Minsuk, S. B. (2005). Toward an Open-Ended and Mechanically Realistic Model of Biological Cells. In: Workshop on Artificial Chemistry and Its Applications. The 8th European Conference on Artificial Life (ECAL) Workshop Proceedings. Mathieu Capcarrere (ed.). http://www.sharonminsuk.com/

Toward an Open-Ended and Mechanically Realistic Model of Biological Cells

Sharon B. Minsuk

Konrad Lorenz Institute for Evolution and Cognition Research,
Adolf Lorenz Gasse 2, A-3422 Altenberg, Austria
sharon.minsuk@kli.ac.at
http://www.kli.ac.at/institute-b.html?personal/minsuk

Abstract. With the aim of developing simulated multicellular organisms that develop, reproduce, and evolve, a simple, general, and mechanically realistic model of a biological cell is needed. The cellular Potts model (CPM) has been used to simulate cells of arbitrary shape, and the mechanical interactions between them, and has been shown to capture the fluid dynamic properties of living tissues. However, the CPM was designed to study adhesive cells moving passively within aggregates. To be useful in an open-ended simulation of simple organisms and embryos, the CPM must be generalized to handle cells of low or no adhesion, isolated cells, and directed, actively moving cells. The original CPM contains built-in assumptions that cause it to behave incorrectly under these conditions. Extensions to the CPM are here presented that overcome these limitations, moving toward a generic model.

1 Introduction

Studies of the evolution of embryonic development in living organisms will be aided by models of simple multicellular organisms that develop, reproduce, and evolve in silico. It is important that such models incorporate the material properties of living cells, because these are critical to understanding development and evolution. Embryo development involves cell movement, cell shape change, and tissue formation and remodeling [7, 14] – mechanical processes that must be represented in order to capture embryo dynamics. Models that represent cells as simple circles or even as dimensionless points, or that allow arbitrary cell movement and shape change with no consideration of forces [2, 3, 13], are too simple to reproduce these dynamics. This mechanical aspect of life determines much of the selection pressures to which organisms must adapt (e.g., in locomotion, food gathering, avoiding or resisting predation, or mating), and these mechanical problems have evoked mechanical solutions (e.g., cytoskeletons in eukaryotes; musculoskeletal systems in animals; rigid cell walls and the specialized structures of leaves and flowers in plants). Thus mechanics is central to understanding the evolution of morphology as well as of development.

Other simulation approaches have incorporated detailed models of the mechanical properties of cells and the forces within and between cells [1, 5, 10, 14]. Such models can describe cells quite realistically but are often computation-intensive, and are gen-

erally specific to a single tissue and species, and therefore are not general or open-ended enough to describe a whole organism or its evolution. A fast and relatively simple, yet general and mechanically realistic cell model is needed, sufficient to support model unicellular and simple multicellular organisms.

This paper presents a cellular-automaton-like artificial chemistry, in which two orders of structure are built in from the beginning: second-order structures (biological cells) with their own cell-level properties, and the first-order elements of which they are constructed. The subcomponent "molecules" are not meant to represent simple molecular species, such as lipids or proteins, but larger, supramolecular regions of the cell. The goal is to construct model cells with realistic mechanical behavior, from which realistic cell-cell interactions (third order structure) can emerge.

The model is adapted from the cellular Potts model (CPM) of Glazier and colleagues [5, 9], a model of cell behavior in adhesive aggregates. The CPM, compared to other models in theoretical biology, captures a lot of behavioral realism with relatively simple math, making it both computationally efficient, and (an advantage to the present author) more accessible to a non-physicist. CPM cells have arbitrary and dynamically changing shapes, controlled by forces resulting from the cells' own mechanical properties. In section 2, I describe my implementation of the CPM. Like other models in theoretical biology, the CPM has built-in assumptions that limit its generality. In section 3, I describe certain problems that arise from these assumptions, and extensions to the model that address these problems, making the model more general and open-ended. In section 4, I discuss prospects for future enhancement.

2 Basic Implementation of Glazier's Cellular Potts Model

The CPM universe is an array in which collections of adjacent array elements represent biological cells (Fig. 1(a)). The present implementation uses a 2D hexagonal array. Each array element contains an integer, the cell index. Each cell i consists of all those elements with cell index i, and can be of arbitrary size and shape. The surrounding fluid environment is treated as a special cell, cell 0, with special properties.

