Evolutionary Game Dynamics Driven By Mutations Under Frequency Dependent Selection

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Abstract

Evolutionary game theory and theoretical population genetics are two different fields sharing many common properties. In both fields, theoretical models are built to explore evolutionary dynamics; various evolutionary forces, such as selection, mutation, and random genetic drift, are involved in the modeling. However, in terms of concrete models, evolutionary game theory is often considered to deal with phenotypes, while theoretical population genetics describes genotypes. Is it possible and worth to combine approaches from both fields? We address this question by analyzing the evolutionary dynamics driven by random mutations in the framework of evolutionary game theory. Mutations provide a continuous input of new variability into a population, which is exposed to natural selection. In evolutionary game theory, mutations are often assumed to occur among predefined types. This assumption initially made in the study of behavioral phenotypes (i.e. human behaviors), might be less reasonable in studies at the level of genes or genotypes. An alternative assumption is made in the infinite allele model in theoretical population genetics, where every mutation brings a new allele to the population. However, the resulting evolutionary dynamics based on the infinite allele model has only been studied in the context of neutral and constant selection. In this thesis, we propose an evolutionary game theoretic model, which combines the assumption of infinite alleles and frequency dependent fitness. We investigate the evolutionary dynamics in finite and infinite populations based on this model. The fixation probability of a single mutant, the diversity of a population, and the changes of the average population fitness are strikingly different under constant selection and frequency dependent selection scenarios. These results imply that connecting evolutionary game theory and theoretical population genetics approaches can bring a different and insightful view in understanding evolutionary dynamics.

Kurzfassung

Evolutionäre Spieltheorie und Populationsgenetik sind zwei verschiedene wissenschaftliche Gebiete, die viele gemeinsame Eigenschaften teilen. In beiden Gebieten werden theoretische Modelle zur Beschreibung evolutionärer Dynamiken entwickelt, wobei viele die Evolution treibende Kräfte berücksichtigt werden, wie etwa Selektion, Mutation und zufälliger genetischer Drift. Nichtsdestotrotz beschreibt die evolutionäre Spieltheorie in konkreten Modelen den Phenotyp und die Populationsgenetik den Genotyp. Ist es möglich und nützlich, Ansätze von beiden Gebieten zu verbinden? Wir beantworten diese Frage durch die Analyse von durch Mutationen getriebenen evolutionären Dynamiken im Rahmen von evolutionärer Spieltheorie. Mutationen verursachen einen kontinuierlichen Zufluss von Variabilität in eine Population, die dann natürlicher Selektion ausgesetzt ist. In evolutionärer Spieltheorie werden Mutationen oft innerhalb vordefinierter Typen angenommen. Diese Annahme stammt ursprünglich aus der Studie von Verhaltensmustern (z. B. menschliches Verhalten) und ist auf dem Level von Allelen möglicherweise weniger schlüssig. Eine alternative Annahme wird im Infinite Allele Model gemacht, wo jede Mutation ein neues Allele in die Population einführt. Jedoch wurde die auf dieser Annahme beruhende evolutionäre Dynamik nur im Zusammenhang mit konstanter oder neutraler Selektion untersucht. In dieser Arbeit schlagen wir ein evolutionäres spieltheoretisches Model vor, das die Annahmen des Infiniten Allele Models mit frequenzabhängiger Selektion kombiniert. Wir untersuchen die dem Model zugrundeliegenden evolutionären Dynamiken für endlich und unendlich große Populationen. Die Fixierungswahrscheinlichkeit eines einzelnen Mutantens , die Vielfältigkeit der Population und die Änderungen der mittleren Fitness sind für konstante und frequenzabhängige Fitness erheblich voneinander verschieden. Diese Ergebnisse implizieren, dass die Verbindung von spieltheoretischen und populationsgenetischen Ansätzen neue Einsichten in das Verstehen von evolutionären Dynamiken bringen kann.

Contents

Introduction

1.1 Motivation

Game theory, invented by Neumann and Morgenstern, studies human behavior in strategic decision making [1, 2, 3]. People display different behavior in social interactions. In game theory, those interactions are described by a game, consisting of a group of players and a set of strategies available to each of these players. What players gain or lose for each combination of strategies are called payoffs. As a player may have more than one available action, this raises the question how do players choose their actions in different interactions? In game theoretic models, a basic assumption is rationality. Rational players choose an optimal action to obtain their highest payoffs, taking into account that their co-players will make similar rational decisions [4].

Game theoretic approaches were first introduced to biology in order to study individual interactions in animal populations by Maynard Smith and Price [5, 6, 7, 8, 9]. In biological populations, strategies correspond to heritable traits, and payoffs are mapped to fitness [10]. As Individuals have fixed strategies (heritable traits) in their life time, the assumption of rationality is relaxed. This is known as evolutionary game theory. Here, the term 'fitness' is used to describe different abilities of individuals with different traits to survive and reproduce [11]. Fitness has different components, such as survival and fertility. However, generally only one single component of fitness is studied

for the sake of simplicity. This is not totally unreasonable, as trade-offs often exist between different components of fitness. In evolutionary game theory, fitness is often defined as the average number of offspring from an individual with a certain trait [9].

A classical assumption is constant fitness, which means that fitness of a certain type is a fixed value independent of other types in the population [12, 13]. This assumption was initially made in studies of short-term evolution, where the feedback of the frequencies of different types on the the population dynamics is often ignored. On the contrary, frequency dependent fitness is defined as that the fitness of a type depends not only on its own frequency but also on the frequencies of other types in the population [9, 12]. The possibility that fitness might be frequency dependent was pointed out by Fisher in his discussion on mimicry [14], and later discussed in other experimental and theoretical studies [15, 16]. Assuming constant fitness makes mathematical models more tractable. Thus, this assumption is widely used in many theoretical models. Instead, one of the advantages of using evolutionary game theory to understand evolutionary processes is that it is a study based on frequency dependent fitness [17].

There are many reasons why the concept of frequency dependent selection is popular in evolutionary biology. One important reason is that negative frequency dependent selection has the potential to explain stable polymorphisms. In this case, rare traits have higher fitness, and the fitness of one trait increases when its relative frequency decreases in the population. This pattern has been observed in many biological systems such as the color morphs of flowers [18], the allelic variation at the self-imcompatibility S locus of plants [19], the diverse genotypes of major histocompatibility complex (MHC) genes [20], the high genetic variation of human immunodeficiency virus (HIV) [21], and the polymorphisms of fruitfly foraging behavior [22].

On the other hand, positive frequency dependent selection, where the

fitness of a type increases with its frequency, is also observed in biological systems. For example, rare morphs produce fewer young than the common morphs in wild snails [23], and common warning colors have advantages over rare warning colors in beetles [24]. It is often argued that stable polymorphisms is driven by negative frequency dependent selection, and that positive frequency dependent selection functions in the opposite way. However, there are patterns in natural populations that can not be simply classified into these two scenarios, but the variation of different types is also maintained.

One example is a rock-paper-scissors pattern in mating strategies in common side-blotched lizards [25, 26]. The orange-throated males defeat the blue-throated males, the blue-throated males defeat the yellow-throated males, and the yellow-throated males defeat the orange-throated males. Between any two male types, frequency dependent selection favors one of them. However, for all three male types, the interactions among them form a cyclic dynamics, which leads to the coexistence of the three types. Their proportions fluctuate in the short term, but are similar in the long term. Similar patterns of cyclic dynamics have also been observed among sessile marine invertebrates, like corals competing for space in reef environments [27, 28, 29]. In *Escherichia coli*, colicin-sensitive cells have a growth-rate advantage over colicin-resistant cells, colicin-resistant cells replace colicinogenic cells, and colicinogenic cells kill colicin-sensitive cells [30, 31, 32, 33].

Those types of interactions defined in a simplified model with only two types, might result in different dynamics in a population with more types. Stable polymorphisms can arise from different types of frequency dependent selection, which can be captured by evolutionary game theoretic models.

Besides of studying animal behavior in conflict interactions, evolutionary game theory is also used to understand mutualism and other types of individual interactions [34, 35, 36, 37, 38]. Due to this extensive background, evolutionary game theory is considered to typically deal with phenotypes [39] and

ignore the complexity at the genotype level [6]. Although connections between evolutionary game dynamics and population genetics are possible [36, 40, 41], concrete models with population genetics ingredients in the framework of evolutionary game theory are still rare. This thesis focuses on a model from such a perspective.

Evolutionary dynamics is driven by many different natural forces such as selection, mutation, random genetic drift, and migration [42, 12]. There are many well-established methods to model selection and random genetic drift in infinite and finite populations [43, 44, 45, 46, 47, 36, 48, 49, 50, 51]. Here, we are interested in the impact of mutations on the population dynamics, especially when the fitness of mutants is frequency dependent. In this thesis, we refer this type of mutants to 'frequency dependent mutants'. Mutations can result in different types of changes in different levels of an organism and provide a continuous source of variation in natural populations [12]. We consider frequency dependent mutations in biological populations, and incorporate approaches and concepts from both population genetics and evolutionary game theory.

In evolutionary game theory, it is often assumed that mutations happen between fixed known strategies. In our model, every mutation brings a new type into the population, which is analogous to the basic assumption of the infinite alleles model in population genetics [52, 53]. In the infinite alleles model, it is assumed that every new mutation brings a new allele which does not exist in the population. This is because the probability of back mutation is considered low enough to be negligible, and there are enough novel alleles the original allele can mutate to. There are many theoretical studies based on the infinite alleles model [54, 55, 56, 13]. However, they mainly consider neutral or constant selection so far. Instead, our model is based on frequency dependent selection and refers to any selection intensity (explained in details in Section 1.3.3). We introduce randomness in the fitness of mutants (see

Section 1.4), which allows any possible types of frequency dependent selection in the same evolutionary process.

In this thesis, different quantities of biological interest are investigated based on this model. We study the fixation probability of a single random mutant, the frequency distribution of the number of types existing at the same time, and the change of the population average population fitness. An interesting and central question is whether this new model differs from the corresponding model based on constant selection, and if so, how.

The following parts of the introduction will explain how random genetic drift and selection are addressed in population dynamical models, and how we implement frequency dependent mutants in the evolutionary game theoretic framework. The main body of the thesis will focus on different population dynamical systems based on our frequency dependent mutant model. All models discussed and explained in this thesis focus on a single locus. We compare frequency dependent selection scenarios with constant selection scenarios. The evolutionary dynamics of a population can be strikingly different under the two scenarios. This comparison reveals that evolutionary game theory can provide a different and insightful view on evolutionary problems.

1.2 Infinite and finite populations

Population size has an important impact on the evolutionary dynamics. In an infinite population model, the frequency changes of different types are deterministic due to dynamic rules of the reproduction process. One of these dynamic rules is the replicator dynamics. Here, the frequency of a certain type changes deterministically in proportion to the difference of its own fitness and the average population fitness [57, 58, 59]. The replicator dynamics is a good approximation if the population size is sufficiently large [40].

When the population size is small, the frequencies will fluctuate by chance. The smaller the population is, the greater the frequency fluctuations. In population genetics, this is called random genetic drift [12]. Random genetic drift is considered to play an important role in evolution [60]. Mathematical models have been proposed to capture such stochastic effects [61, 62, 63]. Two models often used to describe finite populations are the Moran process and the Wright-Fisher process. The Moran process describes the evolutionary dynamics in a population with overlapping generations [64, 65], and the Wright-Fisher process corresponds to a population with non-overlapping generations [14, 66]. All the methods used or discussed in this thesis are focused on well-mixed populations, which mathematically corresponds to populations under random mating [40].

1.2.1 Replicator dynamics

In evolutionary game theory, the replicator equations are used to describe a deterministic game dynamics [43, 36, 67]. The Replicator dynamics was introduced by Taylor, Jonker and Zeeman [57, 58] as a dynamic foundation for the concept of evolutionary stable strategies (ESS) [5].

Suppose there are only two types in the population. The frequency of the first type is x and the frequency of the second type is $1 - x$. We denote the

fitness of the first type as W_1, and the fitness of the second type as W_2. The average fitness of the population $\overline{W}$ is given by

$$\overline{W} = xW_1 + (1 - x)W_2. \tag{1.1}$$

We assume that the change in the frequency of the first type is given by the replicator equation,

$$\dot{x} = x\left(W_1 - \overline{W}\right) = x(1 - x)(W_1 - W_2). \tag{1.2}$$

If the fitness of the first type is larger than the average fitness, its frequency will increase. If the fitness of the first type is below the average fitness, its frequency will decrease. The type with a higher fitness will spread in the population.

In a population of n types, the fitness of type i can be written as W_i, and its frequency as x_i, where $i = 1, 2, 3..., n$ and $\sum_{i=1}^{n} x_i = 1$. Generalizing the replicator equations in such a population, the change of the frequency of type i is given by

$$\dot{x}_i = x_i\left(W_i - \overline{W}\right) = x_i \sum_{j=1}^{n} x_j(W_i - W_j). \tag{1.3}$$

The equilibria of the replicator equations can be derived by solving $\dot{x}_i = 0$ for all i. For a population with two types, they are $x = 1$, $x = 0$, and all $x \in (0, 1)$ fulfilling the condition $W_1 = W_2$. To give an analytical solution of the expression $W_1 = W_2$ and the stability of these equilibria, concrete implementation of fitness is required, see Section 1.3.3. The replicator equations in n types are mathematically equivalent to the Lotka-Voltera equations in $n-1$ dimensions, which is used to study predator-prey dynamics [36]. In Chapter 4, which focuses on infinite populations, we use the replicator dynamics.

1.2.2 Moran process and fixation probabilities

The Moran process is one of the simplest stochastic models to describe finite populations [65, 68, 13]. In a Moran process, there are one birth event and one

death event in every time step. Thus, the total population size is constant.

Consider a finite population with N individuals. In every time step, one random individual is chosen to produce one offspring, which in turn replaces one random individual. If the individual chosen to reproduce is under uniform random sampling among all individuals, the process is under neutral evolution. Selection acts on the population dynamics when this sampling depends on the fitness. Under selection, an individual with higher fitness is more likely to be chosen for reproduction.

In a two-type population without mutations, the chosen individual produces an offspring of its own type. In a population with mutations, the chosen individual produces an offspring of its own type with probability $1 - \mu$, and produces an offspring of a new type with probability μ. Here, μ is the mutation rate per individual per time step. In a Moran process, N time steps are one generation. Thus, the mutation rate of the whole population per generation is μ.

As a birth-and-death process, the Moran process can be considered as a finite Markov chain [69, 70], a random process describing a system undergoing transitions between a finite number of possible states. In a Markov Chain, the transition probability to the next state depends only on the current state and not on the transitions before it.
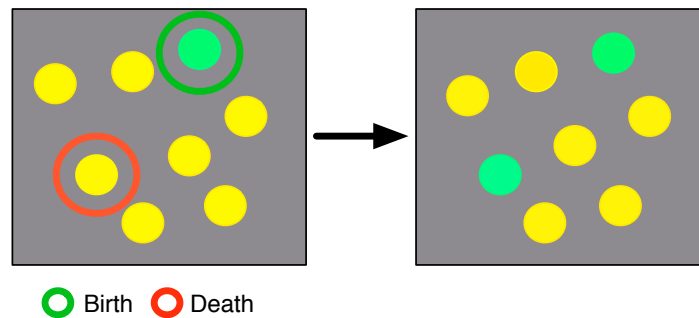
Figure 1.1: The Moran process. Suppose that there are two types in the population, the green mutant type and the yellow wild type, and no further mutations are considered. In every time step, one individual (in this illustration the green one) is chosen at random to reproduce, and one individual (in this illustration one yellow one) is chosen at random to die.

A simple illustration is the case of a population with only two types without mutations ($\mu = 0$), see Fig. 1.1. Suppose a population has yellow type and green type individuals. Here, the population growth of the green type can be defined as a Markov chain, see Fig. 1.2. Every state represents a certain number of the green type individuals. Since there are N individuals in the population, we have $N+1$ states in the Markov chain. The neighboring states are natural numbers. Suppose the current state of the population is state j, where $j = 0, 1, 2..., N$. When a green type individual reproduces and a yellow type individual dies, the population goes from state j to $j+1$. The probability of this transition is denoted as T_j^+. When a green type individual dies and a yellow type individual reproduces, the population moves from state j to state $j-1$. This transition probability is denoted as T_j^-. As in the Moran process, at most one individual reproduces and dies in one time step, the population will move to either one of its two neighboring states, or will stay in the same state in the next time step. Thus, the probability of staying in the same state

is $1 - T_j^+ - T_j^-$.

Since there are no mutations, two absorbing states, state 0 and state N, exist in this Markov Chain. A state is called absorbing, if the system can not leave this state once reaches it [9]. This can be written as $T_0^+ = T_N^- = 0$. Under this assumption, no matter in which state the system initially starts, the population will end up either in state 0 or state N. If the population ends up in state N, we call it the fixation of the green type. The probability of ending in state N, starting from state j, is called fixation probability, ϕ_j [71, 72, 9, 51]. In other words, ϕ_j is the probability of j green type individuals taking over the population, and ϕ_1 is the probability of a single green type individual being fixed in the population.

In a Moran process, the the fixation probability can be written as a recursion equation for the intermediate states [9, 51],

$$
\underbrace{\phi_j = T_j^+ \phi_{j+1} + T_j^- \phi_{j-1} + (1 - T_j^+ - T_j^-)\phi_j}_{} \ .
$$

Transition probability from j to $j+1$ Transition probability from j to $j-1$ Probability of staying in j

Fixation probability in j Fixation probability in $j+1$ Fixation probability in $j-1$

The two absorbing states of the Markov chain give the boundary conditions $\phi_0 = 0$ and $\phi_N = 1$. The recursion equation can be rearranged as

$$
T_j^+ \underbrace{(\phi_{j+1} - \phi_j)}_{a_{j+1}} - T_j^- \underbrace{(\phi_j - \phi_{j-1})}_{a_j} = 0. \tag{1.4}
$$

Denoting $\gamma_j = \frac{T_j^-}{T_j^+}$, we have

$$
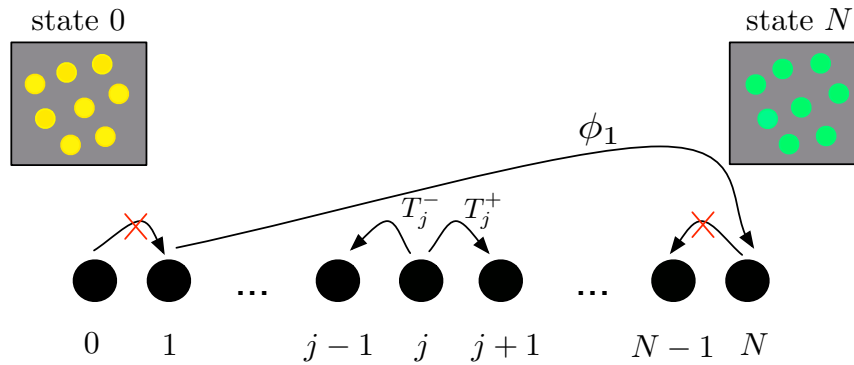a_{j+1} = \gamma_j a_j. \tag{1.5}
$$

Figure 1.2: The Markov chain of a Moran process. In a population with two types (the green type and the yellow type), the state space consists of the possible numbers of green individuals (the numbers in the bottom). The number of green individuals increases by one when one green individual reproduces and one yellow individual dies, remains the same when the two individuals sampled (one to reproduce and one to die) are both the same type, and decreases by one when the one yellow individual reproduces and one green individual dies. Suppose there are j green individuals at the current state. The probabilities that the three events happen are denoted as T_j^+, $1 - T_j^+ - T_j^-$, and T_j^- respectively. Given enough time, the population will end up in state 0 or state N. The probability to eventually go from state 1 to state N is the fixation probability of a single green type, denoted by ϕ_1.

Using the definition of a_j in Eq. 1.4 and Eq .1.5, we obtain

$$
\begin{aligned}
a_1 &= \phi_1 - \phi_0 = \phi_1 \\
a_2 &= \phi_2 - \phi_1 = \gamma_1 \phi_1 \\
&\vdots \\
a_k &= \phi_k - \phi_{k-1} = \phi_1 \prod_{j=1}^{k-1} \gamma_j \\
&\vdots \\
a_N &= \phi_N - \phi_{N-1} = \phi_1 \prod_{j=1}^{N-1} \gamma_j \ .
\end{aligned}
\tag{1.6}
$$

The sum over all a_j is

$$
\begin{aligned}
\sum_{k=1}^{N} a_k &= \phi_1 - \phi_0 + \phi_2 - \phi_1 + \phi_3 - \phi_2 + \ldots + \phi_{N-1} - \phi_{N-2} + \phi_N - \phi_{N-1} \\
&= -\phi_0 + \phi_N = 1.
\end{aligned}
\tag{1.7}
$$

On the other hand, the sum over all a_j can also be written as

$$
\sum_{k=1}^{N} a_k = \phi_1 \left(1 + \sum_{k=1}^{N-1} \prod_{j=1}^{k} \gamma_j \right).
\tag{1.8}
$$

Using Eq. 1.7 and Eq. 1.8, the fixation probability of a single green type individual, ϕ_1, is given by

$$
\phi_1 = \frac{1}{1 + \sum_{k=1}^{N-1} \prod_{j=1}^{k} \frac{T_j^-}{T_j^+}} \ .
\tag{1.9}
$$

For intermediate states i, we have

$$
\begin{aligned}
\phi_i &= \phi_1 - \phi_0 + \phi_2 - \phi_1 + \phi_3 - \phi_2 + \ldots + \phi_{i-1} - \phi_{i-2} + \phi_i - \phi_{i-1} \\
&= \sum_{k=1}^{j} a_k \\
&= \phi_1 \left(1 + \sum_{k=1}^{i-1} \prod_{j=1}^{k} \gamma_j \right) \\
&= \frac{1 + \sum_{k=1}^{i-1} \prod_{j=1}^{k} \gamma_j}{1 + \sum_{k=1}^{N-1} \prod_{j=1}^{k} \gamma_j} \ .
\end{aligned}
\tag{1.10}
$$

Under neutral evolution, all individuals have the same fitness. Thus, we have $T_j^- = T_j^+$ and $\gamma_j = 1$. Putting these in Eq. 1.9 and Eq. 1.10, we obtain $\phi_1 = 1/N$ and $\phi_i = i/N$.

When mutations happen, there are potentially more than two types in the population. No type will be fixed nor exist in the population forever. In such a system, quantities other than fixation probabilities are required to understand the population dynamics.

1.2.3 Wright-Fisher process

In a Wright-Fisher model, discrete generations are considered. Instead of having one individual reproduce in one time step (as in a Moran process), all individuals reproduce at the same time. Thus, one time step is one generation in a Wright-Fisher process. There are two events happening in one time step, reproduction and sampling. In every generation, all individuals reproduce proportionally to their fitness. The descendants form a large offspring pool. In the next generation, all individuals from the previous generation die, and are replaced by a random sample of N individuals from the offspring pool [13].

A population with two types corresponds to a binomial sampling, and a population with more than two types corresponds to a multinomial sampling. If there is no fitness difference, the composition of the population will only be changed by random genetic drift. When the fitness of different types varies, the expected number of offspring of a certain type is in proportion to its fitness.

Similar to a Moran process, a Wright-Fisher process can also be considered with or without mutations. When there are mutations, an individual produces an offspring of its own type with probability $1 - \mu$ and an offspring of a new type with probability μ. Note the unit of μ here is per individual per generation, and the mutation rate of the whole population per generation is

$N\mu$.

