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On aggregation in CA models in biology

Mark S Alber^{1,2} and Audi Kiskowski²

¹ Department of Mathematics, Stanford University, Building 380, MC 2125, Stanford, CA 94305, USA

² Department of Mathematics, University of Notre Dame, Notre Dame, IN 46556, USA

E-mail: malber@math.stanford.edu, malber@nd.edu and mkiskows@nd.edu

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Abstract

Aggregation of randomly distributed particles into clusters of aligned particles is modeled using a cellular automata (CA) approach. The CA model accounts for interactions between more than one type of particle, in which pressures for angular alignment with neighbors compete with pressures for grouping by cell type. In the case of only one particle type clusters tend to unite into one big cluster. In the case of several types of particles the dynamics of clusters is more complicated and for specific choices of parameters particle sorting occurs simultaneously with the formation of clusters of aligned particles.

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1. Introduction

Aggregation and migration are biological phenomena shown by a variety of organisms occurring over a full range of scale, from sub-cellular molecular populations (e.g. actin filaments, molecular collagen structures) to cellular populations (e.g. fibroblasts, myxobacteria) to communities of many organisms (e.g. animal herds, schools of fish) (see, amongst others, Pollard and Cooper (1986), Besseau and Giraud-Guille (1995), Mogilner and Edelstein-Keshet (1996), Cook (1995) and Geigant *et al* (1998)). Spatial distribution and temporal dynamics are obvious factors in such phenomena. The significance of individual orientations, however, has only recently been acknowledged as an important component of aggregation.

Traditionally, cell aggregation has been modeled with partial differential equations that combine elements of random motion with biologically motivated rules that prescribe more ordered motion. These models, however, do not include terms capturing the non-local interactions inherent in a population that moves as a unit. Mogilner and Edelstein-Keshet (1996, 1999) and Mogilner *et al* (1996) realized that angle-dependent alignment of cells could

be more closely modeled by integro-differential partial differential equations which would account for the effect of ‘neighbor’ interactions on each member of the population. Namely, to account for such interactions, one must add up the possibility of encounters with neighbors and weight them with the likelihood of a particular motion, producing an integral. In the special limiting case of nearly complete alignment in the presence of a weak diffusion the angular distribution develops sharp peaks at certain orientations. Mogilner *et al* (1996) suggested using a special peaked ansatz for studying such limiting cases. Notice that, in their paper, emphasis is placed on studying stationary solutions and that peak dynamics is not discussed. The dynamics of peaks can be investigated by first truncating the integral term in the equation and then by using an approach similar to the weak solution method used for the shallow water equation in Alber *et al* (2001).

Only a few authors have worked on alignment models using continuous spatial and angular variables due to inherent difficulties in both the analytical treatment of these models and in the generation of numerical solutions (Dallon and Sherratt 2000). Alternatively, a cellular automata (CA) approach can be used to track the motion of individual cells for direct comparison with biological data.

Cook *et al* (1997) used a CA model of lattice gas type as an alternative to a simplified integro-differential model, which captures the basic type of spatio-angular self-organizational behaviour described in Mogilner *et al* (1996). In their model one particle is identified with one cell, the number of cells is fixed and automaton rules are designed to model the non-local character of the integro-differential equations. In papers by Deutsch (1999a, 1999b), the generation of automaton rules is generalized by maximizing different types of functionals defined on local directional fields. In these models there is only one type of cell and clusters usually grow and unite into one large cluster. Deutsch also added swarming to the model by assuming that particles can stop and by considering local densities of particles at rest. Competition between these different factors also results in cluster formation. These clusters are of the same size, more or less equidistant from each other and are not drifting.

On the other hand, Graner and Glazier (1992) developed a generalized Potts model for studying cell sorting. In their model each cell consists of 100–150 particles and transitional probabilities depend, amongst other things, on the energies of cell–cell interactions. Cell polarity is not incorporated into the model but more than one cell type is needed to establish different cell energies.

In this paper, we consider a model for the spatio-angular movement and interaction of particles of m different types. These particles aggregate in one of two ways and particle behaviour is the result of competition between these two types of movement. Namely, a cell will either align with its neighbors using the directional field or identify with cells of its own type by using the neighborhood density of its own cell type. As a result of this interplay, particles will separate in different ways, depending on the choice of parameters.

In the CA model described in this paper, the clusters formed are confluent collections of particles of the same type moving in the same direction. In a forthcoming paper we will study the formation and subsequent interaction of these clusters with the ultimate goal of using a cluster of aligned particles as a model for a biological cell.

