



MAX-PLANCK-GESELLSCHAFT

# Applying Evolutionary Game Theory in Modeling Life History Evolution and Bacterial Population Dynamics

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## Abstract

Traditional evolutionary theory often treats selective forces from the environment and the adaptation of populations as independent of each other, focusing on the effects of natural selection on population dynamics. The fitness landscape is considered to be static, and adaptation is taken as a process of optimisation. In this thesis, I intend to call attention to the interactions between the environment and biological populations, emphasising the feedbacks from the population to the environment that changes the direction, rate and dynamics of the evolutionary process.

Two general approaches through which populations affect their environment are studied in this thesis. The first one is via life history and demographic architecture of the population. The second one is through interactions among individuals of the same or different types in the population. These two approaches are not inter-exclusive, but rather interact and reinforce each other.

Evolutionary game theory provides a convenient framework of modelling interactions, but it usually takes no account of the life history aspects of the organisms in the population. Demographic models, on the other hand, emphasise the optimisation of life history traits, while neglecting interactions among individuals in the population. One major innovation in this thesis project is to build a system that takes into account both aspects and connects the two theoretical frameworks. This is realised by defining age/life-stage dependent strategies. The behaviours of individuals are conditioned on the age/life-stage of the players involved in the interactions. The dynamics of the system are studied under both deterministic and stochastic frameworks.

Besides an analytical and numerical study of abstract mathematical models, this thesis also includes collaborative projects with experiments in real biological systems. In one modelling project, we show how complex population dynamics can emerge from a simple system of two bacteria species, under frequency dependent selection. Preliminary experimental evidence suggests that the infection and cross-infection of phages might have produced such frequency dependent effects. We continue the investigation in a follow up project.

Covering diverse subjects and employing various methods and mathematical techniques, this thesis summarises my research in the last three years, raises new questions, and opens up opportunities for future investigations.

## Kurzfassung

Die traditionelle Evolutionstheorie behandelt die selektiven Kräfte der Umwelt und die Anpassung von Populationen meistens als voneinander unabhängig. Dabei liegt der Fokus auf den Effekten, die natürliche Selektion auf die Populationsdynamik ausübt. Die Fitnesslandschaft wird als statisch angesehen und Anpassung ist somit ein Optimierungsprozess. In dieser Arbeit zeige ich die Bedeutung der Interaktionen zwischen der Umwelt und natürlichen Populationen und hebe dabei die Rückkopplungen hervor, die die Population auf die Umwelt hat und die die Richtung, Rate und Dynamik des evolutionären Prozesses ändern.

In dieser Arbeit werden zwei generelle Ansätze untersucht, durch welche die Population ihre Umwelt beeinflusst. Der erste Ansatz behandelt die Lebensgeschichte und demografische Struktur der Population. Der Zweite betrachtet die Interaktionen zwischen Individuen der gleichen Spezies oder zwischen verschiedenen Spezies. Diese beiden Ansätze werden hier nicht nur separat betrachtet; vielmehr beeinflussen und verstärken sie sich gegenseitig.

Die Spieltheorie modelliert genau solche Interaktionen. Sie berücksichtigt normalerweise jedoch keine lebenshistorischen Aspekte der Individuen der Population. Demographische Modelle hingegen betonen die Optimierung der lebenshistorischen Merkmale, vernachlässigen gleichzeitig allerdings Interaktionen zwischen Individuen der Population. Eine wesentliche Innovation dieser Doktorarbeit ist die Untersuchung eines Systems, das beide Ansätze berücksichtigt und diese verbindet. Dies wird durch die Definition von alters- bzw. lebensphasensabhängigen Strategien umgesetzt. Das Verhalten von Individuen ist abhängig vom Alter und Lebensstadium der miteinander interagierenden Spieler. Die Dynamik des Systems wird sowohl mit deterministischen als auch stochastischen Modellen untersucht.

Neben rein analytischen und numerischen Betrachtungen abstrakter mathematischer Modelle, beinhaltet diese Arbeit auch Projekte, die direkt auf biologischen Experimenten aufbauen. In einem Projekt zeigen wir, dass unter frequenzabhängiger Selektion ein relativ einfaches System mit zwei Bakterienstämmen zu einer komplexen Populationsdynamik führen kann. Vorläufige experimentelle Daten lassen vermuten, dass Infektionen und Kreuzinfektionen von Phagen zu frequenzabhängigen Effekten führen können. Wir vertiefen daher die Untersuchung des zugrunde liegenden Mechanismus solcher frequenzabhängigen Effekte in einem Kapitel dieser Arbeit.

Diese Arbeit fasst die Untersuchungen meiner Doktorarbeit zusammen, sie umfasst verschiedene Fachgebiete, wendet dabei diverse Methoden und mathematische Techniken an. Gleichzeitig bildet sie den Nährboden für neue Fragen und zeigt somit zukünftige Forschungsarbeiten auf.

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# Introduction

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Mathematical modelling has been playing an important role in analysing and validating the Darwinian theory of evolution by natural selection. For example, one of the greatest early achievements was to show that genetic variation is preserved under the Mendelian hereditary system. The Hardy-Weinberg law shows that the genetic variation needed for natural selection has no intrinsic tendency to diminish. Assuming no selection, mutation, or any other disturbing force such as the randomness in finite size populations, different alleles, once established will remain, and their frequencies will keep unchanged from one generation to the next.

Mathematical modelling also helps us understand quantitatively the evolutionary dynamics of new genetic types. For example, following the emergence of a beneficial mutant, deterministic mathematical models can make predictions on the rate at which the mutant type is incorporated into a population by natural selection. Beyond the deterministic regime, facilitated by probability and stochastic process theory, the role of random fluctuations in gene frequencies can be evaluated, in biological populations of finite sizes. As an example, the probability at which a mutant type fixes in a population, and the time it takes until fixation can be studied using stochastic mathematical models. Furthermore, the emergence and rapid development of the whole field of bioinformatics that currently analyses complexity at the whole genome (and other -omes) level are only possible with the help of mathematical models.

Popular modelling frameworks in evolutionary biology include population genetics, evolutionary game theory, adaptive dynamics, and life-history optimisation. These different modelling frameworks all have their merits and limitations, and they are best applied for solving different problems. In this thesis, evolutionary game theory and life history theory are used. Building on these two existing theoretical frameworks, I try to build a bridge which connects the two fields, facilitating the exchange of ideas. In the following

sections of this introduction, I will first introduce the basic concepts of evolutionary game theory and life history theory, and then introduce the necessity of integrating both.

## 1.1 Evolutionary game theory

### 1.1.1 Classic game theory

Economy is hard to predict. Unlike the weather, a forecast usually does not influence the outcome, a prediction on the economy, especially when it is announced to the public, almost always changes the outcome tremendously. The “mission impossible” of predicting the Austrian economy kept tormenting the economist Oskar Morgenstern, who has been working in the Institute for Business Cycles Research (Institut für Konjunkturforschung) in Vienna in the 1930s. To quote the brilliant metaphor of his own, the never ending chasing game between economists and the economy is like the never ending pursuit of Sherlock Holmes by the infamous Professor Moriarty [Leonard, 2010].

After years of suffering from and broadcasting his trouble with the “impossibility theorem of economic prediction”, Morgenstern was introduced by the Czech mathematician Eduard Čech, to a paper of John von Neumann on parlor games [von Neumann, 1928]. This seminal paper provided the first reliever to Morgenstern’s headache. Furthermore, it eventually led to the important collaboration of von Neumann and Morgenstern [1944], which gave birth to classic game theory.

Among the classical game theory models, the *prisoner’s dilemma* is an interesting case. Using it as an example we introduce a few basic concepts of game theory that is needed later, such as the *strategy*, the *payoff matrix*, and the *Nash Equilibrium*. The scenario of prisoner’s dilemma was nicely described by Poundstone [1992] as the following:

Two members of a criminal-gang are arrested and imprisoned. Each prisoner is in solitary confinement with no means of communicating with the other. The prosecutors lack sufficient evidence to convict the pair on the principal charge. They hope to get both sentenced to a year in prison on a lesser charge. Simultane-

ously, the prosecutors offer each prisoner a bargain. Each prisoner is given the opportunity either to: betray the other by testifying that the other committed the crime, or to cooperate with the other by remaining silent. The offer is:

- If A and B each betray the other, each of them serves 2 years in prison;
- If A betrays B but B remains silent, A will be set free and B will serve 3 years in prison (and vice versa);
- If A and B both remain silent, both of them will only serve 1 year in prison (on the lesser charge).

Important information for predicting the prisoners' behaviours in the story can be summarised in the form of a *payoff matrix*

$$\begin{array}{cc} & \begin{array}{cc} \textit{Betray} & \textit{Cooperate} \end{array} \\ \begin{array}{c} \textit{Betray} \\ \textit{Cooperate} \end{array} & \left( \begin{array}{cc} -2 & 0 \\ -3 & -1 \end{array} \right). \end{array} \quad (1.1)$$

The choices of behaviours that the prisoners can make are called *strategies*. In this case, they could either “betray” the other by testifying the joined crime, or “cooperate” with the other by remaining silent. The entries of the matrix are the *payoffs* from strategy interactions. In this particular case, those are the numbers of years they would serve in prison. The payoff matrix is a very informative way to describe the outcome of strategy interactions.

Forced to play the strategic game against each other, the rational prisoners (let's call them Alice and Bob) need to find the “best reply” to what the other player does. Alice would think like this, “if Bob cooperates, it is better for me to betray, so that I can immediately walk out free; even if he betrays, it is still better to betray as well, two years in prison is nevertheless better than three years. So I should choose to betray no matter what Bob chooses to do”. Unfortunately, Bob is equally rational and thinks the same. Therefore they both choose the “best reply”, betraying each other and thereby serving two years in prison. The two strategies (i.e. “Betray” for Alice and “Betray” for Bob) are said to form a *Nash Equilibrium* pair since each is a best reply

to the other. The choices of Alice and Bob satisfy a minimal consistency requirement: no one has an incentive to deviate.

Paradoxically, the “rational choice” of betraying each other led both prisoners serving two years in jail, which is worse than the situation of serving only one year if they have kept silent. The prisoner’s dilemma shows that sometimes choosing strategies corresponding to the Nash Equilibrium may not produce the best results for the players. It also shows the difficulty of cooperation in general. To cooperate, individuals have to pay a personal cost in order to benefit others. Consequently, the cooperators would have worse payoffs compared with the cheaters, who refuse to pay the cost of cooperation, but still receive the benefits. Therefore, cheaters can invade a population of cooperators, leading the to the unfortunate Nash Equilibrium where everyone has a lower payoff than if they have cooperated.

Interestingly however, cooperation prevails in nature. Natural selection has produced various ways that allow cooperation to evolve [Nowak, 2006b]. A classic example is the food sharing behaviour observed in vampire bats [Wilkinson, 1984]. The bats can only feed on blood and will die after just 70 hours of not eating. Therefore regurgitating blood from the stomach and sharing it with another bat is of great benefit to the receiver but also incurs a great cost to the donor. Cooperation among the bats is maintained by a strategy called “tit-for-tat”. Namely, a bat that has behaved altruistically in the past are helped by the others in the future. A bat that has refused to help the others will get declined, too, when itself is in need of help. Although the nature of the blood sharing behaviour among vampire bats is still under debate [Carter and Wilkinson, 2013], studies of mathematical models have shown that reciprocity in repeated interactions can provide a way of escaping from the prisoner’s dilemma [Hofbauer and Sigmund, 1998; McElreath and Boyd, 2008; Nowak, 2006a].

In the case of the prisoner’s dilemma, the unique Nash Equilibrium is a pure strategy for both players (i.e. always betray). In other games, it can be better to randomise one’s choices rather than sticking to a fixed pure strategy. The children’s game *Rock-Paper-Scissors* provides one interesting example. Following the simple rules that *Rock* smashes *Scissors*, *Scissors* cut *Paper*, and *Paper* wraps *Rock*, the winner gets  $a$  points and the loser loses  $b$

points ( $a, b > 0$ ) in each round of the contest. Written in the form of a payoff matrix, the game summarises to

$$\begin{array}{c} \textit{Rock} \\ \textit{Scissors} \\ \textit{Paper} \end{array} \begin{array}{ccc} \textit{Rock} & \textit{Scissors} & \textit{Paper} \\ \left( \begin{array}{ccc} 0 & a & -b \\ -b & 0 & a \\ a & -b & 0 \end{array} \right) \end{array}. \quad (1.2)$$

In this case, the unique Nash equilibrium for both players is to choose *Rock* or *Scissors* or *Paper* randomly with equal probabilities. Letting chance decide, mixed strategy makes sure the existence of a Nash Equilibrium in any  $n$ -person game, in which each player has a finite set of pure strategies. The proof of the existence of a mixed strategy Nash Equilibrium was given in the classic paper of Nash [1950].

The interesting cyclic dominance of strategies in the *Rock-Paper-Scissors* game is not only an artificial design of a children’s game. It has been observed in many ecosystems in nature, providing an important way of maintaining biodiversity. We discuss this in more detail later, in section 1.1.6 of the introduction.

Work on classic game theory has produced interesting mathematical and economic developments. But it only considers the cases where specific *individuals* of players trying to guess each other’s strategy and find a best reply. Classic game theory confronts difficulties when it comes to deal with problems involving strategy dynamics in *populations*, such as explaining the sex ratio of animal populations and the ritual competition behaviours without a real fight or killing. This leads to the birth of evolutionary game theory.

### 1.1.2 From individuals to populations

“The greatest conceptual revolution in biology... the replacement of typological thinking by population thinking.” – Ernst Mayr

Evolutionary game theory was originally developed by **Maynard Smith and Price** [1973] for explaining the “limited war” among animals. It is not surprising that animals fight for limited resources, such as mates, dominance rights, desirable territories, etc. Through such combats, the winners have

more chances to transmit their genes to the next generation than the losers. Consequently, it is natural to imagine that nature would select for individuals that has the most effective weapons in fighting against competitors. If the rival is killed or seriously injured, the winner would be more likely to spread its genes, and thus the frequency of the reckless type in the next generations should grow. In the long run, however, it would lead to the suicide of the species, if it follows the above mentioned logic.

Fortunately, this is not how nature works. In real animal conflicts, the competitors seldom escalate the war but rather use inefficient weapons or ritualised tactics that do not cause serious damage to any of the contestants. Using an example cited in the original paper of [Maynard Smith and Price \[1973\]](#), in many species of snakes, the males fight by wrestling without using their fangs [[Shaw, 1948](#)]. Peaceful contests like such obviously are good for the overall benefit of the species, but it is puzzling how natural selection achieves those good solutions.

The more complicated interactions in the original work of [Maynard Smith and Price \[1973\]](#) were later on summarised into a simple toy model, called the *Hawk-Dove* game. It describes the interactions of two strategies in a population of players. The payoff matrix is as follows:

$$\begin{array}{cc} & \begin{array}{cc} Hawk & Dove \end{array} \\ \begin{array}{c} Hawk \\ Dove \end{array} & \left( \begin{array}{cc} (v - c)/2 & v \\ 0 & v/2 \end{array} \right) \end{array} \quad (1.3)$$

In the payoff matrix,  $v$  stands for the value of the resource and  $c$  stands for the cost of a devastating fight. It assumes that whenever two *Hawks* meet, or two *Doves*, both are equally likely to win. Therefore their expected payoff are  $(v - c)/2$  and  $v/2$ , respectively. If a *Hawk* and a *Dove* meet, the *Dove* flees with 0 gain and the *Hawk* gets the whole resource  $v$  without any additional cost. Note that  $c > v$ , namely, the cost of conflict exceeds the value of the resource.

Now think in terms of animal *populations*. A homogenous population of *Doves* can be easily invaded by a few *Hawks*, who win all contests without a fight. Conversely, a homogenous population of *Hawks* can also be invaded by a few *Doves*. Although a *Dove* has no gain from flying away in front of

a competitor, it is still better than the negative payoff of *Hawks* who keep tearing at each other. Therefore neither strategy alone is stable in the long run. Evolution will lead to a mixed population of both *Hawks* and *Doves*.

From the example of this extremely simplified *Hawk-Dove* game, we can already see some important differences between classic game theory and evolutionary game theory. In many models of classic game theory, such as the *prisoner's dilemma* game and the *Rock-Paper-Scissors* game, players have perfect knowledge about the rules and the structure of the game. But in evolutionary games, players do not have such knowledge. In addition, compared with the smart and rational players in classic game models, players in evolutionary game theory models normally have bounded rationality. The strategy of an individual is obtained not by rational choice, but by biological inheritance.

Furthermore, classic game theory emphasises the analysis of static solutions, such as the Nash Equilibrium, (i.e., a solution under which no player has anything to gain by changing only their own strategy). In contrast, evolutionary game theory brings more attention to how strategies invade each other, and it also highlights how individuals change their strategy over time based on the comparison of payoffs.

### 1.1.3 Population state

In an infinitely large well mixed population, the state of the population can be represented by a stochastic vector  $\mathbf{x} = (x_1, x_2, \dots, x_n)$  with  $x_i \geq 0$  and  $x_1 + x_2 + \dots + x_n = 1$ . Each element of  $\mathbf{x}$  stands for the frequency of a particular strategy, and  $n$  is the total number of strategies. The total frequencies of all strategies sum up to one. We can therefore denote the set of all states of the population by  $\Delta_n$ , which is a simplex in the  $n$ -dimensional real space  $\mathbb{R}^n$ . It is convenient to represent low dimensional simplexes geometrically, shown in Figure 1.1.

In the case where there are three pure strategies, like the *Rock-Paper-Scissors* game, in a population in which any individual plays only one pure strategy, the state of population can be represented in a  $\Delta_3$  simplex, as illustrated in Figure 1.2.

Now we have summarised the state of the population in a stochastic vector,

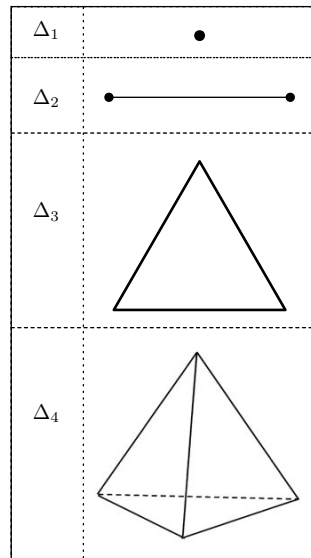


Figure 1.1: Graphical representation of some low dimensional simplexes. (i)  $\Delta_1$  is a point 1 in  $\mathbb{R}^1$ , (ii)  $\Delta_2$  is a line segment joining  $(0,1)$  and  $(1,0)$  in  $\mathbb{R}^2$ , (iii)  $\Delta_3$  is a equilateral triangle with vertices  $(0,0,1)$ ,  $(0,1,0)$  and  $(1,0,0)$  in  $\mathbb{R}^3$ , and (iv)  $\Delta_4$  is a regular tetrahedron with vertices  $(0,0,0,1)$ ,  $(0,0,1,0)$ ,  $(0,1,0,0)$  and  $(1,0,0,0)$  in  $\mathbb{R}^4$ .

and for low dimensional cases, like the *Rock-Paper-Scissors* game, we can conveniently plot the state of population on a simplex. In the next step we study how the state of population changes over time. This brings us to dynamical models of evolutionary processes.

#### 1.1.4 Deterministic evolutionary dynamics

One great leap from static game theory models to dynamical evolutionary game theory models is to assume that populations can evolve, in other words, the relative frequency  $x_i$  of a strategy  $i$  changes over time. From now on, the state vector  $\mathbf{x}(t)$  is time-dependent. We use  $\dot{x}_i(t)$  to denote the speed at which the frequency of strategy  $i$  changes over time. In the deterministic system, the underlying assumption of differentiability (changes are smooth) implies that the population size is infinitely large, or  $x_i$  has to be interpreted as an expected value, rather than a bona fide frequency [Sigmund, 2011].

A great number of game dynamics have been developed to study the evolutionary outcome of strategy interactions, including the replicator dynamics,



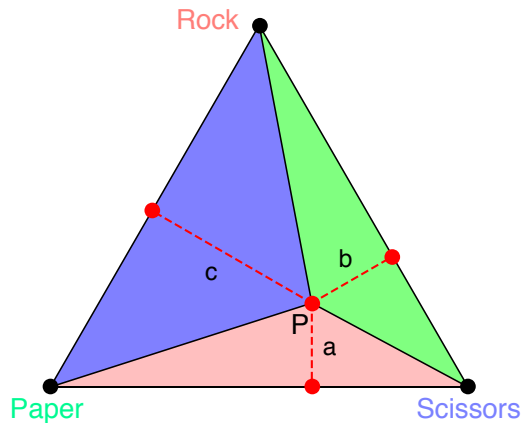


Figure 1.2: Population state represented in a  $\Delta_3$  Simplex. The coordinates of P with respect to the three strategies are equivalent to the heights of the three small triangles of corresponding colours. The sum of the three distances from P to each of the sides are equal to 1 ( $a + b + c = 1$ ). In this way, the frequency of *Rock*, *Paper* and *Scissors* players can be conveniently read from the figure. The state of the population is  $(f_{Rock}, f_{Paper}, f_{Scissors}) = (a, b, c)$ .

the best response dynamics, the payoff projection dynamics and the Brown-von Neumann-Nash dynamics, etc [Sandholm, 2010]. In general, these game dynamics assume that strategies with higher payoff do better. The limiting behaviour of them is often a Nash Equilibrium with additional stability properties [Cressman and Tao, 2014].

Among them the first and most widely used evolutionary dynamics is the replicator dynamics (Eq.1.4). It is originally defined by Taylor and Jonker [1978], and Zeeman [1981], and named by Schuster and Sigmund [1983].

$$\dot{x}_i = x_i \cdot (f_i - \langle f \rangle) \quad (1.4)$$

In equation (1.4),  $f_i$  is the fitness of individuals of the  $i$ -th strategy, and  $\langle f \rangle$  is the average fitness of all individuals in the population. Assuming that payoff from game interactions is translated as reproductive fitness, the replicator dynamics describes the per capita rate of change of the frequency of a strategy  $\dot{x}_i/x_i$  as equal to the difference between its expected payoff  $f_i$  and the average payoff of the population  $\langle f \rangle$ . In other words, if the payoff of a strategy is higher than the population average, its frequency will increase; if the payoff

of a strategy is lower than the population average, its frequency will decrease; if the payoff of a strategy is equal to the population average, the frequency of it will stay. In addition, the greater the payoff difference, the faster the speed of the change. Using matrix notation, the replicator equation can also be written as in Equation (1.5):

$$\dot{x}_i = x_i[(A\mathbf{x})_i - \mathbf{x} \cdot A\mathbf{x}], \quad (1.5)$$

in which  $A$  is the payoff matrix, and  $\mathbf{x}$  is the population state vector. The expected payoff of the  $i$ -th strategy is  $f_i = (A\mathbf{x})_i$ , and the average payoff of the population is  $\langle f \rangle = \mathbf{x} \cdot A\mathbf{x}$ .

An interesting property of the replicator dynamics is that the simplex  $\Delta_n$  (including boundaries and the interior) is *invariant* [Hofbauer and Sigmund, 1998; Sigmund, 2010, 2011]. It means that it is possible to find a lower dimensional subset of the simplex, that any trajectory starting from it will stay on it. This amazing property makes it possible to reduce high dimensional space to foliated surfaces of lower dimensions. It is easier to study the dynamics in lower dimensions and then come back to high dimensions by reconstructing the whole picture. We use this technique both in chapter 2 and chapter 4. Not only the whole simplex, the interior of the simplex  $\text{int}\Delta_n$ , is also invariant. It means that any trajectory starting from the interior of the simplex will stay in the interior forever, and thus it will never touch the boundary. This brings us to the other side of the coin. The nice mathematical property of the invariant of motion may create problems when applied to some biological systems. We come back to this point later in the next section, when discussing stochastic evolutionary dynamics [Sigmund, 2011].

Another interesting and important feature of the replicator equation is its intimate connection with the Lotka-Volterra equation. There exists a mapping from the  $n$  dimensional replicator equation (1.4) to the  $n - 1$  dimensional Lotka-Volterra equation

$$\dot{y}_i = y_i(r_i + \sum_{j=1}^{n-1} d_{ij}y_j), \quad (1.6)$$

in which  $r_i = a_{in} - a_{nn}$ ,  $d_{ij} = a_{ij} - a_{nj}$ , and  $a_{ij}$  is the element in the  $i$ -th row and

the  $j$ -th column of the game payoff matrix  $A$  [Hofbauer and Sigmund, 1998; Sigmund, 2011]. In other words, this connection provides a bridge through which the results about Lotka-Volterra equation and the replicator equation become interchangeable under certain conditions. But on the other hand, the replicator equation focuses on relative changes in population sizes under frequency dependent fitness, while the Lotka-Volterra equation describes populations of changing size. The replicator equation is more readily interpreted in the words of strategy interactions, while the Lotka-Volterra equation is more naturally explained in ecological terms. Through this link, it is possible to connect the replicator dynamics with experimental results [Ellner and Guckenheimer, 2011; May and McLean, 2007; Murray, 2007]. We make use of this connection in Chapter 4.

Apart from the replicator equation, many other evolutionary dynamics have been developed to capture different population dynamics scenarios. For example, the *best reply dynamics* is another widely used and thoroughly studied deterministic evolutionary game dynamics. In contrast with the smooth change of frequencies of strategies through reproduction under the regime of the replicator dynamics, the best reply dynamics assumes that in a large population, a small fraction of the very smart players change their strategy, choosing best replies (not necessarily unique)  $\beta(\mathbf{x})$  to the current mean population strategy  $\mathbf{x}$ . This produces the best reply dynamics:

$$\dot{\mathbf{x}} \in \beta(\mathbf{x}) - \mathbf{x} \tag{1.7}$$

When applied to human interactions, the best reply dynamics can be interpreted as intelligent players respond optimally. In the biological context, it has also been interpreted as biological “explorations”, such as mutations [Sandholm, 2010], although in reality it is unlikely that a mutation happens to be the best response. As a result, when modelling population dynamics in biological systems, the application of the best reply dynamics is much more limited, compared with the widely used replication dynamics. In Figure 1.3 we show that under the same game (implying the same Nash Equilibria), the paths that population state follows can be very different, under different types of population dynamics.

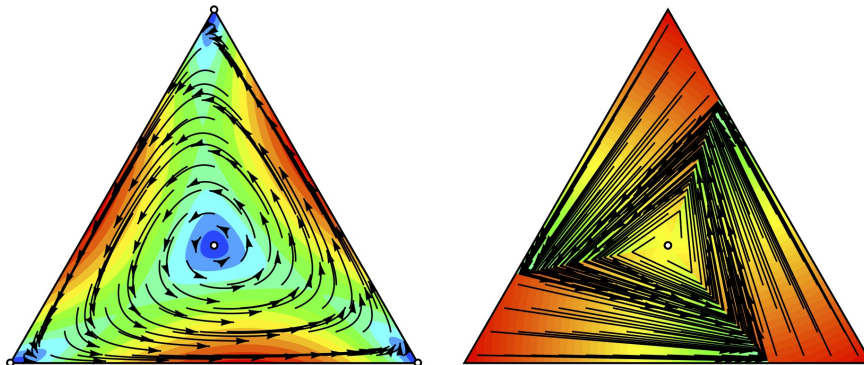


Figure 1.3: The same *Rock-Paper-Scissors* game under different dynamics. We use the payoff matrix as in Equation 1.2 with  $a = 1$  and  $b = 2$ . Because the game is totally symmetric, it does not matter which strategy is on which vertex. The underlying population dynamics are the replicator dynamics (left panel) and the best response dynamics (right panel). This figure is produced using the *Dynamo* package [Sandholm et al., 2012].

### 1.1.5 Stochastic evolutionary dynamics

In section 1.1.4 we introduced some interesting mathematical properties of the replicator dynamics. Among them we mentioned that the interior of the population state simplex is invariant. On one hand, this property provides great convenience in mathematical analysis, but on the other hand, it also implies that if a strategy is present in the population, it will be present forever. The frequency of it may decrease to extremely low but never hit zero. Therefore *extinction is not possible*. This is obviously not true in real biological populations. This example shows us that not all results obtained from the deterministic evolutionary dynamics can be transferred directly to population with finite size.

Although deterministic evolutionary dynamics has many beautiful mathematical properties and it describes population dynamics in very large populations quite well, there is no guarantee that it still provides good approximations in biological systems that are subject to substantial fluctuations in population size. Therefore we continue to explore the role of internal noise and

randomness arising from the limited size of populations under *stochastic evolutionary dynamics*. This modelling framework provides a way to circumvent the “problem of no extinction” by acknowledging the finite size of populations. Now it is possible to ask questions about the evolutionary fate of mutants. For example, one could ask the probability that a mutant spreads and eventually takes over the whole population, or the probability that it goes extinct. In this introduction of the thesis, only the concepts that are used later in Chapter 3 and a few other indispensable ones are introduced to facilitate understanding. A comprehensive introduction to stochastic evolutionary dynamics can be found in the book chapter of [Traulsen and Hauert \[2009\]](#).

In stochastic evolutionary dynamics models it is essential to specify the microscopic mechanisms of strategy transmission. Strategies are most commonly transmitted through reproduction or social learning. Two commonly used stochastic processes of strategy transmission via reproduction are the Moran process [[Moran, 1958](#)] and the Wright-Fisher process [[Fisher, 1930](#); [Wright, 1931](#)]. Both of them have deep roots in population genetics [[Ewens, 2004](#)].

The Moran process has been transferred to evolutionary game theory to model strategy dynamics in populations of overlapping generations [[Nowak et al., 2004](#); [Taylor et al., 2004](#)]. In each time step, one individual gives birth by introducing a copy of itself into the population, followed by the death of a random individual except the newborn to keep population size constant. In this simple birth-death process, the picking of an individual for reproduction is at random, but proportional to the fitness of the individual’s reproductive fitness. In the context of evolutionary games, fitness ( $f$ ) is translated from the payoffs ( $\pi$ ) from strategy interactions. For example, this could be through a linear function, e.g.  $f = 1 - \omega + \omega\pi$ , as in [Nowak et al. \[2004\]](#), or through an exponential function, i.e.  $f = \exp[\omega\pi]$ , as in [Traulsen et al. \[2008\]](#).

In both mapping functions,  $\omega$  denotes the *intensity of selection*. This parameter adjusts the relative importance of selection and random drift in evolutionary processes. Assume that the fitness of the wild type is one, and the fitness of the mutant is  $f$ . In the case where  $\omega = 0$ , for both mapping functions,  $f$  takes the value of one. It means that in this case, selection is absent, and population dynamics is driven by random drift alone. For the

linear mapping function,  $\omega$  has to have an upper bound. This is to make sure that fitness to be nonnegative so that it is biologically meaningful. For the exponential mapping function,  $\omega$  can take any positive value. An important case is when  $\omega \ll 1$ , meaning that all individuals perform approximately equally well. In this case, selection has an effect, but random drift plays the most important role in population dynamics. This scenario is called "weak selection".