An example for a possible transition in a Wright-Fisher process is shown in Fig. 1.3, where a population composed by two types without mutations is considered. The fitness of the green type is W_1, and the fitness of the yellow type is W_2. This process can be characterized by a Markov chain with state space $\{0, ..., N\}$. State i corresponds to the number of green type individuals. There are two absorbing states, state 0 and state N. The transition probability from a state i to a state j, P_{ij} is

$$P_{ij} = \binom{N}{j} \left(\frac{iW_1}{iW_1 + (N - i)W_2} \right)^j \left(\frac{(N - i)W_2}{iW_1 + (N - i)W_2} \right)^{N-j}. \qquad (1.11)$$

Under neutral evolution, the fixation probability of a single individual of the green type is $1/N$.
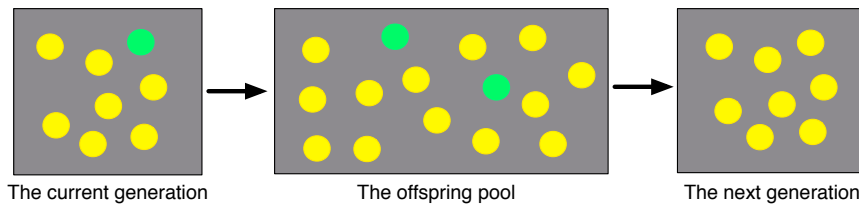
Figure 1.3: A classical Wright-Fisher model is based on a population with two types (the green type and the yellow type) and constant size N. In the current generation, every individual produces a large number of identical offspring, and dies. The reproduction can be neutral or under selection, where in the latter case the number of offspring of an individual is proportional to its fitness. N individuals are sampled at random to form the population in the next generation.

In population genetics, the Moran process is used less frequently than the Wright-Fisher process [13]. However, the Moran process allows explicit analytical solutions for the fixation probabilities, which is difficult for the Wright-Fisher process [73]. In the Moran process, one individual reproduces at one time step, but in the Wright-Fisher process, all individual reproduce at the same time. In an extreme case, the population can come from a single ancestor in one generation (one time step) in a Wright-Fisher process. This is the basic difference of these two processes. For weak selection intensity (see section 1.3.3) and large population size, the dynamics of these two process can be very similar [51, 74]. When selection intensity is strong or population size is small, these two processes can result in very different dynamics (see our publications in Chapter 3). For computer simulations, a Wright-Fisher process is much faster than a Moran process, given the same population size.

In Chapter 2, the Moran process is employed, as it is possible to compare the analytical results with the simulation results for a population with only two types. In Chapter 3, mutations are considered, which results in a much more complex system where analytical solutions are not always possible. We use both the Moran process and the Wright-Fisher process to obtain our simulation results.

1.3 Constant and frequency dependent selection

So far, we have not specified fitness. Is the fitness of an individual of a particular type a constant number? Does it depend on other variables, for example, the composition of the population? How do different fitness specifications effect the evolutionary dynamics? In this section, we discuss different assumptions on fitness configuration and the comparison of those assumptions. The resulting dynamics are discussed in the publications in Chapter $2 - 4$.

1.3.1 Constant selection

In population genetics models, fitness is typically assumed to be constant for haploid populations [42, 61]. Assume that a population has non-overlapping generations with only two types, A and B. The absolute fitness is defined as the average number of offspring that an individual of a certain type has in the next generation. The number of type A individuals in the next generation, N'_A, is given by the product of the number of type A individuals, N_A, and their absolute fitness W_A. The same argument holds for type B, where N'_B and N_B are the number of individuals of type B in the next and the current generation. These can be written as

$$
\begin{aligned}
N'_A &= W_A N_A \\
N'_B &= W_B N_B
\end{aligned}
\tag{1.12}
$$

Given that x_A and x_B are the frequencies of type A and type B in the population, and that x'_A is the frequency of type A in the next generation, we

have

$$
\begin{aligned}
x'_A &= \frac{W_A N_A}{W_A N_A + W_B N_B} \\
&= \frac{W_A x_A}{W_A x_A + W_B x_B} \\
&= \frac{\alpha x_A}{\alpha x_A + 1 - x_A} \, ,
\end{aligned}
\tag{1.13}
$$

where $\alpha = \frac{W_A}{W_B}$. Suppose the fitness of type B is 1 and the relative fitness of type A is $1 + s$. Here, we have $s = \alpha - 1$, and thus $s \geq -1$. In population genetics, s is called selection coefficient [75]. If s is positive, type A has a greater relative fitness than type B, and vice versa. For strict constant selection in a haploid population, s is a constant number. In this case, the dynamics of the population is only density dependent, but not frequency dependent. It is hard to find evidence for strict constant selection in natural populations [16]. However, the assumption that s is independent from the frequencies of different types, or even constant in a haploid population, has proved to be useful in many theoretical and experimental studies [76, 77, 78, 79, 80].

1.3.2 Frequency dependent selection and diploidy

In population genetics, frequency dependent selection arises from sexual reproduction [42, 12, 81]. As most sexual species are diploids, we focus on diploid populations where the fitness of alleles is frequency dependent due to the combination of two alleles at one locus. It is useful to connect the allele frequencies with genotype frequencies. Because frequency dependent selection is on alleles, but the reproduction unit is on genotypes. Suppose A and B are two alleles at the same locus, x_A and $1 - x_A$ are the frequencies of these two alleles. Under random mating, the frequencies and the fitness of different genotypes are given as follow:

Genotype	AA	AB	BB
Fitness	W_{AA}	W_{AB}	W_{BB}
Frequency	x_A^2	$2x_A(1-x_A)$	$(1-x_A)^2$

.

In this table, the fitness of genotype AB and BA is considered identical, and the maternal allele and paternal allele are equally expressed. If the mating is random, the formulation of the genotype frequencies above always holds whether selection is neutral or not. Under neutral evolution ($W_{AA} = W_{AB} = W_{AB}$), the allele and genotype frequencies will remain the same over generations, which is called Hardy-Weinberg equilibrium [82, 83, 84].

The frequencies of genotypes and alleles change when there are fitness differences among the three genotypes. When the allele frequencies do not change (and thus the genotype frequencies remain constant under random mating), we call it an equilibrium of the population. One way to describe the changes of alleles frequencies and to find such an equilibrium is to calculate the fitnesses of alleles. Allele A can be found in genotype AA or AB. The fitness of allele A, W_A, can be written down by summing up the fitness of genotype AA and AB weighted by the frequencies of allele A in them,

$$
\begin{aligned}
W_A &= \frac{2x_A^2}{2x_A^2 + 2x_A(1-x_A)}W_{AA} + \frac{2x_A(1-x_A)}{2x_A^2 + 2x_A(1-x_A)}W_{AB} \\
&= x_A W_{AA} + (1-x_A)W_{AB} \ .
\end{aligned}
$$

(1.14)

Similarly, we have $W_B = x_A W_{AB} + (1-x_A)W_{BB}$. In these two equations, fitness depends linearly on the composition of the population. This method of implementing fitness in diploids is mathematically equivalent to a symmetric pairwise-interaction game in evolutionary game theory, as we will see in the next section.

1.3.3 Frequency dependent selection in evolutionary game theory

Evolutionary game theory is based on the assumption that fitness is frequency dependent, including constant selection as a special case. Frequency dependent selection was initially proposed in population genetics, but it seems to remain a special case. In population genetics, the interpretation of frequency dependent selection on alleles is based on the genetic mechanism of inheritance, for example, diploidy. In evolutionary game theory, frequency dependent selection arises from a different mechanism, the interactions of different types. The differences between these two frameworks in the interpretation of frequency dependent fitness are more obvious in haploid populations, where fitness is typically assumed constant in population genetics models.

Evolutionary games

First, we consider a population with two types (a single haploid locus with two alleles), A and B. The frequencies of these two types are x_A and $1 - x_A$, and the corresponding fitness values are W_A and W_B. The simplest case is when fitness depends linearly on frequencies, where

$$W_A = a x_A + b \left(1 - x_A\right),$$
$$W_B = c x_A + d \left(1 - x_A\right). \tag{1.15}$$

Here, a, b, c and d are coefficients, which can be written down in a matrix as follow

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

The first row refers to type A, and the second row refers to type B.

We can also go the other way around, from matrix to fitness. In evolutionary game theory, different types of individuals interact in a game. The payoffs of individuals in specific pairwise interactions are captured by the payoff matrix. When a type A individual confronts a type A individual, it has a payoff a. Correspondingly, it has a payoff b if interacting with a type B individual, and so forth. In a well-mixed population, the probability to meet an A individual is its frequency, x_A, the probability to meet a B individual is $1 - x_A$. Thus, the average payoff of type A individuals is given by Eq. 1.15. Interestingly, the fitness expressions (Eq. 1.15) in a haploid population are mathematically equivalent to the fitness expressions of alleles in a diploid population (Eq. 1.14), if $b = c$ [59, 85, 41].

A general case is an evolutionary game between more than two types, where the size of the payoff matrix needs to be expanded to accommodate the number of types in the population. In summary, the payoff matrix is one way to implement linear frequency dependent selection. There are also non-linear frequency dependent models in evolutionary game theory [86], but they are not the focus of this thesis.

Stable and unstable equilibria in infinite populations

In Section 1.2.1 (Replicator dynamics), the equilibria of a population were defined as states, where the changes of frequencies of different types are 0. An equilibrium is stable if every trajectory starting near this state always converges towards it [87, 9]. Otherwise, it is unstable. Maynard-Smith and Price proposed a way to identify stable equilibria of the replicator dynamics by comparing the fitness changes around these equilibria [5]. Here, examples are given in the case of two-type games. The replicator equation based on Eqs. 1.15, is

$$\dot{x}_A = x_A(1 - x_A)\left[(a - b - c + d)x_A + b - d\right]. \tag{1.16}$$

There are at most three equilibria for this equation, $x_A = 0$, $x_A = 1$, and $x_A^* = \frac{d-b}{a-b-c+d}$. The third equilibrium x_A^* exists only if $a < c$ and $b > d$ or $a > c$ and $b < d$. Otherwise, x_A^* is not in the interval $[0, 1]$. We discuss the stability of these three equilibria separately (see Fig. 1.4):

- $x_A = 0$. If $W_A < W_B$, the frequency of type A individuals decreases for small x_A. Thus, the population moves to $x_A = 0$, and this equilibrium is stable. Since $W_A = b$ and $W_B = d$ at $x_A = 0$, the condition of stability in this point can be simplified to $b < d$.

- $x_A = 1$. If $W_A > W_B$, the frequency of type A individuals increases for $x_A \approx 1$. The population moves to $x_A = 1$, and the equilibrium is stable. As $W_A = a$ and $W_B = c$ at $x_A = 1$, this equals the condition $a > c$.

- x_A^*. The interior equilibrium is stable, if $\frac{d(W_A - W_B)}{dx_A} < 0$. Let us see how x_A changes in a small environment around x_A^* under this condition. If $x > x_A^*$, $W_A(x) - W_B(x) < W_A(x_A^*) - W_B(x_A^*) = 0$. The frequency of type A will decrease, and the population will move to $x = x_A^*$. If $x < x_A^*$, $W_A(x) - W_B(x) > W_A(x_A^*) - W_B(x_A^*) = 0$. The frequency of type A

will increase, and the population will also move to $x = x_A^*$. Using Eqs. 1.15, we obtain $\frac{dW_A}{dx_A} = a - b$ and $\frac{dW_B}{dx_A} = c - d$. Thus, x_A^* is stable if $a - b < c - d$. Combined with the condition for the existence of this interior equilibrium, we have $a < c$ and $b > d$.
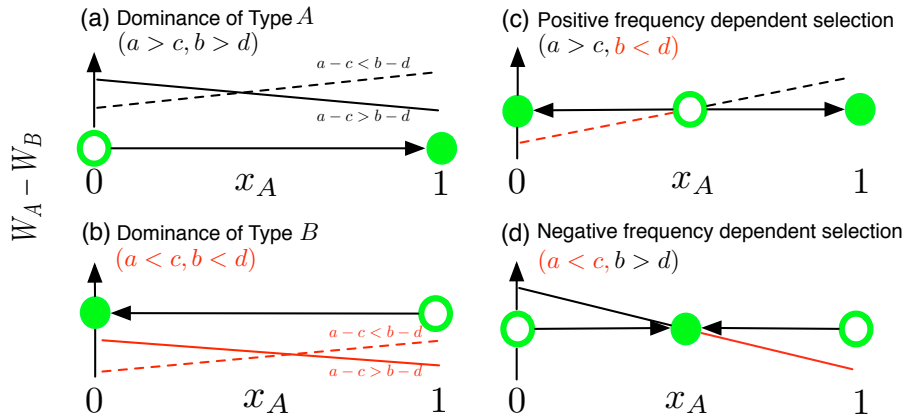

Figure 1.4: The stability of equilibria in an infinite population with two types. The fitness difference between type A and type B, $W_A - W_B$, is a linear function of the frequency of type A, x_A. According to Eqs. 1.15, the fitness difference is $b - d$ at $x_A = 0$, and $a - c$ at $x_A = 1$. The slope of the linear function is larger than 0 if $a - c < b - d$ (dashed lines), or smaller than 0 if $a - c > b - d$ (solid lines). In panel (a) and (b), there are only two equilibria; in panel (c) and (d), there is an interior equilibrium besides of the two boundary equilibria. When $W_A - W_B > 0$, x_A will increase, which is represented by black lines. When $W_A - W_B < 0$, x_A will decrease, which corresponds to red lines. An equilibrium is stable, when the population returns back to this equilibrium after any small deviation, which is shown by direction of the arrows in the x-axis.

Selection intensity and selection coefficient

In an infinite population, the relative fitness of a type can be represented by its average payoff. Those types with higher payoffs will have higher reproduction rates. When the population size is finite, there is another step to map the payoff π to the fitness W. This involves another parameter called selection intensity β. We use an exponential fitness mapping function in all of our finite population models in this thesis [88]. That is

$$W = e^{\beta\pi}, \qquad \beta \geq 0. \tag{1.17}$$

There are many other possible fitness mapping functions, for example, a linear fitness function, $W = 1 - \beta + \beta\pi$ [9]. We use exponential mapping function to avoid negative fitness values for any selection intensities. For small β, the exponential fitness mapping function can be expressed as $W \approx 1 + \beta\pi$. Thus, these two fitness mapping functions are approximately the same if β is small.

One way to understand the meaning of selection intensity in this equation, is to look at the relative fitness difference of two types. Suppose the fitness of the second type is 1. The relative fitness of the first type can be written as $W_1/W_2 = e^{\beta\Delta\pi}$, where $\Delta\pi = \pi_1 - \pi_2$ is the payoff difference. Thus, the relative fitness difference is $e^{\beta\Delta\pi} - 1$. When $\beta = 0$, the relative fitness difference is 0 and unrelated to the payoff difference. This refers to neutral evolution. When $\beta > 0$, the payoff difference $\Delta\pi$ will be transfered into the relative fitness difference. For a fixed $\Delta\pi$, the larger β is, the larger the relative fitness difference is. When β is infinitely large but $\Delta\pi$ is not infinitely small, the selection intensity is infinitely strong.

In Chapter 2, we expand the exponential fitness mapping function in Eq. 1.17 to the second order at $\beta = 0$, and we have $W \approx 1 + \beta\pi + \frac{\beta^2}{2}\pi^2$. If $0 < \beta\Delta\pi \ll 1$, selection is considered to be weak. Weak selection is a particular interesting parameter range. It has attracted a lot of attention in biology

[89, 90, 91]. In addition, analytical solutions are more likely to be obtained under such a condition [92, 93, 94].

In population genetics, selection coefficient s is used to denote the relative fitness difference. If $s = 0$, the two types have the same reproduction rate. If $s = 0.1$, the favored type produces 10% more offspring than the other type. Under neutral evolution, $s = 0$ has the same meaning as $\beta = 0$ in dynamical models. When selection is not neutral, the effects of the two parameters differ. In evolutionary game theory, the definition of the relative fitness difference includes two parts, the difference of payoffs $\Delta\pi$, and the selection intensity β. In population genetics, these two parts are not distinguishable, and are absorbed into a single parameter s.

1.4 Frequency dependent mutant model

1.4.1 Random mutant model with two types

How can the concept of frequency dependent random mutants be incorporated in evolutionary game theory? We start from the simplest case with only two types. Suppose that a mutant type A appears in a population with only wild type B individuals. In evolutionary game theory, the interaction of these two types can be described by a 2×2 payoff matrix,

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

Since the population is initially homogenous, only the payoff entry of a wild type interacting with another wild type, d, is known. There are three unknown payoff entries, a, b and c. Since the fitness of a mutant is unknown and maybe unpredictable, we define a, b and c as random numbers following a certain probability distribution. In the simplest case, we assume that the

three random numbers are taken from the same distribution named as payoff distribution. Mathematically, the payoff distribution can be independent or dependent of d. Here, we assume the latter case, which corresponds to the concept of fitness distribution from population genetics.

1.4.2 Payoff distribution and fitness distribution

In population genetics, mutations are often be classified as deleterious, neutral or advantageous. However, the fitness of mutations is a continuum of effects rather than a group of discrete numbers. The probabilities of these continuous variables follow a distribution within a certain interval, which is called fitness distribution [95, 80]. Different approaches have been used to study the fitness distribution, but it is very difficult to reach a common conclusion about its accurate shape.

The most accurate investigation of fitness distribution is to measure the fitness effects of single mutations. Most of this kind of experiments are done in microorganisms, as they would require too much time in other species [80]. Sanjuan et al. studied mutations caused by single nucleotide substitutions in an RNA virus [96], where the fitness distribution of deleterious mutations is described by a log-normal distribution. Among all mutations, 40% of random mutations are considered lethal. A best fit for beneficial mutations is a gamma distribution. However, since observed beneficial mutations are much less frequent than deleterious mutations, no distribution for the whole range of fitness values is inferred by this study. Cowperthwaite et al. suggested a Gumbel distribution of beneficial fitness effects in RNA [97]. Elena et al. recorded the fitness effects of random insertion mutations in *Escherichia coli* [98]. In this study, the possibility that a strain has more than one insertion mutation can not be excluded. But it is claimed that background mutations are not an important factor due to the low genomic mutation rate. The fre-

quencies of different mutant fitness values follow a compound gamma plus uniform distribution. More than 80% of mutations are classified as deleterious mutations, and no mutations with significant positive effect are identified. Here, we only list some examples, and there are many other similar experiments [99, 100, 101], which lead to various conclusions regarding the fitness distribution. One common problem of measuring the fitness distribution of single mutations is that it is only possible to detect large fitness effects [80]. Thus, a general fitness distribution of mutations with various fitness effects is hard to obtain.

In summary, a general conclusion on the accurate shape of the fitness distribution has not been made, but it is possible to estimate the mean or the percentage of beneficial mutations. Instead of assuming a concrete density function for the payoff distribution (see the definition in last section), we consider an arbitrary distribution $f(x)$, and address either the moments of $f(x)$ (Chapter 2) or the probability that the new payoffs are larger than the payoff of the parent type (Chapter 4).

When we look for the proper quantities to represent the population dynamics, we are especially interested in those which can be obtained independent of the concrete shape of the payoff distribution. For a finite population with only two types, one of such important quantities is the fixation probability ϕ_1 of a random mutant under different selection intensities. In a infinite population with two types, the probability that the average population fitness increases due to a random mutant, has similar properties.

It is worth to point out there is a difference between the fitness distribution in population genetics and the payoff distribution in our model. In population genetics, the concept of fitness distribution is based on constant selection. The fitness of a mutant is one number measured in one time point, and the experiments are repeated many times to infer such a distribution. Under frequency dependent selection, the fitness of a mutant changes with the composition of

the population. Thus, one measurement at one time point can not represent all the properties of the fitness. In our model, we do not assume the fitness of a mutant follows a distribution. Instead, the payoff values, which describe the interactions of the mutant type with the wild type, are obtained from the payoff distribution.

When we choose the payoff distribution, ideally we should consider the shapes or some parameters based on the payoff distributions inferred by the experiments. However, since the concept of frequency dependent selection still needs to be absorbed into such experiments, we assume a null model for the payoff distribution.

1.4.3   Random mutant games with n types

The evolutionary game dynamics with n types of individuals is based on an $n \times n$ payoff matrix. The payoff of a type i individual when it interacts with a type j individual is the entry a_{ij} in the payoff matrix. The average payoff of an i type individual is a function of its corresponding payoffs and the frequencies of all types, $\pi_i = \sum_i^n a_{ij} x_i$. In the payoff matrix, every type is represented by one row (the payoffs of this particular type interacting with different types), and one column (the payoffs of different types interacting with this type). When a mutant appears, the payoff matrix is extended by an additional column and an additional row. When one resident type goes extinct, its corresponding column and row are deleted.

There are different ways to choose the new payoff entries appearing together with a mutant type, see Fig. 1.5. When all the payoff entries in the same row are identical, as in Fig. 1.5(a), we recover the case of constant selection. Only one number is required to describe the mutant type, and this number is related to the payoff of its parent type. In Fig. 1.5(b), the new payoff entries are drawn from a distribution related to the same number which is

not associated to the current payoff entries. In Fig. 1.5(c), the new payoff entries are drawn from the same distribution related to the payoff of the parent type interacting with another parent type. Another option is shown in Fig. 1.5(d), where the payoff of a mutant interacting with any resident type is related to the payoff of the parent type interacting with the same resident type. We think that Fig. 1.5(d) is a more reasonable case in biological applications, because the fitness of a mutant is most close to its parent type compared with other resident types in this case. When there are only two types (the wild type and the mutant type), Fig. 1.5(c) and Fig. 1.5(d) are identical.
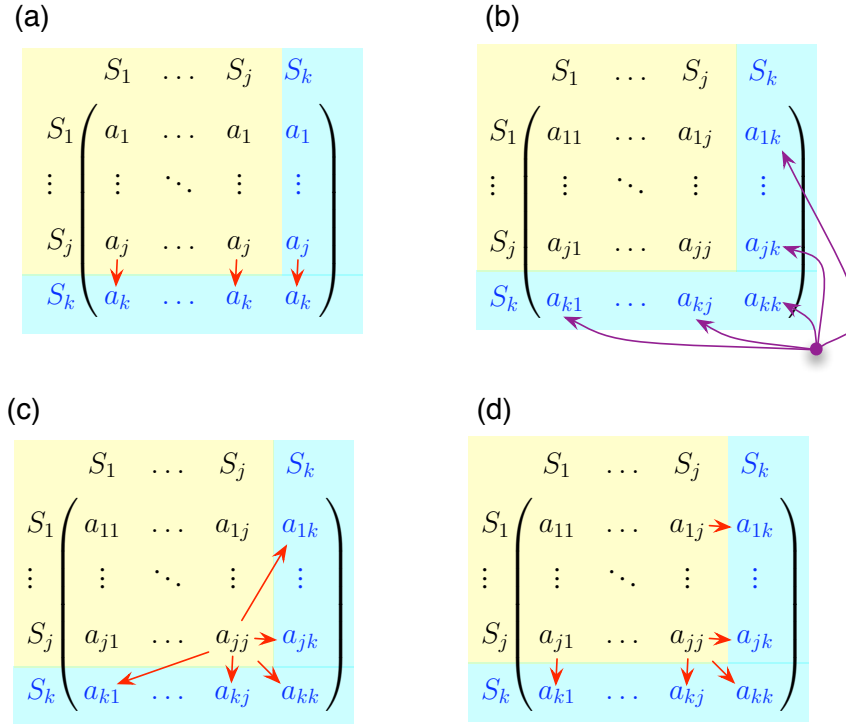
Figure 1.5: Different ways to add a mutant type S_k to the payoff matrix. (a) For constant selection, the new column is identical to all previous columns. The new line is a single random number derived from the parent of the mutated individual. (b) All new payoff entries are chosen from the same distribution with no relation to the mutant's parent. (c) The new payoff entries are chosen from a distribution with mean a_{jj}, where j is the mutant's parent. (d) All new payoff entries are chosen from a distribution with mean of the corresponding payoff entry of the mutant's parent, i.e. a_{ki} has mean a_{ji} and a_{ik} has mean a_{ij}.

