambda\theta}{n} i^*[1+u_1(t)](N-I^*[1+u_2(t)])\Big]\delta t + \delta Z_1(t) \tag{2.69}$$

and
$$I^*[u_2(t+\delta t)-u_2(t)] = \Big[\frac{\lambda\alpha}{n} i^*[1+u_1(t)](N-I^*[1+u_2(t)]) - \mu I^*[1+u_2(t)]\Big]\delta t + \delta Z_2(t). \tag{2.70}$$

on using
$$\lambda I^*\Big(1-\frac{i^*}{n}\Big) - \frac{\lambda\theta}{n} i^*(N-I^*) = 0 \tag{2.71}$$

and
$$\frac{\lambda\alpha}{n} i^*(N-I^*) - \mu I^* = 0, \tag{2.72}$$

and neglecting terms such as u_1^2, u_2^2 and u_1u_2 gives

$$u_1(t+\delta t) = u_1(t) + \Big[\frac{\lambda I^*}{n}\Big(\frac{u_2(t)n}{i^*} - (u_1(t)+u_2(t))\Big) - \frac{\lambda\theta}{n}\Big(u_1(t)N - (u_1(t)+u_2(t))I^*\Big)\Big]\delta t + \frac{\delta Z_1(t)}{i^*} \tag{2.73}$$

and
$$u_2(t+\delta t) = u_2(t) + \Big[\frac{\lambda\alpha}{n} i^*\Big(\frac{u_1(t)N}{I^*} - (u_1(t)+u_2(t))\Big) - \mu u_2(t)\Big]\delta t + \frac{\delta Z_2(t)}{I^*}. \tag{2.74}$$

By considering possible events in the small time interval $(t, t+\delta t)$ and for $i(t)$, $I(t)$ near i^*, I^* we have

$$\Pr\{\delta Z_1 = +1\} \simeq \lambda I^*\delta t, \tag{2.75}$$

$$\Pr\{\delta Z_1 = -1\} \simeq \frac{\lambda\theta}{n} i^*(N-I^*)\delta t,$$

$$\Pr\{\delta Z_2 = +1\} \simeq \frac{\lambda\alpha}{n} i^*(N-I^*)\delta t,$$

and
$$\Pr\{\delta Z_2 = -1\} \simeq \mu I^*\delta t.$$

For example the event $\{\delta Z_2 = +1\}$ corresponds to one additional IDU becoming infected. There are $N-I^*$ susceptible IDUs, each of whom visits shooting galleries with probability approximately $\lambda\delta t$ in the small time interval $[t, t+\delta t]$ and chooses

an infected needle and is infected with probability $\frac{\alpha i}{n}$. Hence

$$\begin{aligned} \mathrm{E}(\delta Z_2) &= (+1)\Pr\{\delta Z_2 = +1\} + (-1)\Pr\{\delta Z_2 = -1\} \qquad (2.76) \\ &\simeq \left[\frac{\lambda\alpha}{n} i^*(N - I^*) - \mu I^*\right]\delta t \\ &= 0. \end{aligned}$$

Similarly $\mathrm{E}(Z_1) = 0$. Also

$$\begin{aligned} \mathrm{Var}(\delta Z_1) &\simeq (+1)^2\Pr\{\delta Z_1 = +1\} + (-1)^2\Pr\{\delta Z_1 = -1\}, \qquad (2.77) \\ &\simeq \lambda I^*\left(1 - \frac{i^*}{n}\right) + \frac{\lambda\theta}{n} i^*(N - I^*)\delta t, \\ &\simeq \left\{2\frac{\lambda\theta}{n} i^*(N - I^*)\right\}\delta t, \end{aligned}$$

and

$$\begin{aligned} \mathrm{Var}(\delta Z_2) &\simeq (+1)^2\Pr\{\delta Z_2 = +1\} + (-1)^2\Pr\{\delta Z_2 = -1\}, \qquad (2.78) \\ &\simeq \left\{\frac{\lambda\alpha}{n} i^*(N - I^*) + \mu I^*\right\}\delta t \\ &\simeq (2\mu I^*)\delta t, \end{aligned}$$

while arguing similarly $\mathrm{Cov}(\delta Z_1, \delta Z_2) \simeq \mathrm{E}(\delta Z_1 \delta Z_2)$ is of order δt^2 and can be ignored.

We can square and cross multiply Equations 2.73 and 2.74 to find σ_1^2, the variance of $u_1(t)$, σ_2^2, the variance of $u_2(t)$ and σ_{12}, the covariance of $u_1(t)$ and $u_2(t)$. We assume that σ_1^2 is constant in time, as is σ_2^2 and the covariance σ_{12} as the system in essentially in an equilibrium situation. Working only to the first order in δt

$$\begin{aligned} \sigma_1^2 &= \sigma_1^2 + \mathrm{Var}(\delta Z_1(t)/i^*) + 2\left[\frac{\lambda I^*}{n}\left(\sigma_{12}\frac{n}{i^*} - (\sigma_{12} + \sigma_1^2)\right)\right. \qquad (2.79) \\ &\quad \left. - \frac{\lambda\theta}{n}\left(\sigma_1^2 N - (\sigma_{12} + \sigma_1^2) I^*\right)\right]\delta t + o(\delta t), \\ \sigma_2^2 &= \sigma_2^2 + \mathrm{Var}(\delta Z_2(t)/I^*) + 2\left[\frac{\lambda\alpha i^*}{n}\left(\sigma_{12}\frac{N}{I^*} - (\sigma_2^2 + \sigma_{12})\right) - \mu\sigma_2^2\right]\delta t + o(\delta t), \end{aligned}$$

(2.80)

and
$$\sigma_{12} = \sigma_{12} + \left[\frac{\lambda I^*}{n}\left(\sigma_2^2\frac{n}{i^*} - (\sigma_2^2+\sigma_{12})\right)\right. \tag{2.81}$$
$$-\frac{\lambda\theta}{n}\sigma_{12}N - (\sigma_2^2+\sigma_{12})I^*$$
$$\left.+\frac{\lambda\alpha i^*}{n}\left(\sigma_1^2\frac{N}{I^*} - (\sigma_{12}+\sigma_1^2)\right) - \mu\sigma_{12}\right]\delta t + o(\delta t),$$

$$\sigma_1^2 = \sigma_1^2 + \frac{2\lambda\theta}{i^*n}(N-I^*)\delta t + 2\left[\frac{\lambda I^*}{n}\left(\sigma_{12}\frac{n}{i^*} - (\sigma_{12}+\sigma_1^2)\right)\right. \tag{2 .82}$$
$$\left.-\frac{\lambda\theta}{n}\left(\sigma_1^2 N - (\sigma_{12}+\sigma_1^2)I^*\right)\right]\delta t + o(\delta t),$$
$$\sigma_2^2 = \sigma_2^2 + \frac{2\mu}{I^*}\delta t + 2\left[\frac{\lambda\alpha i^*}{n}\left(\sigma_{12}\frac{N}{I^*} - (\sigma_2^2+\sigma_{12})\right) - \mu\sigma_2^2\right]\delta t + o(\delta t), \tag{2.83}$$
and
$$\sigma_{12} = \sigma_{12} + \left[\frac{\lambda I^*}{n}\left(\sigma_2^2\frac{n}{i^*} - (\sigma_2^2+\sigma_{12})\right) - \frac{\lambda\theta}{n}\left(\sigma_{12}N - (\sigma_2^2+\sigma_{12})I^*\right)\right. \tag{2.84}$$
$$\left.+\frac{\lambda\alpha i^*}{n}\left(\sigma_1^2\frac{N}{I^*} - (\sigma_{12}+\sigma_1^2)\right) - \mu\sigma_{12}\right]\delta t + o(\delta t).$$

Subtracting off the constant terms, dividing by δt and letting δt tend to zero we deduce that

$$0 = \frac{\lambda\theta}{i^*n}(N-I^*) + \left[\frac{\lambda I^*}{n}\left(\sigma_{12}\frac{n}{i^*} - (\sigma_{12}+\sigma_1^2)\right)\right. \tag{2.85}$$
$$\left.-\frac{\lambda\theta}{n}\left(\sigma_1^2 N - (\sigma_{12}+\sigma_1^2)I^*\right)\right],$$
$$0 = \frac{\mu}{I^*} + \left[\frac{\lambda\alpha i^*}{n}\left(\sigma_{12}\frac{N}{I^*} - (\sigma_2^2+\sigma_{12})\right) - \mu\sigma_2^2\right] \tag{2.86}$$
and
$$0 = \left[\frac{\lambda I^*}{n}\left(\sigma_2^2\frac{n}{i^*} - (\sigma_2^2+\sigma_{12})\right) - \frac{\lambda\theta}{n}\left(\sigma_{12}N - (\sigma_2^2+\sigma_{12})I^*\right)\right. \tag{2.87}$$
$$\left.+\frac{\lambda\alpha i^*}{n}\left(\sigma_1^2\frac{N}{I^*} - (\sigma_{12}+\sigma_1^2)\right) - \mu\sigma_{12}\right].$$

These equations can be solved by standard methods to give expressions for the variances σ_1^2, σ_2^2 and the covariance σ_{12}. From this, using Equations 2.67 and 2.68 we have $\mathrm{Var}(i) = (i^*)^2\sigma_1^2$, $\mathrm{Var}(I) = (I^*)^2\sigma_2^2$ and $\mathrm{Cov}(i,I) = i^*I^*\sigma_{12}$.

Using the mathematical manipulation language Maple, Equations 2.85, 2.86 and 2.87 can be solved although the resulting terms for the variances are alge-

α	i^*	I^*	$\mathbf{Var}(i)$	$\mathbf{Var}(I)$	$\mathbf{Cov}(i, I)$
0.010	939.9	7,964.3	58.5	1,725.0	60.1
0.020	970.0	8,898.0	30.0	1,010.9	30.0
0.030	980.0	9,244.5	20.2	712.7	20.0
0.040	985.0	9,425.3	15.2	550.0	15.0
0.050	988.0	9,536.3	12.2	447.6	12.0
0.060	990.0	9,611.2	10.2	377.4	10.0
0.070	991.4	9,665.4	8.7	326.2	8.5
0.075	992.0	9,687.2	8.2	305.5	8.0
0.080	992.5	9,706.3	7.6	287.2	7.5
0.090	993.3	9,738.3	6.8	256.6	6.6
0.100	994.0	9,764.0	6.1	231.8	6.0

Table 2.1: The effect that varying α, and hence i^* and I^* has on the variances $\mathrm{Var}(i)$, $\mathrm{Var}(I)$ and $\mathrm{Cov}(i, I)$.

braically challenging. It is therefore easier to give values to the parameters λ, α, μ, θ, N and n and explore the effect that these values have on the variances. The variances are tabulated for different values of α and hence i^* and I^* in Table 2.1. The other parameters used are as previously described, in particular N, the number of drug injectors in the population is taken to be 10,000 and n, the number of needles is taken to be 1,000.

This table can only partly describe the complex relationships between the parameter values α, θ, λ and μ, the population sizes N and n, the equilibrium values I^* and i^* and the related variances and covariance. We can however see that I^* increases as α increases. We also have a measure of the random fluctuation around the equilibrium values, given by $\mathrm{Var}(I)$ and $\mathrm{Var}(i)$. We also can see that, for this choice of parameter values as I^* increases, $\mathrm{Var}(I)$ decreases. Thus for lower equilibrium values, there is a greater associated variance and thus there will be a greater chance that the disease will die out. It does seem unlikely that the disease will die out in the drug using population, given the large value of i^* and the small value of the associated variance which show that for these parameter values, virtually all of the needles are infected under equilibrium. This can be

further demonstrated by calculating the coefficient of variation, namely

$$CV(I) = \sqrt{\{\mathrm{Var}(I)\}/I^*}.$$

When $\alpha = 0.075$, as originally suggested by Kaplan, $CV(I) = 0.18$. As this is substantially smaller than 1 then it is unlikely that random movement away from the endemic equilibrium will result in the disease dying out.

2.3 Summary

In this chapter we have introduced a model due to Kaplan (1989) which describes the spread of HIV between IDUs who visit shooting galleries. We have derived an expression for the basic reproductive ratio R_0. R_0 can be thought of as the expected number of secondary infections that will occur when a single infected IDU is introduced into a large population consisting entirely of susceptibles, with syringes uninfected. Similarly R_0 has an interpretation as the expected number of secondary infected syringes caused by introducing a single infected syringe into a similar population. In order to control the disease strategies which lower R_0 can be explored.

We have also shown that there are two possible equilibrium values, one where there are no infected IDUs and no infected needles and a second endemic equilibrium where there are infected IDUs and infected needles. The first equilibrium is always possible, the second is possible if and only if $R_0 > 1$ when it is unique. For $R_0 \leq 1$ the first equilibrium is globally stable. Whatever the initial numbers of infected addicts and infected needles the number of infected addicts and infected needles both tend to zero at large times. For $R_0 > 1$ when the disease is introduced into the population, so $\beta_0 > 0$ or $\pi_0 > 0$ then the numbers of infected syringes and infected addicts tend to their unique endemic equilibrium values.

We have also looked at the introduction of random effects into the analysis of

this model. These effects can be thought of as random fluctuations about the deterministic trajectories. We have derived equations satisfied by the variance and co-variance of these fluctuations about the equilibrium values and numerically evaluated these variances and co-variances. It is important to explore stochastic effects as deterministic models may not be adequate to accurately describe the spread of the disease. In the next chapter we shall go on to develop stochastic simulations of these models for the spread of HIV and AIDS amongst injecting drug users.

Chapter 3

Stochastic Models

3.1 Introduction

Whilst Kaplan's model is deterministic in nature, there are many situations where stochastic models are more appropriate. Deterministic theory does not take into account random fluctuations which may be inherent in the process which is to be studied. Deterministic theory may be sufficient when the population that is to be studied is large and the effect of individual variability will not be so important, but for models studying smaller populations, or models which divide the population into smaller sub-populations stochastic theory may have to be developed. Also the use of a stochastic model may be appropriate even in a situation where the population size is large if the initial number of infectives is small. A stochastic simulation model describing the spread of HIV in a population of IDUs is presented in this chapter. It employs the same assumptions as the previously presented deterministic model to enable direct comparisons between the deterministic and the stochastic models. As there are methodological differences in the development of stochastic and deterministic models, many of the assumptions used in the deterministic model can be relaxed.

3.2 Simulation Models

Monte-Carlo simulation is commonly used by scientists in many fields of research, therefore only a limited introduction will be given. The theory of simulation relies on the generation of pseudo-random numbers, in which a replicable stream of numbers is produced which appear to be randomly distributed over a uniform distribution. A standard method of producing such numbers is the congruential random number generator, where the n^{th} number produced depends on the $(n-1)^{\text{th}}$ where $x_n \equiv (ax_{n-1} + b) \bmod m$. The constants a, b and m are chosen to provided a stream of numbers with desirable properties and x_0 is an arbitrarily chosen seed. The properties looked for in a good psuedo-random number generator include closeness to uniformity over the range of desired values, lack of structure in the data stream and a long period before cycling. Number theory can be used to derive properties of the psuedo-random generator and this is discussed in Morgan (1984). In particular the properties of the NAG random number generator G05CAF is discussed. Ripley (1983) suggests that this generator, which uses the values $a = 13^{13}$, $b = 0$ and $m = 2^{59}$ is acceptable for most purposes and shows that the generator has a period of 2^{57} if the seed is odd. A typical run of the simulations described below use approximately 2^{16} random numbers hence this period is satisfactory. Also the structure of the programs using the random numbers can be thought of as a complex simulation system, in that the number of calls to the random number generator within one loop through the simulation depends on the events that are simulated, which in turn depends on the random numbers generated. Thus the effect of any structure or any cyclic nature in the stream of numbers will be reduced. Therefore, throughout this Thesis, the family of algorithms which use the NAG random number generator G05CAF are employed.

The model takes the form of a Pascal program which is run on a Sun worksta-

tion. In its most basic form the model stores the proportion of the population that is infected and also the proportion of the needles that are infected. The program simulates an IDU visiting a shooting gallery and selecting a needle. Depending on the infectivity status of both the IDU and needle, several events may happen, either an IDU infects a needle, an IDU flushes a needle or a needle infects an IDU. The model also includes infected IDUs dying, leading to an infective immediately being replaced by a susceptible as in Kaplan's model. This unrealistic assumption remains initially to enable comparison between Kaplan's deterministic model and the following stochastic models. This program is a continuous time simulation in that it simulates the time to next event then simulates that event, updating the infected proportions after each event. This program was comprehensively verified using detailed output from a number of runs.

3.2.1 Output from Stochastic Simulations

The output from this program can take several forms, the one of most interest will be the proportion of the IDU population that is infected. Other output can include the proportion of needles infected or the ratio of infected IDUs to infected needles. The ouput can be examined using a standard graphical package such as Splus. Looking at the output from the program it is clearly similar to the deterministic model in that it also appears to be a logistic-type curve starting from close to zero and resulting in almost all of the population becoming infected. Figure 3.1 is one realisation of the stochastic process corresponding to the deterministic model previously described. It uses the standard set of parameters ($\lambda = 5.952 \times 10^{-3}$ visits per hour, $\mu = 1.43 \times 10^{-5}$ deaths per hour, $\alpha = 0.075$, $\theta = 0.25$ and $\gamma = 10$). The parameter γ is constructed from N the IDU population size divided by n, the number of needles available. π will then be constructed as I/N with the initial value for π, π_0 equal to I_0/N. The simulations can only begin with values of π_0 such as $1/N, 2/N, \ldots$. We have

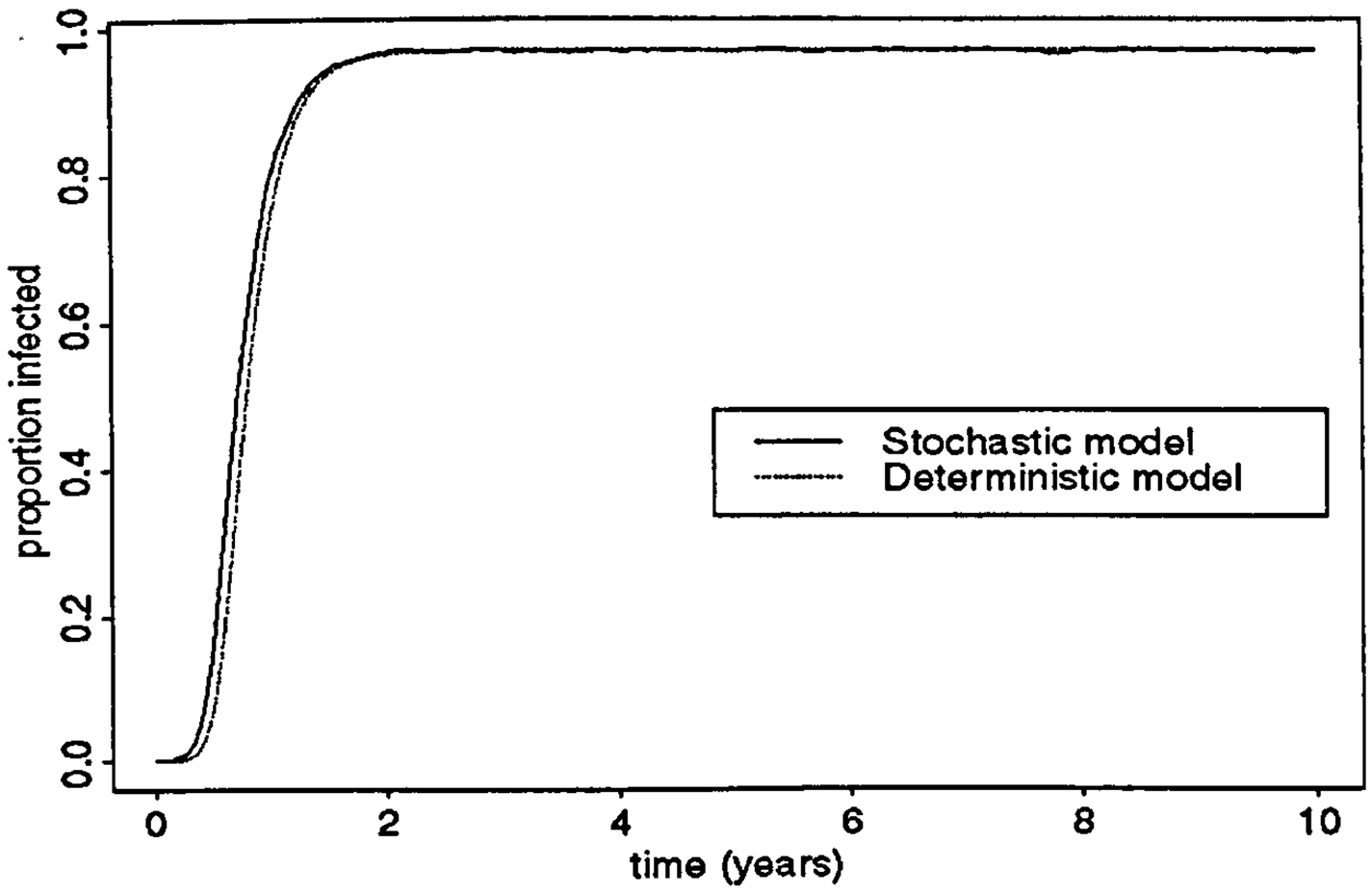

Figure 3.1: One stochastic realisation compared to the corresponding determinic model.

taken $\pi_0 = 1/10,000$ in the realisations portrayed in Figures 3.1 and 3.2, which corresponds to the initial value $\pi_0 = 0.0001$ in the deterministic model. In both the deterministic model and the stochastic models described it is assumed that all needles are initially uninfected.

It is important to note that the deterministic Equations 2.1 and 2.2 imply that the total number of IDUs N and the total number of needles n enter the calculation only through the gallery ratio γ. There is no reason why this should be true for the corresponding stochastic model. Thus for a given value of γ the simulation results are independent of the actual values of N and n for the deterministic model but not for the stochastic model.

As this is a stochastic model and the output from one run of the program will only be one realisation of the process, it is better to examine the output from several realisations. We have simulated the epidemic 50 times using the parameter values and the initial numbers of infected needles and IDUs as in Chapter 2 and in Figure 3.2 we have shown three different realisations of the same epi-

demic process selected to give an idea of the variation between realisations. The

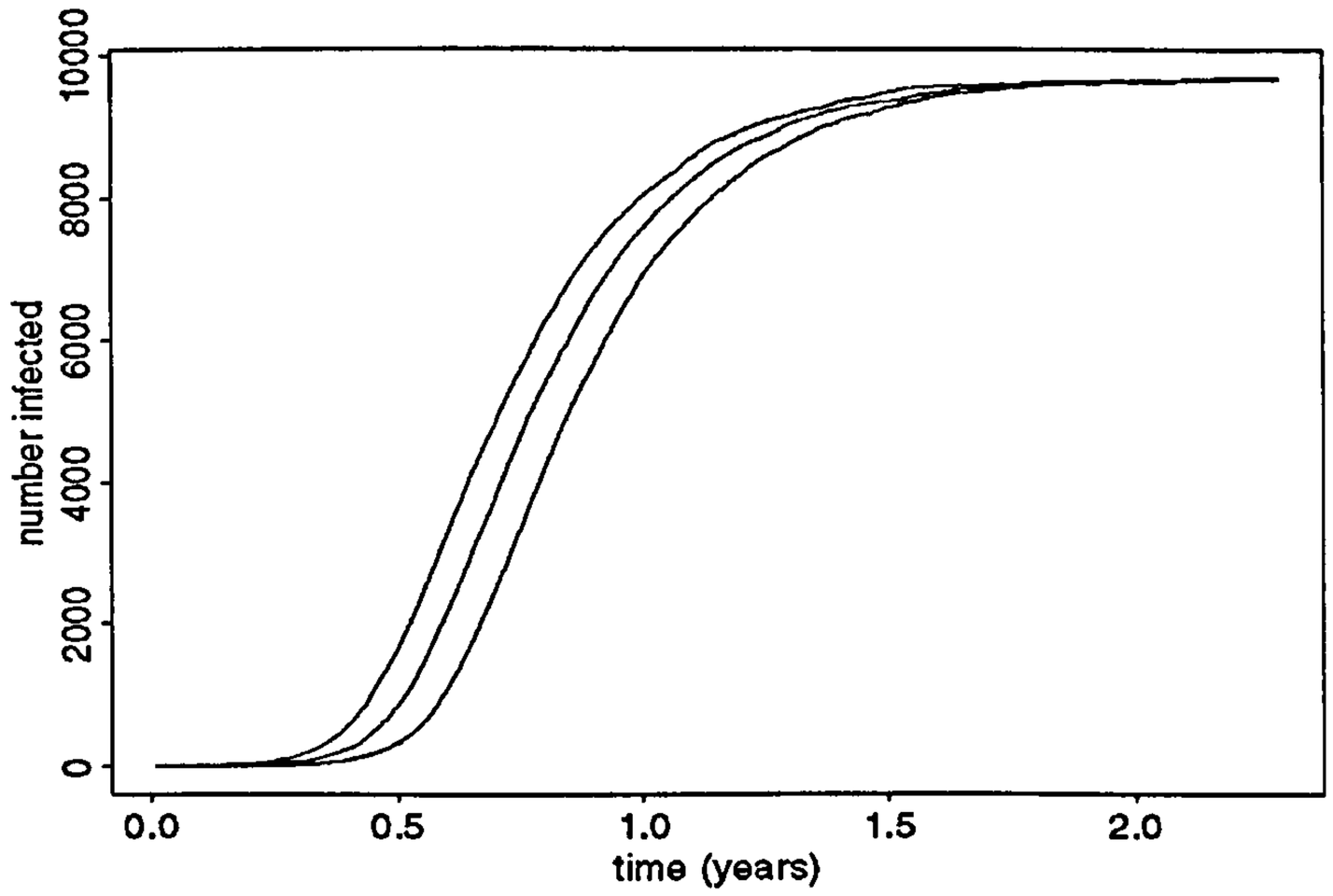

Figure 3.2: Three realisations from the same stochastic process.

stochastic variation will clearly have most influence at the start of an epidemic when the number of infected IDUs and the number of infected needles are small. In Figure 3.3, which explores the initial stages of three realisations using the above parameter set and starting values, we can see that in one realisation the disease spreads quite quickly, that in another the disease spreads at a slower rate and in the third realisation the disease dies out. We need to use summary statistics from several realisations when describing the stochastic process. This output will be summarised as either the mean or median value of a number of simulations along with a measure of the variation about such a mean or median. If we define $\bar{y}^*(t)_k$ as the mean number of infected IDUs at time t calculated from k non-extinct realisations, $\bar{y}^*(t)_k$ can be thought of as an estimate of $\mu_y^*(t)$ which will be a conditional mean number of infected IDUs at time t, conditional on the number of infected IDUs being larger than zero.

$$\mu_y^*(t) = \lim_{k\to\infty} \bar{y}^*(t)_k. \tag{3.1}$$

This stochastic mean is therefore not directly comparable to any of the individual

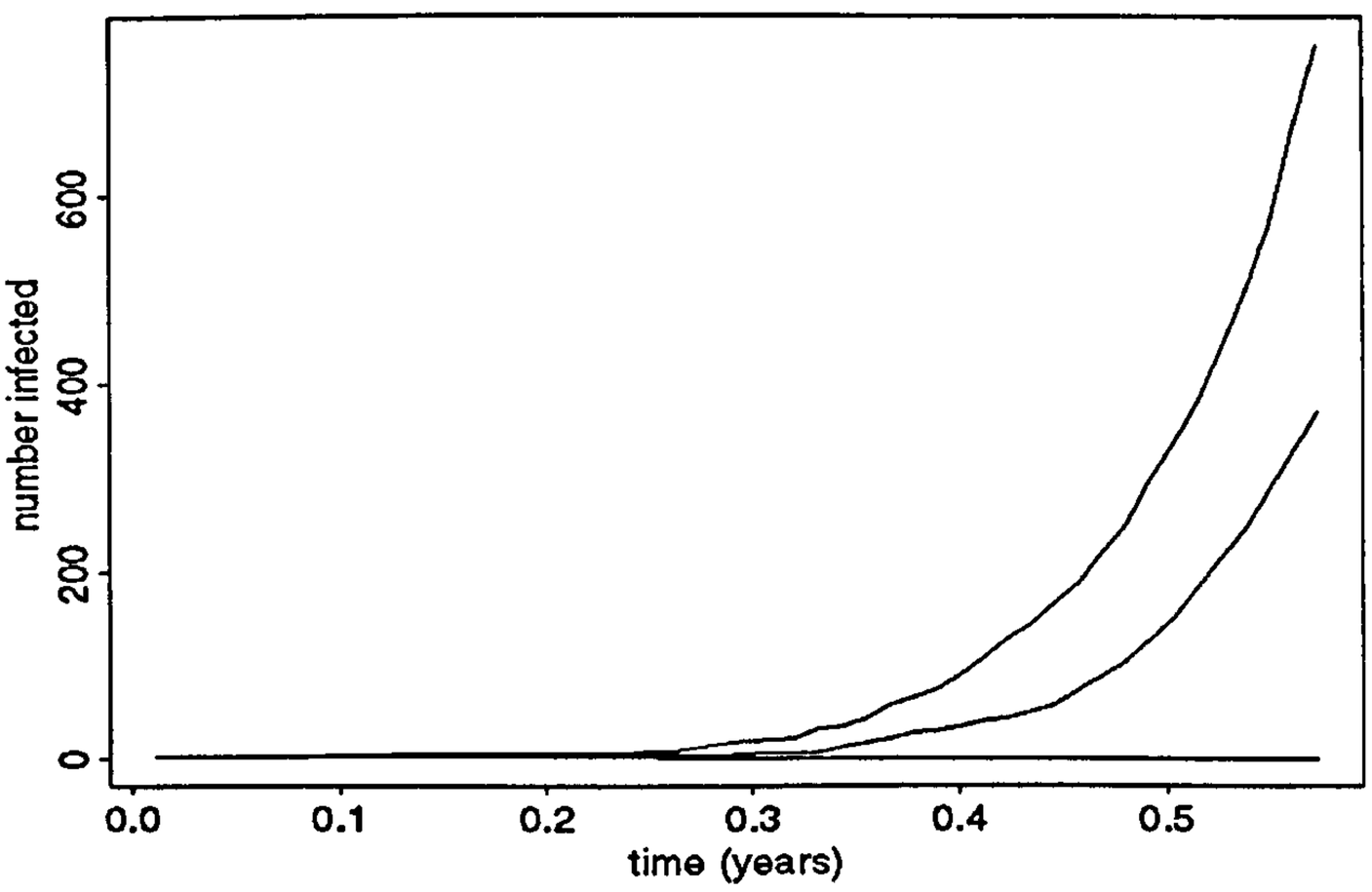

Figure 3.3: Initial stages of three realisations from the same stochastic process.

realisations, as it may well be constructed from several realisations. We can also work with the unconditional mean, which will be affected by the number of zero realisations. The median values can also be examined; these would not attach so much weight to zero realisations. As the distribution of the number of infected individuals and the number of infected needle may well be skew there are attractions to using the median as a measure of location. The median, mean and conditional mean number of IDUs infected over time from 50 simulations are shown in Figure 3.4. To clarify this figure, as the disease begins to spread at the earlier time points both the mean and the conditional mean are greater than the median. This is because the distribution is skew with a tail to the right and zero values from any simulations in which the disease died out would not have such a great effect on the mean values. At the later stages of the disease spread, the median and the conditional mean are almost exactly similar, but the mean value calculated by summing over all realisations includes a zero value corresponding to the realisation in which the disease died out.

In order to construct a measure of the variation it is necessary to understand

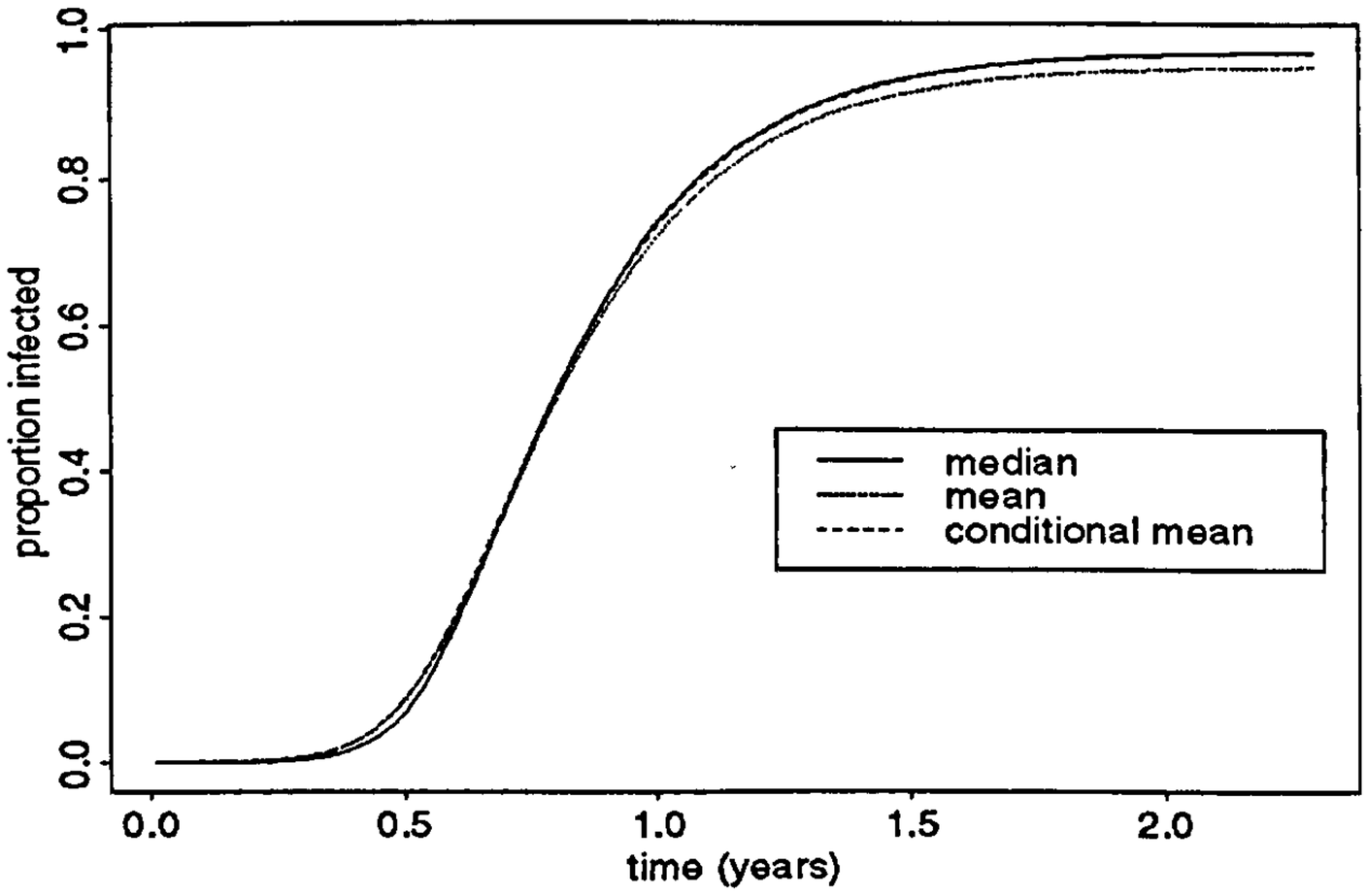

Figure 3.4: Median value from 50 simulations of the same stochastic process compared to the mean and the conditional mean as defined in Equation /msg3.1.

what the distribution of the number of equivalent proportions of infected individuals over different realisations at a fixed time point will be. While more exact representations of the distribution will be explored later, it will be clear that such a distribution will be very skew at earlier values of time and perhaps also bimodal, with one peak corresponding to the zero realisations.

Figure 3.5 describes as a histogram the number of IDUs that are infected after 20 weeks, summarised over 200 realisations with the parameters and starting values as described above. As it is clear that this distribution is skew any confidence intervals involving parametric measures such as the standard deviation will, at best be unsuitable, and at worse give infective proportions less than zero or greater than one. One alternative would be to treat the number of infectives as a binomial distribution with infection comparable to success, although there does not appear to be any theoretical justification for this. The favoured alternative is to look at either the minimum and maximum values across the realisations, or to examine a pair of percentiles constructed from our set of simulated outcomes to give an approximate confidence interval for a single realisation of the process.

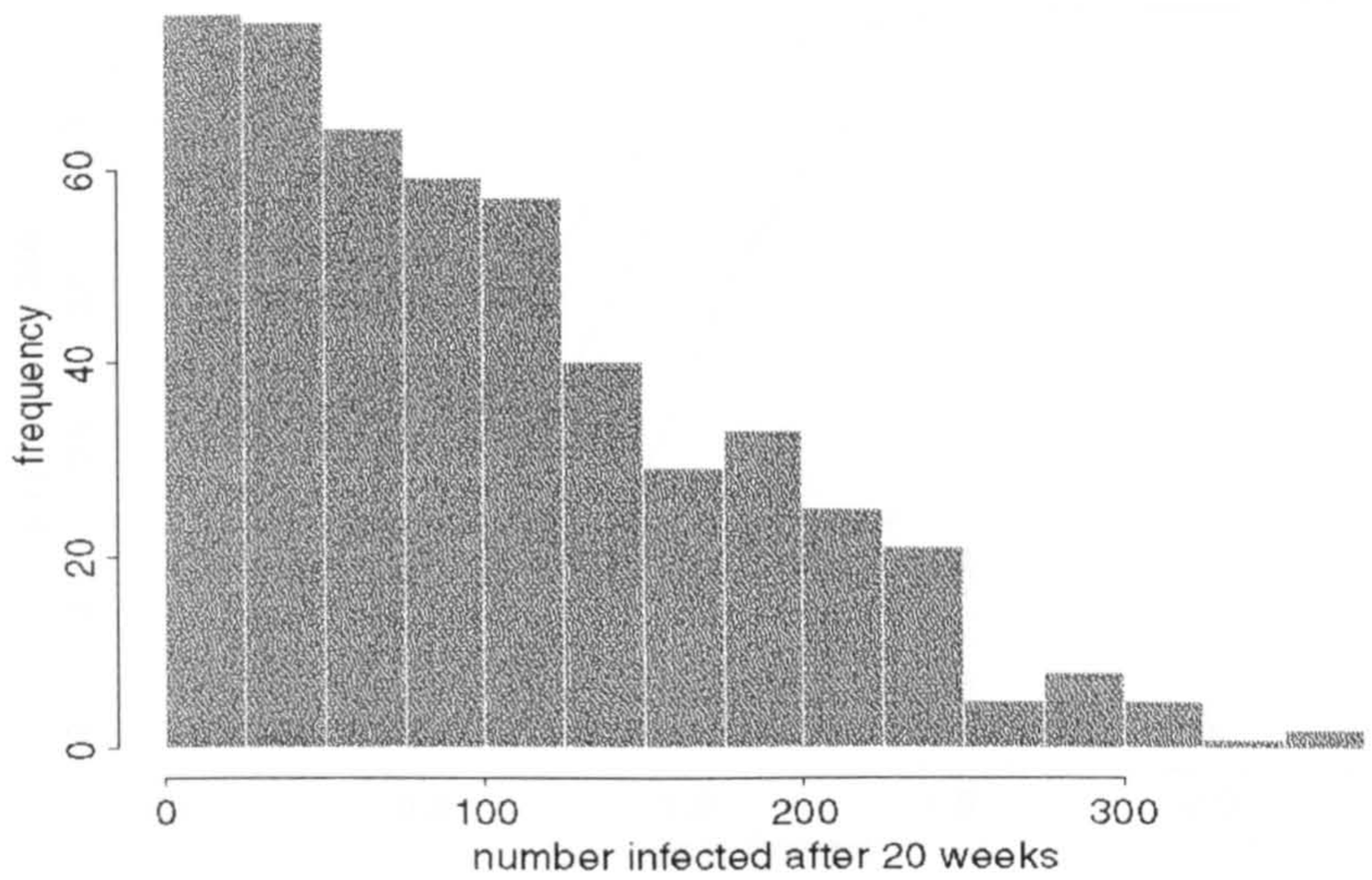

Figure 3.5: Distribution of realisation towards the start of the stochastic process.

Figure 3.6 shows the median, minimum and maximum of 50 realisations, and as can be seen from the minimum values, this collection of realisations did not include a realisation in which the disease dies out.

3.3 Comparable Analytical Models

In this section we shall derive differential equations satisfied by $P_{xy}(t)$, the probability that there are x infected needles and y infected IDUs at time t. Unfortunately these differential equations prove to be analytically intractable. However they can be integrated numerically to give us some insight into the behaviour of the stochastic model over time.

As noted by Bailey (1975, p. 33) 'Deterministic theory is relatively straightforward..., on the other hand, the simple stochastic epidemic, apparently first mentioned explicitly by Bartlett (1949), rapidly leads to complicated mathematical analysis.' There are however some analytical modelling techniques that may be of interest with regard to the model described by Kaplan (1989). Follow-

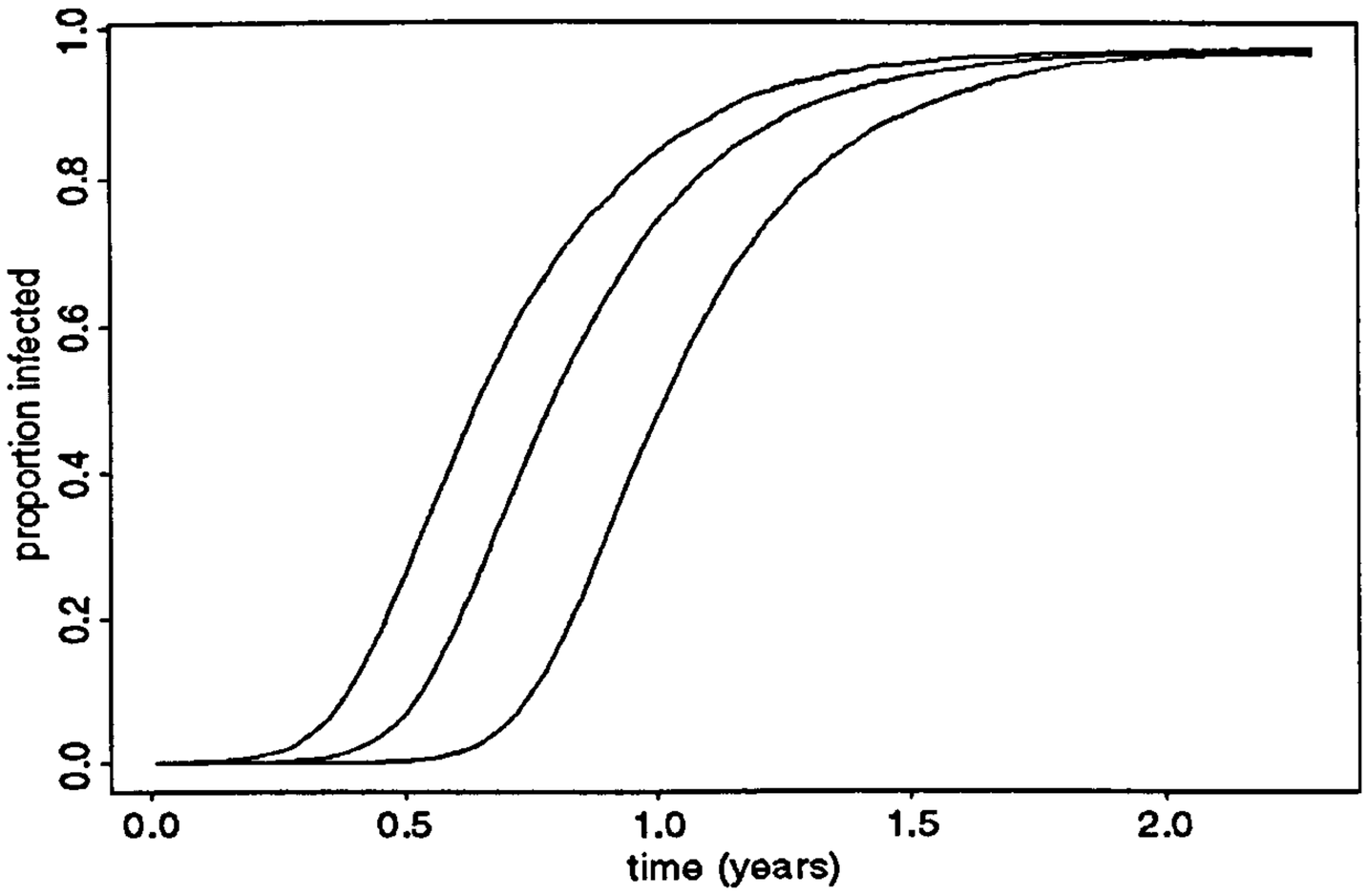

Figure 3.6: Median, minimum and maximum values from 50 realisations of the stochastic process.

ing on from the assumptions in the stochastic simulation model a flow diagram describing the rates of change in the numbers of infected IDUs and needles is presented in Figure 3.7, where the number of infected IDUs and needles are denoted by I and i respectively, and N and n are the total numbers of IDUs and needles respectively. Figure 3.7 illustrates the events that can occur in a small time interval of length δt. It is assumed that only one event can occur in this small time interval, this will be either one needle becoming infected, one needle being flushed, one IDU becoming infected or one infected IDU ceasing to share and therefore is being removed from the population of interest and immediately replace by a susceptible.

