Selection intensity and the time to fixation in evolutionary systems

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Kurzfassung

Prozesse Darwinscher Evolution sind dynamisch, nichtlinear, und unterliegen Fluktuationen. Systeme Darwinscher Evolution können mit wohl etablierten Methoden der statistischen Physik analysiert werden. Die für evolutionäre Veränderungen wesentlichen Mechanismen sind Reproduktion, Mutation und Selektion. Individuen reproduzieren sich und vererben Gene und Merkmale, so dass die Population evolviert. Mutationen treten spontan auf, z.B. durch Fehler in der Reproduktion, wodurch verschiedene neue Typen von Genen oder Merkmalen entstehen können. Selektion wirkt auf verschiedene Typen.

Diese Arbeit konzentriert sich auf Selektion in Systemen, welche den Prinzipien Darwinscher Evolution, sowie Fluktuationen unterliegen. Die Wechselwirkungen verschiedener Typen untereinander können die jeweiligen reproduktiven Raten beeinflussen. Eine wichtige Disziplin, welche solche Wechselwirkungen betrachtet, ist die Spieltheorie. In der evolutionären Spieltheorie identifiziert man verschiedene Typen mit verschiedenen Strategien. Der (spieltheoretische) Erfolg einer Strategie beeinflusst deren reproduktiven Erfolg. Eine wichtige Eigenschaft evolutionärer Spiele ist, dass der evolutionäre Erfolg einer Strategie im Allgemeinen mit der Zusammensetzung der Population variiert.

Der Begriff Fixierung bezeichnet das Ereignis der Übernahme einer Population durch eine Mutation. Hauptsächlich werden in dieser Arbeit die Fixierungszeiten einer mutierten Strategie betrachtet. Sie sind ein Maß für die Zeit, die eine Population benötigt, um von einem Zustand mit nur wenigen zu einem Zustand mit ausschließlich Mutanten zu gelangen.

Selektion kontrolliert die Erfolgsdifferenz zwischen Typen. Dies ermöglicht die Definition verschiedener Regime der Selektion. Ohne Selektion ist Evolution neutral und Fluktuationen dominieren. Ein wichtiger Grenzfall ist schwache Selektion, welche eine gerichtete Veränderung zu diesen zufälligen evolutionären Veränderungen hinzufügt. In dieser Arbeit spielt die Analyse der schwachen Selektion eine bedeutende Rolle in der Klassifikation verschiedener evolutionärer Prozesse. Sie erlaubt eine Vereinfachung der nichtlinearen Systeme und damit eine analytische Beschreibung. Es werden approximative Formulierungen der Fixierungszeiten unter schwacher Selektion präsentiert und die

Universalität dieses Grenzfalls betrachtet. Auf Zwischenskalen kann man beobachten, dass die Fixierungszeit einer vorteilhaften Mutation mit der Selektion ansteigt, obwohl die entsprechende Fixierungswahrscheinlichkeit ebenso größer wird.

Davon ausgehend kann man zur Betrachtung starker Selektion übergehen, so dass Selektion die Dynamik auch in kleinen Systemen dominiert. Hierbei lassen sich Segregationseffekte beobachten: Das Schicksal der Population ist deterministisch durch die Anfangsbedingung bestimmt.

Ein weiterer wichtiger Mechanismus der Evolution ist der Genfluss, welcher z.B. durch Migration zwischen Population der selben Art erzeugt wird. In diesem Zusammenhang kann Migration der Selektion entgegenwirken. In Systemen bistabiler evolutionärer Dynamik kann solch ein Migrations-Selektionsgleichgewicht zu lang stabiler Koexistenz führen. Die vorliegenden Arbeit gibt hier eine quantitative Analyse der dynamischen und statistischen Eigenschaften. Zu diesem Zweck werden die Austerbe- oder Fixierungszeiten des nichtlinear gekoppelten Populationssystems analysiert.

Abstract

Processes of Darwinian evolution are dynamic, nonlinear, and underly fluctuations. A way to analyze systems of Darwinian evolution is by using methods well established in statistical physics. The main mechanisms that are responsible for evolutionary changes are reproduction, mutation, and selection. Individuals reproduce and inherit genes and traits, such that a population evolves. Mutations occur spontaneously, e.g., by errors in reproduction, whereby different new types of genes or traits can emerge. Selection acts on different types.

This thesis focuses on selection in systems that underlie the principles of Darwinian evolution, as well as fluctuations. Once there are different types, their interactions with each other can influence their reproductive rates. One important framework to look at such interactions is game theory. In evolutionary game theory, different types are identified with different strategies, and the payoff of a strategy affects the reproductive success. An important property of evolutionary games is that, in general, the evolutionary success of a strategy varies with the composition of the population.

The event of a mutation taking over a population is called fixation. The quantities mainly considered in this thesis are the fixation times of a mutant strategy. They are a measure for the time a population spends reaching the state of only mutants, when starting from a few.

The role of selection is to control the payoff differences between types, which gives rise to several regimes of selection. In the absence of selection evolution is neutral and fluctuations dominate. An important limit case is weak selection, which introduces a small bias to the random evolutionary changes. In this thesis, weak selection analysis plays an important part in the classification of different evolutionary processes. This allows to simplify the nonlinear dynamical system and thus an analytical description. Here, approximative formulations of the fixation times under weak selection are presented, and the universality of the weak selection regime is addressed. On intermediate scales, one can observe that the average fixation time of an advantageous mutation increases with selection, although the probability of fixation also increases.

One can then move on to strong selection, such that selection dominates the dynamics even in small systems. Here, one can observe segregation effects, where the initial condition determines the fate of the finite population in a deterministic way.

Another important evolutionary mechanism is gene flow, e.g., caused by migration between populations of the same species. In this context, migration can counterbalance selection. In systems with bi-stable evolutionary dynamics, the migration-selection equilibrium can lead to coexistence that is stable for a long time. This thesis gives a quantitative analysis of the dynamical and statistical properties of such a system. To this end, the extinction (fixation) times are analyzed also in the nonlinearly coupled population system.

Thesis overview

This thesis includes the following manuscripts.

- Philipp M. Altrock and Arne Traulsen,
  Fixation times in evolutionary games under weak selection,
  New Journal of Physics **11**, 013012 (2009).

- Bin Wu, Philipp M. Altrock, Long Wang and Arne Traulsen,
  Universality of weak selection,
  Physical Review E **82**, 046106 (2010).
  (*Virtual Journal of Biological Physics Research* **20**(8), 2010).

- Philipp M. Altrock, Chaitanya S. Gokhale and Arne Traulsen,
  Stochastic slowdown in evolutionary processes,
  Physical Review E **82**, 011925 (2010).
  (*Virtual Journal of Biological Physics Research* **20**(3), 2010).

- Philipp M. Altrock and Arne Traulsen,
  Deterministic evolutionary game dynamics in finite populations,
  Physical Review E **80**, 011909 (2009).
  (*Virtual Journal of Biological Physics Research* **18**(2), 2009).

- Philipp M. Altrock, Arne Traulsen, R. Guy Reeves and Floyd A. Reed,
  Using underdominance to bi-stably transform local populations,
  Journal of Theoretical Biology **267**, 62 (2010).

- Philipp M. Altrock, Arne Traulsen and Floyd A. Reed,
  A stochastic model for heterozygote disadvantage in subdivided populations,
  to be submitted, January 2011.

CHAPTER 1

Introduction

The step from describing inert matter
to describing biological life seems enormous,
but maybe it isn't.

Per Bak (How Nature Works)

1.1 Motivation

Fluctuations play an important role in physical and biological systems. In particular, far from equilibrium fluctuations are one of the most fundamental properties commonly observed in many processes of the living world. The rigorous quantitative description of fluctuations is performed in the field of stochastic processes. Its origins lie in the description of Brownian motion, first systematically observed by R. Brown [Brown, 1866]. The mathematical analysis, at least from a physical perspective, started about half a century later, conducted by A. Einstein, M. von Smoluchowski, and P. Langevin [Einstein, 1905; Langevin, 1908; von Smoluchowski, 1906]. What first came along as a rather heuristic chain of arguments guided by genius and intuition led to fundamental physical equations. These equations describe a stochastic process, e.g., position or velocity of a Brownian particle, by microscopic and macroscopic laws accounting for thermal fluctuations. The formalism was later put on a more rigorous basis [Feller, 1968; Kolmogorov, 1956]. Since then, stochastic processes have become unavoidable in successfully describing fundamental processes in physics, chemistry and biological physics, where thermal or quantum fluctuations have to be accounted for, see, e.g., [Gammaitoni et al., 1998; Gardiner, 2008; Krug, 1997; Reimann, 2002; Schnakenberg, 1976; van Kampen, 1997]. Typically, the interactions taken into account here are (quantum-)mechanic or electromagnetic etc., i.e. they are based on the fundamental interactions in physics.

It is, however, notable that in other fields like quantitative social science or biology, a mathematical description can often be formulated as if such physical interactions occur and as if fluctuations are of thermal origin (from a physical point of view, in most cases they are not). Fluctuations can be of thermal origin, but are often generally referred to as demographic fluctuations that simply originate from discreteness and finite size. In the quantitative description of collective motion, social (hierarchical) interactions govern the onset (e.g., movement is induced by imitation), patterns, and phase transitions [Helbing and Molnár, 1995; Romanczuk et al., 2010; Sumpter, 2010; Vicsek et al., 1995]. In Darwinian evolution, the outcome of mutation and selection depends on interactions on many levels, e.g., between molecules, individuals, and/or populations of different species. In both non-physical examples stochasticity can act in a way very similar to physical systems: the formation of patterns in motion can stabilize in a certain regime of fluctuations, or populations can benefit from fluctuations maintaining 'evolutionary freedom' or allowing 'evolutionary revolutions' [Lenormand et al., 2009].

Complexity is another important concept in the natural and social sciences. Systems in which macroscopic properties cannot be predicted by the properties of its microscopic parts alone are characterized as complex. Such complex behavior typically arises in nonlinear dynamical systems, or when problems across a wide range of scales are considered. This is commonly the case in physics, chemistry, and engineering [Haken, 2006], traffic modeling [Helbing, 2001], or modeling stock markets [Farmer et al., 2005], but also omnipresent in adaptive systems, e.g., in the human brain, evolving populations, and ecological networks [Levin, 2002; Schuster, 2002]. When microscopically defined entities such as charged particles, molecules, neurons, or animals, interact in a complex way to form macroscopic patterns in space and/or time, mathematical methods from theoretical physics are well established to make predictions. Moreover, in Darwinian evolution, the fate of biological traits in terms of reproductive success can depend on the interactions with others and with the environment in a complex way.

In a broad sense, this thesis deals with nonlinear dynamics and fluctuations in mathematical models of Darwinian evolution. Although the 'theory of evolution' is now rather a fact than a theory, there are theoretical approaches, which intend to make quantitative predictions that can be tested experimentally. In the beginning of the 20th century a (first) mathematical description of Darwin's exciting approach to biology was on its way. In the century before, C. Darwin and others formulated the fundamental principles of evolution to explain life's diversity by evolutionary mechanisms, which is based on G. Mendel's observations and laws of inheritance [Bateson, 1909]. For the great luck of others, this work was neither very mathematical, nor could Darwin and Mendel know about the molecular mechanisms of inheritance.

In the same way that led theoretical physicist to think about Brownian motion, scientists from various fields started to think about the mathematical formalisms provoked by Mendel's observations and Darwin's theory [Fisher, 1930; Haldane, 1924–1934; Hardy, 1908; Wright, 1931]. Among other topics, the 'modern synthesis' of evolutionary theory [Huxley, 1942] deals with two important aspects. On the one hand, the complexity of the relevant interactions, e.g., genotype-genotype, genotype-phenotype, or phenotype-environment, as well as patterns of inheritance, mutation, and selection have to be analyzed. On the other hand, the formulations of appropriate stochastic processes is of importance [Moran, 1962; Wright, 1931].

Natural selection acts through fitness, which can be measured as an individual's average contribution to the gene (or phenotype) pool at a later point in time. Individuals reproduce, but a population evolves in the space of genomic sequences [Nowak, 2006a; Wright, 1970]. The physical analogy of this high dimensional sequence space (with a genome of length L, it is an L-dimensional lattice) is the phase space. Instead of moving towards states with minimal energy, a population naturally evolves to sites in sequence space with maximal fitness (or at least local optima). The map from each position in sequence space to a reproductive rate is called the fitness landscape. Due to complex interactions between the different types present in a population, the fitness landscape can change while the population is moving across. While a population climbs a hill of the fitness landscape, driven by mutations and selection, the slope itself might change and the peak can even disappear. In general, the fitness of a specific type or strategy depends on the relative densities of the types present. An appropriate framework to model Darwinian evolution under density dependent fitness is evolutionary game dynamics [Hofbauer and Sigmund, 1998; Nowak and Sigmund, 2004].

Game theory itself was established by von Neumann and Morgenstern [1944] as a framework to analyze economic decisions in human behavior. It mathematically analyzes how the success of a strategy depends on other strategies, based on a set of rules. In classical game theory there is a way of finding a static 'equilibrium' in which any participant (player) cannot individually improve by switching to another strategy. Assuming that only rational agents interact, J. Nash could prove that every strategic situation has at least one (mixed) Nash equilibrium [Nash, 1950]. Based on observations in ecology, Hamilton [1967], and Maynard Smith and Price [1973] applied game theoretic arguments to solve problems in explaining sex ratios and conflict situations in animals of the same species. In evolutionary game theory, the concept of rationality is replaced by fitness: The genius of Maynard Smith and Price was to ascribe the so called payoff from a strategic conflict situation to the fitness of individuals. Strategies, in this sense, are genetically hardwired traits, such as body mass, aggressiveness in the competition for

territory, or courtship behavior. A concept that is similar (but not generally identical) to the Nash equilibrium is the evolutionary stable strategy which evaluates the invasiveness of mutant strategies [Maynard Smith and Price, 1973]. In order to come to an evolutionary argument, strategies have to be able to spread in a population by reproduction or cultural learning (imitation). By anticipating that more successful (fitter) strategies spread faster, evolutionary game theory is dynamic [Maynard Smith, 1982].

Individuals in populations play games and reproduce or imitate others. The success in an evolutionary game is mapped to fitness (reproductive rate) or an imitation rate. Hence, successful strategies spread by inheritance or cultural learning due to selection. Depending on the strategic situation under consideration, this results in complex dynamical patterns even if the dynamics is assumed to be deterministic [Hofbauer and Sigmund, 1998; Nowak and May, 1992; Weibull, 1995]. Especially, evolutionary game theory allows to study social dilemma situations under density dependent selection and hence the evolution of cooperation by different mechanisms [Axelrod, 1984; Nowak, 2006b; Nowak and Sigmund, 1998; Ohtsuki et al., 2006; Sachs et al., 2004; Traulsen and Schuster, 2003].

Apart from the study of complex evolutionary game dynamics in deterministic setups more challenges are faced when fluctuations are taken into account. A well defined stochastic process that governs the probabilistic spreading of strategies by natural selection has to include evolutionary mechanisms, i.e. reproduction, mutation, and selection. Although stochastic processes are known in theoretical population genetics [Crow and Kimura, 1970; Ewens, 2004; Moran, 1962], the traditional focus is on models of neutral evolution (all types reproduce at equal rates) or constant selection (different types reproduce at constant but different rates), where mutation rates are the driving mechanism [Drossel, 2001]. Complementary to that, evolutionary game theory focuses on cases where selection changes with the composition of the population [Imhof and Nowak, 2006; Nowak et al., 2004; Nowak and Sigmund, 2004; Santos and Pacheco, 2005; Szabó and Fáth, 2007; Taylor et al., 2004].

This thesis almost exclusively focuses on the role of selection in stochastic evolutionary game dynamics. When fluctuations cannot be neglected, the concept of evolutionarily stable states is lost. What remains are a few absorbing states where the dynamics get stuck, if no further mutations lead away from them: Typically, the absorbing states in such non-invasive processes are those where only one strategy is left. They can be the equivalent of stable or unstable fixed points of the deterministic dynamics. In case of an unstable fixed point, although selection leads away from it, the stochastic dynamics can reach the state with a certain probability. Depending on the microscopic details of the evolutionary process, macroscopic quantities can be found, such as the probability of reaching a particular absorbing state. In addition, one can ask for the average time

needed to reach such a state.

The event of a mutant strategy taking over is called fixation. In general, it is of interest how the statistical properties of fixation events behave with changes in either the strength of selection, or the evolutionary process, by altering the complexity of the strategy space. In the thesis at hand, various new aspects of evolutionary processes concerning the probability of and the average time to fixation are addressed. The first part of the results focuses on dynamics that are based on the success in an evolutionary game, which itself changes with the densities of strategies, see Chapter 2.

One does not need, of course, to think only about strategic interactions to observe complex patterns in evolutionary dynamics. Depending on the interaction, certain variants of genes undergo complex evolutionary changes. Genes are parts of the genome that encode, e.g., for proteins. A variant of a gene is called an allele. In diploid organisms, normally, a parent passes on only half of its genome to the offspring. Hence, a child inherits two copies of each gene; it can have the same or two different alleles. The allelic configuration of the genotype can have an effect on fitness. This results in density dependent changes in fitness, from the perspective of a single alleles [Hartl and Clark, 1997]. Individuals with different alleles on the same gene are called heterozygotes, whereas we speak of homozygotes if the two variants of a gene are identical.

A concrete example is underdominance (heterozygote disadvantage), where heterozygotes suffer from a fitness reduction relative to the homozygotes. Thus, a state with a high density of the allele that causes this disadvantage is typically unstable. If migration between sub-populations of the same genetic background is considered, the question is whether such a state can be stabilized by a selection-migration equilibrium. The resulting bi-stable dynamics have been proposed as a mechanism to establish genetically modified individuals in disease vector species [Curtis, 1968]. Such a nonlinear dynamical system, where migration between sub-populations counterbalances selection, is considered in the second part of this thesis, see Chapter 3. In addition, the impact of demographic fluctuations is addressed: A direct link to findings in the first part can be made by analyzing the mean time of extinction of the genetically modified allele.

The idea of applying
game theory to animals,
and not just the higher primates,
but fish, dung beetles, fireflies,
and pond scum as well,
seemed strange at the time...

Herbert Gintis (Game Theory Evolving)

1.2 Deterministic evolutionary game dynamics

In models of Darwinian evolution it turns out to be very useful to classify interactions within and between populations in terms of strategic interactions between different types or strategies, i.e. in terms of games. The aim of this section is to show why this is the case, to review how complex nonlinear dynamics can emerge, and to give some examples which can guide our intuition. Evolutionary game theory describes evolutionary stability and evolutionary dynamics in populations, where natural selection acts and individuals with different strategies interact [Hofbauer and Sigmund, 1998; Maynard Smith, 1982; Nowak, 2006a; Sandholm, 2010; Weibull, 1995].

In what follows, a brief introduction to non-cooperative games of rational agents is given, which is non-dynamic. Here, solutions can be found by assuming rationality (as explained below). Then, the transition to evolutionary arguments is made by first considering the non-dynamical approach to evolutionary game theory: To find evolutionarily stable strategies rationality can be dropped, but fitness has to be defined. Next, the resulting deterministic nonlinear dynamics are introduced, where differences in fitness are the driving mechanism. Throughout, examples are discussed.

1.2.1 Rational agents

The mathematical theory of games was devised by von Neumann and Morgenstern [1944]. According to Aumann [1987], game theory is an 'interactive decision theory', where agents interact: An agents best action for herself depends on expectations on the actions of other agents, where, at the same time, each of the other agents actions depend on expectations about her. As a result, 'the outcomes in question might have been intended by none of the agents' [Ross, 2010].

Strategic interactions of at least two agents are called games, and agents are referred to as players. In the class of non-cooperative games players optimize their actions solely according to their own interests. If full information about the game is given, and players

are rational and know that the others are rational too (hyper-rationality), then rational players can do three things: (i) rank-order outcomes of actions, especially by (ii) knowing which (sequence of) actions lead to which outcomes, and (iii) select (choose) actions from alternatives according to the above mentioned optimum. The set of all possible actions of a player is called her strategy. The two standard ways to formalize games are extensive form games and normal form games. The former is known to be more general in terms of non-simultaneous decision making as any finite number of agents can interact in arbitrary sequence. Nonetheless, for many of the purposes in evolutionary game dynamics it is sufficient to focus on normal form games.

Normal form games consist of d players, a set of all strategies available to each player (strategy space), and a payoff function for each player [Fudenberg and Tirole, 1991]. The payoff function for a player is a mapping from the cross-product of all players' strategy spaces to that player's set of payoffs. It takes the so called strategy profile, i.e. the d-tuple of strategies chosen by each player, and puts out a real number for each player, called payoff. The question now is: What strategy profile will rational players choose in order to optimize their individual payoffs? For special cases, the answer was given by von Neumann and Morgenstern [1944]. More importantly, Nash [1950] has shown a general way of finding an optimum, the so called Nash equilibrium. Roughly speaking, a Nash equilibrium for rational players is a d-tuple of strategies in which no single player can improve by switching to another strategy. Strategies can be pure, or mixed. Hereby, a mixed strategy is a probability distribution over pure strategies. A mixed strategy is a best reply to itself if no other probability distribution, i.e. no other mixed strategy, leads to a higher payoff for a given player. This leads to the general formulation of a Nash equilibrium, which is defined as the state in which every player chooses a (mixed) strategy that is a best reply to the (mixed) strategies of all other players. The one page publication [Nash, 1950] proves that every finite normal form game has at least one mixed Nash equilibrium. This concept, as well as other concepts that have been developed since, tell us what (hyper-)rational players in states of full information should do when being involved in a strategic interaction.

A case most relevant to the thesis at hand is the class of finite normal form games with two players and two (or more) strategies. The payoffs of such games can be represented by a payoff table, or rather a payoff matrix. This pattern emerges because of the two players, one being the 'row player', the other being the 'column player'. In general, each entry consist of two numbers, the first is the payoff of the column player, the second the payoff of the row player. For general two player games with two strategies, the column player's strategies can be called c_1 and c_2, whereas the row players strategies are called r_1 and r_2. Here, u is the payoff function for the column player, v is the payoff function for

the row player. They both depend on the pair of strategies played. The general payoff matrix reads

$$\begin{array}{c} \\ c_1 \\ c_2 \end{array} \begin{array}{c} \begin{array}{cc} r_1 & r_2 \end{array} \\ \begin{pmatrix} u(c_1,r_1),v(c_1,r_1) & u(c_1,r_2),v(c_1,r_2) \\ u(c_2,r_1),v(c_2,r_1) & u(c_2,r_2),v(c_2,r_2) \end{pmatrix} \end{array}. \tag{1.2.1}$$

If column plays c_1 and row plays r_2, they get $u(s_1,r_2)$ and $v(s_1,r_2)$ respectively. Let $p_c(c_i)$ and $p_r(r_i)$ be the probability distributions (or mixed strategies) of column and row player. Hence, the expected payoff of the column player amounts to $u_i = p_r(r_1)\,u(c_i,r_1) + p_r(r_2)\,u(c_i,r_2)$ when playing strategy c_i. Similarly, the row player expects the payoff $v_i = p_c(c_1)\,v(c_1,r_i) + p_c(c_2)\,u(c_2,r_i)$ when playing strategy r_i.

As an example, consider the two player game 'matching pennies' [Traulsen et al., 2004]. The rules of this game are as follows. The two players simultaneously announce the side of a coin as 'heads' or 'tails'. The according pure strategies for each of them are H (announce heads), and T (announce tails). If the announcements are the same (i.e. (H,H), and (T,T)), the column player wins 1 unit, and the row player loses 1 unit. If the announcements differ (i.e. (T,H), and (T,H)), the row player wins 1 unit, and the column player loses 1 unit. This is an example of a zero-sum game; one player looses what the other gains. The payoff matrix explicitly reads

$$\begin{array}{c} \\ H \\ T \end{array} \begin{array}{c} \begin{array}{cc} H & T \end{array} \\ \begin{pmatrix} 1,-1 & -1,1 \\ -1,1 & 1,-1 \end{pmatrix} \end{array}. \tag{1.2.2}$$

Here, the only mixed Nash equilibrium (a pure one does not exist) is found if both players randomize between the two pure strategies. Because of equal gain and loss, the players play each strategy with probability 1/2, such that the expected payoffs amount to 0. To see why this is the case, we need to find a condition that solves for the probabilities p_c,p_r that either player chooses strategy H, from which follow the probabilities of the strategy T as $1-p_c$,$1-p_r$ consistently. The expected payoffs for, e.g., the column player are given by $u_H = p_r 1 + (1-p_r)(-1)$, and $u_T = p_r(-1) + (1-p_r)1$. From this she wants to maximize her overall expected payoff as she also randomizes her strategy choice: $p_c u_H + (1-p_c)u_T$ when playing H with probability p_c, i.e. $\partial_{p_c}(p_c u_H + (1-p_c)u_T) = 2(2p_r - 1) = 0$. This, and the same argument for the row player lead to $p_r = p_c = 1/2$.

One player's loss does not have to be the other players gain; in general, we do not consider zero-sum games. However, we stick to symmetric games where $u(c_1,r_2) =$

$v(c_2,r_1) = b$, and $v(c_1,r_2) = u(c_2,r_1) = c$, as well as $u(c_1,r_1) = v(c_1,r_1) = a$, and $v(c_2,r_2) = u(c_2,r_2) = d$. This has the notational benefit that we can write down a payoff matrix with singular entries only. In two player games, from now on we differentiate between the two strategies A and B, for which the payoff matrix of the symmetric interaction reads

$$\begin{array}{c} \\ A \\ B \end{array} \begin{array}{c} \begin{array}{cc} A & B \end{array} \\ \begin{pmatrix} a & b \\ c & d \end{pmatrix} \end{array} \tag{1.2.3}$$

This matrix focuses only on the column player and by symmetry we know that the same payoffs hold for the row player. Note that the matching pennies game is not in this class of games because it is a bi-matrix game and does not fulfill the above symmetry. In terms of Nash equilibria, the following situations emerge. Strategy A is a Nash equilibrium if $a \geq c$. Strategy B is a Nash equilibrium if $d \geq b$. If ">" instead of "≥" holds the equilibrium is called strict. If $a < c$, and $d < b$, there exists a mixed Nash equilibrium where the players choose A with probability p, and B with probability $1-p$. Each player expects the payoffs $u_A = p\,a + (1-p)b$, $u_B = p\,c + (1-p)d$. The probability p can be calculated by finding the root of $\partial_q(q\,u_A + (1-q)u_B) = u_A - u_B$, which leads to $p = (d-b)/(a-b-c+d)$.

The solutions to strategic situations like the ones above are based on assuming rationality, full information and, in the games that are of interest for us, simultaneous decisions. The matching pennies game already shows that the outcome of rationality can be somewhat counterintuitive. In fact, it was in such situations that game theorists explored deviations from rationality, such as a limitation of rational choice like the trembling hand and other concepts [Myerson, 1978; Selten, 1975]. For example, a 'perfect strategy' has to take into account that the other players might just occasionally fail to play rational, which can be due to a 'trembling hand, which leads to 'bounded rationality' [Selten, 1990]. This gives rise to evolutionary learning mechanisms, replacing the standard way of 'a priory reasoning' [Hofbauer and Sigmund, 1998]. On top of that, it cannot be generally assumed that the emerging *dynamics* in strategy space always lead to stationary solutions. In this context, it turns out that the matching pennies game belongs to the class of cyclic games [Cressman, 2003; Maynard Smith, 1982]. In the next subsection we give a brief overview over a concept that is especially successful in biology. Similar to classical game theory of rational agents, the concept of evolutionarily stable strategies does not involve dynamics. However, it already includes a very important feature, namely a population of strategically interacting agents.

1.2.2 Evolutionarily stable strategies

A new perspective to and new properties of games have emerged by the work of John Maynard-Smith and George R. Price who could answer the question of why animals of the same species escalate in fights with an observed probability [Maynard Smith and Price, 1973]. Their key assumptions have turned out to be fundamental to evolutionary game theory. To understand the shift in evolutionary game theory the a posteriori categorization by Gintis [2000] is of special appeal. First, instead of an individual choosing from a set strategy, a population (or a society) has a set of strategies. Strategies are hardwired to genes and thus inherited, completely new strategies and games can arise by mutations. Next, the interactions do not take place on a one-shot basis anymore. Instead, individuals of a population are randomly paired repeatedly, to play the game with their genetically determined strategies. Last, Maynard Smith and Price [1973] defined their own equilibrium, namely the set of evolutionarily stable strategies, probably being unaware of the Nash equilibrium concept.

The idea of an evolutionarily stable strategy (ESS) is based on the potential success of invading mutants. In a symmetric n-strategy game between two players, let the pure strategies be $A_1, \ldots, A_n$, and a_{ij} be the the payoff of A_i played against A_j (where the player with A_j receives a_{ji}). Note, that for $A_1 = A$, $A_2 = B$, and thus $a_{11} = a, a_{12} = b, a_{21} = c, a_{22} = d$, (1.2.3) emerges. The strategy A_k is an ESS, for $\forall i \neq k$, if either $a_{kk} > a_{ik}$ holds (which is nothing but the strict Nash equilibrium definition), or $a_{kk} = a_{ik}$, and $a_{ki} > a_{ii}$ hold.

In prose, this means that pure strategy is ESS either if it is best response to itself, or, if any other strategy does equally well, the ESS's payoff against this strategy is greater than this strategy playing against itself. If in the latter statement the 'greater' is replaced by 'greater or equal', the strategy can be called a weak ESS [Nowak, 2006a]. The concepts ESS and Nash equilibrium are tightly linked: Every strict Nash equilibrium is also an ESS. Every ESS is also a weak ESS. Every weak ESS is also a Nash equilibrium.

As an example we consider the game that motivated the ESS concept in the first place. Within species, animals face strategic conflicts over resources that influence their fitness, such as food, territory, or mates. Some of these conflicts tend to escalate, but an interaction between opponents without causing harm can be observed at least as often. In nature there is a healthy mixture between a few escalators and many retreaters, who solve a conflict either by some 'random' process, or retreat when facing an escalator. Why is this so? A small deviation to more escalation would lead to a huge individual fitness advantage of those applying it. A stable coexistence can be explained by combining cost of injury c and benefit of winning b to the more complex pattern of an evolutionary game.

In the standard literature, the two strategies are called hawk H, and dove D. If a hawk meets a dove the hawk simply wins b, the dove gets out with nothing. If two hawks meet, however, the fight escalates such that both have a cost and a benefit with probability one half, i.e. both get $(b-c)/2$. If two doves meet, each wins with a probability one half, receiving the benefit, and no costs occur, both expect a payoff of $b/2$. The symmetric payoff matrix that focuses on the column player (the row player's matrix is just the transpose) now reads

$$\begin{array}{c} \\ D \\ H \end{array} \begin{array}{c} \begin{array}{cc} D & H \end{array} \\ \begin{pmatrix} \frac{b}{2} & 0 \\ b & \frac{b-c}{2} \end{pmatrix} \end{array}. \tag{1.2.4}$$

The assumption here is that the cost exceeds the benefit $c > b$. With what we know so far, we see that neither of the pure strategies D, or H is an ESS. To understand that there is an ESS of mixed strategies, we need some further consideration, including mixed strategies. The variable x_1 denotes the density of strategy D, and x_2 is the density of strategy H, with $x_1 + x_2 = 1$. Hence, the expected payoffs from random pairings with the population are $\pi_D = x_1\, b/2 + x_2\, 0$, and $\pi_H = x_1\, b + x_2\, (b-c)/2$. The condition $\pi_D = \pi_H$ leads to $x_1 = 1 - b/c$. We see that this is an ESS because $a_{11} = b/2 < a_{21} = b$, $a_{22} = (b-c)/2 < a_{12} = 0$.

1.2.3 Replicator dynamics

Hamilton [1967] and especially Maynard Smith and Price [1973] have studied animal conflicts and their evolutionarily stable strategies, based on genetically determined and heritable strategies that are cast into a game. In most cases, the ESS concept can indicate whether a given strategic composition is prone to mutants taking over, or not, given the game that is played between mutants and wildtypes. Also starting from a game, Taylor and Jonker [1978], as well as Zeeman [1980] have introduced an approach to model the actual dynamics from any possible state to (or away from) an evolutionarily stable state by introducing a set of differential or difference equations. The resulting deterministic equation governs the relative spread of continuously changing densities of strategies in continuous or discrete time and is called the replicator equation [Schuster and Sigmund, 1983]. Evolutionary game theory in form of the replicator equation can describe genotype as well as phenotypic evolutionary dynamics [Hofbauer et al., 1979; Hofbauer and Sigmund, 1998; Schuster, 2003].

Say a population consists of n different types, represented by pure strategies $A_1, \ldots, A_n$.

To each strategy A_i we ascribe the relative density x_i (in biology, a relative abundance or density is also called frequency). If the population is very large (infinitely large) the densities are continuous variables, $x_i \in [0,1]$. They can also be understood as the probabilities that a randomly drawn individual has strategy (or is of type) A_i, which implies consistently

$$\Sigma = \sum_{i=1}^{n} x_i = 1. \tag{1.2.5}$$

If we want to come to an evolutionary argument about the increase and decrease of strategies over time by reproduction, we have to ascribe a fitness f_i to each strategy. Given the type A_i, the fitness function f_i is the expected number of offspring of the same type. In this case, the population average fitness is given by

$$\langle f \rangle = \sum_{i=1}^{n} f_i \, x_i, \tag{1.2.6}$$

where $\mathbf{x} = (x_1, \ldots, x_n)^T$, and in general $f_i = f_i(\mathbf{x})$. The general form of the replicator equation is given such that the relative change of density x_i is governed by how well this particular type is doing compared to the population average (in terms of reproductive success), i.e. $\dot{x}_i/x_i = f_i - \langle f \rangle$. The convex set on which the dynamics takes place is the simplex $\mathbf{S}_n$, defined by Eq. (1.2.5). In general terms using the fitness function, the replicator equation simply reads

$$\dot{x}_i = x_i \left(f_i(\mathbf{x}) - \langle f \rangle \right), \tag{1.2.7}$$

which leaves the simplex $\mathbf{S}_n$ invariant, which implies that every solution of Eq. (1.2.7) that starts on $\mathbf{S}_n$ stays on it forever [Hofbauer and Sigmund, 1998], compare to Figure 1.1, where the simplex for $n = 2,3$, and 4 is depicted, respectively.

Suppose that n different types, or subgroups, A_i of a very large population interact in a symmetric game through random pairing. Here, the symmetric game's payoff matrix reads

$$\mathbb{A} = \begin{pmatrix} a_{11} & a_{12} & \ldots & a_{1n} \\ a_{21} & \ldots & \ldots & a_{2n} \\ \vdots & & & \vdots \\ a_{n1} & \ldots & \ldots & a_{nn} \end{pmatrix}. \tag{1.2.8}$$

Hence, in the pairing of an individual playing the pure strategy A_i against one playing

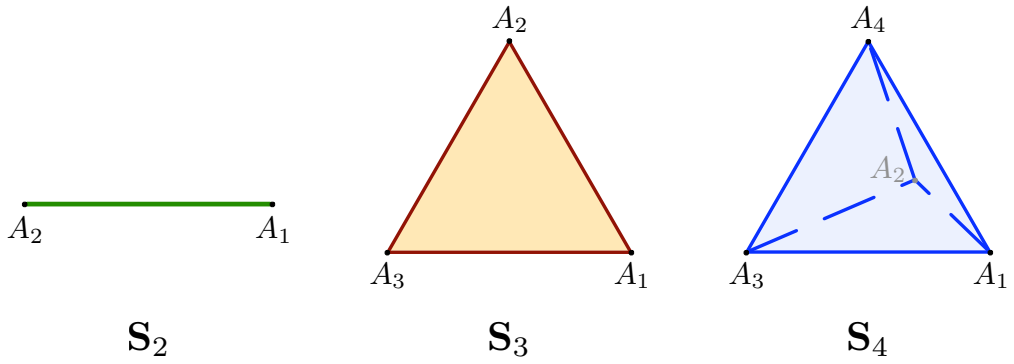

Figure 1.1: The simplex $\mathbf{S}_n$ is defined by all sets of states that fulfill $x_1 + \ldots + x_n = 1$. For two strategies is a line, for three strategies it is the equilateral triangle, for four strategies it is the tetrahedron. In general, for n strategies it is the convex hull of its $n+1$ vertices. The replicator equation leaves the simplex invariant. Each vertex with $x_k = 1$ is identified with its pure strategy A_k.

the pure strategy A_j, the former receives payoff a_{ij}, while the latter receive payoff a_{ji}. An individual with pure strategy A_i that is interacting with an ensemble $\mathbf{q} = (q_1, \ldots, q_n)^T$ of other strategies expects payoff $\pi_{i,\mathbf{q}} = (\mathbb{A}\,\mathbf{q})_i$. A group of individuals with a non-singular strategy profile $\mathbf{p} = (p_1, \ldots, p_n)^T$ interacting with the ensemble $\mathbf{q}$ expects payoff $\pi_{\mathbf{p},\mathbf{q}} = \mathbf{p} \cdot (\mathbb{A}\,\mathbf{q})$. In evolutionary game dynamics modeled by the replicator equation (1.2.7), the rate of increase or decrease of a strategy is proportional to fitness. Typically, a strategy's fitness is equal to (or a monotonically increasing function of) the average payoff of a pure strategy interacting with the entire population as the ensemble of choice. Hence, the fitness of pure strategy A_i is chosen to be $f_i(\mathbf{x}) = (\mathbb{A}\,\mathbf{x})_i$, and the average fitness of the population amounts to $\langle f \rangle = \mathbf{x} \cdot (\mathbb{A}\,\mathbf{x})$. The replicator equation for this standard choice of fitness function thus reads

$$\dot{x}_i = x_i \left(\sum_{j=1}^{n} a_{ij}\, x_j \; - \sum_{i=1}^{n} \sum_{j=1}^{n} x_i\, a_{ij}\, x_j \right). \tag{1.2.9}$$

It is noteworthy that the choice of the f_i is not unique. However, different choices only interfere with the transient dynamics and not with the stability properties of Eq. (1.2.7), as long as fitness is a linear function of payoff.

With this one can make statements about the dynamic variable $\mathbf{x}$ relating it to the Nash equilibrium as well as to the ESS, see [Hofbauer and Sigmund, 1998] and [Nowak, 2006a], and references therein: A point $\mathbf{z} \in \mathbf{S}_n$ is a Nash equilibrium if self interactions

of $\mathbf{z}$ are more or equally successful as any other state $\mathbf{x} \in \mathbf{S}_n$ interacting with $\mathbf{z}$, i.e.

$$\pi_{\mathbf{z}\,\mathbf{z}} \geq \pi_{\mathbf{x}\,\mathbf{z}}. \tag{1.2.10}$$

A point $\mathbf{z}$ on the simplex S_n is called an evolutionarily stable state if

$$\pi_{\mathbf{z}\,\mathbf{x}} > \pi_{\mathbf{x}\,\mathbf{x}} \tag{1.2.11}$$

for all other states $\mathbf{x} \neq \mathbf{z}$, that is if $\mathbf{z}$ is more successful competing with $\mathbf{x}$ than $\mathbf{x}$ competing with itself. The two definitions do not have to be the same. Several important observations arise from combining the replicator dynamics with the Nash equilibrium and the ESS [Hofbauer and Sigmund, 1998; Weibull, 1995], where two of them will be picked up. First, if $\mathbf{z}$ is Lyapunov stable [Strogatz, 2000], then it is a Nash equilibrium in the sense of relation (1.2.10) [Bomze, 1986]. Secondly, if $\mathbf{z}$ fulfills the relation (1.2.11,) it is an asymptotically stable fixed point of the replicator dynamics [Hofbauer et al., 1979; Zeeman, 1980] (the converse is not true [Nowak, 1990]).

A common example of a dynamical systems is the Lotka-Volterra equation that models species interactions [Lotka, 1910; Volterra, 1926]. Like the replicator equation, the Lotka-Volterra equation is a special nonlinear differential equation which puts the growth of biological species or sub-species on the basis of (ecological) interactions, most famously between predators and prey. It has been shown by Hofbauer [1981] that the (cubic) replicator equation (1.2.9) with n strategies can be mapped to a (quadratic) Lotka-Volterra equation with $n-1$ species, using a linear transformation from the compact simplex $\mathbb{S}_n$ to the open half space $\mathbb{R}_+^{n-1}$. Starting from Eq. (1.2.9) consider the new dynamic variable $y_i = x_i/x_n$, with $y_n = 1$, such that

$$\begin{aligned}
\dot{y}_i &= \frac{\dot{x}_i\, x_n - x_i\, \dot{x}_n}{x_n^2} \\
&= \frac{x_i}{x_n}\left[((\mathbb{A}\mathbf{x})_i - \mathbf{x}\cdot(\mathbb{A}\mathbf{x})) - ((\mathbb{A}\mathbf{x})_n - \mathbf{x}\cdot(\mathbb{A}\mathbf{x}))\right] \\
&= y_i\,(\mathbb{A}\mathbf{x})_i \\
&= x_n\, y_i \sum_{j=1}^{n} a_{ij} y_j, \quad (i = 1,\ldots,n-1).
\end{aligned} \tag{1.2.12}$$

The first step applies product and the chain rule, the second step inserts the right hand side of Eq. (1.2.9), and the third step uses that, without loss of generality, we can transform the payoff matrix (1.2.8) such that $a_{nk} = 0$ for all $k = 1,\ldots,n$ [Hofbauer and Sigmund, 1998]. Rescaling time by x_n and setting $r_i = a_{in}$ as the growth or decay rate

of species i, we end up with the Lotka-Volterra equation

$$\dot{y}_i = y_i \left(r_i + \sum_{j=1}^{n-1} b_{ij}\, y_j \right), \tag{1.2.13}$$

which models the growth and decay of $n-1$ species in terms of their relative sizes y_i respecting their interactions $b_{ij} = a_{ij} - a_{nj}$. The relative densities of the strategies x_i exist on [0,1], but, naturally, the relative sizes $y_i = x_i/x_n \in [0,\infty)$ do not have an upper bound. Typically, the replicator equation is cubic, whereas the Lotka-Volterra system is quadratic. Although we almost exclusively think of evolutionary dynamics in terms of strategies and fitness values, the transformation to one of the powerhouses of mathematical ecology is of practical use. The Poincaré-Bendixon theorem leads to the fact that the two-dimensional Lotka-Volterra equation does not allow isolated periodic orbits, compare Bomze [1995] and references therein. This statement can the be transferred to evolutionary games between three strategies, especially when cyclic competition in a rock-paper-scissors fashion is studied [May and Leonard, 1975; Zeeman, 1980]. However, many (non-isolated) cycles can exist, as well as homoclinic and heteroclinic orbits on the simplex $\mathbf{S}_3$, [Hofbauer and Sigmund, 1998]. Before we return to such situation of cyclic competition, all possible scenarios of the replicator dynamics for $n = 2$ are briefly discussed.

1.2.4 Evolutionary game dynamics of two strategies

All evolving organisms face multiple complex strategic situations that can affect their Darwinian fitness: "In the game of life, organisms are the players, their heritable traits provide strategies, their births and deaths are the payoffs, and the environment sets the rules", where the population itself is part of the environment [Vincent and Brown, 2005]. Although it is far from clear whether the strategy space is limited to a few strategies at a time, it is plausible to start a mathematical analysis with only a few evolutionarily competing strategies. This assumption may limit the direct applicability to field biology in some cases, but has been very successful in understanding fundamental aspects of evolutionary dynamics [Nowak, 2006a]. The simplest case emerges for two strategies ($n = 2$), where we will come back to the notation $A = A_1$, and $B = A_2$, with the payoff matrix

$$\mathbb{A} = \begin{pmatrix} a & b \\ c & d \end{pmatrix}. \tag{1.2.14}$$

x is always chosen to be the relative density of strategy A. In the according replicator equation (1.2.7) for $\mathbf{x} = (x_1,x_2)^T$, choosing the fitness function $f_i(\mathbf{x}) = (\mathbb{A}\,\mathbf{x})_i$, it is sufficient to look at $\dot{x} = x\,((\mathbb{A}\mathbf{x})_1 - \mathbf{x}\cdot(\mathbb{A}\mathbf{x}))$; by setting $x_1 = x$, we have $x_2 = 1 - x$. Both strategies evaluate their reproductive success according to random interactions with the entire population. The expected payoffs are

$$\pi_A = (\mathbb{A}\mathbf{x})_1 = a\,x + b(1-x), \tag{1.2.15}$$

$$\pi_B = (\mathbb{A}\mathbf{x})_2 = c\,x + d(1-x), \tag{1.2.16}$$

and the average expected payoff amounts to $\langle\pi\rangle = \mathbf{x}\cdot(\mathbb{A}\mathbf{x}) = x\,\pi_A + (1-x)\pi_B$. We note that $\pi_A - \langle\pi\rangle = (1-x)(\pi_A - \pi_B)$, such that we can write

$$\begin{aligned}\dot{x} &= x\,(1-x)(\pi_A - \pi_B)\\ &= x\,(1-x)(u\,x + v)\end{aligned} \tag{1.2.17}$$

Both expected payoffs are linear, such that that we can generally assume the linear form $\pi_A - \pi_B = u\,x + v$. Naturally, this linear form depends on the payoff matrix (1.2.14), $u = a + d - (b + c)$, and $v = b - d$.

Other choices of linear payoff to fitness mapping are possible. However, they may only change the transient dynamics but not the stability properties of the replicator equation. As an example consider the fitness function $f_i = (1-\beta) + \beta\,(\mathbb{A}\mathbf{x})_i$. The strength by which selection acts on different types or strategies is parameterized by β in form of a convex combination of a background fitness of one and the payoff from the evolutionary game $(\mathbb{A}\mathbf{x})_i$: For $\beta \to 0$, the outcome of the evolutionary game has no effect on the dynamics, the entire simplex consists of neutrally stable fixed points, as, trivially, $\dot{x}_i = 0$ everywhere. If all average payoffs $(\mathbb{A}\mathbf{x})_i$ are positive, $\beta \to 1$ leads to Eq. (1.2.17). In the intermediate regime, the appropriate replicator equation (1.2.7), for $n = 2$, transforms to $\dot{x} = x\,(1-x)\,\beta\,(\pi_A - \pi_B)$. All other terms in the fitness difference $f_i - \langle f\rangle$ vanish, as $\langle f\rangle = x\,f_A + (1-x)f_B$. Hence, for all fitness functions that are linearly increasing in selection intensity, the resulting replicator equation can be rescaled to the form of Eq. (1.2.17). Other choices of deterministic evolutionary game dynamics which, e.g., are based on learning or imitation, as well as so called best response dynamics, have also been studied [Hofbauer and Sigmund, 1998; Sandholm, 2010; Traulsen et al., 2006a; Weibull, 1995].

Evolutionary game dynamics, given by Eq. (1.2.17), reveals a maximum of three fixed points, one in the internal, two on the vertices. The solutions to $\hat{x}_1 = 0$, and $1 - \hat{x}_2 = 0$ always exist. The existence of a solution to $u\,\hat{x}_3 + v = 0$ on the simplex is determined by

the payoff matrix, with $u = a + d - (b + c)$, $v = b - d$. Their stability properties and thus the dynamics between them crucially depends on the payoffs in (1.2.14). The neutral case emerges if $a = c$, and $b = d$, for which the trivial case $\dot{x} = 0$ for all $x \in [0,1]$ holds. Apart from this neutral situation, the three generic scenarios are dominance, bi-stability (coordination), and coexistence, compare to Figure 1.2.

We speak of dominance (in the game theoretic sense, not in the Mendelian sense), if $\hat{x}_1$ is unstable and $\hat{x}_2$ is stable, or if $\hat{x}_1$ is stable and $\hat{x}_2$ is unstable, where $\hat{x}_3 \in (0,1)$ cannot exist. In the former case, any arbitrarily small disturbance from the all B state leads to an all A state, which is true for the payoff rankings $a > c$ and $b > d$. Conversely, the latter case holds for $a < c$ and $b < d$. Part of this class is the non generic case of equal gains from switching, given by $a + d = b + c$ (hence $u = 0$) [Nowak and Sigmund, 1990]. The resulting replicator equation

$$\dot{x} = v\, x\, (1 - x) \tag{1.2.18}$$

describes logistic growth and has the solution

$$x(t) = \frac{1}{1 + \frac{1-x_0}{x_0} \mathrm{e}^{-v(t-t_0)}}, \tag{1.2.19}$$

with the initial condition $x(t_0) = x_0$. If A is the dominant strategy, $v = b - d > 0$, and the time τ_ϵ, needed to get from a small density of A close to fixation, i.e. $x(t_0) = \epsilon \ll 1$, and $x(\tau_\epsilon) = 1 - \epsilon$, is given by

$$\tau_\epsilon = \frac{2}{v} \ln \left[\frac{1 - \epsilon}{\epsilon} \right]. \tag{1.2.20}$$

For sufficiently small ϵ, the fixation time scales as $\tau_\epsilon \sim \ln[1/\epsilon]$.

Bi-stable dynamics emerge in a coordination game, where the payoff rankings are $a > c$, and $b < d$. Hence, strategy A is outperformed by strategy B when rare, but advantageous when at high densities. Consequently, $\hat{x}_1$, and $\hat{x}_2$ are stable fixed points of the replicator dynamics. The outcome of the bi-stable dynamics from any initial condition x_0 between 0 and 1 is determined by the position of the internal unstable fixed point $\hat{x}_3 = -v/u$. If it exists, the unstable fixed point in the interior is located at

$$\hat{x}_3 = \frac{d - b}{a + d - (b + c)}. \tag{1.2.21}$$

If $x_0 < \hat{x}_3$, B dominates, if $x_0 > \hat{x}_3$ A dominates.

Lastly, in an evolutionary game with two strategies A and B, stable coexistence can be

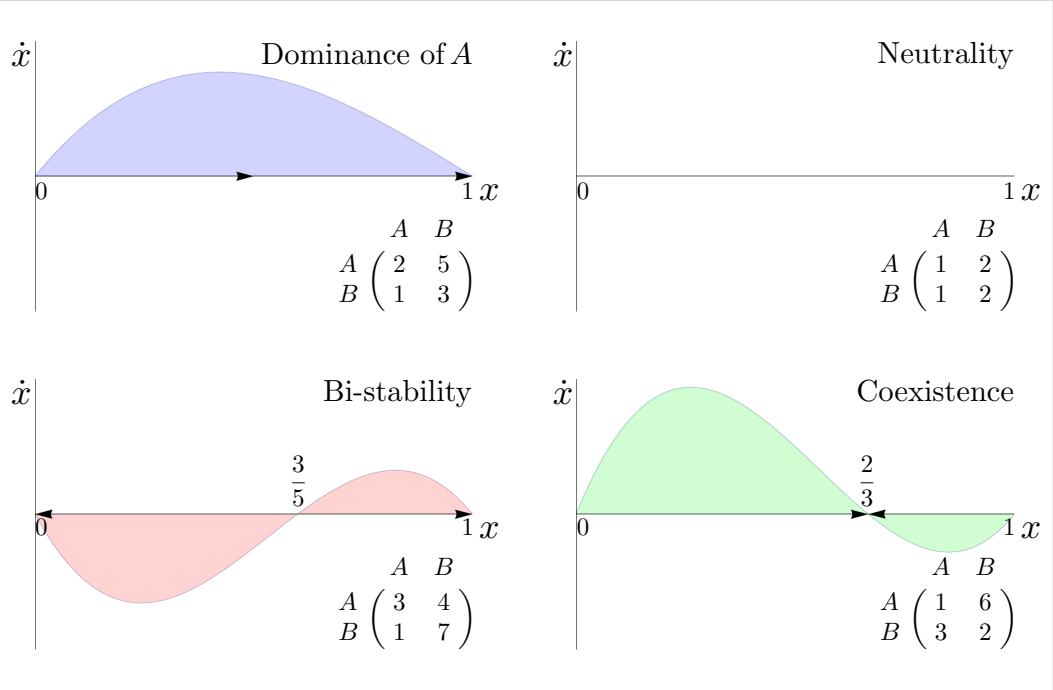

Figure 1.2: Phase diagrams of the replicator equation (1.2.17) for different games. For these numerical examples, the payoff matrices of he symmetric 2×2 game are given explicitly in the figure. If it exists, the position of $\hat{x}_3$, eq. 1.2.21 is given on the simplex $\mathbf{S}_2$ (the [0,1] interval on the x-axis). The arrows indicate the direction of the evolutionary game dynamics.

observed. This is possible for replicator dynamics governed by the payoff matrix (1.2.14) with $a < c$, and $b > d$. It is easy to show that $\hat{x}_1$, and $\hat{x}_2$ are unstable. In this case, $\hat{x}_3$, given by Eq. (1.2.21), is the only stable fixed point.

Note also, that the general form of the right hand side of Eq. (1.2.17) is such that $\hat{x}_3$ cannot be a saddle. This is not naturally the case for any replicator dynamics on the simplex $\mathbf{S}_2$, which is a subset of $\mathbb{R}^1$, but follows here from the choice of the fitness function $f_i = (\mathbb{A}\mathbf{x})_i$. For evolutionary games that account for interactions between pairs the maximal number of internal fixed points of the replicator equation (1.2.9) is one, irrespective of the number of possible strategies [Gokhale and Traulsen, 2010; Hofbauer and Sigmund, 1998].

1.2.5 Cyclic evolutionary games with three strategies

The complexity of evolutionary game dynamics increases with the number of strategies, and new phenomena can emerge. Several widely discussed examples in evolutionary game theory and mathematical ecology are related or can directly be mapped to the dynamics

of the Rock-Paper-Scissors game. Cyclic dominance can play a role in the evolution of mating strategies of lizards [Sinervo and Lively, 1996], and is also observed in the 'chemical warfare' between three strains of the bacterium *E. coli* [Kerr et al., 2002].

A well known child game, Rock-Paper-Scissors is the generic description of cyclic competition: Rock crushes scissors, scissors cut paper, and paper wraps rock. In a pairwise encounter, the winner's payoff is 1 and the loser's payoff is $-s$, but if the two individuals play the same strategy, the payoff of a draw is zero. Hence, the payoff matrix is given as

$$\mathbb{A}_{RPS} = \begin{pmatrix} 0 & -s & 1 \\ 1 & 0 & -s \\ -s & 1 & 0 \end{pmatrix} . \tag{1.2.22}$$

Any payoff matrix describing a cyclic competition of three strategies can be transformed to this form by elementary operations which do not change the stability properties of the replicator equation [Weibull, 1995]. The stability of the center $\hat{\mathbf{x}}(1/3,1/3,1/3)^T \in \mathbf{S}_3$ is controlled by s. Note, that from the Poincaré-Bendixon theorem follows that there cannot be an isolated limit cycle on $\mathbf{S}_3$, hence there cannot be a Hopf-like bifurcation.

