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Bacterial Games

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Abstract. Microbial laboratory communities have become model systems for studying the complex interplay between nonlinear dynamics of evolutionary selection forces, stochastic fluctuations arising from the probabilistic nature of interactions, and spatial organization. Major research goals are to identify and understand mechanisms that ensures viability of microbial colonies by allowing for species diversity, cooperative behavior and other kinds of “social” behavior. A synthesis of evolutionary game theory, nonlinear dynamics, and the theory of stochastic processes provides the mathematical tools and conceptual framework for a deeper understanding of these ecological systems. We give an introduction into the modern formulation of these theories and illustrate their effectiveness focussing on selected examples of microbial systems. Intrinsic fluctuations, stemming from the discreteness of individuals, are ubiquitous, and can have important impact on the stability of ecosystems. In the absence of speciation, extinction of species is unavoidable, may, however, take very long times. We provide a general concept for defining survival and extinction on ecological time-scales. Spatial degrees of freedom come with a certain mobility of individuals. When the latter is sufficiently high, bacterial community structures can be understood through mapping individual-based models, in a continuum approach, onto stochastic partial differential equations. These allow progress using methods of nonlinear dynamics such as bifurcation analysis and invariant manifolds. We conclude with a perspective on the current challenges in quantifying bacterial pattern formation, and how this might have an impact on fundamental research in non-equilibrium physics.

1.1 Introduction

Microbial systems are complex assemblies of large numbers of individuals, interacting competitively under multifaceted environmental conditions. Bacteria often grow in complex, dynamical communities, pervading the earth's ecological systems, from hot springs to rivers and the human body [1]. As an example, in the latter case, they can cause a number of infectious diseases, such as lung infection by Pseudomonas aeruginosa. Bacterial communities, quite generically, form biofilms [1, 2], i.e., they arrange into a quasi-multi-cellular entity where they highly interact. These interactions include competition for nutrients, cooperation by providing various kinds of public goods essential for the formation and maintenance of the biofilm [3], communication through the secretion and detection of extracellular substances [4, 5], chemical warfare [7], and last but not least physical forces. The ensuing complexity of bacterial communities has conveyed the idea that they constitute a kind of "social groups" where the coordinated action of individuals leads to various kinds of system-level functionalities [6].

Since additionally microbial interactions can be manipulated in a multitude of ways, many researchers have turned to microbes as the organisms of choice to explore fundamental problems in ecology and evolutionary dynamics [7, 8, 9]. Much effort is currently devoted to qualitative and quantitative understanding of basic mechanisms that maintain the *diversity of microbial populations*. Hereby, within exemplary models, the formation of dynamic spatial patterns has been identified as a key promoter [10, 11, 12, 13]. In particular, the crucial influence of self-organized patterns on biodiversity has been demonstrated in recent experimental studies [7], employing three bacterial strains that display cyclic competition. The latter is metaphorically described by the game "rock-paper-scissors" where rock smashes scissors, scissors cut paper, and paper wraps rock in turn. For the three bacterial strains, and for low microbes motility, cyclic dominance leads to the stable coexistence of all three strains through self-formation of spatial patterns. In contrast, stirring the system, as can also result from high motilities of the individuals, destroys the spatial structures which results in the take over of one subpopulation and the extinction of the others after a short transient. There is also an ongoing debate in sociobiology how *cooperation* within a population emerges in the first place and how it is maintained in the long run. Microbial communities again serve as versatile model systems for exploring these questions [8, 9]. In those systems, cooperators are producers of a common good, usually a metabolically expensive biochemical product. Hence a successfully cooperating collective of microbes permanently runs the risk to be undermined by non-producing strains ("cheaters") saving the metabolically costly supply of biofilm formation [14, 3]. As partial resolutions to this puzzling dilemma recents studies emphasize nonlinear benefits [8] and population bottlenecks in permanently regrouping populations [9].

This article is intended as an introduction into some of the theoretical concepts which are useful in deepening our understanding of these systems. We will start with an introduction to the language of game theory and after a short discussion of “strategic games” quickly move to “evolutionary game theory”. The latter is the natural framework for the evolutionary dynamics of populations consisting of interacting multiple species, where the success of a given individual depends on the behavior of the surrounding ones. It is most naturally formulated in the language of nonlinear dynamics, where the game theory terms “Nash equilibrium” or “evolutionary stable strategy” map onto “fixed points” of ordinary nonlinear differential equations. Illustrations of these concepts are given in terms of two-strategy games and the cyclic Lotka-Volterra model, also known as the “rock-paper-scissors” game. Before embarking on the theoretical analysis of the role of stochasticity and space we give, in a short chapter 3, some examples of game-theoretical problems in biology, mainly taken from the field of microbiology.

A deterministic description of populations of interacting individuals in terms of nonlinear differential equations misses some important features of actual ecological systems. The molecular processes underlying the interaction between individuals are often inherently stochastic and the number of individuals is always discrete. As a consequence, there are random fluctuations in the composition of the population which can have an important impact on the stability of ecosystems. In the absence of speciation, extinction of species is unavoidable, may, however, take very long times. Chapter 4 starts with some elementary, but very important, notes on extinction times, culminating in a general concept for defining survival and extinction on ecological time scales. These ideas are then illustrated for the rock-scissors-paper game.

Cyclic competition of species, as metaphorically described by the childrens game “rock-paper-scissors”, is an intriguing motif of species interactions. Laboratory experiments on populations consisting of different bacterial strains of E. coli have shown that bacteria can coexist if a low mobility enables the segregation of the different strains and thereby the formation of patterns [7]. In chapter 5 we analyze the impact of stochasticity as well as individuals mobility on the stability of diversity as well as the emerging patterns. Within a spatially-extended version of the May-Leonard model [15] we demonstrate the existence of a sharp mobility threshold [13], such that diversity is maintained below, but jeopardized above that value. Computer simulations of the ensuing stochastic cellular automaton show that entangled rotating spiral waves accompany biodiversity. In our final chapter we conclude with a perspective on the current challenges in quantifying bacterial pattern formation and how this might also have an impact on fundamental research in non-equilibrium physics.

1.2 The language of game theory

1.2.1 Strategic games and social dilemmas

Classical game theory [16] describes the behavior of rational players. It attempts to mathematically capture behavior in strategic situations, in which an individual's success in making choices depends on the choices of others. A classical example of a strategic game is the *prisoner's dilemma*. It can be formulated as a kind of a *public good game* where a cooperator provides a benefit b to another individual, at a cost c to itself (with $b - c > 0$). In contrast, a defector refuses to provide any benefit and hence does not pay any costs. For the selfish individual, irrespective of whether the partner cooperates or defects, defection is favorable, as it avoids the cost of cooperation, exploits cooperators, and ensures not to become exploited. However, if all individuals act rationally and defect, everybody is, with a gain of 0, worse off compared to universal cooperation, where a net gain of $b-c > 0$ would be achieved. This unfavorable outcome of the game, where both play "defect", is called *Nash equilibrium* [17]. The prisoner's dilemma therefore describes, in its most basic form, the fundamental problem of establishing cooperation. It is summarized in the following payoff matrix (for the column player):

P	Cooperator (C)	Defector (D)
C	$b - c$	$-c$
D	b	0

This scheme can be generalized to include other basic types of social dilemmas [18, 19]. Namely, two cooperators that meet are both *rewarded* a payoff $\mathcal{R}$, while two defectors obtain a *punishment* $\mathcal{P}$. When a defector encounters a cooperator, the first exploits the second, gaining the *temptation* $\mathcal{T}$, while the cooperator only gets the *suckers payoff* $\mathcal{S}$. Social dilemmas occur when $\mathcal{R} > \mathcal{P}$, such that cooperation is favorable in principle, while temptation to defect is large: $\mathcal{T} > \mathcal{S}$, $\mathcal{T} > \mathcal{P}$. These interactions may be summarized by the payoff matrix:

P	Cooperator (C)	Defector (D)
C	$\mathcal{R}$	$\mathcal{S}$
D	$\mathcal{T}$	$\mathcal{P}$

Variation of the parameters $\mathcal{T}$, $\mathcal{P}$, $\mathcal{R}$ and $\mathcal{S}$ yields four distinct types of games. The *prisoner's dilemma* arises if the temptation $\mathcal{T}$ to defect is larger than the reward $\mathcal{R}$, and if the punishment $\mathcal{P}$ is larger than the suckers payoff $\mathcal{S}$. As we have already seen above, in this case, defection is the best strategy for the selfish player. Within the three other types of games, defectors are not always better off. For the *snowdrift game* the temptation $\mathcal{T}$ is still higher than the reward $\mathcal{R}$ but the sucker's payoff $\mathcal{S}$ is larger than the punishment $\mathcal{P}$. Therefore, now actually cooperation is favorable when meeting a defector, but defection pays off when encountering a cooperator, and a rational strategy consists of a mixture of cooperation and defection. The snowdrift game derives its name from the potentially cooperative interaction present when two drivers are trapped behind a large pile of snow, and each driver must decide whether to clear a path. Obviously, then the optimal strategy is the opposite of the opponent's (cooperate when your opponent defects and defect when your opponent cooperates). Another scenario is the *coordination game*, where mutual agreement is preferred: either all individuals cooperate or defect as the reward $\mathcal{R}$ is higher than the temptation $\mathcal{T}$ and the punishment $\mathcal{P}$ is higher than sucker's payoff $\mathcal{S}$. Lastly, the scenario of *by-product mutualism* (also called *harmony*) yields cooperators fully dominating defectors since the reward $\mathcal{R}$ is higher than the temptation $\mathcal{T}$ and the sucker's payoff $\mathcal{S}$ is higher than the punishment $\mathcal{P}$.

