International Statistical Review (1994), **62**, 2, pp. 229–243. Printed in Great Britain

Sensitivity and Uncertainty Analysis of Complex Models of Disease Transmission: an HIV Model, as an Example

S.M. Blower and H. Dowlatabadi†

School of Public Health (Epidemiology) 140, Earl Warren Hall, University of California, Berkeley, California 94720, USA. †Department of Engineering & Public Policy, Carnegie Mellon University, Pittsburgh, PA 15213 USA.

Summary

HIV transmission models have become very complex. The behavior of some of these models may only be explored by uncertainty and sensitivity analyses, because the structural complexity of the model are coupled with a high degree of uncertainty in estimating the values of the input parameters. Uncertainty analysis may be used to assess the variability (prediction imprecision) in the outcome variable that is due to the uncertainty in estimating the input values. A sensitivity analysis can extend an uncertainty analysis by identifying which parameters are important in contributing to the prediction imprecision (i.e., how do changes in the values of the input parameters alter the value of the outcome variable). In this paper an uncertainty and a sensitivity analysis are described and applied; both analyses are based upon the Latin Hypercube Sampling (LHS) scheme, which is an extremely efficient sampling design proposed by McKay, Conover & Beckman (1979). The methods described in this paper have not previously been applied to deterministic models of disease transmission, although these models have many characteristics in common with the risk assessment models that the strategies were designed to investigate. The utility of the LHS uncertainty and the LHS/PRC (Latin Hypercube Sampling/Partial Rank Correlation) sensitivity analysis techniques are illustrated by analyzing a complex deterministic model of HIV transmission.

Key words: Uncertainty analysis; Sensitivity analysis; Sampling design; Mathematical models; Epidemiology.

1 Introduction

Mathematical models of disease transmission consist of a series of equations, these equations are formulated based upon specific epidemiological assumptions; such models may be utilized as epidemiological tools (Blower & Medley, 1992). Many models have been formulated to investigate the transmission dynamics of the human immunodeficiency virus (HIV), see for examples: Anderson, Gupta & May, 1991; Anderson, May & McLean, 1988; Blower, 1991; Blower et al., 1991; Dietz & Hadeler, 1988; Jacquez et al., 1988; Koopman et al., 1988; Le Pont & Blower, 1991; May, Anderson & Blower, 1989. The initial simple HIV transmission models have been refined to include behavioral heterogeneity, mixing patterns for the selection of sexual and drug-sharing partnerships and variable infectivity of the virus. The simple transmission models can be solved analytically; however, the behavior of the complex models may only be understood by numerical analysis. Uncertainty analyses and sensitivity analyses are necessary to explore

the behavior of many of these complex models, because the structural complexity of the models are coupled with a high degree of uncertainty in estimating the values of many of the input parameters. Uncertainty analysis may be used to assess the variability (prediction imprecision) in the outcome variable that is due to the uncertainty in estimating the values of the input parameters (Iman & Helton, 1988). A sensitivity analysis can extend an uncertainty analysis by identifying which input parameters are important (due to their estimation uncertainty) in contributing to the prediction imprecision of the outcome variable; therefore, a sensitivity analysis quantifies how changes in the values of the input parameters alter the value of the outcome variable (Iman & Helton, 1988).

One approach to a sensitivity analysis is to use a full factorial sampling design; this sampling scheme uses every value of each parameter and forms every possible combination of parameter values. This analysis has the advantage that the entire parameter space is explored, but this design is extremely time consuming and hence impractical for complex transmission models that contain a multitude of parameters. An alternative sensitivity analysis design, for a K parameter model, is to fix the values of $K-1$ parameters and to vary only the value of the Kth parameter over a specified range. This sensitivity analysis design has the advantage that it is simple and quick, but it suffers from major disadvantages: only one parameter may be varied at a time, only a small region of the K-dimensional parameter space can be explored, and the values of the $K-1$ parameters have to be estimated with a very high degree of precision.

More sophisticated and efficient statistical analysis techniques, that allow for the simultaneous variation of the values of all the input parameters, have been applied to explore the behavior of complex economic, engineering, chemical and physical models. One such technique is based upon Latin Hypercube Sampling (LHS); LHS is a type of stratified Monte Carlo sampling and may be viewed as an extension of Latin Square sampling (Iman & Helton, 1988; McKay, Conover & Beckman, 1979). LHS was first proposed by McKay, Conover and Beckman (1979) to aid in the analysis of evaluating reactor safety. In LHS the estimation uncertainty for each input parameter is modelled by treating each input parameter as a random variable. Probability distribution functions (pdfs) are defined for each parameter, each of the marginal distributions are stratified and the value of each input parameter is then randomly chosen (McKay, Conover & Beckman, 1979). LHS is an extremely efficient sampling design because each value of each parameter is used only once in the analysis. An input vector is generated (composed of the random samples of each of the input parameters) for each computer simulation of the deterministic model. The model is then run N times. Distribution functions for each of the outcome variables can be directly derived, because of the probabilistic selection technique, hence LHS enables the results of a deterministic model to be interpreted within a statistical framework (Iman & Helton, 1988; Iman, Helton & Campbell, 1981a). The distributions may be characterized by simple descriptive statistics; at this stage the LHS uncertainty analysis is complete. A sensitivity analysis may then be performed by calculating partial rank correlation coefficients (PRCC) for each input parameter (sampled by the LHS scheme) and each outcome variable (Iman & Conover, 1980; Iman & Helton 1988; Iman, Helton & Campbell, 1981a).

