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EFFECTS OF SUPERINFECTION AND COST OF IMMUNITY ON HOST-PARASITE CO-EVOLUTION

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Abstract. In this paper, we investigate the cost of immunological up-regulation caused by infection in a between-host transmission dynamical model with superinfection. After introducing a mutant host to an existing model, we explore this problem in (A) monomorphic case and (B) dimorphic case. For (A), we assume that only strain 1 parasite can infect the mutant host. We identify an appropriate fitness for the invasion of the mutant host by analyzing the local stability of the mutant free equilibrium. After specifying a trade-off between the production and recovery rates of infected hosts, we employ the adaptive dynamical approach to analyze the evolutionary and convergence stabilities of the corresponding singular strategy, leading to some conditions for continuously stable strategy, evolutionary branching point and repeller. For (B), a new fitness is introduced to measure the invasion of mutant host under the assumption that both parasite strains can infect the mutant host. By considering two trade-off functions, we can study the conditions for evolutionary stability, isoclinic stability and absolute convergence stability of the singular strategy. Our results show that the host evolution would not favour high degree of immunological up-regulation; moreover, superinfection would help the parasite with weaker virulence persist in hosts.

1. **Introduction.** It is well known that the relationship between hosts and parasites is extremely convoluted [9, 17]. Generally, parasites can be divided into two types: the traditional one is called macroparasite (typically protozoa and helminths); the other one is called microparasite, which is typically smaller, such as viruses and bacteria, and can be directly transmitted between hosts of the same species or even different species [8]. Although parasites harm hosts and possibly cause deaths to the hosts, they live on or in the bodies of the hosts and are dependent on them. Host-parasite co-evolution is still a ubiquitous phenomenon of potential importance to all living organisms, including humans. Many medically relevant diseases (e.g. malaria, AIDS and influenza) are caused by co-evolving parasites. Therefore, better understanding of the co-evolutionary adaptation between parasite "attack strategy" and host "defence strategy" (i.e. immunological response), may result in discovery/development of novel medications and vaccines and thus help save human lives [31].

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In this paper, we are interested in the effect of superinfection and the cost caused by immune response on this co-evolution. Complex immune systems that can target parasites through contact with body fluids are developed in vertebrate animals. Hosts are protected from infection with layered defences of increasing specificity by their immune systems. Hence, the benefits of such defences to a host are obvious. However, according to Lochmiller and Deerenberg [21], the immunological up-regulation response would cause costs in other nutrient-demanding processes such as growth, reproduction, and thermoregulation. Thus, the production rate of an infected individual is a decreasing function of the corresponding disease recovery rate. To explore the impact of this phenomenon on host evolution, Day and Burns[12] proposed the following epidemiological model:

$$\begin{cases} \frac{\mathrm{d}S_1}{\mathrm{d}t} &= b_s S_1 + b_I(c) I_1 - \mu S_1 + c I_1 - \beta S_1 I_1 - \beta S_1 I_2, \\ \frac{\mathrm{d}I_1}{\mathrm{d}t} &= \beta S_1 I_1 + \beta S_1 I_2 - (u + \nu + c) I_1, \\ \frac{\mathrm{d}S_2}{\mathrm{d}t} &= b_s S_2 + b_I(\hat{c}) I_2 - \mu S_2 + \hat{c} I_2 - \beta S_2 I_1 - \beta S_2 I_2, \\ \frac{\mathrm{d}I_2}{\mathrm{d}t} &= \beta S_2 I_1 + \beta S_2 I_2 - (u + \nu + \hat{c}) I_2, \end{cases} \tag{1}$$

where the degree of immunological up-regulation is represented by c ($\hat{c}$) which is the infection clearance rate of resident (mutant) hosts. They assumed that the birth rate by an infected host, $b_I(c)$, is a decreasing function of c. It imposes the fecundity cost of up-regulation (this formulation assumes an instantaneous switch in resource allocation once a host is infected).

However, single infection is very rare in the natural world. Hosts are always attacked by many different parasites simultaneously. Hence, multiple defence mechanisms would also evolve to recognize and neutralize these pathogens [3]. This indicates that the infection can not be as simple as demonstrated by the above mathematical model. The influence of parasites competition on host evolution attracts our attention, and motivates us to develop an epidemiological model with superinfection. Superinfection represents an intermediate level of complexity in the sense that a more virulent parasite can "take over" a host that is already infected with a less virulent strain, but the host will, in effect, harbour only one strain of infection at any time [5, 25, 26, 4]. We utilize a mathematical model with superinfection to analyze the effect of the cost caused by immunologic up-regulation on host-parasite co-evolution.

The rest of this paper is organized as follows. In Section 2, we introduce mutant hosts to a basic superinfection model and explore their invasion in two cases: monomorphic case and dimorphic case. In Section 3, we discuss a *monomorphic case*, by assuming that the mutant host can only be infected by the strain 1 parasite. Local stability of the mutant free equilibrium is analyzed to obtain a fitness function. Then, a trade-off between the production rate of infected hosts and their recovery rate is considered. By employing the adaptive dynamical approaches (see, e.g., [16, 15, 29]), we analyze the evolutionary stability and convergence stability of the corresponding singular strategy, leading to some conditions for continuously stable strategy, evolutionary branching point and repeller. These results show how the convexities of two trade-offs affect the evolutionary and convergence stabilities. Since the other monomorphic case that the mutant hosts can only be infected by strain 2 parasite is symmetric, there is no need to discuss it. In Section 4, we consider a *demographic case* in which the mutant host can be infected by both strains of the parasites. For this case, we define a new fitness to measure the invasion of

mutant hosts with parasite strain 1 and 2, and obtain some conditions for evolutionary stability. Two *trade-offs* are specified by two simple quadratic functions to explore the conditions for possibility of isoclinic stability and absolute convergence stability. We will present some numerical results, respectively. Meanwhile, the value of superinfection rate is varied to observe how it affects the conditions for isoclinic stability and absolute convergence stability, respectively. In Section 5, some discussions on the biological implications of the mathematical results are provided. Moreover, some related problems for future work on this topic are briefly discussed.

2. **A two-parasite strains model within a single host type.** Our resident model is based on a classical SIR framework. We assume that the resident hosts can be infected by two strains of the parasites. The population of susceptible hosts is denoted by S, and the population infected by the parasite strain i is denoted by I_i, where $i = 1, 2$.

A susceptible host can be produced at rate b and die at rate μ. For convenience, the two types of infections are assumed to have the same transmission rate β and death rate δ caused by infection. Moreover, the parasite strain 1 is assumed to have stronger virulence than parasite strain 2. So, individuals infected by parasite strain 2 can be re-infected (superinfection) by contacting the parasite strain 1 and enter the I_1 class with rate φ. With these assumptions, the model takes the form:

$$\begin{cases} \frac{\mathrm{d}S}{\mathrm{d}t} &= bS + f(c_1)I_1 + g(c_2)I_2 + c_1I_1 + c_2I_2 - \mu S - \beta S(I_1 + I_2), \\ \frac{\mathrm{d}I_1}{\mathrm{d}t} &= \beta SI_1 - (\mu + \delta + c_1)I_1 + \beta\varphi I_2 I_1, \\ \frac{\mathrm{d}I_2}{\mathrm{d}t} &= \beta SI_2 - (\mu + \delta + c_2)I_2 - \beta\varphi I_2 I_1. \end{cases} \tag{2}$$

In this model, the parameters c_1 and c_2, which are the recovery rates of resident host, represent the degrees of immunological up-regulation. These two parameters are considered as the traits for each type of infection, respectively. We assume that the birth rates by infected resident hosts, $f(c_1)$ and $g(c_2)$, are decreasing functions of the parameters c_1 and c_2 because of the fecundity cost of up-regulation.

Our model is based on the model (1) in which S either grow or decay exponentially, if there is no infection at all. As in (1), (2) always has the trivial equilibrium $\mathbf{E}_0 = (0, 0, 0)$ instead of an infection-free equilibrium. Also, we find that there may be other three equilibria when $b > \mu$. We will discuss their existences below.

Firstly, when $b > \mu$ and $\mu + \delta > f(c_1)$, there is an equilibrium with infection by parasite strain 1 only:

$$\mathbf{E}_2 = (S,\, I_1,\, I_2) = \Big(\frac{\mu + \delta + c_1}{\beta},\, \frac{(b - \mu)(\mu + \delta + c_1)}{\beta(\mu + \delta - f(c_1)}, 0\Big).$$

Similarly, when $b > \mu$ and $\mu + \delta > g(c_2)$, the model (2) has another equilibrium with infection by parasite strain 2 only:

$$\mathbf{E}_1 = (S, I_1, I_2) = \Big(\frac{\mu + \delta + c_2}{\beta},\, 0,\, \frac{(b - \mu)(\mu + \delta + c_2)}{\beta(\mu + \delta - g(c_2))}\Big).$$

Now, we explore the possibility of coexistence equilibrium $\hat{\mathbf{E}}$. Directly solving for this equilibrium with non-zero components gives $\hat{\mathbf{E}} = (\hat{S}, \hat{I}_1, \hat{I}_2)$ where

$$\begin{aligned}
\hat{S} &= \frac{(\mu+\delta)(c_1 - c_2 + f(c_1) - g(c_2)) + c_2 f(c_1) - c_1 g(c_2)}{\beta[\varphi(b-\mu) + f(c_1) - g(c_2)]}, \\
\hat{I}_1 &= \frac{\beta\hat{S} - (\mu+\delta+c_2)}{\beta\varphi}, \\
\hat{I}_2 &= \frac{(\mu+\delta+c_1) - \beta\hat{S}}{\beta\varphi}.
\end{aligned} \tag{3}$$

By the above formulas, we know that

- $\hat{S}$ is positive if

$$c_1 - c_2 > 0, \quad b > \mu \tag{4}$$

and

$$g(c_2) - f(c_1) > \max\{c_1 - c_2, \varphi(b-\mu)\} > 0; \tag{5}$$

- $\hat{I}_1$ is positive if

$$f(c_1)(c_1 - c_2) + \varphi(b-\mu)c_1 < [(c_1 - c_2) + \varphi(\mu - b)](\mu + \delta); \tag{6}$$

- $\hat{I}_2$ is positive if

$$g(c_2)(c_1 - c_2) + \varphi(b-\mu)c_2 > [(c_1 - c_2) + \varphi(\mu - b)](\mu + \delta). \tag{7}$$

In Appendix A, we show that the coexistence equilibrium $\hat{\mathbf{E}}$ is locally asymptotic stable if the conditions (4)-(7) are satisfied and

$$\frac{c_1 - c_2}{\varphi} - (b - \mu) > 0 \tag{8}$$

holds.

