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Four Phenotype Model of Interaction Between Tumour Cells

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Abstract: Evolutionary game theory has been widely used to simulate tumor processes. Inter-cellular interactions that occur within tumor populations are good examples of biological evolutionary games for space and nutrients. Presented extended model considers four strategies (phenotypes) that can arise by mutations: cells that produce harming substances to gain advantage, cells resistant to these substances, cells that produce growth factor which affects any other cell-kinds and neutral cells. Different equilibrium points, scenarios and spatial versions are also discussed..

1. INTRODUCTION

Game theory has been applied in various branches of science. Starting from economics, where the game theory aroused, through behavioral and social sciences, and ending on linguistic evolution or engineering and military. One of the recent area of applications is biology. Everything started in 1970s when John Maynard Smith combined evolutionary biology and game theory (Maynard Smith, 1982). Evolutionary game theory differs from standard game theory by deviating from rational approach of the competitive players, by treatment of strategies as phenotypes of individuals acquired through the evolution. Moreover the players are members of a population, contained individuals with different phenotypes (strategies), who can cooperate or compete for resources. As a result of different adaptations to the environment and following games through the time (generations) the population can tend to stabilize its structure at the same time gaining stable monomorphism or polymorphism of population's phenotypes. Such state is called evolutionary stable. Whereas evolutionary stable strategy (ESS) is defined as phonotype that, if adopted by the vast majority of a population, will not be displaced by any other phenotype. However opposite situation is very feasible to occur.

Classical game problem studied by Maynard Smith was Hawk-Dove game and it assumed interaction between aggressive and giving up individuals within one population (Maynard Smith, 1982). Relatively to the costs and gains from winning different ratios of both strategies can occur in the studied population.

Interactions between individuals may also happen among tumor cells. Evolutionary game is performed between cells with different phenotypes (both healthy and cancer cells). Main aim of these game theoretic models is to study possibility of coexistence or even domination of newly formed tumor cells, which have acquired new strategies (phenotypes) by mutations. To our knowledge Tomlinson and Bodmer (Tomlinson et al., 1997) first proposed such a model describing inter-cellular interactions including avoidance of apoptosis and production of angiogenic factors. The models that followed described phenomena such as: production of the cytotoxic substances (Tomlinson, 1997), production of growth factors (Bach et al., 2001), invasion and metastasis (Mansury et al., 2006),(Gatenby et al., 2003), radiation bystander effect (Swierniak et al., 2010), resistance to chemotherapy and p53 vaccine (Basanta et al., 2012b), interaction between osteoclasts and osteoblasts (Dingli et al., 2009), tumor-stroma interaction (Gerstung et al., 2011), interaction between different tumors (Basanta et al., 2012a) and others (see (Basanta et al., 2008), (Swierniak et al., 2013) for survey).

In this paper combination and by the same extension of two Tomlinson's models (Tomlinson et al., 1997), (Tomlinson, 1997) is presented. The resulting model shows more complex population in terms of different phenotypes and stronger internal dependencies caused by parameter changing. Author presents hypothesis that as a result of mutation a new phenotype, that gains benefits of harming neighboring cells, may occur and survive in population. The consequence of this phenomena is another phenotype that has acquired possibility to be resistant to harming substances. These two strategies together with neutral one form one of the models presented in (Tomlinson, 1997). The implication of new features is defined by costs and benefits which concern phenotype's fitness in population. The model in (Tomlinson et al., 1997) considers growth factor production by tumor cells. These factors affect both the surrounding cells and the cells that produce them. As a result of such altruistic behavior only producers bear costs of growth factor performance.

Our paper is probably the first model in which interaction between four different phenotypes of cells are illustrated using three dimensional simplexes and time courses. To our knowledge the only other paper in which interaction of four phenotypes was discussed is (Basanta et al., 2011). The authors of (Basanta et al., 2011) however were interested in changes in subpopulations of chosen phenotypes with respect to changes of cost parameters rather than in studying equilibrium between all phenotypes and dynamics of their evolution.

