Coupled within-host and between-host dynamics and evolution of virulence

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Abstract

Mathematical models coupling within- and between-host dynamics can be helpful for deriving trade-off functions between disease transmission and virulence at the population level. Such functions have been used to study the evolution of virulence and to explore the possibility of a conflict between natural selection at individual and population levels for directly transmitted diseases [11]. In this paper, a new coupled model for environmentally-driven diseases is analyzed to study similar biological questions. It extends the model in [3, 7] by including the disease-induced host mortality. It is shown that the extended model exhibits similar dynamical behaviors including the possible occurrence of a backward bifurcation. It is also shown that the within-host pathogen load and the disease prevalence at the positive stable equilibrium are increasing functions of the within- and between-host reproduction numbers ($\mathcal{R}_{w0}$ and $\mathcal{R}_{b0}$), respectively. Optimal parasite strategies will maximize these reproduction numbers at the two levels, and a conflict may exist between the two levels. Our results highlight the role of interdependence of variables and parameters in the fast and slow systems for persistence of infections and evolution of pathogens in an environmentally-driven disease. Our results also demonstrate the importance of incorporating explicit links of the within- and between-host dynamics into the computation of threshold conditions for disease control.

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1. Introduction

It has been shown that models that couple the disease dynamics at the population level and the cell-pathogen dynamics within hosts can generate new insights into host-pathogen interactions (e.g., [1, 7, 8, 10, 11, 12, 15]). Gilchrist and Coombs demonstrated in [11] that nested models can be used to derive the functional relationships between disease transmission and virulence at the population level, and these functions are helpful for studying the evolution of virulence. Particularly, based on the assumptions about the dependence of between-host transmission and disease-induced host mortality on the within-host variables (e.g., pathogen load and cell density), they illustrated the possible occurrence of a conflict between natural selection at the individual and population levels.

The examples considered in [11] also provide specific functional forms for describing the trade-off relationships between disease transmission and pathogen virulence. In one of their examples, the disease transmission rate at the population level β is assumed to be a power function of the within-host pathogen load V , i.e.,

$$\beta(V) = a_1 V^z, \quad z > 0, \quad (1)$$

where a_1 is a positive constant, while the disease-induced host mortality (virulence) α is assumed to be a function of the average density of target cells T within a host given by

$$\alpha(T) = a_2 \left(\frac{1}{T} - \frac{1}{T_0} \right), \quad (2)$$

where T_0 is the density of target cells at the infection-free steady state and a_2 is a positive constant. Under the assumption that the within-host dynamics occur on a much faster time scale than the between-host dynamics, the variables V in Equation (1) and T in Equation (2) can be replaced by their values at the positive steady state, which leads to the following relationship between α and β :

$$\beta(\alpha) = a_1 \left(\frac{\Lambda \alpha}{a_2 k} \right)^z, \quad (3)$$

where Λ and k are parameters associated with the within-host system. Because the qualitative behavior of the function in Equation (3) can be very different for $z > 1$ (concave up) and $z < 1$ (concave down), the two cases generate dramatically different conclusions regarding the direction of natural selection at the within- and between-host levels. That is, while there is no conflict between the two levels of selection when $z \geq 1$, a conflict may exist when $z < 1$.

It is demonstrated in [3, 7] that when a simple within-host model for cell-pathogen interactions is coupled explicitly with an SIE epidemiological model (E for environment), new disease dynamics can emerge. Specifically, when the two models are in isolation, the dynamical behavior of each model is standard and simple in the sense that either the infection-free equilibrium is stable if the respective reproduction number ($\mathcal{R}_{b0}$ or $\mathcal{R}_{w0}$, where the subscripts b and w stand for between-host and within-host respectively) is less than 1, or the unique positive equilibrium exists and is stable if the respective reproduction number is greater than 1. However, when the two models are dynamically coupled, a stable positive equilibrium can be present even when $\mathcal{R}_{b0} < 1$, in which case the disease can persist in the host population. That is, the so called backward bifurcation can appear, which makes the disease control much more difficult (see [2] for a more detailed discussion about backward bifurcation in the context of an invading population). The public health implication of such a backward bifurcation is that the usual threshold condition $\mathcal{R}_{b0} < 1$ for disease elimination no longer holds. Control measures need to bring $\mathcal{R}_{b0}$ to be below another quantity, denoted by $\mathcal{R}_{bL}$, which is smaller than 1. The coupled models are also helpful for identifying critical factors that may contribute to the occurrence of the backward bifurcation, and suggesting the best strategies to achieve the new threshold condition $\mathcal{R}_{b0} < \mathcal{R}_{bL}$ and reduce the size of the “window of opportunity”, $(\mathcal{R}_{bL}, 1)$, for backward bifurcation.

For simplicity, the coupled model in [3] and [7] ignores the disease-induced host mortality. Under this assumption, the dimension of the between-host SIE system can be reduced to two as the total host population $N = S + I$ remains constant for all time. However, this simplification limits the application of the model for the study of certain biological questions such as the evolution of virulence (if the virulence is represented by the host mortality due to the disease). In this paper, we include the disease-induced host death in the SIE epidemiological model. We explore the dynamics of the extended model as well as biological questions related to the evolution of virulence.

For the analysis of the coupled model, we follow the same approach as in previous studies (see, e.g., [1, 3, 11]) and assume that the within-host dynamics are fast compared to the dynamics at the population level, which allows us to analyze the within-host (fast) dynamics first while treating the between-host (slow) variables as constant. We show that the fast system has a unique global attractor (the positive steady state), which allows us to substitute the steady state values of the fast variables into the slow system to study the slow dynamics. The increased dimension of the slow system due to the disease-induced mortality makes the analysis much more challenging. Although only limited analytical results can be derived, numerical simulations are carried out to extend the analytical results. Our analyses show that the dynamics of extended model are similar to those of the model without the disease mortality, including the possibility of a backward bifurcation.

One of the new features in the coupled model in this paper, in comparison with the nested model in [11], is that it deals with an environmentally-driven infectious disease. The results presented in this paper suggest that some of the biological insights obtained in [11] for directly transmitted infectious diseases also apply to environmentally-driven diseases. Specifically, when the transmission function $\beta(V)$ given in Equation (1) and the disease mortality function $\alpha(T)$ given in Equation (2) are used in our model, we find that a conflict between selection at the between- and within-host levels exists for the case when $z < 1$. The links of between-host parameters to the within-host variables can also be used to determine the interdependence of disease transmission and host virulence, and to examine how the optimal virulence may depend on the physiological constraints on parasite production and virulence (see section 3).

