A Stochastic Spatial Model for Tumor Growth

Aashiq N. Dheeraj
A thesis submitted for Honors in Mathematics
Department of Mathematics, Duke University
Durham, North Carolina 27708 USA

April 29, 2014

Acknowledgements

This research was conducted under the supervision of Prof. Richard Durrett (Duke University), and was supported, in part, by the National Science Foundation through Research Training Group grant DMS-0943760 to the Department of Mathematics at Duke University

Abstract

Evolutionary game theory can be used to study the interactions of different cell phenotypes and describe tumor population dynamics. Instead of killing tumor cells, clinical treatment could aim to change the nature of the evolutionary game– enabling healthy cells to outcompete malignant cells. Most applications of evolutionary game theory to tumor growth have considered the tumor as a homogeneously mixing population that is governed by the replicator equation. We model the tumor population as an interacting particle system (IPS), with discrete individuals, stochastic local interactions, and explicit spatial consideration. Using this model, we see how predictions are changed when space is taken into account. In particular, we consider Basanta's work on glioma progression [3], the analysis of multiple myeloma proposed by Dingli *et al.* [8], and Tomlinson's model for tumors containing cytotoxin-producing cells [15]. Our model agrees with Basanta's in that we should have coexistence between the three tumor phenotypes, but the spatial model allows coexistence in a significantly wider region of parameter space. Dingli's tumor population exhibits bistability in a certain parameter regime. Our spatial model predicts a transition between the two stable states at a critical parameter value, so there is no bistability. In Tomlinson's game, the IPS does not allow for coexistence between cell types.

Introduction

The theory of evolutionary games was introduced by John Maynard Smith and George R. Price to study ecological competitions [13]. However 15 years ago, Tomlinson suggested that it could be used to study interactions between tumor cells [14, 15]. More recently, Axelrod, Axelrod, and Pienta [1] explained how the cooperation of cancer and normal cells can bring on mutually beneficial events such as angiogenesis (the development of blood vessels). In a series of papers Basanta and coauthors studied the role of glycolysis in glioma progression and invasion [3, 2]. Dingli *et al.* [8] studied the interactions between osteoclasts, osteoblasts, and tumor cells in multiple myeloma. Finally, we look at Tomlinson and Bodmer's model for a tumor with cells that produce cytotoxin [15].

All of these analyses assume that the population of cells is homogeneously mixing while in reality, each cells compete only with those nearby. Durrett and Levin [9] showed that the introduction of explicit spatial structures can change the qualitative behavior of a game. They consider four different approaches to modeling evolutionary games. The mean field approach assumes that every individual interacts with every other with equal probability. This assumption gives the benefit of often analytically tractable ODE models. Patch models group individuals into homogeneously mixing patches, with possible migration in between, but no other spatial structure. Reaction-diffusion equations have individuals as continuous concentrations that can diffuse through space and interact only locally. Finally, interacting particle systems have discrete individuals and treat space explicitly. There are analytical results that give limiting reaction diffusion equations for interacting particle systems in the hydrodynamic limit [5] [10]. Here, we will consider an IPS model for several games, comparing the results to those of earlier mean-field models.

Materials and Methods

Game Theoretic Model

In evolutionary game theory (EGT), it is common to use an ordinary differential equation (ODE) model based on pairwise interactions. Suppose that we have n cell types. Let x_i denote the fraction of the population that is cell type i. We must have $\sum_{i=1}^{n} x_i = 1$. Then, the state of the population, $\vec{x}$ can be represented as a point on the n-dimensional simplex. The time-evolution of this state is given by the replicator equation. For each i,

$$\dot{x_i} = x_i(W_i - \overline{W})$$

where W_i is the fitness of cell type i and $\overline{W}$ is the average fitness. Suppose that the fitness payoff due to the interaction between cell types depends linearly on the cell proportions. We can write a payoff matrix, G, that captures the results of this interaction. Then $W_i(\vec{x}) = \vec{\mathbf{e}}_i \cdot G\vec{x}$ and $\overline{W} = \vec{x}^{\top} G\vec{x}$.

In this paper, we are chiefly interested in 3-strategy games, with a payoff matrix of the form

$$G = \begin{array}{c} \\ ① \\ ② \\ ③ \end{array} \begin{array}{c} \begin{array}{ccc} ① & ② & ③ \end{array} \\ \begin{pmatrix} a & b & c \\ d & e & f \\ g & h & k \end{pmatrix} \end{array}$$

Entry G_{ij} of the matrix contains the payoff to a user of strategy i when it encounters a user of strategy j.

As shown in Hofbauer and Sigmund [11] adding constants to the columns does not change the replicator dynamics. We can then always subtract the appropriate constants to get the diagonal to be 0.

$$A = \begin{pmatrix} 0 & \alpha & \theta \\ \beta & 0 & \gamma \\ \delta & \rho & 0 \end{pmatrix}$$

To understand the replicator dynamics we can consider the pairwise interactions of the three

types. In general, for a 2 strategy game, we have the matrix

$$A = \begin{pmatrix} 0 & \alpha \\ \beta & 0 \end{pmatrix}$$

If $\beta < 0$ and $\alpha > 0$, Strategy 1 dominates Strategy 2. If $\beta > 0$ and $\alpha < 0$, Strategy 2 dominates Strategy 1. Otherwise, we have an equilibrium where the fitness of Strategy 1 is equal to the fitness of Strategy 2 for some proportions. If the proportion of Strategy 1 users is p, we have an equilibrium at

$$\alpha(1-p) = \beta p$$
$$\bar{p} = \frac{\alpha}{\alpha+\beta}$$

We need α and β have the same sign to have a fixed point (except for the degenerate case where one or both are zero). Consider a perturbation from this equilibrium that introduces more users of Strategy 1, so we have a frequency $\bar{p} + \epsilon$ for $\epsilon > 0$. For stability, we need the fitness of the second type to be greater after this perturbation.

$$\beta\left(\frac{\alpha}{\alpha+\beta} + \epsilon\right) > \alpha\left(\frac{\beta}{\alpha+\beta} - \epsilon\right)$$

Then we have,

$$\alpha + \beta > 0$$

Since α and β had to have the same sign for the fixed point to exist, the equilibrium is stable if and only if $\alpha, \beta > 0$.

When we have a two-strategy equilibrium, we can then check whether the a population of third strategy users can invade. For this, we need the fitness of the third type to be greater than that of the other two at the equilibrium point.

$$\delta\frac{\alpha}{\alpha+\beta} + \rho\frac{\beta}{\alpha+\beta} > \beta\frac{\alpha}{\alpha+\beta} \rightarrow$$

Thus, the invadability condition is,

$$\delta\alpha + \rho\beta > \beta\alpha$$

Spatial Refinement

According to the ODE model, the fitness of a given individual depends upon the state of the population as a whole. However, when individuals are distributed in space, this fitness should only depend upon interactions with nearby neighbors. If the population is homogeneously mixing, all sites are neighbors. The replicator equation can then be viewed as a mean-field approximation to a spatial game. As shown by Durrett and Levine, including spatial effects can have important implications for the dynamics [9].

