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Evolutionary Game Theory and Replicator Dynamics

Applications to Cancer Progression, Immune Response to Viruses and Vaccinating Behaviour

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Abstract

The aim of evolutionary game theory is to describe biological phenomena using mathematical (game theoretical) models. Since about 20 years, evolutionary game theory is used in medicine and biology: Natural processes are modelled with game theory by treating cells as players. In the present thesis fundamental concepts such as Nash equilibria, evolutionarily stable strategies and different game dynamics are explored particularly with regard to applications in medicine. Special attention is paid to explain the relation between game theoretical concepts and the qualitative analysis of differential equations. Models to analyse the progression of multiple myeloma bone disease, virus infections and vaccinating behaviour in humans are presented. Replicator equations are used to estimate the timely course of the multiple myeloma bone disease. A computer simulation shows the effects of several factors on the prognosis of patients. It can also help to determine recommendations for treatment and medical research. The application of Lotka-Volterra equations to describe the immune reaction to viruses is discussed and the model is adapted for more complicated use cases. Stability analysis of rest points yields explanations for different reactions of the immune system. In the last section, imitation dynamics is used to model human vaccinating behaviour. The model is introduced and validated using data on measles incidence and immunisation coverage in the UK from 1980 to 2016.

Kurzfassung

Evolutionäre Spieltheorie nutzt mathematische (spieltheoretische) Modelle zur Beschreibung biologischer Vorgänge. Seit etwa 20 Jahren findet evolutionäre Spieltheorie zunehmend Beachtung in Medizin und Biologie: Zellen werden als Konkurrenten betrachtet und natürliche Vorgänge können realitätsnah modelliert werden. In der vorliegenden Arbeit werden grundlegende Konzepte wie Nash- Gleichgewichte, evolutionär stabile Strategien und verschiedene Spieldynamiken insbesondere im Hinblick auf Anwendungen in der Medizin behandelt. Dabei wird besonderer Wert auf den Zusammenhang zwischen spieltheoretischen Konzepten und der qualitativen Analyse von Differentialgleichungen gelegt. Es werden Modelle zur Analyse des Krankheitsverlaufs des multiplen Myeloms und von Virusinfektionen vorgestellt, außerdem wird ein Modell zur Prognose des Impfverhaltens bei Menschen erörtert. Mithilfe von Replikatorgleichungen wird der zeitliche Verlauf einer Erkrankung an multiplem Myelom bestimmt. Eine Computersimulation zeigt den Einfluss verschiedener Faktoren auf die Prognose von Patienten und Patientinnen und kann Empfehlungen für die Behandlung und medizinische Forschung geben. Die Anwendung von Lotka-Volterra Gleichungen zur Beschreibung von Viruserkrankungen und entsprechenden Immunreaktionen wird diskutiert und das Modell für Spezialfälle adaptiert. Die Stabilitätsanalyse von Gleichgewichtspunkten liefert Erklärungen für verschiedene Reaktionen des Immunsystems. Zur Beschreibung menschlichen Verhaltens wird eine spezielle Spieldynamik, die Imitationsdynamik, genutzt. Das Modell wird hergeleitet und anhand von Daten zur Masernimpfung in Großbritanniern im Zeitraum von 1980 bis 2016 validiert.

Danksagung

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Eidesstattliche Erklärung

Ich erkläre an Eides statt, dass ich die vorliegende Diplomarbeit selbstständig und ohne fremde Hilfe verfasst, andere als die angegebenen Quellen und Hilfsmittel nicht benutzt bzw. die wörtlich oder sinngemäß entnommenen Stellen als solche kenntlich gemacht habe.

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1 Introduction

1.1 Definition of Evolutionary Game Theory

Evolutionary game theory can be defined as "the application of the mathematical theory of games to biological contexts" (Alexander, 2009). When organisms rival for restricted and vital resources such as food, territories or mates, conflicts arise frequently. However, the application of game theory to model these conflicts is not straight forward as classical game theory was developed to model rational behaviour and a rational intellect or conscience cannot be accredited to every animal or organism (van Damme, 1987).
Nevertheless, Maynard Smith & Price (1973) demonstrated the successful use of game theory to describe animal contests in their paper "The Logic of Animal Conflict" (1973). The applications are diverse: Fields included are without limitation sex ratio theory, animal distribution and competition behaviours (Maynard Smith, 1982). Wei et al. (1995) successfully applied game dynamical models to model virus dynamics for HIV, a year later a similar model was applied to the hepatitis B virus infection (Nowak et al., 1996). Brown (2016) suggested using game theory to model eco-evolutionary dynamics, niche construction, ecosystem engineering and viewing cancer as an evolutionary game. Extensive research on cancer from a game theoretical aspect has been done by Wu et al. (2018) and Pacheco et al. (2014).

1.2 A Brief History of Evolutionary Game Theory

In 1944, John von Neumann and Oskar Morgenstern published "The Theory of Games and Economic Behaviour", introducing techniques to analyse games and applications to economic and sociological problems. The first scientist who applied game theory to evolutionary questions was R.A. Fisher in 1930 in order to explain sex ratios in populations. In 1960, R.C. Lewontin considered a population playing against nature. But both Fisher and Lewontin missed a crucial point: The connection between the success and the frequency of a strategy (Sigmund, 2005).
In 1967, William D. Hamiltion applied game theory explicitly to intraspecific competition and frequency-dependent fitness values and in 1970, George Price submitted a paper to the journal *Nature*, investigating the advantages of the strategy "retaliation" in intraspecific conflicts which was reviewed by John Maynard Smith.
It was not until 1973 though, that Maynard Smith and Price published a joint paper, "The Logic of Animal Conflict", which applied Maynard Smith's concept of an evolutionarily stable strategy (ESS) to animal conflicts (Alexander, 2009; Sigmund, 2005). This paper had three fundamental consequences for evolutionary game theory: First, the develop-

ment of ESS and consequently the "marriage of game theory and population dynamics". Second, the use of agent based computer simulation and third, the application of game theoretical results to non-rational players (animals).
With the publication of the book "Evolution and the Theory of Games" in 1982, John Maynard Smith made these results available to a wider audience and he himself became popular as the "father of evolutionary game theory" (Sigmund, 2005). A more recent work giving a detailed introduction to evolutionary game theory and population dynamics is "Evolutionary Games and Population Dynamics" by Hofbauer & Sigmund (1998).

2 Normal Form Games

Let us first introduce some basic game theoretical terminology to model the behaviour of our 'players'. We assume that the behavioural program of each player can be described using a finite set of pure strategies. The definitions below are adapted from Hofbauer & Sigmund (1998).

Definition 2.1. *In a finite normal form game N pure strategies $R_1, \ldots, R_N$ are given. Players may use mixed strategies, i.e. choose these pure strategies with probabilities $p_1, \ldots, p_N$. As there holds $p_i \geq 0$ and $\sum_{i=1}^{N} p_i = 1$, each strategy corresponds to a point p in the simplex*

$$S_N = \left\{ p = (p_1, \ldots, p_N) \in \mathbb{R}^N : \ p_i \geq 0 \text{ and } \sum_{i=1}^{N} p_i = 1 \right\}.$$

The corners of the simplex defined above are the standard unit vectors e_i, each corresponding to a pure strategy R_i, the interior consists of completely mixed strategies with $p_i > 0$. The support

$$C(p) = \{i : \ 1 \leq i \leq N, p_i > 0\}, \ p \in S_N$$

is a proper subset of $\{1, \ldots, N\}$.

Definition 2.2. *The payoff matrix $U = (u_{ij})$ is defined such that the element u_{ij} denotes the payoff of an R_i strategist against an R_j strategist. Hence $(Uq)_i = \sum_{j=1}^{N} u_{ij} q_j$ denotes the expected payoff of an R_i against a q strategist and $p \cdot Uq = \sum_{i,j} u_{ij} p_i q_j$ the expected payoff of a p against a q strategist.*

Another concept frequently used is the notion of "Darwinian fitness":

Definition 2.3. *The term "Darwinian fitness" describes "a relative measure of reproductive success of an organism in passing its genes to the next generation's gene pool" (Mozo, 2018).*

Whenever we use the term "fitness" in the following, we refer to the definition above rather than physical fitness describing health.

Hawks and Doves

A famous example frequently used to illustrate ideas and results in the context of biological game theory is the *Hawk-Dove game*, introduced by Maynard Smith and Price in

1973. The name of the game refers to the character of the contestants rather than the birds themselves. A contestant adopting the hawk strategy will fight as hard as possible and only retreat when being seriously injured. A dove strategist, on the other hand, retreats whenever being confronted and never lets a conflict escalate. Assuming that the winner of a contest obtains a resource of value V and serious injury reduces the individual's fitness by a cost C, one obtains the payoff matrix:

	if it meets hawk	if it meets dove
a hawk receives	$\frac{V-C}{2}$	V
a dove receives	0	$\frac{V}{2}$

The success of either strategy depends on the constitution of the population and the relation between the cost C of injury and profit V for the winner of a contest. In a population consisting mostly of dove strategists, hawk strategists will fare better, as they receive a value V against dove strategists, compared to $\frac{V}{2}$ for dove versus dove confrontations. In a population consisting mostly of hawk strategists, the ratio $\frac{V}{C}$ determines the success of a strategy (Hofbauer & Sigmund, 1998; van Damme, 1987).

- If $V > C$, a hawk strategist does better, as $\frac{V-C}{2} > 0$.
- If $V < C$, neither strategy proves advantageous as strategy $p_1 = Hawk$ fares worse than $p_2 = Dove$, but the dove strategists would be invaded by hawks soon.

The solution is to consider a mixed population, denoting the frequency of hawks with p_H. Then the average increase in fitness for hawks and doves, respectively denotes:

$$p_H \cdot \frac{V-C}{2} + (1-p_H) \cdot V \text{ for hawk strategists}$$
$$(1-p_H) \cdot \frac{V}{2} \text{ for dove strategists}$$

For $p_H = \frac{V}{C}$, equality holds and therefore we expect evolution to lead to the stable state $p_H = \frac{V}{C}$ (Hofbauer & Sigmund, 1998). In the following section the concepts of evolutionarily stable states and Nash equilibria are introduced as tools for analysis.

2.1 Nash Equilibria and Evolutionarily Stable Strategies

A foundational concept of game theory is that of a Nash equilibrium. A strategy q is a Nash equilibrium if it is a *best reply* to itself. It is a strict Nash equilibrium if it is the *unique best reply* to itself. It is named after John Nash who has proved in 1950 that every finite normal form game has at least one Nash equilibrium.

Definition 2.4. *(Hofbauer & Sigmund, 1998)*
A strategy q is said to be a (strict) Nash equilibrium if there holds

$$p \cdot Uq \leq q \cdot Uq \quad (p \cdot Uq < q \cdot Uq) \quad \forall p \neq q. \tag{1}$$

Lemma 2.1. *A strict Nash equilibrium q has to be a pure strategy.*

Proof. Let q be a completely mixed strategy and a strict Nash equilibrium. Then (1) holds for all $p \neq q$, especially for the pure strategies $p = R_i, i \in \{1, \ldots, N\}$, i.e. $(Uq)_i < q \cdot Uq \; \forall i$. As $q_i \geq 0 \; \forall i$ the inequality may be multiplied by q_i, then the sum over i is taken. Factoring out $q \cdot Uq$ and using the property $\sum q_i = 1$ yields the contradiction $0 < 0$.

$$\begin{aligned} \sum_{i=1}^{N} q_i (Uq)_i - \sum_{i=1}^{N} q_i (q \cdot Uq) < 0 \\ \Leftrightarrow \left(1 - \sum_{i=1}^{N} q_i\right)(q \cdot Uq) < 0 \\ \Leftrightarrow 0 < 0 \end{aligned}$$

□

Hawks and Doves

It is easy to show that $q = Hawk = (1, 0)$ is a strict Nash equilibrium if $V > C$. Let us first recall that $U = \begin{pmatrix} \frac{V-C}{2} & V \\ 0 & \frac{V}{2} \end{pmatrix}$.
First, we test q against the only other pure strategy $p = Dove = (0, 1)$. There holds

$$p \cdot Uq = 0 < \frac{V - C}{2} = q \cdot Uq$$

if $V > C$.
Let $p = (p_1, 1 - p_1)$ now be an arbitrary mixed strategy, then there holds

$$\begin{aligned} p \cdot Uq = p \cdot \begin{pmatrix} \frac{V-C}{2} \\ 0 \end{pmatrix} < \frac{V - C}{2} = q \cdot Uq \\ \Leftrightarrow p_1 < 1 \end{aligned}$$

which is always true for a mixed strategy.

If $V < C$, then there is no Nash equilibrium in pure strategies as the best reply to

Dove is *Hawk*, but the best reply to *Hawk* would be *Dove*, therefore neither the hawk nor the dove strategy yield an equilibrium.
There exists a mixed strategy Nash equilibrium, though: $\hat{p} = \left(\frac{V}{C}, \frac{C-V}{C}\right)$. It can easily computed by solving the equation

$$\begin{aligned}(1,0) \cdot \begin{pmatrix} \frac{V-C}{2} & V \\ 0 & \frac{V}{2} \end{pmatrix} \cdot \begin{pmatrix} p_1 \\ 1-p_1 \end{pmatrix} &= (0,1) \cdot \begin{pmatrix} \frac{V-C}{2} & V \\ 0 & \frac{V}{2} \end{pmatrix} \cdot \begin{pmatrix} p_1 \\ 1-p_1 \end{pmatrix} \\ \Leftrightarrow p_1 \cdot \frac{V-C}{2} + (1-p_1) \cdot V &= (1-p_1) \cdot \frac{V}{2} \\ \Leftrightarrow p_1 = \frac{V}{C} &\Rightarrow 1 - p_1 = \frac{C-V}{C}.\end{aligned}$$

However, this equilibrium is not strict and it does not prove that a population applying $\hat{p}$ cannot be invaded by a minority adapting another strategy (Hofbauer & Sigmund, 1998). This consideration leads to the development of the concept of evolutionarily stable strategies.

Definition 2.5. *A strategy $\hat{p} \in S_N$ is evolutionarily stable, if for all $p \in S_N$ with $p \neq \hat{p}$ the inequality*

$$p \cdot U(\varepsilon p + (1-\varepsilon)\hat{p}) < \hat{p} \cdot U(\varepsilon p + (1-\varepsilon)\hat{p}) \tag{2}$$

holds for all $\varepsilon > 0$ that are smaller than an appropriate invasion barrier $\bar{\varepsilon}(p)$.

Hofbauer & Sigmund (1998) give another definition of an evolutionarily stable strategy:

Definition 2.6. *A strategy $\hat{p} \in S_N$ is evolutionarily stable, if and only if it satisfies two conditions:*

1. *equilibrium condition*

$$p \cdot U\hat{p} \leq \hat{p} \cdot U\hat{p} \quad \forall p \in S_N. \tag{3}$$

2. *stability condition*

$$\text{if } p \neq \hat{p} \text{ and } p \cdot U\hat{p} = \hat{p} \cdot U\hat{p}, \text{ then } p \cdot Up < \hat{p} \cdot Up. \tag{4}$$

Lemma 2.2. *The definitions of ESS given above are equivalent.*

Proof. Condition (2) in definition 2.5 is equivalent to:

$$(1-\varepsilon)\underbrace{(\hat{p}\cdot U\hat{p}-p\cdot U\hat{p})}_{I}+\varepsilon\underbrace{(\hat{p}\cdot Up-p\cdot Up)}_{II}>0. \tag{5}$$

- "Definition 2.6 $\Rightarrow$ Definition 2.5".
  $I \geq 0$ denotes the equilibrium condition. If $I = 0$, the stability condition $II \geq 0$ has to hold.
  Let $I = 0$. Then $II \geq 0$ has to hold and (5) holds for all ε.
  Let $I > 0$ hold in the strict sense. Then both $II > 0$ and $II < 0$ are possible. If $II > 0$, (5) follows directly for any $\varepsilon > 0$. If $II < 0$, (5) holds for all $0 < \varepsilon < \bar{\varepsilon}(p) := \frac{I}{I-II}$:

$$\begin{aligned}
&(1-\varepsilon)I+\varepsilon II>0\\
\Leftrightarrow\ &I-\varepsilon(I-II)>0\\
&\Leftrightarrow I>\varepsilon(I-II) \quad |:(I-II)>0\\
&\Leftrightarrow \varepsilon<\frac{I}{I-II}.
\end{aligned}$$

- "Definition 2.5 $\Rightarrow$ Definition 2.6".
  - Case 1: $I \geq 0$ and $II \geq 0$. Both equilibrium and stability condition are fulfilled. ✓
  - Case 2a: $I = 0$ and $II < 0$. ↯ The stability condition does not hold, but this case cannot occur for I, II satisfying (5).

$$\begin{aligned}
&I>\varepsilon(I-II) \quad |:(I-II)>0\\
\Leftrightarrow\ &0>\varepsilon
\end{aligned}$$

    in contradiction to the assumption $\varepsilon > 0$.
  - Case 2b: $I > 0$ and $II < 0$. The equilibrium condition is fulfilled in a strict sense, therefore the stability condition becomes obsolete. ✓

$$\begin{aligned}
&I>\varepsilon(I-II) \quad |:(I-II)>0\\
\Leftrightarrow\ &\varepsilon<\frac{I}{I-II}.
\end{aligned}$$

  - Case 3: $I < 0$ and $II \geq 0$. ↯ Neither equilibrium nor stability condition hold,

but this case cannot occur for I, II satisfying (5).

$$\begin{aligned} & I > \varepsilon(I - II) \quad | : (I - II) < 0 \\ \Leftrightarrow\ & \frac{I}{I - II} < \varepsilon < 1 \\ \Rightarrow\ & I < I - II \Rightarrow II < 0. \end{aligned}$$

in contradiction to the assumption $II \geq 0$.