Fixation probability in the frequency dependent mutation model with two types

2.1 Fixation probability of random mutants under frequency dependent selection

One important concept in evolutionary dynamics is the fixation probability [9]. In a finite population, the success of a type depends not only on selection, but also on the underlying stochastic processes. Fixation is often studied in models, where the fixation or the lost of a mutant type is assumed to happen before the next mutation event [12]. The mutation rate is low enough that most of the time only two types, the mutant type and the wild type, exist in the population at the same time. How small the mutation rate has to be to fulfill such an assumption? It has been shown by numerical simulations that $\mu N^2 \ll 1$ is a sufficient condition if there is no stable coexistence of the two types [102, 103]. The corresponding analytical result was given as $\mu \ll N \ln N$ [104]. If the two types stably coexist, it may take much longer time until one of them get fixed in the population. For such a situation, the mutation rate is necessary to be smaller than $N^{(-1/2)} e^{-N}$ [104].

In finite populations with constant population size, the fixation probability of mutant genes in one locus has been discussed extensively [105, 106, 66,

42]. Under constant selection, an advantageous mutant can be lost, and a deleterious mutant can be fixed. Haldane calculated the fixation probability of a single mutant [105]. The number of offspring of an individual is assumed to follow a Poisson distribution. Only the beneficial mutants have the chance to be fixed. The relative fitness advantage of a beneficial mutant type is s. In a large population, the fixation probability of a single beneficial mutant is approximately $2s$, valid for small selective advantage, $s \ll 1$.

If selection is frequency dependent, mutants can have various fitness properties, instead of being either beneficial or deleterious. A mutant type may be advantageous when it is rare, but its fitness decreases when its frequency increases and it becomes disadvantageous once its frequency reaches a threshold. In such a biological system, the fixation probabilities of mutants are more complicated quantities.

Kimura generalized the model of Haldane to the case of frequency dependent selection in a diploid population under random mating [107, 71]. Suppose the fitness of the wild type homozygote, the mutant homozygote and the heterozygote, are s, $1+s$ and $1+sh$ respectively. If the mutant allele is recessive, the heterozygote has the same fitness as the wild-type homozygote and we have $h = 0$. In the opposite, if the wild-type gene is recessive, the heterozygote has the same fitness as the mutant homozygote and we have $h = 1$. For a nearly recessive mutant allele ($0 < h \ll 1$) with positive selective coefficient ($s > 0$), the fixation probability has been derived [71].

The model proposed by Kimura refers to a specific frequency dependent selection. First, frequency dependent selection arise from symmetric diploidy, where the maternal allele and the paternal allele are assumed to be equally expressed. Second, the assumptions of positive selective coefficient and nearly recessive mutant alleles, make the results valid for an even smaller group of mutants.

In this section, the same question is addressed based on the frequency de-

pendent mutant model in an evolutionary game theoretic framework. A haploid population with two types, the mutant and the wild type, is considered. Frequency dependent selection comes from the interactions of the mutant and the wild type, which are captured by payoff matrices. The new payoff entries introduced by mutations are variables independently drawn from the same payoff distribution. This leads to all types of frequency dependent selection.

Under weak selection, we approximate the fixation probability by the Taylor series expansion at $\beta = 0$. Here, β is the selection intensity (see section 1.3.3). A Taylor series of a function is a polynomial approximation, which is an infinite sum of terms that are calculated from the derivatives of this function at a single point [108]. The first few terms of the Taylor series are often sufficient to approximate a function around that point. The more terms are considered, the more accurate an approximation is. Interestingly, under weak selection the fixation probability of a single mutant only depends on the first moments of the payoff distribution, such as the mean and the variance.

Under strong selection, we classify the interactions of the mutant type and the wild type into different cases, and obtain the fixation probability of a single mutant by summing up the fixation probabilities for all cases. It is shown, that the only thing matters is the probability that the mutant payoff entries are larger than the corresponding payoff entires of its parent type.

For the intermediate selection intensities, simulations are performed based on the Moran process. In the simulations, we need a concrete distribution to generate random payoff entries. Here, we use a Gaussian distribution with mean d, the payoff value of a wild type interacting with another wild type.

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Fixation probabilities of random mutants under frequency dependent selection

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ABSTRACT

Evolutionary game dynamics describes frequency dependent selection in asexual, haploid populations. It typically considers predefined strategies and fixed payoff matrices. Mutations occur between these known types only. Here, we consider a situation in which a mutation has produced an entirely new type which is characterized by a random payoff matrix that does not change during the fixation or extinction of the mutant. Based on the probability distribution underlying the payoff values, we address the fixation probability of the new mutant. It turns out that for weak selection, only the first moments of the distribution matter. For strong selection, the probability that a new payoff entry is larger than the wild type's payoff against itself is the crucial quantity.

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1. Introduction

Evolutionary game theory is a method to study frequency dependent selection in asexual populations (Maynard Smith, 1982; Weibull, 1995; Hofbauer and Sigmund, 1998, 2003; Cressman, 2003; Nowak and Sigmund, 2004). Whenever the fitness of the individuals depends on the composition of the population, the dynamics of the evolving population can be described based on an evolutionary game. Constant selection, where the fitness of a type is fixed, can be considered as a special case in this context, where the payoff depends only on the strategy, but not on the frequencies of other types in the population.

The standard approach to evolutionary game dynamics is the replicator dynamics (Taylor and Jonker, 1978; Hofbauer et al., 1979; Zeeman, 1980). It describes the change in frequency x_i of strategy i as $\dot{x}_i = x_i(\pi_i - \langle \pi \rangle)$, where π_i is the payoff of strategy i and $\langle \pi \rangle$ is the average payoff in the population.

More recently, the focus of research has turned to finite populations. The most popular model for evolutionary game dynamics in finite populations is the frequency dependent Moran process introduced by Nowak et al. (2004). Although, mutations are often disregarded, they can be incorporated without any problems. Typically, the mutations produce types that are predefined in the payoff matrix and one considers the mutation–selection equilibria of the system (Bomze and Buerger, 1995; Nowak et al., 2004; Imhof et al., 2005; Imhof and Fudenberg,

2006; Traulsen et al., 2009; Antal et al., 2009a–c; Van Segbroeck et al., 2009).

Here, we consider a different possibility in which mutants are characterized by a new payoff matrix game with randomly chosen entries. For low mutation rates, only one mutant is present at a time. The average fixation time under neutral selection is N generations. Thus, it is unlikely that several mutants are present at the same time when the mutation rate μ fulfills $\mu \ll N^{-2}$. This estimate holds for situations in which the mutant is advantageous or disadvantageous for all abundances or if it is first disadvantageous and becomes advantageous at high abundances (Antal and Scheuring, 2006). When there is a stable coexistence between the types, however, the average fixation time diverges exponentially with the intensity of selection and the population size. In this case, our approach is only valid when the mutation rates go to zero. When the mutation rate is low, the crucial quantity of the population dynamics is the fixation probability ϕ_1, the probability that a new mutant takes over the population. We address the fixation probability for the simple case of a 2×2 game. The entries of the payoff matrix, however, are chosen from a probability distribution, excluding the interaction of the wild type with itself, which should not be affected by the mutation. But during the course of evolution, the payoff matrix remains fixed. Due to the probabilistic payoff matrix, the fixation probability ϕ itself becomes a random number. Since Kimura (1968) introduced the neutral theory, many evolutionary biologists believe that changes in evolutionary confer only small or even vanishing selective advantages. It is very unlikely that a new mutation leads to a large selective advantage in a well adapted population. Thus, small intensities of selection seem to be biologically highly

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relevant (Ohta, 2002). It turns out that in our case, weak selection approximation corresponds to a moment expansion of the probability distribution, such that only the first few moments of the probability distribution of the payoff values matter. On the other hand, for strong selection the fixation probability is governed by the probability that a random mutant can invade the population.

The remainder of this paper is organized as follows: in Section 2, we recall the Moran process as a standard model of frequency dependent evolutionary dynamics in finite populations. In Section 3, we address payoff matrices with Gaussian distributed entries and generalize the findings to arbitrary distributions in Section 4. Finally, in Section 5 we discuss how our findings relate to fitness distributions found empirically, based on frequency independent selection, and relate our results to this scenario.

2. The Moran process and fixation probabilities

To model frequency dependence, we consider two player games, which can be represented by the payoff matrix

$$\begin{array}{c} \\ A \\ B \end{array} \begin{array}{c} A \quad B \\ \begin{pmatrix} a & b \\ c & d \end{pmatrix}. \end{array}$$

When A interacts with another A, it obtains a, and when it interacts with any B, it obtains b. Similarly, B obtains c or d, when interacting with A or another B, respectively. Assuming there are i type A individuals and $N-i$ type B individuals, the average payoffs of A and B in a mixed population are

$$\pi_A = \frac{i-1}{N-1}a + \frac{N-i}{N-1}b, \tag{1a}$$

$$\pi_B = \frac{i}{N-1}c + \frac{N-i-1}{N-1}d. \tag{1b}$$

Here, we have explicitly assumed that there are no self-interactions. Note that the payoff difference is always a linear function in i,

$$\Delta\pi = \pi_B - \pi_A = ui + v, \tag{2}$$

where $u = (-a+b+c-d)/(N-1)$ and $v = (a-Nb+Nd-d)/(N-1)$. The impact of the game on fitness is determined by the intensity of selection β. While commonly it is assumed that fitness f is a linear function for the payoffs, it is often mathematically more convenient to choose f as an exponential function of the payoff. Both approaches can be justified by mathematical simplicity. But the exponential function allows to address a strong selection limit, that can be relevant in specific biological situations where a certain trait is necessary for survival, e.g. resistance towards toxins. Moreover, the exponential function guarantees that fitness is always positive, even when the payoffs π are negative (Traulsen et al., 2008). This leads to

$$f_A = e^{+\beta\pi_A}, \tag{3a}$$

$$f_B = e^{+\beta\pi_B}. \tag{3b}$$

We consider this game in the context of a frequency dependent Moran process (Nowak et al., 2004; Taylor et al., 2004; Antal and Scheuring, 2006). Suppose there is a finite population of N individuals. One individual is chosen at random, but proportional to fitness, to give birth to a new individual of the same type. Before the new offspring is added, one individual chosen at random is removed to keep the population size constant. The probability to increase the number of type A individuals from i to $i+1$ is T_i^+, and the probability to decrease the number of type A

individuals from i to $i-1$ is T_i^-. For the Moran process, we have

$$T_i^+ = \frac{if_A}{if_A + (N-i)f_B} \frac{N-i}{N}, \tag{4a}$$

$$T_i^- = \frac{(N-i)f_B}{if_A + (N-i)f_B} \frac{i}{N}. \tag{4b}$$

Due to the choice of an exponential function as payoff to fitness mapping, the ratio of the transition probabilities becomes particularly simple,

$$\frac{T_i^-}{T_i^+} = \frac{f_B}{f_A} = e^{+\beta(\pi_B - \pi_A)}. \tag{5}$$

In the absence of mutations, we have $T_0^+ = 0$ and $T_N^- = 0$, cf. Eqs. (4). Thus, there are two absorbing states, the state with all A and the state with all B. The fixation probability ϕ_i describes the probability of i type A individuals to take over the entire population. Obviously, the fixation probabilities fulfill the equation $\phi_i = T_i^- \phi_{i-1} + T_i^+ \phi_{i+1} + (1 - T_i^- - T_i^+)\phi_i$, see e.g. (Goel and Richter-Dyn, 1974) for a full derivation. Solving this recursion with the boundary conditions $\phi_0 = 0$ and $\phi_N = 1$ leads to (Nowak, 2006; Antal and Scheuring, 2006)

$$\phi_i = \frac{1 + \sum_{k=1}^{i-1} \prod_{i=1}^{k} \frac{T_i^-}{T_i^+}}{1 + \sum_{k=1}^{N-1} \prod_{i=1}^{k} \frac{T_i^-}{T_i^+}}. \tag{6}$$

In particular, we are interested in ϕ_1, for which the enumerator is simply one. Together with Eq. (5), we can write ϕ_1 as

$$\phi_1 = \frac{1}{1 + \sum_{k=1}^{N-1} \exp[+\beta \sum_{i=1}^{k} (\pi_B - \pi_A)]}. \tag{7}$$

The two sums in Eq. (7) can be solved analytically, leading to closed expressions for the fixation probabilities (Traulsen et al., 2007a). However, for our numerical and analytical considerations, we consider Eq. (7) in the form given above.

3. Fixation of random mutants

We consider type B as the wild type and type A as the mutant type. Typically, one is interested in the fixation probability of a mutant with fixed values in the payoff matrix. But sometimes, the payoff of the mutant may not be fixed or even unpredictable. For this reason, we focus on payoff matrices with random entries. First, we analyze the case in which the payoff values a, b, and c that describe the mutant's interactions are Gaussian random variables with mean μ and standard deviation σ. Alternative scenarios are discussed below. Note that the payoff matrix is constant, in contrast to the work of Fudenberg and Harris (1992), where the payoff is subject to noise during evolution.

No matter which kind of randomness we consider in the payoff matrix, the fixation probability of a mutant in the population is the expectation value of ϕ_1. Thus, we have to calculate the expectation value of the right hand side of Eq. (7).

When the new payoff values a, b, c are continuous random variables with probability density functions $p(a)$, $p(b)$, and $p(c)$, respectively, we can write the expectation of the fixation probability, Eq. (7), as follows:

$$E(\phi_1) = \iiint \frac{1}{1 + \sum_{k=1}^{N-1} \exp[+\beta \sum_{i=1}^{k} (\pi_B - \pi_A)]} p(a)p(b)p(c)\, da\, db\, dc. \tag{8}$$

For a given population size N, and given probability density functions, this equation can be solved by numerical integration in three dimensions, see Fig. 1. However, the asymptotic for strong
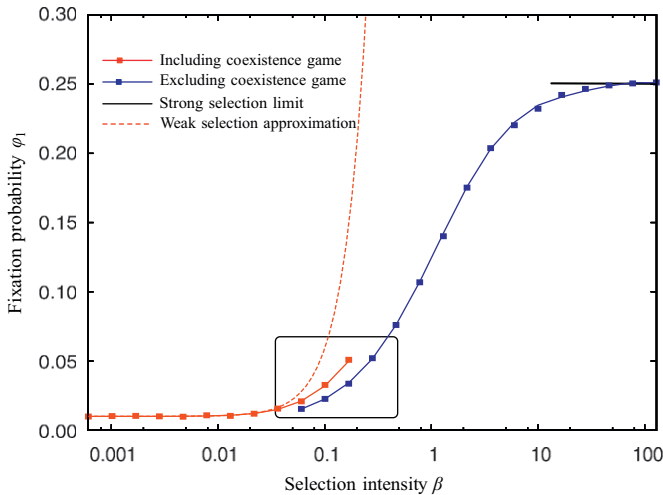
Fig. 1. Fixation probability of a single mutant with random payoff values under different selection intensities. Symbols are simulation results, lines are the numerical solution of Eq. (8). The payoff values are Gaussian distributed with the mean equal to the wild type individual's payoff. We start from a single mutant and wait until it is either lost or it takes over the whole population. The fixation probability is the fraction of runs in which the mutants take over. Coexistence games are only taken into account for weak selection, see text. The box represent the region between strong selection and weak selection (population size $N = 100$, averages over 10^5 runs).

selection, $\beta \to \infty$, can be inferred directly, because for strong selection the fixation probability is either zero or one (Altrock and Traulsen, 2009a). For weak selection, $\beta \ll 1$, we obtain an analytical approximation for the solution of the integrals.

3.1. Weak selection approximation

To address the case of weak selection, we expand the fixation probability ϕ_1, Eq. (7), at $\beta = 0$. First, we expand the exponential function in Eq. (7) up to second order for $\beta \ll 1$,

$$\exp\left[+\beta \sum_{i=1}^{k}(\pi_B - \pi_A)\right] \approx 1 + \beta \sum_{i=1}^{k}(\pi_B - \pi_A) + \frac{\beta^2}{2}\left(\sum_{i=1}^{k}(\pi_B - \pi_A)\right)^2. \tag{9}$$

Hence, we find for the fixation probability

$$\phi_1 \approx \frac{1}{1 + \sum_{k=1}^{N-1}\left(1 + \beta \sum_{i=1}^{k}(\pi_B - \pi_A) + \frac{1}{2}\beta^2(\sum_{i=1}^{k}(\pi_B - \pi_A))^2\right)}$$

$$= \frac{1}{N + \beta \underbrace{\sum_{k=1}^{N-1}\sum_{i=1}^{k}(\pi_B - \pi_A)}_{C_1} + \beta^2 \frac{1}{2}\underbrace{\sum_{k=1}^{N-1}(\sum_{i=1}^{k}(\pi_B - \pi_A))^2}_{C_2}}. \tag{10}$$

After another expansion for $\beta \ll 1$ we obtain

$$\phi_1 \approx \frac{1}{N} - \beta \frac{C_1}{N^2} + \beta^2 \left(\frac{C_1^2}{N^3} - \frac{C_2}{N^2}\right). \tag{11}$$

Note that this expansion is valid for any payoff difference $\pi_B - \pi_A$. For example, let us consider the situation in which $\Delta\pi = \pi_B - \pi_A$ is constant. This occurs for frequency independent selection, but also for $a + d = b + c$, which is often referred to as "equal gains from switching" (Nowak and Sigmund, 1990). In this case, we have $C_1 = N(N-1)\Delta\pi/2$ and $C_2 = N(N-1)(2N-1)\Delta\pi^2/6$. This leads to

$$\phi_1 \approx \frac{1}{N}\left[1 - \beta(N-1)\frac{\Delta\pi}{2} - \beta^2(N^2-1)\frac{\Delta\pi^2}{12}\right]. \tag{12}$$

For a first order expansion to be meaningful, $\beta \ll 1$ is not enough. Instead, we have to ensure $\beta N\Delta\pi \ll 1$.

In principle, we could assume any function for $\pi_B - \pi_A$. The most important case, however, are 2×2 games, which lead to a linear dependence of the payoff difference $\Delta\pi = \pi_B - \pi_A = ui + v$, cf. Eq. (2). In this case, we have

$$C_1 = \sum_{k=1}^{N-1}\sum_{i=1}^{k}(ui+v) = \sum_{k=1}^{N-1}\left(\frac{uk^2}{2} + \frac{(u+2v)k}{2}\right) = u\frac{N(N^2-1)}{6} + v\frac{N(N-1)}{2}. \tag{13}$$

For the second order term in Eq. (10), we obtain

$$C_2 = \frac{1}{2}\sum_{k=1}^{N-1}\left(\sum_{i=1}^{k}(ui+v)\right)^2 = \frac{1}{2}\sum_{k=1}^{N-1}\left(\frac{uk^2}{2} + \frac{(u+2v)k}{2}\right)^2$$

$$= \frac{u^2}{8}\sum_{k=1}^{N-1}k^4 + \left(\frac{u^2}{4} + \frac{uv}{2}\right)\sum_{k=1}^{N-1}k^3 + \left(\frac{u^2}{8} + \frac{uv}{2} + \frac{v^2}{2}\right)\sum_{k=1}^{N-1}k^2$$

$$= N(N-1)\left[u^2\frac{3N^3 + 3N^2 - 2N - 2}{120} + uv\frac{3N^2 + N - 2}{24} + v^2\frac{2N-1}{12}\right]. \tag{14}$$

Thus, we find for the expectation value of ϕ_1 under weak selection

$$E(\phi_1) \approx \frac{1}{N} - \beta \frac{E(C_1)}{N^2} - \beta^2 \frac{E(C_2)}{N^2} + \beta^2 \frac{E(C_1^2)}{N^3}. \tag{15}$$

Note that C_1 is linear in the payoffs, whereas C_2 is quadratic in the payoffs.

So far, this equation is valid for any distribution of payoffs $p(x)$. Next, we focus on the case in which a, b, and c follow Gaussian distributions with mean μ and standard deviation σ^2, $p(x) = (1/\sigma\sqrt{2\pi})\exp[-(x-\mu)^2/2\sigma^2]$. In our expectation value equation (15), we have only terms involving the first and the second moment of the distribution. Using $E(x) = \mu$ and $E(x^2) = \mu^2 + \sigma^2$, we find

$$E(u) = -\frac{d-\mu}{N-1}, \tag{16a}$$

$$E(v) = d - \mu, \tag{16b}$$

$$E(u^2) = \frac{(d-\mu)^2}{(N-1)^2} + \frac{3\sigma^2}{(N-1)^2}, \tag{16c}$$

$$E(v^2) = (d-\mu)^2 + \frac{N^2+1}{(N-1)^2}\sigma^2, \tag{16d}$$

$$E(uv) = -\frac{(d-\mu)^2}{N-1} - \frac{N+1}{(N-1)^2}\sigma^2. \tag{16e}$$

With these terms, Eq. (15) reduces to

$$E(\phi_1) \approx \frac{1}{N} - \beta \frac{N-2}{3N}(d-\mu) + \beta^2 \frac{N-2}{N-1}\frac{16N^2 - 57N + 47}{360N}(d-\mu)^2$$

$$+ \beta^2 \frac{N-2}{N-1}\frac{6N^2 - 7N + 7}{120N}\sigma^2. \tag{17}$$

In the simplest case, the average payoff entry associated with the mutant is identical to the wild type's payoff interacting with himself, such that we have $\mu = d$. Then, the linear term in Eq. (17) vanishes and only a second order weak selection approximation will lead to deviations from the neutral case. We obtain

$$E(\phi_1) \approx \frac{1}{N} + \beta^2 \frac{N-2}{N-1}\frac{6N^2 - 7N + 7}{120N}\sigma^2. \tag{18}$$

Now, the variance σ can be absorbed into the selection intensity. In other words, changing the variance of the Gaussian distribution is equivalent to changing the intensity of selection. In Fig. 1, the quadratic approximation equation (18) is compared to the

numerical solution of the integrals in Eq. (8) and to individual based simulations. For the third order weak selection approximation, we refer to the Appendix.

3.2. Strong selection limit

For strong selection, $\beta \to \infty$, only those mutants that are advantageous from the beginning of their invasion until the time they finally reach fixation take over the population. This means the mutant type A will reach fixation only if $a > c$ and $b > d$, see Eq. (1). In this case, the fixation probability is 1 for $\beta \to \infty$.

However, the fixation probability is not only one for $a > c$ and $b > d$ but also converges to one with $\beta \to \infty$ in coexistence games with $a < c$ and $b > d$ if we have $a + b > c + d$ in addition. This situation occurs for $\mu = d$ with probability $\frac{1}{8}$. However, for such games the average fixation times diverge rapidly with population size and intensity of selection (Antal and Scheuring, 2006; Traulsen et al., 2007a). Thus, for practical purposes we can neglect the fixation in coexistence games under strong selection, as it can hardly ever be observed.

Thus, we only consider $a > c$ and $b > d$ here for the fixation probability. The probability for this payoff ranking is the fixation probability for strong selection. First, let us consider the situation when a, b, and c follow a Gaussian distribution with mean $\mu = d$ and standard deviation σ. The probability that a is larger than c is $\frac{1}{2}$. The probability that b is larger than d is also $\frac{1}{2}$. Therefore, the fixation probability is simply $\frac{1}{4}$, see Fig. 1.

In frequency independent mutant scenarios, the payoff of both types does not depend on its interaction partner, i.e. $a = b$ and $c = d$. In this case, the fixation probability of a random mutant is $\frac{1}{2}$ for $\mu = d$.

3.3. Computer simulations

We simulate the population dynamics exactly as described in Section 2. In each time step, each individual interacts with all others in the population and obtains a payoff. However, our results for weak selection would not change significantly if they interact only with a random subset of the population (Traulsen et al., 2007b; Woelfing and Traulsen, 2009). Then, an individual is selected with probability proportional to its fitness and produces identical offspring. Another individual chosen at random is removed. To compute fixation probabilities, we simulate this birth–death process many times, each time with a new, different payoff matrix. Note that we are combining two sources of randomness, as the fixation process itself and the payoff matrix are stochastic.

