SMR.780 - 44

FOURTH AUTUMN COURSE ON MATHEMATICAL ECOLOGY

(24 October - 11 November 1994)

"A General Solution of the Problem of Mixing of Subpopulations and its Application to Risk- and Age-Structured Epidemic Models for the Spread of AIDS"

Carlos Castillo-Chavez
Biometrics Unit
Cornell University
Ithaca, NY 14853-7801
U.S.A.

These are preliminary lecture notes, intended only for distribution to participants.

STAVROS BUSENBERG

Department of Mathematics, Harvey Mudd College,
Claremont, California 91711, USA

CARLOS CASTILLO-CHAVEZ

· *Biometrics Unit, Center for Applied Mathematics, Cornell University,*
Ithaca, New York 14853-7801, USA

A central aspect in the study of the dynamics of sexually tran ni..ed diseases is that of mixing. The study of the effects of social structure in di ase dynamics has received considerable attention over the last few years as a re ·ilt of the AIDS epidemic. In this paper, we formulate a generalization of the Blythe and Castillo-Chavez social/sexual framework for human interactions through the incorporation of age structure, and derive an explicit expression in terms of a preference function for the general solution to this formulation. We emphasize the role played by proportionate mixing, the only separable solution to this mixing framework, through the discussion of several specific cases, and we formulate an age-structured epidemic model for a single sexually active homosexual population, stratified by risk and age, with arbitrary risk- and age-dependent mixing as well as variable infectivity. In the special case of proportionate mixing in age and risk, an explicit expression for the basic reproductive number is computed.

Keywords: AIDS; HIV transmission; epidemic modelling; mixing problem; proportionate mixing; risk and age structure; basic reproductive number.

1. Introduction

RECENT estimates put the number of HIV-infected individuals (i.e. infected with the human immunodeficiency virus, the aetiological agent for AIDS) at between 800 000 and 1 200 000 in the United States. The World Health Organization estimates the number of HIV carriers worldwide at 5–10 million. The Center for Disease Control in Atlanta (USA) reports, as of December 1990, more than 162 000 cases of 'full-blown' AIDS, of which over 70 000 individuals have died. Estimated costs for the treatment of and caring for individuals with AIDS run into the billions of dollars. This grim scenario has motivated researchers to develop mathematical models to identify and/or improve our understanding of the mechanisms responsible for HIV transmission and for the evaluation of the relative merits of possible control measures. Recent reviews of the literature on models include those of Anderson (1988, 1989), Castillo-Chavez (1989a, b), and Schwager *et al.* (1989), while an extensive study of some of the most recent work

1

on the use of mathematical and statistical modelling of the dynamics of HIV at the individual (immune system) or population level can be found in a recent collection of articles (see Castillo-Chavez, 1989b).

Some of the questions that can be approached through the use of mathematical models (see Hethcote & Yorke, 1984; Anderson, 1988; May & Anderson, 1989; Castillo-Chavez et al., 1988, 1989a, b, e; Diekmann et al., 1990) include: the possibility of invasion (i.e. whether or not a disease can colonize successfully a given population of susceptibles at steady state), the determination of thresholds, the possibility that a disease may reach an endemic state, and whether or not a disease can regulate a population. The preliminary work of several AIDS modelling research groups (see Anderson, 1988; Castillo-Chavez, 1989b) has already made numerous contributions. Researchers have demonstrated that the infectious period distribution with its large mean and variance implies that a rise in seropositivity will precede the rise in AIDS, possibly by years. Furthermore, heterogeneity in infectivity and the possibility of two infectivity peaks (see Francis et al., 1984; Lange et al., 1986; Salahuddin et al., 1984) will have a major effect on the shape of the epidemic curve (see Hyman & Stanley, 1989; Thieme & Castillo-Chavez, 1989, 1991). Selection due to AIDS-induced mortality will decrease the population's mean sexual activity, i.e. the average rate of sexual partner change, and hence make the evaluation of the effectiveness of education programmes difficult (see Castillo-Chavez et al., 1989d; Anderson et al., 1989). The magnitude of the basic reproductive number, or the number of secondary infections generated by a 'typical' infectious individual in a population of susceptibles, in combination with the shape of the incubation period distribution, will have a major effect on the first episode and potentially on the long-term dynamics of HIV as well. Predictions are not possible without an increased understanding of social dynamics (see Hyman & Stanley, 1989; Jacquez et al., 1988; Gupta et al., 1989; Castillo-Chavez et al., 1989c, d; Huang et al., 1991; Cooke et al., 1991; Dietz, 1988; Dietz & Hadeler, 1988; Hadeler, 1989a, b; May & Anderson, 1989; Blythe & Castillo-Chavez, 1989; Castillo-Chavez & Blythe, 1989; Anderson et al., 1989). These researchers have shown that epidemic models can be very sensitive to changes in the sexual/social mixing structures, and that not all of them exhibit the same global dynamics.

Much of this recent work has highlighted the need to study systematically the effects of mixing in disease dynamics. An in-depth study of the effects of mixing requires a suitable axiomatic framework incorporating the natural constraints involved in mixing. Recently, Blythe & Castillo-Chavez (1989) and Castillo-Chavez & Blythe (1989) – hereafter both articles will be referred to as BCC – formulated such a framework for continuously distributed characteristics and found a large class of new solutions to the mixing constraints. Their family of solutions is based on the use of a preference or acceptance function allowing for the incorporation of preference in the mixing process. This family of solutions includes Nold's preferred mixing (see Nold, 1980; Hethcote & Yorke, 1984), proportionate mixing, and like-with-like mixing (see Busenberg & Castillo-Chavez, 1989). Furthermore, BCC have used this family of solutions to illustrate the combined effects on the shape of the mixing function of the interactions among individuals belonging to groups with specified preferences and levels of

risk and the mixing constraints imposed naturally upon this population of interacting groups through their own distribution of sexual activity. These numerical simulations corroborated and extended the numerical results of Hyman & Stanley (1988, 1989). In addition, special representatives of these mixing functions have been incorporated into dynamic models for the sexual spread of HIV. The mathematical analyses and numerical simulations of these models have shown the dramatic effects on disease dynamics of the choice of a mixing function (see Hyman & Stanley, 1989; Anderson *et al.*, 1989; Jacquez *et al.*, 1988; Castillo-Chavez *et al.*, 1989c, d; Huang, 1989; Cooke *et al.*, 1991; Gupta *et al.*, 1989; Huang *et al.*, 1991).

The main objectives of this paper include generalizing the mixing framework (BCC) and deriving an explicit expression for the general solution to the mixing problem for a population stratified by age and level of sexual activity, formulating an age-structured epidemic model for a single homosexually active population with arbitrary social/sexual age-dependent mixing, and computing the reproductive number for a proportionately (in age and risk) mixing population.

This paper is organized as follows. Section 2 axiomatically characterizes the mixing function and describes its role in disease dynamics by deriving an expression for the incidence (which determines the number of new cases per unit time). Section 3 discusses several mixing functions that arise from different constitutive relationships. Section 4 derives an explicit expression for the general solution of the mixing problem in terms of a preference function. Section 5 formulates a general dynamic model for the spread of HIV/AIDS for a homosexually active age- and risk-structured population and computes its basic reproductive number in the case of proportionate mixing. Section 6 discusses the relevance of the results presented in this article, briefly outlines our results on two-sex mixing frameworks, and suggests future directions of research.

2. Mixing framework

The formulation described in this section can be used in the modelling of social or sexual mixing interactions. For example, while the mixing function can describe the proportion of 'dates' between individuals in distinct groups, or can represent the proportion of sexual partnerships or sexual contacts between these individuals, other interpretations are possible. In addition, the mixing function can be generalized to include the geographical distribution or the geographical movement of individuals through the use of 'localized' mixing functions, i.e. functions that represent the proportion of partnerships formed between individuals from clearly defined groups (socially, demographically, etc.) at a particular geographical location. The local geographical heterogeneities can then be linked through the specification of migration or movement matrices (see Sattenspiel, 1987a, b; Sattenspiel & Simon, 1988). Therefore, our approach allows for the specification of a spatial mixing framework. In this paper, however, we concentrate on the study of localized mixing functions. We begin by considering the interactions of a single socially homogeneous group of individuals who are structured according to the following variables: a = age; τ = time (or age) since infection; r = activity or risk level. We let $N(r, a, \tau, t)$ denote the total

population density per unit age, activity, and time since infection, at time t. This population is divided into the following epidemiological classes: S = susceptible; I = asymptomatic or slightly symptomatic infective; A = highly symptomatic infective. This classification is fairly general and includes implicitly the traditional infected, but not infective class E (see Busenberg & Castillo-Chavez, 1989). We assume that τ is a hidden internal variable that does not distinguish individuals other than through their level of infectivity, and perhaps mortality. When modelling the sexual transmission of AIDS, we assume that A-individuals (i.e. individuals with severe symptoms or full-blown AIDS) are sexually inactive and hence that

$$T(r, a, t) = S(r, a, t) + \int_0^\infty I(r, a, \tau, t)\, d\tau$$

represents the total age and activity-level density of a population active in disease transmission contracts. Sexual mixing is defined through the mixing function ρ. Specifically, $\rho(r, a, r', a')$ is the proportion of partners of an (r, a) individual (i.e. a person of activity level r at age a), with (r', a') individuals; $C(r, a, W(T(\cdot, \cdot, t)))$ is the expected or average number of partners per unit time of an (r, a) individual given that the effective population size is $W(T(\cdot, \cdot, t))$ at time t (we assume $C \geq 0$).