Weak selection is a widely used assumption in population genetics. It has also been introduced to evolutionary game theory in the seminal work of [Nowak et al. \[2004\]](#). Many interesting and important results have been derived under weak selection approximations, with the help of perturbation analysis [[Ewens, 2004](#)], such as the change of linkage disequilibrium under weak epistasis [[Hastings, 1985](#)], effects of random drift and selection against heterozygotes across a genetic barrier [[Pialek and Barton, 1997](#)], and the evolutionary dynamics on graphs [[Fu et al., 2009](#)]. Empirical studies also show that most mutations have very small fitness consequences [[Eyre-Walker and Keightley, 2007](#)]. Although the assumption of weak selection is mostly for mathematical convenience, it can be applied appropriately to some biological circumstances.

Even when selection is not weak, results derived under the weak selection approximation can still be insightful in some cases. For example, in populations of infinite size, changing the intensity of selection only results in a rescaling of time, and thus it does not affect the outcome of evolutionary dynamics [[Hofbauer and Sigmund, 1998](#); [Traulsen et al., 2005](#)]. But it is also important to note that in finite populations, the long-term evolutionary outcome obtained under weak selection often cannot be transferred directly to the case of arbitrary intensity of selection, especially when the number of strategies are large [[Wu et al., 2013](#)]. In chapter 3, we study the pattern of fixation probability of a mutant in age structured populations of finite size and fixed demographic structure. In order to keep generality of the results, we calculated the fixation probability numerically, without making the weak selection approximation. But it is a natural approach to obtain more analytical insights when extending the model to the case of multiple age classes in the future.

### 1.1.6 Games in bacterial worlds

Bacterial populations are great systems for applying evolutionary game theory to study the origin and maintenance of biodiversity [Czaran et al., 2002; Durrett and Levin, 1997, 1998; Franzenburg et al., 2013; Kerr et al., 2002; Xavier et al., 2009] and cooperation [Chuang et al., 2009; Gore et al., 2009; Greig and Travisano, 2004; Nadell et al., 2008; Xavier and Foster, 2007]. Compared to large organisms like animals and plants, bacteria have much shorter generation times and larger population sizes, making it convenient for experimental manipulations and quantifications. In addition, the dynamics of bacterial populations display patterns that are also observed in populations of animals and plants, such as the cyclic fluctuations of species frequencies. These patterns can be influenced by many common factors that affect population dynamics of large organisms, too. For example, the spatial and demographic structures of the population, the dispersal of individuals, frequency or density dependent fitness, to name a few. Therefore it is worthwhile to use bacterial populations as model systems for studying and testing ecological and evolutionary theories.

A recent comprehensive review of games in bacterial populations can be found in the book chapter by Frey and Reichenbach [2011], where the authors covered both deterministic and stochastic models integrated with empirical studies. Here we only introduce the necessary background for chapter 4 and chapter 5, focusing on the role of frequency and density dependent interactions on the maintenance of biodiversity.

Negative frequency dependent selection is an important mechanism of the maintenance of biodiversity. One way that produces negative frequency dependent reproductive fitness for different phenotypes or different species is through *cyclic dominance*, like the three strategies in the *Rock-Paper-Scissors* game, which was introduced in section 1.1.1, and its basic population dynamics behaviour under the replicator dynamics and the best response dynamics have been shown in figure 1.3 of section 1.1.4.

Cyclic dominance of strategies have also been known as *non-transitive competition* [Kerr et al., 2002] and *non-hierarchical competition* [Frey and Reichenbach, 2011]. In cyclic dominance, each type (e.g. phenotype, species, strategy) outperform another, but is also itself outperformed by a different

one. This relationship has been found in many ecosystems, including coral reef invertebrates [Buss and Jackson, 1979; Jackson and Buss, 1975], male lizards in the inner Coast Range of California [Sinervo and Lively, 1996], rodents in the high-Arctic tundra in Greenland [Gilg et al., 2003], and in microbial systems, such as different strains of *E. coli* [Kerr et al., 2002; Kirkup and Riley, 2004] and yeast [Paquin and Adams, 1983].

In the *E. coli* system of [Kerr et al., 2002], there are three different strains. One of them is able to produce a toxin called Colicin E2 that acts as a DNA endonuclease. The toxin producing strain (C) kills the sensitive strain (S), which grows faster than the toxin resistant strain (R), because it is costly to produce the immune protein which protects R cells against the toxin. And the R strain grows faster than the C strain, because it involves extra cost to produce the toxin. As a result, the three strains of *E. coli* cyclicly dominate and being dominated by each other, resembling the *Rock-Paper-Scissors* game. In experiments the authors found that limited dispersal and spatially localised interactions are necessary for the coexistence of the three strains. This is consistent with theoretical predictions [Durrett and Levin, 1997; Pagie and Hogeweg, 1999].

Beyond the artificial *E. coli* populations on a Petri dish, the epithelial surfaces of most animals are colonised by diverse microbial communities, which serve many beneficial functions, including pathogen control [Buffie et al., 2012; Fraune et al., 2014; Kamada et al., 2013]. In addition, quantitative studies have shown that the composition of bacterial communities during establishment in neonatal animals are dynamic and complex, but at the same time follow reliable temporal patterns [Franzenburg et al., 2013; Palmer et al., 2007]. However, knowledges about the processes controlling community membership and influencing the establishment of the microbial ecosystem during development are still very limited. In the work of Franzenburg et al. [2013], the temporal pattern that the frequency of the most abundant bacterial species in the stable adult microbiota rises in the beginning or colonisation, and then goes through a large decline rapidly, and then grows up again steadily to a stable dominance. This pattern was captured by the replicator-mutator equation,

$$\dot{x}_i = x_i (f_i - \bar{f}) + \lambda(t) \left( \frac{\bar{f}_i^r}{n-1} - x_i f_i \right), \quad (1.8)$$



where the first term describes changes due to fitness difference with population average, and the second term describes random gain or lose because of all other types proportional to the rate of colonisation.

Although the replicator-mutator equation describes the observed pattern and proposes a tentative mechanism that could produce such pattern, it does not provide detailed information or hypotheses on the microscopic interactions among bacterial cells. It also does not include the influence of population size fluctuation nor density dependent effects. In chapter 4, we integrate both experimental and modelling approaches to investigate the competition dynamics of the two most abundant bacterial species *in vitro*. In experiments, we find that the growth rates of the two interacting bacterial species are frequency dependent. Using mathematical modelling, we show that the frequency dependent growth rates can produce the complex population dynamics patterns observed in the experiments. As a followup, in Chapter 5, we ask what are the mechanisms producing such frequency dependent growth rates. Furthermore, we also try to find out the underlying mechanisms behind the role of *Curvibacter* sp. as a keystone species in the *Hydra* microbiota.

## 1.2 Life History Theory

Life history theory aims to understand the causes and consequences of genetic and environmental variation in life history traits, both within and among species [Flatt and Heyland, 2011]. Historically it has had major successes in explaining the diversity of life history strategies as a result of natural selection, as reviewed comprehensively in the books by Roff [1992] and Stearns [1992]. There are seven most important traits that characterise the life history of a species in classic life history analysis: (1) size at birth, (2) growth pattern, (3) age and size at maturity, (4) number, size, and sex ratio of offspring, (5) age- and size-specific reproductive investment, (6) age- and size-specific mortality schedules, and (7) the length of life [Stearns, 1992]. Taken together in the light of evolution, these life history traits determine Darwinian fitness through two most important fitness components – reproduction and survival.

The idea of tradeoff is a central concept in life history theory. Organisms normally face limited resources, which must be competitively allocated to

different functions, such as growth, reproduction, survival and maintenance. Resources invested into one function can hardly be used also for another, leading to tradeoffs. In the case where selection works on both reproduction and survival, different functions of resource allocation can lead to huge differences in the fixation probability of a mutant, in age structured populations. We study this and evaluate the differences between selecting on reproduction and survival in Chapter 3.

One important feature of models in life history theory is that they allow growth in population size. This is in sharp contrast with evolutionary game models that put more emphasis on the dynamical changes of the frequencies of different strategies. The exponential population growth model (Eq. 1.9) is the simplest and most basic population growth model, in which  $N(t)$  is the number of individuals in the population (or population density, the number of individuals per unit space) at time  $t$ , and  $r$  is the growth rate of the population.

$$N(t) = N(0) \cdot e^{rt} \tag{1.9}$$

When  $r > 0$ , the exponential population growth model produces the result that the size of population will increase exponentially to infinitely large, which is unrealistic. In the book of [Anderson and May \[1992\]](#), the authors explain this problem by comparing it elegantly with Newton's first law of motion:

“A body remains in its state of rest or uniform motion in a straight line, unless acted on by external forces.”

Similarly, in real biological populations, growth cannot go on forever, because the rates of birth and death will change over time. To use the words of [Anderson and May \[1992\]](#),

“A closed population of self-reproducing entities – such as viruses, cells, animals or plants – will grow or decay exponentially at a constant rate, unless a change in conditions alters the per entity birth or death rate.”

This shows that the rates of birth and death are of fundamental importance in describing and predicting population dynamics. Therefore, they are called *vital rates* of the population. The values of these vital rates can be affected

by many factors including frequency and density dependent effects through interactions, as discussed in the previous section. From the genetics and physiological perspective, they can also depend on the age or life stages of the individuals, especially for species with overlapping generations (e.g. humans) and for species with very different stages of life (e.g. insects). This leads us to age and life stage structured population models.

### 1.2.1 Age structured populations models

The most convenient and widely used way of expressing an age-structured population model is by matrix notation. A typical age structured population model as shown in (1.10) is called a Leslie matrix model, named after British ecologist Patrick H. Leslie who popularised age structured models for animal populations [Leslie, 1945, 1948].

$$\begin{pmatrix} n_0 \\ n_1 \\ n_2 \\ n_3 \\ \vdots \\ n_{\nu-1} \end{pmatrix}_{t+1} = \begin{pmatrix} f_0 & f_1 & f_2 & \dots & f_{\nu-2} & f_{\nu-1} \\ s_0 & 0 & 0 & \dots & 0 & 0 \\ 0 & s_1 & 0 & \dots & 0 & 0 \\ 0 & 0 & s_2 & \dots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \dots & s_{\nu-2} & 0 \end{pmatrix} \cdot \begin{pmatrix} n_0 \\ n_1 \\ n_2 \\ n_3 \\ \vdots \\ n_{\nu-1} \end{pmatrix}_t \quad (1.10)$$

We use  $\mathbf{n}_{t+1} = L\mathbf{n}_t$  as a shorthand of equation (1.10), in which  $L$  is called the *Leslie matrix*, or *population projection matrix*. At each time point, the population is represented by a vector  $\mathbf{n}$  with one element for each age class. Each of the elements represents the number of individuals in that age class. The top row of the matrix contains the fecundity of individuals in each of the age classes. The subdiagonal contains probability that an individual in the current age class survives to the next age class.

The Leslie matrix model has a regular form and straight forward interpretations for each of the parameters. In addition, it also has many convenient mathematical properties, which will be introduced later in section 1.2.3. But sometimes it can encounter difficulties, when applied to modelling real biological populations. The first difficulty comes when one has to determine the unit of age for the species under study. Should it be a day, a year or ten years?

It can be hard to justify such particular choices.

The second difficulty is the tradeoff between *model error* and *parameter error* [Ellner and Guckenheimer, 2011]. Model errors are made due to incorrect assumptions. In such age structured population model, it is usually due to an oversimplification of reality. This type of errors can thus be reduced by making the model more complex, e.g., using smaller unit of age and more age classes. But inevitably, parameter error goes up because one needs to estimate more parameter values from the same amount of data. One way of circumventing such difficult tradeoff is to use another type of model that censuses individuals not by their ages, but by life stages. This leads us to the life stage structured population models.

### 1.2.2 Life stage structured population models

Apart from age, individuals can also be classified by their *stage* in the life cycle. For example, it is natural to make such classifications for insects, which have distinct larva, pupa and adult stages. Even for species that have more gradual courses of life history, it can still be desirable to classify the individuals into a few groups according to certain measurable features, such as size or body weight. These features are usually much easier to obtain compared to the age for non-human species. In addition, they often provide the best information for predicting fecundity and probability of survival towards the next period of time. For example, the size, rather than the age of many organisms (i.e., trees, sea turtles, desert tortoise, geese, corals and fish, etc. [Caswell, 2001]), is generally better in predicting the growth, fecundity and mortality.

The life stage structured population models can also be written in the matrix form  $\mathbf{n}_{t+1} = A\mathbf{n}_t$ , in which  $A$  is the population projection matrix. The form is very similar to the Leslie matrix model introduced in the previous section, but with very different meanings.

In age structured models, an individual has to either die or move to the next age class in one step of time. But in stage structured models, an individual can move forwards to later stage classes, or move backwards to earlier stage classes, or stay in the same stage class. In fact, in stage structured models, there essentially is no difference between “survival” and “reproduction”, analogically in the words of age structured models. This is because, for

the population, it does not matter if a small individual is a new born or an older individual who shrank back down to the newborn size. At the level of the population, the number of individuals in each of the stage classes provides complete information about its future prospects, and it does not matter where and how each of the individuals comes from.

As a natural consequence, the shapes of the projection matrices are also different in age and stage structured models. In the Leslie matrix  $L$ , non-zero entries can only be found in the first row (representing reproduction) and the subdiagonal (representing the probability of survival). But for the projection matrix  $A$  in the stage structured population model, in principle, non-zero entries can be found anywhere. In particular, the elements on the diagonal are almost always non-zeros.

### 1.2.3 Useful mathematical properties of matrix population models

Matrix population models provide convenience for mathematical analyses. A pedagogical introduction and detailed derivations and explanations can be found in the classic textbook of Caswell [2001]. More rigorous analysis can be found in the book of Charlesworth et al. [1994]. Here we only list the properties that are used in, or provide important background for Chapter 3.

Given the population *projection matrix*  $A$ , and initial population state vector  $\mathbf{n}(0)$ , the general solution is

$$\mathbf{n}(t) = A^t \mathbf{n}(0). \quad (1.11)$$

The long term behaviour of the population is determined by the dominant right eigenvalue  $\lambda_1$  of the projection matrix, and its corresponding eigenvector  $\mathbf{w}_1$ :

$$\mathbf{n}(t) \rightarrow c_1 \lambda_1^t \mathbf{w}_1, \quad (1.12)$$

where  $c_1$  is the coefficient that satisfies  $\mathbf{n}(0) = \sum_i^{\nu} c_i \mathbf{w}_i$ , in which  $\nu$  is the number of age/stage classes, and  $\mathbf{w}_i$  is the corresponding eigenvector for the eigenvalue  $\lambda_i$ . The symbol ‘ $\rightarrow$ ’ means that as  $t \rightarrow \infty$ , the relative error goes to zero. This tells us that in the long run, the total population size grows

exponentially at rate  $\lambda_1$ , and the population vector becomes proportional to  $\mathbf{w}_1$ . This is called the stable age/stage distribution of the population.

Analogous to that for the right eigenvalues and eigenvectors, there are left eigenvalues and eigenvectors for the projection matrix  $A$  that satisfy  $\mathbf{v}A = \lambda\mathbf{v}$ , where  $\mathbf{v}$  is a row vector. The dominant left eigenvector  $\mathbf{v}_1$  has a biological interpretation as the “reproductive value” of different ages/stages. The reproductive value of an individual was originally defined by Fisher [1930] as “to what extent will persons of this age (or sex), on average, contribute to the ancestry of future generations”. It does so by accounting for the remaining number of offspring he or she will produce discounted by the increase of population size at the time of reproduction of these offspring. More comprehensive explanations and examples are beautifully presented in the books of Caswell [2001] and Houston and McNamara [1999].

### 1.3 Towards the symbiosis between games and life history

Evolutionary game theory introduced in section 1.1 and life history theory introduced in section 1.2 are widely used approaches to modelling of evolutionary processes. However, in classic evolutionary game theory models there is no population demographic structure. The fluctuations in population size are often ignored, too. Life history theory provides a natural and powerful way of studying the demographic structure and size fluctuations of biological populations. But typical approaches take no account of the interactions in the population, relying solely on optimising a set of life history traits to maximise reproductive success. The advantages of the two established theories have the potential to compensate the shortcomings of each other, but a theoretical framework that integrates the two is still missing.

The major goals of the thesis are (1) to build a theoretical framework connecting these two fields, and (2) to apply evolutionary game theory for studying the population dynamics and interactions in real biological systems.

Starting from Chapter 2, we first study the replicator dynamics of evolutionary game interactions in stage structured populations. Game interactions and the demographic structure of biological populations are connected through

“life stage dependent strategies”, which is the most important innovation in this work. With life stage dependent strategies, we are able to study the population dynamics in the novel cases, where the behaviour of an individual is conditioned on its opponent’s life stage, or conditioned on the matching of the life stages of the two. Although these cases are natural in real biological settings, they have not been studied before.

Although accounted for population demographic structure, our model in Chapter 2 did not consider the role of random fluctuations caused by the finite size of real biological populations. We approach this in Chapter 3, building a stochastic model of strategy dynamics in age structured populations. The detailed stochastic processes embedded in the model allow us to evaluate the effects of different targets of selective forces. We show that selecting on reproduction and survival are fundamentally different in age structured populations, which has not been shown in existing theoretical models.

While taking into account both the effects of population demographic structure and size, one limitation of our work in Chapter 3 is that it assumes that the selection is constant, and population size is fixed. Although the assumptions provide convenience for mathematical analyses, they may not be able to capture important features of biological processes. Combining both theory and experiments, we show in Chapter 4 that in bacterial populations, frequency dependent fitness and the growth of population sizes can lead to complex pattern of multiple coexisting states of the population. In order to find out the underlying mechanism of the frequency dependency of growth rates, especially the mechanisms behind the role of *Curvibacter* sp. as a keystone species in the natural microbiota of *Hydra*, we continue our exploration in Chapter 5, in which we postulate that the infection and cross-infection of bacterial phages can provide a way that leads to frequency dependent fitness of bacterial hosts.





# Modeling evolutionary games in populations with demographic structure

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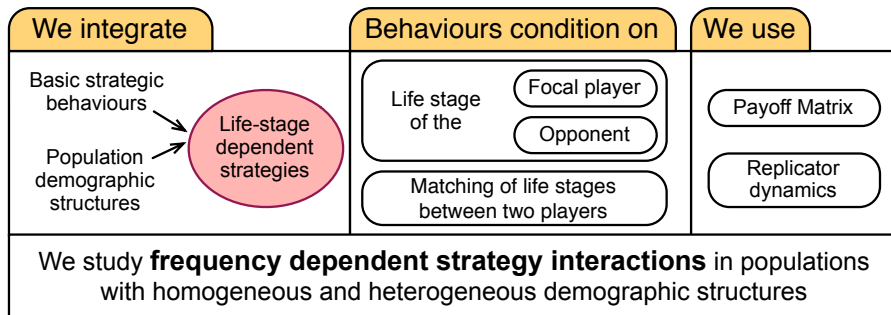
Evolutionary game theory naturally captures the effects of frequency dependent selection, providing a useful framework for studying the evolution of strategic interactions. However, classic evolutionary game models often neglect the life history traits of individuals in the population. This chapter is a first attempt to integrate life history factors into evolutionary game models. We start from defining life-stage dependent strategies by combining basic strategic behaviours with the life history features of individuals in the population. The strategic behaviours of an individual can be conditioned on the current life-stage of itself, or that of the opponent, or the matching of life stages between the two players. We write down the payoff matrices of the interactions between different life-stage dependent strategies, and we study the deterministic replicator dynamics of strategy interactions.

This chapter is based on the publication of Xiang-Yi Li, Stefano Giaimo, Annette Baudisch, and Arne Traulsen with the same title on the *Journal of Theoretical Biology* 380 (2015): 506-515 [Li et al., 2015a]. A detailed summary of the authors' contributions to this publication can be found at the end of this thesis.

## 2.1 Abstract

Classic life history models are often based on optimization algorithms, focusing on the adaptation of survival and reproduction to the environment, while neglecting frequency dependent interactions in the population. Evolutionary

game theory, on the other hand, studies frequency dependent strategy interactions, but usually omits life history and the demographic structure of the population. Here we show how an integration of both aspects can substantially alter the underlying evolutionary dynamics. We study the replicator dynamics of strategy interactions in life stage structured populations. Individuals have two basic strategic behaviours, interacting in pairwise games. A player may condition behaviour on the life stage of its own, or that of the opponent, or the matching of life stages between both players. A strategy is thus defined as the set of rules that determines a player's life stage dependent behaviours. We show that the diversity of life stage structures and life stage dependent strategies can promote each other, and the stable frequency of basic strategic behaviours can deviate from game equilibrium in populations with life stage structures.



## 2.2 Introduction

The evolution of life history traits is of central importance in evolutionary theory. Classic life history theory models often use optimization arguments, focusing on how environmental conditions shape survival and reproduction, and how life history traits affect each other [Roff, 1992; Stearns, 1992, 2000]. But the fitness landscapes of evolving populations are often not static, rather constantly changed by the phenotypic dynamics of the interacting populations [Nowak and Sigmund, 2004]. Therefore, it is necessary to also consider the density and frequency dependent aspects in studying the evolution of life history. Effects of density dynamics on life history evolution have been studied thoroughly [Abrams, 1993; Hastings, 1997; Higgins et al., 1997; Williams and Day, 2003], with recent advancements in particular under the framework of adaptive dynamics [Ernande and Dieckmann, 2004; Ernande et al., 2004; Marty et al., 2011; Meszéna et al., 2001; Metz et al., 1996; Miethe et al., 2009].

Evolutionary Game Theory [Broom and Rychtář, 2013; Hofbauer and Sigmund, 1998; Nowak, 2006a] provides a natural framework that includes frequency dependent selection for modeling evolution in the phenotypic space. But classic evolutionary game theory models often study populations in which an individual's strategic behaviour keeps fixed over the entire life time [Cressman, 1992]. This is largely due to the fact that demographic structure of the population is typically not taken into consideration [for rare exceptions, see Argasinski and Broom, 2013; Cressman, 2003; Day and Taylor, 1996]. By integrating evolutionary game dynamics and life history theory, here we study the interplay of the two fundamental aspects of evolutionary processes. We show that a more intricate dynamics is produced when both aspects are taken into consideration [McNamara, 2013].

In a population where individuals differ in life stages, it is natural that the strategic behaviour can vary accordingly. Since behavioural changes may not necessarily depend on age [Groenendaal et al., 1988], here we adopt the idea of a life stage based model [Caswell, 2001]. For simplicity, we assume that individuals only have two life stages, young and senescent. In addition, we assume that compared to the dynamics of strategic interactions (which is determined by biological reproduction in evolutionary game theory), the update of demographic structure (which reflects chronological ageing) is fast

and thus typically in equilibrium. Therefore, the proportions of young and senescent individuals are constant for each strategic group. These proportions correspond to the elements of the appropriately normalized right eigenvector, corresponding to the leading eigenvalue, of the population projection matrix that contains the vital rates of the relevant group. This vector is proportional to the stable stage distribution of the population [Caswell, 2001]. It should be noted that we have adopted the terminology “young” and “senescent” to suggest that the two stages through which individuals transition can often be interpreted as ages. However, one should keep in mind that our models can be interpreted as composed of two age classes only in cases where the proportion of young individuals is greater than one-half. This is a prerequisite for sustaining population size in the long term.

The replicator equations describe deterministic strategy dynamics in infinitely large, well-mixed populations, serving as the starting point and most standard approach for studying evolutionary game interactions [Hofbauer and Sigmund, 1998; Taylor and Jonker, 1978; Zeeman, 1980]. As a first step of integrating life history structures into evolutionary game dynamics, we start from the very basic and choose the replicator dynamics as the underlying mechanism of strategy updates.

In populations with no demographic structure, a two-player evolutionary game with two strategic behaviours,  $A$  and  $B$  can be written in the form of a payoff matrix.

$$\begin{array}{cc} & \begin{array}{cc} A & B \end{array} \\ \begin{array}{c} A \\ B \end{array} & \begin{pmatrix} a & b \\ c & d \end{pmatrix} \end{array} \tag{2.1}$$

Individuals meet randomly and interact in pairs. If both players play the  $A$  strategy, each of them receives a payoff of  $a$ . If one player plays the  $A$  strategy and the other plays the  $B$  strategy, the  $A$  strategy player receives a payoff of  $b$ , and the  $B$  strategy player receives a payoff of  $c$ . If both players play the  $B$  strategy, they both receive a payoff of  $d$ .

If individuals have distinct young and senescent life stages in the population, their behaviours can be conditioned on the focal player’s life stage, the opponent’s life stage, or the matching of life stages between the two players. In the following, we study these cases separately.

## 2.3 Behaviour conditioned on the player's own life stage

### 2.3.1 Payoff matrix

In a population where individuals have young and senescent life stages and two strategic behaviour options, there can be four different life-stage dependent strategies: always play  $A$  ( $AA$ ), play  $A$  when young but play  $B$  when senescent ( $AB$ ), play  $B$  when young but play  $A$  when senescent ( $BA$ ), and always play  $B$  ( $BB$ ), if an individual's behaviour is determined by its current life stage. In the following we denote the proportions of young individuals in the four strategic subpopulations as  $p_A^A$ ,  $p_A^B$ ,  $p_B^A$ , and  $p_B^B$ , respectively.

If population demography is fixed,  $p_A^A$ ,  $p_A^B$ ,  $p_B^A$  and  $p_B^B$  are constant. Since individuals condition behaviours on their own life stages, the demographic substructures of  $AA$  and  $BB$  individuals do not matter, because these individuals behave in the same way all the time. Therefore the values of  $p_A^A$  and  $p_B^B$  do not appear in the payoff matrix here. Only  $p_A^B$  and  $p_B^A$  affect an individual's payoff.

Now the average payoff for each pair of strategy interactions can be calculated. For example, the average payoff of an  $AB$  individual playing against a  $BA$  individual is  $p_A^B p_B^A b + p_A^B q_B^A a + q_A^B p_B^A d + q_A^B q_B^A c$ , where  $q_A^B = 1 - p_A^B$  and  $q_B^A = 1 - p_B^A$  are frequencies of senescent individuals in the  $AB$  and  $BA$  subpopulations. In this way, the payoff matrix  $M$  of all pairwise interactions can be written as

$$\begin{array}{c}
 \begin{array}{cccc}
 & AA & AB & BA & BB \\
 AA & \left( \begin{array}{c} a \\ p_A^B a + q_A^B c \end{array} \right. & \begin{array}{c} p_A^B a + q_A^B b \\ (p_A^B)^2 a + p_A^B q_A^B (b + c) + (q_A^B)^2 d \end{array} & \begin{array}{c} p_A^B b + q_A^B a \\ p_A^B p_B^A b + p_A^B q_B^A a + q_A^B p_B^A d + q_A^B q_B^A c \end{array} & \begin{array}{c} b \\ p_A^B b + q_A^B d \end{array} \\
 AB & & & & \\
 BA & \begin{array}{c} p_B^A c + q_B^A a \\ c \end{array} & \begin{array}{c} p_B^A p_A^B c + p_B^A q_A^B d + q_B^A p_A^B a + q_B^A q_A^B b \\ p_B^A c + q_B^A d \end{array} & \begin{array}{c} (p_B^A)^2 d + p_B^A q_B^A (b + c) + (q_B^A)^2 a \\ p_B^A d + q_B^A c \end{array} & \begin{array}{c} p_B^A d + q_B^A b \\ d \end{array} \\
 BB & & & & 
 \end{array}
 \end{array}
 \quad (2.2)$$

### 2.3.2 Homogeneous life history

In the special cases where the demographic structures in  $AB$  and  $BA$  subpopulations are identical, namely,  $p_A^B = p_B^A = p$ , the payoff matrix  $M$  can be

simplified to  $M_p$ .

$$M_p = \begin{matrix} & \begin{matrix} AA & AB & BA & BB \end{matrix} \\ \begin{matrix} AA \\ AB \\ BA \\ BB \end{matrix} & \begin{pmatrix} a & pa + qb & pb + qa & b \\ pa + qc & p^2a + pq(b+c) + q^2d & p^2b + pq(a+d) + q^2c & pb + qd \\ pc + qa & p^2c + pq(a+d) + q^2b & p^2d + pq(b+c) + q^2a & pd + qb \\ c & pc + qd & pd + qc & d \end{pmatrix} \end{matrix} \quad (2.3)$$

In the following, we denote the frequencies of  $AA$ ,  $AB$ ,  $BA$  and  $BB$  as  $x_A^A$ ,  $x_A^B$ ,  $x_B^A$  and  $x_B^B$ . Let  $\mathbf{x} = (x_A^A, x_A^B, x_B^A, x_B^B)^T$  denote the population state vector, the average payoff of the four strategies is  $(\pi_A^A, \pi_A^B, \pi_B^A, \pi_B^B)^T = M_p \cdot \mathbf{x}$ . We denote the average payoff the population as  $\langle \pi \rangle = \mathbf{x}^T M_p \mathbf{x}$ ; the replicator equation describing the frequency dynamics of the four strategies is

$$\dot{x}_i^j = x_i^j \cdot (\pi_i^j - \langle \pi \rangle) \quad (2.4)$$

With fixed population demography for  $AB$  and  $BA$  strategies, the replicator dynamics of the four strategies can be represented in the  $S_4$  simplex. As it is difficult to visualize this three-dimensional object, we only illustrate the four surfaces of the simplex for a coexistence game in Figure 2.1a.

For the payoff matrix  $M_p$ , we find  $(M_p \mathbf{x})_1 + (M_p \mathbf{x})_4 = (M_p \mathbf{x})_2 + (M_p \mathbf{x})_3$ . Therefore we can define a function  $V = x_A^A x_B^B / x_A^B x_B^A$ , which satisfies

$$\dot{V} = V[(M_p \mathbf{x})_1 + (M_p \mathbf{x})_4 - (M_p \mathbf{x})_2 - (M_p \mathbf{x})_3] = 0 \quad (2.5)$$

In the interior of  $S_4$ ,  $V$  is an invariant of motion - the value  $V_0$  of the initial condition is always preserved [Hofbauer and Sigmund, 1998; Sigmund, 2010]. For any positive  $V_0$ , the interior of  $S_4$  is foliated by the surface  $W_{V_0}$  given by  $x_A^A x_B^B = V_0 x_A^B x_B^A$ , as shown in Figure 2.1b-c.

