Cellular and Molecular Bioengineering, Vol. 2, No. 3, September 2009 *(© 2009)* pp. 285–294
DOI: 10.1007/s12195-009-0078-2

Rule-Based Simulation of Multi-Cellular Biological Systems—A Review of Modeling Techniques

MINKI HWANG,[1] MARC GARBEY,[2] SCOTT A. BERCELI,[3,4] and ROGER TRAN-SON-TAY[1,5]

[1]Department of Mechanical & Aerospace Engineering, University of Florida, Gainesville, FL 32611, USA; [2]Department of Computer Science, University of Houston, Houston, TX 77004, USA; [3]Department of Surgery, University of Florida College of Medicine, Gainesville, FL 32610, USA; [4]Malcom Randall Veterans Affairs Medical Center, Gainesville, FL 32610, USA; and [5]Department of Biomedical Engineering, University of Florida, Gainesville, FL 32611, USA

(Received 1 May 2009; accepted 28 July 2009; published online 14 August 2009)

Abstract—Emergent behaviors of multi-cellular biological systems (MCBS) result from the behaviors of each individual cells and their interactions with other cells and with the environment. Modeling MCBS requires incorporating these complex interactions among the individual cells and the environment. Modeling approaches for MCBS can be grouped into two categories: continuum models and cell-based models. Continuum models usually take the form of partial differential equations, and the model equations provide insight into the relationship among the components in the system. Cell-based models simulate each individual cell behavior and interactions among them enabling the observation of the emergent system behavior. This review focuses on the cell-based models of MCBS, and especially, the technical aspect of the rule-based simulation method for MCBS is reviewed. How to implement the cell behaviors and the interactions with other cells and with the environment into the computational domain is discussed. The cell behaviors reviewed in this paper are division, migration, apoptosis/necrosis, and differentiation. The environmental factors such as extracellular matrix, chemicals, microvasculature, and forces are also discussed. Application examples of these cell behaviors and interactions are presented.

Keywords—Cellular automata, Agent-based modeling, Individual-based modeling.

INTRODUCTION

Modeling multi-cellular biological systems (MCBS) poses challenges in that the global system behaviors result from individual cell behavior and the interactions among the cells. Cells are live creatures which differentiate, proliferate, move, and die, and these behaviors of living cells constitute the dynamics of MCBS. Moreover, these cell behaviors are influenced by the environmental factors such as extracellular matrix, chemicals, and forces. Modeling MCBS requires incorporating these complex interactions among the individual cells and the environment (Fig. 1).

Modeling approaches for MCBS can be grouped into two categories: continuum models and cell-based models.[7] Continuum models usually take the form of partial differential equations (PDE). One of the advantages of the PDE models is that the model equations provide insight into the relationship among the components in the system (Fig. 2). PDE can be used for modeling all levels of biological systems.[38] However, the continuum models do not catch the discrete nature of MCBS consisting of individual cells, and become cumbersome when modeling complex process involving many variables. On the other hand, the cell-based models such as cellular automata (CA) and agent-based (or individual-based) models (ABM) simulate each individual cell behavior and interactions among them enabling the observation of the emergent system behavior (Fig. 3). Hybrid models combine these two approaches taking the advantages of each method.[24,30]

CA and ABM are based on the local interactions of the members of a population. These individuals might represent plants and animals in ecosystems,[21,48] vehicles in traffic, people in crowds, or autonomous characters in animation and games.[13,29,31] Complex adaptive systems (CAS) are often simulated by ABM. CAS may include (i) reactive units, i.e., units capable of exhibiting systematically different attributes in reaction to changed environmental conditions, (ii) goal-oriented units, i.e., units that are reactive and that direct at least some of their reactions towards the achievement of built-in (or evolved) goals, and (iii) planner units, i.e., units that are goal-directed and that attempt to exert some degree of control over their environment to facilitate achievement of these goals.

