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Stochastic models for the spread of HIV in a mobile heterosexual population

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Abstract

An important factor in the dynamic transmission of HIV is the mobility of the population. We formulate various stochastic models for the spread of HIV in a heterosexual mobile population, under the assumptions of constant and varying population sizes. We also derive deterministic and diffusion analogues for these models, using a convenient rescaling technique, and analyze their stability conditions and equilibrium behavior. We illustrate the dynamic behavior of the models and their approximations via a range of numerical experiments.

Keywords: HIV/AIDS; Mobility; Multiple patches; Epidemiology; Density dependent Markov process; Diffusion approximation

1. Introduction

One of the most urgent public-health problems in developing countries is the AIDS (Acquired Immune Deficiency Syndrome) epidemic, caused by the Human Immunodeficiency Virus (HIV). Since the first cases of AIDS were identified in 1981, the number of HIV infected people and

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AIDS deaths per year has continued to rise rapidly. In 2004, some 40 million people were living with HIV, which has killed over 20 million since 1981 and 3 million in 2003 alone [32]. The epidemic is not homogeneous within geographical regions. Some countries are more affected than others. Even at a country level, there are usually wide variations in infection levels between different provinces, states or districts, and between urban and rural areas. In reality, the national picture is made up of a series of epidemics with their own characteristics and dynamics.

The dynamic transmission of HIV is quite complex and there is no other human infection which has the same epidemiological characteristics with a similar mode of transmission. For instance, the incubation period after infection with HIV is known to be extremely long and is measured in years rather than days (such as in the case of measles, for example). During this period, the individuals stay healthy and can unknowingly transmit the disease to others. In addition, although the disease is known as a sexually transmitted disease, it is also passed on from infected mothers to their babies, and from sharing infected syringes, which is common among injecting drug users. All these factors have made it difficult to understand how this epidemic spreads in the population. The growth of movement among populations further increases the contact between individuals in different patches and, consequently, it might trigger more epidemics. Thus, the migration of people among subgroups has many significant consequences for the outcome of epidemic spread [12,26]. Indonesia in particular, as one of the most populous countries in the world, with a high population mobility among its regions [11], seems to have a high risk for the spread of the epidemic [32]. The number infected has increased sharply, and the prevalence among provinces varies widely.

Mathematical models based on the underlying transmission mechanism of HIV might help the medical and scientific community understand better how the disease spreads in the community. Even though the actual data needed for the models might not be accurate or even available, such modelling is still vital in investigating how changes in the various assumptions and parameter values affect the course of the epidemic [16]. Therefore, by developing such mathematical models, we can to some extent anticipate its spread in different populations and evaluate the potential effectiveness of different approaches for bringing the epidemic under control, and thus help to devise effective strategies to minimize the destruction caused by this epidemic.

Mathematical models for the spread of the HIV/AIDS epidemic have been studied extensively since the first cases were recognized in the late 80s; see for example [9,17,21–23,28,29]. However, this area of study is still challenging, since so many different factors affect the transmission of HIV. Most of the articles have focused on only a single population of constant size, although some studies have stressed the importance of variable population size in epidemic dynamics [9,10,21]. In addition, many models have only focused on a single homosexual population [28], whereas in much of the world, heterosexual contact is the predominant mode of transmission [32]. Finally, the spatial aspect of the epidemic and, related with this, the *mobility* of the population, is often ignored. All these assumptions might limit the application of such models in describing the complex dynamics of the epidemic.

The purpose of this paper is to develop new mathematical models for the spread of HIV that incorporate factors such as mobility, heterosexual transmission and varying population size, which are crucial for countries such as Indonesia, with its many distinct regions. The models will be stochastic in nature, as opposed to the more common deterministic models. However, we will show that the more natural stochastic approach can be approximated well with the traditional

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deterministic approach, which can be analyzed in more detail, in particular with respect to equilibrium behavior. In addition we derive stochastic diffusion approximations, which show that the original process around the equilibrium can be approximated well by an Ornstein–Uhlenbeck process. Both the deterministic and diffusion approximations are derived using the theory of density dependent processes [18,24].

Our models are motivated mostly by the works of Dietz [9] and May et al. [21], both of which formulate deterministic models of HIV spread in a heterogeneous population. They consider the female and male subpopulations separately (individuals are well mixed only in their subpopulation), and assume that HIV transmission is possible only through sexual contact between female and male. There are some differences between the two models: Dietz [9] assumes that the rate of new recruits of susceptibles (for both males and females) is constant, whereas in May et al. [21], this rate is assumed to be proportional to the total population, which varies in time. In Dietz [9], only males choose partners from the female subpopulation. Thus, susceptible males and females become infected at a rate which is proportional to the size of the total female population. On the other hand, May et al. [21] assumes also that females choose partners from the male subpopulation. Therefore, susceptible males are infected relative to the total female population and susceptible females become infected relative to the total male population. Consequently, the models [9] and [21] have slightly different formulations for the infection rate of susceptibles. Furthermore, both study the situation under the assumption of a varying population.

The rest of the paper is organized as follows. In Section 2, we describe the various stochastic models. We start with a single, constant (i.e., a closed system) or varying (i.e., an open system) population with a female and male subpopulation, and then look at the case of a multiple-patch population, incorporating the mobility of people. In Section 3, we present various results from Kurtz [18,19] concerning density dependent processes. In particular, we review under what conditions, and in what manner, such a stochastic process converges to its deterministic and diffusion counterpart. In Section 4, we will use the results from Section 3 to study the dynamics of our stochastic models. This approach has been used recently in the study of epidemic models; see for example [7,6]. Numerical experiments are presented in Section 5. Finally, in Section 6, we summarize our findings and give direction for future research.

2. Models

In this section, we formulate various stochastic models for the spread of HIV in both a single population and in multiple populations, under the assumption of either a constant or varying population size.

2.1. Model with a closed single population

We consider first a closed (constant) single heterosexual population of size N in which all individuals, both females and males, are well mixed in the population. We assume, as in [9] and [21], that a susceptible female gets infected only by an infected male (via sexual contact) and, similarly, a susceptible male gets the infection only from an infected female. A single female or male selects her/his partner (of different sex) randomly from the whole population.

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Let the random variables $S_F(t)$, $I_F(t)$, $S_M(t)$, $I_M(t)$ and $A(t)$ represent the number of susceptible females, infected females, susceptible males, infected males, and the number of AIDS cases at time t, respectively. We assume that a susceptible female (male) will be infected by an infected male (female) at a rate that is proportional to the fraction of infected males (females):

$$\lambda_F = \beta \frac{I_M(t)}{N_M(t)} \quad \left(\lambda_M = \beta \frac{I_F(t)}{N_F(t)}\right), \tag{1}$$

where λ_F and λ_M are called the *forces of infection* (see also Remark 2.1) which is the same as the rate of infection per susceptible defined in Hyman et al. [14], $N_F(t) = S_F(t) + I_F(t)$ and $N_M(t) = S_M(t) + I_M(t)$. We assume that all individuals, including AIDS people, leave the random mixing sexually active population at rate μ (due to natural death or for reasons other than dying). In addition, AIDS people also die from the disease, at rate δ. All individuals that leave the system are replaced (balanced) by inflow of susceptibles, at a proportion α for females and $(1-\alpha)$ for males. Thus, the inflow rates for susceptible females and males are $B_F = \alpha(\mu N + \delta A)$ and $B_M = (1-\alpha)(\mu N + \delta A)$, respectively. The infected individuals develop AIDS at rate γ. This situation can be viewed as a stochastic Susceptible-Infected-Removed (SIR) model; see for example [1]. The scheme is illustrated in Fig. 1.

Remark 2.1 (*Force of Infection*). The parameter β is defined in [9] as the product of the contact rate κ and the probability p that a successive number of contacts leads to infection. The constants κ and p are given as follows: $\kappa = \frac{1}{T}$ per unit time and $p = 1 - (1-h)^{cT}$, where T is the time interval per partnership, c is the average number of sexual contacts per partnership, and h is the probability that one sexual contact between a susceptible and an infected individual leads to infection. Thus, the unit of β is *per time unit* (for the case of HIV/AIDS, the more reasonable unit of β is *per month* [15] or *per year* [5]).

Consider the process $(X(t), t \geqslant 0)$, with

$$X(t) = (S_F(t), I_F(t), S_M(t), I_M(t)),$$

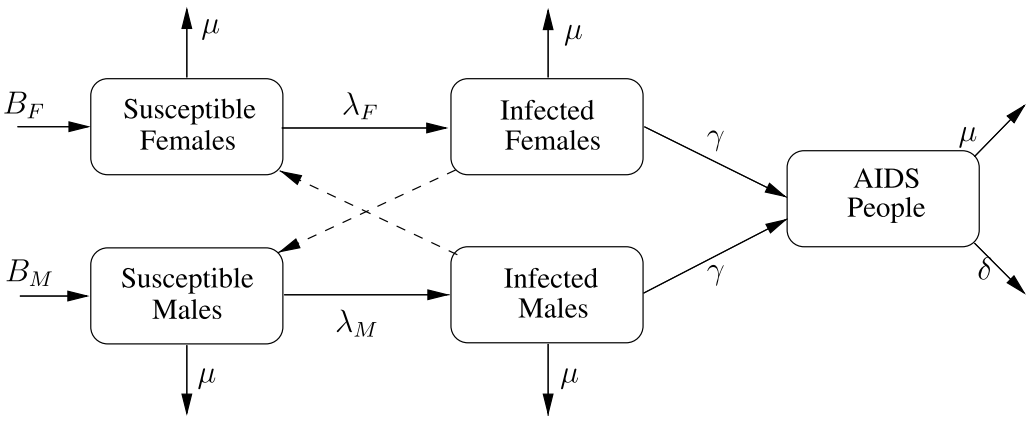

Fig. 1. The scheme of the model. Susceptible females (males) are infected by infected males (females) via sexual contact only, indicated by the dashed arrows.

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which takes values in $E \subset \mathbb{N}^4$, where $\mathbb{N}$ is the set of positive integers (including zero). We model $(X(t), t \geqslant 0)$ as a Continuous Time Markov Chain (CTMC) (see for example [25]), where the transition rates are chosen according to the description above. Thus, we assume that given the whole history $X(s)$, $s \leqslant t$, a future state of the system, $X(t + \Delta t)$, depends only on the current state $X(t)$. In the formulation of the model, we can ignore $A(t)$, since the population size, $N = S_F(t) + I_F(t) + S_M(t) + I_M(t) + A(t)$, is constant for all t. If one is interested in the number of AIDS cases, one can find it from $A(t) = N - S_F(t) - I_F(t) - S_M(t) - I_M(t)$.

