Evolutionary dynamics on multi-dimensional fitness landscapes

Dissertation

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For my parents.

Contents

Kurzfassung

Evolution ist der eine gemeinsame alles verbindende Nenner der Biologie, von individuellen Allelen bis zur Sprache. Darwin glaubte, dass Mathematik eine tiefere Einsicht gewähren kann und bedauerte stets, diese nicht zu haben. Die heutige solide mathematische Grundlage, auf der die Evolution fußt, hätte ihm möglicherweise gefallen. Die Gesetze der Evolution sind durch mathematische Gleichungen darstellbar. Die Beschränkung auf die minimal notwendigen Faktoren sichert Einfachheit. Jedoch ist nicht einmal die genaue Zahl der möglichen Faktoren, z.B. die eine Honigbiene auf der Blumensuche berücksichtigt, bekannt. Wie kann diese Komplexität berücksichtigt werden, wenn das eigentliche Ziel die Beschreibung einfacher biologischer Prinzipien ist? Diese Arbeit betrachtet diese Problemstellung anhand zweier spezieller Szenarien: Statische- und dynamische Fitness-Landschaften. Eine Fitness-Landschaft ist ein Werkzeug zur bildlichen Darstellung der Fitness einer Population in einem Raum, in dem jede Dimension eine die Fitness beeinflussende Eigenschaft ist. Die Population sucht immer nach Maxima in der Fitness-Landschaft. Das ist der Prozess der Adaptation. In einer statischen Fitness-Landschaft ist die Fitness fest, bestimmt durch die Gesamtheit ihrer Eigenschaften. In dieser Arbeit werden Ergebnisse für, die Zeit präsentiert, die eine Population benötigt, um von einem Punkt zu einem anderen zu gelangen, wenn die Wege aus breiten Tälern oder oder schmalen Pfaden besteht. In dynamischen Fitness-Landschaften ist die Fitness abhängig von der Bevölkerungszusammensetzung. Bewegt sich die Population innerhalb der Landschaft, verändert die Landschaft selbst ihre Form und die Maxima können wandern. Um diese Frequenzabhängigkeit zu beschreiben, nutzen wir die evolutionäre Spieltheorie. Traditionell beschreibt die evolutionäre Spieltheorie Zweispielerspiele mit zwei Strategien. In dieser Arbeit werden höhere Dimension durch die Einführung von vielen Spielern und vielen Strategien betrachtet. Wichtige Ergebnisse des Zweispieler-Zweistrategienproblems werden auf viele Spieler verallgemeinert. Schließlich werden diese Ergebnisse für eine mögliche evolutionäre Anwendung der genetischen Schädlingsbekämpfung genutzt.

Abstract

Evolution is the common theme linking everything in biology from individual alleles to languages. Darwin believed that those who were mathematically inclined had a different insight and he regretted not having it. He probably would feel gratified knowing that now evolution has gained a solid mathematical foundation. The general principles of evolution can be represented by precise mathematical equations. Simplicity is invoked by making use of the minimum factors that matter. But we cannot even imagine how many factors a single honeybee takes into account to vouch for a particular flower. How can we take this complexity into account if we aim at retrieving simple tractable explanations of biological principles? This thesis addresses this problem particularly in two scenarios: Static and dynamic fitness landscapes. A fitness landscape is a tool for visualising the the fitness of a population in a space in which each dimension is a trait affecting the fitness. The population is ever searching for fitness maxima on this landscape. This is the process of adaptation. In a static fitness landscape the fitness is fixed, determined by the trait combination. Here we present results pertaining to the time required for a population to move from one point to another on this landscape if the paths consists of broad valleys or narrow ridges. In dynamic fitness landscapes the fitness is a function of the population composition. Hence as the population moves over the landscape the landscape changes shape and the fitness maxima can be eternally moving. To analyse frequency dependence we employ evolutionary game theory. Traditional evolutionary game theory deals with two player games with two strategies. This thesis invokes higher dimensions and non-linearities by studying multiple players and strategies. Important results from the two player two strategy case are generalised to multiple players. Finally we employ this theoretical development to analyse a possible evolutionary application in genetic pest management.

"Nature proceeds little by little from things lifeless to animal life in such a way that it is impossible to determine the exact line of demarcation"

Aristotle, *History of Animals*

1

Introduction

1.1 Evolution of Evolutionary Theory

Evolution is descent with modification. Biological evolution is the change in the form and/or behaviour of organisms over generations (Ridley, 1996). The modifications happen over time and this gives a dynamical aspect to evolution. Evolutionary dynamics is the study of this dynamical system. Dynamical systems have been studied for a long time in mathematics but what distinguishes the study of dynamical systems in biology as compared to other fields is that it is not simply change over time but also from a common ancestor.

The gradual descent with modifications creates variations which are selected by the environment (Ridley, 1996). Some organisms are better "adapted" to the environment that others. The ones that lag behind are left behind in the race of evolution. They go extinct. Observing the finches in the Galápagos archipelago, Charles Darwin was amazed at the different types of beaks which these otherwise similar birds possessed. The causative agent for the different types of beaks was the difference in the type of food which was available on the islands. The different beaks were adaptations to the different food types.

Biological systems are complex dynamical systems. For example the different beaks are no doubt selected by the different food sources but the geographical structure of the environment, the island structure, is also an important contributing factor. Thus the process of adaptation can depend on a number of factors. Traditionally in theoretical studies and for good reasons, the number

of factors considered are kept to a minimum. The aim of this thesis is to explore the high dimensional space of the factors affecting the fitness of an organism. Theoretical biology can range from theoretical ecology, population genetics, epidemiology, theoretical immunology to protein folding, genetic regulatory networks, neural networks, genomic analysis and pattern formation, and much more (Nowak, 2006a). To put the topic of this thesis in perspective, we briefly review the historical theoretical developments. The following does not aim to be an exhaustive account but rather touches upon the main points related to the topic of the thesis.

1.1.1 Darwinism

Charles Darwin converted a speculation which was already in the air into a scientific theory supported by data and observations. From $1831 - 1836$ Charles Darwin served on the *H.M.S. Beagle* as a self-funded naturalist while the ship charted the coastline of South America (Henslow, 1831). Along with the practical experience, Darwin benefited from the scientific literature available during that time period. Sir Charles Lyll's *Principles of Geology* (Lyell, 1998), introduced him to the power of gradual change: how changes over millennia can shape the geological features we see around us such as mountains and valleys. Economic literature such as Adam Smith's *The Wealth of Nations* (Smith, 1776) and Thomas Malthus's *Essay on the Principles of Population* (Malthus, 1798, 1826) influenced Darwin into thinking about biology in an economic framework. Adam Smith introduced the notion of *the invisible hand* where individuals working for their selfish benefit involuntarily contribute to the betterment of the whole society. Malthus proposed that the growth of a population is restricted by the carrying capacity of the environment. For him disasters such as war or famine were the great levelers which curbed the growth of populations.

It took twenty three years for Darwin to gestate the implications of his findings from the voyage and the input from all these ideas. But when Darwin finally published *On the Origin of Species* (Darwin, 1859) and *The Descent of Man* (Darwin, 1871), the result was a revolution in biology as never before. We see the impact of all of Darwin's peers together in a forceful manner and in a biological context in these books. The gradual changes over time shaping up

evolution, the struggle for existence against the forces of nature and the puzzle of co-operation (or the invisible hand?) is all documented in the books. Still what Darwin did not know was the way characters were inherited nor the exact mechanism how this was brought about.

1.1.2   Rise of Mendelism and the dethroning of Darwin

Gregor Johann Mendel (1822-1884) was a student of physics under Charles Doppler at the University of Vienna. Becoming a monk, Mendel continued his scientific exploits in a two hectare garden of the monastery. He studied the variation in pea plants and after seven long years came up with findings which were later to be known as Mendel's Laws of Inheritance. In his publication, Mendel mainly focused on the crosses and hybridization techniques which he had developed but less so on the method of inheritance which he had observed (Mendel, 1866). The study of Mendel was rediscovered by Hugo Marie de Vries (1848-1935) who was studying the stupendous variety in evening primrose. These spontaneous variations, he termed as "mutations". These "mutations" were caused in the heritable elements which too he termed as the "pangenes", later to be known as "genes". De Vries published *The Mutation Theory* in $1900 - 1903$ which had a two pronged effect. Firstly, it brought into focus Mendel's forgotten experiments and an understanding of the principles of heredity. Secondly, it directly challenged the mechanism of evolution as proposed by Darwin. De Vries postulated that evolution may progress not by gradual changes but more often by spontaneous and drastic changes caused due to mutations. The irony of the situation was that the first evolutionary biologists who actually understood Mendel's theories, Bateson, de Vries, Johannsen and T. H. Morgan, downplayed the role of Darwinian selection (Mayr and Provine, 1980). In his time Darwin used to deflect this assault on his theory by the statement *"Natura non facit saltum"* (Nature does not make leaps). According to Darwin, natural selection acts on the variations and selects the best suited of them. The variations themselves are minor whereas natural selection is the major force driving evolution. While differing camps of evolutionary biologists came into being there was a hope for unification in the work of some people like J. Huxley, de Beer, E. B. Ford and J. B. S. Haldane.

1.1.3   The Modern Synthesis and Mathematical Biology

Mutations and selection work in concert. It took twenty years for this idea to sink in. The change was brought about by the realization that the phenotypic traits are not just discretely connected to certain genes but each trait may be the result of the effect of many genes each of which can have multiple alleles. This meant that mutations by themselves could not drive evolution without selection carefully sorting them out and also the scope of mutations relating to a particular trait was increased.

A catalyst in this unification process was the use of a common language, the language of mathematics. Sir Ronald Aylmer Fisher, Sewall Green Wright and John Burdon Sanderson Haldane were at the forefront of this development. These three are the founding fathers of the field of evolutionary theory. This does not mean there were not disagreements between them (Mitchell, 2009). The term "evolutionary/modern synthesis" comes from the book *"Evolution, the modern synthesis"* by Julian Huxley (Huxley, 1942) written much later. The book documents how the unification of Darwinism and Mendelism was brought about during the first half of the twentieth century.

1.1.4   Beyond the synthesis

The synthesis helped the field of evolutionary biology to prosper rapidly. Unequivocally as selection was accepted as a valid force of evolution, it lead to further questions. What exactly is the unit of selection (Mayr, 1997)? Due to rapid growth in the field of molecular biology, many researchers shifted their focus from the individual to the gene. It did not take much time for the same to happen in theory. G. C. Williams proposed that the gene could be the unit of selection (Williams, 1966). This idea was picked up and popularised by Richard Dawkins in his book *"The Selfish Gene"* (Dawkins, 1976). This gene centric view was influential in reviving the second type of selection as proposed by Darwin, the idea of sexual selection (Darwin, 1871; Bowler, 2009).

Nothing defies the laws of physics. Not even natural selection (Mitchell, 2009). With the merger of Mendelism and Darwinism it would have seemed that the dust had settled and science would progress using these new ideas. But

as the evolutionary theory reached mainstream biology and all its neighbouring fields, cries of resistance arose. Stephen Jay Gould (1941 - 2002) along with colleagues pointed out the basic constraints on biology imposed by the physical world. Their view was that along with natural selection and mutations and other biological forces, equal or more importance has to be given to the "accidents" which facilitated the course of evolution. Along with Niles Eldredge (1943-), Gould proposed the concept of *punctuated equilibria* (Eldredge and Gould, 1985; Bak and Sneppen, 1993). It states that evolution while mostly proceeding via gradual changes is also subject to equally shocking 'jerks'. Partial support for this view came from the works of the theoretical biologist Motoo Kimura (1924-1994). He is most famous for his neutral theory of molecular evolution (Kimura, 1968). Kimura proposed that more than selection it would seem that no selection or weak selection (as later Ohta was to show in her "nearly neutral theory of molecular evolution" (Ohta and Gillespie, 1996)) were enough to drive evolution towards polymorphisms which are abundantly seen in Nature. It is often viewed that the neutral theory stands in stark opposition of the theory of natural selection. In fact it does not discount selection but proposes that the variation available for selection to act on is more neutral than having a positive selective effect (Ridley, 1996).

Based on the initial work of Eigen (1971), Eigen and Schuster studied the evolution of RNA based viruses. The virus exists not as an individual organism which has reached a fitness peak, rather the whole virus community was sitting dispersed on a fitness peak. In a series of papers (Eigen and Schuster, 1977, 1978a,b) about the origin of life, the term 'quasi-species' was introduced. The population which is maintained at the mutation-selection equilibrium is known as the quasi-species (Nowak, 1992). Selection acts on the population as a whole (Eigen et al., 1989).

Going back to the the Galápagos archipelago we now see the finches in a new light. On each island a different quasi-species is maintained by the selective constraints while mutations push the population from this adaptation. An equilibrium between the two maintains the populations we see thriving on the islands.

1.2 Scope of the Thesis

The earlier subsection was closed with a few loose ends. For example the use of the term "fitness peak" without actually explaining it. This is because those aspects are the focus of the thesis and hence they are explained here in a bit more detail than the general story of the evolutionary theory so far.

Selection, mutation, drift and migration are known to be the driving forces of evolution. Recently it has been proposed that co-operation may also be another force which drives evolution (Nowak, 2008). All these are but forces and they need to act on some characteristic of the unit of selection (we saw the debate raging over the unit of selection in Section 1.1 and it warrants its own experimental, theoretical and philosophical discussion (Okasha, 2006)). What is driven by these forces is the idea of a fitness. With the vast amount of literature in population genetics, one imagines that this is a concept which does not need clarification. On the contrary fitness as a concept has been highly debated (Haldane, 1932b; Cartwright, 2000; Orr, 2009). A number of definitions have been suggested for the concept of fitness (Ariew and Lewontin, 2004; van der Werf et al., 2009). One idea however which is agreed upon is that the fittest organisms are able to survive long enough to reproduce and pass on their genes to the next generation, more than others. This can be quantified as to how much of passing occurs and then crudely termed as fitness. The reason that this concept needs to be crystal clear is because it forms the cornerstone of evolution. A major component of evolution is selection and selection acts on the difference in fitnesses.

Fisher's Geometric Model. This issue was first addressed by Fisher (1930) in his book *The Genetical Theory of Natural Selection*. In the section "Nature of Adaptation", Fisher proposed a geometric model in which the best combination of n traits is said to be the optimum fitness of an organism and can be imagined as to be at the origin in an n dimensional coordinate system depicting the phenotypic state. Due to a some change in the organism or the environment the organism moves away from the optimum. The way of reaching back to the optimum is the one in question. This is where the phenomenon of mutation reprises its role. Mutations occurring which bring the offset phenotype closer

to the optimum are favoured. A key point in Fisher's model was that different mutations could move the phenotype around in the phenotype space over different distance. Different mutations have different strengths. Hence even if a mutation is in the direction of the optimum it could overshoot it and move into a lower fitness area again.

Wright's Adaptive landscape or Haldane's Meta-populations. Wright considered himself to be primarily a developmental geneticist. His work unlike that of Fishers was based on the importance of gene interactions (Mayr and Provine, 1980) including mutation, selection, migration, multiple alleles etc. (Wright, 1931). He conjured up a fitness landscape which was not phenotype based by rather genotype based. But each gene can have many different allelomorphs so the perfect combination is a perfect allelomorphic combination. For simplicity consider just two genes. On the $x-axis$ we plot all the alleles of one gene and on the $y-axis$ all the alleles of the other gene. This is exactly what Wright plotted in (Wright, 1932) as shown in Figure. 1.1 (a). This is the adaptive fitness landscape as visualized by Sewall Wright (Wright, 1932; Gavrilets, 2004). Wright proposed that populations could split and evolve to different adaptive peaks where the population on a fitter peak out-competes the lesser fit ones. Often only Wright is credited with the invention of the idea of a fitness landscape. In fact Haldane also proposed the idea of meta-populations and how they could evolve to separate adaptive peaks in a genotypic sense (Haldane, 1932a).

Maynard Smith's Sequence Space. In the 1960's John Maynard Smith developed a similar concept of sequence space but this time in the context of proteins (Maynard Smith, 1970). The protein code alphabet consists of the twenty amino acids. For a protein chain of length L there are 20^L possible combinations. Each of these combinations can be represented in an L dimensional space such that the sequences next to each other differ by just a single amino acid. Maynard Smith concocted a recipe for finding adaptive walks in such high dimensional "sequence space". The dimensionality increases as the length of the sequence (L) increases. For example for a three dimensional system we need to represent all the possible combinations in a three dimensional hypercube. According to Maynard Smith, "if evolution by natural selection is
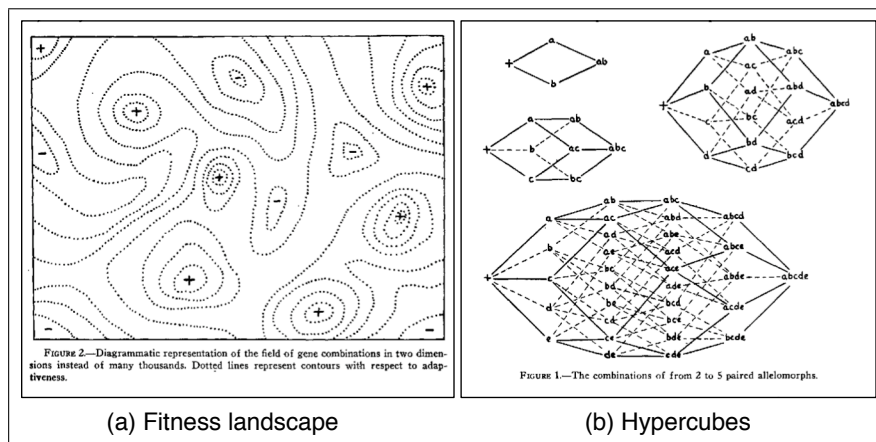
Figure 1.1: **Wright's high dimensional genotypic representation.** Adapted from Wright (1932) Panel (a) shows a simplified two dimensional space of "allelomorphs". The contours represent the scale of the adaptive value. The second panel (b) shows the actual high dimensional genotypic 'hypercubes'. Each of the nodes are the different alleles or as Wright called them, 'allelomorphs'.

to occur, functional proteins (or DNA sequences) must form a continuous network which can be traversed by unit mutational steps without passing through non- functional intermediates" (Maynard Smith, 1970). The landscape thus constructed is also known as "mutational landscape" as the neighbours differ from each other by one mutational step.

   Eigen and Schuster's fusion of landscapes and fitness. Working together, Manfred Eigen and Peter Schuster combined the concepts of sequence space and fitness. If each sequence has its own fitness value and if we add this dimension to the already L dimensional space then we get Wright's Adaptive landscape. In this landscape all the L dimensions are flattened out and we see a mountain range in the dimension of fitness. This range can have peaks and valleys corresponding to the sequences with higher or lower fitnesses. This landscape has been studied in detail by John Gillespie (Gillespie, 1983, 1984a). He was influential in utilizing the strong selection weak mutation (SSWM) assumption in staunch opposition of the neutral theory of Motoo Kimura (Gillespie, 1984b).

   Together these adaptive landscape models (Kauffman and Levin, 1987) are

able to capture the general properties of adaptive evolution as has been seen from experimental studies (Betancourt and Bollback, 2006). Let us review the commonalities between all these visualisations,

– For Fisher it was some trait combination which affected fitness and for Wright it was the genetic makeup which affected fitness. For Maynard Smith it was the different mutational states of a sequence. In all cases, the process involves identifying the variable which affects fitness.

– Fisher used a sphere to demonstrate the idea of the geometrical model for three variables. Wright used only two variables to illustrate an adaptive landscape Fig. 1.1 (a). Although these are for illustrative purposes both of them knew that actually the effective number of variables are many and thus the resulting variable space is high dimensional Fig. 1.1 (b). As noted in (Kauffman and Weinberger, 1989), *"...the concept is very general, and can be used to represent entire organisms or other ensembles of related objects that are "one mutant neighbors" of each other."*

– Fitness adds another dimension to this already high dimensional trait space. This is the dimension which actually gives a shape to the otherwise featureless trait space.

– Change is a major constant in biology. One major assumption with these models was that the fitness landscape remains unchanged. For example Wright constructed the concept of an adaptive landscape assuming that the genotypic fitnesses remain constant over time (Provine, 1986). As the populations moves over the fitness landscape, if the fitness is frequency dependent, then the shape of the landscape will change. The earliest reference to frequency dependent selection is given by Poulton (1884) about the way predators maintain the colour polymorphism in their prey. The explanation of one of the most puzzling of puzzles in biology, evolution and maintenance of sex, is hypothesised to be change. The Vicar of Bray hypothesis suggests that sex helps produce a variability in the phenotypes of the offspring, some of which may be better suited to a change in the ecology of the environment (Ridley, 1993). The Red Queen hypothesis tackles the question at a different level

(van Vaalen, 1973). Sex and the evolutionary existence of males are explained by their ability to preserve the genes which can provide an evolutionary advantage against a changing ecology. Frequency dependent fitness effects have been documented in a number of experimental tests carried out in *Drosophila* (Ayala and Campbell, 1974; Hartl and Clark, 1997) and are proposed to be one of the mechanisms maintaining a high degree of polymorphism for example in the Major Histocompatibility Complex (MHC) (Borghans et al., 2004; Milinski, 2006). Frequency dependence is also a crucial factor when addressing the question of biodiversity (Levin, 2000).

The scope of this thesis is limited to exploring two main themes of these approaches,

– Higher dimensions in static fitness landscapes.

– Higher dimensions in frequency dependent fitness landscapes.

The organisation of these two issues in this thesis is explained in the next section (see Fig. 1.2).

1.3 Thesis Overview

Fisher, Wright and Maynard Smith thought about specific variables affecting fitness. We abstract it further to another level where we just consider them as some variables affecting fitness. In a cultural sense these could be behavioural traits, fads or fashion or on the genetic level they could be particular alleles of a gene, genes, genetic regulatory networks etc. . Hence thinking on a further abstract level we free ourselves from the conditions of the dimensions being genotypically or phenotypically determined. They could be any characteristics which in a certain combination affect fitness.

Chapter 2 is devoted to the question of the speed of adaptation on static landscapes. In it two publications are documented,

2.1 **Chaitanya S. Gokhale**, Yoh Iwasa, Martin A. Nowak, Arne Traulsen,
The pace of evolution across fitness valleys,
Journal of Theoretical Biology, **259**, (2009)
Page 13
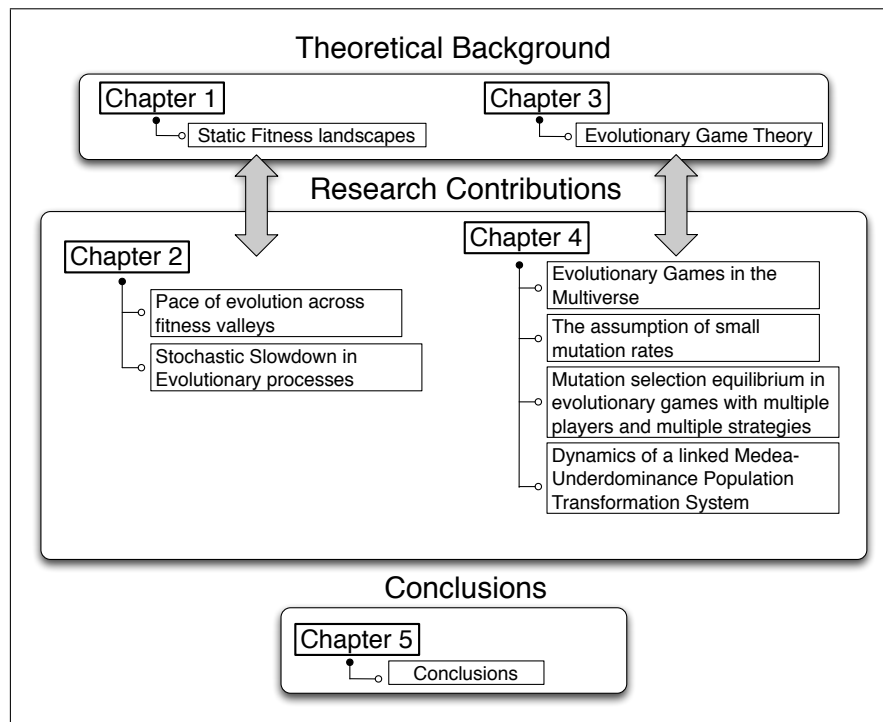
Figure 1.2: **Outline of the thesis.** The thesis layout follows the flow of ideas rather than the chronology of publications. Chapter 1 provides a general background of evolutionary theory and an introduction to static fitness landscapes. Chapter 2 directly follows from the theory of static landscapes. We then move on to the theoretical background of dynamic fitness landscapes and in particular the use of evolutionary game theory in Chapter 3. Chapter 4 includes the publications relating to evolutionary game theory and the Chapter 5 collates all the results together and concludes the thesis with final remarks.

2.2 Philipp M. Altrock, **Chaitanya S. Gokhale**, Arne Traulsen

    Stochastic slowdown in evolutionary processes,

    Physical Review E, **82, 011925**, (2010)

    Page 26

Chapter 3 is an introduction to evolutionary game theory. We move from our discussion of static fitness landscapes to frequency dependent fitness landscapes. For addressing this issue we rely on evolutionary game theory as a tool to study the evolutionary dynamics. In this chapter the basic concepts of evolutionary

game theory pertaining to the scope of this thesis are introduced.

Chapter 4 is an extension of the theory discussed in Chapter 3. It consists of four publications. The first three are theoretical advancements while the fourth is an evolutionary game theoretic analysis of an experimental setup.

4.1 **Chaitanya S. Gokhale**, Arne Traulsen,
    Evolutionary games in the multiverse,
    Proceedings of the National Academy of Sciences, USA, **107**, (2010)
    Page 64

4.2 Bin Wu, **Chaitanya S. Gokhale**, Long Wang, Arne Traulsen,
    How small are small mutation rates?,
    Journal of Mathematical Biology, In revision
    Page 78

4.3 **Chaitanya S. Gokhale**, Arne Traulsen,
    Mutation-selection equilibrium in evolutionary games with multiple players and multiple strategies,
    Submitted
    Page 91

4.4 **Chaitanya S. Gokhale**, R. Guy Reeves, Floyd A. Reed,
    Dynamics of a linked Medea-Underdominance Population Transformation System
    In preparation
    Page 106

Detailed author contributions are reviewed at the end of the thesis in Table 5.1.

"Life is a high-country adventure"

Stuart Kauffman

2

Speed of evolution

2.1 Pace of evolution across fitness valleys

"The problem of evolution as I see it is that of a mechanism by which the species may continually find its way from lower to higher peaks [. . .]. In order that this may occur, there must be some trial and error mechanism on a grand scale [. . .]. To evolve, the species must not be under strict natural selection. Is there such a trial and error mechanism?" (Wright, 1932).

Wright had asked a very interesting question in theoretical population dynamics. How a population which is stuck at one of the many possible local fitness maxima evolve to the global fitness maximum. Fisher, who thought in a much more geometrical way, envisioned that any local fitness maxima would be a point on the slope of another adaptive hill in a higher dimension. Thus given enough time, a population would finally make it to the global maximum. Wright was more in favour of random drift. He believed that by drift populations could reach the foots of other hills and then selection could take over so as to drive the populations uphill towards the peak. In his *Shifting Balance Theory*, Wright postulates that a number of sub-populations could explore the fitness landscapes and as the number of sub-populations increases, the chance that one of them finds the global optimum also increases (Wright, 1932). Once at the global optimum, that sub-population will outcompete all the other types of that species and the species as a whole will have reached the global adaptive peak (Ridley, 1996).

We address the question using the mutational landscape. Mutations during individual reproduction are either ultimately lost (when the mutants go extinct) or fixed in a population (when the mutants take over). The probability that a mutation reaches fixation increases with the relative fitness of the mutant. As the fitness landscape is made up of mutants which are one mutational step away from each other, we can ask the question how long it takes until a number of mutations reach fixation. Of course, this depends on the fitness of the mutants. But in addition, the order of mutations is crucial:

1. If each mutation needs another mutation as a prerequisite to occur, evolution occurs on a single path or ridge in fitness landscape.

2. If the order of mutations is arbitrary, then there are many paths possible along which the mutations are accumulating and evolution typically proceeds faster.
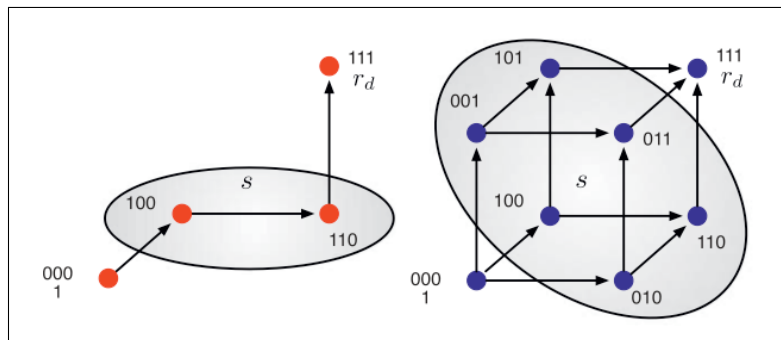
Figure 2.1: **Single path and Hypercube.** Hypothetical fitness paths where only a fixed sequence of mutation can lead to the state of higher fitness (single path) or a multitude of paths lead to the ultimate state (hypercube). The intermediate states are all assumed to have the same fitness s as compared to the fitness of the initial state considered to be 1 and the final state as r_d.

We address the pace of evolution in the two scenarios (see Fig. 2.1) and show how the size of the population affects the way a population evolves. The developed theory allows us to ask when evolution occurs faster on a narrow ridge or through a broad valley with disadvantageous intermediate mutations.

The framework developed here can serve as a reference case for evolution in real fitness landscapes, as it can be easily extended to incorporate the complexity and variation seen in experimental studies, Fig. 2.2. This way of approaching
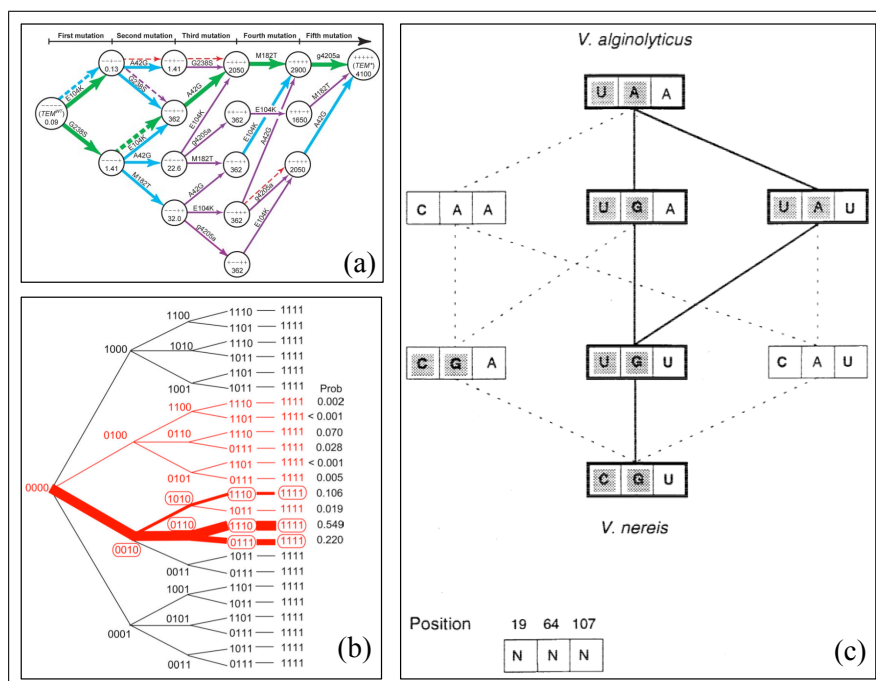
Figure 2.2: **Examples of experimentally constructed fitness landscapes.** The images collated from: (a) Weinreich et al. (2006): Mutational paths in the β lactamase gene conferring resistance to bacteria from β lactam antibiotics where were found to be viable.(b) Lozovsky et al. (2009): The major inferred pathways for the evolution of pyrimethamine resistance. (c) Lee et al. (1997): All paths between the 5srRNA sequences of *Vibrio proteolyticus* and *V. nereis* at the three positions where they differ.

the problem lets us explore the different regimes of mutation rate.

- For **small mutation rates** the population evolves by a process where the mutations occur one after the other, which has been termed periodic selection (Atwood et al., 1951) and theoretically described as the strong-selection weak-mutation regime (Gillespie, 1983, 2004 (2nd edition) (see Fig. 2.3 (a)).
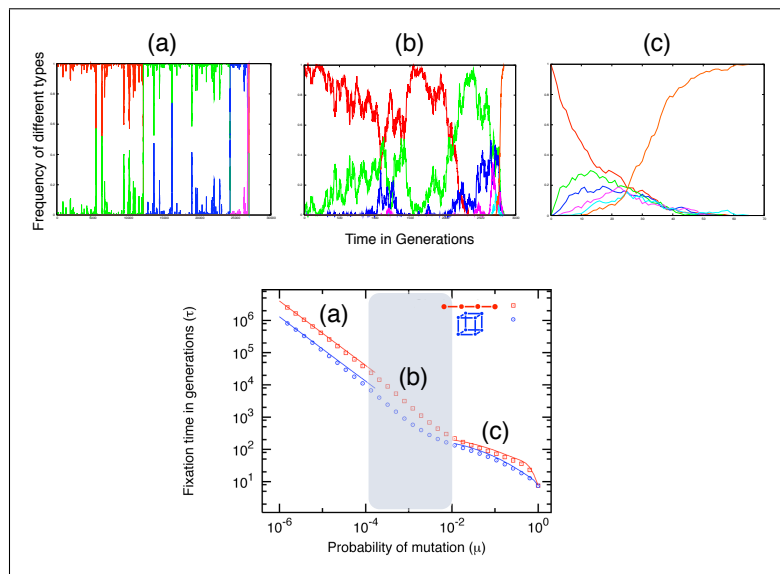
Figure 2.3: **Regimes of mutation rates.** (a) If mutation rates are very low then the system is monomorphic most of the time, occasionally a mutation occurs and it can either go extinct or reach fixation. This scenario can be captured analytically. (b) For intermediate mutation rates multiple mutants can coexist and the situation is difficult to characterise analytically. (c) For high mutation rates the dynamics can be approximated by differential equations again yielding tractable results.

- For **intermediate mutation rates** the population does not move from mutational step to the next as a whole. Instead many mutants are present in the population at the same time. This phenomenon of competition amongst multiple mutants termed as clonal interference or stochastic tunneling has been a subject of in-depth theoretical and experimental studies. (Gerrish and Lenski, 1998; Elena et al., 1998; Elena and Lenski, 2003; Iwasa et al., 2004; Park and Krug, 2007). This process is of importance in studies related to cancer initiation (Iwasa et al., 2004; Michor et al., 2004; Beerenwinkel et al., 2007a,b; Bozic et al., 2010) (see Fig. 2.3 (b)).

- For **high mutation rates** the system we can use ordinary differential equations to capture the behavior of the system (see Fig. 2.3 (c)).

This approach has been used to investigate how different strains of pathogens

can evolve from one another (Alexander and Day, 2010) or how long does it take for a population to acquire complex adaptive traits (Lynch, 2010a,b).

2.1.1 Publication: The pace of evolution across fitness valleys

Chaitanya S. Gokhale, Yoh Iwasa, Martin A. Nowak, Arne Traulsen,

The pace of evolution across fitness valleys

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ABSTRACT

How fast does a population evolve from one fitness peak to another? We study the dynamics of evolving, asexually reproducing populations in which a certain number of mutations jointly confer a fitness advantage. We consider the time until a population has evolved from one fitness peak to another one with a higher fitness. The order of mutations can either be fixed or random. If the order of mutations is fixed, then the population follows a metaphorical ridge, a single path. If the order of mutations is arbitrary, then there are many ways to evolve to the higher fitness state. We address the time required for fixation in such scenarios and study how it is affected by the order of mutations, the population size, the fitness values and the mutation rate.

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1. Introduction

Evolutionary dynamics is based on natural selection, mutation and genetic drift (Nowak, 2006). It can be illustrated as the dynamics of a population in an abstract, typically high-dimensional fitness landscape. Since individuals with higher fitness produce more offspring, the average density of individuals is highest close to the fitness maxima. Many such features as the stationary population density in the fitness landscape or the mutation rate under which a population can still be concentrated around a fitness maximum have been addressed (Eigen and Schuster, 1977; Eigen et al., 1989; Wilke, 2005; Nowak, 1992). An important question is how a population evolves towards a fitness peak via several intermediate states. If the intermediate states have the same fitness as the initial state, then evolution to higher fitness states is neutral at first and thus poses no significant problems (van Nimwegen and Crutchfield, 2000). If the intermediate states have lower fitness than the initial state, then a fitness valley has to be overcome and it is more difficult to reach the fitness peak (Weinreich et al., 2006; Poelwijk et al., 2007). In this case, population stuck on a local peak cannot escape by natural selection alone, because there is no evolutionary trajectory with successively advantageous mutations. Instead, neutral genetic drift becomes important.

Here, we consider the dynamics of these systems from a different perspective. We address the average time a population needs to transfer from one peak to another one. For small mutation rates and finite populations, we calculate this average time analytically. When mutation rates are high, we can describe the system by a set of differential equations and obtain the relevant times from a numerical integration of the differential equations. In this framework, the relevant question is how fast a population evolves (Traulsen et al., 2007).

In particular, we can address the question whether a population evolves faster from one peak to another via d mutations if

 (i) mutations have to occur in a certain order, i.e. only a single evolutionary trajectory is available, or
(ii) the order of the mutations does not matter, i.e. there are $d!$ evolutionary paths.

In the simplest case the intermediate fitness values are identical in both the cases and equal to that of the initial state. Thus the only difference remaining is the number of available paths. When the order of mutations is not fixed then multiple paths are available and the evolutionary dynamics will be faster when compared to a single path. We can then ask the question: Does a population evolve faster on a narrow ridge or a broad valley? This implies that we move away from the simplest case mentioned above and decrease the fitness in the intermediate states of the multiple paths compared to the fitness in the intermediate states of the single path. We show how the pace of evolution depends on the depth of the valley, the number of intermediate states and the size of the population.

In general, evolutionary dynamics depends crucially on the size of the population. In a small population a single mutation will typically reach fixation or extinction before another mutation can

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arise. The population moves as a whole step by step on the fitness landscape. For large populations, even for small mutation rates usually multiple types arise at the same time. This results in a non-zero population density in many states at the same time. For intermediate mutation rates, the population can either move stepwise across the fitness landscape or move several steps without getting concentrated in one of the intermediate states. This phenomenon has been termed stochastic tunneling (Iwasa et al., 2004). If the mutation rates are too small, tunneling does not occur because it is unlikely that a second mutation arises before the first one has reached fixation or has gone extinct. If the mutation rates are high, tunneling occurs trivially, because the system can be approximated by differential equations for the densities in the different states. These different scenarios including the limiting cases of stepwise evolution (typical for small populations) and continuous evolution (typical for large populations) can also be observed when the population size is kept constant, but the mutation rates are increased. For computer simulations increasing the mutation rate is more convenient than simulating huge populations for moderate mutation rates.

One important example for an evolutionary process in which the timescales are of crucial importance is the somatic evolution of cancer (Frank, 2007). Cancer progression has been investigated mathematically since the 1950s (Fisher, 1959; Nordling, 1953; Armitage and Doll, 1954). Of special interest are the tumor suppressor genes (Knudson, 1971; Michor et al., 2004). In a normal cell, there are two alleles of the tumor suppressor gene. The mutation in the first allele is neutral if the second wild-type allele can sufficiently perform the function. Inactivation of both the alleles confers a selective advantage to the cell and can lead to cancer progression. This is an example in which the order of mutations does not matter. Many cancers also require certain particular mutations that initiate cancer growth and pave the way for the accumulation of further mutations (Vogelstein and Kinzler, 2004). Recently, it has been shown that after cancer initiation, a large number of different mutations may be involved in cancer progression (Sjöblom et al., 2006; Wood et al., 2007; Jones et al., 2008a, b). So far, it is unclear if the mutations have to occur in a specific order or if there is more variation in the order (Beerenwinkel et al., 2007; Gerstung and Beerenwinkel, 2008).

For simplicity, we consider only very simple fitness landscapes here in which the fitness in all the intermediate states is identical. In natural systems, these fitness values will differ and also the mutation rate may not be constant. In addition, sometimes the order of mutations will matter and sometimes, it will not. Thus, sometimes a particular mutation will be a prerequisite to obtain a new function, but sometimes new mutations do not require any prerequisites. For example, this is the case in the evolution of resistance to β lactam antibiotics studied by Weinreich (2005) and Weinreich et al. (2006). However, here we focus on a very simple model to highlight the general aspects of the dynamics by analytical and numerical considerations.

This paper is organized as follows. We begin with the description of the two ways to order the mutations, the single path and the hypercube. We then derive analytical approximations of the fixation times for small mutation rates and discuss the effect of the different parameters on the fixation times. Next, we address the dynamics for intermediate and high mutation rates. Finally, we explore biological examples which can be modeled using this approach.

2. Model

To model evolutionary dynamics in a haploid population of size N, we use the Moran process (Nowak, 2006; Moran, 1962). In each time step, one individual is selected at random, but proportional to fitness. It produces one offspring, which replaces a randomly chosen individual. In one generation, each individual reproduces on average once. During reproduction, mutations occur with probability μ. We are interested in the time it takes until d mutations reach fixation in the population, starting from a homogeneous population in the initial state without any mutants. Moreover, we aim to explore the dynamical features of this process. We restrict ourselves to two different cases that allow the derivation of some analytical results.

2.1. Single path

If the mutations can occur only in a particular order, we have a single evolutionary path, see Fig. 1 for an illustration. Individuals in the initial state have fitness $r_0 = 1$ and individuals in the final state have fitness $r_d > 1$. It is instructive to characterize an individual by a string of d sites, which can either be wild-type or mutated. If the order of mutations is fixed, then a particular mutation requires another particular mutation as a prerequisite. For simplicity, we assume that all the $d - 1$ intermediate states have the same fitness $r_j = s < r_d$ $(j = 1, \ldots, d-1)$. For $s < 1$, the joint effect of the set of mutations make up for the loss of fitness caused by the individually deleterious mutations. This can be considered as a very special case of epistasis (Weinreich et al., 2005).

2.2. Hypercube

If the order of mutations does not matter, evolutionary dynamics takes place on a hypercube in d dimensions cf. Fig. 1. Thus, there are 2^d different types of individuals. In the initial state, we have d possible mutations. In the next step, $d - 1$ mutations are available. Consequently, we have $d!$ possible paths to fixation. Again, we assume $r_0 = 1$ and $r_d > 1$. Further, all individuals with some, but not all mutations have fitness $s < r_d$.

If the mutation probability is small, we do not need to make specific assumptions on the mutation process. But when the mutation probability increases, we can no longer be certain that only a single mutation occurs during reproduction. For simplicity, we do not consider the possibility of backward mutations. Although back mutations are often relevant, especially to escape from evolutionary dead ends (DePristo et al., 2007), it is not straightforward to define the speed of evolution in a system with
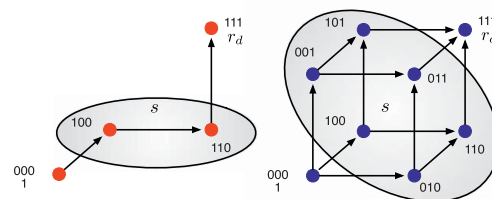
Fig. 1. The order of mutations determines the geometry for evolutionary dynamics, shown here for $d = 3$ sites (e.g. genes, nucleotide sites etc.). If mutations can only occur in a particular order, only a single path is available (left). If the order of mutations is arbitrary, evolutionary dynamics occurs on a hypercube (right). The initial states have fitness 1 and the final states fitness $r \geqslant 1$. All intermediate states are assumed to have the same fitness $s < r$. States are labeled by bit-strings, 0 is an wild-type site and 1 is a mutated site.

backward mutations. This is due to the fact that for sufficiently high mutation rates, fixation in the final state might never occur. Other definitions of the end state of the system become arbitrary to a certain extend. The probability $u_{m \to m+k}$ that the offspring of an individual with m mutations has $m+k$ mutations ($m \leqslant m + k \leqslant d$) is

$$u_{m \to m+k} = \binom{d-m}{k} \mu^k (1-\mu)^{d-m-k}. \tag{1}$$

This equation is valid for the hypercube, where the order of mutations does not matter. Here, $\binom{d-m}{k}$ is the number of different types of mutants with k additional mutations, μ^k is the probability that mutations occur at k sites and $(1-\mu)^{d-m-k}$ is the probability that no mutation occurs at the remaining $d - m - k$ sites. For the single path, there is only one possibility to arrange the $m + k$ mutations. Thus, for $k > 0$, $u_{m \to m+k}$ is identical to Eq. (1), except that the binomial factor has to be dropped. The probability $u_{m \to m}$ that no mutation occurs follows from normalization, $u_{m \to m} = 1 - \sum_{k=1}^{d-m} u_{m \to m+k}$. Our analytical calculations for small mutation rates as well as the considerations for high mutation rates are independent of the precise form of the mutation rates. However, we need to specify the form of the mutation probabilities to perform our numerical simulations for intermediate and high mutation rates.

3. Small mutation rates

3.1. The pace of evolution for small mutation rates

For small mutation probabilities, double mutations can be neglected. Since mutations occur rarely, we can calculate the average time until d mutations are fixed in the population analytically. Let us first address the evolutionary dynamics when mutants with fitness r_m are already present in a resident population of fitness r_w, but no new mutations occur. This scenario is relevant when mutation rates are sufficiently small. The probability to increase the number of mutants from j to $j + 1$ is

$$T_j^+ = \frac{r_m j}{r_m j + r_w(N-j)} \frac{N-j}{N}. \tag{2}$$

Similarly, the number of mutants decreases from j to $j - 1$ with probability

$$T_j^- = \frac{r_w(N-j)}{r_m j + r_w(N-j)} \frac{j}{N}. \tag{3}$$

The probability that k mutants take over the entire population is given by Nowak (2006), Karlin and Taylor (1975), Ewens (2004) and Crow and Kimura (1970)

$$\phi_k\left(\frac{r_m}{r_w}\right) = \frac{1 + \sum_{i=1}^{k-1} \prod_{j=1}^{i} \frac{T_j^-}{T_j^+}}{1 + \sum_{i=1}^{N-1} \prod_{j=1}^{i} \frac{T_j^-}{T_j^+}} = \frac{1 - \left(\frac{r_w}{r_m}\right)^k}{1 - \left(\frac{r_w}{r_m}\right)^N}. \tag{4}$$

If a mutant reaches fixation, the average number of generations this process takes is given by Goel and Richter-Dyn (1974) and Antal and Scheuring (2006)

$$\tau_{\text{fix}}\left(\frac{r_m}{r_w}\right) = \frac{1}{N} \sum_{k=1}^{N-1} \sum_{l=1}^{k} \frac{\phi_l}{T_l^+} \prod_{m=l+1}^{k} \frac{T_m^-}{T_m^+}. \tag{5}$$

For a neutral process with $r_m = r_w$, this reduces to $\tau_{\text{fix}} = N - 1$. For sufficiently large N, this is the maximum conditional fixation time of a mutant. Even for disadvantageous mutants ($r_m < r_w$) the conditional fixation time is smaller than $N - 1$ (Antal and

Scheuring, 2006). Since there are μN mutations per generation, the time between two mutations is $1/\mu N$. Thus, for $\mu \ll N^{-2}$ a mutant reaches fixation before the next one arises and mutations will not occur when a mutant is already present. Thus the population evolves by a process where the mutations occur one after the other, which has been termed periodic selection (Atwood et al., 1951) and theoretically described as the strong-selection weak-mutation regime (Gillespie, 1983, 2004).

The total time τ until a mutation reaches fixation in a population is the sum of the waiting time until a successful mutant occurs and the fixation time of the mutant $\tau = \tau_{\text{wait}} + \tau_{\text{fix}}$. The waiting time is the inverse of the mutation rate divided by the probability that a particular mutant is successful

$$\tau_{\text{wait}}\left(\frac{r_m}{r_w}\right) = \frac{1}{\mu N} \frac{1}{\phi_1\left(\frac{r_m}{r_w}\right)}. \tag{6}$$

For $\mu \to 0$, we have $\tau_{\text{wait}} \to \infty$, but τ_{fix} remains approximately constant. Thus, $\tau \approx \tau_{\text{wait}}$ for small mutation rates. In principle, we could calculate τ_{fix} in the presence of mutations. But since our approximation is only valid for small mutation rates, this will be a minor correction.

For $\mu \ll N^{-2}$, the population is homogeneous most of the time. Only occasionally, a mutant arises and reaches fixation or goes to extinction. The total time until d mutations are fixed in the population is the sum of the waiting times for the successful mutants plus the time of the d fixation events. For a single path with initial fitness 1, intermediate fitness s and final fitness r, we find for the total time τ^S

$$\tau^S = \tau_{\text{wait}}(s) + (d-2)\tau_{\text{wait}}(1) + \tau_{\text{wait}}(r/s) \\ + \tau_{\text{fix}}(s) + (d-2)\tau_{\text{fix}}(1) + \tau_{\text{fix}}(r/s). \tag{7}$$

For small μ, we have $\tau_{\text{fix}} \ll \tau_{\text{wait}}$ and hence the total time can be approximated by

$$\tau^S = \frac{1}{\mu}\left[\frac{1}{N\phi_1(s)} + d - 2 + \frac{1}{N\phi_1(r/s)}\right]. \tag{8}$$

Consider now a "fitness valley", in which the intermediate states have fitness $s < 1$, but the final state has fitness $r > 1$. To move from the fitness peak in the initial state to the fitness state in the final state, first a disadvantageous mutation has to be fixed in the population. Since $\phi_1(s < 1) \ll \frac{1}{N}$, the waiting time of such an event is very long. The waiting time for the neutral mutations, $\tau_{\text{wait}}(1) = 1/\mu$ and the waiting time for a successful mutation, $\tau_{\text{wait}}(r/s)$ are significantly shorter. Thus, τ^S is dominated by $1/\mu N\phi_1(s)$ for $s < 1$ and sufficiently high N in a fitness valley. Fig. 2 shows a good agreement between exact numerical simulations and our analytical approximation for small mutation rates Eq. (8).

If the order of mutations is arbitrary, evolutionary dynamics occurs on a hypercube. In this case, the whole process will be faster, as we have $d!$ possible paths instead of a single one. Now, the waiting times in the different states depend on the number of mutations that are still available. For the total time τ^H, we obtain,

$$\tau^H = \frac{1}{d}\tau_{\text{wait}}(s) + \sum_{k=1}^{d-2} \frac{1}{d-k}\tau_{\text{wait}}(1) + \tau_{\text{wait}}\left(\frac{r}{s}\right) \\ + \tau_{\text{fix}}(s) + (d-2)\tau_{\text{fix}}(1) + \tau_{\text{fix}}\left(\frac{r}{s}\right). \tag{9}$$

Note that the time of the fixations alone is identical for the hypercube and the single path. Neglecting these fixation times for small μ (as $\tau_{\text{fix}} \ll \tau_{\text{wait}}$) yields

$$\tau^H = \frac{1}{\mu}\left[\frac{1}{dN\phi_1(s)} + \sum_{k=1}^{d-2} \frac{1}{d-k} + \frac{1}{N\phi_1(\frac{r}{s})}\right]. \tag{10}$$
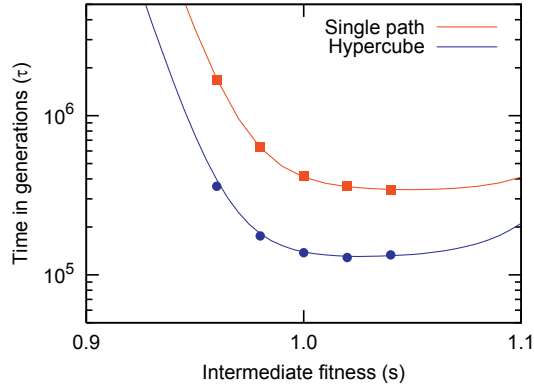
Fig. 2. Fixation time for a single path (squares) and a hypercube (circles) with small mutation rates ($\mu \ll N^{-2}$) for different intermediate fitness values. Evolutionary dynamics is always faster in the hypercube. Solid lines show the analytical approximation for small mutation rates, Eqs. (8) and (10). Numerical simulations shown by symbols agree well with the analytical approximation (population size $N = 100$, mutation rate $\mu = 10^{-5}$, $d = 5$, $r = 1.1$, simulations averaged over a 1000 realizations).
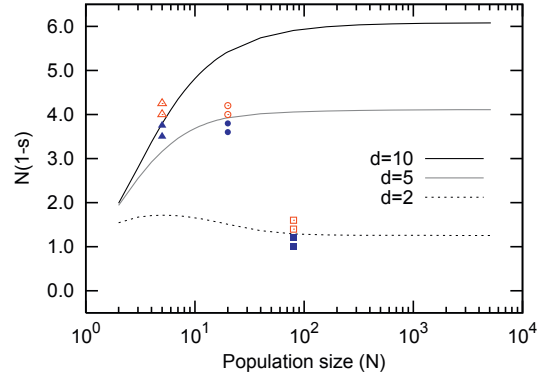

Fig. 3. The figure shows the threshold values for which evolution on a hypercube with fitness $s < 1$ in the intermediate states proceeds as fast as on a single neutral path with $s = 1$. Full lines show $N(1 - s)$ based on the numerical solution of Eq. (11). Above the lines, evolution proceeds faster on the hypercube. Below them, the neutral single path is faster. For $N \to \infty$, the lines converge to a constant, see Eq. (12). The symbols show the results from numerical simulations for $N = 5$ and $d = 10$ (triangles), $N = 20$ and $d = 5$ (circles) as well as $N = 80$ and $d = 2$ (squares). Symbols are open when the single path is faster and filled when the hypercube is faster ($\mu = 10^{-5}$, $r = 1.1$, simulations averaged over a 1000 realizations).

Since $1/(dN\phi_1(s)) < 1/(N\phi_1(s))$ and $\sum_{k=1}^{d-2} 1/(d-k) < \sum_{k=1}^{d-2} 1 = d - 2$ it is obvious that $\tau^H < \tau^S$, i.e. evolutionary dynamics is faster if the order of mutations is arbitrary. For fitness valleys with $s < 1$ and a large population size, τ^H is dominated by $1/d\mu N\phi_1(s)$. As d more mutations are available, this is always faster than the corresponding equation for a single path, see Fig. 2.

3.2. Thresholds of the waiting times

Next, we derive expressions for some interesting thresholds of the waiting times in the limit of small mutation rates. Since evolutionary dynamics is always faster if many paths are available, we now compare a fitness valley in which many paths are available to a single path in which the order of mutations is important, but fitness does not decrease in the course of evolution. The basic question we address here is, whether it is faster to cross a broad valley or a narrow ridge in fitness space. In other words, we compare $\tau^S(s = 1)$ to $\tau^H(s < 1)$. Since we consider only small mutation rates μ, we neglect the fixation times τ_{fix} here, although they will not be identical in the two scenarios. For $s = 1$, the single path is neutral. We decrease s in the hypercube until we have identical waiting times. This yields an implicit expression for s

$$d - 1 + \frac{1}{N}\frac{1 - \frac{1}{r^N}}{1 - \frac{1}{r}} = \frac{1}{dN}\frac{1 - \frac{1}{s^N}}{1 - \frac{1}{s}} + \sum_{k=1}^{d-2}\frac{1}{d - k} + \frac{1}{N}\frac{1 - \left(\frac{s}{r}\right)^N}{1 - \frac{s}{r}}. \quad (11)$$

From this equation, we can numerically determine s for any given N. For large N, Eq. (11) simplifies to

$$d(d - 1) - \sum_{k=1}^{d-2}\frac{d}{d - k} = \frac{1}{N}\frac{1 - \frac{1}{s^N}}{1 - \frac{1}{s}} \approx \frac{e^{N(1-s)-1}}{N(1 - s)}, \quad (12)$$

where we used $(1 - x/N)^{-N} \to e^x$ for large N. Thus, the quantity $N(1 - s)$ becomes constant for large N, see Fig. 3. Thus, we can now say how broad and deep a fitness valley has to be to lead to the same cumulative waiting time as a single neutral path.

Next, we address the effect of the intermediate fitness s, which has an important influence on the cumulative waiting

time τ. Fig. 2 shows how the waiting time decreases with increasing fitness in the intermediate states s. If s comes very close to the fitness in the final state, the waiting time increases. This increase is seen both in the single path and the hypercube. An increase in the intermediate state fitness will not always lead to a reduction in waiting times. Instead, the fixation times reach a minimum when the fitness growth is constant between any two consecutive states (Weinreich and Chao, 2005; Traulsen et al., 2007). For the hypercube, the fastest trajectory will be steeper than on a single path: at first, many mutations are available and a big fitness increase is not necessary. Later, fewer mutations are available and thus, the fitness should increase faster. The precise form of the trajectory will in this case depend on the number of mutations d and the population size N. We note that a similar reasoning can be applied to construct a fitness landscape that allows to cross a fitness valley fastest. The fastest trajectory has the same form regardless if a fitness peak is approached ($r > 1$) or a fitness minimum is approached ($r < 1$). Thus, the fastest way to cross a fitness valley is to descend to the minimum with exponentially decreasing fitness and to increase from the minimum again with exponentially increasing fitness.

