GAME THEORETIC APPROACH TO MATHEMATICAL MODELING OF RADIATION INDUCED BYSTANDER EFFECT

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ABSTRACT
We present a model of radiation induced bystander effect based on the theory of evolutionary games. The model follows the line of reasoning used to describe the so called angiogenic games. We consider three strategies (phenotypes) of cells being exposed to ionizing radiation or more precisely to signals sent by the exposed cells to the unexposed ones. The proposed payoff table of fitness includes costs/profits of bystander effect, choice of apoptotic pathway, producing of growth factors, producing resistance against bystander effect. We discuss the type of equilibrium points (polymorphism of phenotypes) and dynamics leading to equilibrium (replicator dynamics). We present also examples of simulation experiments for various parameters.

KEY WORDS
Biomedical Modeling, Bystander Effect, Evolutionary Games, Cancer Growth

1. Introduction

Non-cooperative game theory starting from its very beginning has been a very practical branch of operation research. Its applications in economics and econometrics, behavioral and social science, engineering and military have created challenges for new formulations and their solutions.

Recently it is observed an increasing interest in game theoretic tools applied in biological and medical sciences especially in genetics and molecular biology, ecology and environmental biology, etiology of diseases and modeling of cell regulatory processes. Evolutionary game theory initiated by John Maynard Smith [1] differs from the standard game theory in its approach to understanding of the mechanism behind the process of strategy formulation. Simply a strategy is not understood as a deliberate course of action but rather as a phenotypic trait and the payoff is an average reproductive success.

Moreover the players are members of a population that compete or cooperate to obtain a larger share of the population. The classical process studied by Maynard Smith named the Hawk-Dove game assumes that the population contains two phenotypes representing two different strategies to access a resource $V$ which affects the reproductive success of the individuals in the population. The first phenotype known as Hawk always escalates the fight until injured (at a cost in fitness equal to $C$) or until the rival retreats while the second one called Dove will retreat if the opponent seems determined to fight. To define a rational equilibrium in this game the concept of an evolutionary stable strategy (ESS) has been introduced in [1]. It is defined as a phenotype that, if adopted by the vast majority of a population, will not be displaced by any other phenotype. One can find relation between ESS and mixed Nash strategies. Simply the ESS defines a point which has a Nash equilibrium property and a stability property. Thus any ESS is a mixed Nash strategy but opposite implication is not true. On the other hand there is a significant difference between ESS and mixed Nash strategy. In the former strategies are genetically encoded, cannot change, and the structure of the game is unclear while in the latter players know the structure of the game and potential strategies of opponents and the game is played many times in the same conditions. In the Hawk-Dove game a Hawk phenotype may be evolutionary stable if the fitness benefit of getting resource is greater than the cost of injuries. In the opposite case the equilibrium between Hawks and Doves defining an ESS depends on the ratio between $V$ and $C$.

Generally if by $E$ we denote an expected payoff in the game, $S$ an evolutionary stable strategy (ESS) and $T$ any alternative strategy then either of the following conditions hold:
E(S,S) > E(T,S) \quad (1)

or

E(S,S) = E(T,S) and E(S,T)\geq E(T,T) \quad (2)

In other words T is neutral strategy against S but S always maintains an advantage over T.

Application of the evolutionary game theory to the mathematical modeling of cancer development is based on the following assertions:

- In organisms cells compete for various resources, tumor and normal cells are players in the game
- Mutations occasionally occur in cell division due to various reasons
- Cancer is a disease where mutated cells oust normal cells in local population

To our knowledge Tomlison [2] first proposed a game theoretic model of interacting tumor cells defining strategies based only on the production rates of cytotoxic metabolites that tumor cells produce. This study has been performed to prove the hypothesis that, as a result of mutations, some tumor cells attempt to gain an advantage by actively harming neighboring cells. This study has been followed by an increasing number of papers in which the evolutionary game theory has been used to study possible circumstances leading to transformation of healthy tissue cells into malignant cancer such as evasion of apoptosis, carcinogenesis, angiogenesis and invasion. The proposed models enable understanding of evolution of the mechanisms to avoid apoptosis [3], scenarios of the angiogenic strategies and games [3], [4], and development of capabilities of invading other tissues and metastasis [5], [6]. Some of these models may lead to new recommendations for anticancer therapies. Although these models do not study the dynamics which may or may not lead to an equilibrium we may use the concept of replicator dynamics [7] to overcome this limitation.

The equation for replicator dynamics may be presented in the following form:

\[ dX_i / dt = X_i (E(e_i) - E \overline{G}) \quad (3) \]

where \( X \) is a vector of strategies with components \( X_i \), \( E(e_i) = E(e_i, X) \) is an expected payoff with one player using pure strategy \( e_i \), and \( E \overline{G} = E(X, X) \).