We can assign probabilities, as shown in the figure, to each event. While each of the probabilities will depend on the number of infected needles i and infected IDUs I, we simplify the notation at point by abbreviating the probabilities to $B_1\delta t$, $D_1\delta t$, $B_2\delta t$ and $D_2\delta t$ respectively. From this flow diagram it is possible to formulate an equation in $P_{x,y}(t)$ where $P_{x,y}(t)$ is the probability that there are x infected needles and y infected IDUs at time t. From this a differential equation

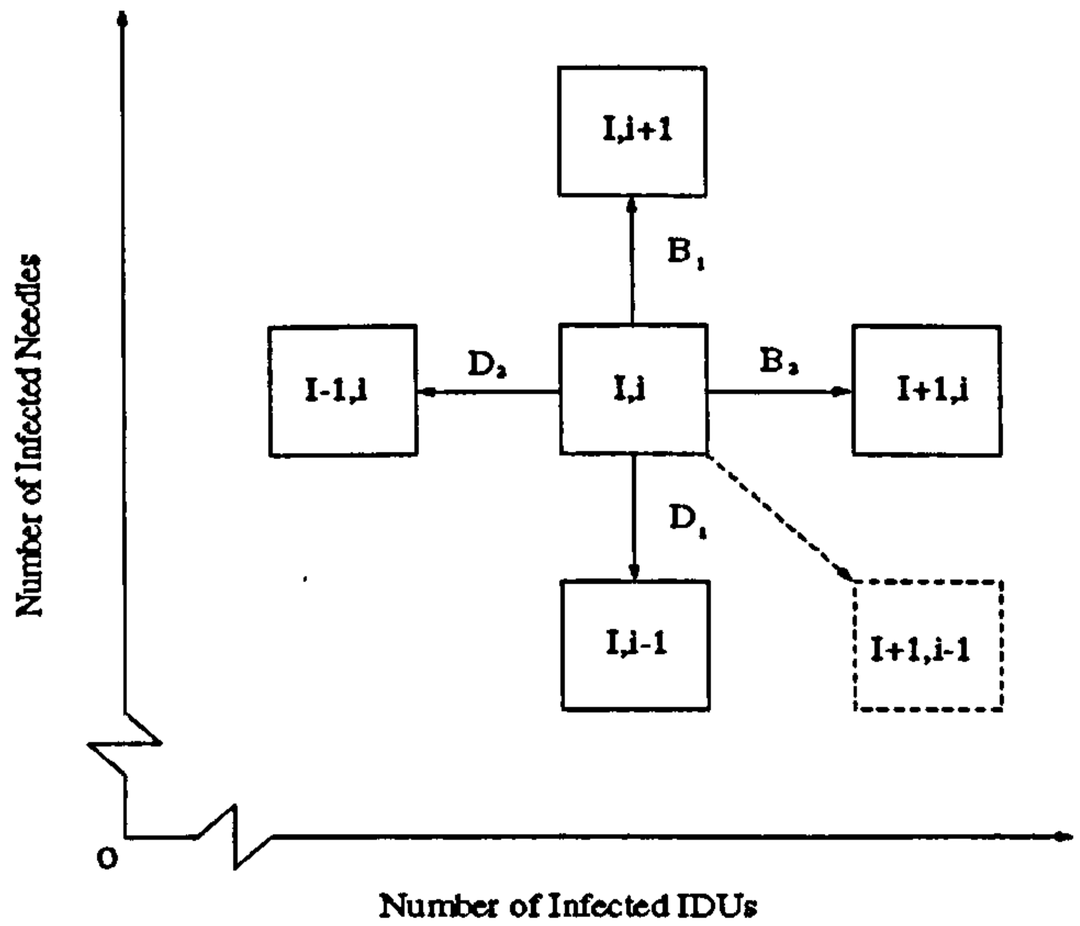

Figure 3.7: Events that can occur in a small time interval of length δt.

describing the rate of change of $P_{x,y}(t)$ can be formulated as

$$\frac{\mathrm{d}P_{x,y}(t)}{dt} = B_1(x-1,y)P_{x-1,y}(t) + B_2(x,y-1)P_{x,y-1}(t) + D_1(x+1,y)P_{x+1,y}(t)$$

$$+ D_2(x,y+1)P_{x,y+1}(t) - R(x,y)P_{x,y}(t)$$

where $R(x,y) = B_1(x,y) + D_1(x,y) + B_2(x,y) + D_2(x,y)$. This equation is equivalently

$$\begin{aligned}\frac{\mathrm{d}P_{x,y}(t)}{dt} = &-\left[\mu y + (N-y)\frac{\lambda\alpha x}{n} + \frac{\lambda\gamma y}{N}(n-x) + \lambda\gamma\left(1-\frac{y}{N}\right)\theta x\right]P_{x,y}(t) \\ &+ \left[\frac{\lambda\gamma y}{N}(n-(x-1))\right]P_{x-1,y}(t) + \left[(N-(y-1))\frac{\lambda\alpha x}{n}\right]P_{x,y-1}(t) \\ &+ \left[\lambda\gamma\left(1-\frac{y}{N}\right)\theta(x+1)\right]P_{x+1,y}(t) + \mu(y+1)P_{x,y+1}(t). \qquad (3.2)\end{aligned}$$

This formulation assumes that the time interval $[t, t+\delta t]$ is small enough that the probability that more than one event occurs in this time interval will be negligible. However in the model described in the previous chapter it is possible for events 1 and 4 to occur simultaneously within a visit to a shooting gallery by a single IDU. So a fifth event corresponding to an IDU becoming infected and

the needle simultaneously becoming flushed will also be considered. Denote the rate at which this multiple event happens by $M(x,y)$. The differential equation in $P_{x,y}(t)$ will now be

$$\frac{\mathrm{d}P_{x,y}(t)}{dt} = B_1(x-1,y)P_{x-1,y}(t) + B_2(x,y-1)P_{x,y-1}(t) + D_1(x+1,y)P_{x+1,y}(t)$$
$$+ D_2(x,y+1)P_{x,y+1}(t) + M(x+1,y-1)P_{x+1,y-1}(t) - R(x,y)P_{x,y}(t) \quad (3.3)$$

where now $R(x,y) = B_1(x,y) + D_1(x,y) + B_2(x,y) + D_2(x,y) + M(x,y)$. We assume that when a susceptible addict injects with an infected syringe the events that the addict is infected and that the syringe is flushed are independent. Thus on a single such injection the probability that both the addict is infected and the syringe is flushed is $\alpha\theta$. The differential equation in $P_{x,y}(t)$ is now equivalently

$$\frac{\mathrm{d}P_{x,y}(t)}{\mathrm{d}t} = \Big[-\lambda\gamma(\alpha+\theta-\alpha\theta)x - (\mu+\lambda)y + \frac{\lambda}{n}(\alpha+\theta-\alpha\theta+1)xy\Big]P_{x,y}(t)$$
$$+ \Big[\frac{\lambda}{n}(n-(x-1))y\Big]P_{x-1,y}(t)$$
$$+ \Big[\frac{\lambda}{n}\alpha(1-\theta)x(N-(y-1))\Big]P_{x,y-1}(t)$$
$$+ \Big[\lambda\gamma(1-\alpha)\theta(x+1)\Big(1-\frac{y}{N}\Big)\Big]P_{x+1,y}(t)$$
$$+ \mu(y+1)P_{x,y+1}(t)$$
$$+ \lambda\gamma\alpha\theta(x+1)\Big(1-\frac{(y-1)}{N}\Big)P_{x+1,y-1}(t). \quad (3.4)$$

This model can be explored by converting this differential equation into one which describes the rate of change of the probability generating function, as described by Bailey (1964). The equation can then be reduced to

$$\frac{\partial\pi(s,z;t)}{\partial t} = \lambda\gamma\Big(((1-\alpha)(1-\theta)-1)s+(1-\theta)\alpha sz+(1-\alpha)\theta+\alpha\theta z\Big)\frac{\partial}{\partial s}\pi(s,z;t)$$
$$+ \Big(\mu(1-z)+\lambda z(s-1)\Big)\frac{\partial}{\partial z}\pi(s,z;t)$$
$$+ \frac{\lambda}{n}\Big((\alpha+\theta-\alpha\theta+1)sz - s^2z - (1-\theta)\alpha sz^2$$

$$- (1-\alpha)\theta z - \alpha\theta z^2\Big)\frac{\partial^2}{\partial s \partial z}\pi(s,z;t) \tag{3.5}$$

where $\pi(s,z;t)$ is the probability generating function of $P_{x,y}(t)$ defined as

$$\pi(s,z;t) = \sum_{x=0}^{n}\sum_{y=0}^{N} P_{x,y}(t)s^x z^y.$$

Solution of this differential equation by conventional techniques does not seem possible although there are some methods that can be used to provide approximate solutions. We can convert the equation in the probability generating function to an equation involving moment generating functions, or for ease of calculation, cumulant generating functions, by using the transformation

$$K(s,z;t) = \log \pi(e^{-s}, e^{-z}; t).$$

Here $K(s,z;t)$ is the joint cumulant generating function. We can now use an approximation of the exponential terms by Taylor series and then equate coefficients. This approximation will result in an infinite system of differential equations involving $\kappa_{ij}(t)$, the mixed cumulants of order (i,j). However this system will not yield a useful solution as its order is infinite. To obtain a practical solution we would have to truncate the system. To do this for some (i,j) it would have be assumed that all cumulants of a higher order will be negligible. As there is no justification for this, we shall explore a different method for solving these analytical equations.

The equations that we are interested in have been reduced to Equation 3.5. Taking the partial derivative with respect to s of both sides of (4) gives

$$\frac{\partial^2 \pi(s,z;t)}{\partial s \partial t} = \lambda\gamma((1-\alpha)(1-\theta) - 1 + (1-\theta)\alpha z)\frac{\partial}{\partial s}\pi(s,z;t)$$

$$+ \lambda\gamma\Big(((1-\alpha)(1-\theta) - 1)s + (1-\theta)\alpha s z$$

$$+ (1-\alpha)\theta + \alpha\theta z\Big)\frac{\partial^2}{\partial s^2}\pi(s,z;t)$$

$$+ \lambda z\frac{\partial}{\partial z}\pi(s,z;t)$$

$$+\left(\mu(1-z)+\lambda z(s-1)\right)\frac{\partial^2}{\partial s\partial z}\pi(s,z;t)$$

$$+\frac{\lambda}{n}\left((\alpha+\theta-\alpha\theta+1)z-2sz-(1-\theta)\alpha z^2\right)\frac{\partial^2}{\partial s\partial z}\pi(s,z;t)$$

$$+\frac{\lambda}{n}\Bigg((\alpha+\theta-\alpha\theta+1)sz-s^2z-(1-\theta)\alpha sz^2$$

$$-(1-\alpha)\theta z-\alpha\theta z^2\Bigg)\frac{\partial^3}{\partial s^2\partial z}\pi(s,z;t). \qquad (3.6)$$

Let X and Y denote respectively the number of infected needles and the number of infected IDUs at time t. When Equation 3.6 is evaluated at $s=1$ and $z=1$ it gives

$$\frac{\mathrm{dE(X)}}{\mathrm{d}t}=-\lambda\gamma\theta\mathrm{E(X)}+\lambda\mathrm{E(Y)}-\frac{\lambda}{n}(1-\theta)\mathrm{E(XY)}.$$

$\frac{\mathrm{dE(Y)}}{\mathrm{d}t}$ and $\frac{\mathrm{dE(XY)}}{\mathrm{d}t}$ can also be found using similar methods, but as in the expression for $\frac{\mathrm{dE(X)}}{\mathrm{d}t}$, they will include second order terms, which when evaluated will include third order terms and so on. There seems to be no justification in aproximating any of the higher order terms with zero, therefore the analytical modelling of this and comparable processes will not be pursued. Indeed for any more realistic models, it would appear that use of analytical methods will be intractable.

3.4 Numerical Solution of Analytical Models

We shall now look at at direct numerical integration of our analytical model using a technique outlined in Renshaw (1991). Consider the differential equations in $P_{x,y}(t)$. These can be solved using numerical methods by approximating them by

$$P_{x,y}(t+\Delta t)=\Big[1-\mu y\Delta t-(N-y)\frac{\lambda(1-\theta)\alpha x}{n}\Delta t-\frac{\lambda\gamma y}{N}(n-x)\Delta t$$

$$-\lambda\gamma(1-\alpha)\Big(1-\frac{y}{N}\Big)\theta x\Delta t-\lambda\gamma\alpha\Big(1-\frac{y}{N}\Big)\theta x\Delta t\Big]P_{x,y}(t)$$

$$+\Big[\frac{\lambda\gamma y}{N}(n-(x-1))\Big]P_{x-1,y}(t)\Delta t$$

$$+\left[(N-(y-1))\frac{\lambda\alpha(1-\theta)x}{n}\right]P_{x,y-1}(t)\Delta t$$

$$+\left[\lambda\gamma(1-\alpha)\left(1-\frac{y}{N}\right)\theta(x+1)\right]P_{x+1,y}(t)\Delta t$$

$$+\mu(y+1)P_{x,y+1}(t)\Delta t$$

$$+\left[\lambda\gamma\alpha\left(1-\frac{(y-1)}{N}\right)\theta(x+1)\right]P_{x+1,y-1}(t)\Delta t$$

$$+o(\Delta t). \tag{3.7}$$

As $P_{x,y}(t),\ 0<x<n,\ 0<y<N$ is essentially a matrix of probabilities of size $(n+1)(m+1)$ recorded at time t, the value of every cell in this matrix at time $t+\Delta t$ can be calculated from the above equation. While not explicitly described by Equation 3.7, the approximation to the differential equations differ slightly when $x=0$, $x=n$, $y=0$ or $y=N$ to include boundary conditions. On the boundary, for example when all IDUs are infected, the rate B_2 will be zero. This is recognised in the following program by assigning values to cells of the matrix such as $P_{x,N+1}(t)$, however as the corresponding rates will all be zero, the assigned value will not be employed when calculating any of the $P_{x,N}(t+\Delta t)$. The value of the matrix at time $t+2\Delta t$ can then be calculated from the matrix at time $t+\Delta t$, and so on. To provide a good approximation Δt must be small. However the accuracy obtained by decreasing the size of Δt is offset by the running time of the program. Program testing and validation has shown that a time increment of $\Delta t=0.01$ hours in a program that simulates the spread of the disease over 10 year is sufficient, the criteria for judging this is whether $\sum_{x=0}^{n}\sum_{y=0}^{N}P_{x,y}(t)$ converges to one at each time step. Approximations can be used where $\sum_{x=0}^{n}\sum_{y=0}^{N}P_{x,y}(t)$ is scaled to one after each time step, although for the simulations that follow this mechanism was not needed. One of the major attractions of this method is that after each time interval, we have $P_{x,y}(t)$ for $0\leq x\leq n,\ 0\leq y\leq N$, which we can view graphically or use to derive a mean. One major disadvantage of this method is the memory that is needed to store a $(N+1)\times(n+1)$ matrix.

The population sizes that have been used in these examples are $N = 100$ and $n = 10$, with initially one infected IDU and no infected needles. This corresponds to $\pi(0) = 0.01$ or $P_{0,1}(0) = 1$. This is simulated using a program developed in Pascal, which again was comprehensively tested and verified, using detailed output from a large number of runs.

In Figures 3.8 to 3.11 we can see the state of the process at times $t = 1$ month, $t = 4$ months $t = 6$ months and $t = 1$ year. As in Chapter 2, the disease spread is triggered by introducing one infected IDU into a population of susceptible IDUs, thus $P_{x,y}(0) = 1$ at $x = 0$, $y = 1$ and $P_{x,y}(0) = 0$ otherwise. Although we are examining a discrete stochastic process such that there can only be x infected needles and y infected IDUs where x and y are integers, the graphical representation of the process is easier to examine using a graphical device which assumes continuity between the x, y points and connects the points $P_{x,y}(t)$ with $P_{x+1,y}(t)$, $P_{x-1,y}(t)$, $P_{x,y+1}(t)$ and $P_{x,y-1}(t)$.

In Figure 3.8, we see that the spike corresponding to one infected IDU and zero infected needles arose from the starting values which triggered the spread of the disease. Later, in Figure 3.9 we see that even though the initial spike is still present, more IDUs have become infected, however the proportion of needles that are infected appears to increase at a higher rate. This again is demonstrated in Figure 3.10 where almost all the needles are likely to be infected but the proportion of the IDU population that has become infected does not appear to have reached an equilibrium. This figure also shows quite clearly that there is a non zero probability that there are no infected IDUs and no infected needles, such that $P_{0,0}(t)$ approximately 0.01. In Figure 3.11 $P_{0,0}(t)$ is still approximately equal to 0.01, but this is difficult to visualise due to the difference in scale between Figures 3.9 and 3.10. However the bulk of the probability is centered on the values, $x = 10$ infected needles and $y = 97$ infected IDUs. These values compare

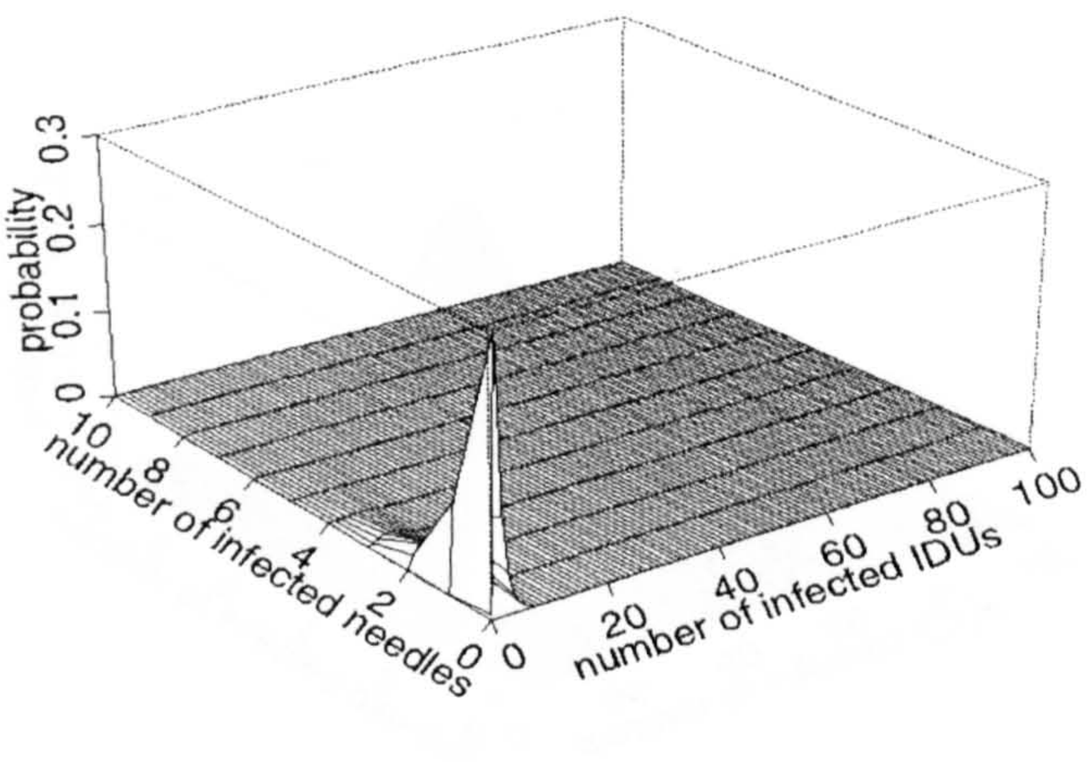

Figure 3.8: $P_{x,y}(t)$ after time $t = 1$ month.

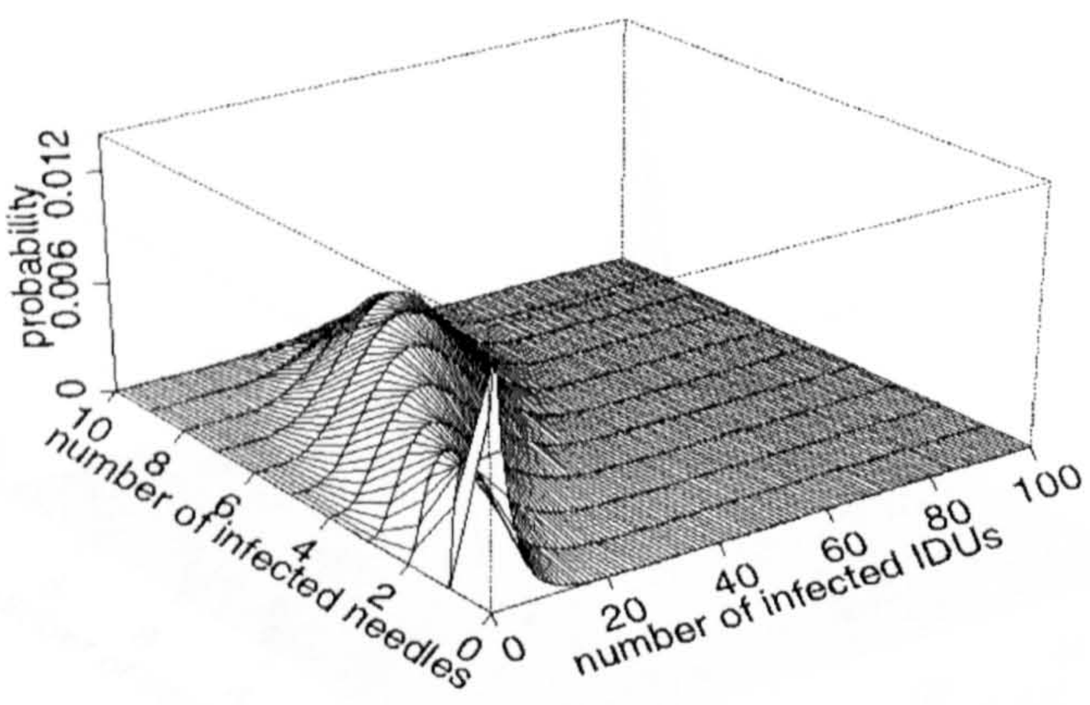

Figure 3.9: $P_{x,y}(t)$ after time $t = 4$ months.

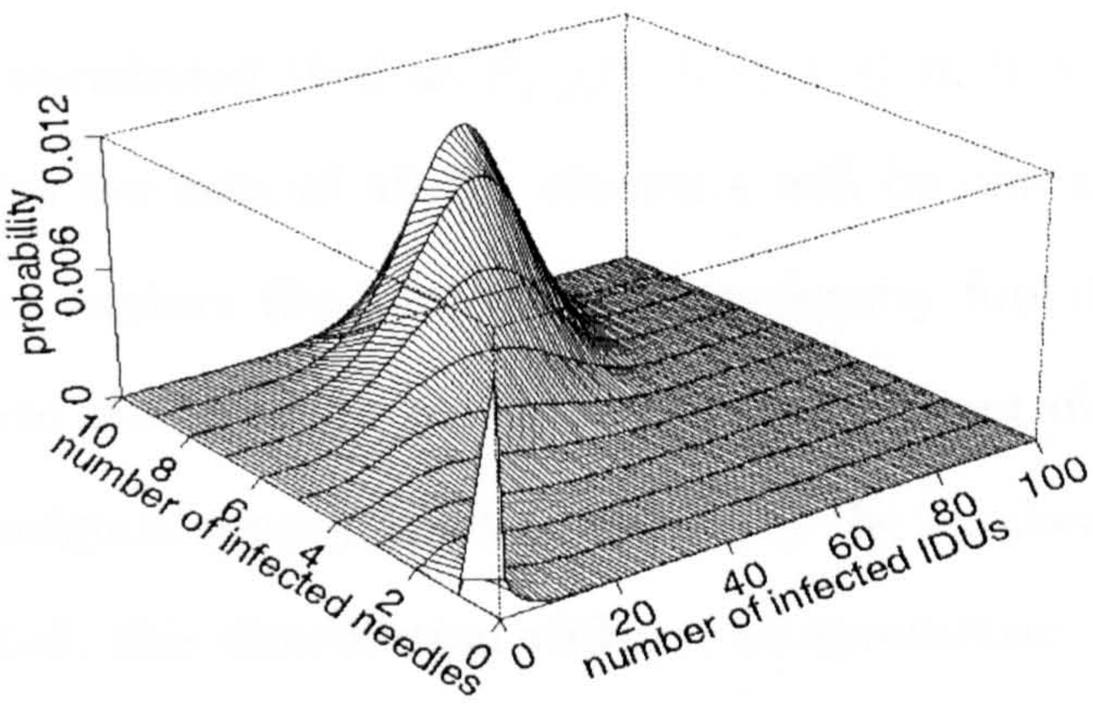

Figure 3.10: $P_{x,y}(t)$ after time $t = 6$ months.

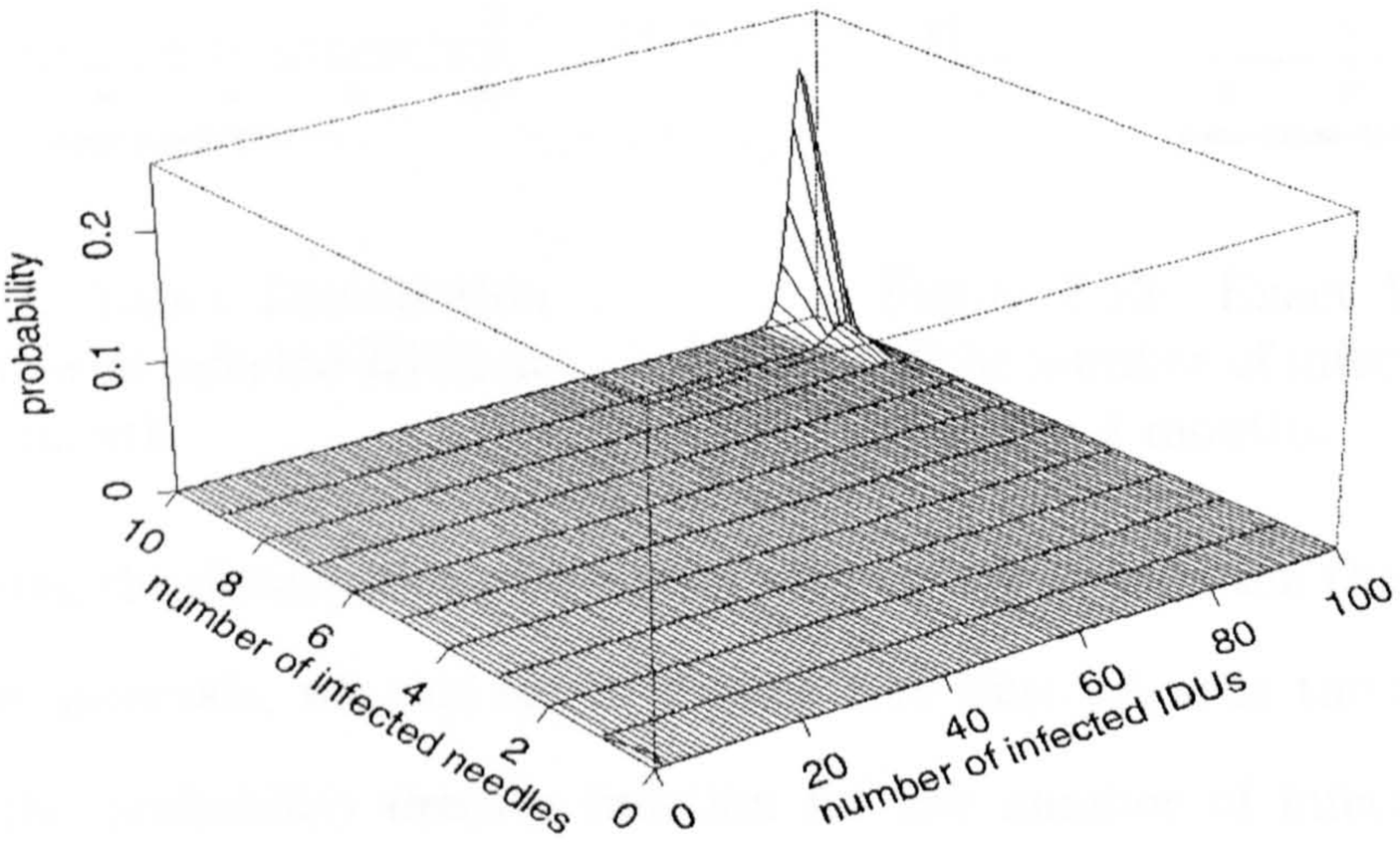

Figure 3.11: $P_{x,y}(t)$ after time $t = 1$ year.

to the deterministic equilibrium values $\beta^* = 0.99$, $\pi^* = 0.969$ for this choice of parameters calculated from Equations 2.3 and 2.4. and also to the equilibrium values obtained from the Monte-Carlo simulations described in Section 3.2.

It should be remembered that as $P_{x,y}(t)$, $0 \leq x \leq n$, $0 \leq y \leq N$ is a matrix of probabilities the sum of all the elements will be one at all times. This means that we can explore the joint probability density function of what is essentially a bivariate distribution. As we now have the exact distribution we can re-examine the mariginal density function related to the number of infected IDUs. As previously noted, this distribution will not be symmetric, and any measure of confidence about where the mean of stochastic realisations is cannot rely on parameters such as the standard deviation.

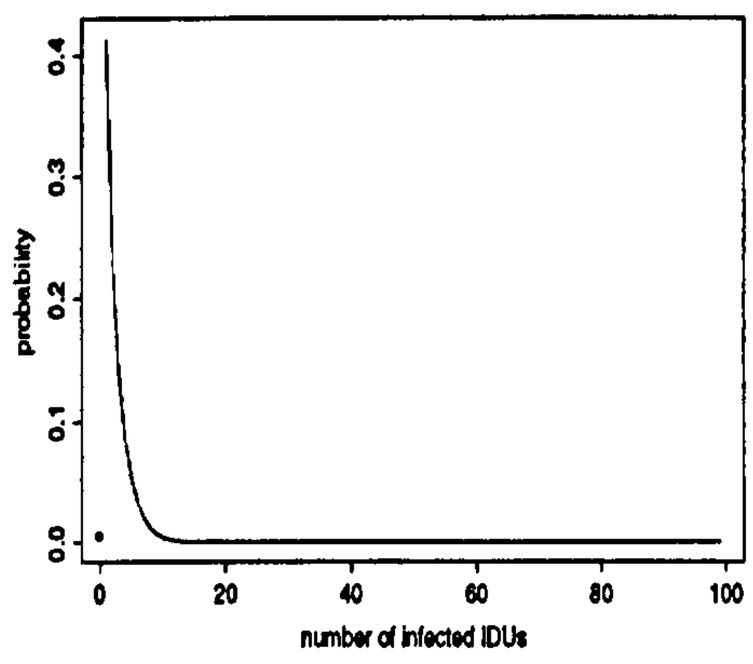

Figure 3.12: Exact Distribution of the number of infected IDUs at time $t = 1$ month.

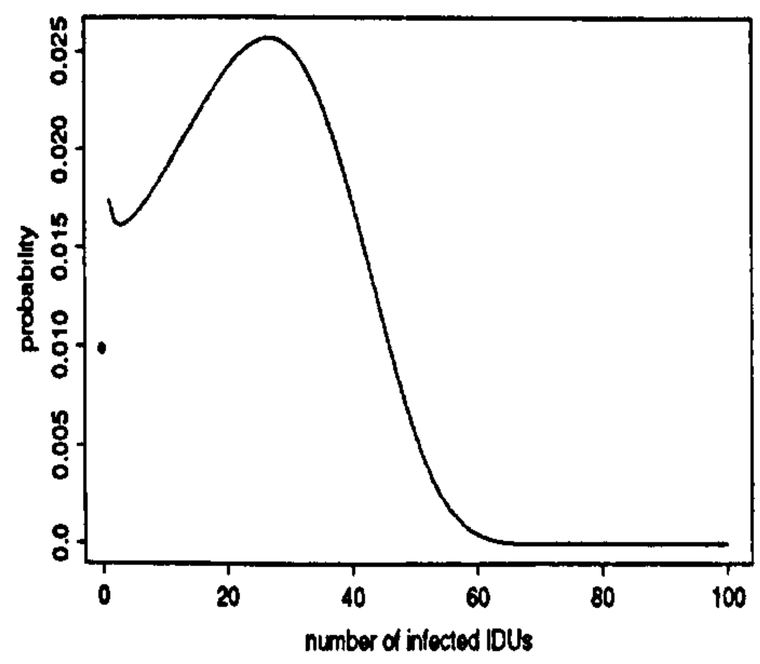

Figure 3.13: Exact Distribution of the number of infected IDUs at time $t = 4$ months.

Examining the distribution of the proportion of the population that is infected at set time intervals, we can see in Figure 3.12 that towards the start of the epidemic the probability density function for the number of infected IDUs is skew, moving on to have, as in Figure 3.13, one peak centered on 25 infected IDUs and a smaller peak at 1 infected IDU which occurs as there is still an effect of the intial values. An additional discrete element is also present which describes the probability that there are zero infected IDUs and zero infected needles. Later

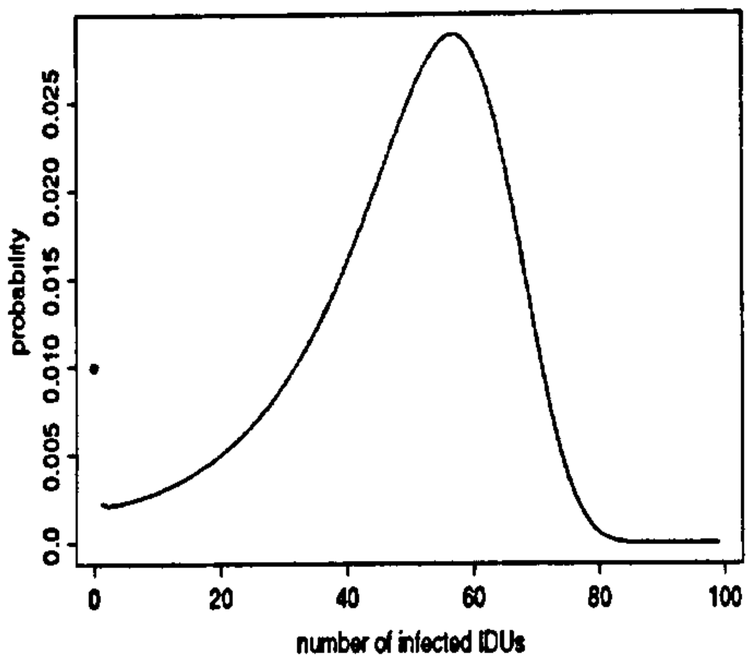

Figure 3.14: Exact Distribution of the number of infected IDUs at time $t = 6$ months.

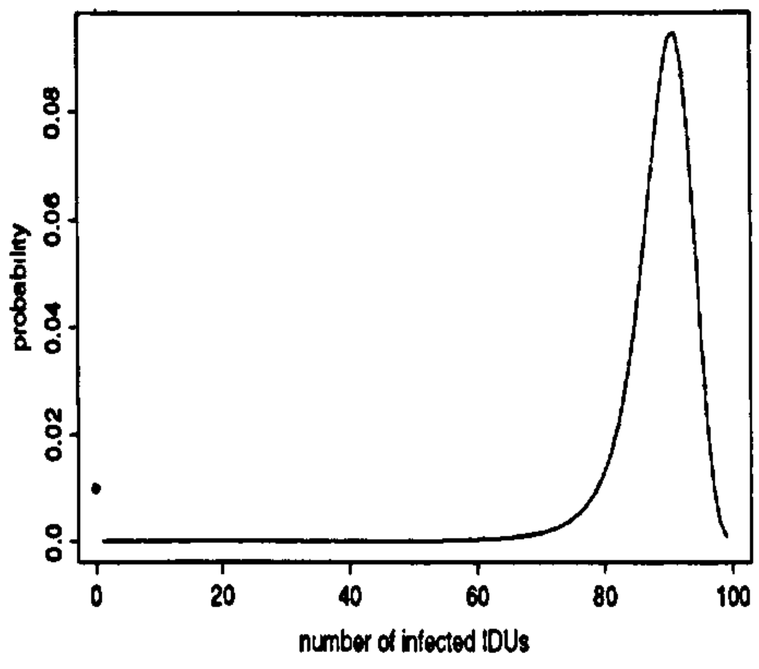

Figure 3.15: Exact Distribution of the number of infected IDUs at time $t = 1$ year.

in the spread of the disease the shape of the distribution is more symmetric apart from the discrete element at zero, as shown in Figures 3.14 and 3.15.

3.5 Extinction of Stochastic Process

3.5.1 Naive Probability of Extinction

As can be seen from Figure 3.11, after a long period of time the bulk of the probability is centered on the cell of the matrix which corresponds to 10 infected needles and 97 infected IDUs. It is also apparent that $P_{0,0}(t)$ is greater than zero. From Figure 3.16 which is a plot of $P_{0,0}(t)$ against time t we can see that for this choice of parameters that $P_{0,0}(t)$ appears to rapidly approach a limit at approximately 0.01. It may possibly be appropriate to describe the probability that the disease dies out, or the probability of extinction, as tending to a limit at 0.01, however a more rigorous analysis reveals that this is not so.

As the epidemic can be thought of as a Markov process, we need to examine the criteria for such an equilibrium value to exist. Consider the embedded Markov Chain associated with this Markov process. (0,0) is clearly an absorbing state

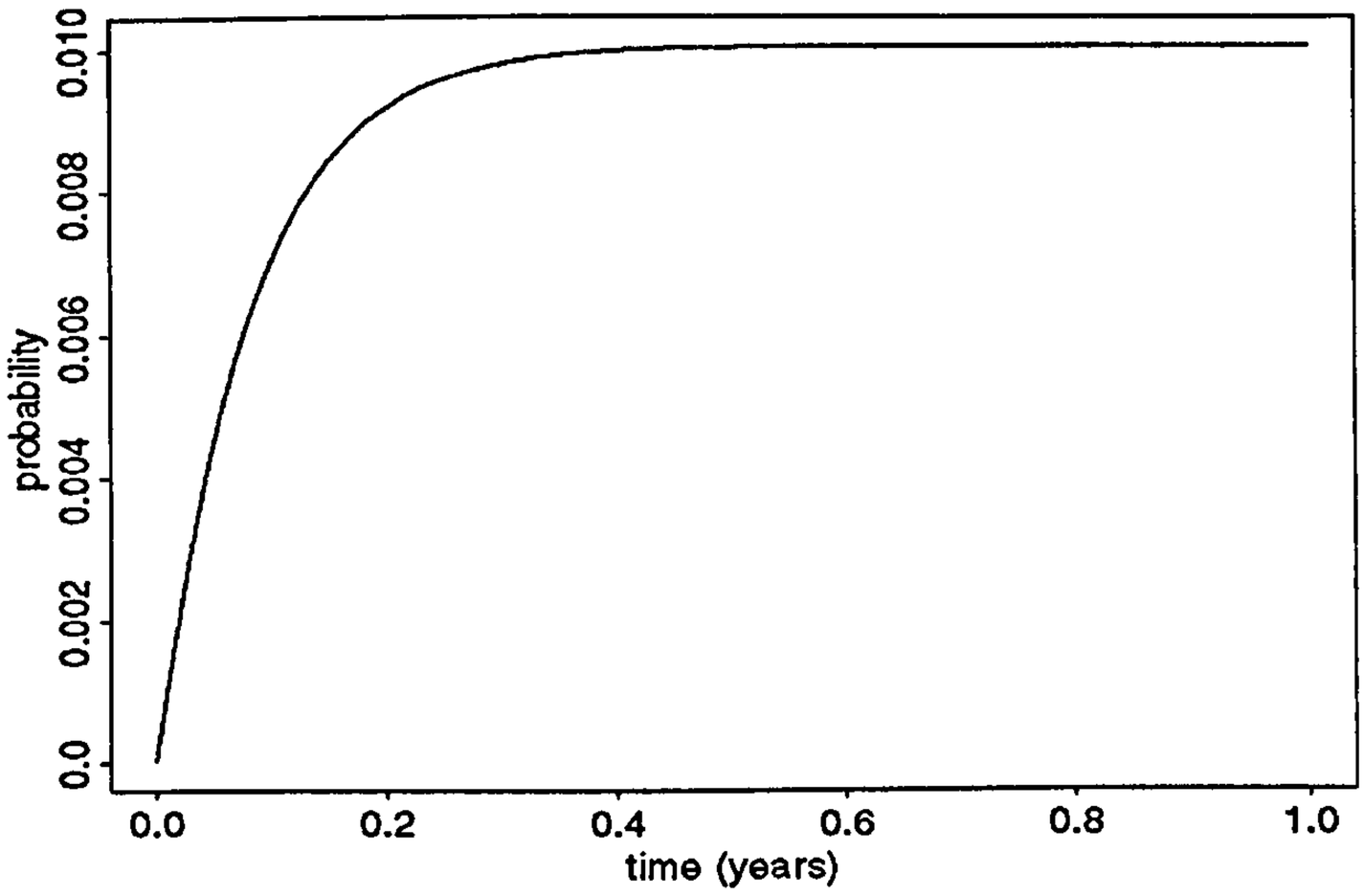

Figure 3.16: $P_{0,0}(t)$ against time t.

and it is clear that (0,0) is reachable from any other state in the (finite) embedded Markov Chain. Hence by standard results on Markov Chains it is straightforward to show that ultimately absorption in this state is certain, that is eventually the number of infected IDUs and the number of infected needles will both be zero. However from calculating $P_{0,0}(t)$ by numerical iteration of Equation 3.7 as to simulate the spread of the disease over a time period of 100 years, the probability of extinction after this time period is still approximately 0.01. We can therefore claim that over a relevant time interval to our problem it may be sensible to define a **quasi**-extinction probability for this choice of parameters. This is the probability that the process has become extinct within a biologically realistic period of time, typically shorter than the expected time to extinction.

3.6 Expected Time to Extinction

We can adapt Equation 3.7 in order to find the expected number of events until extinction occurs and the expected time to extinction. We denote by t_{ij} the expected number of events to extinction given that the initial number of infected

needles is i and the initial number of infected IDUs is j. If we consider the first move away from the starting point, for example moving from (i,j) to $(i+1,j)$ then the expected number of events until extinction occurs starting from $(i+1,j)$ would be $t_{i+1,j}$. If, as before, we denote $B_1(i,j)$ as the rate of transition from state (i,j) to state $(i+1,j)$ we can define $B_1'(i,j) = B_1(i,j)/R(i,j)$ as the probability that the next event is a needle becoming infected. We define the quantities $B_2'(i,j)$, $D_1'(i,j)$, $D_2'(i,j)$ and $M'(i,j)$ similarly. Considering all possible moves we have

$$t_{ij} = B_1'(i,j)(t_{i+1,j}+1) + D_1'(i,j)(t_{i-1,j}+1) + B_2'(i,j)(t_{i,j+1}+1)$$
$$+ D_2'(i,j)(t_{i,j-1}+1) + M'(i,j)(t_{i-1,j+1}+1),$$

or
$$t_{ij} = B_1'(i,j)t_{i+1,j} + D_1'(i,j)t_{i-1,j} + B_2'(i,j)t_{i,j+1} + D_2'(i,j)t_{i,j-1}$$
$$+ M'(i,j)t_{i-1,j+1} + 1 \tag{3.8}$$

as $B_1' + D_1' + B_2' + D_2' + M' = 1$. Clearly $t_{00} = 0$.

We can solve this by attaching starting values to t_{ij} for all $0 \leq i \leq n$ and $0 \leq j \leq N$ and solving the iterative form

$$t_{ij}^{(m+1)} = B_1'(i,j)t_{i+1,j}^{(m)} + D_1'(i,j)t_{i-1,j}^{(m)}$$
$$+ B_2'(i,j)t_{i,j+1}^{(m)} + D_2'(i,j)t_{i,j-1}^{(m)}$$
$$+ M'(i,j)t_{i-1,j+1}^{(m)} + 1 \tag{3.9}$$

for $m = 0, 1, 2\ldots$.

We can also convert this equation into one that gives us the expected time to extinction T_{ij}. As the expected time between two events will be $1/R$

$$T_{ij}^{(m+1)} = B_1'(i,j)T_{i+1,j}^{(m)} + D_1'(i,j)T_{i-1,j}^{(m)}$$
$$+ B_2'(i,j)T_{i,j+1}^{(m)} + D_2'(i,j)T_{i,j-1}^{(m)}$$
$$+ M'(i,j)T_{i-1,j+1}^{(m)} + 1/R. \tag{3.10}$$

We can similarly solve this equation iteratively using a modified version of the program which evaluated $P_{x,y}(t)$ which was discussed in Section 3.4. Again the problem of the boundary conditions is solved due to the values of the rates $B_1'(i,j)$, $B_2'(i,j)$, $D_1'(i,j)$, $D_2'(i,j)$ and $M'(i,j)$ becoming zero on the relevant boundary. In this program we need to decide a criterion for the deciding when the iterative procedure has converged. In this example it was decided that convergence has occurred if the maximum $T_{ij}^{(m+1)} - T_{ij}^{(m)}$ over all i, j is less than some small number. This small number was arbritrarily taken to be 0.001 in the following example.

To explore T_{ij} for various parameter values, let us look first at a choice of parameters where R_0 is close to 1, therefore T_{ij} would be expected to be small. We alter the parameters suggested by Kaplan, making $\lambda = 5.952 \times 10^{-3}$ visits per hour, $\mu = 5 \times 10^{-4}$ deaths per hour, $\alpha = 0.05$ and $\theta = 0.5$, which results in $R_0 = 1.18$. Figure 3.17 plots the values of T_{ij} for the above parameter values after the iterative process was judged to have converged. Again we describe a population of 100 IDUs choosing from 10 needles. We can see from this that the expected time to extinctions are quite large. Looking at the extinction times for

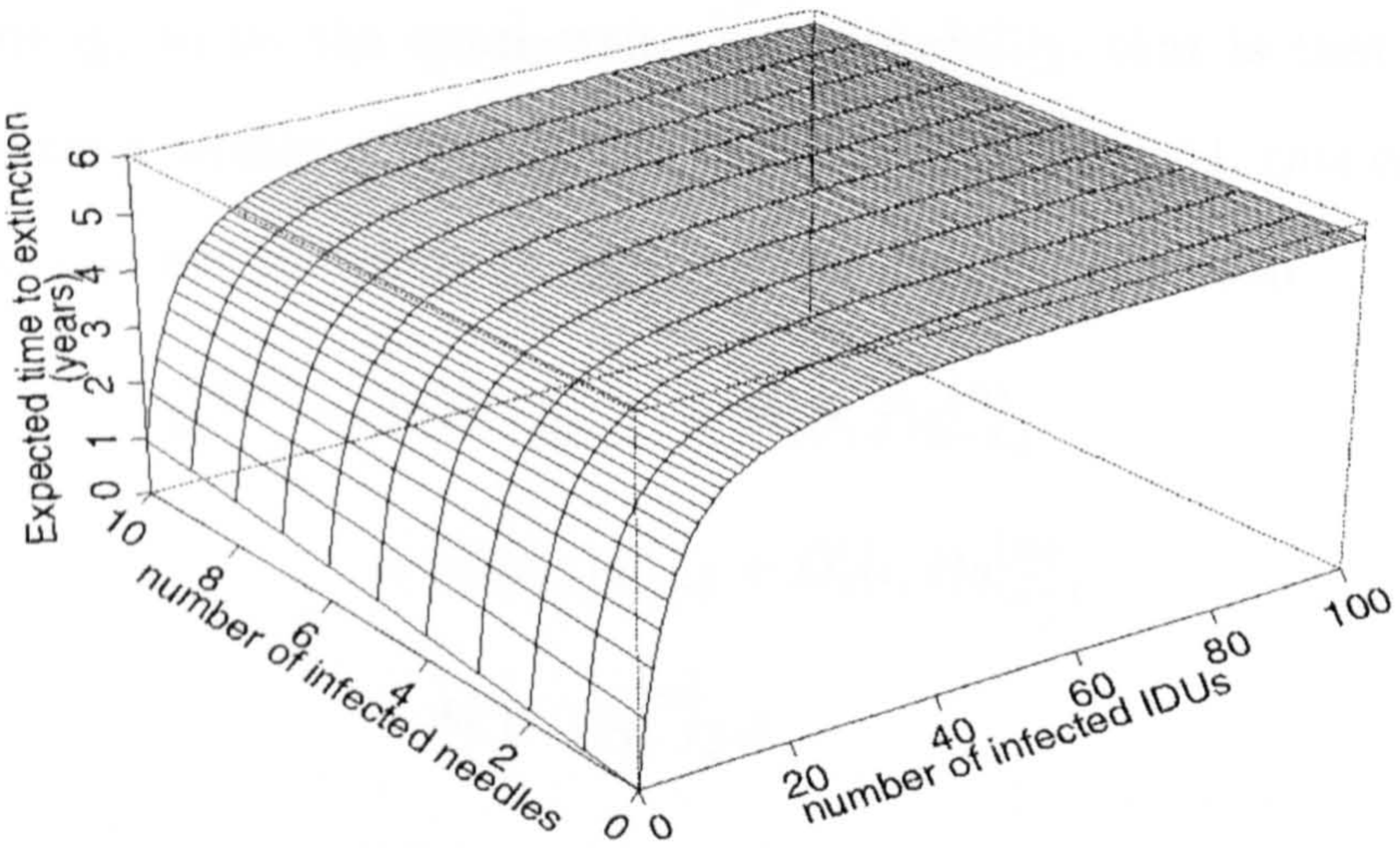

Figure 3.17: Converged values of T_{ij} when $\lambda = 5.952 \times 10^{-3}$ visits per hour, $\mu = 5 \times 10^{-4}$ deaths per hour, $\alpha = 0.05$ and $\theta = 0.5$.