The average payoffs for the pure strategies with densities x_R, x_P, $x_S = 1 - x_R - x_P$, are

$$\begin{aligned} \pi_R &= 1 - x_R - x_P - s\, x_P, \\ \pi_P &= x_R - s(1 - x_R - x_P), \\ \pi_S &= x_P - s\, x_R, \end{aligned} \tag{1.2.23}$$

and the replicator equation reads

$$\dot{x}_X = x_X \left(\pi_X - \langle \pi \rangle \right) , \tag{1.2.24}$$

where $X \in \{R,P,S\}$, and $\langle \pi \rangle = \pi_S + x_R(\pi_R - \pi_S) + x_P(\pi_P - \pi_S)$. The vertices of the simplex $\mathbf{S}_3$ are fixed points that are saddles, and form a heteroclinic cycle together with the edges of $\mathbf{S}_3$ [Hofbauer and Sigmund, 1998]. The three generic cases are $s = 1$ (zero sum), $s < 1$ (positive sum), and $s > 1$ (negative sum).

First, for $s = 1$ we see that $\det \mathbb{A}_{RPS} = 0$, $\langle \pi \rangle = 0$, such that the dynamics are given by $\dot{x}_X = x_X\, \pi_X$. In this case, $\hat{\mathbf{x}}$ is stable, but no orbit converges to it; $\hat{\mathbf{x}}$ is surrounded by infinitely many cycles and for each of these closed orbits the time average is $\hat{\mathbf{x}}$ [Hofbauer and Sigmund, 1998]. There exists a constant of motion $H = x_R\, x_P\, x_S$, with $\dot{H} = H \cdot (\pi_R + \pi_P + \pi_S - 3\,\langle \pi \rangle) = 0$, which only holds under the symmetry condition

$s = 1$.

Next, for the positive sum game with $s < 1$, we have $\det \mathbb{A}_{RPS} = 1 - s^3 > 0$, $\hat{\mathbf{x}}$ is an asymptotically stable fixed point of the dynamics. Any orbit starting from an initial condition in the interior of the simplex converges to $\hat{\mathbf{x}}$.

Lastly, in the negative sum game with $s > 1$, we have $\det \mathbb{A}_{RPS} < 0$. Hence, $\hat{\mathbf{x}}$ is unstable and any orbit starting from an initial condition in the interior of the simplex converges to the heteroclinic cycle on the boundary.

Mathematics without natural history is sterile,
but natural history without mathematics is muddled.

John Maynard Smith (1982)

1.3 Stochastic evolutionary game dynamics

It is natural to assume that a population consists of a finite number of individuals. Instead of the relative densities of strategies, which are continuous variables, one considers integer values representing the number of individuals of a certain type or strategy. Generically, the change of these integer values over time is given by probabilistic laws. On all scales of living systems which are subject to Darwinian evolution we observe reproducing units that do not necessarily fit a continuous description. Genes consist of finite numbers of base pairs, individuals consist of a finite number of cells, and populations are formed by a finite number of individuals. Only in special cases it is justified to assume that evolutionary change is deterministic and described by, e.g., replicator dynamics. In some cases, a stochastic description makes the predictions of the deterministic theory more precise. However, in many cases, it is stochastic evolution itself that gives rise to new phenomena, such as neutral evolution, or maintenance of diversity in cases where the replicator equation predicts extinction of all but one strategy.

1.3.1 Demographic fluctuations in finite populations

One approach is to describe the system by a set of discrete random variables representing the number of individuals of different strategies. Although change in continuous or discrete time is possible, the focus of this thesis is almost exclusively on discrete time dynamics. The system is characterized by a probability density function with a discrete support that describes the variables being at a given time in a certain state. Typically, the systems dynamics are governed by a probability matrix that gives the the probability for a jump in unit time from one state to another. The precise form of these transition probabilities reflects the nature of interactions in the complex system.

Most importantly, the interactions are given by an evolutionary game. In general, if the system has no memory, i.e. it fulfills the Markov property, the temporal change of the probability density can be described by a master equation. From this master equation follows a hierarchy of (stationary) moments, that define the stochastic process. All moments scale with the system size, and especially higher moments, such as the variance, are supposed to vanish with increasing size. This gives rise to a standard approximation scheme; the truncated Kramers-Moyal or system size expansion. Assuming that the

system is large enough to permit an approximate description by continuous random variables, one often analyzes a Fokker-Planck equation the results from an expansion of the master equation in inverse system size. As this expansion take into account only the first two moments called drift and diffusion coefficient, in evolutionary population dynamics it is often called a diffusion approximation. In the limit of infinitely large population size all models are bound to approach a form of deterministic law, e.g., given by the replicator dynamics Eq. (1.2.7).

Another possible approach is to take a set of deterministic differentials equation and modulate a set of parameters by noise. This directly allows a description by a Fokker-Planck equation, or equivalently, by a Langevin equation, if the noise is chosen to be Gaussian white noise. A possible choice is to modulate a parameter u, such that the stochastic modulation over time has zero mean and the autocorrelation of the Wiener process, given by $u\,dt \mapsto u(dt + dW_t)$, where dW_t is the increment of the Wiener process. In states that are absorbing, the noise cannot have an impact as well. Hence, the noise modulation can only be density dependent, it vanishes whenever a strategy dies out. Langevin equations that model stochastic populations dynamics are driven by multiplicative noise.

In many cases, a closed analytical treatment is only possible for special classes of Markov chains or diffusion processes. The focus of this thesis is on the first approach, the body of publications mostly deals with jump processes in discrete time. This section concentrates on an introduction of the important features of this class of Markov chains, linking the transition probabilities to evolutionary game dynamics.

1.3.2 Master equation and moments of the one-step process

Here, an introduction is given to the one-dimensional Markov chains that are commonly used in evolutionary game theory and population dynamics. The case of two strategies A and B in a population of size N can be treated with most rigor. The number of individuals with strategy A is given by $i \in \{0,\ldots,N\}$, from which the number of B follows as $N - i$. With this, we have a stochastic process for the state i. In physical terms, this state can be interpreted as the position of a particle diffusing on a discrete set of states. On the other hand, i/N might as well be the number of molecules of a chemical reactant. If the transition rates follow simple laws, e.g., constant or linearly increasing transition, such processes are well known in physics, see the textbooks by van Kampen [1997] and Gardiner [2008]. In order to capture population dynamics under the influence of Darwinian evolution, the transitions become more complex and are rather known in the field of population genetics [Ewens, 2004; Goel and Richter-Dyn, 1974]. Generally,

when populations in which the numbers of strategies fluctuate are addressed, one-step processes [van Kampen, 1997] are referred to as birth-death processes. This implies that in the time interval Δt, only transitions from the state i to its nearest neighbor states are considered. All other transitions are of order $(\Delta t)^2$ (or higher) and can be neglected. Given what we call the state of the system i, a set of transition probabilities is directly associated, and also sometimes referred to as the state of the process. The range of the process is the discrete set of $N+1$ states between 0, and N. We only consider one-step processes in discrete time. The stationary transition matrix is given by

$$T_{i\to i+1} = T_i^+ \tag{1.3.1}$$

$$T_{i\to i-1} = T_i^- \tag{1.3.2}$$

$$T_{i\to i} = T_i^0 = 1 - T_i^+ - T_i^- \tag{1.3.3}$$

$$T_{i\to i\pm k} = 0,\ k > 1. \tag{1.3.4}$$

To conserve the system to the set $\{0,\ldots,N\}$, an obvious boundary condition is $T_0^- = T_N^+ = 0$, but in many cases we even consider absorbing boundaries, $T_0^\pm = T_N^\pm = 0$. Hence, the transition matrix is nonzero only on the main diagonal and on the two secondary diagonals. We will use these transition rates to simplify the master equation of the system and solve it for the moments of the probability function to get from an initial state to a particular boundary in a certain amount of time.

For the probability $p_i(t)$ to find the process in state i at any time t the master equation is a gain-loss equation. It describes how $p_i(t)$ changes over time, respecting transitions from any other state k

$$\frac{p_i(t+\Delta t)}{\Delta t} = T_{i-1}^+\, p_{i-1}(t) - T_i^-\, p_i(t) + T_{i+1}^-\, p_{i+1}(t) - T_i^+\, p_i(t). \tag{1.3.5}$$

The general function $p_i(t)$ is not of great use for evolutionary questions, as it does not specifically relate to any initial condition. However, we are interested in the statistical properties of reaching a given state M, when starting from any possible initial condition. This particular property of the process is important as $M = 0$, or $M = N$ corresponds to the situation of complete extinctions or complete fixation of strategy A. To this end, we consider the function $P_{M,i}(t)$, which is the conditional probability density that the state M is reached in exactly t time steps, starting from initial state i. The time t itself is a random variable, and hence interest is focused on the mean first passage time through M. For mean first passage problems one typically considers the backward master equation [Gardiner, 2008; Redner, 2001]. Solutions to the forward equation are with respect to the state at time t with some fixed initial state. Complementary, the backward equation

gives solutions for fixed final state and variable initial condition. For $P_{M,i}(t)$, choosing $\Delta t = 1$, the backward master equation, where M is fixed, reads

$$P_{M,i}(t) = \left(1 - T_i^+ - T_i^-\right) P_{M,i}(t-1) + T_i^+ P_{M,i+1}(t-1) + T_i^- P_{M,i-1}(t-1) \quad (1.3.6)$$

The kind of solution to this equation depends on the boundary conditions. For absorbing boundaries, $T_0^\pm = T_N^\pm = 0$, no non-trivial stationary solution exists due to the lack of detailed balance: For instance, $P_{0,i}(t)$ is not the probability of being at the boundary at time t, as t is arbitrary, but the process gets absorbed in 0 after a finite time. In general, if the backward master equation (1.3.6) permits an analytical solution that fully describes the process, it is hard to be found [Goel and Richter-Dyn, 1974]. Thus, one resorts to describing the process by its stationary moments in t, where the R^{th} conditional moment is given by

$$\mathcal{T}_{M,i}^{(R)} = \frac{\sum_{t=0}^{\infty} t^R P_{M,i}(t)}{\sum_{t=0}^{\infty} P_{M,i}(t)}, \quad (1.3.7)$$

where $M = 0$, or $M = N$. The stationary normalization

$$\phi_i^M = \sum_{t=0}^{\infty} P_{M,i}(t) \quad (1.3.8)$$

is the probability that the process reaches M for the first time [Gardiner, 2008; Karlin and Taylor, 1975]. If $M = 0$, or N, ϕ_i^M is called fixation probability [Ewens, 2004; Traulsen and Hauert, 2009]. Obviously, the fixation probability is determined recursively using what follows from Eq. (1.3.6),

$$\phi_i^M = \left(1 - T_i^+ - T_i^-\right) \phi_i^M + T_i^+ \phi_{i+1}^M + T_i^- \phi_{i+1}^M \quad (1.3.9)$$

with appropriate boundary conditions.

A boundary can be reflecting or absorbing. Hence, three classes of processes can be identified. Either, the process has two reflecting, one reflecting and one absorbing, or two absorbing boundaries, where the results presented in this thesis focus on the latter two. In what follows, we briefly introduce the derivation of the moment generating recursions for general transition rates with the boundary conditions $T_0^\pm = T_N^\pm = 0$, and the requirement that the Markov chain is irreducible on the set $\{1, \ldots, N-1\}$. For the probability distribution it follows that $\lim_{t\to\infty} P_{M,i}(t) = 0$ for any $0 < M,i < N$. Similar recursions and results for either only $T_0^\pm = 0$, or only $T_N^\pm = 0$, i.e. for only one absorbing

boundary, see, e.g., the textbook by Goel and Richter-Dyn [1974]. By multiplying the backward equation (1.3.6) with t^R and summation over t, we find

$$\begin{aligned}\sum_{t=0}^{\infty} t^R\, P_{M,i}(t-1) &= \sum_{t=0}^{\infty} (1+t)^R\, P_{M,i}(t) \\ &= \sum_{t=0}^{\infty}\sum_{s=0}^{R} \binom{R}{s} t^s\, P_{M,i}(t) \\ &= \phi_i^M + \phi_i^M \underbrace{\sum_{s=1}^{R-1} \binom{R}{s} \mathcal{T}_{M,i}^{(s)}}_{\mathcal{S}_{M,i}^{(R-1)}} + \phi_i^M\, \mathcal{T}_{M,i}^{(R)}\end{aligned} \tag{1.3.10}$$

where we rearranged the terms of the infinite sum and require $P_{M,i}(s) = 0$ for any $s < 0$. Thus, the recursion for $\mathcal{T}_{M,i}^{(R)}$ depends on all lower conditional moments

$$\begin{aligned}\phi_i^M\, \mathcal{T}_{M,i}^{(R)} =& (1 - T_i^+ - T_i^-)\phi_i^M(1 + \mathcal{T}_{M,i}^{(R)} + \mathcal{S}_{M,i}^{(R-1)}) \\ &+ T_i^+ \phi_{i+1}^M(1 + \mathcal{T}_{M,i+1}^{(R)} + \mathcal{S}_{M,i+1}^{(R-1)}) \\ &+ T_i^+ \phi_{i-1}^M(1 + \mathcal{T}_{M,i-1}^{(R)} + \mathcal{S}_{M,i-1}^{(R-1)}),\end{aligned} \tag{1.3.11}$$

with $\mathcal{T}_{M,0}^{(R)} = \mathcal{T}_{M,N}^{(R)} = 0$. Now, for the mean exit time in $M = N$, $\tau_i^N = \mathcal{T}_{N,i}^{(1)}$, the recursion reads

$$\tau_i^N = \left[(1 - T_i^+ - T_i^-)(1 + \tau_i^N) + T_i^+ \frac{\phi_{i+1}^N}{\phi_i^N}(1 + \tau_{i+1}^N) + T_i^- \frac{\phi_{i-1}^N}{\phi_i^N}(1 + \tau_{i-1}^N)\right] \tag{1.3.12}$$

as $\mathcal{S}_{N,i}^{(0)}$ vanishes. Absorption in $M = 0$ occurs with probability $\phi_i^0 = 1 - \phi_i^N$. An equation similar to Eq. (1.3.12) holds for the mean exit time τ_i^0. The (unconditional) mean life time of the one-step process confined between two absorbing states then amounts to $\tau_i = (1 - \phi_i^N)\tau_i^0 + \phi_i^N \tau_i^N$, for which the recursion reads

$$\tau_i = 1 + (1 - T_i^+ - T_i^-)\tau_i + T_i^+\, \tau_{i+1} + T_i^-\, \tau_{i-1}. \tag{1.3.13}$$

This unconditional mean exit time τ_i is often termed unconditional fixation time. Likewise, τ_i^N is called the conditional fixation time of strategy A.

For non-invasive processes that have two absorbing boundaries, the following general results hold. The fixation probability of A (i.e. reaching $M = N$) starting from any

internal state i is given by

$$\phi_i^N = \frac{1+\sum_{j=1}^{i-1}\prod_{k=1}^{j}\frac{T_k^-}{T_k^+}}{1+\sum_{j=1}^{N-1}\prod_{k=1}^{j}\frac{T_k^-}{T_k^+}}, \tag{1.3.14}$$

which follows from Eq. (1.3.8), see [Traulsen and Hauert, 2009]. For the unconditional fixation time the recursion (1.3.13) solves to

$$\tau_i = \sum_{k=i}^{N-1}\sum_{l=1}^{k}\frac{1}{T_l^+}\prod_{m=l+1}^{k}\frac{T_m^-}{T_m^+} - \tau_1\sum_{k=i}^{N-1}\prod_{m=1}^{k}\frac{T_m^-}{T_m^+}, \tag{1.3.15}$$

$$\tau_1 = \phi_1^N\sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{1}{T_l^+}\prod_{m=l+1}^{k}\frac{T_m^-}{T_m^+}. \tag{1.3.16}$$

The fixation time conditioned on absorption in $M = N$, generally given by Eq. (1.3.12) is

$$\tau_i^N = \frac{1}{\phi_i^N}\sum_{k=i}^{N-1}\sum_{l=1}^{k}\frac{\phi_l^N}{T_l^+}\prod_{m=l+1}^{k}\frac{T_m^-}{T_m^+} - \tau_1^N\frac{\phi_1^N}{\phi_i^N}\sum_{k=i}^{N-1}\prod_{m=1}^{k}\frac{T_m^-}{T_m^+}, \tag{1.3.17}$$

$$\tau_1^N = \sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{\phi_l^N}{T_l^+}\prod_{m=l+1}^{k}\frac{T_m^-}{T_m^+}. \tag{1.3.18}$$

All higher moments follow in a similar way. Especially, the conditional moments are of interest in evolutionary dynamics, as they are connected with extinction or fixation of a mutation. Our particular derivation considers only discrete time events. The analysis of one-step processes in continuos time is similar, recursions for the moments then follow from analyzing the generating function of $P_{M,i}(t)$, and the respective equations associated with the master equation [Goel and Richter-Dyn, 1974; van Kampen, 1997].

The next subsection gives a standard formulation of the transition rates in evolutionary game dynamics in finite populations. Generally, these stationary rates are nonlinear in i and do not allow a closed treatment of Eqs. (1.3.14)–(1.3.18). However, selective differences that introduce a deterministic bias that overlaps with otherwise purely stochastic dynamics effectively change the expectation values of fixation or loss. This is in contrast to the deterministic replicator dynamics in infinitely large populations, where selective differences only affect the intermediate timescales but not the outcome of Darwinian evolution.

1.3.3 Stochastic evolutionary game dynamics

The interactions of the two strategies can be given by a symmetric 2×2 game, such as parameterized in the payoff matrix (1.2.14). The two strategies A and B interact. We have payoff a for the two interacting A individuals. When an A interacts with a B, the former gets payoff b, while the latter gets c. Two B individuals obtain d. Typically, however, in evolutionary game theory, individuals interact with an ensemble of other individuals, which can well be the entire rest of the population. For instance one can obtain an expected payoff from random pairwise interactions. In a system of fixed size N, we can give the number of strategy A by i, and hence the number of strategy B by $N - i$. The expected or average payoffs for the two strategies are

$$\pi_A = \frac{i-1}{N-1}\, a + \frac{N-i}{N-1}\, b, \tag{1.3.19}$$

$$\pi_B = \frac{i}{N-1}\, c + \frac{N-i-1}{N-1}\, d, \tag{1.3.20}$$

excluding self-interactions. Hence, each individual does not interact with a specific counterpart, but rather with a mean-field of others. This is often referred to as the well-mixed population scenario and has its pedigree in the origins in the deterministic description by Maynard Smith [1982].

The choice of a payoff to fitness mapping is crucial in finite systems. In order to describe the statistical properties of evolutionary games in finite populations it has to include a parameter β that quantifies the intensity of Darwinian selection. In general, fitness can be modeled by any non-negative function of the product of selection intensity and payoff, $f(\beta\,\pi) \leq 0$. Fitness is a relative quantity, but typically, the background fitness is chosen to be one, $f(0) = 1$. The increase of a strategy is proportional to its fitness. In order to construct a one-step process (1.3.1)–(1.3.4) that conserves the system size N, one can consider simultaneous birth and death events of individuals. A randomly chosen individual gives birth to an identical copy with a probability proportional to fitness, e.g., $T_{\text{birth of } A} \propto i\, f(\beta\,\pi_A)$. Next, a randomly chosen individual is removed from the population to make way for the offspring. This event typically happens at random without a fitness bias, e.g., $T_{\text{death of } A} \propto i$. The two possible outcomes which actually change the composition of the population are the birth of an A and the death of a B such that i increases by one (T_i^+), or the birth of a B and the death of an A such that i decreases by one (T_i^-). All other events, such as birth and death of the same strategy do not change i, and occur with probability $1 - T_i^+ - T_i^-$. For this particular process, called the Moran process after Moran [1962], also see [Ewens, 2004], the normalized transition rates from state i to states $i+1$, and $i-1$ thus read [Nowak et al., 2004; Taylor et al.,

2004; Wu et al., 2010]

$$T_i^+ = \frac{if(\beta\pi_A)}{if(\beta\pi_A) + (N-i)f(\beta\pi_B)} \frac{N-i}{N}, \tag{1.3.21}$$

$$T_i^- = \frac{(N-i)f(\beta\pi_B)}{if(\beta\pi_A) + (N-i)f(\beta\pi_B)} \frac{i}{N}. \tag{1.3.22}$$

Here, the ratio of transition rates in one state equals the fitness ratio, e.g., $T_i^-/T_i^+ = f(\beta\pi_B)/f(\beta\pi_A)$. The net evolutionary change of this process can be given by the gradient of selection, $T_i^+ - T_i^- \propto i(N-i)(f(\beta\pi_A) - f(\beta\pi_B))$, which is very similar to the replicator dynamics, Eq. (1.2.7).

Other definitions of microscopic transition rates based on selection are common [Altrock and Traulsen, 2009a; Hauert and Szabó, 2005; Traulsen and Hauert, 2009; Traulsen et al., 2007]. They can be fundamentally different in general. However, for neutral evolution, i.e. in the absence of a selective bias $\beta = 0$, they essentially give identical results. Moreover, for weak selection $\beta \ll 1/N$, these processes have some universal properties [Taylor et al., 2006; Wu et al., 2010].

One of these alternative one-step process, namely the Fermi process, is given in Figure 1.3. In the Fermi process two randomly chosen individuals compare their payoffs, and switch strategy with a probability given by the Fermi distribution [Blume, 1993; Szabó and Tőke, 1998]. The selection intensity acts as an inverse temperature, such that for β close to zero (high temperatures), the strategy change is mostly random, but for large β the worse imitates the better with a high probability, and the opposite becomes unlikely. For $\beta = 0$, switching is totally random, which refers to the case of neutral evolution.

1.3.4 Neutral evolution (and the random walk)

The most important reference case in evolutionary biology is neutral evolution. It can explain why a high (genetic) variation in nature exists when selective differences are absent. Using models of neutral evolution, one can explain the diversity of types or strategies (originally on the molecular level) within populations by a dynamic equilibrium between randomly occurring mutations and their neutral fixation or extinction [Kimura, 1968]. In evolutionary biology, it is widely accepted that the vast majority of mutations on the molecular (genetic) level are neutral or nearly neutral [Kimura, 1994; McGill et al., 2006]. Neutral evolution allows a statistical classification in the sense that a beneficial (deleterious) mutation fixates with a higher (lower) probability than a neutral mutation. It also serves as an extension to the concept of evolutionary stability: A strategy is evolutionary stable if selection acts against the complete replacement of this strategy by

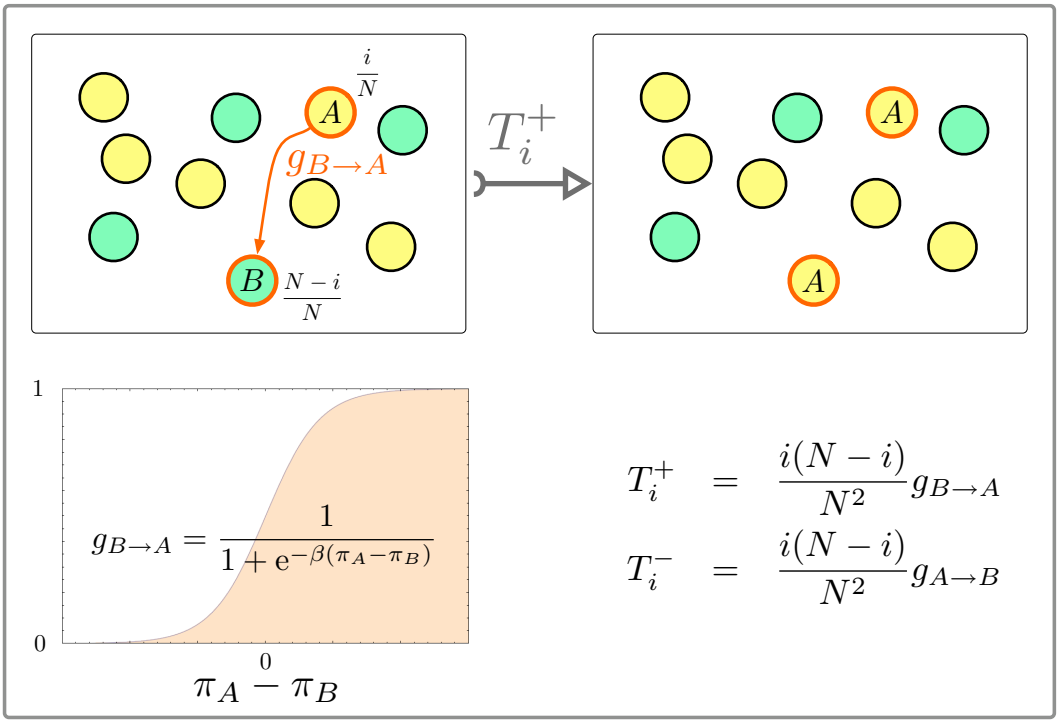

Figure 1.3: The Fermi process as an example of an evolutionary one-step process in a population of fixed size N. In one time step step, two randomly chosen individuals compare their payoff and change their strategy with a probability given by the Fermi distribution. For example a B player switches to strategy A with probability $g_{B\to A}$ as given in the figure at the left bottom. The resulting transition rates are given at the right bottom. The top shows an example where the number of A players i increases by one, which happens with probability T_i^+.

a neutral mutation [Nowak et al., 2004].

For the replicator dynamics in infinitely large populations neutrality means nothing else but that the rate of change in strategy space vanishes trivially everywhere, which does not give a very meaningful prediction for the evolution of a neutral mutation. Perturbations by finite size fluctuations have to be taken into account. Hence, in finite populations the neutral transition rates of the one-step process do not vanish everywhere. Instead, the limit $\lim_{\beta\to 0} f(\beta\pi_A) = \lim_{\beta\to 0} f(\beta\pi_B) = const.$ gives

$$\frac{T_i^-}{T_i^+} = 1 \tag{1.3.23}$$

for neutral evolution, which by no means implies that $T_i^\pm = const.$ Rather than that, under neutrality the transition rates of the evolutionary one-step process with absorbing

boundaries are quadratic in i,

$$T_i^{\pm} = c\,\frac{i\,(N-i)}{N^2}, \tag{1.3.24}$$

where c is a constant often chosen to be one [Ewens, 2004; Nowak, 2006a], see also Eq. (1.3.24). This is a random walk with site dependent hopping rates. Although it is non-isotropic, $T_i^{\pm} \neq T_j^{\pm}$ for $i \neq j$, the symmetries $T_i^{\pm} = T_{N-i}^{\pm}$, and $T_i^{+} = T_i^{-}$ hold.

The fixation probability of the random walk simplifies to

$$\phi_i^N = \frac{i}{N}. \tag{1.3.25}$$

With some more algebra, rearranging the sums in Eq. (1.3.15), the unconditional fixation time is given

$$\tau_1 = \frac{N}{c}\,H_{N-1}, \tag{1.3.26}$$

$$\tau_i = \frac{N}{c}\left[N(N-i)\,s_i + i\,H_{N-1} - N\,H_{i-1}\right]. \tag{1.3.27}$$

Here, $H_k = \sum_{j=1}^{k} 1/j$ are the harmonic numbers that diverge logarithmically in N. We also use the abbreviation $s_i = \sum_{j=1}^{i-1} 1/(j(N-j))$, and note that $H_0 = s_1 = 0$. Likewise, from Eq. (1.3.17), for the conditional fixation time under neutral evolution (in the absence of selection) we find

$$\tau_1^N = \frac{N}{c}(N-1), \tag{1.3.28}$$

$$\tau_i^N = \frac{N}{c}\,\frac{N-i}{i}(\sigma_i + 1), \tag{1.3.29}$$

where $\sigma_i = \sum_{j=1}^{i-1} 1/(N-j)$ with $\sigma_1 = 0$.

It is interesting to see how this compares to the simple random walk with $T_i^{\pm} = 1/2$, and $T_0^{\pm} = T_N^{\pm} = 0$. The unconditional mean exit time of the interval $\{1,\ldots,N-1\}$ now reads

$$\tau_i = (N-i)\,i, \tag{1.3.30}$$

whereas for the conditional mean exit time we find

$$\tau_i^N = \frac{N^2 - i^2}{3}. \tag{1.3.31}$$

The asymptotic scaling behavior of fixation probability and conditional fixation time of

neutral evolution and the simple random walk, if confined between absorbing boundaries, are identical, $\phi_i^N \sim N^{-1}$, $\tau_i^N \sim N^2$ [Altrock et al., 2010a; Antal and Scheuring, 2006; Fisher, 1930]. For the unconditional fixation time (mean life time), this is not true, $\tau_i \sim N \log N$ for the one-step process of neutral evolution, and $\tau_i \sim N$ for the simple random walk.

1.3.5 System size expansion

For all Markov processes, the Chapman-Kolmogorov equation holds as a consistency equation for the joint probability distributions. The master equation is the re-formulation of the Chapman-Kolmogorov equation. It governs the temporal evolution of the probability to occupy a discrete state at a given time respecting the microscopic details of the Markov chain. Due to its complexity, in many cases the master equation itself cannot be solved. In order to be able to find another description that complies with the temporal evolution of a probability density describing the system, one often resorts to an expansion in inverse system size, neglecting terms of higher order in N^{-1}. To this end, continuous spatial and temporal dynamics are assumed, rescaling the state space as $x = i/N$, and the time increment as $\Delta t = 1/N$. This results in a continuous stochastic process on the interval [0,1]. The change from i, the number of type A which is an extensive variable, to the density x being an intensive variable is crucial in the sense that it requires the rescaling of time to lead to a convergent expansion [Gardiner, 2008].

In case of the one-step process, we start from the Markov chain

$$T_{i\to i+1} = \frac{if_A}{if(\beta\pi_A) + (N-i)f(\beta\pi_B)} \frac{N-i}{N} = T_i^+, \tag{1.3.32}$$

$$T_{i\to i-1} = \frac{(N-i)f_A}{if(\beta\pi_A) + (N-i)f(\beta\pi_B)} \frac{i}{N} = T_i^-, \tag{1.3.33}$$

$$T_{i\to i\pm k} = 0, \quad \forall k > 1, \tag{1.3.34}$$

where f_A, f_B are the fitness values of type A, and B, respectively. In discrete space, we define the conditional moments

$$\mathcal{M}_n(i) = \sum_{j=0}^{N} (j-i)^n \, T_{i\to j}, \tag{1.3.35}$$

and require that all such moments with $n > 2$ vanish in the limit of large N. Now the transition to the continuous process allows to describe the system in terms of the temporal change of the conditional moments. Taking $D_n = \langle (x_{t+\Delta t} - x_t)^n \rangle / \Delta t$, such

that for large N [Traulsen et al., 2005]

$$D_n(x) \approx \frac{N}{N^n} \mathcal{M}_n(i), \tag{1.3.36}$$

the drift term becomes

$$D_1(x) \approx T_x^+ - T_x^-, \tag{1.3.37}$$

and the diffusion term is

$$D_2(x) \approx \frac{T_x^+ + T_x^-}{N}. \tag{1.3.38}$$

Eqs. (1.3.35) and (1.3.36) hold in general, Eqs. (1.3.37) and (1.3.38) are a particular result of the one-step process. Especially, for the choice of the density dependent Moran process (1.3.32)–(1.3.34), drift and diffusion can be given in terms of the fitness functions, with $\langle f \rangle = x\, f_A + (1-x) f_B$,

$$D_1(x) \approx x(1-x) \frac{f_A - f_B}{\langle f \rangle}, \tag{1.3.39}$$

$$D_2(x) \approx \frac{x(1-x)}{N} \frac{f_A + f_B}{\langle f \rangle}. \tag{1.3.40}$$

The same drift and diffusion are obtained from a Taylor expansion of the master equation (1.3.5). Setting $\varrho(x,t) = N\, p_i(t)$, in the large N limit the master equation approximately results in the Fokker-Planck equation

$$\dot{\varrho}(x,t) = -\frac{\partial}{\partial x} \left\{ D_1(x)\, \varrho(x,t) \right\} + \frac{1}{2} \frac{\partial^2}{\partial x^2} \left\{ D_2(x)\, \varrho(x,t) \right\}. \tag{1.3.41}$$

This can serve as a starting point for an analysis of stochastic stability and asymptotic behavior [Traulsen et al., 2006b], connecting microscopic stochastic evolutionary game dynamics to the replicator equation with noise [Cremer et al., 2008; Traulsen et al., 2005], as well as allowing a comparison with the diffusion theory in population genetics [Ewens, 2004].

The Fokker-Planck equation (1.3.41) corresponds to a Langevin equation. Using Itô's calculus [Gardiner, 2008; Risken, 1989; van Kampen, 1997], we find

$$dx = x(1-x) \frac{f_A - f_B}{\langle f \rangle} dt + \sqrt{\frac{x(1-x)}{N} \frac{f_A + f_B}{\langle f \rangle}}\, dW(t), \tag{1.3.42}$$

where $dW(t)$ is the increment of the Wiener processes with zero mean and autocorrelation

function $\langle W(t)\, W(s)\rangle = \min\{t,s\}$. We immediately see that in the limit $N \to \infty$ the noise term vanishes and we are left with a replicator equation $\dot{x} \propto x(1-x)(f_A - f_B)$, compare Eq. (1.2.7), provided the average fitness is non-zero.

Nothing in biology makes sense
except in the light of evolution.

Theodosius Dobzhansky

1.4 Population genetics

This is a short overview over the basic population genetic principles used in Chapter 3, which have not been covered in this introduction so far.

A gene, also often referred to as a locus, corresponds to a fixed genetically mappable position on the genome (on a chromosome). Different variants of the same gene are called alleles. Populations genetics studies how distributions of allele frequencies vary over time. In biology, the so called allele frequency is the proportion of all copies of a gene that is made up of a particular gene variant. It is often synonymous with both, the density of a given allele in a very large population (an intensive variable), as well as the number of copies of an allele in a finite population (an extensive variable). Given that individuals in a population reproduce and contribute alleles to their offspring with a certain probability, the important mechanisms for change in allele frequencies are mutation, selection, neutral (i.e., stochastic) change, and gene flow (e.g., caused by mobility of individuals) [Hartl and Clark, 1997]. Some classical aims of populations genetics are, e.g., to understand how polymorphism can be maintained under Darwinian selection and how the process of speciation takes place [Huxley, 1942; Wright, 1931].

The mathematical framework of theoretical population genetics is very similar to that of evolutionary game dynamics [Ewens, 2004; Maruyama, 1977]. However, interest is focused on genes (or alleles) rather that on strategies. If alleles are considered, they usually follow interaction patterns that differ from that of a game, but in some cases, the two descriptions coincide, or can be mapped to each other.

In most cases, the rules by which allele frequencies change comply with Mendelian genetics [Fisher, 1930]. Traditionally, population genetics considers evolution on a fixed but complex fitness landscape, where the evolutionary change is triggered by mutations. Fitness is the expected number of offspring of an individual. The fitness landscape is a mapping from the high dimensional space of all possible genotypes to a real number that measures this expectation value. A population can be seen as a distribution in genotype space, and thus on the fitness landscape. One then asks how the mean and variance of this distribution change over time [Drossel, 2001]. If natural selection acts on genes, or their variants, it is of importance to separate between haploid, diploid or polyploid organisms, as this affects (among other things) the combinatorics that lead to possible

new genotypes. For instance, haploids have only one set of chromosomes, diploids have two. Hence, a diploid organism has two copies of each gene, each of which can have the same or two different variants out of a set of possible alleles.

In general, genotype frequencies are not equal to their corresponding allele frequencies. In haploids, the number of genotypes directly gives the number of alleles. In diploids, the transfer from one to the other depends on the mating pattern [Hartl and Clark, 1997]. We are interested in the evolution of allele frequencies because different alleles have different fitness effects.

1.4.1 Population dynamics under random mating

In diploids, one of the the simplest non-trivial cases emerges when a single gene locus with to variants (alleles) is considered. We denote allele i by A_i, and each individual in a very large population has genotype $A_i\,A_j$, i,j = 1,2. Then, if the ordering does not matter, three generic genotypes are possible: $A_1\,A_1$, $A_1\,A_2 = A_2\,A_1$, and $A_2\,A_2$, with gene frequencies X_1, $2X_2$, and $X_3 = 1 - X_1 - 2X_2$, respectively. Every individual produces gametes during meiosis, which are haploid, i.e. carry only one allele. Diploid offspring are produced by two gametes. The resulting genotype is generated with a probability according to the mating pattern. $A_i\,A_i \times A_i\,A_i$ can produce only $A_i\,A_i$ offspring. Random mating means that offspring from mating of mixed genotypes, such as $A_i\,A_i \times A_i\,A_j$, etc., have a certain genotype with probability given from the according combinatorics, e.g., $A_i\,A_j \times A_i\,A_j$ produces $A_i\,A_j$ with probability 1/2. Hence, the next generation gene frequencies X_i' are given as

$$X_1' = (X_1 + X_2)^2, \tag{1.4.1}$$

$$X_2' = (X_1 + X_2)(X_2 + X_3), \tag{1.4.2}$$

$$X_3' = (X_2 + X_3)^2, \tag{1.4.3}$$

but from then on, in the absence of selection, the frequencies are constant, $X_i'' = X_i'$, with $X_2'X_2' = X_1'X_3'$, [Ewens, 2004]. If

$$X_2^2 = X_1\,X_3 \tag{1.4.4}$$

holds as well, it is sufficient to know the frequency of allele A_1, given by $x = X_1 + X_2$. Hence, all three genotype frequencies can be expressed in terms of the one independent variable x. Then, genotype $A_1\,A_1$ occurs in the population with density x^2, for the other densities see Tab. 1.1. This concept of eliminating the second independent variable, introduced by Hardy [1908], is a fundamental assumption to ease the modeling. Even

though it only properly works throughout the life cycle in the absence of selection, it is assumed in many models that include selection on different genotypes (before applying selection) [Ewens, 2004]. This so called Hardy-Weinberg law serves as the null hypothesis of population genetics.

genotype	$A_1\,A_1$	$A_1\,A_2$	$A_2\,A_2$
fitness	w_{11}	w_{12}	w_{22}
frequency	x^2	$2\,x(1-x)$	$(1-x)^2$

Table 1.1: Hardy-Weinberg equilibrium. Fitness values of genotypes and their frequencies under random mating with two alleles A_1, A_2 (with allele frequencies x, $1-x$).

To come to an (adaptive) evolutionary argument, we have to ascribe fitness values to each genotype, $w_{i,j}$ is thus the constant fitness of genotype $A_i\,A_j$. This is the simplest choice we can make, other choices are possible [Crow and Kimura, 1970]. With this we can write the fitness functions of the alleles as

$$f_1 = w_{11}\,x + w_{12}(1-x), \tag{1.4.5}$$

$$f_2 = w_{12}\,x + w_{22}(1-x), \tag{1.4.6}$$

for allele A_1, A_2, respectively. Then, the average allelic fitness of the population amounts to

$$\langle f\rangle = x\,f_1 + (1-x)f_2. \tag{1.4.7}$$

The evolutionary change in allele frequencies due to reproductive success given by the genotypic fitness values in Tab. 1.1 is given by sampling alleles with replacement between discrete non-overlapping generations according to Wright [1931]. If x is the state of the present generation, in the next generation the frequency changes to $x' = x\,f_1/\langle f\rangle$. Hence, the discrete time dynamics, where time is measured in generations of unit time, for the change in allele frequencies $\Delta x = x' - x$ is given by

$$\Delta x = x\,\frac{f_1 - \langle f\rangle}{\langle f\rangle}. \tag{1.4.8}$$

This is a discrete time version of the replicator equation (1.2.9), corresponding to the

payoff matrix

$$\begin{array}{c} \\ A_1 \\ A_2 \end{array} \begin{array}{c} \begin{array}{cc} A_1 & A_2 \end{array} \\ \begin{pmatrix} w_{11} & w_{12} \\ w_{12} & w_{22} \end{pmatrix} \end{array}. \tag{1.4.9}$$

This direct analogy between the evolution of diploid organisms and evolutionary games only works under the random mating hypothesis in an infinitely large population with Mendelian segregation. It is yet to be seen how far this analogy can be pushed further. In order to cover distortions from Mendelian segregation [Ewens, 2004; Maynard Smith, 1966], more complex strategic interaction patterns may be necessary. The frequencies/payoffs can be adjusted to account for other mating patterns.

1.4.2 Wright-Fisher process

Much like the deterministic theory of population genetics, the stochastic modeling considers time scaled in discrete generations. The individual genes or alleles in generation $t+1$ are sampled with replacement from the ones in generation t. To avoid confusion, instead of referring to individual genes or alleles, we simply refer individuals. This allows a closer comparison with the results for one-step processes in stochastic evolutionary game dynamics, compare to Section 1.3.

In the Wright-Fisher process without mutations, each individual of a population of size N produces a large number of identical offspring, and dies. The next generation of size N is then sampled randomly from this very large offspring pool [Ewens, 2004]. This corresponds to binomial sampling from the present generation. We focus on the situation of two alleles, or types, A_1, and A_2, with fitness values f_1, f_2. The number of A_1 is given as i, the number of A_2 is thus $N-i$. Note that in a diploid population of size n, this corresponds to a total of $N=2n$ individual alleles. We formulate a Markov chain on $\{0,1,\ldots,N\}$, where transitions from state i to any state j are possible, and assume that mutations are so rare that they do not occur before the process gets absorbed in 0, or in N. The probability for a copy of A_1 to occur in the next generation is proportional to the fitness of A_1, and can thus be given by

$$p_{\text{birth of } A} = \frac{i\, f_1}{i\, f_1 + (N-i) f_2}. \tag{1.4.10}$$

Similarly, reproduction of an A_2 happens with probability

$$p_{\text{birth of } B} = \frac{(N-i)f_2}{i\,f_1 + (N-i)f_2}. \tag{1.4.11}$$

The fitness functions are given by Eqs. (1.4.5), (1.4.6), with the replacement $x = i/N$. Hence, the elements of the transition matrix $T_{ji} = T_{i\to j}$, with $i,j \in \{0,\ldots,N\}$, read [Imhof and Nowak, 2006]

$$T_{i\to j} = \binom{N}{j} \left(\frac{x\,f_1}{x\,f_1 + (1-x)f_2}\right)^j \left(\frac{(1-x)f_2}{x\,f_1 + (1-x)f_2}\right)^{N-j}, \tag{1.4.12}$$

$$T_{0\to j} = T_{N\to j} = 0. \tag{1.4.13}$$

The states $\{1,\ldots,N-1\}$ are transient, $\{0,N\}$ are absorbing. The transition rate $T_{i\to j}$ is to be interpreted a the probability that in the next generation, we have j copies of allele A_1, given that in the present generation we have i copies of allele A_1. In discrete time the probability to go from i to j in time t (measured in generations), $\rho(j;i,1)$, fulfills

$$\rho(j;i,t+1) = \sum_{k=0}^{N} T_{k\to j}\,\rho(k;i,t). \tag{1.4.14}$$

The fitness values f_i can be any positive function of the allele frequency x, a special form from random mating is given by Eqs. (1.4.5), (1.4.6). Then, the simplest choice that corresponds to neutral selection is $f_1 = f_2 = 1$, which is equivalent to $w_{11} = w_{12} = w_{22}$ [Crow and Kimura, 1970]. The case of $f_1/f_2 \approx 1/w_{12} \neq 1$ can be obtained for, e.g., $w_{11} = w_{12}$ and $s = w_{12} - w_{22} \ll 1$ by an expansion up to lowest order in s [Ewens, 2004].

In order to make analytical predictions about the statistical properties of the Markov chain given by (1.4.12), (1.4.13) one has to resort to a system size expansion [Kimura, 1994], assuming that the process is approximately well described by the continuous density $x = i/N$. Rescaling time by $\Delta t = 1/N$ as well, and expanding in orders of $1/N$, Eq. (1.4.14) is approximated by the forward Fokker-Planck equation [Ewens, 2004; Gardiner, 2008]

$$\dot{\rho}(x;x_0,t) = -\frac{\partial}{\partial x}\left\{\alpha(x)\,\rho(x;x_0,t)\right\} + \frac{1}{2}\frac{\partial^2}{\partial x^2}\left\{\beta(x)\,\rho(x;x_0,t)\right\}. \tag{1.4.15}$$

The first term accounts for selection (and mutation), the second term models random genetic changes as a diffusion process. The latter phenomenon is often called random drift in population genetics. However, we do not stick to this notation and always refer to it as the diffusion term. Then, the drift term accounts for deterministic part of evolutionary

change due to selection, and reads

$$\alpha(x) = x(1-x)N\frac{f_1(x) - f_2(x)}{xf_1(x) + (1-x)f_2(x)}, \tag{1.4.16}$$

while for the diffusion term one finds

$$\beta(x) = x(1-x)\frac{f_1(x)f_2(x)}{\left(xf_1(x) + (1-x)f_2(x)\right)^2} + \frac{\alpha^2(x)}{N}. \tag{1.4.17}$$

Note the similarities and differences to the system size expansion of the one-step process, Eq. (1.3.41): The drift term takes the same form except for a factor N that can be absorbed by rescaling of time. The diffusion term generally takes a different form, as the Wright-Fisher process starts from a rather different transition matrix.

For our particular process with selection, but without mutations, no stationary distribution exists. The fixation probability $\phi(x_0)$ is the probability that the process exits at $x = 1$ (fixation of allele A_1) after any time when initiated in $x_0 \in (0,1)$. It can be found by considering

$$\phi(x_0) = \int_0^1 d\hat{x}\, \rho(\hat{x}; x_0, t) \tag{1.4.18}$$

and the resulting backward equation

$$0 = \alpha(x_0)\frac{\partial}{\partial x_0}\phi(x_0) + \frac{1}{2}\,\beta(x_0)\,\frac{\partial^2}{\partial x_0^2}\phi(x_0). \tag{1.4.19}$$

This solves to

$$\phi(x_0) = \frac{\int_0^{x_0} dy\, \psi(y)}{\int_0^1 dy\, \psi(y)}, \tag{1.4.20}$$

where

$$\psi(y) = \exp\left\{-2\int^y dz \frac{\alpha(y)}{\beta(z)}\right\}. \tag{1.4.21}$$

In a similar way, considering the backward equation of the generating function one can derive recursions for the moments in time, e.g., for the mean exit times [Ewens, 2004].

1.4.3 Neutral evolution

In the case of neutral evolution, $f_1 = f_2$, the drift term, Eq. 1.4.16, vanishes identically, and the diffusion term simplifies to $\beta(x) = x(1-x)$. Evolution is modeled by the pure diffusion equation on [0,1] with absorbing boundaries,

$$\dot{\rho}(x;x_0,t) = \frac{1}{2}\frac{\partial^2}{\partial x^2}\left\{x(1-x)\,\rho(x;x_0,t)\right\}. \tag{1.4.22}$$

This, and similar equations have been extensively studied by Kimura [1994], an explicit solution exits. It is easy to see that now the fixation probability simply amounts to $\phi(x_0) = x_0$. Under neutral evolution, the conditional mean absorption time, i.e. the average time (measured in generations) spend between 0 and 1, becomes

$$\tau(x_0) = -2\,\frac{(1-x_0)}{x_0}\,\ln[1-x_0]. \tag{1.4.23}$$

A similar result can be obtained for the conditional mean exit times. This links the Wright-Fisher process under diffusion approximation with other evolutionary processes, showing universal behavior in the absence of selection, compare Eqs. (1.3.27), and (1.3.29). This thesis mainly examines the statistical properties of stochastic evolutionary processes under selection. In some cases the influence of selection can be analyzed analytically, e.g., by considering expansion similar to a high temperature expansion in physical systems that respect the bias of selective differences. The interactions that determine selective differences between types can be given either by a genetic background, or by considering evolutionary games. The resulting complex dynamics of the two cases can be very similar.

CHAPTER 2

Fixation events in well mixed populations of finite size

This chapter contains the publications [Altrock and Traulsen, 2009b], [Wu et al., 2010], [Altrock et al., 2010a], and [Altrock and Traulsen, 2009a], in their published format. Each manuscript is given as a section, with a short survey. The previous chapter plays a vital part as motivation and an introduction to the methods used.

2.1 Fixation times in evolutionary games under weak selection

Neutral evolution is the reference case in biology and implies that evolutionary dynamics are random [Kimura, 1994]. In terms of evolutionary game dynamics, weak selection means that an individual's payoffs based on its behavior in strategic interactions with other strategies give only a small correction to the neutral case. This limit case has been transferred from classical population genetics to evolutionary game theory only recently by Nowak et al. [2004]. Weak selection allows to find analytical approximations, e.g., for the probability that a mutation reaches fixation, even in structured populations [Antal et al., 2009; Ohtsuki et al., 2006, 2007b; Tarnita et al., 2009a; Traulsen and Nowak, 2006]. Weak selection results can be obtained by a perturbation analysis that considers additive changes to the neutral evolution due to an expansion in orders of the selection intensity. This is similar to a high temperature expansion in physical systems; selection intensity corresponds to an inverse temperature in statistical mechanics [Traulsen et al., 2006a, 2007]. Most of the recent work focuses on the fixation probability and how it changes with the evolutionary game when selection is weak. In addition, general expressions for the average fixation times have long been known in population genetics [Ewens, 2004; Goel and Richter-Dyn, 1974; Karlin and Taylor, 1975], and mean exit or mean first passage times are routinely analyzed in statistical physics [Gardiner, 2004; Redner, 2001; van Kampen, 1997]. Here, we extend the knowledge of weak selection by particularly

addressing the mean exit times of some widely used stochastic processes that model the dynamics under Darwinian selection in populations of finite size.

We focus on the dynamics of two strategies A and B with a symmetric interaction, as introduced in Chapter 1. The fluctuating variable that characterizes the state of the system is the 'density' i, which is, e.g., the number of A players. Under the well mixed hypothesis, the evolutionary dynamics is governed by the average payoffs π_A, and π_B, both being a function of i. The payoffs π_A and π_B are expectation values from random interactions of the two types (strategies) A and B. In the case of neutral evolution, changes in density only depend on the density itself, compare to 1.3. Under weak selection, the probabilities that the density i changes is proportional to the difference in average payoffs $\Delta\pi = \pi_A - \pi_B$. This difference, as a function of i, is of linear form, namely $\Delta\pi = u\,i + v$. The density dependent term with $u \sim (a + d - (b + c))/N$ evaluates the accumulated success of $A - A$ and $B - B$ versus the accumulated success of $A - B$ and $B - A$. The term that does not depend on the density of A, with $v \sim b - d$, evaluates whether playing A against B, or B against B turns out to be better, irrespective of the composition of the population.

The most relevant case among fixation events emerges when a single mutant, say of type A, invades a population of B. The three important quantities here are (i) the probability that this mutant takes over (fixes) after an arbitrary number of time steps ϕ_1^A, (ii) the conditional mean time of exit for such an event t_1^A, and (iii) the mean lifetime of this process t_1. In Section 1.3, the explicit expressions for these quantities are given for the general evolutionary one-step (birth-death) process with absorbing boundaries.

The common example for a process that involves reproduction and death is the birth-death process introduced by Moran [1962], compare to Section 1.3, Eqs. (1.3.21) and (1.3.22). These processes include a birth and a death event, reproduction is proportional to fitness.

Another possible evolutionary process emerges if one considers imitation. The most famous example for an imitation process is the Fermi process [Blume, 1993; Hauert and Szabó, 2005; Pacheco et al., 2006; Szabó and Tőke, 1998; Traulsen et al., 2006a], compare to Figure 1.3. In each time step two randomly chosen individuals compare payoffs. The probability to choose a random A player is i/N, a random B player is chosen with probability $(N - i)/N$. The probability that one switches and adopts the other's strategy is given by the Fermi function. With a probability greater than $1/2$ the worse imitates the better, whereas with a probability smaller than $1/2$ the better imitates the worse.

Both kind of processes are analyzed in this thesis. For weak selection, the transition probabilities can always assumed to be a linear function of the average payoff. The influence of the selection intensity on the fixation probability ϕ_1^A has been understood

quite well, see ,e.g., [Traulsen et al., 2007], and our focus now is on the fixation times t_1^A and t_1. The goal is to explicitly derive weak selection expressions for the unconditional and conditional fixation times. The final result is deeply connected to a symmetry relation in the conditional fixation times discussed by Antal and Scheuring [2006]; Taylor et al. [2006], see also 2.2.

Relating back to the linear form of the average payoff from above, $\Delta\pi = u\,i + v$, the following surprising simplifications hold under weak selection. The neutral terms of ϕ_1^A, t_1^A, and t_1 only depend on N. Selection is parameterized by β and weak selection thus means $\beta \ll 1/N$. While for the fixation probability ϕ_1^A the correction linear in β depends not only on N, but also on u and v. For the mean life time t_1 the linear correction is proportional to v, whereas for the conditional fixation time t_1^A, it is proportional to u only. We have $t_1^A \approx C_N - u\,D_N\,\beta$ and $t_1 \approx E_N + v\,F_N\,\beta$, where C_N, D_N, E_N, F_N are positive constants involving only N.

With these results we can address the influence of the game parameters a, b, c, and d on the macroscopic statistical properties, as $u \propto a + d - (b + c)$ and $v \propto N(b - d) - a + d$. The weak selection expansion now confirms that in coordination games, i.e. when both strategies are best replies to themselves, both fixation times always decrease with increasing selection, as $u > 0$ and $v < 0$. In addition, when both strategies are a best reply to the other, the system spends more time in the interior and the fixation times increase with increasing selection, as $u < 0$ and $v > 0$. For the seemingly simple case of one strategy performing always better, however, the situation is more diverse, see also Section 2.3.

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Fixation times in evolutionary games under weak selection

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Abstract. In evolutionary game dynamics, reproductive success increases with the performance in an evolutionary game. If strategy A performs better than strategy B, strategy A will spread in the population. Under stochastic dynamics, a single mutant will sooner or later take over the entire population or go extinct. We analyze the mean exit times (or average fixation times) associated with this process. We show analytically that these times depend on the payoff matrix of the game in an amazingly simple way under weak selection, i.e. strong stochasticity: the payoff difference $\Delta\pi$ is a linear function of the number of A individuals i, $\Delta\pi = u\,i + v$. The unconditional mean exit time depends only on the constant term v. Given that a single A mutant takes over the population, the corresponding conditional mean exit time depends only on the density dependent term u. We demonstrate this finding for two commonly applied microscopic evolutionary processes.

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Contents

1. Introduction

Systems in which successful strategies spread by imitation or genetic reproduction can be described by evolutionary game theory. Such models are routinely analyzed in evolutionary biology, sociology, anthropology and economics. Recently, the application of methods from statistical physics to these systems has led to many important insights [1]–[5].

Traditionally, the dynamics is described by the replicator equations, where the growth rate of a strategy is associated with its relative success compared with the population average [6, 7].