### 2.3.3 Heterogeneous life history

Now we study the more general situations where not all strategies have the same proportion of young individuals, i.e. the original payoff matrix  $M$ . If individuals condition behaviour on their own life stages, there is a surface of

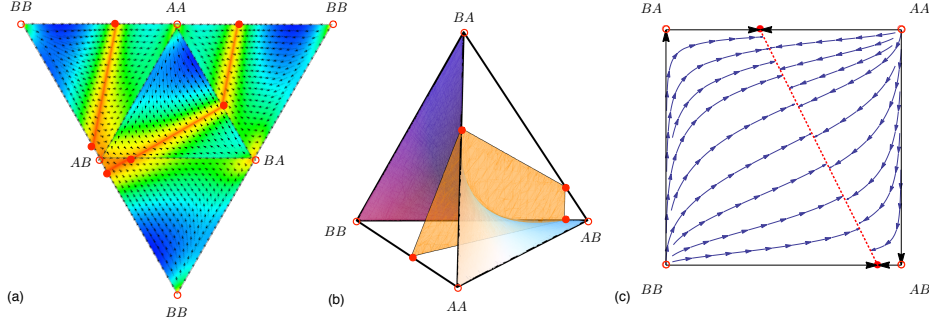


Figure 2.1: (a) Replicator dynamics of a coexistence game on the surface of a  $S_4$  simplex. Game parameters are  $a = -1/3$ ,  $b = 1$ ,  $c = 0$ ,  $d = 1/2$ . The proportion of young individuals in the population is  $p = 2/3$ , identical for all strategies. This figure is produced using the *Dynamo* package [Sandholm et al., 2012]. (b) The saddle-like surface  $W_{V_0}$  given by the solution of  $x_A^A x_B^B = V_0 x_A^B x_B^A$  ( $V_0 = 1$ ) spanned by the edges  $AA - AB - BB - BA - AA$  of the  $S_4$  simplex. The orange surface connected by the four stable fixed points on the edges is a plane of fixed points inside and on the faces of the simplex. (c) The dynamics on the surface  $W_{V_0}$  in (b). Besides the boundary fixed points shown by red circles, all points satisfying  $x_A^A + x_B^A = \frac{9}{5} - 2(x_A^A + x_B^B)$  are equilibria in the interior of the Simplex (red dotted line, which is the intersect of the two surfaces in (b)).

solutions in the  $S_4$  simplex (Figure 2.2a):

$$x_A = x_A^A + p_A^B x_A^B + (1 - p_B^A) x_B^A = \frac{d - b}{a - b - c + d} \quad (2.6)$$

Therefore, regardless of the values of  $p_A^B$  and  $p_B^A$ , the global frequency of  $A$  behaviour  $x_A$  always converges to the intermediate fixed point in a coexistence game, as shown in Figure 2.2b.

If individuals condition their behaviour on their own life stages, there can be more complex conditional strategies coexisting in the population, but the frequency of basic strategic behaviour always converges to the game equilibrium. This holds even if different strategies have different life history, suggest-

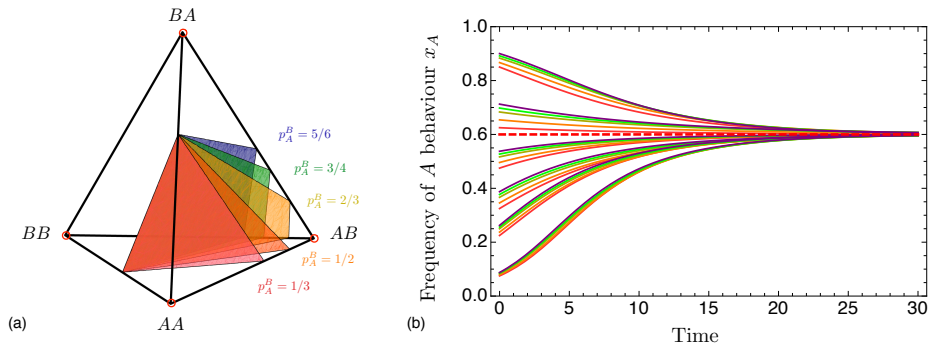


Figure 2.2: The surface of fixed points changes with the change of population demographic structures. But the global frequency of  $A$  behaviour always converges to game equilibrium. (a) The surface of fixed points changes with varying  $p_A^B$ . Game parameters and the value of  $p_B^A$  are identical with those in Figure 2.1. (b) Starting from any initial frequency between 0 and 1, the global frequency of  $A$  behaviour converges to the intermediate game equilibrium. Trajectories of different colours correspond to different values of  $p_A^B$  in (a).

ing that neutral evolution may play an important role in life history evolution under frequency dependence. The diversity of life history can be promoted through strategic interactions, and the diversity of strategies can be promoted through life history.

## 2.4 Behaviour conditioned on the opponent's life stage

### 2.4.1 Payoff matrix

In contrast to the previous case, in which an individual's behaviour is conditioned on its own life stage, one can also condition its behaviour on the opponent's life stage. If an individual senses the life stage of its game opponent and behaves accordingly, there can be four different strategies: play  $A$  with everyone ( $AA$ ), play  $A$  if the opponent is young but play  $B$  if the opponent is senescent ( $AB$ ), play  $B$  if the opponent is young but play  $A$  if the opponent is senescent ( $BA$ ), and play  $B$  with everyone ( $BB$ ). We continue to denote the proportions of young individuals in the four subpopulations as  $p_A^A$ ,  $p_A^B$ ,  $p_B^A$ , and  $p_B^B$ , respectively. The payoff matrix  $\tilde{M}$  for pairwise strategy



interactions can be written as

$$\begin{array}{c}
 \begin{array}{cccc}
 & AA & AB & BA & BB \\
 AA & \left( \begin{array}{c} a \\ p_A^A a + q_A^A c \\ p_A^A c + q_A^A a \\ c \end{array} \right. & \begin{array}{c} p_A^A a + q_A^A b \\ (p_A^B)^2 a + p_A^B q_A^B (b + c) + (q_A^B)^2 d \\ p_B^A p_A^B c + p_B^A q_A^B a + q_B^A p_A^B d + q_B^A q_A^B b \\ p_B^B c + q_B^B d \end{array} & \begin{array}{c} p_A^A b + q_A^A a \\ p_A^B p_B^A b + p_A^B q_B^A d + q_A^B p_B^A a + q_A^B q_B^A c \\ (p_B^A)^2 d + p_B^A q_B^A (b + c) + (q_B^A)^2 a \\ p_B^B d + q_B^B c \end{array} & \left. \begin{array}{c} b \\ p_B^B b + q_B^B d \\ p_B^B d + q_B^B b \\ d \end{array} \right) \\
 AB & & & & \\
 BA & & & & \\
 BB & & & & 
 \end{array}
 \end{array} \quad (2.7)$$

### 2.4.2 Homogeneous life history

If demographic structures are the same for all strategic subpopulations,  $p_A^A = p_A^B = p_B^A = p_B^B = p$ , the payoff matrix  $\tilde{M}$  becomes identical to  $M_p$ , and the replicator dynamics is the same as discussed in section 2.2.

Therefore, in a population where each strategy has the same demographic structure, the interaction dynamics are identical no matter if the behaviours are conditioned on the focal player's life stage, or that of the opponent in pairwise games. One has to examine the microscopic interactions in order to distinguish the two cases.

### 2.4.3 Heterogeneous life history—an example in a Hawk-Dove game

If the proportion of young individuals in one of the strategies becomes different from the others, extinction of one or more strategies can happen, and the global frequency of basic behaviours thereby can diverge from game equilibrium. This is different from the "all-coexist" situation that takes place when behaviour is conditioned on the player's own life stage. In the following, we illustrate this point in a particular coexistence game, the Hawk-Dove game.

In a Hawk-Dove game, two players are involved in a conflict over a valuable resource, but the cost of fighting is greater than the value of the resource. We assume the value of resource is 1, the cost of fighting is  $n > 1$ . If a Hawk meets another Hawk, they fight for the resource and the average payoff for each of them is half of the value reduced by half of the cost of conflict. If a Hawk meets a Dove, the Dove flees to avoid conflict, so that the Hawk gets the whole resource without a fight, and the Dove receives nothing. If

two Doves meet, they share the resource peacefully. In a population without demographic structure, the payoff matrix can be written as

$$\begin{array}{cc}
 & \begin{array}{cc} Hawk & Dove \end{array} \\
 \begin{array}{c} Hawk \\ Dove \end{array} & \left( \begin{array}{cc} (1-n)/2 & 1 \\ 0 & 1/2 \end{array} \right)
 \end{array} \tag{2.8}$$

The frequency of Hawk behaviour in equilibrium is  $1/n$ .

However, in a population with young and senescent life stages, players can condition their behaviours on the life stage of the opponent. In this way, there are again four different strategies in the population. If an individual behaves aggressive to both young and senescent opponents, its strategy is denoted as  $HH$ . If an individual behaves aggressive towards a young opponent but behaves peacefully when it meets a senescent opponent, its strategy is denoted as  $HD$ . If an individual does the opposite by behaving peacefully when facing a young opponent but being aggressive in front of a senescent opponent, its strategy is denoted as  $DH$ . If an individual behaves peacefully in any case, its strategy is denoted as  $DD$ .

If the proportion of young individuals of the four strategies are identical and constant, denoted as  $p$ , the four strategies can all coexist in a variety of states where the frequency of Hawk behaviour  $x_H = x_H^H + px_H^D + (1-p)x_D^H$  is always at game equilibrium  $1/n$  as if demographic structure is absent. This has been discussed above. However, if one of the strategies has a different life-stage structure, starting from the presence of all four strategies, extinction of one or more strategies can happen, and the frequency of Hawk behaviour can diverge from game equilibrium.

For example, assume only  $p_H^H$ , the proportion of young individuals in the  $HH$  subpopulation is different from that of other strategies, which is denoted as  $p$ . The payoff matrix becomes

$$\begin{array}{c}
 \begin{array}{cccc}
 & HH & HD & DH & DD \\
 \begin{array}{c} HH \\ HD \\ DH \\ DD \end{array} & \left( \begin{array}{cccc}
 \frac{1-n}{2} & 1 - \frac{(n+1)p_H^H}{2} & \frac{1-n+(n+1)p_H^H}{2} & 1 \\
 \frac{(1-n)p_H^H}{2} & \frac{p^2(1-np^2)}{2} & p\left(1 - \frac{n(1-p)}{2}\right) & \frac{1+p}{2} \\
 \frac{(n-1)(p_H^H-1)}{2} & \frac{(p-1)(np-2)}{2} & \frac{1-n(p-1)^2}{2} & 1 - \frac{p}{2} \\
 0 & \frac{1-p}{2} & \frac{p}{2} & \frac{1}{2}
 \end{array} \right)
 \end{array} \tag{2.9}
 \end{array}$$

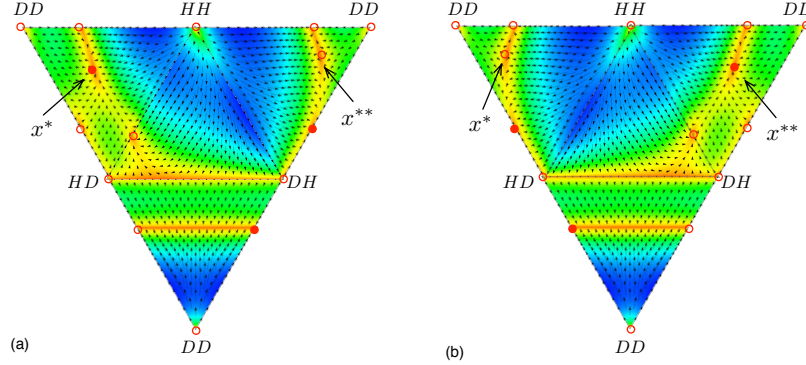


Figure 2.3: Stability of the fixed points  $x^*$  and  $x^{**}$  switches. In both sides, game parameter  $n = 3$ , the proportion of young individuals in the  $HD$ ,  $DH$  and  $DD$  strategy subpopulations are  $p = 0.5$ . In (a), the proportion of young individuals in the  $HH$  strategy is  $p_H^H = 0.3$ , in (b),  $p_H^H = 0.7$ . When  $p_H^H < p$ ,  $x^*$  is stable and  $x^{**}$  is unstable. When  $p_H^H > p$ ,  $x^*$  is unstable and  $x^{**}$  is stable. Figures are produced using the Dynamo package [Sandholm et al., 2012].

We study the interactions of the four strategies in the simplex  $S_4$  using the replicator dynamics. When  $p_H^H \neq p$ , the internal fixed point where all the four strategies coexist disappears. All fixed points are on the surface of the simplex. One, two or three strategies can coexist at the fixed points. Two interesting fixed points are the one where  $HH$ - $HD$ - $DD$  coexist, denoted as  $x^*$ , and the one where  $HH$ - $DH$ - $DD$  coexist, denoted as  $x^{**}$  in the following. Within the regime where the cost of conflict is relatively large,  $n > \frac{1-p_H^H}{p+p_H^H}$  and  $n > \frac{p_H^H}{2-p-p_H^H}$ , the stability of the two fixed points  $x^*$  and  $x^{**}$  switches with the relative size of  $p_H^H$  compared to  $p$ . When  $p_H^H < p$ , the fixed point  $x^*$  is stable and  $x^{**}$  is unstable, but when  $p_H^H > p$ ,  $x^*$  is unstable and  $x^{**}$  becomes stable (Figure 2.3). The expressions for  $x^*$  and  $x^{**}$  and the linear stability analysis of them can be found in Appendix A. More detailed derivations can be found in the Mathematica notebook file in the Supplementary Information.

Whether the frequency of Hawk behaviour at the two fixed points is greater or smaller than  $1/n$  also depends on the relative size of  $p$  and  $p_H^H$ . The frequency of Hawk behaviour at the fixed point  $x^*$  is  $x_H^* = \frac{p((2n^3 - n^2 + 2n + 1)p + (2n^3 + n^2 - 2n - 1)p_H^H)}{((n^2 + 1)p + (n^2 - 1)p_H^H)^2}$ , and the frequency of Hawk behaviour at the

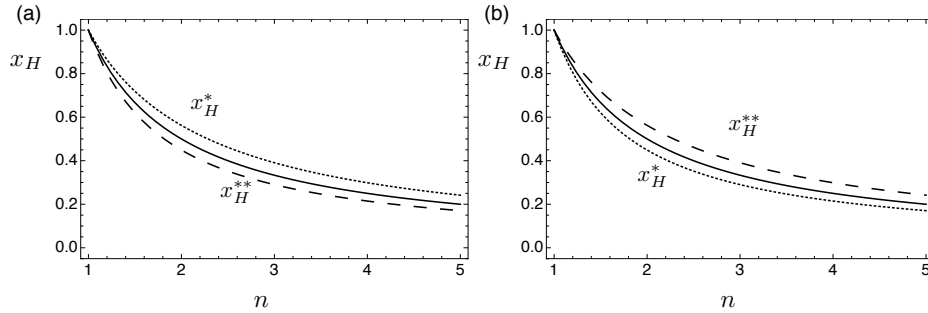


Figure 2.4: The frequency of Hawk behaviour at the fixed point  $x^*$  ( $x_H^*$ ) and the fixed point  $x^{**}$  ( $x_H^{**}$ ) are decreasing functions of  $n$ . (a)  $x_H^* > 1/n > x_H^{**}$  if  $p_H^H < p$ . Here  $p = 0.5$ , and  $p_H^H = 0.3$ . (b)  $x_H^* < 1/n < x_H^{**}$  if  $p_H^H > p$ . Here  $p = 0.5$ , and  $p_H^H = 0.7$ . The frequency of Hawk behaviour is always higher than  $1/n$  at the stable fixed point.

fixed point  $x^{**}$  is  $x_H^{**} = \frac{(1-p)((p-p_H^H)(n^2-2n-1)+2n^3(2-p-p_H^H))}{(p-p_H^H+n^2(p+p_H^H-2))^2}$ . They both are decreasing functions of  $n$ . When  $p_H^H < p$ ,  $x_H^* > 1/n > x_H^{**}$ ; and when  $p_H^H > p$ ,  $x_H^* < 1/n < x_H^{**}$  (Figure 2.4). Therefore regardless of the relative sizes of  $p$  and  $p_H^H$ , the frequency of Hawk behaviour at the stable fixed point is always greater than  $1/n$ , while the frequency of Hawk behaviour at the unstable fixed point is always smaller than  $1/n$ . Intuitively, at the fixed point  $x^*$ , where  $HH$ - $HD$ - $DD$  coexist, an increase of  $p_H^H$  from  $p$  decreases the payoffs of both  $HH$  and  $HD$ , which are the only subpopulations that contain the  $H$  behaviour. In contrast, at the fixed point  $x^{**}$ , where  $HH$ - $DH$ - $DD$  coexist, increasing  $p_H^H$  from  $p$  is of benefit to both  $HH$  and  $DH$ , which are the only subpopulations containing  $H$  behaviour. In this way, the increase or decrease of the abundance of  $H$  behaviour at the fixed points can be intuitively explained by observing the payoff matrix.

## 2.5 Behaviour conditions on the match of life stages

### 2.5.1 Payoff matrix

Besides conditioning one's behaviour on the player's own life stage or that of the opponent, an individual can also condition its behaviour on whether

the opponent is in the same life stage as itself. Therefore in a population with two distinct life stages (young and senescent) and two basic behaviours ( $A$  and  $B$ ), there can be four different strategies: play  $A$  no matter if the opponent is of the same or different life stages ( $AA$ ), play  $A$  if the opponent is of the same life stage, and play  $B$  if the opponent is of the different life stage ( $AB$ ), play  $B$  if the opponent is of the same life stage, and play  $A$  if the opponent is of the different life stage ( $BA$ ), and play  $B$  regardless of whether the opponent is of the same or different life stages ( $BB$ ). The proportion of young individuals in the four strategic subpopulations are  $p_A^A$ ,  $p_A^B$ ,  $p_B^A$ , and  $p_B^B$ . In the following we use  $\sigma$  and  $\rho$  to denote the probability that two individuals of the same or different life stages meet each other. For example, when an  $AA$  individual meets an  $AB$  individual, the probability that they are of the same age is  $\sigma_{AA\leftrightarrow AB} = p_A^A p_A^B + q_A^A q_A^B$ , and the probability that they are of different ages is  $\rho_{AA\leftrightarrow AB} = p_A^A q_A^B + q_A^A p_A^B$ . The payoff matrix  $\hat{M}$  can then be written down as

$$\begin{array}{c} \begin{array}{cccc} & AA & AB & BA & BB \\ AA & \left( \begin{array}{cccc} a & \sigma_{AA\leftrightarrow AB}a + \rho_{AA\leftrightarrow AB}b & \sigma_{AA\leftrightarrow BA}b + \rho_{AA\leftrightarrow BA}a & b \\ \sigma_{AB\leftrightarrow AA}a + \rho_{AB\leftrightarrow AA}c & \sigma_{AB\leftrightarrow AB}a + \rho_{AB\leftrightarrow AB}d & \sigma_{AB\leftrightarrow BA}b + \rho_{AB\leftrightarrow BA}c & \sigma_{AB\leftrightarrow BB}b + \rho_{AB\leftrightarrow BB}d \\ \sigma_{BA\leftrightarrow AA}c + \rho_{BA\leftrightarrow AA}a & \sigma_{BA\leftrightarrow AB}c + \rho_{BA\leftrightarrow AB}b & \sigma_{BA\leftrightarrow BA}d + \rho_{BA\leftrightarrow BA}a & \sigma_{BA\leftrightarrow BB}d + \rho_{BA\leftrightarrow BB}b \\ c & \sigma_{BB\leftrightarrow AB}c + \rho_{BB\leftrightarrow AB}d & \sigma_{BB\leftrightarrow BA}d + \rho_{BB\leftrightarrow BA}c & d \end{array} \right) \\ AB \\ BA \\ BB \end{array} \end{array} \quad (2.10)$$

### 2.5.2 Homogeneous life history

If all strategies have the same proportion of young individuals in the population, denoted as  $p$ , the proportion of senescent individuals in all strategies is  $q = 1 - p$ . Then  $\sigma = p^2 + q^2$ , and  $\rho = 2pq$ , the payoff matrix  $\hat{M}$  reduces to  $\hat{M}_p$

$$\hat{M}_p = \begin{array}{c} \begin{array}{cccc} & AA & AB & BA & BB \\ AA & \left( \begin{array}{cccc} a & \sigma a + \rho b & \sigma b + \rho a & b \\ \sigma a + \rho c & \sigma a + \rho d & \sigma b + \rho c & \sigma b + \rho d \\ \sigma c + \rho a & \sigma c + \rho b & \sigma d + \rho a & \sigma d + \rho b \\ c & \sigma c + \rho d & \sigma d + \rho c & d \end{array} \right) \\ AB \\ BA \\ BB \end{array} \end{array} \quad (2.11)$$

Since  $\sigma + \rho = 1$ , the payoff matrix  $\hat{M}_p$  also satisfies  $(\hat{M}_p \mathbf{x})_1 + (\hat{M}_p \mathbf{x})_4 = (\hat{M}_p \mathbf{x})_2 + (\hat{M}_p \mathbf{x})_3$ . Therefore, it shares the same invariant of motion  $V = x_A^A x_B^B / x_A^B x_B^A$  that corresponds to the payoff matrix  $M_p$  in the interior of the

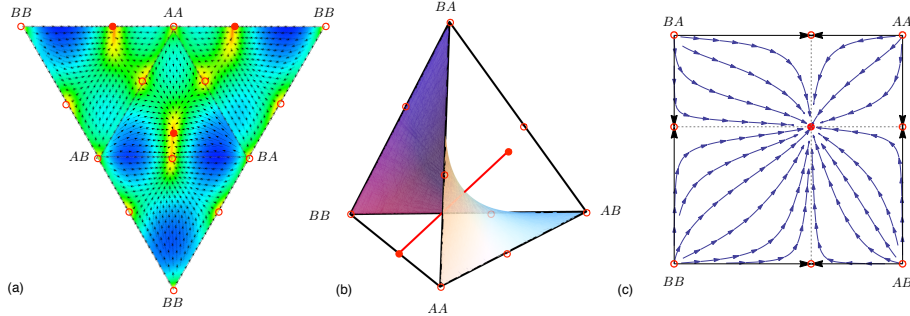


Figure 2.5: a. Replicator dynamics on the surface of a  $S_4$  simplex. Game and life history parameters used are identical to those used in Figure 2.1. This figure is produced using the Dynamo package [Sandholm et al., 2012]. b. The saddle-like surface  $W_k := \{\mathbf{x} \in S_4 : x_A^A x_B^B = k x_A^B x_B^A\}$  ( $k = 1$ ) spanned by the edges  $AA-AB-BB-BA-AA$  of the  $S_4$  simplex. Besides the boundary fixed points shown in red circles, all points that satisfy  $x_A^A + x_A^B = 3/5$ ,  $x_A^B = x_B^A$  and  $x_A^A - x_B^B = 1/5$  are equilibria in the interior of the Simplex (the red circle). Life history and game parameter values used are the same as those in Figure 2.1.

$S_4$  simplex. But the dynamics on the same invariant of motion are different for  $\hat{M}_p$  and  $M_p$ . In the replicator dynamics system that corresponds to  $\hat{M}_p$ , the interior fixed points satisfy  $x_A^A = \frac{(-a+b+c-d)x_A^B - b+d}{a-b-c+d}$ ,  $x_B^A = x_A^B$ , and  $x_B^B = \frac{(-a+b+c-d)x_A^B + a-c}{a-b-c+d}$ . Therefore, the unique interior fixed point on each layer of  $V$  is on the  $AA-BB$  diagonal (Figure 2.5b). Besides the line of interior fixed points, there is a fixed point on each of the vertices and each of the edges of the  $S_4$  simplex. The two stable fixed points shown in Figure 2.5a are at the intersects between the line of interior fixed points and the surface of the simplex. To compare the replicator dynamics that correspond to  $M_p$  and  $\hat{M}_p$ , we embedded the same coexistence game and life history trait that was used in Figure 2.1 and plotted the replicator dynamics on the surface (Figure 2.5a) and interior (Figure 2.5b) of the  $S_4$  simplex.

From the comparisons between Figure 2.1 and Figure 2.5 we can see the differences between conditioning behaviours on the life stages of one of the players, and on the matching of life stages between the two players. In these two figures, all strategies have the same life history (same proportion of young individuals), and the rules are the same for all strategic behaviour interactions.

If one conditions its behaviour on the age of itself or that of the opponent, there is a line of fixed points on each face of the  $S_4$  simplex, any three different strategies can coexist (Figure 2.1). However, if behaviours are conditioned on the matching of life stages, three strategies can coexist only in one special fixed point on the surface (Figure 2.5). But any two strategies can stably coexist when other strategies are not present, which does not hold if behaviours are conditioned on the life stage of the focal player or that of the opponent. In the interior of the  $S_4$  simplex, if behaviours are conditioned on the life stage of the focal player or that of the opponent, there is a whole surface of fixed points that spans in the simplex, crossing through the  $AA-BB \leftrightarrow AA-BA \leftrightarrow AB-BA \leftrightarrow AB-BB \leftrightarrow AA-BB$  edges; in contrast if behaviours are conditioned on the matching of the life stages between players, there is a line of fixed points that extends from the fixed point on the  $AA-BB$  edge to the fixed point on the  $AA-AB-BA$  face of the simplex.

### 2.5.3 Homogeneous and heterogeneous life history – an example in a Stag-Hunt game

In a two-player coordination game with two strategic behaviours, the two behaviours do not stably coexist. However, if behaviours are conditioned on the matching of life stages between the two players, it is possible to have both behaviours simultaneously. For example, in a Stag-Hunt game with the following payoffs from behaviour interactions:

$$\begin{array}{cc} & \begin{array}{cc} \textit{Stag} & \textit{Hare} \end{array} \\ \begin{array}{c} \textit{Stag} \\ \textit{Hare} \end{array} & \left( \begin{array}{cc} 2 & 0 \\ 1 & 1 \end{array} \right) \end{array} \quad (2.12)$$

It is not profitable to go after a hare in a population of stag hunters, and it is too risky to go for a stag alone when all others are chasing hares. Therefore, populations would usually end up with all stag hunters or all hare hunters. In a population with two life stages, a Stag-Hunt game can have four different strategies: hunting stags no matter if the opponent is of the same or different life stage ( $SS$ ), hunting stags if the opponent is of the same life stage, and hunting hares otherwise ( $SH$ ), hunting hares if the opponent is of the same

life stage, and hunting stags otherwise ( $HS$ ), and always hunting hares ( $HH$ ). The dynamics of the frequency of Stag-Hunting behaviour  $x_S$  depends on game interactions, when more than one strategies are present.

$$x_S = x_S^S + x_S^H (p_S^H \mathbf{p} \cdot \mathbf{x} + q_S^H \mathbf{q} \cdot \mathbf{x}) + x_H^S (p_H^S \mathbf{q} \cdot \mathbf{x} + q_H^S \mathbf{p} \cdot \mathbf{x}), \quad (2.13)$$

where  $\mathbf{p} = (p_S^S, p_H^S, p_S^H, p_H^H)$ ,  $\mathbf{q} = (1 - p_S^S, 1 - p_H^S, 1 - p_S^H, 1 - p_H^H)$ , and  $\mathbf{x} = (x_S^S, x_H^S, x_S^H, x_H^H)^T$ . If one of the strategies fixes in the population, the final level of Stag-Hunting behaviour is no more determined by the payoffs from game, but by the life history. If the  $SS$  strategy is fixed,  $x_S = 1$ , if the  $SH$  strategy is fixed,  $x_S = (p_S^H)^2 + (q_S^H)^2$ , if the  $HS$  strategy is fixed,  $x_S = 2p_H^S q_H^S$ , and if the  $HH$  strategy is fixed,  $x_S = 0$ .

Both  $SH$  and  $HS$  strategies can stably preserve both stag-hunting and hare-hunting behaviours. We illustrate this in examples shown in Figure 2.6. In a population with homogeneous life history, all strategies have the same proportion of young individuals in the subgroup. Starting from the presence of all four strategies, the  $SH$  strategy dominates the others and finally fixes in the population (Figure 2.6a). Since behaviours were conditioned on the matching of life stages, when two individuals of the same life stages meets each other, they go for Stag-hunting, and if the two players are of different life stages, they hunt hares instead (Figure 2.6b). If the frequency of young individuals changes in one of the strategy subgroups, the demographic structure of the population becomes heterogeneous. Altering the demographic structure of only one strategy subgroup changes the fitness landscape of all interacting strategies. For example, if we change the proportion of young individuals of the  $SS$  strategy subgroup, starting from the previous coexisting state where all four strategies coexist at equal frequencies, the  $SH$  strategy gains an advantages over all others and fixes in the population (Figure 2.6c). The overall frequency of stag-hunting behaviour first increases from the previous equilibrium, decreases again as the  $HS$  and  $HH$  strategy go extinct, and finally reaches a new equilibrium as  $SH$  fixes in the population (Figure 2.6d).



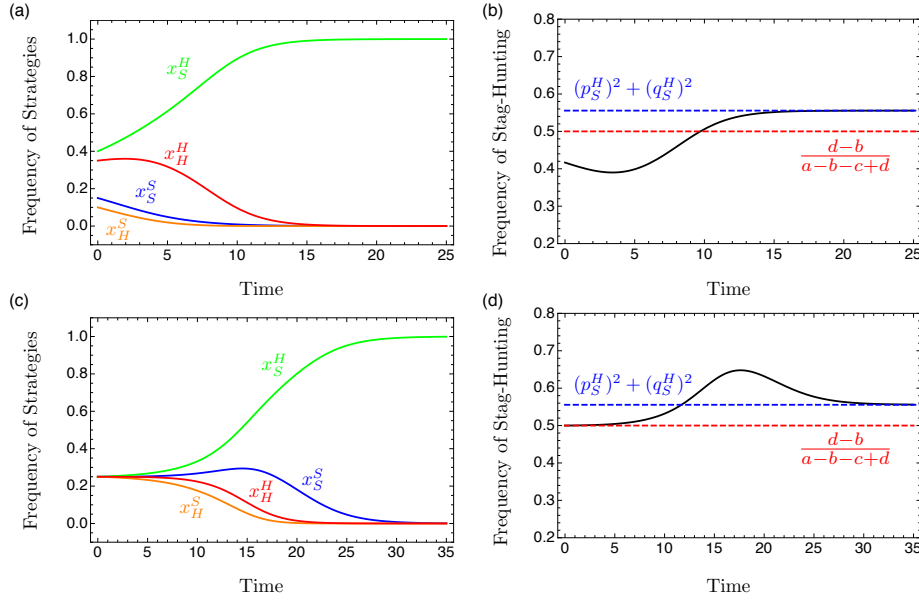


Figure 2.6: Dynamics in a stag-hunt game when the behaviour is conditioned on the matching of life stages. (a) Frequency dynamics of a Stag-Hunt game in a population with two distinct life stages. All strategies have the same proportions of young individuals in the population,  $p = 2/3$ . Initial population structure is:  $x_H^S = 0.1$ ,  $x_S^S = 0.15$ ,  $x_H^H = 0.4$ , and  $x_S^H = 0.45$ . (b) Frequency dynamics of Stag-hunting behaviour. The final frequency of Stag-Hunter behaviour is determined by the demographic structure  $(p_S^H)^2 + (q_S^H)^2$ , rather than the intermediate fixed point of the basic behaviour interaction game,  $(d - b)/(a - b - c + d)$ . (c) Starting from the coexisting state where all strategies have the same frequency and the same proportion of young individuals in the population ( $p = 2/3$ ). If the frequency of young individuals in the  $SS$  strategic group changes ( $p_S^S = 3/4$  in the example), the fitness landscape of all interacting populations change. The  $SH$  strategy takes over the whole population, and all other strategies go extinct. (d) The overall frequency of Stag-Hunting behaviour change to a different equilibrium due to the population dynamics in panel c.

