10.2478/v10170-010-0036-1

Archives of Control Sciences
Volume 21(LVII), 2011
No. 2, *pages 135–150*

Spatial evolutionary games and radiation induced bystander effect

MICHAŁ KRZEŚLAK and ANDRZEJ ŚWIERNIAK

We present an application of evolutionary game theory to modeling of some processes important from oncological point of view. A studied phenomenon is a radiation induced bystander effect, in which three different strategies (phenotypes) of cells take part. The proposed payoff table of fitness, related to environment adaptation and genetic cell behavior, contains costs/profits of bystander effect, choice of apoptotic pathway, producing growth factors and resistance against bystander effect. We consider a game theory model including spatial cells allocation (the game is played on lattice). We discuss also different polymorphic equilibrium points dependent on model parameters, types of spatial games and players distribution.

Key words: evolutionary games, bystander effect, biomathematical modeling, cellular automata, cancer

1. Introduction

Non-cooperative game theory has recently become a powerful tool of analysis of processes and a basis for decision making not only in economy, engineering and military but also in biological, medical and social sciences. The new perspectives in such areas as population genetics, mathematical ecology, molecular and cell biology or even treatment of diseases have been opened by so called evolutionary game theory initiated by John Maynard Smith's works (e.g. [1, 2]). They link mathematical tools of the game theory with Darwinian adaptation and species evolution. In this case players are representatives of the population, and their strategies are determined genetically (phenotypes). Payoffs in this game represent measures of fitness for the given phenotypes as a result of their interaction.

The individuals, compete or cooperate with each other to obtain better access to food supplies, life space or in the fight for females. The classical example and the fundamental evolutionary model is Hawk and Dove game. This game, studied by Maynard Smith

The Authors are with Department of Automatic Control, Silesian University of Technology, Gliwice, Poland. E-mails: krzeslak.michal@gmail.com, andrzej.swierniak@polsl.pl

The second author was partly supported by the Ministry of Science and Higher Education under grant n. NN514411936. We acknowledge biological support of Professors Joanna Rzeszowska and Maria Wideł from our department.

Received 12.04.2011. Revised 29.06.2011.

[2], is a finite nonzero sum game and assumes that the population contains two phenotypes: aggressive (non-outgoing) and compliant. Population members are fighting for a resource V which affects the reproductive success, but they can also achieve wound C (phenotype called Hawk that always takes a fight). This model has been developed into a number of generalizations including spatial effect, taking into account the time reaction or legalist strategy (phenotype can switch between strategies dependent on situation) [3].

Equilibrium in this game is defined by evolutionary stable strategy (ESS [1, 4]). It determines phenotype, which is resistant for inflow of other phenotypes (in result of mutation or environmental migration) and it cannot be repressed by them. However reverse situation is possible, evolutionary stable strategy can stay or even dominate population as an inflow mutant. The phenotypes play the role of pure strategies in standard non-cooperative games, the evolutionary strategies are frequencies of individuals in population (so called strategy profiles) representing these phenotypes and in this sense are analogues of mixed strategies. In addition ESS is always in Nash equilibrium (in mixed strategies), but reverse implication is generally not true [3]. Other differences are character and meaning of the game. In evolutionary games strategies are genetically programmed and they cannot be changed and game structure is not clear. In classical game theory based on Nash equilibrium players know game structure and rules, and the game (in its repeated form [5]) is played many times in the same conditions, while ESS results rather from the iterated game with variant players frequencies in passing generations.

Moreover the Nash strategies are the results of rational analysis while evolutionary strategies are rather due to behavior shaped through natural selection. Good illustration of this difference is the famous Haldane sentence: *I would jump into a river to save two brothers or eight cousin* [2].

More precisely the ESS has two properties:

1. It is a mixed Nash strategy.
2. It is stable.

In the standard game theory the non-zero sum two-person game in normal form is represented by two payoff matrices thus it is also called a bimatrix game. In the evolutionary games the payoffs for players are well defined by one matrix (sice the payoff matrix of the second player may be defined as a transposition of the one for the first player). Let denote this matrix by A and its entries by a_{ij}. Assume that $e_1, \ldots, e_n$ is the set of strategies and $x_i \geqslant 0$ is a frequency of the i-th strategy. Then a vector x is called a strategy (phenotype) profile (average strategy) of the population.