2. The model and analyses

The coupled model considered in this paper is an extension of the model studied in [3, 7] by including a disease-induced death rate for the hosts. This modeling approach can be applied to environmentally-driven infectious diseases such as toxoplasmosis, which is a disease caused by the parasite *Toxoplasma gondii*. The main definitive hosts of the pathogen are members of family Felidae (domestic cats and their relatives). The definitive hosts can become infected either by consumption of infected intermediate hosts (e.g., rats) or by direct ingestion of the parasites existent in a contaminated environment. The within-host system describes the cell-parasite interaction

and keeps track of the densities of uninfected and infected cells as well as the average parasite load within a host (see [16, 17, 18, 20, 21, 22] for similar models of cell-pathogen interactions). The level of environment contamination is dependent on both the number of infected hosts and the average parasite load within a host. The parasites can remain in the environment for several months. Since infected hosts will remain infectious for life, the epidemiological model at the population level is of an SIE type, and the hosts may die from the disease.

The model consists of the following 6 ordinary differential equations:

$$\begin{aligned}
\dot{T} &= \Lambda_c - kVT - mT, \\
\dot{T}^* &= kVT - (m + d)T^*, \\
\dot{V} &= g(E) + pT^* - cV, \\
\dot{S} &= \Lambda_h - \lambda ES - \mu S, \\
\dot{I} &= \lambda ES - (\mu + \delta)I, \\
\dot{E} &= \theta(V)I(1 - E) - \gamma E,
\end{aligned} \tag{4}$$

where $T = T(t)$, $T^* = T^*(t)$ and $V = V(t)$ are the densities of healthy cells, infected cells and parasite load, respectively. $S = S(t)$ and $I = I(t)$ denote the numbers of susceptible and infectious individuals at time t , respectively. The parameters Λ_c , k , m , d , p and c are all positive constants associated with the within-host cell-pathogen interactions, and their definitions are listed in Table 1. We adopt a similar assumption made in [11] on the disease transmission at the population level and assume that the rate of environment contamination is proportional to the number of infected hosts and the parasite load V within a host, which has the form $\theta(V)I$ with $\theta(V)$ being an increasing function of V . Possible functional forms for $\theta(V)$ include $\theta_0 V$ and $\theta_0 V^z$ for $z \neq 1$, where θ_0 and z are positive constants. The parameter γ denotes the rate of pathogen clearance in the environment, λ denotes the per-capita infection rate of hosts in a contaminated environment, Λ_h represents a constant recruitment rate of susceptibles, μ and δ denote the natural and disease-induced death rates, respectively. $E = E(t)$ represents the level of environment contamination at time t ($0 \leq E \leq 1$), or the concentration of the pathogen per unit area of a region being considered. The function $g(E)$ denotes an added rate in the change of parasite load due to the continuous ingestion of parasites by the host from a contaminated environment, and is

assumed to have the following properties:

$$g(0) = 0, \quad g(E) \geq 0, \quad g'(E) > 0, \quad g''(E) \leq 0. \quad (5)$$

One of the simplest forms for $g(E)$ considered in [3, 7] is the linear function $g(E) = aE$, where a is a positive constant. Other forms of $g(E)$ considered in [3] include $g_1(E) = aE/(1+bE)$ with a and b being positive constants and $g_2(E) = aE^q$ ($q < 1$).

2.1. Separation of the fast and slow systems

A common approach to analyzing coupled systems is to take advantage of the different time scales of the processes being modeled. The within-host dynamics usually occurs on a faster time scale than the between-host dynamics. Thus, analytical studies are usually carried out by first computing the positive steady state of the within-host system consisting of the T , T^* and V equations (with E being treated as a constant), and then substituting these steady state values (as functions of E) into the between-host system consisting of the S , I and E equations. This approach of separating time scales can be justified by applying tools in perturbation theory (see [9, 19]). We provide a detailed derivation in this section.

For demonstration purposes we consider the case when $\theta(V) = \theta_0 V$ is a linear function. Introduce a slow time variable $\tau = \epsilon t$, where $0 < \epsilon \ll 1$, and consider the parameters associated with the dynamics at the population level to be small based on the assumption that the between-host dynamics occur on a slower time scale than that of parasite-cell dynamics within the host. Denote $\dot{\cdot} = \frac{d}{dt}$ and $\dot{\cdot}' = \frac{d}{d\tau}$. Let

$$\Lambda_h = \epsilon \tilde{\Lambda}_h, \quad \mu = \epsilon \tilde{\mu}, \quad \delta = \epsilon \tilde{\delta}, \quad \lambda = \epsilon \tilde{\lambda}, \quad \theta_0 = \epsilon \tilde{\theta}_0, \quad \gamma = \epsilon \tilde{\gamma}.$$

Then, the full system can be written as

$$\begin{aligned} \dot{T} &= \Lambda_c - kVT - mT, \\ \dot{T}^* &= kVT - (m + d)T^*, \\ \dot{V} &= g(E) + pT^* - cV, \\ \dot{S} &= \epsilon(\tilde{\Lambda}_h - \tilde{\lambda}ES - \tilde{\mu}S), \\ \dot{I} &= \epsilon(\tilde{\lambda}ES - (\tilde{\mu} + \tilde{\delta})I), \\ \dot{E} &= \epsilon(\tilde{\theta}_0 VI(1 - E) - \tilde{\gamma}E), \end{aligned} \quad (6)$$

or with respect to the slower time τ :

$$\begin{aligned}
\epsilon T' &= \Lambda_c - kVT - mT, \\
\epsilon T^{*'} &= kVT - (m + d)T^*, \\
\epsilon V' &= g(E) + pT^* - cV, \\
S' &= \tilde{\Lambda}_h - \tilde{\lambda}ES - \tilde{\mu}S, \\
I' &= \tilde{\lambda}ES - (\tilde{\mu} + \tilde{\delta})I, \\
E' &= \tilde{\theta}_0VI(1 - E) - \tilde{\gamma}E.
\end{aligned} \tag{7}$$

Using techniques in singular perturbation theory we can analyze system (4) by analyzing the corresponding fast and slow dynamics. The fast dynamics can be analyzed using the system (which we will refer to as fast system) obtained by letting $\epsilon = 0$ in system (6):

$$\begin{aligned}
\dot{T} &= \Lambda_c - kVT - mT, \\
\dot{T}^* &= kVT - (m + d)T^*, \\
\dot{V} &= g(E) + pT^* - cV,
\end{aligned} \tag{8}$$

in which E is considered as a constant parameter. The slow dynamics can be studied using the system obtained by letting $\epsilon = 0$ in system (7) and dropping the ‘tilde’ for ease of notation (which will be referred to as the slow system):

$$\begin{aligned}
S' &= \Lambda_h - \lambda ES - \mu S, \\
I' &= \lambda ES - (\mu + \delta)I, \\
E' &= \theta_0IV(1 - E) - \gamma E,
\end{aligned} \tag{9}$$

in which the fast variables will be replaced by their values at a stable steady state of the fast system (8), provided that the fast system has a unique stable steady state.