In our model, cells are represented as points on the lattice $\mathbb{Z}^d$, initialized to one phenotype. The *neighborhood* of a given cell refers to the von Neumann neighborhood. In 3 dimensions, this consists of the 6 cells with which it shares a face. The *fitness* of a given cell is computed by summing over the payoffs for interactions with each neighbor. The payoffs are taken from the payoff matrix for the particular game under consideration. The time-evolution of the lattice is given by choosing a cell at random and replacing it with one of its neighbors, chosen with probability proportional to fitness. Figure 1 gives a graphical explanation in two dimensions.

There are a few metrics one can use to characterize the behavior of our model. A good way to show coexistence is to look at cell type frequencies over time. If they are stable over long periods of time or have sustained oscillations, this might indicate coexistence. The lattice used must be large enough that stochastic fluctuations in population do not accidentally eliminate a cell type, in which case the predicted dynamics could be far off. As long as this is satisfied, the initial conditions should not matter. In our simulations, cells are initialized randomly to a certain type, as shown in Figure 2. This is true of stochastic models as discussed in Durrett and Levin [9], which have infinite size. The dynamics of interest tend to take place at a characteristic length scale, so the lattice we use must be large enough to capture them. To determine this, we need a metric to quantify the size of the structures we observe in the spatial model. We define the degree of clustering as the ratio of identical neighbor pairs to total neighbor pairs, considering all pairs in the lattice. If the clustering tends to keep increasing, this might indicate that the chosen lattice is not large enough.

After some trial and error, we settled on a lattice of size 75 x 75 x 75 with periodic boundary conditions (torus). Around this size, the clustering statistic for simulations that exhibit coexistence is steady well below 1. In smaller simulations, the clustering statistic goes to 1 and the output is noisier. Initially, simulations were run in 2 dimensions, but the model behaved poorly as the voter model (described below) has no nontrivial stationary distribution in 2 dimensions. Only consensus is possible due to clustering [6].

One can arrive at analytical results for two-strategy games by considering voter model perturbations. Cox, Durrett, and Perkins consider the limiting reaction diffusion equations that arise from perturbations of the voter model [**?**]. The discrete time voter model is a Markov process on the d-dimensional lattice, $\mathbb{Z}^d$. One can think of the model as describing people voting on an issue. Each site is an individual who holds the opinion 0 or 1. The state of the model at time t is $\xi_t : \mathbb{Z}^d \to \{0, 1\}$, with $\xi_t(x)$ giving the opinion of the voter at site x at time t. Let Λ be the entire lattice. Site x will switch states at a rate

$$c(x, \xi_t) = \sum_{y \in \Lambda} p(x, y) \mathbb{I}\left(\xi_t(x) \neq \xi_t(y)\right)$$

where p is a symmetric probability kernel. The indicator $\mathbb{I}\left(\xi_t(x) \neq \xi_t(y)\right)$ is an indicator that is 1 when the state of site y is different from that of site x. In particular, one can let p be the transition function for the symmetric random walk in d dimensions, where $p(x, y) = (2d)^{-1}\mathbb{I}(\mid x - y \mid = 1)$. In this case, a cell only cares about the opinion of adjacent cells, and all adjacent cells are given equal weight. In discrete time, one can consider Moran

updating, where sites are randomly chosen and updated according to the preceding rule.

Analytic results can be obtained in the *weak selection limit*, with a game matrix of the form $\mathbf{1} + \omega A$, where $\mathbf{1}$ is a matrix of 1's, with small $\omega > 0$, and game matrix A. This allows treatment as a voter model perturbation, as the effect of selection is small compared to choosing neighbors uniformly at random. In a pre-print, Rick Durrett shows that introducing space is equivalent to a transformation of the game matrix and replacing the replicator ODE shown earlier with a related PDE. There has been progress made on the three-strategy case, but there are few analytical results to guide the analysis as of now.

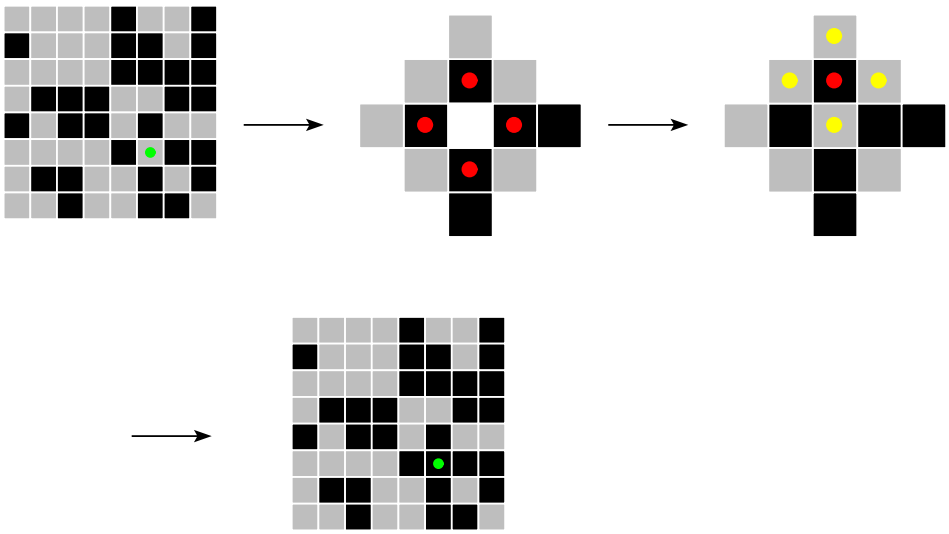
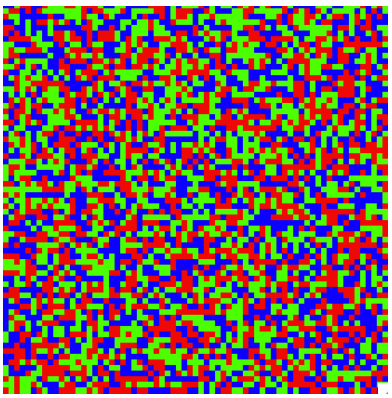


Figure 1: An example of a spatial Moran update. The cell marked green is randomly selected to die. The fitness of each red neighbor is computed using its yellow neighbors (including the dead cell). Finally, the update is made.

Figure 2: An example of a possible initial condition. Red, Green, and Blue represent different cell types.



Results

Case 1: Glioblastoma Game

Basanta *et al.* [3] used EGT to study interactions between different tumor cell phenotypes found in glioblastomas. They were able to explain several observed features of glioma progression, such as a switch to glycolytic respiration. This less efficient type of metabolism is not usually observed in human cells, which perform aerobic respiration. In their model, there are three tumor phenotypes:

1. Autonomous growth (AG) are standard tumor cells that replicate continuously
2. Invasive (INV) cells flee upon encountering another type
3. Glycolytic (GLY) cells use glycolysis for their metabolic needs. This is less efficient than aerobic respiration, and cells generally adopt it when a tumor is insufficiently oxygenated.

We have the following interaction terms, which are assumed to be positive:

- The base payoff is 1. When 2 AG, 2 GLY, or an AG and GLY meet, they split this.
- k : Cost of switching to glycolytic respiration
- n : GLY cells acidify their microenvironment, harming neighboring cells. GLY cells gain payoff n while AG cells suffer cost n. INV cells run away.
- c : Cost of fleeing. INV cells flee from other cell types, obtaining the full base payoff elsewhere. When 2 INV meet, they split c.

