



Spatial evolutionary games with weak selection

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Recently, a rigorous mathematical theory has been developed for spatial games with weak selection, i.e., when the payoff differences between strategies are small. The key to the analysis is that when space and time are suitably rescaled, the spatial model converges to the solution of a partial differential equation (PDE). This approach can be used to analyze all 2×2 games, but there are a number of 3×3 games for which the behavior of the limiting PDE is not known. In this paper, we give rules for determining the behavior of a large class of 3×3 games and check their validity using simulation. In words, the effect of space is equivalent to making changes in the payoff matrix, and once this is done, the behavior of the spatial game can be predicted from the behavior of the replicator equation for the modified game. We say predicted here because in some cases the behavior of the spatial game is different from that of the replicator equation for the modified game. For example, if a rock–paper–scissors game has a replicator equation that spirals out to the boundary, space stabilizes the system and produces an equilibrium.

cancer modeling | public goods game | bone cancer | rock–paper–scissors

Evolutionary games are often studied by assuming that the population is homogeneously mixing, i.e., each individual interacts equally with all the others. In this case, the frequencies of strategies evolve according to the replicator equation. See, e.g., Hofbauer and Sigmund’s book (1). If u_i is the frequency of players using strategy i , then

$$\frac{du_i}{dt} = u_i(F_i - \bar{F}), \quad [1]$$

where $F_i = \sum_j G_{i,j} u_j$ is the fitness of strategy i , $G_{i,j}$ is the payoff for playing strategy i against an opponent who plays strategy j , and $\bar{F} = \sum_i u_i F_i$ is the average fitness. The homogeneous mixing assumption is not satisfied for the evolutionary games that arise in ecology or modeling solid cancer tumors, so it is important to understand how spatial structure changes the outcome of games. The goal of this paper is to facilitate applications of spatial evolutionary games by giving rules to determine the limiting behavior of a large class of 3×3 games.

Our spatial games will take place on the 3D integer lattice \mathbb{Z}^3 . The theory (2, 3) has been developed under the assumption that the interactions between an individual and its neighbors are given by an irreducible probability kernel $p(x)$ on \mathbb{Z}^3 with $p(0) = 0$, that is finite range, symmetric $p(x) = p(-x)$, and has covariance matrix $\sigma^2 I$. Here we will restrict our attention to the nearest neighbor case, in which $p(x) = 1/6$ for $x = (1, 0, 0), (-1, 0, 0), \dots, (0, 0, -1)$.

To describe the dynamics we let $\xi_t(x)$ be the strategy used by the individual at x at time t and let

$$\psi_t(x) = \sum_y G(\xi_t(x), \xi_t(y)) p(y - x)$$

be the fitness of x at time t . In birth–death dynamics, site x gives birth at rate $\psi_t(x)$ and sends its offspring to replace the individual at y with probability $p(y - x)$. In death–birth dynamics, the individual at x dies at rate 1 and is replaced by a copy of the one at y with probability proportional to $p(y - x)\psi_t(y)$. The theory developed in ref. 3 can be applied to both cases. However, to save space we will only consider the birth–death case.

To motivate our study of evolutionary games, we introduce two examples that will be used to illustrate the theory that has been developed.

Examples

A Public Goods Game in Pancreatic Cancer. In this system (4), some cells (type 2’s) produce insulin-like growth factor-II, while other cells (type 1’s) free-ride on the growth factors produced by other cells. Since the 1’s do not have to spend metabolic energy producing the growth factor, they have a higher growth rate. This leads to the following very simple 2×2 game.

$$\begin{array}{cc|c} & 1 & 2 & \\ \hline 1 & 0 & \lambda & \\ 2 & 1 & 1 & \end{array} \quad [2]$$

In words, 2’s give birth at rate 1, independent of what is around them, while 1’s give birth at rate equal to λ times the fraction of neighbors that are of type 1. If $\lambda > 1$ there is a mixed strategy equilibrium for the game $\rho_2 = 1/\lambda$, $\rho_1 = 1 - 1/\lambda$, which is the limit of the solution to the replicator equation when $0 < u_1 < 1$.

Multiple Myeloma. Normal bone remodeling is a consequence of a dynamic balance between osteoclast (OC)-mediated bone resorption and bone formation due to osteoblast (OB) activity. Multiple myeloma (MM) cells disrupt this balance in two ways.

- (i) MM cells produce a variety of cytokines that stimulate the growth of the OC population.
- (ii) Secretion of DKK1 by MM cells inhibits OB activity.

