A STOCHASTIC SPATIAL MODEL FOR TUMOR GROWTH

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1. 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 select out 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, 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 the analysis of multiple myelomas proposed by Dingli [**?**], Basanta's work on glioma progression [**?**], and the robust Hawk-Dove-Retaliator game [**?**] . Our model agrees with Basanta's in that we should have coexistence between the three tumor phenotypes. Dingli's tumor population and the HDR game exhibit 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.

2. Introduction

The theory of evolutionary games was introduced to study ecological competitions [**?**]. However 15 years ago, Tomlinson suggested that it could be used to study interactions between tumour cells [**?**, **?**]. More recently, Axelrod, Axelrod, and Pienta [**?**] have explained how the cooperation of cancer and normal cells can bring on mutually beneficial events such as angiogenesis (the development of blood vessels), Dingli et al (2009) have studied the interactions between osteoclast, osteoblasts, and tumor cells in multiple myeloma, and in a series of papers Basanta and coauthors have studied the role of glycolysis in glioma progression and invasion [**?**, **?**]. All of these analyses assume that the population of cells is homogeneously mixing while in reality, each cells compete only with those nearby. Here we will investigate how predictions change when the space is take into account.

3. Materials and Methods

3.1. **Game Theoretic Model.** First, consider a traditional EGT approach to the modeling. 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,

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

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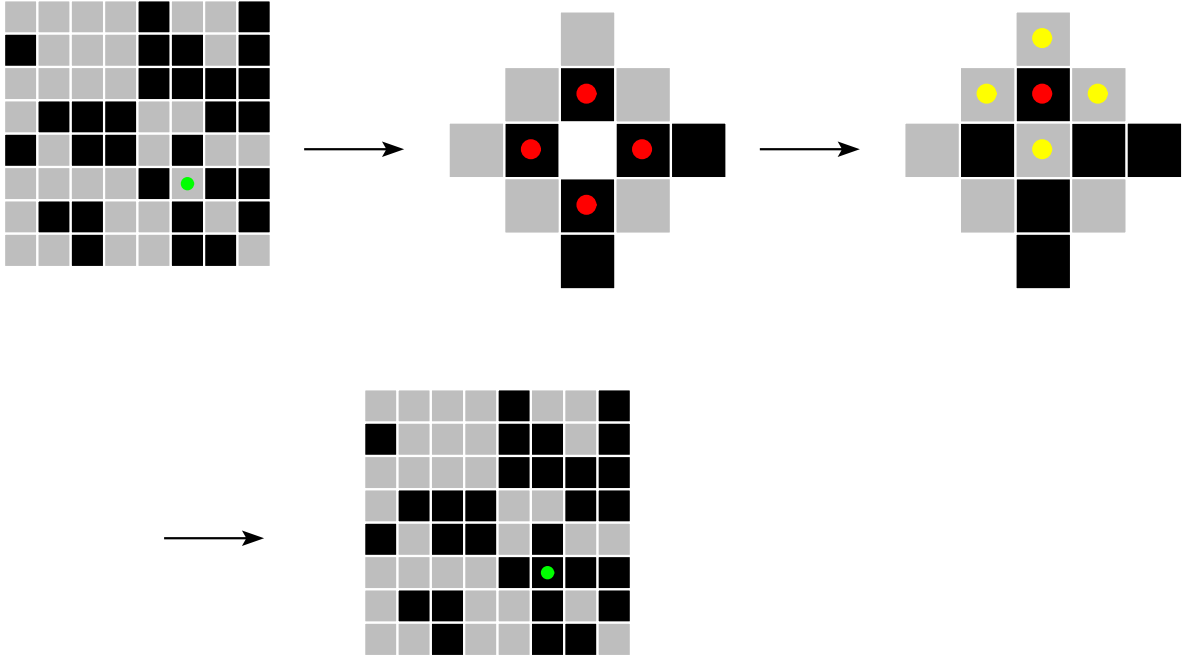
FIGURE 1. An example of a Moran update. The cell marked green is randomly selected to die. The fitness of each red neighbor is computed using its yellow neighbors (including the dead cell). Finally, the update is made.

can write a payoff matrix, U, that captures the results of this interaction. Then $W_i(\vec{x}) = \vec{\mathbf{e}}_i \cdot U\vec{x}$ and $\overline{W} = \vec{x}^\top U\vec{x}$.

3.2. **Spatial Refinement.** According to this model, the fitness of a given individual depends upon the state of the population as a whole. However, this fitness should only depend upon interactions with nearby neighbors. If the population is homogeneously mixing, the composition of the neighbors will look like the state, $\vec{x}$. 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 [**?**].