In each iteration of the simulation, a "Potts move" may occur. An array element, and one of its nearest or second-nearest neighbors, are chosen at random. If they belong to different cells (their cell indices are unequal), the content of the second array element is copied into the first, changing the cell membership of that element. Thus cells change shape by stepwise gain and loss of array elements (Fig. 1(b)-(c)). But the move is accepted only if the cells (other than cell 0) remain simply connected, and only if an energy-minimization criterion is satisfied, as described below.

The energy of the move has three components:

$$\Delta H = \Delta H_{\text{adhesion}} + \lambda_1 \Delta H_{\text{volume}} + \lambda_2 \Delta H_{\text{surface area}} . \quad (1)$$

$\Delta H_{\text{adhesion}}$ measures the energy of changing adhesive contacts. Each cell i has a cell-specific adhesive strength $j_i \geq 0$. Adjacent array elements in cells a and b adhere along their common edge with an adhesive energy $J = -(j_a j_b)^{1/2}$. (J = 0 for elements within a single cell.) H_{adhesion} for a given array element is the sum of all J for all 6 edges of that element. $\Delta H_{\text{adhesion}}$ is the change in adhesive energy caused by the Potts move. Thus

increased contact between sticky cells produces a negative $\Delta H_{adhesion}$ and is favored. Cell 0 has $j_0 = 0$, so cells do not "stick" to the surrounding fluid.

The other terms in ΔH allow cells to maintain their volume and surface area (area and perimeter in this 2D implementation) over time even though each single Potts move changes those values. In living cells, volume is static because water is incompressible, and surface area is constrained because membrane is in finite supply, and under tension. Each cell i has a constant target volume V_i and an actual volume at time t, $v_i(t)$. For cell i, $H_{volume}(t) = (v_i(t) - V_i)^2$. The change in this value is therefore negative (favorable) when the volume approaches V_i, and positive otherwise. The total ΔH_{volume} is the net change for the two cells whose volumes are modified by the move. (Cell 0 is unconstrained: there is no V_0, and $H_{volume}(t) = 0$.) The surface area constraint works exactly the same way, with a target surface area S_i. Thus volume and surface area remain close to their target values, endowing cells with a spring-like resistance to stretch and compression. The constants λ_1 and λ_2 control the relative weights of these constraints, and therefore represent the inelasticity of the cells.

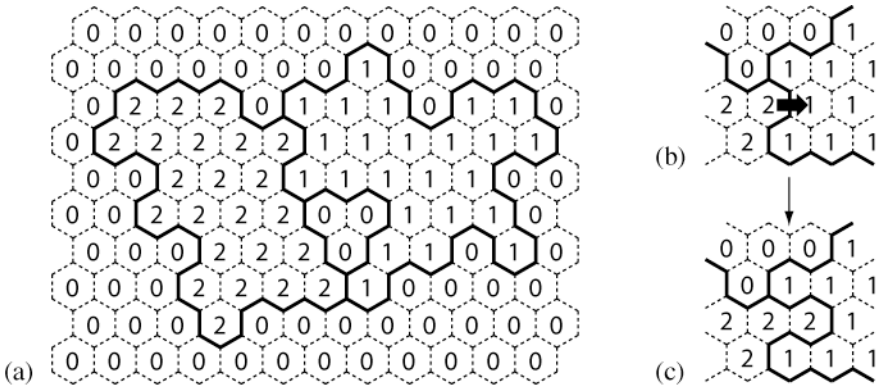

Fig. 1. (a) A section of the array containing two cells surrounded by the fluid environment. (b) Two adjacent array elements have been selected for a Potts move. Thick arrow indicates the direction of the copy. (c) The new configuration that results if the move is accepted.

The Metropolis algorithm is used to prevent the configuration of cells from getting "stuck" in local energy minima [5, 9]: any Potts move with $\Delta H \leq 0$ is automatically accepted, whereas any move with $\Delta H > 0$ is accepted with a probability

$$p = e^{(-\Delta H/T)} . \quad (2)$$

Thus if a Potts move is highly unfavorable (ΔH positive and large), then p approaches 0, and the move will be rejected; but if it is only slightly unfavorable (ΔH positive and small), then $0 < p < 1$, and the move may be accepted. Cells can thus explore their neighborhood to find globally favored configurations. The constant T, the simulation "temperature", controls how easy it is for unfavorable moves to be accepted.

