

Western  Graduate&PostdoctoralStudies

Western University
Scholarship@Western

Electronic Thesis and Dissertation Repository

8-21-2013 12:00 AM

On evolution dynamics and strategies in some host-parasite models

Liman Dai
The University of Western Ontario

Supervisor
Xingfu Zou
The University of Western Ontario

Graduate Program in Applied Mathematics
A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy
© Liman Dai 2013

Follow this and additional works at: <https://ir.lib.uwo.ca/etd>

 Part of the [Dynamic Systems Commons](#), [Ordinary Differential Equations and Applied Dynamics Commons](#), and the [Other Applied Mathematics Commons](#)

Recommended Citation

Dai, Liman, "On evolution dynamics and strategies in some host-parasite models" (2013). *Electronic Thesis and Dissertation Repository*. 1542.
<https://ir.lib.uwo.ca/etd/1542>

This Dissertation/Thesis is brought to you for free and open access by Scholarship@Western. It has been accepted for inclusion in Electronic Thesis and Dissertation Repository by an authorized administrator of Scholarship@Western. For more information, please contact wlsadmin@uwo.ca.

ON EVOLUTIONARY DYNAMICS AND STRATEGIES IN SOME
HOST-PARASITE MODELS
(Thesis format: Integrated Article)

by

Liman Dai

Graduate Program in Applied Mathematics

A thesis submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy

The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

© Liman Dai 2013

Abstract

In this thesis, we use mathematical models to study the problems about the evolution of hosts and parasites. Firstly, we study a within-host age-structured model with mutation and back mutation which is in the form of partial differential equations with double-infections by two strains of viruses. For the case when the production rates of viruses are gamma distributions, the PDE model can be transferred into an ODE one. Then, we analyze our model in two cases: one is without mutation, and the other is with mutation. In the first case, we prove that the two strains of viruses without mutation would die out if both of the individual reproductive numbers are less than one; otherwise, their evolution will comply with competitive exclusion principle meaning that the stronger one will survive finally. In the second case, we verify that they can coexist under some specific conditions in the sense that there exists a coexistence equilibrium which is globally asymptotically stable.

Secondly, we explore the viral evolutionary strategies by using a within-host model under body immune response. We consider two types of trade-offs involving the viral production rate, the host death rate caused by infection (i.e., virulence), and the transmission rate. By choosing appropriate fitness, we show that the evolutionary and convergent stability of an evolutionary singular strategy can be affected by the shapes of the trade-off functions. We also find that the evolutionary branching may occur at the singular strategy for some special trade-off functions. The results imply that the immune response has an important effect on viral evolution. Finally, two classes of trade-off functions are specified which yield some more detailed information on the virus evolutionary strategies.

Thirdly, we investigate the cost of immunological up-regulation caused by infection in a between-host transmission dynamical model with superinfection, which describes disease transmission between a single host and two parasites. After introducing mutant hosts to original model, we explore this problem in two cases: (A) monomorphic case; (B) dimorphic case. For (A), mutant hosts have two possible infections: one is by parasite 1; the other is by parasite 2. In each of these two cases, we identify an appropriate fitness for the invasion of the mutant hosts by analyzing the local stability of the mutant free equilibrium. Then, we consider the trade-off between the production rate of infected hosts and their recovery rate. By employing the adaptive dynamical approach, we analyze the evolutionary stability and convergence stability of this singular point, leading to some the conditions for continuously stable strategy, evolutionary branching point and repeller. For (B), we define a new fitness to measure the invasion of mutant hosts with parasite 1 and 2 by the same method. When the trade-off function is chosen to be linear, we are able to obtain conditions for isoclinic stability and absolute convergence stability through simulations. We find that although immune response is benign to hosts, the host evolution would not favor high degree of immunological up-regulation, implying that an intermediate degree of immunological response will be helpful to the host evolution. Moreover, superinfection would help weaker virulent parasite exist in hosts.

Keywords: hosts, parasites, mutation, global asymptotical stability, evolutionary stable strategy, convergence stable strategy, evolutionary branching, monomorphic, dimorphic.

Co-Authorship Statement

Chapter 2-4 of this thesis consist of the following papers:

Chapter 2: Liman Dai and Xingfu Zou: A within-host age-structured model with mutation between two strains.

Chapter 3: Liman Dai and Xingfu Zou: Within-host viral evolution under body immune response.

Chapter 4: Liman Dai and Xingfu Zou: The effects of superinfection and cost of immunity on host-parasite co-evolution.

The original draft for each of the above articles was prepared by the author. Subsequent revisions were performed by the author and Dr. Xingfu Zou. The analytical and numerical works are performed by the author under the supervision of Dr. Zou.

This thesis is dedicated to my family

For their endless love, support and encouragement!

Acknowledgements

It would have been impossible to write this doctoral thesis without the help and support from many kind people around me, to only a few of whom it is possible to give particular mention here.

Above all, I would like to tender my sincerest gratitude to my supervisor Dr. Xingfu Zou and his family. It is difficult to express how honored I feel as a member of Dr. Zou's research group. Actually, I can still remember the moment when I got the offer from him. There is no doubt that he opened a door for my pursuit of knowledge, particularly in Mathematical Biology. In the past four years, he provided me with an excellent atmosphere for doing research. Meanwhile, his expertise, inspiring guidance, academic rigor, encouragement, and support are throughout my period of study. I strongly believe that the things I learned from him will benefit all my life. Moreover, I would like to thank his family for their hospitality in each of the Christmas, which made me feel less homesick.

I would also like to acknowledge all the members of bio-math and dynamical system groups. In particular, I am thankful to Dr. L. Wahl, Dr. P. Yu and Dr. G. Wild for their insightful advice, extensive comments, and constructive guidance. Flower hour and the dynamical systems seminar taught me how to be a good audience and also a good presenter.

I would like to acknowledge the financial, academic and technical support from the department of Applied Mathematics of Western University for this research. I am also very grateful to Ms. A. Kager, C. MacLean and K. L. Foullong for their support and assistance in these four years.

My office mates and other fellow graduate students, F. Kan, X. Liu, M. Bao, X. Chen, Q. Guo, X. Ji, X. Lai, X. Lin, A. Rahman, J. Ruan, G. Piatkovska, X. Peng, Y.

Tian, A. Walton, F. Wang, X. Wang, J. Xu, X. Xi, Y. Xiao, C. Zhao, W. Zhang, S. Zhao, and Y. Zhang et al., have played important roles in my studies at Western. I highly appreciate all input, help, support, and enjoyment they have offered.

I am thankful to my four best friends: Q. Deng, X. Luo, L. Song, and L. Wang. Cheers for our friendship forever.

My parents and grandparents have given me their unequivocal support throughout, as always, for which my mere expression of thanks likewise does not suffice.

Last, but by no means the least, to my dearest fiance Yu, I am so lucky that you are always there cheering me up and standing by me through the good and bad times. Thank Western for letting us meet by chance!

Contents

Abstract	ii
Co-Authorship Statement	iv
Dedication	v
Acknowledgements	vi
List of Figures	xii
List of Tables	xvii
List of Appendices	xviii
1 Introduction	1
1.1 A between-host model	2
1.2 A within-host model	4
1.3 Adaptive dynamical approaches	7
1.4 Scope of Thesis	10
Bibliography	12
2 A within-host age-structured model with mutation between two strains	18
2.1 Introduction	18
2.2 Model	20

2.3	Equivalent ODE system under Gamma distribution	22
2.4	Basic reproductive number	26
2.5	Equilibria and their stabilities	29
2.5.1	In the absence of mutation	31
2.5.2	With the effect of mutation	34
2.6	Discussion and Conclusion	45
	Bibliography	46
3	Within-host viral evolution under immune control	49
3.1	Introduction	49
3.2	The fitness	52
3.3	Trade off between a and k	55
3.3.1	Exponential function	57
3.3.2	Power function	59
	$n = 1$	59
	$n = 2$	61
3.4	Trade off between β and a	62
3.5	Conclusion and discussion	67
	Bibliography	68
4	The effects of superinfection and cost of immunity on host-parasite co- evolution	72
4.1	Introduction	72
4.2	A two-parasite model within a single host type	75
4.3	Monomorphic cases	77
4.3.1	Mutant hosts with the parasite 1	78
	Evolutionary stability analysis	80

Convergence stability analysis	81
An example	82
4.3.2 Mutant hosts with the parasite 2	86
Evolutionary and convergence stabilities analysis	88
4.4 Dimorphic case	89
Evolutionary stability	95
Isoclinic stability	96
Absolute convergence stability	97
4.5 Discussion	97
Bibliography	100
5 Conclusions and future work	104
5.1 Conclusions	104
5.2 Future work	107
Bibliography	108
A	110
A.1 Solution to the age-structured system	110
A.1.1 If $t \geq a$	110
A.1.2 If $t < a$	111
A.2 Calculate the basic reproductive number of the system (2.8) by next generation method	112
B	114
B.1 The local stability of the equilibrium \bar{E}	114
B.2 Then local stability of the mutant-free equilibrium	119
C	121

C.1 The local stability of the coexistence equilibrium 121
C.2 The local stability of the mutant hosts free equilibrium 124
Bibliography 124

Curriculum Vitae **126**

List of Figures

1.1	Parasite (dashed line) and lymphocyte (solid line) densities for persistent infections with a predator-prey model. Parameter values are $\varphi = 1$, $\sigma = 1$, $c = 5$, $\delta = 1$, and $b = 0.01$	6
1.2	Examples of pairwise invasion plots. Gray shading denotes positive invader growth rate $S_r(m)$, white shading negative $S_r(m)$, the black diagonal lines $S_r(m) = 0$. (a) Evolutionary stable strategy but not convergence stable. Such strategies should be rare in nature: if the strategy is once established it cannot be invaded locally, but it cannot be approached gradually in small steps, either. (b) Evolutionary stable strategy and convergence stable. A possible endpoint of evolution: the strategy can be attained gradually and then it will resist any invaders successfully. (c) Convergence stable strategy but not evolutionary stable, i.e. evolutionary branching. A scenario where a population can become dimorphic: the singular strategy can be established gradually, but then it can be invaded by mutants both above and below the resident strategy at the same time.	8

1.3	Three qualitatively different singular strategies: (a) a local fitness maximum representing a possible endpoint of evolutionary change. (b) Local fitness minimum where evolutionary branching can occur. (c) A degenerate case where the criteria fail because the second order derivative of $S_r(m)$ vanishes, but practically these cases are without significance, since finite evolutionary steps will lead evolution past these points. Fitness is defined here as the expected growth rate of an initially rare mutant and given by the invasion exponent $S_r(m)$	9
2.1	The flow chart of the model.	20
3.1	Basic model of viral infection.	50
3.2	Figures of critical functions. (a). A family of critical functions with different initial values. (b). Critical functions for different values of c . In figure (b), a less concave down (concave) critical function $a_{crit}(k)$ can be caused by a greater stimulation rate c	56
3.3	Exponential function. Where $\phi = 0.043$, $d = 0.01$	58
3.4	Pairwise invasion plots. Only locating in the positive regions, the strategies can invade successfully. Since a vertical line through k^* can entirely lie within the white regions, it is a continuously stable strategy.	59
3.5	Power functions. Where $\alpha = 0.01$, $d = 0.01$	59
3.6	Two pairwise invasion plots when $n = 1$. Since the mutants fitness is a linear function of the mutants strategy, k^* is always an ESS according to the conclusion in [10]. According to our observation, the location of k^* moves to right as α decreases.	60
	(a) $\alpha = 0.1$	60
	(b) $\alpha = 0.01$	60

3.7	Two pairwise invasion plots when $n = 2$. Both of them are continuously stable strategies. Comparing the figure (a) with (b), the location of the evolutionary singular point can be shifted by varying the value of α , which is opposite to the case of $n = 1$	61
	(a) $\alpha = 0.01$	61
	(b) $\alpha = 0.001$	61
3.8	Figures of critical functions. (a). A family of critical functions. (b). The critical functions with different initial values of the variable c . From (b), the greater stimulation rate c can cause the less concave up (convex) critical function.	63
3.9	Specific function. Where $m = 0.5$	64
3.10	A pairwise invasion plot when $n = \frac{1}{2}$. Based on our theories, a^* is a continuously stable strategy.	65
3.11	Two pairwise invasion plots when $n = 2$. (a). We find that there is a "++" above the diagonal on the left and below the diagonal on the right of a_1^* . Also, a vertical line through a_1^* lies entirely within a region marked "++". a_1^* is an evolutionary branching point. (b). A vertical line through a_2^* lies entirely within a region marked "++", so it is a repeller.	66
	(a) a_1^*	66
	(b) a_2^*	66
4.1	Trade off 1: where $b = 0.059883$, $k_1 = 0.075$. $f(c_1)$ is a concave down function.	82

4.2	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 $c_2^*(k_2)$ 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).	84
	(a) $c_1^*(k_1), \varphi = 0.3$	84
	(b) $c_1^*(\varphi), k_1 = 0.5$	84
4.3	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 (4.33) and (4.34) are equal to zero. In figures (c) and (d), the red solid curves represents function (4.43) and the blue dash curves represent function (4.44). In shadows, both conditions (4.38) and (4.39) 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.	98
	(a) $\varphi = 0.05$	98
	(b) $\varphi = 0.05$	98
	(c) $\varphi = 0.5$	98
	(d) $\varphi = 0.5$	98

4.4 **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 (4.43) and the blue dash curve represents function (4.44), too. The golden solid line stands for the formula in inequality (4.40). In two shadows, the conditions for absolute stability can be satisfied. 99

List of Tables

4.1	Descriptions of the variables and parameters in section 4.3.	78
-----	----------------------------------------------------------------------	----

List of Appendices

Solve the age-structure system	110
If $t \geq a$	110
If $t < a$	111
Calculate the basic reproductive number of the system (2.8) by next generation method	112
The local stability of the equilibrium $\bar{\mathbf{E}}$	114
Then local stability of the mutant-free equilibrium	119
The local stability of the coexistence equilibrium	121
The local stability of the mutant hosts free equilibrium	124

Chapter 1

Introduction

Researchers have questioned and studied the outbreak and spread of disease for many years. If scientists could make predictions about diseases, people will be able to evaluate inoculation or isolation plans. This may help to diminish the mortality rate of a particular epidemic. Mathematical modeling of infectious diseases is a tool which has been used to study the mechanisms by which diseases spread, to predict the future course of an outbreak and to evaluate strategies to control an epidemic [14].

Through utilizing mathematics to quantify a disease, we can know the disease better and predict its trend. A physician, Daniel Bernoulli, carried out the earliest account of mathematical modeling of spread of disease in 1766 [6]. A mathematical model is created by Bernoulli [26] to defend the practice of inoculating against smallpox. The calculations from this model showed that universal inoculation against smallpox would increase the life expectancy from 26 years 7 months to 29 years 9 months [7]. Certainly, our modern understanding of germ theory is preceded by Daniel Bernoulli's work. Meanwhile, the modern theoretical epidemiology began with the research of Ronald Ross into the spread of malaria [38, 39, 40]. Following the research of Ronald Ross and others, A. G. McKendrick and W. O. Kermack published their simple deterministic (compartmental) model in 1927 [28]. The model was successful in predicting the behavior of outbreaks which were very similar to that observed in many recorded

epidemics [11].

1.1 A between-host model

In this section, two basic mathematical models, one for between-host and the other for within-host, are further introduced.

In 1927 Kermack and McKendrick [28] proposed a model by dividing a constant population into three compartments [26]: $S(t)$, $I(t)$ and $R(t)$ where

- $S(t)$ is used to represent the number of individuals not yet infected with the disease at time t , or those susceptible to the disease;
- $I(t)$ denotes the number of individuals who have been infected with the disease and are capable of spreading the disease to those in the susceptible category;
- $R(t)$ is the compartment used for those individuals who have been infected and then recovered from the disease. Those in this category are not able to be infected again or to transmit the infection to others.

The flow of this model is described as follows:

$$S \rightarrow I \rightarrow R.$$

Kermack and McKendrick assumed a constant population, $N(t) = S(t) + I(t) + R(t)$. So, their SIR model was the following ordinary differential equations:

$$\begin{cases} \frac{dS(t)}{dt} = -\beta S(t)I(t), \\ \frac{dI(t)}{dt} = \beta S(t)I(t) - \gamma I(t), \\ \frac{dR(t)}{dt} = \gamma I(t), \end{cases} \quad (1.1)$$

where β is the transmission rate and γ is the removal rate of infective individuals [28, 34]. Assume $S(0) = S_0 > 0$ and $I(0) = I_0 > 0$. The corresponding analysis was given in [18, 34], respectively. To measure disease, a quantity \mathcal{R}_0 , basic reproduction number is defined by scientists.

In epidemiology, the basic reproduction number \mathcal{R}_0 of an infection is the number of new cases one case generates on average over the course of its infectious period [20]. Let us take system (1.1) as an example to show how the metric \mathcal{R}_0 works. In system (1.1),

$$\mathcal{R}_0 := \frac{S_0\beta}{\gamma}.$$

- When $\mathcal{R}_0 < 1$, the disease will die out;
- when $\mathcal{R}_0 > 1$ the disease will be able to spread in a population;
- in neither of the above cases, the disease finally dies out of the population, leaving part of population; denoted by S_∞ , untouched by the disease.

The untouched part S_∞ is often referred as the final size of (1.1). It is determined by the equation

$$I_0 + S_0 - \frac{\gamma}{\beta} \ln S_0 = S_\infty - \frac{\gamma}{\beta} \ln S_\infty.$$

Due to I_0 should be sufficiently small, above equation could be approximated by

$$S_0 - \frac{\gamma}{\beta} \ln S_0 = S_\infty - \frac{\gamma}{\beta} \ln S_\infty.$$

In previous epidemic case, the duration of the disease was assumed to be short compared to life expectancy of the host. Thus, any birth and disease-unrelated death could be neglected. Normally, we would like to consider that an endemic disease is habitually in a population [13], which is called endemic case. Furthermore, the long-

term behavior is interesting to us. In mathematics, the corresponding model is

$$\begin{cases} \frac{dS(t)}{dt} = bN - \beta S(t)I(t) - dS, \\ \frac{dI(t)}{dt} = \beta S(t)I(t) - \gamma I(t) - dI(t), \\ \frac{dR(t)}{dt} = \gamma I(t) - dR(t). \end{cases} \quad (1.2)$$

In this case, the basic reproduction rate is a perfect threshold condition to determining the future of disease in epidemiological models. Mathematically, it is a threshold parameter for the stability of an disease-free equilibrium and is related to the peak and final size of a disease [12]. Next generation method is common method to obtain \mathcal{R}_0 . The basic reproductive number \mathcal{R}_0 is defined as the spectral radius of the next generation matrix [19, 18].

From above summary, we can have a rudimentary knowledge of disease dynamics on population level and its analysis approaches. In our thesis, we utilize another method to compute the basic reduction number and compare the results with the value obtained by next generation method.

1.2 A within-host model

Once a pathogen enters a host, it will produce/replicate and infect other target cells within the host. To understand the dynamics of the pathogen population and the interaction with the cells and possibly the immune response, within-host models are typically used. The simplest and most classic within-host model is the following system of

ordinary differential equations [1, 2, 4, 8, 33, 35]:

$$\begin{cases} \frac{dT(t)}{dt} = \lambda - dT - kTV, \\ \frac{dI(t)}{dt} = kTV - \delta I, \\ \frac{dV(t)}{dt} = pI - cV, \end{cases} \quad (1.3)$$

where $T(t)$ is the density of susceptible target cells, $I(t)$ is the density of infected target cells and $V(t)$ is the density of viruses. Here it is assumed that target cells can be produced from a source at a rate λ and die at a rate d . Productively infected cells (I) that are produced by infection produce new viruses at a rate p , and die at a rate δ . The clearance rate of free viruses is c .

The first attempts to model the dynamics of the immune system date from the 1970s [2, 5, 37], and dynamic models for the interaction between parasites and the immune system, based on the analogy with ecological interactions, followed about a decade later [3, 29, 36]. So far, scientists have conducted a large number of studies of within-host dynamics of microparasites. Several of these assume that parasites are resource limited, but it is striking that the majority does not explicitly model dynamics of the immune response of the host [1]. Here, we briefly introduce how this approach, even in a simplified version, takes into account immunological dynamics.

There are a great variety of ways to model immunity in within-host models. However, following the differential equation describing prey dynamics in a Lotka-Volterra predator-prey system [30, 25], similar equations are typically utilized to model the dynamics of the parasite. Thus, several life-stages (such as Plasmodium) of parasites and their resource competition would not be described in models. Then, changes in parasite

density takes the form [1]:

$$\begin{cases} \frac{dx(t)}{dt} = (\varphi - \sigma y)x, \\ \frac{dy(t)}{dt} = c_0 + cxy - \delta y. \end{cases}$$

where x is the density of parasite, y is the density of immune effector, φ is the growth rate of parasite, σ is the killing rate of the hosts by the immune system, c_0 is the lymphocyte baseline production rate, c is the proliferation rate due to the presence of parasites or their antigens, and δ is the lymphocyte death rate. In order to focus researches on the parasites, usually, the simple structure of the immune system is given in within-host models compared with typical models in theoretical immunology. Important oscillations are predicted in this model, which is consistent with the Lotka-Volterra model (see figure 1.1, [1]). If the growth rate of parasite is very low compared with the strength of

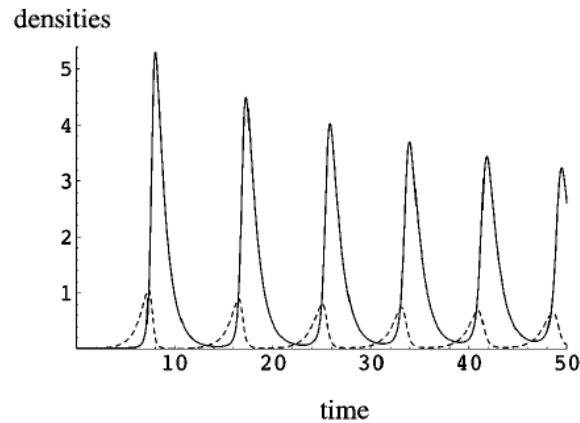


Figure 1.1: Parasite (dashed line) and lymphocyte (solid line) densities for persistent infections with a predator-prey model. Parameter values are $\varphi = 1$, $\sigma = 1$, $c = 5$, $\delta = 1$, and $b = 0.01$.

immune system, instantaneous clearance would occur. Since it occurs before the infection, this model cannot be used to describe an acute infection. This means the parasite never really settles in the host. Therefore, this model can only account for persistent infection [1].

Regardless of types of disease model, however, either hosts or parasites' traits, i.e.

the parameters in models, should never be constants when the evolution of species is taken into account. As a challenge, many traits of a species could affect its evolution.

1.3 Adaptive dynamical approaches

In recent years, a new set of techniques, i.e. adaptive dynamics, has been developed for understanding the long-term consequences of small mutations in the traits expressing certain phenotype [16, 17, 21, 32, 31, 41]. In adaptive dynamics, population dynamics are linked to evolutionary dynamics by incorporating and generalizing the fundamental idea of frequency dependent selection from game theory. By now, many papers used this versatile tool to various evolutionary models. In the following, we introduce the fundamental ideas behind adaptive dynamics.

Two fundamental ideas of adaptive dynamics are that the resident population can be assumed to be in a dynamical equilibrium when new mutants appear, and that the eventual fate of such mutants can be inferred from their initial growth rate when rare in the environment consisting of the resident [41]. This rate is known as fitness to measure the invasion of mutants. The initial exponential growth rate of mutants or the corresponding basic reproductive number is usually referred to as invasion fitness of mutants [17]. In this way, a mathematical model is required to explicitly incorporate the traits undergoing evolutionary change. Meanwhile, both the environment and the population dynamics depending on the environment should be described in the model. Below, we use a monomorphic case as an example to introduce the basic theory.

A monomorphic population is a population consisting of individuals with the same trait. The trait is assumed as a real number without explicit statement differently. Let r and m denote the trait value of the monomorphic resident population and that of an invading mutant, respectively. A function $S_r(m)$ is defined as the *fitness* to measure

the invasion of mutant. By the classical views, evolution is considered an optimization process towards higher value of fitness instead of higher value of trait. So, we need to consider the selection gradient [17, 41] which is defined as the slope of the fitness at $m = r$, $S'_r(r)$. As we know, the mutants may invade successfully if $S_r(m) > 0$; otherwise they may eventually die out. There is linear approximation $S_r(m) = S_r(r) + S'_r(r)(m - r)$, which vanishes whenever $m = r$. In the case $S'_r(r) > 0$, if the mutants are with slightly higher trait values, i.e. $S_r(m) > 0$, they may invade successfully; otherwise they may eventually die out.

The generic outcome of an invasion is that the mutant replaces the resident, and the fitness landscape as experienced by a rare mutant changes [41]. Usually, the outcome of the resulting series of invasions could be determined by pairwise-invasion plots (**PIPs**). The figure 1.2 coming from [41] shows three examples. In the grey area marked with

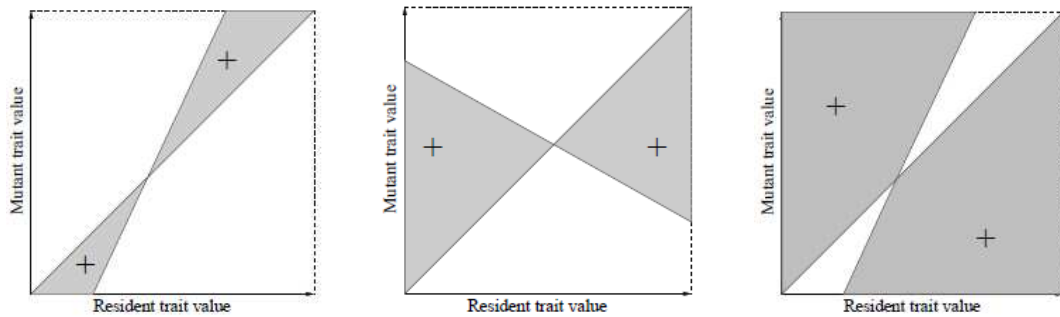


Figure 1.2: Examples of pairwise invasion plots. Gray shading denotes positive invader growth rate $S_r(m)$, white shading negative $S_r(m)$, the black diagonal lines $S_r(m) = 0$. (a) Evolutionary stable strategy but not convergence stable. Such strategies should be rare in nature: if the strategy is once established it cannot be invaded locally, but it cannot be approached gradually in small steps, either. (b) Evolutionary stable strategy and convergence stable. A possible endpoint of evolution: the strategy can be attained gradually and then it will resist any invaders successfully. (c) Convergence stable strategy but not evolutionary stable, i.e. evolutionary branching. A scenario where a population can become dimorphic: the singular strategy can be established gradually, but then it can be invaded by mutants both above and below the resident strategy at the same time.

$+$, $S_r(m) > 0$. So, a resident population with trait value r could be successfully invaded by a mutant if (r, m) locates pair in the grey area.

Obviously, a mutant with a slightly higher trait-value would generically invade and replace the resident if $S'_r(r) > 0$. Thus, the direction of evolutionary change could be determined by the selection of gradient $S_r(r)$. When $S'_r(r)$ vanishes, traits or strategies r^* for which $S'_r(r^*) = 0$ are called *evolutionary singular strategies* [17, 4, 10, 15, 23, 22, 24, 9, 41]. The fitness landscape experienced by a rare mutant would be locally 'flat' near such points. In figure 1.2, the singular strategies are found where the boundary of the region of positive invasion fitness intersects the diagonal. We use three graphs in Figure 1.3 [41] to show three types of singular points.

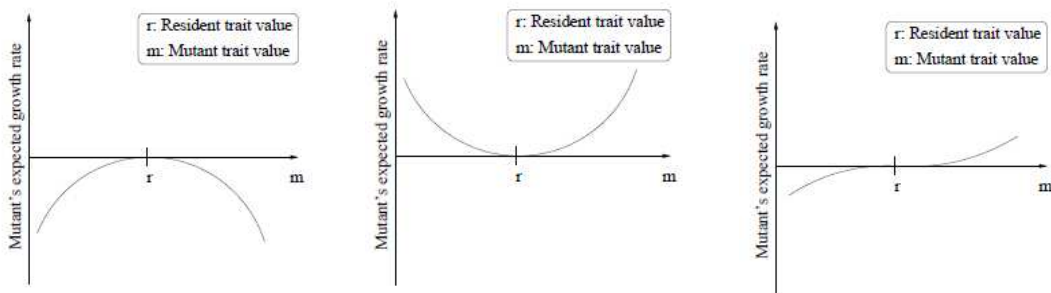


Figure 1.3: **Three qualitatively different singular strategies:** (a) a local fitness maximum representing a possible endpoint of evolutionary change. (b) Local fitness minimum where evolutionary branching can occur. (c) A degenerate case where the criteria fail because the second order derivative of $S_r(m)$ vanishes, but practically these cases are without significance, since finite evolutionary steps will lead evolution past these points. Fitness is defined here as the expected growth rate of an initially rare mutant and given by the invasion exponent $S_r(m)$.

A strategy r^* is an *evolutionary stable strategy (ESS)* if $S_r(m)$ as a function of m has maximum at r^* . Once it established, this trait cannot be invaded by nearby mutants. Mathematically, the strategy would locally maximize fitness if its corresponding second derivative is negative. Thus, at an evolutionary stable strategy r^* we have

$$S''_r(r^*) < 0.$$

Otherwise, the strategy is evolutionary unstable. In the 1.2a and 1.2b of figure 1.2, evolutionary stable strategies are showed since the invasion exponent is negative both

above and below the singular strategy.

A *convergence stable strategy* r^* is a singular strategy that is attracting in the sense that monomorphic populations playing a strategy near r^* can be invaded by mutants closer to it. This means that the selection gradient $S'_r(r)$ in a neighbourhood of r^* must be positive for $r < r^*$ and negative for $r > r^*$ [41]. Hence, the slope of $S'_r(r)$ as a function of r at r^* should be negative, or equivalently

$$\frac{d}{dr} \left(\frac{\partial S_r(m)}{\partial m} \Big|_{r=m} \right) \Big|_{r=r^*} < 0.$$

In figure 1.2, only the 1.2b and 1.2c are convergence stable.

As a result, if a strategy is both evolutionary and convergence stable, it represents a possible endpoint of evolutionary change. However, the singular strategy would be a branching point if it only has convergence stability. In this case, the population will become dimorphic. If neither of these stabilities can be satisfied, it is a repellor.

1.4 Scope of Thesis

We study the effects of mutation and back mutation in a within-host dynamical model in Chapter 2. The phenomena of mutation and back mutation in viruses are briefly described at the beginning of the chapter. After introducing two new terms about mutation and back mutation into the age-structured model in [24], we present the formulation of a new mathematical model with two strain viruses. Then, we utilize linear chain trick to simplify our model and convert the partial differential equations to ordinary differential equations [42, 44]. By following the method to calculate the output in a control system (see Iggidr, Abderrahman et. al. [27]), a basic reproductive number for the model is identified for this model. Furthermore, we study the existences of equilibria and their stability in two situations: one is without mutation and the other is with mutations.

The case in absence of mutation has an infection-free equilibrium and two boundary equilibria. We construct a Lyapunov function and demonstrate that the infection-free equilibrium is globally asymptotic stable if the basic reproductive number is less than 1. Meanwhile, we prove that the stability of the two boundary equilibria complies with the competitive exclusion principle. When considering mutations, the system still have infection-free equilibrium. Moreover, the existence of a coexistence equilibrium is proved in this case when basic reproductive number is larger than 1. When mutations are considered as small perturbations, the globally asymptotic stability of this equilibrium can be established by the average Lyapunov function theory. We end this chapter with a brief discussion about our results.

