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EPIDEMIOLOGICAL MODELS FOR MUTATING PATHOGENS*

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Abstract. We formulate epidemiological models for the transmission of a pathogen that can mutate in the host to create a second infectious mutant strain. The models account for mutation rates that depend on how long the host has been infected. We derive explicit formulas for the reproductive number of the epidemic based on the local stability of the infection-free equilibrium. We analyze the existence and stability of the boundary equilibrium, whose infection components are zero and positive, respectively, and the endemic equilibrium, whose components are all positive. We establish the conditions for global stability of the infection-free and boundary equilibria and local stability of the endemic equilibrium for the case where there is no age structure for the pathogen in the infected population. We show that under certain circumstances, there is a Hopf bifurcation where the endemic equilibrium loses its stability, and periodic solutions appear. We provide examples and numerical simulations to illustrate the Hopf bifurcation.

Key words. epidemic model, pathogen, mutation, infection age, reproductive number, global stability, Hopf bifurcation

AMS subject classifications. 34C32, 34D20, 34D23, 35F99, 92D30

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1. Introduction.

One of the biggest challenges in preventing the spread of infectious diseases is the genetic variations of pathogens. Pathogen mutations that circumvent the protective effects of a patient's immune response are common in infectious diseases such as measles [5], hepatitis B [20], HIV [9], West Nile virus [8], and influenza [18, 23, 24, 25].

The generation or selection of mutants that are a reflection of attempts of the pathogen to resist immune attacks of the host and to survive may occur naturally or in response to treatment with antibodies or antiviral drugs. Pathogens frequently alter their antigen expression to escape the immune defense and ensure the persistent infection in a host [10, 19].

There were only a few existing mathematical models accounting for genetic mutations of a pathogen [2, 3, 11, 17, 21], and little has been done to directly model dynamics of mutations which describe the attempts of the pathogen, after its infection in a host, to escape the immune defense of the host. In this paper, we propose an infection-age-structured dynamic model for a pathogen that can mutate into a second infectious strain in the host. The mutation could be the effect of selective immunologic pressure or possibly adaptation to a more efficiently transmitted or a better replicating pathogen resulting from conversion of the original viral pathogen.

The model formulation for the origin of the pathogen strain is based on a susceptible-infective-recovered (SIR) model with variable infection ages and is governed by partial differential equations (PDEs). The dynamics of the mutant are based on

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an ordinary differential equation (ODE) SIR model. We characterize the threshold conditions of the model epidemic with an explicit formula for the reproductive number of infection, which determines the stability of the infection-free equilibrium. We analyze the stability of boundary equilibria of the model, where some, but not all, of the infection components are zero. We then investigate the existence and stability of the endemic equilibrium, whose components are all positive. We obtain explicit formulas for the endemic equilibrium and the characteristic equation of this equilibrium, which determines its stability. We then consider the special case where the rate at which the pathogen converts to its mutant and the transmission rate of the original pathogen are both independent of infection age. In this simplified situation, the model equations reduce to a system of ODEs. We obtain global stability of the infection-free equilibrium and a unique boundary equilibrium. We show that under certain conditions, the unique endemic equilibrium may undergo a Hopf bifurcation resulting in a periodic solution. We provide examples and numerical simulations to illustrate the stability change of the endemic equilibrium and the Hopf bifurcation.

2. Model formulation. We base our SIR model on the spread of a pathogen that can mutate in the host to create a second, cocirculating, mutant strain. We assume that after a certain period of infection, the original strain, referred to as Strain 1, is selected against in the intrahost selection process and is converted to a mutant, referred to as Strain 2, such that a proportion of the individuals infected by Strain 1 are then carrying Strain 2. Let $S(t)$ be the susceptibles and $i(t,\tau)$ the distribution of infectives infected by Strain 1 with infection stage, or time since infection, τ, such that $\int_{\tau_1}^{\tau_2} i(t,\tau)d\tau$ is the total number of infectives with infection ages between τ_1 and τ_2 [1, 7, 13, 14, 22]. Let $J(t)$ be the infectives infected by Strain 2 and $R(t)$ the group of individuals who are recovered and immune to both strains. We further assume that the genetic difference between the two strains, or the drift of the mutation, is relatively small so that there is perfect cross-immunity; that is, once an individual is recovered from infection by one of the two strains, the individual is immune to both strains.

The dynamics of the transmission in this model are governed by the system

$$
\begin{aligned}
\frac{dS(t)}{dt} &= \mu(S^0 - S(t)) - \left(\int_0^\infty \beta_1(\tau) i(t,\tau)d\tau + \beta_2 J(t)\right) S(t),\\
\frac{\partial i(t,\tau)}{\partial t} + \frac{\partial i(t,\tau)}{\partial \tau} &= -(\mu+\gamma_1) i(t,\tau) - \kappa(\tau) i(t,\tau),\\
i(t,0) &= S(t)\int_0^\infty \beta_1(\tau) i(t,\tau)d\tau,\\
i(0,\tau) &= \psi(\tau),\\
\frac{dJ(t)}{dt} &= \beta_2 J(t) S(t) - (\mu+\gamma_2) J(t) + \int_0^\infty \kappa(\tau) i(t,\tau)d\tau,\\
\frac{dR(t)}{dt} &= \gamma_1 \int_0^\infty i(t,\tau)d\tau + \gamma_2 J(t) - \mu R(t),
\end{aligned}
\tag{2.1}
$$

where μS^0 is the input flow into the susceptible population, μ is the total removal rate which accounts for both natural death and people moving in and out of the susceptible population, γ_1 and γ_2 are the recovery rates from the infection, $\beta_1(\tau)$ and β_2 are the transmission rates of Strain 1 and Strain 2, respectively, $\kappa(\tau)$ is the mutation rate, or the rate at which Strain 1 is converted to Strain 2, and $\psi(\tau)$ is the initial distribution of infectives infected by Strain 1.

3. Thresholds of the epidemic. Assume that the initial distribution of the infectives is zero. Then $E_0 := (S^0, 0, 0)$ is the infection-free equilibrium. As is well known, its stability determines the thresholds of the epidemic [6, 7, 13, 15, 16]. We investigate the local stability of E_0 as follows.

Since the dynamics of $R(t)$ do not affect the evolution of S, i, and J, we omit the equation for $R(t)$ when studying the growth of the epidemic. Linearizing system (2.1) about E_0, by defining the perturbation variables $x(t) = S(t) - S^0$, $y(t,\tau) = i(t,\tau)$, $z(t) = J(t)$, we obtain the system

$$
\begin{aligned}
&\frac{dx(t)}{dt} = -\mu x(t) - \left(\int_0^\infty \beta_1(\tau) y(t,\tau)\, d\tau + \beta_2 z(t)\right) S^0, \\
&\begin{cases} \dfrac{\partial y(t,\tau)}{\partial t} + \dfrac{\partial y(t,\tau)}{\partial \tau} &= -(\mu+\gamma_1) y(t,\tau) - \kappa(\tau) y(t,\tau), \\ y(t,0) &= S^0 \displaystyle\int_0^\infty \beta_1(\tau) y(t,\tau)\, d\tau, \end{cases} \qquad (3.1) \\
&\frac{dz(t)}{dt} = \beta_2 z(t) S^0 - (\mu+\gamma_2) z(t) + \int_0^\infty \kappa(\tau) y(t,\tau)\, d\tau.
\end{aligned}
$$

Let $x(t) = x_0 e^{\rho t}$, $y(t,\tau) = p(\tau) e^{\rho(t-\tau)}$, and $z(t) = z_0 e^{\rho t}$, where x_0, $p(\tau)$, z_0, and ρ are to be determined. Substituting them into (3.1), we obtain the equations

$$\rho x_0 = -\mu x_0 - S^0 \int_0^\infty \beta_1(\tau) p(\tau) e^{-\rho\tau}\, d\tau - \beta_2 S^0 z_0, \tag{3.2}$$

$$\frac{dp(\tau)}{d\tau} = -(\mu+\gamma_1) p(\tau) - \kappa(\tau) p(\tau), \tag{3.3}$$

$$p(0) = S^0 \int_0^\infty \beta_1(\tau) p(\tau) e^{-\rho\tau}\, d\tau, \tag{3.4}$$

$$\rho z_0 = (\beta_2 S^0 - \mu - \gamma_2) z_0 + \int_0^\infty \kappa(\tau) p(\tau) e^{-\rho\tau}\, d\tau \tag{3.5}$$

for $p(\tau) \not\equiv 0$, $x_0 \neq 0$, $z_0 \neq 0$, and ρ.

Equations (3.3) and (3.4) are decoupled from (3.2) and (3.5). Integrating (3.3) from 0 to τ gives

$$p(\tau) = p(0) e^{-(\mu+\gamma_1)\tau - \Delta(\tau)}, \tag{3.6}$$

where $\Delta(\tau) := \int_0^\tau \kappa(v)\, dv$. Substituting (3.6) into (3.4) yields the characteristic equation

$$p(0) = S^0 p(0) \int_0^\infty \beta_1(\tau) e^{-\rho\tau} e^{-(\mu+\gamma_1)\tau - \Delta(\tau)}\, d\tau. \tag{3.7}$$

Defining

$$C(\rho) = S^0 \int_0^\infty \beta_1(\tau) e^{-\rho\tau} e^{-(\mu+\gamma_1)\tau - \Delta(\tau)}\, d\tau,$$

we note that (3.7) has a nonzero solution $p(0)$ if and only if there exists ρ such that $C(\rho) = 1$.

We first consider the case where ρ is a real number. Since

$$C'(\rho) = -S^0 \int_0^\infty \tau \beta_1(\tau) e^{-\rho\tau} e^{-(\mu+\gamma_1)\tau - \Delta(\tau)}\, d\tau < 0,$$

$C(\rho)$ is a decreasing function of ρ. Noticing $\lim_{\rho\to-\infty} C(\rho) = \infty$ and $\lim_{\rho\to\infty} C(\rho) = 0$, if we define the number

$$R_1 := C(0) = S^0 \int_0^\infty \beta_1(\tau) e^{-(\mu+\gamma_1)\tau - \Delta(\tau)} d\tau, \tag{3.8}$$

then there exists a unique real solution ρ to the equation $C(\rho) = 1$, which is negative if $R_1 < 1$ and positive if $R_1 > 1$.