At the level of the individual array elements and Potts moves, the CPM is by no means an explicit model of the components of living cells and their actual mechanical interactions; Potts moves do not represent real events. Rather, they represent a com-

putational shorthand designed to capture the cumulative effects of real forces in many cells over many iterations, producing realistic behavior at the level of the whole cell or tissue. The goal of the CPM, and of the enhancements presented here, is not to test what we know about subcellular structures or events, but to create a phenomenological model with reasonably correct cell-level behavior, which can then be used to study cell-cell and cell-environment interactions.

Simulated cell aggregates (Fig. 2) follow the predictions of Steinberg's hypothesis that differentially adhesive cells, undergoing changing contacts due to random motion, will rearrange passively [4, 5, 12]. Glazier and colleagues have shown that the model performs in accordance with the fluid-dynamic properties of living tissues [9].

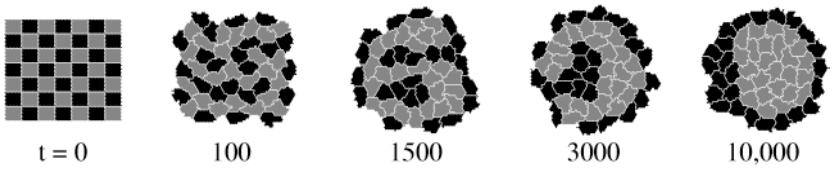

Fig. 2. Basic CPM demonstrating sorting of differentially adhesive cells. Aggregate is initialized at t = 0 as an array of rectangular cells, each composed of 8 rows of 8 hexagons. (Individual hexagons are too small to see at this magnification.) Cells have j = 50 (gray) or j = 10 (black). Time is in Monte Carlo steps, where one Monte Carlo step is as many iterations of the algorithm as there are total array elements in the simulation. Adhesion creates surface tension that causes the aggregate to round up, and to sort, with the less adhesive black cells engulfing the more adhesive gray cells. Note the variable shapes assumed by the cells. Other parameters (for this and all subsequent figures): $V_i = 64$ and $S_i = 55$ for all cells; $\lambda_1 = 4$; $\lambda_2 = 1$; T = 10.

3 Problems and Extensions

3.1 Preventing "Suction"

The CPM was designed to study adhesive cell aggregates [5], but a general purpose model must accommodate isolated cells, and cells with low or no adhesion. Non-adhesive cells in an aggregate should disperse, because no force holds them together, and the compression resistance of neighbors should bias them to move toward open space, in a diffusion-like process. But the experiment (setting all j_i to 0) revealed a previously undocumented anomaly: dispersal is retarded or prevented. The strength of the effect increases with cell size. Cells with $V_i = 16$ disperse gradually. With $V_i = 25$, they disperse more slowly, maintaining a clumped aggregate with a loosely packed boundary, from which individual cells occasionally escape. With $V_i = 64$ (Fig. 3(a)), no cells escape except transiently, and the aggregate boundary is more tightly packed, suggesting surface tension (which should be absent when all adhesion is 0 [4, 5].)

This effect occurs because each Potts move alters the boundaries of two neighboring cells, thereby coupling their movement. By the very nature of the transformation, two cells cannot separate, except by "unzipping" from the edge of their mutual contact area. Thus a kind of suction is present, proportional to the contact area between

the two cells. It is always present, but only noticeable when adhesion is low.

The following "suction-release" algorithm eliminated this effect. After two neighboring array elements have been selected for a Potts move, an electronic coin flip decides which cell is driving the motion – the growing cell or the shrinking cell. If the growing cell is driving the motion, then the algorithm proceeds as usual (because a cell extending a protrusion must push other cells out of the way). But if the shrinking cell is driving the motion, then it should be possible for a gap to open between the two surfaces and fill with the surrounding fluid (because a cell retracting its edge will be followed by another cell only if adhesion pulls the other cell, or if the other cell is under compression and naturally expands into the gap). Therefore the immediate surroundings (the 12 nearest and next-nearest neighbors) are searched for the presence of the environment (cell 0), and if any is found then an alternative Potts move is evaluated, in which the array element vacated by the shrinking cell becomes part of cell 0 instead of part of the original neighbor cell. ΔH for both the original and the alternative move are calculated, and whichever move has the lower ΔH is accepted or rejected as described previously. (When no surrounding fluid is present nearby, it is appropriate for suction to hold the cells together.) The result is shown in Fig. 3(b).

