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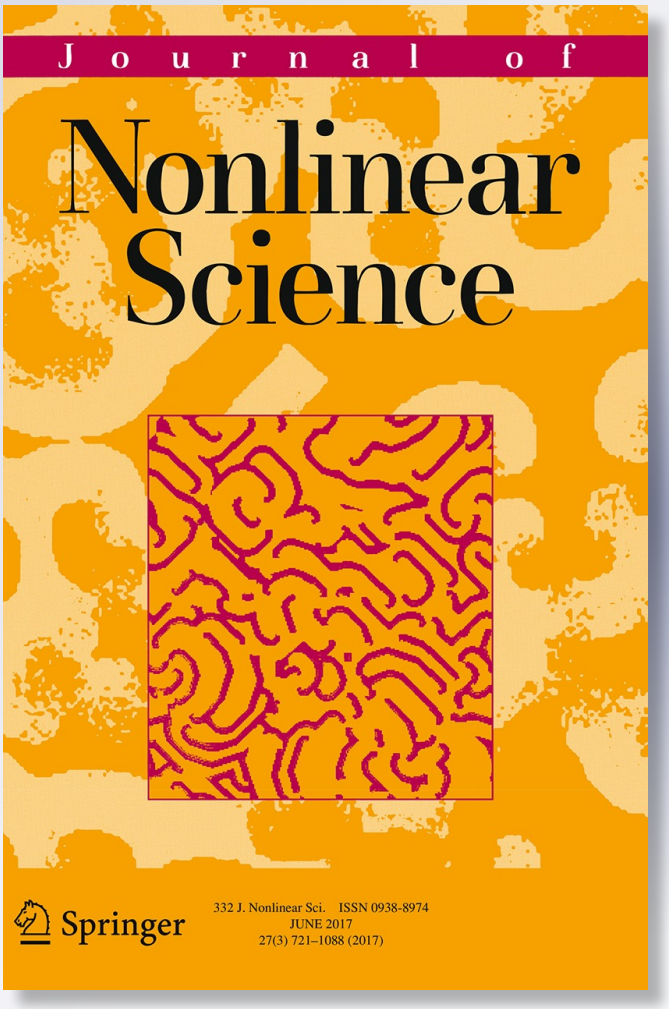

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The Impact of Prophage on the Equilibria and Stability of Phage and Host

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Abstract In this paper, we present a bacteriophage model that includes prophage, that is, phage genomes that are incorporated into the host cell genome. The general model is described by an 18-dimensional system of ordinary differential equations. This study focuses on asymptotic behaviour of the model, and thus the system is reduced to a simple six-dimensional model, involving uninfected host cells, infected host cells and phage. We use dynamical system theory to explore the dynamic behaviour of the model, studying in particular the impact of prophage on the equilibria and stability of phage and host. We employ bifurcation and stability theory, centre manifold and normal form theory to show that the system has multiple equilibrium solutions which undergo a series of bifurcations, finally leading to oscillating motions. Numerical simulations are presented to illustrate and confirm the analytical predictions. The results of this study indicate that in some parameter regimes, the host cell population may drive the phage to extinction through diversification, that is, if multiple types of host emerge; this prediction holds even if the phage population is likewise diverse. This parameter regime is restricted, however, if infecting phage are able to recombine with prophage sequences in the host cell genome.

Keywords SIV model · Bacteriophage · Equilibria · Stability · Hopf bifurcation

Mathematics Subject Classfication 92D30 · 37L10 · 37N25

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1 Introduction

Bacteriophage, viruses that infect bacteria, are the most abundant life form on the Earth, with recent estimates of over 10^{30} viral particles on the planet, largely in marine ecosystems (Hendrix 2002). In particular, phage are believed to outnumber bacterial host cells by about ten to one (Hendrix 2002). The analysis of sequenced prokaryote genomes, however, has revealed another substantial reservoir of phage genetic material: many bacterial species carry between seven and twenty phage genomes within their bacterial DNA (Casjens 2003). This implies that the number of phage genomes inside host cell DNA is of the same order of magnitude as the number of phage genomes (individual free phage) in the environment.

Phage genetic material in bacterial DNA is typically the result of infection by *temperate* bacteriophage. While both temperate and virulent phage have the ability to infect and kill their bacterial host cells, temperate phage have the additional ability to integrate their genetic code into the host cell DNA, leaving the host otherwise unharmed (Stewart and Levin 1984). The phage genome is then replicated when the host cell undergoes fission, and both daughter cells carry a copy of the phage genome. Bacterial cells that carry phage genomes in their DNA are referred to as lysogens.

The copies of phage genetic material carried in bacterial genomes are called prophage, indicating that in future, for example under stressful conditions or when the host cell experiences DNA damage (Stewart and Levin 1984), prophage sequences may be induced to produce phage. During this induction process, the prophage sequence sets in motion the process of killing the lysogen and releasing a large number of viral particles.

The impact of prophage on the evolutionary dynamics of bacteria and phage is particularly intruiguing because of the possibility of recombination. Through this process, newly infecting phage can exchange genetic material with pre-existing prophage in the host cell genome. This process has been well-documented in lactococcal phages in particular (Moineau et al. 1994; Bouchard and Moineau 2000; Durmaz and Klaenhammer 2000; Labrie and Moineau 2007), but has also been recently observed in the most well-studied phage-host system, bacteriophage Lamdba and *E. coli* (Meyer et al. 2012). In one instance, phage Lambda acquired an entirely new protein, a tail fibre, from a prophage sequence in the host genome (Meyer, personal communication). In another, phage ul36 exchanged 79% of its genome with endogenous prophages in the host cell genome (Labrie and Moineau 2007).

This phenomenon raises some significant questions. If many bacterial cells carry the genetic record of seven to twenty previous infections, the bacterial genome carries a substantial arsenal of phage sequences that could be used against it in future. What are the implications of these prophage sequences on the evolutionary dynamics of hosts and phage? What effect does recombination with previous temperate phage have on the evolutionary arm's race? In this contribution, we begin to address these questions by developing a model of host cells and phage, including the possibility that phage in previous generations may leave genetic material in the host genome, as prophage, and that recombination may allow these genes to transfer back to the phage genome at a later time. The main aim of this study is to understand the importance of prophage, and to investigate the striking ability of the virus to use host cells as a time capsule, carrying

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information that may be detrimental to the host cell itself. Although the evolution of humans and their pathogens is clearly outside of the scope of this study, it is important to note that over 8% of the human genome consists of proviral DNA (Casjens 2003), and thus the possibility of carrying an arsenal of viral genes is certainly not limited to bacterial genomes.

In the next section, we develop a full model of host cells and phage, including the influence of prophage and the possibility of recombination. We then examine a reduced model which includes only those populations that may persist as $t \to \infty$. We non-dimensionalize this reduced model, and examine the existence and stability of the equilibria in the non-dimensionalized system. Finally, we investigate the effect of recombination by examining differences in the model behaviour when the recombination rate is set to zero. In the discussion, we highlight several interesting predictions of the model and explore their implications for temperate phages and their hosts.

2 The Model

The model we develop is an S-I-V type model based on a system of nonlinear ordinary differential equations. The model follows the population densities of uninfected bacterial hosts and infected hosts, as well as phage that may infect or lysogenize uninfected hosts.

In general, phage infect host cells through receptor proteins expressed on the surface of the host cell. The phage can only infect if it has a corresponding protein that will bind to the receptor; in tailed phage, for example, the virus carries a tail fibre that must match the host cell receptor in order to infect the cell. For simplicity, in our model each host carries one type of receptor on its surface, either type J or type K; each phage likewise has either a J- or K-type tail fibre, determining the receptor through which it can attach and thus which host cell population it can infect. The phage population densities are denoted P_J and P_K.

Once a phage has attached to the host, the host may become an infected host with probability $(1-p)$ or a lysogen with probability p. Lysogens are considered uninfected cells, but acquire the prophage corresponding to the type of phage that lysogenized them. Each type of uninfected host cell population can thus be written as H_{yz} where $y \in \{O, J, K, JK\}$ represents the type of prophage the cell is carrying (if any) and $z \in \{J, K\}$ represents the type of receptor it is expressing. This yields a total of eight types of uninfected host cells.

If an uninfected host becomes infected, it falls into one of the eight infected population types denoted by I_{yz}, where $y \in \{O, J, K, JK\}$ shows the type of prophage the infected host is carrying, and $z \in \{J, K\}$ defines which type of virus has infected it. We use N to denote the total density of all uninfected and infected cells, $N = \sum H_{yz} + \sum I_{yz}$.

The uninfected bacterial population grows logistically with maximum growth rate λ and carrying capacity K; all infected and uninfected host cells contribute to this carrying capacity. The death rate of uninfected host cells is denoted μ. The parameter β gives the infection rate, assuming mass action kinetics, for both P_J and P_K. Finally, the infected host cells do not reproduce but their death rate is given by δ.

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An infected cell that was infected by a particular type of phage produces phage of the same type, assuming it does not undergo recombination. A unique feature of this model, however, is that infected cells that carry prophage may undergo recombination to produce phage of the prophage type instead. Thus for example a cell of type H_{JK} carries prophage J and expresses receptor K. This cell can only be infected by P_k, and the resulting I_{JK} cell typically produces viral offspring of type P_K. However with probability r, recombination occurs between the infecting phage and the prophage within the bacterial DNA. In this case, the infected cell I_{JK} will produce viral offspring of type P_J.

We assume that infected cells produce new phage at a constant rate f, thus strictly our model captures budding viruses, not lysis in which a burst of phage is released simultaneously (Hubbarde et al. 2007). The clearance rate for the phage is d.

Finally, over evolutionary time, rare mutations allow the evolution of both host receptors and phage tail fibres (see Koskella and Brockhurst 2014 for a recent review). This allows for transitions: rare H_{JJ} individuals, for example, will diversify through mutation to become H_{JK}, expressing an alternate receptor. Likewise P_J can diversify to produce P_K individuals, a process that can require up to four rare mutational substitutions (Meyer et al. 2012).

These stochastic events could be modelled by including deterministic mutation terms in the population dynamics, however this approach has the serious drawback that rare mutational types would be continually generated at low densities – densities corresponding to a fraction of a cell or virus. Including these deterministic approximations in the model can substantially alter the predicted dynamics on realistic time scales, as demonstrated in the final section of the paper. Thus, we take a different approach. We assume that mutation terms are negligible in determining the population dynamics, equilibrium states and stability. However we acknowledge that over evolutionary time scales, these rare transitions do occur, and thus we allow for the existence of populations such as H_{JK}, which may have been produced through the diversification of H_{KK}. In a final section of the paper, we address the implications of diversification by exploring the impact of these rare mutational transitions on the population dynamics.

The complete set of model equations is as follows.

2.1 Uninfected Host Cells

$$
\begin{aligned}
\dot{H}_{OJ} &= \lambda H_{OJ}\left(1-\tfrac{N}{K}\right) - \mu H_{OJ} - \beta P_J H_{OJ},\\
\dot{H}_{OK} &= \lambda H_{OK}\left(1-\tfrac{N}{K}\right) - \mu H_{OK} - \beta P_K H_{OK},\\
\dot{H}_{JJ} &= \lambda H_{JJ}\left(1-\tfrac{N}{K}\right) - \mu H_{JJ} - \beta P_J H_{JJ} + p\beta P_J H_{OJ} + p\beta P_J H_{JJ},\\
\dot{H}_{KK} &= \lambda H_{KK}\left(1-\tfrac{N}{K}\right) - \mu H_{KK} - \beta P_K H_{KK} + p\beta P_K H_{OK} + p\beta P_K H_{KK},\\
\dot{H}_{KJ} &= \lambda H_{KJ}\left(1-\tfrac{N}{K}\right) - \mu H_{KJ} - \beta P_J H_{KJ},\\
\dot{H}_{JK} &= \lambda H_{JK}\left(1-\tfrac{N}{K}\right) - \mu H_{JK} - \beta P_K H_{JK},\\
\dot{H}_{JKJ} &= \lambda H_{JKJ}\left(1-\tfrac{N}{K}\right) - \mu H_{JKJ} - \beta P_J H_{JKJ} + p\beta P_J H_{KJ} + p\beta P_J H_{JKJ},
\end{aligned}
$$

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$$\dot{H}_{JKK} = \lambda H_{JKK}\left(1 - \frac{N}{K}\right) - \mu H_{JKK} - \beta P_K H_{JKK} + p\beta P_K H_{JK} + p\beta P_K H_{JKK}, \tag{2.1}$$

where the dot represents differentiation with respect to time t.

2.2 Infected host cells

$$\begin{aligned}
\dot{I}_{OJ} &= (1-p)\beta P_J H_{OJ} - \delta I_{OJ}, & \dot{I}_{OK} &= (1-p)\beta P_K H_{OK} - \delta I_{OK},\\
\dot{I}_{JJ} &= (1-p)\beta P_J H_{JJ} - \delta I_{JJ}, & \dot{I}_{KK} &= (1-p)\beta P_K H_{KK} - \delta I_{KK},\\
\dot{I}_{KJ} &= (1-p)\beta P_J H_{KJ} - \delta I_{KJ}, & \dot{I}_{JK} &= (1-p)\beta P_K H_{JK} - \delta I_{JK},\\
\dot{I}_{JKJ} &= (1-p)\beta P_J H_{JKJ} - \delta I_{JKJ}, & \dot{I}_{JKK} &= (1-p)\beta P_K H_{JKK} - \delta I_{JKK}.
\end{aligned} \tag{2.2}$$

2.3 Phage

$$\begin{aligned}
\dot{P}_J &= (I_{OJ} + I_{KJ} + I_{JJ} + I_{JKJ})(1-r)f + (I_{JK} + \tfrac{1}{2}I_{JKK}\\
&\quad + \tfrac{1}{2}I_{JKJ} + I_{JJ})rf - dP_J,\\
\dot{P}_K &= (I_{OK} + I_{JK} + I_{KK} + I_{JKK})(1-r)f + (I_{KJ}\\
&\quad + \tfrac{1}{2}I_{JKJ} + \tfrac{1}{2}I_{JKK} + I_{KK})rf - dP_K.
\end{aligned} \tag{2.3}$$

The $\frac{1}{2}$ accompanying the I_{JKK} and I_{JKJ} terms in the last two equations reflects the assumption that when recombination occurs in an infected cell containing both types of prophage, the probability that the infecting phage will recombine with the correct type of prophage to give a different tail fibre is $\frac{1}{2}$.