To determine whether or not the coupled system can generate new disease dynamics, we examine first the dynamics of the fast (within-host) system (8) and the slow (between-host) system (9) in isolation.

2.2. Dynamics of the fast and slow systems in isolation

We show in this section that when the fast and slow systems are in isolation, i.e., when $E = 0$ in (8) and V is a constant in (9), the dynamics of both

systems are standard and simple. Although this feature has been illustrated in [3] for the 2-dimensional between-host system, we provide details in this section as the system here is 3-dimensional.

Specifically, the behavior of the within-host system is determined by the within-host reproduction number

$$\mathcal{R}_{w0} = \frac{kpT_0}{c(m+d)}, \quad (10)$$

where $T_0 = \Lambda_c/m$ is the total amount of target cells in the absence of infection. If $\mathcal{R}_{w0} < 1$ then the infection-free equilibrium $U_0 = (T_0, 0, 0)$ is globally asymptotically stable (g.a.s.), whereas if $\mathcal{R}_{w0} > 1$ then the unique positive equilibrium

$$U_1 = \left(\frac{T_0}{\mathcal{R}_{w0}}, \frac{mT_0}{m+d} \left[1 - \frac{1}{\mathcal{R}_{w0}} \right], \frac{m(\mathcal{R}_{w0} - 1)}{k} \right)$$

is g.a.s. (see [6, 14]).

When the between-host system (9) is in isolation, with V being a constant, the dynamics can be determined by the between-host reproduction number

$$\hat{\mathcal{R}}_{b0} = \frac{\theta_0 V}{\mu + \delta} \frac{\lambda S_0}{\gamma}, \quad (11)$$

where $S_0 = \Lambda_h/\mu$ is the total number of hosts in the absence of infection. The existence and global stability of the steady states can be proved by using Lyapunov Theorem [5]. The two steady states are $W_0 = (S_0, 0, 0)$ (disease-free), which always exists, and

$$W_1 = (S_1, I_1, E_1) = \left(\frac{\theta_0 \Lambda_h V + \gamma(\mu + \delta)}{\theta_0(\lambda + \mu)V}, \frac{\gamma\mu(\hat{\mathcal{R}}_{b0} - 1)}{\theta_0(\lambda + \mu)V}, \frac{\mu(\hat{\mathcal{R}}_{b0} - 1)}{\lambda + \mu\hat{\mathcal{R}}_{b0}} \right),$$

which exists if and only if $\hat{\mathcal{R}}_{b0} > 1$. Introduce the following two Lyapunov functions:

$$\mathcal{L}_0(S, I, E) = S_0 \left(\frac{S}{S_0} - \ln \frac{S}{S_0} - 1 \right) + I + \frac{\mu + \delta}{\theta_0 V} E$$

and

$$\begin{aligned} \mathcal{L}_1(S, I, E) = & S_1 \left(\frac{S}{S_1} - \ln \frac{S}{S_1} - 1 \right) + I_1 \left(\frac{I}{I_1} - \ln \frac{I}{I_1} - 1 \right) \\ & + \frac{(\mu + \delta)E_1}{\theta_0 V(1 - E_1)} \left(\frac{E}{E_1} - \ln \frac{E}{E_1} - 1 \right). \end{aligned}$$

It is easy to verify that $\mathcal{L}_0 \geq 0$ and $\mathcal{L}_1 \geq 0$ in the biologically feasible region $\mathcal{D} = \{(S, I, E) : S, I \geq 0, 0 \leq E \leq 1\}$, with $\mathcal{L}_0 = 0$ and $\mathcal{L}_1 = 0$ only at W_0 and W_1 , respectively. Note that along system (9) we have

$$\begin{aligned} \frac{d\mathcal{L}_0}{dt} &= \left(1 - \frac{S_0}{S}\right) (L - \lambda ES - \mu S) + \lambda ES - (\mu + \delta)I + \frac{\mu + \delta}{\theta_0 V} (\theta_0 IV(1 - E) - \gamma E) \\ &= \mu S_0 \left(2 - \frac{S}{S_0} - \frac{S_0}{S}\right) + \frac{\gamma(\mu + \delta)}{\theta_0 V} (\hat{\mathcal{R}}_{b0} - 1)E - (\mu + \delta)IE \end{aligned}$$

and

$$\begin{aligned} \frac{d\mathcal{L}_1}{dt} &= \left(1 - \frac{S_1}{S}\right) (L - \lambda ES - \mu S) + \left(1 - \frac{I_1}{I}\right) (\lambda ES - (\mu + \delta)I) \\ &\quad + \frac{(\mu + \delta)}{\theta_0 V(1 - E_1)} \left(1 - \frac{E_1}{E}\right) (\theta_0 IV(1 - E) - \gamma E) \\ &= \mu S_1 \left(2 - \frac{S}{S_1} - \frac{S_1}{S}\right) + (\mu + \delta)I_1 \left(3 - \frac{S_1}{S} - \frac{E_1 I}{I_1 E} - \frac{I_1 S E}{S_1 E_1 I}\right) \\ &\quad - \frac{(\mu + \delta)(E - E_1)^2 I}{(1 - E_1)E}. \end{aligned}$$

In region $\mathcal{D}$, if $\hat{\mathcal{R}}_{b0} < 1$ then $d\mathcal{L}_0/dt \leq 0$ with $d\mathcal{L}_0/dt = 0$ only at W_0 , whereas if $\hat{\mathcal{R}}_{b0} > 1$ then $d\mathcal{L}_1/dt \leq 0$ with $d\mathcal{L}_1/dt = 0$ only at W_1 . It follows from Lyapunov Theorem [5] that W_0 is g.a.s. when $\hat{\mathcal{R}}_{b0} < 1$ while W_1 is g.a.s. when $\hat{\mathcal{R}}_{b0} > 1$.

Next, we examine the dynamical behaviors of the within-host system (8) and the between-host system (9) when they are explicitly coupled.

2.3. Disease dynamics of the coupled system

To study the coupled dynamics we consider only the case when $E > 0$. The fast system (8) has the same form as that in [3]. Thus, we omit the detailed analysis and present only the results. Let $U(E) = (T(E), T^*(E), V(E))$ denote the unique positive equilibrium of the fast system (8). For ease of reference, we list below the expressions for the components of $U(E)$:

$$\begin{aligned} V(E) &= \frac{1}{c} \left[g(E) + \frac{pm}{m + d} (T_0 - T(E)) \right], \\ T^*(E) &= \frac{m}{m + d} (T_0 - T(E)), \\ T(E) &= \frac{1}{2} \left(a_1 - \sqrt{a_1^2 - 4a_2} \right), \end{aligned} \tag{12}$$

with

$$a_1 = \frac{(m+d)g(E)}{pm} + T_0 \left(1 + \frac{1}{\mathcal{R}_{w0}}\right), \quad a_2 = \frac{T_0^2}{\mathcal{R}_{w0}}. \quad (13)$$

The global stability of $U(E)$ is shown in [3] and we omit the details here. We observe that the equilibrium parasite load $V(E)$ given in (12) is an increasing function of the quantity $p/(m+d)$, which is the total parasite production and will be used in the next section for the study of evolution of virulence.

