# Entry Title

Cell-based modeling

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# Synonyms

Cell-based modeling; cell-centered modeling; single-cell-based modeling

# Mathematics Subject Classification

92-08; 92C15; 92C17; 92C42; 92C80

# Short Definition

A cell-based model is a simulation model that predicts collective behavior of cell-clusters from the behavior and interactions of individual cells. The inputs to a cell-based model are cell behaviors as observed in experiments or deriving from single cell models, including the cellular responses to cues from the micro-environment. The cell behaviors are encoded in a set of biologically plausible rules that the simulated cells will follow. The outputs of a cell-based model are the patterns and behaviors

that follow indirectly from the cell behaviors and the cellular interactions. Cell-based models resemble agent-based models, but typically contain more biophysically-detailed descriptions of the individual cells.

## Description

Computational and mathematical modeling are becoming central tools in developmental biology, the study of embryonic and post-embryonic development of multicellular animals and plants, and is instrumental in unraveling cellular coordination. A good computational model lays down the biological knowledge in a structured framework, in particular the interactions between the system components. It then predicts the structures and dynamics the interactions between biological components produce, and in this way helps shape new biological hypotheses. Discrepancies between the biological system and the model point at gaps in our understanding, and suggest new experiments whose results will refine our models. Thus, a systematic cycle between model and experiment produces true insights in biological mechanisms, not just in the molecules that are part of the process.

**Cell-based models** start from the premise that cell behavior is central to unraveling biological development. What a cell can do (e.g. move, secrete a signal, etc.) depends of course on what genes it expresses or has access to. However, what it actually *does* depends also on its microenvironment: what signals does it receive from neighboring cells and from the structural proteins these cells secrete? How flexible is the surrounding tissue, and how does the microenvironment change in response to the cells manipulations, e.g., secretion of proteolytic enzymes or pulling and pushing forces?

The collective behavior of tissues then follows a) the behavior of the constituent individual cells, and b) the shapes and patterns produced by these individual behaviors, and c) the responses of the cells to the new environment they have produced collectively.

Cell-based models are instrumental in predicting the collective cell behavior following from individual cell behaviors. The **inputs** to a cell-based model are the experimentally observed cell behaviors and the cellular responses to cues from the micro-environment. These are encoded in a set of biologically plausible rules that the simulated cells will follow. The outputs of the cell-based model are the patterns that follow indirectly from the cell behaviors, e.g., a vascular network (Merks et al 2006). These model **outputs** result from the cellular coordination that follows non-trivially from the cell behaviors and the responses of the cells to the microenvironment they themselves produce. Cell-based methods have been successful in unraveling processes in developmental biology and in biomedicine (reviewed in Merks and Glazier 2005).

Collective and individual cell motility are the main driving forces of animal morphogenesis. The cells in a developing animal swarm, migrate, mix or sort out and divide - thus developing animal tissues essentially behave as living clays in which biological form and pattern arise primarily through cell motility. Hence, most computational techniques focus on providing descriptions of cell motility, and on the forces the individual cells exert on each other.

Cell-based modeling methodologies for animal development differ in the level of detail by which they describe the cells and by the level of detail by which the positions of the cells can be described. Figure 1 schematically depicts the main mathematical representations of cells in common use. *Single-particle* methods describe cells as point particles or as spherical particles. *Multi-particle* methods use a collection of particles to describe a cell and can therefore include more detail on the shape and motility of the cells. A further distinction is made between *lattice-based* methods in which the particles live on the coordinates of a lattice, and *off-lattice* that use real numbers to describe the particle coordinates.