In the past few years, research has focused on stochastic evolutionary game dynamics in finite populations [8]–[22]. In this context, a connection to the weak selection limit of population genetics has been established [8]. Weak selection means that the payoff differences based on different strategic behavior in interactions represent only a small correction to otherwise random dynamics, similar to high temperature expansions in physics. Weak selection is considered as a relevant limit in biology, as most evolutionary changes are driven by small fitness differences [23]. Moreover, it allows analytical approximations that are often impossible when selective differences in payoffs are large [8, 24, 25].

Most of the recent work that uses the weak selection approximation has been focusing on the probability that a certain strategy takes over. The time associated with this process has been calculated [26], but it received considerably less attention so far. Here, we present the weak selection corrections to the conditional and unconditional mean exit or fixation times in evolutionary 2×2 games with N players.

The conditional average time to fixation t_1^A is the expected time a single mutant needs to take over the population, given that such a takeover occurs at all. The unconditional average time of fixation t_1 is the expectation value for the time until the population is homogeneous again after the arrival of a single mutant. This is regardless of whether the mutant type takes

over the population or becomes extinct. Equivalently, the average fixation times for such one-dimensional random walks can also be interpreted as mean first passage times or mean exit times [27]–[29].

Throughout this paper, we use the payoff matrix

$$\begin{array}{c} \\ A \\ B \end{array} \begin{array}{c} \begin{array}{cc} A & B \end{array} \\ \begin{pmatrix} a & b \\ c & d \end{pmatrix} \end{array}. \tag{1}$$

An A player interacting with another A receives a. If it interacts with B, it obtains b. Similarly, B receives c from A and d from other Bs. Thus, the average payoffs are

$$\pi_A(i) = \frac{i-1}{N-1}\, a + \frac{N-i}{N-1}\, b, \tag{2}$$

$$\pi_B(i) = \frac{i}{N-1}\, c + \frac{N-i-1}{N-1}\, d. \tag{3}$$

A quantity that is of particular interest is the difference between the average payoffs,

$$\Delta\pi(i) = \pi_A(i) - \pi_B(i) = u\, i + v, \tag{4}$$

where

$$u = \frac{a+d-(b+c)}{N-1}, \tag{5}$$

$$v = \frac{N(b-d)-(a-d)}{N-1}. \tag{6}$$

We show that under weak selection, the conditional time (t_1^A) during which a single mutant takes over the whole population depends only on u (and, of course, on the population size). The unconditional time (t_1) during which the mutant either takes over the population or reaches extinction depends only on v (and the population size). See figure 1 for an illustration of the relevant quantities.

Our paper is organized as follows: in section 2, we introduce a particular evolutionary process for our analysis. Although our results are valid for a broader class of processes, we only present the full calculation for this evolutionary process. In section 3, we recall the general form of fixation probabilities and times. We discuss neutral selection in section 4 as a prerequisite to the weak selection expansion, which we explore in section 5. In section 6, we address the frequency-dependent Moran process to underline the generality of our findings. The consequences of our analytical results are discussed in section 7.

2. Fermi process

In a finite population of size N with two possible strategies A and B, the state of the system is characterized by the number of type A individuals i. In general, the dynamics is stochastic. In each time step, a randomly chosen individual evaluates its success. It compares this payoff with a second, randomly chosen individual. If this second individual has a higher payoff, the first one switches strategies with probability $p > \frac{1}{2}$. Otherwise, it switches with $p < \frac{1}{2}$. We assume

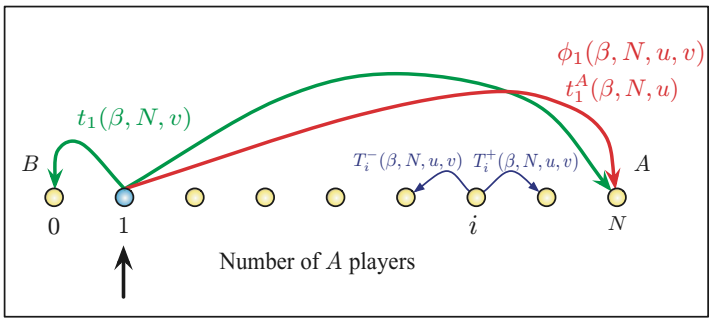

Figure 1. Illustration of the most relevant quantities. We are interested in the evolutionary fate of a single A player. All quantities depend on the intensity of selection β and the population size N. The payoff difference between A and B players is given by $\Delta\pi = u\,i + v$, with i as the number of A players. Both the transition probabilities T_i^+ and T_i^- and the probability that a single A player takes over the population ϕ_1 depend on u and v. But for weak selection, $\beta \ll 1$, the conditional time t_1^A during which a single A player takes over a population of B players only depends on u, whereas the unconditional time t_1 until either A or B has taken over the population only depends on v.

that the switching probability is given by the Fermi distribution. Its shape is controlled by the intensity of selection β, which can be interpreted as an inverse temperature,

$$p_i^{\pm} = \frac{1}{1 + \mathrm{e}^{\mp\beta(\pi_A(i) - \pi_B(i))}} = \frac{1}{1 + \mathrm{e}^{\mp\beta\,\Delta\pi(i)}}. \tag{7}$$

In previous work [30]–[32], there is a different strategy update procedure. The first individual switches to the second's strategy with probability $p_i^{\pm}$. The second individual can also switch to the first individual's strategy with probability $1 - p_i^{\pm}$. This yields a factor 2 in the transition probabilities (and, as will become clear later, a factor $\frac{1}{2}$ in the fixation times). This process also has a proper strong selection limit, i.e. it is possible to examine $\beta \to \infty$. In this latter case, we have $p_i^{\pm} \to \Theta(\Delta\pi(i))$, where $\Theta(x)$ is the step function.

The population size is constant in time, in each time step the state of the system can at most change by one, i.e. from i to $i-1$ or to $i+1$. The transition probabilities $T_i^{\pm}$ to move from i to $i \pm 1$ are

$$T_i^{\pm} = \frac{i}{N}\frac{N-i}{N}\,p_i^{\pm}. \tag{8}$$

The probability to stay in the current state is $1 - T_i^+ - T_i^-$. An important measure of where the system is more likely to move is their ratio,

$$\gamma_i = \frac{T_i^-}{T_i^+} = \mathrm{e}^{-\beta\,\Delta\pi(i)}. \tag{9}$$

This is a quantity that describes the tendency to move from the state i to $i \mp 1$, depending on whether $\gamma_i \gtrless 1$. Of course, $T_i^+ > 0$ is required, which follows from $\beta < \infty$. The $T_i^{\pm}$ and thus the γ_i are invariant under adding a value to each of the payoffs given in (1), whereas multiplying the payoff matrix with a factor λ results in a change in the intensity of selection $\tilde{\beta} = \beta\,\lambda$.

Let us now focus on weak selection, $\beta \ll 1$. In this case, we have

$$p_i^{\pm} \approx \frac{1}{2} \pm \frac{\beta}{4} \Delta\pi(i). \tag{10}$$

Weak selection corresponds to high temperature in Fermi statistics. A Taylor expansion of the γ_i up to first order in β yields $\gamma_i \approx 1 - \beta\, \Delta\pi(i)$. In this case, the probability to move from i to $i+1$ is very similar to the probability to move from i to $i-1$. Weak selection links the Fermi process to a variety of birth–death processes, cf [8, 33].

3. Fixation probabilities and fixation times

From equation (8) it follows that the two pure states all A or all B are absorbing, $T_0^{\pm} = T_N^{\pm} = 0$. In a finite population, we can calculate the probability ϕ_i that the system will fixate to the pure state all A, starting with the mixed state i. Obviously, we have $\phi_0 = 0$ and $\phi_N = 1$. For $0 < i < N$, there is a balance equation for the fixation probabilities, $\phi_i = T_i^- \phi_{i-1} + (1 - T_i^+ - T_i^-)\phi_i + T_i^+ \phi_{i+1}$. This recursion leads to an expression for the fixation probabilities in terms of the γ_i [34]–[36],

$$\phi_i = \frac{1 + \sum_{k=1}^{i-1} \prod_{l=1}^{k} \gamma_l}{1 + \sum_{k=1}^{N-1} \prod_{l=1}^{k} \gamma_l}, \tag{11}$$

which is valid for any birth–death process.

For the Fermi process, the exact equation (9) simplifies matters in an elegant way because the products in equation (11) can be solved,

$$\prod_{l=1}^{k} \gamma_l = \exp\left\{-\beta \sum_{l=1}^{k} \Delta\pi(l)\right\} = \exp\left\{-\beta \left[k^2 \frac{u}{2} + k\left(\frac{u}{2} + v\right)\right]\right\}. \tag{12}$$

Hence, equation (11) simplifies to

$$\phi_i = \frac{1 + \sum_{k=1}^{i-1} \exp\left\{-\beta \left[k^2 \frac{u}{2} + k\left(\frac{u}{2} + v\right)\right]\right\}}{1 + \sum_{k=1}^{N-1} \exp\left\{-\beta \left[k^2 \frac{u}{2} + k\left(\frac{u}{2} + v\right)\right]\right\}}. \tag{13}$$

For large N, the sums in equation (13) can be approximated by integrals, which yields a closed expression for the probabilities ϕ_i [33, 37].

General expressions for the unconditional and conditional mean exit times or average times of fixation, t_1 and t_1^A, are well known, especially for simple, translational invariant random walks [26, 27, 38]. A complete derivation for the average times of fixation in finite systems without translational invariance can be found in [26, 35, 39].

In the following, we will focus on the fixation of a single A mutant in a population of B. Accordingly, the unconditional and conditional fixation times read

$$t_1 = \phi_1 \sum_{k=1}^{N-1} \sum_{l=1}^{k} \frac{1}{T_l^+} \prod_{m=l+1}^{k} \gamma_m \tag{14}$$

and

$$t_1^A = \sum_{k=1}^{N-1} \sum_{l=1}^{k} \frac{\phi_l}{T_l^+} \prod_{m=l+1}^{k} \gamma_m, \tag{15}$$

respectively. Time is measured in elementary time steps here. Thus, in each time step one reproductive event occurs. In biological contexts, it is often more convenient to measure time in generations, such that each individual reproduces once per generation on average. Time in generations is obtained by dividing the number of time steps by the population size N. It is well known that the variance of the exit times under weak selection can be large [39], which has important biomedical implications [40]. Nonetheless, here we concentrate on the expectation values and do not address the distribution of the exit times.

4. Neutral selection

An important reference case is neutral selection, which results from vanishing selection intensity $\beta = 0$ [41]. Neutral selection is a very general limit, which is typically not affected by the details of the evolutionary process. For neutral selection we have $\gamma_i = 1$, that is $T_i^+ = T_i^-$ in any state i. However, we still have $T_i^\pm \neq T_j^\pm$ for $i \neq j$, although the system is symmetric, $T_i^\pm = T_{N-i}^\pm$. This is a difference to the simple random walk in one dimension, which is invariant with respect to translation [29].

For the Fermi process, the neutral transition probabilities are

$$T_i^\pm\Big|_{\beta=0} = \frac{1}{2}\frac{i}{N}\frac{N-i}{N}. \tag{16}$$

We have $T_i^+ = T_i^-$, which leads to $\gamma_i = 1$. From equation (11), it is thus clear that the probability of fixation to A is given by the initial abundance of A,

$$\phi_i\Big|_{\beta=0} = \frac{i}{N}. \tag{17}$$

For the neutral unconditional time of fixation t_1 we get

$$t_1\Big|_{\beta=0} = \frac{1}{N}\sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{2N^2}{l(N-l)} = 2N\,H_{N-1}. \tag{18}$$

Details for this calculation can be found in appendix A. We introduced the shorthand notation for the harmonic numbers $H_{N-1} = \sum_{l=1}^{N-1}\frac{1}{l}$, which diverge logarithmically with N. In the same way we can solve

$$t_1^A|_{\beta=0} = \sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{l}{N}\frac{2N^2}{l(N-l)} = 2N(N-1). \tag{19}$$

For neutral selection, the conditional average time of fixation of a single mutant diverges quadratically with the system size.

5. Weak selection

In this section, we will calculate the linear corrections of the mean exit times or fixation times t_1 and t_1^A under weak selection, $\beta \ll 1$. Of course, all weak selection approximations are valid only if the term linear in β is small compared with the constant term.

The fixation probabilities for small β are

$$\phi_i \approx \frac{i}{N} + \frac{i}{N}(N-i)\frac{(N+i)u+3v}{6}\beta, \tag{20}$$

which has been derived for a variety of evolutionary processes before [8, 10, 12, 35, 36, 42].

Next, we address the weak selection approximation of the fixation times. The expectation value of the unconditional fixation time of a single A mutant in a population of B is in general given by the exact equation (14). With the transition and fixation probabilities of the Fermi process, the unconditional fixation time of absorption at any boundary simplifies to

$$t_1 = \phi_1 \sum_{k=1}^{N-1} \sum_{l=1}^{k} \frac{N^2}{l(N-l)} \left(1 + \mathrm{e}^{-\beta(u\,l+v)}\right) \exp\left\{-\beta \sum_{m=l+1}^{k} \Delta\pi(m)\right\}. \tag{21}$$

The weak selection approximation takes the remarkably simple form (see appendix B for details)

$$t_1 \approx 2\,N H_{N-1} + v\,N\,(N - 1 - H_{N-1})\;\beta \tag{22}$$

with v given in (6). Thus, t_1 depends only on the constant term of the payoff difference. For large N, this yields $v \approx b - d$. That is, for large populations under weak selection, the linear correction of the average fixation time only depends on the advantage (or disadvantage) of the A mutants in the resident population. For $b > d$, invasion of A mutants is likely and slows down the time until the population is homogeneous again. For $d > b$, it is difficult for A to invade a B population and extinction of the mutants is faster than in the neutral case. Note that the payoff entries a and c have no influence on the unconditional fixation time under weak selection corrections. Since fixation is unlikely for weak selection (the probability of fixation of a single A mutant is approximately N^{-1}), the unconditional fixation time is dominated by the fixation to B. In this case, it is enough to discuss the invasion of A mutants.

Next, we address the average time to fixation given that the A mutant takes over the population. With the general result (15) the conditional fixation time of the Fermi process to all A reads

$$t_1^A = \sum_{k=1}^{N-1} \sum_{l=1}^{k} \phi_l \frac{N^2}{l(N-l)} \left(1 + \mathrm{e}^{-\beta(u\,l+v)}\right) \exp\left\{-\beta \sum_{m=1+l}^{k} \Delta\pi(m)\right\}. \tag{23}$$

Its linear approximation turns out to be dependent on the payoffs in a very simple way as well,

$$t_1^A \approx 2\,N(N-1) - u\,N(N-1)\frac{N^2 + N - 6}{18}\,\beta \tag{24}$$

with $u(N-1) = a - b - c + d$. The detailed calculation can be found in appendix B. Since during the fixation process all payoffs are of importance, it is obvious that they all enter here. For example, when it is easy to invade because few mutants have an advantage ($b > d$), but difficult to reach fixation because mutants are disadvantageous once they are frequent ($c > a$), we have $u < 0$ and the conditional time to fixation is larger than neutral. In the last section, we discuss special classes of games to show that, under weak selection, the conditional mean exit times of fixation (or absorption) do not always follow the intuition based on the payoff matrix (1).

6. Frequency dependent Moran process

In this section, we address the generality of the previous findings discussing an alternative evolutionary process. The first model that connects payoffs from a 2×2 game to reproductive fitness using a weak selection approach in finite populations is the frequency dependent Moran process [8, 9]. In this process, an individual is chosen for reproduction with probability

proportional to its fitness $f(i)$. The offspring replaces a randomly chosen individual. The average payoffs (2) and (3) are mapped to the fitness such that $f_A(i) = 1 - \beta + \beta\,\pi_A(i)$ and $f_B(i) = 1 - \beta + \beta\,\pi_B(i)$, where the selection intensity $\beta > 0$ is so small that $f_A(i) > 0$ and $f_B(i) > 0$. The transition probabilities of the standard Moran process read

$$T_i^+ = \frac{i f_A(i)}{i f_A(i) + (N-i) f_B(i)} \frac{N-i}{N}, \tag{25}$$

$$T_i^- = \frac{(N-i) f_B(i)}{i f_A(i) + (N-i) f_B(i)} \frac{i}{N}. \tag{26}$$

Although these transition probabilities are different from those of the Fermi process, they also yield $\gamma_i \approx 1 - \Delta\pi(i)$ and $\prod_{m=l+1}^{k} \gamma_m \approx 1 - \beta \sum_{m=l+1}^{k} \Delta\pi(m)$ for weak selection, $\beta \ll 1$. Thus, the weak selection approximations of the fixation probabilities ϕ_l of the Moran process and the Fermi process are identical, see equation (20). But the weak selection approximations of the transition probabilities are not identical, which leads consequently to different mean exit times. Nevertheless, the results have the same, remarkably simple connection to the payoff matrix (1). The mean exit times or fixation times of the frequency-dependent Moran process are

$$t_1 \approx N H_{N-1} + v\,\frac{N}{2}\,(N + 1 - 2H_N)\;\beta, \tag{27}$$

$$t_1^A \approx N(N-1) - u\,\frac{N^2(N^2 - 3N + 2)}{36}\,\beta. \tag{28}$$

Qualitatively, the dependence on the payoff matrix via u and v is the same as for the Fermi process. Their calculation is analogous to the findings of the previous section, details can be found in appendix B. Note that, comparing with the Fermi process, there is a factor of 2 missing in the neutral terms. However, this can be avoided by rescaling the transition probabilities, without changing the properties of the different processes.

7. Discussion

Finally, let us discuss the implications of our results for general 2×2 games. While we concentrate on the Fermi process here, the discussion is equally valid for the frequency dependent Moran process. An important question is whether the linear correction for weak selection is compatible with the general features of the game and the known asymptotic behavior for large N of the mean exit or fixation times derived by Antal and Scheuring [26]. Clearly, this depends on the payoff matrix of the 2×2 game,

$$\begin{array}{c} \\ A \\ B \end{array} \begin{array}{c} \begin{array}{cc} A & B \end{array} \\ \begin{pmatrix} a & b \\ c & d \end{pmatrix} \end{array}, \tag{29}$$

as the payoffs enter the first exit times of absorption linearly. To analyze the difference from the neutral case we consider the rescaled average times of fixation, $\tau_1(\beta) = t_1(\beta)/t_1(0)$ and $\tau_1^A(\beta) = t_1^A(\beta)/t_1^A(0)$. The rescaled unconditional fixation time reads

$$\tau_1 \approx 1 + \frac{1}{2}\,\frac{N(b-d) - a + d}{N-1}\,\left(\frac{N-1}{H_{N-1}} - 1\right)\,\beta. \tag{30}$$

Accordingly, the rescaled conditional fixation time for absorption at all A is

$$\tau_1^A \approx 1 - \frac{a-b-c+d}{N-1}\,\frac{N^2+N-6}{36}\,\beta. \tag{31}$$

Note that for population sizes $N > 2$ and sufficiently small β, we always have $t_1(0) < t_1^A(0)$. In other words, the average time until the A individual has reached fixation or gone extinct is smaller than the conditional average time until the A individual has reached fixation. For $\beta \to \infty$, the process follows deterministically the intensity of selection and thus both fixation times may coincide, $t_1(\beta \to \infty) \approx t_1^A(\beta \to \infty)$. This ordering of the fixation times is blurred by our rescaling, as we focus only on the change relative to the neutral case.

In the following, we discuss these two expressions for the three generic types of 2×2 games, namely dominance of A ($a > c$ and $b > d$), coexistence of A and B ($a < b$ and $c > d$) and a coordination game ($a > c$ and $b < d$).

7.1. Dominance of A

Consider a game where strategy A is always dominant, i.e. it obtains a larger payoff than B, regardless of the fraction of A in the population. This is the case for $a > c$ and $b > d$. One special case is the Prisoner's dilemma with $b > d > a > c$. The interesting feature of this game is that the social optimum d is not the Nash equilibrium, which is a. For neutral selection, a single A individual goes extinct with probability $1 - N^{-1}$. Thus, the unconditional fixation time τ_1 is dominated by the extinction of A. Since strategy A is favored by selection, increasing the intensity of selection decreases the probability of the extinction of A. Since fixation takes at least $N - 1$ time steps, τ_1 increases with increasing intensity of selection β. For large N, this is obvious from our equation (30), because in this case the quantity $N(b-d) - a + d$ is positive. However, once extinction of A becomes unlikely, increasing β further will lead to a decrease of τ_1.

The discussion of the conditional fixation time τ_1^A is not as straightforward, because the sign of $a - b - c + d$ can be positive or negative. The sign of this quantity is also decisive for the evolutionary dynamics in other contexts, see, e.g., [43]. When the advantage of an A individual is initially large and decreases with the abundance of A ($a - c > b - d > 0$), then the sign of $a - b - c + d$ is positive and τ_1^A decreases with increasing intensity of selection. But when the advantage of strategy A decreases with the number of A individuals ($b - d > a - c > 0$), then τ_1^A increases with increasing intensity of selection. However, this apparently counterintuitive phenomenon (after all, A dominates B) can only be observed for weak selection. For strong selection, τ_1^A decreases again. These results are compatible with the observation that the conditional fixation time scales as $N \ln N$ for large N [26]. In figure 2(a), we show a numerical example for the rescaled average times. We include averages from numerical simulations of the evolutionary process, our linear approximation as well as the exact result that can be obtained from dividing equation (14) by (18) and equation (15) by (19), respectively. The payoff matrix is chosen such that $a + d > b + c$, which means that with increasing intensity of selection τ_1^A decreases and τ_1 increases.

7.2. Coexistence of A and B

As a second class, we consider games in which B is the best reply to A ($c > a$), but A is the best reply to B ($b > d$). Important examples for such games are the Hawk–Dove game [44]

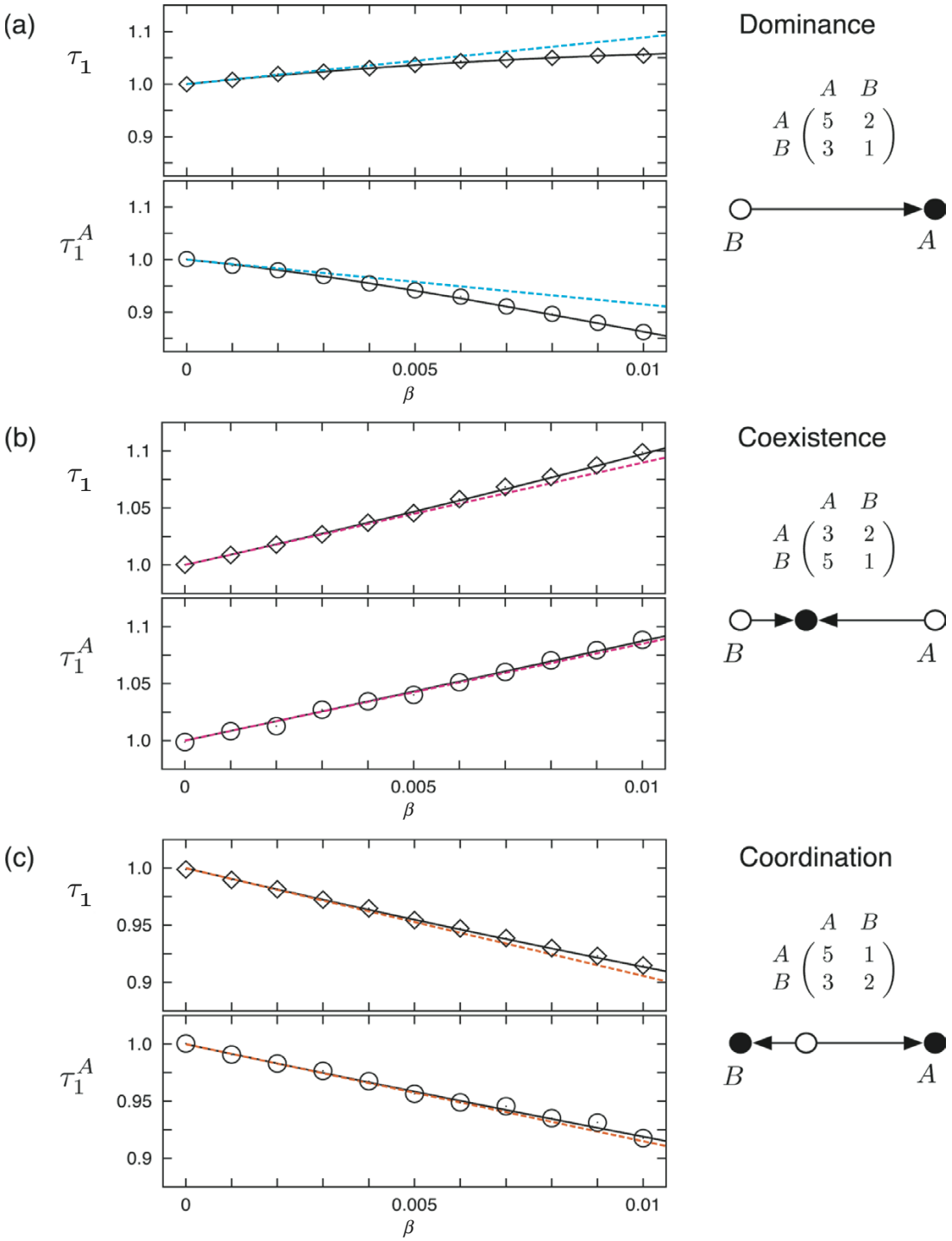

Figure 2. See figure caption on next page.

Figure 2. Expectation values of the rescaled fixation times starting with a single A mutant in a population of B as a function of the selection intensity β. Full lines show the normalized exact solution originating from the exact results (21) and (23). Colored dashed lines are the linear approximations (30) and (31). Symbols show the results from simulations based on 10^7 realizations, which agree nicely with the exact results. Diamonds are for the unconditional averages, circles are for the conditional averages. On the right-hand side, we show the payoff matrices of the three games and illustrate the direction of selection in these games. (a) In a game with dominance of strategy A, the unconditional fixation time increases with the intensity of selection, but the conditional fixation time decreases. (b) For games with stable coexistence, both fixation times increase with the intensity of selection. (c) For coordination games, the two fixation times become shorter when the intensity of selection is increased. In all examples, the population size is $N = 100$.

or the Snowdrift game [45]. For infinite populations, the replicator dynamics predicts a stable coexistence of A and B. In finite populations, the system typically fluctuates around that point until eventually, fluctuations lead to absorption in one of the boundaries [46, 47]. Consequently, the conditional fixation times increase exponentially with the population size [26]. Since $a - b - c + d$ is negative, we also have an increase of τ_1^A with the selection intensity for weak selection. Further, $N(b - d) - a + d$ is positive in large populations, such that also τ_1 increases with the selection intensity. Figure 2(b) shows that the divergence of the exact results is faster than the linear approximation even for weak selection.

7.3. Coordination games

Finally, let us discuss coordination games in which $a > c$ and $b < d$. In these games, A is the best reply to A and B is the best reply to B. The replicator equation of such systems exhibits a bistability: if the fraction of A individuals is sufficiently high in the beginning, the A individuals will reach fixation. Otherwise, B individuals will take over the system. The stronger the intensity of selection, the less likely it is that a single A individual can take over a B population. Consequently, τ_1 should decrease with β. This also follows from our weak selection approximation: in large populations, $N(b - d) - a + d$ is negative and thus τ_1 decreases with the intensity of selection, see equation (30). Perhaps less intuitive, also τ_1^A decreases with β, which results from $a - b - c + d > 0$, cf (30). However, this is again consistent with the observation that τ_1^A scales as $N \ln N$ in large populations. Although the fixation probability of a single A decreases with β, if such an event occurs, it is faster than in the neutral case. A numerical example for this behavior is shown in Figure 2(c).

The numerical examples indicate that the convergence radius of our weak selection expansion is of the order of N^{-1}, which is also known for many systems in population genetics. Although N^{-1} might appear small, this kind of weak selection is the most relevant limit in evolutionary biology, as evolutionary change is typically only connected with small selective differences. We stress that we have made no assumptions on the population size, such that our results are valid for arbitrary N.

Our approach shows under which circumstances the general features of the game are reflected in the fixation times under weak selection. Although the weak selection expansion of the mean exit or fixation times is technically rather tedious, the resulting asymptotic behavior shows remarkable simplicity.

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Appendix A. Finite double sums

Here, we collect some helpful calculations for double sums as they appear in the mean exit times. An important observation is

$$\sum_{k=i}^{N-1}\sum_{l=1}^{k}\frac{f_l}{N-l} = (N-i)\sum_{l=1}^{i-1}\frac{f_l}{N-l} + \sum_{l=i}^{N-1} f_l \tag{A.1}$$

for any function $f_l < \infty$ and $l = 1, \ldots, N-1$. This can be seen by writing the left-hand side term by term, i.e.

$$\begin{aligned}\sum_{k=i}^{N-1}\sum_{l=1}^{k}\frac{f_l}{N-l} &= \frac{f_1}{N-1} + \ldots + \frac{f_i}{N-i} \\ &\quad + \frac{f_1}{N-1} + \ldots + \frac{f_i}{N-i} + \frac{f_{i+1}}{N-(i+1)} \\ &\quad + \ldots \\ &\quad + \frac{f_1}{N-1} + \ldots + \frac{f_i}{N-i} + \ldots + \frac{f_{N-1}}{N-(N-1)} \\ &= (N-i)\sum_{l=1}^{i}\frac{f_l}{N-l} + (N-i-1)\frac{f_{i+1}}{N-(i+1)} + \ldots + f_{N-1} \\ &= (N-i)\sum_{l=1}^{i-1}\frac{f_l}{N-l} + \sum_{l=i}^{N-1} f_l.\end{aligned} \tag{A.2}$$

For the case $i = 1$, the result is especially simple, since the first sum of the right-hand side of equation (A.1) vanishes. This case is of special interest for the computation of t_1^A under neutral selection with $f_l = 1$ and for t_1 with $f_l = 1/l$.

Another finding for double sums with $M \in \mathbb{N}$ and two bounded functions f_k and g_l is

$$\sum_{k=1}^{M}\sum_{l=1}^{k} f_k\, g_l = \sum_{l=1}^{M} g_l \sum_{k=l}^{M} f_k. \tag{A.3}$$

This becomes clear by resorting the terms again,

$$\begin{aligned}\sum_{k=1}^{M}\sum_{l=1}^{k} f_k\, g_l &= f_1 g_1 + f_2(g_1+g_2)+\cdots+f_M(g_1+g_2+\ldots+g_M)\\ &= g_1(f_1+\cdots+f_M)+g_2(f_2+\cdots+f_M)+\cdots+g_M f_M\\ &= \sum_{l=1}^{M} g_l \sum_{k=l}^{M} f_k. \end{aligned} \tag{A.4}$$

Appendix B. Fixation times under weak selection

Here, we calculate the linear corrections of the mean exit times t_1 and t_1^A for the Fermi process in detail, compare equations (21) and (23). We aim at finding these times for weak selection, e.g.

$$t_1 \approx [t_1]_{\beta=0} + \beta \left[\frac{\partial}{\partial\beta} t_1\right]_{\beta=0}. \tag{B.1}$$

The first term follows directly from the calculation in appendix A, see equation (18). Our goal here is to compute the linear term $\left[\frac{\partial}{\partial\beta} t_1\right]_{\beta=0}$.

$$\left[\frac{\partial}{\partial\beta} t_1\right]_{\beta=0} = \sum_{k=1}^{N-1}\sum_{l=1}^{k}\left[\frac{1}{T_l^+}\frac{\partial\phi_1}{\partial\beta}+\phi_1\frac{\partial}{\partial\beta}\frac{1}{T_l^+}\right]_{\beta=0} - \sum_{k=1}^{N-1}\sum_{l=1}^{k}\left[\frac{\phi_1}{T_l^+}\sum_{m=l+1}^{k}\Delta\pi(m)\right]_{\beta=0}, \tag{B.2}$$

where we applied $[\prod_{m=l+1}^{k}\gamma_m]_{\beta=0}=1$ and $[\frac{\partial}{\partial\beta}\prod_{m=l+1}^{k}\gamma_m]_{\beta=0} = -\sum_{m=l+1}^{k}\Delta\pi(m)$. For the fixation probability under weak selection and with $\Delta\pi(l) = u\,l+v$, we have

$$\left[\frac{\partial\phi_l}{\partial\beta}\right]_{\beta=0} = \frac{l}{N}(N-l)\frac{(N+l)u+3v}{6}. \tag{B.3}$$

The weak selection approximation of the inverse of the transition probability T_l^+, compare equation (8), yields

$$\left[\frac{\partial}{\partial\beta}\frac{1}{T_l^+}\right]_{\beta=0} = -\frac{N^2}{l(N-l)}(u\,l+v). \tag{B.4}$$

This leads to

$$\begin{aligned}\left[\frac{\partial}{\partial\beta} t_1\right]_{\beta=0} &= \sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{(N-1)((N+1)u+3v)}{6N}\frac{2N^2}{l(N-l)}\\ &\quad -\sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{1}{N}\frac{N^2}{l(N-l)}(u\,l+v)\\ &\quad -\sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{1}{N}\frac{2N^2}{l(N-l)}\sum_{m=1+l}^{k}(u\,m+v). \end{aligned} \tag{B.5}$$

While the first two double sums can be solved with the help of appendix A, the third term is more complicated. For this more tedious calculation, we refer to appendix C. Eventually, the

solution of the double and triple sums leads to

$$\begin{aligned}\left[\frac{\partial}{\partial\beta}\,t_1\right]_{\beta=0} &= N(N-1)\frac{(N+1)u+3v}{3}H_{N-1} - N(N-1)u - NH_{N-1}v \\ &\quad -N(N-1)\left(\frac{((N+1)u+3v)}{3}H_{N-1} - u - v\right) \\ &= v\,N(N-1-H_{N-1}),\end{aligned} \tag{B.6}$$

where the last step is elementary. Combining this with equation (18) leads finally to the unconditional mean exit time under weak selection, equation (22).

For the conditional fixation time t_1^A, the linear term $\left[\frac{\partial}{\partial\beta}\,t_1^A\right]_{\beta=0}$ reads

$$\left[\frac{\partial}{\partial\beta}\,t_1^A\right]_{\beta=0} = \sum_{k=1}^{N-1}\sum_{l=1}^{k}\left[\frac{1}{T_l^+}\frac{\partial\phi_l}{\partial\beta} + \phi_l\frac{\partial}{\partial\beta}\frac{1}{T_l^+}\right]_{\beta=0} - \sum_{k=1}^{N-1}\sum_{l=1}^{k}\left[\frac{\phi_l}{T_l^+}\sum_{m=l+1}^{k}\Delta\pi(m)\right]_{\beta=0}. \tag{B.7}$$

The only difference compared with the unconditional fixation time, equation (B.2), is the fixation probability ϕ_l instead of ϕ_1. The linear term of the weak selection expansion of ϕ_l is given in equation (B.3). This yields

$$\begin{aligned}\left[\frac{\partial}{\partial\beta}\,t_1^A\right]_{\beta=0} &= \sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{l(N-l)((N+l)u+3v)}{6N}\frac{2N^2}{l(N-l)} - \sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{l}{N}\frac{N^2}{l(N-l)}(u\,l+v) \\ &\quad -\sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{l}{N}\frac{2N^2}{l(N-l)}\sum_{m=l+1}^{k}(u\,m+v).\end{aligned} \tag{B.8}$$

Again, the first two double sums can be solved using the results from appendix A. The third term follows from a calculation which is similar to appendix C, but simpler. This last term reduces to

$$\sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{l}{N}\frac{2N^2}{l(N-l)}\sum_{m=l+1}^{k}(u\,m+v) = N\frac{(N-2)(N-1)}{18}\left((5N+3)u+9v\right). \tag{B.9}$$

Finally, combining the three terms again results in

$$\begin{aligned}\left[\frac{\partial}{\partial\beta}\,t_1^A\right]_{\beta=0} &= \frac{N^2(N-1)}{18}\left((4N+1)u+9v\right) - \frac{N(N-1)}{2}(Nu+2v) \\ &\quad -(N-2)\frac{N(N-1)}{18}\left((5N+3)u+9v\right) \\ &= -u\,N(N-1)\frac{N^2+N-6}{18}.\end{aligned} \tag{B.10}$$

In combination with equation (19), this results in the conditional mean exit time under weak selection, equation (24).

For completeness, we briefly repeat this calculation for the mean exit times of the frequency-dependent Moran process. With the transition probabilities (25) and (26), the fixation probabilities under weak selection are identical to those of the Fermi process, see equation (20). However, the inverse transition probability is different in the weak selection regime, i.e. the linear correction is

$$\left[\frac{\partial}{\partial\beta}\frac{1}{T_l^+}\right]_{\beta=0} = -\frac{N}{l}\Delta\pi(l) = -N\frac{u\,l+v}{l}. \tag{B.11}$$

Hence, for the unconditional mean exit time we have the same starting equation (B.2). But with equation (B.11) this gives

$$\left[\frac{\partial}{\partial\beta}t_1\right]_{\beta=0} = \sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{(N-1)((N+1)u+3v)}{6N}\frac{N^2}{l(N-l)} - \sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{1}{N}N\frac{u\,l+v}{l} - \sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{1}{N}\frac{N^2}{l(N-l)}\sum_{m=1+l}^{k}(u\,m+v), \tag{B.12}$$

which differs from equation (B.5) only in the second double sum. With the previous findings for the Fermi process times, the required calculation is straightforward and results in

$$\left[\frac{\partial}{\partial\beta}t_1\right]_{\beta=0} = v\,\frac{N}{2}\,(N+1-2H_N)\,. \tag{B.13}$$

That is, this linear correction has a different dependence on the system size N.

For the conditional mean exit time the situation is similar. In difference to equation (B.8), the linear correction reads

$$\left[\frac{\partial}{\partial\beta}t_1^A\right]_{\beta=0} = \sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{l(N-l)((N+l)u+3v)}{6N}\frac{N^2}{l(N-l)} - \sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{l}{N}N\frac{u\,l+v}{l} - \sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{l}{N}\frac{2N^2}{l(N-l)}\sum_{m=l+1}^{k}(u\,m+v). \tag{B.14}$$

This leads to

$$\left[\frac{\partial}{\partial\beta}t_1^A\right]_{\beta=0} = -u\,\frac{N^2}{36}\left(N^2-3N+2\right) \tag{B.15}$$

for the linear correction of the conditional mean exit times of the frequency-dependent Moran process.

Appendix C. Finite triple sums

Here, we calculate the triple sum from appendix B, that require some additional steps. Our goal is to solve

$$\sigma = \sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{1}{l(N-l)}\sum_{m=1+l}^{k}\Delta\pi(m). \tag{C.1}$$

For the sum over payoff differences, we have

$$\sum_{m=1+l}^{k}\Delta\pi(m) = \sum_{m=1+l}^{k}(u\,m+v) = f_k - f_l, \tag{C.2}$$

where we introduced the function

$$f_m = m(m+1)\frac{u}{2} + mv, \tag{C.3}$$

which is valid for any integer m. Using partial fraction expansion, $\frac{N}{l(N-l)} = \frac{1}{l} + \frac{1}{N-l}$, we obtain

$$\begin{aligned}\sigma &= \sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{f_k}{l(N-l)} - \sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{f_l}{l(N-l)} \\ &= \frac{1}{N}\underbrace{\sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{f_k}{l}}_{K_1} + \frac{1}{N}\underbrace{\sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{f_k}{N-l}}_{K_2} - \frac{1}{N}\underbrace{\sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{f_l}{l}}_{K_3} - \frac{1}{N}\underbrace{\sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{f_l}{N-l}}_{K_4}. \end{aligned} \tag{C.4}$$

We solve each part separately, starting with the last one. For K_4, we obtain with equation (A.1) from appendix A

$$K_4 = \sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{f_l}{N-l} = \sum_{k=1}^{N-1} f_k = \frac{N-1}{6}N((N+1)u+3v). \tag{C.5}$$

The second last term, K_3, is a sum over a linear function and can be treated with any table of elementary sums, e.g. [48],

$$\begin{aligned}K_3 &= \sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{f_l}{l} = \sum_{k=1}^{N-1}\sum_{l=1}^{k}\left((l+1)\frac{u}{2}+v\right) \\ &= \frac{N-1}{12}N((N+4)u+6v). \end{aligned} \tag{C.6}$$

The remaining two terms require more effort. Both terms, K_1 and K_2, have the same structure regarding functions of k and l. Using equation (A.3), we have

$$K_2 = \sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{f_k}{N-l} = \sum_{l=1}^{N-1}\frac{1}{N-l}\sum_{k=l}^{N-1} f_k \tag{C.7}$$

and

$$K_1 = \sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{f_k}{l} = \sum_{l=1}^{N-1}\frac{1}{l}\sum_{k=l}^{N-1} f_k. \tag{C.8}$$

Hence, we first have to compute the sum $\sum_{k=l}^{N-1} f_k$, which reduces to the solution of elementary sums,

$$\begin{aligned}\sum_{k=l}^{N-1} f_k &= \sum_{k=l}^{N-1} k\left((k+1)\frac{u}{2}+v\right) = \frac{u}{2}\sum_{k=l}^{N-1}k^2 + \left(\frac{u}{2}+v\right)\sum_{k=l}^{N-1}k \\ &= \frac{N-l}{6}\left(N^2+Nl+l^2-1\right)u + 3(N+l-1)v\big) \\ &= \frac{N-l}{6}\left(N^2+Nl+l^2-1\right)u + \frac{N-l}{2}(N+l-1)\,v. \end{aligned} \tag{C.9}$$

Thus, solving equations (C.7) and (C.8) simplifies in solving the elementary sums $\sum_{l=1}^{N-1} l^s$ with $s = 0, 1, 2$, compare [48]. With this, we have

$$\begin{aligned}K_2 &= \frac{N-1}{6}\sum_{l=1}^{N-1}((N+1)u+3v) + \frac{Nu+3v}{6}\sum_{l=1}^{N-1} l + \frac{u}{6}\sum_{l=1}^{N-1} l^2 \\ &= \frac{N-1}{36}\left((11N^2-N-6)u+9(3N-2)v\right). \end{aligned} \tag{C.10}$$

For K_1, we obtain

$$K_1 = \frac{1}{6}\sum_{l=1}^{N-1}\frac{N(N-1)(N+1)u+3N(N-1)v}{l} - \frac{1}{6}\sum_{l=1}^{N-1}\left((l^2-1)u-3(l-1)v\right)$$
$$= \frac{N(N-1)}{6}\left((N+1)u+3v\right)\ H_{N-1} - \frac{N-1}{36}(N-2)((2N+3)u+9v).$$

Summing up the terms, $\sigma = (K_1+K_2-K_3-K_4)/N$, finally yields the result

$$\sigma = \frac{N-1}{6}\left(((N+1)u+3v)H_{N-1}-3(u+v)\right). \tag{C.11}$$

Again, $H_n = \sum_{l=1}^{n} 1/l$ are the harmonic numbers. In equation (B.9), the reasoning is very similar, but only terms of the structure of K_2 and K_4 appear.

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2.2 Universality of weak selection

In Section 2.1 the weak selection (or high temperature) expansion of the fixation times is examined for two of the most common microscopic one-step processes used in evolutionary game theory: the Fermi process and the frequency dependent Moran process. Both describe the change of the composition of a population of size N consisting of two types A and B, and eventually lead to an absorbing state (all A or all B). The difference of the two processes is the following. The Fermi process is based on pairwise imitation: In a comparison of two randomly chosen individuals the probability that the worse imitates the better is given by a certain probability function. The Moran process maps the performance in a strategic situation to reproductive success, a fitness function has to be defined: An individual of a certain type is chosen to produce an identical copy proportional to fitness. This identical offspring then replaces a randomly chosen individual. In these models, the system size N is always constant over time.

An interesting result of stochastic evolutionary game dynamics is the so called one-third rule. It concerns the probability of absorption in a specific state in coordination games, i.e., games where A has a disadvantage when rare, but an advantage when at high densities. The replicator dynamics (1.2.17) of such coordination games has two stable fixed points in 0 and 1, and an unstable fixed point in the interior, given by $x^* \in (0,1)$, compare to Figure 1.2. The value of the fixation probability of a single type A individual in a population of $N-1$ individuals of type B, ϕ_1, can be related to the position of this internal unstable equilibrium. For neutral evolution, we simply have $\phi_1 = 1/N$. If selection acts, the fixation probability of A is larger than neutral, $\phi_1 > 1/N$, if the unstable fixed point is at any value below one third, $x^* < 1/3$ [Imhof and Nowak, 2006; Nowak et al., 2004; Ohtsuki et al., 2007a; Traulsen et al., 2005, 2006a,b]. In a more general consideration Lessard and Ladret [2007] have shown that the one-third rule holds as long as the difference in reproductive success between the two types is not too large, even for more general Markov processes. Then we can say that if the basin of attraction of the all B state is less then half of the size of the basin of the all A state, weak selection favors A.

This gives rise to the question of how universal weak selection results are when comparing different evolutionary Markov processes of the one-step class. In this section we tackle this question by systematically analyzing the fixation probability ϕ_1^A and the conditional mean exit time t_1^A for general versions of the pairwise comparison and the Moran process. In general, the evolutionary change is based on the payoffs π_A and π_B and their difference $\Delta\pi$, and selection is implemented by the parameter β. Universality in this context is to be understood in the widest sense: Starting from different microscopic

evolutionary dynamics, we find universal laws from a perturbation expansion in β, such as the one-third rule. The order up to which such statements of universality can be made is discussed. In addition, we can find simple examples that violate the conditions for the one-third rule.

Our calculations can be simplified by using an identity concerning a symmetry for the conditional moments Antal and Scheuring [2006]; Maruyama and Kimura [1974]; Taylor et al. [2006]: The conditional mean exit times for a single A individual in a population of B is the same as the one for a single B individual in a population of A. This finding does not depend on the underlying strategic pattern and holds for any intensity of selection. However, it only holds for the class of processes where the composition of the population can change at most by one. Especially, the frequency dependent Moran process is considered in this framework.

In the class of general pairwise comparison processes the probability that an individual switches strategy due to imitation is a function of $\Delta\pi$. We call $g(\Delta\pi)$ the imitation probability function. This function has to be nondecreasing, $g'(\Delta\pi) \geq 0$, and nonzero for vanishing payoff difference, $g(0) > 0$. The transition probabilities in state i read

$$T_{i\to i\pm1} = \frac{i}{N}\frac{N-i}{N}\, g(\pm\beta\Delta\pi). \tag{2.2.1}$$

For general Moran processes we have to define a positive function that maps payoff to fitness and involves the intensity of selection, $f(\beta\pi)$. Thus, fitness f is a monotonous function, $f'(\beta\pi) \geq 0$, and we set the baseline fitness to one, $f(0) = 1$. Birth is proportional to fitness, whereas death is random, such that the transition probabilities now read

$$T_{i\to i+1} = \frac{i\, f(\beta\pi_A)}{i\, f(\beta\pi_A) + (N-i) f(\beta\pi_B)}\frac{N-i}{N}, \tag{2.2.2}$$

$$T_{i\to i-1} = \frac{(N-i) f(\beta\pi_B)}{i\, f(\beta\pi_A) + (N-i) f(\beta\pi_B)}\frac{i}{N}. \tag{2.2.3}$$

For both classes of processes the fixation probability and the conditional mean exit time are discussed for $\beta \ll 1/N$. The fixation probabilities are always identical up to first order in β, up to a rescaling. For processes in the pairwise comparison class the fixation probabilities always are identical up to β^2, but for Moran processes with general fitness mapping a similar statement cannot be made. The mean exit times are universal always only up to first order in β. In the cases of universality, the perturbation parameter β can be rescaled by either the logarithmic relative change of the imitation function, $\partial_x[\ln g(x)]_0$, or the absolute slope of the fitness function at the origin, $\partial_x[f(x)]_0$.

The remarkable similarity between different microscopic evolutionary update rules up

to first order in selection intensity follows from the basic assumptions of the evolutionary game dynamics such as that the strategic interaction always is a two player game (for extensions in this direction compare to [Gokhale and Traulsen, 2010]) and that the average payoffs are linear in the density. Thus, universal weak selection properties generally break down when higher orders are considered. Pairwise comparison processes reveal a higher degree of universality, which is based on the fact that the imitation probability functions generally have a higher degree of symmetry than the payoff to fitness mapping of the Moran class.

Universality of weak selection

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Weak selection, which means a phenotype is slightly advantageous over another, is an important limiting case in evolutionary biology. Recently, it has been introduced into evolutionary game theory. In evolutionary game dynamics, the probability to be imitated or to reproduce depends on the performance in a game. The influence of the game on the stochastic dynamics in finite populations is governed by the intensity of selection. In many models of both unstructured and structured populations, a key assumption allowing analytical calculations is weak selection, which means that all individuals perform approximately equally well. In the weak selection limit many different microscopic evolutionary models have the same or similar properties. How universal is weak selection for those microscopic evolutionary processes? We answer this question by investigating the fixation probability and the average fixation time not only up to linear but also up to higher orders in selection intensity. We find universal higher order expansions, which allow a rescaling of the selection intensity. With this, we can identify specific models which violate (linear) weak selection results, such as the one-third rule of coordination games in finite but large populations.

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I. INTRODUCTION

In evolutionary game theory the outcome of strategic situations determines the evolution of different traits in a population [1]. Typically, individuals are hardwired to a set of strategies. The performance in an evolutionary game determines the rate at which strategies spread by imitation or natural selection. Due to differences in payoff, different strategies spread with different rates under natural selection. In infinitely large well-mixed populations this is described by the deterministic replicator dynamics [2–5]. In this set of nonlinear differential equations the intensity of selection, which determines how payoff affects fitness, only changes the time scales but not the direction of selection or the stability properties. In finite populations fluctuations cannot be neglected [6–9]. The dynamics becomes stochastic: selection drives the system into the same direction as the corresponding deterministic process, but sometimes the system can also move into another direction. The strength of selection determines the interplay between these two forces. The absence of selective differences is called neutral selection: moving into one direction is as probable as moving into any other, independent of the payoffs. If selection acts, the transition probabilities become payoff dependent and thus asymmetric. The asymmetry can be the same in each state (constant selection) or state dependent (frequency dependent selection). In general, under frequency dependent selection the probability that one strategy replaces another can be fairly complicated. However, under the assumption of weak selection, some important insights can be obtained analytically [9–16]. It has to be pointed out that these results do, in general, not carry over to stronger selection.

Weak selection describes situations in which the effects of payoff differences are small, such that the evolutionary dynamics are mainly driven by random fluctuations. This approach has a long-standing history in population genetics [17,18]. In evolutionary biology, a phenotype is often found to be slightly advantageous over another phenotype [19,20]. Further, a recent experiment suggests that some aspects of weak selection are reflected in human strategy updating in behavioral games [21]. In the context of evolutionary game dynamics, however, weak selection has only recently been introduced by Nowak *et al.* [9]. The definition of weak selection is unambiguous in the case of constant selection, but there are different ways to introduce such a limit under frequency dependent selection [22].

In the simplest case, frequency dependence can be introduced by an evolutionary game between two types A and B. In a one shot interaction (where strategies are played simultaneously) a type A interacting with another type A receives payoff a, two interacting B types get d each. Type A interacting with B gets b, whereas B obtains c. This symmetric 2×2 game can be described by the payoff matrix

$$\begin{array}{cc} A & B \\ A\begin{pmatrix} a & b \\ c & d \end{pmatrix} \end{array}. \tag{1}$$

Let i denote the number of A individuals in a population of constant size N. Under the assumption of a well-mixed population, excluding self-interactions, the average payoffs for individuals of either type are given by

$$\pi_A = a\frac{i-1}{N-1} + b\frac{N-i}{N-1}, \tag{2}$$

$$\pi_B = c\frac{i}{N-1} + d\frac{N-i-1}{N-1}. \tag{3}$$

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These expectation values are the basis for the evolutionary game. In the continuous limit $N\to\infty$, the state of the system is characterized by the fraction of A individuals $x=i/N$. The dynamics are typically given by the replicator dynamics $\dot{x}=x(1-x)(\pi_A-\pi_B)$, which has the trivial equilibria $\hat{x}=0$ and $\hat{x}=1$. Additionally, there can be a third equilibrium between 0 and 1, given by $x^*=(d-b)/(a-b-c+d)$. In finite populations, the probabilistic description does not allow the existence of equilibrium points anymore. Moreover, the invariance of the replicator dynamics under rescaling of the payoff matrix [5] is lost in finite population models. Typically, the average payoffs are mapped to the transition probabilities to move from state i to other states; only $i=0$ and $i=N$ are absorbing states. When only two types compete and there is only one reproductive event at a time this defines a birth-death process. The transition probabilities from i to $i+1$ and from i to $i-1$ are then denoted by T_i^+ and T_i^-, respectively. They determine the probability of the process to be absorbed at a certain boundary, usually called fixation probability, as well as the average time such an event takes, termed average fixation time.

An important result of evolutionary game dynamics in finite populations under weak frequency dependent selection is the one-third rule. It relates the fixation probability of a single type A individual, ϕ_1, to the position of the internal equilibrium x^* in a coordination game, i.e., when $a>c$ and $d>b$. If selection is neutral, we have $\phi_1=1/N$. If the internal equilibrium is less than 1/3, $x^*<1/3$, then $\phi_1>1/N$. Originally, this weak selection result has been found for large populations in the frequency dependent Moran process [9]. Subsequently, the one-third rule has been derived from several related birth-death processes [23–25] and also for the frequency dependent Wright-Fisher process [26,27], which is still a Markov process, but no longer a birth-death process. In a seminal paper, Lessard and Ladret showed that the one-third rule is valid for any process in the domain of Kingman's coalescence [28], which captures a huge number of the stochastic processes typically considered in population genetics. Essentially, this class of processes describes situations in which the reproductive success is not too different between different types. Thus, the generality of the one-third rule under linear weak selection is well established. Here, we ask a slightly different question: To which order can two birth-death processes be considered as identical under weak selection? Some authors have considered higher weak selection orders for specific processes [29–31]. We investigate two classes of birth-death processes, a general pairwise imitation process motivated by social learning and a general Moran process based on reproductive fitness. In this light, we also discuss cases which violate the one-third rule.

The paper is organized in the following way. In Sec. II we compute the weak selection expansion of the fixation probability in a general case of our two classes of birth-death processes. In Sec. III, we perform the same calculations for the significantly more complicated fixation times. In Sec. IV we discuss our analytical results and conclude. Some detailed calculations can be found in Appendixes A and B.

II. PROBABILITIES OF FIXATION

A birth-death process is characterized by the transition probabilities from each state i to its neighboring states, T_i^+ and T_i^-. We assume that this Markov chain is irreducible on the interior states and we exclude mutations or spontaneous switching from one type to another. Thus, the process gets eventually absorbed at $i=0$ or N. For any internal state, the probability to hit $i=N$ starting from $0<i<N$, ϕ_i, fulfills the recursion equation $\phi_i=(1-T_i^+-T_i^-)\phi_i+T_i^-\phi_{i-1}+T_i^+\phi_{i+1}$ [32–34]. This recursion can be solved explicitly, respecting the boundary conditions $\phi_0=0$ and $\phi_N=1$. For a single A individual in populations of B, the probability to take over the population is [32–34]

$$\phi_1=\frac{1}{1+\sum_{k=1}^{N-1}\prod_{i=1}^{k}\frac{T_i^-}{T_i^+}}. \tag{4}$$

In any model of neutral selection, the transition probabilities of the Markov chain fulfill $T_i^-/T_i^+=1$, and hence the respective fixation probability of a single mutant amounts to $1/N$.

