Computer Simulation Techniques for Shape Composition and Morphogenesis of Biologically Inspired Structures

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Abstract

In this report, a presentation of several computer simulations capable of generating biological-like structures is given. The discussion focuses on the general techniques used to create the simulations, and numerous examples and images of simulated structures. Several simulated cell behaviors will be noted, and the methods of modeling the cells and their environment will be discussed. Of particular interest is a simulator called CompuCell3D, which is an ongoing project that is capable of simulating the morphogenesis of relatively complex biological structures, including the avian limb.

1 Introduction

Before structures of interest are physically synthesized, they are often studied in simulation to gain a more complete understanding of how to create a given structure with a set of desired capabilities. Several approaches have been developed to simulate the formation of various shapes and structures in a biological-like environment. A number of these simulation techniques are discussed in this report, in chronological order of development. The discussion is accompanied with numerous examples and images of different biological-like structures that these simulators are capable of producing. The discussion of each simulation technique includes a general explanation of the mechanisms behind the simulator, as well as models of the implemented cell behaviors and biological environment.

2 Examples of Simulators for Biological-like Structures and Environments

Since the mid-1990's, a number of simulators for studying biological-like structures have been developed. A chronological presentation of several of these simulators follows.

2.1 Multicellular Development of Biological-like Structures (1993-1997)

The simulator developed by Fleischer in [4, 6] models individual cells in a biological-like environment. The goals of the work are to study biological mechanisms in order to eventually create artificial neural networks as well as simulate evolution. The simulations are two dimensional, although it is straightforward to extend them to three dimensions. Hundreds of cells have been simulated. The environment is composed of chemical, mechanical, genetic, and electrical elements. The generation of multicellular structures with emergent properties relies on the initial state being inherited from the parent, intracellular state changes, cell-cell interactions, and cell-environment interactions.

The cells are represented as discrete, circular shaped physical entities. The cells have an asymmetrical structure and the system contains heterogeneous cell types. Two types of proteins occur in cells, one in the cytoplasm and one in the membrane. The behaviors of a cell are based on the cell's internal state and its local environment. Continuous differential equations model the genome of a cell, as well as processes occurring in the environment. Concentrations of different chemicals are present inside the cell, in the cell's membrane, and in the extracellular environment. Various cell behaviors include cell migration, cell differentiation, gradient following, clustering, lateral inhibition, neurite outgrowth, and contact recognition of other cells attached to its membrane. The environment contains diffusing chemicals, mechanical barriers, collisions and adhesions between cells, and adhesive substances. Cells change their states based on cell state equations (the genome). Cell behavior mathematical functions determine the functions that a cell performs. Continuous behaviors include moving, growing, regulating cell size, emitting or absorbing chemicals, and changing the amount of proteins in the membrane. Discontinuous behaviors include cell division, cell death, and emission of a growth cone. Cell

equations of motion determine the growth and movement of a cell based on the forces the cell applies.

Simulation experiments involve neurite path finding, cell differentiation, cyclic behavior for generating ring patterns, chains of cells, skeleton formation, and network building. Images from two of these experiments appear in Figure 1. It is difficult to design a genome for a specific pattern, and it is also difficult to predict a pattern from a genome.

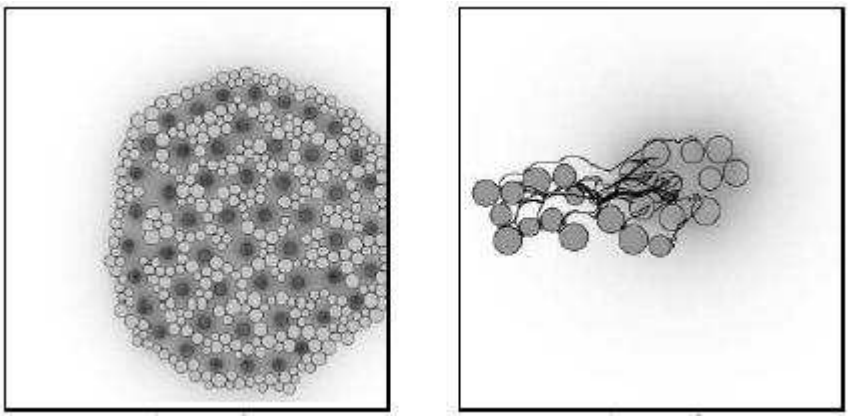

Figure 1. Simulations of skeleton structure (left) and neural network (right) [4].

More simulation examples of Fleischer's work are given in [6]. They are briefly outlined below. In each example, the system begins with a single cell or a few cells which divide and differentiate to generate a multicellular organism.

Chains: The formation of chains of cells is illustrated in Figure 2. Three different cell types comprise the structure: P (progenitor), L (large), and S (small). Only the P cells can divide. A chain is formed from a pattern of two L cells followed by one S cell repeatedly, as shown in the right side of Figure 2. The cells follow gradients of different chemicals to form the chain. Errors and collisions of cells may result in changes to the shape of the structure, such as introducing branches or bends. The size and location of the cells can also be varied in order to alter the shape of the chain.