1.2.2 Evolutionary game theory

Strategic games are thought to be a useful framework in economic and social settings. In order to analyze the behavior of biological systems, the concept of rationality is not meaningful. Evolutionary Game Theory (EGT), as developed mainly by Maynard Smith and Price [20, 21], does not rely on rationality assumptions but on the idea that evolutionary forces like natural selection and mutation are the driving forces of change. The interpretation of game models in biology is fundamentally different from strategic games in economics or social sciences. In biology, strategies are considered to be inherited programs which control the individual's behavior. Typically one looks at a population composed of individuals with different strategies who interact generation after generation in game situations of the same type. The interactions may be described by deterministic rules or stochastic processes, depending on the particular system under study. The ensuing dynamic process can then be viewed as an iterative (nonlinear) map or a stochastic process (either with discrete or continuous time). This naturally puts evolutionary game theory in the context of nonlinear dynamics and the theory of stochastic processes. We will see later on how a synthesis of both approaches helps to understand the emergence of complex spatio-temporal dynamics.

In this section, we focus on a *deterministic description of well-mixed populations*. The term *"well-mixed"* signifies systems where the individual's mobility (or diffusion) is so large that one may neglect any spatial degrees of freedom and assume that every individual is interacting with everyone at the same time. This is a mean-field picture where interactions are given in terms of the average number of individuals playing a particular strategy. Frequently, this situation is visualized as an "urn model", where two individuals from a population are randomly selected to play with each other according to some specified game theoretical scheme. The term *"deterministic"* means that we are seeking a description of populations where the number of individuals $N_i(t)$ playing a particular strategy A_i are macroscopically large such that stochastic effects can be neglected.

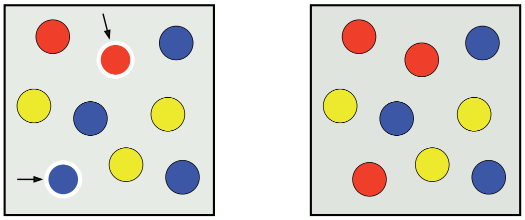

Fig. 1.1. The urn model describes the evolution of well-mixed finite populations. Here, as an example, we show three species as yellow (A), red (B), and blue (C) spheres. At each time step, two randomly selected individuals are chosen (indicated by arrows in the left picture) and interact with each other according to the rules of the game resulting in an updated composition of the population (right picture).

Pairwise reactions and rate equations

In the simplest setup the interaction between individuals playing different strategies can be represented as a reaction process characterized by a set of rate constants. For example, consider a game where three strategies $\{A, B, C\}$ cyclically dominate each other, as in the rock-paper-scissors game: A invades B, B outperforms C, and C in turn dominates over A, schematically drawn in Fig.1.2:

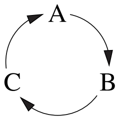

Fig. 1.2. Illustration of cyclic dominance of three states A, B, and C: A invades B, B outperforms C, and C in turn dominates over A.

In an evolutionary setting, the game may be played according to an urn model as illustrated in Fig.1.1: at a given time t two individuals from a population with constant size N are randomly selected to play with each other (react) according to the reaction scheme

$$\begin{aligned} A + B &\xrightarrow{k_A} A + A\,, \\ B + C &\xrightarrow{k_B} B + B\,, \\ C + A &\xrightarrow{k_C} C + C\,, \end{aligned} \tag{1.1}$$

where k_i are rate constants, i.e. probabilities per unit time. This interaction scheme is termed a *cyclic Lotka-Volterra model* [3]. It is equivalent to a set of

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[3] The two-species Lotka-Volterra equations describe a predator-prey system where the per-capita growth rate of prey decreases linearly with the amount of predators

chemical reactions, and in the deterministic limit of a well-mixed population one obtains *rate equations* for the frequencies $(a, b, c) = (N_A, N_B, N_C)/N$:

$$\begin{aligned}\partial_t a &= a(k_A b - k_C c)\,,\\ \partial_t b &= b(k_B c - k_A a)\,,\\ \partial_t c &= c(k_C a - k_B b)\,.\end{aligned} \tag{1.2}$$

Here the right hand sides gives the balance of "gain" and "loss" processes. The phase space of the model is the simplex S_3, where the species' densities are constrained by $a + b + c = 1$. There is a constant of motion for the rate equations, Eq.(1.3), namely the quantity $\rho := a^{k_B} b^{k_C} c^{k_A}$ does not evolve in time [25]. As a consequence, the phase portrait of the dynamics, shown in Fig. 1.3, yield neutrally stable cycles with fixed ρ around the reactive fixed point F. This implies that the deterministic dynamics is oscillatory with the amplitude and frequency determined by the initial composition of the population.

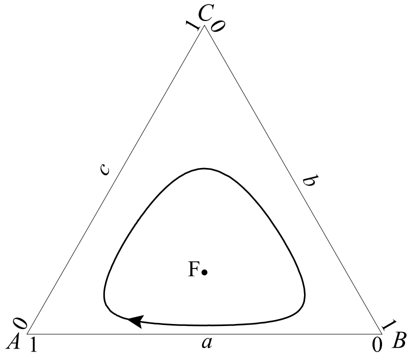

Fig. 1.3. The three-species simplex for reaction rates $k_A = 0.2$, $k_B = 0.4$, $k_C = 0.4$. Since there is a conserved quantity, the rate equations predict cyclic orbits of constant $\rho = a^{k_B} b^{k_C} c^{k_A}$; F signifies the neutrally stable reactive fixed point.

The concept of fitness and replicator equations

Another line of thought to define an evolutionary dynamics, often taken in the mathematical literature of evolutionary game theory [24, 25], introduces the concept of fitness and then assumes that the per-capita growth rate of a strategy A_i is given by the surplus in its fitness with respect to the average fitness of the population. We will illustrate this reasoning for two-strategy

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present. In the absence of prey, predators die, but there is a positive contribution to their growth which increases linearly with the amount of prey present [22, 23].

games with a payoff matrix given by Eq. (1.2.1). Let N_A and N_B be the number of individuals playing strategy A (cooperator) and B (defector) in a population of size $N = N_A + N_B$. Then the relative abundances of strategies A and B are given by

$$a = \frac{N_A}{N}\,, \quad b = \frac{N_B}{N} = (1-a)\,. \tag{1.3}$$

The "fitness" of a particular strategy A or B is defined as a constant *background fitness*, set to 1, plus the *average payoff* obtained from playing the game:

$$f_A(a) := 1 + \mathcal{R}a + \mathcal{S}(1-a)\,, \tag{1.4}$$

$$f_B(a) := 1 + \mathcal{T}a + \mathcal{P}(1-a)\,. \tag{1.5}$$

In order to mimic an evolutionary process one is seeking a dynamics which guarantees that individuals using strategies with a fitness larger than the average fitness increase while those using strategies with a fitness below average decline in number. This is, for example, achieved by choosing the per-capita growth rate, $\partial_t a/a$, of individuals playing strategy A proportional to their surplus in fitness with respect to the average fitness of the population:

$$\bar{f}(a) := a f_A(a) + (1-a) f_B(a)\,. \tag{1.6}$$

The ensuing ordinary differential equation is known as the *standard replicator equation* [24, 25]

$$\partial_t a = \left[f_A(a) - \bar{f}(a)\right] a\,. \tag{1.7}$$

Lacking a detailed knowledge of the actual "interactions" of individuals in a population, there is, of course, plenty of freedom in how to write down a differential equation describing the evolutionary dynamics of a population. Indeed, there is another set of equations frequently used in EGT, called *adjusted replicator equations*, which reads

$$\partial_t a = \frac{f_A(a) - \bar{f}(a)}{\bar{f}(a)}\, a\,. \tag{1.8}$$

The correct form to be used in an actual biological setting may be neither of these standard formulations. Typically, some knowledge about the molecular mechanisms is needed to formulate a realistic dynamics. As we will learn in section 1.3 the functional form of the payoff depends on the microbes' metabolism and is, in general, a nonlinear function of the relative abundances of the various strains in the population.

One may also criticise the assumption of constant population size made in evolutionary game theory. The internal evolution of different traits and the dynamics of the species population size are in fact not independent [26].

Species typical coevolve with other species in a changing environment and a separate description of both, evolutionary and population dynamics, is in general not justified. In particular, a species' population dynamics does not only affect the evolution within each species as considered for example by models of density-dependent selection [27] but population dynamics is also biased by the internal evolution of different traits. One visual example for this coupling are biofilms which permanently grow and shrink. In these microbial structures diverse strains live, interact, and outcompete each other while simultaneously affecting the population size [14]. A proper combined description of the total temporal development should therefore be solely based on isolated birth and death events, as recently suggested in Ref. [28]. Such an approach offers also a more biological interpretation of evolutionary dynamics than common formulations like the Fisher-Wright or the Moran process [29, 30, 31, 32]: fitter individuals prevail due to higher birth rates and not by winning a tooth-and-claw struggle where the birth of one individual directly results in the death of another one.