Moreover denote by:

$$E(e_i, x) = \sum_{j=1}^{n} a_{ij} x_j = e_i{}^T A x \tag{1}$$

an average payoff for the strategy e_i;

by:

$$E(x,x) = \sum_{j=1}^{n} x_i a_{ij} x_j = x^T A x \tag{2}$$

an average payoff for the profile x in the population with such profile;

and by:

$$E(y,x) = \sum_{j=1}^{n} y_i a_{ij} x_j = y^T A x \tag{3}$$

an average payoff of the strategy profile y in the population with the profile x.

The evolutionary stable strategy (ESS) is defined by the strategy profile p such that [4]:

1. $E(p,p) \geqslant E(x,p)$ for any strategy profile x (Nash equilibrium).
2. $E(p,p) = E(x,p) \Rightarrow E(p,x) > E(x,x)$ for any $x \neq p$ (Maynard Smith condition of stability).

Application of the evolutionary game theory to the mathematical modeling of carcinogenesis process is based on the following assertions:

- in organism, cells compete for nutrients, while different kinds of cells are players in the game,
- mutations (appearing in tumor cells) occur in cell division due to various reasons,
- advantage of tumor cells over healthy ones is a signature of cancer.

The one of the first works, where the evolutionary game theory was used to model the interaction behavior of tumor cells, was presented by Tomlinson [6]. The author proposed the model, where one of the phenotypes attempts to gain an advantage by producing the cytotoxic substances. Results show that actively harming neighboring cells may lead to dominance of the local population by the tumor cells. This study has triggered a series of other papers, where evolutionary game theory has been applied to present phenomena of tumor creation by mechanisms of avoidance of apoptosis [7], creation additional capillaries as a result of angiogenesis [7, 8], and development of capabilities of invading other tissues and metastasis [9, 10]. On the other hand, game theory models show only single phenomena occurring in a very complicated process of cancer evolution (results represent quantitave, but not qualitative description). Moreover, the papers usually do not present the system dynamics, which can be analyzed by the replicator dynamic equations [11, 12]

$$\dot{x}_i = x_i \left(E(e_i,x) - E(x,x) \right). \tag{4}$$

In our paper [13] we have extended the idea described above to study a model of radiation induced bystander effects in cell population and to predict its dynamics using replicator equations.

Replicator dynamics is one way to resolve evolutionary stable games. It represents the so called mean-field approach. Another technique which enables study of allocation of players, is called spatial evolutionary game. It combines the evolutionary game theory with machinery of cellular automata or agent based modeling. In this case very important is local players' position with specific strategies and different ways of performance. To our knowledge, one of the first applications of spatial solutions in cancer modeling has been presented by Bach et al [14] as a development of angiogenic game [7]. Spatial version of the motility/evasion game is presented in [15]. Many works demonstrate, that the spatial modeling discloses altruistic and cooperative strategies, and strong discrepancies while compared with the mean-field models (e.g. [16]).

In this paper we demonstrate how the model proposed in [13] could be analyzed using spatial evolutionary games.

2. Spatial evolutionary games

Basic distinctions between the mean-field and the spatial models are lack of perfect mixing, intercellular interactions are dependent of their local arrangement. Instead of, that it is still a simplified model of carcinogenesis, spatial models, based on cellular automata, are next step to discover 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 their origin is the use of cellular automata by such pioneers as von Neumann [17] in conjunction with the classical theory of games. In our paper we follow the line of reasoning presented by Bach et al [14], 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 [14]:

- 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 [14] present three ways of cell mortality:

- synchronous updating – all the cells die simultaneously and they are replaced dependent on the strategy of their neighbours 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. So in one generation from lattice 10% of players are deleted.

In this paper we are using mainly semi-synchronous updating, 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 cells clusters impossible.

Reproduction of removed players (killed cells) is the next step in algorithm. It is understood as the way in which empty place after the cell death is evaded by its neighbors. The authors have suggested two kinds of reproduction:

- Deterministic one – in competition for an empty place the winner is the strongest player (with highest local adaptation - sum of eight scores from cell-cell interaction).
- Probabilistic one – values of fitness (sum of values from pay-off 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 predominate in population.

Additionally we can introduce other two ways of reproduction:

- Quantitative reproduction – pay off updating is found as a sum of fitnesses of players with the same strategy.
- Switching reproduction – when differences between scores are big, quantity reproduction is better option (it is a chance for numerous, but weaker players), in the reverse situation, deterministic reproduction is our choice. In this case in simulation additional correction factor has been added (proportion between minimal and maximal fitness).

