Chemical mediated competition

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September 6, 2013

Abstract

Inspired by the use of hybrid cellular automata in modeling cancer, we introduce a generalization of evolutionary games in which cells produce and absorb chemicals, and the chemical concentrations dictate the death rates of cells and their fitnesses. Our long term aim is to understand how the details of the interactions in a system with n species and m chemicals translate into the qualitative behavior of the system. Here, we study two simple 2×2 games with two chemicals and revisit the two and three species versions of the one chemical colicin system studied earlier by Durrett and Levin [27]. We find that the behavior of our new spatial model can be predicted from that of the mean field differential equation, but it can have different behavior from lattices models in which sites interact with only their nearest neighbors.

1 Introduction

Game theory was invented by John von Neumann and Oscar Morgenstern [1] to study strategic and economic decisions of humans. Maynard Smith and Price [2], see also [3], introduced the concept into ecology in order to explain why conflicts over territory between male animals of the same species are usually of the "limited war" type and do not cause serious damage. Axelrod and Hamilton [4] studied the evolution of cooperation by investigating the Prisoner's dilemma game. Since that time, evolutionary game theory has been used to study many biological problems including host-parasite interactions, ecosystems, animal behavior, social evolution, and human language. For surveys see [5]–[8].

All of the references in the last paragraph study evolutionary games in homogeneously mixing populations, in which case the frequencies (in continuous time) follow the replicator equation. One can argue that long distance connections in human social network imply that spatial effects can be ignored, but this is not true for systems in ecology and cancer. Nowak and May [9, 10] were the first to suggest that spatial structure enhanced the persistence of cooperators in Prisoner's dilemma. Their competition was deterministic and took place on

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the square lattice, but others have considered stochastic systems and competitions taking place on graphs or in finite populations. In the references we list a representative sample of work of this type, [11]–[15]. Dozens of references can be found in [16] and [17].

There have been a number of studies of evolutionary games in spatially distributed populations. However, up to now spatial models have been constructed by declaring that game interactions occur only between a site y chosen at random and a set of neighbors x. If the site y is occupied no change occurs. Here, we will take a different approach: cells produce and absorb chemicals, and the local chemical concentrations dictate the death rates of cells and their fitness. This formulation is inspired by hybrid cellular automata models of cancer. Some examples of this type of modeling can be found in [18]–[24]. Hundreds more can be found in the book by Cristini and Lowengrub [25]. These papers, which study highly detailed models numerically, provide another motivation for this study: we will study simplified systems in order to understand how the details of the interaction translate into the qualitative behavior of the model.

1.1 Motivating example

To explain what we have in mind, we will consider an example first studied by Tomlinson [26]. In this system cells use one of three strategies.

1. Produce a toxic substance.
2. Be resistant to the toxin, but not produce it.
3. Wild type cells that are neither producers nor resistant.

Based on the verbal description, Tomlinson write down the following game matrix.

$$\begin{array}{cccc} & 1 & 2 & 3 \\ 1 & z-e-f+g & z-e & z-e+g \\ 2 & z-h & z-h & z-h \\ 3 & z-f & z & z \end{array} \tag{1}$$

Here G_{ij} is the payoff to a player who plays strategy i against an opponent playing strategy j. Taking the rows in reverse order, z is the baseline fitness while f is the cost to a sensitive cell due to the presence of the toxin. The cost of resistance to the toxin is h. In top row e is the cost of producing the toxin, and g is advantage to a producer when it subjects a sensitive cell.

It is interesting to note that in the same year [26] was published, Durrett and Levin [27] used a spatial model to model the competition two strains of *E. coli*, whose behaviors correspond to strategies 1 and 3 above: one produces colicin to which the other strain is sensitive. In their model, there are also empty cells (denoted by 0). Thinking of a petri dish, their system takes place on the two dimensional lattice. Individuals of type $i > 0$ give birth at rate β_i with their offspring sent to a site chosen at random from the four nearest neighbors of x Each species dies at rate δ_i due to natural causes, while type 3's die at an additional rate γ times the fraction of neighbors of type 1 due to the effect of colicin.

The first step in understanding the behavior of the system is to consider the mean-field version, which takes place on finite square with the neighborhood of each site being the

entire grid. In this case if u_i is the frequency of sites in state i then in the limit as the size of the system goes to ∞ one arrives at differential equation

$$\frac{du_1}{dt} = \beta_1 u_1 u_0 - \delta_1 u_1$$
$$\frac{du_3}{dt} = \beta_3 u_3 u_0 - (\delta_3 + \gamma u_1) u_3$$

In any equilibrium with $u_1, u_3 > 0$ we must have

$$u_0 = \frac{\delta_1}{\beta_1} = \frac{\delta_3 + \gamma u_1}{\beta_3} \tag{2}$$

If we assume $\delta_i < \beta_i$ so that the individual species survive, and

$$\frac{\delta_3}{\beta_3} < \frac{\delta_1}{\beta_1} < \frac{\delta_3 + \gamma}{\beta_3}$$

then we can choose $u_1 \in (0,1)$ so that the second inequality holds and use the first to define u_0. Thus the dynamical system for the evolution of (u_1, u_3) has an interior fixed point in addition to the two boundary equilibria at $(1-\delta_1/\beta,0)$ and $(0, 1-\delta_3/\beta_3)$. Linearizing around the fixed points shows that the interior one is a saddle point while those on the boundary are stable.

Given the properties of the ordinary differential equation (ODE), it is hard to imagine how a colicin producer could arise by mutation in a sensitive population, since in that case their initial density will be small. However, as [27] showed, this can occur in a spatial model. This is consistent with the philosophy of [11]: when the ODE $du_i/dt = \phi_i(u)$ is bistable, the winner in the spatial model is more accurately predicted by the behavior of the partial differential equation (PDE) $du_i/dt = \Delta u_i + \phi_i(u)$.

The situation becomes more interesting when we introduce a type that uses Tomlinson's strategy 2,

$$\frac{du_1}{dt} = \beta_1 u_1 u_0 - \delta_1 u_1$$
$$\frac{du_2}{dt} = \beta_2 u_2 u_0 - \delta_2 u_2$$
$$\frac{du_3}{dt} = \beta_3 u_3 u_0 - (\delta_3 + \gamma u_1) u_3$$

Based on the biology, it is natural to assume

$$\frac{\delta_1}{\beta_1} > \frac{\delta_2}{\beta_2} > \frac{\delta_3}{\beta_3}$$

That is, a cell pays a cost for colicin production or resistance which lowers its ability to compete. These inequalities imply that 3's outcompete 2's and 2's outcompete 1's. If γ is large enough, 1's outcompete 3's and the three species will have a rock-paper-scissors relationship.