The LHS design has been compared with simple random and fractional stratified sampling designs and it has been demonstrated that, if the outcome variable is a monotonic function of each of the input parameters, the LHS design is the most efficient design for estimating the mean value and the population cumulative distribution function (McKay, Conover & Beckman, 1979). Stein (1987) has also compared LHS with simple random sampling and demonstrated that if sample sizes (i.e., the number of computer

simulations) are large, LHS is the most efficient design (i.e., the variance of the estimate of the expectation of the function of the outcome variable is less than if simple random sampling is used), even if the monotonicity assumption does not hold. Iman & Helton (1988) have compared three uncertainty and sensitivity analysis techniques: response surface methodology using input derived from a fractional factorial design, LHS with and without regression analysis, and differential analysis. The same three methods were applied to the analysis of three large computer models. The techniques were compared on the basis of several criteria: ease of implementation, flexibility, estimation of the cumulative distribution function of the outcome variable, and adaptability. Judged on the basis of these criteria, LHS and regression analysis were rated the best techniques (Iman & Helton, 1988). Handcock (1989) also found that LHS can be at least an order of magnitude more efficient than simple random sampling; for example, a LHS scheme with 108 simulations can achieve similar results to a simple random sampling scheme that requires 7,700 simulations (Handcock 1989).

The LHS uncertainty analysis and the LHS/PRCC sensitivity analysis techniques have not previously been applied to deterministic disease transmission models. However, disease transmission models have many characteristics in common with the risk assessment models that these strategies were designed to investigate. The model characteristics may be summarized as follows: (i) the models have many uncertain parameters, (ii) the outcome variables are non-linear functions of the parameters, (iii) the full range of each input parameter needs to be investigated, and (iv) the models are computationally taxing, hence it is desirable to complete the sensitivity analysis with the minimum possible number of computer runs. In this paper the LHS uncertainty and the LHS/PRCC sensitivity analysis techniques are described in detail, and the utility of these techniques are illustrated by analyzing a complex deterministic model of HIV transmission.

2 The HIV transmission model

The deterministic mathematical model used to illustrate the techniques was formulated by one of the authors (SB) to assess the epidemiological consequences of heterosexual, intravenous drug use and perinatal transmission of HIV. The model was designed to reflect the specific transmission dynamics of these three processes in New York City (NYC). The model has been used to suggest a new explanation for the observed intravenous drug use (IVDU) seroprevalence pattern in NYC, and to explore the effect of the heterosexual transmission risk factor on increasing the risk of HIV infection in intravenous drug users (see Blower, 1991 and Blower et al., 1991). The model has also been used to predict future numbers of adult and pediatric AIDS cases in NYC, to assess the variability in these prediction estimates, and to identify the key variables that contribute to this prediction imprecision. The model is deterministic, consequently the prediction imprecision is due to the uncertainty in parameter estimation. The model consists of thirty four ordinary differential equations, containing twenty parameters. These equations define the transmission of the virus within and among ten risk groups (which are represented by ten state variables): eight subpopulations of intravenous drug users and two subpopulations of non-intravenous drug users. A complete presentation of the model and the biological justification of the structure of the model is reported elsewhere (Blower et al. 1991); parameter definitions are given in Table 1. The structural complexity of the model coupled with a high degree of uncertainty in estimating both the values of the input parameters and the initial values of the state variables, necessitated the application of the LHS uncertainty analysis and the LHS/PRC sensitivity analysis.

Table 1

Parameter definitions for the HIV model. All of the transmission efficiencies are conditional on the fact that the partner or needle is infected.

β_{db}	HIV transmission efficiency per buddy partnership
β_{dn}	HIV transmission efficiency per needle injection
β_{fm}	heterosexual transmission efficiency per partnership (female to male)
β_{mf}	heterosexual transmission efficiency per partnership (male to female)
$c_{fb}(t)$	rate of change of sex partners per year (female buddy-users) at time t
$c_{fs}(t)$	rate of change of sex partners per year (female stranger-users) at time t
$c_{fn}(t)$	rate of change of sex partners per year (female non-IVDUs) at time t
$c_{mb}(t)$	rate of change of sex partners per year (male buddy-users) at time t
$c_{ms}(t)$	rate of change of sex partners per year (male stranger-users) at time t
$c_{mn}(t)$	rate of change of sex partners per year (male non-IVDUs) at time t
i_f	rate of sharing needles per year (for female stranger-users)
i_m	rate of sharing needles per year (for male stranger-users)
j_f	rate of change of buddy partners per year (for female buddy-users)
j_m	rate of change of buddy partners per year (for male buddy-users)
q_1	vertical transmission efficiency (seropositive mother, without AIDS)
q_2	vertical transmission efficiency (AIDS mother)
s_a	average adult survival time (years)
s_b	average pediatric survival time (years)
v_a	average adult incubation time (years)
v_b	average pediatric incubation time (years)

3 Methodology

The LHS/PRC technique involves seven steps:

3.1 Define Probability Distribution Functions for Parameters and State Variables

A mathematical model contains a certain number of parameters and state variables, the estimated values for all, or only a subset, of these will be uncertain. In the HIV model all ten state variables and twenty parameters were uncertain; pdfs were assigned to each parameter (see Table 2), the biological justification for the choice of these pdfs is

Table 2

Parameter distribution functions

Parameter	*Min*	*Max*	*Median*	*Standard deviation*	*Function shape*
β_{db}	β_{dn}	1	0·56	0·23	triangular (peak at β_{dn})
β_{dn}	0	1	0·28	0·23	triangular (peak at 0·0)
β_{fm}	0	0·5	0·25	0·15	uniform
β_{mf}	0	0·5	0·25	0·15	uniform
$c_{fb}(t)$	1	11	1	1·74	left skewed
$c_{fn}(t)$	1	20	2·19	2·46	left skewed
$c_{fs}(t)$	1	100	2	20.99	left skewed
$c_{mb}(t)$	1	20	1	3·02	left skewed
$c_{mn}(t)$	1	38	2	4·98	left skewed
$c_{ms}(t)$	1	15	1	2·94	left skewed
i_f	13	5,265	299	1,201	left skewed
i_m	13	3,120	228	738	left skewed
j_f	0	4	1·8	0·77	triangular (peak at 1·0)
j_m	0	4	1·8	0·76	triangular (peak at 1·0)
q_1	0	1	0·28	0·23	triangular (peak at 0·0)
q_2	q_1	1	0·56	0·23	triangular (peak at q_1)
s_a	1·0	5·0	1·0	0·85	left skewed
s_b	0·21	4·8	1·04	1·09	left skewed
v_a	1·36	20	8	3·71	Weibull
v_b	0·1	20	0·33 & 5·5	4·99	mixture of two Weibulls

discussed in detail elsewhere (Blower et al., 1991). The HIV model included specific biological assumptions which resulted in three parameter constraints: (i) heterosexual transmission efficiencies (during a sexual partnership) were assumed to be symmetrical (i.e., β_{mf} was set equal to β_{fm}; hence only nineteen parameters were sampled), (ii) the probability of HIV transmission through needle sharing was assumed to be greater if many needles are shared than if only one was shared (i.e., $\beta_{db} > \beta_{dn}$), and (iii) the probability of a baby being born infected with HIV was assumed to be higher, if the mother had acquired immunodeficiency syndrome (AIDS), than if the mother was infected with HIV, but did not show signs of AIDS (i.e., $q_2 > q_1$).