Thus, we have the following payoff table:

$$A = \begin{array}{c} \\ AG \\ INV \\ GLY \end{array} \begin{array}{c} \begin{array}{ccc} AG & INV & GLY \end{array} \\ \begin{pmatrix} \frac{1}{2} & 1 & \frac{1}{2}-n \\ 1-c & 1-\frac{c}{2} & 1-c \\ \frac{1}{2}+n-k & 1-k & \frac{1}{2}-k \end{pmatrix} \end{array}$$

Adding the appropriate constants, we have,

$$A = \begin{pmatrix} 0 & \frac{c}{2} & k-n \\ \frac{1}{2}-c & 0 & \frac{1}{2}+k-c \\ -(k-n) & \frac{c}{2}-k & 0 \end{pmatrix}$$

1. AG vs INV

$$B = \begin{pmatrix} 0 & \frac{c}{2} \\ \frac{1}{2}-c & 0 \end{pmatrix}$$

(a) If $c \geq \frac{1}{2}$, AG dominates INV.

(b) If $c < \frac{1}{2}$, we have an equilibrium at

$$p_{\text{AG}} = \frac{c}{1-c}$$

$$p_{\text{INV}} = \frac{1-2c}{1-c}$$

The equilibrium is stable, since $0 < c < \frac{1}{2}$.

2. INV vs GLY

$$B = \begin{pmatrix} 0 & \frac{1}{2}+k-c \\ \frac{c}{2}-k & 0 \end{pmatrix}$$

(a) If $k > c - \frac{1}{2}$ and $k > \frac{c}{2}$, INV dominates GLY. This is equivalent to $k > \frac{c}{2}$ for $c \in [0,1]$.

(b) If $k < c - \frac{1}{2}$ and $k < \frac{c}{2}$, GLY dominates INV. This can only occur for $c \geq \frac{1}{2}$, where the condition is equivalent to $k < c - \frac{1}{2}$.

(c) If $k > c - \frac{1}{2}$ and $k < \frac{c}{2}$, we have a stable INV-GLY equilibrium at

$$(\frac{1}{2}+k-c)(1-p) = (\frac{c}{2}-k)p$$

$$\bar{p}_{INV} = \frac{1+2k-2c}{1-c}$$

$$\bar{p}_{GLY} = \frac{c-2k}{1-c}$$

For $c < \frac{1}{2}$, this is equivalent to $k < \frac{c}{2}$

(d) If $k < c - \frac{1}{2}$ and $k > \frac{c}{2}$, we have an unstable INV-GLY equilibrium. This is impossible for $c \in [0,1]$.

3. AG vs. GLY

$$B = \begin{pmatrix} 0 & k-n \\ n-k & 0 \end{pmatrix}$$

(a) If $k > n$, AG dominates GLY

(b) If $k < n$, GLY dominates AG

If $k > n$, AG dominates GLY. If $n < k$, GLY dominates AG.

4. Invadability of AG-INV equilibrium If the fitness of GLY at this fixed point is higher than that of AG and INV, the equilibrium is invadable. We find

$$\begin{aligned} F_{GLY} &= (n-k)\frac{c}{1-c} + (\frac{c}{2} - k)\frac{1-2c}{1-c} \\ &= \frac{cn - kc + c/2 - k - c^2 + 2ck}{1-c} \end{aligned}$$

and

$$F_{INV} = (\frac{1}{2} - c)\frac{c}{1-c}$$

In order to have $F_{GLY} > F_{INV}$, we need

$$k < \frac{cn}{1-c}$$

5. Invadability of INV-GLY equilibrium If the fitness of AG is higher at this fixed point, the equilibrium is invadable. We find

$$\begin{aligned} F_{AG} &= \frac{c}{2}\frac{1+2k-2c}{1-c} + (k-n)\frac{c-2k}{1-c} \\ &= \frac{c/2 + 2kc - c^2 - 2k^2 - cn + 2nk}{1-c} \end{aligned}$$

For the INV frequency,

$$\begin{aligned} F_{INV} &= (\frac{c}{2} - k)\frac{1+2k-2c}{1-c} \\ &= \frac{c/2 + 3kc - c^2 - 2k^2 + kc - k}{1-c} \end{aligned}$$

In order to have $F_{AG} > F_{INV}$, we need the constraint

$$k > \frac{cn}{1-c+2n}$$

We can compute the location of the interior fixed point from the replicator equation. If the 2-species equilibria are invadable, it will be stable.

Let $\vec{p} = \begin{pmatrix} p_1 & p_2 & 1-p_1-p_2 \end{pmatrix}^\top$, noting that the frequencies of all the cell types must add to 1. Then,

$$\vec{W} = A\vec{p} = \begin{pmatrix} \frac{p_2}{2} + p_1 n + \frac{1}{2} - n \\ 1 - c + \frac{p_2 c}{2} \\ p_1 * n + \frac{p_2}{2} + \frac{1}{2} - k \end{pmatrix}$$

The average fitness is given by

$$\overline{W} = \vec{p}^\top A\vec{p} = \frac{1}{2} - k + kp_1 + p_2(1 - c + k) - \frac{p_2^2}{2}(1 - c)$$

To solve for the fixed point, we set $W_1 = \overline{W}$ and $W_2 = \overline{W}$, yielding the internal fixed point

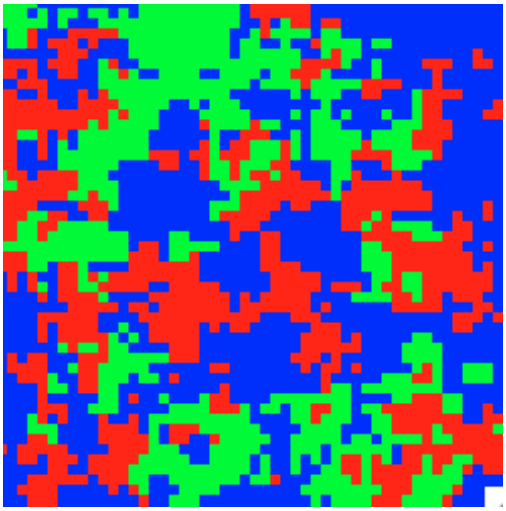
$$p^*_{AG} = \frac{2nk + k - nc - kc}{2n^2}$$
$$p^*_{INV} = \frac{n - k}{n}$$
$$p^*_{GLY} = \frac{kc - k + cn}{2n^2}$$

The coordinates must be in $(0, 1)$, so we have the constraints

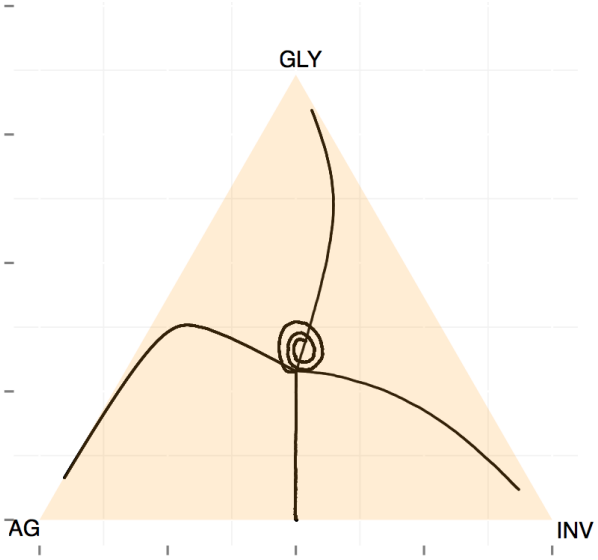
$$k > \frac{cn}{1 - c + 2n} \tag{1}$$
$$k < \frac{cn}{1 - c} \tag{2}$$
$$k < n \tag{3}$$