The follows natural conditions characterize the mixing function:

(i) $\rho \geq 0$;

(ii) $\displaystyle\int_0^\infty \int_0^\infty \rho(r, a, r', a', t)\, dr'\, da' = 1$, if $C(r, a, W(T(\cdot, \cdot, t)))T(r, a, t) \neq 0$;

(iii) $\rho(r, a, r', a', t)C(r, a, W(T(\cdot, \cdot, t)))T(r, a, t) =$
      $\rho(r', a', r, a, t)C(r', a', W(T(\cdot, \cdot, t)))T(r', a', t)$;

(iv) $C(r, a, W(T(\cdot, \cdot, t)))T(r, a, t)C(r', a', W(T(\cdot, \cdot, t)))T(r', a', t) = 0 \Rightarrow$
      $\rho(r, a, r', a', t) = 0.$

Condition (ii) simply says that ρ is a proportion. Condition (iii) states that the total number of contacts of (r, a) individuals with (r', a') individuals equals the total number of contacts of (r', a') individuals with (r, a) individuals (all this is per unit time, age, and time since infection). Condition (iv) says that there is no mixing in the age and activity levels where there are no active individuals. i.e. on the set

$$\Xi = \{(r, a, r', a') : C(r, a, W(T(\cdot, \cdot, t)))T(r, a, t)$$
$$\times C(r', a', W(T(\cdot, \cdot, t)))T(r', a', t) = 0\},$$

where there is no mixing. Condition (iv) arises naturally as will be seen in Section 4, so we proceed to state our results without this assumption until it is required.

In some situations, it is necessary to consider mixing functions ρ, which are Dirac delta-functions (see BCC) or, more generally, distributions or generalized functions. Hence, we are forced to consider solutions to this axiomatic framework

in the space of distributions or generalized functions (see Schwartz, 1966, or Gel'fand & Shilov, 1964). This is easily accomplished by choosing appropriate spaces of test functions whose generic elements we denote by f, and using the following modification to the interpretation of axioms (i) and (iv):

(i′) $\rho \geqslant 0$ in the sense of distributions, i.e.

$$\int_0^x \int_0^x \rho(r, a, r', a')f(r', a')\, dr'\, da' \geqslant 0 \quad \text{for all } f \geqslant 0;$$

(iv′) $\rho = 0$ on a set $\widetilde{\Xi}$, which means

$$\iint_{\widetilde{\Xi}} \rho(r, a, r', a')f(r', a', r, a)\, dr', da', dr\, da = 0 \quad \text{for all } f.$$

In writing the conditions characterizing ρ we have exhibited their functional dependence on (r, a, r', a') and, for notational convenience, have suppressed their dependence on t and T.

Pair formations can involve selectivity by individuals according to age or activity level, they can be random pairings without regard to these variables, or they can be any combination or mixture of the two extremes. A detailed discussion of these possibilities and of the restrictions they place on the mixing function ρ is found in Section 3. The effects of mixing on disease transmission can be modelled through the incidence rate (new infected cases per unit time) or the 'force' of the infection. We begin by letting $\beta(r, a, \tau, r', a')$ denote the probability that a pairing between an (r', a', τ) infective individual and an (r, a) susceptible will lead to the passing of the infection to the susceptible (other interpretations are possible: see Castillo-Chavez et al. (1989c, d) and Cooke et al. (1991)), and by observing that I/T denotes the proportion of contacts of a susceptible with an infective individual. The force of infection term B is therefore given by

$$B(r, a, t) = C\big(r, a, W(T(\cdot, \cdot, t))\big) \int_0^x \int_0^x \int_0^x \beta(r, a, \tau, r', a')$$

$$\times \rho(r, a, r', a', t) \frac{I(r', a', \tau, t)}{T(r', a', t)}\, dr'\, da'\, d\tau, \quad (1)$$

and the incidence rate is given by $S(r, a, t)B(r, a, t)$. In order to simplify the notation, we shall write $C(r, a, W)$ for $C\big(r, a, W(T(\cdot, \cdot, t))\big)$ in the argument that follows. The interpretation of the term is as follows: there are $S(r, a, t)\,\Delta r\,\Delta a$ susceptibles in the class interval $\Delta a \times \Delta r$, and those individuals have $S(r, a, t)C(r, a, W)\,\Delta r\,\Delta a$ contacts per unit time. Of these contacts, $S(r, a, t)C(r, a, W)\rho(r, a, r', a')\,\Delta r\,\Delta a$ are with active individuals in the (r', a') class, and a proportion $I(r', a', \tau, t)/T(r', a', t)$ are with infective individuals. Thus the number of contacts per unit time of (r, a) individuals with infectives in

TABLE 1a

Type & name	Force of infection term $= B(r, at)$		Proposition condition
	$\dfrac{B(r, a, t)}{C(r, a)}$		
(I) Proportionate age mixing	$\displaystyle\iiint_0 \beta(r, a, \tau, r', a')\rho(r, a, r', t)\,\frac{C(r', a')I(r', a', \tau, t)}{\int_0^\infty C(r', a')T(r', a', t)\,da'}\,dr'\,da'\,d\tau$	(ii)	$\displaystyle\iint_0^\infty \rho(r, a, r', a', t)\,da'\,dr' = 1$
			$\displaystyle\iint_0^\infty \frac{\rho(r, a, r', t)C(r', a')T(r', a', t)}{\int_0^\infty C(r', a')T(r', a', t)\,da'}\,da'\,dr' = 1$
(II) Proportionate activity mixing	$\displaystyle\iiint_0 \beta(r, a, \tau, r', a')\bar\rho(r, a, a', t)\,\frac{C(r', a')I(r', a', \tau, t)}{\int_0^\infty C(r'a')T(r', a', t)\,dr}\,dr'\,da'\,d\tau$		$\displaystyle\iint_0^\infty \frac{\bar\rho(r, a, r', t)C(r', a')T(r', a', t)\,da'\,dr'}{\int_0^\infty C(r', a')T(r', a', t)\,dr} = 1$
(III) = (I) + (II) Proportionate mixing	$\dfrac{1}{\displaystyle\iint_0^\infty C(r', a')T(r', a', t)\,da'\,dr'}\displaystyle\iiint_0^\infty \beta(r, a, \tau, r', a')C(r', a')$		$\bar\rho(r, a, t) = 1$
	$\times I(r', a', \tau, t)\,dr'\,da'\,d\tau$		

(IV) Uniform age selectivity	$$\iiint_0 \beta(r,a,\tau,r',a',t)\rho(r,r',a',t)\frac{I(r',a',\tau,t)}{T(r',a',t)}\,dr'\,da'\,d\tau$$	$$\iint_0 \rho(r,r',a',t)\,dr'\,da' = 1$$
(V) Uniform activity selectivity	$$\iiint_0 \beta(r,a,\tau,r',a',t)\rho(a,r',a',t)\frac{I(r',a',\tau,t)}{T(r',a',t)}\,dr'\,da'\,d\tau$$	$$\iint_0 \rho(a,r',a',t)\,dr'\,da' = 1$$
(VI) = (IV) + (V) Uniform age of activity selectivity	$$\iiint_0 \beta(r,a,\tau,r',a',t)\rho(r',a',t)\frac{I(r',a',\tau,t)}{T(r',a',t)}\,dr'\,da'\,d\tau$$	$$\iint_0 \rho(r',a',t)\,dr'\,da' = 1$$
(I) + (V)	Take $\hat\rho(r,a,r',t) = \hat\rho(a,r',t)$ in (I). No r dependence.	These two conditions place severe restrictions on the possible functions $\hat\rho$.
(II) + (IV)	Take $\hat\rho(r,a,a',t) = \hat\rho(r,a',t)$ in (II). No a dependence.	

TABLE 1b

Type & name	Pair symmetry condition (iii) $\rho(r, a, r', a', t)C(r, a)T(r, a, t) = \rho(r', a', r, a, t)C(r', a')T(r', a', t)$
(I) Proportionate age mixing	$\dfrac{\bar{\rho}(r, a, r', t)}{\displaystyle\int_0^\infty C(r', a')T(r', a', t)\,da'} = \dfrac{\bar{\rho}(r', a', r, t)}{\displaystyle\int_0^\infty C(r, a)T(r, q, t)\,da}$
(II) Proportionate activity mixing	$\dfrac{\bar{\rho}(r, a, a', t)}{\displaystyle\int_0^\infty C(r', a')T(r', a', t)\,dr'} = \dfrac{\bar{\rho}(r', a', a, t)}{\displaystyle\int_0^\infty C(r, a)T(r, a, t)\,dr}$
(III) = (I) + (II) Proportionate mixing	$C(r, a)T(r, a, t) = C(r', a')T(r', a', t)$
(IV) Uniform age selectivity	$\rho(r, r', a')C(r, a)T(r, a, t) = \rho(r', r, a)C(r', a')T(r', a', t)$
(V) Uniform activity selectivity	$\rho(a, r', a')C(r, a)T(r, a, t) = \rho(a', r, a)C(r', a')T(r', a', t)$
(VI) = (IV) + (V) Uniform age of activity selectivity	$\bar{\rho}(r', a')C(r, a)T(r, a, t) = \bar{\rho}(r, a)C(r', a')T(r', a', t)$
(I) + (V) (II) + (IV)	These two conditions place severe restrictions on the possible functions $\bar{\rho}$ which we study in Section 4.

the (r', a', τ) class is

$$S(r, a, t)C(r, a, W)\rho(r, a, r', a')\frac{I(r', a', \tau, t)}{T(r', a', t)}\,\Delta a\,\Delta r,$$

and therefore the expected rate of disease transmission due to such contacts with infectives in the $\Delta\tau \times \Delta a' \times \Delta r'$ interval is

$$S(r, a, t)C(r, a, W)\beta(r, a, \tau', r', a')\rho(r, a, r', a')\frac{I(r', a', \tau, t)}{T(r', a', t)}\,\Delta a'\,\Delta r'\,\Delta\tau\,\Delta a\,\Delta r.$$

To find all the disease transmission contacts between susceptibles in the $\Delta a \times \Delta r$ interval with all possible infectives, we sum over $\Delta\tau \times \Delta a' \times \Delta r'$ to get $B(r, a, t)$. Note that the dynamics implied for the susceptible class are given by

$$\frac{\partial S}{\partial t}(r, a, t) + \frac{\partial S}{\partial a}(r, a, t) + \mu(r, a, t)S(r, a, t) = \Lambda(r, a, t, T(a, r, t)) - B(r, a, t),$$

$$(2)$$

where Λ denotes the 'recruitment' rate into the susceptible class, and μ denotes the natural per capita removable rate from sexual activity (due to all causes except severe symptoms or full-blown AIDS). We observe that there are several constitutive forms of the interaction term ρ; examples without age structure can be found in BCC. Tables 1a and 1b illustrate several possibilities, for age- and activity-dependent mixing. These nine general cases include proportionate mixing in the age variable only, proportionate mixing in the activity variable only, and proportionate mixing in both age and activity variables. One of the simplest forms of mixing is that of proportionate or random mixing, which in our present framework includes both variables of age and activity level. It is given by a generalization of the model used for situations without age structure by May & Anderson (1989);

$$\bar{\rho}(r, a, r', a', t) = \frac{C(r', a', W(T(\cdot, \cdot, t)))T(r', a', t)}{\int_0^\infty \int_0^\infty C(r', a', W(T(\cdot, \cdot, t)))T(r', a', t)\,da'\,dr'}$$

$$\text{if } (r, a, r', a') \notin \mathfrak{S} \quad (3)$$

and $\bar{\rho}(r, a, r', a', t) = 0$ if $(r, a, r', a') \in S$. This solution plays an important role in the determination of all possible solutions to the mixing framework (i)–(iv). It will be shown in the next section, all mixing functions are multiplicative perturbations of proportional mixing. Note that proportionate mixing vacuously satisfies condition (iv). This condition prevents us from arbitrarily defining a mixing function for subpopulations that either are not sexually active or that have been depleted of individuals by disease dynamics.