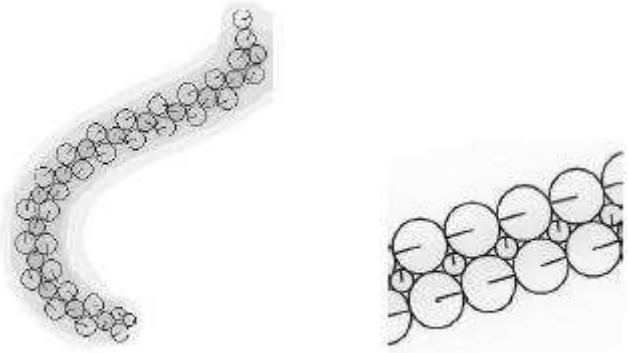

Figure 2. Chain structure (left) and close up of 2-1-2-1 module pattern (right) [6].

Segments: Segmented structures are based on the same 2-1-2-1 pattern discussed in the chain example. Occasionally, an L cell may become an L' cell which emits an inhibitor chemical that prevents nearby L cells from becoming L' cells. The effect of the chemical fades with distance, allowing L cells further down the chain to become L' cells, thus creating a segmented pattern in the structure, as displayed in Figure 3.

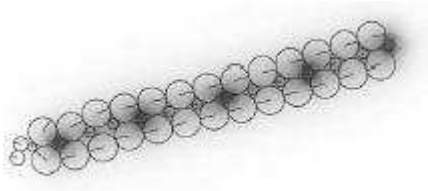

Figure 3. Segment structure [6].

Bending chain: Curled structures are produced as a result of the top cells of a chain contracting in unison while the bottom cells of the chain expand. It is also possible to create a structure with a circular configuration. Examples of curved structures appear in Figure 4. This technique can be used to model the gastrulation process.

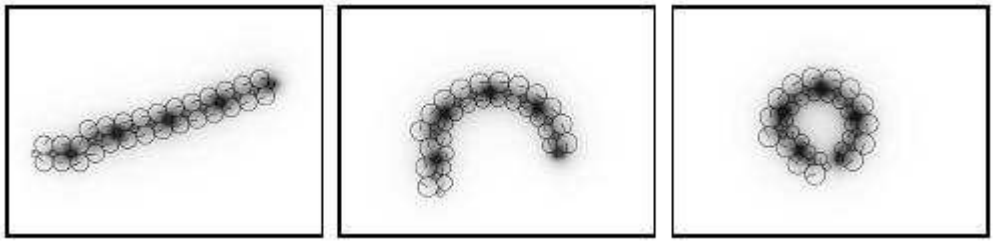

Figure 4. Formation of curled structure, similar to gastrulation [6].

Hierarchical structures: The organisms in Figure 5 result from a two-level hierarchy, where the initial cells divide to create a level, which in turn divide to form another level. Three types of cells form the structure: R, G, and W. The G cells are attracted to the chemical emitted by the R cells. G cells die if they cannot form contact with R cells. Likewise, W cells are attracted to G cells and W cells die if they fail to adhere to G cells.

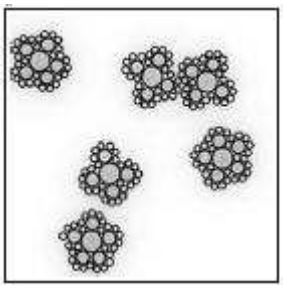

Figure 5. Two-level hierarchical structure [6].

Hierarchical neural network: A two-level neural network is illustrated in Figure 6. As in the other examples, diffusing chemicals drive the process of creating these networks.

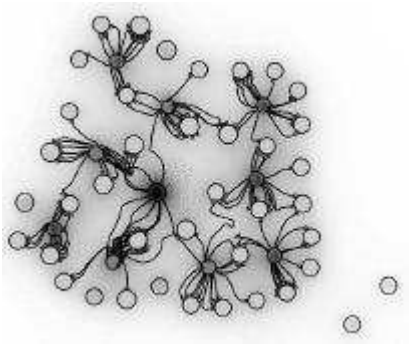

Figure 6. Two-level neural network [6].

Several three-dimensional structures have also been modeled by the simulator. They include clumps of cells, layers of cells, and spiral structures, as shown in Figure 7.

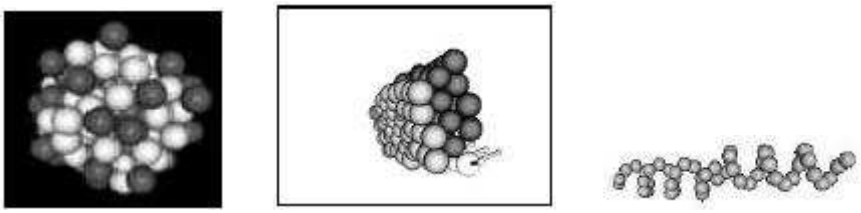

Figure 7. 3D structures: blob, cell layers, and spiral [6].

It is possible to regenerate cells if more than one dies at once, as Figure 8 shows. A surviving neighboring cell is able to divide to regenerate the lost cells.

