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THE ROLE OF INTERVENTIONS IN CANCER EVOLUTION – EVOLUTIONARY GAMES APPROACH

Summary. The objective of this study is to develop and apply a new mathematical model to address the questions of importance for basic cancer research and for practice of oncology: What is the role of diverse kinds of intervention (exposures or treatments) in the evolution of cancer? Can proliferation acceleration make carcinogenesis more likely? Can cell killing create conditions that enable evolution of heterogeneity and therefore increase the viability of the cancer cell population? An important part of the problem we address is whether the genetic heterogeneity in cancer cells exists *ab initio* (before diagnosis and intervention), or it does it evolve following and as a result of the intervention. We believe, based on evidence, that the former is the case, as stated in the following hypothesis:
Positive (stimulating) or negative (cell-killing) treatment modifies pre-cancer and tumor cell heterogeneity through promotion of selection of preexisting cell clones, their phenotypic plasticity and self-organization. We are far from believing that using a new model we are prepared to prove completely this hypothesis. Nevertheless we hope that the new approach based on the theory of evolutionary games, gives an efficient tool for investigation of different aspects related to the hypothesis.

We propose an extension of evolutionary game models which gives possibility to study the role of interventions in cancer evolution. More precisely we endow evolutionary game models with changes of the phenotypes' adjustment during the transient generations within the population. These changes are performed by the parameters in the payoff matrix, which determine the fitness (payoff, adjustment) resulting from different interactions between players (taking into account both the benefits and costs of particular actions and strategies). Alteration of these parameters changes them into functions that simulate (within this model) the changes within the environment and define their different impacts on the fitness. 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 main assumption of the spatial games [2] is that each cell on the lattice is represented by a player following only one strategy. The local payoff for each player is the sum of payoffs due to interactions (according to the payoff matrix) with cells in the neighbourhood. We will refer to this approach as the classical one or SEGT. Cells on the spatial lattice can also be considered as heterogeneous (instead of homogeneous), so that each particular player may contain mixed phenotypes. Spatial games of the type proposed by us [3] are called multidimensional spatial evolutionary games (MSEG). Hence, in MSEG

different degrees of playing a particular strategy are treated as different characteristics that define different phenotypes. It may happen that within the population, all of the players have diverse phenotypes (which probably better describes biological phenomena). In fact, the game is performed on a multidimensional lattice (dependent on the number of defined phenotypes in the model), where each layer represents a particular phenotype (as the frequency of occurrence) of the player.

The payoff matrix does not have to remain constant during the game; the parameters may change and may depend on other factors (e.g. changes in the environment or any other external influence). The model may be extended by yet another parameter r, that represents the amount and the availability of resources like territory, food, drugs etc. For mean-field games r is changed for the entire population at once and does not depend on the current consistency of the population. Spatial games give an opportunity to change r for a group of cells or even for each cell separately. For the spatial application we choose MSEG games since they provide more possibilities of defining different rules for the resources simulation. In this way another lattice is needed, where a different game with different rules is performed.

To explain the role and use of resources in evolutionary game model we start with a classical hawk-dove model [1] analyzed using mixed spatial evolutionary games (MSEG) endowed with. an additional spatial layer representing changes within the environment. Than we use the same approach to study, the so called angiogenic games [4], in the version containing varying external resources. The last model considered in this study is the four phenotype game [5] with two resources representing two different strategies of external interventions. The additional lattice representing the evolution of resources increases only the dimension of the lattice in the MSEG.

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