2. Multi-type CA model for cell aggregation

Traditionally, cell aggregation has been modeled with PDEs that incorporate elements of random motion with biologically motivated rules that prescribe more ordered motion. These models, however, do not include terms capturing the non-local interactions inherent in a population that moves as a unit. Mogilner and Edelstein-Keshet (1996) and Mogilner *et al* (1996)

realized that such phenomena could be more closely modeled by integro-differential partial differential equations which would account for the effect of ‘neighbor’ interactions on each member of the population. To account for such interactions, one must add up the possibility of encounters with neighbors and weight them with the likelihood of a particular motion, naturally producing an integral.

The following simplified model for spatio-angular self-orientation considered in Mogilner and Edelstein-Keshet (1996) and Cook *et al* (1997) captures the basic type of interactions:

$$\frac{\partial C}{\partial t} = \epsilon_1 \Delta_\theta C + \epsilon_2 \Delta_r C + C(K(C) * C)$$

where

$$K(C) * C = \int_D \int_S L(C(r, \theta) - C(r', \theta')) G(r - r', \theta - \theta') C(r', \theta', t) d\theta dr$$

and the density distribution C of a population of cells is a function of space ($r \in D$), orientation ($\theta \in S$) and time t . The spatial domain D may be two- or three-dimensional and is continuous. The first term, in the form of a Laplacian operator in an angular variable θ multiplied by ϵ_1 , represents random angular motion. The second term, in the form of a Laplacian operator in a spatial variable r multiplied by ϵ_2 , represents random walk (diffusion) in a radial direction. The third term is an integral term. One of the functions in the kernel summarizes the biologically motivated condition that small clusters will migrate towards, and be absorbed by, larger clusters and the second function summarizes turning probabilities based on neighbor interactions.

Cook *et al* (1997) also described a CA model. The continuous space D is replaced by a discrete lattice which is periodically extended, and objects are directed particles (vectors) of the same type at each node. No two particles with the same direction can coexist at a node (exclusion principle). Random changes of orientation are introduced by using a Monte Carlo method with a matrix of transitional probabilities which depends on the local directional field. This model has proved both interesting and successful in that, for appropriately chosen coefficients, most of the particles in an initially random directional field will aggregate and align over a finite number of cycles. Altering these coefficients in a continuous way yields bifurcation, the critical points of which can be computed using linear stability analysis (see Mogilner *et al* (1996)).

In this paper movements of particles of m types are studied by considering an interplay between two different ways of aggregating: alignment with neighboring cells by using directional fields and identification with a particular type of particles by using densities of particles of a given type among neighbors. As a result, depending on the choice of parameters, a separation of clusters of aligned particles of different types is observed.

Our goal is to determine a natural size of clusters depending on the initial random distributions. In our model a cluster consists of aligned particles of the same type moving in the same direction. In the case of particles of only one type, clusters tend to unite into one large cluster. In the case of several kinds of particles, the dynamics of the clusters is more complicated.

In what follows we describe in detail a CA model for aggregation of aligned particles of m different types. Consider m square ($n \times n$) lattices with nodes r and with periodic boundary conditions. State space stochastic Boolean variables are

$$S^{(k)} = (s_1^{(k)}, s_2^{(k)}, s_3^{(k)}, s_4^{(k)}) \quad k = 1, \dots, m$$

where $s_i^{(k)} = 1(0)$ indicate one of the four directions in the lattice and

$$\eta^{(k)}(r) = (\eta_1^{(k)}(r), \eta_2^{(k)}(r), \eta_3^{(k)}(r), \eta_4^{(k)}(r)) \quad k = 1, \dots, m$$

denote configurations at node r in m lattices. In this paper we impose an exclusion principle which generalizes a principle from Cook *et al* (1997) to the case of several types of particles, by limiting the sum of densities of particles of all types by four for the same node r :

$$\rho(r) = \sum_{k=1}^m \rho^{(k)}(r) = \sum_{k=1}^m \sum_{i=1}^4 \eta_i^{(k)}(r) \leq 4.$$

Notice that another principle may also be imposed:

$$\rho^{(k)}(r) = \sum_{i=1}^4 \eta_i^{(k)}(r) \leq 4 \quad k = 1, \dots, m.$$

By applying a template, the next neighbors of the node r of type k can be described as follows:

$$N^{(k)}(r) = (r + c_1, r + c_2, r + c_3, r + c_4)$$

where

$$c_1 = (1, 0) \quad c_2 = (0, 1) \quad c_3 = (-1, 0) \quad c_4 = (0, -1).$$

Then local orientation fields are described by the formulae

$$O_{N(r)}^{(k)} = \sum_{i=1}^4 \eta_i^{(k)}(r + c_i) \quad k = 1, \dots, m.$$

One can also calculate local densities of particles of a particular type k by simply summing up the number of particles of this type which are next neighbors of a given node r :

$$D_{N(r)}^{(k)} = \sum_{i=1}^4 \rho^{(k)}(r + c_i).$$

Initially particles are randomly distributed on the lattice. Then interaction and transport steps, to be described below, are applied to every node in the lattices simultaneously.

