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APPLICATION OF EVOLUTIONARY GAMES TO MODELING CARCINOGENESIS

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Abstract. We review a quite large volume of literature concerning mathematical modelling of processes related to carcinogenesis and the growth of cancer cell populations based on the theory of evolutionary games. This review, although partly idiosyncratic, covers such major areas of cancer-related phenomena as production of cytotoxins, avoidance of apoptosis, production of growth factors, motility and invasion, and intra- and extracellular signaling. We discuss the results of other authors and append to them some additional results of our own simulations dealing with the possible dynamics and/or spatial distribution of the processes discussed.

1. **Introduction.** The theory of games provides a very powerful tool for analysis of processes in which decision-making plays an important role. From its very beginning it was mainly applied in economics and econometrics, and soon it was also used successfully to solve problems in behavioural and social sciences, control and process engineering, and military situations. Apart from these applications, new perspectives in biology were introduced by John Maynard Smith and George Price [26-28]. Their ideas linked the mathematical tools of game theory with Darwinian adaptation and species evolution, and initiated a new branch in decision-making mathematics called evolutionary game theory (EGT). This new approach differs from standard game theory by incorporating rational decision-making by the competing players, strategies are treated as phenotypes of individuals in the population acquired through evolution, and payoffs measure a change in the degree of fitness resulting from interactions of the individuals representing different phenotypes. The standard payoff matrix contains different phenotypes (strategies) listed in the first row and the first column, and the appropriate benefits or costs due to interaction between them:

	Phenotype P	Phenotype Q
Phenotype P	A	B
Phenotype Q	C	D

An important remark regarding pay-off matrices is that they can be read vertically or horizontally (from the "column" or "row" player's point of view), and in this paper most of them have the "column player" notation. For instance, in the above

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payoff table the result of interaction between individuals with phenotype Q and phenotype P equals B. If we consider $p(t)$ and $q(t)$ as the frequencies of occurrence for particular strategies within the population, then the average phenotype fitness is:

$$E_p(t) = p(t)A + q(t)C \tag{1}$$

$$E_q(t) = p(t)B + q(t)D \tag{2}$$

and average population fitness:

$$\bar{E}(t) = p(t)E_p + q(t)E_q \tag{3}$$

A classical process studied by John Maynard Smith, named the Hawk-Dove game, assumes that a population contains two phenotypes representing two different strategies to gain resources V (e.g. females, space, nutrients, and as a result also offspring). It should be noted that hawks and doves represent different phenotypes within a population of the same species. To define the results of such a game, the concept of Evolutionary Stable Strategy (ESS) was introduced in [28]. ESS is defined as a phenotype resistant to inflow of other phenotypes (as a result of mutation or environmental migration) and which cannot be repressed by them. However, the opposite situation is possible, so that whenever ESS arises within a population then it can coexist stably with other phenotypes or even dominate the population. One can find a relationship between ESS and mixed Nash strategies; ESS simply defines a point which has a Nash equilibrium property and a stability property. On the other hand, the players in EGT are genetically encoded, cannot change, and the structure of the game is unclear while in standard non-cooperative games the players know the structure and potential strategies of the opponents and the game is played many times in the same conditions. Moreover, the Nash strategies result from rational analysis while evolutionary strategies are rather due to behaviour shaped through natural selection. Thus ESS is a mixed Nash strategy and is stable. If the average payoff for a strategy is defined by E, for ESS by S, and for any other different strategy by s, then the following conditions have to be fulfilled:

$$E(S,S) \geq E(s,S) \tag{4}$$

$$if E(S,S) = E(s,S) then E(S,s) > E(s,s) \tag{5}$$

Application of evolutionary game theory to mathematical modelling of processes during carcinogenesis is based on the following assertions:

- in an organism, cells compete for space and nutrients, while different kinds of cells are players in the game;
- mutation (appearing in tumour cells) occurs in cell division due to various reasons;
- an advantage of tumour cells over healthy ones is a signature of cancer;
- environmental factors can affect different cells to varying degrees.

We follow the line presented in the review of Basanta and Deutsch [6], but as well as reproducing the results presented in that paper we extend them by our additional results of time and space simulations when these were absent in the original papers. We focus attention mainly on examples in which spatial analysis leads to results incompatible with those of mean-field analysis.

2. **Spatial evolutionary games.** EGT is based on the assumption of perfect mixing inside the population and interaction of each pair of strategies at one time. To overcome this simplification, evolutionary games have been transferred into spatial lattices by application of cellular automata techniques where an additional important factor, namely spatial allocation, is included. Although the origin can be found in the pioneering works of von Neuman [38], Nowak and May have usually been granted the name of the fathers of spatial evolutionary games theory (SEGT) [30-32]. In this paper we follow the line presented in [5] with some modifications [23]. Like non-spatial games, spatial games are also iterated. In one place there can be only one cell and there is no free space (each empty place is occupied within one generation). These simplifications and the lack of nutrients allocated in the lattice differ this approach from that in [7], which allows more focusing on cell-cell interaction and the influence of pay-off parameters. As we have mentioned before, the game is played on a lattice forming a torus and in the case of any ties the result is taken randomly. In passing transient generations we proceed according to the following steps [5]:

- payoff updating - the sum of local fitness in cell-cell interactions in the neighbourhood;
- cell mortality - removing a certain number of players;
- reproduction by competition - decision of the cell which strategy will be on an empty place.

Three processes of cell mortality are proposed:

- synchronous updating - all cells die simultaneously and they are replaced dependent on the strategy and payoff of their neighbours before dying;
- asynchronous updating - in each generation a single cell, chosen at random, dies and is replaced;
- semi-synchronous updating - during one generation 10% of cells die randomly.

The next phase is reproduction of newly removed players. Consider an example which is an extract from the lattice with phenotypes defined in Table 1. In that case the local fitness lf_x for cell x with phenotype Q shall be the sum of payoffs from the fitness matrix due to particular interaction of Q_x with the cells in the neighbourhood. Such calculation of the local fitness shall be done for the neighbouring cells to decide which phenotype shall be acquired by the newly reproduced cell according to one of the four types of reproduction below.

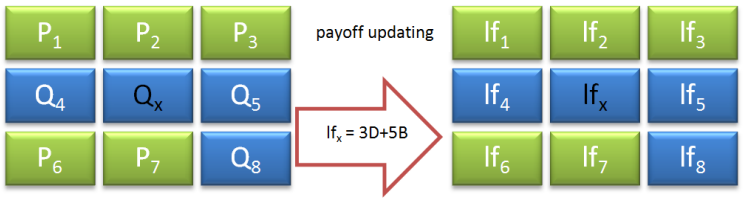

FIGURE 1. Example. Payoff updating

The authors suggest two kinds of reproduction:

- deterministic - the winner is the player with the highest local fitness;
- probabilistic - the local calculated fitness is divided by the total score in the neighbourhood. In this approach the result of competition for an empty place

is more dependent on a better location. Additionally, two other types of reproduction were presented in [23]:

- quantitative - pay-off updating is calculated as the sum of the measures of fitness of players with the same strategy. For this particular example the new phenotype shall be chosen by taking the maximum between the sums of local fitness of cells 1, 2, 3, 6, and 7 (phenotype P) and of cells 4, 5, and 8 (phenotype Q). This kind of reproduction allows weaker cell strategies (in terms of fitness) but locally superiority in numbers to predominate in the population;
- switching - when differences between local scores are crucial then quantitative reproduction shall be chosen (chance for weaker players to overcome the strongest), otherwise the deterministic type is chosen. A threshold factor is introduced to switch between the two types of reproduction which is related to the ratio between minimum and maximum local fitness; this leads to great flexibility in different parameterization of spatial games.

To focus attention we show the results of the original studies together with our results of SEGT-based analysis using semi-synchronous updating, an 8-cell neighbourhood, and different initial lattices.

3. **Replicator dynamics (RD).** As mentioned earlier, EGT has been used in biology to predict the survival of different phenotypes in a population and to explain heterogeneity within neoplastic cell cohorts [2]. To check how and when a population becomes stable it is necessary to simulate phenotype interactions among generations according to a payoff matrix. One way in which the dynamics of transients from an initial to new stable states could be studied is the use of replicator equations [35]. Replicator dynamics describes the speed of changes of the phenotype frequency a by computing the difference between the average fitness for phenotype and that for the entire population. For phenotype P from the pay-off table the replication equation has the following form:

$$\dot{p}(t) = p(t)(E_p - \bar{E}) \tag{6}$$

Since the frequencies for each strategy in the population should be between 0 and 1 (mixed strategies), replicator dynamics can be presented on n-1 dimensional simplexes in the n dimensional spaces of strategies. Different evolutionary game dynamical behaviours with usage of replicator equations were studied in [20].

4. **Hawk-Dove game.**
Evolution and the theory of games [26], J. Maynard Smith 1982

4.1. **Model.** To illustrate the proposed scheme of analysis for all the models reviewed in this paper, we start with the Hawk-Dove game defined by the following payoff table:

	H	D
H	$\frac{V-C}{2}$	0
D	V	$\frac{V}{2}$

4.2. **Phenotypes.**
H – 'Hawk' - escalates and continues until injured or until the opponent retreats
D – 'Dove' - retreats or shares resources with another 'Dove' opponent

4.3. **Model parameters.**
V – benefit that could be gained by competition
C – cost of escalation (injuries)

4.4. **Results of RD.** In [25] Maynard Smith briefly described each interaction:

- Hawk vs. Hawk - each individual has a 50% chance of obtaining the resource V, but the same chance of being injured by the opponent,
- Hawk vs. Dove - since Dove retreats, then Hawk obtains all accessible resources,
- Dove vs. Dove - the resource is shared equally by the two individuals.

The conditions for polymorphism are given by the Bishop-Cannings theorem [12] and defines the situation when all phenotypes coexist in stable equilibrium, i.e. the frequency of occurrences for each phenotype (strategy) shall be greater than 0 and less than 1. For a Hawk-Dove game this condition is satisfied for C greater than V. The expected frequency of Hawks is V/C and of Doves $(1 - V/C)$. An example of the simplex and the time course show an evolutionary stable state for these two phenotypes.

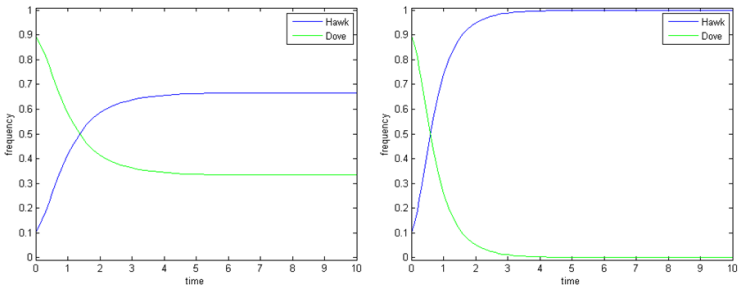

FIGURE 2. Hawk-Dove. Results for (a) $C = 9$, $V = 6$ and (b) $C = 6$, $V = 9$

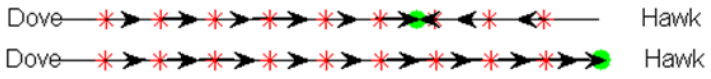

FIGURE 3. Hawk-Dove. Results for (a) $C = 9$, $V = 6$ and (b) $C = 6$, $V = 9$

Simplexes showing different scenarios for different initial frequencies and time courses are presented only for one set of initial frequencies, but they illustrate the dynamics of the population. However, if the implications of Bishop-Cannings' are difficult to analyse it is necessary to check the effect of parameters on a given phenotype (Figure 4), which allows to see the final result, but not dependency on the initial frequencies or the population dynamics. Moreover, only one phenotype can be analysed at the same time.