– Case 4: $I < 0$ and $II < 0$. $\lightning$ This case cannot occur for I, II satisfying (5). If $I < II$, (5) does not hold for all $\varepsilon < 0$ that are smaller than the invasion barrier:

$$\begin{aligned} & I > \varepsilon(I - II) \quad | : (I - II) < 0 \ (I < II) \\ & 0 < \frac{I}{I - II} < \varepsilon. \end{aligned}$$

If $I < II$, the computation leads to a contradiction to the assumption $\varepsilon > 0$:

$$\begin{aligned} & I > \varepsilon(I - II) \quad | : (I - II) > 0 \ (I > II) \\ & 0 > \frac{I}{I - II} > \varepsilon. \end{aligned}$$

□

Lemma 2.3. *If $\hat{p}$ is a strict Nash equilibrium it is an ESS.*

Proof. If $\hat{p}$ is a strict Nash equilibrium it fulfills the equilibrium condition (3) trivially in a strong sense. As equality can never hold for $p \neq \hat{p}$, the stability condition (4) is obsolete. □

Lemma 2.4. *If $\hat{p}$ is an ESS it is a Nash equilibrium.*

Proof. The equilibrium condition (3) is the defintion of a Nash equilibrium. □

Theorem 2.5. *(van Damme, 1987)*
The strategy $\hat{p} \in S_N$ is an ESS if and only if there exists a neighbourhood $W(\hat{p})$ such that

$$\hat{p} \cdot Uq > q \cdot Uq \tag{6}$$

for all $q \in W(\hat{p})$ with $q \neq \hat{p}$.

Proof. Define $p_\varepsilon(q) := (1-\varepsilon)\hat{p}+\varepsilon q$ for $\hat{p}, q \in S_N,\ \varepsilon > 0$. Then $p_\varepsilon \in W(\hat{p})$ for any $q \in S_N$ if ε is sufficiently small. Furthermore, definition 2.5 is equivalent to $\hat{p} \cdot Up_\varepsilon(q) > p_\varepsilon(q) \cdot Up_\varepsilon(q)$

and the if part of the theorem is proven.
Let $\hat{p}$ be an ESS. If $\hat{p}$ is completely mixed ($p_i \neq 0,\ \forall\ i = 1, \ldots, N$), condition (6) holds for $W(\hat{p}) = S_N$, so assume that $\hat{p}$ is not completely mixed. Define

$$S := \{q \in S_N \ : \ q_i = 0 \text{ for some } i, C(q) \neq C(\hat{p})\}.$$

Next, define

$$\begin{aligned} \varepsilon(q) &:= sup\,\{\varepsilon > 0 \ : \ \hat{p} \cdot Up_\varepsilon(q) > q \cdot Up_\varepsilon(q)\} \\ \varepsilon^* &:= inf\,\{\varepsilon(q) \ : \ q \in S\}. \end{aligned}$$

If $q \neq \hat{p}$, then $\varepsilon(q) > 0$ since $\hat{p}$ is an ESS. Further $\varepsilon^* > 0$ since ε is a continuous function and S a compact set. Define $W(\hat{p}) := \{p_\varepsilon(q) \ : \ q \in S, \varepsilon \in [0, \varepsilon^*)\}$. Then W is a neighbourhood of $\hat{p}$ and satisfies the condition of the theorem. □

Lemma 2.6. *Let $\hat{p} \in int\ S_N$ be a Nash equilibrium. Then $\hat{p}$ is an ESS if and only if*

$$\xi \cdot U\xi < 0 \quad \forall\ \xi \neq 0 : \ \sum_{i=1}^{N} \xi_i = 0. \tag{7}$$

Proof.

- Let $\hat{p} \in int\ S_N$ be an ESS according to definition 2.5. Then for all $p \neq \hat{p}$ there holds

  $$p \cdot U(\varepsilon p + (1-\varepsilon)\hat{p}) < \hat{p} \cdot U(\varepsilon p + (1-\varepsilon)\hat{p})$$

  for an appropriate $\varepsilon > 0$.
  This inequality may be rewritten as

  $$(1-\varepsilon)(\hat{p} \cdot U\hat{p} - p \cdot U\hat{p}) + \varepsilon(\hat{p} \cdot Up - p \cdot Up) > 0.$$

  Strategy $\hat{p} \in int\ S_N$ is a Nash equilibrium, hence $(\hat{p} - p) \cdot U\hat{p} = 0$ which implies $(\hat{p} - p) \cdot Up > 0$ and $(\hat{p} - p) \cdot U\hat{p} - (\hat{p} - p) \cdot Up < 0$.
  If we set $\xi := \hat{p} - p$, there holds $\sum_i \xi_i = \sum_i \hat{p}_i - p_i = \sum_i \hat{p}_i - \sum_i p_i = 1 - 1 = 0$ and the claim is proven.

- Let now $\xi \cdot U\xi < 0 \quad \forall\ \xi \neq 0 : \ \sum_{i=1}^{N} \xi_i = 0$ hold.

Set $\xi := \hat{p} - p$ for some $p \neq \hat{p}$. Then

$$\begin{aligned} (\hat{p} - p) \cdot U(\hat{p} - p) &< 0 \\ \hat{p} \cdot U\hat{p} - p \cdot U\hat{p} - \hat{p} \cdot Up + p \cdot Up &< 0 \quad | \cdot (-\varepsilon),\ \varepsilon > 0 \\ -\varepsilon \cdot \hat{p} \cdot U\hat{p} + \varepsilon \cdot p \cdot U\hat{p} + \varepsilon \cdot \hat{p} \cdot Up - \varepsilon \cdot p \cdot Up &> 0 \end{aligned}$$

As $\hat{p}$ is a Nash equilibrium, we may add $\hat{p} \cdot U\hat{p} - p \cdot U\hat{p} \geq 0$ to the left side without changing the inequality. We derive

$$(1 - \varepsilon)(\hat{p} \cdot U\hat{p} - p \cdot U\hat{p}) + \varepsilon(\hat{p} \cdot Up - p \cdot Up) > 0$$

which is the definition of an ESS.

□

Definition 2.7. *A set E is an evolutionarily stable set (ES), if*

$$\forall\ x \in E\ \exists\ \text{a neighbourhood } W(x)\ \text{of } x\ :\quad x \cdot Uy \geq y \cdot Uy \qquad y \in W(x) \cap E \tag{8}$$

$$x \cdot Uy > y \cdot Uy \qquad y \in W(x) \setminus E. \tag{9}$$

Lemma 2.7. *E consists of Nash equilibria, i.e. it is enough to restrict (8) to those y which are best replies to x.*

Proof. Let E be an ES. Let us further assume that $x \in E$ is not a Nash equilibrium, i.e. $\exists\ z \neq x$ such that $x \cdot Ux < z \cdot Ux$. Then $y_\varepsilon := (1 - \varepsilon)x + \varepsilon z$ is in $W(x)$ for sufficiently small ε.

$$\begin{aligned} x \cdot Uy_\varepsilon &> y_\varepsilon \cdot Uy_\varepsilon \quad | - (1 - \varepsilon)x \cdot Uy_\varepsilon \\ \varepsilon x \cdot Uy_\varepsilon &> \varepsilon z \cdot Uy_\varepsilon \quad | : \varepsilon \\ x \cdot Uy_\varepsilon &> z \cdot Uy_\varepsilon \end{aligned}$$

If we now take the limit $\varepsilon \to 0$, we derive

$$x \cdot Ux > z \cdot Ux$$

in contradiction to our assumption that x is not a Nash equilibrium. □

Lemma 2.8. *$\{x\}$ is an evolutionarily stable set if and only if x is an ESS.*

Proof. This result directly follows from Theorem 2.5. □

Summary

The results of the lemmas above are summarised in Fig. 1:

- If $\hat{p}$ is a strict Nash equilibrium it is an ESS.
- If $\hat{p}$ is a Nash equilibrium and additionally satisfies the stability condition (4), it is an ESS.
- If $\hat{p}$ is an ESS it is a Nash equilibrium.

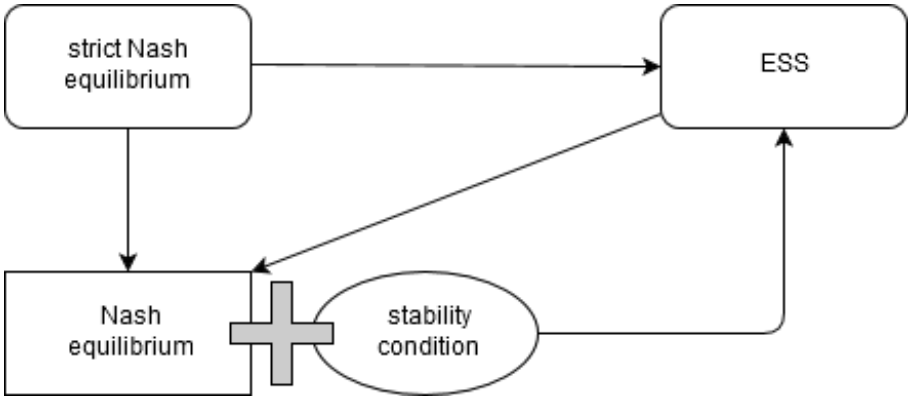

Figure 1: Relationship between Nash equilibria and ESS.

3 Replicator Dynamics

The aim of replicator dynamics is to describe how frequencies of strategies in a population evolve (Hofbauer & Sigmund, 1998). In contrast to the theory of Nash equilibria and ESS in section 2, it is not assumed that individuals may choose to play a mixed strategy, but that there is a heterogenous population of individuals only playing pure strategies (van Damme, 1987).

3.1 The Replicator Equation

Let us first introduce the replicator equation. The following derivation is adapted from Hofbauer & Sigmund (1998).

- Let the population be divided in n types $E_1, \ldots, E_n$ and let $x_1, \ldots, x_n$ denote the frequencies of the types $E_1, \ldots, E_n$.
- Let f_i denote the fitness of type E_i, it is a function of $x = (x_1, \ldots, x_n)$. $\bar{f}(x)$ then denotes the average fitness of the population: $\bar{f}(x) = \sum x_i f_i(x)$.

If the population is sufficiently large, it can be assumed that generations blend in continiously and $x(t)$ can be considered a differentiable function of t. The rate of increase of type E_i, $\frac{\dot{x}_i}{x_i}$, is one way to measure evolutionary success of type E_i. Another way to measure success is to take the difference between the fitness f_i of type E_i and the average fitness $\bar{f}$. Hence we obtain the *replicator equation*

$$\dot{x}_i = x_i(f_i(x) - \bar{f}(x)), \quad i = 1, \ldots, n. \tag{10}$$

For modelling the evolution of a population it is crucial that a trajectory starting in the simplex remains in S_N. The next lemma shows that this is indeed true (van Damme, 1987).

Lemma 3.1. *The simplex S_n is invariant under* (10).

Proof. The replicator equation for each of the n types in the population can be written out in full:

$$\begin{aligned}
\dot{x}_1 &= x_1(f_1(x) - \bar{f}(x)) \\
\dot{x}_2 &= x_2(f_2(x) - \bar{f}(x)) \\
&\vdots \\
\dot{x}_n &= x_n(f_i(x) - \bar{f}(x))
\end{aligned}$$

By taking the sum over all types $1, \ldots, n$ the equation $\sum_{i=1}^{n} \dot{x}_i = \sum_{i=1}^{n} x_i(f_i(x) - \bar{f}(x))$ is derived. Substituting $S = \sum_{i=1}^{n} x_i$, this equation can be written as:

$$\dot{S} = \bar{f} - S\bar{f} \Leftrightarrow \dot{S} = (1 - S)\bar{f}$$

The equation above has $S(t) = 1$ as a solution, therefore the solution of (10) stays in the simplex if it starts there. Furthermore, if $x_i(0) = 0$, then $x_i(t) = 0$ for all t, hence the faces of the simplex S_n and therefore S_n itself are invariant under (10). □

There are several more very convenient characteristics.

Lemma 3.2. *Addition Rule (Hofbauer & Sigmund, 1998)*
The addition of a function $\Psi : S_n \to \mathbb{R}$ to all f_i does not change equation (10) on S_n.

Proof. Let $g_i(x) = f_i(x) + \Psi(x)$. Then

$$\begin{aligned} \bar{g}(x) &= \sum_{i=1}^{n} x_i g_i(x) = \\ &= \sum_{i=1}^{n} x_i f_i(x) + \sum_{i=1}^{n} x_i \Psi(x) = \\ &= \bar{f}(x) + \Psi(x) \quad \text{on } S_n. \end{aligned}$$

Hence $g_i(x) - \bar{g}(x) = f_i(x) + \Psi(x) - \bar{f}(x) - \Psi(x) = f_i(x) - \bar{f}(x)$. □

Lemma 3.3. *Quotient Rule (Hofbauer & Sigmund, 1998)*
For $x_j > 0$ there holds

$$\left(\frac{x_i}{x_j}\right)^{\cdot} = \left(\frac{x_i}{x_j}\right)(f_i(x) - f_j(x)). \tag{11}$$

Proof. The replicator equation (10) reads $\dot{x}_i = x_i(f_i(x) - \bar{f}(x))$ and $\dot{x}_j = x_j(f_j(x) - \bar{f}(x))$ for type i and j, respectively. Applying the quotient rule of derivation leads to:

$$\begin{aligned} \left(\frac{x_i}{x_j}\right)^{\cdot} &= \frac{\dot{x}_i \cdot x_j - x_i \cdot \dot{x}_j}{x_j^2} = \\ &= \frac{x_i \cdot (f_i(x) - \bar{f}(x)) \cdot x_j - x_i \cdot x_j \cdot (f_j(x) - \bar{f}(x))}{x_j^2} = \\ &= \frac{x_i x_j \cdot (f_i(x) - \bar{f}(x) - f_j(x) + \bar{f}(x))}{x_j^2} = \\ &= \left(\frac{x_i}{x_j}\right)(f_i(x) - f_j(x)). \end{aligned}$$

□

The special case of linear f_i is of particular interest to game theory (Hofbauer & Sigmund, 1998). For linear f_i there exists a matrix $A = (a_{ij}) \in \mathbb{R}^{n\times n}$ such that $f_i(x) = (Ax)_i$. In this case, equation (10) can be written as

$$\dot{x}_i = x_i((Ax)_i - x \cdot Ax), \quad i = 1, \ldots, n. \tag{12}$$

The rest points of (12) in *int* S_n are the solutions of

$$(Ax)_1 = \cdots = (Ax)_n \tag{13}$$

$$x_1 + \cdots + x_n = 1 \tag{14}$$

satisfying $x_i > 0$ for $i = 1, \ldots, n$.