If $\rho := \rho_1 + i\rho_2$ is a complex number, where $i = \sqrt{-1}$, then by separating the real and imaginary parts of $C(\rho) = 1$, the real part ρ_1 satisfies

$$1 = S^0 \int_0^\infty \beta_1(\tau) e^{-\rho_1\tau} e^{-(\mu+\gamma_1)\tau - \Delta(\tau)} \cos(\rho_2\tau) d\tau. \tag{3.9}$$

However, since

$$S^0 \int_0^\infty \beta_1(\tau) e^{-\rho_1\tau} e^{-(\mu+\gamma_1)\tau - \Delta(\tau)} \cos(\rho_2\tau) d\tau \le S^0 \int_0^\infty \beta_1(\tau) e^{-\rho_1\tau} e^{-(\mu+\gamma_1)\tau - \Delta(\tau)} d\tau,$$

solution ρ_1 to (3.9) must be negative if $R_1 < 1$. That is, equation $C(\rho) = 1$ can have solutions with negative real part only if $R_1 < 1$.

The solution ρ of $C(\rho) = 1$ can be used to determine $p(\tau)$. The initial values, x_0 and z_0, can now be defined from (3.2) and (3.5). The number R_1 defined in (3.8) is a threshold value for Strain 1 because if $R_1 > 1$ the epidemic for Strain 1 grows, while if $R_1 < 1$ it delays. It is also the number of secondary infective cases generated by infection of Strain 1. We refer to R_1 as the reproductive number for Strain 1.

If initially no one is infected with Strain 1, i.e., $i(t, \tau) = 0$, then $p(\tau) = 0$ for all τ. Equations (3.2) and (3.5) can be reduced to

$$\begin{aligned} \rho x_0 &= -\mu x_0 - \beta_2 S^0 z_0, \\ \rho z_0 &= (\beta_2 S^0 - \mu - \gamma_2) z_0, \end{aligned} \tag{3.10}$$

and they determine threshold conditions for Strain 2. Define

$$R_2 := \frac{\beta_2 S^0}{\mu + \gamma_2}. \tag{3.11}$$

All solutions ρ of system (3.10) are negative if and only if $R_2 < 1$. Therefore, R_2 is a threshold value for Strain 2 and is the number of secondary infective cases generated by infection of Strain 2. We refer to R_2 as the reproductive number of Strain 2.

The thresholds for the epidemic can be summarized as follows.

THEOREM 3.1. *Define the reproductive number, R_0, of infection in the total population by*

$$R_0 := \max\{R_1, R_2\},$$

that is,

$$R_0 = \max\left\{ S^0 \int_0^\infty \beta_1(\tau) e^{-(\mu+\gamma_1)\tau - \Delta(\tau)} d\tau, \quad \frac{\beta_2 S^0}{\mu + \gamma_2} \right\}.$$

Then the infection-free equilibrium E_0 is asymptotically stable if $R_0 < 1$ and is unstable if $R_0 > 1$.

4. Boundary equilibrium. Cocirculating strains of the pathogen compete with each other to infect the susceptible population. When only one strain is present, the solution is on the boundary of the feasibility solution space and we call the stationary solution a boundary equilibrium.

An equilibrium of system (2.1), $(S, i(\tau), J)$, satisfies the system

$$\mu(S^0 - S) - \left(\int_0^\infty \beta_1(\tau) i(\tau) d\tau + \beta_2 J\right) S = 0, \tag{4.1a}$$

$$\frac{di(\tau)}{d\tau} = -(\mu + \gamma_1) i(\tau) - \kappa(\tau) i(\tau), \tag{4.1b}$$

$$i(0) = S \int_0^\infty \beta_1(\tau) i(\tau) d\tau, \tag{4.1c}$$

$$\beta_2 JS - (\mu + \gamma_2) J + \int_0^\infty \kappa(\tau) i(\tau) d\tau = 0. \tag{4.1d}$$

It follows from (4.1d) that if $J = 0$, then $i(\tau) = 0$ for all τ. That is, there does not exist a boundary equilibrium with $i(\tau) \geq 0$ and $J = 0$, and the only boundary equilibrium has $i(\tau) = 0$ for all τ and $J \neq 0$. We denote it as $E_1 := (S_1, i_1(\tau), J_1)$.

Solving (4.1a) and (4.1d), we have

$$S_1 = \frac{\mu + \gamma_2}{\beta_2}, \quad J_1 = \frac{\mu}{\beta_2}\left(\frac{S^0 \beta_2}{\mu + \gamma_2} - 1\right) = \frac{\mu}{\beta_2}(R_2 - 1). \tag{4.2}$$

Thus the boundary equilibrium E_1 exists if and only if $R_2 > 1$.

To study stability of this boundary equilibrium, we linearize system (2.1) about E_1 by letting $x(t) = S(t) - S_1$, $y(t) = J(t) - J_1$, $z(t, \tau) = i(t, \tau)$, and we obtain the system

$$\begin{aligned}
&\frac{dx(t)}{dt} = -\mu x(t) - \beta_2 J_1 x(t) - \beta_2 S_1 y(t) - S_1 \int_0^\infty \beta_1(\tau) z(t, \tau) d\tau, \\
&\frac{dy(t)}{dt} = \beta_2 J_1 x(t) - (\mu + \gamma_2) y(t) + \beta_2 S_1 y(t) + \int_0^\infty \kappa(\tau) z(t, \tau) d\tau, \\
&\begin{cases} \dfrac{\partial z(t, \tau)}{\partial t} + \dfrac{\partial z(t, \tau)}{\partial \tau} = -(\mu + \gamma_1) z(t, \tau) - \kappa(\tau) z(t, \tau), \\ z(t, 0) = S_1 \displaystyle\int_0^\infty \beta_1(\tau) z(t, \tau) d\tau. \end{cases}
\end{aligned} \tag{4.3}$$

Using the same approach as in section 3, we first derive the characteristic equation for E_1,

$$1 = S_1 \int_0^\infty \beta_1(\tau) e^{-\rho\tau} e^{-(\mu + \gamma_1)\tau - \Delta(\tau)} d\tau, \tag{4.4}$$

and define

$$R_b := S_1 \int_0^\infty \beta_1(\tau) e^{-(\mu + \gamma_1)\tau - \Delta(\tau)} d\tau.$$

If $R_b < 1$, then $\lim_{t \to \infty} z(t, \tau) = 0$.

Next we locate the eigenvalues of the following matrix from system (4.3):

$$\begin{bmatrix} -\mu - \beta_2 J_1 & -\beta_2 S_1 \\ \beta_2 J_1 & -(\mu + \gamma_2 - \beta_2 S_1) \end{bmatrix} = \begin{bmatrix} -\mu - \beta_2 J_1 & -\beta_2 S_1 \\ \beta_2 J_1 & 0 \end{bmatrix}.$$

The trace and determinant of this matrix are negative and positive, respectively. Therefore, its eigenvalues both have negative real part.

In summary we have the following.

THEOREM 4.1. *The unique boundary equilibrium*

$$E_1 = (S_1, i_1(\tau), J_1) = \left(\frac{\mu + \gamma_2}{\beta_2},\ 0,\ \frac{\mu}{\beta_2} \left(\frac{S^0 \beta_2}{\mu + \gamma_2} - 1 \right) \right)$$

exists if and only if $R_2 > 1$. *It is locally asymptotically stable if*

$$R_b = \frac{\mu + \gamma_2}{\beta_2} \int_0^\infty \beta_1(\tau) e^{-(\mu+\gamma_1)\tau - \Delta(\tau)} d\tau < 1$$

and is unstable if $R_b > 1$.

If $R_2 > 1$, then $S^0 > (\mu + \gamma_2)/\beta_2 := \tilde{S}_1$. Notice that R_b can be rewritten as $R_b = \tilde{S}_1/S^0 R_1 = R_1/R_2$. When the boundary equilibrium E_1 exists, $R_2 > 1$, and hence $S^0 > \tilde{S}_1$ and $R_b < R_1$. If $R_2 > 1 > R_1$, then $R_b < 1$, which implies that the boundary equilibrium E_1 is asymptotically stable. In the situation where $R_2 > 1$ and $R_1 > 1$, the infection-free equilibrium is unstable and the two strains cannot both die out. If $R_2 > R_1 > 1$, then $R_b < 1$ and the boundary equilibrium E_1 exists and is asymptotically stable. In the last possible case, if $R_1 > R_2 > 1$, then although the boundary equilibrium E_1 exists, it is unstable. This situation may lead to the existence and stability of an endemic equilibrium or other dynamical features of system (2.1).

5. Endemic equilibrium. The cocirculating strains of the pathogen can coexist. The stationary coexistence solution is an endemic equilibrium whose components are all positive.

5.1. Existence of the endemic equilibrium. Let $E^* := (S^*, i^*(\tau), J^*)$ be an endemic equilibrium of system (2.1). It follows from (4.1b) that

$$i^*(\tau) = i^*(0) e^{-(\mu+\gamma_1)\tau - \Delta(\tau)}.$$

By substituting this into (4.1c), we arrive at the equation

$$i^*(0) = i^*(0) S^* \int_0^\infty \beta_1(\tau) e^{-(\mu+\gamma_1)\tau - \Delta(\tau)} d\tau = i^*(0) \frac{S^* R_1}{S^0}. \tag{5.1}$$

Equation (5.1) has a solution $i^*(0) > 0$ if and only if

$$S^* = \frac{S^0}{R_1}. \tag{5.2}$$

It follows from (4.1c) that

$$i^*(0) = S^* W_1,$$

where we define $W_1 := \int_0^\infty \beta_1(\tau) i^*(\tau) d\tau$. Then

$$i^*(\tau) = S^* W_1 e^{-(\mu+\gamma_1)\tau - \Delta(\tau)}. \tag{5.3}$$

Define

$$W_2 := \int_0^\infty \kappa(\tau) i^*(\tau) d\tau = S^* W_1 \int_0^\infty \kappa(\tau) e^{-(\mu+\gamma_1)\tau - \Delta(\tau)} d\tau = S^* W_1 K, \tag{5.4}$$

where

$$K := \int_0^\infty \kappa(\tau) e^{-(\mu+\gamma_1)\tau - \Delta(\tau)} d\tau.$$

The equilibrium equations (4.1a) and (4.1d) can be expressed as

$$\mu S^0 = (\mu + W_1 + \beta_2 J^*)\, S^*, \tag{5.5}$$

$$W_2 = ((\mu + \gamma_2) - \beta_2 S^*)\, J^*. \tag{5.6}$$

Substituting (5.2) into (5.6) yields

$$(\mu + \gamma_2)\left(1 - \frac{\beta_2 S^*}{\mu + \gamma_2}\right) J^* = (\mu + \gamma_2)\left(1 - \frac{R_2}{R_1}\right) J^* = W_2. \tag{5.7}$$

Since $W_2 > 0$, there exists a positive solution J^* of (5.7) if and only if

$$\frac{R_2}{R_1} < 1.$$

Suppose $R_2 < R_1$. Then solving (5.7) for J^* yields

$$J^* = \frac{W_2}{(\mu + \gamma_2)\left(1 - \frac{R_2}{R_1}\right)}. \tag{5.8}$$

Substituting (5.8) into (5.5) gives

$$\mu + W_1 + \beta_2 \frac{W_2}{(\mu + \gamma_2)\left(1 - \frac{R_2}{R_1}\right)} = \frac{\mu S^0}{S^*} = \mu R_1. \tag{5.9}$$

We then substitute (5.4) into (5.9) to obtain

$$W_1 + \frac{\beta_2 S^0 K}{(\mu + \gamma_2)(R_1 - R_2)} W_1 = \mu(R_1 - 1), \tag{5.10}$$

which implies that $W_1 > 0$ if $R_1 > 1$.