2.1.1. Transition rates

We now have a closer look at the transition rates of the CTMC $(X(t), t \geqslant 0)$. In a small time interval Δt we assume that one of the following events occurs: (1) a new susceptible female enters the group of single females, (2) a susceptible female gets infected, (3) a susceptible female dies, (4) an infected female is removed (develops AIDS or dies), (5) a new susceptible male enters the group of males, (6) a susceptible male becomes infected, (7) a susceptible male dies, or (8) an infected male is removed (due to AIDS or natural death). The other possible events are ignored.

Suppose that the system at time t is in state $\mathbf{k} = (s_F, i_F, s_M, i_M)$, $\mathbf{k} \in E$. The transition scheme of the process is described in Fig. 2 (ignoring boundary effects).

Thus, in any small time interval of length Δt, the process jumps from state $\mathbf{k}$ to $\mathbf{k} + l$ with probability $q_{\mathbf{k},\mathbf{k}+l}\Delta t$, where the rates $q_{\mathbf{k},\mathbf{k}+l}$ follow from the formulation above, and are given by

$$q_{\mathbf{k},\mathbf{k}+l} = \begin{cases} \alpha(\mu N + \delta A), & l = \mathbf{e}_1, \\ \beta \frac{i_M}{s_M + i_M} s_F, & l = -\mathbf{e}_1 + \mathbf{e}_2, \\ \mu s_F, & l = -\mathbf{e}_1, \\ (\mu + \gamma) i_F, & l = -\mathbf{e}_2, \\ (1 - \alpha)(\mu N + \delta A), & l = \mathbf{e}_3, \\ \beta \frac{i_F}{s_F + i_F} s_M, & l = -\mathbf{e}_3 + \mathbf{e}_4, \\ \mu s_M, & l = -\mathbf{e}_3, \\ (\mu + \gamma) i_M, & l = -\mathbf{e}_4, \\ 0, & \text{otherwise.} \end{cases} \tag{2}$$

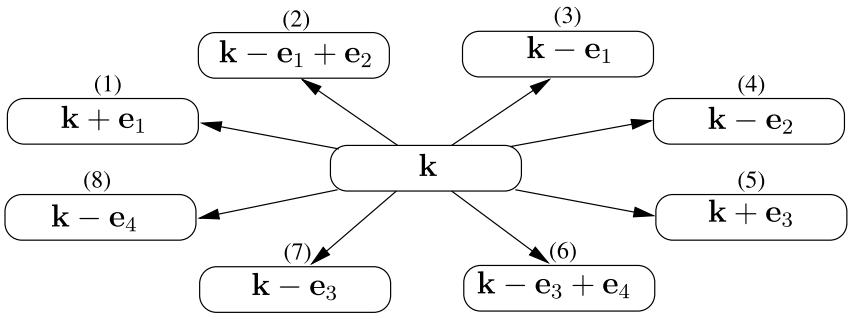

Fig. 2. The transition scheme from state $\mathbf{k}$ to other states, where $\mathbf{e}_i$ represents the ith unit row vector in $\mathbb{N}^4$.

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Note that the process $(X(t), t \geqslant 0)$ has an absorbing state $\mathbf{0}$, and once the process reaches a state where no infection is present (i.e., $I_F(t) = I_M(t) = 0$), it will remain infection free forever, and will eventually end up in $\mathbf{0}$.

2.2. Model with an open single population

In this model, we consider a population size $N(t)$ which varies with time. We have now a slightly different interpretation for the population size. In the constant population case, we include AIDS people in the total population, which makes it possible to formulate the situation as a type of SIR model. With a varying population size, both the female and male subpopulation are simply divided into two groups of susceptibles and infectives, as in the case of the standard SI model. We no longer explicitly consider AIDS people as a part of the population, that is, $N(t) = S_F(t) + I_F(t) + S_M(t) + I_M(t)$. However, if one is interested in the number of AIDS cases at time t, $A(t)$, one can find it from the number of infectives who eventually develop AIDS, that is, $A(t) = \int_0^t \gamma(I_F(s) + I_M(s))\,ds$. We assume as in Dietz [9] that the number of new susceptibles of both females and males arrive into the system at a constant rate $B_F = B_M = B$ (that is, according to a Poisson process with rate B). Thus, the transition scheme is similar to the previous model, but the transition rates of the process are given as follows:

$$q_{\mathbf{k},\mathbf{k}+l} = \begin{cases} B, & l = \mathbf{e}_1, \\ \beta \frac{i_M}{s_M + i_M} s_F, & l = -\mathbf{e}_1 + \mathbf{e}_2, \\ \mu s_F, & l = -\mathbf{e}_1, \\ (\mu + \gamma) i_F, & l = -\mathbf{e}_2, \\ B, & l = \mathbf{e}_3, \\ \beta \frac{i_F}{s_F + i_F} s_M, & l = -\mathbf{e}_3 + \mathbf{e}_4, \\ \mu s_M, & l = -\mathbf{e}_3, \\ (\mu + \gamma) i_M, & l = -\mathbf{e}_4, \\ 0, & \text{otherwise}, \end{cases} \tag{3}$$

Similar to the previous case, this process has an absorbing state $\mathbf{0}$, and once the process reaches the state with no infected individuals, it will remain infection free and will eventually go to $\mathbf{0}$.

2.3. Multiple patch models with varying population size

In order to incorporate mobility effects, we consider individuals residing in many *patches* or *regions*. The population sizes of the patches need not be equal and may vary with time. Individuals may get the infection or transmit the disease during their visit to other patches. People might visit the same patches several times and spend a varying length of time in the visited patches. Suppose v_{rj} denotes the immigration rate of individuals from patch R_r to R_j. The diagram in Fig. 3 illustrates the mobility of people among patches.

We formulate two types of model, assuming that each patch (as in the previous models for a single population) contains a female and a male subpopulation. In the first type of model, we assume that individuals do not actually leave their home patches but that there is an infection force from other patches. In the second type of model, we assume that individuals do leave their home patches and spend a considerable amount of time in the visited patches before they return. They might emigrate

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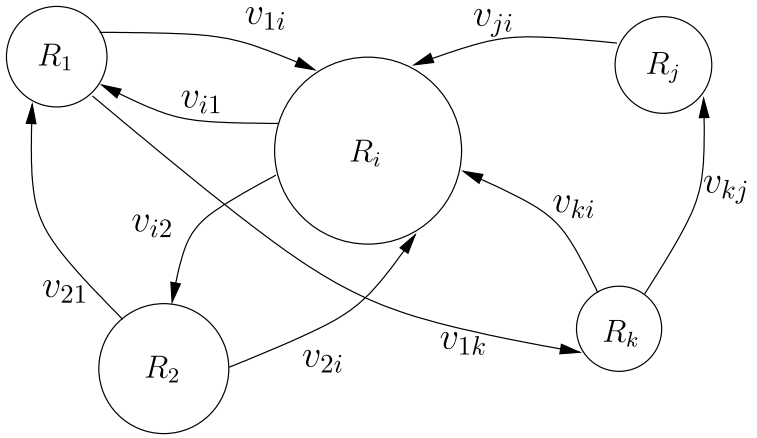

Fig. 3. The scheme for the mobility of people among patches. The size of a circle corresponds to the total population size in that patch.

and stay permanently in a visited patch. We call the first model the *model with a force of infection* and the second model the *model with actual mobility*. We consider both constant and varying population sizes.

In both models there are K patches and each patch contains a female and male subpopulation. Let $S_{\mathrm{F}}^{(r)}(t), I_{\mathrm{F}}^{(r)}(t), S_{\mathrm{M}}^{(r)}(t), I_{\mathrm{M}}^{(r)}(t)$ represent the number of susceptible (infected) females and the number of susceptible (infected) males at time $t \geqslant 0$ in patch r, $r = 1, \ldots, K$, respectively. Define a CTMC $(X(t),\ t \geqslant 0)$ with

$$X(t) = (S_{\mathrm{F}}^{(1)}(t), I_{\mathrm{F}}^{(1)}(t), S_{\mathrm{M}}^{(1)}(t), I_{\mathrm{M}}^{(1)}(t), \ldots, S_{\mathrm{F}}^{(r)}(t), I_{\mathrm{F}}^{(r)}(t), S_{\mathrm{M}}^{(r)}(t), I_{\mathrm{M}}^{(r)}(t), \ldots, S_{\mathrm{M}}^{(K)}(t), I_{\mathrm{F}}^{(K)}(t), S_{\mathrm{M}}^{(K)}(t), I_{\mathrm{M}}^{(K)}(t)).$$

The state of this process is a $4K$-dimensional row vector with elements in $\mathbb{N}$, that is, the state is an element of $\mathbb{N}^{4K}$.