3. Mixing-dependent incidence rates

From equation (1), it is evident that the incidence rate is affected by two parameters: the infectivity and the mixing function. In this section, we begin to analyse the role of mixing in disease dynamics by discussing some specific constitutive forms for the mixing function ρ (for a preliminary mathematical analysis of the effects of variable infectivity, see Thieme & Castillo-Chavez (1989, 1991)). The objective of this section is to illustrate nine general cases that may be useful for modelling purposes. We hope that our brief classification may be of use by making clear the assumptions behind the choice of each mixing function. In the next section, we present a representation theorem that includes all possible solutions to axioms (i)–(iv), and that therefore contains the solutions in this section, although not always in a transparent way. In giving these expressions, we assume, for simplicity, that C does not depend on W, and do not repeat the condition that ρ vanish on the set $\mathfrak{S}$.

(I) *Proportionate mixing in the age variable only.* Individuals in the (r, a) class, when choosing partners, do not show preference for any age group. Consequently, as far as age is concerned, pair formation is a stratified random process. Thus the proportion of contacts of an (r, a) individual (per

capita of active population) with (r', a') individuals is of the form

$$\rho(r, a, r', a')C(r, a) = \bar{\rho}(r, a, r')C(r, a) \frac{C(r', a')T(r', a')}{\int_0^\infty C(r', a')T(r', a')\,\mathrm{d}a'} .$$

that is, contact with age a' individuals is directly related to the proportion of the activity level of such individuals in the total active population across all age groups. This proportion at time t is, of course,

$$\frac{C(r', a')T(r', a', t)}{\int_0^\infty C(r', a')T(r', a', t)\,\mathrm{d}a'} .$$

The force of infection term becomes

$$B(r, a, t) = C(r, a)\int_0^\infty \int_0^\infty \int_0^\infty \beta(r, a, \tau, r', a')\bar{\rho}(r, a, r', t)$$

$$\times \frac{C(r', a')I(r', a', \tau, t)\,\mathrm{d}r'\,\mathrm{d}a'\,\mathrm{d}\tau}{\int_0^\infty C(r', a')T(r', a', t)\,\mathrm{d}a'} .$$

Remark. Note that, because of the presence of the activity-level variable, the integral in the denominator cannot be taken out of the triple integral.

Using the same type of reasoning as in (I) we obtain the following acceptable forms for the mixing function ρ.

(II)   *Proportionate mixing in the activity variable only:*

$$\rho(r, a, r', a') = \bar{\rho}(r, a, a') \frac{C(r, a')T(r', a')}{\int_0^\infty C(r', a')T(r', a')\,\mathrm{d}r'} .$$

(III)   *Proportionate mixing in both the age and partner variables:*

$$\rho(r, a, r', a') = \bar{\rho}(r, a) \frac{C(r', a')T(r', a')}{\int_0^\infty \int_0^\infty C(r', a')T(r', a')\,\mathrm{d}a'\,\mathrm{d}r'} .$$

(I)–(III) assume that the persons selecting partners have criteria of selection which depend on the class to which they belong. We now turn to situations where that is not the case.

(IV)   *Uniform age selectivity:*

$$\rho(r, a, r', a') = \bar{\rho}(r, r', a').$$

Here we assume that individuals in the (r, a) class have the same selection criteria as individuals in any other (r, a^*) class, $a^* \in [0, \infty)$. That is, selection is independent of the age of the individual who is selecting;

however, it does depend on the age of those who are being selected as partners.

(V) *Uniform activity selectivity*:

$$\rho(r, a, r', a') = \bar{\rho}(a, r', a').$$

Here the activity level of the individual does not affect his/her selectivity criteria.

(VI) *Uniform age and activity selectivity*:

$$\rho(r, a, r', a') = \bar{\rho}(r', a').$$

We can combine (I)–(II) with (IV)–(VI) in various ways and obtain nine different forms for the mixing function ρ, which we exhibit in Tables 1a and 1b together with the resulting form of the force of infection which is obtained from (1). We also list the restrictions placed on $\bar{\rho}$ and C by (ii) and (iii). Even though we are singling out these nine possible versions at this stage, the general form of ρ needs only to satisfy conditions (i)–(ii)–(iii), and each of the special cases involves a constitutive assumption concerning the mode of mixing and partner selection. We also note that both ρ and C may be density-dependent, and we are beginning to look at such extensions (see Castillo-Chavez *et al.*, 1989d; Thieme & Castillo-Chavez, 1989, 1991). Finally, we observe that convex linear combinations of mixing functions are mixing functions. Specifically, if $\alpha_1, ..., \alpha_N$ are positive constants such that $\sum_{i=1}^{N} \alpha_i = 1$ and $\rho_1, ..., \rho_N$ are mixing functions, then $\sum_{i=1}^{N} \alpha_i \rho_i$ is a mixing function. This last observation provides a recipe for the construction of a variety of mixing functions; furthermore, it clearly shows that preferred mixing (a convex combination of two mixing functions), contrary to the suggestions of some researchers, does not contain all reasonable possibilities. Specifically, (omitting age) preferred mixing is given by

$$\rho(s, r) = (1 - \alpha) \frac{C(r)T(r)}{\displaystyle\int_0^\infty C(u)T(u)\,du} + \alpha\, \delta(s - r), \tag{4}$$

where δ denotes the Dirac delta-function (see BCC), i.e. it is the convex linear combination of the Dirac delta-function (a mixing function) and proportionate mixing. The two extreme points of this particular convex linear combination (when $\alpha = 0$ or 1) do not obviously represent sociological or mathematical mixing extremes – this was pointed out to us by S. Gupta and R. Anderson – as some researchers have suggested.

We now show how to recover the case of no age-dependence, which yields the original formalism of BCC. To circumvent the fact that we cannot eliminate the variables (a, a') in ρ because (i) and (ii) are then incomparable, we need to assume that the population is not age-structured, so that $T(r, a) \equiv T(r)$ does not depend on a. We further assume that there is a maximum age A, and that

$\rho(r, a, r', a') = 0$ if $a > A$ or $a' > A$, and set

$$\rho(r, a, r', a') = \begin{cases} 0 & \text{if } a > A \text{ or } a' > A, \\ \dfrac{1}{A} \rho(r, r'), & \text{with } \displaystyle\int_0^\infty \rho(r, r') \, dr' = 1, \; \rho(r, r') \geq 0 \quad \text{otherwise.} \end{cases}$$

Conditions (i) and (ii) are then automatically satisfied, (iii) becomes

$$\rho(r, r')C(r)T(r) = \rho(r, r)C(r')T(r'),$$

and we recapture the conditions of BCC. The force of infection term now becomes

$$B(r, t) = S(r, t)C(r) \int_0^\infty \int_0^\infty \beta(r, \tau, r')\rho(r, r', t) \frac{I(r', \tau, t)}{T(r', t)} \, dr' \, d\tau.$$

If β is independent of τ, we can integrate $I(r', \tau, t)$ over τ to get

$$B(r, t) = S(r, t)C(r) \int_0^\infty \beta(r, r')\rho(r, r') \frac{I(r', t)}{T(r', t)} \, dr',$$

where we write $I(r', t)$ for $\int_0^\infty I(r', \tau, t) \, d\tau$. This is the form of the force of infection term used by BCC.

In combining the special cases (I)–(II)–(III) with (IV)–(V)–(VI), we need to avoid conflicting situations. In particular, we cannot have both (I) and (IV) or (VI) holding, and we cannot have (II) and (V) or (VI) holding. However, we can have (I) and (V), and (II) and (IV), holding. There are strong conditions placed on $\bar\rho$ in (I) or (II) by the additional hypotheses (V) or (IV). For (I) and (V), we get $\bar\rho = \bar\rho(a, r')$, and using condition (iii) we must have $\bar\rho = \bar\rho(r')$ only. One solution for $\bar\rho$ is then

$$\bar\rho(r') = \frac{\displaystyle\int_0^\infty C(r', a')T(r', a', t) \, da'}{\displaystyle\iint_0^\infty C(r', a')T(r', a', t) \, dr' \, da'}.$$

Conditions (ii) and (iii) are then automatically satisfied. The force of infection term becomes

$$(I) + (V): \quad B(r, a, t) = \frac{S(r, a, t)C(r, a)}{\displaystyle\iint_0^\infty C(r', a')T(r', a', t) \, dr', \, da'}$$

$$\times \iiint_0^\infty \beta(r, a, \tau, r', a')C(r', a')I(r', a', \tau, t) \, dr', \, da' \, d\tau.$$

Similarly, from (II) + (IV) we get $\bar{\rho} = \bar{\rho}(a')$ only, and one solution for $\bar{\rho}$ then is

$$\bar{\rho}(a') = \frac{\int_0^\infty C(r', a')T(r', a', t)\,dr'}{\int\int_0^\infty C(r', a')T(r', a', t)\,dr'\,da'},$$

with force of infection term

(II) + (V): $B(r, a, t) = \dfrac{S(r, a, t)C(r, a)}{\int\int_0^\infty C(r', a')T(r', a', t)\,dr'\,da'}$

$$\times \int\int\int_0^\infty \beta(r, a, \tau, r', a')C(r', a')I(r', a', \tau, t)\,dr'\,da'\,d\tau,$$

which is identical to that obtained for (I) + (V).

