ISSN 1032-3813
ISBN 0 7326 0769 8

MONASH UNIVERSITY

AUSTRALIA

A COMPUTER SIMULATION OF THE SPREAD OF HEPATITIS C

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Working Paper 8/95
August 1995

DEPARTMENT OF ECONOMETRICS

A Computer Simulation of the Spread of Hepatitis C

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Abstract: The paper presents a generic interactive simulation model for Hepatitis C. The model can be used to predict the long term outcome of existing or custom made cohorts by changing numerous parameters simultaneously. It can also be used to estimate threshold values for parameters and immunisation strategies.

Key words: Epidemics, Simulation, Markov Processes

August 1995

* I am very grateful to Ken Richardson for his helpful comments on several earlier versions of this paper. I also wish to thank Nick Crofts of The Macfarlane Burnet Centre for Medical Research for giving me access to data gathered from the cohort of Victorian Injecting Drug Users.

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1. Introduction

Most simulation models that have been proposed for modelling infectious diseases, *(Ackerman, Elvback and Fox, 1984)* have looked at epidemics such as influenza and measles where the duration of the disease is relatively short compared to an individual's life span. With these diseases, it is also assumed that an individual is infectious only during the illness and that a complete recovery is made. If immunity to that particular strain of infection is not achieved after a single infection, there is a possibility of secondary attacks. Hence, the models allow for the population being divided into susceptibles, infectives and the infected. The latter group (also termed removals) are considered to be non-infectious and hence they do not contribute to the epidemic from that point on. Very few simulation models look into the new wave of epidemics caused by blood borne viruses such as HIV, Hepatitis B and Hepatitis C, where the illness is long term with incubation periods that can stretch to almost a decade, and there is the possibility of being a carrier after recovery (Hepatitis B, C). Most of the models discussed in the literature were also done before the recent revolution of micro-computers and thus, apart from proving to be long and expensive exercises, were also limited by the computer facilities available.

The study of epidemics is made complex by the very large number of parameters that control the dynamics of the spread of disease. Whilst it is extremely difficult to reproduce the complexities of the spread of a disease in a mathematical model, one needs to include the required complexity needed to answer the relevant epidemiological questions. There also should be a balance between complexity and including only parameters that can be quantified and measured. As it is not possible to conduct experiments, epidemiologists have to, by necessity, either observe an epidemic or carry out longitudinal studies in order to collect data. This is particularly a problem with diseases such as Hepatitis C, which was identified less than a decade ago, yet has a natural history which spans nearly three decades. In such cases only part of the information is available and there is little evidence to statistically support some of the conclusions drawn. Whilst it is necessary to ask "what if ?" one cannot always test the questions using experimental trials. The motivation behind this research is to extend the scope of visually interactive PC based simulation to model the spread of epidemics in order to obtain predicted outcomes of current and proposed strategies.

The model proposed is generic and attempts to include several dimensions of complexity in order to be useful to simulate the spread of most infectious diseases. The main objective in building this first model has been to develop a relatively simple simulation model that allows the user to observe the spread of Hepatitis C within a heterogeneous injecting drug using population. Even though the spread of a disease is a continuous process, as the emphasis of the study is to model the individual interactions that lead to the transmission of the agent, the simulation model used is a discrete one. All of the parameters that describe the disease can be set and reset, thus allowing the modelling of diseases which have very different natural histories and mechanics. Parameters that cannot be successfully measured or quantified can still be used to judge the sensitivity of the epidemic to relative changes made. For example, using varying success rates, one could test to establish efficient distribution patterns for limited supplies of vaccinations. It allows numerous interventions to be made during a simulation and also provides a system that allows controlled experimentation by segregating the population. The program provides a graphics interface which is designed to be user friendly and informative.

Due to the complexity and lack of information available on the Hepatitis C epidemic, it was chosen to test adaptability and robustness of the simulation model. The sections that follow cover relevant information on Hepatitis C, the mathematical model used in the simulation, data, preliminary results, conclusions drawn and limitations of the model.

2. The Epidemic

Until the late 1980's, when the Hepatitis C virus (HCV) was identified, chronic liver disease which could not be attributed to the Hepatitis A virus or the Hepatitis B virus was imaginatively classed as non-A, non-B Hepatitis. HCV is a blood borne virus like HIV and is transmitted most efficiently through exposure to blood. Research into Hepatitis C started less than five years ago and, as such, there are many areas of the disease, its transmission and prevalence that are still unclear. Quantitative studies of the natural history of the virus is very limited. Once infected, the virus starts to replicate itself in the liver and this can be detected using a polymerase chain reaction (PCR) within 1-2 weeks. There appears to be a delayed start to the production of antibodies as detection of anti-HCV can take up to 12 weeks. The period up to the detection of antibodies often goes unnoticed as this phase of the disease is mostly asymptomatic. After this phase the individual develops acute Hepatitis. Whilst a minority clear the virus, about 60-90% of people infected with HCV progress to chronic liver disease. At least 20% of these cases go on to develop cirrhosis and liver cancer. Factors involved in the progression of the disease vary from duration of drug use, age, excessive alcohol usage to the genotype of the HCV virus *(Strasser, 1994).* It appears to be the case that some individuals recover from Hepatitis C, but a small proportion become reinfected due to ineffective antibody development.