2. SPATIAL EVOLUTIONARY GAMES

Contrary to the mean-field approach the spatial models avoid perfect mixing, and intercellular interactions are dependent of their local arrangement. In spite of, that it is still a simplified model of carcinogenesis, spatial models, based on cellular automata, create a next step in discovery of new behaviors among cells and give different results than mean-field models. Nowadays, spatial games quickly become very popular, nevertheless it should be remembered that the origin of spatial games is the use of cellular automata by such pioneers as von Neumann in conjunction with the classical theory of games. In our paper we follow the line of reasoning presented by Bach et al (Bach et al., 2003), where spatial tools used in modeling of carcinogenesis is most suited to our expectations.

Similarly to non-spatial games, the spatial ones are also iterated. In passing, transient generations we proceed according to the following steps (Bach et al., 2003):

- payoff updating - sum of local fitness of neighborhood,
- cell mortality - removing a certain number of players,
- reproduction by competition - defining which of the cells (specifically of the strategies) will be on an empty place.

Game is played on the lattice forming torus, and every competition results giving tie are settled randomly.

The authors (Bach et al., 2003) present three ways of cell mortality:

- synchronous updating - all the cells die simultaneously and they are replaced dependent on the strategy of their neighbors before dying.
- asynchronous updating - in each generation a single cell, chosen at random, dies and is replaced.
- semi-synchronous updating - probability of individual cellular mortality is equal to 0.1. Thus in one generation 10% of players are deleted from lattice.

In this paper we are using mainly semi-synchronous updating, since this method allows for the biologically realistic situation. Furthermore simulations show that synchronous updating assumes a global controller of the system, while asynchronous updating implies vanishing of small cell clusters impossible.

Reproduction of removed players (killed cells) is the next stage of the algorithm. The authors have suggested two kinds of reproduction:

- deterministic – in competition for the empty place the winner is the strongest player (with highest local adaptation – sum of eight scores from cell-cell interaction).
- probabilistic – values of adaptation (or sum of values from payoff matrix) for each player are divided by total score in their neighborhood. This local competition, with an appropriate fitness and location, allows cells' strategies with lower fitness, but in better location and locally superior in numbers to dominate in the population.

Additionally we introduce other two ways of reproduction (Krzeslak et al., 2011):

- quantitative reproduction – it is a sum of players adaptations with the same strategy.
- switching reproduction – when differences between scores are big, quantitative reproduction is better option (it is a chance for numerous, but weaker players). Alternatively in the opposite situation, deterministic reproduction is our choice. In this case in simulations an additional correction factor has been added (proportion between minimal and maximal fitness). But it is not our aim to study the role of this factor.

3. ANALYSIS OF THE EXTENDED MODEL

We propose a model which combines the two Tomlinson's models. The first one is the model that assumes production of a substance to harm other cells and the second one considers production of a growth factor which activates e.g. angiogenesis.

More precisely in the first model the author assumes that harming other cells is possible by production of some cytotoxic substances which affect surrounding cells (but not the producer). As an evolutionary response to that feature 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.

The pay-off table has the following form:

Table 1. Pay-off matrix

	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

where phenotypes are defined as follows:
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)
and parameters used to defined the measure of fitness are given by:
z – baseline fitness (set to 1 in the context of the combined model)
e – cost of producing cytotoxin
f – disadvantage of being affected by cytotoxin
g – benefit of harming other cells
h – cost of resistance to cytotoxin
Conditions for stable coexistence of all phenotypes within population, calculated from comparison of expected average fitness are as follows:

$$0 < \frac{h}{f} < 1,\ 0 < \frac{e}{g} - \frac{h}{f} < 1,\ \ 0 < \frac{e}{g} < 1 \qquad (1)$$

These inequalities show that the cost of fitness in interaction with p should be greater than the cost of resistance and that

costs of cytotoxin production should be greater than benefits of harming other cells. If these conditions are fulfilled then the final population will be trimorphic and independent of initial frequencies. The model assures that it is not feasible to reach stable coexistence between q and r phenotype. If we eliminate p from the population, then r receives always baseline value z, but q bores cost of being resistant to cytotoxins. This result has natural explanation since resistance appeared as an evolutionary response to cytotoxins. Apart of the stable state considered above, equilibrium between p, q and p, r may appear in the population too.

