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Journal of Theoretical Biology 234 (2005) 455–470
Journal of Theoretical Biology
www.elsevier.com/locate/yjtbi

Stochastic modeling of nonlinear epidemiology

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Received 19 July 2004; received in revised form 19 November 2004; accepted 22 November 2004

Abstract

The objectives of this paper to analyse, model and simulate the spread of an infectious disease by resorting to modern stochastic algorithms. The approach renders it possible to circumvent the simplifying assumption of linearity imposed in the majority of the past works on stochastic analysis of epidemic processes. Infectious diseases are often transmitted through contacts of those infected with those susceptible; hence the processes are inherently nonlinear. According to the classical model of Kermack and McKendrick, or the SIR model, three classes of populations are involved in two types of processes: conversion of susceptibles (S) to infectives (I) and conversion of infectives to removed (R). The master equations of the SIR process have been formulated through the probabilistic population balance around a particular state by considering the mutually exclusive events. The efficacy of the present methodology is mainly attributable to its ability to derive the governing equations for the means, variances and covariance of the random variables by the method of system-size expansion of the nonlinear master equations. Solving these equations simultaneously along with rates associated influenza epidemic data yields information concerning not only the means of the three populations but also the minimal uncertainties of these populations inherent in the epidemic. The stochastic pathways of the three different classes of populations during an epidemic, i.e. their means and the fluctuations around these means, have also been numerically simulated independently by the algorithm derived from the master equations, as well as by an event-driven Monte Carlo algorithm. The master equation and Monte Carlo algorithms have given rise to the identical results.

Keywords: Stochastic; Nonlinear; Model; Epidemiology

1. Introduction

Modern theories of differential equations have been widely adopted in the analyses, and simulation of biological populations including the evolution of epidemics. This is evidenced by the large amount of systematic treatments of the subject, see, e.g. May (1974), Chiang (1980), Anderson and May (1991), Mode and Sleeman (2000), Ramkrishna (2000), Tan (2000), Brauer and Castillo-Chavez (2001), Murray (2002), Lande et al. (2003), Thieme (2003), Turchin (2003). Both deterministic and stochastic models have been developed. The deterministic models take advantages of modern advancements in nonlinear analysis of low dimension systems. These techniques render it possible to elucidate a number of system characteristics such as bifurcation.

Stochastic algorithms have been developed for analysing two distinct types of noise, internal and external noise (Nicolis and Prigogine, 1977; Hill, 1977; Oppenheim et al., 1977; Gardiner, 1985; van Kampen, 1992; Kimura et al., 1994). External noises are the fluctuations created in an otherwise deterministic system by the application of an external random force, whose stochastic properties are supposed to be known. Internal noise is caused by the fact that the system itself consist of discrete particles and many variables associated with the particles are ignored; it is inherent in the very mechanism by which the process evolves. For this reason, it is often called minimal, or system noises, signifying the

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doi:10.1016/j.jtbi.2004.11.033

Nomenclature

a	rate constant of recovery
D	one-step operator
N_1	random variable representing the susceptible population
N_2	random variable representing the infected population
N_3	random variable representing the recovered population
n_1	realization of random variable, $N_1(t)$
n_2	realization of random variable, $N_2(t)$
n_3	realization of random variable, $N_3(t)$
$\mathbf{N}$	random vector, i.e. $[N_1(t), N_2(t), N_3(t)]$
$\mathbf{n}$	realization of random vector $\mathbf{N}(t)$
$P_{\mathbf{n}}$	probability that the system is at state $\mathbf{n}$ at time t
r	rate constant of infection
t	time
Y	random variable denoting the fluctuations about macroscopic behavior
y	realization of random variable Y

Greek letters

ϕ	macroscopic number of the susceptible population
θ	macroscopic number of the infected population
γ	macroscopic number of the recovered population
λ	transition intensity function
Ψ	joint probability distribution in terms of random vector $\mathbf{Y}$
Ω	total number of population

Subscripts

1	susceptible population (S)
2	infected population (I)
3	recovered population (R)

noises are free from external influences. Small discrete systems governed by a large number of variables often exhibit notable internal fluctuations. Thus, the populations of infected cases at the outbreak and closure of an epidemic are subject to these internal noises, or uncertainties.

The discrete state, continuous-time stochastic processes have been analysed by the master equation (Oppenheim et al., 1977; Gardiner, 1985; van Kampen, 1992) through a probability balance around a particular state of the system by taking into account all mutually exclusive events. The efficacy of this modern methodology of stochastic processes is mainly attributable to its powerful ability to solve the nonlinear master equations through the system-size expansion (van Kampen, 1961, 1976, 1992). This renders it possible to circumvent the simplifying assumption of linearity imposed in the majority, if not all, of the past works.

The impact of the system-size expansion on the analysis of biological processes is enormous as most of them are nonlinear in nature. Indeed, advanced theories of nonlinear differential equations have been widely adopted in the analysis of deterministic characteristics of biological processes. Recent publications of several monumental works in stochastic population dynamics (e.g. Mode and Sleeman, 2000; Tan, 2000; Lande et al., 2003) seem to suggest that there is an urgent need to introduce the nonlinear, stochastic algorithms to the biological community. Transmission of an infectious disease from one individual to another is a known, probably also the simplest, example. The objective of the current exposition is to illustrate the features of formulating the master equations of nonlinear epidemic process and solving them by system-size expansion. This accomplished by means of a relatively simple, widely adopted model of epidemics of Kermack and McKendrick (1927, 1932, 1933), which have had a major influence in the simulating the evolution of epidemics and are still relevant in a broad spectrum of situations. An even-driven Monte Carlo procedure (Gillespie, 1977, 1992; Rajamani et al., 1986) is used in simulating the same process. It has been known to some theoreticians that these two approaches yield the same statistical information including the mean and variance. Nevertheless, the literature lacks such a parallel development that illuminates the foundations and features of these two algorithms.

2. Model formulation

The classic Kermack–McKendrick (1927) model considers the total population to be constant. If a small subgroup of the population is found to be infected with a certain disease, a common interest is to predict the spread of the infection within the population as a function of time. The process depends on a myriad of interacting factors related to the disease in question, the mechanisms of infection, the physical conditions of each individual, and the social and environmental conditions of the population. A mathematical description of this complex process usually relies on a manageable number of system variables. This lumping procedure inevitably

results in a high degree of freedom and fluctuations, or uncertainties, in the predictions (van Kampen, 1992).

Suppose the process of the disease spread is such that the population can be divided into three distinct classes: the susceptibles, S, who can catch the disease; the infectives, I, who have the disease and can transmit it; and the removed class, R, namely, those who have either had and immune from the disease, or, are removed due to death. The process has often been sequentially represented by $S \to I \to R$, or the SIR model in short. For modeling purpose, it will be more illuminating to state the two-step process in the following form:

$$S + I \to 2I,$$

$$I \to R.$$

Note the first step of the process is nonlinear.

In the current work, the master equation describing the spread of the infection within the population as a function of time is developed through the probabilistic population balance. The formulation of the master equation given here follows what has been established by Oppenheim et al. (1977) and van Kampen (1992).

2.1. Model description and assumptions

Let the random variables, $N_1(t)$, $N_2(t)$, and $N_3(t)$, represent the populations of the susceptible, infectious and recovered classes at time t. Consequently, the random vector of the system is $\mathbf{N}(t) = [N_1(t), N_2(t), N_3(t)]$, and the realization of this random vector representing the state of the system at time t is $\mathbf{n}(t) = [n_1(t), n_2(t), n_3(t)]$. Moreover, the probability of the system to be in state $\mathbf{n}$ at time t is denoted by $P_{n_1,n_2,n_3}(t)$ or $P[n_1(t), n_2(t), n_3(t); t]$. The following assumptions are imposed in deriving the master equation governing the transition of the system among various states.

1. The random vector, $\mathbf{N}(t)$, is Markovian, i.e. for any set of successive times, $t_1 < t_2 < \cdots < t_q$, we have $P[\mathbf{N}(t_q) * \mathbf{N}(t_1), \mathbf{N}(t_2), \ldots, \mathbf{N}(t_{q-1})] = P[\mathbf{N}(t_q) * \mathbf{N}(t_{q-1})]$ (see, e.g. Parzen, 1962).
2. The number of conversion from one class to another depends only on the time interval but not time, i.e. it is temporally homogeneous, signifying that $\mathbf{N}(\Delta t)$ and $[\mathbf{N}(t + \Delta t) - \mathbf{N}(t)]$ are identically distributed.
3. The probability of an individual to undergo the infection or the recovery process is proportional to the time interval, $(t, t + \Delta t)$, if the interval, Δt, is sufficiently small.
4. The probabilities of two or more transitions to take place are zero during the time interval, $(t, t + \Delta t)$, so that at most one transition occurs during this period.
5. Individuals in the susceptible class have the same probability of contacting the infected individuals and therefore, have the same probability of transiting to the infectious class. Similarly, the individuals in the infected class have the same probability of being converted to the removed class.

2.2. Transition-intensity functions

On the basis of the assumptions given in the preceding subsection, the transition probability of each event can be written in terms of the transition-intensity function, λ_i $(i = 1, 2)$, is as follows:

$$\begin{aligned}&\Pr[\text{a particular individual in susceptible class}\\&\quad\text{will become an infected due to a}\\&\quad\text{contact with an infected during the}\\&\quad\text{time interval, } (t, t + \Delta t)]\\&\quad = k\,\Delta t + o(\Delta t)\end{aligned} \tag{1a}$$

$$= \lambda_1 n_2\,\Delta t + o(\Delta t), \tag{1b}$$

where $k = \lambda_1 n_2$, signifying the nonlinear nature of the infection process. The probability of a particular individual in susceptible class to get infected is proportional to the population of the infected.

$$\begin{aligned}&\Pr[\text{an infective will recover during the}\\&\quad\text{time interval, } (t, t + \Delta t)]\\&\quad = \lambda_2\,\Delta t + o(\Delta t),\end{aligned} \tag{2}$$

where

$$\lim_{\Delta t \to 0} \frac{o(\Delta t)}{\Delta t} = 0. \tag{3}$$

The definitions of the transition-intensity functions, Eqs. (1) and (2) renders it possible to perform a probabilistic population balance around a particular state of the system by taking into account the mutually exclusive events probably occurring during the evolution of the process.