Now, we turn to the effect of the intermediate fitness s on the individual waiting times. Eqs. (8) and (10) both consist of three terms each. The first term denotes the time required to leave the initial state. The second term is the time spent in moving through all the intermediate states. This second term is independent of s, because the transitions are neutral. The last term denotes the time required to reach the ultimate state from the penultimate state. For small values of s, the probability to fixate the disadvantageous mutation is very small. Thus, the total time is dominated by the first term. When s is increased to a threshold value s_1, then the time for leaving the first state is identical to the waiting time in the intermediate states. For the hypercube, s_1 is given by $(1/d)\tau_{\text{wait}}(s_1) = \sum_{k=1}^{d-2}(1/(d-k))\tau_{\text{wait}}(1)$, which reduces to

$$\frac{1 - \frac{1}{s_1^N}}{1 - \frac{1}{s_1}} = dN\sum_{k=1}^{d-2}\frac{1}{d - k}. \quad (13)$$

This equation can be solved numerically for specific values of N and d. For the single path, the right hand side of this equation has to be replaced by $N(d-2)$. For $s > s_1$, the time to cross the intermediate states is larger than the waiting time in the first state. On the hypercube, we can define a second threshold for which the waiting time in the first state is the same as the time required to reach the final state from the penultimate state. This arises because the effective mutation rate in state 0 is d times larger than the effective mutation rate in state $d-1$. The threshold s_2 is given by $(1/d)\tau_{\text{wait}}(s_2) = \tau_{\text{wait}}(r/s_2)$ or

$$\frac{1}{d}\frac{1-\frac{1}{s_2^N}}{1-\frac{1}{s_2^1}} = \frac{1-\left(\frac{s_2}{r}\right)^N}{1-\frac{s_2}{r}}. \tag{14}$$

Again, s_2 has to be determined numerically. For a single path, the factor d^{-1} in Eq. (14) has to be dropped. Thus, the threshold s_2 occurs for $s > 1$ and is simply given by $s_2 = \sqrt{r}$.

The fixation time is also strongly influenced by the number of mutations d. A larger d increases the length of the path and usually also the fixation times. For the single path, this increase results only from the increase in the time required to cross the intermediate states, because the time for leaving the initial state and the time to reach the final state from the penultimate state are independent of d. The time required to reach the ultimate state from the penultimate state is also independent of d for the hypercube, but the time required to leave the initial state decreases with increasing d. This is because as d increases, there are more states available in the first error class and thus the effective rate of mutation out of the initial state increases. As for the single path, the time to cross the intermediate states increases with d in the hypercube. For the hypercube, this interplay can lead to a non-monotonic dependence of the fixation time on d. For example, for $N = 100$ and $s = 0.95$, the fixation time τ^H decreases with d for $d < 31$, but it increases with d for $d > 31$. In contrast, the fixation time always increases monotonically with d for the single path.

Increasing the fitness of the final state r increases the advantage of the final state over the intermediate states. This will result in the decrease in the time required for the population to make the last move. Increasing r has no effect on the time required to cross the intermediate states or the time required to move away from the initial state. As a result, those two times remain constant even as r increases, both in the single path and the hypercube.

4. Intermediate mutation rates

The analytical approach is only valid as long as the mutation rate is small, $\mu \ll N^{-2}$. For higher mutation rates, the population does not have to consist of at most two different types at any time. Instead, d mutations can be fixed in the population without sequentially fixing one after the other. This process has been termed stochastic tunneling and is of great importance in the context of cancer initiation (Iwasa et al., 2004; Michor et al., 2004; Nowak et al., 2004; Beerenwinkel et al., 2007). Tunneling across fitness valleys is more likely than tunneling across a flat fitness landscape (see Fig. 4). Even for $d = 2$, the evolutionary dynamics is characterized by a doubly stochastic process, which makes analytical approaches tedious (Iwasa et al., 2004). As discussed above, for $\mu N^2 \ll 1$ the population usually contains at most two different types. In this case, the probability of stochastic tunneling will be very small. On the other hand, for $\mu N > 1$, at least one mutant is produced per generation. Thus, the probability of stochastic tunneling approaches 1. For $N^{-2} < \mu < N^{-1}$, the
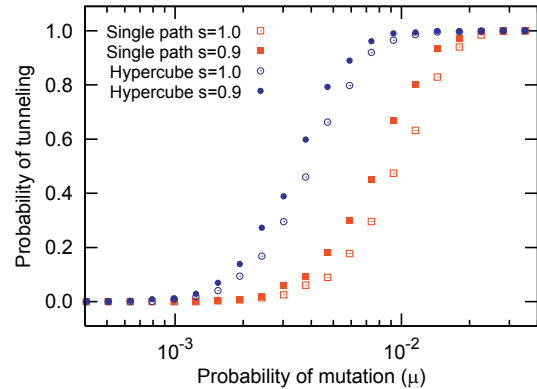
Fig. 4. The probability of tunneling across the hypercube (circles) is larger than in the single path (squares) due to the higher effective mutation rate. The tunneling across the valley denoted by the filled symbols ($s = 0.9$) is always larger than the probability of tunneling across a flat fitness landscape denoted by open symbols ($s = 1.0$). This arises from the fact that the stepwise accumulation of mutations would involve the fixation of a disadvantageous mutation in the first step. All symbols show the probabilities that the population tunnels at least across one state for the single path or at least one error class for the hypercube ($N = 100$, $d = 5$, $r = 1.1$, averaged over a 1000 realizations).
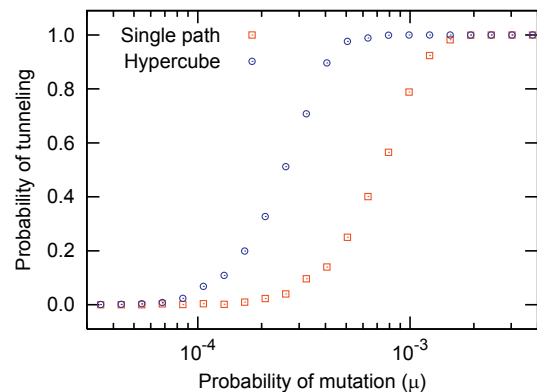
Fig. 5. The probability of tunneling across a neutral hypercube (circles) is always higher than the probability of tunneling across a neutral single path (squares). Here, the probability that the system tunnels across at least one state or one error class is shown for $d = 5$ and $N = 1000$. As expected, for $N\mu > 1$ the probability of tunneling approaches 1. In contrast to our conservative estimate that tunneling can be neglected only as long as the mutation rate is below N^{-2}, even for mutation rates as large as $100N^{-2}$ the probability of tunneling remains close to zero ($s = 1.0$, $r = 1.1$, averaged over a 1000 realizations).

mutations are sometimes fixed sequentially and sometimes via stochastic tunneling. Fig. 5 shows how the tunneling probability increases from 0 to 1 in this interval.

For intermediate mutation rates, it is likely that the population contains more than two different types. The types with beneficial mutations will compete for fixation. This process is termed clonal interference (Crow and Kimura, 1970; Fisher, 1930; Muller, 1932; Gerrish and Lenski, 1998; Park and Krug, 2007). Clonal interference has been considered to slow down adaptation, but recently it has been shown that it can have a positive influence on a rugged fitness landscape (Gerrish and Lenski, 1998; Wilke, 2004; Jain and Krug, 2007).

The states in a single path can be characterized by the number of mutations. In the hypercube, the states are characterized by the types of mutations that have already occurred. Thus, there are many different types that have undergone a specific number of mutations. However, all types that have already accumulated k mutations can be pooled into the error class k. The number of different types in the error class k is given by $\binom{d}{k} = d!/k!(d - k)!$.

In a single path, a population is said to tunnel across a state if it passes through a state without ever reaching fixation in that state. Analogously, in a hypercube a population said to tunnel across an error class if it passes through that error class without ever reaching fixation in it. Within the error classes, tunneling can occur across individual states, but also across several states at once. This means that the whole population passes only across that particular state and not across any other, without ever reaching fixation in that particular state. Tunneling across an error class can also occur in a second way: the population can use all of the available states in the error class, but the total number of individuals in the error class never reaches N. Thus, the probability of tunneling via the individual states is always lower than the probability of tunneling across the error classes. Fig. 6 shows the relation between the different probabilities of tunneling in the hypercube with respect to the rate of mutation μ for the special case $d = 2$.

Due to higher effective rates of mutation, the probability of tunneling across a hypercube is expected to be greater than or equal to the probability of tunneling across a single path. However, numerical simulations reveal that for $d = 2$ the probability of tunneling in a single path is higher than in the hypercube. This is a special case: for $d = 2$ in a hypercube, the number of states into which the initial state can mutate into is 2. The effective rate of mutations is thus twice as much as in the single path. The number of states which can be mutated into next is one, both in the single path and the hypercube. Thus the rate at which the individuals are pushed into the first state is higher in hypercube than in the single path while the rate of individuals being pushed out is the same. Thus there is a higher probability of reaching fixation in the first error class in a hypercube (see Fig. 6). We only observe this effect for $d = 2$, for $d > 2$, the probability of
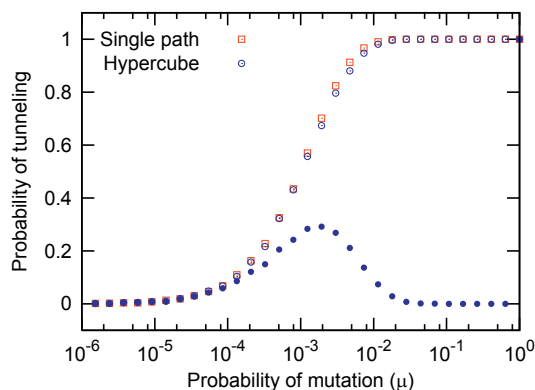
tunneling is higher in a hypercube than in a single path, as expected (see Fig. 4).

5. High mutation rates

For $\mu N > 1$, the stochastic features of the dynamics become less important. In this case, the system can be described by a set of $d + 1$ deterministic differential equations for the fraction $x_k(t)$ of the population that has k mutations (Jain and Krug, 2007). Obviously, we have $\sum_{k=0}^{d} x_k(t) = 1$. Transitions out of state 0 occur with probability $T_{0\rightarrow} = (1 - (x_0/\phi)u_{0\rightarrow0})x_0$, where $\phi = x_0 + (1 - x_0 - x_d)s + x_d r$ is the average fitness of the population. This includes all the reproductive events except for the one where a type 0 is produced. Transitions into state 0 occur with probability $T_{\rightarrow0} = (x_0/\phi)u_{0\rightarrow0}(1 - x_0)$. Thus, the fraction of individuals in the initial state follows the differential equation:

$$\dot{x}_0(t) = \frac{1}{N}\left[\frac{x_0}{\phi}u_{0\rightarrow0}(1 - x_0) - \left(1 - \frac{x_0}{\phi}u_{0\rightarrow0}\right)x_0\right]. \tag{15}$$

The probability that an offspring is of type k is given by $\lambda_k = \sum_{j=0}^{k}(x_j r_j/\phi)u_{j\rightarrow k}$. The difference between the hypercube and the single path only occurs in the quantity $u_{j\rightarrow k}$, which is given above for both cases. The sum in λ_k is over all individuals with k or less mutations and r_j is the fitness of individuals with j mutations. This leads to the differential equation for the fraction of individuals with k mutations

$$\dot{x}_k(t) = \frac{1}{N}[\lambda_k(1 - x_k) - (1 - \lambda_k)x_k], \tag{16}$$

where $k = 0, \ldots, d$. Of course, the special case $k = 0$ recovers Eq. (15). This set of $d + 1$ differential equations describes how the system moves from state $k = 0$ to state $k = d$. In general, only a numerical solution of this system of equations is feasible. While this allows us to infer details of the dynamics, our main interest is the time required for fixation of d number of mutations. Thus, we solve the differential equation numerically using a standard Runge–Kutta algorithm (Press et al., 2007). To find an equivalent to the fixation time in a stochastic simulation, we average between fixation ($x_d = 1$) and the time when there are on average less than 1 individuals outside the final state ($x_d = 1 - 1/N$). Thus, the fixation time is the time when the solution of the differential equation crosses $x_d = 1 - 1/2N$.

Fig. 7 shows an overview of the fixation times, covering the full range of mutation rates. For small mutation rates, we have sequential fixation of mutations and the time can be well approximated by Eqs. (8) and (10). For high mutation rates, the numerical solution of Eq. (16) leads to a good approximation for the fixation times.

6. Discussion

We have determined the average time during which a population moves from a certain initial state to a final state of higher fitness. The initial and the final states are separated by a fixed number of mutations d. The mutations jointly confer a fitness advantage to the final mutant which can be represented by a peak in the fitness landscape. If the intermediate mutations need to occur in a specific order for the evolution of the final mutant then it corresponds to the single path. Otherwise, evolution occurs on a hypercube and there are $d!$ ways of reaching the final state.

We have explored the simplest system in which the fitness in all intermediate states is the same. As expected, the fixation times on a hypercube are shorter than on a single path, due to the

Fig. 6. For $d = 2$, the probability of tunneling across the intermediate state is slightly higher in the single path (squares) than in the hypercube (open circles), shown for $N = 100$ here. This is because the effective mutation rate into the intermediate state is twice as big in the hypercube, leading to a higher probability of fixation. Filled circles show the probability to tunnel across individual states of the hypercube. For $\mu N > 1$, the system always tunnels. In the hypercube, both states are used for this. As expected, we need $\mu \ll N^{-2}$ for the tunneling probability to vanish ($s = 1.0$, $r = 1.1$, averaged over a 1000 realizations).
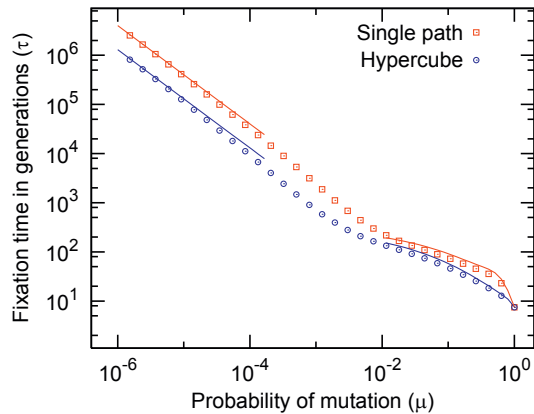
Fig. 7. The fixation times decrease with increasing mutation rate. Fixation always occurs faster on the hypercube (circles) than in the single path (squares). For small mutation rates, mutations fixate sequentially and the fixation time can be well approximated by Eqs. (8) and (10). Here, the fixation times decrease as μ^{-1}. For high mutation rates, the system can be approximated by a set of deterministic differential equations and the simulation results for the fixation times can be approximated based on the numerical solution of Eq. (16). In this case, fixation times decrease in general slower than μ^{-1} with increasing mutation rate (population size $N = 1000$, $d = 5$, $s = 1$, $r = 1.1$, averages over 1000 realizations).

Table 1
The time required for fixation of d mutations in units of 10^{10} generations for a mutation rate of $\mu = 10^{-10}$ based on Eqs. (8) and (10).

N	$d = 3$		$d = 10$	
	Single path	Hypercube	Single path	Hypercube
10^2	2.10999	0.943325	9.10999	2.03896
10^4	2.0011	0.834433	9.0011	1.93007
10^6	2.00001	0.833344	9.00001	1.92898

The intermediate mutations are neutral, $s = 1$. For small mutation rates, the fixation times scale linearly with μ^{-1}. For $N \to \infty$, the fixation time on the single path approaches $\mu^{-1}(d - 1)$ and the fixation time on the hypercube approaches $\mu^{-1}\sum_{k=0}^{d-2}(d - k)$. However, the mutation rates have to decrease with increasing N to make the approximation for the fixation times valid (initial fitness 1.0 and final fitness $r = 1.1$).

presence of multiple paths available in a hypercube. This observation leads to the question: for which parameters does the hypercube show shorter fixation times than the single path, even with an added disadvantage? The fitness in the intermediate states was then set to lower values than the ones in the single path. Up to a certain threshold value of the fitness of the intermediate states, the hypercube shows shorter fixation times than in the single path. The value of the threshold depends on the population size, total number of required mutations and the fitness in the final state.

The fixation times for large populations largely depend on the fitness function and are qualitatively independent of the order of mutations. Let us first focus on a flat landscape: when the intermediate states have a fitness equal to the fitness of the initial wild-type, then for small mutation rates large populations have shorter fixation times than small populations. This is because the neutral rate of evolution does not depend on the population size. But the waiting time for fixation of the last mutation becomes shorter with larger population size. For intermediate mutation rates, tunneling starts earlier in larger populations. This leads to a marked decrease in the fixation time with larger population size. For high mutation rates, the time to fixation is no longer dominated by the time for the first mutant to reach the final state, but by the time until all individuals are in that state. Due to this, for high mutation rates the time required for fixation can be shorter in smaller population as compared to larger populations. Next, we focus on fitness valley: if the fitness landscape consists of a valley with reduced fitness of the intermediate states, small populations have an advantage for small mutation rates, as they can easily leave the initial state and enter the valley. But for high mutation rates, large populations reach fixation faster, because they can explore states within and beyond the fitness valley more easily.

Our numerical simulations reveal that tunneling can be neglected even when the mutation rate exceeds N^{-2}, at least by one order of magnitude. Thus, Eqs. (8) and (10) provide good estimates for the fixation times even in relatively large populations.

Concrete values for fixation times are collected in Table 1. They reveal that even in long-term studies of experimental evolution, it is difficult to observe the consecutive fixation of neutral mutants (Cooper et al., 2003). Consecutive fixation of advantageous mutants, however, is significantly faster. For example, while Table 1 reveals a fixation time of $\sim 10^{11}$ generations on a single path for $d = 10$, $s = 1$ and $N = 10^6$, an optimal choice of the intermediate fitness values (Traulsen et al., 2007) would lead to a fixation time of $\sim 10^7$ generations.

While we have focused on the simplest possible system which allows analytical approximations, experimental studies reveal of course a much higher complexity. Weinreich et al. (2006) studied experimentally the point mutations in the β-lactamase gene of bacteria. β lactam antibiotics are commonly used, but the bacteria can develop resistance to the drugs. Five point mutations in a particular allele of the β-lactamase gene increases the resistance of the bacteria to cefotaxime by a factor of $\sim 100,000$. Theoretically the mutations leading from the wild-type allele to the resistant allele can occur in $5! = 120$ ways. These can be represented by a hypercube of $d = 5$. But in only 18 of the 120 trajectories, the intermediate mutations are either neutral with respect to the initial state or beneficial. Weinreich and colleagues have shown that these have the highest probability of realization. For all beneficial intermediates the fastest way to reach the final state would be when the relative fitness increase between any two consecutive mutations is constant (Traulsen et al., 2007), but usually in nature several different mutations are available and the population first evolves to states that provide the highest selective advantage.

In another experimental study the sequence space of the 5s rRNA of a marine bacterium, *Vibrio proteolyticus* was explored (Lee et al., 1997). The sequences from *Vibrio proteolyticus* and *Vibrio alginolyticus* differ in only four positions. All the possible intermediates were constructed by the authors and the fitness of each was calculated (Chao and McBroom, 1985). Two of the valid intermediates have a fitness lower than the initial wild-type. We have shown how such fitness valleys can be crossed by exploring the phenomenon of tunneling or multiple mutations (for high mutation rates). Thus, the population does not need to move in a Wrightian fashion (the whole population moving as a whole across the valley).

The theory discussed herein deals with basic evolutionary concepts which are important to the kind of biological examples described above. More complex properties of the experimental studies like more general cases of epistasis and compensatory mutations can easily be incorporated, but there is a huge number of possibilities. Even if we are only interested in the ordering of fitness values, we can have up to $2^d!$ distinct epistatic patterns.

Thus, one should rather focus on concrete systems instead. For example, one could simulate the dynamics in a system with experimentally derived fitness values and mutation rates. Not all the paths of a hypercube might be accessible for selection, but still some of them might prove to be significant depending upon the particular values of the parameters, such as fitness values and population size. Our goal here was to characterize the simplest features of the dynamics of a population crossing a fitness valley. This approach can be helpful when more realistic scenarios are addressed.

Acknowledgments

References

Antal, T., Scheuring, I., 2006. Fixation of strategies for an evolutionary game in finite populations. Bull. Math. Biol. 68, 1923–1944.

Armitage, P., Doll, R., 1954. The age distribution of cancer and a multi-stage theory of carcinogenesis. Br. J. Cancer 8, 1–12.

Atwood, K.C., Schneider, K.L., Ryan, F.J., 1951. Periodic selection in *Escherichia coli*. Proc. Natl. Acad. Sci. U.S.A. 37, 146–155.

Beerenwinkel, N., Antal, T., Dingli, D., Traulsen, A., Kinzler, K.W., Velculescu, V.E., Vogelstein, B., Nowak, M.A., 2007. Genetic progression and the waiting time to cancer. PLoS Comput. Biol. 3, e225.

Chao, L., McBroom, S.M., 1985. Evolution of transposable elements: an IS10 insertion increases fitness in *Escherichia coli*. Mol. Biol. Evol. 2, 359–369.

Cooper, T., Rozen, D., Lenski, R.E., 2003. Parallel changes in gene expression after 20,000 generations of evolution in *Escherichia coli*. Proc. Natl. Acad. Sci. U.S.A. 100 (3), 1072–1077.

Crow, J.F., Kimura, M., 1970. An Introduction to Population Genetics Theory. Harper & Row, New York.

DePristo, M.A., Hartl, D.L., Weinreich, D.M., 2007. Mutational reversions during adaptive protein evolution. Mol. Biol. Evol. 24, 1608–1610.

Eigen, M., McCaskill, J., Schuster, P., 1989. The molecular quasi-species. Adv. Chem. Phys. 75, 149–263.

Eigen, M., Schuster, P., 1977. The hypercycle. A principle of natural self-organization. Part A: Emergence of the hypercycle. Die Naturwiss. 64, 541–565.

Ewens, W.J., 2004. Mathematical Population Genetics. Springer, New York.

Fisher, J., 1959. Multiple-mutation theory of carcinogenesis. Nature 181, 651–652.

Fisher, R.A., 1930. The Genetical Theory of Natural Selection. Clarendon Press, Oxford.

Frank, S.A., 2007. Evolutionary Dynamics of Cancer. Princeton University Press, Princeton, NJ.

Gerrish, P.J., Lenski, R.E., 1998. The fate of competing beneficial mutations in a asexual population. Genetica 102/103, 127–144.

Gerstung, M., Beerenwinkel, N., 2008. Waiting time models of cancer progression. Mathematical Population Studies, to appear. arXiv:0807.3638.

Gillespie, J.H., 1983. Some properties of finite populations experiencing strong selection and weak mutation. Am Nat. 121 (5), 691–708.

Gillespie, J.H., 2004. Population Genetics: A Concise Guide, second ed. The Johns Hopkins University Press.

Goel, N., Richter-Dyn, N., 1974. Stochastic Models in Biology. Academic Press, New York.

Iwasa, Y., Michor, F., Nowak, M.A., 2004. Stochastic tunnels in evolutionary dynamics. Genetics 166, 1571–1579.

Jain, K., Krug, J., 2007. Deterministic and stochastic regimes of asexual evolution on rugged fitness landscapes. Genetics 175, 1275–1288.

Jones, S., Chen, W.-D., Parmigiani, G., Diehl, F., Beerenwinkel, N., Antal, T., Traulsen, A., Nowak, M.A., Siegel, C., Velculescu, V.E., Kinzler, K.W., Vogelstein, B., Willis,

J., Markowitz, S.D., 2008a. Comparative lesion sequencing provides insights into tumor evolution. Proc. Natl. Acad. Sci. U.S.A. 105 (11), 4283–4288.

Jones, S., Zhang, X., Parsons, D.W., Lin, J.C.-H., Leary, R.J., Angenendt, P., Mankoo, P., Carter, H., Kamiyama, H., Jimeno, A., Hong, S.-M., Fu, B., Lin, M.-T., Calhoun, E.S., Kamiyama, M., Walter, K., Nikolskaya, T., Nikolsky, Y., Hartigan, J., Smith, D.R., Hidalgo, M., Leach, S.D., Klein, A.P., Jaffee, E.M., Goggins, M., Maitra, A., Iacobuzio-Donahue, C., Eshleman, J.R., Kern, S.E., Hruban, R.H., Karchin, R., Papadopoulos, N., Parmigiani, G., Vogelstein, B., Velculescu, V.E., Kinzler, K.W., 2008b. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science 321 (5897), 1801–1806.

Karlin, S., Taylor, H.M.A., 1975. A First Course in Stochastic Processes, second ed. Academic Press, London.

Knudson, A.G., 1971. Mutation and cancer: statistical study of retinoblastoma. Proc. Natl. Acad. Sci. U.S.A. 68, 820–823.

Lee, T.H., DSouza, L.M., Fox, G.E., 1997. Equally parsimonious pathways through an RNA sequence space are not equally likely. J. Mol. Evol. 45, 278–284.

Michor, F., Iwasa, Y., Nowak, M.A., 2004. Dynamics of cancer progression. Nat. Rev. Cancer 4, 197–205.

Moran, P.A.P., 1962. The Statistical Processes of Evolutionary Theory. Clarendon Press, Oxford.

Muller, H.J., 1932. Some genetic aspects of sex. Am. Nat. 66 (703), 118–138.

Nordling, C., 1953. A new theory on cancer inducing mechanism. Br. J. Cancer 7, 68–72.

Nowak, M.A., 1992. What is a quasispecies? Trends in Ecology and Evolution 7, 118–121.

Nowak, M.A., 2006. Evolutionary Dynamics. Harvard University Press, Cambridge, MA.

Nowak, M.A., Michor, F., Komarova, N.L., Iwasa, Y., 2004. Evolutionary dynamics of tumor suppressor gene inactivation. Proc. Natl. Acad. Sci. U.S.A. 101, 10635–10638.

Park, S.-C., Krug, J., 2007. Clonal interference in large populations. Proc. Natl. Acad. Sci. U.S.A. 104 (46), 18135–18140.

Poelwijk, F.J., Kiviet, D.J., Weinreich, D.M., Tans, S.J., 2007. Empirical fitness landscales reveal accessible evolutionary paths. Nature 445, 383–386.

Press, W.H., Teukolsky, S.A., Vetterling, W.T., Flannery, B.P., 2007. Numerical Recipes 3rd Edition: The Art of Scientific Computing. Cambridge University Press, New York.

Sjöblom, T., Jones, S., Wood, L., Parsons, D., Lin, J., Barber, T., Mandelker, D., Leary, R., Ptak, J., Silliman, N., Szabo, S., Buckhaults, P., Farrell, C., Meeh, P., Markowitz, S., Willis, J., Dawson, D., Willson, J., Gazdar, A., Hartigan, J., Wu, L., Liu, C., Parmigiani, G., Park, B., Bachman, K., Papadopoulos, N., Vogelstein, B., Kinzler, K., Velculescu, V., 2006. The consensus coding sequences of human breast and colorectal cancers. Science 314, 268–274.

Traulsen, A., Iwasa, Y., Nowak, M.A., 2007. The fastest evolutionary trajectory. J. Theor. Biol. 249 (3), 617–623.

van Nimwegen, E., Crutchfield, J., 2000. Metastable evolutionary dynamics: crossing fitness barriers or escaping via neutral paths? Bull. Math. Biol. 62, 799–848.

Vogelstein, B., Kinzler, K., 2004. Cancer genes and the pathways they control. Nat. Med. 10, 789–799.

Weinreich, D., 2005. The rank ordering of genotypic fitness values predicts genetic constraint on natural selection on landscapes lacking sign epistasis. Genetics 171, 1397–1405.

Weinreich, D., Delaney, N., DePristo, M., Hartl, D., 2006. Darwinian evolution can follow only very few mutational paths to fitter proteins. Science 312, 111–114.

Weinreich, D.M., Chao, L., 2005. Rapid evolutionary escape by large populations from local fitness peaks is likely in nature. Evolution 59, 1175–1182.

Weinreich, D.M., Watson, R., Chao, L., 2005. Perspective: sign epistasis and genetic constraint on evolutionary trajectories. Evolution 56 (6), 1165–1174.

Wilke, C., 2004. The speed of adaptation in large asexual populations. Genetics 167, 2045–2053.

Wilke, C., 2005. Quasispecies theory in the context of population genetics. BMC Evol. Biol. 5, 44.

Wood, L.D., Parsons, D.W., Jones, S., Lin, J., Sjöblom, T., Leary, R.J., Shen, D., Boca, S.M., Barber, T., Ptak, J., Silliman, N., Szabo, S., Dezso, Z., Ustyanksky, V., Nikolskaya, T., Nikolsky, Y., Karchin, R., Wilson, P.A., Kaminker, J.S., Zhang, Z., Croshaw, R., Willis, J., Dawson, D., Shipitsin, M., Willson, J.K.V., Sukumar, S., Polyak, K., Park, B.H., Pethiyagoda, C.L., Pant, P.V.K., Ballinger, D.G., Sparks, A.B., Hartigan, J., Smith, D.R., Suh, E., Papadopoulos, N., Buckhaults, P., Markowitz, S.D., Parmigiani, G., Kinzler, K.W., Velculescu, V.E., Vogelstein, B., 2007. The genomic landscapes of human breast and colorectal cancers. Science 318 (5853), 1108–1113.

2.2 Fitter but slower

During the earlier study an interesting counterintuitive characteristic was noted. Consider the following simple setup. There are only two states A and B. The whole population (of size N) currently resides in state B. An individual can move from state B to state A by acquiring a mutation but not vice versa. For the dynamics we make use of the Moran process (Moran, 1962). Each time
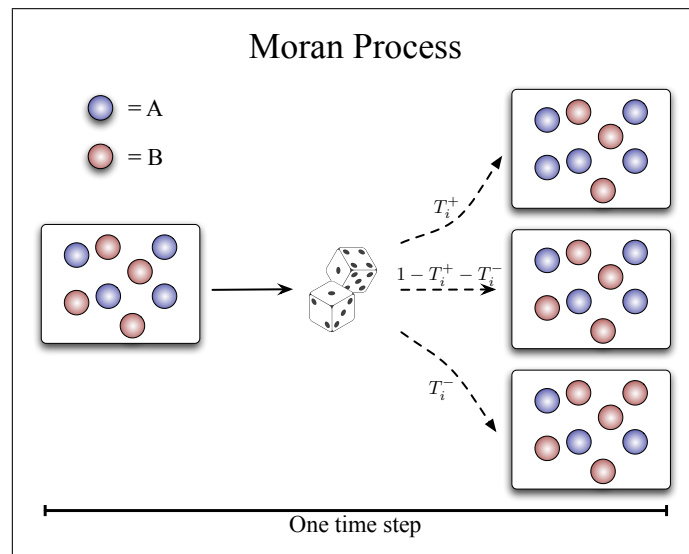
Figure 2.4: **The Moran process.** To describe the dynamics of a population of finite size we resort to stochastic processes. The Moran process is a birth-death process. That is, in time each step a birth event and a death event occur. The population size is maintained constant by a random death. If the population consists of say i A individuals then in one time step the number of A can increase by one (with probability T_i^+) or decrease by one (with probability T_i^-) or stay the same (with probability $1 - T_i^+ - T_i^-$).

step of the Moran process consists of a birth even and a death event. For the whole population to move from state B to state A means that all individuals currently in state B have to acquire the mutation. The mutation rate is given by μ. We consider the limit of small mutation rates such that a mutant reaches its fate (either fixation or extinction) before a new one arises. There are no back mutations from A to B. Thus in our variant of the Moran process in each time step, one of the following three things can happen (see Fig. 2.4),

- **Number of individuals in state A increases by 1.** The number of individuals in state A increases by 1 with probability,

$$T_i^+ = \frac{i}{N}\frac{N-i}{N} + \frac{N-i}{N}\mu\frac{N-i}{N}. \qquad (2.1)$$

The increase can happen in two ways. The first term gives the probability when an A state individual is chosen for reproduction and a B for death. The second term gives the probability when a B is chosen for reproduction, but mutates to A and again a B is chosen for death.

- **Number of individuals in state A decreases by 1.** The number in state A decreases only if a B is chosen for reproduction and it does not mutate and an A is chosen for death. This event happens with probability,

$$T_i^- = \frac{N-i}{N}(1-\mu)\frac{i}{N}. \qquad (2.2)$$

- **No change in either state.** This happens with probability $1-T_i^+-T_i^-$.

Hence in each reproductive step there is a bias towards producing an individual with a mutation (see Fig. 2.5). Intuitively we expect that the average
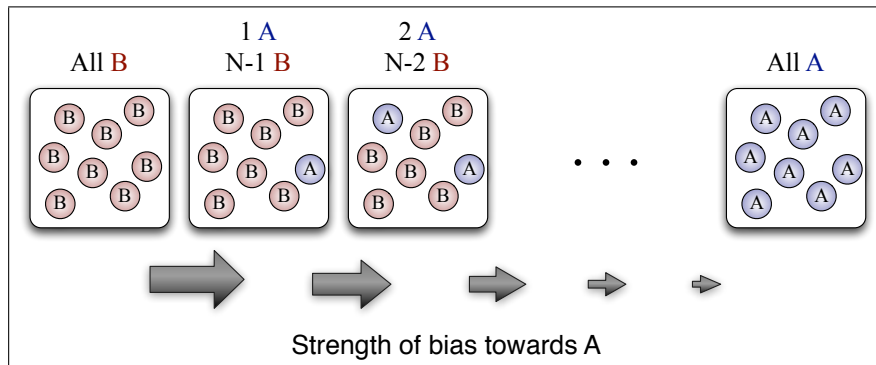
Figure 2.5: **Bias towards** A**.** Throughout the process there is a frequency dependent bias towards moving to an all A state. It diminishes in strength as the system gets closer to an all A state. Yet the time time required to get to the final state is greater than without such a bias.

conditional time required for the fixation of a single A individual in a population of $N-1$ B individuals should be smaller than in a balanced process in

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

Increases

Decreases

Figure 2.6: **Effect of increasing bias on components of conditional fixation time** τ_1^N**.** The expression gives us the exact conditional fixation time τ_1^N for the Moran process beginning with a single mutant. If we introduce a frequency dependent bias such that we have $T_i^+ > T_i^-$, then we see that the ratio of transition probabilities and the inverse of T_l^+ decrease. On the contrary, the fixation probability, ϕ_l^N, increases. The effect of this tug of war is an increase in the conditional fixation time for a small bias.

which there is no bias. However, we observe that for a small bias the average conditional fixation time is larger than that of a balanced process (without bias).

To go to the heart of this counterintuitive observation we must dissect out the quantity of interest, the conditional fixation time. Conditional fixation time means given that the mutant does fix, what is the time required for the population to reach a state where all individuals are mutants. For the Moran process we can exactly calculate the conditional fixation time from a formula which is well known for such a birth-death process (Moran, 1962; Goel and Richter-Dyn, 1974; Ewens, 1979; Landauer and Büttiker, 1987; Antal and Scheuring, 2006; Traulsen and Hauert, 2009) (see Fig. 2.6). In the following publication we observe what happens to this quantity of interest as we introduce a small bias to the system. Even a simpler process than directed mutations can exhibit such counter-intuitive behaviour. All it requires is a slight asymmetry in the transition probabilities (T_i^+ and T_i^-).

2.2.1 Publication: Stochastic slowdown in evolutionary processes

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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.

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 con-

sider 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

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

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

In the following, we discuss different choices of f_A and f_B, as well as closely related, but simplified asymmetric transition rates.
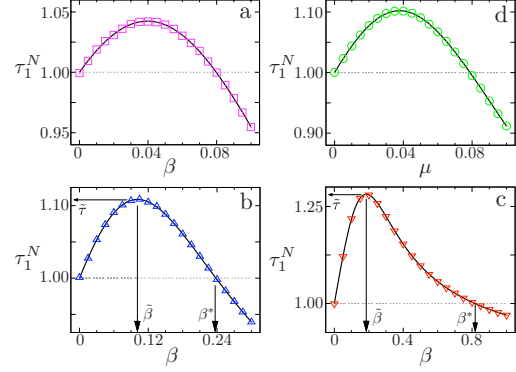
FIG. 1. (Color online) The conditional mean exit time $\tau_1^N / \tau_1^N(0)$ (normalized) as a function of the bias (selection intensity) β, or the mutation rate μ, for the four different models discussed in the main text. Symbols are simulations, lines show Eq. (4). (a) Moran process with $a = -0.1$ 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 non-trivial 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

$$\phi_i^N = \begin{cases} \dfrac{1}{\phi_1^i} \dfrac{\phi_1^{i^*}}{\phi_1^{i^*}(N - i^*)\gamma^{i^*} + 1} & \text{if } i \leq i^*, \\[3mm] \dfrac{\phi_1^{i^*}(i - i^*)\gamma^{i^*} + 1}{\phi_1^{i^*}(N - i^*)\gamma^{i^*} + 1} & \text{if } i \geq i^*, \end{cases} \tag{10}$$

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
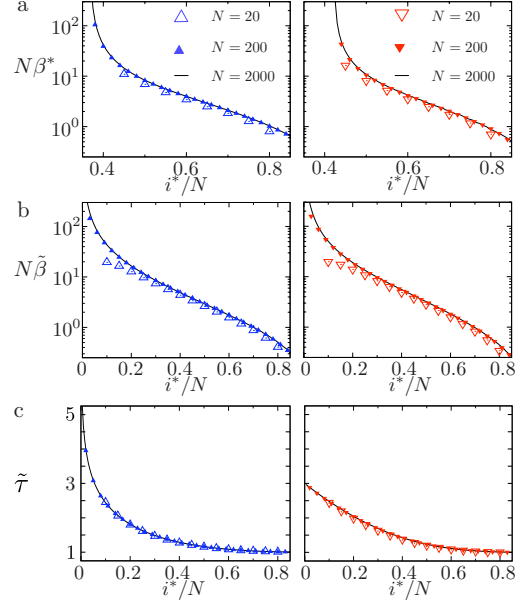
FIG. 2. (Color online) Scaling with system size for the two models with step like asymmetry: Parabolic-step model Eq. (9) [Fig. 1(b)] on the left, constant-step model Eq. (12) with $c = 1/2$ [Fig. 1(c)] on the right. (a) The threshold value $N\beta^*$, defined by $\tau_1^N(\beta^*) = \tau_1^N(0)$. Note 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 slow-down? 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 slow-down 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
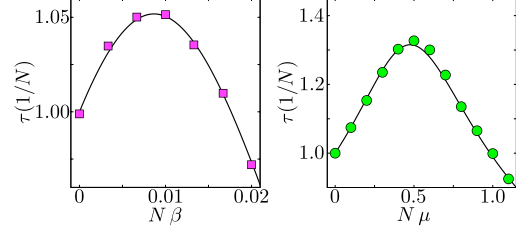
FIG. 3. (Color online) The conditional mean exit time (normalized) for the Wright-Fisher model with $N=1000$, as a function of the rescaled bias (selection intensity, mutation rate). The line shows the analytical diffusion approximation result Eq. (24), namely $\tau(N^{-1})/(2N-1)$. Symbols are simulation 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.

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}.

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]

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

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.

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

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

and obtain

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

with

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

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

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

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

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

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

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

As $\widetilde{D}_2(0) = [(N-1)\mu + 1]\mu$, $\widetilde{D}_2(1) = 1 - \mu$, and $\lim_{\mu \to 0} \widetilde{D}_2(x_0) = x_0$, 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.

[1] N. G. v. Kampen, *Stochastic Processes in Physics and Chemistry*, 2nd ed. (Elsevier, Amsterdam, 1997).

[2] C. W. Gardiner, *Handbook of Stochastic Methods*, 3rd ed. (Springer, New York, 2004).

[3] W. Feller, *An Introduction to Probability Theory and its Applications*, 3rd ed. (Wiley, New York, 1968).

[4] S. Karlin and H. M. A. Taylor, *A First Course in Stochastic Processes*, 2nd ed. (Academic, London, 1975).

[5] P. A. P. Moran, *The Statistical Processes of Evolutionary Theory* (Clarendon Press, Oxford, 1962).

[6] N. Goel and N. Richter-Dyn, *Stochastic Models in Biology* (Academic Press, New York, 1974).

[7] R. Landauer and M. Büttiker, Phys. Rev. B **36**, 6255 (1987).

[8] M. E. Fisher, IBM J. Res. Dev. **32**, 76 (1988).

[9] M.-O. Hongler and P. R. Parthasarathy, Phys. Lett. A **372**, 3360 (2008).

[10] P. Reimann, Phys. Rep. **361**, 57 (2002).

[11] W. J. Ewens, *Mathematical Population Genetics* (Springer,

New York, 2004).

[12] G. Szabó and C. Hauert, Phys. Rev. Lett. **89**, 118101 (2002).

[13] T. Antal and I. Scheuring, Bull. Math. Biol. **68**, 1923 (2006).

[14] M. A. Nowak, A. Sasaki, C. Taylor, and D. Fudenberg, Nature (London) **428**, 646 (2004).

[15] D. Helbing, Physica A **193**, 241 (1993).

[16] P. Schuster, in *Evolutionary Dynamics: Exploring the Interplay of Selection, Accident, Neutrality, and Function* (Oxford University Press, New York, 2003).

[17] G. Szabó and G. Fáth, Phys. Rep. **446**, 97 (2007).

[18] J. C. Claussen and A. Traulsen, Phys. Rev. Lett. **100**, 058104 (2008).

[19] M. Berr, T. Reichenbach, M. Schottenloher, and E. Frey, Phys. Rev. Lett. **102**, 048102 (2009).

[20] C. P. Roca, J. A. Cuesta, and A. Sanchez, Phys. Life. Rev. **6**, 208 (2009).

[21] M. Kimura, Nature (London) **217**, 624 (1968).

[22] T. Ohta, Proc. Natl. Acad. Sci. U.S.A. **99**, 16134 (2002).

[23] Y. M. Kaniovski, J. Evol. Econ. **10**, 545 (2000).

[24] A. Traulsen, J. C. Claussen, and C. Hauert, Phys. Rev. Lett. **95**, 238701 (2005).

[25] C. R. Doering, K. V. Sargsyan, and L. M. Sander, Multiscale Model. Simul. **3**, 283 (2005).

[26] S. Redner, *A Guide to First-Passage Processes* (Cambridge University Press, Cambridge, England, 2001).

[27] C. Taylor, D. Fudenberg, A. Sasaki, and M. A. Nowak, Bull. Math. Biol. **66**, 1621 (2004).

[28] C. Taylor, Y. Iwasa, and M. A. Nowak, J. Theor. Biol. **243**, 245 (2006).

[29] P. M. Altrock and A. Traulsen, New J. Phys. **11**, 013012 (2009).

[30] L. A. Imhof and M. A. Nowak, J. Math. Biol. **52**, 667 (2006).

[31] T. Maruyama, in *Lecture Notes in Biomathematics* (Springer, Berlin, 1977), Vol. 17.

[32] R. Bürger, *The Mathematical Theory of Selection, Recombination, and Mutation* (Wiley, New York, 2000).

[33] A. Traulsen, J. M. Pacheco, and L. A. Imhof, Phys. Rev. E **74**, 021905 (2006).

[34] F. A. C. C. Chalub and M. O. Souza, Math. Comput. Modell. **47**, 743 (2008).

[35] M. Nei and A. A. K. Roychoudhury, Genetics **74**, 371 (1973).

[36] T. Ohta, Nature (London) **246**, 96 (1973).

[37] T. Ohta, J. Mol. Evol. **44**, S9 (1997).

[38] C. D. Bustamante *et al.*, Nature (London) **416**, 531 (2002).

[39] J. C. Fay, G. J. Wyckoff, and C.-I. Wu, Nature (London) **415**, 1024 (2002).

[40] M. A. Nowak and K. Sigmund, Science **303**, 793 (2004).

[41] M. A. Nowak, Science **314**, 1560 (2006).

[42] J. Cremer, T. Reichenbach, and E. Frey, New J. Phys. **11**, 093029 (2009).

Evolutionary Game Theory

3.1 Introduction

Frequency dependent fitness introduces a strategic aspect to evolution. Evolutionary game theory is the study of biological systems with frequency dependent fitness. Consider the following example.

When introduced, evolutionary game theory was used to model animal conflict situations. We use a classical example of hawks and doves used by May- nard Smith and Price (1973). When fighting over resources say hawks are the ones who escalate the fight. Doves do not fight, instead they share the resource equally. Let the benefit of securing the complete resource be b and the cost for fighting over it be c with the relation $c > b$. This problem can be represented as,

$$
\begin{array}{cc}
 & \begin{array}{cc} \text{Hawk} & \text{Dove} \end{array} \\
\begin{array}{c} \text{Hawk} \\ \text{Dove} \end{array} & \left(\begin{array}{cc} \frac{b-c}{2} & b \\ 0 & \frac{b}{2} \end{array} \right).
\end{array}
\tag{3.1}
$$

The above way of representing the problem is known as the **payoff matrix**. This particular payoff matrix denotes the payoff for the row player and it reads as follows:

(1) **I (row player hawk) meet another hawk.** I will keep on fighting until one of us relents. On winning I will get $b - c$ but as each of us has an equal chance of winning the expected payoff is $(b - c)/2$.

(2) **I (row player hawk) meet a dove.** The opponent being a dove gives in without effort and I get the full benefit b without paying any cost.

(3) **I (row player dove) meet a hawk.** This is the mirror image of (2). Seeing the Hawk I give in and gain nothing, 0.

(4) **I (row player dove) meet another dove.** We both do not want to fight and just split the benefit equally between the two of us, each getting, $b/2$.

As $c > b$, that is the benefit from winning does not cover the cost hence a dove does better in a population dominated by hawks. While the hawks fight each other and get negative payoffs, a dove is better off getting 0. Similarly, if all are doves then it pays to be a hawk and get b instead of $b/2$. Hence there will be a stable co-existence of hawks and doves. The hawk-dove game is a bit misleading because the interactions are described as between species. We can consider the types to be behavioural strategies as being aggressive or docile. Overall this example clarifies the most basic point of evolutionary game theory, frequency dependence. This is the essence of evolutionary game theory (see Fig. 3.1). Frequency independence can be a subset of frequency dependence and hence studying frequency independent selection is a simple special case in evolutionary game theory. But this is an anecdotal explanation and where can it be actually used?

In a recent, resource utilisation experiment with the yeast *Saccharomyces cerevisiae*, conflict between genes SUC2 and suc2 was analyzed (MacLean et al., 2010). Two strains of yeast were used. One with the gene SUC2 secretes an extra-cellular enzyme called invertase which catalyses the hydrolysis of sucrose into glucose and fructose, which can then can be taken up by the cell (Greig and Travisano, 2004; Doebeli and Hauert, 2005; Gore et al., 2009). The strain with gene suc2 does not secrete invertase. Thus, suc2 bearers are free from the manufacturing costs but they can utilise the glucose and fructose made by the SUC2 bearing strain The secretors are termed as "co-operators", while non-secretors as "defectors". In MacLean et al. (2010) the highest average fitness is obtained in a stable coexistence of the two strains. Using the published data
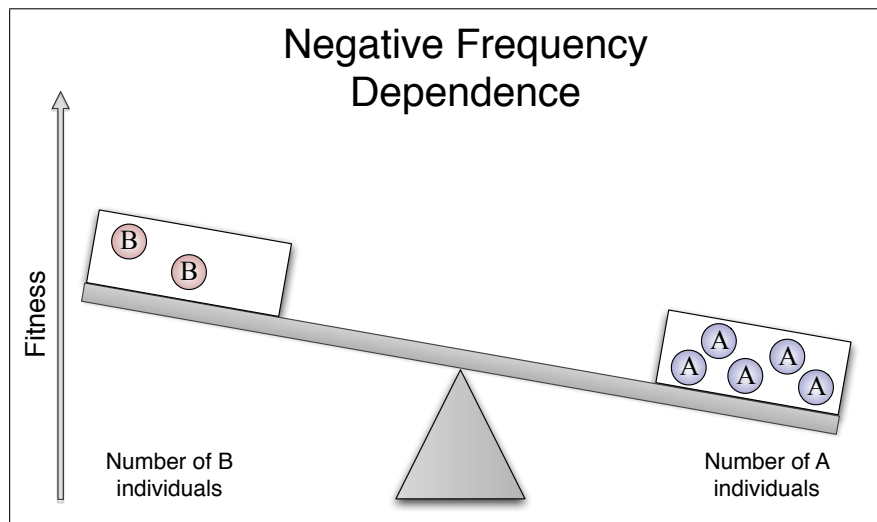
Figure 3.1: **A seesaw model of negative frequency dependence.** If the number of A individuals increases further then the fitness of type A will reduce even more. But having a greater fitness in effect means that the number will increase. Hence now when the number of B players increases the B side will go down i.e. the fitness of B will go down. If we maintain a fixed population size then the increase in B is compensated by a reduction in A. Thus for a small number of A individuals the fitness of A will be greater than that of B. This in particular is an example of what is known as negative frequency dependence, where the lower the frequency, the higher the fitness. Positive frequency dependence means that as the number increases, fitness increases. In general, the position of the pivot is not exactly in the centre.

we can write a payoff matrix for the interactions (Wu et al., 2011),

$$
\begin{array}{cc}
 & \begin{array}{cc} \text{SUC2} & \text{suc2} \end{array} \\
\begin{array}{c} \text{SUC2} \\ \text{suc2} \end{array} & \begin{pmatrix} 0.9475 & 1.03913 \\ 1.03912 & 0.9495 \end{pmatrix}.
\end{array}
\tag{3.2}
$$

We see that it is better to do the opposite of what the other player is doing. Thus this interaction can be studied as the "Hawk-Doves problem" encountered earlier.

The first use of indirect game theoretical arguments in biology is attributed to Fisher (1930). He was intrigued by the question, why the sex ratio in mammals is usually $1 : 1$? He noticed that the fitness of a male is greater in a

population consisting of more females than males and vice versa. The relative frequencies of both the sexes will thus tend to balance each other (the seesaw in Fig. 3.1 would be balanced). The fitness of a sex depends on its relative frequency in the population. The use of formal game theoretic arguments in biology was pioneered by R. C. Lewontin (1961). John Maynard Smith championed game theory in biology and described how it can be used to aptly describe animal conflict and other biologically strategic scenarios (Maynard Smith and Price, 1973; Maynard Smith, 1982). From the interactions between genes or cells (Axelrod et al., 2006; Basanta et al., 2008), between individuals (microbes to humans) or communities (Axelrod, 1984; Turner and Chao, 1999; Archetti, 2000; Turner, 2005; Frey, 2010) and even across species like host-parasite interactions (Vickery and Poulin, 2010), all can be captured by evolutionary games.

The word 'evolutionary' in this sense is not limited to biological evolution but can also describe cultural evolution, dealing with the evolution of behaviours and ideas (Hofbauer and Sigmund, 1998; Vincent and Brown, 2003; Kandori et al., 1993). One of the most important applications of evolutionary game theory has been in the research of evolution and maintenance of co-operation and eusociality. The problem of co-operation is typically represented by a payoff matrix with the following structure,

$$
\begin{array}{c}
\begin{array}{cc} C & D \end{array}\\
\begin{array}{c} C \\ D \end{array}\left(\begin{array}{cc} b-c & -c \\ b & 0 \end{array}\right),
\end{array}
\tag{3.3}
$$

where C and D stand for the strategies, co-operate and defect. As earlier the matrix gives the payoffs for the row player. If the row player is a co-operator then he/she has to pay the cost for co-operation $-c$. The benefit of co-operation b is obtained only if the other player co-operates. Since the lower row of the payoffs is consistently higher than the upper row of payoffs, it makes sense for the row player to play the strategy D instead of C. Assuming that the column player is at least as smart as the row player, both of them will choose to play D. The social optimum, where both of them would have co-operated would have resulted in a payoff of $b-c$ to each. Instead the search for an individual optimum led the players to obtain 0.

An economic analysis of the scenario clearly reveals that co-operation will be eliminated from the population. How could then a behaviour which costs the acting individual and benefits another have evolved by natural selection? In the seminal paper by Axelrod and Hamilton (1981) the problem of co-operation was analysed based on artificial players. There are numerous examples of co-operation in a natural setting:

- When viruses infect the same cell they compete for the available resources (Turner and Chao, 1999; Turner, 2005). "Cheater" viruses get rid of the genes for utilising resources which are available from other viruses and thus prey on the common good.

- Evolution and maintenance of multi-cellular life forms requires the co-operation of the composing cells (Nowak, 2006a). Evolution of cancer is about the breakdown of co-operation amongst the cells (Dingli and Nowak, 2006).

- Minnows demonstrate predator inspection behaviour (George, 1961). An ingenious experiment in which sticklebacks inspect a cichlid model was done by Milinski (1987, 1988, 1990) where a pair of fish are locked in a dilemma. Who will take the greater risk while inspecting the fish? A similar experiment was carried out in guppies (Dugatkin, 1988, 1990, 1997).

- Males of the Lance-tailed manakins participate in complex group courtship displays which benefit only the alpha male (DuVal, 2007). This raises the question of why do the subordinate males take part in the ritual.

- Blood meal sharing in vampire bats is a classic example where vampire bats can regurgitate blood meal for others who did not get enough (Wilkinson, 1984).

- Humans and other social organisms seem to be at the pinnacle of co-operation. Just as there is rampant incidents of cheating and selfish behaviour, there are also occurrences of long sustained co-operation amongst humans (Smith, 1776; Wedekind and Milinski, 1996; Milinski and Wedekind,

1998; Milinski et al., 2001; Fehr and Gächter, 2002; Fehr and Rockenbach, 2004; Sommerfeld et al., 2007; Henrich et al., 2006; Sigmund, 2007; Kummerli et al., 2007; Fehr et al., 2008; Gächter and Herrmann, 2009; Traulsen et al., 2010).

Using games such as the Prisoners Dilemma, Snowdrift game etc. this problem has been analysed in great depth. An in-depth discussion on this problem is beyond the scope of this thesis and hence we just briefly refer to this application of evolutionary game theory. For these and other interesting types of games, see Gintis (2000) or Sigmund (2010).

The names of these games come from short anecdotes like the "Hawk-Dove". They represent human economic conflict situations as was useful in classical game theory. Maynard Smith took the notations from classical game theory (von Neumann and Morgenstern, 1944) like the payoff matrix but developed a new logic for the analysis of games in a biological context. The games could be thus used as a proxy for animal conflict situations (Maynard Smith and Price, 1973). The development of evolutionary game theory is split into two parts, the static analysis initialised by Maynard Smith and the dynamical analysis developed by Taylor and Jonker (1978), Zeeman (1980), Schuster and Sigmund (1983), Hofbauer (1985) and Hofbauer and Sigmund (1988), as well as many others.

3.2 Evolutionarily Stable Strategies

In "The Logic of Animal Conflict" published by John Maynard Smith and George Price in Nature in 1973, they introduce a condition for a strategy to be evolutionarily stable. But what does it mean to be evolutionarily stable? To get to the heart of the question we do away with particular examples. In an abstract way consider just two strategies A and B. In an infinite population of A players imagine that a very small fraction of them start playing strategy B. What is the condition for A to oppose this invasion of B? If we find a certain condition and A satisfies that condition then we say that strategy A is an *evolutionarily stable strategy* (ESS).

Let us find this condition. As before we write down a payoff matrix for the game,

$$
\begin{array}{c}
\begin{array}{cc} A & B \end{array} \\
\begin{array}{c} A \\ B \end{array}
\begin{pmatrix} a_1 & a_0 \\ b_1 & b_0 \end{pmatrix}.
\end{array}
\tag{3.4}
$$

The matrix denotes the payoffs for the row player. The payoff entries are written so that we immediately know where they belong in the matrix. The small a is a payoff entry for strategy A and the subscript denotes if the other player is A, given by 1, or not, given by 0. Now from this infinitely large population let the frequency of the players playing strategy A be x. Hence the frequency of players playing strategy B is given by $1 - x$. The game matrix denotes the interaction of two players. Hence an A player can meet another A player or a B player. The probability of meeting a player of a certain strategy is the frequency of that strategy. This is because we have assumed a well mixed population (Maynard Smith and Price, 1973). In genetical terms this would mean random mating. For example when an A player meets another A player (this will be with probability x) then the focal A player gets a_1 according to the payoff matrix. From this we can calculate the average payoffs to both the strategies, namely π_A and π_B as,

$$
\pi_A = a_1 x + a_0(1 - x) \tag{3.5}
$$

$$
\pi_B = b_1 x + b_0(1 - x). \tag{3.6}
$$

If the average payoff of strategy A is always larger than that of strategy B then B will not be able to invade A,

$$
\pi_A > \pi_B
$$
$$
a_1 x + a_0(1 - x) > b_1 x + b_0(1 - x). \tag{3.7}
$$

Since we have assumed that the frequency of the invading B players is very small, we can cancel the terms with $1 - x$ as $x \approx 1$. Thus we arrive at the condition,

$$
a_1 > b_1 \tag{3.8}
$$

If we are dealing with a quirky situation where $a_1 = b_1$, then we need to restart our analysis at the earlier inequality (3.7). In this case we cancel a_1 terms with b_1 terms and are left with the condition,

$$a_0 > b_0 \quad \text{(given that } a_1 = b_1) \tag{3.9}$$

Thus for strategy A to be an **ESS** either of the following conditions must be met,

- $a_1 > b_1$ or $a_1 = b_1$ and $a_0 > b_0$.

- $a_1 > b_1$ or $a_1 = b_1$ and $a_0 \geq b_0$ also termed as **"weak ESS"** (Thomas, 1984, 1985).

An intuitive understanding of an ESS is that a focal strategy (A) has to do better when playing against itself (A) than when compared to another strategy (B) playing against the focal strategy (A). If somehow this barrier is broken and the invading strategy (B) pushes through, then the focal strategy (A) should do better when playing against the invading strategy (B) as compared to the invading strategy (B) against itself (B).

There is a deeper relationship between ESS and the traditional concept of Nash equilibrium (Nash, 1950) (see Fig. 3.2). In classical game theory strategy A would be a **strict Nash** equilibrium when an A playing against itself is better than B playing against A i.e. $a_1 > b_1$. Strategy A is a **Nash** equilibrium if it performs against itself at least as well as B performs against it, i.e. $a_1 \geq b_1$. A Nash equilibrium in short is the equilibrium from where no player can improve his or her payoff by switching strategies unilaterally (Nash, 1950).