## 2.6 Discussion and conclusion

In this study, population demographic structures are integrated into evolutionary game dynamics in a way that is similar to so called role games [Hofbauer and Sigmund, 1998; Sigmund, 2010]. The life stages in our study are similar to the “roles” in role games, but with two important differences. Firstly, in role games, an individual has different sets of behaviours at different positions, e.g. the behavioral options of a striker and a goalie are quite different. But in our study, individuals always have the same set of basic strategic behaviours even in different life stages. Second, in role games, individuals in one role only interact with those in the other role. But in our study, an individual can play with anyone else in random pairs. An important shared feature between our design and the role games is that an individual’s life stage or role is independent of its current strategic behaviour. Therefore, the payoff from the game does not affect an individual’s probability of playing different roles in role games, and it does not affect the population demographic structure in our settings. This leads to some similar properties of our model and of role games, e.g. the existence of an invariant of motion when all strategic subgroups share the same demographic structure.

Role games readily capture the characteristics in many social and biological scenarios, where two populations are distinct in their sets of strategies but not separable. Examples include conflicts between owner and intruder, parents and offspring, wife and husband, queen and worker bees [Hofbauer and Sigmund, 1998]. Our model, featured by life-stage dependent strategies, may apply to many real world systems, including human societies. For example, compared to most of the adult age groups, children and the elderly differ remarkably in their level of cooperative behaviours [Gutiérrez-Roig et al., 2014]. Similar to cooperation, trust has also been found to increase almost linearly from early childhood to the beginning of adulthood [Sutter and Kocher, 2007]. Not yet fully developed cognitive and strategic abilities have been suggested to explain those behaviours observed in children [Gutiérrez-Roig et al., 2014]. In contrast, the elderly exhibit greater concern for the welfare of others [Bass et al., 1998], behave more idealistically when making ethical judgements [Hartikainen and Torstila, 2004], and show much higher level of cooperation [Gutiérrez-Roig et al., 2014]. Those are ascribed to the improvement in social

reasoning with age, which allows the elderly to “make more use of higher-order reasoning schemes”, and thus be more willing to make compromises, to acknowledge the need for considering multiple perspectives and to admit the limits of knowledge [Grossmann et al., 2010]. Apart from human societies, life history traits of different species differ greatly across the tree of life [Jones et al., 2014]. Behaviours and the patterns of interaction vary, and may play a crucial role to produce the great diversity in relative fecundity and mortality of different species.

In the framework of the replicator dynamics, population size is infinitely large, well mixed, all strategies have the same death rate, and the payoffs are translated into reproduction rates. However, in real biological populations, reproduction rates often do not solely depend on frequency, but also on density. Density dependent evolutionary stable strategies in populations without substructure have been studied by [Cressman, 1990a,b] as well as by [Cressman and Dash, 1987]. Besides density dependent reproduction rates, payoff may affect other aspects of population dynamics as well. For instance, individuals with higher payoff could be less sensitive to density limiting factors and thus have higher carrying capacities [Novak et al., 2013].

In addition, it is important to study the case in which payoff feeds back to population structure via chronological ageing. In populations with pre and/or post-reproductive stages, the timing of entering and staying in the reproductive phase is very often not only determined by genetics, but by nutrients, population density, dominance-specific behaviours and other factors that are strongly affected by social interactions [Jorgenson et al., 1993; Komers et al., 1997; Wootton, 1987]. Theoretical and empirical studies have also shown that increased reproduction does not necessarily decrease lifespan [Baudisch, 2005; Baudisch and Vaupel, 2012; Partridge et al., 2005], and extended life span does not necessarily reduce reproduction [Holehan and Merry, 1986; Shanley and Kirkwood, 2000], suggesting the potential for strategy evolution to change population demographic structure through payoff from interactions in the population.

One of the most straightforward ways for payoff from interactions among individuals in the population to affect ageing is through nutrition. Successful strategies in competition can increase the amount of available nutrient for

animals that employ these strategies. However, the way that payoff interacts with life history evolution can still be complicated even under the simple assumption that payoff is linearly translated into the amount of nutrition. On the one hand, nutrition is one of the ultimate reproductive timing factor for many species. Richer nutrition leads to younger age at first reproduction, higher frequency of subsequent reproductive events, and better quality of gametes [Gunasekera et al., 1995; Luquet and Watanabe, 1986,?; Sadleir, 1973; Schreck et al., 2001]. On the other hand, restricted calorie intake may extend life span, retard age-related chronic disease [Heilbronn and Ravussin, 2003; Koubova and Guarente, 2003], and provide the chance of preserving reproductive value when famine and other transient stress is over [Holliday, 1989; Shanley and Kirkwood, 2000]. Therefore it is not necessarily true that higher payoff or more nutrient intake leads to greater reproductive success, if reproductive stage structure and ageing is taken into consideration.

In this work we study the strategy dynamics of two basic behaviours in a population with two life stages only (young and senescent). It would be natural to extend it to more general cases, with multiple strategies and more complex life history. [Argasinski and Broom, 2013] approach this by introducing a continuous version of the discrete Leslie Matrix and a concept for large age classes. The authors also study the cases with multiple strategies and multiple populations. We plan to present an analysis of the polymorphic and monomorphic equilibria in populations with more general age structures separately, emphasising the potential impact of different life histories.

To conclude, in this study we have developed a framework that integrates life history into game strategies by conditioning basic strategic behaviours on life stages. We studied the replicator dynamics of life stage dependent strategies in a population with young and senescent life stages. In the simple settings with two basic strategic behaviours  $A$  and  $B$  and two life stages, we analysed the cases where basic strategic behaviours are conditioned on the life stage of the focal player, the opponent, or the matching of life stages between the two players. For each of the three cases, we have defined the specific life stage dependent strategies, written down the payoff matrix, and studied the replicator dynamics in populations with homogeneous and heterogeneous life history. In populations with homogeneous life history, if basic strategic

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behaviours are conditioned on the life stage of either of the players, the two payoff matrices become identical, and thus share the same dynamics on the the invariant of motion in the interior of the  $S_4$  simplex. If behaviours are instead conditioned on the matching of life stages between two game players, the invariant of motion is the same, but the dynamics on it changes. In populations with heterogeneous life history, new equilibria of the population dynamics can emerge, and the global frequency of basic strategic behaviours can be different from the game equilibrium.



# Life history sways the evolutionary fate of mutants

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In the previous chapter we studied the replicator dynamics in populations with demographic structure. With the underlying assumptions of infinitely large population size and the absence of mutation, we analysed the frequency dynamics of standing phenotypic variations. In this chapter, we move on to study the population dynamics in age-structured populations with finite sizes, taking into account the effects of stochasticity and mutation. We aim at finding out how demographic structure of the population affects the evolutionary fate of a beneficial mutant under constant selection. Would the mutant be more likely to fix in a population that is younger or older? Does it make a difference if natural selection works on reproduction or survival, or both?

This chapter is based on a working manuscript in collaboration with Shun Kurokawa, Stefano Giaimo, and Arne Traulsen. A detailed summary of the authors' contributions to this project can be found at the end of this thesis.

## 3.1 Abstract

In this work we study the effects of demographic structure on evolutionary dynamics, when selection works on reproduction, survival, or both. In contrast with the previously discovered pattern that the fixation probability of a neutral mutant decreases while population becomes younger, we show that a mutant with constant selective advantage may have a maximum and/or a minimum of fixation probability in populations with an intermediate frequency of young individuals. This highlights the importance of life history and demographic structure in studying evolutionary dynamics. It also shows the fundamental differences between selecting on reproduction and on survival when age structure is present. In addition, we evaluate the relative importance

of size and structure of the population in determining the fixation probability of the mutant. Our work lays the foundation for studying also density and frequency dependent effects in populations where demographic structures cannot be neglected.

## **3.2 Introduction**

The emergence and subsequent dynamics of mutants play important roles in determining the trajectory of evolution. The fate of a mutant is strongly influenced by its relative fitness. The fitness of a mutant, or rather, the fitness landscape of the whole population is not static, but ever changing under influences of many factors, including density and frequency dependent effects [Nowak and Sigmund, 2004].

In the past years, life history has been gaining its recognition as of fundamental importance in determining the trajectory of evolutionary dynamics (Blute, personal communication). Depicting the trajectories of survival and reproduction along the lifespan, life history is well known to have great influence on evolution in general [Charlesworth, 2001; Nunney, 1991, 1996; Vindenes et al., 2009]. Besides, life history also modulates the actual effect that an increase in survival or reproduction has on the population growth rate, and it accounts for part of the effective size of the population [Charlesworth et al., 1994; Engen et al., 2005]. For the frequency dependent case, it has been shown that life stage dependent strategic interactions can promote diversity and push the distribution of strategic behaviours away from the equilibrium determined by interactions alone [Li et al., 2015a]. However, it is not obvious if certain demographic structures of the population would promote or obstruct the spread and fixation of a beneficial mutant. This is the problem of our interest in the present work, which may be the first step towards further studies of stochastic effects of the frequency dependent case.

Pioneer work on this topic includes papers by Felsenstein [1971] and Emigh [1979a,b]. One major goal of this previous work was to understand the evolutionary dynamics in populations with overlapping generations. Overlapping generation models are biologically more relevant to many species of interest including humans, but they are inevitably associated with increased com-



plexity, due to age or stage structure of the population. To fully capture the demographic architecture of age-structured populations, not only the absolute number and frequency of the mutant matter, but also its distribution across different age classes. One important concept to note here is the reproductive value. The reproductive value of an individual was originally defined by Fisher [1930] as “to what extent will persons of this age (or sex), on average, contribute to the ancestry of future generations”. It does so by accounting for the remaining number of offspring he or she will produce discounted by the increase of population size at the time of reproduction of these offspring. More comprehensive explanations and examples are beautifully presented in the books of Caswell [2001] and Houston and McNamara [1999]. In populations with demographic structure, individuals of different age have different reproductive value. Consequently, the evolutionary fate summarised by the fixation probability of a mutant, i.e. the probability that it ultimately takes over the entire population, can vary greatly in populations with overlapping generations, in contrast to the case where population demographic structure is absent.

The pioneer researchers have made great analytical contributions under various assumptions, such as large population size [Emigh, 1979a,b; Felsenstein, 1971], neutral [Emigh, 1979a] or weak selection [Emigh, 1979b], extreme demographic structures [Emigh, 1979a,b; Felsenstein, 1971], etc. Under these conditions, good approximations can be made to facilitate mathematical analysis. For example, if the sizes of subsequent age classes differ greatly or are very close to each other, it is cogent to approximate hypergeometric sampling with binomial sampling in order to capture the process of individuals entering the next age class. With impressive analytical dexterity, these pioneers successfully summarised the vast complexity into a few easily understood parameters, such as the “effective population number” [Felsenstein, 1971] and the “average reproductive value” [Emigh, 1979a] and used those for describing evolutionary dynamics.

However beautifully analysed, the original work did not achieve the impact it deserves in our opinion. This is maybe due to the inevitable mathematical complexity or limited applicability dictated by stringent underlying assumptions. With the help of current increased computational power, we show that

there are still surprises left uncovered in the original model first described in [Felsenstein \[1971\]](#), even in the simplest case with only two age classes in a well-mixed population and constant selection.

In the following we first describe the model, recall the fixation probability of a neutral mutant in the first age class as a benchmark, and then we analyse the pattern of fixation probability of a beneficial mutant in populations with diverse demographic structures. We explore one by one the evolutionary consequences of selecting on reproduction, survival and both. Finally, we evaluate the relative importance of structure and size in determining the fixation probability of a beneficial mutant.

### 3.3 Model description

#### 3.3.1 Life history and population update rules

Here we describe the life history features of individuals and updating rules of the population, as illustrated in Figure 3.1. In contrast with the original model of [Felsenstein \[1971\]](#), we have fewer age classes, while adding different sources of selective forces. Consider a haploid population in which individuals can live up to age two at maximum. The numbers of individuals in age-one (young) and age-two (old) are constant, denoted as  $N_1$  and  $N_2$ , respectively. In each time step, all individuals produce large amounts of offspring, proportional to their fitness. Among them, only  $N_1$  survive and become the next generation of young individuals. Similarly, only  $N_2$  of the young individuals at the previous time step survive to enter the old age class. All old individuals die and are removed from the population. The recruitment of young individuals from the pool of new born offspring is treated as a process of sampling *with* replacement (similar to the classic Wright-Fisher process), while the recruitment of old individuals from young ones is treated as sampling *without* replacement. This is to account for the majority cases when  $N_1$  is not extremely greater than, or very close to  $N_2$ . The fitness of mutant is assumed to be constant, and greater than the fitness of the wild type, which is normalised to one. Selection may work on reproduction (fitter individuals have more offspring), survival (fitter individuals have higher probability to survive to age two), or a combination of both.

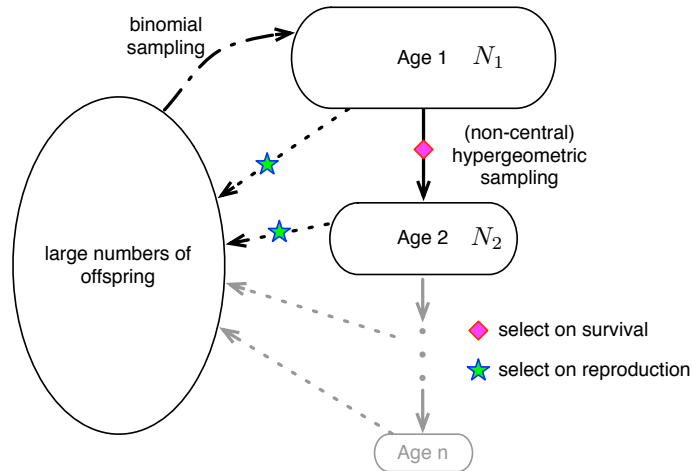


Figure 3.1: Population update rules. The number of individuals in the first and second age classes are fixed ( $N_1$  and  $N_2$ ). Individuals produce large amounts of offspring proportional to their fitness, if selection works on reproduction. Otherwise they all produce the same amounts of offspring. Entering of the first age class of the offspring follows binomial sampling, assuming that the number of offspring is much greater than  $N_1$ . Entering of the second age class of the age-one individuals follows hypergeometric sampling. If selection works on survival, fitter individuals have a higher probability to survive to the next age class. Consequently, the sampling process becomes non-central hypergeometric sampling. Compared to the original model described by Felsenstein [1971], we use only two age classes for simplicity, while the original model has an arbitrary  $n$  age classes. In addition, we explore the difference of selecting on reproduction, selecting on survival, and selecting on both. These different sources of selective forces are not described in Felsenstein’s original model.

### 3.3.2 Fixation probability of a selectively neutral mutant

We denote the state of the population at time  $t$  as a tuple  $x_1 x_2^{(t)}$ , in which  $x_1$  is the number of mutants in the young age class, and  $x_2$  is the number of mutants in the old age class. The transition probability from  $x_1 x_2^{(t)}$  to  $x_1 x_2^{(t+1)}$  is

$$p[x_1 x_2^{(t)} \rightarrow x_1 x_2^{(t+1)}] = B \left( x_1^{(t+1)}; N_1, \frac{x_1^{(t)} + x_2^{(t)}}{N_1 + N_2} \right) H \left( x_2^{(t+1)}; N_1, x_1^{(t)}, N_2 \right), \quad (3.1)$$

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where  $B(k; n, q) = \binom{n}{k} q^k (1 - q)^{n-k}$  denotes the probability of obtaining  $k$  mutants in  $n$  draws with replacement, and  $q$  is the frequency of mutants in the population. We use this binomial sampling to model the process of for picking  $N_1$  individuals from the offspring pool in order to form the new young age class. Similarly,  $H(k; N, K, n) = \binom{K}{k} \binom{N-K}{n-k} / \binom{N}{n}$  denotes the probability of obtaining  $k$  mutants in  $n$  draws without replacement, in which  $N$  is the total number of individuals, and  $K$  is the current number of mutants. We use this hypergeometric sampling for drawing  $N_2$  young individuals that enter the old age class in the next time step. There are  $(N_1 + 1)(N_2 + 1)$  different states of the age-structured population, therefore the state transition matrix  $\hat{P}$  (with elements  $p[x_1 x_2^{(t)} \rightarrow x_1 x_2^{(t+1)}]$ ) has the dimension  $(N_1 + 1)(N_2 + 1) \times (N_1 + 1)(N_2 + 1)$ . The fixation probability vector  $\hat{\rho} = (\rho_{00}, \rho_{01}, \dots, \rho_{0N_2}, \rho_{10}, \rho_{11}, \dots, \rho_{1N_2}, \dots, \rho_{N_1 0}, \rho_{N_1 1}, \dots, \rho_{N_1 N_2})$  contains the fixation probabilities of the mutant type from each of the  $(N_1 + 1)(N_2 + 1)$  distinct population states.

The transition matrix  $\hat{P}$  is stochastic and has unique eigenvalue 1. Due to the absence of mutation, we have  $\rho_{00} = 0$  and  $\rho_{N_1 N_2} = 1$ . In practice, we can thus remove the first row and first column of the transition matrix  $\hat{P}$  to form a new transition matrix  $P$  which corresponds to the fixation probability vector  $\rho$ , which is  $\hat{\rho}$  having the first element 0 removed. To calculate  $\rho$ , we compute the eigenvector that corresponds to eigenvalue 1 of the transition matrix  $P$  numerically, and then normalise it by setting  $\rho_{N_1 N_2}$  to 1.

As a benchmark for later comparisons, we show in Figure 3.2 the fixation probability of a single neutral mutant arising from the young age class. We can see that a neutral mutant is more likely to reach fixation in populations with more old individuals than in populations with more young individuals.

A natural explanation of this pattern is the differentiated reproductive value in the population. In an age-structured population, the fixation probability of a neutral mutation equals the initial frequency of the mutant subpopulation weighted by reproductive values [Emigh, 1979a]. The reproductive value of an individual of a given age expresses the contribution of this individual to the future ancestry of the population. To compute reproductive values, one can use a matrix population model [Caswell, 2001]. That is a square matrix which contains the vital rates (i.e. survival and fertility) of the population

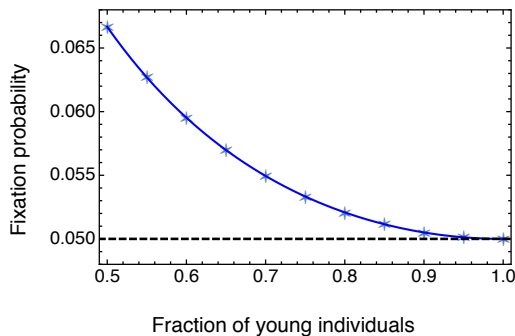


Figure 3.2: Fixation probability of a neutral mutant in a population of total size 20. Symbols are results from numerical calculation (based on the transition matrix), the solid line is the known analytical solution (see Appendix A). Dashed line marks the fixation probability when age structure is absent. There are two age classes in this example, therefore the frequency of young individuals ranges from 0.5 to 1. The neutral mutant has higher probability to reach fixation in populations with more old individuals than in populations with more young individuals.

organised by demographic class. In the case of an age-structured population, the first row of the matrix contains the fertilities of each age class. The fertility at the top of column  $k$  gives the number of offspring born to an individual in age class  $k$  which successfully enters the first age class at the next time step. The subdiagonal of the matrix contains the age-specific survival probabilities. The entry with coordinates  $(j+1, j)$  contains the fraction of individuals in age class  $j$  at time  $t$  that will be in age class  $j+1$  at time  $t+1$ . All other matrix entries are zero. The matrix population model can be right-multiplied by the population state vector. The result of this multiplication is the projection of the population state to the next time step. If this operation is reiterated, then the vector representing the population state eventually becomes proportional to the leading right eigenvector of the matrix population model. At this point, the population is in a demographically stable state and its growth rate corresponds to the leading eigenvalue of the matrix. With appropriate scaling, the leading left eigenvector gives the reproductive value of each age class. As this model only involves matrix algebra, it is entirely deterministic. In our case, the matrix population model is a  $2 \times 2$  matrix, as we only have two age classes. As we assume a constant size, the leading eigenvalue of this matrix

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must be unity. Using the description of the life history in our population given in Section 3.3.1 and setting  $N_2 = N - N_1$ , our matrix population model is

$$\begin{pmatrix} N_1/N & N_1/N \\ N_2/N_1 & 0 \end{pmatrix}. \quad (3.2)$$

The right eigenvector of this matrix corresponding to the eigenvalue of unity is  $e_R = (N_1/N, N_2/N)^T$ . This vector is already scaled to give the stable age distribution in the asymptotic population. The corresponding left eigenvector  $e_L = (N/N_1, 1)$  gives the reproductive values. With these two vectors, we can now give reproductive value weights to the initial frequency of a neutral mutant of young age in our population at demographic stability. The mutant's reproductive value thus equals to  $N/N_1$ . The reproductive value in the total population is the population size  $N$  multiplied by the scalar product  $e_L \cdot e_R$ , which is the reproductive value at stability in the unit size population. Taking the ratio of the initial mutant reproductive value to the total reproductive value in the population, we obtain  $1/(N_1(2 - N_1/N))$ , which corresponds to the fixation probability of the mutant [Emigh, 1979a]. The derivative of this last quantity with respect to  $N_1$  is  $-\frac{2N(N-N_1)}{N_1^2(N_1-2N)^2}$ , which is strictly negative. Therefore, the fixation probability of a neutral mutant has decrease as the frequency of young individuals increases.

Another way to understand this pattern is to calculate directly the age-structure dependent fixation probability. Denote  $f$  as the frequency of young individuals in the population, the fixation probability of a single mutant in a population of size  $N$  is  $1/((Nf(2 - f)))$ . A derivation of this fixation probability can be found in 7.2.1.)

To set the basis for later comparisons, we have derived the fixation probability of a neutral mutant in the first age class. In the following we focus on the population dynamics and fixation probability of a beneficial mutant that has a constant selective advantage  $r > 1$ . We explore one by one the effects of selecting on reproduction, survival and both.

### 3.4 Selection on reproduction

If selection only works on reproduction, the mutant produces  $r$  times more offspring compared to the wild type. The transition probability from state  $x_1 x_2^{(t)}$  to  $x_1 x_2^{(t+1)}$  is then

$$p[x_1 x_2^{(t)} \rightarrow x_1 x_2^{(t+1)}] = B\left(x_1^{(t+1)}; N_1, \frac{r(x_1^{(t)} + x_2^{(t)})}{r(x_1^{(t)} + x_2^{(t)}) + N_1 - x_1^{(t)} + N_2 - x_2^{(t)}}\right) H\left(x_2^{(t+1)}; N_1, x_1^{(t)}, N_2\right) \quad (3.3)$$

It seems difficult to find a closed form of the fixation probability without making a substantial number of additional assumptions, such as approximating the (noncentral) hypergeometric distribution with a binomial distribution, which requires that  $N_{i+1}$  is either very small or close to  $N_i$  [Emigh, 1979a,b]. Nevertheless, we can obtain valuable analytical insights from calculating  $E[x_1^{(t+1)} + x_2^{(t+1)}]$ , the expected total number of mutants in the next time step (Details in 7.2.2.1).

$$E[x_1^{(t+1)} + x_2^{(t+1)}] = \frac{x_1^{(t)} N_2}{N_1} + \frac{r(x_1^{(t)} + x_2^{(t)}) N_1}{(r-1)(x_1^{(t)} + x_2^{(t)}) + N_1 + N_2} \quad (3.4)$$

Although  $E[x_1^{(t+1)} + x_2^{(t+1)}]$  is not a proxy of the fixation probability per se, it illustrates an important aspect of the fixation dynamics.

Given that the total size of the population is fixed, age structure of the population is determined by the relative numbers of young and old individuals. Replacing  $N_2$  with  $N - N_1$ , we observe a minimum of the expected number of mutants in the next time step, where  $dE[x_1^{(t+1)} + x_2^{(t+1)}]/dN_1 = 0$ . The corresponding number of young individuals is

$$N_1^* = \sqrt{x_1^{(t)} N \left(1 + \frac{N - x_1^{(t)} - x_2^{(t)}}{r(x_1^{(t)} + x_2^{(t)})}\right)} \quad (3.5)$$

Therefore, the fixation probability of the mutant could in principle also have a minimum in populations with an intermediate fraction of young individuals (Details in 7.2.2.2). In addition, the frequency of young individuals corresponding to the minimum fixation probability should decrease with  $r$ , the relative fitness of the mutant. We confirm these analytical results numerically

in a population of total size 20, as shown in Figure 3.3.

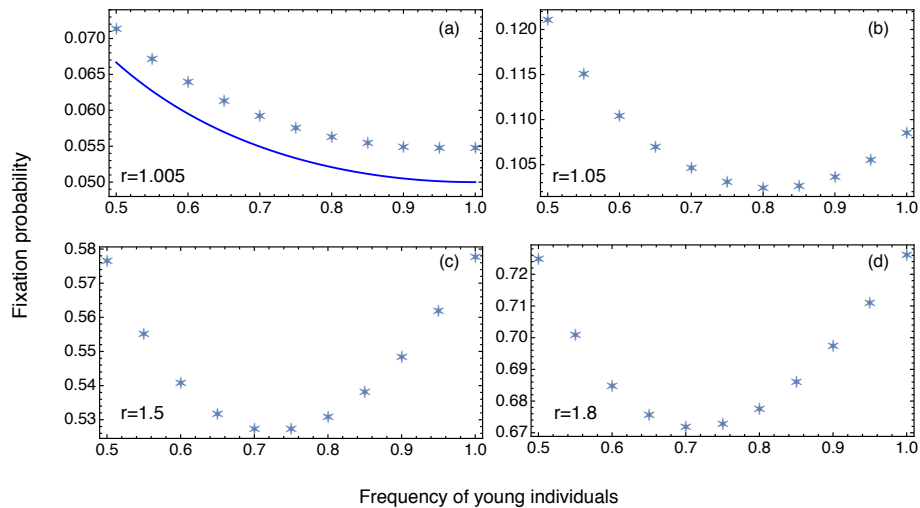


Figure 3.3: Constant selection on reproduction in a population with fixed total size of 20. Symbols represents the fixation probability of a single young mutant with fitness  $r$ . The solid line in the first panel represents the fixation probability in the neutral case when  $r = 1$ . There is always a minimum of the fixation probability for intermediate frequency of young individuals. The frequency of young individuals at the minimum decreases when  $r$  increases.

### 3.5 Selection on survival

If selection only works on survival, the mutant type has the same fecundity as the wild type, but is  $r$  times more likely to survive to age-two. Because of the selective advantage of the mutant, the survival step follows the non-central hypergeometric distribution instead of the standard hypergeometric distribution. The total number of sampling events ( $N_2$ ) is fixed, individuals are sampled one by one, and there is competition among individuals. Under these conditions, we have to use Wallenius' noncentral hypergeometric distribution rather than Fisher's noncentral hypergeometric distribution [Fog, 2008b]. In



this case, the transition probability from state  $x_1x_2^{(t)}$  to  $x_1x_2^{(t+1)}$  is

$$p[x_1x_2^{(t)} \rightarrow x_1x_2^{(t+1)}] = B\left(x_1^{(t+1)}; N_1, \frac{x_1^{(t)} + x_2^{(t)}}{N_1 + N_2}\right) H^W\left(x_2^{(t+1)}; N_1, x_1^{(t)}, N_2, r\right), \quad (3.6)$$

in which  $H^W$  is Wallenius' noncentral hypergeometric distribution, for which closed form implementations are numerically cumbersome [Fog, 2008a].

When the selective advantage of the mutant  $r$  is small,  $H^W$  can be approximated by the corresponding standard hypergeometric distribution, and thus the fixation probability of the mutant is similar to that of the neutral case (Figure 3.4a). However, when  $r$  is large, we observe a remarkable increase of the fixation probability in populations with an intermediate frequency of young individuals (Figure 3.4b-d).

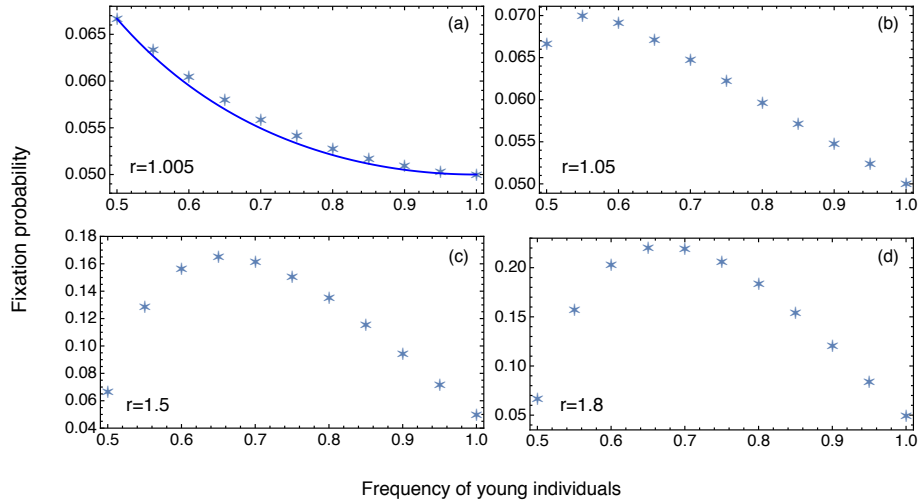


Figure 3.4: Constant selection on survival in a population with a total fixed size of 20. Symbols represent the fixation probability of one single mutant in the young age class with fitness  $r$ . The solid line in the first panel represents the fixation probability in the neutral case, when  $r = 1$ . When  $r$  is small, the fixation probability decreases monotonically, resembling the neutral case. But when  $r$  becomes larger, there is an intermediate maximum of fixation probability. The corresponding frequency of young individuals increase when  $r$  increases.

Although we cannot calculate the exact fixation probability analytically due to the complexity associated with the Wallenius' noncentral hypergeo-

metric distribution, it is still possible to understand intuitively the pattern of having a maximum of fixation probability in populations with intermediate frequency of young individuals.

