Extinction thresholds in deterministic and stochastic epidemic models

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The basic reproduction number, $R_0$, one of the most well-known thresholds in deterministic epidemic theory, predicts a disease outbreak if $R_0 > 1$. In stochastic epidemic theory, there are also thresholds that predict a major outbreak. In the case of a single infectious group, if $R_0 > 1$ and $i$ infectious individuals are introduced into a susceptible population, then the probability of a major outbreak is approximately $1 - \left(\frac{1}{R_0}\right)^i$. With multiple infectious groups from which the disease could emerge, this result no longer holds. Stochastic thresholds for multiple groups depend on the number of individuals within each group, $i_j, j = 1, \ldots, n$, and on the probability of disease extinction for each group, $q_j$. It follows from multitype branching processes that the probability of a major outbreak is approximately $1 - q_1^{i_1} \cdots q_n^{i_n}$. In this investigation, we summarize some of the deterministic and stochastic threshold theory, illustrate how to calculate the stochastic thresholds, and derive some new relationships between the deterministic and stochastic thresholds.

Keywords: multitype branching processes; reproduction numbers

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1. Introduction

The basic reproduction number $R_0$ is a well-known threshold in deterministic epidemic theory. Diekmann et al. [11] and van den Driessche and Watmough [13,14] derived methods to calculate the basic reproduction number based on the next-generation matrix. This method depends on linearization of the system of ordinary differential equations (ODEs) near the disease-free equilibrium (DFE) and is referred to as the next-generation matrix approach. Alternate but equivalent thresholds, derived by Heesterbeek and Roberts [19,31], relate to the control of a particular type of infected or infectious group $i$ and are referred to as type reproduction numbers, $T_i$. These thresholds have been applied to many deterministic epidemic models to predict either disease extinction $R_0 < 1$ (or $T_i < 1$) or disease persistence $R_0 > 1$ (or $T_i > 1$).

Thresholds for probability of disease extinction exist for the stochastic counterpart of the ODE model, a continuous-time Markov chain (CTMC) model, where time is continuous but the
random variables are discrete. These stochastic thresholds are closely related to the deterministic thresholds but depend on the initial number of infectious individuals for each type $i$. The theory depends on continuous-time branching processes. Application of this theory to epidemics goes back to the work of Whittle in 1955 [32], who derived the probability of a major outbreak for the susceptible–infectious–recovered (SIR) model when the population size is large and a small number of infectious individuals are introduced. In Whittle’s approximation, if $I(0) = i$ infectious individuals are introduced into the population, then the probability of a major outbreak is

$$1 - \left( \frac{1}{R_0} \right)^i$$

(1)

or, alternately, the probability of disease extinction is $(1/R_0)^i$ [32]. Important assumptions in this approximation are that each infected individual gives ‘birth’ to a new infectious individual independent of others and each individual has the same probability of giving ‘birth’. These assumptions are implicit in Galton–Watson theory, also referred to as Bienaymé–Galton–Watson theory (named after the three investigators who contributed to the discrete stochastic theory) [2,18,21,27,30]. For a small number of infectious individuals and a large population size, these assumptions may be realistic and indeed the approximation (1) is very good in many cases. Estimates for probability of extinction based on branching processes have been applied frequently to populations, genetics, cellular processes (e.g. [5,12,17,21,23,29,33]), and recently to epidemics on networks (e.g. [6,8,28]). Aside from the applications of branching processes to epidemics on networks, there have been much fewer applications to epidemics with multiple infectious groups or stages [7,12,16].

The goals of this investigation are to review some classical results on epidemic thresholds and to verify some new results that relate the deterministic and stochastic thresholds. In addition, we illustrate the deterministic and stochastic thresholds in some well-known epidemic models. In the following section, the dynamics of the classic deterministic SIR model are summarized and Whittle’s approximation to probability of disease extinction is derived. In the SIR model, there is one infectious group. In Section 3, the deterministic thresholds, basic reproduction number, $R_0$, and type reproduction numbers, $T_i$, are summarized for multiple infectious groups. It is shown for two groups $i = 1, 2$ that either $T_i < R_0 < 1$, $T_i = 1 = R_0$, or $1 < R_0 < T_i$. The theory and underlying assumptions required to apply Bienaymé–Galton–Watson branching processes (BGWbp) are summarized. In Section 4, the deterministic and stochastic extinction theory is applied to some well-known epidemic models with multiple infectious groups.

2. One infectious group

2.1. Deterministic SIR model

In the classic SIR epidemic model with $S =$ susceptible individuals, $I =$ infectious individuals, and $R =$ recovered and immune individuals, the model is a system of three ODEs:

$$\dot{S} = \Lambda - dS - \beta \frac{S}{N} I,$$

$$\dot{I} = \beta \frac{S}{N} I - dI - \gamma I - \alpha I = I \left( \beta \frac{S}{N} - [d + \gamma + \alpha] \right),$$

$$\dot{R} = \gamma I - dR.$$  

(2)

The parameter $\Lambda$ is the immigration/birth rate, $\beta SI/N$ is the rate of new infections (frequency-dependent incidence rate), $d$ is the natural death rate, $\gamma$ is the recovery rate, and $\alpha$ is the
The formula for the basic reproduction number follows directly from the differential equation in (2) when \( S \approx N \). This same basic reproduction number applies to SIS and SIR models. Although in these latter models there is temporary immunity and individuals return to the susceptible group. If \( R_0 \leq 1 \), then solutions approach the DFE, whereas if \( R_0 > 1 \), solutions approach the endemic equilibrium [24].

2.2. Stochastic SIR model

The corresponding CTMC SIR model can be defined in terms of the infinitesimal transition probabilities for the stochastic process \( \tilde{X}(t) = (S(t), I(t), R(t)) \), \( t \in [0, \infty) \),

\[
p_a \rightarrow b(\Delta t) = \text{Prob}[\tilde{X}(t + \Delta t) = b|\tilde{X}(t) = a] = P(a, b)\Delta t + o(\Delta t).
\]

The random variables \( S, I, \) and \( R \) are discrete and the process is time-homogeneous. For simplicity, the same notation for the random variables is used as in the deterministic model. The transitions and their rates are summarized in Table 1.

To derive a stochastic threshold for disease extinction, the Markov chain process, summarized in Table 1, is again approximated near the DFE. The dynamics of \( I \) are of interest when the susceptible population size \( S \) is near the DFE and the initial number of infectives is small. We assume \( S(t) = \bar{S} \), \( R(t) = 0 \), and the events associated with \( I(t) \) are independent. The assumption of independent events in this Markov process is the most restrictive and leads to a BGWbp [2,18,21,27,30]. An estimate for the probability of disease extinction,

\[
P_0 = \lim_{t \to \infty} \text{Prob}[I(t) = 0],
\]

can be obtained from the offspring probability-generating function (pgf) for \( I \). The infectious population either ‘hits zero’ (an absorbing state) or grows rapidly. Thus, it is not necessary to let \( t \to \infty \) to observe extinction.

The offspring pgf for infectious individuals is defined when there is initially one infectious individual, \( I(0) = 1 \). The probability of a death or recovery of an infectious individual is \( p_0 = (d + \gamma + \alpha)/(\beta + d + \gamma + \alpha) \). The probability of a birth (successful transmission) of an infectious individual is \( p_2 = \beta/(\beta + d + \gamma + \alpha) \). In the continuous-time process, a birth is not accompanied by a death, so there are two infectious individuals following a successful transmission. The

| Description    | State transition \( a \to b \) | Rate \( P(a, b) \) |
|----------------|---------------------------------|--------------------|
| Birth of \( S \) | \( (S, I, R) \to (S + 1, I, R) \) | \( \Lambda \)       |
| Death of \( S \) | \( (S, I, R) \to (S - 1, I, R) \) | \( dS \)            |
| Infection      | \( (S, I, R) \to (S - 1, I + 1, R) \) | \( \beta SI/N \)    |
| Recovery       | \( (S, I, R) \to (S, I - 1, R + 1) \) | \( \gamma I \)     |
| Death of \( I \) | \( (S, I, R) \to (S, I - 1, R) \) | \( (d + \alpha)I \) |
| Death of \( R \) | \( (S, I, R) \to (S, I, R - 1) \) | \( dR \)            |
offspring pgf, \( f : [01] \to [0, 1] \), equals
\[
f(u) = p_2 u^2 + p_0 \\
= \frac{\beta u^2 + d + \gamma + \alpha}{\beta + d + \gamma + \alpha}
\]
(e.g. [2,18,21,23,27]). The mean number of offspring per infectious individual is given by
\[
m = f'(1) = \frac{2\beta}{\beta + d + \gamma + \alpha}.
\]
With a small number of infectious individuals, the BGWbp hits zero (disease extinction) or multiplies rapidly (disease outbreak). The occurrence of one of the two outcomes depends on \( m \).
If \( m \leq 1 \), then
\[
\lim_{t \to \infty} \text{Prob}\{I(t) = 0\} = 1
\]
and if \( m > 1 \), there exists a unique fixed point of \( f \), \( f(q) = q \), \( 0 < q < 1 \) such that
\[
P_0 = \lim_{t \to \infty} \text{Prob}\{I(t) = 0\} = q^i,
\]
where \( I(0) = i \) [2,18,21,27,30]. The three cases, \( m < 1 \), \( m = 1 \), and \( m > 1 \) are referred to as subcritical, critical, and supercritical, respectively. Of course, the BGWbp is only applicable at the beginning of the infection process because of the underlying assumptions.