When we compare our analytical results to computer simulations, a further difficulty appears: formally, we are always considering a Markov chain with two absorbing states $i = 0$ and $i = N$. Eventually, we will end up in one of them. But the time until we reach these states diverges with the intensity of selection and the population size if $a < c$ and $d < b$ (Antal and Scheuring, 2006; Traulsen et al., 2007a; Altrock and Traulsen, 2009b), see above. Thus, we have two choices: either, we include coexistence games and say that no fixation has occurred if we have waited for a very long time and still both types are present. However, then we cannot expect that our numerical results coincide with the analytical theory, because only the latter approach takes the possibility of fixation in coexistence games into account. This approach is appropriate when selection is not too strong. For strong selection, alternatively, we can exclude coexistence games from the beginning, both in our numerical solution of the integrals in Eq. (8) and in our simulations. If we do this and assume that fixation never occurs in coexistence games,

we find a convergence for strong selection towards a fixation probability of $\frac{1}{4}$.

As shown in Fig. 1, the simulations and the numerical results agree nicely both under strong selection and weak selection if we take these complications into account. However, under strong selection the fixation probability from simulations temporarily exceeds the strong selection limit. The reason is that in those games in which wild type only slightly dominates the mutant, the latter may still occasionally reach fixation. This makes the fixation probability of the mutant type slightly higher than it should be theoretically. For $\beta \to \infty$, however, the fixation probability converges to $\frac{1}{4}$, as expected.

4. Alternative fitness distributions

So far, we have concentrated on Gaussian distributed payoff entries. Next, we relax this restriction and consider more general distributions. It turns out that for weak selection, only the first moments of the distribution matter, whereas for strong selection, fixation is governed by the probability that a payoff value is larger than the average. Thus, our results from above generalize easily to general distributions.

4.1. Weak selection approximation

The weak selection approximation equation (17) corresponds to a moment expansion of the probability distribution: For the linear term, only the difference between average μ and the wild type's payoff against himself d matters. For the quadratic term, we have to take into account the second moment as well. Thus, Eq. (17) holds for any distribution with mean μ and standard deviation σ. The same reasoning holds when we take higher order terms in β into account, see Appendix. When $\mu = d$, the moments of the distribution matter up to the order of our approximation in β, see Fig. 2.
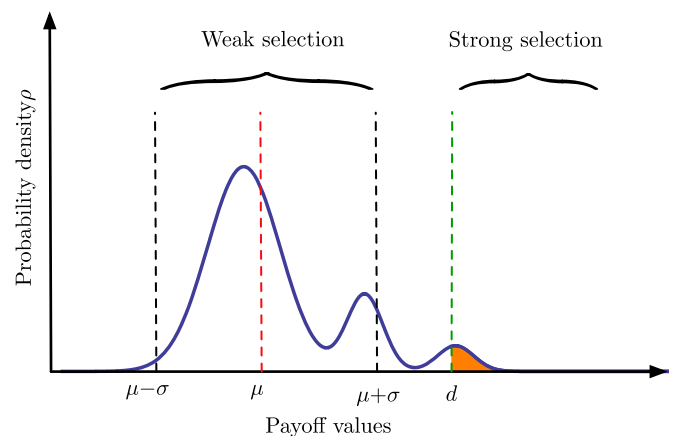

Fig. 2. The probability of fixation of a random mutant for general payoff value distributions is determined by different properties of the distribution. For weak selection, the fixation probability is determined by the first moments of the distribution of the new payoff values a, b and c. If we approximate up to second order, only d-μ, the difference between mean μ and the wild type's payoff d against itself and the standard deviation σ affect the fixation probability. For strong selection, the fixation probability of mutant type is determined by the product of the probability that the mutant is advantageous when it invades, $b > d$ and the probability that it is advantageous when it is frequent, $a > c$. The latter probability is $\frac{1}{2}$ and the former probability is given by the shaded part of the distribution in the figure.

4.2. Strong selection limit

For strong selection, $\beta \to \infty$, only those mutants whose fitness always exceeds that of the wild type, will eventually reach fixation. In game theory, such types are called dominant. The probability of the mutant type to be dominant is based on the fitness distribution.

If a, b, and c follow a symmetric distribution p with mean μ and standard deviation σ, and $\mu = d$, we obtain the same strong selection limit as for the Gaussian distribution with $\mu = d$, see Section 3.2. This is because in our strong selection argument, we only have to consider the probability that a certain payoff entry is larger than another one or larger than the mean. If the fitness distribution is asymmetric or $\mu \neq d$, this argument no longer holds and different strong selection limits will be reached under special fitness distributions. Since both a and c are chosen from the same distribution, the probability p_1 that a is larger than c, and thus the probability that the new mutant dominates when it has high abundance, is simply $p_1 = \int_{-\infty}^{\infty} p(x)p(y)\Theta(x-y)\,dx\,dy = 0.5$, where $\Theta(x-y)$ is the step function. Therefore, the only influence of the details of the distribution occurs through the payoff entry b. The mutant will be dominant if in addition b is larger than d, which is the condition that the mutant is advantageous when it enters the population. This occurs with probability $p_2 = \int_d^{\infty} p(x)\,dx$. For $d = \mu$ and distributions in which the median is equal to the mean, we obtain $p_2 = \frac{1}{2}$. But in general, the value of p_2 depends on the precise shape of the distribution, see Fig. 2, and the fixation probability is given by $p_1 p_2$.

For example, let us assume a, b, and c follow an exponential distribution with mean λ, e.g. $p(a) = (1/\lambda)\exp[-a/\lambda]$, such that $a, b, c \geq 0$. Thus, we obtain

$$p_2 = \lambda^{-1} \int_d^{\infty} \exp\left[-\frac{x}{\lambda}\right]dx = \exp\left[-\frac{d}{\lambda}\right].$$

Even for $\lambda = d$, we have $p_2 = \exp[-1] \approx 0.368$. Thus, the probability that the mutant dominates the wild type is $p_1 p_2 = \exp[-1]/2 \approx 0.184$. The asymptotic limit of the fixation probability for strong selection, $\beta \to \infty$, is also $p_1 p_2$. For $\lambda = d/\ln 2$, we would obtain the same asymptotic limit as for the Gaussian distribution.

5. Discussion

We have introduced a model in which a new mutant in asexual population is characterized by a new payoff matrix. We have calculated the probability that such a mutant interacting with the wild type in a novel, unpredictable way can take over a population. This depends on the details of the interactions, which are in our case based on the distribution of payoff values. How does this relate to the usual approaches of population genetics that discuss fitness distributions? One simplifying assumption of evolutionary game theory is that individuals are haploid and reproduction is asexual. So we should first aim at e.g. comparing to experimental data from bacteria.

Recent works in population genetics have attempted to measure fitness distributions experimentally (Zeyl and DeVisser, 2001; Cowperthwaite et al., 2005; Kassen and Bataillon, 2006). Also in our case, we have a distribution of fitness values, reflected by the entries of a payoff matrix. However, our model is looking at the invasion and fixation of mutants from a different perspective. The first and most important point is the way we define fitness. Mutations bring variety, and fitness is to describe the advantages of one type over others. In the traditional population genetic view, fitness is typically constant, but our model considers fitness under frequency dependent selection. The evolutionary dynamics under
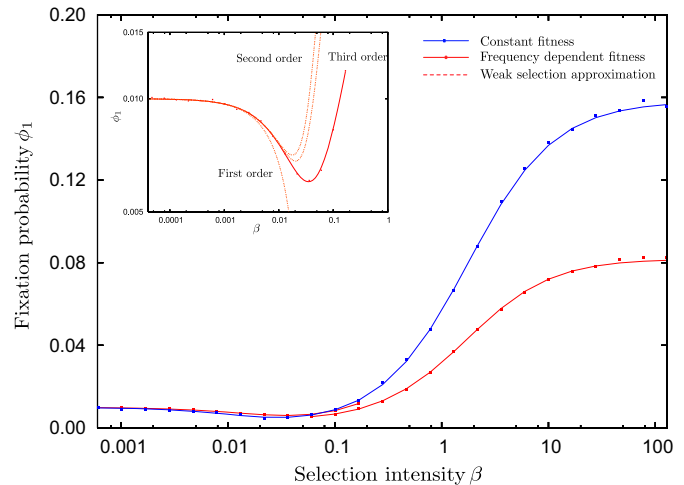

Fig. 3. In the main panel, we compare the probability of fixation under constant fitness and frequency dependent fitness. Here, wild type's payoff against itself d is larger than mean μ of the Gaussian random variables in the payoff matrix ($d = 2, \mu = 1$). This is consistent with the notion in population genetics that deleterious mutants are more common than beneficial ones. For weak selection, the dynamics under both approaches are similar. However, the scenarios under strong selection are quite different. In the inset, we show the weak selection approximations of the fixation probability under frequency dependent fitness. As the probability to be deleterious is higher, the fixation probability of a random mutant decreases first with the intensity selection, before it starts to increase again. It is obviously that the approximation becomes more accurate when higher order terms are considered. In particular, the linear term cannot capture the fixation probability when the intensity of selection is increased here (population size $N = 100$, averages over 10^5 runs).

these two approaches will be quite different, especially when selection is not weak, see Fig. 3. For constant fitness, a mutant in an asexual population is either advantageous or disadvantageous compared to the wild type. Therefore, the fixation or extinction of the mutant type is usually fast for strong selection. But for frequency dependent fitness, mutant and wild type may coexist with each other for a long time. This occurs when a mutant performs better than the wild type when it is rare, but the wild type has a fitness advantage when the mutant is frequent. One would expect that frequency dependence is the rule rather than the exception, because the success of a strategy typically depends on the actions and abundance of others.

The distribution of fitness values is a central concept in population genetics. Gillespie (1983) and Orr (2002, 2003) have proposed that the fitness distribution of beneficial mutants would be approximately exponential. Alternative distributions like gamma distribution, L-shaped distribution and slightly bell-shaped distribution are also considered to be possible. The fitness distribution is a function of the environment and thus it is influenced by many factors, such as the adaption of the wild type to the environment. It also makes a difference if only single-step mutations are considered or if also mutants with several mutations are taken into account. However, these attempts are typically based on the assumption of fixed fitness values. If fitness is frequency dependent, as in our model, the selective advantage of a novel type depends on its frequency. A new mutation may be able to invade, but not to take over the population. Alternatively, new mutants may be disadvantageous, but turn highly successful when they have crossed a certain threshold.

Payoff matrices with random entries have been considered before: in a seminal paper, Fudenberg and Harris (1992) have shown that a game with time-dependent random payoff matrix can be described by a stochastic form of the replicator equation. They have argued that the system spends most time in the vicinity of the risk dominant equilibrium. This is the strategy with

the larger basin of attraction under positive frequency dependent selection. The approach of Fudenberg and Harris leads to much faster convergence to the risk dominant equilibrium than the approach of Kandori et al. (1993), looking at mutations only under strong selection. Our model assumes that the nature of interactions, i.e. the payoff matrix, does not change in time, whereas Fudenberg and Harris (1992) consider a situation in which fitness is not only frequency, but also time dependent, such that fixation probabilities are not meaningful.

Berg and Engel (1998) as well as Galla (2007) have considered random bimatrix games with a large number of strategies to address the number of Nash equilibria and the fraction of strategies contributing to mixed Nash equilibria. Eriksson and Lindgren (2001) have asked what kind of strategies is most successful if the payoff matrix is chosen at random and change in every round of game. These papers either consider large numbers of strategies, sophisticated decision processes or temporal changes of the payoff matrix that do not affect the identity of the strategies. Our approach is different in many aspects: players do not switch between strategies or choose a particular way to play in each game. Rather, they play a fixed strategy that they also pass on to their offspring. We consider an ensemble of fixed games and explore how the probability that a mutant can take over a population depends on that ensemble. It turns out that the dependence on the underlying distribution of interaction parameters corresponds to a moment expansion for weak selection and to an integral of a part of the fitness distribution for strong selection.

Acknowledgements

Appendix A. Third order weak selection

The third order expansion of the fixation probability of a single mutant under weak selection is calculated here. We consider the fitness as frequency dependent. First, we expand the exponential function in Eq. (7) for $\beta \ll 1$,

$$\exp\left[+\beta \sum_{i=1}^{k}(\pi_B-\pi_A)\right] \approx 1+\beta \sum_{i=1}^{k}(\pi_B-\pi_A)+\frac{\beta^2}{2}\left(\sum_{i=1}^{k}(\pi_B-\pi_A)\right)^2$$
$$+\frac{\beta^3}{6}\left(\sum_{i=1}^{k}(\pi_B-\pi_A)\right)^3. \tag{19}$$

Then, Eq. (7) can be written as

$$\phi_1 \approx \frac{1}{N+\beta C_1+\beta^2 C_2+\beta^3 \underbrace{\frac{1}{6}\sum_{k=1}^{N-1}\left(\sum_{i=1}^{k}(\pi_B-\pi_A)\right)^3}_{C_3}}, \tag{20}$$

where C_1 and C_2 are defined as Eqs. (13) and (14) in the main text. Expanding Eq. (20) for $\beta \ll 1$, we have

$$\phi_1 \approx \frac{1}{N}-\beta\frac{C_1}{N^2}+\beta^2\left(\frac{C_1^2}{N^3}-\frac{C_2}{N^2}\right)-\beta^3\left(\frac{C_1^3}{N^4}-\frac{2C_1 C_2}{N^3}+\frac{C_3}{N^2}\right). \tag{21}$$

As $\pi_B-\pi_A = ui+v$, cf. Eq. (2), we have

$$C_3 = \frac{1}{6}\sum_{k=1}^{N-1}\left(\sum_{i=1}^{k}(ui+v)\right)^3$$

$$= N\left[u^3\frac{15N^6-42N^4+35N^2-8}{630}+u^2v\frac{5N^5-3N^4-10N^3+5N^2+5N-2}{240}\right]$$
$$+N\left[uv^2\frac{12N^4-15N^3-10N^2+15N-2}{240}+v^3\frac{N(N-1)^2}{24}\right]. \tag{22}$$

When we assume that a, b, c follow an arbitrary distribution $f(x)$ with mean μ, variance σ^2 and skewness γ, the fixation probability under weak selection is the expectation value of ϕ_1,

$$E(\phi_1) \approx \frac{1}{N}-\beta\frac{E(C_1)}{N^2}+\beta^2\left(\frac{E(C_1^2)}{N^3}-\frac{E(C_2)}{N^2}\right)-\beta^3\left(\frac{E(C_1^3)}{N^4}-\frac{2E(C_1 C_2)}{N^3}+\frac{E(C_3)}{N^2}\right). \tag{23}$$

Compared with the second order approximation where only the first and the second moment of the distribution are involved, we need to include the third moment of the distribution $E(x^3) = \mu^3+3\mu\sigma^2+\gamma$. Then, we obtain four new terms beside those in Eq. (16)

$$E(u^3) = -\frac{(d-\mu)^3}{(N-1)^3}-\frac{9(d-\mu)\sigma^2}{(N-1)^3}+\frac{\gamma}{(N-1)^3}, \tag{24a}$$

$$E(v^3) = (d-\mu)^3+\frac{3(N^2+1)}{(N-1)^2}(d-\mu)\sigma^2-\frac{N^3-1}{(N-1)^3}\gamma, \tag{24b}$$

$$E(u^2v) = \frac{(d-\mu)^3}{(N-1)^2}+\frac{5N-1}{(N-1)^3}(d-\mu)\sigma^2-\frac{\gamma}{(N-1)^2}, \tag{24c}$$

$$E(uv^2) = -\frac{(d-\mu)^3}{N-1}-\frac{3N^2-1}{(N-1)^3}(d-\mu)\sigma^2+\frac{(N^2-1)}{(N-1)^3}\gamma. \tag{24d}$$

With all the items in Eqs. (16) and (24), the fixation probability for a mutant in Eq. (23) becomes

$$E(\phi_1) \approx \frac{1}{N}-\beta\frac{N-2}{3N}(d-\mu)+\beta^2\frac{N-2}{N-1}\frac{16N^2-57N+47}{360N}(d-\mu)^2$$
$$+\beta^2\frac{N-2}{N-1}\frac{6N^2-7N+7}{120N}\sigma^2$$
$$-\beta^3\frac{N-2}{(N-1)^2}\frac{32N^4-345N^3+1106N^2-1347N+530}{15120N}(d-\mu)^3$$
$$-\beta^3\frac{N-2}{(N-1)^2}\frac{12N^4-293N^3+546N^2-541N+288}{5040N}(d-\mu)\sigma^2$$
$$+\beta^3\frac{N-2}{(N-1)^2}\frac{32N^4-177N^3+182N^2-255N+194}{15120N}\gamma. \tag{25}$$

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2.2 Generalizing the definition of the payoff distribution

The payoff distribution is an important concept in our frequency dependent mutant model. As there is no general conclusion on the shape of the payoff distribution from experiments, we assume an arbitrary distribution. Initially, a Gaussian distribution with mean η and variance σ^2 was considered. We analytically calculated the fixation probability of a single mutant under weak and strong selection. Under weak selection, it turns out only the mean and the variance matter, if ϕ_1 is expanded to the second order. This expression of ϕ_1 can be further simplified if $\eta = \mu$, where the mean of the new payoff entries is the payoff of a wild type interacting with another wild type. Under strong selection, ϕ_1 only depends on the probability that a new payoff entry is larger than the initial wild type payoff, $\eta > d$.

There are two important results: First, assuming a concrete shape of the distribution is not necessary for our analysis under weak and strong selection; Second, the relation of the mean payoffs of the mutant η and the payoff of its parents d, is an important parameter for the fixation probability for weak and strong selection (also see Eq. 17 in the paper in Sec. 2). According to these resutls, we generalize the definition of the payoff distribution in our frequency dependent mutant model. It can be any distribution with first moments, such as mean η and variance σ^2. A new parameter θ is defined for the payoff distribution. Here, $\theta = \int_d^\infty f(x)dx$, where $f(x)$ is the probability density function of random payoff entries.

Interestingly, θ corresponds to the beneficial mutation rate under the constant selection scenario. This is a key expression in Chapter 4, where infinite populations are considered. As η, σ^2 and θ are all statistical properties of a distribution, it is more plausible to obtain these values than the concrete shapes of a distribution in experiments.

Diversity in the frequency dependent mutation model with many types

Polymorphism refers to the coexistence of at least two types in the same population [109, 75, 110]. These can be different genotypes or phenotypes. Polymorphism is commonly observed in natural populations. For example, green and red morphs occur in the same population of the pea aphid [112]. In social insects, different morphological forms with a specialized function exist in the same sex within an individual colony [113]. Allele diversity at MHC genes are reported in three-spined stickleback, mouse, human and other species [111, 114, 115, 116]. However, the basic mechanisms maintaining polymorphisms are still under debate [111]. Various mechanisms like host-parasite coevolution [117, 112], sexual selection [118, 119, 111], and heterozygote advantage [120, 121] are proposed to contribute to the maintenance of polymorphisms, where negative frequency dependent selection is often involved. For example, in the host-parasite coevolution, host and parasite genotypes are considered to have a selective advantage when they are rare [122]. In sexual selection, some individuals (usually females) prefer to mate with particular phenotypes or genotypes when they are rare [123].

In natural populations, stable coexistence may arise from various complex interactions between different types (see Section 1.1). Negative frequency

dependent selection is only one of them. As the fitness of mutants is unknown or unpredictable before their appearance, it is hard to impose a particular type of frequency dependence among the mutant type and resident types. Instead, we assume the payoff entries introduced by mutations as random variables, and thus include all types of interactions. In this chapter, we are interested in the origin and the maintenance of the stable coexistence of different types based on our frequency dependent mutant model.

We consider dynamic processes starting from homogenous populations. The evolutionary dynamics unfolds for continuous mutations without predefined fitness. The diversity of a population is under the interplay of mutation and selection. As we are interested in polymorphisms stabilized by selection rather than the presence of several mutants simultaneously driven by high mutation rates, we focus on low mutation rates (see Section 2.1).

For the same mutation rates, we compare the population dynamics under constant selection and frequency dependent selection. For weak selection, the diversity under these two scenarios is similar due to large random genetic drift. Polymorphism arises when the selection intensity becomes stronger under frequency dependent selection, while the opposite pattern occurs under constant selection. Interestingly, although our model allows for an infinite number of mutations over evolutionary time, the diversity of the population typically remains at an intermediate level with only a few coexisting types.

3.1 Diversity under neutrality

One important assumption in our frequency dependent model is that every mutation brings a new game to the population. This corresponds to the assumption of the infinite alleles model, where every mutation results in a new allele in the population [42, 124, 12]. When the mutation rate is low enough, a stationary state will be reached by the population given sufficient

time. In a population with mutations, the frequencies of different types are always changing. A population remains at a stationary state in the sense that the probabilities to observe a certain number of types do not change. These probabilities can be the measure of diversity levels of a population. Under neutral selection, they were derived by Ewens sampling formula [54].

Ewens sampling formula (ESF) describes the probability distribution of a configuration of alleles from a selectively neutral locus, when a sample of N_s individuals is drawn from a population with size N [12]. As a sampling theory, ESF was initially proposed for the Wright-Fisher process (see Section1.2.3). Starting from the probability that two sampled individuals are the same type, it gives a group of sampling properties. According to ESF, the probability of m different alleles present in the population $P(m)$, is given by

$$P(m) = \begin{bmatrix} N_s \\ m \end{bmatrix} \theta^m / S_{N_s}(\theta), \tag{3.1}$$

where $\begin{bmatrix} N_s \\ m \end{bmatrix}$ are the unsigned Stirling numbers of the first kind, and $S_{N_s}(\theta) = \prod_{i=0}^{N_s-1}(\theta + i)$ [13, 108]. The unsigned Stirling numbers of the first kind arises in the framework of permutation theory. They are the coefficients of the rising factorial, $x(x+1)\cdots(x+N_s-1) = \sum_{m=0}^{N_s} \begin{bmatrix} N_s \\ m \end{bmatrix} x^m$ [108]. For a haploid Wright-Fisher process, we have $\theta = 2N\mu$. For a haploid Moran process, the parameter θ is $N\mu$, because random genetics drift in a Moran process is twice as strong as in a Wright-Fisher process under neutral evolution [125].

In our frequency dependent mutant model, we address the population dynamics from near neutral selection to strong selection. The results obtained under near neutral selection in our model, are captured by ESF (see Fig. 3 and Supplementary Figures in the publication included in the next section), in the same way as for the constant selection case.

3.2 Diversity under frequency dependent selection for various selection intensities

Publication: Emergence of stable polymorphisms driven by evolutionary games between mutants

Weini Huang, Bernhard Haubold, Christoph Hauert, and Arne Traulsen

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ARTICLE

Emergence of stable polymorphisms driven by evolutionary games between mutants

Weini Huang[1], Bernhard Haubold[2], Christoph Hauert[3] & Arne Traulsen[1]

Under neutrality, polymorphisms are maintained through the balance between mutation and drift. Under selection, a variety of mechanisms may be involved in the maintenance of polymorphisms, for example, sexual selection or host-parasite coevolution on the population level or heterozygote advantage in diploid individuals. Here we address the emergence of polymorphisms in a population of interacting haploid individuals. In our model, each mutation generates a new evolutionary game characterized by a payoff matrix with an additional row and an additional column. Hence, in general, the fitness of new mutations is frequency-dependent rather than constant. This dynamical process is distinct from the sequential fixation of advantageous traits and naturally leads to the emergence of polymorphisms under selection. It causes substantially higher diversity than observed under the established models of neutral or frequency-independent selection. Our framework allows for the coexistence of an arbitrary number of types, but predicts an intermediate average diversity.

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Evolutionary dynamics is characterized by the interplay of mutation, selection and random drift[1–4]. Evolutionary experiments in microbes provide powerful demonstrations of all these forces at work[5–8]. Typically, it is assumed that mutants with a random fitness value, which remains constant throughout, arise and either go extinct or reach fixation[9]. Advantageous mutations can quickly reach fixation in the population. However, such events are too rare to substantially increase genetic diversity over time[10–12]. Evolutionary game theory provides an alternative perspective on evolutionary change, by modelling the fitness of a mutant as a function of the frequencies of all types of individuals in the population. For example, a mutant may be advantageous at the beginning of an invasion, but its fitness may drop below the residents' fitness when it reaches a certain abundance[2,4,13,14]. In such models, the number of types is usually fixed from the outset[13,15]. This corresponds to two (or few) allele models in population genetics[1,3].