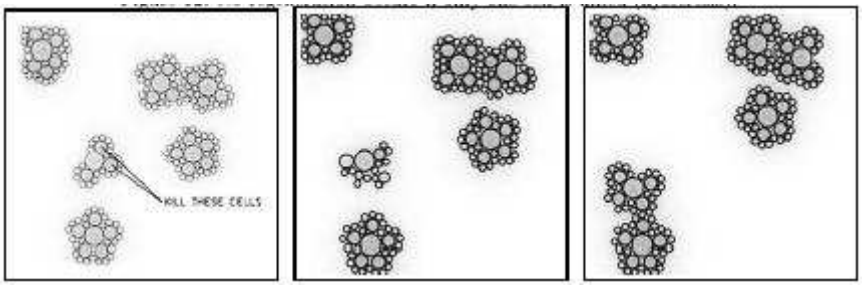

Figure 8. Regeneration of structure after death of two cells [6].

A reaction-diffusion model can serve as a pre-pattern for growth of structures, as illustrated in Figure 9. Cells grow in the dark areas and avoid the lighter areas, creating a patterned structure.

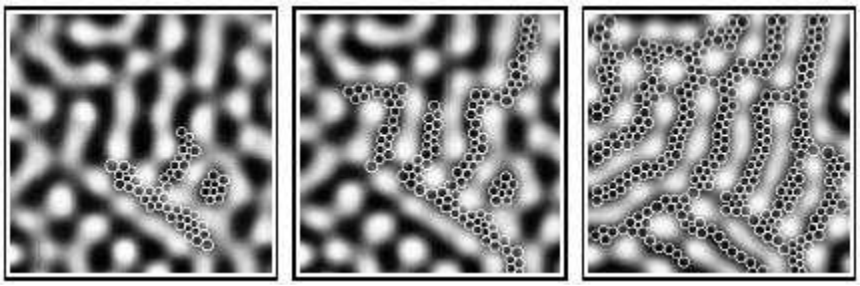

Figure 9. Cells following a pattern created by a reaction-diffusion system [6].

2.2 Cellular Texture Generation (1995)

Fleischer et. al. applied the simulator described in the previous section to rendering 3D surfaces of objects [5]. Surface details such as scales, feathers, thorns, and fur are modeled. This work combines aspects of particle systems, developmental biology models, and reaction-diffusion mechanisms. The elements modeling the objects are small 3D cells that are confined to the surface of the object. A cell is a generalized particle and each cell has a position, orientation, shape, and state vector containing parameters such as chemical concentrations in a reaction-diffusion environment. Cell programs, which are first order differential equations, are implemented to modify a cell's state and describe how the cell's state changes over time. The cell programs implement various cell behaviors, including go to surface, die if too far from surface, align with vector field, align with neighbors, maintain unit quaternion, adhere to other cells, divide until surface covered, and set size relative to surface feature size. Cell programs represent a collection of constraints, which are modeled by an energy function to be minimized. A particle converter translates information about the particles (cells) and the environment into the geometry and parameters necessary to render the objects. Cell size and number varies depending on the level of detail of the object. Fewer cells are used to model more distant objects, and more cells are used for closer objects in order to display more detail. Cells that contain only a small amount of a given chemical will form into bumps, while cells containing a larger amount of a certain chemical will develop into thorns. Two examples of objects rendered using this method, a thorny head and a bear, are shown in Figure 10. Future work includes modeling objects while they are moving and changing shape.

Figure 10. Thorny head (left) and bear (right) [5].

2.3 Simulation of Amoeba-like Structures (1996)

In Hogeweg's work [14], a three-dimensional hybrid cellular automata/partial differential equations model is used to simulate the structure and behavior of amoeba-like creatures. Basic morphogenesis can be obtained by production of and chemotaxis to cAMP and cellular adhesion. In order to minimize the free energy of the amoeba, their cell membranes are deformed. The

simulations involve stream and mound formation, cell sorting, and slug migration, as shown in Figure 11. Approximately 800 cells are used in the simulations. The entire morphogenetic process can be completed without any change of parameters. It is interesting to note that cells move faster when they are in clusters than when they are isolated.