For the SIR model, it is easy to see that \( R_0 < 1 \) (or \( R_0 = 1 \) or \( R_0 > 1 \)) if and only if (iff) \( m < 1 \) (or \( m = 1 \) or \( m > 1 \)). In addition, the fixed point of \( f \) in the case \( m > 1 \) is \( q = 1/R_0 \). Hence, the classic approximation of Whittle [32] holds: for \( I(0) = i \) and \( R_0 > 1 \), the probability of a major outbreak is given by Equation (1).

In the case of multiple infectious groups, methods for calculating thresholds for disease extinction in deterministic and stochastic models are summarized in the next section.

3. Multiple infectious groups

3.1. Deterministic thresholds

We summarize briefly the next-generation matrix method for calculating the basic reproduction number. More details can be found in Diekmann et al. [11] and van den Driessche and Watmough [13,14]. Let \( \tilde{I} = (I_1, \ldots ,I_n)^T \) denote the vector of infected or infectious individuals, where tr means transpose of the vector. Linearizing the system of differential equations about the DFE yields \( d\tilde{I}/dt = J\tilde{I} \), where \( J = F - V \) is the Jacobian matrix evaluated at the DFE. Matrix \( F \) contains terms that represent new infections and matrix \( V \) contains the remaining terms, such as the rate of recovery and transitions between infected groups. The next-generation matrix is \( K = FV^{-1} \). The basic reproduction number is the spectral radius of \( K \), that is, \( R_0 = \rho(K) \). Five sufficient conditions (A1)–(A5) (p. 31 [13] or p. 161 [14]) guarantee that the DFE is locally asymptotically stable if \( R_0 < 1 \). Biologically, \( R_0 \) is the asymptotic per-generation growth rate [11,20].

The type reproduction numbers also depend on the next-generation matrix \( K \). We summarize the method described by Heesterbeek and Roberts [19,31]. Let \( e_j \) be the \( j \)th unit column vector and \( P_j \) be the \( n \times n \) matrix with all zeroes except the diagonal element \( p_{jj} = 1 \). In the first generation, the number of infections of type \( j \) is \( e_j^T K e_j = k_{jj} \). In the second generation, the number of infections
of type $j$ is $e_j^T \mathbb{K}[(I - P_j)\mathbb{K}] e_j$, where $\mathbb{K}$ is the $n \times n$ identity matrix. In generation $n$, the number of infections of type $j$ is $e_j^T \mathbb{K}[(I - P_j)\mathbb{K}] e_j$. In general, the type reproduction number for control of the single group $I_j$ is

$$T_j = e_j^T \mathbb{K} \sum_{k=0}^{\infty} [(I - P_j)\mathbb{K}]^k e_j = e_j^T \mathbb{K} [(I - (I - P_j)\mathbb{K})^{-1} e_j,$$

provided $\rho((I - P_j)\mathbb{K}) < 1$ and $\mathbb{K}$ is irreducible [19,31]. If $n = 1$, such as in the SIR model, the type reproduction number $T_1 = R_0$. If $n = 2$, there are two type reproduction numbers, one for each group. They can be expressed as

$$T_1 = k_{11} + \frac{k_{12}k_{21}}{1 - k_{22}} \quad \text{and} \quad T_2 = k_{22} + \frac{k_{12}k_{21}}{1 - k_{11}}. \quad (3)$$

Irreducibility of $\mathbb{K}$ requires $k_{12}k_{21} \neq 0$ and existence of $T_i$ requires $k_{ij} < 1$, $j \neq i$, $i,j = 1,2$. In general, a type reproduction number can be defined for a subset of the entire group, $\{1,2,\ldots,n\}$ [19,31]. In particular, $T_{\{1,\ldots,n\}} = R_0$.

Roberts and Heesterbeek [31] verified that $1 - R_0$ and $1 - T_i$ have the same sign; either both are negative, positive, or zero. For two groups, it can be easily shown that one of the following holds:

$$T_i < R_0 < 1 \quad \text{or} \quad T_i > R_0 > 1 \quad \text{or} \quad T_i = R_0 = 1. \quad (4)$$

The relationships in (4) can be verified by comparing $R_0$ with $T_i$ and using the fact that both $T_i$ and $R_0$ are either less than, equal to, or greater than one.

We verify the relationships in (4) for $T_1$, where $0 \leq k_{22} < 1$ and $k_{12}k_{21} \neq 0$. The basic reproduction number equals

$$R_0 = \frac{k_{11} + k_{22}}{2} + \frac{\sqrt{(k_{11} - k_{22})^2 + 4k_{12}k_{21}}}{2}. \quad (5)$$

Suppose $R_0 < 1$. Consider

$$R_0 - T_1 = \frac{k_{22} - k_{11}}{2} + \frac{\sqrt{(k_{11} - k_{22})^2 + 4k_{12}k_{21}}}{2} - \frac{k_{12}k_{21}}{1 - k_{22}}. \quad (5)$$

If the right side of Equation (5) is positive, then $T_1 < R_0 < 1$ and the first inequality in (4) holds. Therefore, suppose the right side is nonpositive and by rearranging this inequality one obtains

$$\sqrt{(k_{11} - k_{22})^2 + 4k_{12}k_{21}} \leq k_{11} - k_{22} + 2\frac{k_{12}k_{21}}{1 - k_{22}}. \quad (6)$$

Squaring both sides of (6) and simplifying yields

$$1 \leq k_{11} + \frac{k_{12}k_{21}}{1 - k_{22}} = T_1, \quad (7)$$

a contradiction since $T_1 < 1$. A similar proof applies in the case $R_0 > 1$.

The relationship in (4) is biologically reasonable. The inequality $1 < R_0 < T_i$ implies that more effort is required to control a single infectious group if $R_0 > 1$, than to control both groups simultaneously (reducing $R_0$). Extensions of these deterministic thresholds to models with periodic or heterogeneous environments can be found in references [3,4,20].
3.2. Stochastic thresholds

We summarize briefly some of the theory of continuous-time, multitype BGWbp that relates to probability of ultimate extinction [2,21,22,27,30]. A more detailed introduction to branching processes and applications can be found in references [2,12,17,18,21–23,27].

Let \( \{\tilde{I}(t) : t \in [0, \infty)\} \) be a collection of discrete-valued vector random variables, \( \tilde{I}(t) = (I_1(t), \ldots, I_n(t))^\nu \). For convenience and simplicity, we use the same notation for the random variables as for the deterministic variables. Assume that individuals of type \( i \) give ‘birth’ to individuals of type \( j \) and that the number of offspring produced by type \( i \) does not depend on the number of offspring produced by other individuals of type \( i \) or type \( j, j \neq i \); they are independent. In addition, individuals of type \( i \) have the same offspring pgf (independent and identically distributed, iid). Let \( \{Y_{ji}\}_{j=1}^n \) denote the offspring random variables for type \( i, i = 1, \ldots, n \) so that \( Y_{ji} \) is the number of offspring of type \( j \) produced by type \( i \). Denote the probability that one individual of type \( i \) gives birth to \( k_j \) individuals of type \( j \) as

\[
P_i(k_1, \ldots, k_n) = \text{Prob}[Y_{i1} = k_1, \ldots, Y_{in} = k_n].
\]

The offspring pgf for type \( i \) given \( I_i(0) = 1 \) and \( I_j(0) = 0, j \neq i, f_i : [0, 1]^n \to [0, 1] \), is defined as

\[
f_i(u_1, \ldots, u_n) = \sum_{k_1=0}^{\infty} \cdots \sum_{k_n=0}^{\infty} P_i(k_1, \ldots, k_n) u_1^{k_1} \cdots u_n^{k_n}.
\]

There is always a fixed point at \( 1 = (1, 1, \ldots, 1) \), i.e. \( f_i(1, \ldots, 1) = 1 \).

We assume that each \( f_i \) is not simple, that is, each \( f_i \) is not a linear function of the \( u_j \) and \( f_i(0) \neq 0 \), that is,

\[
f_i(u_1, u_2, \ldots, u_n) \neq \sum_{j=1}^{n} a_j u_j.
\]

The expectation matrix \( \mathbb{M} = [m_{ji}] \) is an \( n \times n \) nonnegative matrix such that the element \( m_{ji} \) is the expected number of offspring of type \( j \) produced by an individual of type \( i \):

\[
m_{ji} = \frac{\partial f_i}{\partial u_j}|_{u=1} < \infty.
\]

In addition, we assume that matrix \( \mathbb{M} \) is irreducible.