Using the primary experimental literature for *E. coli* and phage lambda, we have determined realistic parameter values for the system above, and are using this newly developed model to investigate the complex dynamics of temperate phage and prophage along several lines of enquiry. For the analytical work presented in this contribution, however, system (2.1)–(2.3) can be reduced by noting that if phage populations are nonzero, over time host cells acquire, but never lose, prophage. It is straightforward to show that in the limit as $t \to \infty$, all the host cells acquire both types of prophage in their DNA. For the analysis of equilibria and stability, therefore, we can neglect the transient dynamics of prophage acquisition, and focus on the populations remaining at this limit. We thus consider the following reduced model:

$$\begin{aligned}
&\textbf{Uninfected host cells}: \begin{cases}
\dot{H}_{JKJ} = \lambda H_{JKJ}\left(1 - \frac{N}{K}\right) - \mu H_{JKJ} - \beta P_J H_{JKJ} + p\beta P_J H_{KJ}\\
\qquad + p\beta P_J H_{JKJ},\\
\dot{H}_{JKK} = \lambda H_{JKK}\left(1 - \frac{N}{K}\right) - \mu H_{JKK} - \beta P_K H_{JKK} + p\beta P_K H_{JK}\\
\qquad + p\beta P_K H_{JKK};
\end{cases}\\
&\textbf{Infected host cells}: \begin{cases}
\dot{I}_{JKJ} = (1-p)\beta P_J H_{JKJ} - \delta I_{JKJ},\\
\dot{I}_{JKK} = (1-p)\beta P_K H_{JKK} - \delta I_{JKK};
\end{cases}\\
&\textbf{Phage}: \begin{cases}
\dot{P}_J = I_{JKJ}(1-r)f + \frac{1}{2}(I_{JKK} + I_{JKJ})rf - dP_J,\\
\dot{P}_K = I_{JKK}(1-r)f + \frac{1}{2}(I_{JKJ} + I_{JKK})rf - dP_K,
\end{cases}
\end{aligned} \tag{2.4}$$

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Table 1 Parameters for the phage-host system

P	Definition	Values	References
λ	Birth rate of host cells	27.36 day^{-1}	Suresh et al. (2009)
μ	Death rate of host cells	1.02 day^{-1}	Wang et al. (2010) and Manuel et al. (2014)
δ	Death rate of infected cells	27.27 day^{-1}	De Paepe and Taddei (2006)
d	Virus clearance rate	13.88 day^{-1}	De Paepe and Taddei (2006)
p	Probability with which virus becomes prophage	0.5	
r	Probability of recombination with prophage	0.0001	
β	Infection rate	1.5×10^{-6}ml virus^{-1}day^{-1}	Weitz et al. (2005)
f	Rate at which infected cells produce virus	144.6 virus cell^{-1} day^{-1}	De Paepe and Taddei (2006)
K	Carrying capacity of host cells	1×10^7 cell ml^{-1}	

where N is now simply $N = H_{JKJ} + H_{JKK} + I_{JKJ} + I_{JKK}$. The parameters λ, μ, β, p, δ, f, r and d take positive real values, and $0 < p < 1$, $0 < r < 1$. The parameter values, listed in Table 1, have been chosen from the primary experimental literature as denoted in the references. The recombination probability is unknown, but assumed to be rare. The prophage acquisition probability is expected to vary widely with environmental conditions; we take $p = 0.5$ for simulation studies. The carrying capacity can be varied over several orders of magnitude, depending on experimental protocols, however this parameter scales out in the non-dimensionalized system. The **P** in the table stands for 'parameter'.

3 Dimensionless Model and Well-Posedness of Solutions

3.1 Dimensionless Model

In order to simplify the analysis in the following sections, we first apply scaling on the state variables, the parameters and time to obtain a dimensionless model. To achieve this, introducing the following scaling: $H_{JKJ} = K\,x_1$, $H_{JKK} = K\,x_2$, $I_{JKJ} = K\,x_3$, $I_{JKK} = K\,x_4$, $P_J = \frac{\delta}{(1-p)\beta}\,x_5$, $P_K = \frac{\delta}{(1-p)\beta}\,x_6$, and $\tau = \delta\,t$, into the simple six-dimensional model (2.4) yields the dimensionless system (where we still use the dot to indicate differentiation with respect to the new time τ for brevity):

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$$
\begin{aligned}
\dot{x}_1 &= x_1\big[A(1-x_1-x_2-x_3-x_4)-B-x_5\big],\\
\dot{x}_2 &= x_2\big[A(1-x_1-x_2-x_3-x_4)-B-x_6\big],\\
\dot{x}_3 &= x_1\,x_5-x_3,\\
\dot{x}_4 &= x_2\,x_6-x_4,\\
\dot{x}_5 &= (F+R)\,x_3+R\,x_4-D\,x_5,\\
\dot{x}_6 &= R\,x_3+(F+R)\,x_4-D\,x_6,
\end{aligned}
\tag{3.1}
$$

where the new parameters A, B, D, F and R take positive values, defined by

$$
A=\tfrac{\lambda}{\delta},\quad B=\tfrac{\mu}{\delta},\quad D=\tfrac{d}{\delta},\quad F=\tfrac{f(1-r)(1-p)\beta K}{\delta^2},\quad R=\tfrac{fr(1-p)\beta K}{2\delta^2}. \tag{3.2}
$$

With the parameter values given in Table 1, these new dimensionless parameters take the typical values: $A=1.0033$, $B=0.0374$, $D=0.509$, $F=2.9164(1-p)$, $R=0.0001458(1-p)$. For example, taking $p=0.5$, we have $F=1.4582$ and $R=0.00007292$.

3.2 Well-Posedness of Solutions

First, we show the well-posedness of solutions of system (3.1). We have the following theorem.

Theorem 3.1 *All solutions of system* (3.1) *are non-negative if the initial conditions are non-negative. Furthermore, they are bounded.*

To prove the positivity of the solutions, we need the following lemma.

Lemma 3.2 (Proposition 1.1 in Chepyzov and Vishik 2002) *The cone* R^n_+ *is invariant for the flow generated by the differential equation,* $\frac{d\mathbf{x}}{dt}=\mathbf{f}(\mathbf{x})$, *if and only if the function* $\mathbf{f}(\mathbf{x})$ *is quasi-positive, i.e. for every* $i=1,2,\ldots,n$ *the function* $f_i(x_1,\ldots,0,\ldots,x_n)\geq 0$, *where* 0 *stands at the* i*th position and* $x_j\geq 0$ *for* $j\neq i$.

Proof The non-negativity of solutions of system (3.1) is obvious by verifying the conditions given in Lemma 3.2. To prove the boundedness of solutions, we first construct the Lyapunov function, $L_1=\sum_{i=1}^4 x_i+\frac{1}{F+2R}(x_5+x_6)$, which is positive definite for $(x_1,x_2,x_3,x_4,x_5,x_6)\neq(0,0,0,0,0,0)$. Then differentiating L_1 with respect to τ and then using (3.1), we obtain $\left.\frac{\mathrm{d}L_1}{\mathrm{d}\tau}\right|_{(3.1)}=\sum_{i-1}^4\frac{\mathrm{d}x_i}{\mathrm{d}\tau}+\frac{1}{F+2R}\left(\frac{\mathrm{d}x_5}{\mathrm{d}\tau}+\frac{\mathrm{d}x_6}{\mathrm{d}\tau}\right)=(x_1+x_2)\big[(A-B)-A(x_1+x_2+x_3+x_4)\big]-\frac{D}{F+2R}(x_5+x_6)$. There are two cases.

Case 1 $A\leq B$. In this case, $\left.\frac{\mathrm{d}L_1}{\mathrm{d}\tau}\right|_{(3.1)}<0$ for $\big\{(x_1,x_2,x_3,x_4,x_5,x_6)\big|\,x_1+x_2+x_5+x_6\neq 0\big\}$; but $\left.\frac{\mathrm{d}L_1}{\mathrm{d}\tau}\right|_{(3.1)}=0$ for $\big\{(x_1,x_2,x_3,x_4,x_5,x_6)\big|\,x_1=x_2=x_5=x_6=0\big\}$. So, we only need to consider the second subcase for which the third and fourth equations (3.1) become $\dot{x}_i=-x_i$, $i=3,4$, implying that $\lim_{\tau\to\infty}x_i=0$, $i=3,4$. Thus, by LaSalle's (1976) invariant principle, we know that the conclusion is true for

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the subcase. Combining the two subcases, we conclude that the origin of system (3.1) is globally asymptotically stable (GAS), attracting all solutions of the system.

Case 2 $A > B$. For this case, it is easy to see that $\left.\frac{\mathrm{d}L_1}{\mathrm{d}\tau}\right|_{(3.1)} < 0$ when $x_1+x_2+x_3+x_4 > 1-\frac{B}{A}$. Therefore, in the cone R^6_+, all the solutions are attracted into the trapping region Ω_1, defined by $\Omega_1 := \left\{(x_1, x_2, x_3, x_4, x_5, x_6) \,\middle|\, x_1 + x_2 + x_3 + x_4 \le 1 - \frac{B}{A}\right\}$. Now, within Ω_1, where $x_3 + x_4 \le 1 - \frac{B}{A}$, we want to show that x_5 and x_6 are also bounded. Consider the second Lyapunov function: $L_2 = \frac{x_5+x_6}{F+2R}$. Then,

$$\left.\frac{\mathrm{d}L_2}{\mathrm{d}\tau}\right|_{(3.1)} = \frac{\mathrm{d}x_5}{\mathrm{d}\tau} + \frac{\mathrm{d}x_6}{\mathrm{d}\tau} = x_3 + x_4 - \frac{D}{F+2R}(x_5 + x_6) \le 1 - \frac{B}{A} - \frac{D}{F+2R}(x_5 + x_6),$$

where $x_3 + x_4 \le 1 - \frac{B}{A}$ has been used, which implies that $\left.\frac{\mathrm{d}L_2}{\mathrm{d}\tau}\right|_{(3.1)} < 0$ if $x_5 + x_6 > \frac{(A-B)(F+2R)}{AD}$. Therefore, for $A > B$, together with Ω_1, we define an attracting region Ω as

$$\Omega := \left\{\left(x_1, x_2, x_3, x_4, x_5, x_6\right) \,\middle|\, x_1+x_2+x_3+x_4 \le 1-\frac{B}{A},\quad x_5 + x_6 \le \frac{(A-B)(F+2R)}{AD}\right\}, \tag{3.3}$$

and then all solution trajectories of system (3.1) are attracted into Ω.

Combining the discussions in Cases 1 and 2 completes the proof for Theorem 3.1. □

Now we consider the equilibrium solutions, their stability and bifurcations of the model (3.1). First, note that due to symmetry, the system has an invariant manifold, defined by

$$\mathrm{I}_1 := \left\{(x_1, x_2, x_3, x_4, x_5, x_6) \middle| x_1 = x_2, x_3 = x_4, x_5 = x_6\right\}. \tag{3.4}$$

which implies that in order for the dynamics of system (3.1) to be confined on this invariant manifold, the initial point must chosen on this manifold. Though it is mathematical interesting, this exactly symmetric initial condition is very unlikely to occur in nature. Therefore, here we concentrate on the analysis of the full six-dimensional system (3.1), and in fact the dynamics on invariant manifold I_1 is a special case of the general system. Hence, we omit the analysis of the dynamics on I_1, however we summarize results in a corollary after Theorem 4.1 for the general system. Also, we present the bifurcation diagram for the dynamics on I_1 in Fig. 2b to allow comparison with that of system (3.1) given in Fig. 2a.

