Limit Behavior of Pair Formation for A Large Dissolution Rate

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ABSTRACT

Considerable amount of research has been conducted on the general theory of stochastic epidemic models. Recently, in the study of the transmission dynamics of sexually-transmitted diseases (STD's), emphasis has been put not only on individuals but also on pairs of individuals. STD's cannot been transmitted between non-infected individuals, consequently, non-infected pairs provide temporary periods of immunity which can have substantial effect on disease dynamics. In this article, we formulate a pair-formation stochastic model that provides a generalization of the general epidemic model. Our model can be formulated as a process in which the transmission rates associated with pair-formation, pair dissolution, and infection can be realized as a Markov process. Furthermore, by providing the the appropriate semi-group characterization of this stochastic processes, we make the mathematical results and the analytic tools developed for Markov processes available for the study of pair-formation models for STD's. Finally, we show the connection between classical processes and pair-formation models.

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1. Introduction

The mathematical theory of epidemics began with the work of Bernoulli (1760). In 1889, the Russian Physician P. D. En'ko (see Dietz 1988a) constructed the first binomial model (wrongly attributed to Reed). The so-called Reed-Frost models are still widely used in the fields of theoretical and applied epidemiology. Sir Ronald Ross (1991) (but see also the work of Brownlee, 1907; MacKendrick 1912, 1926) introduced the mass-action law in epidemiology, the concept of an epidemiological threshold, and the first mathematical model for the spread of vector-transmitted diseases (malaria). In his writings, Ross discussed the potential consequences of non-homogeneous mixing, demography, seasonality, genetic variability, and geographical distribution on disease dynamics. Ross understood the effects on mixing of interacting populations with variable population size. Furthermore, he was completely aware that his modeling approach for vector-transmitted diseases was applicable (that is mathematically equivalent) to the study of the transmission dynamics of STD's. Despite the efforts of Ross, most mathematical models for STD's ignored the role of variable population size and its role on mixing. Practical and theoretical questions associated with the study of the dynamics of the HIV/AIDS epidemic have brought the issues associated with heterogeneity in mixing to 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(1988b), Blythe and Castillo-Chavez (1989), Castillo-Chavez and Blythe (1989), Busenberg and Castillo-Chavez (1989, 1991), Castillo-Chavez and Busenberg (1991), Castillo-Chavez *et al.* (1991, 1992), and Blythe *et al.* (1991) have raised important questions as to the appropriateness of classical epidemic models in addressing the effects of heterogeneity in disease dynamics. The situation is quite similar in the clas-

sical stochastic epidemiological literature although some important efforts in this direction are being developed. Lefevre and Picard (1990) introduce a multipopulation general epidemic model to study nonhomogeneous mixing, however, they assume that group-specific contact rates are constant and ignore the dynamics of pairs.

In this manuscript, we provide a realistic and flexible stochastic framework for the spread of STD's that incorporate the dynamics of pairs. The development of our epidemic models is based on methods common to percolation and interacting particle systems (see Liggett, 1985) as implemented – in spatially dominated epidemic processes – by Cox and Durrett (1988).

2. Model Formulation

We begin with a multipopulation epidemic model. Suppose the total population consists of $L + N$ homogeneous groups indexed by $m_1, m_2, ...,$ m_L; $f_1, f_2, ..., f_N$. Here m_i denotes the i-th group of males and f_j denotes the j-th group of females. Each group consists of susceptibles and infectives. Each infective may be removed permanently because of death from the disease at a rate depending on the group index. In the model of Lefevre and Picard (1990), each pair of individuals contact each other at a rate that also depends on their group indexes. After contact–in Lefevre and Picard's model–each pair is immediately dissolved and susceptibles become infected if their partners are infected. The epidemic ends when there are no more infectives in the population.

The model in this paper extends the general stochastic epidemic model by adding the dynamics of pairs. We have the same $L + N$ groups of males and females indexed by $m_1, m_2, ..., m_L$ and $f_1, f_2, ..., f_N$ respectively. At each step in this process individuals may remain single or paired. Homosexually active couples are allowed within our modeling framework. Each

individual can either be susceptible (status 0) or infectives (status 1).

Our model makes use of a multidimensional random process $\{\xi_t : t \geq 0\}$. The components of ξ_t are the number of singles or pairs of each type at time t . The detailed indexing of this process is provided later in this article. At this point, it suffices to say that ξ_t contains the following information: (1) The number of (m_i, f_j)-pairs, i.e., the pair involving a male from i-th group and female from j-th group; (2) The number of $(m_i, m_{i'})$-pairs, i.e., the pair involving a male from i-th group and male from i'-th group; (3) The number of $(f_j, f_{j'})$-pairs, i.e., the pair involving a female from j-th group and female from j'-th group; (4) The number of single males in i-th group; (5) The number of single females from the j-th group; (6) All individuals are classified also by their epidemiological status. For example, for an (m_i, f_j)-pair, we need to record the epidemiological status of each member of the pair. Single individuals need also to be classified by their epidemiological status as ξ_t will record the total number of susceptible and infective individuals of each type at time t.