2.3.1. Model with a force of infection

To formulate the first model, let β_{rj} denote the infection rate of susceptibles in patch r by infected individuals from patch j and $\beta_r = \beta_{rr}$ the infection rate within patch r. Then, the transition rates for this situation ($r = 1, 2, \ldots, K$) are given as follows: For a constant population size

$$q_{\mathbf{k},\mathbf{k}+l} = \begin{cases} \alpha(\mu N^{(r)} + \delta A^{(r)}), & l = \mathbf{e}_{4r-3}, \\ \sum_{j=1}^{K} \beta_{rj} \frac{i_{\mathrm{M}}^{(j)}}{n_{\mathrm{M}}^{(j)}} s_{\mathrm{F}}^{(r)}, & l = -\mathbf{e}_{4r-3} + \mathbf{e}_{4r-2}, \\ \mu s_{\mathrm{F}}^{(r)}, & l = -\mathbf{e}_{4r-3}, \\ (\mu+\gamma) i_{\mathrm{F}}^{(r)}, & l = -\mathbf{e}_{4r-2}, \\ (1-\alpha)(\mu N^{(r)} + \delta A^{(r)}), & l = \mathbf{e}_{4r-1}, \\ \sum_{j=1}^{K} \beta_{rj} \frac{i_{\mathrm{F}}^{(j)}}{n_{\mathrm{F}}^{(j)}} s_{\mathrm{M}}^{(r)}, & l = -\mathbf{e}_{4r-1} + \mathbf{e}_{4r}, \\ \mu s_{\mathrm{M}}^{(r)}, & l = -\mathbf{e}_{4r-1}, \\ (\mu+\gamma) i_{\mathrm{M}}^{(r)}, & l = -\mathbf{e}_{4r}, \\ 0, & \text{otherwise}, \end{cases} \tag{4}$$

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with a constant $N^{(r)} = n_{\mathrm{F}}^{(r)}(t) + n_{\mathrm{M}}^{(r)}(t) + A^{(r)}(t)$, where $n_{\mathrm{F}}^{(r)}(t) = s_{\mathrm{F}}^{(r)}(t) + i_{\mathrm{F}}^{(r)}(t)$ and $n_{\mathrm{M}}^{(r)}(t) = s_{\mathrm{M}}^{(r)}(t) + i_{\mathrm{M}}^{(r)}(t)$. A vector $\mathbf{e}_m$ is the mth unit vector in $\mathbb{N}^{4K}$. For the case of varying population size

$$q_{\mathbf{k},\mathbf{k}+l} = \begin{cases} B, & l = \mathbf{e}_{4r-3}, \\ \sum_{j=1}^{K} \beta_{rj} - \frac{i_{\mathrm{M}}^{(j)}}{n_{\mathrm{M}}^{(j)}} s_{\mathrm{M}}^{(r)}, & l = -\mathbf{e}_{4r-3} + \mathbf{e}_{4r-2}, \\ \mu s_{\mathrm{F}}^{(r)}, & l = -\mathbf{e}_{4r-3}, \\ (\mu+\gamma) i_{\mathrm{F}}^{(r)}, & l = -\mathbf{e}_{4r-2}, \\ B, & l = \mathbf{e}_{4r-1}, \\ \sum_{j=1}^{K} \beta_{rj} \frac{i_{\mathrm{F}}^{(j)}}{n_{\mathrm{F}}^{(j)}} s_{\mathrm{M}}^{(r)}, & l = -\mathbf{e}_{4r-1} + \mathbf{e}_{4r}, \\ \mu s_{\mathrm{M}}^{(r)}, & l = -\mathbf{e}_{4r-1}, \\ (\mu+\gamma) i_{\mathrm{M}}^{(r)}, & l = -\mathbf{e}_{4r}, \\ 0, & \text{otherwise}, \end{cases} \tag{5}$$

with a varying size $n^{(r)}(t) = n_F^{(r)}(t) + n_M^{(r)}(t)$. Note that with these notations, if there is only one patch ($r,j = 1$), the transition rates have the same form as those in the previous models for an open and closed single population.

2.3.2. Model with actual mobility

In this model, we assume that people physically visit other patches. During their visit the infected individuals can transmit the disease to the susceptibles in the visited patches, and susceptibles visiting a patch might get the infection from the infected individuals in a visited patch. This situation is modelled by considering people moving from one patch to another without any forces of infection from outside a patch; however we do have a force of infection within a patch. The force of infection within a patch may differ from patch to patch. We consider for this situation a varying population size only, since it is more realistic. The transition rates of the process are given by

$$q_{\mathbf{k},\mathbf{k}+l} = \begin{cases} B, & l = \mathbf{e}_{4r-3}, \\ \beta_i \frac{i_{\mathrm{M}}^{(r)}}{n_{\mathrm{M}}^{(r)}} s_{\mathrm{F}}^{(r)}, & l = -\mathbf{e}_{4r-3} + \mathbf{e}_{4r-2}, \\ \mu s_{\mathrm{F}}^{(r)}, & l = -\mathbf{e}_{4r-3}, \\ \rho_{rj} \frac{U^{(r)}}{n^{(r)}} s_{\mathrm{F}}^{(r)}, & l = -\mathbf{e}_{4r-3} + \mathbf{e}_{4j-3}, \\ \rho_{rj} \frac{U^{(r)}}{n^{(r)}} i_{\mathrm{F}}^{(r)}, & l = -\mathbf{e}_{4r-2} + \mathbf{e}_{4j-2}, \\ (\mu+\gamma) i_{\mathrm{F}}^{(r)}, & l = -\mathbf{e}_{4r-2}, \\ B, & l = \mathbf{e}_{4r-1}, \\ \beta_i \frac{i_{\mathrm{F}}^{(r)}}{n_{\mathrm{F}}^{(r)}} s_{\mathrm{M}}^{(r)}, & l = -\mathbf{e}_{4r-1} + \mathbf{e}_{4r}, \\ \mu s_{\mathrm{M}}^{(r)}, & l = -\mathbf{e}_{4r-1}, \\ \rho_{rj} \frac{U^{(r)}}{n^{(r)}} s_{\mathrm{M}}^{(r)}, & l = -\mathbf{e}_{4r-1} + \mathbf{e}_{4j-1}, \\ \rho_{rj} \frac{U^{(r)}}{n^{(r)}} i_{\mathrm{M}}^{(r)}, & l = -\mathbf{e}_{4r} + \mathbf{e}_{4j}, \\ (\mu+\gamma) i_{\mathrm{M}}^{(r)}, & l = -\mathbf{e}_{4r}, \\ 0, & \text{otherwise}, \end{cases} \tag{6}$$

with $n^{(r)} = n_{\mathrm{F}}^{(r)} + n_{\mathrm{M}}^{(r)}$.

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3. Density dependence and diffusion approximation

To study the dynamic behavior of the stochastic models formulated previously, we present some results developed by Kurtz [18,19]. These results also justify to some extent the use of deterministic models, which is quite common in modelling the epidemic spread, whereas the real situation is in fact a random process.

Definition 3.1. A one-parameter family of CTMCs $(X^{(N)}(t), t \geqslant 0)$ with state space $E \subset \mathbb{Z}^d$ and transition rates (q_{ij}) is called *density dependent* if there exists a continuous function $f(x, l) : \mathbb{R}^d \times \mathbb{Z}^d \to \mathbb{R}$, such that

$$q_{k,k+l} = Nf\left(\frac{k}{N}, l\right), \qquad l \neq 0 \quad \text{and} \quad k, l \in \mathbb{Z}^d.$$

Suppose $(X(t) = X^{(N)}(t), t \geqslant 0)$ is a density dependent process (from now on we drop the superscript N). By rescaling with N we obtain another a CTMC $(X_N(t), t \geqslant 0)$ called the *density process*. Thus,

$$X_N(t) = \frac{1}{N}X(t).$$

It turns out that under certain mild conditions $(X_N(t))$ converges to a deterministic process that is the solution of a system of first order ODEs that is governed by the following function F:

$$F(x) = \sum_{l \in \mathbb{Z}^d} lf(x, l). \tag{7}$$

Theorem 3.1 (Deterministic Approximation)**.** *Suppose that there exists* (1) *an open set* $E \subset \mathbb{R}^d$ *where the function* $f(x, l)$ *is bounded for each* l *and* (2) *the function* F *is Lipschitz continuous on* E. *Then, for every trajectory* $(x(\tau, x_0), \tau \geqslant 0)$ *satisfying the following system of ODEs*

$$\frac{\mathrm{d}}{\mathrm{d}\tau}x(\tau, x_0) = F(x(\tau, x_0)),$$
$$x(0, x_0) = x_0, \quad x(\tau, x_0) \in E, \quad 0 \leqslant \tau \leqslant t,$$

$\lim_{N\to\infty} X_N(0) = x_0$ *implies for every* $\delta > 0$,

$$\lim_{N\to\infty} \mathbb{P}\left(\sup_{\tau \leqslant t} |X_N(\tau) - x(\tau, x_0)| > \delta\right) = 0, \quad \textit{for every } t \geqslant 0.$$

The proof is given in [18].

Theorem 3.1 implies that the process $(X_N(t))$ can be approximated to first order by a deterministic process, for large N. If the density process $(X_N(t))$ is initially close to x_0, it will tend to stay close to the trajectory $(x(\tau, x_0), \tau \leqslant t)$ in some appropriate time-interval, subject to small random oscillations about the path.

It is even possible to describe the behavior of the random fluctuations of the density process $(X_N(t), t \geqslant 0)$ around its deterministic approximation. This is done via a diffusion approximation, which is governed by two $d \times d$ matrices $G = G(x) = (g_{ij}(x))$ and $H = H(x) = (h_{ij}(x))$ defined by

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$$g_{ij}(x) = \sum_{i=1}^{d}\sum_{j=1}^{d} l_i l_j f(x,l), \quad \text{where} \quad l = (l_1,\ldots,l_d) \in \mathbb{Z}^d,$$

and

$$h_{jk}(x) = \frac{\partial F_j(x)}{\partial x_k}.$$

Note that $H(x)$ is simply the Jacobian matrix of $F(x)$.

Theorem 3.2 (Diffusion Approximation)**.** *Suppose $F(x)$ is bounded and Lipschitz continuous on E. Suppose $G(x)$ is also bounded, and uniformly continuous on E. Suppose that*

$$\lim_{N\to\infty} \sqrt{N}(X_N(0) - x_0) = z.$$

Then, as $N \to \infty$, the family of processes $(Z_N(t), t \geqslant 0)$, defined by

$$Z_N(t) = \sqrt{N}(X_N(t) - x(t,x_0)), \quad 0 \leqslant t \leqslant s,$$

converges weakly in $D[0,t]$ to a Gaussian diffusion $(Z(t), t \geqslant 0)$ with initial value $Z(0) = z$ and with characteristic function $\mathbb{E}\mathbf{e}^{i\theta\cdot Z(t)} \equiv \psi(t,\theta)$ that satisfies

$$\frac{\partial \psi}{\partial t}(t,\theta) = -\frac{1}{2}\sum_{j=1}^{d}\sum_{k=1}^{d} \theta_j\theta_k g_{jk}(x(t,x_0))\psi(t,\theta) + \sum_{j=1}^{d}\sum_{k=1}^{d} \theta_j h_{jk}(x(t,x_0))\frac{\partial \psi}{\partial \theta_k}(t,\theta). \tag{8}$$

For every t, $Z(t)$ has a multivariate Gaussian/normal distribution whose mean vector and covariance matrix is easily determined. In particular, the mean vector of $Z(t)$ is given by

$$\mu = \mathbb{E}Z(t) = M(t)z, \tag{9}$$

where $M(t) = \mathbf{e}^{\int_0^t H_s \mathrm{d}s}$, that is, the unique solution to

$$\frac{\mathrm{d}M(t)}{\mathrm{d}t} = H(t)M(t), \quad \text{with } M(0) = I. \tag{10}$$