In this section we focus on the weak selection approximation of Eq. (4). We do this for two different approaches to evolutionary game theory: imitation dynamics and selection dynamics. In the former case, strategy spreading is based on pairwise comparison and imitation, in the latter it results from selection proportional to fitness and random removal. The most prominent examples are the Fermi process and the Moran process, respectively.

A. Pairwise comparison

In a pairwise comparison process, two individuals are chosen randomly to compare their payoffs from the evolutionary game [Eqs. (2) and (3)]. One switches to the other strategy with a given probability (see Fig. 1). If selection is neutral, this probability is constant. If selection acts, the larger the payoff difference, the higher the probability that the worse imitates the better. But typically there is also a small chance that the better imitates the worse. Otherwise, only the strategy of the more successful individual is adopted. This would lead to a dynamics that is stochastic in the time spent in each interior state but deterministic in direction [24]. Thus, given that all interior states are transient, the fixation probabilities are either 0 or 1, and there is no basis to discuss a weak selection limit.

Selection is parametrized by the intensity of selection $\beta\geq 0$. As a first example we consider the Fermi process [24,35,36]. Let the two randomly selected individuals X and Y have payoffs π_X and π_Y. Then X adopts Y's strategy with probability $g_{\mathrm{Fermi}}(\pi_Y-\pi_X)=1/(1+e^{-\beta(\pi_Y-\pi_X)})$. Thus, the transition probabilities of an evolutionary game with payoffs [Eqs. (2) and (3)] are given by

$$T_i^{\pm}=\frac{i}{N}\frac{N-i}{N}\frac{1}{1+\exp^{\mp\beta(\pi_A-\pi_B)}}. \tag{5}$$

The probability to stay in state i is $1-T_i^--T_i^+$. The Fermi process is closely related to the Glauber dynamics [37]. If we define individuals' energy as the exponential function of payoff, then the Fermi process can be mapped onto the Ising

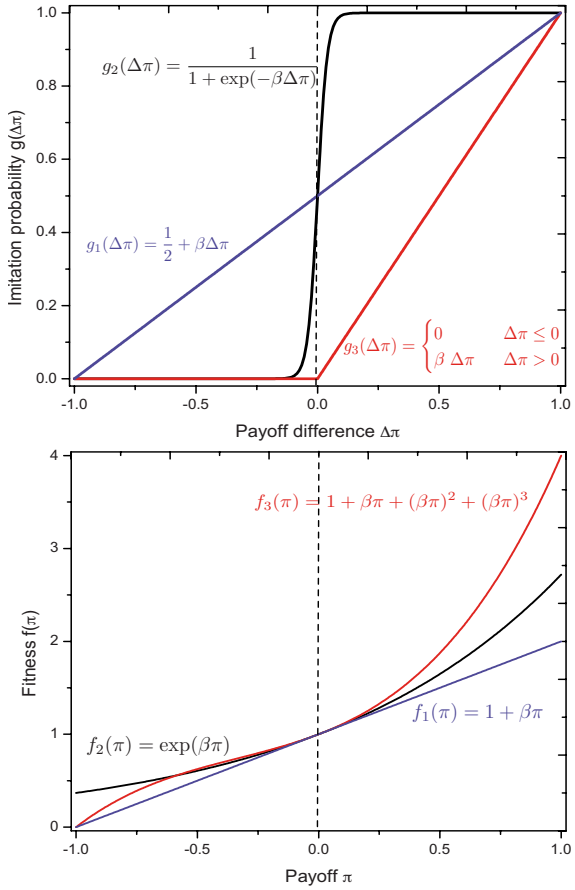

FIG. 1. (Color online) Upper panel: pairwise comparison processes are characterized by the probability $g(\Delta\pi)$ to imitate the strategy of someone else based on the payoff difference $\Delta\pi$. With increasing payoff difference, the imitation probability becomes higher, $g'(\Delta\pi) \geq 0$. Weak selection implies a Taylor expansion at $\Delta\pi=0$. Thus, it can only be invoked for functions that are differentiable in 0. The figure shows three examples of imitation probability functions, $g_1(\Delta\pi)$ is a linear function (selection intensity $\beta=0.5$), and $g_2(\Delta\pi)$ is the Fermi function ($\beta=50$). For the imitation function $g_3(\Delta\pi)$, a meaningful weak selection limit does not exist since $g_3(\Delta\pi)$ is not differentiable in 0. Because $g_3(\Delta\pi)=0$ for $\Delta\pi<0$, the associated stochastic process would be stochastic in time but deterministic in direction. All through the paper, we focus on imitation functions that are differentiable in 0. Lower panel: Moran processes are characterized by a payoff to fitness mapping $f(\pi)$. Fitness is a nondecreasing function of the payoff, $f'(\pi) \geq 0$. The figure shows three examples for payoff to fitness mappings (selection intensity $\beta=1$ for all three functions).

model. The Fermi process has the comfortable property that the ratio of transition probabilities simplifies to $T_i^-/T_i^+ = e^{-\beta(\pi_A-\pi_B)}$, such that the products in Eq. (4) can be replaced by sums in the exponent. Defining $u=(a-b-c+d)/(N-1)$ and $v=(Nb-Nd-a+d)/(N-1)$, such that $\pi_A-\pi_B=ui+v$, leads to

$$\phi_1(\beta) = \frac{1}{1+\sum_{k=1}^{N-1} \exp\left\{-\beta\left[k^2\frac{u}{2} + k\left(\frac{u}{2}+v\right)\right]\right\}}. \quad (6)$$

For large N, the sum can be replaced by an integral, leading to a closed expression [24]. For weak selection, $N\beta \ll 1$, Eq. (6) can be approximated by

$$\phi_1 \approx \frac{1}{N} + \frac{(N-1)[(N+1)u+3v]}{6N}\beta. \quad (7)$$

This can also be obtained directly from $T_i^-/T_i^+ \approx 1-\beta(\pi_A-\pi_B)$. The fixation probability under weak selection is greater than in the neutral case if the term linear in β is positive, $Nu+u+3v>0$. In particular, for a coordination game in a large population, this implies $x^*<1/3$. Thus, natural selection favors the mutant strategy if the invasion barrier is less than one-third, which is the well-known one-third rule [9,24,25,28,30]. It holds when the fixation probability in a large but finite population can be approximated up to linear order in selection intensity.

Can we make general statements based on an expansion of ϕ_1 concerning the probability of switching strategies, $g(\Delta\pi)$? In a general framework, the probability that X switches to the strategy of Y, given the difference in their payoffs, $\Delta\pi=\pi_X-\pi_Y$, is governed by the intensity of selection. We call $g(\Delta\pi)$ the imitation probability function of a general pairwise comparison process. In a well-mixed population, the transition probabilities read

$$T_i^{\pm} = \frac{i}{N}\frac{N-i}{N} g(\pm\beta\Delta\pi). \quad (8)$$

The larger the payoff difference, the more likely the worse individual switches to the strategy of the better. Therefore, the imitation function is nondecreasing, $g'(\Delta\pi) \geq 0$. Additionally, if the payoffs of the two chosen individuals are equal, the neutral probability of switching is nonzero, $g(0)>0$ (otherwise, the process does not allow a meaningful definition of weak selection because it would always deterministically follow the direction of selection). The fixation probability for this general pairwise comparison process can be expanded to the second order (see Appendix A 1),

$$\phi_1 \approx \frac{1}{N} + C_1\beta + C_2\beta^2, \quad (9)$$

where

$$C_1 = \frac{(N-1)[(N+1)u+3v]}{6N}\frac{2g'(0)}{g(0)} \quad (10)$$

and

$$C_2 = [u^2(N+1)(N+2) + 15uv(N+1) + 30v^2] \times \frac{(N-1)(N-2)}{360}\left(\frac{2g'(0)}{g(0)}\right)^2. \quad (11)$$

C_1 is proportional to the increase of the imitation function at $\Delta\pi=0$ (see Fig. 2). Note that for large N, $C_1>0$ is equivalent to $Nu+3v>0$, which for large N further simplifies to

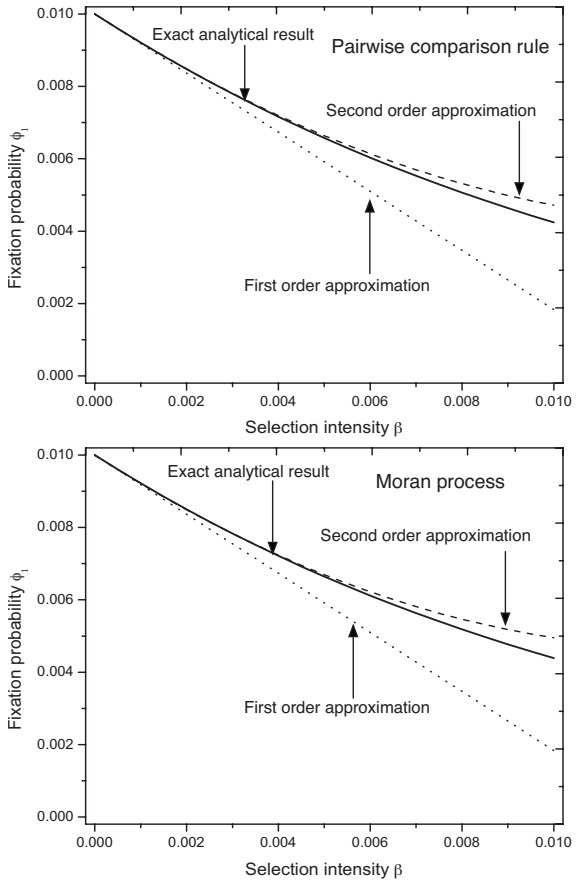

FIG. 2. Approximation of the fixation probability of a single mutant under weak selection. Upper panel: pairwise comparison process with the Fermi function $1/(1+\exp[-\beta\Delta\pi])$ as an imitation function. As shown in the main text, up to the second order the approximation is valid for any imitation function $g(\beta\Delta\pi)$ after appropriate rescaling of the selection intensity β. Lower panel: Moran process with fitness as a linear function of the payoff, $f=1+\beta\pi$. Any other function leads to the same first-order approximation after rescaling of β. However, the second order depends on choice of the function transforming payoff to fitness. Exact analytical results are numerical evaluations of Eq. (4). (Parameters $N=100$, $\beta=1$, $a=4$, $b=1$, $c=1$, and $d=5$ in both panels).

$x^*<1/3$. Thus, the one-third rule holds for all pairwise comparison processes that fulfill $g'(0)\neq 0$, and $g(0)>0$. Moreover, C_1 is proportional to $2g'(0)/g(0)$, while C_2 is proportional to the square of this quantity. Thus, $2g'(0)/g(0)$ can be absorbed into the selection intensity by proper rescaling. Therefore, the more rapid the increases of the imitation function at $\Delta\pi=0$, the stronger is the sensitivity of the fixation probability to changes in average payoff. For low switching probabilities in the neutral case, $\Delta\pi=0$, we have a fixation probability that changes rapidly when the payoff difference becomes important, $\Delta\pi\neq 0$. While most previous models have either considered $g(0)=0$ (which lies out of the scope of our approach because it does not lead to a reasonable definition of weak selection) or $g(0)=0.5$ (which is the default case), some authors have also explored imitation functions with other values of $g(0)$. For example, Szabó and Hauert used the imitation function $g(x)=1/(1+e^{-x+\alpha})$, where α is a constant [38]. In this case $2g'(0)/g(0)=2/[1+\exp(-\alpha)]$; thus, an increase in α is equivalent to an increase in the (small) selection intensity.

Now it is straightforward to come up with an imitation function that leads to a violation of the one-third rule, for example, $g(\Delta\pi)=1/(1+\exp\{-\Delta\pi^3\})$. Obviously, $g(\beta\Delta\pi)$ satisfies the conditions $g'(\beta\Delta\pi)\geq 0$, and $g(0)\neq 0$. Further, both the first- and the second-order expansions vanish. Therefore, the fixation probability under weak selection can only be approximated as

$$\phi_1 \approx \frac{1}{N} + C_3\beta^3, \tag{12}$$

where C_3 can be derived in the same way as C_1 and C_2. In special games, the sign of C_3 can also change at $x^*=1/3$, but in general this will not be the case due to the complicated dependence of C_3 on u and v. In more general terms, the one-third rule is not sustained whenever the linear approximation of $g(\beta\Delta\pi)$ vanishes.

B. Moran process

In the frequency dependent Moran process the payoff π, given in Eqs. (2) and (3), is mapped to fitness f, as illustrated in Fig. 1. In each reproductive event, one individual is selected for reproduction (producing an identical offspring) proportional to fitness. To keep the size of the population to the constant value N, a randomly chosen individual is removed from the population subsequently. As in pairwise comparison processes, the state i can at most change by one per time step.

In the simplest case, fitness is a linear function of payoff. With a background fitness of one, the fitnesses of types A and B read $f_A=1+\beta\pi_A$ and $f_B=1+\beta\pi_B$, respectively. The quantity $\beta\geq 0$ serves as the intensity of selection. Note that β is bound such that fitness never becomes negative. The probability that the number of A individuals increases by 1, $i\to i+1$, is given by

$$T_i^+ = \frac{if_A}{if_A+(N-i)f_B}\frac{N-i}{N}. \tag{13}$$

The other possible transition, $i\to i-1$, occurs with probability

$$T_i^- = \frac{(N-i)f_B}{if_A+(N-i)f_B}\frac{i}{N}. \tag{14}$$

When selection is neutral, $\beta=0$, we have $T_i^\pm = i(N-i)/N^2$. Up to linear order in β the Moran process has the same fixation probability as the Fermi process [Eq. (7)], such that in this approximation the one-third rule is fulfilled. This is because under first-order weak selection, T_i^-/T_i^+ is again a linear function of the payoff difference.

In general, let fitness be *any* non-negative function of the product of payoff and selection intensity, $f(\beta\pi)$, which fulfills $f'(\beta\pi)\geq 0$. For simplicity, we assume that the baseline fitness $f(0)$ is 1. The transition probabilities in a population with types A and B read

$$T_i^+ = \frac{if(\beta\pi_A)}{if(\beta\pi_A)+(N-i)f(\beta\pi_B)}\frac{N-i}{N}, \tag{15}$$

$$T_i^- = \frac{(N-i)f(\beta\pi_B)}{if(\beta\pi_A)+(N-i)f(\beta\pi_B)}\frac{i}{N}. \tag{16}$$

Note that $T_i^-/T_i^+ = f(\beta\pi_B)/f(\beta\pi_A)$. Up to second order in β, the fixation probability of a single A mutant in a population of B is (see Appendix A 2)

$$\phi_1 \approx \frac{1}{N} + D_1\beta + D_2\beta^2, \tag{17}$$

where

$$D_1 = (N-1)\frac{(N+1)u+3v}{6N}f'(0) \tag{18}$$

and

$$\begin{aligned} D_2 = {} & [u^2(N+1)(N+2)+15uv(N+1)+30v^2]\frac{(N-1)(N-2)}{360} \\ & \times f'(0)^2 - [(2a^2+4ab+4cd-10d^2)+(11d^2+2cd-c^2 \\ & -3b^2-6ab-3a^2)N+(a^2+2ab+3b^2-c^2-2cd \\ & -3d^2)N^2]\frac{(N-1)}{24N^3}[f'(0)^2-f''(0)], \end{aligned} \tag{19}$$

with u and v as above. Note that the first-order term depends on payoff differences only, but the second-order term also depends on the payoff values directly. An example for such an approximation is shown in Fig. 2. The first-order term D_1 is proportional to the increase in fitness at $\pi=0$, $f'(0)$. The first-order term D_1 is proportional to $Nu+3v$ for large N. Hence, the one-third rule holds for every Moran model for which $f'(0)$ does not vanish under weak selection. Additionally, $f'(0)$ can be absorbed into the selection intensity by rescaling: changing this rate is equivalent to changing the intensity of selection. Note that this is not possible with D_2, where not only the slope but also the curvature of the fitness function at the origin play a role. However, when the exponential fitness function $f=\exp(\beta\pi)$ is employed [39], the second term of Eq. (19) vanishes. This allows us to incorporate $f'(0)$ into the selection intensity even for the second-order term.

Again, we conclude the section with an example where the one-third rule is violated. Consider the fitness function $f(\beta\pi)=1+\beta^3\pi^3$, which obviously satisfies $f(0)=1$, and $f'(\beta\pi)\geq 0$. Both first- and second-order corrections in β vanish, $D_1=D_2=0$. Therefore, the first nontrivial approximation of the fixation probability is

$$\phi_1 \approx \frac{1}{N} + D_3\beta^3. \tag{20}$$

If D_3 changes sign at $x^*=1/3$, we recover the one-third rule. This is only the case for very special games. In analogy to the previous section, the general one-third rule does not hold anymore.

III. TIMES OF FIXATION

In this section we address the conditional fixation time τ_i^A. In a finite population of $N-i$ individuals of type B and i individuals of type A, τ_i^A measures the expected number of imitation or birth-death events until the population consists of type A only under the condition that this event occurs. In general, the probability $P_i^A(t)$ that after exactly t events the process moved from any i to N, which is the all A state, obeys the master equation $P_i^A(t)=(1-T_i^+-T_i^-)P_i^A(t-1)+T_i^-P_{i-1}^A(t-1)+T_i^+P_{i+1}^A(t-1)$. The average fixation time $\tau_i^A=\sum_{t=0}^{\infty}tP_i^A(t)/\phi_i$ is the stationary first moment of this probability distribution, resulting from a recursive solution of $\phi_i\tau_i^A=(1-T_i^+-T_i^-)\phi_i\tau_i^A+T_i^-\phi_{i-1}(\tau_{i-1}^A+1)+T_i^+\phi_{i+1}(\tau_{i+1}^A+1)$. In a similar way one can find $\tau_i^B=\sum_{t=0}^{\infty}tP_i^B(t)/(1-\phi_i)$, such that the average total lifetime of the Markov process amounts to $\phi_i\tau_i^A+(1-\phi_i)\tau_i^B$ [32,40,41]. Following Sec. II B we restrict our analysis to the biologically most relevant case $i=1$, which yields [32,40]

$$\tau_1^A = \sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{\phi_l}{T_l^+}\prod_{m=l+1}^{k}\frac{T_m^-}{T_m^+}. \tag{21}$$

Maruyama and Kimura [42], Antal and Scheuring [41], as well as Taylor *et al.* [43] showed that the conditional fixation time of a single mutant of either type is the same, $\tau_1^A=\tau_{N-1}^B$. This remarkable identity holds for any evolutionary birth-death process and is thus valid for any 2×2 game and for any selection intensity. However, for $j>1$ we have $\tau_j^A \neq \tau_{N-j}^B$ unless β vanishes. Since τ_1^A and τ_{N-1}^B are identical up to any order in β, we obtain

$$\left[\frac{\partial^n}{\partial\beta^n}\tau_1^A\right]_{\beta=0} = \left[\frac{\partial^n}{\partial\beta^n}\tau_{N-1}^B\right]_{\beta=0} \tag{22}$$

for any n. This symmetry can help to obtain several properties of the expansion of the conditional fixation time [Eq. (21)], without brute force calculations.

A. Pairwise comparison

Let us first consider the fixation time in the special case of the Fermi process [Eq. (5)]. When the selection intensity vanishes, $\beta=0$, we have $\tau_1^A(0)=2N(N-1)$ [13,33]. When selection is weak, $N\beta\ll 1$, the conditional fixation time is approximately $\tau_1^A\approx\tau_1^A(0)+\partial_\beta\tau_1^A(\beta)|_{\beta=0}\beta+\partial_\beta^2\tau_1^A(\beta)|_{\beta=0}\beta^2/2$. For the Fermi process, the first-order term is then given by [13]

$$\left[\frac{\partial}{\partial\beta}\tau_1^A\right]_{\beta=0} = -uN(N-1)\frac{N^2+N-6}{18}, \tag{23}$$

where u stems from $\pi_A-\pi_B=ui+v$ (compare Appendix B 1). The first-order expansion of τ_1^A is only proportional to the i

dependent term u in this special case. This can also be seen from a symmetry argument [41,43]: since $\tau_1^A = \tau_{N-1}^B$, the fixation time does not change under $a \leftrightarrow d$ and $b \leftrightarrow c$. Since u, but not v, is invariant under this exchange of strategy names, τ_1^A can depend under linear weak selection only on u, but not on v. The second-order term of the conditional fixation time for the Fermi process yields

$$\left[\frac{d^2}{d\beta^2}\tau_1^A\right]_{\beta=0} = E_1 u^2 + E_2 uv + E_3 v^2, \tag{24}$$

where

$$E_1 = -\frac{(N-2)(N-1)N}{5400}(180 - 122N + 177N^2 + 59N^3),$$

$$E_2 = -\frac{N^2(6 - 7N + N^3)}{18},$$

$$E_3 = \frac{1}{N}E_2. \tag{25}$$

Now, in contrast to the first-order expansion [Eq. (23)], both u and v enter. An interesting relation is $E_3 = E_2/N$. In the following, we show that this is found for any pairwise comparison process and not only in the special case of the Fermi process.

For general pairwise comparison processes under neutral selection, the conditional fixation time is $\tau_1^A(0) = N(N-1)/g(0)$, where $g(0) > 0$. When selection acts [Eq. (8)], the transition probabilities become dependent on the derivative of the imitation function, $g'(0) \geq 0$. We are now interested in the imitation function's influence on the first- and second-order terms in β. In general, the first-order term in β reads

$$\frac{\partial}{\partial\beta}\tau_1^A = \sum_{|\alpha|=1}\sum_{k=1}^{N-1}\sum_{l=1}^{k} h_\alpha, \tag{26}$$

$$h_\alpha = \left(\frac{\partial^{\alpha_1}}{\partial\beta^{\alpha_1}}\frac{1}{T_i^+}\right)\left(\frac{\partial^{\alpha_2}}{\partial\beta^{\alpha_2}}\phi_l\right)\left(\frac{\partial^{\alpha_3}}{\partial\beta^{\alpha_3}}\prod_{m=l+1}^{k}\frac{T_m^-}{T_m^+}\right), \tag{27}$$

with the multi-index $\alpha = (\alpha_1, \alpha_2, \alpha_3)$, $|\alpha| = \alpha_1 + \alpha_2 + \alpha_3$ (see Appendix B 1 for details of the calculation). The general structure of this term is determined by h_α, which is linear in u and v, as $|\alpha|$ equals 1. Thus, $\partial_\beta \tau_1^A|_{\beta=0} = F_1 u + F_2 v$ is also of this form, where F_1 and F_2 only depend on the population size N. With the same symmetry argument as above, based on [41,43], we can conclude that $F_2 = 0$. This yields

$$\tau_1^A = \tau_{N-1}^B \approx \frac{N(N-1)}{g(0)} + F_1 u\beta. \tag{28}$$

We can now calculate the payoff independent term F_1 for any $g(\Delta\pi)$ from the special case $u=1$ and $v=0$, which reads

$$F_1 = -\frac{g'(0)}{g(0)^2}N(N-1)\frac{N^2 + N - 6}{18}. \tag{29}$$

Here, β can be rescaled by $g'(0)/g(0)^2$. Changing $g'(0)$ or $g(0)$ is equivalent to changing the selection intensity appropriately. In particular, when $u > 0$, which is true, e.g., for coordination games such as the stag-hunt game [44], the conditional time it takes on average for a mutant type to take over decreases with the intensity of selection. Moreover, for $a > c$ and $b > d$ in combination with $u < 0$, a mutant which is always advantageous over the wild type needs longer to reach fixation than a neutral mutant. This phenomenon, termed stochastic slowdown in [45], occurs in any imitation process since Eq. (28) only depends on u.

For the second-order term in the expansion in β we can write

$$\frac{\partial^2}{\partial\beta^2}\tau_1^A = \sum_{|\alpha|=2}\sum_{k=1}^{N-1}\sum_{l=1}^{k} h_\alpha, \tag{30}$$

where h_α is of the form $G_1 u^2 + G_2 uv + G_3 v^2$. Thus, $\partial_\beta^2 \tau_1^A|_{\beta=0}$ is also of this form, where the G_i's only depend on N. Again, we consider the transformations $a \leftrightarrow d$ and $b \leftrightarrow c$ which correspond to exchanging the names of the strategies. For the transformed game, we obtain $\partial_\beta^2 \tau_{N-1}^B|_{\beta=0} = G_1 u^2 + G_2 u\tilde{v} + G_3 \tilde{v}^2$ with $\tilde{v} = (Nc - Na - d + a)/(N-1)$. Using Eq. (22), we obtain $G_2 u(v - \tilde{v}) + G_3(v^2 - \tilde{v}^2) = 0$. With $v + \tilde{v} = -Nu$, we then get $G_3 = G_2/N$—the symmetry discussed above for a special case holds for any imitation function. Eventually, the second-order term in β for general imitation probability is given by

$$\frac{\partial^2}{\partial\beta^2}\tau_1^A = G_1 u^2 + G_2 uv + \frac{G_2}{N}v^2. \tag{31}$$

The special cases $u=1, v=0$, as well as $u=0, v=1$, allow us to compute G_1 and G_2 explicitly. Thus, we have (see Appendix B 1)

$$G_1 = -\frac{(N-2)(N-1)N}{5400}(180 - 122N + 177N^2 + 59N^3) \times\left\{\frac{2[g'(0)]^2}{g(0)^3}\right\} - \frac{N^2(N-1)(2N-1)}{6}\left[\frac{g''(0)}{g(0)^2}\right], \tag{32}$$

$$G_2 = -\frac{N^2(6 - 7N + N^3)}{18}\left\{\frac{2[g'(0)]^2}{g(0)^3}\right\} - N^2(N-1)\frac{g''(0)}{g(0)^2}. \tag{33}$$

Obviously, Eq. (31) does not allow a rescaling of the intensity of selection. Instead, the properties of the imitation function enter in a more intricate way. An example of this approximation is shown in Fig. 3.

B. Moran process

To close this section, we consider the Moran process, where selection at birth is proportional to fitness and selection at death is random. For neutral selection $\beta = 0$, it is well known that $\tau_1^A(0) = N(N-1)$ [13,33,41]. When selection is weak $\beta \ll 1$, the conditional mean fixation time is approximately $\tau_1^A \approx \tau_1^A(0) + \partial_\beta \tau_1^A|_{\beta=0}\beta$. For the Moran process with linear fitness function, $f_A = 1 + \beta\pi_A$, we have $\partial_\beta \tau_1^A|_{\beta=0} = -uN^2(N^2 - 3N + 2)/36$ (compare [13,43]). The first-order

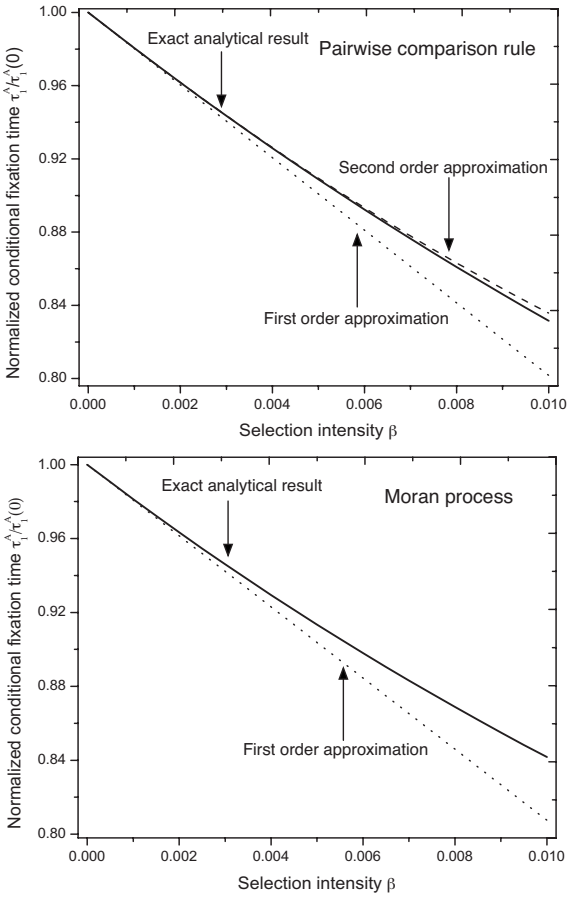

FIG. 3. Weak selection approximation of the conditional fixation time of a single mutant, the exact result is given in Eq. (21). Upper panel: the approximations are shown for the Fermi process, but they would be identical up to the second order for any other pairwise comparison process after appropriate rescaling of the selection intensity. Lower panel: for any Moran process the first-order approximation is independent of the precise function mapping payoff to fitness (here it is linear). Any higher order approximation depends on the details of the function. Note that the first-order approximation in the two panels is not identical due to a difference in the dependence on population size N (same parameters as in Fig. 2).

expansion of τ_1^A again depends only on u, but not on v. This can be shown based on [41,43] or explicitly [13].

With general fitness mapping $f(\beta\pi)$ with transition rates (15) and (16), we have

$$\left[\frac{\partial}{\partial\beta}\tau_1^A(\beta)\right]_{\beta=0} = -f'(0)N^2\frac{N^2-3N+2}{36}u, \qquad (34)$$

which allows a rescaling of the intensity of selection when τ_1^A is approximated up to linear order.

With general fitness function $f(x)$, it becomes unwieldy to calculate higher order terms in β. However, the general calculations are similar to that of the general pairwise comparison rules. Equation (19) reveals that already the second-order expansion of the fixation probability ϕ_1 with general fitness mapping is tedious in form. Thus, the equivalent terms for the fixation time τ_1^A are even more complicated and do not lead to further insight in this case. Since it would be only an academic exercise to calculate them, we do not give them explicitly here. It is clear that the weak selection approximation is not universal over a large class of processes in second order in the fixation times.

IV. DISCUSSION

In the past years, weak selection has become an important approximation in evolutionary game theory [9–15]. Weak selection means that the game has only a small influence on evolutionary dynamics. In evolutionary biology and population genetics, the idea that most mutations confer small selective differences is widely accepted. In social learning models, it refers to a case where imitation is mostly random, but there is a tendency to imitate others that are more successful. Since weak selection is the basis of many recent results in evolutionary dynamics [10,11,46–48], it is of interest how universal these results are. It has been shown that they are remarkably robust and the choice of evolutionary dynamics has only a small impact in unstructured populations [28,49]. In structured populations, however, the choice of evolutionary dynamics can have a crucial impact on the outcome [11,47,50–54]. For example, for a prisoner's dilemma on a graph under weak selection, cooperation may be favored by a death-birth process while it is never favored by a birth-death process. In a well-mixed population, however, the transition probabilities for those two processes are identical; thus, they lead to the same result. However, in general, spatial structure has a less pronounced effect under weak selection than under strong selection [53,54].

We have addressed the question as to what extent two evolutionary processes can be considered as identical by investigating the fixation probability and the fixation time. For any given 2×2 payoff matrix, we have considered two classes of evolutionary processes: pairwise comparison and Moran processes. An interesting special case is the Moran process with exponential fitness mapping, which is equivalent to the Fermi process (a special case of the pairwise comparison rule) in terms of fixation probabilities.

For the fixation probability, the first-order term in the selection intensity always has the same form, given that it does not vanish. In addition, regardless of the choice of imitation functions, two pairwise comparison processes are always identical up to second-order weak selection in the fixation probabilities. For the Moran processes, an equivalent statement does not hold. Recently, a paper has shown that in 3×3 games under weak selection, the Fermi update rule can be quite different from the Moran process and the local update rule (an imitation process with linear imitation function [23]), while the Moran process and the local update rule are

more similar to each other [55]. Our result shows that for weak selection in 2×2 games, these three processes can be mapped to each other by an appropriate rescaling of the intensity of selection.

For the first-order approximation of the average fixation time, there are differences in the dependence on the system size, but all processes depend on the game in the same way. This follows from a symmetry in fixation times [41,43]. For higher orders in the intensity of selection, a simple rescaling of the selection intensity does not exist for the fixation times and a general statement on the relation between two processes cannot be made.

The robustness of weak selection results, i.e., the invariance to changes of the underlying stochastic process, found in the linear approximation is remarkable but follows from basic assumptions on evolutionary dynamics. Moreover, the universality of weak selection breaks down when higher order terms are discussed.

ACKNOWLEDGMENTS

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APPENDIX A: THIRD ORDER EXPANSION OF THE FIXATION PROBABILITIES

Here, we expand the fixation probability ϕ_1 for general birth-death processes up to the third order. Let $\gamma_i=T_i^-/T_i^+$ and

$$\left[\frac{\partial^s}{\partial\beta^s}\gamma_i\right]_{\beta=0}=p_{si}. \tag{A1}$$

Note that the first index of p_{si} refers to the order of the derivative and the second index gives the position in state space. We expand Eq. (4) to the third order under weak selection $\gamma_i\approx 1+p_{1i}\beta+p_{2i}\beta^2/2+p_{3i}\beta^3/6$. Hence, we have

$$\prod_{i=1}^{k}\gamma_i\approx 1+\underbrace{\sum_{j=1}^{k}p_{1j}}_{L_{1k}}\beta+\underbrace{\left[\sum_{j=1}^{k}(p_{2j}-p_{1j}^2)+\Big(\sum_{j=1}^{k}p_{1j}\Big)^2\right]}_{L_{2k}}\frac{\beta^2}{2}$$
$$+\underbrace{\left[\sum_{j=1}^{k}p_{3j}+3\left(\sum_{j=1}^{k}p_{1j}\right)\left(\sum_{s=1}^{k}p_{2s}\right)-3\sum_{j=1}^{k}p_{1j}p_{2j}\right]}_{L_{3k}}\frac{\beta^3}{6}. \tag{A2}$$

Then, the fixation probability can be written as

$$\phi_1\approx\left(N+\beta\underbrace{\sum_{k=1}^{N-1}L_{1k}}_{Q_1}+\frac{\beta^2}{2}\underbrace{\sum_{k=1}^{N-1}L_{2k}}_{Q_2}+\frac{\beta^3}{6}\underbrace{\sum_{k=1}^{N-1}L_{3k}}_{Q_3}\right)^{-1} \tag{A3}$$
$$\approx\frac{1}{N}-\frac{Q_1}{N^2}\beta+\left[\frac{Q_1^2}{N^3}-\frac{Q_2}{2N^2}\right]\beta^2-\left[\frac{Q_1^3}{N^4}-\frac{Q_1Q_2}{N^3}+\frac{Q_3}{6N^2}\right]\beta^3. \tag{A4}$$

This now serves as a starting point for our particular processes with certain choices of $\gamma_i=T_i^-/T_i^+$ and particular p_{si} resulting from this.

1. General pairwise comparison process

For general switching probabilities in a pairwise comparison process, we have

$$p_{1i}=-\frac{2g'(0)}{g(0)}\Delta\pi_i, \tag{A5}$$

$$p_{2i}=\left(\frac{2g'(0)}{g(0)}\Delta\pi_i\right)^2, \tag{A6}$$

$$p_{3i}=-2\frac{6[g'(0)]^3-3g(0)g'(0)g''(0)+g(0)^2g'''(0)}{g(0)^3}(\Delta\pi_i)^3. \tag{A7}$$

Inserting these quantities into Eqs. (A2) and (A3) leads to

$$Q_1=-\frac{2g'(0)}{g(0)}\sum_{k=1}^{N-1}\sum_{i=1}^{k}\Delta\pi_i, \tag{A8}$$

$$Q_2=\left(\frac{2g'(0)}{g(0)}\right)^2\sum_{k=1}^{N-1}\left(\sum_{i=1}^{k}\Delta\pi_i\right)^2, \tag{A9}$$

$$Q_3=2\frac{6[g'(0)]^3+3g(0)g'(0)g''(0)-g(0)^2g'''(0)}{g(0)^3}\times\sum_{k=1}^{N-1}\sum_{i=1}^{k}(\Delta\pi_i)^3-\frac{24(g'(0))^3}{g(0)^3}\times\sum_{k=1}^{N-1}\left(\sum_{i=1}^{k}\Delta\pi_i\right)\Big(\sum_{s=1}^{k}(\Delta\pi_s)^2\Big). \tag{A10}$$

Here, Q_1 and Q_2 have been calculated in the main text. Note that they only depend on $g'(0)/g(0)$, whereas Q_3 also depends on higher order derivatives of the imitation function. Thus, two pairwise comparison processes that are identical in first order are also identical in second order. Only in third order, differences start to emerge.

Let us briefly come back to our example of an imitation function that violates the one-third rule, $g(x)=[1+\exp(-x^3)]^{-1}$. In this case, we have $g(0)=1/2$,

$g'(0)=g''(0)=0$, and $g'''(0)=3/2$. Thus, both Q_1 and Q_2 vanish and the third-order expansion of the fixation probability is

$$\phi_1 \approx \frac{1}{N}+\frac{N-1}{60N}[(N+1)(3N^2-2)u^3+15(N+1)Nu^2v + 30(N+1)uv^2+30v^3]\beta^3. \quad \text{(A11)}$$

2. Moran processes

For the Moran processes with general fitness functions, we have $p_{1i}=-f'(0)\Delta\pi_i$ and $p_{2i}=2[f'(0)]^2\pi_A\Delta\pi_i-f''(0)(\pi_A+\pi_B)\Delta\pi_i$. Inserting these quantities into Eqs. (A2) and (A3) leads to

$$Q_1=-f'(0)\sum_{k=1}^{N-1}\sum_{i=1}^{k}\Delta\pi_i,$$

$$Q_2=\{[f'(0)]^2-f''(0)\}\sum_{k=1}^{N-1}\sum_{i=1}^{k}(\pi_A^2-\pi_B^2) + [f'(0)]^2\sum_{k=1}^{N-1}\left(\sum_{i=1}^{k}\Delta\pi_i\right)^2. \quad \text{(A12)}$$

Thus, the first- and the second-order expansions of the fixation probability of such processes are given in Eqs. (18) and (19), respectively. In particular, for $f(\pi)=1+\pi^3$, both p_{1i} and p_{2i} vanish and $p_{3i}=-6(\pi_A^3-\pi_B^3)$. In Eq. (A3), this yields

$$\phi_1=\frac{1}{N}+\underbrace{\frac{1}{N^2}\sum_{k=1}^{N-1}\sum_{i=1}^{k}(\pi_A^3-\pi_B^3)}_{D_3}\beta^3+o(\beta^3), \quad \text{(A13)}$$

where

$$D_3=[1/60N(N-1)^2][-3c^2d(N-2)(1+N)(2N-1) - 3cd^2(N-2)(N+1)(3N-4)+6a^2b(N-2)(N^2-2N+2)+a(a^2+3b^2)(N-2)(3N^2-6N+1)-c^3(1+N)\times(3N^2-2)+2b^3(1+N-9N^2+6N^3) - d^3(N-2)(29-39N+12N^2)].$$

APPENDIX B: TIMES OF FIXATION

General expressions for the first- and second-order expansions of the fixation time for the birth-death process have been given in Eqs. (26) and (30). Based on these, we show the results for the general pairwise comparison rule first and then discuss the Moran process.

1. General pairwise comparison process

For the first-order term of the fixation time [Eq. (26)], each h_α on the right-hand side is proportional to $g'(0)/g^2(0)$. Thus, the first-order term of the fixation time is of the form $Rg'(0)/g^2(0)$. In particular, when $g(\Delta\pi)$ is the Fermi function, $g'(0)/g^2(0)$ is 1. Hence, the first order of the fixation time for the Fermi process is R [cf. Eq. (23)]. This leads to the first-order expansion of the fixation time for general pairwise comparison rule [Eq. (29)].

For the second order, we write Eq. (30) explicitly as

$$\frac{\partial^2}{\partial\beta^2}\tau_1^A=\underbrace{\sum_{k=1}^{N-1}\sum_{l=1}^{k}h_{(2,0,0)}}_{K_1}+\underbrace{\sum_{k=1}^{N-1}\sum_{l=1}^{k}h_{(0,2,0)}}_{K_2}+\underbrace{\sum_{k=1}^{N-1}\sum_{l=1}^{k}h_{(0,0,2)}}_{K_3} + \underbrace{2\sum_{k=1}^{N-1}\sum_{l=1}^{k}h_{(1,1,0)}}_{K_4}+\underbrace{2\sum_{k=1}^{N-1}\sum_{l=1}^{k}h_{(1,0,1)}}_{K_5}+\underbrace{2\sum_{k=1}^{N-1}\sum_{l=1}^{k}h_{(0,1,1)}}_{K_6}. \quad \text{(B1)}$$

As shown in the main text, the second-order term is of the form $G_1u^2+G_2uv+(G_2/N)v^2$. Letting $u=1$ and $v=0$ leads to

$$K_1=\frac{N^2(N-1)(2N-1)}{6}\frac{2[g'(0)]^2-g(0)g''(0)}{g(0)^3},$$

$$K_2=-\frac{N^2(N-2)(N-1)(17+63N+16N^2)}{2700}\frac{2[g'(0)]^2}{g(0)^3},$$

$$K_3=\frac{N(-120+4N+350N^2-65N^3-290N^4+121N^5)}{1800}\times\frac{2[g'(0)]^2}{g(0)^3},$$

$$K_4=-\frac{N^3(N^2-1)}{12}\frac{2[g'(0)]^2}{g(0)^3},$$

$$K_5=\frac{N^3(2-3N+N^2)}{9}\frac{2[g'(0)]^2}{g(0)^3},$$

$$K_6=-\frac{N^2(2+25N-15N^2-25N^3+13N^4)}{180}\frac{2[g'(0)]^2}{g(0)^3} \quad \text{(B2)}$$

after some tedious calculations using the identity $\Sigma_{k=1}^{M}\Sigma_{l=1}^{k}=\Sigma_{l=1}^{M}\Sigma_{k=l}^{M}$ [56]. Summing these K_i's leads to G_1 in Eq. (32). On the other hand, letting $u=0$ and $v=1$ yields

$$K_1=N(N-1)\frac{2[g'(0)]^2-g(0)g''(0)}{g(0)^3},$$

$$K_2=\frac{N^2(N-1)(N-2)}{18}\frac{2[g'(0)]^2}{g(0)^3},$$

$$K_3=\frac{N(4N^3-15N^2+17N-6)}{18}\frac{2[g'(0)]^2}{g(0)^3},$$

$$K_4=-\frac{N^2(N-1)}{2}\frac{2[g'(0)]^2}{g(0)^3},$$

$$K_5 = \frac{N(N-1)(N-2)}{2}\frac{2[g'(0)]^2}{g(0)^3},$$

$$K_6 = -\frac{N^2(N-1)(N-2)}{3}\frac{2[g'(0)]^2}{g(0)^3}. \tag{B3}$$

Adding these K_i's yields G_2/N as in Eq. (33). Thus, the quantities in Eq. (31) are finally derived.

2. Moran processes

For Moran processes, the approach is fully equivalent to pairwise comparison processes. However, the results do not only depend on payoff differences u and v but also on the full payoff matrix with entries a, b, c, and d. This makes the calculations a matter of diligence and leads to quite long expressions, but not to additional insights. Thus, we do not give details of the derivation here.

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2.3 Stochastic slowdown in evolutionary processes

The result of Section 2.1 leads to an interesting observation that is now examined and discussed in further detail. One of the main assumptions in evolutionary game theory is that in the limit of weak selection all relevant quantities depend on the payoff difference $\Delta\pi = u\,i + v$ in a linear way. The parameter β, termed selection intensity, introduces a bias which vanishes in the limit $\beta \to 0$ (neutral evolution). Hence, in many cases evolutionary game dynamics model a random walk on $\{0,1,\ldots,N\}$, biased by selection, between (absorbing) boundaries 0, N. Of special interest here is the conditional mean exit time of such a biased random walk to get to a particular absorbing state from its most distant non-absorbing state. This expectation value can be a non-monotonous function of β. If this bias decreases with the density $u < 0$, it has a maximum. For sufficiently large v, this essentially means that a random walker that is biased toward a certain boundary spends longer on average than its unbiased counterpart. This becomes clear when observing that in confined random walks, the unbiased mean exit time is constant in system size $C_N \sim N^2$, whereas an approximation that accounts for the bias linear in β always takes the form $-u\,D_N\,\beta$, where $D_N \sim N^4$. This property is universal, see Section 2.2. Thus, one can model game theoretic setups in which one type always has a selective advantage, be it in reproductive success or in the probability to be imitated, but on average the advantageous type spreads slower in the population than a neutral type that does not have any advantage disadvantage. From our intuition this should not be the case, as the associated probability of absorption increases with the bias. We have termed this effect stochastic slowdown; it is an essential feature of the conditional moments given in Section 1.3. It can occur if a positive bias decreases with increasing density i of advantageous mutants.

In systems that do not have state dependent transition rates, $\Delta\pi = v$, which corresponds to constant selection in evolutionary biology, this slowdown cannot be observed; the state dependence is crucial. We construct a simplified model with absorbing boundaries which is a caricature of the standard microscopic evolutionary dynamics. State dependence of the transition probabilities is introduced by a step function: Below a certain threshold there is a bias and above the threshold the bias vanishes. Bias here means that moving toward the absorbing boundary of interest is more likely than moving away from it. The slowdown is thus sensitively dependent on the threshold value. The mean exit time is not a monotonous function of the bias parameter β, which gives rise to discuss three different features: First, there is a non-trivial value of β where the mean exit time is again equal to the one of unbiased random walk, β^*. Next, if slowdown occurs, the mean exit time has a maximal value $\tilde{\tau}$ at a given bias $\tilde{\beta}$. All three quantities can be considered as a

function of the asymmetry threshold. The values of the bias $\tilde{\beta}$ and β^* asymptotically scale with the inverse system size, $\beta^*,\tilde{\beta} \sim N^{-1}$; this is a typical weak selection result. The maximal value $\tilde{\tau}$, however, does not scale with N; the relative amplitude of the slowdown remains constant if the system size increases.

There is a parameter regime of stochastic slowdown for every microscopic one-step process that resembles a biased random walk with at least one absorbing boundary. The question is whether this also holds for other Markov chains. A widely used Markov chain in theoretical population genetics is the Wright-Fisher process [Ewens, 2004; Fisher, 1930; Haldane, 1924–1934; Wright, 1970], see Chapter 1. Instead of single events of reproduction and death, which corresponds to overlapping generations, here, one time step corresponds to one generation: All N individuals produce a large number of offspring proportional to their fitness, and die. The next generation is then a random sample from this huge offspring pool. This corresponds to binomial sampling proportional to fitness [Imhof and Nowak, 2006]. For this class of processes the master equation for the distribution of transition times does not yield solvable recursions for the moments, such as the conditional mean exit time. Nevertheless, for large N it is meaningful to perform an expansion in system size assuming that all but the first two moments of the resulting continuous process vanish [Ewens, 2004; van Kampen, 1997], see Section 1.4. This is analogous to the truncated Kramers-Moyal expansion [Risken, 1989]. Again, with positive but state dependent bias in this Markov process the conditional mean exit time of a single mutant increases with weak but increasing bias. The non-monotonic behavior can be shown analytically in the diffusion approximation for large system size.

For all processes considered in this thesis, the parameter range required for the slowdown in mean exit times can be predicted analytically by considering an expansion up first order in bias. This is corroborated by extensive simulations of the microscopic processes.

Stochastic slowdown in evolutionary processes

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We examine birth-death processes with state dependent transition probabilities and at least one absorbing boundary. In evolution, this describes selection acting on two different types in a finite population where reproductive events occur successively. If the two types have equal fitness the system performs a random walk. If one type has a fitness advantage it is favored by selection, which introduces a bias (asymmetry) in the transition probabilities. How long does it take until advantageous mutants have invaded and taken over? Surprisingly, we find that the average time of such a process can increase, even if the mutant type always has a fitness advantage. We discuss this finding for the Moran process and develop a simplified model which allows a more intuitive understanding. We show that this effect can occur for weak but nonvanishing bias (selection) in the state dependent transition rates and infer the scaling with system size. We also address the Wright-Fisher model commonly used in population genetics, which shows that this stochastic slowdown is not restricted to birth-death processes.

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I. INTRODUCTION

Birth-death processes belong to the simplest stochastic models and are applied in a variety of fields [1–6]. In physics these processes are connected, e.g., to the study of one-dimensional classical diffusion in disordered media, anomalous transport, and molecular motors [7–10]. In evolutionary biology, birth-death processes are commonly applied to model the evolution of traits with different reproductive fitness that are under natural selection [5,11]. In the context of evolutionary game theory, this particular class of Markov chains has been used to model the spreading of successful strategies in a population of small size [12–20]. Naturally, the limit of weak selection is considered to be important in biology. It describes situations in which the effects of payoff differences are small, such that the evolutionary dynamics are mainly driven by random fluctuations. While this approach has a long standing history in population genetics [21,22], in the context of evolutionary game dynamics it has been introduced only recently [14]. Often, from the discrete stochastic process a continuous limit or diffusion approximation is motivated, where typically the impact of the relevant parameters and time scales can be studied more easily [11,23–25]. Here, we consider the Moran process from theoretical population genetics and related processes. We address the speed of evolution when a resident population is taken over by mutants that are more fit. Under the low mutation rates that typically occur in biology, a mutant type either goes extinct or takes over the population before another mutation arises. Thus, for many purposes it is sufficient to address the evolution of two types in a one-dimensional system.

In the following, we first recall general properties of birth-death processes (Sec. II) and then address asymmetry in the transition probabilities (Sec. III). In Sec. IV, we then consider a more general Markov process to highlight that our main finding is not a special property of birth-death processes.

II. STATE DEPENDENT BIRTH-DEATH PROCESS

A one-dimensional birth-death process in position i can move to $i-1$ or $i+1$ with probabilities T_i^- and T_i^+. With probability $1-T_i^- - T_i^+$, the process stays in state i. We assume $T_0^\pm = T_N^\pm = 0$, such that $i=0$ and $i=N$ are absorbing states. In discrete time, the probability to reach boundary N in t steps, starting from any i, obeys the master equation [6].

$$P_i^N(t) = (1 - T_i^+ - T_i^-)P_i^N(t-1) + T_i^- P_{i-1}^N(t-1) + T_i^+ P_{i+1}^N(t-1). \tag{1}$$

The stationary conditional n^{th} moment of $P_i^N(t)$ is given by

$$(\phi_i^N)^{-1} \sum_{t=0}^{\infty} t^n P_i^N(t). \tag{2}$$

The normalization constant, $\phi_i^N = \Sigma_{t=0}^{\infty} P_i^N(t)$, is the probability that the process gets absorbed at boundary N, called fixation probability in population genetics. For ϕ_i^N a recursion is obtained from Eq. (1), $\phi_i^N = (1-T_i^+ - T_i^-)\phi_i^N + T_i^- \phi_{i-1}^N + T_i^+ \phi_{i+1}^N$. With the boundary conditions $\phi_0^N = 0$ and $\phi_N^N = 1$, the solution reads [4]

$$\phi_i^N = \frac{1 + \sum_{k=1}^{i-1} \prod_{m=1}^{k} \frac{T_m^-}{T_m^+}}{1 + \sum_{k=1}^{N-1} \prod_{m=1}^{k} \frac{T_m^-}{T_m^+}}. \tag{3}$$

A measure for the duration of the process is the conditional mean time to absorption (average fixation time) τ_i^N, i.e., the first moment of $P_i^N(t)$. This gives the average number of time steps until one of the two absorbing states is reached, starting

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from any i [7,13]. A recursion for τ_i^N is obtained by multiplying each side of Eq. (1) with t and summing over all t [6], which yields $\phi_i^N \tau_i^N = (1-T_i^+-T_i^-)\phi_i^N \tau_i^N + T_i^- \phi_{i-1}^N (\tau_{i-1}^N+1) + T_i^+ \phi_{i+1}^N (\tau_{i+1}^N+1)$. A similar recursion can be found for the conditional mean exit time τ_i^0, such that the mean life time of the process amounts to $\tau_i^0+\tau_i^N$. Solving recursively with the boundary conditions $\tau_0^N=0$ and $\tau_N^N=0$, leads to the conditional mean time to reach state N, starting from $i=1$,

$$\tau_1^N = \sum_{k=1}^{N-1} \sum_{l=1}^{k} \frac{\phi_l^N}{T_l^+} \prod_{m=l+1}^{k} \frac{T_m^-}{T_m^+}. \tag{4}$$

One common example for a birth-death process with absorbing states 0 and N is the homogenous random walk, $T_i^\pm = c \leq 1/2$ for $0<i<N$ and $T_0^\pm = T_N^\pm = 0$ [26]. This leads to $\phi_i^N = i/N$ and $\tau_1^N = (N^2-1)/(6c)$. The reference case of population genetics is neutral evolution, where the symmetric transition probabilities are state dependent, $T_i^\pm = i(N-i)/N^2$. This results in $\phi_i^N = i/N$ and $\tau_1^N = N(N-1)$ [5,11].

III. BIASED TRANSITION PROBABILITIES

In this section, we examine how the state dependent transition probabilities influence the conditional mean exit time. We consider processes in which a parameter β continuously introduces a bias toward moving into one direction: for $\beta=0$ the transition probabilities are symmetric, $T_i^+ = T_i^-$, but for $\beta>0$, an asymmetry arises, $T_i^+ \geq T_i^-$. In evolutionary dynamics, β is usually referred to as the intensity of selection. It governs the selective advantage (or disadvantage) of mutants in a wild-type population of finite size. Intuitively, it is clear that the time τ_1^N does not depend trivially on β, cf. Eq. (4). With increasing β, the probability ϕ_i^N increases, but both $1/T_i^+$ and T_i^-/T_i^+ decrease in our setup. Thus, the average time τ_1^N can increase or decrease with β. In other words, despite increasing the tendency to move in the direction of a given boundary in each state, the conditional average time until this boundary is reached can still increase.

In the Moran process, an individual selected for reproduction proportional to fitness produces identical offspring that replaces a randomly selected individual from the population. We consider the evolution of two types A and B in a finite population of size N. Type A (with fitness f_A) is usually referred to as the mutant type, B (with fitness f_B) is called the wild type. Let i be the number of individuals of type A, such that $N-i$ is the number of B individuals. In general, the transition probabilities are

$$T_i^+ = \frac{i f_A}{i f_A + (N-i) f_B} \frac{N-i}{N},$$

$$T_i^- = \frac{(N-i) f_B}{i f_A + (N-i) f_B} \frac{i}{N}. \tag{5}$$

In the following, we discuss different choices of f_A and f_B, as well as closely related, but simplified asymmetric transition rates.