As illustrated in Day's works [10, 11], the condition $c_1 > c_2$ reflects that the virulence of parasite strain 1 is stronger than that of parasite strain 2, which is in agreement with our hypothesis.

Our goal is to study the host-parasite co-evolution under the effect of superinfection and immune response. To this end, we assume that a mutant host emerges due to some reasons such as drug resistance, or radiation, etc in the following sections. Furthermore, the discussion is divided into two cases: (i) the mutant hosts can only be infected by one of these two strains of parasites; and (ii) the mutant hosts can be infected by both strains of parasites.

3. **Monomorphic case.**

According to Gandon et al. [14], mutant hosts may obtain some new characters which can help them be immune to parasites. This suggests a scenario which assumes that a mutant host can only be infected by one parasite strain. Then, there are two possible infections in mutant hosts. Furthermore, it is assumed that the infected mutant hosts cannot infect resident hosts.

To be specific and without loss of generality, let us assume that parasite strain 1 can infect mutant host. As a natural extension of model (1) and (2), our new model with the above scenario incorporated is given by the following system of differential equations:

$$\begin{cases} \frac{\mathrm{d}S_1}{\mathrm{d}t} & = bS_1 + f(c_1)I_{11} + g(c_2)I_{12} + c_1I_{11} + c_2I_{12} - \mu S_1 \\ & \quad -\beta S_1(I_{11} + I_{12} + I_{21}), \\ \frac{\mathrm{d}I_{11}}{\mathrm{d}t} & = \beta S_1(I_{11} + I_{21}) - (\mu + \delta + c_1)I_{11} + \beta\varphi I_{12}I_{11}, \\ \frac{\mathrm{d}I_{12}}{\mathrm{d}t} & = \beta S_1 I_{12} - (\mu + \delta + c_2)I_{12} - \beta\varphi I_{12}I_{11}, \\ \frac{\mathrm{d}S_2}{\mathrm{d}t} & = bS_2 + f(c_{1h})I_{21} + c_{1h}I_{21} - \beta S_2(I_{21} + I_{11}) - \mu S_2, \\ \frac{\mathrm{d}I_{21}}{\mathrm{d}t} & = \beta S_2(I_{11} + I_{21}) - (\mu + \delta + c_{1h})I_{21}, \end{cases} \tag{9}$$

where the meanings of the variables and parameters are in Table 1.

Notation	Meaning
S_1	Abundance of susceptible residents
S_2	Abundance of susceptible mutants
I_{11}	Abundance of residents infected by the parasite strain 1
I_{12}	Abundance of residents infected by the parasite strain 2
I_{21}	Abundance of mutants infected by the parasite strain 1
I_{22}	Abundance of mutants infected by the parasite strain 2
b	Birth rate of a host
μ	Background mortality rate of a host
β	Infection rate of a host
δ	Disease induced death rate per host
φ	Superinfection rate per host
c_1 (c_{1h})	Recovery rate of a resident (mutant) host infected by parasite strain 1
c_2 (c_{2h})	Recovery rate of a resident (or mutant) host infected by parasite strain 2

TABLE 1. **Descriptions of the variables and parameters in section 3.**

To explore the survivability of such a mutant host that can only be infected by parasite strain 1, firstly we need to define its fitness. To this end, we consider the stability of the mutant free equilibrium $\tilde{\mathbf{E}} = (\tilde{S}_1, \tilde{I}_{11}, \tilde{I}_{12}, 0, 0))$ for this system (9) where $\tilde{S}_1 = \hat{S}$, $\tilde{I}_{11} = \hat{I}_1$, $\tilde{I}_{12} = \hat{I}_2$ with $\hat{S}$, $\hat{I}_1$ and $\hat{I}_2$ given in (3). Based on the criteria determining the local stability of $\tilde{\mathbf{E}}$ (see detail in Appendix. B), we define the fitness of the mutant hosts that can only be infected by parasite strain 1 as

$$\begin{aligned} \mathbf{F}(c_{1h}, c_1, c_2) =& (b-\mu)(\mu+\delta+c_{1h}) + \frac{f(c_{1h})-\mu-\delta}{\varphi(b-\mu)+f(c_1)-g(c_2)}[\frac{1}{\varphi}(c_1-c_2)(\mu+\delta \\ & - g(c_2)) - (b-\mu)(\mu+\delta+c_2)]. \end{aligned} \tag{10}$$

Since the parasite strain 2 has no effect on mutant hosts, we take c_2 as a positive constant value in this case. Denote $g(c_2) = \bar{g}$, where $\bar{g}$ is a positive constant. As the immunological up-regulation would decrease the fecundity of the hosts, $\bar{g}$ should be less than b. So, the fitness function (10) can be simplified to

$$\begin{aligned} \mathbf{F}(c_{1h}, c_1) =& (b-\mu)(\mu+\delta+c_{1h}) + \frac{f(c_{1h})-\mu-\delta}{\varphi(b-\mu)+f(c_1)-\bar{g}}[\frac{1}{\varphi}(c_1-c_2)(\mu+\delta-\bar{g}) \\ & - (b-\mu)(\mu+\delta+c_2)]. \end{aligned} \tag{11}$$

In order to predict the host-parasite co-evolution trend, we utilize the adaptive dynamical methods [15] to analyze this fitness functions. At first, we need to find singular points, i.e., the values of c_1 at which the gradient of the fitness function

with respect to c_1 vanish. This means that we need to solve the following equation for c_0:

$$\begin{aligned}&\frac{\partial \mathbf{F}(c_{1h}, c_1)}{\partial c_{1h}}\Big|_{c_{1h}=c_1}\\ =&b-\mu+\frac{f'(c_1)}{\varphi(b-\mu)+f(c_1)-\bar{g}}[\frac{1}{\varphi}(c_1-c_2)(\mu+\delta-\bar{g})-(b-\mu)(\mu+\delta+c_2)]\\ =&0.\end{aligned} \tag{12}$$

Assume that c_1^* is a positive solution of (12). It follows from (12) that

$$f'(c_1^*)=\frac{(\mu-b)[\varphi(b-\mu)+f(c_1^*)-\bar{g}]}{\frac{1}{\varphi}(c_1^*-c_2)(\mu+\delta-\bar{g})-(b-\mu)(\mu+\delta+c_2)}. \tag{13}$$

Associated with (13) is the following ordinary differential equation

$$f'(c_1)=\frac{(\mu-b)[\varphi(b-\mu)+f(c_1)-\bar{g}]}{\frac{1}{\varphi}(c_1-c_2)(\mu+\delta-\bar{g})-(b-\mu)(\mu+\delta+c_2)}. \tag{14}$$

A solutions of the ODE (14) is referred to as a critical function with respect to the fitness function $F(c_{1h}, c_1)$, and is denoted by $f_{crit}(c_1)$. Thus, the trade-off $f(c_1)$ should have the same derivative as $f_{crit}(c_1)$ does at c_1^*. Thus, the critical function $f_{crit}(c_1)$ carries some information about the trade-off $f(c_1)$ near c_1^*.

3.1. **Evolutionary stability analysis.** Now, we study the evolutionary stability of this singular point c_1^*. Following the adaptive dynamical approach [15], evolutionary stability of c_1^* is determined by the sign of

$$\mathcal{E}_1 : = \frac{\partial^2 \mathbf{F}(c_{1h}, c_1)}{\partial c_{1h}^2}\Big|_{c_{1h}=c_1=c_1^*} = \tilde{\mathbf{F}}_2 f''(c_1^*), \tag{15}$$

where

$$\tilde{\mathbf{F}}_2 = \frac{\frac{1}{\varphi}(c_1^*-c_2)(\mu+\delta-\bar{g})-(b-\mu)(\mu+\delta+c_2)}{\varphi(b-\mu)+f(c_1^*)-\bar{g}}.$$

According to Eq. (13), the formula of $\tilde{\mathbf{F}}_2$ can be further rewritten as

$$\tilde{\mathbf{F}}_2=\frac{\mu-b}{f'(c_1^*)}. \tag{16}$$

Because of the conditions (4), (5) and (7), one can easily see that $\tilde{\mathbf{F}}_2$ is positive. Indeed, (4) implies that $\mu-b<0$. By (5),

$$\bar{g}-f(c_1^*)>\max\{c_1^*-c_2, \varphi(b-\mu)\}>0,$$

and thus, $\varphi(b-\mu)+f(c_1^*)-g<0$. Furthermore, 7 leads to

$$\frac{1}{\varphi}(c_1^*-c_2)(\mu+\delta-\bar{g})-(b-\mu)(c_2+\mu+\delta)<0.$$

Combining the above, we conclude that

$$f'(c_1^*)=\frac{(\mu-b)[\varphi(b-\mu)+f(c_1^*)-\bar{g}]}{\frac{1}{\varphi}(c_1^*-c_2)(\mu+\delta-\bar{g})-(b-\mu)(\mu+\delta+c_2)}<0.$$

So, the sign of $\mathcal{E}_1$ only depends on the sign of $f''(c_1^*)$. If $f''(c_1^*)<0$ (i.e. $f(c_1)$ is concave down at c_1^*), then $\mathcal{E}_1<0$ and thus, the singular point c_1^* is an evolutionary stable strategy.