$j = 1$ infected IDUs we see that T_{ij} ranges from 9,500 to 15,165 hours, 395 to 631 days, for $1 \leq i \leq n$. On substituting more realistic parameter values, which will in turn increase R_0, the iterative process does not appear to converge in a reasonable time scale. This can be demonstrated by looking at the values of $T_{0,1}$, the expected time to extinction when there is one infected IDU and no infected needles. The iterative process has not converged when $T_{0,1}$ reaches 1,000 years, which suggests that $T_{0,1}$ is very large. Although $P_{0,1}(t) \simeq 0.01$ for $0 < t < 100$ years, or in other words, the probability of extinction in a reasonable time interval is 0.01, it is the expected time to extinction that we are evaluating. In the majority of realisations, the number of infected IDUs approaches the deterministic equilibrium, and from then the time to extinction would be extremely large. This should be reflected in the magnitude of $T_{0,1}$. From this we can assume that, for realistic parameter values, the expected time to extinction is of large enough magnitude that we are justified in defining a quasi-equilibrium probability and a quasi-probability of extinction.

3.6.1 Quasi-Extinction Probability

If we define q_{ij} to be the quasi-extinction probability, that is that the process becomes extinct within a 'biologically realistic' time interval, this can be found in a similar manner to before by applying the iterative equation

$$\begin{aligned} q_{ij}^{(m+1)} = {} & B_1'(i,j)q_{i+1,j}^{(m)} + D_1'(i,j)q_{i-1,j}^{(m)} \\ & + B_2'(i,j)q_{i,j+1}^{(m)} + D_2'(i,j)q_{i,j-1}^{(m)} \\ & + M'(i,j)q_{i-1,j+1}^{(m)} \end{aligned}$$

The only true solution to this iterative process is $q_{i,j} = 1$ for $0 \leq i \leq n, 0 \leq j \leq N$, as $q_{ij}^{(m+1)} \geq q_{ij}^{(m)}$ for all i, j. However on using $q_{ij} = 1$ for $i = 0$ and $j = 0$ and $q_{ij} = 0$ otherwise as initial values for the iteration, the iterative process

apparently approaches a limit. For the parameter values suggested by Kaplan discussed in Chapter 2 we have Figure 3.18, which shows $q^*_{ij} = q^{(m+1)}_{ij}$ when the maximum difference $|q^{(m+1)}_{ij} - q^{(m)}_{ij}| < 10^{-12}$. We can see from this that the

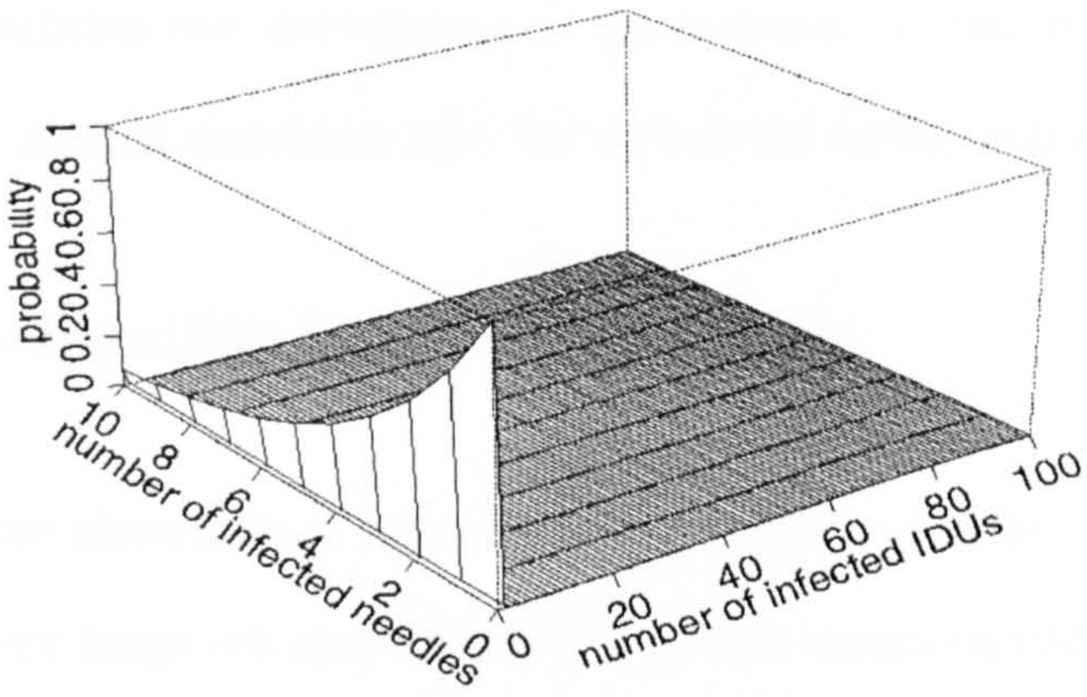

Figure 3.18: q^*_{ij} for parameter values as discussed in Chapter 2.

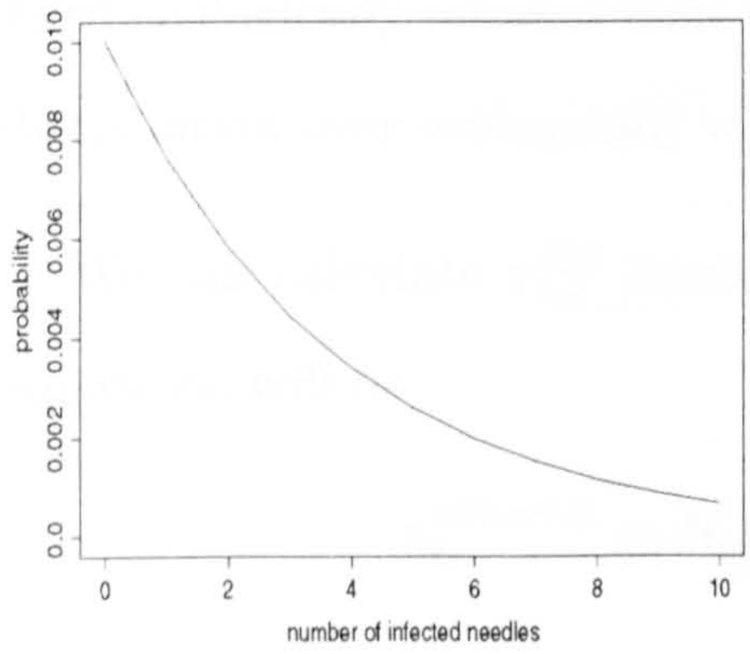

Figure 3.19: q^*_{ij}, $j = 1$.

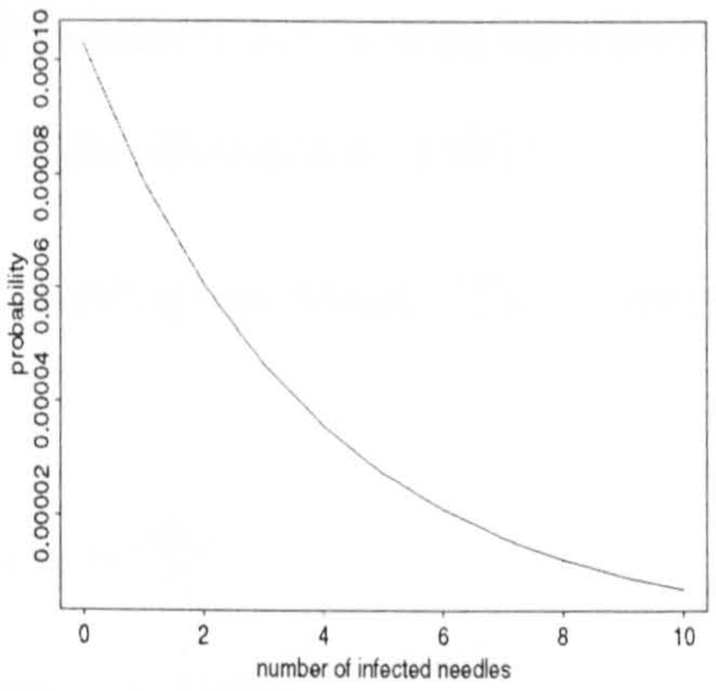

Figure 3.20: q^*_{ij}, $j = 2$.

quasi-probability of extinction only appears to be non-negligible when there is initially only one infected IDU. On plotting q^*_{1j} for $0 \leq i \leq n$ for $j = 1$ and for $j = 2$ as in Figures 3.19 and 3.20 we see that when $j = 1$ the quasi-extinction probability when there is one infected IDU and no infected needles is just greater

than 0.01 with the quasi-extinction probabilities for 1 or more infected needles in decreasing magnitude almost reaching zero for an initial value of ten infected needles, and the quasi-extinction probability when there are two infected IDUs and no infected needles slightly greater than 0.0001. For this case the quasi-extinction probabilities are decreasing in magnitude as the number of infected needles increases, almost reaching zero for an initial value of ten infected needles.

3.6.2 Quasi-Equilibrium Probabilities

Given that we have shown that for sensible parameter values, the expected time to extinction is very large we can define $\pi_{x,y}^{(Q)}$ as the quasi-equilibrium probability. A precise definition for this will be

$$\pi_{x,y}^{(Q)} = \lim_{M\to\infty} \{(1/M) \times \text{ number of realizations containing}$$

$$\text{exactly } x > 0 \text{ needles and } y > 0 \text{ IDUs}\}.$$

Here the limit is taken over a large number M of realisations of the epidemic at a fixed ecologically relevant time T. Therefore $\pi_{x,y}^{(Q)}$ is effectively a true equilibrium distribution over ecologically relevant periods of time (Renshaw, 1991).

We can calculate $\pi_{x,y}^{(Q)}$ iteratively as in the preceding sections. The iterative equations will be

$$\begin{aligned}\pi_{ij}^{(Q)(n+1)} = {} & B_1'(i,j)\pi_{i+1,j}^{(Q)(n)} + D_1'(i,j)\pi_{i-1,j}^{(Q)(n)} \\ & + B_2'(i,j)\pi_{i,j+1}^{(Q)(n)} + D_2'(i,j)\pi_{i,j-1}^{(Q)(n)} \\ & + M'(i,j)\pi_{i-1,j+1}^{(Q)(n)}\end{aligned}$$

and we can see that solving these equations for the parameter values suggested by Kaplan, that the three dimensional plot of $\pi_{ij}^{(Q)}$, as shown in Figure 3.21 is similar to that of Figure 3.11, $P_{ij}(t)$ for $t = 10,000$ hours.

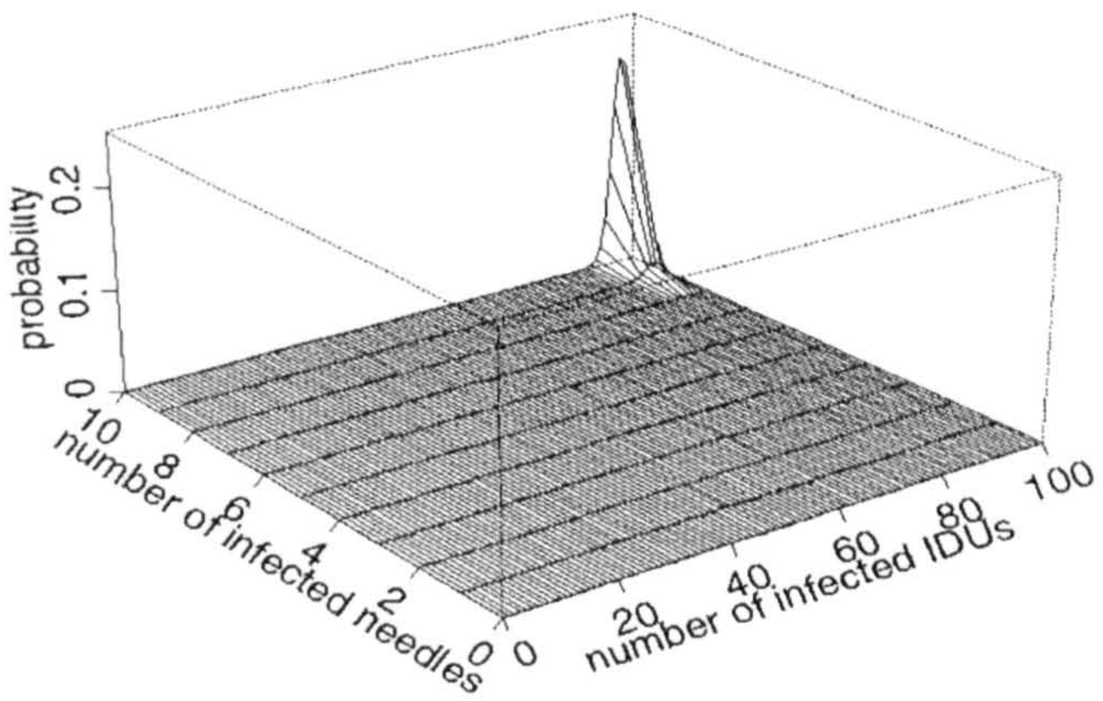

Figure 3.21: $\pi_{ij}^{(Q)}$. Parameter values as discussed in Chapter 2.

3.7 Summary

To summarise, we have shown that even in this most basic of systems, a tractable analytical stochastic model may not exist. However we have a stochastic simulation model and a numerical solution to the analytical stochastic model which can both be compared to Kaplan's deterministic model. In using the stochastic model we have to work with many realisations before definitive conclusions can be drawn and any stochastic mean of the process should be accompanied by a measure of the variation.

We have also shown that this stochastic model has the properties of a Markov model, with the particular property that eventually the disease will die out. The expected time until the disease dies out has been evaluated for different parameter values, and as this expected time is very large, we are justified into defining quasi-equilibrium probabilities. We show that the quasi-equilibrium probabililities are similar to those found in both the stochastic simulation model and the deterministic model. We now have a building block from which we can develop

more sophisticated models which will more realistically mirror the spread of HIV amongst IDUs.

Chapter 4

Biologically Relevant Models

4.1 Introduction

In this chapter we shall continue to study the spread of HIV among a homogeneously mixing population of IDUs who visit shooting galleries. Some of the assumptions previously used such as needles remaining infectious until they are flushed by an uninfected IDU are explored and adapted, creating more biologically relevant, but still homogeneous, models.

4.2 Compartmental Models

The previous models only describe the proportion of the IDU population that is infected with HIV. If we introduce the population size dynamics we then need at least two categories with which to describe IDUs, infected or susceptible. Infection with HIV and the progression to AIDS can be more realistically modelled by introducing more categories. Peterson *et al.* (1990) stratify the IDU population by various stages of the disease into six compartments, as shown in Figure 4.1 and use this as a framework for their simulation models. Kaplan's initial deterministic model in which the population size is held constant can be thought of as a simplification of Peterson's in that the Acute Infection, Asymptomatic,

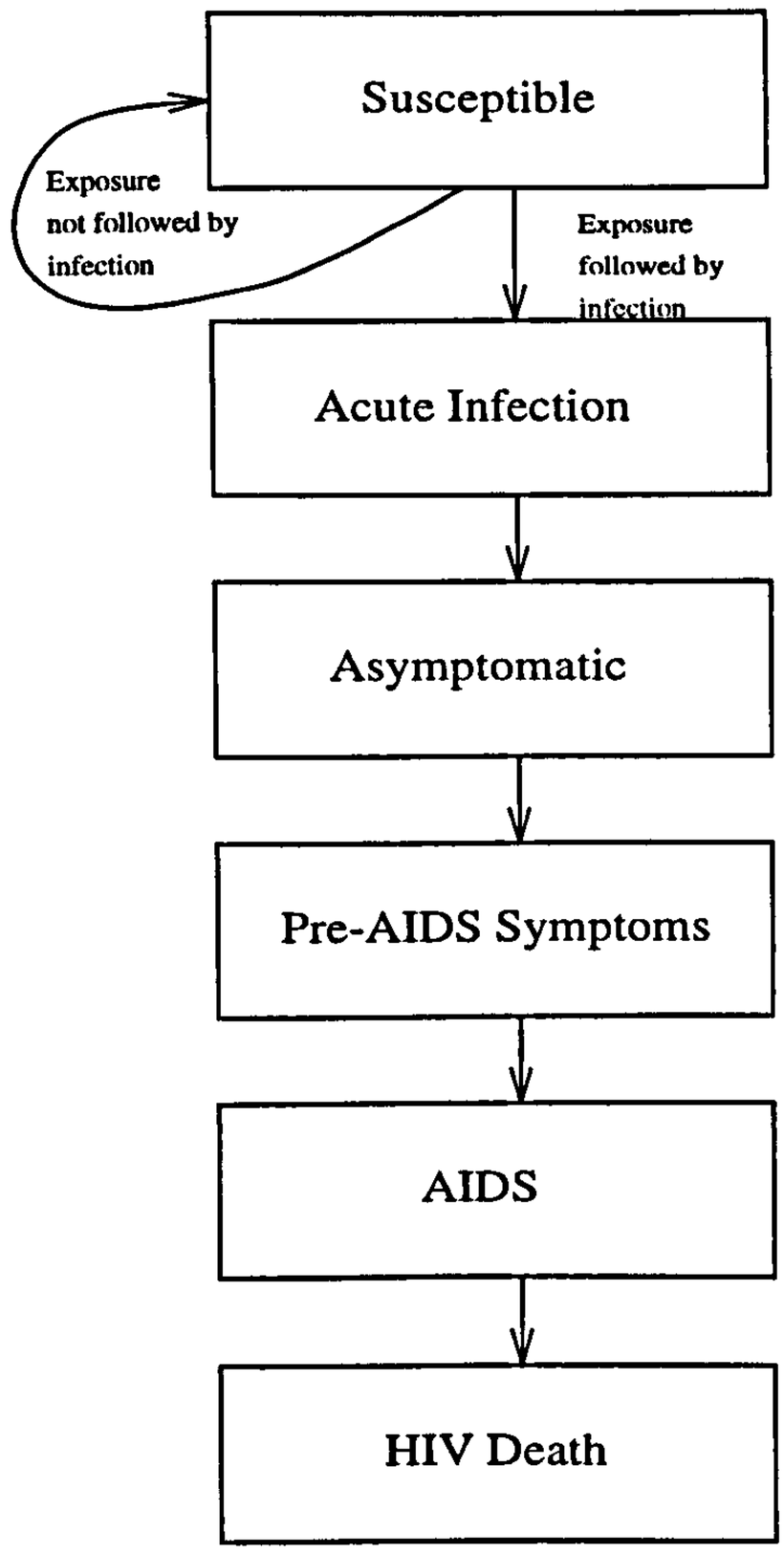

Figure 4.1: Compartments used by Peterson *et al.* to describe the stages of HIV/AIDS. Adapted from Peterson *et al.* (1990).

Pre-AIDS, AIDS and Death compartments are collapsed into a single infected compartment and death is not included. With these six compartments it is now possible to attach different parameters for IDUs in different stages of the infection. For example the visiting rate λ may be different for IDUs in the different compartments. Returning to the model with only two compartments, susceptible and infective, we can adapt our model to include different visiting rates for susceptibles and infectives.

If we assume that susceptible IDUs visit shooting galleries at rate λ_1 and infected IDUs visit at rate λ_2 then we can reformulate the deterministic model to be

$$\frac{\mathrm{d}\beta(t)}{\mathrm{d}t} = \lambda_2\gamma\pi[1-\beta(t)] - \lambda_1\gamma(1-\pi(t))\theta\beta(t)$$

and
$$\frac{\mathrm{d}\pi(t)}{\mathrm{d}t} = (1-\pi(t))\lambda_2\beta(t)\alpha - \pi(t)\mu. \tag{4.1}$$

which can be re-expressed in terms of i and I;

$$\frac{\mathrm{d}i(t)}{\mathrm{d}t} = \lambda_2\left(1-\frac{i(t)}{n}\right)I(t) - \lambda_1\theta\frac{i(t)}{n}(N-I(t))$$

and
$$\frac{\mathrm{d}I(t)}{\mathrm{d}t} = (N-I(t))\frac{\lambda_1 i(t)\alpha}{n} - \mu I(t). \tag{4.2}$$

This assumes that there are only two classes of IDU; susceptible and infected. It would be much more realistic to assume that there will be three classes; susceptible, as before but two classes for the infected IDUs, those who know that they are infected, and therefore may alter their sharing rate, and those who are infected but do not know, and therefore their sharing rate would be similar to that of a susceptible IDU (Rhodes *et al.*, 1993). If we assume that pI infected IDUs know that they are infected and therefore $(1-p)I$ IDUs do not know that they are infected then Equations 2.1 and 2.2 will now be adapted to

$$\frac{\mathrm{d}i(t)}{\mathrm{d}t} = (\lambda_1(1-p)+\lambda_2 p)\left(1-\frac{i(t)}{n}\right)I(t) - \lambda_1\theta\frac{i(t)}{n}(N-I(t))$$

and
$$\frac{\mathrm{d}I(t)}{\mathrm{d}t} = (N-I(t))\frac{\lambda_1 i(t)\alpha}{n} - \mu I(t). \tag{4.3}$$

We can also adapt the assumption that only susceptible IDUs can flush an infected needle. If we now assume that a susceptible IDU flushes an infected needle with probability θ_1 and an infected IDU flushes an infected needle with probability θ_2 then Equations 2.1 and 2.2 will now be further adapted to

$$\frac{\mathrm{d}i(t)}{\mathrm{d}t} = (\lambda_1(1-p)+\lambda_2 p)\left(1-\frac{i(t)}{n}\right)I(t) - \lambda_1\theta_1\frac{i(t)}{n}(N-I(t))$$
$$-(\lambda_1(1-p)+\lambda_2 p)\theta_2\frac{i(t)}{n}I(t)$$

and
$$\frac{\mathrm{d}I(t)}{\mathrm{d}t} = (N-I(t))\frac{\lambda_1 i(t)\alpha}{n} - \mu I(t). \tag{4.4}$$

From Figures 4.2 and 4.3 we can see the effect that p and λ_2 have on the spread

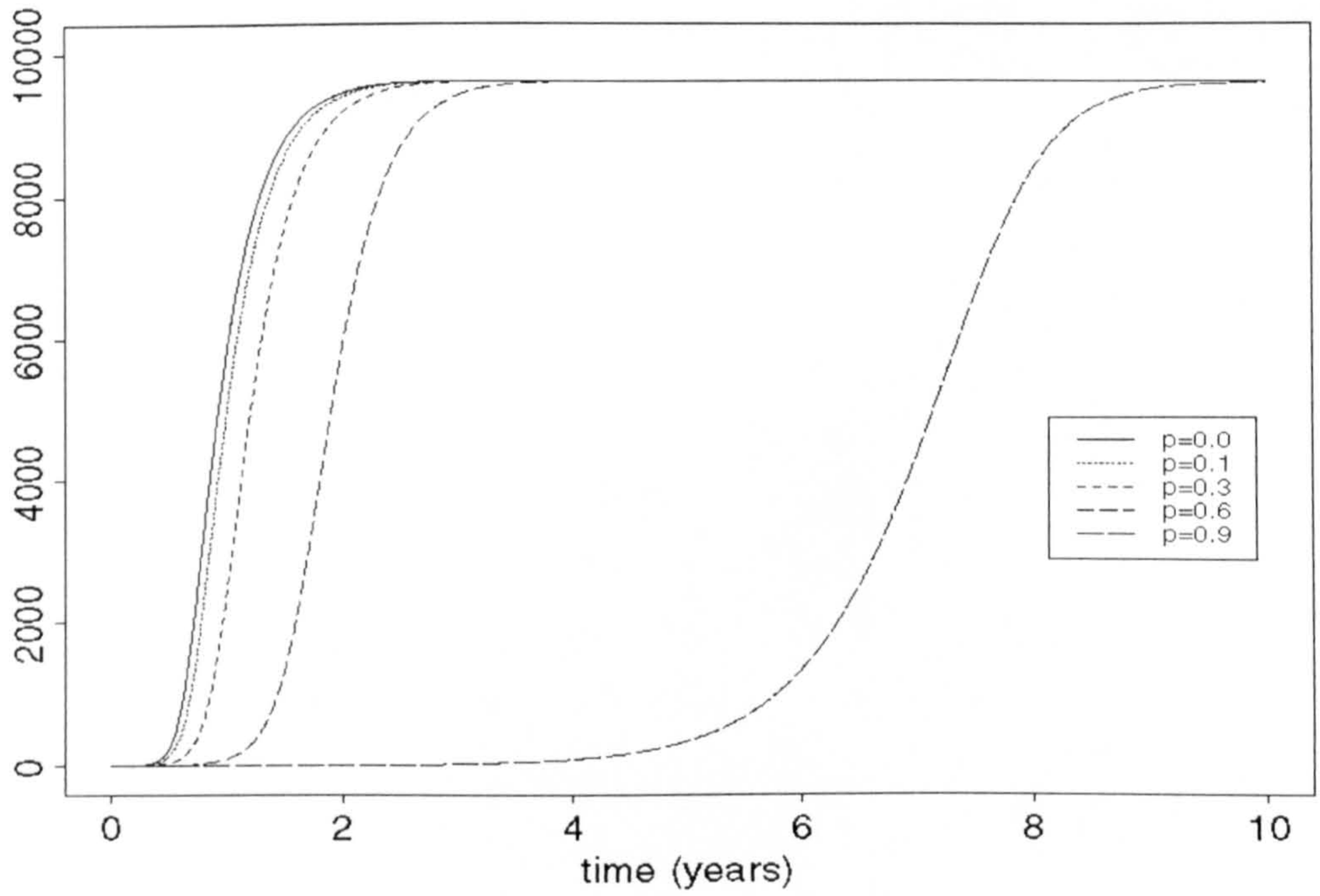

Figure 4.2: The number of IDUs infected over time, using Equations 4.4 to describe the spread of the disease with different values of p when $\lambda_2 = 0$. See text for remaining parameter values.

of the disease. These figures assume that an IDU visits shooting galleries and shares injecting equipment on average once a week, and that an infected IDU continues to share injecting equipment for an average 8 years after infection. We therefore have $\lambda_1 = 5.952 \times 10^{-3}$ visits per hour and $\mu = 1.43 \times 10^{-5}$ deaths per hour. As before, $\alpha = 0.075$, $\theta_1 = 0.25$, $\theta_2 = 0$, the size of the IDU population will be $N = 10,000$, these IDUs choosing at random from $n = 1,000$ needles. As introduction of one infective into the susceptible population triggers the spread of the disease, we have that $\pi(0) = I(0)/N = 0.0001$.

In Figure 4.2 we assume that $\lambda_2 = 0$, that is that when IDUs know that they are infected they cease injecting. When $p = 0$, this model is identical to that described by Equations 2.1 and 2.2 where none of the infected IDUs know that they are infected. On increasing p we see that the disease spreads more slowly throughout the population, when $p = 0.9$ we see that it takes at least seven years

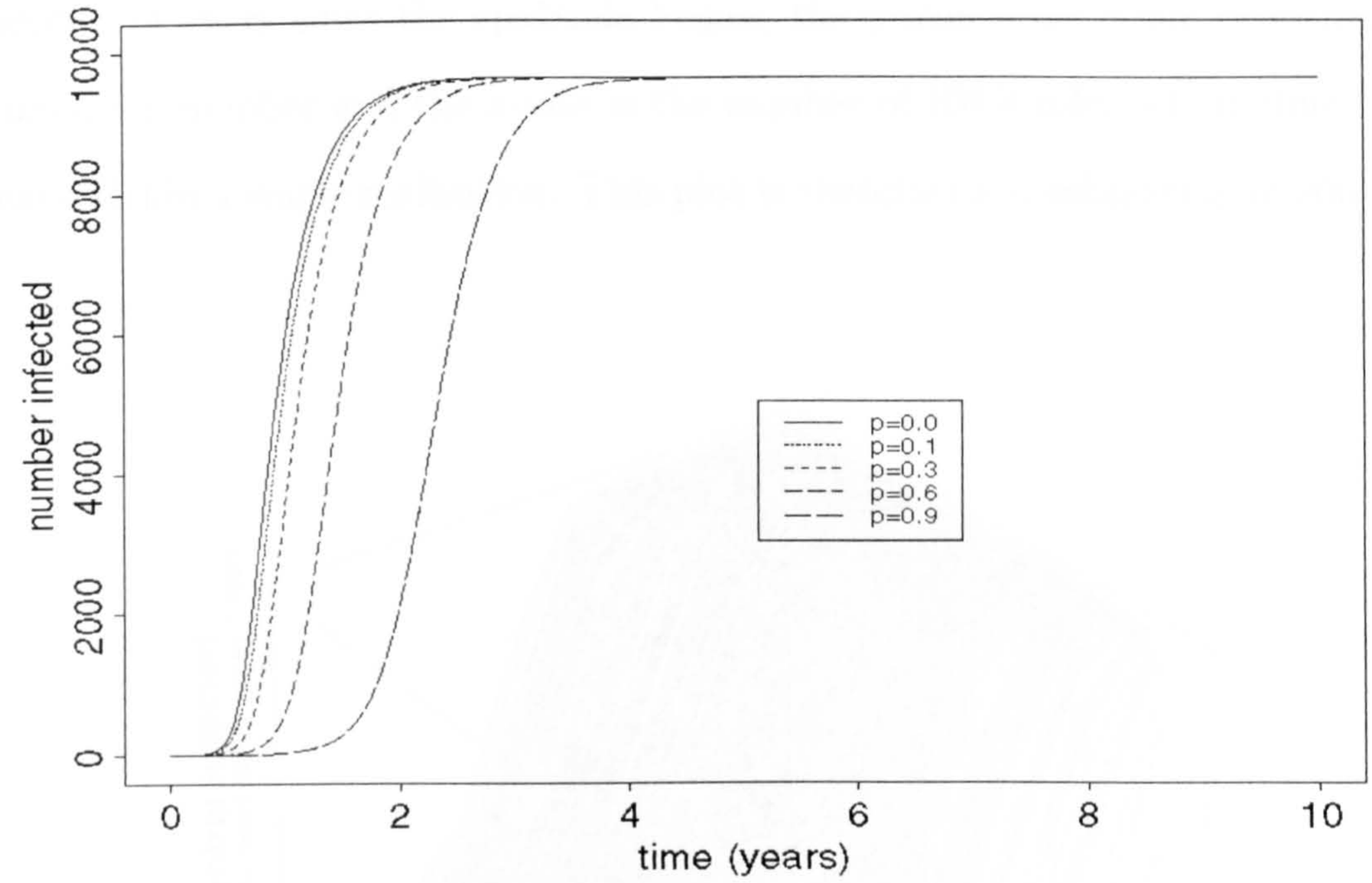

Figure 4.3: The number of IDUs infected over time, using Equation 4.4 to describe the spread of the disease with different values of p when $\lambda_2 = 1.49 \times 10^{-2}$ visits per hour. See text for remaining parameter values.

before half of the population become infected. We can also see this effect in Figure 4.3, where IDUs who now know that they are infected only share injecting equipment on average once a month. Although the endemic equilibrium value does not depend on λ_2 or p, when none of the IDUs know that they are infected, so that $p = 0$, the initial spread of the disease is faster.

However when a stochastic simulation model is created which mirrors the deterministic model, we see a difference between the stochastic and deterministic models. When the disease spreads slowly in the deterministic model, the probability that the disease dies out in the corresponding stochastic model increases. This can be demonstrated by exploring 200 stochastic simulations using the parameters as in Figure 4.2 with $p = 0.9$, that is that 90% of infected IDUs know that they are infected and that IDUs who know that they are infected cease injecting. To summarise the results from these simulations, we can present a 3

dimensional plot, as shown in Figure 4.4, where the x-axis corresponds to the number of years since the epidemic began, the y-axis is an index denoting the simulation number and the z-axis is the number of IDUs infected, at time $t = x$ years within a single realisation. This plot is therefore a combination of 200 time

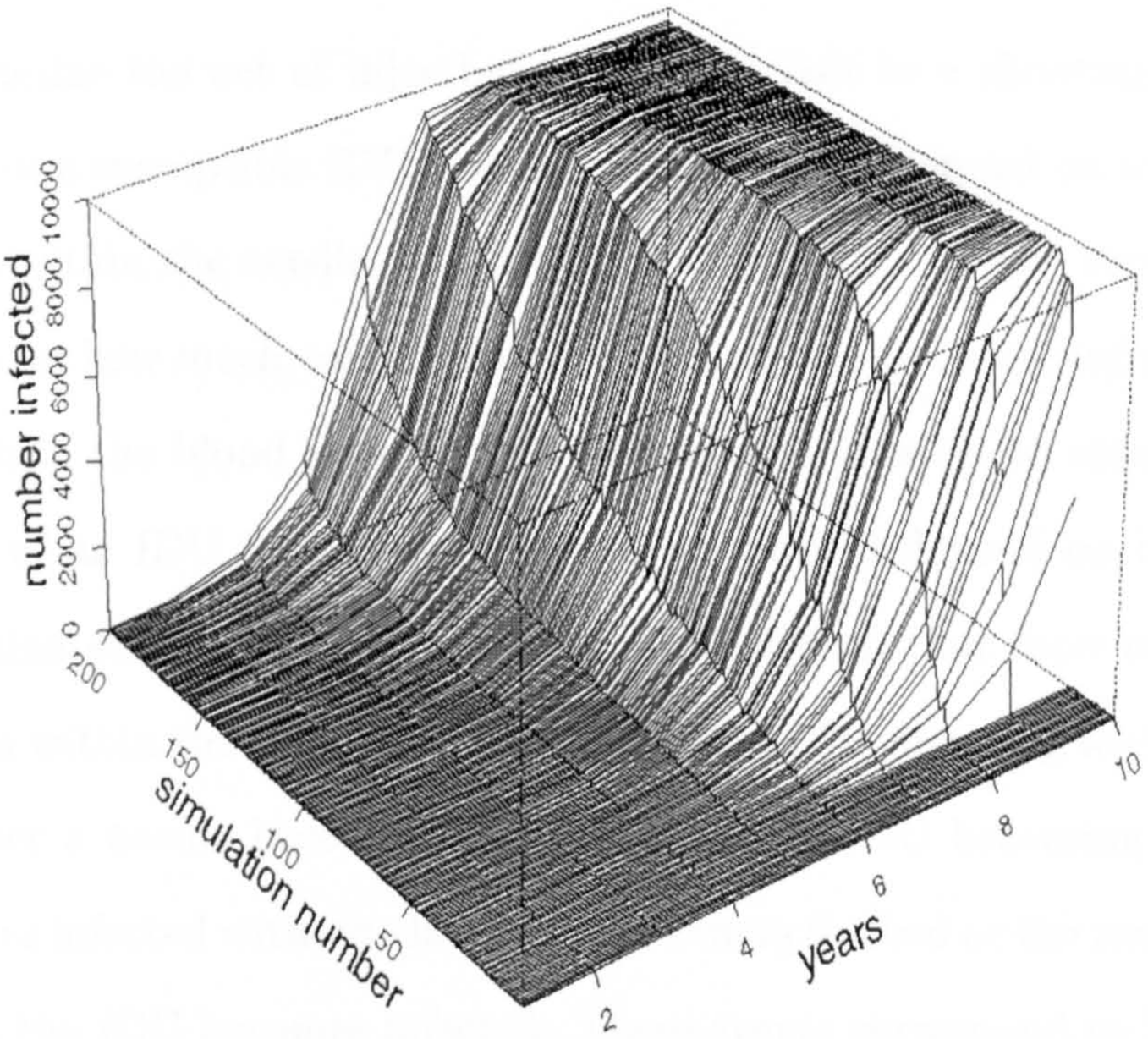

Figure 4.4: The results from 200 realisations of a stochastic simulation model, with transmission dynamics similar to the deterministic model described by Equations 4.4.

series plots, and for clarity, the simulation results are sorted by the number of infected IDUs after 5 years. We note from this that some simulations result in the disease dying out, and out of the 200 simulations there were 19 in which there were no infected IDUs after 10 years, that is the disease will die out within 10 years with approximate probability 0.1.

4.3 Flushing and Infection

Returning to the deterministic model first proposed by Kaplan, we can now examine the flushing process further. Within the act of a single IDU injecting with one needle, the needle may be flushed and the IDU may become infected. This is incorporated in Equations 2.1 and 2.2.

If we examine the act of injecting within one visit to a shooting gallery, the probability of a susceptible IDU becoming infected will depend on the infectivity of the virus within the needle, which will be discussed in a later section but will also depend on how much contaminated blood previously contained in the needle is injected into the blood stream. It would also be sensible to assume that the probability of an IDU flushing an infected needle will depend on how much of this contaminated material has been injected. It is clear that three related events may happen within the single act of an uninfected IDU injecting with an infected needle, either a needle becomes flushed without an IDU becoming infected, an IDU becomes infected without the needle becoming flushed or the needle becomes flushed and the IDU becomes infected. These events correspond to Equation 3.1 in the analytical stochastic model.

For clarity, suppose that a single susceptible IDU injects once with an infected needle. Let P_1 be the probability that the needle becomes flushed and the IDU becomes infected, let P_2 be the probability that the needle becomes flushed but the IDU remains uninfected and let P_3 be the probability that the IDU becomes infected without the needle being flushed. In a similar fashion to the numerical solution to the stochastic model we wish to attach a probability that the 'null' event happens, that is with probability P_4 we have that the uninfected IDU remains uninfected, and the needle remains infected. We can now describe the spread of the disease with the equations

$$\frac{\mathrm{d}i(t)}{\mathrm{d}t} = \lambda\left(1 - \frac{i(t)}{n}\right)I(t) - \lambda(P_1 + P_2)\frac{i(t)}{n}(N - I(t))$$

and
$$\frac{\mathrm{d}I(t)}{\mathrm{d}t} = (N - I(t))\lambda\frac{i(t)}{n}(P_1 + P_3) - I(t)\mu. \tag{4.5}$$

We can now consider the case where α and θ are in some way related. If we suppose that both α and θ are related to the amount of infective material in the blood, which we will assume at the moment depends only on the amount of blood in the needle, then we can contrast two possible scenarios.

If the needle contains a large amount of blood then it is assumed that α, the probability of infection, will be large as there will be a large amount of infectious material injected into the IDU. We also assume that under this scenario, θ, the probability that the needle is rendered uninfectious, is small, as when there is a lot of infectious material in the needle the act of injecting will be less likely to remove all such material.

Under the alternative scenario, such that the needle contains a small amount of blood, then α will be small as there may not be enough infectious material present in the needle to result in a new infection and θ will be large as it will be more likely that using the needle will render it uninfectious.

We can summarise these two scenarios by creating an equation describing a possible relationship between α and θ. If we produce a graph with α as the x-axis and θ as the y-axis, then we can plot the point $(\alpha = 0.075, \theta = 0.25)$. We can also create a hypothetical point, $(\alpha = 0, \theta = 1)$, which describes an extreme version of scenario 2 above, where there is so little blood left in the needle that infection very unlikely, and that when the needle is re-used, it will almost certainly be rendered uninfectious. Thus we have two points, and, in the absence of any data, we can assume that there is a linear relationship between α and θ. A straight line which goes through these two points will have the equation $\theta = 1 - 10\alpha$, which is valid for $0 \leq \alpha \leq 0.1$. This line is plotted in Figure 4.5 below. Thus we can

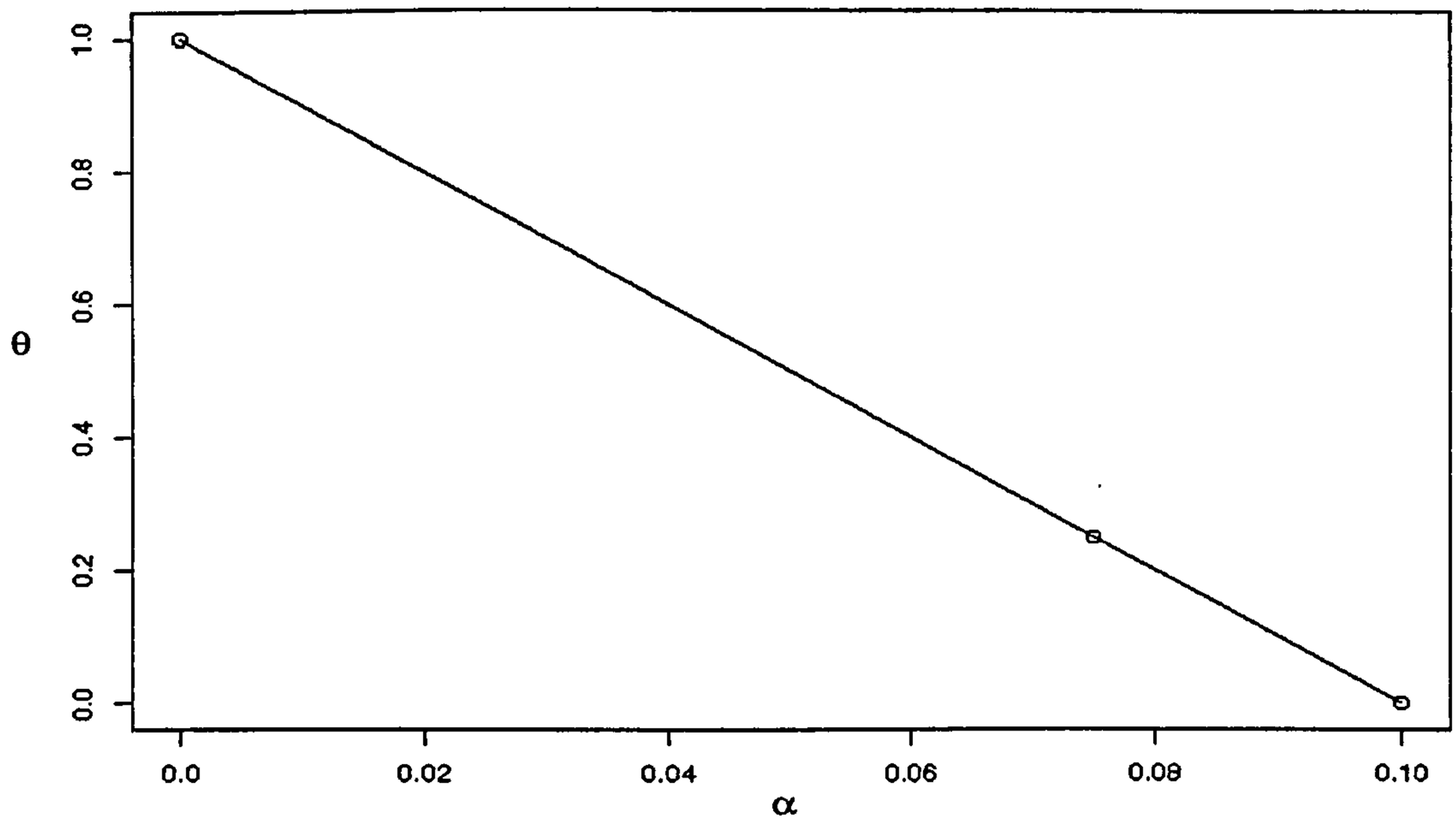

Figure 4.5: Plot of α against θ.

explore the effect that the amount of blood in the needle has on the probabilities P_1, P_2, P_3 and P_4, described in Table 4.1, and thus the spread of the virus. In Figure 4.6, we present the results using the deterministic model presented above when using different values for α. Using the relationship $\theta = 1 - 10\alpha$, and varying α from 0 to 0.1, we can plot the proportion of the population that will be infected after intervals of one year. From Figure 4.6 we can see that when $\alpha = 0$, that is when the amount of blood in the needle is so small that infection becomes practically impossible, then the disease dies out. We also see that if the amount of blood left in the needle increases, that is α increases and θ decreases, then the disease spreads quicker. We also note that this differs from the case when α varies independently from θ, this is due to the combined effect of θ decreasing and α increasing, both of which factors result in the disease spreading more rapidly.

We can also look at R_0, the basic reproductive number which is now given by $R_0 = \dfrac{\lambda(P_1 + P_3)}{\mu(P_1 + P_2)}$. The steady state values will be $I^* = 0$ and $i^* = 0$ or

α	θ	P_1	P_2	P_3	P_4
0.00	1.0	0.000	1.000	0.000	0.000
0.01	0.9	0.009	0.891	0.001	0.099
0.02	0.8	0.016	0.784	0.004	0.196
0.03	0.7	0.021	0.679	0.009	0.291
0.04	0.6	0.024	0.567	0.016	0.384
0.05	0.5	0.025	0.475	0.025	0.475
0.06	0.4	0.024	0.376	0.036	0.564
0.07	0.3	0.021	0.279	0.049	0.651
0.08	0.2	0.016	0.184	0.064	0.736
0.09	0.1	0.009	0.091	0.081	0.819
0.10	0.0	0.000	0.000	0.100	0.900

Table 4.1: The effect that varying α, and hence θ, has on the probabilities P_1, P_2, P_3 and P_4.

$$i^* = n\frac{\lambda(P_1+P_3)-\mu(P_1+P_2)}{\lambda(P_1+P_3)}$$

and

$$I^* = N\frac{\lambda(P_1+P_3)-\mu(P_1+P_2)}{\lambda(P_1+P_3)-\mu(P_1+P_2)+\mu}. \tag{4.6}$$

The first equilibrium is always possible, the second is possible only when $R_0 \geq 1$.