1.2.3 Nonlinear dynamics of two-player games

This section is intended to give a concise introduction into elementary concepts of nonlinear dynamics [33]. We illustrate those for the evolutionary dynamics of two-player games characterized in terms of the payoff matrix, Eq.(1.2.1), and the ensuing replicator dynamics

$$\partial_t a = a(f_A - \bar{f}) = a(1-a)(f_A - f_B)\,. \tag{1.9}$$

This equation has a simple interpretation: the first factor, $a(1-a)$, is the probability for A and B to meet and the second factor, $f_A - f_B$, is the fitness advantage of A over B. Inserting the explicit expressions for the fitness values one finds

$$\partial_t a = a(1-a)\big[\mu_A(1-a) - \mu_B a\big] =: F(a)\,, \tag{1.10}$$

where μ_A is the relative benefit of A playing against B and μ_B is the relative benefit of B playing against A:

$$\mu_A := \mathcal{S} - \mathcal{P}\,, \qquad \mu_B := \mathcal{T} - \mathcal{R}\,. \tag{1.11}$$

Eq.1.10 is a one-dimensional nonlinear first-oder differential equation for the fraction a of players A in the population, whose dynamics is most easily analyzed graphically. The sign of $F(a)$ determines the increase or decrease of the dynamic variable a; compare the right half of Fig.1.4. The intersections of $F(a)$ with the a-axis (zeros) are *fixed points*, a^*. Generically, these intersections are with a finite slope $F'(a^*) \neq 0$; a negative slope indicates a stable fixed point while a positive slope an unstable fixed point. Depending on some *control parameters*, here μ_A and μ_B, the first or higher order derivatives of F

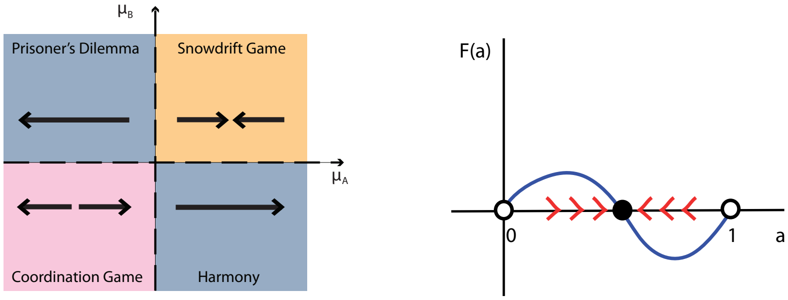

Fig. 1.4. Classification of two-player games. *Left:* The black arrows in the control parameter plane (μ_A, μ_B) indicate the flow behavior of the four different types of two-player games. *Right:* Graphically the solution of a one-dimensional nonlinear dynamics equation, $\partial_t a = F(a)$, is simply read off from the signs of the function $F(a)$; illustration for the snowdrift game.

at the fixed points may vanish. These special parameter values mark "threshold values" for changes in the flow behavior (*bifurcations*) of the nonlinear dynamics. We may now classify two-player games as illustrated in Fig.1.4.

For the prisoner's dilemma $\mu_A = -c < 0$ and $\mu_B = c > 0$ and hence players with strategy B (defectors) are always better off (compare the payoff matrix). Both players playing strategy B is a Nash equilibrium. In terms of the replicator equations this situation corresponds to $F(a) < 0$ for $a \neq 0$ and $F(a) = 0$ at $a = 0, 1$ such that $a^* = 0$ is the only stable fixed point. Hence the term "Nash equilibrium" translates into the "stable fixed point" of the replicator dynamics (nonlinear dynamics).

For the snowdrift game both $\mu_A > 0$ and $\mu_B > 0$ such that $F(a)$ can change sign for $a \in [0, 1]$. In fact, $a^*_{\text{int}} = \mu_A/(\mu_A + \mu_B)$ is a stable fixed point while $a^* = 0, 1$ are unstable fixed points; see the right panel of Fig.1.4. Inspection of the payoff matrix tells us that it is always better to play the opposite strategy of your opponent. Hence there is no Nash equilibrium in terms of pure strategies A or B. This corresponds to the fact that the boundary fixed points $a^* = 0, 1$ are unstable. There is, however, a Nash equilibrium with a *mixed strategy* where a rational player would play strategy A with probability $p_A = \mu_A/(\mu_A + \mu_B)$ and strategy B with probability $p_B = 1 - p_A$. Hence, again, the term "Nash equilibrium" translates into the "stable fixed point" of the replicator dynamics (nonlinear dynamics).

For the coordination game, there is also an interior fixed point at $a^*_{\text{int}} = \mu_A/(\mu_A + \mu_B)$, but now it is unstable, while the fixed points at the boundaries $a^* = 0, 1$ are stable. Hence we have *bistability*: for initial values $a < a^*_{\text{int}}$ the flow is towards $a = 0$ while it is towards $a = 1$ otherwise. In the terminology of strategic games there are two Nash equilibria. The game harmony corresponds to the prisoner's dilemma with the roles of A and B interchanged.

1.3 Games in microbial metapopulations

Two of the most fundamental question that challenge our understanding of evolution and ecology are the origin of *cooperation* [34, 35, 36, 4, 5, 37, 8, 9] and *biodiversity* [38,39,40, 7, 6]. Both are ubiquitous phenomena yet conspicuously difficult to explain since the fitness of an individual or the whole community depends in an intricate way on a plethora of factors, such as spatial distribution and mobility of individuals, secretion and detection of signaling molecules, toxin secretion leading to inter-strain competition and changes in environmental conditions. It is fair to say that we are still a far way off from a full understanding, but the versatility of microbial communities makes their study a worthwhile endeavor with exciting discoveries still ahead of us.

Cooperation

Understanding the conditions that promote the emergence and maintenance of cooperation is a classic problem in evolutionary biology [41,42,21]. It can be stated in the language of the prisoners dilemma. By providing a public good, cooperative behavior would be beneficial for all individuals in the whole population. However, since cooperation is costly, the population is at risk from invasion by “selfish” individuals (cheaters), who save the cost of cooperation but can still obtain the benefit of cooperation from others. In evolutionary theory many principles were proposed to overcome this dilemma of cooperation: repeated interaction [36,41], punishment [36,43], or kin discrimination [44,14]. All of these principles share one fundamental feature: They are based on some kind of selection mechanism. Similar to the old debate between “selectionists” and “neutralists” in evolutionary theory [45], there is an alternative. Due to random fluctuations a population, initially composed of both cooperators and defectors, may (with some probability) become fixed in a state of cooperators only [46].

There has been an increasing number of experiments using microorganisms trying to shed new light on the problem of cooperation [34,35,8,9]. Here, we will shortly discuss a recent experiment on “cheating in yeast” [8]. Budding yeast prefers to use the monosaccharides glucose and fructose as carbon sources. If they have to grow on sucrose instead, the disaccharide must first be hydrolyzed by the enzyme invertase. Since a fraction of approximately $1 - \epsilon = 99\%$ of the produced monosaccharides diffuses away and is shared with neighboring cells, it constitutes a public good available to the whole microbial community. This makes the population susceptible to invasion by mutant strains that save the metabolic cost of producing invertase. One is now tempted to conclude from what we have discussed in the previous sections that yeast is playing the prisoner’s dilemma game. The cheater strains should take over the population and the wild type strain should become extinct. But, this is not the case. Gore and collaborators [8] show that the dynamics is rather described as a snowdrift game, in which cheating can be profitable, but is not necessarily the best strategy if others are cheating too. The explanation given is that the growth rate as a function of glucose is highly concave and, as a consequence, the fitness function is *non-linear* in the payoffs [4]

$$f_C(x) := \Big[\epsilon + x(1-\epsilon)\Big]^{\alpha} - c\,, \tag{1.12}$$

$$f_D(a) := \Big[x(1-\epsilon)\Big]^{\alpha}\,, \tag{1.13}$$

with $\alpha \approx 0.15$ determined experimentally. The ensuing phase diagram, Fig. 1.5 as a function of capture efficiency ϵ and metabolic cost c shows an altered intermediate regime with a bistable phase portrait, i.e. the hallmark of a snowdrift game as discussed in the previous section. This explains the experimental observations. The lesson to be learned from this investigation is that defining a payoff function is not a trivial matter, and a naive replicator dynamics fails to describe biological reality. It is, in general, necessary to have a detailed look on the nature of the biochemical processes responsible for the growth rates of the competing microbes.

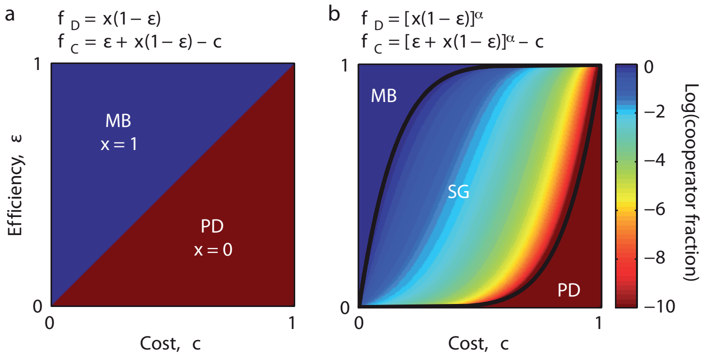

Fig. 1.5. Game theory models of cooperation in sucrose metabolism of yeast. **a)** Phase diagram resulting from fitness functions f_C and f_D linear in the payoffs. This model leads to fixation of cooperators ($x = 1$) at low cost and/or high efficiency of capture ($\epsilon > c$, implying that the game is mutually beneficial (MB)) but fixation of defectors ($x = 0$) for high cost and/or low efficiency of capture ($\epsilon < c$, implying that the game is prisoners dilemma (PD)). **b)** A model of cooperation with experimentally measured concave benefits yields a central region of parameter space that is a snowdrift game (SG), thus explaining the coexistence that is observed experimentally ($\alpha = 0.15$). Adapted from Ref. [8]

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[4] Note that ϵ is the fraction of carbon source kept by cooperators solely for themselves and $x(1-\epsilon)$ is the amount of carbon source shared with the whole community. Hence, the linear growth rate of cooperators and defectors would by $\epsilon + x(1-\epsilon) - c$ and $x(1-\epsilon)$, respectively, where c is the metabolic cost for invertase production.

Pattern formation

Investigations of microbial pattern formation have often focussed on one bacterial strain [47,48,49]. In this respect, it has been found that bacterial colonies on substrates with a high nutrient level and intermediate agar concentrations, representing "friendly" conditions, grow in simple compact patterns [50]. When instead the level of nutrient is lowered, when the surface on which bacteria grow possesses heterogeneities, or when the bacteria are exposed to antibiotics, complex, fractal patterns are observed [47, 51, 52]. Other factors that affect the self-organizing patterns include motility [53], the kind of bacterial movement, e.g., swimming [54], swarming, or gliding [55, 56], as well as chemotaxis and external heterogeneities [57]. Another line of research has investigated patterns of multiple co-evolving bacterial strains. As an example, recent studies looked at growth patterns of two functionally equivalent strains of *Escherichia coli* and showed that, due to fluctuations alone, they segregate into well-defined, sector like regions [48, 58].