The ESS analysis tell us whether a particular configuration of the population is resistant to invasion by a small number of mutants. But how do we know if the population can even reach that configuration in the first place? For this we look at the dynamics of the system.
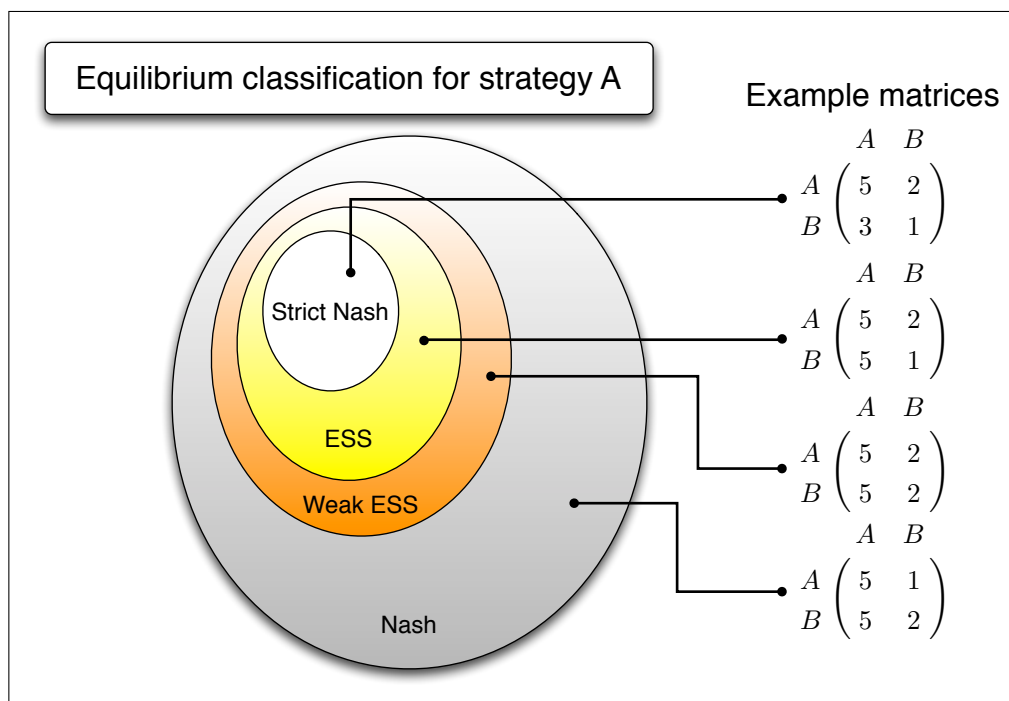
Figure 3.2: **Equilibrium classification for strategy A.** Denoting the logical relationships between ESS and Nash equilibria. All strict Nash equilibria are ESS which are all weak ESS which are all Nash but the reverse is not always true.

3.3 Evolutionary Game Dynamics

Traditionally evolutionary game theory deals with phenotypic traits. *"Evolutionary game theory, [. . .], describes evolution in phenotype space"* (Nowak and Sigmund, 2004). The different phenotypic traits are termed as strategies (like the earlier secretors and non-secretors). In this section we describe the dynamics of such strategies. Although evolutionary game theory is developed from the theory of games in economics (von Neumann and Morgenstern, 1944), it forgoes an important assumption of game theory: rationality. In evolutionary game theory natural selection is the dominant force. Individuals are born with fixed strategies. They interact with each other and receive payoffs according to a payoff matrix based on their strategies. Strategies which get the higher payoff are said to be more successful than those which do not. These successful strategies

spread in the population at the cost of other weaker strategies. Understanding this process is the mainstay of evolutionary game dynamics (Sandholm, 2010).

Difference and Differential equations (Box 3.3)

Before delving into game dynamics let us turn back to Malthus for a moment. Malthus proposed one of the earliest models of population growth now known as the Malthusian growth model or often the simple exponential growth model.

Consider an organism which increases in number exponentially (e-fold) at every time step. If the number of organisms at time t is p_t then the number at the next time step $t + 1$ is given by,

$$p_{t+1} = ep_t \qquad (3.10)$$

If we know the initial condition, i.e. the number at $t = 0$ then we can calculate the number of organisms at any time t exactly as,

$$p_t = e^t p_0 \qquad (3.11)$$

This type of equation is known as a difference equation as it uses the information from discrete time-points and calculates the differences to arrive at the final position specified in this example by t.

If time is measured continuously rather than in discrete time steps then we use a differential equation instead of a difference equation. For the above type of system we can write a differential equation as,

$$\frac{dp}{dt} = rp \qquad (3.12)$$

For the sake of concise notation we use $\dot{p} = \frac{dp}{dt}$, where the dot denotes the derivative taken with respect to time. The solution of this differential equation is obtained by integrating it, which leads to,

$$p(t) = e^{rt} p(0), \qquad (3.13)$$

where $p(t)$ and $p(0)$ are the frequencies at the respective time points.

Taylor and Jonker (1978) and Zeeman (1980) extended the realm of evolutionary game theory to include dynamics. This was a major leap forward in the field of evolutionary game theory. They introduced a differential equation (see Box 3.3) based on the quasi-species equation initially developed by Eigen

and Schuster (1977) (Eigen et al., 1989). The quasi-species equation does not include frequency dependent fitness but mutations. Excluding mutations but including frequency dependent fitness we arrive at the replicator equation (see Fig. 3.3). A simultaneous generalisation of these two equations leads to the replicator-mutator equation which includes frequency dependent fitness as well as mutations (Stadler and Schuster, 1992; Bomze and Buerger, 1995; Nowak and Komarova, 2001; Page and Nowak, 2002) (see Fig. 3.3). All these equations tell us how the strategies replicate and how their frequencies change over time.

$$\dot{x}_i = \sum_{j=1}^{n} x_j f_i(\mathbf{x}) q_{ji} - x_i \bar{f}$$

Replicator-Mutator equation

Neglecting mutations   Neglecting frequency dependent fitness

$$\dot{x}_i = x_i f_i(\mathbf{x}) - x_i \bar{f}$$

Replicator equation

$$\dot{x}_i = \sum_{j=1}^{n} x_j f_i q_{ji} - x_i \bar{f}$$

Quasispecies equation

$\dot{x}$ Frequency of type i

q_{ji} Mutation probability from j to i

$\bar{f}$ Average fitness of the population

f_i Frequency independent fitness of type i

$f_i(\mathbf{x})$ Frequency dependent fitness of type i

Figure 3.3: **Replicator and quasi-species equations as special cases of the Replicator-Mutator equation.** The quasi-species equation includes mutations between types but the fitness of the types are frequency independent. In the replicator equation the fitnesses of types is frequency dependent but there is no chance for mutations. Hence while a certain type can go extinct in replicator dynamics it may not in quasi-species dynamics if it is fuelled by mutations from some other type. Including both frequency dependent and mutations leads to the replicator-mutator equation.

3.3.1 Replicator Dynamics

At the core of evolutionary game theory lies the replicator equation. The replicator equation allows the frequencies of the different types in the population to determine the fitness landscape rather than setting the fitness of each type to be constant (Constant fitness is a special case of the replicator dynamics).

Let us take a bottom-up approach to the replicator equation. As before, consider two types in an infinitely large population, A and B. The frequency of type A is given by x_A and that of type B by x_B. Since these are the only two types in the population, the frequencies sum up to one, i.e. $x_A + x_B = 1$. Each type has an average fitness denoted by f_A and f_B. How this fitness is actually derived is a question pertaining to the particular context of the model we are studying. For our purpose we just consider fitness in its meaning, a quantitative measure of the ability of that type to pass on to the next generation. We consider the case of frequency dependent fitness. Hence we have $f_A(\mathbf{x})$ and $f_B(\mathbf{x})$ as the fitnesses. The bold $\mathbf{x}$ denotes that it is a vector, a set of frequencies of both the types ($\mathbf{x} = \{x_A, x_B\}$), as the fitness can depend on the frequencies of both the types. Considering the classical selection ideas we know that if this fitness is greater than the average fitness of the population then the frequency of that type increases over time and vice versa. Using this information we write down a set of two differential equations for the two types as follows,

$$\dot{x}_A = x\left(f_A(\mathbf{x}) - \bar{f}\right) \tag{3.14}$$

$$\dot{x}_B = y\left(f_B(\mathbf{x}) - \bar{f}\right). \tag{3.15}$$

We keep the population size constant by defining $\bar{f} = x_A f_A + x_B f_B$. This is just the average fitness of the population. Since we know that there are only two types in the population, we have $x_B = 1 - x_A$. Substituting these values of $\bar{f}$ and x_B in Eq. (3.14) we can use only one equation instead of the two to describe the dynamics of the whole system,

$$\dot{x}_A = x_A(1 - x_A)\left[f_A(\mathbf{x}) - f_B(\mathbf{x})\right]. \tag{3.16}$$

For the sake of simplicity we consider $x = x_A$ and thus $x_B = 1 - x$. Also remembering that the fitnesses are frequency dependent, we drop the functional

notation of the fitnesses and write a cleaner equation as,

$$\dot{x} = x(1-x)\left(f_A - f_B\right).$$

Here, one differential equation suffices. In general, if we have n different types in the population then we need a system of $n-1$ differential equations,

$$\dot{x}_i = x_i \left[f_i(\mathbf{x}) - \bar{f}\right]$$

where $i = 1, 2, \ldots n-1$ and the average population fitness is now $\bar{f} = x_1 f_1(\mathbf{x}) + x_2 f_2(\mathbf{x}) \ldots + x_n f_n(\mathbf{x}) = \sum_{i=1}^{n} x_i f_i(\mathbf{x})$ where x_i and f_i is the frequency and fitness of type i respectively. This is the replicator equation.

The solution of the replicator equation can be viewed in a $n-1$ dimensional space. For example, the solution for a two type case can be plotted on a single line, for three types we would need a two dimensional space and so forth. This way of representing the solution space is known as a simplex (see Box 3.3.1).

Simplex (Box 3.3.1)

In dynamical systems a simplex is a tool for visualizing how the dynamics of a system proceeds. We saw how the replicator equation can be used to study the dynamics of systems with n different types.

For simplicity consider $n = 2$ and let the two types be A and B as considered earlier. We can represent the state of the population by the frequencies of these two types. Either the population can be homogeneous for A (i.e. $x_A = 1$ and $x_B = 0$) or for B i.e. $x_A = 0$ and $x_B = 1$. Consider these two states to be represented by two points. The line joining them denotes the different possible compositions of the population. For example at the midpoint of the line, both the types will have the same frequency i.e. $x_A = x_B = 0.5$.

Figure 3.4: A system with n types can be represented by an $n - 1$ dimensional simplex. For $n = 2$ the simplex is a line. For $n = 3$ an equilateral triangle and for $n = 4$ a tetrahedron.

Now if we consider $n = 3$, with three types A, B and C then we represent it by a two dimensional simplex, an equilateral triangle. Again the midpoint of the simplex is where the frequencies are equal, i.e. $x_A = x_B = x_C = 1/3$.

An Italian statistician Bruno de Finetti used the triangular simplex to graph the frequencies of the genotypes for a diploid population with two alleles. In that sense the vertices correspond to the states where the population is homogeneous for a genotype (say aa, AA or aA). This simplex is known in population genetics as the de Finetti diagram.

In 1983, Peter Schuster and Karl Sigmund unified fields ranging from ecology to population genetics and prebiotic evolution to sociobiology in their most basic theoretical characteristic (Schuster and Sigmund, 1983). All these fields are essentially dynamical systems. Schuster and Sigmund abstracted out the essence of these systems and looked plainly at the dynamics. They pointed out that all these different models lead to the same class of differential equations and thus a unified equation could be used to describe the essence of these systems.

They named it the replicator equation by taking inspiration from the notion of 'replicators' from Dawkins (1982). Further Hofbauer and Sigmund (1998) also showed that the set of replicator equations for n strategies are mathematically equivalent to the well known Lotka Volterra equations for $n - 1$ species in ecology. The dynamical equations developed by Lotka and Volterra pre-date the replicator equation by almost half a century (Lotka, 1920; Volterra, 1928). In a sense, *"Ecology is the godfather of evolutionary game theory"* (Hofbauer and Sigmund, 1998).

Ultimately what the equations tell us is that the change in frequency of a certain type over time depends on its frequency, fitness and the average fitness of the population. If $f_i(\mathbf{x}) - \bar{f} > 0$ then the frequency will increase over time. If $f_i(\mathbf{x}) - \bar{f} < 0$ then it will decrease.

Due to this generality of the replicator equations we have not called the different types as "strategies". They will be considered as strategies once we connect this dynamical framework to evolutionary game theory. The evolutionary game is introduced in the dynamics via fitness.

Two strategies

We have defined fitness to be a function of the frequency of the different types. In section 3.2 we encountered a similar entity, payoffs, denoted by Eqs. (3.5). For completeness let us repeat the equations,

$$\pi_A = a_1 x + a_0(1 - x)$$
$$\pi_B = b_1 x + b_0(1 - x).$$

The coefficients belong to a two player game matrix with two strategies i.e. a 2×2 game. In the simplest case we consider the fitness of a strategy to be the payoff (which is already frequency dependent). Thus,

$$f_A = \pi_A \qquad (3.19)$$
$$f_B = \pi_B. \qquad (3.20)$$

The dynamical equation for two strategies is as given earlier by Eq. (3.17),

$$\dot{x} = x(1 - x)(f_A - f_B)$$

where $\dot{x}$ describes the change in the frequency of strategy A.

Of particular interest are the cases when $\dot{x} = 0$. This means that the frequency of A does not change. Hence the system has reached an equilibrium. Thus we look when $\dot{x} = 0$, which is equivalent to,

$$x(1-x)(f_A - f_B) = 0 \qquad (3.21)$$

There are three possible solutions to this equation, strategy A goes extinct, $x = 0$ or the whole population consists of A players, $x = 1$ and lastly when the two strategies have equal fitness, $f_A = f_B$ (Bishop and Cannings, 1976). Graphically we can plot the equation and see when it is equal to zero (see Figs. 3.5 and 3.6). As x increases, if the solution of the replicator equation intersects the zero line from above, then the intersection is known as a stable equilibrium (filled circle Figs. 3.5 and 3.6). If instead it intersects from below then it is an unstable equilibrium (open circle Figs. 3.5 and 3.6). In other words, if the derivative of the solution at the intersection is negative then the equilibrium is stable, if it is positive then it is unstable. For a small perturbation from the stable equilibrium the system returns to the stable equilibrium. For a small perturbation from an unstable equilibrium the system runs away from the unstable equilibrium in the direction of the perturbation.

The possible outcomes can thus be represented using the simplices (see Box 3.3.1) as shown in Figs. 3.5 and 3.6. What do these outcomes mean in terms of the evolutionary game?

(i) **Dominance**

  (a) Dominance of A. The population will eventually lead to a state where everyone is playing strategy A. This is possible if $a_1 > b_1$ and $a_0 > b_0$. This leads to $f_A > f_B$. Intuitively it means that it is always better to play strategy A regardless of which strategy the other player is playing (Fig. 3.5 (a)).

  (b) Dominance of B. This is a mirror image of the earlier case. In this situation it is always better to play strategy B i.e. the fitness of strategy B is always greater than that of A, $f_A < f_B$. This will be true if $a_1 < b_1$ and $a_0 < b_0$ (Fig. 3.5 (b)).
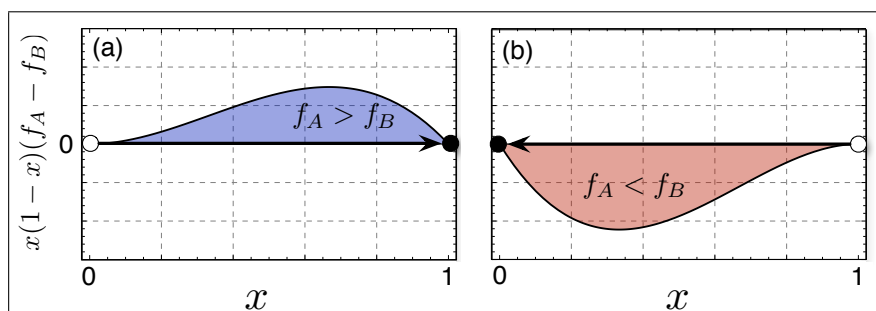
Figure 3.5: **Examples of dominance in a two player game with two strategies.** Let x be the frequency of strategy A. Scenario (a) is possible when either strategy is always fitter than the other, A fitter than B for (a) and vice versa for (b). In the simplex notation, the filled dots are the stable equilibria and the unfilled dots are the unstable equilibria. The arrows shows the direction of selection.

(ii) **Coexistence**. Co-existence of two strategies is possible if each strategy has an advantage when rare. When A is rare then we have $f_A > f_B$ but when A becomes abundant then $f_A < f_B$. That is when $a_1 < b_1$ and $a_0 > b_0$. It means that it is always best to play the strategy which is not being played by the other player (Fig. 3.6 (a)).

(iii) **Bi-stability**. Bi-stability refers to the condition where the pure states of the system, all A and all B, are stable. This is possible when a strategy has an advantage when abundant. That is $f_A > f_B$ when A is abundant but $f_A < f_B$ when it is rare. In this situation it is profitable to play the same strategy as your opponent as $a_1 > b_1$ and $a_0 < b_0$ (Fig. 3.6 (b)).

(iv) **Neutrality**. Under neutrality both the strategies do equally well and it does not matter which strategy we use. The payoffs you get when playing either strategy are equal irrespective of the strategy of your opponent. Hence $a_1 = b_1$ and $a_0 = b_0$. This leads to $f_A = f_B$.

For co-existence and bi-stability we see that the inequality between the fitnesses of the two strategies changes sign. The exact frequency of strategy A where this switch occurs can be explicitly calculated (the filled circle in Fig. 3.6 (a) and the open circle in Fig. 3.6 (b)). Let us call this frequency x^*. If the system
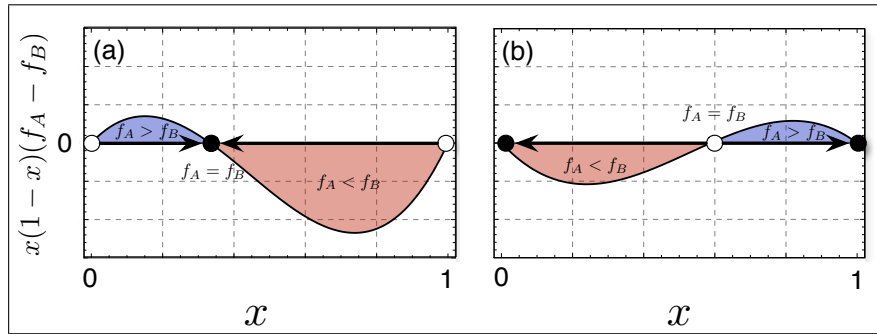
Figure 3.6: **Examples of co-existence and bi-stability in a two player game with two strategies.** Let x be the frequency of strategy A. (a) If each strategy is fitter than the other when it is rare then this leads to the co-existence of the two strategies. (b) Bi-stability is observed when above a certain frequency of A (open circle), A does better and below it B does better i.e. scenario (b). As in the earlier figure, the filled dots are the stable equilibrium and the unfilled are the unstable. The arrows shows the direction of selection.

is at that exact point then the fitnesses of both strategies are equal, $f_A = f_B$. Equating the two fitnesses, $f_A = f_B$, we get,

$$x^* = \frac{b_0 - a_0}{a_1 - a_0 - b_1 + b_0}$$

(3.22)

This frequency of strategy A, x^* is the turning point of the dynamics. For a coexistence game if the frequency of A drops below this point then strategy A does better than strategy B and above it, it does worse. Similarly, for a bi-stability game strategy B is better off below this point but strategy A does better above this point.

Multiple strategies

Consider the following biological example. Strains of *Escherichia coli* competing for resources have been studied by Kerr et al. (2002) and Czaran et al. (2002). K is a killer strain which produces a toxin harmful to strain S. Thus K will eventually out-compete S. Considering having and not having the toxin as two strategies, we can represent this interaction by a payoff matrix for a two player game with two strategies. But this is not the complete story. Another strain R

can be present, which is resistant to the toxin produced by K but pays the cost of resistance. Due to the cost the growth rate of R is slower than that of S. Now we have three strategies. To formally describe the game we need to write a 3×3 payoff matrix.

Thus in principle the number of strategies in a population may not be limited to just two or three. Again forgoing with examples we consider n arbitrary strategies $(1, 2 \ldots n)$ competing with each other. Now we need a larger $n \times n$ payoff matrix,

$$\begin{array}{c} \\ 1 \\ 2 \\ \vdots \\ n \end{array} \begin{array}{cccc} 1 & 2 & \ldots & n \\ \begin{pmatrix} a_{1,1} & a_{1,2} & \ldots & a_{1,n} \\ a_{2,1} & a_{2,2} & \ldots & a_{2,n} \\ \vdots & \vdots & \ddots & \vdots \\ a_{n,1} & a_{n,2} & \ldots & a_{n,n} \end{pmatrix} \end{array} \tag{3.23}$$

The payoff entries are with two subscripts denoting the payoff to the first when interacting with the second. For example $a_{1,2}$ is the payoff obtained by an individual of strategy 1 playing against another individual of strategy 2. This is still a two player game. The dynamics is described by the replicator equation Eq. (3.18),

$$\dot{x}_i = x_i \left[f_i(\mathbf{x}) - \bar{f} \right]$$

where the average fitness of a strategy i is,

$$f_i(\mathbf{x}) = a_{i,1} x_1 + a_{i,2} x_2 \ldots + a_{i,n} x_n = \sum_{j=1}^{n} a_{i,j} x_j$$

and the average fitness of the population is given by

$$\bar{f} = x_1 f_1 + x_2 f_2 \ldots + x_n f_n = \sum_{i=1}^{n} x_i f_i(\mathbf{x}).$$

The dynamics now occurs on an $n - 1$ dimensional simplex (see Box 3.3.1).

3.3.2 Finite Populations

Traditional analysis in evolutionary games has relied on the assumption of an infinite population size (Maynard Smith and Price, 1973; Taylor and Jonker, 1978; Maynard Smith, 1982; Hofbauer and Sigmund, 1998, 2003). Analysing finite populations is mathematically challenging and earlier only a few scientists ventured into that field, but recently rapid advances have been made (Riley, 1979; Schaffer, 1988; Fogel et al., 1998; Ficci and Pollack, 2000; Schreiber, 2001; Nowak and Sigmund, 2004; Nowak et al., 2004; Taylor et al., 2004; Wild and Taylor, 2004; Traulsen et al., 2005, 2006a; Antal and Scheuring, 2006; Fudenberg et al., 2006; Traulsen and Nowak, 2007; Wild and Traulsen, 2007; Hauert et al., 2008; Antal et al., 2009c; Hashimoto and A., 2009; Altrock and Traulsen, 2009; Altrock et al., 2010; Gokhale and Traulsen, 2010). Why should we consider finite populations? Firstly, it is realistic. Secondly, considering finite populations is a natural way of introducing noise in the deterministic dynamics considered earlier.

First let us specify the evolutionary game. Consider a finite population of size N. The individuals have one of the two strategies, A or B. The number of players playing strategy A is given by i and the remaining $(N - i)$ play B. The game being played is given by,

$$
\begin{array}{cc}
 & \begin{array}{cc} A & B \end{array} \\
\begin{array}{c} A \\ B \end{array} & \begin{pmatrix} a_1 & a_0 \\ b_1 & b_0 \end{pmatrix}.
\end{array}
\qquad (3.24)
$$

The average payoffs of the strategies A and B are given by π_A and π_B,

$$
\begin{aligned}
\pi_A &= \frac{i-1}{N-1}a_1 + \frac{N-i}{N-1}a_0 \\
\pi_B &= \frac{i}{N-1}b_1 + \frac{N-i-1}{N-1}b_0.
\end{aligned}
\qquad (3.25)
$$

Note that in the replicator dynamics case the payoff values were multiplied by frequencies but here we have to deal with the actual number of individuals. Due to this we need to exclude the focal individual from the payoffs. Hence if the focal individual is an A strategist then it can interact with $i - 1$ other A individuals out of $N - 1$ individuals and obtain a payoff of a_1.

In the traditional framework the payoffs are directly considered as the fitnesses of the respective strategies. Now we introduce a tunable parameter which controls the effect of the game on the fitness termed as the selection intensity (see Box 3.3.2).

Payoff to fitness mapping. Box (3.3.2)

Until now we considered the trivial payoff to fitness mapping for strategy i, $f_i = \pi_i$ (the average fitness is exactly the same as the average payoff obtained from the game). But fitness can depend on the payoff in many other ways. For some systems we may know the exact relationship between payoff to fitness but in other cases we can only speculate. Two of the many such mappings which are particularly useful are,

- $f_i = 1 - w + w\pi_i$ where the parameter w is bound by 0 and 1 (Nowak et al., 2004). This w is known as the intensity of selection. If it is 1 then we have $f_i = \pi_i$ and the game determines the fitness completely. Instead if it is 0 then we have $f_i = 1$ for all i and we face neutrality.

- $f_i = e^{\beta \pi_i}$ introduced by Traulsen et al. (2008) (also see (Aviles, 1999)). In this case, β plays the role of intensity of selection just as w did earlier. Just as previously, as payoff increases so does fitness. Also when $\beta = 0$ we observe neutral drift. For weak selection (small β) we can approximate the exponential function by a linear function and obtain all the results we have obtained until now for weak selection. For strong selection the definition using w proves to be unwieldy for analytical calculations. Instead, β can take any positive value. Also as the exponential function returns a positive value for any exponent, we can easily analyse payoff matrices with negative entries.

We consider the following mapping,

$$f_A = 1 - w + w\pi_A \qquad (3.26)$$
$$f_B = 1 - w + w\pi_B, \qquad (3.27)$$

where the parameter w is the intensity of selection. It controls the effect of the game on fitness. This helps us move through a range of selection intensities. For $w = 0$ selection is weak and for $w = 1$ it is strong.

Now we move on to the dynamics. We deal with the finite populations by considering stochastic processes developed in population biology. Two such processes are the Wright Fisher process and the Moran process.

- Fisher had implicitly proposed a process which was formally presented by Wright and came to be known as the Wright-Fisher process (Fisher, 1930; Wright, 1931). In this process each individual from a population of size N produces a large number of offspring proportional to fitness. From this large number of offsprings, a random sample of N individuals is drawn to obtain the next generation. Thus each time step in a Wright-Fisher process is of the order of a generation.

- The Australian statistician Moran (1962) introduced a birth-death process later known as the Moran process. Each time step of the Moran process consists of two events, a birth and a death event. For birth an individual is chosen at random. This individual produces an identical copy of itself. For death, again an individual is chosen at random from the population and is eliminated. In this way the population size remains constant. Thus each time-step of a Moran process can change the composition of the population, one individual at a time. In all, N such steps make up a generation.

Earlier in Chapter 2 (Section 2.2) we encountered a variant of the Moran process which included mutations. For our current purpose we will be using another variant of the Moran process to illustrate the dynamics. In this process when an individual is chosen for birth the choice is biased towards the type with higher fitness. This is just a bias, we cannot say where the system will move with certainty. Thus, we resort to probabilities. In each time step, one of the following three things can happen (see Fig. 2.4),

- **Number of A individuals increases by 1.** The number of A individuals can increase only if an A is chosen for reproduction and a B for death. This happens with probability,

$$T_i^+ = \frac{if_A}{if_A + (N-i)f_B} \frac{N-i}{N}. \tag{3.28}$$

The first fractional part is the probability of choosing an individual for reproduction. The probability of choosing an A proportional to its fitness is $if_A/(if_A+(N-i)f_B)$. The second fraction is to choose an individual for death. The probability of choosing a B individuals by chance is $(N-i)/N$.

- **Number of A individuals decreases by 1.** The number of A individuals can decrease only if an A is chosen for death and a B for reproduction. This happens with probability,

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

(3.29)

- **Number of A individuals remains the same.** This occurs with probability $1 - T_i^+ - T_i^-$.

In biology, often it is of interest to know how invasive an allele, a gene or even a species is. If it does invade, then will it go to fixation and wipe out the wild-type? Armed with the transition probabilities we now ask a similar question: in a population of j A individuals and $N-j$ B individuals what is the probability then that at a later time point the whole population will be of A individuals. This is known as the fixation probability of strategy A starting with j individuals, $\rho_A(j)$. A closed form expression for this probability in the Moran process is well known from the theory of birth-death processes (Goel and Richter-Dyn, 1974; Nowak, 2006a; Traulsen and Hauert, 2009),

$$\rho_A(j) = \frac{1 + \sum_{k=1}^{j-1} \prod_{i=1}^{k} \frac{T_i^-}{T_i^+}}{1 + \sum_{k=1}^{N-1} \prod_{i=1}^{k} \frac{T_i^-}{T_i^+}}.$$

(3.30)

If we begin with a single A player i.e. $j = 1$ then the fixation probability is $\rho_A(1)$ (see Fig. 3.7). Putting $j = 1$ we get,

$$\rho_A(1) = \frac{1}{1 + \sum_{k=1}^{N-1} \prod_{i=1}^{k} \frac{T_i^-}{T_i^+}}.$$

(3.31)

Note that $\frac{T_i^-}{T_i^+} = \frac{f_B}{f_A}$. If we have $f_A = f_B$, i.e. the case of neutrality when both the strategies are just neutral variants of each other the fixation probability reduces to $\rho_A(j) = j/N$. Thus we observe neutral drift where if we begin

with a single mutant then the probability of that mutant taking over the whole population is just as good as any other individual, $\rho_A(1) = 1/N$. Since for most of the analysis we deal with the fixation probability of a single mutant for simplicity we drop the functional notation and refer to the fixation probability as simply ρ_A. Similarly we can calculate the fixation probability of strategy B as ρ_B (Fig. 3.7). Formally the probability that 1 B individual reaches fixation is equal to the probability that $N-1$ A individuals do not reach fixation. That is,

$$
\begin{aligned}
\rho_B &= 1 - \rho_A(N-1) \\
&= 1 - \frac{1 + \sum_{k=1}^{N-2} \prod_{i=1}^{k} \frac{T_i^-}{T_i^+}}{1 + \sum_{k=1}^{N-1} \prod_{i=1}^{k} \frac{T_i^-}{T_i^+}} \\
&= \frac{1}{1 + \sum_{k=1}^{N-1} \prod_{i=1}^{k} \frac{T_i^-}{T_i^+}} \left(\prod_{i=1}^{N-1} \frac{T_i^-}{T_i^+} \right) \\
&= \rho_A \prod_{i=1}^{N-1} \frac{T_i^-}{T_i^+}.
\end{aligned}
\tag{3.32}
$$
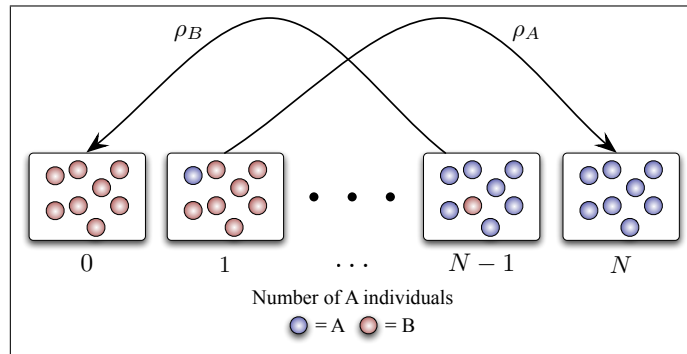
Figure 3.7: **Fixation probabilities.** The probability that a single A individual will take over the whole population is known as the fixation probability of A given by ρ_A. Similarly we can calculate the fixation probability of a single B individual in a population of $N-1$ A individuals as ρ_B. If the two strategies are neutral with respect to each other then these fixation probabilities are just $1/N$.

3.3.3 One Third Rule

A strategy being favoured by selection means that the fixation probability is greater than neutral. Considering strategy A that means we need to check if,

$$\rho_A > \frac{1}{N}. \tag{3.33}$$

For weak selection the product in the fixation probability can be approximated by a sum,

$$\rho_A \approx \frac{1}{N} + \frac{w}{N^2} \underbrace{\sum_{m=1}^{N-1} \sum_{j=1}^{m} (\pi_A - \pi_B)}_{\Gamma}. \tag{3.34}$$

It is then apparent that for $\rho_A > 1/N$, Γ should be greater than zero. That is,

$$\sum_{m=1}^{N-1} \sum_{i=1}^{m} \pi_A > \sum_{m=1}^{N-1} \sum_{i=1}^{m} \pi_B.$$

Substituting the values of π_A and π_B from Eqs. (3.25),

$$\sum_{m=1}^{N-1} \sum_{i=1}^{m} \left(\frac{i-1}{N-1} a_1 + \frac{N-i}{N-1} a_0 \right) > \sum_{m=1}^{N-1} \sum_{i=1}^{m} \left(\frac{i}{N-1} b_1 + \frac{N-i-1}{N-1} b_0 \right).$$

This can be simplified to,

$$a_1(N-2) + a_0(2N-1) > b_1(N+1) + 2b_0(N-2). \tag{3.35}$$

We thus arrive at Inequality 3.35 which is the condition in finite populations and depending only on the relationship between payoff values. For a large N this reduces to $a_1 + 2a_0 > b_1 + 2b_0$, which is equivalent to,

$$\frac{1}{3} > \frac{b_0 - a_0}{a_1 - a_0 - b_1 + b_0} = x^*, \tag{3.36}$$

calculated as the position of the possible internal equilibrium in Eq. (3.22). The internal equilibrium x^* can be in the interior if $a_1 > b_1$ and $a_0 < b_0$ (a bi-stability game) or if $a_1 < b_1$ and $a_0 > b_0$ (a co-existence game). The condition means that if a strategy at frequency *one third* has a fitness greater than the fitness of the other strategy then the fixation probability of that strategy is greater than neutral. This special relation between the internal equilibrium and the condition

for a strategy to have a fixation probability greater than neutrality is termed as the one-third rule (Nowak et al., 2004; Traulsen et al., 2006b; Imhof and Nowak, 2006; Ohtsuki et al., 2007; Bomze and Pawlowitsch, 2008). This rule is valid for all process which fall in the domain of Kingman's coalescence (Lessard and Ladret, 2007)

3.3.4 Risk Dominance

Having $\rho_A > 1/N$ means that the fixation probability of A is greater than neutral. As A approaches fixation at some time point we have $N - 1$ A individuals and 1 B individual. Now if $\rho_B > 1/N$ then the fixation probability of B will be greater than neutral. Hence it is necessary to determine which strategy has a higher fixation probability. Usually we ignore mutations between strategies. Selection and mutations work in tandem and maintain the population at the mutation selection equilibrium but if the mutation rate is very low then we can calculate the approximate stationary distribution by using the fixations probabilities as a proxy. In short we want to know which strategy is more likely to replace the other. Using Eqs. (3.31) and (3.32) we get,

$$\frac{\rho_B}{\rho_A} \quad = \quad \prod_{i=1}^{N-1} \frac{T_i^-}{T_i^+}. \tag{3.37}$$

Let the ratio of transition probabilities be γ_i. Then we have,

$$\gamma_i = \frac{T_i^-}{T_i^+} = \frac{f_B}{f_A} = \frac{1 - w + w\pi_B}{1 - w + w\pi_A} \approx 1 - w(\pi_A - \pi_B), \tag{3.38}$$

where we have assumed that selection is very weak that is $w \ll 1$. Substituting in Eq. (3.37) we get,

$$\frac{\rho_B}{\rho_A} \quad \approx \quad \prod_{i=1}^{N-1} 1 - w(\pi_A - \pi_B)$$

$$= \quad 1 - w \sum_{i=1}^{N-1} (\pi_A - \pi_B).$$

Substituting the values of π_A and π_B from Eqs. (3.25),

$$\frac{\rho_B}{\rho_A} \quad \approx \quad 1 - w \underbrace{\sum_{i=1}^{N-1} \left(\frac{i-1}{N-1}a_1 + \frac{N-i}{N-1}a_0 - \frac{i}{N-1}b_1 - \frac{N-i-1}{N-1}b_0 \right)}_{\Phi}.$$

Hence we have $\rho_A > \rho_B$ if $\Phi > 0$ which reduces to,

$$N(a_0 + a_1) - 2a_1 > N(b_0 + b_1) - 2b_0. \tag{3.39}$$

This result holds for a large number of birth-death processes for weak selection (Nowak et al., 2004; Antal et al., 2009a) and also for some special processes at any intensity of selection (Antal et al., 2009a). In the limit of a large population size we can ignore the terms without N and thus get,

$$a_1 + a_0 > b_1 + b_0 \tag{3.40}$$

Thus if the above inequality is fulfilled then for a large population under weak selection, strategy A will have a higher fixation probability than strategy B. This condition is also known as risk dominance (Harsanyi and Selten, 1988; Kandori et al., 1993). Intuitively risk dominant strategy is the one which you choose if you have no information about your opponent's strategy. In other words it just means knowing which is your safest bet.

4

Evolution in the multiverse

4.1 Evolutionary games in the multiverse

Stander (1992) has described the hunting behaviour of lionesses on the open semi-arid plains of Namibia. Individual hunting tactics of lionesses were analysed from 486 independent group hunts. The lionesses hunt in packs and employ the flush and ambush technique (see Fig. 4.1). Some lie in ambush while others flush out the prey from the flanks and drive them towards the ones waiting in ambush. This technique needs an interaction of more than two players to succeed.

Similarly, we interact with innumerable people at the same time, directly or indirectly. Some interactions may be pair-wise, but others are not. In real life, we may typically be engaged in many person games instead of a disjoined collection of two person games (Hamilton, 1975). Evolutionary game theory which we have discussed until now has been about two player games. It becomes mathematically more demanding when we try to include more players. Hamilton (1975) illustrates the theoretical challenges of multiplayer games as, *"The theory of many-person games may seem to stand to that of two-person games in the relation of sea-sickness to a headache."* A special class of multiplayer games has been experimentally and theoretically studied by economists and sociologists to study social behaviour of individuals. Such a typical "public goods game" consists of participants who have an option of contributing to a common pot. The sum is shared equally amongst all participants. Numerous variants
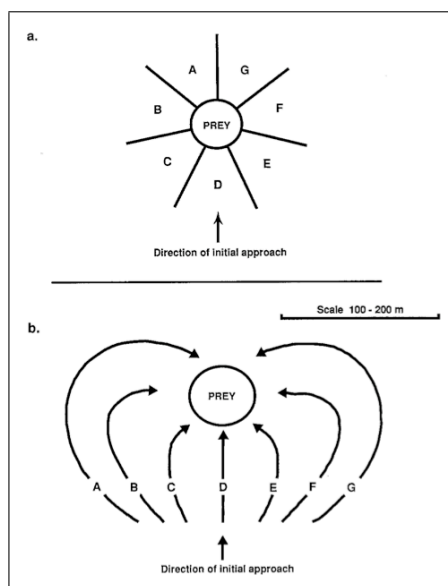
Figure 4.1: **Flush and Ambush.** Taken from Stander (1992) this sketch describes the flush and ambush technique used by the lionesses in Etosha National Park. Top panel reflects the position of the lionesses from the point of view of the prey. The bottom panel shows the attack positions of the lionesses. $A - B$ form the left flank while $F - G$ are the right flank. $C - D - E$ take the centre position. This hunting set-up is not possible with just two lionesses.

of this basic set-up have been explored (Wedekind and Milinski, 2000; Milinski et al., 2001; Anderson and Franks, 2001; Hauert et al., 2002; Semmann et al., 2003; Milinski et al., 2006; Rockenbach and Milinski, 2006; Hauert et al., 2007; Milinski et al., 2008; Santos et al., 2008; Pacheco et al., 2009; Souza et al., 2009; van Veelen, 2009; Traulsen et al., 2010; Connor, 2010). We develop some general conditions for multiplayer games with multiple strategies with simplicity in mind (Kurokawa and Ihara, 2009; Gokhale and Traulsen, 2010). To refrain from repeating the word "multi" for player and strategies we use the short form "games in the multiverse" for these kind of games.

Let us begin with the well known scenario of two player games with two strategies and add one more player to this setting. The changes which happen are reviewed below,

- The payoff matrix for a 2×2 games is a square matrix whereas for a

$2 \times 2 \times 2$ player game it is an extended table of permutations (see Fig. 4.2).

- The dynamics for a 2×2 proceeds on a simplex which is one dimensional, a single line. Even for $2 \times 2 \times 2$ games there are only two strategies and thus the simplex is a single line.

- There are five possible outcomes for a 2×2 game, as shown in Fig. 4.2. As the number of player increases the possible internal equilibrium points also increase. For $2 \times 2 \times 2$ games all the scenarios from 2×2 games are possible and in addition there is a possibility of having two equilibria in the interior, one stable one unstable (see Fig. 4.2).

Adding a player to the usual setting increases the complexity. The level of complexity increases as more and more players are added. In this project we examine this complexity and extract simple relations from it.

There were two main analytical advances in evolutionary game theory in the study of finite populations for two player games with two strategies.

1. When is the fixation probability of a strategy is greater than neutral (One Third rule) (Sub-section 3.3.3)?

2. When is the fixation probability of a strategy is greater than the fixation probability of the other strategy (Risk Dominance) (Sub-section 3.3.4)?

We develop general conditions for multiplayer games and two strategies without compromising on simplicity. Using the infinite population size assumption we also calculate the maximum number of internal equilibria of a given game with multiple player and multiple strategies.
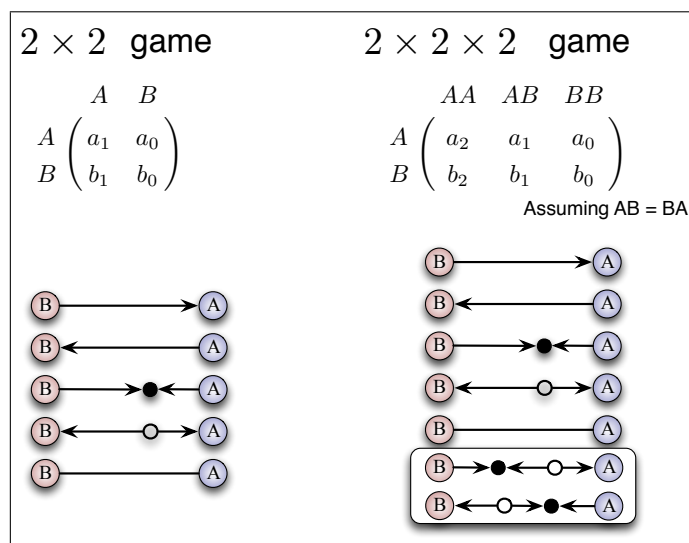
Figure 4.2: **Comparing two player games with three player games for two strategies.** Writing the payoffs for three player games cannot be done in a square payoff matrix as two player games. Instead it is a table of permutations of a player playing with 2 other players. For two player games there are five possible outcomes. As the payoffs are linear in x there can be at most a single internal equilibrium. For three player games the payoffs are not linear in x but of degree 2 leading to at most two possible solutions in the interior of the simplex.

4.1.1 Publication: Evolutionary games in the multiverse

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Evolutionary games in the multiverse

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Evolutionary game dynamics of two players with two strategies has been studied in great detail. These games have been used to model many biologically relevant scenarios, ranging from social dilemmas in mammals to microbial diversity. Some of these games may, in fact, take place between a number of individuals and not just between two. Here we address one-shot games with multiple players. As long as we have only two strategies, many results from two-player games can be generalized to multiple players. For games with multiple players and more than two strategies, we show that statements derived for pairwise interactions no longer hold. For two-player games with any number of strategies there can be at most one isolated internal equilibrium. For any number of players d with any number of strategies n, there can be at most $(d-1)^{n-1}$ isolated internal equilibria. Multiplayer games show a great dynamical complexity that cannot be captured based on pairwise interactions. Our results hold for any game and can easily be applied to specific cases, such as public goods games or multiplayer stag hunts.

evolutionary dynamics | multiplayer games | multiple strategies | replicator dynamics | finite populations

G ame theory was developed in economics to describe social interactions, but it took the genius of John Maynard Smith and George Price to transfer this idea to biology and develop evolutionary game theory (1–3). Numerous books and articles have been written since. Typically, they begin with an introduction about evolutionary game theory and go on to describe the Prisoner's Dilemma, which is one of the most intriguing games because rational individual decisions lead to a deviation from the social optimum. In an evolutionary setting, the average welfare of the population decreases, because defection is selected over cooperation. How can a strategy spread that decreases the fitness of an actor but increases the fitness of its interaction partner? Various ways to solve such social dilemmas have been proposed (4, 5). In the multiplayer version of the Prisoner's Dilemma, the public goods game, a number of players take part by contributing to a common pot. Interest is added to it and then the amount is split equally among all, regardless of whether they have contributed or not. Because only a fraction of one's own investment goes back to each player, there is no incentive to deposit anything. Instead, it is tempting only to take the profits of the investments of others. This scenario has been analyzed in a variety of contexts (6, 7). The evolutionary dynamics of more general multiplayer games has received considerably less attention, and we can guess why from the way William Donald Hamilton put it: "The theory of many-person games may seem to stand to that of two-person games in the relation of sea-sickness to a headache" (8). Only recently, this topic has attracted renewed interest (9–14).

As shown by Broom et al. (9), the most general form of multiplayer games, a straightforward generalization of the payoff matrix concept, leads to a significant increase in the complexity of the evolutionary dynamics. Although the evolution of cooperation is an important and illustrative example, typically it does not lead to very complex dynamics. On the other hand, intuitive explanations for more general games are less straightforward, but only they illustrate the full dynamical complexity of multiplayer games (9).

To approach this complexity, we discuss evolutionary dynamics in finite as well as in infinite populations. For finite populations, we base our analysis on a variant of the Moran process (15), but under weak selection our approach is valid for a much wider range of

evolutionary processes (see next section). We begin by recalling the well-studied two-player two-strategy scenario. Then, we increase the number of players, which results in a change in the dynamics and some basic properties of the games. For infinitely large populations, we explore the dynamics of multiplayer games with multiple strategies and illustrate that this new domain is very different as compared to the two-player situation (see also ref. 9). We provide some general results for these multiplayer games with multiple strategies. The two-strategy case and the two-player scenario are then a special case, a small part of a larger and more complex multiverse.

Model and Results

Two-player games with two strategies have been studied in detail, under different dynamics and for infinite as well as for finite population sizes. Typically, two players meet, interact, and obtain a payoff. The payoff is then the basis for their reproductive success and hence for the change in the composition of the population (2). This framework can be used for biological systems, where strategies spread by genetic reproduction, and for social systems, where strategies spread by cultural imitation.

Consider two strategies, A and B. We define the payoffs by α_i, where α is the strategy of the focal individual and the subscript i is the number of remaining players playing A. For example, when an A strategist meets another person playing A she gets a_1. She gets a_0 when she meets a B strategist. This leads to the payoff matrix

$$
\begin{array}{c|cc}
 & A & B \\
\hline
A & a_1 & a_0 \\
B & b_1 & b_0
\end{array}
\qquad [1]
$$

Some of the important properties of two-player games are:

(*i*) Internal equilibria. When A is the best reply to B ($a_0 > b_0$) and B is the best reply to A ($b_1 > a_1$), the replicator dynamics predicts a stable coexistence of both strategies. Similarly, when both strategies are best replies to themselves, there is an unstable coexistence equilibrium. A two-player game with two strategies can have at most one such internal equilibrium.

(*ii*) Comparison of strategies. In a finite population, strategy A will replace B with a higher probability than vice versa if $Na_0 + (N-2)a_1 > (N-2)b_0 + Nb_1$. This result holds for the deterministic evolutionary dynamics discussed by Kandori et al. (16), for the Moran process and a wide range of related birth-death processes under weak selection (15, 17), and for some special processes for any intensity of selection (17). However, Fudenberg et al. (18) obtain a slightly different result for an alternative variant of the Moran process under

nonweak selection. For large populations, the condition above reduces to risk dominance of A, $a_1 + a_0 > b_1 + b_0$.

(iii) Comparison with neutrality. For weak selection, the fixation probability of strategy A in a finite population is larger than neutral $(1/N)$ if $(2N-1)a_0 + (N-2)a_1 > (2N-4)b_0 + (N+1)b_1$. For a large N, this means that A has a higher fitness than B at frequency $1/3$, termed the one-third law (19–21). The 1/3 law holds under weak selection for any process within the domain of Kingman's coalescence (22).

Often interactions are not between two players but between whole groups of players. Quorum sensing, public transportation systems, and climate preservation represent examples of systems in which large groups of agents interact simultaneously. Starting with the seminal work of Gordon and Hardin on the tragedy of the commons (23, 24), such multiplayer games have been analyzed in the context of the evolution of cooperation (25–28), but general multiplayer interactions have received less attention (see, however, refs. 9–13).

We again assume there to be two strategies, A and B. We can also maintain the same definition of the payoffs as α_i. As there are $d-1$ other individuals, excluding the focal player, i can range from 0 to $d-1$. We can depict the payoffs α_i in the form

Opposing A players	$d-1$	$d-2$	...	k	...	0
A	a_{d-1}	a_{d-2}	...	a_k	...	a_0
B	b_{d-1}	b_{d-2}	...	b_k	...	b_0

. [2]

However, for multiplayer games an additional complication arises. Consider a three-player game $(d = 3)$. Let the focal player be playing A. As $d = 3$ there are $d - 1 = 2$ other players. If one of them is of type A and the other of type B, there can be the combinations AAB or ABA. Do these two structures give the same payoffs? Or, in a more general sense, does the order of players matter? If order does matter, the payoffs are in a d-dimensional discrete space, as illustrated by Fig. 1. There are numerous examples where the order of the players is very important. In a game of soccer, it is necessary to have a player specialized as the goal keeper in the team. But it is also impor-
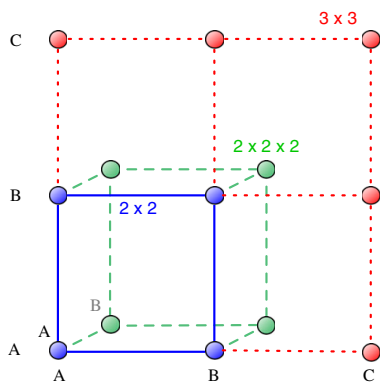
Fig. 1. For 2 × 2 games, the payoff matrix has 4 entries. If we increase the number of strategies, the payoff matrix grows in size. For example, the payoff matrix of a 3 × 3 game has 9 entries. If we increase the number of players, the payoff matrix becomes higher-dimensional. For example, two-strategy games with three players are described by 2 × 2 × 2 payoff structures with 8 entries. In general, a d-player game with n strategies is described by n^d payoff values.

tant that the goal keeper is at the goal and not acting as a center-forward. A biological example has been studied by Stander in the Etosha National Park (29). The lionesses hunt in packs and employ the flush-and-ambush technique. Some lie in ambush while others flush out the prey from the flanks and drive them toward the ones waiting in ambush. This technique needs more than two players to be successful. Some lionesses always display a particular position to be a preferred one (right flank, left flank, or ambush). The success rate is higher if the lionesses are in their preferred positions. Thus, the ordering of players matters here.

To address situations in which the order of players matters, we have to make use of a tensor notation for writing down the payoffs which offers the flexibility to include higher dimensions of the payoff matrix. Consider a tensor β with d indices defined as follows: $\beta_{i_0, i_1, i_2, i_3, \dots i_{d-1}}$, where the first index denotes the focal player's strategy. Each of the indices represents the strategy of the player in the position denoted by its subscript. The index i can represent any of the n strategies. Thus, the total number of entries will be n^d. This structure is the multiplayer equivalent of a payoff matrix (see ref. 9 and Fig. 1). Consider, for example, a game with three players and two strategies (A and B). If the order of players matters, then the payoff values for strategy A are represented by β_{AAA}, β_{AAB}, β_{ABA}, and β_{ABB}. This increase in complexity is handled by the tensor notation but is not reflected in the tabular notation (**2**). But as long as interaction groups are formed at random, we can transform the payoffs such that they can be written in the form of **2** (*SI Text*). In this case, the payoffs are weighted by their occurrence to calculate the average payoffs. For example, in our three-player games, a_1 has to be counted twice (corresponding to β_{AAB} and β_{ABA}). If we would consider evolutionary games in structured populations instead of random-interaction group formation, then the argument breaks down and the tensor notation cannot be reduced.

In the case of d-player games with two strategies, we can then write the average payoff π_A obtained by strategy A in an infinite population as $\pi_A = \sum_{k=0}^{d-1} \binom{d-1}{k} x^k (1-x)^{d-1-k} a_k$, where x is the fraction of A players. An equivalent equation holds for the average payoff π_B of strategy B. The replicator equation of a two-player game is given by ref. 30:

$$\dot{x} = x(1-x)(\pi_A - \pi_B). \quad [3]$$

Obviously, there are two trivial fixed points when the whole population consists of A ($x = 1$) or B ($x = 0$). In d-player games, both π_A and π_B can be polynomials of maximum degree $d-1$ (see *SI Text*). This implies that the replicator equation can have up to $d-1$ interior fixed points. In the two-strategy case, these points can be either stable or unstable. The maximum number of stable interior fixed points possible is $d/2$ for even d and $(d-1)/2$ for odd d; see also refs. 9 and 10, where it is shown that all these scenarios are also attainable. For $d = 2$, π_A and π_B are polynomials of degree 1; hence, there can be at most one internal equilibrium, which is either unstable (coordination games) or stable (coexistence games). For $d = 3$, there can also be a second interior fixed point. If one of them is stable, the other one must be unstable. This can lead to a situation in which A is advantageous when rare (the trivial fixed point $x = 0$ is unstable), and becomes disadvantageous at intermediate frequencies but advantageous again for high frequencies, as in multiplayer stag hunts (11).

For a d-player game to have $d-1$ interior fixed points, the quantities $a_k - b_k$ and $a_{k+1} - b_{k+1}$ must have different signs for all k. However, this condition is necessary (because the direction of selection can only change $d-1$ times if the payoff difference $a_k - b_k$ changes sign $d-1$ times), but not sufficient (*SI Text*). Pacheco and coauthors have studied public goods games in which a threshold frequency of cooperators is necessary for

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producing any public good (11, 12). The payoff difference changes sign twice at this threshold value and hence there can be at most two internal equilibria.

A d-player game has a single internal equilibrium if $a_k - b_k$ has a different sign from $a_{k+1} - b_{k+1}$ for a single value of k: In this case, A individuals are disadvantageous at low frequency and advantageous at high frequency (or vice versa). If $a_k - b_k$ changes sign only once, then the direction of selection can change at most once. Thus, this condition is sufficient in infinite populations.

Now we deviate from the replicator dynamics, where the average payoff of a strategy is equated to reproductive fitness, and turn our attention to finite populations. In this case, the sampling for π_A and π_B is no longer binomial but hypergeometric (*SI Text*). In finite populations, the intensity of selection measures how important the payoff from the game is for the reproductive fitness. We take fitness as an exponential function of the payoff, $f_A = \exp(+w\pi_A)$ for A players and $f_B = \exp(+w\pi_B)$ for B players (31). If $w \gg 1$, selection is strong and the average payoffs dictate the outcome of the game, whereas if $w \ll 1$, then selection is weak and the payoffs have only marginal effect on the game. This choice of fitness recovers the results of the usual Moran process introduced by Nowak et al. (15) and simplifies the analytical calculations significantly under strong selection (31). However, for nonweak selection, other payoffs to fitness mappings lead to slightly different results (18). We employ the Moran process to model the game, but our results hold for any birth-death process in which the ratio of transition probabilities can be approximated under weak selection by a term linear in the payoff difference in addition to the neutral result. In the Moran process, an individual is selected for reproduction at random but proportional to its fitness. The individual produces identical offspring. Another individual is chosen at random for death. With this approach, we can address the basic properties of d-player games with two strategies generalizing quantities from 2×2 games.

Does A replace B with a higher probability than vice versa? Comparing the fixation probabilities of a single A or B individual, ρ_A and ρ_B, we find that $\rho_A > \rho_B$ is equivalent to

$$\sum_{k=0}^{d-1} (Na_k - a_{d-1}) > \sum_{k=0}^{d-1} (Nb_k - b_0) \qquad [\mathbf{4}]$$

(*SI Text*). For $d = 2$, we recover the risk dominance from above. For large N, the condition reduces to (13)

$$\sum_{k=0}^{d-1} a_k > \sum_{k=0}^{d-1} b_k. \qquad [\mathbf{5}]$$

These two conditions are valid for any intensity of selection in our variant of the Moran process.

The one-third law for two-player games is not valid for a higher number of players (*SI Text*). Instead, the condition we obtain for the payoff entries is not directly related to the internal equilibrium points (as opposed to the two-player case, which makes the one-third law special). For weak selection, we show in *SI Text* that $\rho_A > 1/N$ is equivalent to

$$\sum_{k=0}^{d-1} [N(d-k) - k - 1]a_k > \sum_{k=0}^{d-1} [(N+1)(d-k)b_k - (d+1)b_0]. \qquad [\mathbf{6}]$$

For large population size this reduces to (13)

$$\sum_{k=0}^{d-1} (d-k)a_k > \sum_{k=0}^{d-1} (d-k)b_k, \qquad [\mathbf{7}]$$

which is the one-third law from above for $d = 2$. Inequality **7** means that the initial phase of invasion is of most importance: The factor $d - k$ decreases linearly with k, and the payoff values with small indices k are more important than the payoff values with larger indices. Thus, the payoffs relevant for small mutant frequencies determine whether the condition is fulfilled. In other words, the initial invasion is crucial to obtain a fixation probability larger than $1/N$.

In general, conditions **5** and **7** are independent of each other. When **5** is satisfied and **7** is not satisfied, both fixation probabilities are less than neutral ($1/N$). But when **5** is not satisfied and **7** is satisfied, both ρ_A and ρ_B are larger than neutral ($1/N$). This scenario is impossible for two-player games.

Let us now turn to multiplayer games with multiple strategies. As illustrated in Fig. 1, the payoff matrix of a two-player game increases in size when more strategies are added. If more players are added, the dimensionality increases. Now we address the evolutionary dynamics of such games. Again we assume that interaction groups are formed at random, such that only the number of players with a certain strategy—but not their arrangement—matters. The replicator dynamics of a d-player game with n possible strategies can be written as a system of $n - 1$ differential equations:

$$\dot{x}_j = x_j(\pi_j - \langle \pi \rangle), \qquad [\mathbf{8}]$$

where x_j is the frequency of strategy j, π_j is the fitness of strategy j, and $\langle \pi \rangle = \sum_{j=1}^{n} x_j \pi_j$ is the average fitness. The evolution of this system can be studied on a simplex with n vertices, S_n. The simplex S_n is defined by the set of all of the frequencies which follow the normalization $\sum_{j=1}^{n} x_j = 1$. The fixed points of this system are given by the combination of frequencies of the strategies which satisfy $\pi_1 = \cdots = \pi_n$. The vertices of the simplex where x_j is either equal to 1 or 0 are trivial fixed points. In addition, there can be, for example, fixed points on the edges or the faces of the simplex. We speak of fixed points in the interior of the simplex when all payoffs are identical at a point where all frequencies are nonzero, $x_j > 0$ for all j. The internal equilibria are of special interest, because they may represent points of stable biodiversity. For example, three strains of *Escherichia coli* competing for resources have been studied (32, 33). K is a killer strain which produces a toxin harmful to S; R does not produce toxin but is resistant to the toxin of K. The sensitive strain S is affected by the toxin of K. These three strains are engaged in a kind of rock-paper-scissors game. K kills S. S reproduces faster than R, not paying the cost for resistance. R is superior to K, being immune to its toxin. The precise nature of interactions determines whether biodiversity is maintained in an unstructured population (30, 34). In our context, this is reflected by the existence of an isolated internal fixed point.

