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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 (Gilchrist and Coombs, 2006). In this paper, a new coupled model for environmentally-driven diseases is analyzed to study similar biological questions. It extends the model in Cen et al. (2014) and Feng et al. (2013) 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 inter-dependence 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.

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., [1,7,8,10–12,15]). 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.,

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

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

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

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 Eq. (1) and T in Eq. (2) can be replaced by their values at the positive steady state, which leads to the following relationship between α and β:

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

where Λ and k are parameters associated with the within-host system. Because the qualitative behavior of the function in Eq. (3) can be

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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 Eq. (1) and the disease mortality function $\alpha(T)$ given in Eq. (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 [16–18,20–22] 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 six 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

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