Simulations can be expanded by study of the impact of the size and the type of neighborhood. In [14] neighborhood size is defined in the von Neumann sense (4 neighbors of the cell are taken into account). Other possibilities include the so called Moore neighborhood (8 neighbors), which is used in our simulations, or extended Moore neighborhood (24 neighbors).

3. Radiation induced bystander effect

In the last few years it has appeared that cells exposed to ionizing radiation and other genotoxic agents can release signals that induce effects in non-targeted neighboring cells

very similar those observed in them, phenomena known as bystander effects. These signals are transmitted to the neighboring non-hit cells by intercellular gap-junction communication or are released outside the cell, in the case of cultured cells into the medium. Bystander effects are now understood as phenomena in which irradiated cells communicate signals which lead to damage in nearby, non-irradiated bystander cells and ultimately contribute to destabilization of their genome, processes which must be of importance for the development of secondary cancers and possibly for delayed side effects [18]. The whole story complicates since the signaling is mutual, and irradiated cells can also receive signals from non-irradiated neighbors. Bystander effect or more precisely radiation induced bystander effect has been widely reviewed in literature (e.g. [18, 19, 20]). Most experiments show a decrease in survival of unirradiated bystander cells, but some studies of the influence of unirradiated or lowdose-irradiated cells on those irradiated with higher doses show that intercellular bystander signaling can also increase the survival of irradiated cell populations. The bystander effect induced by factors and signals issued by directly irradiated cells leads to reduction in survival of adjacent cells, i.e. cells that have not been exposed to radiation. Of the different types of damage, DNA breaks have been studied most systematically in both directly-irradiated and bystander cells. Double strand breaks induced by ionizing radiation are considered as the most dangerous lesion for cell survival and induction of genomic instability. Single strand breaks, which appear not only as a direct result of radiation but also as intermediates in base and nucleotide excision repair of DNA or during normal replication, are much more frequent and if not rejoined they can be converted into double strand breaks, postulated to be one of the mechanisms responsible for cell killing after irradiation.

The effect has been well documented in a variety of biological systems exposed to low doses of alpha, gamma and *X* radiation. Nevertheless, the mechanisms responsible for bystander effect are complicated and still unclear though there are evidences that in intercellular signalling reactive oxygen species, nitric oxide, cytokines such as interleukin 8 or TGF-β are used, and the important role is played by gap junction communication and presence of soluble mediators. Factors issued by irradiated cells may constitute a risky element of genomic instability induction, i.e. lead to mutation and the second neoplasia. Therefore, for this reason and for the capability of influence both for tumor and healthy cells, the bystander effect implies positive and negative consequences of radiation at comparable doses.

In the radiation induced bystander effect, from modeling point of view couple of intrinsic properties are observable. One of them is genomic instability, i.e. delayed effect of changing and death in distant generations. Another one is possibility of radio resistance acquired at low doses. Observable is also bidirectional way of phenomena working. First, irradiated cells harm surrounding cells. Second, it is possible to increase a count of surrounding no radiated cells. Third, visible and possible are growth of cells that have received a high dose of radiation through signalling from cells irradiated by low-doses. The next interesting phenomenon, on the intercellular interaction, is the fact that in the in vivo case one can observe cell interactions by paracrine signalling. Neoplastic transformation increases linearly with the radiation dose in cultured cells and animals, but

the dose-response relationship varies with strain, gender, and tissue/organ in the case of mice, while in cancer patients cured with radiotherapy the risk of secondary stomach and pancreatic cancer, but not that of secondary bladder, rectal, or kidney cancer is related to the radiation dose received. All these effects result from cellular responses to irradiation, and are therefore closely related to the bystander effects discussed above.

Mechanisms responsible for the bystander effect are therefore quite complicated and not definitely known. Game theoretical model, presented in the next chapter, is based on very simple assumptions of the process. Nevertheless, they allow for observations of complicated and various responses and results of intercellular signalling and communication.

4. Game theoretic model of bystander effect

A game theoretic model which we have proposed [13] may be viewed as a follower of the angiogenic model [8]. The model presented in this paper has been slightly modified. We consider three different strategies/phenotypes of cells:

- escape to apoptosis – in the strategy profile its frequency will be denoted by X (and in simulations by blue color),
- production of growth and mutation factors – the frequency in the strategy profile denoted by Y (in simulations: green color),
- neutrality – the frequency of appearance in the strategy profile denoted by Z (in simulation: red color).