On the other hand, the covariance matrix, $\Sigma(t)$, of $Z(t)$ is given by

$$\Sigma(t) = M(t)\left(\int_0^t M(s)^{-1}G(x(s,x_0))(M(s)^{-1})^T \mathrm{d}s\right)M(t)^T, \tag{11}$$

which is the unique solution to

$$\frac{\mathrm{d}\Sigma(t)}{\mathrm{d}t} = H(t)\Sigma(t) + \Sigma(t)H(t)^T + G(x(t,x_0)), \quad \text{with } \Sigma_0 = \Sigma(0) = 0. \tag{12}$$

If $X_N(0)$ and x_0 are chosen to be equal to an equilibrium point x^* of the ODE system in Theorem 3.1, one can be far more precise in specifying the approximating diffusion. Namely, in that case $(Z(t))$ is an Ornstein–Uhlenbeck (OU) process (i.e., a stationary, Gaussian, and Markovian process), with local drift matrix $H(x^*)$ and local covariance matrix $G = G(x^*)$. In particular, $Z(t)$ has a normal distribution with zero mean and a covariance matrix Σ which is given by the solution of (12) with $\frac{\mathrm{d}\Sigma_t}{\mathrm{d}t} = 0$; see [4]. It follows that $X_N(t)$ has an approximate normal distribution with

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$$\mathrm{Var}(X_N(t)) \approx \frac{1}{N}\Sigma, \tag{13}$$

and the mean, obtained by setting $z = \sqrt{N}(X_N(0) - x_0)$, is given by

$$\mathbb{E}X_N(t) \approx x^*. \tag{14}$$

Therefore, we can approximate the equilibrium distribution of the process $(X(t),\ t \geqslant 0)$ by a multivariate normal distribution with mean vector $\mu = NX_2^*$ and covariance matrix $N\Sigma$. For more general results of density dependent processes, we refer the reader to see Refs. [3,24].

4. Analysis

In this section we analyze the stochastic models formulated in Section 2 by using the results in Section 3, and predict their dynamic behavior via their deterministic and diffusion counterparts.

4.1. Closed single population

To study the behavior of $(X(t), t \geqslant 0)$ with the transition rates $q_{\mathbf{k},\mathbf{k}+l}$ as given in (2), we show that it is a density-dependent Markov process, parameterized by the population size N. By scaling with N, we obtain a scaled Markov process $(X_N(t), t \geqslant 0)$ with $X_N(t) = \frac{1}{N}X(t) = \frac{1}{N}(S_{\mathrm{F}}(t), I_{\mathrm{F}}(t), S_{\mathrm{M}}(t), I_{\mathrm{M}}(t))$. Define the function f as follows

$$f(\mathbf{x}, l) = \begin{cases} \alpha(\mu + \delta z), & \text{if } l = \mathbf{e}_1, \\ \beta \frac{y_2}{y_1+y_2} x_1, & \text{if } l = -\mathbf{e}_1 + \mathbf{e}_2, \\ \mu x_1, & \text{if } l = -\mathbf{e}_1, \\ (\mu+\gamma)x_2, & \text{if } l = -\mathbf{e}_2, \\ (1-\alpha)(\mu+\delta z), & \text{if } l = \mathbf{e}_3, \\ \beta \frac{x_2}{x_1+x_2} y_1, & \text{if } l = -\mathbf{e}_3 + \mathbf{e}_4, \\ \mu y_1, & \text{if } l = -\mathbf{e}_3, \\ (\mu+\gamma)y_2, & \text{if } l = -\mathbf{e}_4, \\ 0, & \text{otherwise}, \end{cases} \tag{15}$$

with $\mathbf{x} = \frac{\mathbf{k}}{N} = (x_1, x_2, y_1, y_2)$ and $z = 1 - (x_1 + x_2 + y_1 + y_2)$. Then, one can check that $q_{\mathbf{k},\mathbf{k}+l} = Nf(\mathbf{x}, l)$. Therefore, $(X(t), t \geqslant 0)$ is, by Definition 3.1, a density dependent process. The corresponding function F is derived from (15) and (7):

$$F(\mathbf{x}) = \begin{pmatrix} \alpha(\mu+\delta z) - \beta \frac{y_2}{y_1+y_2} x_1 - \mu x_1, \\ \beta \frac{y_2}{y_1+y_2} x_1 - (\mu+\gamma)x_2 \\ (1-\alpha)(\mu+\delta z) - \beta \frac{x_2}{x_1+x_2} y_1 - \mu y_1 \\ \beta x_2 y_1 - (\mu+\gamma)y_2 \end{pmatrix}. \tag{16}$$

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The function F is Lipschitz continuous. So, the dynamic behavior of the process $(X_N(t), t \geqslant 0)$, see Theorem 3.1, can be approximated by a system of first order ODEs

$$\mathbf{x}'(t) = F(\mathbf{x}), \tag{17}$$

as $N \to \infty$.

4.2. Equilibria and their stability

From now on we assume for simplicity that $\alpha = \frac{1}{2}$ (i.e., females and males enter the population in equal proportion). Solving $F(X) = 0$ in (16) gives three equilibrium points, two of which fall in the positive quadrant: the *disease-free* equilibrium and the *positive endemic* equilibrium. Let $X^* = (x_1^*, x_2^*, y_1^*, y_2^*)$ denote a generic equilibrium of the system (17).

4.2.1. Disease-free equilibrium

The disease-free equilibrium is given by

$$X_1^* = \left(x_1^* = \frac{1}{2}, x_2^* = 0, y_1^* = \frac{1}{2}, y_2^* = 0\right). \tag{18}$$

In the absence of the disease ($x_2 = y_2 = 0$), the fraction of susceptibles of both females and males will reach a constant number: $x_1 = x_1^* = \frac{1}{2}$ and $y_1 = y_1^* = \frac{1}{2}$, respectively. We are interested in whether in the early epidemic spread (after a few infected people are present) the number of infectives will grow or die out. The following result sheds some light onto this. Here, the basic quantity R_0 serves the same role as the *basic reproduction rate* in epidemiology.

Theorem 4.1. *Let $R_0 = \frac{\beta}{\mu+\gamma}$. The disease-free equilibrium X_1^* in (18) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

Proof . The Jacobian matrix of (16) is given by

$$H(\mathbf{x}) = \begin{pmatrix} -\frac{\delta}{2} - \beta a_3 - \mu & -\frac{\delta}{2} & -\frac{\delta}{2} + \beta a_3 a_4 & -\frac{\delta}{2} - \beta a_4(1-a_3) \\ \beta a_3 & -(\mu+\gamma) & -\beta a_3 a_4 & \beta a_4(1-a_3) \\ -\frac{\delta}{2} + \beta a_1 a_2 & -\frac{\delta}{2} - \beta a_2(1-\beta a_1) & -\frac{\delta}{2} - \beta a_1 - \mu & -\frac{\delta}{2} \\ -\beta a_1 a_2 & \beta a_2(1-a_1) & \beta a_2 & -(\mu+\gamma) \end{pmatrix}, \tag{19}$$

where $a_1 = \frac{x_2}{x_1+x_2}$, $a_2 = \frac{y_1}{x_1+x_2}$, $a_3 = \frac{y_2}{y_1+y_2}$, and $a_4 = \frac{x_1}{y_1+y_2}$.

Evaluating (19) at X_1^* yields

$$H(X_1^*) = \begin{pmatrix} -\frac{\delta}{2} - \mu & -\frac{\delta}{2} & -\frac{\delta}{2} & -\frac{1}{2}\delta - \beta \\ 0 & -(\mu+\gamma) & 0 & \beta \\ -\frac{\delta}{2} & -\frac{1}{2}\delta - \beta & -\frac{\delta}{2} - \mu & -\frac{\delta}{2} \\ 0 & \beta & 0 & -(\mu+\gamma) \end{pmatrix}. \tag{20}$$

If the real parts of all the eigenvalues of this matrix are negative, then the disease-free steady-state is locally asymptotically stable. The matrix (20) has four eigenvalues

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$$r_1 = -\mu, \quad r_2 = -(\mu+\delta), \quad r_3 = -(\beta+\mu+\gamma), \quad r_4 = -(\mu+\gamma)+\beta. \tag{21}$$

Therefore, the stability of this equilibrium is determined by the last eigenvalue r_4, since the other eigenvalues are always negative for the non-negative parameters β, γ, μ, δ. Thus, the disease-free equilibrium is *stable* if and only if $r_4 = -(\mu+\gamma)+\beta < 0$ ($R_0 < 1$) and it is *unstable* if and only if $r_4 = -(\mu+\gamma)+\beta > 0$ ($R_0 > 1$). □

4.2.2. Positive endemic equilibrium

The endemic equilibrium is given by

$$X_2^* = (x_1^* = \rho, x_2^* = \eta, y_1^* = \rho, y_2^* = \eta), \tag{22}$$

where $\rho = \frac{\Gamma}{2\Delta}$, $\eta = \frac{(R_0-1)\Gamma}{2\Delta}$ with $\Gamma = \mu+\delta$ and $\Delta = R_0\Gamma + \gamma(R_0-1)$. It is clear from (22) that the system (17) has a positive-endemic equilibrium if and only if $R_0 > 1$. The Jacobian matrix for the positive-endemic equilibrium is

$$H(X_2^*) = \begin{pmatrix} -\frac{\delta}{2} - \beta\Omega - \mu & -\frac{\delta}{2} & -\frac{\delta}{2} + \beta\Omega\Phi & -\frac{\delta}{2} - \beta\Phi(1-\Omega) \\ \beta\Omega - \mu & -\mu-\gamma & -\beta\Omega\Phi & \beta\Omega(1-\Phi) \\ -\beta\Omega\Phi & -\frac{\delta}{2} - \beta\Omega(1-\Phi) & -\frac{\delta}{2} - \beta\Phi - \mu & -\frac{\delta}{2} \\ -\beta\Omega\Phi & \beta\Omega(1-\Phi) & \beta\Phi & -\gamma-\mu \end{pmatrix}, \tag{23}$$

with $\Omega = \frac{\rho}{\rho+\eta}$ and $\Phi = \frac{\eta}{\rho+\eta}$.