Here we ask the more general question of whether there are internal equilibria in d-player games with n strategies. If so, then how many internal equilibria are possible? It has been shown that for a two-player game with any number of strategies n there can be at most one isolated internal equilibrium (30, 35). In *SI Text*, we demonstrate that the maximum number of internal equilibria in d players with n strategies is

$$(d-1)^{n-1}. \qquad [\mathbf{9}]$$

The maximum possible number of internal equilibria increases as a polynomial in the number of players, but exponentially in the number of strategies. For example, for $d = 4$ and $n = 3$, the maximum number of internal equilibria is 9 (see Fig. 2). Note that for $d = 2$ we recover the well-known unique equilibrium. For $n = 2$, we recover the maximum of $d - 1$ internal equilibria (see above). Of course, not all of these equilibria are stable. Broom et al. have shown which patterns of stability are attainable for general three-player three-strategy games (9).

This illustrates that many different states of biodiversity are possible in multiplayer games, whereas in two-player games only

Fig. 2. Evolutionary dynamics in a simplex with the maximum number of internal equilibria for $d = 4$ players and $n = 3$ strategies as given by $(d-1)^{n-1} = 9$. On the dashed cubic curve, we have $\pi_1 = \pi_3$. On the full cubic curve, we have $\pi_2 = \pi_3$. When both lines intersect in the interior of the simplex, we have an internal equilibrium.

Fig. 3. The probabilities of observing the different numbers of internal equilibria, 0 to $(d-1)^{n-1}$, as the system gets more complex in the number of strategies n and the number of players d. Random games are generated by choosing the payoff entries a_k, b_k, ... from a uniform distribution. If we consider that the order does matter and generate the random games based on the entries of a payoff structure with n^d entries, then the probability of observing a particular number of equilibria is only slightly lower (averages over 10^8 different games with uniformly chosen payoff entries a_k, b_k, ...).

a single one is possible. This is a crucial point when one attempts to address the question of biodiversity with evolutionary game theory. In the previous example, the studies dealing with *E. coli*, consider the system as a $d = 2$ player game with three strategies. Do we really know that $d = 2$? If strains are to be engineered to stably coexist, then multiple interactions ($d > 2$) would open up the possibility of multiple internal fixed points instead of the single one for $d = 2$.

If we choose a game at random, what is the probability that the game has a certain number of internal equilibria? To this end, we take the following approach: We generate many random payoff structures in which all payoff entries are uniformly distributed random numbers (36). For each payoff structure, we compute the number of internal equilibria. It turns out that games with many internal equilibria are the exception rather than the rule. For example, the probability of seeing two or more internal equilibria in a game with four players and three strategies is ≈24%. The probability that a randomly chosen game has the maximum possible number of equilibria decreases with increasing number of players and number of strategies (see Fig. 3). Also, the probability of having a single equilibrium decreases. Instead, we obtain several internal equilibria in the case of more than two players. For two-player games, the probability of seeing an internal equilibrium at all decreases roughly exponentially with the number of strategies. This poses an additional difficulty in coordinating in multiplayer games, because several different solutions may be possible that look quite similar at first sight.

Discussion

Multiplayer games with multiple strategies is what we find all around. We interact with innumerable people at the same time, directly or indirectly. Some interactions may be pairwise, but others are not. In real life, we may typically be engaged in many-person games instead of a disjoined collection of two-person games (8). The evolution and maintenance of cooperation,

problems pertaining from group hunting to deteriorating climate, all are fields for a multiple number of players (29, 37, 28, 38). They can have different interests and hence use different strategies. There are other cases such as the maintenance of biodiversity where multiplayer interactions may lead to a much richer spectrum for biodiversity than the commonly analyzed two-player interactions. The presence of multiple stable states also contributes to the intricate dynamics observed in the maintenance of biodiversity (39). Multiplayer games may help to improve our understanding of such systems. The problem of handling multiple equilibria is not just limited to biological games but also appears in economics (40, 41). Many insights can be obtained by studying two-player games, but it blurs the complexity of multiplayer interactions. Here we have derived some basic rules which apply to multiplayer games with two strategies for finite as well as infinite populations and discussed the number of internal equilibria in d-player games with n strategies which determine how the dynamics proceeds.

This theory can be applied to all kinds of games with any number of players and strategies and can thus be easily applied to public goods games, multiplayer stag hunts, or multiplayer snowdrift games. We believe that this opens up avenues where we can get analytical descriptions of situations which are thought to be very complex, and further discussions of these issues will prove to be fruitful due to the intrinsic importance of multiplayer interactions. We conclude this approach by quoting Hamilton again: "A healthy society *should* feel sea-sick when confronted with the endless internal instabilities of the 'solutions', 'coalition sets', etc., which the theory of many-person games has had to describe" (8).

1. Maynard Smith J, Price GR (1973) The logic of animal conflict. *Nature* 246:15–18.
2. Maynard Smith J (1982) *Evolution and the Theory of Games* (Cambridge Univ Press, Cambridge, UK).
3. Nowak MA (2006) *Evolutionary Dynamics* (Harvard Univ Press, Cambridge, MA).
4. Nowak MA (2006) Five rules for the evolution of cooperation. *Science* 314:1560–1563.
5. Taylor C, Nowak MA (2007) Transforming the dilemma. *Evolution* 61:2281–2292.

6. Ostrom E (1990) *Governing the Commons: The Evolution of Institutions for Collective Action* (Cambridge Univ Press, Cambridge, UK).
7. Hauert C, De Monte S, Hofbauer J, Sigmund K (2002) Volunteering as Red Queen mechanism for cooperation in public goods games. *Science* 296:1129–1132.
8. Hamilton WD (1975) *Biosocial Anthropology*, ed Fox R (Wiley, New York), pp 133–155.
9. Broom M, Cannings C, Vickers GT (1997) Multi-player matrix games. *Bull Math Biol* 59:931–952.
10. Hauert C, Michor F, Nowak MA, Doebeli M (2006) Synergy and discounting of cooperation in social dilemmas. *J Theor Biol* 239:195–202.
11. Pacheco JM, Santos FC, Souza MO, Skyrms B (2009) Evolutionary dynamics of collective action in N-person stag hunt dilemmas. *Proc Biol Sci* 276:315–321.
12. Souza MO, Pacheco JM, Santos FC (2009) Evolution of cooperation under N-person snowdrift games. *J Theor Biol* 260:581–588.
13. Kurokawa S, Ihara Y (2009) Emergence of cooperation in public goods games. *Proc Biol Sci* 276:1379–1384.
14. van Veelen M (2009) Group selection, kin selection, altruism and cooperation: When inclusive fitness is right and when it can be wrong. *J Theor Biol* 259:589–600.
15. Nowak MA, Sasaki A, Taylor C, Fudenberg D (2004) Emergence of cooperation and evolutionary stability in finite populations. *Nature* 428:646–650.
16. Kandori M, Mailath GJ, Rob R (1993) Learning, mutation, and long run equilibria in games. *Econometrica* 61:29–56.
17. Antal T, Nowak MA, Traulsen A (2009) Strategy abundance in 2×2 games for arbitrary mutation rates. *J Theor Biol* 257:340–344.
18. Fudenberg D, Nowak MA, Taylor C, Imhof LA (2006) Evolutionary game dynamics in finite populations with strong selection and weak mutation. *Theor Popul Biol* 70: 352–363.
19. Nowak MA, Sigmund K (2004) Evolutionary dynamics of biological games. *Science* 303:793–799.
20. Ohtsuki H, Bordalo P, Nowak MA (2007) The one-third law of evolutionary dynamics. *J Theor Biol* 249:289–295.
21. Bomze I, Pawlowitsch C (2008) One-third rules with equality: Second-order evolutionary stability conditions in finite populations. *J Theor Biol* 254:616–620.
22. Lessard S, Ladret V (2007) The probability of fixation of a single mutant in an exchangeable selection model. *J Math Biol* 54:721–744.
23. Gordon HS (1954) The economic theory of a common-property resource: The fishery. *J Polit Econ* 62:124–142.

24. Hardin G (1968) The tragedy of the commons. *Science* 162:1243–1248.
25. Hauert C, Schuster HG (1997) Effects of increasing the number of players and memory size in the iterated Prisoner's Dilemma: A numerical approach. *Proc R Soc Lond B Biol Sci* 264:513–519.
26. Kollock P (1998) Social dilemmas: The anatomy of cooperation. *Annu Rev Sociol* 24: 183–214.
27. Rockenbach B, Milinski M (2006) The efficient interaction of indirect reciprocity and costly punishment. *Nature* 444:718–723.
28. Milinski M, Sommerfeld RD, Krambeck HJ, Reed FA, Marotzke J (2008) The collective-risk social dilemma and the prevention of simulated dangerous climate change. *Proc Natl Acad Sci USA* 105:2291–2294.
29. Stander PE (1992) Cooperative hunting in lions: The role of the individual. *Behav Ecol Sociobiol* 29:445–454.
30. Hofbauer J, Sigmund K (1998) *Evolutionary Games and Population Dynamics* (Cambridge Univ Press, Cambridge, UK).
31. Traulsen A, Shoresh N, Nowak MA (2008) Analytical results for individual and group selection of any intensity. *Bull Math Biol* 70:1410–1424.
32. Kerr B, Riley MA, Feldman MW, Bohannan BJM (2002) Local dispersal promotes biodiversity in a real-life game of rock-paper-scissors. *Nature* 418:171–174.
33. Czárán TL, Hoekstra RF, Pagie L (2002) Chemical warfare between microbes promotes biodiversity. *Proc Natl Acad Sci USA* 99:786–790.
34. Claussen JC, Traulsen A (2008) Cyclic dominance and biodiversity in well-mixed populations. *Phys Rev Lett* 100:058104.
35. Bishop DT, Cannings C (1976) Models of animal conflict. *Adv Appl Probab* 8:616–621.
36. Huang W, Traulsen A (2010) Fixation probabilities of random mutants under frequency dependent selection. *J Theor Biol* 263:262–268.
37. Levin SA, ed (2009) *Games, Groups and the Global Good* (*Springer Series in Game Theory*) (Springer Berlin, Heidelberg).
38. Broom M (2003) The use of multiplayer game theory in the modeling of biological populations. *Comments Theor Biol* 8:103–123.
39. Levin SA (2000) Multiple scales and the maintenance of biodiversity. *Ecosystems* 3: 498–506.
40. Kreps DM (1990) *Game Theory and Economic Modelling* (*Clarendon Lectures in Economics*) (Oxford Univ Press, New York).
41. van Damme E (1994) Evolutionary game theory. *Eur Econ Rev* 38:847–858.

Supporting Information

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1. Multiple Players with Two Strategies

1.1. Infinite Populations. We first address the replicator dynamics of multiplayer games with two strategies. If an A player interacts with k other A players, it obtains the payoff a_k. If a B player interacts with k A players, it obtains the payoff b_k. In an infinitely large population in which the fraction of A players is x, the probability that an A player interacts with k other A players is

$$\binom{d-1}{k}x^k(1-x)^{d-1-k}. \qquad \text{[S1]}$$

Here, $\binom{d-1}{k}$ is the number of possibilities of arranging the players. Thus, the average payoffs of A and B are given by

$$\pi_A = \sum_{k=0}^{d-1}\binom{d-1}{k}x^k(1-x)^{d-1-k}a_k$$
$$\pi_B = \sum_{k=0}^{d-1}\binom{d-1}{k}x^k(1-x)^{d-1-k}b_k. \qquad \text{[S2]}$$

These average payoffs are subject to the condition that the order of the players does not matter. For example, in a $d = 3$ game, let the player in the first position play A. Then, the remaining two players can play a combination of A and B. The possible combinations are AAB and ABA. By writing the payoffs in the above-mentioned manner, we assume that such combinations have the same payoffs.

If the order of players does matter, then the payoff values are given by $\beta_{i_0,i_1,i_2,i_3,\ldots i_{d-1}}$. Here, i_0 is the strategy of the focal player. The i_p are the strategies of the type in position p. For random matching of players, we can map the $\beta_{i_0,i_1,i_2,i_3,\ldots i_{d-1}}$ to modified payoffs $\tilde{a}_k$ and $\tilde{b}_k$ without changing the average payoffs of the strategies. As an example, for $d = 4$, we have the modified payoffs $\tilde{a}_k$ and $\tilde{b}_k$ as

$$\tilde{a}_0 = \beta_{A,B,B,B} \qquad\qquad \tilde{b}_0 = \beta_{B,B,B,B}$$
$$\tilde{a}_1 = \frac{\beta_{A,A,B,B}+\beta_{A,B,A,B}+\beta_{A,B,B,A}}{3} \quad \tilde{b}_1 = \frac{\beta_{B,A,B,B}+\beta_{B,B,A,B}+\beta_{B,B,B,A}}{3}$$
$$\tilde{a}_2 = \frac{\beta_{A,A,A,B}+\beta_{A,A,B,A}+\beta_{A,B,A,A}}{3} \quad \tilde{b}_2 = \frac{\beta_{B,A,A,B}+\beta_{B,A,B,A}+\beta_{B,B,A,A}}{3}$$
$$\tilde{a}_3 = \beta_{A,A,A,A} \qquad\qquad \tilde{b}_3 = \beta_{B,A,A,A}. \qquad \text{[S3]}$$

We just need to substitute the above payoffs in place of a_k and b_k in Eq. S2 to take into account the effect of the arrangement of players. For any number of players such a generalization can be easily obtained. Thus, the evolutionary dynamics under random-interaction group formation remains unaffected by the fact that the order of players does matter. When interaction groups are not formed at random, this argument will, of course, fail in most cases.

The following analysis deals with π_A and π_B as in Eq. S2, but it also holds when the order of players matters but interaction groups are formed at random. The replicator equation is thus given by (1, 2)

$$\dot{x} = x(1-x)(\pi_A - \pi_B). \qquad \text{[S4]}$$

Both π_A and π_B are polynomials of degree $d-1$. This implies that the replicator equation can have up to $d-1$ interior fixed points (3).
Maximum number of interior fixed points. For a d-player game to have $d-1$ interior fixed points, the quantities $a_k - b_k$ and $a_{k+1} - b_{k+1}$ must have different signs for all k. For example, in a three-player

game with $a_0 = +1$, $a_1 = -\lambda$, $a_2 = +1$ and $b_0 = -1$, $b_1 = +\lambda$, $b_2 = -1$, we have two internal equilibria at $\frac{1}{2}(1 \pm \sqrt{\frac{\lambda-1}{\lambda+1}})$ for $\lambda > 1$. However, this condition is necessary (because the direction of selection can only change $d-1$ times if the payoff difference $a_k - b_k$ changes sign $d-1$ times), but not sufficient. For example, in the above three-player game, there are no internal equilibria for $\lambda < 1$.
Single interior fixed point. A d-player game has a single internal equilibrium if $a_k - b_k$ has a different sign from $a_{k+1} - b_{k+1}$ for a single value of k: In this case, A individuals are disadvantageous at low frequency and advantageous at high frequency (or vice versa). If $a_k - b_k$ changes sign only once, then the direction of selection can obviously at most change once. Thus, this condition is sufficient.

1.2. Finite Populations. Let us now turn to the evolutionary dynamics in finite populations. In a population of size N with j individuals of type A, the probability of choosing a group that consists of k A players and $d-1-k$ B players is given by a hypergeometric distribution. The probability that an A player interacts with k other A players is given by

$$H(k,d;j,N) = \frac{\binom{j-1}{k}\binom{N-j}{d-1-k}}{\binom{N-1}{d-1}}. \qquad \text{[S5]}$$

This leads to the average payoffs

$$\pi_A = \sum_{k=0}^{d-1}\frac{\binom{j-1}{k}\binom{N-j}{d-1-k}}{\binom{N-1}{d-1}}a_k$$
$$\pi_B = \sum_{k=0}^{d-1}\frac{\binom{j}{k}\binom{N-j-1}{d-1-k}}{\binom{N-1}{d-1}}b_k. \qquad \text{[S6]}$$

We assume that strategies spread by a frequency-dependent Moran process (4–6). The fitness is given by $f_A = \exp(+w\pi_A)$ for A players and $f_B = \exp(+w\pi_B)$ for B players, where w measures the intensity of selection (7). For $w \ll 1$, selection is weak. For $w \gg 1$, selection is strong and only the fitter type reproduces. In the Moran process, an individual is selected for reproduction at random but proportional to its fitness. The individual produces identical offspring. Another individual is chosen at random for death. Consider j individuals of type A in a population of size N. The number of A individuals increases with probability T_j^+ from j to $j+1$ if an A individual is selected for reproduction and a B individual dies. We have

$$T_j^+ = \frac{jf_A}{jf_A+(N-j)f_B}\frac{N-j}{N} \qquad \text{[S7]}$$

$$T_j^- = \frac{(N-j)f_B}{jf_A+(N-j)f_B}\frac{j}{N}. \qquad \text{[S8]}$$

The fixation probability of a single A individual in a population of N is given by (8)

$$\rho_A = \frac{1}{1 + \sum\limits_{m=1}^{N-1} \prod\limits_{j=1}^{m} \frac{T_j^-}{T_j^+}}. \qquad \text{[S9]}$$

For the ratio of transition probabilities, we have

$$\frac{T_j^-}{T_j^+} = \frac{f_B}{f_A} = e^{-w(\pi_A - \pi_B)} \approx 1 - w(\pi_A - \pi_B). \qquad \text{[S10]}$$

The approximation is valid for weak selection, $w \ll 1$. Note that this is the only approximation we make, such that our result is valid for any birth-death process with

$$\frac{T_j^-}{T_j^+} \approx 1 - w(\pi_A - \pi_B). \qquad \text{[S11]}$$

For weak selection, the product in the fixation probabilities can be approximated by a sum, which leads to

$$\rho_A \approx \frac{1}{N} + \frac{w}{N} \underbrace{\sum_{m=1}^{N-1} \sum_{j=1}^{m} (\pi_A - \pi_B)}_{\Gamma}. \qquad \text{[S12]}$$

In *Appendix A*, we show that

$$\Gamma = \frac{1}{d(d+1)} \left[N^2 \left(\sum_{k=0}^{d-1} (d-k)(a_k - b_k) \right) - N \left(\sum_{k=0}^{d-1} (k+1)a_k + \sum_{k=1}^{d-1} (d-k)b_k - d^2 b_0 \right) \right]. \qquad \text{[S13]}$$

As seen from Eq. S12, a strategy is favored by selection; that is, it has a fixation probability larger than $1/N$ if $\Gamma > 0$. For any N, $\Gamma > 0$ can be represented by

$$\sum_{k=0}^{d-1} \left[N(d-k) - k - 1 \right] a_k > \sum_{k=0}^{d-1} \left[(N+1)(d-k)b_k - (d+1)b_0 \right]. \qquad \text{[S14]}$$

For $d = 2$, this condition reduces to the condition $(2N-1)a_0 + (N-2)a_1 > (2N-4)b_0 + (N+1)b_1$, exactly as developed by Nowak et al. (9). For a large population size, the condition can be simplified to

$$\sum_{k=0}^{d-1} (d-k)a_k > \sum_{k=0}^{d-1} (d-k)b_k. \qquad \text{[S15]}$$

In large populations, we have $\rho_A > 1/N$ if the condition Eq. S15 is fulfilled. In the usual case of $d = 2$, the fixation probability of strategy A is larger than $1/N$ if $2a_0 + a_1 > 2b_0 + b_1$. This can be rearranged to

$$x^* = \frac{b_0 - a_0}{a_1 - a_0 - b_1 + b_0} < \frac{1}{3}. \qquad \text{[S16]}$$

This is the 1/3-law first derived in ref. 9: A mutant takes over the population with probability larger than neutral if the mutant is advantageous when it has reached a fraction of 1/3. Condition Eq. S15 represents a generalization of the 1/3 law for general d-player games.

We can also compare the fixation probability ρ_A of a single A player to the fixation probability ρ_B of a single B player. It has been shown (7, 8) that

$$\frac{\rho_B}{\rho_A} = \prod_{j=1}^{N-1} \frac{T_j^-}{T_j^+} = \exp \left[\underbrace{-w \sum_{j=1}^{N-1} (\pi_A - \pi_B)}_{\Phi} \right]. \qquad \text{[S17]}$$

Note that if our previous approximation Eq. S11 holds, then we obtain $\frac{\rho_B}{\rho_A} \approx 1 - w\Phi$. Because we do not make any further ap-

proximations, our calculation remains valid for any birth-death process fulfilling Eq. S11 under weak selection. As shown in *Appendix B*,

$$\Phi = \frac{N}{d} \sum_{k=0}^{d-1} (a_k - b_k) + b_0 - a_{d-1}. \qquad \text{[S18]}$$

From Eq. S17, it is clear that $\rho_A > \rho_B$ if $\Phi > 0$. This is equivalent to the condition

$$\sum_{k=0}^{d-1} (Na_k - a_{d-1}) > \sum_{k=0}^{d-1} (Nb_k - b_0). \qquad \text{[S19]}$$

Note that this condition is valid for any intensity of selection for the process we use. For weak selection, it is valid for all processes with $\frac{T_j^-}{T_j^+} \approx 1 - w(\pi_A - \pi_B)$. For $d = 2$, expression Eq. S19 reduces to $(N-2)(a_1 - b_0) > N(b_1 - a_0)$, which is the risk dominance condition developed in ref. 10 for finite population size (see also ref. 11 for the generality of this finding). For a large population, the condition can be further simplified:

$$\sum_{k=0}^{d-1} a_k > \sum_{k=0}^{d-1} b_k. \qquad \text{[S20]}$$

For two-player games, this reduces to risk dominance, $a_0 + a_1 > b_0 + b_1$.

We can also incorporate mutations, which will complicate the transition probabilities. For symmetric mutation rates, $\mu_{A \to B} = \mu_{B \to A}$, the condition $\rho_A > \rho_B$ is equivalent to a higher average abundance of A compared to B given that $\mu_{A \to B}$ and $\mu_{B \to A}$ are small. For $d = 2$, it has recently been shown that the abundance condition does in fact depend neither on the mutation rate nor on the intensity of selection (11). For $d > 2$, this statement no longer holds, which can be seen from the high mutation limit: If the mutation rates are very high, then the system will be driven toward the point where the two abundances are identical. The dynamics at this point, however, does not depend on the parameters in the same way as $\rho_A > \rho_B$ when it comes to d-player games.

2. Multiplayer Games with Multiple Strategies

2.1. Infinite Populations. In the full multiverse, we have multiple players playing multiple strategies. We are interested in the maximum number of internal equilibria of a system, which will help us understand the general features of the dynamics. Consider a system with d players with n possible strategies. Here we resort to the payoff values as given by $\beta_{i_0, i_1, i_2, i_3, \ldots i_{d-1}}$, because for random group formation a system where the order of players does matter can always be reduced to a system where the order does not matter. Here, i_0 is the strategy of the focal player. The i_p are the strategies of the type in position p. Then the average payoff of the focal player is given by

$$\pi_{i_0} = \sum_{i_1=1}^{n} \sum_{i_2=1}^{n} \cdots \sum_{i_{d-1}=1}^{n} \left(\prod_{k=i_1}^{i_{d-1}} x_k \right) \beta_{i_0, i_1, i_2, i_3, \ldots i_{d-1}}. \qquad \text{[S21]}$$

From this it is clear that each variable x_k is at most of degree $d-1$. Also, as there are n strategies, we have $i_0 = (1, 2, \ldots, n)$, that is, n such multivariate polynomials. Each multivariate polynomial is in $n-1$ variables (because of the normalization $\sum_{l=1}^{n} x_l = 1$). At the fixed points, all these polynomials will be equal. Hence, if we subtract one of the polynomials (say π_n) from all, we have a system of $n-1$ multivariate polynomials, $\Delta \pi_{i_0}$, equal to zero (where i_0 goes from 1 to $n-1$). In each variable x_k, the multivariate polynomial $\Delta \pi_{i_0}$ is at most of degree $d-1$. Hence, there

are at most $d - 1$ roots of $\Delta\pi_{i_0}$ in x_k. Because this is valid for all $n - 1$ functions of $\Delta\pi_{i_0}$, there can be up to $(d - 1)^{n-1}$ simultaneous roots of all $\Delta\pi_{i_0}$. These are the interior fixed points of the replicator dynamics. Thus, there can be at most

$$(d-1)^{n-1} \qquad \text{[S22]}$$

fixed points in the interior of the system. This holds for the full system but also for any subspace in which fewer strategies are available. For example, a game with $d = 3$ players and $n = 4$ strategies has up to 8 fixed points in the interior of the simplex S_4. On the faces of the simplex S_4, represented by the simplex S_3, there can be up to 4 fixed points.

We now have an analytical method to deduce the maximum number of internal equilibria. The question that now arises is: With what probability do we see this maximum number of equilibria? We address the problem by generating 10^8 payoff matrices where the payoff values a_k, b_k, ..., are drawn from a uniform distribution for different configurations of d and n. As discussed in the main text, the probability of obtaining the maximum number of internal equilibria in a game with random payoff entries reduces as the complexity increases in d as well as n.

An example for d = 4 and n = 3. In this section, we describe the parameters of Fig. 2 in the main text. The number of players $d = 4$ and the number of strategies $n = 3$. The total number of payoff values is therefore n^d, which is 81. Thus, for each strategy there are 27 payoff values. This is the number of values we have to consider when the order of player matters. If the payoffs are the same for different arrangements then we reduce the payoff values, but we have to weight them by the number of their occurrence. Consider the three strategies to be A, B, and C. Solving the replicator equation using the average payoffs calculated from the payoffs from Table S1, we numerically obtain 9 fixed points in the interior of the simplex. At these points, the frequencies of all of the strategies are nonzero and the average payoff to each strategy is equal.

2.2. Finite Populations. For finite populations and more than two strategies, few analytical tools are available. The average abundance under weak selection can be addressed using tools from coalescence theory (12, 13).

For small mutation rates, the dynamics reduces to an embedded Markov chain on the pure states of the system [see Fudenberg and Imhof (14) for a proof]. Essentially, this means that the dynamics is governed by dynamics on the edges of the simplex S_n where only two strategies are present. This result can be applied in a variety of contexts (15–17).

Both approaches can be adapted to d-player games.

Appendix A

Condition for the Comparison of One Strategy with Neutrality. We first repeat the condition to prove

$$\sum_{m=1}^{N-1}\sum_{j=1}^{m}(\pi_A - \pi_B)$$
$$= \frac{1}{d(d+1)}\left[N^2\left(\sum_{k=0}^{d-1}(d-k)(a_k - b_k)\right) \right. \qquad \text{[S23]}$$
$$\left. - N\left(\sum_{k=1}^{d-1}(k+1)a_k + \sum_{k=1}^{d-1}(d-k)b_k - d^2 b_0\right)\right],$$

where the payoffs are defined in Eq. S6. Because all of the a_ks come from π_A and all of the b_ks come from π_B, we can solve each separately. For π_A we have to show that

$$\sum_{m=1}^{N-1}\sum_{j=1}^{m}\sum_{k=0}^{d-1}\frac{\binom{j-1}{k}\binom{N-j}{d-k-1}}{\binom{N-1}{d-1}}a_k = \sum_{k=0}^{d-1}\frac{N^2(d-k)-N(k+1)}{d(d+1)}a_k.$$
$$\text{[S24]}$$

Because this should hold for any choice of a_ks, we must show that

$$\sum_{m=1}^{N-1}\sum_{j=1}^{m}\frac{\binom{j-1}{k}\binom{N-j}{d-k-1}}{\binom{N-1}{d-1}} = \frac{N^2(d-k)-N(k+1)}{d(d+1)}. \qquad \text{[S25]}$$

We take out the factor $\binom{N-1}{d-1}^{-1}$ on the left-hand side and get back to the full expression only at the end. We consider the quantity

$$\sum_{m=1}^{N-1}\sum_{j=1}^{m}\binom{j-1}{k}\binom{N-j}{d-k-1}. \qquad \text{[S26]}$$

Using the identity $\sum_{m=1}^{N-1}\sum_{j=1}^{m} = \sum_{j=1}^{N-1}\sum_{m=j}^{N-1}$, we obtain

$$\sum_{m=1}^{N-1}\sum_{j=1}^{m}\binom{j-1}{k}\binom{N-j}{d-k-1}$$
$$= \sum_{j=1}^{N-1}\sum_{m=j}^{N-1}\binom{j-1}{k}\binom{N-j}{d-k-1} \qquad \text{[S27]}$$
$$= \sum_{j=1}^{N-1}\binom{j-1}{k}\binom{N-j}{d-k-1}(N-j),$$

where we performed the sum over m. Let us use the factor $N - j$ to split this expression into two sums. The first sum with the factor N is given by

$$\Sigma_1 = N\sum_{j=1}^{N-1}\binom{j-1}{k}\binom{N-j}{d-k-1}. \qquad \text{[S28]}$$

We change the summation index by one, $i = j - 1$, and then extend the sum up to $N - 1$,

$$\Sigma_1 = N\sum_{i=0}^{N-2}\binom{i}{k}\binom{N-i-1}{d-k-1}$$
$$= N\left[\sum_{i=0}^{N-1}\binom{i}{k}\binom{N-i-1}{d-k-1} - \binom{N-1}{k}\binom{0}{d-k-1}\right].$$
$$\text{[S29]}$$

The last term is zero as long as $d - k - 1 > 0$, that is, $k < d - 1$. We can now apply a variant of Vandermonde's convolution, $\sum_{i=0}^{l}\binom{l-i}{m}\binom{q+i}{n} = \binom{l+q+1}{m+n+1}$ (18), on the first term and obtain for $k < d - 1$ the result $\Sigma_1 = N\binom{N}{d}$. For the special case of $k = d - 1$, we start from Eq. S28,

$$\Sigma_1 = N\sum_{j=1}^{N-1}\binom{j-1}{d-1}\binom{N-j}{0} = N\sum_{j=1}^{N-1}\binom{j-1}{d-1}. \qquad \text{[S30]}$$

Using the identity $\sum_{j=1}^{N-1}\binom{j-1}{d-1} = \binom{N-1}{d}$, we obtain $\Sigma_1 = N\binom{N-1}{d} = (N-d)\binom{N}{d}$. To summarize, we have for Σ_1

$$\Sigma_1 = \begin{cases} N\binom{N}{d} & \text{for } 0 \le k < d-1 \\ N\binom{N-1}{d} = (N-d)\binom{N}{d} & \text{for } k = d-1 \end{cases} . \quad \textbf{[S31]}$$

The second sum in Eq. S27 involving the additional factor j can be rewritten as

$$\Sigma_2 = \sum_{j=1}^{N-1} j\binom{j-1}{k}\binom{N-j}{d-k-1}$$
$$= (k+1)\sum_{j=1}^{N-1}\binom{j}{k+1}\binom{N-j}{d-k-1}, \quad \textbf{[S32]}$$

where we have used $j\binom{j-1}{k} = (k+1)\binom{j-1}{k+1}$. We again shift the summation index by one, $i = j-1$, and extend the sum up to $N-1$,

$$\Sigma_2 = (k+1)\sum_{i=0}^{N-2}\left[\binom{i+1}{k+1}\binom{N-i-1}{d-k-1}\right]$$
$$= (k+1)\sum_{i=0}^{N-1}\left[\binom{i+1}{k+1}\binom{N-i-1}{d-k-1}\right]$$
$$- (k+1)\left[\binom{N}{k+1}\binom{0}{d-k-1}\right]. \quad \textbf{[S33]}$$

The last term is zero for $k < d-1$. For the first term, we can apply the same variant of Vandermonde's convolution as above, $\sum_{i=0}^{l}\binom{l-i}{m}\binom{q+i}{n} = \binom{l+q+1}{m+n+1}$, and obtain

$$\Sigma_2 = (k+1)\binom{N+1}{d+1}. \quad \textbf{[S34]}$$

For $k = d-1$, we again start from Eq. S32, which yields

$$\Sigma_2 = d\sum_{j=1}^{N-1}\binom{j}{d}\binom{N-j}{0} = d\sum_{j=1}^{N-1}\binom{j}{d} = d\binom{N}{d+1}. \quad \textbf{[S35]}$$

We slightly rearrange these two results to a common binomial,

$$\Sigma_2 = \begin{cases} (k+1)\dfrac{N+1}{d+1}\binom{N}{d} & \text{for } 0 \le k < d-1 \\ \dfrac{d}{d+1}(N-d)\binom{N}{d} & \text{for } k = d-1 \end{cases} . \quad \textbf{[S36]}$$

Combining these results with Eq. S31, we obtain

$$\Sigma_1 - \Sigma_2 = \binom{N}{d}\frac{1}{d+1}\times\begin{cases} N(d-k)-k-1 & \text{for } 0 \le k < d-1 \\ N-d & \text{for } k = d-1 \end{cases} . \quad \textbf{[S37]}$$

Note that these two expressions have the same form, such that we obtain a single expression for $\Sigma_1 - \Sigma_2$ or, equivalently, for Eq. S27,

$$\sum_{m=1}^{N-1}\sum_{j=1}^{m}\binom{j-1}{k}\binom{N-j}{d-k-1} = \Sigma_1 - \Sigma_2 = \binom{N}{d}\frac{N(d-k)-k-1}{d+1}. \quad \textbf{[S38]}$$

Together with the common factor $\binom{N-1}{d-1}^{-1}$, we obtain

$$\sum_{m=1}^{N-1}\sum_{j=1}^{m}\frac{\binom{j-1}{k}\binom{N-j}{d-k-1}}{\binom{N-1}{d-1}} = \frac{N^2(d-k)-N(k+1)}{d(d+1)}, \quad \textbf{[S39]}$$

which is Eq. S25.

The sums over π_B can be solved in a similar way. In that case, the special case is $k = 0$ rather than $k = d-1$, which also indicates the symmetry of the result. For the sums over π_B, we obtain

$$\sum_{m=1}^{N-1}\sum_{j=1}^{m}\frac{\binom{j}{k}\binom{N-j-1}{d-k-1}}{\binom{N-1}{d-1}} = \begin{cases} \dfrac{N(N-d)}{d+1} & \text{for } k = 0 \\ \dfrac{N(N+1)(d-k)}{d(d+1)} & \text{for } 1 \le k \le d-1 \end{cases} . \quad \textbf{[S40]}$$

Appendix B

Condition for the Comparison of Two Strategies. The statement to prove is

$$\sum_{j=1}^{N-1}(\pi_A - \pi_B) = \frac{N}{d}\sum_{k=0}^{d-1}(a_k - b_k) + b_0 - a_{d-1}. \quad \textbf{[S41]}$$

As the a_ks are contributed only by π_A and the b_ks only by π_B, we first need to show that

$$\sum_{j=1}^{N-1}\pi_A = \frac{N}{d}\sum_{k=0}^{d-1}a_k - a_{d-1}, \quad \textbf{[S42]}$$

with the payoffs from Eq. S26. This holds for any choice of a_ks. Thus, we only have to show that

$$\frac{1}{\binom{N-1}{d-1}}\sum_{j=1}^{N-1}\binom{j-1}{k}\binom{N-j}{d-k-1}$$
$$= \begin{cases} \dfrac{N}{d} & \text{for } 0 \le k < d-1 \\ \dfrac{N}{d}-1 & \text{for } k = d-1 \end{cases} . \quad \textbf{[S43]}$$

The sum has been solved above, cf Eq. S28, where we have shown that $\sum_{j=1}^{N-1}\binom{j-1}{k}\binom{N-j}{d-k-1} = \binom{N}{d}$ for $0 \le k < d-1$ and $\sum_{j=1}^{N-1}\binom{j-1}{k}\binom{N-j}{d-k-1} = \frac{N-d}{N}\binom{N}{d}$ for $k = d-1$. Using the identity $\binom{N}{d} = \frac{N}{d}\binom{N-1}{d-1}$, we directly obtain Eq. S43.

The equivalent condition for π_B can be derived based on a similar argument. As above, we have $k = 0$ as the special case instead of $k = d-1$ in the equivalent of Eq. S43,

$$\frac{1}{\binom{N-1}{d-1}}\sum_{j=1}^{N-1}\binom{j}{k}\binom{N-j-1}{d-k-1} = \begin{cases} \dfrac{N}{d}-1 & \text{for } k = 0 \\ \dfrac{N}{d} & \text{for } 0 < k \le d-1 \end{cases} . \quad \textbf{[S44]}$$

1. Taylor PD, Jonker L (1978) Evolutionary stable strategies and game dynamics. *Math Biosci* 40:145–156.
2. Hofbauer J, Sigmund K (1998) *Evolutionary Games and Population Dynamics* (Cambridge Univ Press, Cambridge, UK).
3. Hauert C, Michor F, Nowak MA, Doebeli M (2006) Synergy and discounting of cooperation in social dilemmas. *J Theor Biol* 239:195–202.
4. Moran PAP (1962) *The Statistical Processes of Evolutionary Theory* (Clarendon, Oxford).
5. Ewens WJ (2004) *Mathematical Population Genetics* (Springer, New York).

6. Nowak MA, Sigmund K (2004) Evolutionary dynamics of biological games. *Science* 303:793–799.
7. Traulsen A, Shoresh N, Nowak MA (2008) Analytical results for individual and group selection of any intensity. *Bull Math Biol* 70:1410–1424.
8. Nowak MA (2006) *Evolutionary Dynamics* (Harvard Univ Press, Cambridge, MA).
9. Nowak MA, Sasaki A, Taylor C, Fudenberg D (2004) Emergence of cooperation and evolutionary stability in finite populations. *Nature* 428:646–650.
10. Kandori M, Mailath GJ, Rob R (1993) Learning, mutation, and long run equilibria in games. *Econometrica* 61:29–56.
11. Antal T, Nowak MA, Traulsen A (2009) Strategy abundance in 2×2 games for arbitrary mutation rates. *J Theor Biol* 257:340–344.
12. Antal T, Ohtsuki H, Wakeley J, Taylor PD, Nowak MA (2009) Evolution of cooperation by phenotypic similarity. *Proc Natl Acad Sci USA* 106:8597–8600.
13. Antal T, Traulsen A, Ohtsuki H, Tarnita CE, Nowak MA (2009) Mutation-selection equilibrium in games with multiple strategies. *J Theor Biol* 258:614–622.
14. Fudenberg D, Imhof LA (2006) Imitation process with small mutations. *J Econ Theory* 131:251–262.
15. Imhof LA, Fudenberg D, Nowak MA (2005) Evolutionary cycles of cooperation and defection. *Proc Natl Acad Sci USA* 102:10797–10800.
16. Hauert C, Traulsen A, Brandt H, Nowak MA, Sigmund K (2007) Via freedom to coercion: The emergence of costly punishment. *Science* 316:1905–1907.
17. Van Segbroeck S, Santos FC, Lenaerts T, Pacheco JM (2009) Reacting differently to adverse ties promotes cooperation in social networks. *Phys Rev Lett* 102: 058105.
18. Graham RL, Knuth DE, Patashnik O (1994) *Concrete Mathematics* (Addison-Wesley, Reading, MA), 2nd Ed.

Table S1. The reduced payoff table for the $d = 4$ and $n = 3$ game in Fig. 2 in the main text

Weight (Total 27)	1	3	3	3	6	3	1	3	3	1
Configuration	AAA	AAB	AAC	ABB	ABC	ACC	BBB	BBC	BCC	CCC
A	−9.30	3.83	3.86	−1.03	−1.00	−0.96	0.10	0.33	0.16	0.20
B	0.10	−1.03	0.13	3.83	−1.00	0.16	−9.30	4.06	−0.96	0.20
C	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.20	0.00	0.00

In total, there would be $n^d = 3^4 = 81$ payoff entries. For each strategy, we would have had 27 entries. But when we consider that the ordering does not matter, we just weight each configuration by the different ways of ordering; for example, there are three orderings for *AAB*, that is, *AAB*, *ABA*, and *BAA*. In this way, we reduce the number of payoff entries from 81 to 30.

4.2 The assumption of "small" mutation rates

Until now we dealt with selection. Now in this project, we incorporate mutations as well. Mutations or random explorations seem to be inherent in human nature. Mutations and selection work in concert to develop the population to a possible equilibrium state. Traditionally analyzing multiplayer games with mutations is possible if we assume the mutation rate to be negligible (Fudenberg and Imhof, 2008). Consider the situation when we have three strategies A, B and C. Every time a reproductive event occurs, there is a small probability μ that the offspring will be of a random strategy and not necessarily like the parent. The average time between two mutations is thus μ^{-1}. We also know that the time for fixation of a single neutral mutant is $N(N-1)$ (Antal and Scheuring, 2006). Therefore if the mutation probability, μ, is much smaller than N^{-2} then the time between two mutations will be much larger than the time required for either extinction or fixation of a single mutant. Thus at a time we will have to deal with only two strategies. For two strategies we can calculate exactly the fixation probability of a mutant in finite populations (Nowak, 2006a) even for multiplayer games (Gokhale and Traulsen, 2010). For small mutation rates the transition probabilities between different strategies consist of just the fixation probabilities. For example for the three strategies A, B and C the transition matrix, $\mathbf{T}$ looks like,

$$\mathbf{T} = \begin{pmatrix} 1 - \rho_{AB} - \rho_{AC} & \rho_{AB} & \rho_{AC} \\ \rho_{BA} & 1 - \rho_{BA} - \rho_{BC} & \rho_{BC} \\ \rho_{CA} & \rho_{CB} & 1 - \rho_{CA} - \rho_{CB} \end{pmatrix} \tag{4.1}$$

where the fixation probability of strategy A in a population consisting predominantly of strategy B is given by ρ_{AB}. Each element of the matrix denotes the probability of the row strategy to move into the column strategy. Strategy A (first row) can either stay in an all A population (first column) or move to a population of B (second column) individuals or in a population of C (third column) individuals. Since these are the only three probable events, the sum of all elements in a row is one. To find which strategy does the best at the mutation

selection equilibrium we need to know which strategy has the highest frequency on an average in the stationary distribution. The stationary distribution of the system is given by the normalised right eigenvector for the largest eigenvalue of the transition matrix $\mathbf{T}$. However this analysis is only valid for small mutation rates. The question asked in this section is,

- How small do the mutation rates have to be so that the error due to the approximation is below a tolerable threshold?

This issue was can be tackled by using time scale separation analysis based on Antal and Scheuring (2006). Since then this approach has been used extensively in many papers to explore the the dynamics of strategies in the limit of strong selection and weak mutations (Imhof et al., 2005; Fudenberg and Imhof, 2006; Traulsen and Nowak, 2007; Hauert et al., 2007, 2008; Van Segbroeck et al., 2009; Sigmund et al., 2010). Our approach takes the route of the stationary distribution. If we let the system evolve for a long time it will reach an equilibrium state such that we can denote it by a distribution of the frequencies of the different strategies. For small mutation rates this distribution is approximated by the ones based on the fixation probabilities. We check for the difference between these two distributions. To check mathematically if the approximation is "good" we calculate the total variation distance between the distributions.

Herein we also provide a numerically accessible bound which can be calculated for any given system of two player games and two strategies. Hence now it is possible to determine exactly how low the mutation rate should be to reduce the error below a certain threshold.

4.2.1 Publication: How small are small mutation rates?

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How small are small mutation rates?

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We consider evolutionary game dynamics in finite population of size N. When mutations are rare, the population is monomorphic most of the time. Occasionally a mutation arises. It can either reach fixation or go extinct. The evolutionary dynamics of the process under small mutation rates can be approximated by an embedded Markov chain on the pure states. Here we analyze how small the mutation rate should be to make the embedded Markov chain a good approximation by calculating the difference between the real stationary distribution and the approximated one. While for a coexistence game it is *necessary* that the mutation rate μ is less than $N^{-1/2} \exp[-N]$ to ensure that the approximation is good, for *all other* games, it is *sufficient* if the mutation rate is smaller than $(N \ln N)^{-1}$. Our results also hold for a wide class of imitation processes under arbitrary selection intensity.

Keywords: Evolutionary game theory, Mutation rates, Perturbation analysis

I. INTRODUCTION

For evolutionary dynamics in finite populations with mutations, one can think of the evolutionary dynamics on two time scales. In the short run, what is the likelihood that a single mutant or a group of mutants takes over a population? If there is a single A type individual in a population of type B, the probability of fixation of A is termed ϕ_A. This quantity has been analytically characterized in population genetics [9, 11, 22] and has more recently also been applied to evolutionary games [7, 14, 24–26, 30, 31]. On a longer time scale, one can address the average abundance of the available strategies over time [2–4, 29]. [14], following the work of [12, 13] and [21], have developed an approach to deal with this issue. For small mutation rates, the time required for a mutation to occur is much larger than that required for fixation itself. Thus there are at most two strategies in the population simultaneously most of the time. In this case the original stochastic evolutionary process can be approximated by an embedded Markov chain on those states where the population is homogeneous for one strategy. The probability of transition from one homogenous population to another is the corresponding mutation rate multiplied by the fixation probability of the mutant strategy. For simplicity, we assume that all mutation rates are identical.

In particular, when there are only 2 types of strategies, A and B, the 2×2 payoff matrix is given by

$$
\begin{array}{c}
\begin{array}{cc} A & B \end{array} \\
\begin{array}{c} A \\ B \end{array}
\begin{pmatrix} a & b \\ c & d \end{pmatrix},
\end{array} \qquad (1)
$$

where, a is the payoff of A against A, b is the payoff of A against B, c is the payoff of B against A, and finally, d is

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the payoff of B against B. In a well mixed population, an individual interacts with all other individuals with the same probability. Excluding self interactions, the average payoff for each individual of each strategy is given by

$$
\pi_A(i) = a \frac{i-1}{N-1} + b \frac{N-i}{N-1} \qquad \text{and} \qquad (2)
$$

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

Here, i is the number of individuals playing strategy A. Since often the payoff difference is of interest, we substitute $\pi_A(i) - \pi_B(i)$ by $ui + v$, where $u = \frac{a-b-c+d}{N-1}$ and $v = \frac{N(b-d)-a+d}{N-1}$.

In this case, the pure population states are 'All play A' and 'All play B'. The transition probability from 'All play A' to 'All play B' is the mutation rate μ times the fixation probability of strategy B, ϕ_B. In analogy to this, the transition probability from 'All play B' to 'All play A' is the mutation rate μ times the fixation probability of strategy A, ϕ_A. Thus, the stationary distribution for this Markov chain is

$$
\left(\frac{\phi_A}{\phi_A + \phi_B}, \frac{\phi_B}{\phi_A + \phi_B} \right) \qquad (4)
$$

The first element is the average proportion of time spent in state "All play A" while the second element is the average proportion of time spent in state "All play B". This approach opens up a way to analytically investigate the evolutionary dynamics under mutation, selection and drift provided the mutation rate is sufficiently small [17, 18, 27, 34, 35]. However, how small do the mutation rates have to be? Numerical simulations and time scale separation analysis show that $\mu N^2 \ll 1$ ensures the validity of the approach if the game does not show any stable coexistence [1, 17, 33]. However, time scale arguments are often viewed as intuitive tools from physics and are hard to cast

into the form of a mathematical proof. Moreover, they do not provide a precise bound for the mutation rate.

Here, by perturbation analysis, we analytically investigate how small the mutation rate must be to make this embedded Markov chain a good approximation of the original one. To this end, we use the total variation distance of probability measures to measure the quality of the approximation of the stationary distribution. For simplicity, we employ the Fermi process [5, 28, 31], a specific yet widely used imitation process. In contrast with the result by time scale separation analysis, we show that for all games except for the coexistence game, it is *sufficient* that the mutation rate is smaller than $(N \ln N)^{-1}$ to ensure that the approximation of small mutation rates is good, i.e. $\mu N \ln N \ll 1$ relaxing $\mu N^2 \ll 1$. For a coexistence game, however, it is *necessary* that the mutation rate μ is less than $N^{-1/2} \exp[-N]$. Our result is also valid for other imitation processes with continuous derivative of the imitation function [36] as well as for the Moran process with different fitness mappings [32, 36]. For any birth death processes with mutations, we also provide a numerically accessible quantity to determine how small the mutation rate should be to make the approximation good.

II. THE FERMI PROCESS WITH MUTATIONS

The Fermi process is a particular birth-death process used to model evolutionary game dynamics in a finite population. In each time step, a random individual is selected. With probability $\mu < 1/2$, a mutation or exploration event occurs and the focal individual chooses the opposite strategy. With probability $1 - \mu$, no mutation occurs. In this case, the focal individual compares its payoff to another randomly chosen individual. If the focal player is playing A and the other plays B, then the focal player adopts the strategy of the other player with probability

$$\frac{1}{1 + \exp\left[+\beta\left(\pi_A(i) - \pi_B(i)\right)\right]} \qquad (5)$$

where β is the intensity of selection. For small β, selection is weak and strategy changes occur almost at random. For large β, only strategies with higher payoff are adopted. Let i be the number of strategy A individuals in the population. Then the transition probabilities from i to $i \pm 1$, $T_i^{\pm}$, are given by

$$T_i^+ = (1-\mu)\frac{i}{N}\frac{N-i}{N}\frac{1}{1 + \exp\left[-\beta(\pi_A(i) - \pi_B(i))\right]} + \mu\frac{N-i}{N}$$
$$T_i^- = (1-\mu)\frac{i}{N}\frac{N-i}{N}\frac{1}{1 + \exp\left[+\beta(\pi_A(i) - \pi_B(i))\right]} + \mu\frac{i}{N}. \quad (6)$$

The probability to stay in state i is $1 - T_i^+ - T_i^-$.

When the mutation rate is nonzero, this Markov process has no absorbing states. Our birth-death process satisfies the detailed balance condition

$$\psi_{j-1}T_{j-1}^+ = \psi_j T_j^- \qquad \text{for} \qquad 1 \le j \le N \qquad (7)$$

where ψ_j is the probability that the system is in state j [8, 16, 20]. The stationary distribution is given by (see Appendix A)

$$\psi_j = \frac{\frac{T_0^+}{T_j^-}\prod_{i=1}^{j-1}\frac{T_i^+}{T_i^-}}{1 + \sum_{k=1}^{N}\frac{T_0^+}{T_k^-}\prod_{i=1}^{k-1}\frac{T_i^+}{T_i^-}}, \quad 1 \le j \le N. \qquad (8)$$

where the empty product is one, $\prod_{i=1}^{0}\frac{T_i^+}{T_i^-} = 1$. For $j = 0$, we obtain

$$\psi_0 = \frac{1}{1 + \sum_{k=1}^{N}\frac{T_0^+}{T_k^-}\prod_{i=1}^{k-1}\frac{T_i^+}{T_i^-}}. \qquad (9)$$

For $\mu \to 0$, we have $T_0^+ = \mu = T_N^- \to 0$ and thus $\psi_0 \to \left(1 + \prod_{i=1}^{N-1}\frac{T_i^+}{T_i^-}\right)^{-1}$. On the other hand, the numerators of Eq. (8) approach zero for $1 < j < N$ due to $\mu \to 0$. Thus ψ_j approach zero as $\mu \to 0$ for $1 < j < N$. Considering the normalization condition, $\sum_{j=0}^{N}\psi_j = 1$, we have $\psi_N \to 1 - \psi_0$. Therefore, the ratio between ψ_0 and ψ_N is $\frac{\psi_0}{\psi_N} = \prod_{i=1}^{N-1}\frac{T_i^+}{T_i^-}$. Since $\prod_{i=1}^{N-1}\frac{T_i^+}{T_i^-} = \phi_B/\phi_A$ [24], this recovers Eq. (4).

III. ESTIMATING THE ERROR IN THE APPROXIMATION OF THE STATIONARY DISTRIBUTION

For our Markov chain, all possible stationary distributions form a set S denoted by

$$S = \{(\psi_0, \psi_1 \cdots \psi_N) \,|\, \psi_i \ge 0, \sum_{i=0}^{N}\psi_i = 1\}. \qquad (10)$$

We follow [10] (See also [6, 19, 23]) to define a measure for the similarity of two such distributions.

Definition: Let $z = (z_0, z_1 \cdots z_N)$ and $w = (w_0, w_1 \cdots w_N) \in S$ be two distributions. The total variation distance $d_{TV}(z, w)$ between v and w is defined by

$$d_{TV}(z, w) = \frac{1}{2}\sum_{i=0}^{N}|z_i - w_i| \qquad (11)$$

In particular, two distributions are identical if and only if the total variation distance between them is zero. If they are maximally different, we have $d_{TV}(z, w) = 1$. We use this total variation distance as a measure for the quality of the approximation based on the embedded Markov chain described above.

As discussed above, we have from Eqs. (8) and (9)

$$\lim_{\mu \to 0}\psi_0(\mu) = \frac{\phi_B}{\phi_A + \phi_B}$$
$$\lim_{\mu \to 0}\psi_i(\mu) = 0 \quad \text{for} \quad 0 < i < N$$
$$\lim_{\mu \to 0}\psi_N(\mu) = \frac{\phi_A}{\phi_A + \phi_B} \qquad (12)$$

This is consistent with the approach of [14], Eq. (4), which can be viewed as a zeroth order term of an approximation for small mutation rates.

Up to first order, $\psi_j(\mu)$ can be approximated by

$$\psi_j(\mu) \approx \psi_j(0) + \frac{d}{d\mu}\psi_j(0)\mu. \tag{13}$$

Our goal is to show under which circumstances the second term can be neglected compared to the first one. Based on Eqs. (8) and (9), we can address the derivative in Eq. (13) (See Appendix B 1), which involves the terms

$$\frac{d}{d\mu}\psi_0(\mu)|_{\mu=0} = -(\psi_0(0))^2 (C_1 + C_2) \tag{14}$$

$$\frac{d}{d\mu}\psi_j(\mu)|_{\mu=0} = \left(\frac{1}{T_j^-}\prod_{i=1}^{j-1}\frac{T_i^+}{T_i^-}\right)\Big|_{\mu=0}\psi_0(0), \quad 0 < j < N, \tag{15}$$

where

$$C_1 = \left(\sum_{k=1}^{N-1}\frac{1}{T_k^-}\prod_{i=1}^{k-1}\frac{T_i^+}{T_i^-}\right)\Big|_{\mu=0} \tag{16}$$

$$= \sum_{k=1}^{N-1}\frac{N^2\{1+\exp[(uk+v)\beta]\}}{k(N-k)}$$

$$\times \exp\left[\left(\frac{u}{2}(k-1)^2 + \left(\frac{u}{2}+v\right)(k-1)\right)\beta\right] \tag{17}$$

and

$$C_2 = \frac{d}{d\mu}\left(\prod_{i=1}^{N-1}\frac{T_i^+}{T_i^-}\right)\Big|_{\mu=0} \tag{18}$$

$$= N\exp\left[\left(\frac{N-1}{2}(uN+2v)\right)\beta\right]$$

$$\times \exp[-v\beta]\,(1-\exp[(uN+2v)\beta])$$

$$\times \sum_{i=1}^{N-1}\frac{\exp[-ui\beta]}{i} \tag{19}$$

Here, we have replaced $\pi_A(i) - \pi_B(i)$ by $ui + v$. The normalization of the distribution, $\sum_{j=0}^{N}\psi_j = 1$, is determined by the zeroth order term, cf. Eq. (12). Thus, we have $\sum_{j=0}^{N}\frac{d}{d\mu}\psi_j = 0$, which implies

$$\frac{d}{d\mu}\psi_N(\mu)|_{\mu=0} = -\sum_{j=0}^{N-1}\frac{d}{d\mu}\psi_j(\mu)|_{\mu=0} \tag{20}$$

We emphasize that Eqs. (14),(15),(16),(18), and (20) are valid for all the birth death processes with mutations. Eqs. (17) (19) are the special cases obtained by substituting the transition probabilities for the Fermi process, Eqs. (6).

In the following, we denote $\boldsymbol{\psi}(\mu) = (\psi_0(\mu), \cdots, \psi_N(\mu))$ and $\boldsymbol{\psi}(0) = \lim_{\mu\to 0}\boldsymbol{\psi}(\mu)$. Next, we state our main theorem.

Theorem:
Assume that the population size N is sufficiently large compared to the product of the selection intensity β and the payoff entries in Eq. (1). Evolutionary game dynamics is given by the Fermi process described above.

Given an arbitrary $\varepsilon > 0$, for all games with $a > c$ or $d > b$ there exists a $\mu^* = \varepsilon/G_1(N)$, with $G_1(N)$ of the order of $N\ln N$, such that if the mutation rate fulfills $\mu < \mu^*$, then $d_{TV}(\boldsymbol{\psi}(\mu), \boldsymbol{\psi}(0)) < \varepsilon$.

For games with $a < c$ and $d < b$, however, there exists $\mu^* = \varepsilon/G_2(N)$, where $G_2(N)$ is of order $\sqrt{N}\exp[N]$, such that if $d_{TV}(\boldsymbol{\psi}(\mu), \boldsymbol{\psi}(0)) < \varepsilon$ then $\mu < \mu^*$.