We introduce a spatial stochastic model to study differences in the spatial case. 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, consisting of the 2-4 cells with which it shares an edge. 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 at random. Each neighbor has probability of being chosen proportional to its fitness.

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

FIGURE 2. An example of a possible initial condition. Red, Green, and Blue represent different cell types. In spatial games, the arrangement and proportion of different cell types is generally unimportant in determining the outcome.
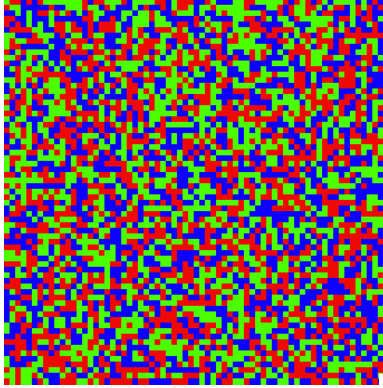
eliminate a cell type, in which case the predicted dynamics could be far off. As long as this is satisfied, the initial conditions should not matter. This is true of stochastic models as discussed in Durrett and Levin [**?**], which have infinite size. The dynamics of interest tend to take place at a 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. 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 cell groups would inevitably clump until one or the other was edged out by chance.

3.3. **Analytic Results in Two Dimensions.** 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, $\mathbb{Z}_2^d$. 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. Individuals are randomly selected, and there is a stochastic rule for updating the preference. The interaction between an individual and its neighbors is given by a symmetric probability kernel $p(x)$ on $\mathbb{Z}^d$.

The results hold 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. It can be shown that introducing space is equivalent to a transformation of the game matrix and replacing the replicator ODE shown earlier with a related PDE.

4. RESULTS

4.1. **Case 1: Glioma Progression.** Basanta *et al.* 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. In their model, there are three tumor phenotypes: autonomous growth (AG), invasive (INV),

and glycolytic metabolism (GLY). Glycolytic metabolism is less efficient than aerobic respiration, and cells generally adopt it when a tumor is insufficiently oxygenated. Let k represent the fitness cost of switching to glycolytic respiration. GLY cells tend to acidify the pH of the surrounding microenvironment, granting a payoff n to themselves, as well as a cost n to non-GLY cells. Finally, INV cells are expected to flee upon encountering another type. They should obtain the base payoff minus the cost of motility, c. Thus, we have the following payoff table.

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

As shown in Hofbauer and Sigmund, adding constants to the columns does not change the replicator dynamics. Thus, we can always have zeroes along the diagonal, adding appropriate constants.

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

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 reduced matrix

$$
B = \begin{pmatrix} 0 & a \\ b & 0 \end{pmatrix}
$$

If $b < 0$ and $a > 0$, Strategy 1 dominates Strategy 2. If $b > 0$ and $a < 0$, 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

$$
a(1 - p) = bp
$$

$$
\bar{p} = \frac{a}{a + b}
$$

We need a and b 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 so that $p > \bar{p}$. The fitness of the first type will be given by $a(1 - p)$ and that of the second will be bp. The equilibrium is stable iff $a, b > 0$, as otherwise we would have $a(1 - p)$ ¿ bp, and the first type would further increase in frequency.

1. AG vs INV

$$
B = \left(\begin{array}{cc}
0 & \frac{c}{2} \\
\frac{1}{2} - c & 0
\end{array} \right)
$$

AG dominates INV for $c \geq \frac{1}{2}$. Otherwise, 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

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

If $k > \frac{c}{2}$ and $k > c - \frac{1}{2}$, INV dominates GLY. Since $c < 1$, $k > \frac{c}{2}$ is sufficient. If $k < c - \frac{1}{2}$, GLY dominates INV. Otherwise, we have a fixed point.

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

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

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

This point is stable for $k < \frac{c}{2}$ and $k > c - \frac{1}{2}$. We have already assumed these in getting this point, so it is stable whenever it exists.

3. AG vs. GLY

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

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

In his 2008 paper, Basanta considers the replicator dynamics for this system, without considering spatial effects. He computes the location of an internal fixed point and gives constraints for its existence. As shown by Hofbauer and Sigmund, if there is an evolutionarily stable internal fixed point, then it is globally stable. We can either check if the third type can invade the two type equilibria computed above, or just find a fixed point and compute its stability directly.

In order to characterize the fixed point, we compute it from the replicator equation, linearize around it, and consider the eigenvalues of the Jacobian. 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

$$p^* = \begin{pmatrix} \dfrac{2nk + k - nc - kc}{2n^2} \\ \dfrac{n - k}{n} \\ \dfrac{kc - k + cn}{2n^2} \end{pmatrix}$$

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

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

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 [?]. The existence of such a point in the mean-field ODE suggests that coexistence is possible in the stochastic spatial model [?]. Thus, we expect AG, INV, and GLY to coexist for some parameter regime in our model.