Table 1. Payoff matrix

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

The payoff matrix represents fitness measures which are defined by the following parameters of the model:

k – represents a cost of apoptosis/profit from bystander effect,
j – is a measure of profit of cell contact with growth factors,
i – represents a cost of producing the growth factors,
p – represents cost/advantage from resistance to bystander effect.

Both k and p may be either positive or negative.

For the strategy protocol

$$x = [X\ Y\ Z]^T \tag{5}$$

we have the following average payoffs:

$$\begin{aligned} E(e_1,x) &= 1-k+jY, \\ E(e_2,x) &= 1+j-i-pX, \\ E(e_3,x) &= 1-pX+jY. \end{aligned} \tag{6}$$

The conditions of polymorphism i.e. the scenario in which all three phenotypes coexist in equilibrium are given by the Bishop-Cannings' theorem [21] which, roughly speaking, extorts equality of average fitness for all phenotypes. For the payoff matrix defined by table 1 it leads to the following constraints imposed on the model parameters:

$$\begin{aligned} &0<X<1, \quad 0<k/p<1, \\ &0<Y<1, \quad 0<(j-i)/j<1, \quad i<j, \\ &0<Z<1, \quad 0<1-k/p-(j-i)/j<1, \quad 0<(j-i)/j+k/p<1. \end{aligned} \tag{7}$$

Replicator dynamics is defined by the following equations:

$$\begin{aligned} \dot{X} &= X\left(E\left(e_1,x\right)-E\left(x,x\right)\right), \\ \dot{Y} &= Y\left(E\left(e_2,x\right)-E\left(x,x\right)\right), \\ \dot{Z} &= Z\left(E\left(e_3,x\right)-E\left(x,x\right)\right). \end{aligned} \tag{8}$$

Taking into account that:

$$Z = 1-X-Y \tag{9}$$

we have a system of two nonlinear differential equation defined on the simplex in the plane. For example the first equation has the form:

$$\begin{aligned} \dot{X} = &-(1-k)X^3-((2+2j-i-k-p)Y+(2-k-p)Z-(1-k))X^2 \\ &-((1-i+j)Y^2+Z^2+(2+2j-i)YZ-(1-k+j)Y-(1-k)Z)X. \end{aligned} \tag{10}$$

Numerical solutions of the replicator dynamics equations show, that population can achieve whole range of behaviors dependent on parameters [13]. We have found evolutionary stable states in the form of trimorphism, dimorphism or even monomorphism depending on initial frequencies. What is even more interesting, the equilibrium point, if it exists, may be either an attractor or a repellor. In this paper we use the replicator dynamics equations only to compare the time behavior of mean field results with the results of the space evolutionary games.

5. Results and analysis of simulations

In spatial games, because of the diversity in game parametrization, we present only few selected parameters of models and types of mortality, reproduction and payoff updating. Those cases include semi-synchronic actualization with 10% of mortality, correction factor (switching reproduction) giving results closer to quantity reproduction, lattice 30×30, 10000 generations and eight neighbors. Furthermore, each result will be confronted with simple mean-field solution (replicator dynamics) for the same initial frequencies and payoff matrix (analysis of the mean-field results may be found in [13]). Figure 1 presents initial location of players on the lattice and results of mean-field game, which leads to stable polymorphism in population.

Similar results have been obtained in probabilistic and switching reproduction, wherein for the last one some stable and regular structures can be noted (see Fig. 2). From biological side probabilistic reproduction gives most expectable results (decreasing count of X and Y cells), on the other hand the worst case (death of the host) are represented by deterministic reproduction.

The related mean-field game assumes population dimorphism (Fig. 3) between Y and Z (no results of radiation therapy). In this case most interesting results are given by probabilistic and switching reproductions (Fig. 4). The probabilistic reproduction shows predomination of X cells, wherein for mean-field game X cells are repressed. Switching reproduction gives the most expected results from the host viewpoint, i.e. dramatic decrease of mutating cells.

Figures 5 and 6 show that for the same parameters, but for different initial frequencies similar results to figure 4 are obtained. This indicates that initial frequencies and location of cells were not so different from the previous example or that dominating factor is related to the payoff matrix.

Diversity and complexity of spatial games may lead to qualitatively comparable results with mean-field games (Fig. 2, 7 and 8) or completely different results (Fig. 3, 4, 5 and 6). An example shown in Fig. 8 represents the situation where mutating cells completely disappear. We can expect also that the minimal number of irradiated cells is left in the body or that Z cells are predominating. In the last case even switching reproduction gave different results compared with other simulations.

