Relaxing homogenous mixing within a SR network model of adaptive cancer treatment
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Introduction

Recently [1] game theory has been used to inspire and model an innovative [2] and effective [3] cancer treatment. Such adaptive treatment (AT) copes with the fact that all treatments to metastatic cancer select for treatment resistance. It does so by reducing the administered dosage in a personalized manner, informed by evolutionary or ecological theory. The treatment thereby delays the onset of treatment resistance by exploiting the competition between treatment sensitive and treatment resistant cancer cells. This paper reframes such a model as a SR network model. This makes it easier to create collaborations with network scientists and allows the use of well-established definitions and results within network science. This paper relaxes the assumption of homogenous mixing, which is traditional within game theory. Mixing is a crucial variable within the cancer, particularly in the here relevant competition between sensitive and resistant cells. Accounting for non-homogenous mixing of cancer cells is a great improvement to the realism of models of cancer and here the perspective of network science can be beneficial.

Method

Model

Consider cancer cells saturated in the space of a torus grid. Some of these cells are susceptible to treatment (S) and some are resistant (R), respectively type 1 and 2.[1] The fitness of type *i* as a result of interacting with type *j* is given by entry A_{ij} in 2x2 fitness matrix A.[2] In contrast to homogenous mixing any cancer cell interacts only with its direct neighbors. On the grid these are the 4 direct neighbors on any side. Death of a cancer cell and the birth of a new cell to replace it is collapsed into one event of "imitation". The neighbor that a cell imitates is decided by lottery where the number of lottery tickets each neighbor has is equal to the fitness of the neighbor's type interacting with the type of this cell. To prevent that the state of a checkerboard is a sink, we include the cell itself as well as a participant (i.e. neighbor) in this lottery. With this inclusion there is some inertia, i.e. some probability that the cell does not die and gets replaced. A small probability of mutation wherewith one cell mutates into the other type is also added. Here it is only relevant to account for whether a location has a cancer cell of type 1 (S) or 2 (R).

In a well-mixed, large population the types of the neighbors of any cell are on average the proportion of types in the population. This deviates from observations where the cancer is not well-mixed in space. We observe the sum of the number of neighbors of either type for all cancer cells of each type. The resulting four counts divided by their sum gives the empirical frequency of one type interacting with another. These empirical frequencies (I_B) at any one particular time point can be divided by the frequencies expected in a homogenously mixed population (I_A) and multiplied with the fitness matrix to represent the average effect of type *j* on type *i* with these deviating rates of interaction in a second fitness matrix (B). This represents the first model.

In a second model I account for the fact that some cells have only neighbors of the same type such that the probability of the type of cell in that location to change equals only the

[1] The fact that treatments of metastatic cancers fail attests to the latter irrespective of the underlying biology.
[2] A constant is added to A such that 1 is its lowest element and it is therewith benchmarked.

mutation rate. Such cells are not participants in interesting lotteries and in this second model I exclude them from my analysis. As such only the so-called "interface" remains wherein the two different cell types interact with one another. I prefix the states S and R with again S and R to encode such sensitivity to change within this interface or resistance to change outside of the interface – a property of the neighborhood as opposed to the cell itself – creating 4 states: SS, RS, SR and RR.

Particularly the first SR model differs from the traditional (as e.g. in [4], figure 10.6) in that the R state is not permanent. Additionally, the perspective is different. Usually the states relate the patient to a disease whereas now it relates the disease to a treatment. As such R is in contrast the bad and S the good state from the perspective of the patient.

Analysis

In a non-spatial evolutionary game, populations converge to an evolutionary stable strategy (ESS) in almost all cases. An ESS is calculable from the fitness matrix [5]. This short paper considers only one fitness matrix: A(S,R) = [3 1; 1 2]. The sensitive type is more fit than the resistant type (by 1). This represents the cost of resistance [2]. Interaction between different types is less fit than interaction with the same type (asymmetrically by 1 for R with S and 2 for S with R). This represents a cost of competition, of co-existence, e.g. analogous to the fact that multi-tasking decreases efficiency. The latter can also be relaxed, yielding A(S,R)=[2 2; 1 1] instead after benchmarking *A* such that the minimal element is 1. Both provide realistic fitness matrices with a cost of resistance, and possibly a cost to inter-type competition, which AT aims to exploit.

Analysis of the dynamics of a non-spatial game can inform those of a spatial game under certain conditions [6] and can thus be predictive. Fitness matrix B in model 1 and 2 represents a non-spatial game that is in a sense equivalent to the particular state of the spatial game at a particular time point. We analyze this non-spatial game B to forecast the spatial implementation.

$B=A*I_B/I_A$ (using element-by-element multiplication and division)
I_B/I_A : the factor difference in (observed and expected) interaction rates.

Results and discussion

The first model correctly predicts the dynamics in the following manner. The fitness matrix A(S,R) = [3 1; 1 2] has two attracting states, the fixation of either type. The game's interior Nash equilibrium is the boundary point of two 'basin's of attraction' on either side. On either side of it the dynamics in the non-spatial variant go to the end of that same side. The same happens in the spatial variant where the dynamics move away from such a same point calculated in fitness matrix *B* and with a speed increasing with the distance, yielding predictability. The second model gives insight into particular states yet was not predictive as its dynamics are later and then faster.