Using this information, we have the replicator behavior in different parameter regimes.
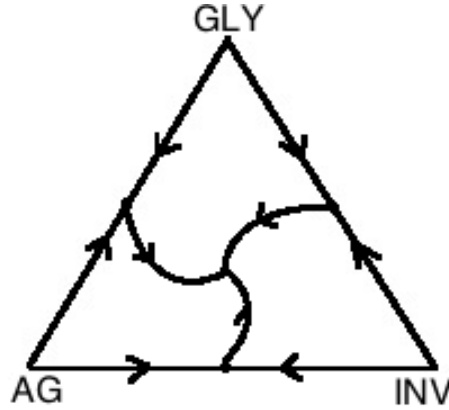
(A) Phase Portrait has attracting fixed point, implying coexistence

4.2. **Case 2: Multiple Myeloma.** In a 2009 paper, Dingli applies EGT to multiple myeloma evolution [?]. 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 [?]. 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.

$$A = \begin{array}{c} \\ OC \\ OB \\ MM \end{array} \begin{array}{c} OC \quad OB \quad MM \end{array} \\ \left(\begin{array}{ccc} 0 & a & b \\ e & 0 & -d \\ c & 0 & 0 \end{array} \right)$$

Dingli reduces the above matrix, A, to the minimal matrix, B, through the projective transformation $B_{ij} = \frac{A_{ij}}{\phi_j}$ where $\phi = \left(e \quad a \quad \frac{be}{c} \right)$. This yields the minimal matrix $B =$
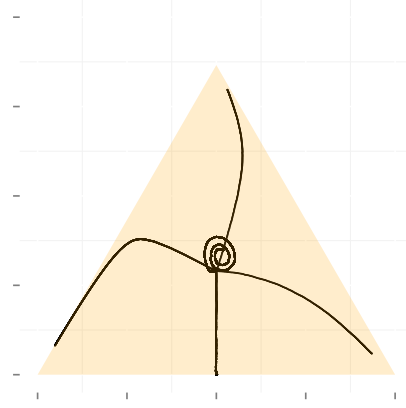
Phase Diagram for $k = 0.5$
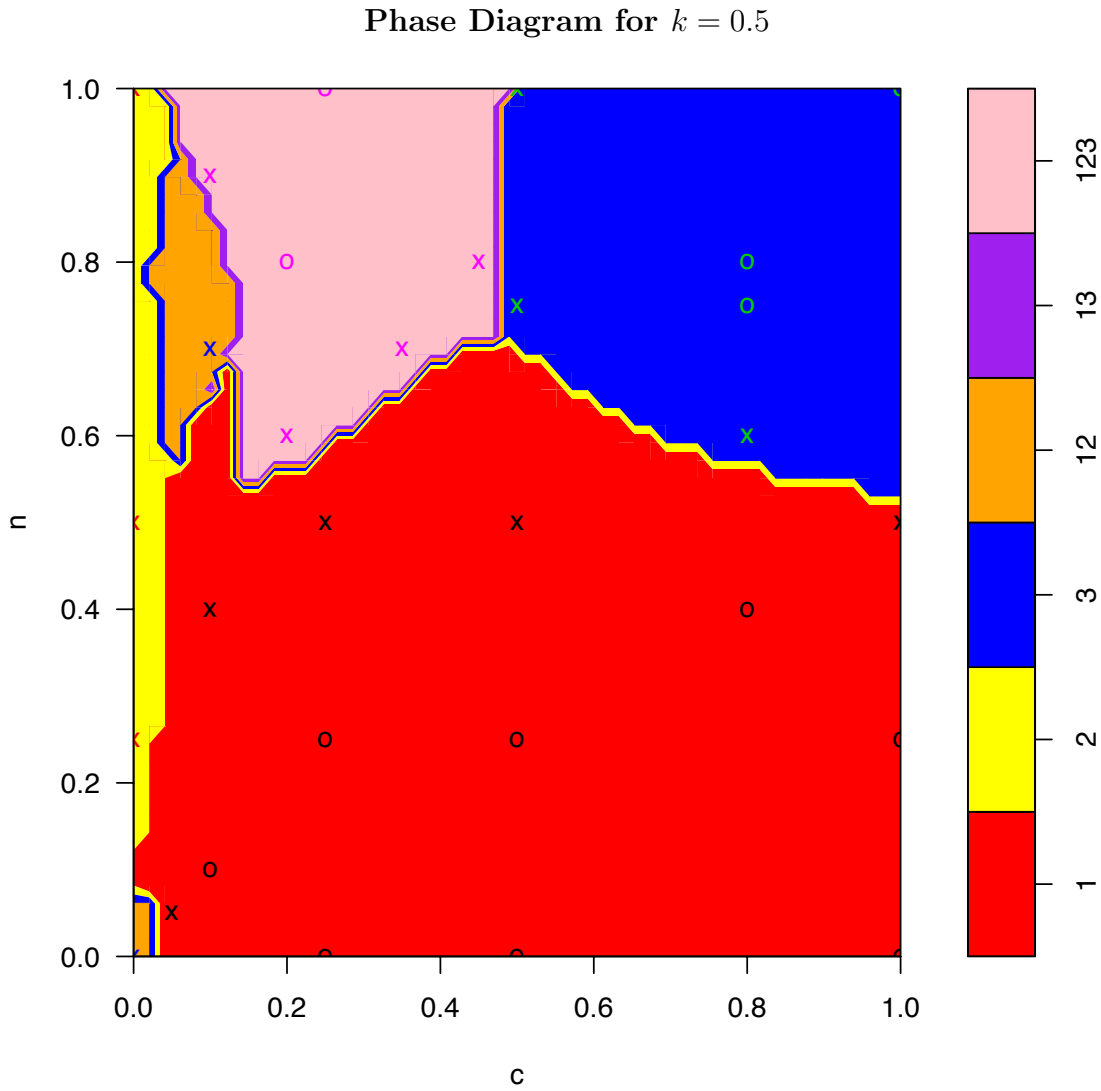
FIGURE 4. Parameter regimes in spatial Glioblastoma game for $k = 0.5$. The numbers 1, 2, and 3 correspond to AG, INV, and GLY respectively. Multiple numbers indicate coexistence
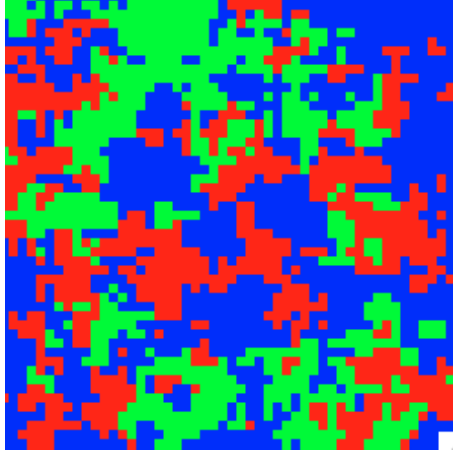
(A) Sample Output. Cells of type AG are red, INV green and GLY blue.