Interaction is performed according to the following transition probabilities:

$$A_{s,s'}(O_{N(r)}^{(k)}) = \begin{cases} \frac{M(s')}{Z(s)} & \text{if } \rho(s') = \rho(s) \\ 0 & \text{else} \end{cases} \quad (2.1)$$

where

$$M(s') = \exp \left(\sum_{k=1, \dots, m} (\beta_k (O_{N(r)}^{(k)} \otimes s') + \gamma_k \rho^{(k)}(r) D_{N(r)}^{(k)}) \right)$$

the normalization factor $Z(s)$ is chosen such that

$$\sum_{s', \rho(s') = \rho(s)} A_{s,s'}(O_{N(r)}^{(k)}) = 1$$

and

$$O_{N(r)}^{(k)} \otimes s' : N_0^5 \times S \rightarrow N_0$$

is a bilinear functional. In this paper we choose $O_{N(r)}^{(k)} \otimes s' := \langle O_{N(r)}^{(k)}, s' \rangle$ which favours parallel orientation (for details see Deutsch (1999a, 1999b)). The parameters β_k and γ_k control alignment and aggregation, respectively. Notice that, in the case of $O_{N(r)}^{(k)} = 0$, a random discrete walk is used.

Transport is implemented as follows. Particles move along their directions to the next neighbors:

$$\eta_i^{(k)}(r) \rightarrow (\eta_i^{(k)}(r))^T := \eta_i^{(k)}(r - c_i).$$

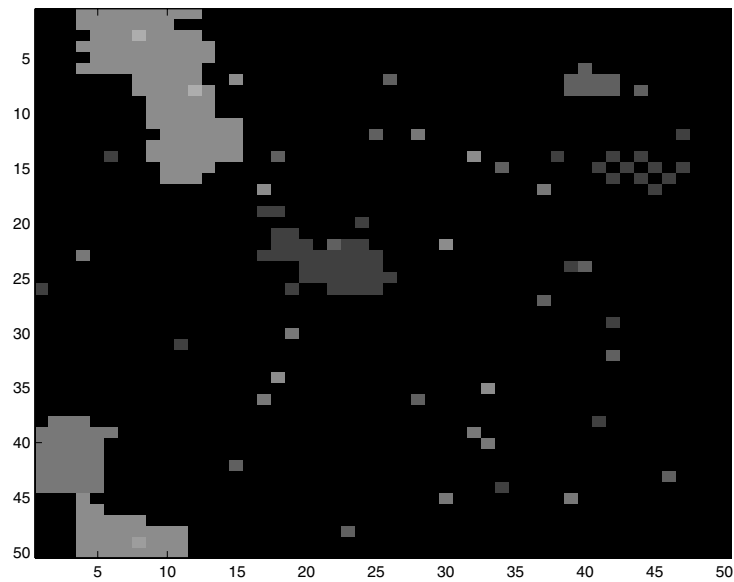


Figure 1. Distribution of particles of type I after 150 cycles. The following values of the parameters were used: $\beta_1 = 2.8$; $\beta_2 = 2.75$; $\gamma_1 = 0.2$; $\gamma_2 = 0.3$.