The preceding discussion has, in part, introduced sensitivity analysis, in that it describes the spread of the disease when a combination of parameters vary. We will perform more in depth sensitivity analyses in a later chapter.

4.4 The Cleaning of Needles

In exploring the circumstances in which a needle can lose its infectivity, Kaplan (1989) considers the case where there is both flushing by uninfected IDUs and cleaning by both uninfected and infected IDUs. Let ξ be the probability that a needle is effectively cleaned by an IDU, Equations 2.1 and 2.2 can now be reformulated as

$$\frac{\mathrm{d}i(t)}{\mathrm{d}t} = \lambda(1-\xi)I(t) - \lambda\frac{i(t)}{n}[N-(N-I(t))(1-\theta)(1-\xi)]$$

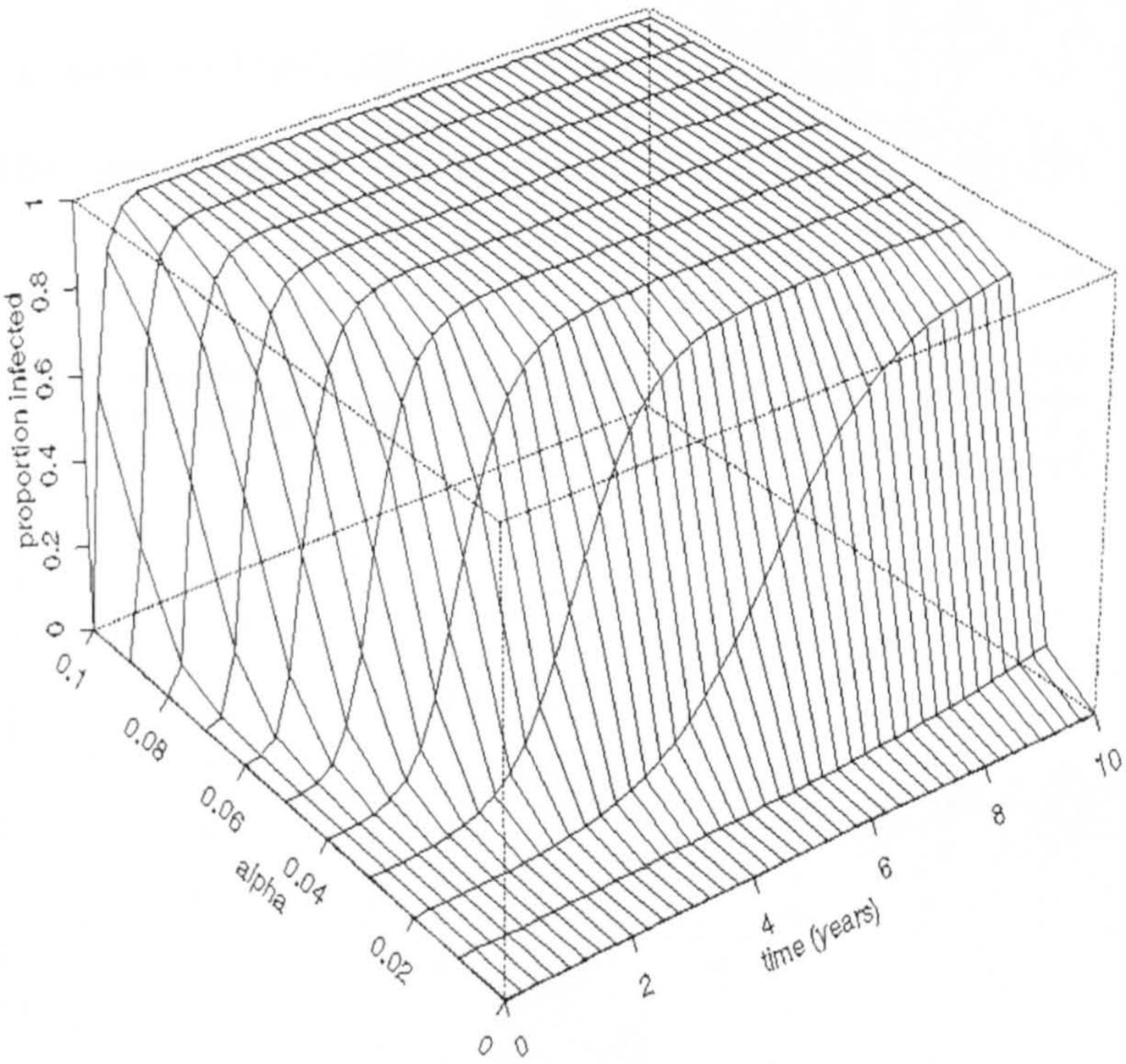

Figure 4.6: The number of IDUs infected over time, using Equations 4.5 to describe the spread of the disease. $P_1 = \alpha\theta$, $P_2 = (1-\alpha)\theta$, $P_3 = \alpha(1-\theta)$ and $\theta = 1 - 10\alpha$, for different values of α.

$$\text{and} \qquad \frac{\mathrm{d}I(t)}{\mathrm{d}t} = (N - I(t))\lambda\frac{i(t)}{n}\alpha - I(t)\mu. \tag{4.7}$$

This assumes that the needle is cleaned after the IDU has used it. It would be more realistic to assume that the needle is cleaned before an IDU uses it. Greenhalgh and Hay (1997) incorporte this assumption and adapt Equations 4.7 to obtain Equations 4.8.

$$\frac{\mathrm{d}i(t)}{\mathrm{d}t} = \lambda I(t) - \lambda\frac{i(t)}{n}[N - (N - I(t))(1-\theta)(1-\xi)]$$

$$\text{and} \qquad \frac{\mathrm{d}I(t)}{\mathrm{d}t} = (N - I(t))\lambda(1-\xi)\frac{i(t)}{n}\alpha - I(t)\mu. \tag{4.8}$$

It is worth noting that the effect of cleaning the needle before injecting results in a change in the differential equation which describes the number of infected IDUs

at time t. However the values of $I(t)$ over time are the same whether Equations 4.7 or Equations 4.8 are employed. This will be due to the needle remaining infectious at a constant level between the two acts of IDUs injecting with it. This may not be the case if the needle loses its infectivity over time. Figure 4.7 shows

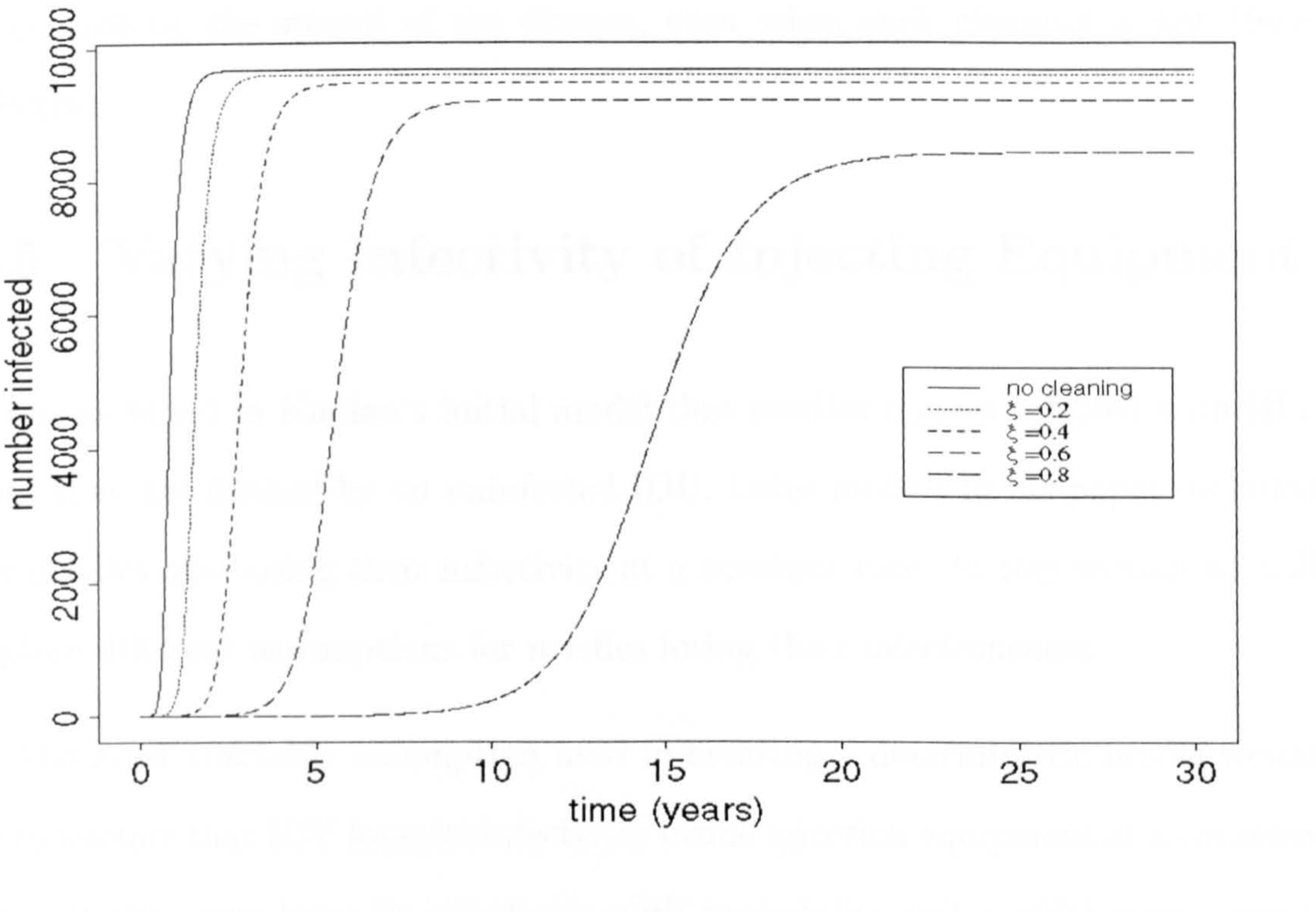

Figure 4.7: The number of IDUs infected over time, using Equation 4.7 to describe the spread of the disease.

the effect that varying ξ, the probability that the needle is effectively cleaned after use. We can see that as ξ increases, the rate at which the disease spreads decreases. Kaplan reformulates R_0 as $R_0(\xi)$ and shows that the relationship can be described as

$$R_0(\xi) = \frac{\lambda(1-\xi)\alpha}{(1-(1-\theta)(1-\xi))\mu}. \tag{4.9}$$

Thus $R_0(\xi)$ can be reduced below 1 if

$$\xi > 1 - \left[\frac{\lambda\alpha}{\mu} + 1 - \theta\right]^{-1}, \tag{4.10}$$

that is for the parameters used in Figure 4.8, if $\xi > 0.97$. We should note that

when $\xi = 0.8$ although the disease still spreads throughout the population the time that it takes for half the population to become infected is over 15 years. In a corresponding stochastic model with $\xi = 0.8$ the number of realisations where the disease dies out will be significant. This demonstrates that control strategies which encourage effective cleaning of injecting equipment may be successful in controlling the spread of the disease, even when such cleaning is not 100% effective.

4.5 Varying Infectivity of Injecting Equipment

It was assumed in Kaplan's initial model that needles remain infected with HIV until they are flushed by an uninfected IDU. Later models in his paper included the needles also losing their infectivity at a constant rate. In this section we will explore different assumptions for needles losing their infectiousness.

The most tractable assumption used in creating a deterministic model would be to assume that HIV loses its infectivity inside injection equipment at a constant rate. If the virus loses its infectivity with probability $\varphi\delta t + o(\delta t)$ over a small time interval of length δt the original equations can be reformulated as

$$\frac{\mathrm{d}i(t)}{\mathrm{d}t} = \lambda I(t) - \lambda\frac{i(t)}{n}\left[N + \frac{n\varphi}{\lambda} - (N - I(t))(1-\theta)\right]$$

and

$$\frac{\mathrm{d}I(t)}{\mathrm{d}t} = (N - I(t))\lambda\frac{i(t)}{n}\alpha - I(t)\mu. \tag{4.11}$$

This implies that a needle remains infectious on average for a time period equal to $1/\varphi$. This also implies that in the absence of needle being flushed and new needles becoming infected the number of infected needles decreases exponentially. The model also assumes that α, the probability that an IDU becomes infected given exposure to an infected needle, remains constant. This deterministic model can be numerically solved as in Figure 4.8, and R_0 is given by

$$R_0(\varphi) = \frac{\lambda\alpha}{\mu\left(\theta + \frac{n\varphi}{N\lambda}\right)}. \tag{4.12}$$

We can see from Figure 4.8 that when the term corresponding to needle losing

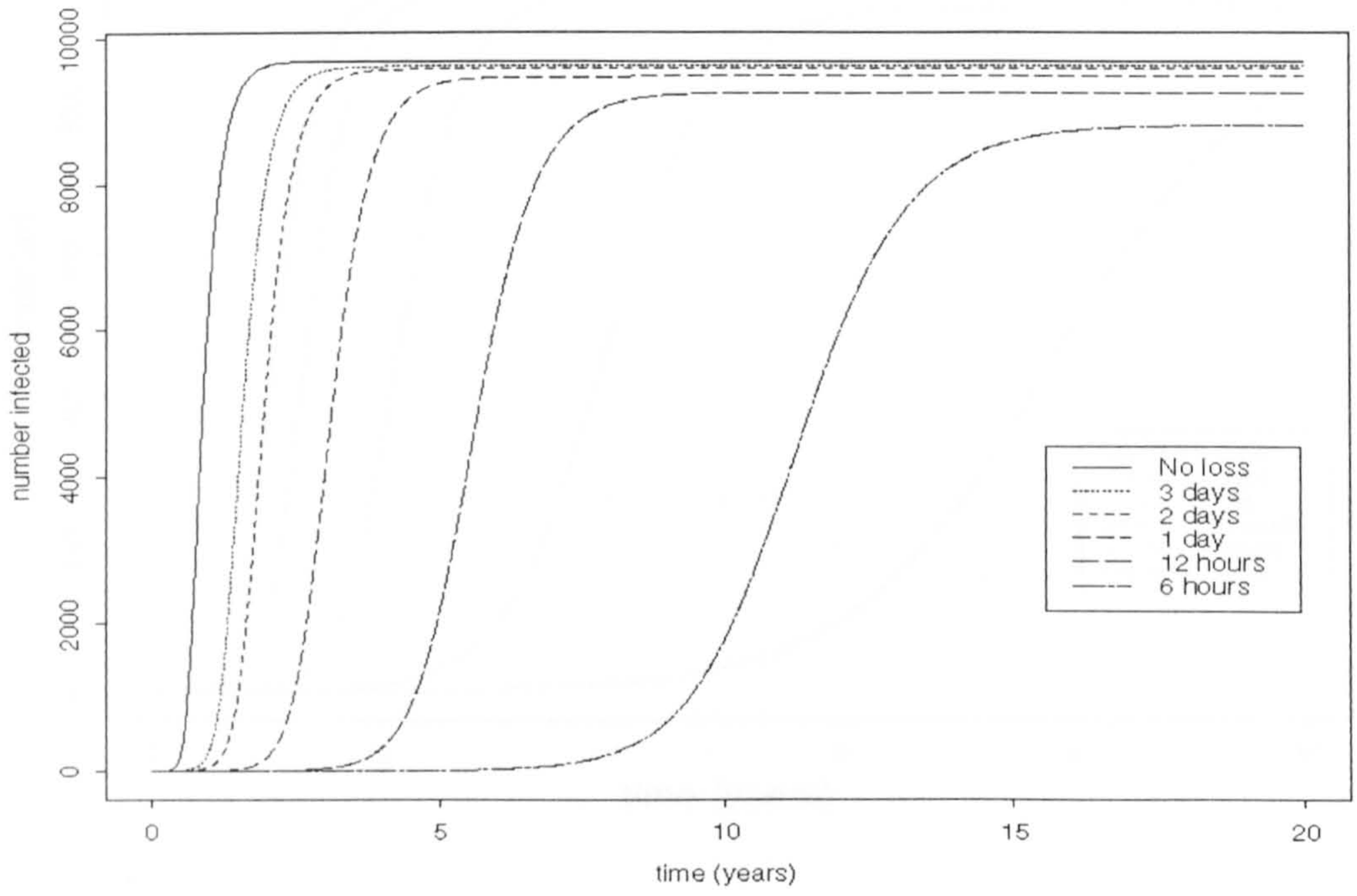

Figure 4.8: The number of IDUs infected over time, using Equation 4.19 to describe the spread of the disease, with different values for φ, ranging from $\varphi^{-1}=$ 6 hours to $\varphi^{-1}=$ 3 days.

its infectivity is introduced the disease spreads at a slower rate. If we assume that an infected needle remains infectious on average for six hours, without any external influences, then the disease will take as long as 12 years to infect 50% of the population. What is more interesting is that even when the needles remain infectious for average periods as long as three days, there is still a noticeable effect on the rate at which the disease spreads. We shall now explore the infectivity of an infectious needle further.

It is possible to assume a time delay in the term corresponding to the needle losing its infectivity. If we assume that a needle remains infectious for exactly τ hours we can model this quite simply with a stochastic simulation model. Figure

4.9 below demonstrates the results when it is assumed that a needle is infectious for a constant time period τ. This figure plots the median values, as described in

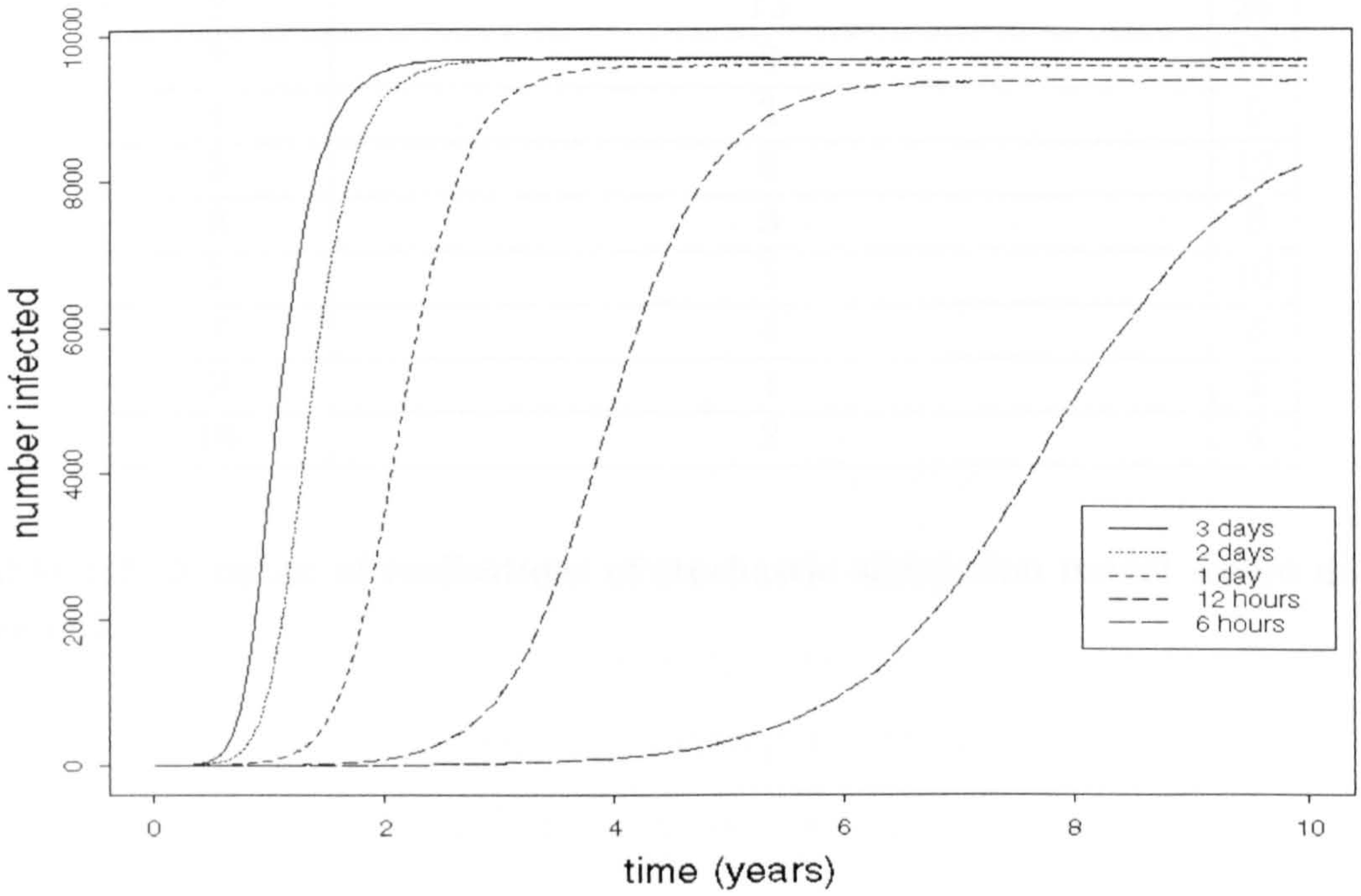

Figure 4.9: The median number of IDUs infected over time from 50 realisations of a stochastic simulation model in which an infected needle is infectious for a fixed time period τ, for different values of τ. Parameter values as discussed in Chapter 2.

Chapter 3, over 50 simulations. It is worth noting that by plotting the median values, we do not see that there are simulations where the disease dies out. Table 4.2 presents the number of realisations in which the disease dies out after 10 years, for various values of τ.

From Table 4.2, we see that when the needle is infectious for only one hour, almost half of the simulations resulted in the disease dying out. To examine this further, we can present the results from the 50 simulations in one 3-dimensional plot, as in Figure 4.10. In this plot, the x-axis is time, and the z-axis is the number infected at time $t = x$. For clarity, this plot is created after sorting the 50 realisations, indexed in the y-axis, by the number that were infected after 10

τ (hours)	Number of realisations where disease dies out	%
1	23	46
2	13	26
3	8	16
4	3	6
5	6	12
6	3	6
7	5	10
8	4	8
9	1	2
10	2	4

Table 4.2: Number of realisations of stochastic simulation model where disease dies out.

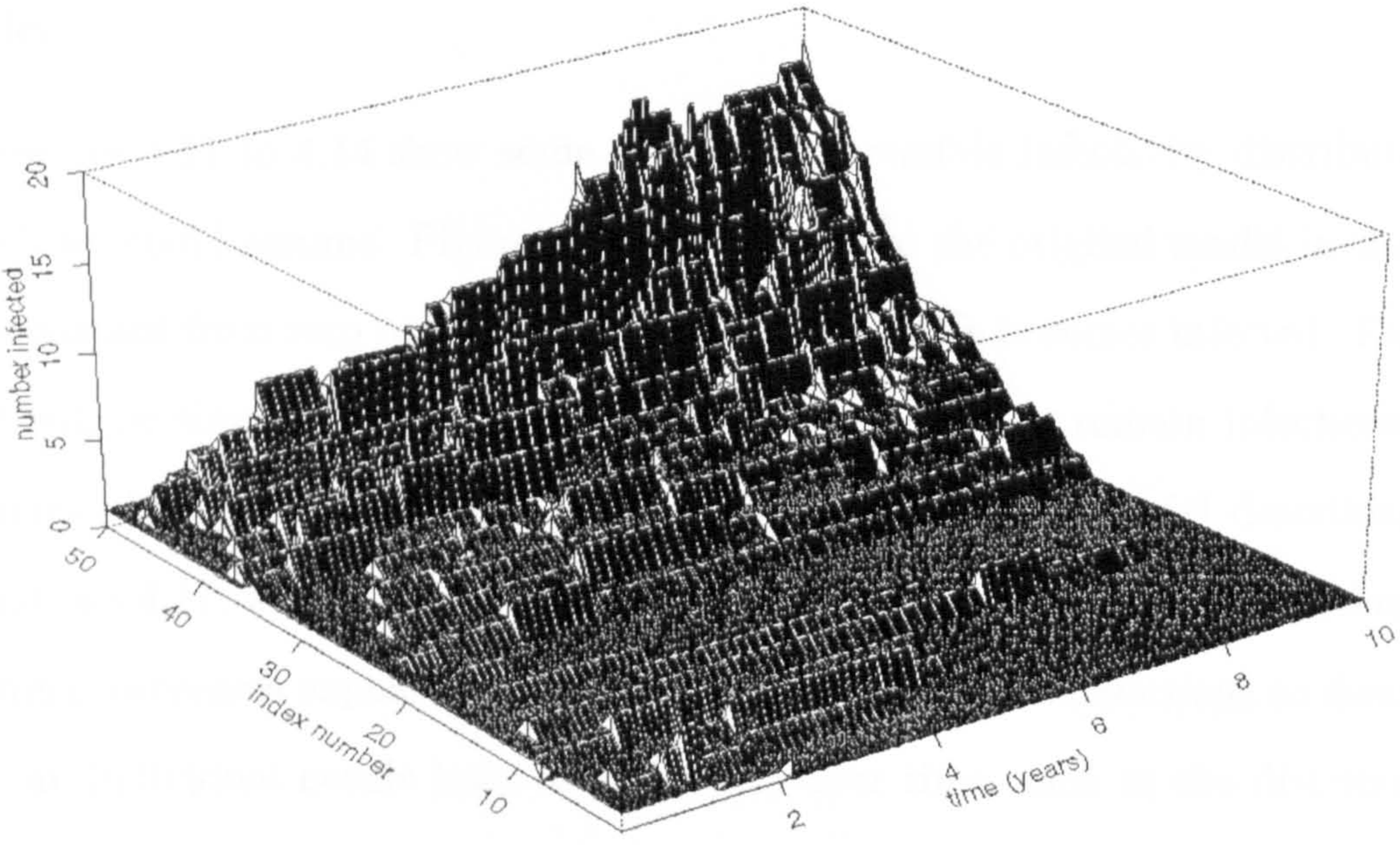

Figure 4.10: The results from 50 realisations of a stochastic simulation model, when the needle is infectious for one hour.

years. We then see that not only are there many realisations where the disease dies out, but there are also realisations where the number of infected people increased from one, and then still died out.

To explore the infectivity of the needles further, we must reconsider the infection process, described by the probability α. In the previous model, where α is a constant, we have the infectivity of needle as a Boolean variable, with β describing the proportion of such needles that are infected. If we now assume that the infectivity of needles is more than just a category such as present or absent, but an actual continuous variable, i.e. the infectivity of a needle can be measured (perhaps biologically by the strength of the virus or the amount of the virus in the needle) then it can be assumed that this infectiousness will decrease over time. This can be modelled by attaching the α variable to the infected needle and letting this take a distributional form. Different distributional forms for α can be created, and they can easily be incorporated into our stochastic simulation model.

Figures 4.11 to 4.14 show some examples of possible infectivity distributions which we could assume. Figure 4.11 corresponds to the original model in that α is a constant from zero to infinity hours after the needle becomes infected. Figure 4.12 will be similar to the stochastic model where needles remain infectious for τ hours after infection. Figure 4.13 will be similar to the model described by Equations 4.11, where the number of infected needles, free from new infections or flushing, decreases exponentially. We can also use other distributions to describe how an individual needle loses its infectivity over time, such as the distribution shown in Figure 4.14. Figure 4.15 compares the spread of the disease under two assumptions, firstly that a needle remains infectious for on average 3 days in the absence of flushing, with the infectivity decreasing as in Figure 4.13, and secondly that the needle remains infectious until it is flushed. We can see from

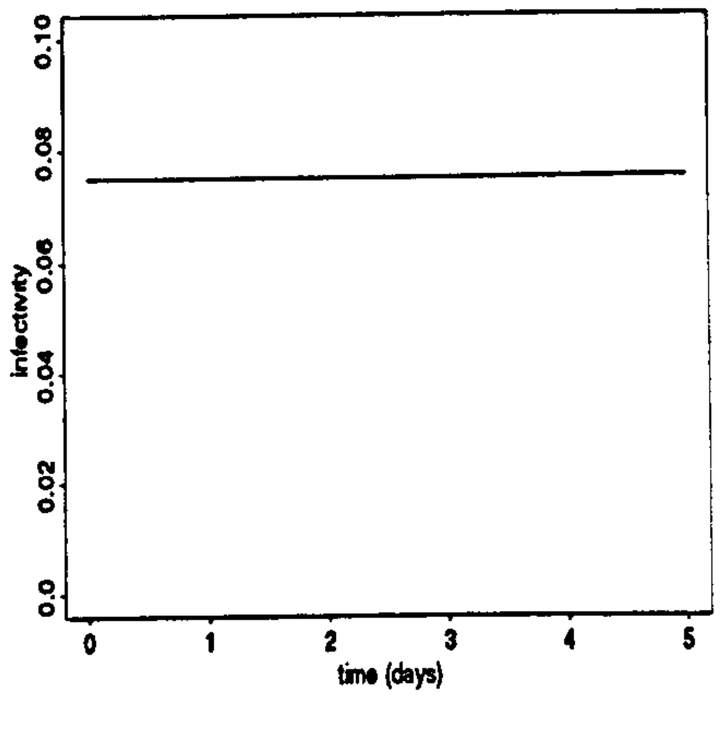

Figure 4.11: Constant infectivity.

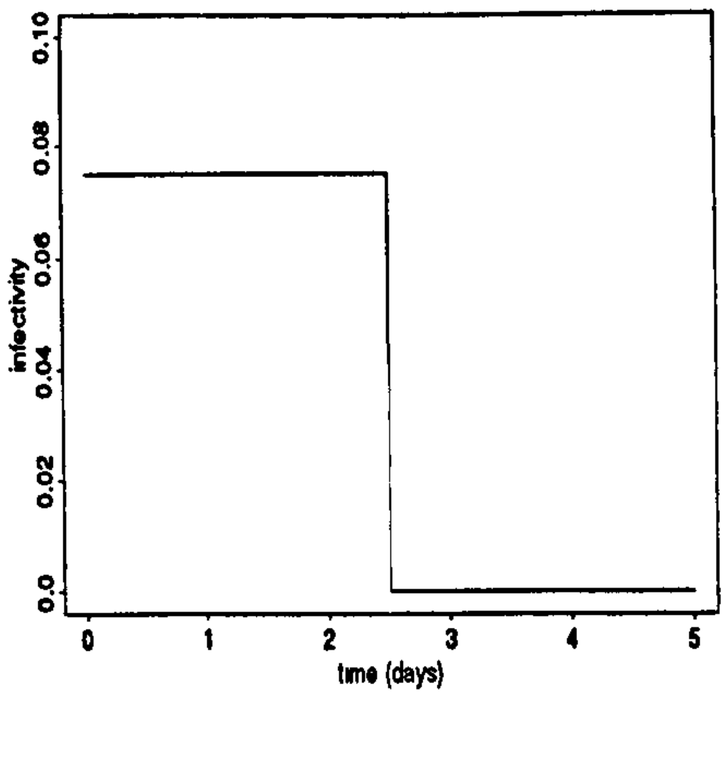

Figure 4.12: Constant infectivity for τ days then decreases to zero.

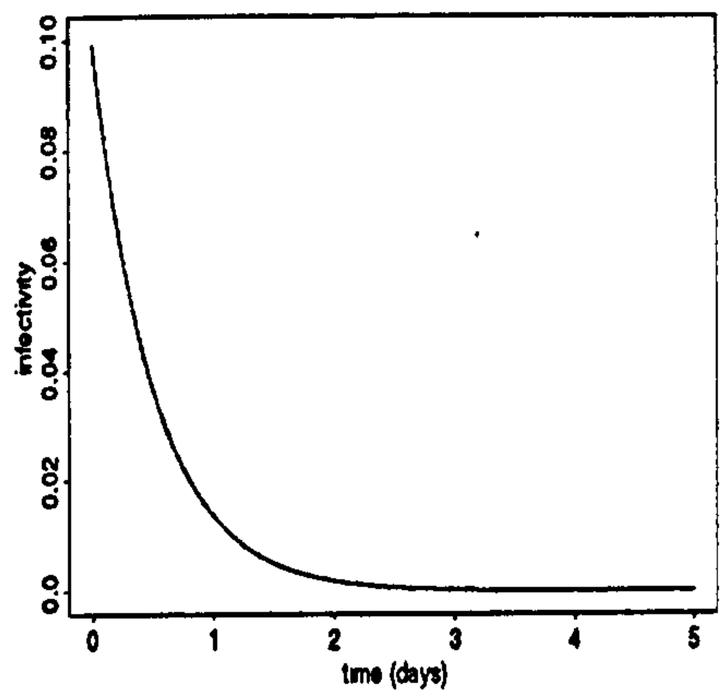

Figure 4.13: Exponential infectivity.

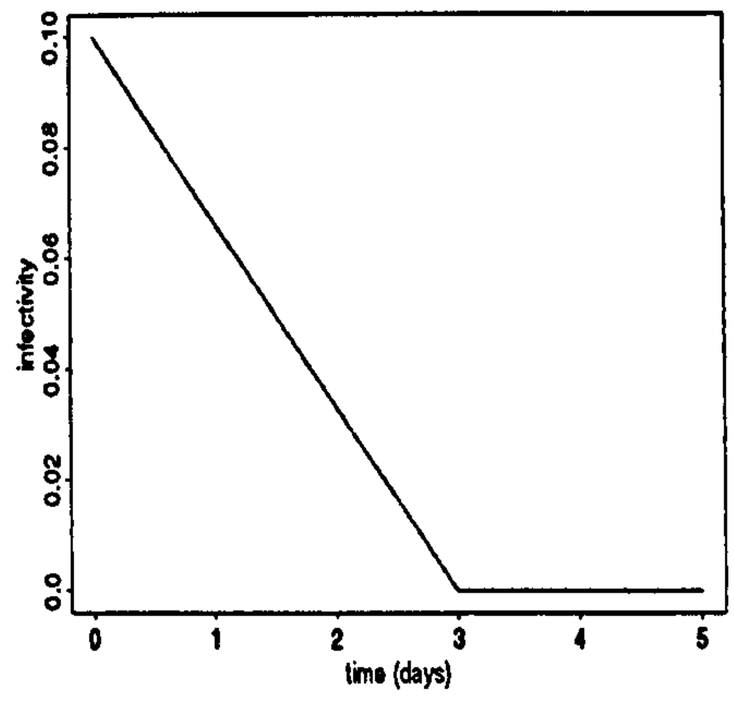

Figure 4.14: Simulated distributional form for the infectivity.

this figure that when the infectivity of the needle follows the distribution shown in Figure 4.14, the disease spreads at a slower rate and apparently reaches a lower equilibrium value.

We have already presented a scenario where both the probability of a susceptible IDU flushing an infectious needle and the probability of a susceptible IDU becoming infected when injecting with an infectious needle are related to the amount of virus left in the needle. In that model we assumed that the amount of virus present was related to the amount of blood in the needle. We now wish to alter this assumption so that the amount of virus in the needle will also be

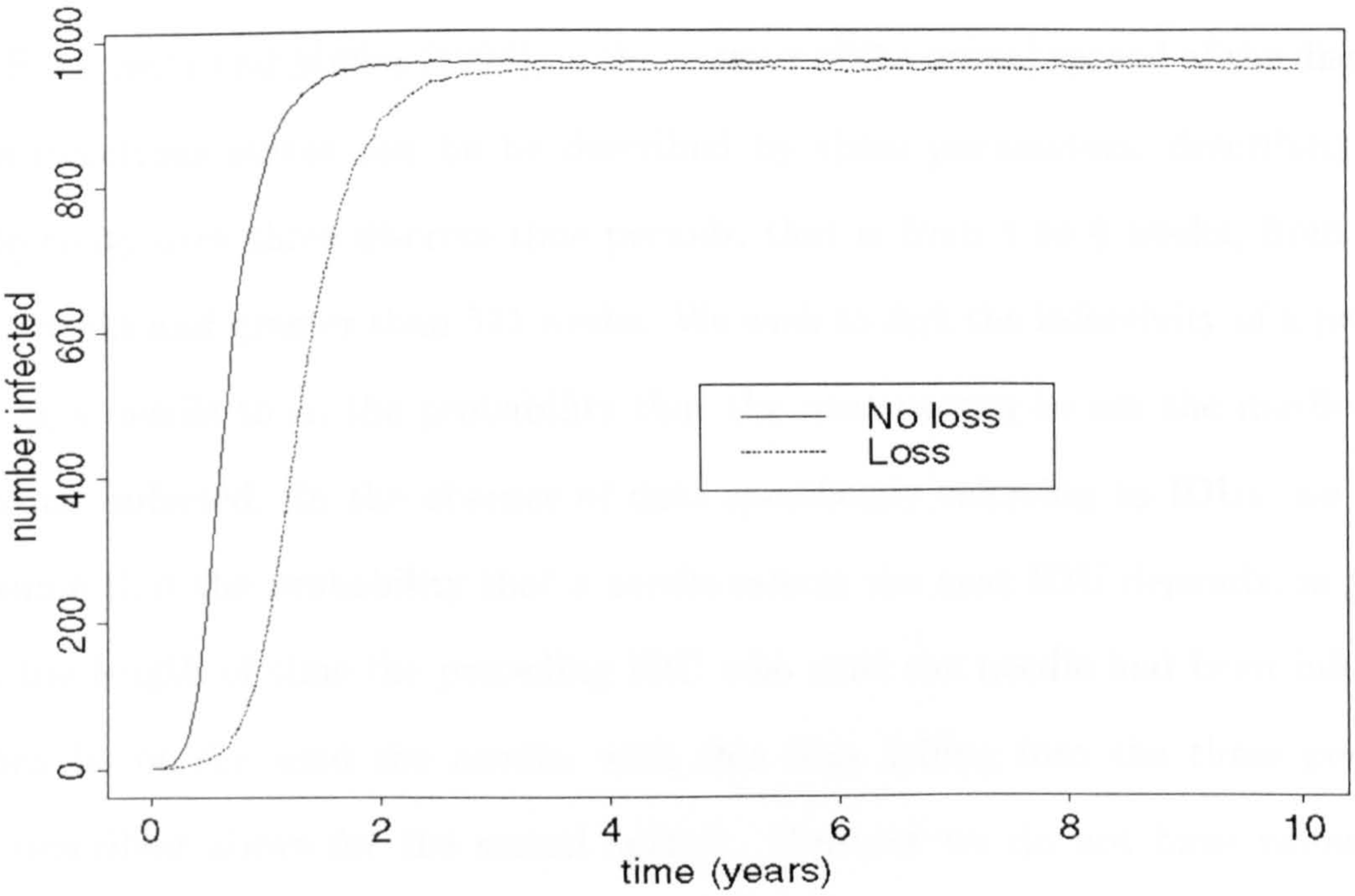

Figure 4.15: The median values from 50 realisations of a stochastic simulation model where the infectivity of an IDU is described by Figure 4.14 (loss), compared to the original model (no loss).

related to the infectivity of the person that infected the needle.

Returning to Peterson's model in which infected people are classified into more than one 'infected' state, we can incorporate some of the effects of stratifying the infected IDU population into our model, in particular we can make the infectivity of an IDU dependent dependent on the length of time than an IDU has been infected with AIDS. The simplest form of stratification would be to assume that an IDU is infectious at a very high level immediately on becoming infected, then for a long period, corresponding to an infected IDU being asymptomatic, such an IDU will then be infectious at a lower level, eventually returning to a high level of infectiousness when Pre-AIDS symptoms or AIDS appears. It should be noted however that this simplified model of infectivity may not adequately describe the complex virological processes that are yet to be fully understood. In creating a more sophisticated form for α, we must reconsider our interpretation of μ; the

rate at which infected IDUs cease sharing.

From Seitz and Müller (1994), in the context of the sexual spread of the disease, the infectious status can be be described by three parameters, describing the infectivity over three discrete time periods, that is from 1 to 6 weeks, from 7 to 511 weeks and greater than 511 weeks. We wish to link the infectivity of a person using a needle to α, the probability that the next person to use the needle will become infected. In the absence of data specifically referring to IDUs, we may assume that the probability that a needle infects the next IDU depends, in part, on the length of time the preceding IDU who used the needle had been infected when he or she used the needle, with this time falling into the three periods as described above for the sexual spread. However we do not have values for the probabilities that we are interested in, but it seems sensible to assume that the ratio of infectiousness over the three periods is the same for needle sharing transmission as it is for sexual transmission.

The ratio of infectiousness over the three periods is 169:1:25, for periods of 7:504:l, where l is the length of time in weeks an IDU lives after developing clinical AIDS (Seitz and Müller, 1994). If we now assume that a typical newly HIV infected IDU continues sharing for 12 years, that is 624 weeks, then $l = 113$. We can therefore combine the infectivity ratios derived from heterosexual transmission from male to female with the corresponding time periods to create infectivity values for IDUs, keeping $\alpha = 0.075$ as a weighted mean value. Thus we have the infectivity values to be 0.5509, 0.00326 and 0.08198 for the three consecutive stages of HIV infection. We can explore the effect that such values have on the spread of the disease using stochastic simulation techniques previously described. Figure 4.16 compares the summarised results from 100 realisations of the stochastic simulation model using the 3-stage infectivity distribution previously described with the original model presented in Chapter 2. The parameters

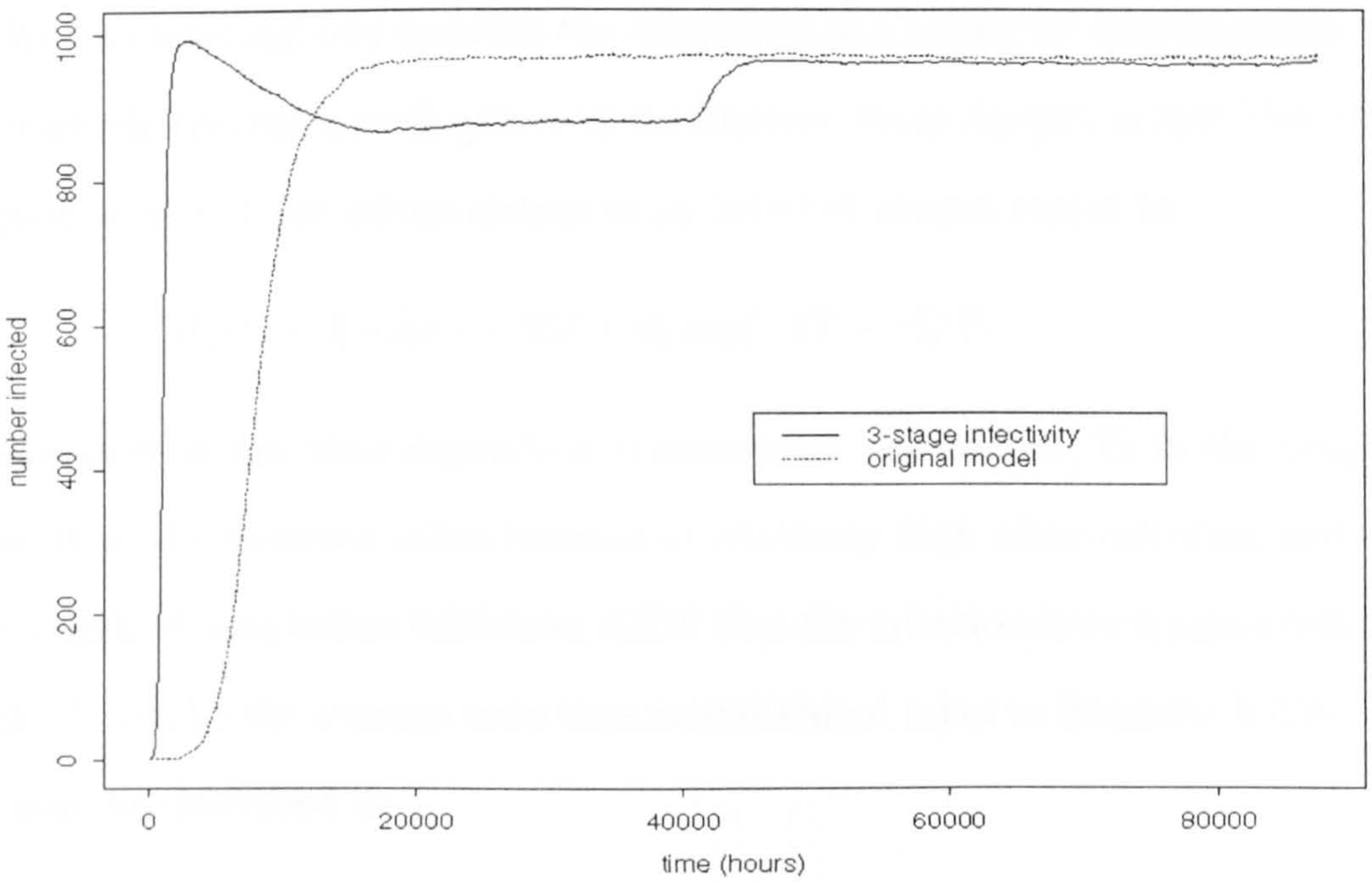

Figure 4.16: The median values from 50 realisations of a stochastic simulation model where the infectivity of an IDU is described by 3 stages, compared to the original model.

used are those used in Figure 2.1, that is $\alpha = 0.075$, $\theta = 0.25$, $\gamma = 10$ and $\lambda = 5.952 \times 10^{-3}$, which is equivalent to an IDU visiting a shooting gallery once a week. The value of μ in our present model corresponds to infected IDUs continuing to share for 12 years after becoming infected. This compares with 8 years in the original model, although this difference will have a negligible effect on the spread of the disease. We see that the disease spreads more rapidly to begin with as newly infected IDUs have high viraemia, however when the number of infected IDUs decreases due to the stochastic equivalent of the mortality 'rate' μ, the new susceptibles are introduced into a population where most of the infected IDUs are not as infectious, and hence the probability that a needle chosen at random will be infectious will be less. After about 10 years the originally infected cohort develops AIDS and there is little difference between the equilibrium prevalence in the two models, although the three stage infectious period appears to have a

slightly lower equilibrium value.

We can alternatively describe the infectivity of a needle by referring once more to research into the sexual spread of the disease. From Anderson and May (1991) a good model of the infectiousness of an infected person would be

$$\beta(\tau) = \beta_0 \exp(-\tau/T_0) + \beta_1 \exp[-(T-\tau)/T_1] \tag{4.13}$$

where $\beta(\tau)$ is the time-dependent transmission probability, T_0 is the length of time that the person's infectiousness is relatively high after infection and T_1 is the length of time before full blown AIDS that the infectiousness is again relatively high. T will be the average time that an individual takes to incubate AIDS. Thus α_0 may be described as

$$\alpha_0(\tau) = \alpha_1 \exp(-\tau/T_0) + \alpha_2 \exp[-(T-\tau)/T_1] \qquad \text{for } \tau < T \tag{4.14}$$

and
$$\alpha_0(\tau) = \alpha_2 \text{ for } \tau > T. \tag{4.15}$$

This can be incorporated into the stochastic simulation model, although values for the parameters α_1 and α_2 will need to be estimated. There will be a range of possible values for these parameters, although we wish to make two restrictions to make comparisons with the model immediately previously presented. Thus we wish the infectivity to average 0.5509 over the first 7 weeks, then also to average 0.08198 for the period between 511 weeks and death at 624 weeks. Hence we then have $T = 624$ weeks, $T_0 = 7$ weeks and $T_1 = 113$ weeks.

