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"A Probabilistic Model of Mixing and Pair Formation with Applications to Epidemiology"

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A Probabilistic Model of Mixing and Pair Formation with Applications to Epidemiology

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ABSTRACT

The increases in sexually-transmitted disease incidence rates such as those for gonorrhea, the continued growth of HIV/AIDS, and the lack of effective vaccines in the near future, have increased our need to better understand the processes associated with disease transmission. The bulk of the mathematical research in the study of STD dynamics has made use of deterministic models. The close scrutiny of the assumptions associated with the development of classical deterministic epidemiological models has led various investigators to their reformulation. The effects of social dynamics through the processes of pair-formation and dissolution have now been incorporated. New deterministic models that explicitly incorporate pairs of individuals and follow their dynamics are the object of intensive research investigations. In this paper we formulate a probability evolution model that incorporates pair dynamics using the mixing/pair-formation formalism of Busenberg and Castillo-Chavez (1989, 1991) and Castillo-Chavez and Busenberg (1992). We incorporate this formalism in combination with the modeling approach used in interacting particle systems (which has great generality and flexibility) to the study of stochastic epidemics. Our work is preliminary, as the main objective of this article is to formulate the stochastic analogs of pair-formation deterministic models. By exploiting the additive (rather than the multiplicative) version of Busenberg and Castillo-Chavez' representation theorem for pair-formation solutions, we introduce new forms of frequency-dependent mixing/pair-formation, in which partners are allowed to incorporate their preferences. Analytical results for stochastic models are usually very difficult to obtain. Fortunately, we now have access to fast, powerful and flexible computing facilities. Large scale simulations are conducted using the Cornell Theory Center's supercomputer with the purpose of illustrating the flexibility and simplicity of our approach.

KEYWORDS : stochastic processes, epidemics, pair-formation, STD's, Monte Carlo simulations, interacting particle systems, HIV/AIDS, social networks.

1. INTRODUCTION

The most recent mathematical studies of the transmission dynamics of sexually-transmitted diseases (STD's) have put emphasis on pairs of individuals. Non-infected pairs provide temporary periods of immunity, as STD's cannot be transmitted between non-infected individuals. The effects of temporary periods of immunity in disease dynamics may be substantial and, consequently, they need to be evaluated. Due to ethical and economical reasons, mathematical models play an important role in this process. The uncertainties associated with STD dynamics including partnership selection, degree of sexual-activity, type of sexual activity, etc. may be at least partially stochastic in nature. Furthermore, the necessity of precise estimates demand the development of methods for measuring the variability in our estimates. These estimates are possible with the use of stochastic models. Unfortunately, at present we do not have a stochastic formalism that allows for the simultaneous incorporation of heterogeneous mixing and pair-dynamics. In Section 2, we introduce the additive version of the mixing formalism of Busenberg and Castillo-Chavez (1989, 1991) and Busenberg and Castillo-Chavez (1992), which encompasses all mixing solutions. In addition, we provide an alternative systematic approach for the generation of a large class of frequency-dependent solutions. In Section 3, we briefly introduce our probabilistic models: an stochastic Markov process. We provide a specific formulation of the general epidemic stochastic model with pairing developed for the study of STD-dynamics. In Section 4, possible connections between stochastic and deterministic frameworks are highlighted. Because the structure of the transition probabilities in the model are very complicated, it is hopeless to get analytical results for this model and hence, in Section 5, we conduct simulations using Cornell's Theory Center Supercomputer to illustrate the possible applications of the general stochastic epidemiological model with pairing. Because we do not want to burden the reader with complex theoretical mathematical results, we provide in the Appendix, a summary of the mathematical results needed to justify the abstract formulation of the model used in this manuscript.

2. Mixing and Preference Matrices

Sir Ronald Ross developed the first model for the dynamics of vector-transmitted diseases to study problems associated with the control of malaria. Ross understood the effects potential mixing effects on disease dynamics due to heterogenous mixing between individuals belonging to subpopulations with variable population size. He was also aware that modeling approaches used in the study of the dynamics of vector-transmitted diseases were applicable — —that is, mathematically equivalent — —to those needed to study the transmission dynamics of STD's. Despite the importance of Ross' work, most mathematical models for STD's ignored the role of variable population size and, consequently, they also ignored frequency-dependent mixing.

Practical and theoretical questions relevant to the transmission dynamics of HIV/AIDS have placed the study of heterogeneous mixing at the forefront of research (see Castillo-Chavez, 1989; Gabriel *et al.* 1990). The recent work on the effects of the processes of pair-formation and dissolution on the dynamics of STD's by Dietz (1988), Dietz and Hadeler (1988), Busenberg and Castillo-Chavez (1989, 1991), Castillo-Chavez and Busenberg (1992), Castillo-Chavez *et al.* (1991, 1992) and Blythe *et al.* (1991) has raised important questions as to the appropriateness of classical epidemic models for the study of the effects of heterogeneous mixing in disease dynamics. In this section, we use Castillo-Chavez and Busenberg's idea (1992) of perturbing Ross solutions to construct a large class/description of mixing/pair-formation frequency dependent matrices. However, the perturbations stressed in this article (as opposed as those previously highlighted by Castillo-Chavez and Busenberg, 1992) are additive rather than multiplicative. We note that our formalism does not depend on either choice. However, we have now been able to use additive perturbations to generate a rather large and interesting class of solutions which we introduce later in this manuscript. We begin with the definition of a mixing matrix:

Def Let the letters m and f to denote the parameters associated with single males and single females and let b_i^m and b_i^f denote the rates of pair-formation. The matrix $(p_{ij}(t), q_{ji}(t))$ is called a mixing/pair-formation matrix if it satisfies the following properties at all times:

(A1) $0 \leq p_{ij} \leq 1, 0 \leq q_{ji} \leq 1;$

(A2) $\sum_{j=1}^{N} p_{ij} = 1 = \sum_{i=1}^{L} q_{ji};$

(A3) $b_i^m T_i^m p_{ij} = b_j^f T_j^f q_{ji}, \; i = 1, \cdots, L, \; j = 1, \cdots, N;$

(A4) If $b_i^m b_j^f T_i^m T_j^f = 0$ for some i and/or j, then $p_{ij} = q_{ji} = 0$.

Ross solutions are the only separable solutions, that is, they are the only solutions of the form $\bar{p}_i \bar{p}_j$ and $\bar{q}_k \bar{q}_l$. In fact, these solutions can be computed explicitly. They are of the form $p_{ij} = \bar{p}_j$ and $q_{ji} = \bar{q}_i$ where

$$\bar{p}_j = \frac{b_j^f T_j^f}{\sum_{i=1}^{L} b_i^m T_i^m}, \; \bar{q}_i = \frac{b_i^m T_i^m}{\sum_{j=1}^{N} b_j^f T_j^f}; \; j = 1, \cdots, N \text{ and } i = 1, \cdots, L. \tag{1}$$

In Busenberg and Castillo-Chavez (1989, 1991), the concepts of frequency-dependent and frequency-independent preference are introduced through the "preferential" budgeting of pair-formation rates (see Blythe *et al.* 1991). In this paper we introduce an alternative concept of frequency-dependent preference that is directly constructed from Ross solutions. Here is an alternative definition of a preference matrix:

Def Given the Ross solution $\bar{p}_j$, $1 \leq j \leq N$ and $\bar{q}_i$, $1 \leq i \leq L$, associated with $L \times N$ interacting populations, we let the $L \times N$ matrix $A = (\alpha_{ij})$ denote a preference matrix iff

(i) $\sum_{j=1}^{N} \alpha_{ij}\bar{p}_j = 0$, $1 \leq i \leq L$,

(ii) $\sum_{i=1}^{L} \alpha_{ij}\bar{q}_i = 0$, $1 \leq j \leq N$,

(iii) $\alpha_{ij} \geq -1$, $1 \leq i \leq L$, $1 \leq j \leq N$.

If we let $\Pi = \{(\bar{p}_j\bar{q}_i) : i = 1, 2,...,L; j = 1,2,...N\}$ denote the set of all preference matrices, we can establish the following results:

Lemma 1. Π is a nonempty convex set.

Proof: The zero matrix, i.e., $\alpha_{ij} = 0$, $\forall$ i, j $\in \Pi$. Convexity is proved as follows: let A_i, i = 1, 2 $\in \Pi$ and let $\lambda_i \geq 0$, i = 1, 2 be such that $\lambda_1 + \lambda_2 = 1$. A simple computation shows that the convex linear combinations $\lambda_1 A_1 + \lambda_2 A_2 \in \Pi$, that is, they satisfy (i), (ii) and (iii).