The Hepatitis C virus is known to be a major cause of chronic hepatitis, cirrhosis and liver cancer. HCV is documented to be ten times more transmissible than HIV *(Kaldor, 1994)* and as a result prevention strategies such as education on cleaning of injecting equipment have not been as effective slowing the spread of HCV as was the case for HIV. Although sexual and perinatal transmission may occur, the most efficient form of transmission of HCV is through needle sharing. Hence, injecting drug usage is the major risk factor. For the same reason, there is a very high prevalence and rate of incidence of HCV amongst the prison population. Studies have shown that HCV prevalence amongst the injecting drug using community to be between 60-80% with an annual rate of incidence of 15-20% *(Kaldor, 1994), (Wodak and Crofts, 1993).* With data suggesting that at least 20-30,000 people begin injecting drugs per year, it is estimated that there are nearly 150,000 people infected with HCV as a direct result of injecting drug use in Australia *(Crofts and Wodak, 1993).* In 1994, up to the end of November, there were 7798 new cases of Hepatitis C reported to the National Notifiable Diseases Surveillance Authority and were the highest number of notifications amongst all the diseases monitored (The Sunday Age, 4 December 1994). Cohort studies have shown that within two years of beginning to inject, up to 40% have already been infected, and there is almost 90% HCV prevalence amongst individuals who have injected drugs for over a period of five years *(Wodak and Crofts, 1993).* In the injecting drug using (IDU) population, the factors that have been found to be correlated with infection of HCV are duration of drug use, prison history and the type of drug used *(Crofts and Wodak, 1993).*

As reliable assays for testing anti-HCV were not available before, screening of donated blood for HCV was introduced only in 1990. There is still no generally accepted testing strategy for HCV. Most laboratories develop their own diagnostic strategy taking into account the limitations of the available anti-HCV assays *[Locarnini, 1994).* Clinical practitioners have to base their diagnosis and treatment on such tests, clinical symptoms and case histories.

At present, the only treatment available for HCV is Interferon which has unpleasant side effects. Until now, the approved duration of Interferon treatment was 6 months. Due to poor response rates and high relapse rates, it is now being tested on courses up to 2 years. Treatment beyond 6 months has been found to give better response rates *(McCaughan, 1994).*

Six main genotypes of the HCV virus have been identified to date. These are classified as types 1a, 1b, 2a, 2b, 3 and 4. Studies suggest that there is a correlation between genotypes and factors such as clinical symptoms and treatment effects *(Strasser, 1994).* It is suggested that the reason many infected with HCV fail to develop effective antibodies in order to clear the virus is multiple genome infection. The theory being that the genomes alternate their dominance, thus changing the antigens produced whilst the body keeps attempting to develop antibodies. The genotype profile found in Australia is similar to that found in Scotland, where types 1a and 3 are the most common, and differs from the USA, France and Japan, where only type 1b appears to be found (*Swanston and Reed, 1994).*

3. The Model

The model described in the paper is one that would be described as a stochastic micro population model i.e. it follows the history of distinct individuals. It is loosely based on the Reed-Frost model (Ackerman et al, 1984) but allows for more heterogeneity amongst the individuals and more dimensions to the disease itself. Apart from the probability of being infected, it also allows for different rates of progression of the illness itself, thus allowing for the inclusion of non-infectious states during latent periods of the illness. The system itself is treated as a finite-state stochastic process. In reality, the time between transitions is also stochastic (semi-Markov) but by taking relatively small time units vis-a-vis the length of the disease, this condition is relaxed and hence the process is treated as Markov (See Appendix 1- Assumptions). Unlike most infections, where susceptibles become infected and move through the various phases of the disease until they die or recover and be immune to reinfection, with HCV, the situation is more complicated. There appear to be transitions into and out of most states. There are also some individuals who stay permanently in what would normally be considered to be a transient state i.e. this state becomes an absorbing state for some of the population whilst others transit to the next stage of the disease.

3.1 The States and Transitions

For the purpose of developing the structure and dynamics of the model, seven states have been used. Several states that describe chronic liver disease due to Hepatitis C have been combined into one state. With the terminology, Sero-positive/negative indicates the antibody status and PCR +/- indicates the presence or absence of the HCV virus in the liver i.e. the virus is replicating in the liver and hence such an individual is infectious. It is also assumed that if $i < j$, then state j is beyond state i in terms of the progress of the disease. That is to say that state i is a more desirable state than state j.