OC cells produce osteoblast-activating factors that stimulate the growth of MM cells, whereas MM cells are not affected by the presence of OB cells. These considerations led Dingli et al. (5) to the following game matrix. Here, $a, b, c, d, e > 0$.

Significance

Game theory, which was invented to study strategic and economic decisions of humans, has for many years been used in ecology and more recently in cancer modeling. In the applications to ecology and cancer, the system is not homogeneously mixing, so it is important to understand how space changes the outcome of evolutionary games. Here, we present rules that can be used to determine the behavior of a wide class of three-strategy games. In short, the behavior can be predicted from the behavior of the replicator equation for a modified equation. This theory will be useful for a number of applications.

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$$\begin{array}{ccccc}
 & OC & OB & MM & \\
 OC & 0 & a & b & \\
 OB & e & 0 & -d & \\
 MM & c & 0 & 0 &
 \end{array} \quad [3]$$

There are many other systems to which our methods can be applied. See, e.g., refs 6–10.

1. Review of Existing Theory

We will study the dynamics of spatial games under the assumption of weak selection, i.e., when the game matrix

$$\bar{G}(i, j) = \mathbf{1} + wG_{i,j},$$

where $\mathbf{1}$ is a matrix of all 1's and w is small. Since multiplying a game matrix by a constant or adding a constant to all of the entries in a column does not change the behavior of the replicator equation, \bar{G} and G are equivalent from that point of view.

Mathematical results for spatial games require that we take a limit in which $w \rightarrow 0$. However, simulations will show that the predictions are accurate in some cases when $w = 1/2$. Bozic et al. (11) calculated that the actual selective advantage provided by typical somatic mutations in human tumors is 0.004, so our results can be applied to evolutionary games arising from the study of cancer.

When $w = 0$, either version of the dynamics reduces to the voter model, a system in which each site at rate 1 changes its state to that of a randomly chosen neighbor. The key to our analysis is that our spatial evolutionary game is a voter model perturbation in the sense of Cox, Durrett, and Perkins (2). To make it easier to compare with ref. 2 and the follow-up paper (3) that applied the theory to evolutionary games, we will let $w = \varepsilon^2$. Here, we will simply state the facts that we will use. The reader can find the details in ref. 3.

The key to the study of voter model perturbations is a result that says when we scale space by ε and runtime at rate ε^{-2} , then the spatial model converges to the solution of a partial differential equation (PDE). In order to state the result, we need to define the mode of convergence. Pick a small $r > 0$ and divide space $\varepsilon\mathbb{Z}^d$ into boxes with side ε^r . Given an $x \in \mathbb{R}^d$, let $B^\varepsilon(x)$ be the box that contains x , and let $\bar{u}_i^\varepsilon(t, x)$ be the fraction of sites in state i in $B^\varepsilon(x)$ at time $t\varepsilon^{-2}$. We say that the spatial model converges to $u(t, x)$, if for any L

$$\sup_{x \in [-L, L]^d} |\bar{u}_i^\varepsilon(t, x) - u_i(t, x)| \rightarrow 0 \quad \text{as } \varepsilon \rightarrow 0.$$

Theorem 1. Suppose $d \geq 3$. Let $v_i: \mathbb{R}^d \rightarrow [0, 1]$ be continuous with $\sum_{i \in S} v_i = 1$. If the initial conditions $\xi_0^\varepsilon \rightarrow v_i$ in the sense described above then $\xi_{\varepsilon^{-2}t}^\varepsilon$ converges to the solution of the system of partial differential equations:

$$\frac{\partial}{\partial t} u_i(t, x) = \frac{\sigma^2}{2} \Delta u_i(t, x) + \phi_i(u(t, x))$$

with initial conditions $u_i(0, x) = v_i(x)$.

The reaction term $\phi_i(u)$ in Theorem 1 is a constant times the replicator equation for the modified game $H = G + A$, where

$$A_{i,j} = \theta(G_{i,i} + G_{i,j} - G_{j,i} - G_{j,j}).$$

Note that if we add c_k to column k , the perturbation matrix A is not changed.