In Chapter 3, we utilize the classic adaptive dynamical approach [23, 21] to further discuss how a strain of viruses succeeds under the immune response of hosts in evolution when mutations happen. Firstly, we introduce a mutant strain into a within-host model with CTL response and analyze the local stability of its mutant free equilibrium. The critical value that can decide its stability is defined as the fitness for the mutant strain of viruses. Then, two parameters are chosen as variables and two relevant trade-offs are studied in this fitness function, respectively. The first trade-off involves the infected cell death rate and the disease transmission rate, and the second trade-off is between the virion production rate and the mortality of infected cells. At first, we discuss the existence conditions of an evolutionary singular point for two cases, respectively. Then, we analyze the evolutionary stability and convergence stability of this point. Examples are provided revealing insight to our theoretical results in both cases, respectively. Based on our mathematical conclusions, we discuss their corresponding biological implications in the end and mention some related problems to broaden this topic.

We study the host-parasite co-evolution under immune response on population level

in Chapter 4. In Section 4.2, we analyze the local stability of coexistence equilibrium in a two parasites and one host strain model. Then, a mutant host is introduced to this model. We explore the invasion of the mutant hosts in two cases, monomorphic case and dimorphic case. In Section 4.3, we discuss two possible infections of mutant hosts, one is by parasite 1; the other is by parasite 2. The critical value for local stability of corresponding mutant-free equilibrium is defined as the fitness of mutant hosts. We study the evolutionary and convergence stabilities of evolutionary singular strategies through utilizing the adaptive dynamical approaches [23, 21, 43] in these two cases, respectively. We also investigate on how the convexities of two trade-offs affect the evolutionary and convergence stabilities. In Section 4.4, a dimorphic case is studied. We define a new fitness to measure the invasion of mutant hosts with parasite 1 and 2 and obtain the conditions for evolutionary stability. Two trade-offs are specified by two simple linear functions to explore the conditions for isoclinic stability and absolute convergence stability. We show some numerical conclusions, 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 4.5, some discussions on the biological implications of the mathematical results are provided. Moreover, some related problems for future work on this topic are discussed.

Bibliography

- [1] Alizon, S. and van Baalen, M. (2008). Acute or chronic? within-host models with immune dynamics, infection outcome, and parasite evolution. *The American Naturalist*, 172(6):E244–E256.
- [2] Anderson, R. M. and May, R. M. (1979). Population biology of infectious diseases: Part I. *Nature*, 280(5721):361.

- [3] Antia, R., Levin, B. R., and May, R. M. (1994). Within-host population dynamics and the evolution and maintenance of microparasite virulence. *American Naturalist*, pages 457–472.
- [4] Ball, C. L., Gilchrist, M. A., and Coombs, D. (2007). Modeling within-host evolution of HIV: mutation, competition and strain replacement. *Bulletin of mathematical biology*, 69(7):2361–2385.
- [5] Bell, G. I., Perelson, A. S., and Pimbley, G. H. (1978). *Theoretical immunology*, volume 8. M. Dekker.
- [6] Bernoulli, D. (1760). Essai d'une nouvelle analyse de la mortalité causée par la petite vérole et des avantages de l'inoculation pour la prévenir. *Histoire de l'Acad. Roy. Sci.(Paris) avec Mém. des Math. et Phys. and Mém*, pages 1–45.
- [7] Bernoulli, D. and Blower, S. (2004). An attempt at a new analysis of the mortality caused by smallpox and of the advantages of inoculation to prevent it. *Reviews in Medical Virology*, 14(5):275–288.
- [8] Boer, R. J. D. and Perelson, A. S. (1998). Target cell limited and immune control models of HIV infection: a comparison. *Journal of Theoretical Biology*, 190(3):201–214.
- [9] Boldin, B. and Diekmann, O. (2008). Superinfections can induce evolutionarily stable coexistence of pathogens. *Journal of mathematical biology*, 56(5):635–672.
- [10] Boldin, B., Geritz, S. A. H., and Kisdi, E. (2009). Superinfections and adaptive dynamics of pathogen virulence revisited: a critical function analysis. *Evolutionary Ecology Research*, 11(2):153–175.
- [11] Brauer, F. and Castillo-Châavez, C. (2012). *Mathematical models in population biology and epidemiology*. Springer.

- [12] Brauer, F., van den Driessche, P., and Wu, J. (2008). *Lecture Notes in Mathematical Epidemiology*. Springer.
- [13] Britton, N. F. (2003). *Essential mathematical biology*. Springer.
- [14] Daley, D. J., Gani, J., and Gani, J. J. M. (2001). *Epidemic modelling: an introduction*, volume 15. Cambridge University Press.
- [15] Day, T. and Burns, J. G. (2003). A consideration of patterns of virulence arising from host-parasite coevolution. *Evolution*, 57(3):671–676.
- [16] Dieckmann, U. and Law, R. (1996). The dynamical theory of coevolution: a derivation from stochastic ecological processes. *Journal of mathematical biology*, 34(5-6):579–612.
- [17] Diekmann, O. (2004). A beginners guide to adaptive dynamics. *Banach Center publications*, 63:47–86.
- [18] Diekmann, O. and Heesterbeek, J. A. P. (2000). *Mathematical epidemiology of infectious diseases*. Wiley Chichester.
- [19] Diekmann, O., Heesterbeek, J. A. P., and Metz, J. A. J. (1990). On the definition and the computation of the basic reproduction ratio r_0 in models for infectious diseases in heterogeneous populations. *Journal of mathematical biology*, 28(4):365–382.
- [20] Fraser, C., Donnelly, C. A., Cauchemez, S., Hanage, W. P., Kerkhove, M. D. V., Hollingsworth, T. D., Griffin, J., Baggaley, R. F., Jenkins, H. E., and Lyons, E. J. (2009). Pandemic potential of a strain of influenza a (h1n1): early findings. *science*, 324(5934):1557–1561.

- [21] Geritz, S. A. H., Mesze, G., and Metz, J. A. J. (1997a). Evolutionarily singular strategies and the adaptive growth and branching of the evolutionary tree. *Evolutionary ecology*, 12(1):35–57.
- [22] Geritz, S. A. H., Mesze, G., and Metz, J. A. J. (1997b). Evolutionarily singular strategies and the adaptive growth and branching of the evolutionary tree. *Evolutionary ecology*, 12(1):35–57.
- [23] Geritz, S. A. H., Metz, J. A. J., Kisdi, É., and Meszéna, G. (1997c). Dynamics of adaptation and evolutionary branching. *Physical Review Letters*, 78(10):2024–2027.
- [24] Gilchrist, M. A., Coombs, D., and Perelson, A. S. (2004). Optimizing within-host viral fitness: infected cell lifespan and virion production rate. *Journal of theoretical biology*, 229(2):281–288.
- [25] Goel, N. S., Maitra, S. C., and Montroll, E. W. (1971). On the volterra and other nonlinear models of interacting populations. *Reviews of modern physics*, 43(2):231.
- [26] Hethcote, H. W. (2000). The mathematics of infectious diseases. *SIAM review*, 42(4):599–653.
- [27] Iggidr, A., Mbang, J., and Sallet, G. (2007). Stability analysis of within-host parasite models with delays. *Mathematical Biosciences*, 209(1):51–75.
- [28] Kermack, M. D. and Mckendrick, A. G. (1927). Contributions to the mathematical theory of epidemics. Part I. In *Proc. R. Soc. A*, volume 115, pages 700–721.
- [29] Konishi, T., Shinohara, K., Yamada, K., and Sasaki, Y. (1996). Acetyl-coa carboxylase in higher plants: most plants other than gramineae have both the prokaryotic and the eukaryotic forms of this enzyme. *Plant and Cell Physiology*, 37(2):117–122.

- [30] Lotka, A. J. (1910). Contribution to the theory of periodic reactions. *The Journal of Physical Chemistry*, 14(3):271–274.
- [31] Marrow, P., Dieckmann, U., and Law, R. (1996). Evolutionary dynamics of predator-prey systems: an ecological perspective. *Journal of Mathematical Biology*, 34(5-6):556–578.
- [32] Matessi, C. and Pasquale, C. D. (1996). Long-term evolution of multilocus traits. *Journal of Mathematical Biology*, 34(5-6):613–653.
- [33] May, R. M. and Anderson, R. M. (1991). Infectious diseases of humans: dynamics and control.
- [34] Murray, J. D. (2002). *Mathematical biology*, volume 2. springer.
- [35] Nowak, M. A. and Bangham, C. R. M. (1996). Population dynamics of immune responses to persistent viruses. *Proc. Natl. Acad. Sci. USA*, 85:3509.
- [36] Nowak, M. A., May, R. M., and Anderson, R. M. (1990). The evolutionary dynamics of HIV-1 quasispecies and the development of immunodeficiency disease. *Aids*, 4(11):1095–1104.
- [37] Perelson, A. S. and Oster, G. F. (1979). Theoretical studies of clonal selection: minimal antibody repertoire size and reliability of self-non-self discrimination. *Journal of theoretical biology*, 81(4):645–670.
- [38] Ross, R. (1916). An application of the theory of probabilities to the study of a priori pathometry. Part I. *Proceedings of the Royal Society of London. Series A*, 92(638):204–230.
- [39] Ross, R. and Hudson, H. P. (1917). An application of the theory of probabilities to

- the study of a priori pathometry. Part II. *Proceedings of the Royal Society of London. Series A*, 93(650):212–225.
- [40] Ross, R. and Hudson, H. P. (1918). An application of the theory of probabilities to the study of a priori pathometry. Part III. *Proceedings of the Royal Society of London. Series A*, 93(650):225–240.
- [41] Shapiro, A. F. (2000). A hitchhikers guide to the techniques of adaptive nonlinear models. *Insurance: Mathematics and Economics*, 26(2):119–132.
- [42] Smith, H. L. (1995). Monotone dynamical systems: An introduction to the theory of competitive and cooperative systems. *Bulletin of the American Mathematical Society*, 33(2):203–210.
- [43] Svernumsgen, T. O. and Kisdi, É. (2009). Evolutionary branching of virulence in a single-infection model. *Journal of theoretical biology*, 257(3):408–418.
- [44] Yuan, Z. H. and Zou, X. F. (2010). Global threshold property in an epidemic model for disease with latency spreading in a heterogeneous host population. *Nonlinear Analysis: Real World Applications*, 11(5):3479–3490.

Chapter 2

A within-host age-structured model with mutation between two strains

2.1 Introduction

Viruses using RNA (ribonucleic acid) as their genetic material are called RNA viruses. They can cause extraordinary tough human diseases, such as HIV, hepatitis C, SARS and influenza, due to their high infection rates. Comparing to DNA virus, they have more rapid mutation rates [4, 2]. In the case of HIV-1, a point mutation occurs with probability 0.25 during every cycle of replication [7, 13]. This is one reason why it is difficult to develop effective vaccines to prevent diseases caused by this kind of viruses [17]. Furthermore, in the virion evolution, the fitter strain, which may produce offspring faster than others, can beat others due to selection. However, errors always occur during reproduction, which lead to mutations. As a result, the competitive balance may be shifted as a result of mutation sometimes. With selection of medical treatment, not only forward mutants but also backward mutants could survive in viral evolution because of their drug resistance surveillance [14].

Mathematical models are commonly used to study the diseases caused by RNA viruses, particularly HIV, for over 25 years [11, 12, 10]. The research achievements about within-host virus disease models are fruitful. Their conclusions illustrate that two strains of viruses without mutation can coexist only if they have the same basic reproductive rates, which are very difficult to actualize in the real world. However, if mutations are considered, the situation changes. The within-host model about two strains has a unique coexistence equilibrium. Its global stability was proved when mutations are treated as small perturbations [6, 1, 9]. However, ordinary differential equations are too idealised to study the viral infection and production. Therefore, motivated by the model

$$\left\{ \begin{array}{l} \frac{dT}{dt} = s - dT(t) - kT(t)V(t), \\ \frac{\partial T^*}{\partial a} + \frac{\partial T^*}{\partial t} = -\delta(a)T^*(a, t), \\ \frac{dV}{dt} = \int_0^\infty p(a)T^*(a, t)da - cV(t), \\ T^*(0, t) = kV_1(t)T(t), \quad t \geq 0. \end{array} \right. \quad (2.1)$$

in the paper of Nelson and et al. [8], we will extend the research by introducing an mutant strain of viruses into this age-structured model and considering forward mutation and back mutation between these two strains of viruses in this chapter.

The rest of this chapter is organized as follows. In the next section, we present the formulation of mathematical model. In Sections 2.3 and 2.4, we utilize linear chain trick to simplify our model and convert the partial differential equations to ordinary differential equations and work out the basic reproductive number for this model. In Section 2.5, we study the equilibria and their stability in two situations; one is without mutation and the other is with mutation. Finally, we end this chapter with brief discussions about our results.

2.2 Model

We assume that the state variables are T (the population of susceptible host cells), $T_i^*(a, t)$ (the population of target cells infected by virus i with age of infection a at time t), V_i (the population of virus i), where $i = 1, 2$. Uninfected cells are produced at constant rate b , die at rate d . After infection at constant rate β_i by strain i , they progress to the productively infected class. There are two death rates during this class. One is a constant background death rate m_i , and the other is an infection dependent mortality rate $\mu_i(a)$. Then, the infected cells can produce virus at an infection dependent rate $p_i(a)$. Free viruses are cleared at a constant rate c_i . Meanwhile, we suppose that the mutation and back mutation happen between the two strains of viruses at rate ϵ_1 and ϵ_2 , respectively. The corresponding disease transmission diagram is shown in the following figure:

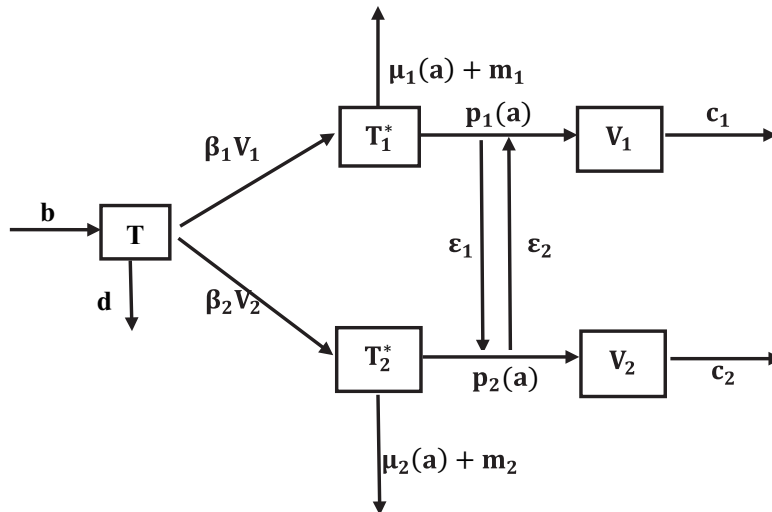


Figure 2.1: The flow chart of the model.

Translating the diagram in Figure 2.1 into equations, our model takes the form:

$$\left\{ \begin{array}{l} \frac{dT}{dt} = b - dT(t) - \beta_1 T(t)V_1(t) - \beta_2 T(t)V_2(t), \\ \frac{\partial T_1^*}{\partial a} + \frac{\partial T_1^*}{\partial t} = -(\mu_1(a) + m_1)T_1^*(a, t), \\ \frac{\partial T_2^*}{\partial a} + \frac{\partial T_2^*}{\partial t} = -(\mu_2(a) + m_2)T_2^*(a, t), \\ \frac{dV_1}{dt} = (1 - \epsilon_1) \int_0^\infty p_1(a)T_1^*(a, t)da + \epsilon_2 \int_0^\infty p_2(a)T_2^*(a, t)da - c_1 V_1(t), \\ \frac{dV_2}{dt} = (1 - \epsilon_2) \int_0^\infty p_2(a)T_2^*(a, t)da + \epsilon_1 \int_0^\infty p_1(a)T_1^*(a, t)da - c_2 V_2(t), \\ T_1^*(0, t) = \beta_1 V_1(t)T(t), \\ T_2^*(0, t) = \beta_2 V_2(t)T(t), t \geq 0. \end{array} \right. \quad (2.2)$$

The system (2.2) will be reduced into DDE. By the method of characteristics, the following two partial differential equations with boundary conditions

$$\begin{aligned} \frac{\partial T_1^*}{\partial a} + \frac{\partial T_1^*}{\partial t} &= -(\mu_1(a) + m_1)T_1^*(a, t), \\ \frac{\partial T_2^*}{\partial a} + \frac{\partial T_2^*}{\partial t} &= -(\mu_2(a) + m_2)T_2^*(a, t), \\ T_1^*(0, t) &= \beta_1 V_1(t)T(t), \\ T_2^*(0, t) &= \beta_2 V_2(t)T(t), t \geq 0, \end{aligned}$$

can be solved and their solutions are:

$$T_1^*(a, t) = \begin{cases} \beta_1 V_1(t-a)T(t-a)\sigma_1(a), & t \geq a, \\ 0, & t < a, \end{cases} \quad (2.3)$$

$$T_2^*(a, t) = \begin{cases} \beta_2 V_2(t-a)T(t-a)\sigma_2(a), & t \geq a, \\ 0, & t < a, \end{cases} \quad (2.4)$$

where $\sigma_1(a) = e^{-\int_0^a (\mu_1(\xi) + m_1) d\xi}$ and $\sigma_2(a) = e^{-\int_0^a (\mu_2(\xi) + m_2) d\xi}$ (see details in Appendix A.1).

Substituting (2.3) and (2.4) into (2.2), the system (2.2) can be rewritten as:

$$\left\{ \begin{array}{l} \frac{dT}{dt} = b - dT(t) - \beta_1 T(t)V_1(t) - \beta_2 T(t)V_2(t), \\ \frac{dV_1}{dt} = \beta_1(1 - \epsilon_1) \int_0^t p_1(a)T(t-a)V_1(t-a)\sigma_1(a)da \\ \quad + \beta_2\epsilon_2 \int_0^t p_2(a)T(t-a)V_2(t-a)\sigma_2(a)da - c_1 V_1(t), \\ \frac{dV_2}{dt} = \beta_2(1 - \epsilon_2) \int_0^t p_2(a)T(t-a)V_2(t-a)\sigma_2(a)da \\ \quad + \beta_1\epsilon_1 \int_0^t p_1(a)T(t-a)V_1(t-a)\sigma_1(a)da - c_2 V_2(t). \end{array} \right. \quad (2.5)$$

For convenience, we assume that $\mu_i(a)$ is just a constant μ_i . So, there is $\sigma_i(a) = e^{-(\mu_i+m_i)a}$, where $i = 1, 2$. Replacing variables in the integration ($u = t - a$, $da = -du$, $t - u = a$; and let $a = u$), above system (2.5) is transformed into

$$\left\{ \begin{array}{l} \frac{dT}{dt} = b - dT(t) - \beta_1 T(t)V_1(t) - \beta_2 T(t)V_2(t), \\ \frac{dV_1}{dt} = \beta_1(1 - \epsilon_1) \int_0^t p_1(t-a)e^{-(\mu_1+m_1)(t-a)}T(a)V_1(a)da \\ \quad + \beta_2\epsilon_2 \int_0^t p_2(t-a)e^{-(\mu_2+m_2)(t-a)}T(a)V_2(a)da - c_1 V_1(t), \\ \frac{dV_2}{dt} = \beta_2(1 - \epsilon_2) \int_0^t p_2(t-a)e^{-(\mu_2+m_2)(t-a)}T(a)V_2(a)da \\ \quad + \beta_1\epsilon_1 \int_0^t p_1(t-a)e^{-(\mu_1+m_1)(t-a)}T(a)V_1(a)da - c_2 V_2(t). \end{array} \right. \quad (2.6)$$

2.3 Equivalent ODE system under Gamma distribution

For convenience to show our main idea, we assume that two strains have same natural death rate and disease remove rate, i.e., $\mu_1 = \mu_2 = \mu$ and $m_1 = m_2 = m$. Moreover, according to the properties of production rate, we select the Gamma distribution [19], which can approximate to many other frequently used distribution, for $p_1(a)$ and $p_2(a)$:

$$p_1(a) = p_2(a) = p_{\alpha,n}(a) = \frac{\alpha^{n-1}}{(n-1)!} e^{-\frac{a}{\alpha}}, \quad (2.7)$$

where α is a positive real number and n is an integer that is greater than 1. Denoting

$$\widehat{\alpha} = \frac{\alpha}{1 + (\mu + m)\alpha},$$

so

$$[1 + (\mu + m)\alpha]^n = \left(\frac{\alpha}{\widehat{\alpha}}\right)^n.$$

We can rewrite the last two equations in (2.6) as:

$$\begin{aligned} \frac{dV_1}{dt} &= (1 - \epsilon_1) \left(\frac{\widehat{\alpha}}{\alpha}\right)^n \int_0^t B_1(a) p_{\widehat{\alpha},n}(t-a) da + \epsilon_2 \left(\frac{\widehat{\alpha}}{\alpha}\right)^n \int_0^t B_2(a) p_{\widehat{\alpha},n}(t-a) da - c_1 V_1, \\ \frac{dV_2}{dt} &= (1 - \epsilon_2) \left(\frac{\widehat{\alpha}}{\alpha}\right)^n \int_0^t B_2(a) p_{\widehat{\alpha},n}(t-a) da + \epsilon_1 \left(\frac{\widehat{\alpha}}{\alpha}\right)^n \int_0^t B_1(a) p_{\widehat{\alpha},n}(t-a) da - c_2 V_2, \end{aligned}$$

where $B_i(t) = \beta_i V_i(t) T(t)$, $i = 1, 2$.

Let

$$\begin{aligned} x_j(t) &= \widehat{\alpha} \left(\frac{\widehat{\alpha}}{\alpha}\right)^n \int_0^t B_1(a) p_{\widehat{\alpha},j}(t-a) da, \\ y_j(t) &= \widehat{\alpha} \left(\frac{\widehat{\alpha}}{\alpha}\right)^n \int_0^t B_2(a) p_{\widehat{\alpha},j}(t-a) da, \end{aligned}$$

for $j = 1, 2, \dots, n$. Then for $j \in \{2, \dots, n\}$

$$\begin{aligned} \frac{dx_j(t)}{dt} &= \widehat{\alpha} \left(\frac{\widehat{\alpha}}{\alpha}\right)^n \int_0^t \frac{(j-1)(t-a)^{j-2}}{(j-1)! \widehat{\alpha}^j} e^{-\frac{(t-a)}{\widehat{\alpha}}} B_1(a) da \\ &\quad - \widehat{\alpha} \left(\frac{\widehat{\alpha}}{\alpha}\right)^n \int_0^t \frac{(t-a)^{j-1}}{(j-1)! \widehat{\alpha}^{j+1}} e^{-\frac{(t-a)}{\widehat{\alpha}}} B_1(a) da \\ &= \frac{1}{\widehat{\alpha}} [x_{j-1}(t) - x_j(t)]. \end{aligned}$$

Similarly, $j = 1, 2, \dots, n$,

$$\frac{dy_j(t)}{dt} = \frac{1}{\widehat{\alpha}} [y_{j-1}(t) - y_j(t)].$$

For $j = 1$, we have

$$\begin{aligned} x_1(t) &= \widehat{\alpha} \left(\frac{\widehat{\alpha}}{\alpha} \right)^n \int_0^t B_1(a) \frac{1}{\widehat{\alpha}} e^{-\frac{(t-a)}{\widehat{\alpha}}} da, \\ y_1(t) &= \widehat{\alpha} \left(\frac{\widehat{\alpha}}{\alpha} \right)^n \int_0^t B_2(a) \frac{1}{\widehat{\alpha}} e^{-\frac{(t-a)}{\widehat{\alpha}}} da, \end{aligned}$$

yielding

$$\begin{cases} \frac{dx_1(t)}{dt} = \beta_1 \left(\frac{\widehat{\alpha}}{\alpha} \right)^n V_1(t) T(t) - \beta_1 \left(\frac{\widehat{\alpha}}{\alpha} \right)^n \int_0^t \frac{1}{\widehat{\alpha}} e^{-\frac{(t-a)}{\widehat{\alpha}}} V_1(a) T(a) da, \\ \phantom{\frac{dx_1(t)}{dt}} = \beta_1 \left(\frac{\widehat{\alpha}}{\alpha} \right)^n V_1(t) T(t) - \frac{1}{\widehat{\alpha}} x_1(t), \\ \frac{dy_1(t)}{dt} = \beta_2 \left(\frac{\widehat{\alpha}}{\alpha} \right)^n V_2(t) T(t) - \frac{1}{\widehat{\alpha}} y_1(t) \end{cases}$$

Thus, with $p_1(a)$ and $p_2(a)$ specified by (2.7), the system (2.6) is equivalent to the following system of ordinary differential equations:

$$\begin{cases} \frac{dT}{dt} = b - dT - \beta_1 T V_1 - \beta_2 T V_2, \\ \frac{dx_1}{dt} = \beta_1 \left(\frac{\widehat{\alpha}}{\alpha} \right)^n V_1 T - \frac{1}{\widehat{\alpha}} x_1, \\ \frac{dx_2}{dt} = \frac{1}{\widehat{\alpha}} (x_1 - x_2), \\ \phantom{\frac{dx_2}{dt}} \vdots \\ \frac{dx_n}{dt} = \frac{1}{\widehat{\alpha}} (x_{n-1} - x_n), \\ \frac{dy_1}{dt} = \beta_2 \left(\frac{\widehat{\alpha}}{\alpha} \right)^n V_2 T - \frac{1}{\widehat{\alpha}} y_1 \\ \frac{dy_2}{dt} = \frac{1}{\widehat{\alpha}} (y_1 - y_2), \\ \phantom{\frac{dy_2}{dt}} \vdots \\ \frac{dy_n}{dt} = \frac{1}{\widehat{\alpha}} (y_{n-1} - y_n), \\ \frac{dV_1}{dt} = \frac{(1-\epsilon_1)}{\widehat{\alpha}} x_n + \frac{\epsilon_2}{\widehat{\alpha}} y_n - c_1 V_1, \\ \frac{dV_2}{dt} = \frac{(1-\epsilon_2)}{\widehat{\alpha}} y_n + \frac{\epsilon_1}{\widehat{\alpha}} x_n - c_2 V_2. \end{cases} \quad (2.8)$$

In the rest of this chapter, we only need to study the ODE system (2.8).

It is easy to prove (e.g. by Smith [15], page 81, Theorem 2.1) that for a nonnegative

initial set, the corresponding solution of (2.8) remains non-negative.

Lemma 2.3.1 *The system (2.8) is dissipative, i.e. there is a forward-invariant compact set $\bar{\Gamma} \subset \mathbb{R}_+^{2n+3}$ such that every solution eventually enters $\bar{\Gamma}$.*

Proof Adding equations about $\frac{dT}{dt}$, $\frac{dx_1}{dt}$ and $\frac{dy_1}{dt}$ in (2.8) gives

$$\begin{aligned} & \frac{d}{dt} \left[T + \left(\frac{\alpha}{\alpha} \right)^n x_1 + \left(\frac{\alpha}{\alpha} \right)^n y_1 \right] \\ &= b - dT - \frac{\alpha^n}{\alpha^{n+1}} (x_1 + y_1) \\ &\leq b - d^* \left[T + \left(\frac{\alpha}{\alpha} \right)^n x_1 + \left(\frac{\alpha}{\alpha} \right)^n y_1 \right] \end{aligned}$$

where $d^* = \min\{d, \frac{1}{\alpha}\}$. Thus, $\limsup_{t \rightarrow \infty} [T + (\frac{\alpha}{\alpha})^n x_1 + (\frac{\alpha}{\alpha})^n y_1] \leq \frac{b}{d^*}$. Similarly, we can obtain that

$$\limsup_{t \rightarrow \infty} (x_j + y_j) \leq \frac{b}{d^*} \left(\frac{\alpha}{\alpha} \right)^n, \quad j = 2, 3, \dots, n,$$

$$\limsup_{t \rightarrow \infty} (V_1 + V_2) \leq \frac{b}{c\alpha d^*} \left(\frac{\alpha}{\alpha} \right)^n,$$

and

$$\limsup_{t \rightarrow \infty} T \leq \frac{b}{d}.$$

Consequently, the feasible region is given by:

$$\begin{aligned} \bar{\Gamma} = \{ & (T, x_1, x_2, \dots, x_n, y_1, y_2, \dots, y_n, V_1, V_2) \in \mathbb{R}_+^{(2n+3)} \mid \\ & \left. \begin{aligned} & T \leq \frac{b}{d}, \quad T + \left(\frac{\alpha}{\alpha} \right)^n x_1 + [1 + (\mu + m\alpha)]^n y_1 \leq \frac{b}{d^*}, \\ & x_i + y_i \leq \frac{b}{d^*} \left(\frac{\alpha}{\alpha} \right)^n, \quad V_1 + V_2 \leq \frac{b}{c\alpha d^*} \left(\frac{\alpha}{\alpha} \right)^n, \\ & i = 2, \dots, n. \end{aligned} \right\} \end{aligned} \quad (2.9)$$

It can be verified that $\bar{\Gamma}$ in (2.9) is positively invariant with respect to (2.8). Dissipativity now follows by noticing that all the above bounds are independent of the initial condition.

2.4 Basic reproductive number

It is easy to see that

$$E_0 = \left(\frac{b}{d}, 0, 0, \dots, 0 \right) \quad (2.10)$$

is an equilibrium of (2.8) which is called the infection-free equilibrium. The basic reproductive number of the model is closely related to the stability of the E_0 .

For ODE models, the next generation matrix is typically utilized to calculate reproductive number. See, e.g., van den Driessche and Watmough [18]. Here we choose an alternative approach developed in Iggidr et al [3] to calculate this important number because this approach can reveal some special relation of the two virus strains for the model (2.8)

Following [3], we now rewrite (2.8) as

$$\begin{cases} \frac{dT}{dt} = b - dT - \beta_1 TV_1 - \beta_2 TV_2, \\ \frac{dx}{dt} = Ax + \beta_1 TV_1 B, \\ \frac{dy}{dt} = Ay + \beta_2 TV_2 B, \\ \frac{dV}{dt} = D_1 x + D_2 y - cV, \end{cases} \quad (2.11)$$

where $x = (x_1, x_2, \dots, x_n)^T$, $y = (y_1, y_2, \dots, y_n)^T$, $V = (V_1, V_2)^T$, $c = (c_1, c_2)$, $B = \left(\frac{\alpha}{\alpha} \right)^n e_1(n)$,

$$D_1 = \begin{pmatrix} 0 & 0 & \dots & \frac{(1-\epsilon_1)}{\alpha} \\ 0 & 0 & \dots & \frac{\epsilon_1}{\alpha} \end{pmatrix}, \quad D_2 = \begin{pmatrix} 0 & 0 & \dots & \frac{\epsilon_2}{\alpha} \\ 0 & 0 & \dots & \frac{(1-\epsilon_2)}{\alpha} \end{pmatrix},$$

$$A = \begin{pmatrix} -\frac{1}{\alpha} & 0 & 0 & \dots & \dots & 0 \\ \frac{1}{\alpha} & -\frac{1}{\alpha} & 0 & \dots & \dots & 0 \\ 0 & \frac{1}{\alpha} & -\frac{1}{\alpha} & \dots & \dots & 0 \\ \vdots & \vdots & \ddots & \ddots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \ddots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & \dots & -\frac{1}{\alpha} \end{pmatrix},$$

and $e_1(n) = (1, 0, \dots, 0)^T$ that is an $n \times 1$ column.