4 Equilibrium Solutions, Stability and Bifurcations of System (3.1)

To find the equilibrium solutions of (3.1), we first find four possible groups from the first two equations of (3.1) (i.e. setting $\dot{x}_1 = \dot{x}_2 = 0$): (i) $x_1 = x_2 = 0$, (ii)

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$x_1 = 1 - \frac{B}{A} - x_3 - x_4 - \frac{x_5}{A},\ x_2 = 0$, (iii) $x_1 = 0,\ x_2 = 1 - \frac{B}{A} - x_3 - x_4 - \frac{x_6}{A}$; and

$$\text{(iv)} \begin{cases} A(1 - x_1 - x_2 - x_3 - x_4) - B - x_5 = 0, \\ A(1 - x_1 - x_2 - x_3 - x_4) - B - x_6 = 0, \end{cases} \implies x_5 = x_6.$$

Obviously, Group (i) gives the equilibrium solution $\mathrm{E}_0 : (0, 0, 0, 0, 0, 0)$. For Group (ii), it follows from $x_2 = 0$ that either $x_3 = 0$, or $x_1 = \frac{D}{F+R}$, the former yields an equilibrium solution: $\mathrm{E}_{1\mathrm{a}} : (1 - \frac{B}{A}, 0, 0, 0, 0, 0)$; while the latter results in another equilibrium solution:

$$\mathrm{E}_2 : \ \big(D^*, 0, D^*F^*, 0, F^*, R^*F^*\big), \ \text{ where } D^* = \tfrac{D}{F+R},\ R^* = \tfrac{R}{F+R},$$
$$F^* = \frac{(F+R)(A-B) - AD}{F+R+AD}. \tag{4.1}$$

Similarly, Group (iii) gives two equilibrium solutions: $\mathrm{E}_{1\mathrm{b}} : \ (0,\ 1 - \frac{B}{A},\ 0, 0, 0, 0)$, and

$$\mathrm{E}_3 : \ \big(0,\ D^*,\ 0, D^*F^*,\ R^*F^*,\ F^*\big). \tag{4.2}$$

Finally, for Group (iv), we have $x_6 = x_5$, for which we obtain by a simple manipulation that either $x_5 = 0$, or $x_1 = x_2 = \frac{D}{F+2R}$. For $x_5 = 0$, we have $x_3 = x_4 = x_5 = x_6 = 0$ and $x_1 + x_2 = 1 - \frac{B}{A}$, which yields an equilibrium line segment:

$$\mathrm{E}_1 : \ (x_1,\ x_2,\ 0,\ 0,\ 0,\ 0), \quad \text{satisfying } x_1 + x_2 = 1 - \tfrac{B}{A},\ x_1 \geq 0,\ x_2 \geq 0. \tag{4.3}$$

It is easy to see that the equilibrium solutions $\mathrm{E}_{1\mathrm{a}}$ and $\mathrm{E}_{1\mathrm{b}}$ are special cases of the equilibrium E_1 ($\mathrm{E}_{1\mathrm{a}}$ and $\mathrm{E}_{1\mathrm{b}}$ are the two end points of E_1). Hence, in the following, we shall include the $\mathrm{E}_{1\mathrm{a}}$ and $\mathrm{E}_{1\mathrm{b}}$ into the discussion of E_1. While for the second case in Group (iv), namely $x_5 \neq 0$, we have a positive equilibrium, given by

$$\mathrm{E}_4 : \ \big(D^{**}, D^{**}, D^{**}F^{**}, D^{**}F^{**}, F^{**}, F^{**}\big),$$
$$\text{where } D^{**} = \tfrac{D}{F+2R},\ .F^{**} = \tfrac{(F+2R)(A-B)-2AD}{F+2R+2AD}. \tag{4.4}$$

Carrying out stability analysis on the above equilibrium solutions and considering bifurcations among these equilibrium solutions, we obtain the following theorem, in which the definitions are used:

$$\begin{aligned}
&\mathrm{E}_{1\mathrm{s}} : \ \big(s\big(1 - \tfrac{B}{A}\big),\ (1-s)\big(1 - \tfrac{B}{A}\big),\ 0,\ 0,\ 0,\ 0\big), \\
&\mathrm{E}_{1(1-\mathrm{s})} : \ \big((1-s)\big(1 - \tfrac{B}{A}\big),\ s\big(1 - \tfrac{B}{A}\big),\ 0,\ 0,\ 0,\ 0\big), \\
&B^* = \frac{2D^*}{\big[1 + \sqrt{(1-2s)^2 + 4s(1-s)R^{*2}}\big]}, \quad \text{for } s \in \big[0, \tfrac{1}{2}\big], \\
&B_{\mathrm{H}}^{(1)} = A\big[1 - \tfrac{2D}{F}\big(1 + 2RD^{**}\big)\big] - \tfrac{2R(1+D)}{F}, \\
&B_{\mathrm{H}}^{(2)} = A - \frac{2A[(F+2R)(F+2R+2AD)(D^2+3D+1)+4A^2D^3]}{(F+2R)[(F+2R-A)^2-(1+4D)A^2]}.
\end{aligned} \tag{4.5}$$

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Theorem 4.1 *For system (3.1), the trivial equilibrium* E_0 *is GAS for* $B \geq A$*, and unstable for* $B < A$*. At the transcritical point* $B = A$*, the equilibrium (line segment)* E_1 *emerges from* E_0*. The equilibrium points on this equilibrium line segment between* $\mathrm{E}_{1\mathrm{s}}$ *and* $\mathrm{E}_{1(1-\mathrm{s})}$ *are GAS for* $B \in (A(1-B^*), A)$ *and become unstable for* $B < A(1-B^*)$*, indicating that the whole equilibrium line segment* E_1 *(i.e. every point on this line segment) is GAS for* $B \in (A(1-D^*), A)$*, while only the middle point on* E_1 *is GAS for* $B \in (A(1-2D^{**}), A)$*. The equilibria* E_2 *and* E_3 *are always unstable for positive parameter values. The equilibrium* E_4 *is asymptotically stable for* $B_{\mathrm{H}}^{(1)} < B < A\big(1-D^{**}\big)$ *if* $A \geq \frac{F+2R}{1+\sqrt{1+4D}}$*; or* $\max\big\{B_{\mathrm{H}}^{(1)}, B_{\mathrm{H}}^{(2)}\big\} < B < A\big(1-2D^{**}\big)$ *if* $A < \frac{F+2R}{1+\sqrt{1+4D}}$*. Hopf bifurcation occurs from* E_4 *at* $B = B_{\mathrm{H}}^{(1)}$ *when* $A \geq \frac{F+2R}{1+\sqrt{1+4D}}$*, or at* $B = \max\big\{B_{\mathrm{H}}^{(1)}, B_{\mathrm{H}}^{(2)}\big\} < A\big(1-\frac{2D}{F+2R}\big)$ *when* $A < \frac{F+2R}{1+\sqrt{1+4D}}$*.*

Remark 1 Analogous to the basic reproductive number, we define $\mathcal{R}_{\mathrm{H}}$ as the number of host cells produced by a single host cell in its lifetime, assuming the bacterial cell density is initially far from the carrying capacity and phage are absent. Clearly $\mathcal{R}_{\mathrm{H}} = \frac{\lambda}{\mu} = \frac{A}{B}$, and thus $\mathcal{R}_{\mathrm{H}} < 1$ ($\mathcal{R}_{\mathrm{H}} > 1$) is equivalent to $B > A$ ($B < A$). For convenience in this paper, we use B, rather then $\mathcal{R}_{\mathrm{H}}$, as a perturbation parameter in the analysis and bifurcation diagrams.

Proof To find stability of the equilibrium solutions, we use the Jacobian of system (3.1). First, evaluating the Jacobian at the equilibrium E_0 results in the characteristic polynomial, $P_0(\xi) = (\xi - A + B)^2(\xi+1)^2(\xi+D)^2$, which indicates that E_0 is asymptotically stable for $B > A$ and becomes unstable for $B < A$. Moreover, E_0 is GAS for $B \geq A$, as shown in the proof of Theorem 3.1 for Case 1. The critical point is $B = A$.

For equilibrium E_1, using $x_1 \in \big[0, 1-\frac{B}{A}\big]$ as a free variable, we substitute E_1 into the Jacobian of (3.1) to obtain the characteristic polynomial, $P_1(\xi) = \xi\,(\xi + A - B)(\xi^4 + b_1\,\xi^3 + b_2\,\xi^2 + b_3\,\xi + b_4)$, where

$$
\begin{aligned}
&b_1 = 2(1+D), \qquad b_2 = (1+D)^2 + 2D - \big(1-\tfrac{B}{A}\big)\big(F+R\big),\\
&b_3 = (1+D)\big[2D - \big(1-\tfrac{B}{A}\big)\big(F+R\big)\big],\\
&b_4 = F(F+2R)x_1\big(1-\tfrac{B}{A}-x_1\big) + D\big[D - \big(1-\tfrac{B}{A}\big)\big(F+R\big)\big].
\end{aligned}
$$

E_1 is asymptotically stable if the following conditions hold: $b_1 > 0$, $b_4 > 0$, $\Delta_2 = b_1 b_2 - b_3 > 0$ and $\Delta_3 = b_3\,\Delta_2 - b_4\,b_1^2 > 0$. Note that $b_1 > 0$ is satisfied. Also note that the above conditions imply that $b_2 > 0$ and $b_3 > 0$. However, $b_3 > 0$, i.e. $1-\frac{B}{A} < \frac{2D}{F+R}$, or $B > A(1-2D^*)$, guarantees $b_2 > 0$. Moreover, under the condition $b_3 > 0$, we can show that

$$
\begin{aligned}
\Delta_2 = {}& 2(1+D)\big[(1+D)^2 + 2D - \big(1-\tfrac{B}{A}\big)(F+R)\big]\\
&- (1+D)\big[2D - \big(1-\tfrac{B}{A}\big)(F+R)\big] = 2(1+D)^3 + b_3 > 0,
\end{aligned}
$$

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and

$$\begin{aligned}\Delta_3 &= (b_1b_2 - b_3)b_3 - b_4b_1^2\\ &= (1+D)^2\Big\{\big[2D - \big(1-\tfrac{B}{A}\big)(F+R)\big]^2 + 2(1+D)^2\big[2D - \big(1-\tfrac{B}{A}\big)(F+R)\big]\\ &\quad + 4D^2 - 4F(F+2R)x_1\big(1-\tfrac{B}{A}-x_1\big)\Big\}\\ &\geq (1+D)^2\Big\{\big[2D - \big(1-\tfrac{B}{A}\big)(F+R)\big]^2 + 2(1+D)^2\big[2D - \big(1-\tfrac{B}{A}\big)(F+R)\big]\\ &\quad + 4D^2 - F(F+2R)\big(1-\tfrac{B}{A}\big)^2\Big\}\\ &= (1+D)\Big[(1+D)\big(1-\tfrac{B}{A}\big)^2R^2 + 2(D^2+4D+1)\,b_3\Big] > 0.\end{aligned}$$

Thus, the only remaining condition for stability is $b_4 > 0$. To verify this condition, let $x_1 = s\,(1-\frac{B}{A})$, $s \in [0, 1]$. Then, we have the equivalent condition:

$$b_4 = s(1-s)\,F(F+2R)\big(1-\tfrac{B}{A}\big)^2 - D(F+R)\big(1-\tfrac{B}{A}\big) + D^2 > 0.$$

First note that when $1-\frac{B}{A} < \frac{D}{F+R}$, i.e. $B > A(1-D^*)$, $b_4 > 0$ for any $s \in [0, 1]$, implying that any point on the equilibrium line segment $x_1 + x_2 = 1 - \frac{B}{A}$ is asymptotically stable for $B > A(1-D^*)$.

Next, consider $B \leq A(1-D^*)$. In this case, it is easy to see that not every point on the equilibrium line segment is stable. For example, when $B = A(1-D^*)$, $b_4 = 0$ if $s = 0$ or $s = 1$. In other words, these two points become critical points and must be excluded from the set of stable equilibrium points. That is, when $B = A(1-D^*)$, except for the two end points, every point on the equilibrium line segment is asymptotically stable. If we further decrease B from $A(1-D^*)$, we would expect more unstable points to appear on the equilibrium line segment. In fact, since $0 \leq s(1-s) = \frac{1}{4} - \big(s-\frac{1}{2}\big)^2 \leq \frac{1}{4}$, b_4 attains its minimum at $s = 0$ for which $(x_1, x_2) = \big((1-\frac{B}{A}), 0\big)$, or at $s = 1$ for which $(x_1, x_2) = \big(0, (1-\frac{B}{A})\big)$; and its maximum at $s = \frac{1}{2}$ for which $x_1 = x_2 = \frac{1}{2}(1-\frac{B}{A})$. At the minimum value obtained when $s = 0$, or $s = 1$, $b_4 > 0$ requires that $B > A(1-D^*)$; while at its maximum value when $s = \frac{1}{2}$, it follows from $b_4 > 0$ that $B > A(1-2D^{**})$. The above discussions indicate that the two end points of the equilibrium line segment E_1 are asymptotically stable for $A(1-D^*) < B < A$, while the middle point of the equilibrium line segment is asymptotically stable for $A(1-2D^{**}) < B < A$, implying that the two end points have the smallest stability interval, while the middle point has the largest stability interval. Any other points on the equilibrium line segment E_1 has stability interval between these two.

More precisely, for each value of $s \in [0, \frac{1}{2}]$, there exists an equilibrium point, E_{1s}, defined in (4.5) and due to symmetry, there also exists another equilibrium point, $\mathrm{E}_{1(1-s)}$ [also defined in (4.5)]. Then, the equilibrium points on the line segment E_1 between these two equilibrium points, E_{1s} and $\mathrm{E}_{1(1-s)}$, are asymptotically stable for $A(1-B^*) < B < A$, and becomes unstable for $B < A(1-B^*)$, where B^* is determined from the inequality $b_4 > 0$. So, for each value of $s \in [0, \frac{1}{2}]$, we can find

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a critical value B^* from $b_4 > 0$ such that

$$1 - \frac{B}{A} < \frac{D\left[F+R-\sqrt{(F+R)^2-4s(1-s)F(F+2R)}\right.}{2s(1-s)F(F+2R)} = \frac{2D^*}{\left[1+\sqrt{(1-2s)^2+4s(1-s)R^{*2}}\right]} \equiv B^*, \tag{4.6}$$

where $B^* \in [D^*, 2D^{**}]$ for $s \in \left[0, \frac{1}{2}\right]$. It is easy to see that B^* is monotonically increasing as s is varied from 0 to $\frac{1}{2}$, and thus B^* is a one-to-one function of s on $s \in [0, \frac{1}{2}]$. Also note that the above condition guarantees $b_3 > 0$ since $1 - \frac{B}{A} < B^* < 2D^*$.

