



Universität zu Köln

Mathematisch-Naturwissenschaftliche Fakultät

Masterarbeit
zur Erlangung des akademischen Grades
Master of Education

**Population dynamics of cooperation and cheating in bacteria: A
game-theoretical approach in discrete time**

Lehramt an Gymnasien und Gesamtschulen
Unterrichtsfach Physik

Erstgutachter*in: Prof. Dr. Joachim Krug

vorgelegt von:

Lukas Laroche (Matrikelnummer: 7349225)

S-Mail: llaroche@smail.uni-koeln.de

Contents

1	Introduction	2
2	Game Theory - A general introduction	4
3	Evolutionary Game Theory	6
3.1	History of Evolutionary Game Theory	6
3.2	Fundamentals and mathematical description	7
3.2.1	Fundamentals	7
3.2.2	Mathematical description - Game theory in continuous time	9
3.3	Game theory in discrete time	13
3.3.1	Fixed points	14
4	Evolutionary game theory and antibiotic resistance	17
4.1	Antibiotic resistance	17
4.1.1	Antibiotic classes and their mechanism of action	18
4.1.2	Resistance mechanisms	18
4.2	Bacterial cheating	20
5	A game theory model in discrete time based on Yurtsev et al.	25
5.1	Game dynamic in the Yurtsev-model	29
5.2	Chaotic behaviour of the Yurtsev-dynamic	31
5.2.1	Chaos in dynamical systems	31
5.2.2	Chaos in the Yurtsev-dynamic	34
6	Discussion	37
6.1	Summary of main findings	37
6.2	The role of chaos in biological systems	37
6.3	Clinical implications	38
6.4	Limitations of the thesis	39

Chapter 1

Introduction

The World Health Organization (WHO) identifies antibiotic resistance as one of the ten most significant challenges to global health [34]. According to estimates, 1.14 million deaths worldwide in 2021 were attributable to bacterial antibiotic resistance [29, 34]. However, the problem is not limited to resistant bacterial strains. Research has demonstrated that susceptible strains are able to withstand concentrations that are many times higher than the minimum inhibitory concentration (MIC) when cultivated together with resistant cells [57, 10]. This phenomenon underscores that resistance mechanisms are highly cooperative.

A notable illustration of such a cooperative behaviour is the β -lactam resistance in *Escherichia coli*, which has been attributed to the production of the enzyme β -lactamase as a *public good*, identified by Yurtsev et al. [57, 8]. The population dynamic between *cooperators*, who produce the public good, and *cheaters*, who use it, can be described in broad terms by the *Evolutionary Game Theory*.

This thesis examines the population dynamics of resistant and sensitive bacteria, as described by Yurtsev et al. [57], employing game theory in discrete time. By analyzing this model, the thesis aims to demonstrate how varying the antibiotic concentrations and costs of resistance shift the population dynamics from stable coexistence (*snowdrift game*) to unpredictable, chaotic regimes.

A key analytical finding of this work is the demonstration of unstable coexistence and chaos within a two-strategy discrete-time game. Standard evolutionary game theory in discrete time relies on constant payoff matrices. These matrices inherently preclude such dynamics for two interacting phenotypes. However, this thesis demonstrates that introducing highly non-linear, frequency-dependent fitness functions chaotic regimes.

The thesis is structured as follows: The second chapter gives a general introduction into Game Theory, followed by a mathematical introduction to evolutionary game theory in Chapter Three. The theoretical framework of evolutionary game theory is connected with antibiotic resistance in Chapter Four. Chapter Five gives

an introduction into the Yurtsev et al.-model and its connection to the game theory in discrete time. The thesis concludes with a discussion of the primary results in the sixth chapter.

Chapter 2

Game Theory - A general introduction

During the 1920s, the mathematician John von Neumann worked on a mathematical framework to describe and analyze games [30, 24]. His work forms the basis for a breakthrough theory in economics, which he and the economist Oskar Morgenstern developed less than twenty years later: The Game Theory [33, 24, 43]. The objective of their study was to examine the behaviour and strategy of individuals in competitive situations [43], such as economic decisions [33]. Accordingly, an analysis of individual behaviour is essential for finding answers to fundamental questions in economics and understanding economic mechanisms [31]. This chapter does not offer a mathematical introduction to game theory. This will be addressed in subsequent sections of the thesis, as it aligns more closely with the subject matter.

The fundamental assumption of the theory is a competitive scenario among individuals, each of whom employs a strategy and attains a payoff from the game [8, 43, 31, 30, 33, 24, 38, 21]. A game is simply defined and described by its rules [32, 24]. Each player of the game possesses a set of strategies, from which they can select [38]. A strategy is defined as the fundamental principles that guide a player's decisions [32]. In other words, it is a plan for every conceivable condition that guides the player's action [38, 43].

Depending on the selected strategy, each player receives a payoff from the game [30, 33, 38, 21, 8, 43], which is described by a payoff function [38]. Evidently, this can be a monetary benefit in economic contexts. In general, however, it is a benefit to the individual who wins [31]. A fundamental question in Game Theory concerns the strategy an individual should use to maximize their own payoff [30, 33, 24, 38, 21, 31]. According to von Neumann and Morgenstern, an individual who strives for maximum payoff is acting *rationally* [31, 21].

However, the payoff does not solely depend on the player's own strategy, but

also on that of their opponents [30, 33, 38, 21, 8, 43], since each player pursues a maximum payoff, which results in a conflict [31, 21]. A simple example of such a game is rock-paper-scissors [8, 43]. Each player has the ability to choose between three strategies. Each of them wins against another strategy, while losing to the third. To illustrate, rock is the winner against scissors, but loses to paper. Therefore, the own strategy alone does not determine the outcome of the game.

However, the theory has long since gone beyond economics and found its way into other scientific disciplines. One example is the evolutionary game theory.

Chapter 3

Evolutionary Game Theory

3.1 History of Evolutionary Game Theory

The initial ideas of applying game theory in biology emerged in the late 1950s [26]. For instance, in 1958, Fisher had the idea of using game theory to describe predator-prey interactions [26, 13]. However, it was the research of Hamilton, Trivers and others that had a significantly greater influence in the field [26, 33]. For example, Hamilton used game theory in a 1967 paper to describe sex allocation [19, 26, 43]. A primary outcome of his research was the demonstration that a 1:1 ratio between males and females does not necessarily represent the optimal scenario for an individual, based on the number of offspring. Especially when mating is limited to a local area, and inbreeding is prevalent, another ratio may prove more advantageous for an individual [19, 43]. Four years later, Trivers employed game theory to analyze reciprocal altruism during evolution [49]. He used the example of cleaning fish and warning cries by birds, and demonstrates that altruism can be a successful strategy during evolution.

Nonetheless, John Maynard Smith and George Price are widely regarded as the pioneers of evolutionary game theory, because of a paper published in 1973 in *Nature* [33, 26], which led to a substantially higher interest in this field [26]. They considered why conflicts among animals do not lead to serious injuries [44, 26]. Evidently, the population obtains an advantage, but Smith and Price also thought about an individual advantage [44, 26]. To give evidence of this, they considered different models: In the initial model, there is a possibility of injury to animals from one another, in the second one, such injury is impossible [44]. The authors modeled conflicts between individuals with different moves. For each move, the individuals can select whether to inflict harm on their opponent, refrain from doing so, or retreat. The authors determined probabilities for which of these choices would be played, depending on what had been played previously. The rules

which determine the possibilities can be seen as strategies [44]. The individuals also yield a payoff from the game, which can be regarded as reproductive success. However, the costs associated with injury or energy loss during the conflict are also taken into account [44]. The findings of the modeling demonstrate that it is preferable for an individual to refrain from inflicting harm on their opponent or to retreat [44]. In this context, Smith and Price introduced the evolutionary stable strategy (ESS): This strategy is defined in the following manner: No mutant can invade a population where most members adopt this strategy [44, 26, 48, 43, 8]. This strategy is a fundamental concept in evolutionary game theory.

Since then, the number of publications in this field has increased significantly and game theory is being applied in various areas of biology, especially where the reproductive success is frequency-dependent [26]. Therefore, the following section will examine the fundamentals and mathematical description of game theory using an example.

3.2 Fundamentals and mathematical description

An exemplary illustration of the implementation of game theory can be observed in the interactions between bacteria [8, 57]. In the following sections, this example introduces the (mathematical) fundamentals of game theory.

3.2.1 Fundamentals

A simple illustration of this context is the interaction of two phenotypes, A and B (fig. 3.1) [33]: The phenotype A is able to move, while B is not. In this particular instance, the ability to move is advantageous, thereby enhancing fitness. When the fitness is constant, the population is expected to converge on all A . However, it is important to note that mobility comes with costs. However, in cases where population density is high, the ability to move becomes a disadvantage: The individuals will be stuck in the traffic (fig. 3.1). Nevertheless, they have to pay the costs for the mobility. The fitness of phenotype A declines with increasing individual number. Therefore, the fitness of phenotype A is frequency-dependent.

In the context of evolutionary games, the fitness corresponds to payoff [33, 8]. Successful individuals have a higher reproductive success. As demonstrated in the example, the result of the game provides information about the evolution of the population [8, 43]. A good strategy in the game is more successful since offspring employ the same strategy as their parents [8, 48]. Of course, in evolutionary context, the concepts of self-interest and rationality are not sensible. Consequently,

Constant selection:



Frequency-dependent selection:

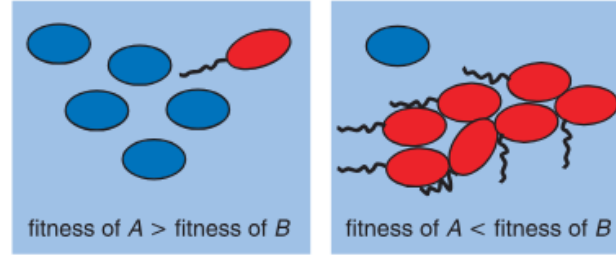


Figure 3.1 Constant vs. frequency dependent selection. Individual A is able to move, while B is not. Constant fitness means, that the fitness is independent of the fraction of a phenotype in the population. In the frequency dependent selection, the fitness depends on the fraction. When only a few individuals are able to move, mobility goes hand in hand with high fitness. When, on the other hand, many individuals are able to move, this becomes a disadvantage. Adapted from [33].

the self-interest is replaced by the concept of fitness, and the rationality is superseded by population dynamics [42].

Considering the population dynamic (Fig. 3.2), five different kinds of games can be distinguished [33, 8].

Cases one and two are the least complex. The population will converge to either all A or all B if the fitness of one phenotype is consistently higher than that of the other. The phenotype with higher fitness is referred to as *dominance*. Such dominant phenotypes represent Evolutionary stable strategies [33, 8].

The third kind of game is *bistability*. The coexistence of both phenotypes at a particular point is possible, but it is not stable. Nonetheless, a minor disruption can result in the extinction of either the A or the B population [33, 8].

In contrast, when fitness is frequency dependent, the population will attain a state wherein both phenotypes or strategies coexist stably. This type of game is referred to as *coexistence*. The point of stable coexistence is termed a *fixed point* [33] or an *equilibrium* [8]. The population will always revert to this point when disturbed, since no strategy can achieve dominance. This dynamic is also referred to as *snowdrift game* [33, 8]. The analogy comes from two drivers who are stuck behind a snowdrift. Each of them has the option to stay in the car or get out and clean the path. If both drivers stay in the car, they will remain stuck behind the

Frequency-dependent selection dynamics
between two strategies, A and B

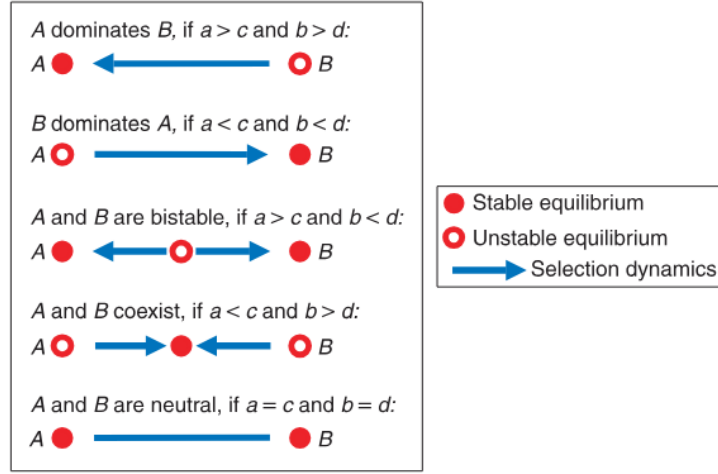


Figure 3.2 Five different outcomes for games between A and B are possible. The outcome depends on the fitness: a is the payoff individual A yields when playing against A. b is the payoff A yields when playing against B. B yields the payoff c when playing against A and d when playing against B. Adapted from [33].

snowdrift. If both parties leave the vehicle, both will pay the costs for cleaning the path. It can thus be concluded that the best strategy is to do the opposite of what the other driver is doing.