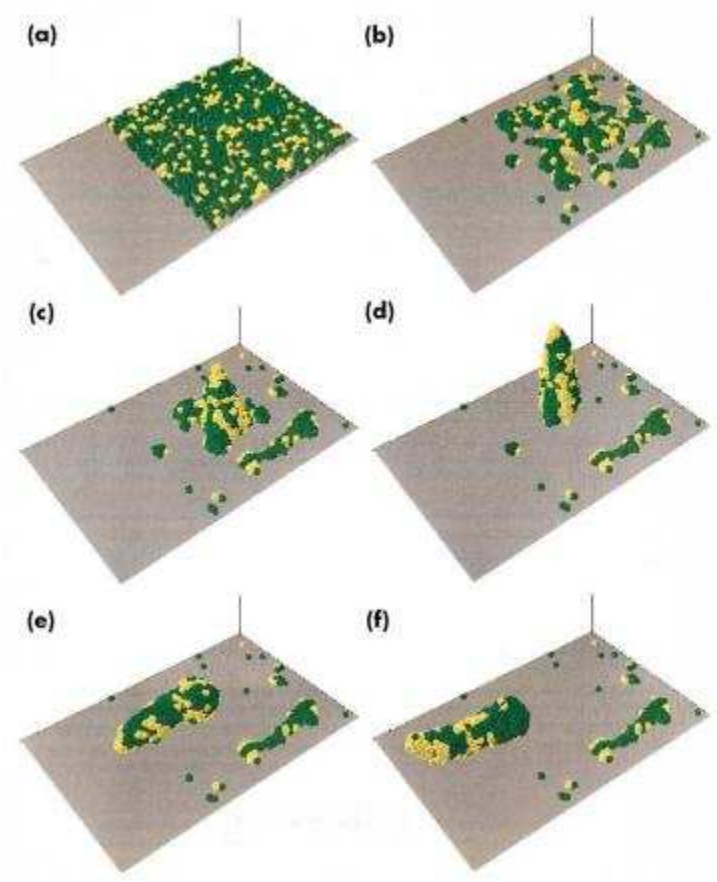

Figure 11. Forming amoeba streams, mounds, and slugs [14].

2.4 Multicellular Organisms and Differentiation (1998)

In the work of [7], the focus is on the creation of emergent spatial patterns of differentiated cells. The model for differentiation is based on biochemical reactions within each individual cell, cell-cell interactions in a medium containing diffusing chemicals, cell division, and cell adhesion. Cells divide and grow by using one of the chemicals as nutrient to build the cell body. Cell adhesion occurs between two cells of the same type that are within a specified distance threshold. Differentiation results from the amplification of fluctuations and the increasing number of cells. The system becomes stabilized with the coexistence of different cell types. One simulation involves the emergence of a layered cluster of cells. The structure begins as a single cell of type 0, which divides and the structure develops into a type 0 cluster. As the structure grows, the central cells differentiate into type 1 and type 2 cells. The type 2 cells further differentiate into type 3 cells, which form the core of the structure. A ring pattern consisting of 3 layers results, as shown in Figure 12. The formation of the structure is not based on diffusion of chemicals,

rather, it is based on growth over time. The inner core continues to grow and eventually the ring pattern is broken. A small cluster is broken off and moves away from the mother structure. The process is repeated, thus establishing a life cycle of a multicellular organism. Another simulation demonstrates the robustness of the system, as illustrated in Figure 13. A damaged part of the structure is regenerated. The growth in the damaged area is stronger. Death of the organism is implemented by a halting of the system. At this point, a life cycle is completed, and the next generation can begin.

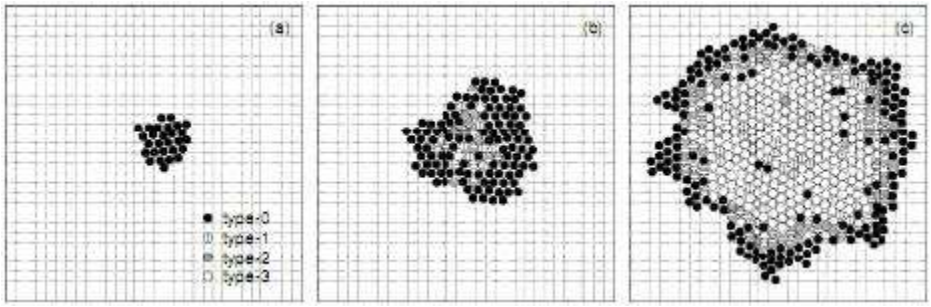

Figure 12. Creation of cell cluster of 4 different cell types [7].

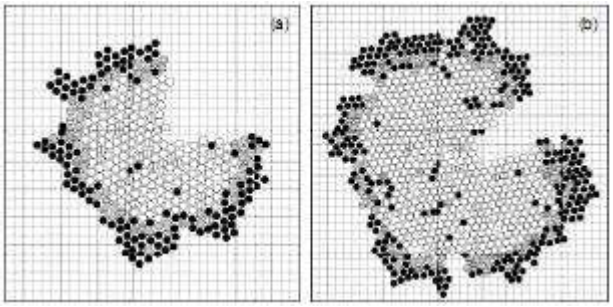

Figure 13. Repairing a damaged cluster [7].

2.5 Morphogenesis from Cell Adhesion and Cell Differentiation (2000)

Most of the examples discussed here involve diffusion and chemical gradients, however, the morphogenesis of the structures in [9] are based on cell adhesion and differentiation. The basis of the model is a receptor-mediated differential adhesion mechanism. Cell adhesion is modeled by a two-scale asynchronous CA (cellular automata) framework. One scale is the local CA rules, and the other refers to the scale of the biotic cells, which are comprised of as many as 80 CA cells. A cell moves by extending and retracting its cell membrane. The model also incorporates cell death from squeezing, cell growth from stretching, and cell division based on cell volume. An evolutionary process (i.e., genetic algorithm) is used to derive the specific structures at the microscopic level. The fitness is based on the difference in gene expression among all the cells. The organisms generated by this technique are two-dimensional and consist of around 128 cells. Several different modes of morphogenesis are achieved, including gastrulation-like engulfing, budding and elongation, intercalation and stretching, meristematic growth, and the cooperation between cell growth, cell differentiation, and cell death. These processes are illustrated in Figure 14.