To prove the global stability of E_1, we construct the Lyapunov function.

$$V_1 = x_1 - x_{1\mathrm{E}} - x_{1\mathrm{E}} \ln \frac{x_1}{x_{1\mathrm{E}}} + x_2 - x_{2\mathrm{E}} - x_{2\mathrm{E}} \ln \frac{x_2}{x_{2\mathrm{E}}} + x_3 + x_4 + p_1 x_5 + p_2 x_6 \tag{4.7}$$

where $x_{1\mathrm{E}} = s(1 - \frac{B}{A})$, $x_{2\mathrm{E}} = (1-s)(1 - \frac{B}{A})$, and

$$p_1 = \begin{cases} \frac{s}{(1-s)F+R}, & s \in \left[0, \frac{1}{2}\right], \\ \frac{s}{sF+R}, & s \in \left(\frac{1}{2}, 1\right], \end{cases} \qquad p_2 = \begin{cases} \frac{1-s}{(1-s)F+R}, & s \in \left[0, \frac{1}{2}\right], \\ \frac{1-s}{sF+R}, & s \in \left(\frac{1}{2}, 1\right], \end{cases}$$

Due to symmetry, we may only consider $s \in [0, \frac{1}{2}]$. Then, differentiating V_1 with respect to τ and using (3.1) yields

$$\begin{aligned}
\left.\frac{\mathrm{d}V_1}{\mathrm{d}\tau}\right|_{(3.1)} &= \frac{\mathrm{d}x_1}{\mathrm{d}\tau} - \frac{x_{1\mathrm{E}}}{x_1}\frac{\mathrm{d}x_1}{\mathrm{d}\tau} + \frac{\mathrm{d}x_2}{\mathrm{d}\tau} - \frac{x_{2\mathrm{E}}}{x_2}\frac{\mathrm{d}x_2}{\mathrm{d}\tau} + \frac{\mathrm{d}x_3}{\mathrm{d}\tau} + \frac{\mathrm{d}x_4}{\mathrm{d}\tau} \\
&\quad + \frac{1}{(1-s)F+R}\left[s\frac{\mathrm{d}x_5}{\mathrm{d}\tau} + (1-s)\frac{\mathrm{d}x_6}{\mathrm{d}\tau}\right] \\
&= (x_1 - x_{1\mathrm{E}})\left[(A-B) - A(x_1+x_2+x_3+x_4) - x_5\right] \\
&\quad + (x_2 - x_{2\mathrm{E}})\left[(A-B) - A(x_1+x_2+x_3+x_4) - x_6\right] \\
&\quad + x_1 x_5 - x_3 + x_2 x_6 - x_4 \\
&\quad + \frac{s}{(1-s)F+R}\left[(F+R)x_3 + Rx_4 - Dx_5\right] \\
&\quad + \frac{1-s}{(1-s)F+R}\left[Rx_3 + (F+R)x_4 - Dx_6\right] \\
&= -A\left(1 - \frac{B}{A} - x_1 - x_2 - x_3 - x_4\right)^2 \\
&\quad - A(x_3+x_4)\left(1 - \frac{B}{A} - x_1 - x_2 - x_3 - x_4\right) \\
&\quad - \frac{(1-2s)F}{(1-s)F+R}x_3 - \left[\frac{B}{A} - 1 + \frac{D}{(1-s)F+R}\right]\left[sx_5 + (1-s)x_6\right].
\end{aligned}$$

Note that we have assumed that all solutions are attracted into the trapping region Ω [see (3.3)] in which $x_1 + x_2 + x_3 + x_4 \le 1 - \frac{B}{A}$. Thus, when $B > A(1 - \bar{B})$, where

$$\bar{B} = \frac{D}{(1-s)F+R} \in \left[\frac{D}{F+R}, \frac{2D}{F+2R}\right] \equiv [D^*, D^{**}], \tag{4.8}$$

$\left.\frac{\mathrm{d}V_1}{\mathrm{d}\tau}\right|_{3.1} \le 0$ and equals zero only if $x_5 = x_6 = 0$, and $x_1 + x_2 + x_3 + x_4 = 1 - \frac{B}{A}$. But when $x_5 = x_6 = 0$, the third and fourth equations of (3.1) yield $x_3(\tau) \to 0$

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and $x_4(\tau) \to 0$ as $\tau \to \infty$. Thus, $\left.\frac{\mathrm{d}v_1}{\mathrm{d}\tau}\right|_{3.1} = 0$ only if $x_1 + x_2 = 1 - \frac{B}{A}$, leading to the equilibrium E_1. Further, by applying LaSalle's (1976) invariance principle, we conclude that the equilibrium point on the line segment E_1, defined by $\big(s(1-\frac{B}{A}),\ (1-s)(1-\frac{B}{A}),\ 0,\ 0,\ 0,\ 0\big)$, is GAS for $A(1-\bar{B}) < B < A$.

It remains to be shown that the $\bar{B}$ used in proving the global stability of E_1 is equivalent to the B^* used in proving the local stability of E_1. To achieve this, we solve for s in terms of B^* using (4.6) and also solve for s in terms of $\bar{B}$ using (4.8), and then equate the resulting expressions to obtain

$$\frac{1}{2}\left\{1 - \sqrt{1 + \frac{4(F+R)D^{**}}{FB^*}\left[\frac{D^*}{B^*} - 1\right]}\right\} = \frac{F+R}{F}\left[1 - \frac{D^*}{\bar{B}}\right]$$

from which we obtain

$$\bar{B} = \frac{2D}{F+2R+\sqrt{F\left(\frac{2D}{B^*} - F\right)\left(\frac{2D^{**}}{B^*} - 1\right)}}, \quad \text{for } B^* \in [D^*,\ 2D^{**}].$$

It is easy to see that $\bar{B} = D^*$ and $\bar{B} = 2D^{**}$ when $B^* = D^*$ and $B^* = 2D^{**}$, respectively. Further, we have

$$\frac{\mathrm{d}\bar{B}}{\mathrm{d}B^*} = \frac{\frac{F\,(F+R)}{F+2R}\left(\frac{2D}{B^*}\right)^2\left(\frac{2D^*}{B^*} - 1\right)}{\left[F+2R+\sqrt{F\left(\frac{2D}{B^*} - F\right)\left(\frac{2D^{**}}{B^*} - 1\right)}\right]^2\sqrt{F\left(\frac{2D}{B^*} - F\right)\left(\frac{2D^{**}}{B^*} - 1\right)}} > 0,$$

for $B^* \in [D^*, 2D^{**}]$, indicating that $\bar{B}$ is a continuous, monotonically increasing function of B^* and thus one-to-one on the interval $B^* \in [D^*, 2D^{**}]$. This shows that $\bar{B}$ is equivalent to B^*, and thus we will use B^* in the following for both local and global stability analyses.

Summarizing the above discussions shows that the equilibrium points on the equilibrium line segment E_1 between E_{1s} and $\mathrm{E}_{1(1-s)}$ are GAS for $B \in \big(A(1-B^*), A\big)$. This clearly indicates that the whole equilibrium line segment (i.e. every point on the line segment) is GAS for the minimum stability interval, only the middle point of the equilibrium line segment reaches the maximal stability interval, and other equilibrium points on this equilibrium line segment gain a global stability interval between these two extremes. The result is illustrated in Fig. 1a–c, as well as in the bifurcation diagram shown in Fig. 2a.

Next, evaluating the Jacobian of (3.1) on the equilibrium solutions E_2 and E_3 yields the same characteristic polynomial:

$$\begin{aligned} P_{2/3}(\xi) = (\xi+1)(\xi+D)\Big(\xi - \tfrac{F^*}{F+R}\Big)\Big\{&\xi^3 + \tfrac{(F+R)(1+D)+AD}{F+R}\,\xi^2 \\ &+ \tfrac{AD[(F+R)(1+D)+AD^2+(F+R)(A-B)]}{(F+R)(F+R+AD)}\,\xi + \tfrac{D[(F+R)(A-B)-AD]}{F+R}\Big\}, \end{aligned}$$

which clearly indicates that the equilibria E_2 and E_3 are always unstable when $B < A(1-D^*)$.

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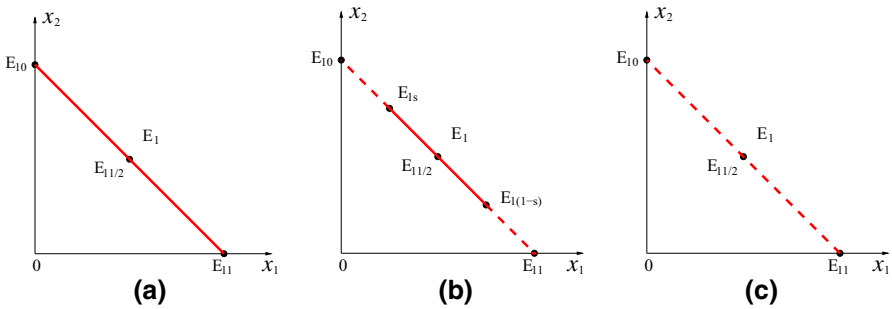

Fig. 1 Equilibrium line segment E_1: **a** every point on E_1 is asymptotically stable for $B \in \big(A(1-D^*), A\big)$, **b** the points between E_{1s} and $E_{1(1-s)}$ are asymptotically stable for $B = B^*$, and **c** only the middle point on E_1 is asymptotically stable for $B = A(1-2D^{**})$

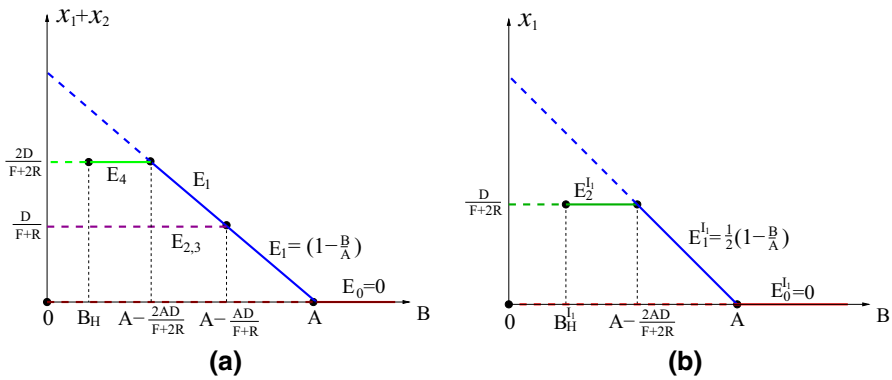

Fig. 2 **a** Bifurcation diagram for system (3.1), showing the equilibrium solutions E_0 (in *red*), E_1 (in *blue*), $E_{2/3}$ (in *purple*) and E_4 (in *green*), and **b** bifurcation diagram restricted on the invariant manifold I_1, showing the equilibrium solutions $E_0^{I_1}$ (in *red*), $E_1^{I_1}$ (in *blue*) and $E_2^{I_1}$ (in *green*); with *solid* and *dotted lines* to denote stable and unstable equilibrium solutions, respectively (Color figure online)

Finally, consider the stability of the equilibrium E_4. Similarly, evaluating the Jacobian of (3.1) on this equilibrium solution we obtain $P_4(\xi) = P_{4a}(\xi)\, P_{4b}(\xi)$, where

$$P_{4a}(\xi) = \xi^3 + (1+D)\,\xi^2 + \frac{2RD}{F+2R}\,\xi + \frac{FD[(F+2R)(A-B)-2AD]}{(F+2R)(F+2R+2AD)},$$
$$P_{4b}(\xi) = \xi^3 + \frac{(F+2R)(1+D)+2AD}{F+2R}\,\xi^2 + \frac{2AD[(F+2R)(1+D)+2AD^2+(F+2R)(A-B)]}{(F+2R)(F+2R+2AD)}\,\xi + \frac{D[(F+2R)(A-B)-2AD]}{F+2R}.$$

Note that the existence condition for E_4 requires $(F+2R)(A-B)-2AD > 0$, which guarantees that all the coefficients in $P_{4a}(\xi)$ and $P_{4b}(\xi)$ are positive. Therefore, the stability of E_4 is determined by $\Delta_{2a} > 0$ and $\Delta_{2b} > 0$, where

$$\Delta_{2a} = \frac{D\{2R(1+D)(F+2R+2AD)-F[(F+2R)(A-B)-2AD]\}}{(F+2R)(F+2R+2AD)},$$

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$$\Delta_{2b} = \frac{D}{(F+2R)^2(F+2R+2AD)}\big\{2A\big[\big((F+2R)(1+D)^2+2AD^2\big)(F+2R+2AD) + D(F+2R)^2\big] + (A-B)(F+2R)[(1+4D)A^2-(F+2R-A)^2\big\}.$$

From $\Delta_{2a} = 0$, we can solve for B to obtain a Hopf critical point $B_{\mathrm{H}}^{(1)}$ [see (4.5)]. Thus, $\Delta_{2a} > 0$ for $B_{\mathrm{H}}^{(1)} < B < A(1-2D^{**})$. To have $\Delta_{2b} > 0$, we need to consider two cases.

Case (i) $A \geq \frac{F+2R}{1+\sqrt{1+4D}}$. For this condition, $(1+D)A^2-(F+2R-A)^2 \geq 0$, and so $\Delta_{2b} > 0$.

Case (ii) $A < \frac{F+2R}{1+\sqrt{1+4D}}$. In this case, $(1+D)A^2-(F+2R-A)^2 < 0$, and thus $\Delta_{2b} > 0$ for $B_{\mathrm{H}}^{(2)} < B < A(1-2D^{**}$, where $B_{\mathrm{H}}^{(2)}$ is defined in (4.5).