Lemma 3.4. *(Hofbauer & Sigmund, 1998)*
The addition of a constant c_j to the j-th column of A does not change (12) *on S_n.*

Proof. The replicator equation for a linear fitness function f_i reads

$$\dot{x}_i = x_i((Ax)_i - x \cdot Ax) = x_i((Ax)_i - \sum_k x_k(Ax)_k), \quad i = 1, \ldots, n$$

The term $(Ax)_i$ may be written as

$$(Ax)_i = \sum_{k=1}^{n} a_{ik}x_k.$$

Adding a constant c_j to the j-th column yields

$$\begin{aligned}(\tilde{A}x)_i &= a_{i1}x_1 + \ldots + (a_{ij} + c_j)x_j + \ldots + a_{in}x_n = \\ &= a_{i1}x_1 + \ldots + a_{ij}x_j + \ldots + a_{in}x_n + c_jx_j = \\ &= (Ax)_i + c_jx_j.\end{aligned}$$

Replacing the corresponding terms in the replicator equation completes the proof:

$$\begin{aligned}\dot{x}_i &= x_i((\tilde{A}x)_i - \sum_k x_k(\tilde{A}x)_k) = \\ &= x_i((Ax)_i + c_j x_j - \sum_k x_k(Ax)_k - \underbrace{\sum_k x_k\, c_j x_j}_{=1}) = \\ &= x_i((Ax)_i - \sum_k x_k(Ax)_k) = \\ &= x_i((Ax)_i - x \cdot Ax)\end{aligned}$$

□

By adding appropriate constants it is possible to transform A into a simpler form (e.g. having 0 in the diagonal).

Lemma 3.5. *(Hofbauer & Sigmund, 1998)*
The projective transformation $x \to y$

$$y_i = \frac{x_i c_i}{\sum_j x_j c_j} \quad c_j > 0$$

transforms (12) *into the replicator equation with matrix* $(a_{ij}c_j^{-1})$. *A rest point* $p \in intS_n$ *can thereby be moved to the barycentre* $\left(\frac{1}{n}, \ldots, \frac{1}{n}\right)$ *of* S_n *without changing its nature.*

Proof.
Taking the derivative of y_i yields

$$\begin{aligned}\dot{y}_i &= \frac{\dot{x}_i c_i \cdot \sum_j x_j c_j - x_i c_i \cdot \sum_j \dot{x}_j c_j}{\left(\sum_j x_j c_j\right)^2} = \\ &= \frac{x_i c_i((Ax)_i - x \cdot Ax) \cdot \sum_j x_j c_j - x_i c_i \sum_j x_j c_j((Ax)_j - x \cdot Ax)}{\left(\sum_j x_j c_j\right)^2} = \\ &= y_i \cdot ((Ax)_i - \sum_j y_j (Ax)_j).\end{aligned}$$

Replacing $\tilde{a}_{ij} = \frac{a_{ij}}{c_j}$ in the replicator equation $\dot{y}_i = y_i((\tilde{A}y)_i - y \cdot \tilde{A}y)$ yields

$$\begin{aligned}\dot{y}_i &= y_i(\sum_j \frac{a_{ij}}{c_j}\frac{x_j c_j}{\sum_j x_j c_j} - \sum_i \frac{x_i c_i}{\sum_j x_j c_j}\sum_j \frac{a_{ij}}{c_j}\frac{x_j c_j}{\sum_j x_j c_j}) = \\ &= \frac{y_i}{\sum_j x_j c_j}((Ax)_i - \sum_i x_i c_i \sum_j \frac{a_{ij}x_j}{\sum_j x_j c_j}) = \\ &= \frac{y_i}{\sum_j x_j c_j}((Ax)_i - \sum_i y_i (Ax)_i).\end{aligned}$$

These terms are identical except for the scaling factor $\frac{1}{\sum_j x_j c_j}$ which can be fixed by scaling the time variable accordingly. □

3.2 Game Theory and Replicator Dynamics

The objective of this chapter is to interpret replicator dynamics in a game theoretical context. It will be explained how the differential equation corresponds to the underlying normal form game and how the concepts of Nash equilibria and stability measures for rest points coincide. This section mainly follows chapter 7 of Hofbauer and Sigmund (1998).

- Let us recall that there is an underlying normal form game in N pure strategies $R_1, \ldots, R_N$ with a payoff matrix U.
- Any strategy corresponds to a point in S_N; therefore the types $E_1, \ldots, E_n$ coincide with n points $p^1, \ldots, p^n \in S_N$.
- The *state* of the population is given by the frequencies x_i of type E_i which is a point $x \in S_n$.
- The entries a_{ij} of the fitness matrix $A \in \mathbb{R}^{n \times n}$ are given by the payoff of a p^i-strategist against a p^j-strategist, namely

$$a_{ij} = p^i \cdot U p^j$$

- The fitness $f_i(x)$ of type E_i can then be computed as

$$f_i(x) = \sum_j a_{ij} x_j = (Ax)_i$$

and the replicator equation (10) can be written in the easier form (12):

$$\dot{x}_i = x_i((Ax)_i - x \cdot Ax), \quad i = 1, \ldots, n \quad (12)$$

3.2.1 Nash Equilibria and Evolutionarily Stable States

Before we can investigate the relation between rest points of the replication equation and Nash equilibria we need to define Nash equilibria in this context and introduce evolutionarily stable states.

Definition 3.1. *A point $\hat{x} \in S_n$ is a Nash equilibrium (with respect to payoff matrix A) if*

$$x \cdot A\hat{x} \leq \hat{x} \cdot A\hat{x} \quad \forall\ x \in S_n. \tag{15}$$

Definition 3.2. *(compare theorem 2.5) A point $\hat{x} \in S_n$ is an evolutionarily stable state if*

$$\hat{x} \cdot Ax > x \cdot Ax \quad \forall\ x \neq \hat{x} \text{ in a neighbourhood of } \hat{x}. \tag{16}$$

Theorem 3.6. *(Hofbauer & Sigmund, 1998)*

1. *If $\hat{x} \in S_n$ is a Nash equilibrium of the game described by the payoff matrix A, then $\hat{x}$ is a rest point of* (12).
2. *If $\hat{x}$ is the ω-limit of an orbit $x(t)$ in int S_n, then $\hat{x}$ is a Nash equilibrium.*
3. *If $\hat{x}$ is Lyapunov stable, then it is a Nash equilibrium.*

Proof. (Hofbauer & Sigmund, 1998)

1. Let $\hat{x}$ be a Nash equilibrium. Then there exists a constant c such that $(A\hat{x})_i = c$ for all i with $\hat{x}_i > 0$. Hence $\hat{x}$ satisfies the equations (13)-(14) for a rest point in the face spanned by the e_i with $i \in supp(\hat{x})$.
2. Assume that $x(t) \in S_n$ converges to $\hat{x}$, but that $\hat{x}$ is not a Nash equilibrium. Then there exists an i and an $\varepsilon > 0$ such that $(A\hat{x})_i - \hat{x} \cdot A\hat{x} > \varepsilon$. Hence $\frac{\dot{x}_i}{x_i} > \varepsilon$ holds for t sufficiently large, which is not possible.
3. Assume that $\hat{x}$ is Lyapunov stable, but not a Nash equilibrium. Then there exists an i and an $\varepsilon > 0$ such that $(Ax)_i - x \cdot Ax > \varepsilon$ for all x in a neighbourhood of $\hat{x}$ For such x the component $\dot{x}_i$ increases exponentially which is a contradtiction to Lyapunov stability.

□

Theorem 3.7. *(Hofbauer & Sigmund, 1998)*
If $\hat{x}$ is an evolutionarily stable state for the game with payoff matrix A, then it is an asymptotically stable rest point of (12).

Proof. (Hofbauer & Sigmund, 1998)
The theorem is proven by showing that the function $P(x) = \prod x_i^{\hat{x}_i}$ is a strict local Lyapunov function for (12).

1. $P(x)$ has a unique maximum point $\hat{x}$. This follows from Jensen's inequality (68) applied to the strictly convex function $f = -log$:

$$\begin{aligned} log(P(x)) - log(P(\hat{x})) &= \sum_{i=1}^{n} \hat{x}_i log \frac{x_i}{\hat{x}_i} = \sum_{\substack{i=1 \\ \hat{x}_i>0}}^{n} \hat{x}_i log \frac{x_i}{\hat{x}_i} \\ &\leq log \sum_{\substack{i=1 \\ \hat{x}_i>0}}^{n} x_i \leq log \sum_{i=1}^{n} x_i = log\ 1 \\ &= 0. \end{aligned}$$

   As log is strictly increasing, there follows $P(x) \leq P(\hat{x})$ with equality only when $x = \hat{x}$.

2. If $P > 0$, then $\dot{P} > 0$ for all $x \neq \hat{x}$ in some neighbourhood of $\hat{x}$.
   For all $x \in S_n$ with $x_i > 0$ whenever $\hat{x}_i > 0$ there holds $P > 0$ and

$$\begin{aligned} \frac{\dot{P}}{P} = (log\ P)^{\cdot} = \Big(\sum \hat{x}_i log\ x_i\Big)^{\cdot} = \sum_{\hat{x}_i>0} \hat{x}_i \frac{\dot{x}_i}{x_i} = \sum \hat{x}_i((Ax)_i - x \cdot Ax) = \\ = \hat{x} \cdot Ax - x \cdot Ax, \end{aligned}$$

   which is positive if $\hat{x}$ is evolutionarily stable. Hence P is a strict local Lyapunov function for (12) according to Lyapunov's theorem (see theorem A.1).

□

Hawks and Doves

For this example we assume that the different types in the population correspond to the pure strategies of the underlying normal form game ($A = U$ and $n = N$). Let us recall the payoff matrix for the Hawk and Dove game:

$$U = \begin{pmatrix} \frac{V-C}{C} & V \\ 0 & \frac{V}{2} \end{pmatrix}.$$

Inserting $A = U$ into equation (12) assuming $x_1 = x$ and $x_2 = 1 - x$ yields

$$\dot{x} = \frac{1}{2}x(1-x)(V - Cx) \tag{17}$$

with rest points $\bar{x}_1 = (0, 1)$, $\bar{x}_2 = (1, 0)$ and $\bar{x}_3 = \left(\frac{V}{c}, \frac{C-V}{C}\right)$ corresponding to the two strict Nash equilibria in pure strategies and the mixed strategy Nash equilibrium, respectively. This result illustrates the statement of theorem 3.6.1.

3.3 The Lotka-Volterra Equation and Replicator Dynamics

The Lotka-Volterra model serves as the basic model for the dynamics of multiple interacting species. It was first introduced by Alfred Lotka who used it to describe chemical reactions in 1910. In 1926, Vito Volterra published the same equations for modeling the effect of fishery in the Adriatic on predator and prey fish. In the case of two populations, the Lotka-Volterra model is often called "predator-prey model", but applications are diverse and include host-parasite dynamics as well as foodchains and cyclic competition in higher dimensions (Goel et al., 1971).

Definition 3.3. *The general Lotka-Volterra equation for n populations reads*

$$\dot{x}_i = x_i \left(r_i + \sum_{j=1}^{n} a_{ij} x_j \right) \quad i = 1, \ldots, n \tag{18}$$

with

$$\begin{aligned} x_i &\ldots \textit{densitiy of population } i \\ r_i &\ldots \textit{intrinsic growth or decay rates, respectively} \\ a_{ij} &\ldots \textit{effect of the } j\textit{-th on the } i\textit{-th population} \end{aligned}$$

$A = (A_{ij})$ *is called interaction matrix.*

The state $x = (x_1, \ldots, x_n)$ is an element of the space

$$\mathbb{R}^n_+ = \{x = (x_1, \ldots, x_n) \in \mathbb{R}^n \ : \ x_i \geq 0 \text{ for } i = 1, \ldots, n\},$$

whereas the replicator equation is an equation on the simplex S_n. Nonetheless it can be shown that the replicator equation in n variables is equivalent to the Lotka-Volterra equation in $n - 1$ variables.

Theorem 3.8. *(Hofbauer & Sigmund, 1998)*
There exists a differentiable, invertible map from $\hat{S}_n = \{x \in S_n \ : \ x_n > 0\}$ *onto* $\mathbb{R}_+^{n-1}$ *mapping the orbits of the replicator equation* (12) *onto the orbits of the Lotka-Volterra equation*

$$\dot{y}_i = y_i \left(r_i + \sum_{j=1}^{n-1} a'_{ij} y_j \right), \quad i = 1, \ldots, n-1 \tag{19}$$

where $r_i = a_{in} - a_{nn}$ *and* $a'_{ij} = a_{ij} - anj$.

Proof. (Hofbauer, 1981; Hofbauer & Sigmund, 1998)

- The $n-1-$ dimensional Lotka-Volterra equation is defined on $\mathbb{R}_+^{n-1}$. Set $y_n = 1$. Then $\mathbb{R}_+^{n-1} \to \hat{S}_n$ via the transformation

$$x_i = \frac{y_i}{\sum_{j=1}^n y_j}.$$

- The inverse transformation $\hat{S}_n \to \mathbb{R}_+^{n-1}$ is then defined as

$$y_i = \frac{y_i}{y_n} = \frac{x_i}{x_n}.$$

- Let us assume that y_i fulfills the Lotka-Volterra equation (19). Then there holds

$$\begin{aligned}
\dot{x_i} &= \frac{\dot{y}_i \cdot \sum_j y_j - y_i \cdot \sum_j \dot{y}_j}{\left(\sum_j y_j\right)^2} = \\
&= x_i \left(a_{in} - a_{nn} + \sum_{j=1}^{n-1} (a_{ij} - a_{nj}) \frac{x_j}{x_n} - \sum_{j=1}^{n} x_j \left(a_{jn} - a_{nn} + \sum_{k=1}^{n-1} (a_{jk} - a_{nk}) \frac{x_k}{x_n} \right) \right) = \\
&= x_i \left(\sum_{j=1}^{n} a_{ij} x_j - \sum_{j=1}^{n} x_j \sum_{k=1}^{n} a_{jk} x_k \right) \frac{1}{x_n} = \\
&= x_i \left((Ax)_i - x \cdot Ax \right) \frac{1}{x_n}
\end{aligned}$$

  if we set the last row of A, $a_{nj} = 0$ for all j. This can always be achieved due to lemma 3.4. The term $\frac{1}{x_n}$ can be removed by a change in velocity.

- Let us now assume that x_i fulfills the replicator equation (12) and $a_{nj} = 0 \ \forall \ j$.

Then there holds

$$\begin{aligned}
\dot{y}_i = \left(\frac{\dot{x_i}}{x_n}\right) &= \left(\frac{x_i}{x_n}\right)((Ax)_i - (Ax)_n) = \\
&= y_i \left(\sum_{j=1}^{n} a_{ij}x_j - \sum_{j=1}^{n} a_{nj}x_j\right) = \\
&= y_i \left(\sum_{j=1}^{n} a_{ij}y_j\right) x_n = \\
&= y_i \left(a_{in}y_n + \sum_{j=1}^{n-1} a_{ij}y_j\right) x_n = \\
&= y_i \left(a_{in} + \sum_{j=1}^{n-1} a_{ij}y_j\right) x_n
\end{aligned}$$

where the second equality follows from the quotient rule (lemma 3.3). Again, x_n can be removed by a change in velocity.

□

Therefore results about the replicator equation can be directly transferred to the Lotka-Volterra equation and vice versa.

4 Asymmetric Games

So far, only the symmtric case of evolutionary games has been considered. Most real world contests, however, are not symmetrical: Strategies and payoffs differ depending on a contestant's position. For example, these differences can be due to size, gender, age or the status in a group (van Damme, 1987). In this chapter, concepts such as Nash equilibria will be extended to the asymmetric case and replicator dynamics to describe the evolution of asymmetric populations will be discussed.