This matrix has four eigenvalues

$$r_1 = \frac{1}{2}(B_1 + \sqrt{\Theta_1}), \quad r_3 = \frac{1}{2}(B_2 + \sqrt{\Theta_2}),$$
$$r_2 = \frac{1}{2}(B_1 - \sqrt{\Theta_1}), \quad r_4 = \frac{1}{2}(B_2 - \sqrt{\Theta_2}),$$

where

$$B_1 = -\mu - \frac{\gamma}{2} - \frac{\beta}{2},$$
$$B_2 = -\frac{1}{2}(\beta+\delta-\gamma),$$
$$\Theta_1 = \frac{1}{4}(\beta-\gamma)^2 + \frac{\gamma\beta}{R_0^2},$$
$$\Theta_2 = \frac{1}{4}(\beta^2+\gamma^2+\delta^2) - \frac{\gamma}{2}(\beta+\delta) - \frac{\beta\delta}{2} + \frac{\beta}{R_0}\left(\delta + \left(1-\frac{1}{R_0}\right)(\gamma-\beta)\right).$$

If $R_0 > 1$, it follows that $B_1, B_2 < 0$. Therefore, $\mathrm{Re}(r_2)$ and $\mathrm{Re}(r_4)$ are always negative. We need to show that for some β, μ, γ, $\delta > 0$, $\mathrm{Re}(r_1)$ and $\mathrm{Re}(r_3)$ are also negative. If $\Theta_1 \leqslant 0$ and $\Theta_2 \leqslant 0$, $\mathrm{Re}(r_1) = B_1 < 0$ and $\mathrm{Re}(r_3) = B_2 < 0$. Now, suppose that $\Theta_1 > 0$ and $\Theta_2 > 0$. Let $C_1 = -B_1 > 0$ and let $C_2 = -B_2$. Then, we obtain

$$\Theta_1 - C_1^2 = -\gamma\beta\left(1 - \frac{1}{R_0^2}\right) - \mu(\mu+\gamma+\beta) < 0 \tag{24}$$

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and

$$\Theta_2 - C_2^2 = \left(1 - \frac{1}{R_0}\right)((\mu+\gamma)(\gamma-\beta) - \beta\delta) < 0. \tag{25}$$

From (24), we have $\Theta_1 - C_1^2 < 0 \Longleftrightarrow 0 < \Theta_1 < C_1^2 \Longleftrightarrow 0 < \sqrt{\Theta_1} < C_1$. Thus, $-C_1 + \sqrt{\Theta_1} = B_1 + \sqrt{\Theta_1} < 0$, which implies $\mathrm{Re}(r_1) < 0$. From (25), we have $\Theta_2 - C_2^2 < 0 \Longleftrightarrow 0 < \Theta_2 < C_2^2 \Longleftrightarrow 0 < \sqrt{\Theta_2} < C_2$. Thus, $-C_2 + \sqrt{\Theta_2} = B_2 + \sqrt{\Theta_2} < 0$, which implies $\mathrm{Re}(r_3) < 0$. We summarize these findings in the following theorem.

Theorem 4.2. *The endemic equilibrium X_2^* exists iff $R_0 > 1$, and it is locally asymptotically stable.*

4.2.3. Diffusion approximation

The approximating OU process $(Z(t), t \geqslant 0)$ around the equilibrium point X_2^* has local drift matrix $H(X_2^*)$ in (23), and local covariance matrix $G(X_2^*)$, defined in Theorem 3.2, as follows

$$G(X_2^*) = \begin{pmatrix} g_{11} & g_{12} & 0 & 0 \\ g_{21} & g_{22} & 0 & 0 \\ 0 & 0 & g_{33} & g_{34} \\ 0 & 0 & g_{43} & g_{44} \end{pmatrix}, \tag{26}$$

where

$$\begin{aligned}
g_{11} &= \frac{1}{2}(\mu+\delta z) + \beta\frac{y_2^*}{y_1^*+y_2^*}x_1^* + \mu x_1^*, \\
g_{12} &= g_{21} = -\beta\frac{y_2^*}{y_1^*+y_2^*}x_1^*, \\
g_{22} &= \beta\frac{y_2^*}{y_1^*+y_2^*}x_1^* + (\mu+\gamma)x_2^*, \\
g_{33} &= \frac{1}{2}(\mu+\delta z) + \beta\frac{x_2^*}{x_1^*+x_2^*}y_1^* + \mu y_1^*, \\
g_{34} &= g_{43} = -\beta\frac{x_2^*}{x_1^*+x_2^*}y_1^*, \\
g_{44} &= \beta\frac{x_2^*}{x_1^*+x_2^*}y_1^* + (\mu+\gamma)y_2^*.
\end{aligned}$$

Therefore, we can approximate the equilibrium distribution of the process $(X(t), t \geqslant 0)$ by a multivariate normal distribution, see (14) and (13), with mean $\mu = NX_2^*$ and covariance matrix $N\Sigma$.

4.3. Open single population

To derive a deterministic analogue, as in the previous model, we show that the process $(X(t), t \geqslant 0)$ with the transition rates $q_{\mathbf{k},\mathbf{k}+l}$ as given in (3) is a density-dependent Markov process parameterized by $V = \frac{2B}{\mu}$. We will see shortly that this constant corresponds to the total population size in the disease-free equilibrium. Define $\mathbf{x} = \frac{\mathbf{k}}{V} = (x_1(t), x_2(t), y_1(t), y_2(t))$. Then, we can write

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$$q_{\mathbf{k},\mathbf{k}+l} = Vf(\mathbf{x}, l),$$

where $f(\mathbf{x}, l)$ is given by

$$f(\mathbf{x}, l) = \begin{cases} \frac{\mu}{2}, & l = \mathbf{e}_1, \\ \beta \frac{y_2}{n_M} x_1, & l = -\mathbf{e}_1 + \mathbf{e}_2, \\ \mu x_1, & l = -\mathbf{e}_1, \\ (\mu + \gamma) x_2, & l = -\mathbf{e}_2, \\ \frac{\mu}{2}, & l = \mathbf{e}_3, \\ \beta \frac{x_2}{n_F} y_1, & l = -\mathbf{e}_3 + \mathbf{e}_4, \\ \mu y_1, & l = -\mathbf{e}_3, \\ (\mu + \gamma) y_2, & l = -\mathbf{e}_4, \\ 0, & \text{otherwise}, \end{cases} \tag{27}$$

with $n_F = x_1 + x_2$ and $n_M = y_1 + y_2$. Therefore, the process $(X(t), t \geqslant 0)$ is a density dependent Markov process. As the parameter $V \to \infty$, by Theorem 3.1, the dynamic behavior of the scaled Markov process $(X_V(t), t \geqslant 0)$ can be approximated by a system of first order ODEs $\mathbf{x}' = F(\mathbf{x})$, with $F(\mathbf{x})$ defined as follows:

$$F(\mathbf{x}) = \begin{pmatrix} \frac{\mu}{2} - \beta \frac{y_2}{n_M} x_1 - \mu x_1 \\ \beta \frac{y_2}{n_M} x_1 - (\mu + \gamma) x_2 \\ \frac{\mu}{2} - \beta \frac{x_2}{n_M} y_1 - \mu y_1 \\ \beta \frac{x_2}{n_M} y_1 - (\mu + \gamma) y_2 \end{pmatrix}. \tag{28}$$

Again, we examine the dynamic behavior of the deterministic model around its equilibrium points.

4.4. Equilibrium points and analysis

This system also has two equilibrium points: the disease-free and the endemic equilibrium. As in the previous model, the disease-free equilibrium is

$$X_1^* = \left(x_1^* = \tfrac{1}{2}, x_2^* = 0, y_1^* = \tfrac{1}{2}, y_2^* = 0\right). \tag{29}$$

The Jacobian matrix of (28) is of the form

$$H(X_1^*) = \begin{pmatrix} -\beta\Lambda - \mu & 0 & \beta\Psi & -\beta\Psi(1-\Lambda) \\ \beta\Lambda & -\mu - \gamma & -\beta\Psi & \beta\Psi(1-\Lambda) \\ \beta\Delta\Theta & -\beta\Theta(1-\Delta) & -\beta\Delta - \mu & 0 \\ -\beta\Delta\Theta & \beta\Theta(1-\Delta) & \beta\Delta & -\mu - \gamma \end{pmatrix}, \tag{30}$$

with $\Lambda = \frac{y_2}{y_1+y_2}$, $\Psi = \frac{x_1}{y_1+y_2}$, $\Delta = \frac{x_2}{x_1+x_2}$ and $\Theta = \frac{y_1}{x_1+x_2}$. Evaluated at the disease-free equilibrium (29), we obtain

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$$H(X_1^*) = \begin{pmatrix} -\mu & 0 & 0 & -\beta \\ 0 & -\mu-\gamma & 0 & \beta \\ 0 & -\beta & -\mu & 0 \\ 0 & \beta & 0 & -\mu-\gamma \end{pmatrix}, \tag{31}$$

This matrix (31) has four eigenvalues (two of which are equal)

$$r_1 = r_2 = -\mu, \quad r_3 = -\beta-\mu-\gamma, \quad \text{and} \quad r_4 = \beta-\mu-\gamma. \tag{32}$$

Thus, the stability of this equilibrium is determined by r_4, since the other eigenvalues are always negative for the non-negative parameters β, γ, μ, δ. Hence, the disease-free equilibrium is *stable* if and only if $r_4 = \beta-\mu-\gamma < 0$ ($R_0 = \frac{\beta}{\mu+\gamma} < 1$) and it is *unstable* if and only if $\beta-\mu-\gamma > 0$ ($R_0 > 1$).