During the mean duration of its lifetime, a virion of the first strain can actually generate a Dirac input $b\beta_1/c_1d$ in the second controlled system $x' = Ax + \beta_1TV_1B$ (see [3]). This input then generates secondary viruses given by formula:

$$\frac{b\beta_1}{c_1d} \int_0^{+\infty} D_i e^{tA} B dt = \frac{b\beta_1}{c_1d} D_i (-A^{-1}) B, \quad i = 1, 2.$$

Since

$$-A^{-1} = \begin{pmatrix} \widehat{\alpha} & 0 & 0 & \dots & \dots & 0 \\ \widehat{\alpha} & \widehat{\alpha} & 0 & \dots & \dots & 0 \\ \widehat{\alpha} & \widehat{\alpha} & \widehat{\alpha} & \dots & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \widehat{\alpha} & \widehat{\alpha} & \widehat{\alpha} & \dots & \dots & \widehat{\alpha} \end{pmatrix},$$

we obtain

$$\begin{aligned}
 D_1(-A^{-1})B &= \begin{pmatrix} 0 & 0 & \dots & \frac{1-\epsilon_1}{\widehat{\alpha}} \\ 0 & 0 & \dots & \frac{\epsilon_1}{\widehat{\alpha}} \end{pmatrix} \begin{pmatrix} \widehat{\alpha} & 0 & \dots & 0 \\ \widehat{\alpha} & \widehat{\alpha} & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ \widehat{\alpha} & \widehat{\alpha} & \dots & \widehat{\alpha} \end{pmatrix} \begin{pmatrix} 0 \\ 0 \\ \vdots \\ (\frac{\widehat{\alpha}}{\alpha})^n \end{pmatrix}, \\
 &= \begin{pmatrix} (1 - \epsilon_1)(\frac{\widehat{\alpha}}{\alpha})^n \\ \epsilon_1(\frac{\widehat{\alpha}}{\alpha})^n \end{pmatrix}.
 \end{aligned}$$

Therefore, based on the input $b\beta_1/c_1d$, two fractions in offsprings are given by

$$\mathbf{R}_{11} = (1 - \epsilon_1)\left(\frac{\widehat{\alpha}}{\alpha}\right)^n \frac{b\beta_1}{c_1d}, \quad \mathbf{R}_{12} = \epsilon_1\left(\frac{\widehat{\alpha}}{\alpha}\right)^n \frac{b\beta_1}{c_1d} \quad (2.12)$$

both of which result from virus one.

Similarly, the numbers of offspring of strains 1 and 2 produced by a single virion of strain 2 are given respectively by

$$\mathbf{R}_{21} = \epsilon_2\left(\frac{\widehat{\alpha}}{\alpha}\right)^n \frac{\beta_2b}{c_2d}, \quad \mathbf{R}_{22} = (1 - \epsilon_2)\left(\frac{\widehat{\alpha}}{\alpha}\right)^n \frac{\beta_2b}{c_2d} \quad (2.13)$$

Now, assume that a single virus particle is brought into a host, and let p (q) be the probability that this initially invaded virion is strain 1 (strain 2). Then $p + q = 1$, and all new viruses resulted from this virion are distributed among the two strains by the following formula:

$$\begin{pmatrix} \mathbf{R}_{11} & \mathbf{R}_{12} \\ \mathbf{R}_{21} & \mathbf{R}_{22} \end{pmatrix} \begin{pmatrix} p \\ q \end{pmatrix} = \begin{pmatrix} p\mathbf{R}_{11} + q\mathbf{R}_{12} \\ p\mathbf{R}_{21} + q\mathbf{R}_{22} \end{pmatrix}$$

Therefore, the total number of new virions resulted from the initial single virion is the

L_1 norm of the above vector, i.e.,

$$\begin{aligned} & \left\| \begin{pmatrix} p\mathbf{R}_{11} + q\mathbf{R}_{12} \\ p\mathbf{R}_{21} + q\mathbf{R}_{22} \end{pmatrix} \right\|_1 = (p\mathbf{R}_{11} + q\mathbf{R}_{12}) + (p\mathbf{R}_{21} + q\mathbf{R}_{22}) \\ & = p(\mathbf{R}_{11} + \mathbf{R}_{21}) + q(\mathbf{R}_{12} + \mathbf{R}_{22}) = p\mathbf{R}_1 + q\mathbf{R}_2 \end{aligned}$$

where

$$\mathbf{R}_1 = \mathbf{R}_{11} + \mathbf{R}_{12} = \frac{\beta_1 b}{c_1 d} \left(\frac{\widehat{\alpha}}{\alpha} \right)^n, \quad \mathbf{R}_2 = \mathbf{R}_{21} + \mathbf{R}_{22} = \frac{\beta_2 b}{c_2 d} \left(\frac{\widehat{\alpha}}{\alpha} \right)^n. \quad (2.14)$$

account for the individual reproductive numbers of strain 1 and strain 2 virus respectively. Thus, the basic reproductive number of the model (2.8) is obtained by taking the maximum over all possible initial distribution:

$$\begin{aligned} \mathbf{R}_0 &= \max_{p+q=1} \left\| \begin{pmatrix} \mathbf{R}_{11} & \mathbf{R}_{12} \\ \mathbf{R}_{21} & \mathbf{R}_{22} \end{pmatrix} \begin{pmatrix} p \\ q \end{pmatrix} \right\|_1 \\ &= \left\| \begin{pmatrix} \mathbf{R}_{11} & \mathbf{R}_{12} \\ \mathbf{R}_{21} & \mathbf{R}_{22} \end{pmatrix} \right\|_1 = \max\{\mathbf{R}_{11} + \mathbf{R}_{12}, \mathbf{R}_{21} + \mathbf{R}_{22}\} = \max\{\mathbf{R}_1, \mathbf{R}_2\} \end{aligned}$$

This conclusion is consistent with the result obtained by using the next generation method, see details in Appendix A.2.

2.5 Equilibria and their stabilities

We already knew that the system (2.8) has the infection-free equilibrium $E_0 = (b/d, 0, 0, \dots, 0)$.

The following theorem discusses the stability of the virus-free equilibrium E_0 .

Theorem 2.5.1 *If $\mathbf{R}_0 < 1$, the infection-free equilibrium E_0 is globally asymptotically stable on \mathbb{R}_+^{2n+3} .*

Proof Let us consider the stability of infection-free equilibrium E_0 in $\bar{\Gamma}$ under the con-

dition $\mathbf{R}_0 < 1$. We construct the Lyapunov function as follows:

$$\mathcal{V} = T_0 \left(\frac{T}{T_0} - \ln \frac{T}{T_0} - 1 \right) + \left(\frac{\alpha}{\widehat{\alpha}} \right)^n \left\{ \sum_{i=1}^n (x_i + y_i) + V_1 + V_2 \right\}.$$

Calculating the derivative of \mathcal{V} along trajectories of (2.8), we obtain:

$$\begin{aligned} \frac{d\mathcal{V}}{dt} &= \frac{dT}{dt} \left(1 - \frac{T}{T_0} \right) + \left(\frac{\alpha}{\widehat{\alpha}} \right)^n \left[\beta_1 \left(\frac{\widehat{\alpha}}{\alpha} \right)^n V_1 T - c_1 V_1 + \beta_2 \left(\frac{\widehat{\alpha}}{\alpha} \right)^n V_2 T - c_2 V_2 \right] \\ &= b - dT - b \frac{T_0}{T} + dT_0 + \beta_1 V_1 T_0 + \beta_2 V_2 T_0 - c_1 \left(\frac{\alpha}{\widehat{\alpha}} \right)^n V_1 - c_2 \left(\frac{\alpha}{\widehat{\alpha}} \right)^n V_2 \\ &= b \left(1 - \frac{T}{T_0} - \frac{T_0}{T} \right) + \left[\beta_1 \left(\frac{\widehat{\alpha}}{\alpha} \right)^n \frac{b}{dc_1} - 1 \right] \left(\frac{\alpha}{\widehat{\alpha}} \right)^n c_1 V_1 + \left[\beta_2 \left(\frac{\widehat{\alpha}}{\alpha} \right)^n \frac{b}{dc_2} - 1 \right] \left(\frac{\alpha}{\widehat{\alpha}} \right)^n c_2 V_2 \\ &= b \left(1 - \frac{T}{T_0} - \frac{T_0}{T} \right) + (\mathbf{R}_1 - 1) \left(\frac{\alpha}{\widehat{\alpha}} \right)^n c_1 V_1 + (\mathbf{R}_2 - 1) \left(\frac{\alpha}{\widehat{\alpha}} \right)^n c_2 V_2. \end{aligned}$$

Notice that $1 - T/T_0 - T_0/T \leq 0$ and the equality holds if and only if $T = T_0$, $V_1 = 0$ and $V_2 = 0$. Thus, $\frac{d\mathcal{V}}{dt} \leq 0$ if $\mathbf{R}_0 < 1$; and $\frac{d\mathcal{V}}{dt} = 0$ is if and only if (T, x, y, V) is at E_0 . Therefore, we can conclude that the virus free equilibrium E_0 is globally asymptotically stable in the positive orthant.

When $\mathbf{R}_0 > 1$, either $\mathbf{R}_1 > 1$ or $\mathbf{R}_2 > 1$. If $\mathbf{R}_1 > 1$, then there is the single-strain equilibrium $E_1 = (\widehat{T}^1, \widehat{x}_1^1, \dots, \widehat{x}_n^1, 0, \dots, 0, \widehat{V}_1^1, 0)$ given by

$$\widehat{T}^1 = \frac{c_1}{\beta_1} \left(\frac{\alpha}{\widehat{\alpha}} \right)^n, \quad \widehat{x}_l^1 = \widehat{\alpha} f(\widehat{T}^1) \left(\frac{\widehat{\alpha}}{\alpha} \right)^n, \quad l = 1, \dots, n, \quad \widehat{V}_1^1 = \frac{f(\widehat{T}^1)}{c_1} \left(\frac{\widehat{\alpha}}{\alpha} \right)^n, \quad (2.15)$$

where $f(\widehat{T}^1) = b - d\widehat{T}^1$. In parallel, if $\mathbf{R}_2 > 1$, then there is the single-strain equilibrium $E_2 = (\widehat{T}^2, 0, \dots, 0, \widehat{y}_1^2, \dots, \widehat{y}_n^2, 0, \widehat{V}_2^2)$ given by

$$\widehat{T}^2 = \frac{c_2}{\beta_2} \left(\frac{\alpha}{\widehat{\alpha}} \right)^n, \quad \widehat{y}_l^2 = \widehat{\alpha} f(\widehat{T}^2) \left(\frac{\widehat{\alpha}}{\alpha} \right)^n, \quad l = 1, \dots, n, \quad \widehat{V}_2^2 = \frac{f(\widehat{T}^2)}{c_2} \left(\frac{\widehat{\alpha}}{\alpha} \right)^n, \quad (2.16)$$

where $f(\hat{T}^2) = b - d\hat{T}^2$. In the sequel, we will discuss the stability of E_1 and E_2 , and possible positive (coexistence) equilibrium. We distinguish the case when the mutation is absent and the case when the mutation are present.

2.5.1 In the absence of mutation

First, let us consider the case $\epsilon_1 = \epsilon_2 = 0$. Since \mathbf{R}_1 and \mathbf{R}_2 depend on many model parameters, the critical case $\mathbf{R}_1 = \mathbf{R}_2$ is sensitive in the sense that a small change of any model parameter would destroy this identity. Thus, for practical purpose, we exclude this case in our discussion.

Note that $\mathbf{R}_i = \frac{b}{d} \frac{1}{\hat{T}^i}$ for $i = 1, 2$. Thus

$$\mathbf{R}_1 > \mathbf{R}_2 \quad \text{iff} \quad \hat{T}^1 < \hat{T}^2 \quad (2.17)$$

The following theorem establish the global stability of E_1 or E_2 , depending which strain has larger basic reproduction number.

Theorem 2.5.2 *Assume that $\mathbf{R}_0 > 1$.*

- (i) *If $\mathbf{R}_1 > \mathbf{R}_2$ and $\mathbf{R}_1 > 1$, then E_1 is globally asymptotically stable with respect to positive initial conditions.*
- (ii) *If $\mathbf{R}_2 > \mathbf{R}_1$ and $\mathbf{R}_2 > 1$, then E_2 is globally asymptotically stable with respect to positive initial conditions.*

Proof We only need to prove (i), since (ii) is parallel to (i). We construct a Lyapunov function on

$$\mathbf{H} := \{(T, x_1, y_1, x_2, y_2, \dots, x_n, y_n, V_1, V_2) \in \mathbb{R}^{(2n+3)} \mid T, x_i, y_i, V_1, V_2 > 0, i = 1, 2, \dots, n\}$$

as follows:

$$\begin{aligned} \mathcal{L} = & \hat{T}^1 \left(\frac{T}{\hat{T}^1} - \ln \frac{T}{\hat{T}^1} - 1 \right) + \left(\frac{\alpha}{\hat{\alpha}} \right)^n \left[\sum_{i=1}^n \hat{x}_i^1 \left(\frac{x_i}{\hat{x}_i^1} - \ln \frac{x_i}{\hat{x}_i^1} - 1 \right) + \hat{V}_1^1 \left(\frac{V}{\hat{V}_1^1} \right. \right. \\ & \left. \left. - \ln \frac{V}{\hat{V}_1^1} - 1 \right) + \sum_{i=1}^n y_i + V_2 \right]. \end{aligned}$$

Then, the derivative of \mathcal{L} along the trajectories of (2.8) is calculated as below:

$$\begin{aligned} \frac{d\mathcal{L}}{dt} &= \frac{dT}{dt} \left(1 - \frac{\hat{T}^1}{T} \right) + \left(\frac{\alpha}{\hat{\alpha}} \right)^n \left[\dot{x}_1 \left(1 - \frac{\hat{x}_1^1}{x_1} \right) + \sum_{i=2}^n \dot{x}_i \left(1 - \frac{\hat{x}_i^1}{x_i} \right) + \dot{V}_1 \left(1 - \frac{\hat{V}_1^1}{V_1} \right) \right. \\ & \left. + \sum_{i=1}^n \dot{y}_i + \dot{V}_2 \right] \\ &= f(T) \left(1 - \frac{\hat{T}^1}{T} \right) - (\beta_1 T V_1 + \beta_2 T V_2) \left(1 - \frac{\hat{T}^1}{T} \right) + \left(\frac{\alpha}{\hat{\alpha}} \right)^n \left[\beta_1 V_1 T \left(\frac{\hat{\alpha}}{\alpha} \right)^n \right. \\ & \quad - \frac{1}{\hat{\alpha}} x_1 - \beta_1 V_1 T \left(\frac{\hat{\alpha}}{\alpha} \right)^n \frac{\hat{x}_1^1}{x_1} + \frac{1}{\hat{\alpha}} \hat{x}_1^1 + \frac{1}{\hat{\alpha}} (x_1 - x_2) - \frac{1}{\hat{\alpha}} \frac{\hat{x}_2^1}{x_2} x_1 + \frac{1}{\hat{\alpha}} \hat{x}_2^1 + \frac{1}{\hat{\alpha}} (x_2 - x_3) \\ & \quad - \frac{1}{\hat{\alpha}} \frac{\hat{x}_3^1}{x_3} x_2 + \frac{1}{\hat{\alpha}} \hat{x}_3^1 + \cdots + \frac{1}{\hat{\alpha}} (x_{n-1} - x_n) - \frac{1}{\hat{\alpha}} \frac{\hat{x}_n^1}{x_n} x_{n-1} + \frac{1}{\hat{\alpha}} \hat{x}_n^1 - \frac{1}{\hat{\alpha}} \frac{\hat{V}_1^1}{v_1} x_n + c \hat{V}_1^1 + \frac{1}{\hat{\alpha}} x_n \\ & \quad \left. - c_1 V_1 + \beta_2 V_2 T \left(\frac{\hat{\alpha}}{\alpha} \right)^n - \frac{1}{\hat{\alpha}} y_1 + \frac{1}{\hat{\alpha}} (y_1 - y_2) + \cdots + \frac{1}{\hat{\alpha}} (y_{n-1} - y_n) + \frac{1}{\hat{\alpha}} y_n - c_2 V_2 \right] \end{aligned}$$

$$\begin{aligned}
 &= f(T)\left(1 - \frac{\hat{T}^1}{T}\right) + \beta_1 V_1 \hat{T}^1 + \beta_2 V_2 \hat{T}^1 + \left(\frac{\alpha}{\hat{\alpha}}\right)^n \left[\frac{n}{\hat{\alpha}} \hat{x}_n^1 - \beta_1 V_1 T \left(\frac{\hat{\alpha}}{\alpha}\right)^n \frac{\hat{x}_1^1}{x_1} \right. \\
 &\quad \left. - \frac{1}{\hat{\alpha}} \frac{\hat{x}_2^1}{x_2} - \frac{1}{\hat{\alpha}} \frac{\hat{x}_3^1}{x_3} - \dots - \frac{1}{\hat{\alpha}} \frac{\hat{x}_n^1}{x_n} - \frac{\hat{V}_1^1}{V_1} x_n + c_1 \hat{V}_1^1 - c_1 V_1 - c_2 V_2 \right] \\
 &= f(T)\left(1 - \frac{\hat{T}^1}{T}\right) + \beta_2 V_2 \hat{T}^1 - c_2 \left(\frac{\alpha}{\hat{\alpha}}\right)^n V_2 + \frac{\hat{x}_n^1}{\hat{\alpha}} \left(\frac{\alpha}{\hat{\alpha}}\right)^n [(n+1) \\
 &\quad - \frac{V_1 T \hat{x}_1^1}{\hat{V}_1^1 \hat{T}^1 x_1} - \frac{x_1}{x_2} - \frac{x_2}{x_3} - \frac{x_3}{x_4} - \dots - \frac{x_{n-1}}{x_n} - \frac{\hat{V}_1^1 x_n}{V_1 \hat{x}_n^1}] \\
 &= f(T)\left(1 - \frac{\hat{T}^1}{T}\right) + \beta_2 V_2 \hat{T}^1 - \beta_2 V_2 \hat{T}^2 - f(\hat{T}^1)\left(1 - \frac{\hat{T}^1}{T}\right) + \frac{\hat{x}_1^1}{\hat{\alpha}} \left(\frac{\alpha}{\hat{\alpha}}\right)^n [(n+2) \\
 &\quad - \frac{\hat{T}^1}{T} - \frac{V_1 T \hat{x}_1^1}{\hat{V}_1^1 \hat{T}^1 x_1} - \frac{x_1}{x_2} - \frac{x_2}{x_3} - \frac{x_3}{x_4} - \dots - \frac{x_{n-1}}{x_n} - \frac{\hat{V}_1^1 x_n}{V_1 \hat{x}_n^1}] \\
 &= (f(T) - f(\hat{T}^1))\left(1 - \frac{\hat{T}^1}{T}\right) + \beta_2 V_2 (\hat{T}^1 - \hat{T}^2) + \frac{\hat{x}_1^1}{\hat{\alpha}} \left(\frac{\alpha}{\hat{\alpha}}\right)^n [(n+2) - \frac{\hat{T}^1}{T} \\
 &\quad - \frac{V_1 T \hat{x}_1^1}{\hat{V}_1^1 \hat{T}^1 x_1} - \frac{x_1}{x_2} - \frac{x_2}{x_3} - \frac{x_3}{x_4} - \dots - \frac{x_{n-1}}{x_n} - \frac{\hat{V}_1^1 x_n}{V_1 \hat{x}_n^1}]
 \end{aligned}$$

It is obvious that

$$[f(T) - f(\hat{T}^1)]\left(1 - \frac{\hat{T}^1}{T}\right) = d(\hat{T}^1 - T)\left(1 - \frac{\hat{T}^1}{T}\right) \leq 0.$$

By (2.17), the second term of right part is nonpositive. Moreover, the relation of isomeric and geometric means implies that

$$\frac{\hat{T}^1}{T} + \frac{V_1 T \hat{x}_1^1}{\hat{V}_1^1 \hat{T}^1 x_1} + \frac{x_1}{x_2} + \frac{x_2}{x_3} + \frac{x_3}{x_4} + \dots + \frac{x_{n-1}}{x_n} + \frac{\hat{V}_1^1 x_n}{V_1 \hat{x}_n^1} \geq (n+2).$$

Thus, we have proved $\frac{d\mathcal{L}}{dt} \leq 0$; and $\frac{d\mathcal{L}}{dt} = 0$ if and only if state is at the equilibrium E_1 . Then, we can conclude that E_1 is globally asymptotically stable in \mathbf{H} and the proof is completed.

This theorem shows that when the basic reproduction number is larger than 1, then competition exclusion would be the generic result in the absence of mutation, implying

that coexistence is in general impossible. Taking (i) as an example, if $\mathbf{R}_1 > \mathbf{R}_2$ and $\mathbf{R}_1 > 1$, then regardless of whether $\mathbf{R}_2 < 1$ or $\mathbf{R}_2 > 1$, E_1 is globally asymptotically stable, meaning that strain 1 will win the competition. Therefore there will no coexistence equilibrium.

2.5.2 With the effect of mutation

In this section, we investigate the effect of the mutations by assuming that $\epsilon_1 > 0$ and $\epsilon_2 > 0$. The first result along this line is that the co-existence equilibrium becomes possible due to the presence of mutations,

Theorem 2.5.3 *Assume $\epsilon_1 > 0$ and $\epsilon_2 > 0$. If one of the following conditions holds, then the model system (2.8) has a unique positive equilibrium \bar{E} :*

(i) $\mathbf{R}_1 > 1$ and $\mathbf{R}_2 > 1$;

(ii) $\mathbf{R}_2 < 1$ but $\mathbf{R}_1 > 1 + \frac{c_2 k}{c_1}(1 - \mathbf{R}_2)$;

(iii) $\mathbf{R}_1 < 1$ but $\mathbf{R}_2 > 1 + \frac{c_1 k}{c_2}(1 - \mathbf{R}_1)$,

where k is a positive constant to be determined by a quadratic equation in the proof of the theorem.

Proof If a positive equilibriums exists, its components are given by

$$\begin{aligned}\bar{x}_n &= \bar{x}_{n-1} = \cdots = \bar{x}_1 = \widehat{\alpha}\beta_1\bar{T}\bar{V}_1\left(\frac{\widehat{\alpha}}{\alpha}\right)^n, \\ \bar{y}_n &= \bar{y}_{n-1} = \cdots = \bar{y}_1 = \widehat{\alpha}\beta_2\bar{T}\bar{V}_2\left(\frac{\widehat{\alpha}}{\alpha}\right)^n, \\ \bar{T} &= \frac{b}{d + \beta_1\bar{V}_1 + \beta_2\bar{V}_2}.\end{aligned}$$

with \bar{V}_1 and \bar{V}_2 being determined by

$$\begin{cases} \frac{\beta_1(1-\epsilon_1)b}{(d+\beta_1\bar{V}_1+\beta_2\bar{V}_2)}\left(\frac{\bar{\alpha}}{\alpha}\right)^n\bar{V}_1 + \frac{\beta_2\epsilon_2b}{(d+\beta_1\bar{V}_1+\beta_2\bar{V}_1)}\left(\frac{\bar{\alpha}}{\alpha}\right)^n\bar{V}_2 = c_1\bar{V}_1 \\ \frac{\beta_2(1-\epsilon_2)b}{(d+\beta_1\bar{V}_1+\beta_2\bar{V}_2)}\left(\frac{\bar{\alpha}}{\alpha}\right)^n\bar{V}_2 + \frac{\beta_1\epsilon_1b}{(d+\beta_1\bar{V}_1+\beta_2\bar{V}_2)}\left(\frac{\bar{\alpha}}{\alpha}\right)^n\bar{V}_1 = c_2\bar{V}_2. \end{cases} \quad (2.18)$$

By simplification, the equations (2.18) can be rewritten as

$$\begin{cases} \mathbf{R}_{11}c_1\bar{V}_1 + \mathbf{R}_{21}c_2\bar{V}_2 - c_1\bar{V}_1\left(1 + \frac{\beta_1}{d}\bar{V}_1 + \frac{\beta_2}{d}\bar{V}_2\right) = 0, \\ \mathbf{R}_{12}c_1\bar{V}_1 + \mathbf{R}_{22}c_2\bar{V}_2 - c_2\bar{V}_2\left(1 + \frac{\beta_1}{d}\bar{V}_1 + \frac{\beta_2}{d}\bar{V}_2\right) = 0. \end{cases} \quad (2.19)$$

After calculating, we can further rewrite them as follows:

$$\begin{cases} (\mathbf{R}_{11} - 1)c_1c_2\bar{V}_1\bar{V}_2 + \mathbf{R}_{21}c_2^2\bar{V}_2^2 - c_1c_2\bar{V}_1\bar{V}_2\left(\frac{\beta_1}{d}\bar{V}_1 + \frac{\beta_2}{d}\bar{V}_2\right) = 0, \\ \mathbf{R}_{12}c_1^2\bar{V}_1^2 + (\mathbf{R}_{22} - 1)c_1c_2\bar{V}_1\bar{V}_2 - c_1c_2\bar{V}_1\bar{V}_2\left(\frac{\beta_1}{d}\bar{V}_1 + \frac{\beta_2}{d}\bar{V}_2\right) = 0. \end{cases} \quad (2.20)$$

Subtracting the second equation in (2.20) from the first one leads to

$$\mathbf{R}_{21}c_2^2\bar{V}_2^2 - \mathbf{R}_{12}c_1^2\bar{V}_1^2 + (\mathbf{R}_{11} - \mathbf{R}_{22})c_1c_2\bar{V}_1\bar{V}_2 = 0. \quad (2.21)$$

Because $\bar{V}_1 \neq 0$, it can be transformed into

$$\mathbf{R}_{21}c_2^2\left(\frac{\bar{V}_2}{\bar{V}_1}\right)^2 + (\mathbf{R}_{11} - \mathbf{R}_{22})c_1c_2\left(\frac{\bar{V}_2}{\bar{V}_1}\right) - \mathbf{R}_{12}c_1^2 = 0. \quad (2.22)$$

Setting $z = \bar{V}_2/\bar{V}_1$, the equation (2.22) becomes the quadratic equation

$$a_2z^2 + a_1z + a_0 = 0, \quad (2.23)$$

where

$$a_0 = -\mathbf{R}_{12}c_1^2, \quad a_1 = (\mathbf{R}_{11} - \mathbf{R}_{22})c_1c_2, \quad a_2 = \mathbf{R}_{21}c_2^2.$$

Note that if $\epsilon_1 = 0 = \epsilon_2$, then $\mathbf{R}_{12} = 0 = \mathbf{R}_{21}$ and hence $a_0 = 0 = a_2$, and thus, (2.23) can not have a positive root and thus, (2.8) can not have a positive equilibrium. But now, we have assumed $\epsilon_1 > 0$ and $\epsilon_2 > 0$, implying $\mathbf{R}_{21} > 0$ and $\mathbf{R}_{12} > 0$. Hence $a_0 < 0$ and $a_2 > 0$, implying that the quadratic equation (2.23) has one positive root, denoting it by k , corresponding to a non-zero solution (\hat{V}_1, \hat{V}_2) of (2.19) with \bar{V}_1, \bar{V}_2 having the same sign.

Substituting $V_2 = kV_1$ into (2.19) gives

$$\begin{cases} \mathbf{R}_{11}c_1\bar{V}_1 + \mathbf{R}_{21}c_2k\bar{V}_1 - c_1\bar{V}_1\left(1 + \frac{\beta_1}{d}\bar{V}_1 + \frac{\beta_2}{d}k\bar{V}_1\right) = 0, \\ \mathbf{R}_{12}c_1\bar{V}_1 + \mathbf{R}_{22}c_2k\bar{V}_1 - c_2k\bar{V}_1\left(1 + \frac{\beta_1}{d}\bar{V}_1 + \frac{\beta_2}{d}k\bar{V}_1\right) = 0. \end{cases}$$

from which, we obtain the following expression for \bar{V}_1 :

$$\bar{V}_1 = \frac{[(\mathbf{R}_1 - 1)c_1 + (\mathbf{R}_2 - 1)c_2k]d}{(c_1 + kc_2)(\beta_1 + k\beta_2)}. \quad (2.24)$$

Therefore, $\bar{V}_1 > 0$ provided that at least one of the three conditions stated in the theorem holds. The proof is completed.

So far, we proved the existence of the positive equilibrium \bar{E} as ϵ changes. Furthermore, we begin the analysis with the two boundary equilibria E_1 and E_2 to investigate the origin of the equilibrium \bar{E} . Denoting vector field of the system (2.8) by $g(X, \epsilon)$, we find that $g(E_i, 0) = 0$, where $i = 1, 2$. Then, if $\frac{\partial g}{\partial X}(E_i, 0)$ is invertible, we can establish a unique equilibrium $E_i(\epsilon)$ near E_i by implicit function theorem for small ϵ . So, let's verify our conjecture.

Proposition 2.5.4 *Assume the equilibrium E_i exists (i.e., $\mathbf{R}_i > 1$). $\frac{\partial g}{\partial X}(E_i, 0)$ are invertible for $i = 1, 2$, respectively.*

Proof Firstly, we consider the situation for E_1 . The Jacobian matrix of linearized sys-

tem (2.8) at E_1 is given by

$$J = \begin{pmatrix} J_1(n) & J_2(n) \\ 0 & J_4(n) \end{pmatrix}.$$

where,

$$J_1(n) = \begin{pmatrix} -\beta_1 \left(\frac{\hat{\alpha}}{\alpha}\right)^n \hat{V}_1^1 & 0 & 0 & \cdots & 0 & -\beta_1 \hat{T}^1 \\ \beta_1 \left(\frac{\hat{\alpha}}{\alpha}\right)^n \hat{V}_1^1 & -\frac{1}{\alpha} & 0 & \cdots & 0 & \beta_1 \left(\frac{\hat{\alpha}}{\alpha}\right)^n \hat{T}^1 \\ 0 & \frac{1}{\alpha} & -\frac{1}{\alpha} & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & -\frac{1}{\alpha} & 0 \\ 0 & 0 & 0 & \cdots & \frac{1}{\alpha} & -c_1 \end{pmatrix}_{(n+1) \times (n+1)},$$

$$J_2(n) = \begin{pmatrix} 0 & 0 & \cdots & 0 & -\beta_2 \hat{T}^1 \\ 0 & 0 & \cdots & 0 & 0 \\ 0 & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 0 & 0 \\ 0 & 0 & \cdots & 0 & 0 \end{pmatrix}_{(n+1) \times n},$$

and

$$J_4(n) = \begin{pmatrix} -\frac{1}{\alpha} & 0 & \cdots & 0 & \beta_1 \left(\frac{\hat{\alpha}}{\alpha}\right)^n \hat{T}^1 \\ \frac{1}{\alpha} & -\frac{1}{\alpha} & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & -\frac{1}{\alpha} & 0 \\ 0 & 0 & \cdots & \frac{1}{\alpha} & -c_2 \end{pmatrix}_{n \times n}.$$

Then, $\det(J) = \det(J_1(n)) \det(J_4(n))$. This means that, if both $\det(J_1(n))$ and $\det(J_4(n))$ do not equal zero, the determinant of J at E_1 is nonzero. Next, we will prove that neither of $\det(J_1(n))$ and $\det(J_4(n))$ is zero.