NO:	STATE DESCRIPTION	COMMENTS
1	Sero(-) PCR(-)	Healthy (non-HCV)
2	Sero(-) PCR(+)	Initial stages (1-2 weeks from infection)
3	Sero(+) PCR(-)	No virus replication detected
4	Sero(+) PCR(+)	Clinical Hepatitis C (at approx.12 weeks)
5	Chronic Liver Disease	Including Cirrhosis and liver cancer
6	Death from HCV	Death as a direct result of above
7	Death from non-HCVcauses	Death by causes other than HCV

State 1 contains the susceptibles. State 2 is a short phase where although the individual is infected, and the virus is already replicating itself, there has not been enough antibodies generated to give a positive antibody test. Whilst this state is entered into within 1-2 weeks of infection, most infected individuals go through this phase without realising they have been infected. From state 2 rather than always progress to state 4, which is clinical HCV, some individuals make a transition to state 3, where the body appears to have halted the replication of the virus and as such the infection is dormant. From here there appear to be three routes:

i. individuals manage to clear the virus completely and stay immune i.e. they stay in state 3 permanently until death by other causes.

ii. individuals manage to clear the virus but do not have enough antibodies to ensure immunity and hence return to being a susceptible in state 1.

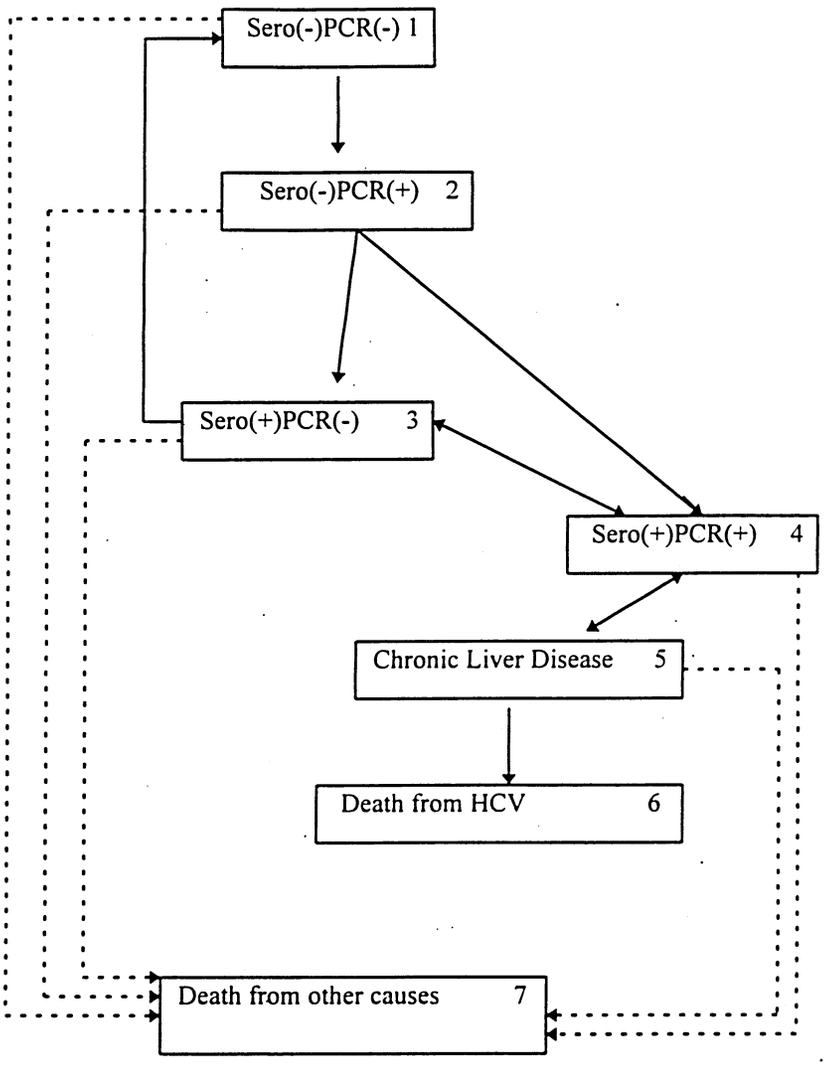
iii. the dormant virus starts replicating again and the individual progresses onto clinical HCV in state 4.