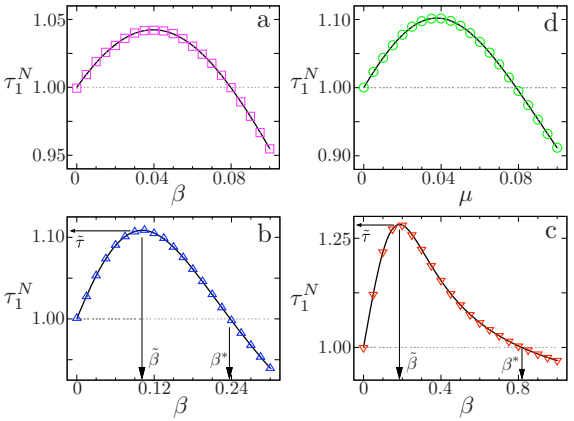

FIG. 1. (Color online) The conditional mean exit time $\tau_1^N/\tau_1^N(0)$ (normalized) as a function of the bias (selection intensity) β, or the mutation rate μ, for the four different models discussed in the main text. Symbols are simulations, lines show Eq. (4). (a) Moran process with $a=-0.1$ and $b=2$, see Eq. (7). (b) Parabolic-step process with $i^*=11$, Eq. (9). (c) Constant-step process with $i^*=9$ and $c=0.5$, Eq. (12). (d) Birth-death process with directed mutations, Eqs. (15) and (16). The quantities $\tilde{\tau}$, $\tilde{\beta}$, and β^* indicate the maximal relative increase of τ_1^N, the according bias parameter, and the nontrivial value of β where $\tau_1^N = \tau_1^N(0)$, respectively (also compare Fig. 2). The system size is $N=20$ in all panels, averages taken over 10^7 realizations.

A. Constant fitness

In the simplest case, the fitness of mutants is constant and does not depend on their abundance [11]. In our model, this can be parametrized as $f_A=1+\beta$ and $f_B=1-\beta$. In this case, the fixation probability of a single mutant is [11]

$$\phi_1^N = (1-\gamma)/(1-\gamma^N), \tag{6}$$

where $\gamma=(1-\beta)/(1+\beta)$. Up to linear order in β we have $\phi_1^N \approx N^{-1} + \beta(N-1)N^{-1}$. The larger the fitness advantage, the more likely the evolutionary takeover. For stronger selection ($\beta>0$) an advantageous mutant is expected to fixate faster compared to neutral ($\beta=0$).

B. Linear density dependence

In general, the fitness of the two types will depend on their abundance. For example, the fitness f of each type can change linearly with i, $f_A=1+\beta(ai+b)$ and $f_B=1-\beta(ai+b)$. The bias β is bound such that fitness never becomes negative. Then, the transition probabilities are

$$T_i^\pm = \frac{1 \pm \beta(ai+b)}{N-\beta(ai+b)(N-2i)} \frac{i(N-i)}{N}. \tag{7}$$

We have $T_0^\pm = T_N^\pm = 0$, such that both boundaries are absorbing [14,27]. For $a<0$ and $aN+b>0$, type A is always fitter than type B, $f_A>f_B$, but the conditional mean exit time τ_1^N is larger than neutral in a certain parameter range, compare Fig. 1(a). In this case, a mutant that is fitter than the rest of the population needs more time to take over the population than

a less fit mutant. Intuitively, this should not be the case. The linear approximation of τ_1^N for $\beta \ll N^{-1}$ (weak selection) reads

$$\tau_1^N \approx N(N-1) - a\frac{N^2(N^2-3N+2)}{18}\beta, \tag{8}$$

see [28,29]. Note that the linear approximation of the conditional mean exit time depends only on the parameter a, but not on b, which holds for any system size. Hence, for small bias β and $a<0$, the conditional average time grows with increasing β. This is an effect from state dependent fitness in finite populations, as it cannot occur for $a=0$.

The ratio T_i^-/T_i^+ is a measure of the stochastic flow. Stochastic slowdown can occur if this ratio changes with the position (abundance of A) i, leading to an asymmetry. When β becomes larger, τ_1^N decreases again with β, which is the strong selection behavior one would expect, compare Fig. 1(a).

C. Steplike asymmetry

Is there a simpler process with similar characteristics? Indeed, we can introduce asymmetry also as a step in the fitness of the two types in our Moran process. This leads to parabolic transition probabilities with an additional steplike discontinuity,

$$T_i^{\pm} = \frac{i(N-i)}{N^2}(1 \pm \beta\Theta[i^*-i]), \tag{9}$$

where $\Theta[x]$ is the step function ($\Theta[x<0]=0$ and $\Theta[x\geq 0]=1$). The integer i^* is the location of the step. This process has the fixation probabilities

$$\phi_i^N = \begin{cases} \dfrac{1}{\phi_1^i}\dfrac{\phi_1^{i^*}}{\phi_1^{i^*}(N-i^*)\gamma^{i^*}+1} & \text{if } i \leq i^*, \\ \dfrac{\phi_1^{i^*}(i-i^*)\gamma^{i^*}+1}{\phi_1^{i^*}(N-i^*)\gamma^{i^*}+1} & \text{if } i \geq i^*, \end{cases} \tag{10}$$

where $\phi_1^k=(1-\gamma)/(1-\gamma^k)$ is the probability to get from 1 to k, and $\gamma=(1-\beta)/(1+\beta)$. Note that this general formula reduces to the standard fixation probability for constant fitness in the case of $i^*=N$, cf. Eq. (6). For weak bias, $\beta \ll 1/N$, we have $\gamma \approx 1-2\beta$, as well as

$$\phi_i^N \approx \frac{i}{N} + \frac{\beta}{N^2}\begin{cases} i[(N(1+2i^*-i)-i^*(1+i^*)] & \text{if } i \leq i^*, \\ (N-i)i^*(1+i^*) & \text{if } i > i^*. \end{cases} \tag{11}$$

ϕ_i^N increases with β in this approximation, whereas γ decreases with β. Hence, the mean exit time can also increase in an appropriate parameter range. The average delay of the absorption is rather high in this case, cf. Fig. 1(b), where it is 10%. Fig. 2(c) illustrates that even a delay of 400% is possible, but this delay decreases with increasing i^*.

An even simpler model with stochastic slowdown is the constant-step process

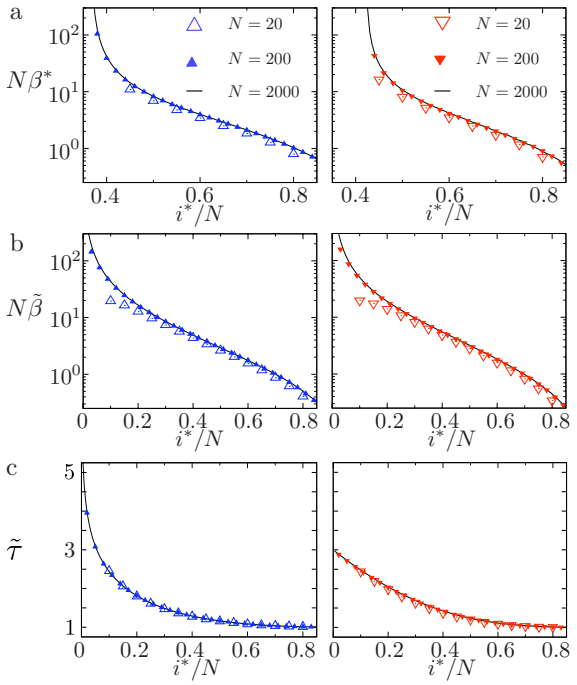

FIG. 2. (Color online) Scaling with system size for the two models with step like asymmetry: Parabolic-step model Eq. (9) [Fig. 1(b)] on the left, constant-step model Eq. (12) with $c=1/2$ [Fig. 1(c)] on the right. (a) The threshold value $N\beta^*$, defined by $\tau_1^N(\beta^*)=\tau_1^N(0)$. Note that $\beta \leq 1$ permits a minimal value of i^*/N only relatively far from zero. (b) $N\tilde{\beta}$, defined as the bias parameter where the mean exit time τ_1^N is maximal. When plotted against the asymmetry parameter i^*, both models approach a limit curve with growing size N. This suggests that nontrivial values of β^* and $\tilde{\beta}$ can be found for any system size N after appropriate rescaling: the asymptotic scaling relations are $\tilde{\beta} \sim N^{-1}$, and $\beta^* \sim N^{-1}$. (c) The maximal increase of the mean exit time (normalized), $\tilde{\tau} = \tau_1^N(\tilde{\beta})/\tau_1^N(0)$, quickly approaches a limiting curve with growing N. This suggests the asymptotic scaling relation $\tilde{\tau} \sim N^0$. Open symbols $N=20$, filled symbols $N=200$, lines $N=2000$.

$$T_i^{\pm} = c(1 \pm \beta\Theta[i^*-i]) \quad \text{if } 0 < i < N, \tag{12}$$

and $T_0^{\pm}=T_N^{\pm}=0$, with $i^* \leq N$, and the constant c chosen such that $T_i^+ + T_i^- \leq 1$. Clearly, the fixation probability of this process obeys Eqs. (10) and (11). Then, the remaining sums can be expressed by means of the exact form of ϕ_i^N, respecting that $1/T_l^+$ only gives contributions different from $1/c$ if $l \leq i^*$. The conditional mean exit time τ_1^N can now be written in the form

$$\tau_1^N = \frac{\phi_1^N}{c}\sum_{k=1}^{i^*}\sum_{l=1}^{k}\frac{\gamma^{k-l}(1+\gamma)}{2\phi_1^l} + \frac{\phi_1^N}{c}\sum_{k=i^*+1}^{N-1}\sum_{l=1}^{i^*}\frac{\gamma^{i^*-l}(1+\gamma)}{2\phi_1^l} + \frac{\phi_1^N}{c}\sum_{k=i^*+1}^{N-1}\sum_{l=i^*}^{k-1}\left[(k-l)\gamma^{i^*} + \frac{1}{\phi_1^{i^*}}\right]. \tag{13}$$

With $\gamma \approx 1-2\beta$ and Eq. (11) this leads to

$$\tau_1^N \approx \frac{N^2-1}{6c} + \frac{(N-i^*)(N-1-i^*)i^*(1+i^*)}{3Nc}\beta. \quad (14)$$

The constant contribution is that of the homogenous random walk. The correction linear in β is always greater than or equal to zero, i.e., within the range of this approximation it just adds a positive value to the symmetric part. Also note that $\tau_1^N(\beta=0,i^*,c)$ serves as an upper bound for the mean exit time if $i^* \geq N-1$. Hence, below a certain threshold of the bias, τ_1^N is always greater than or equal to the homogenous random walk between absorbing boundaries. This is surprising as the process defined by Eq. (12) fulfills $T_i^+ \geq T_i^-$, and thus never gives a disadvantage to movement toward the boundary $i=N$. Moving into the direction of N is always at least as likely as moving into the opposite direction in this setup. In this particular process, the stochastic slowdown can be quite large, cf. Figs. 1(c) and 2(c).

What is the effect of system size on this stochastic slowdown? Let β^* denote the upper bound of the parameter β for which $\tau_1^N(\beta) > \tau_1^N(0)$, which is the parameter range in which slowdown can be observed. Additionally, with $\tilde{\beta}$ we denote the parameter value of maximal slowdown of the exit time τ_1^N. They change with N and i^* in both models with a steplike asymmetry, Eqs. (9) and (12). The expansions linear in β are valid if $N\beta \ll 1$ [13,27,29]. In Figs. 2(a) and 2(b) we show that with increasing system size N, the quantities $N\tilde{\beta}(i^*)$ and $N\beta^*(i^*)$ approach limiting curves if β is rescaled appropriately. Thus, stochastic slowdown does not rely on small system size, but β^* and $\tilde{\beta}$ asymptotically scale as N^{-1}. However, the maximal relative increase of the mean exit time itself, $\tilde{\tau} = \tau_1^N(\tilde{\beta})/\tau_1^N(0)$, does not scale with system size, $\tilde{\tau} \sim N^0$, as illustrated in Fig. 2(c).

D. Directed mutations

To stress the generality of the effect of stochastic slowdown in asymmetric birth-death processes we briefly discuss a model with directed mutations. Fitness does not need to be position/state dependent to observe stochastic slowdown in population genetics. As above we consider two types, A and B, in a population of size N, both having the same reproductive fitness. In one reproduction step of this Moran process, type B mutates to type A with a probability μ, back-mutations are excluded. This introduces asymmetry in the transition rates,

$$T_i^+ = \left(\frac{i}{N} + \mu\frac{N-i}{N}\right)\frac{N-i}{N}, \quad (15)$$

$$T_i^- = \left(\frac{N-i}{N}(1-\mu)\right)\frac{i}{N}, \quad (16)$$

where i is the abundance of A. Obviously, $T_N^\pm = T_0^- = 0$, but with directed mutations we have $T_0^+ \geq 0$. The process has one absorbing boundary. The ratio of the transition probabilities is $T_m^-/T_m^+ \approx 1-\mu N/m$, for mutation rates $\mu \ll 1/N^2$. For larger μ, the dependence on the inverse mutation rate makes the calculation of an approximation of Eq. (4) unwieldy. As μ increases we expect that A has an advantage during reproduction and hence, the conditional fixation time (that a single mutant takes over before going temporarily extinct) should decrease. Nevertheless, we observe an increase in the value of τ_1^N, see Fig. 1(d). The time shows a maximum when μ is close to N^{-1}.

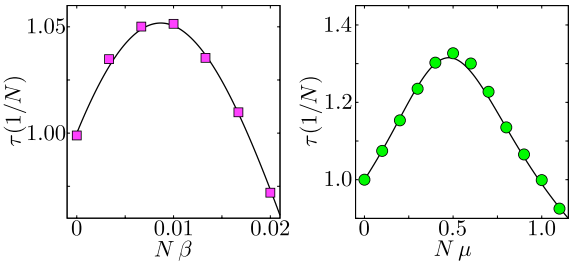

FIG. 3. (Color online) The conditional mean exit time (normalized) for the Wright-Fisher model with $N=1000$, as a function of the rescaled bias (selection intensity, mutation rate). The line shows the analytical diffusion approximation result Eq. (24), namely $\tau(N^{-1})/(2N-1)$. Symbols are simulation results. Left: The state dependent fitness model, Eq. (17) (2×10^6 realizations, $a=-0.1$, $b=N|a|$). For relatively small bias β slowdown is observed. Right: The directed mutations model, Eq. (A1) (5×10^5 realizations). Here, a strong slowdown effect can be observed over a wide range of the bias, $N\mu \leq 1$. This is due to the different nature of the directed mutation process, which has only one absorbing boundary.

A more general process is given in the Appendix. There, we derive an expression for the fixation probability in a Wright-Fisher model with directed mutations. Although this quantity increases with μ, the associated conditional mean exit time also increases in a certain parameter range, compare Fig. 3.

IV. STATE DEPENDENT WRIGHT-FISHER PROCESS

The phenomenon of stochastic slowdown is not restricted to birth-death processes. It also occurs in the Wright-Fisher process that is commonly used in population genetics [11,30]. Again, we consider a population of two types A and B. If i is the abundance of A, the fitness of each type is $f_A = 1+\beta(ai+b)$, and $f_B = 1-\beta(ai+b)$, respectively. Birth-death processes, such as the Moran model considered above, deal with one reproductive event at a time. Now, one time step of the Wright-Fisher process corresponds to one generation where all individuals reproduce: In each generation, the N individuals reproduce a large number of offspring proportional to fitness. The new generation of size N is a random sample from this offspring pool, which corresponds to binomial sampling proportional to fitness. The transition probability to go from i to j A individuals reads [30]

$$T_{i\to j} = \binom{N}{j}\left(\frac{if_A}{if_A+(N-i)f_B}\right)^j\left(\frac{(N-i)f_B}{if_A+(N-i)f_B}\right)^{N-j}. \quad (17)$$

For this process, a closed treatment is not possible. Apart from simulations, for large N a diffusion approximation leads

to analytical results [11,31–34]. With $x=i/N$, the process is approximately described by the Langevin equation $dx = D_1(x)dt + \sqrt{D_2(x)}dW(t)$, where $W(t)$ is the Wiener process with zero mean and autocorrelation $\langle W(t)W(s)\rangle = \min(t,s)$ [1]. The drift term $D_1(x)$ can be written as

$$D_1(x) = x(1-x)N\frac{f_A(x) - f_B(x)}{xf_A(x) + (1-x)f_B(x)}. \tag{18}$$

For the diffusion term $D_2(x)$ we find

$$D_2(x) = x(1-x)\frac{f_A(x)f_B(x)}{(xf_A(x) + (1-x)f_B(x))^2} + \frac{D_1^2(x)}{N}. \tag{19}$$

If the initial fraction of A types is x_0, the probability of absorption in $x=1$ (fixation probability) reads

$$\phi(x_0) = \frac{S(x_0)}{S(1)}, \tag{20}$$

where

$$S(x) = \int_0^x dy\, \exp\left[-\int_0^y dz \frac{2D_1(z)}{D_2(z)}\right]. \tag{21}$$

If there is no bias, $\beta=0$, we have $f_A(x)=f_B(x)$ and hence $D_1(x)=0$. Thus, consistently with the previous section, we obtain $\phi(i/N)=i/N$. For sufficiently weak bias, $N\beta \ll 1$, we have

$$\frac{2D_1(z)}{D_2(z)} \approx 4N(aNz+b)\beta, \tag{22}$$

which leads to

$$\phi(x_0) \approx x_0 + \frac{2x_0(1-x_0)N[aN(1+x_0)+3b]}{3}\beta. \tag{23}$$

The conditional mean time this process takes to exit at $x=1$, $\tau(x_0)$, can be obtained from the associated backward Fokker-Planck equation [11],

$$\tau(x_0) = N\int_0^{x_0} dx t_1(x,x_0) + N\int_{x_0}^1 dx t_2(x,x_0), \tag{24}$$

where

$$t_1(x,x_0) = 2\frac{\phi(x)}{D_2(x)}\frac{1-\phi(x_0)}{\phi(x_0)}S(x)\exp\left[\int_0^x dz \frac{2D_1(z)}{D_2(z)}\right],$$

$$t_2(x,x_0) = 2\frac{\phi(x)}{D_2(x)}(S(1)-S(x))\exp\left[\int_0^x dz \frac{2D_1(z)}{D_2(z)}\right]. \tag{25}$$

For weak bias Eq. (22) holds, as well as $S(x) \approx x - 2/3Nx^2(aNx+3b)\beta$. This results in

$$\tau(1/N) \approx 2N(N-1)\ln\left[\frac{N}{N-1}\right] - \frac{2}{9}(N-1)\left(C_1 + C_2 \ln\left[\frac{N-1}{N}\right]\right)\beta, \tag{26}$$

with

$$C_1 = a(7N^2 + 13N + 6) + 18b,$$

$$C_2 = 6N(aN(N+2) + 3b).$$

For large N, the right hand side of Eq. (26) simplifies, leading to

$$\tau(1/N) \approx 2N - 1 - a\frac{2N^2(N-3)}{9}\beta. \tag{27}$$

Hence, we can predict an increase of $\tau(1/N)$, in the case of state dependent bias with $a<0$, also for the Wright-Fisher process, in particular when A always has a fitness advantage over B, see Fig. 3. This goes along with the findings for the Moran model in the previous section. Thus, the slowdown effect can also be observed in the traditional framework of population genetics, where times of fixation (or rather extinction) have been considered typically for constant selection [11,35].

V. DISCUSSION

This paper addresses several stochastic evolutionary processes asking how long an advantageous mutation needs to take over. We have first concentrated on birth-death processes which model population dynamics with successive reproductive events, like the Moran process. However, the phenomenon of stochastic slowdown is also present in more general Markov processes, e.g., the Wright-Fisher process from population genetics. Stochastic slowdown is relevant in the invasion and fixation of beneficial traits with small state dependent selective advantage, which is typically assumed in evolutionary biology [36]. However, consequences of weak, but nonvanishing selection are hard to reveal in empirical studies, as the dynamics are still dominated by random genetic drift and averages over large ensembles are necessary. Biological examples of weak selection include amino acid substitutions which are only slightly advantageous or deleterious [37–39]. Weak state dependent fitness changes (such as the thresholds we discuss in our model with steplike asymmetry) may help explain situations in which a substitution is likely, but takes a very long time.

Our finding also has applications in evolutionary game theory [40–42]: When a group of cooperative individuals is eventually driven to extinction by defectors, this process may take longer than the corresponding neutral process, although the defectors always have a fitness advantage. This observation is closely related to the fact that the conditional fixation time of an advantageous mutation is the same as the conditional fixation time of a deleterious mutation [28,35].

To sum up, we have shown that an asymmetric bias in a random walk, which is generic in population genetics, can lead to a counterintuitive observation that an advantageous mutant needs longer to take over the population than a neutral mutant in the same system. This is a property of weakly biased systems, i.e., weak selection, and is recovered for any system size if the intensity of selection is rescaled with N^{-1}. The relative maximal increase in time itself is independent of the system size. Especially in the state dependent Moran or Wright-Fisher process, this can have a crucial impact on macroscopic observable quantities.

ACKNOWLEDGMENTS

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APPENDIX: STATE DEPENDENT WRIGHT-FISHER PROCESS WITH DIRECTED MUTATIONS

Consider a finite population of size N, which consists of two types A and B. Both types have the same reproductive rate, which is set to one. In one generation, each type produces a large number of identical offspring proportional to its abundance. Additionally, a directed mutation from B to A can occur with probability μ. The next generation of size N is a random sample from the offspring pool. The transition matrix reads

$$T_{i\to j}=\binom{N}{j}\left(\frac{i}{N}+\mu\frac{N-i}{N}\right)^{j}\left(\frac{N-i}{N}(1-\mu)\right)^{N-j}. \quad \text{(A1)}$$

The conditional moments of this Markov chain are given by [11]

$$\mathcal{M}_n(i)=\sum_{j=0}^{N}(j-i)^n T_{i\to j}. \quad \text{(A2)}$$

In a diffusion approximation we rescale the state space as $x=i/N$, and the timescale as $\Delta t=1/N$, such that for large system size and weak bias the process is well described by the first two moments, $D_k=\langle(x_{t+\Delta t}-x_t)^k\rangle/\Delta t$, i.e.,

$$D_k(x)=\frac{N}{N^k}\mathcal{M}_k(i), \quad \text{(A3)}$$

$k=1,2$. For the given Markov chain Eq. (A1), the drift and diffusion terms read

$$D_1(x)=\mu N(1-x), \quad \text{(A4)}$$

$$D_2(x)=(1-x)[(1-x)(N-1)\mu^2+(1-2x)\mu+x]. \quad \text{(A5)}$$

Next, we derive a closed expression for the probability that the process exits at $x=1$ without hitting the non-absorbing boundary $x=0$ first, starting form x_0, $\phi(x_0)$, Eq. (20). The general expressions Eqs. (20) and (21), as well as Eqs. (24) and (25) hold. However, due to the different nature of this process, where only one absorbing boundary at $x=1$ exists, these quantities have a slightly different meaning.

We define $2D_1(x)/D_2(x)=2N\mu/\tilde{D}_2(x)$, where

$$\tilde{D}_2(x)=(1-x)(N-1)\mu^2+(1-2x)\mu+x, \quad \text{(A6)}$$

and obtain

$$I_1(z)=\int dz\frac{2D_1(z)}{D_2(z)}=-\nu\ln\tilde{D}_2(z) \quad \text{(A7)}$$

with

$$\nu=\frac{2N\mu}{\mu[(N-1)\mu+2]-1}. \quad \text{(A8)}$$

Now, with $D_2(0)=\tilde{D}_2(0)$ and

$$I_2(y)=\exp\{-[I_1(y)-I_1(0)]\}=\left[\frac{\tilde{D}_2(y)}{D_2(0)}\right]^{\nu} \quad \text{(A9)}$$

we can calculate the second integral in Eq. (21),

$$S(x)=\int_0^x dy I_2(y)=\frac{1}{D_2^{\nu}(0)}\frac{\tilde{D}_2^{\nu+1}(x)-\tilde{D}_2^{\nu+1}(0)}{1-\mu[2-\mu+N(2+\mu)]}. \quad \text{(A10)}$$

Hence, the fixation probability, Eq. (20), reads

$$\phi(x_0)=\frac{\tilde{D}_2^{\nu+1}(x_0)-\tilde{D}_2^{\nu+1}(0)}{\tilde{D}_2^{\nu+1}(1)-\tilde{D}_2^{\nu+1}(0)}. \quad \text{(A11)}$$

As $\tilde{D}_2(0)=[(N-1)\mu+1]\mu$, $\tilde{D}_2(1)=1-\mu$, and $\lim_{\mu\to 0}\tilde{D}_2(x_0)=x_0$, we have $\lim_{\mu\to 0}\phi(x_0)=x_0$. Up to first order in mutation rate, we see that $\phi(x_0)$ increases with increasing bias,

$$\phi(x_0)\approx x_0-(2Nx_0\ln x_0)\mu. \quad \text{(A12)}$$

With expressions (A10) and (A11) the conditional mean exit time, Eq. (24), can be tackled as well. However, we do not address the conditional mean exit time analytically, as its explicit form is elaborate and does not lead to further insight. From a numerical solution [Eq. (24)] and from simulations [Eq. (A1)] the mean exit time of a single mutant, $\tau(1/N)$, as a function of μ is shown in Fig. 3.

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2.4 Deterministic evolutionary game dynamics in finite populations

Weak selection does not have to be the only limit case that allows to analytically examine statistical properties of a finite population under Darwinian evolution. An important question has been whether it is possible to introduce a microscopic evolutionary process that can use the parameter β to interpolate between weak and arbitrarily strong selection. Under strong selection in the sense that we discuss here, we require that the fittest are always selected and the least fit are alway removed. Such a limit case is difficult to establish for the density dependent Moran process introduced in Section 1.3, because arbitrarily high values of β can lead to negative values, if $f(\beta\pi)$ is linear and $\pi < 0$. On the other hand, choosing an exponential fitness function, which would ensure $f(\beta\pi) > 0$, the classical Moran process considers random removal of individuals to ensure that the population size remains constant. This also hinders a deterministic limit. To overcome this, we introduce a variant of the Moran process that leads to fully deterministic evolutionary dynamics in finite populations consisting of two strategies. When the interplay of more than two strategies is considered the outcome of strong selection is more complex; whether the dynamics is fully deterministic or not depends crucially on the game parameters and the initial condition. The traditional framework has two major difficulties with the introduction of strong selection

First, selection at birth is proportional to a positive fitness function. The fact that the fitness function actually allows a strong selection limit $\beta \to \infty$ is crucial. For example the commonly used function $f = 1 \pm \beta\pi$, where π is the payoff, does only allow this limit for particular cases of π. The choice $f = \exp\{\pm\beta\pi\}$, however, allows a strong selection limit and has the same linear properties for $\beta \ll 1/N$.

Secondly, even if selection at birth always chooses the fittest for reproduction, typically, there is a probability that an individual of the very same type is randomly selected to be withdrawn. Thus, death events have to be made nonrandom. For this we can define a fitness at death that is reciprocal to fitness a birth, we chose $f^{-1} = \exp\{\mp\beta\pi\}$. Large values of $\beta \gg 1/N$ increas the chances of the most successful type to reproduce and decreases the chances of this type to be removed. In terms of Section 2.2, this new process belongs to the universality class of the Fermi process.

In evolutionary games with two strategies the strong selection limit now leads to deterministic behavior. Depending on the ranking of the average payoffs of different types, which changes with the composition of the population, the probability that the currently advantageous type spreads goes to one. The final state of the evolutionary dynamics is, of course, highly sensitive to the strategic situation. If one type always has an advantage it fixes with certainty. If the two strategies are best replies to themselves the

deterministic outcome depends on the initial condition, which is similar to the prediction of the replicator dynamics in infinitely large populations [Weibull, 1995]. In both cases the mean exit time converges to the distance to the boundary which is finally reached. If the two strategies are best replies to each other the system gets trapped around the coexistence state predicted by the replicator dynamics and the exit time diverges.

If three strategies are considered and they cyclically compete in a Rock-Paper-Scissors like fashion [Hofbauer and Sigmund, 1998; May and Leonard, 1975], the situation is more complex. In such games, cyclic behavior can be observed, as paper wraps rock, scissors cut paper, and rock crushes scissors. Such a situation, the outcome of the strong selection limit is more diverse. This is due to the fact that there can be more than one state of the system where the composition of the population is such that the payoff hierarchy is not unique. Hence, even with $\beta \to \infty$, either birth, removal or both remain stochastic, but the transition probabilities only depend on the composition and not on the actual payoffs. In a simplified cyclic competition of strategies, where the only parameter is the ratio of gain to loss s, three generic cases emerge on the state space, which is the simplex $\mathbf{S}_3$. The simplex $\mathbf{S}_3$ is the convex set of the three variables representing the densities of the three strategies, which sum up to one, compare Section 1.2, Figure 1.1. As we consider evolutionary games in finite populations, not every point of S^2 can be accessed, we are dealing with the discrete equivalent. Depending on the only free parameter of the simplified evolutionary Rock-Paper-Scissors, s, three different cases emerge in the strong selection limit.:

(i) $s = 1$: Fixation remains stochastic for initial conditions on a central set of states. Outside of this set, when one strategy is almost lost, for the two remaining strategies we observe a deterministic process.

(ii) $s < 1$: The state space is again divided into two sets. On an outer set, fixation is deterministic but depends strongly on the initial condition. On an inner set, the system spirals inwards and settles on a cycle (or rather on the discrete equivalent of a cycle).

(iii) $s > 1$: Fixation becomes fully deterministic but the outcome is highly sensitive to the initial condition and depends on s.

Deterministic evolutionary game dynamics in finite populations

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Evolutionary game dynamics describes the spreading of successful strategies in a population of reproducing individuals. Typically, the microscopic definition of strategy spreading is stochastic such that the dynamics becomes deterministic only in infinitely large populations. Here, we present a microscopic birth-death process that has a fully deterministic strong selection limit in well-mixed populations of any size. Additionally, under weak selection, from this process the frequency-dependent Moran process is recovered. This makes it a natural extension of the usual evolutionary dynamics under weak selection. We find simple expressions for the fixation probabilities and average fixation times of the process in evolutionary games with two players and two strategies. For cyclic games with two players and three strategies, we show that the resulting deterministic dynamics crucially depends on the initial condition in a nontrivial way.

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I. INTRODUCTION

Evolutionary game dynamics results from the transfer of economic ideas to biology [1–4]. In economics, rational players try to find the best strategy to maximize their payoffs. In biology, those individuals who use the best strategy obtain the highest reproductive fitness and spread in the population.

Traditionally, evolutionary game dynamics is considered in infinitely large, well-mixed populations. This typically leads to the replicator dynamics, a system of nonlinear differential equations governing the evolutionary dynamics [5–8]. For any composition of the population, the replicator dynamics determines deterministically the direction and velocity of evolutionary dynamics. The replicator dynamics can be derived from microscopic models of strategy spreading, which are typically stochastic [9–13]. The precise definition of strategy spreading between individuals can have decisive consequences for the dynamics, in particular in structured populations [14–21].

Since microscopic models of strategy spreading are typically stochastic, evolutionary game dynamics in finite populations can only be characterized in a probabilistic way. The most important quantities are the probability that a mutant takes over a population and the average time for this process [22–25]. Different models for strategy spreading have been proposed. A popular model is to choose two players, Harry and Sally, at random and to let Harry adopt the strategy of Sally with probability given by the Fermi function, $(1+\exp[+\beta(\pi^H-\pi^S)])^{-1}$, where π^H is the payoff of Harry and π^S is the payoff of Sally [26–29]. The parameter β measures the intensity of selection. For $\beta \ll 1$, selection is weak and strategy spreading is essentially random. For $\beta \gg 1$, selection is strong and only strategies that are more successful will be imitated. For $\beta \to \infty$, the direction of the process for two strategies becomes deterministic and thus the fixation probability is either 0 or 1. However, even in this case, the process is only semideterministic as the time of fixation remains stochastic [29].

Here, we introduce a variant of the Moran process, which leads to a fully deterministic evolutionary process in finite populations under strong selection. For weak selection, we essentially recover the transition probabilities of the standard frequency-dependent Moran process under weak selection.

We describe evolutionary game dynamics in symmetric 2×2 games defined by the general payoff matrix,

$$\begin{array}{c} \\ A \\ B \end{array} \begin{array}{c} \begin{array}{cc} A & B \end{array} \\ \begin{pmatrix} a & b \\ c & d \end{pmatrix} \end{array} . \tag{1}$$

An A player will obtain a when playing against another A or b when playing against B. Choosing strategy B results in either obtaining c (against A) or d (against B).

The average payoffs are obtained from pairwise interactions with all other individuals in the population of size N. This is the standard assumption and refers to the fact that the population is well-mixed; i.e., there is no explicit population structure. Excluding self interactions, this leads to

$$\pi_i^A = \frac{i-1}{N-1}a + \frac{N-i}{N-1}b, \tag{2}$$

$$\pi_i^B = \frac{i}{N-1}c + \frac{N-i-1}{N-1}d, \tag{3}$$

where i is the current number of A players in the population. Individuals with higher average payoffs produce offspring (or are imitated) with a higher probability. Thus, reproductive success is based on the payoff from the game. The intensity of selection β controls the importance of success in the game for reproductive success. The larger the intensity of selection, the stronger the influence of the average payoff difference on reproductive fitness.

The paper is organized in the following way. In Sec. II we introduce the birth-death process as a general framework of evolutionary dynamics between two types in finite, well-

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mixed populations. In particular, we address the probability and times of absorption. In Sec. III we give three explicit analytical forms for the microscopic dynamics and we discuss the possibility to analyze strong selection in each case. We show that the standard Moran process and a previous generalization do not allow a fully deterministic strong selection limit and propose a generalization of the Moran process with selection at birth as well as selection at death. In Sec. IV we perform the strong selection limit analytically for the process. In Sec. V we consider the process with selection at birth and death for two player games with three strategies, namely, the rock-paper-scissors game. Finally, in Sec. VI we conclude and discuss our findings.

II. EVOLUTIONARY GAME DYNAMICS IN FINITE POPULATIONS

In this section, we recall some important properties of stochastic evolutionary game dynamics in finite populations. For simplicity, we restrict ourselves to birth-death processes in which the number of A players can change at most by ± 1 in each update step.

Let i be the number of A players in a population of size $N>2$. The number of B players is given by $N-i$. The transition probabilities to go from i to $i+1$ and to $i-1$ are denoted by $T_i^+(\beta)$ and $T_i^-(\beta)$, respectively. The probability to stay in the current state is thus $1-T_i^+(\beta)-T_i^-(\beta)$. These microscopic details do not have to be specified further at this point. The only requirement is that the expressions for $T_i^\pm(\beta)\neq 0$ are analytic in system size, payoffs and intensity of selection. It is also assumed that the population size remains constant. Mutations are excluded such that a strategy that is lost will not reappear in the system.

In the continuous limit $N\to\infty$, the state of the system $x=i/N$ becomes a continuous variable, strategy A can have any abundance, and we recover a deterministic differential equation [9–13]. This allows computation of the fixed points of the system. There are always fixed points at $x=0$ and $x=1$. In addition, there can be a third fixed point at $x^*=(d-b)/(a-b-c+d)$, which is unstable when $a>c$ and $b<d$ and stable when $a<c$ and $b>d$.

In finite population models, stochasticity does not allow the definition of fixed points. However, the boundaries $i=0$ and $i=N$ are absorbing due to the absence of mutations, $T_0^+(\beta)=0$ and $T_N^-(\beta)=0$. For recurrent Markov chains [$T_i^\pm(\beta)>0$ for $0<i<N$], the system will eventually be absorbed at the boundaries. The probability $\phi_i^A(\beta)$ that a given number $i<N$ of A players will reach the absorbing boundary at $i=N$ is an important quantity to describe the process. In addition to this fixation probability, the unconditional and conditional fixation times, $t_i(\beta)$ and $t_i^A(\beta)$, characterize the stochastic process [24,30–32]. These two average times are the expectation values of the number of time steps it needs either to reach any homogenous state (all A or all B) or to reach fixation at all A under the condition that this event occurs. In the following we recall recursions for these three quantities, which can be solved regardless of the details of the birth-death process. Each solution is only based on the microscopic transition probabilities $T_i^\pm(\beta)$.

A. Fixation probability

The probability of fixation $\phi_i^A(\beta)$ describes the probability that i A mutants in a population of $N-i$ B players will reach fixation at all A. Since the homogenous states are absorbing, we have $\phi_0^A(\beta)=0$ as well as $\phi_N^A(\beta)=1$. For all the intermediate states we can write a balance equation for the probability to fixate at all A ($i=N$),

$$0=T_i^-(\beta)(\phi_{i-1}^A(\beta)-\phi_i^A(\beta))+T_i^+(\beta)(\phi_{i+1}^A(\beta)-\phi_i^A(\beta)). \tag{4}$$

With the boundary conditions $\phi_0^A(\beta)=0$ and $\phi_N^A(\beta)=1$, this can be solved recursively [4,24]. We obtain

$$\phi_i^A(\beta)=\frac{1+\sum_{k=1}^{i-1}\prod_{m=1}^{k}\frac{T_m^-(\beta)}{T_m^+(\beta)}}{1+\sum_{k=1}^{N-1}\prod_{m=1}^{k}\frac{T_m^-(\beta)}{T_m^+(\beta)}}. \tag{5}$$

The probability to fixate at the pure state all B starting from i A players is given by $\phi_i^B(\beta)=1-\phi_i^A(\beta)$.

B. Unconditional average fixation time

The average time (measured in elementary time steps) it needs to reach fixation at one of the homogenous states ($i=0$ or $i=N$) starting with i players of type A is denoted by $t_i(\beta)$. Obviously, $t_0(\beta)=0$ and $t_N(\beta)=0$. The unconditional fixation times also fulfill a balance equation with the transition probabilities describing the rate of change,

$$t_i(\beta)=1+T_i^-(\beta)t_{i-1}(\beta)+(1-T_i^+(\beta)-T_i^-(\beta))t_i(\beta)+T_i^+(\beta)t_{i+1}(\beta). \tag{6}$$

This is a recursion equation for the unconditional mean exit times or average times of fixation. Its solution reads as [32,33]

$$t_i(\beta)=\sum_{k=i}^{N-1}\sum_{l=1}^{k}\frac{1}{T_l^+(\beta)}\prod_{m=l+1}^{k}\frac{T_m^-(\beta)}{T_m^+(\beta)}-t_1(\beta)\sum_{k=i}^{N-1}\prod_{m=1}^{k}\frac{T_m^-(\beta)}{T_m^+(\beta)}, \tag{7}$$

$$t_1(\beta)=\phi_1^A(\beta)\sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{1}{T_l^+(\beta)}\prod_{m=l+1}^{k}\frac{T_m^-(\beta)}{T_m^+(\beta)}. \tag{8}$$

Next, we address the time it takes to reach a particular absorbing state.

C. Conditional average fixation time

Under the condition that the process reaches the absorbing state all A, $i=N$, the average time of fixation starting from i, is $t_i^A(\beta)$. Following [24], we start from the recursion

$$\phi_i^A(\beta)t_i^A(\beta)=T_i^-(\beta)\phi_{i-1}(\beta)[t_{i-1}(\beta)^A+1]+[1-T_i^+(\beta)-T_i^-(\beta)]\phi_i^A(\beta)[t_i^A(\beta)+1]+T_i^+(\beta)\phi_{i+1}(\beta)[t_{i+1}(\beta)+1]. \tag{9}$$

The conditional average fixation time is conditioned upon fixation at all A, which occurs with probability $\phi_i^A(\beta)$. Thus,

the product of probability and conditional time of fixation appears in the recursion. There can be a finite expectation value even for vanishing fixation probability because $\phi_i^A(\beta)t_i^A(\beta)\to 0$ does not imply $t_i^A(\beta)\to 0$. For the average fixation time under the condition of absorption at all A we find [24,32,34,35]

$$t_i^A(\beta)=\frac{1}{\phi_i^A(\beta)}\sum_{k=i}^{N-1}\sum_{l=1}^{k}\frac{\phi_l^A(\beta)}{T_l^+(\beta)}\prod_{m=l+1}^{k}\frac{T_m^-(\beta)}{T_m^+(\beta)} - t_1^A(\beta)\frac{\phi_1^A(\beta)}{\phi_i^A(\beta)}\sum_{k=i}^{N-1}\prod_{m=1}^{k}\frac{T_m^-(\beta)}{T_m^+(\beta)}, \tag{10}$$

$$t_1^A(\beta)=\sum_{k=1}^{N-1}\sum_{l=1}^{k}\frac{\phi_l^A(\beta)}{T_l^+(\beta)}\prod_{m=l+1}^{k}\frac{T_m^-(\beta)}{T_m^+(\beta)}. \tag{11}$$

There is an analogous expression for the fixation time under the condition that strategy B gets fixed in the population, $t_i^B(\beta)$ [32].

As expressions (5), (7), and (10) are functions of the $T_i^{\pm}(\beta)$, the study of a strong selection limit has to be performed in the transition probabilities. In the next section, we introduce a process with the analytical strong selection limit $T_i^+(\beta\to\infty)\to 1$ and $T_i^-(\beta\to\infty)\to 0$ (or the other way around), and we show that the resulting dynamics is fully deterministic in this limit.

III. MORAN PROCESS

A. Selection at birth and random death

A standard model for evolutionary dynamics in finite populations is the frequency-dependent Moran process [22]. This process incorporates the following steps: an individual is selected at random but proportional to its fitness. This individual produces identical offspring. The offspring replaces an individual randomly selected for death. Fitness f is a convex combination of the average payoffs from the game, π_i^A and π_i^B, and a background fitness, which is usually set to one. Thus, we have $f_i^A(\beta)=1-\beta+\beta\pi_i^A$ and $f_i^B(\beta)=1-\beta+\beta\pi_i^B$. The quantity $0\le\beta\le\beta_{\max}\le 1$ determines the intensity of selection. The transition probabilities of the Moran process are thus given by

$$T_i^+(\beta)=\underbrace{\frac{if_i^A(\beta)}{if_i^A(\beta)+(N-i)f_i^B(\beta)}}_{\text{Selection at birth}}\times\underbrace{\frac{N-i}{N}}_{\text{Random death}}, \tag{12a}$$

$$T_i^-(\beta)=\underbrace{\frac{(N-i)f_i^B(\beta)}{if_i^A(\beta)+(N-i)f_i^B(\beta)}}_{\text{Selection at birth}}\times\underbrace{\frac{i}{N}}_{\text{Random death}}. \tag{12b}$$

Selecting proportional to fitness implies that fitness is positive. Thus, for payoff matrices with negative entries, the intensity of selection β cannot exceed a threshold $\beta_{\max}$. This process does not have a generic deterministic limit with arbitrarily strong selection intensity and remains stochastic with random death.

A possibility to extend the Moran process to higher intensities of selection is to choose fitness as an exponential function of the payoff; i.e., $f_i^A(\beta)=\exp(+\beta\pi_i^A)$ and $f_i^B(\beta)=\exp(+\beta\pi_i^B)$ [36,37]. Now, the intensity of selection β can be any positive number. For $\beta\to\infty$, the fitter individual is always selected for reproduction [compare Eqs. (12a) and (12b)]. The direction of the process becomes deterministic. But due to random death, the system can remain longer or shorter in a particular state. Thus, the process remains stochastic in what concerns the times to fixation. With two strategies, we have a semideterministic process with deterministic direction and stochastic speed [29]. If there are more than two strategies, random death can also change the composition of the less fit types in the population. This can affect the direction of selection as the fittest type can change due to frequency-dependent selection.

B. Selection at birth and death

Here, we introduce a birth-death process that recovers the usual results for weak selection but also leads to fully deterministic asymptotic behavior for strong selection. The process has deterministic microscopic dynamics if the $T_i^{\pm}(\beta)$ are zero or one. As in the standard Moran process, we assume that selection at birth is proportional to fitness. In addition to producing less offspring, individuals with a lower fitness now have a higher probability to die. A simple way to incorporate this is to select at death proportional to inverse fitness. To ensure that fitness is a positive number, we follow the approach discussed above and define fitness as an exponential function of the payoff. This leads to the transition probabilities

$$T_i^+(\beta)=\underbrace{\frac{ie^{+\beta_b\pi_i^A}}{ie^{+\beta_b\pi_i^A}+(N-i)e^{+\beta_b\pi_i^B}}}_{\text{Selection at birth}}\times\underbrace{\frac{(N-i)e^{-\beta_d\pi_i^B}}{ie^{-\beta_d\pi_i^A}+(N-i)e^{-\beta_d\pi_i^B}}}_{\text{Selection at death}}, \tag{13a}$$

$$T_i^-(\beta)=\underbrace{\frac{(N-i)e^{+\beta_b\pi_i^B}}{ie^{+\beta_b\pi_i^A}+(N-i)e^{+\beta_b\pi_i^B}}}_{\text{Selection at birth}}\times\underbrace{\frac{ie^{-\beta_d\pi_i^A}}{ie^{-\beta_d\pi_i^A}+(N-i)e^{-\beta_d\pi_i^B}}}_{\text{Selection at death}}. \tag{13b}$$

β_b is the intensity of selection at birth and β_d is the intensity of selection at death. For $\beta_d=0$, we recover the process discussed in Sec. III A. It is known that under weak selection many birth-death processes have the same general properties [25,38,39]. Especially, for $\beta_{b,d}\ll 1$ the behavior of the Moran process is recovered [29,30].

For simplicity, we assume $\beta=\beta_b=\beta_d$ in the following. The transition probabilities can be written as

$$T_i^+(\beta)=\frac{i}{i+(N-i)e^{-\beta\Delta\pi_i}}\frac{N-i}{ie^{-\beta\Delta\pi_i}+N-i}, \tag{14a}$$

$$T_i^-(\beta)=\frac{N-i}{ie^{+\beta\Delta\pi_i}+N-i}\frac{i}{i+(N-i)e^{+\beta\Delta\pi_i}}. \tag{14b}$$

Thus, as far as the payoffs are concerned, the transition probabilities only depend on the difference between the

frequency-dependent average payoffs, $\Delta\pi_i = \pi_i^A - \pi_i^B$.

The case of $\Delta\pi_i = 0$ is a form of neutral selection. In this case, the transition probabilities are $T_i^{\pm}(\beta) \equiv (N-i)/N^2$, for arbitrary β. Note that for neutral selection, moving into one direction is equally probable as moving into the other $T_i^+(0) = T_i^-(0)$. But the probability to leave a given interior state changes with i, $T_i^{\pm}(0) \neq T_j^{\pm}(0)$ for $i \neq j$.

For arbitrary β, the ratio of the transition probabilities reduces to an exponential function of the payoff difference,

$$\frac{T_i^-(\beta)}{T_i^+(\beta)} = e^{-2\beta\Delta\pi_i}. \tag{15}$$

Hence, the fixation probabilities of the process can be approximated with the closed expressions derived in [28] after rescaling the intensity of selection by a factor of 2. From this, it is clear that the usual weak selection behavior is recovered.

IV. STRONG SELECTION

For strong selection, $\beta \to \infty$, the asymptotic behavior of the transition probabilities depends only on the sign of the payoff difference. We focus on the generic cases $\Delta\pi_i \lessgtr 0$ to discuss this limit. The limiting cases can be obtained from Eqs. (14a) and (14b) and yield

$$\lim_{\beta\to\infty} T_i^+(\beta) = \begin{cases} 0 & \text{for } \Delta\pi_i < 0 \\ 1 & \text{for } \Delta\pi_i > 0 \end{cases}, \tag{16}$$

as well as

$$\lim_{\beta\to\infty} T_i^-(\beta) = \begin{cases} 1 & \text{for } \Delta\pi_i < 0 \\ 0 & \text{for } \Delta\pi_i > 0 \end{cases}. \tag{17}$$

Since $\lim_{\beta\to\infty}(T_i^+(\beta) + T_i^-(\beta)) = 1$, the probability to stay in the state i $(0 < i < N)$ vanishes for $\beta \to \infty$ and nontrivial payoff difference, $\Delta\pi_i \neq 0$. Thus, we have a fully deterministic process for arbitrary population size. With this, we consider the fixation probability $\phi_i^A(\beta)$ and average fixation times $t_i(\beta)$ and $t_i^A(\beta)$ in the limiting case of strong selection. In the following let $\phi_i^A(\infty)$ as well as $t_i(\infty)$ and $t_i^A(\infty)$ denote the finite asymptotic $(\beta \to \infty)$ values of the fixation probability and times. We identify them in terms of the initial frequency i, depending on the average payoff difference for the process introduced above under strong selection.

A. Fixation probability

Starting with equation (4) and inserting the limiting cases of $T_i^{\pm}(\beta)$ leads to

$$\phi_i^A(\infty) = (\lim_{\beta\to\infty} T_i^-(\beta))\phi_\infty^A(i-1) + (\lim_{\beta\to\infty} T_i^+(\beta))\phi_\infty^A(i+1). \tag{18}$$

That is, in the strong selection limit we have a very simple recursion for the asymptotic value of the fixation probability, depending on the sign of the payoff difference $\Delta\pi_i$. When strategy A dominates strategy B $(a > c$ and $b > d)$, we have $\Delta\pi_i > 0$. For $0 < i < N$, this yields $\lim_{\beta\to\infty} T_i^-(\beta) = 0$, and $\lim_{\beta\to\infty} T_i^+(\beta) = 1$, which results in $\phi_i^A(\infty) = 1 - \delta_{0,i}$. In other words, the probability to reach the state with all B individuals is zero, except if there are no A individuals initially. Equivalently, for dominance of strategy B we obtain $\phi_i^A(\infty) = \delta_{N,i}$. More interesting cases are found when $\Delta\pi_i$ changes its sign, which occurs at $i^* = (N(d-b)+a-d)/(a-b-c+d)$ when $a > c$ and $d > b$ or when $a < c$ and $d < b$. These are two important classes of games: coordination games and coexistence games.

Let us first focus on coordination games $(a > c$ and $d > b)$. In these games, the threshold value i^* cannot be crossed for infinitely large systems with deterministic dynamics [40]. For finite systems under strong selection, we observe something similar. The payoff difference $\Delta\pi_i$ changes sign from negative to positive and selection points always away from i^* toward the boundaries. Depending on the initial condition $i \gtrless i^*$, the fixation probability $\phi_i^A(\infty)$ is one or zero.

(i) If $i < i^*$, $\Delta\pi_i$ is negative and with Eqs. (16) and (17) we have $\phi_i^A(\infty) = \phi_{i-1}^A(\infty)$. We start the recursion for the fixation probabilities with $\phi_1^A(\infty) = \phi_0^A(\infty) = 0$. This yields $\phi_{i<i^*}^A(\infty) = 0$.

(ii) For $i > i^*$, $\Delta\pi_i$ is positive and Eqs. (16) and (17) yield the recursion $\phi_i^A(\infty) = \phi_{i+1}^A(\infty)$. Starting with the maximal i we obtain $\phi_{N-1}^A(\infty) = \phi_N^A(\infty) = 1$ and thus $\phi_{i>i^*}^A(\infty) = 1$.

(iii) If i^* happens to be an integer value and the system starts there, the first step has equal probabilities, $T_{i^*}^+(\beta) = T_{i^*}^-(\beta) = \frac{1}{2}$. This leads to $\phi_{i^*}^A(\infty) = \frac{1}{2}$.

In summary, for the fixation probability we find

$$\phi_i^A(\infty) = \begin{cases} 0 & \text{for } i < i^* \\ \frac{1}{2} & \text{for } i = i^* \\ 1 & \text{for } i > i^* \end{cases}. \tag{19}$$

This is clearly what is to be expected because A is selected for $i > i^*$ and B is selected for $i < i^*$, (see Fig. 1). Dominance of strategy A can be seen as a special case of coexistence with $i^* < 0$.

Next, we consider coexistence games with $a < c$ and $d < b$. In this case, $\Delta\pi_i$ changes sign from positive to negative and selection points always away from the boundaries toward i^*. For strong selection, the system gets trapped and fixation never occurs.

(i) If i^* is an integer, the system switches from i^* to $i^* \pm 1$ with equal probability. From $i^* \pm 1$, it always returns to i^*.

(ii) If i^* is not an integer, we observe deterministic flipping between the two neighboring states $i_1 < i^*$ and $i_2 > i^*$.

Since fixation never occurs in coexistence games, it does not make sense to compute the asymptotic value of the fixation probability. Formally, the probability to get absorbed in all A converges to 1 if $i^* > N/2$ and to 0 otherwise. However, it turns out that the fixation times diverge.

B. Unconditional average fixation time

The average time it takes for a number i of A players to either become extinct or take over the population, $t_i(\beta)$, can

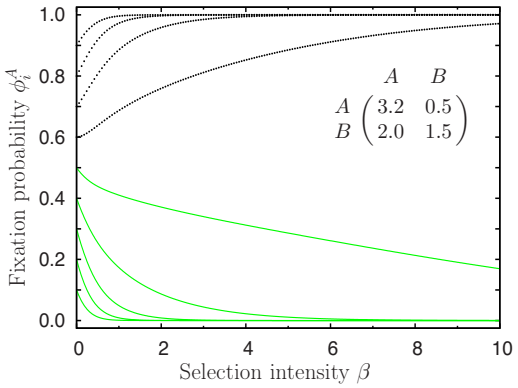

FIG. 1. (Color online) The fixation probability as a function of selection intensity for a coordination game ($a>c$, $b<d$), given by Eq. (5), with selection at birth and death [Eqs. (14a) and (14b)]. From the payoff matrix given in the figure, we obtain $i^*=\frac{17}{22}+\frac{5}{11}N$, which gives $i^*\approx 5.32$ for our numerical example with $N=10$. With increasing selection intensity β, for any $l<i^*$ we have $\phi_l^A(\beta)\to 0$ (full lines), whereas for any $m>i^*$ we have $\phi_m^A(\beta)\to 1$ (dotted lines). The $\phi_i^A(\beta)$ for each i can be identified via its neutral value $\phi_i^A(0)=\frac{i}{N}$.