If there is an equilibrium in which all $u_i > 0$, we must have

$$u_0 = \frac{\delta_1}{\beta_1} = \frac{\delta_2}{\beta_2} = \frac{\delta_3 + \gamma u_1}{\beta_3}$$

which is impossible. In contrast, as shown in [27], the three species coexist in the spatial model. It is intersting to note that after the three species coexistence was predicted it was found in laboratory experiments, see [28], [29].

In **Tomlinson' model**, if we assume that the system is homogeneously mixing then the densities follow the replicator equation ([5], Section 7.1.)

$$\frac{du_i}{dt} = u_i(F_i - \bar{F})$$

where $F_i = \sum_j G_{i,j}u_j$ is the average fitness of the ith strategy and $\bar{F} = \sum_j u_j F_j$ is the average fitness. As computed in [26], there is an interior equilibrium if

$$e < g \qquad h < f \qquad \frac{e}{g} > \frac{h}{f} \tag{3}$$

and its location is

$$\bar{u} = (h/f, 1 - e/g, e/g - h/f). \tag{4}$$

Strategy 3 always dominates 2 (in their two strategy subgame). If we make the natural assumption $g > e$ (the benefit from toxin production outweighs the cost) then strategy 1 dominates 3. Finally, if we assume

$$h < e \quad \text{and} \quad h < e - g + f \tag{5}$$

then 2 dominates 1 and we again have a cyclic relationship between competitors. From the form of the replicator equation it is easy to see that the dynamics are not changed by adding a constant to each column in the game matrix G, so we can make the diagonal entries 0, When we do this, G has the form of generalized rock paper scissors game (here $a_i, b_i > 0$)

$$\begin{pmatrix} 0 & h-e & g-e \\ e-g+f-h & 0 & -h \\ e-g & h & 0 \end{pmatrix} = \begin{pmatrix} 0 & -a_2 & b_3 \\ b_1 & 0 & -a_3 \\ -a_1 & b_2 & 0 \end{pmatrix}$$

The initial assumptions $h > 0$ and $g > e$, with the conditions in (5) imply that our matrix has the desired sign pattern. In this case, Theorem 7.7.2 in [5], describes the asymptotic behavior

Theorem 1. *Let* $\Gamma = b_1b_2b_3 - a_1a_2a_3$.

- *If* $\Gamma = 0$ *then there is a one parameter family of periodic orbits.*
- *If* $\Gamma < 0$*, trajectories spiral out toward the boundary.*
- *If* $\Gamma > 0$ *then there is a globally attracting fixed point for* H.

Tomlinson [26] gives simulation result for a number of examples in his paper. In one set $g = 0.2$, $e = 0.15$, and $h = 0.1$ while f varies. Here $g > e > h$. We will have

$$h < e - g + f \quad \text{if} \quad 0.1 < 0.15 - 0.2 + f \quad \text{or} \quad f > 0.15$$

When this holds we have $f > h$ and $e/g = 3/4 > 2/3 > h/f$. His table reports the following results about the limiting behavior:

f	u_1	u_2	u_3
0.25	0.400	0.250	0.350
0.24	0.417	0.250	0.333
0.23	0.435	0.250	0.315
0.22	0.457	0.250	0.293
0.21	1	0	0

It is not hard to check that the values given for u_1, u_2 and u_3 in the first four rows correspond to the fixed point in (4), e.g., $\bar{u}_2 = 1 - e/g = 0.25$. To check the conditions of Theorem 1, we compute

$$\begin{aligned} \Gamma = b_1b_2b_3 - a_1a_2a_3 &= (e + f - g - h)h(g - e) - (g - e)(e - h)h \\ &= (g - e)h(f - g) \end{aligned}$$

Since $g > e$ and $h > 0$, the interior fixed point is attracting if $f > g$, i.e., $f > 0.2$. The discrepancy in the last line is not surprising. When $f = 0.2$ the interior fixed point is surrounded by a one parameter family of periodic orbits, so when $f \approx 0.2$ numerical solution of the differential equation becomes delicate.

2 Our model

In the two models considered above, only the nearest neighbors of a colicin producing cell are affected, while in reality the chemical will diffuse. With this in mind we reformulate the model. As before, each site of the lattice is occupied by a cell that is in state $\xi(x) \in \{1, 2, \ldots m\}$. In addition, there are ℓ chemical species with concentration given by R_i, which are modeled by reaction diffusion partial differential equations:

$$\frac{dR_i}{dt} = D_i \Delta R_i + \lambda_i - \nu_i R_i + \mu_{i,\xi(x)} - d_{i,\xi(x)} R_i. \tag{6}$$

Here D_i is the diffusion constant for chemical i, λ_i is the rate at which it enters the system, ν_i is the rate at which it breaks down, $\mu_{i,k}$ is the rate at which it is produced by cells of type k, and $d_{i,k}$ is the rate it is consumed by cells of type k. To avoid boundary effects, we employ periodic boundary conditions on the PDE and the particle system model we will soon describe.

In the colicin example above, there is only one chemical which is produced by type 1's and affects type 3's. This is just one of many possibilities. In Gerlee and Anderson's model [22] for the emergence of the glycolytic phenotype, there are three chemicals: glucose, oxygen,

and hydrogen ion concentration. In their work, the PDEs are more biologically accurate and the behavior of the cells is dictated by a complicated network. However, as mentioned earlier, one of our motivations is to study simplified hybrid cellular automata in order to find general results to predict their qualitative behavior.

The sites in our model follow evolutionary game dynamics. In the terminology used in [15] (and many other works) these are generalized death-birth dynamics. The word generalized refers to the fact that death occurs at a rate that depends on the chemical concentrations:

$$\delta_k = \eta_k + \sum_i t_{k,i} R_i, \tag{7}$$

where η_k is a constant and $t_{k,i} \geq 0$ is a measure of the toxicity of chemical i to species k. When a cell of type k dies it is replaced by a neighbor cell that is chosen with probability proportional to its fitness:

$$f_k = \gamma_k + \sum_i b_{k,i} R_i, \tag{8}$$

Note that in contrast to Tomlinson's game dynamics, the fitness of a cell depends on the chemical concentrations rather than on the types of their neighbors.