Solving (5.10) for W_1 yields

$$W_1 = \frac{\mu\,(R_1 - 1)\,(R_1 - R_2)\,(\mu + \gamma_2)}{((\mu + \gamma_2)\,(R_1 - R_2) + \beta_2 K S^0)}. \tag{5.11}$$

W_2 can be determined by substituting (5.11) into (5.4). Finally, substituting W_2 and W_1 into (5.3) and (5.8), we obtain the expression for the unique positive endemic equilibrium.

THEOREM 5.1. *If $R_1 > 1$ and $R_1 > R_2$, then there exists a unique endemic equilibrium $E^* = (S^*, i^*(\tau), J^*)$ given by*

$$S^* = \frac{S^0}{R_1}, \quad i^*(\tau) = \frac{S^0 W_1}{R_1} e^{-(\mu+\gamma_1)\tau - \int_0^\tau \kappa(v)dv}, \quad J^* = \frac{K S^0 W_1}{(\mu + \gamma_2)\,(R_1 - R_2)}, \tag{5.12}$$

where W_1 is defined in (5.11).

5.2. Stability of the endemic equilibrium. We investigate the local stability of the endemic equilibrium, E^*, by linearizing system (2.1) about E^*. Let $x(t) = S(t) - S^*$, $y(t,\tau) = i(t,\tau) - i^*(\tau)$, and $z(t) = J(t) - J^*$. The linearization results in the perturbation equations

$$
\begin{aligned}
&\frac{dx(t)}{dt} = -\left(\mu + W_1 + \beta_2 J^*\right) x(t) - \beta_2 S^* z(t) - S^* \int_0^\infty \beta_1(\tau) y(t,\tau) d\tau, \\
&\begin{cases} \dfrac{\partial y(t,\tau)}{\partial t} + \dfrac{\partial y(t,\tau)}{\partial \tau} &= -(\mu+\gamma_1) y(t,\tau) - \kappa(\tau) y(t,\tau), \\ y(t,0) &= S^* \displaystyle\int_0^\infty \beta_1(\tau) y(t,\tau) d\tau + W_1 x(t), \end{cases} \qquad (5.13) \\
&\frac{dz(t)}{dt} = \beta_2 J^* x(t) - (\mu+\gamma_2) z(t) + \beta_2 S^* z(t) + \int_0^\infty \kappa(\tau) y(t,\tau) d\tau.
\end{aligned}
$$

Suppose $x = x_0 e^{\rho t}$, $y = \hat{y}(\tau) e^{\rho(t-\tau)}$, and $z = z_0 e^{\rho t}$. Substituting these variables into system (5.13) and solving for $\hat{y}(\tau)$, with initial condition $\hat{y}(0)$, leads to the system

$$
\begin{aligned}
&(\rho + \mu + W_1 + \beta_2 J^*) x_0 + \beta_2 S^* z_0 + S^* \int_0^\infty \beta_1(\tau) \hat{y}(\tau) e^{-\rho\tau} d\tau = 0, \\
&-\beta_2 J^* x_0 + (\rho + \mu + \gamma_2 - \beta_2 S^*) z_0 - \int_0^\infty \kappa(\tau) \hat{y}(\tau) e^{-\rho\tau} d\tau = 0, \qquad (5.14) \\
&\hat{y}(\tau) = \left(S^* \int_0^\infty \beta_1(\tau) \hat{y}(\tau) e^{-\rho\tau} d\tau + W_1 x_0 \right) e^{-(\mu+\gamma_1)\tau - \Delta(\tau)}.
\end{aligned}
$$

We simplify these notations by defining the functions

$$
\begin{aligned}
H(\rho) &:= \int_0^\infty \beta_1(\tau) \hat{y}(\tau) e^{-\rho\tau} d\tau, & Q(\rho) &:= \int_0^\infty \kappa(\tau) \hat{y}(\tau) e^{-\rho\tau} d\tau, \\
P_1(\rho) &:= \int_0^\infty \beta_1(\tau) e^{-\rho\tau} e^{-(\mu+\gamma_1)\tau - \Delta(\tau)} d\tau, & P_2(\rho) &:= \int_0^\infty \kappa(\tau) e^{-\rho\tau} e^{-(\mu+\gamma_1)\tau - \Delta(\tau)} d\tau.
\end{aligned}
$$

Multiplying $\hat{y}(\tau)$ in (5.14) by $\beta_1(\tau)e^{-\rho\tau}$ and $\kappa(\tau)e^{-\rho\tau}$, respectively, and then integrating from 0 to ∞ yields

$$
H(\rho) = \frac{W_1 P_1(\rho)}{1 - S^* P_1(\rho)} x_0 \qquad (5.15)
$$

and

$$
Q(\rho) = \left(S^* H(\rho) + W_1 x_0\right) P_2(\rho) = \left(\frac{S^* W_1 P_1(\rho)}{1 - S^* P_1(\rho)} + W_1 \right) P_2(\rho) x_0. \qquad (5.16)
$$

Substituting (5.15) and (5.16) into system (5.14), we obtain the characteristic equation

$$
\left(\rho + \mu + \beta_2 J^* + \frac{W_1}{1 - S^* P_1(\rho)} \right) (\rho + \mu + \gamma_2 - \beta_2 S^*) + \left(\beta_2 J^* + \frac{W_1 P_2(\rho)}{1 - S^* P_1(\rho)} \right) \beta_2 S^* = 0 \qquad (5.17)
$$

and arrive at the following result.

THEOREM 5.2. *The endemic equilibrium, given in* (5.12)*, is locally asymptotically stable if all roots, ρ, of the characteristic equation* (5.17) *have negative real part.*

The results obtained for the two-strain SIR model (2.1) are summarized in Table 1. The stability of the endemic equilibrium is not listed because it requires knowledge of the roots of the characteristic equation (5.17) and we have not established the explicit criterion.

TABLE 1

The existence conditions for the boundary and endemic equilibria, E_1 and E^*, and stability conditions for the infection-free and boundary equilibria, E_0 and E_1. These conditions are based on the relations between the two reproductive numbers, R_1 and R_2, for the two strains.

	$R_1 < 1$, $R_2 < 1$	$R_2 < 1 < R_1$	$R_1 < 1 < R_2$	$1 < R_1 < R_2$	$1 < R_2 < R_1$
E_0	stable	unstable	unstable	unstable	unstable
E_1	does not exist	does not exist	stable	stable	unstable
E^*	does not exist	exists	does not exist	does not exists	exists

6. Constant mutation rate. Because (5.17) is a transcendental equation, it is difficult to determine when all the roots of the characteristic equation have negative real part and, hence, whether the endemic equilibrium is stable. To gain insight into the transmission dynamics of the disease governed by system (2.1), we consider the special case where the mutation rate from Strain 1 to Strain 2 is constant and where the infection rate of Strain 1 is independent of the infection stages. We define these constant rates as $\kappa(\tau) := k$ and $\beta_1(\tau) := \beta_1$.

Let the total infectives be $I(t) := \int_0^\infty i(t,\tau)d\tau$. Integrating the equation for $i(t,\tau)$ in (2.1) with respect to τ and using the initial condition $i(t,0)$ reduces the system of PDEs to the system of ODEs,

$$\frac{dS}{dt} = \mu(S^0 - S) - \beta_1 IS - \beta_2 JS, \tag{6.1a}$$

$$\frac{dI}{dt} = \beta_1 SI - (\mu + \gamma_1 + k)I, \tag{6.1b}$$

$$\frac{dJ}{dt} = \beta_2 SJ - (\mu + \gamma_2)J + kI. \tag{6.1c}$$

The reproductive numbers of Strains 1 and 2, R_1 and R_2, for system (6.1) are

$$R_1 = \frac{S^0\beta_1}{\mu + \gamma_1 + k}, \qquad R_2 = \frac{S^0\beta_2}{\mu + \gamma_2}. \tag{6.2}$$

The only boundary equilibrium with $I = 0$ and $J > 0$ exists if $R_2 > 1$ and it has the same expression as in section 4. This boundary equilibrium is stable if $R_1 < R_2$ and is unstable if $R_1 > R_2$.

We now establish existence and local stability of the endemic equilibrium of system (6.1).

For $\kappa(\tau) = k$, the term K defined in (5.4) becomes

$$K = \frac{k}{\mu + \gamma_1 + k}. \tag{6.3}$$

Substituting (6.2) and (6.3) into (5.12), we obtain the endemic equilibrium, $E^* = (S^*, I^*, J^*)$, with

$$\begin{aligned} S^* &= \frac{\mu + \gamma_1 + k}{\beta_1}, \\ I^* &= \frac{\mu\big(S^0\beta_1 - (\mu + \gamma_1 + k)\big)\big(\beta_1(\mu + \gamma_2) - \beta_2(\mu + \gamma_1 + k)\big)}{\beta_1\big(\beta_1(\mu + \gamma_2) - \beta_2(\mu + \gamma_1)\big)(\mu + \gamma_1 + k)}, \\ J^* &= \frac{\mu k\big(S^0\beta_1 - (\mu + \gamma_1 + k)\big)}{\big(\beta_1(\mu + \gamma_2) - \beta_2(\mu + \gamma_1)\big)(\mu + \gamma_1 + k)}. \end{aligned} \tag{6.4}$$

By solving (6.1) for an endemic equilibrium, we have the equivalent solution

$$\begin{aligned} S^* &= \frac{S^0}{R_1}, \\ I^* &= \frac{\mu(\mu+\gamma_1+k)(R_1-1)(R_1-R_2)}{\beta_1\big(kR_1+(\mu+\gamma_1)(R_1-R_2)\big)}, \\ J^* &= \frac{\mu k S^0(R_1-1)}{(\mu+\gamma_2)\big(kR_1+(\mu+\gamma_1)(R_1-R_2)\big)}. \end{aligned}$$

Hence E^* exists if and only if $R_1 > 1$ and $R_1 > R_2$.