To describe ξ_t, we index the components of ξ_t or more abstractly the general configuration ξ in terms of demographic types (singles or pairs) with their attached epidemiological status. Here we are dealing with a finite number of types. These types are called sites as we borrow the terminology associated with interacting particle systems. The number attached to each site gives the number of pairs or the number of singles of the type or types associated with the site. For $\nu = 0$ or 1, we use (f_j, ν) to denote the type of singles from the f_j group with status ν. Similarly, we use $(m_i, \mu; f_j, \nu)$ to denote the type of pairs of males from group m_i with status μ and females from group f_j in status ν, $(m_i, \mu; m_{i'}, \mu')$ for the pairs of males where one is from group m_i with status μ and the other is from group $m_{i'}$ with status

μ' and $(f_j, \nu; f_{j'}, \nu')$ for the pairs of females where one is from group f_j with status ν and the other is from group $f_{j'}$ with status ν'. Let S denote the set of all such types. Then, ξ_t, as a vector with indexes in S, is a function on S with values in $Z^+ = \{0, 1, 2, ...\}$. If $s \in S$, $\xi_t(s)$ is the value of ξ_t at component s. If X denote the set of all such functions on S and if $|S|$ denotes the number of members in S then X is just a subset of a $|S|$ dimensional lattice. As time t changes, singles may form pairs and pairs may dissolve and a disease may be transmitted (in pairs). The system $\{\xi_t\}$ can be seen as a series of changing elements in the set X. Each element of X is a possible state of the system.

The dynamics of the system is described by the rates at which the system changes. These rates are a set of nonnegative numbers $\{c(\xi, \eta) : \xi \neq \eta, \xi, \eta \in X\}$. Each $c(\xi, \eta)$ is the rate at which the system changes from ξ to η, i.e.,

$$P(\xi_{t+h} = \eta | \xi_t = \xi) = c(\xi, \eta)h + o(h), \forall t \geq 0$$

In Section 3, we specify these rates for a multipopulation general epidemic model and an epidemic model with pairing. The main mathematical results of the general model interpreted as a Markov process through its semigroup characterization are presented in Section 4. The construction of the process with its mathematical formalization are given in the appendix. In Section 5, we show that the general epidemic model can be viewed as the limit of our pair formation models when the dissolution rates tend to infinity.

3. Model/Framework Formulation: Special Cases

In this section, we give two specified version of our model before introducing the most general models. Suppose S and X are as in Section 2. The change transition, or flip rates for the system is given by the set of

nonnegative numbers $\{c(\xi,\eta) : \xi \neq \eta, \xi, \eta \in X\}$. For $\xi \in X, A, B \subset S$ and $A \cap B = \emptyset$, we define $\xi_B^A \in X$ as

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

If we think of ξ as a finite dimensional vector with components indexed through members in S, then ξ_B^A is another finite dimensional vector. ξ_B^A is obtained from ξ in the following way: we add 1 to those components with index in (index) set A and subtract 1 to those components with index in (index) set B. For example, if we let $A = \{(m_1, 0; f_2, 1)\}$ and $B = \{(m_1, 0), (f_2, 1)\}$, then ξ_B^A accounts for the fact that a susceptible male from group m_1 and an infective female from group f_2 form a pair (have a sexual contact) and there is no disease transmission. For simplicity, we discard the brace and write , for example, $\xi^{(m_1,0;f_2,1)}_{(m_1,0),(f_2,1)} = \xi^{\{(m_1,0;f_2,1)\}}_{\{(m_1,0),(f_2,1)\}}$. Thus, $\xi^{(m_1,1;f_2,1)}_{(m_1,0),(f_2,1)}$ accounts for the fact that a susceptible male from group m_1 and an infective female from group f_2 form a pair (have a sexual contact) and there is disease transmission.

General Epidemic Model Suppose $\delta_{m_i}(\delta_{f_j})$ denotes the death rate of an infective male (female) from group $m_i(f_j)$ and β_{m_i,f_j} , $\beta_{m_i,m_{i'}}$, $\beta_{f_j,f_{j'}}$ denote the contact rates between male-female, male-male and female-female respectively. Furthermore, let

$$c(\xi, \xi_{(m_i,1)}) = \delta_{m_i}\xi((m_i,1))$$

$$c(\xi, \xi_{(f_j,1)}) = \delta_{f_j}\xi((f_j,1))$$

$$c(\xi, \xi^{(g,\mu\vee\nu),(h,\mu\vee\nu)}_{(g,\mu),(h,\nu)}) = \beta_{g,h}\xi((g,\mu))\xi((h,\nu)), \mu \neq \nu$$

$$c(\xi,\eta) = 0, \text{ else}$$

where $g, h \in \{m_1, m_2, ..., m_L; f_1, f_2, ..., f_N\}$, $\mu, \nu \in \{0, 1\}$ and $\mu \vee \nu$ denote the maximum of μ and ν. Then, $\{\xi_t\}$ gives the multipopulation general epidemic process described by Lefevre and Picard (1990).