2.3. Master equation

The three mutually exclusive events leading to the evolution of the state of the system include the following:

(a) a susceptible is infected,
(b) a infective person is recovered and
(c) none of the above events take place.

As illustrated in Fig. 1, the probabilities that these three exclusive events will lead the system to state n as

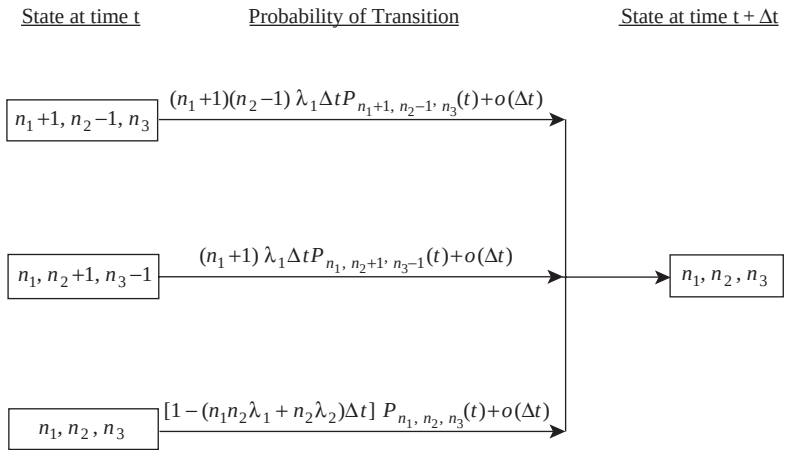

Fig. 1. Probability balances involving three mutually exclusive events in the time interval $(t, t+\Delta t)$.

arbitrary time $(t+\Delta t)$ can be written as

$$\begin{aligned}&\Pr\text{[the system will transfer into state}\\&\quad\mathbf{n}\text{ from another due to the infection}\\&\quad\text{of a susceptible during the time}\\&\quad\text{interval }(t,t+\Delta t)]\\&\quad=\lambda_1(n_1+1)(n_2-1)\Delta t P_{n_1+1,n_2-1,n_3}(t)+o(\Delta t).\end{aligned}\tag{4}$$

$$\begin{aligned}&\Pr\text{[the system will transfer into state}\\&\quad\mathbf{n}\text{ from another due to the recovery}\\&\quad\text{of infected during the time interval }(t,t+\Delta t)]\\&\quad=\lambda_2(n_2+1)\Delta t P_{n_1,n_2+1,n_3-1}(t)+o(\Delta t).\end{aligned}\tag{5}$$

$$\begin{aligned}&\Pr\text{[the system will remain at the}\\&\quad\text{state }\mathbf{n}\text{ during the time interval, }(t,t+\Delta t)]\\&\quad=[1-(\lambda_1n_1n_2+\lambda_2n_2)\Delta t]P_{n_1,n_2,n_3}(t)+o(\Delta t).\end{aligned}\tag{6}$$

By summing all the probabilities, we obtain the probability that the system is at state $\mathbf{n}$ at arbitrary time $(t+\Delta t)$ as follows:

$$\begin{aligned}&P_{n_1,n_2,n_3}(t+\Delta t)\\&\quad=(n_1+1)(n_2-1)\lambda_1\,\Delta t\,P_{n_1+1,n_2-1,n_3}(t)\\&\qquad+(n_2+1)\lambda_2\,\Delta t\,P_{n_1,n_2+1,n_3-1}(t)\\&\qquad+(1-(n_1n_2\lambda_1+n_2\lambda_2)\Delta t)P_{n_1,n_2,n_3}(t).\end{aligned}\tag{7}$$

By rearranging the above equation and taking the limit as $\Delta t\to 0$, we obtain the following master equation:

$$\begin{aligned}\frac{\mathrm{d}P_{n_1,n_2,n_3}(t)}{\mathrm{d}t}&=(n_1+1)(n_2-1)\lambda_1P_{n_1+1,n_2-1,n_3}(t)\\&\quad+(n_2+1)\lambda_2P_{n_1,n_2+1,n_3-1}(t)\\&\quad-(n_1n_2\lambda_1+n_2\lambda_2)P_{n_1,n_2,n_3}(t).\end{aligned}\tag{8}$$

For convenience, the one-step operator, D, is defined through its effect on arbitrary function $f(n)$ as (van Kampen, 1992)

$$\begin{aligned}&Df(n)=f(n+1),\quad D^{-1}f(n)=f(n-1)\quad\text{and}\\&D^2f(n)=f(n+2).\end{aligned}\tag{9}$$

The master equation can be rewritten compactly in terms of the step operator as follows

$$\begin{aligned}\frac{\mathrm{d}P_n(t)}{\mathrm{d}t}&=\lambda_1[D_{n_1}D_{n_2}^{-1}n_1n_2-n_1n_2]P_n(t)\\&\quad+\lambda_2[D_{n_2}D_{n_3}^{-1}n_2-n_2]P_n(t).\end{aligned}\tag{10}$$

2.4. System-size expansion

The solution of the master equation, i.e. Eq. (8) or (10), leads to the joint probability distribution of the populations of the three classes of individuals, $P_{\mathbf{n}}(t)$. It is worth noting that Eq. (10) comprises a set of ordinary differential equations with the joint probability function, $P_{\mathbf{n}}(t)$, as its unknown. Each equation in the set represents a particular outcome of $\mathbf{n}$; thus, solving Eq. (10) for the joint probability distribution of an exceedingly large number of all possible $\mathbf{n}$'s is extremely difficult, if not impossible. In practice, however, it often suffices to determine only the expressions that govern a limited number of moments, especially the first and second moments, of the resultant population distribution. These expressions yield the means, variances, and covariances that can be correlated or compared with the experimental data.

Eq. (10) is nonlinear, thereby preventing the moments to be evaluated by averaging techniques or joint probability generating function techniques (see, e.g. Chiang, 1980). This difficulty is circumvented by resorting to the system-size expansion, a rational approximation technique based on the power-series expansion (van Kampen, 1961, 1976, 1992). The technique gives rise to the deterministic macroscopic

equations and the equations of fluctuations for the master equation.

To apply the system-size expansion, a suitable expansion parameter must be identified in the master equation, specifically in the transition intensity functions. The expansion parameter must govern the size of the fluctuations, and therefore, the magnitude of the jumps, or transitions. The macroscopic features are determined by the average behavior of all particles, while internal fluctuations are caused by the discrete nature of matter. Hence, we expect the fluctuations to be relatively small when the system size is large. The system size has been proposed as an expansion parameter because it measures the relative importance of the fluctuations (van Kampen, 1961, 1976).

For a linear system, fluctuations are of the order of $\Omega^{1/2}$ in a collection of Ω entities. As a result, their effect on the macroscopic properties is of the order of $\Omega^{-1/2}$ (van Kampen, 1976). In the system under consideration, therefore, we expect that the joint probability, $P_{\mathbf{n}}$, will have a sharp maximum around the macroscopic value, $\mathbf{n} = \Omega\Phi(t)$, with a width of the order of $\Omega^{1/2}$. Here, $\Phi(t)$ is a vector whose elements are the mean numbers of the three individual classes, $\phi(t)$, $\theta(t)$, and $\gamma(t)$, or the solution of the macroscopic equations as will be elaborated later. To exploit these characteristics of the system, a new random vector $\mathbf{Y}(t)$ is defined as follows

$$N_1(t) = \Omega\phi(t) + \Omega^{1/2} Y_1(t), \tag{11}$$

$$N_2(t) = \Omega\theta(t) + \Omega^{1/2} Y_2(t), \tag{12}$$

$$N_3(t) = \Omega\gamma(t) + \Omega^{1/2} Y_3(t). \tag{13}$$

The equations of realizations of these expressions are given, respectively, by

$$n_1(t) = \Omega\phi(t) + \Omega^{1/2} y_1(t), \tag{14}$$

$$n_2(t) = \Omega\theta(t) + \Omega^{1/2} y_2(t), \tag{15}$$

$$n_3(t) = \Omega\gamma(t) + \Omega^{1/2} y_3(t). \tag{16}$$

Accordingly, the joint probability of n_1, n_2, and n_3, i.e. $P_{\mathbf{n}}(t)$, is now transformed into that of y_1, y_2, and y_3, i.e. $\Psi_y(t)$.