The values of the ten state variables (at time zero) reflected the sizes of the ten risk groups at the beginning of the epidemic. The complex interdependencies of eight of the state variables (the eight groups of intravenous drug users) are shown in Fig. 1. The initial values of these eight state variables were not statistically independent: for each simulation run the total population size of intravenous drug users (at time zero) was maintained at 200,000 individuals and the sex ratio (at time zero) was kept constant at 3:1 (males:females), (for a biological justification of these constraints see Blower et al., 1991). The initial sizes of the eight risk groups of intravenous drug users were generated by using six independent probability functions; the functions and the sampling design are shown in Fig. 1 (it can be seen that only four of the eight intravenous drug using risk groups were randomly sampled). The two remaining state variables (the male and female sex partners of intravenous drug users, who do not use intravenous drugs themselves) were assigned

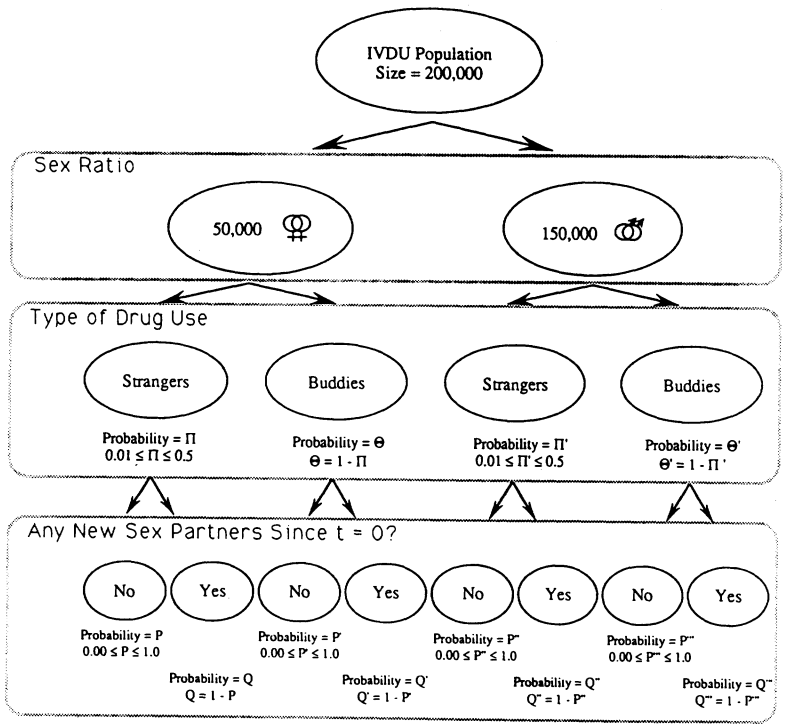

Figure 1. *Setting the initial values of the intravenous drug using (IVDU) risk groups. The IVDU population (at time zero) was set to 200,000 individuals, in each simulation; however, the sizes of the eight risk groups of intravenous drug users varied from run to run. As, the diagram above shows, not all of the subgroups were independent of each other. The sizes of the eight subgroups were defined by the six probability functions shown above.*

(at time zero) by sampling from a seventh pdf. The size of the female subpopulation (F) was sampled over the range 100,000 to 150,000 and the size of the male subpopulation (M) was then assigned: $M = 200{,}000 - F$. Hence, the initial values of the ten state variables (risk groups) were generated from seven pdfs.

3.2 Calculate the number of simulations (N)

The LHS design involves sampling without replacement; therefore, if only K draws are to be made (where K equals the number of uncertain variables) the Kth draw would be predetermined. Hence, the lower limit to the value of N (where N equals the number of simulations) should be at least $K + 1$. An exact formula to calculate N does not exist in the literature; although, an inequality that has to be satisfied ($N > 4/3K$) has been empirically established (McKay, Conover & Beckman, 1979). The appropriate sample size (N) for a specific analysis should also be determined by the desired significance level for the partial rank correlation coefficients. In the present analysis, N was set to 100.

3.3 Divide the range of each of the K parameters into N equi-probable intervals

The range of each parameter was divided into N non-overlapping equiprobable intervals (where N is the number of simulations) and each interval was sequentially assigned a sampling index from 1 to N (see Fig. 2). The parameter being sampled is x, therefore there are N sample values of x: $x_1, x_2 \ldots x_N$. The limits of each interval ($x^i_{\min}$