In the limit of very large selective advantage  $r$ , basically all mutants in the young age class will be selected to survive into the old age class, if  $N_2$  is greater than the total number of mutants. Otherwise,  $N_2$  mutants will survive and enter the old age class. Therefore,  $E[x_2^{(t+1)}] \approx \min(x_1^{(t)}, N - N_1)$ . When  $N_1$  is small ( $N_1 < N - x_1^{(t)}$ ), as  $N_1$  increases by 1,  $E[x_2^{(t+1)}] = x_1^{(t)}$  does not change; but when  $N_1$  is large ( $N_1 > N - x_1^{(t)}$ ), as  $N_1$  increases by 1,  $E[x_2^{(t+1)}] = N - N_1$  decreases by 1. On the other hand, because there is no selection on reproduction, the expected number of young mutant in the next time step  $E[x_1^{(t+1)}]$  is simply proportional to the global frequency of mutants in the whole population,  $E[x_1^{(t+1)}] = N_1(x_1^{(t)} + x_2^{(t)})/N$ . As  $N_1$  increases by 1,  $E[x_1^{(t+1)}]$  increases by  $(x_1^{(t)} + x_2^{(t)})/N$ , which is between 0 and 1. This is irrespective of the value of  $N_1$ . Taken together, the expected number of mutants in the next time step is  $E[x_1^{(t+1)} + x_2^{(t+1)}] = E[x_1^{(t+1)}] + E[x_2^{(t+1)}]$ . Since  $0 \leq E[x_1^{(t+1)}] \leq 1$ ,  $E[x_2^{(t+1)}] \approx 0$  when  $N_1$  is small but  $E[x_2^{(t+1)}] \approx -1$  when  $N_1$  is large, we expect  $E[x_1^{t+1} + x_2^{(t+1)}]$  to first increase and then decrease, as  $N_1$  increases.

### 3.6 Selection on both reproduction and survival

From previous sections, we can see that if selection only works on survival, a beneficial mutant has a minimal probability to get fixed in populations with intermediate level of young individuals. But if selection works on survival and when the selective advantage of the mutant is sufficiently large, there is a maximum of the fixation probability when the frequency of young individuals is intermediate.

If selection works on both reproduction and survival, we assume that a beneficial mutant may not only produce more offspring, but also is more likely to survive to the next age. This double effects could result from the fact that the mutant allocates extra payoff to both reproduction and survival. Consider a mutant that has increased access to food resources compared to the wild type. As a result, she may choose to (or be genetically programmed to) consume the extra food immediately, thereby allocating most of the benefits to reproduction and relatively little to improving her chance of surviving to the next

round of reproduction. On the other hand, she may choose to save most of the food for provision, thereby has little improvement in reproduction, but large increase in the chance of survival. There exists an established body of allocation theory, with different functional forms for allocating limited resource to reproduction and survival. This further leads to different patterns of ageing in different species and populations. For a recent review, see [Baudisch and Vaupel \[2012\]](#). In the case where selection works on both reproduction and survival, and the mutant allocates its payoff benefit to both, the transition probability from state  $x_1x_2^{(t)}$  to  $x_1x_2^{(t+1)}$  is

$$\begin{aligned}
 & p[x_1x_2^{(t)} \rightarrow x_1x_2^{(t+1)}] \\
 & = B \left( x_1^{(t+1)}; N_1, \frac{r_1(x_1^{(t)} + x_2^{(t)})}{r_1(x_1^{(t)} + x_2^{(t)}) + N_1 - x_1^{(t)} + N_2 - x_2^{(t)}} \right) H^W \left( x_2^{(t+1)}; N_1, x_1^{(t)}, N_2, r_2 \right),
 \end{aligned}
 \tag{3.7}$$

in which  $r_1$  and  $r_2$  represent that the mutant produces  $r_1$  times offspring compared to the wild type, and is  $r_2$  times more likely to survive to the next age.

The major purpose of this work is not to compare different allocating patterns but rather to demonstrate the effects of different selective forces. We therefore choose arbitrarily the simple case where  $r_1 = r_2$  to study the model, as [Altrock and Traulsen \[2009\]](#) did in studying the evolutionary dynamics of stochastic birth-death processes. (In 7.2.3, we show an example of the effects of allocating benefits between reproduction and survival following a linear pattern, where  $r_1$  and  $r_2$  are different. Following the same method, the effects of allocating benefits in other ways can be studied.)

From the numerical calculation results (for the special case that  $r_1 = r_2 = r$ ) show in Figure 3.5, we see the pattern of fixation probability of a single mutant in the young age class has combined effects from both selecting on reproduction and on survival. On one hand, the value of the fixation probability is more similar to the case that selection works solely on reproduction. (Note that the end points in the first and the third panel are identical, when the effect of age structure disappears.) On the other hand, the pattern of having an apparent maximum of the fixation probability in populations with intermediate frequency of young individuals, is more similar to the case when selection works solely on survival.

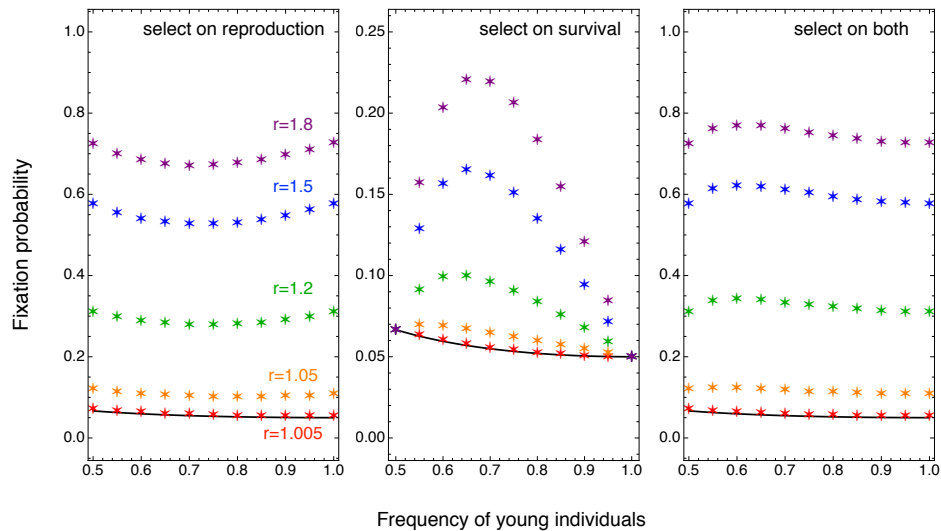


Figure 3.5: A comparison between selecting on reproduction, survival and both. The figure shows the fixation probability of a single beneficial mutant in the young age class. Solid lines represent the fixation probability in the neutral case, when  $r = 1$ . The pattern of selecting on both reproduction and survival shows a combined effect. The magnitude of the fixation probability across different age structures is closer to the case when selecting solely on reproduction, but the shape of having an intermediate maximum when  $r$  is large is similar to selecting on survival (note the different scale on the  $y$ -axis). Total population size  $N = 20$ .

### 3.7 Comparing the effects of population size and demographic structure

The relative importance of population size and demographic population structure in determining the fixation probability depends crucially on the relative fitness of the mutant. If the relative fitness of the mutant is very small, population size has a larger effect, but if the fitness of the mutant is large, the demographic structure of the population plays an essential role (Figure 3.6). The pattern of having an intermediate minimum of fixation probability when selecting on reproduction is preserved irrespective to population size. The intermediate maximum of the fixation probability when selecting on survival exists when the relative fitness of the mutant is not too small.

Another interesting observation is that the fixation probability of a sin-

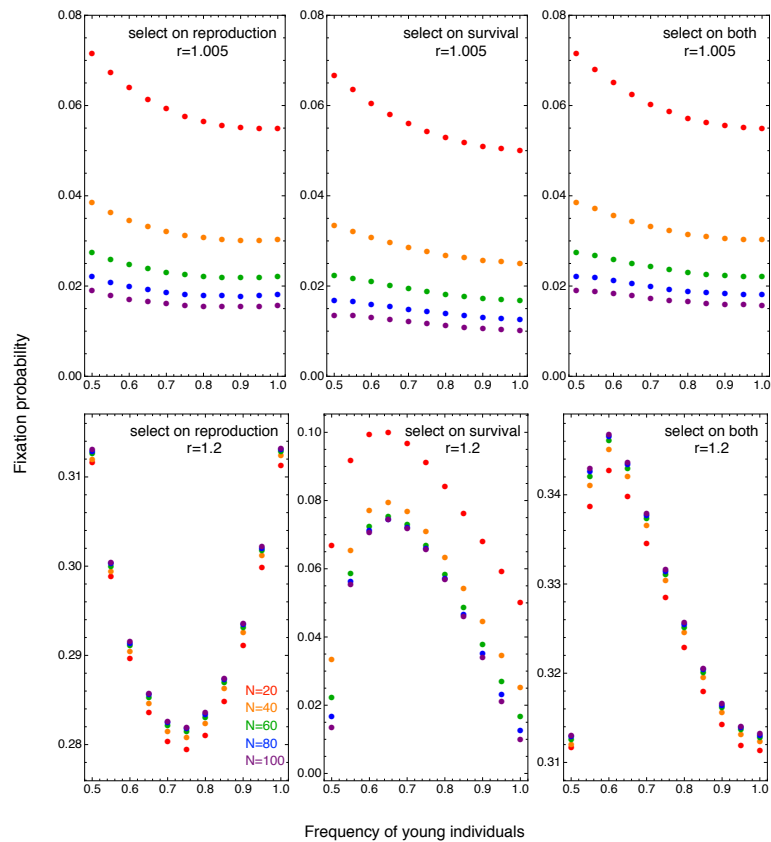


Figure 3.6: Population size has a larger effect if the relative fitness advantage of the mutant is small. Demographic population structure has a larger effect if the relative fitness of the mutant is large. Symbols of different colours represent different population size. Color coding is consistent in all panels.

gle mutant is higher in larger populations compared to smaller populations, when  $r$  is large, and when selecting on reproduction or both reproduction and survival. This is a feature of the Wright-Fisher process (Details in Appendix 7.2.4).

### 3.8 Discussion and conclusion

Although it is clear that the likelihood of incorporating a beneficial mutation in the gene pool is a function of the life history architecture of the population, little has been done to pinpoint the direct effects of different life history patterns on promoting or hindering adaptive evolution. In this work we ap-

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proach this problem building on the basis of the seminal Felsenstein model of populations with overlapping generations [Felsenstein, 1971]. We explore the effects of different sources of evolutionary forces, including selecting on reproduction, survival and a combination of both. We also study the relative importance of the size and demographic structure of the population.

First, our work reveals fundamental differences between selecting on reproduction and survival in populations with age structures. The differences are remarkable even in the simple case where the population is spatially well-mixed, and neither density nor frequency affects the relative fitness of the mutant. It is known that in well-mixed populations under constant selection, selecting on reproduction or survival is equivalent when mutation is absent [Ewens, 2004; Kaiping et al., 2014]. In spatial structured populations, selecting on reproduction and survival are different in general, but it is possible to produce the same effects. For example, under the Moran process scheme, selecting on reproduction with a birth-death updating rule is still equivalent to selecting on survival with a death-birth updating rule, in any populations with “homogeneous” structures (e.g., lattices, cycles, and island models) and symmetric dispersal [Taylor et al., 2011]. It is worthwhile to note that in degree-heterogeneous graphs, the fixation probability of an advantageous mutant depends crucially on if selection works on reproduction or survival [Antal et al., 2006; Hindersin and Traulsen, 2015; Kaveh et al., 2015]. Even when selection works only on reproduction, the sequence of birth and death events can lead to completely different evolutionary dynamics [Kaveh et al., 2015; Zukewich et al., 2013]. For almost any random graph, a selectively advantageous mutant almost always has higher-than-neutral fixation probability if birth takes places before death, but has lower-than-neutral fixation probability if death happens first [Hindersin and Traulsen, 2015]. Although the differences of selecting on reproduction and survival is relatively well recognised and studied in spatially structured populations, less is known in populations with demographic structure.

Here we show that even under constant selective advantage, life history of individuals in the population makes the evolutionary dynamics differ drastically with different sources of selective forces. In the future, it would be interesting to go beyond the simple case of constant selection and investi-

gate the effects of density and frequency dependent fitness of the mutants. Under the well-mixed condition, low density favours individuals who direct their efforts towards exploring the ecological environment and thereby maximising their reproduction rates. But under high density conditions, since most resources have already been absorbed into the population, it is more efficient to direct one's effort towards exploiting other population members through interactions [Blute, 2011]. Usually, the successfulness of a strategy is not determined by its nature alone, but on the presence and frequency of other strategies in the population. Density and frequency effects are hardly disconnected from each other in natural populations, and it is often needed to take both into account in order to capture the important features of evolutionary dynamics, especially when there is noteworthy changes in population size [Huang et al., 2015; Li et al., 2015b; Novak et al., 2013]. Under the framework of Evolutionary Game Theory, elegant conditions such as the 1/3 rule have been obtained [Imhof and Nowak, 2006; Lessard and Ladret, 2007; Nowak et al., 2004], under which strategies such as cooperation via direct reciprocity can evolve in the first place. But it is unclear if such conditions still hold in populations with demographic structures. Therefore it is interesting to study the coevolution between population demography and strategy interactions in future works.

In natural populations, species display an enormous variety of different life history patterns [Jones et al., 2014]. It is very often that mutations affect the fitness of individuals in both reproductive and survival aspects. A classical example is the thoroughly discussed ornamented train of male peacocks, which are sublimely beneficial in terms of mating success, but at the same time tremendously costly when it comes to the chance of escaping from a predator. Another beautiful example is the shape of wings in migrating birds. Pointed wings are aerodynamically desirable for fast and long-distance flights [Berthold, 1996; Bowlin and Wikelski, 2008; Hedenström, 2002; Minias et al., 2015; Mönkkönen, 1995]. But on the other hand, they reduce the manoeuvrability that help birds with foraging and courtship displays [Alatalo et al., 1984; Swaddle and Lockwood, 2003]. Precisely due to the high benefits and high costs of pointed wings, the change of selective pressure leads to the change of wing morphology in bird populations. This has been observed in

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many passerine species, e.g. the fast evolution of stonechats *Saxicola torquata* in response to changing environmental conditions [Baldwin et al., 2010]. It is interesting also to note that evolution can go to great detail in balancing the cost and benefits of a single morphological trait, and life history serves as a channel through which evolutionary forces fine tune the balance. As an example and also a demonstration of its plastic potential, it is found that the juveniles of migrating birds have less pointed wings compared to adults. This is due to the fact that juveniles are more naive and thus more vulnerable to predators. Under elevated predation pressure, improved manoeuvrability is more important than migration performance, particularly in the early stage of life [Pérez-Tris and Tellería, 2001]. For more examples of the amazing variety in survival and reproduction trajectories over the life course across species, Jones et al. [2014] provides a recent review.

In this work we focus on the simple case of two age classes. We have shown how the fixation probability of a mutation with effect on certain components of the life history is influenced by the demographic structure of the resident population, i.e. the relative frequency of young versus adult individuals. We note that a natural interpretation of the same results can also be given in terms of the rate of ageing that characterizes the resident population. In fact, the relative abundances of young and adult individuals depend on the probability of newborn survival to young age and the probability of surviving from young age to old age. Ageing is defined as an age related deterioration in survival. Ageing features in a large number of species and is one of the most salient life history traits. It follows from the definition of ageing that, in our model, populations that are composed by a higher fraction of young individuals are characterized by a higher rate of ageing (i.e. stronger deterioration in survival with age). Conversely, populations with a higher representation of old individuals may possess no ageing at all or even negative ageing (i.e. survival does not decline but it may even increase with age, see Baudisch and Vaupel [2012] and Jones et al. [2014]).

In this way, our results can be directly linked with the effect that an important life history trait exerts on adaptive evolution. If natural selection works on reproduction, for any beneficial mutant, intermediate rates of ageing always reduce fixation probability, although the chance of fixation may be higher in



populations with low or negative rates of ageing, depending on the difference in fitness between the mutant and the wild type. If natural selection works on survival and the fitness difference between the beneficial mutant and the wild type is not too small, there is a maximum of fixation probability in populations with intermediate rates of ageing, while in populations with extreme positive or negative rates of ageing, the fixation probability of the beneficial mutant is reduced. If natural selection works on both survival and reproduction, depending on how fitness advantages are allocated and the magnitude of the fitness difference between mutant and the wild type, complex patterns with multiple extrema of the fixation probability with respect to the rate of ageing can emerge.

To summarize, in this work we have studied the direct effects of population demographic structures on stochastic evolutionary dynamics, under the constant selection regime. Using a model with two age classes and constant population size, we have compared the fixation probability of mutants under different population demographic structures. Different targets of selective forces, as well as the relative impacts of the size and structure of the populations are also evaluated in our analyses. Through this work, we hope to call attention to the importance of considering life history when studying evolutionary dynamics. Facilitated by modern computational power, now we have the opportunity to delve into many interesting questions that were technically not approachable a few decades ago. Our work opens up new directions for future research, including the coevolution of population structure, resource allocation and strategic dynamics, the impacts of demography on the rate of adaptive evolution, and the density/frequency dependent fitness effects in populations with different life history patterns.



# Which games are growing bacterial populations playing?

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In previous chapters we integrate biological factors into evolutionary game theory models by taking into account life history traits of individuals and demographic structures of populations. But these models do not apply to any specific species or biological system. In this chapter, we apply evolutionary game theory to explain population dynamics of bacteria in double-culture experiments. Classic evolutionary game theory models focus on the frequency dynamics of the different strategies, neglecting the density effects. But in bacterial communities, both the frequencies and densities of different species can change rapidly, and have profound ecological influences. We link the effects of population growth with evolutionary game theory by incorporating frequency dependent growth rates in the Lotka-Volterra equation. Our working model captures the main features of the population dynamics observed in experiments, including the population size expansion and alternative coexisting states.

This chapter is based on the publication [Li et al., 2015b], coauthored by Cleo Pietschke, Sebastian Fraune, Philipp M. Altrock, Thomas C.G. Bosch and Arne Traulsen. A detailed summary of the authors' contributions to this publication can be found at the end of this thesis.

## 4.1 Abstract

Microbial communities display complex population dynamics, both in frequency and absolute density. Evolutionary game theory provides a natural approach to analyse and model this complexity by studying the detailed interactions among players, including competition and conflict, cooperation and

coexistence. Classic evolutionary game theory models typically assume constant population size, which often does not hold for microbial populations. Here we explicitly take into account population growth with frequency dependent growth parameters, as observed in our experimental system. We study the *in vitro* population dynamics of the two commensal bacteria (*Curvibacter* sp. (AEP1.3) and *Duganella* sp. (C1.2)) that synergistically protect the metazoan host *Hydra vulgaris* (AEP) from fungal infection. The frequency dependent, nonlinear growth rates observed in our experiments indicate that the interactions among bacteria in co-culture are beyond the simple case of direct competition or, equivalently, pair-wise games. This is in agreement with the synergistic effect of anti-fungal activity observed *in vivo*. Our analysis provides new insight into the minimal degree of complexity needed to appropriately understand and predict coexistence or extinction events in this kind of microbial community dynamics. Our approach extends the understanding of microbial communities and points to novel experiments.

## 4.2 Introduction

From protists to humans, all animals and plants are inhabited by microbial organisms. There is an increasing appreciation that these resident microbes influence evolutionary important traits (e.g., fitness) of their hosts [McFall-Ngai et al., 2013; Sommer and Bäckhed, 2013]. The host and its associated microbiota do not evolve independently, but form a metaorganism that evolves as a whole under natural selection [Brucker and Bordenstein, 2013; Zilber-Rosenberg and Rosenberg, 2008]. The microbial organisms affect host fitness in various ways. They contribute by enhancing digestion and mediating energy balance via nutrient absorption [Douglas et al., 2001; Gustafsson and Laurell, 1959; Nicholson et al., 2012; Yatsunenko et al., 2012], controlling pathogenic reactions [Buffie et al., 2012; Fraune et al., 2014; Kamada et al., 2013], stimulating stem cell turnover [Jones et al., 2013] and the maturation of immune systems [Mazmanian et al., 2005; Weiss et al., 2012], and potentially triggering normal development of organs [Montgomery and McFall-Ngai, 1994; Rawls et al., 2004]. They even promote hybrid lethality/sterility and thus contribute to speciation [Brucker and Bordenstein, 2013]. Despite the well-accepted im-

portance of microbiota to the normal functioning of the host, the molecular and cellular mechanisms controlling interactions within the metaorganisms are poorly understood and many key interactions between the associated organisms remain unknown [Prosser et al., 2007]. Moreover, the applications of theoretical frameworks to improve the understanding of the ecological interactions among microbiota and between host and microbiota are still very limited. Notable exceptions include Blaser and Kirschner [2007]; Bucci and Xavier [2014]; Marino et al. [2014]; Schluter and Foster [2012]; Stein et al. [2013].

There exists an established body of ecological theory for the population dynamics of large organism, such as plants and animals. But whether these theories also apply to the dynamics of microorganisms is largely unknown, yet seldom questioned [Prosser et al., 2007]. Compared to large organisms, bacteria not only differ greatly in the small physical size and high growth rate, but also in the drastic changes of population size. These differences are most profound during neonatal host development, while the microbiota establish. There has been comparably little theoretical development for the interaction dynamics of size fluctuating bacterial populations [Hallatschek et al., 2007; Melbinger et al., 2010]. A recent study showed that microbiota colonization patterns during host development display complex dynamics, which cannot be explained with standard models of density independent competition [Franzenburg et al., 2013]. This study also showed that the microbiota composition in fresh water *Hydra* hatchlings changed greatly during development. A highly variable initial stage was followed by transient adult-like phase in which the microbial composition was temporarily very similar to the stable adult microbiota, yet only retained for a short time. The adult microbiota composition only reappear after further drastic changes. Remarkably, a similar “in-out-in” colonization pattern of adult-like microbiota composition was also observed in human infants [Palmer et al., 2007].

Even more interestingly, the complex microbiota in *Hydra* prevents infection by the filamentous fungus *Fusarium* sp. [Fraune et al., 2014]. Using a germ free *Hydra* model it was shown, that germ free polyps were highly susceptible to fungal infection, while restoring the complex microbiota in gnotobiotic polyps prevented infection. Testing single bacterial isolates from *Hy-*

*dra* in mono-associations revealed that none of the tested bacterial colonizers alone was able to provide full antifungal resistance. In contrast, resistance, as observed in control polyps, was achieved in polyps di-associated with the two most dominant bacterial colonizers, *Curvibacter* sp. and *Duganella* sp., by exhibiting a strong synergistic effect [Fraune et al., 2014]. This finding provides compelling evidence for the importance of bacteria-bacteria interactions in the normal functioning of *Hydra* associated microbiota.

Besides empirical evidence, ecological theories are indispensable to our understanding of the full complexity in the host-microbiota interplay. Evolutionary game theory takes its root in classic game theory, but focuses on the frequency dynamics of strategies in populations instead of the quality of competing strategies themselves. Therefore it is especially suited for studying microbial population dynamics on the ecological time scale, where the fitness landscapes of different types are constantly changing [Nowak and Sigmund, 2004], and thus selection is frequency dependent [Frey and Reichenbach, 2011; Kerr et al., 2002; Rainey and Rainey, 2003]. In the case of deterministic dynamics, there exists a strong link between game dynamics and ecological dynamics. The game theoretical replicator equation is mathematically closely related to the ecological Lotka-Volterra equation with linear growth rates [Hofbauer and Sigmund, 1998]. The replicator equation focuses on relative changes in population size under frequency dependent fitness, which can provide conceptual insights into the microscopic interactions between individual bacteria cells. The Lotka-Volterra equation describes populations of changing size. Therefore it can be conveniently linked to experiments [Ellner and Guckenheimer, 2011; May and McLean, 2007; Murray, 2007]. In the case of two interacting species, the replicator dynamics and the competitive Lotka-Volterra equations predict competitive exclusion, i.e., extinction of one type, or coexistence at a unique state of population composition.

Considering the classic Lotka-Volterra equation as the potential framework to understand bacterial interaction reveals limitations in modeling the population dynamics of the two most abundant bacterial species that interact synergistically to protect the *Hydra* host from pathogenic infection. We show that the patterns observed in our experiments require a more detailed consideration of bacteria-bacteria interactions. This includes growth rates

that nonlinearly depend on the relative abundance of different species in the exponential growth phase.

Compared to human and other more complex model species, the early metazoan *Hydra* provides a comparably simple system with a genetically determined bacterial community colonizing the surface of ectodermal epithelium [Fraune and Bosch, 2007]. Therefore, it serves as a powerful model organism for studying the interactions between the host and its bacterial community [Bosch, Thomas CG, 2013; Fraune and Bosch, 2010]. In addition, the synergistic interaction between the two dominant bacteria species is especially exciting. It provides anti-fungal protection to the host that cannot be achieved by either of the bacteria when associated with the host alone [Fraune et al., 2014]. In a first attempt to quantitatively understand the host-microbial interaction, here we determine the mechanisms of bacterial interactions without the host's influence. We performed double culture experiments *in vitro* with the two most abundant actors in the *Hydra* microbiota. In order to develop a mathematical model for this scenario, here we propose general principles governing the interactions within the microbiota. We start by adding frequency dependent growth rates into the Lotka-Volterra framework and infer the possible dynamics for linear and quadratic frequency dependent growth rates and then put these results into the context of our empirical data. These data suggests interactions between multiple players as one possible mechanism of the interactions among individual bacterial cells, which can lead to the global population dynamics qualitatively similar to the one observed in our experiments.

### 4.3 Materials and methods

We study the interactions between the two species of Betaproteobacteria *Curvibacter* sp. AEP1.3 (*C*) and *Duganella* sp. C1.2 (*D*). Both bacteria belong to the order of Burkholderiales, while *C* represents a Comamonadaceae and *D* an Oxalobacteraceae [Fraune et al., 2014]. We chose these two bacteria because (i) they are naturally found in the bacterial community of the freshwater polyp *Hydra vulgaris* (AEP), and are the two most abundant species in the microbiota (*C*:75.6% and *D*:11.1%) [Fraune et al., 2014]; (ii) the synergis-

tic interaction between the two bacteria species effectively provides anti-fungal protection for the host [Fraune et al., 2014]; and (iii) the morphology of their colonies can be distinguished from each other on agar plates.

### 4.3.1 Monoculture and double culture experiments

To determine the growth rate in monocultures, we inoculated for each bacterium 50 ml R2A medium with 10 concentrations between  $2.0 \times 10^3$  and  $1.0 \times 10^5$  cfu/ml of *C* or *D* of an overnight culture. The cell numbers of each bacteria were estimated by counting the colony forming units (cfu), and was cross-checked with optical density (OD) measurements at OD600 = 0.1 ( $1.0 \times 10^8$  cfu/ml for *C* and  $2.0 \times 10^7$  cfu/ml for *D*). In double culture experiments, we kept a total initial concentration of  $1.0 \times 10^5$  cfu/ml and applied a gradient of different initial frequencies of species *C* and *D*. Over the course of three days, three times a day, we measured the OD600 of the cultures and plated two dilutions, which were adjusted individually to the optical density, on R2A agar plates. After two days we counted the number of colonies of *D* and after four days those of *C*. This difference in counting times was due to different growth rates of the two bacteria on agar plates (Figure 4.1).

### 4.3.2 Data preparation and analysis

For cell culture growth over time in both monocultures and double cultures, we calculated growth rate functions by applying a linear regression to the log-linear transformed data. The goodness of fit was calculated using the (adjusted)  $R^2$  [Draper and Smith, 1998; Kvalseth, 1985]. In monoculture experiments for both species, we tested the dependency of growth rate in the exponential growth phase on a gradient of initial cell densities.

In double culture experiments for both species, we tested linear, quadratic and cubic functions of growth rate on a gradient of initial frequencies. These three different model hypotheses were then compared using Akaike Information Criterion (AIC) [Bozdogan, 1987] and Bayesian Information Criterion (BIC) [Burnham and Anderson, 2004; Posada and Buckley, 2004], based on the likelihood functions of a normally distributed error term in the linear regression model. The most appropriate models were chosen with the agreement



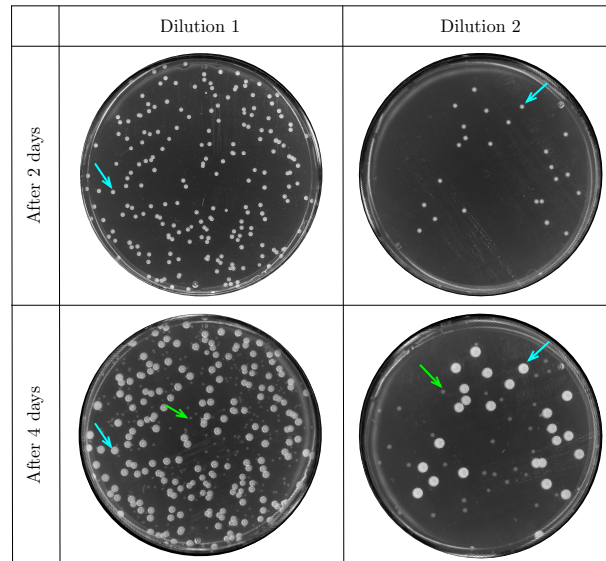


Figure 4.1: We quantify the density of *Curvibacter* sp. and *Duganella* sp. by the method of counting colony forming units (*cfu*). At each time point, we took a sample of the bacterial culture and perform a series of dilutions. The diluted samples were then plated on a petri dish with solid agar medium. After two days, the fast growing *Duganella* sp. (indicated by cyan arrows) already formed clear and distinct colonies on the plates. After four days, the slow growing *Curvibacter* sp. (indicated by green arrows) also formed distinct colonies. Under the assumption that one colony was formed by one single founder cell in the medium, we can calculate the cell densities of each of the two bacteria species in the original sample by adjusting the numbers of colonies with corresponding dilution factors.

between both AIC and BIC tests.

In double culture experiments, if the cell density value was missing for one of the species at a certain point of time during the exponential growth phase, this data point was excluded when plotting the growth trajectories. But the cell density of the species that did have a valid count can still be used for calculating growth rate.

## 4.4 Mathematical model

Our mathematical model is directly motivated by experimental observations. We analyzed the growth trajectories of the double culture experiments of *Curvibacter* sp. ( $C$ ) and *Duganella* sp. ( $D$ ), the two most abundant species that interact synergistically to protect the *Hydra* host from fungal infection. Depending on the initial condition, one of the two species eventually becomes

dominant in frequency (Figure 4.2). This resembles a coordination game [Nowak, 2006a], which is characterised by an unstable intermediate fixed point and two stable boundary fixed points. However, the submissive species does not go extinct but keeps growing in absolute density. This is a key feature, which is usually neglected in game theoretic models where only changes in frequency, fixation and respective extinction are considered.

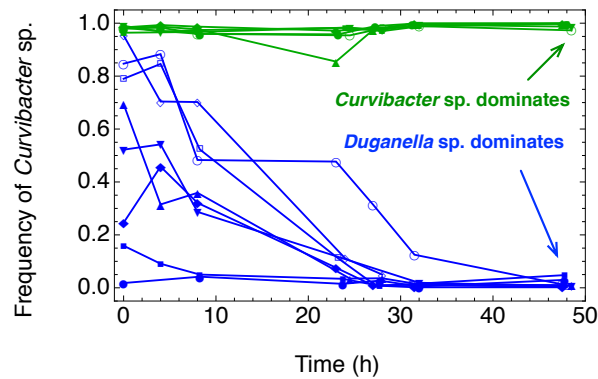


Figure 4.2: Change of the frequency of *Curvibacter* sp. in double cultures with *Duganella* sp. The frequency of *Curvibacter* sp. approaches the 0 or 1 boundaries over time, depending on the initial frequency of both types. If the culture was inoculated with a high frequency of *Curvibacter* sp., the frequency of it remains high (green trajectories), otherwise *Duganella* sp. quickly outgrows and eventually pushes the frequency of *Curvibacter* sp. towards 0 (blue trajectories). This resembles the dynamics in a coordination game, where the two homogeneous populations are stable.