A common first step in understanding the workings of a spatial model is to see what happens when the spatial aspect is eliminated. Taking the diffusion rates $D_i \to \infty$ in equation (6), and letting x_j be the fraction of cells of type j, the concentration of chemical i evolves according to the ODE:

$$\frac{dR_i}{dt} = \lambda_i - \nu_i R_i + \sum_m (\mu_{i,j} - R_i d_{i,j}) x_j, \tag{9}$$

In equilibrium $dR_i/dt = 0$ so we have

$$R_i = \frac{\lambda_i + \sum_j \mu_{i,j} x_j}{\nu_i + \sum_j d_{i,j} x_j}. \tag{10}$$

If we now ignore correlations between neighbors, then we have the following ODE for the frequencies x_j,

$$\begin{aligned} \frac{dx_j}{dt} &= -\delta_j x_j \sum_{k \neq j} \frac{x_k f_k}{\sum_n x_n f_n} + \sum_{k \neq j} \delta_k x_k \frac{x_j f_j}{\sum_n x_n f_n}, \\ &= \sum_{k \neq j} \frac{x_k x_j (\delta_k f_j - \delta_j f_k)}{\sum_n x_n f_n}. \end{aligned} \tag{11}$$

When $\delta_j \equiv 1$ this looks like the replicator equation but the fitnesses are not linear in the frequencies

$$f_k = \gamma_k + \sum_i c_{k,i} R_i = \gamma_k + \sum_i c_{k,i} \frac{\lambda_i + \sum_j \mu_{i,j} x_j}{\nu_i + \sum_j d_{i,j} x_j}$$

Generalizing from the replicator equation, we have equilibrium if the ratio f_j/δ_j is constant. In general this is a system of cubic equations compared to the linear equations that come from the replicator equation. However, as the reader will see in the next two sections, the equations can be solved in some cases and accurately predict the behavior of the spatial model.

3 Implementation

To numerically solve the initial boundary value problems in (6) describing the chemical dynamics we use a two dimensional square lattice with spacing, $h << 1$, between neighboring lattice nodes. For the temporal discretization of (6) we employ the modified Euler [30] method, which is of second order in time and can be written as an explicit Runge-Kutta. A standard second order finite difference scheme is also utilized for the spatial discretization of the Laplacian operator. The resulting numerical scheme does not require the inversion of a matrix at each time iteration hence it is fast. We have used $h = 0.01$ and $\tau = 0.001$ as the stable time step for the PDE updates.

In order to simulate the continuous time Markov chain model describing the particle system dynamics, the corresponding discrete time approximation is used. Sites die with probability τ_s times their death rate and when they die are replaced by a neighbor proportional to its fitness. When the fitnesses are computed we use the values of the neighbors at the previous time step. For this study we have used $\tau_s = 0.01$, that is we update the particle system once for every ten PDE updates. This is done to reduce the amount of work, while keeping the number of collisions (i.e., situations in which a site and its neighbor are both updated) relatively small, thus approximating better the behavior of the continuous time process.

4 Simple two species examples

We begin with two examples that illustrate the possibilities of coexistence and competitive exclusion in the case of two species and two chemicals. In these examples, neither species produces chemicals so $\mu_{i,k} = 0$ and the toxicities $t_{k,i} \equiv 0$, so the death rates $\delta_k = \eta_k$ are frequency independent. In addition, we assume that the death rates η_k and the constants γ_k in the fitness function do not depend on k, and the decay rates $\nu_i = 0$. With these conditions, the mean-field condition for equilibrium is $f_1 = f_2$ and we can drop the γ_k's to write

$$\begin{aligned}&\frac{c_{1,1}\lambda_1}{d_{1,1}x + d_{1,2}(1-x)} + \frac{c_{1,2}\lambda_2}{d_{2,1}x + d_{2,2}(1-x)}\\ &= \frac{c_{2,1}\lambda_1}{d_{1,1}x + d_{1,2}(1-x)} + \frac{c_{2,2}\lambda_2}{d_{2,1}x + d_{2,2}(1-x)}\end{aligned}$$

In this case multiplying each side by the product of the denominators gives a linear equation:

$$\alpha_{1,1}x + \alpha_{1,2}(1-x) = \alpha_{2,1}x + \alpha_{2,2}(1-x) \tag{12}$$

where the constants

$$\alpha_{i,j} = c_{i,1}\lambda_1 d_{2,j} + c_{i,2}\lambda_2 d_{1,j}$$

If when we set $x = 0$ in the denominator, we have

$$\frac{c_{1,1}\lambda_1}{d_{1,2}} + \frac{c_{1,2}\lambda_2}{d_{2,2}} > \frac{c_{2,1}\lambda_1}{d_{1,2}} + \frac{c_{2,2}\lambda_2}{d_{2,2}} \tag{13}$$

then 1 will be more fit than 2 when the frequency of 1's is small, so the frequency of 1's will increase. If in addition

$$\frac{c_{1,1}\lambda_1}{d_{1,1}} + \frac{c_{1,2}\lambda_2}{d_{2,1}} < \frac{c_{2,1}\lambda_1}{d_{1,1}} + \frac{c_{2,2}\lambda_2}{d_{2,1}} \tag{14}$$

then 2's will be more fit than 1's when the frequency of 1's is close to 1, and the fitness of 1's will decrease. When both (13) and (14) hold, (12) will have a solution in $(0, 1)$ that will be an attracting fixed point. If we reverse the inequalities in (13) and (14) then there is an unstable fixed point in (0,1). We will now consider an example of each situation.

4.1 Two species example with coexistence

In this example, we take the diffusion constant $D_i = 0.003$, which is inspired by the diffusion constant for oxygen in the model of [22]. Both chemicals enter the system at rate $\lambda_i = 0.1$, neither is produced $\mu_{i,j} \equiv 0$, and the decay rates are $\nu_i = 0$. The toxicity coefficients $t_{k,i} = 0$ and the death rates $\eta_k = 1$. The consumption rates $d_{i,k}$ and the coefficients $c_{k,i}$ that determine the fitnesses are given by

$$d = \begin{pmatrix} 0.525 & 0.225 \\ 0.125 & 0.425 \end{pmatrix} \qquad c = \begin{pmatrix} 0.8 & 0.7 \\ 0.6 & 0.9 \end{pmatrix}$$

with the constants in the definition of f_k in (8) given by $\gamma_k = 0.1$. Since $0.8 + 0.7 = 1.5 = 0.6 + 0.9$ it is easy to see that in this example the inequalities in (13) and (14) hold

$$\frac{0.8}{0.125} + \frac{0.7}{0.425} < \frac{0.6}{0.125} + \frac{0.9}{0.425} \quad \text{and} \quad \frac{0.8}{0.525} + \frac{0.7}{0.225} < \frac{0.6}{0.525} + \frac{0.9}{0.225}$$

so we expect coexistence. For an intuitive explanation note that type i is more fit when chemical i is present but type i also consumes more of chemical i so it will prefer to be around the opposite type. Simulations in Figure 1 show coexistence and confirm that that chemical 2 has a greater concentration near sites occupied by species 1 and vice versa.