The *Escherichia* Col E2 system

Several Colibacteria such as *Escherichia coli* are able to produce and secrete specific toxins called Colicines that inhibit growth of other bacteria. Kerr and coworkers [7] have studied three strains of *E. coli*, amongst which one is able to produce the toxin Col E2 that acts as an DNA endonuclease. This poison producing strain (C) kills a sensitive strain (S), which outgrows the third, resistant one (R), as resistance bears certain costs. The resistant bacteria grow faster than the poisonous ones, as the latter are resistant and produce poison, which is yet an extra cost. Consequently, the three strains of *E. coli* display cyclic competition, similar to the children's game rock-paper-scissors.

When placed on a Petri-dish, all three strains coexist, arranging in time-dependent spatial clusters dominated by one strain. In Fig. 1.6, snapshots of these patterns monitored over several days are shown. Sharp boundaries between different domains emerge, and all three strains co-evolve at comparable densities. The patterns are dynamic: Due to the non-equilibrium character of the species' interactions, clusters dominated by one bacterial strain cyclically invade each other, resulting in an endless hunt of the three species on the Petri-dish. The situation changes considerably when putting the bacteria in a flask with additional stirring. Then, only the resistant strain survives, while the two others die out after a short transient time.

These laboratory experiments thus provide intriguing experimental evidence for the importance of spatial patterns for the maintenance of biodiversity. In this respect, many further questions regarding the spatio-temporal interactions of competing organisms under different environmental conditions lie ahead. Spontaneous mutagenesis of single cells can lead to enhanced fitness under specific environmental conditions or due to interactions with other

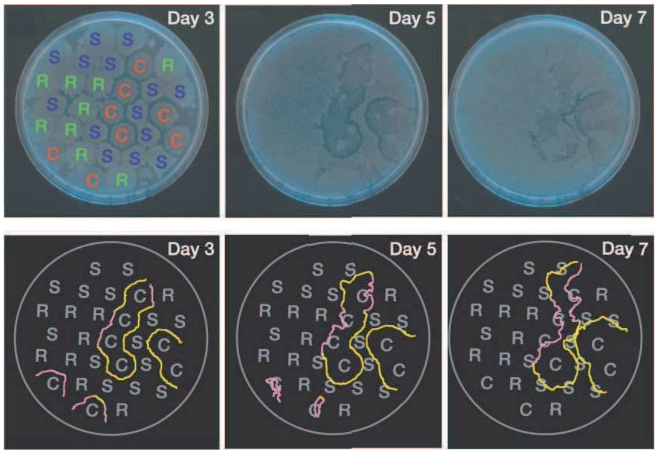

Fig. 1.6. The three strains of the *Escherichia* Col E2 system evolve into spatial patterns on a Petri-dish. The competition of the three strains is cyclic (of rock-paper-scissors type) and therefore non-equilibrium in nature, leading to dynamic patterns. The picture has been modified from [7].

species. Moreover, interactions with other species may allow unfit, but potentially pathogenic bacteria to colonize certain tissues. Additionally, high concentrations of harmless bacteria may help pathogenic ones to nest on tissues exposed to extremely unfriendly conditions. Information about bacterial pattern formation arising from bacterial interaction may therefore allow to develop mechanism to avoid pathogenic infection.

1.4 Stochastic dynamics in well-mixed populations

The machinery of biological cells consists of networks of molecules interacting with each other in a highly complex manner. Many of these interactions can be described as chemical reactions, where the intricate processes which occur during the encounter of two molecules are reduced to reaction rates, i.e. probabilities per unit time. This notion of stochasticity carries over to the scale of microbes in a manifold way. There is *phenotypic noise*. Due to fluctuations in transcription and translation, phenotypes vary even in the absence of genetic differences between individuals and despite constant environmental conditions [59, 60]. In addition, phenotypic variability may arise due to various external factors like cell density, nutrient availability and other stress conditions. A general discussion of phenotypic variability in bacteria may be found in recent reviews [61,62,63,64]. There is *interaction noise*. Interactions between individuals in a given population, as well as cell division and cell death, occur at random points in time (following some probability distribution) and lead to discrete steps in the number of the different species. Then, as noted long ago by Delbrück [65], a deterministic description, as discussed in the previous section, breaks down for small copy numbers. Finally, there is *external noise* due to spatial heterogeneities or temporal fluctuations in the environment. In this section we will focus on *interaction noise*, whose role for extinction processes in ecology has recently been recognized to be very important, especially when the deterministic dynamics exhibits neutral stability [66, 67, 68] or weak stability [69, 46]. After a brief and elementary discussion of extinction times we will introduce a general concept for defining survival and extinction on ecological time-scales. The concept of extinction will be illustrated for the stochastic dynamics of the cyclic Lotka-Volterra model [67].

1.4.1 Extinction times and classification of coexistence stability

For a deterministic system, given an initial condition, the outcome of the evolutionary dynamics is certain. However, processes encountered in biological systems are often stochastic. For example, consider the degradation of a protein or the death of an individual bacterium in a population. To a good approximation it can be described as a stochastic event which occurs at a probability per unit time (rate) λ, known as a stochastic *linear death process*. Then the population size $N(t)$ at time t becomes a random variable, and its time evolution becomes a set of integers $\{N_\alpha\}$ changing from N_α to $N_\alpha - 1$ at particular times t_α; this is also called a realization of the stochastic process. Now it is no longer meaningful to ask for *the* time evolution of a particular population, as one would do in a deterministic description in terms of a rate equation, $\partial_t N = -\lambda N$. Instead one studies the time evolution of an ensemble of systems or tries to understand the distribution of times $\{t_\alpha\}$. A central quantity in this endeavor is the probability $P(N, t)$ to find a population of size N given that at some time $t = 0$ there was some initial ensemble of populations. Assuming that the stochastic process is Markovian, its dynamics is given by the following master equation:

$$\partial_t P(N, t) = \lambda(N + 1)P(N + 1, t) - \lambda N P(N, t)\,. \tag{1.14}$$

A master equation is a "balance equation" for probabilities. The right hand side simply states that there is an increase in $P(N, t)$ if in a population of size $N + 1$ an individual dies with rate λ, and a decrease in $P(N, t)$ if in a population of size N an individual dies with rate λ. Master equations can be analyzed by standard tools from the theory of stochastic processes [70, 71].

A quantity of central interest is the average extinction time T, i.e. the expected time for the population to reach the state $N = 0$. This state is also called an *absorbing state* since (for the linear death process considered here) there are only processes leading into but not out of this state. The expected extinction time T can be obtained using rather elementary concepts from probability theory. Consider the probability $Q(t)$ that a given individual is still alive at time t conditioned on that it was alive at some initial time $t = 0$. Since an individual will be alive at time $t + dt$ if it was alive at time t and did not die within the time interval $[t, t + dt]$ we immediately obtain the identity

$$Q(t + dt) = Q(t)(1 - \lambda t) \quad \text{with} \quad Q(0) = 1\,. \tag{1.15}$$

The ensuing differential equation (in the limit $dt \to 0$), $\dot{Q} = -\lambda Q$ is solved by $Q(t) = e^{-\lambda t}$. This identifies $\tau = 1/\lambda$ as the expected waiting time for a particular individual to die. We conclude that the waiting times for the population to change by one individual is distributed exponentially and its expected value is $\tau_N = \tau/N$ for a population of size N; note that each individual in a population has the same chance to die. Hence we can write for the expected extinction time for a population with initial size N_0

$$T = \tau_{N_0} + \tau_{N_0-1} + \cdots + \tau_1 = \sum_{N=1}^{N_0} \frac{\tau}{N} \approx \tau \int_1^{N_0} \frac{1}{N}\, dN = \tau \ln N_0\,. \tag{1.16}$$

We have learned that for a system with a “drift” towards the absorbing boundary of the state space the expected time to reach this boundary scales, quite generically, logarithmically in the initial population size, $T \sim \ln N_0$. Note that within a deterministic description, $\dot{N} = -\lambda N$, the population size would exponentially decay to zero but never reach it, $N(t) = N_0 e^{-t/\tau}$. This is, of course, flawed in two ways. First, the process is not deterministic and, second, the population size is not a real number. Both features are essential to understand the actual dynamics of a population at low copy numbers of individuals.

Now we would like to contrast the linear death process with a “neutral process” where death and birth events balance each other, i.e. where the birth rate μ exactly equals the death rate λ. In a deterministic description one would write

$$\partial_t N(t) = -(\lambda - \mu) N(t) = 0 \tag{1.17}$$

and conclude that the population size remains constant at its initial value. In a stochastic description, one starts from the master equation

$$\partial_t P(N,t) = \lambda(N+1)P(N+1,t) + \lambda(N-1)P(N-1,t) - 2\lambda N P(N,t)\,. \tag{1.18}$$

Though this could be solved exactly using generating functions it is instructive to derive an approximation valid in the limit of a large population size, i.e. $N \gg 1$. This is most easily done by simply performing a second order Taylor expansion without worrying to much about the mathematical validity of such an expansion. With

$$(N \pm 1)P(N \pm 1, t) \approx NP(N,t) \pm \partial_N \big[NP(N,t)\big] + \frac{1}{2}\partial_N^2 \big[NP(N,t)\big]$$

one obtains

$$\partial_t P(N,t) = \lambda \partial_N^2 \big[NP(N,t)\big]\,. \tag{1.19}$$

Measuring the population size in units of the initial population size at time $t = 0$ and defining $x = N/N_0$, this becomes

$$\partial_t P(x,t) = D\partial_x^2\big[xP(x,t)\big] \tag{1.20}$$

with the "diffusion constant" $D = \lambda/N_0$. This implies that all time scales in the problem scale as $t \sim D^{-1} \sim N_0$; this is easily seen by introducing a dimensionless time $\tau = Dt$ resulting in a rescaled equation

$$\partial_\tau P(x,\tau) = \partial_x^2\big[xP(x,\tau)\big]\ . \tag{1.21}$$

Hence for a (deterministically) "neutral dynamics" the extinction time, i.e. the time reaching the absorbing state $N = 0$, scales, also quite generically, linear in the initial system size $T \sim N_0$.