4. General form of the interaction term

In the previous section, several special forms of the interaction term ρ were derived on the basis of constitutive assumptions concerning the pair formation mechanism. Here we pursue another path and examine the mathematical implications of the conditions (i)–(iv) on ρ. We will derive the general form of ρ and, in the process, also show that the particular forms of ρ that we discussed in the previous section enjoy certain special mathematical properties. The relations that we derive for ρ will allow us to construct a variety of different mixing/pairing functions without having to return to the basic axioms (i)–(iv).

Recall that one solution of (i)–(iv) is given by the total proportionate-mixing pairing function $\rho = \bar{\rho}$, where, for $(r, a, r', a) \notin \bar{\Xi}$,

$$\bar{\rho}(r, a, r', a', t) = \frac{C(r', a')T(r', a, t)}{\int\int_0^\infty C(u, v)T(u, v, t)\,du\,dv}. \tag{5}$$

Since the expression $C(r, a)T(r, a, t)$ will appear often in our computations, and since it can be treated as a parameter only, we use the simplified notation

$$f(r, a) = C(r, a)T(r, a, t), \tag{6}$$

where the variable t is suppressed in f for notational convenience. Thus, from (5),

$$\bar{\rho}(r, a, r', a') = \frac{f(r', a')}{\int\int_0^\infty f(u, v)\,du\,dv}. \tag{7}$$

A useful relation, which is obtained by integrating (iii) over the variables r' and a' and using condition (ii), is

$$C(r, a)T(r, a, t) = \int\int_0^\infty \rho(r', a', r, a)C(r', a')T(r', a', t) \, dr' \, da', \tag{8}$$

which we can also write as

$$f(r, a) = \int\int_0^\infty \rho(r', a', r, a)f(r', a') \, dr', \, da'. \tag{9}$$

A mixing function ρ is called *separable* if it can be written in the form

$$\rho(r, a, r', a') = \rho_1(r, a)\rho_2(r', a'). \tag{10}$$

The total proportionate mixing function $\bar{\rho}$ is separable, and our first result shows that there are no other separable mixing/pairing functions. Although the proof of this result has appeared in Busenberg & Castillo-Chavez (1989) it is repeated here, as proportionate mixing plays a fundamental role in our analysis.

THEOREM 4.1   *The only separable mixing function ρ satisfying conditions* (i)–(iv) *is the total proportionate mixing function $\bar{\rho}$ given by* (5).

Proof. Suppose that ρ is given by (10). Then, from (ii), outside the set Ξ, we have

$$\rho_1(r, a) = \frac{1}{\displaystyle\int\int_0^\infty \rho_2(r', a') \, dr', \, da'} = k \quad \text{(a constant)},$$

and therefore $\rho(r, a, r', a') = k\rho_2(r', a')$. Substituting this in (9), we obtain

$$f(r, a) = k\rho_2(r, a) \int\int_0^\infty f(r', a') \, dr' \, da'.$$

Hence,

$$k\rho_2(r, a) = \frac{f(r, a)}{\displaystyle\int\int_0^\infty f(r', a') \, dr' \, da'},$$

that is, $\rho = \bar{\rho}$. Since we have already shown that $\bar{\rho}$ satisfies (i)–(ii)–(iii) (and, incidentally, it vacuously satisfies (iv)), the proof is complete.   □

The next lemma will help in the construction of general mixing function ρ.

LEMMA 4.2   *The general solution ρ of* (i)–(ii)–(iii) *has the form*

$$\rho(r, a, r', a') = \bar{\rho}(r', a') + \psi(r, a, r', a'), \tag{11}$$

where ψ satisfies

$$\psi \geq -\bar{\rho}, \quad \int\int_0^{\infty} \psi(r, a, r', a')\,dr'\,da' = 0, \quad \int\int_0^{\infty} \psi(r', a', r, a)f(r', a')\,dr'\,da' = 0,$$

$$\psi(r, a, r', a')f(r, a) = \psi(r', a', r, a)f(r', a'). \tag{12}$$

Proof. These properties of ψ follow easily by substituting the form (11) into (i), (ii), (iii), and (7), and using the fact that both ρ and $\bar{\rho}$ must satisfy these relations. $\square$

The next result gives us a general representation formula for the mixing function ρ.

THEOREM 4.3 *Let* $\phi(r, a, r', a') \geq 0$ *be symmetric in the* (r, α) *and* (r', a') *variables*, $\phi(r, a, r', a') = \phi(r', a', r, a)$, *and let* $\int\int_0^{\infty} \bar{\rho}(r', a')\phi(r, a, r', a')\,dr'\,da' = 1$. *Then*

$$\rho(r, a, r', a') = \bar{\rho}(r', a')\phi(r, a, r', a') \tag{13}$$

is a mixing function. Conversely, every mixing function ρ *is given by the form* (13), *where* ϕ *is symmetric and satisfies the hypotheses of the theorem.*

Proof. Suppose that ϕ satisfies the hypotheses and ρ is given by (13). Then it is clear that $\rho \geq 0$, so (i) holds. Also (ii) holds automatically. Finally,

$$\rho(r, a, r', a')f(r, a) = \bar{\rho}(r', a')\phi(r, a, r', a')f(r, a)$$

$$= \bar{\rho}(r', a')\phi(r, a, r', a')\bar{\rho}(r, a)\int\int_0^{\infty} f(r, a)\,dr\,da$$

$$= \bar{\rho}(r, a)\phi(r', a', r, a)\bar{\rho}(r', a')\int\int_0^{\infty} f(r, a)\,dr\,da$$

$$= \bar{\rho}(r', a', r, a)f(r', a'),$$

so (iii) holds.

Conversely, let ρ be an arbitrary mixing function and let

$$\phi(r, a, r', a') = \begin{cases} 0 & \text{if } \bar{\rho}(r', a') = 0, \\ \rho(r, a, r', a')/\bar{\rho}(r', a') & \text{otherwise.} \end{cases}$$

Note that $\rho(r, a, r', a')$ vanishes outside the support of $f(r, a)f(r', a')$ by property (IV); hence, it vanishes where $\bar{\rho}(r', a') = 0$. Then, by (iii),

$$\rho(r, a, r', a')f(r, a) = \bar{\rho}(r', a')\phi(r, a, r', a')f(r, a) = \rho(r', a', r, a)f(r', a')$$

$$= \bar{\rho}(r, a)\phi(r', a', r, a)f(r', a').$$

Hence, $\phi(r, a, r', a') = \phi(r', a', r, a)$ since $\bar{\rho}(r', a')f(r, a) = \bar{\rho}(r, a)f(r', a')$.
Thus ϕ must be symmetric. Clearly, $\phi \geq 0$ by (i), and, outside $\mathfrak{S}$,

$$\int\int\limits_{0}^{\infty} \phi(r, a, r', a')\bar{\rho}(r', a') \, dr', \, da' = \int\int\limits_{0}^{\infty} \rho(r, a, r', a') \, dr' \, da' = 1.$$

This completes the proof. $\square$

Thus, in the construction of mixing functions, we seek to find non-negative symmetric functions which satisfy the integral condition in the hypotheses of the theorem. These symmetric functions are arbitrary except for this integral condition. Since we already have found several special forms for the mixing function ρ, we might seek an explicit formula allowing us to construct arbitrary mixing functions as perturbations of particularly convenient special forms. We will proceed to give such a representation. We start by noting that condition (iii) on ρ can be written as

$$\rho(r, a, r', a')\bar{\rho}(r, a) = \rho(r', a', r, a)\bar{\rho}(r', a').$$

Letting $\text{supp } \bar{\rho} = \{(r, a) \in \mathbb{R}^2_+ : \bar{\rho}(r, a) > 0\}$,   we note that, for all (r', a'), $\rho(r', a', r, a)\bar{\rho}(r', a') = 0$ if $(r, a) \notin \text{supp } \bar{\rho}$ and $\rho(r, a, r', a')\bar{\rho}(r, a) = 0$ for all (r, a) when $(r', a') \notin \text{supp } \bar{\rho}$. Thus, $\text{supp } \rho = \{(r, a, r', a') \in \mathbb{R}^4_+ : \rho(r, a, r', a') > 0\}$ and the set

$$\mathfrak{U} = \{(r, a, r', a') : (r, a) \in \text{supp } \bar{\rho} \text{ and } (r', a') \notin \text{supp } \bar{\rho};$$

$$\text{or } (r, a) \notin \text{supp } \bar{\rho} \text{ and } (r', a') \notin \text{supp } \bar{\rho}\}$$

satisfy

$$\text{supp } \rho \cap \mathfrak{U} = \varnothing.$$

However, in the context of our model, ρ can be assigned arbitrary non-negative values on the set $\hat{\mathfrak{U}} = \{(r, a, r', a') : (r, a) \notin \text{supp } \bar{\rho} \text{ and } (r', a') \notin \text{supp } \bar{\rho}\}$, since the activity level $f = cT$ is zero on $\bar{S}$. Thus, we can normalize ρ, without loss of generality, by requiring the following condition in addition to (i), (ii), and (iii):

(iv) $\text{supp } \rho \subset \{(r, a, r', a') : (r, a) \in \text{supp } \bar{\rho} \text{ and } (r', a') \in \text{supp } \bar{\rho}\} \equiv \mathcal{A}$.

Clearly, from (iv), $\rho(r, a, r', a') = 0$ if either $\bar{\rho}(r, a) = 0$ or $\bar{\rho}(r', a') = 0$. Henceforth, our mixing functions will satisfy (i)–(iv). These observations, together with the additional condition (iv), gives a useful representation formula for any mixing function ρ.