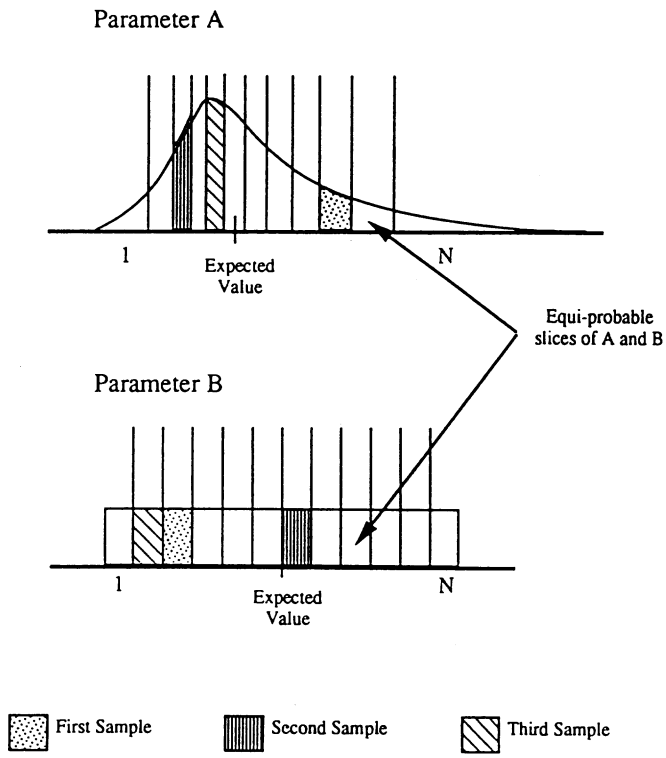

Figure 2. *Creating and sampling the equi-probable intervals. In the Latin Hypercube Sampling design, each parameter is defined in terms of a probability density function (pdf). These pdfs are sliced into N equi-probable intervals—where N is the number of simulations. For each simulation a value for each parameter is selected from one of these intervals at random, and without replacement.*

and $x^i_{\max}$; where i, the sampling index number is $1, 2, \ldots N$) have to be ascertained. Define the pdf of parameter x to be $f(x)$, the integral of $f(x)$ to be $F(x)$ and the inverse of $F(x)$ to be $F^{-1}(x)$. If the function is normalized then:

$$[F(x)]_{x_{\min}}^{x_{\max}} = 1.$$

The area under each equiprobable interval is equal to $1/N$, which is 0·01 in the current analysis.

$$1/N = \int_{x^i_{\min}}^{x^i_{\max}} f(x)\,dx = F(x^i_{\max}) - F(X^i_{\min}).$$

The lower interval limit of the first interval ($x^1_{\min}$) is set equal to the minimum value of the range of $f(x)$, and the upper interval limit ($X^1_{\max}$) is determined from the evaluation of:

$$x^i_{\max} = F^{-1}[F(x^i_{\min}) + 1/N].$$

Interval limits for the remaining intervals are calculated by setting the minimum value for the next interval ($X^{i+1}_{\min}$) to be equal to the maximum value for the previous interval ($X^i_{\max}$) and repeating the whole process.

3.4 Create the LHS table

The LHS design involves random sampling without replacement; every equiprobable interval of each input variable is sampled once. An LHS table is generated as an $N*K$ matrix, where N is the number of simulations and K is the number of sampled input variables. The LHS design was first proposed by McKay, Conover & Beckman (1979); a computer program, based upon this methodology, is available for generating LHS tables (Iman & Shortencarier, 1984). N sampling indices of the first variable are paired randomly with N sampling indices of the second variable, these N pairs are then paired randomly with the N values of the third variable, random pairing continues until all K input variables are included and the $N*K$ matrix has been generated (Iman, Helton & Campbell, 1981a; McKay, Conover & Beckman, 1979). The LHS design was originally proposed for models, where all of the input variables were statistically independent. Iman & Conover (1982) have extended the initial methodology to incorporate statistical dependencies. The new method replaces the random pairing of the N values of each input parameter with restricted pairing (Iman & Conover, 1982). This new technique may be appropriate for both independent variables (because restricted pairing can reduce spurious correlations and ensure that all the rank correlations are close to zero) and dependent variables (because restricted pairing can induce the desired rank correlation between input variables) (Iman & Conover, 1982; Iman & Davenport, 1982; Iman & Helton, 1988).

Stein (1987) has suggested that the restricted pairing technique might be an inappropriate method for generating joint distribution functions; for example, if two input parameters are related in a non-monotonic fashion, then inducing dependencies through rank correlation coefficients is inappropriate. Stein (1987) proposed a new method for incorporating dependencies among the input variables, so that each sample vector has approximately the correct joint distribution (if sample sizes are large). His method is as follows. Assume that the joint distribution of the random vector $\mathbf{X}$ of the K input

variables is given by F; F_k is the cumulative distribution function of $\mathbf{X}_k$ and $\mathbf{X}_{jk}$ is the kth component of the jth vector. Assume that it is possible to produce N iid vectors of these input variables, $\mathbf{Y}_1, \ldots, \mathbf{Y}_N$, with each $\mathbf{Y}_i$ having the correct joint distribution F. Form an $N * K$ matrix with these vectors, each $\mathbf{Y}_i$ is a row in this matrix. Then replace (for $k = 1, \ldots, K$) each element of the kth column of this matrix by its rank in the column; assume each input parameter is continuous and hence there are no ties. Call the new matrix of ranks R and the jkth element of this matrix is referenced as r_{jk}. The LHS table is now formed by generating a new matrix, the jkth element of this matrix is defined by:

$$Z_{jk} = F_k^{-1} N^{-1} (r_{jk} + \xi_{jk} - 1)$$

where ξ_{jk} $(j = 1, \ldots, N; k = 1, \ldots, K)$ be NK iid random variables, uniformly distributed on $[0, 1]$. It should be noted that if all the input parameters are independent, then this approach will also produce the correct joint distribution. This technique uses more than the rank correlation structure to approximate the actual joint distribution, however as Stein (1987) discusses the approach may suffer from two disadvantages: (1) if the analytical solution of F_k^{-1} (the inverse cumulative distribution fucntion of $\mathbf{Y}_k$) cannot be obtained, then F_k^{-1} has to be simulated, this simulation process may require an extremely large number of computer runs. (2) If N is too small then this sampling process may not reflect adequately the actual joint distribution. See Stein (1987) for a further discussion of this method.

The LHS table that was generated for the HIV model was a $100 * 26$ matrix (100 simulations $*$ 19 parameters plus seven pdfs for the state variables at time zero—see Section 3.1); the coefficients in the matrix were the sampling indices for the pdfs of the twenty six pdfs.