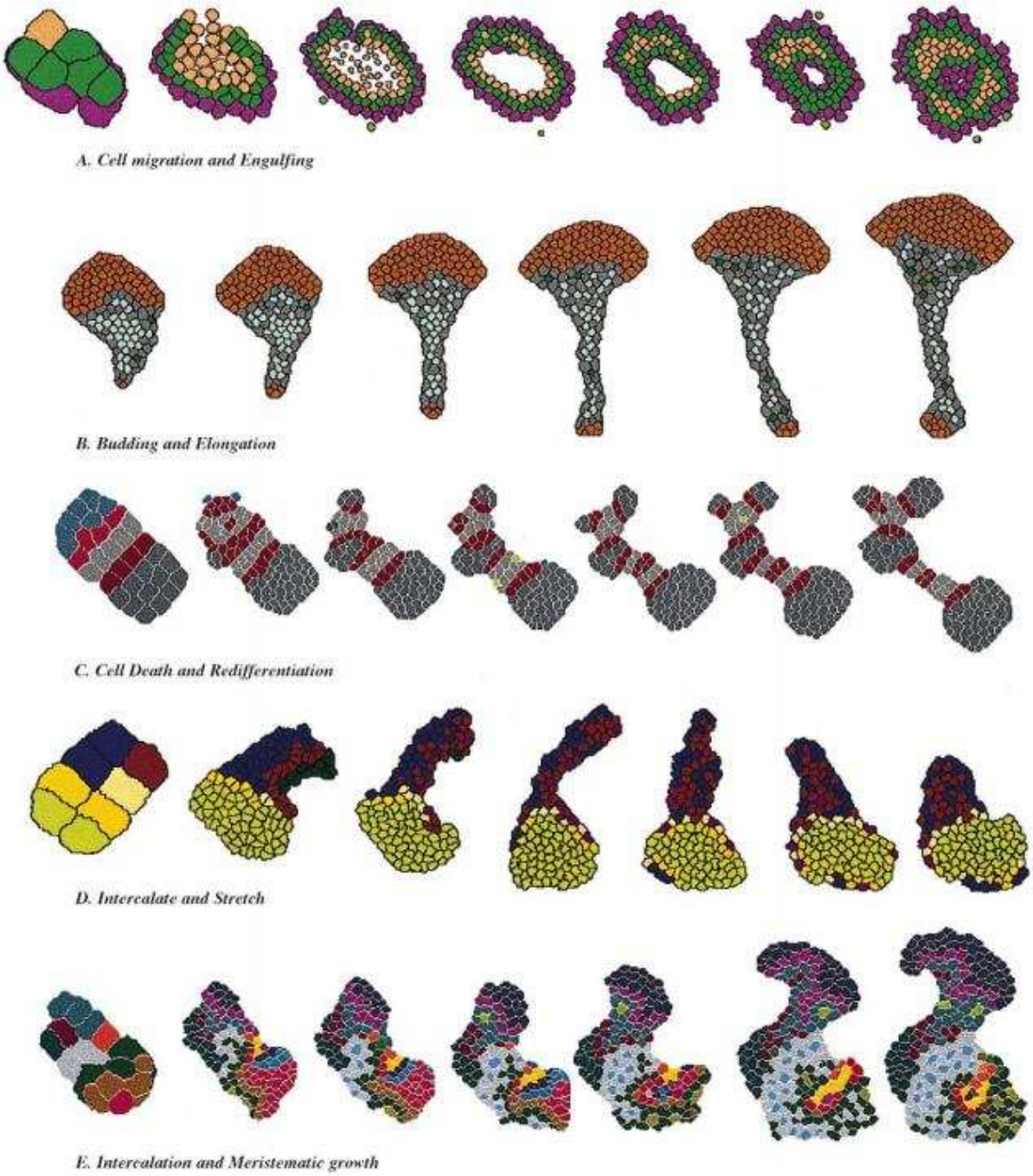

Figure 14. Various modes of morphogenesis [9].

2.6 Programming Self Assembly with Origami and Paper Folding (2002)

The work presented in [13] involves a sheet of identically programmed cells that assemble into a predefined shape. The global shape is specified by the Origami Shape Language. These irregularly-shaped cells are distributed randomly and densely. Communication between cells is

confined to a small local neighborhood, similar to communication of cellular automata. The final shape emerges from these local interactions among cells. The shape formation process is based on several biologically inspired primitives. Chemical gradients serve as an estimate of the distance from the chemical source. A cell can use a neighborhood query to gather values of a gradient. Polarity inversion can be performed to reverse the apical-basal polarity of a cell. Cell-cell contact enables communication by physical contact. Flexible folding refers to the act of a cell contracting fibers to change the shape of the sheet. In one simulation, a sheet of 4000 cells, with an average neighborhood size of 15, was folded into a cup shape, as shown in Figure 15. Other simulations involved forming an envelope structure as well as various patterns and repeated sequences.