After adding the third column of $\det(J_1(n))$ to its second column and expanding the new determinant along its third row, we achieve the following equation:

$$\det(J_1^{(n)}) = \left(-\frac{1}{\widehat{\alpha}}\right) \det \begin{pmatrix} -\beta_1 \left(\frac{\widehat{\alpha}}{\alpha}\right)^n \widehat{V}_1^1 & 0 & 0 & \cdots & 0 & -\beta_1 \widehat{T}^1 \\ \beta_1 \left(\frac{\widehat{\alpha}}{\alpha}\right)^n \widehat{V}_1^1 & -\frac{1}{\widehat{\alpha}} & 0 & \cdots & 0 & \beta_1 \left(\frac{\widehat{\alpha}}{\alpha}\right)^n \widehat{T}^1 \\ 0 & \frac{1}{\widehat{\alpha}} & -\frac{1}{\widehat{\alpha}} & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & -\frac{1}{\widehat{\alpha}} & 0 \\ 0 & 0 & 0 & \cdots & \frac{1}{\widehat{\alpha}} & -c_1 \end{pmatrix}_{n \times n}.$$

Arguing similarly as before, we have

$$\det(J_4(n)) = \left(-\frac{1}{\widehat{\alpha}}\right) \det \begin{pmatrix} -\frac{1}{\widehat{\alpha}} & 0 & \cdots & 0 & \beta_1 \left(\frac{\widehat{\alpha}}{\alpha}\right)^n \widehat{T}^1 \\ \frac{1}{\widehat{\alpha}} & -\frac{1}{\widehat{\alpha}} & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & -\frac{1}{\widehat{\alpha}} & 0 \\ 0 & 0 & \cdots & \frac{1}{\widehat{\alpha}} & -c_2 \end{pmatrix}_{(n-1) \times (n-1)}.$$

Repeating these steps $n - 2$ times, we obtain

$$\det(J_1(n)) = \left(-\frac{1}{\widehat{\alpha}}\right)^{(n-2)} \det \begin{pmatrix} -d - \beta_1 \widehat{V}_1^1 & 0 & -\beta_1 \widehat{T}^1 \\ \beta_1 \widehat{V}_1^1 \left(\frac{\widehat{\alpha}}{\alpha}\right)^n & -\frac{1}{\widehat{\alpha}} & \beta_1 \widehat{T}^1 \left(\frac{\widehat{\alpha}}{\alpha}\right)^n \\ 0 & \frac{1}{\widehat{\alpha}} & -c_1 \end{pmatrix} = (-1)^{(n-1)} \frac{\beta_1 \widehat{V}_1^1 c_1}{\widehat{\alpha}^{(n-1)}} \neq 0,$$

and

$$\det(J_4(n)) = \left(-\frac{1}{\widehat{\alpha}}\right)^{(n-2)} \det \begin{pmatrix} -\frac{1}{\widehat{\alpha}} & \beta_1 \widehat{T}^1 \left(\frac{\widehat{\alpha}}{\alpha}\right)^n \\ \frac{1}{\widehat{\alpha}} & -c_2 \end{pmatrix} = (-1)^{(n-2)} \frac{c_2 \beta_1 - \beta_1 c_1}{\beta_1 \widehat{\alpha}^{(n-1)}} \neq 0.$$

under the assumption $c_1 \neq c_2$. Therefore, the determinant of Jacobian matrix J is nonzero at E_1 .

In the same way, we can demonstrate that $\det(J) \neq 0$ at E_2 . Hence, $\frac{\partial g}{\partial X}(E_i, 0)$ are invertible for all $i = 1, 2$.

When $\mathbf{R}_2 < 1$, only E_1 exists in absence of mutation. Obviously, the positive equilibrium \bar{E} bifurcates from the equilibrium E_1 when mutation happens. However, the situation about the origin of \bar{E} becomes more complicated when $\mathbf{R}_2 > 1$. Next, we will analyze the case when (2.17) holds (i.e. $\mathbf{R}_1 > \mathbf{R}_2$) to find out whether \bar{E} is equal to $E_1(\epsilon)$ or $E_2(\epsilon)$.

Define that

$$P(\epsilon) = \begin{pmatrix} 1 - \epsilon_1 & \epsilon_1 \\ \epsilon_2 & 1 - \epsilon_2 \end{pmatrix},$$

which is a mutation matrix and

$$P(\epsilon) = I + Q(\epsilon),$$

where $Q(\epsilon) = \begin{pmatrix} -\epsilon_1 & \epsilon_1 \\ \epsilon_2 & -\epsilon_2 \end{pmatrix}$ is a matrix with positive off-diagonal entries. Each row of Q sums to zero. Since $\bar{x}_n = \bar{x}_{n-1} = \dots = \bar{x}_1$ and $\bar{y}_n = \bar{y}_{n-1} = \dots = \bar{y}_1$, then the rest of equations when system (2.8) equals to zero except the first equation can be simplified to

$$K\bar{V}\bar{T} - B\bar{T}^* = 0, \quad (2.25)$$

$$P(\epsilon)B\bar{T}^* - M\bar{V} = 0, \quad (2.26)$$

where

$$K = \begin{bmatrix} \beta_1 \left(\frac{\widehat{\alpha}}{\alpha}\right)^n & 0 \\ 0 & \beta_2 \left(\frac{\widehat{\alpha}}{\alpha}\right)^n \end{bmatrix}, \quad B = \begin{bmatrix} \frac{1}{\widehat{\alpha}} & 0 \\ 0 & \frac{1}{\widehat{\alpha}} \end{bmatrix}, \quad M = \begin{bmatrix} c_1 & 0 \\ 0 & c_2 \end{bmatrix}.$$

Substitute $B\bar{T}^* = K\bar{V}\bar{T}$ into (2.26) :

$$(M^{-1}P(\epsilon)K - \frac{1}{\bar{T}})\bar{V} = 0.$$

Denote

$$A(\epsilon) = \begin{bmatrix} \frac{\beta_1(1-\epsilon_1)}{c_1} \left(\frac{\widehat{\alpha}}{\alpha}\right)^n & \frac{\beta_2\epsilon_2}{c_2} \left(\frac{\widehat{\alpha}}{\alpha}\right)^n \\ \frac{\beta_1\epsilon_1}{c_1} \left(\frac{\widehat{\alpha}}{\alpha}\right)^n & \frac{\beta_2(1-\epsilon_2)}{c_2} \left(\frac{\widehat{\alpha}}{\alpha}\right)^n \end{bmatrix}.$$

Then,

$$\left[A(\epsilon) - \frac{1}{\bar{T}}\right]\bar{V} = 0.$$

Finally, the problem about a positive solution become the existence of positive eigenvalue associated with positive eigenvector of matrix $A(\epsilon)$. Calculating

$$\begin{vmatrix} \frac{\beta_1(1-\epsilon_1)}{c_1} \left(\frac{\widehat{\alpha}}{\alpha}\right)^n - \lambda & -\frac{\beta_2\epsilon_2}{c_2} \left(\frac{\widehat{\alpha}}{\alpha}\right)^n \\ -\frac{\beta_1\epsilon_1}{c_1} \left(\frac{\widehat{\alpha}}{\alpha}\right)^n & \frac{\beta_2(1-\epsilon_2)}{c_2} \left(\frac{\widehat{\alpha}}{\alpha}\right)^n - \lambda \end{vmatrix} = 0, \quad (2.27)$$

we obtain

$$\lambda_1(\epsilon) = \frac{[\frac{\beta_1}{c_1}(1-\epsilon_1) + \frac{\beta_2}{c_2}(1-\epsilon_2)] + \sqrt{[\frac{\beta_1}{c_1}(1-\epsilon_1) + \frac{\beta_2}{c_2}(1-\epsilon_2)]^2 + 4\frac{\beta_1\beta_2}{c_1c_2}(1-\epsilon_1-\epsilon_2)}}{2\left(\frac{\widehat{\alpha}}{\alpha}\right)^n}, \quad (2.28)$$

and

$$\lambda_2(\epsilon) = \frac{[\frac{\beta_1}{c_1}(1-\epsilon_1) + \frac{\beta_2}{c_2}(1-\epsilon_2)] - \sqrt{[\frac{\beta_1}{c_1}(1-\epsilon_1) + \frac{\beta_2}{c_2}(1-\epsilon_2)]^2 + 4\frac{\beta_1\beta_2}{c_1c_2}(1-\epsilon_1-\epsilon_2)}}{2\left(\frac{\widehat{\alpha}}{\alpha}\right)^n}. \quad (2.29)$$

Because of $\lambda_1(\epsilon) > 0 > \lambda_2(\epsilon)$, the principle eigenvalue $\lambda_1(\epsilon)$ owns a positive eigenvector by Perron-Frobenius theorem. In addition, it is easy to find that $\lambda_1(0) = \hat{T}^1$ and $\lambda_2(0) = \hat{T}^2$. Thus, $E_2(\epsilon)$ is nonpositive and the unique positive equilibrium \bar{E} equals $E_1(\epsilon)$ when $\mathbf{R}_1 > \mathbf{R}_2 > 1$.

In the following, the average Lyapunov function method is utilized to analyze the stability of the equilibrium \bar{E} .

Theorem 2.5.5 *When $\mathbf{R}_1 > \mathbf{R}_2 > 1$, \bar{E} is globally asymptotically stable in \mathbf{H}' for all $\epsilon \in [0, \bar{\epsilon}]$.*

Proof Before the whole proof, we define a new set

$$\Gamma = \bar{\Gamma} \times [0, \epsilon_0].$$

It is clear that Γ is compact and forward invariant under system (2.8).

We will use the same Lyapunov function

$$\begin{aligned} \mathcal{L} = & \hat{T}^1 \left(\frac{T}{\hat{T}^1} - \ln \frac{T}{\hat{T}^1} - 1 \right) + \left(\frac{\alpha}{\hat{\alpha}} \right)^n \left[\sum_{i=1}^n \hat{x}_i^1 \left(\frac{x_i}{\hat{x}_i^1} - \ln \frac{x_i}{\hat{x}_i^1} - 1 \right) + \hat{V}_1^1 \left(\frac{V}{\hat{V}_1^1} \right. \right. \\ & \left. \left. - \ln \frac{V}{\hat{V}_1^1} - 1 \right) + \sum_{i=1}^n y_i + V_2 \right]. \end{aligned}$$

as before. Calculate $\frac{d\mathcal{L}}{dt}$ along the trajectories of system (2.8)

$$\begin{aligned} \frac{d\mathcal{L}}{dt} &= [f(T) - f(\hat{T}^1)] \left(1 - \frac{\hat{T}^1}{T} \right) + \beta_2 V_2 (\hat{T}^1 - \hat{T}^2) + \frac{\hat{x}_1^1}{\hat{\alpha}} \left(\frac{\alpha}{\hat{\alpha}} \right)^n \left[(n+2) - \frac{\hat{T}^1}{T} \right. \\ &\quad \left. - \frac{V_1 T \hat{x}_1^1}{\hat{V}_1^1 \hat{T}^1 x_1} - \frac{x_1}{x_2} - \frac{x_2}{x_3} - \frac{x_3}{x_4} - \dots - \frac{x_{n-1}}{x_n} - \frac{\hat{V}_1^1 x_n}{V_1 \hat{x}_n^1} \right] - \left(\frac{\alpha}{\hat{\alpha}} \right)^n \frac{\hat{V}_1^1}{V_1} \left(\frac{-\epsilon_1}{\hat{\alpha}} x_n \right. \\ &\quad \left. + \frac{\epsilon_2}{\hat{\alpha}} y_n \right) \\ &= [f(T) - f(\hat{T}^1)] \left(1 - \frac{\hat{T}^1}{T} \right) - \frac{\hat{x}_1^1}{\hat{\alpha}} \left(\frac{\alpha}{\hat{\alpha}} \right)^n \left[\frac{\hat{T}^1}{T} + \frac{V_1 T \hat{x}_1^1}{\hat{V}_1^1 \hat{T}^1 x_1} + \frac{x_1}{x_2} + \frac{x_2}{x_3} \right. \\ &\quad \left. + \frac{x_3}{x_4} + \dots + \frac{x_{n-1}}{x_n} + (1 - \epsilon_1) \frac{\hat{V}_1^1 x_n}{V_1 \hat{x}_n^1} - (n+2)(1 - \epsilon_1)^{\frac{1}{n+2}} \right] - \beta_2 V_2 (\hat{T}^2 - \hat{T}^1) \\ &\quad + \frac{1}{\hat{\alpha}} (n+2) \left[1 - (1 - \epsilon_1)^{\frac{1}{n+2}} \right] \left(\frac{\alpha}{\hat{\alpha}} \right)^n \hat{x}_n^1 - \frac{1}{\hat{\alpha}} \left(\frac{\alpha}{\hat{\alpha}} \right)^n \epsilon_2 y_n \end{aligned}$$

$$\begin{aligned}
 &\leq [f(T) - f(\hat{T}^1)]\left(1 - \frac{\hat{T}^1}{T}\right) - \frac{\hat{x}_1^1}{\hat{\alpha}}\left(\frac{\alpha}{\hat{\alpha}}\right)^n \left[\frac{\hat{T}^1}{T} + \frac{V_1 T \hat{x}_1}{\hat{V}_1 \hat{T}^1 x_1} + \frac{x_1}{x_2} + \frac{x_2}{x_3}\right. \\
 &\quad + \frac{x_3}{x_4} + \dots + \frac{x_{n-1}}{x_n} + (1 - \epsilon_1) \frac{\hat{V}_1^1 x_n}{V_1 \hat{x}_n^1} - (n+2)(1 - \epsilon_1)^{\frac{1}{n+2}} \left. \right] - \beta_2 V_2 (\hat{T}^2 - \hat{T}^1) \\
 &\quad + \frac{1}{\hat{\alpha}}(n+2)[1 - (1 - \epsilon_1)^{\frac{1}{n+2}}] \left(\frac{\alpha}{\hat{\alpha}}\right)^n \hat{x}_n^1
 \end{aligned}$$

By Lemma 5 in [6], we can find $\epsilon_a, \eta > 0$ such that $V_1(t) + V_2(t) > \eta$ for all $\epsilon \in [0, \epsilon_a]$ and all sufficiently large t when (2.17) holds. Let $\gamma = \beta_2(\hat{T}^2 - \hat{T}^1)$, then

$$\beta_2(\hat{T}^2 - \hat{T}^1)V_2 = \gamma V_2 \geq \gamma(\eta - V_1).$$

Then, the following inequality

$$\begin{aligned}
 \frac{d\mathcal{L}}{dt} &\leq (f(T) - f(\hat{T}^1))\left(1 - \frac{\hat{T}^1}{T}\right) - \frac{\hat{x}_1^1}{\hat{\alpha}}\left(\frac{\alpha}{\hat{\alpha}}\right)^n \left[\frac{\hat{T}^1}{T} + \frac{V_1 T \hat{x}_1^1}{\hat{V}_1 \hat{T}^1 x_1} + \frac{x_1}{x_2} + \frac{x_2}{x_3}\right. \\
 &\quad + \frac{x_3}{x_4} + \dots + \frac{x_{n-1}}{x_n} + (1 - \epsilon_1) \frac{\hat{V}_1^1 x_n}{V_1 \hat{x}_n^1} - (n+2)(1 - \epsilon_1)^{\frac{1}{n+2}} \left. \right] - \gamma\eta + \gamma V_1 \\
 &\quad + \frac{1}{\hat{\alpha}}(n+2)[1 - (1 - \epsilon_1)^{\frac{1}{n+2}}] \left(\frac{\alpha}{\hat{\alpha}}\right)^n \hat{x}_n^1.
 \end{aligned}$$

would hold in Γ for all $\epsilon \in [0, \epsilon_a]$.

Suppose a positive constant ϵ_b can satisfy

$$1 - \epsilon_1 \in \left(\frac{1}{2}, 1\right], \quad \frac{1}{\hat{\alpha}}(n+2)[1 - (1 - \epsilon_1)^{\frac{1}{n+2}}] \left(\frac{\alpha}{\hat{\alpha}}\right)^n \hat{x}_n^1 - \gamma\eta \leq -\frac{\gamma\eta}{4}$$

for all $\epsilon \in [0, \epsilon_b]$. Denote $\bar{\epsilon} = \min(\epsilon_a, \epsilon_b)$. Thus, for any $\epsilon \in [0, \bar{\epsilon}]$, we obtain that

$$\begin{aligned}
 \frac{d\mathcal{L}}{dt} &\leq (f(T) - f(\hat{T}^1))\left(1 - \frac{\hat{T}^1}{T}\right) - \frac{\hat{x}_1^1}{\hat{\alpha}}\left(\frac{\alpha}{\hat{\alpha}}\right)^n \left[\frac{\hat{T}^1}{T} + \frac{V_1 T \hat{x}_1^1}{\hat{V}_1 \hat{T}^1 x_1} + \frac{x_1}{x_2} + \frac{x_2}{x_3}\right. \\
 &\quad + \frac{x_3}{x_4} + \dots + \frac{x_{n-1}}{x_n} + (1 - \epsilon_1) \frac{\hat{V}_1^1 x_n}{V_1 \hat{x}_n^1} - (n+2)(1 - \epsilon_1)^{\frac{1}{n+2}} \left. \right] - \frac{\gamma\eta}{4} + \gamma V_1
 \end{aligned}$$

A sufficiently large N is chosen such that

$$\frac{1}{\alpha}(n+2)[1 - (1 + \epsilon q_{11})^{\frac{1}{n+2}}] \left(\frac{\alpha}{\bar{\alpha}}\right)^n \hat{x}_n^1 - \gamma\eta + \gamma V_1 < N,$$

for all solutions of (2.8) in Γ and all $\epsilon \in (0, \bar{\epsilon}]$. Meanwhile, let $\delta_1 > 0$ be such that

$$[f(T) - f(\hat{T}^1)] \left(1 - \frac{\hat{T}^1}{T}\right) < -(N+1),$$

for all $T < \delta_1$ and all $\epsilon \in (0, \bar{\epsilon}]$. It is easy to show that there exists a $\delta_2 > 0$ such that

$$\begin{aligned} & -\frac{\bar{x}_1}{\alpha} \left(\frac{\alpha}{\bar{\alpha}}\right)^n \left[\frac{\hat{T}^1}{T} + \frac{V_1 T \hat{x}_1^1}{\hat{V}_1^1 \hat{T}^1 x_1} + \frac{x_1}{x_2} + \frac{x_2}{x_3} + \frac{x_3}{x_4} + \dots + \frac{x_{n-1}}{x_n} \right. \\ & \left. + (1 - \epsilon_1) \frac{\hat{V}_1^1 x_n}{V_1 \hat{x}_n^1} - (n+2)(1 + \epsilon q_{11})^{\frac{1}{n+2}} \right] < -(N+1) \end{aligned}$$

for all $\frac{x_n}{V_1} < \delta_2$ and all $\epsilon \in (0, \bar{\epsilon}]$. At last, we can find a $\delta_3 > 0$ to make $-\frac{\gamma\eta}{4} + \gamma V_1 < -\frac{\gamma\eta}{8}$ for all $V_1 < \delta_3$ and all $\epsilon \in (0, \bar{\epsilon}]$. Denote

$$\hat{\Gamma}_\delta = \{(T, x_1, y_1, x_2, y_2, \dots, x_n, y_n, V_1, V_2) \in \mathbf{H} \cap \Gamma \mid T \geq \delta_1, x_n \geq \delta_2 V_1, V_1 \geq \delta_3\}.$$

If $(T, x_1, y_1, x_2, y_2, \dots, x_n, y_n, V_1, V_2) \in (\mathbf{H} \cap \Gamma) \setminus \hat{\Gamma}_\delta$ and all $\epsilon \in (0, \bar{\epsilon}]$, at least one of following results holds:

- (1) $T < \delta_1$, then $\frac{d\mathcal{L}}{dt} \leq -(N+1) + N = -1$;
- (2) $\frac{x_n}{V_1} < \delta_2$, then $\frac{d\mathcal{L}}{dt} \leq -(N+1) + N = -1$;
- (3) $V_1 < \delta_3$, then $\frac{d\mathcal{L}}{dt} \leq -\frac{\gamma\eta}{8}$.

Therefore, for all $(T, x_1, y_1, x_2, y_2, \dots, x_n, y_n, V_1, V_2) \in (\mathbf{H} \cap \Gamma) \setminus \hat{\Gamma}_\delta$ and all $\epsilon \in [0, \bar{\epsilon}]$, there is

$$\frac{d\mathcal{L}}{dt} \leq 0.$$

It is easy to see that nonnegative function $\mathcal{L}(T, x_1, y_1, \dots, x_n, y_n, V_1, V_2, \epsilon)$ is continuous and bounded on set $\hat{\Gamma}_\delta \times [0, \bar{\epsilon}]$ since that $T, x_1, y_1, \dots, x_n, y_n, V_1, V_2$ are bounded away from zero. Thus, it can reach a finite positive maximum:

$$\rho := \max_{\hat{\Gamma}_\delta \times [0, \bar{\epsilon}]} \mathcal{L}(T, x_1, y_1, \dots, x_n, y_n, V_1, V_2, \epsilon) > 0$$

Define a new set

$$\begin{aligned} \Gamma_\delta = \{ & (T, x_1, y_1, x_2, y_2, \dots, x_n, y_n, V_1, V_2) \in \mathbf{H} \cap \Gamma \mid \mathcal{L}(T, x_1, y_1, \dots, x_n, y_n, \\ & V_1, V_2, \epsilon) \leq \rho, \forall \epsilon \in [0, \bar{\epsilon}] \}. \end{aligned}$$

Then, we obtain that $\hat{\Gamma}_\delta \subset \Gamma_\delta \subset \mathbf{H} \cap \Gamma$. That Γ_δ is closed can be implied by the continuity of \mathcal{L} . Thus, it is compact in \mathbf{H} .

In the following, we need to show that all solutions of (2.8) in \mathbf{H} enter and remains in Γ_δ for all large time. Because Γ is an absorbing set for all $\epsilon \geq 0$, without loss of generality, we need to prove this for all solutions in Γ .

Let $\Phi(t) = (T, x_1, y_1, x_2, y_2, \dots, x_n, y_n, V_1, V_2) \in \mathbf{H} \cap \Gamma$ be a solution of (2.8) for some fixed $\epsilon \in [0, \bar{\epsilon}]$. It's easy to verify that the inequality $\frac{d\mathcal{L}}{dt} \leq 0$ holds in set $\Gamma \setminus \hat{\Gamma}_\delta$. Because of $\mathcal{L} \geq 0$, there exists a $t_0 \geq 0$ such that $\Phi(t_0) \in \hat{\Gamma}_\delta \subset \Gamma_\delta$. Next, we will prove that $\Phi(t) \in \Gamma_\delta$ for all $t \geq t_0$. For the sake of contradiction, let's assume that there is a $t_1 > t_0$ such that $\Phi(t_1) \notin \Gamma_\delta$. Then there should be a $t_2 \in [t_0, t_1)$ such that $\Phi(t_2) \in \Gamma_\delta$ and $\Phi(t) \notin \Gamma_\delta$ for all $t \in (t_2, t_1]$. On the one hand, we have that

$$\mathcal{L}(\Phi(t_2), \epsilon) \leq \rho < \mathcal{L}(\Phi(t_1), \epsilon)$$

by definition of Γ_δ . But, on the other hand, for all $t \in (t_2, t_1]$, we have $\Phi(t) \notin \Gamma_\delta$ and consequently $\Phi(t) \notin \hat{\Gamma}_\delta$ so that $\frac{d}{dt} \mathcal{L}(\Phi(t), \epsilon) = \frac{d\mathcal{L}}{dt} < 0$. This contradiction shows that

$\Phi(t) \in \Gamma_\delta$ for all $t \geq t_0$.

Let us define

$$\mathbf{H}' = \{(T, x_1, y_1, x_2, y_2, \dots, x_n, y_n, V_1, v_2) \in \mathbb{R}^{(2n+3)} \mid T + \sum_i x_i + V_1 > 0, \\ i = 1, 2, \dots, n\} \supset \mathbf{H}.$$

Since $E_1(0) \in \text{Int}\mathbf{H}'$ is globally asymptotically stable in \mathbf{H}' for $\epsilon = 0$ when $\mathbf{R}_1 > \mathbf{R}_2 > 1$. Then, the condition (H1) of Corollary 2.3 in the paper [5, 16] holds. As a result, \bar{E} (or $E_1(\epsilon)$) is globally asymptotically stable in \mathbf{H}' for all $\epsilon \in [0, \bar{\epsilon}]$ if $\mathbf{R}_1 > \mathbf{R}_2 > 1$.

2.6 Discussion and Conclusion

In this chapter, we have studied the within-host age-structured model of two strains. Different with the multiple-strains model in [6], we used an age-structured model to study the coexistence between two strains of viruses. Fortunately, under some assumptions, we can restore the information about viral infection age to new variables. Then, our age-structured model were transformed into a stage model. To understand the process that begins with viral attachment and end with the release of new viruses better, we treated our stage model as a controlled system to gain the corresponding basic reproductive number. Comparing the numerical conclusion in [8], we proved the global stabilities of two boundary equilibria without the effects of mutations. Moreover, if both boundary equilibria exist, we demonstrated that their evolution would comply with competitive exclusion principle that the stronger one will survive finally. Furthermore, we discussed the existence and stability of the unique positive equilibrium when the forward and backward mutations were considered. We explained how these two strains coexist with the help of small mutation rates in mathematics. Meanwhile, the coexisted equilibrium would be globally asymptotically stable if the mutation is considered as a

small perturbation.

As we all know, the mutation rates cannot be always fixed in the viral evolution. Even there is a small change in environment, it can alter the direction of the evolution of viruses. So, we are interested in the case when natural selection is considered. Since mutation rates can change as times goes by, how would these changes affect the viruses evolution? This could be also a very interesting problem as our future work. Furthermore, if mutation rates exceed these critical values, will these stabilities change or not? Although we found that it would not in our simulations, we cannot assert that it is globally asymptotically stable with any values of mutations. The corresponding mathematical demonstration is necessary.

Bibliography

- [1] Drake, J. W. and Holland, J. J. (1999). Mutation rates among RNA viruses. *Proceedings of the National Academy of Sciences*, 96(24):13910–13913.
- [2] Iggidr, A., Kamgang, J. C., Sallet, G., and Tewa, J. J. (2006). Global analysis of new malaria intrahost models with a competitive exclusion principle. *SIAM Journal on Applied Mathematics*, 67(1):260–278.
- [3] Iggidr, A., Mbang, J., and Sallet, G. (2007). Stability analysis of within-host parasite models with delays. *Mathematical Biosciences*, 209(1):51–75.
- [4] Klein, D. W., Prescott, L. M., and Harley, J. (1999). *Microbiology*. Boston: Wcb.
- [5] Kon, R. and Iwasa, Y. (2007). Single-class orbits in nonlinear Leslie matrix models for semelparous populations. *Journal of mathematical biology*, 55(5-6):781–802.
- [6] Leenheer, P. D. and Pilyugin, S. S. (2008). Multistrain virus dynamics with mutations: a global analysis. *Mathematical Medicine and Biology*, 25(4):285–322.

- [7] Mansky, L. M. and Temin, H. M. (1995). Lower in vivo mutation rate of human immunodeficiency virus type 1 than that predicted from the fidelity of purified reverse transcriptase. *Journal of virology*, 69(8):5087–5094.
- [8] Nelson, P. W., Gilchrist, M. A., Coombs, D., Hyman, J. M., and Perelson, A. S. (2004). An age-structured model of hiv infection that allows for variations in the production rate of viral particles and the death rate of productively infected cells. *Math. Biosci. Eng*, 1(2):267–288.
- [9] Nowak, M. A. (2002). From quasispecies to universal grammar. *Zeitschrift für physikalische Chemie*, 216(1/2002):5.
- [10] Nowak, M. A. and May, R. M. (2000). *Virus dynamics: mathematical principles of immunology and virology*. Oxford university press.
- [11] Perelson, A. S., Kirschner, D. E., and Boer, R. D. (1993). Dynamics of HIV infection of CD4⁺ T cells. *Mathematical Biosciences*, 114(1):81–125.
- [12] Perelson, A. S. and Nelson, P. W. (1999). Mathematical analysis of HIV-1 dynamics in vivo. *SIAM review*, 41(1):3–44.
- [13] Preston, B. D., Poiesz, B. J., and Loeb, L. A. (1988). Fidelity of HIV-1 reverse transcriptase. *Science*, 242(4882):1168–1171.
- [14] Shafer, R., Rhee, S. Y., Pillay, D., Miller, V., Sandstrom, P., Schapiro, J., Kuritzkes, D., and Bennett, D. (2007). HIV-1 protease and reverse transcriptase mutations for drug resistance surveillance. *Aids*, 21(2):215.
- [15] Smith, H. L. (1995). Monotone dynamical systems: An introduction to the theory of competitive and cooperative systems. *Bulletin of the American Mathematical Society*, 33(2):203–210.

- [16] Smith, H. L. and Waltman, P. (1999). Perturbation of a globally stable steady state. *Proceedings of the American Mathematical Society*, 127(2):447–453.
- [17] Steinhauer, D. A. and Holland, J. J. (1987). Rapid evolution of RNA viruses. *Annual Reviews in Microbiology*, 41(1):409–431.
- [18] van den Driessche, P. and Watmough, J. (2002). Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical biosciences*, 180(1):29–48.
- [19] Yuan, Z. H. and Zou, X. F. (2010). Global threshold property in an epidemic model for disease with latency spreading in a heterogeneous host population. *Nonlinear Analysis: Real World Applications*, 11(5):3479–3490.

Chapter 3

Within-host viral evolution under immune control

3.1 Introduction

In the last decades, scientists provided a simple system of differential equations [2, 3, 5, 17, 19]:

$$\begin{aligned}\dot{T} &= \lambda - dT - kTV, \\ \dot{I} &= kTV - \delta I, \\ \dot{V} &= pI - cV,\end{aligned}\tag{3.1}$$

to study the dynamics of human immunodeficiency virus, hepatitis C virus, hepatitis B virus and cytomegalovirus infections in vivo. Target cells (T) that are susceptible to infection are infected by viruses (V) with a constant rate k . They assumed that target cells can be produced from a source at a rate λ and die at a rate d . Productively infected cells (I) that are produced by infection produce new viruses at a rate p , and die at a rate δ . The clearance rate of free viruses is c . This detail is showed in the Figure 3.1 [20].

In the meantime, however, immune system is activated to fight against viruses. De-

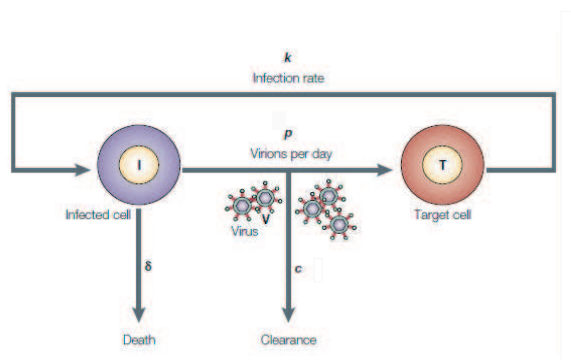


Figure 3.1: Basic model of viral infection.

pending on the characteristics of the infection agents, the most effective mechanisms are used by immune system. Both viral particles and infected cells are the goals of adaptive immunity. Antibodies offer the most important mechanism against viral particles; while the cytotoxic mechanisms play a most significant role against infected cells. In this paper, we only discuss the cytotoxic mechanisms, particularly in cytotoxic T-lymphocyte (CTL) response. A cell-mediated response to specific foreign antigens associated with cells are provided by cytotoxic T-lymphocytes (CTLs), also called killer T cells. As being activated by recognition of specific antigen on a cell, CTLs release the cytotoxins perforin, granzymes, and granulysin. Apoptosis can be induced in two ways: one is through the action of perforin; the other way is via the cell-surface interactions between T cells and infected cells.

We incorporate CTL response into a basic model of virus infection and investigate its effect on viral evolution. Usually, people treat the parameters as constants and analyze the stabilities of corresponding equilibria in population dynamics. However, viruses evolve to adapt the defense from hosts in nature. In the paper of Perelson and et al. [12], the viral burst size is chosen as viral fitness. Considering the competition between resident and mutant strains, we define the fitness of mutants based on analysis about the local stability of the mutant-free equilibrium in our model. Then, the viral

evolution will be explored in trait space in this chapter. It means that a trait is selected as the evolutionary strategy of each strain. Although viruses mutate quickly and randomly, only suitable strains can escape immune response and survive finally [18, 14, 16, 4]. So, strategies that they choose can be vitally important for their destinies. The two strategies: the viral production rate and the virulence, will be taken as variables in the fitness function and studied, respectively.

An increment of the value of one strategy may cause variation of the other. To explore the relation of strategies, we consider two trade-offs. The first one is between virion production rate and mortality of infected cells, which is taken as viral virulence. Nutrient from host cells consumed by virus is used to replicate itself, so the death rate of infected cells will be assumed to increase as viral production increasing. There are a number of reasons to expect that a virus utilizes the resources of its host in order to produce viral proteins in the process of replication. Because of the loss of cell resources and possible cytotoxic effects of viral proteins, the death rate of cells is likely increased [21, 13, 15]. We take this mortality as production-dependent. The trade-off between the infected cell death rate and the disease transmission rate is also considered. According to previous researches [8, 1, 6, 22], an increase in transmission rate can only evolve with a parallel increase in virulence, which is assumed to increase with virulence and eventually converge towards an upper limit. Due to lack of accurate experimental data, we only study the general cases instead of some specific functions. By the classical adaptive dynamical approach, (Gertiz, Kisdi et al., [11, 10]), we have obtained some information on how the CTL response shape these two types of trade-offs and affect the viral evolution.