Subsequently, the new random vector, $\mathbf{Y}$, the new joint probability distribution, $\Psi_y(t)$, and the one-step operator, D, defined in Eq. (9) are substituted into the master equation, Eq. (10). By expanding the right-hand side of the resultant expression into a Taylor's series, the master equation in terms of the new variables is obtained as given below (Appendix A).

$$\begin{aligned}
&\frac{\partial\Psi}{\partial t} - \Omega^{1/2}\frac{\mathrm{d}\phi}{\mathrm{d}t}\frac{\partial\Psi}{\partial y_1} - \Omega^{1/2}\frac{\mathrm{d}\theta}{\mathrm{d}t}\frac{\partial\Psi}{\partial y_2} - \Omega^{1/2}\frac{\mathrm{d}\gamma}{\mathrm{d}t}\frac{\partial\Psi}{\partial y_3} + \cdots \\
&\quad = \lambda_1\left\{\left[1 + \Omega^{-1/2}\left(\frac{\partial}{\partial y_1} - \frac{\partial}{\partial y_2}\right)\right.\right. \\
&\qquad \left. + \frac{1}{2}\Omega^{-1}\left(\frac{\partial}{\partial y_1} - \frac{\partial}{\partial y_2}\right)^2 + \cdots\right] \\
&\qquad \times [\phi\theta\Omega^2 + (\phi y_2 + \theta y_1)\Omega^{3/2} + y_1 y_2\Omega] \\
&\qquad \left. - [\phi\theta\Omega^2 + (\phi y_2 + \theta y_1)\Omega^{3/2} + y_1 y_2\Omega]\right\}\Psi \\
&\qquad + \lambda_2\left\{\left[1 + \Omega^{-1/2}\left(\frac{\partial}{\partial y_2} - \frac{\partial}{\partial y_3}\right)\right.\right. \\
&\qquad \left. + \frac{1}{2}\Omega^{-1}\left(\frac{\partial}{\partial y_2} - \frac{\partial}{\partial y_3}\right)^2 + \cdots\right] \\
&\qquad \left. \times (\Omega\theta + \Omega^{1/2} y_2) - (\Omega\theta + \Omega^{1/2} y_2)\right\}\Psi.
\end{aligned} \tag{17}$$

2.5. Macroscopic and Fokker–Planck equations

Collecting the terms of order $\Omega^{1/2}$ in the right-hand side of Eq. (17) gives rise to the following expressions governing the evolution of the macroscopic behavior of the system (Appendix A).

$$\frac{\mathrm{d}\phi}{\mathrm{d}t} = -\lambda_1'\phi\theta, \tag{18}$$

$$\frac{\mathrm{d}\theta}{\mathrm{d}t} = \lambda_1'\phi\theta - \lambda_2\theta, \tag{19}$$

$$\frac{\mathrm{d}\gamma}{\mathrm{d}t} = \lambda_2\theta, \tag{20}$$

where the constant, λ_1', correspond to the parameter λ_1, normalized with Ω:

$$\lambda_1 = \lambda_1'\Omega^{-1}. \tag{21}$$

This substitution ensure that λ_1' and λ_2 are of the same order of magnitude, which is necessary in collecting terms of order in this procedure. Similarly, collecting the terms of order Ω^0 gives the following linear Fokker–Planck equation, signifying the fluctuations of the system (Appendix B).

$$\frac{\partial\Psi}{\partial t} = -\sum_{i,j} A_{ij}\frac{\partial}{\partial y_i}(y_j\Psi) + \frac{1}{2}\sum_{i,j}\left(B_{ij}\frac{\partial^2\Psi}{\partial y_i\partial y_j}\right), \tag{22}$$

where

$$A = \begin{bmatrix} A_{11} & A_{12} & A_{13} \\ A_{21} & A_{22} & A_{23} \\ A_{31} & A_{32} & A_{33} \end{bmatrix} = \begin{bmatrix} -\theta\lambda_1' & -\phi\lambda_1' & 0 \\ \theta\lambda_1' & \phi\lambda_1' - \lambda_2 & 0 \\ 0 & \lambda_2 & 0 \end{bmatrix} \tag{23}$$

and

$$B = \begin{bmatrix} B_{11} & B_{12} & B_{13} \\ B_{21} & B_{22} & B_{23} \\ B_{31} & B_{32} & B_{33} \end{bmatrix} = \begin{bmatrix} \phi\theta\lambda_1' & -\phi\theta\lambda_1' & 0 \\ -\phi\theta\lambda_1' & \phi\theta\lambda_1' + \theta\lambda_2 & -\lambda_2\theta \\ 0 & -\lambda_2\theta & \lambda_2\theta \end{bmatrix}. \quad (24)$$

Multiplying Eq. (22) by Y_k, $k = 1, 2, 3$, and integrating the resultant expression yield the equation for the first moments, i.e. means, of the random variables, Y_i's,

$$\frac{\mathrm{d}}{\mathrm{d}t}E[Y_k] = \sum_{j=1}^{3} A_{kj}E[Y_j], \quad k = 1, 2, 3. \quad (25)$$

By substituting Eqs. (23) and (24) into the above equation and expanding the resultant equation, the explicit expressions for the equations governing the means of individual Y_i's are generated as follows

$$\frac{\mathrm{d}}{\mathrm{d}t}E[Y_1] = (-\theta\lambda_1')E[Y_1] + (-\phi\lambda_1')E[Y_2], \quad (26)$$

$$\frac{\mathrm{d}}{\mathrm{d}t}E[Y_2] = (\theta\lambda_1')E[Y_1] + (\phi\lambda_1' - \lambda_2)E[Y_2], \quad (27)$$

$$\frac{\mathrm{d}}{\mathrm{d}t}E[Y_3] = \lambda_2 E[Y_2]. \quad (28)$$

Multiplying Eq. (22) by Y_iY_j, $i, j = 1, 2, 3$, and integrating the resultant expression give the equation for the second moments, Y_iY_j's, as

$$\frac{\mathrm{d}}{\mathrm{d}t}E[Y_iY_j] = \sum_{k=1}^{3} A_{ik}E[Y_kY_j] + \sum_{k=1}^{3} A_{jk}E[Y_iY_k] + B_{ij}, \quad i, j = 1, 2, 3. \quad (29)$$

By substituting Eqs. (23) and (24) with $i = j$ into the above equation and expanding the resultant equation, the explicit expressions for the equations governing the variances of individual Y_i's are generated as follows (Appendix B)

$$\frac{\mathrm{d}}{\mathrm{d}t}E[Y_1^2] = 2(-\theta\lambda_1')E[Y_1^2] + 2(-\phi\lambda_1')E[Y_1Y_2] + \phi\theta\lambda_1', \quad (30)$$

$$\frac{\mathrm{d}}{\mathrm{d}t}E[Y_2^2] = 2(\theta\lambda_1')E[Y_1Y_2] + 2(\phi\lambda_1' - \lambda_2)E[Y_2^2] + \phi\theta\lambda_1' + \lambda_2\theta, \quad (31)$$

$$\frac{\mathrm{d}}{\mathrm{d}t}E[Y_3^2] = 2\lambda_2 E[Y_2Y_3] + \lambda_2\theta. \quad (32)$$

By substituting Eqs. (23) and (24) into Eq. (29) and expanding the resultant equations, the explicit expressions for the equations governing the individual covariances, Y_iY_j, are generated as follows (Appendix B)

$$\frac{\mathrm{d}}{\mathrm{d}t}E[Y_1Y_2] = (\phi\lambda_1' - \lambda_2 - \theta\lambda_1')E[Y_1Y_2] + (-\phi\lambda_1')E[Y_2^2] + (\theta\lambda_1')E[Y_1^2] - \phi\theta\lambda_1', \quad (33)$$

$$\frac{\mathrm{d}}{\mathrm{d}t}E[Y_1Y_3] = (-\theta\lambda_1')E[Y_1Y_3] + (-\phi\lambda_1')E[Y_2Y_3] + \lambda_2 E[Y_1Y_2], \quad (34)$$

$$\frac{\mathrm{d}}{\mathrm{d}t}E[Y_2Y_3] = (\theta\lambda_1')E[Y_1Y_3] + (\phi\lambda_1' - \lambda_2)E[Y_2Y_3] + \lambda_2 E[Y_2^2] - \lambda_2\theta. \quad (35)$$

3. Simulation

The epidemic model presented in the preceding section has been simulated by two approaches. The first relies on the solution of the governing equations for the first and second moments of the random variables derived from the master equations and the second resorts to the event-driven Monte Carlo algorithm. The values of the parameters characterizing the dynamics of infection, i.e. the transition-intensity functions, are taken prior to the simulations, as discussed below.

3.1. Assessment of system parameters

In 1978 in the British medical journal, *The Lancet*, there was a report with detailed statistics of a flu epidemic in a boys boarding school with a total of 763 boys (Murray, 2002). Of these 512 were confined to bed during the epidemic, which lasted from January 22nd to February 4th, 1978. There was one infected boy at the beginning of the epidemic. This report contains data that match closely with the SIR model.

The process of interest is characterized by the transition-intensity functions, λ_i's, defining the probabilities of transitions of each type of population per unit time. If the fraction of population converted per unit time is taken to represent the intensity function, its significance is equivalent to the deterministic rate constant of the specific rate. In other words, from the change in the population of a particular class i due to the conversion of type i during the time interval, $(t, t + \Delta t)$, we have

$$-R_i = \lim_{\Delta t \to 0} \frac{n_i - [n_i - n_i\lambda_i\Delta t + o(\Delta t)]}{\Omega\Delta t} = \lambda_i \frac{n_i}{\Omega},$$

where Ω stands for the system size, i.e. the total initial population; and $-R_i$, the population converted attributable to transition type i per unit time. A detailed discussion of the relationship between the rate constant

and the intensity function can be found in van Kampen (1992). According to Murray (2002), the rate constants for the two types of transitions described in a SIR model are:

Rate constant of infection spread, $r = 0.00218/\text{day}$,

Rate constant of recovery, $a = 0.44036/\text{day}$.

3.2. Simulation based on the master equations

From the system size expansion of master equations presented in the preceding section we obtain Eqs. (18)–(20), Eqs. (26)–(28), and Eqs. (30)–(35). To simulate the temporal profile of the epidemic, all the above differential equations form Eqs. (18)–(35) have been solved simultaneously using a MATLAB command, ode45, a software package based on Gear's method of solving a set of ordinary differential equations (Petzold and Hindmarsh, 1997). Among these equations, Eqs. (18)–(20) are for the means; Eqs. (30)–(32), for the variance; and Eqs. (33)–(35), for covariance.