In the last possible instance, the fitness of both phenotypes is always equal, i.e. every point is a fixed point.

The subsequent section will discuss the mathematical description of evolutionary games.

3.2.2 Mathematical description - Game theory in continuous time

The example above is considered again. In the following, x_A denotes the fraction of phenotype A in the population, also referred to as *frequency* [33]. The frequency of phenotype B is denoted by x_B . Therefore, the vector $\vec{x} = (x_A, x_B)$ describes the composition of the population, while $f_A(\vec{x})$ represents the fitness of A and $f_B(\vec{x})$ that of B [33]. The number of individuals varies from one generation to another, depending on their fitness. The variation in the number of individuals, denoted by N , is expressed as:

$$\dot{N}_A = N_A \cdot f_A(\vec{x}) \quad \dot{N}_B = N_B \cdot f_B(\vec{x}). \quad (3.1)$$

The frequency of A and B in the population is

$$x_A = \frac{N_A}{N_A + N_B} \quad x_B = \frac{N_B}{N_A + N_B}. \quad (3.2)$$

The differentiation of equation (3.2) describes how the frequency changes over time.

The condition $x_A + x_B = 1$ holds at all times [33]. Therefore, the equation can be simplified by defining $x_A = x$ and $x_B = 1 - x$. The expressions can be written in dependence on the *average fitness* ϕ of the population:

$$\dot{x}_A = x_A \cdot [f_A(\vec{x}) - \phi] \quad \dot{x}_B = x_B \cdot [f_B(\vec{x}) - \phi] \quad (3.3)$$

with

$$\phi = x_A \cdot f_A(\vec{x}) + x_B \cdot f_B(\vec{x}). \quad (3.4)$$

Expressions (3.3) are known as *replicator equations*, which are fundamental equations in the field of evolutionary game theory [33]. These equations describe the dynamics of the population. The *replicator equation* demonstrates: The frequency of A decreases when the fitness of A is less than the average fitness, and increases when the fitness of A is higher than the average fitness. For the frequency of B , the analogous case applies.

However, the equation $x_A + x_B = 1$ results in a simplification of equation (3.3):

$$\dot{x} = x(1 - x)[f_A(x) - f_B(x)] \quad (3.5)$$

which describes the dynamics of the population in a single function. This indicates that the development of x is contingent on the difference between $f_A(x)$ and $f_B(x)$.

Fixed points and equilibria

It is of greater interest to consider the behaviour of x_A when $f_A(x) = f_B(x)$, than to examine the increase or decrease of x_A when $f_A(x) > f_B(x)$ or $f_A(x) < f_B(x)$. As previously discussed, this leads to the *fixed points* or *equilibria* at which the frequency of A and B is constant (Fig. 3.3) [33, 8], i.e. $\dot{x} = 0$.

For the replicator equation, that's trivially true for $x = 0$ and $x = 1$ and also for every $x \in (0, 1)$, leading to $f_A(x) = f_B(x)$. The last case is termed *inner equilibrium* or *fixed point* [33, 8]. Furthermore, it is necessary to distinguish between stable and unstable fixed points, that is, between coexistence and bistability [33, 8]. The right-hand side of (3.5) is to be defined as a function $f(x)$, i.e. $f(x) = \dot{x}$. A fixed point is stable under the condition

$$f'(x^*) < 0$$

Frequency-dependent selection of two strategies, A and B

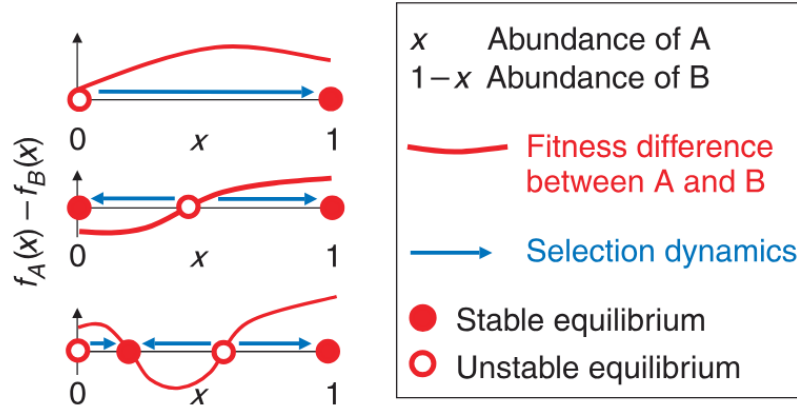


Figure 3.3 Plot of the frequency x from A against the fitness difference between the phenotypes. The figure shows different types of equilibria and the behaviour of the population around them. For equal fitness $f_A(x) = f_B(x)$ equilibria appear, which can be stable or unstable. Adapted from [33].

with x^* the fixed point and $f'(x^*)$ the derivative of $f(x^*)$. A fixed point is unstable if

$$f'(x^*) > 0.$$

In the following sections, a more detailed discussion of the dynamics of the equilibria will be presented.

Payoff matrix

The replicator equation demonstrates the dynamics of the population. However, it is necessary to establish a more precise definition of fitness to make assumptions regarding the dynamics. The fitness of the individuals is contingent on their own phenotype [8, 33]. However, the outcome may also be contingent on the phenotype they are playing against, as well as the payoff of a player is determined by their own strategy and that of their opponent [30, 33, 38, 21, 8, 43]. In order to ascertain the fitness of an individual against each phenotype, a payoff matrix is a straightforward method [8, 33, 44, 43]:

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

In this context, a denotes the fitness of A when playing against A , b denotes the fitness of A when playing against B and so on. With the payoff or fitness matrix, it is possible to find an expression for the fitness of A and B [33]:

$$f_A = a \cdot x + b \cdot (1 - x) \quad f_B = c \cdot x + d \cdot (1 - x). \quad (3.6)$$

Assuming a well-mixed population with random encounters, the frequency x is the probability of meeting individual A and $(1 - x)$ is the probability of meeting B [33]. Inserting these fitness functions into the replicator equation (3.3) leads to [33]:

$$\dot{x} = x \cdot (1 - x)[(a - b - c + d) \cdot x + b - d] \quad (3.7)$$

As mentioned before, the equation $f_A(x) = f_B(x)$ results in a fixed point. It follows from (3.6), that

$$x^* = \frac{d - b}{a - b - c + d} \quad (3.8)$$

is a fixed point. Biologically sensible is only the case where $x^* \in [0, 1]$. Substituting u for $(d - b)$ and v for $(a - c)$ results in

$$x^* = \frac{u}{v + u}.$$

For the condition $x^* \in [0, 1]$ to be valid, u and v must have the same sign. That is, a fixed point just exists if

$$a > c \wedge d > b \quad (3.9)$$

or

$$a < c \wedge d < b. \quad (3.10)$$

Depending on the components of the fitness matrix, the five population dynamics described previously (Fig. 3.2) can be mathematically determined [33, 8]:

1. If $a \geq c$ and $b \geq d$, individual A always has the higher or same fitness and will dominate B . This requires one strict inequality for one of the greater-than-or-equal-to conditions. This results in $x = 1$ and phenotype B dies out. A is then the ESS, and B is not able to invade the population. There is no inner fixed point, because neither (3.9) nor (3.10) holds.
2. On the other hand, B can also dominate A . In this case $a \leq c$ and $b \leq d$, again with one strict inequality. Then phenotype B is the ESS and analogue to case 1., there is no inner fixed point. [8, 3]
3. If $a > c$ and $b < d$, A and B are bistable, which implies that $x = 0$ and $x = 1$ are stable. But there is also an unstable inner equilibrium for $x \in (0, 1)$, defined by (3.8) [33, 8]. To which side the system converges when it is deviated from the

unstable equilibrium depends on the initial fraction. $x_0 < x^*$ results in $x = 0$, so all B . But if $x_0 > x^*$, the population converges to all A , i.e. $x = 1$.

4. A and B can also stably coexist (snowdrift game), when $a < c$ and $b > d$. In this case equation (3.8) is a stable equilibrium.

5. In the fifth scenario, the composition of the population does not change when $a = c$ and $b = d$. That is, every fraction x is a fixed point [33].

The mathematical description so far refers to game theory in continuous time. However, as will be demonstrated subsequently, serial dilution experiments also play an important role in biology. This implies that, in addition to a description in continuous time, a description in discrete time is necessary.

3.3 Game theory in discrete time

The description of the game theory in discrete time is analogous to the game theory in continuous time. However, while *Malthusian fitness* is employed in the context of continuous time, *Wrightian fitness* is employed in discrete time [56]. The fitness matrix is given by

$$\begin{array}{cc} & \begin{array}{cc} A & B \end{array} \\ \begin{array}{c} A \\ B \end{array} & \begin{pmatrix} \alpha & \beta \\ \gamma & \delta \end{pmatrix} \end{array}$$

with x the fraction of the phenotype A . The number of individuals with the phenotype A after one time step is given by

$$N_A(t+1) = N_A(t) \cdot [\alpha \cdot x(t) + \beta \cdot (1 - x(t))]. \quad (3.11)$$

The equation can also be written depending on the frequency

$$x(t+1) = \frac{(x(t) \cdot \alpha + (1 - x(t)) \cdot \beta) \cdot N_A(t)}{((x(t) \cdot \alpha + (1 - x(t)) \cdot \beta) \cdot N_A(t) + (x(t) \cdot \gamma + (1 - x(t)) \cdot \delta) \cdot N_B(t))} \quad (3.12)$$

with $N_B(t)$ the number of individuals with phenotype B at time t , analogous to the number of individuals with phenotype A . This results in the replicator equation in discrete time:

$$x(t+1) = \frac{x(t) \cdot (x(t) \cdot \alpha + (1 - x(t)) \cdot \beta)}{x(t) \cdot (x(t) \cdot \alpha + (1 - x(t)) \cdot \beta) + (1 - x(t)) \cdot (x(t) \cdot \gamma + (1 - x(t)) \cdot \delta)} \quad (3.13)$$

In order to gain a more precise understanding of the population dynamic, it is necessary to examine the fixed points in greater detail, with particular reference to the inner fixed point.

3.3.1 Fixed points

The fixed points or equilibria fractions can be calculated by solving the equation $x(t+1) = x(t)$, because at the fixed point, the resistant fraction does not change from one time step to another. This results in three fixed points, analogous to the continuous time:

$$x_1^* = 0 \quad (3.14)$$

$$x_2^* = 1 \quad (3.15)$$

$$x_3^* = \frac{\delta - \beta}{\delta - \beta + \alpha - \gamma}. \quad (3.16)$$

Even in discrete time, the right-hand side of (3.13) is defined as a function $f(x)$, i.e. $f(x) = x(t+1)$. The stability of the fixed points can again be analyzed by examining the derivative of the function $f(x)$ at the fixed point x^* as shown in [16]:

$$|f'(x^*)| < 1 \Rightarrow \text{stable} \quad (3.17)$$

$$|f'(x^*)| > 1 \Rightarrow \text{unstable} \quad (3.18)$$

Whether the equilibria are stable or not depends on the ratio of the parameters α, β, γ and δ . In the following, the focus is especially on the inner equilibrium x_3^* . For a biologically sensible scenario, the conditions (3.9) and (3.10) must be valid for α, β, γ and δ . For the stability analysis, the derivative at the inner fixed point, hereinafter referred to as x^* , is necessary:

$$f'(x^*) = \frac{2\alpha\delta - \alpha\beta - \gamma\delta}{\alpha\delta - \beta\gamma} = \frac{(\alpha - \gamma) \cdot (\delta - \beta)}{\alpha\delta - \beta\gamma} + 1 \quad (3.19)$$

According to (3.9) and (3.10), two cases are possible for the derivative:

1. $\alpha > \gamma$ and $\delta > \beta$
2. $\alpha < \gamma$ and $\delta < \beta$.

Assuming the first case, the denominator is positive, because $\alpha\delta > \beta\gamma$. For the numerator, then the following applies:

$$2\alpha\delta - \alpha\beta - \gamma\delta > 2\alpha\delta - \alpha\beta - \alpha\delta = \alpha(\delta - \beta) > 0. \quad (3.20)$$

So the numerator is also positive, which means that the entire fraction is positive.

Assuming the second case, the denominator is negative, because $\alpha\delta < \beta\gamma$. The same applies to the numerator as in the first scenario:

$$2\alpha\delta - \alpha\beta - \gamma\delta < 2\alpha\delta - \alpha\beta - \alpha\delta = \alpha(\delta - \beta) < 0. \quad (3.21)$$

Both the numerator and the denominator are negative, so the entire fraction is positive. That is, in both cases the derivative is positive and never less than zero, i.e., $f'(x^*) > 0$.