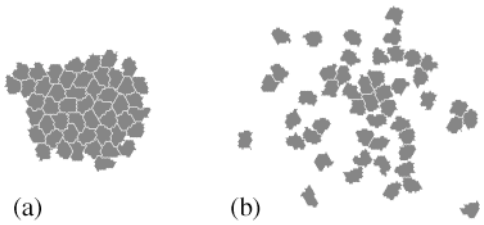

Fig. 3. Cell aggregates initialized as rectangular arrays as in Fig. 2, except $j_i = 0$ for all cells. (a) In the original CPM, aggregate is still intact at t = 10,000 despite complete absence of adhesion. (b) In the CPM with suction-release algorithm, running under identical parameters, cells at t = 10,000 have dispersed.

3.2 Cell Translocation: Respecting Newton's Third Law

The CPM was designed to model passive rearrangements of cells due to differential adhesion, but a general purpose model must also be able to handle active cell movement, an important component of morphogenesis. In the CPM, the path of cell movement is not a completely predictable consequence of the explicit parameters, but is the sum of small, randomly-directed displacements. As long as motion is passive, the net result is a slow, randomly-directed drift. But when active, directed motion is added to the model, this drift becomes amplified into a directional migration that should not occur except under special circumstances requiring additional assumptions.

The initial selection of neighboring elements for each potential Potts move, and hence the direction of each potential move, is random. As long as acceptance/rejection of moves is not directionally biased, the resulting movement will also be directionally random. Bias comes from forces external to a cell: adhesive attractions from neighbors, or resistance of neighbors to compression. A cell's own internal forces

(arising from V_i and S_i) are non-directional. Thus an isolated cell experiencing no external forces undergoes only unbiased drift. This nonetheless gradually accumulates a noticeable translocation (Fig. 4(a)).

Furthermore, when two cells impose directional forces on one another, equal and opposite forces should push or pull the cells in opposite directions (Newton's third law). But each Potts move violates this rule. For example, in Fig. 1(b)-(c), an array element is added to the right edge of cell 2, so this cell's center of mass shifts slightly to the right. That same array element is eliminated from the left edge of cell 1, so this cell's center of mass likewise shifts to the right. Thus the cells' movements have a component not arising from the forces between the cells. As long as movement is passive, in the absence of an externally imposed directional bias, this will result in directionally random drift, often unnoticeable in large aggregates. But when active motion is introduced, it has large, unintended consequences.

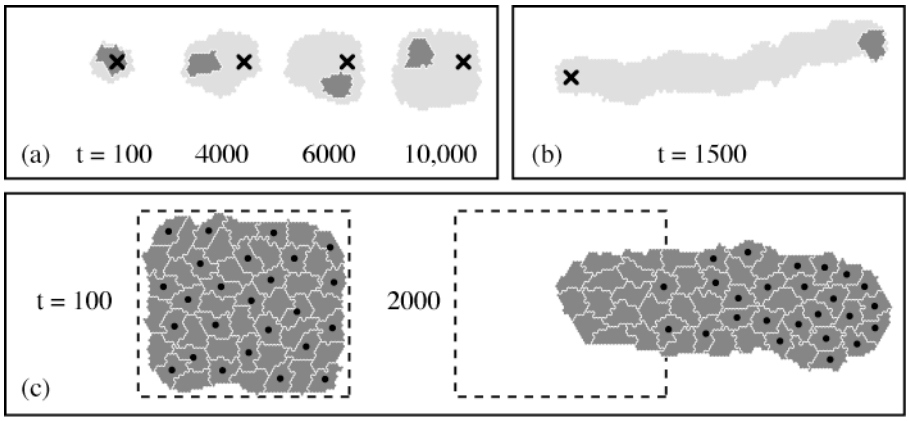

Fig. 4. Translocation in the absence of force in the original CPM. (a) An isolated cell experiences only internal, non-directional forces, but nonetheless drifts. The X indicates the location of the cell center at t = 0, and the light gray background shows the cumulative trail of all array elements the cell passes over during the run. (b) Imposition of a statistical bias on acceptance/rejection of moves causes active, persistent directional motion, although the forces are exactly the same as in (a). (c) An adhesive aggregate (j_i = 50 for all cells) in which half of the cells (those whose centers are marked with a black dot) are subjected to the same statistical bias as the cell in (b); unmarked cells move non-directionally. The dashed box marks the original position of the aggregate.