The rest of this chapter is as follows. In Section 3.2, we first present the mathematical model, and then analyze the local stability of the mutant free equilibrium and define the fitness of mutant viruses. In Section 3.3, the trade-off involving the infected

cell death rate and the disease transmission rate is studied. In Section 3.4, we discuss the trade-off between the virion production rate and the mortality of infected cells. In addition to the theoretical results, examples are given for both cases. In the end, some discussions on the biological implications of the mathematical results are given; moreover, some related problems about future work on this topic are discussed.

3.2 The fitness

We use bilinear function to replace Holling Type II function in the model of Nowak and Wodarz' [22] and obtain the following one strain within-host model:

$$\begin{cases} \dot{x} = \gamma - dx - \beta xv, \\ \dot{y} = \beta xv - ay - pyz, \\ \dot{v} = ky - uv, \\ \dot{z} = cyz - bz, \end{cases} \quad (3.2)$$

where the variables and parameters are explained as below:

x : Abundance of uninfected cells;

y : Abundance of infected cells;

v : Abundance of free viruses;

z : Abundance of CTLs;

γ : Birth rate of healthy cells;

d : Natural death rate of healthy cell;

c : A stimulant rate of CTLs;

p : A killing rate of infected cells;

β : Infection rate;

a : Death rate of infected cell;

k : Virus production rate;

u : Virus clearance rate;

b : Death rate of CTL.

This model always has an infection-free equilibrium $\mathbf{E}_0 = \left(\frac{\gamma}{d}, 0, 0, 0\right)$. It also has an immune-free equilibrium

$$\mathbf{E} = \left(\frac{au}{k\beta}, \frac{k\gamma\beta - aud}{ka\beta}, \frac{k\gamma\beta - aud}{ua\beta}, 0\right).$$

If the immune mediated basic reproduction number

$$\mathcal{R}_1 = \frac{\gamma\beta k}{aud} - \frac{b\beta k}{duc} > 1,$$

a unique positive equilibrium $\bar{\mathbf{E}} = (\bar{x}, \bar{y}, \bar{v}, \bar{z})$ exists, where

$$\bar{x} = \frac{\gamma}{d+\beta\bar{v}}, \quad \bar{y} = \frac{b}{c}, \quad \bar{v} = \frac{k}{u}\bar{y}, \quad \bar{z} = \frac{1}{p}\left(\frac{k}{u}\beta\bar{x} - a\right), \quad (3.3)$$

We have demonstrated in Appendix B.1 that this positive equilibrium $\bar{\mathbf{E}}$ of system (3.2) is locally asymptotic stable under the condition $\mathcal{R}_1 = \frac{\gamma\beta k}{aud} - \frac{b\beta k}{duc} > 1$.

Next, assumed that a mutant strain is introduced, and accordingly the system (3.2) is naturally modified to the following two strain model

$$\begin{cases} \dot{x} &= \gamma - dx - \beta xv_1 - \tilde{\beta} xv_2, \\ \dot{y}_1 &= \beta xv_1 - ay_1 - py_1 z, \\ \dot{v}_1 &= ky_1 - uv_1, \\ \dot{z} &= (cy_1 + \tilde{c}y_2)z - bz, \\ \dot{y}_2 &= \tilde{\beta} xv_2 - \tilde{a}y_2 - \tilde{p}y_2 z, \\ \dot{v}_2 &= \tilde{k}y_2 - \tilde{u}v_2. \end{cases} \quad (3.4)$$

A mutant-free equilibrium of the system (3.4) is:

$$\tilde{\mathbf{E}} = \left(\frac{\gamma}{d + \beta \tilde{v}_1}, \frac{b}{c}, \frac{k}{u} \tilde{y}_1, \frac{1}{p} \left(\frac{k\beta}{u} \tilde{x} - a \right), 0, 0 \right).$$

We have proved that this equilibrium is locally asymptotic stable if $\det(\mathbf{J}_{22}) > 0$ and it becomes unstable if $\det(\mathbf{J}_{22}) < 0$ (see details in Appendix B.2). This implies that the mutant strain can invade successfully if $\det(\mathbf{J}_{22}) < 0$. As such, it is natural and reasonable to define $-\det(\mathbf{J}_{22})$ as the fitness of mutant strain viruses:

$$\begin{aligned} \mathbf{W} &\triangleq -\det(\mathbf{J}_{22}) \\ &= \tilde{k}\tilde{\beta}\tilde{x} - (\tilde{a} + \tilde{p}\tilde{z})\tilde{u} \\ &= \tilde{k}\tilde{\beta}\frac{\gamma}{d+\beta\tilde{v}_1} - \tilde{u}\left[\tilde{a} + \frac{\tilde{p}}{p}\left(\frac{k\beta}{u}\tilde{x} - a\right)\right] \\ &= \tilde{k}\tilde{\beta}\frac{\gamma}{d+\beta\tilde{v}_1} - \tilde{u}\left[\tilde{a} + \frac{\tilde{p}}{p}\left(\frac{k\beta\gamma c}{duc+k\beta b} - a\right)\right] \\ &= \left(\tilde{k}\tilde{\beta}u - \frac{\tilde{p}}{p}k\beta\tilde{u}\right)\frac{\gamma c}{duc+k\beta b} + \tilde{u}\left(\frac{\tilde{p}}{p}a - \tilde{a}\right). \end{aligned} \quad (3.5)$$

From above, it is easy to see that the value of the fitness depends on the difference between two basic reproductive numbers of resident strain and mutant strain with CTL response. If the mutants have bigger reproductive number, the value of fitness is posi-

tive, which means that the mutant strain can invade successfully in the future. Different with the fitness in [12], the competitiveness of both strains can be reflect in our fitness.

3.3 Trade off between a and k

In this section, the trade-off between the viral production rate and the mortality of infected cells is studied. Because viruses need to consume nutrient from host cells to replicate themselves, the replication will increase the death rate of infected cells. Meanwhile, possible cytotoxic effect of their proteins can also raise the mortality [7, 3, 12]. Thus, the mortality of infected cells is taken as production-dependent $a(k)$. So, different strategies will have corresponding values of mortality. For convenience, we assume the rest of parameters for the mutant strain to be the same as the quantities for the resident strain. Therefore, the fitness function about this trade-off is written as

$$W(k, \tilde{k}) = (\tilde{k} - k) \frac{\beta\gamma uc}{duc + k\beta b} + u[a(k) - a(\tilde{k})]. \quad (3.6)$$

Firstly, when the fitness gradient vanishes:

$$\left. \frac{\partial W}{\partial \tilde{k}} \right|_{\tilde{k}=k} = \frac{\beta\gamma uc}{duc + \beta bk} - ua'(k) = 0.$$

The solutions of this equation define as evolutionary singular points. The above equation can be written as the following ordinary differential equation:

$$a'(k) = \frac{\beta\gamma c}{duc + \beta bk}. \quad (3.7)$$

The solutions of this differential equation are defined as critical functions $a_{crit}(k)$. Thus, the trade-off function is tangential to one of the critical functions at a corresponding

evolutionary singular point. The numerical solutions of (3.7) by giving a range of initial values of k are shown in the Figure 3.2a. Furthermore, we vary the stimulation rate c to observe the changes of one critical function in the Figure 3.2b. It is found

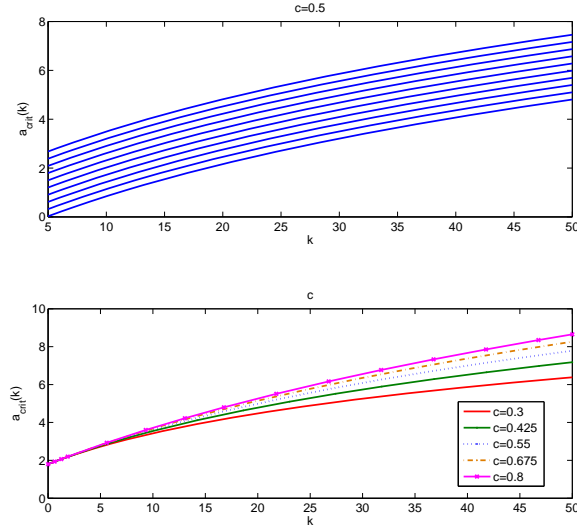


Figure 3.2: **Figures of critical functions.** (a). A family of critical functions with different initial values. (b). Critical functions for different values of c . In figure (b), a less concave down (concave) critical function $a_{crit}(k)$ can be caused by a greater stimulation rate c .

that the greater the stimulation rate c is, the less concave down (concave) the critical function $a_{crit}(k)$ is in the Figure 3.2b. Moreover, the stimulation rate c can also govern the shape of the trade-off function by adjusting the critical functions.

Suppose k^* is an evolutionary singular point. If

$$\left. \frac{\partial^2 W}{\partial \tilde{k}^2} \right|_{\tilde{k}=k=k^*} = -ua''(k^*) < 0,$$

it is evolutionary stable. Obviously, this singular point is evolutionary stable when the trade-off function $a(k)$ is all concave up (convex) or locally concave up at k^* .

The condition for convergence stable strategy is as below:

$$\begin{aligned} \frac{d}{dk} \left(\frac{\partial W}{\partial \tilde{k}} \Big|_{\tilde{k}=k} \right) \Big|_{k=k^*} &= \frac{\partial^2 W}{\partial k \partial \tilde{k}} \Big|_{\tilde{k}=k=k^*} + \frac{\partial^2 W}{\partial \tilde{k}^2} \Big|_{\tilde{k}=k=k^*} \\ &= -\frac{\beta^2 b \gamma u c}{(duc + \beta b k^*)^2} - u a''(k^*) < 0. \end{aligned}$$

Since $a''_{crit}(k^*) = -\frac{\beta^2 b \gamma c}{(duc + \beta b k^*)^2} < 0$, the above condition is equivalent to

$$a''_{crit}(k^*) < u a''(k^*). \quad (3.8)$$

So, if the trade-off function is concave up or locally concave up at k^* , then it is a convergence stable strategy.

At k^* , if the trade-off function is all convex (concave up) or partial convex at k^* , this evolutionary singular point is a continuously stable strategy, which is both evolutionary and convergence stable. If only (3.8) holds, this evolutionary singular point is an evolutionary branching point. Otherwise, it is a repellor when neither of them holds.

Next, two particular types of trade-off functions are introduced to discuss this problem, with a hope to gain more detailed information about these strategies.

3.3.1 Exponential function

Denote $a(k) = d e^{\phi k}$, where ϕ is a scaling factor to reflect the sensitivity of infected cells to virus production. To find an evolutionary singular point, we solve the following equation about k :

$$\frac{\partial W}{\partial \tilde{k}} \Big|_{\tilde{k}=k} = \frac{\beta \gamma c u}{duc + k \beta b} - u d \phi e^{\phi k} = 0. \quad (3.9)$$

Suppose that k^* is a solution of (3.9), then

$$\frac{\beta \gamma c}{d \phi} e^{-\phi k^*} - \beta b k^* - duc = 0. \quad (3.10)$$

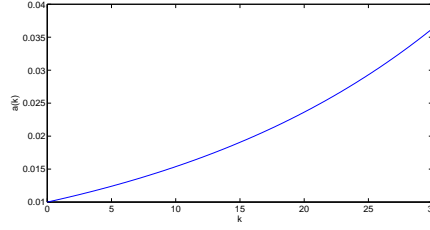


Figure 3.3: **Exponential function.** Where $\phi = 0.043$, $d = 0.01$.

Let us discuss the existence of k^* . Denote

$$f(k) = \frac{\beta\gamma c}{d\phi} e^{-\phi k} - \beta b k - d u c.$$

Since $f(k)$ is a decreasing function of k , k^* is a positive solution of (3.9) if

$$f(0) = \frac{\beta\gamma c}{d\phi} - d u c \geq 0.$$

So, the equation (3.9) has a unique positive solution k^* when $\phi \leq \frac{\beta\gamma}{d^2 u}$. Then, the evolutionary and convergence stability of this strategy is analyzed.

Because that both

$$\left. \frac{\partial^2 \mathbf{W}}{\partial \tilde{k}^2} \right|_{\tilde{k}=k^*} = -u d \phi^2 e^{\phi k^*} < 0$$

and

$$\left. \frac{d}{dk} \left(\frac{\partial \mathbf{W}}{\partial \tilde{k}} \right) \right|_{\tilde{k}=k} \Big|_{k=k^*} = -\frac{\beta^2 \gamma c u b}{d u c + k^* \beta b} - u d \phi^2 e^{\phi k^*} < 0$$

hold, the viral production rate k^* is both the evolutionary and convergence stable, i.e., a continuously stable strategy.

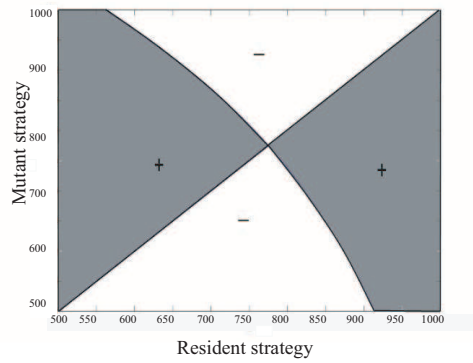


Figure 3.4: **Pairwise invasion plots.** Only locating in the positive regions, the strategies can invade successfully. Since a vertical line through k^* can entirely lie within the white regions, it is a continuously stable strategy.

3.3.2 Power function

In this part, we utilize power functions of the form

$$a(k) = \alpha k^n + d, \quad n \geq 1 \dots$$

to describe the relationship between the virus production rate and the mortality of infected cells.

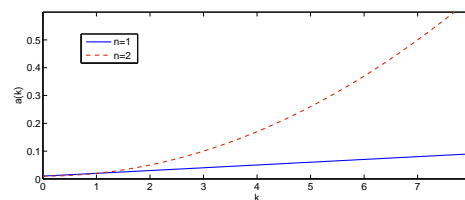


Figure 3.5: **Power functions.** Where $\alpha = 0.01, d = 0.01$.

$$n = 1$$

By solving the equation

$$\left. \frac{\partial W}{\partial \tilde{k}} \right|_{\tilde{k}=k} = \frac{\beta\gamma cu}{duc + k\beta b} - u\alpha = 0 \quad (3.11)$$

for k , we obtain that the unique positive root:

$$k^* = \frac{(\beta\gamma - \alpha du)c}{\beta b \alpha}.$$

under the condition $\beta\gamma - \alpha du > 0$. Then, the cross derivative and the second derivative with respect to \tilde{k} of the fitness are calculated, respectively, at k^* as

$$\left. \frac{d}{dk} \left(\left. \frac{\partial W}{\partial \tilde{k}} \right|_{\tilde{k}=k} \right) \right|_{k=k^*} = -\frac{\beta^2 \gamma cub}{(duc + k^* \beta b)^2} = -\frac{bu\alpha^2}{\gamma c} < 0,$$

and

$$\left. \frac{\partial^2 W}{\partial \tilde{k}^2} \right|_{\tilde{k}=k^*} = 0.$$

According to the conclusion in [10], k^* is an evolutionary stable strategy. Since it also satisfied the condition for convergence stable strategy, k^* is a continuously stable strategy.

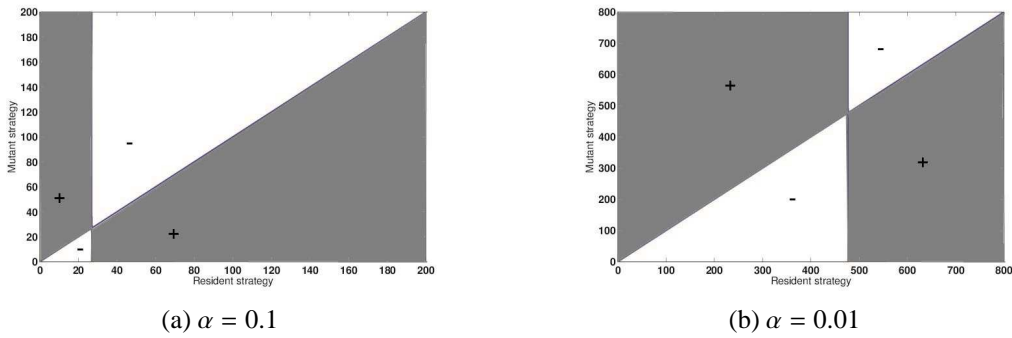


Figure 3.6: **Two pairwise invasion plots when $n = 1$.** Since the mutants fitness is a linear function of the mutants strategy, k^* is always an ESS according to the conclusion in [10]. According to our observation, the location of k^* moves to right as α decreases.

$n = 2$

In such a case, the equation as below:

$$\frac{\partial W}{\partial \tilde{k}} \Big|_{\tilde{k}=k} = \frac{\beta\gamma cu}{duc + k\beta b} - 2u\alpha k = 0,$$

is simplified to

$$2b\beta\alpha k^2 + \alpha du^2 ck - \beta\gamma uc = 0. \tag{3.12}$$

This quadratic equation has a unique positive solution:

$$k^* = \frac{-du^2 c\alpha + \sqrt{(du^2 c\alpha)^2 + 2\beta^2 b\alpha\gamma uc}}{2b\beta\alpha}.$$

Then, we discuss the evolutionary and convergence stability of this singular point. Since

$$\frac{d}{dk} \left(\frac{\partial W}{\partial \tilde{k}} \Big|_{\tilde{k}=k} \right) \Big|_{k=k^*} = -\frac{\beta^2\gamma cub}{(duc + k^*\beta b)^2} - 2\alpha uk^* < 0,$$

and

$$\frac{\partial^2 W}{\partial \tilde{k}^2} \Big|_{\tilde{k}=k=k^*} = -2\alpha uk^* < 0,$$

this singular point k^* is a continuously stable strategy for viruses (see the Figure 3.7).

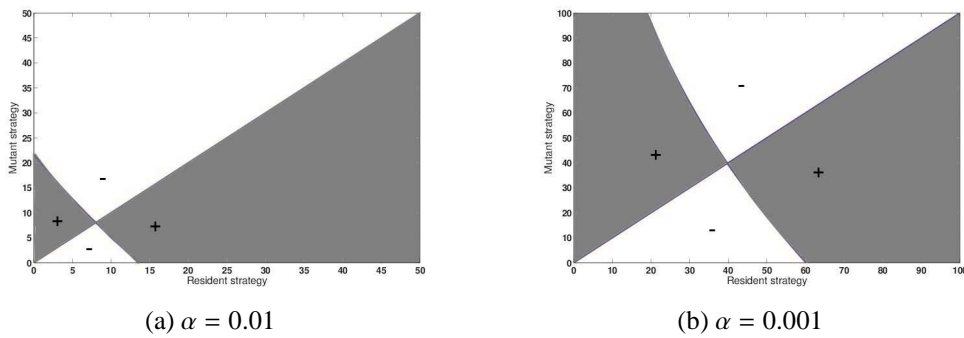


Figure 3.7: **Two pairwise invasion plots when $n = 2$.** Both of them are continuously stable strategies. Comparing the figure (a) with (b), the location of the evolutionary singular point can be shifted by varying the value of α , which is opposite to the case of $n = 1$.

3.4 Trade off between β and a

The trade-off between the disease transmission rate and the viral virulence is studied in this section. The larger death rate of infected cell can result in increase of the transmission rate. The other parameters are assumed to be the same for two strains. So, the fitness takes the form:

$$W(a, \tilde{a}) = (\beta(\tilde{a}) - \beta(a)) \frac{\gamma ck u}{duc + kb\beta} - u(\tilde{a} - a).$$

An evolutionary singular point a^* is the solution of the following equation:

$$\left. \frac{\partial W}{\partial \tilde{a}} \right|_{\tilde{a}=a^*} = \beta'(a^*) \frac{\gamma ck u}{duc + kb\beta(a^*)} - u = 0,$$

which is equivalent to

$$\beta'(a^*) = \frac{duc + kb\beta(a^*)}{\gamma ck}.$$

The second differential equation illustrates that the trade-off function is tangential to its solution, i.e., the critical function $\beta_{crit}(a)$, at the point a^* . The numerical solutions of (3.7) are simulated by giving a range of initial values of a in the Figure 3.8a. Furthermore, there are five curves of critical functions with different stimulation rates c in the Figure 3.8b, respectively. It is shown that the convexity of a critical function $\beta_{crit}(a)$ can be affected by the stimulation rate c . Thus, the stimulation rate c can also shape this trade-off function through corresponding critical functions.

Next, we focus on the biologically evolutionary and convergence stability of the point a^* . When the following inequality

$$\left. \frac{\partial^2 W}{\partial \tilde{a}^2} \right|_{\tilde{a}=a^*} = \beta''(a^*) \frac{\gamma ck u}{duc + kb\beta(a^*)} < 0.$$

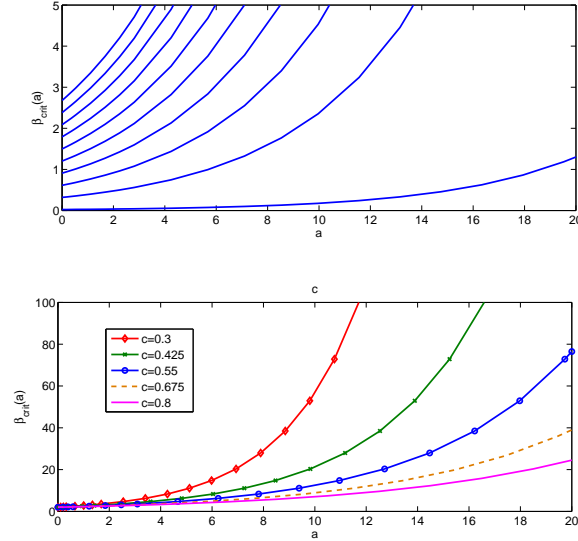


Figure 3.8: **Figures of critical functions.** (a). A family of critical functions. (b). The critical functions with different initial values of the variable c . From (b), the greater stimulation rate c can cause the less concave up (convex) critical function.

holds, the point a^* is evolutionary stable. So, it is demonstrated that the evolutionary singular point a^* is an evolutionary stable strategy if the trade-off function $\beta(a)$ is all concave down (concave) or locally concave down at this point.

A convergence stable strategy a^* should satisfy the following condition:

$$\begin{aligned} \frac{d}{da} \left(\frac{\partial W}{\partial \bar{a}} \Big|_{\bar{a}=a} \right) \Big|_{a=a^*} &= \frac{\partial^2 W}{\partial a \partial \bar{a}} \Big|_{\bar{a}=a=a^*} + \frac{\partial^2 W}{\partial \bar{a}^2} \Big|_{\bar{a}=a=a^*} \\ &= -(\beta'(a^*))^2 \frac{\gamma c k^2 b u}{(duc + kb\beta(a^*))^2} + \beta''(a^*) \frac{\gamma c k u}{duc + kb\beta(a^*)} < 0. \end{aligned}$$

from which we obtain

$$\beta''(a^*) < \beta''_{crit}(a^*), \quad (3.13)$$

where $\beta''_{crit}(a^*) = \frac{b}{kc^2\gamma^2}(duc + kb\beta(a^*))$. Thus, we can conclude that the singular point a^* is a continuously stable strategy when the trade-off function $\beta(a)$ is all concave down (concave) or locally concave down at this point. Otherwise, there could be two possibilities: if the critical function is less concave down than the trade-off function at a^* , it

is an evolutionary branching point; or it is a repeller.

An example.

We assume that the trade-off function is a power function [8]:

$$\beta(a) = ma^n, \quad n = 1, 2, \dots$$

where m is an arbitrary positive constant. Evolutionary singular strategies are the solu-

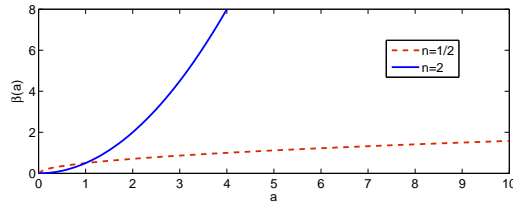


Figure 3.9: **Specific function.** Where $m = 0.5$.

tions of the following equation:

$$\left. \frac{\partial W}{\partial \tilde{a}} \right|_{\tilde{a}=a} = mna^{n-1} \frac{\gamma kcu}{duc + kmba^n} - u = 0,$$

which can be transformed to:

$$kbm \cdot a^n - mn\gamma ck \cdot a^{n-1} + duc = 0. \quad (3.14)$$

Since the existence of the solutions of the equation (3.14) is too complicated to discuss when $n \geq 5$, a positive solution a^* is assumed to exist under some special conditions. Let us study evolutionary and convergence stability of such a strategy.

Consider the two conditions as below:

$$\begin{aligned} \frac{d}{da} \left(\left. \frac{\partial W}{\partial \tilde{a}} \right|_{\tilde{a}=a} \right) \Big|_{a=a^*} &= mn(n-1)(a^*)^{n-2} \frac{ckuy}{duc+kmb(a^*)^n} - (mn(a^*)^{n-1})^2 \frac{bck^2uy}{(duc+kmb(a^*)^n)^2}, \\ &= \frac{ckuymn(a^*)^{n-2}}{(duc+kmb(a^*)^n)^2} [(n-1)duc - kmb(a^*)^n] \end{aligned} \quad (3.15)$$

and

$$\left. \frac{\partial^2 W}{\partial \tilde{a}^2} \right|_{\tilde{a}=a^*} = mn(n-1)(a^*)^{n-2} \frac{cku\gamma}{duc + kmb(a^*)^n}. \quad (3.16)$$

The expressions (3.15) and (3.16) show that the singular point a^* is a continuously stable strategy if $n < 1$. When $n \geq 1$, the sign of the function (3.15) depends on the quantity of $(n-1)duc - kmb(a^*)^n$. Because of $kmb(a^*)^n = mnck\gamma(a^*)^{n-1} - duc$, the value of the function $nduc - mck\gamma(a^*)^{n-1}$ can also decide the sign of the function (3.15).

In the sequel, we choose two values for n to demonstrate our results.

For $n = \frac{1}{2}$, the equation (3.14) is rewritten as

$$kmb \cdot a^{\frac{1}{2}} - \frac{1}{2}myck \cdot a^{-\frac{1}{2}} + duc = 0.$$

This equation has a unique positive solution for a :

$$a^* = \left[\frac{-duc + \sqrt{(duc)^2 + 2myckkmb}}{2kmb} \right]^2.$$

Substituting this a^* into (3.15) and (3.16), the singular point a^* can be proved to be a continuously stable strategy (see the Figure 3.10).

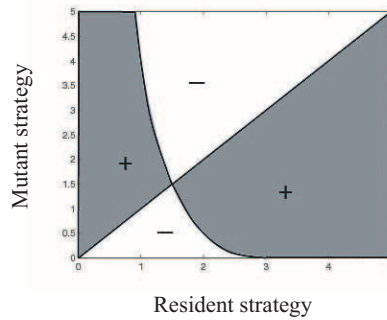


Figure 3.10: A pairwise invasion plot when $n = \frac{1}{2}$. Based on our theories, a^* is a continuously stable strategy.

When $n = 2$, the equation (3.14) takes the form:

$$k b m \cdot a^2 - 2 m \gamma c k \cdot a + d u c = 0,$$

which has two positive roots:

$$a_1^* = \frac{m n c k \gamma + \sqrt{(m c k \gamma)^2 - k m b d u c}}{k b m},$$

and

$$a_2^* = \frac{m n c k \gamma - \sqrt{(m c k \gamma)^2 - k m b d u c}}{k b m},$$

when $m \geq \frac{d u b}{c k \gamma}$.

In this case, neither root can be evolutionary stable. After putting a_i^* , $i = 1, 2$, into the condition (3.15), respectively, we demonstrate that the root a_1^* is convergence stable, but the other root a_2^* is not. Therefore, the singular point a_1^* is an evolutionary branching point (see the Figure 3.11a) and the point a_2^* is a repellor (see the Figure 3.11b).

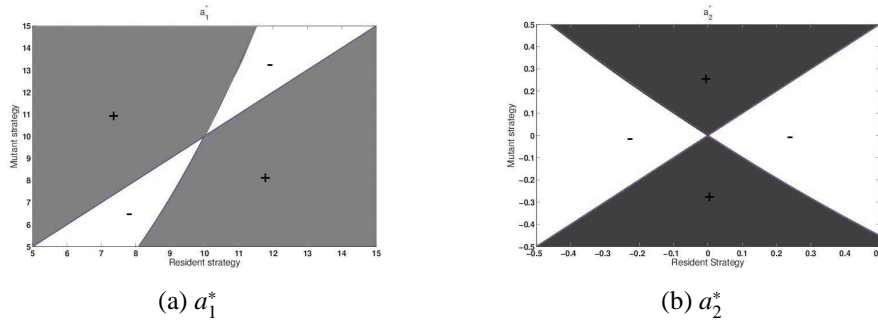


Figure 3.11: **Two pairwise invasion plots when $n = 2$.** (a). We find that there is a "+" above the diagonal on the left and below the diagonal on the right of a_1^* . Also, a vertical line through a_1^* lies entirely within a region marked "+". a_1^* is an evolutionary branching point. (b). A vertical line through a_2^* lies entirely within a region marked "+", so it is a repellor.

3.5 Conclusion and discussion

In this chapter, viral evolution was studied from two types of trade-offs: one is between viral production rate and virulence; the other is between virulence and transmission rate. We chose the critical value of the local stability of the mutant free equilibrium, which was obtained from a within-host model with CTL response, as the fitness to measure the invasion of mutant strain viruses. Then, the effects of the two trade-off functions were discussed through the fitness, respectively. According to the adaptive dynamical approach, evolutionary singular strategies were found from the equations when the gradients of fitness is set to zero. To explore their evolutionary and convergent stability, the geometrical properties of the two trade-off functions were studied by comparing corresponding critical functions at evolutionary singular points, respectively.

In the first trade-off, viruses choose their production rate as the evolutionary strategy. With the effect of CTL response, the existence of the evolutionary branching was demonstrated in a large portion of the parameter space, where the local concavity of the trade-off is more than $\frac{1}{u}$ times that of the critical functions. This result does illustrate the diversity of virus strains. Too concave up (convex) trade-off results in an evolutionary stable strategy, whereas too concave down (concave) trade-off results in a repellor.

For the second trade-off, the viral evolutionary strategy was represented by the viral virulence, i.e., the death rate of infected cells. The CTL response still played a significant role in viral evolution through shaping the trade-off. In this case, too concave down (concave) trade-off results in an evolutionary stable strategy; otherwise it is a repellor. We excluded the existence of the evolutionary branching in the examples. Therefore, neither a too high nor too low degree of virulence would be favored by the virus evolution. Due to the choice of our simple functions in the examples, the existence of evolutionary branching was not observed. However, in a between-host model

with superinfection [6], the authors utilize the logistic growth and a specific trade-off function.

We point out that our model can be improved many ways. For example, instead of the bilinear function, the Holling Type II function can be utilized to describe immune response. Meanwhile, the relationship between viral production rate and disease transmission rate can be researched as a new trade-off in a nested model. According to the paper [9], higher rate of production implies higher clearance rate. Thus, the trade-off between viral production rate and its corresponding clearance is also an interesting topic for us. Furthermore, the impact caused by the cost of body immune response should be taken into account when considering the host-virus co-evolution.