Epidemic Model with Pairing In this model, the contact rate used in the general epidemic model is decomposed into two to include pairing with possible immediate infection and pairing without immediate transmission. Furthermore, pairs are allowed to dissolve. As in the general epidemic model, an infective male(female) from group $m_i(f_j)$ dies at rate $\delta_{m_i}(\delta_{f_j})$. Individuals from group g and h (g and h can be any m_i or f_j) form pairs at the rate $\beta_{g,h}$. When one member of a pair is infective and the other is not, the probability that infection takes place is $\alpha_{g,h}$, while $g - h$ pair divorce at the rate $\sigma_{g,h}$. The epidemic ends, as in the general epidemic model, as soon as there are no more infectives in all groups. However, the process does not terminate in this case because the processes of pair formation and dissolution continue. A deterministic analog of this model can be found in Dietz(1988b). This epidemic model with pairing is therefore defined by the following transition rates

$$
\begin{aligned}
c(\xi, \xi_{(m_i,1)}) &= \delta_{m_i}\xi((m_i, 1)), \\
c(\xi, \xi_{(f_j,1)}) &= \delta_{f_j}\xi((f_j, 1)), \\
c(\xi, \xi^{(h,\nu)}_{(m_i,1;h,\nu)}) &= \delta_{m_i}\xi((m_i, 1; h, \nu)), \\
c(\xi, \xi^{(g,\mu)}_{(g,\mu;f_j,1)}) &= \delta_{f_j}\xi((g, \mu; f_j, 1)), \\
c(\xi, \xi^{(g,\mu\vee\nu;h,\mu\vee\nu)}_{(g,\mu),(h,\nu)}) &= \beta_{g,h}\,\alpha_{g,h}\,\xi((g, \mu))\xi((h, \nu)), \mu \neq \nu \\
c(\xi, \xi^{(g,\mu;h,\nu)}_{(g,\mu),(h,\nu)}) &= \beta_{g,h}(1 - \alpha_{g,h})\xi((g, \mu))\xi((h, \nu)), \mu \neq \nu \\
c(\xi, \xi^{(g,\mu;h,\nu)}_{(g,\mu),(h,\nu)}) &= \beta_{g,h}\,\xi((g, \mu))\xi((h, \nu)), \mu = \nu
\end{aligned}
$$

$$c(\xi, \xi^{(g,\mu),(h,\nu)}_{(g,\mu;h,\nu)}) = \sigma_{g,h}\xi((g,\mu;h,\nu))$$

$$c(\xi,\eta) = 0, \text{ else}$$

where $g, h \in \{m_1, m_2, ..., m_L; f_1, f_2, ..., f_N\}$ and $\mu, \nu \in \{0, 1\}$. As noted by Dietz (1988b), the probability of transmission depends on $\sigma_{.,.}$, that is , it depends on how long a couple remains a couple. In Section 5, we show that the General Epidemic model is just a special case of the pair formation model of this section. It is indeed obtained as a limiting model when all $\sigma_{g,h}$ tend to infinity and all $\alpha_{g,h}$ tend to 1.

4. The General Epidemic Model with Pairing

We give the description of the general model in this section. First, we let

$$\mathcal{N}_0 \equiv \{h | h : S \longrightarrow \{-1, 0, 1\} \text{ is a function } \}$$

denote the set of all possible changes of the system and let

$$\mathcal{N}_1(\xi) \equiv \{\eta \in X : \eta - \xi \equiv h \in \mathcal{N}_0\}, \forall \xi \in X$$

denote the set of all possible states to which ξ may change in one step.

Denote $c : X \times X \longrightarrow [0, \infty)$ denote a function satisfying the following conditions:

(i) $c(\xi, \eta) \geq 0, \forall \xi \neq \eta \in X$;

(ii) $\sum_{\eta \neq \xi} c(\xi, \eta) < \infty, \forall \xi \in X$;

(iii) $\sum_{\eta \in X} c(\xi, \eta) = 0, \forall \xi \in X$;

(iv) $c(\xi, \eta) = 0, \forall \eta \notin \mathcal{N}_1(\xi), \xi \in X$;

(v) The recruitment rate has a linear bound in terms of the total population. Explicitly, let $\mathcal{N}_{new}(\xi) = \{\eta : ||\eta||_{total} > ||\xi||_{total}\}$, where $||.||_{total}$ denote the number of total individuals present in the configuration. Then, there

are constants $C_1 > 0$ and $C_2 > 0$ such that

$$\sum_{\eta \in \mathcal{N}_{new}(\xi)} c(\xi, \eta) \leq C_1 + C_2 ||\xi||_{total}, \forall \xi \in X.$$

The general result is that infectious processes with transition rates defined by (i)-(v) can be realized as a Markov process and a semigroup characterization of this process is possible making the results and analytic tools of the theory of Markov processes available for the analysis of these epidemic models.

For $\xi, \eta \in X$, let

$$d(\xi, \eta) = ||\eta - \xi|| = \max\{|\eta(s) - \xi(s)| : s \in S\}$$

With this metric, X becomes a locally compact and separable metric space and if we let

$$||\xi|| = \max\{\xi(s) : s \in S\},$$

and $B(X)$ denote the set of all bounded functions on X with norm

$$||f|| = \sup_{\xi \in X} |f(\xi)|, f \in B(X),$$

then $B(X)$ becomes almost the appropriate Banach space in which we can study these processes.