Based on $\mu + \beta_2 J^* = \mu S^0/S^* - \beta_1 I^*$, the characteristic equation for system (6.1) has the form

(6.5)
$$\left(\rho + \mu R_1 + \frac{\gamma_1+\mu+k}{\rho}\beta_1 I^*\right)(\rho+\mu+\gamma_2-\beta_2 S^*) + \left(\beta_2 J^* + \frac{k}{\rho}\beta_1 I^*\right)\beta_2 S^* = 0.$$

This can be expressed as

$$\rho^3 + a_1\rho^2 + a_2\rho + a_3 = 0,$$

where

$$\begin{aligned} a_1 &:= \mu R_1 + \mu + \gamma_2 - \beta_2 S^* = \mu\frac{S^0}{S^*} + k\frac{I^*}{J^*}, \\ a_2 &:= \mu R_1(\mu+\gamma_2-\beta_2 S^*) + (\mu+\gamma_1+k)\beta_1 I^* + \beta_2^2 J^* S^* \\ &= \beta_1^2 S^* I^* + \beta_2^2 S^* J^* + \mu\frac{S^0}{S^*}k\frac{I^*}{J^*}, \\ a_3 &:= \left((\mu+\gamma_2)\beta_1 - \beta_2(\mu+\gamma_1)\right)(\mu+\gamma_1+k)I^* = \beta_1 S^* k\frac{I^*}{J^*}\left(\beta_1 I^* + \beta_2 J^*\right). \end{aligned}$$

Since $a_1 > 0$ and $a_3 > 0$, it follows from the Routh–Hurwitz criterion that all characteristic roots of (6.5) have negative real part if and only if $a_1 a_2 > a_3$.

A straightforward calculation yields

(6.6)
$$\begin{aligned} a_1 a_2 - a_3 &= \mu\frac{S^0}{S^*}\left(\beta_1^2 S^* I^* + \beta_2^2 S^* J^* + \mu\frac{S^0}{S^*}k\frac{I^*}{J^*}\right) + \mu\frac{S^0}{S^*}\left(k\frac{I^*}{J^*}\right)^2 + kS^* I^*\beta_2(\beta_2-\beta_1) \\ &= \frac{\mu(R_1-1)(R_1-R_2)}{(\sigma_1+k)R_1-\sigma_1 R_2}\left(\mu R_1(\sigma_1+k)^2 + \frac{\mu\sigma_2 R_2^2 k}{R_1-R_2}\right. \\ &\qquad\qquad \left. - \frac{k\sigma_2 R_2\big(R_1(\sigma_1+k)-R_2\sigma_2\big)}{R_1^2}\right) \\ &\quad + \frac{\mu(R_1-R_2)}{R_1^2}(\mu\sigma_2 R_1^3 + \sigma_2^2(R_1-R_2)R_1) \\ &= \frac{\mu(R_1-1)(R_1-R_2)}{R_1^2\big((\sigma_1+k)R_1-\sigma_1 R_2\big)}(c_2k^2 + c_1 k + c_0), \end{aligned}$$

where

$$\sigma_1 := \mu + \gamma_1, \quad \sigma_2 := \mu + \gamma_2,$$

$$c_0 := \mu\sigma_1^2 R_1^3 + \sigma_2 R_1\big(\mu R_1^2 + \sigma_2(R_1 - R_2)\big)\frac{\sigma_1(R_1 - R_2)}{R_1 - 1},$$

$$c_1 := 2\mu\sigma_1 R_1^3 + \frac{\mu\sigma_2 R_1^2 R_2^2}{R_1 - R_2} + \frac{\sigma_2 R_1^2\big(\mu R_1^2 + \sigma_2(R_1 - R_2)\big)}{R_1 - 1} - \sigma_2 R_2(\sigma_1 R_1 - \sigma_2 R_2),$$

$$c_2 := \mu R_1^3 - \sigma_2 R_1 R_2.$$

Hence all roots of (6.5) have negative real part if $c_2k^2 + c_1k + c_0 > 0$, and at least one of the roots of (6.5) has positive real part if $c_2k^2 + c_1k + c_0 < 0$.

We summarize the results in the following theorem.

THEOREM 6.1. *When the mutation rate is constant, the dynamical behavior of epidemic model* (6.1) *can be described as one of the following cases:*

1. *If we define* $R_0 := \max\{R_1, R_2\}$ *and* $R_0 < 1$, *then the infection-free equilibrium,* $E_0 := (S^0, 0, 0)$, *is the only equilibrium and is locally asymptotically stable. If* $R_0 > 1$, *then* E_0 *is unstable.*
2. *If* $R_1 < 1 < R_2$, *or* $1 < R_1 < R_2$, *the only boundary equilibrium, given by*

$$E_1 := \left(\tilde{S}, 0, \tilde{J}\right) = \left(S^0 R_2,\ 0,\ \frac{\mu S^0}{\sigma_2 R_2}(R_2 - 1)\right), \tag{6.7}$$

   exists and is locally asymptotically stable. In this case, the endemic equilibrium, E^*, *does not exist.*
3. *If* $R_2 < 1 < R_1$, *the endemic equilibrium,* E^*, *exists and is the only nontrivial equilibrium. It is locally asymptotically stable if* $c_2k^2 + c_1k + c_0 > 0$ *and unstable if* $c_2k^2 + c_1k + c_0 < 0$.
4. *If* $1 < R_2 < R_1$, *the boundary equilibrium,* E_1, *exists but is unstable. The endemic equilibrium,* E^*, *exists and is locally asymptotically stable if* $c_2k^2 + c_1k + c_0 > 0$ *and unstable if* $c_2k^2 + c_1k + c_0 < 0$.

6.1. The global stability of the equilibria. In this section we establish that when the infection-free equilibrium and the boundary equilibrium of system (6.1) are locally asymptotically stable, they are globally stable.

THEOREM 6.2.

1. *If the infection-free equilibrium,* E_0, *is locally asymptotically stable, then it is globally stable; that is,* E_0 *is globally asymptotically stable if* $R_0 < 1$.
2. *If* $R_1 < 1 < R_2$, *the only boundary equilibrium,* E_1, *given in* (6.7), *is globally asymptotically stable.*

Proof. It follows from (6.1b) that

$$I(t) = I(0)e^{\int_0^t \beta_1 S(\tau)d\tau - (\mu+\gamma_1+k)t}$$

for all $t \geq 0$. Hence, the hyperplane $I = 0$ is invariant for system (6.1).

If $R_1 < 1$, we can further show that the hyperplane attracts all solutions started in the first octant, $S \geq 0$, $I \geq 0$, $J \geq 0$. That is, $\lim_{t\to\infty} I(t) = 0$. It can be seen from (6.1a) that $dS/dt \leq \mu(S^0 - S)$ and hence $S(t) \leq S^0 + S(0)e^{-\mu t}$ and from (6.1b) that

$$\begin{aligned} I(t) &\leq I(0)e^{\int_0^t \beta_1\left(S^0 + S(0)e^{-\mu\tau}\right)d\tau - (\mu+\gamma_1+k)t} = I(0)e^{(\mu+\gamma_1+k)(R_1-1)t + \frac{\beta_1 S(0)}{\mu}\left(1-e^{-\mu t}\right)} \\ &\leq I(0)e^{\frac{\beta_1 S(0)}{\mu}}e^{(\mu+\gamma_1+k)(R_1-1)t} \to 0 \end{aligned}$$

as $t \to \infty$.

Based on the attractiveness of the hyperplane $I = 0$, to prove the global asymptotic stability of the infection-free equilibrium E_0 or the boundary equilibrium E_1 in the first octant, it suffices to show that these two equilibria are globally asymptotically stable in the hyperplane $I = 0$.

We first show that all the solutions of (6.1) in the hyperplane $I = 0$ approach E_0 if $R_0 < 1$. We use the Lyapunov function V_1 defined by

$$V_1(S, J) := J + S - S^0 - S^0 \ln \frac{S}{S^0}$$

for system (6.1). Along the trajectories of system (6.1) in the hyperplane $I = 0$ we have

$$\begin{aligned}
\left.\frac{dV_1}{dt}\right|_{(6.1)} &= (\beta_2 S - (\mu + \gamma_2))\, J + \frac{S - S^0}{S}\left(\mu(S^0 - S) - \beta_2 JS\right) \\
&= -\frac{\mu(S - S^0)^2}{S} + \left(S^0\beta_2 - (\mu + \gamma_2)\right) J \\
&= -\frac{\mu(S - S^0)^2}{S} + J(R_2 - 1)\sigma_2 < 0
\end{aligned}$$

if $R_2 < 1$. Hence it follows from Lyapunov stability theory that E_0 is globally asymptotically stable.

We next assume $R_1 < 1 < R_2$ and show the global stability of the boundary equilibrium $E_1 = (\tilde{S}, 0, \tilde{J})$. We use

$$V_2(S, J) = J - \tilde{J} - \tilde{J} \ln \frac{J}{\tilde{J}} + S - \tilde{S} - \tilde{S} \ln \frac{S}{\tilde{S}}$$

as a Lyapunov functions for system (6.1). In the hyperplane $I = 0$,

$$\begin{aligned}
\left.\frac{dV_2}{dt}\right|_{(6.1)} &= (\beta_2 S - (\mu + \gamma_2))\,(J - \tilde{J}) + \frac{\mu(S^0 - S)(S - \tilde{S})}{S} - (S - \tilde{S})\beta_2 J \\
&= \beta_2(S - \tilde{S})(J - \tilde{J}) + \frac{\mu(S^0 - S)(S - \tilde{S})}{S} - (S - \tilde{S})\beta_2 J \\
&= -\beta_2(S - \tilde{S})\tilde{J} + \frac{\mu(S^0 - S)(S - \tilde{S})}{S} \\
&= -\frac{S - \tilde{S}}{S}\left(S\beta_2\tilde{J} - \mu(S^0 - S)\right) = -\frac{S - \tilde{S}}{S}\left((\beta_2\tilde{J} + \mu)S - \mu S^0\right) \\
&= -\frac{S - \tilde{S}}{S}\left(\frac{\mu S^0}{\tilde{S}}S - \mu S^0\right) = -\frac{\mu S^0(S - \tilde{S})^2}{\tilde{S}S} \le 0.
\end{aligned}$$

The maximum invariant subset of the set $\left\{(S, I, J) \;\middle|\; \frac{dV}{dt} = 0\right\}$ in the hyperplane $I = 0$ contains only E_1. Then it follows from the LaSalle invariance principle that E_1 is globally asymptotically stable on the hyperplane $I = 0$. □

Note that we have not been able to prove the global stability of the boundary equilibrium E_1 for the case $1 < R_1 < R_2$.