POSSIBLE TRANSITIONS FOR HCV: (Indicated by +)
(Transitions not possible Indicated by 0)

state	1	2	3	4	5	6	7
1	+	+	0	0	0	0	+
2	0	+	+	+	0	0	+
3	+	0	+	+	0	0	+
4	0	0	+	+	+	0	+
5	0	0	0	+	+	+	+
6	0	0	0	0	0	+	0
7	0	0	0	0	0	0	+

To complicate matters further, the model must allow for some individuals to alternate between states 3 and 4 for a very long time, even till death by other causes, going through repeated cycles of controlling the virus and redeveloping Hepatitis C. Some of the individuals in state 4 progress further to state 5, Chronic Liver Disease, which is an amalgamation of Chronic Hepatitis, Cirrhosis and Liver Cancer. Some will recover from this phase and return to state 4 and then to state 3 . State 7 contains individuals who die from other (natural) causes.

TRANSITION DIAGRAM



3.2 Parameters used in the Model

The parameters used are

1. Initial transition rates
2. Interaction (mixing) factor
3. Immunisation factor
4. Treatment factor
5. Number of infectives in each group (1-4 are given as probabilities)

The factors that were considered in order to divide the population into different risk categories were:

a) Duration of drug use;
b) Type of drug used;
c) Prison History;
d) Blood transfusion before screening for HCV was introduced;
e) Mediterranean origin.
f) Age;
g) Other health problems such as excessive use of alcohol.

The population is divided into several groups. It is assumed that individuals interact only within their group (Appendix I). Each group encompasses a combination of the characteristics listed above so that individuals within a group have similar risk factors. As such, each group has a unique transition matrix associated with it. Heterogeneity within groups is allowed by introducing three further parameters, namely, the interaction factor, the immunisation factor and the treatment factor. The interaction factor gives the proportion of group members the individual in question has contact (shares needles) within a single time period. The purpose of this parameter is to allow for each individual in a group to have a marginally higher or lower probability of infection than the average probability of infection for that group. Apart from breaking down the necessity to have homogeneity within groups, it also allows for the modelling of a sudden change to an individual's behaviour. The immunisation factor allows for all or a proportion of healthy individuals to be immunised against the disease. The estimated effectiveness of the immunisation is used as the immunisation factor. This parameter could also be used to include natural or acquired immunity to the disease. The treatment factor influences the rate at which individuals progress to worse states of the disease once infection has taken place. Apart from using the parameter to experiment with treatment effects, it could also be interpreted as changes to lifestyle leading to better or worse state of general health. e.g. reducing excess use of alcohol or contracting another liver disorder.

3.3 Calculating the probability of becoming infected

The probability of a healthy individual becoming infected at any given time is calculated using the following parameters:
1. The probability of becoming infected by a single contact with an infective. In HCV terms this is a measure of the level of risk exposed to by injecting. As the groups are based on behavioral characteristics, each group has a unique probability associated with injecting and is given by the group transition matrix.
2. The interaction factor. In the case of HCV, this parameter measures the frequency of sharing needles. There could be multiple contacts with the same individuals.
3. The immunisation factor.
4. The percentage of infectives in group.

Let G be a group of the population.
If x is a susceptible and $x \in G$, let:

$N_G(t)$ = number in G at time t;
$n_G(t)$ = number of infectives in G at time t;
p_G = probability of a susceptible in group G becoming infected through a single contact with an infective from group G;
m_x = the number of contacts x makes with individuals in the group between time t and t+1, $\forall$ t;
i_x = the reduction in the probability of infection (as a proportion) for the susceptible x due to x being immunised. This is the immunisation factor of x or the immunisation efficacy.

3.3.1. Introducing the interaction and prevalence factors

Let $c_x(t)$ denote the number of contacts made with infectives, by the susceptible x, between the times t and t+1.
then $c_x(t) = m_x.n_G(t)/ N_G(t)$.
Hnce the probability of *not* becoming infected by *all* contacts made between time t and (t+1)
$= (1- p_G)^{c_x(t)}$
Hence the probability of x becoming infected during time t,

$$p_x(t) = 1 - [(1-p_G)^{m_x.n_G/ N_G(t)}].$$

3.3.2. Introducing the immunisation factor

The probability of the susceptible x becoming infected, adjusted for immunisation is

$$_i p_X(t) = p_X(t)[1 - i_X]$$

3.3.3 Numerical example:

Let $x \in G$.
The probability of infection through a single contact with an infective = 0.03
The percentage of infectives in G at time t = 70
The mean number of interactions per time unit (a fortnight)for x = 2.
The probability of x becoming infected during the next fortnight =

$$p_X(t) = 1 - [(1-p_G)^{m_X \cdot n_G / N_G(t)}]$$

$$= 1 - [(1-0.03)^{2 \times 0.7}] = 0.04$$

If x is immunised and the efficacy of the vaccine is 80%, then the probability of becoming infected during the next fortnight is