3.2. **Convergence stability analysis.** Firstly, let us calculate the cross-derivative $\mathcal{M}_1$ of the fitness $\mathbf{F}$:

$$\mathcal{M}_1 = \frac{\partial^2 \mathbf{F}(c_{1h},c_1)}{\partial c_1 \partial c_{1h}}\Big|_{c_{1h}=c_1=c_1^*} = \tilde{\mathbf{F}}_{12}[f'(c_1^*)]^2 + \tilde{\mathbf{F}}_{11} f'(c_1^*),$$

where

$$\tilde{\mathbf{F}}_{12} = \frac{-\tilde{\mathbf{F}}_2}{\varphi(b-\mu)+f(c_1^*)-\bar{g}}, \quad \tilde{\mathbf{F}}_{11} = \frac{\frac{1}{\varphi}(\mu+\delta-\bar{g})}{\varphi(b-\mu)+f(c_1^*)-\bar{g}}.$$

For the convergence stability of c_1^*, we need to consider

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}c_1}\left(\frac{\partial \mathbf{F}(c_{1h},c_1)}{\partial c_1}\Big|_{c_{1h}=c_1}\right)\Big|_{c_1=c_1^*} &= \mathcal{E}_1 + \mathcal{M}_1 \\ &= \tilde{\mathbf{F}}_2 f''(c_1^*) + \tilde{\mathbf{F}}_{12}[f'(c_1^*)]^2 + \tilde{\mathbf{F}}_{11} f'(c_1^*). \end{aligned} \tag{17}$$

Differentiating Eq. (14) and simplifying, we obtain

$$f''_{crit}(c_1^*) = \frac{(\mu-b)-\frac{1}{\varphi}(\mu+\delta-\bar{g})}{\frac{1}{\varphi}(c_1^*-c_2)(\mu+\delta-\bar{g})-(b-\mu)(\mu+\delta+c_2)} * f'(c_1^*).$$

Thus, the right hand side of (17) can actually be expressed as

$$\mathcal{E}_1 + \mathcal{M}_1 = \tilde{\mathbf{F}}_2[f''(c_1^*) - f''_{crit}(c_1^*)].$$

Therefore, if

$$f''(c_1^*) < f''_{crit}(c_1^*), \tag{18}$$

then $\mathcal{E}_1 + \mathcal{M}_1 < 0$. Thus, c_1^* is a convergence stable strategy if the trade-off $f(c_1)$ is more concave down than the critical function $f_{crit}(c_1)$ at the singular point c_1^*. This indicates that c_1 would evolve toward c_1^* from its neighbourhood in this case.

From the above analysis, we conclude that if the trade-off $f(c_1)$ is locally concave down at c_1^* and more concave down than the critical function $f_{crit}(c_1)$ at c_1^*, this evolutionary singular point c_1^* is a continuously stable strategy, which is both evolutionary and convergence stable; otherwise, it is an evolutionary repeller, meaning a singular strategy from which an initially monomorphic population evolves away (for the definition, see [15]). If the trade-off is not locally concave down at c_1^* but (18) still holds, c_1^* should be an evolutionary branching point. In addition, if the trade-off $f(c_1)$ is all concave down or locally concave down at c_1^* but the inequality (18) is violated, the problem will be so complicated that we will not discuss here.

3.3. **An example.** To demonstrate our results obtained above, we choose a specific trade-off function. To make life easy, we choose the following simple concave down polynomial of degree 2:

$$f(c_1) = b - k_1 c_1^2, \tag{19}$$

where $k_1 > 0$. Due to the biological meaning, we only consider the situation $c_1 > 0$.

Substitute the expression of $f(c_1)$ into the fitness function (11):

$$\begin{aligned} \mathbf{F}(c_{1h},c_1) = {} & (b-\mu)(\mu+\delta+c_{1h}) + \tfrac{b-k_1c_{1h}^2-\mu-\delta}{\varphi(b-\mu)+b-k_1c_1^2-\bar{g}}[\tfrac{1}{\varphi}(c_1-c_2)(\mu+\delta-\bar{g}) \\ & -(b-\mu)(\mu+\delta+c_2)]. \end{aligned}$$

According to previous theoretical conclusion, the singular point should be evolutionary stable if it exists. The convergence stability will need further discussion by applying our previous result.

To find the evolutionary singular point(s), we need to solve the following equation resulting from setting the fitness gradients $\left[\frac{\partial \mathbf{F}}{\partial c_{1h}}\right]_{c_{1h}=c_1}$ to zero:

$$b-\mu-\frac{2k_1c_1}{\varphi(b-\mu)+b-k_1c_1^2-\bar{g}}[\frac{1}{\varphi}(c_1-c_2)(\mu+\delta-\bar{g})-(b-\mu)(\mu+\delta+c_2)]=0, \tag{20}$$

Equation (20) can be simplified into a quadratic equation:

$$a_{12}c_1^2+a_{11}c_1+a_{10}=0, \tag{21}$$

where

$$\begin{aligned} a_{12} &= k_1[(b-\mu)+\tfrac{2}{\varphi}(\mu+\delta-\bar{g})],\\ a_{11} &= -2k_1[\tfrac{c_2}{\varphi}(\mu+\delta-\bar{g})+(b-\mu)(\mu+\delta+c_2)],\\ a_{10} &= -[\varphi(b-\mu)+(b-\bar{g})](b-\mu). \end{aligned}$$

Note that

$$\begin{aligned} \Delta_1 \quad := \quad & 4k_1^2[\tfrac{c_2}{\varphi}(\mu+\delta-\bar{g})+(b-\mu)(\mu+\delta+c_2)]^2\\ & +4k_1[(b-\mu)+\tfrac{2}{\varphi}(\mu+\delta-\bar{g})][\varphi(b-\mu)+(b-\bar{g})](b-\mu). \end{aligned}$$

Due to the complexity of these coefficients, the problem about the existence of a singular point needs to be discussed in many cases. We only explore one case in this paper.

If

$$0<\bar{g}<\min\{b,\frac{\varphi}{2}(b-\mu)+(\mu+\delta)\}, \tag{22}$$

then $a_{12}>0$, $a_{11}<0$, $a_{10}<0$ and $\Delta_1>0$, and consequently, (21) has a unique positive root which is given by

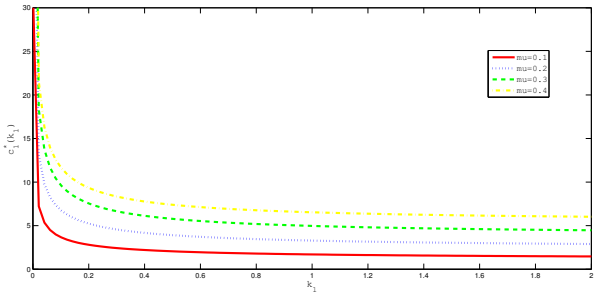
$$c_1^*=\frac{k_1[\frac{c_2}{\varphi}(\mu+\delta-\bar{g})+(b-\mu)(\mu+\delta+c_2)]+\sqrt{\Delta_1}}{k_1[(b-\mu)+\frac{2}{\varphi}(\mu+\delta-\bar{g})]},$$

Since $f''(c_1^*)=-2k_1<0$, c_1^* is an evolutionary stable strategy. Under the conditions of (22) and (7), it is easy to show that

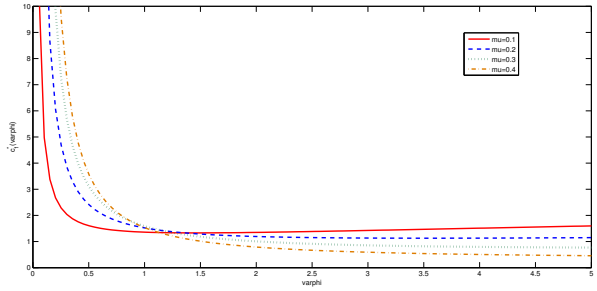
$$f''_{crit}(c_1^*)=\frac{(\mu-b)-\frac{1}{\varphi}(u+\delta-\bar{g})}{\frac{1}{\varphi}(c_1^*-c_2)(u+\delta-\bar{g})-(b-\mu)(\mu+\delta+c_2)}>0>f''(c_1^*).$$

Thus, this singular point c_1^* is also convergence stable.

In this case, the impact of the cost of immunological up-regulation k_1 and the superinfection rate φ on c_1^* can be reflected by the formula of c_1^*. For example, fixing φ or k_1 at some value, Figure 1 gives some plots of c_1^* as function of k_1 or φ. From Fig. 1, we observe that c_1^* decreases very fast as k_1 or φ increases at low level. In Figure 1(a), the curve moves up as the mortality of infected hosts increases. When the level of superinfection maintains at some value, this is significant. The evolutionary increases in the degree of up-regulation in host will thereby be selected by evolutionary increases in μ by the parasite. However, it would become more complicated when the level of superinfection is also changing.