The fixed point is unstable when $\alpha > \gamma$ and $\delta > \beta$. That means the population is bistable, because $\alpha\delta > \beta\gamma$ and the numerator is positive, so the fraction in $f'(x^*)$ is positive and $f'(x^*) > 1$. But if $\alpha < \gamma$ and $\delta < \beta$, the denominator, and thus the entire fraction in $f'(x^*)$, becomes negative. $f'(x^*)$ itself cannot be negative, therefore it must be the case that $f'(x^*) < 1$. That means that the inner fixed point is stable, so both phenotypes coexist. Two examples of those scenarios are shown in fig. 3.4.

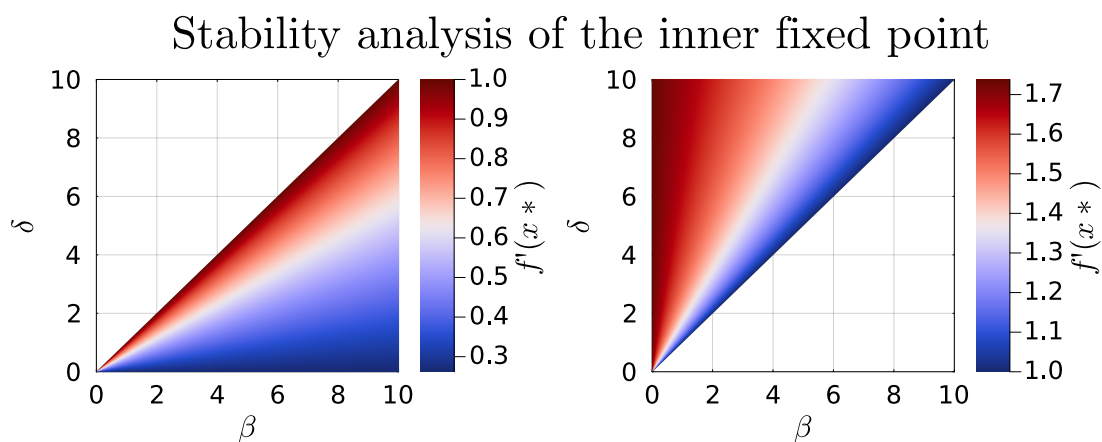


Figure 3.4 Two examples of the population dynamics in discrete time. The left plot shows the stable inner fixed point for $\alpha = 1.1$ and $\gamma = 4.2$. The right plot shows the unstable inner fixed point for $\alpha = 4.2$ and $\gamma = 1.1$. The color map represents the value of the derivative $f'(x^*)$. In the white regions there, is no valid inner fixed point, because neither 3.9 nor 3.10 hold.

How the population dynamics and the stability of the inner fixed point depend on the ratio between the parameters is also shown in fig. 3.5. As demonstrated in this section, alternative scenarios are not feasible. At least there is always one stable fixed point, which has not to be an inner fixed point. For the inner fixed point is always $f'(x^*) > 0$. The plot confirms the criteria for the stability of fixed points and also shows that there is no fixed point if $b > d$ and $a > c$ or $a < c$ and $b < d$.

The question now, however, is: When do such scenarios occur in nature? A typical example can be found in populations that contain both antibiotic-resistant and sensitive bacteria [8, 57].

Replicator Dynamics: Inner Fixed Point Analysis

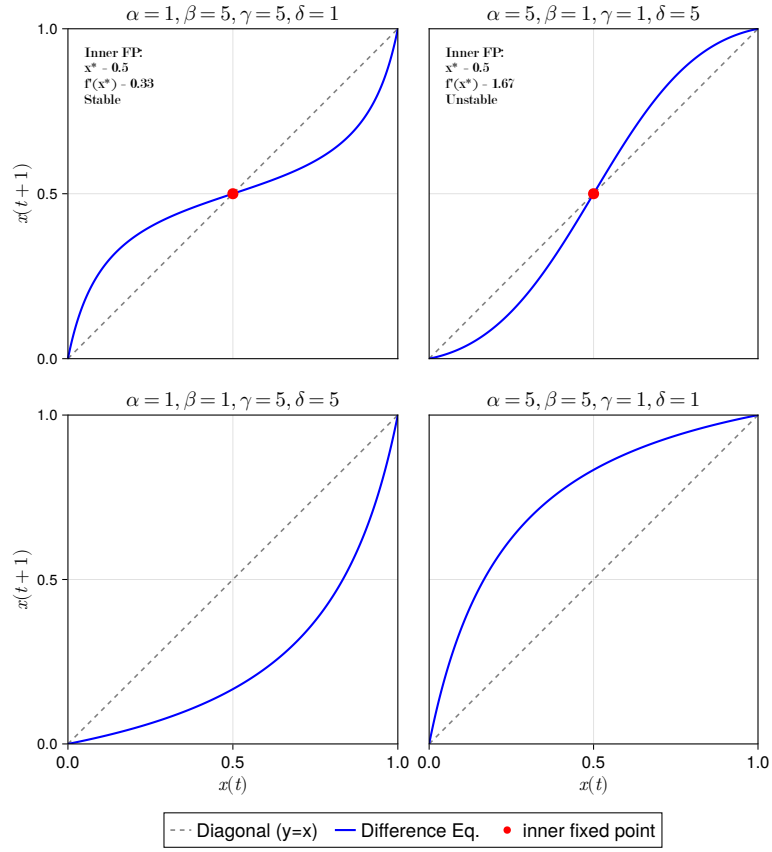


Figure 3.5 Replicator dynamic in discrete time, depending on the ratio between the parameters. Four examples for different ratios.

Chapter 4

Evolutionary game theory and antibiotic resistance

In more general terms, circumstances arise that may be regarded as an evolutionary game between a producer and a non-producer [8]. The producer generates a 'public good': A compound, which leads to a benefit for both the producer and non-producer. As a consequence, the producer has to pay the costs for the production. Nevertheless, as will be demonstrated later, it could be an advantage of being a producer. For example, in terms of antibiotic resistance. Such a game could be the interaction between antibiotic-resistant and sensitive bacteria [8, 57].

4.1 Antibiotic resistance

Antibiotic resistance is a major problem in clinics and the community [55]. According to the World Health Organization, antibiotic resistance increases and is widespread, especially in gram-negative bacteria [34]. Between 2018 and 2023, the resistance increased in 40% of the antibiotic-pathogen combinations [34]. Resistance often occurs because of the high growth rate and high mutation rate in bacteria [53]. All antibiotic classes are affected by antibiotic resistance [25].

A key factor of resistance spreading is the exchange of genetic information between bacteria [53, 50], for example, through horizontal gene transfer [25].

But the definition of resistance is not uniform. While with biological methods even small changes in susceptibility can be detected, within the context of a pharmacy or medicine, just huge changes of the minimal inhibitory concentration (MIC) are relevant [27].

However, of greater significance is the question of which classes of antibiotics are distinguishable and how they function, in order to describe the mechanism of action of resistance.

4.1.1 Antibiotic classes and their mechanism of action

In general, antibiotics interfere with bacterial growth or essential processes for survival [53]. Based on this, it is possible to distinguish two kinds of antibiotics. *Bacteriostatic* antibiotics inhibit bacterial growth while *bactericidal* ones kill the bacteria [53]. Antibiotics are often produced by bacteria or fungi in order to kill nearby microbes [53]. For example, some β -lactam antibiotics like penicillin and cephalosporins are produced by fungi. But nowadays, they are optimized semisynthetically.

Antibiotics can attack different targets. Because of clarity, just three possible mechanisms will be shortly discussed. The first class of antibiotics blocks the protein synthesis in bacteria by blocking ribosome-action [53, 55]. Because of the complexity of protein synthesis and the diversity of steps in ribosome-action, there are a lot of different possible targets for antibiotics [53]. An example of such an antibiotic class is kanamycin.

A second class of antibiotics targets the DNA replication and DNA repair [53, 55]. Antibiotics of this class inhibit the DNA enzyme gyrase. This enzyme uncoils DNA for replication by cleaving it [53]. Antibiotics like Ciprofloxacin bind to the enzyme and inhibit the repair of the DNA, which leads to even more double-strand-breaks. The cells are dying because of the emergency repair system [53].

The third and for the thesis most important mechanism is the impact on the cell wall biosynthesis [53, 55, 7]. The cell wall synthesis of the bacteria is disturbed by inhibiting important enzymes for the crosslinking of the peptidoglycan layers [53, 55, 7]. These enzymes are also called penicillin-binding proteins (PBP), because antibiotics like penicillin block them with a covalent binding [7]. The name also reveals an example of such antibiotics: β -lactam antibiotics like penicillin are part of this class [7, 53].

But with the diversity of antibiotic-actions also comes a diversity of resistance mechanisms.

4.1.2 Resistance mechanisms

Bacteria have already developed different mechanisms to resist the effects of antibiotics (fig. 4.1); already shortly after the introduction of new antibiotics, resistance mechanisms emerge [53, 55, 1]. A common answer to antibiotic treatment is to pump them out of the cell [53, 55, 50]. Antibiotics are only effective when reaching their target site. When the concentration in the cytoplasm is too low, they are ineffective [53]. With additional efflux pumps, bacteria can pump the antibiotic out of the cell to lower the concentration [53].

A second resistant mechanism is to change the target structure of the antibiotics [53, 55, 50]. An example is the resistance against antibiotics, which attack the

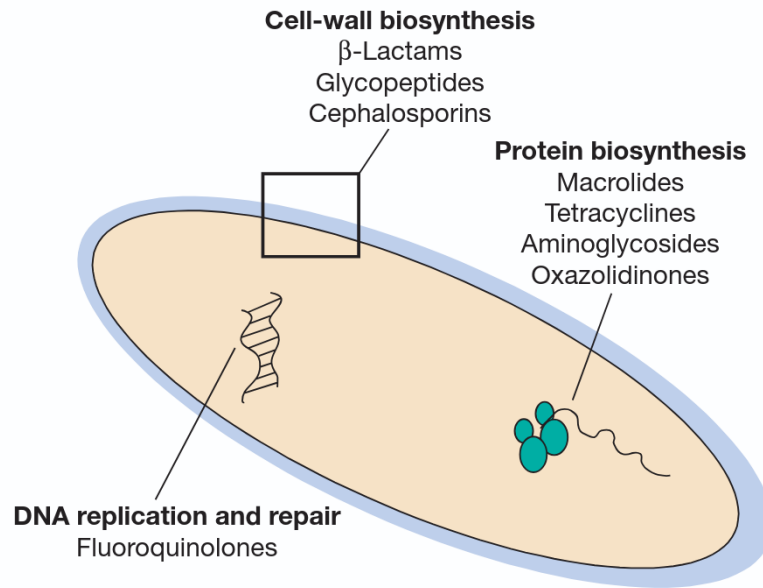


Figure 4.1 Examples for classes of antibiotic resistance and affected antibiotics. Adapted from [53].

protein synthesis: The bacteria methylate parts of the ribosome, so the antibiotics cannot bind [50], as the affinity of them for the ribosomes is reduced [53]. Target change also occurs in response to treatment with β -lactam antibiotics, in case that the affinity to the penicillin binding proteins is lowered [53]. An example is the widespread resistance of *Staphylococcus aureus* against the most β -lactam antibiotics [53, 46].

Another β -lactam resistance mechanism is to destroy the antibiotic. An example is the hydrolysis of β -lactam by the enzyme β -lactamase, which is produced by the resistant bacteria (fig. 4.2) [53, 55, 27, 7, 50]. The β -lactamase is released in the periplasm [53, 27] or the extracellular space [27], so the β -lactam antibiotics do not reach their target. The enzyme is very effective and can hydrolyze high amounts of antibiotics [53].

The production of such enzymes can be seen as a cooperative behaviour [57, 8, 17]. The resistant bacteria break down the antibiotic, while the sensitive bacteria benefit from it and can survive in even high antibiotic concentrations. Such a cooperative behaviour will be discussed in the following section on the example of β -lactam resistance.

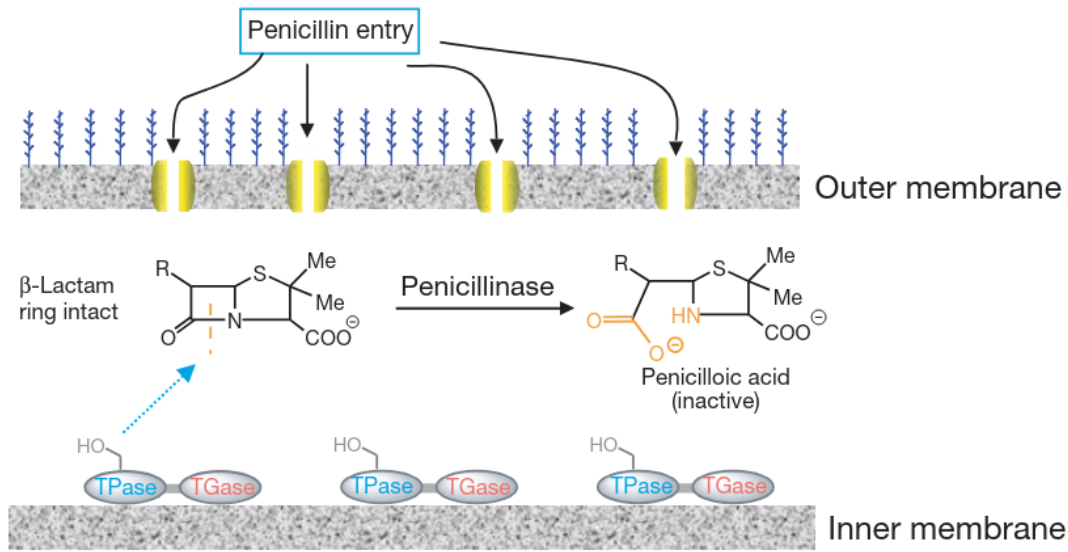


Figure 4.2 Hydrolysis of penicillin by the β -lactamase enzyme penicillinase. The β -lactamase is released into the periplasm. It hydrolyses the antibiotics, so they can not bind the penicillin-binding proteins in the cytoplasmic membrane. The shown bacterium is gram-negative. Adapted from [53].