For the proof of this *Theorem*, we have to infer when the total variation between the distribution with and without mutation is smaller than ε. By Eqs. (11) and (13), we have

$$d_{TV}(\boldsymbol{\psi}(\mu), \boldsymbol{\psi}(0)) = \frac{1}{2}\left[\sum_{i=0}^{N}|\psi_i'(0)|\right]\mu \tag{21}$$

Replacing $\psi_N'(0)$ by Eq. (20) leads to

$$d_{TV}(\boldsymbol{\psi}(\mu), \boldsymbol{\psi}(0)) = \frac{1}{2}\left[\sum_{i=0}^{N-1}|\psi_i'(0)| + |\sum_{i=0}^{N-1}\psi_i'(0)|\right]\mu$$

$$\leq \frac{1}{2}\left[\sum_{i=0}^{N-1}|\psi_i'(0)| + \sum_{i=0}^{N-1}|\psi_i'(0)|\right]\mu$$

$$= \sum_{i=0}^{N-1}|\psi_i'(0)|\mu \tag{22}$$

First, note that $\psi_i'(0) > 0$ for $i = 1, \ldots, N-1$, cf. Eq. (15). Thus, we have

$$\sum_{i=1}^{N-1}|\psi_i'(0)| = \sum_{i=1}^{N-1}\psi_i'(0)$$

$$= \left(\sum_{i=1}^{N-1}\frac{1}{T_i^-}\prod_{k=1}^{i-1}\frac{T_k^+}{T_k^-}\right)\Big|_{\mu=0}\psi_0(0)$$

$$= C_1\psi_0(0). \tag{23}$$

On the other hand, we have

$$|\psi_0'(0)| = (\psi_0(0))^2\,|C_1 + C_2| \tag{24}$$

Taking Eq. (23) and (24) into Expression.(22) as well as considering $\psi_0(0) \leq 1$ leads to

$$d_{TV}(\boldsymbol{\psi}(\mu), \boldsymbol{\psi}(0)) = \left(|C_1 + C_2|\psi_0(0) + C_1\right)\psi_0(0)\mu$$

$$\leq \left(|C_1 + C_2| + C_1\right)\mu \tag{25}$$

C_1 is positive as seen directly from the definition Eq. (16). For C_2, it is positive when $uN + 2v < 0$ and it is negative otherwise. However, for the game fulfilling $uN + 2v > 0$,

we can look at a transformed game in which A and B are exchanged. This leads to $\tilde{u} = u$ and $\tilde{v} = (N(c - a) - d + a)/(N - 1)$. Using $v + \tilde{v} = -\tilde{u}N$ leads to $\tilde{u}N + 2\tilde{v} < 0$. Since the exchange of strategies does not affect our general result, we thus always consider the game satisfying $uN + 2v < 0$. In this case, both C_1 and C_2 are positive, yielding

$$d_{TV}(\boldsymbol{\psi}(\mu), \boldsymbol{\psi}(0)) \leq \left(2C_1 + C_2\right)\mu \qquad (26)$$

Thus, the scaling of $2C_1 + C_2$ with N allows us to asses how the total variation distance scales with N. For games except for the coexistence game, we can derive an upper bound for the mutation rate: $2C_1 + C_2$ is smaller than a quantity $G_1(N)$ of order $N \ln N$ for large N (See Appendix B 2 a and Appendix B 2 b). Hence, we have $d_{TV}(\boldsymbol{\psi}(\mu), \boldsymbol{\psi}(0)) \leq G_1(N)\mu$. For any $\varepsilon > 0$, we define $u^* = \varepsilon/G_1(N)$ and whenever $u < u^*$, the error we are making when considering the stationary distribution without mutations instead of the one with mutations is smaller than ε, $d_{TV}(\boldsymbol{\psi}(\mu), \boldsymbol{\psi}(0)) < \varepsilon$. Since we can specify an upper bound for u^*, the condition is sufficient.

For the coexistence game ($a < c$ and $b > d$), we only find a lower bound: $2C_1 + C_2$ is greater than a quantity $G_2(N)$ of order $\sqrt{N} \exp[N]$ for large N (See Appendix B 2 c). For any $\varepsilon > 0$, we can define $u^* = \varepsilon/G_2(N)$. Only when $u < u^*$, the error of our approximation is small, $d_{TV}(\boldsymbol{\psi}(\mu), \boldsymbol{\psi}(0)) < \varepsilon$.

This completes the proof of our *Theorem*.

Corollary: As per the above *Theorem*, for games with $a > c$ or $d > b$, i.e. 2×2 games except for the coexistence game, if μ is smaller than the error ε times $(N \ln N)^{-1}$, then $d_{TV}(\boldsymbol{\psi}(\mu), \boldsymbol{\psi}(0)) < \varepsilon$. Thus $\mu < \varepsilon (N \ln N)^{-1}$ is a sufficient condition to ensure that the embedded Markov chain is a good approximation of the original one. In analogy to this, for coexistence game, the *Theorem* implies that $\mu < \varepsilon \exp[-N]N^{-1/2}$ is only a necessary condition.

In the following we investigate what the mutation rate should be for neutral evolution, $\beta = 0$. In this case, the selection is absent and the strategies evolve due to mutation and neutral drift. Eq. (24) still holds since we do not employ β to obtain Eq. (24). In this case, we have $C_2 = 0$ and

$$\begin{aligned} C_1 &= \sum_{i=1}^{N-1} \frac{2N^2}{i(N-i)} \\ &= 2N \sum_{i=1}^{N-1} \left(\frac{1}{i} + \frac{1}{N-i}\right) \\ &= 4NH_{N-1} \end{aligned} \qquad (27)$$

where $H_{N-1} = \sum_{i=1}^{N-1} 1/i$ is the Harmonic number, which is of order $\ln N$ for large N. Therefore $2C_1 + C_2$ is of order $N \ln N$ for large N. ¿From Eq. (26), we have that mutation rate of order $(N \ln N)^{-1}$ is sufficient to make the approximation good.

Finally, we address the validity of our approach for other processes. The Fermi process is a special imitation process whose imitation function is the Fermi function, Eq. (5).

For a general imitation function, we show the *Theorem* is also valid, provided the first order derivative of the imitation function is continuous (See Appendix C).

IV. DISCUSSION AND CONCLUSION

We have investigated how small the mutation rate should be to make the stationary distribution obtained with a mutation rate going to zero a good approximation of the "real" stochastic process with nonzero mutation rate. For a non-coexistence game, it is *sufficient* that the mutation rate is smaller than a quantity of the order of $(N \ln N)^{-1}$. For a coexistence game, however, it is *necessary* that the mutation rate μ is less than a quantity of the order of $\left(\sqrt{N}\right)^{-1} \exp[-N]$. These results are valid for any nonzero selection intensity. When the selection intensity vanishes, the mutation rate μ of order $(N \ln N)^{-1}$ is *sufficient* to make the approximation good. Therefore, we can say that the order of μ, which makes the approximation good, does not change compared to the neutral case provided the game allows no coexistence.

For a non-coexistence game, our results can also be interpreted in a time scale separation analysis framework: For large population size N, the conditional fixation time is of order $N \ln N$ [1]. On an average the time between two mutations is $1/\mu$. The embedded Markov chain is valid as long as there are at most two strategies in the population, i.e. $1/\mu \gg N \ln N$. Thus time scale separation analysis also yields $\mu \ll (N \ln N)^{-1}$.

To formulate the problem mathematically, we introduced the total variation distance to measure how "good" the embedded Markov chain is compared to the original one. We can also introduce other measures of distances. A natural question arises: How much does the definition of the distance influence the results? In analogy to Eq. (11), the distance between z and w induced by the $p-$Norm is given by

$$\|z - w\|_p = \left(\sum_{i=0}^{N} |z_i - w_i|^p\right)^{\frac{1}{p}}, \quad p \geq 1 \qquad (28)$$

In particular, we have $\|\boldsymbol{\psi}(\mu) - \boldsymbol{\psi}(0)\|_1 = 2d_{TV}(\boldsymbol{\psi}(\mu), \boldsymbol{\psi}(0))$ by the definition of the total variation distance. Since $\|\boldsymbol{\psi}(\mu) - \boldsymbol{\psi}(0)\|_p \leq \|\boldsymbol{\psi}(\mu) - \boldsymbol{\psi}(0)\|_1$ for $p > 1$ as well as $d_{TV}(\boldsymbol{\psi}(\mu), \boldsymbol{\psi}(0)) \leq G_1(N)\mu$ for a non-coexistence game, we have $\|\boldsymbol{\psi}(\mu) - \boldsymbol{\psi}(0)\|_p \leq 2G_1(N)\mu$ for $p > 1$. By identical arguments, the *Theorem* is also valid for non-coexistence games under this definition of distance. For a coexistence game, however, we have $\|\boldsymbol{\psi}(\mu) - \boldsymbol{\psi}(0)\|_p \geq \|\boldsymbol{\psi}(\mu) - \boldsymbol{\psi}(0)\|_1/(N+1)$ for $p > 1$. In analogy to the above discussion, the *Theorem* should be reformed by replacing $G_2(N) = \sqrt{N} \exp[N]$ by $\exp[N]/\sqrt{N}$. Therefore, our *Theorem* is robust with respect to the definition of distance for a non-coexistence game while needs reformation for a coexistence game. But the reformed theory illustrates that the critical mutation rate

for a coexistence game decreases more rapidly compared to that of the non-coexistence games. Thus the results are qualitatively robust with respect to the definition of the distance.

We have shown that the *Theorem* is not only valid for the Fermi process, but also for a general imitation process with continuous derivative of the imitation function [36]. By definition an imitation process involves an imitator and a role model and the strategy of the role model can be adopted by the imitator. Individuals are more likely to imitate those with higher fitness. This has been termed as 'monotonicity' in [15]. In addition, the *Theorem* is also valid for the Moran process with continuous differentiable fitness mappings. The proof is quite similar to that of the general imitation process and thus we do not show it in the appendix. For the Moran process, the monotonicity of the payoff to fitness mapping is also needed. This ensures that individuals with higher payoff have more chance to reproduce.

Since the proof of the *Theorem* depends only on C_1 and C_2 as defined in Eqs. (16) and (18) and the triangle inequality used in Eq. (22), Eq. (25) is valid for general evolutionary processes that can be described by a birth death process with mutations. The Moran processes with different fitness functions are of this kind [36]. Therefore, for any such process, given the error bound ε, the critical mutation bound that ensures that the approximation by the embedded Markov chain is good, i.e., $d_{TV}(\boldsymbol{\psi}(\mu), \boldsymbol{\psi}(0)) \leq \varepsilon$, is $\varepsilon / (|C_1 + C_2| + C_1)$. In other words, the numerical value of $|C_1 + C_2| + C_1$ is sufficient to determine the critical mutation bound. Considering that $|C_1 + C_2| + C_1$ is numerically accessible, it paves the way to determine the critical mutation bound. This mutation bound for the Fermi process is given in Appendix B 3

In contrast with the 2×2 games, it would be challenging to address what the mutation rate has to be for more than two strategies. For multi-strategy games it is difficult to obtain the exact stationary distribution. However, when there are at most two strategies in the population, then pairwise competition between all strategies is the main force of selection, therefore, our results for 2×2 can still shed light on how small the mutation rate should be. In fact, for $n \times n$ games, we optimistically speculate that our *Theorem* is also valid, whenever there are no stable internal equilibria in the simplex and the sub-simplices.

ACKNOWLEDGEMENT

Appendix A: The stationary distribution

Here, we recall the calculation of the stationary distribution ψ_j for a one dimensional birth-death process without absorbing states [8, 16, 20]. The stationary distribution fulfills the detailed balance condition $\psi_{j-1} T_{j-1}^+ = \psi_j T_j^-$. We rearrange this to

$$\psi_j = \frac{T_{j-1}^+}{T_j^-} \psi_{j-1}. \tag{A1}$$

Therefore

$$\psi_1 = \frac{T_0^+}{T_1^-} \psi_0$$
$$\psi_2 = \frac{T_1^+}{T_2^-} \psi_1 = \frac{T_0^+ T_1^+}{T_2^- T_1^-} \psi_0$$
$$\psi_3 = \frac{T_2^+}{T_3^-} \psi_2 = \frac{T_0^+ T_1^+ T_2^+}{T_3^- T_1^- T_2^-} \psi_0. \tag{A2}$$

In general, we have

$$\psi_j = \frac{T_0^+}{T_j^-} \prod_{i=1}^{j-1} \frac{T_i^+}{T_i^-} \psi_0, \qquad 1 \leq j \leq N. \tag{A3}$$

On the other hand, $\sum_{j=0}^{N} \psi_j = 1$. Thus, we have

$$1 = \sum_{j=0}^{N} \psi_j = \psi_0 \left(1 + \sum_{j=1}^{N} \frac{T_0^+}{T_j^-} \prod_{i=1}^{j-1} \frac{T_i^+}{T_i^-} \right) \tag{A4}$$

and hence

$$\psi_0 = \frac{1}{1 + \sum_{j=1}^{N} \frac{T_0^+}{T_j^-} \prod_{i=1}^{j-1} \frac{T_i^+}{T_i^-}}. \tag{A5}$$

Therefore, by Eq.(A2)

$$\psi_j = \frac{\frac{T_0^+}{T_j^-} \prod_{i=1}^{j-1} \frac{T_i^+}{T_i^-}}{1 + \sum_{k=1}^{N} \frac{T_0^+}{T_k^-} \prod_{i=1}^{k-1} \frac{T_i^+}{T_i^-}}, \quad 1 \leq j \leq N. \tag{A6}$$

Appendix B: Estimating the critical mutation rate for the Fermi process

In this section, we consider the first order term of the Taylor approximation of the stationary distribution for small mutation rates. This provides part of the proof of the *Theorem* in the main text.

1. The first order term of the stationary distribution in the mutation rate

We calculate the first order expansion of the stationary distribution at state 0 under small mutation. Since $T_N^- =$

$\mu = T_0^{+'}$, we have

$$\psi_0(\mu) = \frac{1}{1 + \mu \left(\sum_{k=1}^{N-1} \frac{1}{T_k^-} \prod_{i=1}^{k-1} \frac{T_i^+}{T_i^-} \right) + \prod_{i=1}^{N-1} \frac{T_i^+}{T_i^-}} \quad \text{(B1)}$$

Thus, $\frac{d}{d\mu}\psi_0|_{\mu=0}$ is given by

$$\frac{d}{d\mu}\psi_0|_{\mu=0} = -\psi_0^2(0) \left[\underbrace{\left(\sum_{k=1}^{N-1} \frac{1}{T_k^-} \prod_{i=1}^{k-1} \frac{T_i^+}{T_i^-} \right)|_{\mu=0}}_{C_1} \right.$$
$$\left. + \underbrace{\frac{d}{d\mu} \left(\prod_{i=1}^{N-1} \frac{T_i^+}{T_i^-} \right)|_{\mu=0}}_{C_2} \right] \quad \text{(B2)}$$

This equation is valid for all evolutionary birth-death processes. Substituting Eq.(6) into C_1 yields

$$C_1 = \sum_{k=1}^{N-1} \frac{N^2 \{1 + \exp[(uk+v)\beta]\}}{k(N-k)} \prod_{i=1}^{k-1} \exp[(ui+v)\beta]$$
$$= \sum_{k=1}^{N-1} \frac{N^2 \{1 + \exp[(uk+v)\beta]\}}{k(N-k)} \exp\left[\sum_{i=1}^{k-1} (ui+v)\beta \right]$$
$$= \sum_{k=1}^{N-1} \frac{N^2 \{1 + \exp[(uk+v)\beta]\}}{k(N-k)} \exp\left[\left(\frac{u}{2}k + v \right)(k-1)\beta \right]$$
$$\quad \text{(B3)}$$

Next, we address C_2. Let $g(\mu) = \prod_{i=1}^{N-1} \frac{T_i^+}{T_i^-}$, therefore $\ln g(\mu) = \sum_{i=1}^{N-1} (\ln T_i^+ - \ln T_i^-)$. The derivative of this quantity is given by $\frac{d}{d\mu} \ln g(\mu) = \frac{g'(\mu)}{g(\mu)}$, which results in $C_2 = \frac{d}{d\mu}g(\mu)|_{\mu=0} = g(0)\frac{d}{d\mu}\ln g(\mu)|_{\mu=0}$. On the other hand, $\frac{d}{d\mu} \ln g(\mu) = \sum_{i=1}^{N-1} \left(\frac{T_i^{+'}}{T_i^+} - \frac{T_i^{-'}}{T_i^-} \right)$. Therefore,

$$C_2 = \prod_{i=1}^{N-1} \left(\frac{T_i^+}{T_i^-} \right)|_{\mu=0} \sum_{i=1}^{N-1} \left(\frac{T_i^{+'}}{T_i^+} - \frac{T_i^{-'}}{T_i^-} \right)|_{\mu=0}. \text{(B4)}$$

By Eq.(6), we have $T_i^{+'}|_{\mu=0} = \frac{N-i}{N} - T_i^+|_{\mu=0}$ and $T_i^{-'}|_{\mu=0} = \frac{i}{N} - T_i^-|_{\mu=0}$. Substituting these expressions into Eq.(B4) yields

$$C_2 = \prod_{i=1}^{N-1} \left(\frac{T_i^+}{T_i^-} \right)|_{\mu=0} \sum_{i=1}^{N-1} \left(\frac{N-i}{NT_i^+} - \frac{i}{NT_i^-} \right)|_{\mu=0} \quad \text{(B5)}$$

$$= \exp\left[\sum_{i=1}^{N-1} (ui+v)\beta \right]$$
$$\times \left[\sum_{i=1}^{N-1} \frac{N\{1 + \exp[-\beta(ui+v)]\}}{i} \right.$$
$$\left. - \sum_{i=1}^{N-1} \frac{N\{1 + \exp[\beta(ui+v)]\}}{N-i} \right]$$
$$= \exp\left[\left(u\frac{(N-1)N}{2} + v(N-1) \right)\beta \right]$$
$$\times \left[\sum_{i=1}^{N-1} \frac{N\{1 + \exp[-\beta(ui+v)]\}}{i} \right.$$
$$\left. - \sum_{i=1}^{N-1} \frac{N\{1 + \exp[\beta(u(N-i)+v)]\}}{i} \right]$$
$$\quad \text{(B6)}$$

where we have exchanged the summation variable in the second sum, $i \leftrightarrow N-i$. Next, we can drop common terms in the two sums and arrive at

$$C_2 = N \exp\left[\left(\frac{N-1}{2}(uN+2v) \right)\beta \right]$$
$$\times \exp[-v\beta] \left(1 - \exp[(uN+2v)\beta] \right)$$
$$\times \sum_{i=1}^{N-1} \frac{\exp[-ui\beta]}{i} \quad \text{(B7)}$$

2. Scaling of the first order term with N

Next, we estimate the order of $2C_1 + C_2$. To facilitate the calculation, we classify the 2×2 games by the payoff difference parameters, u and v

Classification of the game	
Neither u nor v is zero	(i) $u < 0$ and $v < 0$
	(ii) $u < 0$ and $v > 0$, coexistence game
	(iii) $u < 0$ and $v > 0$, non-coexistence game
	(iv) $u > 0$ and $v > 0$
	(v) $u > 0$ and $v < 0$, coordination game
	(vi) $u > 0$ and $v < 0$, non-coordination game
Either u or v is zero	(vii) $u = 0$ and $v < 0$
	$(viii)$ $u = 0$ and $v > 0$
	(ix) $u > 0$ and $v = 0$
	(x) $u < 0$ and $v = 0$
Both u and v are zero	(xi) $u = 0$ and $v = 0$

With this classification, we have to prove that for case (ii), i.e. the coexistence game, $2C_1 + C_2$ is greater than $G_2(N)$ which is of order $\sqrt{N} \exp[N]$, whereas for all the other cases, $2C_1 + C_2$ is less than $G_1(N)$ which is of order $N \ln N$. We only show the calculations for case (i) (ii) and (v), for the rest of the cases it can be proved by identical techniques. For case (xi) though, it is identical with the case without selection intensity. Further, without loss of generality, we assume that the payoff entries are of order 1. Thus u is of the order of $1/N$ and v as well as $\lambda = uN + 2v < 0$ are of order 1 when N is large. On the other hand, for large N, $\lambda < 0$ is equivalent to the risk dominance condition of strategy B. Also, since β can be absorbed into the payoff entries in the transition probabilities, we let β be one for simplicity.

a. Dominance of strategy B with $u < 0$ and $v < 0$

For C_1, we have

$$
\begin{aligned}
C_1 &= \sum_{i=1}^{N-1} \frac{N^2 \left(1 + \exp[ui + v]\right)}{i(N-i)} \\
&\quad \exp\left[\frac{u}{2}(i-1)^2 + \left(\frac{u}{2} + v\right)(i-1)\right] \\
&< \sum_{i=1}^{N-1} \frac{2N^2}{i(N-i)} \exp\left[\frac{u}{2}(i-1)^2 + \left(\frac{u}{2} + v\right)(i-1)\right] \\
&< 2N^2 \sum_{i=1}^{N-1} \frac{1}{i(N-i)} \\
&= 2N \left(\sum_{i=1}^{N-1} \frac{1}{i} + \sum_{i=1}^{N-1} \frac{1}{N-i}\right) \\
&= 4N H_{N-1}
\end{aligned}
$$
(B8)

The Harmonic number H_{N-1} is of order $\ln N$ for large N, thus C_1 is smaller than a quantity of order $N \ln N$.

For C_2, we have (with $\lambda = uN + 2v < 0$)

$$
\begin{aligned}
C_2 &= N \exp\left[\frac{N-1}{2}\lambda - v\right] (1 - \exp[\lambda]) \sum_{k=1}^{N-1} \frac{\exp[-uk]}{k} \\
&\leqslant N \exp\left[\frac{N-1}{2}\lambda - v\right] (1 - \exp[\lambda]) \exp[-u(N-1)] \sum_{k=1}^{N-1} \frac{1}{k} \\
&= N \exp\left[\frac{N-1}{2}\lambda - v\right] (1 - \exp[\lambda]) \exp[-u(N-1)] H_{N-1}
\end{aligned}
$$
(B9)

$u < 0$ is of order $1/N$ and $\lambda < 0$ is of order 1. Thus, $N \exp\left[\frac{N-1}{2}\lambda - v\right] (1 - \exp[\lambda]) \exp[-u(N-1)] H_{N-1}$ is of order $N \ln N \exp[-N]$, which is much smaller than $N \ln N$. Thus, C_2 can be neglected compared to C_1; $G_1(N) = 8N H_{N-1} > 2C_1 + C_2$ scales at most with $N \ln N$.

b. Coordination game with $u > 0$ and $v < 0$

To estimate the order of C_1, let

$$
F(i) = \frac{u}{2}i^2 + \left(\frac{u}{2} + v\right)i,
$$
(B10)

We have $F(0) = 0$ and $F(N-1) = (N-1)(uN + 2v)/2 = (N-1)\lambda/2 < 0$. On the other hand, $F''(i) = \frac{u}{2}$. Since $u > 0$, $F(i)$ is a convex function which implies

$$
\begin{aligned}
F(i) &= F\left(\frac{i}{N-1}(N-1) + \left(1 - \frac{i}{N-1}\right)0\right) \\
&\leq \frac{i}{N-1}F(N-1) + \left(1 - \frac{i}{N-1}\right)F(0) \\
&\leq 0,
\end{aligned}
$$
(B11)

where equality holds for $i = 0$ only. Therefore for C_1, we have

$$
\begin{aligned}
C_1 &= \sum_{i=1}^{N-1} \frac{N^2 \left(1 + \exp[ui + v]\right)}{i(N-i)} \\
&\quad \exp\underbrace{\left[\frac{u}{2}(i-1)^2 + \left(\frac{u}{2} + v\right)(i-1)\right]}_{F(i-1)} \\
&< \sum_{i=1}^{N-1} \frac{N^2 \left(1 + \exp[ui + v]\right)}{i(N-i)} \\
&< \sum_{i=1}^{N-1} \frac{N^2 \left(1 + \exp[u(N-1) + v]\right)}{i(N-i)} \\
&= N \left(1 + \exp[u(N-1) + v]\right) \left(\sum_{i=1}^{N-1} \frac{1}{i} + \sum_{i=1}^{N-1} \frac{1}{N-i}\right) \\
&= 2 \left(1 + \exp[u(N-1) + v]\right) N H_{N-1}
\end{aligned}
$$
(B12)

(B13)

Considering that u and v are of order $1/N$ and 1. C_1 is less than a quantity of order $N \ln N$.

For C_2, since $u > 0$, we have

$$
\begin{aligned}
C_2 &= \\
&N \exp\left[\frac{N-1}{2}\lambda - v\right] (1 - \exp[\lambda]) \sum_{k=1}^{N-1} \frac{\exp[-uk]}{k} \\
&\leqslant N \exp\left[\frac{N-1}{2}\lambda - v\right] (1 - \exp[\lambda]) \exp[-u] \sum_{k=1}^{N-1} \frac{1}{k} \\
&= N \exp\left[\frac{N-1}{2}\lambda - v\right] (1 - \exp[\lambda]) \exp[-u] H_{N-1}
\end{aligned}
$$
(B14)

In analogy to the order analysis for Eq. (B9), C_2 is much smaller than C_1. Hence, $2C_1 + C_2$ scales with N as $N \ln N$. Thus our quantity $G_1(N)$ in the proof is $4 \left(1 + \exp[u(N-1) + v]\right) N H_{N-1}$.

c. Coexistence of strategy A and B with $u < 0$ and $v > 0$

We show that for a coexistence game, $2C_1 + C_2$ is greater than a quantity of order $\sqrt{N}\exp(N)$. For C_1, we have

$$
\begin{aligned}
C_1 &= \sum_{i=1}^{N-1} \frac{N^2\left(1 + \exp\left[ui+v\right]\right)}{i(N-i)} \exp\left[\frac{u}{2}(i-1)^2 + \left(\frac{u}{2}+v\right)(i-1)\right] \\
&> 4\sum_{i=1}^{N-1} \exp\left[ui+v\right]\exp\left[\frac{u}{2}(i-1)^2 + \left(\frac{u}{2}+v\right)(i-1)\right] \\
&= 4\sum_{i=1}^{N-1} \exp\left[\frac{u}{2}i^2 + \left(\frac{u}{2}+v\right)i\right] \\
&= 4\exp\left[-\frac{u}{2}\left(\frac{1}{2}+\frac{v}{u}\right)^2\right]\sum_{i=1}^{N-1}\exp\left[\frac{u}{2}\left(i+\frac{1}{2}+\frac{v}{u}\right)^2\right]
\end{aligned}
$$

When the population size N is large, we can set $x = i/(N-1)$ and approximate the sum in the above equation by an integral,

$$
(N-1)\int_0^1 \exp\left[-\frac{1}{2}\left(\sqrt{-u}\left((N-1)x+\frac{1}{2}+\frac{v}{u}\right)\right)^2\right]dx
\tag{B17}
$$

Let $t = \sqrt{-u}[(N-1)x+\frac{1}{2}+\frac{v}{u}]$, then the above integral is

$$
\begin{aligned}
&\frac{1}{N-1}\sqrt{-\frac{2\pi}{u}} \\
&\times\left[\Phi\left(\sqrt{-u}\left(N-\frac{1}{2}+\frac{v}{u}\right)\right)-\Phi\left(\sqrt{-u}\left(\frac{1}{2}+\frac{v}{u}\right)\right)\right]
\end{aligned}
\tag{B18}
$$

where $\Phi(x) = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^x e^{-t^2/2}\,dt$ is the cumulative distribution function of the Gaussian distribution. For a coexistence game, $ui+v = 0$ has a solution i between 1 and $N-1$. Thus $-\frac{v}{u} \le N-1$. With this, we have $0 < N - \frac{1}{2}+\frac{v}{u}$. Hence, $\sqrt{-u}\left(N-\frac{1}{2}+\frac{v}{u}\right)$ is of order $+\sqrt{N}$ and approaches $+\infty$ as the population size N goes to infinity. Thus, $\Phi\left(\sqrt{-u}\left(N-\frac{1}{2}+\frac{v}{u}\right)\right)$ approaches 1 as N approaches infinity. Similarly, a coexistence game implies $0 < -\frac{v}{u}$ and thus $\sqrt{-u}\left(\frac{1}{2}+\frac{v}{u}\right)$ scales as $-\sqrt{N}$. Therefore, the second term $\Phi\left(\sqrt{-u}\left(\frac{1}{2}+\frac{v}{u}\right)\right)$ approaches 0 as N approaches infinity. This means that the sum in Eq. (B16) is larger than $\sqrt{-\frac{2\pi}{u}}$ for large N, yielding a lower bound for C_1,

$$
C_1 > 4\sqrt{-\frac{2\pi}{u}}\exp\left[-\frac{u}{2}\left(\frac{1}{2}+\frac{v}{u}\right)^2\right].
\tag{B19}
$$

Now, $u < 0$ scales as $1/N$, whereas v becomes independent of N for large N. Hence, C_1 scales as $\sqrt{N}\exp[N]$, i.e. it increases more than exponentially with N. For C_2, the order estimation is identical to Eq.(B9), C_2 becomes infinitely small for large N. Therefore, $2C_1 + C_2$ scales

as $\sqrt{N}\exp[N]$ and the mutation rate has to go to zero rapidly to ensure that the approximation remains good when the population size is increased. Thus $G_2(N)$ is $8\sqrt{-\frac{2\pi}{u}}\exp\left[-\frac{u}{2}\left(\frac{1}{2}+\frac{v}{u}\right)^2\right]$.

3. A numerically accessible bound for the mutation rate

In this part of the Appendix, we show, for a given non-coexistence game, how the critical mutation rate depends on the payoff entries. By the proof provided above, this mutation rate is $(2C_1)^{-1}\varepsilon$ for large population size, where ε is the given tolerance of the error. Thus we only need to derive the relationship between C_1 and the payoff entries.

For coordination games, Eq. (B13) provides such a relationship. For dominance games, however, it is not straightforward from Eq. (B8). But based on Eq. (B8), we have

$$
C_1 < \sum_{i=1}^{N-1}\frac{2N^2}{i(N-i)}\exp\left[\frac{u}{2}(i-1)^2 + \left(\frac{u}{2}+v\right)(i-1)\right]
\tag{B20}
$$

By the Cauchy-Schwarz inequality,

$$
\begin{aligned}
C_1 < &\left(\sum_{i=1}^{N-1}\frac{2N^2}{i(N-i)}\right)^{\frac{1}{2}} \\
&\left(\sum_{i=1}^{N-1}\underbrace{\exp\left[\frac{u}{2}(i-1)^2 + \left(\frac{u}{2}+v\right)(i-1)\right]}_{R(i-1)}\right)^{\frac{1}{2}}
\end{aligned}
\tag{B21}
$$

By using $\sum_{i=1}^{N-1}R(i-1) = \sum_{i=0}^{N-2}R(i) = \sum_{i=1}^{N-1}R(i) + R(0) - R(N-1)$, the above inequality can be rewritten as

$$
\begin{aligned}
C_1 < &\left(\sum_{i=1}^{N-1}\frac{2N^2}{i(N-i)}\right)^{\frac{1}{2}} \\
&\times\left(\sum_{i=1}^{N-1}\exp\left[\frac{u}{2}i^2 + \left(\frac{u}{2}+v\right)i\right]\right. \\
&\left. +1 - \exp\left[(N-1)\frac{Nu+2v}{2}\right]\right)^{\frac{1}{2}}
\end{aligned}
\tag{B22}
$$

The first factor of the r.h.s of the inequality, by Eq. (27), scales as $2\sqrt{N\ln N}$. The second factor is similar to the expressions obtained by Eqs. (B15) (B16) (B17) (B18). It can be approximated by the square root of

$$
\begin{aligned}
&\exp\left[-\frac{u}{2}\left(\frac{1}{2}+\frac{v}{u}\right)^2\right]\sqrt{-\frac{2\pi}{u}} \\
&\left[\Phi\left(\sqrt{-u}\left(N-\frac{1}{2}+\frac{v}{u}\right)\right)-\Phi\left(\sqrt{-u}\left(\frac{1}{2}+\frac{v}{u}\right)\right)+1\right]
\end{aligned}
$$

for large N where $\Phi(x)$ is the standard Gaussian distribution function. Thus

$$C_1 < 2\sqrt{N \ln N} \sqrt[4]{-\frac{2\pi}{u}} \exp\left[-\frac{u}{4}\left(\frac{1}{2} + \frac{v}{u}\right)^2\right]$$
$$\times \sqrt{\Phi\left(\sqrt{-u}\left(N - \frac{1}{2} + \frac{v}{u}\right)\right) - \Phi\left(\sqrt{-u}\left(\frac{1}{2} + \frac{v}{u}\right)\right) + 1}$$
(B23)

This allows to estimate a numerical value for the critical mutation bound for given payoff entries of a non-coexistence game and error tolerance without the need to evaluate sums. If the system is not too large such that sums can be evaluated numerically, the first line of Eq. (B13) gives a more precise estimate.

Appendix C: Estimating the critical mutation rate for general imitation processes

For the general imitation process with mutations, an individual is picked up from the well mixed population of size N. With probability $1 - \mu$, imitation occurs: The focal individual imitates another random individual with a probability $g(\beta\Delta\pi_i)$, where $\Delta\pi_i = \pi_A - \pi_B$ and β is the selection intensity. Here $g(x)$ is an increasing function. This implies that the more successful the opponent is, the more likely the focal individual imitates it. With probability $\mu < 1/2$, mutation or exploration occurs: The focal individual switches to the opposite strategy.

In analogy to the transition probabilities given by Eq. (6), we have

$$T_i^+ = (1 - \mu)\frac{i}{N}\frac{N-i}{N}g(+\beta\Delta\pi_i) + \mu\frac{N-i}{N}$$
$$T_i^- = (1 - \mu)\frac{i}{N}\frac{N-i}{N}g(-\beta\Delta\pi_i) + \mu\frac{i}{N}.$$
(C1)

and $1 - T_i^+ - T_i^-$. In this Appendix, we show that the *Theorem* is also valid for a wide class of imitation processes. The only technical requirement is that the imitation function is increasing and that its derivative is continuous.

1. The form of the first order term

For the general imitation process with mutations, we still have C_1 and C_2 defined in Eqs. (16) and (18). For C_1, we obtain

$$C_1 = \left(\sum_{i=1}^{N-1}\frac{1}{T_i^-}\prod_{k=1}^{i-1}\frac{T_k^+}{T_k^-}\right)|_{\mu=0}$$
$$= \sum_{i=1}^{N-1}\frac{N^2}{i(N-i)}\frac{1}{g(-\beta\Delta\pi_i)}\prod_{k=1}^{i-1}\frac{g(+\beta\Delta\pi_k)}{g(-\beta\Delta\pi_k)}$$
(C2)

By making use of the identity $x = \exp[\ln x]$ for $x = \prod_{k=1}^{i-1}\frac{g(+\beta\Delta\pi_k)}{g(-\beta\Delta\pi_k)}$, we arrive at

$$C_1 = \sum_{i=1}^{N-1}\frac{N^2}{i(N-i)}\frac{1}{g(-\beta\Delta\pi_i)}\exp\left[\sum_{k=1}^{i-1}\ln\left[\frac{g(+\beta\Delta\pi_k)}{g(-\beta\Delta\pi_k)}\right]\right]$$
(C3)

For C_2, note that the derivation of Eq. (B5) is independent of the imitation function given, thus it is valid for all imitation processes. We have

$$C_2 = \prod_{k=1}^{N-1}\left(\frac{T_k^+}{T_k^-}\right)|_{\mu=0}\sum_{k=1}^{N-1}\left(\frac{N-k}{NT_k^+} - \frac{k}{NT_k^-}\right)|_{\mu=0}$$
$$= \prod_{k=1}^{N-1}\frac{g(+\beta\Delta\pi_k)}{g(-\beta\Delta\pi_k)}\sum_{k=1}^{N-1}\frac{N}{N-k}\left(\frac{1}{g(+\beta\Delta\pi_{N-k})} - \frac{1}{g(-\beta\Delta\pi_k)}\right)$$
$$= \exp\left[\sum_{k=1}^{N-1}\ln\left[\frac{g(+\beta\Delta\pi_k)}{g(-\beta\Delta\pi_k)}\right]\right]$$
$$\times \sum_{k=1}^{N-1}\frac{N}{N-k}\left(\frac{1}{g(+\beta\Delta\pi_{N-k})} - \frac{1}{g(-\beta\Delta\pi_k)}\right)$$
(C4)

For C_2, if $\frac{1}{g(+\beta\Delta\pi_{N-k})} - \frac{1}{g(-\beta\Delta\pi_k)}$ is non-negative for all the k, then C_2 is non-negative. Since $g(x)$ is an increasing function, this is equivalent to $\Delta\pi_{N-k} \leq -\Delta\pi_k$, i.e., $uN + 2v \leq 0$. If this is not the case, we can exchange strategy A and B, as described in the main text. This yields a transformed game which fulfills $\tilde{u}N + 2\tilde{v} \leq 0$ without influencing the main results. Therefore, we always consider the case for $uN + 2v \leq 0$, such that both C_1 and C_2 are non-negative.

2. Scaling of the first order term with N

To estimate the order of $2C_1 + C_2$, we absorb the selection intensity β into the payoff difference term in analogy to the proof above, i.e. we formally set $\beta = 1$. The quantity u is of order $1/N$ and v is of order 1. Without loss of generality (see above), $uN + 2v \leq 0$ is also assumed to ensure $C_2 > 0$.

For the coordination game, $u > 0$ and $v < 0$, we only need to prove that $2C_1 + C_2$ is less than a quantity of order $N \ln N$. For C_1, we have

$$C_1 = \sum_{i=1}^{N-1}\frac{N^2}{i(N-i)}\frac{1}{g(-\Delta\pi_i)}\exp\left[\sum_{k=1}^{i-1}\ln\left[\frac{g(\Delta\pi_k)}{g(-\Delta\pi_k)}\right]\right]$$
$$< \sum_{i=1}^{N-1}\frac{N^2}{i(N-i)}\frac{1}{g(-\Delta\pi_N)}\exp\left[\sum_{k=1}^{i-1}\ln\left[\frac{g(\Delta\pi_k)}{g(-\Delta\pi_k)}\right]\right]$$
(C5)

By Lagrange mean value theorem, for every $1 \leq k \leq N-1$

there exists $\xi_k \in [0,1]$, s.t.

$$
\ln\left[g\left(\Delta\pi_k\right)\right] - \ln\left[g\left(-\Delta\pi_k\right)\right]
$$
$$
= uN\frac{g'(uN\xi_k + v)}{g(uN\xi_k + v)}\left(\Delta\pi_k - (-\Delta\pi_k)\right)
$$
$$
\leq 2uN\frac{M}{g(v)}\Delta\pi_k \tag{C6}
$$

where M is the maximum of $g'(x)$ for $x \in [v, uN+v]$. Since v and $uN+v$ are of order 1, M only depends on the imitation function and payoff entries rather than the population size N for large N. Thus we can consider it to be of order 1 in what concerns the scaling of N. On the other hand, since $g'(x)$ is continuous as we assume, there exists $y^* \in [0,1]$ such that $M = g'(y^*) > 0$. Therefore, $uN\frac{M}{g(v)} > 0$ becomes independent of N for large N. This implies

$$
C_1 < \sum_{i=1}^{N-1}\frac{N^2}{i(N-i)}\frac{1}{g\left(-\Delta\pi_N\right)}\exp\left[2uN\frac{M}{g(v)}\sum_{k=1}^{i-1}\Delta\pi_k\right] \tag{C7}
$$

Therefore, it degenerates to Eq. (B12) for coordination game of the Fermi process. Following the proof therein, finally we arrived at

$$
C_1 < 2\frac{1}{g\left(-\Delta\pi_N\right)}NH_{N-1}. \tag{C8}
$$

Since $g(-\Delta\pi_N) = g(-uN - v)$ is only dependent on the imitation function and the payoff entries, it is independent of N. Thus, C_1 is smaller that a quantity of order $N\ln N$.

Next, we consider C_2. We have

$$
C_2 = \exp\underbrace{\left[\sum_{k=1}^{N-1}\ln\left[\frac{g(\Delta\pi_k)}{g(-\Delta\pi_k)}\right]\right]}_{D_1}
$$
$$
\underbrace{\sum_{k=1}^{N-1}\frac{N}{N-k}\left(\frac{1}{g(\Delta\pi_{N-k})} - \frac{1}{g(-\Delta\pi_k)}\right)}_{D_2}, \tag{C9}
$$

which is a product of $\exp[D_1]$ and D_2. For D_1, we have

$$
D_1 = \sum_{k=1}^{N-1}\ln\left[\frac{g(\Delta\pi_k)}{g(-\Delta\pi_k)}\right]
$$
$$
= \sum_{k=1}^{N-1}\ln\left[g(\Delta\pi_k)\right] - \sum_{k=1}^{N-1}\ln\left[g(-\Delta\pi_k)\right]
$$
$$
= \sum_{k=1}^{N-1}\ln\left[g(\Delta\pi_k)\right] - \sum_{k=1}^{N-1}\ln\left[g(-\Delta\pi_{N-k})\right]
$$
$$
= \sum_{k=1}^{N-1}\left(\ln\left[g(\Delta\pi_k)\right] - \ln\left[g(-\Delta\pi_{N-k})\right]\right) \tag{C10}
$$

Again, by Lagrange mean value theorem, for every $1 \leq k \leq N-1$, there exists $\zeta_k \in [0,1]$, s.t.

$$
\ln\left[g\left(\Delta\pi_k\right)\right] - \ln\left[g\left(-\Delta\pi_{N-k}\right)\right]
$$
$$
= uN\frac{g'(uN\zeta_k + v)}{g(uN\zeta_k + v)}\left(\Delta\pi_k - (-\Delta\pi_{N-k})\right)
$$
$$
\leq uN\frac{M}{g(v)}\left(uN + 2v\right) \tag{C11}
$$

where $M > 0$ is the maximum of $g'(x)$ on $[v, uN+v]$ as defined above. Thus we have

$$
\sum_{k=1}^{N-1}\ln\left[\frac{g(\Delta\pi_k)}{g(-\Delta\pi_k)}\right] < u(N-1)N\frac{M}{g(v)}\left(uN + 2v\right) \tag{C12}
$$

Remembering that $uN + 2v$ is negative and of order 1, $u(N-1)N\frac{M}{g(v)}\left(uN + 2v\right)$ is smaller than zero and of order N for large N. Therefore, $\exp\left[\sum_{k=1}^{N-1}\ln\left[\frac{g(\Delta\pi_k)}{g(-\Delta\pi_k)}\right]\right]$ is smaller that a quantity of order $\exp[-N]$.

For D_2, since $u > 0$, $\Delta\pi_k$ is increasing with k. In addition, $g(x)$ is increasing, we have

$$
\frac{1}{g(+\Delta\pi_{N-k})} - \frac{1}{g(-\Delta\pi_k)} = \frac{g(-\Delta\pi_k) - g(+\Delta\pi_{N-k})}{g(-\Delta\pi_k)g(+\Delta\pi_{N-k})}
$$
$$
< \frac{g(-\Delta\pi_k) - g(+\Delta\pi_{N-k})}{g(-\Delta\pi_N)g(+\Delta\pi_0)} \tag{C13}
$$

By Lagrange mean value theorem, there exists $\eta_k \in [0,1]$ s.t.

$$
g\left(-\Delta\pi_k\right) - g(\Delta\pi_{N-k})
$$
$$
= g'\left(-\Delta\pi_k + \eta_k\left(-\Delta\pi_k - \Delta\pi_{N-k}\right)\right)\left(-\Delta\pi_k - \Delta\pi_{N-k}\right)
$$
$$
< -H\left(uN + 2v\right) \tag{C14}
$$

where $H > 0$ is the maximum of $g'(x)$ on $[-v, +v]$, where $\Delta\pi_k$ and $-\Delta\pi_k$ lie. In analogy to previous discussion, it is independent of N when N is large. Thus we have

$$
\frac{1}{g(+\Delta\pi_{N-k})} - \frac{1}{g(-\Delta\pi_k)} < \frac{-H\left(uN + 2v\right)}{g(-uN - v)g(v)} \tag{C15}
$$

Further, we have

$$
\sum_{k=1}^{N-1}\frac{N}{N-k}\left(\frac{1}{g(+\Delta\pi_{N-k})} - \frac{1}{g(-\Delta\pi_k)}\right)
$$
$$
< \left(\frac{-H\left(uN + 2v\right)}{g(-uN - v)g(v)}\right)\sum_{k=1}^{N-1}\frac{N}{N-k}
$$
$$
= \left(\frac{-H\left(uN + 2v\right)}{g(-uN - v)g(v)}\right)NH_{N-1} \tag{C16}
$$

Note that $\frac{-H(uN+2v)}{g(-uN-v)g(v)}$ positive and independent of N for large N. D_2 is smaller than a quantity of order $N\ln N$. Finally, $C_2 = \exp[D_1]D_2$ is of order $N\ln N\exp[-N]$; it becomes infinitely small for large N. This means that the

scaling of $2C_1 + C_2$ is determined by the scaling of C_1 and thus the critical mutation rate scales as $N \ln N$.

For the coexistence game and dominant game, the procedure of the proof for general imitation function is also identical to that of the coordination game: For C_1, we make use of Lagrange mean value theorem to establish a relationship

between $\ln\left[\frac{g(\Delta\pi_k)}{g(-\Delta\pi_k)}\right]$ and $\Delta\pi_k$, then it can be deduced by the proof the corresponding game for the Fermi process. For C_2, for all games, it is infinitely small for large population size. The proof is identical with that of the coordination game for general imitation function.

[1] Antal T, Scheuring I (2006) Fixation of strategies for an evolutionary game in finite populations. Bull Math Biol 68:1923–1944

[2] Antal T, Nowak MA, Traulsen A (2009) Strategy abundance in 2x2 games for arbitrary mutation rates. J Theor Biol 257:340–344, doi:10.1016/j.jtbi.2008.11.023

[3] Antal T, Ohtsuki H, Wakeley J, Taylor PD, Nowak MA (2009) Evolution of cooperation by phenotypic similarity. Proc Natl Acad Sci USA 106:8597–8600

[4] Antal T, Traulsen A, Ohtsuki H, Tarnita CE, Nowak MA (2009) Mutation-selection equilibrium in games with multiple strategies. J Theor Biol 258:614–622, doi:10.1016/j.jtbi.2009.02.010

[5] Blume LE (1993) The statistical mechanics of strategic interaction. Games and Economic Behavior 5:387–424

[6] Brémaud P (1999) Markov chains: Gibbs fields, Monte Carlo simulation, and queues. Springer, Verlag

[7] Chalub FA, Souza MO (2009) From discrete to continuous evolution models: A unifying approach to drift-diffusion and replicator dynamics. Theoretical Population Biology 76:268–277

[8] Claussen JC, Traulsen A (2005) Non-Gaussian fluctuations arising from finite populations: Exact results for the evolutionary Moran process. Phys Rev E 71:025,101(R)

[9] Crow JF, Kimura M (1970) An Introduction to Population Genetics Theory. Harper and Row, New York, NY

[10] Durrett R (1996) Probability: theory and examples. Citeseer

[11] Ewens WJ (2004) Mathematical Population Genetics. Springer, NY

[12] Foster D, Young P (1990) Stochastic evolutionary game dynamics. Theo Pop Biol 38:219–232

[13] Fudenberg D, Harris C (1992) Evolutionary dynamics with aggregate shocks. J Econ Theory 57:420–441

[14] Fudenberg D, Imhof LA (2006) Imitation process with small mutations. J Econ Theory 131:251–262

[15] Fudenberg D, Imhof LA (2008) Monotone imitation dynamics in large populations. J Econ Theory 140:229–245

[16] Gardiner CW (2004) Handbook of Stochastic Methods, 3rd edn. Springer, NY

[17] Hauert C, Traulsen A, Brandt H, Nowak MA, Sigmund K (2007) Via freedom to coercion: the emergence of costly punishment. Science 316:1905–1907

[18] Imhof LA, Fudenberg D, Nowak MA (2005) Evolutionary cycles of cooperation and defection. Proc Natl Acad Sci USA 102:10,797–10,800

[19] Kallenberg O (2002) Foundations of modern probability. Springer, Verlag

[20] Kampen NGv (1997) Stochastic Processes in Physics and Chemistry, 2nd edn. Elsevier, Amsterdam

[21] Kandori M, Mailath GJ, Rob R (1993) Learning, mutation, and long run equilibria in games. Econometrica 61:29–56

[22] Karlin S, Taylor HMA (1975) A First Course in Stochastic Processes, 2nd edn. Academic, London

[23] Levin DA, Peres Y, L Wilmer E (2009) Markov chains and mixing times. American Mathematical Society

[24] Nowak MA (2006) Evolutionary Dynamics. Harvard University Press, Cambridge, MA

[25] Nowak MA, Sasaki A, Taylor C, Fudenberg D (2004) Emergence of cooperation and evolutionary stability in finite populations. Nature 428:646–650

[26] Ohtsuki H, Hauert C, Lieberman E, Nowak MA (2006) A simple rule for the evolution of cooperation on graphs. Nature 441:502–505

[27] Sigmund K, De Silva H, Traulsen A, Hauert C (2010) Social learning promotes institutions for governing the commons. Nature 466:861–863, doi:10.1038/nature09203

[28] Szabó G, Tőke C (1998) Evolutionary Prisoner's Dilemma game on a square lattice. Phys Rev E 58:69

[29] Tarnita CE, Ohtsuki H, Antal T, Fu F, Nowak MA (2009) Strategy selection in structured populations. J Theor Biol 259:570–581, doi:10.1016/j.jtbi.2009.03.035

[30] Taylor C, Fudenberg D, Sasaki A, Nowak MA (2004) Evolutionary game dynamics in finite populations. Bull Math Biol 66:1621–1644

[31] Traulsen A, Nowak MA, Pacheco JM (2006) Stochastic dynamics of invasion and fixation. Phys Rev E 74:011,909

[32] Traulsen A, Shoresh N, Nowak MA (2008) Analytical results for individual and group selection of any intensity. Bull Math Biol 70:1410–1424, doi:10.1007/s11538-008-9305-6

[33] Traulsen A, Hauert C, De Silva H, Nowak MA, Sigmund K (2009) Exploration dynamics in evolutionary games. Proc Natl Acad Sci USA 106:709–712, doi:10.1073/pnas.0808450106

[34] Van Segbroeck S, Santos FC, Lenaerts T, Pacheco JM (2009) Reacting differently to adverse ties promotes cooperation in social networks. Phys Rev Lett 102:058,105

[35] Wang J, Wu B, Chen X, Wang L (2010) Evolutionary dynamics of public goods games with diverse contributions in finite populations. Phys Rev E 81:056,103

[36] Wu B, Altrock PM, Wang L, Traulsen A (2010) Universality of weak selection. Phys Rev E 82:046,106

4.3 Mutation selection equilibrium in evolutionary games.

Multiplayer games are the representations of many social dilemmas. Even for multiplayer games we can use the replicator equation with a complicated payoff structure to derive the time evolution of the strategies. This includes only the effect of selection. Including mutations in a given evolutionary game is relatively easy if we assume the mutation rate to be very small. This allows us to derive important quantities such as fixation probabilities with relative mathematical ease. For high mutation rates the concept of fixation itself becomes problematic and so does fixation probability. Even with high mutation rates, if a system continues to evolve for a long time then we can calculate the average frequency of a strategy. This average frequency of a strategy in the stationary distribution (hereafter termed as abundance) for arbitrary mutation rates has been calculated previously by Antal et al. (2009a,b,c). The procedure can even be applied in some cases when a population is structured (Tarnita et al., 2009). The analysis has remained possible only for two player games.

We develop an approach for estimating the abundance for multiple players and multiple strategies.. The theory hinges on the calculation of the following term, the average change in the frequency of strategy k under weak selection ($\delta \ll 1$),

$$\langle \Delta x_k^{sel} \rangle_\delta.$$

Once we know this then we can add the effect of mutations (u) which gives us the abundance of a strategy (here strategy k) in the mutation-selection equilibrium (Antal et al., 2009a,b,c) as,

$$\langle x_k \rangle_\delta = \frac{1}{n} + N \frac{1-u}{u} \langle \Delta x_k^{sel} \rangle_\delta \qquad \boxed{4.2}$$

For the calculations we employ tools from coalescence theory (Kingman, 1982a,b,c, 2000; Wakeley, 2008). Small mutation rates make sense in genetical sense but for cultural traits such as fashion or plastic behaviour, high mutation rates are more realistic (Traulsen et al., 2010; Grujic et al., 2010). The theory developed herein can be used for a variety of applications ranging from finding the abundance of alleles in an allelic polymorphism to the best strategy in a social setting.
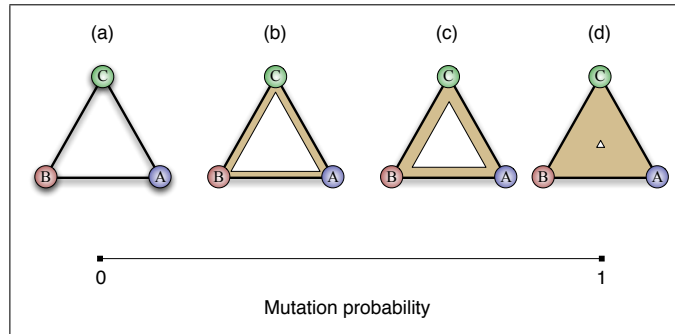
Figure 4.3: **Available space in the simplex with increasing mutation probability.** In infinitely large populations as mutation probability increases, the area where a stable coexistence is possible decreases. (a) If a population is at a certain homogeneous state, all A, all B or all C then it will stay there forever. For very low mutation rate if a system is in a homogeneous state then occasionally a mutant arises and the edges of the simplex are explored. (b) For sufficiently high mutation rates the system leaves the edges. the possible space for a stable coexistence becomes constricted (white interior). (c) As mutation probability increases the system is driven towards a state of eternal heterogeneity where all strategies coexist. (d) For a mutation probability of 1 all three strategies coexist at equal frequencies in the center of the simplex at $\left(\frac{1}{3}, \frac{1}{3}, \frac{1}{3}\right)$.

4.3.1 Publication: Mutation selection equilibrium in multiplayer games with multiple strategies

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Submitted

Mutation-selection equilibrium in evolutionary games with multiple players and multiple strategies

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Evolutionary game theory is an abstract and simple, but very powerful way to model evolutionary dynamics. Even complex biological phenomena can sometimes be abstracted to simple two player games. But often, the interaction between several parties determines evolutionary success. In this case, one can resort to multiplayer games, which are inherently more complicated than the usual two-player games, yet they can yield simple results. In this manuscript we derive the composition of a multiplayer multiple strategy system in the mutation-selection equilibrium. This results in a simple expression which can be obtained by recursions using coalescence theory. This approach can be modified to suit a variety of contexts, e.g. to find the equilibrial frequencies of a finite number of alleles in a polymorphism or the equilibrial frequencies of different strategies in a social dilemma in a cultural context.

Keywords: multi-player game theory, multiple strategies, coalescence theory, mutation-selection equilibrium

I. INTRODUCTION

Game theory was originally developed in the field of economics to study strategic interactions amongst humans [48]. The "agents" who play against each other have a set of "strategies" to choose from. The payoff which an agent gets depends on its own strategy and the strategy of the opponent. A player can decide which strategy to play against an opponent of a given strategy.

In evolutionary game theory players are born with fixed strategies instead, [25] which are considered to be inherited traits. As usual, we assume a population game in which every player effectively plays against the average opponent. The success of a strategy depends on the number of players of that strategy and also the number of players with other strategies. A classical example is the Lotka-Volterra equation [16, 24, 47]. If the number of wolves increases then the numbers of hares will decrease in turn leading to a decrease in the number of wolves. Evolutionary game dynamics studies the change in the frequencies of the strategies [28], which depends on mutation selection and drift.

A recurrent and obvious question asked in the study of games is which is the best strategy? Assuming an infinitely large population we can approach this question by the traditional replicator dynamics [16]. The frequency of a strategy will increase if its average payoff is greater than the average payoff of the whole population. That is, if the individuals of a particular strategy are doing better on average than the individuals of other strategies then that strategy spreads. The average payoff of a strategy is also dependent on the frequency of the strategy. For finite populations one must resort to stochastic descriptions [7, 29, 37]. One important quantity is the fixation probability. Consider two strategies A and B in a population of size N. Let the population be almost homogenous for B with only a single A. If there is no fitness difference amongst the strategies, i.e. selection is neutral, then the probability that the A individual will take over the entire population is $1/N$. If this probability is greater than $1/N$ we say that strategy A is favoured by selection. When there are multiple strategies in the population, then a pairwise comparison between the fixation probabilities of all the strategies will reveal which is the most abundant strategy [9, 12, 13, 38, 45]. This analysis requires the assumption of low mutation rates.

When mutations become more frequent then the concept of fixation itself is problematic and hence also that of fixation probability. In such a case we resort to the average frequency of a strategy which is maintained at the mutation-selection balance. This has been termed as the abundance of a strategy [3].

Consider n strategies which are effectively neutral against each other. In such a case the abundance of all the strategies in the stationary state will be just $1/n$. Usually there are fitness differences between the strategies. In such a case if the abundance of a strategy is greater than that of all the other strategies then we can say it is favoured under the effects of mutation, selection and drift. Hence for n strategies, the kth strategy will be favoured if the abundance of k is greater than $1/n$. Calculating the abundance of a strategy is a non-trivial exercise even when assuming weak selection. [3] have developed such an approach based on coalescence theory for the case of two player games and n strategies. Under certain conditions and weak selection, one can calculate the most abundant strategy for arbitrary mutation rates even in structured populations [2, 42, 43] and bimatrix games [31].

Usually two players interactions are studied in evolutionary game theory. The analysis of Antal et al. also is for two player games. The interactions which we usually use as examples in evolutionary game theory are in general multiplayer interactions making the systems non-linear [30]. Evolutionary dynamics of multi-player games has received growing interest in the recent years [10–

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12, 22, 26, 32, 33, 36, 39, 46]. We extend the approach developed by [3] for two player games and multiple strategies to multi-player population games. We show that in the limit of weak selection it is possible to calculate analytical results for n strategies and d players for arbitrary mutation rates. For a three player game the mathematical analysis is described in detail. It is followed by an example with simulations supporting the analytical result. Lastly we discuss how the methodology can be extended for d player games and argue that a general approach is possible, but tedious.

II. ABUNDANCES IN THE STATIONARY STATE FOR THREE PLAYER GAMES

[3] have developed an approach to find the abundances of n strategies in a two player game ($d = 2$). For a two player game even with n strategies, the payoff values can be represented in the usual payoff matrix form. They can be represented as quantities with two indices, $a_{k,h}$. We increase the complexity first by adding one more player ($d = 3$). This adds another index for the third player's strategy set, $a_{k,h,i}$. To calculate the average change in the frequency of a strategy we thus need to take into account this payoff 'tensor'.