Address correspondence to Roger Tran-Son-Tay, Department of Mechanical & Aerospace Engineering, University of Florida, Gainesville, FL 32611, USA. Electronic mail: rtst@ufl.edu

CA and ABM belong to bottom up approach. The individual cells are represented explicitly and local rules of behavior are given to them. Historically, Conway's Game of Life[22] is one of the most famous examples of CA. One of the most successful applications of CA is the work of Pomeau and coworkers[17] that computed the Navier–Stokes equations on hexagonal lattice. However, one of the big differences between biological systems and physical systems such as gas or flow of particles is that each element in biological systems is a living entity that can have a fairly complex system of rules, and may depend not only on local environment but also on global factors.

This review focuses on the cell-based models of MCBS, and especially, the technical aspect of the rule-based simulation method for MCBS is reviewed. How to implement the cell behaviors and their interactions with other cells and with the environment into the computational domain is discussed, and application examples from recent publications are introduced.

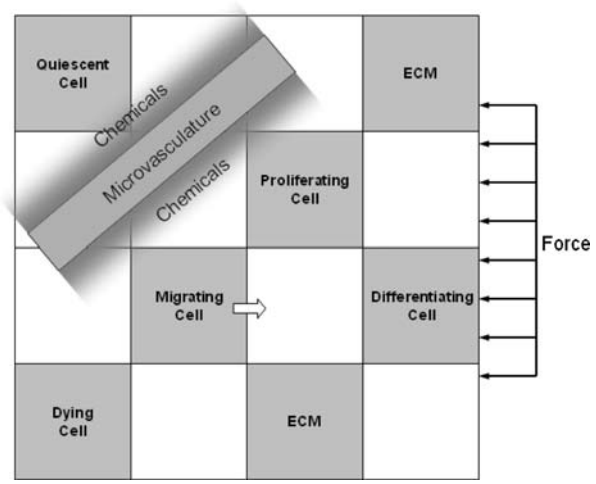

FIGURE 1. Schematic of computational domain of rule-based simulation for MCBS. The cell behaviors include proliferation, migration, apoptosis/necrosis, differentiation. The environmental factors include extracellular matrix, chemicals, microvasculature, and forces.

CELLULAR AUTOMATA AND AGENT-BASED MODELING

CA and ABM are two of the widely used methodologies for rule-based simulation of MCBS.[1,8,11,15,49,50]

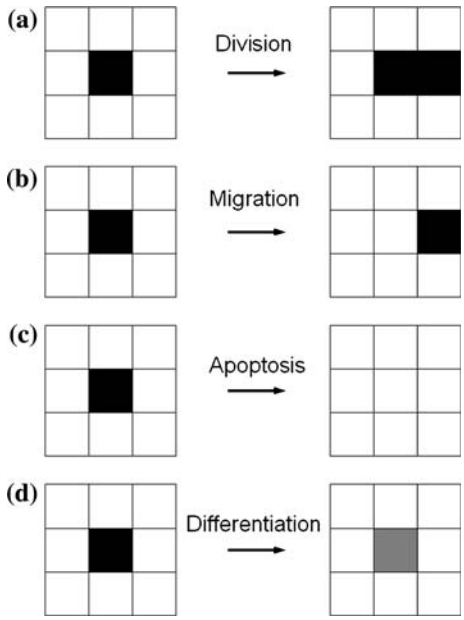

FIGURE 3. Schematic of cell behavior implementation on the lattice. Black and grey elements represent cells. White elements represent empty spaces. (a) When a cell divides, a new cell is created. (b) When a cell migrates, the location of the cell changes. (c) When a cell dies, the cell disappears from the lattice. (d) When a cell differentiates, the cell becomes a different cell.