Finally, there are processes like the snowdrift game where the deterministic dynamics drives the population towards an interior fixed point well separated from the absorbing boundaries, $x = 0$ and $x = 1$. In such a case, starting from an initial state in the vicinity of the interior fixed point, the stochastic dynamics has to overcome a finite barrier in order to reach the absorbing state. This is reminiscent to a chemical reaction with an activation barrier which is described by an Arrehnius law. Hence we expect that the extinction time scales exponentially in the initial population size $T \sim \exp N_0$.

These simple arguments on dependence of the mean extinction time T of competing species on the system size N can now be used to define a general framework to distinguish neutral from selection-dominated evolution. For a selection-dominated parameter regime, instability leads to steady decay of a species, and therefore to fast extinction [72, 73, 13]: The mean extinction time T increases only logarithmically in the population size N, $T \sim \ln N$, and a larger system size does not ensure much longer coexistence. This behavior can be understood by noting that a species disfavored by selection decreases by a constant rate. Consequently, its population size decays exponentially in time, leading to a logarithmic dependence of the extinction time on the initial population size. In contrast, stable existence of a species induces $T \sim \exp N$, such that extinction takes an astronomically long time for large populations [72,73,46]. In this regime, extinction stems from large fluctuations that cause sufficient deviation from the (deterministically) stable coexistence. These large deviations are exponentially suppressed and hence the time until a rare extinction event occurs scales exponentially in the system size N. Then coexistence is maintained on ecologically relevant time-scales which typically lie below T. An intermediate situation, i.e., when T has a power-law dependence on N, $T \sim N^\alpha$, signals dominant influences of stochastic effects and corresponds to neutral evolution. Here the extinction time grows considerably, though not exponentially, in increasing population size. Large N therefore clearly prolongs coexistence of species but can still allow for extinction within biologically reasonable time-scales. Summarizing these considerations, we have proposed a quantitative classification of coexistences stability in the presence of absorbing states, which is presented in the following Box [13]:

Classification of coexistence stability

Stability: If the mean extinction time T increases faster than any power of the system size N, meaning $T/N^\alpha \to \infty$ in the asymptotic limit $N \to \infty$ and for any value of $\alpha > 0$, we refer to coexistence as stable. In this situation, typically, T increases exponentially in N.

Instability: If the mean extinction time T increases slower than any power in the system size N, meaning $T/N^\alpha \to 0$ in the asymptotic limit $N \to \infty$ and for any value of $\alpha > 0$, we refer to coexistence as unstable. In this situation, typically, T increases logarithmically in N.

Neutral stability: Neutral stability lies in between stable and unstable coexistence. It emerges when the mean extinction time T increases proportional to some power $\alpha > 0$ of the system size N, meaning $T/N^\alpha \to \mathcal{O}(1)$ in the asymptotic limit $N \to \infty$.

The strength of the above classification lies in that it only involves quantities which are directly measurable (for example through computer simulations), namely the mean extinction time and the system size. Therefore, it is generally applicable to stochastic processes, e.g. incorporating additional internal population structure like individuals age or sex, or where individuals interaction networks are more complex, such as lattices, scale-free networks or fractal ones. In these situation, it is typically impossible to infer analytically, from the discussion of fixed points stability, whether the deterministic population dynamics yields a stable or unstable coexistence. However, based on the scaling of extinction time T with system size N, differentiating stable from unstable diversity according to the above classification is feasible. In Section 1.5, we will follow this line of thought and fruitfully apply the above concept to the investigation of a rock-paper-scissors game on a two-dimensional lattice, where individuals mobility is found to mediate between stable and unstable coexistence.

1.4.2 Cyclic three-strategy games

As we have learned in the previous section, the coexistence of competing species is, due to unavoidable fluctuations, always transient. Here we illustrate this for the cyclic Lotka-Volterra model (rock-scissors-paper game) introduced in the section on Evolutionary Game Theory 1.2.2 as a mathematical description for non-transitive dynamics. Like the original Lotka-Volterra model the deterministic dynamics of the rock-scissors-paper game yields oscillations along closed, periodic orbits around a coexistence fixed point. These orbits are neutrally stable due to the existence of a conserved quantity ρ. Including noise in such a game it is clear that eventually only one of the three species will survive [67, 74, 75, 76]. However, it is far from obvious which species will most likely win the contest. Intuitively, one might think, at a first glance, that it pays for a given strain to have the highest reaction rate and hence strongly dominate over its competitor. As it turns out, however, the exact opposite strategy is the best [77]. One finds what could be called a “law of the weakest”: When the interactions between the three species are (generically) asymmetric, the “weakest” species (i.e., the one with the smallest reaction rate) survives at a probability that tends to one in the limit of a large population size, while the other two are guaranteed to extinct.

The reason for this unexpected behavior is illustrated in Fig.1.7, showing a deterministic orbit and a typical stochastic trajectory. For asymmetric reaction rates, the fixed point is shifted from the center Z of the phase space (simplex) towards one of the three edges. All deterministic orbits are changed in the same way, squeezing in the direction of one edge. In Fig.1.7 reaction rates are chosen such that the distance λ_A to the a-edge of the simplex, where A would win the contest, is smallest. The important observation here is that because of simple geometric reasons λ_A is smallest because the reaction rate k_A is smallest! Intuitively, the absorbing state which is reached from this edge has the highest probability of being hit, as the distance λ from the deterministic orbit towards this edge is shortest. Indeed, this behavior can be validated by stochastic simulations complemented by a scaling argument [77].

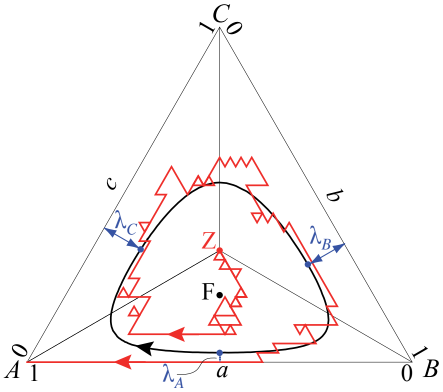

Fig. 1.7. The phase space S_3. We show the reactive fixed point F, the center Z, as well as a stochastic trajectory (red). It eventually deviates from the ‘outermost’ deterministic orbit (black) and reaches the absorbing boundary. λ_A, λ_B and λ_C (blue/dark gray) denote the distances of the ’outermost’ orbit to the boundaries. Parameters are $(k_A, k_B, k_C) = (0.2, 0.4, 0.4)$ and $N = 36$. Figure adapted from Ref. [77].

1.5 Spatial games with cyclic dominance

Spatial distribution of individuals, as well as their *mobility*, are common features of real ecosystems that often come paired [78]. On all scales of living organisms, from bacteria residing in soil or on Petri dishes, to the largest animals living in savannas - like elephants - or in forests, populations' habitats are spatially extended and *individuals interact locally* within their neighborhood. Field studies as well as experimental and theoretical investigations have shown that the locality of the interactions leads to the self-formation of complex spatial patterns [78, 79, 80, 81, 11, 82, 83, 7, 84, 85, 86, 87, 88, 89, 90, 91]. Another important property of most individuals is *mobility*. For example, bacteria swim and tumble, and animals migrate. As motile individuals are capable of enlarging their district of residence, mobility may be viewed as a mixing, or stirring mechanism which "counteracts" the locality of spatial interactions.

The role of mobility in ecosystems

The interplay between mobility and spatial separation on the spatio-temporal development of populations is one of the most interesting and complex problems in theoretical ecology [78, 79, 80, 82, 84, 13]. If *mobility is low*, locally interacting populations can exhibit involved spatio-temporal patterns, like traveling waves [92], and for example lead to the self-organization of individuals into spirals in myxobacteria aggregation [92] and insect host-parasitoid populations [11]. In contrast, *high mobility* results in well-mixed systems where the spatial distribution of the populations is irrelevant [13]. In this situation, spatial patterns do no longer form: The system adopts a spatially uniform state, which therefore drastically differs from the low-mobility scenario. Pioneering work on the role of mobility in ecosystems was performed by Levin [10], who investigated the dynamics of a population residing in two coupled patches: Within a deterministic description, he identified a critical value for the individuals' mobility between the patches. Below the critical threshold, all subpopulations coexisted, while only one remained above that value. Later, more realistic models of many patches, partly spatially arranged, were also studied; see e.g. Refs. [11,82,83,93] as well as references therein. These works shed light on the formation of patterns, in particular traveling waves and spirals. However, patch models have been criticized for treating the space in an "implicit" manner (i.e. in the form of coupled habitats without internal structure) [39]. In addition, the above investigations were often restricted to deterministic dynamics and thus did not address the spatio-temporal influence of noise. To overcome these limitations, Durrett and Levin [38] proposed to consider interacting particle systems, i.e. stochastic spatial models with populations of discrete individuals distributed on lattices. In this realm, studies have mainly focused on numerical simulations and on deterministic reaction-diffusion equations, or coupled maps [12, 38, 39, 84, 40, 94, 95, 96, 89].

Cyclic dominance in ecosystems

An intriguing motif of the complex competitions in a population, promoting species diversity, is constituted by three subpopulations exhibiting cyclic dominance, also called non-transitive competition. This basic motif is metaphorically described by the rock-paper-scissors game, where rock crushes scissors, scissors cut paper, and paper wraps rock. Such non-hierarchical, cyclic competitions, where each species outperforms another, but is also itself outperformed by a remaining one, have been identified in different ecosystems like coral reef invertebrates [97], rodents in the high-Arctic tundra in Greenland [98], lizards in the inner Coast Range of California [99] and microbial populations of colicinogenic *E. coli* [7, 100]. As we have discussed in section 1.3, in the latter situation it has been shown that spatial arrangement of quasi-immobile bacteria on a Petri-dish leads to the stable coexistence of all three competing bacterial strains, with the formation of irregular patterns. In stark contrast, when the system is well-mixed, there is spatial homogeneity resulting in the take over of one subpopulation and the extinction of the others after a short transient.

