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Game Theory and Cancer

Using Game Theory to Model Host-Tumor Interactions

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Master's Thesis Spring 2013

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Spring 2012

Abstract

Cancer can be seen as an evolutionary disease, where natural selection works on the cells in an organism to promote traits that are detrimental to the organism. Evolutionary game theory (EGT) is a field using the methods of game theory, which is usually concerned with the behaviour of rational agents, to model adaptive systems. The basis for EGT is that the stable rest points of the adaptive system correspond to stable equilibrium solutions to related games.

EGT has been used to model the cellular evolution in cancer with focus on the interactions between different cancer cells, and between cancer cells and normal cells. This thesis is an attempt to model the relationship between the host and the cancer cells using game theory.

Simplified systems of differential equations simultaneously describing the cellular evolution within organisms as well as organismal evolution are presented, and a correspondence between stable rest points of these systems and stable equilibrium solutions to a class of extensive games are shown.

The game theoretical models are applied to modified versions of cell-cell interaction games from the literature. The results show that it is evolutionarily plausible for multicellular organisms to develop tactical elements in their anti-cancer strategies.

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Acknowledgements

I'd like to thank my main supervisor Geir Kjetil Sandve for the suggestion of this interresting subject and valuable feedback along the way. I'd also like to thank my co-supervisor Eivind Hovig for help and information concerning the biology of cancer and to Paul Torvund for help regarding the complexities of game theory. Furthermore a big thanks goes out to my fellow graduate students at the Biomedical Research Group for help and great company along the way.

I'd also like to thank my family and friends for support, and especially Peder and Synne for their help in the finishing steps of this thesis.

Part I

Introduction

Chapter 1

Outline

This thesis is about the application of game theory to cancer modelling. The idea is to see the relationship between an organism and its cells as a game where the cells act in their self interest and the organism acts in its self interest. Cancer cells in this context is seen as cell with a 'strategy' that is good for the cell itself, but bad for the organism.

In order to establish this idea in proper form, a few steps have to be taken.

- Firstly, a mathematical consept of a game is established, this is done in the next chapter in the introduction to game theory.
- To apply the theory of games to biology, evolutionary game theory is introduced
- Lastly the evolutionary aspects of cancer is introduced, needed to apply to evolutionary game theory to cancer

Naturally, a full introduction to game theory, evolutionary game theory and the evolutionary biology of cancer is to much for the background material of a Master's thesis. I will therefore limit the presentation of the fields to the bare minimum neede for for this thesis to be reasonably mathematically self contained, and for a reader with some experience in the fields to know the terminology and notation used. For more detailed introductions, the reader is referenced to existing litterature.

Chapter 2

Game Theory

The name game theory is deceptive in two ways. Firstly, it implies that it is only useful for analyzing games of the which most people are familiar such as chess, bridge or poker. Although it can be used for this, the concept of a game in game theory is much more abstract and game theory has a wide range of applications such as finance, politics, linguistics and, important for this thesis, biology. Secondly the name implies a light subject while game theory is often very complex both in it's applied and pure form. A full account of game theory and it's applications is therefore more suited for a book format then the introduction of a Master's thesis, so I will limit this introduction to the framework and interpretation of game theory that is important for this thesis. For a full introduction to the subject see [28][29]. Although the mathematics become complicated and abstract there is usually an intuitive concept behind. The goal of this introduction is to clarify the mathematical language I use in the thesis and connect them to the intuitive concepts they represent.

2.1 Extensive Games

Extensive games[21] are games that explicitly define the order of moves in a game as well as it's strategies and payoffs. In this thesis I use the definition from [28] (framed definitions are taken from [28]).

Definition 1. ([28] Def 200.1[1]) An extensive game with perfect information has the following components.

- A set N (the set of players).
- A set H of sequences (finite or infinite) that satisfies the following three properties.
  - The empty sequence is a member of H.
  - If $(a^k)_{k=1,\dots,K} \in H$ (where K may be infinite) and $L < K$ then $(a^k)_{k=1,\dots,L} \in H$

– If an infinite sequence $(a^k)_{k=1}^{\infty} satisfies (a^k)_{k=1,\dots,L} \in H$ for every positive integer L then $(a^k)_{k=1}^{\infty} \in H$.

(Each member of H is a history; each component of a history is an action taken by a player.) A history $(a^k)_{k=1,\dots,K} \in H$ is terminal if it is infinite or if there is no $a^K + 1$ such that $(a^k)_{k=1,\dots,K+1} \in H$. The set of terminal histories is denoted Z .

- A function P that assigns to each nonterminal history (each member of H
  Z) a member of $N \cup \{c\}$. (P is the player function, $P(h)$ being the player who takes an action after the history h. If $P(h) = c$ then chance determines the action taken after the history h.)
- A function f_c that associates with every history h for which $P(h) = c$ a probability measure $f_c(|h)$ on $A(h)$, where each such probability measure is independent of every other such measure. ($f_c(a|h)$ is the probability that a occurs after the history h.)
- For each player $i \in N$ a partition $\mathscr{I}_i$ of $\{h \in H : P(h) = i\}$ with the property that $A(h) = A(h')$ whenever h and h' are in the same member of the partition. For $I_i \in \mathscr{I}_i$ we denote by $A(I_i)$ the set $A(h)$ and by $P(I_i)$ the player $P(h)$ for any $h \in I_i$. ($\mathscr{I}_i$ is the information partition of player i; a set $I_i \in \mathscr{I}_i$ is an information set of player i.)
- For each player $i \in N$ a payoff function $\pi_i : Z \to \mathbb{R}$

The interpretation of this is that at each possible history $h \in H$, a player $P(h)$ can choose between the actions in $A(h)$ where an action $a \in A(h)$ leads to a new history $h_2 = (h, a)$ where a player $P(h_2)$ chooses between the actions in $A(h)$. The game continues in this way until a terminal history $h_t \in Z$ is reached. Each player $p \in P$ then gets the payoff $\pi_P(h_t)$. The goal for each player is to maximize it's own payoff, or in other words that the game should end up in a terminal history with a high payoff. The game is complicated by the fact that at each history $h \in H$, the player $p = P(h)$ does not know exactly which is the current history, only which information partition $I_p \in \mathscr{I}_i$ it is in.

Example 1. Chess. The game of chess can be defined as an extended game by:

- The white and black player $N = (W, B)$
- H is every sequence of legal moves in chess. The terminal $Z \subset H$ is every history leading to checkmate or remis
- The function P is defined by
  - $P(\emptyset) = W$, meaning that white starts the game.

  - $P(h) = W$ when the length of the history h is divisible by two and $P(h) = B$ when it is not.

- The set $A(h)$ is every legal move available to $P(h)$ after the history h
- The information partitions $I_W = \{\{h\} \mid P(h) \in W\}$ and $I_B \{\{h\} \mid P(h) \in W\}$, meaning that at each stage in the game, the players exactly what has happened up to that point.
- The payoff function

$$\pi_W(h) = \begin{cases} 1 & \text{if } h \text{ represents white check mating black} \\ 0 & \text{if } h \text{ represents black check mating white} \\ 1/2 & \text{if } h \text{ represents remis} \end{cases}$$

  and opposite for $\pi_B(h)$

Example 2. A coin toss game with two players, where one player chooses either Tails (T) or Heads (H) and wins if a subsequent coin toss gets the same outcome can be described by the following.

- Two players $N = \{A, B\}$
- The histories $H = \{\emptyset, (H), (T), (H,H), (H,T), (T,H), (T,T)\}$ where the terminal histories are $Z = \{(H,H), (H,T), (T,H), (T,T)\}$
- $P(\emptyset) = A$, $P((H)) = P((T)) = c$
- The probability function

$$f_c((H,H)|(H)) = f_c((H,T)|(H)) = f_c((T,H)|(T)) = f_c((T,T)|(T)) = 0.5$$

- $\mathcal{I}_A = \{\emptyset\}$ and $\mathcal{I}_B = \emptyset$
-

$$\begin{aligned} \pi_A((H,H)) = \pi_A((T,T)) &= \pi_B((H,T)) = \pi_B((T,H)) &= 1 \\ \pi_A((H,T)) = \pi_A((T,H)) &= \pi_B((H,H)) = \pi_B((T,T)) &= 0 \end{aligned}$$

When two players make a move at the same time, one can model this as one player moving first, but where the second player does not know what the other player has chosen. I show this using the Rock, Scissor Paper game.

Example 3. In the Rocks, Scissor, Paper game, two players simultaneously choose between three strategies: rocks(r), paper (p) or scissors (s). If both choose the best strategy it's a tie, otherwise rock beats scissors, scissors beats paper and paper beats rock.

- The players $N = \{A, B\}$

- $H = \{\emptyset, (R), (P), (S), (R,R), (R,P), (R,S), (P,R), (P,P), (P,S), (S,R), (S,P), (S,S)\}$ and $Z = \{(R,R), (R,P), (R,S), (P,R), (P,P), (P,S), (S,R), (S,P), (S,S)\}$
- $P(\emptyset) = A$, $P((R)) = P((P)), P((S)) = B$
- $\mathscr{I}_A = \{\{\emptyset\}\}$, $\mathscr{I}_B = \{\{(R), (P), (S)\}\}$
-

$$\begin{aligned}
\pi_i((R,R)) = \pi_i((P,P)) = \pi_i((S,S)) = 1/2 \ \ \forall i \in \{A,B\} \\
\pi_A((R,P)) = \pi_A((P,S)) = \pi_A((S,R)) = 0 \\
\pi_B((R,P)) = \pi_B((P,S)) = \pi_B((S,R)) = 1 \\
\pi_A((P,R)) = \pi_A((S,P)) = \pi_A((R,S)) = 1 \\
\pi_B((P,R)) = \pi_B((S,P)) = \pi_B((R,S)) = 0
\end{aligned}$$

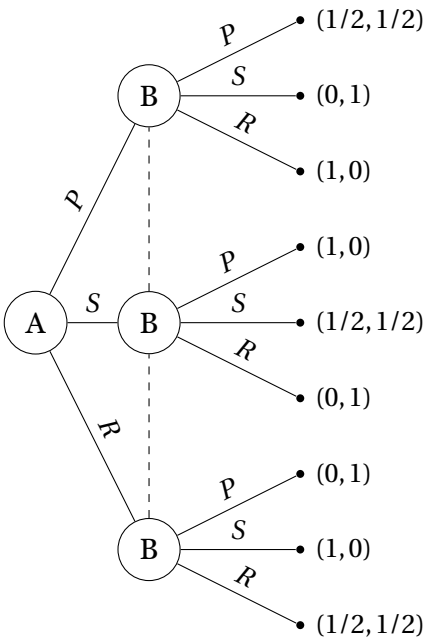
This framework for defing games is a bit cumbersome, but it is very flexible, and it is hard to imagine anything that can be considered a game which can not be modelled in this framework. The graphical representation of games make the concepts more intuitive.

2.2 Graphical Representation

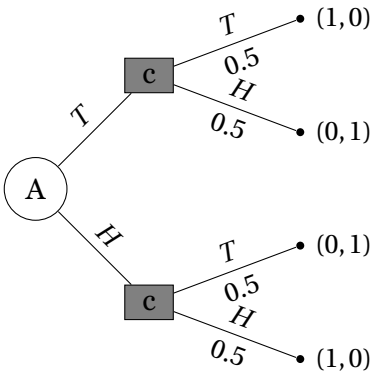
When H is a finite set, the game can be represented visually as a graph. In this thesis I use the following rules to define a graph for a game $\Gamma =< N, H, P, f_c, (\mathscr{I}_i), (\pi_i) >$:

- Each history $h \in H$ is represented as a node on the graph.
- Each node h in H/Z is labeled by the value of the player function of that node $P(h)$.
- For each node $h \in H$ the action set $A(h)$ is represented by an edge from h to the node representing (h, a) for all $a \in A(h)$. The edges are labeled as the action a it represents.
- The information partitions are represented by a dotted line between all the histories in a partition
- The chance probability distributions f_c are represented by labels below the action edges corresponding to the probability of that action.
- Each terminal history $h_t \in Z$ is labelled with a tuple representing the payoff $\pi_i(h_t)$ for all players $i \in N$

Example 4. The Rock, Scissor, Paper game from example example 3 can be represented by the graph:



The coin toss game from example 2 can be represented as:



2.3 Strategies and Outcomes

A game $\Gamma =< N, H, P, f_c, (\mathscr{I}_i), (\pi_i) >$ describes what can happen in a game, or in other words the rules of the game. To describe what actually happens in a game a concept of a strategy, or game plan, is needed. The most intuitive form of strategy in an extensive game is that of a pure strategy:

Definition 2. ([28] Def 203.1) A pure strategy of player $i \in N$ in an extensive game $< N, H, P, f_c, (\mathscr{I}_i), (\pi_i) >$ is a function that assigns an action in $A(I_i)$ to each information set $I_i \in \mathscr{I}_i$.

A pure strategy is thus a predefined choice defined for all possible situations the player can be in during a game. An extension of this

concept, where players are allowed to randomize their choices is given by the following definition:

Definition 3. ([28] Def 212.1) A behavioral strategy of player i is a collection $(\beta_i(I_i))_{I_i \in \mathcal{I}_i}$ of independent probability measures, where $\beta_i(I_i)$ is a probability measure over $A(I_i)$

A behavioral strategy gives a probability to each action in the action set of each information set in the game.

Pure strategies can be seen as a behavioural strategy where all the probability distributions give probabilities either 1 or 0 to each action.

Together, a strategy for each player in a game is called a *strategy profile*. If a strategy profile for a game is given, the outcome of the game $O(s)$, defined as a probability distribution over the terminal histories, can be calculated.

Example 5.

$$s_A(\{\emptyset\}) = R$$
$$s_B(\{(R),(S),(P)\})P$$

are pure strategies for A and B in the rock, paper, scissors game. Together they make the strategy profile $s = (s_A, s_B)$ with the outcome

$$O(s)(h) = \begin{cases} 1 & \text{if} h = (R,P) \\ 0 & \text{otherwise} \end{cases}$$

The collections $s_A = (\beta_A(\emptyset))$ and $s_B = (\beta_B(\{R,S,P\}))$ where, for $I_A = \emptyset$, $I_B = \{(R),(P),(S)\}$,

$$\beta_A(I_A)(R) = \beta_A(I_A)(P) = \beta_A(I_A)(S) = 1/3 \tag{2.1}$$
$$\beta_A(I_B)(R) = \beta_A(I_B)(P) = \beta_A(I_B)(S) = 1/3 \tag{2.2}$$
$$\tag{2.3}$$

are behavioural strategies for A and B in the RPS game. The outcome is a probability distribution $O(s)$ over Z where

$$O(s)((h_t)) = 1/9 \ \forall h_t \in Z$$

Definition 4. The expected payoff for player i for a strategy profile s is defined as:

$$E_i(s) = \sum_{h_t \in Z} O(s)(h_t)\pi_i(h_t)$$

2.3.1 Game Equilibrium

One of the most fundamental concepts in game theory is that of a game equilibrium. An equilibrium of a game is a strategy profile that fulfils certain criteria. The most important equilibrium concept is that of a Nash Equilibrium [26].