To obtain parameter estimates for α_1 and α_2 we note that from the structure of Equation 4.14, the effect of any values of α_2 will be minimal over the first few weeks of the infectivity distribution. Thus

$$\frac{1}{T_0}\int_0^{T_0} \alpha_1 \exp\left(-\frac{z}{T_0}\right)\mathrm{d}z = \frac{\alpha_1}{T_0}\left[-T_0 \exp\left(-\frac{z}{T_0}\right)\right]_0^{T_0},$$

$$= \alpha_1(1-e^{-1}),$$

hence $\alpha_1(1-e^{-1}) = 0.5509$, or $\alpha_1 = 0.8715$.

Similarly we have $\alpha_2(1 - e^{-1}) = 0.08198$ therefore $\alpha_2 = 0.1297$. We note that the average infectivity over the 12 years that an IDU is assumed to be infectious will be 0.03. This distribution is presented in Figure 4.17. Figure 4.18 compares

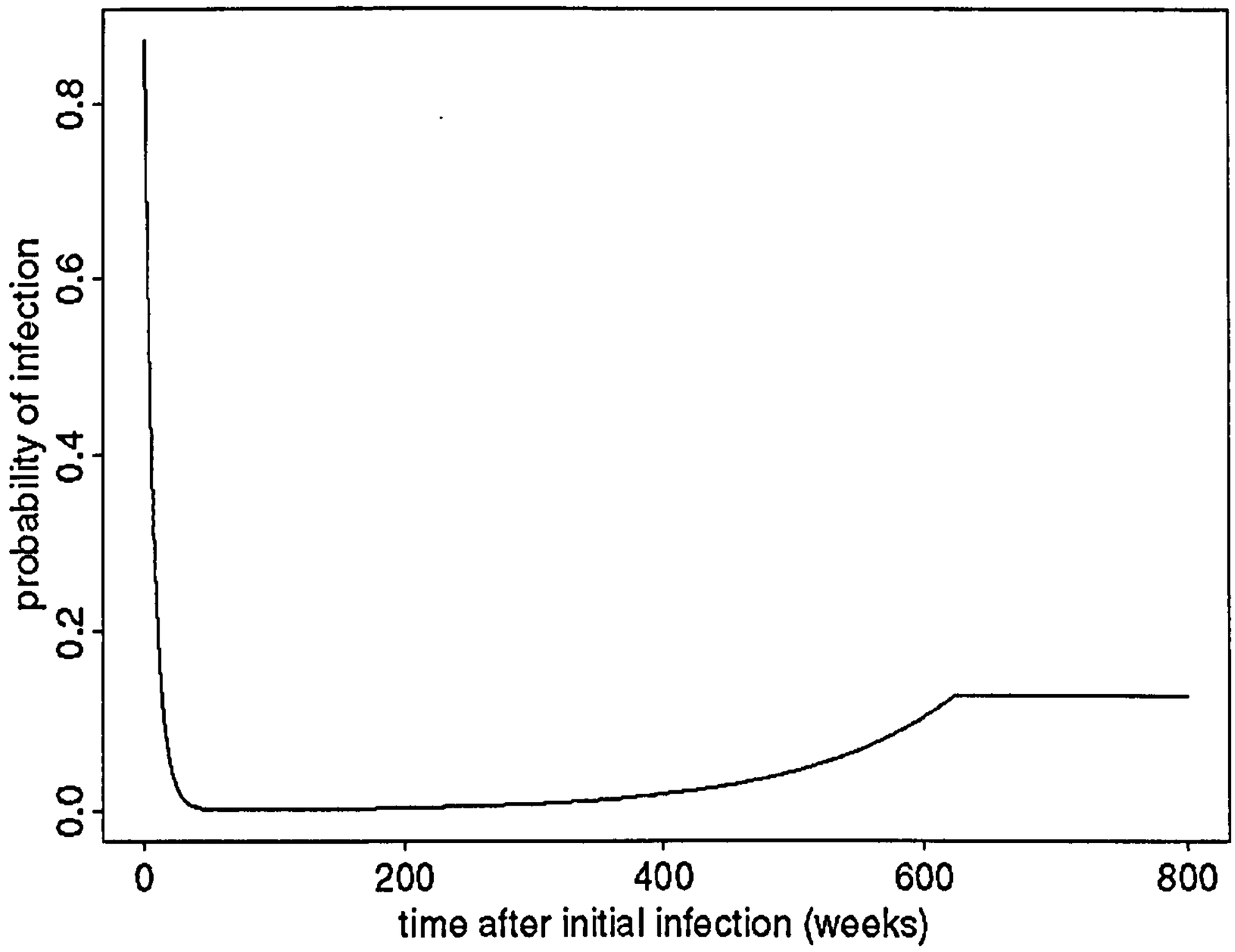

Figure 4.17: Simulated infectivity distribution.

the results of the model which involves an infectiousness distribution with that of the original model. This pattern is qualitatively similar to the results for the model which uses the discrete 3-stage infectiousness as demonstrated in Figure 4.16, although this time it is not clear that the equilibrium level is similar to the model with the three stage infectious period.

From our work it does not appear that needles losing their infectivity by other means apart from flushing has a large influence on the equilibrium number of infected IDUs over time. On the other hand the 3-stage infectious period does appear to have a big initial effect, reflecting the high level of infectiousness when

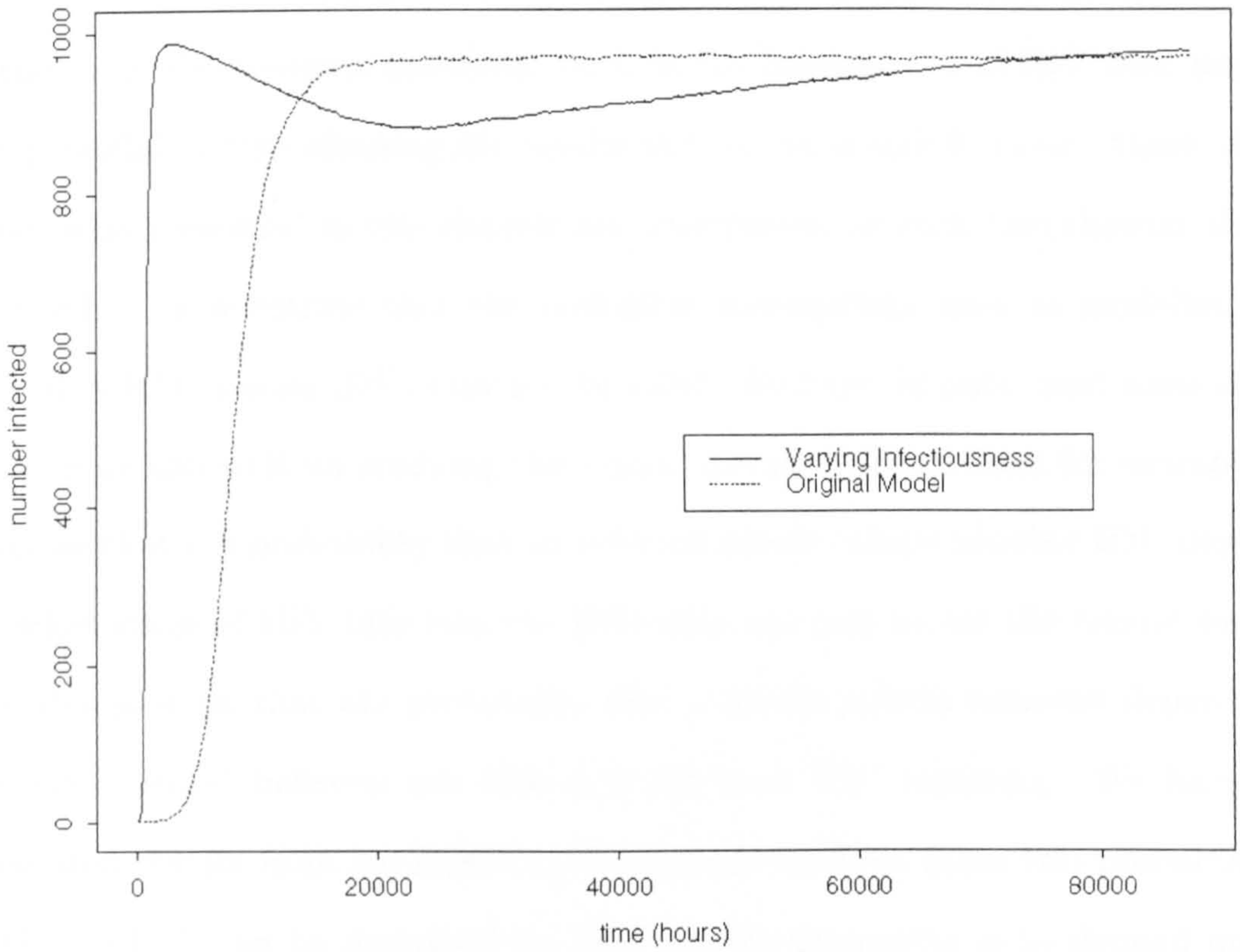

Figure 4.18: The median values from 50 realisations of a stochastic simulation model where the infectivity of an IDU is described by a distribution, following Anderson and May (1991), compared to the original model.

an IDU becomes infected. However on considering some of the other assumptions used in this model, when these assumptions are replaced by more realistic ones the rate at which needles lose their infectivity may be of more importance.

4.6 Summary

In this chapter we explored some of the assumptions that Kaplan used in creating his original model. We presented different scenarios which we believe may be more realistic, and we used both stochastic and deterministic models to explore the effect that varying the original assumptions may have on the spread of the disease. The scientific literature on the spread of HIV through shared injecting

equipment has not greatly increased our knowledge of the transmission dynamics. This is particular true about our knowledge of the virological processes occurring within a needle between injections, such as the inactivation of HIV over time or the probability that cleaning the needle will render it uninfectious. Many of the extensions presented in this chapter are speculative, as such this chapter should be used to demonstrate that the biological assumptions used in modelling the spread of HIV among IDUs may not be valid. We have, in part, used some of the knowledge gained from studying the sexual spread of the disease, for example we propose that the probability that an infected needle infects another IDU depends on what stage of HIV infection the IDU who was last to use the needle was at. We also propose that the probability that a needle infects someone depends on the time period between one IDU and the next IDU injecting. We have not presented results from stochastic models which combine these two probabilities, both of which can be described by allowing the parameter α to depend on the time since the last injection.

To combine these two virological processes would be to lend credence to some of the parameter estimates and assumptions used in this chapter. Even in the simpler models, such as Kaplan's original model, we are using parameters, such as α which we cannot estimate with any certainty, and we are approximating biological processes, such as the needle not remaining infectious *ad infinitum*, with a simplified mechanism such as flushing. In the more advanced models there will be less information available on the mechanisms described and parameters used.

We conclude this chapter however by noting that the assumptions made in the simpler models may be flawed. They may perhaps be relevant in assessing public health campaigns such as needle exchanges or the distribution of bleach to clean injecting equipment. Indeed Kaplan has used his mathematical models to decribe

how the needle exchange in New Haven, USA has reduced the number of infected needles in circulation and the incidence of new HIV cases. We do however suggest that such models should be strengthened by the extensions described above, if the additional parameters can be estimated.

Chapter 5

Parameter Values used in Describing the Spread of HIV via Needle Sharing

5.1 Introduction

In the models previously described, social and biological processes were simplified and described by small sets of parameters. An extension to these models will be made in a later chapter. These will serve to improve on the simple interpretation of the sociological processes, changing the assumption that all IDUs select injecting equipment at random from all shooting galleries. We have essentially introduced all parameters that are of importance in modelling the biological processes involved in the spread of HIV via shared injecting equipment, therefore a discussion of these parameters and the effect that they have on the spread of the disease seems pertinent.

Little is known about the biological parameters that have previously been described as the literature on modelling drug injecting and HIV is sparse. In this chapter and the next we discuss the estimation of parameters used in the preceding models, drawing on both the established literature and data taken from an unpublished study of IDUs in Glasgow. We begin in this chapter by looking

at the sociological parameters and then we examine the parameters describing the biological processes acting on an infected needle. We leave discussion of the parameter α until Chapter 6.

5.2 Estimating the Prevalence of Injecting Drug Use

It is clearly important to have accurate estimates of the number of IDUs to be able to predict the spread of HIV, however many estimates in the past have been based on untestable assumptions. Hartnoll *et al.* (1985) describe methods for estimating the number of drug users in a London borough. At that time, the major source of official data on drug users came from the Home Office Addict Notification system, where GPs were required to notify the Home Office about anybody they suspected to be addicted to a range of opiates or cocaine. Hartnoll demonstrated that only about 20% of drug users were actually notified, hence he suggested that applying a multiplier factor of five to the 'official' data to obtain a more accurate estimate. This method of estimating the proportion of the total population observed from one data source by examining a second, apparently random, sample was similar to capture-recapture methods used in estimating the size of animal populations where it is impractical to count the whole population.

Seber (1992) describes how such a population size can be estimated by catching a sample of animals, marking then releasing them, and then recapturing another sample, from which the number of animals found in both samples, or overlaps, can be used to give an estimate of the proportion of total population that were caught in the first sample. When estimating the size of a drug using population, data from various agencies such as a drug treatment agency and the police data on misuse of drugs convictions are used and the overlap between the data sets is examined. Using such methods assumes that the two data sets are independent,

an assumption that cannot be tested and may not be justified. To improve on the two sample procedure, Parker *et al.* (1984) used data from three samples to estimate the prevalence of heroin use on the Wirral peninsular in 1984.

Frischer (1993*a*) extends this theory to use data from four data sources, within which dependencies can be specified. Data on IDUs were supplied by the police, treatment agencies, needle exchanges and the HIV test register. This data was arranged into a 2^4 cross-classification table corresponding to presence or absence in the four samples with a missing cell corresponding to absence in all four samples. Log-linear analysis was used to test for any dependencies and a model which specified such dependencies was used to give an estimate of the missing cell from which an estimate of the total population size was derived. Using such techniques, Frischer yields an estimate of 8,494 (95% confidence interval 7,491 - 9,721) IDUs in Glasgow in 1990. It should be noted however that there are many caveats to be considered when using capture-recapture methods to estimate the size of drug using populations (Hay, 1997), particularly in relation to the difference in definition between drug use and drug injecting.

As Haw (1985) estimated the number of IDUs in Glasgow to be 5,000 in 1985, it can be assumed the the number of IDUs rapidly increased towards the end of that decade. Whether or not the number is still increasing is yet to be explored, but it is thought that AIDS may have a threefold effect of decreasing the IDU population, by IDUs dying of the disease, IDUs ceasing to share or inject and persons liable to begin injecting drugs not doing so.

Indeed Caulkins and Kaplan (1991) improve on Kaplan's original 'Needles that Kill' (NTK) model by assuming more general influx and removal rates. This open model can be used to show the effect that HIV may have on the population size, with particular reference to creating a model describing the baseline population from which public health campaigns can be evaluated.

Caulkins and Kaplan describe the population size by the following equation

$$\frac{dN(t)}{dt} = c_B N(t)^{\nu} - \mu_B N(t) \tag{5.1}$$

where c_B is the recruitment rate proportionality constant, ν is nonnegative and strictly less than one, μ_B is the rate at which current users exit the population, and $N(t)$ is the size of the IDU population at time t. This equation can, of course, be solved analytically giving

$$N(t) = \left[\frac{c_B}{\mu_B} + \left(N(0)^{1-\nu} - \frac{c_B}{\mu_B}\right)e^{-\mu_B(1-\nu)t}\right]^{1/(1-\nu)} \tag{5.2}$$

which approaches a steady state size of

$$N(\infty) = \left(\frac{c_B}{\mu_B}\right)^{1/1-\nu}. \tag{5.3}$$

This can be explored numerically using parameters suggested, which describe the size of the IDU population of the USA which has an estimated steady state population size of 750,000, with

$$\mu_B = \frac{100,000}{750,000} \cong 0.133 \tag{5.4}$$

and for any given value of ν

$$c_B = \frac{100,000}{750,000^{\nu}}. \tag{5.5}$$

The model assumes that these two parameters will change instantaneously at some time point due to the introduction of AIDS from μ_B and c_B to μ_A and c_A respectively. The subscripts B and A on the parameters denote respectively those parameter values before and after the introduction of AIDS. This assumption does simplify the model, and as we are interested only in the steady state population size there seems no justification to complicate the model further.

Assuming that the parameters change at time $t = 0$, the population size as a function of time would be

$$N(t) = \left[\frac{c_A}{\mu_A} + \left(\frac{c_B}{\mu_B} - \frac{c_A}{\mu_A}\right)e^{-\mu_A(1-\nu)t}\right]^{1/(1-\nu)} \tag{5.6}$$

The new steady state population size will be

$$\begin{aligned} N_A(\infty) &= \left(\frac{c_A}{\mu_A}\right)^{1/1-\nu} \\ &= \left(\frac{c_A}{c_B}\frac{\mu_B}{\mu_A}\right)^{1/1-\nu}\left(\frac{c_B}{\mu_B}\right)^{1/1-\nu} \\ &= \left(\frac{c_A}{c_B}\frac{\mu_B}{\mu_A}\right)^{1/1-\nu} N_B(\infty). \end{aligned} \tag{5.7}$$

This can also be explore numerically, with varying estimates for the parameters.

Even in the case of AIDS not affecting the recruitment rate, $c_A = c_B$, and $\mu_A = \mu_B + \frac{1}{8}$

$$N_A(\infty) \cong \left(\frac{1}{2}\right)^{1/1-\nu}\left(\frac{c_B}{\mu_B}\right)^{1/1-\nu} \tag{5.8}$$

which can be interpreted as the population size decreasing by at least 50 percent. This is shown in Figure 5.1, with a starting population of 750,000 and a recruitment rate proportionality constant, $\nu = 0.5$.

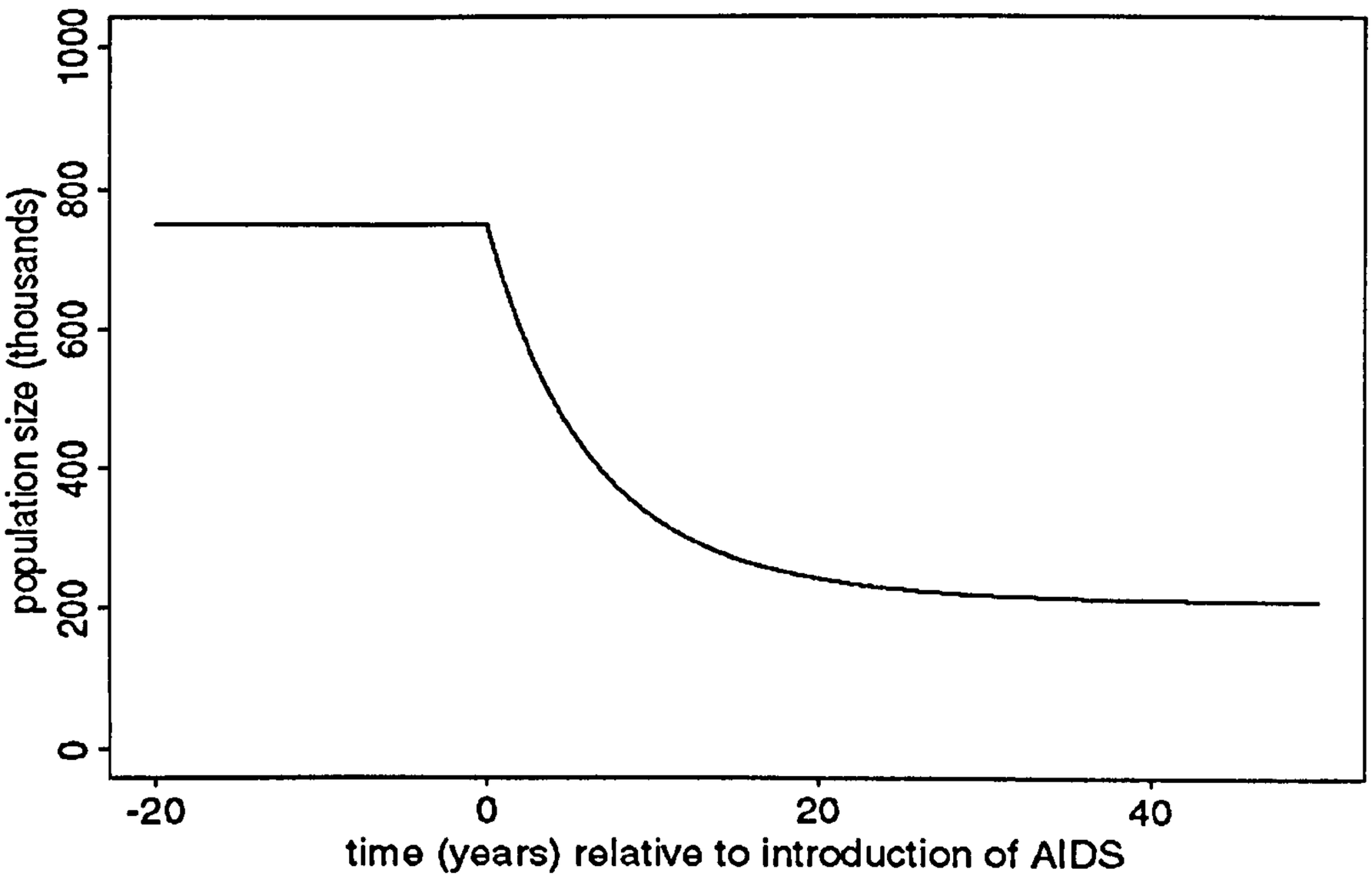

Figure 5.1: Size of IDU population before and after the introduction of HIV/AIDS, using Equation 5.1 which has been adapted from Caulkins and Kaplan (1991). Parameter values as in text.

Caulkins and Kaplan go on to include these population size dynamics into the NTK framework of equations. In order to do this they switch from modelling the HIV prevalence in a population of unspecified size to modelling the absolute numbers of infected or susceptible sharing IDUs. Again they show the dramatic effect that HIV has on the size of an IDU population.

In 1995, over ten years since HIV was first detected in Glasgow, the size of the city's IDU population appears not to have been seriously affected by deaths from AIDS (Bloor *et al*, 1993). This may, in part, be due to the continued low prevalence of HIV in Glasgow (Taylor, *et al.* 1994). The situation may be different in Dundee where the HIV prevalence within the IDU population has been estimated at 27% (Haw *et al.* 1996). Many of these IDUs were at greatest risk from infection between 1982 and 1987. Thus the number of deaths due to AIDS is of a greater magnitude than that of Glasgow and hence a model which includes the population decreasing beacuse of AIDS, such as that of Caulkins and Kaplan, may be more appropriate.

It will be of interest to discuss how the size of the IDU population may change in a city where the prevalence of HIV is low. As data concerning the rate at which drug users become drug injectors, and also the rate at which they cease injecting is sparse, we only briefly introduce population size modelling by describing a very basic model.

In common with any population size model, there will be several forces acting on the size of the needle sharing population. There will be a rate at which drug users commence an injecting career and begin sharing and there will be a rate at which IDUs cease sharing or injecting. People may begin drug injecting and needle sharing for sociological reasons such as peer pressure, and other reasons such as the purity of available drugs. Indeed there are great geographical differences in the preferred route of drug taking between Scotland and the rest of the UK

(Department of Health, 1997), thus the size of IDU populations may differ both spatially and over time. There will be other reasons why people cease injecting, such as through death, either from AIDS or from other causes, or just because they wish to stop sharing, either due to HIV directly as they are infected, or indirectly as they do not wish to become infected. Indeed many IDUs enrol in methadone maintenance programs to reduce the risk of becoming infected and many injectors obtain clean needles from needle exchanges in order to avoid sharing. There may also be movement in and out of a geographical area by IDUs. Indeed the epidemics previously described begin when one or more infected IDUs are introduced into a population of susceptibles.

In the absence of data concerning the number of people beginning to inject we may wish to simplify the influx rate to be a constant κ. This assumes that a certain percentage of each age cohort has an innate predisposition for injecting drug use. We can also assume that the per IDU rate of ceasing sharing is a constant μ per unit time. It should be stressed that in this chapter μ refers not just to IDUs dying from AIDS, but also IDUs dying from other causes as well as simply ceasing to share. There has been recent interest in Glasgow in the mortality rate of drug users due to accidental death from overdose. Thus in modelling the population size the mortality rate of IDUs in the absence of HIV can be assumed to be larger than that of the general population that does not inject (Frischer *et al*, 1997).

5.3 Parameter Estimates from the Existing Literature

There have been few papers which explore the spread of HIV through needle sharing. In this section we review some of these papers to compare the different interpretion of the sociological and biological processes and the values attached

to the parameters that are employed in the respective models. We initially examinine the different parameters individually before, in a later chapter, undertaking a sensitivity analysis in a similar fashion to Blower *et al.* (1991). This deterministic model aims to more completely describe the transmission dynamics of HIV within New York City, by including heterosexual, injecting drug use and perinatal transmission of HIV. This complex model involved 34 differential equations employing twenty biological/behavioural transmission parameters, although some of these were not of interest in describing the transmission dynamics via sharing injecting equipment. In this analysis, single parameter values are replaced by ranges of values simulated from a postulated distributions. Thus the combined effect of parameters can be explored and the importance of the values of different parameters in relation to the number of infected IDUs can be examined.

5.3.1 Parameters Describing the IDU Population Size and the Number of Shooting Galleries

Kaplan, in conjunction with Caulkins, Heimer and O'Keefe presented a range of scenarios which could be modelled using his framework of differential equations, know as 'Needles that Kill'; Kaplan (1989), Caulkins and Kaplan (1991), Kaplan and Heimer (1992*a*), Kaplan and O'Keefe (1993). In the initial paper, it was assumed that the number of IDUs was large, thus $N = 200,000$, reflecting the size of the injecting population of New York. While the number of needles was not explicitly described, it was assume that this parameter was related to N, such that m, the number of needles was assumed to be between $10N$ and $N/10$ and $\gamma = N/m$, the gallery ratio between 0.1 and 10. Apart from the open NTK model, where a much larger population size was modelled, Kaplan's models only refer to the proportion of the population that is infected and the number of needles relative to the number of IDUs, thus it can be assumed that for all Kaplan's models the population size is large, therefore justifying the deterministic

approach. Other deterministic models assume that that the population is of a similar magnitude to that described by Kaplan.

5.3.2 Parameters Describing the Rate at which an IDU Ceases Sharing

Studies of people with HIV and AIDS were used to estimate μ, the rate at which infected IDUs ceased sharing injection equipment. Estimates of the mean incubation period varied from 8 years to 10 years, thus μ was assumed to be either 1/8 or 1/10. However this did not include IDUs ceasing injecting for reasons other than death, therefore these estimates may inflate the true length of time an IDU remains injecting after infection with HIV. In fact as discussed earlier Caulkins and Kaplan estimate the rate at which IDUs cease injecting in the absence of HIV and AIDS as roughly 0.1333 in the USA. We may wish to combine this estimate with the above estimates of the rates at which HIV infected IDUs cease sharing due to developing clinical AIDS to give a total rate at which infected injectors cease sharing of 0.2333 to 0.2583. These rates include ceasing sharing due to non-AIDS related reasons and ceasing sharing due to developing clinical AIDS. In fact even these rates are underestimates as some individuals will discover that they are HIV positive from the results of HIV antibody tests before the end of their incubation period and some will cease sharing due to fear of catching HIV and AIDS rather than actually catching it. Both of these factors will act to increase still further the rate at which HIV infected individuals cease sharing injection equipment.

In Blower's sensitivity analysis an incubation period and a survival period were modelled. Thus the incubation period was described by a Weibull distribution and the survival distribution by a left skewed distribution, the former ranging from 1.36 to 20 years, median value 8 years, and the latter ranging from 1 to 5 years, median value 1 year.

Peterson *et al.* (1990) use a compartmental model to describe the HIV progression. If the compartments 'Acute Infection', 'Asymptomatic' and 'pre-AIDS symptoms' are collapsed into a single HIV compartment, then on average an infected IDU is in this compartment for just under 10 years and in the AIDS compartment for 2 years.

5.3.3 Parameters Describing the Rate at which an IDU Shares Needles

Peterson *et al.* elaborate on Kaplan's sharing rate λ by simultaneously modelling the progression from monthly, through weekly, to daily injecting and the different forms of sharing, of which shooting galleries is only one. As male and female IDUs were treated separately in Blower's model and sharing was in the context of random sharing with a stranger, or more structured sharing with a 'buddy' an exact representation of λ could not be extracted from this paper, however for male random sharing, a left skewed distribution was postulated, with a minimum of 13 and a maximum of 5,265 times per year, approximately once a month to 14 times a day.

5.3.4 Parameters Describing the Infectiousness of a Needle

In Kaplan's 1989 paper, the probability of an infected needle being flushed by a susceptible IDU was initially set to 0.25. This assumption has been heavily criticised and experiments have shed doubts on whether flushing actually occurs (Kaplan, private communication). In later papers Kaplan assumes no flushing (Kaplan and O'Keefe, 1993). Instead he uses the parameter θ to denote the probability that an addict effectively cleans a needle before use. From needle exchange data this was estimated to be 0.84 for New Haven, Connecticut, USA. An informal sensitivity analysis of this parameter for values of θ in the range

0.21-0.84 suggested that, in the context of needle exchanges reducing the number of new infections, the model was not particularly sensitive to this value.

The rate at which HIV loses its infectivity within a needle in Kaplan's original paper was estimated from Resnick *et al.* (1986). It was noted that HIV can retain its infectivity for more than three days when dried and held at room temperature and it can remain active for more than a week in an aqueous environment. There is considerable uncertainty about this parameter, indeed the effect that the length of time the person who rendered the needle infectious has themself been infectious may considerably affect the length of time the virus can retain its infectivity within a needle. Stephens *et al.* (1995) note that HIV can be cultured from syringes twenty eight days after they were loaded with HIV infected blood.

In Allard's (1990) more theoretical paper, it is noted from previous studies that although the frequency of injecting is variable, the vast majority of users are daily users and that a high proportion share needles. Allard dismisses the inclusion of θ to describe flushing of an infectious needle by a susceptible IDU as premature, suggesting that experimentation could be used to establish the existence of this mechanism.

5.4 Data Extracted from Research in Glasgow

Behavioural data has been collected on IDUs in Glasgow, from which certain parameters which are of use when modelling the spread of HIV can be estimated. This data was collected using a questionnaire which asked questions not only about injecting and needle sharing, but also sexual activity. The infection probability, about which there may possibly be the most uncertainty, warrants separate discussion, and a estimate of this probability will be presented in the next chapter.

In 1990 over 500 IDUs were questioned about their injecting and sharing prac-

Frequency of injecting per month	Number of IDUs (N=503)	Number of injecting events per month	Number of injecting events per year for 503 IDUs
0	4	0	0
0.5	7	3.5	38.5
2	4	8	88
4	2	8	88
10	17	170	1,870
20	20	400	4,400
30	63	1,890	20,790
75	215	16,125	177,375
150	171	25,650	282,150
Total		44,254.5	486,799.5

Table 5.1: The frequency of injecting. Adapted from Goldberg *et al.* (1995).

tices. This sample came from various parts of the city, and attempts were made to avoid any bias by sampling both from drug treatment agencies and also IDUs who were approached in the street. Tables 5.1 and 5.2 show the reported frequency of injecting and needle sharing within a typical month during the six months prior to interview. This data is taken from Goldberg *et al.* (1995).

Other studies have cast doubts on self-reported sharing rates from IDUs, particularly Kaplan (1991) and McKeganey *et al.* (1996). Kaplan argues in his paper that his data corresponding to attendees at needle exchanges may be biased to be too low by social desirability considerations. See also Stimson *et al.* (1988) who argue that there may be bias in self reported sharing rates either too low due to social desirability considerations or too high as addicts may exaggerate the extent of their sharing to gain access to needle exchanges. McKeganey *et al.* note that low reported rates of sharing in a preceding time period may hide the fact that many IDUs would still be prepared to share as IDUs who respond negatively to questions about there sharing practices say that they would share when prompted with vignettes describing realistic circumstances such as not having a clean nee-

Frequency of injecting per month	Number of IDUs (N=503)	Number of injecting events per month	Number of injecting events per year for 503 IDUs
0	290	0	0
0.5	87	43.5	487.5
2	44	88	968
4	23	92	1,012
10	19	190	2,090
20	9	180	1,980
30	9	270	2,970
75	15	11,255	12,375
150	7	1,050	115,500
Total		3,038.5	33,423.5

Table 5.2: The frequency of needle sharing. Adapted from Goldberg *et al.* (1995).

dle when the IDU has drugs and is desperate to inject. However we assume that the ratio of sharing to non-sharing injectors in this sample is the same as that in the more general injecting population Approximately 40% of injectors report sharing. The most recent estimate of the number of injectors in Glasgow comes from Frischer *et al.* (1993*a*), who suggest that there are roughly 8,494 IDUs in Glasgow, hence we estimate the number of IDUs who share injecting equipment at approximately 3,597.

The data presented above in Tables 5.1 and 5.2 may be misleading, due to the unequal classification size of responses, for example IDUs reporting sharing about once a week may have shared from four times in the last month to about seven times in the last month, while those that report sharing about once a day, may actually share anything from twenty five to forty five times a month. This classification is subjective, but we can approximately map the eight possible responses from the questionnaire onto a scale which denotes the number of days a month that an IDU shares. We again have to subjectively decide the lower and upper limits for this scale, thus we assume that an IDU can share from 0.5 times

Questionnaire response	Number of sharing days per month	Discrete approximation
Less than once per month	0.5	0.5
Once to three times a month	1-3	2
About once a week	4-7	4
Two to three times a week	8-14	10
Four to six times a week	15-24	20
About every day	25-45	30
Two to three times a week	46-105	75
Four or more times a day	106-200	150

Table 5.3: Continuous sharing frequencies. Adapted from Goldberg *et al.* (1995).

a month to 200 times a month. We can demonstrate the mapping that was used in Table 5.3.

From the scale that the questionnaire responses were mapped onto we can construct an approximate probability density function $f(x)$ to describe the probability that an IDU selected at random shares x times a month. This can be achieved using the DISCRETE subcommand in the statistical package MINITAB's probability distribution commands. To obtain approximately the frequency of sharing for the 3,597 IDUs who share we can sample randomly from this distribution to give the Figure 5.2. While Figure 5.2 cannot be taken as completely accurate, it does demonstrate that few IDUs share very frequently. Indeed compared to the value of λ that has been assumed in the previous chapters, only 388 IDUs can be thought of as sharing weekly. Almost 1,000 IDUs share more often than this and over 2,000 IDUs share less frequently, but as the distribution is quite skew there are a small number of IDUs who share very often. Thus the mean value that on average injectors share roughly once a week is quite accurate.

We will again use the reported sharing rates in the next chapter, but we note that although the majority of IDUs share less than once a week, from Table 5.3 the mean number of times an IDU who does report sharing injecting equipment

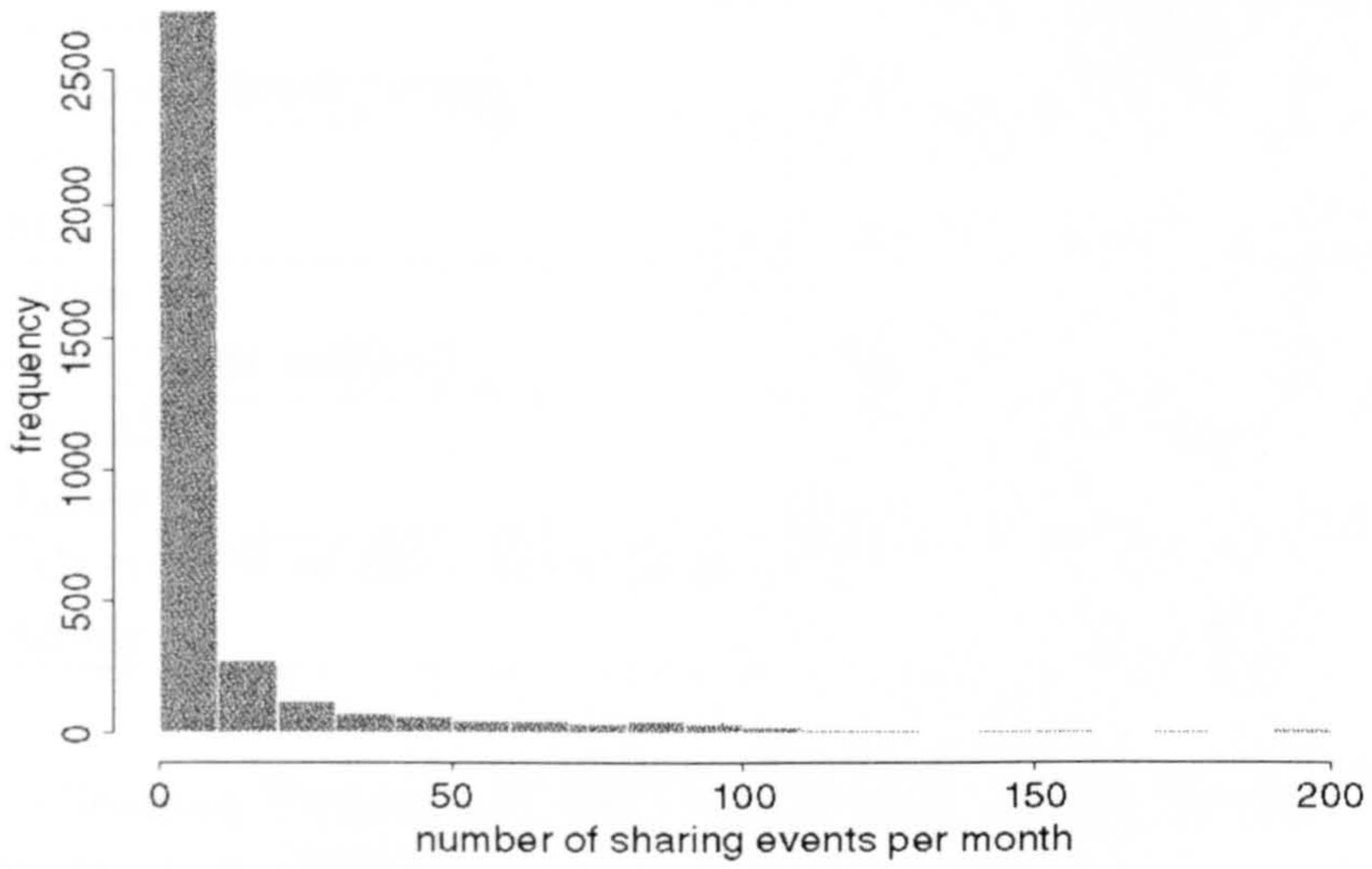

Figure 5.2: Approximate sharing frequency (per month) of 3,597 IDUs.

shares in a month can be calculated, thus a needle-sharing IDU shares on average fourteen times a month.

The cleaning practices of IDUs whom shared injecting equipment can be explored. IDUs employ various methods in order to clean previously used needles, some of which may not render the needle free from HIV. Studies have shown that the most efficient methods of cleaning needles were to use either boiling water, alcohol or bleach, however doubt still remains as to whether these methods always clean the needle or if IDUs are carrying out these procedures in the correct fashion

While various methods of cleaning injection equipment were described in a sample of 200 IDUs in Glasgow, from Table 5.4 44.2% used an efficient cleaning practice such as boiling water, bleach or alcohol. If we employ the terminology from Kaplan's later papers, such that ξ describes the probability of effective cleaning, we therefore have an estimate of this probability.

Frischer *et al.* (1997) explored the mortality of IDUs within Glasgow and present the annual mortality of IDUs as 1.77%. This estimate is lower than

	Monthly	Weekly	Daily	Total
Clean always boiling water/bleach/alcohol	63	20	9	92
Clean always hot water	57	29	22	108
Clean always cold water/other method	13	2	7	22
Clean mostly all methods	6	5	2	13
Clean about 50% of the time or less all methods	3	3	0	6

Table 5.4: Cleaning Practices of Monthly, Weekly and Daily Sharers. Adapted from Goldberg *et al.* (1995).

previous estimates such as Bucknall *et al.* (1986) and Skidmore *et al.* (1990), and suggest that this is due to the increased knowledge of the size of the IDU population. Data on the length of time between an IDU becoming infected with HIV and the time that they die may be used to estimate the increased mortality due to HIV, Frischer estimates this mortality rate at 3.8%, but it should be noted that the interpretation of this mortality rate differs from that of both Kaplan and Peterson, as Frischer's increased mortality rate does not account for the incubation period of HIV/AIDS.

5.5 Summary

In this chapter we have examined the parameters that we have previously employed in the deterministic and stochastic models presented in the preceding chapters. We have shown that from the existing literature, the existance of flushing may be questionable, and that θ may be better described as the probability that a needle is effectively cleaned. We have described the forces acting on the size of the IDU population and shown that the outflow rate μ at which IDUs cease sharing injection equipment consists of more than one process as in the

absence of HIV, IDUs have a higher rate of mortality that the general public and HIV/AIDS itself contributes to this outflow rate as infected individuals may cease sharing because they develop AIDS or due to fear of AIDS. Caulkins and Kaplan formulated models in which HIV and AIDS may have a dramatic effect in lowering the number of IDUs in a particular area, however in Glasgow over the last 10 years there does not appear to have been a serious decline in the numbers of IDUs. Any lowering of the number of needle sharing IDUs may be better attributable to the success of public health campaigns, including the introduction of methadone prescribing. In the next chapter we will examine the remaining parameter α, the probability of a susceptible IDU becoming infected after using an infected needle once.

Chapter 6

Estimating the Probability of Infection

6.1 Introduction

In the preceding chapters we have developed models which described the spread of HIV in a population of IDUs. We have shown that the number of infected IDUs depends on the parameter values, in particular α, the probability that an IDU becomes infected with HIV after injecting with an infected needle. In this chapter we review the existing literature and then use data from various sources in Glasgow, collected in 1990, to create an estimate for α.

Little is known about the value that this parameter should take, and in the preceding chapters $\alpha = 0.075$, the value suggested by Kaplan in 1989, was used without question. Kaplan justifies this value as it is within the range of estimates of the probability of becoming infected following unprotected receptive anal intercourse. In a later paper, Kaplan and Heimer (1992*b*) use the formulation of the steady state values of π and β and data collected from a study of IDUs who attend a needle exchange to produce an estimate for α. The result of such analysis is to lower the estimate of α to 0.0066. This was seen as an improvement on previous estimates of α which were derived from studies of health care workers who had needlestick injuries while treating known AIDS or HIV posi-

tive patients, giving estimates of between 1/300 and 1/200 (Friedland and Klein, 1987; Leentvaar-Kuijpers *et al.*, 1990; Marcus, 1988). These estimates based on needlestick injuries can really be thought only to be a lower bound for α as the amount of blood involved when an addict injects with a syringe exceeds that involved in needlestick injuries.

More recently, other authors have suggested that Kaplans value of 0.075 was an overestimate, suggesting that $\alpha \simeq 0.01$. In Allard's (1990) paper, which focusses on the infection process, a conservative value of α is given as 0.005, derived again from needlestick injuries, although scenarios where $\alpha = 0.05$ are discussed. Peterson *et al.* (1990) also use 0.005 as an estimate of α, again from needlestick injury data, although they perform a sensitivity analysis on this value by describing the effect that changing α from 0.001 to 0.05 has on HIV prevalence in a stochastic simulation.

In the sensitivity analysis of Blower *et al.* (1991) a triangular probability distribution was assumed for the probability of becoming infected on using infected injecting equipment. This distribution had a peak at zero and ranged from zero to one with a median value of 0.28. These values ensured that although the majority of simulations would have low infection probabilities, there would be some with high probabilities. Kretzschmar and Wiessing (1998) assume that the infectivity of HIV varies over the course of infection. They note that Jacquez *et al.* (1994) argue that infectiousness is very high in the first 6-8 weeks of infection (in the order of 0.1 to 0.3 per contact) then it stays low (0.0001 to 0.001 per contact). Hence they assume a two stage process of infectivity; in the first 60 days after infection infectivity is set to 0.5 per contact, after that it is 0.001 per contact. As they assume that an IDU will continue to infect for approximately 10 years after becoming infected then their representation of the infectivity is similar to the average infectivity of 0.01 per contact as estimated by Kaplan and Heimer.

6.2 The Probability of HIV Transmission among IDUs in Glasgow

Two quantities that are frequently used to give an estimate of the effect that HIV has in an area are prevalence and incidence. The prevalence of HIV in the IDU population at a given point in time is defined as the total number of HIV positive IDUs divided by the number of IDUs. This can be estimated from sampling known IDUs and using the proportion of those sampled who are HIV positive as an estimate of the prevalence of HIV in the whole IDU population. This may give an incorrect estimate if the IDUs sampled are not representative of the more general IDU population.

The incidence of HIV in a given year is defined as the number of new infections that occurred in that year, again divided by the number of IDUs. This again can be estimated by taking a sample of IDUs and exploring how many of them became HIV positive that year, and then scaling up this estimate to correspond to the estimated total number of IDUs. However, due to the long latent period, many people infected with the virus do not find out until several years later, hence incidence is more accurately estimated retrospectively. Goldberg *et al.* (1995) suggest that the prevalence and incidence of HIV in Glasgow are both low. They combine data from various studies of the Glasgow IDU population including the behavioural and seroprevalence study to give an estimate of the probability that a single sharing event will result in a new HIV infection.

Taylor *et al.* (1994) estimated the incidence of HIV infection among IDUs in Glasgow in 1990 to be low. Without formally describing a confidence interval they estimate the value to be between 0% and 0.2%. If the upper limit of this interval is used and the incidence of HIV in Glasgow in 1990 is assumed to be 0.2% then the number of new infections in 1990 can be estimated as $n\hat{p}_1$ where n is the number of IDUs who were not infected with HIV at the start of 1990 and

$\hat{p}_1 = 0.002$. Using the upper limit of the interval can be justified as the findings from this research can be thought of as the 'worst case scenario'. The prevalence of HIV in in Glasgow 1990 was estimated at 1.8%, therefore the number of infected IDUs that year can be estimated as $\hat{N}\hat{p}_2$ where $\hat{N}$ is an estimate of the population size of IDUs and $\hat{p}_2 = 0.018$. The estimated number of uninfected IDUs will be $\hat{N}(1 - \hat{p}_2)$. From Frischer (1993*a*) there are an estimated 8,494 IDUs in Glasgow hence we can combine these estimates to give an estimate of the number of new infections in 1990 as $\hat{p}_1\hat{N}(1 - \hat{p}_2)$ or $0.002 \times 8,494 \times (1 - 0.018) = 16.68$.