The total number of initial populations, Ω, is set 763 and the initial ratio of the susceptible to infected population is taken to be 762:1 while the initial number of recovered population is taken to be 0. Since the number of the three types of populations are known at the outset, the initial values for variances and covariances are zero.

3.3. Monte Carlo simulation

Linear or nonlinear dynamic processes have been simulated either deterministically or stochastically by Monte Carlo procedures. It is worth noting that a well-developed class of Monte Carlo simulation procedures essentially share identical computational bases with the master-equation algorithm presented in the preceding sections. Specifically, the assumptions of Markov property and temporal homogeneity of the random variables lead to the definitions of transition-intensity functions (see, e.g. Gillespie, 1977, 1992). As discussed in the Model Formulation section, probability balances of various events on the basis of these intensity functions give rise to the master equations. In the Monte Carlo simulation, the system's state is simulated by a step-wise, random-walk scheme based on the same intensity functions.

Process systems or phenomena can be simulated by time- and event-driven Monte Carlo procedures (see, e.g. Rajamani et al., 1986). The difference between these two procedures is in the manner of updating the time clock of the evolution of the system. The time-driven procedure advances the simulation clock by a prespecified time increment, Δt, which is sufficiently small so that at most one event will occur in this interval. The probability of an event occurring is determined by the nature and magnitudes of the transition-intensity functions. In contrast, the event-driven procedure updates the simulation clock by randomly generating the waiting time, τ_w, which has an exponential distribution (Karlin and Taylor, 1981); this distribution signifies that a population transition takes place completely randomly. At the end of each waiting interval, one event will occur, and the state to which the system will transfer is also determined by the nature of the transition-intensity functions.

The process of interest here, i.e. disease spread, has been simulated by the event-driven procedure; it is usually computationally faster than the time-driven procedure. The simulation starts with a given initial distribution of population; the essential task is to obtain the probability distributions of the infective numbers at any subsequent times. To determine the system transition in each time step, two random numbers are generated for two different purposes. The first random number in (0, 1), i.e. r_1, is for estimating the waiting time during which a possible transition of the system's state will take place. The second random number in (0, 1), i.e. r_2, is for identifying the transition type.

3.3.1. Waiting time

Let $T_{\mathbf{n}}$ be the random variable representing the waiting time of the population system of interest at state $\mathbf{n}$ prior to its transition due to the transformation of an infected person, and let τ_w be the realization of $T_{\mathbf{n}}$. Moreover, let $G_{\mathbf{n}}(\tau_w)$ be the probability that no transition occurs during the time interval, τ_w. Thus

$$G_n(\tau_w) = \Pr(T_n \geqslant \tau_w) \tag{36}$$

which can be expressed as (see Appendix C)

$$G_n(\tau_w) = \exp[-(n_1 n_2 \lambda_1 + n_2 \lambda_2)\tau_w]. \tag{37}$$

The complement of $G_{\mathbf{n}}(\tau_w)$,

$$H_n(\tau_w) = 1 - G_n(\tau_w) \tag{38}$$

expresses the cumulative probability distribution of $T_{\mathbf{n}}$ up to τ_w. The probability-density function of $T_{\mathbf{n}}$, i.e.

$$h(\tau_w) \equiv \frac{\mathrm{d}H_n(\tau_w)}{\mathrm{d}\tau_w}.$$

Therefore, has the following exponential form (see Appendix C).

$$h(\tau_w) = (n_1 n_2 \lambda_1 + n_2 \lambda_2)\exp[-(n_1 n_2 \lambda_1 + n_2 \lambda_2)\tau_w]. \tag{39}$$

Note that, $H_{\mathbf{n}}(\tau_w)$ is the probability function of $T_{\mathbf{n}}$.

Eq. (39) indicates that, to estimate the waiting time of the disease spread, τ_w, a sequence of exponentially distributed random numbers must be generated. The sequences of the computer-generated random numbers, however, are usually uniformly distributed in interval [0, 1]. This uniform distribution, therefore, need be transformed into the exponential distribution, which can be accomplished by defining a new random variable,

denoted by U, whose realization, denoted by u, assumes the value of $H_{\mathbf{n}}(\tau_w)$ at τ_w (see, e.g. Gillespie, 1992), i.e.

$$u = H_n(\tau_w) = 1 - \exp[-(n_1 n_2 \lambda_1 + n_2 \lambda_2)\tau_w] \quad (40)$$

or, inversely,

$$\tau_w = \frac{-1}{-(n_1 n_2 \lambda_1 + n_2 \lambda_2)} \ln[1-u]. \quad (41)$$

It can be verified that if the waiting time, $T_{\mathbf{n}}$, whose realization is τ_w, is exponentially distributed, then the random variable, U, whose realization is u, is uniformly distributed over interval [0, 1] (Appendix D).

3.3.2. Probabilities of two possible transitions

After residing in state $\mathbf{n} = (n_1, n_2, n_3)$ for a waiting time of τ_w, the system will transfer to one of its adjacent states. During the process, the transition intensities of the spread of disease from state (n_1, n_2, n_3) to state $(n_1 - 1, n_2 + 1, n_3)$ and $(n_1, n_2 - 1, n_3 + 1)$ are λ_1 and λ_2, respectively; these infection and recovery process are the exact equivalent of the system transitions from states $(n_1 + 1, n_2 - 1, n_3)$ and $(n_1, n_2 + 1, n_3 - 1)$ to state (n_1, n_2, n_3). The probability of the system transferring from state (n_1, n_2, n_3) to $(n_1 - 1, n_2 + 1, n_3)$ during the process is

$$Q_1 = \frac{n_1 n_2 \lambda_1}{n_1 n_2 \lambda_1 + n_2 \lambda_2}. \quad (42)$$

Similarly, the probability of the system transferring from state (n_1, n_2, n_3) to $(n_1, n_2 - 1, n_3 + 1)$ during process is

$$Q_2 = \frac{n_2 \lambda_2}{n_1 n_2 \lambda_1 + n_2 \lambda_2}. \quad (43)$$

Since the sum of Q_1 and Q_2 is 1, the reaction type can be identified by the randomly generated number, r_2. Specifically, r_2 falling within the interval,

$$\left[0, \frac{n_1 n_2 \lambda_1}{n_1 n_2 \lambda_1 + n_2 \lambda_2}\right] \quad (44)$$

implies that a susceptible person is infected; r_2 falling within the interval,

$$\left[\frac{n_1 n_2 \lambda_1}{n_1 n_2 \lambda_1 + n_2 \lambda_2}, 1\right] \quad (45)$$

implies that an infected person recovered.

3.3.3. Simulation algorithm

A step-wise description of the event-driven procedure is given below.

1. Choose an initial population size, and let the number of replications, Ω, be the sum of initial healthy and infected population. Start the random walk from this state.

2. Select the total length of time of each simulation, T_f. For convenience, T_f has been selected as 20 days.

3. Determine the length of waiting time, τ_w. First, generate a random number, r_1, from a uniform distribution in [0, 1]; then, calculate τ_w, for a system's transition at state (n_1, n_2, n_3) according to Eq. (41).

4. Update the computer clock by letting $t = t + \tau_w$.

5. Calculate the transition probabilities that the system will transfer from state $\mathbf{n}$ to the other states, Q_i's, by Eqs. (42) and (43). Then, generate another random number, r_2, from a uniform distribution in [0, 1]. Determine the transition type by examining in which interval given by Eqs. (44) and (45) is r_2 located.

6. Repeat steps 3–5 until the total time exceeds T_f; this terminates one replication of simulation.

7. Repeat steps 2–6 for Ω (763 times) times, and store the resultant number of people of type i during the jth replication at time t, $n_{ij}(t)$. This yields the mean number of people of type i at time t, i.e.

$$E[N_i(t)] = \frac{\sum_{j=1}^{\Omega} n_{ij}}{\Omega}. \quad (46)$$

The variance of population of type i at time t can be calculated from its definition, i.e.

$$Var[N_i(t)] = \frac{\sum_{j=1}^{\Omega} (n_{ij} - E[N_i(t)])^2}{\Omega - 1}. \quad (47)$$

The covariance around the means between two types of population, i and j, at time t can be calculated from its definition, i.e.

$$Cov[N_i(t), N_j(t)] = \frac{\sum_{h=1}^{\Omega}\sum_{k=1}^{\Omega} (n_{ih} - E[N_i(t)])(n_{jk} - E[N_j(t)])}{\Omega - 1}. \quad (48)$$

As mentioned at the outset of this section, both the Monte Carlo simulation and the simulation based on the master equations adopted in the current work are rooted in the identical set of transition-intensity functions derived from the same set of assumptions. Thus, integrating the equations for the first and second moments of the master equations, Eqs. (26)–(35) for the process, is expected to generate results nearly identical to those from the Monte Carlo simulations, i.e. Eqs. (46)–(48).

4. Results and discussion

A stochastic analysis of the proposed model has yielded the transition probabilities or, more specifically, transition-intensity functions, of spread of infection and recovery among the population. This renders it possible to derive the nonlinear master equations of the model through stochastic population balance and to derive the

event-driven Monte Carlo procedure for the model, both of which enable the model to be simulated independent of each other.

4.1. Simulation based on the master equations

Figs. 2–4 present the temporal profiles of epidemic spread from the infectives to susceptibles with 763 total initial population and an initial ratio of the susceptibles to infectives of 762:1. It is observed that the number of healthy population decreases continuously to a constant value, as the population of infective class increases to a maximum value and then decreases and reaches to zero eventually. The recover population increases steadily over the entire period.