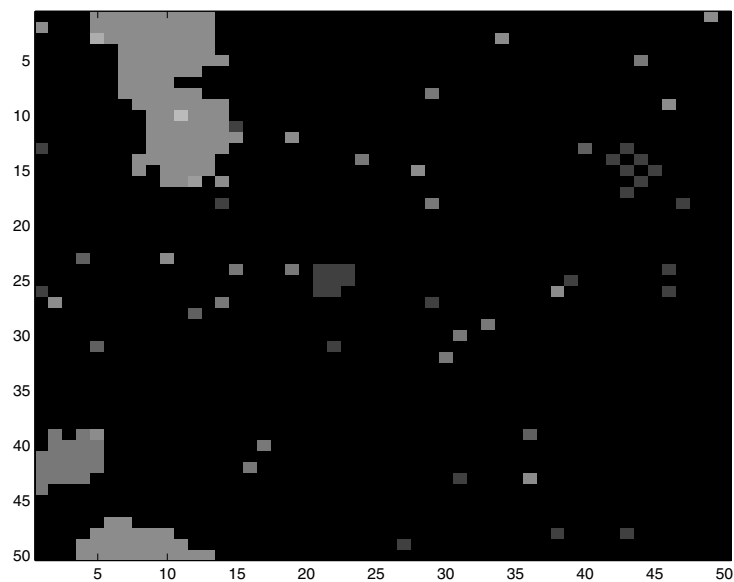


Figure 2. Distribution of particles of type I after 200 cycles. The following values of the parameters were used: $\beta_1 = 2.8$; $\beta_2 = 2.75$; $\gamma_1 = 0.2$; $\gamma_2 = 0.3$.

In what follows we demonstrate a general algorithm by describing numerical results in the case of particles of two different types.

In the numerical experiments described in figures 1 and 2 we consider two 50×50 lattices with 30% of nodes occupied initially by particles of each type. Different scales of grey indicate particles moving in one of four directions. Systematic investigation of the ranges of parameters

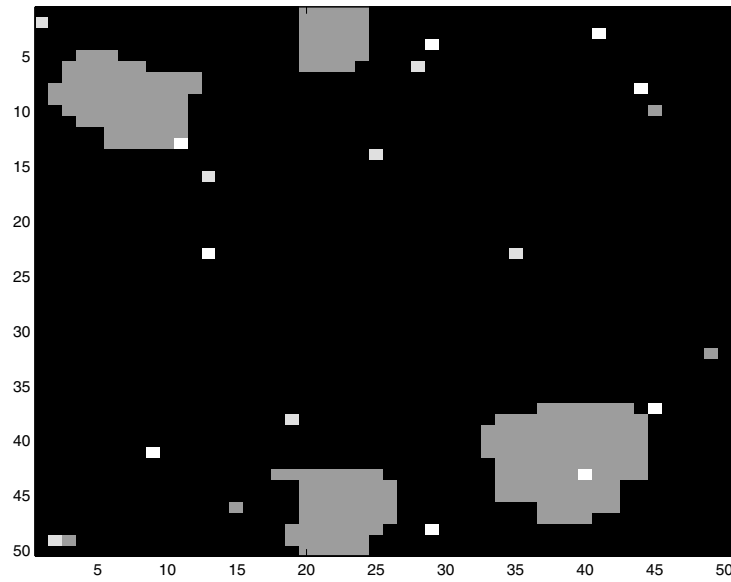


Figure 3. Distribution of particles of type I after 500 cycles. The following values of the parameters were used: $\beta_1 = 3.1$; $\beta_2 = 2.75$; $\gamma_1 = 0.2$; $\gamma_2 = 0.3$.

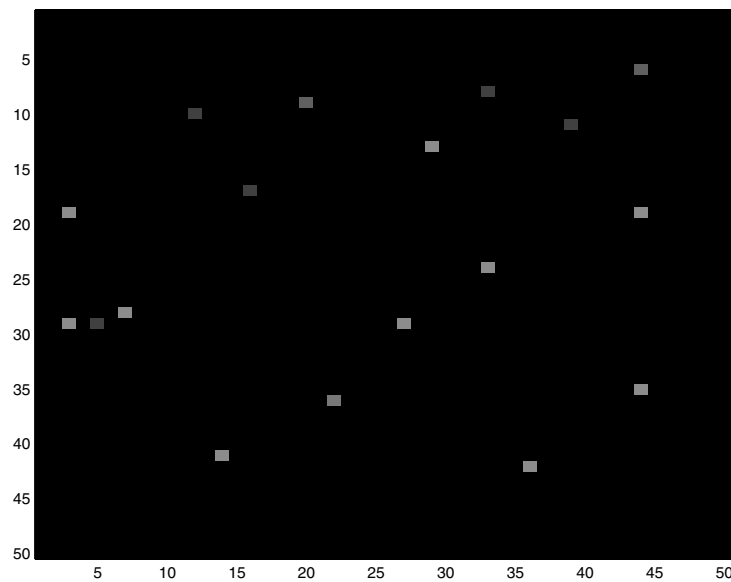


Figure 4. Distribution of particles of type II after 500 cycles. The following values of the parameters were used: $\beta_1 = 3.1$; $\beta_2 = 2.75$; $\gamma_1 = 0.2$; $\gamma_2 = 0.3$.

resulted in values of β_k and γ_k which yield clustering in both lattices. Running code for only 150 steps results in clearly visible clusters of aligned particles of different sizes. Notice that checkerboard patterns are also present, but they are not stable and disappear after 500 steps. Figure 2 demonstrates the evolution of the clusters after 200 steps.