As part of a World Health Organisation study of IDUs and HIV risk, 503 Glasgow IDUs were interviewed about their sharing patterns. The reported sharing frequencies as discussed in Section 5.4 have been presented in Table 5.2. From the reported sharing frequencies of the 503 IDUs that were interviewed, we can obtain an estimate for the total number of sharing events that occurred in Glasgow in 1990. As there were an estimated 8,494 IDUs, there would have been an estimated $\frac{8,494}{503} \times 33,423.5 = 564,412$ sharing events assuming that the sample is drawn at random from the whole IDU population. Hence although the number of sharing events has been estimated at more than half a million, they only resulted in around 17 new infections, which implies that the probability that a single sharing event would have resulted in a new infection in 1990 was $\frac{16.68}{564,412}$ or 2.96×10^{-5}.

It may be unrealistic to assume that the sharing patterns of the IDUs that have been included in the sample will be representative of the whole IDU population. Although Haw *et al.* (1992) stress the importance of multi-site sampling, there are often difficulties in obtaining a representative sample. As two thirds of this sample were recruited from needle exchanges or treatment agencies the sample may be biased towards those who are more willing to share injecting equipment, therefore extrapolating the sharing frequency of those sampled may result in an

overestimate for the total number of sharing events, and hence an underestimate for the derived probability of infection occurring.

While the point estimate derived above may be of interest in explaining the continued low prevalence of HIV in Glasgow, it will useful to attach a confidence interval to this estimate. We can assume that the parameters previously described are estimates of unknown values, and that these values can be thought of as following a given probability distribution. Using distribution theory we can explore the variance of such estimates. We can assume that both the number of infected IDUs and the number of new infections in 1990 will follow a binomial distribution. Hence we have that the number of new infections will be $\mathrm{B}(n, p_1)$, which results in a variance of $np_1(1-p_1)$ which is estimated by $\hat{n}\hat{p_1}(1-\hat{p_1}) = 0.001996\hat{n}$ where as before n is the number of uninfected IDUs. Similarly the number of infected IDUs will be $\mathrm{B}(N, p_2)$ as before with estimated variance $0.0177\hat{N}$. If we assume that N, the total number of IDUs is normally distributed then we can use Monte-Carlo methods to estimate the variance of i, the number of new infections in 1990. To obtain a value of the distribution which i follows, we first generate a random variate from a distribution which describes the population size. Frischer *et al.* (1993*a*) quote a non symmetric confidence interval derived using the likelihood interval method (Cormack, 1992). We approximate this by a normal distribution with mean 8,494 and standard deviation 568. The RANDOM function in the statistical package MINITAB, was used to obtain 1,000 random variates from a normal distribution with the specified parameters. Figure 6.1 is adapted from a histogram describing the distribution of the sampled variates.

We can then use $\hat{N}^{(1)}$, the first estimate of the population size to create the binomial distribution $\mathrm{B}(\hat{N}^{(1)}, \hat{p}_2)$ from which an estimate of the number of infected IDUs can be sampled. We can divide this estimate by $\hat{N}^{(1)}$ to get a value, $\hat{p}_2^{(1)}$, from the distribution for the HIV prevalence. As $\hat{n}^{(1)} = (1-\hat{p}_2^{(1)})\hat{N}^{(1)}$ will be a

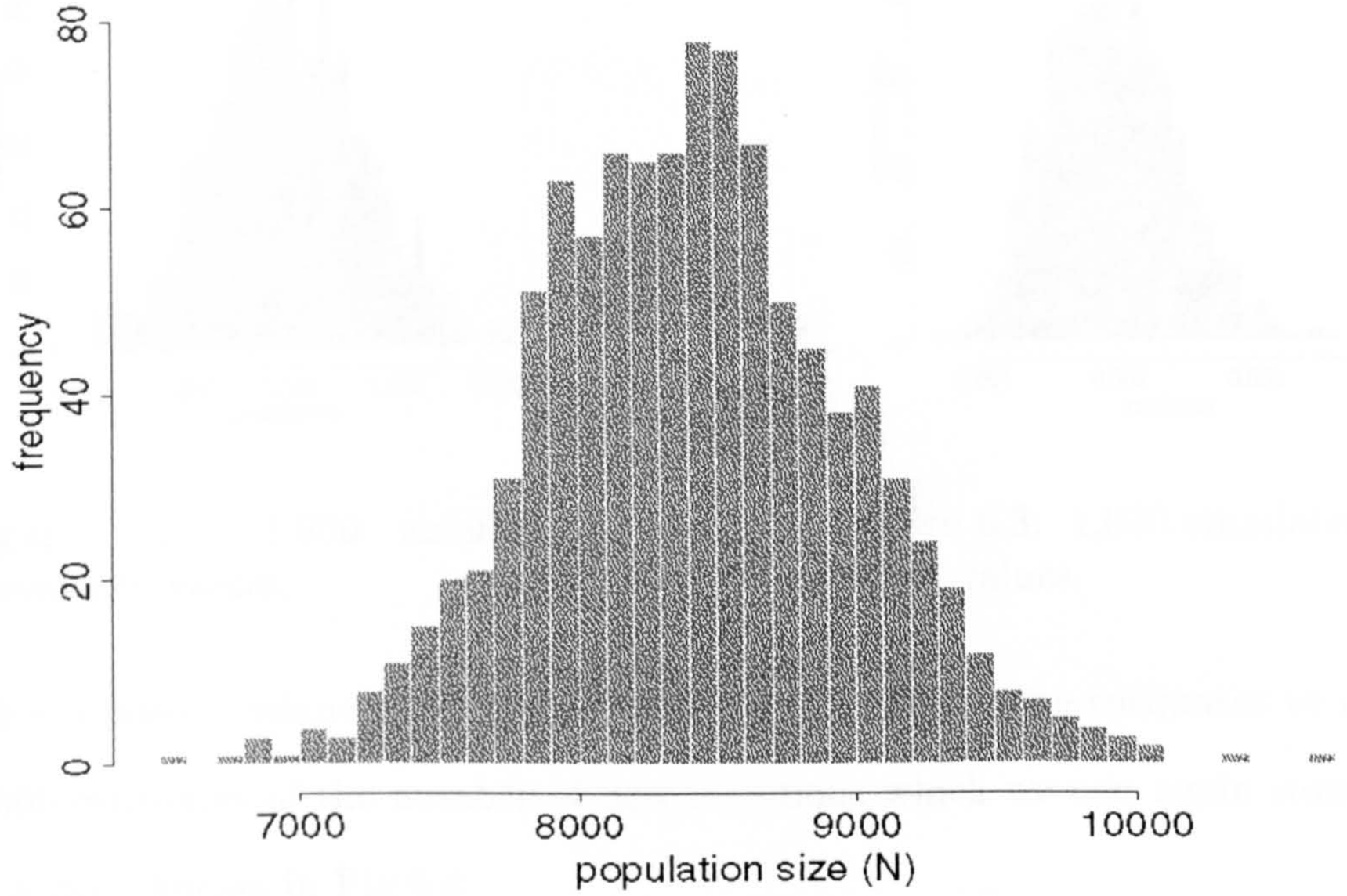

Figure 6.1: Simulated Numbers of IDUs from the N(8,494, 568) distribution.

sample value for the number of uninfected IDUs, we can randomly sample from a $B(\hat{n}^{(1)}, \hat{p}_1)$ distribution to obtain a sample value that will be an estimate of the number of new infections in 1990. Similarly dividing this value by $\hat{n}^{(1)}$ we will get a value $\hat{p}_1^{(1)}$ from the assumed incidence distribution. Hence if we combine $\hat{N}^{(1)}, \hat{p}_1^{(1)}$ and $\hat{p}_2^{(1)}$ to get $\hat{i}^{(1)} = \hat{p}_1^{(1)}\hat{N}^{(1)}(1-\hat{p}_2^{(1)})$ then $\hat{i}^{(1)}$ will be an estimate of the number of new infections in 1991. If we construct $\hat{i}^{(3)}$, ... $\hat{i}^{(2)}$to $\hat{i}^{(1000)}$ in a similar manner, we can approximate the 95% confidence interval limits of a sample from the distribution that describes the number of new infections by the 5th percentile and 95th percentile of the distribution given by $\hat{i}^{(1)}$, $\hat{i}^{(1)}$ ... $\hat{i}^{(1000)}$ arranged in ascending order. From Figure 6.3 we can see that the sampled values follow a symmetric distribution, therefore we can approximate the mean by the median value of $i^{(1)}$ ... $i^{(1000)}$.

If we use the values quoted in Taylor *et al.* (1994), $\hat{p}_1 = 0.002$, $\hat{p}_2 = 0.018$, we can summarise the distributions of the prevalence, and incidence as follows.

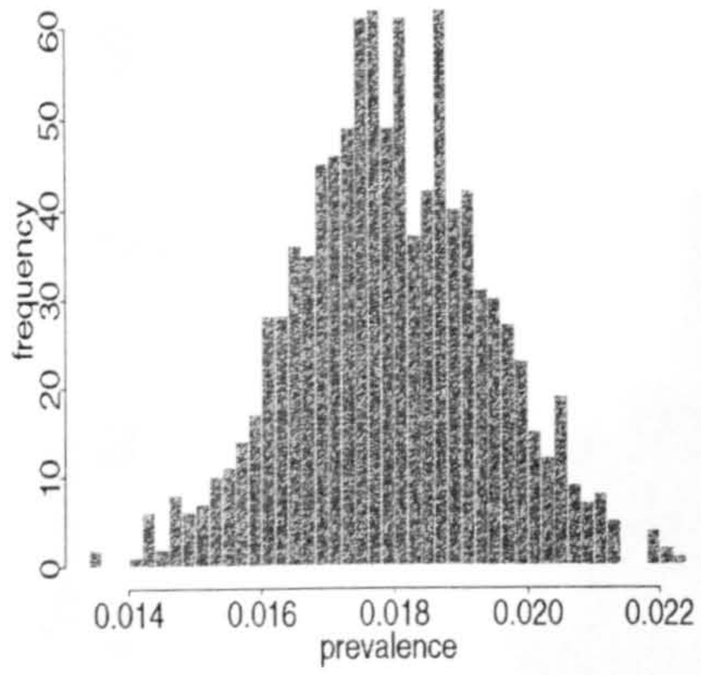

Figure 6.2: 1,000 simulated prevalence values.

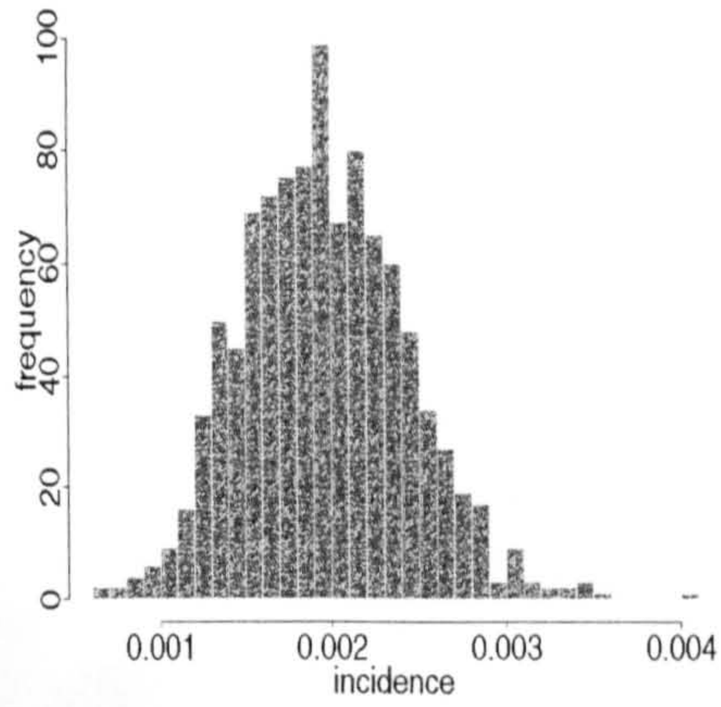

Figure 6.3: 1,000 simulated incidence values.

We can also combine these values with the population size estimates to give us 1,000 estimates of the number of new infections which we can again summarise as a distribution in Fig 6.4.

We can use the data from Table 5.2 to construct a discrete distribution using the RANDOM command in MINITAB with the DISCRETE subcommand. The distribution will be very skew reflecting the fact that many IDUs do not report needle sharing. The distribution will also be discrete, as the questionnaire responses were categorical data. To obtain an estimate of the total amount of sharing for a population size N we can simply repeat the random sampling from the distribution constructed from Table 5.2 N times and sum the N values. We will therefore have a continuous distribution for the total amount of sharing, which would more accurately describe the distribution of the amount of sharing compared with simply multiplying the values in Table 5.2 by the population size. In a similar manner to that described above for calculating the mean number of new infections, we can use $\hat{N}^{(1)}$, the first value sampled from the population size distribution so sample $\hat{N}^{(1)}$ times from the reported sharing distribution. Taking the sum of these values will result in $\hat{S}^{(1)}$, which will be the first value from a series of values that can be thought of as describing the total number of sharing

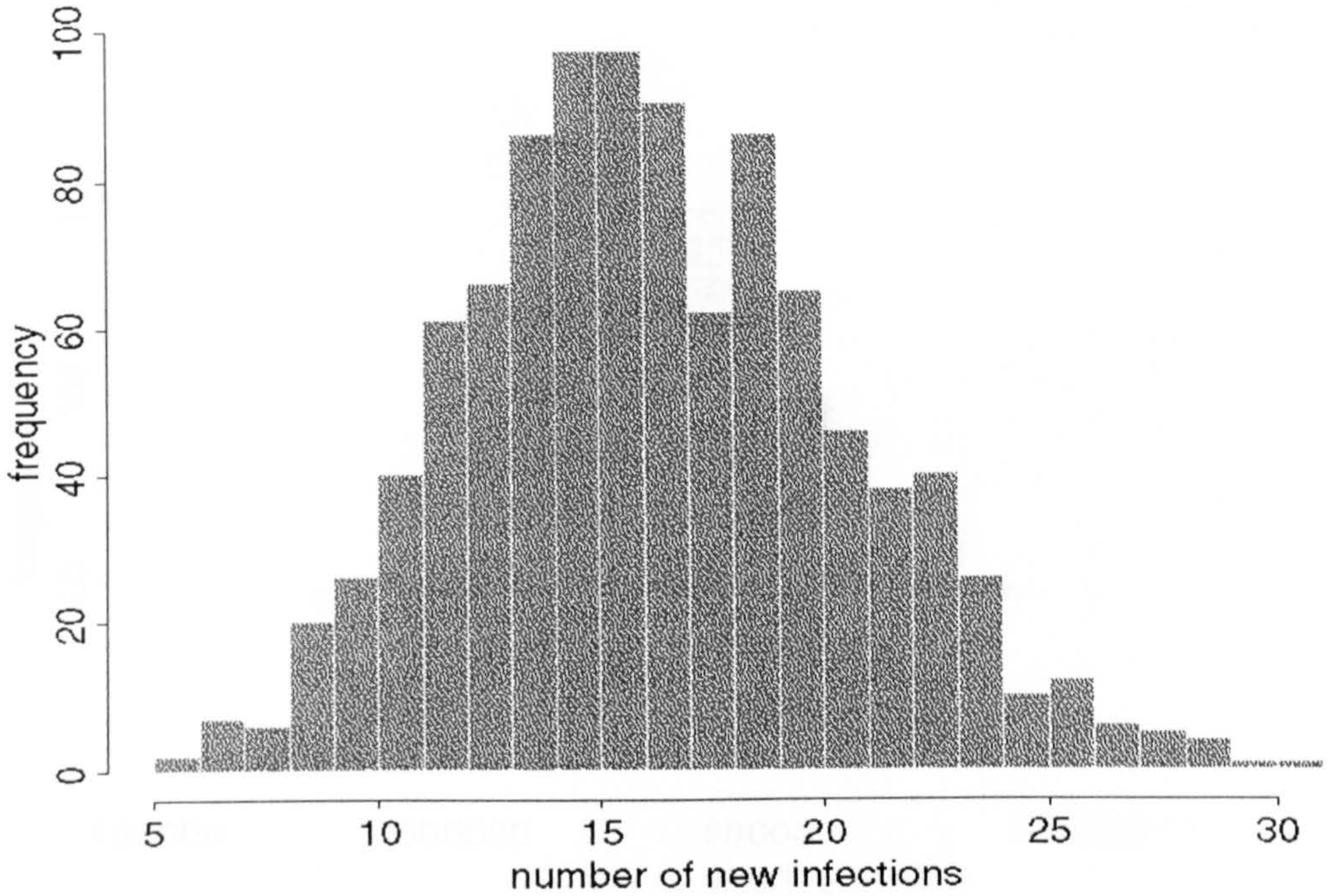

Figure 6.4: 1,000 simulated number of new infections.

events over a period of a month in a population whose size has been estimated. As the sampled IDUs have been injecting on average 5.5 months out of the preceding 6 months we can multiply this value by 11 to obtain an estimate $\hat{S}^{(1)}$ for the total sharing for the complete year. Again after repeating this process 1,000 times we will have $\hat{S}^{(1)}$, $\hat{S}^{(2)}$, ... $\hat{S}^{(1000)}$ and we can obtain an estimated mean value for the total number of sharing events and an approximate 95% confidence interval as before. We can estimate that there were 561,968 sharing events in 1990, 95% confidence interval [477,235, 646,613]. The associated distribution is shown in Figure 6.5.

This can be compared to Table 5.2, which describes the sharing frequencies reported by the sample of 503 IDUs. All that remains to obtain a series of estimates of the probability that sharing a needle results in a new infection is to divide the values for the number of new infections shown as a histogram in Figure 6.3, by the corresponding values for the number of sharing events described by

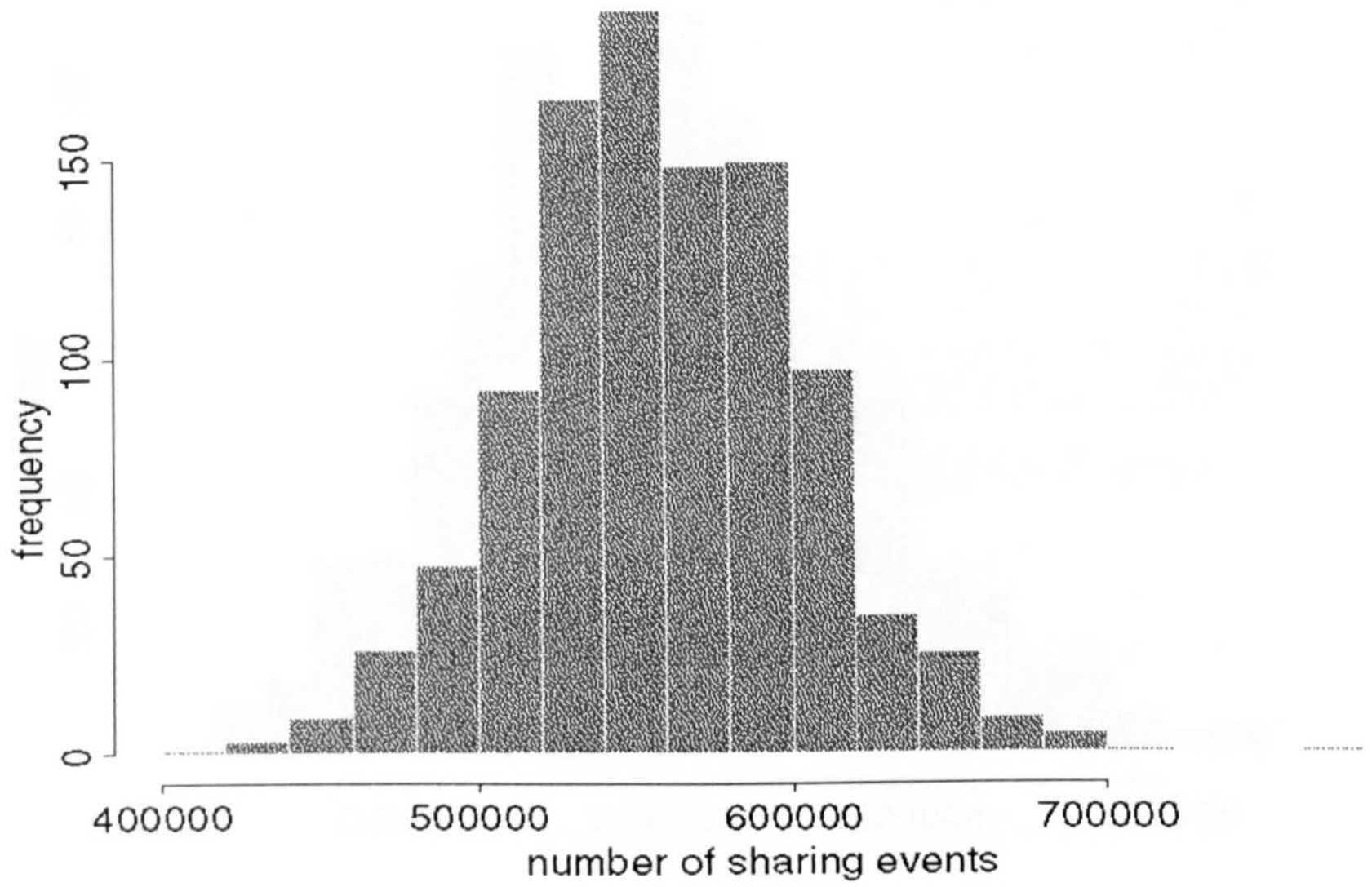

Figure 6.5: 1,000 simulated numbers of sharing events.

Figure 6.6 and find the mean value, the 5th percentile and the 95th percentile as before. Thus q, the probability that sharing a needle in Glasgow in 1990 would result in a new infection is estimated as 2.95×10^{-5}, 95% confidence interval $[1.56 \times 10^{-5}, 4.39 \times 10^{-5}]$. The distribution is reasonably symmetric and is shown in Figure 6.6.

Although the preceding analysis is based on several assumptions that cannot be tested, and the confidence intervals that were obtained are approximate and not statistically robust, it was carried out to demonstrate how low the probability of becoming infected through a single sharing act was.

Even at the higher confidence limit, 4.39×10^{-5}, the value appears to be extremely low. If the sharing pattern of IDUs were completely random which would correspond to the homogeneous mixing model in Chapter 3 and infected IDUs were equally distributed throughout the population, then only 1.8% of the reported 561,968 sharing events, or 10,115, would involve any risk of infection.

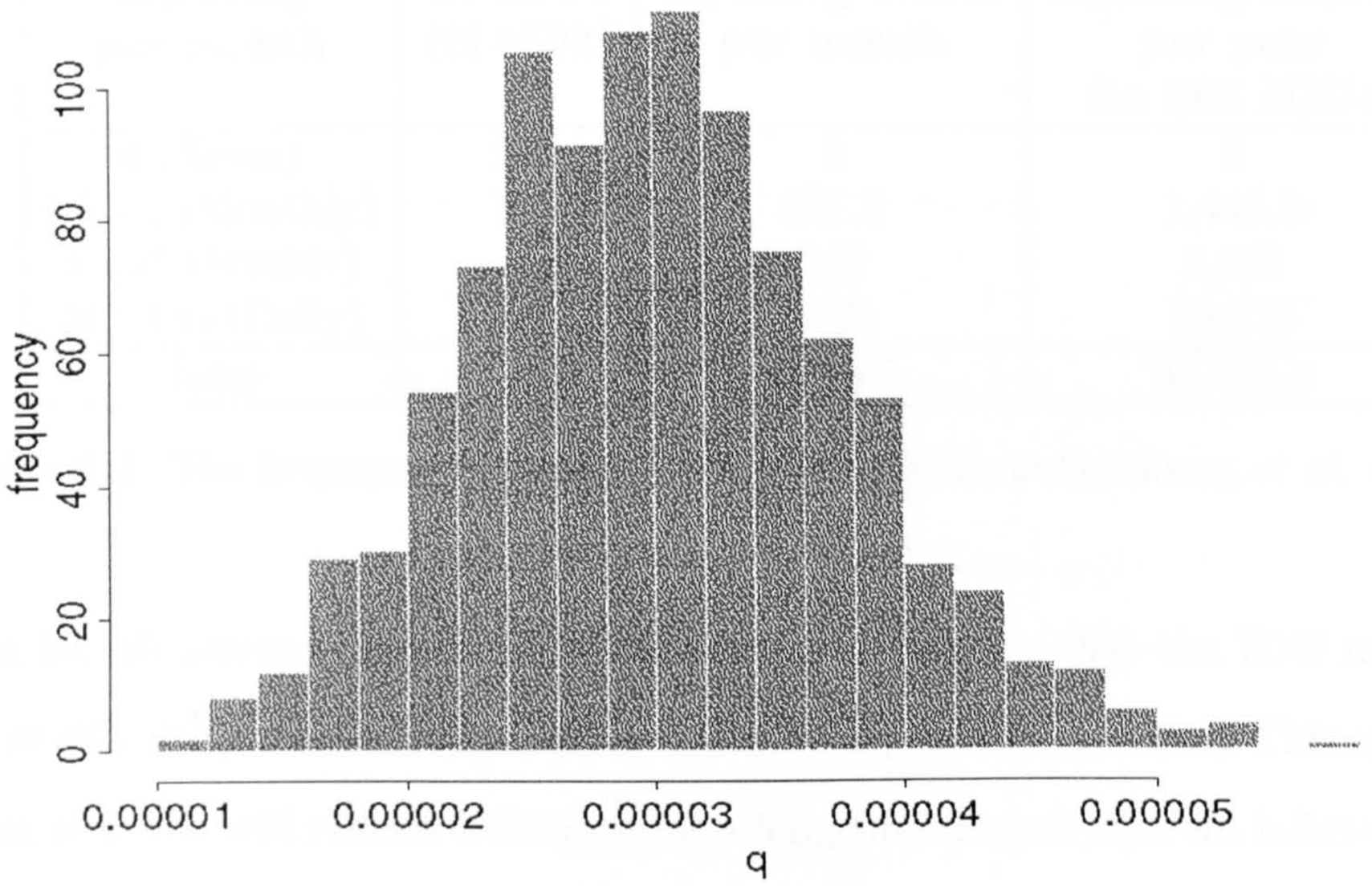

Figure 6.6: 1,000 simulated values of q.

	Monthly	Weekly	Daily	Total
Efficient Cleaning Practice	63	20	9	92
Inefficient Cleaning Practice	57	29	22	108

Table 6.1: Cleaning Practices of IDUs adapted from Goldberg *et al.* (1995).

Given that the shared needle had previously been used by an infected IDU, then there would be several factors that would influence the infectivity of the needle. As in Chapter 4, these can be summarised by three parameters, α, which depends on the amount of blood left in the needle and the viral load of such blood, τ, the time interval between injections and ξ, the probability that the needle is cleaned effectively between injections.

The reported cleaning practices of a sample of 200 IDUs is summarised in Table 6.1, adapted from Goldberg *et al.* (1995). From this table the probability that an IDU cleaned the injecting equipment effectively is 0.46, although daily sharers were less likely to use effective cleaning methods. Therefore 5,462 out of

Frequency of injecting per month	Number of IDUs (N=503)	Number of injecting events per month	Number of injecting events per year for 503 IDUs
0 (Never)	290	0	0
0.5 - 2 (Monthly)	131	131.5	1,446.5
4 - 10 (Weekly)	42	282	3,102
20 - 150 (Daily)	40	2625	28,875
Total		3,038.5	33,423.5

Table 6.2: The frequency of needle sharing adapted from Goldberg *et al.* (1995).

the 10,115 sharing events can be thought of as risky in that the IDU may not have effectively cleaned the needle and may be exposed to the virus. This assumes that a needle will remain infectious for a long time period after an infected IDU injects with it. We can then estimate α, the probability of infection given that the IDU is exposed to HIV as $\frac{16.68}{5,462} = 0.00305$. This may be an underestimate as those IDUs who share equipment more frequently appear to be less likely to effectively clean their needles. It may also tend to underestimate the probability of infection as even inefficient cleaning may do some good.

6.3 Derivation of the Infection Probability in a Stratified Population

The assumption that all IDUs mix homogeneously is likely to be unrealistic as IDUs who share more frequently will be more likely to share with other IDUs who share more frequently and vice-versa. If we stratify the population into three groups, those who share monthly, those who share weekly and those who share daily, we can explore heterogeneous mixing. If we amalgamate the categories in Table 5.2 we obtain Table 6.2. If we now assume that the population of IDUs is split into these four categories, we can define $\hat{\alpha}_D$ as the estimated probability that an uninfected IDU who shares injecting equipment daily will become infected

after using an infected needle, estimated from the data for those that share daily, with a similar definition for $\hat{\alpha}_M$ and $\hat{\alpha}_W$. As we are only interested in IDUs that share, we wish to ignore the category that does not share.

As before, i, the expected number of new infections, can be calculated as $i = p_1 N(1 - p_2)$. If s is the number of sharing events then q, the probability that a single injecting act will result in a new infection will be $\frac{i}{s}$. Out of the s sharing events, assuming that each needle had only been used previously by one IDU, then $p_2 s$ events would have occurred with a needle from an infected person. If ξ is the probability of effective cleaning of the needle, then $(1 - \xi)p_2 s$ will be the expected number of sharing events that can be thought of as risky, in that the needle was previously used by an infected person and was not effectively cleaned. We therefore have

$$\alpha = \frac{i}{(1-\xi)p_2 s} = \frac{p_1 N(1-p_2)}{(1-\xi)p_2 s}. \tag{6.1}$$

For the group that shares monthly, there were an estimated 1446.5 sharing events in that year for the 131 IDUs in the sample of 503 who reported monthly sharing, which, if the sharing patterns were extrapolated onto the whole population, there would be $\frac{131}{503} \times 8,494 = 2,212$ IDUs in the population who share monthly. The total number of sharing events for monthly sharers in 1990 would be $\frac{2,212}{131} \times 1,446.5 = 24,425$. It would seem sensible to assume that IDUs who share more often would be at greater risk of being infected with the virus, which would imply that the HIV prevalence and incidence in the group who reported daily sharing would be higher than that in the group who share monthly. If we calculate these values within the monthly sharing group by weighting the population prevalence and incidence by $\bar{s}_M$, the average monthly number of sharing events per IDU reported in Table 6.2 then the number of existing infected people in the monthly group will be $\frac{131.5}{3,038.5} \times 152.89 = 6.62$, therefore p_2, the prevalence will be $\frac{6.62}{2,212} = 2.99 \times 10^{-3}$, assuming that each injection is equally likely to cause infection. In

	Never	Monthly	Weekly	Daily
N	4,897	2,212	709	675
s	0	24,426	52,382	487,603
$\bar{s}$	0	11.042	73.882	722.374
new infecteds (i)	0	0.722	1.548	14.412
p_1	0	3.274×10^{-4}	2.228×10^{-3}	0.02655
infecteds (I)	0	6.616	14.190	132.086
p_2	0	2.991×10^{-3}	0.020	0.196
ξ	0	0.525	0.4081	0.29
α		2.081×10^{-2}	2.495×10^{-3}	2.127×10^{-4}

Table 6.3: Estimated parameter values.

addition the number of new infections can be calculated as $\frac{131.5}{3,038.5}\times 16.68 = 0.72$. Therefore the incidence in the monthly group will be $\frac{0.72}{(1-2.99\times10^{-3})\times 2,212} = 3.27\times10^{-4}$. From Table 6.1 we have that c, the probability of effective cleaning, will be estimated by $\frac{63}{120} = 0.525$. Our estimate of $\hat{\alpha}_M$ can then be calculated from the data on monthly sharers by Equation 6.1. We can summarise this calculation, and the calculation of α_W and α_D as follows in Table 6.3.

As can be seen from Table 6.3, the assumption that the prevalence and incidence of HIV within the three groups is weighted by $\bar{s}$ then we have that α, when calculated using the data for those IDUs that share monthly, is larger than α calculated with data on weekly sharers which in turn is larger than α calculated using data on daily sharers.

The value of α calculated above can be directly compared with the value α quoted in Kaplan's deterministic model, Equations 2.1 and 2.2, and also the parameter used in the stochastic simulation models described in Chapter 3. This parameter is a biological parameter which depends only on factors such as the infectivity of the virus therefore calculating α using different data sets corresponding to independent factors such as the rate at which IDUs share injecting equipment should result in similar values. If the methodology behind our esti-

mate of α is correct, then we should be able to explore incidence and prevalence values for monthly, weekly and daily sharers which will give a common value for α.

Equation 6.1 can be reformulated in terms of the actual number of infected IDUs at the beginning of 1990, I, and the number of IDUs that become infected during that year i. We have

$$\alpha = \frac{iN}{(1-\xi)Is} \tag{6.2}$$

which when splitting the population into 3 groups will be

$$\alpha_M = \frac{i_M N_M}{(1-\xi_M) I_M s_M}$$

$$\alpha_W = \frac{i_W N_W}{(1-\xi_W) I_W s_W} \tag{6.3}$$

and $$\alpha_D = \frac{i_D N_D}{(1-\xi_D) I_D s_D}.$$

We have data from which we can estimate the parameters N_M, N_W, N_D, ξ_M, ξ_W, ξ_D, s_M, s_W and s_D, and we also know that

$$i_M + i_W + i_D = i_T \tag{6.4}$$

and $$I_M + I_W + I_D = I_T,$$

where i_T and I_T are the total number of new infected IDUs in 1990 and the number of infected IDUs at the beginning of 1990 respectively, both parameters can be estimated from the data. Hence setting $\alpha_M = \alpha_W = \alpha_D$ estimated from the combined data we have a system of five equations in six unknowns. A solution to the five equations can be found in terms of one of the other unknowns i_M, i_W, i_D, I_M, I_W and I_D. The system of equations described above were solved using the mathematical computation system MAPLE, using i_M as the variable that the unknown variables were solved in terms of. The justification behind the choice of i_M is that it is thought that this value would be the smallest. The

parameter values described above were used. We have a value for α determined to be 3.04×10^{-3} by using the data collected from the sample of 503 IDUs before they were split into groups by their sharing activities. We recognise that this is an estimated value, for which we have provided an approximate measure of the uncertainty of the estimate as previously described. We also have estimates of the total number of new infections in 1990 from Taylor *et al.* (1994) and the total number of infected people at the start of 1990, within which publications the relevant authors discuss the uncertainty in these estimates. Having discussed this, we still use this estimated value in our system of equations and the estimated number of original and new infections.

The system of equations were repeatedly solved for different values of i_M, but it was found that only two discrete values of i_M, $i_M = 1$ and $i_M = 2$ resulted in solutions that were feasible and that the range of feasible solutions for non-discrete values for i_M was when $i_M < 2.2$. Table 6.4 is a range of feasible solutions for $1 \leq i_M \leq 2.2$. It should be noted here that we approximating a set of discrete values by a set of continuous values; that is the number of infected IDUs and the number of new infections can only be integers. This is similar to approximating stochastic models which describe the number of infected individuals with deterministic models.

There may be constraints that we want to put on the variables to achieve biological relevance. One constraint that may be desirable is that the number of new infections in each group is less than the number of existing infections in that group, as described by Constraint 6.5.

$$\begin{aligned} i_M &< I_M \\ i_W &< I_W \\ i_D &< I_D \end{aligned} \tag{6.5}$$

i_M	i_W	i_D	I_M	I_W	I_D
1.0	11.65	4.03	62.70	87.60	2.59
1.1	10.75	4.84	68.97	80.81	3.10
1.2	9.84	5.64	75.25	74.03	3.61
1.3	8.94	6.44	81.52	67.25	4.13
1.4	8.04	7.24	87.79	60.46	4.64
1.5	7.14	8.04	94.06	53.67	5.16
1.6	6.23	8.85	100.33	46.89	5.67
1.7	5.33	9.65	106.60	40.11	6.18
1.8	4.43	10.45	112.87	33.32	6.70
1.9	3.53	11.25	119.14	26.54	7.22
2.0	2.62	12.06	125.41	19.75	7.73
2.1	1.72	12.86	131.68	12.97	8.24
2.2	0.82	13.66	137.95	6.18	8.75

Table 6.4: Range of feasible soultions for $1 \leq i_M \leq 2.2$.

On closer inspection of the definition of incidence and prevalence in this chapter, we will see that it is possible that the number of new infections in a group for a given year can be greater than the number of infected people at the start of the year. Indeed, looking at many conventional models of disease spread, including Kaplan's deterministic model the number of new infections can be greater than the original number of infections. Therefore Constraint 6.5 may not be relevant.

Under conventional mixing models stratified by sexual mixing rates in the case of the sexual spread of a disease, it can be shown that the proportion of infected people in the group with the highest sexual activity rate will have the highest number of new infections. Although it is known that IDUs do not select a person with whom to share injecting equipment with at random and that the number of different people they share with may not be strictly correlated with the frequency with which they share, it is assumed that the fraction of new infections in the group that shares daily will be greater than that in the group that shares weekly which in turn will be greater than in the group that shares monthly as described by Constraint 6.6.

$$\frac{i_M}{N_M} < \frac{i_W}{N_W} < \frac{i_D}{N_D} \tag{6.6}$$

Without exploring the relationship between IDUs sharing patterns before and after infection with HIV, we cannot assume that the sharing patterns of infected IDUs will be the same as the sharing patterns of uninfected IDUs. Indeed it can be argued that knowledge of HIV infection may affect the sharing rates of IDUs, as explored in Chapter 4. Therefore an assumption that the fraction infected with HIV at the start of the year in the group that shares daily will be greater than that of the weekly sharers which is in turn greater than that of the monthly sharers, as described by Constraint 6.7, may be questionable.

$$\frac{I_M}{N_M} < \frac{I_W}{N_W} < \frac{I_D}{N_D}. \tag{6.7}$$

We can show the range of feasible solutions in terms of the prevalence and incidence values in Table 6.6 graphically in Figures 6.7 and 6.8 where the y axis describes incidence and prevalence of HIV amongst IDUs respectively numbers of infected IDUs for a solution set determined by a value of i_M on the x axis. From

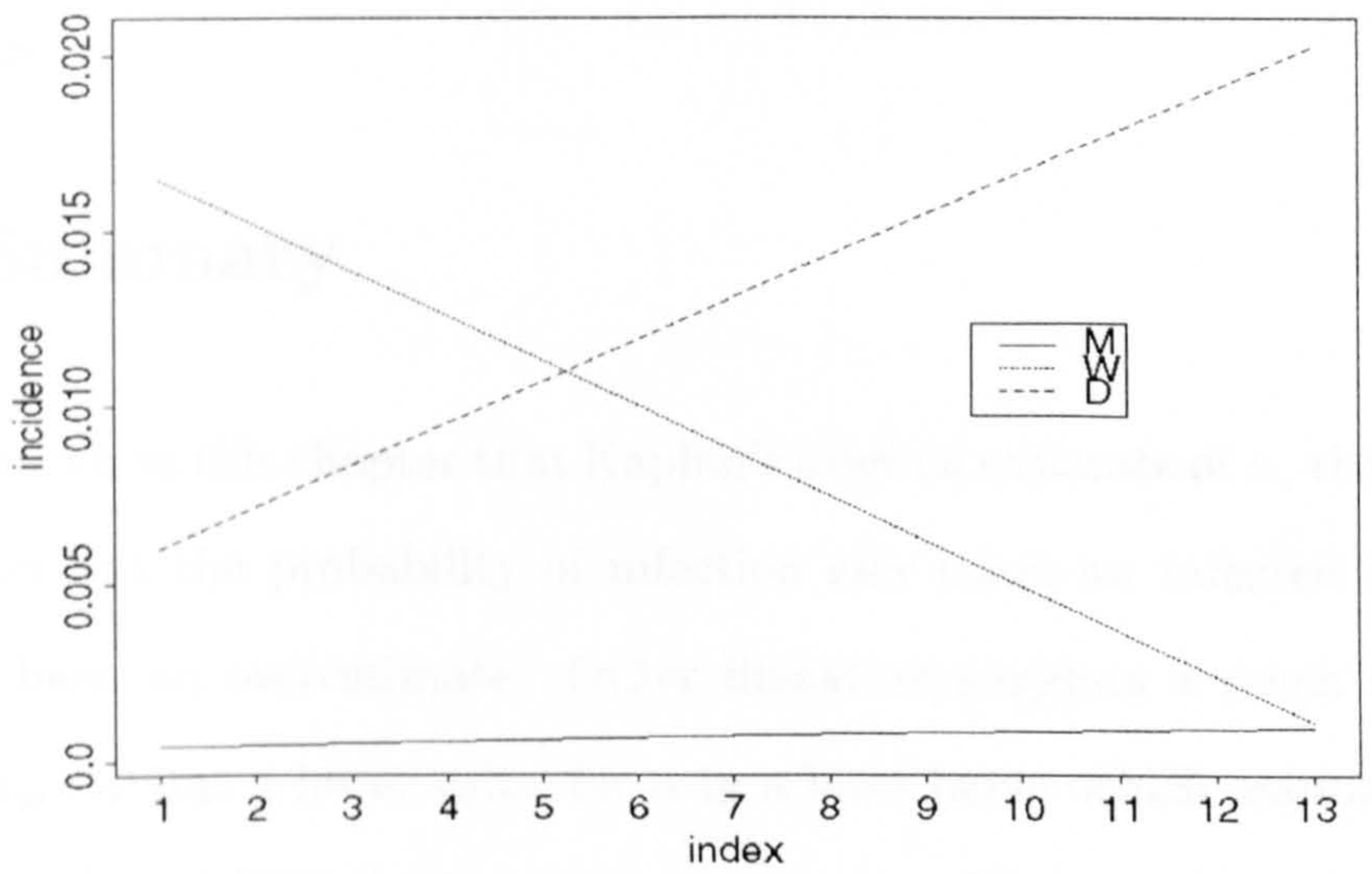

Figure 6.7: Range of incidence values, for $1 < i_M < 2.4$.

these figures, we can see from Figure 6.7 that there exists a range of solutions

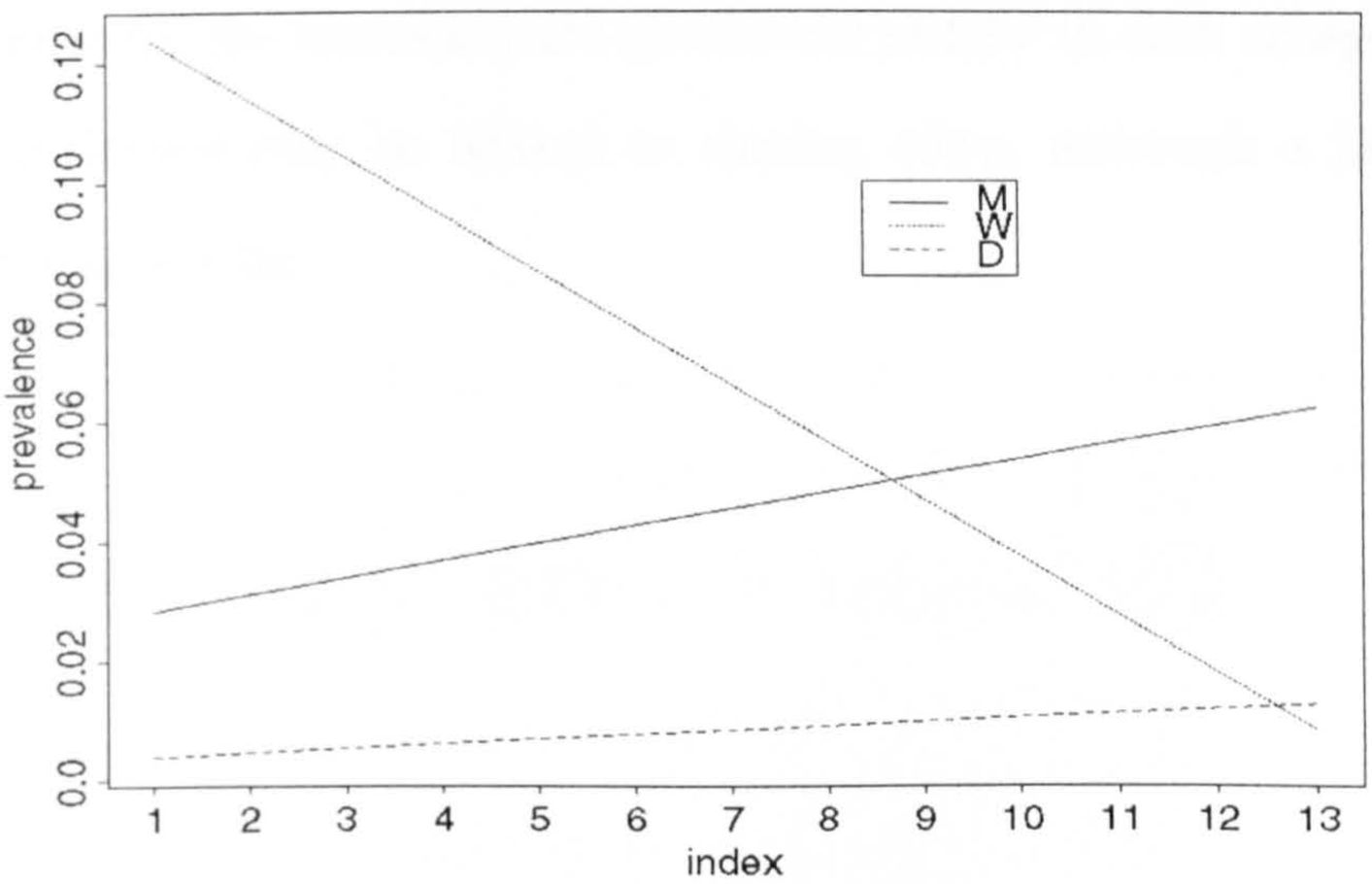

Figure 6.8: Range of prevalence values, for $1 < i_M < 2.4$.

which satisfy Constraint 6.6, but from Figure 6.8, there is no range of solutions that statisfies Constraint 6.7. Or in other words, there is a range of values in which the incidence is higher in the groups that share more often, however the prevalence at the start of the year was never greater in these groups. This may be due to IDUs changing their sharing practices when they are aware of their HIV status.

6.4 Summary

We have shown in this chapter that Kaplan's original estimate of α, the parameter which described the probability of infection afer using an infected needle may well have been an overestimate. Other literature suggests a much lower value and Kaplan obtains a lower value for α in a later paper which assumed that the number of infected IDUs had reached equilibrium. We have derived an estimate of α using data collected on IDUs in Glasgow in 1990, along with an estimate of the number of IDUs. We have also stratified the population by sharing rates, and shown that our estimate of α is broadly consistent when daily, weekly and

monthly sharers are analysed separately. Indeed when examining the range of possible values for the incidence and prevalence of HIV in each category, we find that high incidence may be related to sharing often, although a high existing prevalence may not be.