We now consider the dynamical behavior of the slow system (9) with V being replaced by the expression for $V(E)$ given in (12). The initial condition for (9) is assumed to be positive, i.e., $S(0) > 0$, $I(0) > 0$ and $E(0) > 0$.

Although only the case of $E > 0$ will be considered for the analysis of the slow system, it is useful to point out the following limiting behavior of the $V(E)$ component of $U(E)$ as $E \rightarrow 0$:

$$V(0) = \lim_{E \rightarrow 0} V(E) = \begin{cases} 0 & \text{for } \mathcal{R}_{w0} \leq 1, \\ \frac{m(\mathcal{R}_{w0} - 1)}{k} & \text{for } \mathcal{R}_{w0} > 1. \end{cases} \quad (14)$$

Moreover, $V(E)$ is an increasing function of E (see Figure 1).

Figure 1: Plot of the $V(E)$ component of the positive steady state $U(E)$ of the fast system (8) for various values of $\mathcal{R}_{w0}$. It shows that $V(E)$ is an increasing function of E , and that the larger $\mathcal{R}_{w0}$ the higher $V(E)$.

For ease of presentation, we state the results for the slow system only for the case of $\mathcal{R}_{w0} > 1$. In this case, the quantity $V(0) = m(\mathcal{R}_{w0} - 1)/k$

represents the parasite load within a host at the initial stage of environmental contamination. The reproduction number for the between-host system (9) is denoted by $\mathcal{R}_{b0}$ and defined as

$$\mathcal{R}_{b0} = \frac{\theta_0 V(0)}{\mu + \delta} \frac{\lambda S_0}{\gamma}. \quad (15)$$

Clearly, $\mathcal{R}_{b0}$ is well defined as $V(0) > 0$ for $\mathcal{R}_{w0} > 1$. The biological interpretation of the expression of $\mathcal{R}_{b0}$ is clear by noticing that $\theta_0 V(0)/(\mu + \delta)$ denotes the average units of environmental contamination produced by one infected host in a completely “susceptible” environment ($E = 0$) during the entire infectious period of the host ($1/\mu$). The factor $\lambda N/\gamma$ denotes the average number of infected hosts produced by one unit of environmental contamination during the entire period of contamination ($1/\gamma$) in a susceptible population ($S = N$).

The following stability result regarding the infection-free equilibrium $W_0 = (S_0, 0, 0)$ of system (9) is easy to prove.

Theorem 1. *W_0 is l.a.s. if $\mathcal{R}_{b0} < 1$ and unstable if $\mathcal{R}_{b0} > 1$.*

2.3.1. Existence of positive equilibria of the slow system

For the existence and stability of an endemic equilibrium, it is much more difficult to prove analytically than the case without disease-induced host death, in which case the dimension of the system can be reduced to 2 and only the I and E variables need to be considered. For the 3-dimensional system here, we provide only partial analytic proofs and extend the results by numerical simulations.

Let $\hat{W} = (\hat{S}, \hat{I}, \hat{E})$ denote a positive equilibrium of (9) (i.e., $\hat{S} > 0$, $\hat{I} > 0$ and $\hat{E} > 0$). For ease of notation, introduce the quantity

$$\mathcal{R}_{b1} = \frac{\theta_0 \lambda S_0}{(\mu + \delta) \gamma}, \quad (16)$$

which is similar to $\mathcal{R}_{b0}$ but with $V(0)$ being replaced by 1. Then

$$\hat{S} = \frac{\Lambda_h}{\lambda \hat{E} + \mu}, \quad \hat{I} = \frac{\gamma \mu \mathcal{R}_{b1} \hat{E}}{\theta_0 (\lambda \hat{E} + \mu)}, \quad (17)$$

and $\hat{E}$ is a solution of the equation $F(E) = G(E)$ for $0 < E < 1$, where

$$F(E) = \frac{1 - E}{c} \left[g(E) + \frac{pm}{m + d} (T_0 - T(E)) \right], \quad G(E) = \frac{\lambda E}{\mu \mathcal{R}_{b1}} + \frac{1}{\mathcal{R}_{b1}}. \quad (18)$$

Equivalently, $\hat{E}$ is a zero of the function $H(E)$, where

$$H(E) = F(E) - G(E). \quad (19)$$

It can be shown that F , G and H have the following properties

$$F(0) = \frac{m(\mathcal{R}_{w0} - 1)}{k}, \quad F(1) = 0, \quad G(0) = \frac{1}{\mathcal{R}_{b1}}, \quad G(1) = \frac{\lambda}{\mu\mathcal{R}_{b1}} + \frac{1}{\mathcal{R}_{b1}},$$

and

$$H(0) = V(0)\left(1 - \frac{1}{\mathcal{R}_{b0}}\right), \quad H(1) = -\frac{\lambda}{\mu\mathcal{R}_{b1}} - \frac{1}{\mathcal{R}_{b1}} < 0. \quad (20)$$

Moreover, the second derivative of $H(E)$ has the property:

$$H''(E) < 0. \quad (21)$$

The condition (21) implies that $H(E)$ has at most two zeros, and that the number of zeros depends on the maximum of the $H(E)$ function, which we denote by $H_{\max}$, i.e.,

$$H_{\max} = \max_{0 \leq E \leq 1} H(E).$$

Let $\hat{E}_1$ and $\hat{E}_2$ denote the two possible zeros of $H(E)$ in $(0, 1)$ with $\hat{E}_1 \leq \hat{E}_2$, and let $\hat{W}_i = (\hat{S}_i, \hat{I}_i, \hat{E}_i)$ ($i = 1, 2$) denote the corresponding equilibria of system (9), where $\hat{S}_i$ and $\hat{I}_i$ are functions of $\hat{E}_i$ given in (17). From the properties of $H(E)$ as described in (20) and (21), the following result on the existence of positive equilibria can be established.