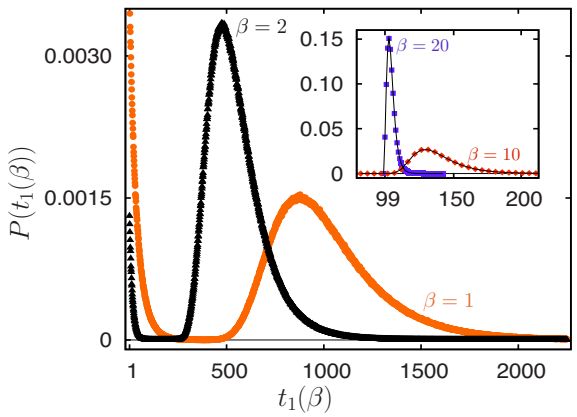

FIG. 2. (Color online) Dominance of strategy A. We show the probability distribution of the unconditional fixation time (measured in elementary time steps) of a single A player in a population of $N-1$ B players. For $\beta=1$ and $\beta=2$, the distribution has two peaks corresponding to the two absorbing boundaries. For stronger selection (inset), the probability that the advantageous A individual goes extinct becomes small and fixation takes at least $N-1$ time steps. In this case, the distribution becomes single peaked. For $\beta\to\infty$, the distribution converges to a delta peak at $t_1(\infty)=N-1$ (payoff matrix $a=2.2$, $b=1.5$, $c=2$, and $d=0.5$, population size $N=100$, and histograms obtained from 10^7 realizations. Lines are guides to the eyes).

be found by solving Eq. (6) recursively. To examine the limit of strong selection, we perform the limit on both sides of the balance equation, assuming that there exists an asymptotic value $t_i(\infty)$ of the unconditional fixation time. With the previous analysis of the transition probabilities, this leads to

$$t_i(\infty)=1+(\lim_{\beta\to\infty} T_i^-(\beta))t_{i-1}(\infty)+(\lim_{\beta\to\infty} T_i^+(\beta))t_{i+1}(\infty). \tag{20}$$

This strong selection recursion has to be analyzed for the two different cases of behavior at the threshold i^*, coordination and coexistence. Again, we first examine the coordination game ($a>c$ and $d>b$).

(i) For $i<i^*$, the payoff difference is negative, $\Delta\pi_i<0$. The recursion amounts to $t_i(\infty)=1+t_{i-1}(\infty)$ because $T^+(i)\to 0$ whereas $T_i^-(\beta)\to 1$. With $t_0(\infty)=0$ at the boundary we have $t_1(\infty)=1$, $t_2(\infty)=1+t_1(\infty)=2$, and eventually $t_i(\infty)=i$.

(ii) For $i>i^*$ the payoff difference is $\Delta\pi_i>0$. The recursion from Eq. (20) is $t_i(\infty)=1+t_{i+1}(\infty)$. The transition probabilities $T^{\pm}(i)$ behave exactly in the opposite way as before. The time starting from next to the absorbing boundary is $t_{N-1}(\infty)=1+t_N(\infty)=1$. Hence, we have $t_{N-k}(\infty)=k$, or with $k=N-i$, the unconditional average time is $t_i(\infty)=N-i$.

(iii) If the threshold is an integer and the system is initiated there the number of steps needed to fixate is i^* or $N-i^*$ with equal probability. Thus, we can compute the average time with the previous findings, $t_{i^*}(\infty)=(i^*+N-i^*)/2=N/2$.

In summary, depending on the starting point i^*, the asymptotic value for the unconditional average fixation time in a coordination game is

$$t_i(\infty)=\begin{cases} i & \text{for } i<i^*, \\ \dfrac{N}{2} & \text{for } i=i^*, \\ N-i & \text{for } i>i^*. \end{cases} \tag{21}$$

In the strong selection limit $t_i(\infty)$ converges to the distance between initial state and the final state, as expected from deterministic motion.

We can also infer the dynamics for games in which one strategy dominates. When strategy A dominates, we can formally set $i^*<0$ and obtain $t_i(\infty)=N-i$ (cf. Fig. 2). When strategy B dominates, the equivalent procedure yields $t_i(\infty)=i$.

In case of a coexistence game, the system gets trapped around i^* and cannot reach the absorbing boundaries. As expected, the recursions lead to $t_i(\infty)\to\infty$.

C. Conditional average fixation time

If i A players take over the population, the asymptotic fixation time under this condition, $t_i^A(\infty)$, can be obtained by solving the balance [Eq. (9)] recursively. However, this situation is more complex as we have to consider the fixation probability and the conditional fixation time in a combined way. Introducing the asymptotic value $\theta_i^A(\infty)=\phi_i^A(\infty)t_i^A(\infty)$, recursion (9) yields

$$\theta_i^A(\infty)=(\lim_{\beta\to\infty} T_i^-(\beta))(\theta_{i-1}^A(\infty)+\phi_\infty^A(i-1)) + (\lim_{\beta\to\infty} T_i^+(\beta))(\theta_{i+1}^A(\infty)+\phi_\infty^A(i+1)). \tag{22}$$

The formulation of a similar equation for $\theta_i^B(\infty)=(1$

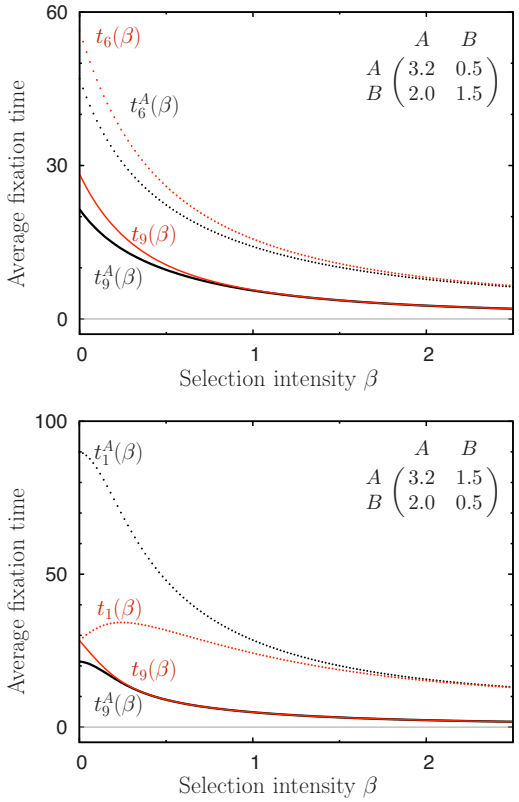

FIG. 3. (Color online) Unconditional $[t_i(\beta)]$ and conditional $[t_i^A(\beta)]$ average fixation times (measured in elementary time steps) as a function of the intensity of selection for a coordination game (top) and a game in which A dominates (bottom). The payoff matrices of the games are given in the figures, the population size is $N=10$. Top: in a coordination game ($a>c$, $b<d$), the conditional and unconditional fixation times converge to $N-i$ for $\beta\to\infty$ if initially more than $i^*=117/22\approx 5.32$ individuals play A [compare Eq. (21)]. The lines show the initials states $i=6$ (dotted lines) and $i=9$ (full lines). Bottom: when A dominates B ($a>c$, $b>d$), the unconditional fixation time $t_1(\beta)$ first increases with β. For any initial condition i, $t_i(\beta)$ and $t_i^A(\beta)$ converge to $N-i$ in the limit of strong selection. The initials states are $i=1$ (dotted lines) and $i=9$ (full lines).

$-\phi_i^A(\infty))$ $t_i^B(\infty)$ is straightforward. Both are analyzed regarding the different behaviors at either side of the threshold i^*.

For the coordination game the system reaches the absorbing boundaries after a finite time.

(i) If $i>i^*$, the system fixates at $i=N$ with probability $\phi_i^A(\infty)=1$. Thus, $\theta_i^A(\infty)=t_i^A(\infty)$ and we recover the same recursion as for the unconditional fixation time. This yields $t_i^A(\infty)=t_i(\infty)=N-i$ (see Fig. 3).

(ii) If $i<i^*$, the system fixates at $i=0$, $\phi_i^A(\infty)=0$. Thus, we cannot formulate a meaningful recursion for $t_i^A(\infty)$. In this case we observe $T_i^-(\beta)\to 1$, $T_i^+(\beta)\to 0$, and we can only make a statement for $t_i^B(\infty)$, which results in $t_i^B(\beta)=i$.

(iii) If $i=i^*$ is an integer, the system is not fully deterministic as fixation of A and fixation of B are observed with equal probability $\frac{1}{2}$. In this case, we obtain $t_{i^*}^A(\infty)=N-i^*$ and $t_{i^*}^B(\infty)=i^*$.

In a regime where A always performs better than B the unconditional fixation time $t_i^A(\infty)$ is equal to the conditional fixation time $t_i(\infty)$ (see Fig. 3). Equivalently, when B always performs better, we have $t_i^B(\infty)=t_i(\infty)$.

For a coexistence game, the system does not reach any of the boundaries but is always dragged toward i^*, as discussed before. Recursion (22) for $t_i^A(\infty)$ or its equivalent for $t_i^B(\infty)$ is not meaningful here because they contain the fixation probabilities. However, in this case all fixation times diverge with β.

In this section, we have derived asymptotic values for the birth-death process with selection at birth and selection at death. We have identified the underlying games that lead to a fully deterministic process in the limit of strong selection. As we have seen, the difference of the average payoffs $\Delta\pi_i$ as a function of the relative abundance of type A plays an important role.

V. GAMES WITH THREE STRATEGIES

Here, we demonstrate that the process we have introduced above leads to rather simple and often deterministic dynamics even in more complex situations. We focus on games with two players and three strategies with cyclic dominance [41–51].

Cyclic dominance among three strategies corresponds to rock-paper-scissors games, where each strategy can be beaten by another one: rock crushes scissors, scissors cut paper, and paper wraps rock. In general, the payoff for winning does not have to be equal to the payoff for losing, which leads to nonzero-sum games. For simplicity, we set the payoff for a tie to zero. Setting the winners payoff to one and the losers payoff to $-s\leq 0$, the 3×3 payoff matrix reads as

$$\begin{array}{c} \\ R \\ P \\ S \end{array}\begin{array}{c} \begin{array}{ccc} R & P & S \end{array} \\ \begin{pmatrix} 0 & -s & 1 \\ 1 & 0 & -s \\ -s & 1 & 0 \end{pmatrix} \end{array} . \tag{23}$$

For infinite populations, the state of the system is defined by the frequencies of the three strategies, x_R, x_P, and x_S. Thus, the state space is the simplex $S_3\subset\mathbb{R}^2$, an equilateral triangle between the three states all R, all P, and all S. Apart from the three trivial equilibria, the replicator dynamics has an interior equilibrium at $(x_R,x_P,x_S)^*=(\frac{1}{3},\frac{1}{3},\frac{1}{3})$, which follows from the symmetry of the system. The parameter s determines whether the interior equilibrium is asymptotically stable (the system spirals inwards toward the interior fixed point for $s<1$) or unstable (the system spirals out toward a heteroclinic cycle along the boundaries for $s>1$). In the zero-sum game with $s=1$, the system oscillates around the interior equilibrium with the Hamiltonian $-x_Rx_Px_S$ being a constant of motion [4,8].

In finite, well-mixed populations, the state space is only a subset of $(N+1)(N+2)/2$ states within the simplex S_3 (cf. Fig. 4). Moreover, the dynamics is typically stochastic. Prop-

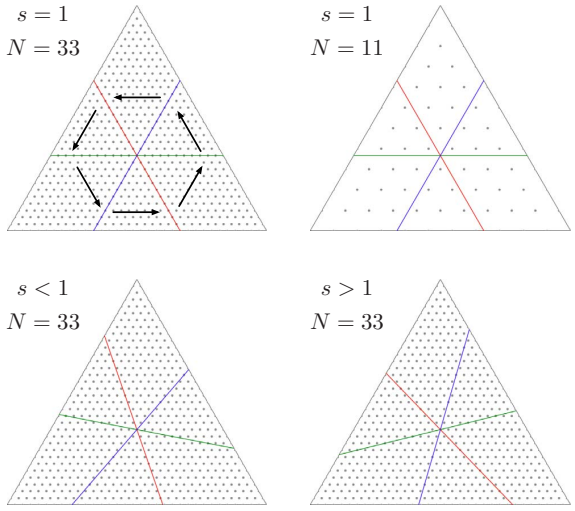

FIG. 4. (Color online) The discrete simplex of the rock-paper-scissors game for the different ranges of s. The three strategies are arranged in such a way that cyclic dominance is counterclockwise. For $N=33$ and $s=1$ (top left), the three lines of equal payoffs defined by Eqs. (34) are parallel to the boundaries of the simplex. Changing the population size to $N=11$ (top right) does not change these lines but only the state space of the system indicated by dots. For example, the system can no longer access the center of the simplex. With decreasing s, the three lines of equal payoffs are rotated clockwise (bottom left, $s=0.5$). With increasing s, these lines are rotated counterclockwise (bottom right, $s=2.5$). Only in special cases, the three lines of equal payoffs defined by Eqs. (34) intersect with the possible states of the system. The arrows in the upper left figure indicate the direction of selection as it is induced by the cyclic dominance of the three strategies.

erties such as the average drift for a Moran process or the average time to reach the absorbing boundaries are attainable for weak selection [46,50]. To analyze the strong selection limit, we adopt the evolutionary process with selection at birth and death discussed above for 2×2 games. Starting with the payoffs from Eq. (23) in a well-mixed population the average payoffs read as

$$\pi_R = i_S - i_P s, \tag{24}$$

$$\pi_P = i_R - i_S s, \tag{25}$$

$$\pi_S = i_P - i_R s, \tag{26}$$

where i_R, i_P, and $i_S=N-i_R-i_P$ are the number of individuals playing rock, paper, or scissors in a population of size N, respectively. Individuals are selected proportional to fitness at birth and proportional to inverse fitness at death, both with the intensity of selection β. The fitness of strategy X is given by $f_X=\exp[+\beta\pi_X]$. The dynamics on the discrete finite set of states is governed by six transition probabilities in each state. The transition probabilities in each state (i_R,i_P,i_S) to change to one of the six neighboring states are thus given by

$$T_{Y\to X}(i_R,i_P,i_S) = \underbrace{\frac{i_X f_X}{\sum_Z i_Z f_Z}}_{\text{birth}} \times \underbrace{\frac{i_Y f_Y^{-1}}{\sum_Z i_Z f_Z^{-1}}}_{\text{death}}, \tag{27}$$

where X, Y, and Z stand for R, P, or S. Note that the probability to stay in the given state is given by $T_{R\to R}(i_R,i_P,i_S)+T_{P\to P}(i_R,i_P,i_S)+T_{S\to S}(i_R,i_P,i_S)$. For strong selection, $\beta\to\infty$, the system moves from each state into one direction with probability one unless two payoffs are identical. In the following we address how this direction depends on the payoffs in each state and on the parameter s.

Let us first assume that for given state (i_R,i_P,i_S), we have the unique ordering of the average payoffs from Eqs. (24)–(26). Let π_1 denote the largest and π_3 denote the lowest value, i.e., $\pi_1>\pi_2>\pi_3$. The number of individuals playing the according strategies can be denoted as i_1, i_2, and i_3. For $T_{3\to 1}$, we have

$$T_{3\to 1} = \frac{i_1 e^{\beta\pi_1}}{i_1 e^{\beta\pi_1} + i_2 e^{\beta\pi_2} + i_3 e^{\beta\pi_3}} \times \frac{i_3 e^{-\beta\pi_3}}{i_1 e^{-\beta\pi_1} + i_2 e^{-\beta\pi_2} + i_3 e^{-\beta\pi_3}} \tag{28}$$

$$= \frac{i_1}{i_1 + i_2 e^{-\beta(\pi_1-\pi_2)} + i_3 e^{-\beta(\pi_1-\pi_3)}} \times \frac{i_3}{i_1 e^{-\beta(\pi_1-\pi_3)} + i_2 e^{-\beta(\pi_2-\pi_3)} + i_3}, \tag{29}$$

where $\pi_1-\pi_2>0$, $\pi_1-\pi_3>0$, as well as $\pi_2-\pi_3>0$. For $\beta\to\infty$, this leads to

$$\lim_{\beta\to\infty} T_{3\to 1} = 1. \tag{30}$$

All the other transition probabilities vanish. In each reproductive event, an individual with the largest payoff replaces an individual with the smallest payoff. This holds for any unique ordering of the three payoffs.

If the payoffs are not in unique order, that is, if two or more payoffs are equal, at least two probabilities become nontrivial. This yields the following three scenarios:

(i) for $\pi_1>\pi_2=\pi_3$, the individual with the highest average payoff is certainly selected at birth. But selection at death will remove an individual playing one of the two remaining strategies with probability given by their abundance. We find

$$\lim_{\beta\to\infty} T_{2\to 1} = \frac{i_2}{i_2+i_3}, \tag{31a}$$

and

$$\lim_{\beta\to\infty} T_{3\to 1} = \frac{i_3}{i_2+i_3}. \tag{31b}$$

Obviously, we have $T_{2\to 1}+T_{3\to 1}=1$.

(ii) For $\pi_1=\pi_2>\pi_3$, the individual with the lowest payoff is selected for death with certainty, but selection at birth is still probabilistic. It is easy to see that

$$\lim_{\beta\to\infty} T_{3\to 1} = \frac{i_1}{i_1 + i_2}, \tag{32a}$$

and

$$\lim_{\beta\to\infty} T_{3\to 2} = \frac{i_2}{i_1 + i_2}. \tag{32b}$$

Thus, $T_{3\to 1} + T_{3\to 2} = 1$.

(iii) For $\pi_1 = \pi_2 = \pi_3$, selection is stochastic at birth and at death. In this case, we find

$$\lim_{\beta\to\infty} T_{X\to Y} = \frac{i_X}{N}\frac{i_Y}{N}. \tag{33}$$

As expected, we have $\Sigma_{X,Y} T_{X\to Y} = 1$.

These results are valid if two or more payoffs are equal at a given lattice site, which is only obvious for $s=1$ and might not occur for any lattice site at all in the general case of $s \neq 1$.

With Eqs. (24)–(26), we can compute the point sets in the simplex where two or all three average payoffs are equal, depending on the value of s. For $\pi_R = \pi_P = \pi_S$ this is only the center of the simplex, independent of s. For two payoffs being equal, we obtain the three linear equations

$$\pi_R = \pi_S \quad \text{at} \quad i_P(s+2) = N - i_R(1-s),$$

$$\pi_S = \pi_P \quad \text{at} \quad i_P(s-1) = Ns - i_R(1+2s),$$

$$\pi_R = \pi_P \quad \text{at} \quad i_P(2s+1) = N(1+s) - i_R(2+s). \tag{34}$$

However, it is not obvious at which of the discrete states (i_R, i_P, i_S) we can observe equal average payoffs of two strategies if the loser's payoff is not equal to -1 and especially if the system size is not a multiple of three (compare Fig. 4).

For simplicity we thus concentrate on the case of N being a multiple of three. In general, the strong selection behavior of the system is determined by the transition probabilities near the lines of equal average payoffs. When the population size N is a multiple of three, the dynamics for the three different cases of $s=1$, $s<1$, or $s>1$ is as follows:

(i) for $s=1$, we have $\pi_R = \pi_S$ at $i_P = N/3$, $\pi_S = \pi_P$ at $i_R = N/3$, and $\pi_R = \pi_P$ at $i_S = N/3$. Hence, there is always stochastic movement induced by Eqs. (31a), (31b), (32a), (32b), and (33). Apart from these points, the direction of selection is indeed deterministic, which means that an individual with higher payoff always replaces an individual with a lower one. In certain regimes, near the corners of the simplex and along the edges the initial condition determines the final state where the system fixates. In a much larger area, however, the system fixates stochastically. In Fig. 5 we illustrate this by showing one fixation probability obtained from numerical simulations of the birth-death process. Due to the symmetry of the system, this fixation probability can either be ϕ^R, ϕ^P, or ϕ^S.

For $s<1$, the lines where payoffs are equal rotate clockwise in our setup of cyclic dominance. In general, no states of the finite population system coincide with the lines of equal payoffs (except for special cases) (see Fig. 4). But as soon as the process crosses these lines, it changes direction.

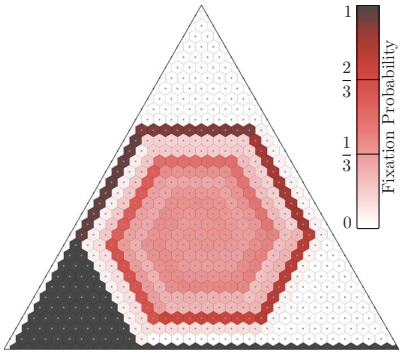

FIG. 5. (Color online) Zero-sum rock-paper-scissors game. We show the probability that the system fixates at the lower right corner, e. g., ϕ^R, in a system with $N=33$, and $s=1$ for strong selection $\beta\to\infty$, depending on the initial state (i_R, i_P, i_S): as discussed in the main text, fixation is stochastic. Near the corners and along the edges fixation is deterministic. In a central area of the simplex, the system spirals out in a probabilistic fashion. The closer the initial condition is to the center, the closer the probability to get absorbed in a given state is to one-third (fixation probabilities obtained from numerical simulations over 10^4 realizations).

Near the corners and on the edges the system fixates deterministically, but in a central area the process spirals inwards if it does not hit the boundary of the system. However, it turns out that there is a largest limit cycle (LLC) depending on s and N and that there can be several other limit cycles inside the LLC. We demonstrate this finding as it is obtained from numerical simulations in Fig. 6, showing one sample trajectory that ends as the LLC. Note that the term cycle actually refers to a hexagon.

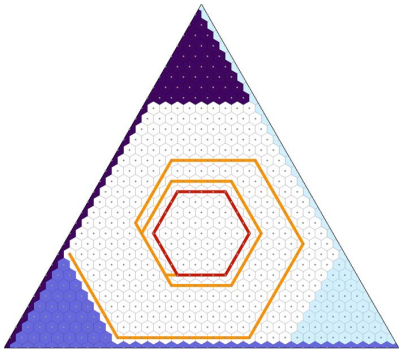

FIG. 6. (Color online) Positive-sum rock-paper-scissors game. For a population size of $N=33$ and $s=0.5$, the dynamics is such that fixation does not occur in a central area, but it is deterministic near the corners. For instance, any initial condition in the darkest area will lead to the pure state at the lower left. The white area marks the sites from which, chosen as initial condition, the system does not fixate but approaches a closed cycle. We show an example trajectory of the system that ends on the largest of these cycles (central hexagon) starting from the initial state $(i_R, i_P, i_S) = (1, 9, 23)$. Inside this largest cycle, there are other cycles such that every site except the center is already on such a cycle.

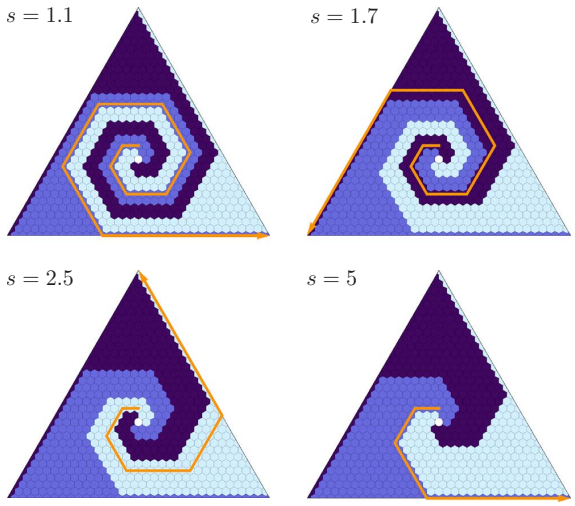

FIG. 7. (Color online) Negative-sum rock-paper-scissors game. Deterministic fixation for a population of size $N=33$ and different $s>1$. The dynamics is deterministic everywhere, except in the center (white dot), where all three payoffs are the same. Depending on the initial state, the system fixates to a given pure state. This is indicated by the three different shadings. For instance, when the system is initially at a site in darkest shading, it will fixate to the pure state at the lower left with probability one. We show one example trajectory (arrow) starting from the initial state $(i_R, i_P, i_S) = (10, 13, 10)$. By increasing s, we can vary the state that is ultimately reached by the system.

For $s>1$, as the lines of equal payoffs rotate counterclockwise (Fig. 4) the system spirals outwards in a deterministic fashion. The movement is no longer deterministic only near the corners and along the edges but everywhere (except for the center) (compare Fig. 7. This means that if $s>1$, we observe deterministic fixation depending on the initial condition.

In this section, we have shown that a birth-death process with exponential payoff to fitness mapping and selection at birth and death is able to induce deterministic movement in the strong selection limit even in 3×3 games. For the transition probabilities $T_{Y\to X}$ this limit can be performed analytically. It turns out that the microscopic dynamics is dependent only on the hierarchy of the average payoffs. As for finite systems an analytic description of the fixation probabilities (and times) is lacking; further examination of this system has to be numerical. Under strong selection the patterns that emerge show a very interesting regularity; it turns out that apart from population size, the results are dependent on the parameter s.

VI. DISCUSSION

The standard approaches to evolutionary game dynamics such as the Moran process or pairwise comparison based on the Fermi rule lead to stochastic dynamics in finite populations [12]. Even if the direction of selection becomes deterministic, the time scale typically remains stochastic and leads to a distribution of the average fixation or mean exit times [29]. Moreover, these standard approaches do not lead to a deterministic direction of selection in games with more than two different strategies [52]. Here, we have introduced a process with selection at birth and at death. This process allows to interpolate between weak selection, usually considered in evolutionary biology, and arbitrary strong selection, such that in the extreme case the worst performing individual is always replaced by a copy of the best performing individual. This kind of selection is sometimes used in evolutionary optimization [36,53]. While the limiting case itself may not be of most interest for real biological or social systems, which are always subject to stochastic noise, we have discussed the most important features of this limit. In particular, it reveals speed limits of evolutionary dynamics in 2×2 games that stochastic dynamics cannot cross and shows that in games with more than two strategies, the limiting deterministic dynamics can have a crucial dependence on the initial conditions.

ACKNOWLEDGMENT

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CHAPTER 3

Stability in structured populations with heterozygote disadvantage

Here, the manuscripts [Altrock et al., 2010b], and [Altrock et al., 2011] are discussed. Each of the following two sections is headed by a survey that serves as an additional motivation and summarizes the main findings. Both sections deal with different aspects of a complex evolutionary system: A model is studied where gene flow mediated by migration between sub-populations of the same kind counterbalances selection.

In the first part, the stability properties of the deterministic equations are considered. By certain symmetry arguments one can characterize a bifurcation pattern, evolutionary stability is controlled by the rate of migration between the sub-populations. Consequences of symmetry loss due to a change in parameter space are discussed.

In the second part, we specifically address demographic fluctuations by defining a two-dimensional variant of the density dependent Moran process. The evolutionary process is subject to migration between two sub-populations. Assuming Mendelian segregation allows one to model the system as if individual alleles are reproducing. Size asymmetry can be tackled, which leads to the extreme case of an evolving island population of finite size which is coupled to a static continent of infinite size. Due to migration, there can be a set of states where the direction of selection is reversed in the island population.

First, we give an introduction to aspects of the model that are common for both following sections. Underdominance refers to a certain fitness configuration in diploid organisms. We consider two alleles A and B of a single gene (i.e., on a single locus). We will denote A the mutant type, and call B the wildtype. An application of this theory is the genetic transformation of insect populations, where a standard genetics notation for the wildtype allele is thus $+$, whereas the mutant, or transformed allele can be denoted by T [Hartl and Clark, 1997].

genotype	$A\,A$	$A\,B$	$B\,B$
name	*mutant homozygote*	*heterozygote*	*wildtype homozygote*
fitness	ν	ω	1
frequency	x^2	$2\,x(1-x)$	$(1-x)^2$

Table 3.1: Two alleles on a single locus. Genotypes are given with their fitness values relative to wildtype fitness. A is the mutant, or transformed allele, B is the wildtype allele. In an infinitely large population, the allele frequency of A can be give as $x \in [0.1]$, the frequency of B as $1-x$. Under random mating, the continuous variable x fully characterizes a single population. For $\nu < 1$, we speak of fitness asymmetry.

Given that there are only two alleles, four generic fitness configurations are possible, compare to Table 3.1.

(*i*) For $\nu = \omega = 1$, we are in the domain of neutral evolution, where evolutionary change can only occur due to finite size fluctuations, see Section 1.4. In the following we assume that there are selective difference for the three genotypes, $\nu \neq \omega \neq 1$.

(*ii*) The cases $\nu > \omega > 1$, or $\nu < \omega < 1$ are called directional selection. One of the alleles always has a fitness advantage, the allele frequency shifts in one direction.

(*iii*) The case of heterozygote advantage is also called overdominance, $\omega > 1$, $\omega > \nu$. The allele frequency x has a stable equilibrium

$$x^* = \frac{\omega - 1}{2\omega - 1 - \nu}, \tag{3.0.1}$$

as a mutant has a fitness advantage when rare, but a disadvantage when abundant. Mutant and wildtype alleles coexist, often in form of heterozygotes.

(*iv*) The complement to overdominance is underdominance, which corresponds to the fitness configuration $\omega < \nu \leq 1$ [Fisher, 1922; Haldane, 1924–1934; Wright, 1931]. This is also called heterozygote disadvantage. In this case there is an unstable equilibrium at x^*, given by Eq. (3.0.1), which refers to bi-stable evolutionary dynamics: The mutant is lost when it appears at a frequency below x^*, but fixates for initial conditions above the unstable point.

The notation of overdominance and underdominance is not to be confused with the term dominance or recessiveness in the laws of Mendelian inheritance [Hartl and Jones, 1998]. Overdominance and underdominance refer to fitness configurations, whereas dominant/recessive mainly refers to a genotype-phenotype mapping.

It is the aim of this section to analyze how stable equilibria can arise in structured populations with underdominance. The focus is on infinitely large populations that admit a deterministic description. The system is analyzed by considering the deterministic version of the Wright-Fisher process, which models the evolutionary change of allele

frequencies by sampling alleles with replacement between discrete and non-overlapping generations. The change of allele frequency in the next generation is proportional to the frequency in the present generation

$$x' = x \frac{f_A(x)}{\langle f \rangle}, \tag{3.0.2}$$

where x, and x' are the frequencies of allele A in the present and the next generation, respectively.

In the analysis of the deterministic system we focus on a dynamical scheme in discrete non-overlapping generations, which is more traditional approach in population genetics [Hartl and Clark, 1997]. However, there is a strong relation between discrete and continuous time evolutionary dynamics; the fixed points are the same [Maynard Smith, 1982]. If one performs the limit of infinitesimally small time steps, an adjusted replicator dynamics in continuous time can be found [Weibull, 1995]. The difference between choosing the timescale as either discrete generations or single reproductive events at any time is important for the definition of a stochastic process. The stochastic model we chose in Section 3.2 is a variant of the frequency dependent Moran process [Taylor et al., 2004]. Hence, in the stochastic model we are in the regime of overlapping generations.

3.1 Using underdominance to bi-stably transform local populations

The simplest case of a structured population emerges when two sub-populations with genetically identical properties are considered. The state space of the two sub-populations is two dimensional, given by the two dynamic variables (x_1,x_2), with $x_i \in [0,1]$. In order to capture the gene flow due to migration between two sub-populations, the rate of migration from each of the two populations is given by a pair of two parameters m_1,m_2.

There the simplest scenario assumes symmetry in migration rates, $m = m_1 = m_2$. In this latter case, a critical migration rate can be found analytically such that for migration rates below the critical point, there exist non-trivial stable fixed points of the evolutionary dynamics. The coupling of the two populations is nonlinear. Introducing the migration mixed variables $\tilde{x}_i = (1-m)x_i + m\,x_j$ with $i \neq j$, the discrete time dynamics are given by

$$x_i' = \tilde{x}_i \frac{f_A(\tilde{x}_i)}{\langle f_i \rangle}, \tag{3.1.1}$$

with $\langle f_i \rangle$ being the average fitness in population i, respecting the gene flow due to migration.

For the symmetric fitness configuration $1 = \nu > \omega$, two critical values for the migration rate can be calculated analytically,

$$\mu_1 = \frac{1-\omega}{4}, \tag{3.1.2}$$

$$\mu_2 = \frac{3-\sqrt{5+4\,\omega}}{4}. \tag{3.1.3}$$

For $m < \mu_2$, there are two stable equilibria on the diagonal $x_1 = 1 - x_2$. The symmetric properties $m_1 = m_2$ and $\nu = 1$ can be relaxed to come to a more general classification. Depending on the deviation from the fully symmetric case, on can then classify the system in terms of the maximal number of stable fixed points. To this end, a phase diagram can be given, depending on the two difference variables $1 - \nu$ and $m_1 - m_2$.

A motivation to study bi-stable evolutionary dynamics in structured populations has its pedigree in inventing genetic means for genetic pest management. Linked underdominant alleles have been proposed to stably render insect resistant to diseases (with a refractory genetic construct producing the resistance). The aim is to prevent the transmission of a disease, e.g., malaria, to humans [Curtis, 1968]. In general, this can be achieved by a sufficiently high release number of genetically transformed individuals in a wildtype population. Our analysis addresses how such releases can lead to the desired outcome of establishing the transformed type in a local population by respecting gene flow from, or to another population. By taking into account asymmetries in fitness configuration and migration pattern, as well as the average fitness in each sub-population, an optimal release strategy can be found.

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Using underdominance to bi-stably transform local populations

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ABSTRACT

Underdominance refers to natural selection against individuals with a heterozygous genotype. Here, we analyze a single-locus underdominant system of two large local populations that exchange individuals at a certain migration rate. The system can be characterized by fixed points in the joint allele frequency space. We address the conditions under which underdominance can be applied to transform a local population that is receiving wildtype immigrants from another population. In a single population, underdominance has the benefit of complete removal of genetically modified alleles (reversibility) and coexistence is not stable. The two population system that exchanges migrants can result in internal stable states, where coexistence is maintained, but with additional release of wildtype individuals the system can be reversed to a fully wildtype state. This property is critically controlled by the migration rate. We approximate the critical minimum frequency required to result in a stable population transformation. We also concentrate on the destabilizing effects of fitness and migration rate asymmetry. Practical implications of our results are discussed in the context of utilizing underdominance to genetically modify wild populations. This is of importance especially for genetic pest management strategies, where locally stable and potentially reversible transformations of populations of disease vector species are of interest.

1. Introduction

1.1. Overview

In population genetics, underdominance, also known as heterozygote disadvantage or homozygote advantage, refers to the fitness configuration where diploid individuals with heterozygote genotypes have a lower fitness than the corresponding homozygous genotypes. It is thus the opposite of overdominance or heterozygote advantage. Here lower fitness is defined as having on average relatively fewer descendants in the following generation.

The properties of underdominant polymorphisms have long been well described for a single population and are characterized by an unstable equilibrium (Fisher, 1922; Wright, 1931, 1941; Haldane, 1942; Wiener, 1942). Thus, a mutant allele that is less fit when heterozygous does not have the capacity to increase in frequency when rare and is predicted to be lost from the population. However, in an underdominant fitness configuration, an allele is predicted to proceed to fixation when starting at a frequency greater than the unstable equilibrium value, $\hat{p}$. Therefore, in a single population, underdominance sets up a type of evolutionary bi-stable switch where a population is expected to exist in one of two stable states of allele frequency, $p=0$ or $p=1$. We use + to denote a wildtype allele and T to denote a genetically modified construct (or mutant allele). In a single population, the latter has frequency p while the former is at frequency $1-p$. The alleles are underdominant with respect to each other if the fitness of the heterozygote, w_{T+}, is less than both homozygote fitnesses, $w_{T+} < w_{++}$ and $w_{T+} < w_{TT}$, Fig. 1(a). Assuming random mating in a single population, the average fitness of the modified allele is $f_T(p) = w_{TT}p + w_{T+}(1-p)$ (i.e. the T allele will be paired with another T at frequency p which will result in a fitness of w_{TT}; at frequency $1-p$, it will be paired with a wildtype allele, leading to a fitness of w_{T+}). Equivalently, the average fitness of a wildtype allele is $f_+(p) = w_{++}(1-p) + w_{T+}p$. At the unstable equilibrium, with both alleles present, the two average allele fitnesses are equal to each other, $f_T(\hat{p}) = f_+(\hat{p})$. At this point, $\hat{p}$, the two alleles are thus neither increasing or decreasing in frequency relative to each other. By substituting the above relationship, this predicts that the ratio of alleles at this equilibrium is equal to the inverse ratio of fitness differences between the respective homozygotes and the heterozygote,

$$\frac{\hat{p}}{1-\hat{p}} = \frac{w_{++} - w_{T+}}{w_{TT} - w_{T+}}. \quad (1)$$

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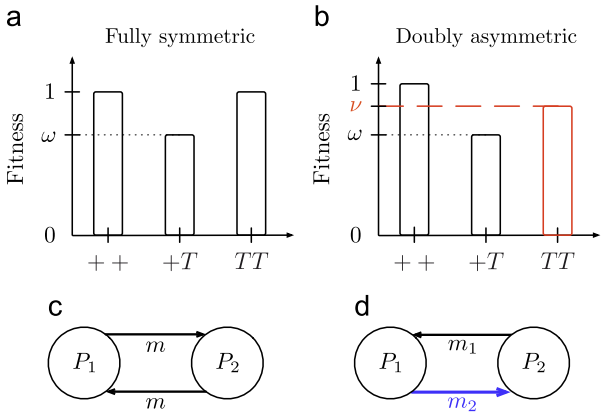

Fig. 1. (a) Genotype configuration of underdominance with the fitness of the homozygotes set to one, $w_{++}=w_{TT}=1$. The reduced fitness of the heterozygote, $w_{T+}=\omega$, is a positive number which is less than one. (b) Migration between the two populations. In each generation, migrants come and go with the rate m ($0\le m<0.5$), such that the fraction of immigrants in each population is m. (c) Genotype configuration of underdominance in the asymmetric case. The fitness of the wildtype homozygotes is 1. The fitness of the transgenic type homozygotes is $v\le 1$. The underdominant fitness of the heterozygotes is $\omega<v$. (d) Non-symmetric migration between the two populations. For each generation, the contributions of immigrants to the next generation in each of the two populations with p_1, p_2 are $m_1<0.5$ and $m_2<0.5$, respectively.

This can be rearranged into the more familiar form of

$$\hat{p}=\frac{w_{++}-w_{T+}}{w_{++}-2w_{T+}+w_{TT}}, \tag{2}$$

cf. Li (1955) and Hartl and Clark (1989). Note that, without loss of generality, we set the fitness of the wildtype homozygote to one, $w_{++}=1$. All other fitnesses are positive numbers relative to this value.

Chromosomal rearrangements, such as translocations and inversions, are classic examples of potentially underdominant mutations. The offspring of heterozygous individuals are predicted to have high rates of segmental aneuploidy (disrupted number of gene copies) in their offspring. This can result in lethality of the offspring and thus partial sterility of the heterozygote, which reduces fitness (Snell, 1946). It has long been recognized that, with underdominance, the probability of fixation of a new, rare mutant is exceedingly small in populations of more than a few individuals (Wright, 1941; Kimura, 1962; Bengtsson and Bodmer, 1976; Lande, 1979). Yet it is clear that mutations, including translocations, with potential underdominant effects accumulate between species and are common even among some closely related species (Bush et al., 1977; White, 1978). Several models have been proposed to try to explain this discrepancy (Bengtsson and Bodmer, 1976; White, 1978; Hedrick, 1981; Walsh, 1982). This is discussed in Nachman and Searle (1995) and Rieseberg (2001).

Rather than addressing the probability of naturally establishing underdominant variants as in the "chromosomal speciation" literature cited above, we focus on artificially establishing underdominant polymorphisms and the stability of these systems once established. In contrast to the predicted loss of polymorphism in a single population, when there are migrants between multiple populations an underdominant polymorphism can be stably maintained. In the case where different neighboring populations are at high and low allele frequencies, respectively, the offspring of rare migrants tend to be heterozygous. Due to their lower fitness, the rarer allele tends to be removed from the population resulting in different migration-selection equilibria in the neighboring populations. However, if migration rates between the populations are sufficiently high, the rarer allele is not removed at a sufficient rate by selection. As a result the underdominant polymorphism becomes destabilized. An analytic solution describing this critical point of destabilization, as a function of the strength of selection and the migration rate between the two demes, has been described in a fully symmetric model (Karlin and McGregor, 1972a), and for the limiting case of migration in a single direction where homozygotes are at different fitness values and the allele frequency in one of the populations is fixed at zero (Lande, 1985). Diffusion approximations describing this property have been made for the two-deme model (Barton and Rouhani, 1991). Also, a traveling wave approximation (Fisher, 1937) has been used to describe the conditions permissible for the establishment and spread, despite underdominance, of an allele in continuous habitats with a higher homozygous genotype fitness (Barton, 1979; Piálek and Barton, 1997; Soboleva et al., 2003). However, we do not mean to imply that underdominance is commonly responsible for the maintenance of polymorphism in natural structured populations. In addition to neutral mutations (Kimura, 1968), and mutation-selection balance (Haldane, 1924), there are many other forms of selection that can maintain polymorphism among demes, especially local adaptation, e.g., Nagylaki and Lou (2001), Lenormand (2002), and Bürger (2009). Here, with underdominance, we focus on the most efficient release strategy to achieve a stable local transformation and cases with fitness and/or migration rate asymmetry.

Part of our motivation to focus on the stability of established underdominant differences is the proposal to use underdominance as a means to genetically transform wild populations with desirable alleles, e.g., to render insects resistant to diseases to prevent their transmission to humans (Curtis, 1968). In essence, releases of individuals are made that result in a population allele frequency in the wild greater than $\hat{p}$. The transformation of the population is then predicted to proceed by natural selection without additional releases or intervention. This has the desirable properties of reversibility and geographic stability. Releases of wildtype alleles resulting in a frequency lower than $\hat{p}$, Eq. (2), are predicted to ultimately remove all modified alleles from the wild population. Additionally, in certain situations, modified alleles are not expected to spread far beyond the initial release range nor be lost from the wild. This can be an important consideration for initial testing of refractory effector constructs (e.g., Ito et al., 2002) in field trials and for non-native invasive disease vectors that threaten susceptible species (e.g., Warner, 1968); local populations can be stably transformed to be refractory while a wildtype state is maintained in the vectors native range. Despite intensive work to this end in the 1970–1980s, using radiation induced chromosomal rearrangements, this approach ultimately failed. This is partially because the genetically modified homozygous individuals suffered from dramatically reduced fitness relative to wildtypes (e.g., Foster et al., 1972; Lorimer et al., 1972; Boussy, 1988, and references therein; see also Harewood et al., 2010). However, with new, more precise molecular genetic technologies, there is a growing interest in systems, including underdominance, that have the capacity to transform wild populations (Davis et al., 2001; Sinkins and Gould, 2006; Magori and Gould, 2006; Gould, 2008).

In the second part of the introduction we introduce a simplified symmetrical model governing the dynamics of an underdominant polymorphism in two populations of infinite size coupled by migration. We review the bifurcation pattern and the linear stability analysis that allows one to find and classify the different equilibria. Although all stable equilibria and some

unstable ones can be calculated, a full phase portrait can only be obtained by supporting numerical methods. In Section 2 we give a quantitative estimate for the basin of attraction emerging in the presence of the non-trivial stable equilibria. In Section 3 we briefly discuss how the pattern in average fitness may affect the outcome of a transformation. In Section 4 we then discuss situations with broken symmetry, i.e. when there is unequal migration between the two populations and/or unequal homozygote fitnesses. Section 5 is a further discussion of our results and gives suggestions for practical applications. Finally, Section 6 serves as a summary.

1.2. Wright–Fisher dynamics

Here, we introduce the equations governing the dynamics of the system as it evolves from one generation to the next. This is based on the Wright–Fisher model, i.e. sampling alleles with replacement between discrete non-overlapping generations (Wright, 1931), in two coupled infinitely large populations. In the single population example, the contribution of an allele to the next generation is the allele's average fitness multiplied by its frequency in the present generation. This product is divided by the total average fitness of all alleles in the population, $\overline{w}$, to normalize it to a frequency from zero to one. Thus, the expected frequency of allele T in the next generation, p', is proportional to the frequency in the present generation, p,

$$p' = \frac{f_T(p)}{\overline{w}}\, p, \tag{3}$$

where $\overline{w} = f_T(p)p + f_+(p)(1-p)$ is the total average fitness. Note that the average fitnesses are independent of the specific evolutionary model and could also be directly used in alternative systems such as the Moran model with overlapping generations.

In the two population case we have to account for migration rate, m, which is defined as the proportion of immigrant individuals entering a population prior to mating. This implies that $1-m$ is the fraction of non-migrants each generation. For symmetric interactions see Fig. 1(b). The genotypic fitnesses are fixed values: given the value of the reduced heterozygote fitness $w_{T+} = \omega < 1$, the simplest case emerges when both homozygote fitnesses are set to one, $w_{++} = w_{TT} = 1$ (Fig. 1(a)). The average fitness of an allele changes with its frequency: in population $i = 1,2$, let p_i, and $1-p_i$ be the frequencies of alleles T (a modified allele) and + (wildtype), respectively. The wildtype allele has average fitness $f_+(p_i) = 1-p_i+\omega p_i$, whereas the average modified allelic fitness amounts to $f_T(p_i) = p_i+\omega(1-p_i)$, compare to the previous subsection. Due to equal homozygote fitnesses, $w_{++} = w_{TT} = 1$, we have the symmetry property $f_T(p) = f_+(1-p)$. Taking migration into account, in population i, the frequency of allele T is $(1-m)p_i + mp_j$. As we express the average fitness of allele + in terms of the frequency of allele T, the total average fitness in population i is

$$\begin{aligned}\overline{w_i}(p_i,p_j) = {} & [(1-m)p_i + mp_j]f_T((1-m)p_i + mp_j) \\ & + [(1-m)(1-p_i) + m(1-p_j)]f_+((1-m)p_i + mp_j),\end{aligned} \tag{4}$$

where $j \neq i$. The state of the system is characterized by the two population allele frequencies p_1 and p_2 ($0 \le p_1, p_2 \le 1$), which evolve from one generation to the next as

$$p_1'(p_1,p_2) = \frac{[(1-m)p_1 + mp_2]f_T((1-m)p_1 + mp_2)}{\overline{w_1}(p_1,p_2)}, \tag{5}$$

$$p_2'(p_1,p_2) = \frac{[(1-m)p_2 + mp_1]f_T((1-m)p_2 + mp_1)}{\overline{w_2}(p_2,p_1)}. \tag{6}$$

We now focus on the equilibrium points of the dynamics, namely we are interested in all points with $\Delta p_i = p_i' - p_i = 0$ for $i = 1,2$, depending on ω and m. Some of these fixed points are independent of the parameters, others only emerge in a certain parameter range. Trivial equilibrium points are $(\hat{p}_1,\hat{p}_2) = (0,0)$ and $(\hat{p}_1,\hat{p}_2) = (1,1)$, where both populations are fixed for the wildtype or the modified allele. In the symmetric case, there is also an unstable equilibrium or a saddle point (depending on m) at $(\frac{1}{2},\frac{1}{2})$. These three fixed points do not change position for any pair of parameters ω and m. For $m = 0$, the system behaves as two single populations and all nine possible combinations of fixed points exist (e.g., $(\frac{1}{2},1)$, $(0,\frac{1}{2})$, etc.). For $m > 0$, we take the symmetry of the system into account. This allows for solving only one equation, for instance $\Delta p_1 = 0$. With this, we find two fixed points on the axis $(p_1, 1-p_1)$, namely $(\hat{p}_1,\hat{p}_2) = (x_i, 1-x_i)$, $i = 1,2$, where

$$x_{1,2} = \frac{1}{2} \pm \frac{\sqrt{(1-\omega)(1-\omega-4m)}}{2(1-\omega)(1-2m)}. \tag{7}$$

Note that with $m = 0$, this reduces to the two fixed points $(\hat{p}_1,\hat{p}_2) = (1,0)$ or $(0,1)$. For $m > 0$, the solution is real valued if $(1-\omega)(1-\omega-4m) \ge 0$. The first term is always positive, but the second term becomes zero at critical value of the migration rate m, where a bifurcation occurs

$$\mu_1(\omega) = \frac{1-\omega}{4}. \tag{8}$$

The interior solutions (7) exist for $m \le \mu_1(\omega)$.

A linear stability analysis of these fixed points yields a second critical point, μ_2 (see Appendix A), given by

$$\mu_2(\omega) = \tfrac{1}{4}(3 - \sqrt{5+4\omega}). \tag{9}$$

Note that we have $\mu_2(\omega) < \mu_1(\omega)$ for underdominance, $\omega < 1$. For $m < \mu_1(\omega)$, one eigenvalue of the Jacobian associated with the fixed point is negative. For $m < \mu_2(\omega)$, the second eigenvalue becomes negative and a new pair of stable equilibria arises. They are located on the diagonal $(p_1, 1-p_1)$ in the joint allele frequency space.

The bifurcation pattern is three-dimensional, given by the coordinates (p_1,p_2,m) for a given heterozygote fitness ω. In Fig. 2(a) we use a projection to the plane (p,m), where p simultaneously stands for p_1 and p_2. In both planes, the pattern looks the same, which is due to the symmetry of the system. Although the second bifurcation obeys this symmetry as well, we are not able to calculate its actual shape – and thus the position of the associated unstable fixed points – analytically. The set of all possible internal equilibria, from analytical predictions as well as from numerical root finding, is given in Fig. 2(b). Fig. 2(c) shows how the two bifurcation points depend on the fitness of the heterozygotes ω.

In Fig. 3 we show several slices of the (p_1,p_2)-plane for different pairs of parameters (ω,m); the phase portrait changes with the control parameter m. Note that we have $\mu_2(\omega) < \mu_1(\omega)$ for $\omega < 1$. For $m < \mu_1(\omega)$, we have $\lambda_1 < 0$. In addition for $m < \mu_2(\omega)$, we get $\lambda_2 < 0$. A new pair of stable internal equilibria arises. They are located on the diagonal $(p_1,1-p_1)$ in the state space.

In Appendix B, we further discuss the system, also showing that for sufficiently low migration rates, the dynamics are well captured by a linearized system of equations. This is especially interesting for further analytical examinations that go beyond the scope of this manuscript, e.g., when a larger system of interacting populations is considered.

Taking advantage of the symmetry in the system of two populations coupled by migration allows one to analytically calculate the emergence of stable internal equilibria depending on the heterozygote's fitness ω. With the additional aid of numerical methods we can also find the saddle points. In the next section we discuss the pattern in more detail, addressing the problem of

finding the basins of attraction that belong to the internal stable equilibria.

In Appendix C, we present results when considering three alleles with underdominance, which necessarily becomes more complicated and has implications for transformation strategies. However, in certain situations bi-stable population transformations are still possible, even if underdominance is not present between all pairs of alleles. Also, in the two population case, even at the non-trivial stable equilibria, if only underdominance is present, alleles are expected to be lost and the system returns to the two-allele case. This suggests that in certain contexts the results for a two-allele system are applicable to systems with initially more than two alleles.

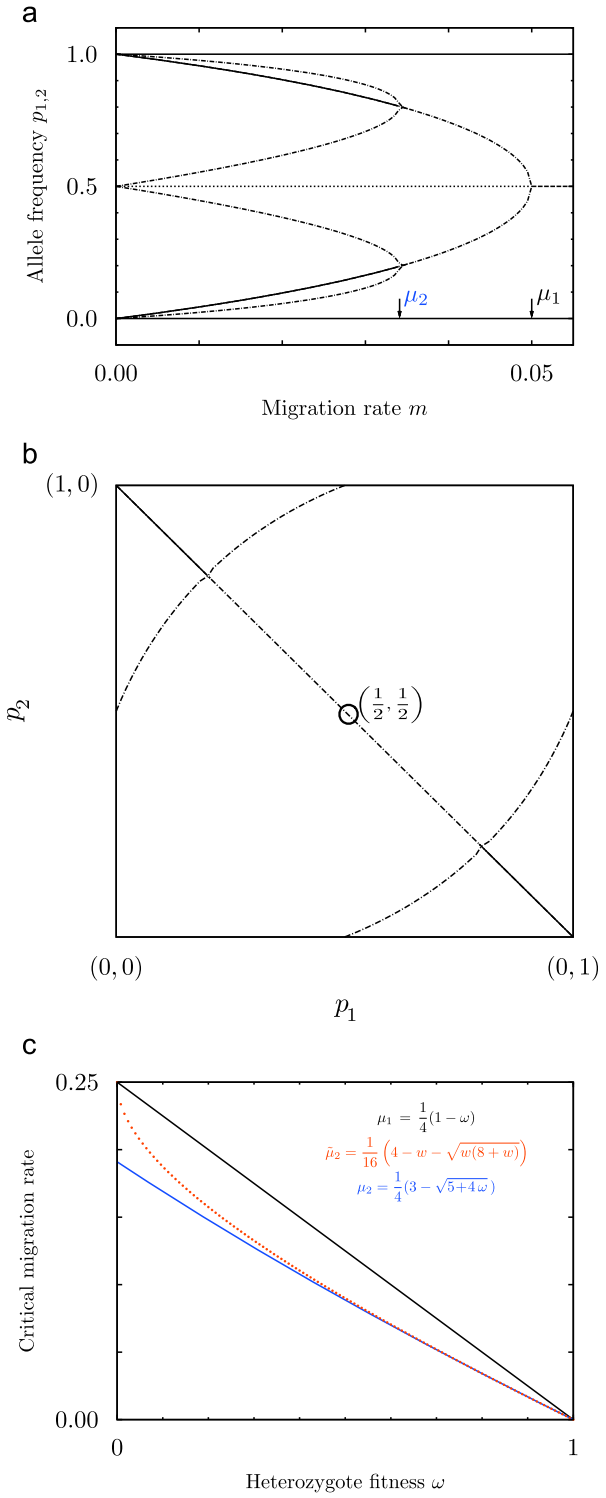

Fig. 2. (a) Projection of the bifurcation diagram showing the allele frequency $p_{1,2}$ in one of the two populations as a function of the control parameter m. The positions of the critical points $\mu_1(\omega)=0.05$ and $\mu_2(\omega)\approx 0.0341$ are indicated by arrows. (b) Projection of the bifurcation diagram to the state space, i.e. the positions of equilibria for any migration rate. Dashed lines and curves describe unstable, dashed-dotted curves describe saddle, and full curves and lines describe stable fixed points in both figures. In both, (a) and (b), the fitness of the heterozygote's is fixed to $\omega=0.8$. Note the difference to Karlin and McGregor (1972a), where a figure of this bifurcation wrongly suggests a different pattern. (c) The two critical points of the fully symmetric system, μ_1 (black), and μ_2 (shaded), and the approximation of the latter stemming from the linearized system, $\tilde{\mu}_2$ (dotted), as a function of the fitness of the heterozygotes $(+T)$, ω. While μ_1 is a linear function in ω, μ_2 and $\tilde{\mu}_2$ exhibit square root behavior (compare inset and Eqs. (8), (9), and (33) in the main text). $\tilde{\mu}_2$ approaches μ_2 for ω sufficiently large; The difference vanishes for $\omega\to 1$.

2. The basin of attraction

What is the region in the state space where the system is attracted to a non-trivial stable equilibrium? Once the two non-trivial stable equilibria are present, i.e. for $0<m<\mu_2(\omega)$ there is a region where the system, once initiated there, will ultimately reach one of the stable equilibria along $(x_i,1-x_i)$, Eq. (7). This region is the basin of attraction. Here, we give two estimates of this subset of the state space and compare it to simulations.

Consider the boundaries of the system. In one population the frequency of the transgenic type is fixed to zero or one, and in the other it can have any value between zero and one. Due to the symmetry in homozygote fitnesses and migration rate, we only have to consider those parts of the boundaries where for instance $p_2=0$, as in this case $p_2=1$ follows directly from that.