Bibliography

- [1] Alizon, S. (2008). Transmission-recovery trade-offs to study parasite evolution. *The American Naturalist*, 172(3):E113–E121.
- [2] Anderson, R. M. and May, R. M. (1979). Population biology of infectious diseases: Part I. *Nature*, 280(5721):361.
- [3] Ball, C. L., Gilchrist, M. A., and Coombs, D. (2007). Modeling within-host evolution of HIV: mutation, competition and strain replacement. *Bulletin of mathematical biology*, 69(7):2361–2385.
- [4] Bocharov, G., Ludewig, B., Bertolotti, A., Klenerman, P., Junt, T., P. Krebs, T. L., Fraser, C., and Anderson, R. M. (2004). Underwhelming the immune response: effect of slow virus growth on CD8⁺-T-lymphocyte responses. *Journal of virology*, 78(5):2247–2254.
- [5] Boer, R. J. D. and Perelson, A. S. (1998). Target cell limited and immune control

- models of HIV infection: a comparison. *Journal of Theoretical Biology*, 190(3):201–214.
- [6] Boldin, B., Geritz, S. A. H., and Kisdi, E. (2009). Superinfections and adaptive dynamics of pathogen virulence revisited: a critical function analysis. *Evolutionary Ecology Research*, 11(2):153–175.
- [7] Coombs, D., Gilchrist, M. A., Percus, J., and Perelson, A. S. (2003). Optimal viral production. *Bulletin of mathematical biology*, 65(6):1003–1023.
- [8] Day, T. and Burns, J. G. (2003). A consideration of patterns of virulence arising from host-parasite coevolution. *Evolution*, 57(3):671–676.
- [9] De Paepe, M. and Taddei, F. (2006). Viruses' life history: towards a mechanistic basis of a trade-off between survival and reproduction among phages. *PLoS biology*, 4(7):e193.
- [10] Geritz, S. A. H., Mesze, G., and Metz, J. A. J. (1997a). Evolutionarily singular strategies and the adaptive growth and branching of the evolutionary tree. *Evolutionary ecology*, 12(1):35–57.
- [11] Geritz, S. A. H., Metz, J. A. J., Kisdi, É., and Meszéna, G. (1997b). Dynamics of adaptation and evolutionary branching. *Physical Review Letters*, 78(10):2024–2027.
- [12] Gilchrist, M. A., Coombs, D., and Perelson, A. S. (2004). Optimizing within-host viral fitness: infected cell lifespan and virion production rate. *Journal of theoretical biology*, 229(2):281–288.
- [13] Gustin, K. E. and Sarnow, P. (2001). Effects of poliovirus infection on nucleocytoplasmic trafficking and nuclear pore complex composition. *Science Signaling*, 20(1):240.

- [14] Huang, G., Yokoi, H., Takeuchi, Y., Kajiwara, T., and Sasaki, T. (2011). Impact of intracellular delay, immune activation delay and nonlinear incidence on viral dynamics. *Japan Journal of Industrial and Applied Mathematics*, 28(3):383–411.
- [15] Lenardo, M. J., Angleman, S. B., Bounkeua, V., Dimas, J., Duvall, M. G., Graubard, M. B., Hornung, F., Selkirk, M. C., Speirs, C. K., and Trageser, C. (2002). Cytopathic killing of peripheral blood CD4⁺ T lymphocytes by human immunodeficiency virus type 1 appears necrotic rather than apoptotic and does not require env. *Journal of virology*, 76(10):5082–5093.
- [16] Liu, W. M. (1997). Nonlinear oscillations in models of immune responses to persistent viruses. *Theoretical population biology*, 52(3):224–230.
- [17] May, R. M. and Anderson, R. M. (1991). Infectious diseases of humans: dynamics and control.
- [18] Milstein, O., Hagin, D., Lask, A., Reich-Zeliger, S., Shezen, E., Ophir, E., Eidelstein, Y., Afik, R., Antebi, Y. E., and Dustin, M. L. (2011). Ctls respond with activation and granule secretion when serving as targets for t-cell recognition. *Blood*, 117(3):1042–1052.
- [19] Nowak, M. A. and Bangham, C. R. M. (1996). Population dynamics of immune responses to persistent viruses. *Proc. Natl. Acad. Sci. USA*, 85:3509.
- [20] Perelson, A. S. (2002). Modelling viral and immune system dynamics. *Nature Reviews Immunology*, 2(1):28–36.
- [21] Schneider, R. J. and Shenk, T. (1987). Impact of virus infection on host cell protein synthesis. *Annual review of biochemistry*, 56(1):317–332.
- [22] Wodarz, D. and Nowak, M. A. (2000). Immune responses and viral phenotype:

do replication rate and cytopathogenicity influence virus load? *Computational and Mathematical Methods in Medicine*, 2(2):113–127.

Chapter 4

The effects of superinfection and cost of immunity on host-parasite co-evolution

4.1 Introduction

It is well known that the relationship between hosts and parasites is extremely convoluted [5, 14]. 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 [4]. Although parasites harm hosts and possibly cause death, 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 detailed understanding of the co-evolutionary adaptation between parasite "attack

strategy” and host ”defence strategy” (i.e. immunological response), may result in the development of novel medications and vaccines and thus help save human lives [24].

In this chapter, we are interested in the effect of superinfection and the cost caused by immune response on this co-evolution. Complex immune systems are developed in vertebrate animals that can target parasites through contact with body fluids. Hosts are protected from infection with layered defenses of increasing specificity by their immune systems. So, the benefits of such defences to a host are obvious. However, according to the argument in the paper [18], 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 [8] provided an epidemiologic model:

$$\begin{cases} \frac{dS_1}{dt} = b_s S_1 + b_I(c)I_1 - \mu S_1 + cI_1 - \beta S_1 I_1 - \beta S_1 I_2, \\ \frac{dI_1}{dt} = \beta S_1 I_1 + \beta S_1 I_2 - (u + \nu + c)I_1, \\ \frac{dS_2}{dt} = b_s S_2 + b_I(\hat{c})I_2 - \mu S_2 + cI_1 - \beta S_2 I_1 - \beta S_2 I_2, \\ \frac{dI_2}{dt} = \beta S_2 I_1 + \beta S_2 I_2 - (u + \nu + \hat{c})I_2, \end{cases} \quad (4.1)$$

where the degree of immunological up-regulation is represented by c (\hat{c}), the infection clearance rate of a resident (mutant) host. 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 our real world. Hosts are always attacked by many different parasites simultaneously. So, multiple defence mechanisms would also evolve to recognize and neutralize these pathogens [1]. Thus, the infection can not be so simple as demonstrated by the above mathematical model. The influence of

parasites competition on host evolution attracts our attention. We develop an epidemiological model with superinfection. Superinfection represents an intermediate level of complexity in the sense that a more virulent parasite of infection 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 one time [3, 21, 22, 2]. We utilize this 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 chapter is organized as follows. In Section 4.2, we introduce mutant hosts to a basic superinfection model and explore their invasion in two cases, monomorphic case and dimorphic case. In Section 4.3, we discuss two possible infections of mutant hosts, one is by parasite 1; the other is by parasite 2. The local stabilities of their corresponding equilibria are analyzed to obtain fitness. We study the evolutionary and convergence stabilities of evolutionary singular strategies through utilizing the adaptive dynamical approaches [13, 11, 23] in two cases, respectively. We also focus on how the convexities of two trade-offs affect the evolutionary and convergence stabilities. In Section 4.4, a dimorphic case is studied. We define a new fitness to measure the invasion of mutant hosts with parasite 1 and 2, and obtain the conditions for evolutionary stability. Two trade-offs are specified by two simple quadratic functions to explore the conditions for isoclinic stability and absolute convergence stability. We show some numerical conclusions, 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 4.5, 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.

4.2 A two-parasite 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 i is denoted by I_i , where $i = 1, 2$.

The 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 parasites 1 are assumed to have stronger virulence than parasites 2. So, individuals infected by type 2 parasite can be re-infected (superinfection) by contacting the type 1 parasites and enter the I_1 class with rate φ . With these assumptions, the model takes the form:

$$\begin{cases} \frac{dS}{dt} = bS + f(c_1)I_1 + g(c_2)I_2 + c_1I_1 + c_2I_2 - \mu S - \beta S(I_1 + I_2), \\ \frac{dI_1}{dt} = \beta S I_1 - (\mu + \delta + c_1)I_1 + \beta\varphi I_2 I_1, \\ \frac{dI_2}{dt} = \beta S I_2 - (\mu + \delta + c_2)I_2 - \beta\varphi I_2 I_1. \end{cases} \quad (4.2)$$

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 (4.1) in which S either grow or decay exponentially. As in (4.1), (4.2) 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 1 only:

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

Similarly, when $b > \mu$ and $\mu + \delta > g(c_2)$, the model (4.2) has another equilibrium with infection by parasite 2 only:

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

Now, we explore the possibility of coexistence equilibrium \hat{E} . Directly solving for this equilibrium with non-zero components give:

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

By the formulas for \hat{S} , \hat{I}_1 and \hat{I}_2 , we know that

- if

$$c_1 - c_2 > 0, \quad b > \mu \tag{4.3}$$

and

$$g(c_2) - f(c_1) > \max\{c_1 - c_2, \varphi(b - \mu)\} > 0, \tag{4.4}$$

\hat{S} is positive;

- if

$$f(c_1)(c_1 - c_2) + \varphi(b - \mu)c_1 < [(c_1 - c_2) + \varphi(\mu - b)](\mu + \delta), \tag{4.5}$$

\hat{I}_1 is positive;

- if

$$g(c_2)(c_1 - c_2) + \varphi(b - \mu)c_2 > [(c_1 - c_2) + \varphi(\mu - b)](\mu + \delta), \quad (4.6)$$

\hat{I}_2 is positive.

In appendix C.1, we show that the coexistence equilibrium $\hat{\mathbf{E}}$ is locally asymptotic stable if the conditions (4.3)-(4.6) and

$$\frac{c_1 - c_2}{\varphi} - (b - \mu) > 0 \quad (4.7)$$

hold.

As illustrated in Day [6, 7], the condition $c_1 > c_2$ reflects that the virulence of parasite 1 is stronger than that of parasite 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, so we assume that the mutant hosts emerge because of 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 types of parasites; and (ii) the mutant hosts can be infected by both two types parasites.

4.3 Monomorphic cases

According to the paper by Gandon et al [10], mutant hosts may obtain some new characters which can help them 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, the infected mutant hosts are assumed not to infect resident hosts.

4.3.1 Mutant hosts with the parasite 1

At first, we study the case that only parasites 1 can infect mutant hosts. As a natural extension of model (4.1) and (4.2), our new model with the above scenario incorporated is given by the following system of differential equations:

$$\left\{ \begin{array}{l} \frac{dS_1}{dt} = bS_1 + f(c_1)I_{11} + g(c_2)I_{12} + c_1I_{11} + c_2I_{12} - \mu S_1 - \beta S_1(I_{11} + I_{12} + I_{21}), \\ \frac{dI_{11}}{dt} = \beta S_1(I_{11} + I_{21}) - (\mu + \delta + c_1)I_{11} + \beta\varphi I_{12}I_{11}, \\ \frac{dI_{12}}{dt} = \beta S_1I_{12} - (\mu + \delta + c_2)I_{12} - \beta\varphi I_{12}I_{11}, \\ \frac{dS_2}{dt} = bS_2 + f(c_{1h})I_{21} + c_{1h}I_{21} - \beta S_2(I_{21} + I_{11}) - \mu S_2, \\ \frac{dI_{21}}{dt} = \beta S_2(I_{11} + I_{21}) - (\mu + \delta + c_{1h})I_{21}, \end{array} \right. \quad (4.8)$$

where the meanings of the variables and parameters are in Table 4.1.

Notation	Meaning
S_1	Abundance of susceptible residents
S_2	Abundance of susceptible mutants
I_{11}	Abundance of residents infected by the parasites 1
I_{12}	Abundance of residents infected by the parasites 2
I_{21}	Abundance of mutants infected by the parasites 1
I_{22}	Abundance of mutants infected by the parasites 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 1
c_2 (c_{2h})	Recovery rate of a resident (or mutant) host infected by parasite 2

Table 4.1: Descriptions of the variables and parameters in section 4.3.

To explore the survivability of such a mutant host that can only be infected by strain 1 parasite, firstly we need to define its fitness. To this end, we consider the stability of

the equilibrium of mutant hosts free for this system (4.8):

$$\begin{aligned}\tilde{\mathbf{E}} &= (\tilde{S}_1, \tilde{I}_{11}, \tilde{I}_{12}, \tilde{S}_2, \tilde{I}_{21}) \\ &= \left(\frac{(\mu+\delta)(c_1-c_2+f(c_1)-g(c_2))+c_2f(c_1)-c_1g(c_2)}{\beta[\varphi(b-\mu)+f(c_1)-g(c_2)]}, \frac{\beta\tilde{S}_1-(\mu+\delta+c_2)}{\beta\varphi}, \frac{(\mu+\delta+c_1)-\beta\tilde{S}_1}{\beta\varphi}, 0, 0 \right).\end{aligned}$$

Based on the criteria for the local stability of $\tilde{\mathbf{E}}$, the fitness of the mutant hosts that can be infected by parasite 1 is defined as:

$$\begin{aligned}\mathbf{F}(c_{1h}, c_1, c_2) &= (b - \mu)(\mu + \delta + c_{1h}) + \frac{f(c_{1h}) - \mu - \delta}{\varphi(b - \mu) + f(c_1) - g(c_2)} \left[\frac{1}{\varphi}(c_1 - c_2)(\mu + \delta - g(c_2)) \right. \\ &\quad \left. - (b - \mu)(\mu + \delta + c_2) \right]\end{aligned}\tag{4.9}$$

(see detail in Appendix C.2).

Since the parasite 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. Due to the immunological up-regulation would decrease the fecundity of hosts, \bar{g} should be less than b . So, the fitness (4.9) can be simplified to

$$\begin{aligned}\mathbf{F}(c_{1h}, c_1) &= (b - \mu)(\mu + \delta + c_{1h}) + \frac{f(c_{1h}) - \mu - \delta}{\varphi(b - \mu) + f(c_1) - \bar{g}} \left[\frac{1}{\varphi}(c_1 - c_2)(\mu + \delta - \bar{g}) \right. \\ &\quad \left. - (b - \mu)(\mu + \delta + c_2) \right]\end{aligned}\tag{4.10}$$

In the following, we utilize the adaptive dynamical methods [12] to examine whether this fitness functions can be optimized.

At first, we need to find singular points, i.e. the solutions when the fitness gradient

$$\begin{aligned}&\left[\frac{\partial \mathbf{F}(c_{1h}, c_1)}{\partial c_{1h}} \right] \Big|_{c_{1h}=c_1} \\ &= b - \mu + \frac{f'(c_1)}{\varphi(b - \mu) + f(c_1) - \bar{g}} \left[\frac{1}{\varphi}(c_1 - c_2)(\mu + \delta - \bar{g}) - (b - \mu)(\mu + \delta + c_2) \right],\end{aligned}\tag{4.11}$$

is equals to zero. Assume that c_1^* is a positive solution of (4.11), that is, c_1^* is a singular

point. It follows from (4.11) that

$$f'(c_1^*) = \frac{(\mu - b)[\varphi(b - \mu) + f(c_1^*) - \bar{g}]}{\frac{1}{\varphi}(c_1^* - c_2)(\mu + \delta - \bar{g}) - (b - \mu)(\mu + \delta + c_2)}. \quad (4.12)$$

Associating with (4.12) is the following ordinary differential equation

$$f'(c_1) = \frac{(\mu - b)[\varphi(b - \mu) + f(c_1) - \bar{g}]}{\frac{1}{\varphi}(c_1 - c_2)(\mu + \delta - \bar{g}) - (b - \mu)(\mu + \delta + c_2)}. \quad (4.13)$$

A solutions of which 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 be the slope of $f_{crit}(c_1)$ at c_1^* . Then, the critical function $f_{crit}(c_1)$ can help us better know the trade-off $f(c_1)$.

Evolutionary stability analysis

Now, we study the evolutionary stability of this singular point c_1^* . Following the adaptive dynamical approach [12], its evolutionary stability can be decided by the sign of

$$\mathcal{E}_1 = \left. \frac{\partial^2 \mathbf{F}(c_{1h}, c_1)}{\partial c_{1h}^2} \right|_{c_{1h}=c_1=c_1^*} = \tilde{\mathbf{F}}_2 f''(c_1^*), \quad (4.14)$$

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 the equation (4.12), the formula of $\tilde{\mathbf{F}}_2$ can be rewritten as

$$\tilde{\mathbf{F}}_2 = \frac{\mu - b}{f'(c_1^*)}. \quad (4.15)$$

Because of the conditions (4.3) and (4.5), it is easy to show that $\tilde{\mathbf{F}}_2$ is positive. 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.

Convergence stability analysis

Firstly, let us calculate the cross-derivative \mathcal{M}_1 of the fitness \mathbf{F} :

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

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

$$\begin{aligned} \left. \frac{d}{dc_1} \left(\left. \frac{\partial \mathbf{F}(c_{1h}, c_1)}{\partial c_1} \right|_{c_{1h}=c_1} \right) \right|_{c_1=c_1^*} &= \mathcal{E}_1 + \mathcal{M}_1 \\ &= \tilde{\mathbf{F}}_2 f''(c_1^*) + \tilde{\mathbf{F}}_{12} [f'(c_1^*)]^2 + \tilde{\mathbf{F}}_{11} f'(c_1^*). \end{aligned} \quad (4.16)$$

Noticing that

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

the right hand side of (4.16) can actually be expressed as

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

Therefore, if

$$f''(c_1^*) < f''_{crit}(c_1^*), \quad (4.17)$$

then $\mathcal{E}_1 + \mathcal{M}_1 < 0$. Thus, according to the conclusion of [13], 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^* . It means that c_1 would evolve to 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 a repellor. If the trade-off is not locally concave down at c_1^* but (4.17) 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 (4.17) is violated, the problem will be so complicated that we will not discuss here.

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:

$$f(c_1) = b - k_1 c_1^2, \quad (4.18)$$

where $k_1 > 0$, see (4.1) for its graph for $c_1 > 0$.

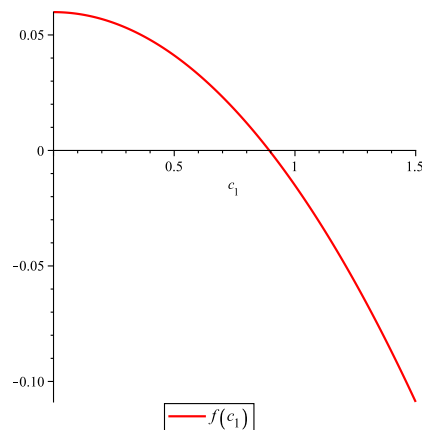


Figure 4.1: **Trade off 1:** where $b = 0.059883$, $k_1 = 0.075$. $f(c_1)$ is a concave down function.

Substitute the expression of $f(c_1)$ into the fitness function (4.10):

$$\begin{aligned} \mathbf{F}(c_{1h}, c_1) = & (b - \mu)(\mu + \delta + c_{1h}) + \frac{b - k_1 c_{1h}^2 - \mu - \delta}{\varphi(b - \mu) + b - k_1 c_1^2 - \bar{g}} \left[\frac{1}{\varphi} (c_1 - c_2)(\mu + \delta - \bar{g}) \right. \\ & \left. - (b - \mu)(\mu + \delta + c_2) \right]. \end{aligned}$$

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:

$$b - \mu - \frac{2k_1 c_1}{\varphi(b - \mu) + b - k_1 c_1^2 - \bar{g}} \left[\frac{1}{\varphi} (c_1 - c_2)(\mu + \delta - \bar{g}) - (b - \mu)(\mu + \delta + c_2) \right] = 0, \quad (4.19)$$

Equation (4.19) can be simplified into a quadratic equation:

$$a_{12} c_1^2 + a_{11} c_1 + a_{10} = 0, \quad (4.20)$$

where

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

Note that

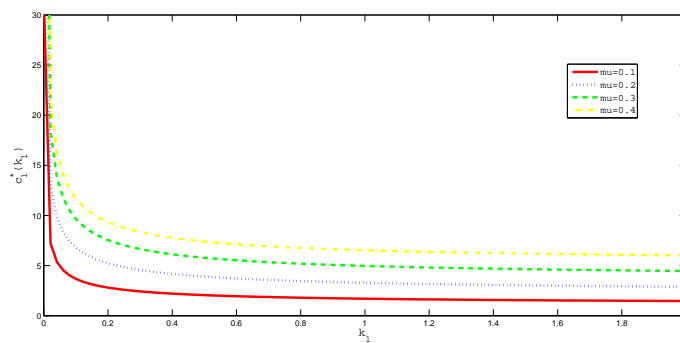
$$\begin{aligned} \Delta_1 := & 4k_1^2 \left[\frac{c_2}{\varphi} (\mu + \delta - \bar{g}) + (b - \mu)(\mu + \delta + c_2) \right]^2 \\ & + 4k_1 \left[(b - \mu) + \frac{2}{\varphi} (\mu + \delta - \bar{g}) \right] [\varphi(b - \mu) + (b - \bar{g})](b - \mu). \end{aligned}$$

Thus, if $0 < \bar{g} < \min\{b, \frac{\varphi}{2}(b - \mu) + (\mu + \delta)\}$, then $a_{12} > 0$, $a_{11} < 0$, $a_{10} < 0$ and $\Delta_1 > 0$,

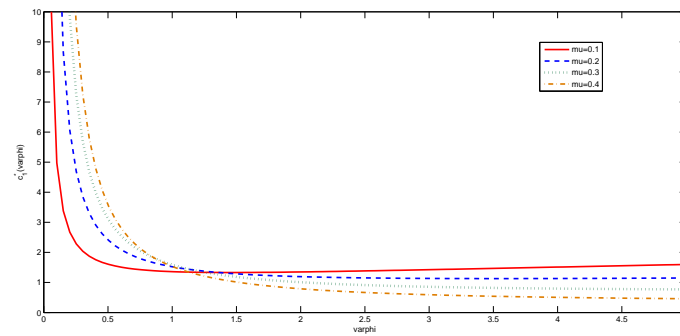
and consequently, (4.20) has a unique positive root which is given by

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

In this situation, the impact of the cost of immunological up-regulation k_1 and the superinfection rate φ on c_1^* can be reflected by the above formula. For example, fixing φ or k_1 at some value, Figure 4.2 gives some plots of c_1^* as function of k_1 or φ . Therefore,



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



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

Figure 4.2: **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 $c_2^*(k_2)$ 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).

it is straightforward to observe that the value of c_1^* keeps decreasing until reaches a certain value when the variable is increasing in the Figures 4.2a and 4.2b respectively. In Figure 4.2a, the curve is moving up as the mortality of infected hosts increasing. When the level of superinfection maintains in some value, this is significant. The evolutionary increases in the degree of up-regulation in host will be thereby selected by evolutionary increases in μ by parasite. However, it would become more complicated when the level of superinfection is also changing.

If $(b - \mu) + \frac{2}{\varphi}(\mu + \delta - \bar{g}) = 0$, i.e. $a_{12} = 0$, then (4.20) has no positive root because $a_{11} < 0$ and $a_{10} < 0$.

If $b > \bar{g} > \frac{\varphi}{2}(b - \mu) + (\mu + \delta)$, then $h(c_1) = a_{12}c_1^2 + a_{11}c_1 + a_{10}$ is concave down because of $a_{12} < 0$. Taking Δ_1 as a function of \bar{g} , i.e. $\Delta_1(\bar{g})$, we can find that its quadratic coefficient is positive. Meanwhile, straightforward verifications show that

$$\Delta_1(0) > 0, \Delta_1'(0) < 0; \quad \Delta_1\left(\frac{\varphi}{2}(b - \mu) + (\mu + \delta)\right) > 0, \Delta_1'\left(\frac{\varphi}{2}(b - \mu) + (\mu + \delta)\right) < 0,$$

and

$$\Delta_1\left((\mu + \delta) + \frac{\varphi}{c_2}(b - \mu)(\mu + \delta - c_2)\right) < 0. \quad (4.21)$$

According to the properties of quadratic function, we can infer that

$$(\mu + \delta) + \frac{\varphi}{c_2}(b - \mu)(\mu + \delta - c_2) > \frac{\varphi}{2}(b - \mu) + (\mu + \delta) > 0. \quad (4.22)$$

There could not have a positive root when $\bar{g} \leq (\mu + \delta) + \frac{\varphi}{c_2}(b - \mu)(\mu + \delta - c_2)$, i.e. $a_{11} \leq 0$.

If $b > \bar{g} > (\mu + \delta) + \frac{\varphi}{c_2}(b - \mu)(\mu + \delta - c_2)$, we can have $a_{11} > 0$ and $a_{12} < 0$ due to (4.22). Through calculation, we obtain $\Delta_1'(b) > 0$. So,

1. if $\Delta_1(b) < 0$, there is no real root;
2. if $\Delta_1(b) = 0$, there is no real root either;

3. if $\Delta_1(b) > 0$, there are three possible situations:

(1) when $\Delta_1(\bar{g}) < 0$, we cannot have any positive roots;

(2) when $\Delta_1(\bar{g}) = 0$, we can only have a positive root

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

(3) when $\Delta_1(\bar{g}) > 0$, we can have two positive roots c_1^* and

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

Since the existence conditions are extremely complicated, it is not easy to find a set of values of parameters to meet all of them for us. Thus, we only show above theoretical conclusions.

4.3.2 Mutant hosts with the parasite 2

Now, we study the case that only parasites 2 can infect mutant hosts. With this assumption, the model building on (4.1) and (4.2) is given by the following system of ordinary differential equations:

$$\begin{cases} \frac{dS_1}{dt} = bS_1 + f(c_1)I_{11} + g(c_2)I_{12} + c_1I_{11} + c_2I_{12} - \mu S_1 - \beta S_1(I_{11} + I_{12} + I_{22}), \\ \frac{dI_{11}}{dt} = \beta S_1 I_{11} - (\mu + \delta + c_1)I_{11} + \beta \varphi I_{12} I_{11}, \\ \frac{dI_{12}}{dt} = \beta S_1 (I_{12} + I_{22}) - (\mu + \delta + c_2)I_{12} - \beta \varphi I_{12} I_{11}, \\ \frac{dS_2}{dt} = bS_2 + g(c_{2h})I_{22} + c_{2h}I_{22} - \beta S_2 (I_{22} + I_{12}) - \mu S_2, \\ \frac{dI_{22}}{dt} = \beta S_2 (I_{12} + I_{22}) - (\mu + \delta + c_{2h})I_{22}, \end{cases} \quad (4.23)$$

where the meanings of the variables and parameters are explained in Table 4.1.

Since the parasite 1 has no effect on mutant hosts in this case, we take c_1 as a

positive constant. Denote $f(c_1) = \bar{f}$, where \bar{f} is a positive constant. Due to that fact that the immunological up-regulation would decrease the fecundity of hosts, $\bar{f} < b$ will be assumed in the sequel.

By similar consideration to that in Section 4.3.1, we can obtain the fitness of mutant hosts with parasite 2:

$$\begin{aligned} \mathbf{G}(c_{2h}, c_2) &= (b - \mu)(\mu + \delta + c_{2h}) + \frac{g(c_{2h}) - \mu - \delta}{\varphi(b - \mu) + \bar{f} - g(c_2)} \left[\frac{1}{\varphi}(c_1 - c_2)(\bar{f} - \mu - \delta) \right. \\ &\quad \left. + (b - \mu)(\mu + \delta + c_1) \right]. \end{aligned} \quad (4.24)$$

The gradient of fitness is

$$\begin{aligned} &\left[\frac{\partial \mathbf{G}(c_{2h}, c_2)}{\partial c_{2h}} \right] \Big|_{c_{2h}=c_2} \\ &= b - \mu + \frac{g'(c_2)}{\varphi(b - \mu) + \bar{f} - g(c_2)} \left[\frac{1}{\varphi}(c_1 - c_2)(\bar{f} - \mu - \delta) + (b - \mu)(\mu + \delta + c_1) \right]. \end{aligned} \quad (4.25)$$

The evolutionary singular points are then determined by setting the gradient to zero and solving the resulting equation for c_2 . We assume that c_2^* is such a positive singular point. From (4.25), we then have

$$g'(c_2^*) = \frac{(\mu - b)[\varphi(b - \mu) + \bar{f} - g(c_2^*)]}{\frac{1}{\varphi}(c_1 - c_2^*)(\bar{f} - \mu - \delta) + (b - \mu)(\mu + \delta + c_1)}. \quad (4.26)$$

Associated to (4.26) is the following ordinary differential equation

$$g'(c_2) = \frac{(\mu - b)[\varphi(b - \mu) + \bar{f} - g(c_2)]}{\frac{1}{\varphi}(c_1 - c_2)(\bar{f} - \mu - \delta) + (b - \mu)(\mu + \delta + c_1)}, \quad (4.27)$$

a solution of which is referred to as a critical function, and is denoted by $g_{crit}(c_2)$. Thus, the trade-off should a slope of the critical function $g_{crit}(c_2)$ at c_2^* . Then, the trade-off $g(c_2)$ can be studied through the critical function $g_{crit}(c_2)$.

Next, we discuss the evolutionary stability of the singular point c_2^* .

Evolutionary and convergence stabilities analysis

Let

$$\mathcal{E}_2 = \left. \frac{\partial^2 \mathbf{G}(c_{2h}, c_2)}{\partial c_{2h}^2} \right|_{c_{2h}=c_2=c_2^*} = \tilde{\mathbf{G}}_2 g''(c_2^*), \quad (4.28)$$

where

$$\begin{aligned} \tilde{\mathbf{G}}_2 &= \frac{\frac{1}{\varphi}(c_1^* - c_2^*)(\bar{f} - \mu - \delta) + (b - \mu)(\mu + \delta + c_1^*)}{\varphi(b - \mu) + \bar{f} - g(c_2^*)} \\ &= \frac{\mu - b}{g'(c_2^*)}. \end{aligned}$$

Due to the condition (4.3), $\tilde{\mathbf{G}}_2$ is positive. Thus, the sign of $g''(c_2^*)$ fully determines the signs of \mathcal{E}_2 . If $g''(c_2^*) < 0$, i.e. $g(\cdot)$ is locally concave down at c_2^* , \mathcal{E}_2 is negative, then c_2^* is an evolutionary stable strategy.

For the convergence stability of c_2^* , we need to consider

$$\begin{aligned} \left. \frac{d}{dc_2} \left(\left. \frac{\partial \mathbf{G}(c_{2h}, c_2)}{\partial c_1} \right|_{c_{2h}=c_2} \right) \right|_{c_2=c_2^*} &= \mathcal{E}_2 + \mathcal{M}_2 \\ &= \tilde{\mathbf{G}}_2 g''(c_2^*) + \tilde{\mathbf{G}}_{12} [g'(c_2^*)]^2 + \tilde{\mathbf{G}}_{11} g'(c_2^*) \\ &= \tilde{\mathbf{G}}_2 [g''(c_2^*) - g''_{crit}(c_2^*)]. \end{aligned} \quad (4.29)$$

Therefore, if $g''(c_2^*) < g''_{crit}(c_2^*)$, c_2^* is a convergence stable strategy if the trade-off $g(c_2)$ is more concave down than the critical function $g_{crit}(c_2)$ at the singular point c_2^* . It means that c_2 would evolve to c_2^* from its neighbourhood in this case.

Actually, both monomorphic cases are based on a assumption that one parasite can evolve but the other can not. This is a very ideal assumption. Definitely, we can explore the host-parasite co-evolution when mutant hosts can be either infected by parasite 1 or by parasite 2 which both evolve. The corresponding analysis can be implemented similarly as the case in [23]. Thus, a pair of singular point is a solution, at which both fitness gradients vanish. The discussion about its evolutionary and convergence stability could be our future project. Alternatively, we will study the case that mutant hosts can be infected by both parasite 1 and 2 in next section.