In our paper we extend the idea described above to study a model of radiation induced bystander effect which has recently attained great interest both from biological and clinical point of view. This effect which we shortly describe in the next section is strongly related with the carcinogenesis process but may be also used to improve some radiotherapy protocols.

**2. Radiation induced bystander effect**

Bystander effects or more precisely radiation based bystander effects have been widely reviewed in literature (e.g. [8], [9]). They are defined as "inductions of biological effects in cells that are not directly traversed by a charged particle but are in close proximity to cells that are". The effects have been well documented in a variety of biological systems exposed to low doses of alpha, gamma and X radiation. Nevertheless the mechanisms behind these phenomena are still unclear. The precise signaling molecules have not been completely identified though there is evidence that reactive oxygen species, nitric oxide, cytokines such as interleukin 8 or TGFβ are involved in the process, and the important role is played by gap junction communication and presence of soluble mediators.

In the classical target theory only cells directly exposed to radiation are believed to be in danger of DNA damage. The discovery of the radiation induced bystander effect has changed this point of view. Allowing cell-cell and cell-matrix communication means that cells not directly exposed to radiation but receiving damage signals from irradiated cells can suffer DNA damage as well.

The radiation induced bystander effect may have both beneficial and harmful effects of radiation at comparable doses. The former are mainly related to increase of apoptotic inductions in cancer cells which have not been directly treated by radiation therapy. The latter include induction of second cancers, perturbations in tissue control, immediate and delayed mutations in non-exposed cells, induction of genomic instability. Genomic instability induced by bystander effect has been observed both in \textit{in vivo} and \textit{in vitro} cells, occurs at very high frequency and is non-clonal. Although the bystander effect has been induced in the population of cells exposed to very low doses it is shown to be in high range independent of dose. It seems that it appears as the response to a signal that radiation is in the system. On the other hand experimental results in which bystander effect and genome instability have introduced significant nonlinearities in dose dependent behaviors are reported. Some of the authors suggest that there exists an increase of the bystander effect with the dose in the area of low doses which saturates at some level.

The mechanism of the bystander effect mediated mainly by soluble factors seems to be very complex and
involves multiple pathways. Probably there exist multiple signaling cascades involving both initiating event and sequential steps mediating the process. Although a couple of genes have been identified engaged in the signaling pathways their biological significance are far from being recognized. A game theoretic model which will be proposed in the next section does not attempt to be a systematic approach to description and understanding of the phenomena behind and resulting from the bystander effect. It demonstrates only the possibility of quite simple reasoning based on the simplified assumptions dealing with the process which enable observation of quite complex and differentiated responses of different cells to radiation or more precisely signaling resulting from it.

3. The model of the bystander game

A model which we propose is in many points similar to the model of angiogenic game discussed by Tomlinson and Bodmer [3]. In this paper we focus our attention on the possible fate of cancer cell population under bystander signaling. The similar model could be constructed for normal cells. We consider three different strategies/phenotypes of cells:

1. Choice of the apoptosis pathway leading to controlled suicide by a fraction of the population.
2. Production of growth and mutation factors leading to high proliferation and evasion/migracy behavior

The proposed payoff table for the game of the bystander is presented beneath.

<table>
<thead>
<tr>
<th>Strategies</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>1+k</td>
<td>1-j-i+p</td>
<td>1+p</td>
</tr>
<tr>
<td>Y</td>
<td>1-j+k</td>
<td>1-j</td>
<td>1+j</td>
</tr>
<tr>
<td>Z</td>
<td>1+j+k</td>
<td>1-j</td>
<td>1</td>
</tr>
</tbody>
</table>

The frequency of cells type 1 is equal to X, that of type 2 is Y and that of type 3 is Z.

The model may be used to study the possibility of stable coexistence of different phenotypes (polymorphism) possible in the population in which only three such phenotypes are considered.

In the table:
p – represents a difference between the profit of resistance against the bystander effect and the cost of producing the resistance.

Both k and p may be either positive or negative. In the table we have introduced the following values of parameters: k=0.1, i=0.4, j=0.8, p=0.4 which have been chosen for one of the simulation experiments in which one stable equilibrium point has been found. The expected pay-offs are then:

\[
E(1) = 1 + k + jY \\
E(2) = 1 + j - i + pX \\
E(3) = 1 + pX + jY
\]

At any triple polymorphism:

\[
E(1) = E(3), \quad \text{i.e. } X = k/p \\
E(2) = E(3), \quad \text{i.e. } Y = (j-i)/j \\
Z = 1 - X - Y
\]

For stable triple polymorphism in the population each frequency should be contained in interval (0,1). It means that the following relations should be satisfied:

\[
0 < X < 1 \\
0 < k/p < 1 \quad \text{(6)}
\]

i.e. for positive p,

\[
0 < k < p \quad \text{(7)}
\]

for negative p,

Similarly:

\[
0 < Y < 1 \\
0 < (j-i)/j < 1 \quad \text{(9)}
\]

i.e.