4.2 Bacterial cheating

Studies have shown that β -lactam resistance in *Escherichia coli* is a highly cooperative process: Sensitive bacteria can survive even high amounts of antibiotics when growing together with resistant bacteria [8, 57, 10]. Consequently, the β -lactamase can be seen as a *public good*, from which both sensitive and resistant bacteria benefit. But the resistant bacteria have to pay the costs for producing the enzyme. The sensitive bacteria can save these costs, while still benefiting from the enzyme. Nevertheless, when the antibiotic concentration is high and the fraction of resistant bacteria is low, it is an advantage to produce the enzyme, which is, being resistant [8, 57]. The β -lactamase is released in the periplasm [53, 27], so the producer cells have a preferred access to it [57, 17].

Yurtsev et al. [57] analyzed the population dynamics of such a population by coculturing two strains of *E. coli* bacteria: One sensitive strain and an isogenic resistant strain, with an additional plasmid that encodes β -lactamase. In their experiments, they let the culture grow in a medium with $100 \frac{\mu g}{ml}$ ampicillin for 23 hours to saturation (saturation occurs within the 23 hours, not exactly after 23 hours). After that, they measured the fraction of resistant cells using flow cytometry (fig. 4.3), before diluting the culture by a factor 100. The antibiotic

concentration is the same every day. They let the culture grow again to saturation for 23 hours, so the final cell density is also the same every day. The whole procedure was repeated for eight days (fig. 4.3).

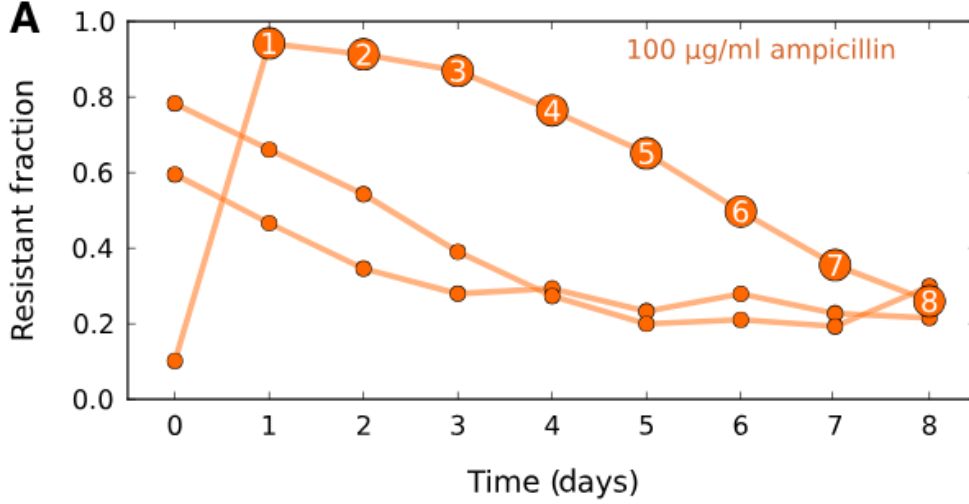


Figure 4.3 *Evolution of resistant fraction for three cultures with different initial resistant fractions. The fractions after 23 h were measured with flow cytometry. After that, they were diluted by a factor 100 into fresh media with $100 \frac{\mu\text{g}}{\text{ml}}$ ampicillin as culture for the next day. Adapted from [57]*

First of all, the results show that sensitive bacteria can live together with resistant bacteria, even in high antibiotic concentrations. In their experiment, the sensitive bacteria survived concentrations 50 times higher than the minimum inhibitory concentration [57]. In each of the three scenarios shown in fig. 4.3, the fraction of the resistant cells settle in ~ 0.25 . But against the expectation, the resistant fraction does not strictly evolve to the equilibrium in every scenario. When starting with a fraction below the equilibrium fraction, it overshoots the fixed point and increases to ~ 0.95 . From there, it converges to the equilibrium. The resistant cells never die out, because the β -lactamase is located in the periplasmic space [53, 27], so they have a priority access to the enzyme [57, 17].

Yurtsev et al. [57] analyzed the population dynamics more precisely by using difference equation maps (fig. 4.4). Those demonstrate the dependence of the final fraction from the initial fraction of resistant bacteria. By applying the difference equation repeatedly, the population dynamics can be estimated. To plot the difference equation, Yurtsev et al. used multiple cultures with different initial fractions of resistant cells. They measured the final fraction after a single day. Each curve demonstrates different antibiotic concentrations. As expected, for higher antibiotic concentrations, the equilibrium fraction is higher. The equilibria

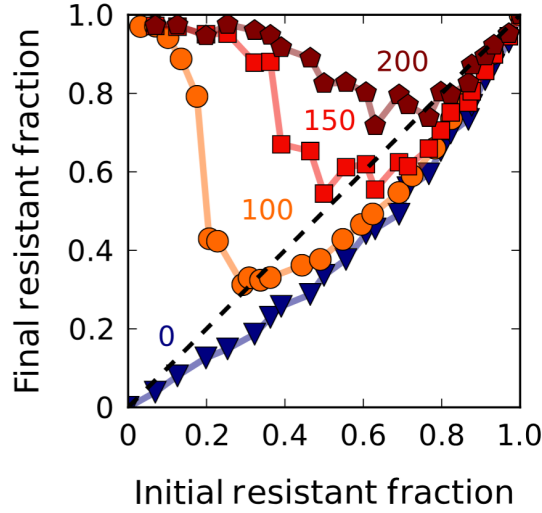


Figure 4.4 *Difference equation map of the experiments from Yurtsev et al. [57]. Each curve represents another antibiotic concentration, marked by the colored numbers. For each concentration 24 different initial fractions were used. After 23 h, the final fraction was measured, i.e., each datapoint represents the growth of the resistant fraction within 23 hours. The intersections with the diagonal line represent the fixed points. Adapted from [57].*

or fixed points are given by the intersection of the difference equation map with the diagonal [57]. The dynamic of the system with a stable inner equilibrium reminds of the snowdrift game [57, 8]. But the overshoot shows that it's much more complicated than that [57].

To describe the dynamic of the population, the authors introduced a system of three differential equations (4.1)–(4.3) [57].

$$\frac{dN_R}{dt} = \gamma_R \cdot N_R \quad (4.1)$$

$$\frac{dN_S}{dt} = \begin{cases} \gamma_S \cdot N_S & A < MIC \\ -\gamma_D \cdot N_S & A \geq MIC \end{cases} \quad (4.2)$$

$$\frac{dA}{dt} = -V_{max} \cdot N_R \cdot \frac{A}{A + K_M} \quad (4.3)$$

with

- γ_R : growth rate of the resistant bacteria
- γ_S : growth rate of the sensitive bacteria
- γ_D : death rate of the sensitive bacteria
- MIC : minimal inhibitory concentration (MIC)

A : antibiotic concentration

V_{max} : maximum rate of antibiotic degradation per cell

K_M : Michaelis-Menten-constant

N_S : number of sensitive cells

N_R : number of resistant cells

The degradation of the antibiotic is described by Michaelis-Menten kinetics. In case of the experiments, the resistant bacteria are growing constantly with the growth rate $\gamma_R = 1.1 h^{-1}$, while the sensitive bacteria are growing with $\gamma_S = 1.265 h^{-1}$ for $A < MIC$. When $A \geq MIC$, they are dying with the death rate $\gamma_D = 2.8 h^{-1}$. (fig. 4.5). During the lag phase when transferred into fresh media, the bacteria are neither dying nor growing. The constants V_{max} , MIC and K_M

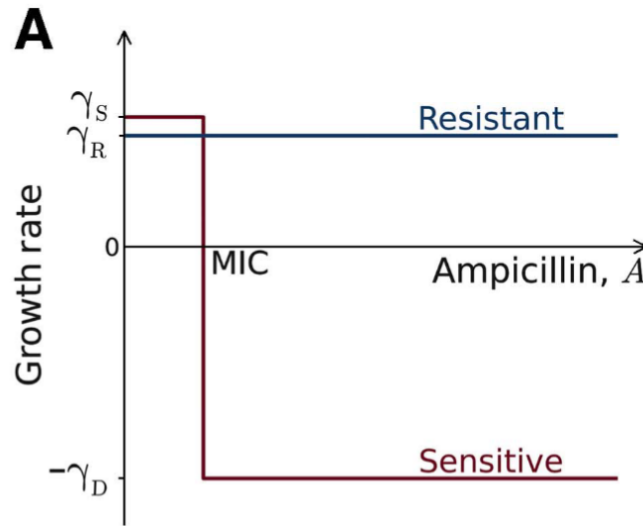


Figure 4.5 *Growth rate of the bacteria depending on the antibiotic concentration. Adapted from [57].*

were determined by fitting an expression for the equilibrium fraction, resulting from the differential equations, against the experimentally determined resistant equilibrium fraction at different ampicillin concentrations [57]. The growth and death rates, as well as the lag phase, were measured. With the constants, the authors solved the differential equations numerically and mapped the difference equations (fig. 4.6).

As mentioned before, the dynamic of the system reminds of the snowdrift game, except the overshoot. So it seems it should be possible to describe the population dynamics by a game theoretical approach in discrete time: Instead of a continuous timescale and continuous change of the resistant fraction, we have

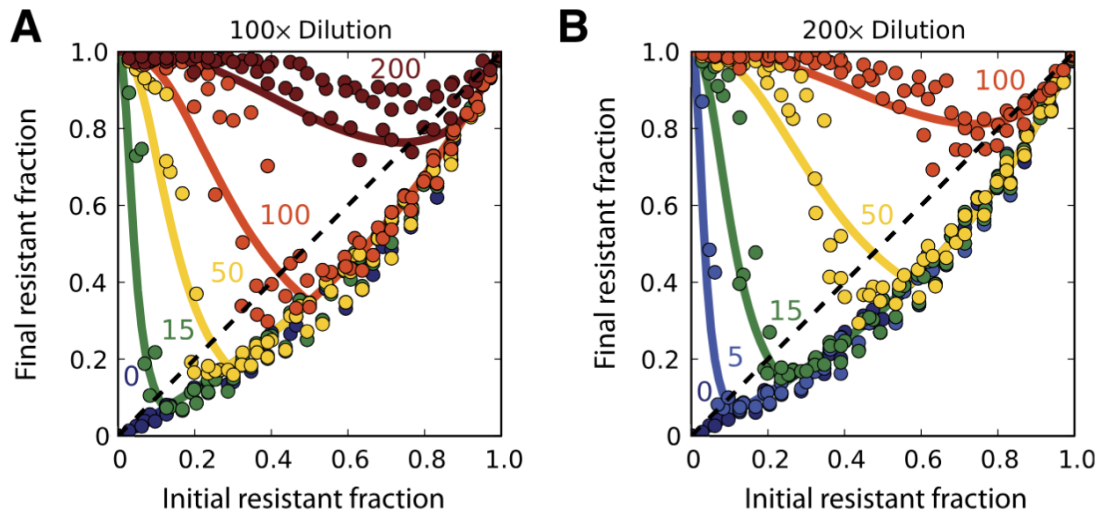


Figure 4.6 *Experimental and predicted difference equations for two dilution factors. The solid curves represent the numerical solution of the model using parameters fitted from the equilibrium data. Different antibiotic concentrations are indicated by colored numbers. Adapted from [57].*

an initial fraction every day and a final fraction after 23 hours, that is, a serial dilution experiment. The following section is an attempt to analyze the dynamics of the model using discrete-time game theory.

Chapter 5

A game theory model in discrete time based on Yurtsev et al.