Here we present a model where each mutation generates a new evolutionary game characterized by a payoff matrix with an additional row and an additional column. This represents a generalization that is analogous to the infinite-alleles model that has mainly been considered in the context of neutral or constant selection so far[3]. This approach results in substantially higher diversity than observed under the established models of neutral or frequency-independent selection and permits the coexistence of an arbitrary number of types, but predicts an intermediate average diversity.

Results

Description of the model. We propose an approach where every mutation leads to a new game between the mutant and the residents. We use stochastic evolutionary game dynamics with n types of individuals in a finite population of size N (refs 16,17). Interactions between individuals are captured by an $n \times n$ payoff matrix. The payoff of a type i individual when it interacts with a type j individual is the entry a_{ij} in the payoff matrix. The average payoff of an individual determines its fitness and is a function of the frequencies of all types. In our model, any new mutation increases the number of types in the game. We assume that mutant m inherits the payoff entries of its parent p, subject to Gaussian noise. Thus, the mutant's payoff against type j, a_{mj}, has mean a_{pj}, and the payoff of type j against the mutant, a_{jm}, has mean a_{jp}. If there are n resident types when the mutant appears, the $n \times n$ payoff matrix is extended by an additional column (the payoff entries of residents interacting with the mutant) and an additional row (the payoff entries of the mutant interacting with residents) (Fig. 1). Conversely, when type j goes extinct, row j and column j in the payoff matrix are deleted, such that it is reduced to an $(n-1) \times (n-1)$ matrix. Our reference scenario is frequency-independent (constant) selection, where each type has a fixed fitness. In this special case, each row in the payoff matrix consists of identical numbers, $a_{ij} = a_{ik}$ for all i, j, and k.

Mutant games between two types. First, we consider the case of a single mutant B in a homogeneous population of A-types. Fitness differences depend on the distribution of payoff values and on the intensity of selection w. To avoid negative fitness values, we assume that fitness is an exponential function of the average payoff multiplied by w (see Methods). Under constant selection with Gaussian distributed payoffs around the parent type payoff, the probability for an advantageous mutation is 50%. For frequency-dependent selection, 50% of the mutants are also initially advantageous. In 25% of the cases, the mutants' fitness is greater than that of the wild type regardless of the mutants' abundances. In these cases, the mutants will take over the population deterministically for strong selection w, or large population size N. Some of these mutations increase the average fitness and some of them will decrease it, the latter representing Prisoner's Dilemmas[13]. This game is characterized by a
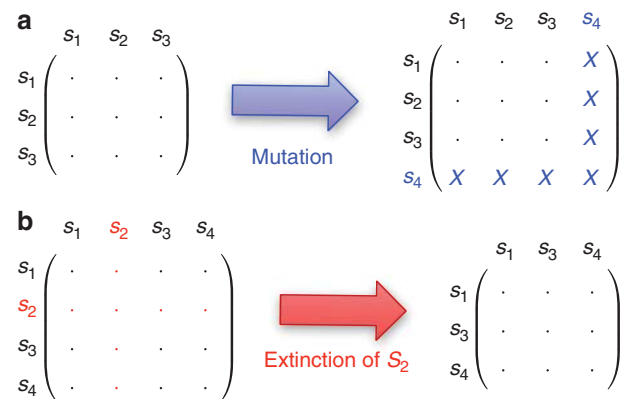

Figure 1 | Dynamic payoff matrices. Mutant games are characterized by growing and shrinking payoff matrices, as shown in this example with 3 and 4 types. All elements of the payoff matrix can be different, whereas for the special case of constant selection payoff entries in each row are identical. (**a**) A mutation increases the dimension of the payoff matrix from 3 to 4. The new column describes interactions of the previous types with the new mutant, whereas the new row describes the interactions of the new mutant with the previous types. (**b**) Extinction of a type S_2 decreases the dimension of the payoff matrix from 4 to 3. Whenever a type goes extinct, the corresponding row and column of the payoff matrix are deleted.

specific ordering of payoffs, $a_{BA} > a_{AA} > a_{BB} > a_{AB}$, a situation that is typically described as interactions between cooperators (type A) and defectors (type B). The payoff ordering implies that defectors always have higher fitness and tend to spread, but this decreases the average fitness of the population. Another 25% of the mutations are initially advantageous but lose this advantage once they become abundant and hence promote coexistence, which is reminiscent of the Hawk–Dove game[13] or the Snowdrift game[18] and characterized by the payoff ordering $a_{BA} > a_{AA} > a_{AB} > a_{BB}$. The remaining 50% of the mutants are disadvantageous at low frequencies and will typically be lost. However, for weak selection, $w \ll 1/N$, the stochastic nature of the process allows even slightly disadvantageous mutants to invade and fix. Conversely, advantageous mutants can also be lost for the same reason. The corresponding fixation probabilities can be calculated from a moment expansion of the distribution of payoffs[19].

Mutant games between n types. Here we focus on a more general case of a continuously evolving population. New types appear and old types go extinct. No type can be fixed in the population forever. Instead of looking at the fixation probability of a certain type, we will focus on the evolutionary dynamics in such a population and see under which conditions a stable polymorphism can naturally emerge.

In population genetics, frequency-dependent selection in diploids has been considered in the past, but the focus has been on special cases such as symmetric overdominance[20,21]. In evolutionary game theory, it is argued that frequency-dependent selection is generic, with constant selection describing a special case[2,14,16]. Our model allows us to address the consequences of frequency-dependent selection. We focus on the average number of different types simultaneously present in the population. The interactions can be any two-player game, leading to any kind of linear frequency dependence.

Whereas previous models of evolutionary games with variable numbers of types were based on deterministic dynamics[22–25], we focus on the more general case of stochastic evolutionary dynamics.
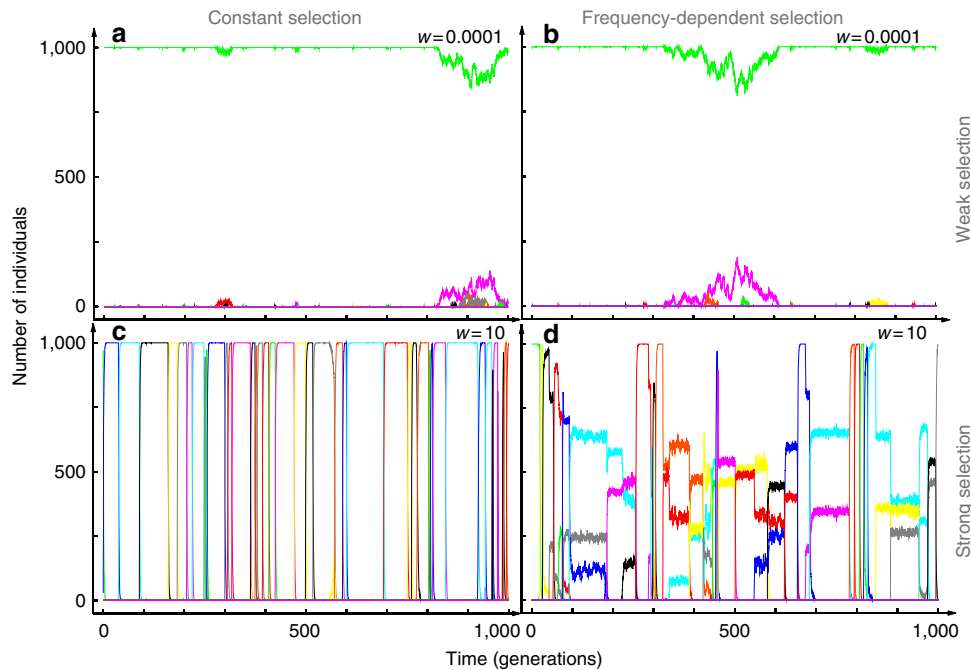
Figure 2 | Sample trajectories of the evolutionary dynamics in a Moran process. The left panels are for constant selection and the right panels are for frequency-dependent selection. Top: for weak selection, $w = 0.0001$, the dynamics with constant selection (**a**) is similar to that with frequency-dependent selection (**b**), because possible coexistences disappear due to genetic drift. As on average μ/N mutations appear per generation, μ neutral fixation events are expected per generation, and a single type dominates over $1/\mu$ generations. Bottom: for strong constant selection, $w = 10$, successive fixation events of the 50% advantageous mutants are observed (**c**), the expected number of such events per generation is $N\mu/2$. For frequency-dependent fitness (**d**), pairwise coexistences are stable over long periods of time. Additional mutants can arise and lead to the coexistence of 3 or even more types (population size $N = 1,000$, mutation rate $\mu = 10^{-4}$ per time step, all simulations start from a monomorphic state).

We consider a Moran process in a population of constant size N. In every time step, one individual is randomly chosen proportional to its fitness, and produces a mutant with probability μ or an identical offspring with probability $1 - \mu$. A randomly chosen individual in the population is replaced by this offspring. The fitness of a given individual is determined from its interactions within the population (see Methods). Mutations increase and extinctions decrease the dimension of the payoff matrix (Fig. 1). To ensure that the selection intensity is independent with evolutionary time, we normalize the payoff matrix after each mutation and after each extinction such that the highest absolute payoff value equals one.

Diversities under constant selection and mutant games. An example for the different dynamics arising through mutant games compared with constant selection is shown in Fig. 2. For weak selection, $Nw \ll 1$, the extinction times are of the order of N generations and frequency-dependent selection is not markedly different from constant selection. However, for larger populations or higher intensity of selection w, stable alliances can coexist for a long time[26]. Mutants can affect the population by (i) destroying existing alliances and taking over the population, (ii) enabling one of the residents or a new alliance of residents to take over or (iii) leading to another stable alliance together with a subset of the resident types or all of them. Only if the mutant type enters the population without displacing any resident, does the number of types increase. Nonetheless, frequency-dependent selection leads to a significant increase in the diversity of the population compared with neutral or constant selection. The balance between selection and drift is governed by the product of the selection intensity and the population size. For fixed selection intensity, the smaller the population, the larger the genetic drift. For fixed population size, the smaller the selection intensity, the larger the genetic drift. Here we assess the effect of genetic drift

by varying the selection intensity in a population of fixed size (see Methods).

To further analyse diversity, let us recall population genetics under weak selection. Under neutrality and low mutation, the average number of different types, which can sometimes increase by mutation and always decreases by extinction, is described by Ewens' sampling formula[27] (see Methods). To ensure that there can be an equilibrium between mutations and extinctions, we must assume $\mu \ll N^{-1}$. In large populations, this condition is violated and the diversity is substantially higher. Even in this case, frequency-dependent selection leads to more diversity than constant selection (see Methods). Our weak selection results recover Ewens' sampling formula, both under constant and frequency-dependent selection. However, for strong selection, the results are strikingly different in these two cases. For constant selection, diversity decreases with increasing intensity of selection, because the extinction and fixation times become shorter. In contrast, increasing the selection intensity under frequency-dependent selection stabilizes alliances between different types and typically increases diversity (Fig. 3). For small mutation rates, $\mu \ll N^{-2}$, neutral mutations go extinct on a faster timescale than new mutations arise, but polymorphisms may still exist for a long time. Mutations lead to transitions between monomorphic states or coexistence states involving 2,3,4 or more types under strong selection (Fig. 4). The stationary distribution of these coexistence states can be computed based on the transition probabilities (see Methods). This recovers our results for the distribution of the number of coexisting types (Fig. 3). Evolutionary dynamics selects stable polymorphisms, but diversity is an emergent property because our mutant games lead to all possible payoff matrices.

The nature of the games. As soon as more than two types coexist, we can also analyse the interactions of each pair of types. Here we focus
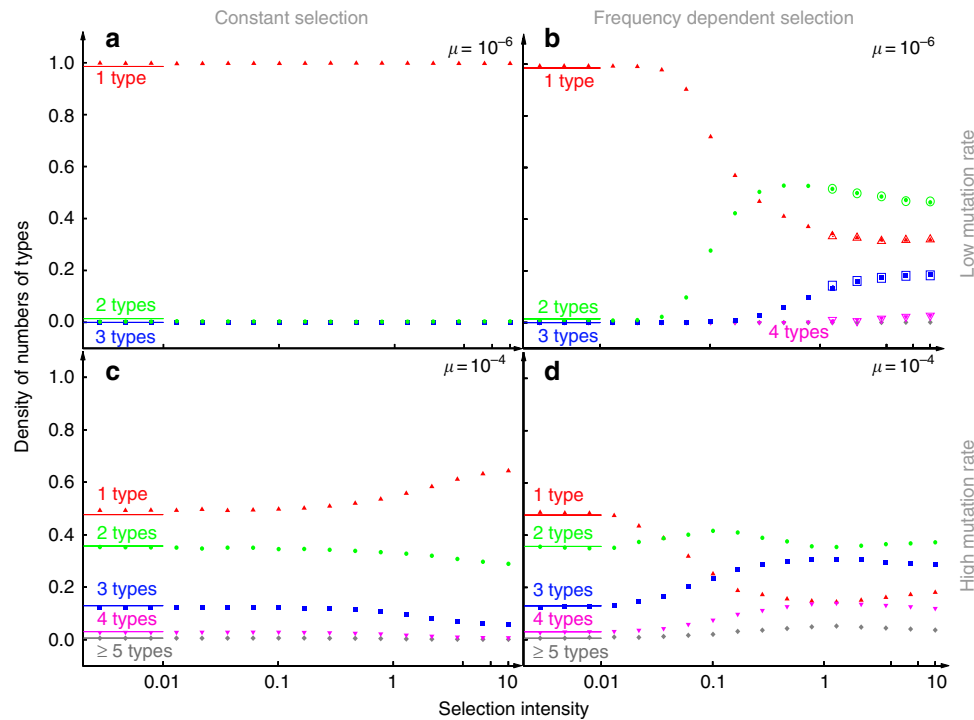
Figure 3 | Distribution of the number of types. The probability of observing a certain number of coexisting types is shown for different selection intensities. As expected, our simulations (filled symbols) agree with Ewens' sampling formula under weak selection (lines). The top panels show a low mutation rate, $\mu = 10^{-6}$ per time step. For constant selection (**a**), diversity decreases slightly with increasing intensity of selection. For frequency-dependent selection (**b**), diversity increases substantially with increasing intensity of selection. For strong selection, we can alternatively compute the stationary distribution from the transitions between the different polymorphisms (Fig. 3 (open symbols)). Although the number of types is not limited in our model, there are typically 4 or less types coexisting in our simulations at the same time. The bottom panels show higher mutation rates, $\mu = 10^{-4}$ per time step, where the diversity under neutral selection is already high. Under frequency-independent selection (**c**) diversity increases compared with (**a**), owing to the increasing mutation rate. But frequency-dependent selection (**d**) increases diversity further compared with constant fitness (**c**) or lower mutation rates (**b**) (population size $N = 1,000$, averages obtained over 500 independent realizations and 10^7 generations per realization. All simulations begin in a monomorphic state, averages start after 25,000 generations).

on 2×2 subgames of the observed 3×3 games. As a polymorphism of n types usually arises from a previous polymorphism of $n-1$ types, the vast majority of the 2×2 subgames (~90%) show stable coexistences. However, there is a small fraction of 2×2 games in which one type dominates over the other. In particular, when viewed in isolation, a few of these pairs engage in Prisoner's Dilemma interactions (~1%). Despite the metaphorical power of the Prisoner's Dilemma in the theory of evolution of cooperation, there is a striking lack of empirical cases described by this model[28]. The relative rarity of Prisoner's Dilemma relationships occurring in mutant games seems to corroborate the dearth of empirical evidence for it. Besides, restricting the analysis to pairwise interaction in this way can be misleading, because any pair of individuals represents just a subset of a more complex interacting community of many types. For example, they could be part of a rock-scissors-paper-type cyclic dominance hierarchy that is known for its capacity to support coexistence[29,30]. In contrast, ~10% of pairwise interactions represent Snowdrift games, which do not mandate the presence of further types or other mechanisms to account for polymorphisms. Hence the Snowdrift game seems a biologically appealing and possibly more relevant framework to address cooperation[18].

Discussion

Complex communities can only be observed when the intensity of selection is strong, which means that the rate of adaptation of a population to external conditions is relatively high. HIV evolution, host-parasite coevolution, or antibiotic resistance are examples

for high selective pressures. Moreover, intraclonal polymorphism is frequently observed in bacterial species[31,32]. Our mutant games show an intriguing resemblance to recent observations in long-term evolutionary experiments with *Escherichia coli*: When kept in a constant environment, these bacteria alternate between monomorphic phases and coexistence of up to a handful of distinct genotypes for hundreds of generations[32], similar to our strong selection case in Fig. 2.

Frequency-dependent selection is a recurrent theme in evolutionary biology, with applications as diverse as Fisher's explanation of the 1:1 sex ratios[33], sympatric speciation[34], and the allelic diversity of the immune system driven by host parasite coevolution[35]. In each case, the most important consequences for the evolutionary process arise through frequency dependence and, in particular, through stable polymorphisms. In our model, any mutation produces a new game between mutant type and resident types, which takes the full spectrum of frequency dependence into account. It is straightforward to extend our framework to diploid populations, where pairwise games correspond to the interactions of two alleles at one locus[21] (see Methods), and frequency-dependent selection arises from diploidy rather than interaction between different genotypes.

Under constant selection, the average fitness of a population keeps increasing (neglecting occasional dips due to the stochastic fixation of disadvantageous mutants), which contrasts with the proposed mutant games where frequency-dependent selection may result in an increase as well as a decrease of fitness. Evolutionary
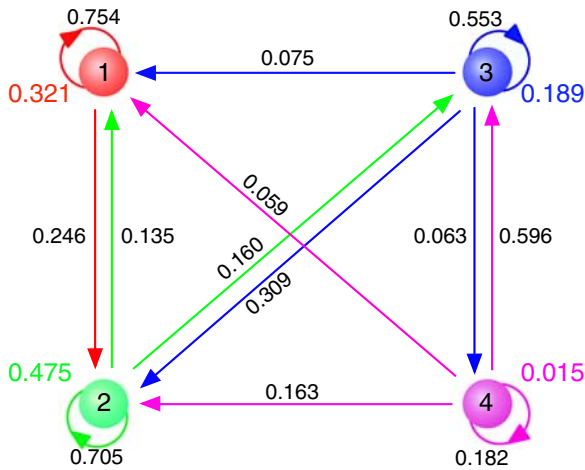
Figure 4 | Transition probabilities between different levels of diversity.
The consequences of mutations for the diversity are described by transition probabilities for low mutation rates under strong selection. The transition probability between different levels of diversity results from the appearance of a mutant. Each circle marks a certain number of coexisting types and the probability that the population is in this state (cf. to Fig. 3b), arrows mark the probabilities of the transitions between these states after the appearance of a mutant. A mutation can only increase the diversity by at most one type, but this probability decays rapidly with the number of coexisting types. A new mutation can also lead to a decrease in the diversity to any level. Here we show the transitions for up to four coexisting types under strong selection; as illustrated in Fig. 3b, the probability to be in states with $n>4$ under strong selection is negligible for the present parameter combination. (population size $N=1,000$, mutation rate $\mu=10^{-6}$ per time step, selection intensity $w=10$, averages obtained over 500 independent realizations and 10^7 generations per realization after a transient period of 25,000 generations. All simulations start from a monomorphic state).

processes represent an optimization to a changing environment[14], but in addition, evolutionary trajectories are constrained through inheritance and mutations. Mutant games capture all these effects in a concise framework and present a complementary perspective on the emergence of polymorphisms and the degree of diversity.

Methods

Payoff and fitness. In evolutionary game theory, the fitness of individuals is determined through games, that is, interactions with other individuals. In our case, the game is characterized by a payoff matrix. If only two types, S_1 and S_2, interact, the payoff matrix is given by

$$
\begin{array}{cc}
 & \begin{array}{cc} S_1 & S_2 \end{array} \\
\begin{array}{c} S_1 \\ S_2 \end{array} & \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}.
\end{array}
\qquad (1)
$$

In our model, the payoff is determined from interactions with all other individuals in the population, excluding self interactions. Thus, the payoff of type S_1 is $\pi_1 = (i-1)/(N-1)a_{11} + (N-i)/(N-1)a_{12}$, where i is the number of S_1 individuals in the population. Equivalently, we have $\pi_2 = i/(N-1)a_{21} + (N-i-1)/(N-1)a_{22}$ for the payoff of type S_2. To avoid the complications of negative fitness, we define the fitness, f_j, of type j as an exponential function of its payoff π_j, $f_j = \exp[+w \cdot \pi_j]$. Here w ($0 \le w < \infty$) controls the selective differences between players with different payoffs[36]. If $a_{11} = a_{12}$, and $a_{21} = a_{22}$, the payoffs are independent of interactions and are only determined by the type of the individuals. This special case corresponds to constant selection, where the fitness of one type does not depend on the frequency of the types in the population. Neutral selection corresponds to $w=0$ or to $a_{11} = a_{21} = a_{12} = a_{22}$.

In a population of n types, we use a $n \times n$ matrix to describe the payoffs. When a mutant appears, an additional column and row are added to the matrix to describe the additional interactions. In the general frequency-dependent case, $2n+1$ new

payoff matrix entries have to be defined. In contrast, for constant selection, only one new variable is needed to describe the fitness of a mutant. There are several ways to generate these new variables. Suppose that m is the mutant type, j is a resident type, and p is the mutant's parent type. In the simplest case, the payoffs of the mutant m against the resident types j, a_{mj}, and the payoffs of the resident types against the new mutant, a_{jm}, are chosen randomly and independently of the current types from some probability distributions. But it is more natural, if the mutants are similar to their parents by inheriting some aspects of their payoff entries. To this end, we randomly choose the payoff of the mutant against a certain resident from a distribution around its parent's payoff against that resident. Although we can take arbitrary distributions for the payoff entries in our model, we focus on the simplest case, where the payoff entries of the offspring are Gaussian distributed around its parent's payoff entries. In other words, the mean of the new payoff entries a_{mj} for the mutant m is given by the payoff a_{pj} of its parent type p against a type j individual. An equivalent rule holds for the payoff of the resident types against a mutant, the new payoff entries a_{jm} have mean a_{jp}. For the Gaussian distribution, a change in the variance corresponds to a change in the intensity of selection[19]. Thus, we always set the variance to one.

This approach implies that mutations with selective advantage are favoured, such that the average fitness increases over time. In our case, this would mean that the effective intensity of selection is also increasing, making the system nonstationary. To avoid this effect, we rescale the payoff matrix by dividing it by the largest absolute value of all payoff entries after every mutation and every extinction.

With the full information on the payoffs, we can calculate the fitness of all types in the population based on the payoff matrix. For example, type j obtains the payoff $\pi_j = (\sum_{k=1}^{d} a_{jk} i_k - a_{jj})/(N-1)$ where i_k is the number of type k individuals in the population and d is the number of types.

Moran dynamics. The Moran process describes the evolutionary dynamics in a finite population with overlapping generations[16,36,37]. We start with a homogeneous population with constant size $N=1,000$ and payoff $a_{11}=1$. In every time step, one individual is chosen randomly in proportion to its fitness, and produces an identical offspring with probability $1-\mu$ or a mutant with probability μ. The offspring then replaces a randomly chosen individual. In nature, mutation rates can range from 10^{-8} to 10^{-3} per base, per generation[38]. Although mutation rates are not affected by local population size, the effect of mutation rates on diversity is directly related to it. To investigate realistic mutation rates in our model, we consider it based on the population size N. As our primary interest is diversity driven by selection rather than diversity driven by mutations, we focus on low mutation rates here. When the mutation rate is high, $\mu > 1/N$, the differences between the population dynamics under frequency-dependent and constant selection are less obvious, as the diversity is mainly driven by mutation. In the case of $\mu = 1/N$, frequency-dependent selection still leads to higher diversity, compared with constant selection (Supplementary Fig. S1). In either case diversity tends to decrease for strong selection, which becomes more pronounced for higher mutation rates (Fig. 3; Supplementary Fig. S1). The reason is that there are only relatively few coexistence games and mutant types may destabilize them—and the stronger the selection, the faster this occurs.