Lemma 2. Let $A = (\alpha_{ij})$ denote the preference matrix associated with the Ross solution $\bar{p}_j$, $1 \leq j \leq N$ and $\bar{q}_i$, $1 \leq i \leq L$. Define a matrix as follows:

$$p_{ij} \equiv (1 + \alpha_{ij})\bar{p}_j \quad \text{and} \quad q_{ji} \equiv (1 + \alpha_{ij})\bar{q}_j \tag{2}$$

for $1 \leq i \leq L$, $1 \leq j \leq N$, then, (p_{ij}, q_{ji}) is a mixing/pair-formation matrix.

Proof: Since $\sum_j \bar{p}_j = 1$ and $\sum_j \alpha_{ij}\bar{p}_j = 0$ then $\sum_j p_{ij} = 1$ for all i's and similarly $\sum_i q_{ji} = 1$ for all j's. Because $\alpha \geq -1$ then all p_{ij} and q_{ji} are positive and (A1) and (A2) are satisfied. Using the fact that Ross solutions satisfy (A3) and (A4) then one easily shows that the the elements of this mixing matrix $\{(p_{ij},q_{ji})\}$ also satisfy these mixing axioms. Therefore the matrix (p_{ij}, q_{ji}) is a mixing/pair-formation matrix.

Lemma 3. If (p_{ij}, q_{ji}) is a mixing/pair-formation matrix then it has an associated Ross solution $\bar{p}_j$, $1 \leq j \leq N$ and $\bar{q}_i$, $1 \leq i \leq L$. For any mixing/pair-formation matrix we can compute a preference matrix $A = (\alpha_{ij})$ such that (p_{ij}, q_{ji}) is given by Equation 2.

Proof: Let $I = \{i : c_i T_i^m \neq 0\}$ and $J = \{j : b_j T_j^f \neq 0\}$. For $i \in I$ and $j \in J$, $c_i T_i^m \bar{p}_j = b_j T_j^f \bar{q}_i > 0$ from the definition of a Ross solution. Thus the ratios

$$\frac{p_{ij}}{\bar{p}_j} = \frac{q_{ji}}{\bar{q}_i}$$

are strictly positive. If we denote them by $1 + \alpha_{ij}$, then

$$p_{ij} = (1 + \alpha_{ij})\bar{p}_j \text{ and } q_{ji} = (1 + \alpha_{ij})\bar{q}_i$$

for $i \in I$ and $j \in J$. If for some i and j, where either $i \in I$ or $j \in J$, we have that $p_{ij} = q_{ji} = \bar{p}_j = \bar{q}_i = 0$ then we let $\alpha_{ij} \equiv 0$. Thus, formula (2) holds for all i and j. Furthermore, one can easily verify that $A = (\alpha_{ij})$ is a preference matrix.

Lemmas 2 and 3 imply that mixing/pair-formation matrices are determined by their associated preference matrix set. Ross solutions are independent of the activity of their own subgroups (separable solutions) and, consequently, their corresponding preference matrix is $A \equiv 0$ (the zero matrix). There is no preference in this case. If the term $\alpha_{ij} > 0$ in the preference matrix $A = (\alpha_{ij})$, then we have that $p_{ij} > \bar{p}_j$ and $q_{ji} > \bar{q}_i$. We say in this case that i and j prefer each other. If $\alpha_{ij} > 0$ then from the definition of preference matrix, we know that there is an i′ such that $\alpha_{i'j} < 0$. Consequently, $p_{i'j} < \bar{p}_j$

and $q_{ji'} < \bar{q}_{i'}$ and we say that individuals from groups i prefer j more than i′ (or that i′ and j do not prefer each other–they actually try to avoid each other). The definition of preference matrix and Lemma 1 make the structure of Π clear but there are obviously many ways in which one can choose a preference matrix A. Here we present a simple yet general way of selecting frequency-dependent preference matrices:

We begin with a Ross solution $\bar{p}_j$, $1 \leq j \leq N$ and $\bar{q}_i$, $1 \leq i \leq L$ and define the following quantities:

$$\hat{p}_j \equiv \bar{p}_1 \cdots \bar{p}_{j-1}\bar{p}_{j+1} \cdots \bar{p}_N \text{ and } \hat{q}_i \equiv \bar{q}_1 \cdots \bar{q}_{i-1}\bar{q}_{i+1} \cdots \bar{q}_L, \tag{3}$$

and let s^i, t_j be real numbers such that $-1 \leq s^i t_j \hat{q}_i \hat{p}_j$ and $\sum_i s^i = \sum_j t_j = 0$. For a given Ross solution, the elements of the preference matrix A are defined by

$$\alpha_{ij} = s^i t_j \hat{q}_i \hat{p}_j, \ \forall \text{ i, j} \tag{4}$$

Note that by definition α_{ij}(the elements of A) ≥ -1 and that individuals from group i and j prefer each other if and only if $s^i t_j > 0$.

3. Probabilistic Models

Classical deterministic models for the sexual spread of STD's such as gonorrhea among heterosexual populations can be found in Hethcote and Yorke (1984) while classical and pair-formation models under a unified mixing framework for the spread of STD's can be found in Blythe *et al.* (1991) and references therein. A stochastic version of one of the deterministic models found in Blythe *et al.* (1991) is provided below. This formulation uses the modeling approach common to interacting particle systems. Hence, it has great generality and flexibility.

General Notation

Let $X = \{0, 1, \cdots, L\} \times \{0, 1\} \times \{0, 1, \cdots, N\} \times \{0, 1\} \backslash \{0\} \times \{0, 1\} \times \{0\} \times \{0, 1\}$ and consider the stochastic process $\xi_t : X \to \{0, 1, 2, \cdots\}$, $t \geq 0$. For $x = (i, \mu; j, \nu) \in X$, our interpretation of this process is as follows:

(1) The labels μ and ν represent the eepidemiological status of the individuals. Specifically, $0 \equiv$ susceptible and $1 \equiv$ infected. The labels i and j represent labels for the groups of males and females.

(2) For $i > 0$ and $j > 0$, $\xi_t(i, \mu; j, \nu)$ gives the number of pairs where the male is of the i-th type and has epidemiological status μ and the female is of the j-th type and has status ν at time t;

(3) Singles are labeled by triplets. However, to keep the domain fixed we use four coordinates and set either i or j equal to zero. Specifically, if $i > 0$ and $j = 0$, then $\xi_t(i, \mu; 0) \equiv \xi_t(i, \mu; 0, 0) \equiv \xi_t(i, \mu; 0, 1)$ denotes the number of single males with status μ in the i-th subpopulation at time t. Similarly, if $i = 0$ and $j > 0$, then $\xi_t(0; j, \nu) \equiv \xi_t(0, 0; j, \nu) \equiv \xi_t(0, 1; j, \nu)$ denotes the number of single females with status ν in the j-th subpopulation at time t.

Let $S \equiv \{0, 1, 2, \cdots\}^X$ and let $c : S \times S \to (0, \infty)$ be a real-valued function--the flip rate--to be specified later. We view $\{\xi_t : t \geq 0\}$ as a S-valued Markov process with flip rate $c(.,.)$, i.e., if $\xi_t = \xi$ for some $t \geq 0$ then $c(\xi, \eta)$ denotes the instantaneous rate at which ξ_t may change to the state η. The generator of this process is

$$\Omega f(\xi) = \sum_{\eta} c(\xi, \eta)(f(\eta) - f(\xi)), \tag{5}$$

where f is a continuous function on S. Thus,

$$\frac{d}{dt} Ef(\xi_t) = E \sum_{\eta} c(\xi, \eta)(f(\eta) - f(\xi_t)). \tag{6}$$

Model Specification

In this section, we follow the notation used in Blythe *et al.* (1991) for the specification of analog deterministic models for gonorrhea transmission, consequently, there is recovery from the disease. Transmission may occurred only while paired with an infected partner. $T_i^m(\xi)$ denotes the number of single uninfected males (time is omitted from ξ) of type i (at time t) that is, $T_i^m(\xi) = \xi(i, 0; 0) + \xi(i, 1; 0)$. Similarly, $T_j^f(\xi)$ denotes the number of single uninfected females of type j at time t that is, $T_j^f(\xi) = \xi(0; j, 0) + \xi(0; j, 1)$. Axiom (A3) implies that the pair formation rates $\{b_i^m(\xi), b_j^f(\xi): i, j\}$ must satisfy the following relationship (that is, they are conserved) which is obtained by summing both sides of (A3) over both indices:

$$\sum_{i=1}^{L} b_i^m(\xi), T_i^m = \sum_{j=1}^{N} b_j^f(\xi), T_j^f \ . \tag{7}$$