6. Remarks

We have proposed an evolutionary game theoretic model of radiation induced bystander effect in tumor cell populations. Results from spatial modeling show that they may be different than mean-field results based on replicator dynamics. Developing spatial model arises enormous range of parameterization possibilities how to play the game (way of reproduction, deleting players, type of neighborhood, restriction of lattice, players location). Therefore, results of replicator equations are less dependent on initial frequency and are independent of a chosen way of the allocation.

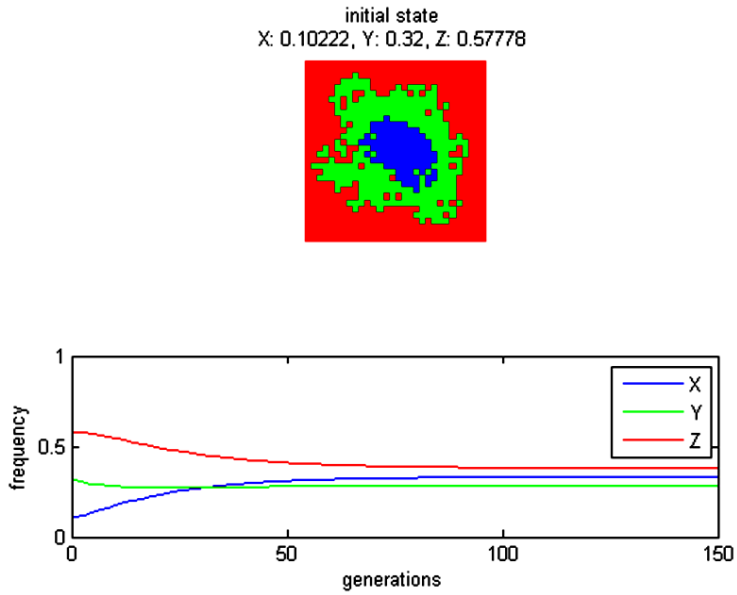

Figure 1. Initial distribution and replicator dynamics for parameters $i = 0.5$, $j = 0.7$, $k = 0.1$, $p = 0.3$.

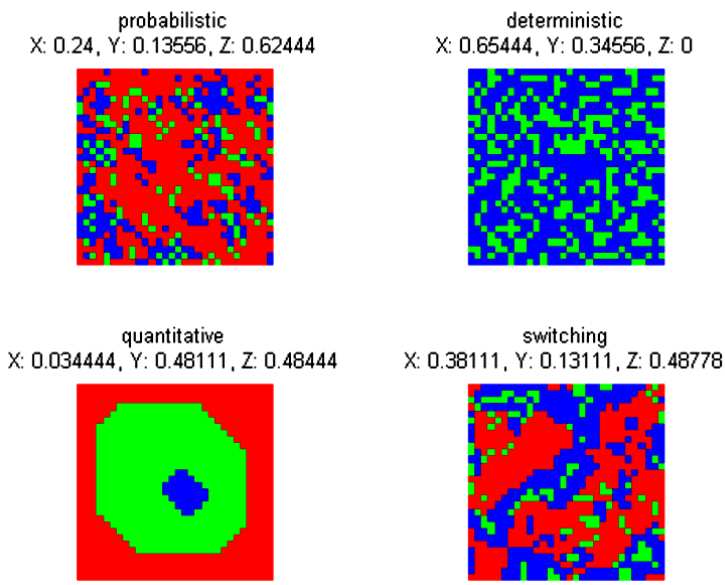

Figure 2. Results of simulations of spatial evolutionary game model for parameters $i = 0.5$, $j = 0.7$, $k = 0.1$, $p = 0.3$, and different forms of reproduction.