Chapter 7

Uncertainty and Sensitivity Analyses

7.1 Introduction

In the preceding two chapters we examined the values that the various parameters employed when modelling the spread of HIV via shared injecting equipment may take. We wish now to demonstrate the effect that varying these parameters may have on the spread of the disease. Unlike Chapters 2 and 4, where we varied parameters in isolation, in this chapter we will examine the combined effect of varying several parameters simultaneously. In order to do this we postulate distributions for these different parameters. Then using sets of values sampled from each of these distributions we can examine the proportion of infected IDUs over time as found by numerically solving the differential equations. We perform uncertainty and sensitivity analyses on some of the previously presented models by examining the output values obtained when using different combinations of the parameters. We conclude this chapter by discussing some of the policy implications of the results.

A mathematical model of disease transmission can be seen as a system in which a set of input values combine to give a single value or series of output values. The key epidemiological parameter R_0 can also be viewed as such a system. The

estimation of the parameter values employed in the system is often subject to uncertainty therefore it may be more appropriate to treat each input parameter as a random variable with a corresponding probability density function. An uncertainty analysis, similar to that presented in Chapter 6 which was used to examine the infection parameter α, measures the effect that this uncertainty in the input parameters has on the output parameter. A sensitivity analysis extends the uncertainty analysis by exploring the sensitivity of the output parameter to the uncertainty of the input values.

There are several distinct stages involved in both an uncertainty and a sensitivity analysis. After postulating the distributions of the input parameters, a sampling design must be decided upon. The number of simulations that will be used in the analyses must also be decided before repeated solving of the model using the parameter values sampled from the postulated distributions. It is at this point that the uncertainty and the sensitivity analyses differ. Within the uncertainty analysis the resultant output values are examined, often using non-parametric measures of dispersion such as percentiles. In the sensitivity analysis the correlation between the input values and the output values is examined, again often using a non-parametric measure of correlation such as the partial rank correlation coefficient (Kendall and Stuart, 1979).

There are several sampling designs that can be used in a sensitivity analysis, ranging from simple random sampling to a full factorial sampling design. The latter is time consuming, especially in models that employ many parameters, whereas the former can be shown to be inefficient (Stein, 1987). Latin Hypercube Sampling (LHS) has been used by Blower and Dowlatabadi (1994) in examining their complex HIV transmission model which employed twenty behavioural and biological transmission parameters in a system of thirty four differential equations to describe the spread of HIV within interacting heterosexual and drug injecting

populations (Blower *et al.*, 1991). We wish to undertake similar analyses on the model proposed by Kaplan (1989). We do not, however, use the LHS design, not because of the added complexity, but because efficiency will not be as pertinent when analysing a simpler deterministic model such as those previously examined within this Thesis. We also wish to employ a simple random sampling design as we have previously constructed numerical distributions for some of the relevant parameters. We can therefore sample directly from the distribution which we presented in Figure 5.2 to describe the number of sharing episodes per month.

The effect of using a simple random sampling design on the uncertainty analysis may be to reduce the variation in the output values, as it is possible that the full range of the input values might not be sampled. A sensitivity analysis which uses non-parametric measures of correlation should not be affected because the correlation of the ranks between a monotonically increasing or decreasing range of input values and a monotonically increasing or decreasing output value should be present regardless of the sampled input values, at least in the context of Kaplan's model and the possible range of input parameter values.

7.2 The HIV Transmission Model

The simple model presented by Kaplan (1989) was described in Chapter 2. This model was explored using a set of parameter values as suggested by Kaplan. A notable feature of the model was that, using most combinations of the parameters suggested in Kaplan's original paper, almost every drug injector in the population became infected. This may be because the model is too simplistic, however the high values of α employed in the initial examination of the model must now be thought of as questionable in the light of more recent work such as Kaplan and O'Keefe (1993). In addition, the process of flushing may not be the best way of approximating the complex biological, physical and virological processes that

occur when a drug injector, infected or otherwise, injects with a previously used needle. Also the model ignores the natural turnover of needles. The effect of including this would be to decrease the fraction of needles which are infected and hence indirectly the fraction of addicts who are infected. We can now re-examine this model using what are now thought to be more realistic parameter values, and this exercise will be useful in explaining which parameters within the model have the most influence on the results.

Both analyses view a mathematical model as a system into which we feed a set of input parameters and out of which we obtain an output parameter. In the case of the model that Kaplan intially presented, there are five input parameters, λ, γ, θ, α and μ. As stated in Chapter 2, the output from these models can either be the proportion of needles or the proportion of IDUs that are infected, and both these output values change over time. To obtain a single series of output values, we ignore the proportion of infected needles and concentrate on the proportion of infected needles. If we examine this proportion at time $t = 1, 2, ...20$ years we have 20 separate output values. We can then include each output value in the sensitivity analysis separately.

7.3 Probability Distribution Functions for Parameters

To construct probability density functions for the distributions of the various input parameters we combine information taken from the literature as described in Chapter 5 and with the previously derived values for the 'rate of sharing' parameter also described in Chapter 5. We use at this stage the distribution for the values of α as proposed by Blower and Dowlatabadi. Table 7.1 describes the minimum value, the maximum value, the median value and the standard deviation of the distributions that we now assume these parameters take. Figures 7.1 to

Parameter	Units	Min	Max	Median	Standard deviation
α		0.004	0.884	0.334	0.244
γ		0.013	9.447	1.278	2.795
λ	Visits per Month	0.331	189.0	1.971	25.40
θ		0.021	0.997	0.550	0.301
μ^{-1}	Years	0.511	13.45	2.844	2.853

Table 7.1: Parameter Distribution Summary Statistics.

7.5 are histograms of 100 values sampled at random from these distributions.

The distribution of λ, the rate at which an IDU shares needles, is adapted from Goldberg *et al.* (1995). There has been a slight alteration to the distribution as shown in Chapter 5 which was derived from a discrete distribution adapted from the eight questionnaire responses as described in Table 5.3. This distribution was still discrete in that it could only take the value 0.5 or integer values between 1 and 200 for the number of sharing events per month. Many drug users reported sharing needles less than once per month and this was reflected in the high probability that a random variate sampled from this distribution was 0.5. As the sensitivity analysis looks at the correlation between these values and the output values of the model, we wish now to slightly change the 'sharing' distribution by adding an independent normal distribution, N(0,0.25) to this discrete distribution to obtain a continuous distribution. Thus when examining correlations, in particular the rank correlations, there will not be so many tied values. It is, of course, possible to obtain negative values for λ when we combine these distributions, however we discarded any negative values and continued sampling until we obtained the required number of variates. As the number of discarded values was small, this procedure introduced only a small amount of bias into the distribution.

As suggested in Chapter 6, the value of α can be estimated from known values such as the HIV incidence, the HIV prevalence and the rate of sharing in a

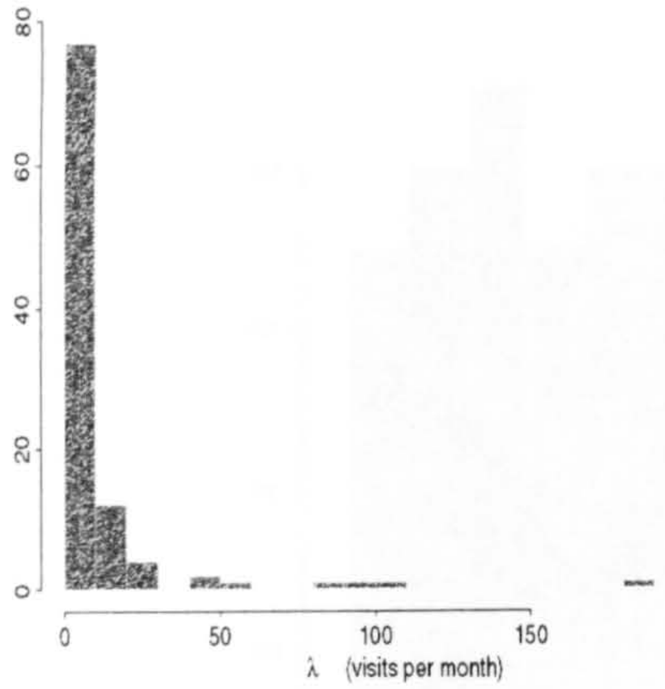

Figure 7.1: Simulated values for λ.

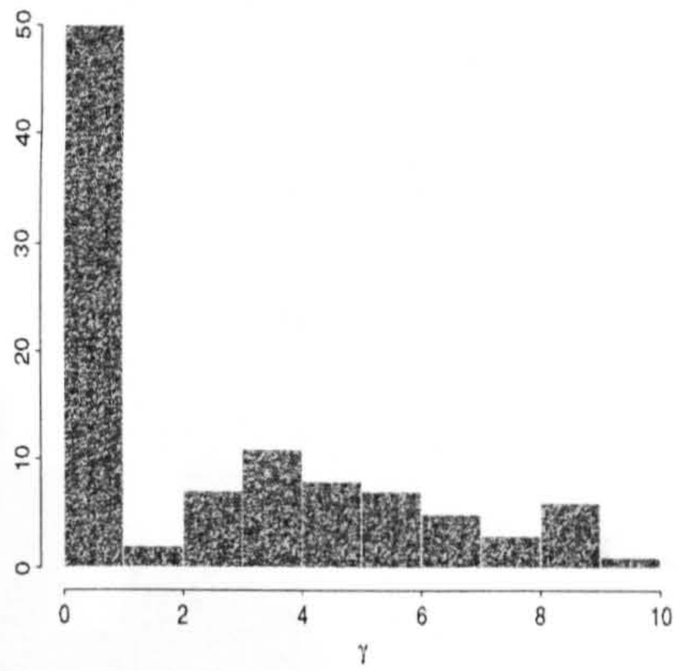

Figure 7.2: Simulated values for γ.

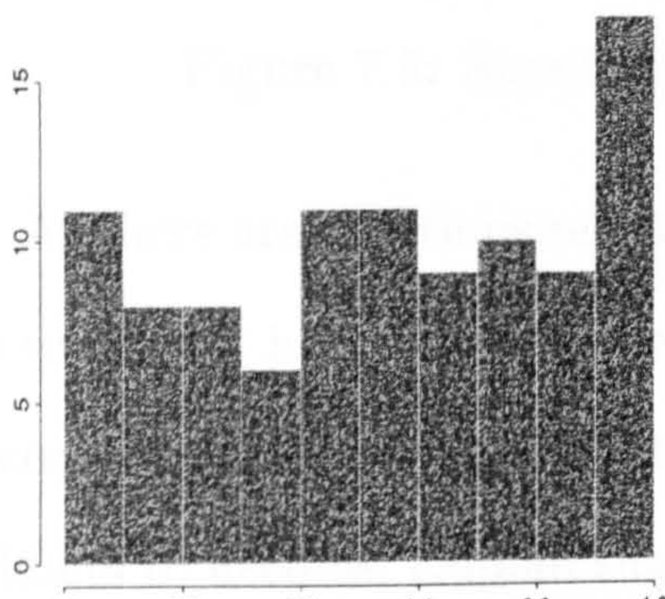

Figure 7.3: Simulated values for θ.

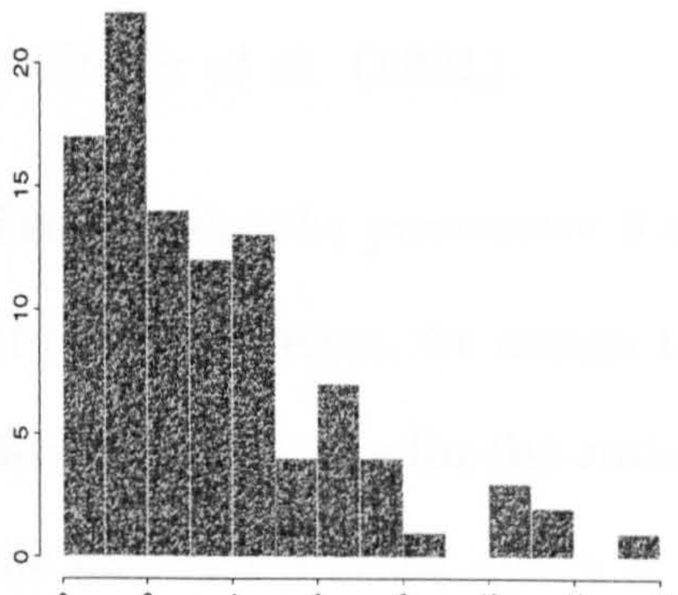

Figure 7.4: Simulated values for μ.

population of drug injectors of known size. As distributions can be attached to each of these values we can obtain a distribution for the estimated parameter. If we use this distribution for α, with a mean value of 0.00316, we find that most of the deterministic realisations will have $R_0 < 1$ so the disease will die out. This is clearly unsatisfactory as we know that AIDS persists in that population, it is the reason why we are studying it. We therefore, at this stage, employ the triangular distribution for the infection parameter α as employed by Blower *et al.*; 100 sampled values from this distribution are shown in Figure 7.5. This sampled distribution has the much higher mean value of 0.37 (median value 0.33).

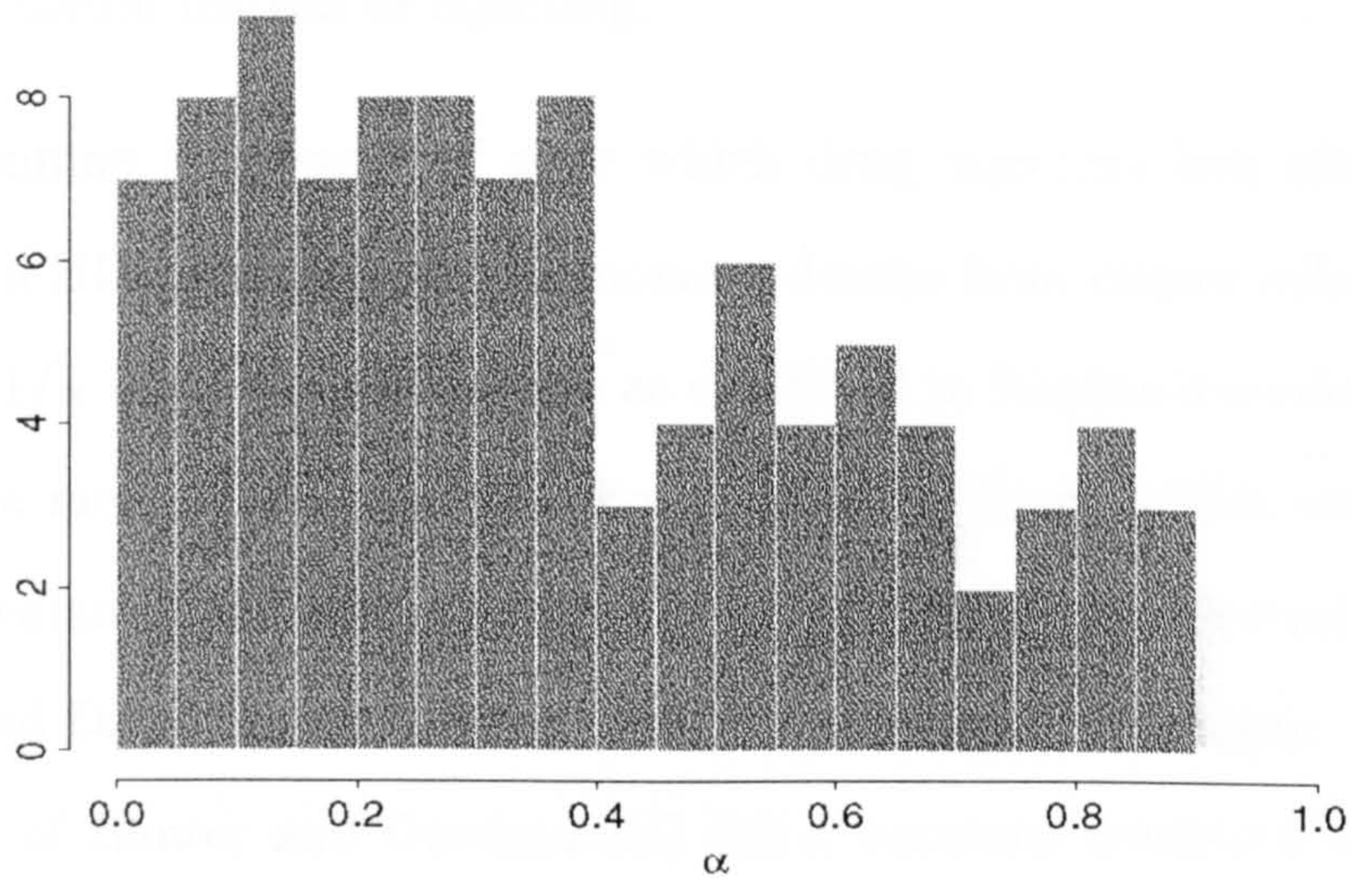

Figure 7.5: Simulated values for α from Blower *et al.* (1991).

As there are questions relating to the validity of employing the parameter θ and as we do not have any firm idea about the value of this parameter, we assign to θ a continuous uniform distribution with values between 0 and 1. As for the ratio of addicts to needles, Kaplan suggests values which lie between $\gamma = 0.1$ and $\gamma = 10$, therefore we use these values as upper and lower bounds of the distribution. We wish to include values of γ which correspond to an excess of needles over IDUs and also values of γ in which there are less needles than IDUs. We can therefore split the distribution into two sections, one which is a continuous uniform distribution from 1 to 10 and the other which is $\gamma = 1/G$ where G also is a continuous uniform distribution from 1 to 10. We obtain half the required number of values sampled at random from each of these distributions independently and then randomly order these values to avoid a pattern in the simulated values.

The remaining parameter μ is harder to attach a distribution to as we have described, in Chapter 5, that the rate at which drug injectors cease sharing injecting equipment can depend on several related parameters, including the incubation period of HIV and survival rate of those with AIDS, and also the rate at which

drug users cease using drugs or change their method of using them, for example by smoking heroin instead of injecting.

If we examine the length of time which drug injectors live after becoming infected with HIV, ignoring for the moment deaths from causes other than HIV, this will be $1/\mu$ using the parameters as described in Kaplan's model (1989). We can take the mean of this distribution to be eight years, which corresponds to both the median of the Weibull distribution describing the survival distribution in Blower and Dowlatabadi and the value of μ suggested by Kaplan. The Weibull distribution of Blower and Dowlatabadi has a standard deviation of 3.71 years, so we employ this shape parameter. We therefore independently sample a value for $1/\mu$ from the normal distribution with mean 8 and standard deviation 3.71 years for each simulation.

We also need to recognise that IDUs may cease sharing for reasons other than death due to HIV/AIDS. Caulkins and Kaplan (1991) include this rate in their models, but sociological research such as McKeganey and Barnard (1992) shows that there are many reasons why people cease sharing. Although we wish to include this in our sensitivity and uncertainty analyses, we have no clear idea how this should be done. We assume that an IDU will continue to inject for only a proportion of this time, and within that time the IDU could have died from other causes. As we have no strong belief about the values that this proportion would take, we assume the distribution of the proportion has a uniform distribution between 0 and 1. We therefore combine the Normal distribution described above with this uniform distribution and, to avoid obtaining a negative or zero simulated value for the rate at which drug injectors cease sharing, we censor this combined distribution at 0.5, in other words, if the value of μ simulated is less than 0.5 we discard it and continue to sample at random until we have the required number of values. Thus the mean of the combined distribution of the length of time an

IDU continues to share after becoming infected will be approximately four years. This is consistent with combining the results of the models of Kaplan (1989) and Caulkins and Kaplan (1991) where the times until an infected IDU stops sharing due to AIDS-related and other causes are independent exponential distributions with rates 1/8 years^{-1}. Thus the combined time until an infected IDU stops sharing from any cause has mean four years, which agrees with the mean of our distribution.

7.4 Uncertainty Analyses

Now that we have created distributions for the five parameters we can go on to undertake both the uncertainty analysis and the sensitivity analysis. We have sampled 100 times from each of the distributions and used them in the system of differential equations to give 100 series of output values describing the prevalence of HIV in the IDU population or in needles. Although Blower and Dowlatabadi sample 100 times, our decision to employ this number was made to ease calculation of non-parametric measures of dispersion such as percentiles. Because of the added efficiency, the Latin Hypercube Sampling/partial rank correlation coefficient sensitivity analysis can be used with a lower number of simulations than simple random sampling. As the number of simulations used within the analysis depends on the number of input variables, in a less sophisticated model such as Kaplan's, this number of simulations may be excessive. We do however need to balance the number of simulations with the lack of efficiency in the sampling design which we are use. In employing 100 simulations we note that our analysis is not as sophisticated as that of Blower and Dowlatabadi such that we are not specifically searching for input parameters whose effect on output values as measured by the correlaton coefficient is statistically significant, rather we are looking for relatively high absolute value correlation cofficients.

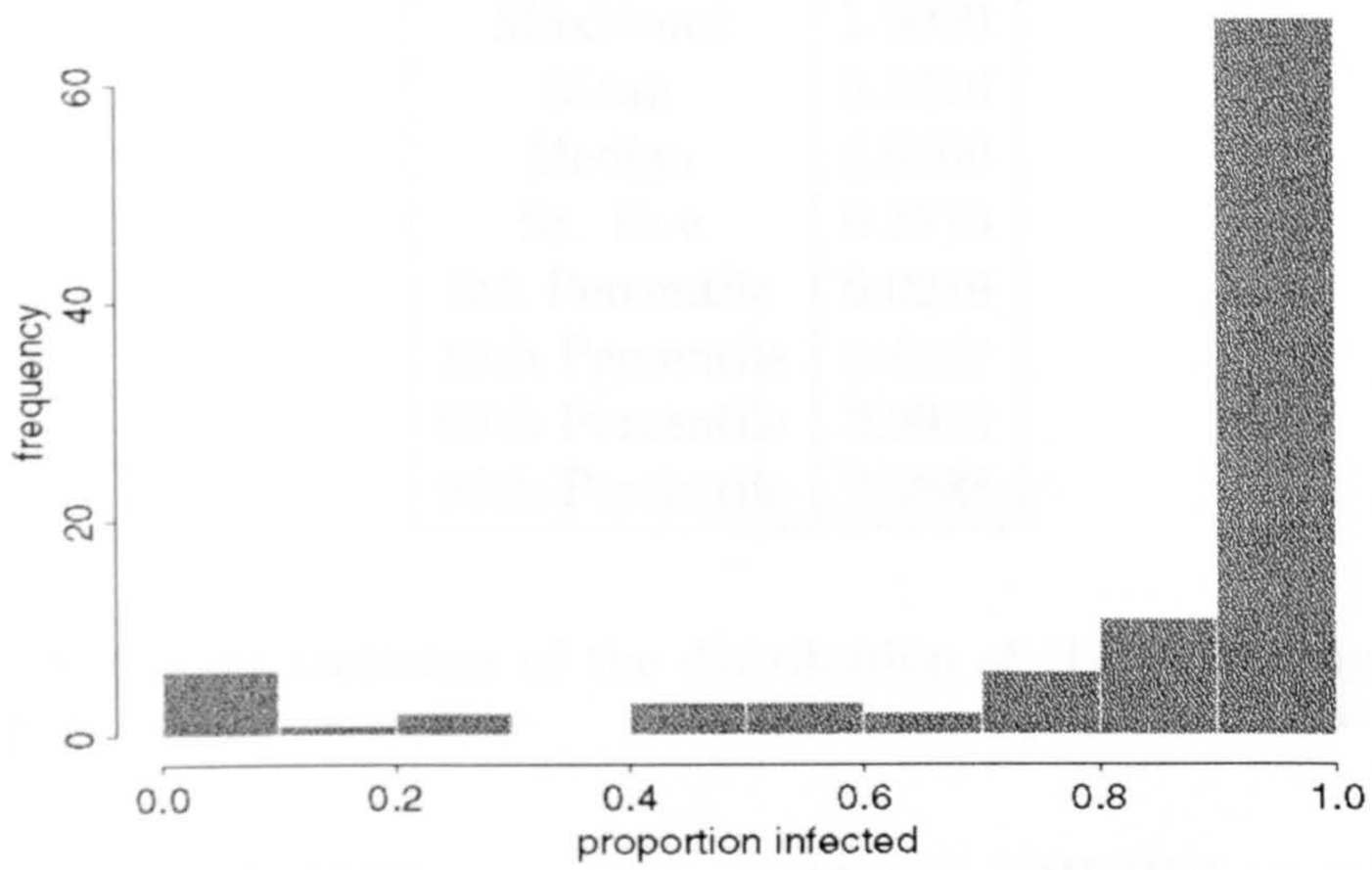

Figure 7.6: Proportion of IDUs infected from 100 simulations.

From 100 simulations of Kaplan's model, we can rank the 100 series of prevalence values by the value after 20 years. Thus we can easily obtain percentile values, including the median values over time. It should be noted that where summary statistics are calculated, the median value is calculated as the average of the 50th and the 51st ranks, whereas for simplicity, the slightly smaller values of the 50th ranked realisation are used as an approximation to the median in the figures. In Figure 7.6 we present the proportion of the IDU population that is infected after 20 years. We can see that this distribution is skew to the right, although there are some simulations in which the disease does not appear to have spread throughout the susceptible population. Table 7.2 presents the summary statistics of that distribution. In a similar way from the 100 sets of sampled parameter values from Kaplan's model we can calculate R_0 for each parameter set. Then we can also rank the 100 series of prevalence values by R_0. In Figure 7.7 we present the proportion of infected IDUs over time for the set of parameters values which result in the approximate median value of the distribution of output values at time $t = 20$ years and those which result in the approximate median value for R_0. Although the values of R_0 are quite similar for both sets of input values,

Minimum	0.0000
Maximum	1.0000
Mean	0.8316
Median	0.9500
St. Dev	0.2719
5th Percentile	0.0219
10th Percentile	0.4187
90th Percentile	0.9975
95th Percentile	0.9988

Table 7.2: Summary statistics of the distribution of the proportion of infected IDUs after 20 years.

41.58 compared with 49.62, as are the equilibrium IDU HIV prevalence values, we can see that the rate at which the disease spreads differs between the two deterministic realisations. This is possibly due to the absence of the parameter γ in both the expressions for R_0 and π^*. We also present, along with the approximate median value, the approximate 90th and 95th percentiles of the distribution in Figure 7.8 and the approximate 5th and 10th percentile values in Figure 7.9. From these figures we see that although looking at the median values suggests that the majority of IDUs will become infected with HIV, there is considerable uncertainty in the prevalence values over time, and, as we will show in a later section, it is possible that the disease may die out.

7.5 Sensitivity Analyses

The output values, as summarised in the last section, can now be used within the sensitivity analysis. In order to explore which input parameter has the most effect on the proportion of infected IDUs over time, we need to use a measure of correlation which is both non-parametric, as we can clearly see from Figure 7.6 that the simulated prevalence values are not normally distributed, and which can examine the five input parameters simultaneously. We therefore use the

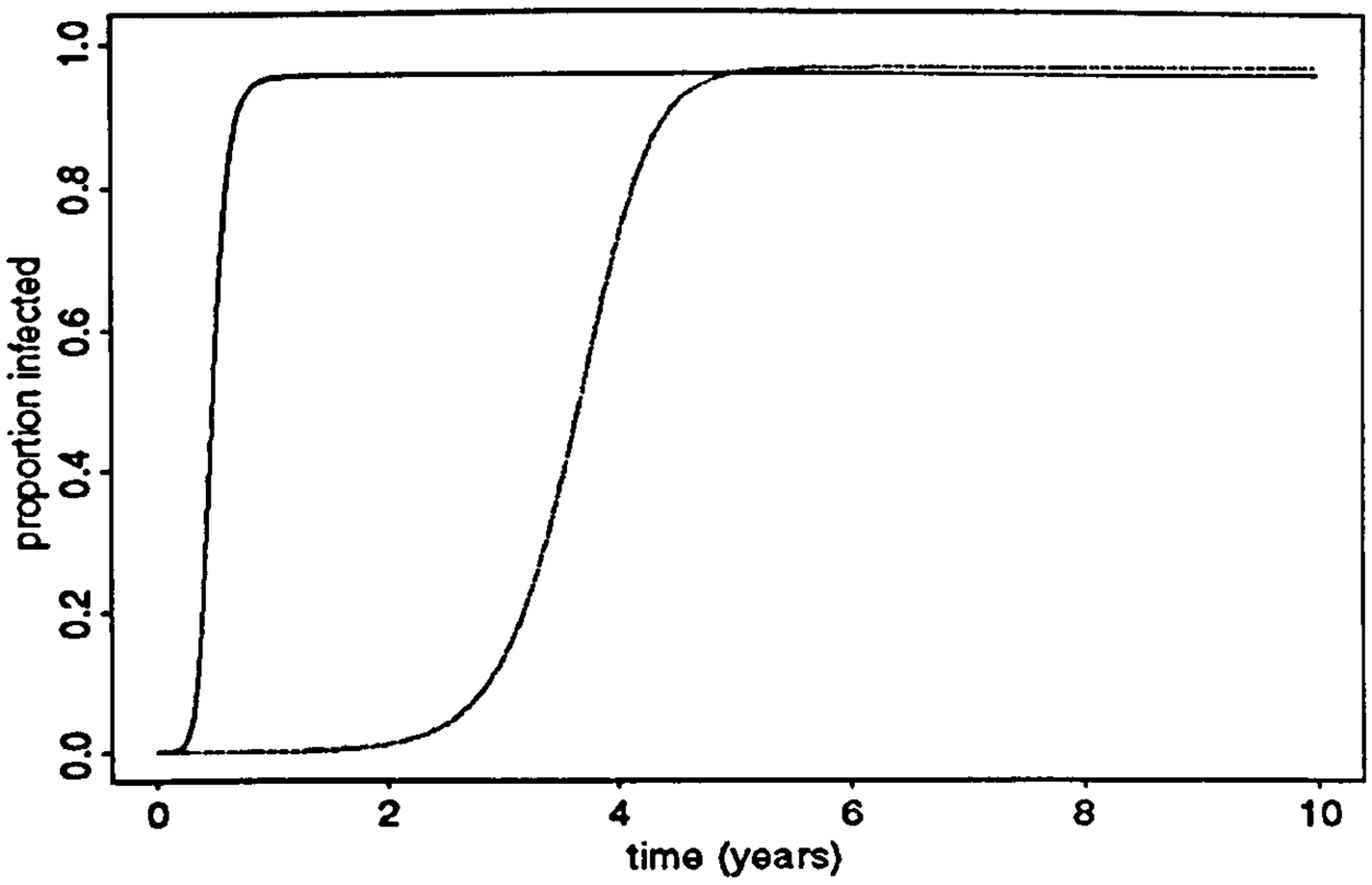

Figure 7.7: Deterministic realisation which results in the approximate median prevalence after 20 years (solid line) and the approximate median value of R_0 (broken line).

partial rank correlation coefficient. Blower and Dowlatabadi (1994), describe in an appendix how the coefficients can be calculated, however the statistical package SPSS can be used. In essence, partial correlation coefficients can be used to isolate the correlation between two variables within a larger set of variables. Therefore although all five parameters may be correlated with the output values, those which are not directly being compared can be thought of as being held at their median value and therefore not affecting the correlation coefficient. Table 7.3 presents the partial rank correlation coefficients between the five input parameters and the proportion of IDUs that are infected after 1, 2, 3, 4, 5, 10, 15 and 20 years.

We can see from this table that the rate at which IDUs share needles is the parameter which is the most highly correlated with the proportion of infected IDUs from 1 to 20 years. The biological parameter α is also highly correlated with the infected proportion. We note that the rate at which IDUs cease injecting becomes more correlated with the proportion infected after the disease has been

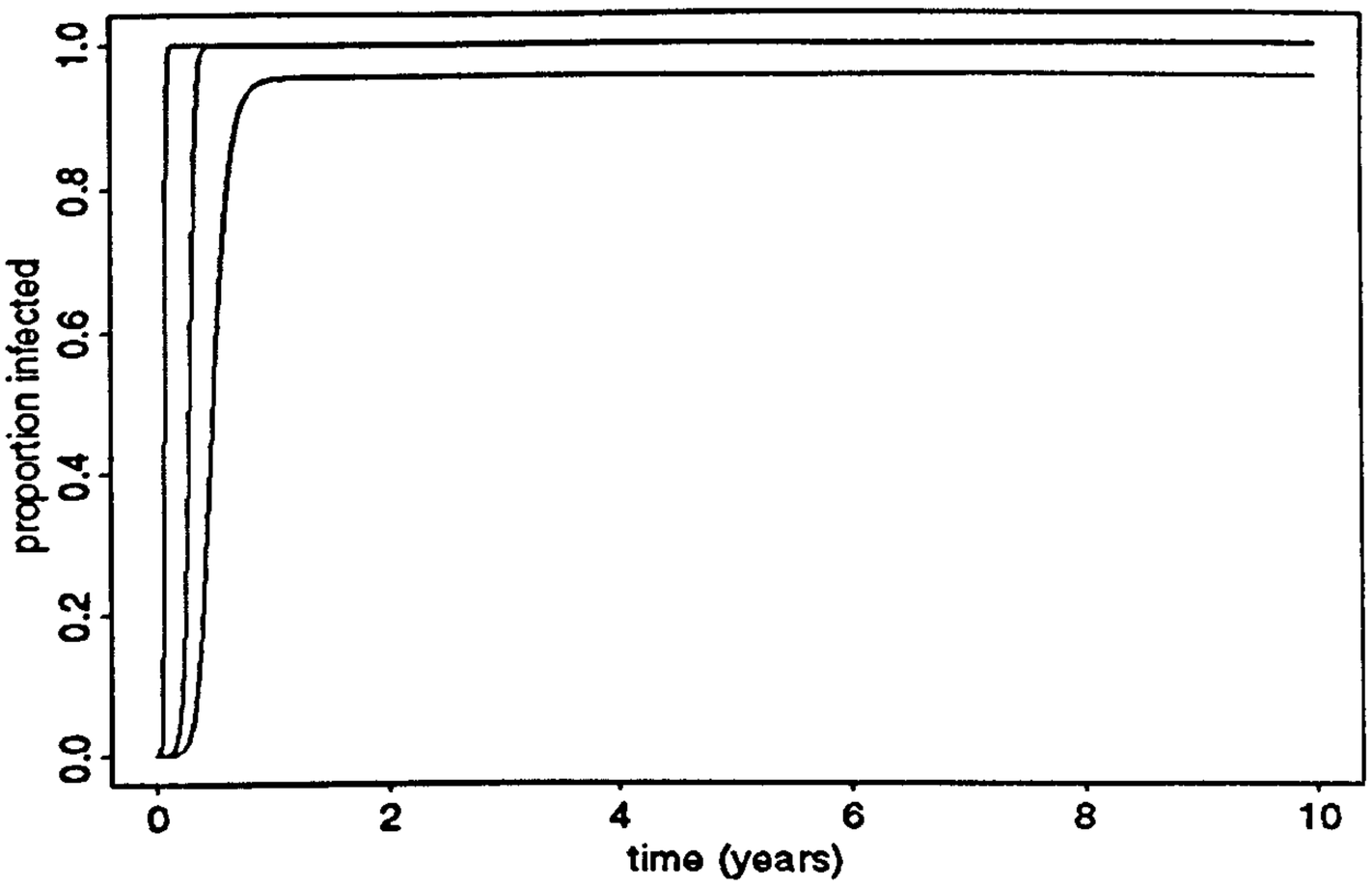

Figure 7.8: Approximate median, 90th and 95th percentile realisations ranked by HIV prevalence after 20 years.

spreading for a few years. The low values of the correlation between γ and the output values towards the later stages of the epidemic will again be due to the absence of this parameter from the equilibrium value π^*. We note, perhaps surprisingly, that the parameter θ does not appear to be correlated with the proportion of people that become infected. This is mirrored by the scenario analysis of Kaplan and O' Keefe (1993).

We can extend the sensitivity analysis by including the cleaning of needles.

Years	α	γ	λ	μ	θ
1	0.6539	0.4845	0.9173	-0.3613	-0.3217
2	0.6500	0.3799	0.9067	-0.4169	-0.3260
3	0.6464	0.3253	0.8915	-0.4865	-0.3069
4	0.6774	0.3033	0.8961	-0.5486	-0.2755
5	0.6954	0.2947	0.8987	-0.5856	-0.2453
10	0.7280	0.2261	0.9035	-0.6733	-0.1188
15	0.7269	0.1483	0.9024	-0.6950	-0.0688
20	0.7230	0.1260	0.8998	-0.6968	-0.0065

Table 7.3: Partial rank correlations between the various parameter values used within simulations and the proportion of infected IDUs at time $t = 1$ to 20 years.

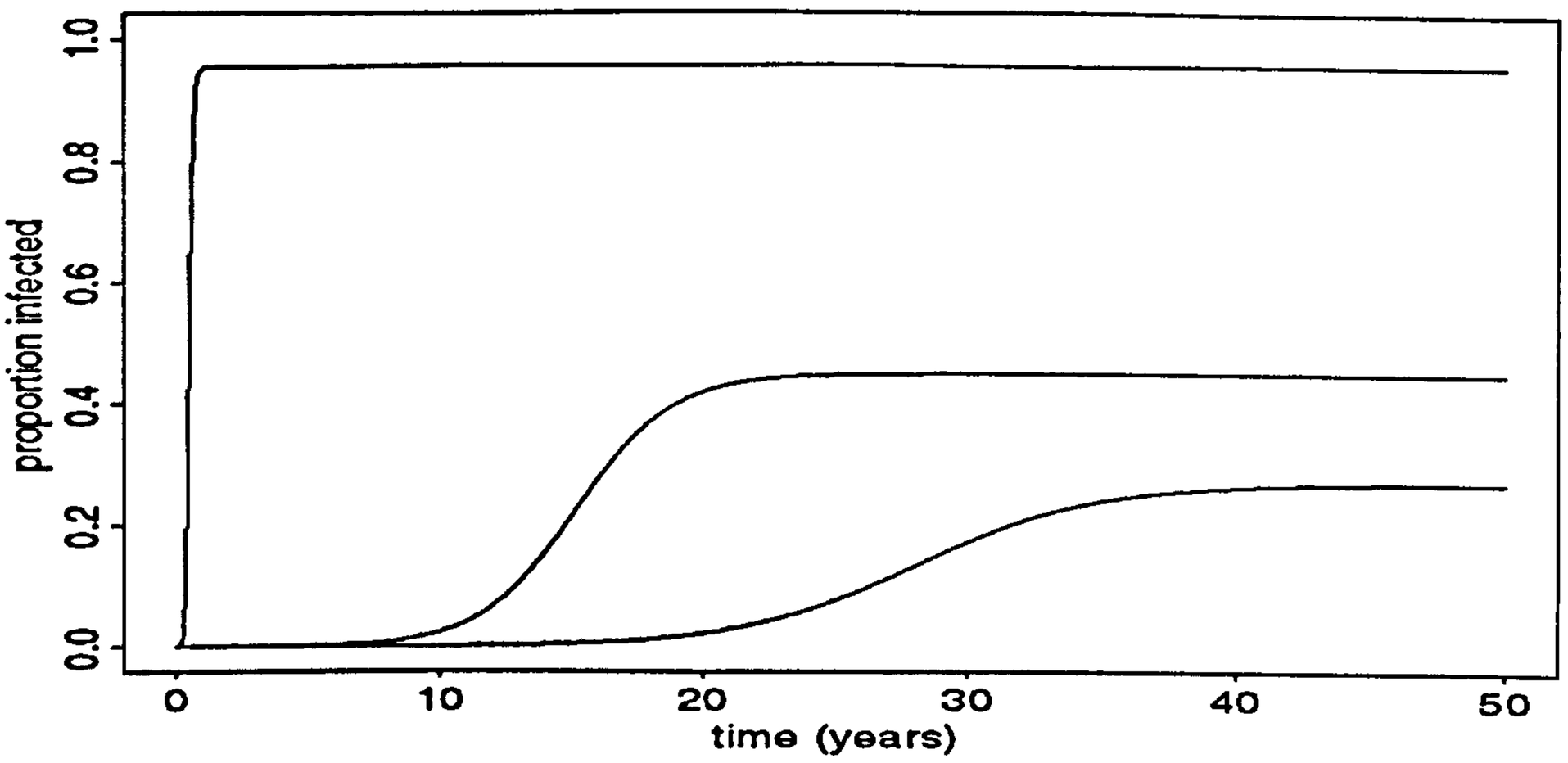

Figure 7.9: Approximate median, 5th and 10th percentile realisations ranked by HIV prevalence after 20 years.

The deterministic model has previously been presented as Equations 4.7. We used the same distributions as before for the parameters α, γ, λ, μ and θ, and use a uniform distribution from zero to one for ξ, the probability that an IDU effectively cleans a needle after use. Again, 100 simulations were used, and the output from the sensitivity analyses could be examined at different values of time t. Table 7.4 presents the Partial Rank Correlation Coefficients between the six input parameters and the proportion of IDUs that are infected after 1, 2, 3, 4, 5, 10, 15 and 20 years.

We can see from this table that when the cleaning of needles is included within the deterministic model, the relative partial rank correlation between the prevalence values and the input variables decreases. Although again, λ, the rate at which IDUs share needles is the most correlated with the prevalence, the parameter which describes the probability that an IDU cleans a needle is more correlated than the infection probability. Thus the two parameters which can be altered by control strategies such as providing bleach to clean needles, and needle exchanges, which lower the rate at which IDUs share needles, are the two that are the most

Years	α	γ	λ	μ	θ	ξ
1	0.4579	0.4047	0.8273	-0.2465	-0.1540	-0.5629
2	0.4877	0.3575	0.8254	-0.2772	-0.1363	-0.5691
3	0.4869	0.3268	0.8235	-0.2796	-0.1382	-0.5772
4	0.4964	0.3108	0.8236	-0.2926	-0.1326	-0.5875
5	0.5070	0.2809	0.8239	-0.3314	-0.1240	-0.5943
10	0.5227	0.1754	0.8107	-0.4184	-0.0452	-0.5699
15	0.5279	0.1604	0.8137	-0.4396	-0.0145	-0.5660
20	0.5416	0.1198	0.8173	-0.4673	-0.0032	-0.5634

Table 7.4: Partial Rank Correlations between the various parameter values used within simulations and the proportion of infected IDUs at time $t = 1$ to 20 years.

correlated with the population prevalence and therefore have the most effect on the future spread of the disease.

7.6 Uncertainty Analyses of π^* and β^*

In the previous section we examined the proportion of IDUs that become infected at different time periods after the disease has been introduced into the population. To do this we had to numerically solve the differential equations at the different time points as analytical solutions were not available. In this section we can examine two values which are related to this mathematical model of disease spread; the equilibrium proportions of infected IDUs and infected needles. Both of these have an analytical representation as shown in Equations 2.3 to 2.5, which are the basic models that do not include the cleaning of needles. Greenhalgh and Hay (1997) present the related equilibrium values when cleaning is present.

We can therefore undertake uncertainty and sensitivity analyses on the basic reproductive number and both sets of equilibrium values. Although in the previous section, it was possible for the disease to die out within the time period we were interested in, in this section there will be combinations of parameters for which R_0 will be less than one, giving only the zero equilibrium values. Thus when

	π^*	β^*
Minimum	0.0029	0.0079
Maximum	1.00	1.00
Mean	0.86	0.91
Median	0.95	0.98
St. Dev	0.21	0.16
5th Percentile	0.37	0.55
10th Percentile	0.56	0.74
90th Percentile	1.00	1.00
95th Percentile	1.00	1.00

Table 7.5: Summary statistics of the distributions of π^* and β^*.

examining the equilibrium values, we will only perfom the sensitivity analysis on those realisations corresponding to sets of parameter values where $R_0 \geq 1$.

As the output values in these analyses are now functions as opposed to simulations and are easier to calculate, we can now work with a larger number of values. For the remainder of this chapter we have used 10,000 values for each of the input parameters and the output parameters. When using the distributions previously described in this chapter, in particular the distribution for the infectivity parameter α as proposed by Blower *et al.* (1991), there were 549 cases in which the equilibrium values were zero, rising to 1,901 when cleaning is included. Figure 7.10 presents the equilibrium values for the proportion of infected IDUs when cleaning is not present, whereas Figure 7.11 presents the corresponding equilibrium values for the proportion of infected needles. The summary statistics of these two distributions are presented as Table 7.5.

It should be noted that only the endemic equilibrium distributions are presented in the graph. It should also be noted that in both these cases the applicability of a sensitivity analysis lessens as these output values are a function of the input parameters. This situation may also be true for $\pi(t)$ when $t < \infty$ as although we are not able to solve Equations 2.1 and 2.2, we can perhaps assume

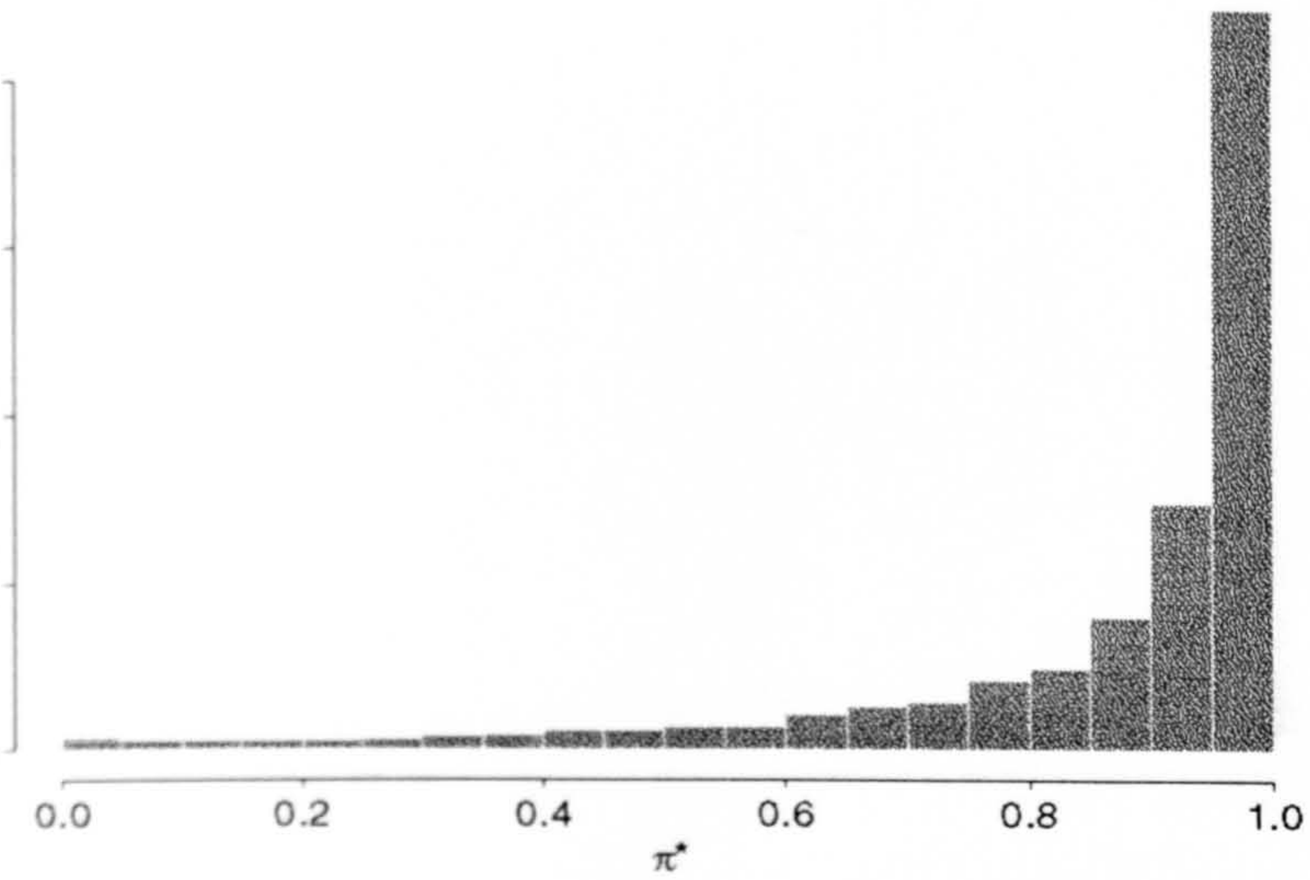

Figure 7.10: Distribution of π^*: cleaning not present.