Table 1. Simulation results for the public goods game

λ	4/3	3/2	3	3.5	4
Original game	0.11	0.25	0.75	0.83	0.89
$w = 1/2$	0.01	0.19	0.79	0.88	0.96
$w = 1/10$	0.00	0.16	0.82	0.92	0.98
$w \rightarrow 0$ limit	0	0.17	0.83	0.93	1

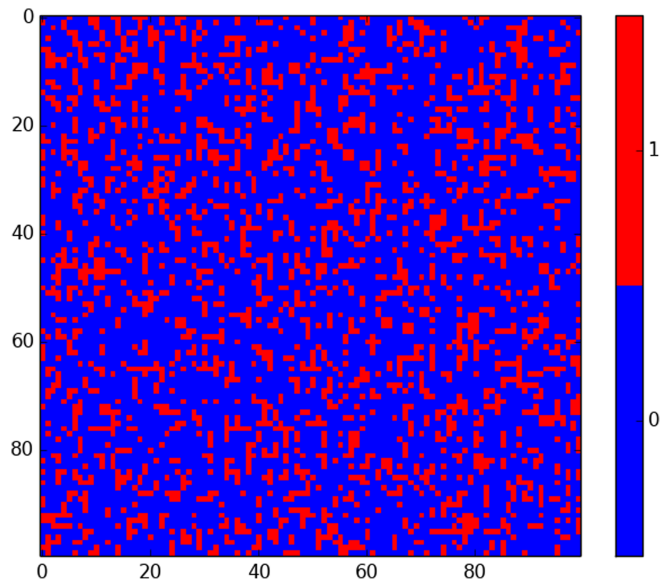


Fig. 1. Simulation of the original public goods game G_1 with $\lambda = 3$. Here and in Figs. 4, 5, and 7, the picture gives the state of slice through a $100 \times 100 \times 100$ grid. Visually there is very little spatial structure in equilibrium. The correlation $\rho_{11} = 0.006657$.

The idea that the reaction term is the replicator equation for a modified games is inspired by Ohtsuki and Nowak (12), who found a similar result for the ordinary differential equation that arises from the pair approximation. See section 5 of ref. 3 for more on this connection. As in the work of Tarnita et al. (13, 14), θ depends only on the spatial structure, and not on the entries in the game matrix. In the 3D nearest-neighbor case it is known that $\theta \approx 0.5$. See section 4 of ref. 3 for more details.

2. Public Goods Game

Since the behavior of the replicator equation and of the weak selection limit for birth–death updating are not changed if we subtract a constant from each column, so we can restrict our attention to 2×2 games of the form

$$\begin{array}{cc}
 \mathbf{1} & \mathbf{2} \\
 \mathbf{1} & 0 \quad b. \\
 \mathbf{2} & c \quad 0
 \end{array} \quad [4]$$

Let u denote the frequency of strategy 1. In a homogeneously mixing population, u evolves according to the replicator equation Eq. 1:

$$\begin{aligned}
 \frac{du}{dt} &= u\{b(1-u) - ub(1-u) - (1-u)cu\} \\
 &= u(1-u)[b - (b+c)u] \equiv \phi_R(u).
 \end{aligned} \quad [5]$$

Note that $\phi_R(u)$ is a cubic with roots at 0 and at 1. If there is a fixed point in $(0, 1)$, it occurs at $\rho = b/(b+c)$.

A method for analyzing all 2×2 games is described in section 6 of ref. 3, so we will only consider the public goods game and suppose that $\lambda > 1$. Subtracting 1 from the second column, the game G becomes

$$\begin{array}{cc}
 G_1 & \mathbf{1} & \mathbf{2} \\
 \mathbf{1} & 0 & b = \lambda - 1. \\
 \mathbf{2} & c = 1 & 0
 \end{array}$$

In the three-dimensional nearest-neighbor case, the transformed game is given by H :

$$\begin{array}{cc}
 H_1 & \mathbf{1} & \mathbf{2} \\
 \mathbf{1} & 0 & \bar{b} = (3/2)\lambda - 2. \\
 \mathbf{2} & \bar{c} = 2 - \lambda/2 & 0
 \end{array}$$