The second model in general describes paracrine production of growth factor (GF) including angiogenesis promoters. In this model the pay-off table is defined in the following way:

Table 2. Pay-off matrix

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

where phenotypes are given as:
A+ - cell produces growth factors (paracrine fashion)
A- - cell does not produce growth factors (baseline)
and parameters used to defined the measure of fitness are given by:
i – cost of proangiogenic factor production
j – benefit of receiving growth factor

To reach stable dimorphism between phenotypes, the cost of producing growth factors i should 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 opposite situation (j < i) A- is a strategy which is evolutionarily stable and dominates in the population.

By combining the phenotypes of these two models we obtain a model with four phenotypes. The biological meaning of this model is obvious. The reason why it has not been analysed previously is probably related to technical problems with analysis of the three dimensional simplexes which is a consequence of the resulting space of strategies. The model contains four different strategies/phenotypes of cells:

1. Cell produces the growth factor and the benefit impacts on all neighbors and cell itself;
2. Cell produces a cytotoxic substance against nearby cells;
3. Cell is resistant to the cytotoxic substance;
4. Strategy which shall be considered as a baseline (neither produces the cytotoxic substance, resistance to it, nor growth factor).

The frequency of cell type 1 is equal to A, that of type 2 is P, that of type 3 is Q and the last one's frequency is equal to R (in some sense it is also relevant to A-).

Table 3. Proposed pay-off matrix

Strategies	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

Although the model is an intermediate extension of the previously discussed models it allows also for more general biological interpretation. This model may be used to study interactions, between different cells' strategies among two different models. In terms of tumor cells the sum of A-type and P-type may be considered, since Q-type does not make any damage to other cells and R-type is neutral. On the other hand phenotype A could be considered as cells responsible for immune system, so then P and Q-type shall be tumor cells. In general model represents implications of interactions between diverse cells' phenotypes and feasible stable coexistence.
The expected pay-offs (the sum of the products of frequency and pay-off) are then:

$$E(1) = 1 - i + j - f \cdot P \quad (2)$$

$$E(2) = 1 - e + j \cdot A - f \cdot P + g \cdot (A + P + R) \quad (3)$$

$$E(3) = 1 - h + j \cdot A \quad (4)$$

$$E(4) = 1 + j \cdot A - f \cdot P \quad (5)$$

To achieve quadruple equilibrium following relations should be satisfied:

$$E(1) = E(2) = E(3) = E(4) \quad (6)$$

$$E(1) = E(4) \rightarrow A = (j - i)/j \quad (7)$$

$$E(3) = E(4) \rightarrow P = h/f \quad (8)$$

$$E(2) = E(3) \rightarrow Q = (g - e)/g \quad (9)$$

$$R = 1 - A - P - Q \quad (10)$$

Therefore, for a polymorphism (coexistence) of all strategies, each frequency should be contained in interval (0,1).

It has to be added that calculated formulas for frequencies could be applied only when the above-mentioned conditions are satisfied. In other cases the results could lead to equilibrium point which may be either an attractor or a repeller, to any other than quadrupled stable polymorphism, to monomorphism or even to unstable populations. To track the evolution of different phenotypes in the population it is feasible to simulate equations for replicator dynamics (Hofbauer et al., 1979). They show how frequencies of different strategies change in time, thereby influencing the composition of studied population. Some examples of the phase portraits (since A+P+R+Q=1, then the graphical representation could be shown as a simplex) are presented on the following figures together with their spatial counterparts:

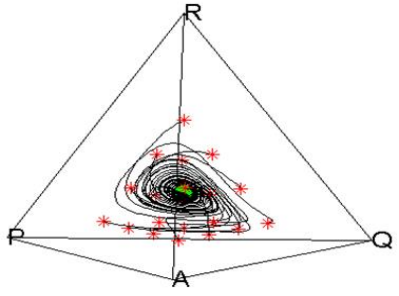

Fig. 1. Parameters: i = 0.3, j=0.4, f=0.4, g=0.4, e=0.3, h=0.1

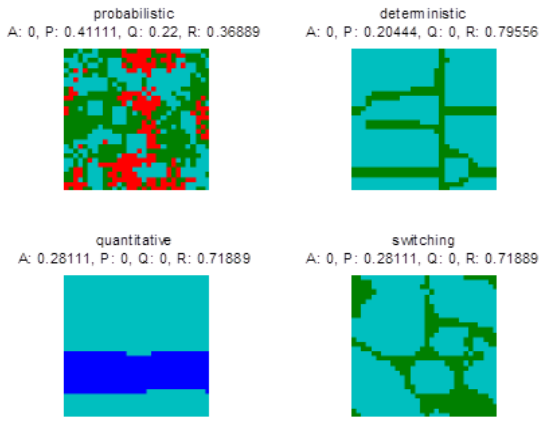

Fig. 2. Parameters: i = 0.3, j=0.4, f=0.4, g=0.4, e=0.3, h=0.1

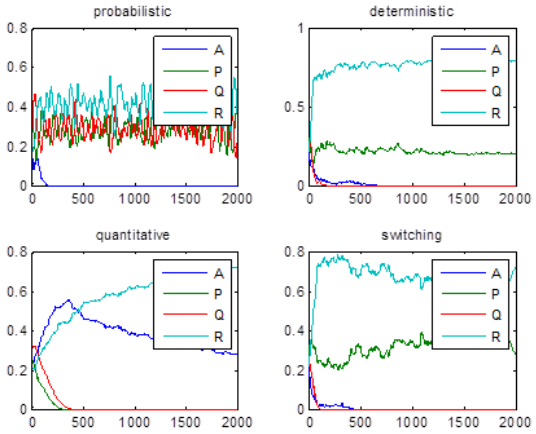

Fig. 3. Parameters: i = 0.3, j=0.4, f=0.4, g=0.4, e=0.3, h=0.1

For inference analysis in this game the result when all phenotypes coexist is taken as a reference one (Fig. 1 and Fig. 2). Relatively to this result the cost of the cytotoxic production has been increased by 0.1 and equals to the benefits of harming the neighbors. Similarly, the adaptation of P-cells has been decreased and at the same time one of the polymorphic conditions has been not fulfilled. Because of that, P-phenotype almost disappears from the population, but the same effect is observed for Q-cells. It could be explained by self-correlation between these two phenotypes – in fact the main assumption of the model is that Q-cells arise as the evolutionary reaction to the toxic substance produced by P-phenotype. It is also observable within the expected results for quadromorphic population. Fraction of phenotype P is directly proportional to the cost of resistance h and inversely proportional to the losses of interaction with toxic substances f. Namely the more the cells are wounded (including the P-cells contact with another P-cell and excluding the contact with the resistant Q-cells) by cytotoxic substance, the adjustment of the phenotype P decreases.