4.4 Dimorphic case

In this section, we assume that both parasites can infect mutant hosts *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 (4.1) and (4.2):

$$\left\{ \begin{array}{l} \frac{dS_1}{dt} = bS_1 + f(c_1)I_{11} + g(c_2)I_{12} + c_1I_{11} + c_2I_{12} - \mu S_1 - \beta S_1(I_{11} + I_{12} + I_{21} + I_{22}), \\ \frac{dI_{11}}{dt} = \beta S_1(I_{11} + I_{21}) - (\mu + \delta + c_1)I_{11} + \beta\varphi I_{12}I_{11}, \\ \frac{dI_{12}}{dt} = \beta S_1(I_{12} + I_{22}) - (\mu + \delta + c_2)I_{12} - \beta\varphi I_{12}I_{11}, \\ \frac{dS_2}{dt} = bS_2 + f(c_{1h})I_{21} + g(c_{2h})I_{22} + c_{1h}I_{21} + c_{2h}I_{22} - \beta S_2(I_{21} + I_{11} + I_{12} + I_{22}) - \mu S_2, \\ \frac{dI_{21}}{dt} = \beta S_2(I_{11} + I_{21}) - (\mu + \delta + c_{1h})I_{21}, \\ \frac{dI_{22}}{dt} = \beta S_2(I_{12} + I_{22}) - (\mu + \delta + c_{2h})I_{22}, \end{array} \right. \quad (4.30)$$

where the meanings of the variables and parameters are in Table 4.1. Trade-offs $f(c_1)$ and $g(c_2)$ are still decreasing function.

The mutant host-free equilibrium of (4.30)

$$\begin{aligned} \mathbf{E}_3 &= (\tilde{S}_1^*, \tilde{I}_{11}^*, \tilde{I}_{12}^*, \tilde{S}_2^*, \tilde{I}_{21}^*, \tilde{I}_{22}^*) \\ &= \left(\frac{(\mu+\delta)(c_1-c_2+f(c_1)-g(c_2))+c_2f(c_1)-c_1g(c_2)}{\beta[\varphi(b-\mu)+f(c_1)-g(c_2)]}, \frac{\beta\tilde{S}_1^*-(\mu+\delta+c_2)}{\beta\varphi}, \frac{(\mu+\delta+c_1)-\beta\tilde{S}_1^*}{\beta\varphi}, 0, 0, 0 \right), \end{aligned}$$

exists under conditions (4.3)-(4.7). And the quantities of positive components are the same as before.

The local stability of this mutant host-free equilibrium \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 C.2. When the conditions (4.3)-(4.7) hold, the local stability of the equilibrium \mathbf{E}_3 will depend on the signs of the eigenvalues of the matrix \mathbf{J}_{22}^* . So, we only need to analyze the eigenvalues of \mathbf{J}_{22}^* .

Calculating the characteristic equation gives

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

Hence, the characteristic equation of \mathbf{J}_{22}^* is

$$A_0\lambda^3 + A_1\lambda^2 + A_2\lambda + A_3 = 0, \quad (4.31)$$

where

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

and

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

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

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

The necessary and sufficient conditions, under which all the roots of the polynomial (4.31) have negative real parts, are given by $\Delta_2 > 0$ and $\Delta_3 > 0$ according to the well-known Hurwitz criterion. So, the mutant host-free equilibrium \mathbf{E}_3 would lose its local stability so that the mutant hosts have a chance to invade resident hosts successfully if either $\Delta_2 > 0$ or $\Delta_3 > 0$ is violated. Moreover, the sign change of $\Delta_2 = 0$ results in Hopf

bifurcation around \mathbf{E}_3 for system (4.30) while $A_3 > 0$ (see Theorem 2 in [25]). However, it is difficult for us to construct a fitness on the corresponding periodic solution of such a Hopf bifurcation. So, we have to exclude this case.

The above observation suggests that $-A_3$ is a reasonable measurement of the fitness for the mutant hosts with two parasites. This means that the mutant hosts can invade resident hosts successfully only if $-A_3 > 0$. As such, we choose the following fitness function $T(c_{1h}, c_{ch}, c_1, c_2)$:

$$\begin{aligned}
 & T(c_{1h}, c_{ch}, c_1, c_2) \\
 &= \frac{1}{\varphi}[(\mu + \delta + c_1) - \beta\tilde{S}](g(c_{2h}) + c_{2h})(\mu + \delta + c_{1h}) \\
 &\quad - [\frac{1}{\varphi}(c_1 - c_2) - (b - \mu)](\mu + \delta + c_{1h})(\mu + \delta + c_{2h}) \\
 &\quad + \frac{1}{\varphi}[\beta\tilde{S} - (\mu + \delta + c_2)](f(c_{1h}) + c_{1h})(\mu + \delta + c_{2h}).
 \end{aligned} \tag{4.32}$$

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

$$\begin{aligned}
 & \left[\frac{\partial T}{\partial c_{1h}} \right]_{(c_{1h}, c_{2h})=(c_1, c_2)} \\
 &= \frac{1}{\varphi}[(\mu + \delta + c_1) - \beta\tilde{S}(c_1, c_2)](g(c_2) + c_2) - [\frac{1}{\varphi}(c_1 - c_2) - (b - \mu)](\mu + \delta + c_2) \\
 &\quad + \frac{1}{\varphi}[\beta\tilde{S}(c_1, c_2) - (\mu + \delta + c_2)](f'(c_1) + 1)(\mu + \delta + c_2)
 \end{aligned} \tag{4.33}$$

and

$$\begin{aligned}
 & \left[\frac{\partial T}{\partial c_{2h}} \right]_{(c_1, c_{2h})=(c_1, c_2)} \\
 &= \frac{1}{\varphi}[(\mu + \delta + c_1) - \beta\tilde{S}(c_1, c_2)](g'(c_2) + 1)(\mu + \delta + c_1) \\
 &\quad - [\frac{1}{\varphi}(c_1 - c_2) - (b - \mu)](\mu + \delta + c_2) + \frac{1}{\varphi}[\beta\tilde{S}(c_1, c_2) - (\mu + \delta + c_2)](f(c_1) + c_1).
 \end{aligned} \tag{4.34}$$

The evolutionary singular points are determined by

$$\begin{aligned} \left[\frac{\partial \mathbf{T}}{\partial c_{1h}} \right] \Big|_{(c_{1h}, c_{2h})=(c_1, c_2)} &= 0, \\ \left[\frac{\partial \mathbf{T}}{\partial c_{2h}} \right] \Big|_{(c_{1h}, c_{2h})=(c_1, c_2)} &= 0. \end{aligned} \quad (4.35)$$

If $(\tilde{c}_1^*, \tilde{c}_2^*)$ is a solution of (4.35), $(\tilde{c}_1^*, f(\tilde{c}_1^*))$ and $(\tilde{c}_2^*, g(\tilde{c}_2^*))$ are called an evolutionarily singular species pair.

Although we can obtain the expressions of $f'(c_1)$ and $g'(c_2)$ by transforming the two equations of (4.35), the slopes $f'(c_1)$ and $g'(c_2)$ only give us partial information of $f(c_1)$ and $g(c_2)$ near \tilde{c}_1^* and \tilde{c}_2^* . Thus, the critical functions cannot be constructed in dimorphic case.

According to the paper of Kisdi [15], if this singular pair cannot be invaded by mutant hosts with either parasites, it is locally evolutionary stable. This can be implied by the following two conditions:

$$\frac{\partial^2 \mathbf{T}(c_{1h}, c_{2h}, c_1, c_2)}{\partial c_{1h}^2} \Big|_{(c_{1h}, c_{2h}, c_1, c_2)=(\tilde{c}_1^*, \tilde{c}_2^*, \tilde{c}_1^*, \tilde{c}_2^*)} < 0, \quad (4.36)$$

and

$$\frac{\partial^2 \mathbf{T}(c_{1h}, c_{2h}, c_1, c_2)}{\partial c_{2h}^2} \Big|_{(c_{1h}, c_{2h}, c_1, c_2)=(\tilde{c}_1^*, \tilde{c}_2^*, \tilde{c}_1^*, \tilde{c}_2^*)} < 0. \quad (4.37)$$

In dimorphic case, the convergence stability become very difficult and may be affected by the relative speed of evolution in the two hosts [9, 19, 17].

Firstly, we identify conditions for 'isoclinic stability'. Assuming that the evolution of parasite 2 is prevented by keeping $c_2 = \tilde{c}_2^*$. Then, by the generalization of the

monomorphic case, c_1 would evolve to \tilde{c}_1^* from its neighbourhood if

$$\begin{aligned}
 & \left. \frac{d}{dc_1} \left(\frac{\partial \mathbf{T}(c_{1h}, c_{2h}, c_1, c_2)}{\partial c_1} \right) \right|_{c_{1h}=c_1} \Big|_{c_1=\tilde{c}_1^*} \\
 = & \left. \frac{\partial^2 \mathbf{T}(c_{1h}, c_{2h}, c_1, c_2)}{\partial c_{1h}^2} \right|_{(c_{1h}, c_{2h}, c_1, c_2)=(\tilde{c}_1^*, \tilde{c}_2^*, \tilde{c}_1^*, \tilde{c}_2^*)} + \left. \frac{\partial^2 \mathbf{T}(c_{1h}, c_{2h}, c_2, c_2)}{\partial c_1 \partial c_{1h}} \right|_{(c_{1h}, c_{2h}, c_1, c_2)=(\tilde{c}_1^*, \tilde{c}_2^*, \tilde{c}_1^*, \tilde{c}_2^*)} \\
 < & 0.
 \end{aligned} \tag{4.38}$$

Similarly, c_2 is set to \tilde{c}_2^* , c_1 would evolve to \tilde{c}_1^* if

$$\begin{aligned}
 & \left. \frac{d}{dc_1} \left(\frac{\partial \mathbf{T}(c_{1h}, c_{2h}, c_1, c_2)}{\partial c_1} \right) \right|_{c_{2h}=c_2} \Big|_{c_2=\tilde{c}_2^*} \\
 = & \left. \frac{\partial^2 \mathbf{T}(c_{1h}, c_{2h}, c_1, c_2)}{\partial c_{2h}^2} \right|_{(c_{1h}, c_{2h}, c_1, c_2)=(\tilde{c}_1^*, \tilde{c}_2^*, \tilde{c}_1^*, \tilde{c}_2^*)} + \left. \frac{\partial^2 \mathbf{T}(c_{1h}, c_{2h}, c_1, c_2)}{\partial c_2 \partial c_{2h}} \right|_{(c_{1h}, c_{2h}, c_1, c_2)=(\tilde{c}_1^*, \tilde{c}_2^*, \tilde{c}_1^*, \tilde{c}_2^*)} \\
 < & 0.
 \end{aligned} \tag{4.39}$$

However, 'isoclinic stability' is neither necessary nor sufficient condition for convergence stability if both parasites evolve [19, 20].

Next, we discuss the conditions for absolutely convergence stability [20]. In this case, we assume two traits of parasites in mutant hosts are independent. Suppose the most extreme path is constructed in the neighbourhood of $(\tilde{c}_1^*, \tilde{c}_2^*)$, which brings the system as far away from $(\tilde{c}_1^*, \tilde{c}_2^*)$ as possible. Then, the singularity is necessarily convergence stable because no trajectory can diverge. Therefore, its convergence is termed absolute convergence [16]. If

$$\begin{aligned}
 & \left(\frac{\partial^2 \mathbf{T}(c_{1h}, c_{2h}, c_1, c_2)}{\partial c_{1h}^2} + \frac{\partial^2 \mathbf{T}(c_{1h}, c_{2h}, c_2, c_2)}{\partial c_1 \partial c_{1h}} \right) \left(\frac{\partial^2 \mathbf{T}(c_{1h}, c_{2h}, c_1, c_2)}{\partial c_{2h}^2} + \frac{\partial^2 \mathbf{T}(c_{1h}, c_{2h}, c_1, c_2)}{\partial c_2 \partial c_{2h}} \right) \\
 > & \left| \frac{\partial^2 \mathbf{T}(c_{1h}, c_{2h}, c_1, c_2)}{\partial c_2 \partial c_{1h}} \frac{\partial^2 \mathbf{T}(c_{1h}, c_{2h}, c_1, c_2)}{\partial c_1 \partial c_{2h}} \right|
 \end{aligned} \tag{4.40}$$

holds at the singularity and (4.38), (4.39) are satisfied, then $(\tilde{c}_1^*, \tilde{c}_2^*)$ absolute convergence stable.

Next, these approaches are utilizing to obtain more details in this case.

Evolutionary stability

Let us analyze the condition of evolutionary stability. Note that

$$\begin{aligned} & \left. \frac{\partial^2 \mathbf{T}(c_{1h}, c_{2h}, c_1, c_2)}{\partial c_{1h}^2} \right|_{(c_{1h}, c_{2h}, c_1, c_2) = (\tilde{c}_1^*, \tilde{c}_2^*, \tilde{c}_1^*, \tilde{c}_2^*)} \\ &= [\beta \tilde{S}(\tilde{c}_1^*, \tilde{c}_2^*) - (\mu + \delta + \tilde{c}_2^*)] f''(\tilde{c}_1^*). \end{aligned} \quad (4.41)$$

Under the conditions (4.3), (4.4), (4.5), and (4.6), $\tilde{S}(\tilde{c}_1^*, \tilde{c}_2^*) - (\mu + \delta + \tilde{c}_2^*)$ is positive. Thus, the condition (4.36) can be met at \tilde{c}_1^* when trade-off $f(c_1)$ is concave down or locally concave down at \tilde{c}_1^* .

Similarly, under the conditions (4.3), (4.4), (4.5), and (4.6), there is

$$\begin{aligned} & \left. \frac{\partial^2 \mathbf{T}(c_{1h}, c_{2h}, c_1, c_2)}{\partial c_{1h}^2} \right|_{(c_{1h}, c_{2h}, c_1, c_2) = (\tilde{c}_1^*, \tilde{c}_2^*, \tilde{c}_1^*, \tilde{c}_2^*)} \\ &= [(\mu + \delta + \tilde{c}_1^*) - \beta \tilde{S}(\tilde{c}_1^*, \tilde{c}_2^*)] g''(\tilde{c}_2^*) \\ &< 0 \end{aligned} \quad (4.42)$$

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

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

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 **ESS** in this case. Next, we discuss the conditions for isoclinic stability and absolute convergence respectively.

Isoclinic stability

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

$$\begin{aligned}
 & \left. \frac{d}{dc_1} \left(\frac{\partial \mathbf{T}(c_{1h}, c_{2h}, c_1, c_2)}{\partial c_1} \right) \right|_{c_{1h}=c_1} \Big|_{c_1=\tilde{c}_1^*} \\
 = & [\beta \tilde{\mathcal{S}}(\tilde{c}_1^*, \tilde{c}_2^*) - (\mu + \delta + \tilde{c}_2^*)] f''(\tilde{c}_1^*) + \frac{1}{\varphi} \left(1 - \beta \frac{\partial \tilde{\mathcal{S}}}{\partial c_1} \Big|_{(c_1, c_2)=(\tilde{c}_1^*, \tilde{c}_2^*)} \right) (g(\tilde{c}_2^*) + \tilde{c}_2^*) \quad (4.43) \\
 & - \frac{1}{\varphi} (f'(\tilde{c}_1^*) + 1) (\mu + \delta + \tilde{c}_2^*) \beta \frac{\partial \tilde{\mathcal{S}}}{\partial c_1} \Big|_{(c_1, c_2)=(\tilde{c}_1^*, \tilde{c}_2^*)},
 \end{aligned}$$

and

$$\begin{aligned}
 & \left. \frac{d}{dc_1} \left(\frac{\partial \mathbf{T}(c_{1h}, c_{2h}, c_1, c_2)}{\partial c_1} \right) \right|_{c_{1h}=c_1} \Big|_{c_1=\tilde{c}_1^*} \\
 = & [(\mu + \delta + \tilde{c}_1^*) - \beta \tilde{\mathcal{S}}(\tilde{c}_1^*, \tilde{c}_2^*)] g''(\tilde{c}_2^*) - \frac{1}{\varphi} (g'(\tilde{c}_2^*) + 1) \beta \frac{\partial \tilde{\mathcal{S}}}{\partial c_2} \Big|_{(c_1, c_2)=(\tilde{c}_1^*, \tilde{c}_2^*)} \quad (4.44) \\
 & + \frac{1}{\varphi} \left(\beta \frac{\partial \tilde{\mathcal{S}}}{\partial c_2} \Big|_{(c_1, c_2)=(\tilde{c}_1^*, \tilde{c}_2^*)} - 1 \right) (f(\tilde{c}_1^*) + \tilde{c}_1^*),
 \end{aligned}$$

where

$$f'(\tilde{c}_1^*) = -2k_1^* \tilde{c}_1^*, \quad f''(\tilde{c}_1^*) = -2k_1^*,$$

$$g'(\tilde{c}_2^*) = -2k_2^* \tilde{c}_2^*, \quad g''(\tilde{c}_2^*) = -2k_2^*,$$

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

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

According to previous discussion, $(\tilde{c}_1^*, \tilde{c}_2^*)$ is isoclinic stable when both (4.43) and (4.44) are negative.

Since the two functions are difficult to be simplified, we can only give some numerical results in Figure 4.3. After fixing the values of parameters, we show the corresponding singularity in Figures 4.3a and 4.3c, which are with different superinfection

rate respectively. In Figure 4.3b and 4.3d, the two conditions for isoclinic stability can be met in shadow areas. By comparing Figure 4.3b and Figure 4.3d, we find that the shape of the shadowed area could be changed by varying the superinfection rate.

Absolute convergence stability

For this pair of quadratic trade-off functions, we have

$$\begin{aligned}
 & \left. \frac{\partial^2 \mathbf{T}(c_{1h}, c_{2h}, c_1, c_2)}{\partial c_2 \partial c_{1h}} \right|_{(c_{1h}, c_{2h}, c_1, c_2) = (\tilde{c}_1^*, \tilde{c}_2^*, \tilde{c}_1^*, \tilde{c}_2^*)} \\
 = & -\frac{1}{\varphi} \beta \frac{\partial \tilde{\delta}}{\partial c_2} \Big|_{(c_1, c_2) = (\tilde{c}_1^*, \tilde{c}_2^*)} \left(g(\tilde{c}_2^*) + \tilde{c}_2^* \right) + \frac{1}{\varphi} (\mu + \delta + \tilde{c}_2^*) \\
 & + \frac{1}{\varphi} \left(\beta \frac{\partial \tilde{\delta}}{\partial c_2} \Big|_{(c_1, c_2) = (\tilde{c}_1^*, \tilde{c}_2^*)} - 1 \right) (f'(\tilde{c}_1^*) + 1) (\mu + \delta + \tilde{c}_2^*)
 \end{aligned} \tag{4.45}$$

and

$$\begin{aligned}
 & \left. \frac{\partial^2 \mathbf{T}(c_{1h}, c_{2h}, c_1, c_2)}{\partial c_2 \partial c_{1h}} \right|_{(c_{1h}, c_{2h}, c_1, c_2) = (\tilde{c}_1^*, \tilde{c}_2^*, \tilde{c}_1^*, \tilde{c}_2^*)} \\
 = & \frac{1}{\varphi} \beta \frac{\partial \tilde{\delta}}{\partial c_1} \Big|_{(c_1, c_2) = (\tilde{c}_1^*, \tilde{c}_2^*)} \left(f(\tilde{c}_1^*) + \tilde{c}_1^* \right) - \frac{1}{\varphi} (\mu + \delta + \tilde{c}_1^*) \\
 & + \frac{1}{\varphi} \left(1 - \beta \frac{\partial \tilde{\delta}}{\partial c_1} \Big|_{(c_1, c_2) = (\tilde{c}_1^*, \tilde{c}_2^*)} \right) (g'(\tilde{c}_2^*) + 1) (\mu + \delta + \tilde{c}_1^*).
 \end{aligned} \tag{4.46}$$

Although we choose quadratic functions to simplify the problem, the second conditions for absolute stability is still very complicated. To show that this condition is feasible, a numerical result is showed in Figure 4.4. We only plot the first quadrant, because the data for simulation in other regions has no biological meaning. The three conditions (4.38), (4.39) and (4.40) can be met in the two shadows. We find that this condition is very sensitive to value of each parameter.

4.5 Discussion

In this chapter, we studied the host-parasite co-evolution on population level. Superinfection and a trade-off involving production rate by infected hosts and their recovery rate were considered in the basic *SIR* model with two parasites and one host strain. We

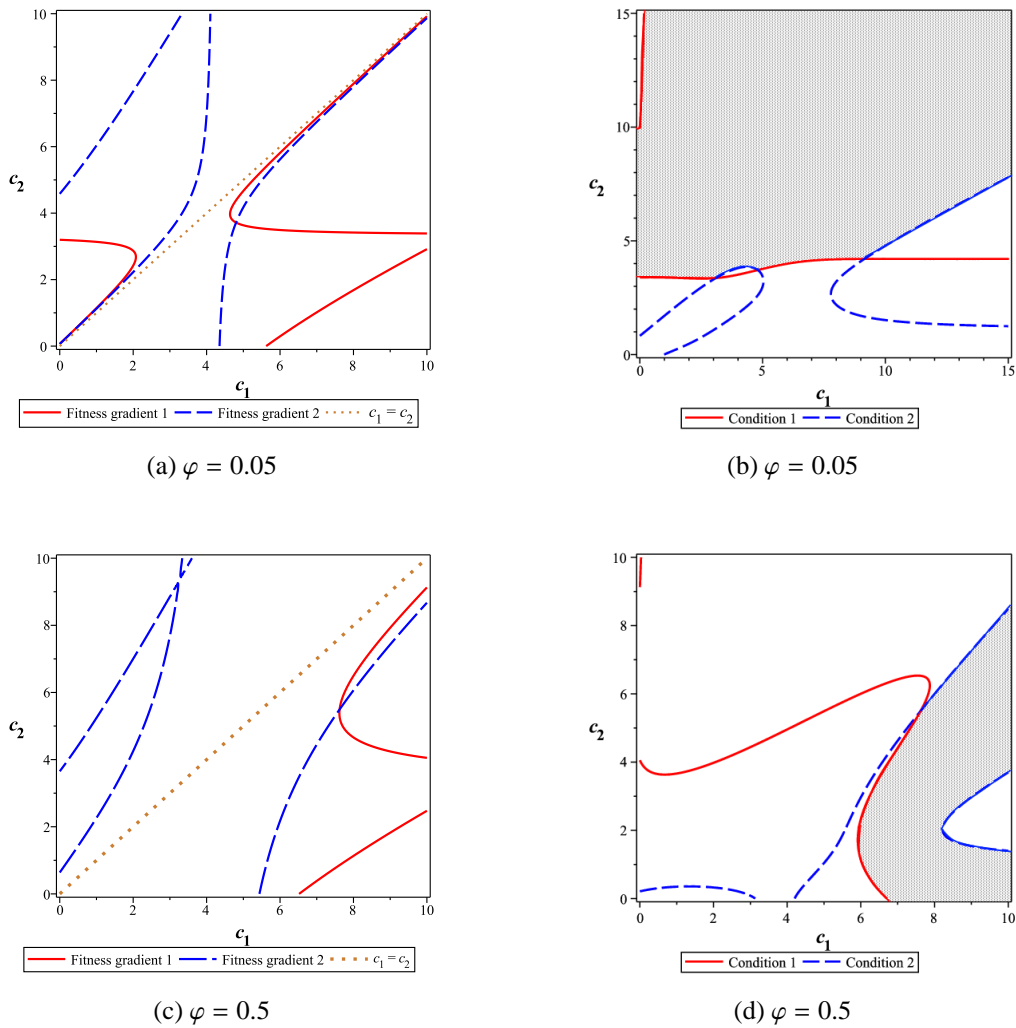


Figure 4.3: **Singularity and Isoclinic stability:** when $\delta = 0.95$, $b = 10$, $\beta = 0.4$, $\mu = 0.2$, $k_1 = 0.5$, and $k_2 = 0.8$. We only observe the regions in first quadrant. In figure (a) and (b), we plot the solutions when (4.33) and (4.34) are equal to zero. In figures (c) and (d), the red solid curves represents function (4.43) and the blue dash curves represent function (4.44). In shadows, both conditions (4.38) and (4.39) 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.

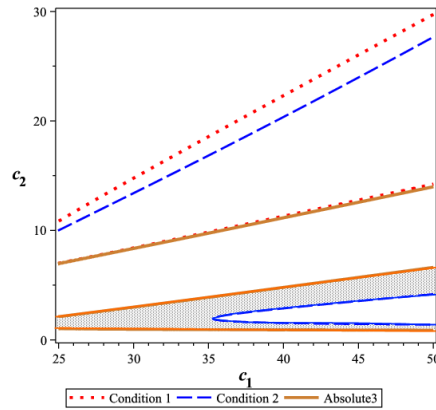


Figure 4.4: **Absolute stability:** when $\delta = 0.3$, $\varphi = 10$, $b = 2$, $\beta = 0.4$, $\mu = 0.2$, $k_1 = 0.1$, and $k_2 = 0.8$. The red dot curve represents function (4.43) and the blue dash curve represents function (4.44), too. The golden solid line stands for the formula in inequality (4.40). In two shadows, the conditions for absolute stability can be satisfied.

obtained a positive equilibrium that parasite 1 and 2 can coexist in resident hosts and proved its local stability. Furthermore, we introduced mutant hosts into our model and discussed its invasion in monomorphic and dimorphic case, respectively.

In monomorphic case, the critical value that can decide the local stabilities of the mutant host-free equilibria was define as the fitness of the invasion of mutant hosts with a infection. Since mutant hosts could be infected by parasite 1 or 2, there were two possible infections. For each type of infection, we obtained evolutionary singular points when fitness gradients were equal to zero. And the evolutionary and convergence stabilities were analyzed respectively. In our examples, we observed how the cost of immunological up-regulation and superinfection rate changes the value of singular points in each case.

Comparing with the conclusions of Day and Burns [13], superinfection trends to help parasite 1 and 2 to coexist and keep evolving in hosts. Meanwhile, it makes host-parasite co-evolution more difficult to study. Besides, our results suggest that the degree of immune response can affect the future of the host evolution. As the degree of

immunological response increasing, its cost from up-regulation would also increase. However, nutrients are limited for consuming in a host. Although immune response is benign to hosts, the host evolution would not favor 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 hosts with both parasite 1 and 2 was explored. A new fitness with four types of traits was defined. In this case, the conditions for an evolutionary stable singularity was easily obtained. However, the convergence stability in multiple-dimension problem become complicated. Instead, we studied isoclinic and absolute convergence stability. For convenience, the trade-offs were specified by two simple quadratic functions. And the numerical results were showed.

In both monomorphic and dimorphic case, superinfection was found to help parasite 2 with weaker virulence exist and keep evolving in hosts.

However, we only discuss the evolution on 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. Moreover, Day and Burns discussed another trade-off between transmission rate and clearance rate, based on much evidence that quicker host death is caused by the parasites with increased transmission rate, in [13]. In the future, we could also consider this trade off, and compare results with our conclusion to know the host-parasite co-evolution better. Being confined to the limited approaches in dimorphic adaptive dynamics, so many ideal assumptions are provided to simplify the complex analysis. But they may not be realistic. Therefore, we need to modify our model and make it closer to real world in the upcoming project.

Moreover, we find that the convergence stability for multiple dimension is significantly complicated. Especially, the absolute convergence stability is too ideal to be met in real world. Hence, there are many works that we can do to help to fill this gap.

Bibliography

- [1] Beck, G. and Habicht, G. S. (1996). Immunity and the invertebrates. *Scientific American*, 275(5):60–66.
- [2] Boldin, B. and Diekmann, O. (2008). Superinfections can induce evolutionarily stable coexistence of pathogens. *Journal of mathematical biology*, 56(5):635–672.
- [3] Boldin, B., Geritz, S. A. H., and Kisdi, E. (2009). Superinfections and adaptive dynamics of pathogen virulence revisited: a critical function analysis. *Evolutionary Ecology Research*, 11(2):153–175.
- [4] Combes, C. (2005). *The art of being a parasite*. University of Chicago Press.
- [5] Darwin, C. (1859). *On the origin of species*, volume 484. John Murray, London.
- [6] Day, T. (2002). On the evolution of virulence and the relationship between various measures of mortality. *Proceedings of the Royal Society of London. Series B: Biological Sciences*, 269(1498):1317–1323.
- [7] Day, T. (2003). Virulence evolution and the timing of disease life-history events. *Trends in Ecology & Evolution*, 18(3):113–118.
- [8] Day, T. and Burns, J. G. (2003). A consideration of patterns of virulence arising from host-parasite coevolution. *Evolution*, 57(3):671–676.
- [9] Dieckmann, U. and Law, R. (1996). The dynamical theory of coevolution: a derivation from stochastic ecological processes. *Journal of mathematical biology*, 34(5–6):579–612.
- [10] Gandon, S., van Baalen, M., and Jansen, V. A. A. (2002). The evolution of parasite virulence, superinfection, and host resistance. *The American Naturalist*, 159(6):658–669.

- [11] Geritz, S. A. H., Mesze, G., and Metz, J. A. J. (1997a). Evolutionarily singular strategies and the adaptive growth and branching of the evolutionary tree. *Evolutionary ecology*, 12(1):35–57.
- [12] Geritz, S. A. H., Mesze, G., and Metz, J. A. J. (1997b). Evolutionarily singular strategies and the adaptive growth and branching of the evolutionary tree. *Evolutionary ecology*, 12(1):35–57.
- [13] Geritz, S. A. H., Metz, J. A. J., Kisdi, É., and Meszéna, G. (1997c). Dynamics of adaptation and evolutionary branching. *Physical Review Letters*, 78(10):2024–2027.
- [14] Hall, B. and Hallgrímsson, B. (2008). *Strickberger's evolution*. Jones & Bartlett Learning.
- [15] Kisdi, E. (2006). Trade-off geometries and the adaptive dynamics of two co-evolving species. *Evolutionary Ecology Research*, 8(6):959–973.
- [16] Leimar, O. (2002). Evolutionary change and darwinian demons. *Selection*, 2(1):65–72.
- [17] Leimar, O. (2009). Multidimensional convergence stability. *Evolutionary Ecology Research*, 11(2):191–208.
- [18] Lochmiller, R. L. and Deerenberg, C. (2000). Trade-offs in evolutionary immunology: just what is the cost of immunity? *Oikos*, 88(1):87–98.
- [19] Marrow, P., Dieckmann, U., and Law, R. (1996). Evolutionary dynamics of predator-prey systems: an ecological perspective. *Journal of Mathematical Biology*, 34(5-6):556–578.
- [20] Matessi, C. and Pasquale, C. D. (1996). Long-term evolution of multilocus traits. *Journal of Mathematical Biology*, 34(5-6):613–653.

- [21] May, R. M. and Nowak, M. A. (1994). Superinfection, metapopulation dynamics, and the evolution of diversity. *Journal of Theoretical Biology*, 170(1):95–114.
- [22] Mosquera, J. and Adler, F. R. (1998). Evolution of virulence: a unified framework for coinfection and superinfection. *Journal of Theoretical Biology*, 195(3):293–313.
- [23] Svernungsen, T. O. and Kisdi, É. (2009). Evolutionary branching of virulence in a single-infection model. *Journal of theoretical biology*, 257(3):408–418.
- [24] Woolhouse, M. E. J., Webster, J. P., Domingo, E., Charlesworth, B., and Levin, B. R. (2002). Biological and biomedical implications of the co-evolution of pathogens and their hosts. *Nature genetics*, 32(4):569–577.
- [25] Yu, P. (2005). Closed-form conditions of bifurcation points for general differential equations. *International Journal of Bifurcation and Chaos*, 15(04):1467–1483.

Chapter 5

Conclusions and future work

5.1 Conclusions

Our whole thesis studies the evolution of hosts and parasites. Firstly, a within-host age-structured dynamical model was used to explore the viral mutation phenomena. For convenience, the PDE model was transformed into an ODE system by defining the production rates of virus are gamma distributions in the chapter 2. To obtain the basic reproductive number of this system, the method of controlled system to calculate output was utilized. After the discussion about the existence and globally asymptotical stability of the infection-free equilibrium, the existences and stabilities of other equilibria were analyzed in two cases of mutation rates, respectively.