Next, we analyze the endemic equilibrium. The endemic equilibrium is of the form

$$X_2^* = (x_1^* = \xi_1, x_2^* = \xi_2, y_1^* = \xi_1, y_2^* = \xi_2), \tag{33}$$

where $\xi_1 = \frac{\mu}{2(\beta-\gamma)}$, and $\xi_2 = \frac{\mu(R_0-1)}{2(\beta-\gamma)}$. So, a positive endemic equilibrium occurs if and only if $R_0 > 1$. The Jacobian matrix evaluated around this positive endemic equilibrium X_2^* has four eigenvalues:

$$s_1 = \frac{1}{2}(B_3 + \sqrt{\Theta_3}), \quad s_3 = \frac{1}{2}(B_4 + \sqrt{\Theta_4}),$$
$$s_2 = \frac{1}{2}(B_3 - \sqrt{\Theta_3}), \quad s_4 = \frac{1}{2}(B_4 - \sqrt{\Theta_4}),$$

where

$$B_3 = -\mu - \frac{1}{2}(\beta+\gamma),$$
$$B_4 = -\frac{1}{2}(\beta-\gamma),$$
$$\Theta_3 = \frac{1}{4}(\beta^2+\gamma^2) + \beta\gamma\left(\frac{1}{R_0^2} - \frac{1}{2}\right),$$
$$\Theta_4 = \frac{1}{4}(\beta^2+\gamma^2) + \frac{\beta}{R_0}\left(\frac{1}{R_0} - 1\right)(\beta-\gamma) + \beta\gamma\left(\frac{1}{R_0} - \frac{1}{2}\right).$$

Since $R_0 > 1 \iff \beta > \mu+\gamma \iff \beta-\gamma > 0$, we have B_3, $B_4 < 0$. Let $C = -B > 0$, then

$$\Theta_3 - C_3^2 = \beta\gamma\left(\frac{1}{R_0^2} - 1\right) - \mu(\beta+\mu+\gamma), \tag{34}$$

and

$$\Theta_4 - C_4^2 = \frac{\beta}{R_0}\left(\frac{1}{R_0} - 1\right)(\beta-\gamma). \tag{35}$$

Since $R_0 > 1$, Eq. (34) implies $\Theta_3 - C_3^2 < 0 \iff 0 < \Theta_3 < C_3^2 \iff 0 < \sqrt{\Theta_3} < C_3$. Thus, $-C_3 + \sqrt{\Theta_3} = B_3 + \sqrt{\Theta_3} < 0$, which gives $\mathrm{Re}(r_1) < 0$. Also, from (35), we have $\Theta_4 - C_4^2 < 0 \iff 0 < \Theta_4 < C_4^2 \iff 0 < \sqrt{\Theta_4} < C_4$. Thus, $-C_4 + \sqrt{\Theta_4} = B_4 + \sqrt{\Theta_4} < 0$, which implies $\mathrm{Re}(r_3) < 0$. We summarize these findings in the following theorem.

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Theorem 4.3. *The disease-free equilibrium* X_1^* (29) *is locally asymptotically stable if* $R_0 < 1$ *and unstable if* $R_0 > 1$. *A stable positive endemic equilibrium* X_2^* (5) *exists iff* $R_0 > 1$.

Thus both the open and closed population models, under the assumption of both constant and variable population size, have the same stability conditions: the disease-free equilibrium is stable if $R_0 < 1$, otherwise, it is unstable, and the endemic equilibrium occurs when $R_0 > 1$ and it is stable. The differences are only in the size of the endemic equilibrium and the eigenvalues of the corresponding Jacobian matrix.

This reproduction number R_0 can be also derived by using the definition introduced in [8,31]. When the results (Theorem 2, [31]) are applied to the models for single population both constant and varying population size, one gets the same threshold condition as Theorem 4.1 and Theorem 4.2. For the case where the infection rates from an infected female to a susceptible male (say β_1) and from an infected male to a susceptible female (β_2) are different [21], the reproduction number is given by $R_0 = \frac{\sqrt{\beta_1\beta_2}}{\mu+\gamma}$.

4.5. Multiple patch models

To study the dynamic behaviour of the multiple patch models presented in Section 2, we apply the deterministic and diffusion approach, as in the case of a single population. We construct a density Markov process by scaling with a certain parameter, and derive a deterministic model to approximate the scaled process. The deterministic analogues of those two multiple patch models are given next.

4.5.1. Model with a force of infection

For the multiple patch model with constant population size; if all patches have equal size N, we can use this parameter as a scale factor for all random variables in the process. However, for the case where the patches have unequal size, all random variables are scaled by the total population size $N = \sum_{r=1}^{K} N^{(r)}$ and we define an extra constant $c^{(r)} = \frac{N^{(r)}}{N}$ for each r. Thus, one can obtain $q_{k,k+l} = Nf(\mathbf{x}, l)$, $r = 1, \ldots, K$ where f is given as follows

$$f(\mathbf{x},l) = \begin{cases} \alpha(\mu c^{(r)} + \delta z^{(r)}), & l = \mathbf{e}_{4r-3}, \\ \sum_{j=1}^{K} \beta_{rj} \frac{y_2^{(j)}}{n_{\mathrm{M}}^{(j)}} x_1^{(r)}, & l = -\mathbf{e}_{4r-3} + \mathbf{e}_{4r-2}, \\ \mu x_1^{(r)}, & l = -\mathbf{e}_{4r-3}, \\ (\mu+\gamma) x_2^{(r)}, & l = -\mathbf{e}_{4r-2}, \\ (1-\alpha)(\mu c^{(r)} + \delta z^{(r)}), & l = \mathbf{e}_{4r-1}, \\ \sum_{j=1}^{K} \beta_{rj} \frac{x_2^{(j)}}{n_{\mathrm{F}}^{(j)}} y_1^{(r)}, & l = -\mathbf{e}_{4r-1} + \mathbf{e}_{4r}, \\ \mu y_1^{(r)}, & l = -\mathbf{e}_{4r-1}, \\ (\mu+\gamma) y_2^{(r)}, & l = -\mathbf{e}_{4r}, \\ 0, & \text{otherwise}, \end{cases} \tag{36}$$

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with $n_{\mathrm{F}}^{(r)} = x_1^{(r)} + x_2^{(r)}$, $n_{\mathrm{M}}^{(r)} = y_1^{(r)} + y_2^{(r)}$, and $z^{(r)} = 1 - (n_{\mathrm{F}}^{(r)} + n_{\mathrm{M}}^{(r)})$.

As $N \to \infty$, we can apply again the results of Kurtz and derive the following deterministic analogue, for the process with transition rates (4):

$$\begin{aligned}
\frac{\mathrm{d}x_1^{(r)}}{\mathrm{d}t} &= \alpha(\mu c^{(r)} + \delta z^{(r)}) - \sum_{j=1}^{K} \beta_{rj} \frac{y_2^{(j)}}{n_{\mathrm{M}}^{(j)}} x_1^{(r)} - \mu x_1^{(r)}, \\
\frac{\mathrm{d}x_2^{(r)}}{\mathrm{d}t} &= \sum_{j=1}^{K} \beta_{rj} \frac{y_2^{(j)}}{n_M^{(j)}} x_1^{(r)} - (\mu + \gamma) x_2^{(r)}, \\
\frac{\mathrm{d}y_1^{(r)}}{\mathrm{d}t} &= (1-\alpha)(\mu c^{(r)} + \delta z^{(r)}) - \sum_{j=1}^{K} \beta_{rj} \frac{x_2^{(j)}}{n_{\mathrm{F}}^{(j)}} y_1^{(r)} - \mu y_1^{(r)}, \\
\frac{\mathrm{d}y_2^{(r)}}{\mathrm{d}t} &= \sum_{j=1}^{K} \beta_{rj} \frac{x_2^{(j)}}{n_{\mathrm{F}}^{(j)}} y_1^{(r)} - (\mu + \gamma) y_2^{(r)},
\end{aligned}$$

with $z^{(r)} = c^{(r)} - n_{\mathrm{F}}^{(r)} - n_{\mathrm{M}}^{(r)}$.

For the varying population case, the ODEs version of the stochastic model is derived by parameterizing each random variable of the process $(X(t), t \geqslant 0)$ (with the transition rates (5)) with the parameter $V = \frac{2B}{\mu}$ (as in the single varying population model). The deterministic system is given by the following equations:

$$\begin{aligned}
\frac{\mathrm{d}x_1^{(r)}}{\mathrm{d}t} &= \frac{\mu}{2} - \sum_{j=1}^{K} \beta_{rj} \frac{y_2^{(j)}}{n_{\mathrm{M}}^{(j)}} x_1^{(r)} - \mu x_1^{(r)}, \\
\frac{\mathrm{d}x_2^{(r)}}{\mathrm{d}t} &= \sum_{j=1}^{K} \beta_{rj} \frac{y_2^{(j)}}{n_{\mathrm{M}}^{(j)}} x_1^{(r)} - (\mu + \gamma) x_2^{(r)}, \\
\frac{\mathrm{d}y_1^{(r)}}{\mathrm{d}t} &= \frac{\mu}{2} - \sum_{j=1}^{K} \beta_{rj} \frac{x_2^{(j)}}{n_{\mathrm{F}}^{(j)}} y_1^{(r)} - \mu y_1^{(r)}, \\
\frac{\mathrm{d}y_2^{(r)}}{\mathrm{d}t} &= \sum_{j=1}^{K} \beta_{rj} \frac{x_2^{(j)}}{n_{\mathrm{F}}^{(j)}} y_1^{(r)} - (\mu + \gamma) y_2^{(r)},
\end{aligned}$$

with $n_{\mathrm{F}}^{(r)}$ and $n_{\mathrm{M}}^{(r)}$ defined as before.

4.5.2. Model with actual mobility

As explained previously, for the model with actual mobility we only consider the case under a varying population size. The ODE analogue of this model is given, after scaling the process $(X(t), t \geqslant 0)$ (with transition rates in (6)) with $V = \frac{2B}{\mu}$, by the following system:

$$\begin{aligned}
\frac{\mathrm{d}x_1^{(r)}}{\mathrm{d}t} &= \frac{\mu}{2} - \beta_r \frac{y_2^{(r)}}{n_{\mathrm{M}}^{(r)}} x_1^{(r)} - \mu x_1^{(r)} + \sum_{j=1}^{K} \rho_{rj} \frac{u^{(j)}}{n^{(j)}} x_1^{(j)} - \frac{u^{(r)}}{n^{(r)}} x_1^{(r)}, \\
\frac{\mathrm{d}x_2^{(r)}}{\mathrm{d}t} &= \beta_r \frac{y_2^{(r)}}{n_{\mathrm{M}}^{(r)}} x_1^{(r)} - (\mu + \gamma) x_2^{(r)} + \sum_{j=1}^{K} \rho_{rj} \frac{u^{(j)}}{n^{(j)}} x_2^{(j)} - \frac{u^{(r)}}{n^{(r)}} x_2^{(r)},
\end{aligned}$$

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$$\frac{dy_1^{(r)}}{dt} = \frac{\mu}{2} - \beta_r \frac{x_2^{(r)}}{n_F^{(r)}} y_1^{(r)} - \mu y_1^{(r)} + \sum_{j=1}^{K} \rho_{rj} \frac{u^{(j)}}{n^{(j)}} y_1^{(j)} - \frac{u^{(r)}}{n^{(r)}} y_1^{(r)},$$

$$\frac{dy_2^{(r)}}{dt} = \beta_r \frac{x_2^{(r)}}{n_F^{(r)}} y_1^{(r)} - (\mu + \gamma) y_2^{(r)} + \sum_{j=1}^{K} \rho_{rj} \frac{u^{(j)}}{n^{(j)}} y_2^{(j)} - \frac{u^{(r)}}{n^{(r)}} y_2^{(r)},$$

where $n^{(r)} = n_F^{(r)} + n_M^{(r)}$.