\[
i < j \quad \text{(10)}
\]

and

\[
0 < Z < 1 \\
0 < 1 - k/p - (j-i)/j < 1 \quad \text{(11)}
\]

i.e.
\[ 0 < (j-i)/j + k/p < 1 \]  

\[ (12) \]

The triple polymorphism is not a general rule, sometimes it may be not feasible. Moreover even if it exists it may be unstable, in other words the equilibrium point, if it exists, may be either an attractor or a repiler. To track the evolution of different genotypes (strategies) in the population we may simulate equations for replicator dynamics. They explain how the fitness of each phenotype changes in time to attain an equilibrium or in other words how the different types of cells can adopt genetically-determined survival strategies being exposed to radiation or to bystander effect induced by radiation.

Such equations are given by:

\[
\begin{align*}
\frac{dX}{dt} &= X(E(1) - E(G)) \\
\frac{dY}{dt} &= Y(E(2) - E(G)) \\
\frac{dZ}{dt} &= Z(E(3) - E(G))
\end{align*}
\]

where \( E(G) \) is an expected payoff in the game under evolutionary stable strategies.

For example for the first strategy we obtain:

\[
\begin{align*}
\frac{dX}{dt} &= -(1+k)X^3 - ((2-i+2j+k+p)Y + (2+k+p)Z - (1+k))X^2 + \\
&- ((1-i+j)Y^2 + (2-i+j)YZ - (1+j+k)Y - (1+k)Z)X
\end{align*}
\]

\[ (13) \]

The equations for \( Y \) and \( Z \) are similar and the system is quite difficult for analysis. Nevertheless the simulation experiments are not too complex and give quite a reasonable estimation of qualitative behavior of the population dynamics depending on the parameters.

We have observed that depending on parameters triple polymorphism may be stable or unstable. In the former case the genotype strategies do not oscillate before reaching equilibrium. In the latter case depending on the initial frequencies of genotypes it is possible to reach monomorphism or dimorphism. It means that one or two (from three) genotypes are eliminated from the population.

Some examples of the phase portraits are presented on the figures 1–5:

Figure 1. Parameters: \( i=0.5, j=0.7, k=0.1, p=0.3 \)

Figure 2. Parameters: \( i=0.4, j=0.8, k=-0.1, p=-0.4 \)

In the first example we have a stable triple polymorphism, in the second case it is unstable but there are two locally stable dimorphism points. In the latter case the parameters \( k \) and \( p \) become negative that means that negative effects of irradiation are greater than profits from bystander signaling.
The important finding is the observed variability of possible behaviors of phenotypes in the cell population disturbed by the bystander effect. It is caused not only by changes of parameters describing the fitness of phenotypes but also by different initial distribution of these phenotypes in the population.

Nevertheless dimorphism between $X$ and $Z$ is possible also for positive values of these parameters (see fig.3). In this case change of signs of $p$ and $k$ implies two possible monomorphic equilibriums (fig.4). different scenarios depending on the initial

Yet another combination of parameters results to two distribution of phenotypes in the investigated population (fig.5).

4. Conclusions

We have proposed a game theoretic model of radiation induced bystander effect. The model assumes an existence of three possible phenotypes (strategies) in the population of cells being exposed to radiation or unexposed but disturbed by the bystander effect. This model has only qualitative meaning but enables observation of different behaviors depending on the assumed parameters. Moreover using replicator dynamics equations the fate of different phenotypes and evolution of strategies leading to genetic survival may be studied. Although the results of simulations confirm high sensitivity of both asymptotic and transient behaviors on parameter changes we are far from suggestion that it is a property of the process rather than the model. Nevertheless during biological experiments a great variability of responses has been observed and we believe that the model will help to understand more mechanisms behind radiation induced bystander effects, the more that some of the simulation results could be transformed into biological phenomena. Space effects may be incorporated in the model by adopting a spatial game approach i.e. by considering competition of the neighboring cells on a lattice in discrete time (similarly as in [5]). In this case different scenarios could be proposed. First of all actualization of the state of the lattice describing the way in which the cells are eliminated could be done in synchronic, asynchronous or semi-synchronic form. On the other hand reproduction resulting from the fitness may be deterministic, probabilistic, quantitative or switched. Simulation experiments performed by us lead to different
behaviors than in the non-spatial case. It is however too early to discuss which approach is more reasonable. Yet another problem which could be easily adopted in the proposed approach is related to the observed dependence of the bystander effects on the dose of irradiation. One of possibilities is to connect the values of fitness parameters, especially $k$ and $p$ with the dose of irradiation. The results of simulations for different values of parameters may be than translated onto changes in phenotypes which in turn allows to built hypothesis on the relation between the dose and the bystander effect.

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References