When a mutation occurs, we generate the payoff matrix according to the method described above. We record the number of individuals of different types in every time step, which gives a straightforward picture of the population dynamics over time. As the system evolves for a long time, we record the number of types in every generation. To avoid dependence on the initial condition, we excluded the data of the first 25,000 generations (see the captions of figures) in the averages. To compare constant fitness and frequency-dependent fitness, we run simulations in both cases, which only differ in the process for generating payoff matrices.

The results under weak selection reflect the usual statistical properties of genetic data samples. The probability of m different alleles present in the population under neutral selection, $P(m)$, can be calculated by Ewens' sampling formula, $P(m) = \begin{bmatrix} N \\ m \end{bmatrix} \theta^m / S_N(\theta)$, where $S_N(\theta) = \Pi_{i=0}^{N-1}(\theta + i)$, and $\begin{bmatrix} N \\ m \end{bmatrix}$ are the unsigned Stirling numbers of the first kind[3,39]. For a haploid Moran process, as in our case, the parameter θ is $N\mu$.

Transition probabilities between different coexistence states. Let us consider selection scenarios generated by introducing mutants. Under strong selection and low mutation rates, a population is usually in an equilibrium where different types coexist with each other. The appearance of a new mutant during a phase of coexistence can lead to establishment of a new alliance with the new mutant as an additional type, formation of a new alliance with fewer types (which may include the mutant type or not), replacement of one type from the previous alliance with the new mutant, or extinction of the mutant.

Here we infer the probabilities of these selective consequences under the Moran process. We assume a mutation rate $\mu \ll N^{-2}$. In this case, the average time of waiting for a new mutant is much longer than the average time a population needs to reach a new equilibrium after a mutation. We start simulations from a homogeneous population. Mutants show up at random. After a mutant appears, we wait until the population reaches a new equilibrium, and infer whether the

5

diversity has decreased, increased or been maintained. Each state is characterized only by the number of coexisting types. For example, state one represents that the population is homogeneous, and state two represents that there are two types coexisting. We are interested in the probability that a population changes from one state to another. The transition matrix between different states T is obtained by averaging over the evolutionary trajectories. The element t_{ij} denotes the transition probability from i to j coexisting types. For low mutation rates, t_{ij} is very small for $j>i+1$. The fraction of time that the population spends in each state of diversity is then given by the stationary distribution of the Markov chain determined by the transition matrix T (Fig. 4).

Population size. For fixed selection intensity, the smaller the population size is, the larger the genetic drift. For fixed population size, the smaller the selection intensity is, the larger the genetic drift. Thus, the stochastic effect from the small population size is similar to a smaller intensity of selection. Instead of having two parameters that lead to the same effect, we focussed our discussion on the case of $N=1,000$ for various intensities of selection. Focussing on variable selection intensities is computationally less costly than varying the population size. For both the Moran process and the Wright–Fisher process, the required CPU time scales with the population size, but not with the intensity of selection. For comparison, we also carried out simulations for $N=100$, where the same patterns of difference between frequency-dependent selection and constant selection are observed (Supplementary Fig. S2).

Diploid populations. The evolutionary game dynamics for Mendelian populations has been studied in detail in the past[40–42]; the interaction of two alleles at a diploid locus can be interpreted as a special kind of two-player game, which has a symmetric payoff matrix[43–45]. Suppose there are two types of alleles, allele A and allele B. The fitness of a homozygous individual AA is w_{AA}, the fitness of a BB individual is w_{BB} and the fitness of a heterozygous individual AB is w_{AB}. This can be formalized as

$$\begin{array}{cc} & \begin{array}{cc} A & B \end{array} \\ \begin{array}{c} A \\ B \end{array} & \begin{pmatrix} w_{AA} & w_{AB} \\ w_{AB} & w_{BB} \end{pmatrix}. \end{array}$$

When $w_{AA}>w_{AB}$ and $w_{BB}>w_{AB}$, it corresponds to under-dominance, where heterozygous individuals have a lower fitness than homozygous individuals. When $w_{AA}<w_{AB}$ and $w_{BB}<w_{AB}$, a condition of over-dominance is described. A diploid population with more than two types of alleles at a single locus can be described by a symmetric $n \times n$ matrix, where n is the number of different alleles and matrix element w_{ij} represents the fitness of a diploid individual with genotype ij.

We have simulated the dynamics of such a diploid population under different selection intensities based on the Moran process (Supplementary Fig. S3). In every time step, one allele is replaced, and thus the time for one generation is twice as long as the one in a haploid Moran model. Under the same mutation rate, the diversity of a diploid population (Supplementary Fig. S3a) is higher compared with the frequency-dependent case in a haploid population (Fig. 4b). This is because symmetry of the payoff matrix $w_{ij}=w_{ji}$ favours coexistence of different types. In the simplest case with only two alleles, a coexistence game corresponding to over-dominance has the ordering of payoffs, $w_{AA}<w_{AB}$ and $w_{BB}<w_{AB}$. Suppose allele A is a random mutant from allele B, and the payoffs of the new genotypes, w_{BB} and w_{AB}, are random variables with mean w_{BB}. Thus, the probability to have a coexistence of these two alleles is 37.5%, which is larger than 25%, the probability to have a coexistence in a two-allele haploid model. In the diploid approach, the fitness of a genotype ij, w_{ij} is a constant number, and does not change with the composition of the frequencies of different genotypes (but the fitness of an allele is frequency dependent). Hence, this kind of frequency dependence corresponds to constant selection in a haploid population. To introduce frequency dependence on this level leads to serious mathematical intricacies[40,43,45,46].

Wright-Fisher dynamics. In the Wright-Fisher Model, all individuals produce a large number of offspring proportional to their fitness. Then, all individuals from the previous generation die, and are replaced by N new individuals sampled at random from the offspring pool. This corresponds to a multinomial sampling of offspring. The expected number of offspring of a certain type, j, in the next generation is proportional to its fitness. Neglecting mutations, the expected number of type j is $N(i_j f_j)/\sum_{k=1}^{d} i_k f_k$, where, i_j and f_j are the number of individuals and the fitness of type j. If there is no difference in fitness between types in the population, the expected number of individuals of the different types is constant and the composition of the population will only be changed by random drift. When we consider mutations, the probability that an offspring mutates is μ. On average, there are $N\mu$ new mutants in the population per generation.

We analyse the same quantities in the Wright–Fisher process as above in the Moran process. We see similar patterns in the differences between constant selection and frequency-dependent selection (Supplementary Fig. S4). However, for very strong selection, diversity decreases in our set-up. This can be understood as follows: consider a stable coexistence between two types. If a fluctuation leads the system away from this point, one type has a slight payoff advantage, which causes

a large fitness advantage owing to our exponential payoff to fitness mapping. Such a fluctuation can lead to the immediate fixation of one type in the next generation and thus destroy the stable coexistence quickly.

Again, under weak selection and low mutation rates, we recover the diversity given by Ewens' sampling formula. Under neutral selection, random drift in a Moran process is twice as strong as in a Wright–Fisher process[47]. Thus, we have $\theta=2N\mu$ in Ewens' sampling formula for the Wright–Fisher process.

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Author contributions

W.H. and A.T. devised the model. W.H. B.H., C.H., and A.T. analysed the model and wrote the paper.

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Supplementary Information for

Emergence of stable polymorphism driven by evolutionary games between mutants

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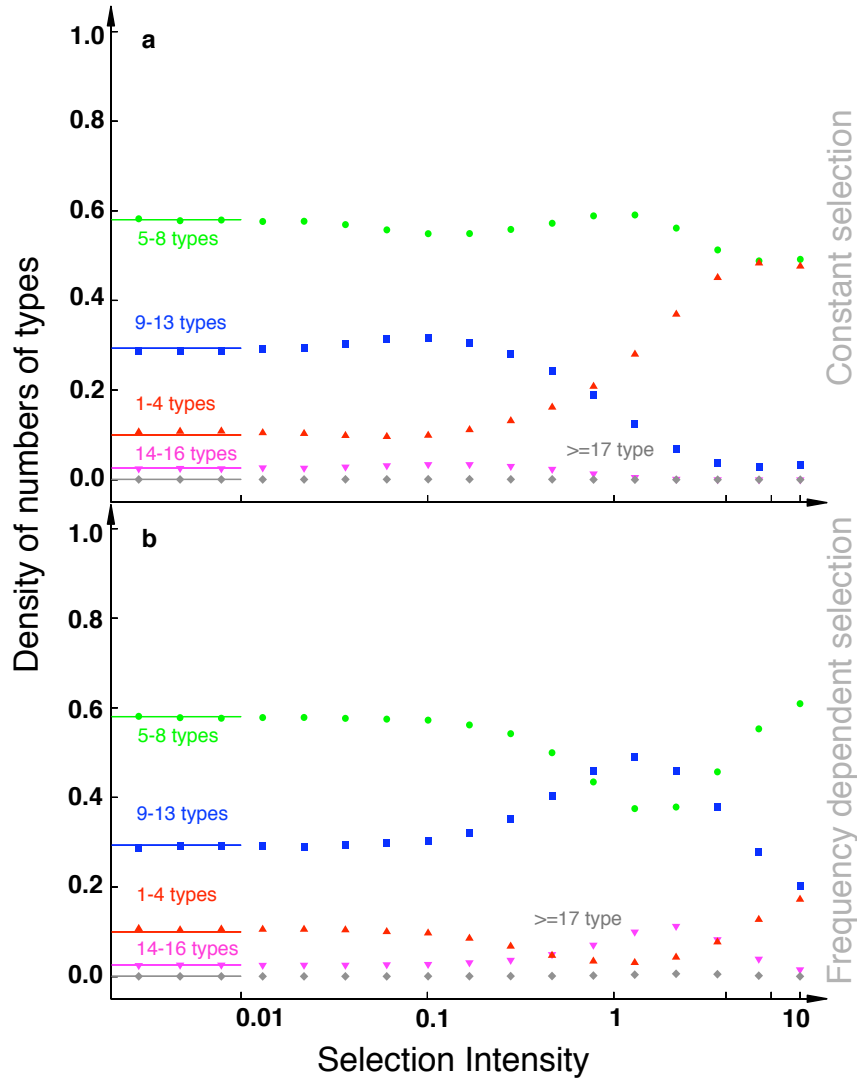
Supplementary Figure S1: **Distribution of the number of types under high mutation rates.** The expected number of types for different selection intensities is shown in a Moran process with a high mutation rate, $\mu = 1/N$. The symbols are simulation results, and the lines are Ewens' sampling formula under neutral selection. Under neutral or weak selection, the diversity is much higher than for smaller mutation rates, both for constant selection (top) and frequency-dependent selection (bottom). It is unlikely that any type occurs with a high frequency, and it is most likely to observe a comparatively large number of low-frequency types. For strong selection, the diversity under frequency-dependent selection is much higher compared with constant selection (population size $N = 1000$, mutation rate $\mu = 10^{-3}$ per time step, average over 500 independent realizations, and 10^7 time steps, after an initial period of 25000 time steps).
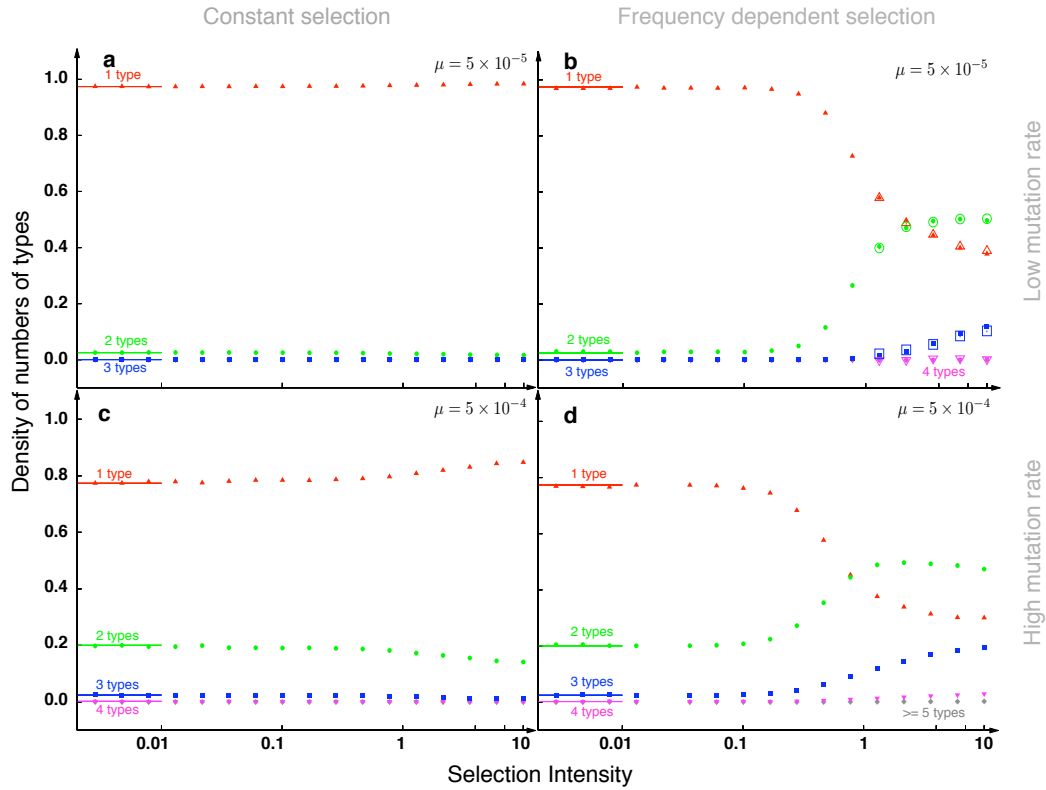
Supplementary Figure S2: **Distribution of number of types for a small population.** The expected number of different types for different selection intensity is shown under a Moran process for $N = 100$, the case of $N = 1000$ is shown in the main text. As for $N = 1000$, our simulations (filled symbols) agree with Ewens' sampling formula under weak selection (lines). The top panels show a low mutation rate, $\mu = 5 \times 10^{-5}$ per time step. The bottom panels show a higher mutation rate, $\mu = 5 \times 10^{-4}$ per time step. For constant selection (left), diversity decreases when selection becomes stronger. For frequency dependent selection (right), from nearly neutral selection to extremely strong selection, the number of types coexisting in the population for most of the time increases. (population size $N = 100$, averages obtained over 500 independent realizations and 10^6 generations per realization, where the data of first $25N$ generations are excluded).

3
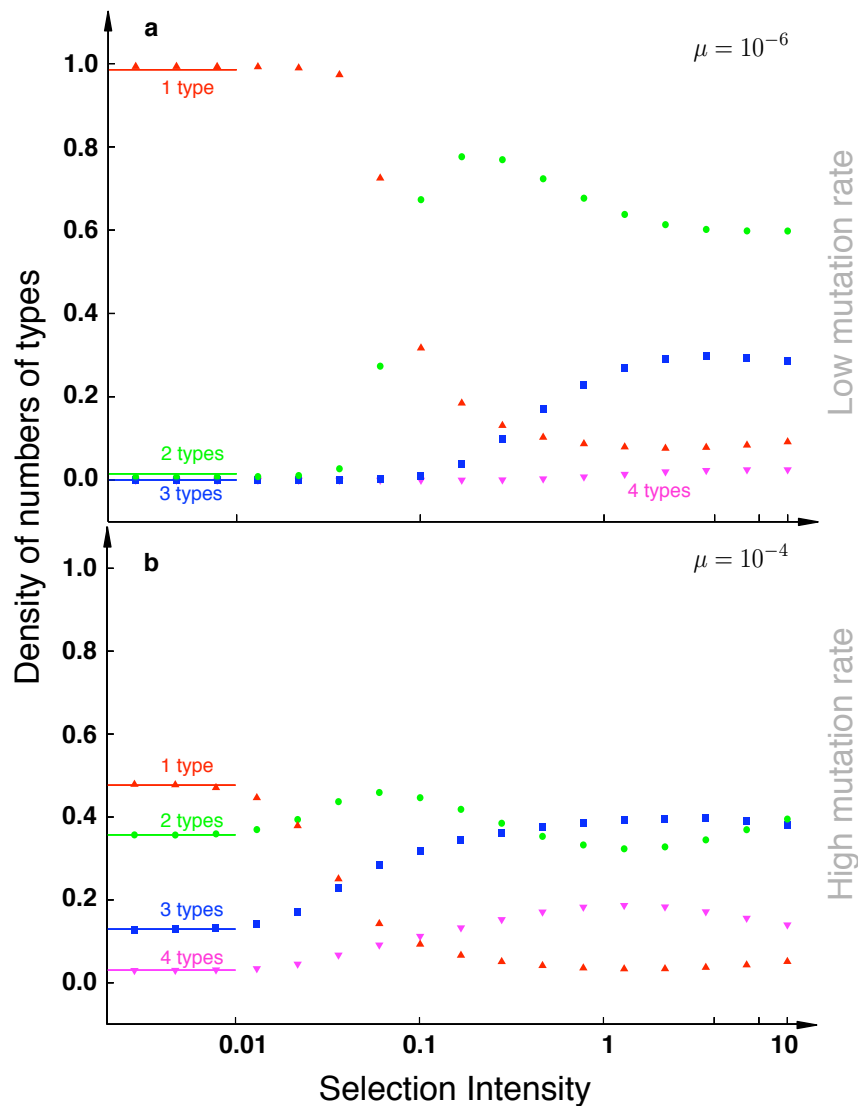
Supplementary Figure S3: **Distribution of number of types in a diploid population under a Moran process.** The symbols are simulation results, and the lines represent Ewens' sampling formula. The top panel shows a low mutation rate, $\mu = 10^{-6}$ per time step. The bottom panel shows a higher mutation rate, $\mu = 10^{-4}$ per time step. From nearly neutral selection to extremely strong selection, the number of types which stably coexist in the population increases (population size $N = 1000$, averages obtained over 500 independent realizations and 10^7 generations per realization, where the data of first 25000 generations are excluded).
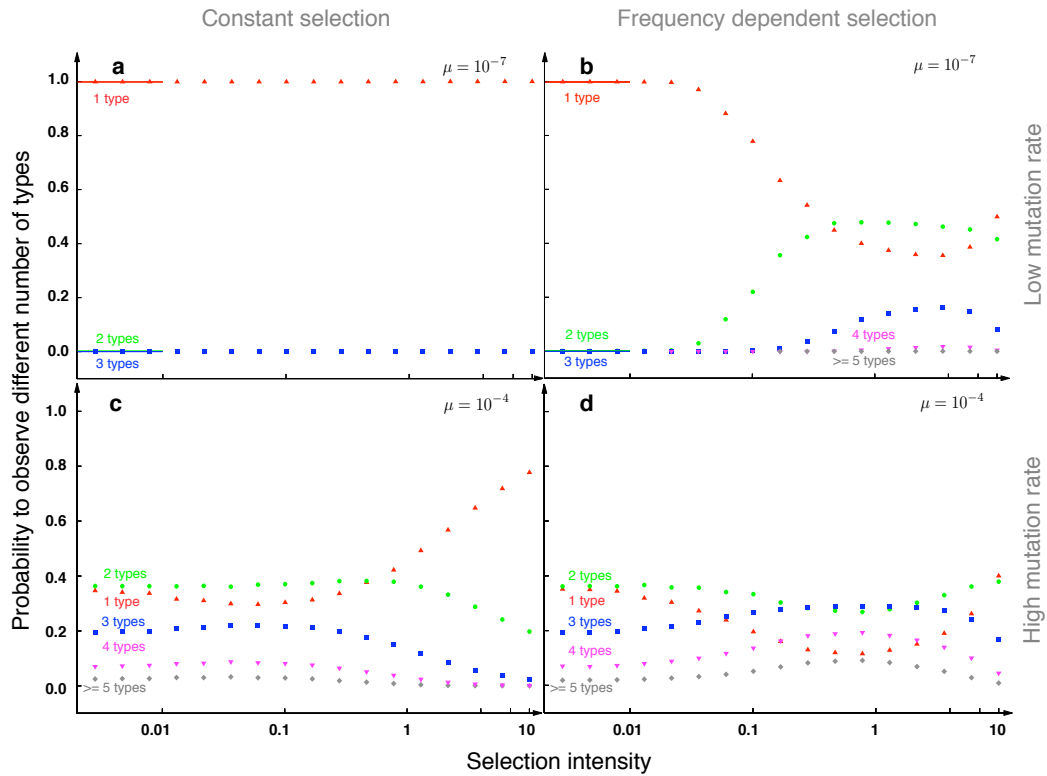
Supplementary Figure S4: **Distribution of number of types under a Wright-Fisher process.** The expected number of different types for different selection intensities is shown here. The symbols are simulation results, and the lines are Ewens' sampling formula derived for neutral selection. For constant selection (left), diversity decreases when selection becomes strong. For frequency dependent selection (right), from nearly neutral selection to extremely strong selection, the number of types coexisting in the population for most of the time increases. The decrease of diversity for very high selection intensity is due to the effect that even minimal fluctuations can quickly destroy stable coexistence under strong selection in the Wright-Fisher process (population size $N = 1000$, average over 500 independent realizations, and 10^7 generations per realization, where the data of first 25000 generations are excluded).

3.3   Rescaling the average fitness

Under the interplay of mutation and selection, the population dynamics differs for different selection intensities. Under strong selection, frequency dependent selection leads to higher diversity than constant selection. In this part, we will discuss the change of the average fitness under strong selection.

In Section 3.2, we assume that the payoff entires of the offspring are Gaussian distributed around its parent's payoff entries. The beneficial mutation rate under frequency dependent selection is $\theta = 0.5$ (see the definition of θ in Section 2.2). Under constant selection, mutants with higher fitness take over the whole population sequentially, and thus the average fitness of the population increases. Interestingly, for frequency dependent selection, we also observe an increase of the average fitness over time for $\theta = 0.5$. This might be related to the increase of fitness values, which is exponential under our fitness mapping function, $F = e^{\beta\pi}$. Here, F, β and π are the fitness value, the selection intensity and the payoff value respectively.

On one hand, this brings a difficulty in our computer simulations, since we are interested in stationary properties, but fitness quickly increases in this way. The more generations realized in one simulation, the large the fitness values become. However, since we look at the stationary distribution of allele frequencies, it is necessary to simulate a certain number of generations in one realization to obtain stable results. To solve this problem, we normalize the payoff matrix after every mutation and every extinction such that the highest absolute payoff value equals one.

One the other hand, the observation that the average fitness increases under $\theta = 0.5$ leads to some interesting questions. How does the average fitness of the population change due to frequency dependent mutations? Can the average fitness decrease under certain conditions? Is this change related to the beneficial mutation rate θ? We carry out the same simulations without

normalizing the payoff values under different θ in finite populations. They show that the average fitness can decrease if the beneficial mutation rate is small enough. To have a further and more accurate understanding of this question, we turn back to a deterministic system with infinite population size. In the next chapter, we analytically calculate the probability that the average fitness increases after a random mutation in a population with two types. Simulations are performed for populations with more than two types, see Chapter 4.

Average fitness in the frequency dependent mutation model in infinite populations

4.1 The average population fitness

The average fitness of a population (shortened as the average fitness in the following context) is also called mean population fitness, and defined as the sum of the fitness of different types weighted by their frequencies [75, 12]. Fitness is considered as the average number of offspring from a certain type of individuals, and the reproduction unit is the individual rather than the population. Hence, comparing the average fitness between different populations may make limited sense. Instead, the changes of the average fitness of the same population over time is a more interesting quantity from the perspective of evolutionary dynamics.

These changes have different causes: a fluctuating environment can result in fluctuations in the total number of offspring of all types, mutations or migration can bring new types of individuals into the population, and the average fitness can change because the frequencies of different types change under selection and random genetics drift. To seperate the effects of different factors, we consider the change of the average fitness due to frequency dependent mutations in infinite populations in a constant environment.