Given the assumptions on \( f_i \) and \( \mathbb{M} \) (\( f_i \) is not simple, \( \mathbb{M} \) is irreducible), it follows that the magnitude of the spectral radius of \( \mathbb{M} \), \( \rho(\mathbb{M}) = m \) determines whether the probability of ultimate extinction is one or less than one [2,18,30]. If \( \rho(\mathbb{M}) < 1 \) (subcritical process), then the probability of ultimate extinction of the process is one, that is,

\[
\lim_{t \to \infty} \text{Prob}[\tilde{I}(t) = 0] = 1.
\]

If \( \rho(\mathbb{M}) = m > 1 \) (supercritical process), then there exists a unique fixed point of the pgfs, \( 0 < q_j < 1 \), \( [f_i(q_1, \ldots, q_n) = q_i] \), such that if \( I_j(0) = i_j \), then

\[
\mathbb{P}_0 = \lim_{t \to \infty} \text{Prob}[\tilde{I}(t) = 0] = q_1^{i_1} \cdots q_n^{i_n} < 1.
\]

The preceding probability follows because of the assumption of independence. In the critical case, \( \rho(\mathbb{M}) = 1 \), the continuous-time BGWbp ultimately has probability of extinction one, but since the BGWbp is only an approximation of the CTMC process, we are only interested in the subcritical and supercritical cases.
4. Examples with multiple infectious groups

We consider some well-known deterministic epidemic models from the literature: SEIR, vector-host, stage-structured, and treatment [9,13]. We formulate the corresponding CTMC model and define the offspring pgf for the infectious groups. In the case of a vector–host model, the type reproduction number is defined and a new result on the probability of disease extinction is expressed in terms of the type reproduction number \( T_1 \). In addition, new results for the SEIR and treatment models on the probability of disease extinction are expressed in terms of \( R_0 \). Numerical examples are presented for each of the models.

4.1. SEIR model

4.1.1. Deterministic model

The classic SEIR epidemic model has the following form:

\[
\begin{align*}
\dot{S} &= \Lambda - dS - \beta \frac{S}{N} I, \\
\dot{E} &= \beta \frac{S}{N} I - \nu E - dE, \\
\dot{I} &= \nu E - (d + \gamma + \alpha)I, \\
\dot{R} &= \gamma I - dR.
\end{align*}
\]

This model is similar to the SIR model, except that it includes an exposed or latent group \( E \), with \( 1/\nu \) being the average latent period. The basic reproduction number, calculated via the next-generation matrix approach for the \( E \) and \( I \) groups [13,14], is the spectral radius of the next-generation matrix

\[
\mathbb{K} = \begin{bmatrix}
\frac{\beta \nu}{(\nu + d)(d + \gamma + \alpha)} & \frac{\beta}{d + \gamma + \alpha} \\
0 & 0
\end{bmatrix}.
\]

That is,

\[
R_0 = \frac{\beta \nu}{(\nu + d)(d + \gamma + \alpha)}.
\]

The type reproduction numbers cannot be defined since \( \mathbb{K} \) is reducible. It is not possible to control the disease through stages \( E \) or \( I \) alone; both \( E \) and \( I \) must be controlled to eliminate the disease. The dynamics of the SEIR model are well known [26]. If \( R_0 \leq 1 \), then the DFE with \( \bar{S} = \Lambda/d = \bar{N} \) is globally asymptotically stable and if \( R_0 > 1 \), there exists a unique endemic equilibrium that is globally asymptotically stable [26].

4.1.2. Stochastic model

The transition probabilities for the corresponding CTMC SEIR model are defined in Table 2. In the CTMC model, there are four discrete random variables and the transitions to and from group \( E \) are included. As in the calculation of the basic reproduction number [13], offspring pgfs for the multitype branching process can be defined for the variables \( E \) and \( I \). Assume that \( S(0) = \bar{S} \),
The probability of ultimate disease extinction is approximately $P = 0.1$. Given $E(0) = 1$ and $I(0) = 0$, is

$$f_1(u_1, u_2) = \frac{vu_2 + d}{v + d}$$

and the offspring pgf for $I$, given $E(0) = 0$ and $I(0) = 1$, is

$$f_2(u_1, u_2) = \frac{\beta u_1 u_2 + d + \gamma + \alpha}{\beta + d + \gamma + \alpha}.$$ 

The expectation matrix for this BGWbp is

$$\mathbb{M} = \begin{bmatrix} 0 & \frac{\beta}{\beta + d + \gamma + \alpha} \\ \frac{v}{v + d} & \frac{\beta}{\beta + d + \gamma + \alpha} \end{bmatrix}. $$

The pgfs $f_i$ are not simple and matrix $\mathbb{M}$ is irreducible. According to the Jury conditions [1], $\rho(\mathbb{M}) < 1$ iff

$$\text{trace}(\mathbb{M}) < 1 + \det(\mathbb{M}) < 2, \quad (8)$$

where $\text{trace}(\mathbb{M}) = \beta / (\beta + d + \gamma + \alpha)$ and $\det(\mathbb{M}) = -\beta v / [(v + d)(\beta + d + \gamma + \alpha)].$ The second inequality in the Jury conditions (8) is easily satisfied, $\det(\mathbb{M}) < 1.$ The first inequality holds iff $\mathcal{R}_0 < 1$, that is,

$$\rho(\mathbb{M}) < 1 \quad \text{iff} \quad \rho(\mathbb{K}) < 1. \quad (9)$$

The fixed point of the offspring pgfs in the case $\mathcal{R}_0 > 1$ is found by setting $f_i(q_1, q_2) = q_i, \ i = 1, 2,$ and solving for $q_i.$ This leads to unique solution in the set $(0, 1)^2:\n
\begin{align*}
q_1 &= \frac{v}{v + d \mathcal{R}_0} + \frac{d}{v + d}, \\
q_2 &= \frac{1}{\mathcal{R}_0}.
\end{align*}

The probability of ultimate disease extinction is approximately $P = q_1 q_2$, given $E(0) = i_1$ and $I(0) = i_2$. The same result as Whittle [32] is obtained for probability of a major outbreak in the case $I(0) = i$ and $E(0) = 0$, Equation (1). The probability $q_1$ can be interpreted epidemiologically. Given one exposed individual, either that individual dies with probability $d / (v + d)$ or survives with probability $v / (v + d)$ to become infectious. Then the infectious individual successfully transmits an infection with probability $q_2 = 1 / \mathcal{R}_0$. Note that $q_2 < q_1.$ This is biologically

| Description               | State transition $\mathbf{a} \rightarrow \mathbf{b}$ | Rate $P(\mathbf{a}, \mathbf{b})$ |
|---------------------------|----------------------------------------------------|----------------------------------|
| Birth of $S$              | $(S, E, I, R) \rightarrow (S + 1, E, I, R)$       | $\Lambda$                       |
| Death of $S$              | $(S, E, I, R) \rightarrow (S - 1, E, I, R)$       | $dS$                            |
| Death of $R$              | $(S, E, I, R) \rightarrow (S, E, I, R - 1)$       | $dR$                            |
| Infection                 | $(S, E, I, R) \rightarrow (S - 1, E + 1, I, R)$   | $\beta SI/N$                    |
| Latent to infectious      | $(S, E, I, R) \rightarrow (S, E - 1, I, R)$       | $\gamma E$                      |
| Recovery                  | $(S, E, I, R) \rightarrow (S, E - 1, R + 1)$      | $dE$                            |
| Death of $E$              | $(S, E, I, R) \rightarrow (S, E - 1, I, R)$       | $(\alpha + d)I$                 |
| Death of $I$              | $(S, E, I, R) \rightarrow (S, E - 1, R)$          | $\gamma E$                      |

Table 2. State transitions and rates for the CTMC SEIR epidemic model.
reasonable, since the disease is more likely to persist if individuals are already infectious rather than merely exposed to the disease.

4.1.3. Numerical example

A numerical example illustrates the close agreement between the predicted probability of extinction \( P_0 \) and an estimate obtained from simulation of sample paths. Let \( \Lambda = 1, d = 0.005, \beta = 0.2, \nu = 0.1, \gamma = 0.05, \) and \( \alpha = 2d. \) Then \( \bar{S} = 200, R_0 = 3.66, \) and \( \rho(\mathcal{M}) = 1.35. \) The stable endemic equilibrium for the ODE model is \((\hat{S}, \hat{E}, \hat{I}, \hat{R}) = (48.5, 7.21, 11.1, 111).\) Prior to stabilization at the endemic equilibrium, there is a disease outbreak that exceeds the endemic values (Figure 1). Applying the formula for the fixed point of the offspring pgfs yields \((q_1, q_2) = (0.3076, 0.2730).\)

In Table 3, the probability of disease extinction \( P_0 \) is computed, then compared to the estimate obtained from the proportion of sample paths (out of 10,000) in which the sum \( E(t) + I(t) \) hits zero (disease extinction) prior to reaching an outbreak size of 20. If exposed and infectious individuals exceed 20, it is considered an outbreak.