Consider the following linear operator $A : B(X) \longrightarrow B(X)$ be such that

$$Af(\xi) = \sum_{\eta \in X} c(\xi, \eta)[f(\eta) - f(\xi)], \xi \in X,$$

on $B(X)$ and let $\hat{C}(X) \subset B(X)$ consist of all functions $f : X \longrightarrow R$ such that $\lim_{||\xi|| \to \infty} f(\xi) = 0$. The restriction of the norm to $\hat{C}(X)$

$$||f|| = \sup_{\xi \in X} |f(\xi)|, f \in \hat{C}(X),$$

makes $\hat{C}(X)$ Banach space too. $\hat{C}(X)$ is the space in which we formulate the result needed for the formal construction of the above epidemic process.

Theorem 4.1: There is a family of linear operators $\{S_t : t \geq 0\}$ on $\hat{C}(X)$ and a $X-$valued random process $\{\xi_t : t \geq 0\}$ such that

(1) $S_{t+s} = S_s S_t$;

(2) $S_0 = I$ the identity map;

(3) $\lim_{t\to 0} S_t f = f, \forall f \in \hat{C}(X)$;

(4) $S_t f \geq 0, \forall t \geq 0, f \geq 0$;

(5) $||S_t f|| \leq ||f||, \forall f \in \hat{C}(X)$;

(6) $Af = \lim_{t\to 0} \frac{1}{t}\{S_t f - f\}$;

(7) $\frac{d}{dt} S_t f = AS_t f = S_t Af$;

(8) $S_t f(\xi) = E_\xi f(\xi_t), \xi \in X$.

(9) If we denote the transition function of $\{\xi_t : t \geq 0\}$ as $\{P^t(\xi, \eta) : \xi, \eta \in X\}$, then $\sum_\eta P^t(\xi, \eta) = 1$.

Properties (1)-(3) imply that the set of linear operators $\{S_t : t \geq 0\}$ is a strongly continuous semigroup. Property (6) implies that the operator A is the generator of the semigroup. The process ξ_t defined by the set of transition rates satisfying (i)-(iv) generates a strongly continuous semigroup on $\hat{C}(X)$. The proof of this result is outlined in the Appendix.

5. Classical and Pair-Formation Epidemic Models

In this section, we apply the construction of the epidemic process as outlined in Section 5, to show a key connection between classical infectious and pair formation models. As a special case, the result below implies that the Epidemic Model with Pairing of Section 3 converges, when the transmission probabilities $\alpha_{g,h} = 1$ (or $\alpha_{g,h}$ go to 1 uniformly), to the General Epidemic model as dissolution rates tend to infinity.

We start with a simultaneous description of both models. Let $X_s = \{\xi \in X : \xi(g,\mu;h,\nu) = 0, \forall g,h,\mu,\nu\}$ be the set of all states or sites with no pairs. Here, g,h denote any individual or site (see Section 3). In the classical infectious models there are no pairs and, consequently, they can be seen as X_s-valued random processes. The General Epidemic Model of Section 3 corresponds to the case where $c(\xi,\eta) = 0$ if ξ or $\eta \notin X_s$. Thus, all models without pairing can be described by setting $c(\xi,\eta) = 0$ if ξ or η is not in X_s in those models with pairing.

For models with pairs, we decompose the pairing rates, $c(\xi,\eta)$, into several parts. The first part, $c_0(.,.)$, is the change rate within X_s (instantaneous pairing rate). The second part, $c_{1+}(.,.)$, is the instantaneous pairing rate with disease transmission. The third part, $c_{1-}(.,.)$, is the pairing rate without disease transmission. The forth part, $\sigma c_2(.,.)$, is the dissolution rate with parameter σ. Finally, the fifth part, $c_3(.,.)$, consists of other changes which are not affected as σ tends to infinity. We note that $c_0(.,.)$ is due only to the initial contact and whether or not a more permanent relationship is formed depends. We can write the above descriptions as

$$c_0(\xi,\eta) = 0, \text{ if } \xi \notin X_s \text{ or } \eta \notin X_s$$

$$c_{1+}(\xi,\eta) = 0, \text{ if } \eta \neq \xi^{(g,\mu\vee\nu;h,\mu\vee\nu)}_{(g,\mu),(h,\nu)}, \mu \neq \nu$$

$$c_{1-}(\xi,\eta) = 0, \text{ if } \eta \neq \xi^{(g,\mu;h,\nu)}_{(g,\mu),(h,\nu)}$$

$$c_2(\xi,\eta) = 0, \text{ if } \eta \neq \xi^{(g,\mu),(h,\nu)}_{(g,\mu;h,\nu)}$$

where $\mu \vee \nu$ denote the maximum of μ and ν. We assume that $c_3(.,.)$ as any other change rate, $= 0$ when η is any one of the above exceptional states. In above definition, we assume that $\xi \neq \eta$ and that all $c_0(.,.)$,$c_1(.,.)$, $c_2(.,.)$ and $c_3(.,.)$ satisfy conditions (i)-(v) of Section 4.