4.2 Two species, competitive exclusion

The only change from the first example is that in the matrix of consumption rates d_{ik} has been changed to have larger entries off the diagonal

$$d = \begin{pmatrix} 0.225 & 0.525 \\ 0.425 & 0.225 \end{pmatrix} \qquad c = \begin{pmatrix} 0.8 & 0.7 \\ 0.6 & 0.9 \end{pmatrix}.$$

In this example that the inequalities in (13) and (14) are reversed

$$\frac{0.8}{0.525} + \frac{0.7}{0.225} < \frac{0.6}{0.425} + \frac{0.9}{0.225} \quad \text{and} \quad \frac{0.8}{0.225} + \frac{0.7}{0.425} > \frac{0.6}{0.225} + \frac{0.9}{0.425}.$$

The interior equilibrium is unstable, so this is case 2 of Durrett and Levin [11]. Based on this analogy we predict that the two species will separate and the winner will be dictated by the direction of interface separating the two species.

Figure 2 confirms the segregation. Intuitively this occurs since species i consumes more of chemical i but is more fit when the other chemical is high, so species i will prefer to be around its type. Panels (b) and (c) of Figure 3 show the concentration of the two chemical species at the final time confirming that chemical i has a greater concentration near sites occupied by species i.

5 Colicin

We now return to the example that motivated our investigation.

5.1 Two species

In this case, we have one chemical (colicin) with $\lambda_1 = 0$, $\nu_1 > 0$, and $\mu_{1,1} > 0$. The constants $c_{1,j} = d_{1,j} = 0$ $t_{1,1} = 0$ and $t_{3,1} > 0$. In words the first species produces colicin which increases the death rate of the second one, which for consistency with earlier discussion and in preparation for the next example, we call species 3. Our choices imply that

$$f_i = \gamma_i \quad \delta_1 = \eta_1 \quad \delta_3 = \eta_3 + t_{3,1}R_1$$

There is a cost of producing colicin so we assume

$$\frac{\gamma_1}{\eta_1} < \frac{\gamma_3}{\eta_3} \tag{15}$$

Using (10), we see that in equilibrium $R_1 = \mu_{1,1}x/\nu_1$. So by (11) the mean-field differential equation for fraction of type 1 is

$$\frac{dx}{dt} = \frac{x(1-x)(\delta_3 f_1 - \delta_1 f_3)}{xf_1 + (1-x)f_3} \tag{16}$$

In equilibrium

$$(\eta_3 + t_{3,1}\mu_{1,1}x/\nu_1)\gamma_1 = \eta_1\gamma_3$$

Let $\alpha = t_{3,1}\mu_{1,1}/\nu_1$. In order to have an interior fixed point we need

$$\frac{\gamma_1}{\eta_1} > \frac{\gamma_3}{\eta_3 + \alpha} \tag{17}$$

When $x \approx 0$, $dx/dt < 0$ in (16) by (15), while for $x \approx 1$, $dx/dt > 0$ by (17), so the interior fixed point is unstable. Thus by the reasoning in the previous example, in the spatial model the victor will be determined by the direction of movement of interfaces.

To check this prediction by simulation, we investigate a concrete example. As usual, we take the diffusion constant $D_1 = 0.003$. The other positive parameters are $\mu_{1,1} = 0.525$, $\nu_1 = 0.4$, $\gamma_1 = 0.25$, $\gamma_3 = 0.6$, $t_{3,1} = 0.65$, $\eta_1 = 0.25$, and $\eta_3 = 0.2$. With the current parameters

$$\begin{array}{ccc} \gamma_3/\eta_3 & \gamma_1/\eta_1 & \gamma_3/(\eta_3+\alpha) \\ \frac{0.6}{0.2} = 3 & \frac{0.25}{0.25} = 1 & \frac{0.6}{0.2+0.853125} = 0.5697 \end{array}$$

so there is an interior fixed point. Figure 4 shows a simulation on a 200×200 grid. The colicin producers rapidly eliminate the sensitive strain.

5.2 Three species

We turn now to the three species system. Generalizing the previous example $\lambda_1 = 0$, $\nu_1 > 0$, and $\mu_{1,1} > 0$, $c_{1,j} = d_{1,j} = 0$, $t_{1,1} = t_{2,1} = 0$ and $t_{3,1} > 0$. Our choices imply that

$$f_i = \gamma_i \quad \delta_1 = \eta_1,\ \delta_2 = \eta_2,\ \delta_3 = \eta_3 + t_{3,1}R_1$$

There is a cost of producing colicin, and the sensitive strain would be doomed if it was not stronger than the resistant strain in the absence of colicin, so we assume

$$r_1 < r_2 < r_3 \tag{18}$$

where $r_i = \gamma_i/\eta_i$

Again in equilibrium $R_1 = \mu_{1,1}x_1/\nu_1$. Ignoring the denominator in the mean-field equation, which is just a time change, and writing $\alpha = t_{3,1}\mu_{1,1}/\nu_1$ the three equations for equilibrium are

$$\begin{aligned}
0 = \frac{dx_1}{dt} &= x_1x_2(\eta_2\gamma_1 - \eta_1\gamma_2) + x_1x_3[(\eta_3 + \alpha x_1)\gamma_1 - \eta_1\gamma_3] \\
0 = \frac{dx_2}{dt} &= x_2x_1(\eta_1\gamma_2 - \eta_2\gamma_1) + x_2x_3[(\eta_3 + \alpha x_1)\gamma_2 - \eta_2\gamma_3] \\
0 = \frac{dx_3}{dt} &= x_3x_1[\eta_1\gamma_3 - (\eta_3 + \alpha x_1)\gamma_2] + x_3x_2[\eta_2\gamma_3 - (\eta_3 + \alpha x_1)\gamma_2]
\end{aligned}$$

Moving the first term in the first equation and the second term in the second equation to the left, we see that for this to hold we want:

$$x_1x_2(\eta_1\gamma_2 - \eta_2\gamma_1) = x_1x_3[(\eta_3 + \alpha x_1)\gamma_1 - \eta_1\gamma_3] = x_2x_3[\eta_2\gamma_3 - (\eta_3 + \alpha x_1)\gamma_2]$$

The first term is positive since $r_2 > r_1$. If we let $\bar{r}_3 = \gamma_3/(\eta_3 + \alpha x_1)$ then for the second and third to be positive we need $r_1 > \bar{r}_3$ and $\bar{r}_3 > r_2$, which is impossible, so there is no interior fixed point.