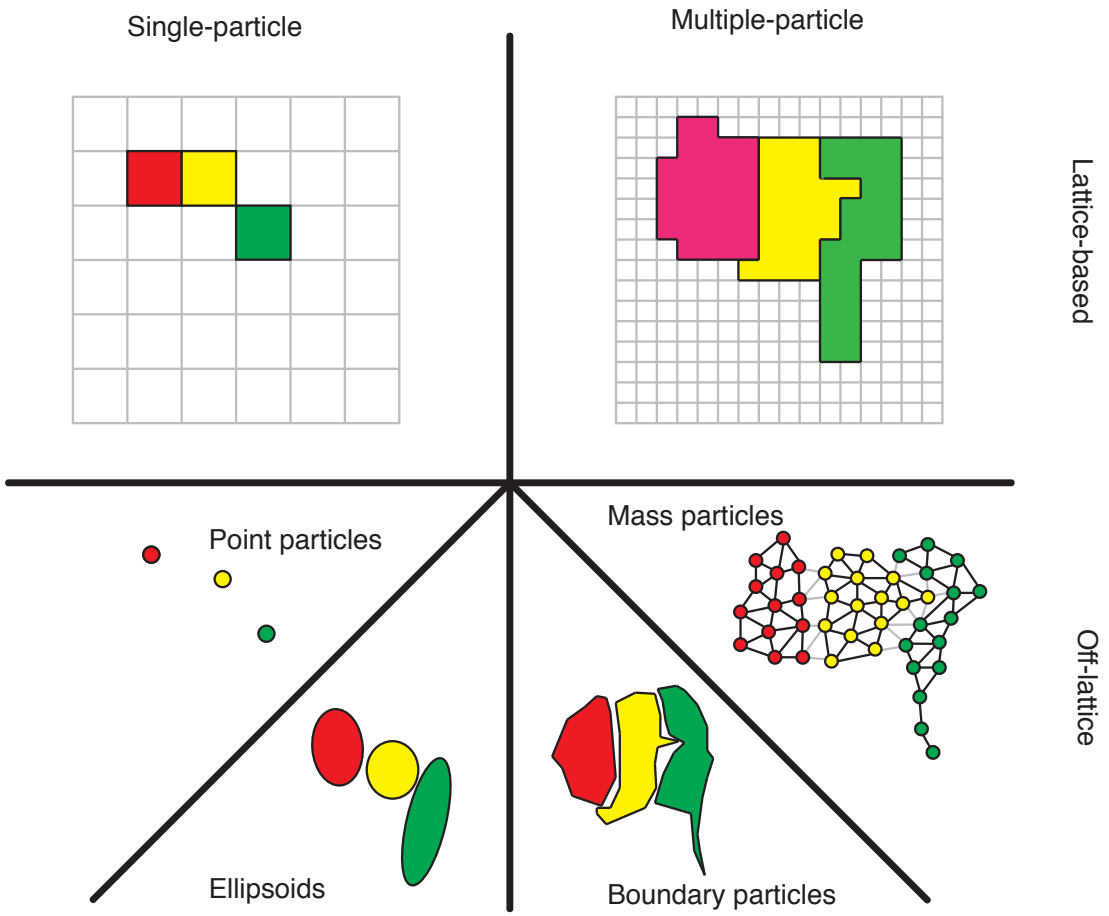


**Fig. 1.** Schematic depiction of common cell representations in cell-based modeling methodologies. The same configuration of three cells is shown in a single-particle, lattice-based model (e.g. lattice gases), in a multi-particle lattice-based model (e.g., the Cellular Potts model), in a single-particle, off-lattice model, and in a multiparticle off-lattice model. Single-particle, off-lattice models describe cells either as point particles or as ellipsoids. Multiparticle, off-lattice models can describe the boundaries of the cells or the cells' interiors.

From a computational perspective, these methods differ in the way the cells are represented in memory and in the algorithms used, and therefore each has its own advantages and disadvantages. In lattice-based methods determining the neighbors of cell is straightforward (just look at adjacent lattice sites), while inserting a cell during cell division is difficult because the surrounding tissue must be shifted over the whole lattice. In an off-lattice method finding neighbors is challenging - in a naive algorithm