![Graph](image)

Figure 1. One sample path of the CTMC SEIR model and the ODE solution. Parameter values are \( \Lambda = 1, d = 0.005, \beta = 0.25, \nu = 0.1, \gamma = 0.05, \) and \( \alpha = 2d \) with initial conditions \( S(0) = 200, E(0) = 0, I(0) = 2, \) and \( R(0) = 0. \) The stable equilibrium of the ODE model is \((\hat{S}, \hat{E}, \hat{I}, \hat{R}) = (48.5, 7.21, 11.1, 111). \) An outbreak occurs with probability \( 1 - P_0 = 0.926. \)

| \( e_0 \) | \( i_0 \) | \( P_0 \) | Approx. |
|---|---|---|---|
| 1 | 0 | 0.3076 | 0.3085 |
| 0 | 1 | 0.2730 | 0.2863 |
| 1 | 1 | 0.0840 | 0.0890 |
| 2 | 0 | 0.0946 | 0.0932 |
| 0 | 2 | 0.0745 | 0.0741 |
4.2. Vector–host model

4.2.1. Deterministic model

Consider the following vector–host model with $S$ and $I$ susceptible and infectious hosts, $S + I = H$, and $M$ and $V$ susceptible and infectious vectors. More complex vector–host models have been applied to malaria and dengue, where the mosquitoes are the vector (e.g. [10,15]). A simple vector–host model takes the following form:

\[
\begin{align*}
\dot{S} &= \Lambda - dS + \gamma I - \beta_h \frac{S}{H} V,
\dot{I} &= \beta_h \frac{S}{H} V - (d + \gamma)I,
\dot{M} &= \Gamma - \mu M - \beta_m M \frac{I}{H},
\dot{V} &= \beta_m M \frac{I}{H} - \mu V.
\end{align*}
\]  

(10)

The transmission rate from vector to host is $\beta_h SV/H$ and from host to vector is $\beta_m MI/H$. The coefficient $\beta_h = ab$ and $\beta_m = ac$, where $a$ is the number of bites per vector per time, $b$ is the per-bite vector to host transmission probability, and $c$ = per-bite host to vector transmission probability. Transmission in model (10) is limited by the number of hosts so that the transmission rates depend on the proportion of susceptible and infectious hosts ($S/H$ or $I/H$). The DFE for host and vector is $\bar{S} = \Lambda/d = \bar{H}$ and $\bar{M} = \Gamma/\mu$. The basic reproduction number is calculated from the next-generation matrix,

\[
K = \begin{bmatrix} 0 & \frac{\beta_h}{\mu} \\ \frac{\beta_m}{d + \gamma} & \frac{\bar{M}}{H} \end{bmatrix}
\]

so that

\[
R_0 = \sqrt{\frac{\beta_h \beta_m}{\mu (d + \gamma) \bar{H}}} = \sqrt{\frac{\beta_h \hat{\beta}_m}{\mu (d + \gamma)}},
\]

where $\hat{\beta}_m = \beta_m \bar{M}/\bar{H}$. The type reproduction numbers are the square of the basic reproduction number [31],

\[
T_i = R_0^2, \quad i = 1, 2.
\]

(11)

The same amount of control is needed for either the vector or host population. The relationships shown in (4) between $T_i$ and $R_0$ clearly apply to this example.

4.2.2. Stochastic model

Now, consider a CTMC model for this vector–host system (10). The transition rates are defined in Table 4. Assume $S(0) = \bar{S}$ and $M(0) = \bar{M}$ are sufficiently large. If $I(0) = 1$ and $V(0) = 0$, the offspring pgf for $I$ is

\[
f_1(u_1, u_2) = \frac{\hat{\beta}_m u_1 u_2 + d + \gamma}{\hat{\beta}_m + d + \gamma}.
\]
Similarly, the offspring pgf for $V$ given $I(0) = 0$ and $V(0) = 1$ is

$$f_2(u_1, u_2) = \frac{\beta_h u_1 u_2 + \mu}{\hat{\beta}_h + \mu}.$$

The expectation matrix for this branching process is

$$\mathbb{M} = \begin{bmatrix} \hat{\beta}_m & \beta_h \\ \hat{\beta}_m + d + \gamma & \hat{\beta}_m + d + \gamma \beta_h + \mu \\ \hat{\beta}_m + d + \gamma & \hat{\beta}_m + d + \gamma \beta_h + \mu \end{bmatrix}.$$ 

Matrix $\mathbb{M}$ is irreducible. The spectral radius of $\mathbb{M}$ equals

$$\rho(\mathbb{M}) = \frac{\hat{\beta}_m}{\beta_m + d + \gamma} + \frac{\beta_h}{\hat{\beta}_m + d + \gamma}.$$ 

It is straightforward to verify $\rho(\mathbb{M}) < 1$ iff $\mathcal{R}_0 = \rho(\mathbb{K}) < 1$.

For the supercritical case $\rho(\mathbb{M}) > 1$, the fixed point of the offspring pgfs on $(0, 1)^2$ can be found by setting $f_i(q_1, q_2) = q_i$ for $i = 1, 2$. The fixed point can be expressed in terms of the type reproduction number $T_1$, defined in (11), as follows:

$$q_1 = \frac{(\beta_h + \mu)(d + \gamma)}{\beta_h(\hat{\beta}_m + d + \gamma)} = \frac{\hat{\beta}_m}{\hat{\beta}_m + d + \gamma} \frac{1}{\hat{\beta}_m + d + \gamma T_1} + \frac{d + \gamma}{\hat{\beta}_m + d + \gamma},$$

$$q_2 = \frac{\mu(\hat{\beta}_m + d + \gamma)}{\hat{\beta}_m(\beta_h + \mu)} = \frac{\beta_h}{\beta_h + \mu} \frac{1}{T_1} + \frac{\mu}{\hat{\beta}_m + d + \gamma}.$$ 

The value of $q_1$ is the sum of two terms that can be interpreted as follows: an infectious host will either (1) transmit the disease to a susceptible vector with probability $\hat{\beta}_m/(\hat{\beta}_m + d + \gamma)$ or (2) die or recover before transmission with probability $(d + \gamma)/(\hat{\beta}_m + d + \gamma)$. If the disease transmission is successful, then the probability of transmission from host to host is $1/T_1$. Similarly, the value of $q_2$ has an epidemiological interpretation: an infectious vector either (1) transmits the disease to a susceptible host with probability $\beta_h/(\beta_h + \mu)$ or (2) dies with probability $\mu/(\beta_h + \mu)$. If there is a transmission from vector to host, then the probability that the disease is transmitted from an infectious vector to susceptible vector is $1/T_1$. 

---

Table 4. State transitions and rates for the CTMC vector–host model.

| Description               | State transition $a \rightarrow b$ | Rate $P(a, b)$ |
|---------------------------|------------------------------------|---------------|
| Host birth                | $(S, I, M, V) \rightarrow (S + 1, I, M, V)$ | $\Lambda$     |
| Death of $S$              | $(S, I, M, V) \rightarrow (S - 1, I, M, V)$ | $dS$          |
| Host infection            | $(S, I, M, V) \rightarrow (S - 1, I + 1, M, V)$ | $\beta_S V / H$ |
| Host recovery             | $(S, I, M, V) \rightarrow (S + 1, I - 1, M, V)$ | $\gamma I$   |
| Death of $I$              | $(S, I, M, V) \rightarrow (S, I - 1, M, V)$ | $dI$          |
| Vector birth              | $(S, I, M, V) \rightarrow (S, I, M + 1, V)$ | $\Gamma$     |
| Death of $M$              | $(S, I, M, V) \rightarrow (S, I, M - 1, V)$ | $\mu M$      |
| Vector infection          | $(S, I, M, V) \rightarrow (S, I, M - 1, V + 1)$ | $\beta_m I / H$ |
| Death of $V$              | $(S, I, M, V) \rightarrow (S, I, M, V - 1)$ | $\mu V$      |
Table 5. Probability of disease extinction $P_0$ and numerical approximation (Approx.) based on 10,000 sample paths of the CTMC vector–host model with parameter values $\lambda = 0.5$, $d = 0.005$, $\gamma = 0.1$, $\Gamma = 500$, $\mu = 0.5$, and $\beta_m = 0.2 = \beta_h$, and initial conditions $I(0) = i_0$, $V(0) = v_0$, $S(0) = 100$, and $M(0) = 1000$.

| $i_0$ | $v_0$ | $P_0$ | Approx. |
|-------|-------|-------|---------|
| 1     | 0     | 0.1746| 0.1762  |
| 0     | 1     | 0.7518| 0.7573  |
| 1     | 1     | 0.1312| 0.1342  |
| 2     | 0     | 0.0305| 0.0332  |
| 0     | 2     | 0.5652| 0.5619  |

Alternately, applying the first expressions for $q_1$ and $q_2$, the probability of disease extinction given $I(0) = i_0$ and $V(0) = v_0$ can be written as

$$P_0 = q_1^{i_0} q_2^{v_0} = \left[ \frac{d + \gamma}{\beta_h} \right]^{i_0} \left[ \frac{\mu}{\beta_m} \right]^{v_0} \left[ \frac{\beta_h + \mu}{\beta_m + d + \gamma} \right]^{i_0 - v_0}. \quad (12)$$

Except for notation, the expression in (12) was obtained by Bartlett in 1964 [7].