For the game-theoretical analysis of the model, it's necessary to find an expression for the number of resistant and sensitive bacteria after one time step (23 h). To do this, the differential equations must be solved (5.1)–(5.3). To simplify the equations initially, it's possible to use an easier model from Yurtsev et al. [57], which assumes a constant degradation rate of the antibiotic:

$$\frac{dN_R}{dt} = \gamma_R \cdot N_R \quad (5.1)$$

$$\frac{dN_S}{dt} = \begin{cases} \gamma_S \cdot N_S & A < MIC \\ -\gamma_D \cdot N_S & A \geq MIC \end{cases} \quad (5.2)$$

$$\frac{dA}{dt} = -V_{max} \cdot N_R \quad (5.3)$$

The constants from the original paper [57] are given in Table 5.1. Finding the

γ_R	γ_S	γ_D	V_{max}	MIC
1.1 h^{-1}	1.265 h^{-1}	2.8 h^{-1}	$10^6 \frac{\text{molecules}}{\text{cell} \cdot \text{second}}$	$100 \frac{\mu\text{g}}{\text{ml}}$

Table 5.1 Constants used in the model from Yurtsev et al. γ_R is the growth rate of the resistant bacteria, γ_S is the one for the sensitive bacteria for $A < MIC$, γ_D is the death rate of the sensitive bacteria for $A \geq MIC$ and V_{max} is the hydrolysis rate [57].

solution of the differential equations can be done numerically, but also an analytical solution is possible [57].

Integration of equation (5.1) leads to

$$N_R(t) = N_R(0) \cdot e^{\gamma_R \cdot t} = N_{total} \cdot x_0 \cdot e^{\gamma_R \cdot t}, \quad (5.4)$$

with N_{total} the initial total number of bacteria and x_0 the initial fraction of resistant bacteria. The number of resistant bacteria is growing exponentially, because they are not affected by the antibiotic. The saturation time

$$T_{sat} = \frac{1}{\gamma_r} \cdot \log \left(\frac{N_{sat}}{N_{total}} \right), \quad (5.5)$$

of the culture is given by an equilibrium state

$$\frac{N_{Rf}}{N_{sat}} = \frac{N_{Ri}}{N_{total}} \Leftrightarrow \frac{N_{Rf}}{N_{Ri}} = \frac{N_{sat}}{N_{total}} \quad (5.6)$$

with $N_{Rf} = N_{Ri} \cdot e^{\gamma_r T_{sat}}$, the final number of resistant cells, N_{Ri} the initial number of resistant cells and N_{sat} the bacterial number at saturation and N_{total} the initial total bacteria number [57]. That is an approximation of the saturation time, because it is valid for the long-term dynamics of the model, but not for every population state. Nevertheless, it can be seen as a constant and a good enough approximation for the model.

Inserting equation (5.4) into (5.3) and integrating the expression leads to

$$A(t) = A_{init} - \frac{V_{max} \cdot N_{total} \cdot N_R(0)}{\gamma_r} \cdot (e^{\gamma_r t} - 1) \quad (5.7)$$

with $N_R(0)$, the initial number of resistant cells. The expression describes the antibiotic degradation. Subsequently, the integration of (5.2) yields an expression for the number of sensitive bacteria N_S . But it is necessary to distinguish between two scenarios: The sensitive bacteria start growing only when the antibiotic concentration is below the MIC. The time until that point is reached is defined by [57]

$$\tau = \frac{1}{\gamma_r} \cdot \log \left(1 + \frac{(A_{init} - MIC) \cdot \gamma_r}{V_{max} \cdot x_t \cdot N_{total}} \right). \quad (5.8)$$

From this point, they are growing until saturation. Consequently, when the antibiotic degradation is too slow and $\tau \geq T_{sat}$, the sensitive bacteria die, while they have a growth phase, when $\tau < T_{sat}$. The number of sensitive bacteria is then given by

$$N_S(t) = \begin{cases} N_S(0) \cdot e^{-\gamma_D \cdot T_{sat}} & \tau \leq T_{sat} \\ N_S(0) \cdot e^{\gamma_S \cdot (T_{sat} - \tau) - \gamma_D \cdot \tau} & \tau > T_{sat} \end{cases}. \quad (5.9)$$

That means, there must be a threshold frequency at which the dying-phase switches to a growth phase, i.e., the antibiotic concentration passes the MIC. The threshold

frequency is defined by

$$T_{sat} = \tau(x) \quad (5.10)$$

$$\Leftrightarrow \frac{1}{\gamma_R} \cdot \log\left(\frac{N_{sat}}{N_{total}}\right) = \frac{1}{\gamma_R} \cdot \log\left(\frac{B}{x} + 1\right) \quad (5.11)$$

$$\Leftrightarrow \frac{N_{sat}}{N_{total}} = 1 + \frac{B}{x} \quad (5.12)$$

$$\Leftrightarrow x := x_{tf} = \frac{B}{\frac{N_{sat}}{N_{total}} - 1}. \quad (5.13)$$

with

$$B = \frac{(A_{init} - MIC) \cdot \gamma_R}{V_{max} \cdot N_{total}}$$

These solutions show the population dynamics over the period between two transfers. For the dynamics of the resistant bacteria from one transfer to the next, an iterated map $x_{n+1} = f(x_n)$, with n being the number of transfers, can be defined:

$$f(x) = \frac{f_R \cdot x}{f_R \cdot x + f_S(x) \cdot (1 - x)}, \quad (5.14)$$

with $f_R = e^{\gamma_R \cdot T_{sat}}$ the discrete time fitness of the resistant bacteria, which is independent of density. $f_S(x)$ is the discrete time fitness of the sensitive bacteria, which depends on the initial fraction of resistant bacteria x :

$$f_S(x) = \begin{cases} e^{-\gamma_D \cdot T_{sat}} & x \leq x_{tf} \\ e^{\gamma_S \cdot (T_{sat} - \tau(x)) - \gamma_D \cdot \tau(x)} & x > x_{tf} \end{cases}. \quad (5.15)$$

But the replicator equation in discrete time discussed in section 3.3 is a linear model. The derivative of the fixed point is always positive, so an overshoot of the dynamic is not possible. However, the model from Yurtsev et al. is not linear in x and cannot be described by a fitness matrix.

Nevertheless, an analysis of the fixed-point dynamics provides further information about the population dynamics. Plotting the difference equation map (??) demonstrates the fixed points of the system (fig. 5.1). For the analysis of the dynamic an initial antibiotic concentration of $20 \frac{\mu g}{ml}$ is assumed, instead of $100 \frac{\mu g}{ml}$ as in the original paper. That is, because the simplified model used here, does not consider a lag-phase at which the bacteria are neither growing nor dying. However, if the same antibiotic concentration is assumed, the degradation is too slow, and the sensitive bacteria do not start growing fast enough.

As previously discussed, the stability of the fixed points can be analyzed by examining the derivative of the function $f(x) = x(n+1)$ at the fixed points x^* .

Population dynamic of the model from Yurtsev et al.

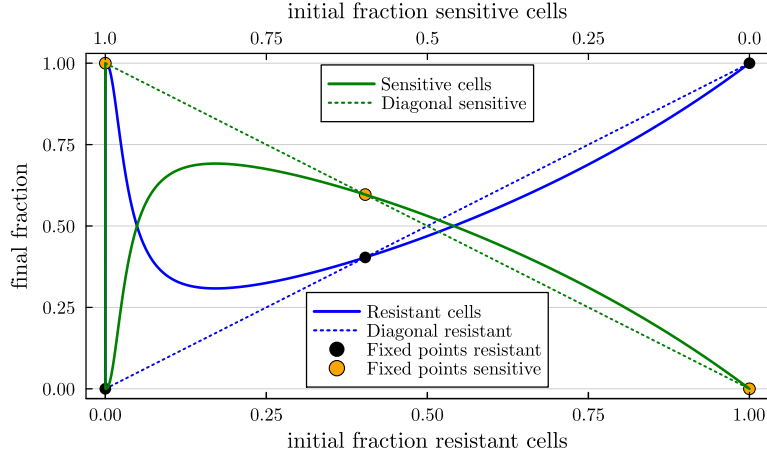


Figure 5.1 The blue line shows the dynamic of the resistant fraction as a difference map. The green line shows the dynamic of the sensitive fraction and depends on the upper x -axis. The intersections with the diagonals represent the fixed points of the system. As plotting parameters, the parameters from the paper are used, except the antibiotic concentration, which is in this case $A_{init} = 20 \frac{\mu g}{ml}$

For the used parameters, this leads to one stable inner equilibrium at

$$x^* = \frac{B}{e^{\frac{\gamma_R \cdot T_{sat} \cdot (\gamma_S - \gamma_R)}{\gamma_D + \gamma_S}} - 1} \approx 0.403 \quad (5.16)$$

with two unstable fixed points at $x = 0$ and $x = 1$. This is also shown in Figure fig. 5.1. However, as demonstrated later, this is not always the case: The stability of the fixed point changes under different conditions.

At the threshold frequency, where the dynamic of the sensitive bacteria changes, the function is continuous but not differentiable; because of the chosen plotting parameters, the threshold frequency is at very low fractions (fig. 5.2).

In the subsequent section, the dynamics of the system will be analyzed more precisely in terms of game theory.

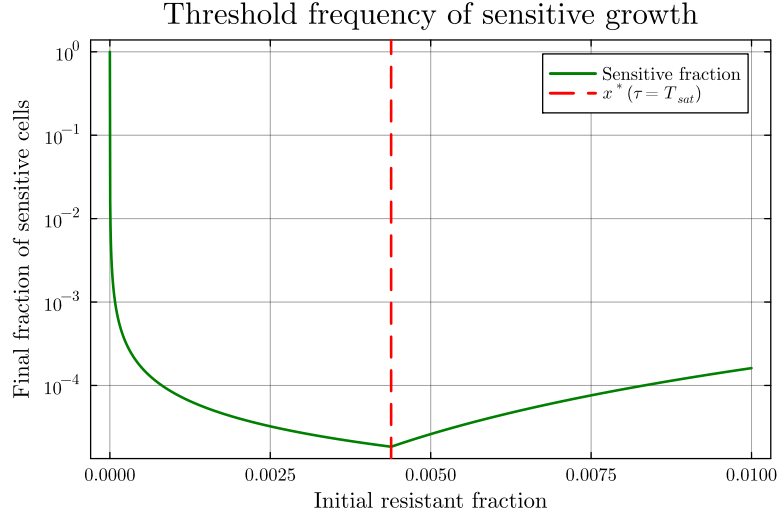


Figure 5.2 *Threshold frequency of the sensitive growth. The red dashed line marks the point where the degradation time equals the saturation time. The green line describes the sensitive fraction around the threshold frequency.*

5.1 Game dynamic in the Yurtsev-model

As already discussed, it is not possible to describe the Yurtsev-model with a simple payoff matrix and a linear game dynamic. Instead, it's possible to define fitness functions f_R and $f_S(x)$ for the resistant and sensitive bacteria as mentioned before. Those fitness functions describe the dynamics of the population. The fitness of the resistant bacteria is constant, while the fitness of the sensitive bacteria depends on the time $\tau(x_t)$, until the antibiotic concentration is below the MIC.

The ampicillin resistance is also associated with costs for protein synthesis. That means the growth rate of the resistant bacteria is lower than the growth rate of the sensitive bacteria, depending on the used plasmid. It is also possible to quantify the costs of resistance. While the growth rate of the sensitive bacteria in the Yurtsev-model is $\gamma_S = 1.265 h^{-1}$, the growth rate of the resistant bacteria, is in general, $\gamma_R = \gamma_S \cdot (1 - c)$. c denotes the cost of resistance and is, by definition, dimensionless. Those values can be used to calculate the fitness of the resistant and sensitive bacteria. Depending on the fitness values, scenarios similar to those in section 3.2.2 can be distinguished:

1. The *resistant bacteria dominate* if the sensitive bacteria are not able to invade the population, but the resistant bacteria are able to do so.

That is, $f_R \geq f_S(1) \wedge f_R > f_S(0)$.

2. Similarly, the *sensitive bacteria dominate* if $f_R < f_S(1) \wedge f_R \leq f_S(0)$.

3. Both phenotypes *stably coexist* when both are able to invade, i.e., $f_R <$

$f_S(1) \wedge f_R > f_S(0)$, and the population converges to a fixed point without oscillating. This was verified by running the system, i.e., the difference equation, 500 times and examining whether the fraction changed from one step to the next.