	π^*	β^*
Minimum	0.0001	0.0000
Maximum	1.00	1.00
Mean	0.81	0.48
Median	0.92	0.47
St. Dev	0.24	0.28
5th Percentile	0.25	0.05
10th Percentile	0.44	0.10
90th Percentile	1.00	0.87
95th Percentile	1.00	0.92

Table 7.6: Summary statistics of π^* and β^* when cleaning of needles is included.

that the proportion infected over time can only be a function, perhaps extremely complex, of the input values.

We also present the distribution of the equilibrium values when cleaning is present in Figures 7.12 and 7.13, and Table 7.6 presents the summary statistics.

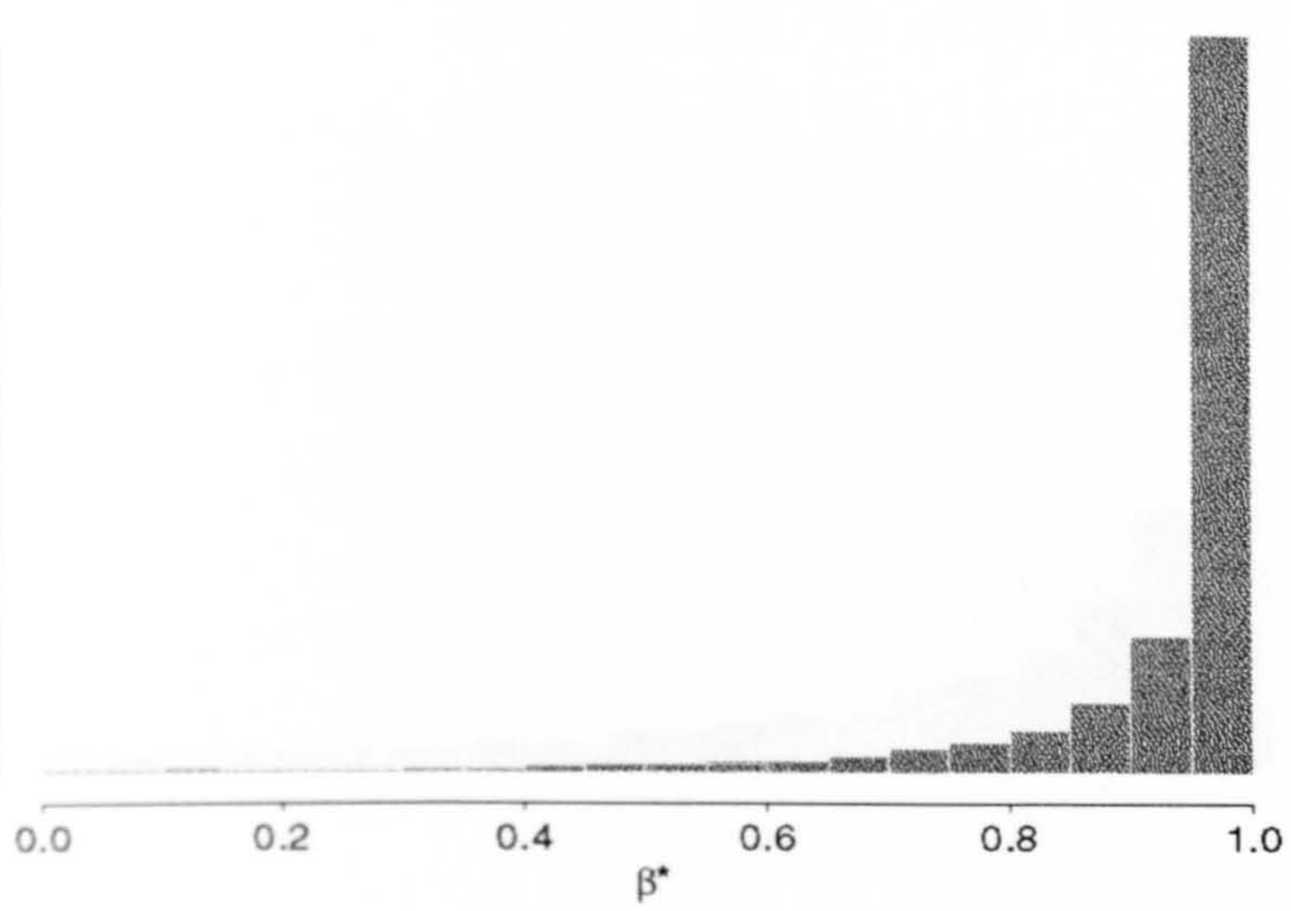

Figure 7.11: Distribution of β^*: cleaning not present.

	α	γ	λ	μ	θ
π^*	0.7968	-0.0086	0.9287	-0.7866	-0.0348
β^*	0.7293	-0.0221	0.8976	-0.7154	-0.6924

Table 7.7: Partial Rank Correlations between the various parameter values used within simulations and the equilibrium values π^* and β^*.

7.7 Sensitivity Analyses of π^* and β^*

We performed a sensitivity analysis for both the equilibrium proportion of infected needles and infected IDUs. We again calculated partial rank correlation coefficients for the ranks of the infected proportions against the input parameters. Table 7.7 presents these partial rank correlation coefficients for Kaplan's original model. It is again clear from these tables that the equilibrium proportion of infected IDUs is not highly correlated with the parameters γ and θ. This is expected in the case of γ as the parameter does not appear in the equation for π^*. What is more interesting however is that the equilibrium proportion of infected needles is correlated with the flushing parameter θ, demonstrating that the presence of flushing may lower the number of infected needles in a population, but within

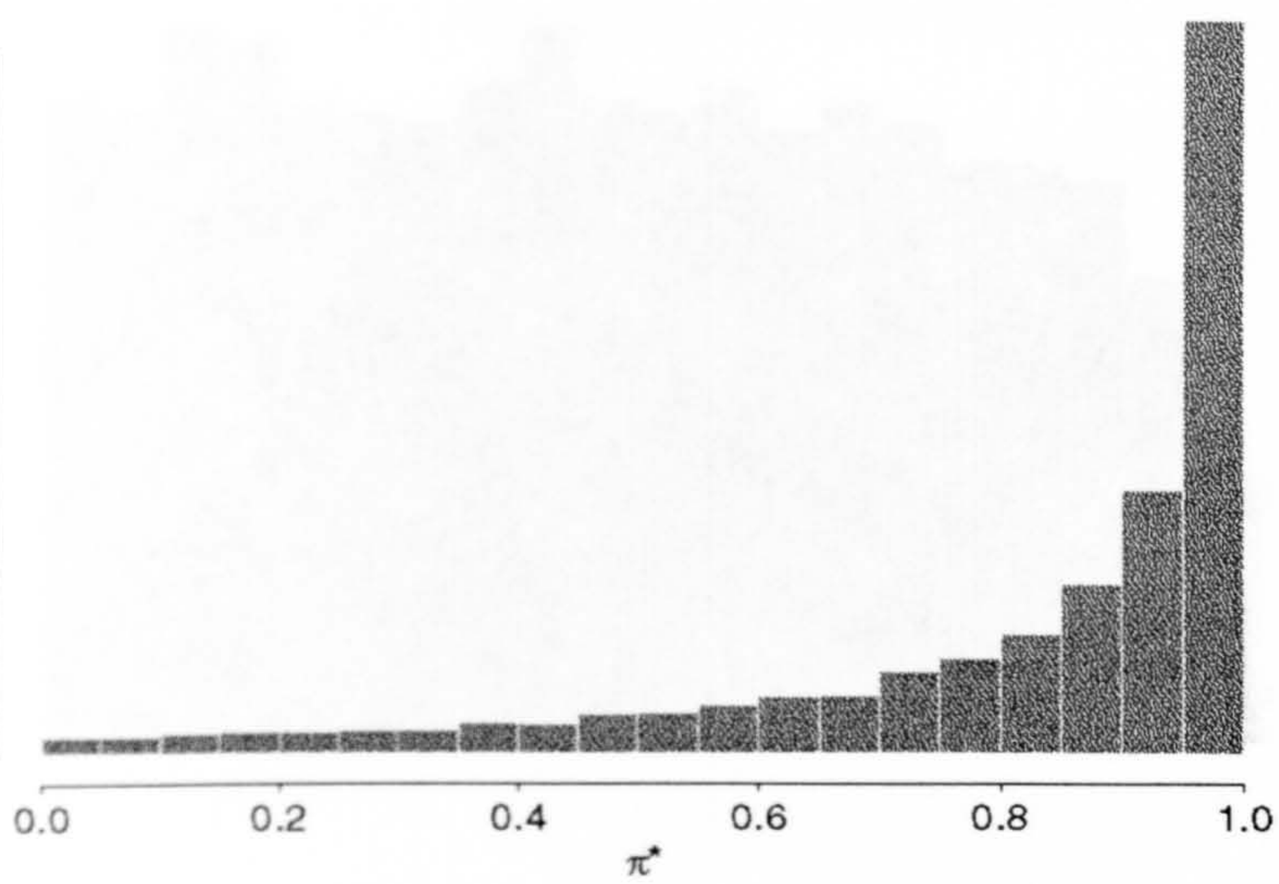

Figure 7.12: Distribution of π^* when cleaning is present.

	α	γ	λ	μ	θ	ξ
π^*	0.7213	-0.0121	0.9087	-0.7137	-0.0102	-0.6550
β^*	0.4146	0.0008	0.5855	-0.4137	-0.1383	-0.9508

Table 7.8: Partial Rank Correlations between the various parameter values used within simulations and the equilibrium values π^* and β^* when cleaning of needles is present.

Kaplan's model, this does not have much effect on the HIV prevalence in the IDU population. Again, the rate at which IDUs share needles is the parameter which is the most highly correlated with the infected IDU equilibrium proportion.

The partial rank correlation coefficients for when cleaning of needles is included within the model are presented as Table 7.8. Again, neither γ nor θ appears to be correlated with the equilibrium IDU infected proportion, however the inclusion of cleaning in the model does alter the partial rank correlations between both equilibria and the other parameters. When cleaning is not present, the correlations between α, λ and μ and the two equilibria are quite similar, showing that there is a strong link between the processes that give rise to levels of infection in the IDU and needle populations. When cleaning is present, the parameter which

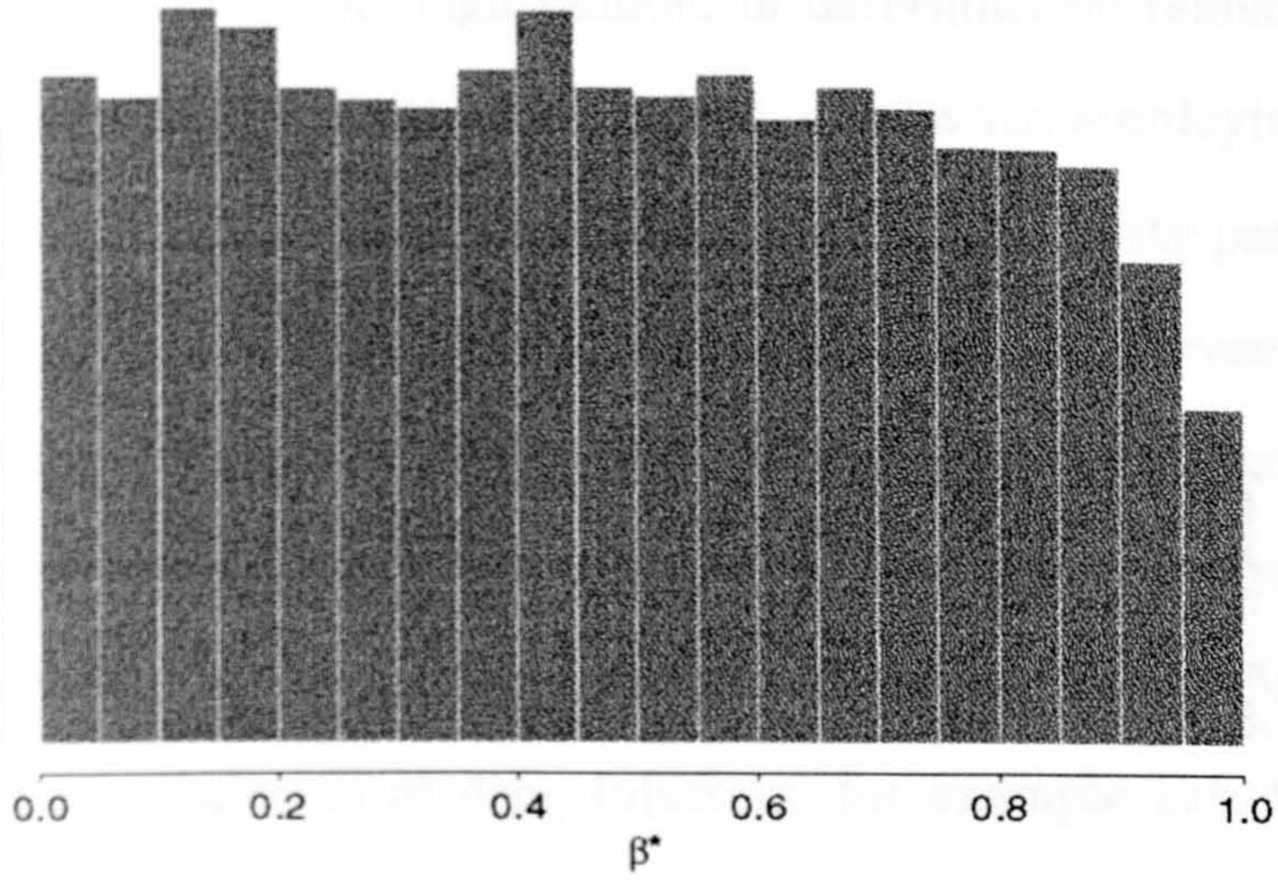

Figure 7.13: Distribution of β^* when cleaning is present.

describes the probability that a needle is effectively cleaned is the most highly correlated parameter, in terms of the equilibrium proportion of infected needles. Also, the correlations between both the sharing and the infection parameters with β^* are much lower, demonstrating the relative effect that cleaning can have on the proportion of infected needles.

7.8 Discussion

Clearly the models explored within these sensitivity and uncertainty analyses can only encapsulate some of the complex dynamics of the spread of HIV amongst drug injectors. However, just as Kaplan's initial models had a direct relevance to policy makers so that the legislation regarding needle exchange provision was amended following his research, the added insight of the sensitivity analyes can also be viewed from a health promotion policy perspective.

We have only vaguely touched upon the fact that when using what are now thought to be realistic parameter values, particularly in relation to drug injectors

in Western Europe and North America, there appears to be very little spread of the disease, as reflected by the high number of deterministic realisations where the disease free equilibrium is attained. Indeed, even when employing what may now be thought of as an unrealistic distribution for the infectivity parameter (due to the high median value), there are realisations in which the disease dies out, for example in Section 7.6, approximately 0.5% of realisations resulted in the zero equilbrium values when cleaning was not present, and approximately 2% when cleaning was present. Although there are situations in which HIV can spread rapidly through a population of drug injectors, for example Edinburgh in the early 1980s, there are other areas in which low levels of infection are continuingly being recorded such as Glasgow. This is consistent with the models presented within this chapter as there are some combinations of parameters with which rapid disease spread occurs, mirroring the situation in some areas, whilst other combinations of parameters correspond to much lower rates of disease spread corresponding to other areas.

Within these sensitivity and uncertainty analyses we have explored different types of uncertainty about the various parameters. Apart from studies such as Peterson *et al.* (1990) and Seitz and Müller (1994), the variability in the infection parameter α is seldom discussed, for example the range of values it may take, its variability over time from infection, and how it may vary over time in the blood that remains within a needle after injection. We have also explored parameters that vary under different circumstances, such as the rate at which injectors share needles and the probability that they clean them effectively. On one hand, these analyses show that the variations in these parameters do contribute to very different patterns of disease spread, but what is more heartening is that these two parameters which can be changed by control strategies are, in comparison to the other parameters in these basic models, highly correlated with the equilibrium proportion of infected IDUs. It is clear that effective cleaning of

needles not only lowers the number of infected needles that can be shared, but also lowers the prevalence of HIV in IDUs. It is also clear that a reduction in the rate of sharing of needles is the parameter which is most highly correlated with the equilibrium proportion of infected IDUs, and this can be achieved through the provision of needle exchanges. Although needle exchanges usually operate the principle of one-to-one exchange, these analyses demonstrate that the distribution (as opposed to the exchange) of new, clean needles, which would alter only the parameter γ, should not significantly affect the long-term spread of the disease.

7.9 Summary

In this chapter we returned to the more basic models presented by Kaplan and presented uncertainty and sensitivity analyses on the output from these models. In addition to the considerable uncertainty surrounding the infection parameter α, uncertainty and variability in the other parameters give rise to uncertainty in the proportion of infected IDUs and needles over time, and also in the corresponding equilibrium values. When a lower value for α is used than that which was initially employed by Kaplan, many deterministic realisations describe the disease rapidly dying out. When using a distribution for this parameter as proposed by Blower *et al.* (1991) we can explore the correlation between the parameters and the proportion of infected IDUs or needles. Although in this small system of equations (and in particular when using the simple expressions for the equilibrium values) both infected proportions will be correlated to most of the parameters, two parameters that can be influenced by changes in injecting practice are more highly correlated that others. Thus policies, such as the distribution of bleach with which needles can be cleaned (and therefore increasing the value of the parameter ξ) and the provision of clean needles through needle exchanges or the

increased availability of injecting equipment (and therefore lowering the value of λ) will both decrease the spread of the disease.

Chapter 8

Future Work

8.1 Introduction

In this Thesis we have concentrated on homogeneous models. While the development of these simple models can be used to evaluate control strategies, they perhaps do not have enough realism to comprehensively describe the transmission dynamics of the spread of a disease like HIV in a population of IDUs. The variation in HIV prevalence rates in different areas of the world, and indeed within a country as small as Scotland, confirms that the simple models of Kaplan which rely only a small number of behavioural parameters, may need to be extended to more realistic heterogeneous models.

In Chapter 2 we described Kaplan's determinstic model of the spread of HIV within a population of IDUs. This model was converted into a stochastic model in Chapter 3 and extensions to this basic model, both deterministic and stochastic were presented in Chapter 4. The models described in these three chapters were homogeneous in that all IDUs make a similar random choice from all available needles with which they can inject and they all use injecting equipment at the same rate. Previous models have been described in which the sharing rate is dependent on knowledge of HIV status, although again all IDUs with knowledge of their status use injecting equipment at the same rate.

In Chapter 5 we introduced the concept of heterogeneity, that is IDUs either have a structured sharing pattern, or they have a specific attribute that can be reflected by varying a particular parameter in a mathematical model, such as the sharing rate. We have seen from data collected during a quantitative study that IDUs do not all share at the same rate, and that the probability of cleaning a needle effectively varies over the IDU population. From qualitative studies, such as McKeganey and Barnard (1991) we have also seen that the assumption that all sharing is with needles selected at random from the total number of needles, or in Kaplan's model that IDUs select a shooting gallery at random, is questionable. Indeed, not all IDUs share needles as many use their own set of needles. Other IDUs share only with close friends.

In this chapter we show how the framework of the homogeneous models presented by Kaplan could be extended into more realistic models by allowing IDUs to inject with a needle which was not randomly selected from the complete needle population. These models can therefore, in one sense, be considered heterogenous. We present the models as ideas for future work and therefore we do not delve beneath the abstract representation of the suggested transmission dynamics as mathematical models, partly because we feel that the variability in the parameter values employed in such models would make any realisations unreliable, as demonstrated in the preceding chapters. Thus in this chapter we suggest the direction that future work could take, first by extending the homogeneous models to create a link between an IDU and a needle, and then going on to include the varying of sharing rates and a structured sharing pattern.

8.2 Sharing and Injecting: The Linking of Needles to IDUs

There are differences between injecting with a needle previously used by another IDU and injecting with a needle obtained elsewhere, such as from a needle exchange. When using a needle that has not been used by another IDU there is no risk of infection, and indeed continued use of such a needle, or continued use of any uninfected needle will not lead to infection. This scenario is similar the models of Dietz and Hadeler (1988) in which they describe the sexual spread of a disease within a population that is subject to pair formation. The authors note 'if two susceptible individuals form a pair then they can be considered temporarily immune as long as they do not separate and have no contacts with other partners'. Similarly we have that if an IDU injects with only their own equipment, or does not obtain injecting equipment from other IDUs but from somewhere such as a pharmacy or a needle exchange, they can also be thought of as immune. The models presented by Dietz and Hadeler that describe the sexual spread of a disease can be adapted to describe the spread of HIV among IDUs.

The concepts of pair formation and pair separation will need adapting when we are examining the spread of disease among IDUs that share needles. We are interested in needles only when they belong to an IDU as we assume that when an IDU no longer wants to keep a needle then it will either be given to another IDU or destroyed. That is an IDU/needle pair will terminate when the needle is destroyed or given to another IDU, which itself will be the beginning of a new partnership. Hence pair formation and pair separation can be combined into a single act which will be the transferral of a needle from one IDU to another.

8.3 The Needle Transference Rate

The rate at which this transferral happens can be defined as in Dietz and Hadeler's models as φ, such that $\varphi(y_i, x_{jk})$ is the rate at which an IDU of type i, takes a needle from an IDU of type k who has a needle of type j. Thus i, j and k will be zero or one, referring to uninfected or infected respectively. There are immediate simplifications that can be made, such as that an IDU will not be able to tell the infectivity status of another IDU or of a needle. It can also perhaps be assumed that whether or not an IDU is infected makes no difference to whether he or she is likely to share needles, although the success of public health campaigns such as increased testing of IDUs for HIV and the prescribing of methadone for those who are known to be HIV positive may make this assumption unrealistic. If IDUs do not change their sharing patterns on becoming infected then we have that $\varphi(y_i, x_{jk})$ is independent of i,j and k and hence can be expressed as $\varphi(y, x)$. We also have to describe how this rate depends on the population size. If we define:

$y_0(t)$ as the number of uninfected IDUs that do not have their own injecting equipment at time t;

$y_1(t)$ as the number of infected IDUs that do not have their own injecting equipment at time t;

$x_{00}(t)$ as the number of uninfected IDUs that have uninfected injecting equipment at time t;

$x_{01}(t)$ as the number of infected IDUs that have uninfected injecting equipment at time t;

$x_{10}(t)$ as the number of uninfected IDUs that have infected injecting equipment at time t and

$x_{11}(t)$ as the number of infected IDUs that have infected injecting equipment at time, t

then the rate of transferral of injection equipment can depend on both $\sum y_i(t)$ and $\sum x_{jk}(t)$. Several functions of these values can be considered. We require that $\varphi(y,0) = 0$ for all $y \geq 0$ and $\varphi(0,x) = 0$ for all $x \geq 0$. That is the rate at which needles are transferred is zero when there are no IDUs with needles, hence no needles, or there are no IDUs without needles. We could require that φ is increasing in y, or $\partial\varphi(y,x)/\partial y \geq 0$, that is the rate at which needles are transferred will increase with the number of IDUs that are lacking needles. We could also require that the rate at which needles are transferred will increase as the number of IDUs with needles increases, or $\partial\varphi(y,x)/\partial x \geq 0$.

We need also to make an assumption about how the transference rate increases as both x and y increase. It may be sensible to assume that it increases proportionally to y, that is for a fixed total number of IDUs with needles if y doubles then $\varphi(y,x)$ doubles, or $\varphi(\alpha y,x) = \alpha\varphi(y,x)$. This will be true if the number of IDUs with needles is much greater than the number of IDUs without. Under this scenario there is no competition between IDUs that do not have a needle to get one from someone that has. If the converse is true, that is the number of IDUs without needles is much greater than that of those with then it may be sensible to assume $\varphi(y,\alpha x) = \alpha\varphi(y,x)$. As in many models describing processes such as pair formation or disease spread, the rate $\varphi(y,x)$ may not be easily described. In particular a function such as $\varphi(y,x) = \text{const.}xy$ may not be suitable as this would mean that the rate of pair formations increase quadratically with population density. A transference rate similar to a minimum law of pair formation in a sexual spread model can be employed, for example

$$\varphi(y,x) = \frac{\rho y_i x_{jk}}{x_{00} + x_{01} + x_{10} + x_{11}}.$$

We now can express the numbers of infected and uninfected IDUs with or without

Parameter	Description
κ_y	recruitment rate of IDUs
μ_x	the rate at which needles are disposed of by an IDU
μ_{y0}	rate at which uninfected IDUs cease injecting drugs
μ_{y1}	rate at which infected IDUs cease injecting drugs
ρ_1	the rate at which an IDU obtains a needle from a pharmacy
ρ_2	the rate at which an IDU gives or takes a needle to or from another IDU
θ	flushing probability
α	infection probability
λ	rate of injecting within pair

Table 8.1: Description of parameters employed in the model as described in Equation 8.1.

their own injecting equipment by the following set of six differential equations:

$$\dot{y}_0 = \kappa_y - \mu_{y0}y_0 + \mu_x(x_{00}+x_{10}) + \frac{\rho_2(y_0+y_1)(x_{00}+x_{10})}{x_{00}+x_{01}+x_{10}+x_{11}} - \rho_2 y_0 - \rho_1 y_0,$$

$$\dot{y}_1 = -\mu_{y1}y_1 + \mu_x(x_{01}+x_{11}) + \frac{\rho_2(y_0+y_1)(x_{01}+x_{11})}{x_{00}+x_{01}+x_{10}+x_{11}} - \rho_2 y_1 - \rho_1 y_1,$$

$$\dot{x}_{00} = -\mu_{y0}x_{00} - \mu_x x_{00} + \frac{\rho_2(y_0x_{01}-y_1x_{00})}{x_{00}+x_{01}+x_{10}+x_{11}} + \lambda\theta x_{10} + \rho_1 y_0,$$

$$\dot{x}_{10} = -\mu_{y0}x_{10} - \mu_x x_{10} + \frac{\rho_2(y_0x_{11}-y_1x_{10})}{x_{00}+x_{01}+x_{10}+x_{11}} - \lambda\theta x_{10} - \lambda\alpha x_{10},$$

$$\dot{x}_{01} = -\mu_{y1}x_{01} - \mu_x x_{01} + \frac{\rho_2(y_1x_{00}-y_0x_{01})}{x_{00}+x_{01}+x_{10}+x_{11}} - \lambda x_{01} + \rho_1 y_1,$$

and

$$\dot{x}_{11} = -\mu_{y1}x_{11} - \mu_x x_{11} + \frac{\rho_2(y_1x_{10}-y_0x_{11})}{x_{00}+x_{01}+x_{10}+x_{11}} + \lambda x_{01} + \lambda\alpha x_{10}. \tag{8.1}$$

The definition of parameters is given in Table 8.1. We assume that immediately on acquiring injecting equipment an IDU will inject with it, so that ρ_1 and ρ_2 can also be thought of as injecting rates. There are several processes described within this model, for example one describes the rate at which needles are brought into the community from a pharmacy and another describes the rate at which needles are disposed of. These processes are described using the parameters ρ_1 and μ_x

respectively. A third process describes needles being transferred between IDUs. *This is caused by an IDU who does* not currently have a needle obtaining one from an IDU who does. Over a small *time interval of length dt the number of* uninfected IDUs without injecting equipment will increase when uninfected IDUs with either infected or uninfected equipment give their equipment to another IDU. Thus the number of uninfected IDUs without injecting equipment will increase by

$$\frac{\rho_2(y_0+y_1)(x_{00}+x_{10})}{x_{00}+x_{01}+x_{10}+x_{11}}\mathrm{d}t.$$

This increase will be offset by the number of uninfected IDUs without injecting equipment who have received a needle from another IDU in the small time period $[t, t+\mathrm{d}t]$, which will be $\rho_2 y_0 \mathrm{d}t$. The number of uninfected IDUs without injecting equipment will similarly decrease when an IDU without injecting equipment obtains a needle from a pharmacy. The second equation which describes the rate of change of infected IDUs without injection equipment has a similar explanation. Although Equations 8.1 have been simplified by combining similar terms, the number of uninfected IDUs with uninfected injection equipment will similarly increase when uninfected IDUs without equipment acquire uninfected equipment either from a pharmacy or from another IDU, and will similarly decrease when any IDU without equipment takes a needle from an uninfected IDU with uninfected equipment. Similar increases and decreases will occur for the other three infected/uninfected IDU/needle combinations. The other processes are those described in Kaplan's model, that is the events that happen on injection such as flushing, infection of needle or infection of IDU (which in this model can happen only when a needle belongs to an IDU), and the death of IDUs.

Although this model appears to be far more complex than that described by Kaplan, we have only included a few more parameters. However, as shown in the previous chapter, there is considerable variability in the parameters employed in

the simpler models, and as yet data from qualitative and quantitative studies of IDUs' sharing behaviour have not been in a form that is immediately useful in these pair formation models. We have demonstrated however that models to describe the sexual spread of a disease, particularly those which include pair formation, can be easily adapted to extend Kaplan's simple deterministic model.

8.4 Linkage Models which include Borrowing Injecting Equipment and Shooting Galleries

In the previous section we created a link between an IDU and a needle, and now we will extend the previous model to include IDUs using needles that they are not linked to. Thus we can alter the equations presented above to include borrowing, which will be defined as the temporary use of a needle that belongs to another person and we can also incorporate the use of shooting galleries, which will be similar to Kaplan's model in that it is assumed that there is a fixed number of needles m within these shooting galleries and the proportion of the needles available from the shooting galleries that are infected at time t will be $\beta(t)$. We alter our definition of λ, the rate of sharing within a pair to be λ_1 and define λ_2 to be the rate at which an IDU borrows a needle from another IDU and gives it back to them and λ_3 to be the rate at which an IDU visits a shooting gallery. Note that only IDUs who do not own injecting equipment are assumed to borrow needles from another or visit shooting galleries. Thus we can augment the previous system of equations by including the visiting of shooting galleries and the borrowing of needles to obtain

$$\dot{\beta} = \frac{\lambda_3}{m}((1-\beta)y_1 - \theta\beta y_0),$$

$$\dot{y_0} = \kappa_y - \mu_{y0}y_0 + \mu_x(x_{00}+x_{10}) + \frac{\rho_2(y_0+y_1)(x_{00}+x_{10}) - \lambda_2\alpha y_0(x_{10}+x_{11})}{x_{00}+x_{01}+x_{10}+x_{11}}$$

$$-(\rho_1+\rho_2)y_0 - \lambda_3\alpha\beta y_0,$$

$$\dot{y}_1 = -\mu_{y1}y_1 + \mu_x(x_{01} + x_{11}) + \frac{\rho_2(y_0 + y_1)(x_{01} + x_{11}) + \lambda_2\alpha y_0(x_{10} + x_{11})}{x_{00} + x_{01} + x_{10} + x_{11}}$$

$$- (\rho_1 + \rho_2)y_1 + \lambda_3\alpha\beta y_0,$$

$$\dot{x}_{00} = -\mu_{y0}x_{00} - \mu_x x_{00} + \frac{\rho_2(y_0x_{01} - y_1x_{00}) - \lambda_2 y_1 x_{00} + \lambda_2\theta y_0 x_{10}}{x_{00} + x_{01} + x_{10} + x_{11}}$$

$$+ \lambda_1\theta x_{10} + \rho_1 y_0,$$

$$\dot{x}_{10} = -\mu_{y0}x_{10} - \mu_x x_{10} + \frac{\rho_2(y_0x_{11} - y_1x_{10}) - \lambda_2\theta y_0 x_{10} + \lambda_2 y_1 x_{00}}{x_{00} + x_{01} + x_{10} + x_{11}}$$

$$- \lambda_1\theta x_{10} - \lambda_1\alpha x_{10},$$

$$\dot{x}_{01} = -\mu_{y1}x_{01} - \mu_x x_{01} + \frac{\rho_2(y_1x_{00} - y_0x_{01}) - \lambda_2 y_1 x_{01} + \lambda_2\theta y_0 x_{11}}{x_{00} + x_{01} + x_{10} + x_{11}}$$

$$- \lambda_1 x_{01} + \rho_1 y_1,$$

and

$$\dot{x}_{11} = -\mu_{y1}x_{11} - \mu_x x_{11} + \frac{\rho_2(y_1x_{10} - y_0x_{11}) - \lambda_2\theta y_0 x_{11} + \lambda_2 y_1 x_{01}}{x_{00} + x_{01} + x_{10} + x_{11}}$$

$$+ \lambda_1 x_{01} + \lambda_1\alpha x_{10}. \tag{8.2}$$

Whilst a package such as SOLVER could easily be used to solve these differential equations and to examine the number of infected IDUs with or without injecting equipment, values for the various parameters described above must be estimated. Additionally in this more complex heterogeneous model, estimates must be obtained for the number of IDUs initially with or without needles, along with the behavioural parameter values we assign to each group. In Glasgow injecting is far more common than actual sharing, as is shown by Tables 5.1 and 5.2. Thus it can be assumed the act of an injector (without injecting equipment) obtaining injecting equipment used previously by another IDU happens less often than injecting with a needle obtained from a pharmacy or a needle which was already in the IDU's possession.

In this section we combined the model presented earlier in this chapter, in which disease spread only occurred within the framework of pair formation be-

tween an IDU and a needle, with the transmission dynamics proposed by Kaplan. Within this combined model, we not only have to estimate values for the parameters described in the previous chapters, but we would now also need to quantify the rate that an IDU borrows a needle from another user as opposed to visiting a shooting gallery. We would also have to quantify the rate at which an IDU obtains clean needles from either a pharmacy or a needle exchange.

8.5 Summary

Within this chapter we have proposed some extensions to Kaplan's basic model which include heterogeneity in the rate at which IDUs inject and heterogeneity in where they obtain a needle, either from a shooting gallery, from a friend/partner, a pharmacy, or one that they had previously been the only person to use. We have presented a deterministic framework for examining these heterogeneous disease transmission dynamics. We do not attempt to present the results from realisations, rather we suggest that these models may form the basis for future work. Although the models presented in this chapter are more realistic than those presented in earlier chapters, there are still some improvements that can be made to allow them to become even more realistic, perhaps by additionally including some of the features of the models presented in Chapter 4, such as the cleaning of needles or the loss of infectivity within a needle over time. Future work may also try to create models in which a reduction of the availability of clean injecting equipment from pharmacies would increase the rate at which IDUs share or models that effectively describe needle exchanges where both the disposing of used injecting equipment and the obtaining of clean needles will happen simultaneously.

Chapter 9

Discussion and Conclusions

9.1 Introduction

In this Thesis, the use of mathematical models in understanding the transmission dynamics of HIV spread via the sharing of injecting equipment has been explored. A simple model presented by Kaplan (1989) was used as a framework from which we examined various extensions, both by attempting to make some of the assumptions more realistic, but also by converting the deterministic model into a stochastic model. We discuss, at length, the parameters that such models employ and seek to use data from a sample of IDUs from Glasgow to estimate the probability that a single injection with an infected needle will result in a new infection. We performed uncertainty and sensitivity analyses on these models, and demonstrated that the uncertainty in the parameter values prevents accurate predictions of the future prevalence of HIV / AIDS. Finally we discussed how the simple models of Kaplan could be extended into heterogeneous models by considering the pair formation models of Dietz and Hadeler (1988).

9.2 Deterministic Models

Kaplan's deterministic model, presented in 1989, was the first model to describe the spread of HIV among IDUs. Although this simple model failed to describe some of the more complex transmission dynamics of HIV spread, it was useful in evaluating control strategies, particularly needle exchanges. This was reflected in the change in legislation in the State of Connecticut to legalise needle exchanges following his work. In Chapter 2 we described this model, and showed that the disease can only spread if the basic reproductive ratio of infection R_0 is greater than 1. We noted that, using the parameters initially suggested by Kaplan, the vast majority of IDUs become infected in quite a short time period.

We provided some analytical results for this deterministic model, first by showing that there exist equilibrium values for the proportion of IDUs that are infected, and also equilibrium values for the proportion of infected needles. We demonstrated that if $R_0 \leq 1$ then the equilibrium values are both zero. If $R_0 > 1$ then there exists a non-zero equilibrium. We then showed that the disease-free equilibrium is locally stable for $R_0 < 1$ and unstable for $R_0 > 1$ and that the endemic equilibrium was locally stable whenever it exists. Next we went on to show global stability results. We showed that the disease-free equilibrium was globally stable for $R_0 \leq 1$. For $R_0 > 1$ provided the disease was present initially the fractions of infected needles and addicts always tended to their unique endemic equilibrium values. By introducing stochastic variation around the deterministic trajectory, we showed that for the parameter values suggested by Kaplan, it is unlikely that such a stochastic trajectory will hit either of the axes corresponding to zero infected IDUs or zero infected needles.

By comparing Kaplan's model with a framework proposed by Peterson *et al.* (1990) to describe the different stages of infection with HIV and the disease AIDS, we created a deterministic model in which infected IDUs are considered

separately from uninfected IDUs. Thus we could make Kaplan's model more realistic by including a behavioural change by an IDU on learning that they have become infected. We presented deterministic realisations in which infected IDUs share less often than uninfected IDUs, something which behavioural studies of IDUs suggest.

The infectivity of a needle was examined further using deterministic modelling techniques. Initial models assume that the act of injecting with an infected needle may actually flush the needle of infectious material. We therefore extended Kaplan's model to assume that only blood from an uninfected IDU could do this. We further examined flushing by postulating that both the probability that a needle infects an IDU and that an IDU flushes that needle are linked to the amount of infectious equipment, so that as the infection probability increases, the flushing probability would decrease. We continued to assume that the infectivity of a needle depends on the amount of infectious material within it by presenting models in which this infectivity varies over time from injection. We also presented a model in which the initial infectiousness of a needle would depend on the length of time the person who infected it had been infected with HIV. This mirrored the more recent scientific opinion that an infected person is much more infectious just after infection with the virus. This was done both by using a three-stage infectivity distribution, then a model suggested by Anderson and May (1991). Some of these more complex models employed stochastic modelling techniques. Additionally within Chapter 4 we demonstrated the effect that cleaning a needle, either before or after injecting, has on the spread of the disease.

9.3 Stochastic Models

While the deterministic models were easier to create and analyse, we noted that stochastic models may be needed to more accurately describe the spread of the

disease. In Chapter 3 we presented a stochastic representation of Kaplan's model and aimed to explore it in a threefold manner; analytically, numerically and using Monte-Carlo simulation methods. We soon found the analytical models that we had created to reflect Kaplan's model were intractable, therefore we abandoned this approach in favour of the more computer intensive methods. In the Monte-Carlo simulation models, a suite of Pascal programs were created to model the scenario as described by Kaplan and, as mentioned in the preceding section, to model some of the extensions such as the varying infectivity of the needle over time. These models were extensively verified. It became clear when using the Monte-Carlo simulation models that, in a similar manner to the deterministic models, most runs resulted in the majority of IDUs quickly becoming infected. What also became clear was that it was possible that the disease may die out. Thus when comparing the output from a series of stochastic realisations to that from the deterministic realisation, due consideration must be made of the possibility that such a series of realisations includes situations where the disease did not spread.

We examined this further by numerically solving the analytical model. To do this we considered the various events that could happen in a small time interval; an uninfected IDU becomes infected, an infected IDU leaves the population and is immediately replaced by an uninfected one, an uninfected needle becomes infected and a needle gets cleaned. We also noted that it is possible for a needle to get cleaned at the same time as an IDU becomes infected. After developing a matrix framework for the number of infected IDUs and needles, we noted that the epidemic spread can be thought of as a Markov process in which the state corresponding to zero infected IDUs and zero infected needles is an absorbing state. Thus eventually the disease must die out. This seemed to contradict our numerical solution of the stochastic model in which the disease prevalence appeared to reach an equilibrium similar to Kaplan's deterministic equilibrium. In

our numerical solutions, we did however note that there was a small probability that the disease would die out. We examined these apparent equilibrium values further by attempting to numerically calculate the time to extinction of the stochastic process. We demonstrated that, particularly when there was one or more infected IDUs, the time to extinction was extremely large. Thus we felt justified in defining quasi-extinction probabilities and quasi-equilibrium values which considered the process over a biologically realistic time period. Using these, we showed that there was indeed a non-negligible probability that the disease dies out within a realistic time period, and that there exist equilibrium values in which the majority of IDUs and needles become infected, confirming what we found in the deterministic and the Monte-Carlo simulation models.

9.4 Parameter Estimation

Even though the most basic model by Kaplan only employed five parameters, there was considerable uncertainty about the values that these parameters took. Indeed later versions of Kaplan's models dismiss the presence of flushing. In Chapters 5 and 6 we discussed the parameter values that can be found from the existing literature, complementing them with data from a behavioural and seroprevalence study of Glasgow IDUs. In the first of these chapters we explored the parameters describing the size of the IDU population and the dynamics acting on it, such as death from HIV and death from other causes, as well as drug users starting or ceasing to inject drugs. While HIV may have a large impact on the size of the IDU population in other areas, we have found no evidence of this in Glasgow; indeed the size of the IDU population has increased since HIV was first detected. We also show that although there is a large population of IDUs that regularly injects, not all of them share needles. Additionally many IDUs practice safer injection techniques such as cleaning needles with bleach or boiling water.

We used this information in deriving an estimate for the probability than an IDU becomes infected after injecting with an infected needle. We did this by first estimating how many injections occurred in the year 1990, using the data described above. We note that although there will have been over half a million injections, very few new infections occurred. After accounting for the fact that not all injections will have involved shared injecting equipment, that a proportion of injections will have occurred after effective cleaning, and finally that due to the low HIV prevalence amongst Glasgow IDUs in 1990 only a small percentage of needles will have been used by an infected IDU, we estimate that the probability of infection is lower than that suggested by the literature.

We examined the variability in the parameter values by performing both an uncertainty analysis and a sensitivity analysis in Chapter 7. We showed that there is considerably uncertainty in the future prevalence of HIV in an IDU population and that the disease often dies out before an epidemic can occur. We showed in the sensitivity analyses that the two behavioural parameters that can be altered by control strategies have a greater influence on the spread of the disease than some other parameters. The provision of clean needles through needle exchanges or pharmacies removes the need to share needles and should decrease the value of the corresponding parameter and thus the spread of the disease, similarly an increase in the cleaning of needles will also slow down, and possible avert, epidemic spread.

9.5 Future Work

In Chapter 8 we proposed future work by extending homogenous models to create a link between an individual IDU and a needle. This was done by comparing the needle sharing spread of the disease to the sexual spread of the disease where pair formation is present. Deterministic models were presented in which interacting

populations of IDUs with or without injecting equipment are subject to the same transmission dynamics as presented in Kaplan's model. Although this more complex model can be analysed numerically, there still exists the problem about the uncertainty of the parameters that such a model employs. We therefore do not explore this heterogeneous model at length, preferring only to suggest one or two improvements, such as including the borrowing of injecting equipment where it is immediately returned. We do however note that even these models are far from realistic.

Future work should therefore focus on extending models to include further realistic representations of heterogeneity, either using deterministic models or stochastic models. Models such as those proposed by Kretzschmar and Wiessing (1998) go some way to improve the models presented in this Thesis by assuming a social structure amongst IDUs, in which an IDU shares with close friends or buddies. They propose this structure after examining detailed information gathered on IDUs' contact patterns in the Netherlands, thus being a case where the models are led by the data, and not vice versa. This is an example of the collaborative approach involving both mathematical modellers and drug-use researchers proposed by Blower and Medley (1992). This collaboration has to be two-sided; it will not be sufficient for more and more realistic models to be created by mathematical modellers without a better understanding of the values that the parameters used in such models would take, both from biological and virological research, but also from behavioural research into IDUs.

9.6 Conclusions

We started this Thesis by noting that although research into HIV is multi-faceted, including complex models describing the sexual spread of the disease and behavioural and seroprevalence studies of IDUs, there have been few attempts to

marry the developing expertise and available information into realistic models of the spread of HIV amongst IDUs. While attempting to definitively fill this gap may been over ambitious, especially when some of the more complex transmission dynamics have yet to be accurately quantified, we have demonstrated the usefulness of some of the simpler models in evaluating control strategies such as needle exchanges. We have presented an in-depth examination of a simple deterministic model, and attempted to analytically examine an equivalent stochastic model. Resorting instead to exploring this stochastic model using Monte-Carlo methods we could demonstrate how the model could be improved. We noted the difficulties in using seroprevalence and behavioural data within these mathematical models, however we were successful in obtaining an estimate for the probability that an IDU becomes infected after injecting with an infected needle.

It is difficult to imagine that the complex transmission dynamics of the spread of HIV, especially amongst a population about which so little is know as the population of injecting drug users, will ever be described by a single model. Indeed the search for an all encompassing model may not be relevant. Just as this Thesis has concentrated on a few key aspects of the disease spread and improved our understanding in these areas, future research should focus on specific questions, thus providing more pieces of the jigsaw puzzle that the scientific knowledge about HIV appears to be, some fifteen years on from the discovery of the virus. Hopefully some of the missing pieces, the cure or an effective vaccine, will soon be discovered.

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