Definition 5. A Nash equilibrium of an extensive game is a strategy profile s^* that fulfils the following criterium:

$$E_i(s_i^*, s_{-i}^*) \geq E_i(s_i, s_{-i}^*)$$

I denote by $NE(\Gamma)$ the set of strategy profiles which are Nash Equilibria for the game Γ

In words, a Nash Equilibria is a strategy profile such that no player can benefit from unilaterally changing his strategy.

2.3.2 Subgames

Given a set of histories H and a history $h \in H$, let $H|_h$ define the set of histories after h: $H|_h = h' \mid (h, h') \in H$.

Definition 6. An *independent history* in a game $\Gamma =< N, H, P, f_c, (\mathscr{I}_i), (\pi_i) >$ is a history $h \in H$ such that

- $\{h\} \in \mathscr{I}_{P(h)}$
- If $h' \in H|_h$ then the information set $I \in \mathscr{I}_{P((h,h'))}$ containing (h, h') has the following property:

$$\forall i \in I \, \exists h' \in H|_h \mid i = (h, h')$$

An independent history is then a history h in the game where the the player $P(h)$ knows exactly which history it is in, and for every history h' following h the player $P(h')$ knows that the game has been in history h.

Definition 7. ([28] Def 97.1 [2]) Given an extensive game $\Gamma =< N, H, P, f_c, (\mathscr{I}), (\pi) >$. For every history $h \in H$ such that $\{h\} \in \mathscr{I}_{P(h)}$, the *subgame of* Γ *following* h is the game: The subgame of $\Gamma =< N, H, P, f_c, (\mathscr{I}), (\pi) >$ that follows the independent history h is the extensive game $\Gamma(h) =< N, H|_h, P|_h, f_c|_h, (\mathscr{I}_i|h), (\pi_i|h) >$ where $H|_h$ is the set of sequences h' of actions for which $(h, h') \in H$, $P|_h$ is defined by $P|_h(h') = P(h, h')$ for each $h \in H|_h$, $f_c|_h$ associates with every history $h' \in H|_h$ for which $P|_h(h') = c$, $\mathscr{I}_i|h = \{I_i \in \mathscr{I}_i : h' in H|_h \forall h' \in I_i\}$ and $\pi_i|_h$ is defined by $\pi_i|_h(h') = \pi_i(h, h')$

A subgame of Γ following h can then be seen as the game starting from history h in Γ. The following important concept was introduced by Selten [30].

Definition 8. ([28] Def. 97.2 [3]) A *subgame perfect Nash equilibrium* (SPNE) of a game Γ is a strategy profile s^* such that $s^*|_h$ is a Nash equilibrium of $\Gamma|_h$ for all independent history h in Γ

A SPNE is then a Nash Equilibrium where at each point in the game, if a player knows exactly what history it is in, it plays a Nash Equilibria in the subgame following that history.

2.4 Symmetric Two-Player games

A special class of games that is of special importance to Evolutionary Game Theory is the one-shot symmetric two-player games (STG). These are games with two players where the roles of the players can be interchanged without changing the dynamics of the game. In an STG, each player has only one information set, and the action set on each set is equal.

Definition 9. Given a set Σ and a function $f : \Sigma \times \Sigma \to \mathbb{R}$, the symmetric two player game generated by the set Σ, f denoted $STG(\Sigma, f)$ is the game given by:

- Two players $N = A, B$
- The histories $H = I_A \cup I_B \cup Z$ where

$$\begin{aligned} I_A &= \{\emptyset\} \\ I_B &= \{(a) : a \in \Sigma\} \\ Z &= \left\{(a^1, a^2) : a^1, a^2 \in \Sigma\right\} \end{aligned}$$

- $P(\emptyset) = A$, $P(h) = B \forall h \in I_B$
- The empty probability distribution f_c
- The information partitions $\mathcal{I}_A = \{I_A\}$, $\mathcal{I}_B = \{I_B\}$
- The payoff functions $\pi_A((a^1, a^2)) = \pi_B((a^2, a^1)) = f(a^1, a^2) \ \forall a^1, a^2 \in \Sigma$

An S2G with finite strategy space Σ can be represented as by a table showing the payoff value for each combination of strategies $s \in \Sigma^2$. Each column and each row represents a strategy and the elements in the table represent the payoff for a player when playing the strategy represented by the row if the other player plays the strategy represented by the column.

	R	S	P
R	1/2	1	0
S	0	1/2	1
P	1	0	1/2

Table 2.1: Rock, Scissor, Paper

Example 6. The rock,scissor, paper game from example example 3 is a symmetric two player game $STG(\Sigma, f)$ where $\Sigma = \{R, P, S\}$ and payoff function described by the table.

Since each player has only one information set in an STG, the behavioural strategies are just a probability distribution over the trait set Σ.

Definition 10. Given two sets $\Sigma^1, stsp2$ and two functions $f1 : \Sigma^1 \times \Sigma^2 \to \mathbb{R}$ and $f2 : \Sigma^2 \times \Sigma^1 \to \mathbb{R}$, the *Leader-Follower* game $LF((\Sigma^1, \Sigma^2), (f1, f2))$ is defined as the extensive game $\Gamma :< N, H, P, f_c, (\mathcal{I}_i), (\pi_i) >$ where:

- Two players $N = \{A, B\}$
- The histories $H = \{\emptyset\} \cup \{(a) | a \in \Sigma^1\} \cup Z$ where $Z = \{(a^1, a^2) | a^1 \in \Sigma^1, a^2 \in \Sigma^2\}$
- The player function P where

$$P(\emptyset) = A$$
$$P(h) = B \ \forall h \in \{(a) | a \in \Sigma^1\}$$

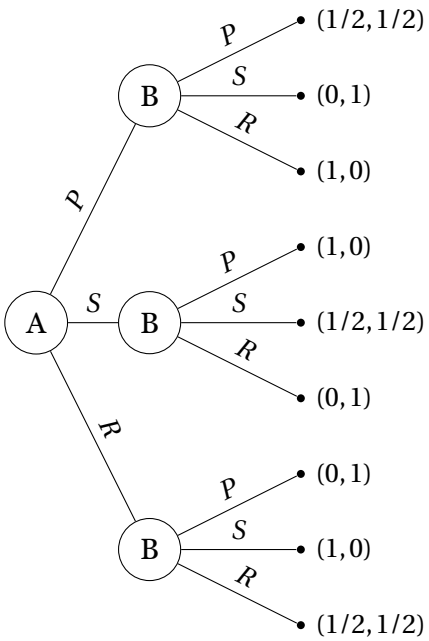
- $f_c = \emptyset$
-

$$\mathcal{I}_A = \{\{(a)\} | a \in \Sigma^1\}$$
$$\mathcal{I}_B = \{\{(a^1, a^2)\} | a^1 \in \Sigma^1, a^2 \in \Sigma^2\}$$

- Tha payoff functions:

$$\pi_A((a^1, a^2)) = f1(a^1, a^2)$$
$$\pi_B((a^1, a^2)) = f2(a^2, a^1)$$

Example 7. The Leader-Followerversion of the rock scissor game $LF((\{R, S, P\}, \{R, S, P\}), f_A, f_B)$ is given by the game tree:



Here player A and B knows which strategy A has chosen. The only rational strategy for player B is then $\alpha = \{((R) : P), ((S) : R), ((P) : S)\}$ which ensures him a payoff of 1. Player A can not expect any payoff no matter what strategy it chooses. Thus any strategy profile where player B chooses α is a subgame perfect Nash Equilibrium.

2.5 Population Games

Another concept that is important for EGT is population games. Population games are description of games where a large group of players have the same role. The payoff for each player depends on which strategy it chooses and on what strategies the rest of the population chooses, but not on which player does what.

Definition 11. A population game $\Gamma_P =< \Sigma, F >$ consists of a trait space Σ and a payoff function F where:

- The trait set Σ is the possible strategies for each player
- The function $F : \Sigma^{\times} X \to \mathbb{R}$, where $F(\sigma, x)$ is the payoff to a player with strategy σ when the population is in state x. Here X is the possible population states where a population state is a distribution over the strategy space Σ given by $(x_i)_{i \in \Sigma} \mid \sum_{i \in \Sigma} x_i = 1$. A population state can therefore be seen as a probability distribution over Σ

Chapter 3

Evolutionary Games

In evolutionary game theory, the interpretation of a game is different from classical game theory. Where game theory traditionally models rational agents choosing strategies to maximize their payoff, evolutionary game theory models players? who are programmed to play a certain strategy in a game where a player's payoff represents his darwinian fitness. Often these two processes end up with the same result. The basis for much of EGT lies in the replicator equation, developed by Taylor and Jonker [31].

Definition 12. ([31] The replicator equation for a population game $< \Sigma, F >$ is the system of differential equations given by:

$$\dot{x}_i = x_i(F_i(x) - \sum_{j \in \Sigma} x_j F_j(x))$$

where x_i denotes the proportion of the population playing strategy i.

I include a derivation of the replicator equation here, since a modified version of the equation is used in this thesis. The replicator equation is used in different fields of EGT [**replicatoreqs**] including economics, biology and linguistics, and there are therefore different derivations for the same equation. I include here a version outlined in [31], based on the language and formalism from [35].

Derivation 1. (based on [35] p. 71-73) Let $P(t)$ be a population of replicator, called units from now, at time p, and let Σ be a set of traits which the units can have. $p_i(t)$ is the number of units in the population which have the trait $i \in \Sigma$ and $x_i(t) = p_i(t)/p(t)$ be the proportion of units with trait $i \in \Sigma$. Each unit have a birth rate β and a death rate δ. The birth rate for a unit with strategy is given by a constant baseline birth rate β_0 and a term given by the result of a population game with payoff function F. Thus $\beta_i(t) = \beta_0 + F(i, x(t))$. The death rate is equal for all units. It is assumed that the offspring of a unit inherits the parent units trait. Thus the number

of units with trait i after a time difference? dt is given by:

$$\begin{aligned} p_i(t+dt) &= p_i(t) + p_i(t)(\beta_0 + F(i,x(t)) - \delta)\,dt \\ \frac{p_i(t+dt) - p_i(t)}{dt} &= p_i(t)(\beta_0 + F(i,x(t)) - \delta) \\ \dot{p}_i &= p_i(\beta_0 + F(i,x) - \delta) \end{aligned}$$

And the total number of units $p(t)$ is given by:

$$\begin{aligned} \dot{p} &= \sum_{i \in K} \dot{p}_i \\ \dot{p} &= \sum_{i \in K} (p_i(\beta_0 - \delta) + p_i F(i,x)) \\ \dot{p} &= p(\beta_0 - \delta) + \sum_{j \in K} p_j F(j,x)) \end{aligned}$$

By the division rule for differentiation the time derivative of x_i is then given by:

$$\begin{aligned} \dot{x}_i &= \frac{\dot{p}_i p - p_i \dot{p}_i}{p^2} \\ \dot{x}_i &= \frac{p_i(\beta_0 + F(i,x) - \delta)p - p_i(p(\beta_0 - \delta) + \sum_{j \in K} p_j F(j,x))}{p^2} \\ \dot{x}_i &= x_i \frac{(\beta_0 + F(i,x) - \delta)p - (p(\beta_0 - \delta) + \sum_{j \in K} p_j F(j,x))}{p} \\ \dot{x}_i &= x_i((\beta_0 + F(i,x) - \delta) - (\beta_0 - \delta + \sum_{j \in K} x_j F(j,x))) \\ \dot{x}_i &= x_i(F(i,x) - \sum_{j \in K} x_j F(j,x)) \end{aligned}$$

Which is the replicator equation.

There are a some important things to note about the replicator equation and it's derivation.

- The population size need to be big in order that it is plausible for p_i and x_i to be differentiable functions of time.
- The equation is not dependent on the base birthrate and death rate
- The equation says nothing about what the replicators are. In this thesis, both cells and organisms are considered to be replicators
- The replicators' traits are assumed to 'breed true', meaning that the offspring of a replicator inherits the trait of it's parent with 100 percent probability. This excludes the possibility of mutations, and the effects of sexual reproduction.

The replicator equation assumes that the population is big enough that one can view the population state as a differentiable function of time. The replicator equation describes the dynamics of a biological system when the fitness of a trait depends on the makeup of the population. This dependency can take many forms, but in most uses it is thought of as being the result of random matching of a symmetric game [35]

Definition 13. A random matching of a symmetric two-player game $\Gamma = STG(\Sigma, \pi)$, denoted by $RM(\Gamma)$ is a population game $< (F_i), \Sigma >$ where: $F_i(x) = E_i(x)$.

The fitness of a strategy, or trait, in a random matching game is the expected payoff from playing the associated STG against a random opponent from the population. The replicator equation of a random matching game can then be interpreted as follows.

- Each member of the population is randomly paired with another member of the population to play a symmetric game
- The payoff a member receives from the symmetric game represents its fitness , or expected number of viable offspring.
- The offspring of a member inherits the member's trait
- By the law of large numbers the average number of offspring for the members with a given trait is proportional with the expected payoff from the symmetric game.

Theorem 1. *([18]) Every Symmetric Nash equilibrium of a symmetric two-player game corresponds to a rest point in the replicator equation of the derived random matching game. Every stable rest point in the derived replicator equation is a Nash Equilibrium of the symmetric two player game.*

A rest point corresponding to a mixed Nash Equilibrium is called a *polymorphic equilibrium*, meaning that more than one trait is present in the population in an equilibrium.

Definition 14. The support of a population state x is the set of strategies $j \in \Sigma$ such that x_j is not zero.

$$supp(x) = \{j \in stsp \mid x_j \neq 0\}$$

Theorem 2. *Every rest point x^* of the replicator equation corresponds to a Nash Equilibrium of a population game restricted to $supp(x^*)$.*

$$\dot{x}^* = 0 \Rightarrow x^*_{|supp(x^*)} \in NE(< supp(x^*), F_{|supp(x^*)} >)$$

3.0.1 Classification of symmetric 2×2 games

A general STG with two strategies can be described by the payoff matrix: $W = \begin{pmatrix} a & b \\ c & d \end{pmatrix}$ Based on the ordering of the payoff values the number and nature of the Nash equilibria.

Domination If $a > c \wedge b > d$ strategy 1 dominates strategy 2 and the only nash equilibrium is $(1,1)$. Correspondingly if $a < c \wedge b < d$ strategy 2 dominates strategy 1 and the only Nash equilibrium is $(2,2)$.

Coordination If $a > c \wedge b < d$ there are two pure strategy Nash equilibria: $(1,1)$ and $(2,2)$,and a mixed strategy Nash equilibrium given by $p = q = \frac{d-b}{a+d-b-c}$. Both pure equilibria represent a stable rest point in the derived dynamics. The mixed strategy equilibrium is unstable, and a small perturbation to either side leads to the fixation of the fixation of one of the strategies.