In the neighborhood of the boundaries, we expect the components of the (two-dimensional) flow parallel to the boundaries to be similar to the (one-dimensional) flow along the boundaries. Wherever the flow along the boundaries vanishes there are points of vanishing flow of the quasi-one-dimensional system. They can be stable or unstable, depending on the slope of the one-dimensional flow at these points, $\partial_p\Delta p_1(p,0)$, or $\partial_p\Delta p_2(0,p)$. Their position will give an estimate of where the basin of attraction meets the boundaries, assuming low migration. Consequently, we need the solutions of the one-dimensional system, $\Delta p_1(\rho,0)=\Delta p_2(0,\rho)=0$, which are given by

$$\rho_{\pm}=\frac{3-m(1-\omega)-3w\pm\sqrt{(1-\omega)(1+m^2(1-\omega)-2m(3+\omega)-\omega)}}{4(1-m)(1-\omega)}. \tag{10}$$

If both equilibria exist $\rho_-\le\rho_+$. Additionally, $(\rho_-,0)$ is unstable, since $\partial_p\Delta p_1(p,0)|_{p=\rho_-}>0$ and hence $(\rho_-,0)$ is a naïve minimum of a possible initial condition at the boundary that leads to the stable equilibrium $(x_2,1-x_2)$, compare Eq. (7) and Fig. 4. Thus, possible estimates for the regions where the dynamics leads to one of the stable equilibria given by the coordinates $(x_i,1-x_i)$, Eq. (7), for $0\le m<\mu_2(\omega)$, are rectangles, for example the one limited by the four points $(\rho_-,0),(1,0),(1,1-\rho_-)$ and $(\rho_-,1-\rho_-)$, cf. Fig. 4. At high migration rates this increasingly underestimates the basin. In addition, we can give another estimate, which is the deltoid (kite) limited by the four points $(\frac{1}{2},\frac{1}{2}),(1,1-\rho_-),(1,0)$, and $(\rho_-,0)$. For low migration this in an overestimate of the basin of attraction, which itself is obtained by numerical simulations, see Fig. 4.

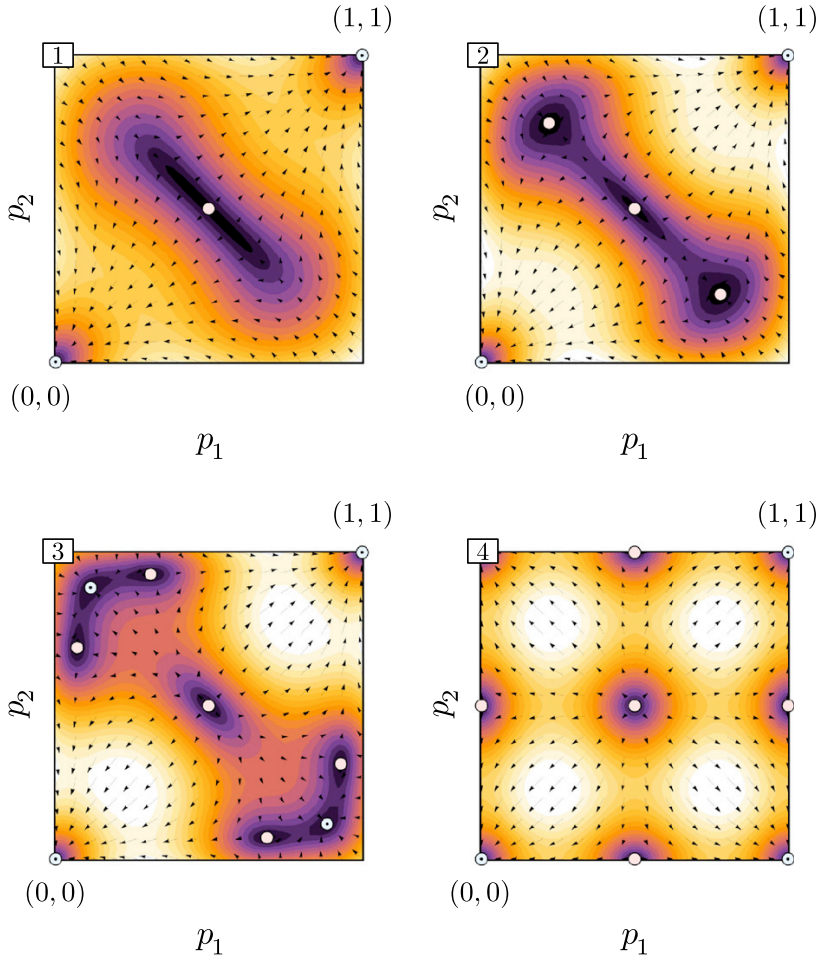

Fig. 3. For the bifurcation pattern with fixed heterozygotes fitness $\omega = 0.5$ and critical points $\mu_1 = 0.125$ and $\mu_2 \approx 0.0886$, four slices (1–4) with different migration rates m are shown. In each of them the state space of the system, ($[0,1] \times [0,1]$), is depicted with a phase portrait (arrows) and the absolute rate of change $\sqrt{(\Delta p_1)^2 + (\Delta p_2)^2}$ (shading). The darker the shading the slower the dynamics, the brighter the faster. The equilibrium points are given by disks. Empty disks are unstable (or saddles), disks with a dot are the stable equilibria. (1) For $m = 0.13$ there exist only the two trivially stable equilibria at (0,0) and (1,1) as well as the saddle fixed point at the center (0.5,0.5). (2) If migration rate decreases below μ_1, for $m = 0.1$, we observe two new saddles along the axis $(p_1, 1-p_1)$, cf. Eq. (7), and the center becomes fully unstable. (3) For migration below μ_2, $m = 0.07$, the former saddles at $(x_{1,2}, 1-x_{1,2})$, Eq. (7), become stable and four new equilibria (also saddles) emerge, cf. Figure 1 of Barton and Rouhani (1991). Although they also obey the mirror symmetry, for the four new unstable points an analytical description of their positions is cumbersome; we only locate them via numerical root finding algorithms. (4) For vanishing migration rate the case of two distinct populations with underdominance is recovered.

3. Average fitness

Do the patterns of reduced average fitness affect the strategy for achieving transformation? For the symmetric model, the mean population fitness at the central unstable equilibrium can be found by substituting $\hat{p}_i = \frac{1}{2}$ into Eq. (4). This results in $\overline{w_i} = (1+\omega)/2$. Near this point is the optimal strategy for transforming a target population with a minimum release of individuals (see Section 5). However, this is also the point where mean population fitness is at its lowest. At the approximate threshold for transformation with a single population release,

$$(p_1, p_2) = (\rho_-, 0), \tag{11}$$

the average fitness in each population is

$$\overline{w_i}(\rho_-, 0) = \tfrac{1}{4}(1-m)(3-m+\omega(1+m) - \sqrt{(1-\omega)((1-\omega)(1+m^2)-2m(3+\omega))}), \tag{12}$$

which only results in a small increase in mean fitness except at very high migration rates, see Fig. 5, where the approximation is less accurate and stability of the system is almost lost. Thus, the strategy to minimize release numbers probably has more advantages than maximizing average population fitness during the transformation.

Interestingly, the mean population fitness at the stable non-trivial fixed point, where the system is in migration-selection equilibrium, appears to be independent of the heterozygote fitness, ω. This point is given by $\hat{p}_{1,2} = x_{1,2}$, Eq. (7). The point is stable for $0 < m < \mu_2$, Eq. (9). Substituting this into Eq. (4) yields $\overline{w_i} = 1-2m$, which is only a function of the migration rate. Intuitively, if heterozygotes are less fit then the rarer allele will have a lower frequency, at equilibrium, in the population, producing fewer heterozygotes each generation. Conversely, if heterozygotes are more fit the rarer allele will attain a higher frequency producing more heterozygotes each generation. The number of heterozygotes produced and their fitness cancel out in

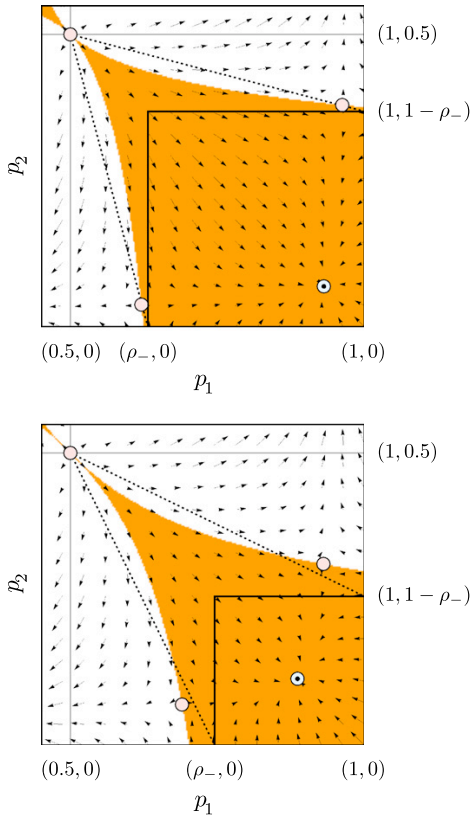

Fig. 4. We show the basin of attraction for heterozygotes fitness of $\omega=0.5$ ($\mu_2(0.5)\approx 0.0886$) in the lower right quarter of the state space. The migration rates are $m=0.05$ (top) and $m=0.07$ (bottom). The basin in darker shading results from simulations of the dynamic system in discrete time, Eqs. (5) and (6). The thick lines are estimates from the reduction to the one-dimensional flow along the boundaries, cf. Eq. (10): The square in full lines is a conservative underestimate, whereas the quadrilateral limited by the dashed lines and the boundaries serve as an overestimate when p_2 is not too small and p_1 is not too high (in natural populations, the migration rate ensures these properties). Although migration is low, it becomes clear that with m increasing both estimates become conservative in a neighborhood of the ρ_- boundaries.

terms of the average effect in the population. This is similar to the effects of deleterious mutations at mutation-selection equilibrium, in which case the average fitness of a population is only a function of the mutation rate (Haldane, 1937).

4. Unequal homozygote fitnesses and non-symmetric migration

So far all results are based on the symmetry of the system of two coupled populations with an underdominant locus. In this section, we show how the phase portrait changes for non-symmetric migration between the two populations and if restriction of the model to equal homozygote fitnesses is relaxed, see Fig. 1(c). We allow migrants in one population, coming from the other, to have an abundance m_i, with $m_1 \neq m_2$ in general, see Fig. 1(d). For example, migration bias can arise between upstream (or upwind) and downstream (downwind) populations, in the direction of an invasive front with a demographic expansion, or when migration occurs between populations of unequal size. Typically, the genetically modified type suffers from a fitness reduction compared to the wildtype with a fitness of one (Boussy, 1988). This reduction results in a lower fitness $w_{TT}=v$,

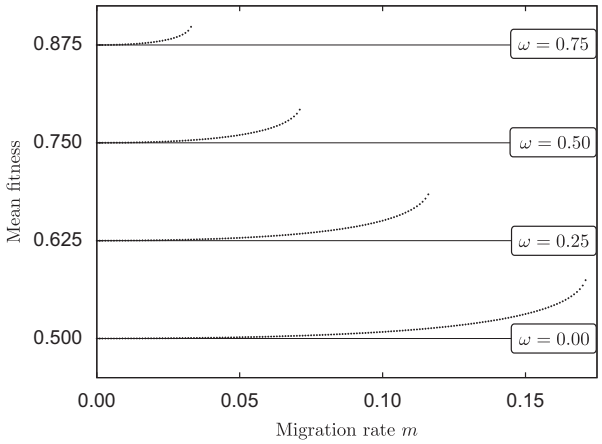

Fig. 5. Total mean population fitness of the central unstable equilibrium, $\overline{w}=(1+\omega)/2$ (full lines), and of the one-dimensional edge approximation for single population release, Eq. (12) (dotted curves), are shown with four different values of heterozygote fitness ω (values given in the figure) η=1. The two estimates are essentially equal except at relatively high migration rates.

with $0<\omega<v\leq 1$. Discarding the simplifying assumptions that lead to a high degree of symmetry disrupts the symmetrical arrangement of the phase portrait. As a result, the critical values in parameter space and thus the stable equilibria can no longer be calculated analytically.

With $w_{+T}=\omega$, $w_{TT}=v$, and $w_{++}=1$, the respective average allelic fitnesses in population i are

$$f_+(p_i)=1-p_i+\omega p_i, \tag{13}$$

$$f_T(p_i)=vp_i+\omega(1-p_i) \tag{14}$$

for wildtype + and modified type T. Note that both fitness functions are linear in p, but in general $f(mp)\neq mf(p)$. Nevertheless, observe that $f((1-m)p_i+mp_j)=(1-m)f(p_i)+mf(p_j)$ holds for all values of ω and v. More importantly, $f_T(p)$ equal to $f_+(1-p)$ no longer holds either, which is due to loss of symmetry in homozygote fitness. Similar to Eq. (4) the average fitness in population i thus reads

$$\begin{aligned}\overline{w_i}(p_i,p_j)=&(1-m_i)^2[p_if_T(p_i)+(1-p_i)f_+(p_i)]\\&+m_i(1-m_i)[p_if_T(p_j)+(1-p_i)f_+(p_j)]\\&+(1-m_i)m_i[p_jf_T(p_i)+(1-p_j)f_+(p_i)]\\&+m_i^2[p_jf_T(p_j)+(1-p_j)f_+(p_j)],\end{aligned} \tag{15}$$

where $j\neq i$. As we consider infinitely large populations with random mating taking place after migrants are exchanged, m_j neither gives a contribution to $\overline{w_i}$ nor does it directly influence the frequency of allele T in the next generation, p_i':

$$p_1'(p_1,p_2)=\frac{(1-m_1)^2p_1f_T(p_1)+(1-m_1)m_1(p_1f_T(p_2)+p_2f_T(p_1))+m_1^2p_2f_T(p_2)}{\overline{w_1}(p_1,p_2)}, \tag{16}$$

$$p_2'(p_1,p_2)=\frac{(1-m_2)^2p_2f_T(p_2)+(1-m_2)m_2(p_1f_T(p_2)+p_2f_T(p_1))+m_2^2p_1f_T(p_1)}{\overline{w_2}(p_2,p_1)}. \tag{17}$$

From the shift in fixed points and rate of allele frequency change, when considering a phase portrait (Fig. 6) we can see that unequal migration rates result in a loss of bilateral symmetry. Unequal homozygote fitnesses result in a loss of rotational

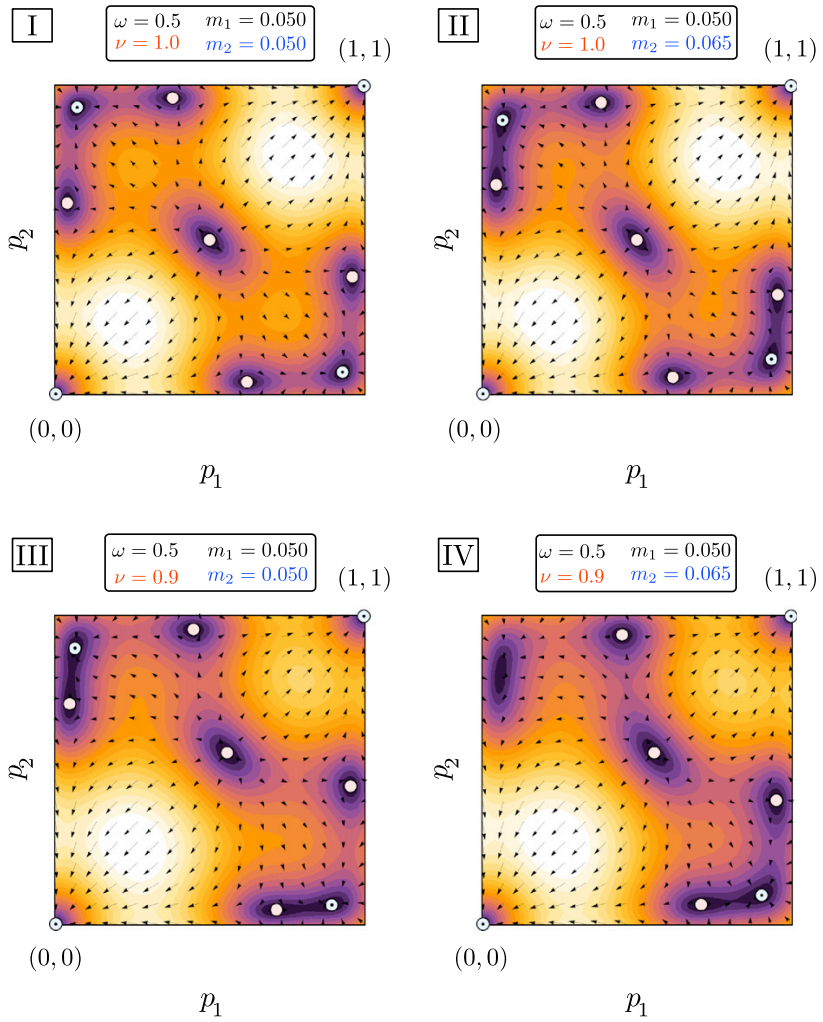

Fig. 6. Symmetry breaking. We show four different scenarios with different degrees of symmetry. ω denotes the fitness of the heterozygotes, v is the fitness of the transgenic homozygous type, which is equal or less than the fitness of the wildtype, with fitness of one. In population $i=1,2$, the frequency of immigrants which contribute to the next generation is m_i. The exact values of fitnesses and migration rates are given in the boxes above each plot. Disks indicate equilibrium points; empty disks are unstable (or saddle points), disks with a dot are stable equilibria. (I) Maximal symmetry is maintained when the fitness of both homozygotes is equal to one and migration is symmetric, $m_1=m_2$. In this example there is a point symmetry and one finds two symmetry axes. The important symmetry here is $p_1 \to 1-p_1$. (II) When migration is asymmetric both symmetry axes are lost, but there is still a point symmetry in the center (0.5,0.5). (III) For symmetric migration but lower fitness of the transgenic homozygotes, $\omega < v < 1$, the point symmetry and the important symmetry axis are lost. The unstable equilibrium in the central area is shifted along the axis (p_1,p_1). (IV) For unequal migration rates and unequal homozygotes fitness all symmetry is lost, but the central unstable equilibrium remains at the axis (p_1,p_1). In this case, only one non-trivial fixed point is stable.

symmetry. With both of these effects, all forms of symmetry are lost as illustrated in Fig. 6 (IV). Furthermore, from this asymmetry it becomes apparent that situations exist where a stable, local transformation of a less fit allele is possible in only one of the two coupled populations. The stability properties under symmetry distortion can be represented in a "phase diagram" Fig. 7. From this example it can also be seen that both unequal migration rates and unequal homozygote fitnesses are required to result in non-trivial stability in only one of the two populations. In this doubly asymmetric case, higher migration rates and lower homozygote fitnesses can result in single population stability outside the range of parameter values necessary for symmetric stability in two populations: e.g., the lower right tip of zone B in Fig. 7 has a lower homozygote fitness and a higher migration rate than is found for any area of zone A. In this regime, lower homozygote fitnesses are counterbalanced to some degree by higher emmigration and lower immigration rates.

As homozygote fitnesses become more asymmetrical, the non-trivial stable fixed points move closer to the boundaries of the system. Solving (16) for the edge of the system, $p_2=0$, as done in Section 2 for the fully symmetrical model, and assuming stationarity, $\Delta p_1 = 0$, gives the non-trivial solutions

$$\rho_{\pm} = \frac{2+v(1-m)-\omega(3-m) \pm \sqrt{(v-\omega)^2(1+m)-2m(2v(1-\omega)+v^2-\omega^2)}}{2(1-m)(2\omega-v-1)}, \tag{18}$$

where ρ_+ is stable and ρ_- is the unstable internal fixed point in the one-dimensional system. Setting $\rho_- = \rho_+$, the point, where stability is lost according to the flow along the edge (when the argument in the square root is zero), gives

$$\mu_3(\omega,v) = \frac{v(2-2\omega+v)-\omega^2-2\sqrt{v(1+v-2\omega)(v-\omega^2)}}{(v-\omega)^2}. \tag{19}$$

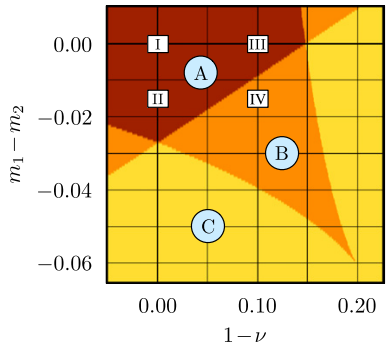

Fig. 7. Phase diagram of a system of two populations with an underdominant allele coupled by two migration rates. We show the difference of migration rates, m_1-m_2, on the ordinate and the difference in homozygote fitnesses, $w_{++}-w_{TT}=1-\nu$, on the abscissa. For each pair of these differences, we evaluate whether the system reaches an internal (non-trivial) stable fixed point, given it has been initiated inside the basin of attraction (compare Fig. 4). The system has been simulated using Eqs. (16) and (17). We can identify three different phases: (A) The system has two internal stable fixed points (darkest shading). (B) The system has only one internal stable fixed point (intermediate shading). (C) The system does not have any internal stable fixed point (light shading). We also link back to Fig. 6 and locate the plots in this phase diagram: (I) Full symmetry is maintained, cf. Fig. 3. (II) The system is moved along the axis of equal homozygote fitness, $1-\nu=0$. (III) The system is moved along the axis of equal rates of migration, $m_1-m_2=0$. (IV) No symmetry is maintained and we find only one internal stable fixed point.

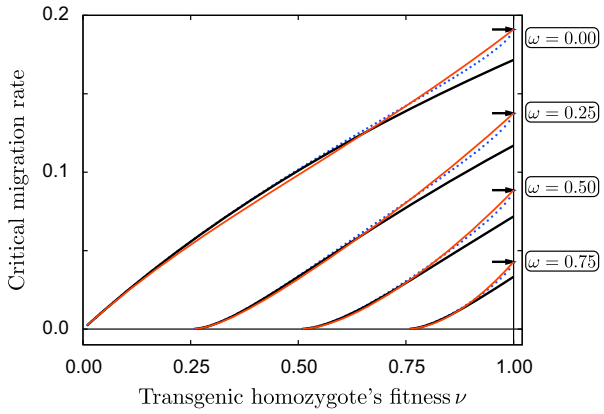

Fig. 8. Critical migration rates with unequal homozygote fitnesses for a range of illustrative heterozygote fitness values, ω. The right edge of the plot, $\nu=1$, corresponds to μ_2 in the fully symmetric model ($\nu=1$, arrows). As the *TT* homozygote fitness declines relative to the wildtype, ++, the critical migration rate also declines as the system is destabilized. This has been determined numerically (dots) and the simulated result approaches the approximation analytically, derived from the edge of the system for smaller ν (black). A simple non-linear weighted average approximates critical values of m across the range of ν and ω (shaded), compare Eq. (20).

This is an approximation of the critical migration rate allowing stability in the case of unequal homozygote fitnesses. As can be seen in Fig. 8 this edge-approximation works very well when $\nu<(\omega+1)/2$ or when the transgenic homozygote fitness is less than the average of the heterozygote and wildtype fitnesses. Above this area there is an increasing deviation as the symmetric critical migration rate μ_2 is approached. An *ad hoc* non-linear weighted average between μ_2 and μ_3 of

$$\mu_w(\omega,\nu)=\mu_3(\omega,\nu)(1-\nu)+\frac{\mu_2(\omega)(\nu-\omega)^2}{(1-\omega)^2} \tag{20}$$

gives a good fit across the entire range.

It can also be casually observed in Fig. 6 that the central unstable equilibrium always falls along the $p_1=p_2$ axis despite various forms of parameter asymmetry. Solving Eqs. (16) and (17) for an unstable fixed point along this axis (similar to Appendix A) yields

$$\hat{p}_1=\hat{p}_2=\frac{1-\omega}{1-2\omega+\nu}. \tag{21}$$

Thus, the central unstable equilibrium is independent of migration and identical to the unstable equilibrium in the single population case, Eq. (2). This makes intuitive sense if one considers that this is also the stable equilibrium point in the case of overdominance (i.e. heterozygote advantage) and that at this equilibrium all populations should arrive at the same allele frequency. At this point the migrants between populations have no effect on changing allele frequencies.

5. Discussion

At high and very low migration rates the dynamics of the two population system approaches that of a single population system, either as two independent populations or as a single combined population. Here we have explored the interesting cases between these two extremes where the dynamics are more complex. A two-population single-locus system can have up to nine equilibrium points, two of which can be non-trivially stable. We have focused on the conditions of this non-trivial stability and how the system can arrive at these points. First, however, it is important to be clear about the assumptions and limitation of the necessarily simplified model.

The system described here assumes selection acting on a single locus, which is appropriate for certain kinds of chromosomal rearrangements, such as paracentric inversions and fusions, discussed by Lande (1979), and single gene effects, similar to Rh factor, e.g., Wiener (1942). Yet, in general the biological examples provided for underdominance are reciprocal chromosomal translocations, which of course involves two (or more) loci. In plants, fungi and protists that undergo alternation of generations where diploid stages are separated by multicellular haploid gametophytes, unbalanced translocations can be lethal at the gametophyte stage (Ray et al., 1997). In this simple case of complete lethality, the system behaves as a single locus with $\omega=\frac{1}{2}$ (Wright, 1941). In typical animals, gametes that have an unbalanced set of chromosomes can function normally and produce a zygote (Snell, 1946). Thus, there is a small chance that two unbalanced gametes could complement each other upon fertilization, so unbalanced zygotic lethality in animals can behave as a single locus with ω slightly greater than $\frac{1}{2}$ (Wright, 1941). Of course, even with full unbalanced lethality, other factors in various species such as competition among offspring, parental care, some fraction of vegetative reproduction, and/or alternate chromosome segregation patterns can result in an effective ω substantially greater than one-half (Lande, 1979). However, if an organism with an unbalanced translocation can survive to reproduce, as is perhaps the case with some human diseases and translocations that involve smaller chromosomal regions, e.g., Koochek et al. (2006), then the system can no longer be expected to behave according to the single-locus model presented here.

Another important limitation is the simplifying assumption of an infinitely large population size, where only migration and selection are the sole determinants of allele frequency change. A finite population will ultimately reach the absorbing states at $p_1=p_2=0$ or $p_1=p_2=1$. However, the time until these points are reached may be very large, in particular when the corresponding deterministic system has stable interior fixed points and selection

is relatively strong. An interesting question in this case is how long until a local transformation is lost and, in the case of asymmetry, what are the relative likelihoods of ultimate fixation for the wildtype versus transgenic alleles. This is briefly presented in Appendix D.

If a stable transformation of a population is possible, from an applied point of view, ρ_- from Eq. (10) gives the approximate minimum frequency that must be surpassed to result in a stable transformation, by releasing the transgenic construct into a single target population. In order to attain a target frequency p^*, releases must be made of size $P=p^*/(1-p^*)$ relative to the wild population (i.e. after the release of P individuals homozygous for a modified allele into a wildtype population of relative size 1, the allele frequency becomes $p^*=P/(1+P)$. This function increases steeply towards positive infinity as $p^*\to 1$, thus small differences in p^* can have large effects and, for practical reasons, larger p^*'s should be avoided. Because of this, stable transformations might be more efficiently achieved with smaller, asymmetrical releases into both populations (i.e. closer to the central unstable equilibrium point, which is at the tip of all basins of attraction, Fig. 4). For example, starting at $p_1=p_2=0$, a total of a twofold equivalent of a single wildtype population is required for equal releases into two populations to result in the central unstable point, $p_1^*=p_2^*=\frac{1}{2}$ (with equal homozygote fitness). While a larger minimum of a fourfold equivalent is required to enter the basin of attraction by a single population release, if for example the threshold, Eq. (10), is at $p^*=0.8$. Specifically, the proposed minimal-number strategy is a p^* close to, but less than, $\hat{p}$, Eq. (2), in non-target, neighboring populations, and a p^* close to, but greater than, $\hat{p}$ in the target population. Estimating the central equilibrium point has the advantage of less uncertainty due to its independence from rates of migration, see Section 4. However, the basin near the central equilibrium is a smaller target area and entering near there raises the risk of accidentally transforming both populations or only the non-target population. If this is an undesirable outcome, it must also be considered. These calculations naïvely assume released individuals are equivalent to wildtype in terms of mating success and that both sexes will be released. In reality it is likely that released individuals are less fit and may even be discriminated against by wild female mate choice (Lance et al., 1998; McInnis et al., 1996), and that (in many disease vectoring insect species) releases of only males would be made necessitating more than one generation of release to achieve $p^*>\frac{1}{2}$. However, the basic strategy of more efficient transformations closer to the central equilibrium remains unchanged.

Sterile insect technique (SIT) is a widely used and in some cases very successful genetic pest management (GPM) approach where the goal is suppression and elimination of the wild population, rather than transforming the population, and incidentally often requires larger release sizes than those predicted here for underdominant transformation (Asman et al., 1981; Krafsur, 1998). However, SIT can be less effective in species that have high density-dependant population size regulation such as mosquitoes, i.e. a high reproductive potential allowing a rapid rebound from a small number of individuals (Prout, 1978; Dye, 1984). In contrast, underdominant mediated population transformation may have advantages in species with high density-dependant regulation. Part of the original interest in underdominance was due to its potential population suppression effects, similar to SIT, rather than population replacement, e.g., Vanderplank (1944) and Laven (1969). This population suppression is greatest near unstable equilibriums where the mean population fitness is minimized (Serebrovskii, 1940). One potential problem in a species with low density dependence is that during an underdominant transformation the wild population size may start to decline as the populations transits through low average fitnesses near unstable equilibria (see Section 3). This population size effect is dependent on additional fecundity parameters not modeled here, but it is easy to imagine that the target population may become more susceptible to immigration from other wild populations during this phase (similar to a "migrational meltdown," Ronce and Kirkpatrick, 2001; Tufto, 2001). Hence, it may be difficult to locally transform certain species in such a case. However, in species with high reproductive potential, where only a few individuals can quickly produce enough descendants to return to carrying capacity, this should not be as large of an issue because the population is continuously maintained near carrying capacity. This is precisely the situation where SIT can be very ineffective. Thus, underdominant mediated population transformation is an excellent alternative to SIT in GPM strategies because the two approaches are likely most effective at opposite ends of the density-dependent spectrum. Note also that at mid-spectrum the two methods might be usefully combined to first reduce the wild population by SIT, followed by population replacement by underdominance.

6. Summary

In summary, Section 1 introduces the problem and gives the criteria permissible to a stable transformation in a single target population, which is a function of the migration rate, Eq. (9). This is based on a stability analysis (Appendix A). Appendix B extends this approach to a simplified linear treatment of the dynamics, which can be useful in more complicated and realistic population models beyond the simple two-deme system analyzed here. In Appendix C we illustrate underdominant dynamics for more than two alleles, which in some cases is similar to the expectations of a two-allele system.

In Section 2 we identify the full basin of attraction numerically and approximate it analytically. For a stable local transformation, this is important when considering release strategies.

In Section 3 we determine the effect of a local population transformation on the average fitness of the population. Counter-intuitively we find that average fitness is independent of the genotypic fitness parameters and only a function of the migration rate.

In Section 4 we analyze cases of asymmetric fitness and/or asymmetric migration rates, which generally act to destabilize the system. Initially surprising results are that there are cases where stable-local transformations are only possible in one of the populations and the central unstable equilibrium is independent of migration. We also derive an approximation for critical migration rates permissive to stability with asymmetric fitness, Eq. (19).

The expected sensitivity to fecundity of underdominance complements alternative population management techniques. This, and other consequences of the model for practical use are discussed in Section 5: In general there is very little difference in fitness for alternative strategies to enter the basin of attraction. In future studies of finite populations the fecundity of the organism can be included in the model to directly quantify this effect.

Finally, in Appendix D we give numerical results from simulations of stable transformations in finite populations. We find that if effective population sizes are large (≈ 100 diploid individuals) and the system is not near critical boundaries (migration rates and heterozygote fitnesses are relatively low) a local transformation can remain stable for a very long time (for more than 10^4 generations). If homozygotes for the modified allele are only slightly less fit than the wildtype allele, the finite system is likely to ultimately result in loss of the modified allele from both populations, rather than fixation in both.

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Appendix A. Linear stability analysis

A system similar to Eqs. (4)–(6) can be found in Karlin and McGregor (1972a) (see also Karlin and McGregor, 1972b), where a linear stability analysis has also been performed. Here we briefly repeat this procedure. Additionally, this formalism can also be applied to the linearized system (Appendix B), and used to solve for the central unstable equilibrium along the (x_i,x_j) axis in the asymmetric model (Section 4).

Linear stability analysis reveals whether a fixed point of a dynamical system is attracting or repelling (Hofbauer and Sigmund, 1998; Strogatz, 2000; Murray, 2007). The idea is the following: Given an equilibrium point, if we perturb the system, will it move away from that point or return to it? This property is expressed by the eigenvalues of the Jacobian matrix at the equilibrium point $(\hat{p}_1,\hat{p}_2)$, $\mathbb{J}|_{(\hat{p}_1,\hat{p}_2)}$. The Jacobian matrix is the matrix of all partial derivatives,

$$\mathbb{J}(x,y)=\begin{pmatrix}\left.\frac{\partial\Delta p_1}{p_1}\right|_{(x,y)} & \left.\frac{\partial\Delta p_1}{p_2}\right|_{(x,y)}\\ \left.\frac{\partial\Delta p_2}{p_1}\right|_{(x,y)} & \left.\frac{\partial\Delta p_2}{p_2}\right|_{(x,y)}\end{pmatrix}, \tag{22}$$

where $\Delta p_i=p_i'-p_i$, see Eqs. (5) and (6). Assuming that the perturbation is small and that the Jacobian does not vanish, we obtain a linear equation that governs the temporal evolution of that perturbation. Its solutions can be written as a superposition of eigenmodes, $\propto e^{\lambda_k t}$, where λ_k is the kth eigenvalue of the Jacobian. Thus, a perturbation will become smaller over time if all eigenvalues are negative. As soon as a single eigenvalue is positive, the perturbation increases and the corresponding equilibrium point is not stable. The eigenvalues govern the behavior of the system in a vicinity of an equilibrium point (Strogatz, 2000). The explicit form of our Jacobian at $(x_i,1-x_i)$, Eq. (7), is

$$\mathbb{J}(x_1,1-x_1)=\begin{pmatrix}\frac{\omega-1-m(w-6)-6m^2}{(1-2m)^2} & \frac{m(2m+\omega)}{(1-2m)^2}\\ \frac{m(2m+\omega)}{(1-2m)^2} & \frac{\omega-1-m(w-6)-6m^2}{(1-2m)^2}\end{pmatrix}, \tag{23}$$

which is the same for $i=1$ or 2, due to the symmetry of the system. The eigenvalues are the solutions of the characteristic polynomial $\det(\mathbb{J}-\lambda\mathbb{I})=0$. They are given by

$$\lambda_1=-\frac{1-\omega-4m}{1-2m}, \tag{24}$$

$$\lambda_2=-\frac{1-\omega+2m(2m-3)}{(1-2m)^2}. \tag{25}$$

Both roots are always real valued. A local bifurcation occurs when a parameter change causes the stability of an equilibrium to change, such that new equilibria can arise. Stability changes when the λ_k change signs. Thus, we can compute the critical points from $\lambda_1=0$, and from $\lambda_2=0$. In the former case, we obtain $\mu_1(\omega)=(1-\omega)/4$. The latter case yields the critical point of the second bifurcation,

$$\mu_2(\omega)=\tfrac{1}{4}(3-\sqrt{5+4\omega}), \tag{26}$$

where we can neglect the second branch of the root due to consistency.

Appendix B. Linearized dynamics

The original symmetric system, Eqs. (5) and (6), is of the shorthand form $p_i'(p_1,p_2)=\varphi_i(p_1,p_2)/\overline{w_i}(p_1,p_2)$. A fixed point of the dynamics occurs if $\Delta p_i(p_1,p_2)=p_i'(p_1,p_2)-p_i=0$. The position of fixed points and the stability properties do not change if we examine $\delta p_i(p_1,p_2)=\Delta p_i(p_1,p_2)\overline{w_i}(p_1,p_2)=\varphi_i(p_1,p_2)-\overline{w_i}(p_1,p_2)p_i(p_1,p_2)$. This condition is quadratic in the control parameter m and can be rearranged as $(i\neq j)$

$$\begin{aligned}\delta p_i(p_1,p_2)=&(1-\omega)p_i(3p_i-2p_i^2-1)\\&-(4(1-p_i)p_i-\omega(1-2p_i)^2)(p_i-p_j)m\\&+(1-\omega)(1-2p_i)(p_i-p_j)^2m^2.\end{aligned} \tag{27}$$

Note that only the relative coordinate, (p_i-p_j), scales with m. The above set of equations has exactly the same fixed points as the system (5) and (6). However, the Jacobian matrix and its eigenvalues are of different form. Namely, the latter now read

$$\hat{\lambda}_1=-1+\omega+4m, \tag{28}$$

$$\hat{\lambda}_2=-\frac{1-\omega+2m(2m-3)}{1-2m}, \tag{29}$$

i.e. $\hat{\lambda}_i=(1-2m)\lambda_i$, compare Eqs. (24) and (25). With $\hat{\lambda}_{1,2}=0$ solved for m, this leads again to the critical points from Appendix A, see also Eqs. (8) and (9).

Up to linear order in m we have approximately $\delta p_i\approx\delta^L p_i(p_1,p_2)=(1-\omega)p_i(3p_i-2p_i^2-1)-(4(1-p_i)p_i-\omega(1-2p_i)^2)(p_i-p_j)m$, such that $\delta^L p_i(p_1,p_2)=0$, solved along the diagonal $(p_1,1-p_1)$ leads to the pair of internal equilibria $(\hat{p}_1,\hat{p}_2)=(y_i,1-y_i)$ given by

$$y_{1,2}=\frac{1}{2}\pm\sqrt{(1-4m)}\frac{\sqrt{(1-\omega)(1-\omega-4m)}}{2(1-\omega)(1-2m)}, \tag{30}$$

which only differ from Eq. (7) by the factor of $\sqrt{1-4m}$ in the second term. The eigenvalues of the Jacobian $\mathbb{J}(y_i,1-y_i)$, computed similar to Appendix A, read

$$\tilde{\lambda}_1=\hat{\lambda}_1=-1+\omega+4m, \tag{31}$$

$$\tilde{\lambda}_1=\frac{1+16m^2-2m(4-\omega)-\omega}{1-4m}. \tag{32}$$

The condition $\tilde{\lambda}_1=0$ yields (once more) $\tilde{\mu}_1(\omega)=\mu_1(\omega)=(1-\omega)/4$ for the first critical point. Moreover, $\tilde{\lambda}_2=0$ gives

$$\tilde{\mu}_2(\omega)=\tfrac{1}{16}(4-\omega-\sqrt{\omega(8+\omega)}), \tag{33}$$

such that if migration rate is lower than $\tilde{\mu}_2(\omega)$, we observe stable internal fixed points of the dynamics described by Eq. (27) up to linear order. In Fig. 2(c) we compare the second critical point of the original system with its equivalent from the approximation linear in m. Note that for $\omega<1$, we have $\mu_2(\omega)<\tilde{\mu}_2(\omega)$, whereas $\tilde{\mu}_2(\omega)-\mu_2(\omega)\to 0$ for $\omega\to 1$. If ω is above 0.012, the relative error $|\tilde{\mu}_2-\mu_2|/(\tilde{\mu}_2+\mu_2)$ is smaller than 10%, i.e. the prediction of stable internal equilibria is relatively robust to cutting away information on higher order migration effects.

Appendix C. Three alleles

Here we introduce a third allele, R, to the system at frequency q. Thus, the frequency of the original wildtype allele now becomes $1-p-q$. In the most general case the RR homozygote has a unique homozygote fitness of v_{RR} and we now write the TT homozygote

fitness as v_{TT} relative to a wildtype homozygote fitness of one. The corresponding heterozygote fitnesses are ω_{+T}, ω_{+R}, and ω_{RT}.

The average fitnesses of the three alleles can be written as

$$f_T = v_{TT}p + \omega_{RT}q + \omega_{+T}(1-p-q), \tag{34}$$

$$f_+ = (1-p-q) + \omega_{+T}p + \omega_{+R}q, \tag{35}$$

$$f_R = v_{RR}r + \omega_{RT}p + \omega_{R+}(1-p-q). \tag{36}$$

In general, the expected frequency of the ith allele in the next generation, p_i', is the product of the alleles frequency p_i and fitness f_i normalized by the sum of this product over all alleles,

$$p_i' = \frac{f_i}{\sum_j p_j f_j} p_i. \tag{37}$$

With three alleles, the fixed points along the edges of the simplex, where the frequency of one allele is zero, are equivalent to the corresponding two-allele case presented above. The remaining internal fixed point can be found by setting the three averages fitnesses equal to each other and solving the set of simultaneous linear equations. This gives the coordinates of the central unstable (assuming underdominance) equilibrium as

$$\hat{p} = \frac{1}{\alpha} v_R(\omega_{T+}-1) + \omega_{R+}(\omega_{R+} - \omega_{T+} - \omega_{RT}) + \omega_{RT} \tag{38}$$

and

$$\hat{q} = \frac{1}{\alpha} \omega_{T+}^2 + v_T(\omega_{R+}-1) + \omega_{RT} - \omega_{T+}(\omega_{R+} + \omega_{RT}), \tag{39}$$

where

$$\alpha = \omega_{T+}^2 - v_R - v_T(1 + v_R - 2\omega_{R+}) + 2\omega_{T+}(v_R - \omega_{R+} - \omega_{RT}) + (\omega_{R+} - \omega_{RT})^2 + 2\omega_{RT} \tag{40}$$

which exists if both $\hat{p} > 0$, $\hat{q} > 0$ and $\hat{p} + \hat{q} < 1$.

If there is three-way underdominance between all alleles, the minimum transformation threshold for the modified allele can be lower than if a pair of alleles are considered individually, Fig. 9A. In terms of transformation strategies, if a linked effector gene results in a substantial fitness cost, a population transformation might be more achievable by a two step process, first transforming the population with a sightly less fit modified allele; then transforming the modified population with a combined underdominant-effector construct. Similarly, if there are multiple wildtype alleles that together have a heterozygous fitness advantage, the transformation threshold is higher than if it is inferred with respect to a single wildtype allele, Fig. 9B. Regardless of how many alleles are in underdominance with respect to each other, in this system, fixation of the modified allele $p=1$ is stable if its homozygous fitness is greater than both of its heterozygote fitnesses, $v_T > \omega_{T+}$ and $v_T > \omega_{RT}$, and bi-stability with wildtype can be maintained even if there is no underdominance with respect to the third allele. This is illustrated in Fig. 9C and D.

Three alleles predict a maximum of seven fixed points in a single population. This predicts a maximum of 7^2 fixed points,

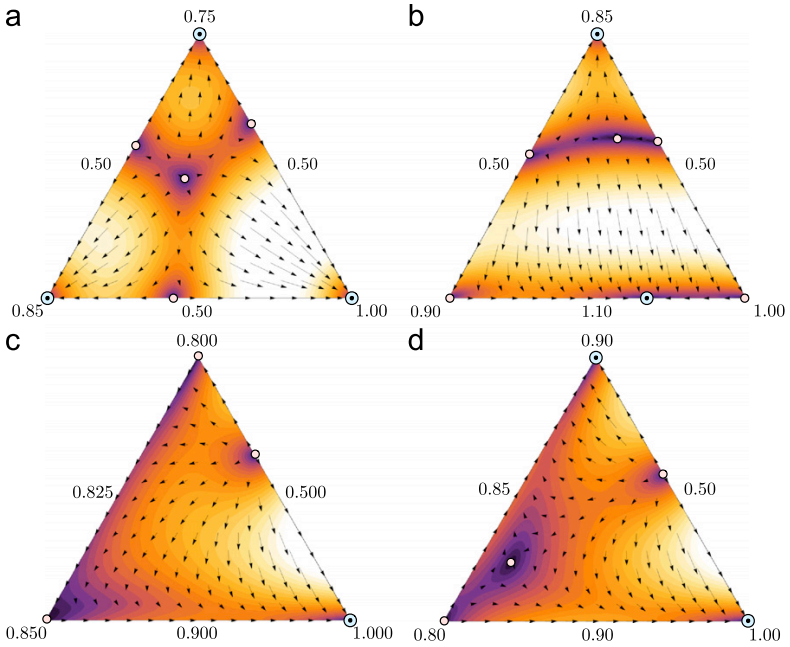

Fig. 9. Dynamics of a three-allele model in a single population. The shading indicates rate of change in joint allele frequencies on a scale from dark (slow) to light (fast). Arrows indicate direction of change. Unstable equilibria as well as saddles are indicated with an empty disk, stable fixed points are black dotted disks. At the vertexes of the simplex the population is fixed for one of the three alleles, and the corresponding allele is lost from the population at points along the opposing edge. In all four panels the representation is wildtype + in the lower right corner, type R in the lower left corner, and type T in the top corner. The genotypic fitness values are given in each panel: near the vertices the homozygote fitnesses ($v_{++}=1, v_{RR}, v_{TT}$), along the edges the heterozygote fitnesses ($\omega_{+R}, \omega_{RT}, \omega_{+T}$). (A) Full three-way underdominance. $\omega_{+R}=\omega_{RT}=\omega_{+T}=0.5$, and $v_{++}=1, v_{RR}=0.85, v_{TT}=0.75$. With fitness asymmetry among the homogenous genotypes, the central unstable point moves towards higher frequencies of the less fit genotypes. (B) Overdominance between two wildtype alleles. $\omega_{+R}=1.1, \omega_{RT}=\omega_{+T}=0.5$, and $v_{++}=1, v_{RR}=0.9, v_{TT}=0.85$. Overdominance between the remaining alleles raises the transformation threshold of the modified allele. (C) $\omega_{+R}=0.9, \omega_{RT}=0.825, \omega_{+T}=0.5$, and $v_{++}=1, v_{RR}=0.85, v_{TT}=0.8$. If directional selection with R exists with fitness increasing away from a less fit TT homozygote, fixation of T is unstable despite heterozygote disadvantage (underdominance) with wildtype. This may provide insight into how some types of underdominant changes can evolve between species, by transiting via intermediate alleles. (D) $\omega_{+R}=0.9, \omega_{RT}=0.85, \omega_{+T}=0.5$, and $v_{++}=1, v_{RR}=0.8, v_{TT}=0.9$. If directional selection exists and RR is less fit than the other homozygotes, underdominance can remain bi-stable between TT and wildtype ++.

when migration rates are low, in a coupled two-deme system. Nine of these points can be stable equilibria (three are trivial fixations), one central point is unstable and all others are saddle points, if they exist for a given migration rate. Since a two-dimensional simplex exists for each population ($\mathcal{S}^2$) the joint state space for the coupled populations is four-dimensional ($\mathcal{S}^2 \times \mathcal{S}^2$); however, the state space is not simply a pentachoron simplex ($\mathcal{S}^4$, a four-dimensional triangle) but exists over a broader area. This is because the allele frequencies, when considered jointly for both populations, can be at any position within their respective $\mathcal{S}^2$'s (also, allele frequencies do not sum to one when considered jointly for both populations). This is analogous to the simpler case in Fig. 3 where an $\mathcal{S}^1 \times \mathcal{S}^1$, for two alleles in two populations, exists on a two-dimensional square rather than an $\mathcal{S}^2$ triangle. If a dimension is assigned to each allele frequency in each population, we can say the $\mathcal{S}^1 \times \mathcal{S}^1$ coupled system is in a plane across $\mathbb{R}^4$ rather than the $\mathcal{S}^2$ plane in $\mathbb{R}^3$, but both are two-dimensional. Similarly $\mathcal{S}^2 \times \mathcal{S}^2$ is distributed across $\mathbb{R}^6$ rather than as $\mathcal{S}^4$ in $\mathbb{R}^5$, but both $\mathcal{S}^2 \times \mathcal{S}^2$ and $\mathcal{S}^4$ are four-dimensional.

Even with three-way pairwise underdominance, at a stable migration-selection equilibrium there cannot be more alleles present than the number of populations (a detailed argument is given in Karlin and McGregor, 1972a), so even if migration rates in the two-deme model are permissive to stable maintenance of polymorphism, one of the three alleles is expected to be lost. Thus, starting from the point of view of a fully underdominant system in stable equilibrium, the critical migration rates derived for the two-allele case are applicable even if additional underdominant alleles are possible. To illustrate three alleles in two populations we modify p and q in Eqs. (34)–(36) to read, after migration, as $p_1 = (1-m)p_1 + mp_2$ and $q_1 = (1-m)q_1 + mq_2$ for the first population and the corresponding terms are also written for allele frequencies in second population, where, for example, p_1 is the frequency of p in population 1, and m is the fraction of migrants each generation as given previously for the two-allele case. The stable maintenance of two alleles (in underdominance) in two coupled populations for this three-allele system is illustrated in Fig. 10.

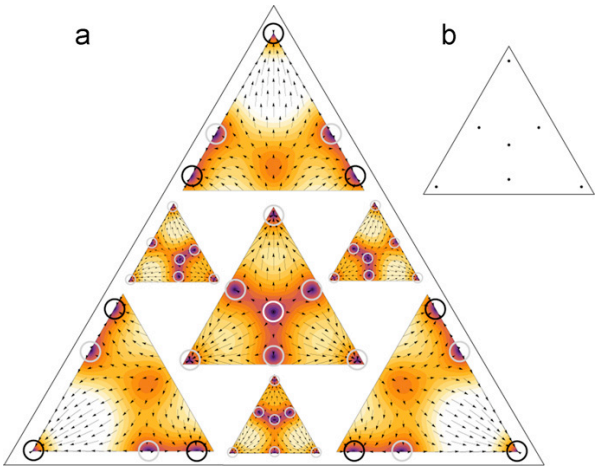

Fig. 10. A schematic illustrating the fixed points and their stability in slices of the four-dimensional state space of three alleles in two populations. (A) A useful visualization in this context is a two-dimensional simplex for population 1 ($\mathcal{S}_1^2$), and at each point within this simplex an additional two-dimensional simplex also exists for population 2 ($\mathcal{S}_2^2$, four total dimensions). Consider the large outlined triangle to be $\mathcal{S}_1^2$, within this illustrative $\mathcal{S}_2^2$'s are arranged according to their relative positions within $\mathcal{S}_1^2$. In this example, all homozygotes have equal fitnesses, all heterozygotes have half the fitness of the homozygotes (cf. Fig. 9A), and the migration rate is $m=0.06$. The approximate positions of fixed points are indicated with open circles, which may not exist in precisely these illustrative slices, but are expected to be nearby in the four-dimensional space. The central unstable equilibrium is outlined in white, saddle points in gray, and stable equilibria in black. Note that some points that appear to be stable equilibria in two dimensions are actually saddle points in four dimensions. At this migration rate six of the 49 possible fixed points have merged and disappeared, so a total of 43 fixed points are indicated. Of interest are the non-trivial stable fixed points on the outside edges of the "corner" $\mathcal{S}_2^2$'s, where the allele is at a high frequency in one population and at low frequency in the alternate population. (B) The actual positions of the internal simplexes in panel A are indicated as points within the first population simplex. Except for the central point, these are closer to the edges than can be shown in A.

Appendix D. Fluctuations

Ultimately, in populations of finite size, the concept of stability is not applicable any more. The only two absorbing states are complete fixation or complete loss of one of the alleles. However, with underdominance, the loss of polymorphism in coupled populations may take a very long time if population sizes are large and selection is very strong relative to migration. For a given set of parameter values, if a polymorphism is stable in infinite populations, we can ask the question of how long until polymorphism is lost in finite populations. To answer this we have provided illustrative examples from simulations using Kimura's pseudosampling method (Kimura, 1980): Pseudosampling rescales a uniform random variate to have the same variance of that expected under genetic drift as an approximation to the diffusion of alleles in a finite population. The change in an allele's frequency due to deterministic forces, here selection and migration, is then adjusted in each generation. The adjustment is according to the appropriately scaled random variate. This method is a computationally efficient and gives reasonably accurate approximation of genetic drift (Kimura, 1980). Some illustrative results for various configurations in parameter space are given in Fig. 11. Simulations have been performed with alleles starting at the non-trivial stable equilibrium point (in a deterministic sense) and were jointly iterated each generation until the difference in allele frequencies between the populations collapsed to less than 1% and the minor allele frequency in each population was less than 1%. We set a maximum upper time bound of 10^5 generations in the simulations, and for plotting purposes have a maximum of 10^4 generations. Because of this bound, an expectation cannot be accurately calculated. Instead we show a range of more informative lower percentiles for the time until loss. As modeled here, if the population size is large (>100 diploid individuals) and parameter configurations are far from critical boundaries, a difference in allele frequencies can be maintained for 10^4 generations with a probability greater than 99%. As population sizes decrease, or critical boundaries are approached (with increasing migration, and/or heterozygote fitness, and/or decreasing asymmetric homozygote fitness) the time until loss monotonically decreases.

Note that the evolution of modifying factors such as mate choice discrimination or genetic suppression can be quite rapid in circumstances where there is strong selection (e.g., Soans et al., 1974; McInnis et al., 1996; Charlat et al., 2007). Because of this we are hesitant to make predictions beyond 10^4 generations.

If the two-deme system is fully symmetrical, $v=1$, fixation or loss of the T allele in both populations is equally likely. However, it is found that with even small asymmetries in homozygote fitnesses, $v<1$, the probability of fixation of the allele corresponding to the less fit homozygote is dramatically reduced. The proportion of fixation out of the total number that were fixed or lost within the time period considered was 9×10^{-3} for $v=0.98$, 8×10^{-4} for $v=0.97$. No fixations were observed out of 10^4 replicates for $v\leq0.96$. It is likely that genetically modified organisms resulting in underdominance will have reduced fitness relative to wildtypes. This provides a degree of fail-safe into the

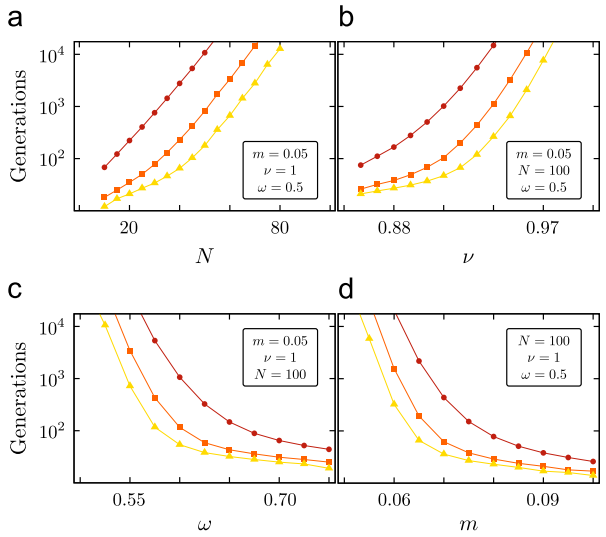

Fig. 11. Time until loss of underdominant polymorphism in populations of finite size. Results from 10,000 simulated replicates are plotted. The 50th percentile is represented by dark circles, the lower 5th percentile by medium shaded squares, and the 1st percentile by light triangles (color in the on-line version). Unless otherwise indicated, all points are plotted with $\omega = 0.5$, $v = 1$, $m = 0.05$, and the diploid population size $N = 100$. All times are in generations. (A) The destabilizing effect of small population sizes is illustrated. (B) The destabilizing effect of unequal homozygote fitnesses. (C) The effect of increasing heterozygote fitness. (D) The effect of increasing migration rates.

reversibility of the system; when a local population transformation is disrupted, it is much more likely that the genetic modification will be lost from the wild rather than achieving full fixation.