The May-Leonard model

In ecology competition for resources has been classified [101] into two broad groups, *scramble* and *contest*. Contest competition involves direct interaction between individuals. In the language of evolutionary game theory the winner in the competition replaces the looser in the population (Moran process). In contrast, scramble competition involves rapid use of limiting resources without direct interaction between the competitors. The May-Leonard model [15] of cyclic dominance between three subpopulations A, B and C dissects the non-transitive competition between these into a contest and a scramble step. In the contest step an individual of subpopulation A outperforms a B through "killing" (or "consuming"), symbolized by the ("chemical") reaction $AB \to A\oslash$, where $\oslash$ denotes an available empty space. In the same way, B outperforms C, and C beats A in turn, closing the cycle. We refer to these contest interactions as selection and denote the corresponding rate by σ. In the scramble step, which mimics a finite carrying capacity, each member of a subpopulation is allowed to reproduce only if an empty space is available, as described by the reaction $A\oslash \to AA$ and analogously for B and C. For all subpopulations, these reproduction events occur with rate μ, such that the three subpopulations equally compete for empty space. To summarize, the reactions that define the May-Leonard model (selection and reproduction) read

$$\begin{aligned} AB &\xrightarrow{\sigma} A\oslash\,, \qquad & A\oslash &\xrightarrow{\mu} AA\,, \\ BC &\xrightarrow{\sigma} B\oslash\,, \qquad & B\oslash &\xrightarrow{\mu} BB\,, \\ CA &\xrightarrow{\sigma} C\oslash\,, \qquad & C\oslash &\xrightarrow{\mu} CC\,. \end{aligned} \tag{1.22}$$

Let $a,\ b,\ c$ denote the densities of subpopulations $A,\ B$, and C, respectively. The overall density ρ then reads $\rho = a + b + c$. As every lattice site is at most occupied by one individual, the overall density (as well as densities of each subpopulation) varies between 0 and 1, i.e. $0 \leq \rho \leq 1$. With these notations, the rate equations for the reactions (1.22) are given by

$$\begin{aligned} \partial_t a &= a\left[\mu(1-\rho) - \sigma c\right], \\ \partial_t b &= b\left[\mu(1-\rho) - \sigma a\right], \\ \partial_t c &= c\left[\mu(1-\rho) - \sigma b\right]. \end{aligned} \tag{1.23}$$

The phase space of the model is organized by fixed point and invariant manifolds. Equations (1.23) possess four absorbing fixed points. One of these (unstable) is associated with the extinction of all subpopulations, $(a_1^*, b_1^*, c_1^*) = (0, 0, 0)$. The others are heteroclinic points (i.e. saddle points underlying the heteroclinic orbits) and correspond to the survival of only one subpopulation, $(a_2^*, b_2^*, c_2^*) = (1, 0, 0), (a_3^*, b_3^*, c_3^*) = (0, 1, 0)$ and $(a_4^*, b_4^*, c_4^*) = (1, 0, 0)$, shown in blue (dark gray) in Fig. 1.8. In addition, there exists a *reactive* fixed point, indicated in red (gray) in Fig. 1.8, where all three subpopulations coexist (at equal densities), namely $(a^*, b^*, c^*) = \frac{\mu}{3\mu+\sigma}(1, 1, 1)$.

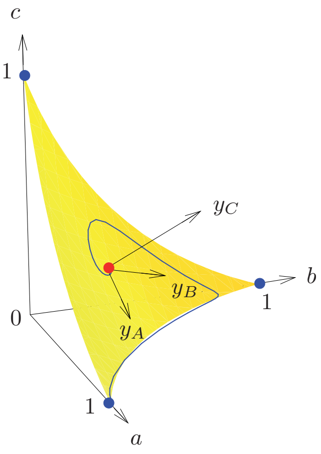

Fig. 1.8. The phase space of the May-Leonard model. It is spanned by the densities a, b, and c of species A, B, and C. On an invariant manifold (yellow), the flows obtained as solutions of the rate equations (1.23) (an example trajectory is shown in blue) initially in the vicinity of the reactive fixed point (red) spiral outwards, approaching the heteroclinic cycle which connects three trivial fixed points (blue). Adapated from Ref. [103].

For a non-vanishing selection rate, $\sigma > 0$, Leonard and May [15] showed that the reactive fixed point is unstable, and the system asymptotically approaches the boundary of the phase space (given by the planes $a = 0$, $b = 0$, and $c = 0$). There, they observed *heteroclinic orbits*: the system oscillates between states where nearly only one subpopulation is present, with rapidly increasing cycle duration. While mathematically fascinating, this behavior was recognized to be unrealistic [15]. For instance, as discussed in section 1.4, the system will, due to finite-size fluctuations, always reach one of the absorbing fixed points in the vicinity of the heteroclinic orbit, and then only one population survives.

The spatially extended May-Leonard model

As discussed above, in the experiments by the Kerr group [7] crucial influence of self-organized patterns on biodiversity has been demonstrated, employing three bacterial strains that display cyclic competition. Here, from theoretical studies, we show that cyclic competition of species can lead to highly non-trivial spatial patterns as well as counterintuitive effects on biodiversity. To this end we analyze the stochastic spatially-extended version of the May-Leonard model [13], as illustrated in Fig. 1.9. We adopt an interacting particle description where individuals of all subpopulations are arranged on a lattice. Let L denote the linear size of a 2-dimensional square lattice (i.e. the number of sites along one edge), such that the total number of sites reads $N = L^2$. In this approach, each site of the grid is either occupied by one individual or empty, meaning that the system has a finite carrying capacity, and the reactions are then only allowed between *nearest neighbors*. In addition, we endow the individuals with a certain form of mobility. Namely, at rate ϵ all individuals can exchange their position with a nearest neighbor. With that same rate ϵ, any individual can also hop on a neighboring empty site. These “microscopic” exchange processes lead to an effective diffusion of the individuals described by a macroscopic diffusion constant $D = \epsilon/2L^2$. For simplicity, we consider equal reaction rates for selection and reproduction, and, without loss of generality,

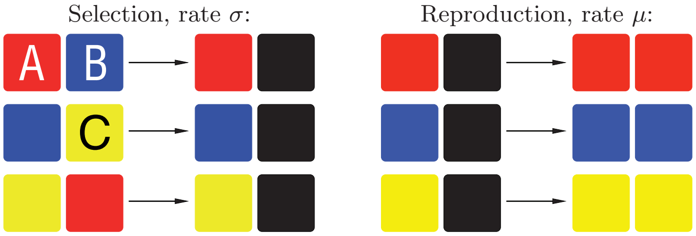

Fig. 1.9. Individuals on neighboring sites may react with each other according to the rules of cyclic dominance (selection; contest competition), or individuals may give birth to new individuals if they happen to be next to an empty site (reproduction; scramble competition).

set the time-unit by fixing $\sigma = \mu \equiv 1$. From the phase portrait of the May-Leonard model it is to be expected that an asymmetry in the parameters yields only qualitative but not quantitative changes in the system's dynamics. The length scale is chosen such that the linear dimension of the lattice is the basic length unit, $L \equiv 1$. With this choice of units the diffusion constant measures the fraction of the entire lattice area explored by an individual in one unit of time.

Typical snapshots of the steady states are shown in Fig. 1.10 [5]. When the mobility of the individuals is low, one finds that all species coexist and self-arrange by forming patterns of moving spirals. Increasing the mobility D, these structures grow in size, and disappear for large enough D. In the absence of spirals, the system adopts a uniform state where only one species is present, while the others have died out. Which species remains is subject to a random process, all species having equal chances to survive in the symmetric model defined above.

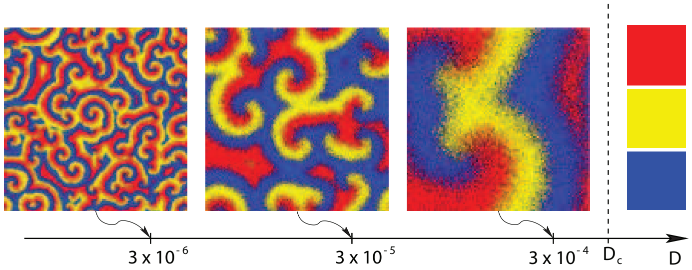

Fig. 1.10. Snapshots obtained from lattice simulations are shown of typical states of the system after long temporal development (i.e. at time $t \sim N$) and for different values of D (each color, blue, yellow and red, represents one of the species and black dots indicate empty spots). Increasing D (from left to right), the spiral structures grow, and outgrow the system size at the critical mobility D_c: then, coexistence of all three species is lost and uniform populations remain (right). Figure adapted from Ref. [13].

The transition from the reactive state containing spirals to the absorbing state with only one subpopulation left is a non-equilibrium phase transition [102]. One way to characterize the transition is to ask how the extinction time T, i.e. the time for the system to reach one of its absorbing states, scales with system size N. In our analysis of the role of stochasticity in section 1.4 we have found the following classification scheme. If $T \sim N$, the stability

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[5] You may also want to have a look at the movies posted on `http://www.theorie.physik.uni-muenchen.de/lsfrey/research/fields/biological_physics/2007_004/`. There is also a Wolfram demonstration project which can be downloaded from the web: `http://demonstrations.wolfram.com/BiodiversityInSpatialRockPaperScissorsGames/`.

of coexistence is marginal. Conversely, longer (shorter) waiting times scaling with higher (lower) powers of N indicate stable (unstable) coexistence. These three scenarios can be distinguished by computing the probability P_{ext} that two species have gone extinct after a waiting time $t \sim N$:

$$P_{\mathrm{ext}} = \mathrm{Prob}\,[\text{only one species left after time } T \sim N] \ . \tag{1.24}$$

In Fig. 1.11, the dependence of P_{ext} on the mobility D is shown for a range of different system sizes, N. Increasing the system size, a sharpened transition emerges at a critical value $D_c = (4.5 \pm 0.5) \times 10^{-4}$. Below D_c, the extinction probability P_{ext} tends to zero as the system size increases, and coexistence is stable in the sense defined in section 1.4. In contrast, above the critical mobility, the extinction probability approaches one for large system size, and coexistence is unstable. As a central result, the agent-based simulations show that there is a critical threshold value for the individuals' diffusion constant, D_c, such that a low mobility, $D < D_c$, guarantees coexistence of all three species, while a high mobility, $D > D_c$, induces extinction of two of them, leaving a uniform state with only one species [13].