This was the case in the model of Durrett and Levin, but their model had coexistence. If we assume that

$$\bar{r}_3 < r_1 < r_2 < r_3$$

then the competitors have the same rock-paper scissors relationship. 2 beats 1, 3 beats 2, and 1 beats 3. For this reason we expected to find coexistence in the new model with diffusion but after many tries we have failed to find even one example for which this holds. Figure 5 shows the results of a typical simulation. As usual, we take the diffusion constant $D_1 = 0.003$. Most of the other positive parameters are the same as in the previous example $\mu_{1,1} = 0.525$, $\nu_1 = 0.4$, $\gamma_1 = 0.25$, $\gamma_3 = 0.6$, $\eta_1 = 0.25$, and $\eta_3 = 0.2$. Here we have increased the death rate colicin coefficient, $t_{3,1}$, from 0.65 to 0.8 in order to compensate for the fewer initial number of colicin producers. The new species has $\gamma_2 = 0.37$ and $\eta_2 = 0.29$, i.e., $r_2 = 0.37/0.29 = 1.276$ so (18) holds. The parameters here were chosen by simulating a system with strips of each of the three types on a torus in order to confirm that when the types were put down in the order 1, 2, 3, all of the interfaces move to the left (Fig. 6). However in the simulation starting from a random initial configuration the 1's cannot advance against the 3's because the 2's are mixed in with them and reduce the colicin concentration.

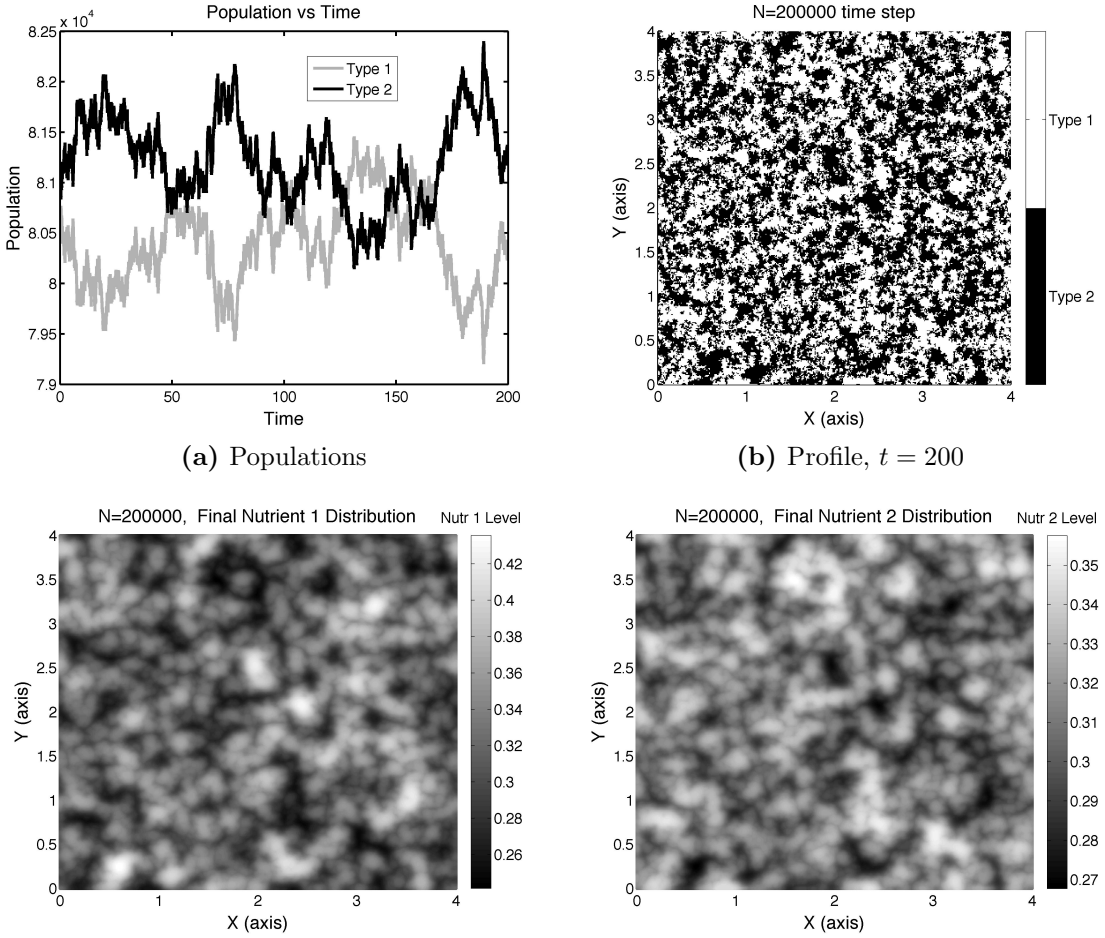
5.3 Removing diffusion

In going from the system studied by Durrett and Levin, we have made two changes: we have replaced the birth-death dynamics by an evolutionary game and we have introduced diffusion of colicin. To try to determine what is responsible for the change in behavior, we will consider a version of the evolutionary game in which fitnesses $f_i = \gamma_i$ and individuals of type i die at rates η_1, η_2, and $\eta_3 + t_{3,1}\phi_1$ where ϕ_1 is the fraction of the four nearest neighbors in state 1.

Figure 7 shows a simulation of the system with $\gamma_1 = 1$, $\gamma_2 = 3$, $\gamma_3 = 7$, $\eta_1 = 0.8$, $\eta_2 = 1.6$, $\eta_3 = 1$, and $t_{3,1} = 16.5$.

$$\frac{\gamma_3}{\eta_3 + t_{3,1}} = \frac{7}{17.5} < \frac{\gamma_1}{\eta_1} = 1.25 < \frac{\gamma_2}{\eta_2} = 1.6 < \frac{\gamma_3}{\eta_3} = 7,$$

so we have the rock-paper scissors relationship. As the simulation shows the three species segregate and coexist. Here as in [27] the densities oscillate. These fluctuations will be reduced when the system size is increased.