(a) $c_1^*(k_1)$, $\varphi = 0.3$



(b) $c_1^*(\varphi)$, $k_1 = 0.5$

FIGURE 1. Dependence of the value of evolutionary singular point on the cost of immunological up-regulation k_1 and the superinfection rate φ, where $\delta = 0.095$, $b = 0.6$, $c_2 = 0.3$, and $\bar{g} = 0.15$. From two figures, both $c_1^*(k_1)$ and $c_1^*(\varphi)$ are decreasing functions in first quadrant. In (a) and (b), the four curves are obtained by varying the value of μ, respectively. In (a), the curves are moved up when μ increases. However, the movement in (b) are in two direction and more complicated than it in (a).

We point out that the monomorphic case is based on an assumption that one parasite strain can evolve but the other can not. This is a very ideal assumption. Definitely, one can explore the host-parasite co-evolution when mutant hosts can be either infected by parasite strain 1 or by parasite strain 2 and both strains evolve. The corresponding analysis can be implemented similarly to the case in [29]. Accordingly, a singular point is a pair of (c_1, c_2) at which both fitness gradients vanish. The investigation of the evolutionary and convergence stability for such a singular point constitutes an interesting and worthwhile project, which is left for a future work. In the next section, we will, instead, consider the case that mutant host can be infected by both parasite strain 1 and 2.

4. **Dimorphic case.** In this section, we assume that *both* parasites can infect mutant hosts but *without superinfection*. We also assume the infected mutant hosts

will not infect resident hosts. With these assumptions, we arrive at the following model along the line of (1) and (2):

$$\begin{cases} \frac{\mathrm{d}S_1}{\mathrm{d}t} &= bS_1 + f(c_1)I_{11} + g(c_2)I_{12} + c_1I_{11} + c_2I_{12} - \mu S_1 - \beta S_1(I_{11} + I_{12} \\ & \quad +I_{21} + I_{22}), \\ \frac{\mathrm{d}I_{11}}{\mathrm{d}t} &= \beta S_1(I_{11} + I_{21}) - (\mu + \delta + c_1)I_{11} + \beta\varphi I_{12}I_{11}, \\ \frac{\mathrm{d}I_{12}}{\mathrm{d}t} &= \beta S_1(I_{12} + I_{22}) - (\mu + \delta + c_2)I_{12} - \beta\varphi I_{12}I_{11}, \\ \frac{\mathrm{d}S_2}{\mathrm{d}t} &= bS_2 + f(c_{1h})I_{21} + g(c_{2h})I_{22} + c_{1h}I_{21} + c_{2h}I_{22} - \beta S_2(I_{21} + I_{11} + I_{12} \\ & \quad +I_{22}) - \mu S_2, \\ \frac{\mathrm{d}I_{21}}{\mathrm{d}t} &= \beta S_2(I_{11} + I_{21}) - (\mu + \delta + c_{1h})I_{21}, \\ \frac{\mathrm{d}I_{22}}{\mathrm{d}t} &= \beta S_2(I_{12} + I_{22}) - (\mu + \delta + c_{2h})I_{22}, \end{cases} \tag{23}$$

where the meanings of the variables and parameters are in Table 1. Trade-offs $f(c_1)$ and $g(c_2)$ are still decreasing functions.

Now, under conditions (4)-(8), System (23) has the mutant host free equilibrium $\tilde{\mathbf{E}}_3 = (\tilde{S}_1, \tilde{I}_{11}, \tilde{I}_{12}, 0, 0, 0))$ where $\tilde{S}_1 = \hat{S}$, $\tilde{I}_{11} = \hat{I}_1$, $\tilde{I}_{12} = \hat{I}_2$ with $\hat{S}$, $\hat{I}_1$ and $\hat{I}_2$ given in 3. The local stability of this mutant host free equilibrium $\tilde{\mathbf{E}}_3$ is determined by the eigenvalues of the Jacobian matrix:

$$\mathbf{J}^* = \begin{pmatrix} \mathbf{J_{11}} & \mathbf{J_{12}^*} \\ 0 & \mathbf{J_{22}^*} \end{pmatrix}$$

at the equilibrium $\mathbf{E}_3$, where

$$\mathbf{J_{22}^*} = \begin{pmatrix} b - \mu - \beta(\tilde{I}_{11} + \tilde{I}_{12}) & f(c_{1h}) + c_{1h} & g(c_{2h}) + c_{2h} \\ \beta\tilde{I}_{11} & -(\mu + \delta + c_{1h}) & 0 \\ \beta\tilde{I}_{12} & 0 & -(\mu + \delta + c_{2h}) \end{pmatrix}.$$

and $\mathbf{J_{11}}$ is exactly the same as in Appendix. B. When the conditions (4)-(8) hold, the local stability of the equilibrium $\tilde{\mathbf{E}}_3$ will depend on the eigenvalues of the matrix $\mathbf{J_{22}^*}$. Thus, we only need to analyze the eigenvalues of $\mathbf{J_{22}^*}$.

Calculating the characteristic equation gives

$$\begin{aligned} |\lambda \mathrm{I} - \mathbf{J}_{22}^*| = &-\frac{1}{\varphi}[(\mu + \delta + c_1) - \beta\tilde{S}] \begin{vmatrix} -c_{1h} - f(c_{1h}) & -g(c_{2h}) - c_{2h} \\ \lambda + (\mu + \delta + c_{1h}) & 0 \end{vmatrix} \\ &+ [\lambda + (\mu + \delta + c_{2h})] \begin{vmatrix} \lambda - (b - \mu) + \frac{1}{\varphi}(c_1 - c_2) & -c_{1h} - f(c_{1h}) \\ -\frac{1}{\varphi}[\beta\hat{S} - (\mu + \delta + c_2)] & \lambda + (\mu + \delta + c_{1h}) \end{vmatrix}. \end{aligned}$$

Hence, the characteristic equation of $\mathbf{J_{22}^*}$ is

$$A_0\lambda^3 + A_1\lambda^2 + A_2\lambda + A_3 = 0, \tag{24}$$

where

$$
\begin{aligned}
A_0 =& 1 > 0,\\
A_1 =& (\mu+\delta+c_{2h}) + (\mu+\delta+c_{1h}) - (b-\mu) + \frac{1}{\varphi}(c_1-c_2) > 0,\\
A_2 =& -\frac{1}{\varphi}[(\mu+\delta+c_1) - \beta\tilde{S}]\big(g(c_{2h})+c_{2h}\big) + \big[\frac{1}{\varphi}(c_1-c_2) - (b-\mu)\big](\mu+\delta+c_{1h})\\
&-\frac{1}{\varphi}[\beta\tilde{S} - (\mu+\delta+c_2)]\big(f(c_{1h})+c_{1h}\big) + (\mu+\delta+c_{1h})(\mu+\delta+c_{2h})\\
&+\big[\frac{1}{\varphi}(c_1-c_2) - (b-\mu)\big](\mu+\delta+c_{2h}),\\
A_3 =& -\frac{1}{\varphi}[(\mu+\delta+c_1) - \beta\tilde{S}]\big(g(c_{2h})+c_{2h}\big)(\mu+\delta+c_{1h})\\
&+\big[\frac{1}{\varphi}(c_1-c_2) - (b-\mu)\big](\mu+\delta+c_{1h})(\mu+\delta+c_{2h})\\
&-\frac{1}{\varphi}[\beta\tilde{S} - (\mu+\delta+c_2)]\big(f(c_{1h})+c_{1h}\big)(\mu+\delta+c_{2h}).
\end{aligned}
$$

Corresponding to the cubic polynomial in (24), there are the following three quantities needed for applying the Ruth-Hurwitz criteria:

$$
\begin{aligned}
\Delta_1 =& 1 > 0,\\
\Delta_2 =& A_2A_1 - A_3\\
=& [(\mu+\delta+c_{2h}) + \frac{1}{\varphi}(c_1-c_2) - (b-\mu)]\Big\{(\mu+\delta+c_{1h})(\mu+\delta+c_{2h})\\
&+(\mu+\delta+c_{2h})\big[\frac{1}{\varphi}(c_1-c_2) - (b-\mu)\big] - \frac{1}{\varphi}[(\mu+\delta+c_1) - \beta\tilde{S}]\big(g(c_{2h})+c_{2h}\big)\Big\}\\
&[(\mu+\delta+c_{1h}) + \frac{1}{\varphi}(c_1-c_2) - (b-\mu)]\Big\{(\mu+\delta+c_{1h})(\mu+\delta+c_{2h})\\
&+(\mu+\delta+c_{1h})\big[\frac{1}{\varphi}(c_1-c_2) - (b-\mu)\big] - \frac{1}{\varphi}[\beta\tilde{S} - (\mu+\delta+c_2)]\big(f(c_{1h})+c_{1h}\big)\Big\},\\
\Delta_3 =& A_3\Delta_2.
\end{aligned}
$$

The necessary and sufficient conditions, under which all the roots of (24) have negative real parts, are given by $\Delta_2 > 0$ and $\Delta_3 > 0$ according to the well-known Hurwitz criterion. This means that if $\Delta_2 > 0$ and $\Delta_3 > 0$, then $\tilde{\mathbf{E}}_3$ is asymptotically stable, implying that a small number of mutant hosts can not get established.

If either $\Delta_2 > 0$ or $\Delta_3 > 0$ is violated, the mutant host free equilibrium $\tilde{\mathbf{E}}_3$ would lose its local stability so that the mutant hosts have a chance to invade resident hosts. When $A_3 > 0$, it is known that the sign change of Δ_2 (also of Δ_3) would result in Hopf bifurcation around $\tilde{\mathbf{E}}_3$ for system (23) (see Theorem 2 in Yu [28]), causing solutions to oscillate about $\tilde{\mathbf{E}}_3$. The S_2, I_{21} and I_{22} components of such oscillatory solutions would become *negative* in some time intervals. On the other hand, using the standard approach, one can easily show that solutions to (23) with non-negative initial values remains non-negative, leading to a contradiction. Therefore, loss of stability of $\mathbf{E}_3$ can only occur through the sign change of A_3 from positive to negative. Based on this observation, it is natural to choose $-A_3$ as a measurement of the fitness for the mutant hosts with two parasite strains, in the sense that the mutant hosts can invade resident hosts successfully only if $-A_3 > 0$.