We further assume the existence of an underlying mixing/pair-formation matrix $(p_{ij}(\xi), q_{ij}(\xi))$ of the type described in Section 2. To specify the flip rates we use the following notation. For $\xi \in S$, $A \subset X$, $B \subset X$ and $A \cap B = 0$, we define $\xi_B^A \in S$ as

$$\xi_B^A(x) = \begin{cases} \xi(x) + 1 & \text{if } x \in A \\ \xi(x) - 1 & \text{if } x \in B \ . \\ \xi(x) & \text{otherwise} \end{cases}$$

If we change the notation slightly and now use the letters m and f to denote the parameters associated with uninfected males and females and M and F to denote those associated with infected males and females then one defines the flip rate c(., .) as follows (here γ, δ, and σ are constant parameters):

(a) Pair-formation

For $i > 0, j > 0$,

$$c(\xi, \xi_{(i,\mu;0),(0;j,\nu)}^{(i,\mu;j,\nu)}) = b_j^f(\xi)\xi(0;j,\nu)p_{ji}^f(\xi)\frac{\xi(i,\mu;0)}{\xi(i,\mu;0) + \xi(i,1-\mu;0)} \ .$$

(b) Pair-dissolution (σ denotes the pair-dissolution rate)

For $i > 0, j > 0$,

$$c(\xi,\ \xi^{(i,\mu;0),(0;j,\nu)}_{(i,\mu;j,\nu)}) = \sigma_{\nu\mu}\xi(i,\ \mu;\ j,\ \nu).$$

(c) Transmission (δ denotes the transmission coefficient–transmission may occur only while paired)

For $i > 0, j > 0$,

$$c(\xi,\ \xi^{(i,1;j,1)}_{(i,0;j,1)}) = \delta_F\xi(i,\ 0;\ j,\ 1),\ c(\xi,\ \xi^{(i,1;j,1)}_{(i,1;j,0)}) = \delta_M\xi(i,\ 1;\ j,\ 0).$$

(d) Recovery (γ denotes the recovery rate)

For $i > 0, j > 0$,

$$c(\xi,\ \xi^{(i,0;j,0)}_{(i,0;j,1)}) = \gamma_F\xi(i,\ 0;\ j,\ 1),\ c(\xi,\ \xi^{(i,0;j,0)}_{(i,1;j,0)}) = \gamma_M\xi(i,\ 1;\ j,\ 0),$$

$$c(\xi,\ \xi^{(i,1;j,0)}_{(i,1;j,1)}) = \gamma_F\xi(i,\ 1;\ j,\ 1),\ \ c(\xi,\ \xi^{(i,0;j,1)}_{(i,1;j,1)}) = \gamma_M\xi(i,\ 1;\ j,\ 1).$$

while for single infected individuals we have

$$c(\xi,\ \xi^{(i,0;0)}_{(i,1;0)}) = \gamma_M\xi(i,\ 1;\ 0),\ c(\xi,\ \xi^{(0;j,0)}_{(0;j,1)}) = \gamma_F\xi(0;\ j,\ 1);$$

furthermore, for $i > 0, j > 0$ we have the combined recovery rate

$$c(\xi,\ \xi^{(i,0;j,0)}_{(i,1;j,1)}) = \gamma_{FM}\xi(i,\ 1;\ j,\ 1).$$

(e) Removal (μ denotes the removal rate from sexual activity)

For $i > 0, j > 0, \mu, \nu$,

$$c(\xi,\ \xi^{(i,\mu;0)}_{(i,\mu;j,\nu)}) = \mu_f\xi(i,\ \mu;\ j,\ \nu),\ c(\xi,\ \xi^{(0;j,\nu)}_{(i,\mu;j,\nu)}) = \mu_m\xi(i,\ \mu;\ j,\ \nu),$$

while for the removal rate of single individuals we have that

$$c(\xi,\ \xi_{(i,\mu;0)}) = \mu_m\xi(i,\mu\ ;\ 0),\ c(\xi,\ \xi_{(0;j\nu)}) = \mu_f\xi(0;\ j,\ \nu).$$

(f) Recruitment (all "recruited individuals are susceptible)

For i > 0, j > 0,

$$c(\xi, \xi^{(i,0;0)}) = \Lambda_i^m, \ c(\xi, \xi^{(0;j,0)}) = \Lambda_j^f$$

(g) Other

For any other $\eta \neq \xi$,, we assume $c(\xi, \eta) = 0$ and $c(\xi,\xi) = -\sum_{\xi \neq \eta} c(\xi, \eta)$.

4. Comparison with deterministic approaches

From the theory of stochastic processes one knows that the specification of the flip rate c(., .) uniquely determines a Markov process. To see the relation between this stochastic system and the deterministic system in Castillo-Chavez et al. (1991), we let the function f be such that $f(\xi) = \xi(i,0;j,1)$ for some i > 0, j > 0. From the construction of the flip rate, we know

$$f(\eta) - f(\xi) = \begin{cases} 1 & \text{pair, recovery} \\ -1 & \text{disolution, removal, transmission.} \\ 0 & \text{otherwise} \end{cases} \tag{8}$$

We observe that the following type of relationship

$$E b_j^f(\xi_t)\, \xi_t(0;j,1)\, p_{ji}^f(\xi_t) \frac{\xi_t(i,0;0)}{\xi_t(i,0;0) + \xi_t(i,1;0)}$$

$$= b_j^f(\xi_t) p_{ji}^f(\xi_t) \frac{\xi_t(i,0;0)}{\xi_t(i,0;0) + \xi_t(i,1;0)} E\xi_t(0;j,1), \tag{9}$$

does not hold in general. However, it may be aproximately satisfied when the subpopulation sizes are large enough and

$$b_j^f(\xi_t) p_{ji}^f(\xi_t) \frac{\xi_t(i,0;0)}{\xi_t(i,0;0) + \xi_t(i,1;0)}$$

is nearly a constant. In this case, the deterministic system will be a good approximation for the stochastic system. By carefully arranging terms one gets from Equation (6) the following equation for the expected number of (M,f)-pairs $\pi_{ji}^{Mf}(t) = E\xi_t(i, 1; j, 0)$:

$$\frac{d}{dt}E\xi_t(i, 1; j, 0) = Eb_j^f(\xi_t)\xi_t(0; j, 1)p_{ji}^f(\xi_t)\frac{\xi_t(i,0;0)}{\xi_t(i,0;0) + \xi_t(i,1;0)} + \gamma_M E\xi_t(i, 1; j, 1)$$

$$- [\mu_f + \mu_M + \sigma_{Mf} + \delta_F + \gamma_F]E\xi_t(i, 0; j, 1). \tag{10}$$

Other equations can be written similarly. For example, the equation for $E\xi_t(i, 0; j, 1) = \pi_{ji}^{Fm}(t)$ involves the following nonlinearity

$$Eb_j^f(\xi_t)\ \xi_t(0; j, 1)\ p_{ji}^f(\xi_t)\frac{\xi_t(i,0;0)}{\xi_t(i,0;0) + \xi_t(i,1;0)}$$

and can be easily written after a few appropriate modifications.

5. Simulation of the process $\{\xi_t : t \geq 0\}$

From the construction of the flip rates we know that

$$c(\xi) = \sum_{\eta \in S} c(\xi, \eta) < \infty.$$

We let the sequence $0 = \rho_0 < \rho_1 < \rho_2 < \cdots$ denote the jump times of the process. Then $\tau_n = \rho_n - \rho_{n-1}$ has exponential distribution with rate $c(\xi_{\sigma_{n-1}})$ and we can simulate the process using the following procedure:

(i) Set the initial state ξ_0 and assume that a sequence of n jump times $0 = \sigma_0 < \sigma_1 < \cdots < \sigma_n$ and their corresponding states ξ_{σ_i}, $1 \leq i \leq n$ have been determined.

(ii) Get τ_{n+1} from exp $\{c(\xi_{\sigma_n})\}$ and let $\sigma_{n+1} = \sigma_n + \tau_n$.

(iii) Set $\xi_{\sigma_{n+1}} = \eta$ with probability $\dfrac{c(\xi_{\sigma_n}, \eta)}{c(\xi_{\sigma_n})}$.

(iv) Define $\xi_t = \xi_{\sigma_n}$ for $\sigma_n \leq t < \sigma_{n+1}$.