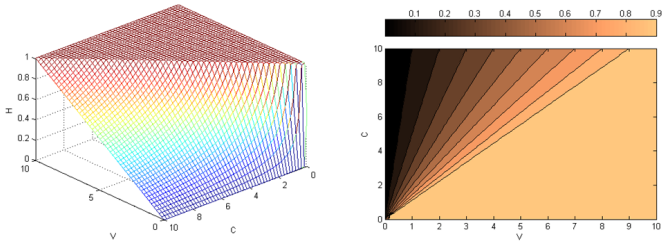

FIGURE 4. The influence of parameters C and V on the Hawks phenotype

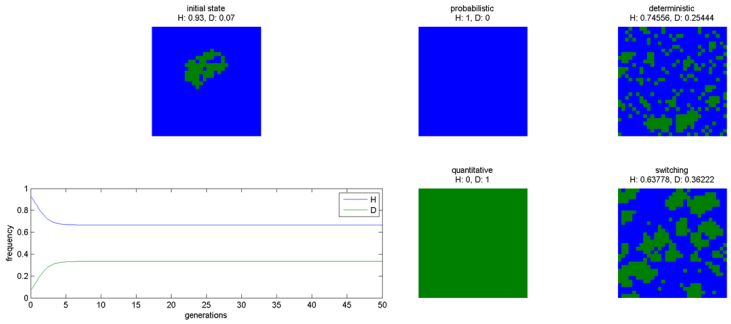

FIGURE 5. Hawk-Dove. Results for $C = 9$ and $V = 6$

4.5. **Results of SEGT.** The previously mentioned algorithm for SEGT analysis could also be applied to the classical Hawk-Dove game.

Deterministic and switching reproductions gave the same results as their mean-field counterparts. On the other hand probabilistic and quantitative methods, which could be interpreted as 'the winner takes all' and 'the strongest group wins' respectively, disagreed with the mean-field analysis due to the better fitness of Doves in groups and the better fitness of Hawks as individuals. The same result can be obtained when Hawks are underrepresented in the initial population.

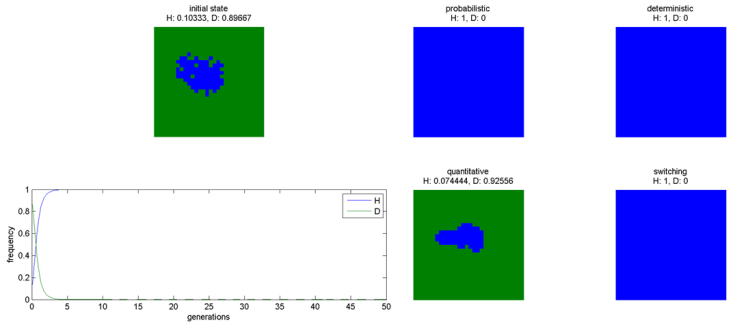

FIGURE 6. Hawk-Dove. Results for $C = 6$ and $V = 9$ illustrate the opposite situation.

TABLE 1. Idiosyncratic summary of models reviewed in this paper.

Reference	Game type	Cancer Phenomena	No. M.	No. P.	Graphical Representation	Add. Info
I. P. M. Tomlinson, W. F. Bodmer 1997 [37]	Non-spatial	avoiding apoptosis, production of growth factors	2	5	-	-
I. P. M. Tomlinson 1997 [36]	Non-spatial	Production of/resistance to cytotoxins	4	5	-	Table with final results for various configurations.
L.A. Bach et al 2001 [4]	Non-spatial	production of growth factors	1	2	time courses	Three-players interaction
L.A. Bach et al 2003 [5]	Spatial	production of growth factors	2	2	parameter-phenotype Charts	-
Y. Mansury, M. Diggory, T.S. Deisboeck 2005 [25]	Spatial	invasion and migration	1	2	-	phenotype-genotype link
D. Basanta et al 2008 [10]	Non-spatial	invasion and migration	1	3	two parameters-phenotype charts dependency	-
D. Basanta, H. Hatzikirou, A. Deutsch 2008 [7]	Spatial	invasion and migration	1	2	parameter-phenotype chart	Spatial model does not depend on payoff matrix
D. Dingli et al 2009 [16]	Non-spatial	bone cancer	1	3	time courses, simplexes	Therapeutic recommendation
D. Basanta et al 2010 [9]	Non-spatial	invasion and migration	1	4	two parameters-phenotype charts	Speed of population dominance. Therapeutic recommendation
A. Swierniak, M. Krzeslak 2010 [34]	Non-spatial	bystander effect	1	3	simplexes, time courses	-
M. Gerstung, H. Nakhoul, N. Beerenwinkel 2011 [19]	Non-Spatial	general phenomena	1	4	simplexes	Fitness matrix as affine function.
M.Krzeslak, A.Swierniak 2011 [23]	Spatial	bystander effect	1	3	simplexes, time courses (RD), cellular allocation (SEGT)	
D. Basanta, R. A. Gatenby, A. R. A. Anderson [7]	Non-spatial	evolutionary double bind	1	3	time courses	Parameters are time dependent (Heaviside function)
M.Krzeslak, A.Swierniak 2012 [22]	Non-spatial	avoiding apoptosis, production of cytotoxic and growth factors	1	4	simplexes, time courses	3-dimensional simplex
D. Basanta et al 2012 [11]	Non-spatial	prostate cancer tumour-stroma interactions	1	3	time courses, two parameters- phenotype charts dependency	therapeutic recommendation

5. **EGT based models in cancer analysis.** To our knowledge, the first work in which evolutionary game theory was used to model the interaction behaviour of tumour cells , was presented by Tomlinson and Bodmer [37], who proposed the model where one of the phenotypes attempts to gain an advantage by producing cytotoxic substances. The results show that actively harming neighbouring cells may lead to dominance of the local population by the tumour cells. This study triggered a series of other papers, and below we overview the features of the models discussed in these publications and present the main results. We append to this analysis our results obtained by SEGT and RD tools if absent in the original study. The purpose of Table 1 is to provide an idea of the predominant trends in game theory modelling, without the pretence of completeness.

6. **Avoidance of apoptosis.**
Modeling the consequences of interactions between tumour cells [37], I. P. M. Tomlinson, W. F. Bodmer 1997

6.1. **Model.** To prevent apoptosis (programmed cell death) cells can produce growth factors in a paracrine fashion, or in an autocrine fashion when a tumour has become too large for paracrine communication. A paracrine growth factor can also affect independent cells in terms of producing factors.

	k	m	n
k	$1-a+b$	$1+b+c$	$1+b$
m	$1-a$	$1+c$	1
n	$1-a$	$1+c$	1

6.2. **Phenotypes.**
k – cell produces a growth factor to prevent apoptosis (paracrine fashion)
m – cell produces a growth factor to prevent apoptosis (autocrine fashion)
n – cell is dependent on a paracrine growth factor

6.3. **Model parameters.**
a – the cost of producing a paracrine growth factor
b – the benefit of receiving paracrine growth factor
c – includes the cost and the benefit of producing an autocrine factor. Since independence from the growth factor is rather advantageous then c shall be positive, but scenarios with c negative shall be also considered.

6.4. **Results of RD.** According to the payoff matrix, phenotype n is better adapted than phenotype k (for $a>0$) but less well adapted in interaction with phenotype m (for $c>0$). So when parameters a and c are positive the population stabilizes with domination of phenotype m (even when a and c are very small). When c is smaller than 0 then phenotype n is evolutionary stable, since the altruistic phenotype k bears the costs of producing paracrine factors. When $a=0$, then the evolutionary fitness of phenotypes k and n is equal and m is the strongest phenotype in the population. But if $a=0$ and $c<0$ then stable dimorphism, strongly dependent on initial frequencies of occurrences, can exist between k and n. A similar situation, but between n and m, can appear when $a>0$ and $c=0$.

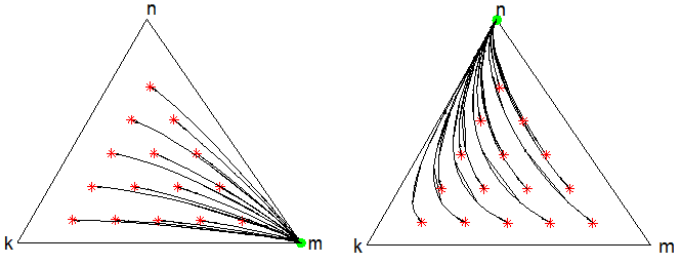

FIGURE 7. Avoidance of apoptosis. Results for (a) $a>0$, $c>0$, (b) $a>0$, $c<0$

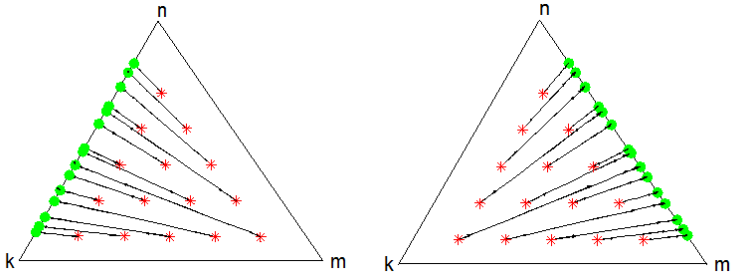

FIGURE 8. Avoidance of apoptosis. Results for (a) $a = 0$, $c<0$, (b) $a>0$, $c = 0$

6.5. **Results of SEGT.** When $a = 0$, then the evolutionary fitness of phenotypes k and n is equal and m is the strongest phenotype in the population. But if $a = 0$ and $c<0$ then stable dimorphism, strongly dependent on initial frequencies of occurrences, can exist between k and n. A similar situation, but between n and m, can appear when $a>0$ and $c = 0$.

7. **Production of growth factors.**
Modeling the consequences of interactions between tumour cells [37] I. P. M. Tomlinson, W. F. Bodmer 1997

7.1. **Model.** This model in general describes the paracrine production of a growth factor (GF), including angiogenesis promoters. It is quite similar to the previous one, but in this case there is no phenotype that produces GFs in an autocrine fashion

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

7.2. **Phenotypes.**
$A+$ – cell produces an angiogenesis factor (paracrine fashion)
$A-$ – cell does not produce growth factors (baseline)

7.3. **Model parameters.**
i – cost of angiogenesis factor production
j – benefit of receiving growth factor

7.4. **Results of RD.** To reach stable dimorphism between phenotypes, the cost of producing growth factors i shall be smaller than the benefit j. The resulting frequencies of occurrences are then dependent on the ratio of the differences between the benefit and the cost. In the situation ($j<i$) $A-$ is a strategy which is evolutionarily stable and dominates the population.

7.5. **Results of SEGT.** First we consider the situation when the costs of growth factor production are greater than the benefits. In this situation the mean-field model returns a population of $A-$ types, and the same result is obtained for the spatial game both in the case when $A+$ is interpreted as a new type that has arisen in the population and in the opposite situation. When the costs are less than the benefits, then in the mean-field game it is feasible to reach a stable dimorphic population that depends on the exact values of parameters i and j. A similar effect is observed in the spatial game.

8. **Production of and resistance to cytotoxic substances.**
Game-theory Models of Interactions Between Tumor Cells [36] I. P. M. Tomlinson 1997

8.1. **Model.** The author assumes that harming other cells is possible by production of cytotoxic substances which affect surrounding cells (but not the producers). As a response, some cells can acquire genetic resistance. Both production of substances and resistance are costly, but a phenotype that produces cytotoxins is able to gain some advantage in contact with non-resistant cells

	p	q	r
p	$z-e-f+g$	$z-h$	$z-f$
q	$z-e$	$z-h$	z
r	$z-e+g$	$z-h$	z

8.2. **Phenotypes.**
p – cell produces a cytotoxic substance against adjacent cells
q – cell is resistant to the cytotoxic substance
r – cell neither produces the cytotoxic substance nor is resistant (baseline)

8.3. **Model parameters.**
z – baseline fitness
e – cost of producing cytotoxins
f – disadvantage of being affected by cytotoxins
g – benefit of harming other cells
h – cost of resistance to cytotoxins

8.4. **Results of RD.** Conditions for stable coexistence of all phenotypes within the population, calculated from comparison of expected average fitness:

$$0<\frac{h}{f}<1, 0<\frac{e}{g}-\frac{h}{f}<1, 0<\frac{e}{g}<1 \tag{7}$$

These inequalities show that the cost of fitness in interaction with p shall be greater than the cost of resistance and that the costs of cytotoxin production shall be greater than the benefits of harming other cells. If these conditions are fulfilled then the final population shall be trimorphic and independent of initial frequencies. The model assures that it is not feasible to reach stable coexistence between the q and r phenotypes. If we eliminate p from the population, then r always has the

baseline value z, but q bears the cost of being resistant to cytotoxins. This result has a natural explanation since resistance appeared as an evolutionary response to cytotoxins. Apart from the stable state considered above, equilibrium between p, q and p, and r may also appear in the population.