3.5 Sample the values of the input parameters & perform the N simulations

The LHS table was used to generate a 100 by 30 (100 simulations $*$ twenty parameters plus ten state variables at time zero) input matrix. The sampling indices in the LHS table were replaced by the values of the parameters and the state variables by using the pdfs shown in Table 2; the sampling constraints ($\beta_{db} > \beta_{dn}$ and $q_2 > q_1$—see Section 3.1) were satisfied at this stage. The values of β_{dn} and q_1 were determined by simply replacing the sampling indices with the corresponding values from the pdfs given in Table 2. For the ith simulation (where $i = 1, \ldots, N$) the minimum possible value of β_{db}^i was set to the value of β_{dn}^i and the minimum possible value of q_2^i was set to the value of q_1^i. The values of β_{db}^i and q_2^i were then sampled using the appropriate sampling indices from the LHS table; however, the indices referred to a different pdf for each simulation run. The pdfs of the sampled values for β_{dn} and β_{db} are presented in Fig. 3. Two features of this figure should be noted. First, that although the two parameters can assume values in the range from 0 to 1, their values β_{dn}^i and β_{db}^i for each run i, satisfy the constraint $\beta_{db} > \beta_{dn}$. Second, that while the sampled values for β_{dn} are as defined in Table 2 (triangular, with a peak at 0·0), the sampled values for β_{db} do not have to resemble the pdf defined in Table 2 (triangular with a peak at β_{dn}). In practice, the shape of the pdf for β_{db} will vary according to the LHS table being used; each time β_{dn} is changed, β_{db} will also change. The sampling indices for the seven probability functions were used to sample the values of five of the state variables at time zero (see Section 3.1). The initial values of the remaining five state variables (at time zero) were then generated, they were perfectly inversely correlated to the five sampled state variables (see Section 3.1). This input matrix was then used to generate 100 runs of the HIV model; the Runga–Kutta 4th order numerical method was used in the simulations.

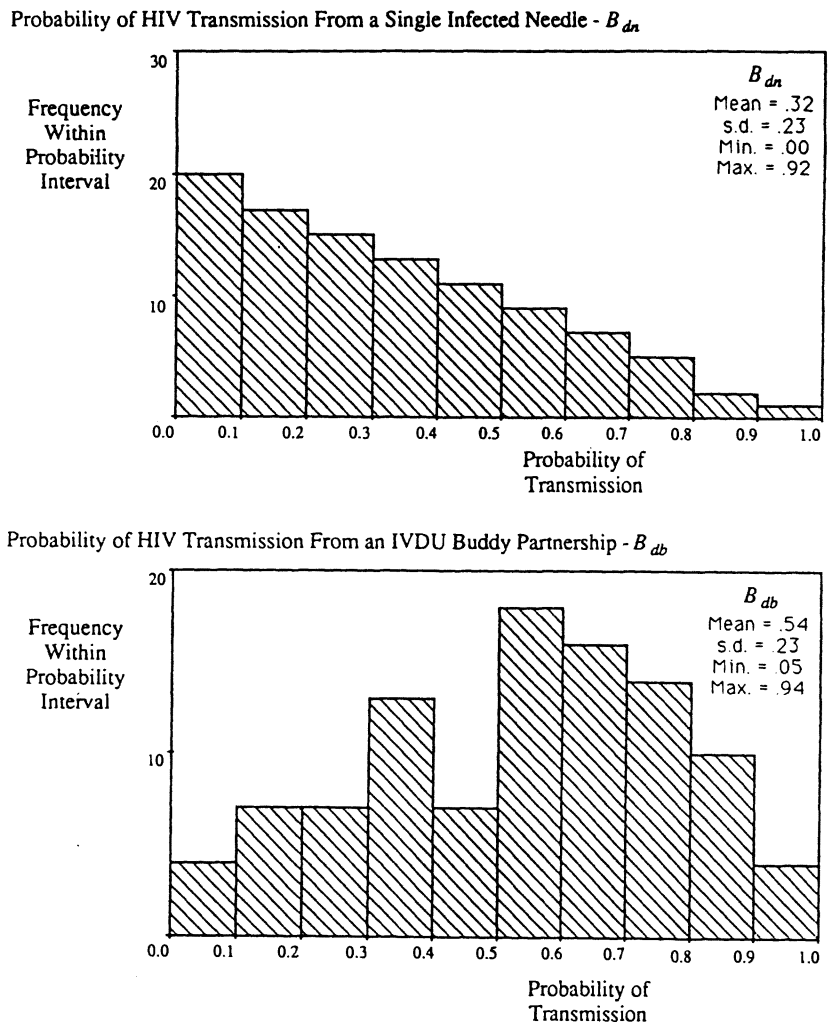

Figure 3. *Histograms of HIV IVDU transmission probabilities; the sampling constraint $\beta_{db} > \beta_{dn}$ holds (i.e., in a buddy partnership more than one needle is shared). In preparing the data for the ith run of the model, β^i_{dn} was selected from a triangular distribution, (with its minimum value and peak at zero), and β^i_{db} was selected from a triangular distribution, (with a minimum value and peak set equal to β^i_{dn}). Hence, in the two histograms shown above, β_{dn} is triangular and β_{db} is skewed to the right.*

3.6 Analysis of Model Outcomes: Uncertainty Analysis

The results of the simulation runs of the model consist of N observations of each outcome variable. Distribution functions for each of the outcome variables can be directly derived and characterized by simple descriptive statistics. Any particular run of the model is unlikely to have all the key parameters at the various extrema which would be necessary for the whole system to be at an absolute minimum or maximum value; consequently, the N observations correspond to a range of probable outcomes rather than the absolute lower and upper bounds of the system. At this stage the uncertainty analysis is complete, the variability (prediction imprecision) in the outcome variable that is due to the parameter and state variable estimation uncertainty has been determined. The results from the uncertainty analysis of the HIV model are discussed in a later section.