$$_i p_X(t) = p_X(t)[1 - i_X]$$
$$= 0.04\ (1-0.8)$$
$$= 0.008$$

3.4 Introducing the treatment factor

The treatment effect reduces the transition probabilities to higher states by a constant factor (the treatment factor) and correspondingly equally increases the transition probabilities to all other states, including the present one.
For $x \in G$ and is in state j at time t
Let $p_{xjk}(t)$ = transition probability of moving from state j to state k during t and t+1.
$\mathbf{Px}$ = transition matrix for x.
τ_{xj} = treatment factor of individual x when in state j;
Revision of transition probabilities to incorporate treatments
$_\tau p_{xjk}(t)$ = revised transition probability

$$_\tau p_{xjk}(t) = p_{xjk}(t) \cdot \tau_{jx} \qquad s > k > j;\ s = \text{number of states}$$

$$_\tau p_{xjk}(t) = p_{xjk}(t) \left[(1 - \tau_{jx} \cdot \sum_{l>j} p_{xjl}) / \sum_{l>j} p_{xjl} \right] \qquad k < j+1$$

3.4.1 Numerical example:

Let $x \in G$ and be in state 3. If the 3rd row of the transition matrix of x is

(0.1 0 0.69 0.2 0 0 0.01)

and the treatment factor of x is 60%, then the revised transition probabilities to states high than 3 are:

$$_\tau p_{x34}(t) = 0.2 \times 0.6 = 0.12$$
$$_\tau p_{x35}(t) = 0 \times 0.6 = 0$$
$$_\tau p_{x36}(t) = 0 \times 0.6 = 0$$
$$_\tau p_{x37}(t) = 0.01 \times 0.6 = 0.006$$

$$\sum_{k>3} {}_\tau p_{x3k}(t) = 0.126$$

The revised transitions probabilities for states up to and including 3 are:

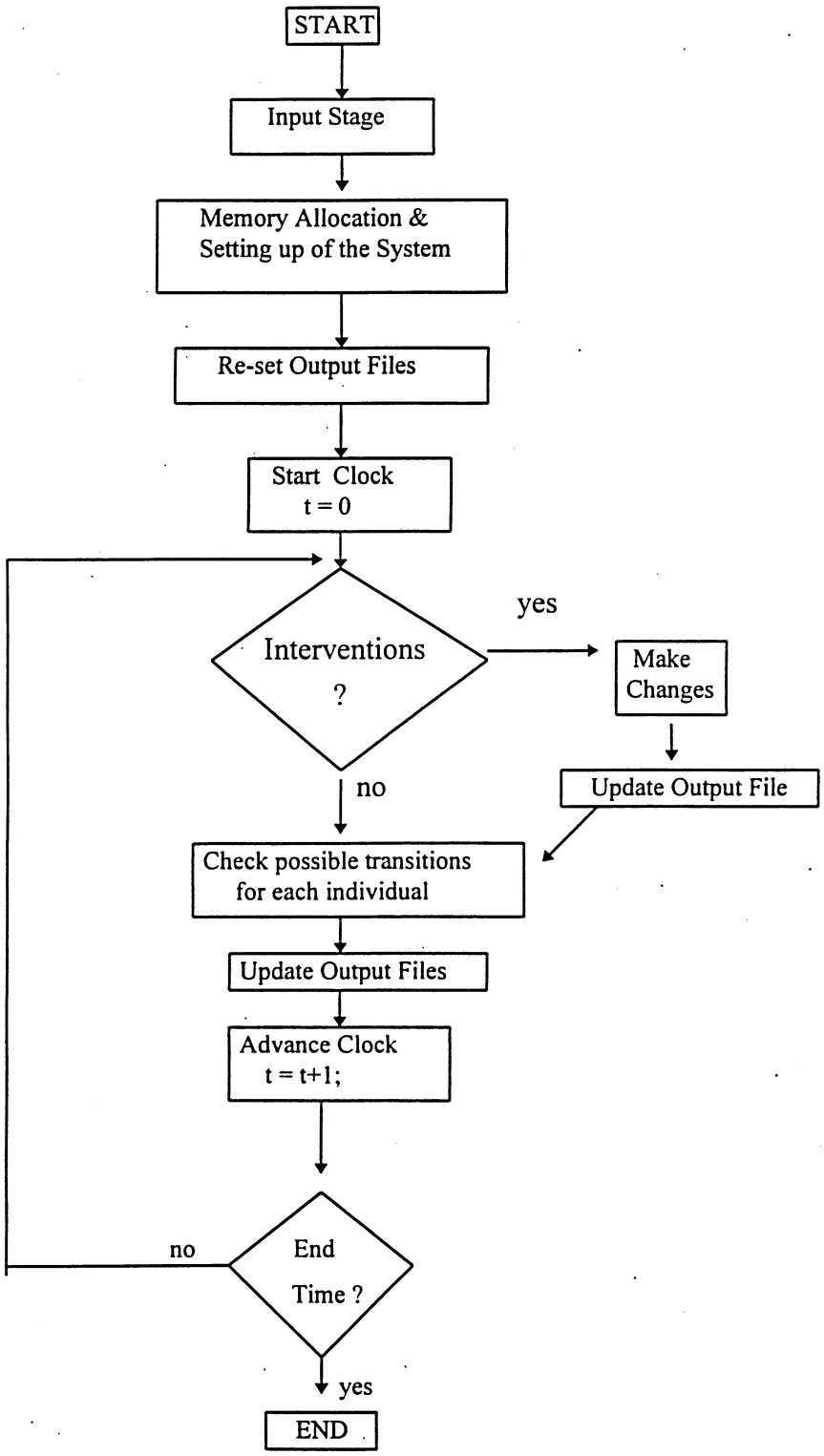
$$_\tau p_{x31}(t) = 0.1 \times (1-0.126)/(0.1 + 0.69) = 0.1 \times 0.874/0.79 = 0.111$$
$$_\tau p_{x32}(t) = 0 \times 0.874/0.79 = 0$$
$$_\tau p_{x33}(t) = 0.69 \times 0.874/0.79 = 0.763$$