(B) Some sample trajectories plotted on the simplex

$$\begin{pmatrix} 0 & 1 & \beta \\ 1 & 0 & -\delta \\ \beta & 0 & 0 \end{pmatrix}.$$ The projective transformation moves any internal fixed point into the barycenter of the simplex without changing the replicator dynamics or stability [**?**]. 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 bistability between an OB-OC equilibrium and an OC-MM equilibrium.

In the spatial case, things look different.

5. Conclusion

We have created a stochastic spatial model for a generic evolutionary game and applied it to the interplay of phenotypes in tumor growth. Our model shows that explicit spatial considerations can change the qualitative behavior of an evolutionary game. On the other hand, if there is bistability, spatial considerations show a transition between stable fixed points.

(A) Sample Phase Portrait for $\beta < 1 and \beta + \delta < 1$
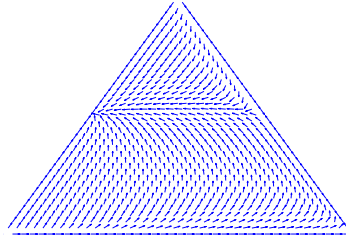
(B) Sample Phase Portrait for $\beta < 1 and \beta + \delta > 1$
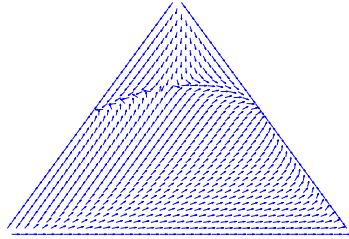
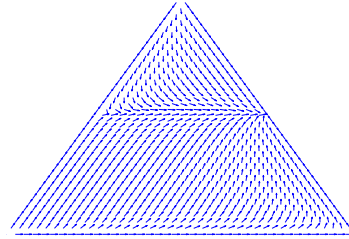(C) Sample Phase Portrait for $\beta > 1$

FIGURE 7. Parameter regimes in spatial Myeloma Game. The numbers 1, 2, and 3 correspond to OC, OB, and MM respectively. Two numbers together indicate coexistence