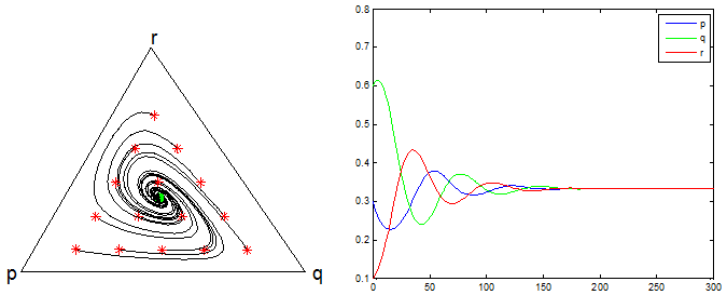

FIGURE 9. Interaction between tumor cells. The results for $e = 0.2$, $g = 0.3$, $h = 0.26$ and $f = 0.8$

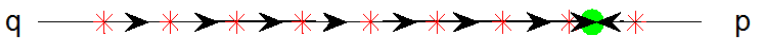

FIGURE 10. Evolutionary stable state between p and q for $h = 0.3$, $e = 0.1$, $f = 0.6$, $g = 0.3$

8.5. **Model.**

	p	r	s
p	$z-e+g-f$	$z-f$	$z-e+g-h$
r	$z-e+g$	z	$z-e+g-h$
s	$z-e-f$	$z-f$	$z-e-h$

8.6. **Phenotypes.**
p– cell produces a cytotoxic substances against adjacent cells
s – cell is resistant and at the same time cell produces a cytotoxic substances
r – cell neither produces a cytotoxic substance nor is resistant (baseline)

8.7. **Model parameters.**
z – baseline fitness (for the rest of the games this is usually 1)
e – cost of producing a cytotoxin
f – disadvantage of being affected by a cytotoxin
g – benefit of harming other cells
h – cost of resistance to a cytotoxin

8.8. **Results of RD.** We modified the model of interaction between p and s types presented by Tomlinson [36]. Since the s phenotype is resistant to cytotoxins, then p shall not receive any advantage g from harming other cells. As for the previous model, we can compare the expected results to compute conditions for stable polymorphism, and the only difference is in the second inequality:

$$1<\frac{e}{g}-\frac{h}{f}<2 \tag{8}$$

Simulations and analysis of the pay-off matrix enable us to conclude that when e is greater or equal to g, then phenotype s shall be displaced from the population. In that case dominance of type r or stable dimorphism between p and r shall occur (depending on the ratio between g and e).

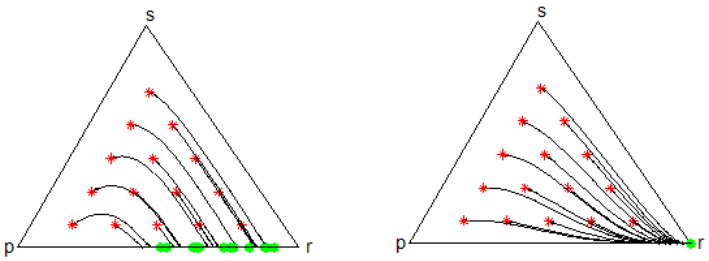

FIGURE 11. Results for (a) large and (b) small difference between g and e

As shown in Figure 11a, the result is dependent on the initial frequencies. It is feasible to reach stable coexistence between p and s, but only in the case when h is equal to f. When h is greater than f then p is the strategy that dominates, otherwise s is the strongest evolutionary strategy. In the case of r and s, stable coexistence should appear when $g = e + h = f$.

8.9. **Results of SEGT.** We consider only the first model, i.e. the situation when production of cytotoxins and resistance have occurred separately in the phenotypes. For one set of parameters, two different initial lattices are taken into consideration (Figures 12-13).

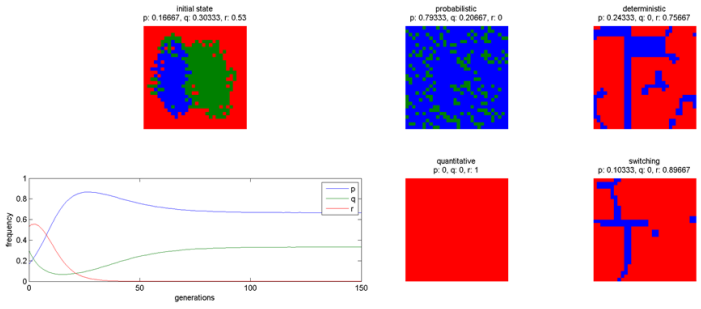

FIGURE 12. Results for $e = 0.1$, $g = 0.3$, $h = 0.3$ and $f = 0.6$

The results of RD are shown only for comparison, and differ for different initial lattices and more specifically for different initial frequencies. Only the case of probabilistic competition agrees qualitatively with the mean-field model, and the remaining three types of reproduction lead to definitely different results. For the first initial lattice the results show coexistence of p and r, with strong dominance of the latter, and for the second it is feasible to obtain a trimorphic population with some stable groups of neutral cells. The existence of phenotype r in the population and even its

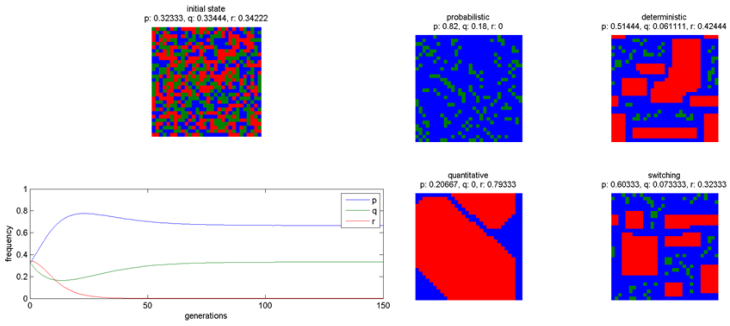

FIGURE 13. Results for $e = 0.1$, $g = 0.3$, $h = 0.3$ and $f = 0.6$ with different initial lattice

strong domination can be explained similarly as in the Hawk-Dove game: in interaction between two cells with type r the fitness value is the largest one within the payoff matrix. Use of another set of parameters $(e = 0.2, g = 0.3, h = 0.26, f = 0.8)$ shows that for probabilistic reproduction it is feasible to reach similar, although unstable, results as for the mean-field game. Since the results for different initial lattices are very similar, we present only one of them.

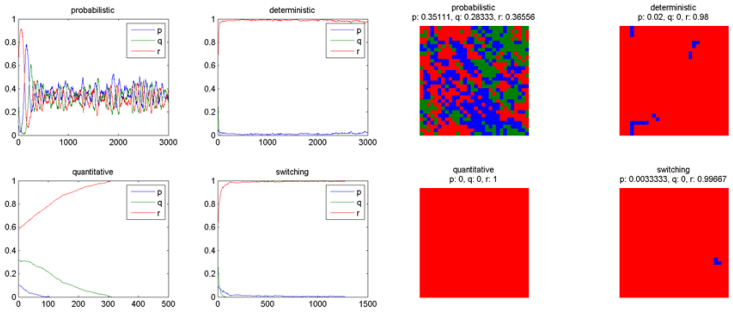

FIGURE 14. Results for $e = 0.2$, $g = 0.3$, $h = 0.26$ and $f = 0.8$

8.10. **Biological aspects.** The model implies that cells could develop a mechanism to produce a cytotoxic substance to gain space and nutrients. One biological example could be the Warburg effect, that describes transition from aerobic to glycolytic metabolism; the latter is less efficient but produces acid which harms surrounding cells as a side effect. In the Tomlinson's game parameter e could correspond to the loss of adjustment due to less effective glycolytic metabolism, f to loss associated with being in acid environment, and g to benefits for acid producers to aerobic cells [6].

9. **Production of growth factors (three players game).**
An evolutionary-game model of tumour cell interactions: possible relevance to gene therapy [4] L.A. Bach, S.M. Bentzen, J. Alsner, F. B. Christiansen 2001

9.1. **Model.** This model is an extension of the previous one with the same phenotypes and parameters, but instead of two players directly interacting here there are three players. The model assumes that to benefit from the growth factors some synergy is needed. Because of this parameter j is only applied when at least two $A+$ cells interact at one time.

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

9.2. **Phenotypes.**
$A+$ – cell produces growth factors (paracrine fashion)
$A-$ – cell does not produce growth factors (baseline)

9.3. **Model parameters.**
i– cost of proangiogenic factor production
j – benefit of receiving growth factor

9.4. **Results of RD.** When benefits are twice smaller than costs, then $A-$ can dominate the population independently of initial frequencies.

FIGURE 15. Angiogenic game. Result for $j<2i$

If $j = 2i$, then for initial frequencies of $A+$ smaller than 50% the result is the same so the population concerns only the $A-$ phenotype. However, when the initial frequencies of $A+$ are greater than 50% it is feasible to reach stable dimorphism with equal frequencies of occurrence.

FIGURE 16. Angiogenic game. Result for $j = 2i$

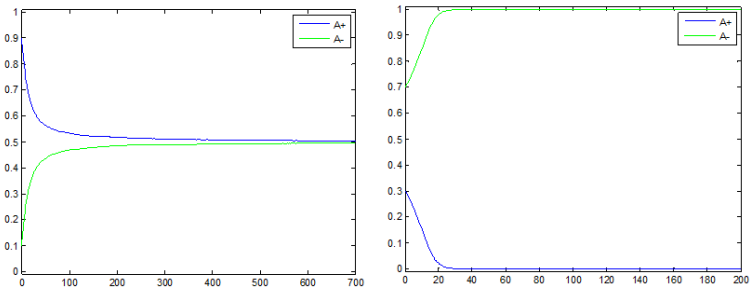

FIGURE 17. Angiogenic game. Time courses for $j = 2i$

If $j>2i$, two different situations can occur in the population, and as in the previous case the resulting points are strongly dependent on initial frequencies. When the initial frequency of $A+$ is less than 30% then again the game leads to domination of the $A-$ phenotype because an unstable internal equilibrium forms a barrier between these two stable points. The authors compare the results to similar phenomena that were observed in their biological experiments.

FIGURE 18. Angiogenic game. Result for $j>2i$

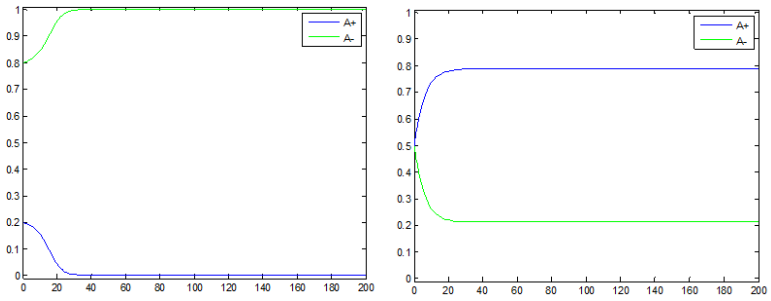

FIGURE 19. Angiogenic game. Time courses for $j>2i$

9.5. **Biological aspects.** According to the authors, the most interesting result of this model is the existence of an equilibrium point which behaves as a repeller. From the therapeutic point of view this feature suggests the possibility that gene therapy needs to decrease the fraction of mutated cells below a certain level.