Let

$$c_\sigma(\xi,\eta) = c_0(\xi,\eta) + c_{1+}(\xi,\eta) + c_{1-}(\xi,\eta) + \sigma c_2(\xi,\eta) + c_3(\xi,\eta) \qquad (5.1)$$

where $\sigma > 0$ is a parameter. Then, $c_\sigma(.,.)$ also satisfies conditions (i)-(v) of Section 4.

The model determined by the above set $\{c_\sigma(.,.)\}$ is very general and covers the Epidemic Model with Pairing of Section 3 as a special case. Here for simplicity, we assume that only one parameter goes to infinity. The result is the same for multiparameter models as long as the dissolution rates tend to infinity uniformly. From Section 4 and the Appendix, $c_\sigma(.,.)$ determines a Markov process $\{\xi^\sigma_\cdot\}$ with its Feller semigroup $\{S^\sigma_t\}$. The discussion below addresses the question of what is the limit of $\{\xi^\sigma_\cdot\}$ when σ tends to infinity ?

Intuition says that the population of pairs become nearly extinct if dissolution rates become large. $\{\xi^\sigma_t : t \geq 0\}$ is close to the infectious process and the contact and infectious rates come from both pairing and transmission. The construction given in the Appendix shows that the framework works according to our intuition.

Let $\{\xi^\sigma_\cdot\}$ be the process of this section and start this process at $\xi^\sigma_0 = \xi \in X_s$, i.e., there are no pairs at the beginning. Let τ_1 be the first time a pair appears, i.e.,

$$\tau_1 = \inf\{t \geq 0 : \xi^\sigma_t \notin X_s\}$$

and let τ_1' be the first time the system gets back to X_s, i.e.,

$$\tau_1' = \inf\{t \geq \tau_1 : \xi^\sigma_t \in X_s\}$$

Since σ influences only pairs (from the definition of $c_\sigma(.,.)$), τ_1 is independent of σ. In general, we let

$$\tau_k = \inf\{t \geq \tau'_{k-1} : \xi^\sigma_t \notin X_s\}$$

and let τ_k' be the first time the system gets back to X_s, i.e.,

$$\tau_k' = \inf\{t \geq \tau_k : \xi_t^\sigma \in X_s\},$$

therefore, $\tau_{k+1} - \tau_k'$ is independent of σ. At time τ_k, a pair is formed in the system, i.e. $\xi_{\tau_k}^\sigma \notin X_s$. We introduce a corresponding contact interaction as that it consider pairing as contact, that is to say, the duration of the pair is zero. When it is pairing with transmission, they contact with transmission. After contact, they dissolve immediately. Also, when it is pairing without transmission, they meet and dissolute without anything left. In the following lemma, we use $\xi_{\tau_k}^{\sigma,p,c}$ to denote this types of interaction.

Lemma 5.1 : Suppose

$$c_2(\xi,\eta) > 0, \text{ when } \xi(g,\mu;h,\nu) > 0, \eta = \xi_{(g,\mu;h,\nu)}^{(g,\mu),(h,\nu)}, \forall g,h,\mu,\nu$$

Then, for any k and $\epsilon > 0$, there is a $\Delta > 0$ such that for all $\sigma > \Delta$ we have

$$P(0 < \tau_k' - \tau_k < \epsilon) > 1 - \epsilon$$

$$P(\xi_{\tau_k'}^\sigma = \xi_{\tau_k}^{\sigma,p,c}) > 1 - \epsilon$$

where $\xi_{\tau_k}^{\sigma,p,c}$ is obtained from $\xi_{\tau_k}^\sigma$ from partnership of duration zero.

Proof: For the time gap, we use (5.1) and note that the rate of the associated exponential random variable tends to infinity. That is, events happens infinitely fast or equivalently given $\epsilon > 0$ $\tau_k' - \tau_k < \epsilon$ with high probability. We choose σ large enough so that the probability of pair dissolution is greater than $1 - \epsilon$. Hence the event that nothing but dissolution happens during $(\tau_k, \tau_k']$ has a very high probability (see (A1) in the appendix). This completes the proof of the Lemma.

The change rate associated with the limiting system is obtained as in the above discussion for the corresponding contact interaction, that is, for partnerships of duration zero. Let $c_{1+}^{pc}(.,.)$ on X_s be defined as

$$c_{1+}^{pc}(\xi, \xi_{(g,\mu),(h,\nu)}^{(g,\mu\vee\nu),(h,\mu\vee\nu)}) = c_{1+}(\xi, \xi_{(g,\mu),(h,\nu)}^{(g,\mu\vee\nu;h,\mu\vee\nu)})$$

and

$$c(\xi,\eta) = c_0(\xi,\eta) + c_{1+}^{pc}(\xi,\eta) \tag{5.2}$$

for all $\xi \neq \eta, \xi, \eta \in X_s$, while $c(\xi,\xi)$ is specified by the relationship

$$\sum_{\eta} c(\xi,\eta) = 0.$$

To fit the general model of Section 3, we define $c(\xi,\eta)$ as 0 when either of ξ or η is not in X_s. From Section 3 and the appendix, $c(.,.)$ determines a Markov process $\{\xi_.\}$ and its Feller semigroup $\{S_t\}$. The convergence result that follows is the main mathematical result of this article. It shows that our model behaves at it should.