We calculate the abundance of a strategy at the mutation-selection equilibrium. We begin by checking if there is a change in the frequency of a strategy, say k on average, due to selection. The average change under weak selection is given by

$$\langle \Delta x_k^{sel} \rangle_\delta = \frac{\delta}{N} \left(\sum_{h,i} a_{k,h,i} \langle x_k x_h x_i \rangle - \sum_{h,i,j} a_{h,i,j} \langle x_k x_h x_i x_j \rangle \right),$$
(1)

where the angular brackets denote the average in the neutral stationary state. The δ (selection intensity) as a lower index on the left hand side, however, denotes that the average is obtained under (weak) selection. If we pick three individuals in the neutral stationary state, then the probability of the first one to have strategy k, the next one h and the last i, is given by the angular brackets in the first sum, $\langle x_k x_h x_i \rangle$. Furthermore, $a_{k,h,i}$ denotes the payoff values obtained by a strategy k player when pitted against two other players of strategy h and i. For n strategies the sums run from 1 to n. This equation is the special case of a $d = 3$ player game. The derivation for arbitrary d is given in A. The above equation is similar to the replicator equation, which is also based on the difference between the average payoff of a strategy and the average payoff of the population, but as we will see below here the averages on the right hand side also include mutations.

To incorporate mutations in the process, we write the total expected change due to mutation and selection as

$$\Delta x_k^{tot} = \Delta x_k^{sel}(1 - u) + \frac{u}{N} \left(\frac{1}{n} - x_k \right).$$
(2)

The first term is the change in the frequency in the absence of mutation. In presence of mutations, the second term shows that the frequency can increase by $1/(nN)$ by random mutation and decrease by x_k/N due to random death. A mutation means that with a certain probability u, the strategy k can mutate to any of the n strategies.

We are interested in the abundance of a strategy in the stationary state. In the stationary state, the average change in frequency is zero, $\langle \Delta x_k^{tot} \rangle_\delta = 0$, as the mutations are balanced by selection. Averaging Equation 2 under weak selection thus gives us

$$\langle x_k \rangle_\delta = \frac{1}{n} + N \frac{1-u}{u} \langle \Delta x_k^{sel} \rangle_\delta.$$
(3)

This is our quantity of interest, the abundance of a strategy when the system has reached the stationary state. For $d = 2$ player games, this quantity is given by [3]. For the abundance of a strategy to be greater than neutral, $\langle x_k \rangle_\delta > \frac{1}{n}$, the change in frequency in the stationary state due to selection must be greater than zero, $\langle \Delta x_k^{sel} \rangle_\delta > 0$.

Thus, we need to resolve the right hand side of Equation 1. Consider the first term in the brackets. In the neutral stationary state the number of combinations in the sums reduces due to symmetry, e.g. $\langle x_i x_j x_j \rangle = \langle x_j x_i x_j \rangle = \langle x_j x_j x_i \rangle$. Hence, we need to calculate only three different terms, $\langle x_1 x_1 x_1 \rangle$, $\langle x_1 x_2 x_2 \rangle$ and $\langle x_1 x_2 x_3 \rangle$. Also for d player games, the terms in the sums are reduced. For the second term in the brackets we need to calculate five different types of averages, $\langle x_1 x_1 x_1 x_1 \rangle$, $\langle x_1 x_2 x_2 x_2 \rangle$, $\langle x_1 x_1 x_2 x_2 \rangle$, $\langle x_1 x_1 x_2 x_3 \rangle$ and $\langle x_1 x_2 x_3 x_4 \rangle$. These averages are derived in the B. Using an approach from coalescence theory, we derive s_i, the probability that i individuals chosen from the stationary state all have the same strategy. Hence s_4 is the probability that four individuals chosen in the stationary state all have the same strategy. If there are in all n strategies, then the probability that all have exactly strategy 1 is s_4/n. Hence $\langle x_1 x_1 x_1 x_1 \rangle = \langle x_2 x_2 x_2 x_2 \rangle = \dots = \langle x_n x_n x_n x_n \rangle = s_4/n$. Conversely, $\bar{s}_i$ is the probability that if we choose i individuals in the stationary state, each has a unique strategy. Knowing these averages helps us resolve Eq. (1),

$$\langle \Delta x_k^{sel} \rangle_\delta = \frac{\delta \mu (L_k + M_k \mu + H_k \mu^2)}{N n^4 (1 + \mu)(2 + \mu)(3 + \mu)}$$
(4)

where $\mu = Nu$ and L_k, M_k and H_k are functions consisting only of the number of strategies n and the payoff values $a_{k,h,i}$ (see B). Using this and evaluating Eq. (3) gives us the abundance of the kth strategy.

$$\langle x_k \rangle_\delta = \frac{1}{n} \left[1 + \frac{\delta(N - \mu)(L_k + M_k \mu + H_k \mu^2)}{n^3 (1 + \mu)(2 + \mu)(3 + \mu)} \right].$$
(5)

This expression is valid for large population sizes, $N\delta \ll 1$ and any constant $\mu = Nu$.

We arrive at the result with an implicit assumption that there are at least four strategies. For $n \leq d$, each player cannot have a unique strategy and hence we need to set the corresponding terms to zero (see B). If there are less than $n = 4$ strategies then $\bar{s}_4$ vanishes. This does not affect

our general result as the affected terms in L_k, M_k and H_k simply vanish. In general Eq. (5) is valid for all of the n strategies.

FIG. 1. The average change in the frequency of strategy k due to selection, $\langle \Delta x_k^{sel} \rangle_\delta$ for a three player game. Notice first the similarity to the replicator equation where also we look at how a strategy is faring compared to the population. The first term in the bracket is analogous to the average fitness of strategy k. If we pick three individuals in the stationary state, then the probability that the first one has strategy k, second h and the third i is given by $\langle x_k x_h x_i \rangle$ (dashed box). Even for n strategies there are only three possible combinations, either all can have the same strategy, a pair has the same strategy or all three have different strategies. These probabilities were calculated by [3]. The s_i's appearing in the averages are the probabilities that if we choose i individuals from the stationary distribution then they all have the same strategy. The second term in the bracket is analogous to the average fitness of the population in the stationary state. For this we need to pick four individuals and look for all the different combinations (solid box). For n strategies, five combinations can explain all the different configurations. These range from all the individuals having the same strategy $\langle x_1 x_1 x_1 x_1 \rangle$ to all having a different strategy $\langle x_1 x_2 x_3 x_4 \rangle$ (B). For the latter, we calculate $\bar{s}_i$, the probability that we choose i individuals from the stationary distribution and each of them has a unique strategy. For a general d player game we need to pick d individuals for the first term and $d+1$ for the second.

III. AN EXAMPLE FOR THREE PLAYER GAMES WITH THREE STRATEGIES

To illustrate the analytical approach we explore an evolutionary three player game with three strategies A, B and C. Let our focal individual play strategy A. The other two player can play any of the three strategies. This can lead to a potential complication. Consider the combinations AAB or ABA. If the order of players does not matter, then both these configurations give the same payoffs but if they do matter then we need to consider them separately. Here we assume random matching, and hence the order drops out

(e.g. AAB and ABA are equally likely). We consider an arbitrary game as denoted in Table I.

We need to calculate the average change in the frequency of strategy A due to selection, i.e. Eq. (1). We denote the co-efficients of the averages in the first sum by α_1, α_2 and α_3. Hence for example, $\alpha_3 = a_{A,B,C} + a_{A,C,B}$. Similarly for the second sum we have β_1 to β_4 (Note that $\beta_1 = \alpha_1 = a_{A,A,A}$). Thus we have,

$$\sum_{h,i} a_{A,h,i} \langle x_A x_h x_i \rangle = \alpha_1 \langle x_A x_A x_A \rangle + \alpha_2 \langle x_A x_B x_B \rangle + \alpha_3 \langle x_A x_B x_C \rangle \quad (6)$$

and

$$\sum_{h,i,j} a_{h,i,j} \langle x_A x_h x_i x_j \rangle = \beta_1 \langle x_A x_A x_A x_A \rangle + \beta_2 \langle x_A x_B x_B x_B \rangle$$
$$+ \beta_3 \langle x_A x_A x_B x_B \rangle + \beta_4 \langle x_A x_A x_B x_C \rangle. \quad (7)$$

Note that the term $\langle x_A x_B x_C x_D \rangle$ which would appear with a factor β_5, does not appear, as we have only three strategies and thus $\bar{s}_4 = 0$. This also alters the definition of $\langle x_A x_A x_B x_C \rangle$ and $\langle x_A x_A x_B x_B \rangle$ (see Figure 1, all terms dependent on $\bar{s}_4$ are affected).

We know the form of L_k, M_k and H_k from B as,

$$L_k = n^2 \left[2\alpha_1(n-1) + 3\alpha_2 - 2\beta_2 - \beta_3 \right] \quad (8)$$
$$M_k = n \left[(3n-3)\alpha_1 + (n+3)\alpha_2 + 3\alpha_3 - 3\beta_2 - 2\beta_3 - \beta_4 \right] \quad (9)$$
$$H_k = n(\alpha_1 + \alpha_2 + \alpha_3) - (\beta_1 + \beta_2 + \beta_3 + \beta_4 + \beta_5) \quad (10)$$

With L_k, M_k and H_k as above, Eq. (5) for $n = 3$ reduces to,

$$\langle x_A \rangle_\delta = \frac{1}{3} \left[1 + \frac{\delta(N-\mu)(L_k + M_k\mu + H_k\mu^2)}{27(1+\mu)(2+\mu)(3+\mu)} \right]. \quad (11)$$

This gives us the abundance of strategy A at the mutation selection equilibrium. Repeating the procedure for strategies B and C gives the analytical lines in Figure 2. Although the analytical solutions are valid for large population sizes only, we still see a good agreement between the simulation and theory results, even for a population size as small as 60.

IV. ABUNDANCES IN $d > 3$ PLAYER GAMES.

We can repeat the whole procedure for $d = 4$ player games with n strategies. The formula for the abundance remains the same, Eq. (3), but the average change due to selection, Eq. (1), becomes more complicated. We need to add an index in the sums,

$$\langle \Delta x_k^{sel} \rangle_\delta = \frac{\delta}{N} \Big(\sum_{l,m,n} a_{k,l,m,n} \langle x_k x_l x_m x_n \rangle$$
$$- \sum_{l,m,n,o} a_{l,m,n,o} \langle x_k x_l x_m x_n x_o \rangle \Big) \quad (12)$$

The first term is comparatively simple as we already know all the different ways of picking four individuals. For the second

Weights (Total 9)	1	2	2	1	2	1
	AA	AB	AC	BB	BC	CC
A	2	1	2	1	1	3
B	3	1	1	1	1	1
C	1	5	1	1	1	2

TABLE I. An example payoff table for $d = 3$ and $n = 3$. Consider a three player game with three strategies A, B and C. The strategy of the focal individual is in the column on the left. For example the payoff received by a C individual when playing in a configuration of CAB is 5. From the focal individual's point of view there are two ways of this configuration CAB and CBA as it is twice as likely as compared to e.g. CAA. Hence we weight that payoff value by 2 when calculating the average payoff of strategy C.
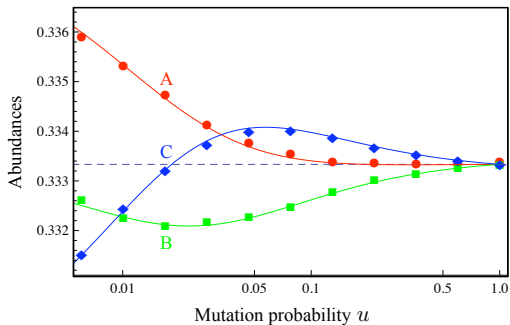
FIG. 2. For a three player game with three strategies $(d = 3; n = 3)$ we plot the average abundances of the three strategies as a function of the mutation probability u. The payoff table from Table I is used. The lines are the solutions of Eq. (3) and the symbols are the simulation results for the three strategies. Although the calculations are valid for large populations we see a good agreement even for a population size of $N = 60$ (selection intensity $\delta = 0.001$, simulation points are obtained averaging over 100 independent runs, each over 10^8 time steps after a transient phase of N time steps).

term we need to know the different possible combinations of strategies when picking five individuals from the neutral stationary state.

For d players and n strategies we can construct an expression analogous to Equation. 1. Consider for example the strategies played by d individuals denoted by, $r_1, r_2, r_3 \ldots r_d$. Note that each of these can be a strategy from the strategy set $1, 2, 3 \ldots n$. Let p be our strategy of interest. Then the expression for the change of strategy p

due to selection is given by,

$$\langle \Delta x_p^{sel} \rangle_\delta = \frac{\delta}{N} \Big(\sum_{r_2, \ldots r_d} a_{p, r_2, \ldots r_d} \langle x_p x_{r_2} x_{r_3} \ldots x_{r_d} \rangle$$
$$- \sum_{r_1, \ldots r_d} a_{r_1, r_2, \ldots r_d} \langle x_p x_{r_1} x_{r_2} \ldots x_{r_d} \rangle \Big)$$
(13)

where the sums range as usual from 1 to n (A). Solving this and plugging it in Eq. (3) gives the generalized expression for the abundance of strategy p for an n strategy, d player game. We see that in the first sum the averages are for choosing d players but for the second its $d + 1$. Hence we need to calculate the probabilities of the form s_{d+1}, but s_{d+1} depends on s_d. Thus we have to solve the expression recursively e.g. for $d = 6$, we will need to pick 7 players at most and we must solve the expression for $d = 2, 3, 4, 5, 6$ before (but $d = 2$ has been solved by [3] and $d = 3$ in this manuscript). As d increases calculating s_{d+1} is not enough and we will also need to calculate terms such as $\bar{s}_{d+1}$ which is already the case for $d = 3$.

V. SPECIAL CASE: TWO STRATEGIES, n = 2

Games with two strategies have been very well studied. In two player games with two strategies, one strategy can replace another with a higher probability if the sum of its payoff values is greater than the sum of the payoff values of the other strategy. This is valid under small mutation rates for deterministic evolutionary dynamics [17]. The result also holds for for different dynamical regimes under specific limits of selection intensity and mutation rates [1, 8, 29]. Recently it has been shown that this result can be generalized for d player games with two strategies [10, 22].

Hence the condition which we find for d player games should be identical to $L_k > 0$ derived in this manuscript for d players. We check this for $d = 3$,

$$L_k = 2^2 \left[2\alpha_1(2 - 1) + 3\alpha_2 - 2\beta_2 - \beta_3 \right] \quad (14)$$
$$= 4[2a_{1,1,1} + 3(a_{1,1,2} + a_{1,2,1} + a_{1,2,2})$$
$$- 2(a_{1,1,2} + a_{1,2,1} + a_{2,1,1} + a_{2,2,2})$$
$$- a_{1,2,2} - a_{2,1,2} - a_{2,2,1}] \quad (15)$$

Thus $L_k > 0$ is equivalent to,

$$2a_{1,1,1} + a_{1,1,2} + a_{1,2,1} + 2a_{1,2,2} > 2a_{2,1,1} + a_{2,1,2} + a_{2,2,1} + 2a_{2,2,2}$$
(16)

If we assume that the order of players does not matter then we have $a_{1,1,2} = a_{1,2,1}$ and $a_{2,1,2} = a_{2,2,1}$. This yields

$$a_{1,1,1} + a_{1,1,2} + a_{1,2,2} > a_{2,1,1} + a_{2,1,2} + a_{2,2,2}, \quad (17)$$

which is exactly the condition that has been obtained previously using different methods and different notation by [22], see also [10].

VI. DISCUSSION

Public goods games are often used as examples of multi-player games. In the beginning there were the cooperators and defectors. Then came the punishers and then the loners [11, 41]. Now we talk about second order punishers, pool and peer punishers [38] and more. Studying these systems for small mutation rates and arbitrary selection intensity is almost becoming standard [9, 12, 13, 38, 45]. In the limit of weak selection our method allows to find out which strategy is most abundant for arbitrary mutation rates.

Yet, another important aspect of most social dilemmas and many other biological examples is that they involve multiple-players [4, 23, 27, 40]. [2, 3] have made use of the coalescence approach to characterize the mutation process under neutrality and then apply it under weak selection to two player games with n strategies ($n \times n$). Here we extend the approach to d player games with n strategies.

We give an example for an $n \times n \times n$ game and derive the analogous expressions for abundances of the strategies for arbitrary mutation rates. When we increase the number of players to d the payoff matrix becomes a d dimensional object. We run into the problem of whether the order of players matters or not. Either way this does not influence our results but notation-wise it is easier if the order of players does not matter. Adding a new player adds a new index to the payoff values. For calculating the abundance we need to assess Eq. (13). For solving the two sums in Eq. (13) we need to know the different combinations of choosing d players and $d+1$ players from the neutral coalescent stationary state.

To illustrate the complexity of the situation take for example s_4. This is the probability that four chosen individual have the same strategy. In C we have shown that deriving s_4 depends on s_3 which depends on s_2 in turn. Hence in general to derive s_{d+1}, we need to know $s_d, s_{d-1}, s_{d-2} \ldots, s_2$. In addition, $\bar{s}_{d+1}$ is the probability that $d+1$ individuals chosen in the stationary state all have different strategies. If $n < d$ then $\bar{s}_{d+1}$ is zero and hence the terms dependent on it need to be recalculated. After recalculation the terms which are affected either vanish or are automatically adjusted such that the result can be written again in the form for L_k's, M_k's and H_k's. However, for a d player game, $d-2$ intermediate terms such as M_k appear.

For two strategies, L_k reduces to the general condition derived in [10, 22] and again holds for arbitrary d. For H_k for any number of strategies we conjecture that it will always be of the form $n\left(\sum_{r_2,\ldots r_d} a_{p,r_2,\ldots r_d}\right) - \left(\sum_{r_1,r_2,\ldots r_d} a_{r_1,r_2,\ldots r_d}\right)$ from Eq. (13). Addressing a generalization for d player games is not a fundamental problem of the approach but requires a tedious recursive effort and poses a notational challenge. At the coalescence level the problem rests on permutations and combinations.

Arbitrary mutation rates can be interpreted in different ways. In the social learning context [44] it can be thought of as the exploration rate where the players experiment with different strategies. Small mutation rates are most relevant

in population genetic contexts where the strategies can be thought of as alleles. While most people think of evolutionary game theory as a phenotypic approach, one can as well consider evolutionary games on the level of genes [5, 14–16, 34, 35]. The abundances of the alleles can be calculated in the limit of neutrality and assuming the infinite alleles model by the Ewens sampling formula. The approach developed herein is not based on the assumption of infinite alleles; the recursions can be performed for any given number of alleles n.

Making use of our approach we can precisely determine the composition of a population with a finite number of different types under weak selection for arbitrary mutation rates. Another convenient way of finding the strategy which performs the best is the limit of small mutation rates. For small mutation rates, the system spends most of its time in a monomorphic state. We can approximate the system by just looking at fixation probabilities of the different types. Our approach illustrates that the interaction of d players is significantly more complex than the usual two player games. General multiplayer games pose exciting challenges way beyond the usual intricacies of public goods games.

Appendix A: Deriving the average change due to selection

We begin the Appendix by first deriving the average change in the frequency of a strategy under selection for an arbitrary number of players (d) and strategies (n). In B, we consider the special case $d = 3$. The more technical calculations based on coalescence theory can be found in Section C.

Let us begin with the simple case of a two player game. The payoff matrix for a two player game, $\mathbf{A}$ with n strategies is an $n \times n$ matrix,

$$
\mathbf{A} = \begin{array}{c} \\ 1 \\ 2 \\ \vdots \\ n \end{array}
\begin{array}{cccc} 1 & 2 & \ldots & n \end{array}
\left(\begin{array}{cccc}
a_{1,1} & a_{1,2} & \ldots & a_{1,n} \\
a_{2,1} & a_{2,2} & \ldots & a_{2,n} \\
\vdots & \vdots & \ddots & \vdots \\
a_{n,1} & a_{n,2} & \ldots & a_{n,n}
\end{array}\right) \tag{A1}
$$

The average fitness of strategy 1 can be written down as,

$$
\mathbf{f}_1 = 1 + \delta\left(\sum_{h=1}^{n} a_{1,h} x_h\right) \tag{A2}
$$

where the leading 1 is the baseline fitness and $\delta > 0$ is the intensity of selection. The variable x_h is the frequency of players with strategy h, $\sum_{h=1}^{n} x_h = 1$. We assume that the δ is so small that the fitness is always positive. Similarly, for

a three player game the payoffs have an additional index. Thus we can write the average fitness of strategy 1 as,

$$\mathbf{f}_1 = 1 + \delta \left(\sum_{h,i} a_{1,h,i} \left(x_h x_i \right) \right) \tag{A3}$$

As usual, the sums run from 1 to n, the number of strategies. Continuing up to d players we now consider $r_2 \ldots r_d$ the strategies of players $2 \ldots d$ as the strategy of one of the players is set to p, i.e. $r_1 = p$. We see that the average payoff of strategy p can be written as,

$$\mathbf{f}_p = 1 + \delta \left(\sum_{r_2,\ldots,r_d} a_{p,r_2,\ldots,r_d} \left(x_{r_2} x_{r_3} \cdots x_{r_d} \right) \right) \tag{A4}$$

The average payoff of the whole population is given by $\mathbf{F}$ as,

$$\mathbf{F} = \sum_{p=1}^{n} x_p \mathbf{f}_p \tag{A5}$$

Now we need to consider the dynamics of the process. The Moran process is used, where in each time-step an individual is chosen proportional to its fitness to reproduce and a randomly chosen individual dies. With probability $1 - u$ the individual chosen for reproduction produces an exact copy as itself, but with probability u, a mutation occurs and the offspring can be any of the n strategies.

If the abundance of a strategy is greater than $1/n$, then it is favoured at the mutation-selection equilibrium. To calculate the abundance of strategy p we begin with the average number of offsprings of an individual of strategy p, which is given by,

$$\omega_p = 1 - \frac{1}{N} + \frac{1}{N} \frac{\mathbf{f}_p}{\mathbf{F}}. \tag{A6}$$

The first term captures the survival of the parent. The second and third terms refer to the random death and fitness proportional reproduction. For $\delta \ll 1$, we have,

$$\omega_p \approx 1 + \frac{\delta}{N} \left[\left(\sum_{r_2,\ldots,r_d} a_{p,r_2,\ldots,r_d} \left(x_{r_2} x_{r_3} \cdots x_{r_d} \right) \right) - \left(\sum_{r_1} x_{r_1} \sum_{r_2,\ldots,r_d} a_{r_1,r_2,\ldots,r_d} \left(x_{r_2} x_{r_3} \cdots x_{r_d} \right) \right) \right] \tag{A7}$$

The change in the frequency of strategy p, x_p, due to selection is given by,

$$\Delta x_p^{sel} = x_p \omega_p - x_p. \tag{A8}$$

The vector $\mathbf{x} = (x_1, \ldots, x_n)$ contains all possible frequency compositions of the system. The system will be in state $\mathbf{x}$ with probability $Q_\delta(\mathbf{x})$. Hence by averaging Δx_p^{sel} in the

leading order of δ we obtain,

$$\langle \Delta x_p^{sel} \rangle \approx \sum_{\mathbf{x}} \Delta x_p^{sel} Q_\delta(\mathbf{x})$$
$$= \delta \sum_{\mathbf{x}} \left(\frac{1}{N} x_p \left[\left(\sum_{r_2,\ldots r_d} a_{p,r_2,\ldots r_d} \left(x_{r_2} x_{r_3} \ldots x_{r_d} \right) \right) \right. \right.$$
$$\left. \left. - \left(\sum_{r_1,r_2,\ldots r_d} a_{r_1,r_2,\ldots r_d} \left(x_{r_1} x_{r_2} x_{r_3} \ldots x_{r_d} \right) \right) \right] \right) Q_\delta(\mathbf{x}) \tag{A9}$$

Thus we reach the expression for the average change in the frequency of strategy p due to selection in the stationary state as,

$$\langle \Delta x_p^{sel} \rangle_\delta = \frac{\delta}{N} \left\langle x_p \left[\left(\sum_{r_2,\ldots r_d} a_{p,r_2,\ldots r_d} \left(x_{r_2} x_{r_3} \ldots x_{r_d} \right) \right) \right. \right.$$
$$\left. \left. - \left(\sum_{r_1,r_2,\ldots r_d} a_{r_1,r_2,\ldots r_d} \left(x_{r_1} x_{r_2} x_{r_3} \ldots x_{r_d} \right) \right) \right] \right\rangle$$
$$= \frac{\delta}{N} \left(\sum_{r_2,\ldots r_d} a_{p,r_2,\ldots r_d} \langle x_p x_{r_2} x_{r_3} \ldots x_{r_d} \rangle \right.$$
$$\left. - \sum_{r_1,r_2,\ldots r_d} a_{r_1,r_2,\ldots r_d} \langle x_p x_{r_1} x_{r_2} x_{r_3} \ldots x_{r_d} \rangle \right) \tag{A10}$$

Notice the form of a replicator like equation in the above terms. We look for the difference between the average payoff of a strategy and the average payoff of the population. The first sum consists of a product of d frequencies while the second sum requires a product of $d+1$. Particularly, we consider the case $d = 3$. For strategy k the average change due to selection is given by

$$\langle \Delta x_k^{sel} \rangle_\delta = \frac{\delta}{N} \left(\sum_{h,i} a_{k,h,i} \langle x_k x_h x_i \rangle - \sum_{h,i,j} a_{h,i,j} \langle x_k x_h x_i x_j \rangle \right). \tag{A11}$$

Next, we will consider the special case of $d = 3$ in more detail.

Appendix B: Three player games

1. Choosing a set of players

To solve Eq. (A11) we need to solve the two sums on the right hand side. The first sum can be solved using the technique derived by [3]. For the second sum we need to know the different forms of the averages possible. Using symmetry arguments such as $\langle x_1 x_2 x_2 x_3 \rangle = \langle x_1 x_2 x_3 x_3 \rangle$ (this is valid because we average under neutrality) only five different kinds of averages are required, $\langle x_1 x_1 x_1 x_1 \rangle$, $\langle x_1 x_2 x_2 x_2 \rangle$, $\langle x_1 x_1 x_2 x_2 \rangle$, $\langle x_1 x_1 x_2 x_3 \rangle$ and $\langle x_1 x_2 x_3 x_4 \rangle$. The quantities

$\langle x_1 x_1 x_1 x_1 \rangle$ and $\langle x_1 x_2 x_3 x_4 \rangle$ are derived in section C based on coalescence theory. The rest of the averages can be written down as,

(i) Three of a kind, $\langle x_1 x_2 x_2 x_2 \rangle$.

$$\langle x_1 x_2 x_2 x_2 \rangle = \left\langle \left(1 - \sum_{i=2}^{n} x_i \right) x_2 x_2 x_2 \right\rangle$$
$$= \langle x_1 x_1 x_1 \rangle - \langle x_1 x_1 x_1 x_1 \rangle - (n-2)\langle x_1 x_2 x_2 x_2 \rangle$$
$$= \frac{\langle x_1 x_1 x_1 \rangle - \langle x_1 x_1 x_1 x_1 \rangle}{n-1} \qquad (B1)$$

(ii) Two pairs, $\langle x_1 x_1 x_2 x_2 \rangle$.

$$\langle x_1 x_1 x_2 x_2 \rangle = \left\langle (1 - x_2 - \sum_{i=3}^{n} x_i) x_1 x_2 x_2 \right\rangle$$
$$= \langle x_1 x_2 x_2 \rangle - \langle x_1 x_2 x_2 x_2 \rangle - (n-2)\langle x_1 x_1 x_2 x_3 \rangle \qquad (B2)$$

(iii) Single pair, $\langle x_1 x_1 x_2 x_3 \rangle$.

$$\langle x_1 x_1 x_2 x_3 \rangle = \left\langle \left(1 - x_2 - x_3 - \sum_{i=4}^{n} x_i \right) x_1 x_2 x_3 \right\rangle$$
$$= \langle x_1 x_2 x_3 \rangle - 2\langle x_1 x_1 x_2 x_3 \rangle - (n-3)\langle x_1 x_2 x_3 x_4 \rangle$$
$$= \frac{\langle x_1 x_2 x_3 \rangle - (n-3)\langle x_1 x_2 x_3 x_4 \rangle}{3}. \qquad (B3)$$

Thus we can write all averages in terms of $\langle x_1 x_1 x_1 x_1 \rangle$, $\langle x_1 x_2 x_3 x_4 \rangle$ and the known quantities from [3],

$$\langle x_1 x_2 x_2 x_2 \rangle = \frac{\langle x_1 x_1 x_1 \rangle - \langle x_1 x_1 x_1 x_1 \rangle}{n-1}$$
$$\langle x_1 x_1 x_2 x_2 \rangle = \langle x_1 x_2 x_2 \rangle - \langle x_1 x_2 x_2 x_2 \rangle - (n-2)\langle x_1 x_1 x_2 x_3 \rangle$$
$$\langle x_1 x_1 x_2 x_3 \rangle = \frac{\langle x_1 x_2 x_3 \rangle - (n-3)\langle x_1 x_2 x_3 x_4 \rangle}{3}$$
$$\qquad (B4)$$

From [3] we know the form of,

$$\langle x_1 x_1 x_1 \rangle = \frac{s_3}{n}$$
$$\langle x_1 x_2 x_2 \rangle = \frac{s_2 - s_3}{n(n-1)}$$
$$\langle x_1 x_2 x_3 \rangle = \frac{1 - 3s_2 + 2s_3}{n(n-1)(n-2)}, \qquad (B5)$$

where the probability that if we choose i individuals from the stationary state of a neutral coalescent then all i have the same strategy is s_i. The quantities s_2 and s_3 have been previously derived in [3]. For completeness we repeat the derivation in Section C. In Section C s_4 is calculated, which is the probability of choosing four individuals from the neutral stationary state and all have the same strategy. If there are n strategies then the probability that all four have strategy 1 is s_4/n. Thus $\langle x_1 x_1 x_1 x_1 \rangle = s_4/n$. Similarly, the probability that all four have different strategies is $\bar{s}_4$. The exact case when the first individual has strategy 1, second has 2, third has 3 and the fourth has 4 is just $\langle x_1 x_2 x_3 x_4 \rangle = \bar{s}_4/(n(n-1)(n-2)(n-3))$. Using this information we can get the expression for all the five averages as,

$$\langle x_1 x_1 x_1 x_1 \rangle = \frac{s_4}{n}$$
$$\langle x_1 x_2 x_2 x_2 \rangle = \frac{s_3 - s_4}{n(n-1)}$$
$$\langle x_1 x_1 x_2 x_2 \rangle = \frac{\bar{s}_4 + 3s_4 - 8s_3 + 6s_2 - 1}{3n(n-1)}$$
$$\langle x_1 x_1 x_2 x_3 \rangle = \frac{1 - 3s_2 + 2s_3 - \bar{s}_4}{3n(n-1)(n-2)}$$
$$\langle x_1 x_2 x_3 x_4 \rangle = \frac{\bar{s}_4}{n(n-1)(n-2)(n-3)}. \qquad (B6)$$

The quantities s_2, s_3, s_4 and $\bar{s}_4$ are derived in Section C. Substituting these values in the above set of equations yields,

$$\langle x_1 x_1 x_1 \rangle = n(n+\mu)(2n+\mu)(3+\mu)C$$
$$\langle x_1 x_2 x_2 \rangle = n\mu(n+\mu)(3+\mu)C$$
$$\langle x_1 x_2 x_3 \rangle = n\mu^2(3+\mu)C$$
$$\langle x_1 x_1 x_1 x_1 \rangle = (n+\mu)(2n+\mu)(3n+\mu)C$$
$$\langle x_1 x_2 x_2 x_2 \rangle = \mu(n+\mu)(2n+\mu)C$$
$$\langle x_1 x_1 x_2 x_2 \rangle = \mu(n+\mu)^2 C$$
$$\langle x_1 x_1 x_2 x_3 \rangle = \mu^2(n+\mu)C$$
$$\langle x_1 x_2 x_3 x_4 \rangle = \mu^3 C. \qquad (B7)$$

where $C = \left[n^4(1+\mu)(2+\mu)(3+\mu) \right]^{-1}$.

2. Number of strategies with respect to the number of players

Now that we know the form of the averages, we can begin expanding the sums from Eq. (A11), first for $d = 3$ and for $n > 3$. Consider the first sum,

$$\sum_{h,i} a_{k,h,i}\langle x_k x_h x_i \rangle = \langle x_1 x_1 x_1 \rangle a_{k,k,k} + \langle x_1 x_2 x_2 \rangle \sum_{\substack{h,i \\ k \neq h = i \neq k \\ h = k, i \neq k \\ i = k, h \neq k}} a_{k,h,i}$$
$$+ \langle x_1 x_2 x_3 \rangle \sum_{\substack{h,i \\ k \neq h \neq i \neq k}} a_{k,h,i}. \qquad (B8)$$

For the ease of notation we denote the co-efficients on the right hand side by $\alpha_1 = a_{k,k,k}$, $\alpha_2 = \sum_{\substack{h,i \\ k \neq h = i \neq k \\ h = k, i \neq k \\ i = k, h \neq k}} a_{k,h,i}$,

$\alpha_3 = \sum_{\substack{h,i \\ k \neq h \neq i \neq k}} a_{k,h,i}$. Hence, we have,

$$\sum_{h,i} a_{k,h,i}\langle x_k x_h x_i \rangle = \langle x_1 x_1 x_1 \rangle \alpha_1 + \langle x_1 x_2 x_2 \rangle \alpha_2 + \langle x_1 x_2 x_3 \rangle \alpha_3.$$
$$\qquad (B9)$$

Similarly, the second sum in Eq. (A11) becomes,

$$\sum_{h,i,j} a_{h,i,j}\langle x_k x_h x_i x_j\rangle = \langle x_1 x_1 x_1 x_1\rangle\beta_1 + \langle x_1 x_2 x_2 x_2\rangle\beta_2$$
$$+\langle x_1 x_1 x_2 x_2\rangle\beta_3 + \langle x_1 x_1 x_2 x_3\rangle\beta_4$$
$$+\langle x_1 x_2 x_3 x_4\rangle\beta_5 \qquad (B10)$$

Note that $\beta_1 = \alpha_1$. Substituting the expressions for the averages from Eqs. (B7),

$$\frac{\sum_{h,i} a_{k,h,i}\langle x_k x_h x_i\rangle}{C} = n(n+\mu)(2n+\mu)(3+\mu)\alpha_1$$
$$+n\mu(n+\mu)(3+\mu)\alpha_2$$
$$+n\mu^2(3+\mu)\alpha_3$$
$$= 6n^3\alpha_1 + n\left[2n^2\alpha_1 + 3n(3\alpha_1 + \alpha_2)\right]\mu$$
$$+n\left[n(3\alpha_1 + \alpha_2) + 3(\alpha_1 + \alpha_2 + \alpha_3)\right]\mu^2$$
$$+n(\alpha_1 + \alpha_2 + \alpha_3)\mu^3 \qquad (B11)$$

for the first sum. For the second sum,

$$\frac{\sum_{h,i,j} a_{h,i,j}\langle x_k x_h x_i x_j\rangle}{C} = (n+\mu)(2n+\mu)(3n+\mu)\alpha_1$$
$$+\mu(n+\mu)(2n+\mu)\beta_2$$
$$+\mu(n+\mu)^2\beta_3 + \mu^2(n+\mu)\beta_4 + \mu^3\beta_5$$
$$= 6n^3\alpha_1 + n^2(11\alpha_1 + 2\beta_2 + \beta_3)\mu$$
$$+n(6\alpha_1 + 3\beta_2 + 2\beta_3 + \beta_4)\mu^2$$
$$+(\alpha_1 + \beta_2 + \beta_3 + \beta_4 + \beta_5)\mu^3. \qquad (B12)$$

Going back to our original Equation (A11) and organising it in powers of μ, we obtain,

$$\frac{N\langle\Delta x_k^{sel}\rangle_\delta}{\delta C} = \left(\sum_{h,i} a_{k,h,i}\langle x_k x_h x_i\rangle\right.$$
$$\left.-\sum_{h,i,j} a_{h,i,j}\langle x_k x_h x_i x_j\rangle\right)$$
$$= \underbrace{\left[n^2(2\alpha_1(n-1) + 3\alpha_2 - 2\beta_2 - \beta_3)\right]}_{L_k}\mu$$
$$+\underbrace{\left[n((3n-3)\alpha_1 + (n+3)\alpha_2 + 3\alpha_3 - 3\beta_2 - 2\beta_3 - \beta_4))\right]}_{M_k}\mu^2$$
$$+\underbrace{\left[n\mathcal{A} - \mathcal{B}\right]}_{H_k}\mu^3 \qquad (B13)$$

where $\mathcal{A} = \alpha_1 + \alpha_2 + \alpha_3 = \sum_{h,i} a_{k,h,i}$ and $\mathcal{B} = \beta_1 + \beta_2 + \beta_3 + \beta_4 + \beta_5 = \sum_{h,i,j} a_{h,i,j}$. Notice that the co-efficients of the different orders of μ consist only of the number of strategies and the payoff values. Let the coefficients of μ, μ^2 and μ^3 be denoted by L_k, M_k and H_k. Thus we get to the following result.

$$\langle\Delta x_k^{sel}\rangle_\delta = \frac{\delta\mu(L_k + M_k\mu + H_k\mu^2)}{Nn^4(1+\mu)(2+\mu)(3+\mu)} \qquad (B14)$$

Next we consider $d = 3$ and $n = 3$. In this case the sums in Eq. (A11) are,

$$\sum_{h,i} a_{k,h,i}\langle x_k x_h x_i\rangle = \langle x_1 x_1 x_1\rangle\alpha_1 + \langle x_1 x_2 x_2\rangle\alpha_2 + \langle x_1 x_2 x_3\rangle\alpha_3$$
$$(B15)$$

and

$$\sum_{h,i,j} a_{h,i,j}\langle x_k x_h x_i x_j\rangle = \langle x_1 x_1 x_1 x_1\rangle\alpha_1 + \langle x_1 x_2 x_2 x_2\rangle\beta_2$$
$$+\langle x_1 x_1 x_2 x_2\rangle\beta_3 + \langle x_1 x_1 x_2 x_3\rangle\beta_4. \qquad (B16)$$

Thus $\bar{s}_4 = 0$ and we do not have the term $\langle x_1 x_2 x_3 x_4\rangle$. This changes the averages, $\langle x_1 x_1 x_2 x_2\rangle$ and $\langle x_1 x_1 x_2 x_3\rangle$ as they were dependent on $\langle x_1 x_2 x_3 x_4\rangle$ (see Eqs. (B6)). Eqs. (B7) do not change, but $\beta_5 = 0$. Solving the two sums using these expressions and evaluating Eq. (A11), specifically for $n = 3$,

$$\frac{N\langle\Delta x_k^{sel}\rangle_\delta}{\delta C} = \left(\sum_{h,i}^{3} a_{k,h,i}\langle x_k x_h x_i\rangle - \sum_{h,i,j}^{3} a_{h,i,j}\langle x_k x_h x_i x_j\rangle\right)$$
$$= 9\left[4\alpha_1 + 3\alpha_2 - 2\beta_2 - \beta_3\right]\mu$$
$$+3\left[6\alpha_1 + 6\alpha_2 + 3\alpha_3 - 3\beta_2 - 2\beta_3 - \beta_4\right]\mu^2$$
$$+\left[3\mathcal{A} - \mathcal{B}\right]\mu^3 \qquad (B17)$$

which can be written in the form of Eq. (B14).

Finally for $d = 3$ and $n = 2$ the sums in Eq. (A11) consist only of the following terms,

$$\sum_{h,i}^{2} a_{k,h,i}\langle x_k x_h x_i\rangle = \langle x_1 x_1 x_1\rangle\alpha_1 + \langle x_1 x_2 x_2\rangle\alpha_2.$$
$$(B18)$$

and

$$\sum_{h,i,j}^{2} a_{h,i,j}\langle x_k x_h x_i x_j\rangle = \langle x_1 x_1 x_1 x_1\rangle\alpha_1 + \langle x_1 x_2 x_2 x_2\rangle\beta_2$$
$$+\langle x_1 x_1 x_2 x_2\rangle\beta_3 \qquad (B19)$$

The form of the averages does not change from the general form given in Eqs. (B6) except for $\langle x_1 x_1 x_2 x_2\rangle$ which depends on $\bar{s}_4$. Due to $n = 2$, $\bar{s}_4 = 0$ and also $\beta_5 = \beta_4 = 0$. For this special case thus, we have

$$\frac{N\langle\Delta x_k^{sel}\rangle_\delta}{\delta C} = \left(\sum_{h,i}^{2} a_{k,h,i}\langle x_k x_h x_i\rangle - \sum_{h,i,j}^{2} a_{h,i,j}\langle x_k x_h x_i x_j\rangle\right)$$
$$= 4\left[2\alpha_1 + 3\alpha_2 - 2\beta_2 - \beta_3\right]\mu$$
$$+2\left[(3\alpha_1 + 5\alpha_2 - 3\beta_2 - 2\beta_3)\right]\mu^2$$
$$+\left[2\mathcal{A} - \mathcal{B}\right]\mu^3 \qquad (B20)$$

which can be cast in the form of Eq. (B14).

This case is actually very well studied. For multiple players and two strategies it has been recently shown that the condition for strategy A replacing strategy B with a higher

probability simply depends on the sums of the payoff values of the two strategies [10, 22]. This result is valid for random matching of players and small mutation rates. In our case, the condition for small mutation rates is obtained by checking the condition $L_k > 0$, i.e.,

$$4(2\alpha_1 + 3\alpha_2 - 2\beta_2 - \beta_3) > 0. \tag{B21}$$

Inserting the definitions of α_1, α_2, β_1 and β_2 and rearranging leads to

$$2a_{1,1,1} + a_{1,1,2} + a_{1,2,1} + 2a_{1,2,2} > 2a_{2,1,1} + a_{2,1,2} + a_{2,2,1} + 2$$

Under random matching we have $a_{1,1,2} = a_{1,2,1}$ and $a_{2,1,2} = a_{2,2,1}$. Thus, this is equivalent to

$$a_{1,1,1} + a_{1,1,2} + a_{1,2,2} > a_{2,1,1} + a_{2,1,2} + a_{2,2,2} \tag{B23}$$

which is the condition derived in [10, 22]. When we do the same analysis for $n = 2$ and increasing d, and compare the L_k for each d, we will find a general form of the condition already given in [10, 22] for small mutation rates.

Appendix C: Calculating probabilities based on Coalescence Theory

In the coalescence approach, we take a sample from the present generation and look back in time with respect to the sample. Consider two copies of a gene. Sometime back in the past they come together to a common ancestor. This means the lineages of the two copies "coalesce" back in time. In general if we have a sample of d individuals from the present then sometime back the lineages of two of the individuals will coalesce and there will be $d-1$ individuals. In all thus there will be $d-1$ coalescence events until we arrive at the most recent common ancestor, the root of the coalescent. [18–21] showed that the mathematical process of joining lineages leading up to the common ancestor can be analytically understood. He also showed that the coalescent encompassess a broad class of population dynamics models including Wright-Fisher and Moran processes.

There are three assumptions of the most basic coalescent theory [49],

- The population is not subdivided or structured.

- The population size remains constant over time.

- Genetic differences have no effect on the fitness of an individual. In our case this means that different strategies have the same fitness, the neutral case.

We follow the approach developed in [2, 3]. In a neutral Moran process two individuals will have the same ancestor in one update step with probability $2/N^2$. We use a continuous time limit by rescaling the time such that $\tau = t(2/N^2)$. We determine the results for a large, but finite population size N.
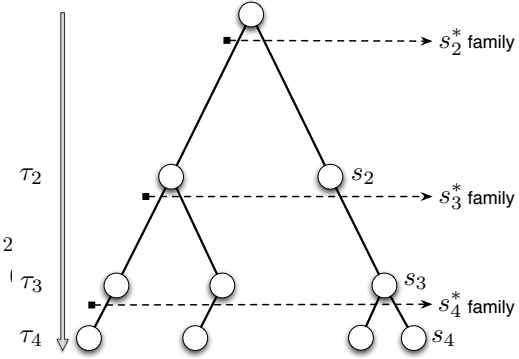
FIG. 3. The coalescent as it evolves through time. The probability that at time τ_i the i individuals have the same strategy is given by s_i. Immediately after τ_i there are $i+1$ individuals. The strategy configuration at that time point depends if s_i was 1 or not. If not then exactly what was the configuration? All these factors determine the possible configuration of the immediate $i+1$ individuals and these different possibilities are grouped in the s_{i+1}^* family.

The beauty of the coalescence process lies in the separation of the genealogical part and the mutation process. This is due to the assumption of neutrality. Mutations occur at the rate of $\mu/2$ where $\mu = Nu$ and u is the probability with which the offspring obtains any one of the n strategies at random. The mutation probability u can range from 0 to 1, but when the mutation probability is 1 then the strategies would oscillate. Hence we rescale the mutation rate by $1/2$. It has been shown by [19, 20] that when N is large, the coalescent time is exponentially distributed as,

$$f_i(\tau) = \binom{i}{2} e^{-\binom{i}{2}\tau}. \tag{C1}$$

On each trajectory no mutation occurs in time τ with probability

$$\gamma = e^{-\frac{\mu}{2}\tau}. \tag{C2}$$

1. Calculation of s_2

First we repeat the derivations of [3] for completeness of the process. Also this will help simplify the terminologies used in the next subsection. The quantity s_2 is the probability that two individuals chosen randomly in a neutral coalescent process have the same strategy. According to the coalescent back in time there was a single common ancestor of the two chosen individuals. Immediately after the ancestor split there were two individuals of the same type. Thus the s_2^* family consists of only one configuration, a pair of identical individuals. From then onwards to τ_2 mutations

can play a role. Hence, the probability that the two individuals drawn have identical strategies when at the s_2^* family level they have identical strategies, is given by $s_2^{*[2]}$,

$$s_2^{*[2]}(\tau) = \gamma^2 + \frac{2}{n}\gamma(1-\gamma) + \frac{1}{n}(1-\gamma)^2. \quad \text{(C3)}$$

The index $[2]$ in the superscript describes the composition of the configuration. In this case denoting that both the individuals are of the same strategy. The terms on the right hand side from first to last can be described as follows. (i) None of the trajectories mutate and hence the individuals have identical strategies with probability 1. (ii) At least one mutation occurs on one of the trajectories and the chance that the new strategy is identical to the other is $1/n$. As there are two trajectories this can happen in 2 ways. (iii) When both the trajectories mutate the first one gets some strategy with probability 1 and the second also mutates to the same strategy with probability, $1/n$.

This has to be weighted by the probability that we begin with two identical individuals at the s_2^* family level. As this is the only possible configuration, the probability is 1. Further we also need to integrate with the coalescent time density (Eq. (C1)) to finally get s_2 as,

$$s_2 = 1 \int_0^\infty s_2^{*[2]}(\tau)f_2(\tau)d\tau$$
$$= \frac{n+\mu}{n(1+\mu)}. \quad \text{(C4)}$$

This is a the case of a k-allele Moran model with replacement [6].

2. Calculation of s_3

Now we take a step further. What is the probability that three randomly chosen individuals will have the same strategy ? The distribution of coalescent times is given by the density function for the coalescent event for three individuals which is given by $f_3(\tau) = 3e^{-3\tau}$.

Similarly as above we first investigate the s_3^* family. At time τ_2 in the coalescent tree, one of the two individuals splits. Thus in the s_3^* family, two individuals will always have identical strategies. In all there can be only two configurations, all three are identical or two have the same strategy and the third differs.

We consider the two cases separately. If all three individuals have the same strategy at the s_3^* family level, then the probability that they have identical strategies after time τ is,

$$s_3^{*[3]}(\tau) = \gamma^3 + \frac{3}{n}\gamma^2(1-\gamma) + \frac{3}{n^2}\gamma(1-\gamma)^2 + \frac{1}{n^2}(1-\gamma)^3. \quad \text{(C5)}$$

If two individuals have the same strategy and the third one is different at the s_3^* family level, then the probability that

they have identical strategies after time τ is given by,

$$s_3^{*[2|1]}(\tau) = 0\ \gamma^3 + \frac{1}{n}\gamma^2(1-\gamma) + \frac{3}{n^2}\gamma(1-\gamma)^2 + \frac{1}{n^2}(1-\gamma)^3$$
$$= \frac{1}{n}\gamma^2(1-\gamma) + \frac{3}{n^2}\gamma(1-\gamma)^2 + \frac{1}{n^2}(1-\gamma)^3. \quad \text{(C6)}$$

In the superscript the index $[2|1]$ denotes that two individuals are of the same strategy and one is of a different strategy. In this case we see that the first term for all three trajectories not mutating vanishes. This is because when we begin with the case when all the individuals do not have identical strategies, they cannot be identical later in time if no mutation occurs.

To get the full probability s_3 we need to weight the above two cases with the probabilities of their realizations. Three individuals will be the same at the s_3^* family level if the two individuals at τ_2 are identical. This happens with probability s_2. The probability that they are not the same is thus $1-s_2$. Putting in these weights and integrating over all possible times, we get s_3 as

$$s_3 = s_2 \int_0^\infty s_3^{*[3]}(\tau)f_3(\tau)d\tau + (1-s_2)\int_0^\infty s_3^{*[2|1]}(\tau)f_3(\tau)d\tau$$
$$= \frac{(n+\mu)(2n+\mu)}{n^2(1+\mu)(2+\mu)}. \quad \text{(C7)}$$

3. Calculation of s_4
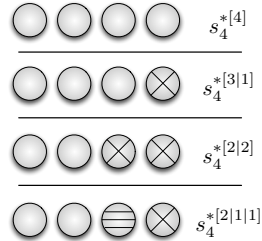
FIG. 4. **The s_4^* family.** All possible starting configurations where there are 4 individuals. Two of them have the same strategy. The figure shows all the possible combinations for the remaining two individuals.

Here we calculate s_4, i.e. the probability that four randomly chosen individuals have the same strategy out of a collection of n strategies.

We are interested in the probability that the four leaves of the coalescent have the same strategy, cf. Fig. C.3. At time τ_3, two of the four trajectories coalesce with rate 1. Hence there is a coalescence at rate 6, and the density function is given as, $f_4(\tau_4) = 6e^{-6\tau_4}$. Before the bifurcation occurs at τ_3 the three players can have the same strategy with probability s_3 or at least one is different with probability $1-s_3$.

If the three players have the same strategy then immediately after the coalescence there will be four players with the same strategy. If the three player do not have the same strategy then there are three different possible configurations. This is the family of configurations we denote by s_4^*. Thus beginning with four individuals of different configurations we are interested in the probability that after time τ all four of them will have the same strategy.

The s_4^* family consists of four cases:

- Four identical individuals (Fig. C.4 , $s_4^{*[4]}$). In this case they will be the same at time τ_4 if none of them mutate. If one of them mutates that can happen with probability $4(\gamma)^3(1-\gamma)$ and they are the same with probability $1/n$. Similarly, we can write down when two or three or all can mutate and we get the expression,

$$s_4^{*[4]}(\tau) = \gamma^4 + \frac{4}{n}\gamma^3(1-\gamma) + \frac{6}{n^2}\gamma^2(1-\gamma)^2$$
$$+ \frac{4}{n^3}\gamma(1-\gamma)^3 + \frac{1}{n^3}(1-\gamma)^4. \tag{C8}$$

- Three of a kind (Fig. C.4 , $s_4^{*[3|1]}$). If only three are the same then if no one mutates its impossible for all four to be the same at time τ_4. Similarly we can argue what happens if one, two, three or all four mutate and we get the expression for $s_4^{*[3|1]}$,

$$s_4^{*[3|1]}(\tau) = \frac{1}{n}\gamma^3(1-\gamma) + \frac{3}{n^2}\gamma^2(1-\gamma)^2$$
$$+ \frac{4}{n^3}\gamma(1-\gamma)^3 + \frac{1}{n^3}(1-\gamma)^4. \tag{C9}$$

- Two pairs (Fig. C.4 , $s_4^{*[2|2]}$). At least two need to mutate such that we can end up with four identical individuals. Additionally the two mutating must belong to the same pair. The last two terms are the same as before.

$$s_4^{*[2|2]}(\tau) = \frac{2}{n^2}\gamma^2(1-\gamma)^2 + \frac{4}{n^3}\gamma(1-\gamma)^3$$
$$+ \frac{1}{n^3}(1-\gamma)^4. \tag{C10}$$

- Single pair (Fig. C.4 , $s_4^{*[2|1|1]}$). At least two mutations are necessary for all four individuals to have the same strategy. The two mutations have to be on the trajectory of the non-paired individuals. Again the last two terms are the same as before.

$$s_4^{*[2|1|1]}(\tau) = \frac{1}{n^2}\gamma^2(1-\gamma)^2 + \frac{4}{n^3}\gamma(1-\gamma)^3$$
$$+ \frac{1}{n^3}(1-\gamma)^4. \tag{C11}$$

To obtain the final probability s_4 (all four individuals have the same strategy), we combine all the above scenarios. But we need to weight each of the scenarios with the probability of the realization of the starting configuration. E.g. if the system reaches the state of all individuals having the same strategy from the second element of the s_4^* family, i.e. $s_4^{*[3|1]}$, then we have to weight it by the probability of that configuration, three of the same type and one different, Fig C.4. This is possible if at τ_3 we do not have all three of the same type, but they must be of one of the the type $\langle x_1 x_2 x_2 \rangle$ or $\langle x_2 x_1 x_2 \rangle$ or $\langle x_2 x_2 x_1 \rangle$. Not only this, but the bifurcation should occur at one of the two identical types (x_2) and not the different type (x_1), the probability of which is $\frac{2}{3}$. Thus we have to weight $s_4^{*[3|1]}$ by $\frac{2}{3} \times (s_2 - s_3) \times 3$. We calculate these weights for all the family members of s_4^* and thus get an expression for s_4 as,

$$s_4 = s_3 \int_0^\infty s_4^*(\tau)f_4(\tau)d\tau + 2(s_2 - s_3)\int_0^\infty s_4^{*[3|1]}(\tau)f_4(\tau)d\tau$$
$$+ (s_2 - s_3)\int_0^\infty s_4^{*[2|2]}(\tau)f_4(\tau)d\tau$$
$$+ (1 - 3s_2 + 2s_3)\int_0^\infty s_4^{*[2|1|1]}(\tau)f_4(\tau)d\tau$$
$$= \frac{(3n+\mu)(2n+\mu)(n+\mu)}{n^3(1+\mu)(2+\mu)(3+\mu)}. \tag{C12}$$

4. Calculation of $\bar{s}_4$

Here we calculate the probability $\bar{s}_4$ of picking four individuals in the stationary state all having different strategies. As before we can have four different starting configurations, the same as shown in Figure C.4.

Hence basically now we want to calculate the probability that starting with each of the s_4^* family members what is the probability of ending with all different individuals:

- Four identical individuals (Fig. C.4 , $\bar{s}_4^{*[4]}$). We term the probability to start with four identical strategy individual to four different strategy individuals to be $\bar{s}_4^{*[4]}$. For four to be different at least three have to mutate. It can be calculated as follows,

$$\bar{s}_4^{*[4]}(\tau) = 4\gamma(1-\gamma)^3\frac{(n-1)(n-2)(n-3)}{n^3}$$
$$+ (1-\gamma)^4\frac{(n-1)(n-2)(n-3)}{n^3}. \tag{C13}$$

- Three of a kind (Fig. C.4 , $\bar{s}_4^{*[3|1]}$). For all four individuals to be different now we need at least two individuals to mutate as we already have one individuals

of a different type. Hence,

$$\bar{s}_4^{*[3|1]}(\tau) = 3\gamma^2(1-\gamma)^2\frac{(n-2)(n-3)}{n^2}$$
$$+4\gamma(1-\gamma)^3\frac{(n-1)(n-2)(n-3)}{n^3}$$
$$+(1-\gamma)^4\frac{(n-1)(n-2)(n-3)}{n^3}. \quad \text{(C14)}$$

- Two pairs (Fig. C.4 , $\bar{s}_4^{*[2|2]}$). Here again we need at least two individuals to mutate for all the individuals to be different. Of the two individuals mutating each should be of different types. Hence, in all there are 4 such combinations.

$$\bar{s}_4^{*[2|2]}(\tau) = 4\gamma^2(1-\gamma)^2\frac{(n-2)(n-3)}{n^2}$$
$$+4\gamma(1-\gamma)^3\frac{(n-1)(n-2)(n-3)}{n^3}$$
$$+(1-\gamma)^4\frac{(n-1)(n-2)(n-3)}{n^3}. \quad \text{(C15)}$$

- Single pair (Fig. C.4 , $\bar{s}_4^{*[2|1|1]}$). For this starting configuration a single mutation is enough to create all different individuals provided it happens in one of the paired individuals. If two individuals are to mutate, then except for the two unpaired individuals together, all other groupings of two can give four different in-

dividuals, hence in 5 different ways,

$$\bar{s}_4^{*[2|1|1]}(\tau) = 2\gamma^3(1-\gamma)\frac{(n-3)}{n} + 5\gamma^2(1-\gamma)^2\frac{(n-2)(n-3)}{n^2}$$
$$+4\gamma(1-\gamma)^3\frac{(n-1)(n-2)(n-3)}{n^3}$$
$$+(1-\gamma)^4\frac{(n-1)(n-2)(n-3)}{n^3}. \quad \text{(C16)}$$

To get the final probability $\bar{s}_4$ we need integrate all the different starting configurations over the coalescent time density and add them all together. Hence,

$$\bar{s}_4 = s_3\int_0^\infty \bar{s}_4^*(\tau)f_4(\tau)d\tau + 2(s_2-s_3)\int_0^\infty \bar{s}_4^{*[3|1]}(\tau)f_4(\tau)d\tau$$
$$+(s_2-s_3)\int_0^\infty \bar{s}_4^{*[2|2]}(\tau)f_4(\tau)d\tau$$
$$+(1-3s_2+2s_3)\int_0^\infty \bar{s}_4^{*[2|1|1]}(\tau)f_4(\tau)d\tau$$
$$=\frac{\mu^3(n-1)(n-2)(n-3)}{n^3(1+\mu)(2+\mu)(3+\mu)}. \quad \text{(C17)}$$

Due to the notational challenge, possible errors can arise hence to check our results, we simulated a neutral Moran process and computed the different averages, $\langle x_1x_1x_1x_1\rangle$, $\langle x_1x_2x_2x_2\rangle$, $\langle x_1x_1x_2x_2\rangle$, $\langle x_1x_1x_2x_3\rangle$ and $\langle x_1x_2x_3x_4\rangle$. These quantities depend on all the probabilities calculated in the Appendix namely s_2, s_3, s_4 and $\bar{s}_4$. The results of the simulation and analytical method are shown in Figure C.5.