10. **Production of growth factors (spatial model).**
Spatial Evolutionary Games of Interactions among Generic Cancer Cells [5] L.A. Bach, D. J. T. Sumpter, J. Alsner, V. Loeschcke 2003

10.1. **Model.**

	$Gr+$	$Gr-$
$Gr+$	$1+b+e-c$	$1+d$
$Gr-$	$1+b-c$	1

10.2. **Phenotypes.**
$Gr+$ – cell produces an angiogenesis factor (paracrine fashion)
$Gr-$ – cell does not produce growth factors (baseline)

10.3. **Model parameters.**
b – benefit of usage of growth factor by the producer phenotype
c – cost of growth factor production
d – benefit of receiving the growth factor by the non-producer phenotype
e – benefit of receiving the growth factor by the producer phenotype

10.4. **Model description.** The authors recall the growth factor-producing model [36] with different parameters and consider details of the benefits of receiving a growth factor. For example, the $Gr+$ phenotype gets advantage b from its own production of the growth factors, but also benefits e in interactions with other cells with the same phenotype. $Gr-$ also gains some advantage from the growth factors (parameter d). Because of separate parameters for different interactions it is possible to simulate more scenarios (such as a synergy effect). The authors present a spatial model with three types of updating the lattice: synchronous (all cells die simultaneously), asynchronous (in each generation only a single cell is updated), or semi-synchronous (each cell has an equal chance to die). Two rules of updating are also presented: deterministic ("winner takes all" - only a cell with the highest local maximum score is allowed to reproduce), or probabilistic (the payoff for each cell is divided by the sum of local payoffs which gives a chance for cells with lower fitness, but superior in numbers). The size of the neighbourhood is considered to be: 4, 8 or 24 neighbours. The condition of polymorphic equilibrium is given by:

$$0<\frac{b-c}{d-e}<1 \tag{9}$$

10.5. **Results of RD.** As well as different spatial results because of different configurations, the authors also analyse and compare results between the spatial and the mean-field (non-spatial) model and all results are compared for $Gr+$ as a function of parameters b or d. The main difference occurs for larger values of b and rather smaller values of d. Additionally, the authors test their spatial algorithm on two classical games, Hawk-Dove and Prisoner's Dilemma. Unfortunately the influence of the initial allocation was not checked. An interesting extension of the authors' analysis could be performed by changing parameters e and d, for constant b and c, both equal to 0.5 for the mean-field model. Let us identify b and c with j and i from the previous model. For $i = j$ (here $b = c$) $A+$ (here $Gr+$) dominates the population. Since in this model e and d are different, then it is feasible to reach a population of only the $Gr+$ type when e is greater than d, which is impossible for the previous model.

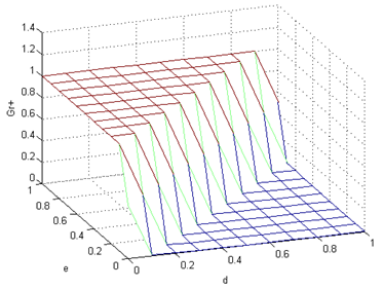

FIGURE 20. Influence of parameters e and d on phenotype $Gr+$

10.6. **Results of SEGT.** We consider three cases: dominance of $Gr+$, and two different populations included both phenotypes. The parameters were set to $b = 0.7, c = 0.5, d = 0.7$ and within these three examples e was changed from 0.2, to 0.3 and up to 0.5. The results are qualitatively similar for both the mean-field and

the spatial models, and moreover the effect of the value of parameter e on the final results shows that interaction between cells of the same phenotype is also important.

11. **Proliferation and migration (spatial model).**
Evolutionary game theory in an agent-based brain tumor model: Exploring the 'Genotype-Phenotype' link [25] Y. Mansury, M. Diggory, T.S. Deisboeck 2005

11.1. **Model.**

	A	B
A	α	β
B	δ	γ

	A	B
A	$\uparrow$	$\uparrow\uparrow$
B	$\uparrow\uparrow$	$\uparrow\uparrow\uparrow$

11.2. **Phenotypes.**
A– cell is proliferative
B– cell is of the migratory type

11.3. **Model description.** The model is a combination of an agent-based spatial model with the game theory approach, which is an extension of their previous work [24]. The authors explore the link between phenotype and genotype; they claim that all previous evolutionary models have been considered only in terms of phenotype specification and that their model provides the starting point for exploring genotype-phenotype connections. Their first table describes phenotype pay-offs for each interaction using game theory, and three genotype pay-off tables are presented: gap-junction communication, proliferation activity, and migration activity. To link the cells' genotypes to their phenotypes, the authors suggest that the extent of cell-cell gap-junction communication affects its phenotypic behaviour. The spatial part consists also of nutrient supplies. Instead of cell death due to toxicity, cells can perform the following actions: proliferate, invade, or become quiescent.

11.4. **Model results.** The authors examine the impact of changing A-A payoffs on the tumour's average spatial-temporal expansion velocity and distinguish different phases when A-A interaction is changing. The model presented may be considered as an extension of existing models or only as referring to typical game theory. Despite the fact that this model does not provide the possibility to study stable equilibrium like other game theory models, it focuses on the dynamics of tumour growth which is more related to cellular automata.

12. **Proliferation and migration (role of glycolysis).**
Evolutionary game theory elucidates the role of glycolysis in glioma progression and invasion [10] D. Basanta, M. Simon, H. Hatzikirou, A. Deutsch 2008

12.1. **Model.** The authors assume that in the initial stage all cancer cells are specified by autonomous growth, and then because of evolutionary acquisition are able to switch to anaerobic glycolysis or to become increasingly motile and invasive. In comparison with the previous models, this one is less general (the phenomena described are more specific) but at the same time is more complex. Moreover, one parameter is used as a cost and a benefit for the same interaction ($AG - GLY$).

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

12.2. **Phenotypes.**
AG– cell is characterized by autonomous growth
INV – cell is motile and invasive
GLY – cell can switch to anaerobic glycolysis for energy production

12.3. **Model parameters.**
k – cost of switching to glycolytic metabolism
n – cost for a non-glycolytic cell to live in an acid environment / benefit for a glycolytic cell of increasing the ambient acidity
c – cost of motility (reduced proliferation rate)

12.4. **Model description.** When AG interacts with AG - (AG, AG) - then both cells have to share available resources (since the baseline is 1 then it is $1/2$ for each cell). (AG, INV) - AG receives full resources, since INV cells have to move. The (AG, GLY) - situation is similar to interaction between two AGs, but additionally there is a cost of the acidic environment. All interactions for the INV phenotype are common and come down to the cost of invasiveness. (GLY, AG) - GLY cells bear the cost of switching to anaerobic glycolysis, but also gain an advantage related to the existence of other non-glycolytic phenotypes in an acid environment.

12.5. **Results of RD.** From comparison of average fitness per phenotype it is feasible to calculate the expected payoffs:

$$INV = 1 - \frac{k}{n}, AG = \frac{2kn + k - ck - cn}{2n^2}, GLY = 1 - INV - AG \tag{10}$$

To obtain conditions for a stable, trimorphic population it is necessary to check whether each of the phenotypes is greater than 0 and less than 1. The authors

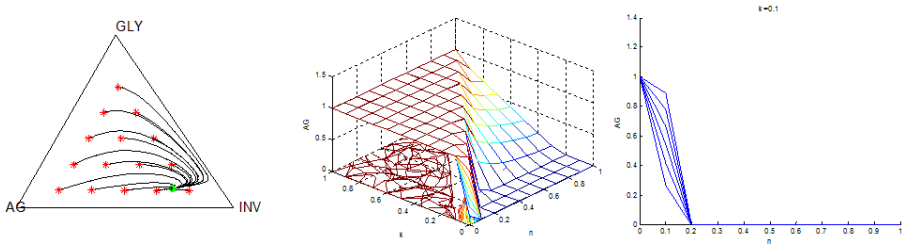

FIGURE 21. (a) Example of stable trimorphic population (b) The influence of parameters k and n on AG phenotype with $c = 0.6$ (c) The influence of n on AG phenotype with $c = 0.6$ and $k = 0.1$

suggest to confirm conditions for stable polymorphism by running simulations with different parameters due to the complexity of the equation for AG. This is a suitable approach for searching for points of stable coexistence of all phenotypes, because in this case the stable point does not depend on initial frequencies. However, as we have shown before the results could be different because of initial frequencies. Moreover, for this kind of analysis and representation of results it is not feasible to

check if the population is stable. The results indicate that phenotype AG is favoured by large values of k and small values of n. Figure 21b shows how phenotype INV

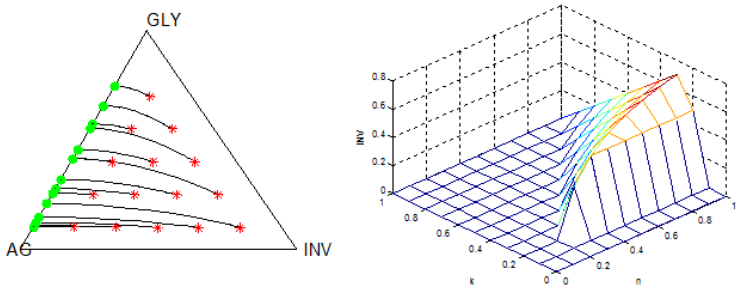

FIGURE 22. (a) Possible influence of different initial frequencies (b) The influence of parameters k and n on INV phenotype with $c = 0.6$

changes in the case of different values of k and n: it is favoured for small values of k and for large values of n. By simple analysis of the pay-off matrix it appears that a similar set of parameters can also favour the GLY phenotype. The explanation for this could be an impact of parameter c which for this test equals 0.6 which could be enough to make INV phenotypes better adapted than GLY (also because of 1 as baseline fitness) and the latter has enhanced fitness due to the relative large value of parameter n, which has a cross-influence on the AG phenotype. The model is more difficult for analysis compared to the previously described models. The results tend to be sensitive to parameter changes; for instance a change of c from 0.2 to 0.5 can push the population structure from a stable state between AG and INV to a stable coexistence of all phenotypes.

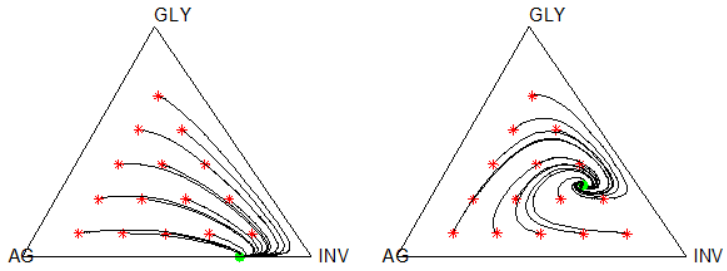

FIGURE 23. Proliferation-migration. Results for $c = 0.2$ and $c = 0.5$

12.6. **Results of SEGT.** The first scenario that we consider is for stable trimorphism (Figure 24). As we can see, the results for both models are qualitatively similar, but only for deterministic and switching reproduction. The interesting finding is that the results of switching reproduction contain the AG phenotype, while probabilistic reproduction shows coexistence between INV and GLY, and quantitative dominance of the INV phenotype. The results suggest different conclusions, and only probabilistic reproduction leads to the same state as in the mean-field model.