The envelopes of standard deviation around the means in Figs. 2–4 are indicative of the internal, or system, fluctuations (van Kampen, 1992) or inherent uncertainties in the numbers of susceptible, infective and recovered classes during the infection spread process. In a stable system, the standard deviation of population of either susceptibles or infectives class attains the maximum, or maxima, because the state of the system is usually well defined at the outset of the process and the uncertainties decline eventually until it vanishes upon stabilization (Carmichael, 1999). The uncertainties are caused by the discrete nature of the system and is particular notable when the population is increasing and decreasing. Therefore, two maxima are observed for the fluctuations of the infected population, each corresponds to an inflection point in the mean trajectory. The master equations resulting from the stochastic analysis

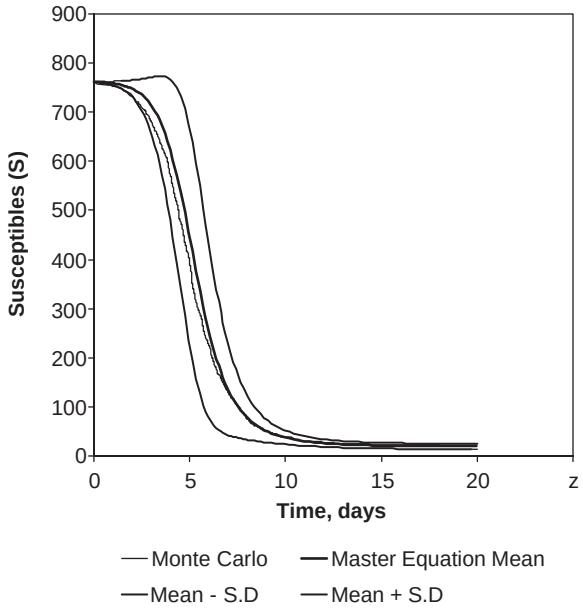

Fig. 2. Temporal profile of the susceptibles population with their standard deviation envelop by master-equation. Also included is a single simulation from the Monte Carlo procedure.

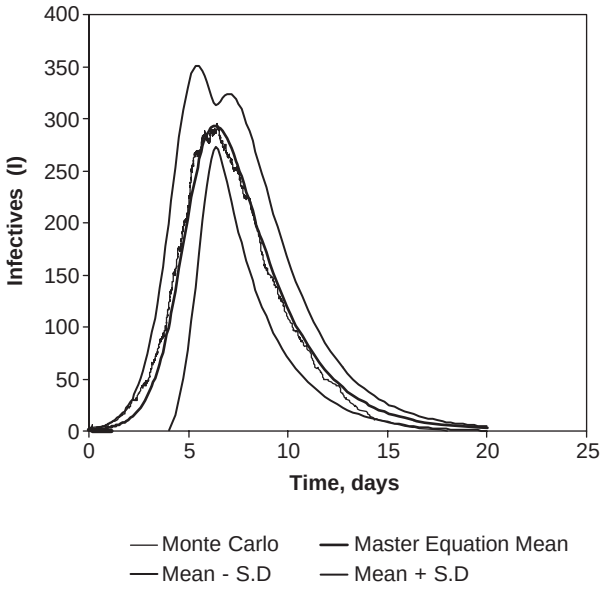

Fig. 3. Temporal profile of the infected population with their standard deviation envelop by master-equation. Also included is a single simulation from the Monte Carlo procedure.

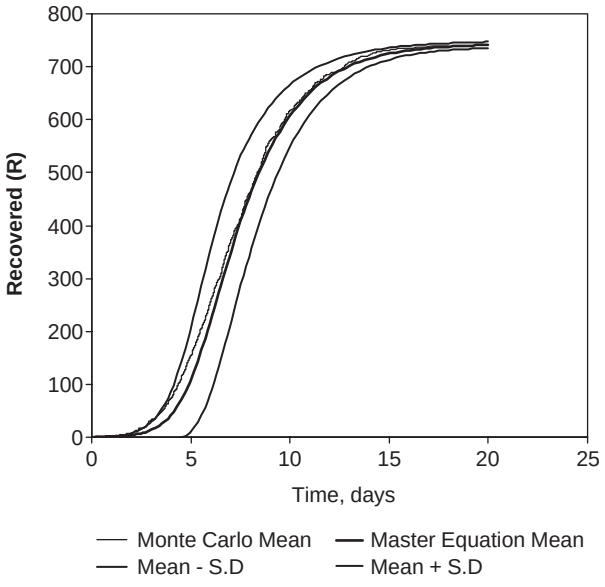

Fig. 4. Temporal profile of the recovered population with their standard deviation envelop by master-equation. Also included is a single simulation from the Monte Carlo procedure.

of a complex process facilitate the estimation of these minimum fluctuations. The parameters in the equations, e.g. the intensity functions, are presumed to depend only on the major variables of the system and to be independent of the variables of secondary importance. Neglecting these secondary variables is, in essence, the source of internal noises that should be appropriately

analysed stochastically. For the current work, the transition-intensity functions correspond to the infection and recovery rates of its deterministic counter parts.

The standard deviations around the means in Figs. 2–4 are indicative of the internal noises which govern the minimum scattering expected of a measured variable. The appreciable internal fluctuations are characteristic of a mesoscopic, discrete system (van Kampen, 1992). Since a process usually evolves under the influence of external variables and their fluctuations, the observed fluctuations are expected to be higher than the internal fluctuations predicted by the model.

Unlike the fluctuations and noises induced by external disturbances, the system's inherent fluctuations, i.e. internal noises, are extremely difficult, if not impossible, to reduce. These inherent fluctuations or noises can indeed be substantial under some conditions as mentioned earlier.

The master-equation algorithm reveals the minimum system fluctuations and is not restricted by the linearity of the process. As presented in the current work, the system-size expansion procedure has given rise to a powerful algorithm for solving or simulating various nonlinear stochastic processes.

As indicated earlier, the discrete nature of infection process is the source of the fluctuations; therefore, the magnitude of intrinsic fluctuations depends on the population. Note that the random variables, Y_1, Y_2, and Y_3, in Eqs. (11)–(13) have been defined based on the premise that the internal fluctuations around the macroscopic means are inversely proportional to the square root of the total population in the system, Ω.

To illuminate the evolutions of the probability distribution of a specific population, three-dimensional representation of the stochastic process from master equation algorithm is shown in Fig. 5 for infective class.

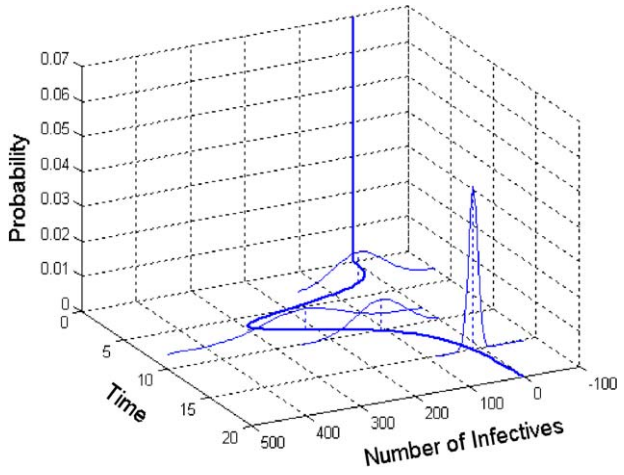

Fig. 5. Three-dimensional representation of stochastic process for infective population.

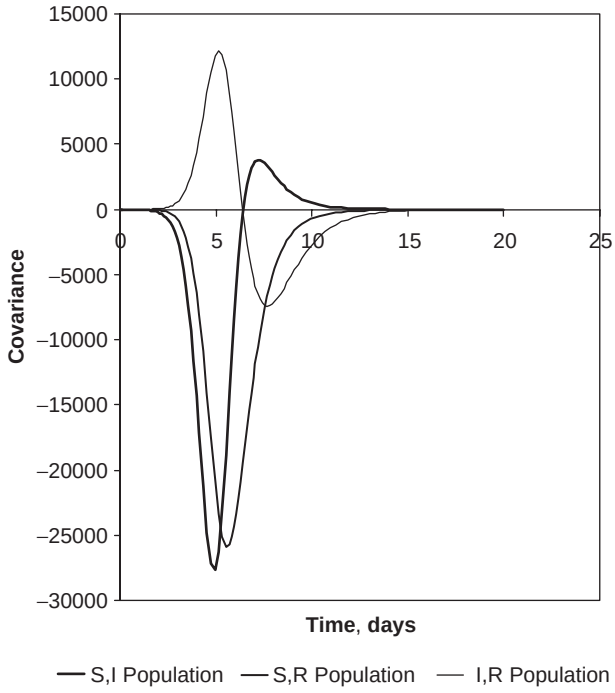

Fig. 6. Temporal evolutions of the three covariances from the simulation of population containing 762 initial susceptibles and 1 infected by the master-equation algorithm.

The uncertainties are developed by assuming normal distributions of three random variables. Three-dimensional figures for the susceptible and recovered classes are posted on the web under the title "3D Figures" at: home.olemiss.edu/~cmchengs/SIR_Model/.

The covariances around the means between the three types of population are plotted in Fig. 6; note that the interactions between the three types of population can be appreciable. The covariances, similar to the variances, are quantities which cannot be evaluated a priori by a deterministic model. Note that the minimum fluctuation of the infected class during the process take place at about 5 days. This time corresponds to zero covariances, Y_1Y_2 and Y_2Y_3, as shown in Fig. 6 and Eq. (31).