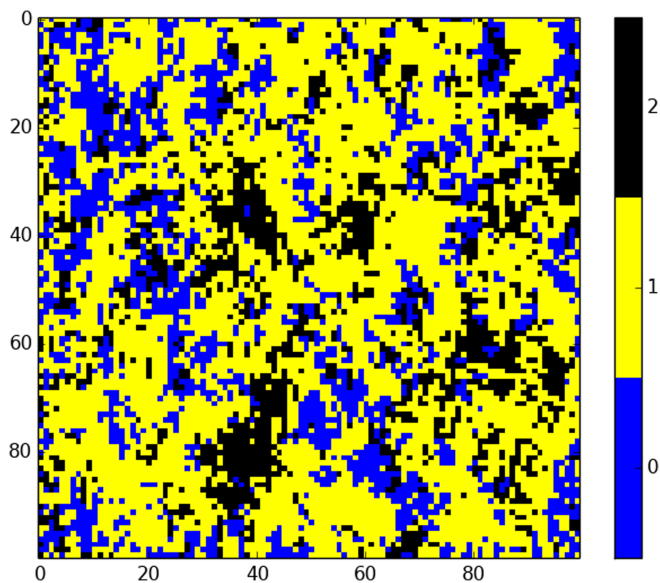


Fig. 4. Final state in the simulation in Fig. 3. Note that there is significant spatial correlation in contrast to the simulation of the public goods game in Fig. 1. Here, $\rho_{11} = 0.1775$, $\rho_{22} = 0.2256$ and $\rho_{33} = 0.2031$.

G_3	1	2	3	H_3	1	2	3
1	0	1	-2	1	0	3	-4.5
2	-3	0	2	2	-5	0	4
3	3	-2	0	3	5.5	-4	0

Fig. 3 shows that spatial structure stabilizes the unstable rock-paper-scissors example, i.e., the densities stay bounded away from 0. The apparent periodic behavior will disappear when a large enough system is simulated. For a discussion of this, see section 5 of a 1998 paper by Durrett and Levin (18). As explained in *SI Appendix, Section S3*, sufficiently large means that the side of the cube is much larger than the correlation length. Fig. 4 shows a picture of the final state in the simulation run that produced Fig. 3.

5. Stag Hunt

To prepare for the discussion of bistable 3×3 games, we begin with a 2×2 example.

	<i>Stag</i>	<i>Hare</i>
<i>Stag</i>	4	0
<i>Hare</i>	2	1

To explain the matrix: You can go hunt Stag (a large male deer), but if you go alone, then you have no chance to get one. If you hunt Hare and the other player hunts Stag, you get to keep all the rabbits. If you hunt Hare and the other player does also, then you split the kill.

If we transform so that there are 0's on the diagonal and replace the strategy names by numbers, the game becomes G . The modified game is H .

G	1	2	H	1	2
1	0	-1	1	0	-0.5
2	-2	0	2	-2.5	0

In H , $(\rho_1, \rho_2) = (1/6, 5/6)$ is an unstable equilibrium. If $u_1 > 1/6$, the first strategy becomes more attractive and increases further.

It was shown in section 6 of ref. 3 that if $\rho_1 < 1/2$, then the 1's take over the system. This is proved by considering the limiting PDE for the local density of strategy 1, which is

$$\frac{du}{dt} = \sigma^2 u'' / 2 + \phi(u) \quad \text{with} \quad \phi(u) = u(1-u)[b - (b+c)u],$$

where $b = -0.5$, $c = -2.5$. When $b, c < 0$, this equation has a traveling wave solution that moves with velocity v

$$u(t, x) = w(x - vt), \quad u(-\infty) = 1, \quad u(\infty) = 0.$$

The 1's take over if and only if $v > 0$, which is equivalent to $\int_0^1 \phi(x) dx > 0$. Since ϕ is a cubic with zeros at 0 and 1, this holds if and only if the interior equilibrium $\rho = b/(b+c) < 1/2$.

Fig. 5 gives a visual explanation of the difference between interfaces in the public goods and stag hunt games. For an explanation of the relevance of the behavior of interfaces to properties of stochastic spatial models, see the 1999 paper by Molofsky et al. (19).

6. Multiple Myeloma

The original matrix, which we will call G_4 , is given in Eq. 3. The modified game has entries

H_4	1	2	3
1	0	A	B
2	E	0	$-D'$
3	C	F	0

where $A = (1 + \theta)a - \theta e$, $E = (1 + \theta)e - \theta a$, $B = (1 + \theta)b - \theta c$, $C = (1 + \theta)c - \theta b$, $D = (1 + \theta)d$, and $F = \theta d$. The modification of the game does not change the sign of D , but it puts a positive entry F in $G_{3,2}$. It may also change the signs of one or two of the other four nonzero entries. Noting that $A < 0$ if $e > (1 + \theta)a/\theta$ while $E < 0$ if $e < \theta a/(1 + \theta)$, we see that if one of these two entries is negative, the other one is positive. The same holds for B and C , so there are nine possibilities for the signs of A, B, C, E and a wide variety of possible behaviors for the spatial game that are not found in the replicator equation. In particular it is possible for all three strategies to coexist in the spatial model, but not in the replicator equation. These possibilities were systematically considered in section 9.1