4.2.3. Numerical example

The probability of extinction $P_0$ is illustrated in a numerical example with the following parameter values: $\lambda = 0.5$, $d = 0.005$, $\gamma = 0.1$, $\Gamma = 500$, $\mu = 0.5$, and $\beta_m = 0.2 = \beta_h$. The DFE values for hosts and vectors are $\bar{S} = 100$ and $\bar{M} = 1000$ with type reproduction number $T_i = 7.62$. The fixed point in $(0, 1)^2$ of the generating functions is $(q_1, q_2) = (0.1746, 0.7518)$. Table 5 gives the probability of extinction $P_0$ for different initial values and the corresponding proportion of sample paths (out of 10,000) of the CTMC model in which the total number of infectives ($I(t) + V(t)$) hits zero before reaching a value of 50, a minimal outbreak size. The numerical approximation shows good agreement with $P_0$. A sample path of the CTMC model in which an outbreak occurs is illustrated in Figure 2.

4.3. Stage-structured model

4.3.1. Deterministic model

Consider the following stage-structured model with $m$ stages of infection:

$$\dot{S} = \Lambda - dS - \sum_{k=1}^{m} \beta_k \frac{S}{N} I_k,$$

$$\dot{I}_1 = \sum_{k=1}^{m} \beta_k \frac{S}{N} I_k - (\nu_1 + d_1) I_1,$$

$$\dot{I}_i = \nu_{i-1} I_{i-1} - (\nu_i + d_i) I_i, \quad i = 2, 3, \ldots, m,$$

$$\dot{R} = \nu_m I_m - dR,$$

where $N = S + \sum_{i=1}^{m} I_i + R$. Susceptible individuals progress through $m$ stages of infection before recovery, $\nu_m = \gamma$, and during each stage an individual is infectious. Natural mortality
plus disease-related mortality may occur in each of the infectious stages, \( d_i = d + \alpha_i \). The DFE value is \( \bar{S} = \Lambda/d \). The same model (except for notation) was considered by van den Driessche and Watmough [13].

The basic reproduction number was calculated by van den Driessche and Watmough [13], where

\[
F = \begin{bmatrix}
\beta_1 & \beta_2 & \cdots & \beta_m \\
0 & 0 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
0 & 0 & \cdots & 0
\end{bmatrix}
\]

and

\[
V^{-1} = \begin{bmatrix}
\frac{1}{v_1 + d_1} & 0 & \cdots & 0 \\
\frac{v_1}{(v_1 + d_1)(v_2 + d_2)} & \frac{1}{v_2 + d_2} & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
\frac{v_1 v_2 \cdots v_{m-1}}{(v_1 + d_1)(v_2 + d_2) \cdots (v_m + d_m)} & \frac{v_2 \cdots v_{m-1}}{(v_1 + d_1)(v_2 + d_2) \cdots (v_m + d_m)} & \cdots & \frac{1}{v_m + d_m}
\end{bmatrix}.
\]

Thus, \( R_0 = \rho(FV^{-1}) = \rho(\mathbb{K}) \) is

\[
R_0 = \frac{\beta_1}{v_1 + d_1} + \frac{\beta_2 v_1}{(v_1 + d_1)(v_2 + d_2)} + \cdots + \frac{\beta_m v_1 \cdots v_{m-1}}{(v_1 + d_1)(v_2 + d_2) \cdots (v_m + d_m)}.
\]

4.3.2. Stochastic model

The corresponding CTMC stage-structured model can be defined in terms of the transition probabilities (Table 6). Suppose that \( S(0) = \bar{S} \) is sufficiently large and \( R(0) = 0 \). Let \( I_i(0) = 1 \) and
Table 6. State transitions and rates for the CTMC stage-structured model.

| Description            | State transition a → b | Rate $P(a, b)$                        |
|------------------------|------------------------|---------------------------------------|
| Birth of $S$           | $(S, \ldots, R) \rightarrow (S + 1, \ldots, R)$ | $\Lambda$                             |
| Death of $S$           | $(S, \ldots, R) \rightarrow (S - 1, \ldots, R)$ | $dS$                                 |
| Infection $I_j$        | $(S, I_1, \ldots) \rightarrow (S - 1, I_1 + 1, \ldots)$ | $\sum_{k=1}^{m} \beta_kSI_k/N$       |
| Stage $j \rightarrow j + 1$ | $(\ldots, I_j, \ldots) \rightarrow (\ldots, I_j - 1, I_{j+1} + 1, \ldots)$ | $v_j I_j$                             |
| Recovery $I_m$         | $(\ldots, I_m, R) \rightarrow (\ldots, I_m - 1, R + 1)$ | $v_m I_m$                             |
| Death of $R$           | $(S, \ldots, R) \rightarrow (S, \ldots, R - 1)$ | $dR$                                 |

$I_j(0) = 0$ for $j \neq i$. Then the offspring pgf for $I_i$, is

$$f_i(u_1, \ldots, u_m) = \frac{\beta_i u_1 u_i + v_i u_{i+1} + d_i}{\beta_i + v_i + d_i}, \quad i = 1, \ldots, m - 1.$$ 

For stage $m$, $I_m(0) = 1$ and $I_j(0) = 0, j = 1, \ldots, m - 1$, the offspring pgf for $I_m$ is

$$f_m(u_1, \ldots, u_m) = \frac{\beta_m u_1 u_m + v_m + d_m}{\beta_m + v_m + d_m}.$$ 

The expectation matrix for this branching process is an $m \times m$ matrix,

$$\mathbf{M} = \begin{bmatrix}
2\beta_1 & \beta_2 & \cdots & \beta_m \\
\beta_1 + v_1 + d_1 & \beta_2 + v_2 + d_2 & \cdots & \beta_m + v_m + d_m \\
\beta_1 + v_1 + d_1 & \beta_2 + v_2 + d_2 & \cdots & 0 \\
0 & 0 & \cdots & 0 \\
0 & 0 & \cdots & \beta_m + v_m + d_m \\
\end{bmatrix}.$$ 

For two infectious groups, $m = 2$, the expectation matrix simplifies to

$$\mathbf{M} = \begin{bmatrix}
2\beta_1 & \beta_2 \\
\beta_1 + v_1 + d_1 & \beta_2 + v_2 + d_2 \\
\beta_1 + v_1 + d_1 & \beta_2 + v_2 + d_2 \\
\end{bmatrix}.$$ 

The $2 \times 2$ matrix $\mathbf{M}$ satisfies $\rho(\mathbf{M}) < 1$ iff the Jury conditions (8) hold. Through some algebraic manipulations it is straightforward to derive conditions for the second inequality in the Jury conditions [25]:

$$\det(\mathbf{M}) < 1 \iff \frac{\beta_1}{v_1 + d_1} < 1.$$ 

In addition, conditions for the first inequality in the Jury conditions [25] are

$$\text{trace}(\mathbf{M}) < 1 + \text{det}(\mathbf{M}) \iff R_0 < 1.$$ 

Hence, the relationship between the spectral radii of the two matrices $\mathbf{M}$ and $\mathbf{K}$ holds, Equation (9).
Unfortunately, even for the case $m = 2$, an analytical expression cannot be obtained for the fixed point $(q_1, q_2)$ of the offspring pgfs in the supercritical case, $\rho(\mathcal{M}) > 1$. The fixed point and probability of extinction are illustrated in the following numerical example.

4.3.3. Numerical example

Let $\Lambda = 1$, $d = 0.005$, $\beta_1 = 0.4$, $\beta_2 = 0.1$, $\nu_1 = 0.2$, $\nu_2 = 0.05$, $d_1 = 0.02$, and $d_2 = 0.01$. Then $R_0 = 3.33$ and $\rho(\mathcal{M}) = 1.52$. Initial conditions are $S(0) = \bar{S} = 200$, $R(0) = 0$. The fixed point of the pgfs is $(q_1, q_2) = (0.1943, 0.4268)$. Table 7 is a summary of the probability of disease extinction $P_0$ and the numerical approximation based on the proportion of sample paths of the CTMC model in which the infectious population $(I_1(t) + I_2(t))$ hits zero prior to reaching a size of 20, the minimal outbreak size. One sample path of the CTMC stage-structured model is graphed with the solution of the ODE model in Figure 3 when $I_1(0) = 1 = I_2(0)$.