In summary, we conclude that the equilibrium E_4 is asymptotically stable if

$$\begin{aligned} B_{\mathrm{H}}^{(1)} < B < A(1-2D^{**}) \text{ for } A \geq \frac{F+2R}{1+\sqrt{1+4D}}, \\ \max\big\{B_{\mathrm{H}}^{(1)},\ B_{\mathrm{H}}^{(2)}\big\} < B < A\big(1-2D^{**}\big) \text{ for } A < \frac{F+2R}{1+\sqrt{1+4D}}. \end{aligned} \tag{4.9}$$

Hopf bifurcation may occur from E_4 at $B = B_{\mathrm{H}}^{(1)}$ or $B = B_{\mathrm{H}}^{(2)}$. □

To end this section, based on Theorem 4.1 we describe the dynamics on the invariant manifold I_1 in the following corollary. In this case, there is no equilibria $\mathrm{E}_{2/3}$, and E_1 becomes $\mathrm{E}_1^{\mathrm{I}_1}$. Define

$$\begin{aligned} &\mathrm{E}_0^{\mathrm{I}_1}:\ (0,\ 0,\ 0), \qquad \mathrm{E}_1^{\mathrm{I}_1}:\ \big(\tfrac{A-B}{2A},\ 0,\ 0\big), \qquad \mathrm{E}_2^{\mathrm{I}_1}:\ \big(D^{**},\ D^{**}F^{**},\ F^{**}\big), \\ &B_{\mathrm{H}}^{\mathrm{I}_1} = A - \frac{2A\{[(F+2R)(1+D)^2+2AD^2](F+2R+2AD)+D(F+2R)^2\}}{(F+2R)[(F+2R-A)^2-(1+4D)A^2]}. \end{aligned} \tag{4.10}$$

Corollary 4.2 *For system (3.1) with $x_1 = x_2$, $x_3 = x_4$, $x_5 = x_6$ (i.e. restricted on the invariant manifold I_1), the trivial equilibrium $\mathrm{E}_0^{\mathrm{I}_1}$ is GAS for $B \geq A$, and unstable for $B < A$. At the transcritical point $B = A$, the equilibrium $\mathrm{E}_1^{\mathrm{I}_1}$ emerges from $\mathrm{E}_0^{\mathrm{I}_1}$ and is GAS for $A(1-2D^{**}) < B < A$. It becomes unstable for $0 < B < A(1-2D^{**})$. At the transcritical point $B = A(1-2D^{**})$, the equilibrium $\mathrm{E}_2^{\mathrm{I}_1}$ bifurcates from $\mathrm{E}_1^{\mathrm{I}_1}$, and is asymptotically stable for $B_{\mathrm{H}}^{\mathrm{I}_1} < B < A(1-2D^{**})$, where $B_{\mathrm{H}}^{\mathrm{I}_1}$ denotes a Hopf critical point. If $A \geq \frac{F+2R}{1+\sqrt{1+4D}}$ or $A < \frac{F+2R}{1+\sqrt{1+4D}}$ but $B_{\mathrm{H}}^{\mathrm{I}_1} \leq 0$, there is no Hopf bifurcation and $\mathrm{E}_2^{\mathrm{I}_1}$ is stable for $0 \leq B < A(1-2D^{**})$. Only if $A < \frac{F+2R}{1+\sqrt{1+4D}}$ and $B_{\mathrm{H}}^{\mathrm{I}_1} > 0$, then can a Hopf bifurcation occur from $\mathrm{E}_2^{\mathrm{I}_1}$, leading to a family of limit cycles.*

The bifurcation diagrams for the general system (3.1) and the invariant manifold I_1 are shown in Fig. 2a, b, respectively, where B_{H} denotes either $B_{\mathrm{H}}^{(1)}$ or $B_{\mathrm{H}}^{(2)}$. A comparison between these two bifurcation diagrams reveals that the equilibria $\mathrm{E}_{2/3}$ disappear on the invariant manifold I_1, which forces $x_2 = x_1$, $x_4 = x_3$ and $x_6 = x_5$, and therefore $\mathrm{E}_{2/3}$ become E_4.

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5 Effects of Recombination: $R = 0$

A key novel feature of the model developed here is recombination, the ability of infecting virus to exchange genetic material with prophage in the host cell genome. To isolate the effects of recombination, we can compare the bifurcation analysis above with analogous results obtained in the case when the recombination rate, $r = 0$ ($R = 0$ in the non-dimensionalized system).

Setting $R = 0$ in (3.1) we have

$$\begin{aligned}
\dot{x}_1 &= x_1\big[A(1 - x_1 - x_2 - x_3 - x_4) - B - x_5\big],\\
\dot{x}_2 &= x_2\big[A(1 - x_1 - x_2 - x_3 - x_4) - B - x_6\big],\\
\dot{x}_3 &= x_1 x_5 - x_3, \quad \dot{x}_4 = x_2 x_6 - x_4,\\
\dot{x}_5 &= F x_3 - D x_5, \qquad \dot{x}_6 = F x_4 - D x_6,
\end{aligned} \tag{5.1}$$

Again, we have the invariant manifold, described by (3.4) and the dynamics on this manifold are described by system (3.1) restricted to the invariant manifold I_1 with $R = 0$. However, for this special case, there exist two additional invariant manifolds, described by

$$\begin{aligned}
\mathrm{I}_2 &:= \big\{(x_1, x_2, x_3, x_4, x_5, x_6)\big|x_2 = x_4 = x_6 = 0\big\},\\
\mathrm{I}_3 &:= \big\{(x_1, x_2, x_3, x_4, x_5, x_6)\big|x_1 = x_3 = x_5 = 0\big\}.
\end{aligned} \tag{5.2}$$

These two invariant manifolds have some interesting properties, different from the general model. In the following, we first consider the three invariant manifolds and then briefly discuss the general case.

5.1 Invariant Manifolds

First, for the invariant manifold I_1, simply setting $R = 0$ in Corollary 4.2 we have the following corollary.

Corollary 5.1 *For system (5.1) restricted to the invariant manifold I_1, the trivial equilibrium $\mathrm{E}_0^{\mathrm{I}_1}$ is GAS for $B \geq A$, and unstable for $B < A$. At the transcritical point $B = A$, the equilibrium $\mathrm{E}_1^{\mathrm{I}_1}$ emerges from $\mathrm{E}_0^{\mathrm{I}_1}$ and is GAS for $A(1 - 2D/F) < B < A$. It becomes unstable for $0 < B < A(1 - 2D/F)$. At the transcritical point $B = A(1 - 2D/F)$, the equilibrium $\mathrm{E}_2^{\mathrm{I}_1}$ bifurcates from $\mathrm{E}_1^{\mathrm{I}_1}$, and is asymptotically stable for $B_{\mathrm{H}}^{\mathrm{I}_1} < B < A(1 - 2D/F)$, where $B_{\mathrm{H}}^{\mathrm{I}_1}$ denotes a Hopf critical point; and $B_{\mathrm{H}}^{\mathrm{I}_1} = 0$ (meaning no Hopf critical point exists) if $A \geq \frac{F}{1+\sqrt{1+4D}}$, and $B_{\mathrm{H}}^{\mathrm{I}_1} = A - \frac{2A\{[F(1+D)^2+2AD^2](F+2AD)+DF^2\}}{F(F^2-2FA-4DA^2)}$ if $A < \frac{F}{1+\sqrt{1+4D}}$, at which $\mathrm{E}_2^{\mathrm{I}_1}$ loses stability and a family of limit cycles bifurcates.*

The bifurcation diagram shown in Fig. 2b is still valid here provided we set $R = 0$ in the figure.

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Next, we consider the invariant manifolds I_2 and I_3 which can be combined into the study of the following unified system:

$$\dot{u}_1 = u_1\left[A - B - A(u_1 + u_2) - u_3\right], \quad \dot{u}_2 = u_1 u_3 - u_2, \quad \dot{u}_3 = F u_2 - D u_3, \tag{5.3}$$

which has three equilibrium solutions:

$$\begin{aligned} &\mathrm{E}_0^{\mathrm{I}_{2/3}}:\ (0,0,0), \quad \mathrm{E}_1^{\mathrm{I}_{2/3}}:\ \left(1-\tfrac{B}{A},\,0,\,0\right),\\ &\mathrm{E}_2^{\mathrm{I}_{2/3}}:\quad \left(\tfrac{D}{F},\ \tfrac{D[F(A-B)-AD]}{F(F+AD)},\ \tfrac{F(A-B)-AD}{F+AD}\right). \end{aligned} \tag{5.4}$$

Define

$$B_{\mathrm{H}}^{\mathrm{I}_{2/3}} = A - \frac{A\left[F(F+AD)(D^2+3D+1)+A^2D^3\right]}{F\left[F^2-A(F+AD)\right]}. \tag{5.5}$$

Then, we have the following theorem. Its proof is similar to that for Theorem 4.1 and thus omitted here for brevity.

Theorem 5.2 *For system (5.3), the trivial equilibrium* $\mathrm{E}_0^{\mathrm{I}_{2/3}}$ *is GAS for* $B \geq A$*, and unstable for* $B < A$*. At the transcritical point* $B = A$*, the equilibrium* $\mathrm{E}_1^{\mathrm{I}_{2/3}}$ *emerges from* $\mathrm{E}_0^{\mathrm{I}_{2/3}}$ *and is GAS for* $A(1-D/F) < B < A$*. It becomes unstable for* $0 < B < A(1-D/F)$*. At the transcritical point* $B = A(1-D/F)$*, the equilibrium* $\mathrm{E}_2^{\mathrm{I}_{2/3}}$ *bifurcates from* $\mathrm{E}_1^{\mathrm{I}_{2/3}}$*, and is asymptotically stable for* $B_{\mathrm{H}}^{\mathrm{I}_{2/3}} < B < A(1-D/F)$*, where* $B_{\mathrm{H}}^{\mathrm{I}_{2/3}}$ *denotes a Hopf critical point. If* $A \geq \frac{2F}{1+\sqrt{1+4D}}$ *or* $A < \frac{2F}{1+\sqrt{1+4D}}$ *but* $B_{\mathrm{H}}^{\mathrm{I}_{2/3}} \leq 0$*, then no Hopf bifurcation occurs and* $\mathrm{E}_2^{\mathrm{I}_{2/3}}$ *is stable for* $0 \leq B < A(1-D/F)$*. Only if* $A < \frac{2F}{1+\sqrt{1+4D}}$ *and* $0 < B_{\mathrm{H}}^{\mathrm{I}_{2/3}} < A(1-D/F)$*, then can a Hopf bifurcation occur from* $\mathrm{E}_2^{\mathrm{I}_{2/3}}$*, leading to a family of limit cycles.*

The bifurcation diagram is depicted in Fig. 3a.

5.2 General Model

The analysis on the general model (5.1) is similar to that for the model (3.1) in which $R \neq 0$. The four equilibrium solutions are given by

$$\begin{aligned} &\mathrm{E}_0^0{:}(0,\ 0,\ 0,\ 0,\ 0,\ 0),\\ &\mathrm{E}_1^0{:}(x_1,\ x_2,\ 0,\ 0,\ 0,\ 0), \quad x_1 + x_2 = 1,\\ &\mathrm{E}_2^0{:}\left(\tfrac{D}{F},\ 0,\ \tfrac{D[F(A-B)-AD]}{F(F+AD)},\ 0,\ \tfrac{F(A-B)-AD}{F+AD},\ 0\right),\\ &\mathrm{E}_3^0{:}\left(0,\ \tfrac{D}{F},\ 0,\ \tfrac{D[F(A-B)-AD]}{F(F+AD)},\ 0,\ \tfrac{F(A-B)-AD}{F+AD}\right),\\ &\mathrm{E}_4^0{:}\left(\tfrac{D}{F},\ \tfrac{D}{F},\ \tfrac{D[F(A-B)-2AD]}{F(F+2AD)},\ \tfrac{D[F(A-B)-2AD]}{F(F+2AD)},\ \tfrac{F(A-B)-2AD}{F+2AD},\ \tfrac{F(A-B)-2AD}{F+2AD}\right), \end{aligned} \tag{5.6}$$

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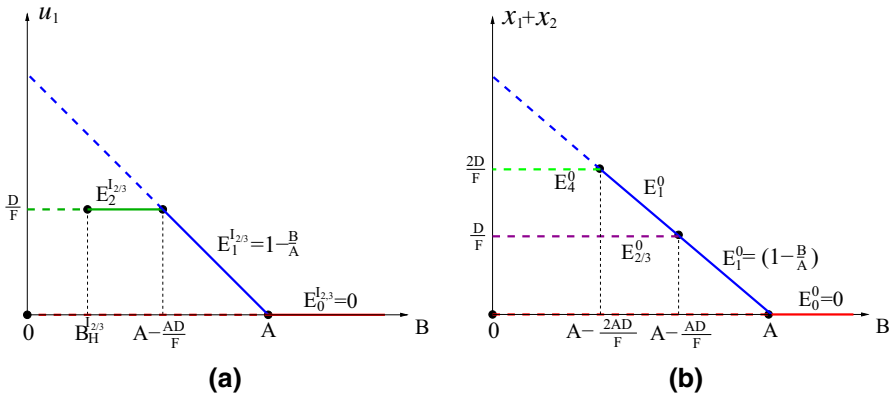

Fig. 3 **a** Bifurcation diagram for system (5.3), showing the equilibrium solutions $E_0^{I_{2/3}}$ (in *red*), $E_1^{I_{2/3}}$ (in *blue*) and $E_2^{I_{2/3}}$ (in *green*), and **b** bifurcation diagram for system (5.1), showing the equilibrium solutions E_0^0 (in *red*), E_1^0 (in *blue*), $E_{2/3}^0$ (in *purple*) and E_4^0 (in *green*); with *solid* and *dotted lines* to denote stable and unstable equilibrium solutions, respectively (Color figure online)

where the superscript 0 denotes $R = 0$. The stability of these equilibrium solutions is similar to that of system (3.1). The only significant difference is that now for the special case $R = 0$, the Hopf critical point of E_4 coincides with its transcritical point. In other words, the equilibrium E_4^0 is always unstable once it bifurcates from E_1^0. Therefore, there is no Hopf bifurcation from E_4^0, but there may exist persistent oscillating motions when E_4^0 becomes unstable. Without presenting the detailed analysis, we state a theorem below for system (5.1) and show its bifurcation diagram in Fig. 3b.