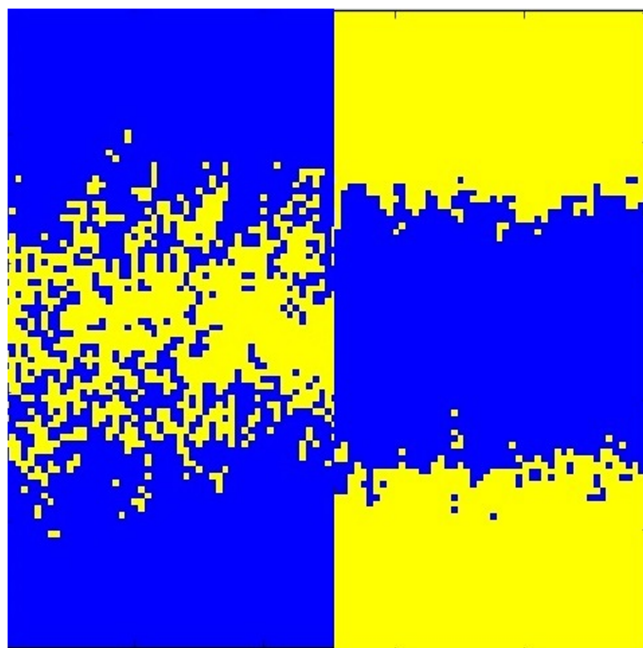


Fig. 5. The simulations were started with a strip of one strategy in between two strips of the opposite type. In the public goods game, on the left the interface melts down, and we have coexistence. In the Stag Hunt, on the right, the interface stays tight.

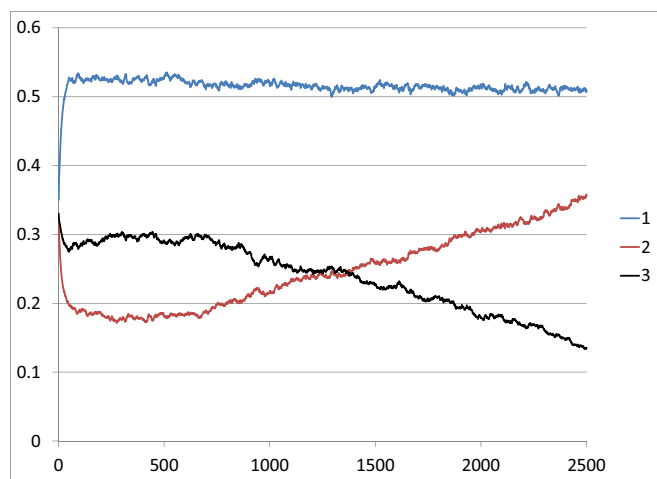


Fig. 6. Frequencies versus time in a $100 \times 100 \times 100$ simulation of the weak selection multiple myeloma game $1 + (1/3)G_4$, with $a = e = 2$, $d = 1$, and $b = c = 1.25$. Note that the frequencies first get close to the unstable fixed point at $(0.531, 0.306, 0.1633)$ and then start heading toward the boundary equilibrium.

of ref. 3. The dramatic differences between the properties of the spatial game and the replicator equation cast doubt on the proposed insights into therapy that emerge from the analysis of Dingli et al. (see the discussion that begins on page 1,134 of ref. 5).

Here, our interest in this model is as an example with bistability. Suppose that $A, B, C, E > 0$ and $DC/BE > F/A$, which holds for the original game entries. Results from ref. 3, which are described in *SI Appendix, Section S4*, show that there are three cases:

Case 1. $C/E > 1 - F/A$. The replicator equation converges to the 1,3 equilibrium.

Case 2. $1 - F/A > C/E > 1 - DC/BE$. There is an interior fixed point that is a saddle point, and the replicator equation exhibits bistability.

Case 3. $1 - DC/BE > C/E$. The replicator equation converges to the 1,2 equilibrium.

In our simulation of case 2 we take $a = e = 2$, $d = 1$, and vary $b = c$. The perturbed game is very simple in this case: $A = E = a = e$, $B = C = b = c$, $D = 1.5$, $F = 0.5$. Since $B = C = c$ the condition for case 2 is

$$1 - \frac{0.5}{2} > \frac{c}{2} > 1 - \frac{1.5}{2},$$

or $1.5 > c > 0.5$. When $c = 1.5$, the 1,3 equilibrium wins. When $c = 1$, the 1,2 equilibrium wins. In principle we could find the value of c where the limiting equilibrium changes by showing that the limiting system of PDE has traveling wave solutions and finding the parameter value where the velocity changes sign, but this seems to be difficult mathematical problem.