3.7 Analysis of Model Outcomes: Sensitivity Analysis

The N observations of each outcome variable may be used to assess the sensitivity of the outcome variables to the estimation uncertainty in the input parameters. The pdfs of the input variables for a disease transmission model are rarely normally distributed and the outcome variables are generally non-linear functions of the input variables; hence, non-parametric tests of ranked data are necessary (Conover 1980). In the LHS scheme, all of the parameters are varied simultaneously and the input parameters are often interdependent; therefore, PRCC can be used to evaluate the statistical relationships. Calculation of PRCC enables the determination of the statistical relationships between each input parameter and each outcome variable while keeping all of the other input parameters constant at their expected value (Conover, 1980). This procedure enables the independent effects of each parameter to be determined, even when the parameters are correlated. A PRCC indicates the degree of monotonicity between a specific input variable and a particular outcome variable; therefore only outcome variables that are monotonically related to the input parameters should be chosen for this analysis (Conover, 1980; Iman & Helton, 1988; Iman & Conover 1980). Monotonicity can be assessed by examining scatterplots, each input variable should be plotted against each outcome variable. The sign of the PRCC indicates the qualitative relationship between each input variable and each output variable. The magnitude of the PRCC indicates the importance of the uncertainty in estimating the value of the input variable in contributing to the imprecision in predicting the value of the outcome variable. The relative importance of the input variables can be directly evaluated by comparing the values of the PRCC. Calculation of PRCC is shown in Appendix A.

4 Results for the HIV Transmission Model

4.1 Uncertainty Analysis

The LHS uncertainty technique was used to explore the effect of the uncertainty in estimating the values of the input variables on the prediction precision of two outcome variables: the cumulative number of adult and pediatric AIDS cases at the end of thirty years. The empirical frequency distributions for these two outcome variables were directly derived from the results of the uncertainty analysis, these distributions are presented and discussed elsewhere (Blower et al., 1991). The descriptive statistics for these distributions are given in Table 3. The results indicate that the prediction precision of the model is

Table 3.
Descriptive statistics from the uncertainty analysis

	Cumulative number of aids cases in 30 years	
	Adult cases	Pediatric cases
Minimum	49,134	246
Maximum	347,420	161,615
Mean	238,571	37,330
Median	257,085	22,663
Variance	$4{\cdot}7 * 10^9$	$1{\cdot}2 * 10^9$
5th percentile	116,422	1,780
95th percentile	333,932	108,173

fairly low, due to the high degree of estimation uncertainty for the initial values of the input variables. This technique enables the degree of prediction imprecision to be quantified, and used as a basis for comparing the expected results (i.e., the models' predictions) with the observed results. The predictions of the HIV model have been compared with the cumulative number of adult and pediatric AIDS cases that have been observed in NYC (Blower et al., 1991).

4.2 Sensitivity Analysis

PRCC were calculated between each of the input parameters and two outcome variables: the cumulative number of adult and pediatric AIDS cases at the end of thirty years. Scatterplots (of each input parameter against each outcome variable) were generated and examined to check that the assumption of monotonicity was satisfied. These PRCC were used to identify the key input variables that contributed to the prediction imprecision; the PRCC results are presented in Table 4. It can be found from Table 4 that the uncertainties in estimating the values of three parameters (the two heterosexual transmission efficiencies and the average adult incubation period) are the most critical in affecting the prediction precision of the future number of adult AIDS cases. The estimation uncertainty of these three parameters are also critical in contributing to the prediction precision of the number of pediatric AIDS cases, however in this case the vertical transmission efficiency is also of great importance (see Table 4). The results of the sensitivity analysis can be used to focus data collection effort because the analysis identifies which parameters (due to their estimation uncertainty) are important in the prediction precision of adult AIDS cases.

The sign of the PRCC identifies the specific qualitative relationship between the input and the output variable; the qualitative relationships are the same for all of the key variables, except the average incubation periods. The positive value of the PRCC for the majority of the variables implies that when the value of the input variable increases, the future number of AIDS cases will also increase. The future number of AIDS cases decreases as the average incubation period lengthens, because even though individuals

Table 4

Partial rank correlation coefficients

Adult cases		Pediatric cases	
Parameter	PRCC	Parameter	PRCC
β_{mf} & β_{fm}	0·84***	q_1	0·77***
v_a	−0·72***	β_{mf} & β_{fm}	0·77***
β_{db}	0·35***	v_a	0·51***
$c_{fn}(0)$	0·29**	X_{4f}	0·36***
$c_{mn}(0)$	0·29**	$c_{mb}(0)$	0·36***
$c_{mb}(0)$	0·25*	s_a	0·35***
$c_{ms}(0)$	0·23*	v_b	−0·30**
i_m	0·22*	$c_{ms}(0)$	0·28**
$c_{fs}(0)$	0·21*	$X_{3f}(0)$	0·20*
β_{dn}	0·20*		

The PRCCs are between the input values of the biological-behavioural transmission parameters and the output values (the cumulative number of adult and pediatric AIDS cases in 30 years). The results are significant at the 0·05 level (*), the 0·01 level (**) or the 0·001 level (***).

remain infectious for a longer period and consequently can infect more individuals, the rate of progression to disease decreases. The epidemiological implications of these PRCC results are discussed in detail elsewhere (Blower et al., 1991).

5 Discussion

The uncertainty analysis described in this paper is based upon the assumption that the input parameters are statistically independent, hence the LHS scheme uses marginal distributions. However, if some of the input parameters are statistically dependent and consequently certain combinations of parameters are actually more likely to occur than others, then it is necessary to sample from the appropriate joint distribution function (as described in Section 3.4). If the parameters are statistically dependent and marginal distributions are used then the output from the uncertainty analysis will not reflect adequately the prediction imprecision of the model. Therefore, before an uncertainty analysis is undertaken it should be checked that the assumptions of statistical independence of the input parameters are satisfied by analyzing the available data, or else it should be clearly stated that the model is being used as a thought experiment (sensu Blower & Medley 1991) to assess the independent effects of each input parameter. Furthermore, several independent Latin Hypercube samples could be obtained and analyzed. Replicated sampling will have two benefits: (i) replicates will contain different combinations of parameter values, consequently any effects that are due to unlikely combination of parameter values will be diluted, and (ii) the outputs from the replicates can be used to obtain standard errors for the outcome variables of interest (Iman & Conover 1980).