Constant selection in haploid populations

There are many theoretical studies addressing this question for constant selection in haploid populations, or frequency dependent selection based on diploidy. In a haploid population with two types, the average fitness is non-decreasing under strong constant selection [12]. When a mutant type with lower fitness appears, it will be removed from the population under strong selection, and the average fitness remains the same. When an advantageous mutation happens, it can take over the population and increases the average fitness. Thus, in total, the average fitness in a haploid population will increase over time.

This result can also be derived mathematically. Here, we give an example of a haploid population of infinite size and discrete generations. Suppose there are two types, A and B in the population. The fitness of type A is W_A and the fitness of type B is W_B. In the current generation, the frequencies of type A and B are x_A and x_B respectively. The average fitness of the whole population in the current generation can be written as $\overline{W} = x_A W_A + x_B W_B$. The variance of the fitness in the population, denoted as σ_W^2, is $x_A W_A^2 + x_B W_B^2 - (x_A W_A + x_B W_B)^2$.

Now we look at the frequencies and the average fitness in the next generation, x_A', x_B' and $\overline{W}'$. According the definition in Eq. 1.13 in Chapter 1.3.1, we have

$$x_A' = \frac{x_A W_A}{x_A W_A + x_B W_B}$$

and

$$x_B' = \frac{x_B W_B}{x_A W_A + x_B W_B} \ .$$

Thus, the average fitness in the next generation is

$$\overline{W}' = x_A' W_A + x_B' W_B = \frac{x_A W_A^2 + x_B W_B^2}{x_A W_A + x_B W_B} \ .$$

The difference between the average fitness in the current and the next generation can be written as

$$
\begin{aligned}
\overline{W}' - \overline{W} &= \frac{x_A W_A^2 + x_B W_B^2}{x_A W_A + x_B W_B} - (x_A W_A + x_B W_B) \\
&= \frac{x_A W_A^2 + x_B W_B^2 - (x_A W_A + x_B W_B)^2}{x_A W_A + x_B W_B} \\
&= \frac{\sigma_W^2}{\overline{W}} \ .
\end{aligned}
$$

As the variance of the fitness is non-negative and the average fitness is always positive, the difference of the average fitness between the next generation and the current generation is always larger than or equal to 0. Thus, the average fitness remains the same or increases over generations in a haploid population under strong constant selection.

Diploid populations and Fisher's fundamental theorem

Under frequency dependent selection, the effects of mutations on the average fitness are more complicated. In population genetics, frequency dependent selection arises in Mendelian populations (Chapter 1.3.2). One well-known study on diploid populations is Fisher's fundamental theorem of natural selection [14].

The fundamental theorem of natural selection was first formulated in the second chapter of Fisher's book *The Genetical Theorem of Natural selection*. It is stated that "*the rate of increase in fitness of any organism at any time is equal to its genetic variance in fitness at that time*" [14] . There are many standard assumptions in the fundamental theorem [126, 127]: for the one-locus case, it assumes a limited number of allele types withouts mutations; the fitness of alleles linearly depend on the allele frequencies, but the fitness of the genotypes are fixed values; discrete generations are considered for an infinite population without genetic drift.

Suppose there are n types of alleles in one locus, allele 1, 2, ..., n. The frequency of allele i is x_i, where $i \in \{1, 2, ..., n\}$. Genotype ij consists of allele i and allele j with order, and its frequency and fitness are x_{ij} and W_{ij} respectively. In the fundamental theorem, genotype ij and genotype ji are considered to be identical, which leads to $x_{ij} = x_{ji}$ and $W_{ij} = W_{ji}$. Thus, the frequency of genotype ij without allelic order is $2x_{ij}$ when $i \neq j$, and $x_i = \sum_j x_{ij}$. The average fitness of the whole population, $\overline{W}$, is $\sum_i \sum_j x_{ij} W_{ij}$. Suppose the frequency of genotype ij with order in the next generation is x_{ij}'. The change of the average fitness between the next generation and the current generation is

$$\Delta \overline{W} = \sum_i \sum_j (x_{ij}' - x_{ij}) W_{ij}, \tag{4.1}$$

as the genotype fitness W_{ij} is a fixed value. The change of the average fitness can be positive or negative according to this definition. Interestingly, this seems to disagree with the conclusion of the fundamental theorem, which states that the average fitness will always increase in such a model [14, 128, 127].

Price and Ewens pointed out that there was an universal misunderstanding on the Fisher's fundamental theorem in population genetics [129, 127]. The change of the average fitness referred in the fundamental theorem is not the total change of the average fitness, but a partial change only related to the change of the genotype frequency, $x_{ij}' - x_{ij}$ in Eq. 4.1. The fundamental theorem considers a special situation, where W_{ij} can be written as

$$W_{ij} = \overline{W} + \alpha_i + \alpha_j. \tag{4.2}$$

Here, α_i is called the average effect of the allele i, and assumed to be a fixed value. For all allele types, $\sum_i x_i \alpha_i = 0$. Ewens proofed that $\overline{W}$ is exactly equal to the additive genetic variance, $\sum_i \sum_j x_{ij} (\alpha_i + \alpha_j)^2$, which is a non-negative value, under all assumptions above [127].

Obviously, Eq. 4.2 is not a general case. In a diploid population with n alleles, there exist $n(n+1)/2$ genotypes. Thus, the degree of freedom on the left side of this equation is $n(n+1)/2$, but the degree of freedom on the right side of this equation is $n+1$. The genotype fitness can not be written as Eq. 4.2 in all situations. In a summary, Fisher's fundamental theorem describes the change of the average fitness in a special case. How does the average fitness changes under frequency dependent selection is still an unanswered question.

Here, we consider a haploid population, where frequency dependent selection comes from the interaction of different types (Chapter 1.3.3). In this chapter, we extend our frequency dependent mutant model to infinite populations, where the population dynamics is captured by the replicator equations. For a model with only two types, we calculate the probabilities that the average fitness increases, decreases and remains the same according to the payoff distribution. Interestingly, it is only related to the probability that a mutant payoff entry exceeds the payoff of its parent under frequency dependent selection, θ (see the detailed definition in Section 2.2).

For a model with more than two types, we numerically simulate the evolutionary processes based on the replicator equations. We assume that every mutation brings a new game and thus a new group of replicator equations. A new mutation happens immediately after the population reaches the equilibrium, which is given by the current group of replicator equations and the initial composition of the population. This corresponds to low mutation rates, where the time a population needs to reach an equilibrium is shorter than the waiting time for the next mutation.

4.2 Random frequency dependent mutations can decease the average fitness

Submitted Paper (in revision): The impact of random frequency-dependent mutations on the average population fitness

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The impact of random frequency-dependent mutations on the average population fitness

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Abstract

In addition to selection, the process of evolution is accompanied by stochastic effects, such as changing environmental conditions, genetic drift and mutations. Commonly it is believed that without genetic drift, advantageous mutations quickly fixate in a halpoid population due to strong selection and lead to a continuous increase of the average fitness. This conclusion is based on the assumption of constant fitness. However, for frequency dependent fitness, where the fitness of an individual depends on the interactions with other individuals in the population, this does not hold. We propose a mathematical model that allows to understand the consequences of random frequency dependent mutations on the dynamics of an infinite large population. The frequencies of different types change according to the replicator equations and the fitness of a mutant is random and frequency dependent. To capture the interactions of different types, we employ a payoff matrix of variable size and thus are able to accommodate an arbitrary number of mutations. We assume that at most one mutant type arises at a time. The payoff entries to describe the mutant type are random variables obeying a probability distribution which is related to the fitness of the parent type. We show that a random mutant can decrease the average fitness under frequency dependent selection, based on analytical results for two types, and on simulations

1

for n types. Interestingly, in the case of at most two types the probabilities to increase or decrease the average fitness are independent of the concrete probability density function. Instead, they only depend on the probability that the payoff entries of the mutant are larger than the payoff entries of the parent type.

Background

Mutations provide a continuous source of variation in natural populations, on which natural selection can act. When fitness is assumed to be constant, only those mutations with higher fitness values will be fixed in a haploid population under strong selection and negligible random drift. Thus, the average fitness of the population would monotonically increase in evolutionary time. There have been numerous hypotheses why this is not what is observed in nature: for instance, environmental changes require new adaptions [1, 2] or coevolution can imply continuous adaptation without increasing the average fitness [3–5]. However, these are not aspects that we intend to include here. Instead, we focus on a haploid population in a constant environment, and explore frequency dependent fitness, which can be described by evolutionary game theory [6–11]. In this framework, the fitness of a type depends on the frequencies of other types of individuals in the population. We address the very general question of how the average fitness changes when it is driven by random mutations under frequency dependent selection.

The fitness effects of new mutations have gained significant attention both in experimental research and theoretical work [12, 13]. In experiments, the distribution of fitness effects depends on several aspect of the experimental setup, e.g. how well adapted the organism is to the environment and whether only single mutants or also double mutants (mutants differing from the wild type by two mutations) are considered. Different shaped distributions were proposed to capture the fitness distributions of random mutants under constant selection [14–17]. The concrete shape of fitness distributions of spontaneous mutations varies between species and even within the same species on different parts of DNA [18]. Although no common conclusion on this has been obtained yet – and a universal fitness distribution may as well not exist – it is often possible to estimate some general properties, such as the proportion

of advantageous mutations and the mean value of the fitness of the mutations [19, 20].

The concept of random distributed and frequency dependent fitness of mutations can be addressed by evolutionary game theory [21], which considers evolutionary processes under frequency dependent selection [22]. In this framework, a population of interacting individuals is considered. In the simplest case of linear frequency dependence, the interactions of different types of individuals are captured by a payoff matrix for a game. Those types which are more successful in the game will have a higher reproduction rate. We introduce a payoff matrix with variable size to capture mutations and extinctions. The new payoff entries introduced by mutations are independently drawn from a probability distribution, which corresponds to the concept of randomly distributed fitness. By tracking the dynamics of the payoff matrix and the compositions of the population, we are able to investigate several aspects of an evolving system, such as the average fitness changes of the population, the impact of the fitness distribution on these changes and the expected level of diversity.

Results
Dynamics for populations with two types

Let us start with a population of a resident wild type (R) and a mutant type (M). Suppose the fitness of a wild type in a homogenous population is d. For constant selection, the fitness distribution is simply a one dimensional distribution around d. For frequency dependent selection, the fitness of a mutant must be defined based on more than a single number. We can write it as an evolutionary game based on a 2×2 payoff matrix with three new payoff entries, a, b and c

$$\begin{array}{c} \\ \begin{array}{cc} \text{M} & \text{R} \end{array} \\ \begin{array}{c} \text{M} \\ \text{R} \end{array} \begin{pmatrix} a & b \\ c & d \end{pmatrix}. \end{array}$$

When a mutant and a wild type interact, the mutant obtains fitness a, and the wild type obtains c. When a mutant meets another mutant, it obtains b. Following the concept of randomly distributed fitness of mutations, the entries a, b and c are defined as random variables. We assume that a, b and c independently follow the same probability distribution

3

given by a probability density function $f(x)$. While this is the simplest possibility, it may be more realistic to assume correlations between the payoff entries characterizing each type, i.e. between a and b as well as between c and d (see below, section Games with equal gains from switching). However, in the extreme case of $a = b$ and $c = d$, this would recover the case of constant selection, so we expect that such correlations would lead to results intermediate between constant and frequency dependent selection. We discuss how this distribution affects the changes in the average fitness during the evolutionary process. It turns out, the probability $\theta = \int_d^\infty \mathrm{d}x\, f(x)$ that a payoff entry is larger than the fitness of the wild type (the parent type in the case of n types) d, is of particular interest and determines the change in the average fitness when initially only a single type is present. Remarkably, all other aspects of the fitness distribution turn out to be irrelevant for this observable.

The dynamics of evolving populations of interacting individuals shows stochastic fluctuations when selection is weak and when populations are small. In addition, stochasticity can arise based on environmental changes or stochastic effects due to mutations. As we are interested in the effects of frequency dependent selection, we only consider stochasticity arising from random frequency dependent mutations and use the replicator equations to model evolutionary dynamics. The frequency of a certain type changes deterministically according to the difference of its own fitness to the average fitness in the population.

Suppose x is the frequency of the mutant type and $1 - x$ the frequency of the wild type, respectively. We can define the fitness of the mutant type, W_1, and the fitness of the wild type, W_2, as

$$
\begin{aligned}
W_1 &= ax + b(1 - x), \\
W_2 &= cx + d(1 - x),
\end{aligned} \tag{1}
$$

where a, b, c, and d are the entries in the payoff matrix. The average fitness of the population $\overline{W}$ is given by

$$
\overline{W} = xW_1 + (1 - x)\, W_2. \tag{2}
$$

If the fitness of the mutant type is larger than the average fitness, its frequency will increase. If the fitness of the mutant type is below the average fitness, its frequency will decrease. We follow the usual assumption that the change of the frequency of the mutant type is given by

4

the replicator equation [23–25]

$$\dot{x} = x\left(W_1 - \overline{W}\right) = x\left(1 - x\right)\left(W_1 - W_2\right). \tag{3}$$

The change of the wild type frequency follows immediately as $-\dot{x}$. This dynamics is fully determined by the entries of the payoff matrix. Different constellations of the payoff entries cause different dynamical patterns. In the following, we discuss all generic cases of two-type interactions and how the average fitness of the population changes under the different situations.

First, we analyze the case where the mutant has higher fitness than the wild type for all frequencies x. This is the case for $a > c$ and $b > d$. The wild type goes extinct and the mutant type will be fixed in the population. Thus, the average fitness $\overline{W}$ in the new equilibrium $x = 1$ is given by the payoff entry of the mutant type interacting with itself, a. We are interested in the probability, that the fitness of the population is increased after the fixation of the mutant. This becomes a conditional probability of $a > d$ given that $a > c$ and $b > d$. Applying Bayes Rule, this can be expressed as

$$\begin{aligned}
p(\overline{W}(1) > d \mid a > c, b > d) &= p(a > d \mid a > c, b > d) \\
&= \frac{p(a > d, a > c, b > d)}{p(a > c, b > d)} \\
&= \frac{p(a > d, a > c)}{p(a > c)}.
\end{aligned} \tag{4}$$

We assume that the random variables a, b and c are independently derived from the same probability distribution. Hence, b does not depend on a or on c. Thus, the probability of $b > d$ is independent from the probability that $a > d$, which is used in Eq. (4). Since a and c are sampled from the same distribution, we have $p(a > c) = 1/2$ in the denominator. For the numerator, we have

$$\begin{aligned}
p(a > d, a > c) &= \int_d^\infty \mathrm{d}a \int_{-\infty}^a \mathrm{d}c\, f(c)f(a) \\
&= \int_d^\infty \mathrm{d}a\, F(a)\, F'(a) \\
&= \frac{1}{2} - \frac{F(d)^2}{2},
\end{aligned} \tag{5}$$

5

where $F(x)$ is the cumulative distribution function of a random variable with probability density function $f(x)$. As the probability that one of the new payoff entries a, b, c is greater than the wild type fitness d is $\theta = \int_d^\infty dx\, f(x) = 1 - F(d)$. Using this expression in Eq. (5), we arrive at

$$p(\overline{W}(1) > d \mid a > c, b > d) = 2\theta - \theta^2. \tag{6}$$

Strikingly, this only depends on θ, and is independent of the concrete choice of the probability density function $f(x)$. In population genetics, beneficial mutation rates are measured based on the concept of constant fitness, where the fitness of the mutant and the fitness of the wild type are both constant numbers. However, if we consider frequency dependent fitness, a new parameter is needed to represent the proportion of beneficial mutations. One option arising from our approach is to compare the payoff value of the mutant with the payoff value of the wild type when they are confronted by the same opponent. Since θ is the probability that the new payoff value of the mutant is larger than the wild type's payoff d, it corresponds to the probability that a mutation is beneficial under the constant selection scenario. If θ can be measured, the probability that the average fitness is increased by a random mutant is independent of the payoff distribution according to Eq. (5). But different choices of probability density functions $f(x)$ will result in different values of θ, thus leading to different probabilities to increase the average fitness.

Next, we assume that a mutant type occurs with lower fitness than the wild type. With frequency dependence, there are two situations for such a mutant type. The mutant type can either have lower fitness than the wild type for all frequencies, or it can have a lower fitness only for small frequencies. In both cases, the mutant will go extinct and the average fitness will remain unchanged, since a mutant type is supposed to arise with a small amount.

Finally, a mutant type could be initially advantageous compared to wild types, but turn to be disadvantageous when it has reached a certain frequency. This occurs for $a < c$ and $b > d$. In this case neither the wild type nor the mutant type can take over the population, but there exists a mixed equilibrium consisting of mutant types at a frequency $x^* = \frac{b-d}{b-d-a+c}$ and wild types at a frequency $1 - x^*$. In this coexistence equilibrium, the fitness of the wild type subpopulation is equal to the fitness of the mutant type subpopulation. The average

fitness of the system in the equilibrium is given by

$$\overline{W}(x^*) = ax^* + b(1 - x^*) = \frac{bc - ad}{b - d - a + c}. \tag{7}$$

Again, we ask for the probability of having a coexistence game that increases the average fitness. This is the conditional probability that $\overline{W}(x^*) > d$ given that $a < c$ and $b > d$, which can be written as

$$
\begin{aligned}
&p(\overline{W}(x^*) > d \mid a < c, b > d) \\
&= p\left((b - d)(c - d) > 0 \mid a < c, b - d > 0\right) \\
&= p\left(c > d \mid a < c\right) \\
&= \frac{p\left(c > a, c > d\right)}{p\left(c > a\right)}
\end{aligned} \tag{8}
$$

This is identical to Eq. (4) if one exchanges $a \leftrightarrow c$. Since a and c have the same distribution, we recover the result from Eq. (6),

$$p(\overline{W}(x^*) > d \mid a < c, b > d) = 2\,\theta - \theta^2. \tag{9}$$

In other words, the probability to increase fitness is the same in a coexistence game as in a game where the mutant dominates the wild type.

Let us now combine the results and consider the changes of the average fitness over all types of interactions. The probability to increase the fitness due to a new mutation is given by

$$
\begin{aligned}
p(\overline{W} > d) = &\underbrace{p(\overline{W} > d \mid a > c, b > d)}_{2\theta - \theta^2} \underbrace{p(a > c, b > d)}_{\frac{\theta}{2}} \\
&+ \underbrace{p(\overline{W} > d \mid a < c, b > d)}_{2\theta - \theta^2} \underbrace{p(a < c, b > d)}_{\frac{\theta}{2}} \\
&+ \underbrace{p(\overline{W} > d \mid b < d)}_{0} \underbrace{p(b < d)}_{1 - \theta} \\
= &\, 2\,\theta^2 - \theta^3
\end{aligned} \tag{10}
$$

In a similar manner, we can calculate the probability to decrease the average fitness due to a new mutation. When the mutant dominates the wild type, the average fitness may still

7

decrease. This is exactly what happens in the Prisoner's Dilemma [26, 27]. Equivalently to the calculation above, we have

$$
\begin{aligned}
p(\overline{W}(1) < d \mid a > c, b > d) &= \frac{p(a < d, a > c, b > d)}{p(a > c, b > d)} \\
&= \frac{p(a < d, a > c)}{p(a > c)} \\
&= (1 - \theta)^2.
\end{aligned}
\tag{11}
$$

For the probability to decrease the average fitness in a coexistence game, we find

$$
p(\overline{W}(x^*) < d \mid a < c, b > d) = (1 - \theta)^2.
\tag{12}
$$

Thus, using a calculation similar to Eq. (10), the overall probability to decrease the average fitness is given by

$$
p(\overline{W} < d) = \theta - 2\theta^2 + \theta^3.
\tag{13}
$$

Also the probability to maintain a constant average fitness can be calculated in this way. For continuous fitness distributions, there are no strictly neutral mutations. As the fitness of the wild type is a specific value of the continuous random variable, the probability of having a strict neutral mutation, the fitness of which is equal to the fitness of the wild type, is 0. Thus, the average fitness is only maintained when the mutant goes extinct, which occurs with probability

$$
p(\overline{W}(0) = d) = p(b < d) = 1 - \theta
\tag{14}
$$

We discussed the changes of the average fitness in a two-type population under frequency dependent selection above. Under constant selection, the average fitness will increase with probability θ and decrease with probability 0. As for frequency dependent selection, it will remain constant with probability $1 - \theta$. Fig. 1 illustrates these results and compares frequency dependent selection to constant selection for all values of θ. For frequency dependent selection, there is an intersection point θ_*, where the probability to increase the average fitness and to decrease the average fitness are equal. Using Eq. (10) and Eq. (13), this becomes $2\theta_*^2 - \theta_*^3 = \theta_* - 2\theta_*^2 + \theta_*^3$, and we have $\theta_* = \frac{\sqrt{2}-1}{\sqrt{2}}$. Small values of θ are typically considered to

8

be of biological relevance. In this case, frequency dependent selection tends to decrease the average fitness: for $\theta < \frac{\sqrt{2}-1}{\sqrt{2}}$, it is more likely that the average fitness of the population is decreased by a single random frequency dependent mutation; for $\theta > \frac{\sqrt{2}-1}{\sqrt{2}}$, it is more likely that it is increased.

Frequency-dependent selection can arise from different mechanisms. In a haploid population, frequency-dependent selection are caused by the interactions of different types. In this case, the fitness of a particular type depends on the frequency of its own and other types in the population. However, in a diploid population, frequency dependent selection on alleles can arise also from the interactions of two alleles at one locus [8, 28, 29]. Thus, our model can be easily extended to a diploid population in such a case, which leads to different results for the average change in fitness, see Appendix.

Games with n types

So far, we have discussed the change of the average fitness of a population consisting of at most two types. However, when two types coexist in a stable polymorphism, an additional type can enter the population and persist. To describe the interaction of individuals in a population with more than two types, we extend the 2×2 payoff matrix to a $n \times n$ payoff matrix A, where n is the number of types in the population. The entry in the i-th row and the j-th column, A_{ij} represents the fitness of an i-type individual interacting with a j-type individual. The fitness of type i on average can be written as $W_i(x) = \sum A_{ij} x_j$, where $j = 1, 2, 3..., n$, and x_j is the frequency of type j, such that $\sum_{j=1}^{n} x_j = 1$.

In our model, n is not a fixed number. When a type goes extinct, the corresponding row and column are deleted in the payoff matrix. Thus, the value of n decreases by one. When a mutation occurs, one row and one column are added to describe the interactions of the mutant type and resident types, which increases the size of the payoff matrix by one. The new entries introduced by a mutation are generated based on the assumption that the interactions between the mutant type m and any resident type i are similar to those between the parent type p and the resident type i. In our case, we assume a_{mj} is a random variable which is drawn from a probability density function $f(x)$ and is larger than a_{pj} with probability θ.

Since the complexity of the population dynamics increases considerably with the number

of types, it would be difficult to obtain the changes of the average fitness in a polymorphic population of $n > 2$ types analytically. Therefore, we use the replicator equations to simulate the dynamics of the system with several types. We start the simulation from a homogenous population. However, since we are interested in the average fitness changes and other stationary quantities averaged over a long time period, the initial number of types has no effects on the results. The time intervals are sufficiently small that at most one mutant type can appear during one time interval. The probability that a resident type i produces a mutant type is $\mu x_i W_i(\mathrm{x}) / \overline{W}(\mathrm{x})$, where $i = 1, 2, 3, ..., n$. Thus the probability that a mutant arises from a resident type i increases with the fitness of this type. However, for the whole population, the probability that a mutant type appears is just the mutation rate, $\sum_{i=1}^{n} \mu x_i W_i(\mathrm{x}) / \overline{W}(\mathrm{x}) = \mu$.

We can chose arbitrary mutation rates in our simulations. However, when the mutation rate is very high, a population might experience a new mutation when it is still in a non-equilibrium state triggered by the previous mutation. In this case, the fate of a mutant is not only driven by selection, but also by the interplay of mutations. Since we are interested in the fitness consequences of frequency dependent selection, we choose the mutation rate small enough such that a population disturbed by a mutation reaches the new equilibrium before the next mutation arises.