The revised row is

(0.111 0 0.763 0.120 0 0 0.126)

4. The Simulation program

The program is coded in C and uses a three phase simulation executive which was developed at the University of Lancaster, England. The executive provides the simulation clock and the cyclic system which facilitates the progression of time. All the functions relating to the mechanics of the spread the disease, the interventions and the graphical display have been coded separately and compiled as a single project using Turbo C (Borland).
Flow diagram of computer program:



The simulation model is a visually interactive one. It allows the user to intervene at any time so as to simultaneously change values of parameters. The system is entirely input driven. Parameters such as population size, number of groups, number of states, possible transitions and other factors which affect the rate of transition are all treated as variables. These values are read from text files at the start of a run and,as such, the model uses dynamic memory allocation.
The entities used in the model are individuals. Based on the overall risk factors each individual displays, the population is divided into a number of groups where each group has a unique transition matrix.

The attributes of the individuals are
1. Identification number
2. Status of infection
3. Group number
4. Other characteristics of relevance at entry to cohort (e.g. age,duration of injecting drug use, primary drug)
5. Interaction factor
6. Immunisation factor
7. Treatment factor

Each time unit corresponds to two weeks and interventions are allowed at the start of any time period. The program uses two input files. The first input file defines the system whilst the other lists the cohort. Output files generated by the program list all the transitions, a summary of the numbers in each state within each group and details of interventions made.

5. Data and Results

The main objectives of this stage of the analysis were
i. to ensure the results produced were representative of the progress of the disease and the spread of the epidemic;
ii. to test the sensitivity of the main parameters used;
iii. to determine the limitations of this model.

5.1 Cohorts used in Simulation

As it was not possible to access a data set large enough to contain the desired variability, it was decided that a data set would be generated using published results of cohort studies conducted in Australia. Microsoft Excel was used to generate the cohort. In order to experiment with parameters such as transition rates, immunisation factors etc., several cohorts were also designed to portray the necessary characteristics and variability.

5.2 Results:

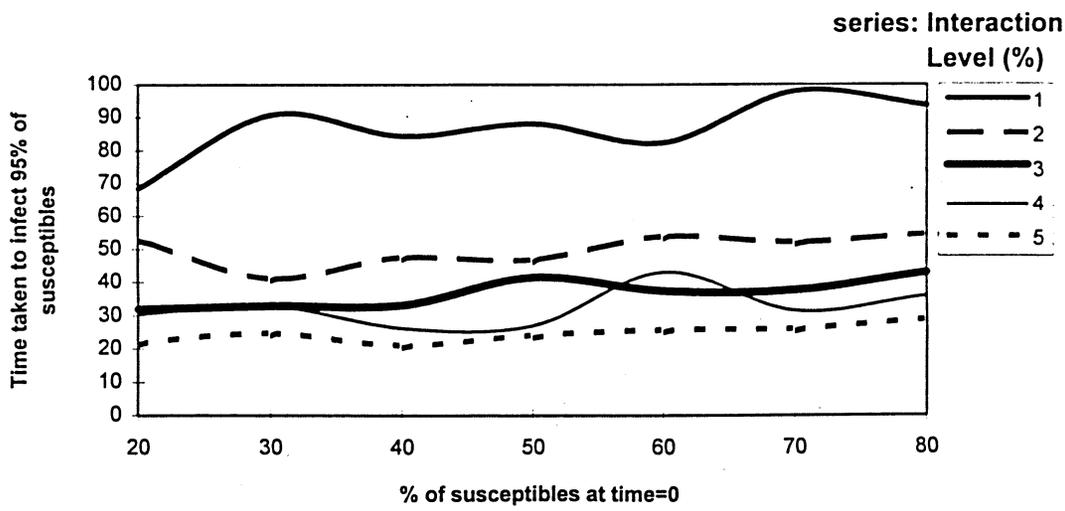


Figure 5.2.1: varying the % of susceptibles at time=0

(Probability of infection from a contact with an infective kept constant at 1%)

The test measure that was used to determine the effect of each of the parameters on the spread of the infection was the time taken to infect 95% of the susceptible population. The spread of the infection was simulated in cohort and the results were cross tabulated.