As such, we choose the following fitness function $\mathbf{T}(c_{1h}, c_{ch}, c_1, c_2)$:

$$\begin{aligned}
&\mathbf{T}(c_{1h}, c_{ch}, c_1, c_2)\\
=&\frac{1}{\varphi}\big[(\mu+\delta+c_1)-\beta\tilde{S}\big]\big(g(c_{2h})+c_{2h}\big)\big(\mu+\delta+c_{1h}\big)\\
&-\big[\frac{1}{\varphi}(c_1-c_2)-(b-\mu)\big]\big(\mu+\delta+c_{1h}\big)\big(\mu+\delta+c_{2h}\big)\\
&+\frac{1}{\varphi}\big[\beta\tilde{S}-(\mu+\delta+c_2)\big]\big(f(c_{1h})+c_{1h}\big)\big(\mu+\delta+c_{2h}\big).
\end{aligned} \tag{25}$$

To proceed further, we calculate the derivatives of $T(c_{1h}, c_{ch}, c_1, c_2)$ as below:

$$\begin{aligned}
&\Big[\frac{\partial\mathbf{T}}{\partial c_{1h}}\Big]\Big|_{(c_{1h},c_{2h})=(c_1,c_2)}\\
=&\frac{1}{\varphi}\big[(\mu+\delta+c_1)-\beta\tilde{S}(c_1,c_2)\big]\big(g(c_2)+c_2\big)-\big[\frac{1}{\varphi}(c_1-c_2)-(b-\mu)\big]\big(u+\delta+c_2\big)\\
&+\frac{1}{\varphi}\big[\beta\tilde{S}(c_1,c_2)-(\mu+\delta+c_2)\big]\big(f'(c_1)+1\big)\big(\mu+\delta+c_2\big),
\end{aligned} \tag{26}$$

$$\begin{aligned}
&\Big[\frac{\partial\mathbf{T}}{\partial c_{2h}}\Big]\Big|_{(c_1,c_{2h})=(c_1,c_2)}\\
=&\frac{1}{\varphi}\big[(\mu+\delta+c_1)-\beta\tilde{S}(c_1,c_2)\big]\big(g'(c_2)+1\big)\big(\mu+\delta+c_1\big)\\
&-\big[\frac{1}{\varphi}(c_1-c_2)-(b-\mu)\big]\big(\mu+\delta+c_2\big)+\frac{1}{\varphi}[\beta\tilde{S}(c_1,c_2)-(\mu+\delta+c_2)]\big(f(c_1)+c_1\big).
\end{aligned} \tag{27}$$

The evolutionary singular point is determined by

$$\begin{cases}
\Big[\dfrac{\partial\mathbf{T}}{\partial c_{1h}}\Big]\Big|_{(c_{1h},c_{2h})=(c_1,c_2)}=0,\\
\Big[\dfrac{\partial\mathbf{T}}{\partial c_{2h}}\Big]\Big|_{(c_{1h},c_{2h})=(c_1,c_2)}=0.
\end{cases} \tag{28}$$

If $(\tilde{c}_1^*, \tilde{c}_2^*)$ is a solution of (28), $(\tilde{c}_1^*, f(\tilde{c}_1^*))$ and $(\tilde{c}_2^*, g(\tilde{c}_2^*))$ are called an evolutionary singular species pair.

Although we can obtain the expressions of $f'(c_1)$ and $g'(c_2)$ by solving equations of (28), these formulas for $f'(c_1)$ and $g'(c_2)$ can only give us *partial information* of $f(c_1)$ and $g(c_2)$ near $\tilde{c}_1^*$ and $\tilde{c}_2^*$. Thus, the notion of critical functions is not applicable in dimorphic case.

4.1. **Evolutionary stability.** According to Kisdi [18], if this singular pair cannot be invaded by mutant hosts with either of the parasites, it is *locally evolutionary stable*. Here a strategy is said to be a local (global) ESS if the equilibrium at this strategy is a local (global) ecologically stable equilibrium (see Definition 1 in [1]). This can be implied by the following two conditions:

$$\frac{\partial^2\mathbf{T}(c_{1h},c_{2h},c_1,c_2)}{\partial c_{1h}^2}\Big|_{(c_{1h},\,c_{2h},\,c_1,\,c_2)=(\tilde{c}_1^*,\,\tilde{c}_2^*,\,\tilde{c}_1^*,\,\tilde{c}_2^*)}<0, \tag{29}$$

and

$$\frac{\partial^2\mathbf{T}(c_{1h},c_{2h},c_1,c_2)}{\partial c_{2h}^2}\Big|_{(c_{1h},\,c_{2h},\,c_1,\,c_2)=(\tilde{c}_1^*,\,\tilde{c}_2^*,\,\tilde{c}_1^*,\,\tilde{c}_2^*)}<0. \tag{30}$$

Note that

$$\begin{aligned} & \frac{\partial^2 \mathbf{T}(c_{1h},c_{2h},c_1,c_2)}{\partial c_{1h}^2}\Big|_{(c_{1h},\,c_{2h},\,c_1,\,c_2)=(\tilde{c}_1^*,\,\tilde{c}_2^*,\,\tilde{c}_1^*,\,\tilde{c}_2^*)} \\ = \;& \big[\beta\tilde{S}(\tilde{c}_1^*,\tilde{c}_2^*)-(\mu+\delta+\tilde{c}_2^*)\big]f''(\tilde{c}_1^*). \end{aligned} \tag{31}$$

Under the conditions (4), (5), (6) and (7), $\tilde{S}(\tilde{c}_1^*,\,\tilde{c}_2^*)-(\mu+\delta+\tilde{c}_2^*)$ is positive. Thus, the condition (29) can be satisfied at $\tilde{c}_1^*$ when trade-off $f(c_1)$ is concave down or locally concave down at $\tilde{c}_1^*$.

Similarly, if $g(c_2)$ is concave down or locally concave down at $\tilde{c}_2^*$, there holds

$$\begin{aligned} & \frac{\partial^2 \mathbf{T}(c_{1h},c_{2h},c_1,c_2)}{\partial c_{2h}^2}\Big|_{(c_{1h},\,c_{2h},\,c_1,\,c_2)=(\tilde{c}_1^*,\,\tilde{c}_2^*\,\tilde{c}_1^*,\,\tilde{c}_2^*)} \\ = \;& \big[(\mu+\delta+\tilde{c}_1^*)-\beta\tilde{S}(\tilde{c}_1^*,\tilde{c}_2^*)\big]g''(\tilde{c}_2^*) \\ < \;& 0 \end{aligned} \tag{32}$$

under the conditions (4), (5), (6) and (7).

Therefore, this evolutionary singularity is an evolutionary stable strategy if both trade-offs are concave down or locally concave down at $(\tilde{c}_1^*,\,\tilde{c}_2^*)$.

4.2. **Isoclinic stability.** In dimorphic case, the convergence stability becomes very difficult and it involves the relative speed of evolution between the two hosts [13, 23, 20]. But "isoclinic stability" (see [18] for the notion) is a bit easier to determine, and is now explored as below. Assuming that the evolution of parasite 2 is prevented by keeping $c_2=\tilde{c}_2^*$, we can treat it as the monomorphic case. Therefore, if

$$\begin{aligned} & \frac{\mathrm{d}}{\mathrm{d}c_1}\Big(\frac{\partial \mathbf{T}(c_{1h},c_{2h}^*,c_1,c_2^*)}{\partial c_1}\Big|_{c_{1h}=c_1}\Big)\Big|_{c_1=\tilde{c}_1^*} \\ =& \frac{\partial^2 \mathbf{T}(c_{1h},c_{2h},c_1,c_2)}{\partial c_{1h}^2}\Big|_{(c_{1h},\,c_{2h}\,c_1,\,c_2)=(\tilde{c}_1^*,\,\tilde{c}_2^*,\,\tilde{c}_1^*,\,\tilde{c}_2^*)} \\ & + \frac{\partial^2 \mathbf{T}(c_{1h},c_{2h},c_2,c_2)}{\partial c_1\partial c_{1h}}\Big|_{(c_{1h},\,c_{2h},\,c_1,\,c_2)=(\tilde{c}_1^*,\,\tilde{c}_2^*,\,\tilde{c}_1^*,\,\tilde{c}_2^*)} \\ <& 0 \end{aligned} \tag{33}$$

holds, c_1 would evolve toward $\tilde{c}_1^*$ from its neighbourhood. Similarly, when c_1 is set to $\tilde{c}_1^*$, c_2 would evolve toward $\tilde{c}_2^*$ if

$$\begin{aligned} & \frac{\mathrm{d}}{\mathrm{d}c_2}\Big(\frac{\partial \mathbf{T}(c_{1h}^*,c_{2h},c_1^*,c_2)}{\partial c_2}\Big|_{c_{2h}=c_2}\Big)\Big|_{c_2=\tilde{c}_2^*} \\ =& \frac{\partial^2 \mathbf{T}(c_{1h},c_{2h},c_1,c_2)}{\partial c_{2h}^2}\Big|_{(c_{1h},\,c_{2h},\,c_1,\,c_2)=(\tilde{c}_1^*,\,\tilde{c}_2^*,\,\tilde{c}_1^*,\,\tilde{c}_2^*)} \\ & + \frac{\partial^2 \mathbf{T}(c_{1h},c_{2h},c_1,c_2)}{\partial c_2\partial c_{2h}}\Big|_{(c_{1h},\,c_{2h},\,c_1,\,c_2)=(\tilde{c}_1^*,\,\tilde{c}_2^*,\,\tilde{c}_1^*,\,\tilde{c}_2^*)} \\ <& 0. \end{aligned} \tag{34}$$

We point that when both parasites evolve, however, "isoclinic stability" is neither necessary nor sufficient condition for convergence stability [23, 24].