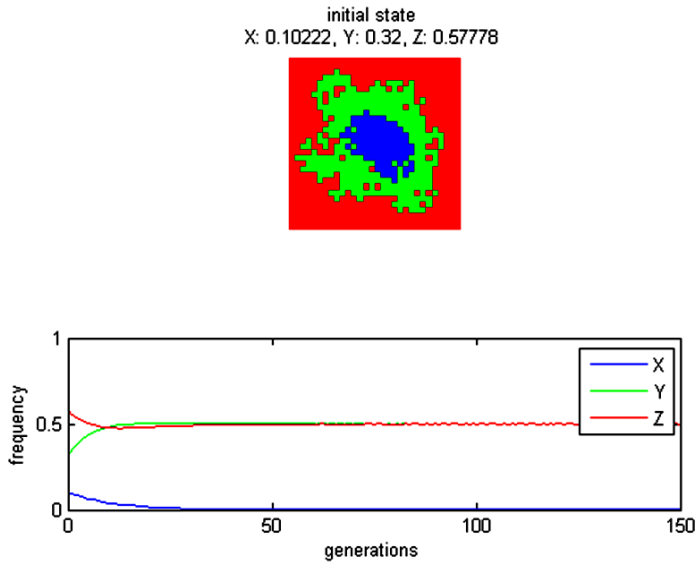

Figure 3. Initial distribution and replicator dynamics for parameters $i = 0.4$, $j = 0.8$, $k = 0.1$, $p = -0.4$.

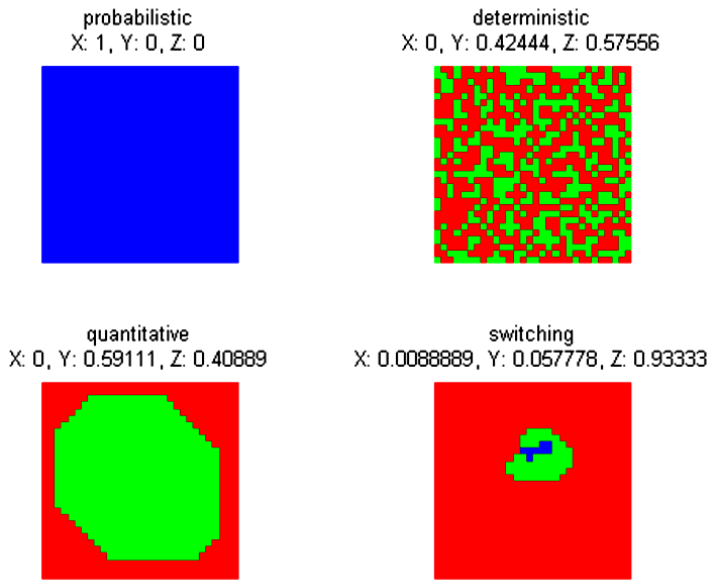

Figure 4. Results of simulations of spatial evolutionary game model for parameters $i = 0.4$, $j = 0.8$, $k = 0.1$, $p = -0.4$, and different forms of reproduction.

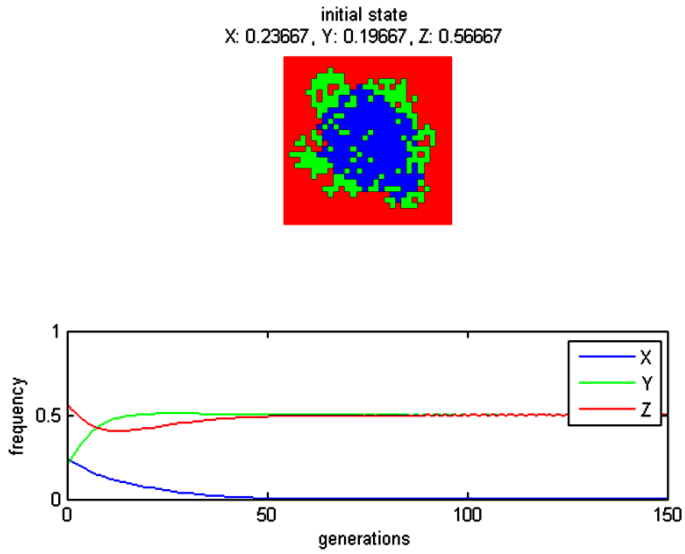

Figure 5. Initial distribution and replicator dynamics for parameters $i = 0.4$, $j = 0.8$, $k = -0.1$, $p = -0.4$.