Based on these experimental findings, we propose a mathematical model building on the classic Lotka-Volterra competition dynamics, which is mathematically closely related to the replicator equation in game theory models Hofbauer and Sigmund [1998]. In our model, the maximum growth rates in the exponential growth phase of the bacterial culture are frequency dependent. This model of *in vitro* bacterial interactions in growing populations serves as a basis for making comparisons with the *in vivo* scenarios influenced by the host.

#### 4.4.1 Lotka-Volterra competition model with linear frequency dependent growth rates

The population dynamics in two-species Lotka-Volterra competition models is been thoroughly discussed in textbooks [May and McLean, 2007; Murray,

2007]. Those models assume that the two species only compete for the same limited resources, e.g. the same food, or space with unrestricted nutrient provision, or territory which is directly related to food resources, but the two species do not interact otherwise. Then the dynamics are given by the following growth equations:

$$\begin{aligned}\dot{C} &= \left( r_C - \frac{r_C}{K_C}C - \frac{r_D}{K_C}D \right) C \\ \dot{D} &= \left( r_D - \frac{r_D}{K_D}D - \frac{r_C}{K_D}C \right) D\end{aligned}\tag{4.1}$$

Both species exhibit logistic growth when cultured alone. The value of growth rates  $r$  and carrying capacities  $K$  are positive constants. Equations (4.1) predict that the two species can coexist only when exactly  $r_C K_C = r_D K_D$ . Otherwise, the species with higher  $rK$  value wins the competition, and the other species goes extinct (competitive exclusion).

We depart from this simple case and consider the case where growth rates  $r_C$  and  $r_D$  are frequency dependent linear functions. The frequency of  $C$  is denoted as  $x$  ( $x = C/(C + D)$ ), and the frequency of  $D$  is thus  $1 - x$ , in the double culture system. Therefore  $r_C$  and  $r_D$  can be written as linear functions of  $x$ :

$$\begin{aligned}r_C(x) &= \gamma_0 + \gamma_1 x \\ r_D(x) &= \delta_0 + \delta_1 x\end{aligned}\tag{4.2}$$

Since the growth rates  $r_C$  and  $r_D$  are the maximum growth rates reached at the exponential growth phase, they are always positive. Consequently, we require  $\gamma_0$ ,  $\delta_0$ ,  $\gamma_0 + \gamma_1$ , and  $\delta_0 + \delta_1$  to be positive. Then the population dynamics is described by a set of modified Lotka-Volterra equations, with linear frequency dependent growth rates and interaction coefficients. This is equivalent to logistic growth functions with frequency dependent competition coefficients. In the following, we assume constant carrying capacity for both species,  $K_C = K_D = K$ . For constant and linear growth rates, it is straightforward to generalize our findings to  $K_C \neq K_D$ . There are four steady states

– three boundary cases  $(0, 0)$ ,  $(0, K)$ ,  $(K, 0)$ , and the mixed solution:

$$(C^*, D^*) = \left( \frac{\delta_0 - \gamma_0}{\gamma_1 - \delta_1} K, \frac{\gamma_0 - \delta_0 + \gamma_1 - \delta_1}{\gamma_1 - \delta_1} K \right) \quad (4.3)$$

The mixed solution is only biologically meaningful if  $0 < C^*, D^* < 1$ . The relation  $C^* > 0$  implies that the growth rates of the two species have to intersect at an intermediate frequency. For the overall dynamics, there are four qualitatively different cases, as illustrated in Figure 4.3.

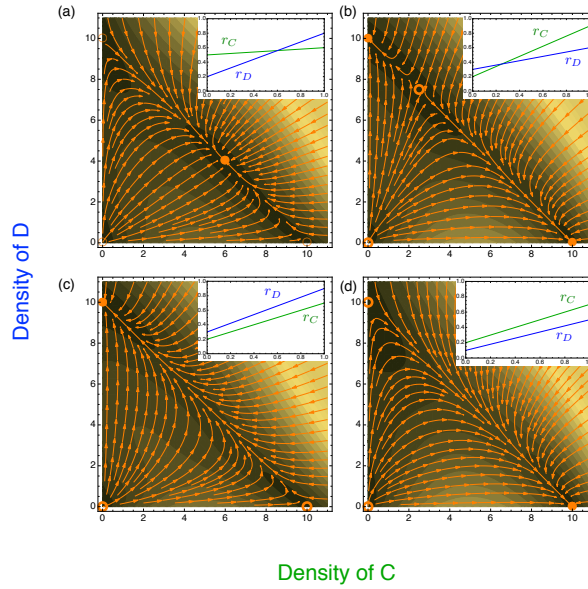


Figure 4.3: Population growth with linear frequency dependent growth rates, cf. Eqs. (4.2). The four main panels show the population dynamics. The insets show the corresponding linear frequency dependent growth rate functions, in which the  $x$ -axis represents the frequency of  $C$ . In the main panels, filled circles are stable fixed points and open circles are unstable fixed points. The orange arrows show the stream line trajectories of the population dynamics starting from a variety of initial states. The gradient background captures the speed of change. In (a) and (b), the growth rate functions cross in the range  $(0, 1)$ , leading to a mixed steady state  $(C^*, D^*)$ . (a) If  $r_C(0) > r_D(0)$  and  $r_C(1) < r_D(1)$ ,  $(C^*, D^*)$  is stable ( $r_C = 0.5 + 0.1x$ ,  $r_D = 0.2 + 0.6x$ ). (b) If  $r_C(0) < r_D(0)$  and  $r_C(1) > r_D(1)$ ,  $(C^*, D^*)$  is unstable ( $r_C = 0.2 + 0.7x$ ,  $r_D = 0.3 + 0.3x$ ). (c) If  $r_C(x) < r_D(x)$  for all  $x$ , there is no interior fixed point and only  $(0, K)$  is stable ( $r_C = 0.2 + 0.5x$ ,  $r_D = 0.3 + 0.6x$ ). (d) If  $r_C(x) > r_D(x)$  for all  $x$ , there is no interior fixed point and only  $(K, 0)$  is stable ( $r_C = 0.2 + 0.5x$ ,  $r_D = 0.1 + 0.4x$ ).

The set of points  $C + D = K$  satisfy the condition  $\dot{C} + \dot{D} = 0$ , therefore

it is an invariant manifold [Hofbauer and Sigmund, 1998; Wiggins, 2003] of the dynamics. Once this invariant manifold has been reached, the population dynamics will not lead away from it. Let  $f = |C_0 + D_0 - K|$  be the distance from any point  $(C_0, D_0)$  on the plane spanned by  $C$  and  $D$  to this invariant manifold. This distance decreases monotonically regardless of the initial condition  $(C_0, D_0)$  off the  $C + D = K$  manifold:

$$\dot{f} = \frac{C_0 + D_0 - K}{|C_0 + D_0 - K|} (\dot{C}_0 + \dot{D}_0) = -|C_0 + D_0 - K| \left( r_C(x) \frac{C_0}{K} + r_D(x) \frac{D_0}{K} \right) < 0. \quad (4.4)$$

Note that this holds regardless of the functional form of the original frequency dependent growth rates used in our model  $r_C(x)$  and  $r_D(x)$ .

We can determine the local stability of the fixed points from the signs of the eigenvalues of the Jacobian matrix at the fixed points [Hofbauer and Sigmund, 1998; Strogatz, 2000]. The fixed point at  $(0, K)$  is stable if  $\gamma_0 < \delta_0$ . The fixed point at  $(K, 0)$  is stable if  $\gamma_0 + \gamma_1 > \delta_0 + \delta_1$ . Intuitively, these points are stable if the resident type grows faster than the invading type. In Figure 4.3 (panel a) we illustrate the case where the growth rates  $r_C(x)$  and  $r_D(x)$  intersect in the interval  $(0, 1)$ , and  $r_C(0) > r_D(0)$ . Then the fixed points where one species goes extinct  $(K, 0)$  and  $(0, K)$  are unstable. On the one-dimensional stable manifold  $C + D = K$ , the stability of fixed points alternate. Hence, the internal fixed point  $(C^*, D^*)$  is stable. The other cases in Figure 4.3 (panel b-d) can be analyzed in the same way.

#### 4.4.2 Quadratic growth rates

In order to obtain multiple intersections of the frequency dependent growth rates in the range  $(0, 1)$ , the simplest possibility is that one of the growth rate function is linear and the other is quadratic in species frequency. Therefore, we assume a quadratic term in the growth rate function of species  $D$ , and keep  $r_C(x)$  and the population dynamics in Eqs. (4.1) unchanged,

$$r_D(x) = \delta_0 + \delta_1 x + \delta_2 x^2 \quad (4.5)$$

Depending on whether  $r_D(x)$  has a maximum or a minimum, there are two different cases allowing the growth rate functions to intersect twice in

the frequency range  $(0, 1)$ . To have two intersections of  $r_C(x)$  and  $r_D(x)$  within  $(0, 1)$ , the function  $r_C(x) - r_D(x)$  must have two roots in the same range. Besides the two boundary solutions  $(0, K)$  and  $(K, 0)$ , there are now two intermediate solutions on the manifold  $C + D = K$ , given by

$$(C_1^*, D_1^*) = \frac{K}{2\delta_2} (\gamma_1 - \delta_1 + \Omega, 2\delta_2 + \delta_1 - \gamma_1 - \Omega) \quad (4.6)$$

and

$$(C_2^*, D_2^*) = \frac{K}{2\delta_2} (\gamma_1 - \delta_1 - \Omega, 2\delta_2 + \delta_1 - \gamma_1 + \Omega) \quad (4.7)$$

where  $\Omega = \sqrt{(\gamma_1 - \delta_1)^2 + 4(\gamma_0 - \delta_0)\delta_2}$ .

Similar to the cases where  $r_C(x)$  and  $r_D(x)$  are linear functions of  $x$ , all trajectories lead to the invariant manifold  $C + D = K$ . The stability of fixed points alternates on this one-dimensional line. Conditioned on whether  $r_D(x)$  has a maximum or a minimum, there are two different stability patterns on the manifold. The stability patterns are illustrated in Figure 4.4. When the quadratic function  $r_D(x)$  has a maximum ( $\delta_2 < 0$ ), the two eigenvalues of the Jacobian matrix at  $(0, K)$  are  $-\delta_0 < 0$  and  $\gamma_0 - \delta_0 > 0$ . The two eigenvalues at  $(K, 0)$  are  $-\gamma_0 - \gamma_1 < 0$  and  $-\gamma_0 - \gamma_1 + \delta_0 + \delta_1 + \delta_2 < 0$ . Therefore,  $(0, K)$  is unstable and  $(K, 0)$  is stable. Thus, the intermediate fixed point  $(C_1^*, D_1^*)$  is stable and  $(C_2^*, D_2^*)$  is unstable, as shown in Figure 4.4 (panel a). The stability of fixed points when  $r_D(x)$  has a minimum can be analyzed in the same way, as shown in Figure 4.4 (panel b). When the carrying capacity values  $K_C$  and  $K_D$  are not equal, the fixed points can still be calculated analytically, but  $(C_1^*, D_1^*)$  and  $(C_2^*, D_2^*)$  do not always both fall in the first quadrant.

## 4.5 Results

Let us now come to a comparison of our theoretical model and our experiments. The two bacteria species *Curvibacter* sp. and *Duganella* sp. were mixed with different initial frequency combinations and inoculated from a total concentration of  $1.0 \times 10^5$  cfu/ml. Depending on the initial condition, the frequency of one of the species becomes much higher than the frequency of the other (Figure 4.2), resembling the scenario of positive frequency dependent selection in a coordination game. However, the absolute concentrations of both

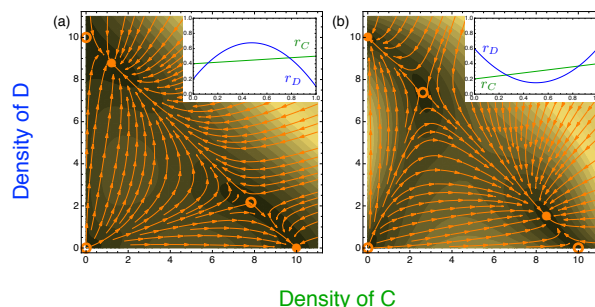


Figure 4.4: Population growth with quadratic growth functions, cf. Eq. (4.5). Schematic phase trajectories near the steady states when frequency dependent growth rate functions intersect twice. There always are a stable node  $(C_1^*, D_1^*)$  and a saddle point  $(C_2^*, D_2^*)$  in the first quadrant. The insets represent the frequency dependent growth rates, in which the  $x$ -axis is the frequency of  $C$ . There are two general cases in which  $r_C$  and  $r_D$  intersect twice. In (a), the quadratic growth rate has a maximum due to  $\delta_2 < 0$  ( $r_C = 0.4 + 0.1x$ ,  $r_D = 0.2 + 2x - 2.1x^2$ ). In (b), the quadratic growth rate has a minimum due to  $\delta_2 > 0$  ( $r_C = 0.2 + 0.2x$ ,  $r_D = 0.6 - 1.8x + 1.8x^2$ ).

species increased over time in any case. The observed bacterial population dynamics is different from competitive exclusion in the sense that the advantageous species cannot entirely take over the population. The submissive species kept growing in absolute number despite the decrease in frequency.

We first confirmed experimentally that the maximum growth rates of the two bacteria did not change with the initial density in monoculture experiments (Figure 4.5a). The maximum growth rates of *Curvibacter* sp. and *Duganella* sp. in monoculture inoculated with a gradient of initial densities are fitted to constant functions  $r_C = 0.146$  ( $R^2 = 0.998$ ), and  $r_D = 0.420$  ( $R^2 = 0.996$ ). This suggests that differences in the growth rate in double cultures (Figure 4.5b) depend on the frequency combinations of the two species, rather than their absolute densities.

The frequency dependent growth rate of *Curvibacter* sp. in double culture is fitted to a linear function  $r_C = 0.049x + 0.128$  (adjusted  $R^2 = 0.970$ ), and the growth rate of *Duganella* sp. in double culture is fitted to a quadratic function  $r_D = -0.825x^2 + 0.898x + 0.080$  (adjusted  $R^2 = 0.972$ ), shown in Figure 4.5b. For both  $r_C$  and  $r_D$ , we fitted the data to linear, quadratic and cubic functions. The models of best fit are chosen by both finite sample corrected Akaike information Criterion [Bozdogan, 1987] and Bayesian information Criterion [Burnham and Anderson, 2004; Posada and Buckley, 2004]. The carrying

capacity values  $K$  of both bacteria are  $5.9 \times 10^8$  cfu/ml, which is the median of all double culture experiments (shown as the red line in Figure 4.6).

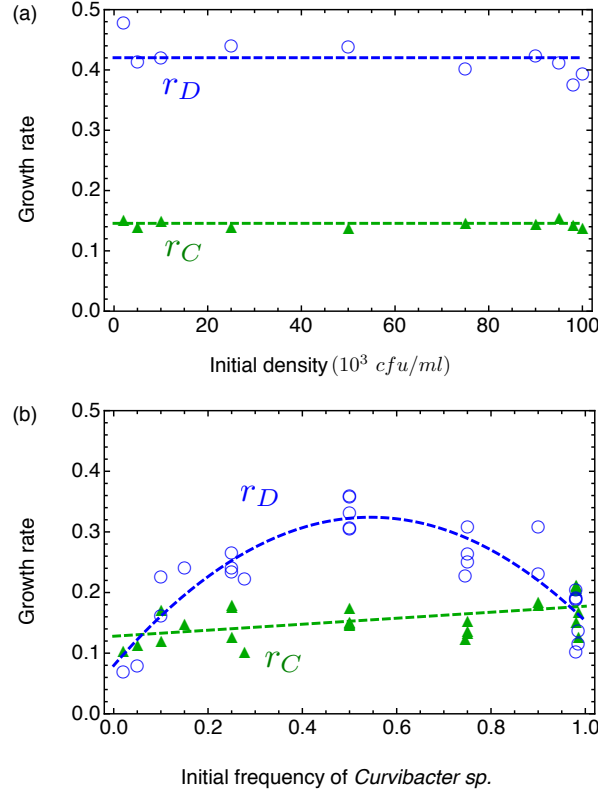


Figure 4.5: (a) The growth rates of *Curvibacter* sp. and *Duganella* sp. do not depend on initial density in monoculture experiments.  $r_C = 0.146$  ( $R^2 = 0.998$ ),  $r_D = 0.420$  ( $R^2 = 0.996$ ). (b) The growth rate at exponential growth phase change with initial frequencies in double cultures. This depends on the frequencies of both types, not necessarily in linear fashion. The frequency dependent growth rates of *Curvibacter* sp. were fitted to a linear function  $r_C = 0.049x + 0.128$  (adjusted  $R^2 = 0.970$ ), and that of *Duganella* sp. were fitted to a quadratic function  $r_D = -0.825x^2 + 0.898x + 0.080$  (adjusted  $R^2 = 0.972$ ). The presence of *Duganella* sp. affects the growth rate of *Curvibacter* sp., but not substantially. In contrast, *Curvibacter* sp. has strong inhibiting effects on the growth rate of *Duganella* sp., across a wide range, even at very low frequency.

From the comparison between growth rates in monoculture and double culture experiments, we observe that the presence of *Duganella* sp. does not profoundly influence the growth rates of *Curvibacter* sp., across a wide range of initial frequencies. But interestingly, the presence of *Curvibacter* sp. greatly influences the growth rate of *Duganella* sp., even at very low frequency (2%).



When the initial frequency of *Curvibacter* sp. approaches 0 in double culture experiments, the growth rates of *Duganella* sp. do not converge to its growth rate when cultured alone. This disproportionately large effect of *Curvibacter* sp. on the system indicates its role as a keystone species [Mills et al., 1993; Paine, 1995] in the simplified microbiota.

Inserting the parameters measured from experiments, the phase plane dynamics obtained from Eqs. (4.1) is shown in Figure 4.6.

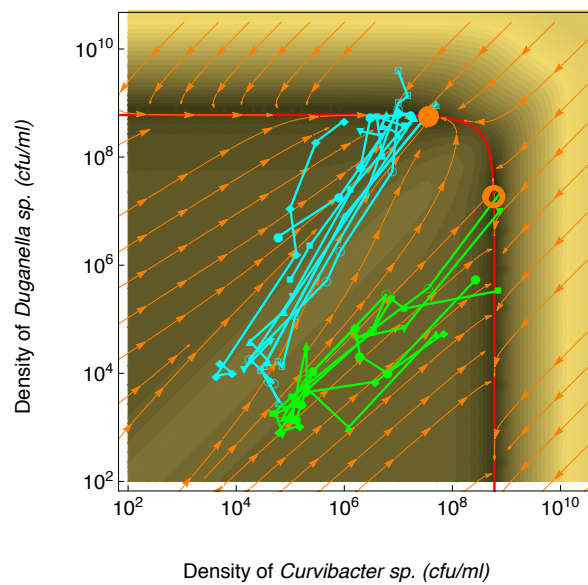


Figure 4.6: Growth trajectories plotted on the phase plane predicted by the model. The green trajectories lead to the unstable interior fixed point where *Curvibacter* sp. dominates in frequency. The cyan trajectories lead to the stable interior fixed point where *Duganella* sp. dominates. Filled and empty circles are stable and unstable fixed points, respectively. The red line is the invariant manifold  $C + D = K$ . The darkness of the contour plot represents the speed of change. The fast region along the diagonal represented by light colors separates the trajectories and pushes them to the two distinct fixed points in the interior. Near fixed points the speed of change is very low, therefore the two bacteria can coexist for a long time even near the internal unstable fixed point.

## 4.6 Discussion

Growth is important for bacterial populations. In comparison to larger organisms the size of bacterial populations can fluctuate greatly and rapidly. Drastic changes occur particularly during the colonization of new environments.

Such new environments can be abiotic systems like deep-sea hydrothermal vents [Alain et al., 2004; Guezennec et al., 1998], and biotic systems, including neonatal invertebrate hosts [Franzenburg et al., 2013] and vertebrate hosts [Palmer et al., 2007]. The composition of host associated microbiota play an important role in the development and functioning of the host [Goldmann et al., 1978]. Prior work has shown that the colonization processes display fast growth and complex dynamics of the microbiota composition. Interesting examples include the in-out-in colonization pattern of the adult-like microbiota composition, observed in *Hydra* and human babies [Palmer et al., 2007]. In addition, the “division of labor” like dynamics in marine bacteria that colonize the chitin substratum [Baty et al., 2000], the life-cycle like dynamics of *Pseudomonas* biofilms that connect extrinsic structure and intrinsic protein expression [Sauer et al., 2002], and cross-feeding and spatial partitioning of biofilm spaces between ecotypes [Poltak and Cooper, 2011] are also interesting examples of complex bacterial population dynamics during colonization of new environments. More examples of bacterial interactions in biofilms during the colonization of new environments can be found in the review by Hall-Stoodley et al. [Hall-Stoodley et al., 2004]. Despite the wealth of intriguing empirical discoveries, theoretical work that informs about principal mechanisms and leads to synthesis and integration of the available data is still limited [Prosser et al., 2007].

Although various models have been developed to describe the time dynamics of bacterial growth, most of them only focus on the growth of one single species [Buchanan et al., 1997; Koch, 1982; Kompala et al., 1986]. On the other hand, bacterial inter-species interactions are often studied in systems that have been intentionally excluded from notable fluctuations of population density [Frey and Reichenbach, 2011; Kerr et al., 2002; Schluter and Foster, 2012]. In this way, species frequencies instead of absolute densities are used to describe population dynamics. For example, in the work of Kerr et al. [Kerr et al., 2002], the authors studied the spatial interactions of three strains of *Escherichia coli*. It was found that when interactions are localized, the dynamics of the three strains resemble a “rock-paper-scissors” game, with the colicin-resistant strain beating the colicin-producing strain, the colicin-producing strain beating the colicin-sensitive strain, and the colicin-sensitive

strain outgrowing the colicin-resistant strain. This provided compelling support for game theoretical predictions in microbial ecology and evolution. However, the total population size was kept relatively constant on static agar plates. Therefore frequency alone was sufficient to describe the population dynamics observed.

In contrast to populations that have been kept in constant size for theoretical convenience, here we analyze the dynamics in growing bacterial populations. We show that it is necessary to take into account both frequency and density to fully characterize the interaction dynamics. Considering microbial density alone, the growth curves of both *Curvibacter* sp. and *Duganella* sp. resemble logistic growth. Solely from the frequency perspective, the two bacteria seem to play a coordination game. Only in the interplay of the two effects we can aptly describe the full picture. Our analysis reveals a system with two intermediate fixed points where both species coexist only if we look at both frequency and density dynamics together.

In evolutionary game theory, the vast majority of studies consider cases where the population size is either constant or where the system can be recast into a form where population growth does not affect the outcome. When it comes to growing populations – as in our case – many concepts and definitions become more cumbersome. Consequently, experimental and quantitative description also become more delicate. For example, the typical definition of cooperative traits is that they increase the fitness of others at a fitness cost to self. But this increase could refer to the relative abundance or the absolute abundance. The former is commonly assumed in the evolutionary game theory literature, while the latter is commonly found in the experimental evolution literature. In other words, interactions could either influence the relative abundance or the absolute abundance in a variety of ways that has not yet been fully addressed by theoretical models.

In classic logistic growth under the Lotka-Volterra dynamics, or equivalently, the game theoretical replicator dynamics, the growth rates in exponential growth phase (simply denoted as growth rates in the following) are usually assumed to be constant [Berryman, 1992; Hanson and Tuckwell, 1981; Tsoularis and Wallace, 2002; Verhulst, 1838]. The overall density dependent change in population size can be introduced by altering the carrying capacity

of the system. This alteration can arise from inter-specific and intra-specific competition. For example, the carrying capacity could theoretically be determined by an evolutionary game [Novak et al., 2013]. In our case, we have seen that the growth rates are affected much more by bacterial interactions than the carrying capacities. Such growth rates can be frequency dependent due to interactions in the population other than direct competition [Hibbing et al., 2009].

A recent modeling study showed that social interactions between antibiotic-tolerant and antibiotic-sensitive bacteria can lead to patterns of multiple stability and thus explained how the microbiota composition can switch after antibiotic treatment [Bucci et al., 2012]. Linear frequency dependent growth rates have also been reported in a study of microbial random phase variation, which influences bacterial survival in changing environments [Wolf et al., 2005]. A particularly interesting finding was reported by Trosvik *et. al.* [Trosvik et al., 2008]. There the authors found a parabolic interaction relationship between *Bacteroides uniformis* and *Escherichia coli*, similar to our case. In our experimental system, the growth rate of *Duganella* sp. depends on the frequency of *Curvibacter* sp. also in a parabolic way. In the study by Trosvik *et. al.*, *E. coli* had a positive effect on *B. uniformis* only to a certain point in the range of frequency, and then the effect turned out to be detrimental. Mechanistically, the positive effect of *E. coli* at low frequency might result from the removal of residual oxygen from the growth medium [Hagen et al., 1982], given that *B. uniformis* is strictly anaerobic. But when the frequency of *E. coli* became higher, the authors argued that direct competition might outweigh the benefits from oxygen removal, and thus limits the growth of *B. uniformis* [Trosvik et al., 2008].

In our case, *Curvibacter* sp. has an overall suppression effect on the growth of *Duganella* sp. in double cultures. This effect is nonlinearly frequency dependent, most remarkably when the frequency difference of the two species is large. This is consistent with the situation *in vivo*. Inside the *Hydra* host, *Curvibacter* sp. has absolute dominance in abundance, despite that *Duganella* sp.'s faster growth rate when cultured alone [Fraune et al., 2014]. We have shown in the analysis that direct pairwise interactions between two bacterial cells are not enough to capture the complexity of the system. This leads us

to consider the possibility that bacterial cells are involved in “multiplayer” interactions [Gokhale and Traulsen, 2010, 2014; Kurokawa and Ihara, 2009]. In these scenarios, multiple bacterial cells interact with each other at the same time. Studies have shown that bacteria can form nanotubes with multiple other cells and exchange molecules with each other [Dubey and Ben-Yehuda, 2011; Sanchez, 2011]. This could be the physical basis of bacterial multiplayer games. In the simple system we have studied, at least a three-player game of degree two [Ohtsuki, 2014] is needed to account for the observed quadratic nonlinearity in frequency dependent payoffs. An example of a three-player game that produces similar population dynamics pattern of two alternative intermediate equilibria can be found in Appendix Figure (7.3). Other alternative explanations include the effect of phage infection in the system. Our hypothesis is that the phage that infects *Curvibacter* sp. at a population equilibrium level may switch its host to *Duganella* sp. and thus induces an outbreak event that reduces its Malthusian growth rate by increased mortality. Testing of this hypothesis is an extension of this project. Since frequency dependent interactions can lead to multiple coexistence states Gokhale and Traulsen [2010], this effect could contribute to the tremendous microbial diversity coexisting with the numerically dominant few in natural environments, known as the “rare biosphere” [Sogin et al., 2006].

To conclude, in this study we show that it is necessary to consider both frequency and density dynamics in bacterial populations with noteworthy density fluctuations. Using a mathematical model, we examined the effects of linear and quadratic frequency dependent growth rates in Lotka-Volterra dynamics. The interaction patterns of the system are richer with additional intermediate fixed points when frequency dependent growth rate functions intersect more than once. Most importantly, our empirical data provide compelling evidence that the maximum growth rate can be a non-linear function of frequency, without effects of density limitation. This strongly indicates that there must be mechanisms other than direct pairwise interactions (including competition for a limiting resource) among the growing bacterial populations. Such complex patterns provide a mechanism for the maintenance of vast microbial diversity in the natural environment. Our study focuses on the interactions among growing bacterial populations without the effect of host or other environmen-

tal factors, serving as a null model for studying higher-level interactions.

# The invisible player

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In the previous Chapter, we found nonlinear frequency dependent growth rates of two most abundant bacteria (*Curvibacter* sp. and *Duganella* sp.) of the *Hydra* microbiota in an artificial environment. The nonlinear frequency dependent growth rates lead to complex population dynamics with alternative coexisting states. However, the mechanistic causes of such phenomenon are still unclear. Phages have been suggested to play important roles in mediating bacterial interactions. In our experimental system, it has been found that for each of the bacteria, there is an associated phage that is integrated in the bacterial genome (Tim Lachnit, personal communication). Surprisingly, the phage that associated with *Curvibacter* sp. can also cross infect *Duganella* sp. Here, we build a mathematical model of bacterial-phage interactions that recovers the nonlinear frequency dependent growth rates observed in experiments.

This chapter is based on a working paper in collaboration with Tim Lachnit. This project has both experimental and modeling parts, but only the modeling part is presented here. A detailed summary of the authors' contributions to this project can be found at the end of this thesis.

## 5.1 Introduction

“I can imagine nothing more terrifying than an Eternity filled with men who were all the same. The only thing which has made life bearable...has been the diversity of creatures on the surface of the globe. – T.H. White, *The Book of Merlyn*”

Naturalists have always been fascinated by the beautiful coexistence of diverse life forms on earth. It has been a long tradition that we seek the ways that generate, maintain and promote such splendour of biodiversity in

nature. For example, the pioneer work of Gause [1932] in yeast, combining experiments and mathematical modeling, suggests that given enough time, one species will always outcompete the other, driving the submissive species to extinction. This forms the cornerstone of “*Gause’s principle*”, which has later been coined with the name “*the competitive exclusion principle*” by Hardin [1960], stating that two species competing for the same resource cannot stably coexist in the same area at the same time.

However logically sound, the predictions of the theory have been challenged by observations, particularly in aquatic ecosystems. Despite their great diversity in species and different phenotypes within the same species, most of the phytoplankton compete for the same small set of nutrients. How could a great number of species coexist in a nutritionally poor environment, while competing on the same set of resources? This question raised by Hutchinson [1961] was later named after him as the “*Hutchinson’s paradox*”.

Some of the potential solutions of the paradox have already been put forward in the seminal paper of Hutchinson [1961] himself. For example, he argued that predation and the constant changes of the environment might have kept natural systems far away from equilibria, and the subtle heterogeneities in space, such as the gradient of light intensity and the Langmuir spirals in the wind drift, might have created diversified niches for different species. More explanations and conditions have been proposed, studied with mathematical models and tested by experiments [Cadotte, 2007; Chesson, 2000; Narwani et al., 2013; Shea et al., 2004; Sommer, 1984; Welborn et al., 1996]. Although there might still be some small unsolved issues, the general impression is that biologists have well deciphered Hutchinson’s paradox.