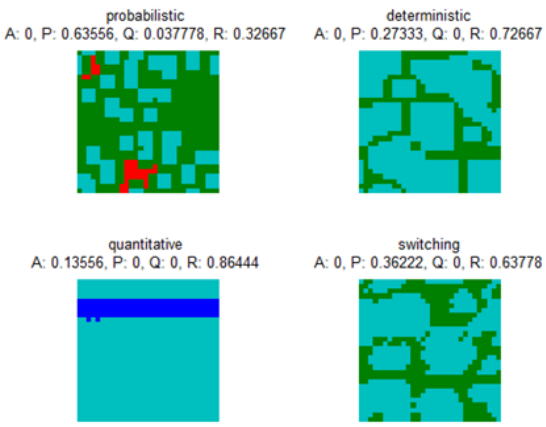

Fig. 4. Parameters: i = 0.3, j=0.4, f=0.4, g=0.4, e=0.3, h=0.2

Similarly with phenotype Q, fraction of which depends on the ratio of the parameters related strictly to phenotype P. So the greater benefits g from the harming of the neighboring cells the greater adaptation of Q phenotype. This can be explained that in contact between P with Q, the former does not receive the benefits. On the other hand when parameter g is relatively high (e.g. 0.7) then P is the dominant strategy in the population displacing all remaining phenotypes (it is the same for the spatial games, which show that when strategy has got high adaptation then independently of the type of the game it is a dominant one). Coming back to the results, when e equals g then P and Q cells are displaced from the population, and the game is played between A and R phenotypes in similar terms as in the angiogenic game. Within the reference results the neutral phenotype R is the dominative one, then P and also Q appear for the spatial game (Fig. 2). There is no obvious explanation of these results, since phenotype R is not better adjusted neither in contact with the rest of phenotypes nor itself. In the case of the second game (for increased e) phenotype R also dominates for deterministic and quantitative reproductions (the result similar as for non-spatial game). The difference has occurred in probabilistic reproduction, where Q-type has been displaced from the population. Alternatively spatial games could be presented in a way similar to mean-field models. Those outcomes are more focused on the dynamics of the model trough the passing generations than on the spatial structures. In that way Fig. 3 shows how frequencies of occurrences of each phenotypes are changing in time up to the state showed on the Fig. 2. What is more the former also confirms the observations and analysis done for the latter and indicates even more clearly the sensitivity with respect to the different reproductions.

For another analysis the cost of resistance has been increased by 0.1 compared to the reference model (Fig. 4). In this case also one of the polymorphic conditions is not satisfied and R-type is no longer in the population (however in the spatial game it is still dominant phenotype). P-cells have increased their frequency of occurrence twice, while Q and A do not change. It shows how difficult is to perform analyses of the possible results only by studying the pay-off table without

game simulation (however the number of different parameter sets could be also vast).

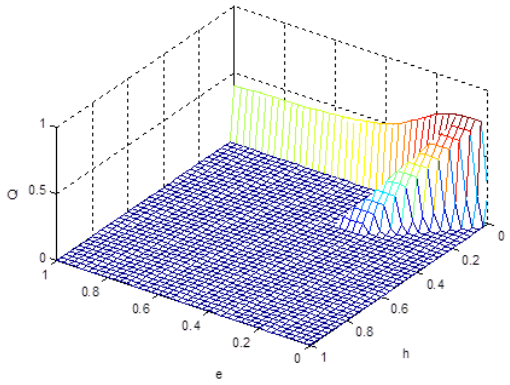

Fig. 5. Phenotypes Q and P for parameters: i=0.4, j=0.4, f=0.4, g=0.4

The analysis could be supported by generation the final frequency of occurrences for parameter changes. This kind of representation does not allow to study the dynamic of phenotype changes in time, however it is feasible to check the impact of two different parameters for one phenotype at the same time. For example on Fig. 5 (rest of the parameters as in the reference result) an interesting case has arisen for h=0 - phenotype Q decreases while parameter e increases. For P-phenotype it can be traced, that if e is greater than 0.4 then P is always 0. It could be related to the fact that value of g in that case equals to 0.4. Increasing g up to 0.7 gives also surprising results.

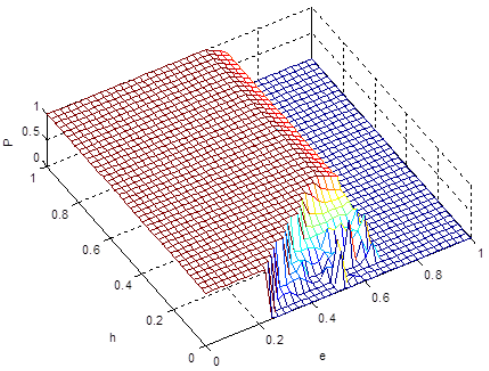

Fig. 6. Phenotype P for parameters: i=0.4, j=0.4, f=0.4, g=0.7

As it is shown on Fig. 6 the dominance of P-type remains longer than in previous cases, however for small values of h there are some irregularities. In that case the equilibrium point is a repeller even if the conditions for quadruple polymorphism are satisfied. Interesting results are also for spatial games. There are not any oscillations, however they differ significantly from the previous results. For e=0.3 and h=0.1 (still g equals 0.7) the P-phenotype dominates independently of the reproduction type. In this case increasing e and decreasing h results in re-domination of phenotype R for deterministic and probabilistic reproduction.