Table 7. Probability of disease extinction $P_0$ and numerical approximation (Approx.) based on 10,000 sample paths of the CTMC stage-structured model with parameter values $\Lambda = 1$, $d = 0.005$, $\beta_1 = 0.4$, $\beta_2 = 0.1$, $\nu_1 = 0.2$, $\nu_2 = 0.05$, $d_1 = 0.02$, and $d_2 = 0.01$, and initial conditions $S(0) = \bar{S} = 200$, $R(0) = 0$, $I_1(0) = i_1$, and $I_2(0) = i_2$.

| $i_1$ | $i_2$ | $P_0$ | Approx. |
|-------|-------|-------|---------|
| 1     | 0     | 0.1943| 0.1932  |
| 0     | 1     | 0.4268| 0.4295  |
| 1     | 1     | 0.0829| 0.0839  |
| 2     | 0     | 0.0378| 0.0387  |
| 0     | 2     | 0.1822| 0.1836  |

Figure 3. One sample path of the stochastic model and the ODE solution of the stage-structured model. Parameter values are $\Lambda = 1$, $d = 0.005$, $\beta_1 = 0.4$, $\beta_2 = 0.1$, $\nu_1 = 0.2$, $\nu_2 = 0.05$, $d_1 = 0.02$, and $d_2 = 0.01$ with initial conditions $S(0) = \bar{S} = 200$, $R(0) = 0$, $I_1(0) = i_1$, and $I_2(0) = i_2$. The basic reproduction number is $R_0 = 3.33$. The ODE model has a stable equilibrium at $(\hat{S}, \hat{I}_1, \hat{I}_2, \hat{R}) = (53.7, 3.33, 11.1, 111)$. A major outbreak occurs with probability $1 - P_0 = 0.917$. 
4.4. Treatment model

4.4.1. Deterministic model

A model for tuberculosis (TB) with treatment was formulated by Castillo-Chavez and Feng [9]. TB is a bacterial infection caused by *Mycobacterium tuberculosis*. Antibiotics are used to treat infected patients. But when treatment methods are inadequate or incomplete, then drug-resistant strains develop [9]. The model of Castillo-Chavez and Feng [9] considers two strains of TB, drug-sensitive and drug-resistant strains. Susceptible individuals are exposed to either the sensitive or resistant strains and enter the exposed or latent group, $E_1$ or $I_2$. Disease-related mortality occurs for infectious individuals of both types, $d_i = d + \alpha_i$. Treatment does not work for the drug-resistant strain. Therefore, latent and infectious individuals with the drug-sensitive strain are treated at rates $r_1$ and $r_2$, respectively. Treatment for latent individuals may be inadequate $pr_2$ or result in the development of resistance (incomplete treatment), $qr_2$. Thus, in only a proportion $(1 - p - q)$ of those treated will the treatment be effective. Treated individuals $T$ may become infected with either strain, but are less likely to become infected with the drug-sensitive strain than susceptible individuals, $\beta_T \leq \beta_1$.

The model of Castillo-Chavez and Feng [9] (except for notation) takes the following form:

\[
\begin{align*}
\dot{S} &= \Lambda - dS - \beta_1 \frac{S}{N} I_1 - \beta_2 \frac{S}{N} I_2, \\
\dot{E}_1 &= \beta_1 \frac{S}{N} I_1 + \beta_T \frac{T}{N} I_1 - \beta_2 \frac{E_1}{N} I_2 - (d + v_1 + r_1)E_1 + pr_1 I_1, \\
\dot{I}_1 &= v_1 E_1 - (d_1 + r_2)I_1, \\
\dot{T} &= -\beta_T \frac{T}{N} I_1 - \beta_2 \frac{T}{N} I_2 + r_1 E_1 + (1 - p - q)r_2 I_1 - dT, \\
\dot{E}_2 &= \beta_2 \frac{(S + E_1 + T)}{N} I_2 + qr_2 I_1 - (d + v_2)E_2, \\
\dot{I}_2 &= v_2 E_2 - d_2 I_2. \\
\end{align*}
\]  

(13)

The total population size is $N = S + E_1 + I_1 + T + E_2 + I_2$. The DFE value for susceptibles is $\dot{S} = \Lambda/d$. When treatment fails and treated individuals are not considered as new infections [13], then the Jacobian matrices $F$ and $V$ for the latent and infectious groups $(E_1, E_2, I_1, I_2)$, evaluated at the DFE, are

\[
F = \begin{bmatrix} 0 & 0 & \beta_1 & 0 \\ 0 & 0 & 0 & \beta_2 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \quad \text{and} \quad 
V = \begin{bmatrix} d + v_1 + r_1 & 0 & -pr_2 & 0 \\ 0 & d + v_2 & -qr_2 & 0 \\ -v_1 & 0 & d_1 + r_2 & 0 \\ 0 & -v_2 & 0 & d_2 \end{bmatrix}.
\]

The next-generation matrix $K = FV^{-1}$ is

\[
K = \begin{bmatrix} 
\frac{\beta_1 v_1}{(d + v_1 + r_1)(d_1 + r_2) - v_1 pr_2} & 0 & * & 0 \\
\frac{\beta_2 v_1 v_2 qr_2}{d_2(d + v_2)(d + v_1 + r_1)(d_1 + r_2) - v_1 pr_2} & \frac{\beta_3 v_2}{d_2(d + v_2)} & * & * \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 
\end{bmatrix}.
\]
The transition rates for a CTMC treatment model are given in Table 8. To define the offspring pgfs

\[ R = \max \left\{ \frac{\beta_1 v_1}{(d + v_1 + r_1)(d_1 + r_2) - v_1 pr_2}, \frac{\beta_2 v_2}{d_2(d + v_2)} \right\} = \{ R_1, R_2 \}. \]

The threshold \( R_1 \) is the one derived by van den Driessche and Watmough [13]. If there is no drug-sensitive strain and no treatment, i.e. \( E_1(0) = 0 = I_1(0) \), \( T(0) = 0 \), then the drug-sensitive strain will not develop and the system (13) reduces to three ODEs in \( S, E_2, \) and \( I_2 \). In this case, if \( R_2 > 1 \), there is a unique endemic equilibrium for the reduced system. See [9] for a more thorough analysis of this model.

4.4.2. Stochastic model

The transition rates for a CTMC treatment model are given in Table 8. To define the offspring pgfs for the branching process, assume \( S(0) = \bar{S}, T(0) = 0, \) and \( \bar{S} \) is sufficiently large. In addition, let the initial values for \((E_1(0), I_1(0), E_2(0), I_2(0)) = (\delta_{i1}, \delta_{i2}, \delta_{i3}, \delta_{i4}) \), where \( \delta_{ij} \) is the Kronecker delta symbol, \( \delta_{ij} = 0 \), for \( i \neq j \) and \( \delta_{ii} = 1 \). Next, the four offspring pgfs are defined. For \( i = 1 \), the offspring pgf for \( E_1 \) is

\[ f_1(u_1, u_2, u_3, u_4) = \frac{v_1 u_2 + d + r_1}{v_1 + d + r_1}. \]

For \( i = 2 \), the offspring pgf for \( I_1 \) is

\[ f_2(u_1, u_2, u_3, u_4) = \frac{\beta_1 u_1 u_2 + pr_2 u_1 + qr_2 u_3 + d_1 + (1 - p - q)r_2}{\beta_1 + d_1 + r_2}. \]

For \( i = 3 \), the offspring pgf for \( E_2 \) is

\[ f_3(u_1, u_2, u_3, u_4) = \frac{v_2 u_4 + d}{v_2 + d}. \]

For \( i = 4 \), the offspring pgf for \( I_2 \) is

\[ f_4(u_1, u_2, u_3, u_4) = \frac{\beta_2 u_3 u_4 + d_2}{\beta_2 + d_2}. \]