4.2. Simulation based on the Monte Carlo procedure

Monte Carlo simulations have yielded results essentially indistinguishable from those generated from the master equations, i.e. those shown in Figs. 2–4. As discussed earlier, this is expected since the algorithms based on the event-driven Monte Carlo procedure and master equations derived in the present work are rooted in the identical assumptions, i.e. the Markov property and temporal homogeneity of the random variables. These assumptions lead to the definitions of transition-intensity functions which are the cornerstones of the

formulation of the master equations and of the Monte Carlo procedure. Three traces from the Monte Carlo simulations, one for each population, are in Figs. 2–4 for comparison.

Although the master-equation algorithm and the Monte Carlo algorithm share common assumptions, they are independent of each other. The fact that the two algorithms have yielded essentially the same results implies that both indeed define the evolution of dynamic process in a precisely equivalent way. The master-equation algorithm generates the equations governing the statistical moments of the process, which can be readily varied to cover a wide range of initial conditions, whereas the Monte Carlo procedure will require far more computational time and storage space under such circumstances.

The current model adopts the essential concepts of a nonlinear epidemic model for analysing the spread of infection of a system. This master-equation algorithm, along with its system-size expansion, involves the stochastic probability balance of the three type of populations; the resultant master equation should yield not only the deterministic evolution of infected population reported by influenza epidemic, but also the fluctuations, or uncertainties inherited in the prediction or measurement.

5. Concluding remarks

The spread of an epidemic from the susceptibles to the infected have been estimated through a nonlinear stochastic analysis. Subsequently, this has given rise to the master equations subject to system-size expansion and to the event-driven Monte Carlo procedure for numerical representation of the model. The master equations are capable of estimating not only the means, but also the variances, or fluctuations, of three classes of population and the covariances between them. Explicit expressions governing the variances and covariance have been derived to demonstrate the efficiency of the master-equation algorithm and concomitant system-size expansion in the analysis, modeling and simulation of nonlinear stochastic processes.

The validity of the model is amply demonstrated by numerically calculating the evolution of population of both types and their fluctuations over time through two simulation algorithms, one based on the master equations and the other based on the event-driven Monte Carlo procedure. These two algorithms are implemented totally independently of each other but with the same set of system parameters, i.e. the transition-intensity functions. Hence, it is indeed remarkable that the two algorithms have yielded essentially identical results.

Appendix A. Derivation of the macroscopic equations by system-size expansion

For convenience, the random variables of the system, i.e. Eqs. (11)–(13) in the text, are reproduced below.

$$N_1(t) = \Omega^{1/2}\phi(t) + \Omega^{1/2}\,Y_1(t), \tag{A.1}$$

$$N_2(t) = \Omega^{1/2}\theta(t) + \Omega^{1/2}\,Y_2(t), \tag{A.2}$$

$$N_3(t) = \Omega^{1/2}\gamma(t) + \Omega^{1/2}\,Y_3(t). \tag{A.3}$$

The realizations of these random variables can be written, respectively, as

$$n_1(t) = \Omega\phi(t) + \Omega^{1/2}y_1(t), \tag{A.4}$$

$$n_2(t) = \Omega\theta(t) + \Omega^{1/2}y_2(t), \tag{A.5}$$

$$n_3(t) = \Omega\gamma(t) + \Omega^{1/2}y_3(t). \tag{A.6}$$

Recall in the context of deriving the master equation that the state or dependent variable of interest is the joint probability of the population distribution, $P_{\mathbf{n}}(t)$, and the realizations of random variables at time t, i.e., n_1, n_2, and n_3 at the reference state, is regarded to be invariant with respect to time. Consequently, the time derivatives of Eqs. (A.4), (A.5), and (A.6) are, respectively,

$$\frac{\mathrm{d}y_1}{\mathrm{d}t} = -\Omega^{1/2}\frac{\mathrm{d}\phi}{\mathrm{d}t}, \tag{A.7}$$

$$\frac{\mathrm{d}y_2}{\mathrm{d}t} = -\Omega^{1/2}\frac{\mathrm{d}\theta}{\mathrm{d}t}, \tag{A.8}$$

$$\frac{\mathrm{d}y_3}{\mathrm{d}t} = -\Omega^{1/2}\frac{\mathrm{d}\gamma}{\mathrm{d}t}. \tag{A.9}$$

The left-hand side of Eq. (22) in the text, therefore, can be rewritten as

$$\begin{aligned}\frac{\mathrm{d}P_n(t)}{\mathrm{d}t} &= \frac{\mathrm{d}\Psi_y(t)}{\mathrm{d}t}\\ &= \frac{\partial\Psi}{\partial t} + \frac{\partial\Psi}{\partial y_1}\frac{\mathrm{d}y_1}{\mathrm{d}t} + \frac{\partial\Psi}{\partial y_2}\frac{\mathrm{d}y_2}{\mathrm{d}t} + \frac{\partial\Psi}{\partial y_3}\frac{\mathrm{d}y_3}{\mathrm{d}t}\\ &= \frac{\partial\Psi}{\partial t} - \Omega^{1/2}\frac{\partial\Psi}{\partial y_1}\frac{\mathrm{d}\phi}{\mathrm{d}t}\\ &\quad - \Omega^{1/2}\frac{\partial\Psi}{\partial y_2}\frac{\mathrm{d}\theta}{\mathrm{d}t} - \Omega^{1/2}\frac{\partial\Psi}{\partial y_3}\frac{\mathrm{d}\gamma}{\mathrm{d}t}.\end{aligned} \tag{A.10}$$

The step operator, D_n^{-1}, changes n_1 into (n_1+1) and therefore, y_1 into

$$(y_1 + \Omega^{-1/2}).$$

Hence, it can be expanded into Taylor's series as

$$D_{n_1} = 1 + \Omega^{-1/2}\frac{\partial}{\partial y_1} + \frac{1}{2}\Omega^{-1}\frac{\partial^2}{\partial y_1^2} + \cdots \tag{A.11}$$

Similarly

$$D_{n_1}^{-1} = 1 - \Omega^{1/2}\frac{\partial}{\partial y_1} + \frac{1}{2}\Omega^{-1}\frac{\partial^2}{\partial y_1^2} - \cdots, \tag{A.12}$$

$$D_{n_1}^{2} = 1 + 2\Omega^{-1/2}\frac{\partial}{\partial y_1} + 2\Omega^{-1}\frac{\partial^2}{\partial y_1^2} + \cdots, \tag{A.13}$$

$$D_{n_2} = 1 + \Omega^{-1/2}\frac{\partial}{\partial y_2} + \frac{1}{2}\Omega^{-1}\frac{\partial^2}{\partial y_2^2} + \cdots, \tag{A.14}$$

$$D_{n_2}^{-1} = 1 - \Omega^{1/2}\frac{\partial}{\partial y_2} + \frac{1}{2}\Omega^{-1}\frac{\partial^2}{\partial y_2^2} - \cdots, \tag{A.15}$$

$$D_{n_3}^{-1} = 1 - \Omega^{1/2}\frac{\partial}{\partial y_3} + \frac{1}{2}\Omega^{-1}\frac{\partial^2}{\partial y_3^2} - \cdots \tag{A.16}$$

Substituting Eqs. (A.4)–(A.6) and Eqs. (A.10)–(A.16) into Eq. (10) in the text yields

$$\begin{aligned}
&\frac{\partial \Psi}{\partial t} - \Omega^{1/2}\frac{\mathrm{d}\phi}{\mathrm{d}t}\frac{\partial \Psi}{\partial y_1} - \Omega^{1/2}\frac{\mathrm{d}\theta}{\mathrm{d}t}\frac{\partial \Psi}{\partial y_2} - \Omega^{1/2}\frac{\mathrm{d}\gamma}{\mathrm{d}t}\frac{\partial \Psi}{\partial y_3} \\
&\quad = \lambda_1\left\{\left[1 + \Omega^{1/2}\left(\frac{\partial y}{\partial y_1} - \frac{\partial y}{\partial y_2}\right)\right.\right. \\
&\qquad \left.\left. + \frac{1}{2}\Omega^{-1}\left(\frac{\partial y}{\partial y_1} - \frac{\partial y}{\partial y_2}\right)^2 + \cdots\right]\right. \\
&\qquad \times \left[\phi\theta\Omega^2 + (\phi y_2 + \theta y_1)\Omega^{3/2} + y_1 y_2 \Omega\right] \\
&\qquad \left. - \left[\phi\theta\Omega^2 + (\phi y_2 + \theta y_1)\Omega^{3/2} + y_1 y_2 \Omega\right]\right\}\Psi \\
&\qquad + \lambda_2\left\{\left[1 + \Omega^{1/2}\left(\frac{\partial y}{\partial y_2} - \frac{\partial y}{\partial y_3}\right)\right.\right. \\
&\qquad \left.\left. + \frac{1}{2}\Omega^{-1}\left(\frac{\partial y}{\partial y_2} - \frac{\partial y}{\partial y_3}\right)^2 + \cdots\right]\right. \\
&\qquad \left. \times \left(\Omega\theta + \Omega^{1/2} y_2\right) - \left(\Omega\theta + \Omega^{1/2} y_2\right)\right\}\Psi.
\end{aligned} \tag{A.17}$$

Due to the nonlinear nature of the infection process, the magnitudes of the parameters, λ_1 and λ_2 differ by a factor of the system size, Ω; thus, we can define the normalized parameter, λ_1', as follows:

$$\lambda_1 = \lambda_1'\Omega^{-1}. \tag{A.18}$$

Substituting this expression into right-hand side of Eq. (A.17) and expanding the resultant expression and then Collecting the resultant terms of order $\Omega^{1/2}$ from that expression leads to

$$\begin{aligned}
&-\Omega^{1/2}\frac{\mathrm{d}\phi}{\mathrm{d}t}\frac{\partial \Psi}{\partial y_1} - \Omega^{1/2}\frac{\mathrm{d}\theta}{\mathrm{d}t}\frac{\partial \Psi}{\partial y_2} - \Omega^{1/2}\frac{\mathrm{d}\gamma}{\mathrm{d}t}\frac{\partial \Psi}{\partial y_3} \\
&\quad = \lambda_1'\left[\phi\theta\frac{\partial \Psi}{\partial y_1} - \phi\theta\frac{\partial \Psi}{\partial y_2}\right] + \lambda_2\left[\theta\frac{\partial \Psi}{\partial y_2} - \theta\frac{\partial \Psi}{\partial y_3}\right]
\end{aligned} \tag{A.19}$$

The terms in the above expression have to be valid for various . $\partial\psi/\partial y_1$, $\partial\psi/\partial y_2$ and $\partial\psi/\partial y_3$. As a result, Eq. (A.19) reduces to the following three expressions:

$$\frac{\mathrm{d}\phi}{\mathrm{d}t} = -\lambda_1'\phi\theta, \tag{A.20}$$

$$\frac{\mathrm{d}\phi}{\mathrm{d}t} = -\lambda_1'\phi\theta - \lambda_2\theta, \tag{A.21}$$

$$\frac{\mathrm{d}\gamma}{\mathrm{d}t} = \lambda_2\theta \tag{A.22}$$

which are the macroscopic equations of the system, i.e. Eqs. (18), (19), and (20), respectively, in the text.