Anti-Coordination If $a < c \wedge b > d$ there are two non-symmetric pure strategy Nash equilibria: $(1,2)$ and $(2,1)$ and one symmetric mixed strategy Nash equilibrium: $p = q = \frac{d-b}{a+d-b-c}$. The mixed strategy equilibrium represents a stable rest point.

A similar classification exists for three strategy games[10], where there are 33 different classes.

3.1 Non Deterministic Models

Chapter 4

Cancer from an Evolutionary Perspective

Cancer is a common and deadly disease [20]. The There are many aspects of cancer that are relevant to an evolutionary analysis, but I will focus here on only on those that are essential to the understanding of this thesis. In the first section I will introduce the multistep process of cancer and the traits known as the 'hallmarks of cancer'. In the second section I will discuss the evolutionary relationship between the organism and the cell as the unit of selection. For a general introduction to the biology of cancer, I refer the reader to the book by Weinberg [36]. And for specificaly evolutionary perspectives of cancer see: [1]

4.1 The Somatic Evolution of Cancer

Cancer can be seen as a evolution of the somatic cells within an organism, where cells acquire mutations and the selection pressure between cells selects for advantageous mutations [27]. The complexity of this evolutionary process is gradually being elucidated, seeing that the cellular environment within the body, often called the *microenvironment*, has impact on the evolutionary process[22].

4.1.1 The Hallmarks of Cancer

In [17] (and later [16]) Hanahan and Weinberg defined a set of cellular traits common in cancer cells as Hallmarks of Cancer. These traits are important for the somatic evolution of cancer, because cancer cells need to acquire them in order to become fully malignant.

Sustaining Proliferative Signaling The cell growth in normal tissue is a controlled process. Cells are dependent on proliferative signals to grow and divide. The production of these signals is usually tightly controlled, and cancer cells need to escape this control. Common mechanisms for this includes producing its own proliferative signals, manipulating other cells

to produce proliferative signals or become more sensitive to the signals by expressing more of the receptors for the signals on the cell wall.

Evading Growth Suppressors Growth suppressors are signals with the opposite effect of proliferative signals. Growth suppressors signals the cell to stop proliferating. Cancer cells can evade this mechanism by becoming insensitive to them.

Resisting Cell Death Cells in the body are programmed to self destruct under various circumstances. Many of the common steps in cancer progression are supposed to trigger this mechanism, among them genomic instability and abundance of growth factors. In order to survive the cells need to circumvent this program.

Inducing Angiogenesis Somatic cells receive nutrients and oxygen from the bloodstream. When the tumor size increases, the limited supply make the cells suffer from lack of nutrients and oxygen. For continued growth of the tumor the cancer cells need to activate vascularisation of the tumor. Mutations which activate, directly or indirectly, signalling to endothelial cells to produce new vasculature gives tumors the possibility to increase further in size.

Enabling Replicative Immortality Somatic cells does not have limitless replicative potential. For each cell division the telomeres at the ends of each chromosome shortens. The telomeres are important for the structural integrity of the chromosomes, so when they become to short, a senescence or apoptosis program is initiated. If these programs are compromised in the cell, the cell continues to replicate leading to genomic instability . This will in most cases lead to lower fitness for the cell, but this instability can also lead to advantageous mutations which can, given that the cell regains genomic stability, lead to a fitness increase and a higher degree of variability in the cell population. Mutations that reactivate the telomerase gene, which is active in immortal stem cells and germ-line-cells, can stop the telomerase degeneration and give the cell replicative immortality.

Activating Invasion and Metastasis Different organs are separated by boundaries which prevent cells from one organ to migrate to another. These boundaries serve to contain tumours from spreading. Tumors that are contained to non-vital organs are seldom lethal. In order to become fully malignant tumors need to cross the barrier. In epithelial cancer this means penetrating the basement membrane. If cancer cells are able to access either the bloodstream or the lymphatic system, they can spread to remote organs. In order to do this they must have mutations enabling them to survive in the bloodstream and also to survive in a remote organ.

Avoiding Immune Destruction Both the innate and the adaptive immune system is involved in the hosts defence against cancer [12]. NK-cells and macrophages from the innate immune system produce anti-angiogenic factors, produce cytotoxic substances and induces apoptosis in cancer cells. T-cells from the adaptive immune system also induces tumor cell death by various mechanisms. Resistance to these immune responses are needed for cancer cells to survive.

4.2 Cancer Effects on Organismal Fitness

When viewing the organism as the unit of selection, cancer has a negative effect on the fitness. As such it is natural to ask why it is so common. The field of evolutionary medicine offers some general rules for why we are vulnerable to disease. Explanations include (adopted from [15] Chapter 11, and [1] Box 1):

"Selection Does not operate to maximize Health or Longevity" [15] While cancer has high morbidity, it does not necessarily have a big impact on fitness. Most cancer rates grow exponentially with age [32] [1]. This is an effect of the multistep nature of cancer, but is also an indication that selection has favoured organisms that does not get cancer in reproductive life stages.

"Co-evolution with pathogens"[1] Many cancer types are associated with infections of various microbial life forms [25][3][33]. The evolutionary relationship between human organisms and microbial life forms often take the form of arms races. Thus when some microbes benefit from inducing cancerogenic phenotypes in cells, this mechanism can prevail even though the host evolves defences against it since the microbes can evolve counter-mechanisms against it.

"Constraints on Evolution" [1] Many of the cancer associated genes are highly conserved across many multicellular species, implying that they are connected with the 'core machinery' of multicellularity. Germ line mutations in this machinery have a very low probability of giving a fitness advantage, even if they lower cancer risk, since they

"An Evolutionary Mismatched or Novel Environment"[15] In rapidly changing environments, the forces of evolution might not be strong enough to ensure that everyone is at a fitness maximum. The novel mutagenic substances introduced by human culture increase cancer risk, but the body has not yet evolved to cope with this increased risk.

[1] At very high ages(≈ 100) the rates go down

The Result of an Evolutionary Trade Off Mechanisms to prevent cancer can be envisioned that are more effective than what humans have. The idea of an evolutionary trade off suggests that such a mechanism could have negative side effects which outweigh the reduced cancer risk.

Chapter 5

A Review of Game Theory in Cancer Modelling

The Beginning

The first attempt to model cancer-interactions using game-theory was done in 1997 by Tomlinson and Bodmer's article "Modelling the consequences of interactions between tumour cells" [34]. They argue that "... some mutations might cause tumour cells to adopt strategies that involve interacting with other cells in the tumour" and use evolutionary game theory (EGT) to model two plausible scenarios where this is the case. The first scenario they model is one with two strategies concerning the production of growth factor (GF). A+ cells produces a GF that gives them and the cells they interact with a benefit (j), while A- does not. Production of the growth factor represents a cost (i) to the A+ cells. This gives the payoff **??** on page ??:

	A+	A-
A+	$1-i+j$	$1-i+j$
A-	$1+j$	1

Table 5.1: Growh Factor

The proportion (x_{A+}) of A+ cells in equilibrium is then:

$$x_{A+} = \frac{1-(1-i+j)}{(1-i+j)-(1-i+j)-(1+j)+1)} = \frac{i-j}{j} = 1-\frac{i}{j}$$

This shows that a polymorphic equilibrium can occur if the cost of producing the growth factor is smaller than the benefit it gives.

The second model includes paracrine GF-producers (PGF), autocrine GF-producers (AGF) and a wild-type (W). a denotes the cost of producing the paracrine GF and b the benefit of receiving it. b denotes the net benefit from producing the autocrine GF. The payoff table is given in **??** on page ??:

In this case the PGF-strategy is dominated by the wild type if the cost of producing the GF is non-zero. And the wild type is dominated by the autocrine GF-strategy if the net benefit of producing GF is positive.

	PGF	AGF	W
PGF	$1-a+b$	$1-a$	$1-a$
AGF	$1+b+c$	$1+c$	$1+c$
W	$1+b$	1	1

Table 5.2: Angiogenesis

The article gives two important insights. That a polymorphic equilibrium between different traits can exist in the cancer population and that traits that are good for the tumor as a whole, will not prevail if it is disadvantageous to the cell itself.

In [19] Tomlinson shows that even traits that are detrimental to the tumor as a whole can be selected for. Here he models a scenario where one cell-type (P) produces a cytotoxin which is harmful (f) to the cells it interacts. The production of the cytotoxin incurs a production cost (e) and a benefit from affecting others (g). The model also includes cells (R) that are resistant to the cytotoxin at a cost (h) to itself, and a wild type (W) which neither produces nor is resistant to the cytotoxin.

	P	R	W
P	$1-e-f+g$	$1-h$	$1-f$
R	$1-h$	$1-h$	1
W	$1-f$	1	1

Table 5.3: Cytotoxin Production (modified from [19])

which gives the equilibrium frequencies:

$$x_P = \frac{h}{f}$$
$$x_R = \frac{e}{g} - \frac{h}{f}$$
$$x_W = 1 - \frac{e}{g}$$

The calculation shows that, depending on the value of the costs, all polymorphisms except between the resistant and wild type strategies are possible. He also shows that this can also be the case when the different types have different replicative advantages independent of the other frequencies of cell-types.

Bach et al. [5] add a spatial aspect to GF-model of [19] by giving each cell a 3-neighbourhood consisting of itself and two other cells. A cell will only get benefits from GF if two of the three cells in its 3-neighbourhood produces it. This leads to a 3-player game instead of the 2-player game in Tomlinson's model. The payoff table is given in **??** on page ??:

	A+,A+	A+,A-	A-,A+	A-,A-
A+	$1-i+j$	$1-i+j$	$1-i+j$	$1-i$
A-	$1+j$	1	1	1

Table 5.4: 3-player Growth Factor Game

leads to two equilibrium values for the proportion (x_{A+}) of A+ cells:

$$x_{A+}^{h*} = \frac{1+\sqrt{1-2i/j}}{2}$$
$$x_{A+}^{l*} = \frac{1-\sqrt{1-2i/j}}{2}$$

which both disappear at when $j < 2i$, leading to extinction of A+ cells. For $j >= 2i$, the x_{A+}^{h*} will be an attractor for all frequencies $x_{A+} > x_{A+}^{l*}$, while 0 will be an attractor for $x_{A+} < x_{A+}^{l*}$.

The novel result from this model was that even if the benefit is over twice as large as the cost, the survival of the A+ cells depends on the initial frequencies of cell-types. In addition to a stable equilibrium where the frequency of A+ type cells is above 0.5, there is an unstable equilibrium with the A+ frequency below 0.5. If the initial A+ frequency is below this equilibrium, the A+ cells will go extinct while a polymorphic equilibrium will be reached if it is above. The authors notes that "During tumorigenesis, it must be assumed that local collaboration is possible which may allow this critical threshold to be crossed locally." This article shows that taking (spatial considerations/three player game) can alter the dynamics of the model, drastically.

An explicitly spatial adaption of the same model was introduced in [6]. In the spatial model, cells are organized in a 100×100 grid. For each time step, some cells are killed, according to an update rule, and replaced by a cell in it's neighbourhood according to a revision protocol. Different update rules and revision protocols were considered as well as different definitions of a cells neighbourhood. With synchronous updating (SU) a fixed number of cells were killed each iteration, with asynchronous updating one cell was killed each iteration, and with semi-synchronous updating each cell had a fixed probability of being killed each round. Deterministic and probabilistic revision protocols were also considered. In both cases each cell in the killed cells neighbourhood gets a fitness defined as the sum of the payoffs of games played with each other cell in its neighbourhood. In the deterministic protocol, the cell with the highest fitness gets to replace the killed cell, while in the probabilistic protocol, the cells have a probability proportional to its fitness to replace it. The neighbourhood definitions considered were: the Von Neumann-neighbourhood consisting of the cells 4 neighbours, the Moore neighboorhood consisting of the cells 8 nearest neighboors, and the extended Moore-neighbourhood consisting of the nearest 15 neighbours. Simulations with the different combinations of revision protocol, update rule and neighbourhood size were run, with focus

on semi-synchronous updating and probabilistic revision protocol, since those were considered more biologically relevant. Different adaptations of the game were also simulating, corresponding to the hawk-dove game and the prisoners dilemma game. They found that with deterministic revision protocol, the cooperative types could prevail where they did not in the non-spatial game. But with semi-synchronous updating and probabilistic revision protocol, the results resembled those from the non-spatial game. They noted that the dependency of results on design decisions like neighbourhood size, update rule and revision protocol were a problem with the model.

Glycolysis and Invasion

Glycolysis is the lysis of oxygen to produce energy usually used by cells in hypoxic condition. It is less effective than mitochondrial metabolism, and produces cytotoxic waste, but is still seen in many cancers even in normoxic conditions [13]. In [14], Gatenby et al. proposed that glycolysis "confers a selective growth advantage on transformed cells because it allows them to create an environment toxic to competitors but relatively harmless to themselves". Basanta et al [8] used this hypothesis in a EGT-model. Three different cell types, all of which has acquired autonomous growth (AG) are modeled. The GLY-type uses Glycolysis, the INV-type is an invasive phenotype while the AG is a "normal" tumor cell with autonomous growth. Using glycolysis confers a cost (k) to the GLY-type in all interactions, but the acidity it produces gives a benefit (n) when interacting with an AG-type cell. The INV-type has a cost (c) of motility, but does not suffer any cost of acidity when interacting with a GLY-type cell. The AG-type has a cost of acidity (n) when interacting with a GLY-type cell. The cells compete resources of value 1 which has to be shared when two stationary cells interact.

	AG	INV	GLY
AG	$1/2$	1	$1/2-n$
INV	$1-c$	$1-c/2$	$1-c$
GLY	$1/2-k+n$	$1-k$	$1/2-k$

Table 5.5: Glycolysis Game

In the case where only AG and INV cells exists, the equilibrium-frequency of INV cells is given by:

$$x_{\mathrm{INV}} = \frac{1-2c}{1-c}$$

That means that a polymorphic equilibrium can be reached as long as $0 < c < 1/2$, while $c \geq 1/2$ leads to fixation of AG. In the case of all three interacting the equilibrium-frequencies x_{INV} of INV and x_{AG} of AG cells

are:

$$x_{\text{INV}} = 1 - \frac{k}{n}$$
$$x_{\text{AG}} = \frac{2kn + k - ck - cn}{2n^2}$$

The frequency of the INV-type will thus not depend on the cost of motility, only on the acidity-cost of the AG-type, and the glycolysis cost of the GLY-type. The authors note that "... conditions favouring anaerobic glycolysis also favour tumour invasion".