4. If the conditions in 3. are given, but the system oscillates, *unstable coexistence* appears.

The results are shown in fig. 5.3. As expected, for higher concentrations and

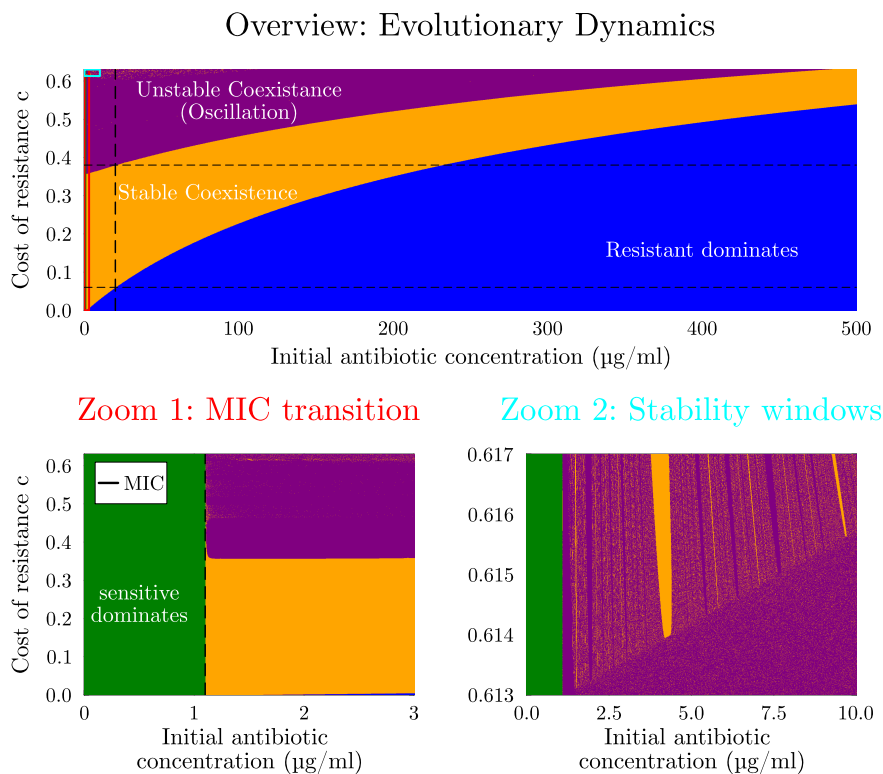


Figure 5.3 Evolution of the game dynamic in the Yurtsev-model for changing antibiotic concentration and costs of resistance. Zoom 1 shows the dynamic for small antibiotic concentrations (red rectangle). Zoom 2 shows windows of stability in the area of unstable coexistence (blue rectangle). The vertical dashed line in the upper plot marks the antibiotic concentration $A = 20 \frac{\mu g}{ml}$. The horizontal ones mark the transitions from one phase to another for the mentioned antibiotic concentration.

lower costs for resistance, the snowdrift game dynamic changes to a resistance dominance. For the values in the paper from Yurtsev et al., the plot shows a resistant dominance ($c \approx 0.13$; $A_{init} = 100 \frac{\mu g}{ml}$). The reason is that the lag time is not taken into account in (5.1)–(5.3), during which the antibiotic is degraded without cell death. When the antibiotic concentration is below the MIC, the sensitive bacteria dominate (Zoom 1, 5.3). For increasing costs of resistance and higher antibi-

otic concentrations, the sensitive and resistant bacteria stably coexist. However, at even higher resistance costs, stable coexistence shifts to unstable coexistence. Nevertheless, zooming in on the area reveals windows of stability within the area of unstable coexistence (Zoom 2, 5.3). This means that the population oscillates, but also returns to a stable condition. This is an important result: When both resistant and sensitive bacteria are able to invade, but oscillate between different frequencies, an unstable coexistence is possible, with $f'(x^*) < -1$. As shown in section 3.3.1, this is not possible in game theory in discrete time.

Instead, the dynamic reminds of a chaotic dynamic. The subsequent section will thus be dedicated to a more thorough analysis of the population dynamic.

5.2 Chaotic behaviour of the Yurtsev-dynamic

5.2.1 Chaos in dynamical systems

History and examples of chaotic dynamics

Henri Poincaré, a French mathematician, can be seen as the founding father of the chaos theory [35]. At the end of the 19th century, he studied three-body problems and their orbits. Unlike before, he examines the behaviour of trajectories resulting from sets of initial points. As his work shows, very complicated trajectories were possible. In the following decades, many mathematicians worked on chaotic systems. But it wasn't until computer-aided simulations became possible that interest in chaotic processes in physical systems began to grow [35]. Only then did it become clear how relevant the chaotic evolution of time is in practice.

But chaotic dynamics are more widespread than one might initially assume. The systems themselves where chaotic behaviour appears are often quite simple [35]. There are many examples from different fields of physics, where chaotic behaviour appears [35, 40]. One example from fluid dynamics comes from an experiment by Shaw in 1984 [35, 39]. For his experiment, he observed a steady but slow flow of water from a faucet. Below the faucet, a measuring device records the time when a water drop passes. This provides a dataset with discrete time $t_1, t_2, \dots, t_n$ at which the drops passed the measuring device. Time intervals between two drops are determined by $\Delta t = t_n - t_{n-1}$. When the flow rate is slow enough, the intervals between two drops are all equal. But for increasing flow rates, the time intervals become periodic: A long interval follows a short one, i.e. $\Delta t = t_n - t_{n-2}$. For even higher flow rates, the periods are also getting longer (e.g. a period sequence $\Delta t_1, \Delta t_2, \Delta t_3, \Delta t_1, \dots$). A further increase in the flow rate leads to a chaotic behaviour of the system.

Chaos is also possible in medical systems. The intervals between heartbeats are showing a chaotic behaviour in healthy hearts [15]. A non-chaotic or lower-

chaotic behaviour can suggest heart failure [36]. For example, a study analyzed the electrocardiograph recordings from 61 patients with a high cardiovascular risk [52]. The results showed that low-dimensional chaos can predict lethal ventricular fibrillation at least 12 hours before it appears. The scientists used an algorithm to analyze the chaotic behaviour of heartbeat intervals. But such systems in medicine are also complex and often can not be described easily by chaos, but by non-linear dynamics in general, [51].

Also, in biological systems, chaos appears, for example, in synthetic microbial communities [23] and in microbial food webs with two prey bacterial strains and one predator ciliate [4].

Definition of chaos

But what exactly is chaos? In general, chaos is defined by the *sensitive dependence on initial conditions* [41, 35, 20, 18, 47]. This means that two trajectories whose initial values are infinitesimally close to each other diverge exponentially over time [11, 41, 35, 20, 47]. Mathematically that means, $x_1(t)$ and $x_2(t)$ are two trajec-

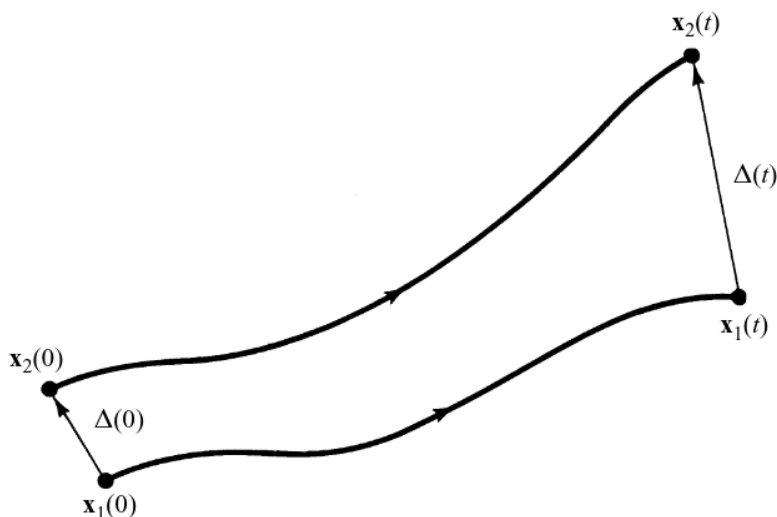


Figure 5.4 *Sensitive dependence on initial conditions.* $x_1(t)$ and $x_2(t)$ are time dependent trajectories. The distance between them at $t = 0$ is arbitrarily small. The distance between them increases with time. The time-dependent distance is given by $\Delta(t)$. Adapted from [35]

ries in continuous time with initial distance $|\Delta(0)|$ (fig. 5.4) and $|\Delta(0)| \rightarrow 0$ [35]. In general, at time t , the distance is $|\Delta(t)|$. When $\frac{|\Delta(t)|}{|\Delta(0)|} \sim \exp(\lambda \cdot t)$ for $\lambda > 0$, the system is sensitive to initial conditions, i.e., chaotic.

More generally, in discrete time, this leads to $dx_n \sim \exp(\lambda n) \cdot dx_0$, where dx_n is the distance between two points after n iterations by a given map. The rate of divergence of the initial points of the trajectories can be established by the *Lyapunov exponent* λ [11, 35, 54] in the following way [35, 11]:

$$\lambda = \lim_{n \rightarrow \infty} \left[\frac{1}{n} \cdot \ln \left| \frac{dx_n}{dx_0} \right| \right]. \quad (5.17)$$

An infinitesimally small distance between the trajectories leads to

$$\frac{dx_n}{dx_0} = \frac{d}{dx_0} \cdot f^n(x_0) = \prod_{i=0}^{n-1} (f'(x_i)). \quad (5.18)$$

That means for the Lyapunov exponent in discrete time

$$\lambda = \lim_{n \rightarrow \infty} \left[\frac{1}{n} \cdot \sum_{i=0}^{n-1} (\ln |f'(x_i)|) \right]. \quad (5.19)$$

For continuous time, the Lyapunov exponent is defined analogously [35]

$$\lambda = \lim_{t \rightarrow \infty} \left[\frac{1}{t} \cdot \ln \left| \frac{dx_t}{dx_0} \right| \right] \quad (5.20)$$

with the time t and dx_t , the distance between the trajectories at time t .

A positive *Lyapunov exponent* indicates a high sensitivity to initial conditions [20, 35, 11, 54, 18]. That is, the system is chaotic. However, it is also important to note that, according to other studies, the sensitive dependence on initial conditions alone is not sufficient to identify chaos; rather, a second condition — such as bifurcation or period doubling — must also be present [11]. But the most common condition is sensitive dependence on initial conditions.

This also leads to the fact that chaotic systems are unpredictable in the long run [41, 20, 35, 47]. Even small deviations in the initial conditions have a major impact on the course of the trajectories. A famous example comes from Lorenz, who analysed the long-term prediction of weather, i.e. atmospheric conditions [35, 47, 28]. He showed that atmospheric conditions are chaotic and introduced the famous *butterfly effect*: Even a small disturbance like the flap of a butterfly may lead to large effects in the system [11, 47], e.g. in atmospheric conditions [35]. Nevertheless, chaos is deterministic [20, 11, 41, 35, 47], and therefore differs fundamentally from stochastic dynamics.

But chaotic systems are also not periodic [20, 35, 47]: The trajectories in the phase space are not closed and do not intersect but come back to previous states, arbitrarily close without coming back to the exact state. Nevertheless, the

trajectories never run to infinity; they are in a bounded region [20, 35, 47]. This is possible with an attractor in a fractal, i.e. not an integer dimension, called a *strange attractor* [15, 35, 20, 18, 47]. This is the common case, but a chaotic attractor does not always have to be fractal [35]. That will not be discussed more precisely. The *strange attractor* evolves with stretching and folding of the phase space by the dynamic evolution, which leads to the fractal dimension [35, 20, 47]. The stretching results in the exponential divergence of initial points, and the folding leads to the bounded orbit.

Nevertheless, chaotic systems can exhibit windows of periodicity [35, 6]. In continuous time, chaos is only possible for dimension ≥ 3 [35]. In discrete time, chaos can also appear for dimension one, when the map is noninvertible. If it is invertible, dimension ≥ 2 is necessary. A typical way that leads the system into chaos is the period doubling of the system [35]: At some parameter values, a fixed point becomes unstable and a period two trajectory appears. Further period doubling results then in chaos.

The dynamic of the model from Yurtsev et al. [57] will be analysed more precisely in the following section, in terms of chaotic behaviour.

5.2.2 Chaos in the Yurtsev-dynamic

For the analysis of the dynamic, the difference map of the Yurtsev-model (??) was iterated three thousand times per cost of resistance, to stabilize the system. Another 100 values were plotted against the costs of resistance (fig. 5.5). The first three thousand values were not plotted, because they show the way to the attractor [35], while the trajectory on the attractor is relevant for the analysis.

Looking at the costs of resistance relative to the proportion of resistant cells reveals highly complex dynamics (fig. 5.5). For low costs of resistance, the system evolves to a stable fixed point. But for higher costs of resistance, the system starts oscillating between two fractions. Such *period doublings* occur again for even higher costs of resistance. So at some point the system starts oscillating with period four, eight and so on, evolving apparently to deterministic chaos.

The interval length between the period doubling points is getting smaller (table 5.2). More precisely, the ratio between two consecutive intervals converges to the Feigenbaum-constant $\delta = 4.669201609\dots$ [12]. This is shown in Table 5.2. The Feigenbaum constant is calculated by the ratio between the length of consecutive intervals between period doubling points.