THEOREM 4.4   Let $\phi : \mathbb{R}^4_+ \to \mathbb{R}$ be measurable and jointly symmetric, i.e. $\phi(r, a, r', a') = \phi(r', a', r, a)$, and suppose that

$$\int\int\limits_{0}^{\infty} \bar{\rho}(r', a')\phi(r, a, r', a') \, dr' \, da' \leq 1,$$

and

$$\int\int\limits_{0}^{\infty} \bar{\rho}(r, a)\left(\int\int\limits_{0}^{\infty} \bar{\rho}(r', a')\phi(r, a, r', a') \, dr' \, da'\right) dr \, da < 1.$$

Let

$$\rho_1(r, a) = 1 - \int\!\!\int_0^\infty \bar{\rho}(r', a')\phi(r, a, r', a')\, dr'\, da'. \tag{14}$$

Then

$$\rho(r, a, r', a') = \bar{\rho}(r', a')\left(\frac{\rho_1(r, a)\rho_1(r', a')}{\int_0^\infty \int_0^\infty \bar{\rho}(r', a')\rho_1(r', a')\, dr'\, da'} + \phi(r, a, r', a')\right) \tag{15}$$

is a mixing function. Conversely, for every mixing function ρ, there exists a ϕ that satisfies the hypotheses of the theorem such that ρ is given by (15) with ρ_1 defined by (14).

Proof. Let ϕ satisfy the hypotheses of the theorem and define ρ_1 via (14). From (14), we get

$$\int\!\!\int_0^\infty \bar{\rho}(r', a')\rho_1(r, a)\, dr\, da = 1 - \int\!\!\int_0^\infty \bar{\rho}(r, a)\int\!\!\int_0^\infty \bar{\rho}(r', a')\phi(r, a, r', a')\, dr'\, da' > 0,$$

and ρ as given by (15) is well defined. The assumptions on ϕ and equation (13) imply that $\rho_1(r, a) > 0$ and thus that the mixing function ρ as given by (15) is greater than or equal to 0. Further, $\rho(r, a, r', a') = 0$ whenever $\bar{\rho}(r', a') = 0$, so $\rho(r, a, r', a')/\bar{\rho}(r', a')$ is well defined on the support of $\bar{\rho}$ and is jointly symmetric. Thus ρ satisfies conditions (iii) and (iv). Finally, from (14) and (15), ρ satisfies condition (ii), and hence it is a mixing function.

In order to prove the converse, we first note that condition (iv) implies that $\rho(r, a, r', a')/\bar{\rho}(r', a')$ is well defined and non-negative. Hence, conditions (i) and (ii) guarantee the existence of an $\varepsilon(r, a) > 0$ and a subset Q of $\mathbb{R}_+^4$ of positive measure such that $\rho/\bar{\rho} > \varepsilon(r, a)$ on Q. Further, since $\rho(r, a, r', a')/\bar{\rho}(r', a') = \rho(r', a', r, a)/\bar{\rho}(r, a)$ in $\mathscr{A}$ by (ii)–(iv), then $\rho(r', a', r, a)/\bar{\rho}(r, a) > \varepsilon(r, a)$ in subset Q. Hence the set Q is symmetric in (r, a) and (r', a'). We now let

$$\tilde{Q} = \{(r, a) : (r, a, r', a') \in Q \text{ for some } (r', a') \in \mathbb{R}_+^2\},$$

and let $\chi_{\tilde{Q}}$ denote the characteristic function of this set. Define

$$\rho_1(r, a) = \varepsilon\chi_{\tilde{Q}}(r, a)\int\!\!\int_0^\infty \chi_{\tilde{Q}}(u, v)\bar{\rho}(u, v)\, du\, dv,$$

$$\rho_1(r', a') = \varepsilon\chi_{\tilde{Q}}(r', a')\int\!\!\int_0^\infty \chi_{\tilde{Q}}(u, v)\bar{\rho}(u, v)\, du\, dv,$$

where ε, based on the above discussion, can be chosen independently of (r, a) and (r', a'). Then $\rho_1 \geq 0$ is measurable and

$$\frac{\rho_1(r, a)\rho_1(r', a')}{\int\!\!\int_0^\infty \bar{\rho}(r, a)\rho_1(r, a)\, dr\, da} = \varepsilon\chi_{\tilde{Q}}(r, a)\chi_{\tilde{Q}}(r', a'),$$

which is symmetric in (r, a) and (r', a'). If we now let

$$\phi(r, a, r', a') \equiv \frac{\rho(r, a, r', a')}{\bar{\rho}(r', a')} - \frac{\rho_1(r, a)\rho_1(r', a')}{\displaystyle\int\int_0^\infty \bar{\rho}(r, a)\rho_1(r, a)\, dr\, da} \cdot \frac{\rho(r, a, r', a')}{\bar{\rho}(r', a')}$$

$$- \frac{\rho_1(r, a)\rho_1(r', a')}{\displaystyle\int\int_0^\infty \bar{\rho}(r, a)\rho_1(r, a)\, dr\, da},$$

then ϕ is symmetric in (r, a) and (r', a'), that is, $\phi(r, a, r', a') = \phi(r', a', r, a)$, and (14) holds. Finally, from (14), we get

$$\int\int_0^\infty \bar{\rho}(r, a)\left(\int\int_0^\infty \bar{\rho}(r', a')\phi(r, a, r', a')\, dr'\, da'\right) dr\, da$$

$$= 1 - \int\int_0^\infty \bar{\rho}(r, a)\rho_1(r, a)\, dr\, da < 1,$$

and the proof is complete. $\square$

One especially interesting class of mixing functions comes from the choice $\phi(r, a, r', a') = \alpha\phi(r - a, r' - a')$, where ϕ is even in both variables jointly, $\alpha > 0$, and

$$\int\int_0^\infty \bar{\rho}(r', a')\phi(r - r', a - a')\, dr'\, da' < \infty.$$

Then (15) yields a mixing function, provided that

$$0 < [1 - \alpha\bar{\rho} * \phi(r, a)][1 - \alpha\bar{\rho} * \phi(r', a')]\alpha\phi(r - r', a - a')$$

$$\times \left(1 - \alpha\int\int\int\int_0^\infty \bar{\rho}(r, a)\bar{\rho}(r', a')\phi(r - r', a - a')\, dr\, da\, dr'\, da'\right), \quad (16)$$

where

$$\bar{\rho} * \phi(r, a) = \int\int_0^\infty \bar{\rho}(r', a')\phi(r - r', a - a')\, dr'\, da'. \quad (17)$$

This condition is satisfied whenever

$$1 - \alpha\bar{\rho} * \phi(r, a) > 0, \quad (18)$$

since $\alpha\phi \geq 0$ and (17) implies that the last term in (16) is positive. These observations yield the following corollary which is the age-structured version of the neighbourhood mixing function of BCC.

COROLLARY 4.5 *Let* $\phi \geqslant 0$, $\phi : \mathbb{R}^2 \to \mathbb{R}_+$ *be jointly even, i.e.* $\phi(r, a) = \phi(-r, -a)$, *and suppose that, for some* $\alpha > 0$,

$$\alpha \int\!\!\int_0^{\infty} \bar{\rho}(r', a')\phi(r - r', a - a')\, dr'\, da' < 1 \quad \text{for } r, a \in [0, \infty). \tag{19}$$

Then

$$\rho(r, a, r', a') = \bar{\rho}(r', a')\left(\frac{\rho_1(r, a)\rho_1(r', a')}{\displaystyle\int\!\!\int_0^{\infty} \bar{\rho}(r, a)\rho_1(r, a)\, dr\, da} + \alpha\phi(r - r', a - a') \right) \tag{20}$$

is a mixing function, where

$$\rho_1(r, a) = 1 - \alpha \int\!\!\int_0^{\infty} \bar{\rho}(r', a')\phi(r - r', a - a')\, dr'\, da'.$$

Theorems 4.3 and 4.4 and Corollary 4.5 can be used to construct mixing functions of varying degrees of complexity. We shall give examples of such functions in the next section.

Theorem 4.1 gave a mathematical characterization of the total proportionate mixing function appearing in case (III) of Table 1. There are similar characterizations of the other cases in that table. For example, the mixing function in case (II), proportionate activity mixing has the form

$$\rho(r, a, r', a') = \bar{\rho}(r, a, a')\bar{\rho}(r', a'), \tag{21}$$

and $\bar{\rho}$ is independent of the variable r'. Conversely, if we assume that

$$\rho(r, a, r', a') = \rho_1(r, a, a')\rho_2(r', a'), \tag{22}$$

then from (9) we obtain

$$f(r, a) = \rho_2(r, a) \int\!\!\int_0^{\infty} \rho_1(r', a', a)f(r', a')\, dr'\, da' = \rho_2(r, a)g(a).$$

Using this in (22), we get

$$\rho(r, a, r', a') = \frac{\rho_1(r, a, a')}{g(a)} f(r, a),$$

which implies that ρ is of the form given by (21), where

$$\bar{\rho}(r, a, a') = \frac{\rho_1(r, a, a')}{g(a)} \int\!\!\int_0^{\infty} f(u, v)\, du\, dv.$$

Thus the proportionate activity mixing term (21) is the unique mixing term with the separability property given in (22). Here uniqueness is modulo regrouping of terms in the product in (22) and the cancellation of common factors. Similar characterizations hold for the other cases given in Tables 1a and 1b.

The results in this section can be specialized to the case where there is no age structure in the population. In this simpler setting, they yield new results concerning the mixing function $\rho(r, r')$ studied by BCC. We give here two of these results that allow for the easier construction of mixing functions in this simpler setting that follows from assuming no age dependence in Theorems 4.3 and 4.4.

COROLLARY 4.6 $\rho(r, r')$ *is a mixing function if and only if there exists a symmetric function* $\phi(r, r') \leqslant 0$ *such that*

$$\int_0^\infty \rho(r')\phi(r, r')\,\mathrm{d}r' = 1.$$

and

$$\rho(r, r') = \bar{\rho}(r')\phi(r, r'). \tag{23}$$

COROLLARY 4.7   *Let* $\phi : \mathbb{R}_+^2 \to \mathbb{R}_+$ *be measurable and symmetric, and suppose that*

$$\int_0^\infty \bar{\rho}(r')\phi(r, r')\,\mathrm{d}r' \leqslant 1 \quad and \quad \int_0^\infty \bar{\rho}(r')\int_0^\infty \bar{\rho}(r')\phi(r, r')\,\mathrm{d}r'\,\mathrm{d}r \leqslant 1.$$

Letting

$$\rho_1(r) = 1 - \int_0^\infty \bar{\rho}(r')\phi(r, r')\,\mathrm{d}r', \tag{24}$$

we find that

$$\rho(r, r') = \bar{\rho}(r)\left(\frac{\rho_1(r)\rho_1(r')}{\displaystyle\int_0^\infty \bar{\rho}(r)\rho_1(r)\,\mathrm{d}r} + \phi(r, r')\right) \tag{25}$$

is a mixing function. Conversely, for every mixing function ρ, *there exists* ϕ *satisfying the above hypothesis such that* ρ *is given by* (25), *with* ρ_1 *defined by* (24).