4.1 Bimatrix Games

In a symmetric game, the players' start positions are the same, they have identical sets of strategies and payoffs. The game can therefore be described by one $n \times n$ payoff matrix. For players in asymmetric games, on the other hand, the starting position matters. If this scenario is restricted to pairwise encounters and a finite set of pure strategies, we speak of bimatrix games (Pfeiffer, 2014).
Players can be in different positions I and II: A contestant in position I has n, a contestant in position II has m pure strategies. The corresponding payoffs are stored in matrices $A \in \mathbb{R}^{n\times m}$ and $B \in \mathbb{R}^{m\times n}$, respectively. If a player in position I uses strategy i against a player in position II using strategy j, the payoff for player I is given by a_{ij}, the payoff for player II is given by b_{ji}.
A mixed strategy for contestant I coincides with a point p in the simplex S_n, a mixed strategy for contestant II with a point q in simplex S_m. The corresponding payoffs for a p versus a q player are then given by $p \cdot Aq$ and $q \cdot Bp$, respectively.

Definition 4.1. *(Hofbauer & Sigmund, 1998)*
A pair $(\hat{p}, \hat{q}) \in S_n \times S_m$ is called a Nash equilibrium, if it satisfies the equations

$$p \cdot A\hat{q} \leq \hat{p} \cdot A\hat{q} \quad \forall\ p \in S_n \tag{20}$$

$$\text{and } q \cdot B\hat{p} \leq \hat{q} \cdot B\hat{p} \quad \forall\ q \in S_m. \tag{21}$$

It is called a strict Nash equilibrium, if strict inequalities hold in (20) and (21) for $p \neq \hat{p}$ and $q \neq \hat{q}$.

In other words, the pair $(\hat{p}, \hat{q})$ is a Nash equilibrium, if $\hat{p}$ is a best answer to $\hat{q}$ and vice versa. The following lemma can be transferred almost directly from the symmetric case (compare lemma 2.1).

Lemma 4.1. *(Hofbauer & Sigmund, 1998)*
A strict Nash equilibrium $(\hat{p}, \hat{q})$ consists of pure strategies.

Proof. Assume that $(\hat{p}, \hat{q})$ is a strict Nash equilibrium with $\hat{p} \neq e_i$ for any vertex of S_n. Then (20) has to hold for any $p \in S_n,\ p \neq \hat{p}$ and especially for $p = e_i$. As $\hat{p}_i \geq 0$ for all i, the inequality may be multiplied by $\hat{p}_i$ without changing its sign. Then the sum over i is taken. Factoring out $\hat{p} \cdot A\hat{q}$ and using the property $\sum_{i=1}^{n} \hat{p}_i = 1$ yields the contradiction $0 < 0$.

$$\begin{aligned} \sum_{i=1}^{n} \hat{p}_i \cdot (A\hat{q})_i - \sum_{i=1}^{n} \hat{p}_i \cdot (\hat{p} \cdot A\hat{q}) < 0 \\ \Leftrightarrow \left(1 - \sum_{i=1}^{n} \hat{p}_i\right) \cdot (\hat{p} \cdot A\hat{q}) < 0 \\ \Leftrightarrow 0 < 0. \end{aligned}$$

□

4.2 Game Dynamics

In a similar approach as in section 3 we introduce differential equations for asymmetric games. The derivation below follows Hofbauer & Sigmund (1998).

- Players in position I form population X, players in position II form population Y.
- Let the populations be divided in types $E_i,\ i = 1, \ldots, n$ and $F_j,\ j = 1, \ldots, m$, respectively. Let $x \in S_n$ denote the frequencies of the types E_i in population X and $y \in S_m$ the frequencies of the types F_j in population Y.
- The average fitness of population X is denoted by $x \cdot Ay$ and the average fitness of population Y is denoted by $y \cdot Bx$.

Equating the rate of increase $\frac{\dot{x}_i}{x_i}$ of type E_i to the difference between its payoff and the average payoff leads to the first equation (22). Applying the same thought to population Y leads to the second equation (23).

$$\dot{x}_i = x_i((Ay)_i - x \cdot Ay) \qquad i = 1, \ldots, n \tag{22}$$

$$\dot{y}_i = y_i((Bx)_j - y \cdot Bx) \qquad j = 1, \ldots, n \tag{23}$$

The state space $S_n \times S_m$ is invariant under (22)-(23) (compare lemma 3.1). The boundary faces of $S_n \times S_m$ are obtained by setting some x_i or y_j to zero. Every one of those faces can then be divided into boundary and interior- the boundary formed by faces again.

Hence there is no loss of generality in restricting (22)-(23) to sets of the type

1. $S_n \times \{f_1\}$ with $f_1 = \{1, 0, \ldots, 0\} \in S_m$
2. int $S_n \times S_m$.

The formulas above describe two cases

1. at least one population consists of only one type
2. both populations consist of several types

and all other restrictions of this type are of the same form (Hofbauer & Sigmund, 1998). The first case leads to the dynamics

$$\dot{x}_i = x_i(a_{1i} - \sum_{j=1}^{n} a_{1j}x_j). \tag{24}$$

The idea that type i will succeed over the other types in the long term if its payoff a_{1i} is higher than the average payoff comes quite naturally and this is indeed the case:

Lemma 4.2. *Whenever a_{1i} in equation (24) is not maximal, there holds $x_i \to 0$.*

Proof. see Hofbauer & Sigmund (1998) □

Let us now consider case 2. The rest points in the interior $int\ S_n \times S_m$ are solutions of

$$(Ay)_1 = \ldots = (Ay)_n \qquad \sum_{j=1}^{m} y_j = 1 \tag{25}$$

$$(Bx)_1 = \ldots = (Bx)_m \qquad \sum_{i=1}^{n} x_i = 1 \tag{26}$$

and are strictly positive. There are two possible cases:

- $n > m$. Solutions of (25) only exist if matrix A is degenerate. Solutions of (26) form a linear manifold of dimension $n-m$. Hence the set of restpoints in $intS_n \times S_m$ is either empty or contains an $(n-m)-$dimensional subset.
- $n = m$. In this case, an isolated rest point can exist. If it exists, it is unique and cannot be a source or a sink (Hofbauer & Sigmund, 1998).

4.2.1 Nash Equilibria and Stability

In the special case $n = m = 2$, we can assume without loss of generality (see lemma 3.4) that matrices A and B are of the form

$$A = \begin{pmatrix} 0 & a \\ b & 0 \end{pmatrix}, \quad B = \begin{pmatrix} 0 & c \\ d & 0 \end{pmatrix}.$$

Equations (22)-(23) reduce to

$$\dot{x} = x(1-x)(a-(a+b)y) \tag{27}$$
$$\dot{y} = y(1-y)(c-(c+d)x) \tag{28}$$

and have a unique mixed equilibrium in the interior: $P = \left(\frac{c}{c+d}, \frac{a}{a+b}\right)$. Schuster & Sigmund (1981) have reached a qualitative result about this equilibrium:

Theorem 4.3. *(Schuster & Sigmund, 1981)*
Let the matrices A and B describe a 2×2 bimatrix game with a unique and completely mixed Nash equilibrium. This equilibrium is a stable fixed point of the system (22)-(23) *that is not asymptotically stable. The orbits of* (22)-(23) *are closed and have the Nash equilibrium as their time average.*

Proof. (Schuster & Sigmund, 1981)
We only consider the cases $ab < 0$ and $cd > 0$ as otherwise $\dot{x}$ or $\dot{y}$, respectively, do not change sign and x (y) would either be constant or converge to 0 or 1. To analyse the stability of rest point P, the Jacobian matrix of (27)-(28) is evaluated at P

$$J = \begin{pmatrix} 0 & -(a+b)\frac{cd}{(c+d)^2} \\ -(c+d)\frac{ab}{(a+b)^2} & 0 \end{pmatrix}$$

and the eigenvalues are computed:

$$\lambda_{1,2} = \pm\sqrt{\frac{abcd}{(a+b)(c+d)}}$$

Under the assumption that $ac > 0$ holds, P is a saddle and the theorem of Poincaré-Bendixon A.3 implies that there is no closed orbit in the interior of the unit square. Depending on the sign of a, either $(1,0), (0,1), (0,0)$ or $(1,1)$ are sinks and almost all orbits in the interior will have these sinks as ω-limits. If $ac < 0$, the eigenvalues $\lambda_{1,2}$ are imaginary and P is of center type. Then the interior rest point $P = \left(\frac{c}{c+d}, \frac{a}{a+b}\right)$ of

(27)-(28) is stable, but not asymptotically stable. Consider the function

$$V(x,y) = x^c(1-x)^d y^{-a}(1-y)^{-b}$$

which has a unique maximum at P. Furthermore there holds

$$\dot{V} = \frac{\partial V}{\partial x}\dot{x} + \frac{\partial V}{\partial y}\dot{y} = 0,$$

hence V is constant along every orbit. The orbits are level curves of V and therefore periodic and closed. Equation (27) is equivalent to

$$\frac{\dot{x}}{x(1-x)} = a - (a+b)y = \log \frac{\dot{x}}{1-x}$$

Integrating along an orbit of period T, using $x(0) = x(T)$ yields

$$\begin{aligned} 0 = \log \frac{x(t)}{1-x(t)} \Big|_{t=0}^{T} &= aT - (a+b)\int_0^T y(t)dt \\ \Rightarrow \frac{1}{T}\int_0^T y(t)dt &= \frac{a}{a+b}. \end{aligned}$$

The identity for the time average of x follows analogously. □

The following result can be transferred directly from the symmetric case (see theorem 3.6):

Theorem 4.4. *(Hofbauer & Sigmund, 1998)*

1. *If $(\hat{x},\hat{y}) \in S_n \times S_m$ is a Nash equilibrium of the game described by the payoff matrix A, then $\hat{x}$ is a rest point of* (27)-(28).
2. *If $(\hat{x},\hat{y})$ is the ω-limit of an orbit in int $S_n \times S_m$, then $(\hat{x},\hat{y})$ is a Nash equilibrium.*
3. *If $(\hat{x},\hat{y})$ is Lyapunov stable, then it is a Nash equilibrium.*

4.2.2 Nash-Pareto pairs

There is no straightforward way to extend the concept of evolutionarily stable strategies to asymmetric games as mixed strategy Nash equilibria for bimatrix games cannot be evolutionarily stable. However, it was shown by Schuster & Sigmund (1981) that a unique mixed strategy Nash equilibrium is an asymptotically stable rest point of the

dynamics (22)-(23) (see theorem 4.3), therefore these mixed equilibrium points have to be evolutionarily relevant in some sense.

This can be solved by introducing *Nash-Pareto pairs*, a concept relaxing the notion of an ESS for mixed strategy equilibria of bimatrix games. (Hofbauer & Sigmund, 1998).

Definition 4.2. *A pair of strategies (p, q) is called a Nash-Pareto pair for an asymmetric game with payoff matrices A and B if two conditions hold:*

1. *Equilibrium condition:*

$$p \cdot Aq \geq x \cdot Aq \text{ and} \tag{29}$$
$$q \cdot Bp \geq y \cdot Bp \quad \forall\ (x, y) \in S_n \times S_m \tag{30}$$

2. *Stability condition: For all states $(x, y) \in S_n \times S_m$ for which equality holds in 1, there holds*

$$\text{if } x \cdot Ay > p \cdot Ay \text{ then } y \cdot Bx < q \cdot Bx \tag{31}$$
$$\text{and if } y \cdot Bx > q \cdot Bx \text{ then } x \cdot Ay < p \cdot Ay. \tag{32}$$

The first condition simply ensures that the pair (p, q) is a Nash equilibrium. If there was another strategy (x, y) such that both players could maximise their payoffs at the same time, they would surely switch to it and (p, q) would not be stable in any sense. The idea behind the second condition is that it is impossible for both players to benefit from a switch concurrently- one of them will always be put at disadvantage (Hofbauer & Sigmund, 1998).

Summary

Figure 2 below is adapted from Schuster et al. (1981) and describes the development of the game theoretical model and its connection to game dynamics. Figure 3 illustrates lemmas 3.6 and 4.4: In the symmetric as well as in the asymmetric case, there is a relationship between the concept of a Nash equilibrium and the results of the qualitative analysis of the differential equations associated with game dynamics.

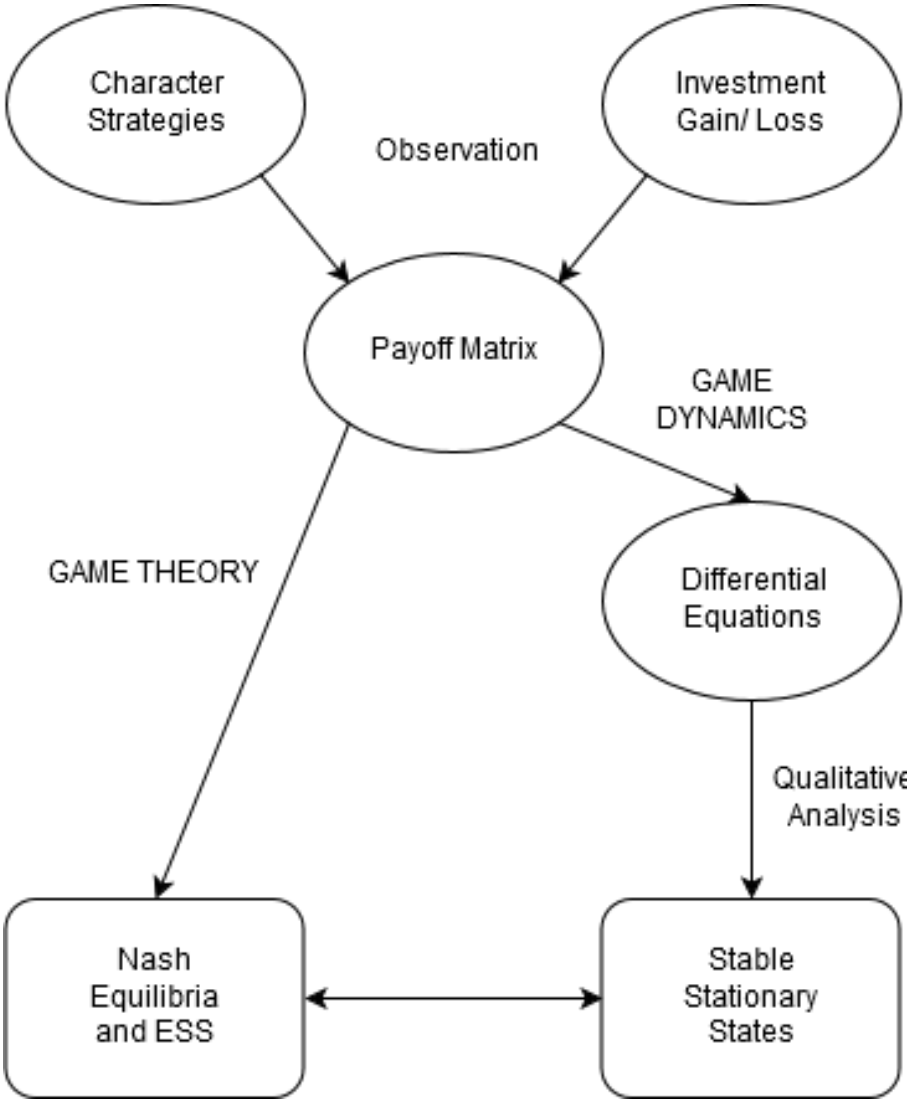

Figure 2: Game Theory and Game Dynamics.

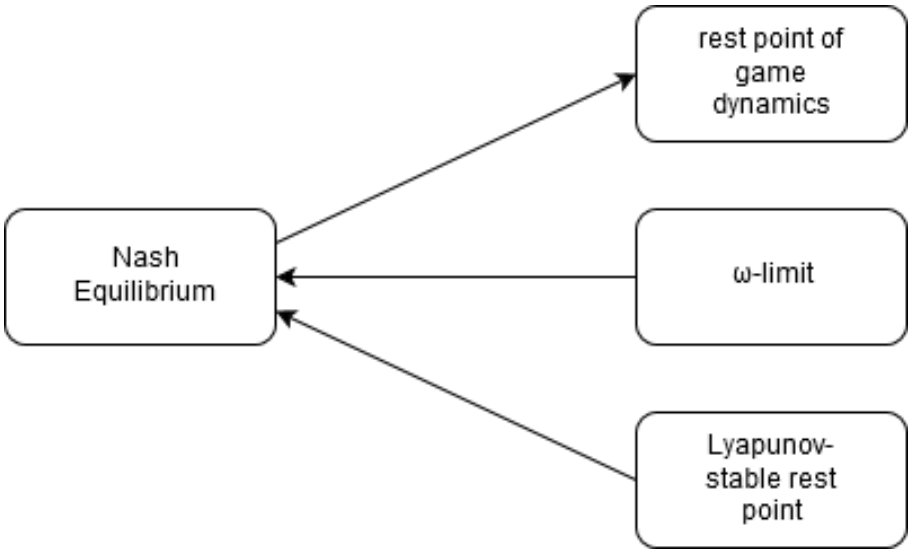

Figure 3: Rest points and Nash equilibria.