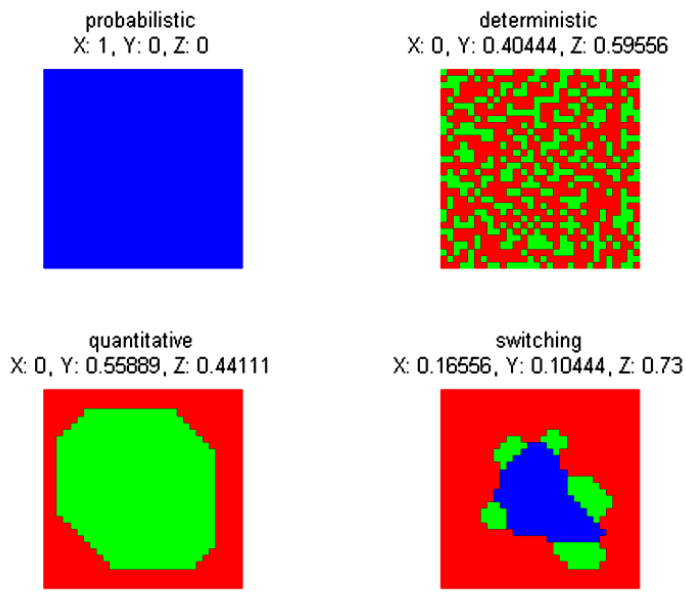

Figure 6. Results of simulations of spatial evolutionary game model for parameters $i = 0.4$, $j = 0.8$, $k = -0.1$, $p = -0.4$, and different forms of reproduction.

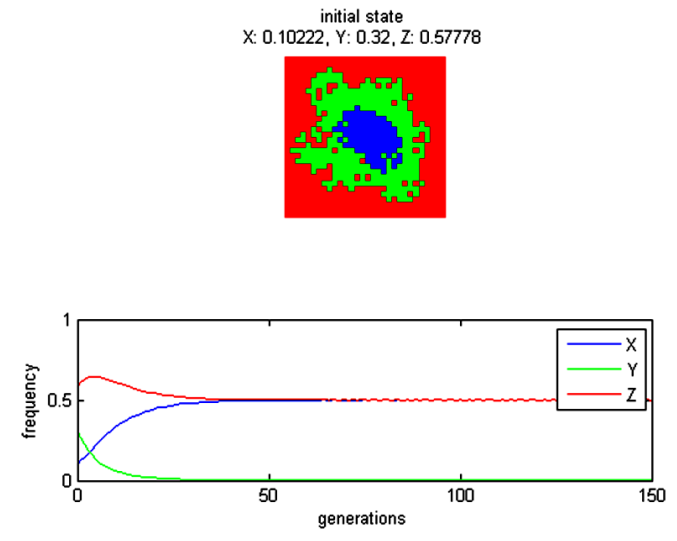

Figure 7. Initial distribution and replicator dynamics for parameters $i = 0.6$, $j = 0.5$, $k = 0.2$, $p = 0.4$.

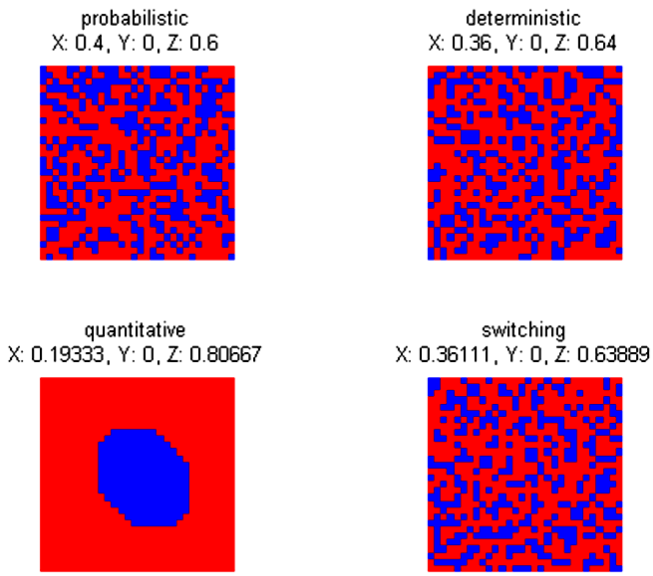

Figure 8. Results of simulations of spatial evolutionary game model for parameters $i = 0.6$, $j = 0.5$, $k = 0.2$, $p = 0.4$, and different forms of reproduction.

Spatial games show that cooperation and forming common cells clusters are possible. Moreover, this kind of models may better describe some phenomena, however they are not completely deterministic models. In reproduction stage and during ties some random effects are shown. The case of single player surrounded by other players with different strategies is a very good example. According to the payoff matrix evolutionary stable strategy is a strategy of single player. If so, with some amount of luck and mortality of surrounding players it has a chance to dominate the population.