To conveniently demonstrate the above general results, we use two simple quadratic functions $f(c_1)=b-k_1^*c_1^2$ and $g(c_2)=b-k_2^*c_2^2$, where $k_1^*<k_2^*$, for the two trade-offs respectively. Obviously, the corresponding evolutionary singularity is a locally evolutionary stable strategy in this case.

Substituting the specified trade-offs into the conditions of isoclinic stability, we obtain

$$\begin{aligned}
&\tfrac{\mathrm{d}}{\mathrm{d}c_1}\Big(\tfrac{\partial \mathbf{T}(c_{1h},c_{2h},c_1,c_2)}{\partial c_1}\Big|_{c_{1h}=c_1}\Big)\Big|_{c_1=\tilde{c}_1^*}\\
=\;&\big[\beta\tilde{S}(\tilde{c}_1^*,\tilde{c}_2^*)-(\mu+\delta+\tilde{c}_2^*)\big]f''(\tilde{c}_1^*)+\tfrac{1}{\varphi}\Big(1-\beta\tfrac{\partial\tilde{S}}{\partial c_1}\Big|_{(c_1,c_2)=(\tilde{c}_1^*,\tilde{c}_2^*)}\Big)\big(g(\tilde{c}_2^*)+\tilde{c}_2^*\big)\\
&-\tfrac{1}{\varphi}\big(f'(\tilde{c}_1^*)+1\big)\big(\mu+\delta+\tilde{c}_2^*\big)\beta\tfrac{\partial\tilde{S}}{\partial c_1}\Big|_{(c_1,c_2)=(\tilde{c}_1^*,\tilde{c}_2^*)}
\end{aligned}\tag{35}$$

and

$$\begin{aligned}
&\tfrac{\mathrm{d}}{\mathrm{d}c_1}\Big(\tfrac{\partial \mathbf{T}(c_{1h},c_{2h},c_1,c_2)}{\partial c_1}\Big|_{c_{1h}=c_1}\Big)\Big|_{c_1=\tilde{c}_1^*}\\
=\;&\big[(\mu+\delta+\tilde{c}_1^*)-\beta\tilde{S}(\tilde{c}_1^*,\tilde{c}_2^*)\big]g''(\tilde{c}_2^*)-\tfrac{1}{\varphi}(g'(\tilde{c}_2^*)+1)\beta\tfrac{\partial\tilde{S}}{\partial c_2}\Big|_{(c_1,c_2)=(\tilde{c}_1^*,\tilde{c}_2^*)}\\
&+\tfrac{1}{\varphi}\Big(\beta\tfrac{\partial\tilde{S}}{\partial c_2}\Big|_{(c_1,c_2)=(\tilde{c}_1^*,\tilde{c}_2^*)}-1\Big)\big(f(\tilde{c}_1^*)+\tilde{c}_1^*\big),
\end{aligned}\tag{36}$$

where

$$\begin{aligned}
f'(\tilde{c}_1^*)=-2k_1^*\tilde{c}_1^*,\quad f''(\tilde{c}_1^*)=-2k_1^*,\\
g'(\tilde{c}_2^*)=-2k_2^*\tilde{c}_2^*,\quad g''(\tilde{c}_2^*)=-2k_2^*,
\end{aligned}$$

$$\begin{aligned}
\beta\tfrac{\partial\tilde{S}(c_1,c_2)}{\partial c_1}\Big|_{(c_1,c_2)=(\tilde{c}_1^*,\tilde{c}_2^*)} =\;&\tfrac{(\mu+\delta)[1+f'(\tilde{c}_1^*)]+\tilde{c}_2^*f'(\tilde{c}_1^*)-g(\tilde{c}_2^*)}{\varphi(b-\mu)+f(\tilde{c}_1^*)-g(\tilde{c}_2^*)}\\
&-\tfrac{(\mu+\delta)[\tilde{c}_1^*-\tilde{c}_2^*+f(\tilde{c}_1^*)-g(\tilde{c}_2^*)]+\tilde{c}_2^*f(\tilde{c}_1^*)-\tilde{c}_1^*g(\tilde{c}_2^*)}{\big[\varphi(b-\mu)+f(\tilde{c}_1^*)-g(\tilde{c}_2^*)\big]^2}f'(\tilde{c}_1^*),
\end{aligned}$$

and

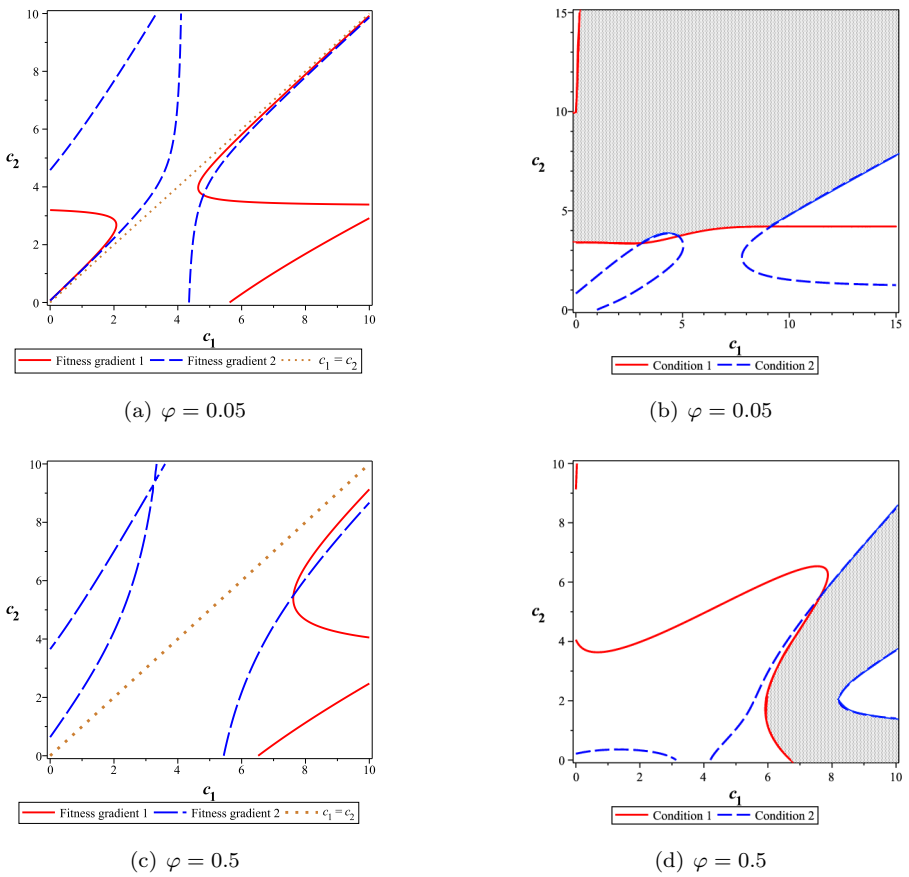
$$\begin{aligned}
\beta\tfrac{\partial\tilde{S}(c_1,c_2)}{\partial c_2}\Big|_{(c_1,c_2)=(\tilde{c}_1^*,\tilde{c}_2^*)} =\;&\tfrac{(\mu+\delta)[-1-g'(\tilde{c}_2^*)]+f(\tilde{c}_1^*)-\tilde{c}_1^*g'(\tilde{c}_2^*)}{\varphi(b-\mu)+f(\tilde{c}_1^*)-g(\tilde{c}_2^*)}\\
&-\tfrac{(\mu+\delta)[\tilde{c}_1^*-\tilde{c}_2^*+f(\tilde{c}_1^*)-g(\tilde{c}_2^*)]+\tilde{c}_2^*f(\tilde{c}_1^*)+\tilde{c}_1^*g(\tilde{c}_2^*)}{\big[\varphi(b-\mu)+f(\tilde{c}_1^*)-g(\tilde{c}_2^*)\big]^2}g'(\tilde{c}_2^*).
\end{aligned}$$

According to previous discussion, $(\tilde{c}_1^*,\tilde{c}_2^*)$ is isoclinic stable when both (35) and (36) are negative.

Since the above two formulas are not easy to be further simplified, we give some numerical results in Figure 2 to observe the effects of two key parameters. After fixing the values of parameters, we show the corresponding singularity in Figures 2(a) and 2(c), which are plotted with respect to different superinfection rates. In Figure 2(b) and 2(d), the two conditions for isoclinic stability can be met in shadow areas. By comparing Figure 2(b) and Figure 2(d), we find that the shape of the shadowed area could be changed by varying the superinfection rate.