Theorem 5.3 *For system* (5.1)*, the trivial equilibrium* E_0^0 *is GAS for* $B \geq A$*, and unstable for* $B < A$*. At the transcritical point* $B = A$*, the equilibrium (line segment)* E_1^0 *emerges from* E_0^0*. The equilibrium points on this equilibrium line segment between* $E_{1r}^0 = \left(s(1-\frac{B}{A}),\ (1-s)(1-\frac{B}{A}),\ 0,\ 0,\ 0,\ 0\right)$ *and* $E_{1(1-s)}^0 = \left((1-s)(1-\frac{B}{A}),\ s(1-\frac{B}{A}),\ 0,\ 0,\ 0,\ 0\right)$ *are GAS for* $B \in (A(1-B^{0*}), A)$*, where* $B^{0*} = \frac{D}{(1-s)(F+R)}$*, and become unstable for* $B < A(1-B^{0*})$*. The equilibria* $E_{2/3}^0$ *and* E_4^0 *are always unstable for positive parameter values.*

6 Additional Two Invariant Manifolds Showing the Effects of Recombination

In simulation, it has been shown that for system (3.1) or system (5.1) trajectories may converge to the unstable equilibrium solutions $E_{2/3}$ for $A(1-2D^{**}) < B < A(1-D^*)$ [$R = 0$ for system (5.1)], if the initial condition is chosen in the form of $(*, 0, *, 0, *, *)$ where $*$ denotes nonzero entries, as shown in Fig. 5 [for system (3.1)] and Fig. 7a [for system (5.1)]. This seems to contradict the results of our stability analysis. A careful consideration shows that the equilibrium solution E_2 of system (3.1) or (5.1) is in the form of $(*, 0, *, 0, *, *)$. Moreover, the second and fourth equations of the two systems are given as $\dot{x}_2 = x_2(\cdots)$ and $\dot{x}_4 = x_2x_6 - x_4$. This clearly shows that the dynamical

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solutions of the two equations remain as $x_2 = x_4 = 0$ if the initial conditions involve $x_2(0) = x_4(0) = 0$. Therefore, starting from the initial condition given in the form of $(*, 0, *, 0, *, *)$, the dynamics of the system are actually restricted to the following invariant manifold:

$$\mathrm{I}_{24} := \big\{(x_1, x_2, x_3, x_4, x_5, x_6)\big| x_2 = 0, x_4 = 0\big\}, \tag{6.1}$$

and dynamics on this invariant manifold are described by the following equations:

$$\begin{aligned}
\dot{x}_1 &= x_1\big[A(1 - x_1 - x_3) - B - x_5\big],\\
\dot{x}_3 &= x_1 x_5 - x_3,\\
\dot{x}_5 &= (F + R)\, x_3 - D\, x_5,\\
\dot{x}_6 &= R\, x_3 - D\, x_6,
\end{aligned} \tag{6.2}$$

This system has three equilibrium solutions: $\mathrm{E}_0 : (0, 0, 0, 0)$, $\mathrm{E}_1 : (1 - \frac{B}{A}, 0, 0, 0)$, and $\mathrm{E}_2 : \ (D^*, D^*F^*, F^*, R^*F^*)$. Note that now we do not have equilibrium solutions E_3 and E_4. We have the following theorem. The proof is straightforward and omitted here.

Theorem 6.1 *For system (6.1), the trivial equilibrium* E_0 *is GAS for* $B \geq A$*, and unstable for* $B < A$*. At the transcritical point* $B = A$*, the equilibrium* E_1 *bifurcates from* E_0*, and is GAS for* $A(1 - D^*) < B < A$*.* E_2 *loses its stability at the critical point* $B = A(1 - D^*)$ *at which the equilibrium* E_2 *emerges and is asymptotically stable for* $B_{\mathrm{H}} < B < A(1 - D^*)$*, where* $B_{\mathrm{H}} = 0$ *if* $A \geq \frac{2(F+R)}{1+\sqrt{1+4D}}$*, and* $B_{\mathrm{H}} = A - \frac{A[(1+3D+D^2)(F+R)(F+R+AD)+A^2D^3]}{(F+R)[(F+R)^2-A(F+R+AD)]}$ *if* $A < \frac{2(F+R)}{1+\sqrt{1+4D}}$.

Similarly, we can define another invariant manifold:

$$\mathrm{I}_{13} := \big\{(x_1, x_2, x_3, x_4, x_5, x_6)\big| x_1 = 0, x_3 = 0\big\}, \tag{6.3}$$

and can obtain a similar dynamics for this sub-system. We omit the details for brevity.

7 Hopf Bifurcations

In this section, we consider Hopf bifurcations which may occur in the models discussed in previous sections, including the three-dimensional symmetric model on the invariant manifold I_1, the special three-dimensional symmetric model (5.3) on the invariant manifolds $\mathrm{I}_{2/3}$, and the six-dimensional asymmetric model (3.1). For convenience, we call the three-dimensional symmetric model on the invariant manifold I_1 as system $(3.2)_{\mathrm{I}_1}$ Note that we'll not consider the special three-dimensional symmetric system on the invariant manifold I_1 for model (5.1), since the analysis is exactly the same as that for system $(3.2)_{\mathrm{I}_1}$. We also do not consider the special six-dimensional asymmetric model (5.1), simply because it does not have Hopf bifurcation.

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7.1 Hopf Bifurcation in the three-Dimensional Symmetric Model $(3.2)_{\mathrm{I}_1}$

For system $(3.2)_{\mathrm{I}_1}$, there exist three equilibrium solutions: $\mathrm{E}_0^{\mathrm{I}_1}$, $\mathrm{E}_1^{\mathrm{I}_1}$ and $\mathrm{E}_2^{\mathrm{I}_1}$. It has been shown that $\mathrm{E}_0^{\mathrm{I}_1}$ is GAs for $B \geq A$, and becomes unstable for $B < A$. Equilibrium $\mathrm{E}_1^{\mathrm{I}_1}$ bifurcates from $\mathrm{E}_0^{\mathrm{I}_1}$ at the transcritical point $B = A$, and is GAS for $A(1-2D^{**}) < B < A$, and becomes unstable for $B < A(1-2D^{**})$. At the transcritical point $B = A(1-2D^{**})$, $\mathrm{E}_2^{\mathrm{I}_1}$ emerges from $\mathrm{E}_1^{\mathrm{I}_1}$ and stable for $B_{\mathrm{H}}^{\mathrm{I}_1} < B < A(1-2D^{**})$, where $B_{\mathrm{H}}^{\mathrm{I}_1} = 0$ if $A \geq \frac{F+2R}{1+\sqrt{1+4D}}$ (no Hopf bifurcation). Therefore, the only possible bifurcation from $\mathrm{E}_2^{\mathrm{I}_1}$ is Hopf bifurcation when $A < \frac{F+2R}{1+\sqrt{1+4D}}$, and the Hopf critical point $B_{\mathrm{H}}^{\mathrm{I}_1}$ is given in (4.10).

Theorem 7.1 *For system* $(3.2)_{\mathrm{I}_1}$, *Hopf bifurcation can only occur from the equilibrium solution* $\mathrm{E}_2^{\mathrm{I}_1}$ *at the critical point* $B_{\mathrm{H}}^{\mathrm{I}_1}$ *if* $A < \frac{F+2R}{1+\sqrt{1+4D}}$. *The Hopf bifurcation is supercritical and thus the bifurcating limit cycles are stable.*

Proof For convenience, let

$$\begin{aligned} &C_1 = F + 2R, \qquad C_2 = C_1 + 2AD, \\ &C_3 = C_1(C_1 - 2A) - 4A^2 D = \Big(A + \tfrac{C_1}{\sqrt{1+4D}-1}\Big)\Big(\tfrac{C_1}{\sqrt{1+4D}+1} - A\Big). \end{aligned} \tag{7.1}$$

Then, at the Hopf critical point $B_{\mathrm{H}}^{\mathrm{I}_1}$, system $(3.2)_{\mathrm{I}_1}$ has one negative eigenvalue r_1, and a purely imaginary pair $\pm i\,\omega_c$, where

$$r_1 = -(1+D) - \tfrac{2AD}{C_1}, \qquad \omega_c = \sqrt{\tfrac{2AD(1+D)C_2}{C_3}} \quad \Big(0 < A < \tfrac{F+2R}{1+\sqrt{1+4D}}\Big). \tag{7.2}$$

Now based on the associated eigenvectors of the above eigenvalues, introducing the following affine transformation,

$$\begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = \begin{pmatrix} \frac{D}{C_1} \\ \frac{D[(F+2R)(A-B)-2AD]}{C_1 C_2} \\ \frac{(F+2R)(A-B)-2AD}{C_2} \end{pmatrix} + \begin{bmatrix} -\frac{DC_2}{(1+D)C_1C_2} & \frac{\omega_c C_3}{2A(1+D)C_1C_2} & \frac{DC_3}{(1+D)C_1^3} \\ \frac{D}{C_1} & \frac{\omega_c}{C_1} & -\frac{C_2}{C_1^2} \\ 1 & 0 & 1 \end{bmatrix} \begin{pmatrix} y_1 \\ y_2 \\ y_3 \end{pmatrix}, \tag{7.3}$$

and the time scale $\tau_1 = \omega_c \tau$ as well as the perturbation $B = B_{\mathrm{H}}^{\mathrm{I}_1} - \alpha$, into system $(3.2)_{\mathrm{I}_1}$, we obtain

$$\begin{aligned} \frac{\mathrm{d}y_1}{\mathrm{d}\tau_1} &= y_2 + (\alpha_{11} y_1 + \alpha_{12} y_2)\alpha + (\cdots) + \sum_{i+j+k=2} a_{ijk}\, y_1^i y_2^j y_3^k, \\ \frac{\mathrm{d}y_2}{\mathrm{d}\tau_1} &= -\,y_1 + (\alpha_{21} y_1 + \alpha_{22} y_2)\alpha + (\cdots) + \sum_{i+j+k=2} b_{ijk}\, y_1^i y_2^j y_3^k, \\ \frac{\mathrm{d}y_3}{\mathrm{d}\tau_1} &= -\tfrac{r_1}{\omega_c}\, y_3 + (\cdots) + \textstyle\sum_{i+j+k=2} c_{ijk}\, y_1^i y_2^j y_3^k. \end{aligned} \tag{7.4}$$

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where $(\cdots)$ denotes other terms involving α which are not needed for computing the normal form, and a_{ijk}, b_{ijk} and c_{ijk} are coefficients expressed in terms of the original parameters A, B, D, F and R. Here,

$$\alpha_{11} = -\frac{D(1+D)C_1^3C_2C_3}{\alpha^*(C_1+2AD)^2}, \qquad \alpha_{22} = \frac{DC_1C_3[(1+D)C_1^2C_2+C_3(C_1+2AD)]}{\alpha^*(C_1+2AD)^2},$$
$$\alpha_{12} = \frac{\omega_1(1+D)C_1^3C_3^2}{2\alpha^*A(C_1+2AD)^2}, \qquad \alpha_{21} = -\frac{\omega_c DC_1C_3[(1+D)C_1^2C_2+C_3(C_1+2AD)]}{\alpha^*(1+D)(C_1+2AD)^2},$$
$$\alpha^* = (1+D)C_1C_3(DC_1+C_2) + 2AD\big[(1+D)C_1^2C_2 + C_3(C_1+2AD)\big].$$

Then we can apply the formulas and algorithms developed in Yu (1998), Yu and Huseyin (1988) to obtain the normal form up to third order terms as follows:

$$\frac{\mathrm{d}\rho}{\mathrm{d}\tau_1} = \rho\big(v_0\,\alpha + v_1\,\rho^2 + \cdots\big), \qquad \frac{\mathrm{d}\theta}{\mathrm{d}\tau_1} = \omega_c + t_0\,\alpha + t_1\,\rho^2 + \cdots, \tag{7.5}$$

where v_i is called the ith focus values, and v_0 and t_0 are given by Yu and Huseyin (1988)

$$v_0 = \tfrac{1}{2}\,(\alpha_{11}+\alpha_{22}) = \frac{DC_1C_3^2}{2\alpha^*(C_1+2AD)} > 0,$$
$$t_0 = \tfrac{1}{2}\,(\alpha_{12}-\alpha_{21}) = \frac{\omega_c C_1C_3\{(1+D)^2C_1^2C_3+2AD[(1+D)C_1^2C_2+C_3(C_1+2AD)]\}}{4\alpha^*A(1+D)(C_1+2AD)^2}, \tag{7.6}$$

and v_1 and t_1 can be obtained by executing the Maple program given in Yu (1998). Since the sign of v_1 determines the stability of bifurcating limit cycles (i.e. to determine whether the Hopf bifurcation is supercritical or subcritical), we present v_1 here, given by $v_1 = \frac{v_{1n}}{v_{2d}}$, in which

$$\begin{aligned} v_{1n} = &-DC_3\big\{D_1C_3^4 + 2A\,(D_2+2D_3)\,C_3^3 + 8(1+D)A^3(D_4+2D_5)\,C_3^2 \\ &+ 32(1+D)^2A^5(D_6+2D_7)\,C_3 + 128D(1+D)^2A^7(D_8+2D_9)\big\}, \\ v_{1d} = &\,D_{10}\big\{(1+D)^2C_3^2 + 2A(D_{11}+2D_{12})C_3 \\ &+ 32D(1+D)A^3\big[(1+2D)(F+2R) + 2D(1+D)A\big]\big\} \\ &\times\big\{(1+D)^2C_3^2 + 2A(D_{13}+2D_{14})C_3 + 8D(1+D)A^3\big[(1+2D)\tilde{F} \\ &+ 2D(1+D)A\big]\big\}, \end{aligned} \tag{7.7}$$

where C_3 is given in (7.1), and other coefficients D_i's are given below.