5 Imitation Dynamics

Replicator dynamics model natural selection via inheritence of behaviour, which is not an appropriate assumption for human populations. In a human society it is much more likely that successful behaviour is imitated by others (Hofbauer & Sigmund, 1998). Children start mimicking the actions of their parents at a very young age and continue to adapt other (more successful) ways for the rest of their lives. There are various reasons for this behaviour that are explored in specialised literature for psychology. In this chapter, a model for imitation behaviour will be introduced and its similarity to replicator dynamics explored.

Imitation Rules

Assume we have a symmetric game with an $n \times n$ payoff matrix A and $R_1, \dots, R_n$ pure strategies. At time t, these pure strategies are adapted by a population of players with frequency $x_i(t)$ and the state of a population is thereby given by a point in the simplex $x \in S_n$. The payoff of a R_i strategist is given by $(Ax)_i$ and the average payoff is given by $x \cdot Ax$.

Suppose now that one player is picked out and is challenged to change his or her strategy. He or she then samples another player randomly and mimics his or her strategy with a certain probability. This scenario is described by the equation

$$\dot{x}_i = x_i \sum_j [f_{ij}(x) - f_{ji}(x)] x_j \tag{33}$$

where f_{ij} is defined as the rate at which a R_j strategist switches to R_i and it is assumed that $f_{ij}(x)$ depends on the expected payoff: $f_{ij}(x) = f((Ax)_i, (Ax)_j)$. The function f is called imitation rule.

Imitate the better

The simplest imitation rule one can use is "imitate the better". It reads

$$f(u, v) = \begin{cases} 0, & u < v \\ 1, & u > v \end{cases}. \tag{34}$$

The disadvantage of this rule, however, is its discontinuity.

Proportional Imitation Rule

This rule says "imitate actions that perform better, with a probability proportional to the expected gain" (Hofbauer & Sigmund, 1998). We define

$$f(u,v) = \Phi(u-v) \text{ with } \Phi \text{ monotonically increasing and} \tag{35}$$

$$\Psi(u-v) = \Phi(u-v) - \Phi(-u+v) \text{ with } \Psi \text{ odd and strictly increasing} \tag{36}$$

The imitation equation then reads

$$\dot{x}_i = x_i \sum_j x_j \Psi((Ax)_i - (Ax)_j). \tag{37}$$

With the choice $\Phi(u) = max(0,u)$ we obtain $\Psi(u) = u$ and the replicator equation (12):

$$\dot{x}_i = x_i((Ax)_i - x \cdot Ax).$$

In the limit case $\alpha \to 0$ the "imitate the better" rule is obtained. It has been shown by Björnerstedt & Weibull (1996) that the proportional imitation rule is in some way optimal. In section 6.3 we will use these dynamics to model vaccination behaviour in humans.

Other Imitation Rules

There are other versions of equation (33), e.g. with functions f only depending on the success of the imitated player or the imitating player, respectively. These have been studied by Björnerstedt & Weibull (1996) in more detail.

6 Applications

6.1 Modeling Multiple Myeloma Bone Disease

Cancer is a collective term for "diseases in which abnormal cells divide without control and can invade nearby tissues" (U.S. Department of Health and Human Services, 2018). Multiple myeloma (MM) begin with a chain of mutations in white blood cells, plasma cells that normally produce antibodies (Raab et al., 2009). Researchers have shown that a "supportive" bone marrow microenvironment plays an essential role in the pathogenesis of multiple myeloma, therefore evolutionary game theory can be used to better understand the interactions between tumour cells and the environment. The mutant cells may be seen as intruders to a population of normal cells (Pacheco et al., 2014).
Pacheco, Santos and Dingli (2014) have motivated the application of evolutionary game theory to model tumour progression and used it to describe the dynamics of multiple myeloma. In order to do this, several assumptions need to be made:

1. The normal as well as the mutant cell population need to be large enough to replace absolute numbers with cell frequencies.

2. Every cell interacts with any other cell. This assumption restricts the use of evolutionary game theory to tumours with high cell motility. Hence, the proposed model cannot be applied to solid tumours, but it is feasible for blood cells and multiple myeloma (MM), especially.

Overview of cell types involved

- osteoblast (OB) cells: bone formation
- osteoclast (OC) cells: bone resorption
- multiple myeloma (MM) cells: malignant tumour cell

6.1.1 Normal Bone Remodelling

In a healthy bone marrow, the bone metabolism is determined by a dynamic balance between osteoclast (OC) cells and osteoblast (OB) cells, OC cells responsible for bone resorption and OB cells responsible for bone formation. The interaction between these two types is complex and depends on cytokines, small proteins that affect communication between cells (Pacheco et al., 2014; U.S. Department of Health and Human Services, 2018).

According to Pacheco, Santos and Dingli (2014), this dynamic balance can be modeled assuming there is a game with a stable balance between the two populations OC and OB. In this case, the payoff matrix reads:

$$A = \begin{pmatrix} 0 & a \\ e & 0 \end{pmatrix}, \quad a, e > 0.$$

There is no pure Nash equilibrium with respect to A, but a mixed one for $(\hat{x}_1, \hat{x}_2) = \left(\frac{a}{a+e}, \frac{e}{a+e}\right)$. Let x_1 denote the frequency of OC cells and x_2 the frequency of OB cells. The replicator equations then read:

$$\dot{x}_1 = x_1(ax_2 - (a+e)x_1x_2) \tag{38}$$

$$\dot{x}_2 = x_2(ex_1 - (a+e)x_1x_2) \tag{39}$$

with rest points $\bar{x}^1 = (0,1), \bar{x}^2 = (1,0)$ and $\bar{x}^3 = (\frac{a}{a+e}, \frac{e}{a+e})$.

Stability Analysis

To analyse the stability of the rest points, we compute the Jacobi matrix for the system (38)-(39)

$$J(x) = \begin{pmatrix} ax_2 - 2(a+e)x_1x_2 & ax_1 - (a+e)x_1^2 \\ ex_2 - (a+e)x_2^2 & ex_1 - 2(a+e)x_1x_2 \end{pmatrix}. \tag{40}$$

Substituting $\bar{x}^1$ yields

$$J(\bar{x}^1) = \begin{pmatrix} a & 0 \\ -a & 0 \end{pmatrix}$$

with eigenvalues $\lambda_1 = 0$ and $\lambda_2 = a > 0$, hence $\bar{x}^1$ is unstable. Substituting $\bar{x}^2$ yields

$$J(\bar{x}^2) = \begin{pmatrix} 0 & -e \\ 0 & e \end{pmatrix}$$

with eigenvalues $\lambda_1 = 0$ and $\lambda_2 = e > 0$, hence $\bar{x}^2$ is unstable, too. Inserting $\bar{x}^3$, on the other hand, leads to

$$J(\bar{x}^3) = \begin{pmatrix} -\frac{ae}{a+e} & 0 \\ 0 & -\frac{ae}{a+e} \end{pmatrix}$$

with eigenvalue $\lambda = -\frac{ae}{a+e} < 0$ and is therefore a stable rest point of (38)-(39).

6.1.2 Pathological Bone Turnover

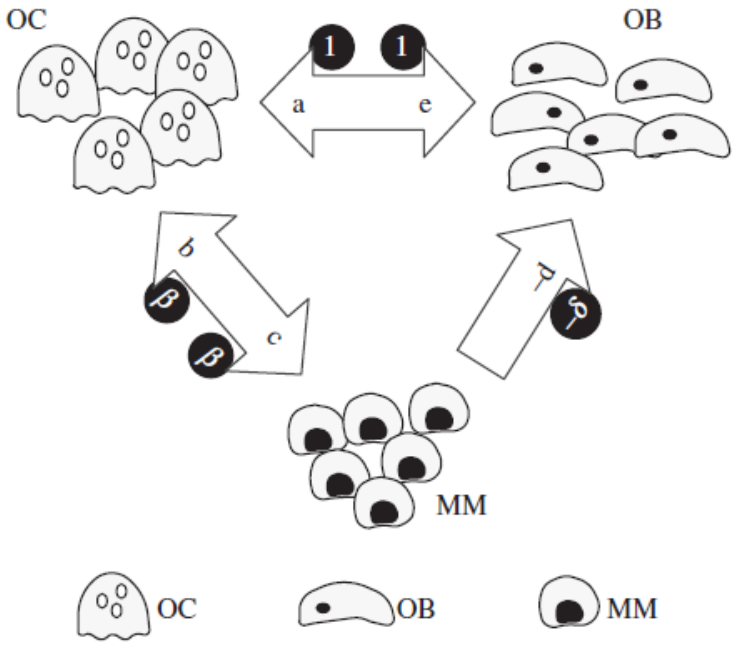

Figure 4: Schematic representation of pathological bone turnover. From "The ecology of cancer from an evolutionary game theory perspective" by J. M. Pacheco, F. C. Santos, and D. Dingli, 2006, *Interface Focus, 4*(4) p. 5.

The transformation of plasma cells into malignant tumour cells is a complex process and requires several mutations (Raab et al., 2009). Let us therefore assume that the first myeloma (MM) cell has already appeared. The presence of MM cells now disrupts the equilibrium between OC and OB cells in several ways (see Fig: 4):

- MM cells:
  - produce cytokines that activate OC cells and increase bone resorption,
  - produce cytokines that suppress OB activity (bone formation) and
  - are unaffected by the presence of OB cells.
- OC cells stimulate increase of MM cells.
- Interactions between same cell types are neutral.

A more precise description of the types of messenger substances secreted and the influence on each cell type is omitted here due to space reasons but can be found in Pacheco, Santos, and Dingli (2014).

Knowing the dependencies above, the model for OB and OC cells can be expanded to include MM cells and the new payoff matrix reads:

$$A = \begin{pmatrix} 0 & a & b \\ e & 0 & -d \\ c & 0 & 0 \end{pmatrix}, \quad a, b, c, d, e > 0.$$

Applying a projective transformation does not change the nature of the rest points (see theorem 3.5), and taking $\beta = \frac{c}{e}$ and $\delta = \frac{dc}{be}$ yields the minimum payoff matrix containing only two unknowns:

$$A_{min} = \begin{pmatrix} 0 & 1 & \beta \\ 1 & 0 & -\delta \\ \beta & 0 & 0 \end{pmatrix}, \quad \beta, \delta > 0.$$

Let x_1 denote the frequency of OC cells, x_2 of OB, and x_3 of MM cells. Then the system of replicator equations (12) for A_{min} reads:

$$\dot{x}_1 = x_1(x_2 + \beta x_3 - 2x_1x_2 - 2\beta x_1x_3 - \delta x_2x_3) \tag{41}$$

$$\dot{x}_2 = x_2(x_1 - \delta x_3 - 2x_1x_2 - 2\beta x_1x_3 - \delta x_2x_3) \tag{42}$$

$$\dot{x}_3 = x_3(\beta x_1 - 2x_1x_2 - 2\beta x_1x_3 - \delta x_2x_3) \tag{43}$$

6.1.3 Simulation

The parameter β denotes the ratio $\frac{\text{increase of MM activity}}{\text{increase of OB activity (bone formation)}}$. Therefore the expected behaviour in the case $\beta < 1$ would be a decline of MM cells and a return to the healthy equilibrium between OC and OB cells. The case $\beta > 1$ describes a reduced activity of OB cells, i.e. bone formation, and a heavier tumour load. In this case we expect the restpoint between OC and MM to be stable.

To analyse the behaviour in the case $\beta = 1$, let us include δ in our consideration. The parameter δ denotes the ratio $\beta \cdot \frac{\text{suppression of OB cells (bone formation)}}{\text{increase of OC activity (bone resorption)}}$. High δ corresponds to suppressed bone formation, while bone resorption is increased, which can be observed clinically as myeloma- induced osteoporosis Pacheco et al. (2014). High δ will accelerate the progress of the disease, while low δ can slow it down.

The expectations above were tested by simulating the evolution of the dynamical system (41)-(43) over time. This was done using Matlab 2017b on a Samsung Chronos 7 computer, the code used for generating the images below can be found in appendix A.2. For the simulation it has been assumed that a mutation has already occured (1% of observed cells are MM cells); this scenario has been tested for a number of parameters.

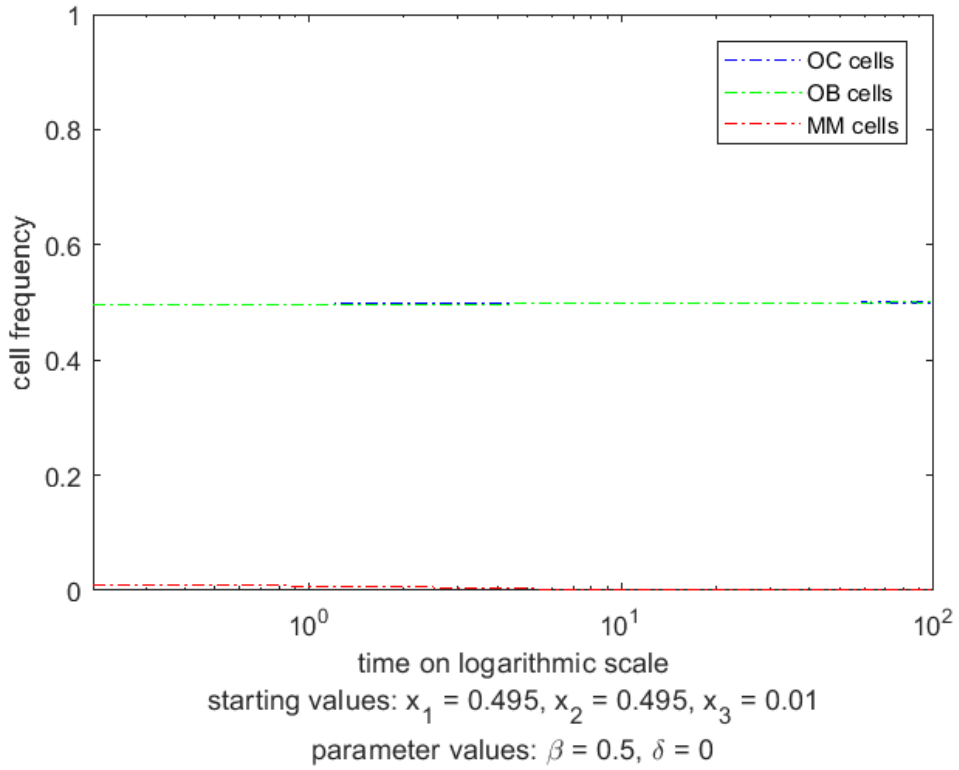

Figure 5: Stable equilibrium between OC and OB cells.