Active motion is the creation of a directional bias in cell motion, sometimes persistent, by the cell's own control over its locomotion. In Fig. 4(b), a statistical bias has been imposed on the acceptance/rejection of Potts moves, favoring acceptance of moves toward the right. This results in distinct directional migration, although forces driving this motion are not explicitly present in the model. Clearly this can only be justified by assuming the presence of a substrate and of the cell's ability to crawl on that substrate. In the absence of such a substrate, the cell should be unable to migrate.

Another feature of such migrating cells is that they drag non-migrating cells along with them. In Fig. 4(c), the same statistical bias has been applied to half of the cells in

an adhesive aggregate. The active cells sort to the front of the aggregate and drag the other cells along with them because of adhesion. Thus the whole aggregate migrates. For living cells in the absence of a substrate this could not occur, since migrating cells could only move forward by pushing other cells an equal distance backward – the aggregate should sort, but remain stationary. Migration of the whole aggregate only makes sense if the biased cells crawl on a substrate, pulling the unbiased cells.

This very method was used by Hogeweg and colleagues [8, 11] to model chemotactic migration in cells of the slime mold *Dictyostelium* during several developmental stages. This was valid for the earliest stage, when individual cells migrate through the soil [11], because a substrate is present and the mechanics of crawling was not the object of their study. But the model is no longer valid during migration of the *Dictyostelium* "slug" [11], in which a mass of thousands of cells migrates as a unit, or during the transformation from slug to fruiting body [8], because most of the cells in a slug have no substrate except each other. In a model of active cell migration generated by forces between a cell and its surroundings, cells should remain stationary in the absence of such forces, and cells exerting forces on each other should obey Newton's third law. Only then can the active migration be meaningful.

I now present two quite different approaches to solving these problems of locomotion. Neither approach alone was able to provide a complete solution, but a hybrid algorithm using both methods resulted in improved motion, requiring no assumed substrate and able to accommodate active motion.

Method 1: Constraining Center of Mass. The cell volume and surface area of living cells are properties that remain stable over time, but in the CPM, the inherent nature of Potts moves is such that each accepted move changes these values. These values are kept stable by constraining each one to its target value, V_i and S_i, respectively. Each is represented by its own term in equation 1, minimizing the difference between the actual value and its target, so that the values change with each move, but remain stable over time. The cell translocation problem can be viewed as an inappropriate drift of a cell's center of mass unrelated to the forces applied. Thus the center of mass can be treated the same way as volume and surface area – as a quantity that should remain stable over time even though each accepted move changes its value. By constraining it to a target value, the drift can be eliminated.

This is implemented exactly like the other constraints, except that a cell's center of mass is a vector, $(cx_i(t), cy_i(t))$. With the simplifying assumption of constant density, a cell's mass is simply its volume, and the center of mass is the mean of the coordinates of all the array elements in the cell. A target center of mass, (Cx_i, Cy_i), is defined for each cell i, equal to the cell's actual center at the time of initialization. In the absence of external forces, this is kept constant. A constraint term is added to equation 1 to minimize the distance between a cell's actual center and its target center, $H_{center}(t) = (cx_i(t) - Cx_i)^2 + (cy_i(t) - Cy_i)^2$. Thus an isolated cell can wiggle, but never drifts (Fig. 5(a)). This is true even when active motion is introduced by the imposition of a directional bias (Fig. 5(b)), as it should be, because there is no substrate which the cell can adhere to and crawl on. Directional motion as seen in Fig. 4(b) will now require the *explicit* definition of such a substrate and a crawling mechanism.

By itself, this center of mass constraint would prevent all cell displacement. In or-

der to allow displacement in response to forces from neighboring cells, the target centers must be explicitly updated. This is always done reciprocally, moving the target centers of two cells in opposite directions. Subcomponents of ΔH are used to determine how far to move each cell, as follows. First, two cells are pushed apart whenever the growing cell is pushed outward by its own volume and surface area constraints; i.e., when the contribution of only the growing cell to ($\Delta H_{volume} + \Delta H_{surface\ area}$) is negative. The push occurs along the line between the two cells' target centers.