In [7] this model is adapted to describe glioblastoma multiforme. A INV-GLY phenotype is introduced as well as an angiogenic parameter (α) representing the benefit of having access to vasculature. The INV-GLY type acts as a GLY type when interacting with AG and INV cells, and as an INV type when interacting with a GLY type. The glycolytic types (GLY, INV-GLY) produces an angiogenic factor (an IDHD-1 mutation is taken to affect both glycolytic type and angiogenic type), which is positive when interacting with an AG type, but negative when interacting with a glycolytic type since the resulting vasculature will be leaky. The authors

	AG	INV	GLY	IVN-GLY
AG	$1/2 + \alpha/2$	1	$1/2 - n + \alpha$	$1/2 - n + \alpha$
INV	$1 - c$	$1 - c/2$	$1 - c/3$	$1 - c/3$
GLY	$1/2 - k + n + \alpha$	$1 - k + \alpha/2$	$1/2 - k + \alpha/4$	$1 - k + \alpha/2$
INV-GLY	$1/2 - k + n + \alpha$	$1 - k + \alpha/2$	$1 - c/3 - k + \alpha/2$	$1 - c/6 - k + \alpha/2$

Table 5.6: Glycolysis Game 2

ran simulations on the corresponding replicator equations with parameters taken to be relevant to a sGLM scenario. They found that at low α the INV type became dominant, but as α increased $INV - GLY$ took over dominance and the time before it reached domination decreased. The more important access to vasculature is, the more aggressive the tumor will be.

In [24] Mansury et al. adds a game theoretic module to a spatial-temporal model they developed in [23]. The original model described how cancer cells proliferates and migrates depending on microenvironemental factors. With the use of game theory they were able to extend the model to include interactions between genotypically different cancer cells. The extended model consist of type A and type B cells. Type A cells are more likely to proliferate, while type B cells are more likely to migrate. A cell's migrational and proliferative inclination is not only determined by it's genotype but is also affected by gap-junction channels it forms with other cells. This is incorporated into the model by a game-theoretic payoff matrix which describes how the cell-cell interactions affect migratory and proliferative inclination. These payoff-matrices is incorporated into the model by using these values to modify each cell's probability to migrate or proliferate depending on the the type of it's neighbouring cells.

5.0.1 Cooperation

One of the central themes in game theory is cooperation. Under which circumstances can individual agents acting in self-interest end up cooperating with each other. In [4] Axelrod et. al. investigates this theme in a cancer population and looks at scenarios in which cooperation between genotypically different cancer cells can make the cancer as a whole reach the hallmarks of cancer. They mention angiogenesis, production of growth factors and metastasis as ... For example, if one subclone has a angiogenesis promoting? mutation, other subclones in the cancer population will benefit from that as well. And if one subclone produces a paracrine growth factor, that will benefit other cells as well.

Interaction with normal cells

In [11] Dingli modelled the interaction between multiple-myeloma (MM) (cancer) cells, osteoclasts and osteoblasts using a game-theory payoff-matrix. Osteoclasts and osteoblasts are cells in the bone marrow that are responsible for bone resorption and formation respectively. In a healthy individual, the interactions between these cells leads to an equilibrium where they balance each other out. But when these cells interact with MM- cells, the equilibrium is disturbed. In addition to the interactions between OC and OB cells (a,e), the interactions considered in this article is cytokines released by MM-cells that stimulates the growth of OC-cells (b); a possible negative effect on OB-cells caused by the secretion of DKK1 by MM-cells (d); and a positive effect on MM-cells caused by production of growth factors by the OC-cells (c). This leads to the payoff-table given in table 5.7: From this they showed that if $\frac{c}{e} > 1$ the OB-cells will go extinct

	OC	OB	MM
OC	0	a	b
OB	e	0	$-d$
MM	c	0	0

Table 5.7: MM Game

which leads to bone-loss. If $\frac{d}{b}$ is large, the OB cells will go extinct faster than MM cells take over, leading to bone loss without a big tumor.

Anderson et. al. [2] used a game theory model in addition to a HDC model to investigate microenvironmental independence in tumors. The model consisted of microenvironment-dependent (mED) and microenvironment-independent (mEI) cells. mEI cells were given a constant fitness of h while mED cells had baseline fitness minus the cost (c) of getting resources from the mE which increased when interacting with other mED cells. This gave the payoff table 5.8 (with $n = 2$).

which gives the proportion (p) of mEI cells at equilibrium:

$$p = \frac{(1-2c)-h}{h+(1-2c)-(1-c)-h} = \frac{1-2c-h}{-c} = \frac{2c+h-1}{c}$$

	mED	mEI
mED	$1-2c$	$1-c$
mEI	h	h

Table 5.8: Microenvironmental Independence

which shows that the proportion of mEI cells increases as the cost of relying on the mE increases. When $c >= 1-h$ the mEI cells dominates the mE cells.

In [9] they develop this model further by introducing stromal cells. The stromal cells can get co-opted by the mED cells to interact with them in a mutualistic manner, giving them both a payoff of a. That gives the following payoff table table 5.9 (note that a payoff of d has been added to the mED, mEI interaction):

	S	mED	mEI
S	0	a	0
mED	$1-c+a$	$1-2c$	$1-c+d$
mID	$1-h$	$1-h$	$1-h$

Table 5.9: Microenvironmental Independence 2

They used the replicator equations leading from this payoff table to do simulations investigating how the different parameters affected the equilibrium distribution. They found that coexistence of all three types were possible for a small subset of parameter-space. They also found that varying the parameters could change the dominance from mED to mEI cells. They also ran a simulation where the parameters were changed mid-stream, from favouring mED cells to favouring mEI cells. The population then changed from being dominated by mED to being dominated by mEI.

Chapter 6

Problem Statement

In this thesis I will investigate whether it is possible and useful tomodel the host-tumor relationship using a game theory framework. Previous works using game theory in cancer modelling have focused solely on cell-cell interactions and only cells have been considered as active agents. Here I will extend this framework, by using methods from evolutionary game theory, to include interactions between the host and the cancer cells.

Part II

Method

Chapter 7

General Framework

An organism is thought to represent a multicellular organism. Each organism is associated with a population of cells. This population is thought to represent either the whole organism, or an organ or part of an organ that is separated from the rest of the organism. A cell is thought to represent a member of the cell population associated with an organism. An organism possesses a trait, or strategy, that determines some of it's function. A cell also possesses a trait which determines some of it's function. The premise of the model is that:

- Some part of an organism's fitness is determined both by it's trait and of the traits of the cells in it's cell population
- Some part of a cell's fitness is determined both by it's trait and by the trait of the organism it is part of

A basic example which fits this description is:

- The organism represents a human being
- The cell population represents a part of the small intestine of the human
- The cell traits are either:
  - Stay on the lining of the intestinal tract and absorb nutrients and pass it along to the bloodstream (normal function)
  - Stay inside the crypt and absorb nutrients from the bloodstream and proliferate (abnormal function)
- The organism traits are either:
  - Have an immune system that seeks out cells with abnormal function and kill them
  - Don't have such an immune system

The fitness of the organisms is then partly determined by it's trait, since the immune system is costly and because it runs the risk of the immune system misinterpreting and start attacking normal cells. It is also determined by

the trait of it's cell population, because cells with normal function does a job for the organism increasing it's fitness, while the abnormal cells just use nutrients and doesn't provide a useful function. Similarly the fitness of a cell is determined by it's trait, since an abnormal cell will proliferate and thus have a high reproduction rate, while a normal cell will not proliferate and thus have a reproduction rate of 0. It is also affected by the organism trait since an abnormal cell will be killed if the organism has the immune trait, giving it low fitness, while it will be able to continue proliferating if it doesn't.

I will denote these concepts in the following way:

- The role of an organism is denoted by O and the role of a cell will be denoted by C
- The possible traits of an organism is denoted by Σ^O and the possible traits of a cell is denoted by Σ^C
- The size of the organismal trait space is denoted m_O and the size of the cellular trait space m_C
- The contribution to an organism's fitness is given by the function $g : \Sigma^O \times \Sigma^C \to \mathbb{R}$
- The contribution to a cell's fitness is given by the function $f : \Sigma^C \times \Sigma^O \to \mathbb{R}$

A cellular cancer trait can then be consider a trait which gives the cell a high payoff, but reduces the payoff of the organism it resides in.

The fitness functions g and f above can be considered the payoffs from an interaction between a single cell and an organism. Since an organism has a population of cells, fitness should be influenced by each cell in the population and thus be a function of the cell population state. I choose to let this function be the average payoff from an interaction with each cell in the population.

Letting $X = \left\{(x_i)_{i\in\Sigma^C} \mid \sum_{i\in\Sigma^C} x_i = 1\right\}$ represent the population state space of a cell population, the fitness function for organisms is given by:

$$G_j(x) = \sum_{i\in\Sigma^C} x_i g(j, x_i) \tag{7.1}$$

(7.2)

Similarly the fitness of a cell should represent the value of the interaction with the organism it is in. (In frequency dependent **??** dynamics the interaction will include another cell as well). The fitness for a cell in an organism with organismal trait $j \in \Sigma^O$ is then a function of the cell strategy $i \in \Sigma^C$. $F_j : \Sigma^C \to \mathbb{R}$

$$F_j(i) = f(i, j)$$

7.1 Dynamics

7.1.1 Organismal Dynamics

I consider a population of organisms, which reproduce asexually. This is not biologically correct for humans, or indeed most multicellular organisms, but including the mechanisms of sexual selection complicates matters. The birthrate is given by a baseline rate β_O plus an interaction dependent birth rate given by the fitness function G in the previous section. Thus the birthrate of an organisms with trait $j \in \Sigma^O$ with a cell population in state $x \in X$ the birth rate is given by $\beta_O + G_j(x)$. An organisms birth rate is thus determined by it's trait as well as the makeup of its cell population. The death rate is considered to be constant and given by δ_O. The offspring of an organism inherits the organism's trait, but not its cell population; Each new organism starts out with a cell population where all cells have the same trait which is considered the normal trait. This represents the fact that the evolution in a somatic cell population does not affect the genome of the germ line cells.

Each organism's cell population also have a dynamic. A cell's reproduction rate is given by the base line rate β_C and a term determined by the fitness function from the last section. Thus for a cell with trait $i \in \Sigma^C$, in an organism with trait $j \in \Sigma^O$ and in a cell population in state $x \in X$, the birth rate is given by $\beta_C + F_i(j, x)$. The death rate is fixed at δ_O. Normally the offspring of a cell inherits the cell's trait, but in some cases a mutation occurs giving the offspring another trait from the trait space. I make different assumptions as to how these mutations occur, which lead to different dynamics. The whole system can then be described by the following:

- Ω is the population of organisms
- $\mathscr{C} = \{\mathscr{C}_\omega \mid \omega \in \Omega\}$ a set containing a cell population for each organism
- $\Sigma = (\Sigma^C, \Sigma^O)$ a cellular trait space and an organismal trait space
- The cellular state space $X \subseteq \Delta^{m_c}$
- A cellular fitness function for each cellular strategy $(F_i)_{i \in \Sigma^C}$
- An organismal fitness function for each organismal strategy $(G_j)_{j \in \Sigma^O}$

In this thesis I will make the assumption that each cell population is sufficiently large that they can be considered infinite and that the population state in a cell population can be considered a differentiable function of time. Thus the cell dynamics in each organism can be represented by a system of differential equations. I will deal first with the dynamics leading from the assumption that the cells' fitness are frequency independent, then see what happens when cell-cell interactions are considered.

7.1.2 Assumptions

This is a very simplified description of how the dynamics. There are several of the aspects considered in section 4.2 that are not included.

In this model the death rate is constant, while the reproduction rate varies according to the interactions. This does not represent the fact that cancer can be a deadly disease and therefore affect the death rate of the organism. Similarly, different organismal traits might affect the death rate of cells, for example an immune response. The choice to let the death rate be fixed is motivated by two notions. One is that letting the birth rate vary is most common in evolutionary game theory, and the a fixed death rate keeps most in line with the current literature. Secondly, both birth and death rates can be affected and varying both would lead to unnecessary complications.

The model also assumes that the baseline birth rate is constant throughout the lifetime of an organism. This is not the case for humans who have a limited reproductive age. An interpretation of the model that accounts for this is that a death in this model means reaching the end of the reproductive age.

To make the system representable by ordinary differential equations I also make the assumption that the cellular dynamics are sufficiently faster than the organismal dynamics that the cell populations can be seen as instantaneously reaching stable equilibrium points.

Chapter 8

Frequency Independent Cell Dynamics

I will here consider the dynamics when a cell's fitness is independent of the population state of the cell population it inhabits. The cellular fitness is then a function only of its trait and its organism's trait. The fitness function in an organism with organismal trait $j \in \Sigma^O$ can then be written $F_j : \Sigma^C \to \mathbb{R}$, where $F_j(i)$ gives the fitness of a cell with cellular trait $i \in \Sigma^C$ in an organism with organismal trait $j \in \Sigma^O$.

The replicator equation definition 12 for the cellular dynamics in an organism with organismal trait j then becomes:

$$\dot{x}_i = x_i(F_j(i) - \sum_{k \in \Sigma^C} x_k F_k) \; \forall i \in \Sigma^C$$

The only stable rest point of this dynamic is that where the fittest cell trait is fixated. This stable rest point is given by $x^*(j)$ where:

$$x^*(j)_i = \begin{cases} 1 & \text{if } i = \alpha_j \\ 0 & \text{otherwise} \end{cases}$$

where

$$\alpha_j = \underset{k \in \Sigma^C}{\operatorname{argmax}} f(k, j)$$

Assuming that a small mutation rate continuously perturb the system from rest points such that the system ends up in the stable rest point, and that this happens so much faster than the organismal reproduction, the population state of an organism with organismal trait j will always be in state $x^*(j)$. Thus, using equation 7.1 the fitness of an organism with trait

$j \in \Sigma^O$ can be given as:

$$\begin{aligned} W_j &= G_j(x^*(j)) \\ &= \sum_{i \in \Sigma^C} x^*(j)_i g(j, x^*(j)_i) \\ &= g(j, \alpha_j) \end{aligned}$$