Theorem 5.1: suppose $\{\xi_.^\sigma\}$ and $\{\xi_.\}$ are the processes determined by (5.1) and (5.2) respectively. Then, as $\sigma \to \infty$, $\xi_.^\sigma$ converges to $\xi_.$ in distribution.

The proof of the Theorem is based on Theorem 2.5 on page 167 in Ethier and Kurtz (1986). It suffices to show that

$$\lim_{\sigma\to\infty} Ef(\xi_t^\sigma) = Ef(\xi_t), \forall t \geq 0 \tag{5.3}$$

where $f \in \hat{C}(X)$ and $\xi \in X_s$.

A detailed proof of (5.3) can be found in Luo (1990). Here we just point out the general idea. For any fixed time t, the number of pairings is bounded independently of σ. The time space graphs $\{\xi_s^\sigma, 0 \leq s \leq t\}$ and

$\{\xi_s, 0 \leq s \leq t\}$ are at approximately in the same location and will be close to each other as σ tends to infinity. Therefore, ξ_t^σ and ξ_t are close for large σ and hence $Ef(\xi_t^\sigma)$ is close to $Ef(\xi_t)$.

6. Discussion

Here we only considered infectious processes with two stages: healthy and infected. In practical application, we may have to consider several stages of infection. From Section 4 and the appendix, we see that the construction of our model does not depend on the number of stages. Our model and our results will hold for infectious processes with finitely many stages. Models that allow for the incorporation of age-dependent heterogeneously mixing populations can be similarly developed. Our framework provides the necessary theoretical background for further exploration of general stochastic models with pairing. To apply our models to practical situations, we need to specify the flip rate matrix $c(.,.)$. If the flip rate matrix has a simple structure then we can apply (7) in Theorem 4.1 to the analysis of various statistics. For complicated systems with large number of parameters, the representation theorem of Section 4 provides the theoretical foundation for needed simulations. In this paper, we have used the mass-action law to model pair-formation. This was done with the purpose of showing the connection between models that follow pairs and the (classical) general stochastic epidemic model. The use of the mass-action law is however not considered appropriate in many realistic situation. Generalized mass-action laws have been developed by Busenberg and Castillo-Chavez (1989, 1991) and Castillo-Chavez and Busenburg (1991). Modifications to the framework of this article to take into account arbitrary mixing/pair formation patterns –generalized mass-action laws– can be accomplished without dif-

ficulty and will be published elsewhere. Supercomputers in combination with modern numerical analysis techniques will help us gain further insight into these processes. We expect to pursue the numerical exploration of this model in the near future.

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Appendix

I: Process Construction

In this Appendix, we give the construction of the process from the change rates $\{c(.,.)\}$. Let S, X, $\mathcal{N}_0$, $\mathcal{N}_1(\xi)$ and function $c : X \times X \longrightarrow [0,\infty)$ be as in Section 3 . For $m = 1, 2, 3, ...$, let

$$X^m \equiv \{\xi \in X : \xi(s) \leq m, \forall s \in S\}$$

and truncate the function c as follows

$$c^m(\xi,\eta) = \begin{cases} c(\xi,\eta) & \text{if } \xi \neq \eta \text{ and } \xi,\eta \in X^m \\ 0 & \text{if } \xi \neq \eta \text{ and one of them is not in } X^m \\ -\sum_{\zeta \neq \xi} c^m(\xi,\zeta) & \text{if } \eta = \xi \end{cases}$$

We construct a series of Markov processes $\{\xi_t^m : t \geq 0\}$ approaching the required process in the limit. First, for each $m \geq 1, k \geq 0$ and $\xi \in X$, let $\tau_{m,k}^{\xi}$ be the exponential distributed random variable with rate $-c^m(\xi,\xi)$. Let $Y_{m,k}^{\xi}$ be the $\mathcal{N}_0$ -valued random variable such that

$$P(Y_{m,k}^{\xi} = h) = -\frac{c^m(\xi,\xi+h)}{c^m(\xi,\xi)}. \qquad (A.1)$$

We assume that all these random variables are independent. Let $\xi \in X$. We construct all processes $\{\xi_t^m : t \geq 0\}$ starting at ξ at the same time. The idea is to use $\tau_{m,k}^{\xi}$'s to decide the time gaps among jumps and use $Y_{m,k}^{\xi}$'s to choose landing site. In order to tie these processes together, we always use the random variable with the lower index if possible. Thus, for any $m < n$, the processes $\xi_\cdot^m$ and $\xi_\cdot^n$ will move together until the first time $\mathcal{N}_1(\xi_t^m)$ is not contained in X^m, i.e., the first time the process $\xi_\cdot^m$ can jump out of X^m.