6.2. Hopf bifurcation near the endemic equilibrium. We know from Theorem 6.1 that if $R_2 < 1 < R_1$ or $1 < R_2 < R_1$, the boundary equilibrium either does not exist or is unstable, and the positive endemic equilibrium is asymptotically stable if $c_2k^2 + c_1k + c_0 > 0$ and is unstable if $c_2k^2 + c_1k + c_0 < 0$. We now show that as the

endemic equilibrium loses stability, periodic solutions can bifurcate from the endemic equilibrium.

To investigate the bifurcation and to simplify the mathematical analysis, we study the bifurcation in terms of the mutation rate k and the two basic reproductive numbers R_1 and R_2 and assume that individuals infected by the two strains have the same recovery rate $\gamma_1 = \gamma_2 := \gamma$, and hence $\sigma_1 = \sigma_2 := \sigma$. Under these assumptions, and after some tedious algebraic manipulations, (6.6) becomes

(6.8)
$$a_1a_2 - a_3 = \mu(R_1 - 1)(R_1 - R_2)\Big(\mu - \frac{\sigma R_2}{R_1^2}\Big)k + \sigma\mu^2 R_1(2R_1 - R_2 - 1) + \frac{\mu\sigma^2(R_1 - R_2)^2}{R_1}.$$

All terms in (6.8) are positive except $\mu - \sigma R_2/R_1^2$. If $\mu R_1^2 \geq \sigma R_2$, then $a_1a_2 > a_3$. It follows from the Routh–Hurwitz criterion that the endemic equilibrium E^* is locally asymptotically stable.

Suppose $\mu R_1^2 < \sigma R_2$. We define a critical number k_0 as

$$k_0 = \frac{\sigma\mu R_1^3(2R_1 - R_2 - 1) + \sigma^2(R_1 - R_2)^2 R_1}{(R_1 - 1)(R_1 - R_2)(\sigma R_2 - \mu R_1^2)} \tag{6.9}$$

such that E^* is locally asymptotically stable if $k < k_0$ and is unstable if $k > k_0$. For $k = k_0$, the characteristic equation (6.5) for the linearization of system (6.1) has two pure imaginary roots. The parameter k can be used as a bifurcation parameter such that as k passes through k_0, a Hopf bifurcation occurs and a periodic solution bifurcates from the endemic equilibrium.

The reproductive numbers R_1 and R_2 can also be used as bifurcation parameters. Rewrite $a_1a_2 - a_3$ as a quadratic function of $R_1 - R_2$:

$$a_1a_2 - a_3 = \mu d_2(R_1 - R_2)^2 + \mu d_1(R_1 - R_2) + \mu d_0,$$

where

$$\begin{aligned} d_0 &:= \sigma\mu R_1(R_1 - 1), \\ d_1 &:= (R_1 - 1)(\mu - \sigma/R_1)k + \sigma\mu R_1, \\ d_2 &:= \sigma^2/R_1 + \sigma(R_1 - 1)k/R_1^2. \end{aligned}$$

Fixing R_1 and then solving the equation $d_2(R_1 - R_2)^2 + d_1(R_1 - R_2) + d_0 = 0$ for R_2 yields the two solutions

$$R_2^+ = R_1 + \frac{d_1 + \sqrt{d_1^2 - 4d_2d_0}}{2d_2}, \qquad R_2^- = R_1 + \frac{d_1 - \sqrt{d_1^2 - 4d_2d_0}}{2d_2}.$$

For $R_1 > 1$, $d_2 > 0$ and $d_0 > 0$. If $R_1 > R_2$ and $d_1^2 < 4d_2d_0$, the inequality $a_1a_2 - a_3 > 0$ always holds. The endemic equilibrium, E^*, is locally asymptotically stable. If $d_1^2 > 4d_2d_0$, E^* is locally asymptotically stable provided $0 < R_2 < R_2^-$ or $R_2^+ < R_2 < R_1$ and is unstable provided $R_2^- < R_2 < R_2^+$. As R_2 passes through R_2^- or R_2^+, periodic solutions bifurcate from the endemic equilibrium.

The dynamics of system (6.1) are summarized, based on R_1 and R_2, in Figure 1. We divide the R_1-R_2 plane into five regions. In Region I, $R_1 < 1$ and $R_2 < 1$. The infection-free equilibrium, E_0, is the only equilibrium and is globally asymptotically stable. In both Regions II and III, the boundary equilibrium, E_1, is globally asymptotically stable, whereas the endemic equilibrium, E^*, does not exist in Region II

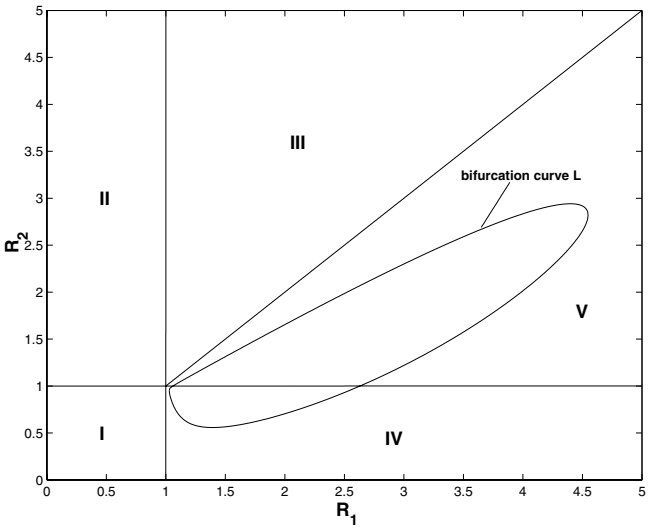

FIG. 1. *Schematic illustrations of dynamical behavior of system* (6.1) *based on the reproductive numbers,* R_1 *and* R_2*. The infection-free equilibrium,* E_0*, is the only equilibrium in Region* I *and is globally asymptotically stable. The boundary equilibrium,* E_1*, exists in Regions* II, III, *and* V*. It is globally asymptotically stable in both Regions* II *and* III *but is unstable in Region* V*. The endemic equilibrium,* E^**, exists in Regions* III, IV, *and* V*. It is unstable in Region* III *and in the interior of the region enclosed by the bifurcation curve* L*. It is locally asymptotically stable in the complement of the region enclosed by curve* L *in* IV *and* V*. For a fixed* R_1 *in the interval of the projection of curve* L *on the* R_1*-axis, as* R_2 *crosses through curve* L*, periodic solutions are bifurcated.*

and exists but is unstable in Region III. While E^* exists in both Regions IV and V and is the only nontrivial equilibrium in Region IV, and E_1 exists but is unstable in Region V, the stability of E^* is determined by the closed bifurcation curve L in these two regions. E^* is unstable and a Hopf bifurcation takes place in the interior of the region enclosed by L. E^* is asymptotically stable elsewhere in Regions IV and V.

We illustrate these results by examples using k, or R_1 and R_2, as bifurcation parameters.

Example 6.1. We use k as a bifurcation parameter and let $\sigma_1 = \sigma_2 = 1/2$, $\mu = 1/100$, $R_1 = 3$, and $R_2 = 2$. System (6.1) becomes

$$\begin{aligned} \frac{dS}{dt} &= \frac{1}{100}(S^0 - S) - \left(\frac{3+6k}{2S^0}I + \frac{1}{S^0}J\right)S, \\ \frac{dI}{dt} &= \frac{3+6k}{2S^0}SI - \frac{1+2k}{2}I, \\ \frac{dJ}{dt} &= \frac{1}{S_0}SJ - \frac{1}{2}J + kI \end{aligned} \tag{6.10}$$

and has the endemic equilibrium

$$E^* = \left(\frac{S^0}{3}, \frac{S^0}{75(1+6k)}, \frac{2kS^0}{25(1+6k)}\right) = (S^*, I^*, J^*).$$

The linearization of system (6.10) at E^* has the characteristic equation

$$f(\rho) = \rho^3 + \frac{59}{300}\rho^2 + \left(\frac{k}{150} + \frac{3}{200}\right)\rho + \frac{k}{300} + \frac{1}{600} = 0. \tag{6.11}$$

The critical number k_0 defined in (6.9) can be determined as $k_0 = 33/52$. Then, if $k < 33/52$, all roots of (6.11) have negative real part, and hence the endemic equilibrium of (6.10) is stable. If $k > 33/52$, there exist two roots with positive real part, and hence the endemic equilibrium of system (6.10) is unstable. For $k = 33/52$, (6.11) has a negative real root and two pure imaginary conjugates:

$$\rho_1 = -\frac{59}{300}, \quad \rho_2 = \frac{\sqrt{13}}{26}i, \quad \rho_3 = -\frac{\sqrt{13}}{26}i.$$

For k greater than, but near $33/52$, (6.11) has a negative real root $\rho_1(k)$ and a pair of complex conjugates $\rho_2(k) = \bar{\rho}_3(k) := \xi(k) + i\eta(k)$. Substituting the complex conjugates into (6.11) and then separating the real and imaginary parts yields the equations for $\xi(k)$ and $\eta(k)$:

$$\begin{aligned} &\xi^3 - 3\xi\eta^2 + \frac{59}{300}\xi^2 - \frac{59}{300}\eta^2 + \frac{k}{150}\xi + \frac{3}{200}\xi + \frac{k}{300} + \frac{1}{600} = 0, \\ &3\xi^2\eta - \eta^3 + \frac{59}{150}\xi\eta + \frac{k}{150}\eta + \frac{3}{200}\eta = 0. \end{aligned} \tag{6.12}$$

By differentiating (6.12) with respect to k, we have

$$\begin{aligned} &\left(3\xi^2 - 3\eta^2 + \frac{59}{150}\xi + \frac{k}{150} + \frac{3}{200}\right)\frac{d\xi}{dk} - \left(6\xi\eta + \frac{59}{150}\eta\right)\frac{d\eta}{dk} + \frac{1}{150}\xi + \frac{1}{300} = 0, \\ &\left(6\xi\eta + \frac{59}{150}\eta\right)\frac{d\xi}{dk} + \left(3\xi^2 - 3\eta^2 + \frac{59}{150}\xi + \frac{k}{150} + \frac{3}{200}\right)\frac{d\eta}{dk} + \frac{1}{150}\eta = 0. \end{aligned} \tag{6.13}$$

Solving (6.13) for $d\xi/dk$ and substituting $k = 33/52$, $\xi = 0$, and $\eta = \sqrt{13}/26$ into the expression of $d\xi/dk$ yields $d\xi/dk = 169/9679 > 0$. Therefore, system (6.10) undergoes a Hopf bifurcation and a periodic solution is bifurcated near $k = 33/52$.