To ensure that the system is indeed chaotic and not only oscillating between high periods, the *sensitive dependence on initial conditions* as a condition for chaos must be examined [41, 35, 20, 18, 47]. As already mentioned, this can be done using the *Lyapunov exponent*: A positive Lyapunov exponent indicates a high sensitivity to initial conditions [20, 35, 11, 54, 18], i.e., chaos. So to check if the

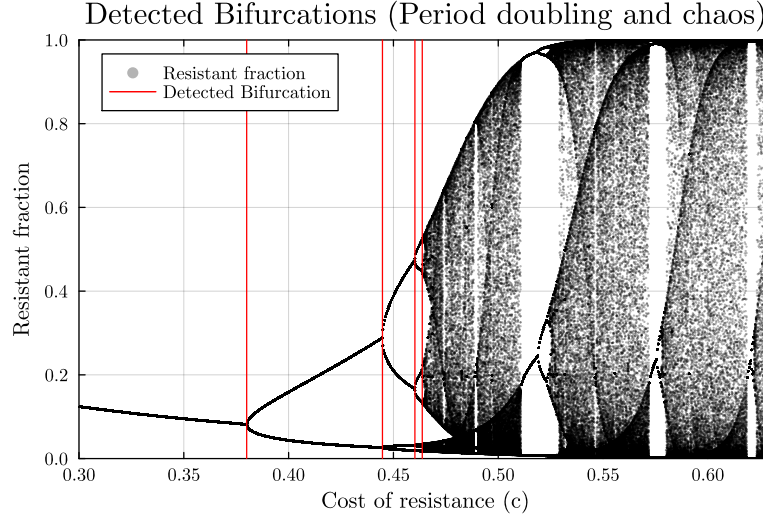


Figure 5.5 *Bifurcation analysis of the resistant population depending on the cost of resistance in the Yurtsev-model. The vertical red lines mark the cost of resistance where period doubling appears. For the plot, the difference map was iterated three thousand times for each cost of resistance to stabilize the system. Another hundred values are plotted to show the trajectory on the attractor.*

system is really chaotic, the Lyapunov exponent λ was calculated for the dynamic with equation (5.19).

The results, depending on the costs of resistance, are shown in fig. 5.6. The horizontal dashed line represents the threshold between chaotic and non-chaotic behaviour.

For low costs of resistance, the Lyapunov exponent is negative, so the system is not chaotic. But near $c = 0.46$, λ becomes positive and the system switches to chaotic behaviour.

But for even higher costs of resistance, the system comes back to a non-chaotic behaviour, before starting again to be chaotic. That means even in the chaotic areas, windows of order appear from time to time. The vertical dashed lines represent points where the Lyapunov exponent gets zero. When the sign of the Lyapunov exponent does not change at these points, the fixed point gets unstable and period doubling occurs. This is also shown in fig. 5.5. But at the first vertical dashed line in fig. 5.6 no period doubling occurs. Instead, it marks the point where stable coexistence appears first. This can be seen in fig. 5.3, where the intersection between the first horizontal dashed line and the vertical line represents this point. The second line represents where period doubling occurs first.

But what do these results mean in a biological context?

n	c_n	Δc_n	δ_n
1	0.379990		
2	0.444762	0.064772	4.184874
3	0.460240	0.015477	4.407407
4	0.463752	0.003512	

Table 5.2 *Period doubling points and convergence to the Feigenbaum constant for the Yurtsev-model. n is the index of the bifurcation point. c_n is the value of the cost at the n -th period doubling. Δc_n is the difference between consecutive bifurcation points. δ_n is the ratio of these differences, which should converge to the Feigenbaum constant.*

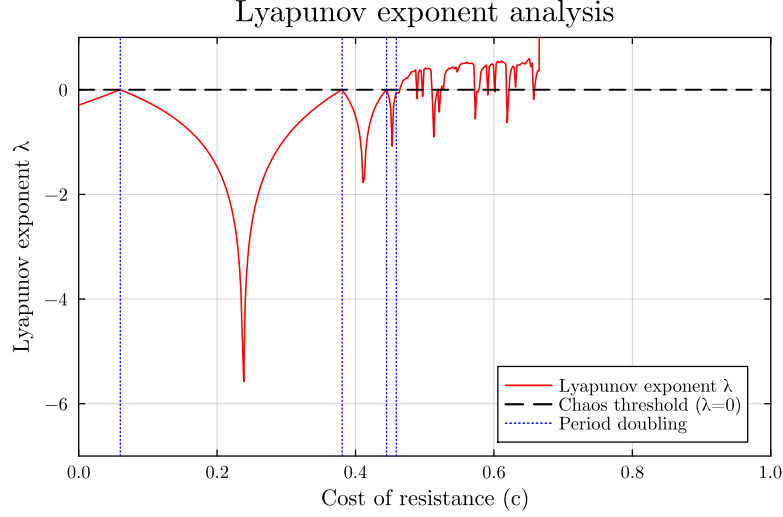


Figure 5.6 *Lyapunov exponent of the population dynamic in the Yurtsev-model*

Chapter 6

Discussion

The results of this study are discussed in the following sections within a biological context.

6.1 Summary of main findings

Yurtsev et al. [57] showed that antibiotic-resistant and sensitive bacteria can co-exist in even high amounts of antibiotics. The dynamic reminds of the game theoretical snowdrift game, but as shown, it is much more complicated than that. The dynamic of the population is highly non-linear. Taking the costs of resistance into account, the dynamic converges from coexistence to oscillating to chaos for higher costs of resistance. A reason for this could be the delayed feedback of the population: The resistant bacteria are degrading the antibiotics, but grow very slowly. When the MIC is reached, the sensitive bacteria start to grow explosively. But in the next time step, they are dying because of the high antibiotic concentration.

6.2 The role of chaos in biological systems

Chaotic dynamical systems are not very rare in biology [37]. Rogers et al. [37] investigated in a meta-analysis the relative abundance of chaos in natural populations. Out of 172 analysed population time series, more than 30 % showed chaotic behaviour. According to the study, chaos is three times more abundant than expected in earlier studies. This shows that long-term prediction in ecology is not always possible, above all in complex ecological systems.

However, even in small and simple systems, chaos occur. As already mentioned Becks et al. [4] demonstrated chaotic behaviour in microbial food webs, consisting of two bacterial prey species and one predator ciliate. They showed that in addition to chaotic behaviour, the system can also exhibit coexistence and stable limit

cycles. Their work showed that chaotic dynamics occur within real-world multi-species systems.

However, in more realistic and complex food webs, chaos also occurs. Benincà et al [5] cultured a food web from the Baltic Sea in a laboratory under constant conditions. The food webs consist of different species, among others, herbivorous and predatory zooplankton and phytoplankton. It was a long-term experiment that lasted approximately 2300 days. The system showed chaotic behaviour and was predictable for only about 15 to 30 days. These are important results for ecosystem management and the estimation of population fluctuations.

In particular, in engineering biology, predictable and repeatable systems are essential [23]. Nevertheless, chaos appears in even low-dimensional synthetic microbial systems. This was shown by Karkaria et al. [23], who analysed under which conditions chaos occurs in those systems consisting of three strains. Analysed parameters involved bacteriocin interactions, intercellular communication and resource competition. Accordingly, the highest probability for chaos occurs, when four *parts*, i.e., bacteriocins or communication molecules, are expressed. For fewer or more parts, the probability is lower. Also, the composition of the parts is relevant: For example, one communication system and a positive bacteriocin regulation leads to a higher probability for chaos. The results are important for future work to prevent chaotic behaviour of synthetic microbial systems. Further investigations have to show if the results are comparable with chaotic attractors in cooperative bacterial interactions like the one analysed in this thesis. But the present results indicate that in cooperative systems, chaos already appears for one part, the β -lactam, and two bacterial strains under antibiotic stress.

The examples listed show that chaotic dynamics are highly relevant in ecology and multi-species populations. This suggests that chaos also plays a significant role in medical fields, such as antibiotic resistance, where cooperative interactions between bacteria can occur, as demonstrated, e.g., by the study by Yurtsev et al. [57]. This thesis supports this assumption. But what does that mean for the clinical implications?

6.3 Clinical implications

Chaos leads to the fact that the evolution of the population is not predictable for the long run [41, 20, 35, 47]. But the evolution of resistant bacteria in populations could be an important factor for drug development [45]. Of course, the evolution of resistant bacteria is much more complicated than in the analysed model: Among others, mutations and horizontal gene transfer have to be taken into account. But nevertheless, the thesis shows that chaos is possible in even simpler populations and the examples in the previous sections showed that in more complicated popu-

lations, even in nature, not only in laboratories, chaos appears. As the dimension increases, chaotic behaviour becomes more probable [22].

The results suggest that periodic antibiotic treatment, similar to the serial dilution experiment, is not necessarily the most effective approach when resistant bacteria are involved, as it has an unpredictable effect on the composition of the population, which makes targeted treatment more difficult.

Furthermore, the windows of stability in fig. 5.3 show that the population dynamic is very sensitive to small changes in the initial antibiotic concentration.

6.4 Limitations of the thesis

Nevertheless, it has to be noted that chaos in the Yurtsev-dynamic occurs only for high costs of resistance about $c = 0.46$, which means that the growth rate of the resistant bacteria is 46 % lower than the growth rate of the sensitive bacteria. In general, the costs for antibiotic resistance are very variable, e.g., depending on the environment [2] and whether or not the bacteria are exposed to antibiotics [2, 14]. An experiment from Foucault et al. [14] showed a 20 % to 38 % reduction of the growth rate from vancomycin-resistant *S. aureus* compared to a sensitive strain. Results in other experiments suggest costs of resistance of just 0.7 % in tetracycline-resistant *E. coli* [9]. The cost of resistance in the present study, where chaos appears, is very high. In general, high costs of resistance can lead to a reversibility of resistance in the population [2]. The reversibility increases with the costs of resistance. Given this context, it is questionable if such high costs of resistance are realistic in the long-term evolution of bacterial populations.

In addition, the model used is highly simplified. Instead of an antibiotic degradation described by Michaelis-Menten kinetics, a constant degradation rate is used, and the lag-time was not taken into account. Furthermore, the saturation-time in the used model is only sensible for long-term dynamics and can just be seen as an approximation. The chaotic dynamics can also be further analyzed and characterized.

Future studies could use more realistic models and attempt to experimentally demonstrate such dynamics.

Bibliography

- [1] E. P. Abraham and E. Chain. “An Enzyme from Bacteria able to Destroy Penicillin”. In: *Nature* 146.3713 (Dec. 1940), pp. 837–837. ISSN: 1476-4687. DOI: 10.1038/146837a0.
- [2] Dan I. Andersson and Diarmaid Hughes. “Antibiotic resistance and its cost: is it possible to reverse resistance?” In: *Nature Reviews Microbiology* 8.4 (Mar. 2010), pp. 260–271. ISSN: 1740-1534. DOI: 10.1038/nrmicro2319.
- [3] Robert Axelrod and William D. Hamilton. “The Evolution of Cooperation”. In: *Science* 211.4489 (Mar. 1981), pp. 1390–1396. ISSN: 1095-9203. DOI: 10.1126/science.7466396.
- [4] Lutz Becks et al. “Experimental demonstration of chaos in a microbial food web”. In: *Nature* 435.7046 (June 2005), pp. 1226–1229. ISSN: 1476-4687. DOI: 10.1038/nature03627.
- [5] Elisa Benincà et al. “Chaos in a long-term experiment with a plankton community”. In: *Nature* 451.7180 (Feb. 2008), pp. 822–825. ISSN: 1476-4687. DOI: 10.1038/nature06512.
- [6] Steven R. Bishop et al. “Applying Chaos Control in Periodic Windows”. In: *Chaos, Solitons & Fractals* 9.8 (Aug. 1998), pp. 1297–1305. ISSN: 0960-0779. DOI: 10.1016/S0960-0779(98)00064-2.
- [7] Karen Bush and Patricia A. Bradford. “ β -Lactams and β -Lactamase Inhibitors: An Overview”. In: *Cold Spring Harbor Perspectives in Medicine* 6.8 (June 2016), a025247. ISSN: 2157-1422. DOI: 10.1101/cshperspect.a025247.
- [8] Peter L. Conlin, Josephine R. Chandler, and Benjamin Kerr. “Games of life and death: antibiotic resistance and production through the lens of evolutionary game theory”. In: *Current Opinion in Microbiology* 21 (Oct. 2014), pp. 35–44. ISSN: 1369-5274. DOI: 10.1016/j.mib.2014.09.004.