However, recent observations in bacteria co-culture experiments bring forward new questions (Chapter 4). The two bacterial species (*Curvibacter* sp. and *Duganella* sp.) were isolated from the natural microbiota of freshwater hydra (*Hydra vulgaris*). In a simple well-mixed liquid culture, the two bacterial species not only coexist for a long time, but also at distinct population states, depending on the initial frequencies at inoculation. It shows that both biodiversity and the diversity of biodiversity can emerge in such extremely simple and spatially homogenous culturing environment. How could this happen? To study this, we started with a mathematical model, building on the



basis of the classic Lotka-Volterra dynamics. Then we realised that in order to have the two distinct internal equilibria, the maximum growth rate, observed at the exponential phase of the growth curve, has to be nonlinearly frequency dependent, at least for one of the bacterial species. Inspired by the model prediction, experiments were designed and then performed by Cleo Pietschke and Sebastian Fraune. Eventually, the nonlinear frequency dependent growth rate of *Duganella* sp. was confirmed in co-culture experiments (Chapter 4, published in [Li et al., 2015b]).

On the other hand, despite that it explains the multiple coexisting states observed in experiments, the nonlinear frequency dependent growth rate itself brings up more fundamental questions. What has made the growth rate of a bacterium, which was supposed to be an intrinsic feature of the species, dependent on the relative abundance of it compared to its competitors in the same environment? What are the interactions in the community that produced such phenomena? And, is the culturing medium really such a simple abiotic environment as we have assumed?

If all assumptions hold (i.e. population is well-mixed, interactions among cells are random, and are confined to direct competition on the same resource), the two bacterial species would not be able to coexist, as indicated by the competitive exclusion principle. On the other hand, if any of the assumptions is relaxed, several mechanisms could potentially explain the coexistence of the two bacteria, including adapting to different spatial niches [Burmølle et al., 2010], interacting in small groups via nanotubes [Dubey and Ben-Yehuda, 2011], interference competition [Amarasekare, 2002], and cross-feeding [Freilich et al., 2011], for a general review, see Hibbing et al. [2009]. But none of the above mentioned mechanisms has been explicitly shown to produce nonlinear frequency dependent growth rates, nor the resultant alternative coexisting states of the population. In addition, our experimental collaborators have so far not found biofilm or nanotube formation, and there is no evidence that the two bacteria species interfere the growth or cross-feed each other (Tim Lachnit, personal communication).

On the other hand, analysis of the genome sequences of the two bacteria revealed an alternative possibility. Tim Lachnit found that the sequence of a prophage integrated in the genome of each of the two bacterial species. Follow-

ing this hint, we isolated phage particles that correspond to the two prophage sequences. This leads us to the hypothesis that the two phages might be the “invisible players” in the system that interact with the two bacterial species and produce the frequency dependent growth rates of them, as observed in experiments.

It has been shown that the interactions among bacteria and the phages which infect them can produce complex population dynamics and are important for both ecosystem functioning [Goodridge and Abedon, 2003; Rohwer and Thurber, 2009] and human health [Faruque et al., 2005a,b; Levin and Bull, 2004]. Phages not only shape the composition of bacterial communities, but also influence the evolution of bacterial genomes by both specialized and generalized transduction of genetic materials among different hosts [Chen and Novick, 2009; Fineran et al., 2009; Mazaheri Nezhad Fard et al., 2011]. Even in the standard *in vitro* cultures of bacteria, the presence of phages can transform the seemingly simple and static artificial culture medium into an evolving and highly dynamic biotic environment [Koskella and Meaden, 2013].

Interactions mediated by phages play important roles in the maintenance of biodiversity in many ecosystems. One of them is via negative frequency dependent selection by “*Killing-the-Winners* (KTW)” [Thingstad, 2000; Winter et al., 2010]. The KTW model considers the dynamics of multiple species of bacteria and phages in lytic interactions, showing that the density of each bacterial host is controlled by the phage that infects it, in a top-down fashion. The simple yet powerful model explains successfully the coexistence of many bacterial species that compete in the same spatial and temporal environment. In addition, it also recovers many empirical observations, such as the 1:10 ratio of the bacterial and viral abundance. But one assumption of the KTW model does not apply to many natural bacterial communities. It assumes that each species of phage only infects one species of bacteria, and one species of bacteria is only infected by one single species of phage.

Evidence has shown that cross-infection between phage and bacteria is common in nature [Holmfeldt et al., 2007; Poullain et al., 2008; Stenholm et al., 2008; Sullivan et al., 2003; Wichels et al., 1998]. Phage infectivity and bacterial resistance are key factors that determine the host range of phages [Duplessis and Moineau, 2001; Hyman and Abedon, 2010; Rakhuba et al., 2010; Riede

et al., 1985]. Although we still know very little about the general principles which determine the relationship of who infects whom, recent studies have uncovered some interesting patterns of the infection networks, such as nested and modular [Flores et al., 2011], as well as multi-scale [Flores et al., 2013] structures.

Taken into account the cross-infection between phages and bacteria, a recent model by Jover et al. [2013] recovers the basic predictions of the KTW model, such as the coexistence of different bacteria by top-down control of phages. In addition, they show that trade-off conditions on the life-history traits of both bacteria and phages are required for stable coexistence. Bacteria with high growth rates are more vulnerable to phage infection, and phages with a wide host range are less effective in infecting bacteria. But the model of Jover et al. [2013] assumes that the infection relationships between bacteria and phages are static, and the evolutionary arms race between bacteria and phages is not considered. More recent studies show that the evolution of host ranges of phages are of fundamental importance in bacterial communities [Chaturongakul and Ounjai, 2014]. In addition, the cross-infection model of Jover et al. [2013] does not predict alternative coexisting states. This indicates that it might be necessary to consider the evolutionary aspect of phage-bacteria interaction, and there might be other interactions except lysis between bacteria and phages.

It has been found that the “*outer membrane vesicles* (OMVs)” of bacteria play important roles in mediating interactions with the environment, including protein secretion, immune and stress response, attachment, and defence against phages. For a recent review, see MacDonald and Kuehn [2012]. The spherical blebs mimic the outer membrane of bacteria, functioning as decoys. Phages are found to have irreversibly bound to, and injected genetic materials into the OMVs [Manning and Kuehn, 2011]. The typical diameter of OMVs ranges from 10nm to 300 nm [MacDonald and Kuehn, 2012]. The relatively large surface to volume ratio makes it very effective to absorb phage particles in the environment. However, no mathematical model has been built to study the role of OMVs in phage-bacteria interactions so far.

To provide a simple explanation of the nonlinear frequency dependent growth rates of bacteria observed in experiments, and the resultant alternative

coexisting states of the bacterial community [Li et al., 2015b], we develop a simple mathematical model of bacterial population dynamics mediated by the activity of phages. We take into account both the evolutionary aspects of cross-infection and the effects of OMVs in the defence of bacteria against phages.

## 5.2 Null model

Before considering the effects of phages adapting to changing frequency of bacterial hosts, and the effects of OMVs as decoys produce by bacteria for defence, we first build a null model that does not include these two factors. It serves as the basis for later comparisons.

Firstly, we describe some basic interactions among different actors in the phage-bacteria interaction system. The actors are two bacteria (*Curvibacter* sp. and *Duganella* sp.) and two phages (*Curvibacter*-phage and *Duganella*-phage). They are denoted as  $C$ ,  $D$ ,  $P_C$ , and  $P_D$  in the following.

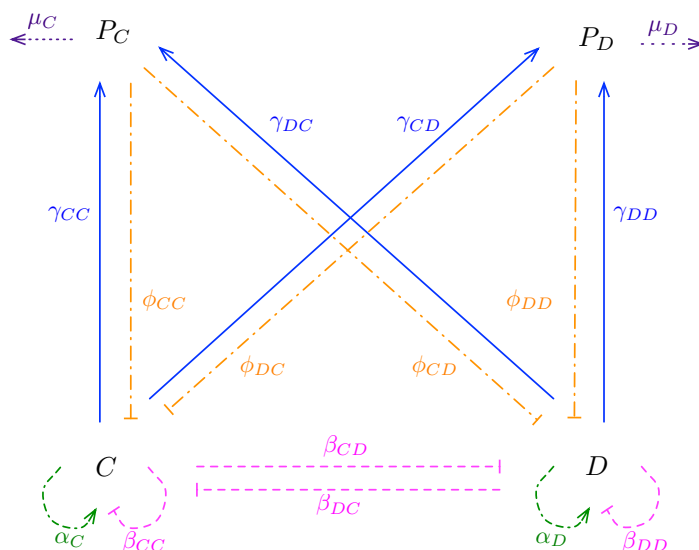


Figure 5.1: Actors and interactions in the phage-bacteria system.

In the null model, we assume all interactions are linear and follow the law of mass action [Ellner and Guckenheimer, 2011]. It does not include stochastic effects, only describing the deterministic dynamics of the system. As il-

illustrated in Figure 5.1, the basic inter-specific and intra-specific interactions include:

1. Reproduction of the two bacteria, at a rate of  $\alpha_C$  for *Curvibacter* sp. and  $\alpha_D$  for *Duganella* sp., respectively;
2. Direct competition:  $\beta_{CC}$  and  $\beta_{DD}$  are the suppression rates of intra-specific competitions,  $\beta_{CD}$  is the rate of suppression from *Curvibacter* sp. to *Duganella* sp., and  $\beta_{DC}$  is the rate of suppression from *Duganella* sp. to *Curvibacter* sp.;
3. Production of phages:  $\gamma_{CC}$  is the production rate of *Curvibacter*-phage from *Curvibacter* sp.,  $\gamma_{DD}$  is the production rate of *Duganella*-phage from *Duganella* sp.,  $\gamma_{CD}$  is the production rate of *Duganella*-phage from *Curvibacter* sp.,  $\gamma_{DC}$  is the production rate of *Curvibacter*-phage from *Duganella* sp.;
4. Death of the bacteria caused by phage infections:  $\phi_{CC}$  and  $\phi_{DD}$  are the rates of death of *Curvibacter* sp. and *Duganella* sp. caused by the infection from their own associated phages,  $\phi_{CD}$  and  $\phi_{DC}$  are the death rate from cross-infections,  $\phi_{CD}$  is the death rate of *Duganella* sp. due to the cross-infection by *Curvibacter*-phage, and  $\phi_{DC}$  is the death rate of *Curvibacter* sp. due to the cross-infection by *Duganella*-phage;
5. Decay of phages:  $\mu_C$  and  $\mu_D$  are the spontaneous decay rates of *Curvibacter* sp. and *Duganella* sp., respectively.

Assuming all parameters are constant, the population dynamics of the four actors can be written in a system of ordinary differential equations:

$$\begin{aligned}
 \dot{P}_C &= \gamma_{CC}C + \gamma_{DC}D - \mu_C P_C \\
 \dot{P}_D &= \gamma_{CD}C + \gamma_{DD}D - \mu_D P_D \\
 \dot{C} &= \alpha_C C - \beta_{CC}C^2 - \beta_{DC}DC - \phi_{CC}P_C C - \phi_{DC}P_D C \\
 \dot{D} &= \alpha_D D - \beta_{DD}D^2 - \beta_{CD}CD - \phi_{DD}P_D D - \phi_{CD}P_C D
 \end{aligned} \tag{5.1}$$

We assume that the population dynamics of phages is much faster than that of the bacteria during the lytic cycle [Delbrück, 1940]. This implies that the first two equations in (5.1) quickly approach their asymptotic states where

$\dot{P}_C = 0$  and  $\dot{P}_D = 0$ . On the fast time scale, while  $P_C$  and  $P_D$  converge to equilibria, the values of  $C$  and  $D$  remain unchanged. On the slow time scale while  $C$  and  $D$  are changing,  $P_C$  and  $P_D$  are assumed to be at their equilibria. The separation of timescales allows us to simplify the analysis by studying the fast and slow systems separately. We can solve the equilibria of the fast system and then insert them into the slow system in order to approximate the population dynamics of bacteria.

After replacing  $P_C$  and  $P_D$  with their unique stable equilibria,

$$\begin{aligned} P_C &= (\gamma_{CC}C + \gamma_{DC}D)/\mu_C \\ P_D &= (\gamma_{CD}C + \gamma_{DD}D)/\mu_D, \end{aligned} \quad (5.2)$$

we can simplify the analysis further by rescaling the system to dimensionless variables [Murray, 2007]. We remove the units from the system of equations by a suitable replacement of variables. In this way, we reduce the number of model parameters, making subsequent analyses simpler. In addition, we can get the general and characteristic properties of the system without relying on specific choices of parameters. The procedures of this standard technique is reviewed in detail by Segel [1972].

By substituting the parameters and variables in the original equations with a more suitable set of variables

$$\begin{aligned} x &= \frac{\beta_{CC}\mu_C\mu_D + \gamma_{CD}\phi_{DC}\mu_C + \gamma_{CC}\phi_{CC}\mu_D}{\alpha_C\mu_C\mu_D} \cdot C \\ y &= \frac{\beta_{DD}\mu_C\mu_D + \gamma_{DC}\phi_{CD}\mu_D + \gamma_{DD}\phi_{DD}\mu_C}{\alpha_D\mu_C\mu_D} \cdot D \end{aligned} \quad (5.3)$$

and parameters:

$$\begin{aligned} \tau &= \alpha_C t \\ \rho &= \frac{\alpha_D}{\alpha_C} \\ a &= \rho \cdot \frac{\beta_{DC}\mu_C\mu_D + \gamma_{DD}\phi_{DC}\mu_C + \gamma_{DC}\phi_{CC}\mu_D}{\beta_{DD}\mu_C\mu_D + \gamma_{DC}\phi_{CD}\mu_D + \gamma_{DD}\phi_{DC}\mu_C} \\ b &= \frac{1}{\rho} \cdot \frac{\beta_{CD}\mu_C\mu_D + \gamma_{CC}\phi_{CD}\mu_D + \gamma_{CD}\phi_{DD}\mu_C}{\beta_{CC}\mu_C\mu_D + \gamma_{CD}\phi_{DC}\mu_C + \gamma_{CC}\phi_{CC}\mu_D} \end{aligned} \quad (5.4)$$

The slow system in (5.1) becomes

$$\begin{aligned}\frac{dx}{d\tau} &= x(1 - x - ay) \\ \frac{dy}{d\tau} &= \rho y(1 - y - bx),\end{aligned}\tag{5.5}$$

in which  $x$  and  $y$  are rescaled abundance of *Curvibacter* sp. and *Duganella* sp.;  $\tau$  is rescaled time;  $a$ ,  $b$ , and  $\rho$  are parameters without units.

This brings us back to the classic case of competitive exclusion [May and McLean, 2007; Murray, 2007]. There are four possible equilibrium states  $(x^*, y^*)$  are  $(0, 0)$ ,  $(1, 0)$ ,  $(0, 1)$  and  $(\frac{1-a}{1-ab}, \frac{1-b}{1-ab})$ . An equilibrium is biologically meaningful if both  $x$  and  $y$  are non-negative. Depending on the relative size of  $a$  and  $b$ , the qualitative structures of the phase plane dynamics are shown in Figure 5.2.

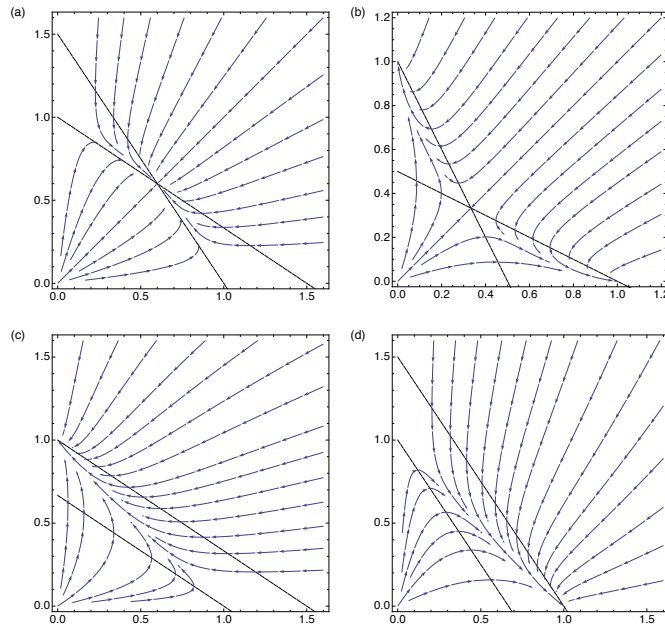


Figure 5.2: Qualitative structures of bacterial interactions.  $x$  and  $y$  axes are the densities of  $x$  and  $y$ , which represent the rescaled densities of *Curvibacter* sp. and *Duganella* sp. Depending on the relative size of parameters  $a$  and  $b$ , the rescaled system either leads to the extinction of one of the bacteria (competitive exclusion), or the coexistence of the two bacteria at a unique equilibrium state. (a)  $a < 1$  and  $b < 1$ , (b)  $a > 1$  and  $b > 1$ , (c)  $a > 1$  and  $b < 1$ , (d)  $a < 1$  and  $b > 1$ .

To sum up the null model, if the production rates of phages depend on bacterial densities in a linear manner, as assumed in the first two equations in (5.1), the population dynamics of the two bacteria recovers the classic case of competitive exclusion.

More importantly, the analysis of the null model tells us that the basic interactions alone are not able to produce frequency dependent growth rates of bacteria, nor the resultant alternative coexisting states of the population. In the following, we build a new model based on the null model, taking into account the evolutionary aspects of phage adapting to hosts and the active defence of the hosts against phage through OMVs.

### 5.3 Working model

First we take into account the evolutionary aspect of phage host range. We assume that phages adapt to bacterial hosts in a frequency dependent manner, because it is the most profitable to adapt to the host species that is the most abundant. Note that this is achieved through natural selection, rather than the “active decisions” of phages. Phages mutate randomly, but only the adapted variations are preserved, and the rest are eliminated from the system. In this ODE model, we only model the overall behaviour of a phage species, neglecting the detailed dynamics of different strains within the same species. Using the dynamics of *Curvibacter*-phage in the null model as an example,

$$\dot{P}_C = \gamma_{CC}C + \gamma_{DC}D - \mu_C P_C \quad (5.6)$$

we add in the effects of adaptation to changing frequencies of bacteria.

For example, as *Duganella* sp. increase in frequency in the population, the *Curvibacter*-phage would be selected to adapt to the more abundant *Duganella* sp. As a consequence, the infection rate to the original host species  $\gamma_{CC}$  decreases by a factor  $1 - \lambda_{DC} \frac{D}{C+D}$ , in which  $0 \leq \lambda_{DC} \leq 1$ . The parameter  $\lambda_{DC}$  adjusts the cost of adapting to the alternative host. We model the early stage of adaptation mainly through the frequency dependent decrease of infection rate to the original host species. Because the time period of adaptation is so short, we assume that the infection rate to the alternative host has not increased substantially. Therefore the term  $\gamma_{DC}D$ , which captures the rate



at which *Curvibacter*-phage is produced from the cross-infection of *Duganella* sp., is kept unchanged.

After taking into account the effects of phage adaptation, we add in the effects of bacterial defence. Using OMVs as decoys is supposed to be a defence mechanism against many different phages in general. To keep the model simple, we assume that phages may have different attachment rates to OMVs, but they do not distinguish between OMVs produced by different bacteria. And we also assume that the two bacteria produce OMVs at equal rates, so that the total density of OMVs is proportional to the total density of bacteria. Therefore the deactivation rates of phages are also proportional to the total density of bacteria. In the null model, we use  $\mu$  to denote the spontaneous decay rate of bacteria:  $\mu_C$  is the spontaneous decay rate of the *Curvibacter*-phage, and  $\mu_D$  is the spontaneous decay rate of the *Duganella*-phage. In the working model, phages are removed not by spontaneous decay, but from the defence activity of bacteria by OMVs. We use  $\tilde{\mu}$  to summarize the attachment rate of phages to OMVs, and the rate at which OMVs are produced by bacteria:  $\tilde{\mu}_C$  is the deactivation rate of the *Curvibacter*-phage, and  $\tilde{\mu}_D$  is the deactivation rate of the *Duganella*-phage.

In the working model, we keep the slow system that describes the density dynamics of bacteria unchanged. Taking both phage adaptation and host defence into account, the fast system describing phage population dynamics in the null model is modified to:

$$\begin{aligned} \dot{P}_C &= \gamma_{CC}C \left(1 - \lambda_{DC} \frac{D}{C+D}\right) + \gamma_{DC}D - \tilde{\mu}_C(C+D)P_C \\ \dot{P}_D &= \gamma_{DD}D \left(1 - \lambda_{CD} \frac{C}{C+D}\right) + \gamma_{DC}C - \tilde{\mu}_D(C+D)P_D \end{aligned} \quad (5.7)$$

A graphical illustration of the modification of the model is shown in Figure 5.3. We analyse the working model in the following.

First, we calculate the equilibrium of the fast system of phage density dynamics:

$$\begin{aligned} P_C^* &= \frac{\gamma_{CC}C^2 + (\gamma_{CC} + \gamma_{DC} - \gamma_{CC}\lambda_{DC})CD + \gamma_{DC}D^2}{\tilde{\mu}_C(C+D)^2} \\ P_D^* &= \frac{\gamma_{DC}C^2 + (\gamma_{DC} + \gamma_{DD} - \gamma_{DD}\lambda_{CD})CD + \gamma_{DD}D^2}{\tilde{\mu}_D(C+D)^2} \end{aligned} \quad (5.8)$$

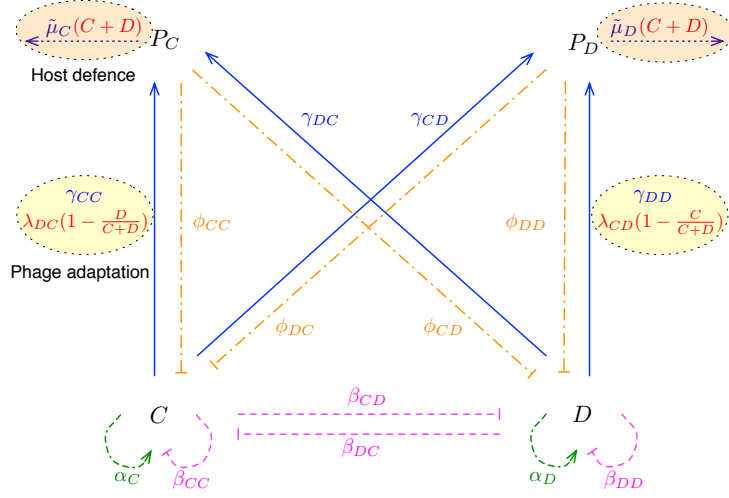


Figure 5.3: Interactions among bacteria and phages. Building on the null model, now we take into account phage adaptation and host defence mechanisms, as shown in the colored circles.

Inserting the equilibrium of the fast system into the slow system, which is kept the same as in the last two equations in (5.1), the slow system of bacterial population dynamics can be arranged into the following form, in which the parameters  $\zeta_0$ ,  $\zeta_1$ ,  $\zeta_2$ ,  $\eta_0$ ,  $\eta_1$ , and  $\eta_2$  are constant:

$$\begin{aligned} \dot{C} &= \left[ \zeta_2 \left( \frac{C}{C+D} \right)^2 + \zeta_1 \left( \frac{C}{C+D} \right) + \zeta_0 \right] C - \beta_{CC}C^2 - \beta_{DC}CD \\ \dot{D} &= \left[ \eta_2 \left( \frac{C}{C+D} \right)^2 + \eta_1 \left( \frac{C}{C+D} \right) + \eta_0 \right] D - \beta_{DD}D^2 - \beta_{CD}CD \end{aligned} \quad (5.9)$$

During the exponential growth phase when the density of bacteria are low, competitions are negligible. Therefore the second order terms of bacterial densities in (5.9) can be ignored. Denote the frequency of *Curvibacter* sp. as  $f$ , which equals  $C/(C+D)$ , and neglecting the competition terms with contains  $C^2$ ,  $D^2$  or  $CD$ , we reach a structure of nonlinear frequency dependent growth rates similar to the experimental observations in Li et al. [2015b]:

$$\begin{aligned} \dot{C} &= (\zeta_2 f^2 + \zeta_1 f + \zeta_0)C \\ \dot{D} &= (\eta_2 f^2 + \eta_1 f + \eta_0)D, \end{aligned} \quad (5.10)$$

with the parameters:

$$\begin{aligned}
\zeta_2 &= -\frac{\gamma_{CC}\lambda_{DC}}{\tilde{\mu}_C}\phi_{CC} - \frac{\gamma_{DD}\lambda_{CD}}{\tilde{\mu}_D}\phi_{DC} \\
\zeta_1 &= -\frac{\gamma_{CC} - \gamma_{DC} - \gamma_{CC}\lambda_{DC}}{\tilde{\mu}_C}\phi_{CC} - \frac{\gamma_{DC} - \gamma_{DD} - \gamma_{DD}\lambda_{CD}}{\tilde{\mu}_D}\phi_{DC} \\
\zeta_0 &= \alpha_C - \frac{\gamma_{DC}}{\tilde{\mu}_C}\phi_{CC} - \frac{\gamma_{DD}}{\tilde{\mu}_D}\phi_{DC} \\
\eta_2 &= -\frac{\gamma_{CC}\lambda_{DC}}{\tilde{\mu}_C}\phi_{CD} - \frac{\gamma_{DD}\lambda_{CD}}{\tilde{\mu}_D}\phi_{DD} \\
\eta_1 &= -\frac{\gamma_{CC} - \gamma_{DC} - \gamma_{CC}\lambda_{DC}}{\tilde{\mu}_C}\phi_{CD} - \frac{\gamma_{DC} - \gamma_{DD} - \gamma_{DD}\lambda_{CD}}{\tilde{\mu}_D}\phi_{DD} \\
\eta_0 &= \alpha_D - \frac{\gamma_{DC}}{\tilde{\mu}_C}\phi_{CD} - \frac{\gamma_{DD}}{\tilde{\mu}_D}\phi_{DD}
\end{aligned} \tag{5.11}$$

But in the work of [Li et al., 2015b], the frequency dependent growth rate of *Curvibacter* sp. is rather linear than quadratic. This implies that  $\zeta_2 \rightarrow 0$ . In the next we integrate experimental results into the mathematical model to recover this observation, and at the same time gain new insights of the biological system from mathematical analysis.

Our preliminary experiment results indicate that it is generally hard for the *Duganella*-phage to infect *Curvibacter* sp. Therefore the value of  $\phi_{DC}$  is very small. Under the condition  $\phi_{DC} \rightarrow 0$ , the form of  $\zeta_2$  becomes:

$$\zeta_2' = -\frac{\gamma_{CC}\lambda_{DC}}{\tilde{\mu}_C}\phi_{CC} \tag{5.12}$$

From the experiments we are certain that *Curvibacter*-phage can infect *Curvibacter* sp., and by lysing the cells of *Curvibacter* sp., infectious particles of *Curvibacter*-phage are produced. Therefore  $\gamma_{CC}$  and  $\phi_{CC}$  must take nonzero values. In order to have  $\zeta_2' \rightarrow 0$ , it requires that  $\lambda_{DC} \rightarrow 0$ . On the other hand, because the frequency dependent growth rate of *Duganella* sp. is quadratic,  $\eta_2$  must be nonzero. This requires that  $\lambda_{CD} > 0$ .

This asymmetry implies that it is very costly for the *Duganella*-phage to switch host and infect *Curvibacter* sp., but it is almost no cost for the *Curvibacter*-phage to switch host and infect *Duganella* sp. Biologically this suggests that the *Curvibacter*-phage is a generalist, and the *Duganella* phage is a specialist. The resulting structure of interactions are shown in Figure 5.4.

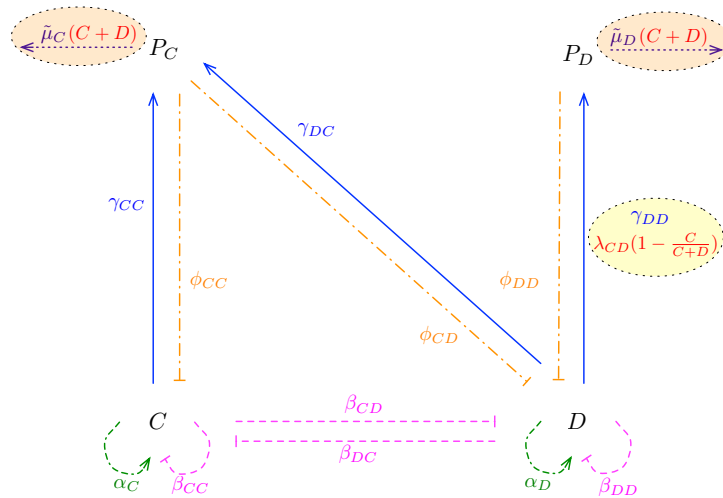


Figure 5.4: Interactions that recover the linear frequency dependent growth rate of *Curvibacter* sp. and the quadratic frequency dependent growth rate of *Duganella* sp. The asymmetry in the infection network shows that the *Curvibacter*-phage plays the role of a generalist and the *Duganella*-phage plays the role of a specialist.

In this work, from analysing the null model we show that simple infection and cross-infection of bacteria by phages in a linear manner cannot produce frequency dependent growth rates. Taking into account the adaptation of phages to the changing frequencies of bacteria hosts, and the active defence of bacteria by producing OMVs, we build a simple mathematical model of phage-bacteria interactions that can produce frequency dependent growth rates of bacteria. Feeding experimental results to the general model, we recover the observation of linear and quadratic frequency dependent growth rates of bacteria in Li et al. [2015b]. In addition, from the mathematical analysis, we gain knowledge on the ecological nature of the two phages, one as a generalist and the other as a specialist.

## 5.4 Discussion

The first interesting finding of this work is that our null model recovers the classic case of competitive exclusion. Although we have brought in additional actors (i.e. the phages) to the system, the overall behavior of the bacterial

population dynamics remains qualitatively the same as if there is no phage involved at all. This tells us that without additional factors, such as adaptation of phages to changing frequencies of bacteria hosts or life history tradeoffs, the fact that phages being able to infect and cross-infect different bacteria species per se do not contribute to the maintenance of biodiversity. This is in agreement with the conclusion of [Jover et al. \[2013\]](#), where the tradeoffs between life-history traits of both bacteria and phages are essential for stable coexistence.

Quantitatively however, the presence of phages can change the outcome of bacterial competition. In the null model, the relative sizes of parameters  $a$  and  $b$  determine which bacterial species dominates the other. The activity of phages may indeed change the outcome of bacterial population dynamics, by changing the values of parameters  $a$  and  $b$ . For example, when phages are not present, one bacteria species may always outcompete the other; but they might be able to coexist if phages are introduced into the system. The two bacteria exclude each other if either  $a$  or  $b$  is greater than one. But if the activity of phages change the values of  $a$  and  $b$ , bringing both to values below one, the two bacteria can stably coexist. However, without explicit experimental designs with phage-free controls, simply from the observation of competitive exclusion, it is not possible to tell if such population dynamics is caused by bacterial competitions alone, or if phages are also involved.