[1] Antal, T., Nowak, M. A., Traulsen, A., 2009. Strategy abundance in 2x2 games for arbitrary mutation rates. J. Theor. Biol. 257, 340–344.
[2] Antal, T., Ohtsuki, H., Wakeley, J., Taylor, P. D., Nowak, M. A., 2009. Evolution of cooperation by phenotypic similarity. Proc. Natl. Acad. Sci. USA 106, 8597–8600.
[3] Antal, T., Traulsen, A., Ohtsuki, H., Tarnita, C. E., Nowak, M. A., 2009. Mutation-selection equilibrium in games with multiple strategies. J. Theor. Biol. 258, 614–622.
[4] Broom, M., 2003. The use of multiplayer game theory in the modeling of biological populations. Comments on Theoretical Biology 8, 103–123.
[5] Cressman, R., 1992. The stability concept of evolutionary game theory. Lecture Notes in Biomathematics 94.
[6] Ewens, W. J., 2004. Mathematical Population Genetics. Springer, NY.
[7] Ficici, S., Pollack, J., 2000. Effects of finite populations on evolutionary stable strategies. In: Whitley, D., Goldberg, D., Cantu-Paz, E., Spector, L., Parmee, I., Beyer, H.-G. (Eds.), Proceedings GECCO. Morgan-Kaufmann, San Francisco, pp. 927–934.
[8] Fudenberg, D., Harris, C., 1992. Evolutionary dynamics with aggregate shocks. J. Econ. Theory 57, 420–441.
[9] Fudenberg, D., Imhof, L. A., 2006. Imitation process with small mutations. J. Econ. Theory 131, 251–262.

[10] Gokhale, C. S., Traulsen, A., 2010. Evolutionary games in the multiverse. Proc. Natl. Acad. Sci. U.S.A. 107 (12), 5500–5504.
[11] Hauert, C., De Monte, S., Hofbauer, J., Sigmund, K., 2002. Volunteering as red queen mechanism for cooperation in public goods games. Science 296, 1129–1132.
[12] Hauert, C., Traulsen, A., Brandt, H., Nowak, M. A., Sigmund, K., 2007. Via freedom to coercion: the emergence of costly punishment. Science 316, 1905–1907.
[13] Hauert, C., Traulsen, A., Brandt, H., Nowak, M. A., Sigmund, K., 2008. Public goods with punishment and abstaining in finite and infinite populations. Biological Theory 3, 114–122.
[14] Hofbauer, J., Schuster, P., Sigmund, K., 1982. Game dynamics in mendelian populations. Biological Cybernetics 43, 51–57.
[15] Hofbauer, J., Sigmund, K., 1984. Evolutionstheorie und dynamische Systeme – Mathematische Aspekte der Selektion. Verlag Paul Parey, Berlin, Hamburg, 22 (SUB GOE).
[16] Hofbauer, J., Sigmund, K., 1998. Evolutionary Games and Population Dynamics. Cambridge University Press, Cambridge.
[17] Kandori, M., Mailath, G. J., Rob, R., 1993. Learning, mutation, and long run equilibria in games. Econometrica 61, 29–56.
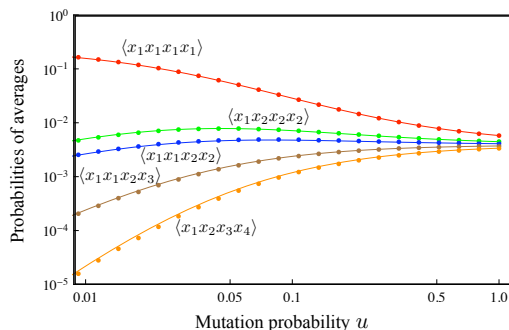
FIG. 5. For a neutral Moran process with four strategies if we pick four individuals from the stationary state then the probability that all of them have the same strategy is given by, s_4, Eq. (C12). For four strategies ($n = 4$), the probability that all four have strategy 1 is $s_4/4$ given by $\langle x_1 x_1 x_1 x_1 \rangle$. Similarly the probabilities for $\langle x_1 x_2 x_2 x_2 \rangle$, $\langle x_1 x_1 x_2 x_2 \rangle$, $\langle x_1 x_1 x_2 x_3 \rangle$ and $\langle x_1 x_2 x_3 x_4 \rangle$ are plotted as a function of the mutation probability for a population size of $N = 40$. The symbols are simulations while the lines are the analytical results.

[18] Kingman, J., 1982. Exchangeability and the evolution of large populations. In: Koch, G., Spizzichino, F. (Eds.), Exchangeability in probability and statistics. North-Holland, Amsterdam, pp. 97–112.

[19] Kingman, J. F. C., 1982. The coalescent. Stochastic Processes and Their Applications 13, 235–248.

[20] Kingman, J. F. C., 1982. On the genealogy of large populations. J. Appl. Probability 19A, 27–43.

[21] Kingman, J. F. C., 2000. Origins of the coalescent. 1974-1982. Genetics 156 (4), 1461–1463.

[22] Kurokawa, S., Ihara, Y., April 2009. Emergence of cooperation in public goods games. Proc. R. Soc. B 276, 1379–1384.

[23] Levin, S. A. (Ed.), 2009. Games, Groups and the Global Good. Springer Series in Game Theory. Springer.

[24] Lotka, A. J., 1910. Contribution to the theory of periodic reactions. J. Phys. Chem. 14 (3), 271–274.

[25] Maynard Smith, J., 1982. Evolution and the Theory of Games. Cambridge University Press, Cambridge.

[26] Milinski, M., Semmann, D., Krambeck, H. J., Marotzke, J., 2006. Stabilizing the earth's climate is not a losing game: Supporting evidence from public goods experiments. Proc. Natl. Acad. Sci. USA 103, 3994–3998.

[27] Milinski, M., Sommerfeld, R. D., Krambeck, H.-J., Reed, F. A., Marotzke, J., 2008. The collective-risk social dilemma and the prevention of simulated dangerous climate change. Proc. Natl. Acad. Sci. USA 105 (7), 2291–2294.

[28] Nowak, M. A., 2006. Evolutionary Dynamics. Harvard University Press, Cambridge, MA.

[29] Nowak, M. A., Sasaki, A., Taylor, C., Fudenberg, D., 2004.

[30] Emergence of cooperation and evolutionary stability in finite populations. Nature 428, 646–650.

[30] Nowak, M. A., Tarnita, C. E., Wilson, E. O., 2010. The evolution of eusociality. Nature 466, 1057–1062.

[31] Ohtsuki, H., 2010. Stochastic evolutionary dynamics of bimatrix games. J. Theor. Biol. 264, 136–142.

[32] Pacheco, J. M., Santos, F. C., Souza, M. O., Skyrms, B., 2009. Evolutionary dynamics of collective action in n-person stag hunt dilemmas. Proc. R. Soc. B 276, 315–321.

[33] Rockenbach, B., Milinski, M., 2006. The efficient interaction of indirect reciprocity and costly punishment. Nature 444, 718–723.

[34] Rowe, G. W., 1987. A dynamic game theory model of diploid genetic system. J Theor Biol 129, 243–255.

[35] Rowe, G. W., 1988. To each genotype a separate strategy - a dynamic game theory model of a general diploid system. J Theor Biol 134, 89–101.

[36] Santos, F. C., Santos, M. D., Pacheco, J. M., 2008. Social diversity promotes the emergence of cooperation in public goods games. Nature 454, 213–216.

[37] Schreiber, S. J., 2001. Urn models, replicator processes, and random genetic drift. Siam J. Appl. Math. 61, 2148–2167.

[38] Sigmund, K., De Silva, H., Traulsen, A., Hauert, C., 2010. Social learning promotes institutions for governing the commons. Nature 466, 861–863.

[39] Souza, M. O., Pacheco, J. M., Santos, F. C., 2009. Evolution of cooperation under n-person snowdrift games. J. Theor. Biol. 260, 581–588.

[40] Stander, P. E., 1992. Cooperative hunting in lions: the role of the individual. Behavioral Ecology and Sociobiology 29, 445–454.

[41] Szabó, G., Hauert, C., 2002. Phase transitions and volunteering in spatial public goods games. Phys. Rev. Lett. 89, 118101.

[42] Tarnita, C. E., Antal, T., Ohtsuki, H., Nowak, M. A., 2009. Evolutionary dynamics in set structured populations. Proc. Natl. Acad. Sci. USA 106, 8601–8604.

[43] Tarnita, C. E., Ohtsuki, H., Antal, T., Fu, F., Nowak, M. A., 2009. Strategy selection in structured populations. J. Theor. Biol. 259, 570–581.

[44] Traulsen, A., Hauert, C., De Silva, H., Nowak, M. A., Sigmund, K., 2009. Exploration dynamics in evolutionary games. Proc. Natl. Acad. Sci. USA 106, 709–712.

[45] Van Segbroeck, S., Santos, F. C., Lenaerts, T., Pacheco, J. M., 2009. Reacting differently to adverse ties promotes cooperation in social networks. Phys. Rev. Lett. 102, 058105.

[46] van Veelen, M., 2009. Group selection, kin selection, altruism and cooperation: When inclusive fitness is right and when it can be wrong. J. Theor. Biol. 259, 589–600.

[47] Volterra, V., 1928. Variations and fluctuations of the number of individuals in animal species living together. J. Cons. int. Explor. Mer 3 (1), 3–51.

[48] von Neumann, J., Morgenstern, O., 1944. Theory of Games and Economic Behavior. Princeton University Press, Princeton.

[49] Wakeley, J., 2008. Coalescent theory: an introduction. Roberts and Company Publishers.

4.4 Evolutionary games and Medea allele dynamics

The previous publications in this thesis dealt with extending the theoretical limits of frequency independent and frequency dependent models of evolution. This publication stands apart as it is an application of the theories developed so far. Herein, evolutionary game theoretic arguments are employed to

1. show how the dynamics of the Medea alleles can be used to an advantage in genetic pest management techniques and

2. explain the evolution of natural Medea elements.

Maternal **e**ffect **d**ominant **e**mbryonic **a**rrest (Medea) is a selfish gene (Hurst et al., 1996; Hurst and Werren, 2001). It was first discovered in *Tribolium* flour beetles (Beeman et al., 1992). The Medea allele increases in frequency at the cost of the wildtype allele. The effect of the Medea allele can be seen if the mating involves a female heterozygous for Medea. The Medea system works by producing a "poison" and a "rescue". Females possessing a Medea allele deposit the "poison" in the germline. If the resulting zygotes do not contain an endogenous rescue then they do not survive; in effect heterozygous (carrier) mothers can effectively kill off their homozygous wildtype offspring (see Fig. 4.4). Thus, Medea elements can increase in frequency in a population, even if they are not beneficial to the organism (Beeman et al., 1992; Wade and Beeman, 1994). The dynamics of the Medea allele have been well studied in theory and in the laboratory (Wade and Beeman, 1994; Smith, 1998). These maternal-effect selfish alleles have also been reported in the mouse (Peters and Barker, 1993; Weichenhan et al., 1996).

A synthetic Medea system has been engineered in *Drosophila melanogaster* that mimics the natural Medea system and has the same invasive properties (Chen et al., 2007). It has been proposed as a transformation system to genetically modify wild populations (Chen et al., 2007). Many proposed genetic pest management approaches rely on the introduction of genetic modifications, such as disease resistance in a vector species, using an evolution based population-transformation system. Gene drive mechanisms, engineered to genetically transform wild populations, are of little use in the real world unless they can be con-

	♀		
	$++$	$+M$	MM
$++$	$\sim$	**!**	$\sim$
$+M$	$\sim$	**!**	$\sim$
MM	$\sim$	$\sim$	$\sim$

♂ (label for rows)

$\sim$ Normal offspring
! $++$ die with probability t

Figure 4.4: **Effect of the Medea allele is seen in offsprings when mothers are heterozygous for Medea.** If the mother is a Medea carrier then she deposits a poison in the germline. Only the offspring who have a copy of the Medea allele can produce the antidote and can survive. Thus the wild-type homozygous offspring of heterozygote parents or of heterozygote mother and wild-type homozygous father are affected.

trolled. While Medea elements can, in theory, transform populations, they are very difficult to control once spread and can wipe out the resident population. Here, we describe the predicted properties of a combined system genetically linking a Medea construct with underdominance. Underdominant systems typically require the release of very large numbers of individuals to result in a stable population transformation but are more likely to be spatially contained and, if desired, completely removed from the wild. When combined with Medea this release threshold can be reduced (see Fig. 4.5). A combination of currently available techniques can results in a system with desirable theoretical properties, which in broad circumstances surpass those of the single systems considered individually. These enhanced properties include more ideal population transformation thresholds with potential reversibility, mutational stability, and enhanced spatial stability.

In small finite populations Medea elements can invade from very low frequencies with elevated probabilities, even with corresponding fitness costs. This

has implications for understanding the evolution of natural Medea elements.
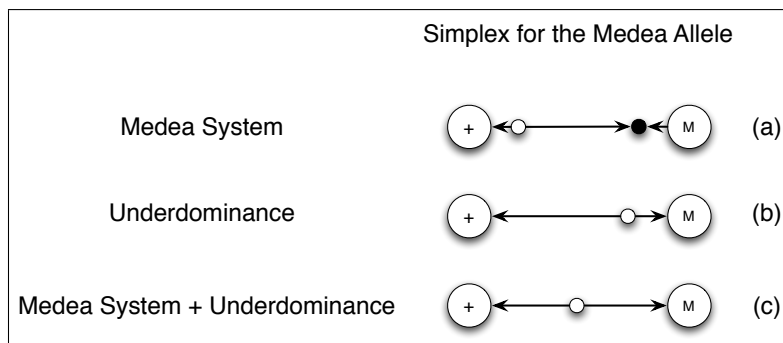
Figure 4.5: **Benefits of a combined Medea-Underdominant system.** (a) The Medea system by itself allows the selfish gene to sweep through the population. If the Medea allele has a small cost then the threshold frequency from where it can sweep through the population is very low. Also due to the cost it will not be able to fix in the population. (b) Underdominant systems usually have very high natural transformation thresholds and very large releases are necessary to overcome them. (c) A combination of Medea and underdominance brings together the best features of both the systems. The high transformation threshold of underdominance is lowered by Medea to practical release frequencies and the Medea element is more controllable.

4.4.1 Publication: Dynamics of a linked Medea-Underdominance Population Transformation System

Chaitanya S. Gokhale, R. Guy Reeves, Floyd A. Reed,
In preparation

Dynamics of a linked Medea-Underdominance
Population Transformation System

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Many proposed genetic pest management approaches rely on the introduction of genetic modifications, such as disease resistance in a vector species, using an evolutionary based population-transformation system. Predominantly, only systems with a single selective element have been envisioned. Here we describe the predicted properties of a combined system genetically linking a Medea construct with underdominance. While Medea elements can, in theory, transform populations with the release of small numbers of individuals, they are poorly suited to being spatially contained or removed from the wild. Conversely, underdominant systems typically require the release of very large numbers of individuals to result in a stable population transformation but are more likely to be spatially contained and can be, if desired, completely removed from the wild. We show that a combination of currently available techniques results in a system with desirable theoretical properties, which in broad circumstances surpass those of the single systems considered individually. These enhanced properties include more ideal population transformation thresholds with potential reversibility, mutational stability, and enhanced spatial stability. Finally, we also show that in small finite populations Medea elements can invade from very low frequencies with elevated probabilities, even with corresponding fitness costs. This has implications for understanding the evolution of natural Medea elements as well as consequences for the use of synthetic Medea in population-transformations.

Keywords: applied evolution, disease elimination, dynamical systems, gene drive, genetic pest management

I. INTRODUCTION

There are cases where the use of genetic methods to modify pest populations can be argued to be preferable to alternatives such as insecticides and classical biological control (release of non-native predators or parasites), for example, tropical conservation settings. Current approaches to developing genetic mechanisms that usefully transform a species, predominantly envisage the development of transgenic constructs that render insect vectors refractory to acting as disease vectors. There has been rapid success in the malaria and dengue fever models (e.g. Ito et al. 2002; Franz et al. 2006; Jasinskiene et al. 2007; Corby-Harris et al. 2010). However, for these refractory constructs to spread effectively into experimental or ultimately wild populations, it is widely recognized that they will need to be linked to elements that, through evolutionary effects over several generations, have the capacity to transform wild populations (reviewed in Sinkins and Gould 2006; see also Hay et al. 2010). There are also broad potential applications of this type of technology beyond insects (e.g. Gould 2008).

The earliest such proposed population-transformation system exploited the predicted underdominant fitness configurations of chromosomal translocations (Curtis 1968). In a single population rarer alleles tend to be heterozygous, with underdominance, where heterozygotes are less fit than homozygotes. Hence a threshold allele frequency arises that

is an unstable equilibrium (Fisher 1922; Wright 1931; Li 1955). Once this threshold is surpassed, for instance with releases of insects with rearranged chromosomes, an allele with underdominant effects is predicted to proceed to fixation within the population and to be stable over the following generations (Fig. 1 A). This process is inherently reversible. If the removal of genetically modified organisms is desired, releases of wildtype individuals that bring the population allele frequency below this threshold is predicted to result in the complete removal of underdominant alleles from the wild. For small migration rates this system also exhibits spatial stability (Karlin and McGregor 1972; Piálek and Barton, 1997; Altrock et al., 2010). This implies that initial wild releases can be made on a restricted local scale where permissions and informed consent for the study (which by nature are geographically restricted) are more possible to attain and more appropriate (cf. Angulo and Gilna 2008). Laboratory generated organisms were generally too unfit to result in useful underdominant constructs. It has proved exceedingly difficult to engineer viable, fit translocated stocks (e.g. Lorimer et al. 1972; Robinson 1977; Boussy 1988). Thus, the low fitness of individuals homozygous for lab engineered chromosomes appeared to be the main disadvantage of utilizing engineered underdominance to stably and reversibly transform wild populations.

In a different kind of genetic system, alleles at multiple loci in Tribolium flour beetle species have been discovered where there is a specific distortion in expected Mendelian transmission (Beeman et al. 1992). These maternal-effect selfish alleles are known as Medea elements and have also been reported in the mouse (Peters and Barker 1993; We-

ichenhan et al. 1996). In Medea systems, by producing both a poison and a rescue, organisms that contain Medea elements can be viable. However, if the poison is deposited by the mother into oocytes and the resulting zygote does not contain an endogenous rescue; heterozygous (carrier) mothers can effectively kill off their homozygous wildtype offspring. Thus, Medea elements can increase in frequency in a population, even if they are not beneficial to the organism in the sense of Darwinian adaptation (Beeman et al. 1992; Wade and Beeman 1994). A synthetic Medea system has also recently been engineered in Drosophila melanogaster that exhibits the properties found in natural Medea systems and has been proposed as a transformation system to genetically modify wild populations (Chen et al. 2007). There is also interest in screening for inducible maternal-effect lethal phenotypes in order to develop Medea systems in additional species (Hay et al. 2010).

Medea elements have very different predicted dynamics from underdominant systems and can potentially invade a population from very low frequencies (Wade and Beeman 1994). This predicts that, with low rates of migration, Medea elements can spread from population to population, possibly species wide. This also implies that it may be very difficult or impossible to reverse Medea transformed population(s) to the wildtype state and remove all genetically modified alleles from the wild. If there is a fitness cost to the organism carrying Medea elements, an unstable threshold equilibrium at a low frequency may arise (Fig. 1 B). This point must be surpassed in order for the Medea effect to overcome the fitness loss and for the allele to rise in frequency in the population, in a manner similar to underdominance. However, this unstable equilibrium can be much lower in frequency than that expected from underdominance between engineered and wildtype chromosomes (i.e. $\ll 50\%$ versus $\gg 50\%$). A fitness cost also predicts a second high-frequency stable equilibrium that the frequency of Medea elements is predicted to approach but is not expected to surpass (Fig. 1 B). Thus, unlike underdominance, Medea is not necessarily predicted to completely fix in a population (Wade and Beeman 1994). However, if the Medea effect is 100% efficient (complete lethality) with a fitness cost a population can still result in all Medea carriers, some of which are heterozygous (e.g. Chen et al. 2007). If a linked effector construct (e.g. disease resistance) is dominant then this may have the desired effect. However, if an effector is recessive, a disease may not be completely eradicated from a population (Boëte and Koella 2002, 2003). Also, if a Medea allele does not achieve complete fixation, matings between heterozygotes still experience a loss of offspring, which provides selective pressure for resistance to Medea to evolve and can disrupt the system (Smith 1998).

We have briefly introduced two very different genetic systems, underdominance and Medea. These are not always mutually exclusive. Underdominance is a result of the organismal fitness associated with the genotypes of an allele. Medea effect results from a selfish genetic process during gametogenesis and formation of the zygote that can be thought of as separate from the underlying organismal

genotype fitnesses (in the adaptive sense). Here, we present some of the predicted dynamics of a combined Medea-underdominant system in a population genetic framework (Fig. 1 C). The effects of combining different types of artificial selective systems have been considered before (Huang et al. 2007), but not this particular combination. We discuss the advantages of this combined system over the individual systems and briefly discuss the feasibility of engineering such a system.
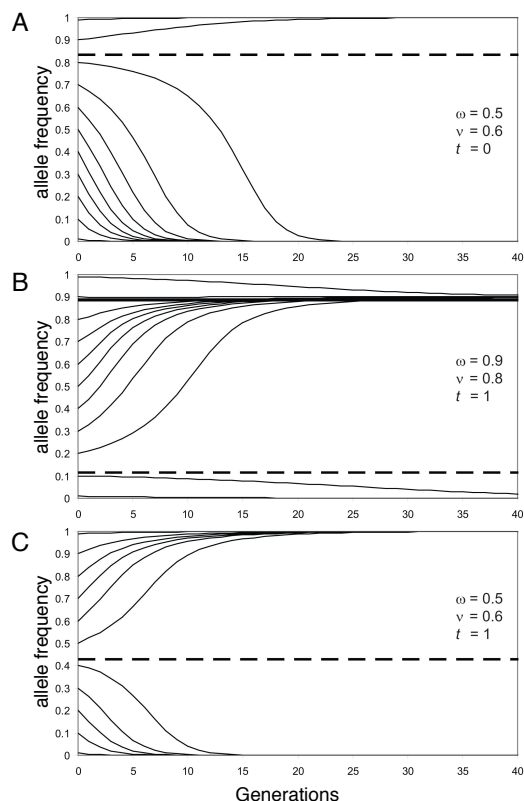

FIG. 1. **Dynamics of Medea and underdominance in a single population.** Example trajectories of allele frequencies over several generations from a range of starting frequencies are plotted, thin solid lines. Allele frequencies, p, are on the y-axis and generations on the x-axis. Discrete, non-overlapping, Wright-Fisher generations were assumed. The underlying genotype frequencies were actually used to calculate trajectories, starting at Hardy-Weinberg equilibrium in the initial generation, and are summarized by reducing them to a corresponding allele frequency. Homozygote fitness is indicated by ν and heterozygote fitness by ω, relative to a wild-type homozygote fitness of 1. The degree of Medea lethality is given by t. An unstable equilibrium is indicated by a dashed line. A stable equilibrium is indicated by a thick line. A) Underdominance with a high transformation threshold. B) Medea with a semi-dominant fitness cost. C) A combination of underdominance and Medea.

II. METHODS AND RESULTS

A. Ideal Minimum Release Sizes

In order to reach a target frequency in a population of $\hat{p}$, releases would have to be made of a minimum size of $R = \hat{p}/(1-\hat{p})$ relative to the wild population size. To cross this boundary and then recross it (i.e. to reverse the population transformation after an engineered allele has reached fixation) requires two releases with a minimum combined size of $R = \hat{p}/(1-\hat{p}) + (1-\hat{p})/\hat{p} = 1/(1-\hat{p}) + 1/\hat{p} - 2$. This function approaches positive infinity at $\hat{p} = 0$ and $\hat{p} = 1$ and has a minimum at $\hat{p} = \frac{1}{2}$, with $R = 2$ (Fig. 2). Thus, an unstable threshold of $\hat{p} = \frac{1}{2}$ is ideal from the perspective of potential population transformation *and* reversibility. It is still much lower than releases sizes used in successful applications of the sterile insect technique (e.g. Asman et al. 1981; Krafsur 1998).

In an actual applications, genotypes will be released instead of alleles. Thus it may be possible to enter the basin of attraction for transformation and reversal at different points in the full genotype space to take advantage of specific dynamics in these two-dimensions. However, the essential consideration remains the same; elements that can invade from arbitrarily low frequencies are all but impossible to reverse and remove from the wild, elements with very high threshold values are difficult to impossible to succesfully establish. Threshold equilibria near the center of the state space are optimal with regard to local spatial stability and reversibility.
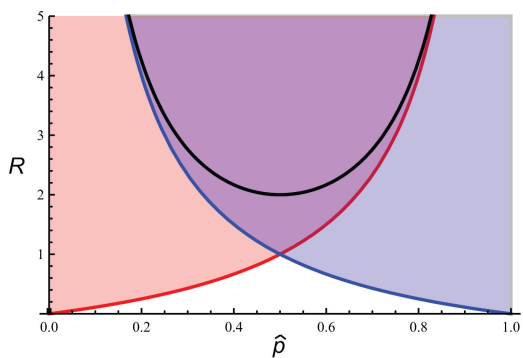
FIG. 2. **Directional and reversible transformation thresholds.** The release size relative to the wild population is given by R. The corresponding threshold allele frequency, an unstable equilibrium, is $\hat{p}$. Simplistically, in order to genetically transform a population, R must be above the red line (in the region of light red or purple). The reverse minimum transformation back to a wildtype state is indicated by the blue line. The combined total release size required for reversibility is above the black line. If releases can be made in the red area but not in the purple area, i.e. very low $\hat{p}$, the system is not reversible. Individual releases that can be made in the purple area (or combined sums above the black line) are reversible.

B. Genotype fitnesses and expected dynamics

When selection is only dependent on the organisms genotype, expected genotype frequencies can be generated under the random mating assumption (Hardy-Weinberg independent pairing of alleles). These frequencies are then adjusted each generation according to their corresponding fitnesses. However, in cases where the action of selection extends over, or is conditional on, more than one generation, this assumption can not be used, and the contribution to the next generation from each genotype class must be accounted for individually. With Medea the action of selection on wildtype homozygotes depends not only on their current state but is also coupled to the maternal genotype. For example, the number of wildtype homozygotes (and thus the allele frequency) expected in the next generation after selection is very different in a population composed entirely of heterozygotes (where all wildtype homozygotes in the next generation are exposed to the Medea effect) versus one near Hardy-Weinberg equilibrium (where only a fraction of wildtype homozygotes are exposed). In both cases the allele frequencies may be identical. Thus, the expected proportions of zygotes produced under random mating are expected to be equal, but not the fitness effects. Here we have a Medea allele, M, and a wildtype allele, $+$; which generate three genotypes, MM, $M+$, and $++$. We set the fitness of the wildtype homozygote, $++$, to 1; use ω to indicate the heterozygote, $M+$, fitness relative to wildtype; and ν to indicate the MM fitness. The parameter t measures the degree of lethality of homozygous wildtype offspring from Medea carrying mothers. This can range from zero, no lethality and no Medea effect, to 1, complete lethality of homozygous wildtype offspring from heterozygote mothers. From Table. I we can calculate the expected frequencies of all three genotypes in the next generation as,

$$\bar{G}x' = \nu\left(x^2 + xy + \frac{y^2}{4}\right)$$
$$\bar{G}y' = \omega\left(xy + yz + 2xz + \frac{y^2}{2}\right) \qquad (1)$$
$$\bar{G}z' = 1\left(z^2 + \frac{yz}{2} + (1-t)\frac{yz}{2} + (1-t)\frac{y^2}{4}\right)$$

where x, y, and z are the frequencies of MM, $M+$, and $++$ respectively in the current generation and x', y', and z' are the expected frequencies in the next generation (note that in Wade and Beeman (1994) differences in fitness were only ascribed to differences in maternal fecundity rather than zygotic genotypes as is done here). The total contribution from all genotypes in the population (i. e., the average fitness) is given by $\bar{G}$. It is the sum of the right hand sides of the set of Eqs. (1) (Hofbauer et al. 1982). Some example dynamics of the expected change in frequency of genotypes in a population are given in Fig. 3.
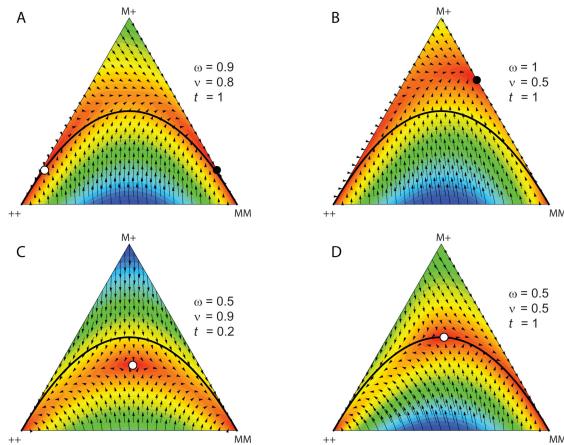
FIG. 3. **Example evolutionary dynamics in infinite populations.** Here the full two-dimensional simplexes are shown for dynamics in changes in genotype frequencies. The corner of each triangle represents 100% frequency of each genotype, which are at intermediate frequencies as distance from the corner increases, and are at a frequency of zero on the opposite edge. The black line indicates Hardy-Weinberg equilibrium for reference. Arrows indicate direction of change and arrow length and background color indicate rate of change (from blue, fast, to red, slow). Stable internal or edge equilibria are indicated with a black circle and unstable or saddle equilibria are indicated with a white circle. A) This represents the conditions given in Fig. 1 B, with a lower unstable equilibria and a stable point on the $M+$ to MM edge where wildtype homozygotes have disappeared from the population. In this case the equilibria are near Hardy-Weinberg. B) This illustrates a case where the sable equilibrium lies far from Hardy-Weinberg. C) An example with a high homozygote fitness and low degree of lethality that has an unstable equilibrium at approximately an allele frequency of $p = 1/2$ in the population ($t = 2 - 2\nu$, see Appendix). D) An example where the unstable equilibrium is at $p = 1/2$ for a high degree of lethality and low homozygote fitness, see Eq. 11.

C. Dynamics at the corners of the system

When an allele is at the extreme limit of being fixed or lost it is expected to be present as either one copy in a heterozygote or as all copies but one, also in a heterozygote. Thus the change in frequency of the heterozygote near $z = 1$ and $x = 1$ gives the conditions for an allele to invade and/or go on to fixation. The slope of y' at $z = 1$ is

$$\frac{\partial y'}{\partial y}\Big|_{z=1} = \frac{\omega}{1} \qquad (2)$$

Thus, the heterozygote fitness must be greater than the wildtype homozygote for the Medea allele to invade. Note that this condition is independent of the maternal lethal parameter t. In smaller finite populations the starting frequency will be at greater initial frequencies and, in this

TABLE I. The expected next generation contribution of individual genotypes in an underdominant Medea system under hard selection.

Parents		Offspring		
♂	♀	MM	$M+$	$++$
$++$	$++$			1
$++$	$M+$		$\omega/2$	$(1-t)/2$
$++$	MM		ω	
$M+$	$++$		$\omega/2$	$1/2$
$M+$	$M+$	$\nu/4$	$\omega/2$	$(1-t)/4$
$M+$	MM	$\nu/2$	$\omega/2$	
MM	$++$		ω	
MM	$M+$	$\nu/2$	$\omega/2$	
MM	MM	ν		

sense, a $t > 0$ will promote invasions. The corresponding dynamic at $x = 1$ is similar,

$$\frac{\partial y'}{\partial y}\Big|_{x=1} = \frac{\omega}{\nu} \qquad (3)$$

The Medea homozygote fitness has to be greater than the heterozygote to go to fixation (in an infinite population), and this condition is independent of t and consistent with underdominance. Using alternative models, Wade and Beemans (1994) and Marshalls (2009) results are also consistent with this condition for invasion and fixation.

D. Average genotype fitnesses

Another way to view the recursion equations is as a frequency multiplied by its fitness then normalized, for example $x' = x f_x / \bar{G}$, where f_x is the average fitness of the MM genotype, according to discrete time replicator dynamics (e.g., section 2.8.1 of Cressman 2003). This allows us to solve for the average fitness of each genotype (known as marginal fitness in population genetics),

$$\frac{\bar{G}x'}{x} = f_x = \nu\left(x + y + \frac{y^2}{4x}\right)$$
$$\frac{\bar{G}y'}{y} = f_y = \omega\left(x + z + \frac{2xz}{y} + \frac{y}{2}\right) \qquad (4)$$
$$\frac{\bar{G}z'}{z} = f_z = z + \frac{y}{2} + (1-t)\frac{y}{2} + (1-t)\frac{y^2}{4z}$$

Using this set of equations we can solve for the fixed points in the two-dimensional simplex as illustrated in Fig. 3. Considering the average fitness of the genotypes in a pairwise fashion, two genotypes are neither increasing or decreasing relative to each other if their average fitnesses are equal, e.g., $f_x = f_y$. If all three of these zero fitness differences intersect in the interior of the simplex an equilibrium (fixed) point exists. Additionally, if one of these curves intersects an edge corresponding to the genotypes being considered (e.g., $f_x = f_y$ on the $z = 0$ edge), a fixed point exists on that edge.

E. Edge dynamics, analytical solutions for $t = 1$

For $t = 0$ the system is governed only by genotypic fitnesses which have well understood properties and reduces to a simpler one dimensional simplex in terms of allele frequency rather than genotypes (e.g., Altrock et al. 2010). Setting $t = 1$ also allows some analytical results to be derived. Along the edges of the simplex, we look separately at $f_x = f_y$, $f_x = f_z$ and $f_y = f_z$ and set the third genotype frequency to zero to solve for equilibria. We find that only , i.e., only the MMM+ edge can posses a fixed point on the boundary. Setting $t = 1$ and solving for x in this case gives a solution of

$$x = \frac{\nu}{2\omega - \nu}. \tag{5}$$

This is a stable solution for all $\omega > \nu$, for $\omega < \nu$, there is no solution within the edge (compare to Eq. 3 above). Since there are no edge fixed points for $t = 0$ (the classic case along the Hardy-Weinberg simplex) this suggests that for $t < 1$ the fixed points will move away from the edge to the interior. This also makes intuitive sense because some wildtype homozygotes should survive if Medea lethality is not 100% and thus $z > 0$. This higher frequency interior equilibrium is expected to remain stable according to the reasoning of small parameters (Karlin and McGregor 1972) and this is confirmed numerically.

F. Internal dynamics, analytical solutions for $t = 1$

Solving $f_x = f_z$ and $f_y = f_z$ for x and y, and realizing that $z = 1 - x - y$, gives the following coordinates of an internal equilibrium, if it exists within the two-dimensional simplex,

$$\hat{x} = \frac{(\omega - 1)^2}{1 + \nu - \omega}$$
$$\hat{y} = \frac{2\omega(1 - \omega)}{1 + \nu - \omega} \tag{6}$$
$$\hat{z} = \frac{\omega^2 - \omega + \nu}{1 + \nu - \omega}$$

Subtracting the frequency from both sides of Eqs. 1 gives the change in genotype frequency per unit time,

$$x' - x = \frac{x f_x}{\bar{G}} - x$$
$$\bar{G}\Delta x = x f_x - x\bar{G}. \tag{7}$$

This can be rescaled by $\bar{G}$ without affecting the dynamical properties of the system. All fixed points remain at the same positions in the state space and flows are rescaled but remain in the same direction. Thus, we can write down the dynamics for all three genotypes in a simplified non-rational form as,

$$\Delta x = x(f_x - \bar{G})$$
$$\Delta y = y(f_y - \bar{G}) \tag{8}$$
$$\Delta z = z(f_z - \bar{G})$$

Using Eqs. 8, the eigenvalues of the Jacobian at the equilibrium point given in Eqs. 5 are

$$\lambda_\pm = \frac{-\nu\omega \pm \sqrt{\nu\left(\nu(2 - \omega)^2 - 4\omega(1 - \omega)^2\right)}}{2(1 + \nu - \omega)}. \tag{9}$$

If $\lambda\pm < 0$ then the equilibrium is stable, if both eigenvalues are positive it is unstable and if the values have opposite signs it is a saddle point.

Of interest is the case where the unstable equilibrium frequency is equal to one half,

$$x + y/2 = 1/2, \tag{10}$$

because this is an ideal transformation threshold according to the reasoning given in the previous section. Substituting the equilibrium values in Eqs. 5 into Eq. 10 gives

$$\nu + \omega = 1 \tag{11}$$

at $t = 1$ (Fig. 3 D). Again, coupled with the reasoning for the stable point on the edge above, for $t < 1$, there may exist two internal equilibria, the lower allele frequency one is unstable and the higher frequency one is stable, this is verified numerically (e.g., Fig. 3) and supported by the Hardy-Weinberg approximation given in the Appendix. However, if $1 > \nu > \omega$ (underdominance) and (Eq. 11) only the unstable internal equilibrium at $p = 1/2$ exists.

G. Dynamics in finite populations with overlapping generations

The Moran process is a tractable birth-death process used to model well-mixed finite populations (e.g. Karlin and Taylor 1975; see Traulsen and Hauert 2009 for a general introduction). Here, in each time step, a single individual is chosen at random to be removed from the population and another individual is chosen for reproduction according to fitness.

One quality of particular interest in Medea systems are the properties of invasion when rare due to the female killing effect. If genotype fitnesses are equal, M alleles are predicted to invade infinitely slowly in infinitely large populations (Eq. (2) and Wade and Beeman 1994). In small finite populations, a single M allele has a greater starting frequency and the wildtype individuals killed by Medea also make up a greater proportion of a smaller population. In larger finite populations, selection is more able to overcome drift when rare, but the allele has a smaller starting frequency. It is not intuitively clear how these trade-offs affect fixation probabilities. The two-dimensional simplex of genotype frequencies prevents us from using standard analytical tools of the Moran model.

To address this, we simulated the trajectories of loss or fixation of initially a single Medea allele present in a heterozygous individual. In each time step a "mother" and "father" are chosen from the population with a probability proportional to their number and relative fitnesses. Conditional on the parental genotypes, an offspring is generated

TABLE II. The expected next generation contribution of individual genotypes in an underdominant Medea system with soft selection.

Parents		Offspring		
♂	♀	MM	$M+$	$++$
$++$	$++$			1
$++$	$M+$		$\omega(1+t)/2$	$(1-t)/2$
$++$	MM		ω	
$M+$	$++$		$\omega/2$	$1/2$
$M+$	$M+$	$\nu(1+t/3)/4$	$\omega(1+t/3)/2$	$(1-t)/4$
$M+$	MM	$\nu/2$	$\omega/2$	
MM	$++$		ω	
MM	$M+$	$\nu/2$	$\omega/2$	
MM	MM	ν		

according to the genotype cross (Table. I) and the degree of Medea lethality (if the offspring dies due to Medea the parents are repicked and another child is generated). Then the resulting offspring replaces a single individual in the population at random. If population sizes are small then, even with a modest fitness cost relative to wildtype of $10-20\%$, a single Medea allele can invade a new population with a probability elevated over that of neutrality. However, heterozygote fitness reductions of 30% or greater help prevent Medea invasion in new populations. The scenario just described represents a "hard selection" regime.

However, if there is resource limiting sibling competition, where a larger number of initial zygotes result, according to fitness, in a smaller number of individuals that survive to reproduction, (and/or remating compensation effects) there can be a "soft selection" scenario (cf. Wade 1985). This case assumes that a given pairing will ultimately produce an offspring (i.e., wildtype homozygotes lost due to Medea are replaced by alternative genotypes, Table. II). This was also modeled as before except that when offspring lethality was encountered offspring were repicked within the pairing instead of picking new parents (i.e., these two scenarios represent the extreme limits of hard and soft selection). This soft selection scenario corresponds to the following recursions,

$$\bar{G}x' = \nu\left(x^2 + xy + \frac{y^2}{4} + t\left(\frac{1}{3}\frac{y^2}{4}\right)\right)$$

$$\bar{G}y' = \omega\left(xy + yz + 2xz + \frac{y^2}{2} + t\left(\frac{yz}{2} + \frac{2}{3}\frac{y^2}{4}\right)\right) \quad (12)$$

$$\bar{G}z' = 1\left(z^2 + \frac{yz}{2} + (1-t)\frac{yz}{2} + (1-t)\frac{y^2}{4}\right).$$

In this second regime, one result that becomes clear is that Medea alleles can invade and fix in a population with a probability that is dramatically elevated over that of neutrality (a similar result is also found in Wade and Beeman 1994). If there is no fitness cost, this probability is approximately a constant $\Phi \approx 1/3$ over a wide range of population sizes (Fig.

4 B). A large heterozygous fitness reduction of $40\%-50\%$ relative to wildtype is required to bring the fixation probability down to approximate neutrality ($\Phi = 1/2N$). Even in an infinite population, a dominant fitness cost as high as 30% can still yield an invasion/fixation trajectory (Fig. 5 A). A closer look at some individual examples reveals a highly asymmetric trajectory. Even when genotype fitnesses are all equal to one, the initial rise in frequency is quite fast, then there is a long time spent waiting at high frequencies before ultimate fixation (Fig. 5 B). This potentially increases the opportunity for alleles resistant to Medea to arise which can destabilize the system and return to a wildtype state (Smith 1998).
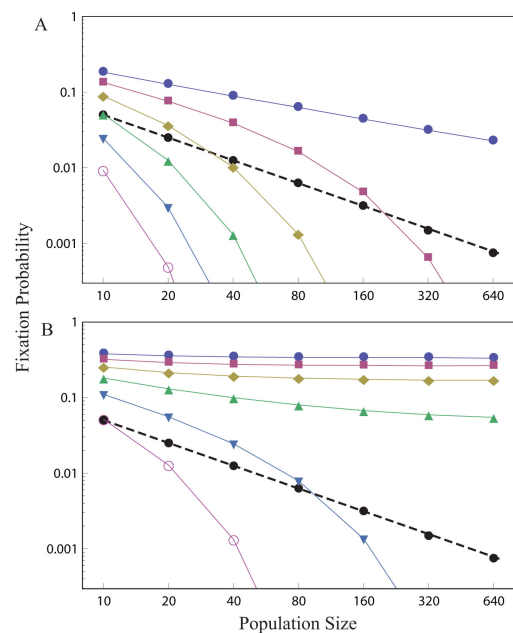

FIG. 4. **The probability of invasion of a Medea allele.** Fixation probability versus diploid population size for a Medea allele starting as a single heterozygote in the population. The probability of fixation under neutrality is given by the black dashed line with circles for reference. A heterozygote fitness equal to homozygotes, $\omega = 1$, is given by the top dark blue line with circles, $\omega = 0.9$ red squares, $\omega = 0.8$ yellow diamonds, $\omega = 0.7$ light blue triangles, $\omega = 0.6$ blue upside down triangles, $\omega = 0.5$ red open circles. A) Fixation probabilities under the standard hard selection model. B) Fixation probabilities under soft selection with, for example, sibling competition.

H. Population structure dynamics

Next we consider a two-deme model of population structure, where two discrete populations of large size are couple by a symmetrical fraction of migrants between the popula-

tions each generation. Genotype frequencies in each population are adjusted each generation for exchanging migrants, at a fraction m, and retaining non-migrants, at fraction $1 - m$. In population i the expected genotype frequency for genotype k after migration (g') is

$$g'_{k,i} = (1 - m)g_{k,i} + mg_{k,j}, \qquad (13)$$

where here $g_{k,i}$ is the frequency of the kth allele in population i and $g_{k,j}$ is the kth allele frequency in population j. These adjusted genotype frequencies can then be substituted into Eqs. 1 and the equivalent recursion for the second population, $g'_{k,j}$, can be found by interchanging i and j in Eq. 13.

Simulations were performed of the two-population system to find the critical migration rate allowing stable differences in allele frequencies between the two populations. To do this the allele frequencies were started at opposite values ($p_1 = 0, p_2 = 1$) with an initial migration rate of zero. The migration rate was slowly incremented in units of 10^{-4}. For each value of migration, the allele frequency recursions were iterated until the difference in allele frequencies between generations was less than 10^{-12} (i.e. effective equilibrium was reached). This process was stopped once the absolute difference in allele frequencies between the two populations fell below 1% and the corresponding migration rate was recorded as the critical migration rate boundary where stability is lost (i.e., at lower migration rates the combined systems will not spread far from a successfully transformed zone, and will be resistant to loss by immigration). Results plotted for a range of fitness and Medea values show that the combined system can have enhanced stability against migration, tolerating higher migration rates while maintaining geographic stability (Fig. 6). However, at $\omega = 0$, there are no heterozygotes reproducing and thus Medea has no effect and the dynamics are equivalent to that expected with only underdominance (Fig. 6).

III. DISCUSSION

The major disadvantage of classical underdominance is its high transformation thresholds. The major disadvantages of Medea systems are their low transformation thresholds and, possibly, a lack of complete fixation within a population if there is a fitness cost. A reduction in homozygote fitness seems to be unavoidable with classically engineered translocations (see also Boussy 1988). Note that radiation induced translocations are rare single events that are then made homozygous, and translocations typically suppress recombination over a neighboring chromosomal region (Dobzhansky 1931, Wallace 1956).

In a Medea system, even with a fitness cost, if migration rates are sufficiently high, once a single population is above a transformation threshold, the accumulation of the M allele in neighboring populations by migration can be sufficient to also raise the neighboring allele frequency above this threshold and the system is expected to spread. Furthermore, in some cases, results from infinite population models

can be misleading when intuitively applied to finite populations. As illustrated above, Medea alleles that are otherwise equivalent to wildtypes in terms of fitness, have an elevated probability of invasion in finite populations with overlapping generations and can even overcome the effects of mild underdominance (Fig. 4). A related caution in using fertility reducing translocations to help limit the spread of Medea is that soft selection can also act to relax the fitness cost of the translocation in addition to promoting the invasiveness and spread of Medea. Thus, the degree of sibling competition and/or remating compensation should be studied for target species to better understand if this may be a relevant factor; e.g. if a singly mated female mosquito predominantly laid all the eggs present in a small pool with density dependant larval mortality (cf. Madder et al. 1983; Dye 1984; Teng and Apperson 2000; see also the discussion of this in Hay et al. 2010). Related examples from Tribolium and mouse can be found in (Beeman and Friesen 1999; Lorenzen et al. 2008, Winking et al. 1991) Perhaps, if Medea alleles were more common across species (as suggested by Beeman and Friesen 1999), they, in conjunction with soft selection, could contribute to explanations of how chromosomal rearrangements accumulate between species despite underdominance (suggested for meiotic drive, Sandler and Novitski 1957; Bengtsson and Bodmer 1976). Thus, local fine-scaled population stratification (in addition to density regulated soft selection within families, Wade and Beeman 1994) may promote the invasion of rare Medea migrants and is an important consideration in the applicability of analytic results.

By linking Medea and underdominance the combined system can result in ideal properties in terms of population transformation ability and reversibility. Medea gives potentially underdominant alleles an "upward boost" at intermediate frequencies, where Medea acts most efficiently, and underdominance can give Medea alleles an "outward push" at lower and higher allele frequencies, where underdominance acts more efficiently (Fig. 1). These complementary properties not only potentially include a transformation threshold closer to $p = 1/2$ (at $\nu + \omega = 1$ for $t = 1$, Eq. 11, or at $t = 2 - 2\nu$, from Eq. A6 using the Hardy Weinberg approximation) for reversibility (Fig. 2), but also the property that the genetic construct can completely fix within a single population and can also be completely removed (if $\nu > \omega < 1$, Fig. 1). Furthermore, a combined system can have enhanced stability against migration along the edges of a transformed zone, even beyond that of underdominance alone, both in terms of preventing unwanted spread of genetic modifications and in maintaining a local transformation against wildtype immigrants (Fig. 6).

The tools already exist to attempt to engineer a system with these combined properties in Drosophila. A Medea poison-rescue element (Chen et al. 2007) could be inserted near a translocation breakpoint that has underdominant properties (a reduction in heterozygote fertility). New approaches have been developed to target insertions to specific points in the genome (such as the $\varphi C31 - attP$ integration system; Bischof et al. 2007) and translocations can

also be designed with breakpoints at specific sites (for example, by using the FRT-FLP system, Beumer et al. 1998; or by double strand breaks and homologous recombination, Egli et al. 2004), so it should be possible to accomplish this insertion close to a breakpoint. If an effector construct designed to provide disease refractoriness has a substantial fitness cost, then even a "fit" translocation that may otherwise be equivalent to wildtype fitness. This system will have a predicted threshold frequency near $p = 1/2$ and may benefit from being combined with a Medea element to give an upward boost to the fitness reducing effector. Since translocations essentially reduce fertility by $1/2$, but not to zero, genetic variation in the wild can introgress into the genetically modified population. This could allow local adaptation to persist in the majority of the genome alongside a targeted genetic transformation. It should also be possible to engineer a system that is resistant to recombination breaking up the linkage both between Medea and the translocation as well as the effector gene (Dobzhansky 1931, Coyne et al. 1993; Sherizen et al. 2005). (Alternative efforts to design a system resistant to disruption by recombination result in a greater fitness cost, Chen et al. 2007.)

There are methods to engineer underdominance with much lower threshold frequencies than the single locus system considered here (two-locus poison-rescue underdominance, Davis et al. 2001); however, this also results in lowered stability against spread by migration. Geographic stability may have particular value both in initial testing of genetically modified vectors and in species conservation applications (e.g. the Galápagos, Bataille et al. 2009, and Hawaiian, Warner 1968, archipelagoes).

In a combined system, if the Medea effect was inactivated by mutation, the presence of a translocation enables reversibility, and possibly stability, to be maintained. However, it can be seen that disruption of the Medea effect in a combined system would shift the system closer to loss of the transgene (compare Fig. 1 C to Fig. 1 A), providing a degree of fail-safe to restore the system to a wildtype state. Also, if a third allele resistant to the female killing Medea effect arose in the population, the presence of underdominance may inhibit a resistance allele from becoming established in the population (Altrock et al. 2010).

We agree that it is not a trivial engineering challenge to combine the two systems in a way that meets optimal fitness combinations. However, we also feel that the combined system described here should not be simply viewed as a baroque second-generation elaboration on existing technologies. A system with these predicted advantages; enhanced spatial stability, reversibility, and robustness to mutation and recombination would be ideal not only for reducing the likelihood of artificial Medea constructs becoming irreversibly established in the wild in model organisms, but additionally for first generation testing of population-transformation systems.

Appendix A: Hardy-Weinberg Approximations

Here we briefly present some general analytic solutions assuming one-dimensional dynamics along Hardy-Weinberg equilibrium within the two-dimensional simplex of genotype frequencies. As described in the main text, this is inadequate to fully describe the system; however, there are some useful approximations that can be made , particulary when t is small and/or ν is large (in these cases the stable points can approach the Hardy-Weinberg axis).

Assuming Hardy-Weinberg equilibrium allows the dynamics to be written in terms of allele frequency. Let the frequency of the Medea allele (M) be written as p with a corresponding fitness f_M and the frequency of the wildtype allele ($+$) is $(1-p)$ with a fitness f_+. The Medea allele is unaffected by (i.e. rescues) maternal induced lethality, thus the average fitness of an M allele is only the relative genotype fitness weighted by the probability of appearing in heterozygote or homozygote form,

$$f_M = p\nu + (1-p)\omega. \tag{A1}$$

The mean population fitness is the sum of the Medea allele's average fitness and the average fitness of the wildtype allele, f_+, weighted by their corresponding frequencies,

$$\bar{w} = pf_M + (1-p)f_+. \tag{A2}$$

The average fitness of the wildtype allele can be written as,

$$f_+ = p\omega + (1-p)(1-pt). \tag{A3}$$

The wildtype allele is heterozygous at frequency p, with a relative fitness of ω. Alternatively, the wildtype allele is paired with another wildtype allele at a frequency of $1-p$, and its average fitness is reduced from 1 by an amount proportional to the frequency of the Medea allele in the popualtion and the degree of lethality due to Medea, pt. Medea lethality only reduces the expected proportion of wildtype homozygotes by t from Medea carrying mothers. In this case we know that one allele in the mother has to be wildtype, given that the offspring is wildtype homozygous, and the chance that this wildtype allele is paired with a Medea allele in the mother is p. The remaining wildtype homozygotes that do not have heterozygous mothers have a relative genotype fitness of 1.

The equilibria in this approximate treatment are found when the two average allele fitnesses are equal, which is

given by

$$f_M - f_+ = -tp^2 + (1 + t + \nu - 2\omega)p - 1 + \omega = 0. \quad \text{(A4)}$$

Solving for p gives the two possible internal equilibria along the Hardy-Weinberg axis (e.g. Fig. 1 B),

$$\hat{p}_\pm = \frac{1 + t + \nu - 2\omega \pm \sqrt{(1 + t + \nu - 2\omega)^2 + 4t(\omega - 1)}}{2t}$$
$$\text{(A5)}$$

Eq. A4 is a quadratic polynomial of the general form $ax^2 + bx + c$. The coefficient of the squared term, a, is $-t$ and t can either be zero or positive. Hence, whenever $t > 0$ the parabola determined by this function will always open downward. Thus, if both roots exist inside the simplex, the lower root (closer to $p = 0$) will always be unstable and the greater root will always be stable for any combination of ν, ω, and $t > 0$.

As described before, a "threshold" unstable equilibrium of $\hat{p}_- = 1/2$ can be thought of as an ideal situation from the standpoint of systems that are stable and reversible in terms of release numbers required to repeatedly cross this threshold. Setting $\hat{p}_- = 1/2$ and solving Eq. 18 for ν results in

$$\nu = 1 - t/2. \quad \text{(A6)}$$

In other words, with this approximation, in order to maintain an unstable equilibrium at $\hat{p}_- = 1/2$, a lower homozygote fitness can be compensated for by a higher degree of Medea lethality (Fig. 3 C and D).

REFERENCES

Altrock, P. M., A. Traulsen, R. G. Reeves, and F. A. Reed 2010 Using underdominance to bi-stably transform local populations. J. Theor. Biol. 267: 62-75.

Angulo, E. and B. Gilna, 2008 International law should govern release of GM mosquitoes. Nature 454: 158.

Asman, S. M., P. T. McDonald, and T. Prout, 1981 Field studies of genetic control systems for mosquitoes. Annu. Rev. Entomol. 26: 289-318.

Barton, N. H., 1979 The dynamics of hybrid zones. Heredity 43: 341-359.

Barton, N. H. and S. Rouhani, 1991 The probability of fixation of a new karyotype in a continuous population. Evolution 45: 499-517.

Bataille, A., A. A. Cunningham, V. Cedeo, M. Cruz, G. Eastwood, et al., 2009 Evidence for regular ongoing introductions of mosquito disease vectors into the Galápagos Islands. Proc. Biol. Sci. 276: 3769-3775.

Beeman, R. W., and K. S. Friesen, 1999 Properties and natural occurrence of maternal-effect selfish genes ("Medea" factors) in the red flour beetle, Tribolium castaneum. Heredity 82: 529-534.

Beeman, R. W., K. S. Friesen and R. E. Denell, 1992 Maternal-effect selfish genes in flour beetles. Science 256: 89-92.

Bengtsson, B. O. and W. F. Bodmer, 1976 On the increase of chromosome mutations under random mating. Theoretical Population Biology 9: 260-281.

Beumer, K. J., S. Pimpinelli, and K. G. Golic, 1998 Induced Chromosomal Exchange Directs the Segregation of Recombinant Chromatids in Mitosis of Drosophila. Genetics 150: 173-188.

Bischof, J., R. K. Maeda, M. Hediger, F. Karch, and K. Basler. 2007 An optimized transgenesis system for Drsophila using germ-line-specific ?C31 integrases. Proc. Natl. Acad. Sci. U.S.A. 104:3312-3317.

Boëte, C. and J. C. Koella, 2002 A theoretical approach to predicting the success of genetic manipulation of malaria mosquitoes in malaria control. Malaria Journal 1: 3

Boëte, C. and J. C. Koella, 2003 Evolutionary ideas about genetically manipulated mosquitoes and malaria control. Trends in Parasitology 19: 32-38.

Boussy, I. A., 1988 A Drosophila model of improving the fitness of translocations for genetic control. Theoretical and Applied Genetics 76: 627-639.

Chen, C. H., H. Huang, C. M. Ward, J. T. Su, L. V. Schaeffer, et al., 2007 A synthetic maternal-effect selfish genetic element drives population replacement in Drosophila. Science 316: 597-600.

Clark, T., 2002 Mosquitoes minus malaria. Nature 419: 429-430.

Corby-Harris, V., A. Drexler, L. W. de Jong, Y. Antonova, N. Pakpour, et al. 2010 Activation of Akt Signaling Reduces the Prevalence and Intensity of Malaria Parasite Infection and Lifespan in Anopheles stephensi Mosquitoes. PLoS Pathog. 6: e1001003.

Coyne, J. A., W. Meyers, A. P. Crittenden, and P. Sniegowski, 1993 The Fertility Effects of Pericentric Inversions in Drosophila melanogaster. Genetics 134: 487-496.

Cressman, R., 2003 Evolutionary dynamics and extensive form games. Massachusetts Institute of Technology Press. Cambridge, Massachusetts.

Curtis, C. F., 1968 Possible use of translocations to fix desirable genes in insect pest populations. Nature 218: 368-369.