Game theoretic models are able to assist in our understanding of radiation induced bystander effect mechanisms, the more that some results of the simulation may well represent biological phenomena. Nevertheless, it is reasonable to remember that, till now, those results are strictly qualitative, not quantitative. Still, spatial evolutionary models are the next stage in improvement modeling of carcinogenesis phenomena. The possible generalization of games is by introduction of the payoff matrix with time dependent variables, or functions of dose concentration (very important in the case of radiation induced bystander effect modeling). In the spatial evolutionary games it is also much easier than in mean-field games to introduce new phenotypes and increase the dimension of the space of strategies.

High sensitivity of the presented models to parameters leads to a fundamental question of their identifiability or at least practical procedure leading to their estimation. At present it is not clear how experimentally one can find or estimate the measures of fitness for different phenotypes and how to adjust parameters of simulation procedures for considered models. We hope to be able to elaborate such recommendations in collaboration with biologists.

References

[1] J. MAYNARD SMITH and G.R. PRICE: The logic of animal conflict. *Nature*, **246** (1973), 15-18.

[2] J. MAYNARD SMITH: Evolution and the theory of games. Cambridge University Press, 1982.

[3] M. MESTERTON-GIBBONS: An introduction to game theoretic modeling. AMS (second edition), 2001.

[4] J. HAIGH: Game theory and evolution. *Advances in applied probability*, **7** (1975), 9-12.

[5] R.J. AUMANN and M.B. MASCHLER: Repeated games with incomplete information. MIT Press, Cambridge, 1995.

[6] I.P.M. TOMLINSON: Game-theory models of interactions between tumor cells. *European J. of Cancer*, **33** (1997), 1495-1500.

[7] I.P.M. TOMLINSON and W.F. BODMER: Modeling the consequences of interactions between tumor cells. *British J. of Cancer*, **75** (1997), 157-160.

[8] L.A. BACH, S.M. BENTZEN. J. ALSDNER and F.B. CHRISTENSEN: An evolutionary-game model of tumor cell interactions: possible relevance to gene therapy. *European J. of Cancer*, **37** (2001), 2116-2120.

[9] D. BASANTA, M. SIMON, H. HATZIKIROU and A. DEUTSCH: Evolutionary game theory elucidates the role of glycolysis in glioma. *Cell Proliferation*, **41** (2008), 980-987.

[10] Y. MANSURY, M. DIGGORY and T.S. DEISBOECK: Evolutionary game theory in an agent-based brain tumor model: exploring the 'genotype-phenotype' link. *J. of Theoretical Biology*, **238** (2006), 146-156.

[11] P.D. TAYLOR and L.B. JONKER: Evolutionarily stable strategies and game dynamics. *Mathematical Biosciences*, **40** (1978), 145-156.

[12] J. HOFBAUER and K. SIGMUND: Evolutionary game dynamics. *Bulletin (New Series) of the American Mathematical Society*, **40**(4), (2003), 479-519.

[13] A. ŚWIERNIAK and M. KRZEŚLAK: Game theoretic approach to mathematical modeling of radiation induced bystander effect. *Proc. of the 16 Nat. Conf. on Applications of Mathematics in Biology and Medicine*, (2010), 99-104.

[14] L.A. BACH, D.J.T. SUMPTER, J. ALSNER and V. LOESCHCKE: Spatial evolutionary games of interaction among generic cancer cells. *J. of Theoretical Medicine*, (2003), 1-12.

[15] D. BASANTA, H. HATZIKIROU and A. DEUTSCH: Studying the emergence of invasiveness in tumors using game theory. *Physical J. B*, **63** (2008), 393-397.

[16] M.A. NOWAK and R.M. MAY: Evolutionary games and spatial chaos. *Nature*, **359** (1992), 826-829.

[17] J. VON NEUMANN: Theory of self reproducing automata. University of Illinois Press, 1966.

[18] J. RZESZOWSKA-WOLNY, W.M. PRZYBYSZEWSKI and M. WIDEL: Ionizing radiation-induced bystander effects, potential targets for modulation of radiotherapy. *European J. of Pharmacology*, **625** (2009), 98-107.

[19] C. MOTHERSILL and C. SEYMOUR: Radiation-induced bystander effects: past history and future directions. *Radiation Research*, **155** (2001), 759-767.

[20] R. IYER and B.E. LEHNERT: Low dose, low-LET ionizing radiation-induced radioadaptation and associated early responses in unirradiated cells. *Mutation Research*, 503 (2002), 1-9.

[21] D.T. BISHOP and C. CANNINGS: Models of animal conflict. *Advances in Applied Probability*, **8** (1976), 616-621.