These constraints are equivalent to the invadability criteria, with the additional stipulation that $k < n$. To double-check the invadability conditions, we can linearize around this fixed point in order to compute its stability. The Jacobian must have negative real part when evaluated at p^*. Solving, p^* is only unstable for $c > 1$, $n > c - \frac{1}{2}$. The term c represents the cost of motility, so it is not biologically realistic for it to be larger than 1, the base payoff. Thus, as long as the fixed point p^* exists, it is stable.

Stable fixed points of the replicator equation on the inside of the simplex are unique and globally asymptotically stable [11]. The existence of such a point in the mean-field ODE suggests that coexistence is possible in the stochastic spatial model [9]. Thus, we expect AG, INV, and GLY to coexist for some parameter regime in our model.

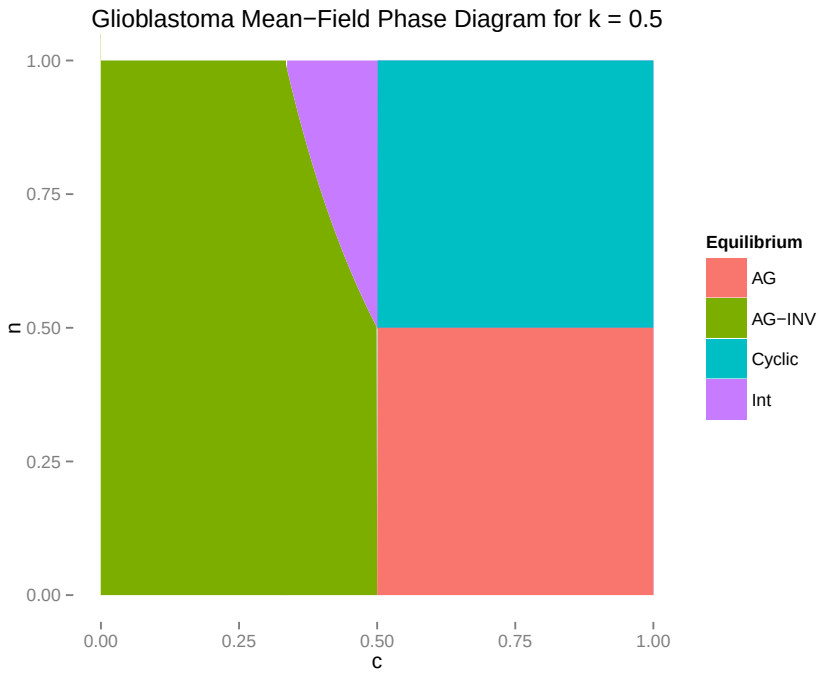


(a) Sample Output. Cells of type AG are red, INV green and GLY blue.

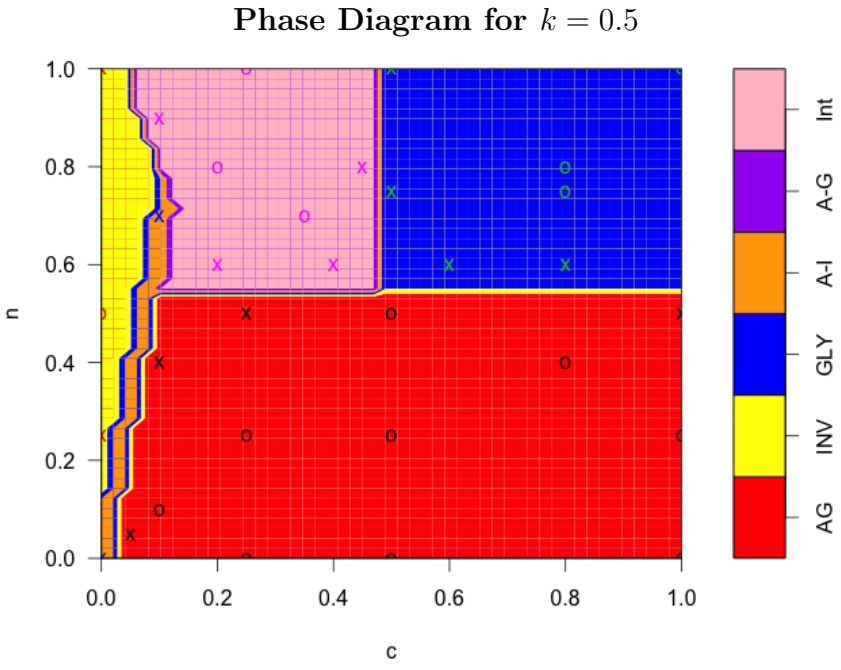


(b) Some sample trajectories of the spatial simulation plotted on the simplex. Each trajectory begins at the center and is for a different choice of parameters.

Figure 3



(a) In the ODE model, coexistence is only possible for a narrow band, indicated by Int. In the cyclic region, GLY beats AG, AG beats INV, and INV beats GLY. AG-INV is a region where two strategies coexist.



(b) Equilibrium cell types for spatial simulation. Simulation was run on a 75^3 lattice with toroidal geometry. The points, both X's and O's, indicate parameter values simulated and used to train an SVM. Points indicated by X's are the support vectors, nearest the decision boundary.

Figure 4: Cell types present at equilibrium in Glioblastoma game for $k = 0.5$

In Figure 3b, we plot some trajectories on the simplex to get a feel for how the frequencies evolve in time. The frequencies seem to approach equilibrium asymptotically, without executing a random walk on the simplex. The stable fixed point is interesting, as we can see the frequencies spiral into the center, where we might expect stochastic fluctuations around the fixed point. It would be interesting to compare these flows to that of the mean-field ODE model in future work. Looking at the actual spatial arrangement of cells in Figure 3a, we see that the degree of clustering has increased compared to the initial condition. Where the three cell types coexisted, clustering stabilized between 0.4 and 0.6, suggesting that the simulation is on a large enough lattice to capture the spatial structure.

Ignoring all behavior except coexistence or lack thereof, we can create a phase diagram from spatial simulation. We want to draw a boundary between points with different qualitative behavior. A natural choice is to draw the boundary such that examples of different categories are divided by a gap that is as wide as possible, so that future classification of unknown points is robust to small perturbations. More specifically, suppose we have points $x_i \in \mathbb{R}^n$, belonging to one of two classes. Consider the convex hull of each class. The boundary we want is the perpendicular bisector of the segment joining the closest points in each convex hull. This is a linear programming problem that creates a classifier called a Support Vector Machine (SVM). This is a non-probabilistic binary linear classifier with an implementation in the R statistical language [7].