- [9] Leen De Gelder et al. “Combining Mathematical Models and Statistical Methods to Understand and Predict the Dynamics of Antibiotic-Sensitive Mutants in a Population of Resistant Bacteria During Experimental Evolution”. In: *Genetics* 168.3 (Nov. 2004), pp. 1131–1144. ISSN: 1943-2631. DOI: 10.1534/genetics.104.033431.
- [10] Lee Alan Dugatkin et al. “Group-beneficial traits, frequency-dependent selection and genotypic diversity: an antibiotic resistance paradigm”. In: *Proceedings of the Royal Society B: Biological Sciences* 272.1558 (Dec. 2004), pp. 79–83. ISSN: 1471-2954. DOI: 10.1098/rspb.2004.2916.
- [11] S. Effah-Poku, W. Obeng-Denteh, and I. K. Dontwi. “A Study of Chaos in Dynamical Systems”. In: *Journal of Mathematics* 2018 (2018), pp. 1–5. ISSN: 2314-4785. DOI: 10.1155/2018/1808953.
- [12] Mitchell J. Feigenbaum. “Quantitative universality for a class of nonlinear transformations”. In: *Journal of Statistical Physics* 19.1 (July 1978), pp. 25–52. ISSN: 1572-9613. DOI: 10.1007/bf01020332.
- [13] Ronald A. Fisher. “Polymorphism and Natural Selection”. In: *The Journal of Ecology* 46.2 (July 1958), p. 289. ISSN: 0022-0477. DOI: 10.2307/2257396.
- [14] Marie-Laure Foucault, Patrice Courvalin, and Catherine Grillot-Courvalin. “Fitness Cost of VanA-Type Vancomycin Resistance in Methicillin-Resistant *Staphylococcus aureus*”. In: *Antimicrobial Agents and Chemotherapy* 53.6 (June 2009), pp. 2354–2359. ISSN: 1098-6596. DOI: 10.1128/aac.01702-08.
- [15] A. L. Goldberger. “Is the Normal Heartbeat Chaotic or Homeostatic?” In: *Physiology* 6.2 (Apr. 1991), pp. 87–91. ISSN: 1548-9221. DOI: 10.1152/physiologyonline.1991.6.2.87.
- [16] Orlando Gomes. “Discrete Dynamics in Evolutionary Games”. In: *Discrete Dynamics in Nature and Society* 2012.1 (Jan. 2012). Ed. by Zuo Nong Zhu. ISSN: 1607-887X. DOI: 10.1155/2012/416789.
- [17] Jeff Gore, Hyun Youk, and Alexander van Oudenaarden. “Snowdrift game dynamics and facultative cheating in yeast”. In: *Nature* 459.7244 (Apr. 2009), pp. 253–256. ISSN: 1476-4687. DOI: 10.1038/nature07921.
- [18] Peter Grassberger and Itamar Procaccia. “Measuring the strangeness of strange attractors”. In: *Physica D: Nonlinear Phenomena* 9.1–2 (Oct. 1983), pp. 189–208. ISSN: 0167-2789. DOI: 10.1016/0167-2789(83)90298-1.
- [19] W. D. Hamilton. “Extraordinary Sex Ratios: A sex-ratio theory for sex linkage and inbreeding has new implications in cytogenetics and entomology.” In: *Science* 156.3774 (Apr. 1967), pp. 477–488. ISSN: 1095-9203. DOI: 10.1126/science.156.3774.477.

- [20] Mathias L. Heltberg et al. “A tale of two rhythms: Locked clocks and chaos in biology”. In: *Cell Systems* 12.4 (Apr. 2021), pp. 291–303. ISSN: 2405-4712. DOI: 10.1016/j.cels.2021.03.003.
- [21] Leonid Hurwicz. “The Theory of Economic Behavior”. In: *The American Economic Review* 35.5 (1945), pp. 909–925. ISSN: 00028282. URL: <http://www.jstor.org/stable/1812602> (visited on 03/06/2026).
- [22] Iaroslav Ispolatov et al. “Chaos in high-dimensional dissipative dynamical systems”. In: *Scientific Reports* 5.1 (July 2015). ISSN: 2045-2322. DOI: 10.1038/srep12506.
- [23] Behzad D. Karkaria et al. “Chaos in synthetic microbial communities”. In: *PLOS Computational Biology* 18.10 (Oct. 2022). Ed. by Christopher Rao, e1010548. ISSN: 1553-7358. DOI: 10.1371/journal.pcbi.1010548.
- [24] Harold W. Kuhn. *Lectures on the Theory of Games (AM-37)*. Annals of Mathematics Studies 37. Princeton: Princeton University Press, 2009. 120 pp. ISBN: 9780691027722.
- [25] D. G. Joakim Larsson and Carl-Fredrik Flach. “Antibiotic resistance in the environment”. In: *Nature Reviews Microbiology* 20.5 (Nov. 2021), pp. 257–269. ISSN: 1740-1534. DOI: 10.1038/s41579-021-00649-x.
- [26] Olof Leimar and John M. McNamara. “Game theory in biology: 50 years and onwards”. In: *Philosophical Transactions of the Royal Society B* 378.1876 (Mar. 2023). ISSN: 1471-2970. DOI: 10.1098/rstb.2021.0509.
- [27] D. M. Livermore. “beta-Lactamases in laboratory and clinical resistance”. In: *Clinical Microbiology Reviews* 8.4 (Oct. 1995), pp. 557–584. ISSN: 1098-6618. DOI: 10.1128/cmr.8.4.557.
- [28] Edward N. Lorenz. “Deterministic Nonperiodic Flow”. In: *Journal of the Atmospheric Sciences* 20.2 (Mar. 1963), pp. 130–141. ISSN: 1520-0469. DOI: 10.1175/1520-0469(1963)020<0130:dnf>2.0.co;2.
- [29] Mohsen Naghavi et al. “Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050”. In: *The Lancet* 404.10459 (Sept. 2024), pp. 1199–1226. ISSN: 0140-6736. DOI: 10.1016/S0140-6736(24)01867-1.
- [30] John von Neumann. “Zur Theorie der Gesellschaftsspiele”. In: *Mathematische Annalen* 100.1 (Dec. 1928), pp. 295–320. ISSN: 1432-1807. DOI: 10.1007/bf01448847.

- [31] John von Neumann and Oskar Morgenstern. “Theory of Games and Economic Behavior”. In: *Theory of Games and Economic Behavior (60th Anniversary Commemorative Edition)*. Princeton University Press, Dec. 2007. Chap. Chapter I. Formulation of the Economic Problem, pp. 1–45. DOI: 10.1515/9781400829460.1.
- [32] John von Neumann and Oskar Morgenstern. “Theory of Games and Economic Behavior”. In: *Theory of Games and Economic Behavior (60th Anniversary Commemorative Edition)*. Princeton University Press, Dec. 2007. Chap. Chapter II. General Formal Description of Games of Strategy, pp. 46–84. DOI: 10.1515/9781400829460.46.
- [33] Martin A. Nowak. *Evolutionary Dynamics: Exploring the Equations of Life*. Harvard University Press, Sept. 2006. ISBN: 9780674023383. DOI: 10.2307/j.ctvjghw98.
- [34] World Health Organization. *Global Antibiotic Resistance Surveillance Report 2025. WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS)*. 1st ed. Geneva: World Health Organization, 2025. 1138 pp. ISBN: 9789240116337.
- [35] Edward Ott. *Chaos in Dynamical Systems*. Cambridge University Press, Aug. 2002. ISBN: 9780511803260. DOI: 10.1017/cbo9780511803260.
- [36] Chi-Sang Poon and Christopher K. Merrill. “Decrease of cardiac chaos in congestive heart failure”. In: *Nature* 389.6650 (Oct. 1997), pp. 492–495. ISSN: 1476-4687. DOI: 10.1038/39043.
- [37] Tanya L. Rogers, Bethany J. Johnson, and Stephan B. Munch. “Chaos is not rare in natural ecosystems”. In: *Nature Ecology & Evolution* 6.8 (June 2022), pp. 1105–1111. ISSN: 2397-334X. DOI: 10.1038/s41559-022-01787-y.
- [38] Andrew Schotter and Gerhard Schwödiauer. “Economics and the Theory of Games: A Survey”. In: *Journal of Economic Literature* 18.2 (1980), pp. 479–527. ISSN: 00220515. URL: <http://www.jstor.org/stable/2723801> (visited on 03/06/2026).
- [39] Robert Shaw. *The Dripping Faucet as a Model Chaotic System*. Aerial Press, Inc., Santa Cruz, CA, 1984. ISBN: 0-942344-05-7.
- [40] J. Singer, Y-Z. Wang, and Haim H. Bau. “Controlling a chaotic system”. In: *Physical Review Letters* 66.9 (Mar. 1991), pp. 1123–1125. ISSN: 0031-9007. DOI: 10.1103/physrevlett.66.1123.
- [41] James E. Skinner. “Low-dimensional Chaos in Biological Systems”. In: *Nature Biotechnology* 12.6 (June 1994), pp. 596–600. ISSN: 1546-1696. DOI: 10.1038/nbt0694-596.

- [42] John Maynard Smith. *Evolution and the Theory of Games*. Cambridge University Press, Oct. 1982. ISBN: 9780511806292. DOI: 10.1017/cbo9780511806292.
- [43] John Maynard Smith. “Evolution and the Theory of Games: In situations characterized by conflict of interest, the best strategy to adopt depends on what others are doing”. In: *American Scientist* 64.1 (1976), pp. 41–45. ISSN: 00030996. URL: <http://www.jstor.org/stable/27847040> (visited on 03/06/2026).
- [44] John Maynard Smith and G. R. Price. “The Logic of Animal Conflict”. In: *Nature* 246.5427 (Nov. 1973), pp. 15–18. ISSN: 1476-4687. DOI: 10.1038/246015a0.
- [45] Morten O. A. Sommer et al. “Prediction of antibiotic resistance: time for a new preclinical paradigm?”. In: *Nature Reviews Microbiology* 15.11 (July 2017), pp. 689–696. ISSN: 1740-1534. DOI: 10.1038/nrmicro.2017.75.
- [46] Min Dong Song et al. “Evolution of an inducible penicillin-target protein in methicillin-resistant *Staphylococcus aureus* by gene fusion”. In: *FEBS Letters* 221.1 (Aug. 1987), pp. 167–171. ISSN: 1873-3468. DOI: 10.1016/0014-5793(87)80373-3.
- [47] Steven H. Strogatz. *Nonlinear Dynamics and Chaos with Student Solutions Manual: With Applications to Physics, Biology, Chemistry, and Engineering, Second Edition*. CRC Press, Sept. 2018. ISBN: 9780429399640. DOI: 10.1201/9780429399640.
- [48] Peter D. Taylor and Leo B. Jonker. “Evolutionary stable strategies and game dynamics”. In: *Mathematical Biosciences* 40.1–2 (July 1978), pp. 145–156. ISSN: 0025-5564. DOI: 10.1016/0025-5564(78)90077-9.
- [49] Robert L. Trivers. “The Evolution of Reciprocal Altruism”. In: *The Quarterly Review of Biology* 46.1 (Mar. 1971), pp. 35–57. ISSN: 1539-7718. DOI: 10.1086/406755.
- [50] Shawn Vasoo, Jason N. Barreto, and Pritish K. Tosh. “Emerging Issues in Gram-Negative Bacterial Resistance”. In: *Mayo Clinic Proceedings* 90.3 (Mar. 2015), pp. 395–403. ISSN: 0025-6196. DOI: 10.1016/j.mayocp.2014.12.002.
- [51] Andreas Voss et al. “Methods derived from nonlinear dynamics for analysing heart rate variability”. In: *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences* 367.1887 (Oct. 2008), pp. 277–296. ISSN: 1471-2962. DOI: 10.1098/rsta.2008.0232.

- [52] T. Vybiral and J.E. Skinner. “The point correlation dimension of R-R intervals predicts sudden cardiac death among high-risk patients”. In: *Proceedings of Computers in Cardiology Conference*. CIC-93. IEEE Comput. Soc. Press, Sept. 1993, pp. 257–260. DOI: 10.1109/cic.1993.378455.
- [53] Christopher Walsh. “Molecular mechanisms that confer antibacterial drug resistance”. In: *Nature* 406.6797 (Aug. 2000), pp. 775–781. ISSN: 1476-4687. DOI: 10.1038/35021219.
- [54] Alan Wolf et al. “Determining Lyapunov exponents from a time series”. In: *Physica D: Nonlinear Phenomena* 16.3 (July 1985), pp. 285–317. ISSN: 0167-2789. DOI: 10.1016/0167-2789(85)90011-9.
- [55] G. Wright. “Bacterial resistance to antibiotics: Enzymatic degradation and modification”. In: *Advanced Drug Delivery Reviews* 57.10 (July 2005), pp. 1451–1470. ISSN: 0169-409X. DOI: 10.1016/j.addr.2005.04.002.
- [56] Bin Wu et al. “Interpretations arising from Wrightian and Malthusian fitness under strong frequency dependent selection”. In: *Ecology and Evolution* 3.5 (Apr. 2013), pp. 1276–1280. ISSN: 2045-7758. DOI: 10.1002/ece3.500.
- [57] Eugene A. Yurtsev et al. “Bacterial cheating drives the population dynamics of cooperative antibiotic resistance plasmids”. In: *Molecular Systems Biology* 9.1 (Jan. 2013). ISSN: 1744-4292. DOI: 10.1038/msb.2013.39.