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3.2 Heterozygote disadvantage in subdivided populations of finite size

The deterministic evolutionary dynamics of heterozygote disadvantage respecting population structure has been well established and studied under various aspects, compare to Section 3.1, as well as works by Karlin and McGregor [1972a] and Karlin and McGregor [1972b]. In contrast, stochastic evolutionary dynamics in structured populations that exhibit heterozygote disadvantage have so far attracted much less attention. Typical approaches to spatially extended evolutionary dynamics consider the individuals on a spatial setting, e.g., on a lattice or network [Hauert and Szabó, 2005; Nowak and May, 1992; Ohtsuki et al., 2006; Perc and Szolnoki, 2010; Szabó and Fáth, 2007; Traulsen and Claussen, 2004]. In order to model coupling between populations of identical genetic background, we have to take a different path. The system of two population exchanging migrants is modeled as one macro-system. Thus, we define a Moran process that only considers one reproductive event at a time, which excludes simultaneous changes in the two sub-populations. Models of interacting populations that occupy patches are no novelty. Typically, infinitely long chains of populations, or growing fronts are considered to study local differentiation Kimura and Weiss [1964], or range expansions, see [Korolev et al., 2010] and references therein.

The two alleles at a single locus are called A and B, and follow the fitness pattern given in Table 3.1. The two populations are of finite sizes, N_1, and N_2. Under random mating, see Section 1.4, we can sufficiently describe the two-population system with the pair of allele numbers (i_1,i_2), where $i_k \in \{0,\dots,N_k\}$. Given the state (i_1,i_2), the five possible transitions are

$$\begin{aligned}
(i_1,i_2) &\to (i_1,i_2)\\
(i_1,i_2) &\to (i_1+1,i_2)\\
(i_1,i_2) &\to (i_1-1,i_2)\\
(i_1,i_2) &\to (i_1,i_2+1)\\
(i_1,i_2) &\to (i_1,i_2-1).
\end{aligned} \tag{3.2.1}$$

The only absorbing states are (0,0), and (N_1,N_2). All other states on the boundaries $(\{0,N\},i_2)$, $(i_1,\{0,N\})$, with $0 < i_k < N_k$, are reflecting for $m > 0$. This two dimensional one step process does not have a non-trivial stationary distribution. However, we can look at histograms of the transient stochastic dynamics, at the probability of fixation or loss of the underdominant allele, and the associated mean fixation or extinction times numerically.

Some of the questions we can address with this model are the following. How does the ratio of loss to fixation depend on the initial condition and on the fitness differences? How long can we expect a successfully transformed local population to maintain the modified allele? If one population is considerably larger than the other, what is the extinction time in the resulting island-continent model?

Whether the system is more likely to exit in (0,0), or (N_1,N_2) depends on the initial condition. For $1 > \nu > \omega$, the central unstable fixed point moves to higher values along the diagonal $x_1 = x_2$, and thus the absorbing state (0,0) is reached with higher probability for most initial conditions. Especially, for systems that reach the corner where the desired allele is fixed only in one population, ultimate loss becomes more likely than complete fixation as the fitness asymmetry increases. Fitness asymmetry provides a kind of fail-safe mechanism. Complete fixation of the genetically modified allele, linked to the underdominant one, becomes unlikely. This is a desired situation in genetic pest management. In fact values of ν below the fitness of wildtype homozygotes are almost exclusively the case, because wildtype homozygotes have already adapted over a long time and are typically most fit.

In agreement with the deterministic prediction, see Section 3.1, the time spent before absorption depends on the value of migration rate. By simulations, a clear separation between two phases can be found. The associated critical value of migration rate is very close to the boundary between two different power law regimes. Below the critical value the process spends a long time in the neighborhood of the state where the allele of interest is fixed in one and almost lost in the other population.

In case of a size asymmetry $N_2 \ll N_1$ we suggest an adiabatic elimination of one dynamics variable: In the large population, the underdominant allele cannot invade, the small population experiences loss to and influx from a large basin of wildtype alleles. The limit case $N_2 \to \infty$ leads to a one-dimensional Markov chain on $\{0,\dots,N_1\}$, where N_1 is reflecting and 0 is absorbing. For such a process an analytical treatment in the spirit of Section 1.3 is possible [Goel and Richter-Dyn, 1974]. In contrast to the typical evolutionary dynamics of two types, compare to Section 1.2, due to migration, there can be a second internal fixed point of the replicator dynamics in the island population. Hence, we observe a reversal of local drift induced by migration between island and continent.

From these findings, conclusions can be drawn concerning the technical difficulties of establishing an underdominant allele which can establish resistance in potential disease vector species.

A stochastic model for heterozygote disadvantage in subdivided populations

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Heterozygote disadvantage, or underdominance, is a component of natural evolution and can be used to establish genetic constructs in wildtype populations. In single populations underdominance leads to bistable evolutionary dynamics: Below a certain mutant frequency the wildtype succeeds. Above this point, the potentially underdominant mutant fixes. In very large subdivided populations that exchange migrants there can be an evolutionary stable state with coexistence of wildtype and modified individuals. This is due to a migration-selection equilibrium (selection against rare recent immigrant alleles that tend to be heterozygous). Here, we focus on the stochastic evolutionary dynamics of such a system, where demographic fluctuations in the two coupled populations are the main source of internal noise. We construct a variant of the Moran process in which the mutant can only fix or become extinct after a certain time. We discuss the influence of fitness, migration rate, and the relative sizes of the two populations on the mean extinction times of a group of underdominant mutants.

Introduction

A population can evolve due to differences in relative reproductive success over a life cycle. Fitness, in an evolutionary genetic sense, is defined as the relative expected number of descendants in the next generation based on an individuals genotype. In diploid organisms, two alleles can result in three genotype combinations, two homozygous genotypes with two copies of the same allele and heterozygotes with one copy of each allelic type. Heterozygote disadvantage in reproductive success is termed underdominance: individuals that have heterozygous genotypes have a lower relative fitness than homozygotes. The fundamental properties of underdominance are well known [1, 2, 3]. One of these is that underdominance acts as an evolutionarily bi-stable switch. An underdominant allele is expected to be lost, if the initial frequency is below a certain threshold, but can also proceed to fixation, if the initial frequency is above this threshold. This threshold frequency is determined by the fitness values of the genotypes involved [4, 5]. The evolutionary dynamics induced by underdominance are similar to the evolutionary dynamics of a coordination game, such as the stag hunt [6, 7, 8, 9].

Under natural conditions underdominance can be caused by chromosomal rearrangements [10]. For example, individuals that are heterozygotes for a reciprocal translocation suffer from reduced fertility due to a disrupted number of copies of genes in the affected chromosomal region (i.e. segmental aneuploidy) [11]. Interestingly, chromosomal rearrangements that can result in underdominance are known to sometimes accumulate between closely related species [12, 13]. Additionally, they may simultaneously contribute to fitness differences and reproductive isolation during speciation [14].

As an artificial genetic construct, underdominance has been proposed as a method to stably establish linked alleles with desirable properties in the wild; for example, rendering insect populations resistant to diseases that otherwise can be transferred to humans (or other species), such as malaria or Dengue fever [15]. The bi-stable nature of the evolutionary dynamics suggests that a sufficient release of transformed individuals will ultimately result in complete fixation of the allele in a population. Additionally, release of sufficient numbers of wildtypes can then bring the population back to its original state, if desired; thus, the system is reversible.

Underdominant polymorphism is eventually lost or completely fixed in single populations. However, it is known that it can become stable at mixed frequencies due to a migration-selection equilibrium in large populations that exchange a fraction of migrants [16, 17, 18]. There is a bifurcation point of the migration rate between two populations below which an underdominant polymorphism is maintained in an infinitely large population. Migration rates above this point result in sufficient mixing that the two population system reduces to a single population and polymorphism is lost. This critical value and the mere existence of migration-selection equilibria sensitively depend on the genotypic (constant) fitness configuration, as well as on migration rate asymmetry [18].

Initial testing of genetic pest management systems is likely to take place on more isolated physical or ecological islands [19, 20, 21], which will also have smaller insect population sizes that may not be well approximated by dynamics under an infinite population assumption. Here, we focus on extending the understanding of underdominant dynamics in multiple demes to include stochastic effects that stem from finite population size. Generations are overlapping in species that do not strictly follow discrete time reproductive patterns. Hence, we concentrate on Moran models describing the stochastic invasion and fixation of transformed or mutant alleles in a system of coupled populations. A Moran process considers a single reproductive event in one time step such that in a population of size N, after N steps each individual has reproduced once on average. If the timescales are such that further mutations that potentially alter the evolutionary dynamics can be excluded, loss or fixation of a given allele are the only possible outcomes. As a simplification of our stochastic model, we assume that the two populations involved in exchanging migrants do this at the same rate. If that is not the case, symmetry is broken further, which lies beyond our scope here. However, we briefly discuss coupled pop-

ulations of different size which results in asymmetric rates of birth and death events between the populations. Relevant questions are: How likely are a certain number of genetically transformed underdominant alleles, released into both populations, to take over or become extinct? How long can we expect a successfully transformed local population to maintain the modified allele, and what is the ratio of outcomes when the system ultimately breaks down (complete loss verses complete fixation in both populations). If one population is much larger than the other, such that the mutant cannot invade, what is the extinction time in the resulting island-continent model?

The manuscript is organized in the following way. The next part of this section briefly repeats the mathematical aspects of evolutionary dynamics in an infinitely large population. Then, we introduce a Moran model in two dimensions. The section ends with the introduction of a one-dimensional island continent model. In the Methods section we first give the precise formulation of the discrete stochastic model in two dimensions and argue how we access its properties by simulations. Secondly, in the Methods we introduce the island-continent model, which allows a prediction for the mean extinction times of the underdominant allele in a small island population. All results are discussed and summarized in the final section.

Replicator dynamics

With B we denote the wildtype allele, whereas A represents a transformed (or mutant) allele. Given a single locus two allele model of diploid organisms, there are three genotypes possible: BB, AB, and AA. We set the average allelic fitness of wildtypes (BB) to 1 and all other fitness values are measured relative to this value; We use ω to parameterize the fitness of heterozygote genotype (AB), and ν to measure the fitness of homozygous mutants (AA). The fitness configuration $\omega < \nu \leq 1$ leads to underdominance or heterozygote disadvantage. Under random mating, we can describe the population by the frequencies of the alleles (i.e., random union of gametes predicts the relative abundance of initial zygotic genotypes in the population before applying selection). For allele A with relative abundance p in a single population, the average fitness is then given by $f_A = \nu\, p + \omega(1-p)$. Likewise, for the wildtype allele B we have $f_B = (1-p) + \omega\, p$. In general, for overlapping generations, a replicator equation describes the change in allele frequency in an infinitely large (well mixed) population in continuous time:

$$\begin{aligned} \dot{p} &= \left(f_A - \overline{f}\right) p \\ &= \left(f_A - f_B\right)(1-p)\, p. \end{aligned} \tag{1}$$

Here, $\dot{p} = dp/dt$ denotes the temporal derivative and $\overline{f} = p\, f_A + (1-p) f_B$ is the total average fitness of the population. The zeros of Eq. (1) give the evolutionarily stable states, $\hat{p}_k$. In the case of underdominance, $\omega < \nu \leq 1$, it is easy to show that $\hat{p}_1 = 0$, $\hat{p}_2 = 1$, or $\hat{p}_3 = (1-\omega)/(1+\nu-2\omega)$, where $\hat{p}_{1,2}$ are stable fixed points and $\hat{p}_3$ is an unstable fixed point.

One way of treating the case of two local populations that exchange migrants is to introduce a parameter m as the rate of migration. In the arbitrarily small time interval dt, the fraction of immigrants entering one population, coming from the other, is $m\, dt$. Hence, $(1-m)dt$ is the fraction of non-migrant individuals. In the two population case, let p_j be the frequency of allele A in population $j = 1, 2$. With migration pumping in alleles from the other population, the mixed frequencies that contribute to the change in p_i over time are consequently $\tilde{p}_j = (1-m)p_j + m\, p_k$, where $k \neq j$ in both populations. The total average fitness in either population can now be given as $\overline{f_i} = \tilde{p}_i\, f_A(\tilde{p}_i) + (1-\tilde{p}_i)\, f_B(\tilde{p}_i)$. Hence, the replicator equation for the coupled system $(i, j = 1, 2,\ i \neq j)$ reads

$$\begin{aligned} \dot{p}_i = &\left(f_A(\tilde{p}_i) - f_B(\tilde{p}_i)\right)(1-\tilde{p}_i)\,\tilde{p}_i \\ &- m\,(p_i - p_j)\,\overline{f_i}. \end{aligned} \tag{2}$$

These dynamic equations follow from Eq. (1), $\dot{p}_i = f_A(\tilde{p}_i)\,\tilde{p}_i - p_i\,\overline{f_i}$ [18]. The number of fixed points and their stability properties are controlled by the rate of migration. The points $(0,0)$ and $(1,1)$ are always stable. Migration has no effect on the diagonal $p_1 = p_2$, because exchanging alleles between populations at equal frequencies results in no change in either of them. For sufficiently small migration rate $p_1 = p_2 = (1-\omega)/(1+\nu-2\omega)$ is an unstable fixed point (a saddle otherwise), similar to the singe population case. Another important result is that for $\nu = 1$, if $m \leq \mu_c = (3 - \sqrt{5+4\,\omega})/4$ there are evolutionary stable states in the interior of the joined allele frequency space, i.e. where A is neither fixed, nor lost. These stable fixed points of the dynamics are located on the symmetry axis, $p_2 = 1 - p_1$. For general fitness values $\nu \leq 1$, this symmetry is broken, but approximations of the critical migration rate μ_c can be made [18].

Moran process

Here, we introduce a Moran model that describes a Markov chain by probabilistic birth and death events in two dimensions. Our main assumption is that mate choice is random. In this case individuals in the population can be thought of as passing through the Hardy-Weinberg expectations at some point in the life-cycle before selection. Hence, we can consider the system as if individual alleles (i.e. gametes) reproduce and die. Reproduction is proportional to fitness, death is random, and population sizes are held constant. Such discrete stochastic processes are commonly examined in evolutionary biology, mostly in one dimension. They are typically used to describe the microscopic evolutionary dynamics in single uncoupled populations of finite size [22, 23, 24], and are particularly famous in evolutionary game theory [25, 26, 27]. From the microscopic dynamics, one is interested in macroscopic quantities such as the probability of extinction starting from a given allele frequency and the associated average extinction time.

Our two populations are of size N_1, N_2, respectively. Hence, the two stochastic variables that jointly describe the state in the two population case are denoted i_1 and i_2, which are the number of individual copies of allele A (type A) in each population. Thus, type B has frequencies $N_1 - i_1$, $N_2 - i_2$, respectively. For convenience we introduce the fractions $x_1 = i_1/N_1$ and $x_2 = i_2/N_2$. For the average allelic fitness functions we can now write

$$f_A(x_j) = \nu\, x_j + \omega\,(1 - x_j)\,, \tag{3}$$

$$f_B(x_j) = (1 - x_j) + \omega\, x_j. \tag{4}$$

For a consistent stochastic model several events have to be considered independently in one time step of the Moran process.

First, with probability α a reproductive event occurs in population 1. With probability $1-\alpha$ a reproductive event occurs in population 2. We can exclude simultaneous reproductive events in both populations. This makes it possible to treat the two population system as one Markov chain with the two absorbing states $(0,0)$, and (N_1, N_2). One population, say the one of smaller size, may change more rapidly than the other. This difference is captured in the rates α and $1-\alpha$. If we think of the α's as reproductive rates, a possible choice is $\alpha \propto N_1/(N_1+N_2)$, and thus $1-\alpha \propto N_2/(N_1+N_2)$. Hence, for the study of two populations of comparable size, it is convenient to set $\alpha = 0.5$. The choice of α does not change the migration-selection equilibria predicted by the replicator system Eq. (2), compare

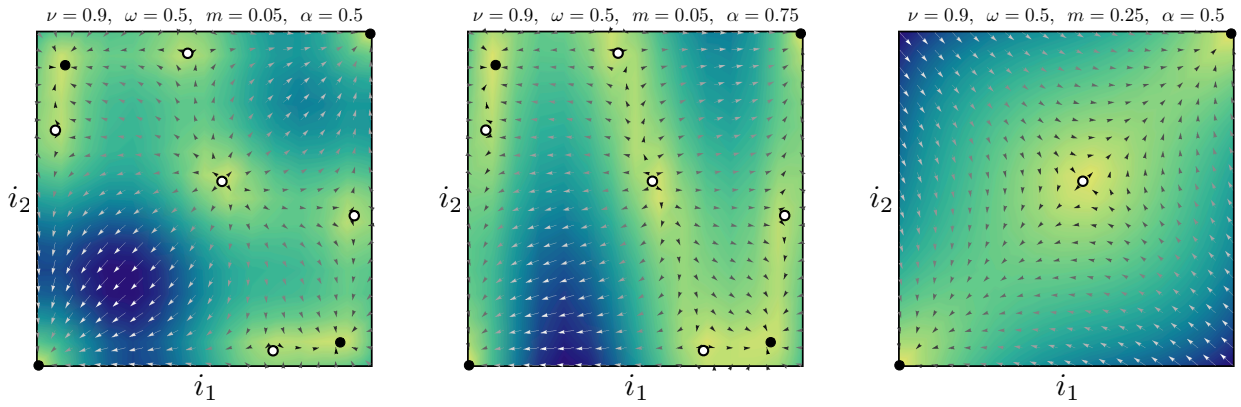

Figure 1: Phase portrait of the stochastic flow ($N_{1,2} = 1000$). The arrows (length rescaled) indicate the highest probable net direction of selection, i.e. the vector $\{(P_1^+ - P_1^-), (P_2^+ - P_2^-)\}^T$. The shading indicates the average speed of selection, namely $[(P_1^+ - P_1^-)^2 + (P_2^+ - P_2^-)]^{1/2}$: The darker she shading, the faster the system is expected to leave the given state. All panels share the same fitness valley with $\omega = 0.5$ and $\nu = 0.9$. Stable fixed points of the replicator dynamics are given by full disks. Unstable fixed points and saddles are given by empty disks. **Left panel**: The migration rate is below the critical value, such that the replicator dynamics has internal stable fixed points. $m = 0.05 < \mu_c$, and the number of alleles changes equally fast in both populations $\alpha = 0.5$. **Central panel**: For the same migration rate, but with one population changing three times as fast compared to the other ($\alpha = 0.75$), the pattern changes. However, number and positions of (stable) fixed points of the replicator dynamics Eq. (2) associated with the parameter choice remains the same. **Right panel**: Stability of the replicator dynamics changes critically with the migration rate m. For sufficiently frequent migrations, $m > \mu_c$, the system proceeds very fast to a simultaneous all or nothing state.

Fig. 1. Only the rates of change between fixed points are increased in the larger population that contains more events per unit time.

Secondly, in population j, an individual allele gives birth to an identical copy with a probability proportional to the average fitness of the allele. In such an event, however, we have to consider that with probability m, the birth giving individual allele is from the other population (i.e., an immigrant). Hence, type A produces an identical offspring with probability proportional to $[(1-m)x_j + m\,x_k] \times f_A((1-m)x_j + m\,x_k)$. A similar probability holds for type B, $[(1-m)(1-x_j) + m(1-x_k)] \times f_B((1-m)x_j + m\,x_k)$.

Thirdly, in each population, the total number of alleles is held constant. This implies that for each birth event, there is an independent death event: a randomly chosen individual allele is removed from the population. A type A allele is removed with probability $x_j = i_j/N$, a type B allele is removed with probability $1 - x_j = (N_j - i_j)/N_j$.

Overall, given the two population state (i_1, i_2), there are five events possible. Four of them involve a change in allele frequency i_1, or i_2. Hence, we have to define four transition probabilities in each state, $\{P_1^{\pm}(i_1, i_2), P_2^{\pm}(i_1, i_2)\}$, such that migration and selection only contribute to birth and not to random death, which occurs independently in each population. Note that, in general, fixation or loss in both populations are the only absorbing states, i.e. $P_j^{\pm}(N, N) = P_j^{\pm}(0, 0) = 0$. Due to migration, there is a non-vanishing flow perpendicular the boundaries in state space. When the allele of interest is lost or fixed only in one population immigrants can push the system back into the interior, where type A is present in both populations, compare to Fig. 1 and Fig. 2.

Island and continent

Above, we introduced an α parameter to allow unequal population sizes. The logical limit of this process is where one population becomes infinite and the other remains finite. This leads to the simplified island and continent situation. Here, the focus is on an island population of relatively small size N that is coupled to an essentially infinite continent population in which the allele of interest is not present (i.e. the wildtype allele is fixed). With this the genetic modification will not invade the continent. This gives rise to a non-vanishing fitness contribution due to migration to the island: With rate m the one-dimensional island system receives wildtype immigrants from, and loses migrants of any type to, the continent. Given the fitness functions Eqs. (3) and (4) the equivalent limit case is $x_2 = i_2/N_2 \to 0$. Applying this limit to the transition rates $\{P_j^{\pm}(i_1, i_2)\}$, the single stochastic variable becomes $i = i_1$, and time can be rescaled such that $\alpha = 1$.

Hence, a one-dimensional Markov chain between $\{0, 1, \ldots, N-1, N\}$, with transition probabilities T_i^+, T_i^-, is generated by $T_i^+ = \lim_{N_2\to\infty} P_1^+(i, i_2)$ and $T_i^- = \lim_{N_2\to\infty} P_1^-(i, i_2)$. However, we have to respect that for instance $\lim_{i_2\to 0} f_X((1-m)i_1 + m\,i_2) = (1-m)f_X(i) + m\,f_X(0)$, $(X = A, B)$, where $f_A(0) = \omega$, and $f_B(0) = 1$. The continent can only contribute to the birth of wildtype homozygotes. For non-vanishing migration between island and continent we have $T_0^- = T_0^+ = T_N^+ = 0$, and $T_N^- > 0$. In the Methods section we show how the moments τ_i^r of the extinction times associated with this process can be determined from a recursion. The r^{th} moment follows successively from

$$\tau_i^r = \sum_{j=1}^{i} \sum_{k=0}^{N-j} \frac{\tau_{N-k}^{r-1}}{T_{N-k}^-} \prod_{l=k+1}^{N-j} T_{N-l}^+ / T_{N-l}^-, \tag{5}$$

where $\tau_i^0 = 1$ is the probability that allele A vanishes in the island population, and τ_i^1 is the mean life time, or average extinction time of allele A.

Methods

Moran process for two coupled populations

Introducing the migration influenced number of A alleles in each population, $\tilde{x}_1 = (1-m)x_1 + m\,x_2$, and $\tilde{x}_2 = (1-m)x_2 + m\,x_1$, where

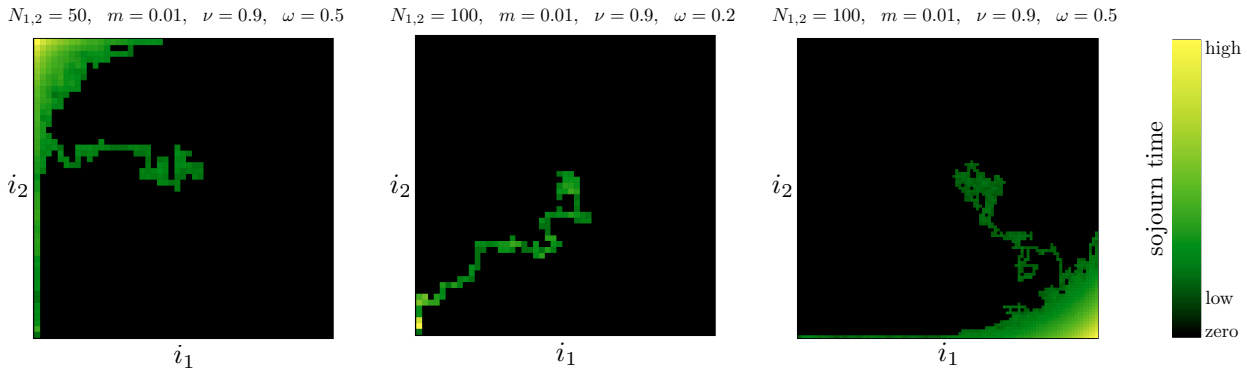

Figure 2: Typical trajectories for the loss of the extinction process of an underdominant allele in a system of two populations of the same size, $N_1 = N_2$. We show different realizations of the two dimensional Markov chain for $\nu = 0.9$, $\alpha = 0.5$, and different N, ω, and m. The initial condition is the unstable equilibrium near the center $i_1 = i_2 \approx N_{1,2}(1-\omega/(1+\nu-2\omega))$ (rounded to an integer), the final state is $(0,0)$ in all three cases. Black states are never visited, colored sites are visited at least once. The brighter the color, the more often the respective state has been visited. **Left panel**: $N_{1,2} = 50$, $m = 0.01$, $\omega = 0.5$. The process typically spends a long time near the $(0, N_2)$, $(N_1, 0)$ corners, where the waiting times are highest. **Central panel**: $N_{1,2} = 50$, $m = 0.2, \omega = 0.2$. The process proceeds fast to extinction of the underdominant allele, but slows down near $(0,0)$. **Right panel**: $N_{1,2} = 100$, $m = 0.01, \omega = 0.5$. The process spends most of the time in the $(N, 0)$ corner. Once it proceeds to extinction, it moves fast.

$x_1 = i_1/N_1$, $x_2 s = i_2/N_2$, the transition probabilities are given by

$$P_1^+(i_1,i_2) = \alpha\,\tilde{x}_1\,\frac{f_A(\tilde{x}_1)}{F_1}(1-x_1), \tag{6}$$

$$P_1^-(i_1,i_2) = \alpha(1-\tilde{x}_1)\frac{f_B(\tilde{x}_1)}{F_1}\,x_1, \tag{7}$$

$$P_2^+(i_1,i_2) = (1-\alpha)\tilde{x}_2\,\frac{f_A(\tilde{x}_1)}{F_2}(1-x_2), \tag{8}$$

$$P_2^-(i_1,i_2) = (1-\alpha)(1-\tilde{x}_2)\frac{f_B(\tilde{x}_2)}{F_2}\,x_2, \tag{9}$$

where $F_1 = \tilde{x}_1 f_A(\tilde{x}_1) + (1-\tilde{x}_1) f_B(\tilde{x}_1)$, and F_2 defined likewise are the total average fitness values in each population respecting migration between them. The probability that the state (i_1, i_2) does not change (e.g. when a type A dies and another type A is born) is thus given by $P^0(i_1,i_2) = 1 - P_1^+(i_1,i_2) - P_1^-(i_1,i_2) - P_2^+(i_1,i_2) - P_2^-(i_1,i_2)$. The only trivial boundary conditions can be formulated on the states of total extinction of one allele, as $P_j^\pm(0,0) = 0$, and $P_j^\pm(N,N) = 0$ for $j = 1, 2$. No non-trivial measure for the probability to find the system in a certain state after a given time exists.

An analytical solution of the moment generating recursions for the stationary moments is unfeasible because of insufficient boundary conditions. For instance the probability of extinction $\phi^0_{i,j}$ after an infinite number of time steps (above a given minimum) fulfills the rate equation $\phi^0_{i,j} = P^0(i,j)\phi^0_{i,j} + P_1^+(i,j)\phi^0_{i+1,j} + P_1^-(i,j)\phi^0_{i-1,j} + P_2^+(i,j)\phi^0_{i,j+1} + P_2^-(i,j)\phi^0_{i,j-1}$. To make predictions about the evolution of the system we directly simulate the stochastic process described by Eqs. (6) – (9).

Lifetime in an island population close to a continent

The average allelic fitness values in the island population of size N are

$$g_A(i) = \omega + \frac{i}{N}(1-m)(\nu-\omega), \tag{10}$$

$$g_B(i) = 1 - \frac{i}{N}(1-m)(1-\omega). \tag{11}$$

Note here that for the rescaled variable $q = (1-m)\,i/N$, we just have $g_A(i) = f_A(q)$, as well as $g_B(i) = f_B(q)$, compare Eqs. (3) and (4). The transition probabilities of the one-dimensional Moran process can be formulated as

$$T_i^+ = (1-m)\,i\,\frac{g_A(i)}{G(i)}\,\frac{N-i}{N}, \tag{12}$$

$$T_i^- = ((1-m)(N-i) + m\,N)\,\frac{g_B(i)}{G(i)}\,\frac{i}{N}, \tag{13}$$

where the normalization (total fitness) is given by $G(i) = (1-m)\,i\,g_A(i) + ((1-m)(N-i) + m\,N)g_B(i)$. Let $f_{n,m}(t)$ be the probability that the process moves from state m to state n after exactly t time steps. For this probability function the master equation

$$\begin{aligned} &f_{n,i}(t+1) - f_{n,i}(t) \\ &= T_i^+ f_{n,i+1}(t) + T_i^-\,f_{n,i-1}(t) - \left(T_i^+ + T_i^-\right) f_{n,i}(t) \end{aligned} \tag{14}$$

holds, for which we can compute the moments in the following way. The only absorbing state is $i = 0$, as $i = N$ is reflecting, $T_N^+ = 0$, $T_N^- \neq 0$ for $m > 0$. We call τ_i^r the r^{th} moment of the life time of the process starting from any $i = 1, 2, \ldots N$. For these moments, the following moment generating recursions hold [22, 24, 28]:

$$r\,\tau_i^{r-1} = \left(T_i^+ + T_i^-\right)\tau_i^r - T_i^+\,\tau_{i-1}^r - T_i^-\,\tau_{i-1}^r, \tag{15}$$

where for the zeroth moment we have $\tau_i^0 = \phi_i^0 = 1$, which is the probability that the system fixes at $i = 0$ after an arbitrary number of (but at least i) steps. Hence, for the mean life time, $\tau_i = \tau_i^1$, i.e. the first moment of the process, we find

$$1 = \left(T_i^+ + T_i^-\right)\tau_i - T_i^+\,\tau_{i-1} - T_i^-\,\tau_{i-1}, \tag{16}$$

which we can solve recursively. Introducing $v_i = \tau_i - \tau_{i-1}$, we get

$$v_i = T_i^+/T_i^-\,v_{i+1} + 1/T_i^-, \tag{17}$$

which, respecting the boundary condition and starting from $v_N = 1/T_N^-$, solves to

$$v_{N-j} = \sum_{k=0}^{j} 1/T_{N-k}^- \prod_{l=k+1}^{j} T_{N-l}^+/T_{N-l}^-. \tag{18}$$

Changing $N-j$ to j (and the upper limits of sum and product accordingly), we see that $\sum_{j=1}^{i} v_j = \tau_i$, such that the mean life time, starting from any $i > 0$, fulfills

$$\tau_i = \sum_{j=1}^{i}\sum_{k=0}^{N-j} \frac{1}{T_{N-k}^-} \prod_{l=k+1}^{N-j} \frac{T_{N-l}^+}{T_{N-l}^-}. \tag{19}$$

Similarly, all moments follow from Eq. (15), leading to Eq. (5) [24].

Results and Discussion

Extinction events in two populations of comparable size

First, let us address the ratio of fixation to loss in the system of two subpopulations of equal size. An ideal case for a locally controlled genetic pest management strategy emerges when the resistant allele A is at high frequency in one local population and at very low frequency in another. We can then ask: Given the situation of almost-all A in one population, and almost-no A in the other, what is the probability of the allele A to become extinct in both populations, $\phi^0_{i,j}$, relative to the probability to reach complete fixation, $\phi^N_{i,j}$? The answer is given in Fig. 3, where we give the ratio $\phi^N_{N-1,1}/\phi^0_{N-1,1}$, for $N_{1,2} = N = 40$, as a function of increasing fitness asymmetry $1-\nu$, with the heterozygote fitness kept constant at $\omega = 0.5$. The ratio of loss to fixation of A approaches zero for sufficiently low fitness ν. The rate of decay decreases with increasing migration rate, which is to be expected as for low values of m the system spends long times in the interior, compare Fig. 4.

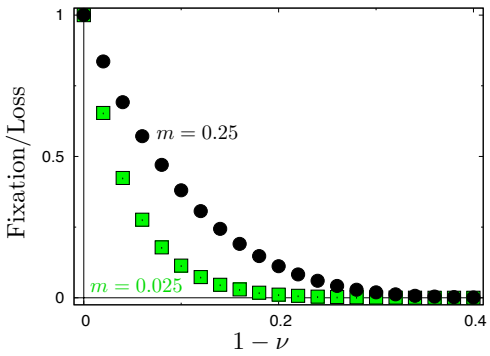

Figure 3: Initial condition near the internal stable state, $i_1 = N-1$, $i_2 = 1$. We show the ratio of fixation to loss of the underdominant allele in a system of two populations of sizes $N_{1,2} = 40$, as a function of the difference of homozygote fitness values $1-\nu$. Results are obtained from 0.5×10^6 independent simulations with a heterozygote fitness of $\omega = 0.5$.

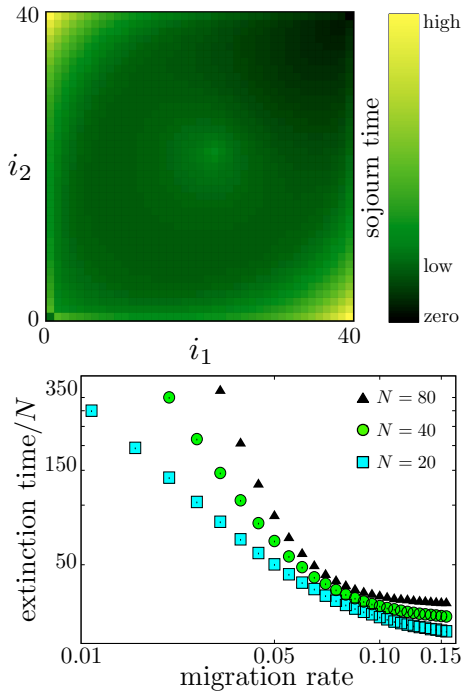

Figure 4: Histogram of the extinction process and the according extinction times as functions of the migration rate in two equally large populations; $N_{1,2} = N$, $\nu = 0.9$, $\omega = 0.5$, $\alpha = 0.5$. The initial condition is the unstable equilibrium near the center $i_1 = i_2 \approx N(1-\omega/(1+\nu-2\omega))$ (rounded to an integer), the final state is $(0,0)$ in all cases. **Top:** Histogram across the entire state space, **conditioned on extinction**, for $N = 40$, $m = 0.025$ (10^6 realizations). For each coordinate we give a record of the time spent. Black sites are never visited, colored sites are visited at least once. The brighter the color, the more often the respective site has been visited. **Bottom;** The mean extinction time in generations (divided by $N_{1,2} = N$, averaged over 10^5 realizations) for three different system sizes as a function of m, in a double logarithmic plot. $N_{1,2} = 20$ (squares), $N_{1,2} = 40$ (circles), $N_{1,2} = 80$ (triangles).

The replicator dynamics in two dimensions predicts a bifurcation pattern and a maximum of nine fixed points (Fig. 1). Number and stability of the interior fixed points are sensitively controlled by migration [18]. A stable interior equilibrium, if it exists, at migration-selection balance is disturbed by the demographic fluctuations and will ultimately result in fixation or loss of one of the alleles. Hence, one is interested in the average extinction time under various parameter configurations. To grasp an idea of how the system behaves in a single realization, we draw three typical stochastic trajectories, Fig. 2. In these examples, an important feature becomes evident. Naively one would expect the system to spend more time near interior stable equilibria. However, the process spends most of its time in the adjacent edges and corners of the joint allele frequency space. The system exits the regions around stable points (e.g. near the $(N_1, 0)$ corner) via the edge rather than on internal trajectories, see Fig. 2. This is because the demographic noise is proportional to $x_i(1-x_i)$ [22]. Hence, in the non-absorbing corners we expect long waiting times, between corners and along the symmetry axis $i_1 = i_2$ the system evolves relatively fast. An example histogram of extinction events is given in Fig. 4. For instance, the mean extinction time in a system with $N_1 = N_2 = 40$ alleles is approximately 1.4×10^4 (or 350 generations) for very small rates of migration. The extinction process spends most of its time near the $(N_1, 0)$ or $(0, N_2)$ corner. For a very long time the underdominant allele is almost fixed in one population and almost lost in the other. However, if migration becomes larger, the length of this quasi-stable period decreases. Above certain population size dependent value of migration ($m \approx 0.06$ for $N_{1,2} = 40$) the slope changes significantly, compare to Fig. 5.

The impact of system size in two equally large populations can now be quantified in terms of the average extinction time of type A. Different sizes $N_1 = N_2$ lead to significantly faster divergence of the extinction time. Fig. 4 indicates that the migration rate below which extinction of the underdominant allele is strongly delayed, (i.e., below the deterministic critical point) shifts the times to higher values with increasing system size.

In general, considering the extinction time as a function of the migration rate reveals the transition from one power law to another in the region of the critical migration rate of the replicator system. Depending on the migration rate, we can identify two regimes. In the first regime, $m < 0.05$ the extinction time scales as $\propto m^{-\gamma_1}$, with $\gamma_1 > 2$. In the second regime, $m > 0.1$ the extinction time scales as $\propto m^{-\gamma_2}$, with $\gamma_2 < 0.5$. The two power law regimes for $N_1 = N_2 = 40$ are given in Fig. 5 for a realistic choice of genotypic fitness values $\nu = 0.9$ and $\omega = 0.5$. This parameter configuration yields a critical value of $\mu_c \approx 0.06$, which can be determined numerically from the replicator equation (2). Fig. 5 analyzes this transition quanti-

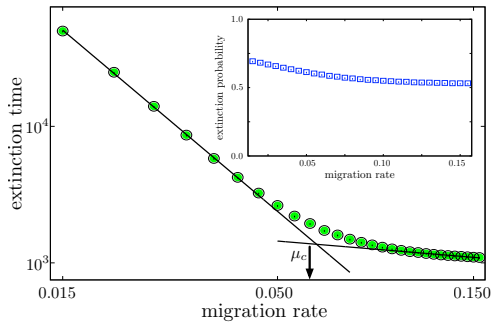

Figure 5: The mean extinction time as a function of the migration rate (10^6 realizations) for $N_{1,2} = 40$, in a double logarithmic plot. Migration reaches from 1.5 to 15 percent, mutant homozygote fitness $\nu = 0.9$, heterozygote fitness $\omega = 0.5$. The initial condition is on the diagonal near the deterministic unstable equilibrium $i_1 = i_2 \approx N(1-\omega)/(1+\nu-2\omega)$. The arrow indicates the value of critical migration rate of the deterministic replicator dynamics, Eq. (2), calculated numerically as $\mu_c \approx 0.06$. **Inset:** The probability of extinction. This probability starts at approximately $2/3$ ($m = 0.015$) and settles to the value 0.531 ($m > 0.1$).

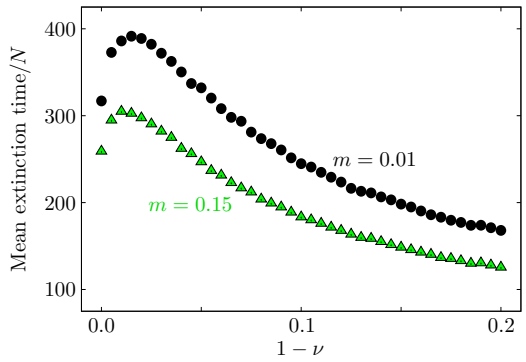

Figure 6: Initial condition near the central unstable point $i_1 = i_2 \approx N(1-\omega/(1+\nu-2\omega))$ (rounded to an integer) with $N = N_{1,2}$. We show the mean extinction time (rescaled by N) as a function of the 'intensity of selection' $1-\nu$ for $N = 100$ and different migration rates (10^5 realizations). The difference between mutant homozygote fitness and heterozygote fitness is held constant, $\nu - \omega = 0.005$. Circles: $m = 0.01$. Triangles: $m = 0.15$.

tatively for $N_{1,2} = 40$. The initial condition is chosen such that $i_1 = i_2$ are at or close to the deterministically unstable equilibrium $i_{1,2} = N(1-\omega)/(1+\nu-2\omega)$, which is near the most efficient release strategy in terms of minimum release numbers [18]. In the regime of low migration, $m < 0.06$, we find $\gamma_1 \approx 2.54$, whereas for $m > 0.06$, we come to $\gamma_2 \approx 0.25$.

For the typical fitness configurations of ω being low and ν being almost one, the extinction probability becomes very high. Although our model refers to the case of strong selection in population genetics [4], we can implement weak selection, where fitness differences are of the order of (or less than) $1/2N$. Choosing $\nu = 1-\delta$ and $\omega = \nu - \delta$ with $\delta \ll 1$ is such an example of weak fitness influence. It is surprising in this context that the extinction time can have a maximum at intermediate values of δ, see Fig. 6. This, however, highly depends on the initial condition, but not on the rate of migration. In the regime of weak selection (small fitness differences), as the system departs from neutrality, there is increasing selective pressure to move away from joint fixation in the two populations. In this case trajectories that may have almost fixed initially continue to segregate and may ultimately become lost, which results in a net increase in fixation times.

Temporary maintenance of polymorphism in an island population

The transition of one population approaching infinite size, while the other remains relatively small, leads to a birth-death process in one dimension. The one-dimensional case can be treated analytically in the sense that we can solve the recursions for the moments. However, the structure of the general solution Eq. (5) does not allow much further insight at this point, an expansion of the ratio T_k^+/T_k^- in orders of m or $\delta = 1-\nu$ does not simplify the products and sums to a satisfying degree. Hence, also here, we analyze the island population mostly numerically, or by simulations.

The transition from high to low migration leads to a local change of the gradient of selection $T_i^+ - T_i^-$, Eqs. (12) and (13). The boundary $i = 0$ is absorbing, while $i = N$ is reflecting,

$$T_N^- = \frac{m(m(1-\omega)+\omega)}{m(m(\nu-2\omega+1)-2(\nu-\omega))+\nu}, \tag{20}$$

which does not depend on the size of the island population. Furthermore, $T_i^+ - T_i^- = 0$ has the trivial solution $i = 0$, and depending on m, ν, and ω, two non-trivial solutions are given by

$$\begin{aligned}\frac{i_{+,-}}{N} =& \frac{(3-m)\omega-(1-m)\nu-2}{2(m-1)(\nu-2\omega+1)} \\ &\pm \frac{\sqrt{\nu\left((1-m)^2\nu-4m\right)+(1+m)^2\omega^2-2(1-m)^2\nu\omega}}{2(m-1)(\nu-2\omega+1)},\end{aligned} \tag{21}$$

which exists if $\nu\left((1-m)^2\nu-4m\right)+(1+m)^2\omega^2 \geq 2(1-m)^2\nu\omega$. Hence, we obtain a point μ_{1D} such that for

$$m < \frac{\nu(\nu+2)-2\nu\omega-\omega^2 \pm 2\sqrt{\nu(1+\nu-2\omega)\,(\nu-\omega^2)}}{(\nu-\omega)^2} \tag{22}$$

the deterministic one-dimensional dynamics has a stable fixed point at i_-/N, and an unstable one at i_+/N. In Fig. 7 we show histograms from simulations of the one-dimensional island model (12) and (13). For different migration rates, we see that the distribution changes significantly: In our example, for very low migration rates the underdominant allele is expected to be maintained in the system for more than 400 generations, when starting from an optimal release of $i = N$.

Summary and Conclusion

We have proposed a very simple model to predict the influence of small system size connected with system size asymmetry on the evolutionary dynamics of an underdominant allele in structured populations. As a first step, the population structure itself is chosen to be as simple as possible: We consider sub-populations of the same kind that exchange migrants at a given rate. This has the benefit of allowing a comparison with the predictions in infinitely large coupled populations [18, 16].

Firstly, for fitness asymmetry, extinction rather than total fixation of the potentially underdominant allele is the most likely outcome, if this allele has been at high frequency in one of the populations. Secondly, we find that the migration rate has a strong impact on the extinction times. Much like in the replicator dynamics, we identify a threshold below which the potentially underdominant allele can be maintained for a rather long time. We have confirmed that with increasing system size, the extinction times diverge for sufficiently low migration rate. Thirdly, the limit case of one population becoming very large also reveals that the underdominant allele can be kept in the small population

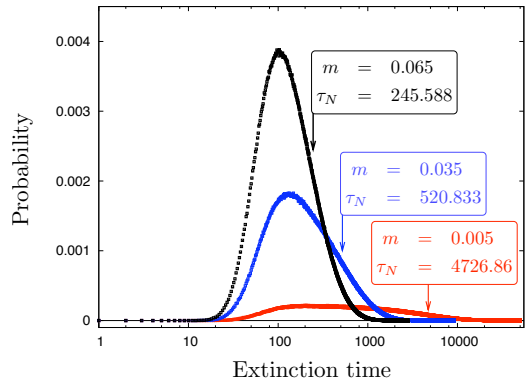

Figure 7: Histograms of the extinction time on an island population for different migration rates in a log-linear plot. The other parameters are $N = 10$, $\nu = 0.85, \omega = 0.5$. The data are from 10^7 independent simulations with initial condition N. In the figure, each arrow indicates the mean extinction time τ_N, Eq. (19) ($r = 0$), where the values from simulation and the exact formula agree nicely.

for long times. This refers to the desired situation in which one is interested in the local establishment of disease resistance (caused by an effector gene), driven by underdominance.

If selection is strong, even in small populations, for migration rates not near critical boundaries, underdominance can maintain a polymorphic state for a very long period of time. This bodes well for using underdominance to control initial testing of genetically modified insects in isolated settings so that the natural species remains untransformed in its broader range. For a wide range of parameter values the system may be stable for so long that additional factors are likely to be more important in ultimately disrupting the system. Such additional factors can be the occurrence of new mutations and/or behavioral changes [29, 30, 31].

However, results from infinite population assumptions may, in some cases, be misleading when observing finite allele frequencies. Under demographic fluctuations with variances that are quadratic in allele frequencies the stochastic process slows down near corners and along edges. Due to this nature of the random drift we observe large waiting times near the corners and transitions along edges, instead of long periods near the stable internal equilibria.

It is likely that genetically modified chromosomes will be less fit than wildtype as homozygotes, see [32] and references therein. This homozygote fitness asymmetry provides a degree of failsafe into the system. If stability is lost, the system is more likely to result in a return to a natural wildtype state, rather than reaching fixation of an artificial genetic modification across demes.

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CHAPTER 4

Conclusions

We see nothing of these slow changes in progress,
until the hand of time has marked the long lapses of ages,
and then, so imperfect is our view
into long past geological ages,
that we only see that the forms of life
are different now from what they formerly where.

Charles Darwin (The Origin of Species)

The results presented in this thesis concern two different approaches in the quantitative description of population dynamics under Darwinian selection. On the one hand, evolutionary game dynamics are considered with respect to the time to fixation of a given strategy. On the other hand, a population genetic system of structured populations is examined.

In the first part, the focus is on stochastic dynamics in evolutionary game theory and the role of selection. Essentially, all models analyze the role of selection acting on different strategies and how this effects the fixation probabilities and average fixation (or extinction) times. They deal with finite populations in which two different classes of one-step processes can be responsible for the evolutionary change. In the Moran class of processes the reproductive success of a strategy is determined by the strategic interactions through a payoff to fitness mapping. In the Fermi class, the population evolves due to individual switching of strategies based on a pairwise comparison. Selection is parameterized by a quantity called selection intensity and evolutionary dynamics can be divided into different regimes.

The regime of neutral evolution has been studied in classical population genetics [Ewens, 2004; Kimura, 1994], and can be compared to the random walk in physics [Gardiner, 2008]. When the bias from selection is weak, many important insights can be obtained from the

weak selection expansion, which corresponds to a high temperature expansion in physical systems. This concerns structured and unstructured systems alike [Gokhale and Traulsen, 2010; Kurokawa and Ihara, 2009; Nowak et al., 2004; Ohtsuki et al., 2006; Tarnita et al., 2009a; Traulsen and Nowak, 2006]. Most analytical results in this regime focus on the fixation probability, and make predictions for in which cases a mutation can be classified as beneficial. In this thesis, contributions to such weakly biased systems in well mixed populations have been presented. First, for the two most common representatives of the classes mentioned above, the weak selection expansion for the average fixation times are given. This reveales an interesting relation between the symmetry of the underlying strategic interactions and the linear perturbation terms. Next, the weak selection expansion is considered in a broader context, addressing the universality of weak selection. The fact that this is been done for well mixed systems leaves the open question of how such considerations will transfer to spatially heterogeneous populations. Approaches to analytically tackle fixation times in weakly biased population dynamics with evolutionary rules on networks are yet to be formulated. Typical weak selection results for fixation times are invariant to changes in the microscopic dynamics. Can this be carried over to systems with spatially heterogeneous interactions? In contrast to well mixed populations, the outcome of evolutionary game dynamics crucially depends on the microscopic rules, e.g., on the sequence of birth and death events in the evolutionary update [Ohtsuki and Nowak, 2006a,b].

The regime of strong selection is less accessible analytically. For instance, the 'low temperature' limit of the one-step processes considered in this thesis in not analytical in the selection intensity. However, a variant of the Moran process is discussed, such that a deterministic strong selection limit is accessible. The resulting dynamics resemble some properties of the deterministic replicator dynamics [Hofbauer and Sigmund, 1998]. The process builds a bridge between the biologically relevant case of weak selection [Bustamante et al., 2002; Fay et al., 2002; Ohta, 1997], and results typically obtained in evolutionary optimization [Mitchell, 1996; Prugel-Bennett and Shapiro, 1994]. Some properties of the fixation probability and fixation times for slightly stronger selection have been discussed recently [Mobilia and Assaf, 2010]. The co-evolutionary nature of evolutionary game theory plays a fundamental role, namely that the advantage or disadvantage of an invading mutant can change with its density [Drossel, 2001]. The asymptotic scaling of the fixation times with system size in this context has been known [Antal and Scheuring, 2006; Cremer et al., 2008], and for weak mutation rates stationary distributions have been found [Claussen and Traulsen, 2005]. On intermediate scales, between weak and strong selection, the average fixation times can behave non-monotonically with increasing bias (selection). In this thesis, it is observed that for

the typical classes of stochastic processes, e.g., for the one-step processes mentioned above, 'stochastic slowdown' can occur. This means that for biased random walks on a (bounded) interval [Goel and Richter-Dyn, 1974; Redner, 2001], the mean exit time increases with the bias, which is only possible if the transition rates depend on the density. It will be interesting to compare the results of interactions between two strategies with appropriately formulated measures in systems with more strategies.

In the second part, this thesis examines structured systems in terms of migration between sub-populations with the same genetic fitness configuration. The goal is a quantitative description of a migration-selection equilibrium with a bi-stable fitness configuration, which can emerge in the case of heterozygote disadvantage in a specific migration regime. The analysis of coupled populations is based on a rather simple scheme with two coupled populations. This has the benefit of being widely traceable analytically in the deterministic case. In addition, the stochastic model can be reduced to an analytically accessible case when one population becomes much larger than the other.

The resulting predictions aim at a technique for genetic pest management. In mosquitos, the bi-stable dynamics can be coupled to a gene that causes resistance against a parasite or a virus, which could prevent the virus from spreading to humans [Curtis, 1968]. Here, future research can include the effect of genotypic interactions that give rise to more complex fitness configurations [Park and Krug, 2010]. This is of special interest in structured populations, e.g., a small island and a large continent population, that exchange migrants. The bi-stable nature of the direction of selection can guarantee some degree of reversibility of such genetically modified systems even in coupled populations. Here, it has to be mentioned that genetic modifications of insects are not new, but usually consider other mechanisms, such as male sterility [Krafsur, 1998]. The approach using heterozygote disadvantage to locally stabilize resistance can act as a complement to those mechanisms. In this context is also desirable to study larger networks of migrant-exchanging populations, where a profound description of heterozygote disadvantage has been lacking so far.

In summary, this thesis is concerned with the process of fixation of a mutant strategy or allele in finite populations, where fluctuations are a major feature. It concentrates on the average time associated with this process. In the limit cases of weak and strong selection, analytical approximations can be made. But also intermediate regimes, as well as migration patterns between populations are analyzed and discussed.

With the methods presented here, we aim at understanding more about the influence of Darwinian selection on stochastic dynamics in finite populations, and thus advance the knowledge of the dynamics of evolution.

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Eidesstattliche Erklärung

Ich erkläre, dass ich die vorgelegte Arbeit – abgesehen von der Beratung durch meinen Betreuer Dr. Arne Traulsen – selbständig und nur unter Benutzung der angegebenen Literatur angefertigt habe.

Die den Veröffentlichungen zugrunde liegende Forschungsarbeit wurde – abgesehen von der Zusammenarbeit mit meinem Betreuer Dr. Arne Traulsen – ausschließlich von mir selbst durchgeführt. Ausnahmen sind die folgenden Veröffentlichungen:

- Bei dem Artikel "Universality of weak selection" war Bin Wu an der quantitativen Analyse beteiligt, Long Wang hat zur Verfassung des Manuskriptes beigetragen.
- Bei dem Artikel "Stochastic slowdown in evolutionary processes" hat Chaitanya S. Gokhale zur Modellbildung beigetragen.
- Bei dem Artikel "Using underdominance to bi-stably transform local populations" trugen Floyd A. Reed zur Modellbildung und Diskussion, R. Guy Reeves zur Literatursichtung und Diskussion bei.
- Bei dem Artikel "A stochastic model for heterozygote disadvantage in subdivided populations" war Floyd A. Reed an Manuskript und Modellbildung beteiligt.

Weiterhin versichere ich, dass die vorliegende Dissertation weder ganz noch zum Teil bei einer anderen Stelle im Rahmen eines Prüfungsverfahrens vorgelegt worden ist.

Diese Arbeit ist unter Einhaltung der Regeln guter wissenschaftlicher Praxis der Deutschen Forschungsgemeinschaft entstanden.

Ich habe keine früheren Promotionsversuche unternommen.

Kiel, den 20. Januar 2011 Philipp Altrock