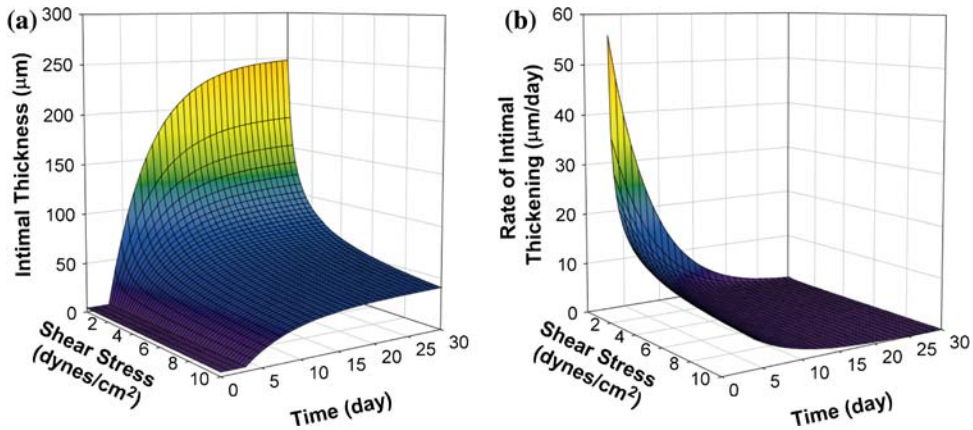

FIGURE 2. Mathematical model of vein graft remodeling induced by shear stress. (a) Intimal thickness as a function of shear stress and time. (b) Rate of intimal thickening as a function of shear stress and time. Taken from Tran-Son-Tay *et al.*[51]

Both methods are believed to have originated from an idea by John von Neumann in the 1940s.[26,53] Later, John von Neumann with the help of Stanislaw Ulam introduced the concept of CA,[11,39,53] and ABM also started to be established by other researchers thereafter.[26] Traditional CA is defined by the following components: a regular discrete lattice, a finite set of cell states, a finite set of neighboring cells, and rules for the transition of cell states.[11] In real-life application of CA, the traditional definition is considered too restrictive, and there have been many relaxations such as non-uniform grid, asynchronous update of the cell states, and extension of the cell neighborhood.[40] ABM is defined in a similar way. ABM is a computational method in which decision-making agents interact with the environment following a set of rules.[6,26] CA and ABM are similar in that the behaviors of cells or agents are governed by the rules in their neighborhood or environment, and generate global behavior of the system emergent from the local interactions. CA, however, seems more mathematical in its formulation. Mathematical rigorousness of the CA can be seen in the graph-CA proposed by O'Sullivan,[40] a new CA introduced to accommodate non-uniform grid whereas the traditional CA is defined on uniform grid. Although the relationship between CA and ABM is not obvious, some researchers think of ABM encompassing CA[18,55] possibly due to the more general definition of ABM.[6] Both CA and ABM have been widely used in the modeling of a variety of systems such as social, economic, and biological systems.[6,26,53] Detailed modeling techniques of these methods applied to MCBS are discussed in the following sections.

LATTICE

Rule-based simulations are usually performed on a lattice system. Cells and other components occupy some of the grid elements and can move from one element to another (Fig. 3). Regular, irregular, or lattice-free approach can be used, and each of these grid systems is discussed in this section.

Regular and Irregular Lattice

In case of regular lattice, the distance between two adjacent elements remain constant over the entire simulation domain, and hence the grid-dependency of the simulation results can be minimized. The lattice can be triangular, square, or hexagonal.[11] Engelberg *et al.*[14] report that, in their simulation of tumor spheroid growth, square grid required a higher order implementation of discrete diffusion compared with hexagonal grid, and generated artifacts that are not present with the hexagonal grid. The size of individual lattice element can be made to be comparable to that of the biological cell,[23,35] or can be any value.[28,47] One biological cell[10,47] or multiple cells[16,33,43] can occupy one lattice element. Piotrowska and Angus[43] report that assigning many biological cells to one lattice site can reduce the total number of lattice sites for a given number of biological cells, and hence the computational time, and provides the flexibility in positioning the newly created cells from cell divisions (Fig. 4).

Cellular Potts model is a type of CA in which one biological cell occupies more than one lattice sites.[1] This model enables the incorporation of the shape change of each cell into the simulation. Jiang *et al.*[32] simulated an avascular tumor growth using an extended large-Q Potts model. "Large-Q" means that the number of possible cell states is comparable to that of the connected subdomains of different cell types.[1] Robertson *et al.*[45] segmented one biological cell into nine sub-compartments enabling different portions of a cell to respond to different stimuli. These sub-compartments can also incorporate cell polarity and sense the spatial gradient of the environment across the cell.