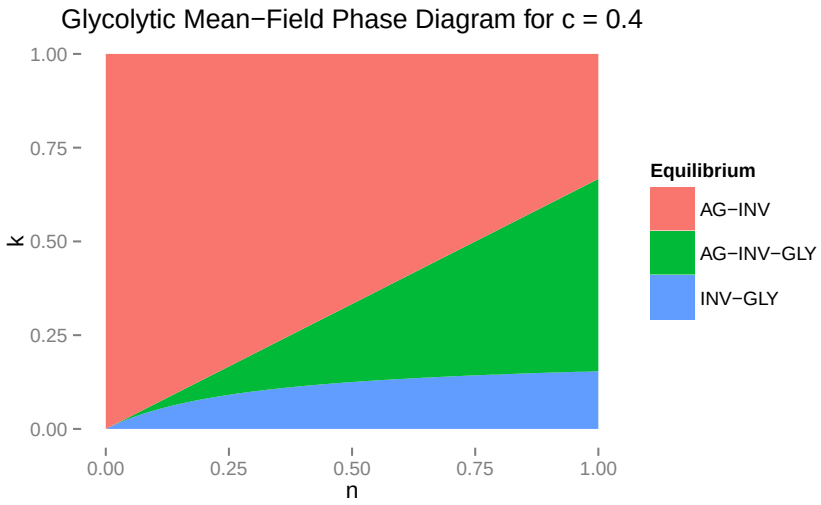
Simulation is time-consuming, so we can use an SVM to draw boundaries based on limited data. In the case of a linear boundary, this is known as the *maximum-margin hyperplane* [4]. Nonlinear boundaries are also possible with kernel techniques. If there exists no hyperplane that can split the data, we can try a *soft* margin that allows misclassification of points, with a specified cost for doing so. The output of the model is not very noisy, and we expect to have few mis-labelled points, so we impose a very strict cost for misclassification when training the model. In our examples, there are usually more than 2 classes, while SVM is a binary classifier. Thus, we consider a series of binary classification problems instead, using the *one-vs-one* method. That is, for k different classes, $k(k-1)/2$ different binary classifiers are trained (for distinguishing between each pair of classes). Majority vote is used to classify new points or draw decision boundaries.

Many important features of the ODE model do not change with the introduction of space. However, based on the results for two species competition, we expected that the introduction of spatial consideration would be like a change in the game matrix – potentially altering the critical values of the parameters. First consider Figure 4, which is in terms of c and n, for $k = 0.5$. Cyclic competition was not observed. In this regime, the Glycolytic cells won. The region where coexistence was possible was much wider, as was the region where AG took over. Coexistence between AG and INV was very rare as a result, with only a small region near $c = 0$. The transition at $k < n$ is similar to the mean-field approximation, where GLY becomes favored over AG. However, the mean-field model suggests there should be cyclic competition where $c > 0.5$, so GLY beats AG, AG beats INV, and INV beats GLY. The transition at $c = 0.5$ is also similar. As expected, all 3 types cannot coexist in the event that AG dominates INV.The equilibrium of INV and GLY is not seen, as for $k = 0.5$, it

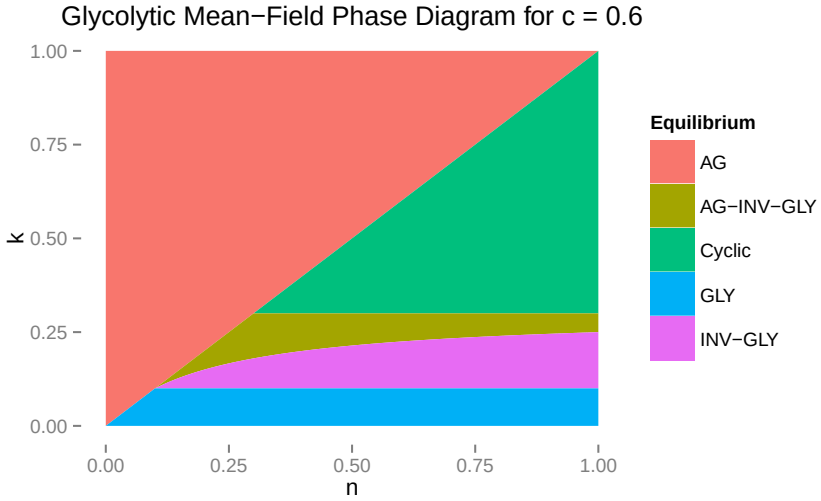
is sufficient that n is positive for AG to be able to invade this equilibrium. One important difference is that coexistence seems to be possible for a wider range of constraints. The constraint $k < cn/(1-c)$ implies that we need

$$n > \frac{1}{2c} - \frac{1}{2}$$

This yields a value of $n > 1$ for $c < \frac{1}{3}$, but the spatial model permits coexistence in this parameter regime. This is consistent with previous work on stochastic spatial models in biology and economics, especially in the prisoner's dilemma[10]. We can have a fugitive species dynamic [12]. Defectors beat cooperators and increase in frequency. Cooperators exist only in small patches. When defectors almost take over, they have lower fitness than that of the cooperator colonies, as there are no cooperators to exploit. The cooperator colonies then grow, but they are exploited by lingering defectors. This gives rise to coexistence that is impossible in a mean-field model. Durrett and Levin showed that the limiting PDE of an IPS model of this system can have a stable interior fixed point with both types, where the mean-field ODE does not [9].



(a) We have two regions with 2-species equilibria, separated by a region in which all three can coexist.



(b) For a large cost of motility, we see more exotic behavior, with potential cyclic competition

Figure 5: Cell types present at equilibrium of mean-field ODE model for indicated parameters

