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Evolutionary games in modeling cancer metastases

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ABSTRACT

Evolutionary game theory (EGT) [Smi73, Smi82] combines mathematical tools of theory of games with Darwinian adaptation and species evolution and may be applied to analysis and simulation of evolutionary changes within different subpopulations due to interactions between them. The result of these interactions (and, possibly, the effect of environment) is a change of the degree of evolutionary adjustment which, in turn, may cause stabilization of the population structure. Using EGT, it is possible to foresee, whether a population tends to be heterogeneous or rather only one phenotype survives and dominates. Introducing changes of the replicator equations (RE) [Hof98] describing the behavior in the population in time allows to follow dynamics of changes. EGT has also been applied to study development of cellular populations since cells, like whole organisms, compete for space and nutrients, exchange signals, cooperate, and show kinds of "altruism" resembling animals in evolution. One of the core properties of evolutionary systems that can be studied with EGT is the presence of an evolutionary stable strategy (ESS) [Smi82], which corresponds to the stable equilibria of the tumor dynamics. Starting from the pioneering works of Tomlinson [Tom97, Tom97a] this machinery was used to model different tumor related phenomena. The EGT models build and test the fundamental understanding of the dynamical interactions underlying tumor population dynamics [McE09, Gal18,Vin05]. The development and study of mathematical models like these has suggested different possible evolutionary therapies including adaptive therapies [Gat03, Gat09].

Basanta et al. [Bas08] were probably the first to use this machinery in modeling phenomena leading to tumor cell invasion and migration. The authors assume that at initial stage cancer cells are specified by autonomous growth and then they can switch to anaerobic glycolysis or become increasingly motile and invasive. It allows to study the circumstances, under which mutations confer increased motility to cells needed for invasion of other tissues and metastasis. In their next paper [Bas10], the authors extended their model by adding phenotype which could switch to anaerobic glycolysis and be motile. Their model is directed to glioblastomas. EGT is based on the assumption of perfect mixing inside the population (mean field approach) and interaction of each pair of strategies. To overcome this simplification and enable analysis of local arrangement and internal interactions in the neighborhood, the evolutionary games have been transferred into spatial lattice by application of cellular automata

techniques, leading to the so called spatial evolutionary game theory. Such approach was also used by Basanta et al. [Bas08a], to deal with the simplified version of their first model, which had only two phenotypes. In our study [Swi13] we have appended analysis of all these three models by RE and SEGT tools (if absent in original study) which allows to give an approximate answer on questions regarding time and place of the switch, leading to tumor migration. If stable equilibria in tumors corresponding to ESS exist , reaching it using available therapies could provide a means for achieving long term stabilization of tumors and subsequent increase in metastasis-free time [Wes18].

In our study we propose more complex EGT models of tumor-tumor cells interactions containing different strategies of dissemination of cancer which take into account results of clinical and medical imaging data. Moreover, we apply new tools of spatial evolutionary tools, proposed by us recently. These tools take into account heterogeneity at the cell level (the so called Mixed Spatial Evolutionary Games – MSEG) and varying in time (and possibly also in space) effects of environment (Evolutionary Games with Resources and Spatial Evolutionary Games with Resources, respectively). In the former case it leads to multilayer structure of the game [Swi16b] and in the latter case to time varying pay-off tables [Swi18].

The main idea that autonomously growing cells because of evolutionary acquisition are able to become motile and invasive and afterwards, disseminate, first, to local and subsequently (or sometimes immediately), to distant sites leads to several questions which could be at least qualitatively answered by game theoretic model. First, we can ask what are factors deciding when and where distant metastases in a given patient will emerge. Based on patient characteristics and radiomics features from PET/CT scans such as metabolic tumor volume and total lesion glycolysis we may construct the pay-off table whose entries measure changes in evolutionary adjustment resulting from interaction of cells representing different phenotypes (division, motility, cell-cell contacts, apoptosis). The mean field approach will enable to predict how changes in these adjustments lead to stable equilibrium between different phenotypes or perhaps result in dominance of some phenotypes in cancer cell population. Additional analysis of replicator dynamics equations (RE) is helpful in finding factors which can prolong the time interval between cancer diagnosis and the first distant metastasis. Nevertheless, analysis of Replicator Dynamics for Games with Resources leads to some new problems since relevant differential equations are time-varying. An important issue which should be taken into account is that, in such games, tumor cells play their own adaptive strategy. Zhao et al [Zhao14] review the recent evidence concerning impact of heterogeneity of tumors on effects of therapy. It has become clear that not only are distinct tumor subclones found to coexist within the same tumor regions, but that metastatic subclones originate from a non-metastatic parental clone in the primary tumor. Additional posttranscriptional and epigenetic changes can potentially further diversify a tumor population, which is also dynamic, as shown in the responses to standard combination regimens, with preexisting minor subclones expanding to dominate at relapse. It is yet another challenge which should be overcome in the stage of defining a game to be played. In the problem of tumor dissemination and colonization of local lymph nodes and distant organs spatial dependencies between cells representing different phenotypes and their movement are crucial in analysis. Thus, the mean field approach will be treated only as the primary but crucial step leading to construction and analysis of spatial evolutionary games (SEGT) based on cellular automata and agent-based systems. Our experience in analysis of such models shows that the type of the reproduction used in the model leads to markedly different outcomes during the simulations of cellular populations evolution [Swi 16a]. Since deterministic reproduction seems to be responsible for direct cell-cell communication and probabilistic reflects rather release of signaling factors into the environment thus the type of intercellular communication seems to be very important for the results generated by the model. In biology reality, the behavior of individual tumor cells is rather a mixture of features, which have been treated as strategies in the game theoretic model mentioned above. A cell with even potentially high level of factors determining a particular feature may not exhibit it because of the intercellular communication in the local environment. This observation led us to introduction of yet

another type of games which we have called Mixed Spatial Evolutionary Games (MSEG) [Swi16b] in which the game is played simultaneously on multilayer lattices. Moreover, by introducing time varying and/or space dependent factors into the pay-off table (so called Games with Resources – [Swi18]) we address the hypothesis that it is possible to prolong the time interval between cancer diagnosis and appearance of distant metastasis. 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.

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