$$\begin{aligned} D_1 &= (1+D)^2(4D^2-D+4), \\ D_2 &= (1+D)(6D^4+23D^3+37D^2+22D+10)(F+2R), \\ D_3 &= (3D^6+47D^5+144D^4+194D^3+135D^2+50D+8)A, \\ D_4 &= (D^6+31D^5+162D^4+271D^3+187D^2+63D+10)(F+2R), \\ D_5 &= (1+D)(11D^5+119D^4+218D^3+121D^2+29D+2)A, \end{aligned}$$

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$$
\begin{aligned}
D_6 &= (2D^6 + 45D^5 + 220D^4 + 276D^3 + 127D^2 + 25D + 2)(F + 2R),\\
D_7 &= D(13D^5 + 128D^4 + 259D^3 + 165D^2 + 42D + 4)A,\\
D_8 &= (D^6 + 21D^5 + 105D^4 + 158D^3 + 93D^2 + 23D + 2)(F + 2R),\\
D_9 &= D(5D^5 + 46D^4 + 101D^3 + 74D^2 + 21D + 2)A,\\
D_{10} &= 2(1 + D)\big[(1 + D)(F + 2R) + 2DA\big]^2,\ D_{11} = (1 + D)(1 + 7D)(F + 2R),\\
D_{12} &= D(5D^2 + 11D + 5)A, \quad D_{13} = (1 + D)(1 + 4D)(F + 2R),\\
D_{14} &= D(2 + D)(1 + 2D)A.
\end{aligned}
$$

Because $C_3 > 0$ due to $A < \frac{F+2R}{1+\sqrt{1+4D}}$ and $D_i > 0$ for all i, so $v_{1n} < 0$ and $v_{1d} > 0$, indicating $v_1 < 0$. Thus, the Hopf bifurcation is supercritical and bifurcating limit cycles are stable, and the approximation of the amplitude of the periodic solutions (limit cycles) can be obtained from the first equation of (7.5) as $\rho = (-\frac{v_0}{v_1}\alpha)^{1/2}$ ($v_0 > 0,\ v_1 < 0,\ \alpha > 0$). This agrees with the simulation presented in Sect. 7. □

7.2 Hopf Bifurcation in the three-Dimensional Symmetric Model (5.3)

Next, we consider the Hopf bifurcation which occurs in the model (5.3) on the invariant manifold $\mathrm{I}_{2/3}$ for the special case $R = 0$. The analysis for this three-dimensional system is similar to that for system $(3.2)_{\mathrm{I}_1}$ given in the previous subsection. Thus, we outline the proof for the following theorem.

Theorem 7.2 *For system (5.3), Hopf bifurcation can only occur from the equilibrium solution* $\mathrm{E}_2^{\mathrm{I}_{2/3}}$ *at the critical point* $B_{\mathrm{H}}^{\mathrm{I}_{2/3}} = A - \frac{AD}{F}$ *if* $A < \frac{2F}{1+\sqrt{1+4D}}$. *The Hopf bifurcation is supercritical and thus the bifurcating limit cycles are stable.*

Proof For system (5.3), at the Hopf critical point $B = B_{\mathrm{H}}^{\mathrm{I}_{2/3}}$, where $B_{\mathrm{H}}^{\mathrm{I}_{2/3}}$ is given in (5.5), the eigenvalues are $r_1 = -(1 + D) - \frac{AD}{F}$, and $\pm i\omega_c$, where $\omega_c = \left(\frac{AD(1+D)(F+AD)}{F^2-AF-DA^2}\right)^{1/2}$. Then using a similar transformation as that given in (7.3) to system (5.3), we obtain a normalized system similar to (7.4). Finally, applying the Maple program (Yu 1998) yields the normal form (7.5), for which

$$
\begin{aligned}
v_0 &= -\frac{DF\tilde{C}_3^2\omega_c}{2(F+AD)[(1+D)^2F^4-(1+D)AF^3-D(2D^2+4D+3)A^2F^2-D^2(2D+3)A^3F-D^3A^4]},\\
t_0 &= -\frac{DF[(1+D)F^3-(1+2D)AF^2+DA^2F+D^2A^3]}{2[(1+D)^2F^4-(1+D)AF^3-D(2D^2+4D+3)A^2F^2-D^2(2D+3)A^3F-D^3A^4]},
\end{aligned}
\tag{7.8}
$$

and $v_1 = \frac{v_{1n}}{v_{2d}}$, where

$$
\begin{aligned}
v_{1n} &= -D\tilde{C}_3\big\{D_1\tilde{C}_3^4 + A\,(D_2 + D_3)\,\tilde{C}_3^3 + (1 + D)A^3(D_4 + D_5)\,\tilde{C}_3^2\\
&\quad + (1 + D)^2A^5(D_6 + D_7)\,\tilde{C}_3 + D(1 + D)^2A^7(D_8 + D_9)\big\},\\
v_{1d} &= D_{10}\big\{(1 + D)^2\tilde{C}_3^2 + A(D_{11} + D_{12})\tilde{C}_3 + 4D(1 + D)A^3\\
&\quad \big[(1 + 2D)F + D(1 + D)A\big]\big\}\big\{(1 + D)^2\tilde{C}_3^2 + A(D_{13} + D_{14})\tilde{C}_3\\
&\quad \times +D(1 + D)A^3\big[(1 + 2D)F + D(1 + D)A\big]\big\}.
\end{aligned}
\tag{7.9}
$$

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Here, $\tilde{C}_3 = C_3 |_{R=0} = F^2 - AF - DA^2 > 0$ due to $A < \frac{2F}{1+\sqrt{1+4D}}$, and D_i's are given in Appendix B with $R = 0$. This shows that $v_1 < 0$, and therefore, the Hopf bifurcation is supercritical and the bifurcating limit cycles are stable. □

7.3 Hopf Bifurcation in the six-Dimensional Asymmetric Model (3.1)

For the general asymmetric model (3.1), to simplify the analysis, except B (i.e. μ), we take the parameter values from Table 1 and choose $p = \frac{1}{2}$, and treat B as a bifurcation parameter. Then, we have the following dimensionless parameter values:

$$A = 1.0033, \quad D = 0.509, \quad F = 1.4582, \quad R = 0.00007292, \tag{7.10}$$

showing that $1.0033 = A > \frac{F+2R}{1+\sqrt{1+4D}} = 0.531777$. Thus, according to Theorem 4.3, Hopf bifurcation may occur at the critical point $B = B_{\mathrm{H}}^{(1)}$ if $B_{\mathrm{H}}^{(1)} < A(1-2D^{**})$. Indeed, at $B = A = 1.0033$, the equilibrium E_0 loses stability and the equilibrium E_1 bifurcates. Then when B is further decreased to cross $B = A(1-2D^{**}) = 0.302965$, the equilibrium E_1 loses stability and bifurcates into equilibrium E_4, which loses stability at the Hopf critical point $B = B_{\mathrm{H}}^{(1)} = 0.302708$, leading to a family of limit cycles. More precisely, we have the following result.

Theorem 7.3 *For the parameter values given in* (7.10)*, system* (3.1) *undergoes a Hopf bifurcation at the critical point* $B_{\mathrm{H}}^{(1)} = 0.302708$. *The Hopf bifurcation is supercritical and thus the bifurcating limit cycles are stable.*

Proof We use normal form theory to prove Theorem 7.3. To obtain the normal form for this case, we first let $B = 0.302708 - \alpha$, where α is a perturbation parameter from the Hopf critical point, and now $\alpha = 0$ defines the Hopf critical point. At the critical point, the equilibrium E_4 given in (4.4) becomes

$$\mathrm{E}_4: \quad (0.349016,\ 0.349016,\ 0.000053,\ 0.000053,\ 0.000151,\ 0.000151),$$

and the linearized system of (3.1) has a pair of purely imaginary eigenvalues and four real negative eigenvalues:

$$\xi = \pm 0.007134\, i, \quad -0.000124, \quad -0.700235, \quad -1.508961, \quad -1.508984.$$

With these eigenvalues, we obtain a set of corresponding eigenvectors, which yields a linear transformation T, and then apply the affine transformation $\mathbf{x} = \mathrm{E}_4 + T\mathbf{y}$, together with $B = 0.302708 - \alpha$, into system $(3.2)_{\mathrm{I}_1}$ to obtain the system

$$\dot{\mathbf{y}} = J\,\mathbf{y} + \mathbf{f}(\mathbf{y}, \alpha), \tag{7.11}$$

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where J is in the Jordan canonical form. Now we can use the formulae to find v_0 and t_0:

$$v_0 = \frac{1}{2}\left[\frac{\mathrm{d}^2 f_1}{\mathrm{d}y_1\,\mathrm{d}\alpha}(\mathbf{0},0) + \frac{\mathrm{d}^2 f_2}{\mathrm{d}y_2\,\mathrm{d}\alpha}(\mathbf{0},0)\right] = 0.065723,$$
$$t_0 = \frac{1}{2}\left[\frac{\mathrm{d}^2 f_1}{\mathrm{d}y_2\,\mathrm{d}\alpha}(\mathbf{0},0) + \frac{\mathrm{d}^2 f_2}{\mathrm{d}y_1\,\mathrm{d}\alpha}(\mathbf{0},0)\right] = 13.901119.$$

Then setting $\alpha = 0$ and executing the Maple program (Yu 1998) on system (7.11) to obtain

$$v_1 = -0.744051 \times 10^2, v_2 = -0.265818 \times 10^8, \quad v_3 = -0.707090 \times 10^{14}, \cdots$$
$$t_1 = -0.325775 \times 10^4, t_2 = -0.194141 \times 10^{10}, \quad t_3 = 0.418827 \times 10^{16}, \cdots$$

and thus the normal form is given by

$$\begin{aligned}\dot{\rho} &= \rho\,(0.065723\,\alpha - 74.405150\,\rho^2 + \cdots),\\ \dot{\theta} &= 0.007134 + 13.901119\,\alpha - 3257.750850\,\rho^2 + \cdots.\end{aligned} \tag{7.12}$$

It follows from $v_1 < 0$ that the Hopf bifurcation is supercritical and so the bifurcating limit cycles are stable, and the approximations of the amplitude and frequency of the motion are given by

$$\rho \approx 0.029721\sqrt{\alpha}, \qquad \omega \approx 0.007134 + 11.023508\,\alpha.$$

The proof of Theorem 7.3 is complete. □

8 Numerical Simulation

To illustrate and confirm these analytical results, simulations for system (3.1) were performed by numerical integration (ODE45 package in MATLAB). Parameter values were as provided in Table 1, with the exception of μ, which was varied to explore the stability regimes illustrated in Fig. 2a through changes in the composite parameter $B = \mu/\delta$. We also tested our predictions in the absence of recombination, which implies $r = 0$ and therefore $R = 0$ in the non-dimensionalized model. Results are plotted as population densities versus time. Unless otherwise noted, we take initial conditions with both types of uninfected host cells and both phage types, thus simulating the invasion dynamics as well as equilibrium conditions.

In Fig. 4a we take $B = 1.02 > A$, such that the system approaches the trivial equilibrium. When B is reduced slightly to $B! = 0.9$, the condition $A(1-D^*) < B < A$ holds, and the system converges, as expected, to equilibrium E_1; only uninfected host cells persist. This is illustrated in Fig. 4b.

Figure 5 illustrates the predicted effect of diversification. In this simulation we take $B = 0.5$, such that $A(1-2D^{**}) < B < A(1-D^*)$. When the initial conditions only include host cells with receptor J (neither H_{JKK} nor I_{JKK} is present), the system

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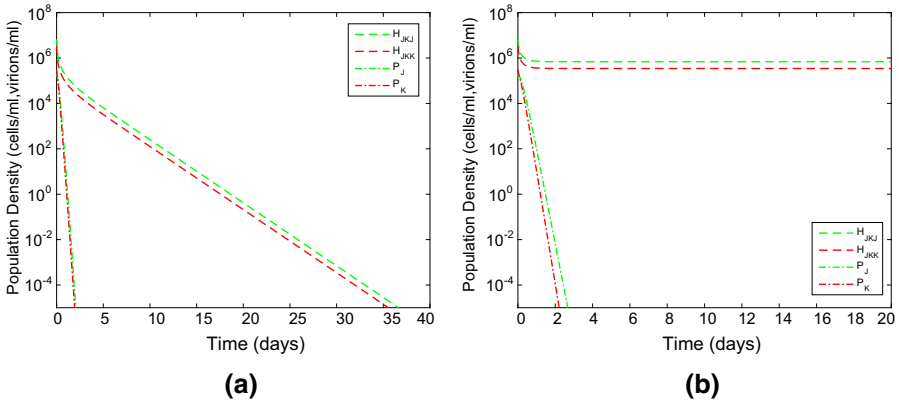

Fig. 4 **a** Time course of system (3.1) with $B = 1.02$. Since $B > A$, the system approaches the trivial equilibrium with all populations going extinct. Other initial conditions were $H_{JKJ} = \frac{2K}{3}$, $H_{JKK} = \frac{K}{3}$, $I_{JKJ} = I_{JKK} = 0$ and $P_J = 2 \times 10^5$, $P_K = 3 \times 10^5$. **b** Time course of system (3.1) with $B = 0.9$, such that $A(1 - D^*) < B < A$. The system converges to E_1 with only uninfected host cells remaining. Other initial conditions were $H_{JKJ} = \frac{2K}{3}$, $H_{JKK} = \frac{K}{3}$, $I_{JKJ} = I_{JKK} = 0$ and $P_J = 2 \times 10^5$, $P_K = 3 \times 10^5$