We first look at the transition probability between different levels of diversity under mutation and selection. Once a mutation occurs it can coexist with all resident types, replace one resident type, outcompete some resident types, or go extinct. The transition matrix T describes this dynamics. Suppose the number of types in the current population is n. The element T_{ni} denotes the transition probability from n to i coexisting types, where $i = 1, 2, 3, ..., n+1$, see Fig. 2. We obtain the values in the transition matrix from numerical simulations. Every transition event triggered by a mutation is recorded and the probability to go from a certain number of types to another number of types is averaged over many realizations. These transition probabilities show some interesting properties. The probability to keep the current diversity (the element in the main diagonal in a row) is always higher than the probabilities to decrease or increase the diversity (all the other elements in the same row), see Fig. 2 and Ref. [30]. Interestingly, for a population consisting of less than

10

4 types, the probability to increase the diversity T_{ii+1} is higher than the probability to decrease the diversity $\sum_{j=1}^{i-1} T_{ij}$ in the parameter regime of Fig. 2. Once the population reaches the threshold of 4 types, this pattern reverses. Thus in the long run the population tends towards an intermediate level of diversity. Furthermore, we observe the ranking, $T_{12} > T_{23} > T_{34} > T_{45}$. This suggests that the probability to reach higher levels of diversity decreases with increasing diversity even for larger number of initial types. The transition probability from one type to a two-type coexistence can be calculated analytically based on the comparison of payoff entries, see above. Thus, $T_{12} = p(a < c)p(b > d) = \theta/2$, which is confirmed by our simulation results of T_{12} under different θ for the n-type model.

For a population with n types, the changes of the average fitness are more complicated, as the interactions between different types are much more diverse than in a two-type population. Even a classification of different types of interactions in such a population is difficult and of limited value to understand the change in average fitness. Instead, we evaluate the changes of the average fitness between these states numerically.

A mutation can increase, maintain, or decrease the diversity level of the population. We present the changes of the average fitness in these three scenarios, see Fig. 3, for those transitions which happen most frequently (see Fig. 2). For small θ, mutants are more likely to obtain lower fitness than their parents type does, in the interactions with the same resident type. This can cause the decrease of the average fitness in all three situations. If θ is sufficiently small, the average fitness will decrease all the time. When θ becomes larger, the average fitness can increase. The larger θ is, the larger the increase is. Thus, our results under the replicator dynamics provide not only the change of the average fitness under a constant θ, but also the direction and magnitude of the average fitness changes. In real systems, one may expect that θ decreases during the adaption of the population. However, e.g. environmental changes could also increase it.

Games with equal gains from switching

So far, we have assumed that the payoff of the mutant interacting with another resident type is derived from the payoff of its parent interacting with the same resident type. In a population with only two types, this leads to the case where the three random payoff entries, a, b and c, are all related to d. As a null model, we have assumed that a, b and c

11

are uncorrelated. While this is the simplest possibility, it may not be the case for concrete biological systems. Therefore, we analyze an different case here which focuses on particular cases of frequency dependence, but includes such correlations.

We focus on an evolutionary game with the payoff matrix

$$
\begin{array}{cc}
& \begin{array}{cc} \text{M} & \text{R} \end{array} \\
\begin{array}{c} \text{M} \\ \text{R} \end{array} & \left(\begin{array}{cc} d + \varepsilon + \delta & d + \delta \\ d + \varepsilon & d \end{array} \right),
\end{array}
$$

where ε and δ are independent random variables with probability distributions $f_\varepsilon(x)$ and $f_\delta(x)$ respectively. ε represents the effect of a mutation on the mutant type, and δ represents the effect of a mutation on those who interact with the mutant type. This game has the property of "equal gains from switching", where the sum of the payoff values in the main diagonal is equal to the sum of the payoff values in the other diagonal [31]. It can arise from the assumption that the two types are close to each other in a continuous phenotype space [32]. The case of $\delta = 0$ corresponds to constant selection. Note that there are no coexistence games when we assume such payoff matrices. If $\varepsilon > 0$, the mutant will take over the population ($d + \varepsilon + \delta > d + \delta$ and $d + \varepsilon > d$), and the new average fitness becomes $\overline{W} = d + \varepsilon + \delta$. Compared with the former average fitness d, the average fitness increases if $\varepsilon + \delta > 0$, and decreases if $\varepsilon + \delta < 0$. If $\varepsilon < 0$, the mutant will be outcompeted by the wild type ($d + \varepsilon + \delta < d + \delta$ and $d + \varepsilon < d$), and the average fitness of the population remains the same.

The probability to increase the average fitness becomes $p(\overline{W} > d) = (1 - \theta_\varepsilon) \cdot 0 + \theta_\varepsilon \cdot p(\varepsilon + \delta > 0 \mid \varepsilon > 0)$, where θ_ε is the probability that ε is larger than 0, and $p(\varepsilon + \delta > 0 \mid \varepsilon > 0)$ is the conditional probability that the sum of ε and δ is larger than 0 given ε is larger than 0. This conditional probability can be written as

$$
\begin{aligned}
p(\varepsilon + \delta > 0 \mid \varepsilon > 0) &= \frac{p(\delta > -\varepsilon, \varepsilon > 0)}{p(\varepsilon > 0)} \\
&= \frac{\int_0^\infty \mathrm{d}x \int_{-x}^\infty \mathrm{d}y \, f_\delta(y) \, f_\varepsilon(x)}{\theta_\varepsilon}.
\end{aligned}
\tag{15}
$$

The values of θ_ε and $p(\varepsilon + \delta > 0 \mid \varepsilon > 0)$, which determine the probability that the average fitness increases, depend on the concrete choice of $f_\varepsilon(x)$ and $f_\delta(x)$. The integrals can only be carried out in special cases.

It is worth to mention there is a difference between games with equal gains from switching and games with independent random payoff entires on the population dynamics. In an infinite population, where genetic drift has no effect on the population dynamics, the resulting dynamics under positive frequency dependent selection and under constant selection are similar, as there are no stable coexistences. Successful mutants will invade and take over the population sequentially. The diversity will only increase if the mutation rate is high enough. On the contrary, when different kinds of interactions, especially negative frequency dependent selection, are allowed (for example, the case with independent random payoff entires), diversity can increase even for lower mutation rates (see above).

Discussion

Mutants with high individual fitness do not necessarily increase the average fitness of the population under frequency dependent selection. Similarly, the mutants which maximize the average fitness of a population are not necessarily those leading to a stable equilibrium in this scenario. An example for a two-type population is that a mutant interacts with the wild type in a game like Prisoners' Dilemma [7,26]. This is a special case of a dominance game, where the defector (the mutant) outcompetes the cooperator (the wild type) and causes a reduction in the average fitness. For example, in the RNA phage $\phi 6$, the competitive interactions among the high multiplicities-of-infection phage (the defector) and the low multiplicities-of-infection phage (the cooperator) in the same host cell are studied, which conforms to the Prisoners' Dilemma [33]. In this experiment, when the defector invades with a low frequency, it has higher fitness than the residents ($c > a$), but the average fitness decreases when the defector becomes fixed ($d > a$).

Since natural selection works on an individual level rather than a population level, it does not always lead to an increase of the average fitness. Our random mutant games model accommodates mutations under frequency-dependent selection, which can result in an increase or decrease in the average fitness, not only for the simplest case of two types but also for an arbitrary number of mutant types. An interesting aspect of our model is that even though it allows for an infinite number of mutant types, it does not result in a continuous growth of diversity in a population, but leads to an intermediate level of diversity [30]. We

assume that the payoffs are constant in time and identical for individuals of the same type. If individuals vary in their payoffs despite being of the same type, the results are altered by this additional source of randomness [34, 35]. In a population with two types, we calculate a particular value θ_*, where the probability that the average fitness increases is equal to the probability it decreases. The exact value of θ_* depends on the concrete implementation of the payoff matrix. An interesting result of our model is that the probability to decrease or increase fitness depends only on a particularly simple property of the fitness distribution. While this may not be of direct relevance to a concrete biological system, it illustrates conceptually that a decreasing fitness may not be counterintuitive even under the simplest possible assumptions of frequency dependence.

We have discussed the changes in the average fitness for an infinite asexual population under mutation and selection. Additional effects occur when the population size becomes finite and genetic drift is not negligible [30]. However, our main observation is that the average fitness at equilibrium can only increase or remain constant by random mutations under constant selection, but also decrease under frequency-dependent selection. This can shed new light on problems in evolutionary biology and leads to the exciting question on the dynamics of the average population fitness in real biological populations. In an asexual finite population, random genetic drift leads to the accumulation of deleterious mutations and an continuous decrease in the average fitness, which is well known as Muller's ratchet [36]. Without any forms of recombination and epistasis, beneficial mutations are the only source to compensate the average fitness decline. Since the probability of increasing the average fitness by random mutations is lower under frequency-dependent selection (see Fig. 1), we must conclude that asexual populations face an even bigger challenge to maintain their average fitnesses under frequency dependent selection than under constant selection in a finite population. This is particularly striking when θ is small, a case that is typically thought of as the biologically most relevant case.

In population genetics, the change of the average fitness has also been studied in diploid systems [37, 38]. However, our approach starting from a different point of view, not only allows the interplay of mutation and selection, but also a wider interpretation of the fitness of heterozygotes. Suppose A and B are two alleles at the same locus. In population genetics, the

fitness of genotype AB and BA is usually considered to be identical, which is a special case in our model called symmetric diploids. However, this does not hold in asymmetric diploids where the maternal allele and paternal allele are not equally expressed. Our model and our analysis allow both cases. In the framework of a well-mixed symmetric diploid population (corresponding to random mating), our result that the average fitness never decreases is consistent with the former statement in population genetics (see Appendix).

Frequency dependent interactions can lead to a decrease of the average fitness of a population during the process of evolution despite natural selection. This is because natural selection works on individual fitness instead of the average fitness of a population.

Appendix
Diploid populations with two alleles

The impact of Mendelian inheritance on the population dynamics has been discussed in the framework of evolutionary game theory before [25, 39–41]. In a diploid population, the combinations of two alleles at a given locus on a pair of homologous chromosomes, can be interpreted by a special two player game. Suppose there are allele A and allele B. The fitness of different genotypes, W_{AA}, W_{AB} and W_{BB} can be described by a 2×2 matrix

$$
\begin{array}{c}
 \quad A \quad \ \ B \\
\begin{array}{c} A \\ B \end{array}
\begin{pmatrix}
W_{AA} & W_{AB} \\
W_{AB} & W_{BB}
\end{pmatrix}.
\end{array}
$$

This is mathematically identical to the game with two types discussed above. Here, W_{AA} corresponds to a, W_{AB} to $c = b$, and W_{BB} to d. For a population initially only with homozygotes BB, the probability of increasing the average fitness $\overline{W}$ caused by a random

new allele A, can be calculated by setting $c = b$ in Eq. (10). This becomes

$$p(\overline{W} > W_{BB}) = \underbrace{p(a > d \mid a > b, b > d)}_{1} \underbrace{p(a > b, b > d)}_{\theta - \frac{\theta^2}{2}}$$

$$+ \underbrace{p(\frac{b^2 - ad}{2b - d - a} > d \mid a < b, b > d)}_{1} \underbrace{p(a < b, b > d)}_{\theta - \frac{\theta^2}{2}}$$

$$+ \underbrace{p(d > d \mid b < d)}_{0} \underbrace{p(b < d)}_{1 - \theta}$$

$$= 2\theta - \theta^2 \tag{16}$$

The probability that the average fitness decreases in such a population is 0, because the diploid AB and the diploid BA is indistinguishable, $c = b$. In asymmetric diploids, where the maternal alleles and paternal alleles are not equally expressed, the average fitness changes are exactly the same as shown in a general case of haploid populations.

Author's contributions

W.H. and A.T. designed the model. W.H., B.W. and A.T. evaluated the model and wrote the manuscript.

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Competing interests

The authors declare no competing interests.

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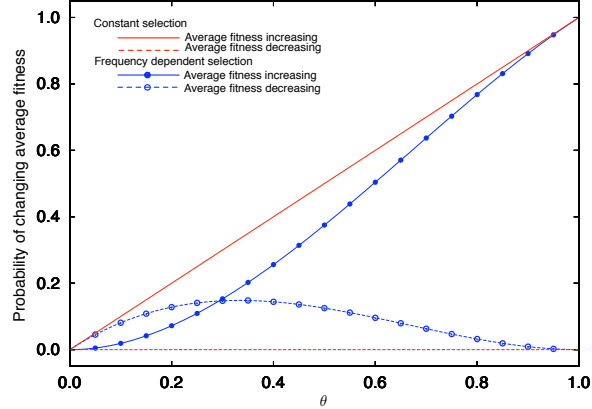37. Fisher RA: *The Genetical Theory of Natural Selection*. Clarendon Press, Oxford 1930.

Figure 1: Probability of increasing or decreasing the average fitness in the new equilibrium after one mutation event in an initial homogenous population. θ is the probability that a random payoff entry of the mutant, a, b or c is larger than wild type initial fitness d. Blue symbols and lines are simulation and analytical results under frequency dependent selection (average over 10^6 runs). Red lines are analytical results under constant selection. For constant selection, the average fitness either increases or is unchanged by a new mutation, where the fraction of mutants that increases fitness is determined by θ. However, under frequency dependent selection, the average fitness of the population in the new equilibrium after a mutation can also decrease. The probability to increase, decrease the average fitness or maintain the same average fitness, depends on θ, for $\theta > \frac{\sqrt{2}-1}{\sqrt{2}}$ the probability to increase the average fitness in the new equilibrium is larger than the probability to decrease it.

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Figure 2: Transition probabilities between different levels of diversity. The entry in row i and column j is the transition probability from a stable coexistence of i types to a stable coexistence of j types, numbers are also color coded. The mutation rate is so low that the transitions between different states are caused by the appearance of a single mutation. The higher the number of coexisting types is, the more difficult the state is to be reached. Here we show the transition for up to six co-existing types ($\theta = 0.5$, averages obtained over 500 independent realizations and 20000 mutations per realization).
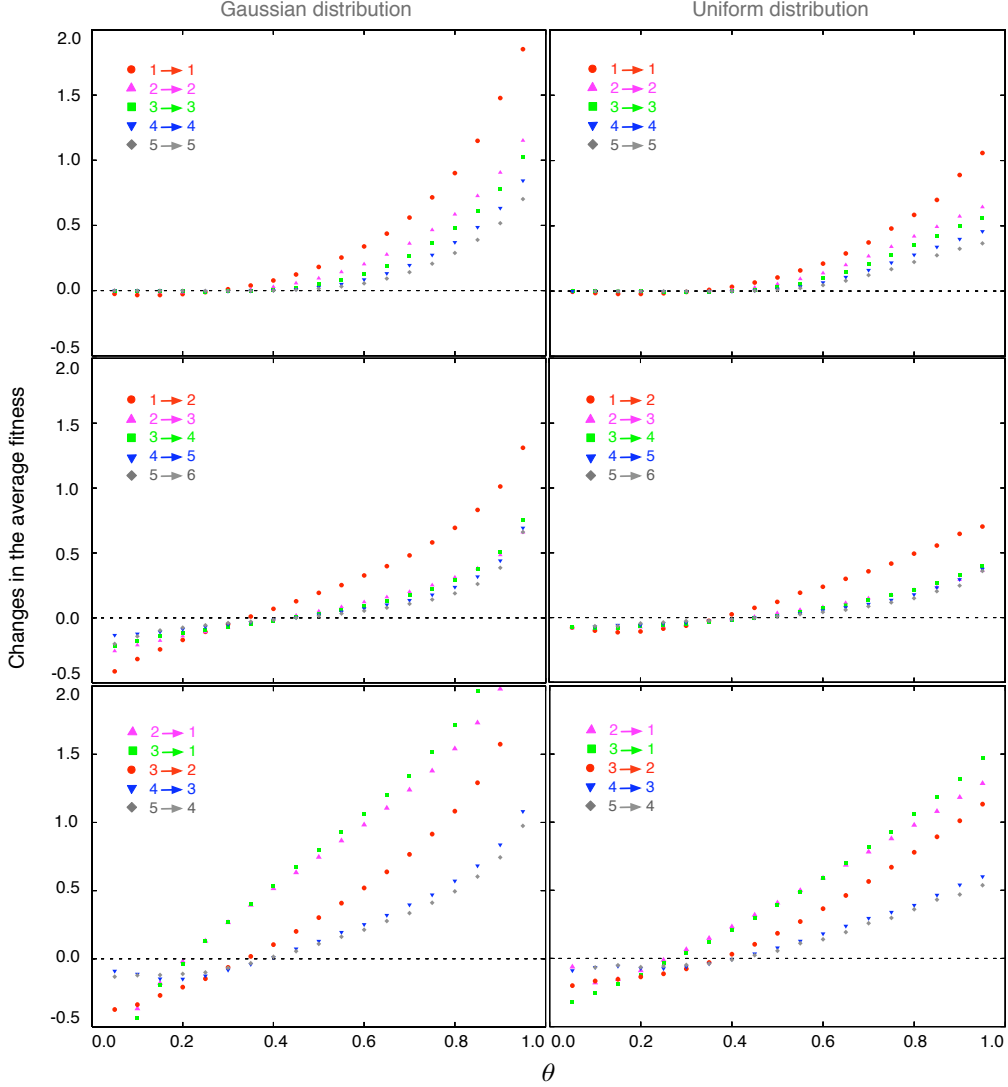
Figure 3: Changes in the average fitness when a population evolves between different levels of diversity under various probabilities that a mutant payoff values is larger than the parent's θ. The symbols are simulation results based on replicator dynamics. The number of different types can either stay the same, increase by one or decrease by any number, because at most a single mutation enters the population. Note that the average fitness of the population in the new equilibrium decreases for small θ in all three cases after a transition. Thus even if a mutant takes over a population, the average fitness can decrease. With increasing θ, the average fitness will increase over time, but the fitness gain reduces with increasing diversity. The difference among results under Gaussian distribution and uniform distribution with the same variance, shows that the absolute changes of the average fitness also depends the concrete shapes of the probability distribution (every symbol is averaged over 500 independent realizations and 20000 mutations per realization. The probability distribution $f(x)$ is Gaussian (left) or uniform (right) with variance 1).

22

CHAPTER 5

Summary and outlook

5.1 Summary

Evolutionary game theoretic models deal with various types of individual interactions, where complicated dynamics at different levels can arise [41]. In this thesis, we present an evolutionary game theoretic model that describes random frequency dependent mutations. The evolutionary dynamics of this system at the population level is explored based on this model.

In our frequency dependent mutation model, the interactions of the mutant types and the resident types are described by a payoff matrix with changing size. Using a payoff matrix to obtain the fitness values of different types implies linear frequency dependent selection [9]. We focus on haploid populations, but our model corresponds to diploid populations if the payoff matrix is symmetric.

Most evolutionary game theoretic models assume that mutations happen between fixed and known types. This means that the number of arising mutations is limited, and the payoff entries of those mutations are predefined. Our model differs from these models in two aspects. First, the new payoff values arising with the presence of mutants are represented by random variables, i. e. values unknown before the mutations appear. We introduce the concept of the payoff distribution, which describes the possible payoff values that a mutant or a resident type can have during their interactions. In population genetics, a corresponding concept is fitness distribution, which is based on

the assumption of constant selection. Second, we assume that every mutation brings a new type into the population. Thus, the number of possible mutations appearing in a population is infinite in a continuous evolutionary process. The same assumption is made in infinite alleles models in theoretical population genetics [54, 52, 12]; typically these models are based on neutral evolution or constant selection.

Our frequency dependent mutation model has striking results in both finite and infinite populations. In finite populations, we have two types of stochasticity, the randomness in the payoff entries and the random genetic drift from the interplay of finite population size and selection intensity. To separate the effects of different types of stochasiticity, we extend our analysis to infinite populations with non-determinstic property. When a mutant type shows up, the new payoff entries are random variables. Until the next mutation happens, the interactions between the mutant type with all the resident types are deterministic.

Mathematical approaches have been used to study evolutionary questions, starting from the work of Fisher and Wright [17, 130, 131]. Under simplified assumptions, for example two-type models or neutral evolution, some properties of a biological system can be obtained analytically. When further complications, ranging from many types to various selection intensities, are considered, computational approaches are often required. In this thesis, both mathematical and computational approaches are employed.

In a finite haploid population with two types, the fixation probability of a random mutant is an important quantity [9]. In the case of weak and strong selection, analytical approximations have been made. The corresponding results reveal an interesting relation of the first moments of the payoff distribution with the fixation probability. For all selection intensities, simulation results are obtained, and comparison is made between these simulations and analytical results.

When more than two types exist in the population, the population dynamics rapidly becomes much more complicated. Important questions we have addressed in the thesis are: does the diversity level of the population always increase when a high number of types becomes possible? What is the mechanism of the origin and maintenance of stable coexistence of different types in the population? We look for the answers in a finite population with unlimited number of types by simulations. Under the interplay of relatively strong selection, random genetic drift, and low rate of mutation, intermediate levels of diversity are maintained under frequency dependent selection. On the contrary, substantially lower diversity is observed under the same conditions when the fitness is assumed to be constant. The stable polymorphism driven by frequency dependent selection, is different from the diversity caused by high mutation rates. When the mutation rate is high, the diversity is the collection of random types staying shortly in the population, but the stable coexistence of different types for a long time period is not observed.

The same patterns are obtained for infinite populations, which is the situation of extremely strong selection. In addition to the diversity of the population, we are also interested in how the average population fitness changes due to random mutations. Again, analytical solutions on the probabilities of increasing or decreasing the average fitness are given for haploid populations with two types. Under constant selection, only mutant types with a fitness advantage can be fixed in the population. Thus, the average fitness may fluctuate in short time, but will always increase in the end. Under frequency dependent selection, the average fitness can also decrease, because interactions resembling the Prisoner's dilemma exist [132]. The relative changes of the average fitness are recorded in a population with unlimited types by computational approaches.

5.2 Outlook

There still remain many questions that can be explored based on this model. In Chapter 3, we have a short discussion about how this model could be extended to diploid populations. For the sake of simplicity, the fitness of a genotype is assumed to be constant, and only the fitness of an allele type is frequency dependent [85, 133]. This is also an assumption for most diploid models in population genetics [12]. It would be interesting to introduce another level of frequency dependent selection on genotypes [126].

In Chapter 3 and Chapter 4, we conclude that the average fitness can increase, decrease or remain the same during the evolutionary process. In a constant environment, this might lead to the flourishing or diminishing of a population. If the average fitness increases, the total number of offsprings in the future may increase. If the average fitness decreases, the population size may decrease accordingly. The fluctuating population size will lead to different strength of random genetic drift. The types which might be lost very fast in a large population, may stay longer in a small population. This effect from changing strength of random genetic drift might play an important role in evolution. The evolutionary dynamics in such a population with changing size due to the changes of the average fitness, would be one of the most exciting subjects to analyze in the future.

In our model, some assumptions are based on the genotypic level, for example the infinite alleles model. Payoff matrices are used to describe the interactions of individuals with different genotypes. However, it may also be possible to extend this model to study the phenotype diversity or species coexistence [10, 134], if reasonable assumptions can be made to capture the corresponding context.

Population genetics is concerned with genotype and gene frequencies [42, 12, 13], and evolutionary game theory is typically considered to deal with phenotypes [9, 135]. In this thesis, we propose a frequency dependent mutant model, which can be used to understand the changes of the genotype frequencies and the resulting dynamics under frequency dependent selection, genetic drift, and random mutations. It covers the case of weak selection, intermediate regimes, and strong selection. Thus, it may help to further develop the connections between theoretical population genetics and evolutionary game theory.

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Declaration

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

Two papers published separately in the Journal of Theoretical Biology (JTB) and Nature Communications (NC), and one submitted paper are included in this thesis.

- For the publication in JTB, Weini Huang(WH) and Arne Traulsen(AT) designed the model, WH performed the simulations, WH and AT did the analysis, and WH and AT wrote the paper.

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