4.3. **Absolute convergence stability.** An absolutely convergence point is a local attractor for all gradual adaptive change. For fitness landscapes of fixed shape, the local fitness maxima are absolutely convergence [19]. In this subsection, we discuss the conditions for absolutely convergence stability for dimorphic case with the fitness function given by (25). In this case, we assume that the two strains in mutant hosts are independent. Based on the theory in [18, 24], if (33), (34) and

$$\begin{aligned}
&\Big(\tfrac{\partial^2\mathbf{T}(c_{1h},c_{2h},c_1,c_2)}{\partial c_{1h}^2}+\tfrac{\partial^2\mathbf{T}(c_{1h},c_{2h},c_2,c_2)}{\partial c_1\partial c_{1h}}\Big)\Big(\tfrac{\partial^2\mathbf{T}(c_{1h},c_{2h},c_1,c_2)}{\partial c_{2h}^2}+\tfrac{\partial^2\mathbf{T}(c_{1h},c_{2h},c_1,c_2)}{\partial c_2\partial c_{2h}}\Big)\\
>\;&\Big|\tfrac{\partial^2\mathbf{T}(c_{1h},c_{2h},c_1,c_2)}{\partial c_2\partial c_{1h}}\;\tfrac{\partial^2\mathbf{T}(c_{1h},c_{2h},c_1,c_2)}{\partial c_1\partial c_{2h}}\Big|
\end{aligned}\tag{37}$$



(a) $\varphi = 0.05$ (b) $\varphi = 0.05$

(c) $\varphi = 0.5$ (d) $\varphi = 0.5$

FIGURE 2. Singularity and Isoclinic stability: when $\delta = 0.95$, $b = 10$, $\beta = 0.4$, $\mu = 0.2$, $k_1 = 0.5$, and $k_2 = 0.8$. We only observe the regions in first quadrant. In figure (a) and (b), we plot the solutions when (26) and (27) are equal to zero. In figures (c) and (d), the red solid curves represents function (35) and the blue dash curves represent function (36). In shadows, both conditions (33) and (34) for isoclinic stability can be met. We adjust the value of superinfection rates φ to observe its effects. When superinfection rate increase, the values of $\tilde{c}_1^*$ and $\tilde{c}_2^*$ also increase. The shadow area has significant change when superinfection rate changes.

hold simultaneously, the point, $(\tilde{c}_1^*, \tilde{c}_2^*)$, is absolute convergence stable (see e.g., [19]).

Note that in (37), the formulas (31) and (32) are still valid and simple, the two cross derivatives are typically more complicated. To illustrate this, we still use the two simple quadratic functions $f(c_1) = b - k_1^* c_1^2$ and $g(c_2) = b - k_2^* c_2^2$, where $k_1^* < k_2^*$ for the two trade-offs respectively. For this pair of quadratic trade-off functions, the

two cross derivatives in (37) become

$$\begin{aligned}
&\frac{\partial^2 \mathbf{T}(c_{1h}, c_{2h}, c_1, c_2)}{\partial c_2 \partial c_{1h}}\Big|_{(c_{1h}, c_{2h}, c_1, c_2)=(\tilde{c}_1^*, \tilde{c}_2^*, \tilde{c}_1^*, \tilde{c}_2^*)} \\
&= -\frac{1}{\varphi}\beta\frac{\partial \tilde{S}}{\partial c_2}\Big|_{(c_1,c_2)=(\tilde{c}_1^*,\tilde{c}_2^*)}\Big(g(\tilde{c}_2^*)+\tilde{c}_2^*\Big)+\frac{1}{\varphi}\big(\mu+\delta+\tilde{c}_2^*\big) \\
&\quad+\frac{1}{\varphi}\Big(\beta\frac{\partial \tilde{S}}{\partial c_2}\Big|_{(c_1,c_2)=(\tilde{c}_1^*,\tilde{c}_2^*)}-1\Big)\big(f'(\tilde{c}_1^*)+1\big)\big(\mu+\delta+\tilde{c}_2^*\big)
\end{aligned} \tag{38}$$

and

$$\begin{aligned}
&\frac{\partial^2 \mathbf{T}(c_{1h}, c_{2h}, c_1, c_2)}{\partial c_2 \partial c_{1h}}\Big|_{(c_{1h}, c_{2h}, c_1, c_2)=(\tilde{c}_1^*, \tilde{c}_2^*, \tilde{c}_1^*, \tilde{c}_2^*)} \\
&=\frac{1}{\varphi}\beta\frac{\partial \tilde{S}}{\partial c_1}\Big|_{(c_1,c_2)=(\tilde{c}_1^*,\tilde{c}_2^*)}\Big(f(\tilde{c}_1^*)+\tilde{c}_1^*\Big)-\frac{1}{\varphi}\big(\mu+\delta+\tilde{c}_1^*\big) \\
&\quad+\frac{1}{\varphi}\Big(1-\beta\frac{\partial \tilde{S}}{\partial c_1}\Big|_{(c_1,c_2)=(\tilde{c}_1^*,\tilde{c}_2^*)}\Big)\big(g'(\tilde{c}_2^*)+1\big)\big(\mu+\delta+\tilde{c}_1^*\big).
\end{aligned} \tag{39}$$

For such simple trade-offs, verification of (37) is still not easy. To show that this condition is feasible, we provide some numerical results in Figure 3. We only plot the first quadrant, because the data for simulation in other regions has no biological meaning. The three conditions (33), (34) and (37) can be met in the two shadows. We find that this condition is very sensitive to the value of each parameter.

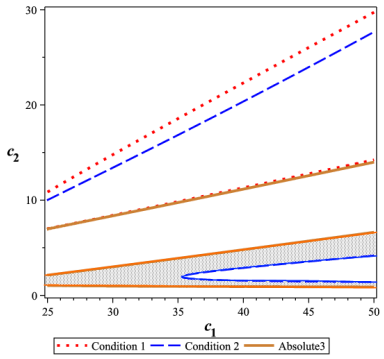


FIGURE 3. Absolute stability: when $\delta = 0.3$, $\varphi = 10$, $b = 2$, $\beta = 0.4$, $\mu = 0.2$, $k_1 = 0.1$, and $k_2 = 0.8$. The red dot curve represents function (35) and the blue dash curve represents function (36), too. The golden solid line stands for the formula in inequality (37). In two shadows, the conditions for absolute stability can be satisfied.

5. **Discussion.** In this paper, we study the host-parasite co-evolution on population level. Superinfection and a trade-off involving production rate by infected hosts and their recovery rate are considered in a basic SIR model with two parasite strains and one host strain. We obtain a positive equilibrium representing the co-existence of parasite strains 1 and 2 in the resident host and prove its local stability.

Furthermore, we introduce mutant host into our model and discuss its invasion in monomorphic and dimorphic cases, respectively.

In monomorphic case, a critical quantity that can decide the local stability of the mutant host-free equilibrium is used as the fitness of the invasion of mutant hosts with an infection. Mutant host can only be infected by one parasite strain, and due to symmetry, we have only discussed the case that the mutant can only be infected by strain 1 parasite. Considering trade-off between the production rate and recovery rate of infected mutant host, we are able to discuss the evolutionary singular strategy and its evolutionary and convergence stabilities are analyzed respectively. In a concrete example, we observe how the cost of immunological up-regulation and superinfection rate affect the singular point.

Comparing with the conclusions of Geritz et al. [16], our results suggest that superinfection trends to help parasite strains 1 and 2 coexist, and impacts the evolution in hosts. Indeed, it makes host-parasite co-evolution more difficult to study. Our results also suggest that the degree of immune response can affect the the host evolution. As the degree of immunological response increases, its cost from up-regulation would concomitantly increase. However, nutrients are limited for consuming in a host. Although immune response is benign to hosts, the host evolution would not favour a high degree of immunological up-regulation. In this way, an intermediate degree of immunological up-regulation would be helpful to host evolution.

Furthermore, the case that mutant host can be infected by *both parasite strains* is also explored. A new fitness with four types of traits is defined. In this case, the conditions for an evolutionary stable singularity is easily obtained. However, due to the higher dimension of the strategy space, the convergence stability becomes much more complicated, and is thus not explored here. Instead, isoclinic and absolute convergence stabilities are discussed. The fact that there are two trade-off functions in this case, offers more possibilities to discuss the above mentioned stabilities. All these are in contrast to the monomorphic case. For convenience, the trade-offs are specified by two simple quadratic functions, and some numerical results are provided to demonstrate the effect of the two key parameters.

In both monomorphic and dimorphic case, superinfection is found to help the parasite strain with a weaker virulence exist and keep evolving in hosts.

We note that we have only discussed the evolution at host level in this paper. Actually, the evolutionary speed of parasites should be quicker than that of hosts. So, a nested model may be a better choice for our further research. We point that Day and Burns [12] discussed another trade-off, the trade-off between transmission rate and clearance rate, based on some evidences that quicker host death is caused by the parasites with larger transmission rate. In the future, we could also consider this trade off, and compare the possible results to gain a better understanding of the host-parasite co-evolution. Due to very limited approaches in dimorphic adaptive dynamics, some ideal assumptions have been used to simplify the analysis, but such assumptions may not be realistic. Therefore, further constructing more reasonable models without sacrificing the mathematical tractability seems to be desirable and meaningful in future research along this line.

As we mentioned above, the convergence stability problem in higher dimensional strategy space is significantly more complicated. In our two-dimensional case, although we simplify all possible conditions, it is still too hard to obtain some analytical results by applying existing theories. Meanwhile, the absolute convergence

stability is too ideal to be met in real world. Hence, much needs to be done to fill this gap in future research on such topics.