Second, cells are pulled together whenever an accepted Potts move is favored by adhesive changes. When an element of the shrinking cell is replaced by the growing cell, contacts with third neighbors may be broken and reformed. Each such contact exchange may be either favorable or unfavorable, depending on j_i for each cell. When the net energy change for all such contacts is favorable (negative), the growing cell pulls those third neighbors with which favorable contacts were made. The growing cell's target center moves along the line from its center to the newly acquired array element (i.e., toward the new adhesive contact points). The adhering cells' target centers move oppositely, and if there are two or more such adhering cells, the amount of pulling force is distributed to each proportionally, according to the energy gain at each contact and the amount of contact (number of edges) with each cell.

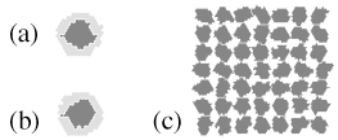

Fig. 5. Cells with constrained centers of mass. (a) An isolated cell as in Fig. 4(a). At t = 4000, cell has not drifted. (b) An isolated cell with biased acceptance/rejection of moves, as in Fig. 4(b). At t = 4000, cell has not migrated. (c) Non-adhesive aggregate as in Fig. 3(b), t = 10,000. Cells no longer disperse across open space, but nudge one another apart by their movements.

For both pulling and pushing interactions, the distance each target center is moved is inversely proportional to the cell's mass (i.e., its target volume). Thus the product of mass and distance is equal and opposite for the two cells, as appropriate for objects experiencing equal and opposite forces. The modified target center locations are taken into account in calculating the distances of the cell centers from their targets after the prospective Potts move, and thus contribute to the calculation of ΔH and the ultimate acceptance or rejection of the move.

Under this algorithm, non-adhesive cells no longer disperse long distances, but only as far as they can push one another (Fig. 5(c)). As they move apart, the contact between them decreases, thus reducing the pushing forces between them. The state of the cells thus approaches that of Fig. 5(a), in which movement is no longer possible without some explicitly defined external force. In an aggregate of adhesive cells, all equally adhesive, the adhesion overcomes these pushing forces and the aggregate simply rounds up, just as in the original CPM – but with one important difference. In the CPM, the aggregate center of mass (the mass-weighted average of the centers of all the cells) drifts considerably. In the modified algorithm, the aggregate center hovers near the aggregate *target* center, which itself remains stationary during the entire

duration of all runs, even while the individual target centers rearrange.

This algorithm unfortunately failed for heterogeneous aggregates – those containing cells of different adhesive strengths, or those in which directional bias was applied to a subset of cells, such as in Fig. 4(c). Depending on the parameters used, cells either were immobilized, or they became elongated and distorted as if subjected to extreme forces. The failure is restricted to cell-cell interactions between the heterogeneous cell types, and only in the aggregate interior, away from the interface with the environment. Many variant algorithms were attempted in order to diagnose and remedy this failure, but no remedy was found. Fortunately, there is an entirely different approach to the problem of drifting centers of mass and drifting aggregates, applicable specifically to cell-cell interactions not involving the environment interface. This approach and the resulting successful hybrid algorithm are described in the next section.

Method 2: Redefining Potts Moves. The basic Potts move produces deviations from ideal behavior: the volume and surface area of a cell, as well as its center of mass, are changed by each Potts move, even though in living cells, they are stable until perturbed. These deviations, although directionally random, would accumulate over time if not prevented. One approach to preventing them is to compensate for them by constraining them to target values – V_i and S_i [5, 9], and, in method 1 above, (Cx_i, Cy_i). An alternative is to use a different type of fundamental individual move that does not produce these deviations in the first place.

In the CPM, a Potts move selects two neighboring points in neighboring cells, and copies one point over the other, causing one cell to acquire a new array element from the other cell (a "Potts copy"). An alternative approach would be to swap the two points instead, causing each cell to lose one array element and gain another (a "Potts exchange"). In a Potts exchange, the movements of the two cells are exactly equal and opposite. Thus the motion obeys Newton's third law inherently, creating no deviation for which to compensate. Even after adding the directional bias of active motion, all cell movements will be balanced by opposite movements of other cells, so all motion will be accounted for without having to invoke additional, undefined forces.