We have implemented several examples of the above procedure using parameters that are roughly similar to those generated by the Cornell Undergraduate Survey on Social and Sexual Patterns (CUSSP, see Castillo-Chavez *et al.* 1992). However, it is not possible for us to obtain estimates of all the parameters because we only have cross-sectional data. To obtain frequency dependent mixing rates, one needs longitudinal data. Here we present the results of some simulations using these data with the sole purpose of illustrating the above simulation procedure. We let L=5 and N=4, that is, we consider 5 groups of males and 4 of females and assume that all of them are sexually-active and hence capable of transmitting a disease such as gonorrhea. The number of single male susceptibles in each group is 106, 106, 126, 251, and 543 respectively. The number of single female susceptibles is 376, 500, 354, and 674. We begin these simulated epidemics by assuming that there are only 10 infectives, single males of type 1 (that is, in the first male group). We further assume no pairs at the begining (t=0) and proceed to specify the necessary parameters. Note however, that the selection of parameters is complicated by the fact that specific constraints must be maintained (see Equation (7) and Axiom A3).

To model heterogeneous mixing among heterosexually-active populations we need at least two groups of females and two of males . If K (number of groups of females) $\equiv N^f$ and L(number of group of males) $\equiv N^m$ are large then some of the mixing probabilities $p_{ij}{}^m(t)$ and $q_{ji}{}^f(t)$ will be small making it difficult to detect, through the use of survey methods, interactions between some groups in the population. The results of our survey (CUSSP) suggests that 4 to 6 groups of each sex represent an upper practical limit on the values of N^f and N^m. It is also hard to estimate inter-group frequency dependent pairing rates even if we had longitudinal data. We proceed to specify frequency-dependent pairing-rates using the approach that is used in the development of epidemiological models for communicable diseases (see Castillo-Chavez *et al.* 1989 and references therein), that is, we use activity levels to characterize the level of interaction between individuals of different groups. The assignment of these acitvity levels is subjective, nevertheless it has proven to be extremely useful in understanding the mechanisms behind the transmission dynamics of diseases such as rubella, measles, and influenza (see Castillo-Chavez *et al.* 1989 and references therein). Here we combine these subjective rating system with the constraint imposed in the form of Equation (7) by Axiom (A3).

We let

ϕ_{ij}^m = denote the affinity score that single male individuals of group i have for females of group j.

ϕ_{ji}^m = denote the affinity score that single female individuals of group j have for males of group j.

$$i = 1, \ldots, N^m;\ j = 1, \ldots, N^f \tag{11}$$

The process of model formulation must include the specification of the pair-formation rates in such a way that Eq (7) is satisfied for all time. This constraint can be met in a number of ways involving some or all of the elements of the sexual-activity vectors $b^m(t)$ and/or $b^f(t)$ which may depend on sub-group population sizes. We further assume that "popular" groups tend to have higher acquisition rates, that being scarce increases the rate for *individuals* in any group, and that we need to satisfy Equation (7) for all time. We define

$$n_i^m(t) = \frac{T_j^m(t)}{\sum\limits_{n=1}^{N^m} T_k^m(t)}, \qquad n_j^f(t) = \frac{T_j^f(t)}{\sum\limits_{l=1}^{N^f} T_l^f(t)} \tag{12}$$

as the fractional contributions of each group to the population of the same sex, and

$$\bar{\phi}_i^m(t) = \sum_{l=1}^{N^f} n_l^f(t)\, \phi_{li}^f, \qquad \bar{\phi}_j^f(t) = \sum_{k=1}^{N^m} n_k^m(t)\, \phi_{kj}^m \tag{13}$$

as the weighted average affinity or activity level associated with each group where the weights are given by the frequency distribution of the opposite-sex types. In Blythe *et al.* (1991) we found the following relationships between the ϕ's and Ross solutions

$$\bar{p}_j = \frac{b_j^f T_j^f}{\sum_{i=1}^{L} b_i^m T_i^m} = \frac{\bar{\phi}_j^f(t)}{\sum\limits_{l=1}^{N^f} \bar{\phi}_l^f(t)}, \tag{14}$$

$$\bar{q}_i = \frac{b_i^m T_i^m}{\sum_{j=1}^{N} b_j^f T_j^f} = \frac{\bar{\phi}_i^m(t)}{\sum\limits_{k=1}^{N^m} \bar{\phi}_k^m(t)}.\ j = 1, \cdots, N \text{ and } i = 1, \cdots, L. \tag{15}$$

If we let

$$b_i^m(t) = \frac{r}{T_i^m(t)} \frac{\bar{\phi}_i^m(t)}{\sum\limits_{k=1}^{N^m} \bar{\phi}_k^m(t)} \tag{16}$$

and

$$b_j^f(t) = \frac{r}{T_j^f(t)} \frac{\overline{\phi}_j^f(t)}{\sum_{l=1}^{N^f} \overline{\phi}_l^f(t)}, \tag{17}$$

where r denotes the encounter rate then Equation (7) is satisfied. However, the above is just a circular argument because in fact

$$r \equiv \sum_{i=1}^{N^m} b_i^m(\xi) = T_i^m = \sum_{j=1}^{N^f} b_j^f(\xi), T_j^f .$$

Here we model r by assuming the existence of constants a and b such that

$$r = a\left(\sum_{k=1}^{N^m} T_k^m(t)\right) + b\left(\sum_{\ell=1}^{N^f} T_\ell^f(t)\right).$$

This assumption allows us to go forward while maintaining the conservartion of partnerships acquistion group rates law.

We notice that if $\overline{\phi}_i^m(t)$ is large then $\overline{q}_i$ is large. Similarly, if $\overline{\phi}_j^f(t)$ is large then $\overline{p}_j$ is also large. If one thinks of the ϕ-elements, ϕ_{li}^f and ϕ_{kj}^m as activity levels then $\overline{\phi}_i^m(t)$'s and $\overline{\phi}_j^f(t)$'s become a measure of group-specific frequency dependent mixing, that is, "popular" groups tend to have higher acquisition rates . These affinities are driven by Ross solutions--a form of proportionate mixing. The modelling is analogous to that used in classical deterministic epidemiological models with age-structure (see Castillo-Chavez *et al.* 1989 and references therein). The ϕ's give a weighted random mixing effect in which more active individuals will encounter more often more active individuals.

On the other hand, the quantities

$$\hat{p}_j = \overline{p}_1 \cdots \overline{p}_{j-1} \overline{p}_{j+1} \cdots \overline{p}_N \text{ and } \hat{q}_i = \overline{q}_1 \cdots \overline{q}_{i-1} \overline{q}_{i+1} \cdots \overline{q}_L,$$

used to generate the type-preference matrix A defined by $\alpha_{ij} = s^i t_j \hat{q}_i \hat{p}_j$ where s^i, t_j are real numbers chosen so that $\alpha_{ij} \geq -1$, provide a measure of frequency-dependent group specific preference. in fact individuals from group i and j prefer each other if and only if $s^i t_j > 0$. Being scarce may decrease an individuals' pair formation rate relative to the the rate of pair-formation for *individuals* in alternative groups, however, these frequency-dependent effects can be easily altered by the proper manipulation of the products $s^i t_j$.

Our simulations are conducted following steps (i) – (iv). We use two sets of parameters (I and II) and model populations with activity levels (ϕ-values) that promote like-with-like mixing. Set I is chosen so that there is strong group preference between males of group 1 and females of group 1 (large ϕ values) and $s^I t_I$ is a product of positive numbers. Set II is chosen so that $s^I t_I$ is negative and we used reduced ϕ values (that is, individuals that like-each other less will also interact less). Specifically, the matrix ϕ is of the form

$$\begin{bmatrix} 0 & \phi^m \\ \phi^f & 0 \end{bmatrix}$$

For set I, we have the following selections:

$$\phi_I^f \equiv \begin{bmatrix} 29.5 & 0.05 & 0.01 & 0.005 & 25.0 \\ 0.0 & 5.0 & 0.0 & 0.1 & 0.01 \\ 0.1 & 0.01 & 54.3 & 9.0 & 10.01 \\ 1.0 & 0.01 & 0.01 & 5.0 & 0.1 \end{bmatrix}$$

$$\phi_I^m \equiv \begin{bmatrix} 9.0 & 0.01 & 0.05 & 0.01 \\ 0.01 & 5.0 & 0.5 & 0.4 \\ 1.0 & 0.01 & 4.0 & 0.5 \\ 0.01 & 1.0 & 0.01 & 4.0 \\ 1.0 & 1.0 & 0.0 & 1.0 \end{bmatrix}$$