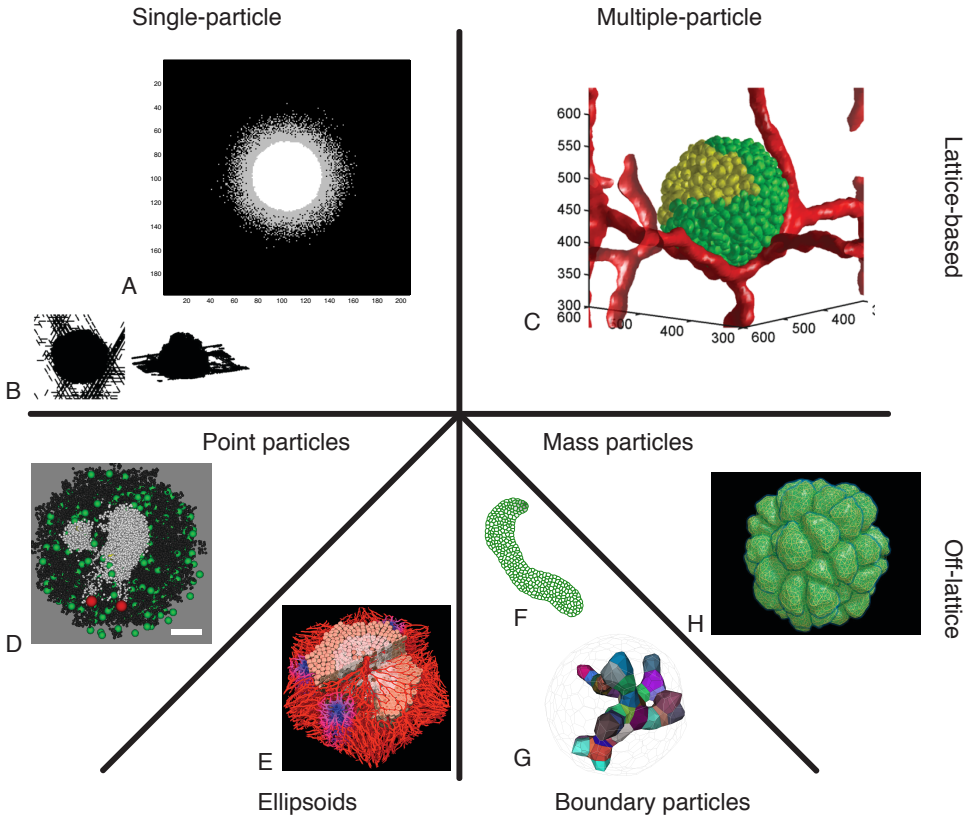


**Fig. 2.** Applications of cell-based modeling in developmental biology: (A) lattice-gas cellular automata model of tumor invasion, with isotropic particles (Hatzikirou et al 2010); (B) three-dimensional lattice-gas cellular automata model of fruiting body formation in myxobacteria, with elongated particles (Sozinova et al 2006); (C) cellular Potts model of vascular tumor growth (Shirinifard et al 2009); (D) Delaunay-Object-Dynamics of germinal center dynamics (Beyer and Meyer-Hermann 2008), scale bar 100 $\mu$m; (E) cell-based, off-lattice model of hepatic tissue expansion during liver regeneration (modified

the positions of all cells would need to be compared with each other - while moving a cell or part of the tissue is easier than in a lattice-based algorithm.

*Single particle methods*

Single-particle methods can describe cells as points on a lattice (Figure 1A), off lattice, as points with real coordinates with the cell boundaries represented by their Voronoi planes (Fig. 1C-1) or as spherical or ellipsoid particles (Figure 1C-2). An example of a lattice-based, single particle cell-based simulation system are lattice gases. Lattice gases have been originally developed for fluid dynamics simulations. Because they model the movement of particles over a lattice and their change of direction due to collisions, they can be applied more generally as agent-based systems and have been used to model cellular interactions and pattern formation in bacterial and animal systems. Deutsch and coworkers have used lattice gases for modeling invasion of tumors (Figure 2A; Hatzikirou et al 2010), and for modeling myxobacterial slime molds (Börner et al 2006), a unicellular organism that aggregates to form mushroom-like fruiting bodies to sporulate.

A limitation of lattice gases is that they cannot straightforwardly represent the shape of individual cells. Therefore Alber and coworkers have taken the lattice gas approach one step further and explicitly represent the rod shaped cells in their lattice gas model, where the interaction rules of the bacteria depend on the relative cell orientation. Their model shows that motile, rod-shaped myxobacteria can aggregate and form fruiting bodies (Figure 2B) due to direct contact dependent interactions causing traffic jams (Sozinova et al 2005).

Lattice gases are a useful for sparse cellular systems with highly motile, swarming cells, in which the shape of individual cells does not need to be described in detail. In most plant or animal or plant tissues the cells partially or completely tesselate the space, and in such cases more detailed descriptions of the tissues are required. Off-

lattice, point methods describe tissues as a set of points in space, where the cells and the contact area between cells is given by a Voronoi tesselation (Schaller and Meyer-Hermann 2004). This method, called Delaunay-Object-Dynamics, models cell motility by moving the points and updating the Voronoi tesselation, and cell division is modelled by duplicating the points. The method has later been extended so it can represent both sparse and dense tissues. In this model of tumor spheroid growth spheres represent isolated cells, and Voronoi tesselations describe denser parts of the tissues (Figure 2D; Schaller and Meyer-Hermann 2005).