Figure 1 depicts the typical dynamics with a particular initialization of this model.[3] The orange line shows the interior Nash equilibrium in the non-spatial case. The light grey line is this same value in the spatial case and the green line, representing the number of sensitive cancer cells, moves away from it. The dark grey line and red line are respectively their complement; the other part of the population. The brown and yellow line respectively represent the first two

[3] Namely 'Initial-State' "dispersed" with .84 'number-of-resistant-cells' within the NetLogo program linked below.

values (the orange non-spatial and light grey spatial interior Nash equilibrium) when only considering the interface (model 2).

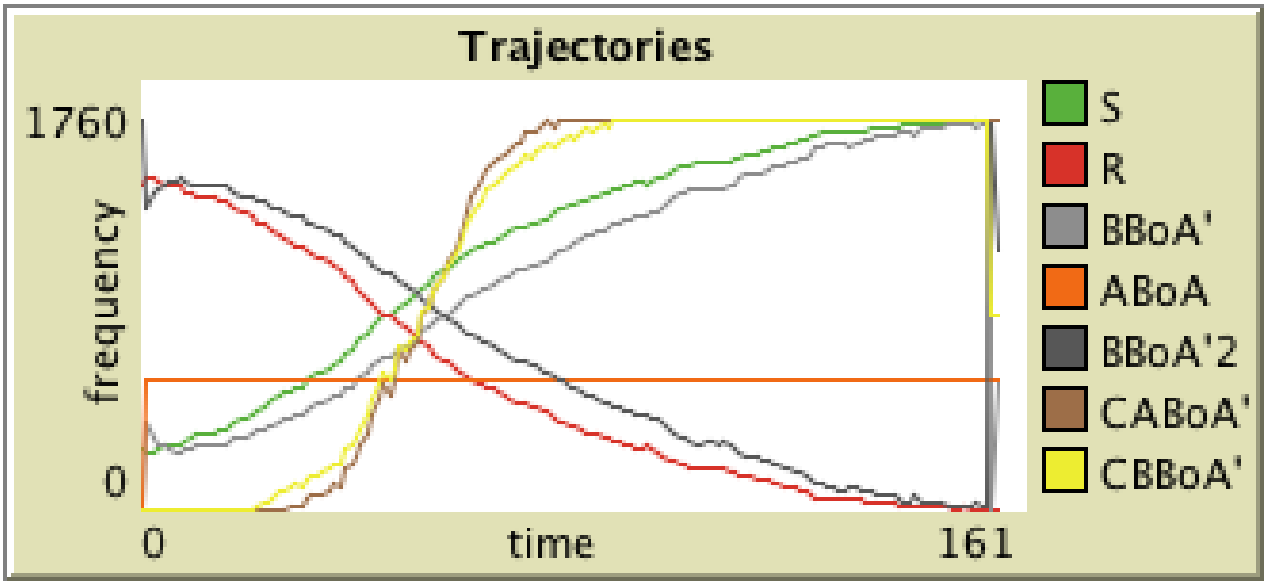

Figure 1. Trajectories from a simulation in NetLogo.

Spatial patterns explain the dynamics of the interior Nash equilibrium of *B* over time (the light grey line) and thereby the prediction. You can imagine that with the cost of competition in the fitness matrix, cells will "want to" interact with their own type, creating interaction that is correlated or assortative. The less frequent or dominant type then also tends to clumps together, interacting with its own type even more frequent. I call this skewness and is similar to the rich club in network science (i.e. of well-connected nodes to be well-connected to each other). The introduced terms correlation and skewness have involved yet precise mathematical definitions[4] omitted in this paper yet present in [10] and the NetLogo [11] program (v. 5.3.1.) that performs the simulation. The program is build on [12] and available as "Software Accompaniment 1 with short network biology paper" within the NetLogo modeling commons (modelingcommons.org).

A dynamic network

The simple grid network under analysis can be collapsed into 2 nodes (S and R), fully connected with 4 directed edges, including self-loops, where all 6 objects are weighted and dynamic in their weights through time. This summarizes at any one particular time point the interaction on the network and is a sufficient basis for the analysis. The second model would split node S and R and their weight into a node sensitive and a node resistant to change based on its environment where the resistant parts are connected only to themselves and their sensitive counterpart.

Wider application

The method here introduced can be applied in general to any network, not just the simple grid network here analyzed. To illustrate I will reproduce and similarly analyze a related spatial model. It will similarly be available as "Software Accompaniment 2 with short network biology paper".

[4] Inspired by [7] and 4CModelling workshop #2 and correlation is mentioned without definition in e.g. [8] and [9].

Conclusion

This paper establishes that the above first model can predict dynamics in a spatial network through dynamic equivalencies to a non-spatial model. In doing so only part of the network is measured. This is a promising basis for the exploration of trends and their subsequent incorporation in models of adaptive cancer treatment and in any network with a similar process.

Future extensions and research

Diagonally adjacent cells as neighbors, the addition of a third type of cancer cell and integration of it with the results of the above and future research, empty grid locations (no cell present), possibly modelled as a type itself, a healthy type that is a non-cancerous cell, analyses of different initial states and different fitness matrices, exploration and analysis of update mechanisms alternative to the "imitation" used here, elements in space (e.g. a blood vessel), creating heterogeneity intrinsic to the space, effects of certain types of cancer cells on the space, e.g. producing and emanating testosterone in cooperative 'TP' prostate cancer cells [5]. Introduce a drug into the space as one of multiple ways to add treatment to the simulation.

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