The construction of $\xi_\cdot^1$ is as follows: choose a sequence $0 = M_0 < M_1 < M_2 < ...$ such that $M_{j+1} - M_j > 2$ for all $j \geq 0$. If $\xi \notin X^{M_1}$, then $\xi_t^1 = \xi, \forall t \geq 0$. We assume $\xi \in X^{M_1}$, then, we define $\xi_t^1 = \xi, \forall 0 \leq t < \tau_{1,0}^\xi$ and $\xi^1_{\tau^\xi_{1,0}} = \xi + Y^\xi_{1,0}$. Denote $t_1 = \tau^\xi_{1,0}$ and $t_2 = t_1 + \tau^{\xi^1_{t_1}}_{1,1}$. For $t_1 < t < t_2$, we define $\xi_t^1 = \xi^1_{t_1}$. Then, define $\xi^1_{t_2} = \xi^1_{t_1} + Y^{\xi^1_{t_1}}_{1,2}$. By an easy induction argument, we can define ξ_t^1 for all $t \geq 0$.

Suppose $\xi_t^i, 0 \leq t < \infty, 1 \leq i \leq m$ are given and define $\xi_t^{m+1} = \xi_t^m$ t until the first time $c^{M_{m+1}}(\xi_t^m, \xi_t^m) \neq c^{M_m}(\xi_t^m, \xi_t^m)$, i.e., the first time ξ_t^{m+1} can jump out of X^{M_m}. ξ_t^{m+1} is defined in the same manner as $\xi_\cdot^1$ was. This completes the definition of all the processes $\{\xi_t^m : t \geq 0, m \geq 1\}$. Finally, for each m, let $\sigma_m = \inf\{t \geq 0 : c^{M_{m+1}}(\xi_t^m, \xi_t^m) \neq c^{M_m}(\xi_t^m, \xi_t^m)\}$. From this construction, the following result follows:

Lemma A.1: For any $n > m$, we have

$$\xi_t^n = \xi_t^m, 0 \leq t \leq \sigma_m .$$

To pass to the limit, we need to establish the following lemma.

Lemma A.2 : σ_m is increasing in m and

$$\lim_{m \to \infty} \sigma_m = \infty \text{ a.s.}$$

Proof: From the definition of $c^m(.,.)$, it is clear that σ_m is increasing in m. To see that $\sigma_m \longrightarrow \infty$, we note that at time $t = \sigma_m$, $\mathcal{N}_1(\xi_t) \subset X^{M_{m+1}} \setminus X^{M_m}$. Let σ'_m be the first time the total population reaches $M_m - 3$. Then, $\sigma_m \geq \sigma'_m$. It suffices to show $\sigma'_m \longrightarrow \infty$.

Let T_0 be the total individuals at the beginning. For $i \geq 1$, let t_i be the i-th time a new individual is added to the populations. Then, $\sigma'_m \geq$

$t_{M_m-3-T_0}$ and the lemma will be proved if we can show that $\lim_{i\to\infty} t_i = \infty$. By the condition (v) in Section 3, $t_{i+1} - t_i$ has a rate no larger than $C_1 + C_2(T_0 + i)$. Suppose τ_i's are independent random variables exponentially distributed with parameter $C_1+C_2(T_0+i)$, respectively. Then, t_i is bounded below by $\sum_{j=0}^{i-1} \tau_j$. Since $\sum_{j=0}^{i-1} E\tau_j = \sum_{j=0}^{i-1} \frac{1}{C_1+C_2(T_0+j)}$ goes to infinity as $i \to \infty$, a standard martingale convergence theorem shows $\sum_{j=0}^{i-1} \tau_j \longrightarrow \infty$ a.s when $i \to \infty$ (see e.g. Luo (1990)). Therefore, the lemma is true.

The required process $\{\xi_t : t \geq 0\}$ is defined as

$$\xi_t = \xi_t^m, t < \sigma_m$$

By Lemma A.1, the process is well defined and by Lemma A.2 the process is defined for all $t \geq 0$.

II: Mathematical Justification

In this section, we show that the process defined in this appendix is determined by the c-function. First we look at the generator and the semigroup determined by the process $\{\xi_t^m : t \geq 0\}$ for each fixed m.

Let X, $B(X)$ and $\hat{C}(X)$ be as in Section 3. Let $A_m : B(X) \longrightarrow B(X)$ be such that

$$A_m f(\xi) = \sum_{\eta \in X} c^m(\xi, \eta)[f(\eta) - f(\xi)], \xi \in X.$$

Then, A_m is a bounded linear operator on $B(X)$. From Ethier and Kurtz (1986) page 162, we know A_m generates a semigroup $\{S_t^m : t \geq 0\}$ on $B(X)$ which can be written as

$$S_t^m f(\xi) = E_\xi f(\xi_t^m), \xi \in X$$

where $\{\xi_\cdot^m\}$ is the process constructed in this Appendix. It is the Markov process corresponding to the semigroup $\{S_t^m : t \geq 0\}$. We summarize the results as follows:

Proposition B.1 : There is a family of linear operators $\{S_t^m : t \geq 0\}$ on $\hat{C}(X)$ such that

(1) $S_{t+s}^m = S_s^m S_t^m$;

(2) $S_0^m = I$ the identity map;

(3) $\lim_{t\to 0} S_t^m f = f, \forall f \in \hat{C}(X)$;

(4) $S_t^m f \geq 0, \forall t \geq 0, f \geq 0$;

(5) $||S_t^m f|| \leq ||f||, \forall f \in \hat{C}(X)$;

(6) $A_m f = \lim_{t\to 0} \frac{1}{t}\{S_t^m f - f\}$;

(7) $\frac{d}{dt} S_t^m f = A_m S_t^m f = S_t^m A_m f$;

(8) $S_t^m f(\xi) = E_\xi f(\xi_t^m), \xi \in X$.