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Appendix A. The Jacobian matrix of the system (2) at its coexistence equilibrium is :

$$\mathbf{J}=\begin{pmatrix} b-\mu-\beta(\hat{I}_1+\hat{I}_2) & f(c_1)+c_1-\beta\hat{S} & g(c_2)+c_2-\beta\hat{S} \\ \beta\hat{I}_1 & \beta\hat{S}-(\mu+\delta+c_1)+\beta\varphi\hat{I}_2 & \beta\varphi\hat{I}_1 \\ \beta\varphi\hat{I}_2 & -\beta\varphi\hat{I}_2 & \beta\hat{S}-(\mu+\delta+c_2)+\beta\varphi\hat{I}_1 \end{pmatrix}$$

$$=\begin{pmatrix} b-\mu-\frac{(c_1-c_2)}{\varphi} & f(c_1)+c_1-\beta\hat{S} & g(c_2)+c_2-\beta\hat{S} \\ -\frac{(\mu+\delta+c_2)-\beta\hat{S}}{\varphi} & 0 & \beta\hat{S}-(\mu+\delta+c_2) \\ \frac{(\mu+\delta+c_1)-\beta\hat{S}}{\varphi} & \beta\hat{S}-(\mu+\delta+c_1) & 0 \end{pmatrix}.$$

So,

$$\begin{aligned}
&|\lambda\mathrm{I}-\mathbf{J}| \\
=&\begin{vmatrix} \lambda-(b-\mu-\frac{c_1-c_2}{\varphi}) & \beta\hat{S}-f(c_1)-c_1 & \beta\hat{S}-g(c_2)-c_2 \\ \frac{(\mu+\delta+c_2)-\beta\hat{S}}{\varphi} & \lambda & (\mu+\delta+c_2)-\beta\hat{S} \\ \frac{\beta\hat{S}-(\mu+\delta+c_1)}{\varphi} & (\mu+\delta+c_1)-\beta\hat{S} & \lambda \end{vmatrix} \\
=&[\lambda-(b-\mu-\frac{c_1-c_2}{\varphi})]\begin{vmatrix} \lambda & (\mu+\delta+c_2)-\beta\hat{S} \\ (\mu+\delta+c_1)-\beta\hat{S} & \lambda \end{vmatrix} \\
&-\frac{(\mu+\delta+c_2)-\beta\hat{S}}{\varphi}\begin{vmatrix} \beta\hat{S}-f(c_1)-c_1 & \beta\hat{S}-g(c_2)-c_2 \\ (\mu+\delta+c_1)-\beta\hat{S} & \lambda \end{vmatrix} \\
&+\frac{\beta\hat{S}-(\mu+\delta+c_1)}{\varphi}\begin{vmatrix} \beta\hat{S}-f(c_1)-c_1 & \beta\hat{S}-g(c_2)-c_2 \\ \lambda & (\mu+\delta+c_2)-\beta\hat{S} \end{vmatrix} \\
=&[\lambda-(b-\mu)+\frac{c_1-c_2}{\varphi}][\lambda^2-(\mu+\delta+c_1-\beta\hat{S})(\mu+\delta+c_2-\beta\hat{S})] \\
&-\frac{(\mu+\delta+c_2)-\beta\hat{S}}{\varphi}[(\beta\hat{S}-f(c_1)-c_1)\lambda-(\mu+\delta+c_1-\beta\hat{S})(\beta\hat{S}-g(c_2)-c_2)] \\
&+\frac{\beta\hat{S}-(\mu+\delta+c_1)}{\varphi}[(\beta\hat{S}-f(c_1)-c_1)(\mu+\delta+c_2-\beta\hat{S})-\lambda(\beta\hat{S}-g(c_2)-c_2)] \\
=&\lambda^3+[\frac{c_1-c_2}{\varphi}-(b-\mu)]\lambda^2-[(\mu+\delta+c_1)-\beta\hat{S}][(\mu+\delta+c_2)-\beta\hat{S}]\lambda \\
&-\frac{(\mu+\delta+c_2-\beta\hat{S})(\beta\hat{S}-f(c_1)-c_1)+(\beta\hat{S}-(\mu+\delta+c_1))(\beta\hat{S}-g(c_2)-c_2)}{\varphi}\lambda \\
&+(b-\mu-\frac{c_1-c_2}{\varphi})[(\mu+\delta+c_1)-\beta\hat{S}][(\mu+\delta+c_2)-\beta\hat{S}] \\
&+\frac{1}{\varphi}(f(c_1)-g(c_2)+c_1-c_2)[(\mu+\delta+c_1)-\beta\hat{S}][(\mu+\delta+c_2)-\beta\hat{S}].
\end{aligned}$$

The characteristic equation is

$$a_0\lambda^3+a_1\lambda^2+a_2\lambda+a_3=0, \tag{40}$$

where

$$
\begin{aligned}
a_0 =& 1 > 0,\\
a_1 =& \frac{c_1 - c_2}{\varphi} - (b - \mu),\\
a_2 =& [(\mu + \delta + c_1) - \beta\hat{S}][\beta\hat{S} - (\mu + \delta + c_2)] + \frac{1}{\varphi}[-(f(c_1) + c_1)(\mu + \delta + c_1)\\
&+ (g(c_2) + c_2)(\mu + \delta + c_2) + \beta\hat{S}(g(c_2) - f(c_1))]\\
=& [(\mu + \delta + c_1) - \beta\hat{S}][\beta\hat{S} - (\mu + \delta + c_2)] + \frac{1}{\varphi}[(\mu + \delta)(g(c_2) - f(c_1) + c_2 - c_1)\\
&+ c_1 g(c_2) - c_2 f(c_1) + \beta\hat{S}(g(c_2) - f(c_1))] > 0,\\
a_3 =& \frac{1}{\varphi}[(\mu + \delta + c_1) - \beta\hat{S}][(\mu + \delta + c_2) - \beta\hat{S}][\varphi(b - \mu) + f(c_1) - g(c_2)] > 0,
\end{aligned}
$$

under the conditions (4)-(7). If (8) holds, we have

$$
\begin{aligned}
\Delta_1 =& \frac{c_1 - c_2}{\varphi} - (b - \mu) > 0,\\
\Delta_2 =& a_2 a_1 - a_3\\
=& \frac{1}{\varphi}[(\mu + \delta)(g(c_2) - f(c_1) + c_2 - c_1) + c_1 g(c_2) - c_2 f(c_1) + \beta\hat{S}(g(c_2) - f(c_1))]\\
&+ \frac{1}{\varphi}[(\mu + \delta + c_1) - \beta\hat{S}][\beta\hat{S} - (\mu + \delta + c_2)][c_1 - c_2 + g(c_2) - f(c_1)] > 0,\\
\Delta_3 =& a_3 \Delta_2 > 0.
\end{aligned}
$$

Now, we have proved that all roots of polynomial equation (40) have negative real parts by Routh-Hurwitz criterion. Therefore, the coexistence equilibrium $\hat{\mathbf{E}}$ is locally asymptotic stable when the conditions (4)-(8) are satisfied.

Appendix B. To study the local stability of the mutant hosts free equilibrium $\tilde{\mathbf{E}}$ in system (9), we need to consider the Jacobian matrix of system (9) at the equilibrium $\tilde{\mathbf{E}}$

$$
\mathbf{J} = \begin{pmatrix} \mathbf{J_{11}} & \mathbf{J_{12}} \\ 0 & \mathbf{J_{22}} \end{pmatrix}
$$

where

$$
\mathbf{J_{11}} = \begin{pmatrix} b - \mu - \beta(\tilde{I}_{11} + \tilde{I}_{12}) & f(c_1) + c_1 - \beta\tilde{S}_1 & g(c_2) + c_2 - \beta\tilde{S}_1 \\ \beta\tilde{I}_{11} & \beta\tilde{S}_1 - (\mu + \delta + c_1) + \beta\varphi\tilde{I}_{12} & \beta\varphi\tilde{I}_{11} \\ \beta\tilde{I}_{12} & -\beta\varphi\tilde{I}_{12} & \beta\tilde{S}_1 - (\mu + \delta + c_2) - \beta\varphi\tilde{I}_{11} \end{pmatrix}
$$

and

$$
\mathbf{J_{12}} = \begin{pmatrix} 0 & -\beta\tilde{S}_1 \\ 0 & \beta\tilde{S}_1 \\ 0 & 0 \end{pmatrix}, \quad \mathbf{J_{22}} = \begin{pmatrix} b - \mu - \beta\tilde{I}_{11} & f(c_{1h}) + c_{1h} \\ \beta\tilde{I}_{11} & -(\mu + \delta + c_{1h}) \end{pmatrix}.
$$

Under the conditions (4)-(8), all eigenvalues of the sub-matrix $\mathbf{J_{11}}$ have negative real parts (by Appendix A). Then, the local stability of the equilibrium $\tilde{\mathbf{E}}$ fully depends on the eigenvalues of the matrix $\mathbf{J_{22}}$. By the condition (4) and making use of the formula for $\tilde{I}$, we can easily verify that the trace of matrix $\mathbf{J_{22}}$ is always negative. Thus the mutant host-free equilibrium $\tilde{\mathbf{E}}$ is locally asymptotic stable,

if and only if $\det \mathbf{J_{22}} > 0$. This implies that a small mutant population infected by strain 1 parasite can invade/persist if and only if $\det \mathbf{J_{22}} < 0$, or equivalently, $-\det \mathbf{J_{22}} > 0$. Such an observation suggests us to choose $-\det \mathbf{J_{22}}$ as a natural measurement of the fitness for the mutant host infected by strain 1 parasite. Straightforward calculation gives the explicit formula in (10).

We point out that there are other choices for fitness in the context of adaptive dynamics. For example, when considering a pathogen mutant, the *basic reproduction ratio* has been frequently used (see, e.g., [27]), while when invasion of a mutant host is considered, *life span* and *basic depression ratio* are used as the respective fitness functions in [7] and [6]. Since this work is motivated by [12], here we choose to follow [12] to use the above quantity which is the threshold for the local stability of $\tilde{\mathbf{E}}$. The theory in [30] seems to suggest that these choices are mathematically equivalent generically and they can all measure the invasion ability, but each has its own merits and drawbacks. Take our choice here as an example, it is along the line of the principal eigenvalue which has also been widely used, and is mathematically more convenient but biologically less relevant than the basic reproduction ration and basic depression ratio. In the ecological context, total growth rate is also often used to measure the fitness of a species, see, e.g., [13, 15, 22].

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