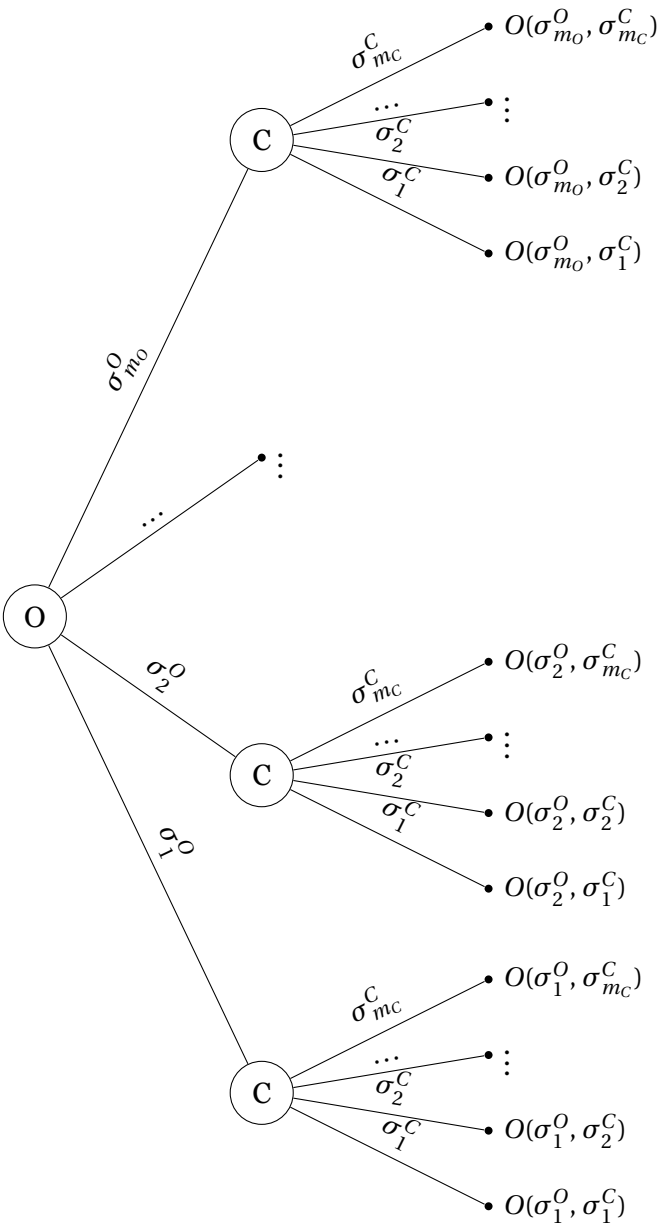
Given these fitness values, the replicator equation for the organismal dynamics, becomes:

$$\begin{aligned} \dot{y}_j &= y_j(W_j - \sum_{k \in \Sigma^O} y_k W_k) \; \forall \, j \in \Sigma^O \\ \dot{y}_j &= y_j(g(j, \alpha_j) - \sum_{k \in \Sigma^O} y_k g(k, \alpha_k)) \; \forall \, j \in \Sigma^O \end{aligned}$$

This system also has only one stable rest point y^* which is given by:

$$y_j^* = \begin{cases} 1 & \text{if } j = \text{argmax}_{k \in \Sigma^O} g(k, \alpha_k) \\ 0 & \text{otherwise} \end{cases}$$

This means that the organismal trait j that has the highest payoff from an interaction with a cell trait that has the highest payoff an interaction with j, will be fixated in the organismal population. This result is corresponds to the subgame perfect equilibrium of a the Leader-Followergamedefinition 10 $LF((\Sigma^O, \Sigma^C), (u, v))$ where the organism role is the leader and the cell role is the follower. Denoting the organismal strategies as $\Sigma^O = (\sigma_1^O, \sigma_2^O, \ldots, \sigma_{m_O}^O)$ and the cellular strategies as, $\Sigma^C = (\sigma_1^C, \sigma_2^C, \ldots, \sigma_{m_C}^C)$, gives the following game tree for the Leader-



Followergame:

8.0.3 Application

Let the cellular trait space include a normal trait $\bar{T}$, which represents normal cell function, and a tumorigenic trait T that represents increased proliferation which gives a fitness advantage a over normal cells and decreases the organismal fitness by d. Thus $\Sigma^C = \{\bar{T}, T\}$.

The organismal trait space includes a passive trait $\bar{P}$ that does not interfere with the cell dynamics; and a punishing trait P that decreases the fitness of tumorigenic cells by p. $\Sigma^O = \bar{P}, P$.

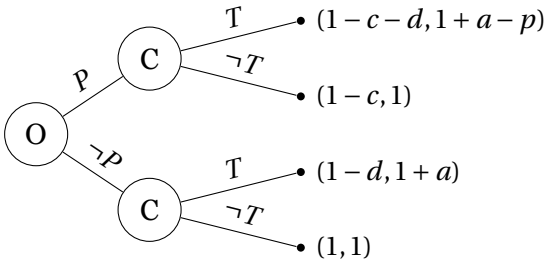
The organismal payoff g and cellular payoff f from an interaction then

becomes:

$$f(\neg T, \neg P) = 1 \qquad f(\neg T, P) = 1$$
$$f(T, \neg P) = 1 + a \qquad f(T, P) = 1 + a - p$$

$$g(\neg P, \neg T) = 1 \qquad g(P, \neg T) = 1 - c$$
$$g(\neg P, T) = 1 - d \qquad g(P, T) = 1 - d - c$$

The Leader-Followergame $LF((\Sigma^O, \Sigma^C), (u, v))$ can be represented by the game tree:



The outcome of this game is dependent on the relationship between the parameters a and p and between c and d. If $p > a$ then C will respond with $\neg T$ to P. If, in addition , $c < d$ O will play P. Otherwise O will play $\neg P$ and C will play T. A punishment strategy is therefore successful if it successfully deters the cells from playing the cancer strategy and at the same time costs less for the organism than the detrimental effect of the cancer cells.

8.0.4 Infrequent Mutations

In the previous model, cellular mutations were thought to occur continuously, thus always perturbing any unstable rest point such that the cellular population always ended up in a stable rest point. In this section I consider the case where tumorigenic mutations only happen occasionally. Ideally, the mutation rates should be defined as a cellular property. The standard way to model it is that each cell division has a given probability of generating a mutant. When the cellular population size is considered infinite, a finite cellular mutation rate would give rise to continuously occurring mutations. I therefore define the mutation rates as an organismal property. I consider first a dynamic where the only mutations considered are from the normal cellular strategy to one of the other cellular strategies.

For interactions given by the strategy spaces Σ^O, Σ^C, where the normal cellular strategy is denoted $\eta \in \Sigma^C$, and payoff functions g, f, I define $\mu_i \; \forall i \in \Sigma^C / \{\eta\}$ as the mutation rate from the normal cell strategy η to the cellular strategy i. When a mutation from η to i occurs, a small part of the cell population mutates to the i strategy. The cellular dynamics will then lead to either η or i fixating in the population, depending on which trait gives the highest fitness. Define $\alpha_j : \Sigma^C / \{\eta\} \to [0, 1]$ for all organismal strategies

$j \in \Sigma^O$ as:

$$\alpha_j(i) = 1 \begin{cases} 1 & \text{if } f(i,j) > f(\eta, j) \\ 0 & \text{otherwise} \end{cases} \tag{8.1}$$

This function determines whether or not a cellular trait i will fixate in the population if the mutation μ_i occurs in an organism with trait $j \in \Sigma^O$.

Dynamics

Let β_O be the baseline birth rate for organisms and δ_O be the death rate. Let $\hat{u}(i,j) = \beta_O + g(i,j)$ be the birth rate of an organism with organismal trait $j \in \Sigma^O$ and a cellular population consisting of cells with cellular trait $i \in \Sigma^C$ Let $p_i^j(t)$ represent the number of organisms with organismal trait j and a cell population with cellular trait i. For cell non-normal cell populations the number of organism s with organismal trait j and cell population with trait i after time $t + dt$ the number is then:

$$p_i^j(t+dt) = p_i^j(t) - p_i^j(t)\delta_O\, dt + p_\eta^j(t)\mu_i\alpha_j(i)\, dt \;\; \forall i \in \Sigma^C / \{\eta\}$$

The first term is the previous number of organisms. The second represents the organisms that die in the time period, while the third represents the number of organisms that had a normal cell population where a mutation lead to the population switching to cellular trait i. The number of organisms with a normal cell population is given by:

$$p_\eta^j(t+dt) = p_\eta^j(t) - p_\eta^j(t)\delta_O\, dt - \sum_{k \in \Sigma^C/\{\eta\}} \mu_k \alpha_j(k) p_\eta^j(t)\, dt + \sum_{k \in \Sigma^C} \hat{u}(j,k) p_k^j(t)\, dt \tag{8.2}$$

The first term is the previous number of organisms, the second is the number of organisms that die in the time period, the third term is the number of organisms where the cell population switches to another trait and the fourth is the number of organisms that are born during the time period.

To simplify the equations I will assume that the population size stays constant by defining the actual birth rate for an organism with trait j and cell population with trait i at time t as:

$$\hat{u}(j,i) \frac{p(t)\delta_O}{\sum_{k \in \Sigma^C} \sum_{l \in \Sigma^O} p_k^l(t)\hat{u}(k,l)}$$

This makes 8.2:

$$p_\eta^j(t+dt) = p_\eta^j(t) - p_\eta^j(t)\delta_O\, dt - \sum_{k \in \Sigma^C/\{\eta\}} \mu_k \alpha_j(k) p_\eta^j(t)\, dt + \sum_{k \in \Sigma^C} \frac{\delta_O p(t) \hat{u}(j,k) p_k^j(t)}{\sum_{k \in \Sigma^C} \sum_{l \in \Sigma^O} p_k^l(t)\hat{u}(k,l)}\, dt$$

This leads to the differential equations:

$$\dot{p}_i^j = -p_i^j \delta_O + p_\eta^j \mu_i \alpha_j(i) \;\; \forall i \in \Sigma^C / \{\eta\}$$
$$\dot{p}_\eta^j = -p_\eta^j \delta_O - \sum_{k \in \Sigma^C / \{\eta\}} \mu_k \alpha_j(k) p_\eta^j + \delta_O p \frac{\sum_{k \in \Sigma^C} \hat{u}(j,k) p_k^j}{\sum_{k \in \Sigma^C} \sum_{l \in \Sigma^O} p_k^l \hat{u}(k,l)}$$

$$\begin{aligned}\dot{p} &= \sum_{i \in \Sigma^C} \sum_{j \in \Sigma^O} \dot{p}_i^j \\ &= -\delta_O p + \sum_{i \in \Sigma^C} \sum_{j \in \Sigma^O} \delta_O p \frac{p_i^j \hat{u}(j,i)}{\sum_{m \in \Sigma^C} \sum_{n \in \Sigma^O} p_m^n \hat{u}(m,n)} \\ &= 0\end{aligned}$$

Let $x_i^j(t) = p_i^j(t)/p(t)$ be the frequency of organisms with organismal trait $j \in \Sigma^O$ and a cell population of cellular trait $i \in \Sigma^C$. Since $\dot{p} = 0$, $\dot{x}_i^j = \frac{\dot{p}_i^j}{p}$, which gives:

$$\dot{x}_i^j = -x_i^j \delta_O + x_\eta^j \mu_i \alpha_j(i) \;\; \forall i \in \Sigma^C / \{\eta\}$$
$$\dot{x}_\eta^j = -x_\eta^j \delta_O - \sum_{k \in \Sigma^C / \{\eta\}} \mu_k \alpha_j(k) x_\eta^j + \delta_O \frac{\sum_{k \in \Sigma^C} \hat{u}(j,k) x_k^j}{\sum_{k \in \Sigma^C} \sum_{l \in \Sigma^O} x_k^l \hat{u}(k,l)}$$

If all the organisms in the population has the same trait $j \in \Sigma^O$, the only equilibrium state is given by (see appendix A.0.1 for the mathematical derivations):

$$x_\eta^j = \frac{\delta_O}{\delta_O + \sum_{i \in \Sigma^C / \{\eta\}} \mu_i \alpha_j(i)}$$
$$x_i^j = \frac{\mu_i \alpha_j(i)}{\delta_O + \sum_{i \in \Sigma^C / \{\eta\}} \mu_i \alpha_j(i)} \forall i \in \Sigma^C / \{\eta\}$$

The average value of $\hat{u}$ is then given by:

$$W_j = \frac{\delta_O \hat{u}(j,\eta) + \sum_{i \in \Sigma^C / \{\eta\}} \hat{u}(j,i) \mu_i \alpha_j(i)}{\delta_O + \sum_{i \in \Sigma^C / \{\eta\}} \mu_i \alpha_j(i)}$$

The only stable equilibrium of the system is fixation of the organismal trait $k \in \Sigma^O$ that maximises W_j:

$$k = \underset{j \in \Sigma^O}{\operatorname{argmax}} W_j \tag{8.3}$$

The stable equilibrium state x^* is given by:

$$x_\eta^k = \frac{\delta_O}{\delta_O + \sum_{i \in \Sigma^C/\{\eta\}} \mu_i \alpha_k(i)}$$
$$x_i^k = \frac{\mu_i \alpha_k(i)}{\delta_O + \sum_{i \in \Sigma^C/\{\eta\}} \mu_i \alpha_k(i)} \forall i \in \Sigma^C/\{\eta\}$$
$$x_i^j = 0 \ \forall j \neq k$$

8.0.5 Game Interpretation

The function $\alpha_j(i)$ 8.1 corresponds to a 'rational' choice for a cell between cellular traits i and η in an organism that has organismal trait $j \in \Sigma^O$. The organismal trait that reaches fixation 8.3 also seems like a 'rational' choice in that it is an optimization. The mutation probabilities is best represented as an assignment from nature. If a mutation occurs and the mutant trait fixates in the cell population, no more mutations will occur, and the organismal fitness is thus detirmened. If however a mutatation occurs and the mutant gets extinct the cell population will still be normal and further mutations are possible. Since the cell choices represents an optimization of the fitness of the trait there and then independent of other traits in the trait space, a cell player's payoff must be defined as the choice it makes there and then. Thus when more than one cellular desicions must be made in the game, these must be made by different cell players. Define the different chance actions as D representing the organism dieing and $(M_i)_{i \in \Sigma^C/\{\eta\}}$ where M_i defines a mutation to celluar strategy i. The

This motivates the extensive form game $\Gamma =< N, H, P, f_c, (\mathcal{I}_i), (\pi_i) >$ given by:

- The infinite countable set of players: $\{O, C_1, C_2, C_3, \ldots\}$
- The histories given by:

$$H = \{\emptyset\} \cup I_M \cup I_C \cup Z$$

where I_M, I_C, Z are defined by. $(j) \in I_M \forall j \in \Sigma^O$ and if h in I_m then:

$$(h, m, \eta) \in I_M \forall m \in M$$
$$.(h, m) \in I_C \forall m \in M$$
$$(h, D, \eta) \in Z$$
$$(h, M_i, i) \in Z \forall i \in \Sigma^C$$

- The player function:

$$P(h) = \begin{cases} O & \text{if } h = \emptyset \\ c & \text{if } |h|\%2 = 1 \\ C_{|h|/2} & \text{if } |h|\%2 = 0 \end{cases}$$

- The probability distribution

$$f_c(M_i|h) = \frac{\mu_i}{\delta_O + \sum_{k\in\Sigma^C/\{\eta\}}} \forall h \in H \mid P(h) = c$$
$$f_c(D|h) = \frac{\delta_O}{\delta_O + \sum_{k\in\Sigma^C/\{\eta\}}} \forall h \in H \mid P(h) = c$$

- The discrete partitions

- The payoff functions $(\pi_i)_{i\in N}$

$$\pi_O((a^1, a^2, \ldots, a^n)) = \begin{cases} \hat{u}(a^1, \eta) & \text{if } a^n = D \\ \hat{u}(a^1, a^n) & \text{otherwise} \end{cases}$$
$$\pi_{C_i}((a^1, a^2, \ldots, a^n)) = \begin{cases} f(a^{(2i+1)}, a^1) & \text{if } 2i < n \\ f(\eta, a^1) & \text{if } 2i = n \\ 0 & \text{if } 2i > n \end{cases}$$

The flow of the game is this:

- The organism is the first to move, playing a strategy from the organismal strategy space

- The cells then make moves sequentially. If a cell plays the normal strategy, the game continues, if it plays one of the other strategies, the game ends. Each cell gets the payoff corresponding to the strategy the organism played (j) and the strategy itself played (i) $f(\sigma^O, \sigma^C)$. The cells that do not get to play recieve a payoff of 0, but this is irrelevent for the outcome.