Appendix B. Derivation of equations governing the first and second moments of fluctuations by the system-size expansion

Collecting the resultant terms of order Ω^0 from Eq. (A.17) leads to

$$\begin{aligned}
\frac{\partial \Psi}{\partial t} &= \lambda_1'\begin{bmatrix} \theta\frac{\partial}{\partial y_1}(y_1\Psi) + \phi\frac{\partial}{\partial y_1}(y_2\Psi) - \phi\frac{\partial}{\partial y_2}(y_2\Psi) - \theta\frac{\partial}{\partial y_2}(y_1\Psi) + \frac{1}{2}\phi\theta\frac{\partial^2}{\partial y_1^2}\Psi \\ -\phi\theta\frac{\partial^2}{\partial y_1 \partial y_2}\Psi + \frac{1}{2}\phi\theta\frac{\partial^2}{\partial y_2^2}\Psi \end{bmatrix} \\
&\quad + \lambda_2\left[\frac{\partial}{\partial y_2}(y_2\Psi) - \frac{\partial}{\partial y_3}(y_2\Psi) + \frac{1}{2}\theta\frac{\partial^2}{\partial y_2^2}\Psi - \theta\frac{\partial^2}{\partial y_2 \partial y_3}\Psi + \frac{1}{2}\theta\frac{\partial^2}{\partial y_3^2}\Psi\right].
\end{aligned} \tag{B.1}$$

This linear Fokker–Planck equation can be rewritten compactly as

$$\frac{\partial \Psi}{\partial t} = -\sum_{i,j} A_{ij}\frac{\partial}{\partial y_i}(y_j\Psi) + \frac{1}{2}\sum_{i,j} B_{ij}\left(\frac{\partial^2 \Psi}{\partial y_i \partial y_j}\right), \tag{B.2}$$

where

$$A = \begin{bmatrix} A_{11} & A_{12} & A_{13} \\ A_{21} & A_{22} & A_{23} \\ A_{31} & A_{32} & A_{33} \end{bmatrix} = \begin{bmatrix} -\theta\lambda_1' & -\phi\lambda_1' & 0 \\ \theta\lambda_1' & \phi\lambda_1' - \lambda_2 & 0 \\ 0 & \lambda_2 & 0 \end{bmatrix} \tag{B.3}$$

and

$$\begin{aligned}
B &= \begin{bmatrix} B_{11} & B_{12} & B_{13} \\ B_{21} & B_{22} & B_{23} \\ B_{31} & B_{32} & B_{33} \end{bmatrix} \\
&= \begin{bmatrix} \phi\theta\lambda_1' & -\phi\theta\lambda_1' & 0 \\ -\phi\theta\lambda_1' & \phi\theta\lambda_1' + \theta\lambda_2 & -\lambda_2\theta \\ 0 & -\lambda_2\theta & \lambda_2\theta \end{bmatrix}.
\end{aligned} \tag{B.4}$$

Multiplying Eq. (B.2) with Y_k, $k = 1, 2, 3$, and integrating the resultant expression yield the equations for the

means of the random variables, Y_k,

$$\frac{d}{dt}E[Y_k] = \sum_{j=1}^{3} A_{kj}E[Y_k], \quad k = 1,2,3 \tag{B.5}$$

which is Eq. (25) in the text. Similarly, multiplying the Eq. (B.2) with Y_iY_j, i, $j = 1,2,3$, and integrating the resultant expression give the equation for the second moments as

$$\frac{d}{dt}E[Y_iY_j] = \sum_{k=1}^{3} A_{ik}E[Y_kY_j] + \sum_{k=1}^{3} A_{jk}E[Y_iY_k] + B_{ij}, \quad i,j = 1,2,3 \tag{B.6}$$

which is Eq. (29) in the text.

Eqs. (B.5) and (B.6) can be expanded, thereby yielding the following expressions governing the means of the fluctuations in terms of the realization of the random variables, Y_k, $k = 1,2,3$:

$$\frac{d}{dt}E[y_1] = A_{11}E[y_1] + A_{12}E[y_2] + A_{13}E[y_3], \tag{B.7}$$

$$\frac{d}{dt}E[y_2] = A_{21}E[y_1] + A_{22}E[y_2] + A_{23}E[y_3] \tag{B.8}$$

$$\frac{d}{dt}E[y_3] = A_{31}E[y_1] + A_{32}E[y_2] + A_{33}E[y_3]. \tag{B.9}$$

Eqs. (B.5) and (B.6) can be expanded, thereby yielding the following expressions governing the variances of the fluctuations in terms of the realization of the random variables, Y_k, $k = 1,2,3$:

$$\frac{d}{dt}E[y_1^2] = 2A_{11}E[y_1^2] + 2A_{12}E[y_2y_1] + 2A_{13}E[y_3y_1] + B_{11}, \tag{B.10}$$

$$\frac{d}{dt}E[y_2^2] = 2A_{21}E[y_1y_2] + 2A_{22}E[y_2^2] + 2A_{23}E[y_3y_2] + B_{22}, \tag{B.11}$$

$$\frac{d}{dt}E[y_3^2] = 2A_{31}E[y_1y_3] + 2A_{32}E[y_2y_3] + 2A_{33}E[y_3^2] + B_{33}. \tag{B.12}$$

Eqs. (B.5) and (B.6) can be expanded, thereby yielding the following expressions governing the covariances of the fluctuations in terms of the realization of the random variables, Y_k, $k = 1,2,3$:

$$\frac{d}{dt}E[y_1y_2] = A_{11}E[y_1y_2] + A_{12}E[y_2^2] + A_{13}E[y_3y_2] + A_{21}E[y_1^2] + A_{22}E[y_1y_2] + A_{23}E[y_1y_3] + B_{12}, \tag{B.13}$$

$$\frac{d}{dt}E[y_1y_3] = A_{11}E[y_1y_3] + A_{12}E[y_2y_3] + A_{13}E[y_3^2] + A_{31}E[y_1^2] + A_{32}E[y_1y_2] + A_{33}E[y_1y_3] + B_{13}, \tag{B.14}$$

$$\frac{d}{dt}E[y_2y_3] = A_{21}E[y_1y_3] + A_{22}E[y_2y_3] + A_{23}E[y_3^2] + A_{31}E[y_2y_1] + A_{32}E[y_2^2] + A_{33}E[y_2y_3] + B_{23}. \tag{B.15}$$

Substituting Eqs. (B.3) and (B.4) into Eqs. (B.10)–(B.15) yields the equations governing the variances and covariances of the realizations of the random variables, Y_k, $k = 1,2,3$, as follows

$$\frac{d}{dt}E[y_1^2] = 2[-\theta\lambda_1']E[y_1^2] + 2[-\phi\lambda_1']E[y_1y_2] + \phi\theta\lambda_1', \tag{B.16}$$

$$\frac{d}{dt}E[y_2^2] = 2(\theta\lambda_1')E[y_1y_2] + 2(\theta\lambda_1' - \lambda_2)E[y_2^2] + \phi\theta\lambda_1' + \lambda_2\theta, \tag{B.17}$$

$$\frac{d}{dt}E[y_3^2] = 2\lambda_2E[y_2y_3] + \lambda_2\theta, \tag{B.18}$$

$$\frac{d}{dt}E[y_1y_2] = (\phi\lambda_1' - \lambda_2 - \theta\lambda_1')E[y_1y_2] + (-\phi\lambda_1')E[y_2^2] + (\theta\lambda_1')E[y_1^2] - \phi\theta\lambda_1', \tag{B.19}$$

$$\frac{d}{dt}E[y_1y_3] = (-\theta\lambda_1')E[y_1y_3] + (-\phi\lambda_1')E[y_2y_3] + \lambda_2E[y_1y_2], \tag{B.20}$$

$$\frac{d}{dt}E[y_2y_3] = (\theta\lambda_1')E[y_1y_3] + (\phi\lambda_1' - \lambda_2)E[y_2y_3] + \lambda_2E[y_2^2] - \lambda_2\theta. \tag{B.21}$$

which are Eqs. (30)–(35), respectively, in the text.