The cell-based models by Drasdo and coworkers (Hoehme et al 2010; Byrne and Drasdo 2009; Drasdo 2000) and Palsson and Othmer (2000) represent cells as spheres or ellipsoids. In these methods the forces the cells exert on each other and on their surroundings result in cell movements, often combined with random motility component. They have been applied to a range of problems including the development of the cellular slime mold *Dictyostelium discoideum* (Palsson and Othmer 2000) and liver development (Figure 2E; Hoehme et al 2010). For a detailed review of this class of off-lattice models, see Galle et al (2006).

*Multiple-particle methods*

A disadvantage of single particle methods is that they often necessarily simplify cell shape to spheres, ellipsoids or Voronoi regions, and that cell motility is simplified as translation of the center of mass of the cell. In reality, most animal cells' move by stochastically extending and retracting membrane sections called pseudopods. A detailed description of the stochastic membrane ruffling driving animal cell motility is required for understanding morphogenetic processes. For example, cells in embryonic tissues can be sort out depending on how strongly they adhere to one another, a process called differential-adhesion cell sorting (Steinberg 2007). Such cell sorting requires a accurate description of stochastic cell movement. Cell-based methods that describe

biological cells as collections of particles or in terms of cell perimeter can describe such stochastic cell motility in much more detail.

*Cellular Potts Model*

The Cellular Potts model (CPM), also known as the Glazier-Graner-Hogeweg model, is a lattice-based Monte-Carlo approach that describes biological cells as spatially-extended patches of identical lattice indices (Figure 1C). Intercellular junctions and cell junctions to the ECM determine adhesive (or binding) energies. The CPM algorithm models pseudopod protrusions by iteratively displacing cell interfaces, with a preference for displacements that reduce a local effective energy H of the configuration. Cells reorganize to favor stronger rather than weaker cell-cell and cell-ECM bonds and shorter rather than longer cell boundaries. Further constraints regulate cell volumes, surface areas, cortical tension, cell shape, and chemotaxis. The Cellular Potts model has been succesfully applied to a wide range of biological problems, including the life cycle of the cellular slime mold *Dictyostelium discoideum* (Maree and Hogeweg 2002), blood vessel development (Merks et al 2006), vascular tumor growth (Shirinifard et al 2009), early chick development (Vasiev et al 2010), and T-cell migration patterns in lymph nodes (Beltman et al 2007).

*Off-lattice multiparticle methods*

More recently, several off-lattice multiparticle methods have been introduced. Alber and coworkers use a coarse-grained approach to model rod-shaped, motile myxobacteria as small collections of around three particles coupled with Hookean springs (Wu et al 2009); an energy-minimization approach, similar to the Cellular Potts model, is used to describe cell motion. Typical multiparticle methods use larger set of particles to describe cells. Newman's subcellular element model (Newman 2005) describes cells as 2D or 3D sets of strongly connected particles (Figure 1). Cells are connected via weak

bonds and cells can migrate or slide along one another by randomly constructing and breaking connections to adjacent cells. Because of the detailed description of the cells' cytoskeleton, the method is suitable for quantitative, rheological descriptions of the visco-elastic properties of cells (Figure 2H; Sandersius and Newman 2008). A similar multiparticle method was introduced by Herman Ramon and coworkers (Liedekerke et al 2010).

Other multiparticle cell-based methods provide more or less detailed, finite-element descriptions of the cell boundaries, combined with continuum descriptions of the cell's interior. Honda and coworkers place vertices at the interfaces between at least three cells. The visco-elastic properties of the cell membranes and the resulting motion of the vertices are described using continuum equations. The method was recently applied to a model of symmetry breaking in the early, pre-implantation mouse embryo (Honda et al 2008). Odell et al (1981) and Sherrard et al (2010) have introduced a similar finite-element model that describes cell surface tensions and describes the cytoplasm as an incompressible fluid. Brodland and Clausi (1994), Hutson et al (2008) (Figure 2G), and Tamulonis et al (2010) add neighbor changes to such tension-based finite element models of cell-boundary dynamics. The immersed boundary method introduced by Rejniak (2007) takes a similar boundary-oriented approach, but resolves both the cellular boundary and in particular the intracellular fluid in more detail. The method describes the cell membrane using a collection of particles connected by springs; the cytoplasm is modeled as a viscous fluid modeled in detail by the Navier-Stokes equations that are solved on a grid.