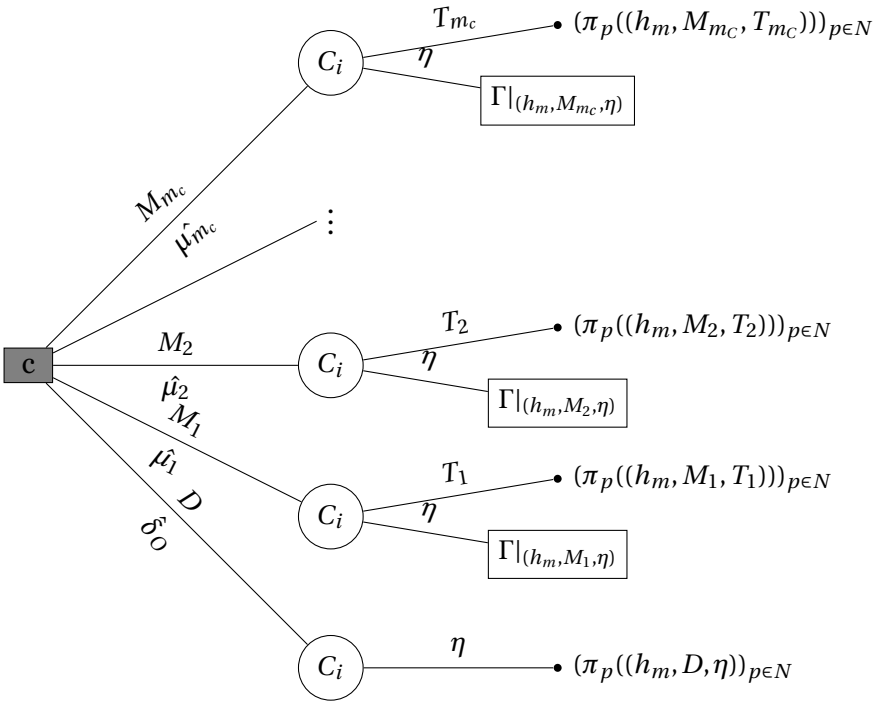
- Between each cell move is a chance move, where either the organism dies D, ending the game, or a mutation M_i occurs which leads to another cell move.

- The organism gets the payoff corresonding to what it plays and what the last cell plays.

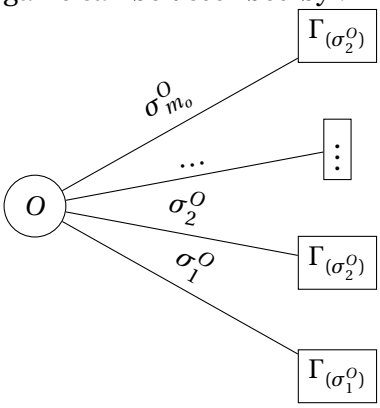
Let $\Gamma|_{h_m}$ be defined as the subgame following a history in I_m . Let the cellular strategies be denoted by $\Sigma^C = (\eta, \sigma_1^C, \sigma_2^C, \ldots, \sigma_{m_C}^C)$ and let M_i denote a mutation to strategy σ_i^C. Let

$$\hat{\mu_i} = \frac{\mu_i}{\delta_O + \sum_{k\in\Sigma^C/\{\eta\}}}$$
$$\hat{\delta_O} = \frac{\delta_O}{\delta_O + \sum_{k\in\Sigma^C/\{\eta\}}}$$

This game can be represented graphically as:



By denoting the organismal strategies: $\Sigma^O = (\sigma_1^O, \sigma_2^O, \ldots, \sigma_{m_O}^O)$, the whole game can be described by :



The outcome of the subgame equilibrium of this game corresponds to the stable rest point of the differential equations. (See appendix A.0.2 for derivation of this result)

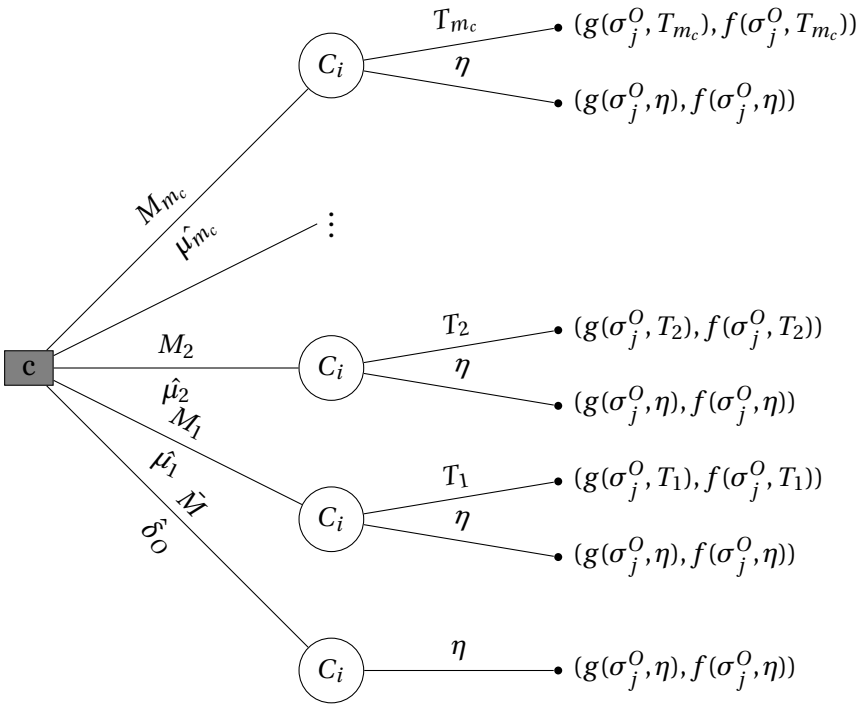
The fact that the cell nodes are divided between different cell players is important since it implies that a the cell players are indifferent to the further developments of the game. This represents ethe lack of foresight that is characteristic of "evolutionary rationality". If each cell desicion was made by the same player, it would be able to consider not choosing one cancerous strategy since by choosing the normal strategy it would have the opportunity of a more advantageous cancerous strategy in the future.

If $\sum_{k\in\Sigma^C/\{\eta\}} \mu_k << \delta_O$, the game can be reduced to a much simpler form

by the approximations:

$$\frac{\mu_i}{\delta_o + \sum_{k \in \Sigma^O / \{\eta\}} \mu_k \alpha_j(k)} \approx \frac{\mu_i}{\delta_O + \sum_{k \in \Sigma^O / \{\eta\}} \mu_k}$$
$$\frac{\delta_O}{\delta_o + \sum_{k \in \Sigma^O / \{\eta\}} \mu_k \alpha_j(k)} \approx \frac{\delta O}{\delta_O + \sum_{k \in \Sigma^O / \{\eta\}} \mu_k}$$

The games $L|_{(\sigma_j^O)}$ can then be represented by the game trees:



The interpretation of this is that the probability that an organism should get a mutation that does not fixate, and then get another mutation is negliable. Therefore the risk of a cancer from a given cancer trait is given just by the probability of getting the mutation to that trait times the probability of that trait fixating (0 or 1) times the reduced fitness to the organism from havin a cell population with that trait. The organism chooses the strategy that minimizes the sum of this risk for all the celluar traits.

Chapter 9

Frequency Dependent Cell Dynamics

9.1 Game Definition

In this section I look at the dynamics when a cell's payoff from an interaction is not not only determined by its own trait and the trait of its organism, but also on the cellular trait of the cell it interacts with. In this context the celluar payoff function from an interaction is a function $f : \Sigma^C \times \Sigma^C \Sigma^O \to \mathbb{R}$, where $f(i, j, k)$ defines the payoff to a cell with celluar trait $i \in \Sigma^C$ interacting with a cell with trait $j \in \Sigma^C$ in an organism with trait k. I chose to let the fitness of a trait be defined as the payoff from random matching of a symmetric two player game against a cell from the same cell population since this is the framework that has been used in the previous literature (chapter 5). The fitness of a cellular trait in an organism with organismal trait j is then given by the function $F_j : \Sigma^C \times X \to \mathbb{R}$, where:

$$F_j(i, x) = \sum_{k \in stspC} f(i, k, j)$$

9.2 Dynamics

The stable equilibrium points of the cell dynamics in an organism then corresponds to a Nash equilibrium of the cellular population game defined by the organism's trait, which again corresponds to the mixed Nash Equilibria in the STG defined by f (theorem 1). Defining the resulting organismal dynamics is not always trivial due to the fact that an STG can have several Nash Equilibria. I will only consider 2 and 3 strategy games here, since the dynamics of these games are well understood [10][35]. I consider first dynamics with only two cellular traits. The celluar population game defined by an organismal trait can then be classified according to [35], being either a coordination, anti-coordination or domination game. Only coordination games have more than one ESS. The two ESS of a coordination game correspond to fixation of either trait. The basins of attractions for the

two ESSes is divided by a third, unstable, Nash equilibrium which acts as an invasion barrier. Thus if one of the traits is fixated in the cell population, the cell population is stable against invasions from the other cell trait. The other classes of two-strategy games has a unique ESS. Given the initial cell population, the resulting stable rest point after a pertrubing mutation can be uniquly determined. Since I assume that all new organisms are born with a cell population where all the cells have a trait $\eta \in \Sigma^C$, this initial cell population is given. Assuming, as in chapter 8, that a small mutation rate is continously pertrubing the celluar populations so that they always end up in the uniquely determined stable rest point, the cell population of an organism with organismal trait $j \in \Sigma^O$ is always $x^*(j)$, where $x^*(j)$ is the uniquly determined stable rest point of the game F_j. Knowing this, the fitness of an organism with organismal trait $j \in \Sigma^O$ can be written:

$$\begin{aligned} W_j &= G_j(x^*(j)) \\ &= \sum_{i \in \Sigma^C} x^*(j)_i g(j,i) \end{aligned}$$

Let y_j be the proportion of organisms in the population with organismal trait $j \in \Sigma$. The replicator equation for the organismal population then becomes:

$$\begin{aligned} \dot{y}_j &= y_j(W_j - \sum_{k \in \Sigma^O} y_k W_k) \; \forall \, j \in \Sigma^O \\ &= y_j(\sum_{i \in \Sigma^C} x^*(j)_i g(j,i) - \sum_{k \in \Sigma^O} y_k \sum_{i \in \Sigma^C} x^*(k)_i g(k,i)) \; \forall \, j \in \Sigma^O \end{aligned}$$

This fitness value is constant for all organismal strategies and thus the only stable rest point for the organismal dynamics is the fixation of the organismal trait $j \in \Sigma^O$ for which W_j is biggest. The only stable rest point for this system is given by:

$$y_j^* = \begin{cases} 1 & \text{if } j = \text{argmax}_{k \in \Sigma^O} \sum_{i \in \Sigma^C} x^*(k)_i g(k,i) \\ 0 & \text{otherwise} \end{cases}$$

9.3 Results

The growth factor production game in chapter 5 is an anti-coordination game when $i < j$, meaning that the production cost of the growth factor is lower than the benefit it gives.

I use this game as a basis for a game including the organism. The cellular trait space is then $\Sigma^C = \{A+, A-\}$. I define two organismal strategies $\Sigma^O = \{\bar{P}, P\}$, where $\bar{P}$ represents a naive strategy that defines the cellular game represented by table 5.1 and P represents a punishing strategy that reduces the fitness of $A+$ cells by p but at a cost c to the organism. Thus the

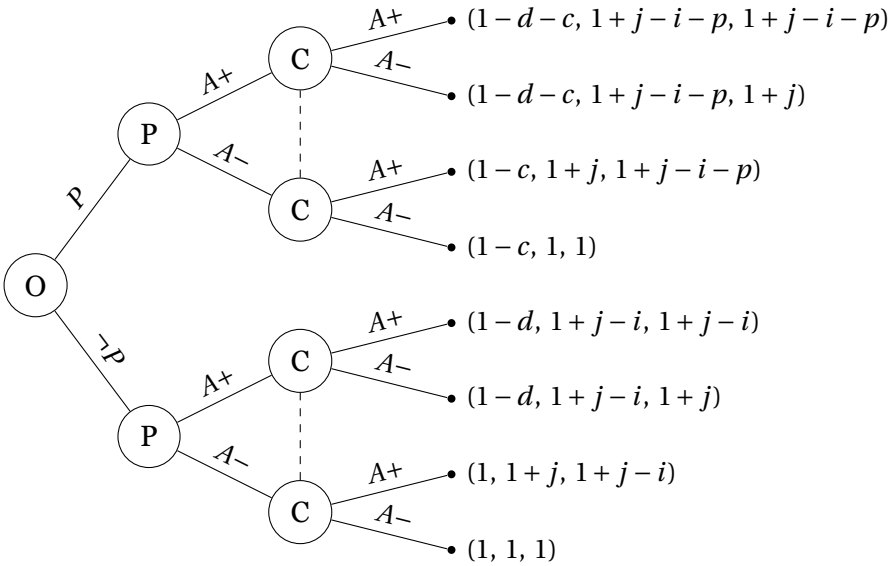
cellular payoff function f is given by:

$$
\begin{aligned}
f(A+, A+, \bar{P}) &= 1 - i + j & \qquad f(A+, A-, \bar{P}) &= 1 - i + j \\
f(A-, A+, \bar{P}) &= 1 + j & \qquad f(A+, A-, \bar{P}) &= 1 \\
f(A+, A+, P) &= 1 - i + j - p & \qquad f(A+, A-, P) &= 1 - i + j - p \\
f(A-, A+, P) &= 1 + j & \qquad f(A+, A-, P) &= 1
\end{aligned}
$$

I let the organismal fitness from interacting with an $A-$ cell, be 1 for $\bar{P}$ organisms and $1 - c$ for P organisms and let the $A+$ cells decrease the organismal fitness by d such that:

$$
\begin{aligned}
g(\bar{P}, A+) &= 1 - d & \qquad g(\bar{P}, A-) &= 1 \\
g(P, A+) &= 1 - d - c & \qquad g(P, A+) &= 1 - c
\end{aligned}
$$

This defines the following game tree, I denote one of the cell players as 'P', meaning population, which is the player that affects the organismal payoff.