5. Age- and risk-based model with variable infectivity: disease transmission in a single population

We now use some of the above observations to formulate the simplest single population model of the $S \to I$ type where there is no recovery from the disease. Since one of our main goals is to model the transmission of HIV, we begin with the more general model as dictated by the transfer diagram $S \to I \to A$, with A denoting those individuals with severe symptoms or with full-blown AIDS. In this section, we deal with a dynamic model of the transmission of HIV/AIDS in a single sexually-active homosexual male population. More general models, especially two-sex models, will be treated in the near future (see Section 6). We base our model on the following assumptions.

- There is a possibly varying recruitment rate Λ into the population.
- The population does not reproduce itself via birth.
- The population internal variables are $a =$ chronological age, $\tau =$ infection age (for the I and A groups), and $r =$ activity level.

With these assumptions. we obtain the following set of equations for $S(r, a, t)$, $I(r, a, \tau, t)$, and $A(r, a, \tau, t)$ describing the disease dynamics:

$$\frac{\partial S}{\partial t} + \frac{\partial S}{\partial a} + \mu(a)S = \Lambda(r, a, t, T(a, r, t)) - B(r, a, t), \tag{26}$$

$$\frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} + \frac{\partial I}{\partial \tau} + [\mu(a) + \xi(a, \tau) + \gamma(a, \tau)]I = 0, \tag{27}$$

$$\frac{\partial A}{\partial t} + \frac{\partial A}{\partial a} + \frac{\partial A}{\partial \tau} + [\mu(a) + \eta(a, \tau)]A = \gamma(a, \tau)I, \tag{28}$$

where

$$S(r, 0, t) = I(r, 0, \tau, t) = A(r, 0, \tau, t) = 0, \qquad I(r, a, 0, t) = B(r, a, t). \tag{29}$$

Here ξ and η denote the disease-induced mortalities, and γ is the rate of entry into the AIDS class. The other parameters are as previously defined, and $(t, a, \tau) \in \mathbb{R}^3_+$.

For this model. we have obtained a general expression which characterizes the basic reproductive number R_0 of the disease. The basic reproductive number is defined as the number of secondary infections generated by a 'typical' infectious individual in a population of susceptibles (for a recent discussion, see Diekmann et al., 1990). The basic reproductive number determines whether or not a disease can invade, and is therefore of utmost epidemiological importance. For arbitrary mixing functions, we cannot determine an explicit expression for R_0 and, therefore we provide only an implicit expression as described in the following discussion.

If $I \equiv A \equiv 0$, then we obtain the disease-free state $(S, 0, 0)$, where S satisfies

$$\frac{\partial S}{\partial t} + \frac{\partial S}{\partial a} + \mu(a)S = \Lambda(r, a, t). \tag{30}$$

If Λ is time independent, then $\Lambda(r, a, t) = \Lambda(r, a)$, and we obtain the steady-state disease-free solution $\bar{S}$ which satisfies

$$\frac{d\bar{S}}{dt} + \mu(a)\bar{S} = \Lambda(r, a), \tag{31}$$

and consequently.

$$\bar{S}(r, a) = \int_0^a \exp\left(-\int_x^a \mu(y)\, dy\right) \Lambda(r, x)\, dx. \tag{32}$$

We want to investigate the stability of $\bar{S}$ and how it is affected by the choice of mixing function ρ. For simplicity. we assume that C is not dependent on the population size; however, much of the analysis that follows extends directly to the case where C does depend on the population size. We note that equation (28) is decoupled from the first two. so we need only to study the system for S and I (equations (26)–(27)). At an endemic equilibrium $(S^*(r, a), I^*(r, a, \tau))$. the incidence rate is given by $B^*(r, a) = k^*(r, a, \rho^*)C(r, a)S^*(r, a)$. where ρ^*

denotes the mixing at equilibrium (i.e. evaluated at (S^*, I^*)) and

$$k^*(r, a, \rho^*) = \int\int_0^x \left(\int_0^{a'} \beta(r, a, \tau, r', a')\mathcal{F}(k^*, r, a, r', a') \, d\tau \right) dr' \, da', \qquad (33)$$

where $\mathcal{F} \equiv \mathcal{F}(k^*, r, a, r', a')$ denotes a nonlinear functional which depends on the particular mixing function ρ^*. Specifically, we have

$$\mathcal{F}(k^*, r, a, r', a') = \frac{\rho^*(r, a, r', a')I^*(r', a', \tau)}{S^*(r', a') + \int_0^x I^*(r', a', \tau) \, d\tau}. \qquad (34)$$

The equations for $S^*(r, a)$ and $I^*(r, a, \tau)$ are

$$\frac{dS^*}{dt} + \mu(a)S^* = \Lambda(r, a) - k^*(r, a, \rho^*)C(r, a)S^*, \qquad (35)$$

$$\frac{\partial I^*}{\partial a} + \frac{\partial I^*}{\partial \tau} + [\mu(a) + \varepsilon(a, \tau) + \gamma(a, \tau)]I^* = 0, \qquad (36)$$

$$I^*(r, a, 0) = k^*(r, a, \rho^*)C(r, a)S^*(r, a). \qquad (37)$$

Equation (35) has the solution

$$S^*(r, a) = \int_0^a \exp\left(-\int_x^a [\mu(y) + k^*(r, y, \rho^*)C(r, y)] \, dy\right) \Lambda(r, x) \, dx, \qquad (38)$$

which can now be substituted in equation (36) to yield a simple linear first-order partial differential equation for I^* which can be integrated along characteristics to yield

$$I^*(r, a, \tau) = \begin{cases} 0, & \text{if } a < \tau, \\ k^*(r, a - \tau, \rho^*)C(r, a - \tau)S^*(r, a - \tau) \\ \times \exp\left(-\int_0^\tau [\mu(a + \sigma - \tau) + \varepsilon(a + \sigma - \tau, \sigma) + \gamma(a + \sigma - \tau, \sigma] \, d\sigma\right) \\ \text{if } a > \tau, \end{cases}$$

$$(39)$$

where $S^*(r, a)$ is given by (38). We now substitute the expressions for S^* and I^* in (33), and note that the form of the nonlinear functional $\mathcal{F}$ depends on the particular mixing function ρ^* used in (33), but that it always has the property that

$$\mathcal{F}(0, r, a, r', a') = 0. \qquad (40)$$

Equation (33) determines the threshold for the existence of an endemic equilibrium solution. First, $k(r, a, \rho^*) \equiv 0$ is always a solution of (33) and this corresponds to the disease-free state. Any other non-negative solution of (33) corresponds to an endemic equilibrium. To gain further understanding of the role of the mixing function in the determination of endemic equilibria, it may be of value to study equation (33) for very specific mixing functions. This is particularly relevant as the recent results of Huang (1989), Huang *et al.* (1991), and Castillo-Chavez *et al.* (1989c, d) have shown that the existence of multiple endemic

equilibria may be due to the combined effects of variable population size and nonsymmetric mixing functions. In the following subsection we compute the threshold for the total proportionate mixing case.

5.1 Threshold for the Total Proportionate Mixing Case

In the total proportionate mixing case, we have

$$\rho(r, a, r', a', t) = \bar{\rho}(r', a', t) = \frac{C(r', a')T(r', a', t)}{\displaystyle\int\int_{0}^{\infty} C(u, v)T(u, v, t)\, du\, dv},$$

which, when substituted in (33) and upon using (38), yields

$$k^*(r, a, \rho^*)$$

$$= H \int\int_{0}^{\infty} \left(\int_{0}^{a'} \beta(r, a, \tau, r', a')C(r', a')I^*(r', a', \tau)\, d\tau\right) dr'\, da'$$

$$= H \int\int_{0}^{\infty} C(r', a')\left\{\int_{0}^{a'} \left[\beta(r, a, \tau, r', a')k^*(r', a' - \tau, \rho^*)C(r', a' - \tau)\right.\right.$$

$$\times \exp\left(-\int_{0}^{\tau} [\mu(a' + \sigma - \tau) + \varepsilon(a' + \sigma - \tau, \sigma) + \gamma(a' + \sigma - \tau, \sigma)]\, d\sigma\right)$$

$$\times \int_{0}^{a'-\tau} \exp\left(-\int_{x}^{a'-\tau} [\mu(y) + k^*(r', y, \rho^*)C(r', y)]\, dy\right) \Lambda(r', x)\, dx\right] d\tau\right\} dr'\, da',$$

(41)

where

$$\frac{1}{H} = \int\int_{0}^{\infty} C(r', a')$$

$$\times \left\{\int_{0}^{a'} \exp\left(-\int_{x}^{a'} [\mu(y) + k^*(r', y, \rho^*)C(r', y)]\, dy\right) \Lambda(r', x)\, dx\right.$$

$$+ \int_{0}^{\infty} \left[k^*(r', a' - \tau, \rho^*)C(r', a' - \tau)\right.$$

$$\times \int_{0}^{a'-\tau} \exp\left(-\int_{x}^{a'-\tau} [\mu(y) + k^*(r', y, \rho^*)C(r', y)]\, dy\right) \Lambda(r', x)\, dx$$

$$\times \exp\left(-\int_{0}^{\tau} [\mu(a' + \sigma - \tau) + \varepsilon(a' + \sigma - \tau, \sigma) + \gamma(a' + \sigma - \tau, \sigma)]\, d\sigma\right)\right] d\tau\right\} dr'\, da'.$$

(42)