Davis, S., N. Bax, and P. Grewe, 2001 Engineered underdominance allows efficient and economical introgression of traits into pest populations. J. Theor. Biol. 7: 83-98.

Dobzhansky, T., 1931 The decrease of crossing-over observed in translocations, and its probable explanation. Am. Nat. 65: 214-232.

Dye, C., 1984 Models for the population dynamics of the yellow fever mosquito Aedes aegypti. J. Anim. Ecol. 53: 247-268.

Egli, D., E. Hafen, and W. Schaffner, 2004 An Efficient Method to Generate Chromosomal Rearrangements by Targeted DNA Double-Strand Breaks in Drosophila melanogaster. Genome Res. 14: 1382-1393.

Fisher, R. A., 1922 On the dominance ratio. Proc. Roy. Soc. Edinburgh 42: 321-341.

Fitz-Earle, M., D. G. Holm and D. T. Suzuki, 1973 Genetic control of insect population. I. Cage studies of chromosome replacement by compound autosomes in Drosophila melanogaster. Genetics 74: 461-475.

Foster, G. G., M. J. Whitten, T. Prout and R. Gill, 1972 Chromosome rearrangements for the control of insect pests. Science 176: 875-880.

Foster, G. G., R. H. Maddern, R. A. Helman, and E. M. Reed, 1985 Field trial of a compound chromosome strain for genetic control of the sheep blowfly Lucilia cuprina. Theoretical and Applied Genetics 70: 13-21.

Franz, A. W. E., I. Sanchez-Vargas, Z. N. Adelman, C. D. Blair, B. J. Beaty, et al., 2006 Engineering RNA interference-based resistance to dengue virus type-2 in genetically-modified Aedes aegypti. Proc. Natl. Acad. Sci. U.S.A. 103: 4198-4203.

Gould, F. 2008 Broadening the application of evolutionarily based genetic pest management. Evolution 62: 500-510.

Haldane, J. B. S., 1942 Selection against heterozygosis in man. Ann. Eugen. 11: 333-340.

Harewood, L, F. Schtz, S. Boyle, P. Perry, M. Delorenzi, et al., 2010 The effect of translocation-induced nuclear re-organization on gene expression. Genome Res. 20: 554-564.

Hay, B. A., C.-H. Chen, C. M. Ward, H. Huang, J. T. Su, and M. Guo, 2010 Engineering the genomes of wild insect popualtions: Challenges, and opportunities provided by synthetic Medea selfish genetic elements. J. Insect Physiol. 56: 1402-1413.

Hofbauer, J., P. Schuster, and K. Sigmund, 1982 Game Dynamics in Mendelian Populations. Biol. Cybern. 43: 51-57.

Huang, Y., K. Magori, A. L. Lloyd and F. Gould, 2007 Introducing transgenes into insect populations using combined gene-drive strategies: Modeling and analysis. Insect Biochem. Molec. 37: 1054-1063.

Huang, Y., A. L. Lloyd, M. Legros, and F. Gould, 2008 Gene-drive in age-structured insect populations. Evolutionary Applications 2: 143-159.

Huang, Y., A. L. Lloyd, M. Legros, and F. Gould, 2010 Gene-drive into insect populations with age and spatial structure: a theoretical assessment. Evolutionary Applications (Early View, published online in advance of print).

Ito, J., A. Ghosh, L. A. Moreira, E. A. Wimmer, and M. Jacobs-Lorena, 2002 Transgenic anopheline mosquitoes impaired in transmission of a malaria parasite. Nature 417: 452-455.

Jasinskiene, N., J. Coleman, A. Ashikyan, M. Salampessy, O. Marinotti, et al., 2007 Genetic control of malaria parasite transmission: threshold levels for infection in an avian model system. Am. J. Trop. Med. Hyg. 76: 1072-1078.

Karlin, S., and J. McGregor, 1972 Application of method of small parameters to multi-niche population genetic models. Theor. Pop. Biol. 3: 186-209.

Karlin, S. and H. M. A. Taylor, 1975 A First Course in Stochastic Processes, 2nd Edition. Academic, London.

Krafsur, E. S., 1998 Sterile insect technique for suppressing and eradicating insect populations: 55 years and counting. J. Ag. Entomol. 15: 303-317.

Lande, R., 1985 The fixation of chromosomal rearrangements in a subdivided population with local extinction and colonization. Heredity 54: 323-332.

Laponte, D. and J. Burgett, 2005 Mosquitoes in Hawaii. Position paper of the Hawaiian Conservation Alliance

Li, C. C. 1955 The Stability of an Equilibrium and the Average Fitness of a Popualtion. Am. Nat. 89: 281-295.

Lorenzen, M. D., A. Gnirke, J. Margolis, J. Garnes, M. Campbell, et al., 2008 The maternal-effect, selfish genetic element Medea is associated with a composite Tc1 transposon. Proc. Natl. Acad. Sci. USA 105: 10085-10089.

Lorimer, N., E. Hallinan, and K. S. Rai, 1972 Translocation homozygotes in the yellow fever mosquito, Aedes aegypti. J. Hered. 63: 158-166.

Madder, D., G. Surgeoner, and B. Helson, 1983 Number of generations, egg production and developmental time of Culex pipens and Culex restuans (Diptera: Culicidae) in southern Ontario. J. Med. Entomol. 20: 275-287.

Magori, K., M. Legros, M. E. Puente, D. A. Focks, T. W. Scott, et al., 2009 Skeeter Buster: A Stochastic, Spatially Explicit Modeling Tool for Studying Aedes aegypti Population Replacement and Population Suppression Strategies. PLoS Neglected Tropical Diseases 3: e508.

Marshall, J. C., J. Pinto, J. D. Charlwood, G. Gentile, F. Santolamazza, et al., 2008 Exploring the origin and degree of genetic isolation of Anopheles gambiae from the islands of So Tom and Prncipe, potential sites for testing transgenic-based vector control. Evolutionary Applications 1: 631-634.

Marshall, J. M., 2009 The effect of gene drive on containment of transgenic mosquitoes. J. Theor. Biol. 258: 250-265.

McGovern, D. P. B., M. R. Jones, K. D. Taylor, K. Marciante, X. Yan, et al. 2010 Fucosyltransferase 2 (FUT2) non-secretor status is associated with Crohn's disease. Hum. Mol. Genet. 19: 3468-3476.

Newburg, D. S., G. M. Ruiz-Palacios, and A. L. Morrow 2005 Human Milk Glycans Protect Infants Against Enteric Pathogens. Annu. Rev. Nutr. 25: 37-58.

Peters, L. L., and J. E. Barker, 1993 Novel inheritance of the murine severe combined anemia and thrombocytopenia (scat) phenotype. Cell 74: 135-142.

Piálek, J. and N. H. Barton, 1997 The spread of an advantageous allele across a barrier: The effects of random drift and selection against heterozygotes. Genetics 145: 493-504.

Pinto, J., M. J. Donnelly, C. A. Sousa, J. malta-Vacas, V. Gill, et al., 2003 An island within an island: genetic differentiation of Anopheles gambiae in So Tom, West Africa, and its relevance to malaria vector control. Heredity 92: 407-414.

Robinson, A. S., 1977 Translocations and a Balanced Polymorphism in a Drosophila Population. Genetica 47: 231-236.

Robinson, A. S. and C. F. Curtis, 1973 Controlled Crosses and Cage Experiments with a Translocation in Drosophila. Genetica 44: 591-601.

Ruvoën-Clouet, N., E. Mas, S. Marionneau, P. Guillon, D. Lombardo, and J. Le Pendu 2006 Bile-salt-stimulated lipase and mucins from milk of 'secretor' mothers inhibit the binding of Norwalk virus capsids to their carbohydrate ligands. Biochem. J. 393: 627-634.

Sandler, L. and E. Novitski, 1957 Meiotic drive as an evolutionary force. Am. Nat. 41: 105-110.

Seager, R. D., F. J. Ayala, and R. W. Marks, 1982 Chromosome Interactions in Drosophila melanogaster. II. Total Fitness. Genetics 102: 485-502.

Sherizen, D., J. K. Jang, R. Bhagat, N. Kato and K. S. McKim, 2005 Meiotic Recombination in Drosophila Females Depends on Chromosome Continuity Between Genetically Defined Boundaries. Genetics 169: 767-781.

Sinkins, S. P., and F. Gould, 2006 Gene drive systems for insect disease vectors. Nat. Rev. Gen. 7: 427-435.

Smith, N. G., 1998 The dynamics of maternal-effect selfish genetic elements. J. Theor. Biol. 191: 173-180.

Soboleva, T. K., P. R. Shorten, A. B. Pleasants, and A. L. Rae, 2003 Qualitative theory of the spread of a new gene into a resident population. Ecol. Model 163: 33-44.

Teng, H. and C. Apperson, 2000 Development and survival of immature Aedes albopictus (Diptera: Culicidae) in the laboratory: effects of density, food and competition on response to temperature. J. Med. Entomol. 37: 40-52.

Traulsen, A. and C. Hauert, 2009 Stochastic evolutionary game dynamics. In Reviews of Nonlinear Dynamics and Complexity, Vol. II, Ed. H. G. Schuster, Wiley-VCH.

Wade, M. J., 1985 Hard selection, soft selection, kin selection, and group selection. Am. Nat. 125: 61-73.

Wade, M. J., and R. W. Beeman, 1994 The Population Dynamics of Maternal-Effect Selfish Genes. Genetics 138: 1309-1314.

Wallace, B., 1956 Studies on irradiated populations of D. melanogaster. J. Genetics 54: 280-293.

Warner, R. E., 1968 The role of introduced diseases in the extinction of the endemic Hawaiian avifauna. Condor 70: 101-120.

Weichenhan, D., W. Traut, B. Kunze, and H. Winking, 1996 Distortion of Mendelian recovery ratio for a mouse HSR is caused by maternal and zygotic effects. Genet. Res. 68: 125-129.

Wiener, A. S., 1942 The Rh factor and racial origins. Science 96: 407-408.

Winking, H., A. Weith, B. Boldyreff, K. Moriwaki, K. Fredga, et al., 1991 Polymorphic HSRs in chromosome 1 of the two semispecies Mus musculus musculus and Mus m. domesticus have a common origin in an ancestral population. Chromosoma 100: 147-151.

Woodworth, B. L., C. T. Atkinson, D. A. LaPointe, P. J. Hart, C. S. Spiegel, et al., 2005 Host population persistence in the face of introduced vector-borne diseases: Hawaii amakihi and avian malaria. Proc. Natl. Acad. Sci. USA 102: 1531-1536.

Wright, S., 1931 Evolution in mendelian populations. Genetics 16: 97-159.

Wright, S., 1941 On the probability of fixation of reciprocal translocations. Am. Nat. 75: 513-522.

Zivkovic, A. M., J. B. German, C. B. Lebrilla and D. A. Mills 2010 Human milk glycobiome and its impact on the infant gastrointestinal microbiota. Proc. Natl. Acad. Sci. USA (PNAS Early Edition)

A

M+

$\omega = 0.7$
$\nu = 0.7$
$t\ = 1$

++   MM

B

$\omega = 1$
$\nu = 1$
$t\ = 1$
$N = 100$

Medea allele frequency

Time Step
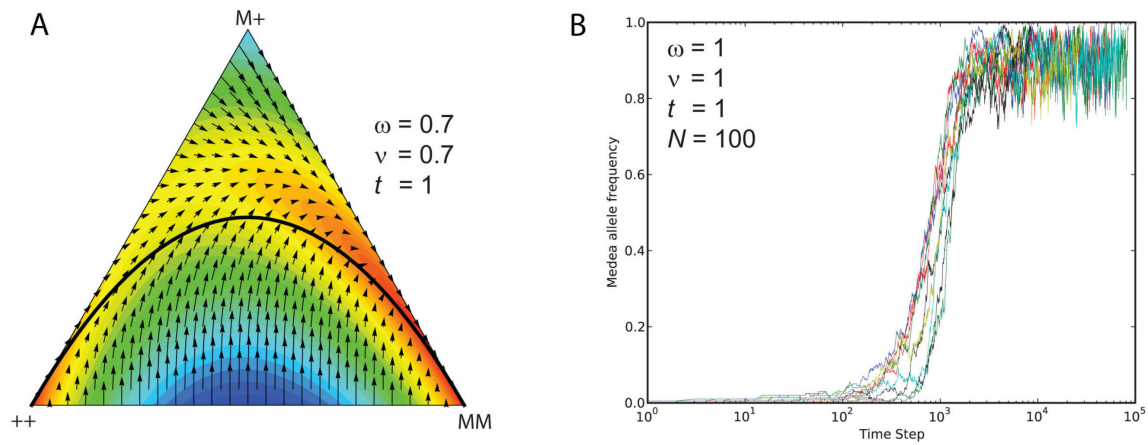
FIG. 5. **Illustrative dynamics for examples of soft selection.** A) A simplex similar to those in Fig. 3 except the soft selection genotype frequency recursions given in Equations 12 are used. B) Example trajectories for 20 replicate simulations. Time steps here refer to a single birth-death replacement under the Moran model. Eleven of the replicate frequencies were lost while rare; nine trajectories achieved fixation but segregated at high frequency for a substantial period of time before fixing (note that time is on a log scale). This may increase the time for alleles resistant to Medea lethality to occur in the population. With underdominance, fixation is rarer but achieved faster.
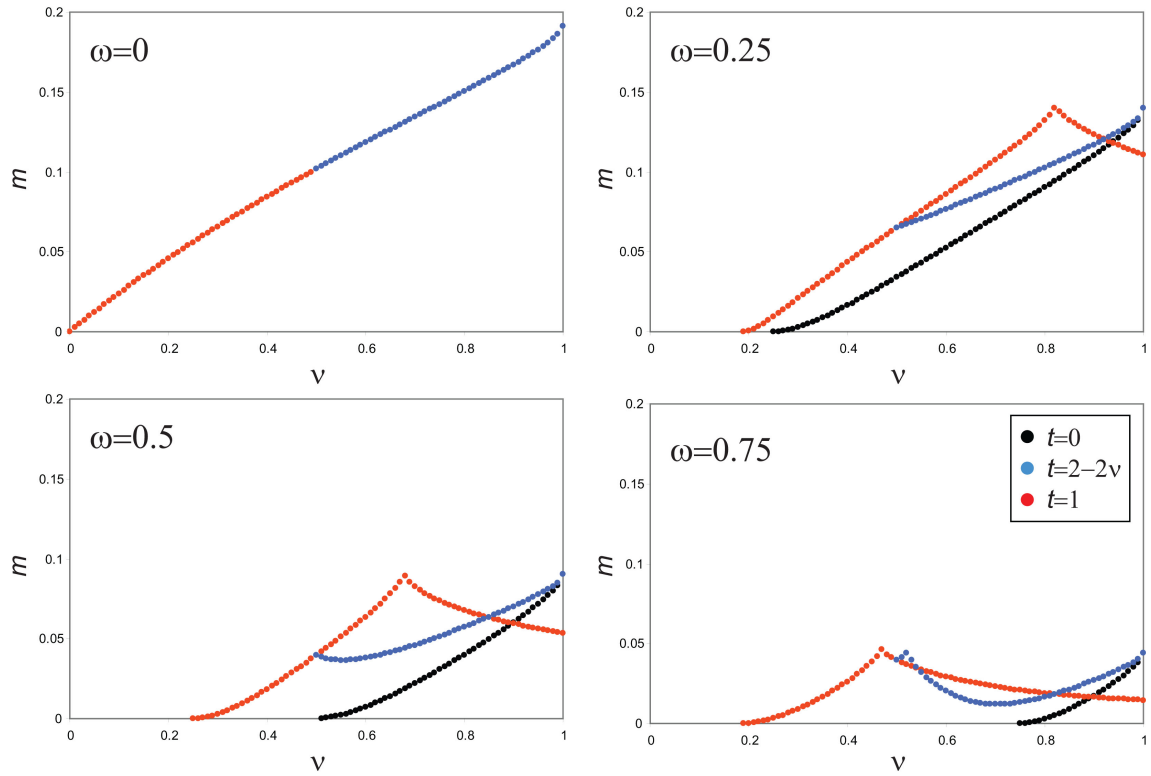
FIG. 6. **Critical migration rates allowing stable local transformations over a range of genotype fitness and Medea parameter configurations.** Migration rates are on the y-axis and homozygous MM fitness on the x-axis for four different heterozygous fitness values. Simulated parameter combination outcomes are indicated with dots. Pure underdominance with no Medea effect ($t = 0$) is plotted in black. Full Medea, 100% lethality ($t = 1$), is plotted in red. Intermediate Medea strengths that maintain an approximate unstable equilibrium at $p = 1/2$ are plotted in blue ($t = 2 - 2\nu$). Note that for $\omega = 0$ the points with Medea exactly correspond to the points without Medea (i.e., Medea has no effect and only underdominance determines the stability).

"It is vain to do with more what can be done with fewer."

William of Occham

(c. 1288-1348)

Summary and Outlook

In the Introduction we mentioned biological systems as complex dynamical systems. The theory of dynamical systems has its roots in Newtonian mechanics (Strogatz, 2000). In dynamical systems we write down a difference or differential equation which has all the parameters crucial for describing the dynamics of a system. Depending on the interactions of those parameters the equation gives us the time development of the system.

Analysing evolutionary dynamics in higher dimensions we face the question, is it is really necessary to include all this complexity? To comment on this question we go through the following argument. Consider the publications based on static fitness landscapes. How long does it take for a population to switch peaks if there are two possibilities, a narrow ridge or a broad valley? A basic requirement of this approach is that there have to be multiple states. If there were just two states then the question becomes irrelevant. Multiple states are very realistic for example in cases where fitness is determined by multiple traits. Accepting this idea, we see that even if one has to go through the valley, it can be faster if there are multiple paths available in it instead of a fixed path with no fitness reduction. Next, a peculiar property relating to the time for fixation is studied. In this case there is no need for multiple states. The whole study is based on a population moving from state B to A with a slight bias for moving towards A. All else being same if there is a small frequency dependent bias for the population to move from one state to the next then the time for fixation is actually larger than if there is no bias. We can extend this knowledge to multiple states and conjecture the following: Imagine a population moving on a flat landscape. Even if there is a small bias for moving in a particular direction for each transition, the time required will be greater than neutral and hence in all it will take longer to cross the landscape as compared to a balanced process.

To study frequency dependent scenarios we use evolutionary game theory. Evolutionary game theory has become quite popular amongst behavioral ecologists, sociologists, philosophers and also back among economists from where game theory originated (Hammerstein and Hagen, 2005). Evolutionary game theory usually deals with two player games with two strategies. The publications relating to evolutionary game theory, collated, in Chapter 4, increase the dimensions of analysis by including multiple players and multiple strategies. Is the analysis of this increased complexity justified?

The evolution and maintenance of co-operation is definitely one of the most active research areas in biology, sociology and economics. Social dilemmas have been extensively analysed using evolutionary game theory (Ostrom, 1990; Nowak, 2006b; Taylor and Nowak, 2007). Using the Prisoners Dilemma and many other such social dilemma games the problem has been tackled both theoretically and experimentally. At the heart of many of these experiments are problems which involve multiple players. Multiplayer games span a wide range of topics, worldwide co-operation to combat global warming, inferring social structure from communities of social animals and even breakdown of co-operation between cells in a multi-cellular organism leading to cancerous growth. The multiplayer versions of these social settings are used in experiments, but theoretical development of general multiplayer games had not received as much attention.

The publications about evolutionary game theory in Chapter 4, aim at incorporating these complexities of multiplayer games:

1. Develop analogous condition to the one third rule and the risk dominance conditions in multiplayer games with two strategies. Sabin Lessard has shown that our conditions are also valid for any process in the Kingman's coalescent (personal communication). Also we calculate the maximum number of equilibria possible in a system with multiple player and multiple strategies for infinitely large populations.

2. The replicator dynamics approach only includes selection. Assuming small mutation rates, many important and analytically accessible quantities like the fixation probability still remain meaningful. We derive a method to

calculate a bound on the mutation rate under which making the assumption minimizes the error under a certain threshold.

3. When mutations are incorporated, it is difficult to quantify how the strategies will fluctuate. We develop a method to calculate the long term frequencies of strategies for arbitrary mutation rates for weak selection. This analysis is also valid for multiple strategies and generalises previous results to multiplayer games.

The analysis reveals that multiplayer games can show different properties than the regular two player games with two strategies. Under mutation selection equilibrium we find that the result is an extension of the framework used for two player games with multiple strategies. Hence we see that depending on the problem being addressed, the addition of multiple parameters is sometimes useful and sometimes redundant. The inclusion of the extra complexity is a matter of what kind of question is being asked. So what more can we add to the theory which has been developed in here so far?

We have come a long way from two players two strategies to multiple players and strategies but almost all this still happens in the same game, the public goods game. A certain game may have an impact on another game in which the same individual(s) is(are) involved. So what about multiple game(s) theory (Bednar and Page, 2007)?. Also earlier we had quoted Nowak and Sigmund (2004) for the inability of evolutionary game theory to describe evolutionary dynamics at the genotypic level. This is true for traditional evolutionary game theory which cannot handle situations when the fitness is a non-linear function such as in genetic conflict situations. The development of multiplayer game theory can tackle this problem as it can incorporate non-linearity via the addition of multiple players.

One of the important mathematical theories in the biological sphere is population genetics. It was thus natural to draw parallels with evolutionary game theory as soon as the latter gained reputation (Rowe, 1987, 1988; Cressman, 2003) as a credible theoretical tool. In comparison evolutionary game theory is looked upon in biology as a tool giving us a good insight into a biological process but at the cost of ignoring the details of the evolutionary process. We

see a different picture when we look at evolutionary game theory from the point of view of economics. A field predominated by classical game theory, evolutionary game theory has first been looked upon to bring unnecessary complications and is thought of to be too complex (Friedman, 1991). However this view has changed in recent years (Hammerstein and Hagen, 2005; Sandholm, 2010). One is warned against going overboard with simplicity by this quote supposedly by Einstein, "Everything should be made as simple as possible, but not simpler."

Evolutionary theory has always been evolutionary dynamics. This is because evolution is a dynamic process, change over time. Evolutionary dynamics which we know of as *population genetics*, *evolutionary game theory*, *adaptive dynamics*, *optimisation theory* etc. are just different faces of the study of dynamical systems. They all describe more or less the same properties. This is so because these different fields make more or less assumptions as per the rules which define them and hence the predictions which they make can be quantitatively more accurate or less. For example, population genetics can handle the complexities of sexual selection, recombination and speciation. In turn it has not analysed themes such as spread of infectious agents, somatic evolution of cancer or the evolution of human language (Nowak, 2006a). We need different evolutionary dynamics to study different systems. Yet qualitatively they all point in the same direction. How do we justify this pluralism? Interdisciplinary studies, like this thesis, try to answer this. Interdisciplinary studies can cover up the shortcomings of one theory by the developments from another or remove the redundancy in one theory by the simplicity of another. An aim of this thesis was to have a dialogue between biology and the basic mathematics of dynamical systems theory using terminology from both the fields.

"Realistic models may describe nature more accurately, but they are less illuminating when explaining principles ..." (Hartl and Clark, 1997). Testing Newton's laws in the real world we understand that they almost never hold. Friction, drag, moisture, viscosity etc. are not taken into account in Newton's equations, yet we can launch a rocket to the moon based on them. The same holds true for evolutionary dynamics.

References

H. K. Alexander and T. Day. Risk factors for the evolutionary emergence of pathogens. *J. R. Soc. Interface*, 7:1455–1474, 2010.

P. M. Altrock and A. Traulsen. Deterministic evolutionary game dynamics in finite populations. *Phys. Rev. E*, 80:011909, 2009.

P. M. Altrock, C. S. Gokhale, and A. Traulsen. Stochastic slowdown in evolutionary processes. *Phys. Rev. E*, 82:011925, 2010.

C. Anderson and N. R. Franks. Teams in animal societies. *Behavioral Ecology*, 12(5):534–540, 2001.

T. Antal and I. Scheuring. Fixation of strategies for an evolutionary game in finite populations. *Bull. Math. Biol.*, 68:1923–1944, 2006.

T. Antal, M. A. Nowak, and A. Traulsen. Strategy abundance in 2x2 games for arbitrary mutation rates. *J. Theor. Biol.*, 257:340–344, 2009a.

T. Antal, H. Ohtsuki, J. Wakeley, P. D. Taylor, and M. A. Nowak. Evolution of cooperation by phenotypic similarity. *Proc. Natl. Acad. Sci. USA*, 106:8597–8600, 2009b.

T. Antal, A. Traulsen, H. Ohtsuki, C. E. Tarnita, and M. A. Nowak. Mutation-selection equilibrium in games with multiple strategies. *J. Theor. Biol.*, 258:614–622, 2009c.

M. Archetti. The origin of autumn colours by coevolution. *J. theor. Biol.*, 205:625–630, 2000.

A. Ariew and R. C. Lewontin. The confusions of fitness. *Brit. J. Phil. Sci.*, 55:347–363, 2004.

K. C. Atwood, K. L. Schneider, and F. J. Ryan. Periodic selection in escherichia coli. *Proc. Natl. Acad. Sci. U.S.A.*, 37:146–155, 1951.

L. Aviles. Cooperation and non-linear dynamics: An ecological perspective on the evolution of sociality. *Evol. Ecol. Research*, 1:459–477, 1999.

R. Axelrod. *The Evolution of Cooperation*. Basic Books, New York, 1984.

R. Axelrod and W. D. Hamilton. The evolution of cooperation. *Science*, 211:1390–1396, 1981.

R. Axelrod, D. E. Axelrod, and K. J. Pienta. Evolution of cooperation among tumor cells. *Proc. Natl. Acad. Sci. USA*, 103(36):13474–13479, 2006.

F.J. Ayala and C.A. Campbell. Frequency-dependent selection. *Annu. Rev. Ecol. Syst.*, 5:115–138, 1974.

P. Bak and K. Sneppen. Punctuated equilibrium and criticality in a simple model of evolution. *Phys. Rev. Letters*, 24:4083, 1993.

D. Basanta, M. Simon, H. Hatzikirou, and A. Deutsch. Evolutionary game theory elucidates the role of glycolysis in glioma progression and invasion. *Cell Prolif.*, 41:980–987, 2008.

J. Bednar and S. Page. Can game(s) theory explain culture ? : The emergence of cultural behavior within multiple games. *Rationality and Society*, 19:65–97, 2007.

R. W. Beeman, K. S. Friesen, and R. E. Denell. Maternal-effect selfish genes in flour beetles. *Science*, 256:89–92, 1992.

N. Beerenwinkel, T. Antal, D. Dingli, A. Traulsen, K. W. Kinzler, V. E Velculescu, B. Vogelstein, and M. A. Nowak. Genetic progression and the waiting time to cancer. *PLoS Comput. Biol.*, 3:e225, 2007a.

N. Beerenwinkel, L. Pachter, B. Sturmfels, S. F Elena, and R. E. Lenski. Analysis of epistatic interactions and fitness landscapes using a new geometric approach. *BMC Evol Biol*, 7:60, 2007b.

A. J. Betancourt and J. P. Bollback. Fitness effects of beneficial mutations: the mutational landscape model in experimental evolution. *Current Opinion in Genetics & Development*, 16:618–623, 2006.

D. T. Bishop and C. Cannings. Models of animal conflict. *Advances in Applied Probability*, 8 (4):616–621, 1976.

I. Bomze and R. Buerger. Stability by mutation in evolutionary games. *Games and Econ. Behav.*, 11:146–172, 1995.

I. Bomze and C. Pawlowitsch. One-third rules with equality: Second-order evolutionary stability conditions in finite populations. *J. Theor. Biol.*, 254:616–620, 2008.

J. A. M. Borghans, J. B. Beltman, and R. J. De Boer. MHC polymorphism under host-pathogen coevolution. *Immunogenetics*, 55:732–739, 2004.

P. J. Bowler. *Evolution. The History of An Idea*. University of California Press, 3rd edition, 2009.

I. Bozic, T. Antal, H. Ohtsuki, H. Carter, D. Kim, S. Chen, R. Karchin, K. W. Kinzler, B. Vogelstein, and M. A. Nowak. Accumulation of driver and passenger mutations during tumor progression. *Proc. Natl. Acad. Sci. U.S.A.*, Early Edition, September 2010.

J. Cartwright. *Evolution and Human Behaviour: Darwinian Perspectives on Human Nature*. Palgrave Macmillan, 2000.

C-H. Chen, H. Huang, C. M. Ward, J. T. Su, L. V. Schaeffer, M. Guo, and B. A. Hay. A synthetic maternal-effect selfish genetic element drives population replacement in drosophila.

Science, 316:597–600, 2007.

R. C. Connor. Cooperation beyond the dyad: on simple models and a complex society. *Phil. Trans. Roy. Soc. London B*, 365:2687–2697, 2010.

R. Cressman. *Evolutionary Dynamics and Extensive Form Games*. MIT Press, Cambridge, MA, 2003.

T. L. Czaran, R. F. Hoekstra, and L. Pagie. Chemical warfare between microbes promotes biodiversity. *Proc. Natl. Acad. Sci. USA*, 99:786–790, 2002.

C. Darwin. *On the origin of species by means of natural selection*. Cambridge-London. Reprinted in Harvard University Press (1964), 1859. 30.

C. Darwin. *The Descent of Man*. John John Murray, London, 1871.

R. Dawkins. *The Selfish Gene*. Oxford University Press, New York, 1976.

R. Dawkins. *The extended phenotype*. Oxford University Press, Oxford, 1982.

D. Dingli and M. A. Nowak. Infectious tumour cells. *Nature*, 443(7):35–36, 2006.

M. Doebeli and C. Hauert. Models of cooperation based on the prisoner's dilemma and the snowdrift game. *Ecology Letters*, 8:748–766, 2005.

L. A. Dugatkin. Do guppies play tit for tat during predator inspection visits ? *Behavioral Ecology and Sociobiology*, 23(6):395–399, 1988.

L. A. Dugatkin. N-person games and the evolution of co-operation: A model based on predator inspection in fish. *J. theor. Biol.*, 142:123–135, 1990.

L. A. Dugatkin. *Cooperation among animals: an evolutionary perspective*. Oxford Univ. Press, 1997.

E. H. DuVal. Adaptive advantages of cooperative courtship for subordinate male lance-tailed manakins. *Am. Nat.*, 169(4):423–432, 2007.

M. Eigen. Selforganization of matter and the evolution of biological macromolecules. *Die Naturwissenschaften*, 58(10):465–523, Oct 1971. 84.

M. Eigen and P. Schuster. The hypercycle. a principle of natural self-organization. part a: Emergence of the hypercycle. *Die Naturwiss.*, 64:541–565, 1977.

M. Eigen and P. Schuster. The hypercycle. a principle of natural self-organization. part b: The abstract hypercycle. *Die Naturwissenschaften*, 65:7–41, 1978a.

M. Eigen and P. Schuster. The hypercycle. a principle of natural self-organization. part c: The realistic hypercycle. *Die Naturwissenschaften*, 65:341–369, 1978b.

M. Eigen, J. McCaskill, and P. Schuster. The molecular quasi-species. *Adv. Chem. Phys.*, 75:

149–263, 1989.

N. Eldredge and S. J. Gould. *Models in Paleobiology*, chapter Punctuated equilibria: an alternative to phyletic gradualism. Freeman Cooper, San Francisco, 1985.

S. F. Elena and R. E. Lenski. Evolution experiments with microorganisms: the dynamics and genetic bases of adaptation. *Nat. Rev. Gen.*, 4:457–469, 2003.

S. F. Elena, L. Ekunwe, N. Hajela, S.A. Oden, and R. E. Lenski. Distribution of fitness effects caused by random insertion mutations in escherichia coli. *Genetics*, 102/103:349–358, 1998.

W. J. Ewens. *Mathematical Population Genetics*. Springer, Berlin, 1979.

E. Fehr and S. Gächter. Altruistic punishment in humans. *Nature*, 415:137–140, 2002.

E. Fehr and B. Rockenbach. Human altruism: economic, neural, and evolutionary perspectives. *Curr Opin Neurobiol*, 14(6):784–790, 2004.

E. Fehr, H. Bernhard, and B. Rockenbach. Egalitarianism in young children. *Nature*, 454 (7208):1079–1083, 2008.

S. Ficci and J. Pollack. Effects of finite populations on evolutionary stable strategies. In D. Whitley, D. Goldberg, E. Cantu-Paz, L. Spector, I. Parmee, and H.-G. Beyer, editors, *Proceedings GECCO*, pages 927–934, Morgan-Kaufmann, San Francisco, 2000.

R. A. Fisher. *The Genetical Theory of Natural Selection*. Clarendon Press, Oxford, 1930.

G. Fogel, P. Andrews, and D. Fogel. On the instability of evolutionary stable strategies in small populations. *Ecol. Model.*, 109:283–294, 1998.

E. Frey. Evolutionary game theory: Theoretical concepts and applications to microbial communities. *Physica A*, 389:4265–4298, 2010.

D. Friedman. Evolutionary games in economics. *Econometrica*, 59(3):637–666, May 1991. 39.

D. Fudenberg and L. A. Imhof. Imitation process with small mutations. *J. Econ. Theory*, 131: 251–262, 2006.

D. Fudenberg and L. A. Imhof. Monotone imitation dynamics in large populations. *J Econ Theory*, 140:229–245, 2008.

D. Fudenberg, M. A. Nowak, C. Taylor, and L.A. Imhof. Evolutionary game dynamics in finite populations with strong selection and weak mutation. *Theor. Pop. Biol.*, 70:352–363, 2006.

S. Gächter and B Herrmann. Reciprocity, culture and human cooperation: previous insights and a new cross-cultural experiment. *Philos Trans R Soc Lond B Biol Sci*, 364(1518): 791–806, 2009.

S. Gavrilets. *Fitness Landscapes & the Origin of Species*. Princeton University Press, 2004.

C. J. W. George. *Behavioral interaction of the pickerel (Esoxniger and Esoxamericanus) and the mosquitofish (Gambusia patruelis)*. PhD thesis, Harvard University, 1961.

P. J. Gerrish and R. E. Lenski. The fate of competing beneficial mutations in a asexual population. *Genetica*, 102/103:127–144, 1998.

J. H. Gillespie. Some properties of finite populations experiencing strong selection and weak mutation. *Am. Nat.*, 121:691–708, 1983.

J. H. Gillespie. Molecular evolution over the mutational landscape. *Evolution*, 38:1116–1129, 1984a.

J. H. Gillespie. The status of the neutral theory. *Science*, 224(4650):732–733, 1984b.

J. H. Gillespie. *Population Genetics : A Concise Guide*. The Johns Hopkins University Press, 2004 (2nd edition).

H. Gintis. *Game Theory Evolving*. Princeton University Press, Princeton, 2000.

N. S. Goel and N. Richter-Dyn. *Stochastic Models in Biology*. Academic Press, New York, 1974.

C. S. Gokhale and A. Traulsen. Evolutionary games in the multiverse. *Proc. Natl. Acad. Sci. U.S.A.*, 107(12):5500–5504, 2010.

J. Gore, H. Youk, and A. van Oudenaarden. Snowdrift game dynamics and facultative cheating in yeast. *Nature*, 459:253–256, 2009.

D. Greig and M. Travisano. The Prisoner's Dilemma and polymorphism in yeast SUC genes. *Biol. Lett.*, 271:S25 – S26, 2004.

J. Grujic, C. Fosco, L. Araujo, J.A. Cuesta, and A. Sanchez. Social experiments in the mesoscale: Humans playing a spatial prisoner's dilemma. *PLoS One*, 5(11):e13749, 2010.

J. B. S. Haldane. A mathematical theory of natural and artificial selection. viii. metastable populations. *Proc. Camb. Philos. Soc.*, 27:137–142, 1932a.

J. B. S. Haldane. *The Causes of Evolution*. Longmans, Green and Co., Ltd, New York, 1932b.

W. D. Hamilton. Innate social aptitudes of man: an approach from evolutionary genetics. In R. Fox, editor, *Biosocial Anthropology*, pages 133–155. Wiley, New York, 1975.

P. Hammerstein and E. H. Hagen. The second wave of evolutionary economics in biology. *Trends in Ecology and Evolution*, 20(11):604–609, 2005.

J. C. Harsanyi and R. Selten. *A general theory of equilibrium selection in games*. MIT Press, Cambridge, 1988.

S. L. Hartl and A. G. Clark. *Principles of Population Genetics*. Sinauer Associates, Inc.,

Sunderland, Massachusetts, third edition, 1997.

K. Hashimoto and Kazuyuki A. Fixation probabilities in evolutionary game dynamics with a two-strategy game in finite diploid populations. *J. Theor. Biol.*, 258, 2009.

C. Hauert, S. De Monte, J. Hofbauer, and K. Sigmund. Volunteering as red queen mechanism for cooperation in public goods games. *Science*, 296:1129–1132, 2002.

C. Hauert, A. Traulsen, H. Brandt, M. A. Nowak, and K. Sigmund. Via freedom to coercion: the emergence of costly punishment. *Science*, 316:1905–1907, 2007.

C. Hauert, A. Traulsen, H. Brandt, M. A. Nowak, and K. Sigmund. Public goods with punishment and abstaining in finite and infinite populations. *Biological Theory*, 3:114–122, 2008.

J. Henrich, R. McElreath, A. Barr, J. Ensminger, C. Barrett, A. Bolyanatz, J. C. Cardenas, M. Gurven, E. Gwako, N. Henrich, C. Lesorogol, F. Marlowe, D. Tracer, and J. Ziker. Costly punishment across human societies. *Science*, 312:1767–1770, 2006.

C. R. Henslow, J. S. to Darwin. Darwin correspondence project. Letter 105, 24 Aug 1831.

J. Hofbauer. The selection mutation equation. *Journal of Mathematical Biology*, 23(1):41–53, December 1985.

J. Hofbauer and K. Sigmund. *The theory of evolution and dynamical systems: Mathematical aspects of selection*. Cambridge University Press, Cambridge, 1988.

J. Hofbauer and K. Sigmund. *Evolutionary Games and Population Dynamics*. Cambridge University Press, Cambridge, 1998.

J. Hofbauer and K. Sigmund. Evolutionary game dynamics. *Bull. Am. Math. Soc.*, 40:479–519, 2003.

G. D. Hurst and J. H. Werren. The role of selfish genetic elements in eukaryotic evolution. *Nat. Rev. Gen.*, 2:597–606, 2001.

L. D. Hurst, A Atlan, and B. O. Bengtsson. Genetic conflicts. *The Quarterly Review of Biology*, 71(3):317–364, 1996.

J. Huxley. *Evolution, the modern synthesis*. Allen and Unwin, London, 1942.

L. A. Imhof and M. A. Nowak. Evolutionary game dynamics in a Wright Fisher process. *J. Math. Biol.*, 52:667–681, 2006.

L. A. Imhof, D. Fudenberg, and M. A. Nowak. Evolutionary cycles of cooperation and defection. *Proc. Natl. Acad. Sci. USA*, 102:10797–10800, 2005.

Y. Iwasa, F. Michor, and M. A. Nowak. Stochastic tunnels in evolutionary dynamics. *Genetics*,

166:1571–1579, 2004.

M. Kandori, G. J. Mailath, and R. Rob. Learning, mutation, and long run equilibria in games. *Econometrica*, 61:29–56, 1993.

S. A. Kauffman and S. Levin. Towards a general theory of adaptive walks on rugged landscapes. *J. theor. Biol.*, 128:11–45, 1987.

S. A. Kauffman and E. D. Weinberger. The NK model of rugged fitness landscapes and its application to maturation of the immune response. *J. theor. Biol.*, 141:211–245, 1989.

B. Kerr, M. A. Riley, M. W. Feldman, and B. J. M. Bohannan. Local dispersal promotes biodiversity in a real-life game of rock-paper-scissors. *Nature*, 418:171–174, 2002.

M. Kimura. Evolutionary rate at the molecular level. *Nature*, 217:624–626, 1968.

J. F. C. Kingman. The coalescent. *Stochastic Processes and Their Applications*, 13:235–248, 1982a.

J. F. C. Kingman. On the genealogy of large populations. *J. Appl. Probability*, 19A:27–43, 1982b.

J. F. C. Kingman. Exchangeability and the evolution of large populations. In G. Koch and F. Spizzichino, editors, *Exchangeability in probability and statistics*, pages 97–112, Amsterdam, 1982c. North-Holland.

J. F. C. Kingman. Origins of the coalescent. 1974-1982. *Genetics*, 156(4):1461–1463, 2000.

R. Kummerli, C. Colliard, N. Fiechter, B. Petitpierre, F. Russier, and L. Keller. Human cooperation in social dilemmas: comparing the snowdrift game with the prisoner's dilemma. *Proc Biol Sci*, 274(1628):2965–2970, 2007.

S. Kurokawa and Y. Ihara. Emergence of cooperation in public goods games. *Proc. R. Soc. B*, 276:1379–1384, 2009.

R. Landauer and M. Büttiker. Diffusive traversal time: Effective area in magnetically induced interference. *Phys. Rev. B*, 36:6255–6260, 1987.

T. H. Lee, L. M. DSouza, and G. E. Fox. Equally parsimonious pathways through an rna sequence space are not equally likely. *J. Mol. Evol.*, 45:278–284, 1997.

S. Lessard and V. Ladret. The probability of fixation of a single mutant in an exchangeable selection model. *J. Math. Biol.*, 54:721–744, 2007.

S. A. Levin. Multiple scales and the maintenance of biodiversity. *Ecosystems*, 3:498–506, 2000.

R. C. Lewontin. Evolution and the theory of games. *J. Theo. Biol.*, 1:382–403, 1961.

A. J. Lotka. Analytical note on certain rhythmic relations in organic systems. *Proc. Natl. Acad. Sci.*, 6:410–415, 1920.

E. R. Lozovsky, T. Chookajorn, K. M. Brown, M. Imwong, P. J. Shaw, S. Kamchonwongpaisan, D. E. Neafsey, D. M. Weinreich, and D. L. Hartl. Stepwise acquisition of pyrimethamine resistance in the malaria parasite. *Proc. Natl. Acad. Sci.*, 106(29):12025–12030, 2009.

C. Lyell. *Principles of Geology*. Penguin Classics, 1998.

M. Lynch. The rate of establishment of complex adaptations. *Mol. Biol. Evol.*, 27(6):1404–1414, 2010a.

M. Lynch. Scaling expectations for the time to establishment of complex adaptations. *Proc. Natl. Acad. Sci. USA*, Early edition, 2010b.

C. MacLean, A. Fuentes-Hernandez, D. Greig, L. D. Hurst, and I. Gudelj. A mixture of "cheats" and "co-operators" can enable maximal group benefit. *PLoS Biology*, 8(9):e1000486, 2010.

T. R. Malthus. *An essay on the Principle of Population*. J. Johnson, in St. Paul's Church-yard, London, 1st edition, 1798.

T. R. Malthus. *An essay on the Principle of Population*. John Murray, 6th edition, 1826.

J. Maynard Smith. Natural selection and the concept of a protein space. *Nature*, 225:563–564, 1970.

J. Maynard Smith. *Evolution and the Theory of Games*. Cambridge University Press, Cambridge, 1982.

J. Maynard Smith and G. R. Price. The logic of animal conflict. *Nature*, 246:15–18, 1973.

E. Mayr. The objects of selection. *Proc. Natl. Acad. Sci. USA*, 94:2091–2094, 1997.

E. Mayr and W. B. Provine, editors. *The Evolutionary Synthesis Perspectives on the unification of biology*. Harvard University Press, Cambridge, Massachusetts and London, England, 1980.

G. Mendel. Versuche über Pflanzen-Hybriden. *Verhandlungen des Naturforscher-Vereins in Brünn*, 10:3–47, 1866. 31.

F. Michor, Y. Iwasa, and M. A. Nowak. Dynamics of cancer progression. *Nat. Rev. Cancer*, 4:197–205, 2004.

M. Milinski. Tit for tat in sticklebacks and the evolution of cooperation. *Nature*, 325(6103):433–435, 1987.

M. Milinski. Games fish play: Making decisions as a social forager. *TREE*, 3(12):325–330, 1988.

M. Milinski. No alternative to tit-for-tat cooperation in sticklebacks. *Anim. Behav.*, 39(5): 989–991, 1990.

M. Milinski. The major histocompatibility complex, sexual selection, and mate choice. *Ann. Rev. Ecol. Evol. Syst.*, 37:159–186, 2006.

M. Milinski and C. Wedekind. Working memory constrains human cooperation in the prisoner's dilemma. *Proc. Natl. Acad. Sci. USA*, 95:13755–13758, 1998.

M. Milinski, D. Semmann, T. C. Bakker, and H. J. Krambeck. Cooperation through indirect reciprocity: image scoring or standing strategy? *Proc. R. Soc. Lond. B*, 268:2495–2501, Dec 2001. ISSN 0962-8452.

M. Milinski, D. Semmann, H. J. Krambeck, and J. Marotzke. Stabilizing the earth's climate is not a losing game: Supporting evidence from public goods experiments. *Proc. Natl. Acad. Sci. USA*, 103:3994–3998, 2006.

M. Milinski, R. D. Sommerfeld, H.-J. Krambeck, F. A. Reed, and J. Marotzke. The collective-risk social dilemma and the prevention of simulated dangerous climate change. *Proc. Natl. Acad. Sci. USA*, 105(7):2291–2294, 2008. doi: 10.1073/pnas.0709546105.

M. Mitchell. *Complexity: A Guided Tour*. Oxford University Press, 2009.

P. A. P. Moran. *The Statistical Processes of Evolutionary Theory*. Clarendon Press, Oxford, 1962.

J. F. Nash. Equilibrium points in n-person games. *Proc. Natl. Acad. Sci. U.S.A.*, 36:48–49, 1950.

M. A. Nowak. What is a quasispecies? *Trends in Ecology and Evolution*, 7:118–121, 1992.

M. A. Nowak. *Evolutionary Dynamics*. Harvard University Press, Cambridge, MA, 2006a.

M. A. Nowak. Five rules for the evolution of cooperation. *Science*, 314:1560–1563, 2006b.

M. A. Nowak. Generosity: A winner's advice. *Nature*, 456(4):579, December 2008.

M. A. Nowak and N. L. Komarova. Towards an evolutionary theory of language. *Trends Cogn. Sci.*, 5(7):288–295, 2001.

M. A. Nowak and K. Sigmund. Evolutionary dynamics of biological games. *Science*, 303: 793–799, 2004.

M. A. Nowak, A. Sasaki, C. Taylor, and D. Fudenberg. Emergence of cooperation and evolutionary stability in finite populations. *Nature*, 428:646–650, 2004.

T. Ohta and J. H. Gillespie. Development of neutral and nearly neutral theories. *Theoretical Population Biology*, 49, 1996.

H. Ohtsuki, P. Bordalo, and M. A. Nowak. The one-third law of evolutionary dynamics. *J. Theor. Biol.*, 249:289–295, 2007.

S. Okasha. The levels of selection debate: Philosophical issues. *Philosophy Compass*, 1:74–85, 2006.

H. A. Orr. Fitness and its role in evolutionary genetics. *Nat. Rev. Gen.*, 10:531–539, 2009.

E. Ostrom. *Governing the Commons: The Evolution of Institutions for Collective Action*. Cambridge Univ. Press, 1990.

J. M. Pacheco, F. C. Santos, M. O. Souza, and B. Skyrms. Evolutionary dynamics of collective action in N-person stag hunt dilemmas. *Proc. R. Soc. B*, 276:315–321, 2009.

K. M. Page and M. A. Nowak. Unifying evolutionary dynamics. *J. Theor. Biol.*, 219:93–98, 2002.

S-C. Park and J. Krug. Clonal interference in large populations. *Proc. Natl. Acad. Sci. U.S.A.*, 104(46):18135–18140, 2007.

L. L. Peters and J. E. Barker. Novel inheritance of the murine severe combined anemia and thrombocytopenia (scat) phenotype. *Cell*, 74(1):135–142, 1993.

E.B. Poulton. Notes upon, or suggested by, the colours, markings and protective attitudes of certain lepidopterous larvae and pupae, and of a phytophagous hymenopterous larva. *Transactions of the Entomological Society of London*, pages 27–60, 1884.

W. B. Provine. *Sewall Wright and evolutionary biology*. University of Chicago Press, Chicago., 1986.

M. Ridley. *The Red Queen: Sex and Evolution of Human Nature*. HarperCollins Publishers, 1993.

M. Ridley. *Evolution*. Wiley-Blackwell, second edition, August 1996.

J. G. Riley. Evolutionary equilibrium strategies. *J. Theor. Biol.*, 76:109–123, 1979.

B. Rockenbach and M. Milinski. The efficient interaction of indirect reciprocity and costly punishment. *Nature*, 444:718–723, 2006.

G. W. Rowe. A dynamic game theory model of diploid genetic system. *J Theor Biol*, 129: 243–255, 1987.

G. W. Rowe. To each genotype a separate strategy - a dynamic game theory model of a general diploid system. *J Theor Biol*, 134:89–101, 1988.

W. H. Sandholm. *Population games and evolutionary dynamics*. MIT Press, Cambridge, MA, 2010.

F. C. Santos, M. D. Santos, and J. M. Pacheco. Social diversity promotes the emergence of cooperation in public goods games. *Nature*, 454:213–216, 2008.

M. Schaffer. Evolutionary stable strategies for a finite population and variable contest size. *J. Theo. Biol.*, 132:469–478, 1988.

S. Schreiber. Urn models, replicator processes, and random genetic drift. *Siam J. Appl. Math.*, 61:2148–2167, 2001.

P. Schuster and K. Sigmund. Replicator dynamics. *J. Theo. Biol.*, 100:533–538, 1983.

D. Semmann, H. J. Krambeck, and M. Milinski. Volunteering leads to rock-paper-scissors dynamics in a public goods game. *Nature*, 425(6956):390–393, 2003. ISSN 1476-4687.

K. Sigmund. Punish or perish? Retaliation and collaboration among humans. *Trends Ecol. Evol.*, 22(11):593–600, 2007.

K. Sigmund. *The calculus of selfishness*. Princeton Univ. Press, 2010.

K. Sigmund, H. De Silva, A. Traulsen, and C. Hauert. Social learning promotes institutions for governing the commons. *Nature*, 466:861–863, 2010.

A. Smith. *An Inquiry into the Nature and Causes of the Wealth of Nations*, volume II. Strahan, London, 1776. 4th edition (1786).

N. G. C. Smith. The dynamics of maternal-effect selfish genetic elements. *J. theor. Biol.*, 191: 173–180, 1998.

R. D. Sommerfeld, H-J Krambeck, D Semmann, and M Milinski. Gossip as an alternative for direct observation in games of indirect reciprocity. *Proc Natl Acad Sci U S A*, 104(44): 17435–17440, 2007.

M. O. Souza, J. M. Pacheco, and F. C. Santos. Evolution of cooperation under n-person snowdrift games. *J. Theor. Biol.*, 260:581–588, 2009.

P. F. Stadler and P. Schuster. Mutation in autocatalytic reaction networks - an analysis based on perturbation theory. *J. Math. Biol.*, 30:597–631, 1992.

P. E. Stander. Cooperative hunting in lions: the role of the individual. *Behavioral Ecology and Sociobiology*, 29:445–454, 1992.

S. Strogatz. *Nonlinear Dynamics and Chaos: With Applications to Physics, Biology, Chemistry, and Engineering (Studies in Nonlinearity)*. Westview Pr, 2000.

C. E. Tarnita, H. Ohtsuki, T. Antal, F. Fu, and M. A. Nowak. Strategy selection in structured populations. *J. Theor. Biol.*, 259:570–581, 2009.

C. Taylor and M. A. Nowak. Transforming the dilemma. *Evolution*, 61:2281–2292, 2007.

C. Taylor, D. Fudenberg, A. Sasaki, and M. A. Nowak. Evolutionary game dynamics in finite populations. *Bull. Math. Biol.*, 66:1621–1644, 2004.

P. D. Taylor and L. Jonker. Evolutionary stable strategies and game dynamics. *Math. Biosci.*, 40:145–156, 1978.

B. Thomas. Evolutionary stability: States and strategies. *Theoretical Population Biology*, 26 (1):49–67, 1984.

B. Thomas. On evolutionarily stable sets. *J. Math. Biology*, 22(1):105–115, 1985.

A. Traulsen and C. Hauert. Stochastic evolutionary game dynamics. In H.-G. Schuster, editor, *Reviews of nonlinear dynamics and complexity*, pages 25–61. Wiley-VCH, 2009.

A. Traulsen and M. A. Nowak. Chromodynamics of cooperation in finite populations. *PLoS One*, 2:e270, 2007.

A. Traulsen, J. C. Claussen, and C. Hauert. Coevolutionary dynamics: From finite to infinite populations. *Phys. Rev. Lett.*, 95:238701, 2005.

A. Traulsen, J. C. Claussen, and C. Hauert. Coevolutionary dynamics in large, but finite populations. *Phys. Rev. E*, 74:11901, 2006a.

A. Traulsen, M. A. Nowak, and J. M. Pacheco. Stochastic dynamics of invasion and fixation. *Phys. Rev. E*, 74:011909, 2006b.

A. Traulsen, N. Shoresh, and M. A. Nowak. Analytical results for individual and group selection of any intensity. *Bull. Math. Biol.*, 70:1410–1424, 2008.

A. Traulsen, D. Semmann, R. D. Sommerfeld, H-J. Krambeck, and M. Milinski. Human strategy updating in evolutionary games. *Proc. Natl. Acad. Sci. U.S.A.*, 107(7):2962–2966, 2010.

P. E. Turner. Cheating viruses and game theory. *American Scientist*, 93:428–435, 2005.

P. E. Turner and L. Chao. Prisoner's Dilemma in an RNA virus. *Nature*, 398:441–443, April 1999.

J. van der Werf, H.-U. Graser, R. Frankham, and C. Gondro, editors. *Adaptation and Fitness in Animal Populations*. Springer, Heidelberg, 2009.

S. Van Segbroeck, F. C. Santos, T. Lenaerts, and J. M. Pacheco. Reacting differently to adverse ties promotes cooperation in social networks. *Phys. Rev. Lett.*, 102:058105, 2009.

L. van Vaalen. A new evolutionary law. *Evolutionary Theory*, 1:1–30, 1973.

M. van Veelen. Group selection, kin selection, altruism and cooperation: When inclusive fitness is right and when it can be wrong. *J. Theor. Biol.*, 259:589–600, 2009.

W. L. Vickery and R. Poulin. The evolution of host manipulation by parasites: a game theory analysis. *Evol Ecol*, 24:773–788, 2010.

T. L. Vincent and J. S. Brown. *Evolutionary Game Theory, Natural Selection, and Darwinian Dynamics*. Cambridge University Press, Cambridge, 2003.

V. Volterra. Variations and fluctuations of the number of individuals in animal species living together. *J. Cons. int. Explor. Mer*, 3(1):3–51, 1928.

J. von Neumann and O. Morgenstern. *Theory of Games and Economic Behavior*. Princeton University Press, Princeton, 1944.

M. J. Wade and R. W. Beeman. The population dynamics of maternal-effect selfish genes. *Genetics*, 138:1309–1314, 1994.

J. Wakeley. *Coalescent theory: An Introduction*. Roberts and Company Publishers, 2008.

C. Wedekind and M. Milinski. Human cooperation in the simultaneous and the alternating prisoner's dilemma: Pavlov versus generous tit-for-tat. *Proc. Natl. Acad. Sci. USA*, 93: 2686–2689, 1996.

C. Wedekind and M. Milinski. Cooperation through image scoring in humans. *Science*, 288: 850–852, 2000.

D. Weichenhan, W. Traut, B. Kunze, and H. Winking. Distortion of mendelian recovery ratio for a mouse HSR is caused by maternal and zygotic effects. *Genet. Res.*, 68(2):125–129, 1996.

D. M. Weinreich, N.F. Delaney, M.A. DePristo, and D.L. Hartl. Darwinian evolution can follow only very few mutational paths to fitter proteins. *Science*, 312:111–114, 2006.

G. Wild and P.D. Taylor. Fitness and evolutionary stability in game theoretic models of finite populations. *Proc. Roy. Soc. Lond. B*, 271:2345–2349, 2004.

G. Wild and A. Traulsen. The different limits of weak selection and the evolutionary dynamics of finite populations. *J. Theor. Biol.*, 247:382–390, 2007.

G. S. Wilkinson. Reciprocal food-sharing in the vampire bat. *Nature*, 308:181–184, 1984.

G. C. Williams. *Adaption and natural selection: A critique of some current evolutionary though*. Princeton Univ. Press, Princeton, 1966.

S. Wright. Evolution in Mendelian populations. *Genetics*, 16:97–159, 1931.

S. Wright. The roles of mutation, inbreeding, crossbreeding and selection in evolution. In *Proc of the 6th International Congress of Genetics*, volume 1, pages 356–366, 1932.

B. Wu, C. S. Gokhale, L. Wang, and A. Traulsen. Different definitions of fitness can lead to

different evolutionary predictions. *In preparation*, 2011.

E. C. Zeeman. Population dynamics from game theory. *in Lecture Notes in Mathematics*, 819: 471–497, 1980.

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Declaration

I hereby declare,

i. that apart from my supervisor, Arne Traulsen's guidance, the content and design of the thesis is my own work.

ii. that the thesis has not been submitted partly or wholly as a part of a doctoral degree to any other examining body. Apart from the included published papers and the submitted papers no other part of the thesis has been published or submitted for publishing. Table. 5.1 categorises the author contributions into the different stages of research.

iii. that the thesis has been prepared according to the rules of Good Scientific Practice of the German Research Foundation.

Chaitanya S. Gokhale

Table 5.1: In alphabetical order: Philipp M. Altrock (PMA), **Chaitanya S. Gokhale (CSG)**, Yoh Iwasa (YH), Martin A. Nowak (MAN) Floyd A. Reed (FAR) Guy R. Reeves (RGR) Arne Traulsen (AT), Long Wang (LW), Bin Wu (BW). **Journals:** Journal of theoretical Biology (JTB), Proceedings of the National Academy of Sciences (PNAS), Physical Review E (PRE)

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Journal of Mathematical Biology

Journal of Theoretical Biology

Proceedings of the National Academy of Sciences, United States of America

On the review board of Santa Fe Institute's Complex Systems Summer School applications

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