Theorem 2. *Let $H = H(E)$ be the function defined in (19) and $\mathcal{R}_{w0} > 1$.*

(a) *For $\mathcal{R}_{b0} < 1$,*

(i) *if $H_{\max} > 0$ then $\hat{W}_1 \neq \hat{W}_2$ both exist;*

(ii) *if $H_{\max} = 0$ then a unique $\hat{W} = \hat{W}_1 = \hat{W}_2$ exists;*

(iii) *if $H_{\max} < 0$ then $\hat{W}$ does not exist.*

(b) *For $\mathcal{R}_{b0} > 1$, a unique $\hat{W}$ exists.*

Numerical simulations show that, when $\mathcal{R}_{b0} < 1$, there is a lower bound $\mathcal{R}_{bL} > 0$ such that

$$\text{Two positive equilibria exist} \iff \mathcal{R}_{bL} < \mathcal{R}_{b0} < 1.$$

Thus, a backward bifurcation as shown in Figure 2 can occur for system (9) once the stability results of these equilibria are confirmed.

2.4. Local stability of the positive equilibria of the slow system

From Theorem 2 we know that the slow system may have zero, one, or two interior equilibrium points depending on parameter values. In this section we provide results on the local stability of these equilibria.

The Jacobian matrix of the slow system (9) at $\hat{W} = (\hat{S}, \hat{I}, \hat{E})$ is

$$J(\hat{W}) = \begin{pmatrix} -\lambda\hat{E} - \mu & 0 & -\lambda\hat{S} \\ \lambda\hat{E} & -(\mu + \delta) & \lambda\hat{S} \\ 0 & \theta_0 V(\hat{E})(1 - \hat{E}) & \theta_0 \hat{I}V'(\hat{E})(1 - \hat{E}) - \theta_0 \hat{I}V(\hat{E}) - \gamma \end{pmatrix},$$

or equivalently

$$J(\hat{W}) = \begin{pmatrix} -\mu\mathcal{R}_{b1}F(\hat{E}) & 0 & -\lambda S_0/(\mathcal{R}_{b1}F(\hat{E})) \\ \mu(\mathcal{R}_{b1}F(\hat{E}) - 1) & -(\mu + \delta) & \lambda S_0/(\mathcal{R}_{b1}F(\hat{E})) \\ 0 & \theta_0 F(\hat{E}) & -\gamma(F(\hat{E}) - \hat{E}F'(\hat{E}))/F(\hat{E}) \end{pmatrix},$$

where $\mathcal{R}_{b1}$ is given in (16). Denote

$$K(E) = F(E) - EF'(E).$$

Then $K'(E) > 0$ for $E > 0$; and thus, $K(\hat{E}) > 0$. The characteristic equation of $J(\hat{W})$ is

$$x^3 + j_2x^2 + j_1x + j_0 = 0,$$

where

$$\begin{aligned} j_2(\hat{W}) &= \gamma K(\hat{E})/F(\hat{E}) + \mu\mathcal{R}_{b1}F(\hat{E}) + \mu + \delta > 0, \\ j_1(\hat{W}) &= \gamma\mu\mathcal{R}_{b1}K(\hat{E}) + \mu(\mu + \delta)\mathcal{R}_{b1}F(\hat{E}) + \gamma(\mu + \delta)K(\hat{E})/F(\hat{E}) - \gamma(\mu + \delta), \\ &= \mu(\mu + \delta)\mathcal{R}_{b1}F(\hat{E}) + \gamma\mu\mathcal{R}_{b1}K(\hat{E}) - \gamma(\mu + \delta)\hat{E}F'(\hat{E})/F(\hat{E}), \\ j_0(\hat{W}) &= \gamma\mu(\mu + \delta)(\mathcal{R}_{b1}K(\hat{E}) - 1). \end{aligned}$$

From the Routh-Hurwitz criterion we know that $\hat{W}$ is unstable if $j_0 < 0$, whereas if $j_0 > 0$ then $\hat{W}$ is l.a.s. when the following conditions are satisfied:

$$j_1 > 0 \quad \text{and} \quad j_1j_2 - j_0 > 0. \quad (22)$$

Let $\hat{E}_1$ and $\hat{E}_2$ denote the solutions of $H(E) = 0$ with $\hat{E}_1 < \hat{E}_2$. It is easy to verify that $K(\hat{E}_1) < \mathcal{R}_{b1}$ and $K(\hat{E}_2) > \mathcal{R}_{b1}$. It follows that $j_0(\hat{W}_1) < 0$ and $j_0(\hat{W}_2) > 0$. Thus, $\hat{W}_1$ is unstable. It is very difficult to check analytically the

inequalities in (22) evaluated at $\hat{W}_2$ due to the complexity of the functions $F(\hat{E})$ and $H(\hat{E})$. A large number of numerical simulations suggest that the inequalities in (22) hold at $\hat{W}_2$; and thus, $\hat{W}_2$ is l.a.s. when it exists. Numerical simulations are also conducted to confirm the following result.

Theorem 3. *Consider the interior equilibria described in Theorem 2.*

(a) *For $\mathcal{R}_{b0} < 1$,*

(i) *if $H_{\max} > 0$ then $\hat{W}_1$ is unstable while $\hat{W}_2$ is l.a.s.;*

(ii) *if $H_{\max} = 0$ then $\hat{W}$ is unique and it is a saddle-node.*

(b) *For $\mathcal{R}_{b0} > 1$, the unique equilibrium $\hat{W}$ is l.a.s.*

2.5. Backward bifurcation

Combining the results in Theorems 2 and 3 we conclude that there is a backward bifurcation for the full system (4). That is, the system has two positive equilibria for $\mathcal{R}_{b0} < 1$ with one being unstable and the other being stable, and a unique stable positive equilibrium for $\mathcal{R}_{b0} > 1$. This is demonstrated in Figure 2. The curve in the figure shows the infected fraction at the positive equilibria of the full system (4) as a function of $\mathcal{R}_{b0}$. The solid and dashed parts of the curve correspond to the stable and unstable equilibria, respectively. Numerical simulations show that there is a lower bound of $\mathcal{R}_{b0}$, labeled by $\mathcal{R}_{bL}$, such that the system has two positive equilibria for $\mathcal{R}_{b0} \in (\mathcal{R}_{bL}, 1)$, and no positive equilibrium for $\mathcal{R}_{b0} < \mathcal{R}_{bL}$. Thus, the threshold value $\mathcal{R}_{b0} = 1$ no longer provides a criterion for disease eradication. The new threshold condition for disease control is $\mathcal{R}_{b0} < \mathcal{R}_{bL}$. The parameter values used in the simulations are suitable for *T. gondii*. For example, $\Lambda_c = 6 \times 10^3$, $k = 1.5 \times 10^{-6}$, $m = 0.3$, $d = 0.15$, $a = 4 \times 10^5$, $c = 60$, $\mathcal{R}_{w0} = 1.1$ ($p = 950$), $\Lambda_h = 4$, $\mu = 0.0004$, $\delta = 0.0004$, $\theta_0 = 1.5 \times 10^{-10}$, and $\gamma = 0.015$.