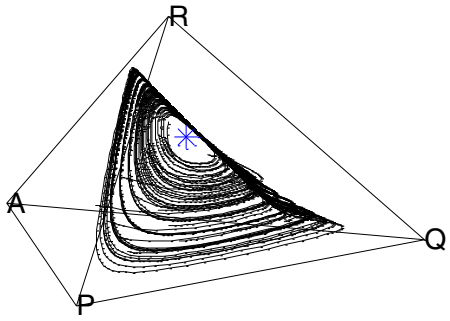

Fig. 7. Parameters: i = 0.3, j=0.4, f=0.4, g=0.7, e=0.525, h=0.025

Quantitative reproduction shows feasible coexistence between phenotypes A and Q. Interesting is that switching reproduction, which relatively to local adjustment diversity uses quantitative or deterministic reproduction, allows for almost full domination of phenotype P, even if in the remaining reproduction types P-type has been displaced from the population. For the same set of parameters it turns out, that quantitative reproduction is very sensitive to random choice of cells for actualization (Fig. 8). So, for the same initial lattice and for exactly the same game parameters the next following executions of the game give different results (one common trait is that P-cells do not exist in the final population). However at the same time switching reproduction, which for some special circumstances depends on the quantitative reproduction, gives almost the same results. The clinical confirmations of presented features are not known. However, the results of experiments performed on cell lines show that despite assurance of the theoretically identical conditions (environment), the response to stress exhibits considerable diversity.

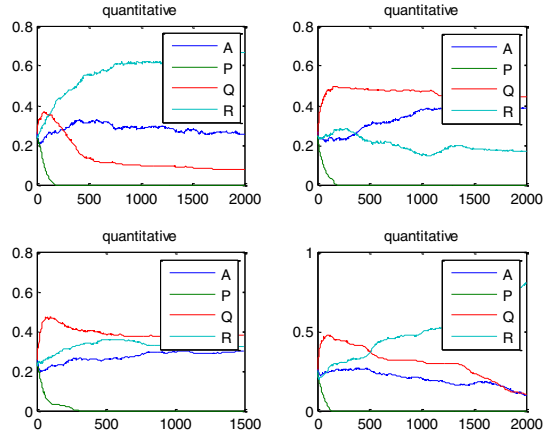

Fig. 8. Different results from quantitative reproduction for the same initial lattice.

4. CONCLUSION

The proposed model is a development of two of the first game theoretic models of carcinogenesis. The model assumes an existence of four possible phenotypes (strategies) in the population of cells that make up tumor. Despite complex analysis of this model due to numerous parameters and relations between cells, the model gives finite number of

diverse results. The one of them is a possibility of stable coexistence between different tumor cells within the population (Hanahan et al., 2000). Unfortunately the results have only qualitative meaning, but enable better understanding of cancer evolution. In similar way other models can be combined (e.g. two models from (Tomlinson et al., 1997)). However, the limitation might be graphical representation of the results. This constrain results from maximum number of strategies equal to four. What is more, any additional strategies (phenotypes), added to the model, would increase internal dependency between parameters, strategies and results. Just as an example additional phenotype M (a cell that produces a factor enabling avoidance apoptosis in autocrine fashion) from (Tomlinson et al., 1997) has been added. From comparison of expected pay-offs and vast number of simulations for different parameters it turns out that it is impossible to get stable polymorphic population with all phenotypes. As we mentioned before the limitation for graphical representation is that for the phase portrait there are points that could describe different populations (e.g. the point exactly in the middle of the portrait could mean that population for instance consists of phenotypes A, P and Q, or only phenotypes M and R, or population with all phenotypes). On the other hand spatial games seem to have no such limitations for graphical representation.