To determine the bifurcation direction, we first discuss the stability of the endemic equilibrium of system (6.10) as $k = 33/52$. Let $x_1 = S - S^*$, $y_1 = I - I^*$, and $z_1 = J - J^*$ to transform the endemic equilibrium to the origin of a new system. Using the linear transformation

$$\begin{aligned} x_1 &= \frac{3125\sqrt{13}}{767}y - \frac{125}{6}z, \\ y_1 &= x + z, \\ z_1 &= \frac{639}{236}x - \frac{1125\sqrt{13}}{3068}y - \frac{539}{39}z, \end{aligned}$$

and rescaling $t = 2\sqrt{13}\,\hat{t}$, we transform the resulting system into

$$\begin{aligned} \frac{dx}{d\hat{t}} &\approx y + 319.95\left(S^0\right)^{-1}xy - 453.74\left(S^0\right)^{-1}xz - 6.93\left(S^0\right)^{-1}y^2 \\ &\quad + 243.20\left(S^0\right)^{-1}yz - 330.96\left(S^0\right)^{-1}z^2, \\ \frac{dy}{d\hat{t}} &\approx -x + 13.55\left(S^0\right)^{-1}xy - 19.22\left(S^0\right)^{-1}xz + 19.36\left(S^0\right)^{-1}y^2 \\ &\quad + 228.07\left(S^0\right)^{-1}yz - 362.37\left(S^0\right)^{-1}z^2, \\ \frac{dz}{d\hat{t}} &\approx -1.42z + 40.63\left(S^0\right)^{-1}xy - 57.62\left(S^0\right)^{-1}xz + 6.93\left(S^0\right)^{-1}y^2 \\ &\quad + 117.39\left(S^0\right)^{-1}yz - 180.40\left(S^0\right)^{-1}z^2. \end{aligned} \tag{6.14}$$

The nonlinear terms of the right-hand side of system (6.14) are quadratic and satisfy the existence conditions of the center manifold theorem [4, 12]. Hence, there exists a manifold $z = h(x, y)$ of system (6.14) which can be expanded as

$$z = h_{20}x^2 + h_{11}xy + h_{02}y^2 + o(r^2), \quad r = \sqrt{x^2 + y^2}, \tag{6.15}$$

where $o(r^2)$ denotes higher order terms and h_{ij} are to be determined.

Substituting (6.15) into system (6.14), we obtain

$$h_{20} = 8.38\left(S^0\right)^{-1}, \quad h_{11} = 11.89\left(S^0\right)^{-1}, \quad h_{02} = -3.50\left(S^0\right)^{-1}.$$

Substituting (6.15) with these h_{ij} again into the first two equations of system (6.14), we have the following equations on the center manifold:

(6.16)

$$\begin{aligned}
\frac{dx}{d\hat{t}} &= y - 6.93\left(S^0\right)^{-1} y^2 + 319.95\left(S^0\right)^{-1} xy - 3802.35\left(S^0\right)^{-2} x^3 - 3357.04\left(S^0\right)^{-2} x^2 y \\
&\quad + 4479.62\left(S^0\right)^{-2} xy^2 - 851.17\left(S^0\right)^{-2} y^3 + o(r^3), \\
\frac{dy}{d\hat{t}} &= -x + 13.55\left(S^0\right)^{-1} xy + 19.36\left(S^0\right)^{-1} y^2 - 161.06\left(S^0\right)^{-2} x^3 \\
&\quad + 1682.70\left(S^0\right)^{-2} x^2 y + 2779.06\left(S^0\right)^{-2} xy^2 - 798.25\left(S^0\right)^{-2} y^3 + o(r^3).
\end{aligned}$$

Consider the function

$$\begin{aligned}
V(x, y) = x^2 + y^2 &- 239.10\left(S^0\right)^{-1} x^3 - 38.71\left(S^0\right)^{-1} xy^2 + 4.42\left(S^0\right)^{-1} y^3 \\
&+ 59133.80\left(S^0\right)^{-2} x^4 - 6381.38\left(S^0\right)^{-2} x^3 y - 151.46\left(S^0\right)^{-2} xy^3 \\
&- 2462.13\left(S^0\right)^{-2} y^4.
\end{aligned}$$

It is positive definite in a small neighborhood of the origin. Along the trajectories of system (6.16),

$$\left.\frac{dV(x, y)}{dt}\right|_{(6.16)} = -1223.33\left(S^0\right)^{-2}(x^2 + y^2)^2 + o(r^4) < 0.$$

Therefore, V is a Lyapunov function for system (6.16) and the trivial solution of system (6.16) is asymptotically stable. It follows from the reducible principle of the center manifold theorem that the trivial solution of system (6.14), and hence the endemic equilibrium of system (6.10), is asymptotically stable for $k = 33/52$. Since the endemic equilibrium is unstable for $k > 33/52$, it follows from the Hopf bifurcation theorem that there exists a stable periodic solution in the neighborhood of the endemic equilibrium of system (6.10).

We illustrate the stable endemic equilibrium ($k < k_0$) and the stable periodic solutions ($k > k_0$) in Figures 2 and 3. In Figure 2, $k = 0.135 < k_0 = 0.6346$, and the endemic equilibrium $E^* = (3.3363, 0.0074, 0.0059)$ is asymptotically stable. In Figure 3, $k = 0.9846 > k_0 = 0.6346$, and the endemic equilibrium E^* is unstable. The solutions quickly converge to the stable periodic solution.

Example 6.2. In this example, we use R_1 and R_2 as bifurcation parameters. Let

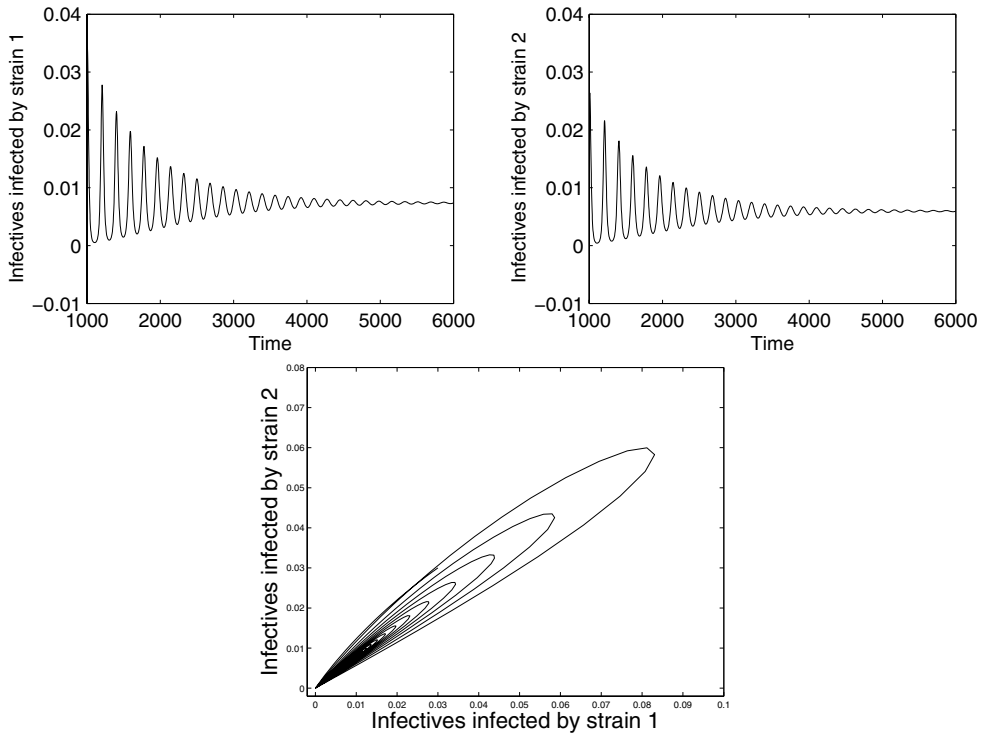

FIG. 2. *The solutions of system* (6.1) *for* $\mu = 0.01$, $\gamma_1 = \gamma_2 = 0.49$, $R_1 = 3$, *and* $R_2 = 2$. *The mutation rate* $k = 0.135$ *is used as a bifurcation parameter and is less than the critical value* $k_0 = 33/52$. *The endemic equilibrium* $(3.3363, 0.0074, 0.0059)$ *is asymptotically stable. The top two figures are the solutions of* I *and* J *versus time* t. *The bottom figure is the projected* I-J *phase plane of the phase space.*

$\sigma_1 = \sigma_2 = 1/10$, $\mu = 1/100$, and $k = 9/10$ in system (6.1), so that we have

$$\begin{aligned} \frac{dS}{dt} &= \frac{1}{100}(S^0 - S) - \left(\frac{R_1}{S^0}I + \frac{R_2}{10S^0}J\right)S, \\ \frac{dS}{dt} &= \frac{R_1}{S^0}SI - I, \\ \frac{dS}{dt} &= \frac{R_2}{10S_0}SJ - \frac{1}{10}J + \frac{9}{10}I. \end{aligned} \tag{6.17}$$

In region $D := \{(R_1, R_2) \mid R_1 > R_2,\ R_1 > 1\}$, the endemic equilibrium of system (6.17) is given by

$$E^* = \left(\frac{S^0}{R_1}, \frac{S^0(R_1 - 1)(R_1 - R_2)}{10(10R_1 - R_2)R_1}, \frac{9S^0(R_1 - 1)}{10(10R_1 - R_2)}\right).$$