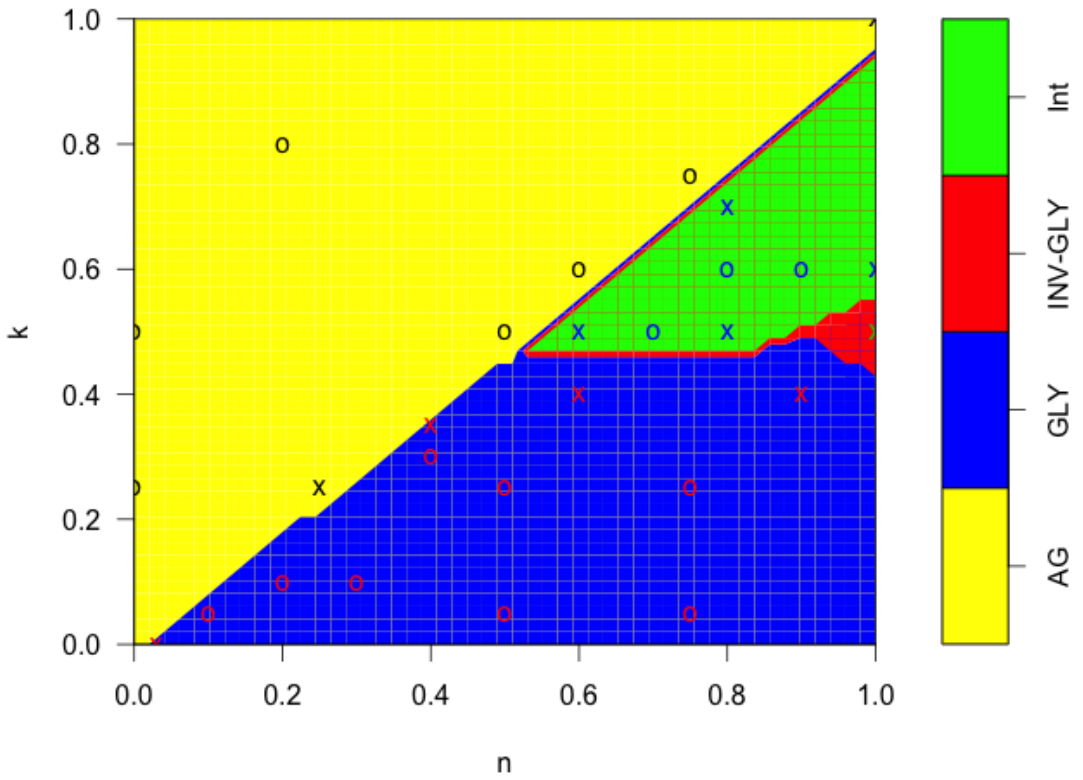


Figure 6: Cell types present at equilibrium in simulated spatial Glioblastoma game

n	k	Δ_{AG}	Δ_{INV}	Δ_{GLY}
0.8	0.4	-0.24	-0.11	0.35
0.8	0.6	-0.44	0.02	0.41
1	0.6	-0.4	-0.02	0.42
0.9	0.6	-0.39	-0.03	0.42
0.7	0.5	-0.42	0.0	0.42
0.8	0.7	-0.5	0.1	0.4
0.6	0.5	-0.62	0.02	0.6

Table 1: Consider simulations where all three cell types coexist. For $c = 0.4$ and given n, k: we compute a Δ for each cell type. This gives the difference between the observed frequencies in the spatial model and the predicted frequencies at the fixed point of the replicator equation.

We can also look at the phase diagram in terms of n and k for fixed c. There are two qualitatively different pictures for $c < \frac{1}{2}$ and $c \geq \frac{1}{2}$, shown in Figure 5. For $c < \frac{1}{2}$, we can either have an AG-INV equilibrium or an INV-GLY equilibrium, with a region of coexistence between all types in between. Spatial simulations shown in Figure 6 suggest that INV does not coexist with AG or GLY almost anywhere. Instead, AG or INV will take over, with a regime where all three coexist in between. Here, coexistence occurs in a narrower parameter regime, for higher values of k. There is a wider range in which GLY takes over. One interesting point is that the invadability condition for the AG-INV equilibrium seems to be unimportant. The transition between AG taking over and other outcomes occurs at the line $k = \frac{c}{1-c}n = \frac{2}{3}n$ in the mean-field case. In simulation, the transition in the spatial case seems to occur at $k = n$, the transition where GLY dominates AG. The region where all 3 coexist in the spatial model corresponds to a region where the fixed point in the replicator ODE does not exist, as the predicted frequency of GLY is negative. Thus, the observed equilibrium frequencies are quite different, as shown in Table 1.

Case 2: Myeloma Game

In a 2009 paper, Dingli *et al.* apply EGT to multiple myeloma evolution [8]. Multiple myeloma (MM) cells interact with the body's osteoclast (OC) and osteoblast (OB) cells, which are important in normal bone remodelling. When there are no MM cells, there is a stable equilibrium between OC and OB cells. MM cells promote the growth of OC cells by secreting osteoclast activating factors (OAF's) like interleukin 1β, RANKL, and MIP-1α. MM cells also hinder OB differentiation by secreting Dickkopf-1 [8]. OC cells produce IL-6 and osteopontin to promote MM growth. The frequency-dependent interactions of the three cell types can be treated as an evolutionary game with a payoff matrix encapsulating the above information. Dingli further assumes that interactions between cells of the same type incur no cost or benefit. We can write the following payoff matrix, which captures the result of these interactions.

$$A = \begin{array}{c} \\ OC \\ OB \\ MM \end{array} \begin{array}{c} \begin{array}{ccc} OC & OB & MM \end{array} \\ \begin{pmatrix} 0 & a & b \\ e & 0 & -d \\ c & 0 & 0 \end{pmatrix} \end{array}$$

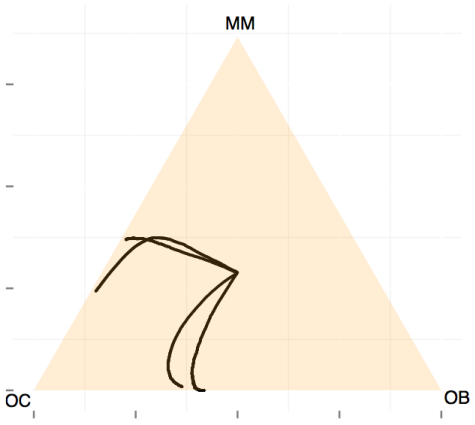
Dingli reduces the above matrix, A, to the minimal matrix, B, through the projective transformation $B_{ij} = \frac{A_{ij}}{\phi_j}$ where $\phi = \begin{pmatrix} e & a & \frac{be}{c} \end{pmatrix}$. This yields a matrix with 2 parameters.

$$B = \begin{pmatrix} 0 & 1 & \beta \\ 1 & 0 & -\delta \\ \beta & 0 & 0 \end{pmatrix}$$

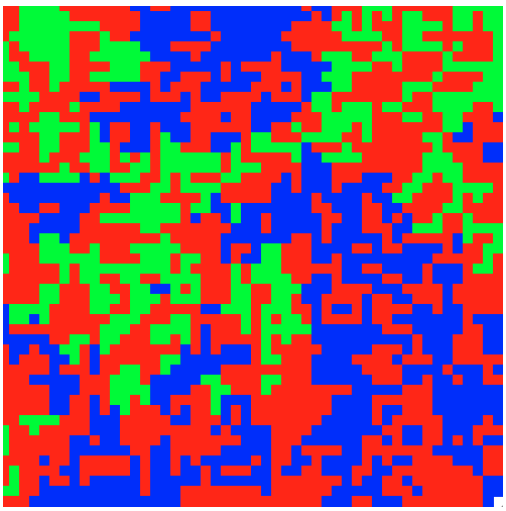
The projective transformation moves the location of the fixed point, without changing the replicator dynamics or stability [11]. The dynamics can be divided into three regimes. For

$\beta < 1$ and $\beta + \delta < 1$, an equilibrium between OC and OB is a globally attracting fixed point. For $\beta > 1$, an OC-MM equilibrium is globally attracting. Finally, for $\beta < 1$ and $\beta + \delta < 1$, we have bi-stability between an OB-OC equilibrium and an OC-MM equilibrium.

In the spatial case, things look different, mainly because of the absence of bi-stability. Instead, for each $\beta < 1$, there is a critical δ at which the equilibrium shifts from OC-OB to OC-MM, seen in Figure 9. Trajectories for both possible equilibria are shown in Figure 7a. The spatial structure shown in Figure 7b is interesting. There is essentially a competition between an OC-MM cluster and an OC-OB cluster. Due to this structure, and the fact that each 2-strategy equilibrium has symmetric payoffs, clustering is very close to 0.5.