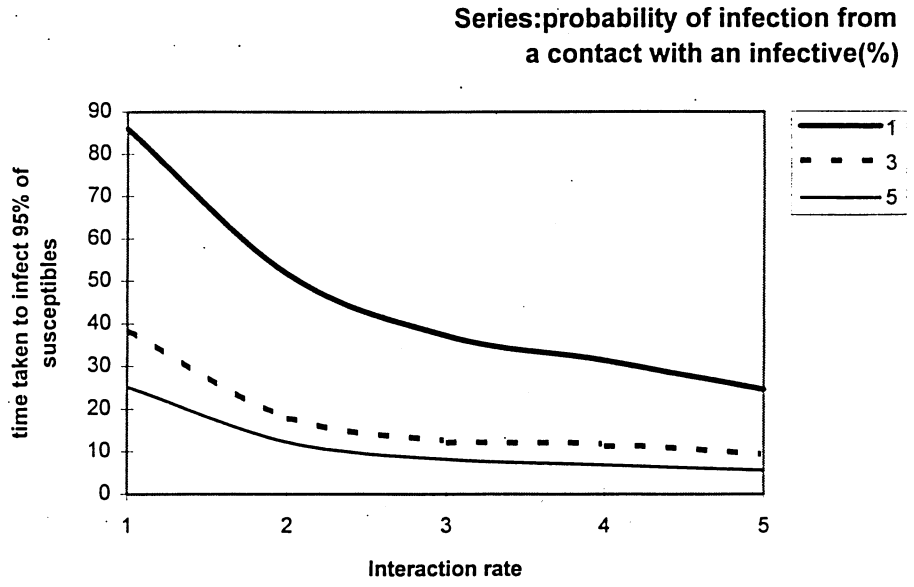


Figure 5.2.2: Varying the interaction rates of the individuals

The results generated show that the spread of the infection is not particularly sensitive to the prevalence rate. As shown in *Figure 5.2.1*, in most cases, the time taken to infect 95% of the susceptibles did not change significantly when the prevalence decreased from 80% - 20%. There was however a noticeable trend in the series generated by the low interaction level of 1%. Once the interaction level increases above 2% this trend becomes less apparent. *Figure 5.2.2* confirms that the spread of the infection is very sensitive to the interaction rates, with clear indication of the infection spreading much more rapidly as the interaction levels increase. There is also a considerable difference in the series based on the probability of infection through a single contact.

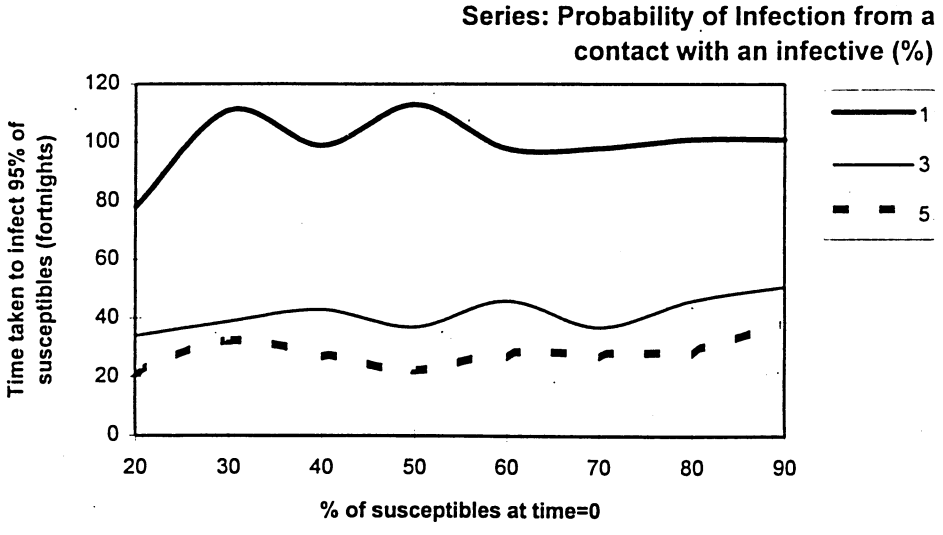


Figure 5.2.3: Varying the prevalence whilst keeping the interaction constant at 1%

Figure 5.2.3 shows the result of keeping the interaction rate constant at 1% and varying the prevalence. Once again whilst the time taken to infect 95% of the susceptibles is not very sensitive to the prevalence, the series show that it is very

sensitive to the probability of infection. *Figure 5.2.4* confirms this by showing that as the probability of infection is increased from 1% to 5% there is a clear impact on the rate at which the disease spreads through the cohort. This graph also indicates that at lower values of the probability of infection, namely 1%-3%, the changes to the interaction rates are marked. It would appear that low interaction and low probability of infection has a considerable impact on the rate of the spread of the disease.