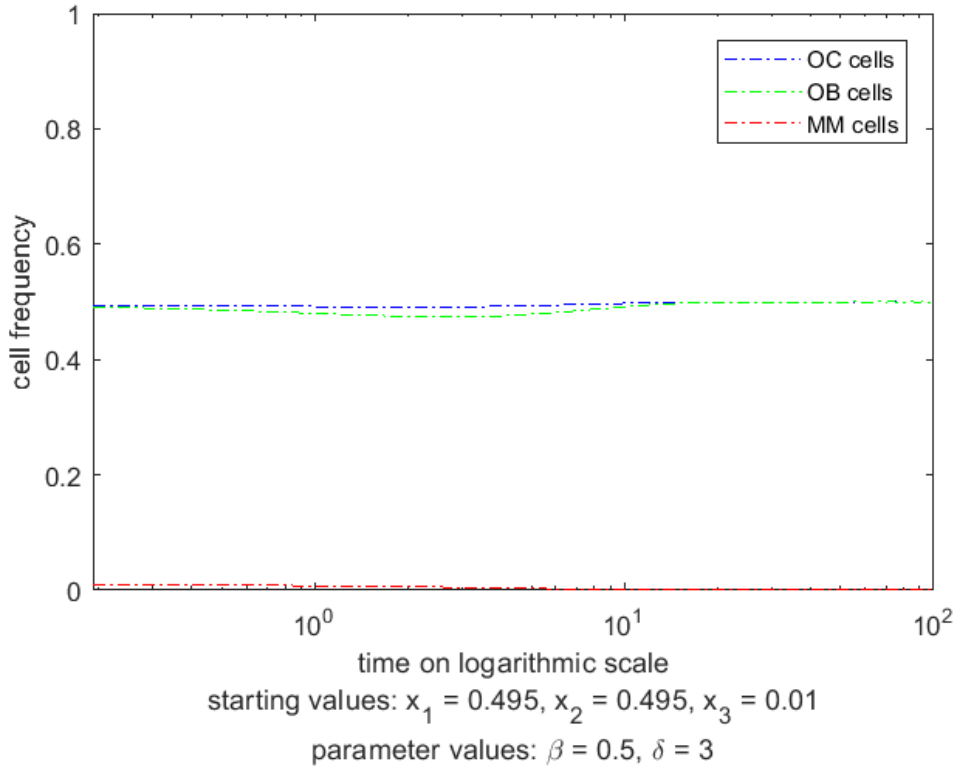

Figure 6: Stable equilibrium between OC and OB cells.

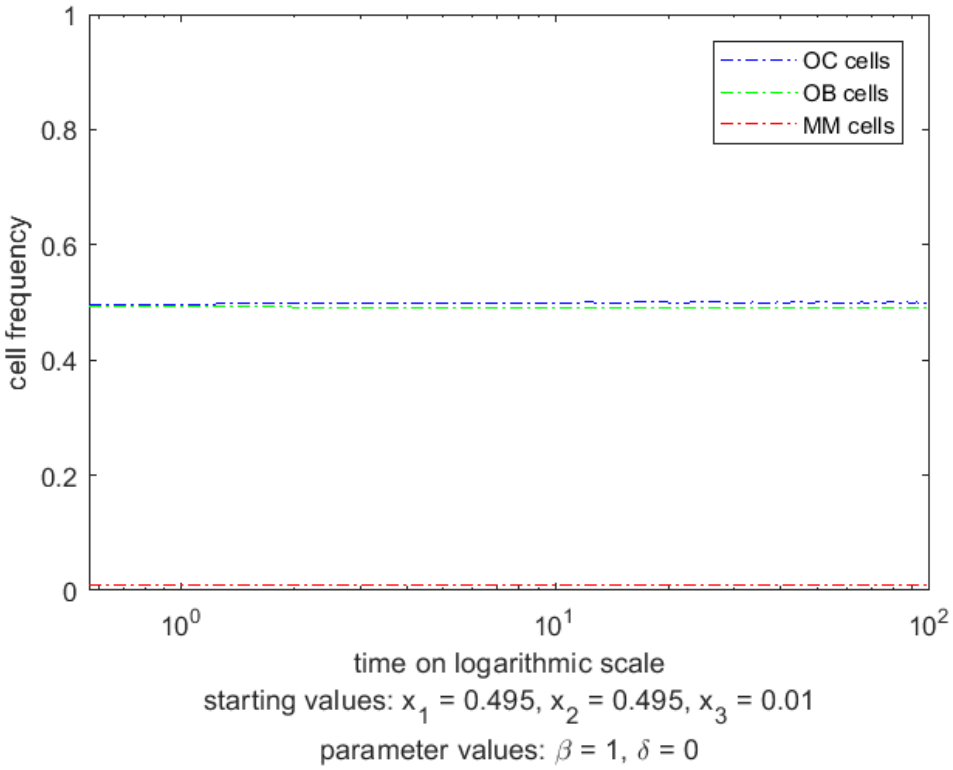

Figure 7: Stable equilibrium between OC and OB cells.

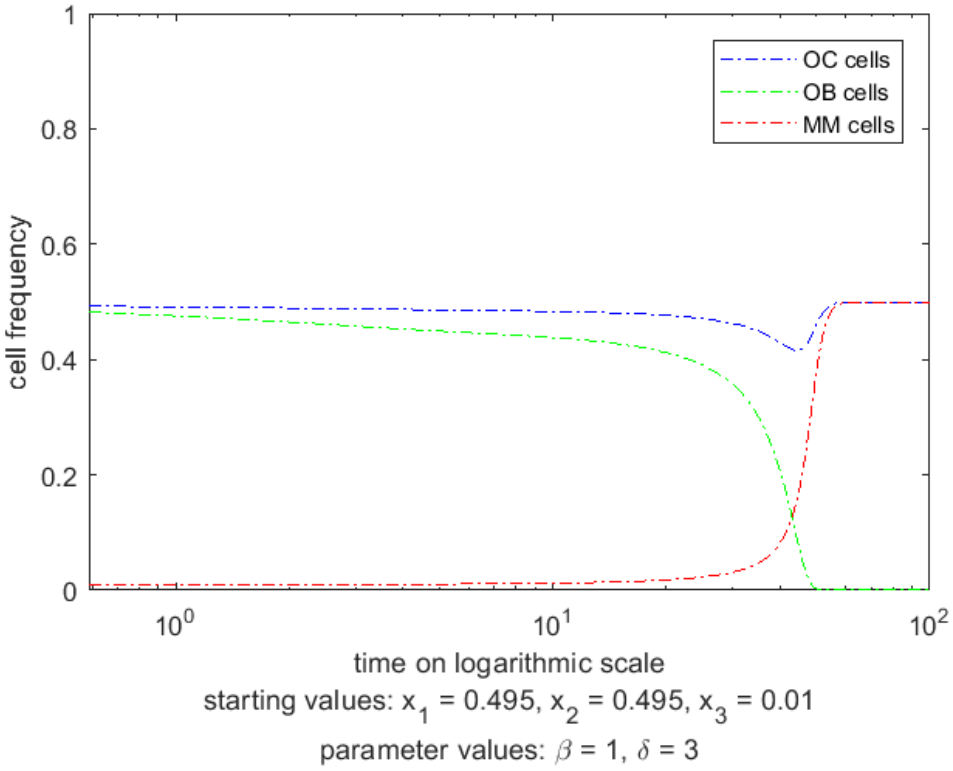

Figure 8: The equilibrium between OC and OB cells is not stable, the dynamics lead to an equilibrium between OC and MM cells.

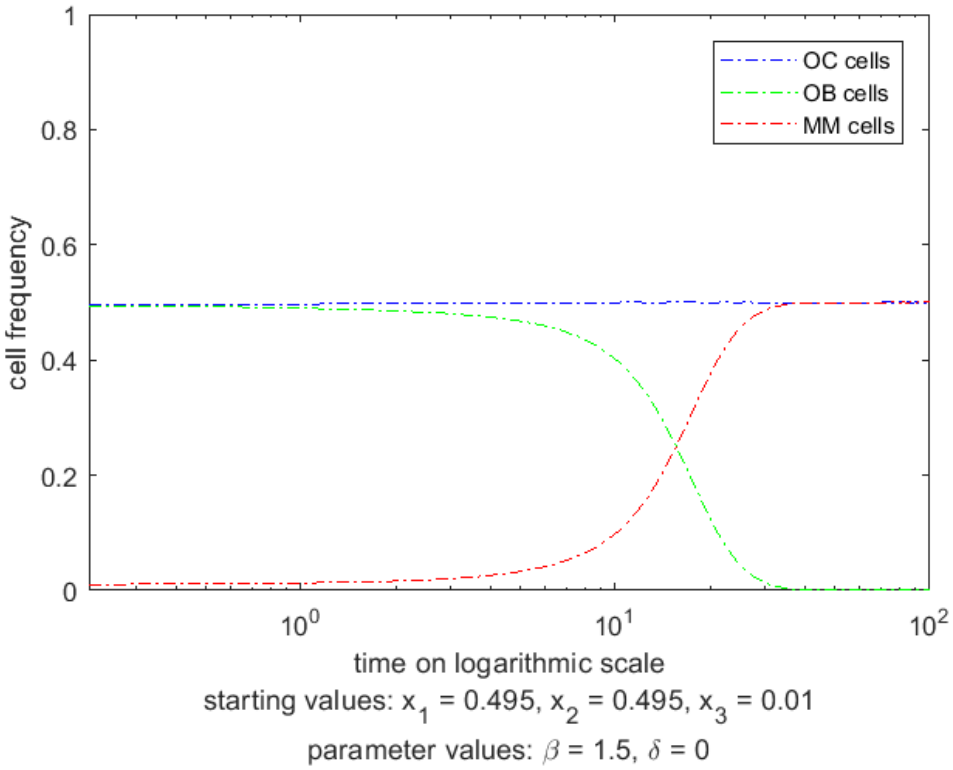

Figure 9: Stable equilibrium between OC and MM cells.

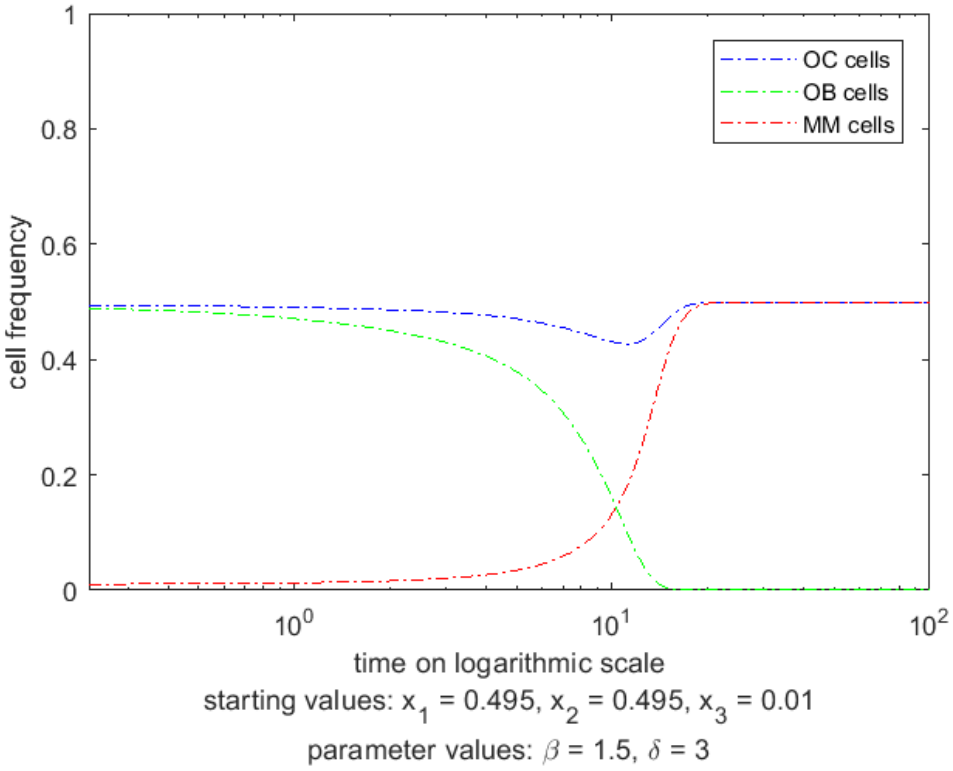

Figure 10: Stable equilibrium between OC and MM cells. Higher δ increases the velocity of MM cell progression.

6.1.4 Results and Recommendations

The results obtained meet the expectations explained in section 6.1.3: If the ratio $\beta < 1$, the disease cannot progress independently from the value of δ. If $\beta = 1$, δ is important: In the limit case $\delta = 0$, the tumour cells cannot reproduce, in the case $\delta > 1$, they do and an equilibrium between OC and MM cells is reached. If $\beta > 1$, δ does not determine whether MM cells spread, but influences the speed of tumour growth positively.

Several conclusions can be drawn from these results:

- The aim of a therapy should be to suppress or reduce β and δ to decrease the speed of myeloma progression.
- Therapy that decreases β, reduces bone destruction and disease progression speed.
- Therapy that decreases δ, reduces the myeloma burden and improves bone mass.
- Therapy that reduces OC growth can indirectly benefit the patient as OC cells contribute positively to MM cell growth.

Pacheco et al. (2014)

Although the dynamics introduced in this chapter describe the evolution of multiple myeloma as observed clinically very well, Pacheco et al. (2014) point out that the parameters (payoff entries a, b, c, d, e) can vary widely between patients. Hence the location of the rest points are patient specific. In the normal case $\beta > 1$, however, the prognosis is very negative, which can also be observed clinically. The model can be extended to include a bone marrow transplant as a therapy, which improves the prognosis significantly (Pacheco et al., 2014).

6.2 Immune Response to Viruses

Viruses are defined as "Intracellular parasites that depend on the host cell to survive and replicate" (Nowak et al., 1996). There are several biologically important questions concerned with viral replication dynamics, virus-host cell interaction and the consequences of immune response. Fenton & Perkins (2010) have explored several basic models describing said dynamics.
In order to do this, some simplifying assumptions have to be made:

1. The virus load determines the severity of the disease.
2. The human immune response is complex and has several components. However, we will only focus on CTL cells (cytotoxic T lymphocytes) that are crucial for the antiviral defense and attack virus- infected cells.
3. CTLs limit virus load.

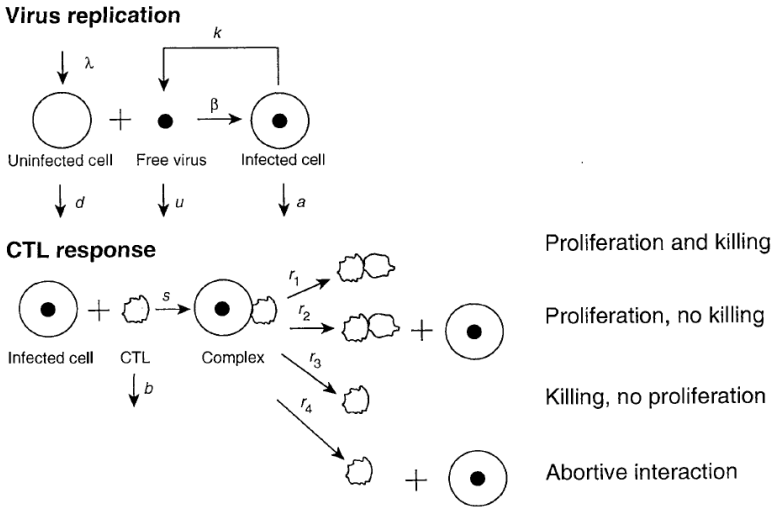

Figure 11: Schematic representation of virus replication and immune response. From "Population dynamics of immune responses to persistent viruses" by M. A. Nowak, S. Bonhoeffer, A. M. Hill, R: Boehme, H. C. Thomas and H. McDade, 1996, *Proceedings of the National Academy of Sciences, 93*(9) p. 75.

Three different models will be explained in detail: The first and easiest one assumes that the virus replicates within the host, the second and third one considers the more complicated relationship shown in figure 11. The next definition is of great importance in epidemology and will be needed throughout the chapter.

Definition 6.1. *The basic reproductive ratio R_0 is defined as the number of newly infected cells arising from any one infected cell.*

6.2.1 Predator-Prey-Model

Fenton & Perkins (2010) regard cells as players in the game immune system versus parasites (e.g. viruses). It is assumed that parasite cells replicate within the host. The model further assumes long-lived immune memory, therefore a constant immune response to viruses. The active cells of the immune system are in the role of the predators, the virus cells are the prey. The variables are defined as follows:

- Let P denote the parasite cell load, and I denote the load of active immune system cells.
- Let α denote the growth rate of the parasite, β the consumption rate of parasites by the immune system, γ the immune system stimulation rate through contact with parasites and δ the decay rate of immune system cells.