Here, we have not proved analytically the existence and the stability of their equilibrium points but we believe that one could derive the reproduction number R_0 by using the concept of next generation matrix introduced in [8] and the results of the method (Theorem 2 and Theorem 4, [31]) to discuss the stability of the equilibria. [13,2] have used the result (Theorem 2, [31]) to analyse the multi compartmental models.

Thus, we only consider the endemic equilibria numerically and use them to derive the diffusion counterparts.

5. Numerical experiments and discussion

In this section, we illustrate the behavior of the various population models and their deterministic and diffusion approximations via a number of numerical experiments. The following parameters are the same in each experiment: The natural death rate is $\mu = 0.02$ (which corresponds to the life expectancy 50 years), the death rate due to AIDS is $\delta = 0.05$ (which means a life expectancy for AIDS people of only 20 years), and the removal rate is $\gamma = 0.08$ (which corresponds to a 12 year infectious period of HIV before AIDS sets in). We always assume $\alpha = \frac{1}{2}$, which implies a 50:50 ratio of females and males in the recruitment of new susceptibles. The other parameter settings are explained in each individual experiment.

5.1. Models for a single population

In these experiments the important parameter is β, since it determines the stability of the disease-free equilibrium (see Section 4 for the threshold condition assuming the parameters μ and γ are fixed). The numerical results in Fig. 4, for the deterministic model with a constant single population, illustrate how crucial the parameter β is.

It can be seen from the two logarithmic plots in Fig. 4(b) and (c) that when R_0 is below the threshold ($R_0 < 1$) the proportion of infectives of both females and males, after a few infectives are introduced in the population, returns to no infection, but it grows away from the disease-free equilibrium if R_0 is above the threshold ($R_0 > 1$).

The value of the parameter β can be set by using the formula in Remark 2.1. In some studies, the value of the infection rate β was estimated in a range 0.48–1.98 *per year* for homo/bisexuals [5] depending on the population investigated. For the purpose of our numerical study, we choose the parameter $\beta = 0.5$ so that $R_0 > 1$ which results in a positive endemic equilibrium. We consider how the stochastic processes converge to their deterministic and diffusion approximation around the equilibrium.

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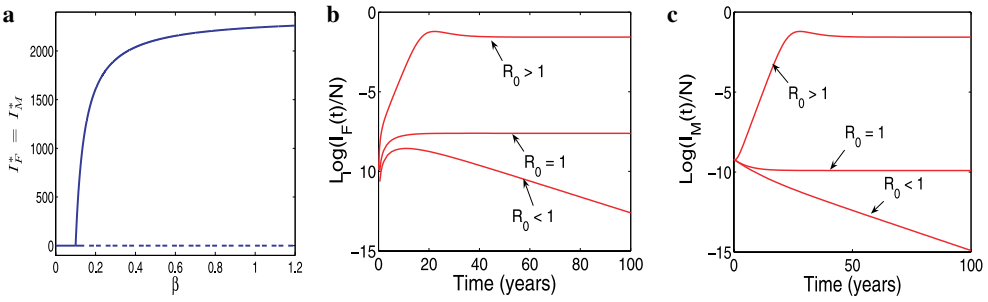

Fig. 4. (a). The stability of the disease-free equilibrium, and the birth of the endemic equilibrium as the parameter β varies. (b) and (c) illustrate how the disease-free equilibrium of the deterministic model behaves for three different values of β, ($0.5(R_0 > 1)$; $0.1(R_0 = 1)$; $0.05(R_0 < 1)$).

5.1.1. Model with a closed single population

For the numerical experiments, we apply the parameter settings above and use the following initial values: 50 000 susceptible females and 50 000 susceptible males, 100 infected males, no infected females, and no AIDS cases. So, the total population size is $N = 100\,100$.

Fig. 5 describes the dynamic behaviour in the male subpopulation (similar results hold for the female subpopulation).

We can see that the stochastic process remains close to the trajectory of its deterministic analogue during a finite time interval. We should note that the process will eventually leave the trajectory and be absorbed in the disease-free equilibrium.

The histograms in Fig. 6 describe the empirical distribution of the number of infectives based on a simulation of the CTMC with transition rates 2 around the equilibrium point of the deterministic process.

These numerical results illustrate that the 'stationary' distribution of the process can be approximated by a normal distribution. The empirical means and standard deviations for the number of infected females (males) are 20 910 and 128.9 (20 914 and 126.7), respectively. From the diffusion approximation, the exact form of the mean $\bar{x} = NX_2^*$ and covariance matrix $N\Sigma$ of $X(t)$ can be calculated from Eqs. (9) and (11), which numerically can be found to be

$$\bar{x} = (5224, 20895, 5224, 20895),$$

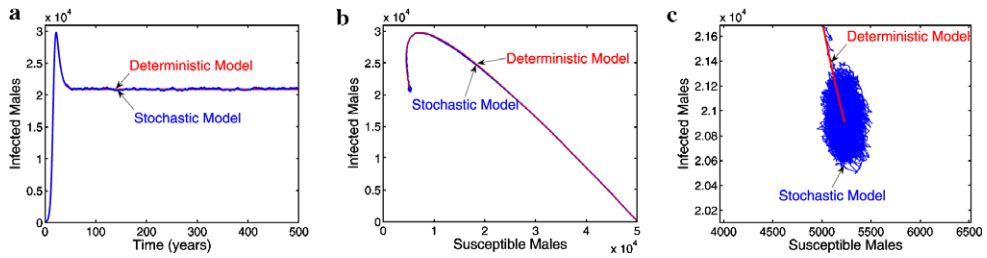

Fig. 5. The behavior of the stochastic model and its deterministic counterpart for Male Subpopulation for long term evolution. (a) The number of male infectives versus time, (b) the dynamic behavior in the male subpopulation, and (c) the graph of (b) around the endemic equilibrium.

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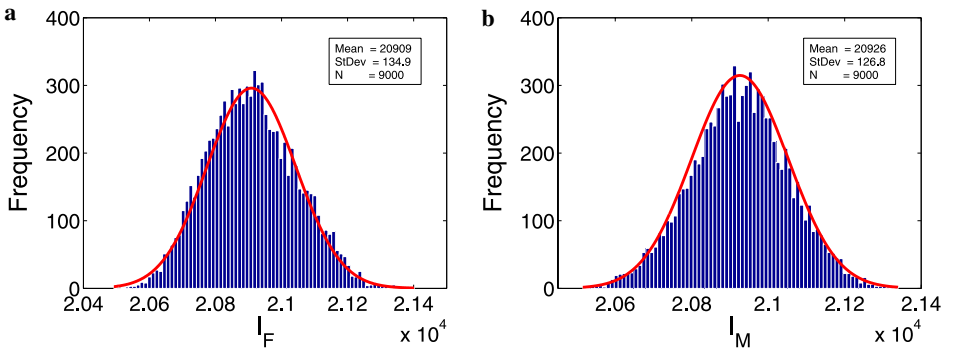

Fig. 6. Endemic distributions of the stochastic model around the endemic equilibrium of its deterministic analogue behave as a normal distribution. (a) The distribution of the number of infected females and (b) the distribution of the number of infected males.

and

$$N\Sigma = N\begin{pmatrix} 0.05256277166437 & -0.00960963034076 & 0.00840185581453 & -0.01661760123708 \\ -0.00960963034076 & 0.17922317018881 & -0.01661760123708 & -0.02293806664514 \\ 0.00840185581453 & -0.01661760123708 & 0.05256277166437 & -0.00960963034076 \\ -0.01661760123708 & -0.02293806664514 & -0.00960963034076 & 0.17922317018881 \end{pmatrix}.$$

The means and standard deviations obtained from the diffusion approximation for the number of infected females (males), which are 20916 and 133.9 for both females and males, are close to the experiment results.

To illustrate the accuracy of this diffusion approximation, we plot the dynamic behavior of the male subpopulation around the equilibrium point, together with its diffusion analogue, see Fig. 7.

We see that the equilibrium distribution of infectives around the endemic equilibrium is closely approximated by a two-dimensional Gaussian distribution derived from the diffusion process.

5.1.2. Model with an open single population

In these experiments we use the same parameters as in the model with a single closed (constant) population. In addition, we set $B = 1000$. Fig. 8 illustrates that the stochastic process for an open single population converges to its deterministic counterpart.

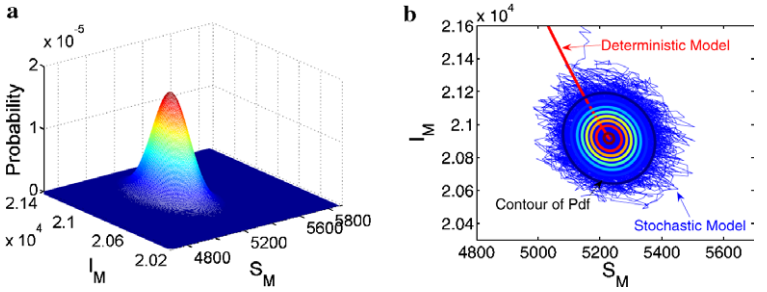

Fig. 7. The stochastic model and its deterministic and diffusion analogues for a constant population size for male subpopulation. (a) The p.d.f of male population corresponding to the diffusion approximation and (b) the stochastic process with its deterministic limit, and the contour lines corresponding to the p.d.f in (a).