Kansal *et al.*[33] used an irregular lattice for CA simulation of brain tumor growth. They used Voronoi tessellation to generate the lattice, and each resulting automaton cell takes the form of polyhedra in three-dimensional space. They also used varying lattice density with higher density at the center to allow the tumor to grow to a large size during the simulation. Due to their varying size of the elements, the number of real cells contained in the automaton cells ranged from roughly 100 to 10^6 depending on the size of the automaton cell.[33] Gevertz and Torquato[25] adopted a similar irregular lattice to investigate the effects of vasculature on early brain tumor growth (Fig. 5).

Lattice-Free Models

In case of lattice-free models, cells can be at any location in the computational domain. The positions of the cells are usually determined by solving equations of motion incorporating the forces acting on the cells.[18,19,46] Rheological properties of the cells also can be included in the simulation.[41] Galle *et al.*[18,19] simulated multi-cellular systems using lattice-free models incorporating contact-dependent regulation mechanisms (Fig. 6). Schaller and Meyer-Hermann[46] simulated steady-state flow equilibrium of skin using an off-lattice agent-based model.

BIOLOGICAL APPLICATIONS OF CA AND ABM

Three of the biologically relevant areas that use CA and ABM frequently for modeling methodology are tissue engineering, tumor growth, and wound healing.

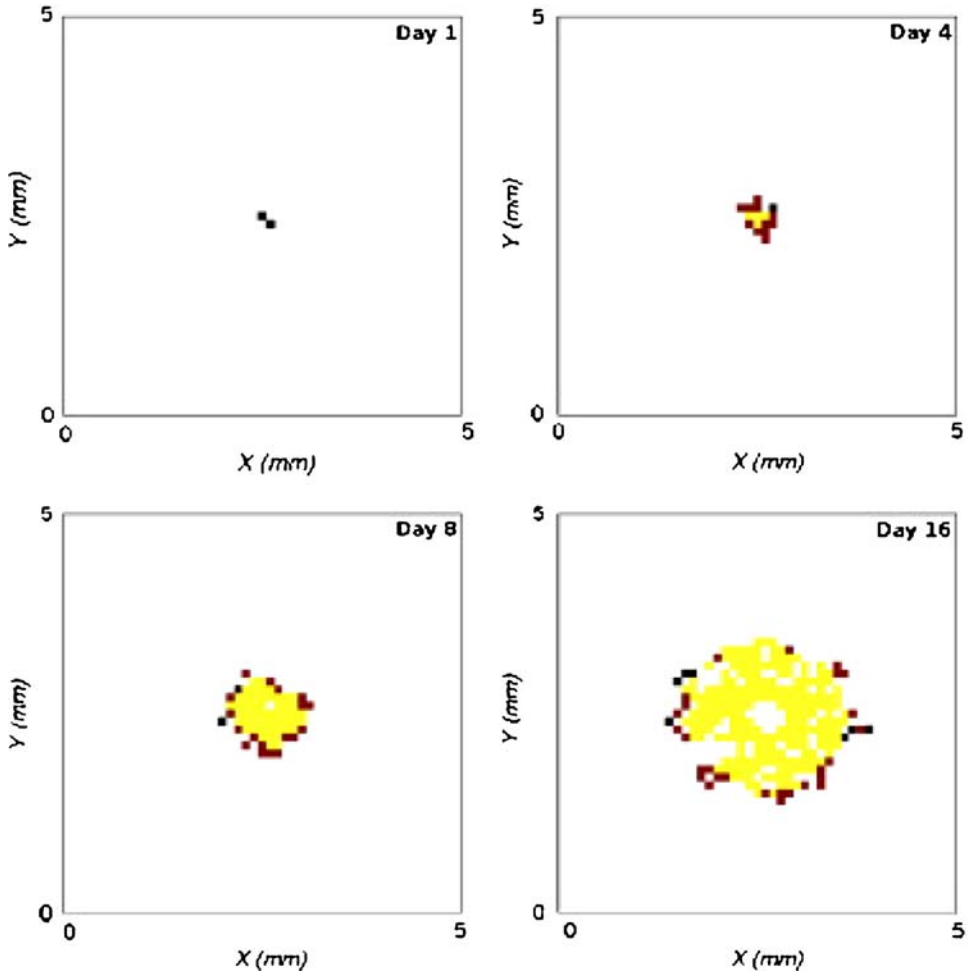

FIGURE 4. Simulation of *in vitro* multicellular spheroid tumor growth. Each lattice site contains 400 biological cells. Cells in aerobic proliferation (black), anaerobic proliferation (red), aerobic quiescence (orange), and anaerobic quiescence (yellow) are shown. Taken from Piotrowska and Angus.[43]