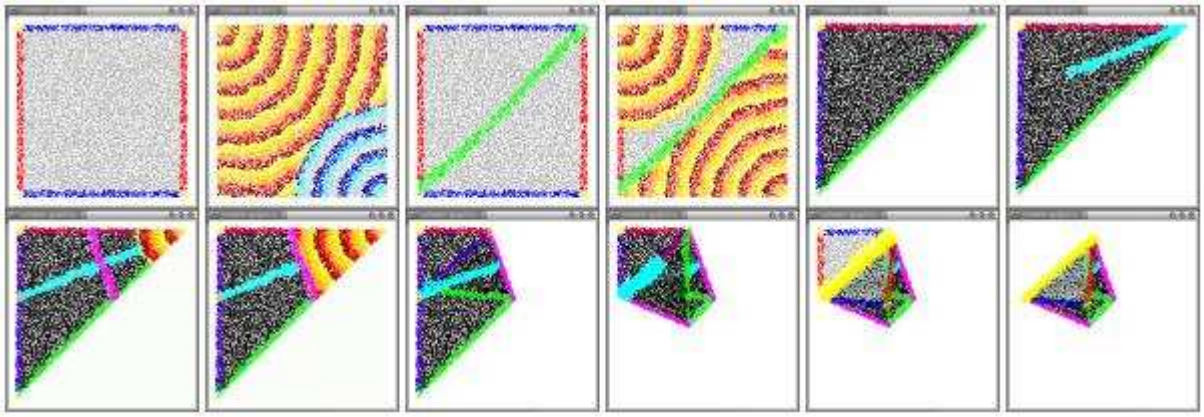

Figure 15. Folding a sheet of cells into a cup [13].

2.7 CompuCell (2003, 2005-present)

The CompuCell project [10] involves the simulation of the morphogenesis of the avian limb. This model consists of three components: the Cellular Potts Model (CPM) defines the behaviors of the cell (such as growth and movement) and its environment, a reaction-diffusion model describes morphogens that diffuse throughout the environment, and an ordinary differential equations framework describes genetic regulation networks and cell differentiation. Various cell behaviors are represented by mathematical constraints and an energy function that is to be minimized. Chemical gradients are created by haptotaxis and chemotaxis of the cells. Several cell functions include interaction between cell membranes, regulation of the cell perimeter, cell growth, cell division, and cell death. The growth of the limb bud is determined by the rate of cell division and the speed of cell movement. The limb space consists of three zones. The apical zone is where growth occurs. In the active zone, the cells arrange into precartilage condensations. In the frozen zone, additional pattern formation ceases and the condensations differentiate into cartilage, which is eventually replaced by bone structure.

CompuCell3D [3] is the three-dimensional version of the simulator modeling skeletal formation in the avian limb. The development of the limb is emergent, rather than preprogrammed. It is based on a cell-centered approach, where the focus is on the behaviors of individual cells collectively influencing higher level behavior, as observed in tissues and organs. Discrete cellular automata are used for controlling interactions of cells and continuous reaction-diffusion

equations are used to model chemical gradients around the cells. The Cellular Potts Model is a grid-based method for simulating the interactions and movement of cells. Both unicellular and multicellular organisms can be simulated. The simulator is able to model the directional movement and structure of rod-shaped bacteria. In addition to reaction-diffusion and the CPM, the simulator also implements a Cell-Type Map for modeling cell differentiation. Each cell is represented by a collection of lattice sites that organize to effect motion and shape changes in the cell. Behaviors such as cell-cell adhesion, cell growth, cell division, cell death, chemotaxis, and haptotaxis are described by an energy equation. The cells modeled in the simulation are approximately 15 micrometers in diameter. The simulation begins with 8 cells, and the final limb structure contains nearly 14,000 cells. Figure 16 illustrates three stages of the avian limb simulation, and well as simulations of somitogenesis and vasculogenesis. Advantages of CompuCell3D over CompuCell are faster computation, less memory usage, and more biological realism. Software, documentation, and publications for the CompuCell3D project can be found at [8].