The left graph in Figure 3 is a time plot of solutions of the full system in the case of $\mathcal{R}_{bL} < \mathcal{R}_{b0} < 1$ with different initial conditions. The parameter values are the same as in Figure 2 except that $a = 6 \times 10^5$, $\mathcal{R}_{w0} = 1.04$ ($p = 932$), and $\lambda = 0.0006$. The time unit is in years. Denote the total host population size by $N(t) = S(t) + I(t)$. We observe that the solutions with lower initial values of $I(0)/N(0)$ converge to 0, whereas the solutions with larger initial values of $I(0)/N(0)$ converge to a positive level of infection. The right graph in Figure 3 is a phase portrait of the full system projected onto

Figure 2: Illustration of the backward bifurcation. It plots the equilibrium fraction $\hat{I}/\hat{N}$ as a function of $\mathcal{R}_{b0}$. For all $\mathcal{R}_{b0}$ in the interval $(\mathcal{R}_{bL}, 1)$, there are two branches with the solid and dashed branches representing the stable and unstable interior equilibria, respectively. The vertical arrows indicate the directions of solutions as time tends to infinity. Depending on the initial conditions, the fraction of infected will converge to either 0 or $\hat{I}/\hat{N}$ on the solid curve.

the (E, V) plane. It is for the case when $\mathcal{R}_{b0} > 1$, in which case the system has a unique interior equilibrium ($\hat{W}$). Parameter values used are the same as in the time plot except that $d = 0.2$, $a = 4000$, $c = 50$, $p = 1000$, and $\delta = 0.00035$. We observe the two distinct time scales of the fast variable (V) and the slow variable (E). Particularly, for all initial conditions, the fast variable V converges quickly to its equilibrium value of the fast system (the slow manifold), followed by the convergence of the slow variable E to its value at the positive equilibrium $\hat{W}$ along the slow manifold.

3. Evolution of virulence

The inclusion of the disease-induced host death in the coupled model allows us to examine biological questions such as those considered in [11], including the evolution of virulence (δ), interdependence and constraints on transmission and virulence, and whether selection at the between- and within-host levels is in accord or in conflict.

In the nested model considered in [11], the disease is transmitted directly

Figure 3: Plots of solutions of the full system (4). The left figure is a time plot for the case of $\mathcal{R}_{b0} < 1$ and it illustrates that solutions will converge to either the infection-free equilibrium or an endemic equilibrium, depending on initial conditions. The figure on the right is a phase portrait (projected onto the (E, V) plane) for the case $\mathcal{R}_{b0} > 1$. It shows that solutions with all initial conditions converge to the unique positive equilibrium $\hat{W}$.

between hosts and the between-host model is given by

$$\begin{aligned} S' &= b(S, I) - \beta SI - \mu S, \\ I' &= \beta SI - (\mu + \delta)I, \end{aligned} \quad (23)$$

where β is the infection transmission rate, and the birth rate $b(S, I)$ is assumed to be a decreasing function of $S + I$. For the purpose of comparison, we have used μ and δ to denote host natural and disease death rates, respectively, in (23). They considered three examples of the exact functions for linking between-host parameters to within-host variables. Here, we focus only on the Example II (see Table 1 in [11]), in which

$$\beta(\hat{V}) = a_1 \hat{V}^z, \quad \delta(\hat{T}) = a_2 \left(\frac{1}{\hat{T}} - \frac{1}{T_0} \right), \quad (24)$$

where a_1 , a_2 and z are positive constants, and $\hat{V}$ and $\hat{T}$ are the values at the positive steady state of the within-host system. It is also assumed that the pathogen-induced bursting mortality $d = d(p)$ is an increasing function of parasite production p . One of the possible functional forms is $d(p) = d_0 p^2$, where d_0 is a positive constant. It is derived in [11] that the burst size, which we denote by Φ , is given by

$$\Phi = \frac{p}{m + d(p)}. \quad (25)$$

It is also assumed that, when other within-host parameters are fixed (e.g., k , c , Λ_c and m), the burst size Φ can be used as a measure of within-host parasite fitness, and that the optimal parasite production p^* maximizes Φ . Equivalently, the within-host reproduction number

$$\mathcal{R}_{w0} = \frac{\Phi k T_0}{c}$$

can be used as the fitness to be optimized. As was done in [11], we assume that there is a physiological maximum for the parasite production rate p , which we denote by $p_{\max}$. Thus, $p^* \leq p_{\max}$.

In the case when $d(p) = d_0 p^2$, $\mathcal{R}_{w0}$ has a unique positive critical point $p_c = \sqrt{m/d_0}$ determined by the equation $\Phi'(p_c) = 0$. Hence,

$$p^* = \min\{p_{\max}, p_c\}. \quad (26)$$

Note that in our model the infection of a host is through a contaminated environment. The rate of contamination is proportional to the number of infected hosts and the per-capita rate of parasite releasing $\theta(V)$, which is linked to the within-host parasite load V . The pathogen virulence to the host $\delta(T)$ is linked to the within-host variable T in the same way as considered in [11].

The optimal parasite production p and its virulence δ determined by the between-host reproduction number $\mathcal{R}_{b0}$ will depend on the choice of the functional forms $\theta(V)$ and $\delta(T)$. For demonstration purposes, we adopt the functional forms in (24) with $\beta(\hat{V})$ replaced by $\theta(\hat{V})$. The steady state values $\hat{V}$ and $\hat{T}$ at $E = 0$ are

$$\hat{V} = \frac{\Lambda_c \Phi}{c} - \frac{m}{k}, \quad \hat{T} = \frac{c}{k \Phi}. \quad (27)$$

Clearly, $\hat{V}$, $\hat{T}$ and Φ are all functions of p . Specifically, $\theta(p) := \theta(\hat{V}(p))$ and $\delta(p) := \delta(\hat{T}(p))$ can be written as

$$\theta(p) = \theta_0 \left(\frac{\Lambda_c \Phi(p)}{c} - \frac{m}{k} \right)^z, \quad \delta(p) = a_2 \left(\frac{k \Phi(p)}{c} - \frac{m}{\Lambda_c} \right). \quad (28)$$

At the population level, we can also assume that selection will favour the parasite production rate that maximizes the between-host reproduction number, which is given by

$$\mathcal{R}_{b0}(p) = \frac{\theta(p)}{\mu + \delta(p)} \cdot \frac{\lambda S_0}{\gamma}.$$

The specific functional forms of $\theta(p)$ and $\delta(p)$ given in (28) also allow us to derive the following interdependence and constraints on the transmission rate and pathogen virulence δ :

$$\theta(\delta) = \theta_0 \left(\frac{\Lambda_c \delta}{a_2 k} \right)^z. \quad (29)$$

By substituting this function $\theta(\delta)$ into $\mathcal{R}_{b0}$ we can rewrite the between-host reproduction number as a function of δ :

$$\mathcal{R}_{b0}(\delta) = \frac{\lambda S_0 \theta_0}{\gamma(\mu + \delta)} \left(\frac{\Lambda_c \delta}{a_2 k} \right)^z, \quad (30)$$

which also provides another expression of $\mathcal{R}_{b0}$ as a function of p by using the second equation in (28):

$$\mathcal{R}_{b0}(p) = \frac{\lambda S_0 \theta_0}{\gamma(\mu + \delta(p))} \left(\frac{\Lambda_c \delta(p)}{a_2 k} \right)^z. \quad (31)$$

The expressions of $\mathcal{R}_{b0}$ given in (30) and (31) can be used to compute the optimal parasite production and virulence.