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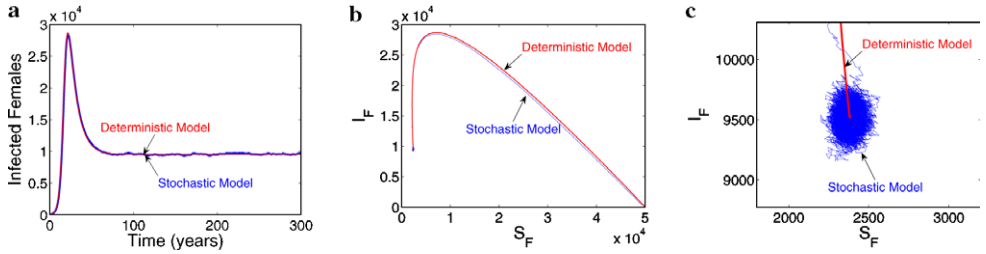

Fig. 8. Stochastic and deterministic model for the female subpopulation. (a) The number of female infectives versus time, (b) the dynamic behavior in the female subpopulation, and (c) the graph of (b) around the endemic equilibrium.

From the diffusion approximation, the mean and covariance of the process $(X(t),\ t \geqslant 0)$ can be approximated using Eqs. (14) and (13). The Gaussian distribution derived from the diffusion process (with $V = 100\,000$) has the mean vector

$$\bar{x} = VX_2^* = (2381, 9524, 2381, 9524),$$

and the covariance matrix $V\Sigma$, with

$$\Sigma = \begin{pmatrix} 0.02415856711539 & 0.00153711928687 & -0.00001949907606 & -0.00725191311387 \\ 0.00153711928687 & 0.10548710082854 & -0.00758259929573 & -0.00982775497753 \\ -0.00001949907606 & -0.00758259929573 & 0.02416688585698 & -0.00075143305884 \\ -0.00725191311387 & -0.00982775497753 & -0.00075143305884 & 0.09606834250022 \end{pmatrix}.$$

Fig. 9 illustrates the accuracy of the diffusion approach in approximating the distribution of susceptibles and infectives around the equilibrium point.

5.2. Multiple patch models

In these numerical experiments we carry out the simulations with $M = 10$ patches in all multiple patch models. We set the initial values to 50 000 susceptibles females and 50 000 susceptibles males for each patch. The infected people – set to be 100 infected males – are assumed to be initially concentrated only in patch 1. Thus, initially no infected individuals are present in other patches. All parameters (except β) have the same values as specified previously.

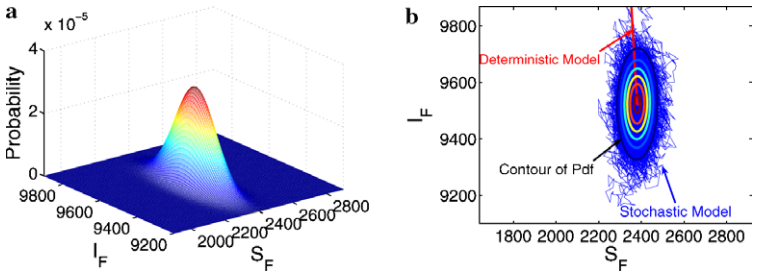

Fig. 9. The stochastic model and its deterministic and diffusion analogue for the female subpopulation using a varying population size. (a) The p.d.f of female population corresponding to the diffusion approximation and (b) the stochastic process with its deterministic limit, and the contour lines corresponding to the p.d.f in (a).

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5.2.1. Models with force of infection

In this model, we assumed that within-patch mixing is stronger (and often considerably stronger) than between-patch mixing, and hence that the between-patch transmission parameters β_{rj} (for $r \neq j$) are small compared to the within-patch transmission parameters β_r (or β_{rr}); see [20]. In addition, the force of infection from the patch where the infection is initially concentrated to is assumed to be stronger than the forces among other patches. We might consider this patch, for example, as a big city where people from other small cities come to visit often. With these assumptions, we set the values of β as follows: $\beta_r = 0.5$, $\beta_{1j} = 0.5$, $j = 1, \ldots, 10$, and $\beta_{rj} = 0.01$, $r = 2, \ldots, 10$, $j = 1, \ldots, 10$.

The following numerical results (see Fig. 10) describe the dynamic behavior of the process and its deterministic analogue in patch 1 for the female subpopulation. This behaviour is similar to that in other patches, for each subpopulation.

We conclude that the stochastic process in the multiple patch model, at least from the numerical evidence, converges to its deterministic version.

To obtain the diffusion approximation, we evaluate the equilibrium points by solving the deterministic counterparts numerically. Then, we determine numerically the mean vectors and the covariance matrices around these equilibria for their multivariate Gaussian distributions. These results can be seen in Tables 1 and 2 for the case of constant population sizes and varying population sizes, respectively.

These calculation are in close agreement with the empirical means and standard deviations obtained by simulating the stochastic process and collecting data after equilibrium has been reached. We summarize in Tables 3 and 4 the sample means and sample standard deviations obtained from a Monte Carlo simulation for a closed and open multiple population, respectively, with the force of infection.

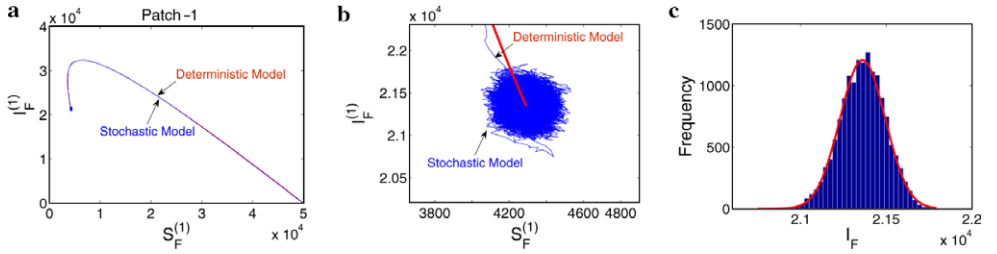

Fig. 10. Stochastic and deterministic model. (a) The dynamic behavior in the female subpopulation in the patch-1, (b) the graph of (a) around the endemic equilibrium, and (c) the distribution of the number of the infected females in the patch-1.

Table 1
Means and standard deviations of the diffusion approximation; for the closed population model

Patches	Infected females		Infected males	
	$\bar{x}$	σ	$\bar{x}$	σ
1	21354	133	21354	134
2–10	22230	135	22230	134

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Table 2
Means and standard deviations of the diffusion approximation; for the open population model

Patches	Infected females		Infected males	
	$\bar{x}$	σ	$\bar{x}$	σ
1	9614	106	9614	98
2–10	9792	103	9792	99

Table 3
Sample means and standard deviations for the model with a constant population size

Patches	Infected females		Infected males	
	$\tilde{\bar{x}}$	$\tilde{\sigma}$	$\tilde{\bar{x}}$	$\tilde{\sigma}$
1	21350	138	21358	130
2	22239	137	22238	139
3	22229	138	22234	142
4	22221	141	22230	135
5	22225	135	22233	135
6	22223	140	22234	133
7	22222	141	22237	134
8	22231	137	22231	136
9	22226	138	22229	140
10	22235	130	22236	135

Table 4
Sample means and standard deviations for the model with a varying population size

Patches	Infected females		Infected males	
	$\tilde{\bar{x}}$	$\tilde{\sigma}$	$\tilde{\bar{x}}$	$\tilde{\sigma}$
1	9600	103	9611	93
2	9802	96	9800	103
3	9783	99	9797	99
4	9776	98	9788	94
5	9790	101	9792	95
6	9792	96	9787	94
7	9776	101	9784	101
8	9791	99	9785	103
9	9801	99	9801	102
10	9795	100	9794	100

5.2.2. Model with actual mobility

For the model with actual mobility, we assume that the forces of infection within a patch are the same for all patches, which is set to $\beta_i = 0.5$. The initial numbers of susceptibles and infectives in each patch are as in the model with force of infection. Here, we assume that the number of people leaving their home patches is equal for all patches (assumed $u_r = 10$ *per capita per year*, $r = 1, \ldots, K$) and they will visit other patches with the same probability.

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Table 5
Means and standard deviations of Multivariate Gaussian distribution

Patches	Infected females		Infected males	
	$\bar{x}$	σ	$\bar{x}$	σ
1–10	9524	98	9524	98

Table 6
Sample means and sample standard deviations from numerical experiments

Patches	Infected females		Infected males	
	$\bar{\bar{x}}$	$\tilde{\sigma}$	$\bar{\bar{x}}$	$\tilde{\sigma}$
1	9476	100	9527	95
2	9499	100	9528	100
3	9500	94	9527	99
4	9505	94	9518	95
5	9536	98	9523	101
6	9538	100	9528	95
7	9527	94	9522	101
8	9542	99	9521	99
9	9455	99	9523	98
10	9492	96	9524	99

The mean vector and standard deviation of the multivariate Gaussian distribution corresponding to the diffusion approximation are obtained in the same way as before, and the corresponding mean vectors and standard deviations obtained from the numerical simulation of the stochastic models are presented in Tables 5 and 6, respectively. Again there is close agreement with the sample means and variances obtained by Monte Carlo simulation.

Thus, the deterministic and diffusion approach can be applied to study the dynamic behavior of the stochastic multiple patch model with the actual mobility.

6. Conclusion and future research

The dynamic behavior of the stochastic models for the spread of HIV presented in this paper are well approximated by their deterministic and diffusion counterparts. We find the same threshold conditions $R_0 = 1$ for a disease-free equilibrium in the case of both an open and closed single population. As $R_0 > 1$ (above threshold), this equilibrium loses its stability and a stable endemic state occurs. The numerical results also indicate that there exists a positive-stable endemic equilibrium in the multiple patch models, although we have not proved this analytically. Although the stochastic models presented in this paper are perhaps too simple to describe the actual spread of HIV, they provide some clues, how e.g., more realistic models can be formulated. Moreover, for future research, it should be feasible to use the deterministic and diffusion approaches to study more complex stochastic models of HIV/AIDS spread; for example, stochastic models in a mobile

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heterogeneous population, classified according to age and sexual behavior [15,28–30], various stages of infectivity [14,22], or (since the disease is primarily a sexually transmitted disease) models that include partnership pattern formation [9,21,27]. Another possible direction for future research is to consider how control strategies may be devised. For example, to find a strategy that provides the greatest reduction in the endemic level of the disease for a given cost, or to find the cheapest strategy that guarantees an upper level of prevalence of HIV in all patches. Finally, taking into account the available statistical data and control strategies into the models will further improve our understanding how the disease spread into the heterogeneous population. However, as many factors of consideration are included in the models, the complexity of the models increases.

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