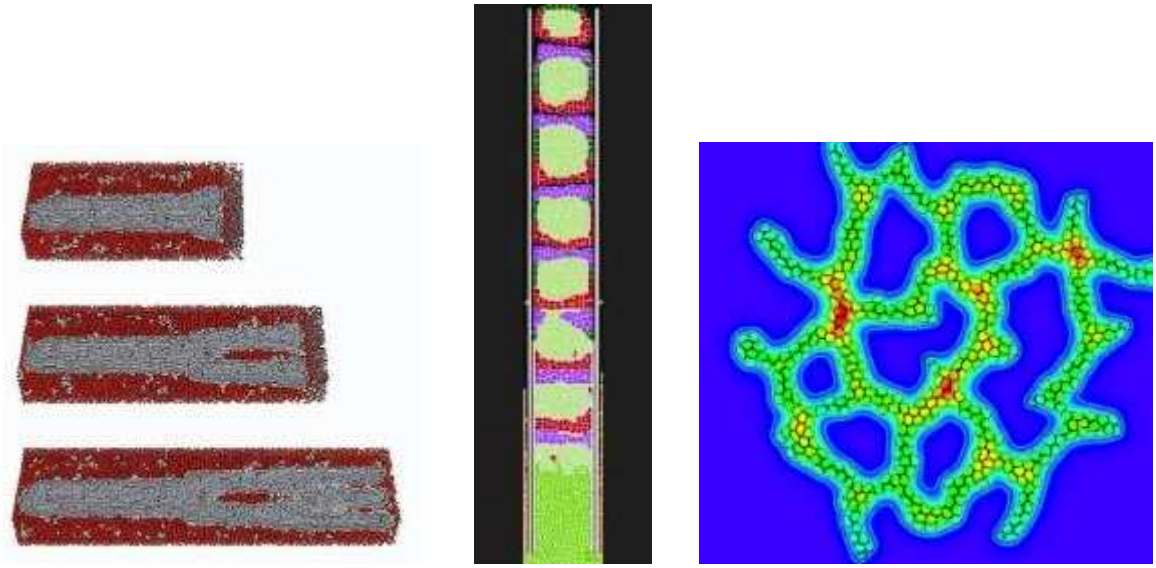

Figure 16. Simulation of avian limb [3], somitogenesis [8], and vasculogenesis [8].

2.8 Bluenome Model (2004)

Bluenome [11] is a 2D cellular automata based model in which an agent is limited to local interactions and an agent's genome consists of a series of rules. After gathering information from its neighbors, an agent finds the closest matching rule in its genome to determine the next action taken. Possible actions include Die, Specialize (where a cell changes its type), Divide, and Move. An artificial world has been simulated [11] in which the goal for an agent is to survive as long as possible. The cells are distributed throughout a grid framework and given an initial amount of food. In order to survive longer, an agent must detect food, move to its location, consume it, and distribute it to the rest of the cells in its body. Each cell is of five possible types: eye, nerve, foot, transport, and structure. Figure 17 depicts a simple agent in an artificial world containing food.

Figure 17. A simple agent searching for food [11].

2.9 Topology Changes and Reaction-Diffusion (2005)

The work of [12] is based on implementing reaction-diffusion equations to effect topological changes in multicellular structures, which in turn act as feedback to the reaction-diffusion system. The simulator consists of reaction-diffusion waves and diffusing chemicals. This framework has been applied to simulating the formation of the gastrointestinal tract, which consists of two layers. The epithelial layer generates the reaction-diffusion waves and the extracellular matrix contains the diffusing chemicals. When the concentration of the activator chemical exceeds a threshold for a certain amount of time, the cells begin to divide. A new link is inserted between the existing cells and this causes the structure to curve at that location. This increasing curvature acts as feedback as it suppresses the reaction-diffusion wave. The fractal patterns generated by this process are illustrated in Figure 18. The diffusion coefficient and division threshold influence the speed of cell growth. The convergence of the growth mechanism is independent of the initial number of cells.

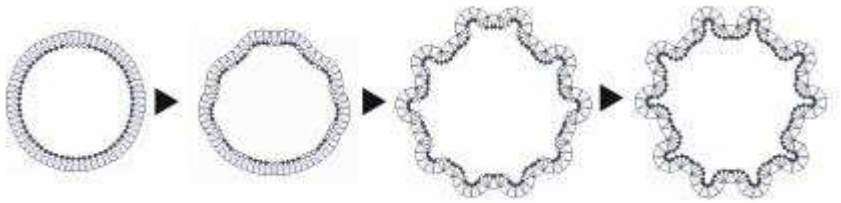

Figure 18. Simulation of gastrointestinal tract formation [12].

2.10 Morphogenesis as Amorphous Computation (2006)

Another technique for programming the formation of structures is to give local instructions to objects representing cells (organizers) [2]. Applications of this research are programming smart matter and controlling robot swarms. The experiments in this work are 2D simulations, however, the author states that the experiments are also possible in 3D. During development, the embryo is divided into compartments. Each compartment is composed of organizers of the same type, and these objects organize the growth of that compartment. A mother organizer generates a daughter organizer in a certain direction by using a grower program which is contained within the organizer. Cells move as a result of adhesion to other cells which are moving. There are two types of signaling in these systems: morphogens emitted locally by organizers and background fields which provide each organizer with global positional information. Two types of morphogens are *sterile*, which inhibits growth, and *poison*, which signals the organizer to die. Cell death can result in carving finer details into the forming structure. Examples of patterns

created through simulation are solid spheres, ellipses, and a microtubule structure. Each of these structures is illustrated in Figure 19. The sphere begins with a starter organizer in the center, which generates organizers uniformly in all directions. An ellipse results from two starters that each emit a different chemical and grow a sphere around it. The growth of microtubules is similar to the formation of the cytoskeleton where filaments grow from the center to the edge of a hollow ball.