$$s_I \equiv \begin{bmatrix} 0.1 \\ -1.1 \\ -0.5 \\ -0.4 \\ 1.9 \end{bmatrix} \quad \text{and} \quad t_I \equiv \begin{bmatrix} 0.3 \\ 1.0 \\ -0.4 \\ -0.3 \end{bmatrix}$$

$$\phi^f_{II} \equiv \begin{bmatrix} 0.05 & 0.05 & 0.01 & 0.005 & 25.0 \\ 0.0 & 5.0 & 0.0 & 0.1 & 0.01 \\ 0.1 & 0.01 & 54.3 & 9.0 & 10.01 \\ 1.0 & 0.01 & 0.01 & 5.0 & 0.1 \end{bmatrix}$$

$$\phi^m_{II} \equiv \begin{bmatrix} 0.06 & 0.01 & 0.05 & 0.01 \\ 0.01 & 5.0 & 0.5 & 0.4 \\ 1.0 & 0.01 & 4.0 & 0.5 \\ 0.01 & 1.0 & 0.01 & 4.0 \\ 1.0 & 1.0 & 0.0 & 1.0 \end{bmatrix}$$

$$s_{II} \equiv \begin{bmatrix} -0.1 \\ 1.1 \\ 0.5 \\ 0.4 \\ -1.9 \end{bmatrix} \quad \text{and} \quad t_{II} \equiv \begin{bmatrix} 0.3 \\ 1.0 \\ -0.4 \\ -0.3 \end{bmatrix}$$

In the parameter set I, we have larger ϕ^m_1 and larger ϕ^f_1. Thus, m_1 and f_1 are very popular or very active (proportionate mixing). In addition, $s^1 t_1 > 0$ gives $\alpha_{11} > 0$ which implies that m_1 and f_1 have strong preference for each other. In the parameter set II, we have smaller ϕ^m_1 and smaller ϕ^f_1. Thus, m_1

and f_1 are not as popular or as active (proportionate mixing) as in the first case. In addition, $s^1t_1 < 0$ gives $\alpha_{11} > 0$ which implies that m_1 and f_1 do not prefer each other. Obviously, these two different set of parameters yield different results. Figures 1 – 6 show that they are indeed significantly different.

6. Conclusions

In this manuscript, we have formulated a probability evolution model that incorporates pair dynamics using the mixing/pair-formation formalism of Busenberg and Castillo-Chavez. We incorporate this formalism in combination with the modeling approach used in interacting particle systems to the study of stochastic epidemics. Our work is preliminary, as the main objective of this article is to formulate the stochastic analogs of pair-formation deterministic models. By exploiting the additive (rather than the multiplicative) version of Busenberg and Castillo-Chavez' representation theorem for pair-formation solutions (1989, 1991), we were able to introduce new forms of frequency-dependent mixing, in which partners are allowed to incorporate their preferences in the process of pairing. We have illustrated our model dynamics using two mixing preferences. The results are as expected and attest to the reliability of the model and the value of simulations. We are currently conducting large scale simulations using the Cornell Theory Center's supercomputer to gain further understanding of the effects of pairing in the stochastic spread of epidemics.

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Appendix

In this appeandix, we explain how to construct a transition semigroup and hence a Markov process using flip rates. Let S be a countable space with its elements denote by lower case Greek letters such as. ξ, η, ζ, $\cdots$. Consider $C = (c(\xi, \eta) : \xi, \eta \in S)$ as a (possibly infinite) matrix where $c(.,.)$ is a function from $S \times S$ to R. For A and B matrices, we define the product AB in the usual way, i.e. the (ξ, η) entry is given by $\sum_{\zeta \in S} a(\xi, \zeta) b(\zeta, \eta)$.

We define the matrix e^{tC} through the following power series

$$e^{tC} = \sum_{n=0}^{\infty} \frac{t^n}{n!} C^n.$$

If we have an infinite series, we assume that this definition is conditional on all infinite series being convergent. Similar convergence properties will be needed in this section. However we do not specify them explicitely. We require some definitions:

Def 1: A matrix $\Omega = (w(\xi, \eta))$ is called a generator if

(i) $w(\xi, \eta) \geq 0, \forall \xi \neq \eta$;

(ii) $\sum_{\eta \in S} w(\xi, \eta) = 0$.

Def 2: A family of matrix $\{P^t = (p^t(\xi, \eta)) : t \geq 0\}$ is called a transition semigroup if

(i) $p^t(\xi, \eta) \geq 0$, $\sum_{\eta} p^t(\xi, \eta) = 1$, $\forall t \geq 0$, $\xi, \eta \in S$;

(ii) $P^{t+s} = P^t P^s$, $t \geq 0$, $t \geq 0$;

(iii) $P^0 = I$;

(iv) $\lim_{t \to 0} P^t = I$.

The following results are standard.

Proposition 1. Suppose $\Omega = (w(\xi, \eta))$ is a generator. Then, $P^t = e^{t\Omega}$ is well defined for all $t \geq 0$ and $\{P^t : t \geq 0\}$ is a transition semigroup.

Proposition 2. Under the condition of Proposition 1 we have

(i) $w(\xi, \eta) = \lim_{t \to 0} \dfrac{P^t(\xi, \eta) - I(\xi, \eta)}{t}$, for all $\xi, \eta \in S$;

(ii) $\dfrac{d}{dt} P^t = \Omega P^t = P^t \Omega$, $t \geq 0$.

Suppose $\{P^t : t \geq 0\}$ is a transition semigroup. We can use Kolmogorov's Theorem to construct a S-valued stochastic process $\{\xi_t : t \geq 0\}$ such that

$$P(\xi_{t_i} = \xi_i, 0 \leq i \leq n) = p^{t_1}(\xi_0, \xi_1) p^{t_2 - t_1}(\xi_1, \xi_2) p^{t_n - t_{n-1}}(\xi_{n-1}, \xi_n) \text{ and}$$

such that it is also a Markov process (see below).

Let C(S) be the space of all function from S to R. Any matrix C can be seen as an operator on C(S), i.e. $C : C(S) \to C(S)$, in the sense

$$Cf(\xi) = \sum_{\eta \in S} c(\xi, \eta)f(\eta), \ \forall \xi \in S$$

Suppose the generator Ω is given and the semigroup and the stochastic process are as in the propositions. We have

$$P^t f(\xi) = Ef(\xi_t)$$

where $\xi_0 = \xi$. Thus,

$$\frac{d}{dt}Ef(\xi_t) = \frac{d}{dt}P^t f(\xi)$$

$$= P^t \Omega f(\xi) = P^t \sum_{\eta} w(\xi,\eta)f(\eta)$$

$$= P^t \sum_{\eta} w(\xi,\eta)[f(\eta) - f(\xi)]$$

$$= E\sum_{\eta} w(\xi_t,\eta)[f(\eta) - f(\xi_t)]$$

Figure Captions:

Fig 1. In this figure there are no infectives at time t = 0. The dynamics are of pure mixing/pair formation. This figure gives the average number of partners that each male individual of group 1 has from time t=0 to t = 4 years (48 months). Note that at the 35-th month the average was about 7.7. The title "with preference" means that we used the parameter set I (see the text for details).