However, replacing all Potts copies with Potts exchanges would not be a viable, complete alternative to method 1. A Potts exchange along the boundary between two (non-environment) cells solves the problem of the two cells moving in the same direction, but a Potts exchange along the boundary of a cell and the environment will still suffer the problem of accumulating drift. Also, Potts exchanges are less flexible, lending themselves to the sliding of cells past one another, but not to cells pulling each other together across a gap, or pushing each other apart to create a gap (as in Fig. 5(c)). But, because method 1 handles these cases well, and because the cases for which method 1 failed lie well within the category where Potts exchanges can do the most good, a hybrid algorithm employing both methods was devised, as follows.

On each iteration, two neighboring points are selected at random. If either point is in cell 0, then a Potts copy is carried out; otherwise an electronic coin flip determines whether a Potts copy, or a Potts exchange, will be carried out. The Potts copies are as described above, including the procedures of method 1 (constraint of cell centers of mass to their targets, and update of the targets in response to external forces).

When a Potts exchange is to be carried out, the two initially selected points are

used only to identify the two neighboring cells in which they lie; a new pair of points is then selected randomly from anywhere along the boundary between the two cells, one on each side of the boundary. Thus the two points to be exchanged may be quite distant from one another but are guaranteed to be adjacent to the boundary, one from each cell. As usual, ΔH is then evaluated to determine acceptance/rejection. ΔH includes adhesion and the surface area constraint (taking into account that two different array elements are being modified instead of just one); but no volume constraint, because during an exchange of array elements the volume of each cell remains constant ($\Delta H_{volume} = 0$). Finally, in contrast to Potts copies, the movement of the cells' centers of mass are automatically equal and opposite, and so need not be constrained. If a Potts exchange is accepted, the target centers are simply moved the same distance and direction as the actual centers, maintaining the relationship between center and target.

Under this algorithm, isolated cells, and aggregates of non-adhesive or equally adhesive cells, behave exactly as under method 1. In addition, heterogeneous aggregates behave properly, not exhibiting the failures of method 1. Differentially adhesive cells sort as in the original CPM, except that the aggregate center remains stationary. Finally, the addition of a directional bias to a subset of cells in an aggregate (Fig. 6) results in a drastically different behavior from that of the original CPM. Now, since all cell translocation, both during Potts copies and during Potts exchanges, must arise from equal and opposite forces, the biased cells sort to one side of the aggregate by pushing the non-biased cells to the other side. This algorithm therefore produces correct motion based on the interactions between the cells, without having to assume a cryptic substrate, and even when active motion is added.

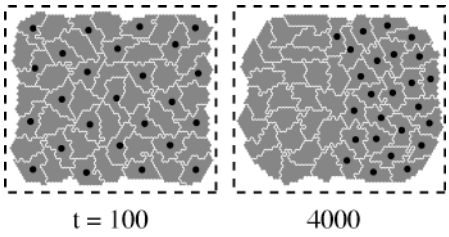

Fig. 6. Algorithm combining Potts copies (with centers of mass constrained) and Potts exchanges. Same parameters as in Fig. 4(c); directionally biased cells are marked, and dashed box indicates original aggregate position. Active cells now advance by pushing the other cells backward, leading to sorting without migration of the aggregate.

4 Conclusions and Future Prospects

I have presented a first step toward a "generic cellular Potts model", the GCPM, a mechanical cell model with generalized properties, exhibiting biologically realistic behavior under a variety of conditions, depending on only those forces explicitly described in the model. This model already produces a rich range of behavior based

on its inherent mechanics, without a genome, a metabolism, or a complex environment, the addition of which will surely add still greater richness.

Several additional enhancements are needed at the mechanical level. CPM cells have boundaries, but no explicit membranes – distinct outer coverings with properties independent from those of the interior. Membranes are the locus of all mechanical and chemical cell-environment interaction, and are a critical component of cellular self-maintenance, and so should be described explicitly. A version of the GCPM including such an explicit description has been developed and will be presented elsewhere. The model should of course be expanded to 3D, as has been done for the original CPM [6, 11]. An improved model of active motion is also necessary. The model now works correctly for passive cell rearrangements and with directionally biased motion, but a bias imposed numerically [8, 11] is an ad hoc description that treats the locomotion mechanism as a black box; instead, it should be described in terms of forces between the cell and its environment, just as the passive movements are. One feature that will be required for such a description is heterogeneity of the cell surface. Cellular control over the properties of different surface domains is not only a requirement for directional motion [14], but is a fundamental feature of numerous aspects of cell structure, physiology, and behavior. These enhancements are currently under development.