The expression on the right-hand side of (41) is fairly complicated; however, it is still possible to derive explicit conclusions from it. Clearly, $k \equiv 0$ is a solution of (41)–(42), and yields the disease-free equilibrium. One case that can be

completely analysed is when

$$\beta(r, a, \tau, r', a') = \beta(\tau, r', a'),$$

that is, the probability of acquiring the disease, given that contact has occurred, does not depend on the age or activity level of the susceptible. In this case, k^* is independent of r and a and can be factored out of the integrals to reduce (41) to

$$
1 = H \int\int_0^{\infty} C(r', a')
$$

$$
\times \left\{ \int_0^{a'} \left[\int_0^{a'-\tau} \exp\left(-k^* \int_x^{a'-\tau} C(r', y)\, dy - \int_x^{a'-\tau} \mu(y)\, dy \right) \Lambda(r', x)\, dx \right. \right.
$$

$$
\times \beta(\tau, r', a') C(r', a' - \tau) \exp\left(- \int_0^{\tau} [\mu(a' + \sigma - \tau) \right.
$$

$$
\left. + \varepsilon(a' + \sigma - \tau, \sigma) + \gamma(a' + \sigma - \tau, \sigma)]\, d\sigma \right) \right] d\tau \Big\} dr'\, da'
$$

$$
\equiv R(k^*). \tag{43}
$$

From (43), it follows that, if $R(0) = R_0 > 1$, where

$$
R_0 = \left\{ \int\int_0^{\infty} C(r', a') \left[\int_0^{a'} \exp\left(- \int_x^{a'} \mu(y)\, dy \right) \Lambda(r', x)\, dx \right] dr'\, da' \right\}^{-1}
$$

$$
\times \int\int_0^{\infty} C(r', a') \left\{ \int_0^{a'} \left[\int_0^{a'-\tau} \exp\left(- \int_x^{a'} \mu(y)\, dy \right) \Lambda(r', x)\, dx\, \beta(\tau, r', a') C(r', a' - \tau) \right. \right.
$$

$$
\left. \times \exp\left(- \int_0^{\tau} [\mu(a' + \sigma - \tau) + \varepsilon(a' + \sigma - \tau, \sigma) + \gamma(a' + \sigma - \tau, \sigma)]\, d\sigma \right) \right] d\tau \Big\} dr'\, da',
$$

$$
\tag{44}
$$

then there exists a $k > 0$ satisfying (43) provided that $C(r, a)$ is not identically zero. Equation (44) provides an explicit expression for the endemic threshold or basic reproductive number R_0.

The basic reproductive number allows us to study the effects of demographic and epidemiological parameters in disease transmission. For example, since R_0 is given by three types of risk- and age-dependent expressions – those involving death-adjusted 'recruitment', those involving time spent in the infectious state (appropriately weighted by infectivity), and those involving average sexual activity – it follows that any uniform increase in these expressions (i.e. any increase in the incubation period, in the mean number of sexual partners, or in the recruitment of susceptibles) will generate an increase in the reproductive number. However, a change in any of these parameters, which represents an average increase over old age and activity classes, need not lead to an increase in R_0, and in fact may cause R_0 to decrease owing to the close coupling between these epidemiological parameters and the age- and activity-dependent de-

mographic parameters. The results concerning uniform increases agree in principle with those found for reproductive numbers for age-independent homogeneously mixing models in which the reproductive number is given as the product of three factors: the mean infectious period, the mean number of sexual partners per unit time, and the average infectivity (see Anderson & May, 1987; Busenberg & Castillo-Chavez, 1989). Also note that the reproductive number, in models in which the mean number of sexual partners depends on the 'recruitment' rate, is a nondecreasing function of this rate (see Busenberg *et al.*, 1989; Castillo-Chavez *et al.*, 1989a, b, c; Thieme & Castillo-Chavez, 1989, 1991), but the lack of an age and activity-level structure makes it impossible to use these simpler age and activity-independent models in the fine tuning and testing of specific control measures. The expression for R_0, given by equation (44), lets us look at the effects of potential control measures that are targeted to individuals of specific age and activity levels.

6. Conclusion

In this paper, we have extended the mixing framework of BCC through the incorporation of age structure, and have found the general solution to the mixing problem for a sexually active homosexual population. This general solution, as well as a number of other results, are new even in the simpler context where there is no age dependence. We have clarified the role of proportionate mixing by showing that it is the only separable solution, and have formulated a general epidemic model for a single age-dependent sexually active homosexual population with distributed activity levels. An explicit expression for the reproductive number for the special case of proportionate mixing has been determined.

Our results show that the reproductive number is a complex nonlinear function of the mixing. Future clarification of the role of the mixing function on the reproductive number may be accomplished by analysing models with specific simple mixing functions (such as those specified in Section 3 or in BCC) and convex linear combinations of them. Some preliminary work in this direction has already begun (see Nold, 1980; Jacquez *et al.*, 1988; BCC; Busenberg & Castillo-Chavez 1989; Castillo-Chavez *et al.*, 1989c; Gupta *et al.*, 1989; Huang, 1989; Huang *et al.*, 1991).

Andrea Pugliese remarks that our mixing framework can be easily generalized to include geographical variability by assuming that each neighbourhood has its own mixing function $p^j(r, a, r', a')$, which now denotes the proportion of contacts between 'typical' (r, a) individuals at neighbourhood j with 'typical' (r', a') individuals. Each of these 'localized' mixing functions satisfies the mixing axioms and hence can be expressed through our representation theorem. In addition, the spatial movement of individuals has to be specified with a migration or movement matrix such as those found in the work of Sattenspiel (1987a, b) and Sattenspiel & Simon (1988). This general framework may be very useful in theoretical considerations; however, its applicability to specific situations is probably extremely limited because of the tremendous number of parameters involved.

The extension of the above framework to two-sex populations is straightforward. We have already determined the general solution to the corresponding two-sex framework (see Castillo-Chavez & Busenberg, 1991; Castillo-Chavez et al., 1991). Our formulation of this two-sex framework (along the lines of the one-sex framework described in this paper) provides an alternative formulation to the problem of pairing (see Dietz & Hadeler, 1988). Models that consider pairs and follow the dynamics of pairs have been studied by Kendall (1949), Fredrickson (1971), Dietz & Hadeler (1988), Dietz (1988), Hadeler (1989a, b), a d Waldstätter (1989). We have formulated analogous models that utilize solutions of our two-sex framework. Our approach (one- and two-sex formulations) has perhaps the added advantage that it allows direct comparison of the dynamics of disease in models that follow pairs and those that do not (i.e. the duration of each partnership is zero) through the use of equivalent pairing (mixing) functions.

Several special solutions to the mixing/pair-formation problem have been proposed (for a review of some of the literature, see Schwager et al., 1989; Sattenspiel & Castillo-Chavez, 1990). In Blythe & Castillo-Chavez (1990a), a table that shows the relationship between these particular solutions and the general solution is provided; specifically formulae for the corresponding ϕ's are provided. In Blythe & Castillo-Chavez (1990b), and Castillo-Chavez & Blythe (1990), specific implementations of the general mixing solution in the context of SIS models are provided.

In the framework presented in this article, we have assumed that all subpopulations interact with each other, that is, that all groups are connected. In Castillo-Chavez & Busenberg (1991), a generalization is provided for disconnected subpopulations (for the case of purely heterosexual populations). A general formulation involving any connectance structure has been provided by Blythe (1990).

Some recent work (Blythe & Castillo-Chavez, 1990; Castillo-Chavez & Busenberg, 1991; Blythe et al., 1991a) has implemented the framework of this paper in population genetics; investigated the connections between our mixing framework and that of Kendall (1949), Fredrickson (1971), McFarland (1972), and Dietz & Hadeler (1988); and has compared the results of stochastic simulations with deterministic mixing functions. Finally, some work has begun on the estimation of these mixing/pair-formation functions (see Blythe et al., 1991b).

REFERENCES

ANDERSON, R. M. 1988 The role of mathematical models in the study of HIV transmission and the epidemiology of AIDS. *J. AIDS* **1**, 241–56.

ANDERSON R. M. 1989 Editorial review: Mathematical and statistical studies of the epidemiology of HIV. *AIDS* **3**, 333–46.

ANDERSON R. M., BLYTHE, S. P., GUPTA, S., & KONINGS, E. 1989 The transmission dynamics of the human immunodeficiency virus type 1 in the male homosexual community in the United Kingdom: The influence of changes in sexual behaviour. *Phil. Trans. R. Soc. Lond.* B **325**, 145–98.

ANDERSON R. M., & MAY, R. M. 1987 Transmission dynamics of HIV infection. *Nature* **326**, 137–42.

BLYTHE, S. P. 1990 Heterogeneous sexual mixing in populations with arbitrarily connected multiple groups. *Math. Pop. Stud.*, to appear.

BLYTHE, S. P., & CASTILLO-CHAVEZ, C. 1989 Like-with-like preference and sexual mixing models. *Math. Biosci.* **96**, 221–38.

BLYTHE, S. P., & CASTILLO-CHAVEZ, C. 1990a The one-sex mixing problem: a choice of solutions? *J. Math. Biol.*, in the press.

BLYTHE, S. P., & CASTILLO-CHAVEZ, C. 1990b Like-with-like mixing and sexually transmitted disease epidemics in one-sex populations. Biometrics Unit Technical Report BU-1078-M, Cornell University.

BLYTHE, S. P., & CASTILLO-CHAVEZ, C. 1990c Scaling of sexual activity. *Nature* **344**, 202.

BLYTHE, S. P., CASTILLO-CHAVEZ, C., & CASELLA, G. 1991a Empirical methods for the estimation for the mixing probabilities for socially structured populations from a single survey sample. Biometrics Unit Technical Report BU-1072-M, Cornell University.

BLYTHE, S. P., CASTILLO-CHAVEZ, C., PALMER, J., & CHENG, M. 1991b Towards a unified theory of mixing and pair formation. Biometrics Unit Technical Report BU-1106-M, Cornell University.

BUSENBERG, S., & CASTILLO-CHAVEZ, C. 1989 Interaction, pair formation and force of infection terms in sexually transmitted diseases. In: *Mathematical and Statistical Approaches to AIDS Epidemiology* (C. Castillo-Chavez. ed.), Lecture Notes in Biomathematics 83. New York: Springer, pp. 289–300.

CASTILLO-CHAVEZ, C. 1989a Some applications of structured models in population dynamics. In: *Applied Mathematical Ecology* (S. A. Leven, T. G. Hallam, & L. J. Gross, eds.), Biomathematics 18. New York: Springer, pp. 450–70.