In the first case, the competition between two viral strains was without mutation. It was demonstrated to comply with the competitive exclusion principle that the one with larger basic reproductive number would survive finally. We considered mutation and back mutation between two viral strains in the second case. The existence of coexistence equilibrium was proved under some specific conditions. Because the mutation rates were considered as small perturbations, we showed that this equilibrium was glob-

ally asymptotically stable through average Lyapunov function theory [4].

In the chapter 3, the adaptive dynamical approaches were utilized to discuss viral evolution. The study was based on a within-host model considering immune response to analyze two types of trade-offs: the one is involving viral production rate and virulence; the other is involving virulence and transmission rate. The critical value that can decide the local stability of the mutant free equilibrium of our system was defined as a fitness to measure the invasion of mutant strain viruses. After substituting two trade-offs in the fitness, respectively, evolutionary singular strategies were found from the equations when fitness gradients were set equal to zero. For their evolutionary and convergent stability, we compared the geometrical properties of the two trade-off functions with corresponding critical functions at those evolutionary singular points, respectively.

Viruses choose their production rate as the evolutionary strategy in the first trade-off. To explain the diversity of viral strains, the existence of evolutionary branching was demonstrated under the effect of CTL response when the local concavity of the trade-off is $\frac{1}{u}$ times more than it of the critical functions. The singular point is an evolutionary stable strategy if its trade-off is all concave up (convex) or partial concave up at this point; otherwise, it is a repellor. Therefore, the speed of viruses replication would help viruses to overcome the immune system of hosts [1].

In the second trade-off, the viral evolutionary strategy was the death rate of infected cells, which represented the viral virulence. It was showed that the CTL response can control viral evolution through shaping the trade-off. A singular strategy was evolutionary stable when the trade-off was all concave down (concave) or partial concave down at this point; whereas too concave up would result in a repellor. Based on our examples, viral evolution would favor neither a too high nor too low degree of virulence. However, the results are more complicated than this when this trade-off is considered in a between-host model with superinfection [2], which denotes a specific function to

the trade-off. Meanwhile, hosts can play a significant role in viral evolution and decide the evolutionary trend of viruses. Hence, we studied the host-parasite co-evolution in the chapter 4.

In chapter 4, the host-parasite co-evolution is discussed on population level. A basic *SIR* model with two parasites and one host strain is utilized to consider the effects of superinfection and a trade-off involving production rate by infected hosts and their recovery rate. We obtained a positive equilibrium that parasite 1 and 2 can coexist in resident hosts and showed its local stability. Furthermore, mutant hosts are introduced into our model to discuss its invasion in monomorphic and dimorphic case, respectively.

In monomorphic case, the critical value for the local stabilities of the mutant host-free equilibria was defined as the fitness of the invasion of mutant hosts with one type of infection, one is infected by parasite 1 and the other is infected by parasite 2. For each type of infection, we obtained evolutionary singular points when fitness gradients vanished. And the evolutionary and convergence stabilities were analyzed respectively. We provided examples to observe how the cost of immunological up-regulation and superinfection rate changes the value of singular points in each case.

In contrast to the conclusions of Day and Burns' in [3], we find that superinfection trends to help parasite 2 to coexist with parasite 1 and keep evolving in hosts. Meanwhile, our results suggest that the future of the host evolution can be decided by the degree of immune response. As the degree of immune response increases, its cost from up-regulation would also increase. However, nutrients are limited for consuming in a host. Although immune response is benign to hosts, the host evolution would not favor a high degree of immunological up-regulation. Therefore, an intermediate degree of immunological up-regulation would be helpful to the host evolution.

Furthermore, we explored the case of mutant hosts with both parasite 1 and 2. A

new fitness with four types of traits was constructed. In this case, we can easily obtain the conditions for an evolutionary stable singularity. In multiple-dimension problem, however, the convergence stability becomes very complicated. We studied isoclinic and absolute convergence stability instead of convergence stability. We specified the trade-offs by two simple linear functions and showed some numerical results.

In both monomorphic and dimorphic case, superinfection was found to help parasite 2 with weaker virulence exist and evolve in hosts.

5.2 Future work

Summarizing the entire article, there are still remaining works to be continued in the future.

In chapter 2, we cannot help to wonder that whether those stabilities will change if mutation rates exceed these critical values. Also, a natural question of whether the mutation rates are always fixed or not arises. In fact, the evolution is a long and endless journey for species. The direction of the evolution of viruses will be altered by a tiny change in our environment. Then, we can study how the changes of mutation rates would effect the viruses evolution as time goes by in the future. Since the triggers of the phenomenon of viral mutation, such as drug resistance, etc, in our model, are ignored, we can also introduce this term to our model to discuss whether our results may be shifted as our future work.

The model is very ideal because of limited mathematical techniques in chapter 3. We can utilize the Holling Type II function to replace the bilinear function to describe immune response for more real realistic in our model. Furthermore, we are interested in a trade-off involving viral production rate and disease transmission rate and plan to study it in the future. Also, the impact caused by the cost of body immune response

should be taken into account into the within-host level.

In chapter 4, we only discuss the evolution on host level. Actually, the evolutionary speed of parasites should be quicker than it of hosts. So, a nested model may be a better choice for our further research. Moreover, another trade-off between transmission rate and clearance rate, based on much evidence that quicker host death is caused by the parasites with increased transmission rate, is discussed by Day and Burns in [3]. Thus, we could also consider this trade off, and compare with our conclusion to deeply know the host-parasite co-evolution. Being confined to the limited approaches in dimorphic adaptive dynamics, so many ideal assumptions are provided to simplify the complex analysis. But they may not be realistic. Therefore, we need to modify our model and make it closer to real world in the upcoming project.

Moreover, we find that the convergence stability for multiple dimension is significantly complicated. Especially, the absolute convergence stability is too ideal to be met in the real world. Hence, there are many works that we can do to help to fill this gap.

Bibliography

- [1] Bocharov, G., Ludewig, B., Bertolotti, A., Klenerman, P., Junt, T., P. Krebs, T. L., Fraser, C., and Anderson, R. M. (2004). Underwhelming the immune response: effect of slow virus growth on CD8⁺-T-lymphocyte responses. *Journal of virology*, 78(5):2247–2254.
- [2] Boldin, B., Geritz, S. A. H., and Kisdi, E. (2009). Superinfections and adaptive dynamics of pathogen virulence revisited: a critical function analysis. *Evolutionary Ecology Research*, 11(2):153–175.
- [3] Geritz, S. A. H., Metz, J. A. J., Kisdi, É., and Meszéna, G. (1997). Dynamics of adaptation and evolutionary branching. *Physical Review Letters*, 78(10):2024–2027.

- [4] Kon, R. and Iwasa, Y. (2007). Single-class orbits in nonlinear Leslie matrix models for semelparous populations. *Journal of mathematical biology*, 55(5-6):781–802.

Appendix A

A.1 Solution to the age-structured system

Let us consider the second equation in system (2.2) and its corresponding boundary condition:

$$\frac{\partial T_1^*}{\partial a} + \frac{\partial T_1^*}{\partial t} = -(\mu_1(a) + m_1)T_1^*(a, t), \quad t \geq 0,$$

$$T_1^*(0, t) = \beta_1 V_1(t)T(t), \quad a \geq 0.$$

Assume $T_1^*(0, a) = 0$. By characteristic line

$$\begin{aligned} \frac{dt}{ds} &= 1, \\ \frac{da}{ds} &= 1, \\ \frac{dT_1^*}{ds} &= -(\mu_1(a) + m_1)T_1^*(a, t), \end{aligned} \tag{A.1}$$

with initial conditions:

A.1.1 If $t \geq a$

$$\begin{aligned} t(0) &= t_0, \\ a(0) &= 0, \end{aligned} \tag{A.2}$$

$$T_1^*(0, t) = \beta_1 V_1(t)T(t).$$

Let $B_1(t) = \beta_1 V_1(t)T(t)$. From (A.2), we can induce that $t = t_0 + s$, and $a = s$. Then, there is $a = t - t_0$. Suppose $T_1^*(a, t) = W(s)$, then $W(0) = T_1^*(0, t_0) = B_1(t_0) = B_1(t - a)$.

That is

$$\frac{dW(s)}{ds} = -(\mu_1(s) + m_1)W(s)$$

So, the general solution for above equation is $W(s) = C_1 e^{\int_0^s (\mu_1(\xi) + m_1) d\xi}$, where C_1 is arbitrary constant. Since $W(0) = C_1$, we have $C_1 = B_1(t - a)$. Then, there is $W(s) = B_1(t - a) e^{-\int_0^s (\mu_1(\xi) + m_1) d\xi}$. That is,

$$T_1^*(a, t) = \beta_1 V_1(t - a)T(t - a) e^{-\int_0^s (\mu_1(\xi) + m_1) d\xi}.$$

A.1.2 If $t < a$

$$t(0) = 0,$$

$$a(0) = a_0, \tag{A.3}$$

$$T_1^*(0, a_0) = 0.$$

From above equations, we have $t = s$, and $a = a_0 + s$. That is $a_0 = a - t$. Then, we can obtain $W(s) = C_2 e^{-\int_0^s (\mu_1(\xi) + m_1) d\xi}$, where C_2 is arbitrary constant. Since $W(0) = T_1^*(0, a_0) = 0$, there is $C_2 = 0$. Therefore, the result $T_1^*(a, t) = 0$ can be acquired.

Overall, the solution is

$$T_1^*(a, t) = \begin{cases} \beta_1 V_1(t - a)T(t - a)\sigma_1(a), & t \geq a, \\ 0, & t < a, \end{cases}$$

where $\sigma_1(a) = e^{-\int_0^a (\mu_1(\xi) + m_1) d\xi}$. By the same method, we can solve

$$\frac{\partial T_2^*}{\partial a} + \frac{\partial T_2^*}{\partial t} = -(\mu_2(a) + m_1)T_2^*(a, t), \quad t \geq 0$$

$$T_2^*(0, t) = \beta_2 V_2(t) T(t), \quad a \geq 0$$

to obtain that:

$$T_2^*(a, t) = \begin{cases} \beta_2 V_2(t-a) T(t-a) \sigma_2(a), & t \geq a, \\ 0, & t < a, \end{cases}$$

where $\sigma_2(a) = e^{-\int_0^a (\mu_2(\xi) + m_2) d\xi}$.

A.2 Calculate the basic reproductive number of the system (2.8) by next generation method

Firstly, we can figure out vectors \mathcal{F} and \mathcal{V} for system (2.8) as follows:

$$\mathcal{F} = \begin{pmatrix} 0 \\ \beta_1 \left(\frac{\alpha}{a}\right)^n V_1 T \\ 0 \\ \vdots \\ 0 \\ \beta_2 \left(\frac{\alpha}{a}\right)^n V_2 T \\ 0 \\ \vdots \\ 0 \\ 0 \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} dT + \beta_1 T V_1 + \beta_2 T V_2 - b \\ \frac{1}{\alpha} x_1 \\ \frac{1}{\alpha} (x_2 - x_1) \\ \vdots \\ \frac{1}{\alpha} (x_n - x_{n-1}) \\ \frac{1}{\alpha} y_1 \\ \frac{1}{\alpha} (y_2 - y_1) \\ \vdots \\ c_1 V_1 - \frac{1-\epsilon_1}{\alpha} x_n - \frac{\epsilon_2}{\alpha} y_n \\ c_2 V_2 - \frac{1-\epsilon_2}{\alpha} y_n - \frac{\epsilon_1}{\alpha} x_n \end{pmatrix}.$$

Since the infected compartments are V_1 and V_2 , F and V should be:

$$F = \begin{bmatrix} \frac{\beta_1 b}{d} \left(\frac{\alpha}{a}\right)^n & 0 \\ 0 & \frac{\beta_2 b}{d} \left(\frac{\alpha}{a}\right)^n \end{bmatrix}, \quad V = \begin{bmatrix} c_1 & 0 \\ 0 & c_2 \end{bmatrix},$$

giving

$$V^{-1} = \begin{bmatrix} \frac{1}{c_1} & 0 \\ 0 & \frac{1}{c_2} \end{bmatrix}.$$

Then, the next generation matrix, FV^{-1} , has the two eigenvalues $\mathbf{R}_i = \frac{\beta_i b}{d c_i} \left(\frac{\alpha}{\bar{\alpha}}\right)^n$, $i = 1, 2$. That is,

$$\mathbf{R}_0 = \max_{i \in \{1, 2\}} \mathbf{R}_i.$$

Appendix B

B.1 The local stability of the equilibrium $\bar{\mathbf{E}}$

The last equation of (3.3) is equivalent to

$$\beta\bar{x} = (p\bar{z} + a)\frac{u}{k}.$$

The Jacobian matrix at the point $\bar{\mathbf{E}}$ is

$$\mathbf{J} = \begin{pmatrix} -d - \beta\bar{v} & 0 & -\beta\bar{x} & 0 \\ \beta\bar{v} & -a - p\bar{z} & \beta\bar{x} & -p\bar{y} \\ 0 & k & -u & 0 \\ 0 & c\bar{z} & 0 & c\bar{y} - b \end{pmatrix}.$$

Because we have $c\bar{y} - b = 0$, $\mu = d + \beta'$ and $\beta\bar{x} = (p\bar{z} + a)\frac{u}{k}$ at $\bar{\mathbf{E}}$, put $\beta' = \beta\bar{v}$ and $\omega = a + p\bar{z}$ into above matrix. It changes to:

$$\mathbf{J} = \begin{pmatrix} -\mu & 0 & -\frac{u\omega}{k} & 0 \\ \beta' & -\omega & \frac{u\omega}{k} & -p\bar{y} \\ 0 & k & -u & 0 \\ 0 & c\bar{z} & 0 & 0 \end{pmatrix}.$$

We notice that all parameters are positive, and $\mu > \beta'$ & $\omega > p\bar{z}$. Then, we need to show that all solutions of the characteristic equation of \mathbf{J} have negative real parts. For this purpose, we regard $\mu, \omega, \frac{k}{a}, c, \beta', a, \bar{v}$ and \bar{z} as independent variables.

The characteristic equation of \mathbf{J} is denoted as

$$|\lambda\mathbf{I} - \mathbf{J}| = \lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4. \quad (\text{B.1})$$

We calculate a_1, a_2, a_3 and a_4 as follows by utilizing the formula (4.3) in the paper of Huang, Yokoi and et al. [1]. Let $h = cp\bar{y}\bar{z}$, and we have

$$\begin{aligned} a_1 &= -\text{tr}(\mathbf{J}) = \mu + (\omega + u), \\ a_2 &= \begin{vmatrix} -mu & 0 \\ \beta' & -\omega \end{vmatrix} + \begin{vmatrix} -\mu & -\frac{u\omega}{k} \\ 0 & -u \end{vmatrix} + \begin{vmatrix} -\mu & 0 \\ 0 & 0 \end{vmatrix} + \begin{vmatrix} -\omega & \frac{u\omega}{k} \\ k & -u \end{vmatrix} \\ &\quad + \begin{vmatrix} -\omega & -p\bar{y} \\ c\bar{z} & 0 \end{vmatrix} + \begin{vmatrix} -u & 0 \\ 0 & 0 \end{vmatrix} \\ &= \mu(\omega + u) + h, \\ a_3 &= - \begin{vmatrix} -\omega & \frac{u\omega}{k} & -p\bar{y} \\ k & -u & 0 \\ c\bar{z} & 0 & 0 \end{vmatrix} + \begin{vmatrix} -\mu & -\frac{u\omega}{k} & 0 \\ 0 & -u & 0 \\ 0 & 0 & 0 \end{vmatrix} - \begin{vmatrix} -\mu & 0 & 0 \\ \beta' & -\omega & -p\bar{y} \\ 0 & c\bar{z} & 0 \end{vmatrix} \\ &\quad - \begin{vmatrix} -mu & 0 & -\frac{u\omega}{k} \\ \beta' & -\omega & \frac{u\omega}{k} \\ 0 & k & -u \end{vmatrix} \\ &= \mu h + (\beta' u \omega + u h), \\ a_4 &= \det(\mathbf{J}) = \begin{vmatrix} -\mu & 0 & -\frac{u\omega}{k} & 0 \\ \beta' & -\omega & \frac{u\omega}{k} & -p\bar{y} \\ 0 & k & -u & 0 \\ 0 & c\bar{z} & 0 & 0 \end{vmatrix} = \mu u h. \end{aligned}$$

Since that $a_i, i = 1, 2, 3, 4$, is a linear function of μ , a necessary and sufficient conditions for all roots of (B.1) have negative real parts are:

$$a_1 > 0, \quad \begin{vmatrix} a_1 & 1 \\ a_3 & a_2 \end{vmatrix} > 0, \quad \begin{vmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ 0 & a_4 & a_3 \end{vmatrix} > 0 \quad a_4 > 0, \quad (\text{B.2})$$

by Routh-Hurwitz criteria. It is easy to find that a_1 and a_4 are positive. Let us analyze other two determinants in (B.2). We have

$$\begin{aligned} \begin{vmatrix} a_1 & 1 \\ a_3 & a_2 \end{vmatrix} &= [\mu(\omega + u) + h] - \mu h - (\beta' u \omega + u h) \\ &= (\omega + u)\mu^2 + (\omega + u)^2 \mu + h\omega - \beta' u \omega \\ &= (\omega + u)\mu^2 + (\omega^2 + u^2 + \omega u)\mu + h\omega + u\omega(\mu - \beta') \\ &> 0, \end{aligned}$$

provided that $\mu > \beta'$.

Consider the third determinant in (B.2) as a function of μ , that is,

$$f(\mu) \triangleq \begin{vmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ 0 & a_4 & a_3 \end{vmatrix} = \begin{vmatrix} a_1(\mu) & 1 & 0 \\ a_3(\mu) & a_2(\mu) & a_1(\mu) \\ 0 & a_4(\mu) & a_3(\mu) \end{vmatrix}.$$

Since a_1, a_2, a_3 and a_4 are all linear with respect to μ , $f(\mu)$ is a polynomial of μ with degree 3. Denote

$$f(\mu) = \mathbf{A}_3 \mu^3 + \mathbf{A}_2 \mu^2 + \mathbf{A}_1 \mu + \mathbf{A}_0, \quad (\text{B.3})$$

where $\mathbf{A}_3, \mathbf{A}_2, \mathbf{A}_1$ and \mathbf{A}_0 do not contain μ . So,

$$\begin{aligned}
 \mathbf{A}_0 &= f(0) = \begin{vmatrix} \omega + u & 1 & 0 \\ \beta' u \omega + uh & h & \omega + u \\ 0 & 0 & \beta' u \omega + uh \end{vmatrix} \\
 &= (\beta' u \omega + uh) \begin{vmatrix} \omega + u & 1 \\ \beta' u \omega + uh & h \end{vmatrix} \\
 &= u\omega h^2 - \beta' u^2 \omega h + h\beta' u \omega^2 - u^2 \omega^2 \beta'^2.
 \end{aligned}$$

And,

$$\begin{aligned}
 \mathbf{A}_1 &= f'(0) \\
 &= \begin{vmatrix} 1 & 1 & 0 \\ h & \mu(\omega + u) + h & \mu + (\omega + u) \\ 0 & \mu uh & \mu h + (\beta' u \omega + uh) \end{vmatrix} \\
 &+ \begin{vmatrix} \mu + \omega + u & 0 & 0 \\ \mu h + \beta' u \omega + uh & \omega + u & \mu + \omega + u \\ 0 & uh & \mu h + \beta' u \omega + uh \end{vmatrix} \\
 &+ \begin{vmatrix} \mu + \omega + u & 1 & 0 \\ \mu h + \beta' u \omega + uh & \mu(\omega + u) + h & 1 \\ 0 & \mu uh & h \end{vmatrix} \\
 &= (\omega + u) \begin{vmatrix} \omega + u & \omega + u \\ uh & \beta' u \omega + uh \end{vmatrix} + h \begin{vmatrix} \omega + u & 1 \\ \beta' u \omega + uh & h \end{vmatrix} \\
 &= (\omega + u)^2 [(\beta' u \omega + uh) - uh] + h[(\omega + u)h - \beta' u \omega - uh] \\
 &= \beta' u \omega + 2\beta' u^2 \omega^2 + h^2 \omega + \beta' u^3 \omega - \beta' u \omega h.
 \end{aligned}$$

As $\mathbf{A}_2 = \frac{f''(0)}{2}$, we obtain

$$\begin{aligned} \mathbf{A}_2 &= \begin{vmatrix} 1 & 0 & 0 \\ h & \omega + u & \omega + u \\ 0 & uh & \beta'u\omega + uh \end{vmatrix} + \begin{vmatrix} \omega + u & 0 & 0 \\ \beta'u\omega + uh & \omega + u & 1 \\ 0 & uh & h \end{vmatrix} + \begin{vmatrix} 1 & 1 & 0 \\ h & h & 1 \\ 0 & 0 & h \end{vmatrix} \\ &= (\omega + u)[(\beta'u\omega + uh) - uh + (\omega + u)h - uh] \\ &= \beta'u\omega^2 + \beta'u^2\omega + \omega^2h + \omega uh. \end{aligned}$$

Then, let us compute \mathbf{A}_3

$$\begin{aligned} \mathbf{A}_3 &= \frac{f'''(0)}{6} = \begin{vmatrix} 1 & 0 & 0 \\ h & \omega + u & 1 \\ 0 & uh & h \end{vmatrix} \\ &= (\omega + u)h - uh = \omega h. \end{aligned}$$

We rewrite the polynomial function $f(\mu)$ in the form of $\omega g(\mu)$, where

$$g'(\mu) = 3h\mu^2 + 2(\beta'u\omega + \beta'u^2 + \omega h + uh)\mu + (\beta'u\omega + 2\beta'u^2\omega + h^2 + \beta'u^3 - \beta'uh).$$

Set $\mu = \beta'$, then we can prove:

$$g'(\beta') = 3h\beta'^2 + 2\beta'^2u\omega + \beta'^2u^2 + \beta'\omega h + \beta'u\omega + 2\beta'u^2\omega + h^2 + \beta'u^3 > 0.$$

Now, the function $g(\beta')$ is demonstrated to be positive.

$$\begin{aligned} g(\beta') &= h(\beta')^3 + \beta'^3u\omega + \beta'^3u^2 + \beta'^2\omega h + uh\beta'^2 + \beta'^2u\omega + 2\beta'^2u^2\omega \\ &\quad + h^2\beta' + \beta'^2u^3 - \beta'^2uh + uh^2 - \beta'u^2h + h\beta'u\omega - u^2\beta'^2\omega \\ &= h(\beta')^3 + \beta'^3u\omega + \beta'^3u^2 + \beta'^2\omega h + \beta'^2u\omega + \beta'^2u^2\omega + h^2\beta' + h\beta'u\omega \\ &\quad + (uh^2 - \beta'u^2h + \beta'^2u^3). \end{aligned}$$

The last term is positive because

$$uh^2 - \beta' u^2 h + \beta'^2 u^3 = u \left[\left(h - \frac{u\beta'}{2} \right)^2 + \frac{3}{4} u^2 \beta'^2 \right] > 0.$$

Thus, there is $g(\beta') > 0$. As a result, it can be concluded that $g(\mu) > 0$ for $\mu > \beta'$. Until now, we have finished the proof of the local stability of the positive equilibrium $\bar{\mathbf{E}}$ for one strain model.

B.2 Then local stability of the mutant-free equilibrium

The Jacobian matrix of the system (3.4) at $\bar{\mathbf{E}}$ is:

$$\tilde{\mathbf{J}} = \begin{pmatrix} -d - \beta\tilde{v}_1 - \tilde{\beta}\tilde{v}_2 & 0 & -\beta\tilde{x} & 0 & 0 & -\tilde{\beta}\tilde{x} \\ \beta\tilde{v}_1 & -a - p\tilde{z} & \beta\tilde{x} & -p\tilde{y}_1 & 0 & 0 \\ 0 & k & -u & 0 & 0 & 0 \\ 0 & c\tilde{z} & 0 & c\tilde{y}_1 + \tilde{c}\tilde{y}_2 - b & \tilde{c}\tilde{z} & 0 \\ \tilde{\beta}\tilde{v}_2 & 0 & 0 & -\tilde{p}\tilde{y}_2 & -\tilde{a} - \tilde{p}\tilde{z} & \tilde{\beta}\tilde{x} \\ 0 & 0 & 0 & 0 & \tilde{k} & -\tilde{u} \end{pmatrix}$$

$$= \begin{pmatrix} -d - \beta\tilde{v}_1 & 0 & -\beta\tilde{x} & 0 & 0 & -\tilde{\beta}\tilde{x} \\ \beta\tilde{v}_1 & -a - p\tilde{z} & \beta\tilde{x} & -p\tilde{y}_1 & 0 & 0 \\ 0 & k & -u & 0 & 0 & 0 \\ 0 & c\tilde{z} & 0 & 0 & \tilde{c}\tilde{z} & 0 \\ \hline 0 & 0 & 0 & 0 & -\tilde{a} - \tilde{p}\tilde{z} & \tilde{\beta}\tilde{x} \\ 0 & 0 & 0 & 0 & \tilde{k} & -\tilde{u} \end{pmatrix}.$$

By observation, its eigenvalues are determined by the following two submatrices:

$$\mathbf{J}_{11} = \begin{pmatrix} -d - \beta\tilde{v}_1 & 0 & -\beta\tilde{x} & 0 \\ \beta\tilde{v}_1 & -a - p\tilde{z} & \beta\tilde{x} & -p\tilde{y}_1 \\ 0 & k & -u & 0 \\ 0 & c\tilde{z} & 0 & 0 \end{pmatrix}$$

and

$$\mathbf{J}_{22} = \begin{pmatrix} -\tilde{a} - \tilde{p}\tilde{z} & \tilde{\beta}\tilde{x} \\ \tilde{k} & -\tilde{u} \end{pmatrix},$$

where the eigenvalues of \mathbf{J}_{11} are all negative when $\mathcal{R}_1 > 1$ (see Appendix B.1). So, the local stability of this mutant free equilibrium only depends on the signs of the eigenvalues of the matrix \mathbf{J}_{22} . The two critical conditions for the negative eigenvalues of two by two matrix are:

$$\text{tr}(\mathbf{J}_{22}) = -\tilde{a} - \tilde{p}\tilde{z} - \tilde{u} < 0,$$

$$\text{det}(\mathbf{J}_{22}) = (\tilde{a} + \tilde{p}\tilde{z})\tilde{u} - \tilde{k}\tilde{\beta}\tilde{x}.$$

If $\text{det}(\mathbf{J}_{22}) > 0$, all eigenvalues of the matrix \mathbf{J}_{22} are negative, i.e., the mutant-free equilibrium is locally asymptotic stable. Otherwise, the stability of $\tilde{\mathbf{E}}$ will be violated.

Appendix C

C.1 The local stability of the coexistence equilibrium

The Jacobian matrix of the system (4.2) 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,

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

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

The characteristic equation is

$$a_0 \lambda^3 + a_1 \lambda^2 + a_2 \lambda + a_3 = 0, \quad (\text{C.1})$$

where

$$\begin{aligned}
a_0 &= 1 > 0, \\
a_1 &= \frac{c_1 - c_2}{\varphi} - (b - \mu), \\
a_2 &= [(\mu + \delta + c_1) - \beta\hat{S}][\beta\hat{S} - (\mu + \delta + c_2)] + \frac{1}{\varphi}[-(f(c_1) + c_1)(\mu + \delta + c_1) \\
&\quad + (g(c_2) + c_2)(\mu + \delta + c_2) + \beta\hat{S}(g(c_2) - f(c_1))] \\
&= [(\mu + \delta + c_1) - \beta\hat{S}][\beta\hat{S} - (\mu + \delta + c_2)] + \frac{1}{\varphi}[(\mu + \delta)(g(c_2) - f(c_1) + c_2 - c_1) \\
&\quad + c_1g(c_2) - c_2f(c_1) + \beta\hat{S}(g(c_2) - f(c_1))] > 0, \\
a_3 &= \frac{1}{\varphi}[(\mu + \delta + c_1) - \beta\hat{S}][(\mu + \delta + c_2) - \beta\hat{S}][\varphi(b - \mu) + f(c_1) - g(c_2)] > 0,
\end{aligned}$$

under the conditions (4.3)-(4.6). If

$$\frac{c_1 - c_2}{\varphi} - (b - \mu) > 0, \quad (\text{C.2})$$

we can prove that

$$\begin{aligned}
\Delta_1 &= \frac{c_1 - c_2}{\varphi} - (b - \mu) > 0, \\
\Delta_2 &= a_2a_1 - a_3 \\
&= \frac{1}{\varphi}[(\mu + \delta)(g(c_2) - f(c_1) + c_2 - c_1) + c_1g(c_2) - c_2f(c_1) + \beta\hat{S}(g(c_2) - f(c_1))] \\
&\quad + \frac{1}{\varphi}[(\mu + \delta + c_1) - \beta\hat{S}][\beta\hat{S} - (\mu + \delta + c_2)][c_1 - c_2 + g(c_2) - f(c_1)] > 0, \\
\Delta_3 &= a_3\Delta_2 > 0.
\end{aligned}$$

Now, we have proved that all roots of polynomial equation (C.1) have negative real parts by Routh-Hurwitz criterion. Therefore, the coexistence equilibrium $\hat{\mathbf{E}}$ is locally asymptotic stable when the conditions (4.3)-(4.6) and (C.2) can be satisfied.

C.2 The local stability of the mutant hosts free equilibrium

Let us study the local stability of the mutant hosts free equilibrium $\tilde{\mathbf{E}}$ in system (4.8).

The Jacobian matrix of system (4.8) is

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

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

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

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

Under the conditions (4.3)-(4.7), all eigenvalues of the matrix \mathbf{J}_{11} are negative in last subsection. Then, the local stability of the equilibrium $\tilde{\mathbf{E}}$ will depend on the signs of the eigenvalues of the matrix \mathbf{J}_{22} . Because of the first inequality in condition (4.3) we can easily obtain that the trace of matrix \mathbf{J}_{22} is always negative. If matrix \mathbf{J}_{22} has positive determinant, the mutant host-free equilibrium $\tilde{\mathbf{E}}$ is locally asymptotic stable. So, when determinant of \mathbf{J}_{22} is negative, the mutant hosts with type 1 infection can successfully establish in evolution; otherwise, mutant hosts will go to extinction in the future.

Therefore, we choose the value $-\det(\mathbf{J}_{22})$ to denote the fitness of the mutant hosts with type 1 infection.

Bibliography

- [1] Huang, G., Yokoi, H., Takeuchi, Y., Kajiwara, T., and Sasaki, T. (2011). Impact of intracellular delay, immune activation delay and nonlinear incidence on viral dynamics. *Japan Journal of Industrial and Applied Mathematics*, 28(3):383–411.

Curriculum Vitae

Liman Dai

Citizenship: Chinese

Post-Secondary Education and Degrees: Ph.D. Candidate, 2011-Present
Applied Mathematics
The University of Western Ontario, London, ON, Canada

Master of Science, 2006-2009
Mathematics and Applied Mathematics
Southwest University, Chongqing, China

Bachelor of Science, 2002-2006
Mathematics and Applied Mathematics
Beijing Institute of Technology, Beijing, China

Honours and Awards: Western Graduate Research Scholarship, 2009-Present

Beijing Excellent Graduate Student for outstanding performance
in Beijing Institute of Technology, 2006

Inspirational Scholarship of Beijing Institute of Technology, 2003-2006

Related Work Experience: Research Assistant, 2011-Present
Applied Mathematics, The University of Western Ontario

Teaching Assistant, 2011-2013
Applied Mathematics, The University of Western Ontario

Poster Representation, 2013
Disease Dynamics 2013 Workshop,
Pacific Institute for the Mathematical Science, British Columbia, Canada

Publications:

L. Dai and W. Wang. The influence of Competition among Vectors on the Disease Dynamics of Malaria. *Journal of Southwest China Normal University (Natural Science)* 2, 31-38, 2009.