The interresting case is when $0 < i < j$ since if $i > j$, $A-$ dominates $A+$ in all cases leading to the outcome $(\bar{P}, A-, A-)$. If however $i < j$, the cellular game under $\bar{P}$ has one stable symmetric equilibrium given by

$$
\begin{aligned}
x^*(\bar{P})_{A-} &= \frac{i}{j} \\
x^*(\bar{P})_{A+} &= 1 - \frac{i}{j}
\end{aligned}
$$

which gives the organism the payoff:

$$\begin{aligned} G_{\bar{P}}(x^*) &= x^*(\bar{P})_{A-} g(\bar{P}, A-) + x^*(\bar{P})_{A+} g(\bar{P}, A+) \\ &= \frac{i}{j} + (1 - \frac{i}{j})(1-d) \\ &= 1 - d + \frac{i}{j} d \end{aligned}$$

The organismal P strategy can lead to two different games dependent on whether or not $i + p > j$. If $i + p < j$ the cellular game is still an anti-coordination game with equilibrium points:

$$\begin{aligned} x^*(P)_{A-} &= \frac{i+p}{j} \\ x^*(P)_{A+} &= 1 - \frac{i+p}{j} \end{aligned}$$

which gives the organismal payoff:

$$\begin{aligned} G_P(x^*) &= x^*(P)_{A-} g(P, A-) + x^*(\bar{P})_{A+} g(P, A+) \\ &= \frac{i+p}{j}(1-c) + (1 - \frac{i+p}{j})(1-c-d) \\ &= 1 - c - d + d\frac{i+p}{j} \end{aligned}$$

The P strategy is then better than $\bar{P}$ if:

$$\begin{aligned} G_P(x^*(P)) &> G_{\bar{P}}(x^*(\bar{(P)}) \\ 1 - c - d + d\frac{i+p}{j} &> 1 - d + \frac{i}{j} d \\ dp &> jc \end{aligned}$$

So the P strategy is better if the fitness cost it gives to the organism times the cellular fitness benefit given by the GF production is less than the extra damage the $A+$ cells give to the organism times the fitness cost the P strategy confers to the $A+$ cells.

If $i + p > j$, the $A-$ trait will fixate in the cell population. The equilibrium point is then:

$$\begin{aligned} x^*(P)_{A-} &= 1 \\ x^*(P)_{A+} &= 0 \end{aligned}$$

which gives the organism the payoff:

$$
\begin{aligned}
G_P(x^*) &= x^*(P)_{A-} g(P, A-) + x^*(\bar{P})_{A+} g(P, A+) \\
&= 1 - c
\end{aligned}
$$

. The P strategy is then better than the $\bar{P}$ if:

$$
\begin{aligned}
G_P(x^*(P)) &> G_{\bar{P}}(x^*(\bar{(}P)) \\
1 - c &> 1 - d + \frac{i}{j} d \\
-c &> -d + \frac{i}{j} d \\
c &< 1 - \frac{i}{j} d
\end{aligned}
$$

Which means if the organsismal cost of the P strategy is less than the negative effect of the $A+$ cells under the $\bar{P}$ strategy.

Taken together, these result says that the P strategy is better than the $\bar{P}$ strategy if:

$$
(i + p < j \ \wedge \ dp > jc) \ \vee \ (i + p \geq j \ \wedge c < 1 - \frac{i}{j} d)
$$

The novel effect here, compared to the frequency independent cell dynamics, is that the relationship between the effects on the organismal payoff and the cellular payoff induced by an organismal strategy is relevant.

9.4 Three cellular strategies

When considering three cellular strategies, the dynamics are more complicated. Three strategy STGs can be classified into 19 different classes of dynamics, depending on how many and where the stable rest points are. As with two strategies, the stable rest point can be determined if the initial population state is known. Describing how this can be determined for each of the 19 categories is out of reach for this, but use an example from the review (chapter 5).

The game described in table 5.5 describes a game between normal cancer cells, glycolytic cancer cells and invasive cancer cells. The conclusion was that the equilbrium proportion of invasive cells was independent of the cost of motility. I use this game as a base for a organsimal-cellular game where the organism has three strategies:

- A naive strategy ($\bar{A}$) leading to a cellular game identical to table 5.5
- A strategy punishing the INV type cells (P_{inv}), subtracting p_{inv} from their fitness, at a cost c_{inv} to the organism

- A strategy punishing the GLY type cells (P_{gly}), subtracting p_{gly} from their fitness, at a cost c_{gly} to the organism

The cellular games is shown in table form in table 9.1. The authors found

$\Gamma_{\tilde{A}}$	AG	INV	GLY
AG	$1/2$	1	$1/2-n$
INV	$1-c$	$1-c/2$	$1-c$
GLY	$1/2-k+n$	$1-k$	$1/2-k$
Γ_{inv}	AG	INV	GLY
AG	$1/2$	1	$1/2-n$
INV	$1-c-p_{\text{inv}}$	$1-c/2-p_{\text{inv}}$	$1-c-p_{\text{inv}}$
GLY	$1/2-k+n$	$1-k$	$1/2-k$
Γ_{gly}	AG	INV	GLY
AG	$1/2$	1	$1/2-n$
INV	$1-c$	$1-c/2$	$1-c$
GLY	$1/2-k+n-p_{gly}$	$1-k-p_{gly}$	$1/2-k-p_{gly}$

Table 9.1: Cellular Glycolysis Game

that given $c<1/2$, there was a polymorphic equilibrium given by:

$$x^*_{\text{AG}} = \frac{2kn+k-ck-cn}{2n^2}$$
$$x^*_{\text{INV}} = 1-\frac{k}{n}$$
$$x^*_{\text{GLY}} = 1-x^*_{\text{AG}}-x^*_{\text{INV}}$$

If $c>1/2$ the AG cell would dominate. This is valid for the $\Gamma_{\tilde{A}}$ game in this case. For the Γ_{inv} game, the coniditon is $c+p_{\text{inv}}<1/2$ and the equilibrium is given by:

$$x^*_{\text{AG}} = \frac{2kn+k-(c+p_{\text{inv}})(k+n)}{2n^2}$$
$$x^*_{INV} = 1-\frac{k}{n}$$
$$x^*_{\text{GLY}} = 1-x^*_{\text{AG}}-x^*_{INV}$$

If $c<1/2$, the equilibrium in the Γ_{gly} game is given by:

$$x^*_{\text{AG}} = \frac{(k+p_{\text{gly}})(2n+1-c)-cn}{2n^2}$$
$$x^*_{INV} = 1-\frac{k+p_{\text{gly}}}{n}$$
$$x^*_{\text{GLY}} = 1-x^*_{\text{AG}}-x^*_{INV}$$

If the condition for a polymorphic equilibrium is not met, the AG cells will dominate. The AG cells represent gives the organisms a baseline fitness 1, while the INV and GLY cells reduce the organismal fitness by d_{inv} and d_{gly} correspondingly. The organismal payoff function g is represented in table 9.2 Assuming that $c < 1/2$ such that $\Gamma_{\bar{A}}$ and Γ_{gly} have polymorphic

	AG	INV	GLY
$\bar{A}$	1	$1-d_{\text{inv}}$	$1-d_{\text{gly}}$
P_{inv}	$1-c_{\text{inv}}$	$1-d_{\text{inv}}-c_{\text{inv}}$	$1-d_{\text{gly}}-c_{\text{inv}}$
P_{gly}	$1-c_{\text{gly}}$	$1-d_{\text{inv}}-c_{\text{gly}}$	$1-d_{\text{gly}}-c_{\text{gly}}$

Table 9.2: Organismal Glycolysis Game

equilibria, the organismal fitness of $\bar{A}$ and P_{gly} is given by:

$$\begin{aligned}
G_{\bar{A}} &= x^*(\bar{A})_{\text{AG}} g(\bar{A}, AG) + x^*(\bar{A})_{INV} g(\bar{A}, INV) + x^*(\bar{A})_{\text{GLY}} g(\bar{A}, GLY) \\
&= \frac{2kn+k-ck-cn}{2n^2} + (1-\frac{k}{n})(1-d_{inv}) + (\frac{k}{n} - \frac{2kn+k-ck-cn}{2n^2})(1-d_{\text{gly}}) \\
&= 1 - d_{\text{inv}} + \frac{k}{n} d_{\text{inv}} - \frac{k}{n} d_{\text{gly}} + \frac{2kn+k-ck-cn}{2n^2} d_{\text{gly}} \\
&= 1 - (1-\frac{k}{n}) d_{\text{inv}} + \frac{k-ck-cn}{2n^2} d_{\text{gly}}
\end{aligned}$$

$$\begin{aligned}
G_{P_{\text{gly}}} &= x^*(P_{\text{gly}})_{\text{AG}} g(P_{\text{gly}}, AG) + x^*(P_{\text{gly}})_{INV} g(P_{\text{gly}}, INV) + x^*(P_{\text{gly}})_{\text{GLY}} g(P_{\text{gly}}, GLY) \\
&= 1 - (1 - \frac{k+p_{\text{gly}}}{n}) d_{\text{inv}} + \frac{(k+p_{\text{gly}})(1-c)-cn}{2n^2} d_{\text{gly}} - c_{\text{gly}}
\end{aligned}$$

If $c + p_{\text{inv}} < 1/2$ such that there is a polymorphic equilibrium inn Γ_{inv} game, the organismal fitness is given by:

$$\begin{aligned}
G_{P_{\text{inv}}} &= x^*(P_{\text{inv}})_{\text{AG}} g(P_{\text{inv}}, AG) + x^*(P_{\text{inv}})_{INV} g(P_{\text{inv}}, INV) + x^*(P_{\text{inv}})_{\text{GLY}} g(P_{\text{inv}}, GLY) \\
&= 1 - (1 - \frac{k}{n}) d_{\text{inv}} + \frac{k-(c+p_{\text{inv}})(k+n)}{2n^2} d_{\text{gly}} - c_{\text{inv}}
\end{aligned}$$

otherwise, AG will dominate and the fitness is given by:

$$\begin{aligned}
G_{P_{\text{inv}}} &= x^*(P_{\text{inv}})_{\text{AG}} g(P_{\text{inv}}, AG) + x^*(P_{\text{inv}})_{\text{INV}} g(P_{\text{inv}}, INV) + x^*(P_{\text{inv}})_{\text{GLY}} g(P_{\text{inv}}, GLY) \\
&= 1 - c_{\text{inv}}
\end{aligned}$$

Comparing the strategy P_{inv} punishing INV cells against the naive strategy

$\bar{A}$ when $c + p_{\text{inv}} < 1/2$ yields:

$$G_{P_{\text{inv}}} > G_{\bar{A}}$$
$$1 - (1 - \frac{k}{n}) d_{\text{inv}} + \frac{k - (c + p_{\text{inv}})(k+n)}{2n^2} d_{\text{gly}} - c_{\text{inv}} > 1 - (1 - \frac{k}{n}) d_{\text{inv}} + \frac{k - ck - cn}{2n^2} d_{\text{gly}}$$
$$\frac{k - (c + p_{\text{inv}})(k+n)}{2n^2} d_{\text{gly}} - c_{\text{inv}} > \frac{k - ck - cn}{2n^2} d_{\text{gly}}$$
$$-\frac{(p_{\text{inv}})(k+n)}{2n^2} d_{\text{gly}} - c_{\text{inv}} > 0$$

Thus, the strategy punishing invasive cells in this game is worse than the naive strategy if it does not punish the invasive cells enough $p_{inv} > 1/2 - c$ to prevent the polymorphic equilibrium. If it does prevent the polymorphic equilibrium, the comparison yields:

$$G_{P_{\text{inv}}} > G_{\bar{A}}$$
$$1 - c_{\text{inv}} > 1 - (1 - \frac{k}{n}) d_{\text{inv}} + \frac{k - ck - cn}{2n^2} d_{\text{gly}}$$
$$c_{\text{inv}} < (1 - \frac{k}{n}) d_{\text{inv}} - \frac{k - ck - cn}{2n^2} d_{\text{gly}}$$

Punishing the invasive cells is better than the naive strategy if the cost to the organism of punishing is less than the total damage done to the organism by the glycolytic and ivasive cell under the naive strategy.

Comparing the strategy punishing the glycolytic cells P_{gly} to the naive strategy $\bar{A}$ yields:

$$G_{P_{\text{gly}}} > G_{\bar{A}}$$
$$1 - (1 - \frac{k + p_{\text{gly}}}{n}) d_{\text{inv}} + \frac{(k + p_{\text{gly}})(1 - c) - cn}{2n^2} d_{\text{gly}} - c_{\text{gly}} > 1 - (1 - \frac{k}{n}) d_{\text{inv}} + \frac{k - ck - cn}{2n^2} d_{\text{gly}}$$
$$\frac{p_{\text{gly}}}{n} d_{\text{inv}} + \frac{(k + p_{\text{gly}})(1 - c) - cn}{2n^2} d_{\text{gly}} - c_{\text{gly}} > \frac{k - ck - cn}{2n^2} d_{\text{gly}}$$
$$\frac{p_{\text{gly}}}{n} d_{\text{inv}} + \frac{p_{\text{gly}}(1 - c)}{2n^2} d_{\text{gly}} - c_{\text{gly}} > 0$$
$$\frac{p_{\text{gly}}}{n} d_{\text{inv}} + \frac{p_{\text{gly}}(1 - c)}{2n^2} d_{\text{gly}} > c_{\text{gly}}$$
$$p_{\text{gly}}(\frac{1}{n} d_{\text{inv}} + \frac{1 - c}{2n^2} d_{\text{gly}}) > c_{\text{gly}}$$

This shows that punishing the glycocolytic cells P_{gly} can be better than the naive strategy $\bar{A}$ as long as the organismal cost of punishing is sufficiently low compared to the effect on the fitness of the punished cells.

The last comparison, between punishing invasive cells enough to

prevent the polymorphic equilibrium and punishing glycolytic cells yields:

$$
\begin{aligned}
G_{P_{\text{inv}}} &> G_{P_{\text{gly}}} \\
1 - c_{\text{inv}} &> 1 - (1 - \frac{k + p_{\text{gly}}}{n}) d_{\text{inv}} + \frac{(k + p_{\text{gly}})(1 - c) - cn}{2n^2} d_{\text{gly}} - c_{\text{gly}} \\
c_{\text{inv}} &< (1 - \frac{k + p_{\text{gly}}}{n}) d_{\text{inv}} - \frac{(k + p_{\text{gly}})(1 - c) - cn}{2n^2} d_{\text{gly}} + c_{\text{gly}}
\end{aligned}
$$

Punishing the invasive cells can be better for the organism than punishing the glycolytics cells, as long as the cost of punishng the invasive cells is lower than the cost of punishing the glycolytic cells combined with the damage of the remaining glycolytic and invasive cells.

Part III

Discussion and Conclusions

Chapter 10

Discussion

The goal of this thesis was to see if it was possible, and useful, to model the host-tumor relationship using a game theory framework. I will here discuss the results.