Appendix C. Derivations of the distribution functions of waiting time

Eq. (6) in the text indicates that the probability of no transition in the small time interval, $(\tau_w, \tau_w + \Delta\tau_w)$, is

$$G_n(\Delta\tau_w) = [1 - (n_1n_2\lambda_1 + n_2\lambda_2)\Delta\tau_w] + o(\Delta\tau_w). \tag{C.1}$$

The Markov property implies that succeeding time intervals, $(0, \tau_w)$ and $(\tau_w, \tau_w + \Delta\tau_w)$, are independent of

each other (see, e.g., Karlin and Taylor, 1975); thus

$$G_n(\tau_w+\Delta\tau_w) = G_n(\tau_w)G_n(\Delta\tau_w) = G_n(\tau_w)[1-(n_1n_2\lambda_1+n_2\lambda_2)\Delta\tau_w]+o(\Delta\tau_w). \quad (C.2)$$

Rearranging the above expression yields

$$G_n(\tau_w+\Delta\tau_w)-G_n(\tau_w) = -G_n(\tau_w)(n_1n_2\lambda_1+n_2\lambda_2)\Delta\tau_w+o(\Delta\tau_w). \quad (C.3)$$

Dividing this expression by $\Delta\tau_w$ and taking the limits as $\Delta\tau_w \to 0$ give

$$\frac{dG_n(\tau_w)}{d\tau_w} = -(n_1n_2\lambda_1+n_2\lambda_2)G_n(\tau_w). \quad (C.4)$$

By integrating this equation, with constant **n**, subject to the initial condition

$$G_n(0)=1, \quad (C.5)$$

we obtain

$$G_n(\tau_w) = \exp[-(n_1n_2\lambda_1+n_2\lambda_2)\tau_w]. \quad (C.6)$$

A more rigorous proof of Eq. (C.6) is given in chapter 14 of Karlin and Taylor (1981)

From the definition of $G_n(\tau_w)$, i.e., Eq. (36) in the text,

$$G_n(\tau_w) = Pr(T_n \geqslant \tau_w), = 1-H(\tau_w) = 1-\int_0^{\tau_w} h(\tau_w)\,d\tau_w. \quad (C.7)$$

Since $H_{\mathbf{n}}(\tau_w)$ is the cumulative probability distribution of $T_{\mathbf{n}}$ up to τ_w, i.e. the probability function of $T_{\mathbf{n}}$ at τ_w, $h(\tau_w)$ which is the derivative of $H_{\mathbf{n}}(\tau_w)$ with respect to τ_w is the probability-density function of $T_{\mathbf{n}}$. Hence

$$\frac{dH_n(\tau_w)}{d\tau_w} = h(\tau_w) = -\frac{dG_n(\tau_w)}{d\tau_w} \quad (C.8)$$

In light of Eq. (C.6), Eq. (C.8) gives rise to

$$h(\tau_w) = (n_1n_2\lambda_1+n_2\lambda_2)\exp[-(n_1n_2\lambda_1+n_2\lambda_2)\tau_w]. \quad (C.9)$$

Eqs. (C.6) and (C.9) are Eqs. (37) and (39) in the text, respectively; the latter signifies that the probability density for the population to make the next transition at τ_w is exponentially distributed.

Appendix D. Random number transformation

For convenience, Eq. (40) in the text is reiterated below.

$$u = H_n(\tau_w) = 1-\exp[-(n_1n_2\lambda_1+n_2\lambda_2)\tau_w]. \quad (D.1)$$

Obviously, $u=0$ at $\tau_w=0$ and $u=1$ when $\tau_w \to \infty$. We are to prove that the random variable, U, whose realization is u, is uniformly distributed in [0, 1].

Since u increases with τ_w monotonically according to Eq. (D.1), there is a one-to-one correspondence between u and τ_w, thereby leading to the expression which can be visualized as signifying that the probabilities of the same event in two different domains are identical; this expression is

$$h(\tau_w)\,d\tau_w = f(u)\,du, \quad (D.2)$$

where $h(\tau_w)$ and $f(u)$ are the probability-density functions of $T_{\mathbf{n}}$ and U, respectively. For transforming a random variable, an equivalent form of Eq. (D.2) is often given to account for a random variation in either positive or negative direction as follows (see, e.g., Casella and Berger, 1990):

$$f(u) = h(\tau_w)\left|\frac{d\tau_w}{du}\right|. \quad (D.3)$$

Eq. (D.2) or, strictly speaking, Eq. (D.3) signifies that the probability-density function of T_{n}, i.e., $h(\tau_w)$, is transformed into that of U, i.e., $f(u)$, such that the probability represented by $h(\tau_w)|d\tau_w|$ and that represented by $f(u)|du|$ are identical.

The function, $h(\tau_w)$, derived in Appendix C and given in the text as Eq. (39) is as follows:

$$h(\tau_w) = (n_1n_2\lambda_1+n_2\lambda_2)\exp[-(n_1n_2\lambda_1+n_2\lambda_2)\tau_w]. \quad (D.4)$$

Solving Eq. (D.1) for τ_w gives

$$\tau_w = \frac{-1}{(n_1n_2\lambda_1+n_2\lambda_2)}\ln[1-u]. \quad (D.5)$$

This is Eq. (41) in the text. By differentiating Eq. (D.5) with respect to u, we obtain

$$\left|\frac{d\tau_w}{du}\right| = \frac{1}{(n_1n_2\lambda_1+n_2\lambda_2)(1-u)} \quad (D.6)$$

Substituting Eqs. (D.4)–(D.6) into Eq. (D.3) leads to

$$f(u) = \exp[-(n_1n_2\lambda_1+n_2\lambda_2)\tau_w]\frac{1}{1-u} = \exp[\ln(1-u)]\frac{1}{1-u} = 1. \quad (D.7)$$

The values of u in the interval, [0, 1], as mentioned at the outset; consequently, the probabilitydensity function of U, i.e., $f(u)$, remains 1 throughout in the interval, [0, 1] as expressed above. In other words, U, the realization of which is u, is a random variable uniformly distributed over this interval; for convenience, the probability function or cumulative probability distribution of U is denoted by $F(u)$. The relationships among $H(\tau_w)$, $h(\tau_w)$, $F(u)$, and $f(u)$ are illustrated in Fig. D1. This figure has been up-loaded to the web along with the three-dimensional figures for the susceptible and recovered classes under the title "Figured1" at: home.olemiss.edu/~cmchengs/SIR_Model/

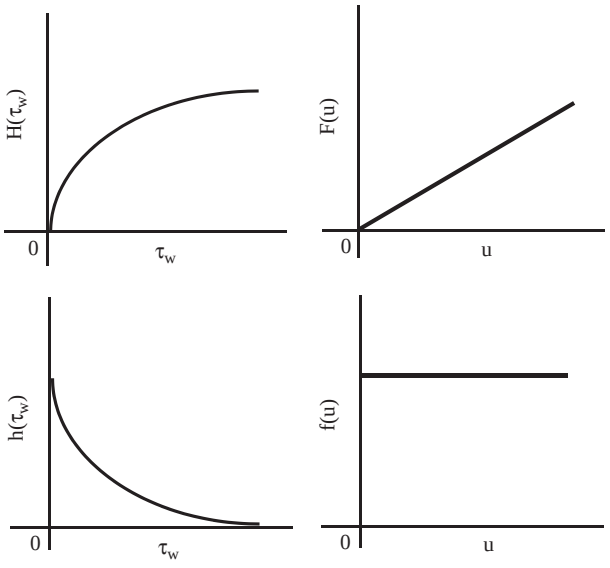

Fig. D1. Relationships among $H(\tau_w)$, $h(\tau_w)$, $F(u)$, and $f(u)$.

Appendix E. Conditional probabilities of the two possible transitions

Expressions are to be derived for the probabilities of the three possible populations transitions from state (n_1, n_2, n_3) to states $(n_1 - 1, n_2 + 1, n_3)$ and $(n_1, n_2 - 1, n_3 + 1)$, during the process, under the condition that the system will make one and only one transition during the time interval, $(t, t + \Delta t)$. The reaction's type is identified from these conditional probabilities upon the generation of a random number, r_2. The condition is imposed because the waiting time must be estimated for the occurrence of one transition prior to the identification of the reaction type. As illustrated in Fig. 1 in the text, the conditional probabilities of the two mutually exclusive events, which transform the system from state n at arbitrary time interval of $(t, t + \Delta t)$ can be written as follows:

[the system will transform from state **n** to another state due to spread of infection form infective to susceptible during the time interval, $(t, t + \Delta t)$]

$$= n_1 n_2 \lambda_1 \Delta t + o(\Delta t). \tag{E.1}$$

Pr [the system will transform from state **n** to another state due recovery from infective to healthy population during the time interval, $(t, t + \Delta t)$]

$$= n_2 \lambda_2 \Delta t + o(\Delta t). \tag{E.2}$$

Since the two events are mutually exclusive, the sum of these two probabilities is 1. Moreover, the probability of the system transferring from state (n_1, n_2, n_3) to state $(n_1 - 1, n_2 + 1, n_3)$ during the process is

$$Q_1 = \frac{n_1 n_2 \lambda_1 \Delta t + o(\Delta t)}{(n_1 n_2 \lambda_1 \Delta t + o(\Delta t)) + (n_2 \lambda_2 \Delta t + o(\Delta t))} = \frac{n_1 n_2 \lambda_1}{n_1 n_2 \lambda_1 + n_2 \lambda_2}. \tag{E.3}$$

Similarly, the probability of the epidemic system transferring from state (n_1, n_2, n_3) to state $(n_1, n_2 - 1, n_3 + 1)$ during the process is

$$Q_2 = \frac{n_2 \lambda_2 \Delta t + o(\Delta t)}{(n_1 n_2 \lambda_1 \Delta t + o(\Delta t)) + (n_2 \lambda_2 \Delta t + o(\Delta t))} = \frac{n_2 \lambda_2}{n_1 n_2 \lambda_1 + n_2 \lambda_2}. \tag{E.4}$$

Eqs. (E.3) and (E.4), are Eqs. (42) and (43), respectively, in the text.

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