The sensitivity analysis described in this paper uses the magnitude of the PRCC to indicate the importance of the uncertainty in estimating the value of the specific input variable in contributing to the prediction imprecision of the outcome variable. As discussed in Section 3.7 a PRCC indicates the degree of monotonicity between the specific input variable and the particular outcome variable. The monotonicity assumptions were satisfied in the analysis of the NYC HIV model; HIV transmission models tend to be fairly stable and do not show chaotic behavior (Bob May, personal communication). However, some other disease transmission models (for example, certain measles models) may exhibit chaotic behavior over certain regions of the parameter space. Consequently, before initiating a sensitivity analysis, it is necessary to conduct preliminary investigations of the behavior of the model; scatterplots of input variables against outcome variables can be used to detect discontinuities (Iman & Helton 1988). If the monotonicity assumptions are not satisfied, then calculation of PRCC is inappropriate. It is possible that certain input parameters may be non-monotonically related to the outcome variable and consequently have a low PRCC, but may produce sizeable changes in the outcome variable; therefore, any input parameters that are non-monotonically related to the outcome variables should be discussed along with the results of the PRCC. In interpreting the results of any sensitivity analysis it should be stressed that the PRCC results are derived from a specific model structure and that similar results may not be obtained from other models.

For some models the pdfs of certain of the input parameters may be unknown, and in these cases it is important to explore distributional effects (i.e., the effect of the pdfs of the input parameters on the values of the outcome variables) (Iman & Conover 1980; Iman, Helton & Campbell 1981a). Multiple uncertainty and sensitivity analyses could be completed, each analysis could include a different set of pdfs. The results of these multiple uncertainty and sensitivity analyses could then be compared to assess the distributional

effects. Iman & Conover (1980) have also developed a weighting scheme for investigating distribution effects without the need for additional computer simulations.

The techniques used in this paper can be extended and coupled with stepwise or rank regression in order to determine how much of the variation in the outcome variables is due to each of the key input variables, that were identified by their PRCC (Iman, Helton & Campbell 1981b). Therefore, the LHS/PRCC sensitivity analysis can be used as an initial step in the construction of response surfaces; the key input variables can be used as the best subset of predictor variables to determine the relationship between the independent and dependent variables (Iman, Helton & Campbell 1981b). The LHS scheme is also an extremely efficient sampling design for investigating response surfaces in stochastic models (see Seaholm et al. 1988 and Seaholm 1988a and 1988b for a discussion of LHS and Monte Carlo models).

The LHS/PRCC sensitivity analysis can be used for exploring models where the outcome variables are time-dependent functions of the input variables (Iman, Helton & Campbell 1981a; Iman & Helton 1988). To carry out such an analysis, the uncertainty and sensitivity analysis could be performed at a series of time steps, rather than only at one point. The results would illustrate (i) how prediction precision decreases with time and (ii) the effect of time on both the values of the PRCC and their relative rankings.

In this paper, we have described and applied techniques that were developed for risk assessment models. We have illustrated the utility of these techniques for epidemiologists and population biologists by analyzing a complex HIV transmission model. We have also discussed how these techniques may be used in a variety of ways to investigate further the effects of parameter and model uncertainty in other complex models. We suggest that the application of these techniques may have considerable utility in the analysis of a wide variety of other complex biological and epidemiological models.

Acknowledgements

We thank Gerald Friedland, Bob Klein, Diana Hartel, Ellie Schoenbaum, Peter Selwyn at the Montefiore Medical Center in the Bronx for data and many helpful discussions on sexual and drug use behavior. I especially thank Roy Anderson, Henry Brady, Jake Freimer, Ed Kaplan, Bob May, Angela McLean, Jim Wiley and two anonymous reviewers for many useful comments and criticisms on earlier drafts of this manuscript. SMB acknowledges gratefully the financial support of the UK Medical Research Council and Zena Stein for computing resources. HD acknowledges gratefully the financial support of the Rockefeller Foundation and Resources for the Future. We especially thank Nelson Freimer for his superb typing and many helpful comments.

Appendix A

PRCC are determined for each input variable and each outcome variable in the following manner. We describe the technique for one outcome variable. First, the outcome vector is added as an additional column in column number $K+1$ to the matrix of input values. The ordinal numbers representing the rank (1 to N) of each of these columns are defined as the set $(r_{1i}, r_{2i}, \ldots, r_{ki}, R_i)$, where i = run number. The average rank $\mu = (1+N)/2$. If two of the input parameters have exactly the same ranking for every run, then only one of the parameters should be used in the calculation of PRCC. A $K+1$ by $K+1$ symmetric matrix (C) may now be defined, with elements c_{ij}.

$$c_{ij} = \frac{\sum_{t=1}^{N} (r_{it} - \mu)(r_{jt} - \mu)}{\sqrt{\sum_{t=1}^{N} (r_{it} - \mu)^2 \sum_{s=1}^{N} (r_{js} - \mu)^2}} \quad i, j = 1, 2, \ldots, K.$$

For the $c_{i,k+1}$ elements R_i replaces r_{jt} and r_{js}. The leading diagonal elements of C are all ones. The matrix B is defined as the inverse of C.

$$B = [b_{ij}] = C^{-1}$$

The PRCC (γ_{iy}) between the ith input parameter and the yth outcome variable is defined as (Kendall & Stewart, 1979):

$$\gamma_{iy} = \frac{-b_{i,K+1}}{\sqrt{b_{ii}b_{K+1,K+1}}}.$$

The significance of a nonzero value of γ_{iy} is tested by computing t_{iy}. The distribution of this variable approximates a Student's T with $N-2$ degrees of freedom:

$$t_{iy} = \gamma_{iy}\sqrt{\frac{N-2}{1-\gamma_{iy}}}.$$

PRCC are then calculated for the second outcome variable.

References

Anderson, R.M., Gupta, S. & May, R.M. (1991). Potential of community-wide chemotherapy or immunotherapy to control the spread of HIV-1. *Nature Lond.* **350,** 356–359.

Anderson, R.M., May, R.M. & McLean, A.R. (1988). Possible demographic consequences of AIDS in developing countries. *Nature* **332,** 228–34.

Blower, S.M. (1991). Behavior changes & stabilization of seroprevalence levels, correlation or causation? *JAIDS* **4,** 920–923.

Blower, S.M., Hartel, D., Dowlatabadi, H., Anderson, R.M. & May, R.M. (1991). Sex, drugs & HIV: a mathematical model for New York City. *Phil. Trans. R. Soc. Lond.* (Series B) **331,** 171–187.