When $c = 1.25$, the 1,2 equilibrium wins (Fig. 6), but takes a long time to do so, suggesting that this value is near the point where the limiting state changes. Fig. 7, which shows the final state of the simulation, shows that we get separation into regions that look like the two possible equilibria, and then the 1,2 regions grow and take over.

7. Summary

In this paper, we have used simulation and heuristic arguments to make predictions about the behavior of games that cannot be

analyzed rigorously using the methods of ref. 3. The main contribution is to describe a procedure for determining the behavior of spatial three-strategy games with weak selection, when the game matrix G has no unstable edge fixed points. One first forms the modified game $H_{ij} = (1 + \theta)G_{ij} - \theta G_{j,i}$, where θ is a constant that depends on the spatial structure, but not on the entries in the game matrix. $\theta \approx 1/2$ in the three-dimensional nearest-neighbor case. The behavior of the spatial game with matrix G can then be predicted from that of the replicator equation for H . We say predicted because in some cases the behavior is not the same.

For three-strategy games without unstable edge fixed points, there are four major types:

1. When there are 1, 2, or 3 stable edge fixed points and they can all be invaded, there is coexistence in the spatial evolutionary game when selection is small. This was proved in ref. 3
2. As first observed by Durrett and Levin (20), when the replicator equation is bistable, i.e., the limit depends on the starting point, the spatial game has a stronger equilibrium that is the limit for generic initial conditions. In two strategy games, the victorious strategy is determined by the direction of movement of the traveling wave solution of the PDE. For three-strategy games, we do not know how to prove the existence of such traveling waves or compute their speeds, but simulations suggest that the same result holds.
3. In the case of rock–paper–scissors games, there is coexistence when the replicator equation converges to the interior fixed point. This was proved in ref. 3 when the game is “almost constant sum.” It is somewhat surprising that when the replicator equation trajectories that spiral out to the boundary, space exerts a stabilizing effect and the three strategies coexist. This result has also been found recently by Ryser and Murgas (10).
4. Last, and least interesting, is the situation in which the replicator equation converges to a boundary fixed point. Simulations show (*SI Appendix, Section S5*) that the same behavior occurs in the spatial evolutionary game.

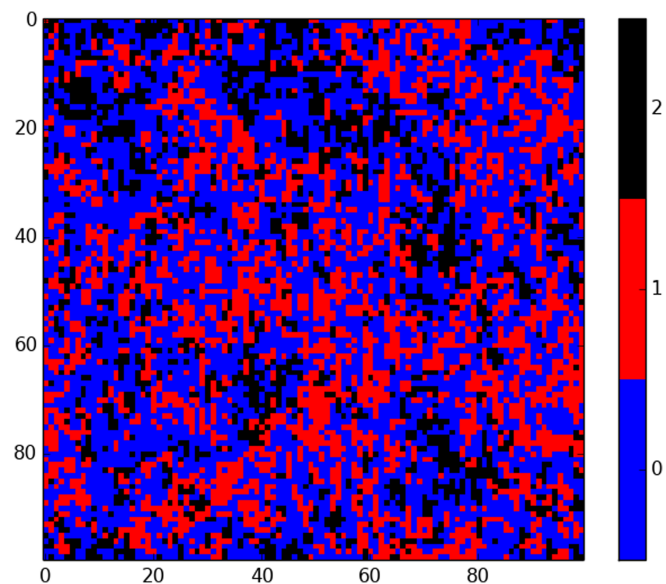


Fig. 7. Picture of final configuration for the simulation in Fig. 6. Note that the blues (1’s) are spread throughout the space, while the reds (2’s) and whites (3’s) are segregated. The correlations $\rho_{11} = 0.1342$, $\rho_{22} = 0.1600$, and $\rho_{33} = 0.1497$ are smaller than those in Fig. 4.

Work remains to be done on three-strategy games with unstable boundary fixed points; however, the work presented here can be used to analyze all of the games in all the papers we have cited except for one example in ref. 10. In many cases the behavior of the spatial game differs from that of the replicator equation, so it is important to consider the impact of spatial structure in order to obtain correct conclusions. The results we have presented here are derived in the limit that the selection $w \rightarrow 0$, but

simulations show that in many cases the conclusions are accurate when $w = 0.1$ or even 0.25 .

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