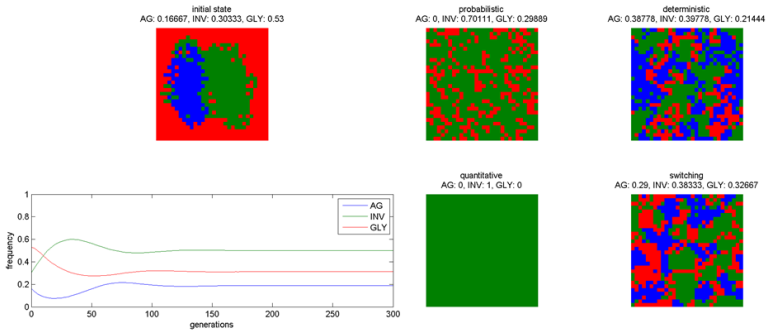

FIGURE 24. Proliferation-migration. Results for $c = 0.5$, $n = 0.4$ and $k = 0.2$

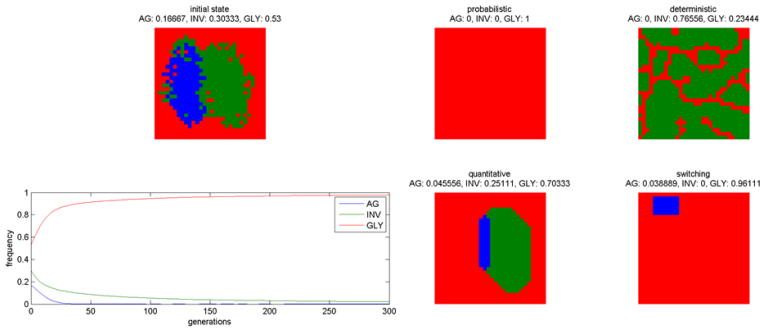

FIGURE 25. Proliferation–migration. Results for $c = 0.7$, $n = 0.4$ and $k = 0.2$

Deterministic reproduction shows that it is feasible to reach a stable dimorphic population of INV and GLY phenotypes, where bigger groups of motile cells are surrounded by glycolytic cells. Yet another interesting result occurs for a dimorphic

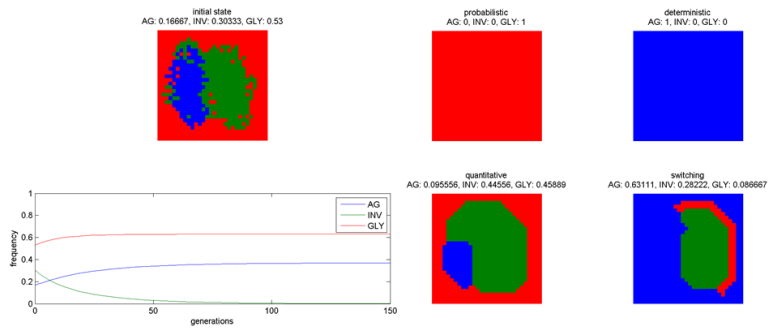

FIGURE 26. Proliferation–migration. Results for $c = 0.6$, $n = 0.1$ and $k = 0.1$

population of AG and GLY phenotypes in the mean-field game (Figure 26). Results for probabilistic and deterministic reproduction are completely different, and

the result for switching reproduction illustrates that glycolytic phenotypes can form stable groups on the edge between motile and proliferative phenotypes.

12.7. **Biological aspects.** The model results suggest that in a population composite of glycolytic cells, invasive cells are better adjusted and that conditions favouring a glycolytic phenotype also promote the occurrence of invasiveness. The frequency of occurrence of invasive cells does not depend on the cost of moving if a polymorphic equilibrium exists between all phenotypes. This phenomenon could indicate one of the basic principles of carcinogenesis: a malignant cancer (with a glycolytic phenotype) will manifest a high invasive phenotype regardless of costs.

13. **Proliferation and migration (spatial model).**
Studying the emergence of invasiveness in tumour using game theory [7] D. Basanta, H. Hatzikirou, A. Deutsch 2008

13.1. **Model.** This model is a simplification (for the spatial case) of the previously described model, without the phenotype GLY. The lattice for a spatial mode contains nutrients (for cell proliferation) which shall be replenished to a given constant value in each time step. Within one lattice site a couple of cells can be inserted and then interact between each other. If a cell is motile and its site is not empty then it shall move to a new location, but only where the cell density is lower than in the origin site, and if the cell is proliferative then it shall divide when the chosen site has enough space. If offspring has been produced, then with a small probability a mutation can occur and a new cell can be changed to the motile type.

	P	M
P	$1/2$	$b-c$
M	b	$b-c/2$

13.2. **Phenotypes.**
P – cell proliferates
M – cell migrates

13.3. **Model parameters.**
b – baseline (in other models set to 1)
c – cost of moving to the next location

13.4. **Results of RD.** In the case of the non-spatial model an equation for motile strategy computed from the Bishop-Cannings theorem is provided:

$$INV = \frac{b-2c}{b-c} \tag{11}$$

However, the authors assume that c is not greater than half of the base payoff b, and in their work it is fixed at 1. (Figure 27a) shows how phenotype P depends on c and b without such an assumption. Moreover, since contact between P and P shall be described as "share resources between two cells", then the payoff for this game could be $b/2$ which provides different results (Figure 27b).

	P	M
P	$b/2$	$b-c$
M	b	$b-c/2$

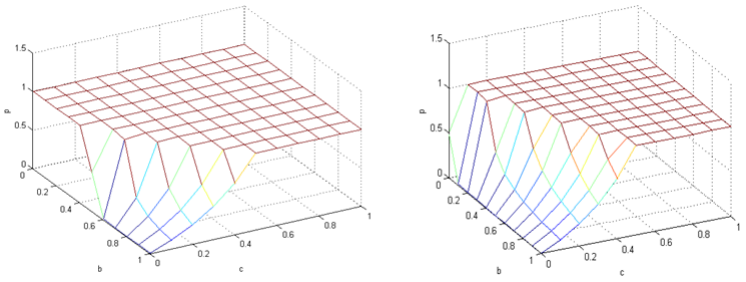

FIGURE 27. The influence of b and c parameters on P phenotype for (a) the original payoff matrix and (b) a modified one matrix

Since the result does not depend on the initial frequency, this way of representation is more convenient especially when the payoff matrix considers only 2 phenotypes and 2 parameters. Two models are presented, game theory and cellular automata, the latter without a game theory payoff matrix. The authors describe a link between the two models which shall be the ratio of nutrients per lattice, the site capacity, and the cost of motility c compared to the maximum fitness benefit.

14. **Multiple myeloma bone disease.**
Cancer phenotype as the outcome of an evolutionary game between normal and malignant cells [16] (see also comments by Mc Evoy [29]) D. Dingli, F. Chalub, F.C. Santos, S. Van Segbroeck, J.M. Pacheco 2009

14.1. **Model.** The situation when IL-6 and osteopontin produced by OC cells stimulate growth of MM cells was considered. The former also receive benefits in interacting with MM because of OAF production. Both net benefits are considered as β. OB cells are affected by the presence of MM cells, whereas the opposite influence does not occur. Also, a positive impact occurs in both directions during interaction between OC and OB cells.

	OC	OB	MM
OC	0	1	β
OB	1	0	-δ
MM	β	0	0

In this case the table is defined for the "row player" (read horizontally)

14.2. **Phenotypes.**
OC – Osteoclast
OB – Osteoblast
MM – multiple myeloma

14.3. **Model parameters.**
β – benefit of interaction between MM and OC cells
δ – negative influence to OB cells because of MM cells

14.4. **Results of RD.** Using this model it is feasible to reach stable polymorphism whenever β is less than 1. Additional variants arise from the sum of β and δ, which, when smaller than 1, implies coexistence between the OB and OC phenotypes. When it is greater than 1 the equilibrium point is a repeller and depending on initial

frequencies the population includes OC and OB or OC and MM phenotypes. The

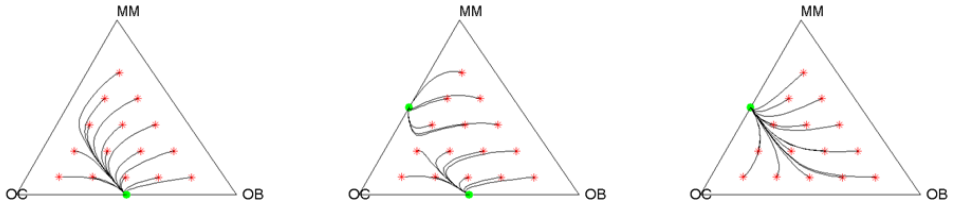

FIGURE 28. Multiple myeloma. Results for (a) $\beta = 1/2$, $\delta = 1/3$, (b) $\beta = 1/2$, $\delta = 1$, (c) $\beta = 2$, $\delta = 0$

third situation is when β>1, then the only possible outcome is a population of OC and MM cells. However, from our tests it appears that this situation is also possible when, for instance, both β, δ are equal to 0.9, a situation when the repeller is near to the point where OC and OB have 50% of the cells in the population. Further, two interesting situations not presented are when β is 0 (with non-zero δ) and when β is equal to 1. From the biological point of view it is rather unlikely that there

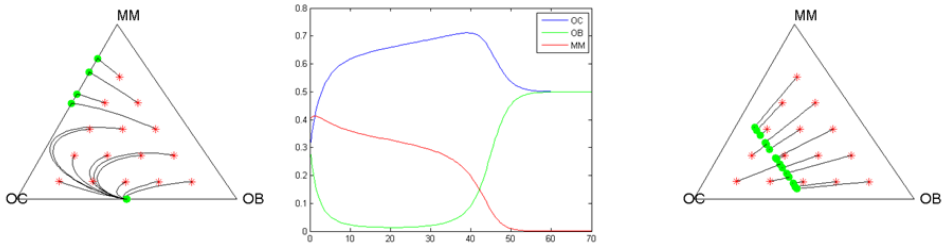

FIGURE 29. Multiple myeloma. Results for (a) $\beta = 0$, $\delta = 2$, (b) (b) time course for $\beta = 0$, $\delta = 2$, (c) $\beta = 1$, $\delta = 0$

is no interaction between MM and OC cells, but on the other hand the results are attractive from the game theory point of view. First, a finite structure of the population depends on initial frequencies. For some of these there exists coexistence of OC and OB, and for the others different final states of MM and OC. Second, as shown by the time course, frequencies can increase and then decrease to the stable state for the OC phenotype or otherwise for the OB-type. In the case of the parameters set $\beta = 1$, $\delta = 0$, which is on the boundary of all conditions which the authors consider, coexistence of all phenotypes is likely within the population and the result depends on initial frequencies. Additional information and explanations regarding this model can be found in [29].

14.5. **Results of SEGT.** We consider the same set of parameters for spatial game as for the mean-field model. And for all cases, except $\beta = 2$, $\delta = 0$ (dimorphic population with MM and OC), for the quantitative reproduction the population is dominated by MM cells and for the other types of reproduction methods unstable coexistence between OB and OC can occur.

14.6. **Biological aspects.** Time courses outcomes from RD dealing with therapeutic recommendations related to reduction of the MM burden are shown. The model gives low chances for elimination of the all MM cells, but that could change by development of new therapies β and δ. In the summary the authors propose that therapies could aim at changing the proportions of different cell types (in this case by the two parameters mentioned), instead of trying to eliminate all cancer cells. From an EGT point of view this means that therapies should focus on changing the dynamics of phenotypes so that normal cells out-compete the cancer cells (a similar strategy is discussed in [4]).

15. **Proliferation and migration (role of glycolysis and IDH1).**
The role of IDH1 mutated tumour cells in secondary glioblastomas: an evolutionary game theoretical view [9] D. Basanta, J.G. Scott, R. Rockne, K. R. Swanson, A. R. A. Anderson 2010

15.1. **Model.** A four-phenotype model characterizing secondary glioblastomas (sGBM) and the role of isocitrate dehydrogenase (1IDH-1) as related to angiogenesis, a hallmark of this disease, is described. The authors extended their previous model [10] by adding a phenotype that could be motile and could switch to anaerobic glycolysis. Within this model a distinction is introduced between the cost of motility for glycolytic and aerobic environments by dividing c by 3. On the other hand α, which represents the benefit of the surrounding vasculature, shall have a lower influence in an anaerobic environment and shall not be available for cells that are moving.

