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Modeling evolutionary effects of anticancer therapies by spatial games with resources

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***Abstract*—We propose an extension of spatial evolutionary games which enables simulation of evolutionary changes in cancer cells population resulting from anticancer therapies treated as external interventions. There are two non-standard issues used in this type of games. The first one is based on the assumption that heterogeneity of tumor populations takes place on the cell level which is realized by the use of multilayer spatial structures. The other one is related to variability of entries of pay-off tables representing changes in external resources which describe anticancer treatment.**

Keywords-evolutionary games, anticancer therapies, heterogeneity.

EXTENDED ABSTRACT

Recent works have focused on the evolutionary dynamics of tumors and point out that factors important at the evolutionary level, like survival and proliferation, are the pivotal points in cancer development as a heterogeneous population with different cells[1]. Moreover, an additional key-factor (for game theory applications) is the impact of the ecosystem or the interactions between tumor cells and their environment enabling modeling changes in the cancer ecosystem in the context of different anti-cancer therapeutic strategies [2]. From the game theory point of view, during simulation changes appear in the frequency of occurrence of parameters or phenotypes, like those in simulations of resources for the mean-field model. Further development of spatial games (as we present here) may provide additional possibilities of simulating therapies (treatments) by affecting different players (as elements on the spatial lattice) at a different level or even in a different way. In particular, elimination of as many cancer cells as possible may not be essentially the best strategy. It may be demonstrated that destroying only some fraction of the cancer cells (with a particular phenotype) may be far more efficient. Thus, using spatial games with additional simulations that impact the game (either by a payoff matrix or spatial structures on the lattice) provides a possibility to study that conclusion using a vast amount of different configurations (especially for various initial lattices and simulated environments). Moreover, we also emphasize strongly that evolutionary games are mainly used to study changes in a tumor's phenotypic heterogeneity and its impact on the evolutionary dynamics of cancer (possibility of different interactions, e.g. cooperation). However, the importance of heterogeneity is at the population level, meaning that the population contains different homogenous cells, which is obviously an important limitation arising (coming) from replication dynamics usage. The application of mixed spatial evolutionary games (MSEG) [3] additionally allows for modeling heterogeneity on the cell level within the population, which may be more appropriate for the biological reality. We propose to endow evolutionary game models with changes of the phenotypes' adjustment during the transient generations performed by the parameters in the payoff matrix which determine the fitness resulting from different interactions between players. These changes represent alteration of access to external resources which, in turn, may describe anticancer treatment. In the case of spatial games, these functions are represented by an additional lattice where another and parallel game based on cellular automata is performed. The additional lattice representing the evolution of resources increases only the dimension of the lattice in the MSEG [4]. Moreover we consider both 2D and 3D spatial structures that, in our opinion, is an exception rather than a rule in literature devoted to simulations of spatial evolutionary games.

To illustrate advantages of our approach to the analysis of combined anticancer therapy we consider the model which is based on two classical models of Tomlinson [5]. The model contains four different strategies/phenotypes of cells:

- A cell produces a growth factor and the benefit impacts all the neighbors and the cell itself (A);
- A cell produces a cytotoxic substance against nearby cells (P);
- A cell is resistant to the cytotoxic substance (Q);
- Strategy which shall be considered as a baseline (no production of the cytotoxic substances, no resistance to it, no growth factor) (R).

Parameters used to defne the measure of fitness are given by:

z: baseline fitness (set to 1 in the context of the model)
e: cost of producing the cytotoxin
f: disadvantage of being affected by the cytotoxin
g: benefit of harming other cells

h: cost of resistance to the cytotoxin
i: cost of proangiogenic factor production
j: beneficial effect of receiving the growth factor
r: external resources stimulating growth (e.g proangiogenic growth factors)
c: external cytotoxic resources (e.g. cytotoxic drugs).

The pay-off matrix for four phenotype model with resources has the following form:

	A	P	Q	R
A	1-i+j+r/2-c/2	1+j-e+g+r/2-c/2	1+j-h+r/2	1+j+r/2-c/2
P	1-i+j-f+r/2-c/2	1-f-e+g+r/2-c/2	1-h+r/2	1-f+r/2-c/2
Q	1-i+j+r/2-c/2	1-e+r/2-c/2	1-h+r/2	1+r/2-c/2
R	1-i+j+r/2-c/2	1-e+g+r/2-c/2	1-h+r/2	1+r/2-c/2

Such model was already analysed by us in the context of mean field games [6]. For a polymorphism (coexistence) of all strategies, each frequency should be contained within the interval (0,1). To track the evolution of different phenotypes in the population, it is feasible to simulate equations for replicator dynamics. They show how frequencies of diffrent strategies change over time, thereby inuencing the composition of the studied population. For inference analysis in this game, the result when all phenotypes coexist is taken as a reference. Relatively to this result the cost of cytotoxic production has been increased by 0.1 and equals to the benefits from harming the neighbors. Similarly, the adaptation of P-cells has been decreased, and at the same time, one of the polymorphic conditions has not been 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 the self-correlation between these two phenotypes in fact, and the main assumption of the model is that Q-cells arise as the evolutionary reaction to the toxic substance produced by P-phenotype. The 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 the cytotoxic substance, the adjustment of the phenotype P decreases. Similarly with phenotype Q, a fraction of which depends on the ratio of the parameters related strictly to phenotype P. So the greater the benefits from the harming of the neighboring cells, the greater the adaptation of Q phenotype. This can be explained by that in contact between P and Q, the formerdoes not receive the bene_ts. Within the reference results, the neutral phenotype R is the dominative one. The analysis could be supported through generating the final frequency of occurrences for parameter changes. This kind of representation does not allow to study the dynamic of phenotype changes in time. The machinery of EGT supported by the replication dynamics enables analysis of the evolution of phenotype structure in time within cell populations; nevertheless, it gives no information about the spatial distribution of these phenotypes in tumors. Such possibilities are created by the methodology of spatial evolutionary games theory (SEGT) [7] which enables a study of players allocation. The lack of perfect mixing is a crucial diffrence between non-spatial and spatial models Within the reference results the neutral phenotype R is the dominative one, then P and also Q appear for the spatial game. There is no obvious explanation for these results since the phenotype R is not better adjusted neither in contact with the rest of phenotypes nor with itself. In the case of the second game (for increased e) the phenotype R also dominates for deterministic and quantitative reproductions (the result similar as for non-spatial game). The diffrence has occurred in the probabilistic reproduction, where Q-type has been displaced from the population. Alternatively spatial games could be presented in a way similar to meanfield models. Those outcomes are more focused on the dynamics of the model through the passing generations than on the spatial structures. Introduction of external resources may result in qualitative changes in the phenotype evolution The idea is to consider effects of those two factors by changing only two parameters (r and c in this case). The in-house software was created to perform simulations in 2D and 3D cases. All simulations were performer for 2D or 3D torus of size 32x32 or 10x10x10 cells.

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