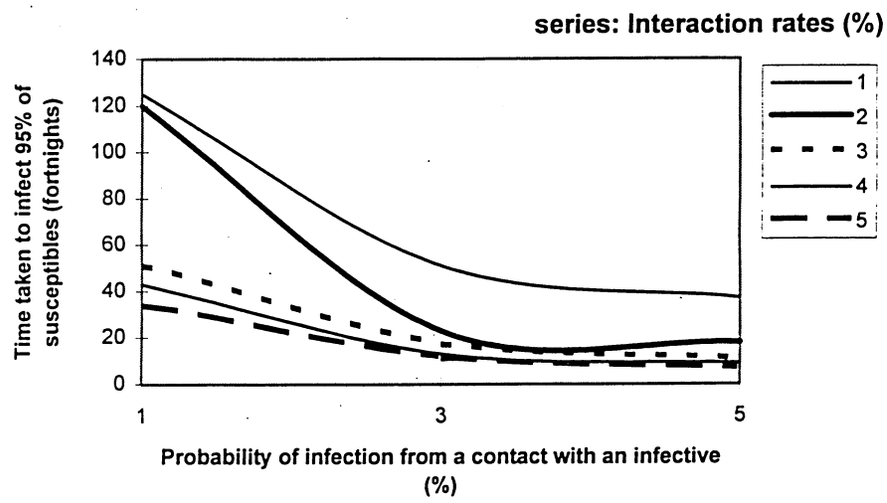


Figure 5.2.4: Varying the probability of infection

Sample result

ID no.	005
Age	25
Sex	Male
Main Drug	Heroin
Duration	2 yrs
Prison history	yes
Sexual Orientation	Bisexual

Time	0	20	26
State	sero-pcr-	sero-pcr+	sero+pcr+
Infectives in group	57%	80%	89%

5.3 Conclusions

The results clearly indicate that the rate at which the infection spreads is extremely sensitive to the interaction rate and the probability of infection through a single contact with an infective. At the same time it shows that it is not very sensitive to the prevalence. This is very encouraging as it suggests,that in spite of the very high prevalence of Hepatitis C in the true population, changes to behaviour that could reduce interaction levels could play an important role in controlling the epidemic.

5.4 Limitations of the existing model

The main limitation that is evident is the use of a closed population. As the results indicate very high sensitivity to relatively small changes to the interaction levels and probability of infection, it may also be useful to allow these parameters not to be limited to integer values. In order to introduce more heterogeneity to the process of becoming infected once exposed, the inclusion of a parameter defining the infectiousness of an infective may be helpful.

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APPENDIX I

Assumptions made in building the model

A1: The population is a closed cohort of injecting drug users.

A2: The time between transitions is taken as being constant.

A3: There is total mixing within groups; ie. every individual may interact with every other member of the same group.

A4: There is no interaction between individuals of different groups.

A5: The probability of infection through a single contact is constant; ie. any contact is considered to be of fixed risk. (In the case of Hepatitis C, "contact" is assumed to be risk associated with injecting in groups such as needle sharing, contaminated surfaces etc.)

A6: The rate of infectiousness of infectives is constant.

A7: There is only one state infected susceptibles can move to ie. the only transitions possible from state 1 are state1-> state1 and state1->state2 . (All the calculations for the probability of not being infected are based on this assumption)

APPENDIX II

Statistics used to generate Cohorts for simulation program

[Extracted from Table 1. Characteristics of injecting drug users interviewed and tested for antibody to Hepatitis C virus, Victorian Injecting Drug Users Cohort Study, 1990-1992. (Croft et al, 1992)]

Population size = 283;

	Mean	*sd*
Age at entry to cohort (years)	*28.4*	*6.6*
Duration of injecting at entry (years)	*9.5*	*6.2*
Age at first injection	*19.2*	*5.7*

	Proportion (%)
Sexual orientation	
Homosexual	*7*
Bisexual	*10*
Heterosexual	*79*
Other (celibate)	*3*
Current primary drug injected	
Opiates	*65*
Amphetamines	*18*
Other	*18*
First drug injected	
Opiates	*50*
Amphetamines	*47*
Other	*3*
Prison History	*34*
Location	
Metropolitan	*88*
Rural	*12*