The physiological maximum of parasite production $p_{\max}$ also imposes a constraint on its maximum virulence at the population level, which is denoted by $\delta_{\max}$. Note that $\delta_{\max}$ can be determined from the maximum of Φ , which is achieved at p^* . Let δ^* denote the optimal virulence determined by the within-host parameters (i.e., it maximizes Φ or equivalently $\mathcal{R}_{w0}$). Then, from (28) we obtain

$$\delta^* = \delta(p^*) = \delta_{\max}. \quad (32)$$

Let $p^\bullet$ and $\delta^\bullet$ denote the optimal parasite production and virulence at the population level, i.e., they maximize the expressions $\mathcal{R}_{b0}(p)$ and $\mathcal{R}_{b0}(\delta)$ given in (30) and (31), respectively, under the given constraints. To demonstrate the possibility of a conflict of selection pressures at the within-host and between-host levels, we discuss only the case when $z < 1$. From (30), the unique critical point of $\mathcal{R}_{b0}(\delta)$ is

$$\delta_c = \frac{z\mu}{1-z}. \quad (33)$$

Thus,

$$\delta^\bullet = \min\{\delta_{\max}, \delta_c\}.$$

Note from (31) that

$$\frac{d\mathcal{R}_{b0}}{dp} = \frac{d\mathcal{R}_{b0}}{d\delta} \frac{d\delta}{dp} = q(\delta_c - \delta) \frac{d\delta}{dp}, \quad (34)$$

where

$$q = \frac{\lambda S_0 \theta_0 (1 - z)}{\gamma \delta (\mu + \delta)^2} \left(\frac{\Lambda_c \delta}{a_2 k} \right)^z.$$

If $\delta_{\max} < \delta_c$, since $\Phi'(p_c) = 0$ and $\Phi'(p) > 0$ for $p < p_c$, from (28) and (31) we know that $\mathcal{R}'_{b0}(p) > 0$ and $\delta'(p) > 0$ for all $p < p_c$. Thus, from (26), p^* is the point where $\mathcal{R}_{b0}(p)$ and $\delta(p)$ achieve their maximum values. It follows that $p^\bullet = p^*$. If $\delta_{\max} > \delta_c$, then from $\delta(p^*) = \delta_{\max} > \delta_c$ and $\delta'(p) > 0$ for $p < p^* = \min\{p_{\max}, p_c\}$, we know that there exists a $p^\bullet < p^*$ such that $p^\bullet = \delta^{-1}(\delta_c)$ and $\mathcal{R}'_{b0}(p^\bullet) = 0$. This is illustrated in Figure 4. The figure shows the curves of $\mathcal{R}_{w0}(p)$ and $\mathcal{R}_{b0}(p)$ for $\delta_{\max} < \delta_c$ (see (a)) and $\delta_{\max} > \delta_c$ (see (b)). The parameter values used are the same as in the time plot of Figure 3 (left) except that $k = 4 \times 10^{-6}$, $\theta_0 = 6 \times 10^{-10}$ and $N(0) = 3 \times 10^5$. The function $d(p) = d_0 p^2$ is used with $d_0 = 0.0005^2$. The value of a_2 is 1 in (a) and 10 in (b). In (a), both curves have a maximum at the same point, i.e., $p^\bullet = p^*$, whereas in (b) we observe that $p^\bullet < p^*$, suggesting a conflict between selection at the two levels.

Figure 4: Plots of $\mathcal{R}_{w0}(p)$ and $\mathcal{R}_{b0}(p)$ for the cases when $\delta_{\max} < z\mu/(1 - z)$ (a) and $\delta_{\max} > z\mu/(1 - z)$ (b). It shows in (b) that $p^\bullet < p^*$, indicating a conflict between natural selection at the two levels.

This analysis suggests that our model provides a similar conclusion as the model in [11] with regard to the evolution of virulence at the population

level (δ) when the functions in (28) are used. That is, natural selection will favour either the maximum level of virulence ($\delta^\bullet = \delta_{max}$) if p_{max} is small or an intermediate level of virulence ($\delta^\bullet < \delta_{max}$) if p_{max} is large.

Although the analysis in section 2.3 is carried out for the case when $\theta(V)$ is a linear function of V , i.e., $z = 1$ in $\theta(V) = \theta_0 V^z$, our numerical results suggest that dynamics of the system (4) when $z > 1$ or $z < 1$ are similar to the case of $z = 1$ provided that the parameter values are reasonable. For example, a backward bifurcation can occur when $\mathcal{R}_{w0} > 1$ and $\mathcal{R}_{bL} < \mathcal{R}_{b0} < 1$. This is demonstrated in Figure 5. This figure shows time plots for $z = 0.95$ (see (a)) and $z = 1.1$ (see (b)). All parameters have the same values as in the time plot of Figure 3 (left) except that $p = 900$ ($\mathcal{R}_{w0} = 1.05$), $d_0 = 0.0004^2$, and $\lambda = 0.0001$ in (a) and 0.0004 in (b). We observe that, depending on initial conditions, the solutions converge to either the disease-free equilibrium or a positive equilibrium.

Figure 5: Time plots of the full model when the functions $\theta(V) = \theta_0 V^z$ and $\delta(T) = a\left(\frac{1}{T} - \frac{1}{T_0}\right)$ are used, and $d = d(p) = d_0 p^2$. The value of z is 0.95 in (a) and 1.1 in (b). It shows that for both z values the system has multiple attractors.