CASTILLO-CHAVEZ, C. (ed.) 1989b *Mathematical and Statistical Approaches to AIDS Epidemiology*, Lecture Notes in Biomathematics 83. New York: Springer.

CASTILLO-CHAVEZ, C., & BLYTHE, S. P. 1989 Mixing framework for social/sexual behavior. In: *Mathematical and Statistical Approaches to AIDS Epidemiology* (C. Castillo-Chavez, ed.), Lecture Notes in Biomathematics 83. New York: Springer, pp. 275–88.

CASTILLO-CHAVEZ, C., & BLYTHE, S. P. 1991 A 'test-bed' procedure for evaluating one-sex mixing frameworks. Biometrics Unit Technical Report BU-1077-M, Cornell University.

CASTILLO-CHAVEZ, C., & BUSENBERG, S. 1991 On the solution of the two-sex problem. In: *Proc. Int. Conf. Differential Equations and Applications to Biology and Population Dynamics* (S. Busenberg & M. Martelli, eds.), Lecture Notes in Biomathematics. Berlin: Springer, in the press.

CASTILLO-CHAVEZ, C., BUSENBERG, S., & GEROW, K. 1991 Pair formation in structured populations. In: *Differential Equations with Applications in Biology, Physics and Engineering* (J. Goldstein, F. Kappel, & W. Schappacher, eds.). New York: Marcel Dekker, in the press.

CASTILLO-CHAVEZ, C., COOKE, K., HUANG, W., & LEVIN, S. A. 1989a On the role of long periods of infectiousness in the dynamics of acquired immunodeficiency

syndrome (AIDS). In: *Mathematical Approaches to Problems in Resource Management and Epidemiology* (C. Castillo-Chavez, S. A. Levin, & C. Shoemaker, eds.), Lecture Notes in Biomathematics 81. New York: Springer, pp. 177–89.

CASTILLO-CHAVEZ, C., COOKE, K., HUANG, W., & LEVIN, S. A. 1989b On the role of long incubation periods in the dynamics of acquired immunodeficiency syndrome (AIDS). Part 1. Single population models. *J. Math. Biol.* **27**, 373–98.

CASTILLO-CHAVEZ, C., COOKE, K., HUANG, W., & LEVIN, S. A. 1989c Results on the dynamics for models for the sexual transmission of the human immunodeficiency virus. *Appl. Math. Lett.* **2** (4), 327–31.

CASTILLO-CHAVEZ, C., COOKE, K., HUANG, W., & LEVIN, S. A. 1989d On the role of long incubation periods in the dynamics of acquired immunodeficiency syndrome (AIDS). Part 2. Multiple group models. In: *Mathematical and Statistical Approaches to AIDS Epidemiology* (C. Castillo-Chavez, ed.), Lecture Notes in Biomathematics 83. New York: Springer, pp. 200–217.

CASTILLO-CHAVEZ, C., HETHCOTE, H. W., ANDREASEN, V., LEVIN, S. A., & LIU, W. M. 1988 Cross-immunity in the dynamics of homogeneous and heterogeneous populations. In: *Mathematical Ecology.* (L. Gross, T. G. Hallam, & S. A. Levin, eds.), Proc. Autumn Course Research Seminars, Trieste. Singapore: World Scientific, pp. 303–16.

CASTILLO-CHAVEZ, C., HETHCOTE, H. W., ANDREASEN, V., LEVIN, S. A., & LIU, W. M. 1989e Epidemiological models with age structure, proportionate mixing, and cross-immunity. *J. Math. Biol.* **27**, 233–58.

COOKE, K. L., ALLERS, D. A., & CASTILLO-CHAVEZ, C. 1991 Mixing patterns and multiple endemic states in models of AIDS. In: *Proc. 2nd Int. Conf. Differential Equations and their Applications*, Rutgers (Ovide Arino, ed.). In the press.

DIEKMANN, O., HEESTERBEEK, J. A. P., & METZ, J. A. J. 1990 On the definition of R_0 in models for infectious diseases in heterogeneous populations. *J. Math. Biol.*, in the press.

DIETZ, K. 1988 On the transmission dynamics of HIV. *Math. Biosci.* **90**, 397–414.

DIETZ, K., & HADELER, K. P. 1988 Epidemiological models for sexually transmitted diseases. *J. Math. Biol.* **26**, 1–25.

FRANCIS, D. F., FEORINO, P. M., BRODERSON, J. R., McCLURE, H. M., GETCHELL, J. P., McGRATH, C. R., SWENSON, B., McDOUGAL, J. S., PALMER, E. L., HARRISON, A. K., BARRÉ-SINOUSSI, F., CHERMANN, J. C., MONTAGNIER, L., CURRAN, J. W., CABRADILLA, C. D., & KALYANARAMAN, V. S. 1984 Infection of chimpanzees with lymphadenopathy-associated virus. *Lancet* ii, 1276–77.

FREDERICKSON, A. G. 1971 A mathematical theory of age structure in sexual populations: Random mating and monogamous marriage models. *Math. Biosci.* **20**, 117–43.

GEL'FAND, I. M., & SHILIV, G. E. 1964 *Generalized Functions*, Vol. 1, New York: Academic Press.

GUPTA, S., ANDERSON, R. M., & MAY, R. M. 1989 Networks of sexual contacts: Implications for the pattern of spread of HIV. *AIDS* **3**, 1–11.

HADELER, K. P. 1989a Pair formation in age-structured populations. *Acta Applicandae Mathematicae* **14**, 91–102.

HADELER, K. P. 1989b Modeling AIDS in structured populations. Invited paper of the 47th Biennial Session of the International Statistical Institute, Paris.

HETHCOTE, H. W., & YORKE, J. A. 1984 *Gonorrhea Transmission Dynamics and Control*, Lecture Notes in Biomathematics 56. New York: Springer.

HUANG, W. 1989 Studies in differential equations and applications. Ph.D. thesis, The Claremont Graduate School, Claremont, California.

HUANG, W., COOKE, K., & CASTILLO-CHAVEZ, C. 1991 Stability and bifurcation for a multiple group model for the dynamics of HIV/AIDS transmission. *SIAM J. Appl. Math.*, in the press.

HYMAN, J. M., & STANLEY, E. A. 1988 A risk-based model for the spread of the AIDS virus. *Math. Biosci.* **90**, 415–73.

HYMAN, J. M., & STANLEY, E. A. 1989 The effect of social mixing patterns on the spread of AIDS. In: *Mathematical Approaches to Problems in Resource Management and Epidemiology* (C. Castillo-Chavez, S. A. Levin, & C. Shoemaker, eds.), Lecture Notes in Biomathematics 81. New York: Springer, pp. 190–9.

JACQUEZ, J. A., SIMON, C. P., KOOPMAN, J., SATTENSPIEL, L., & PERRY, T. 1988 Modelling and analyzing HIV transmission: The effect of contact patterns. *Math. Biosci.* **92**, 119–99.

KENDALL, D. G. 1949 Stochastic processes and population growth. *J. R. Statist. Soc.* Ser. B **2**, 230–64.

LANGE, J. M. A., PAUL, D. A., HUISMAN, H. G., DE WOLF, F., VAN DEN BERG, H., ROIEL, C. A., DANNER, S. A., VAN DER NOORDAA, J., & GOUDSMIT, J. 1986 Persistent HIV antigenaemia and decline of HIV core antibodies associated with transition to AIDS. *Br. Med. J.* **293**, 1459–62.

McFARLAND, D. D. 1972 Comparison of alternative marriage models. In: *Population Dynamics* (T. N. E. Greville, ed.). New York: Academic Press pp. 89–106.

MAY, R. M., & ANDERSON, R. M. 1989 The transmission dynamics of human immunodeficiency virus (HIV). *Phil. Trans. R. Soc. Lond.* B **321**, 565–607.

NOLD, A. 1980 Heterogeneity in disease-transmission modeling. *Math. Biosci.* **52**, 227–40.

SALAHUDDIN, S. Z., GROOPMAN, J. E., MARKHAM, P. D., SARNGAHARAN, M. G., REDFIELD, R. R., McLANE, M. F., ESSEX, M., SLISKI, A., & GALLO, R. C. 1984 HTLV-III in symptom-free seronegative persons. *Lancet* ii, 1418–20.

SATTENSPIEL, L. 1987a Population structure and the spread of disease. *Hum. Biol.* **59**, 411–38.

SATTENSPIEL, L. 1987b Epidemics in nonrandomly mixing populations: a simulation. *Am. J. Phys. Anthropol.* **73**, 251–65.

SATTENSPIEL, L., & CASTILLO-CHAVEZ, C. 1990 Environmental context, social interactions, and the spread of HIV. *Am. J. Hum. Biol.* **2**, 397–417.

SATTENSPIEL, L., & SIMON, C. P. 1988 The spread and persistence of infectious diseases in structured populations. *Math. Biosci.* **90**, 341–66.

SCHWAGER, S. J., CASTILLO-CHAVEZ, C., & HETHCOTE, H. 1989 Statistical and mathematical approaches in HIV/AIDS modeling: a review. In: *Mathematical and Statistical Approaches to AIDS Epidemiology* (C. Castillo-Chavez, ed.), Lecture Notes in Biomathematics 83. New York: Springer, pp. 2–37.

SCHWARTZ, L. 1966 *Théorie des distributions*. Paris:Hermann.

THIEME, H. R., & CASTILLO-CHAVEZ, C. 1989 On the role of variable infectivity in the dynamics of the human immunodeficiency virus. In: *Mathematical and Statistical Approaches to AIDS Epidemiology* (C. Castillo-Chavez, ed.), Lecture Notes in Biomathematics 83. New York: Springer, pp. 157–77.

THIEME, H. R., & CASTILLO-CHAVEZ, C. 1991 On the possible effects of infection-age-dependent infectivity in the dynamics of HIV/AIDS. Submitted to *SIAM J. Appl. Math.*

WALDSTÄTTER, R. 1989 Pair formation in sexually transmitted diseases. In: *Mathematical and Statistical Approaches to AIDS Epidemiology* (C. Castillo-Chavez, ed.), Lecture Notes in Biomathematics 83. New York: Springer, pp. 260–74.