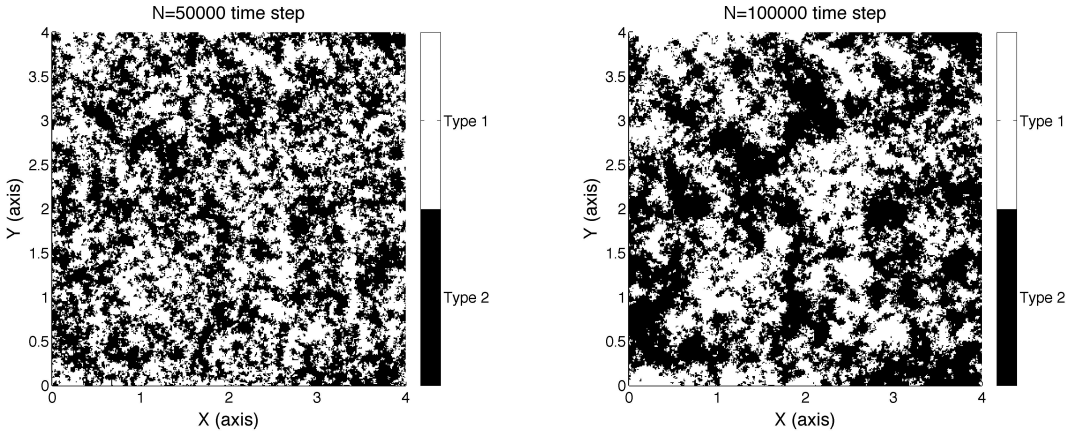
(a) Populations

(b) Profile, $t = 200$

(c) Chemical 1, $t = 200$

(d) Chemical 2, $t = 200$

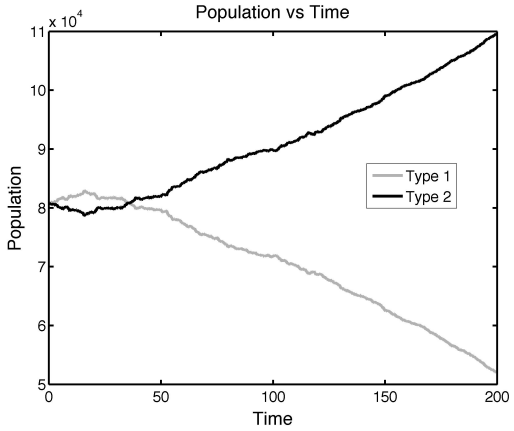
Figure 1: *Simulation of the system described in Section 4.1. The mean-field differential equation has a fixed point in (0,1) that is stable. As the graph of densities in panel (a) shows the system converges to equilibrium. At first glance it may seem that there are large fluctuations in the densities but the numbers on the axis go from 7.9 to* 8.25×10^4*. Panel (b) shows the system at the final time* $t = 200$*. Panels (c) and (d) show the concentration of the two chemicals at the final time.*



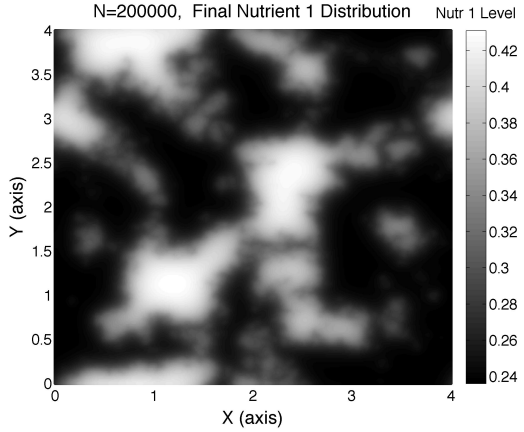
(a) $t = 50$ **(b)** $t = 100$

(c) $t = 150$ **(d)** $t = 200$

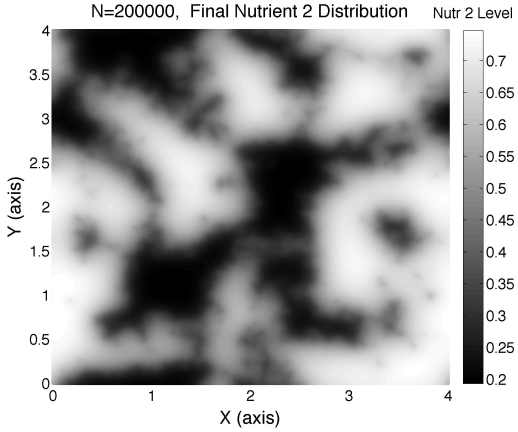
Figure 2: *Simulation of the system described in Section 4.2. The mean-field differential equation has a fixed point in (0,1) that is unstable. As the sequence of images shows the two species segregate.*



(a) Population

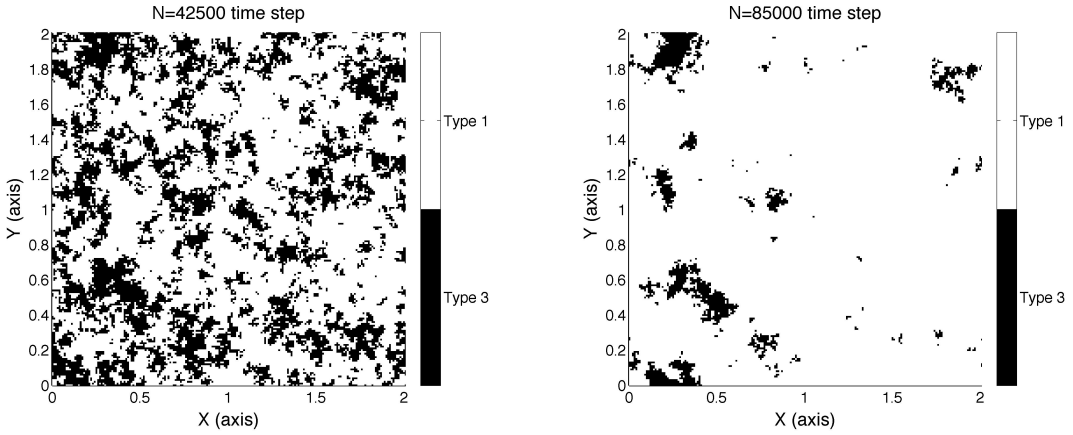


(b) Chemical 1, $t = 200$

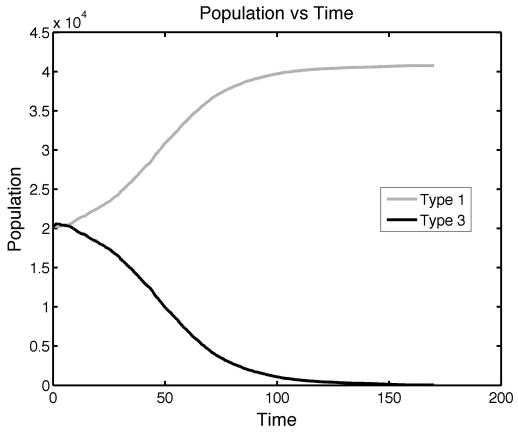


(c) Chemical 2, $t = 200$

Figure 3: *More simulation results for the system from Figure 2. From the snapshots in that figure the direction of movement of the interface is not clear, but panel (a) here shows that the number of type 2's is increasing. Panels (b) and (c) give the concentrations of the two chemicals at the final time.*