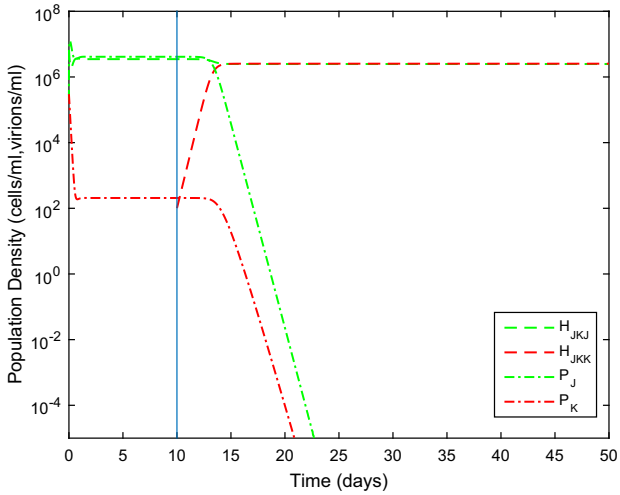

Fig. 5 Time course of system (3.1) with parameters in the range $A(1 - 2D^{**}) < B < A(1 - D^*)$. We take $B = 0.5$ and initial conditions $H_{JKJ} = \frac{2K}{3}$, $H_{JKK} = 0$, $I_{JKJ} = \frac{K}{3}$, $I_{JKK} = 0$ and $P_J = 2 \times 10^5$, $P_K = 3 \times 10^5$. The system initially converges to equilibrium $E_{2/3}$. At time $t = 10$, we introduce $H_{JKK} = 100$, and the system rapidly converges to E_1, eliminating the phage populations

converges to equilibrium $E_{2/3}$, which is unstable in the full system but stable on the invariant manifold with $H_{JKK} = I_{JKK} = 0$. Thus, when the complementary host cell population H_{JKK} is added, the equilibrium loses stability. The system converges to the stable equilibrium E_1 of the full system, and both phage populations decay to zero. Thus the diversification of the host cell population from a single type to multiple types can potentially drive both phage populations to extinction.

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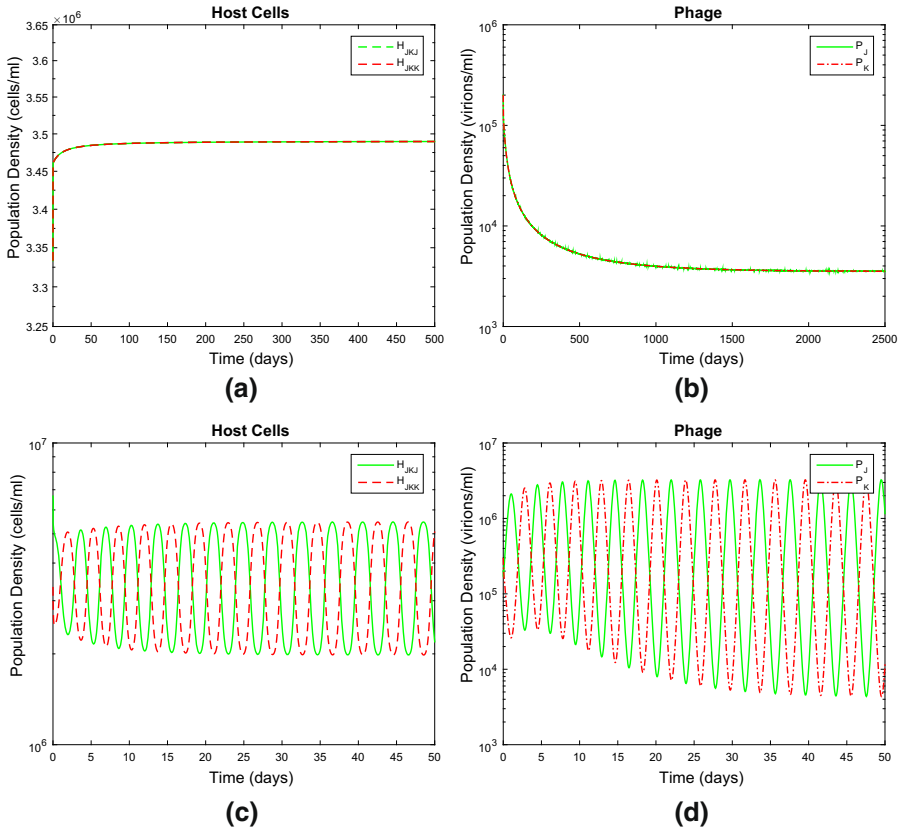

Fig. 6 **a**, **b** show the time course for $B_{\mathrm{H}} < B < A(1-2D^{**})$. Here $B = 0.3028$, with initial conditions $H_{JKJ} = H_{JKK} = \frac{K}{3}$, $I_{JKJ} = I_{JKK} = 0$ and $P_J = P_K = 2 \times 10^5$. The system converges to the stable equilibrium E_4. **c**, **d** show the time course for $0 < B < B_{\mathrm{H}}$. Here $B = 0.25$, with initial conditions $H_{JKJ} = \frac{2K}{3}$, $H_{JKK} = \frac{K}{3}$, $I_{JKJ} = I_{JKK} = 0$ and $P_J = 2 \times 10^5$, $P_K = 3 \times 10^5$. We observe a stable limit cycle

Figure 6 illustrates the cases $B_{\mathrm{H}} < B < A(1-2D^{**})$ and $0 < B < B_{\mathrm{H}}$, respectively. We observe stable convergence to equilibrium E_4, with all populations present (panels (a) and (b)), and a stable limit cycle around E_4 (panels (c) and (d)) as expected. We note that at the parameter values we have chosen from the literature, the parameter regime $B_{\mathrm{H}} < B < A(1-2D^{**})$ is quite narrow, and thus our results predict that oscillations would be commonly observed in natural phage-host systems.

Finally, we numerically investigated the effect of recombination, r. Starting in the regime $B < B_{\mathrm{H}}$, we investigate a situation in which both types of phage are initially present, and the host cells diversify to escape the phage. Thus we begin with type J host cells, and both viral types, but at a later time introduce type K host cells.

In Fig. 7a, the resulting dynamics are shown in the absence of recombination. We see that phage P_K goes extinct early in the simulation because of the lack of type K host cells. Later, when type K host cells are introduced, these host cells compete with

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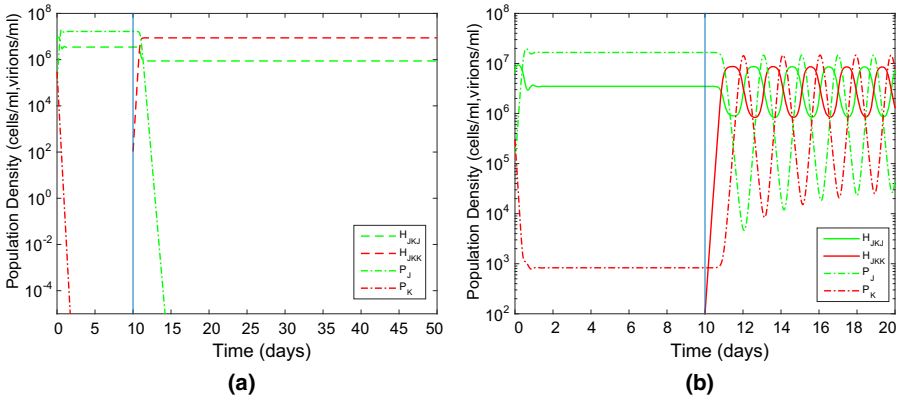

Fig. 7 **a** Extinction of phage in the absence of recombination. A time course is shown for $B = 0.037$, and initial conditions $H_{JKJ} = \frac{2K}{3}$, $H_{JKK} = 0$, $I_{JKJ} = I_{JKK} = 0$ and $P_J = 2 \times 10^5$, $P_K = 3 \times 10^5$. The parameter r was set to zero to analyse the absence of recombination. At time $t = 10$, $H_{JKK} = 100$ is introduced (the host diversifies). Note that phage P_K goes extinct at early times due to the lack of host cells, while P_J goes extinct once the new type of host is introduced. Only uninfected host cells persist. **b** Survival of phage in the presence of recombination. Parameter values and initial conditions are as described for (**a**), with the exception that $r = 0.0001$. Recombination preserves the phage population from extinction

and reduce the population of type J host cells. The uninfected H_{JKJ} population is no longer sufficiently large to maintain phage, and ultimately phage J is also unable to survive. The system converges to E_1.

In contrast, Fig. 7b illustrates the same results in the presence of recombination. Before the introduction of the type K host cells, type K phage is present at low levels due to recombination with prophage in the host cell genome. When type K host cells are introduced, the system approaches a limit cycle in which all populations are present. Thus recombination preserves the phage populations from extinction.

9 Conclusion and Discussion

Figure 2a succinctly summarizes our main results, and in this concluding section we interpret the implications of those results in terms of the original model. Moving along the x-axis of Fig. 2a corresponds, in the original model, to increasing the death rate of host cells. Thus when the death rate is very high (far right), the host cell population cannot sustain itself and the trivial equilibrium is stable. At intermediate death rates, the host cells are able to sustain themselves, and the two types can coexist at any ratio, such that the population densities sum to a constant. However in this region, the host cell density is not sufficient to maintain the phage populations. Further to the left, the host cell population densities are sufficiently high that the phage population can invade, and all host and phage types are present at the stable equilibrium.

Stability analysis generally identifies equilibria that are stable to small perturbations in all population densities. In phage-host systems in nature, however, not all populations may be present, and rare mutations may be required to introduce perturbations for populations that are initially at zero density. Thus perturbations away from

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boundaries at which one or more population densities are zero are qualitatively different from perturbations in other population densities. This consideration motivated us to investigate situations in which not all populations are present initially.

An intriguing prediction emerges from this study when we take this approach. In Fig. 7a, we illustrate a situation in which initially only one type of host, H_{JKJ}, exists. We allow both types of prophage to exist by recombination, although this does not affect the result. If the system is in the parameter regime in the centre of Fig. 2a ($A(1-2D^{**}) < B < A(1-D^{*})$), the system converges to equilibrium $E_{2/3}$; the host population sustains the P_J population, P_K is produced at a low level by recombination, and a mix of H_{JKJ} and I_{JKJ} survive at equilibrium. Now however, if the host diversifies and is able to produce H_{JKK} individuals, the system will converge to equilibrium E_1, which includes only the two uninfected host cell populations. Thus, by diversifying into two distinct populations, the host drives the phage populations to extinction.

This prediction holds even if the phage is equally adept at diversifying; both types of phage are present and nonetheless they do not persist. The underlying issue in this example is that each type of phage requires a certain minimum density of susceptible host cells, such that the basic reproductive ratio for that phage type exceeds one. When only one type of host cell exists, that host type can grow to the carrying capacity, and sustain the corresponding phage type; recombination will stably maintain the other phage. However at the same parameter values, if two host cell types co-exist, neither has sufficient density to maintain their phage predators. Expanding this to a real-world situation with many host and phage types, we predict that host cell populations that are able to diversify, such that only a subset of cells are susceptible to a specific phage type, may be able to drive several phage types to extinction. One caveat is that this phenomenon is only possible in the possibly limited parameter range $A(1-2D^{**}) < B < A(1-D^{*})$. In terms of our original model and parameter values, we find $0.3030 < B < 0.6531$.

A related prediction highlights the effect of recombination, as illustrated in Fig. 7b. In this scenario, we take parameter values in the region $B < A(1-2D^{**})$, and again consider a situation in which initially only one type of host cell exists. In this region, the host cell population stably maintains the corresponding phage population. We then introduce the second host cell population by diversification. If recombination is possible, the system converges to E_4, and we observe all six populations at equilibrium or in an oscillatory pattern. However this result critically depends on recombination. If we set the recombination rate to zero, the system converges to E_1 when the second host cell type is introduced. Thus once again, diversification of the host population can drive the viral population to extinction, but in this parameter regime extinction is only possible if recombination does not occur. In other words, the ability to recombine with prophage in the host genome is critically important to the phage population, and can save the phage from extinction. The condition $B < A(1-2D^{**})$, in terms of the parameter values of the original model, is $B < 0.3030$, and thus we expect this scenario to be relevant to a wide range of host-phage systems.

Overall, the work we present here highlights the importance of prophage and recombination to the equilibria of phage-host systems. Although the model simplifies many aspects of the underlying biology, the clearest direction for future work is to relax the

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assumption that host cells express only one receptor type, as host cells are known to up- and down-regulate various receptors in response to phage pressure (Meyer et al. 2012). Prophage can also confer immunity to further infection (Stewart and Levin 1984), and can be lost from the host genome over time (Stewart and Levin 1984); both of these possibilities should be included in future work.

Finally, we would like to point out that in this paper we focus on the stability and bifurcation of equilibrium solutions, in particular on transcritical and Hopf bifurcations. However, other bifurcations such as saddle-node bifurcations or Bogdanov-Takens (B-T) bifurcations may also occur. For example, for the general six-dimensional system (3.1), at the critical point defined by the condition $(F+2R)(A-B)-2AD=0$, the equilibrium E_1 loses stability at a singularity with a double zero eigenvalue, giving rise to B-T bifurcation. For the special six-dimensional system (5.1), a triple-zero singularity can occur on the equilibrium solution E_1^0 when the condition $F(A-B)-2AD=0$ is satisfied. Also, for modelling, the maximum growth rate λ in (2.4) [or A in the dimensionless system (3.1)] may be different for the two equations. These dynamical analyses will be carried out in our future work.

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