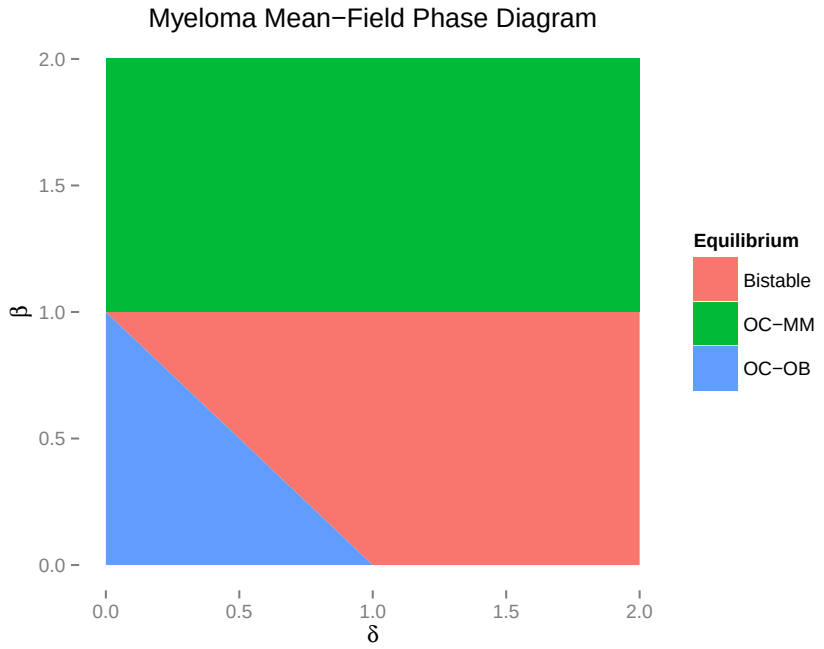


(a) Sample trajectories for each attracting basin from the spatial model. Each trajectory begins at the center and is for a different choice of parameters.

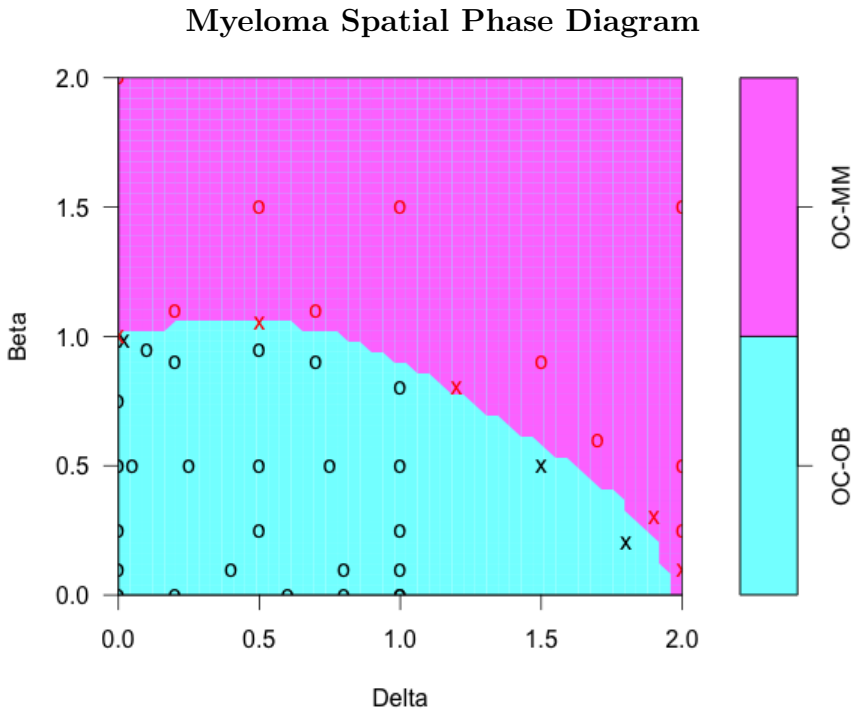


(b) Sample output from simulation before equilibrium. Red are OC, Blue are OB, and Green are MM. OC and MM cluster together, as do OC and OB. One of these two-species combos will take over.

Figure 7



(a) Equilibrium cell types in the ODE model. A region of bistability separates regions where each 2-species equilbrium is globally stable.



(b) Equilibrium cell types in spatial simulation. The region wherethere is an OC-OB equilbrium extends into the bistable region of the ODE model.

Figure 8: Cell types present at equilibrium in Myeloma game

Case 3: Toxin Game

Tomlinson and Bodmer [15]1 consider the following example, where one cell produces a toxin that harms other tumor cells – receiving a payoff.
We have three types of cells

1. Producers (P) secrete a toxin
2. Resistant (R) cells to the above toxin
3. Baseline (B) cells neither produce nor resist the toxin

We have the following interaction terms. All terms are assumed to be positive.

- z : Baseline fitness
- e : Cost of producing toxin
- g : Payoff of poisoning another cell. We have $g > e$, as the toxin would otherwise not be produced.
- h : Cost of resisting the toxin
- f : Effect of toxin on non-resistant cells

We have the payoff matrix,

$$A = \begin{array}{c} \\ P \\ R \\ B \end{array} \begin{array}{c} \begin{array}{ccc} P & R & B \end{array} \\ \begin{pmatrix} z-e-f+g & z-e & z-e+g \\ z-h & z-h & z-h \\ z-f & z & z \end{pmatrix} \end{array}$$

We add constants to each column to set the diagonals to 0. Then, we have the reduced matrix

$$A = \begin{pmatrix} 0 & h-e & g-e \\ f-k-h & 0 & -h \\ e-g & h & 0 \end{pmatrix}$$

As before, we can consider the pairwise interaction of each cell pair.

1. R vs. B
B dominates R since $h > 0$

2. P vs. B
P dominates B since $k > 0$

3. P vs. R

Here, the picture is more interesting. First, suppose that $h > e$.

If $h - e > f - g$, P dominates R.
Otherwise, we have a stable fixed point at

$$p_P^* = \frac{h-e}{f-g}$$
$$p_R^* = \frac{e+f-g-h}{f-g}$$

Now we need to check if this equilibrium is invadable by B. The fitnesses of P and R are equal at the fixed point, so we have

$$F_P = F_R = \frac{(h-e)(e+f-g-h)}{f-g}$$
$$F_B = \frac{h-e}{f-g}(e-g) + \frac{e+f-g-h}{f-g}h$$

If the fitness of B is greater near the equilibrium, the equilbrium is invadable. Note that $f - g > 0$. To meet the invadability condition, $F_B > F_P$, we need

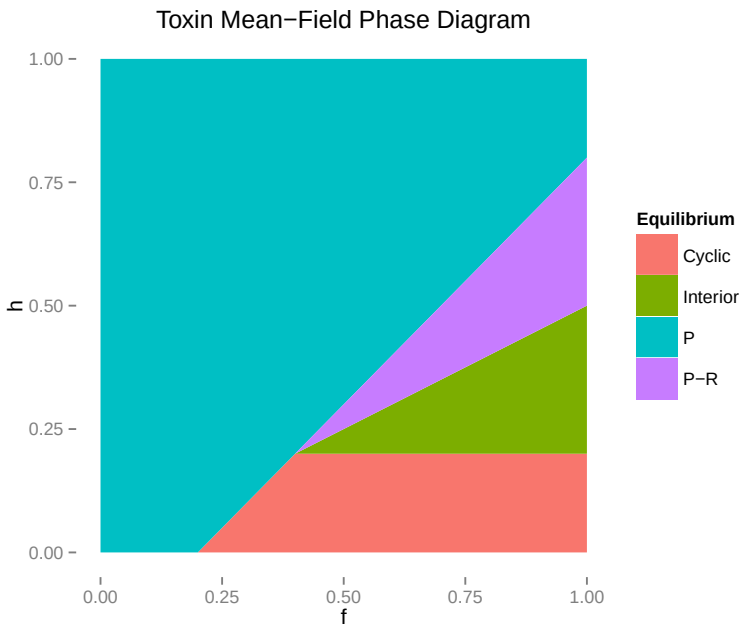
$$\frac{e}{g} > \frac{h}{f}$$

Otherwise, the equilibrium is attracting.