10.1 Possibility

I consider the models in this thesis as a proof of concept of game theoretic models of the host tumor relationship. However, in making the models, I made some assumptions which can have impact on the result. I will discuss their impact, as well as possible methods of overcoming them, here.

10.1.1 Instantanious Cell Dynamics

I assume throughout that the cell populatinon dynamics is fast enough that it can be seen as instantanious compared to the organismal population dynamics.

10.1.2 Infinite Size Populations

Both the cellular and organismal population are assumed to be infinitely large. This assumption is required to use the replicator equation and get deterministic dynamics. The deterministic dynamics is essential to for the population dynamics to mimic completely rational choices. Considering finite population sizes lead to outcomes that can be important for cancer progression.

10.1.3 Spatially Homogenous Populations

The random mathing population games used to model the cell dynamics assumes that the population is homogenous, i.e. that every cell in the population has the same probability of interacting with every other cell in the population. This is not realstic for cell growth where the two offspring of a cell division often ends up as neighbours. When assuming that the offspring inherits the trait of the parent, this implies that every cell is

more likely to interact with a cell of it's own type. This has been raised as a problem of using evolutionary game theory in the modelling of cancer cell dynamics *cite*. The field of evolutionary games on graphs, provide a possible solution to this, but I did not have time to implement it.

10.1.4 Asexual Organismal Reproduction

I assume that the organisms reproduce asexually. This is not valid for most multicellular organisms. An investigation into how sexual reproduction affects the outcome is therfore needed. One of the important aspects that are lost due to this assumption is that of recessive inherited cancer alleles*refr*. In an asexually reproducing population such alleles would not survive, at least not in a infinite population.

10.2 Usefulness

As I see it, the most useful feature fo the game theoretic model is that it provides intuitive insights to the complex host-tumor relationship. The model with frequency dependent cell selection in section 9.4 suggests that multicellular organisms can develop defence mechanisms with tactical elements, i.e. not punishing the cell traits that are most detrimental to the organism, but the traits that lead to the cellular population wich is most detrimental. The models in section 8.0.4 illustrates the differences in level of rationality between cells and organisms in the relationship. The organism can make choices that incorporate knowledge of the probability of different game outcomes, while the cells can only make desicions based on what is best there and then. There are some obsticals to using the model as a method of prediction.

10.2.1 Many Parameters

A number of parameters need to be defined in each model. In a model with m_O organismal strategies and m_C cellular strategies the following parameters must be defined.

- An organismal payoff for each combination of organismal and cellular strategy: $m_O \times m_C$
- A cellular payoff for each combinaiton of cellular and organismal strategy: $m_C \times m_O$, or when frequency dependent cellular selection is considered: a payoff for each combination of an organismal strategy and two cellular strategies: $m_C \times m_C \times m_O$
- For models with infrequent mutations a mutation rate for each non-normal strategy: $m_C - 1$
- For the multistep model, a mutation rate for each combination of cellular strategies: $m_C \times m_C$

The number of parameters make the use of the models to describe real biological scenarios difficult since getting biologically realistic values for these parameters are not trivial.

10.2.2 Abstract Definition of Strategies and Payoffs

The definitions of strategies and payoffs used here is not clearly defined in terms of biological function.

10.2.3 Abstract Game Definition

One of the good features of evolutionary game theory is its simplicity and its intuitive nature. Random matching of symmetrical games gives rise to a simple and easily understandable model. In this work the use of a more abstract game definition than finite 2-player symmetric games was needed, and this removes some of the simplicity. Especially the games considering infrequent mutations (section 8.0.4) led to games which needed an abstract definitions.

10.2.4 Foucus on Phenotype

The strategies or traits are thought to represent the function, or phenotype, of the cell. The link to the genotype is not established, other than assuming that the traits are heritable. It would be useful to look at the problem from a genetic point of view.

Chapter 11

Conclusions

In this thesis I have provided a proof of concept that game theory can be used to model the host-tumor relationship. The models developed shows that it is plausible for the host to have developed tactical cancer defence mechanisms. They also highlight the asymmetrical 'rationaly' relationship between the host and the tumor cells: The host takes the structure of the whole game into consideration while the cells only make 'myopic' decisions, choosing the strategy which is best there and then. The models provide an intuitive interface to complex multilevel differential equations and is a

I hope that this work leads to further research into the subject. imortant further steps are described below.

11.1 Further Work

- Incorporate finite and spatially heterogenous cell populations into the model
- The implications of sexual reproduction should be worked out and preferably included in the model.
- Develop a similar model considering strategies as genotype instead of phenotype
- Investigate methods of finding values for parameters in the model.

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Appendix A

Mathematical Derivations

A.0.1 Infrequent Mutations

I use linearization of the differential equations to find stable restpoints. Let $R = \delta_O$ and $s_v^k = \alpha_v(k)$. and let the organismal and cellular strategies be denoted

$$\Sigma^O = (\sigma_1^O, \sigma_2^O, \ldots, \sigma_{m_O}^O)\Sigma^C = (\eta, \sigma_1^C, \sigma_2^C, \ldots, \sigma_{m_C}^C)$$

and $z_i^j = x_{\sigma_j^C}^{\sigma_i^O}$ and $z_j^0 = x_\eta^{\sigma_j^O}$.

The differential equations defined in section 8.0.4 have equilbrium points $e(v)$ for each strategy $\sigma_v^O \in \Sigma^O$ defined by:

$$e(v)_i^j = 0 \text{ if} i \neq v$$

which means that $\bar{w}_v = \bar{w}$ leadning to:

$$0 = -Re(v)_v^0 - (\sum_k u_k s_v^k) e(v)_v^0 + R_0$$

$$e(v)_v^0 = \frac{R}{R + \sum_k u_k s_v^k}$$

$$0 = -Re(v)_v^j + \mu s_v^j e(v)_v^0 \ \forall j \neq 0$$

$$Re(v)_v^j = \mu s_v^j \frac{R}{R + \sum_k u_k s_v^k} \ \forall j \neq 0$$

$$e(v)_v^j = \frac{\mu s_v^j}{R + \sum_k u_k s_v^k} \ \forall j \neq 0$$

we have the following partial derivatives:

$$\frac{\partial \dot{z}_i^j}{\partial z_k^l} = 0$$
$$\frac{\partial \dot{z}_i^j}{\partial z_i^0} = \mu_j s_i^j$$
$$\frac{\partial \dot{z}_i^j}{\partial z_i^j} = -R_0$$

$$\frac{\partial \dot{z}_i^0}{\partial z_k^l} = -R_0 \frac{\bar{w}_i w_k^l}{\bar{w}^2}$$
$$\frac{\partial \dot{z}_i^0}{\partial z_i^l} = R_0 \frac{w_i^l \bar{w} - \bar{w}_i w_i^l}{\bar{w}^2}$$
$$\frac{\partial \dot{z}_i^0}{\partial z_i^0} = -R_0 - (\sum_n \mu_n s_i^n) + R_0 \frac{w_i^0 \bar{w} - \bar{w}_i w_i^0}{\bar{w}^2}$$

Define $J_{i,j}$ as the matrix:

$$J_{i,j} = \begin{pmatrix} \frac{\partial \dot{z}_i^0}{\partial z_j^0} & \frac{\partial \dot{z}_i^0}{\partial z_j^1} & \frac{\partial \dot{z}_i^0}{\partial z_j^2} & \cdots & \frac{\partial \dot{z}_i^0}{\partial z_j^{m_c}} \\ \frac{\partial \dot{z}_i^1}{\partial z_j^0} & \frac{\partial \dot{z}_i^1}{\partial z_j^1} & \frac{\partial \dot{z}_i^1}{\partial z_j^2} & \cdots & \frac{\partial \dot{z}_i^1}{\partial z_j^{m_c}} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \frac{\partial \dot{z}_i^{m_c}}{\partial z_j^0} & \frac{\partial \dot{z}_i^{m_c}}{\partial z_j^1} & \frac{\partial \dot{z}_i^{m_c}}{\partial z_j^2} & \cdots & \frac{\partial \dot{z}_i^{m_c}}{\partial z_j^{m_c}} \end{pmatrix}$$

$$J_{i,i} = \begin{pmatrix} R\frac{w_i^0(\bar{w}-\bar{w}_i)}{\bar{w}^2} - R - (\sum_n \mu_n s_i^n) & R\frac{w_i^1(\bar{w}-\bar{w}_i)}{\bar{w}^2} & R\frac{w_i^2(\bar{w}-\bar{w}_i)}{\bar{w}^2} & \dots & R\frac{w_i^{m_c}(\bar{w}-\bar{w}_i)}{\bar{w}^2} \\ \mu_1 s_i^1 & -R & 0 & \dots & 0 \\ \mu_2 s_i^2 & 0 & -R & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \mu_{m_c} s_i^{m_c} & 0 & 0 & \dots & -R \end{pmatrix}$$

In a state $e(v)^*$ where $e(v)_i^k = 0 \ \forall i \neq v$ we get $\bar{w}_v = \bar{w}$ and $\bar{w}_i = 0 \ \forall i \neq v$.

And thus

$$J_{v,v} = \begin{pmatrix} -R - (\sum_n \mu_n s_v^n) & 0 & 0 & \dots & 0 \\ \mu_1 s_v^1 & -R & 0 & \dots & 0 \\ \mu_2 s_v^2 & 0 & -R & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \mu_{m_c} s_v^{m_c} & 0 & 0 & \dots & -R \end{pmatrix}$$

$$J_{i,i} = \begin{pmatrix} R\frac{w_i^0}{\bar{w}} - R - (\sum_n \mu_n s_i^n) & R\frac{w_i^1}{\bar{w}} & R\frac{w_i^2}{\bar{w}} & \dots & R\frac{w_i^{m_c}}{\bar{w}} \\ \mu_1 s_i^1 & -R & 0 & \dots & 0 \\ \mu_2 s_i^2 & 0 & -R & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \mu_{m_c} s_i^{m_c} & 0 & 0 & \dots & -R \end{pmatrix}$$

$$\det(J - \lambda I) = \prod_i \det(J_{i,i} - \lambda I)$$

$$\det(J_{v,v} - \lambda I) = (-R - \lambda)^{m_c}(-R - (\sum_n \mu_n s_v^n) - \lambda)$$

$$\begin{aligned} \det(J_{i,i} - \lambda I) &= (R\frac{w_i^0}{\bar{w}} - R - (\sum_n \mu_n s_i^n))(-R - \lambda)^{m_c} - (-R - \lambda)^{m_c - 1}(\sum_j R\frac{w_i^j}{\bar{w}}\mu_j s_i^j) \\ &= (-R - \lambda)^{m_c - 1})((-R - \lambda)(R\frac{w_i^0}{\bar{w}} - R - (\sum_n \mu_n s_i^n)) - \sum_j R\frac{w_i^j}{\bar{w}}\mu_j s_i^j) \end{aligned}$$

The eigenvalues of J is then $\lambda_A = -R$ and $\lambda_B = -R - (\sum_n \mu_n s_v^n)$, which are both negative, and the roots of the quadratic polynominals given by:

$$pJ_{i,i} = (-R - \lambda)(R\frac{w_i^0}{\bar{w}} - R - (\sum_n \mu_n s_i^n)) - \sum_j R\frac{w_i^j}{\bar{w}}\mu_j s_i^j$$

which has negative roots when:

$$\begin{aligned} \bar{w} &> \frac{Rw_i^0 + \sum_j w_i^j \mu_j s_i^j}{R + \sum_j \mu_j s_i^j} \\ \sum_j e(v)_v^j w_v^j &> \frac{Rw_i^0 + \sum_j w_i^j \mu_j s_i^j}{R + \sum_j \mu_j s_i^j} \\ \frac{Rw_v^0 + \sum_j w_v^j \mu_j s_v^j}{R + \sum_j \mu_j s_v^j} &> \frac{Rw_i^0 + \sum_j w_i^j \mu_j s_i^j}{R + \sum_j \mu_j s_i^j} \end{aligned}$$

So the only v such that $e(v)$ is stable is given by:

$$v^* = \underset{i}{\text{argmax}} \frac{R w_i^0 + \sum_j w_i^j \mu_j s_i^j}{R + \sum_j \mu_j s_i^j}$$

A.0.2 Game outcome

If the organism plays strategy σ_i^O, the probability that the cell will play T_j in L_k^i is given by

$$p_k(T_j) = \hat{\mu}_j s_i^j$$

. The probability that the game will continue to L_{k+1}^j is given by:

$$1 - (\hat{R} + \sum \hat{\mu}_j s_i^j)$$

The total probability of the last cell playing strategy T_j is then given by:

$$\begin{aligned} p(T_j) &= \hat{\mu}_j s_i^j (\sum_{k=0}^{\infty} (1 - (\hat{R} + \sum \hat{\mu}_j s_i^j))^k) \\ &= \frac{\hat{\mu}_j s_i^j}{1 - (1 - (\hat{R} + \sum \hat{\mu}_j s_i^j))} \\ &= \frac{\hat{\mu}_j s_i^j}{\hat{R} + \sum \hat{\mu}_j s_i^j} \end{aligned}$$

A.1 Multistep Process

The differential equations:

$$\begin{aligned} \dot{z}_i^0 &= -R_O x_i^0 - (\sum_k q_{0,k} s_i^{0,k}) z_i^0 + R_0 \frac{w_i}{\bar{w}} \\ \dot{z}_i^j &= -R_O z_i^j + \sum_k (q_{k,j} s_i^{k,j} z_i^k - q_{j,k} s_i^{k,j} z_i^j) \;\; \forall \, j \neq = 0 \end{aligned}$$

is invariant in the hyperplanes $h(v)$ given by:

$$h(v) = \left\{ z \in Z \mid z_i^j = 0 \forall \, i \neq v \right\}$$

Rest points in each plane $r(v) \in h(v)$ is given by :

$$0 = -Rz_v^0 - (\sum_{k=1}^{m_c} q_{0,k} s_v^{0,k}) z_v^0 + R\frac{w_v}{\bar{w}}$$

$$0 = -Rz_v^0 - (\sum_{k=1}^{m_c} q_{0,k} s_v^{0,k}) z_v^0 + R$$

$$z_v^0(R + (\sum_k q_{0,k} s_v^{0,k})) = R$$

$$z_v^0 = \frac{R}{R + (\sum_k q_{0,k} s_v^{0,k})}$$

and $\forall j \neq 0$

$$0 = -Rz_v^j + \sum_{k=0}^{m_c} (q_{k,j} s_v^{k,j} z_v^k - q_{j,k} s_v^{k,j} z_v^j)$$

$$Rz_v^j + \sum_{k=1}^{m_c} q_{j,k} s_v^{k,j} z_v^j = \sum_{k=0}^{m_c} q_{k,j} s_v^{k,j} z_v^k$$

$$z_v^j = \frac{\sum_{k=0}^{m_c} q_{k,j} s_v^{k,j} z_v^k}{R + \sum_{k=1}^{m_c} q_{j,k} s_v^{k,j}}$$