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

In this case the table is defined for the row player (read horizontally)

15.2. **Phenotypes.**
AG– cell is characterized by autonomous growth
INV – cell is motile and invasive
GLY – cell can switch to anaerobic glycolysis for energy production
$INV-GLY$ - cell is invasive and glycolytic

15.3. **Model parameters.**
k - cost of switching to glycolytic metabolism
n - cost for a non-glycolytic cell to live in an acid environment / benefit for a glycolytic cell of increasing the ambient acidity
c - cost of motility (reduced proliferation rate)
α angiogenic benefit because of the influence of IDH1 mutant sGBM

15.4. **Results of RD.** As in the previous work, figures are presented showing change of one phenotype caused by changes applied to the parameters. So instead of the proportion and ratio of phenotypes, the authors focus on $INV-GLY$ cells and four sets of values for k and n: (0.01, 0.02), (0.1, 0.2), (0.2, 0.3) and (0.3, 0.4). As an example we present only the results for $k=0.2$ and $n=0.3$: When k and c are relatively small then an influence of α can be strongly recognized. However, except

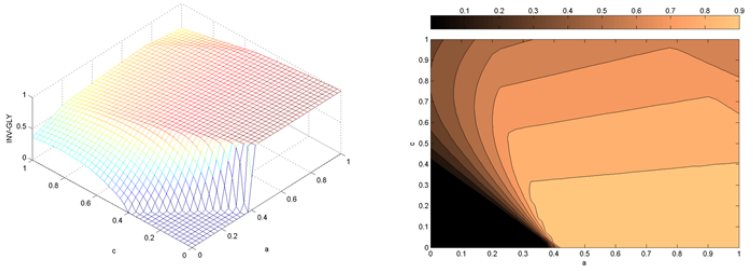

FIGURE 30. The influence of parameters c and a on $INV - GLY$ phenotype with $k = 0.2$ and $n = 0.3$

for the $INV - GLY$ phenotype it is not possible to track the behaviour of other phenotypes, their dynamics, and the possible impact of initial frequencies. Because of this, we present additional simplexes for different set of parameters chosen on the basis of previous figures. It is observed that the population can be in a stable state

FIGURE 31. Results for (a) $c = 0$, $n = 0.3$, $k = 0.2$ and $\alpha = 0.2$ (b) $c = 1$, $n = 0.001$, $k = 0.8$ and $\alpha = 0.8$

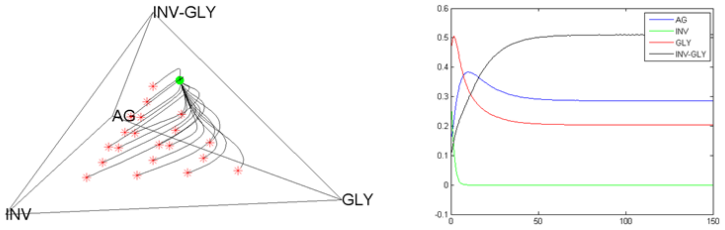

FIGURE 32. Results for $c = 0.1$, $n = 0.02$, $k = 0.01$ and $\alpha = 1$

when INV-type cells dominate, which can be achieved with 0 cost of motility. On the other hand, a similar behaviour for AG cells can be reached by setting a small cost for living in a glycolytic environment (Figure 31). The next figure (Figure 31) shows the possibility of a trimorphic population of AG, GLY and $INV - GLY$. The INV type has been repressed because $c = 1$, but $INV - GLY$ exists in the population and its frequency is the greatest. The dominance of $INV-GLY$ could be explained by analysis of their respective interactions, where the parameter α has a strong influence. It is also important to take into account an interaction among cells of the same type; even if the GLY phenotype is better adapted than $INV - GLY$ the latter has better fitness value in contact with other $INV - GLY$, because the

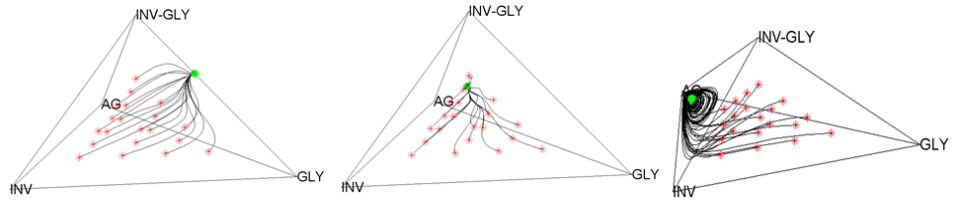

FIGURE 33. Results for (a) $c = 1$, $n = 0.02$, $k = 0.01$ and $\alpha = 0.5$ (b) $c = 1$, $n = 0.6$, $k = 0.8$ and $\alpha = 0.8$ (c) $c = 0.4$, $n = 0.3$, $k = 0.4$ and $\alpha = 0.25$

baseline equal 1. If α has been decreased, then AG cells are weaker in interactions especially with GLY and $INV - GLY$. In the previous figure $\alpha = 1$, now we have decreased it to 0.5 which implies driving AG type out. A stable quadromorphic population is also feasible, particularly for balanced parameters. In addition the model can produce oscillations between the AG, INV and $INV - GLY$ types. The authors considered this possibility but saw no evidence that such oscillations do occur although they considered the possibility that the metabolic activity of the tumour may have a cyclic nature. The speed of $INV - GLY$ domination is also presented, described by the number of time steps for $INV - GLY$ cells to reach 50% of the population the population, but also sped up subtracted from 1000 (tumour with speed 999 needs 1 time step to reach $INV - GLY$ dominance; tumour with speed 0 never achieved this dominance). The results (RD) show the crucial role of parameter α: not only increase dominance of $INV - GLY$ type in this result. The effects of anti-angiogenic treatment are also considered by changing the parameter α during simulation. One of the interesting results is that in the case of low α, increasing this parameter leads to domination of $INV - GLY$ cells in the population, whereas with no increase this phenotype is eliminated.

15.5. **Results of SEGT.** The same or a similar set of parameters has been used to simulate the behaviour of spatial allocation of the phenotypes. In the situation when INV is dominant in the population for the mean-field game, the same results have been obtained for spatial games for all reproduction methods. When c has been changed from 0 to 0.1, which enables phenotype AG to be maintained in the population, only probabilistic reproduction leads to the same results as the mean-field model and the results are qualitatively very similar to the non-spatial counterpart. Evolutionary game modelling with changing parameters for RD and SEGT will be studied more deeply in the frame of another model.

15.6. **Biological aspects.** Angiogenesis (parameter α) could be the most important factor in the dominance of invasive glycolytic phenotypes which is suggested by the results of RD models and clinical imaging. The simulations focused mainly on the glycolytic fraction, since the population of these cells could be observed approximately by clinical imaging.

16. **Radiation induced bystander effect.**
Game theoretic approach to mathematical modeling of radiation induced bystander effect [34] Spatial evolutionary games and radiation induced bystander effect [23] A. Swierniak, M. Krzeslak 2010

16.1. **Model.** The biological phenomenon could be roughly defined as follows: cells exposed to ionizing radiation or other extracellular stresses release signals that induce effects in neighbouring non-irradiated cells which resemble those observed in the targeted cells. A model in game theory terms has been set up based on the angiogenic model [37] and the authors considered tumour cells exposed to the bystander effect.

	X	Y	Z
X	$1-k$	$1-i+j-p$	$1-p$
Y	$1+j-k$	$1-i+j$	$1+j$
Z	$1-k$	$1-i+j$	1

16.2. **Phenotypes.**
X – cell escapes to apoptosis
Y – cell produces a growth factor (paracrine fashion)
Z – cell is neutral (baseline)

16.3. **Model parameters.**
k - represents the cost of apoptosis/profit from the bystander effect
j - is a measure of the profit for the cell of contact with a growth factors
i - represents the cost of producing the growth factors
p - represents the cost/advantage from resistance to the bystander effect

16.4. **Results of RD.** Conditions for stable coexistence of all phenotypes within the population, calculated from the comparison of expected, average fitness:

$$0<\frac{k}{p}<1, i<j, 0<\frac{j-i}{j}+\frac{k}{p}<1 \tag{12}$$

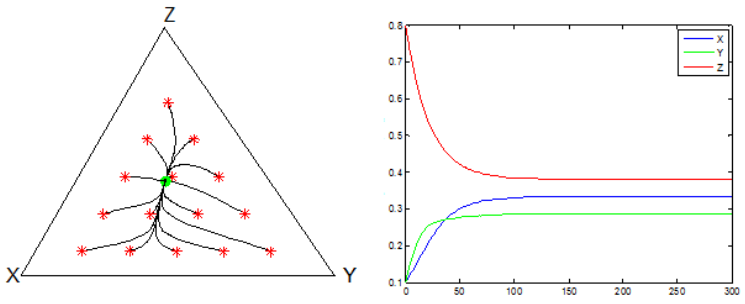

FIGURE 34. Bystander effect. Results for $i = 0.5$, $j = 0.7$, $k = -0.1$ and $p = -0.3$

In the model it is feasible to reach triple polymorphism, but such a relation does not always exist and even if it exists it may be unstable. Different behaviours are due to positive and negative values of k and p. In the case of negative parameters the equilibrium point is an attractor and provides stable coexistence of X, Y and Z phenotypes, but when these parameters are positive the equilibrium point is a repeller and the result depends on initial frequencies. This can lead to dimorphism of the Z and Y or X and Y phenotypes. In the case when the equilibrium point is an attractor, changing parameters causes changes only in the final state. In the case when this point is a repeller then such changes affect two sets of initial frequencies

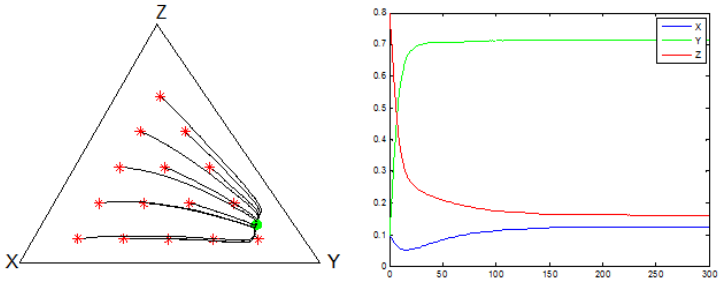

FIGURE 35. Bystander effect. Results for $i = 0.2$, $j = 0.7$, $k = -0.05$ and $p = -0.4$

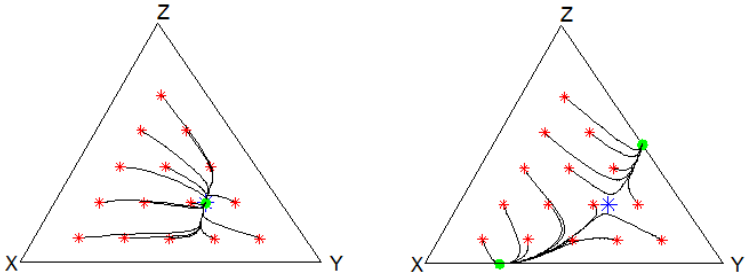

FIGURE 36. Bystander effect. Results for (a) $k = -0.1$ and $p = -0.1$, (b) $k = 0.1$ and $p = 0.1$

that leads to two different final states. This model also admits stable dimorphic

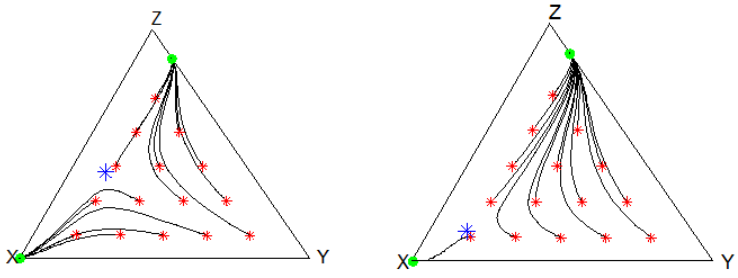

FIGURE 37. Bystander effect. Results for different repellers

coexistence between irradiated cells X and neutral cells Z in the case when the costs of producing a growth factor are greater than the benefits. For positive values of k and p we get two cases in which the population becomes homogenous (monomorphic equilibrium). An equilibrium point within these two cases depends on the ratio of k and p. Increasing this ratio leads to dominance of X and decreasing it to dominance of Z. A situation when Z and Y are in coexistence is obtained when k is positive or when the equilibrium point is close to dominance of the X phenotype (in the repeller case).