A classic Lotka-Volterra model is derived:

$$\frac{dP}{dt} = \alpha P - \beta IP \tag{44}$$

$$\frac{dI}{dt} = \gamma \beta IP - \delta I \tag{45}$$

The model (44)-(45) is a good approximation for some immune system- virus interactions, even though it is quite simple. But as the replication process for most viruses is more complicated, this basic model needs to be modified. The model used by Nowak et al. (1996) to describe the process shown in figure 11 is investigated in the following sections.

6.2.2 Virus Replication

The virus replication model is a classic host- parasite model and contains three variables. It was introduced by Nowak et al. (1996) and models the situation illustrated in figure 11 without immune response.

- Uninfected cells are denoted by x, they are reproduced with rate λ and die with rate d.
- Infected cells are denoted by y, they are reproduced with rate βxv and decline by rate ay.
- Free virus particles are denoted by v, they are reproduced with rate ky and die with rate uv.

The basic reproductive ratio of the virus reads $R_0 = \frac{\beta\lambda k}{adu}$.

The resulting system of differential equations reads:

$$\dot{x} = \lambda - dx - \beta xv \tag{46}$$

$$\dot{y} = \beta xv - ay \tag{47}$$

$$\dot{v} = ky - uv \tag{48}$$

with rest points $x_1^* = \frac{\lambda}{d},\ y_1^* = 0$ and $v_1^* = 0$ and $x_2^* = \frac{au}{\beta k},\ y_2^* = \frac{\lambda}{a} - \frac{du}{\beta k}$ and $v_2^* = \frac{\lambda k}{au} - \frac{d}{\beta}$.

Stability Analysis

To analyse the stability of the rest points, we compute the Jacobi matrix of the system (46)-(48).

$$J = \begin{pmatrix} -d - \beta v & 0 & -\beta x \\ \beta v & -a & \beta x \\ 0 & k & -u \end{pmatrix} \tag{49}$$

Substituting x_1^*, y_1^* and v_1^* yields:

$$J\left(\frac{\lambda}{d}, 0, 0\right) = \begin{pmatrix} -d & 0 & -\frac{\beta\lambda}{d} \\ 0 & -a & \frac{\beta\lambda}{d} \\ 0 & k & -u \end{pmatrix}$$

with eigenvalues $\mu_1 = -d$ and $\mu_{2,3} = -\frac{a+u}{2} \pm \sqrt{\left(\frac{a-u}{2}\right)^2 + auR_0}$. Under the assumption $R_0 = \frac{\beta k\lambda}{dau} < 1$, i.e. less than one newly infected cell arising from any one infected cell, (x_1^*, y_1^*, v_1^*) is a stable rest point. This can be shown as follows:

- $\mu_1 = -d < 0$ follows directly.

- Next we show $\mu_2 < 0$:

$$\begin{aligned}
\mu_2 &= -\frac{a+u}{2} - \sqrt{\left(\frac{a+u}{2}\right)^2 - au + auR_0} \\
&= -\frac{a+u}{2} - \sqrt{\left(\frac{a+u}{2}\right)^2 - au(1-R_0)} \\
&< -\frac{a+u}{2} - \sqrt{\left(\frac{a+u}{2}\right)^2 - au} \\
&= -\frac{a+u}{2} - \frac{a-u}{2} = -a < 0.
\end{aligned}$$

- Last, we prove $\mu_3 < 0$:

$$\begin{aligned}
\mu_3 &= -\frac{a+u}{2} + \sqrt{\left(\frac{a+u}{2}\right)^2 - au + au \cdot R_0} \\
&< -\frac{a+u}{2} + \sqrt{\left(\frac{a+u}{2}\right)^2 - au + au} \\
&= -\frac{a+u}{2} + \frac{a+u}{2} = 0.
\end{aligned}$$

Substituting x_2^*, y_2^* and v_2^* yields:

$$J\left(\frac{au}{\beta k}, \frac{\lambda}{a} - \frac{du}{\beta k}, \frac{\lambda k}{au} - \frac{d}{\beta}\right) = \begin{pmatrix} -\frac{\beta\lambda k}{au} & 0 & -\frac{au}{k} \\ \frac{\beta\lambda k}{au} - d & -a & \frac{au}{k} \\ 0 & k & -u \end{pmatrix}$$

The eigenvalues of this matrix are much harder to compute as a cubic equation has to be solved. Using a computer algebra system one can compute the eigenvalues and show that (x_2^*, y_2^*, v_2^*) is stable if the condition $R_0 > 1$ holds.

6.2.3 Immune Response

The basic model (46)-(47) is now extended with a variable describing the immune response against infected cells.

- The CTL response is denoted by z, the CTL responsiveness is denoted by c. CTL cells decay at rate b and kill infected cells at rate pyz.

The resulting system of differential equations reads:

$$\dot{x} = \lambda - dx - \beta xv \tag{50}$$

$$\dot{y} = \beta xv - ay - pyz \tag{51}$$

$$\dot{v} = ky - uv \tag{52}$$

$$\dot{z} = cyz - bz \tag{53}$$

with rest points $(x_1^*, y_1^*, v_1^*, 0)$ and $(x_2^*, y_2^*, v_2^*, 0)$ as given above and an additional one:

$$x_3^* = \frac{\lambda cu}{cdu + \beta bk}, y_3^* = \frac{b}{c}, v_3^* = \frac{bk}{cu}, z_3^* = \frac{1}{p}\left(\frac{\lambda \beta ck}{cdu + \beta bk} - a\right) \tag{54}$$

Analysis

According to Nowak et al. (1996), there are two cases for the convergence of system (50)-(53) to equilibria:

1. $cy_2^* < b$. Even though the immune system response may be activated, the system will converge to the equilibrium $(x_2^*, y_2^*, v_2^*, 0)$ without immune system response.

2. $cy_2^* > b$. In this case, the system exhibits damped oscillations to the equilibirum

$$\begin{aligned} x_3^* &= \frac{\lambda cu}{cdu + \beta bk} \\ y_3^* &= \frac{b}{c} \\ v_3^* &= \frac{bk}{cu} \\ z_3^* &= \frac{1}{p}\left(\frac{\lambda \beta ck}{cdu + \beta bk} - a\right) \end{aligned}$$

6.2.4 Virus Mutation and Escape

The model can be extended to include virus diversity and escape from the immune system. As the replication time for viruses is quite short, there is a high potential for mutations and therefore diversification. Of course there is a positive correlation between virus load and the number of mutant virus cells that cannot be spotted by the immune system-these cells have a major advantage compared to other virus cells. The full model would exceed the scope of this work, but is explained in detail in Nowak et al. (1996).

6.3 Prediction of Vaccinating Behaviour

Immunisation benefits global health enormously by preventing illnesses, disability and death from diseases such as diphteria, hepatitis B, measles, mumps, rubella or tetanus (World Health Organization, 2017). The World Health Organization's (WHO) goal is to improve vaccine coverage in order to eradicate vaccine-preventable diseases. Due to herd immunity it is not necessary to vaccinate everyone to achieve this goal, but just a certain proportion of the population. There is more than one definition for the term "herd immunity": It is either referred to as the "proportion of subjects with immunity in a given population" or the "reduction of infection or disease in the unimmunised segment as a result of immunising a proportion of the population" (John & Samuel, 2000).
Herd immunity is important in the decision making process of whether to vaccinate a child or not: The decision depends on the perceived risk of infection and the perceived risk of vaccine-related side effects- and the risk of infection apparently depends on the proportion of the population that is vaccinated. This complex process is visualised in figure 12.

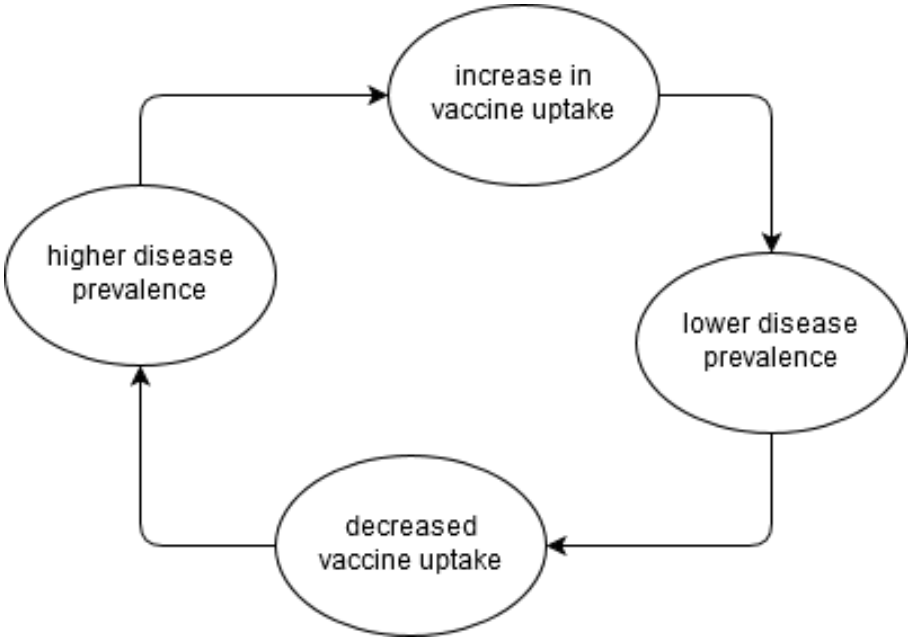

Figure 12: Vaccination Cycle: The more people are vaccinated- the lower the risk for infection- the less likely it is for parents to vaccinate their children- the higher the prevalence.

6.3.1 Vaccinator and Non-Vaccinator Model

To model human vaccination behaviour, some assumptions need to be made.

- Only childhood diseases with lifelong or long-term natural immunity are considered.
- The "players" are the parents who decide on the vaccination of their children.
- Vaccinations are scheduled at a young age and the decision whether to vaccinate is only made once.
- We further assume perfect vaccine efficacy.

Let f_v and f_n denote the perceived payoff for vaccinators and non-vaccinators, respectively. Let r_v and r_i denote the perceived probability of morbidity from the vaccine and upon infection, respectively. Then $f_v = -r_v$ holds. Let $I = I(t)$ denote the disease prevalence at time t and m the sensitivity of vaccinating behaviour to changes in prevalence. The perceived payoff for non-vaccinators can be expressed in terms of disease prevalence:

$$f_n(I) = -r_i m I \tag{55}$$

Individuals randomly sample other members of population at some constant rate σ. The payoff gain (or loss) for switching to the vaccinator strategy is given by

$$\Delta E = f_v - f_n(I) \tag{56}$$

The imitation rule applied in this case is the "proportional imitation rule": imitating better performing actions with a probability proportional to the gain a player can expect (see section 5). Let x denote the frequency of vaccinators and σ the rate at which a vaccinator samples vaccinators. If $\Delta E > 0$, non-vaccinators change to the vaccinator-strategy with probability $\rho \Delta E$:

$$\frac{dx}{dt} = (1-x)\sigma x \rho \Delta E \tag{57}$$

If $\Delta E < 0$, vaccinators may switch to the non-vaccinator strategy. Let $k = \sigma\rho$ denote the combined imitation rate, then the differential equation for x reads

$$\frac{dx}{dt} = kx(1-x)(f_v - f_n(I)) = \tag{58}$$

$$= kx(1-x)(-r_v + r_i m I) \tag{59}$$

The disease prevalence I is determined with a classic SIR- model: S denotes the susceptible individuals of a population, I the infected proportion and R the immune (either

naturally or through vaccination). Let μ denote the mean birth/ death rate per capita, β the transmission rate and $\frac{1}{\gamma}$ the mean duration of infectiousness. We derive the following system of equations:

$$\frac{dS}{dt} = \mu(1-x) - \beta SI - \mu S \tag{60}$$
$$\frac{dI}{dt} = \beta SI - \gamma I - \mu I \tag{61}$$
$$\frac{dR}{dt} = \mu x + \gamma I - \mu R \tag{62}$$
$$\frac{dx}{dt} = kx(1-x)(-r_v + r_i m I) \tag{63}$$

As $S + R + I = 1$, R can be eliminated and system (60)-(63) reduces to

$$\frac{dS}{dt} = \mu(1-x) - \beta SI - \mu S \tag{64}$$
$$\frac{dI}{dt} = \beta SI - \gamma I - \mu I \tag{65}$$
$$\frac{dx}{dt} = \kappa x(1-x)(-1 + \omega I) \tag{66}$$

with $\kappa = kr_v$ and $\omega = \frac{mr_i}{r_v}$.

The model above was introduced by Bauch (2005), who also derived the following results about equilibrium points: The system (64)-(66) admits

- a pure disease free, non-vaccinator equilibrium: $\mathcal{E}_1 = (1, 0, 0)$,
- a pure disease free, vaccinator equilibrium: $\mathcal{E}_2 = (0, 0, 1)$,
- an endemic, non-vaccinator equilbrium $\mathcal{E}_3 = \left(\frac{1}{R_0}, \frac{1}{\omega_0}, 0\right)$ if the basic reproductive ratio $R_0 > 1$ and where $\omega_0 = ((\gamma + \mu)/\mu)/(1 - (1/R_0)))$,
- and an endemic equilibrium with a mixed state of vaccinators and non-vaccinators:

$$\mathcal{E}_4 = \left(\frac{1}{R_0}, \frac{1}{\omega}, 1 - \frac{1}{R_0} - \frac{\gamma + \mu}{\omega\mu}\right)$$

  if $R_0 > 1$ and $\omega > \omega_0$ hold.

6.3.2 Vaccine Scare 1998

In 1998, Andrew Wakefield et al. published a case series in the journal "Lancet", linking the MMR vaccine to autism. Even though the case studies only consisted of a small sample size ($n = 12$) and the results were considered speculative, Wakefield and his colleagues reached wide publicity. Shortly after the publication several studies contradicting

their results and refuting the claimed correlation between MMR vaccinations and autism were published. The other authors and the journal retracted after it was revealed that parents seeking to sue companies producing the vaccine had taken financial influence on Wakefield. The scientists involved are not only charged with ethical misconduct and scientific misinterpretation but also with deliberate fraud. As a result Andrew Wakefield was removed from the UK Medical register.
An implication from this vaccine scare in Europe was a reduced immunisation rate in the following years resulting in a measles outbreak in the early 2000 years. This statement is illustrated in figure 13. In this chapter, we will model the evolution of MMR vaccination rates in the United Kingdom from 1980 to 2016.

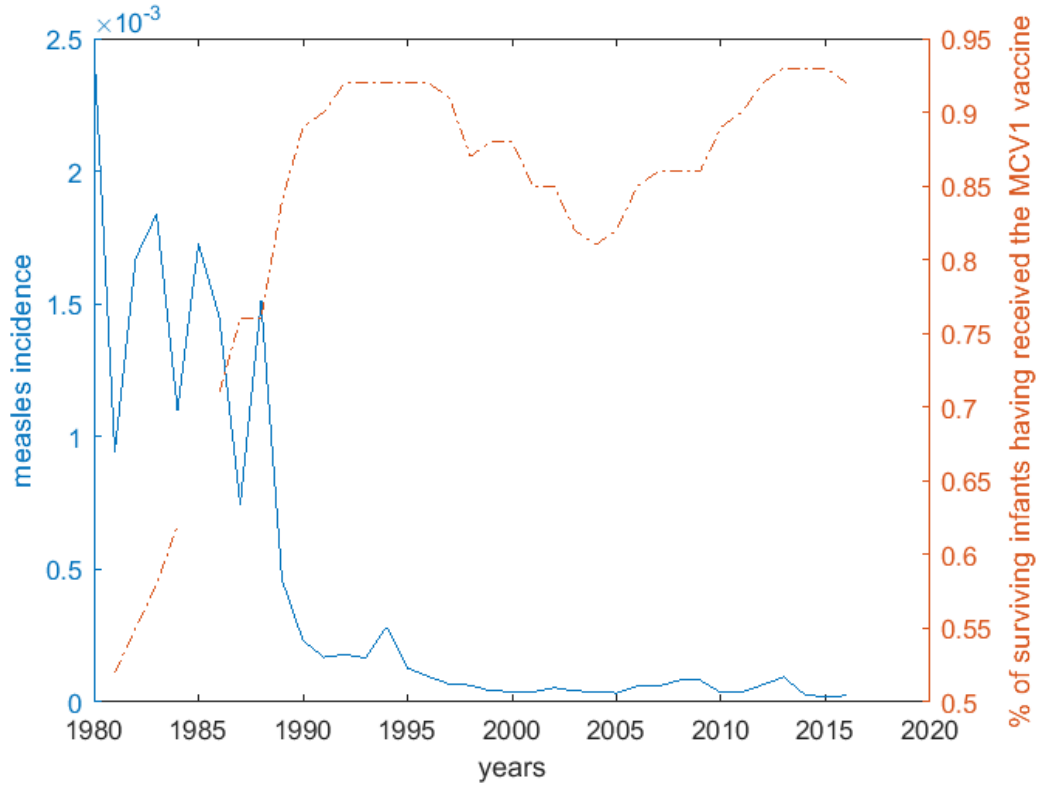

Figure 13: MCV1 vaccination rates and measles incidence in the UK 1980-2016. Data retrieved from WHO.