Previous studies on the “killing-the-winner” (KTW) theory have shown that phages can contribute to the coexistence of bacteria by preferentially killing bacteria with the highest frequency in the population [[Koskella and Meaden, 2013](#); [Thingstad, 2000](#); [Winter et al., 2010](#)]. Through negative frequency dependent selection, the KTW theory provides a mechanism of promoting biodiversity in microbial communities. However, KTW models normally assume that each of the bacterial species is infected by strictly one specialist phage [[Middelboe et al., 2001, 2008](#); [Miki et al., 2008](#); [Thingstad, 2000](#)]. In the original model of [Thingstad \[2000\]](#), the author also assumes that all bacteria compete for the same substrate resource, and are under nonselective predation from the same protozoan predator.

To test the KTW model experimentally and also elucidate the role of predation, in [Middelboe et al. \[2001\]](#), the authors combined simulation and

experimental approaches. The four phage species were isolated from the marine surface water. They are chosen and experimentally confirmed to be host specific. This makes it satisfies the model assumption that one phage only infect one bacteria and one bacteria is infected by only one phage. The results confirmed the strong effects of viral lysis on bacterial population dynamics. The authors also showed from simulations that the nonspecific predation of a common protozoan grazer reduces the amplitudes of bacterial population size fluctuations, but increases the frequency of such fluctuations. Besides bacteria and phages, the model also considers many other factors such as the inflow and outflow of carbon sources, dilution, as well as different nutrition uptake rates by bacteria of different radii. Despite being biologically more realistic, this limits the mathematical tractability of the model.

In the working model, we show that the combined effects of phage adaptation and host defence can produce frequency dependent growth rates of bacteria and the resultant alternative coexisting states. When modeling the adaptation of phages, we use the parameter  $\lambda$  to describe how aptly a phage responds to the fluctuation of relative frequencies of bacteria in the population. Biologically, it captures the fitness cost inflicted by switching to another host. If  $\lambda$  is small, it is cheap for a phage to switch to infecting an alternative host. In our system, it corresponds to the case of the *Curvibacter*-phage. On the other hand, if  $\lambda$  is large, it would be very costly for the phage to switch to another host, especially when the frequency of the alternative host is not very high. In our system, it corresponds to the case of the *Duganella*-phage. This is in agreement with our experimental observations that the *Curvibacter*-phage often cross-infect *Duganella* sp., but not the other way round.

It is important to note that we do not assume explicitly a tradeoff between phage host range and the efficiency of infection, as required in the model of [Jover et al., 2013]. In order to produce alternative coexisting states, for our model the only requirement is that the two quadratic growth rate functions in (5.10) intersect twice within the range of  $0 < f < 1$ . As included in equations (5.11), besides the efficiency of phage infection, many other factors can have an effect, including the rates at which phage particles are produced from lysing different bacteria cells, the costs of switching hosts, reproduction rates of bacteria and the deactivation rates of phages by OMVs. This may explain

the rather equivocal empirical observations on the tradeoffs between phage host range and the efficiency of infection [Avrani et al., 2011; Lennon et al., 2007]. In our model, other factors can also contribute to the maintenance of biodiversity, so it is not that phages with broader host ranges have to be less efficient.

Another interesting finding from our model analysis is that it also requires that bacterial hosts defend themselves against phage infections actively. Across a wide range of environmental habitats, bacteria and phages generally represent the most abundant and genetically diverse groups of organisms [Edwards and Rohwer, 2005; Fraser et al., 2009; Torsvik et al., 2002]. It has been proposed that such diversity is mostly driven by the arms race between phage adaptation and host resistance [Labrie et al., 2010]. Except using OMVs as decoys, there are many other mechanisms through which bacteria defend against bacterial infections. For example, one of the mechanisms is to prevent phages from adsorption by blocking phage receptors [Foster, 2005], or by producing extracellular matrix [Hammad, 1998], or even by producing competitive inhibitors [Destoumieux-Garzón et al., 2005]. Other commonly used strategies include blocking DNA injection, cutting phage nucleic acids, and bacterial suicide through the abortive infection systems [Dy et al., 2014; Labrie et al., 2010]. Although we already have good empirical knowledge on the molecular mechanisms of bacterial defence, little modeling work has been done to compare the effects of different mechanisms on the population dynamics of phages and bacteria quantitatively.

Various factors affect the arms race of phage infectivity and bacterial resistance, including phage adsorption via specific receptors [Chatterjee and Rothenberg, 2012], structural change of both phages and their bacterial host [Mahony and Van Sinderen, 2012], injecting nucleic acids into bacterial cells and defence against degradation [Richter et al., 2012], and the presence of phage resistance plasmid in the host cells [de Vos et al., 1984; Deng et al., 1997]. There are also cases of cryptic phenotypic resistance, where the bacteria remain genetically sensitive, but being able to attain high density as if they are resistant [Bull et al., 2014]. But the costs to either phages or bacteria inflicted in these processes are largely unknown. Albeit accumulating empirical findings, there is still very little modeling work that studies the detailed

mechanisms of these biological processes quantitatively. A rare example is the work of [Smith and Trevino \[2009\]](#), where the authors built a stochastic model of phage-bacteria population dynamics, taking into account the detailed dynamics of multiple phages adsorb to one single host cell. The authors not only simulated the stochastic processes, but also analysed the associated deterministic model, showing that the reproductive number for phage proliferation has to exceed one for the persistence of both phages and bacteria. They also calculated the distribution of the numbers of adsorbed phage on one single bacterial cell.

Beyond the detailed mechanisms of infection and resistance, there is also great need of knowledge on the general principles which determine the set of phages that can infect a bacteria species, and the group of bacteria that a phage can infect. Taking a statistical approach, [Flores et al. \[2011\]](#) performed a detailed metaanalysis of the infection relationships across a wide habitat spectrum. They show that the infection network is featured by a nested structure and the absence of modularity. Findings of general principles like such greatly facilitate modeling works by providing a justified ground to build on. In fact, recent mathematical models of [Jover et al. \[2013\]](#) and [Thingstad et al. \[2014\]](#) are both built on the nested structure. In another modeling work, [Beckett and Williams \[2013\]](#) show that the “nested-modular” interaction networks found in Atlantic Ocean samples can be produced by a simple ODE model of host-phage coevolution, where infectivity depends on genetic matching. See [Weitz et al. \[2013\]](#) for a recent review on phage-bacteria infection networks.

It is also crucial to distinguish and reintegrate interactions that operate on different time scales. In the evolutionary time scale, the arms race between phages and bacteria propelled by mutation and natural selection ultimately drives the generation and maintenance of biodiversity. However, under some experimental conditions, ecological processes such as the Lotka-Volterra dynamics may take up a more important role. For example, the experiments in the work of [Middelboe et al. \[2001\]](#) show that viral lysis only have temporary effects on the population dynamics of the bacterial hosts. Resistance against phages evolved quickly after the initial lysis of sensitive host cells. Consequently, interspecific competitions among the phage-resistant bacterial



strains become the driving force of population dynamics, in only a few generations after the lysis event. But in most cases, the effects of evolution and ecology are combined and hard to separate, as reviewed in [Jessup and Forde \[2008\]](#).

In our working model, the formulation of host range evolution of phages can only capture the initial phase of adaptation, when the decrease of infection rate to the original host species is relatively large, and the increase in the infection rate to the new host species is rather small. This corresponds to the time scale of the experiments in Chapter 4, where we observed frequency dependent growth rates of *Curvibacter* sp. and *Duganella* sp., and the alternative coexisting states of the two bacteria. It has been found experimentally that within the hydra host, *Curvibacter* sp. is the most abundant in frequency, and it plays the role of keystone species in maintaining the composition of host microbiota [[Fraune et al., 2014](#)]. This might be a benefit from hosting the generalist *Curvibacter*-phage, which has little cost to switch to infecting other bacteria when their frequencies become too high.



# Summary and Outlook

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Evolutionary game theory provides a useful framework for studying the evolution of strategic behaviours, such as cooperation and reciprocity. It also contributes to our understanding about many biological phenomena, such as the one to one sex ratio observed in various different species. But classic evolutionary game theory models take very little consideration of the life history traits of individuals nor the demographic structure of populations. In addition, it mainly focuses on the dynamics of frequency, rather than the absolute quantity/density of different phenotypes. But these often neglected factors can play an important role in determining the population dynamics in many biological systems. For example, many insect species experience distinct life stages, performing different ecological functions in each of them. Also, in many microbial communities, such as the human and animal microbiota, the population size of different bacteria can fluctuate considerably within a short period of time. The central theme of this thesis is to integrate indispensable biological factors back into evolutionary game theory models. Sometimes this is necessary in order to capture the essential features of population dynamics, and to elucidate the underlying mechanisms that produce these features.

The first factor we take into consideration is the life history of individuals and the corresponding demographic structure of the population. Life history theory has provided a systematic way to study the evolution of aging, life history tradeoffs, and reproductive schedules. But traditional life history models are often based on optimisation algorithms, neglecting interactions within the population and the resultant changes of the fitness landscape. In Chapter 2, we incorporate these factors into evolutionary game theory through models with life stage dependent strategies. For species with different life stages, an individual can behave differently at different times. In addition, behaviours can be conditioned on the current life stage of the focal individual, that of its opponent, or the matching of life stages between the two. By analysing the

replicator dynamics of life-stage dependent strategies, we show that an integration of life history and evolutionary games can alter the population dynamics substantially. The diversity of life stage structures and life stage dependent strategies can promote each other through interactions in the population. In addition, we show that the distribution of different strategic behaviours at equilibrium can be different from that predicted by game theoretic interactions alone. Starting from the same frequency of a certain behaviour (e.g. cooperation), populations with different demographic structures can evolve towards different states.

Although the replicator dynamics has many convenient mathematical properties (see Chapter 1), it is based on the assumption of infinite population size. But the finiteness of population size and the resultant stochasticity of the system can be important in many biological populations. In order to study the evolutionary fate of mutants and the effects of extinction events, we have to analyse the corresponding stochastic processes. Thus, in Chapter 3 we continue to study the interactions of life history and evolutionary games, but instead of focusing on the average frequency changes of standing variations, we explore the evolutionary fate of beneficial mutants in adaptive evolution. In stochastic population models, the detailed strategy interactions and population state update rules allow us to investigate the effects of different selective forces. We show that the evolutionary fate of a beneficial mutant, characterised by its fixation probability, can differ greatly when natural selection works on reproduction, survival or a combination of both. Moreover, we are able to assess the relative importance of the size and the demographic structure of the populations, in determining the fixation probability of a beneficial mutant.

Although our models in Chapter 3 capture the effects of stochasticity that is absent in the deterministic models in Chapter 2, they have so far not taken into account of frequency dependent selection. On the one hand, adding population demographic structure while keeping constant selection makes it possible to compare our results with those from classic population genetics models; on the other hand, it would be an interesting topic for the future to study the effects of frequency dependent selection in evolutionary games. In fact, frequency dependent selection can be important in determining population dynamics. An example is shown in Chapter 4, where we study the evolution-

ary games between two bacterial species (*Curvibacter* sp. and *Duganella* sp.), which are isolated from the Hydra microbiome. The growth rate of *Duganella* sp. is a quadratic function and the growth rate of *Curvibacter* sp. is a linear function. Incorporating the frequency dependent growth rates into the Lotka-Volterra dynamics, we build a mathematical model that recovers the alternative coexisting states of the two bacteria.

Besides frequency dependent effects, in Chapter 4, we also show the importance of considering the absolute density in characterising population dynamics, especially in populations that can experience considerable size changes. For the same trajectories of population growth in co-culture experiments, if we only look at the frequency dynamics, it resembles the typical case of coordination game. Depending on the initial condition, the frequency of one bacterium approaches one, and the frequency of the other approaches zero. However, if we also look at the population dynamics represented by the changes of density, the picture is completely different. The two competing bacterial species have both increased their absolute density greatly during the course of 60 hours of growth. Even the submissive species has increased its absolute density by a factor of a hundred at the end of the experiments. Taken together frequency and density dynamics, the whole picture of the bacterial games can be illustrated by drawing a parallel to economic inflation. The rich becomes richer and the poor poorer (frequency dynamics), although everybody has more money by the end (density dynamics). The complex population growth pattern arisen from the seemingly simple evolutionary game between two bacteria highlights the fundamental importance of frequency dependent selection on population dynamics.

In Chapter 4, we show that frequency dependent growth rates can produce alternative coexisting states in growing bacterial populations. From mathematical analysis we also show that it is not possible to produce such complex population dynamics by bacterial cells interacting in pairwise games. One potential explanation indicated by preliminary experiments is that there might be invisible players (e.g. phages) involved in the games. In order to find out the microscopic mechanisms that can produce such macroscopic frequency dependent growth rates, we study a model of phage-bacteria interactions in Chapter 5. We show that phages being able to infect and cross-infect bacterial

cells per se do not contribute to the deviation from competitive exclusion of the co-culture system. On the other hand, a combined effect of phage adaptation and bacterial defence can produce frequency dependent growth rate of bacteria and the resultant alternative coexisting states in the population.

In the work presented in the four projects from Chapter 2 to 5, we develop models that rely on as few assumptions as possible, but being able to capture the most important features of the biological systems under investigation, and to facilitate our understanding of the underlying mechanisms. It is tantalising to incorporate more biological factors into evolutionary game theory models and assess their relative importance, but this inevitably increases the complexity and very often reduces the tractability of the models. For example, it would be interesting to study frequency dependent game interactions in age structured populations with selection working on reproduction or survival or a combination of both. This would also connect the questions we studied in Chapter 2 and Chapter 3. However, because of the much increased complexity, we have to make additional assumptions and approximations, such as assuming infinitely large population size and weak selection (the technique is introduced in Chapter 1) in order to gain analytical insights.

Besides incorporating more factors in order to make the models more biologically relevant, another future direction I would like to explore is to simplify models which describe biological phenomena in great detail, so that they might reduce to processes that can be captured by evolutionary games. Another interesting future direction is to develop models that help explain the increasing amount of biological data. Our modelling work should go beyond statistical descriptions, but explain the mechanisms that produce the observed patterns. For example, it would be interesting to develop a mechanistic model that can explain the dynamic “in-out-in” colonisation pattern of the microbiota of neonatal animals, and link it with sequencing data from experiments.

# Appendices

## 7.1 Appendix of Chapter 2

### 7.1.1 Linear Stability Analysis of the fixed points in Figure 2.3 of Chapter 2

The fixed points where three strategies coexist are as following:

1.  $\left( \frac{(n^2-n-2)(-2p+1)}{2n^2(2p_H^H-1)+4(p-p_H^H)}, \frac{(n-1)(n(p+2p_H^H-2)+2p_H^H)}{2n^2(2p_H^H-1)+4(p-p_H^H)}, \frac{(n-1)(n(p+2p_H^H-1)+2(p_H^H-1))}{2n^2(2p_H^H-1)+4(p-p_H^H)}, 0 \right)$
2.  $\left( \frac{(n+1)p}{n^2(p+p_H^H)+p-p_H^H}, \frac{n-1}{n^2(p+p_H^H)+p-p_H^H}, 0, \frac{(n-1)(n(p+p_H^H)+p_H^H-1)}{n^2(p+p_H^H)+p-p_H^H} \right)$
3.  $\left( \frac{(n+1)(p-1)}{n^2(p+p_H^H-2)+p-p_H^H}, 0, \frac{-n+1}{n^2(p+p_H^H-2)+p-p_H^H}, \frac{(n-1)(n(p+p_H^H-2)+p_H^H)}{n^2(p+p_H^H-2)+p-p_H^H} \right)$

In addition, there is a line of fixed points on the  $HD - DH - DD$  surface,  $(0, \frac{n(p-1)x+1}{np}, x, 1 - x - \frac{n(p-1)x+1}{np})$ , independent of  $p_H^H$ . Depending on the values of  $n$ ,  $p$ , and  $p_H^H$ , some of the fixed points may fall out of the  $S_4$  simplex.

The linear stability of the fixed points can be determined by the sign of eigenvalues of the Jacobian matrix evaluated at the fixed points. For example, at the fixed point where  $HH$ ,  $HD$  and  $DD$  coexist, the three eigenvalues of the Jacobian Matrix are:

1.  $-(n-1) \frac{np(1+p) + \sqrt{p} \sqrt{n^2(p^3 - 2p^2 + p + 4(p_H^H)^2) + 4n(-p^2 + p - p p_H^H + 2(p_H^H)^2 - p_H^H) + 4(p - p p_H^H + (p_H^H)^2 - p_H^H)}}{4((n^2+1)p + (n^2-1)p_H^H)}$
2.  $-\frac{(n^2-1)(p-p_H^H)}{2((n^2+1)p + (n^2-1)p_H^H)}$
3.  $-(n-1) \frac{np(1+p) - \sqrt{p} \sqrt{n^2(p^3 - 2p^2 + p + 4(p_H^H)^2) + 4n(-p^2 + p - p p_H^H + 2(p_H^H)^2 - p_H^H) + 4(p - p p_H^H + (p_H^H)^2 - p_H^H)}}{4((n^2+1)p + (n^2-1)p_H^H)}$

The first eigenvalue is always negative. The second eigenvalue is negative when  $p_H^H < p$ , and is positive when  $p_H^H > p$ . The third eigenvalue is negative when  $p_H^H < p$  and  $n > \frac{1-p_H^H}{p+p_H^H}$ , and it is positive when  $p_H^H > p$  or  $n < \frac{1-p_H^H}{p+p_H^H}$ .

Therefore in the case where the cost of conflict is fairly large,  $n > \frac{1-p_H^H}{p+p_H^H}$ , the stability of the fixed point where  $HH$ ,  $HD$  and  $DD$  coexist is determined by the relative size of  $p_H^H$  and  $p$ . If  $p_H^H < p$ , the fixed point is a stable node, if  $p_H^H > p$ , the fixed point is a saddle point.

Another interesting fixed point is where  $HH$ ,  $DH$  and  $DD$  coexist. The three eigenvalues of the Jacobian Matrix are:

1.  $-(n-1) \frac{n(-p^2+3p-2)+\sqrt{1-p}\sqrt{n^2(-p^3+p^2+4(p_H^H-1)^2)-4n(p^2-2p+p_H^H-2)(p_H^H)^2+2p_H^H}-4pp_H^H+4(p_H^H)^2}}{4(n^2(p+p_H^H-2)+p-p_H^H)}$
2.  $-\frac{(n^2-1)(p-p_H^H)}{2(n^2(p+p_H^H-2)+p-p_H^H)}$
3.  $-(n-1) \frac{n(-p^2+3p-2)-\sqrt{1-p}\sqrt{n^2(-p^3+p^2+4(p_H^H-1)^2)-4n(p^2-2p+p_H^H-2)(p_H^H)^2+2p_H^H}-4pp_H^H+4(p_H^H)^2}}{4(n^2(p+p_H^H-2)+p-p_H^H)}$

Like the previous case, the first eigenvalue is always negative. The second eigenvalue is negative when  $p_H^H > p$ , and is positive when  $p_H^H < p$ . The third eigenvalue is negative when  $p_H^H > p$  and  $n > \frac{p_H^H}{2-p-p_H^H}$ , and is positive when  $p_H^H < p$  or  $n < \frac{p_H^H}{2-p-p_H^H}$ . Therefore in the case where  $n > \frac{p_H^H}{2-p-p_H^H}$ , the stability of the fixed point changes with the relative sizes of  $p_H^H$  and  $p$ . If  $p_H^H > p$ , the fixed point is a stable node, if  $p_H^H < p$ , the fixed point is a saddle point.

Taken the stability of the two fixed points together, within the regime where the cost of conflict is relatively large,  $n > \frac{1-p_H^H}{p+p_H^H}$  and  $n > \frac{p_H^H}{2-p-p_H^H}$ , the stability of the two fixed point switches.

When  $p_H^H < p$ , the fixed point at which  $HH, HD, DD$  coexist is stable, and the fixed point at which  $HH, DH, DD$  coexist is unstable. When  $p_H^H > p$ , the  $HH, HD, DD$  fixed point is unstable, and the  $HH, DH, DD$  fixed point is stable. This is illustrated in Figure 2.3.

We solved for the fixed points and performed the linear stability analysis first using the symbolic mathematical software Mathematica 9.0.1 and subsequently verified all results manually. When analysing the switch of stability of the two fixed points where  $HD$  or  $DH$  coexist with the two "pure strategies"  $HH$  and  $DD$ , it is instructive to make use of the built-in "Manipulate" function of Mathematica. For example, one can plot the values of the three eigenvalues with respect to  $n$ , and observe the changes of the signs of the three eigenvalues while changing  $p$  and  $p_H^H$ . Our Mathematica file is available as a Supplementary Material to this paper.



## 7.2 Appendix of Chapter 3

### 7.2.1 Fixation probability of a single mutant in the young age class

Fisher's reproductive value  $v_k$  of an individual in age class  $k$  in an age-structured population with pre-breeding census is [Charlesworth et al., 1994]:

$$v_k = \frac{\lambda^k}{l_k} \sum_{x=k}^{\omega} l_x m_x \lambda^{-x} \quad (7.1)$$

in which  $\lambda$  is the asymptotic growth rate of the population,  $l_k$  is the probability of an individual surviving at least to age class  $k$ ,  $m_k$  is the expected number of offspring in the first age class produced by an individual in the  $k$ -th age class in the last time step, and  $\omega$  is the maximum attainable age. In our specific model of two age classes ( $\omega = 2$ ), the parameter values are,  $\lambda = 1$  (constant population size),  $l_1 = 1$ ,  $l_2 = N_2/N_1$ , and  $m_1 = m_2 = N_1/N$ , where  $N = N_1 + N_2$

We have  $v_1 = 1$  and  $v_2 = N_1/N \equiv f$ . Following Emigh [1979a], the fixation probability of a selectively neutral mutant is

$$\frac{v_1}{v_1 N_1 + v_2 N_2} = \frac{1}{N f (2 - f)}. \quad (7.2)$$

### 7.2.2 Selection on reproduction

#### 7.2.2.1 Expected value of mutants in the next time step

In the following we use  $B(x_1^{(t+1)})$  as the shorthand for  $B\left(x_1^{(t+1)}; N_1, \frac{r(x_1^{(t)} + x_2^{(t)})}{r(x_1^{(t)} + x_2^{(t)}) + N_1 - x_1^{(t)} + N_2 - x_2^{(t)}}\right)$  and  $H(x_2^{(t+1)})$  as the shorthand

for  $H(x_2^{(t+1)}; N_1, x_1^{(t)}, N_2)$ .

$$\begin{aligned}
E[x_1^{(t+1)} + x_2^{(t+1)}] &= \sum_{x_1^{(t+1)}=0}^{N_1} \sum_{x_2^{(t+1)}=0}^{N_2} B(x_1^{(t+1)})H(x_2^{(t+1)})(x_1^{(t+1)} + x_2^{(t+1)}) \\
&= \sum_{x_1^{(t+1)}=0}^{N_1} B(x_1^{(t+1)}) \sum_{x_2^{(t+1)}=0}^{N_2} \left( H(x_2^{(t+1)})x_1^{(t+1)} + H(x_2^{(t+1)})x_2^{(t+1)} \right) \\
&= \sum_{x_1^{(t+1)}=0}^{N_1} B(x_1^{(t+1)}) \left( x_1^{(t+1)} + \frac{x_1^{(t)}N_2}{N_1} \right) \\
&= \frac{x_1^{(t)}N_2}{N_1} + \frac{r(x_1^{(t)} + x_2^{(t)})N_1}{(r-1)(x_1^{(t)} + x_2^{(t)}) + N_1 + N_2}
\end{aligned} \tag{7.3}$$

### 7.2.2.2 $N_1^* < N$ always holds when $r > 1$

$$N_1^* = \sqrt{x_1^{(t)}N \left( 1 + \frac{N - x_1^{(t)} - x_2^{(t)}}{r(x_1^{(t)} + x_2^{(t)})} \right)} \tag{7.4}$$

Requiring  $N_1^* < N$ , we solve the inequality for  $r$ .

$$r > 1 - \frac{x_2^{(t)}N}{(N - x_1^{(t)})(x_1^{(t)} + x_2^{(t)})} \tag{7.5}$$

Starting from one single mutant in the young age class, initially  $x_1^{(t)} = 1$ , and  $x_2^{(t)} = 0$ . Therefore the requirement becomes  $r > 1$ . For advantageous mutants, this requirement is always satisfied.

### 7.2.3 Effects of linear allocation of benefits

Imagine that the mutant allocates its extra benefit in a linear way. Relative to wild types, the mutant has an extra payoff  $s$ . She allocates  $a$  fraction of it to increase her reproduction, and use the rest to improve survival. Therefore her relative fitness for reproduction  $r_1 = 1 + as$ , and her relative fitness for survival  $r_2 = 1 + (1 - a)s$ . In Figure 7.1 we show the effects on fixation probability of this particular way of allocating extra benefits.

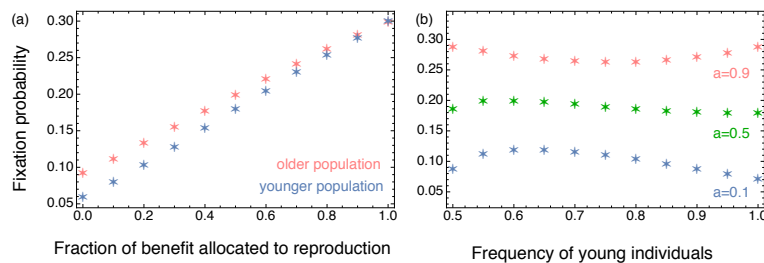


Figure 7.1: Effects on fixation probability of a mutant that has an extra fitness benefit of  $s = 0.2$ . (a) In general the fixation probability increases monotonically with the fraction of benefits allocated to reproduction. In the older population, the frequency of young individual is 0.55, and in the younger population, the frequency of young individual is 0.95. (b) If the fraction of benefits that can be allocated to reproduction is fixed, the fixation probability varies in a non-linear way in populations with different demographic structures.  $a$  is the fraction of extra benefits that is allocated to reproduction. ( $N = 20$ , a Mathematica notebook file for generating this figure can be found in the Supplementary Information).

### 7.2.4 The fixation probability increases with population size in the Wright Fisher process when $r$ is large

When  $r$  is small, the fixation probability of a beneficial mutant decreases with increasing size of the population, approaching  $2(r - 1)$ . But when  $r$  is large, the fixation probability first decreases and then increase again, although the magnitude of increase is rather small, see Figure 7.2.

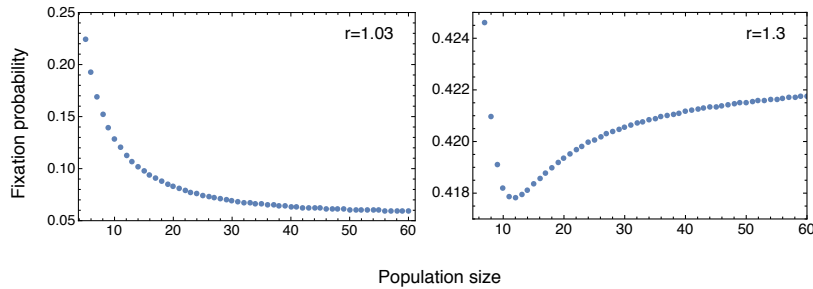


Figure 7.2: Fixation probability of a single beneficial mutant in the Wright-Fisher process. In the left panel when the selective advantage of the mutant is small, as population size grows, the fixation probability approaches the classic result of  $2(r - 1)$ . In the right panel, when the conditions of diffusion approximation are not satisfied, the fixation probability first decreases and then increase again as population size increases.

### 7.3 Appendix of Chapter 4

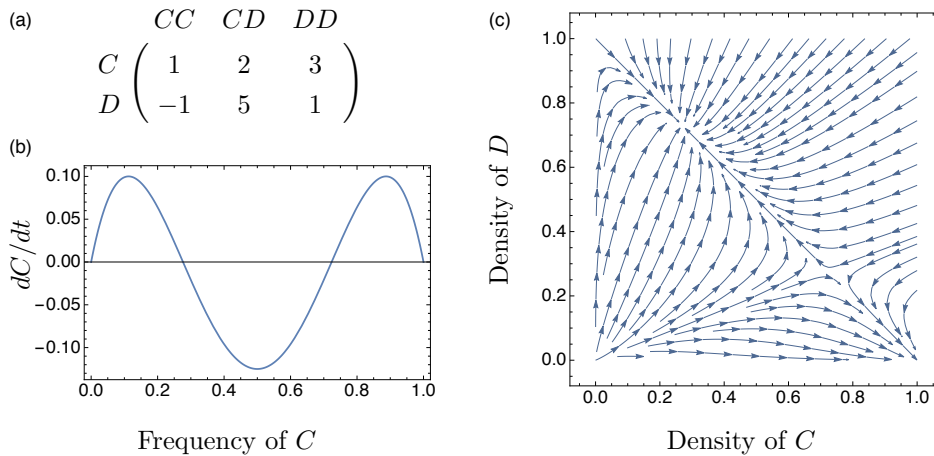


Figure 7.3: A 3-player evolutionary game that produces frequency dependent growth rates and two internal equilibria. The payoff matrix of the three-player game is shown in (a). The two internal equilibria are shown in the frequency (b) and density (c) plots.

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## Curriculum Vitæ

May 04, 1988	Born in Jiyuan, China Nationality: Chinese
2006 – 2010	Bachelor of Science: Biochemistry and Molecular Biology Ocean University of China, Qingdao
2010 – 2012	Erasmus Mundus Master of Science in Marine Biodiversity and Conservation ( <i>summa cum laude</i> ) Master's Thesis: Genome evolution following admixture in invasive sculpins Supervisor: Prof. Dr. Arne Nolte and Prof. Dr. Magda Vincx Universiteit Gent, Gent & Université Pierre et Marie Curie, Paris
2012 – 2015	Ph.D. candidate: Mathematical Biology Supervisor: Prof. Dr. Arne Traulsen Max Planck Institute for Evolutionary Biology, Plön

## Declaration

This thesis is a presentation of my original work, apart from my supervisor, Arne Traulsen's guidance. This thesis has not been submitted partly or wholly as a part of a doctoral degree to any other examining body. This thesis has been prepared according to the Rules of Good Scientific Practice of the German Research Foundation.

Two papers published separately in the Journals *Journal of Theoretical Biology*, and *Journal of the Royal Society Interface*, as well as two chapters based on work in progress, are included in this thesis.

- Published paper [Li et al., 2015a], Chapter 2  
I developed and analysed the model under the supervision of Arne Traulsen. Stefano Giaimo and Annette Baudisch gave valuable inputs from the demographic aspects. All authors wrote the paper together.
- Work in progress, Chapter 3  
I initiated the project, did mathematical analysis and numerical solutions under the supervision of Arne Traulsen. Shun Kurokawa gave important input in the analysis of the model. Stefano Giaimo contributed greatly in the demographic aspects and literature review. All authors write the manuscript together.
- Published paper [Li et al., 2015b], Chapter 4  
I carried out the mathematical modelling. Cleo Pietschke carried out the laboratory work. Cleo Pietschke and I both performed data analysis. Philipp M. Altrock, Sebastian Fraune, Thomas C. G. Bosch and Arne Traulsen conceived the study. All authors participated in the design of the study and contributed to writing the paper.
- Work in progress, Chapter 5  
I work on the modeling part and Tim Lachnit works on the experimental part.