The characteristic equation of the linearization of system (6.17) at E^* is

$$f(\rho) = \rho^3 + a_1\rho^2 + a_2\rho + a_3 = 0, \tag{6.18}$$

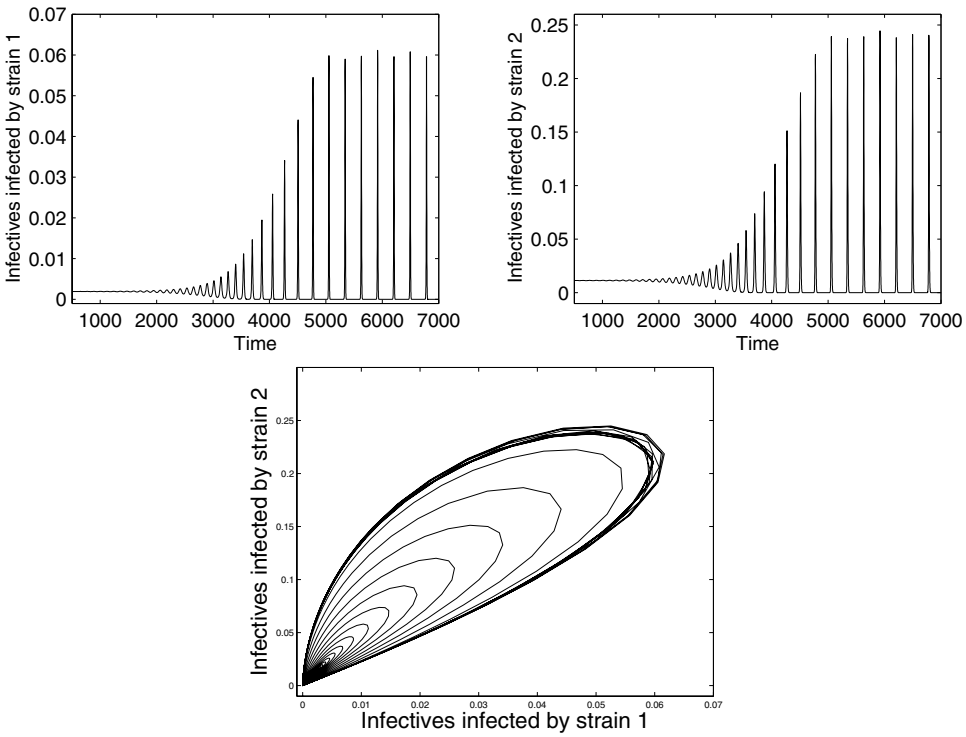

FIG. 3. *All parameters are the same as those in Figure* 2*, except the mutation rate* $k = 0.9846$ *is greater than the critical value* $k_0 = 33/52$*. The endemic equilibrium is unstable and a stable periodic solution is bifurcated from the endemic equilibrium. The top two figures show how the solutions with initial values near the unstable endemic equilibrium rapidly converge to the stable periodic solution. This can be also seen in the bottom figure of the I-J phase plane.*

where

$$a_1 = \frac{R_1^2 + 10R_1 - 10R_2}{100R_1},$$
$$a_2 = \frac{11R_1^2 - 10R_1R_2 - 10R_1 + 9R_2}{1000R_1},$$
$$a_3 = \frac{(R1-1)(R1-R2)}{1000R_1}.$$

E^* is asymptotically stable if

$$a_1a_2 - a_3 = \frac{100R_2^2R_1 - 90R_2^2 - 101R_2R_1^2 + 90R_1R_2 - 10R_1^3R_2 + 11R_1^4}{100000R_1^2} > 0. \tag{6.19}$$

Define function $H(R_2)$ as the numerator in (6.19). Then

$$H(R_2) = (100R_1 - 90)\,R_2^2 - \left(10R_1^3 + 101R_1^2 - 90R_1\right)R_2 + 11R_1^4.$$

The two zeros $R_2^{(1)} < R_2^{(2)}$, for R_1 and R_2, are in D, if

$$Q(R_1) := \left(10R_1^3 + 101R_1^2 - 90R_1\right)^2 - 44R_1^4\,(100R_1 - 90) > 0.$$

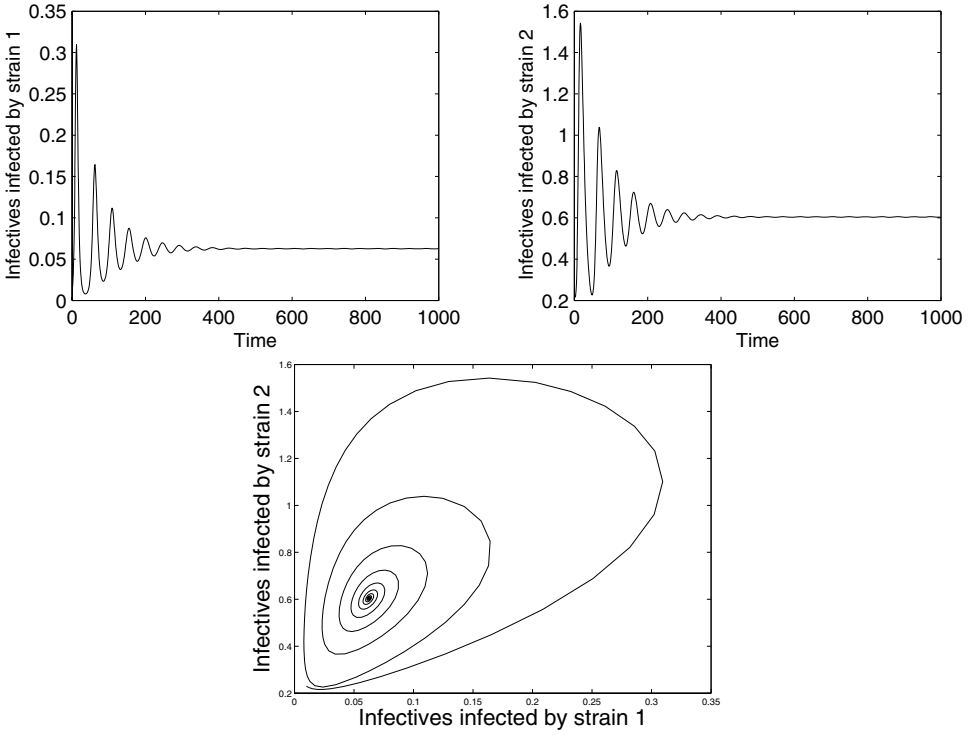

FIG. 4. *The reproductive numbers R_1 and R_2 are used as bifurcation parameters. The parameters $R_1 = 3$, $R_2^{(1)} = 1.5$, and $R_2 = 0.2$ are chosen so that $R_2 < R_2^{(1)}$. Then R_1 and R_2 are in Region* IV *in Figure* 1. *The endemic equilibrium exists and is asymptotically stable.*

Numerical computations verify that $Q(R_1)$ has two zeros, $R_1^{(1)} < R_1^{(2)}$, in the intervals $(1.01, 1.04)$ and $(4.50, 4.60)$, respectively. If $R_1 < R_1^{(1)}$ or $R_1 > R_1^{(2)}$, then $Q(R_1) < 0$, and if $R_1^{(1)} < R_1 < R_1^{(2)}$, then $Q(R_1) > 0$.

Suppose $R_1 < R_1^{(1)}$ or $R_1 > R_1^{(2)}$. Then $Q(R_1) < 0$ and $H(R_2)$ is always positive. If $R_1^{(1)} < R_1 < R_1^{(2)}$, then $Q(R_1) > 0$ and there are two zeros of $H(R_1)$, $R_2^{(1)} < R_2^{(2)}$ in D. If, moreover, $R_2 < R_2^{(1)}$ or $R_2 > R_2^{(2)}$, then $H(R_2) > 0$. Hence, in either case, $H(R_2) > 0$ and E^* is asymptotically stable. However, if $R_1^{(1)} < R_1 < R_1^{(2)}$ but $R_2^{(1)} < R_2 < R_2^{(2)}$, then $H(R_2) < 0$, for R_2 in D, and the endemic equilibrium is unstable.

For each R_1 in the interval $(R_1^{(1)}, R_1^{(2)})$, E^* changes its stability as R_2 increases from 0 to R_1. E^* is stable for R_2 in $(0, R_2^{(1)})$, unstable for R_2 in $(R_2^{(1)}, R_2^{(2)})$, and stable again for R_2 in $(R_2^{(2)}, R_1)$. At $R_2 = R_2^{(1)}$ or $R_2 = R_2^{(2)}$, the roots of characteristic equation (6.18) are imaginary indicating the existence of a periodic solution by Hopf bifurcation theory.

In numerical simulations, we fix $R_1 = 3$. The two roots of $H(R_2) = 0$ are $R_2^{(1)} = 3/2$ and $R_2^{(2)} = 99/35$. The characteristic roots of (6.18), with $R_2^{(1)} = 3/2$, are $\rho = -2/25$, $\rho = \sqrt{5}/20i$, and $\rho = -\sqrt{5}/20i$. The characteristic roots of (6.18), for $R_2^{(2)} = 99/35$, are $\rho = -1/28$, $\rho = \sqrt{2}/25i$, and $\rho = -\sqrt{2}/25i$.