### Table 8. State transitions and rates for the CTMC treatment model.

| Description                        | State transition \( a \rightarrow b \) | Rate \( P(a, b) \) |
|------------------------------------|--------------------------------------|------------------|
| Birth of \( S \)                    | \((S,...,S) \rightarrow (S+1,\ldots)\) | \( A \)          |
| Death of \( S \)                   | \((S,...,S) \rightarrow (S-1,\ldots)\) | \( dS \)         |
| Drug-sensitive infection of \( S \)| \((S,E_1,\ldots) \rightarrow (S-1,E_1+1,\ldots)\) | \( \beta_1 SH_1/N \) |
| Drug-resistant infection of \( S \)| \((S,...,E_2,\ldots) \rightarrow (S-1,...,E_2+1,\ldots)\) | \( \beta_2 SE_2/N \) |
| Resistant infection \( E_1 \)      | \((S,E_1,\ldots,E_2,\ldots) \rightarrow (S,E_1-1,1,\ldots,E_2+1,\ldots)\) | \( \beta_2 E_1E_2/N \) |
| Latent to infectious               | \((S,E_1,I_1,\ldots) \rightarrow (S,E_1-1,I_1+1,\ldots)\) | \( v_1 E_1 \)    |
| Treatment of \( E_1 \)             | \((S,E_1,\ldots,T,\ldots) \rightarrow (S,E_1-1,T+1,\ldots)\) | \( r_1 E_1 \)    |
| Death of \( E_1 \)                 | \((S,E_1,\ldots) \rightarrow (S,E_1-1,\ldots)\) | \( dE_1 \)       |
| Death of \( I_1 \)                 | \((S,...,I_1,\ldots) \rightarrow (S,...,I_1-1,\ldots)\) | \( d_1 I_1 \)    |
| Effective treatment of \( I_1 \)   | \((\ldots,I_1,T,\ldots) \rightarrow (\ldots,I_1-1,T+1,\ldots)\) | \( (1-p-q)r_2 I_1 \) |
| Inadequate treatment of \( I_1 \)  | \((S,E_1,I_1,\ldots) \rightarrow (S,E_1+1,I_1-1,\ldots)\) | \( pr_2 I_1 \)   |
| Treatment resistance \( I_1 \)     | \((\ldots,I_1,T,E_2,\ldots) \rightarrow (\ldots,I_1-1,T,E_2+1,\ldots)\) | \( q r_2 I_1 \)   |
| Drug-sensitive infection of \( T \)| \((S,E_1,\ldots,T,\ldots) \rightarrow (S,E_1+1,T-1,\ldots)\) | \( \beta_2 TH_1/N \) |
| Resistant infection of \( T \)     | \((\ldots,T,E_2,\ldots) \rightarrow (\ldots,T-1,E_2+1,\ldots)\) | \( \beta_2 T I_2/N \) |
| Death of \( T \)                   | \((\ldots,T,\ldots) \rightarrow (\ldots,T-1,\ldots)\) | \( d T \)        |
| Death of \( E_2 \)                 | \((\ldots,E_2,\ldots) \rightarrow (\ldots,E_2-1,\ldots)\) | \( d E_2 \)      |
| Latent to infectious               | \((\ldots,E_2,I_2) \rightarrow (\ldots,E_2-1,I_2+1)\) | \( v_2 E_2 \)    |
| Death of \( I_2 \)                 | \((S,...,I_2) \rightarrow (S,...,I_2-1)\) | \( d_2 I_2 \)    |
Each offspring pgf $f_i$ is not simple. The expectation matrix is

$$M = \begin{bmatrix}
0 & \frac{\beta_1 + pr_2}{\beta_1 + d_1 + r_2} & 0 & 0 \\
\frac{v_1}{v_1 + d + r_1} & \frac{\beta_1}{\beta_1 + d_1 + r_2} & 0 & 0 \\
0 & \frac{q r_2}{\beta_1 + d_1 + r_2} & 0 & \frac{\beta_2}{\beta_2 + d_2} \\
0 & \frac{v_2}{\beta_1 + d_1 + r_2} & \frac{d + v_2}{d + v_2} & \frac{\beta_2}{\beta_2 + d_2}
\end{bmatrix} = \begin{bmatrix} M_1 & 0 \\ \ast & M_2 \end{bmatrix},$$

where $M_1$ and $M_2$ are the $2 \times 2$ matrices in the upper left and lower right corners of $M$ and $0$ is the $2 \times 2$ zero matrix. Matrix $M$ is reducible, so that there is not necessarily a unique fixed point in $q \in (0, 1)^4$ when $\rho(M) > 1$. In fact, there are four fixed points in $(0, 1)^4$ when $\rho(M) > 1$ and these fixed points depend on the magnitude of $\rho(M_i)$, $i = 1, 2$ (shown below). However, the spectral radius of $M$ is consistent with the spectral radius of $K$. That is, we show that the relation (9) holds.

The Jury conditions (8) are applied to each of the matrices $M_1$ and $M_2$. It is clear that $\text{trace}(M_i) > 0$ and $\text{det}(M_i) < 1$ for $i = 1, 2$. Next, through some algebraic simplification of the expressions $\text{trace}(M_i) < 1 + \text{det}(M_i)$ [25], the second condition of the Jury conditions holds if $R_i < 1$, $i = 1, 2$. Hence, $\rho(M_i) < 1$ if $R_i < 1$, $i = 1, 2$ which yields the relation (9).

Next, we show that there are four fixed points of the pgfs in the set $(0, 1)^4$ if $R_0 > 1$ ($\rho(M) > 1$). Of course, one of the fixed points is $q = 1$ which always exists. The remaining three fixed points are defined below. If $R_1 > 1$ ($\rho(M_1) > 1$), then the first fixed point is

$$q'_1 = \frac{v_1}{v_1 + d + r_1} \frac{1}{R_1} + \frac{d + r_1}{v_1 + d + r_1},$$

$$q'_2 = \frac{1}{R_1},$$

$$q'_3 = 1 = q'_4. \tag{14}$$

If $R_2 > 1$ ($\rho(M_2) > 1$), there are two more fixed points in $(0, 1)^4$. The second fixed point is

$$q_1 = 1 = q_2,$$

$$q_3 = \frac{v_2}{d + v_2} \frac{1}{R_2} + \frac{d}{d + v_2},$$

$$q_4 = \frac{1}{R_2}. \tag{15}$$

The third fixed point lies in $(0, 1)^4$,

$$q^*_1 = \frac{v_1 q_2^*}{v_1 + d + r_1} + \frac{d + r_1}{v_1 + d + r_1},$$

$$q^*_3 = \frac{v_2}{d + v_2} \frac{1}{R_2} + \frac{d}{d + v_2},$$

$$q^*_4 = \frac{1}{R_2}. \tag{16}$$
The value of $q_2^*$ is the unique solution in $(0, 1)$ of the quadratic equation $Ax^2 + Bx + C = 0$, where

\[
A = \frac{\beta_1 v_1}{(\beta_1 + d_1 + r_2)(v_1 + d + r_1)},
\]

\[
B = \frac{\beta_1 v_1 + (d_1 + r_2)(v_1 + d + r_1) - pr_2 v_1}{(\beta_1 + d_1 + r_2)(v_1 + d + r_1)},
\]

\[
C(q_3^*) = \frac{pr_2(d + r_1) + [qr_2 q_3^* + d_1 + (1 - p - q)r_2][v_1 + d + r_1]}{(\beta_1 + d_1 + r_2)(v_1 + d + r_1)}.
\]

The values of $q_3^*$ and $q_4^*$ for the third fixed point, given in (16), are the same values as in the second fixed point, defined in (15). If there is no drug-sensitive strain and no treatment, $E_I(0) = 0 = I_1(0)$ and $T(0) = 0$, then, in the CTMC model, the pgfs $f_3$ and $f_4$ apply to the reduced system $(E_2, I_2)$ with $S(0) = \hat{S}$. In this latter case, there is a unique fixed point $(q_2^*, q_4^*) \in (0, 1)^2$ when $\rho(M_2) > 1$ which determines probability of disease extinction.

We verify that the third fixed point $(q_3^*, q_4^*, q_4^*) \in (0, 1)^4$ iff $\mathcal{R}_2 > 1$. As can be seen from the preceding formulas, $A > 0$, $B < 0$, and $C(q_3^*) > 0$ for $q_3^* \in [0, 1]$. Also, $A + B + C(1) = 0$ implies $x = 1$ is a solution of the quadratic equation. The solution $q_3^* \in (0, 1)$ iff $\mathcal{R}_2 > 1$.

Thus, $q_3^* \in (0, 1)$ implies $C(q_3^*) < C(1)$ so that the quadratic equation has two positive roots, $x_1$ and $x_2$, where $q_2^* = x_1 < 1 < x_2$. It follows that $(q_1^*, q_2^*, q_3^*, q_4^*) \in (0, 1)^4$ iff $\mathcal{R}_2 > 1$.

4.4.3. Numerical examples

Three numerical examples illustrate which of the fixed points determine probability of disease extinction. In all of the examples, it is assumed that $S(0) = \hat{S}$ and $T(0) = 0$. In the first example, $\mathcal{R}_2 < 1 < \mathcal{R}_1$, the fixed point (14) determines the probability of extinction. In the second example with $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 > 1$, the fixed points (14) and (16) determine the probability of extinction.

In the third example, with $\mathcal{R}_1 < 1 < \mathcal{R}_2$, $E_1(0) = 0 = I_1(0)$, and either $E_2(0) > 0$ or $I_2(0) > 0$, the fixed point (15) determines the probability of extinction. We vary the transmission rates $\beta_1$ and $\beta_2$ in the numerical examples. All other parameters are $\Lambda = 1$, $d = 0.005$, $\beta_T = 0.25\beta_2$, $r_1 = 0.05 = r_2$, $p = 0.5$, $q = 0.1$, $v_1 = 0.5$, $v_2 = 0.1$, and $d_1 = 1.5d = d_2$. In all three examples, we compute the probability of disease extinction $P_0$ and the numerical approximation based on the proportion of sample paths (out of 10,000) in which the total infected population $\text{Totall}(t) = E_1(t) + I_1(t) + E_2(t) + I_2(t)$ hits zero prior to reaching a size of 20. Twenty infectious individuals is considered as an outbreak.