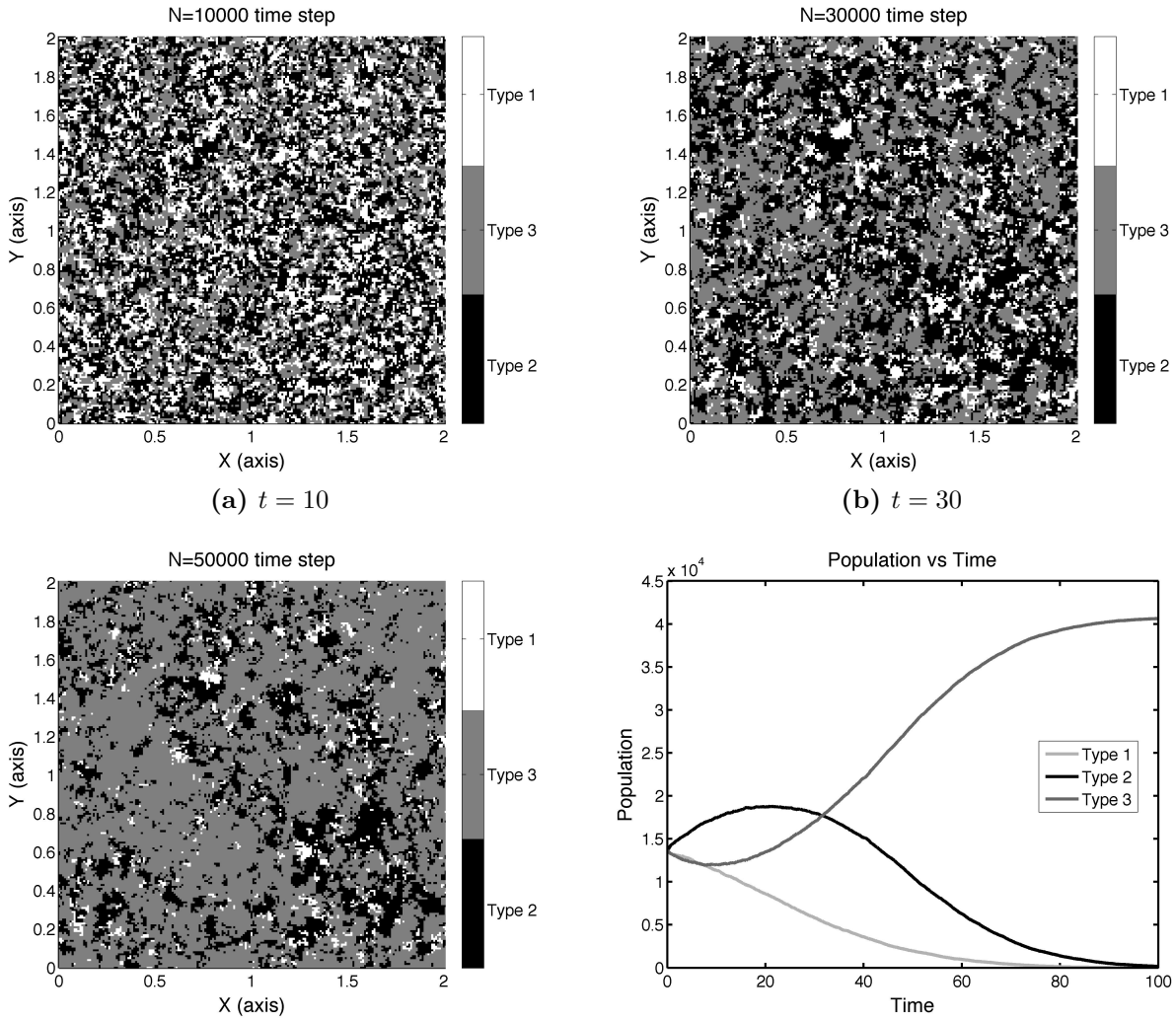


(a) Profile, $t = 42.5$ **(b)** Profile, $t = 85$



(c) Population

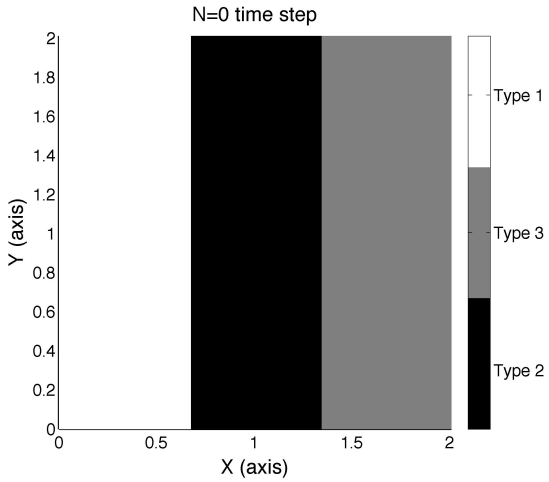
Figure 4: *Simulation of the two species colicin system described in Section 5.1. Note that the colicin producer rapidly eliminates the sensitive strain.*



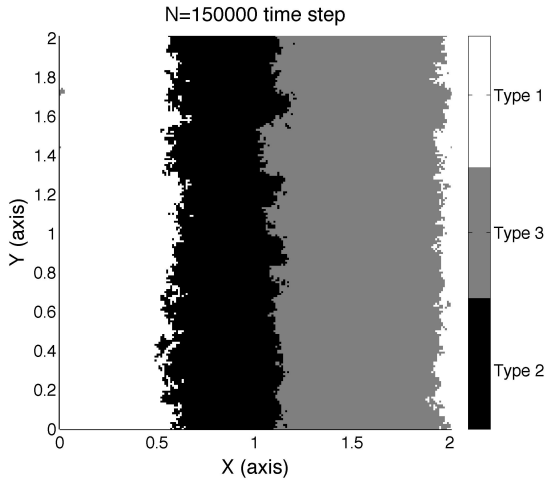
(a) $t = 10$ **(b)** $t = 30$

(c) $t = 50$ **(d)** Population

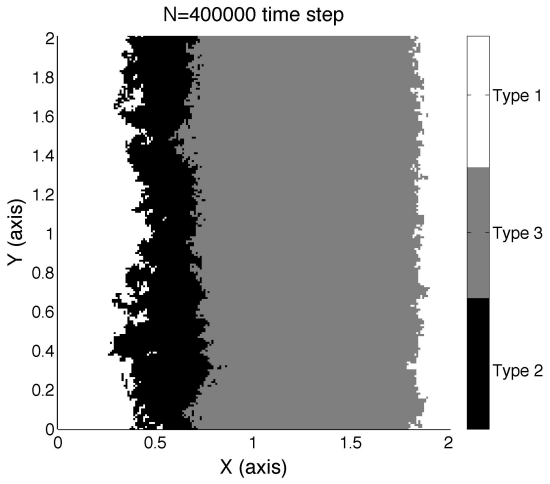
Figure 5: *Simulation of the three species colicin system described in Section 5.2. Note that the 3's separate from the 1's and 2's and then win the competition.*