In Figure 4, $\beta_1 = 0.3$ and $\beta_2 = 0.002$, and $R_2 = 0.2 < R_2^{(1)}$. The endemic equilib-

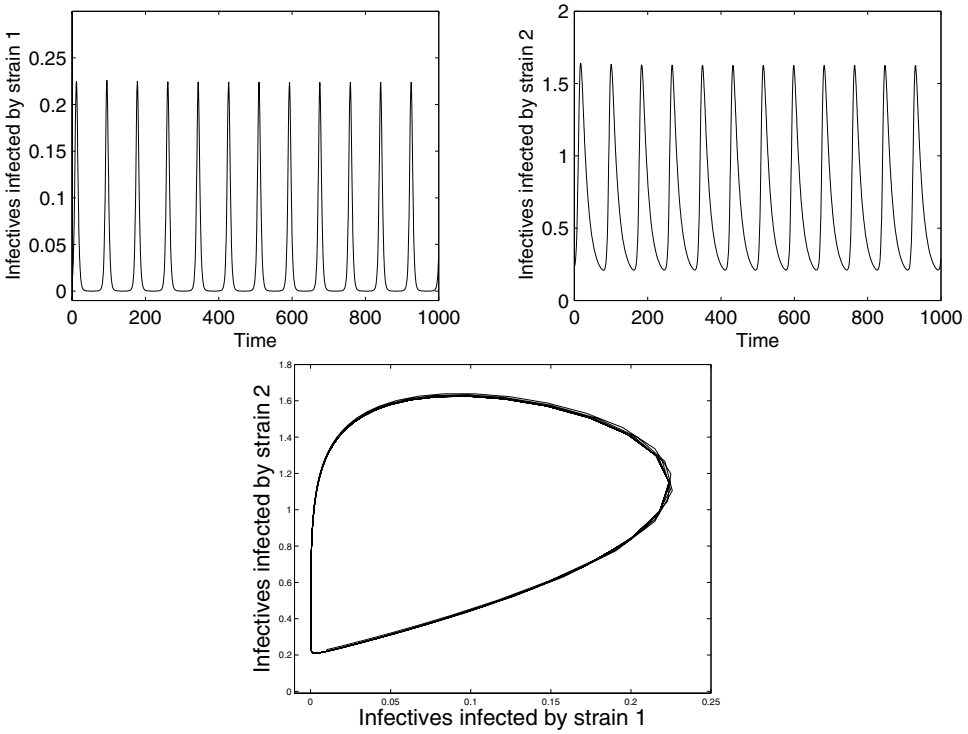

FIG. 5. *The parameters are chosen as in Figure* 4*, except* $R_2 = 2$ *by increasing* β_2 *to* 0.02 *whereas* $\beta_2 = 0.002$ *in Figure* 4*. Then* $R_2^{(1)} < R_2 < R_2^{(2)} = 2.829$*, and* R_1 *and* R_2 *are in the interior of the region enclosed by the bifurcation curve L, in Figure* 1*. The endemic equilibrium loses its stability. A periodic solution is bifurcated and is asymptotically stable.*

rium $E^* = (3.3348, 0.02627, 0.6032)$ is locally asymptotically stable, as is shown. We then increase β_2 to 0.02 so that $R_2 = 2$, which is between $R_2^{(1)}$ and $R_2^{(2)}$. The endemic equilibrium loses its stability and a periodic solution is bifurcated from the endemic equilibrium, as is shown in Figure 5. We continue increasing β_2 to 0.0286 such that $R_2 = 2.8571 > R_2^{(2)}$. The periodic solution disappears and the endemic equilibrium, $E^* = (3.3358, 0.0035, 0.6621)$, regains its stability, as is shown in Figure 6.

7. Concluding remarks. One of the challenges in modeling the spread of infectious diseases is to understand and predict the spread of competing strains of the same pathogen. After a strain of a pathogen infects a host, the mutation can be caused by an attempt of a pathogen to evade the immune defense of the host, the effect of selective immunologic pressure, or possibly adaptation to a more efficiently transmitted or better replicating pathogen.

We have formulated a simple compartmental mathematical model for the competition, mutation, and spread of a pathogen and its mutant strain. The model accounts for a continuous infection-age structure for the original pathogen, and the mutation rate of the pathogen depends on how long the host has been infected.

We model the transmission dynamics of pathogens by a system of partial differential-integral equations. We established conditions for the existence and stability of the infection-free equilibrium, the boundary equilibrium, and the endemic equilibrium. We derived formulas for the reproductive numbers, R_1 and R_2, for the two strains

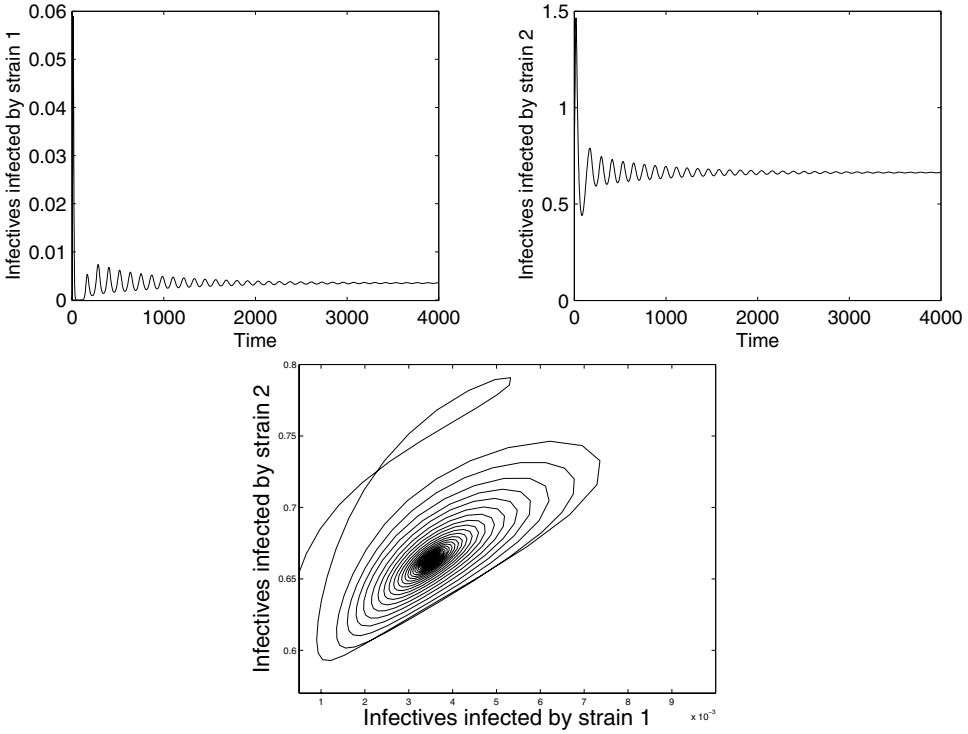

FIG. 6. *The parameters are chosen as in Figure* 4 *except* $\beta_2 = 0.0286$ *so that* $R_2 = 2.857 > R_2^{(2)}$. *Then* R_1 *and* R_2 *are in Region* V *and above the region enclosed by the bifurcation curve* L. *The endemic equilibrium regains its stability.*

based on the local stability of the infection-free equilibrium. We established the conditions for existence of the boundary equilibrium, E_1, where only one strain of the pathogen is in circulation, and the endemic equilibrium, E^*, where both the strain and its mutant are in circulation. We obtained stability conditions for E_1. These conditions, listed in Table 1, are expressed in terms of the two reproductive numbers. We investigated the stability of E^* and derived the characteristic equation of the linearization about E^*. The roots of this transcendental equation determine the stability of E^*.

To gain insight into transmission dynamics of the diseases with mutating strains, we simplified the model to make it more analytically tractable. By assuming the pathogen mutates with a constant rate, the PDE system is reduced into a system of ODEs. For pathogens with a constant mutation rate, we extended the local stability results for the infection-free and boundary equilibria of the ODE system, to prove that if $R_0 < 1$, E_0 is not only locally but also globally asymptotically stable. We also proved that if $R_1 < 1 < R_2$, then E_1 is globally asymptotically stable.

We established explicit conditions for the stability of the endemic equilibrium E^* when the mutation rate is constant. Furthermore, we identified the regions for the parameters where E^* loses its stability and periodic solutions bifurcate from E^*. For the special case where the two strains have the same recovery rate, we proved Hopf bifurcations using either the mutation rate, k, or the reproductive numbers, R_1 and R_2, as bifurcation parameters.

For the case where $R_1 = 3 > R_2 = 2 > 1$, we used k as a bifurcation parameter and identified regions where E_0 and E_1 are both unstable. In Example 6.1, we established a critical value, k_0, such that if $k < k_0$, the endemic equilibrium is asymptotically stable, and if $k > k_0$, the endemic equilibrium is unstable and periodic solutions appear through a Hopf bifurcation. We presented numerical simulations to illustrate that if both reproductive numbers exceed the threshold value, then the mutant cannot completely wipe out the original pathogen strain. We also showed that if the mutation rate is below the critical value, k_0, the two strains can coexist and eventually stay at a constant steady state level. On the other hand, if the mutation rate is above the critical value, k_0, there can be sustained periodic oscillations of the two pathogen strains. This phenomenon may furnish us with an interpretation of periodic appearance of pathogen strains of some diseases, such as influenza, and can provide useful guidance for disease intervention programs. Note that in this example we fixed R_2. Since R_2 is a function of the mutation rate, k, as we vary k we must also adjust the infection rate β_2 in the bifurcation analysis.

We also used R_1 and R_2 as bifurcation parameters, while fixing other parameters, including the mutation rate. Figure 1 illustrates the regions in the R_1-R_2 plane where the equilibria have different dynamics. We identified a closed bifurcation curve, L, for $R_1^{(1)} < R_1 < R_1^{(2)}$, where if R_1 and R_2 are within the curve, the endemic solution is periodic. We showed that for R_1 in the interval $(R_1^{(1)}, R_1^{(2)})$, as R_2 increases and passes through curve L, the stable steady state equilibrium changes its stability and becomes unstable. As R_2 continues to increase and passes through curve L the second time, the steady state equilibrium regains its stability. That is, the curve L identifies the parameter values where the solution undergoes a Hopf bifurcation.

Example 6.2 illustrates the Hopf bifurcation for $R_1^{(1)} < R_1 < R_1^{(2)}$. In Figure 4, (R_1, R_2) is outside the region enclosed by L with R_2 below L. In this case, the endemic equilibrium is asymptotically stable and the two strains eventually coexist at a steady state level with $I^* = 0.0035$. Figure 5 shows how when (R_1, R_2) is within the L the endemic solutions are periodic. In Figure 6, (R_1, R_2) are again outside L, but R_2 is above L. Once again, the two strains can coexist, but the steady state level $I^* = 0.02627$ is much higher than in Figure 4 because the mutant in the latter case has a larger reproductive number.

These examples illustrate the wide range of behavior that can exist when a pathogen mutates in the host to create a second infectious mutant strain. The explicit formulas for the reproductive numbers and the detailed analysis for the existence and stability of the boundary equilibrium can provide insight into the complexity of these epidemics. For the simplified cases where the mutation rate is not infection-age dependent, we were able to establish conditions for the global stability of the infection-free and boundary equilibria. Our analysis of the situation where the steady state equilibrium loses its stability through a Hopf bifurcation, and periodic solutions appear, may also help in understanding similar transitions in epidemics with mutating pathogens.

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