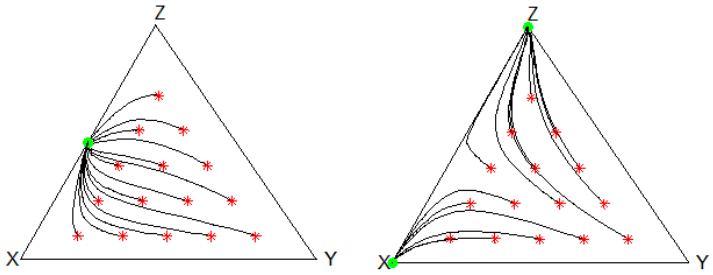

FIGURE 38. Results for (a) $i = 0.6$, $j = 0.5$, $k = -0.2$ and $p = -0.4$ (b) $i = 0.6$, $j = 0.5$, $k = 0.2$ and $p = 0.4$

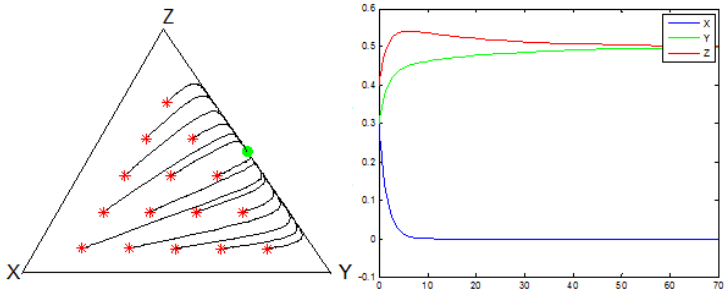

FIGURE 39. An example of a stable dimorphic population between Z and Y cells

16.5. **Results of SEGT.** In most cases the spatial results are qualitatively in agreement with the mean-field model. Differences are significant if the parameters fulfil the previously derived conditions for equilibrium (both attractor and repeller). Deterministic and switching reproductions lead to the same results. Moreover, both

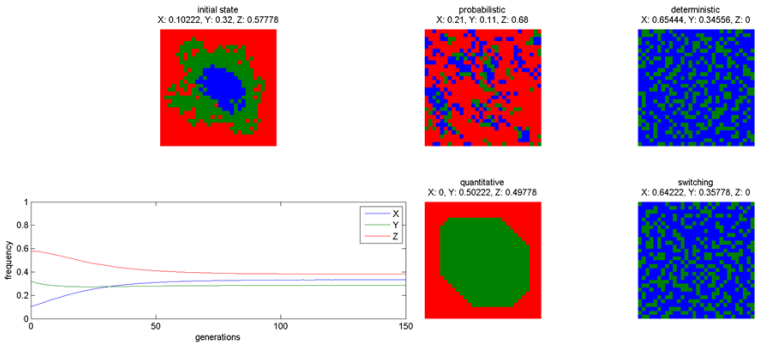

FIGURE 40. Bystander effect. Results for $i = 0.5$, $j = 0.7$, $k = -0.1$ and $p = -0.3$

include a population which contains X and Y cells, although from the mean-field model it seems that the Z type has the best adaptation. Probabilistic reproduction leads to qualitatively similar results as its non-spatial counterpart, but the result

is unstable. When the equilibrium point is a repeller (k and p are positive), then

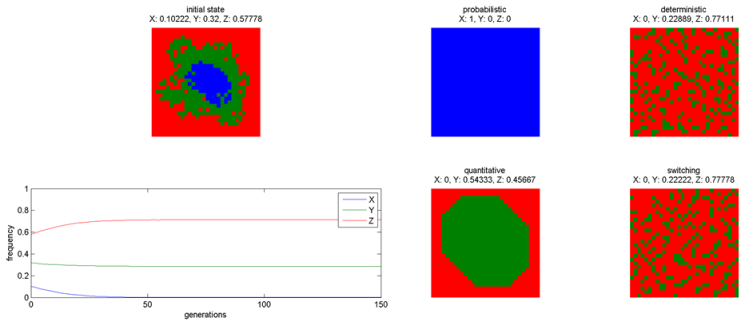

FIGURE 41. Bystander effect. Results for $i = 0.5$, $j = 0.7$, $k = 0.1$ and $p = 0.3$

deterministic and switching reproduction show coexistence of Y and Z, exactly as in the mean-field model. In the case of probabilistic reproduction the results are completely different.

17. **General cell interactions with affine fitness functions.**
Evolutionary Games with Affine Fitness Functions Applications to Cancer [19] M. Gerstung, H. Nakhoul, N. Beerenwinkel 2011

17.1. **Model.**

	H	$T1$	$T2$
H	0	0	0
$T1$	1	-1	$-b-\sigma_1$
$T2$	1	$-b-\sigma_2$	-1

In this case the table is defined for the row player (read horizontally)

17.2. **Phenotypes.**
H – normal cell
$T1$ – tumour cell type 1
$T2$– tumour cell type 2

17.3. **Model parameters.** The parameters are not relevant to any phenomena of real tumours, but were obtained by mathematical calculations from a general affine model.

17.4. **Model description.** Mathematical definitions of affine functions which shall be the function of the expected payoff plus some constant are presented. If the constant is set to 0 (which is a standard game case) then the authors find a strong selection limit, because the fitness is given directly by the expected payoff of the game. If the constant has values slightly smaller than 1 then the affine fitness function can be interpreted as a standard game scaled to an affine game in the weak selection limit. The authors also recall a theorem about the inhomogenous replicator equation with affine fitness function [33] which allows an affine fitness function to be obtained from an equivalent homogeneous replicator equation (however, the dynamics could be different for both the affine and the standard game). Having this in mind, the authors also present a general two-players game with the prisoner's

dilemma as an example. The three player game is presented as the interaction of one healthy and two tumour cells from three different cancer phenotypes. The proposed payoff matrix and fitness vector enable the problem to be transformed to the standard game based on the theorem mentioned above.

17.5. **Model results.** The authors discover a number of different stable points and present results from the replicators dynamics. The model remains quite general without any references to real cancer phenomena.

18. **p53 cancer vaccine and chemotherapy (evolutionary double bind).** Exploiting evolution to treat drug resistance: Combination therapy and the double bind [7] D. Basanta, R. A. Gatenby, A. R. A. Anderson 2012

18.1. **Model.** The double bind is a combination of two therapies such that resistance evolved to one leaves individuals more susceptible to the other. Compared to the other models, the main difference is that resistance can be treated in an autocrine or a paracrine fashion and therefore the cost of treatment targeting p53 is divided by 2 in contact with I-type cells. For simplicity, evolutionary double bind extra costs were set to 1.1 and the costs of treatments are represented by Heaviside step functions multiplied by these extra costs.

	C	I	S
C	$1 - C_c - \alpha d_i(t)$	$1 - C_c - \alpha d_i(t)/2$	$1 - C_c - \alpha d_i(t)$
I	$1 - C_i - \beta d_c(t)$	$1 - C_i - \beta d_c(t)$	$1 - C_i - \beta d_c(t)$
S	$1 - d_c(t) - d_i(t)$	$1 - d_c(t) - d_i(t)/2$	$1 - d_c(t) - d_i(t)$

18.2. **Phenotypes.**
C – cell is resistant to chemotherapy (an autocrine type of resistance)
I – cell is resistant to the p53 vaccine (a paracrine type of resistance)
S – cell is susceptible to both the p53 vaccine and chemotherapy

18.3. **Model parameters.**
C_c – cost of the resistance to chemotherapy
C_i – cost of the resistance to p53 vaccine
$d_c(t)$ – cost of chemotherapy treatment to non-resistant cells
$d_i(t)$ – cost of p53 vaccine treatment to non-resistant cells
α – extra cost of being subjected to p53 vaccine
β – extra cost of being subjected to chemotherapy

18.4. **Results of RD.** Results for different sequences of applying treatments, activation times, and costs are presented. The missing point is the case when both treatments are applied at the same time. As the authors suggest, the extra costs for resistance should be constant and set to 1.1, C_c shall be set to 0.2, and $C_i = 0.4$. We have also considered the case when the costs of the resistance to chemotherapy are greater than those to p53 vaccine (Figure 43). It is found that if both treatments are applied at the same time, then in the former case (C_c>C_i) the population consists only of cells resistant to chemotherapy C, and in the latter (C_c>C_i) a stable dimorphic population of C and I type cells can occur. Time courses for different values of C_i (0.2, 0.3 and 0.4), a constant value of C_c (0.2), and for different sequences of treatments are presented. In the case of chemotherapy applied first, independently from the parameters the population always ends with domination of p53 vaccine-resistant cells. When the p53 treatment is applied first, for C_i

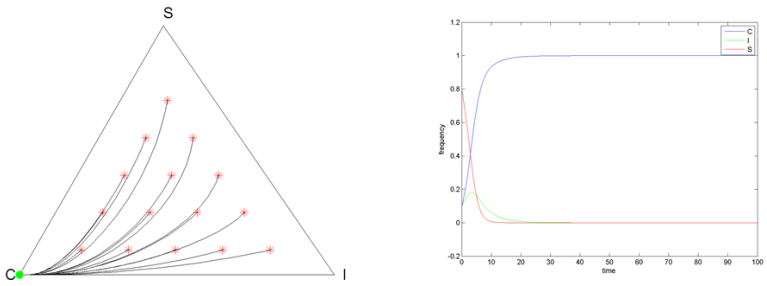

FIGURE 42. Combination therapy. Results for $C_c = 0.2$ and $C_iCi = 0.4$ when both treatments are applied simultaneously

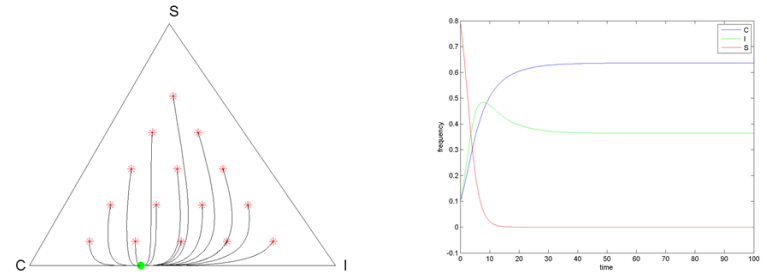

FIGURE 43. Combination therapy. Results for $C_c = 0.4$ and $C_iCi = 0.2$ when both treatments are applied simultaneously

equals 0.2 and 0.4 polymorphic populations of cells resistant to chemotherapy are observed. For C_i equals 0.3, cells resistant to p53 vaccine survive and even dominate the population during chemotherapy. Additionally simulations for C_i=0.2 and C_c=0.4 were performed. And in all cases (even for C_i equal 0.3 and different times of switching between therapies) cells resistant to the second treatment dominate in the population. The conclusion is that sometimes a smaller dose of the drug or vac-

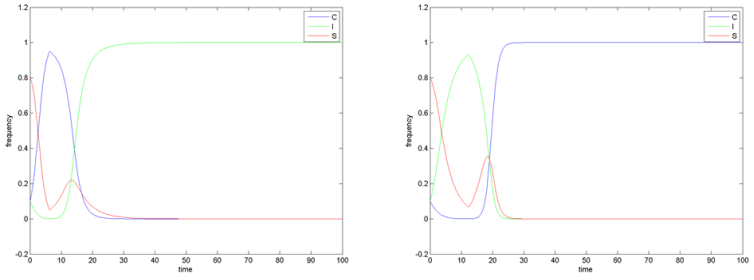

FIGURE 44. Results for $C_c = 0.2$ and $C_i = 0.3$ when (a) chemotherapy is applied first or (b) when p53 vaccine therapy is applied first

cine can lead to a worse tumour fitness. Increasing the cost of the p53 vaccine it can be found that low and higher values of this parameter can lead to similar results:

domination of chemotherapy-resistant cells if the p53 vaccine is applied first. The results show that treatments switching time is more important for the chemotherapy than for p53 treatment. The novel finding of this study is the time dependence of the parameters used to simulate different sequences of the treatments. On the other hand the only place where cells really interact is a common share of resistance to the p53 vaccine. In other cases different phenotypes react to changes in the environment (such as therapies).