In utilizing CA and ABM in tissue engineering, the emphasis is on the controlled production of tissue and elucidating mechanism for differentiation and spatial pattern formation. One of the main targets of using cell-based model is to control the process of tissue growth under the limitation of the reactor.[56] In case of tumor growth simulation, the goal is to understand the mechanism of tumor growth in its different stages, and potentially monitor the effect of medication (drug delivery versus spatial properties and radiotherapy versus cell cycle).[12] For wound healing simulation, CA and ABM are used mainly for understating the roll of vasculature and cell migration in the process, and the mechanism of plaque building.[4,37]

CELL BEHAVIOR

Division, migration, apoptosis, necrosis, and differentiation are among the cell behaviors that are commonly modeled in the rule-based simulations of MCBS. Figure 3 shows an example of how these cell behaviors can actually be implemented on a lattice. Cells are created, moved, removed, or replaced by different cells according to the corresponding cell behaviors. More behaviors can be added (e.g., cell growth) or only some of these behaviors can be chosen to be implemented. Depending on specific biologic applications, these behaviors can be implemented differently (e.g., an empty space can be placed between the two daughter cells after cell division). More detailed information needed for the actual implementation (e.g., probability of cell division) is discussed in this section. By implementing these local cell behaviors, a global behavior of cell population can be observed. As an example, in case of tumor growth simulations, two of the commonly simulated cell behaviors are cell division and cell death. New cells are created mostly at the periphery of the tumor through the cell division which is dependent on nutrient