The GCPM will provide a starting point for improved simulations of living cells and tissues, as well as for richer adaptive simulations of cellular and multicellular evolution. Realistic mechanical constraints on cells' behaviors and capabilities, in an evolutionary scenario, should provide both limits to, and opportunities for, the evolution of solutions to the problems of living in a mechanical world.

Acknowledgments

Many thanks to James Glazier for extensive conversation and advice about the Potts model; to Eirikur Palsson for pointing out the tendency for the Potts model to behave as in Fig. 4(c); and to Camille Stephan-Otto Attolini for discussing and experimenting with the causes of suction. Thanks also to Ulrich Krohs, Elias Khalil, and Igor Popov for comments on the manuscript; and to the Konrad Lorenz Institute for Evolution and Cognition Research for a postdoctoral fellowship providing financial support and the opportunity to do this work.

References

1. Davidson, L.A., Koehl, M.A.R., Keller, R., and Oster, G.F., How do sea urchins invaginate? Using biomechanics to distinguish between mechanisms of primary invagination. *Development*. 121: 2005-2018 (1995).
2. Eggenberger, P., Evolving morphologies of simulated 3d organisms based on differential gene expression, in Fourth European conference on artificial life, P. Husbands and I. Harvey, Editors, MIT Press: Cambridge, MA. p. 205-213 (1997).
3. Fleischer, K. and Barr, A.H., A simulation testbed for the study of multicellular development: the multiple mechanisms of morphogenesis, in Artificial life III: SFI studies in the sciences of complexity, Proc. vol. XVII, C.G. Langton, Editor, Addison-Wesley: New York.

p. 389-416 (1994).
4. Foty, R.A. and Steinberg, M.S., The differential adhesion hypothesis: a direct evaluation. *Dev. Biol.* 278: 255-263 (2005).
5. Glazier, J.A. and Graner, F., Simulation of the differential adhesion driven rearrangement of biological cells. *Phys. Rev. E.* 47: 2128-2154 (1993).
6. Glazier, J.A., Raphael, R.C., Graner, F., and Sawada, Y., The energetics of cell sorting in three dimensions, in Interplay of genetic and physical processes in the development of biological form, D. Beysens, G. Forgacs, and F. Gaill, Editors, World Scientific Publishing Company: Singapore. p. 54-61 (1995).
7. Keller, R., Davidson, L.A., and Shook, D.R., How we are shaped: The biomechanics of gastrulation. *Differentiation.* 71: 171-205 (2003).
8. Marée, A.F.M. and Hogeweg, P., How amoeboids self-organize into a fruiting body: multicellular coordination in *Dictyostelium discoideum*. *Proc. Natl. Acad. Sci. USA*. 98: 3879-3883 (2001).
9. Ouchi, N.B., Glazier, J.A., Rieu, J.-P., Upadhyaya, A., and Sawada, Y., Improving the realism of the cellular Potts model in simulations of biological cells. *Physica A*. 329: 451-458 (2003).
10. Palsson, E. and Othmer, H.G., A model for individual and collective cell movement in *Dictyostelium discoideum*. *Proc. Natl. Acad. Sci. USA*. 97: 10448-10453 (2000).
11. Savill, N.J. and Hogeweg, P., Modelling morphogenesis: from single cells to crawling slugs. *J. Theor. Biol.* 184: 229-235 (1997).
12. Steinberg, M.S., Reconstruction of tissues by dissociated cells. *Science*. 141: 401-408 (1963).
13. Taylor, T.J., From artificial evolution to artificial life. PhD thesis, University of Edinburgh (1999), http://homepages.inf.ed.ac.uk/timt/papers/thesis/
14. Weliky, M., Minsuk, S., Keller, R., and Oster, G., Notochord morphogenesis in *Xenopus laevis*: simulation of cell behavior underlying tissue convergence and extension. *Development.* 113: 1231-1244 (1991).