Also to increase complexity of the model additional player (not strategy/phenotype) could be added (Bach et al., 2001). Within this approach theoretically pay-off matrix has three dimensions, that raises possibility to define different values for different multi-phenotype interactions.

Our model has been evaluated by extensive simulation studies. In this paper we have presented only most representative results. In cooperation with biologists and clinicians from Centre of Oncology, M. Curie Sklodowska Institute Branch Gliwice we have planned a series of experiments on different cancer cell lines enabling estimation of parameters of the model which is a crucial point in verification of the biological meaning of the model and obtained results.

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REFERENCES

Bach, L.A., S.M. Bentzen, J.Alsdner and F.B. Christensen (2001). An evolutionary-game model of tumour-cell interactionsl possible relevance to gene therapy, *Eur. J. Cancer*, **37**, 2116-2120

Bach, L.A., D.J.T. Sumpter, J. Alsner and V.Loeschcke (2003). Spatial evolutionary games of interactions among generic cancer cell. *Journal of Theoretical Medicine*, **5**, 47-58.

Basanta, D. and A. Deutsch (2008). A game theoretical perspective on the somatic evolution of cancer. *Selected Topics in Cancer Modeling: Genesis, Evolution, Immune Competition, and Therapy* (eds. N. Bellomo, M. Chaplain and E. Angelis), 1-16.

Basanta, D., J.G, Scott, R. Rockne, K.R. Swanson and A.R.A. Anderson (2011). The role of IDH1 mutated tumour cells in secondary glioblastomas: an evolutionary game theoretical view. *Phys. Biol*, **8**, 015016.

Basanta, D., J.G. Scott, M.N. Fishman, G. Ayala, S.W. Hayward and A.R.A. Anderson (2012). Investigating prostate cancer tumour-stroma interactions: clinical and biological insights from an evolutionary game, *British J. Cancer*, **106**, 174-181.

Basanta, D., R.A. Gatenby and A.R.A Anderson (2012). Exploiting evolution to treat drug resistance: Combination therapy and the double bind. *Mol. Pharmaceutics*, **9**, 914–921.

Dingli, D., F.A.C.C. Chalub, F.C. Santos, S. Van Segbroec and, J.M. Pacheco (2009). Cancer phenotype as the outcome of an evolutionary game between normal and malignant cells. *British J. Cancer*, **8**, 1-7

Gatenby, R.A. and T.L. Vincent (2003). An evolutionary model of carcinogenesis. *Cancer Res*., **63**, 7028-7033

Gerstung, M., H. Nakhoul and N. Beerenwinkel (2011). Evolutionary Games with Affine Fitness functions: applications to cancer. *Dynamic Games and Applications*, **1**, 370-385.

Hanahan, D. and R.A. Weinberg (2000). The hallmarks of cancer. *Cell*, **100**, 57–70.

Hofbauer, J. and P.Shuster, K.Sigmund (1979). Replicator dynamics. *J. Theor. Biol*. **100**, 553-538

Krześlak, M. and A. Świerniak (2011). Spatial evolutionary games and radiation induced bystander effect. *Archives of Control Sciences*, **21**, 135-150.

Mansury, Y., M. Diggory and T. Deisboeck (2006). Evolutionary game theory in an agent-based brain tumor model: 'exploring the genotype-phenotype link'. *Journal of Theoretical Biology*, **238**, 145-156

Maynard Smith, J. (1982). Evolution and the theory of games. *Cambridge University Press*.

Świerniak, A. and M. Krześlak (2010). Game theoretic approach to mathematical modeling of radiation induced bystander effect. *Proc. 16 National Conf. on Applications of Mathematics in Biology and Medicine, Krynica*, 99-105

Świerniak, A. and M. Krześlak (2013). Application of evolutionary games to modeling carcinogenesis. *Mathematical Biosciences and Engineering*, **3**, 873-911.

Tomlinson, I.P.M. (1997). Game-theory models of interactions between tumour cells. Eur. *J. Cancer*, **33**, 1495-1500

Tomlinson, I.P.M. and W.F. Bodmer (1997). Modelling the consequences of interactions between tumour cells. *British J. Cancer*, **75**, 157-160