(9) If we denote the transition function of $\{\xi_t^m : t \geq 0\}$ as $\{P^t(\xi, \eta) : \xi, \eta \in X\}$, then $\sum_\eta P^t(\xi, \eta) = 1$.

We define a family of linear operators on $\hat{C}(X)$ by

$$S_t f(\xi) = E_\xi f(\xi_t)$$

where ξ_t is defined in this appendix. To complete the mathematical justification we need to show (1)-(9) in Proposition B.1 hold for $\{S_t\}$ and ξ_t.

<u>S_t is well defined</u> We need to show $S_t f \in \hat{C}(X)$ for $f \in \hat{C}(X)$ or

$$\lim_{||\xi||\to\infty} S_t f(\xi) = 0$$

. Indeed, for any $\epsilon > 0$, we have a $M > 0$ such that $||\xi|| \geq M$ implies $|f(\xi)| < \epsilon/2$. For fixed $t > 0$, by the argument in Lemma 5.1, there is a

$\Delta > 0$ such that $P(\xi_t \in X^M) < \epsilon/2||f||$ if $||\xi|| > \Delta$. Thus, for $||\xi|| > \Delta$, we have $|S_t f(\xi)| < \epsilon$, i.e. $\lim_{||\xi||\to\infty} S_t f(\xi) = 0$.

From the definition of $\{S_t\}$, we know (2),(4),(5), (8) and (9) are true for $\{S_t\}$ and ξ_t.

$\{S_t\}$ is a semigroup We first note that from a similar argument as above we have

$$\lim_{m\to\infty} S_t^m f = S_t f$$

Write $S_s^m S_t^m f$ as

$$S_{t+s}^m f = S_s^m S_t^m f = S_s^m [(S_t^m - S_t)f] + S_s^m [S_t f]$$

and take the limit for $m \to \infty$. With (5), we have

$$S_{t+s} f = S_t S_s f$$

i.e. (1) is true.

$\{S_t\}$ is strongly continuous For any fixed $\xi \in X$ and any $\epsilon > 0$, by the argument in Lemma 5.1, we can choose a $m_0 >> 1$ such that $|S_t^{m_0} f(\xi) - S_t f(\xi)| < \epsilon$ for all $0 \le t \le 1$. Thus,

$$S_t f(\xi) = S_t^{m_0} f(\xi) - [S_t^{m_0} f(\xi) - S_t f(\xi)]$$

Letting t go to 0, we know (3) is true for S_t.

Generator of $\{S_t\}$ For $f \in \hat{C}(X), \xi \in X$, let

$$Af(\xi) = \sum_{\eta\in X} c(\xi,\eta)[f(\eta) - f(\xi)]$$

It is easy to see from (iv) that $Af \in \hat{C}(X)$. We are going to show

$$Af = \lim_{t\to 0} \frac{1}{t}\{S_t f - f\}, \forall f \in \hat{C}(X)$$

First, we claim $\lim_{m\to\infty} A_m f(\xi) = Af(\xi)$. Indeed, let m be large enough so that $\xi \in X^m$

$$\begin{aligned} A_m f(\xi) &= \sum_{\eta\in X} c^m(\xi,\eta) f(\eta) \\ &= \sum_{\eta\in X^m} c(\xi,\eta) f(\eta) \\ &= \sum_{\eta\in X} c(\xi,\eta)[f(\eta) - f(\xi)] \\ &\quad - \sum_{\eta\notin X^m} c(\xi,\eta) f(\eta) \\ &\to Af(\xi) \end{aligned}$$

as $m \to \infty$, where we made use condition (iv) in Section 3 and $f \in \hat{C}(X)$. Thus, for any $\epsilon > 0$, we can choose a $M > 0$ such that $|A_m f(\xi) - Af(\xi)| < \epsilon/3$ for all $m \geq M$. Note that $|S_t f(\xi) - S_t^m f(\xi)| \leq 2||f||P(\sigma_m < t) \leq 2||f||P(\sigma_2 < t) = o(t)$ as $t \to 0$. Fix a $m > M + 2$, choose a $\delta > 0$ such that

$$|\frac{1}{t}\{S_t^m f(\xi) - f(\xi)\} - A_m f(\xi)| < \epsilon/3$$

$$\frac{2}{t}||f||P(\sigma_2 < t)| < \epsilon/3$$

for all $t < \delta$. Thus, for $t < \delta$, we have

$$|\frac{1}{t}\{S_t f(\xi) - f(\xi)\} - Af(\xi)| < \epsilon$$

i.e., (6) is true for S_t and A.

From (1) and (6), we have (7) completing the proof.

We conclude that $\{S_t\}$ is a Feller semigroup on $\hat{C}(X)$ and $\{\xi_t\}$ is a Markov process with values in X (see page 169 in Ethier and Kurtz (1986)). These completes the proof for Theorem 2.1.