Blower, S.M. & Medley, G.F. (1992). Epidemiology, HIV & drugs: mathematical models & data. *British Journal of Addiction* **87,** 31–39.

Conover, W.J. (1980). *Practical Nonparametric statistics,* 2nd ed., John Wiley & Sons Inc., New York, NY.

Dietz, K. & Hadeler, K.P. (1988). Epidemiological models for sexually transmitted diseases. *Journal of Mathematical Biology* **26,** 1–25.

Handcock, M.S. (1989). *Latin Hypercube Sampling to improve the efficiency of Monte Carlo Simulations: Theory and Implementation in ASTAP,* IBM Research Division, TJ Watson Research Center, RC 14546.

Iman, R.L. & Conover, W.J. (1980). Small sample sensitivity analysis techniques for computer models, with an application to risk assessment. *Commun. Statist.-Theor. Meth.* **A9**(17), 1749–1874.

Iman, R.L. & Conover, W.J. (1982). A distribution-free approach to inducing rank correlation among input variables. *Commun. Statist.-Simula. Computa.* **11,** 311–334.

Iman, R.L. & Davenport, J.M. (1982). Rank correlation plots for use with correlated input variables. *Commun. Statist.-Simula. Computa.* **11,** 335–360.

Iman, R.L. & Helton, J.C. (1985). *A comparison of uncertainty and sensitivity analysis techniques for computer models.* Sandia National Laboratories. NUREG/CR-3904 SANDA84-1461.

Iman, R.L. & Helton, J.C. (1988). An investigation of uncertainty and sensitivity analysis techniques for computer models. *Risk Analysis* **8,** 71–90.

Iman, R.L., Helton, J.C. & Campbell, J.E. (1981a). An approach to sensitivity analysis of computer models: Part I—Introduction, input variable selection and preliminary variable assessment. *Journal of Quality Technology* **13,** 174–183.

Iman, R.L., Helton, J.C. & Campbell, J.E. (1981b). An approach to sensitivity analysis of computer models: Part II—Ranking of input variables, response surface validation, distribution effect and technique synopsis. *Journal of Quality Technology* **13,** 232–240.

Iman, R.L. & Shortencarier, M.J. (1984). *A Fortran 77 program & users guide for the generation of Latin Hypercubes & random samples for use with computer models.* NUREG/CR-3624, SAND83-365. Sandia National Laboratories, Albuquerque, NM.

Jacquez, J.A., Simon, C.P., Koopman, J., Sattenspiel, L., & Perry, T. (1988). Modelling and analysing HIV transmission: the effect of contact patterns. *Mathematical Biosciences,* **92,** 119–199.

Kendall, M. & Stewart, A. (1979). *The Advanced Theory of Statistics. Volume II.* Hafner Publishing Company, New York.

Koopman, J., Simon, C. & Jacquez, J. et al. (1988). Sexual partner selectiveness effects on homosexual HIV transmission dynamics. *JAIDS* **1,** 486–504.

Le Pont, F. & Blower, S. M. (1991). The supply & demand dynamics of sexual behavior: implications for a heterosexual HIV epidemic. *JAIDS* **4,** 987–999.

May, R.M., Anderson, R.M. & Blower, S.M. (1989). The epidemiology and transmission dynamics of HIV/AIDS. *Daedalus* **118(2),** 163–201.

McKay, M.D., Conover, W.J. & Beckman, R.J. (1979). A comparison of three methods for selecting values of input variables in the analysis of output from a computer code. *Technometrics* **21,** 239–245.

Seaholm, S. (1988a). Latin Hypercube Sampling and the sensitivity analysis of a Monte Carlo epidemic model. *International Journal of Biomedical Computing* **23,** 97–112.

Seaholm, S. (1988b). Software systems to control sensitivity studies of Monte Carlo simulation models. *Computers & Biomedical Research* **21,** 531–550.

Seaholm, S., Yang, J.J. & Ackerman, E. (1988). Order of response surfaces for representation of a Monte Carlo epidemic model. *International Journal of Biomedical Computing* **23,** 113–123.

Stein, M. (1985). *The use of LHS for variance reduction in simulations with many random parameters.* IBM Report RC11166 (#50265) 52385, mathematics, 46 pages.

Stein, M. (1987). Large sample properties of simulations using Latin Hypercube Sampling. *Technometrics* **29,** 143–151.

Résumé

Les modèles d'étude de la diffusion du VIH sont devenus très complexes. Cette complexité étant associée à une forte incertitude dans l'estimation des valeurs des paramètres d'entrée, le comportement de certains de ces modèles ne peut être appréhendé que par des analyses d'incertitude et de sensibilité. L'analyse d'incertitude peut être utilisée pour établir la variabilité (imprécision de la prédiction) de la variable de sortie qui provient de l'incertitude de l'estimation des paramètres d'entrée. Une analyse de sensibilité peut compléter celle d'incertitude en identifiant les paramètres qui ont une influence maximale sur l'imprécision de la prévision (i.e., étude de l'impact des modifications des valeurs des paramètres d'entrée sur la valeur de la variable de sortie). Dans cet article, des analyses d'incertitude et de sensibilité sont décrites et leurs applications sont présentées; les deux analyses s'appuient sur la méthode d'Echantillonnage des Carrés Latins (ECL) qui est un protocole d'échantillonnage extrêmement efficace proposé par McKay, Conover & Beckman (1979). Les méthodes présentées dans ce papier n'ont jamais été appliquées aux modèles déterministes de la dynamique de la diffusion d'une maladie, même si ces modèles ont de nombreuses caractéristiques en commun avec les modèles d'estimation du risque pour lesquelles ces stratégies ont été développées. L'intérêt des analyses d'incertitude par le ECL et de la sensibilité par le ECL/CPR (Echantillonnage des Carrés Latins/Corrélation Partielle de Rang) est mise en évidence par l'analyse d'un modèle déterministe complexe de transmission du VIH.

Mot clefs: Analyse d'incertitude, Analyse de sensibilité, Protocole d'échantillonnage, Modèles mathématiques, Epidémiologie.

[*Received March* 1992, *accepted February* 1993]