When Example I in [11] is used, i.e.,

$$\theta(p) = \theta_0 \left(\frac{\Lambda_c \Phi(p)}{c} - \frac{m}{k} \right), \quad \delta(p) = a_1 \left(\frac{\Lambda}{m} - \frac{c}{k \Phi(p)} \right), \quad (35)$$

the function $\delta(p)$ increases Φ and $\Phi(p)$ achieves its maximum at p^* , which implies that $\delta(p)$ achieves its maximum at p^* . Thus, the within-host optimal virulence satisfies $\delta^* = \delta(p^*)$. At the between-host level, notice that $\mathcal{R}(\delta)$ is an increasing function of δ . Thus, $\mathcal{R}(\delta)$ increases with p . It follows that the

optimal virulence at the population level, $p^\bullet$, is the same as p^* . Therefore, there is no conflict. A similar argument can be used to show that there is no conflict when the Example III in [11] is used.

4. Discussion

Results presented in this paper extend those in [3, 7] by incorporating the parasite virulence in the host (δ) and a nonlinear dependence of parasite releasing rate on parasite load ($\theta(V)$). The extended model (4) makes it possible to obtain additional biological insights into host-parasite interactions that are not possible from the models in [3, 7]. Because the reproduction numbers $\mathcal{R}_{w0}$ and $\mathcal{R}_{b0}$ are functions of parasite production p and virulence δ , respectively, and because the equilibrium values of parasite load $\hat{V}$ and infection prevalence $\hat{I}$ are increasing functions of $\mathcal{R}_{w0}$ and $\mathcal{R}_{b0}$, respectively (see Figures 1 and 2), we can use the expressions of $\mathcal{R}_{w0}$ and $\mathcal{R}_{b0}$ to identify the optimal levels of parasite production and virulence favoured by natural selection.

The inclusion of host disease mortality makes the model analysis much more challenging due to a variable population size. Although only limited analytical results can be obtained, numerical simulations help confirm that the extended model has similar qualitative behaviors as those of the simpler model in [3, 7]. Particularly, the model can still have multiple attractors when $\mathcal{R}_{b0} < 1$ due to a backward bifurcation. As mentioned earlier, the public health implication of this type of bifurcation is that there will be a new threshold quantity $\mathcal{R}_{bL} < 1$ such that control measures for the disease need to reduce the reproduction number $\mathcal{R}_{b0}$ to be below $\mathcal{R}_{bL}$. Equivalently, control programs may focus on increasing $\mathcal{R}_{bL}$ so that the window of opportunity $(\mathcal{R}_{bL}, 1)$ for multiple attractors can be reduced.

One of the key reasons for the occurrence of backward bifurcation in the coupled model is the biological factor represented by $g(E)$, which dynamically links the within-host system to the between-host variable (E). This approach of linking the two processes is biologically reasonable for environmentally-driven infectious diseases. Consider the case in which the pathogens can establish themselves within the host in the absence of an input from the environment, i.e., the within-host reproduction number $\mathcal{R}_{w0}$ is greater than 1. Without a feedback from the population dynamics (i.e., $E = 0$), the within-host pathogen load will reach the steady state value $\hat{V}$. In several studies of coupled models for directly transmitted diseases (e.g., [1, 11]), this steady

state value is used for studying the between-host dynamics (assuming the within-host dynamics to be faster than that at population level). However, when modeling environmentally transmitted diseases such as Toxoplasmosis and Cholera, the pathogen load at the steady state of the within-host system should be affected by the level of environment contamination when $E > 0$ because of the continuous ingestion of pathogens by the host. This modeling framework is similar to the consideration of local population dynamics in a mean-field metapopulation model in ecology. For example, Hanski and Zhang [13] proposed the following metapopulation model with explicit local population dynamics:

$$\begin{aligned}\frac{dN}{dt} &= rN\left(1 - \frac{N}{K}\right) - mN + amNp, \\ \frac{dp}{dt} &= bamNp(1 - p) - ep,\end{aligned}\tag{36}$$

where $p \in [0, 1]$ represents the fraction of occupied habitat patches; N is the typical size of existing local populations; r is the per capita growth rate due to local births and deaths; K is the average carrying capacity; m is the per capita emigration rate; a is the fraction of migrating individuals that survived and reached a new patch; b is the probability that an arriving individual gives rise to a new local population in an empty patch; and e is the extinction rate of local populations. Each habitat patch corresponds to a host with the local populations being the parasites within a host. The fraction of metapopulation occupancy (p) in (36) corresponds to the fraction of infected hosts and/or the level of environment contamination (E), while the local population size N represents the parasite load within a host. The term $amNp$ in the N equation in the system (36) represents an influence of the metapopulation occupancy level p in the local population size.

Our model analysis takes advantage of the two different time scales of within- and between-host dynamics by applying tools from the singular perturbation theory. This, however, requires that the fast system to have a globally asymptotically stable steady state U , so that we can use the steady state expressions of the fast variables in the analysis of the slow system. In the case when the fast system has multiple attractors, either stable steady states or limit cycles, one cannot analyze the slow dynamics by simply substituting a steady state of the fast system into the slow system. Thus, it is necessary to understand the dynamical behaviors of the fast system.

The modeling framework considered in this paper, particularly the ex-

plicit coupling of two population processes, are also applicable to other environmentally-driven infectious diseases such as Hemorrhagic fever with renal syndrome (HFRS), which is a group of clinically similar illnesses caused by hantaviruses. Depending on the biological features of host-pathogen interactions for a specific disease, the differential equations for the within-host system and/or the between-host system may need to be modified. Another approach for modeling the epidemiological and immunological processes is to structure the host population by immune status [4, 10, 12], in which case the model analysis can be very challenging (see, e.g., [10]). Nevertheless, these studies all demonstrated that coupled epidemiological and immunological models are capable of generating new biological insights into the host-pathogen interactions.

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Table 1: Description of parameters and frequently used symbols

Symbol	Description
Λ_c	Recruitment of target cells
k	Per-capita infection rate of cells
m	Per-capita background mortality of cells
d	Per-capita infection-induced mortality rate of cells
p	Parasite production rate by an infected cell
c	Within-host clearance rate of parasites
Λ_h	Recruitment of hosts
μ	Per-capita natural death rate of hosts
δ	Per-capita disease-induced death rate of hosts
λ	Infection rate of individuals at population level
$\theta(V)$	Parasite releasing rate per host
γ	Clearance rate of the environment
$g(E)$	Inoculation rate of host via contacts with the environment
a	The constant in the special functional form $g(E) = aE$
$\mathcal{R}_{w0}$	$= kpT_0/(c(m + d))$, Within-host baseline reproduction number
$\mathcal{R}_{b0}$	$= \lambda N\theta(\tilde{V}(0))/(\gamma\mu)$, Between-host reproduction number if $\mathcal{R}_{w0} > 1$
$\mathcal{R}_{b1}$	$= \lambda N\theta_0/(\gamma\mu)$, similar to $\mathcal{R}_{b0}$ but with $\tilde{V}(0)$ being replaced by 1