*Plant development: symplastic development*

Most cell-based simulation methods focus on simulating collective cell motility in animal development. In plants and some animal tissues (e.g., in epithelia) the relative positions of the cells are practically fixed, and only cell division and changes in cell

shape affect tissue shape. In addition, the rigid cell walls of plant cells play a key role in regulating cell expansion and overall tissue mechanics. Therefore questions in plant development requires a different choice of cell-based modeling method than animal development. A few cell-based simulation techniques have specialized on plant development. *vv-Systems* is a two-dimensional rewriting grammar to model cell division; its has been applied in a number of recent studies on plant development (e.g., Smith et al 2006). vv-Systems often specify a morphological transformation of the tissue as a whole. A cell division algorithm then partitions the resulting space; thus in vv-systems tissue morphologenesis is not necessarily driven by collective cell behavior as in other cell-based methodology. The methods by Corson et al (2009) and Merks et al (2007) (Figure 2F) resemble the off-lattice, animal cell-boundary based methods by Honda et al (2008), Odell et al (1981), and Brodland and Clausi (1994). They keep the cells' relative positions fixed and describe in detail the biomechanical responses of the plant cell wall and the adjacent cell membranes to events in the cells.

*Future developments*

Cell-based computational methods can help unraveling how individual cell behavior and cell interactions drive biological growth and development. They can simulate biological development in amazing detail. A limitation of the computational methods used in cell-based modeling is that making generic statements on the behavior of a model is hard. The simulations must be repeated for large range of parameter values before any generic statement can be made. Recent efforts aim to develop mean-field approximations of cell-based models, such that simplified, analytical models can be derived from cell-based model descriptions (see, e.g., Byrne and Drasdo 2009; Turner et al 2004; Lushnikov et al 2008). Although in such continuum approximations of cell-based models inevitably details are lost, they may eventually assist in deriving analytical approximations of cell-based models.

Another danger in cell-based modeling is that some observations may result from the biological hypothesis represented by the model, while other observation may be the result of model-specific simulation artifacts. Therefore it is important to simulate a model using a range of cell-based modeling methodologies. To do so currently the user must rebuild his or her simulation for each of the available cell-based models. The ongoing cell behavioral ontology (CBO) initiative `http://bioportal.bioontology.org/ontologies/39336` aims to provide a well-defined set of terms for describing the behavior of animal, plant, or bacterial cells. A biological modeling language derived from the CBO would make it possible to define the model entirely in a conceptual language familiar to biologists. This will make it possible to define a model once, and test it in all compatible cell-based modeling packages.

*Cell-based modeling software*

A number of Open Source software packages and programming libraries are available for constructing lattice-based or off-lattice cell-based simulations with relatively little effort.

*CompuCell3D* (`http://www.compucell3D.org`) is an extensive software package for constructing three-dimensional and two-dimensional cell-based simulations based on the Cellular Potts model. Using an XML and Python interface, users can easily construct simulations based on the standard cell behaviors of the Cellular Potts model, e.g. differential adhesion and chemotaxis. Its modular architecture makes it possible to build user-defined cell behaviors using C++. The *Tissue Simulation Toolkit* (`http://sourceforge.net/projects/tst/`) is a C++ library for building two-dimensional Cellular Potts simulations.

*Chaste* (Cancer, heart and soft-tissue environment; Pitt-Francis et al. 2009) provides a set of C++ libraries for developing off-lattice, single-particle cell-based sim-

ulations of animal tissues. It represents cells by its centers and connects cells with virtual springs.

*L-studio* (`http://algorithmicbotany.org/virtual_laboratory/`) is an extensive suite for modeling plants. It includes software for building L-systems and vv-systems simulations of plant tissues.

*VirtualLeaf* (`http://code.google.com/p/virtualleaf/` and Merks et al 2011) implements a plant-specific, cell-based methodology for cell-based plant tissue simulation. Users can define their models by implementing a C++ model description plugin, using objects corresponding a biological entities, including molecules, cells, and cell walls.

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