In the first example, let $\beta_1 = 0.1$ and $\beta_2 = 0.005$. This leads to $\mathcal{R}_1 = 2.58$ and $\mathcal{R}_2 = 0.635$. In the ODE model, a stable endemic equilibrium exists $(\hat{S}, \hat{E}_1, \hat{I}_1, \hat{T}, \hat{E}_2, \hat{I}_2) = (69.8, 1.83, 15.9, 72.4, 1.53, 20.3)$. The first fixed point (14), $(q_1^*, q_2^*, q_3^*, q_4^*) = (0.4489, 0.3883, 1, 1)$, determines probability of disease extinction. Table 9 provides a summary of the probability of disease extinction and the numerical approximation for the branching processes based on small initial values of the drug-sensitive strain, $E_1(0)$ and $I_1(0)$. The extinction results do not depend on the drug-resistant strain for small initial values. In addition, if the initial values of the drug-resistant strain are zero and only the drug-resistant strain is present, then the probability of extinction is one.

In the second numerical example, $\beta_1 = 0.1$ and $\beta_2 = 0.04$, which yields $\mathcal{R}_1 = 2.58$ and $\mathcal{R}_2 = 5.08$. Because $\mathcal{R}_2 > 1$ and $\mathcal{R}_1 > 1$, the two fixed points (14) and (16), $(q_1^*, q_2^*, q_3^*, q_4^*) = (0.4489, 0.3883, 1, 1)$ and $(q_1^*, q_2^*, q_3^*, q_4^*) = (0.3922, 0.3253, 0.2351, 0.1969)$, determine the probability of disease extinction. Table 10 provides a summary of the results for various initial conditions. In addition to recording the proportion of the total number of infectives that hit zero
Table 9. Probability of disease extinction $P_0$ and numerical approximation (Approx.) based on 10,000 sample paths of the CTMC treatment model with parameter values $\Lambda = 1$, $\beta_1 = 0.1$, $\beta_2 = 0.005$, $\beta_T = 0.25\beta_2$, $r_1 = 0.05 = r_2$, $p = 0.5$, $q = 0.1$, $v_1 = 0.5$, $v_2 = 0.1$, and $d_1 = 1.5d = d_2$, and initial conditions $S(0) = S = 200$, $T(0) = 0$, $E_2(0) = 0$, $I_2(0) = 0$, $E_1(0) = e_1$, and $I_1(0) = i_1$.

| $e_1$ | $i_1$ | $P_0$ | Approx. |
|-------|-------|-------|---------|
| 1     | 0     | 0.4489| 0.4458  |
| 0     | 1     | 0.3883| 0.3961  |
| 1     | 1     | 0.1743| 0.1817  |
| 2     | 0     | 0.2015| 0.2114  |
| 0     | 2     | 0.1507| 0.1554  |

Table 10. Probability of disease extinction $P_0$ and numerical approximation (Approx.) based on 10,000 sample paths of the CTMC treatment model with parameter values $\Lambda = 1$, $\beta_1 = 0.1$, $\beta_2 = 0.04$, $d = 0.005$, $\beta_T = 0.25\beta_2$, $r_1 = 0.05 = r_2$, $p = 0.5$, $q = 0.1$, $v_1 = 0.5$, $v_2 = 0.1$, and $d_1 = 1.5d = d_2$ and initial conditions $S(0) = S = 200$, $T(0) = 0$, $E_1(0) = e_1$, $I_1(0) = i_1$, $E_2(0) = e_2$ and $I_2(0) = i_2$.

| $e_1$ | $i_1$ | $e_2$ | $i_2$ | $P_0^a$ | Approx. Totall | $P_0^b$ | Approx. Totb |
|-------|-------|-------|-------|---------|---------------|---------|-------------|
| 1     | 0     | 0     | 0     | 0.3922  | 0.3893        | 0.4489  | 0.4471      |
| 0     | 1     | 0     | 0     | 0.3253  | 0.3233        | 0.3883  | 0.3880      |
| 1     | 1     | 0     | 0     | 0.1178  | 0.1270        | 0.1743  | 0.1790      |
| 0     | 0     | 1     | 0     | 0.2351  | 0.2336        | 1       | 1           |
| 0     | 0     | 0     | 1     | 0.1969  | 0.1956        | 1       | 1           |
| 0     | 0     | 1     | 1     | 0.0463  | 0.0472        | 1       | 1           |
| 1     | 0     | 1     | 0     | 0.0852  | 0.0934        | 0.4489  | 0.4476      |
| 0     | 1     | 0     | 0     | 0.0640  | 0.0688        | 0.3883  | 0.3953      |

$^aP_0$ is computed based on fixed point (16), $(q_1^*, q_2^*, q_3^*, q_4^*) = (0.3922, 0.3253, 0.2351, 0.1969)$.  
$^bP_0$ is computed based on the fixed point (14), $(q_1^{'}, q_2^{'}, q_3^{'}, q_4^{'}) = (0.4489, 0.3883, 1, 1)$.

Figure 4. One sample path of the CTMC treatment model is graphed with the solution of the ODE model. Parameter values are $\Lambda = 1$, $d = 0.005$, $\beta_1 = 0.1$, $\beta_2 = 0.04$, $\beta_T = 0.25\beta_2$, $r_1 = 0.05 = r_2$, $p = 0.5$, $q = 0.1$, $v_1 = 0.5$, $v_2 = 0.1$, and $d_1 = 1.5d = d_2$. The reproduction numbers are $R_1 = 2.58$ and $R_2 = 5.08$. In the ODE model, the stable endemic equilibrium is $(\hat{S}, \hat{E}_1, \hat{I}_1, \hat{T}, \hat{E}_2, \hat{I}_2) = (28.7, 0, 0, 0, 8.16, 109)$. A major outbreak occurs with probability $1 - P_0 = 0.936$. 

\[ S(t), E_1(t), I_1(t); T(t), E_2(t), I_2(t) \]
Table 11. Probability of disease extinction $P_0$ and numerical approximation (Approx.) based on 10,000 sample paths of the CTMC treatment model with parameter values $\Lambda = 1$, $\beta_1 = 0.02$, $\beta_2 = 0.04$, $d = 0.005$, $\beta_T = 0.25\beta_2$, $r_1 = 0.05 = r_2$, $p = 0.5$, $q_1 = 0.5$, $q_2 = 0.1$, and $d_1 = 1.5d = d_2$, and initial conditions $S(0) = \hat{S} = 200$, $T(0) = 0$, $E_1(0) = e_1$, $I_1(0) = i_1$, $E_2(0) = e_2$, and $I_2(0) = i_2$.

| $e_1$ | $i_1$ | $e_2$ | $i_2$ | $P_0$     | Approx. |
|------|------|------|------|----------|---------|
| 1    | 0    | 0    | 0    | 0.8307   | 0.8356  |
| 0    | 1    | 0    | 0    | 0.8120   | 0.8115  |
| 1    | 1    | 0    | 0    | 0.6745   | 0.6770  |
| 0    | 0    | 1    | 0    | 0.2351   | 0.2383  |
| 0    | 0    | 0    | 1    | 0.1969   | 0.1925  |
| 0    | 0    | 1    | 1    | 0.0463   | 0.0470  |
| 1    | 0    | 1    | 0    | 0.1953   | 0.1924  |
| 0    | 1    | 0    | 1    | 0.1599   | 0.1670  |

(Approx. Total) and comparing it with $P_0$ computed from the third fixed point, we record the proportion out of the total in which the drug-sensitive strain hits zero ($\text{Tot}_s(t) = E_1(t) + I_1(t) = 0$) and compare it with $P_0$ computed from the first fixed point. One sample path of the CTMC treatment model and the ODE solution are graphed in Figure 4. This sample path follows the ODE solution which converges to the stable endemic equilibrium $(\hat{S}, \hat{E}_1, \hat{I}_1, \hat{T}, \hat{E}_2, \hat{I}_2) = (28.7, 0, 0, 0, 8.16, 109)$. However, initially, there is an increase in the drug-sensitive strains because $R_1 > 1$.

In the third numerical example, $\beta_1 = 0.02$ and $\beta_2 = 0.04$, which yields $R_1 = 0.515$ and $R_2 = 5.08$. For the ODE model, there exists a stable endemic equilibrium with the drug-resistant strain, the same equilibrium as in the preceding example. The probability of disease extinction is determined by the fixed point (16), $(q_1^*, q_2^*, q_3^*, q_4^*) = (0.8307, 0.8120, 0.2351, 0.1969)$. See Table 11.

5. Summary

Thresholds for disease extinction are well known in the epidemiological literature, especially thresholds based on the basic reproduction number and type of reproduction numbers [11,13, 14,19,31]. For ODE models, these thresholds provide important information about parameter relationships and occurrence of disease outbreaks. The analogous stochastic thresholds are less well known, with the exception of the estimate (1) derived by Whittle [32] (see also [7,12,16]). Information about the probability of an outbreak can be obtained by applying multitype branching processes approximations when there is a small initial number of infectious individuals introduced into a large, entirely susceptible population. We show the usefulness of these probabilities in several epidemic models and show the good agreement between the predicted probability of disease extinction $P_0$ and the numerical approximation based on computing sample paths. In addition, new relationships are derived between the deterministic and stochastic thresholds.

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