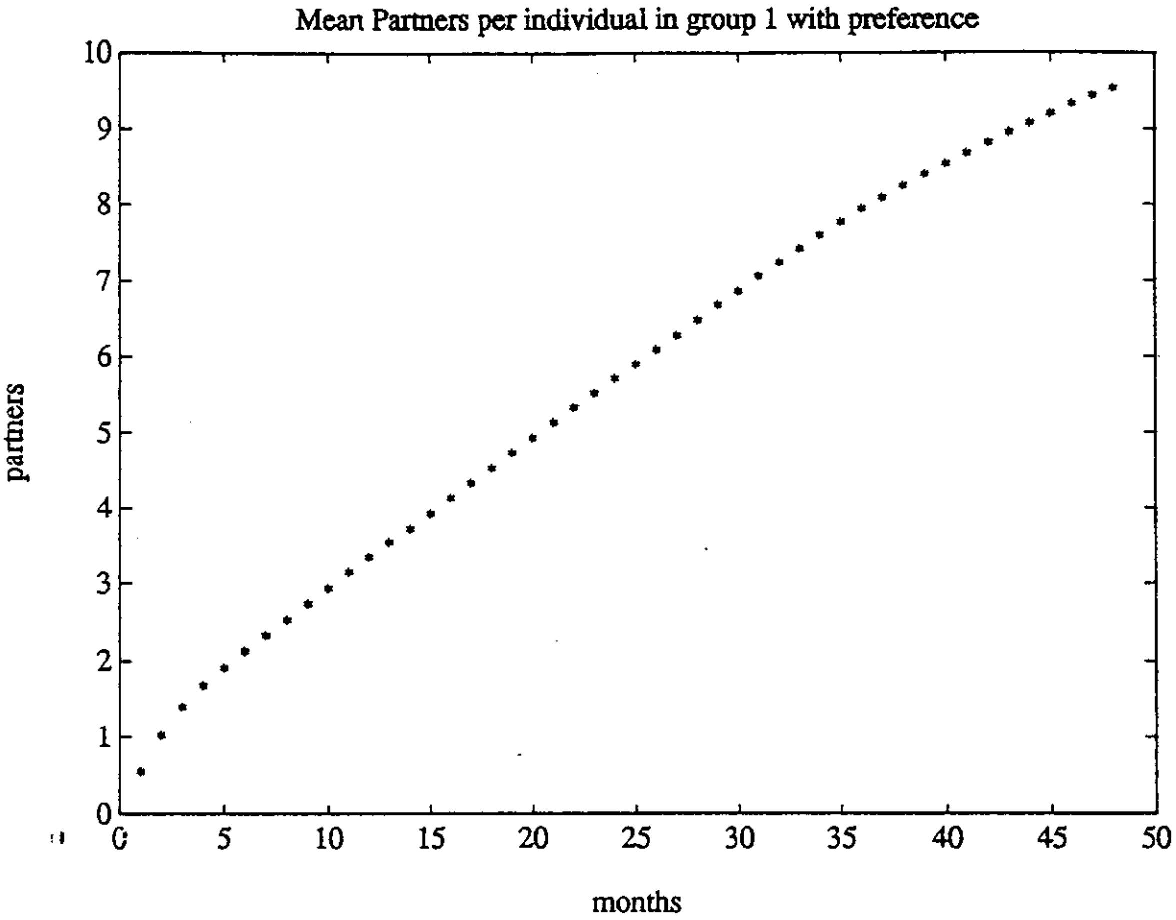
Fig 2. Same as Figure 1 but using the parameter set II (title "without preference"). Note that at the 35-th month the average number of sexual partners is about 0.9.

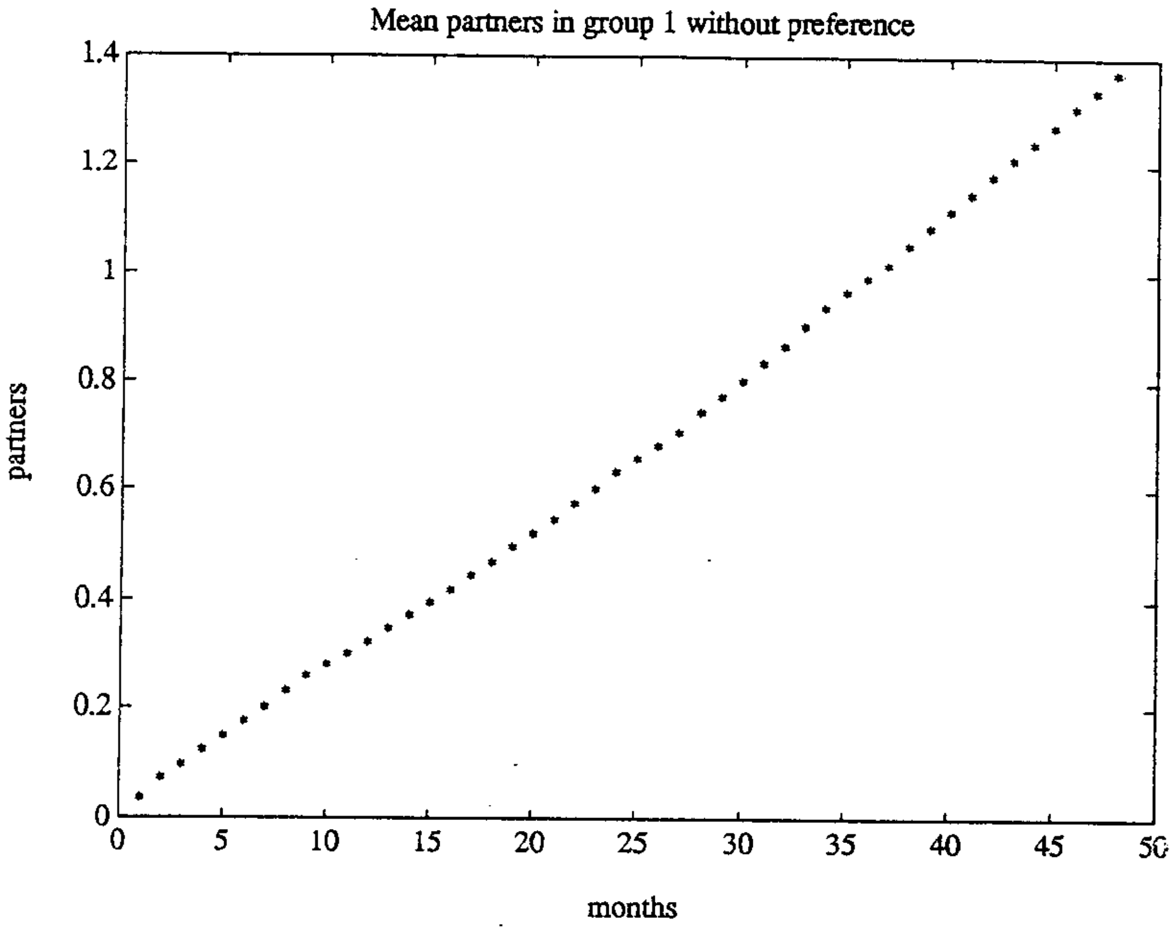
Fig 3. Here we use parameter Set I. We begin with 10 infectives in the first male group. In this graph we show the distribution function of the random time at which the total number of infectives reaches 100. For example, we observe that with probability 0.09, the time at which the total number of infectives reaches 100 is less than 0.66 years.

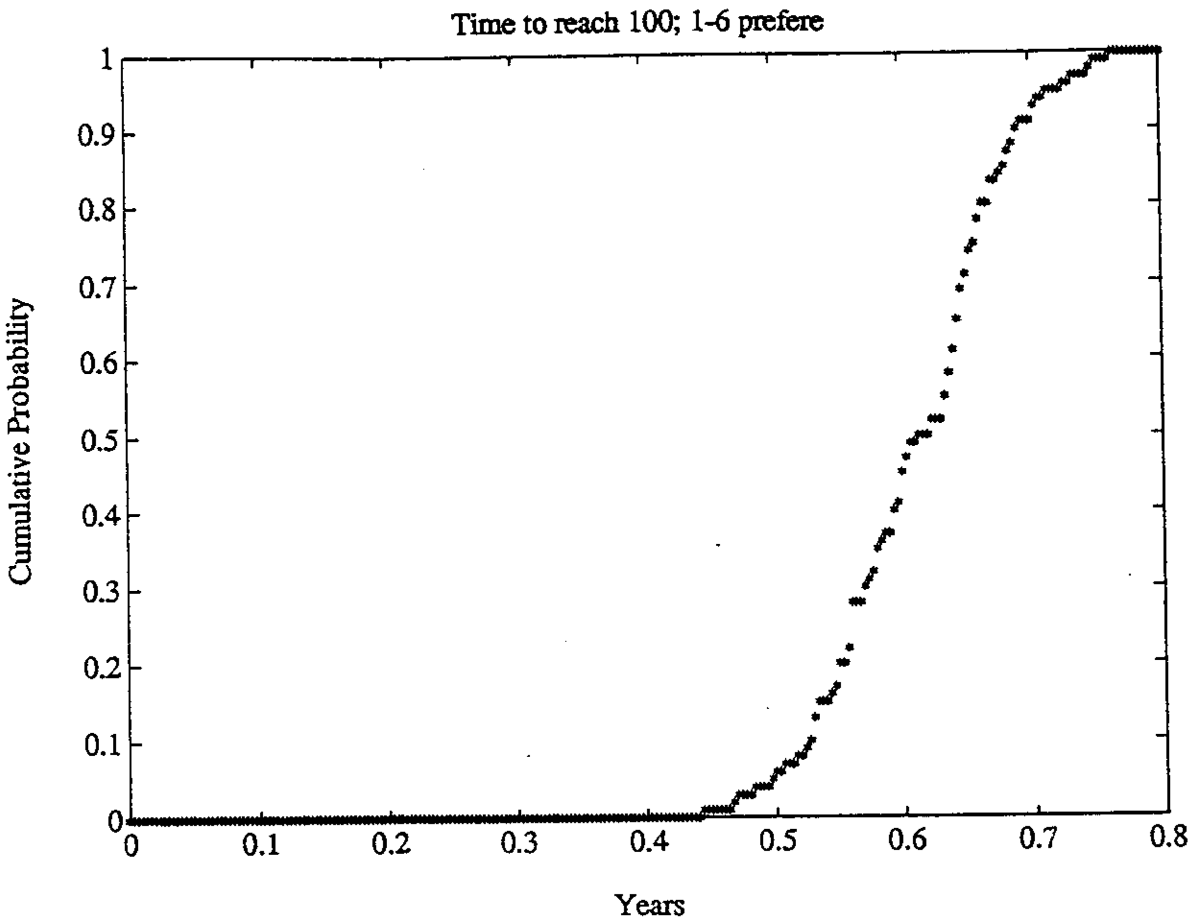
Fig 4. Analogous to Figure 3 but using the parameter Set II ("without preference"). See the text for details.