18.5. **Results of SEGT.** Just for simplification, we consider spatial models only for one time of switching therapies and for parameters set the same as for the base model ($C_c = 0.2, C_i = 0.4$). In the case when both therapies are applied together the result from the spatial game is exactly the same as that from the mean-field model. Within the probabilistic mode, some oscillations of phenotype S can be observed as

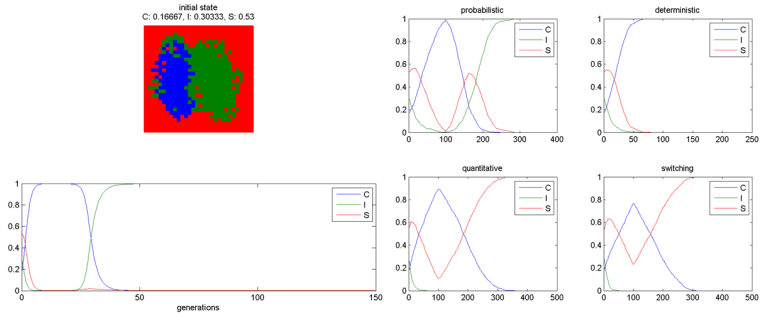

FIGURE 45. Results for $C_c = 0.2$ and $C_i = 0.4$ when both treatments are applied simultaneously

long as C cells exist in the population. After p53 vaccine treatment I cells gain an advantage; this should also be observed for deterministic reproduction, but after p53 vaccine treatment no cells of I-type remain. Dominance of S-type in quantitative and switching reproduction could be possible because of a greater number of initial cells and because of better adaptation of C cells when p53 vaccine is applied. When

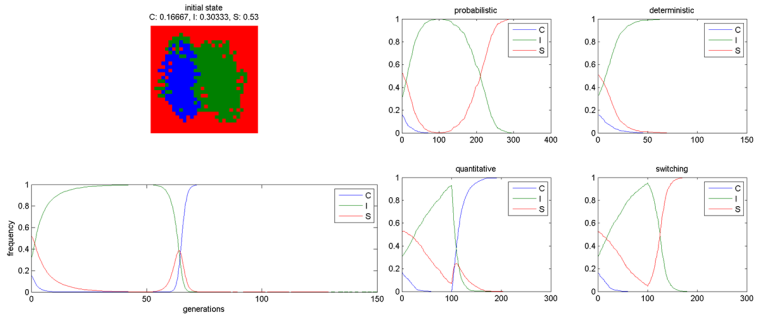

FIGURE 46. Results for $C_c = 0.2$ and $C_i = 0.4$ when p53 vaccine treatment is applied first

chemotherapy is applied later, different results for different reproduction modes are also observed, and as in the previous example they are dependent on the amount of initial cells and adaptation between each phenotype different treatments.

19. **Production of growth and cytotoxic factors.**
Extended game-theoretic model of interaction between tumour cells [22] M. Krzeslak, A. Swierniak 2012

19.1. **Model.** The model presented is an extension and combination of two Tomlinson's models [34, 35] with parameter z set to 1 as in the other models. In one model cells that produce growth factors or cytotoxins, and resistant and neutral cells are considered.

	A	P	Q	R
A	$1-i+j$	$1+j-e+g$	$1+j-h$	$1+j$
P	$1-i+j-f$	$1-f-e+g$	$1-h$	$1-f$
Q	$1-i+j$	$1-e$	$1-h$	1
R	$1-i+j$	$1-e+g$	$1-h$	1

19.2. **Phenotypes.**
$A-$ cell produces the angiogenesis factor (paracrine fashion)
P – cell produces a cytotoxic substance against adjacent cells
Q – cell is resistant to the cytotoxic substance
R – cell neither produces the cytotoxic substance nor is resistant (baseline), shall be also treated as $A-$

19.3. **Model parameters.**
e – cost of producing cytotoxin
f – disadvantage of being affected by cytotoxin
g – benefit of harming other cells
h – cost of resistance to cytotoxin
i – cost of the angiogenesis factor production
j – benefit of receiving growth factor

19.4. **Results of RD.** Conditions for stable coexistence between all phenotypes:

$$j>i, h<f, e<g \tag{13}$$

Example with stable quadrupled polymorphism. It is possible to reach stable coex-

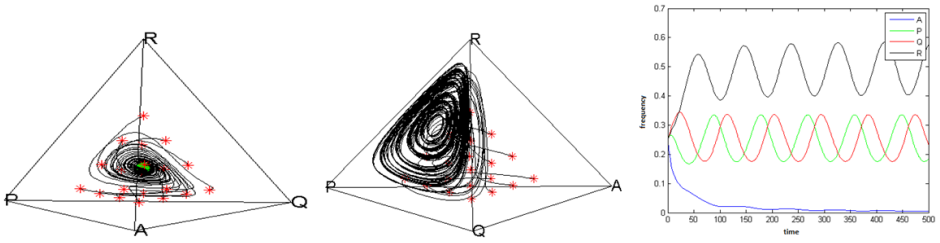

FIGURE 47. 3D simplex of interaction. Results for $j = 0.4$, $f = 0.4$, $g = 0.4$, $e = 0.3$, $h = 0.1$ and (a) $i = 0.3$ (b) $i = 0.4$ (c) time course for $i = 0.4$

istence of all phenotypes in the population. The population can be also dimorphic between A and R types with a weak dependency on initial frequencies (the Q-type could appear with relatively larger initial values of Q and P phenotypes). This state can be easily changed by small increases of parameter h which leads to a trimorphic

population of A, P and Q phenotypes. Other changes of parameter i can lead to oscillations between R, P and Q. Such complexity provides strong dependency on initial frequencies.

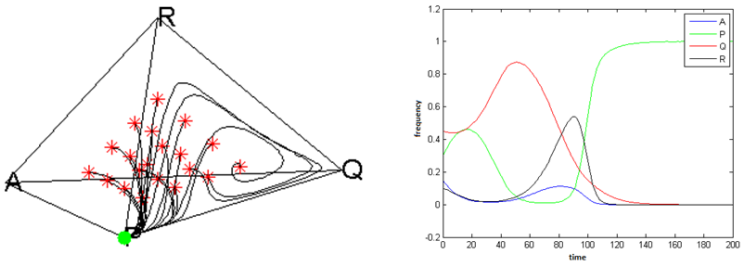

FIGURE 48. 3D simplex of interaction. Results for $i = 0.4$, $j = 0.4$, $f = 0.4$, $g = 0.7$, $e = 0.3$ and $h = 0.1$

19.5. **Results of SEGT.** As in the four-phenotype model of proliferation and motility [9], we consider initial lattices generated randomly. A couple of scenarios for different initial, random lattices were checked for parameter sets leading to P domination and in all cases both spatial and non-spatial models provide the same qualitative results. Differences are observed if more phenotypes can remain in the population (for the mean-field model). The figures presented below show situations where except for R, all phenotypes exist in the population. The spatial counterpart leads to different results and suggests that coexistence with R phenotype is feasible and that moreover R can dominate because of the high fitness value of contacts R with R. As in the previous example, quantitative reproduction leads to different

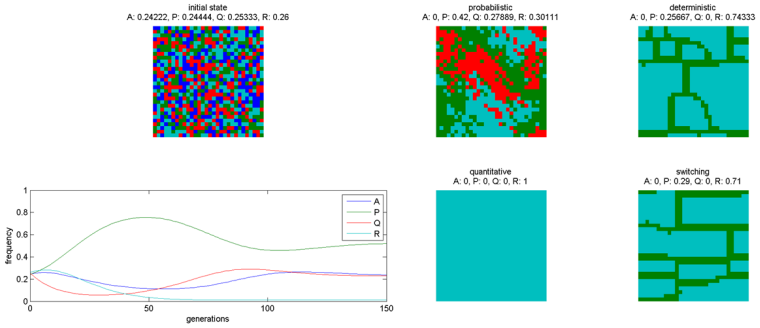

FIGURE 49. Results for $i = 0.3$, $j = 0.4$, $f = 0.4$, $g = 0.4$, $e = 0.3$ and $h = 0.2$

results than in the case of the mean-field model. Comparing with the previous example e has been increased by 0.1 and h decreased by 0.1. Intuitively, this should lead to better adjustment of Q phenotypes and poorer for P, however the mean-field and spatial models give different results.

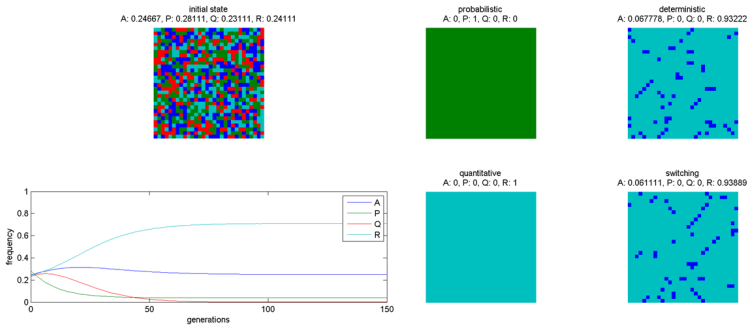

FIGURE 50. Results for $i = 0.3$, $j = 0.4$, $f = 0.4$, $g = 0.4$, $e = 0.4$ and $h = 0.1$

20. **Investigating prostate cancer tumour-stroma interactions.** Investigating prostate cancer tumour-stroma interactions: clinical and biological insights of from an evolutionary game [11] D. Basanta, J.G. Scott, M.N. Fishman, G. Ayala, S.W. Hayward, A. R. A. Anderson 2012

20.1. **Model.** A three-phenotyped evolutionary game to simulate tumour and stroma interactions is presented, using an extension of a previous model [1] with introduction of a stromal population S that can interact with the tumour.

	S	D	I
S	0	α	0
D	$1+\alpha-\beta$	$1-2\beta$	$1-\beta+\rho$
I	$1-\gamma$	$1-\gamma$	$1-\gamma$

In this case the table is defined for the "row player" (read horizontally)

20.2. **Phenotypes.**
S – stroma
D – microenviromentally dependent
I – microenviromentally independent

20.3. **Model parameters.**
α – benefit derived from the cooperation between a S and a D cell
β – cost of extracting resources from the microenvironment
γ – cost of being microenvironmentally independent
ρ – benefit derived by D from paracrine growth factors produced by I cells

20.4. **Model results.** The focus is more on the influence of the parameters than on the different initial frequencies of occurrences. Both tumour phenotypes (D and I) start from 10^{-4} of the population, with the rest being stromal cells. RD results are presented without detailed end values for frequencies and population dynamics, but they show which phenotypes survive in the population for different sets of parameters. The authors also explore in detail the emergence of stromagenic tumours using time evolution based on RD. Additionally, some therapeutic implications similar to those in previous models [7] [9] were introduced.

21. **Summary and conclusions.** The collection of game theoretic models presented here includes numerous examples describing different tumour phenomena. As well as the various biological backgrounds, the mathematical and computational techniques also vary significantly. The common feature for almost all models is an assumption that as an effect of evolution, different types of cells can occur in healthy tissue and that the existence of these phenotypes strongly depends on their evolutionary adaptation and on the changing environmental conditions. Game theoretical models of carcinogenesis, by monitoring the different success of cell adaptations, show how and in which conditions cells are able to coexist with others or to dominate the population by repressing cells with other, weaker strategies. However, it is clear that additionally to the studies of possible cells coexistence it is important to consider different quantitative results of final frequency occurrences of phenotypes in the population. In addition to different initial frequencies and parameters, time and space should also be included in models. In spatial evolutionary games the initial allocation is very important and the time variability is almost exclusively considered in the non-special models. As has been discussed combination of both factors is also possible. Game theory provides a simple way of modelling cellular interactions. The main problems appear to be definition of pay-off matrices which are adequate for the biological issues considered, specifying the proper pay-off matrix, and then the use of replicator equations to study different scenarios. Combining models of different types leads to complexity and difficulty in analysis of results and their interpretation; one example can be observed when a change of measure of fitness of one phenotype affects other seemingly uncorrelated phenotypes. Other approaches to application of game theory both in the mean-field and the spatial version are found in the literature (see e.g. [13], [15], [18]). In this review we have omitted studies in which although a game theoretic approach was used, other tools were adopted to study population dynamics within tumour cohorts or in the tumour-host interface (e.g. [3], [14], [17], [18], [21]). Complete simulation of existing phenomena could be done by studying each model in the non-spatial (both the two players and the three players game which can introduce synergy effects) and the spatial versions (with different ways of reproduction, competition and initial lattice). Appropriate comparison of the results could explain if different parameters or time and spatial distribution are essential for some phenotypes. If a phenotype has a strong adaptation and the ability to overcome other strategies, it may dominate the population independently of its initial frequency or allocation. Despite the complexity of conditions used in different models and the variety of ways of presenting the results, there still exists a gap between the models and biological experiments. Qualitatively, the results can help in understanding tumour evolution and the possible effects of different therapies. Models which demonstrate stable coexistence of different phenotypes can explain the strong heterogeneity of cancer cell populations, while others predict displacement of tumour cells from the population or dominance of mutated cells. On the other hand the results appear to be characterized by strong sensitivity to the values of the parameters used and to the particular modelling procedure, possibly reflecting limitations of present methods.

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