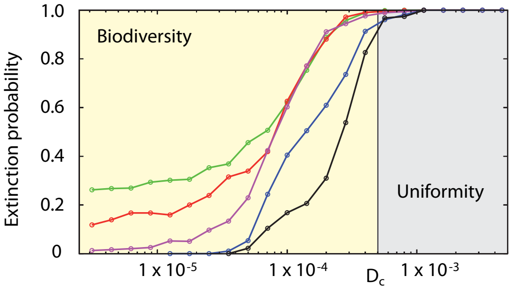

Fig. 1.11. The extinction probability P_{ext} that, starting with randomly distributed individuals on a square lattice, the system has reached an absorbing state after a waiting time $T \sim N$. P_{ext} is shown as function of the mobility D (and $\sigma = \mu = 1$) for different system sizes: $N = 20 \times 20$ (green), $N = 30 \times 30$ (red), $N = 40 \times 40$ (purple), $N = 100 \times 100$ (blue), and $N = 200 \times 200$ (black). As the system size increases, the transition from stable coexistence ($P_{\mathrm{ext}} = 0$) to extinction ($P_{\mathrm{ext}} = 1$) sharpens at a critical mobility $D_c \approx (4.5 \pm 0.5) \times 10^{-4}$. Figure adapted from Ref. [13].

Pattern formation and reaction-diffusion equations

The emergence of spatial patterns, their form, and characteristic features can be understood employing a continuum approach which maps the agent based model to a set of stochastic partial differential equations (SPDE) (often referred to as Langevin equations) [102]:

$$\begin{aligned}\partial_t a(\boldsymbol{r},t) &= D\Delta a(\boldsymbol{r},t) + \mathcal{A}_A[\boldsymbol{a}] + \mathcal{C}_A[\boldsymbol{a}]\xi_A\,,\\ \partial_t b(\boldsymbol{r},t) &= D\Delta b(\boldsymbol{r},t) + \mathcal{A}_B[\boldsymbol{a}] + \mathcal{C}_B[\boldsymbol{a}]\xi_B\,,\\ \partial_t c(\boldsymbol{r},t) &= D\Delta c(\boldsymbol{r},t) + \mathcal{A}_C[\boldsymbol{a}] + \mathcal{C}_C[\boldsymbol{a}]\xi_C\,,\end{aligned} \tag{1.25}$$

where $\boldsymbol{a} = (a, b, c)$ and Δ denotes the Laplacian operator. The first term describes the diffusive motion of each of the individual agents with a macroscopic diffusion constant D. The reaction terms $\mathcal{A}_i[\boldsymbol{a}]$ derived in a Kramers-Moyal expansion [103] are identical - as it must - to the corresponding nonlinear drift term in the diffusion-reaction equation, $\boldsymbol{F}[\boldsymbol{a}] = \mathcal{A}[\boldsymbol{a}]$, which describe coevolution of different species in the absence of spatial degrees of freedom and with a large number of interacting individuals. Noise arises because processes are stochastic *and* population size N is finite. While noise resulting from the competition processes (reactions) scales as $1/\sqrt{N}$, noise originating from hopping (diffusion) only scales as $1/N$. In summary, this gives (multiplicative) Gaussian white noise $\xi_i(\boldsymbol{r},t)$ characterized by the correlation matrix

$$\langle \xi_i(\boldsymbol{r},t)\xi_j(\boldsymbol{r}',t')\rangle = \delta_{ij}\delta(\boldsymbol{r}-\boldsymbol{r}')\delta(t-t') \tag{1.26}$$

and amplitudes depending on the system's configuration:

$$\begin{aligned}\mathcal{C}_A &= \frac{1}{\sqrt{N}}\sqrt{a(\boldsymbol{r},t)\big[\mu(1-\rho(\boldsymbol{r},t)) + \sigma c(\boldsymbol{r},t)\big]}\,,\\ \mathcal{C}_B &= \frac{1}{\sqrt{N}}\sqrt{b(\boldsymbol{r},t)\big[\mu(1-\rho(\boldsymbol{r},t)) + \sigma a(\boldsymbol{r},t)\big]}\,,\\ \mathcal{C}_C &= \frac{1}{\sqrt{N}}\sqrt{c(\boldsymbol{r},t)\big[\mu(1-\rho(\boldsymbol{r},t)) + \sigma b(\boldsymbol{r},t)\big]}\,.\end{aligned} \tag{1.27}$$

The strength of such a continuum description is that it is *generic*, i.e. the form of the equations does not depend on, for example, the precise form of the lattice or the shape and size of individuals' neighborhood as long as it is local. It is the interplay between diffusion, mixing the system locally on a certain length scale, and the reaction kinetics, whose features are encoded by the phase portrait of the well-mixed system, which gives rise to the observed complex dynamics. The stochastic reaction-diffusion equations can be solved numerically. Fig. 1.12 shows the outcome of such a simulation starting from a inhomogeneous initial condition (and using periodic boundary conditions) [13], and compares the results obtained to agent based simulations and deterministic diffusion-reaction equations. The comparison of those snapshots reveals a remarkable coincidence of the patterns obtained from agent based simulations and the continuum approach. As shown in Refs. [102, 103] these similarities in patterns are actually fully quantitative and the spatio-temporal correlations functions for the population densities are almost identical.

The approach of mapping the interacting particle system to the SPDE, (1.26), yields extremely insightful results, as it enables the application of bifurcation theory [104]. Determining the bifurcations that the nonlinear functions

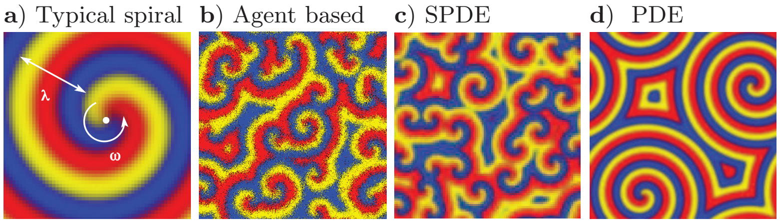

Fig. 1.12. *Spiral patterns.* **a**) Schematic drawing of a spiral with wavelength λ. It rotates around the origin at a frequency ω. **b**) Agent-based simulations for $D < D_c$, when all three species coexist, show entangled, rotating spirals. **c**) Stochastic partial differential equations show similar patterns as agent-based simulations. **d**) Spiral pattern emerging from the dynamics of the deterministic diffusion reaction equation starting from a spatially inhomogeneous initial state. Parameters are $\sigma = \mu = 1$ and $D = 1 \times 10^{-5}$. Figure adapted from Ref. [13].

$\mathcal{A}_i[\boldsymbol{a}]$ exhibit defines universality classes for the emerging patterns. Namely, in the vicinity of bifurcations, the behavior is described by generic normal forms, characterizing each bifurcation type. The resulting universality classes have already been widely studied in the physical and mathematical community, mostly by investigating deterministic partial differential equations, see e.g. Refs. [105, 106, 107] for reviews as well as references therein. Although specific models for competing populations will not yield SPDE that are identical to the general equations studied there, their bifurcation behavior may coincide with an equation that has already been investigated. Consequently, the specific SPDE falls into that universality class, and generic results may be transferred. In the present case of a spatially extended May-Leonard model, projecting the deterministic version of the diffusion-reaction equation, Eq.(1.26), onto the *reactive manifold* M one obtains [13, 102, 103]:

$$\partial_t z = D\nabla^2 z + (c_1 - i\omega)z - c_2(1 + ic_3)|z|^2 z \,. \tag{1.28}$$

Here, we recognize the celebrated *complex Ginzburg-Landau equation* (CGLE), whose properties have been extensively studied in the past [105, 106]. In particular, it is known that in two dimensions the latter gives rise to a broad range of coherent structures, including spiral waves whose velocity, wavelength and frequency can be computed analytically. Remarkably, the results for the spirals' velocities, wavelengths, and frequencies agrees extremely well with those obtained from the agent based simulations [13, 102, 103].

Thus the formulation of the spatial game theoretical model in terms of stochastic diffusion-reaction equations enabled us to reach a comprehensive understanding of the resulting out-of-equilibrium and nonlinear phenomena. Employing a mapping of the diffusion-reaction equation onto the reactive manifold of the nonlinear dynamics it turned out that the dynamics of the coexistence regime is in the same "universality class" as the complex Ginzburg-

Landau equation (CGLE). This fact reveals the generality of the phenomena discussed in this chapter. In particular, the emergence of an entanglement of spiral waves in the coexistence state, the dependence of spirals' size on the diffusion rate, and the existence of a critical value of the diffusion above which coexistence is lost are robust phenomena. This means that they do not depend on the details of the underlying spatial structure: While, for specificity, we have (mostly) considered square lattices, other two-dimensional topologies (e.g. hexagonal or other lattices) will lead to the same phenomena, too. Also the details of the cyclic competition have no qualitative influence, as long as the underlying rate equations exhibit an unstable coexistence fixed point and can be recast in the universality class of the Hopf bifurcations. It remains to be explored what kind of mathematical structure corresponds to a broader range of game-theoretical problems.