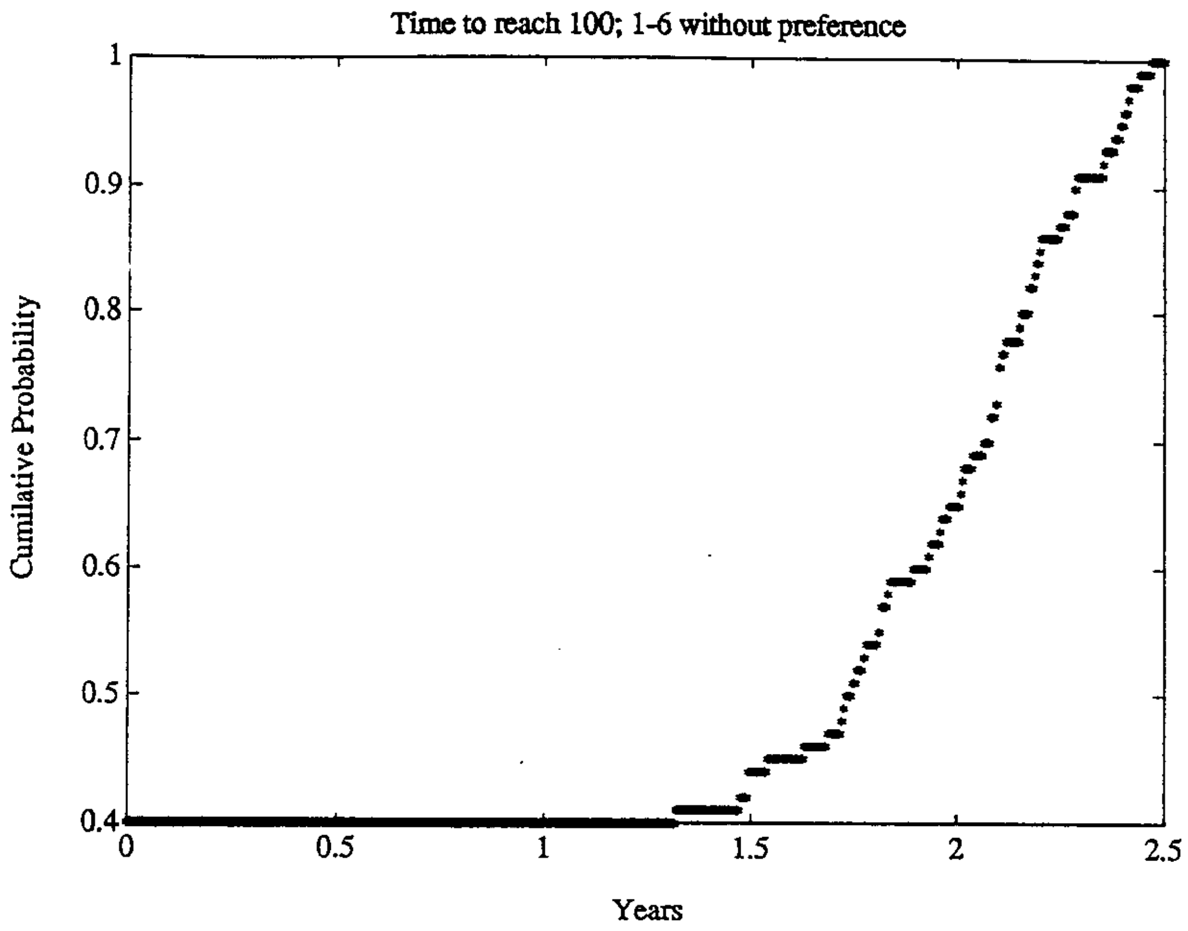
Fig 5. This picture illustrates the distribution of infectives a year and half later. We use parameter Set I. One sees, for example, that the total number of infectives 1.5 years after the start of this epidemic is less than 500 with probability 0.25 or more than 500 with probability 0.75.

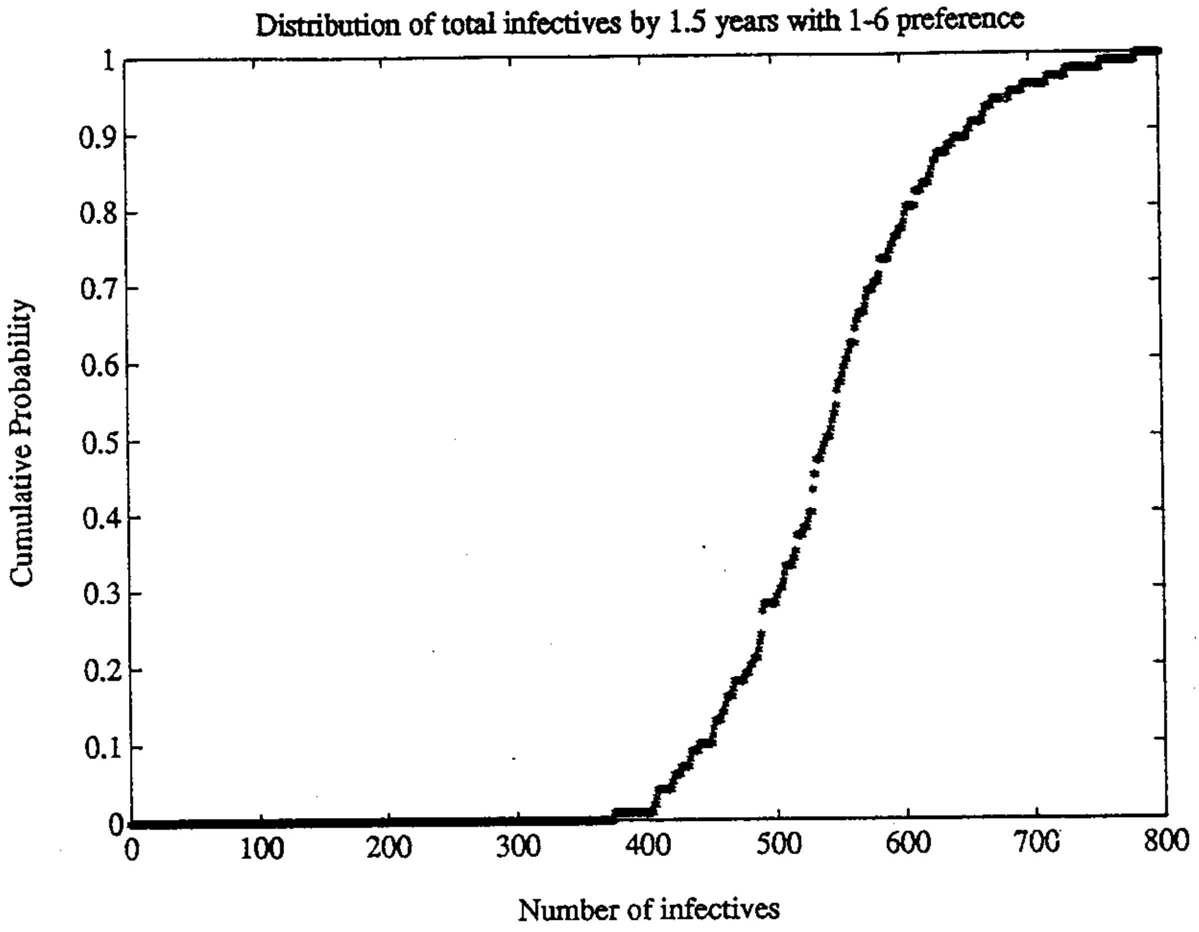
Fig 6. Analogous to Figure 5 but using the parameter Set II.