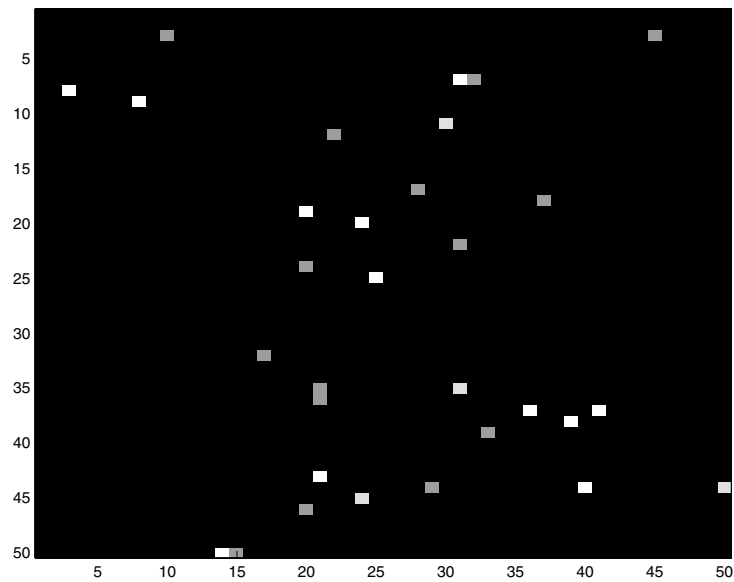


Figure 5. Distribution of particles of type I after 500 cycles. The following values of the parameters were used: $\beta_1 = 2.8$; $\beta_2 = 2.75$; $\gamma_1 = 0.2$; $\gamma_2 = 0.4$.

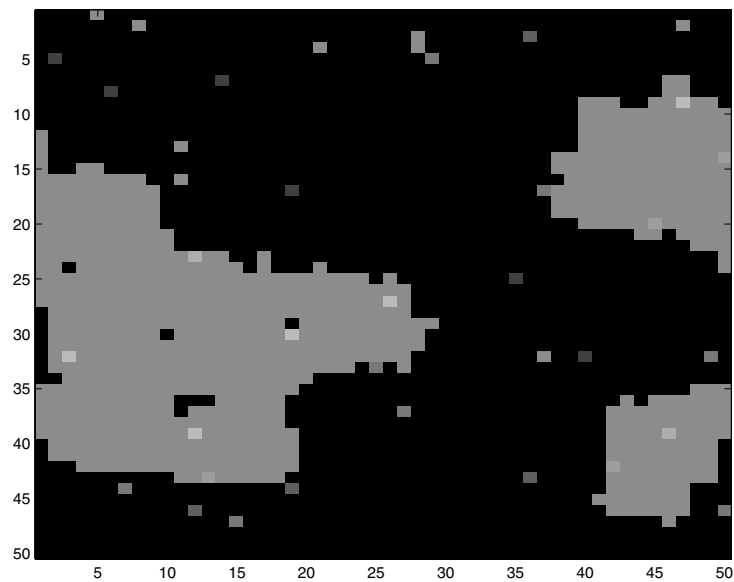


Figure 6. Distribution of particles of type II after 500 cycles. The following values of the parameters were used: $\beta_1 = 2.8$; $\beta_2 = 2.75$; $\gamma_1 = 0.2$; $\gamma_2 = 0.4$; $\delta = 0.6$.

In the numerical experiments described in figures 3–6 two 50×50 lattices are considered, with 40% of nodes occupied initially by particles of each type. These figures demonstrate the large sensitivity of the cluster formation to slight changes in parameters, leading to an imbalance between the alignment and aggregation of particles.

The numerical experiments also describe a switch between two different scales. We start by tracking the motion of individual particles and end up by describing the motion of clusters of aligned particles. After the average size of clusters is stabilized one can use the approach of Graner and Glazier (1992) which involves, amongst other things, the minimization of cell–cell energies. Currently we are working on imposing size restrictions on the clusters of aligned particles with the goal of using clusters for modeling cells. For example, the front end of each cluster can be made more sensitive, which is important in modeling cell–cell interactions, by expanding the directional field to the second, third, fourth, etc, neighbors. Also, clusters can be made longer in one direction for modeling special types of cells, such as fibroblasts on a surface.

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