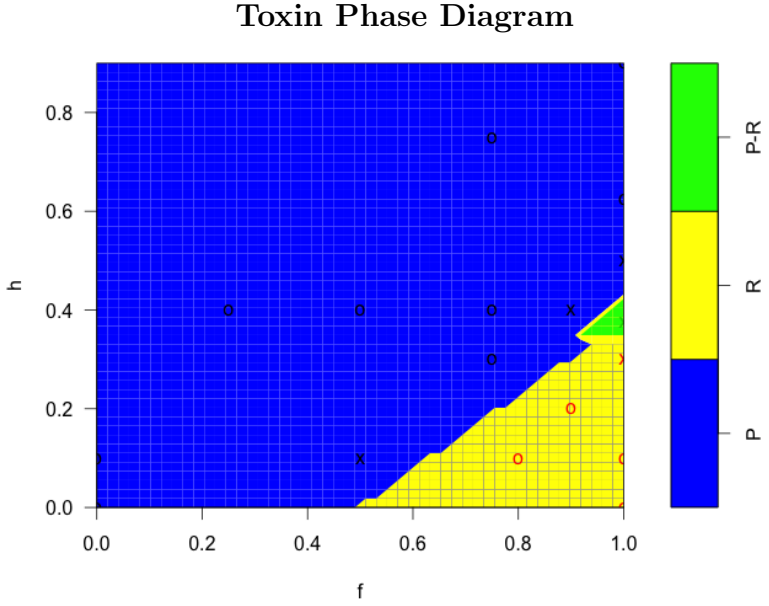
Now, consider $h < e$.

If $h - e > f - g$, we have an unstable fixed point on the P-R boundary, so P will dominate.

Otherwise, R will dominate P, leading to a cyclic competition between the three types, like rock-paper-scissors. Fixing $e = 0.2$ and $g = 0.4$, we can see most qualitatively different behaviors in the mean-field model (Figure 9a).



(a) Equilibrium cell types in mean-field model.



(b) Equilibrium cell types for spatial simulation.

Figure 9: Cell types present at equilibrium in Toxin game for $e = 0.2$ and $g = 0.4$.

In this case, simulations show much less varied behavior than the mean-field model would suggest. There is a transition between regimes where P or R takes over. Three strategies do not coexist anywhere, and there is a slim region where P and R can coexist.

Conclusion

We have introduced a stochastic spatial model for a generic evolutionary game and applied it to the interplay of phenotypes in tumor growth. The mean-field approximation agrees with many of the features of the interacting particle system, including certain critical parameters for which the coexistence changes. The spatial structure facilitated coexistence in the Glioblastoma game, making it possible for a wider range of parameters. On the other hand, structure made coexistence impossible in the Toxin game. In bi-stable systems like the Myeloma game, we can observe a phase transition that depends on the parameters, in lieu of actual bi-stability. In the Glioblastoma and Toxin games, coexistence between two cell types was more uncommon in spatial simulation.

These differences are somewhat expected. Results that derived a limiting PDE assumed weak selection, which was not used in simulation. In addition, the limiting PDE can in general have an altered game matrix.

Tumors are known to exhibit varying degrees of heterogeneity, with multiple cell types in complex spatial arrangements. Spatial considerations can change the qualitative features of an evolutionary game, explaining this coexistence better than a simple mean-field approach. A game-theoretic approach could offer clinical insights into the relationship between cancerous phenotypes. New methods of treatment could attempt to change the parameters of this evolutionary game, enabling the tumor to select malignant phenotypes out on its own.

Bibliography

[1] Robert Axelrod, David E. Axelrod, and Kenneth J. Pienta. Evolution of cooperation among tumor cells. *Proceedings of the National Academy of Sciences*, 103(36):13474–13479, September 2006.

[2] D. Basanta, J.G. Scott, R. Rockne, K.R. Swanson, and A.R.A. Anderson. The role of idh1 mutated tumour cells in secondary glioblastomas: an evolutionary game theoretical view. *Physical Biology*, 8:015016, 2011.

[3] D. Basanta, M. Simon, H. Hatzikirou, and A. Deutsch. Evolutionary game theory elucidates the role of glycolysis in glioma progression and invasion. *Cell Proliferation*, 41(6):980–987, 2008.

[4] Kristin P Bennett and Colin Campbell. Support vector machines: hype or hallelujah? *ACM SIGKDD Explorations Newsletter*, 2(2):1–13, 2000.

[5] J Theodore Cox, Richard Durrett, and Edwin Perkins. Voter model perturbations and reaction diffusion equations. *arXiv preprint arXiv:1103.1676*, 2011.

[6] J Theodore Cox and David Griffeath. Diffusive clustering in the two dimensional voter model. *The Annals of Probability*, pages 347–370, 1986.

[7] Evgenia Dimitriadou, Kurt Hornik, Friedrich Leisch, David Meyer, and Andreas Weingessel. e1071: Misc functions of the department of statistics (e1071), tu wien. r package version 1.5-27, 2011.

[8] D. Dingli, FACC Chulab, F.C. Santos, S. van Sedgebroeck, and J.M. Pacheco. Cancer phenotype as the outcome of an evolutionary game between normal and malignant cells. *British Journal of Cancer*, 101:1130–1136, 2009.

[9] R. Durrett and S. Levin. The importance of being discrete (and spatial). *Theoretical Population Biology*, 46(3):363 – 394, 1994.

[10] Rick Durrett. Coexistence in stochastic spatial models. *Annals of Applied Probability*, 22(3):477–496, 2009.

[11] Josef Hofbauer and Karl Sigmund. *Evolutionary Games and Population Dynamics*. Cambridge University Press, Cambridge, 1998.

[12] Carl Barton Huffaker. Experimental studies on predation: dispersion factors and predator-prey oscillations. *Hilgardia*, 27:343–383, 1958.

[13] J.M. Smith and G.R. Price. The logic of animal conflict. *Nature*, 246:15–18, November 1973.

[14] I.P.M Tomlinson. Game-theory models of interactions between tumour cells. *European Journal of Cancer*, 33:1495–1500, 1997.

[15] I.P.M Tomlinson and W.F. Bodmer. Modeling the interactions between tumor cells. *British Journal of Cancer*, 75:157–160, 1997.