In this chapter, we have mainly focused on the situation where the exchange rate between individuals is sufficiently high, which leads to the emergence of regular spirals in two dimensions. However, when the exchange rate is low (or vanishes), we have seen that stochasticity strongly affects the structure of the ensuing spatial patterns. In this case, the (continuum) description in terms of SPDE breaks down. In this situation, the quantitative analysis of the spatio-temporal properties of interacting particle systems requires the development of other analytical methods, e.g. relying on field theoretic techniques [96]. Fruitful insights into this regime have already been gained by pair approximations or larger-cluster approximations [108, 109, 110, 89]. The authors of these studies investigated a set of coupled nonlinear differential equations for the time evolution of the probability to find a cluster of certain size in a particular state. While such an approximation improves when large clusters are considered, unfortunately the effort for solving their coupled equations of motion also drastically increases with the size of the clusters. In addition, the use of those cluster mean-field approaches becomes problematic in the proximity of phase transitions (near an extinction threshold) where the correlation length diverges. Investigations along these lines represent a major future challenge in the multidisciplinary field of complexity science.

The cyclic rock-paper-scissor model as discussed in this section can be generalized in manifold ways. The model with asymmetric rates turns out to be in the same universality class as the one with symmetric rates [111]. Qualitative changes in the dynamics, however, emerge when the interaction network between the species is changed. For example, consider a system where each agent can interact with its neighbors according to the following scheme:

$$\begin{array}{lll}
AB \xrightarrow{1} AA & AB \xrightarrow{\sigma} A\oslash & A\oslash \xrightarrow{\mu} AA \\
BC \xrightarrow{1} BB & BC \xrightarrow{\sigma} B\oslash & B\oslash \xrightarrow{\mu} BB \\
CA \xrightarrow{1} CC \quad (1.29) & CA \xrightarrow{\sigma} C\oslash \quad (1.30) & C\oslash \xrightarrow{\mu} CC \quad (1.31)
\end{array}$$

Reactions (1.29) describe *direct dominance* in a Moran-like manner, where an individual of one species is consumed by another from a more predominant species, and the latter immediate reproduces. Cyclic dominance appears as A consumes B and reproduces, while B preys on C and C feeds on A in turn. Reactions (1.30) encode some kind of *toxicity*, where one species kills another, leaving an empty site $\oslash$. These reactions occur at a rate σ, and are decoupled from *reproduction*, Eqs. (1.31), which happens at a rate μ. Note that reactions (1.29) and (1.31) describe two different mechanisms of reproduction, both of which are important for ecological systems: In (1.29), an individual reproduces when having consumed a prey, due to thereby increased fitness. In contrast, in reactions (1.31) reproduction depends solely on the availability of empty space. As can be inferred from Fig.1.13 the spatio-temporal patterns sensitively depend on the strength σ of the *toxicity* effect. Actually, as can be shown analytically [112], there is an Eckhaus instability, i.e., a convective instability: a localized perturbation grows but travels away. The instabilities result in the blurring seen in Fig. 1.13.

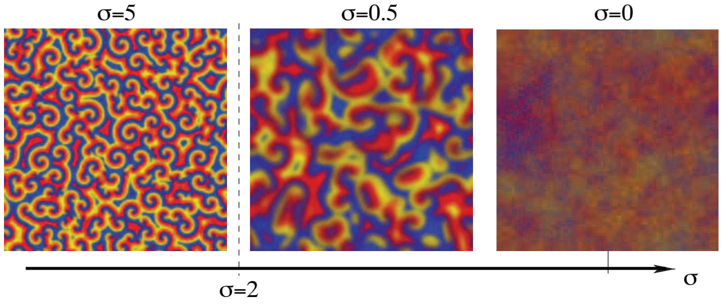

Fig. 1.13. Snapshots of the biodiverse state for $D = 1 \times 10^{-5}$. (a), For large rates σ, entangled and stable spiral waves form. (b), A convective (Eckhaus) instability occurs at $\sigma_E \approx 2$; below this value, the spiral patterns blur. (c), At the bifurcation point $\sigma = 0$, only very weak spatial modulations emerge; we have amplified them by a factor two for better visibility. The snapshots stem from numerical solution of an appropraite SPDE with initially homogeneous densities $a = b = c = 1/4$.

It remains to be explored how more complex interaction networks with an increasing number of species and with different types of competition affect the spatio-temporal pattern formation process. Research along these lines is summarized in a recent review [89].

1.6 Conclusions and Outlook

In this contribution we have given an introduction into evolutionary game theory. The perspective we have taken was that starting from agent-based models the dynamics may be formulated in terms of a hierarchy of theoretical models. First, if the population size is large and the population is well-mixed, a set of ordinary differential equations can be employed to study the system's dynamics and ensuing stationary states. Game theoretical concepts of "equilibria" then map to "attractors" of the nonlinear dynamics. Setting up the appropriate dynamic equations is a non-trivial matter if one is aiming at a realistic description of a biological system. For instance, as nicely illustrated by a recent study on yeast [8], a linear replicator equation might not be sufficient to describe the frequency-dependence of the fitness landscape. We suppose that this is rather the rule than the exception for biological systems such as microbial populations. Second, for well-mixed but finite populations, one has to account for stochastic fluctuations. Then there are two central questions: (i) What is the probability of a certain species to go extinct or become fixated in a population? (ii) How long does this process take? These questions have to be answered by employing concepts from the theory of stochastic processes. Since most systems have absorbing states, we have found it useful to classify the stability of a given dynamic system according to the scaling of the expected extinction time with population size. Third and finally, taking into account finite mobility of individuals in an explicit spatial model a description in terms of stochastic partial differential equations becomes necessary. These Langevin equations describe the interplay between reactions, diffusion and noise which give rise to a plethora of new phenomena. In particular, spatio-temporal patterns or, more generally, spatio-temporal correlations, may emerge which can dramatically change the ecological and evolutionary stability of a population. For non-transitive dynamics, like the rock-scissors-paper game played by some microbes [7], there is a *mobility threshold* which demarcates regimes of maintenance and loss of biodiversity [13]. Since, for the rock-scissors-paper game, the nature of the patterns and the transition was encoded in the flow of the nonlinear dynamics on the reactive manifold, one might hope that a generalization of the outlined approach might be helpful in classifying a broader range of game-theoretical problems and identify some "universality classes".

What are the ideal experimental model systems for future studies? We think that microbial populations will play a major role since interactions between different strains can be manipulated in a multitude of ways. In addition, experimental tools like microfluidics and various optical methods allow for easy manipulation and observation of these systems, from the level of an individual up to the level of a whole population. Bacterial communities represent complex and dynamic ecological systems. They appear in the form of free-floating bacteria as well as biofilms in nearly all parts of our environment, and are highly relevant for human health and disease [26]. Spatial patterns arise from heterogeneities of the underlying "landscape" or self-organized by the bacterial interactions, and play an important role in maintaining species diversity [6]. Interactions comprise, amongst others, competition for resources and cooperation by sharing of extracellular polymeric substances. Another aspect of interactions is chemical warfare. As we have discussed, some bacterial strains produce toxins such as colicin, which acts as a poison to sensitive strains, while other strains are resistant [7]. Stable coexistence of these different strains arises when they can spatially segregate, resulting in self-organizing patterns. There is a virtually inexhaustible complexity in the structure and dynamics of microbial populations. The recently proposed term "socio-microbiology" [113] expresses this notion in a most vivid form. Investigating the dynamics of those complex microbial populations is a challenging interdisciplinary endeavor, which requires the combination of approaches from molecular microbiology, experimental biophysical methods and theoretical modeling. The overall goal would be to explore how collective behavior emerges and is maintained or destroyed in finite populations under the action of various kinds of molecular interactions between individual cells. Both communities, biology as well as physics, will benefit from this line of research.

Stochastic interacting particle systems are a fruitful testing ground for understanding generic principles in non-equilibrium physics. Here biological systems have been a wonderful source of inspiration for the formulation of new models. For example, MacDonald [114] looking for a mathematical description for mRNA translation into proteins managed by ribosomes, which bind to the mRNA strand and step forward codon by codon, formulated a non-equilibrium one-dimensional transport model, nowadays known as the totally asymmetric simple exclusion process. This model has led to significant advances in our understanding of phase transitions and the nature of stationary states in non-equilibrium systems [115, 116]. Searching for simplified models of epidemic spreading without immunization Harris [117] introduced the contact process. In this model infectious individuals can either heal themselves or infect their neighbors. As a function of the infection and recovery rate it displays a phase transition from an active to an absorbing state, i.e. the epidemic disease may either spread over the whole population or vanish after some time. The broader class of absorbing-state transitions has recently been reviewed [118]. Another well studied model is the voter model where each individual has one of two opinions and may change it by imitation of a randomly chosen neighbor. This process mimics in a naive way opinion making [119]. Actually, it was first considered by Clifford and Sudbury [120] as a model for the competition of species and only later named voter model by Holley and Liggett [121]. It has been shown rigorously that on a regular lattice there is a stationary state where two "opinions" coexist in systems with spatial dimensions where the random walk is not recurrent [122, 119]. A question of particular interest is how opinions or strategies may spread in a population. In this context it is important to understand the coarsening dynamics of interacting agents. For a one-dimensional version of the rock-paper-scissors game Frachebourg and collaborators [123, 124] have found that starting from some random distribution, the species organize into domains that undergo (power law) coarsening until finally one species takes over the whole lattice. Generalizing this model to account for species mobility and multiple occupation of each site several distinct pathways to extinction emerge, ranging from annihilating propagating waves to intermittent dynamics arising from heteroclinic orbits [125]. Including mutation the coarsening process is counteracted and by an interesting interplay between equilibrium and non-equilibrium processes a reactive stationary state emerges [126]. Yet another endeavor in non-equilibrium dynamics is to find global variables that provide a characterization of the system. Entropy production has been proposed as a useful observable [127,128], and different principles governing its behavior have been suggested [129, 130], though problems arise from different employed definitions of entropy and approaches to nonequilibrium dynamics [128,131,132]. Recent investigations of the rock-scissors-paper model with mutations show that entropy production can indeed characterize the behavior of population dynamics models. At a critical point the dynamics exhibits a transition from large, limit-cycle like oscillations to small, erratic oscillations. It is found that the entropy production peaks very close to this critical point and tends to zero upon deviating from it [133]. One may hope that, in a similar manner, entropy production may yield valuable information about other models in evolutionary game theory.

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