Using equations (64)-(66), the evolution of vaccinators and measles incidence over the years from 1980 to 2016 was modelled. The results in figure 14 were derived using the parameters $1/\gamma = 22$ days, $1/\mu = 50$ years, $\kappa = 0.0025$ and $\omega = 200000$ in the beginning, increasing the risk of vaccination $40-$fold in 1997 and restoring it to its original value in 2005.

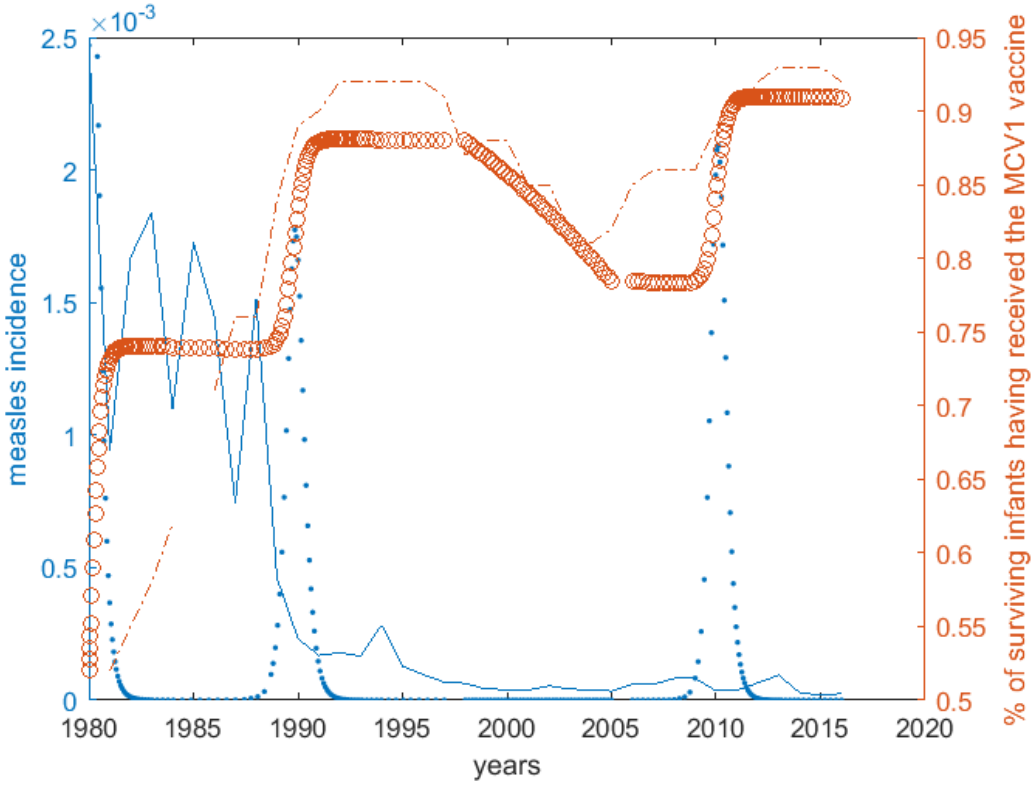

Figure 14: MCV1 vaccination rates and measles incidence in the UK 1980-2016 compared to model result. Data retrieved from WHO.

A Appendix

A.1 Important Results for the Analysis of ODEs

The definitions and results below can be found in any textbook on ordinary differential equations. For example, see Teschl (2012).

Definition A.1.
The $\omega - limit$ of x is the set of all accumulation points of $x(t)$ for $t \to +\infty$:

$$\omega(x) = \{y \in \mathbb{R}^n : x(t_k) \to y \text{ for some sequence } t_k \to +\infty\}. \tag{67}$$

Theorem A.1. *Lyapunov's theorem*
Let $\dot{x} = f(x)$ be a time-independent ODE defined on some subset G of $\mathbb{R}^n$. Let $V : G \to \mathbb{R}$ be continuously differentiable. If for some solution $x(t)$ the derivative $\dot{V}$ of the map $t \to V(x(t))$ satisfies the inequality $\dot{V} \geq 0$, then $\omega(x) \cap G$ is contained in the set $\{x \in G : \dot{V}(x) = 0\}$.
V is called a Lyapunov function.

Theorem A.2. *Jensen's inequality*
If f is a strictly convex function defined on some interval I, then

$$f\left(\sum p_i x_i\right) \leq \sum p_i f(x_i) \tag{68}$$

for all $x_1, \ldots, x_n \in I$ and all $p = (p_1, \ldots, p_n) \in int\ S_n$, with equality if and only if all x coincide.

Theorem A.3. *Poincaré- Bendixon*
Let $y'(t) = f(y(t)$ be a time-independent ODE on an open set $G \subset \mathbb{R}^2$. Let $\omega(y) \neq \emptyset$ be a bounded and closed ω-limit. If $\omega(y)$ does not contain a rest point, then is $\omega(y)$ a closed orbit.

A.2 Matlab Code for simulation in section 6.1

```
close all
clear all
clc

global b d
b = 1.5;
```

```
d = 3;

iter = 100;
x0=[0.495; 0.495; 0.01];
tspan = [0 iter];

[t, x] = ode45(@eoms, tspan, x0);
s=size(x);
x(s(1),:)
semilogx(t,x(:,1),'b-.',t,x(:,2),'g-.',t,x(:,3),'r-.')
axis([0 iter 0 1])
xlabel({'time on logarithmic scale',['starting values: x_1 = ',
    num2str(x0(1)),', x_2 = ', num2str(x0(2)),', x_3 = ',num2str(
    x0(3))], ['parameter values: \beta = ',num2str(b), ', \delta
    = ', num2str(d)]})
ylabel('cell frequency')
legend('OC cells','OB cells','MM cells')
hold on

function xprime = eoms(t,x)
global b d
xprime = [x(1).*(x(2)+b.*x(3)-2.*x(1).*x(2)-2.*b.*x(1).*x(3)-d.*
    x(2).*x(3));
     x(2).*(x(1)-d.*x(3)-2.*x(1).*x(2)-2.*b.*x(1).*x(3)-d.*x(2).*
         x(3));
     x(3).*(b.*x(1)-2.*x(1).*x(2)-2.*b.*x(1).*x(3)-d.*x(2).*x(3))
         ];
end
```

A.3 Matlab Code for simulation in section 6.3

```
close all;
clear all;
clc;

years = 1980:1:2016;
MCVprop = [NaN; 0.52; 0.55; 0.58; 0.62; NaN; 0.71; 0.76; 0.76;
    0.84;0.89; 0.9; 0.92; 0.92; 0.92; 0.92; 0.92;    0.91; 0.87;
```

```
    0.88; 0.88; 0.85; 0.85; 0.82;0.81; 0.82; 0.85; 0.86; 0.86;
    0.86; 0.89; 0.9; 0.92; 0.93; 0.93; 0.93; 0.92];
Measlesprop = [0.002479087;      0.000940919; 0.001671732;
    0.001839113; 0.001100184; 0.001725069; 0.001449472;
    0.000742833; 0.001511535; 0.000459713; 0.00023262;
    0.000168811; 0.00017857; 0.0001667;
    0.00028321;0.000128445;9.65055E-05;6.78804E-05;6.36592E
    -05;4.14934E-05;4.03387E-05;3.79952E-05;5.43328E-05; 4.16385E
    -05;3.92539E-05; 3.46511E-05; 6.08467E-05; 5.96799E-05;
    8.19339E-05; 8.27873E-05; 3.53042E-05; 3.69557E-05; 6.56347E
    -05; 9.45153E-05; 2.84861E-05; 1.82424E-05; 2.49587E-05];


figure(1)
yyaxis right
plot(years, MCVprop,'-.')
xlabel('years')
ylabel('% of surviving infants having received the MCV1 vaccine'
    )
yyaxis left
plot(years, Measlesprop,'-')
ylabel('measles incidence')
global g m k w b

g = 1/0.06;
m = 1/50;
k = 0.0025;
w = 200000;
b = 15*(g+m);

x0=[0.075; 0.00247; 0.52];
tspan = [1980 1997];

[t, x] = ode45(@eoms, tspan, x0);
s=size(x);
x(s(1),:)
```

```
figure(2)
yyaxis left
ylim([0 0.0025])
xlabel('years')
ylabel('measles incidence')
plot(t,x(:,2),'.')
yyaxis right
ylabel('% of surviving infants having received the MCV1 vaccine'
    )
plot(t,x(:,3),'o')
%xlabel('time')
hold on

x1 = x(s(1),:)';
global k1 w1
k1 = 0.1;
w1 = 5000;
tspan2 = [1998 2005];

[t1, x1] = ode45(@eoms1, tspan2, x1);
yyaxis left
xlabel('years')
ylabel('measles incidence')
ylim([0 0.0025])
plot(t1,x1(:,2),'.')
yyaxis right
ylabel('% of surviving infants having received the MCV1 vaccine'
    )
plot(t1,x1(:,3),'o')

s = size(x1);
x2 = x1(s(1),:)';
tspan3 = [2006 2016];

[t2, x2] = ode45(@eoms, tspan3, x2);

yyaxis right
```

```
ylabel('% of surviving infants having received the MCV1 vaccine'
    )
plot(t2,x2(:,3),'o')
yyaxis left
xlabel('years')
ylabel('measles incidence')
ylim([0 0.0025])
plot(t2,x2(:,2),'.')

yyaxis right
plot(years, MCVprop,'-.')
yyaxis left
plot(years, Measlesprop,'-')

function xprime = eoms(t,x)
global g m k w b
xprime = [m.*(1-x(3))-b.*x(1).*x(2)-m.*x(1);
     b.*x(1).*x(2)-g.*x(2)-m.*x(2);
     k.*x(3).*(1-x(3)).*(-1+w.*x(2))];
end

function xprime = eoms1(t,x)
global g m k1 w1 b
xprime = [m.*(1-x(3))-b.*x(1).*x(2)-m.*x(1);
     b.*x(1).*x(2)-g.*x(2)-m.*x(2);
     k1.*x(3).*(1-x(3)).*(-1+w1.*x(2))];
end
```

References

Alexander, J. M. (2009). Evolutionary game theory. In E. N. Zalta (Ed.), *The Stanford Encyclopedia of Philosophy* (Fall 2009 ed.). Metaphysics Research Lab, Stanford University. Retrieved from `https://plato.stanford.edu/archives/fall2009/entries/game-evolutionary/` (Accessed: 2018-05-02)

Bauch, C. T. (2005). Imitation dynamics predict vaccinating behaviour. *Proceedings of the Royal Society B*, *272*, 1669-1675. doi: 10.1098/rspb.2005.3153

Björnerstedt, J., & Weibull, J. W. (1996). Nash equilibrium and evolution by imitation. *The Rational Foundations of Economic Behaviour*, 155-171.

Brown, J. S. (2016). Why darwin would have loved evolutionary game theory. *Proceedings of the Royal Society of London B: Biological Sciences*, *283*(1838). Retrieved from `http://rspb.royalsocietypublishing.org/content/283/1838/20160847` doi: 10.1098/rspb.2016.0847

Fenton, A., & Perkins, S. (2010). Applying predator-prey theory to modelling immune-mediated, within-host interspecific parasite interactions. *Parasitology*, *137*(6), 1027-1038. doi: 10.1017/S003118200999178

Goel, N. S., Maitra, S. C., & Montroll, E. W. (1971). On the volterra and other nonlinear models of interacting populations. *Reviews of Modern Physics*, *43*, 231-276. doi: 10.1103/RevModPhys.43.231

Hofbauer, J. (1981). On the occurrence of limit cycles in the Volterra-lotka equation. *Nonlinear Analysis: Theory, Methods and Applications*, *5*(9), 1003 - 1007. Retrieved from `http://www.sciencedirect.com/science/article/pii/0362546X81900596` doi: https://doi.org/10.1016/0362-546X(81)90059-6

Hofbauer, J., & Sigmund, K. (1998). *Evolutionary games and population dynamics*. Cambridge: Cambridge University Press.

John, T. J., & Samuel, R. (2000). Herd immunity and herd effect: new insights and definitions. *European Journal of Epidemiology*, *16*, 601-606. Retrieved from `https://www.ncbi.nlm.nih.gov/pubmed/11078115` (Accessed: 2018-10-17)

Maynard Smith, J. (1982). *Evolution and the theory of games*. Cambridge University Press. doi: 10.1017/CBO9780511806292

Maynard Smith, J., & Price, G. R. (1973). The logic of animal conflict. *Nature*, *246*, 15-18. doi: 10.1038/246015a0

Mozo, M. V. (2018). *Biology Online Dictionary.* Retrieved from `https://www.biology-online.org/dictionary/Darwinian_fitness` (Accessed: 2018-10-22)

Nowak, M. A., Bonhoeffer, S., Hill, A. M., Boehme, R., Thomas, H. C., & McDade, H. (1996). Viral dynamics in hepatitis B virus infection. *Proceedings of the National Academy of Sciences*, *93*(9), 4398–4402. doi: 10.1073/pnas.93.9.4398

Pacheco, J. M., Santos, F. C., & Dingli, D. (2014). The ecology of cancer from an evolutionary game theory perspective. *Interface Focus*, *4*(4). doi: 10.1098/rsfs.2014.0019

Pfeiffer, P. (2014). Spieldynamiken asymmetrischer Spiele. *Seminar Paper*. (TU Wien)

Raab, M. S., Podar, K., Breitkreutz, I., Richardson, P. G., & Anderson, K. C. (2009). Multiple myeloma. *The Lancet*, *374*, 324-339. doi: 10.1016/S0140-6736(09)60221-X

Schuster, P., & Sigmund, K. (1981). Coyness, philandering and stable strategies. *Animal Behaviour*, *29*, 186-192.

Schuster, P., Sigmund, K., Hofbauer, J., & Wolff, R. (1981). Selfregulation of behavior in animal societies, parts I, II and III. *Biological Cybernetics*, *40*, 1-8, 9-15, 17-25.

Sigmund, K. (2005). John Maynard Smith and evolutionary game theory. *Theoretical Population Biology*, *68*, 7–10. doi: 10.1016/j.tpb.2004.10.002

Teschl, G. (2012). *Ordinary differential equations and dynamical systems.* Providence, Rhode Island: American Mathematical Society.

U.S. Department of Health and Human Services. (2018). *NCI dictionary of cancer terms.* Retrieved from `https://www.cancer.gov/publications/dictionaries/cancer-terms` (Accessed: 2018-04-19)

van Damme, E. (1987). *Stability and perfection of nash equilibria.* Berlin: Springer.

Wei, X., Ghosh, S. K., Taylor, M. E., Johnson, V. A., Emini, E. A., Deutsch, P., ... Shaw, G. M. (1995). Viral dynamics in human immunodeficiency virus type 1 infection. *Nature*, *373*, 117-122. doi: 10.1038/373117a0

World Health Organization. (2017). *Immunization coverage fact sheet 2017.* Retrieved from `http://www.who.int/en/news-room/fact-sheets/detail/immunization-coverage` (Accessed: 2018-10-17)

Wu, A., Liao, D., Kirilin, V., Lin, K.-C., Torga, G., Qu, J., ... Austin, R. (2018, Jan 22). Cancer dormancy and criticality from a game theory perspective. *Cancer Convergence*, *2*(1), 1. Retrieved from https://doi.org/10.1186/s41236-018-0008-0 doi: 10.1186/s41236-018-0008-0

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