(a) $t = 0$

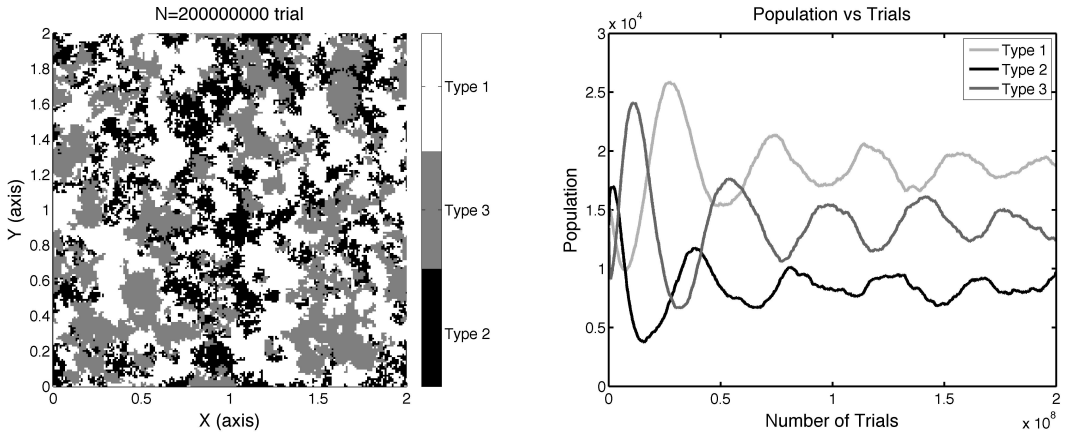


(b) $t = 150$



(c) $t = 400$

Figure 6: *Simulation of the three species colicin system on a torus starting with three strips as describe in Section 5.2. Note that the interfaces move to the left with various positive speeds.*



(a) $N = 2 \times 10^8$ updates **(b)** Population

Figure 7: *Simulation of a version of the three species colicin system in which the chemical does not diffuse. In contrast to the outcome in Figure 5, the three species coexist, as they do in the birth-death dynamics of Durrett and Levin [27].*

References

[1] von Neumann, J., and Morgenstern, O. (1944) *The Theory of Games and Economic Behavior.* Princeton U. Press

[2] Maynard Smith, J., and Price, G.R. (1973) The logic of animal conflict. *Nature.* 401, 268–371

[3] Maynard Smith, J. (1982) *Evolution and the Theory of Games.* Cambridge U. Press

[4] Axelrod, R., and Hamilton, W.D. (1981) The evolution of cooperation. *Science.* 211, 1390–1396

[5] Hofbauer, J., and Sigmund, K. (1998) *Evolutionary Games and Population Dynamics.* Cambridge U. Press

[6] Hofbauer, J., and Sigmund, K. (2003) Evolutionary game dynamics. *Bull. Amer. Math. Soc.* 40, 479–519

[7] Nowak, M.A., and Sigmund, K. (2004) Evolutionary dynamics of biological games. *Science.* 303, 793–799

[8] Nowak, M.A. (2006) *Evolutionary Dynamics.* Belknap Press, Harvard University.

[9] Nowak, R.M., and May, R.M. (1992) Evolutionary games and spatial chaos. *Science.* 359, 826–829

[10] Nowak, M.A., and May, R.M. (1993) The spatial dilemmas of evolution. *Int. J. Bifur. Chaos.* 3, 35–78

[11] Durrett, R., and Levin S. (1994) The importance of being discrete (and spatial). *Theor. Pop. Biol.* 46, 363–394

[12] Killingback, T., and Doebeli, M. (1996) Spatial evolutionary game theory: Hawks and Doves revisited. *Proc. Royal Society B.* 263, 1135–1144

[13] Hauert, C. (2002) Effects of space in 2×2 games. *Int. J. Bifurcation and Chaos.* 12, 1531–1548

[14] Hauert, C., and Doebli, M. (2004) Spatial structure often inhibits the evolution of cooperation in the snowdrift game. *Nature.* 428, 643–646

[15] Ohtsuki, H., Hauert, C., Lieberman, E., and Nowak, M.A. (2006) A simple rule for the evolution of cooperation on networks. *Nature.* 441, 502–505

[16] Ohtsuki, H., and Nowak, M.A. (2008) Evolutionary stability on graphs. *J. Theoretical Biology.* 251, 698–707

[17] Szabó, G., and Fáth, G. (2007) Evolutionary games on graphs. *Physics Reports.* 46, 97–216

[18] Dormann, S., and Deutsch, A. (2002) Modeling of self-organized avascular tumor growth with a hybrid cellular automaton. *In Silico Biology.* 2, 393–406

[19] Alacorn, T., Byrne, H.M., and Maini, P.K. (2003) A multiple scale model for tumor growth. *J. Theor. Biol.* 225, 257–254

[20] Anderson, A.R.A. (2005) A hybrid mathematical model of solid tumor invasion: the importance of cell adhesion. *Mathematical Medicine and Biology.* 22, 163–186

[21] Gerlee, P., and Anderson, A.R.A. (2007) An evolutionary hybrid cellular automation model of solid tumor growth. *J. Theoretical. Biology.* 246, 583–603

[22] Gerlee, P., and Anderson, A.R.A. (2008) A hybrid cellular automaton model of clonal evolution in cancer: The emergence of the glycolytic phenotype. *J. Theoretical. Biology.* 250, 705–722

[23] Deisboeck, T.S., Wang, Z., Macklin, P., and Cristini, V. (2011) Multiscale cancer modeling. *Annual Rev. Biomed. Eng.* 13, 127–155

[24] Rejniak, K.A., and Anderson, A.R.A. (2011) Hybrid models of tumor growth. *Systems Biology and Medicine.* 3, 115–125

[25] Cristini, V., and Lowengrub, J. (2010) *Multiscale Modeling of Cancer.* Cambridge U. Press

[26] Tomlinson, I.P.M. (1997) Game-theory models of interactions between tumor cells. *European J. Cancer.* 33, 1495–1500

[27] Durrett, R., and Levin S. (1997) Alleopathy in spatailly distributed populations. *J. theor. Biol.* 185, 165–171

[28] Kerr, B., Riley, M.A., Feldman, M.W., and Bohannon, B.J.M. (2002) Local dispersal promotes biodiversity in a real-life game of rock-paper-scissors. *Nature.* 418, 171–174

[29] Kirkup, B.C., and Riley, M.A. (2004) Antibiotic-mediated antagonism leads to a bacterial game of rock-paper scissors in vivo. *Nature.* 428, 412–414

[30] Süli, E. and Mayers, D. (2003) *An Introduction to Numerical Analysis.* Cambridge U. Press