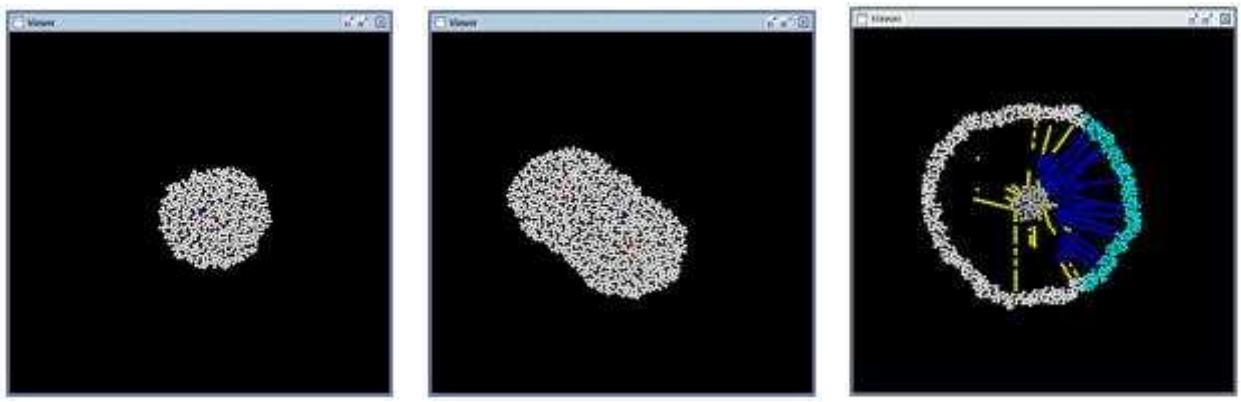

Figure 19. Simulation of sphere, ellipse, and microtubule structures [2].

2.11 Automated Shape Composition Based on Genetic Programming (2008)

In [1], genetic programming is used to determine a mathematical function for producing a particular two dimensional shape. The interactions between cells are driven by chemotaxis, that is, the process of cells emitting chemicals that diffuse into the environment. The cells are autonomous, their actions are based on local information, and they are not aware of the structure of the final shape. The target shape emerges as a result of the aggregation of local interactions and behaviors of the cells. The algorithm focuses on the chemical field around a cell, which is defined as a mathematical expression. Each cell emits a chemical and also computes the cumulative chemical field. A fitness function is used to evaluate the candidate functions for producing a given shape. The simulated shape is compared to the target shape to obtain a fitness value. The functions whose simulated shapes most closely match the target are passed on to the next generation. Crossover and mutation operations are performed on these parent functions. The process repeats until the desired shape is obtained or until the maximum number of generations is reached. Simulations involve 500 cells and examples of shapes produced include ellipse, diamond, boomerang, hourglass, wave, annulus (donut), gear, stripes, and spots. A few of these shapes are shown in Figure 20.

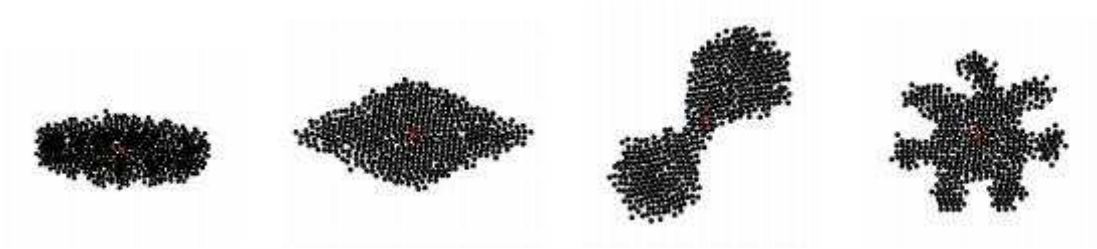

Figure 20. Shapes generated from genetic programming approach (ellipse, diamond, hourglass, gear) [1].

3 Conclusions

This review has presented several different simulation techniques for generating biological-like structures. Most of the simulations involve hundreds or thousands of cells, and the majority of them are two-dimensional, although several of the experimenters are confident that it is straight-forward to adapt the simulations to 3D. Many typical cell behaviors have been simulated, including cell growth, cell adhesion, cell movement, cell differentiation, cell division, cell death, chemotaxis, and haptotaxis. Most of the simulations involve cells that interact locally with neighboring cells, and chemicals diffusing throughout an environment. The cell behaviors are often based on cellular automata or genome-like models, and the chemical environment is typically represented by a reaction-diffusion model with partial differential equations. Many of the shapes generated by these simulators are rather simple, such as a sphere or diamond, although the CompuCell3D project has involved more complex structures, such as the avian limb, somitogenesis, and vasculogenesis. Increasing the complexity of the simulated structures will likely lead to a deeper understanding of the morphogenesis of biological-like structures, that may ultimately result in the ability to move beyond simulation and create physical biologically inspired structures for use in real-world applications.

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