Mean Partners per individual in group 1 with preference
partners
months
0
1
2
3
4
5
6
7
8
9
10
0
5
10
15
20
25
30
35
40
45
50

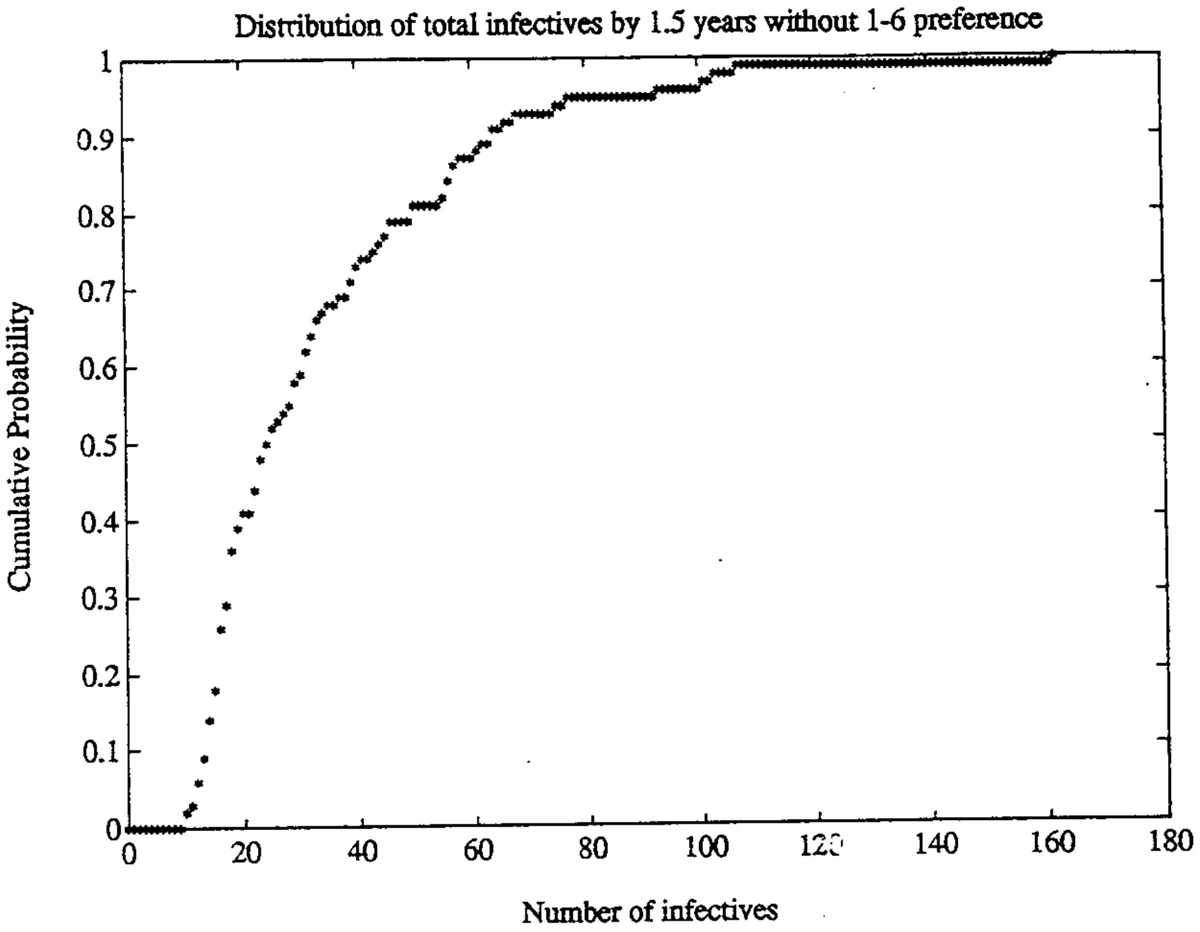

Mean partners in group 1 without preference
partners
months
0
0.2
0.4
0.6
0.8
1
1.2
1.4
0
5
10
15
20
25
30
35
40
45
50


Time to reach 100; 1-6 prefere
Cumulative Probability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
Years


Time to reach 100; 1-6 without preference
Cumilative Probability
1
0.9
0.8
0.7
0.6
0.5
0.4
0
0.5
1
1.5
2
2.5
Years



Distribution of total infectives by 1.5 years with 1-6 preference
Cumulative Probability
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
100
200
300
400
500
600
700
800
Number of infectives


Distribution of total infectives by 1.5 years without 1-6 preference
Cumulative Probability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
80
100
120
140
160
180
Number of infectives

```
   Initial Condition

susceptible singles
106   106   126   251   543   376   500   354   674
infective singles
10      0      0     0   0     0     0     0     0
(s,s) pairs:
   0     0     0     0
   0     0     0     0
   0     0     0     0
   0     0     0     0
   0     0     0     0
(s,i) pairs:
   0     0     0     0
   0     0     0     0
   0     0     0     0
   0     0     0     0
   0     0     0     0
(i,s) pairs
   0     0     0     0
   0     0     0     0
   0     0     0     0
   0     0     0     0
   0     0     0     0
(i,i) pairs
   0     0     0     0
   0     0     0     0
   0     0     0     0
   0     0     0     0
   0     0     0     0
```

Activity Parameter Set I

```
0.0    4.0    0.05
9      5      2
0.0    0.0    0.0      0.0      0.0      0.0       0.0     0.0    0.0
0.1     0.1     0.1     0.1     0.1     0.1      0.1    0.1      0.1
1.1     1.2
 29.5    0.05    0.01    0.005   25.0
0.0    5.0    0.0    0.1    0.01
0.1    0.01 54.3    9.0   10.01
1.0    0.01   0.01   5.0    0.1
9.0     0.01   0.5    0.01
0.01   5.0    0.5    0.4
1.0    0.01   4.0    0.5
0.01   1.0    0.01   4.0
  1.0    1.0    0.0    1.0
0.1  -1.1    -0.5    -0.4    1.9
0.3   1.0   -0.4   -0.3
8.1  2.1    2.1    2.1
5.1  2.1    2.1    2.1
0.05  2.1    2.1    2.1
0.1  2.1    2.1    2.1
20.1  2.1    2.1    2.1
20.1  10.1   10.1   10.1
10.1  10.1   10.1   10.1
10.1  10.1   10.1   10.1
10.1  10.1   10.1   10.1
10.0  10.0   10.0   10.0
10.1  10.1   10.1   10.1
10.1  10.1   10.1   10.1
10.1  10.1   10.1   10.1
10.1  10.1   10.1   10.1
10.1  10.1   10.1   10.1
20.1  20.1   20.1   20.1
20.1  20.1   20.1   20.1
20.1  20.1   20.1   20.1
20.1  20.1   20.1   20.1
20.1  20.1   20.1   20.1
 190.1  190.1
0.0   0.0    0.0
0.0   0.001
0.01    0.0    0.0    0.0    0.1
0.0     0.0    0.01   0.0
0.0
```

Activity Parameter Set II

```
0.0    4.0    0.05
9      5      2
0.0    0.0    0.0     0.0     0.0     0.0      0.0    0.0    0.0
0.1     0.1    0.1     0.1     0.1     0.1     0.1   0.1     0.1
1.1     1.2
 0.05   0.05   0.01   0.005  25.0
0.0    5.0    0.0    0.1    0.01
0.1    0.01 54.3    9.0   10.01
1.0    0.01  0.01   5.0    0.1
0.06     0.01  0.5    0.01
0.01   5.0    0.5    0.4
1.0    0.01   4.0    0.5
0.01   1.0    0.01   4.0
  1.0    1.0    0.0    1.0
-0.1   1.1    0.5    0.4    -1.9
0.3    1.0   -0.4   -0.3
8.1   2.1    2.1    2.1
5.1   2.1    2.1    2.1
0.05   2.1    2.1    2.1
0.1   2.1    2.1    2.1
20.1   2.1    2.1    2.1
20.1  10.1    10.1    10.1
10.1  10.1    10.1    10.1
10.1  10.1    10.1    10.1
10.1  10.1    10.1    10.1
10.0  10.0    10.0    10.0
10.1  10.1    10.1    10.1
10.1  10.1    10.1    10.1
10.1  10.1    10.1    10.1
10.1  10.1    10.1    10.1
10.1  10.1    10.1    10.1
20.1  20.1    20.1    20.1
20.1  20.1    20.1    20.1
20.1  20.1    20.1    20.1
20.1  20.1    20.1    20.1
20.1  20.1    20.1    20.1
 190.1  190.1
0.0   0.0    0.0
0.0   0.001
0.01    0.0    0.0    0.0    0.1
0.0     0.0    0.01   0.0
0.0
```