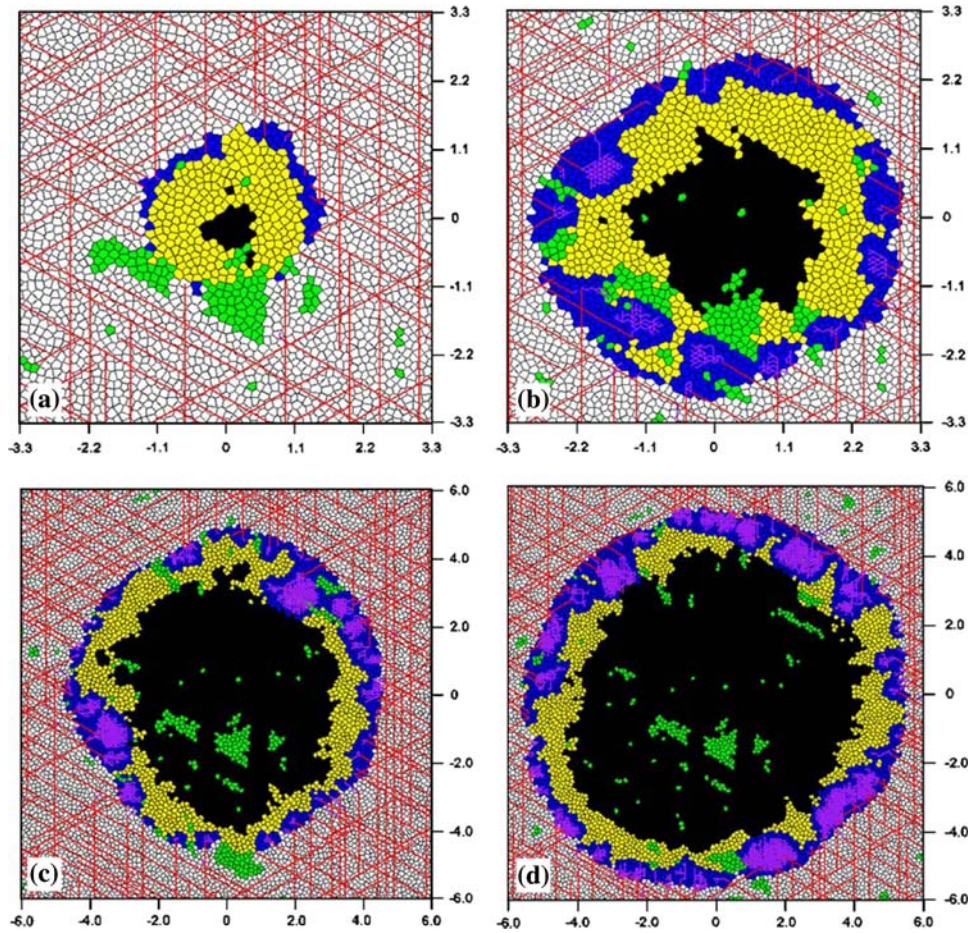

FIGURE 5. Simulation of brain tumor growth under the effects of vasculature. Straight lines are microvascular network. (a) Day 40, (b) day 70, (c) day 100, and (d) day 130. Proliferative cells (blue), hypoxic cells (yellow), necrotic cells (black), and apoptotic cells (green) are shown. Taken from Gevertz and Torquato.[25]

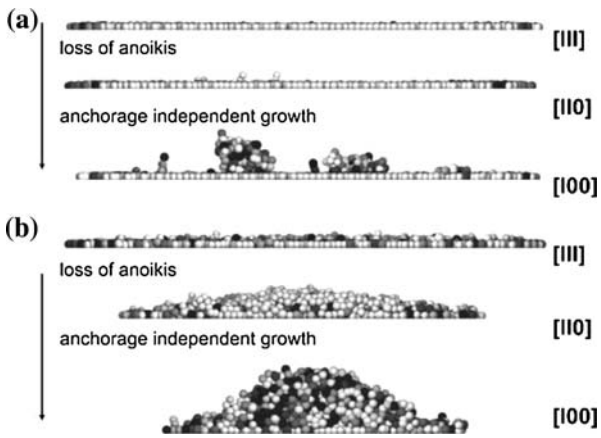

FIGURE 6. Simulation of the growth of epithelial cell populations *in vitro* for cell substrate anchorage of (a) 600 μN/m and (b) 200 μN/m. [III]: contact inhibition, anchorage-dependent growth, and anoikis present. [II0]: contact inhibition and anchorage-dependent. [I00]: contact inhibition. Taken from Galle *et al.*[19]

concentrations. As the tumor grows, nutrient concentrations inside the tumor become lower due to the increasing size of the tumor. When the nutrient concentrations become lower than threshold values, the cells located in the regions of low nutrient concentration are made to die and are added to the necrotic core. In this way, tumor growth simulations usually show the increasing size of the tumor as well as the distinct layers inside the tumor such as necrotic core and proliferating rim.

The rules for the cell behaviors are dependent upon specific biologic applications. Some of the rules found in recent publications are discussed in this section.

Division

Two of the important decisions regarding the cell division are determination of the division probability and where to position the two daughter cells. For the

cell division probability, cells can be programmed to divide after cell cycle time.[10,27,43] Experimentally obtained cell cycle time can be applied.[10,43,52] Each cell can be assigned different cell cycle time based on a normal distribution,[10,43] and in that case, the daughter cells can inherit the cell cycle time of the parent cell.[43] When incremental time step Δt is used for time dependent simulation, the probability of cell division can be applied such that $P_d = \Delta t/t_c$ where P_d is the cell division probability at the time step and t_c is the cell cycle time.[47] The cell division probability can also be calculated based on other parameters such as local nutrient concentration.[16]

Cell cycle can also be modeled. In their model for the epidermis, Schaller and Meyer-Hermann[46] incorporated a cell cycle in which cells can enter different phases depending on the local environment. Walker *et al.*[52] modeled a cell cycle in their simulation of epithelial cells. Jiang *et al.*[32] used a simplified protein regulatory network to model the transition between different phases of the cell cycle in their simulation of avascular tumor growth.

Regarding where to position the two daughter cells, one of the common rules is to position them randomly at the adjacent vacant sites.[9,10,23] Contact inhibition is a commonly used rule which prevents cell division when all the adjacent sites are already filled.[5,9,43] Depending on specific application, the daughter cells can be placed away from each other with a site between them[47] or always adjacent to each other.[42] Pérez and Prendergast[42] assigned different probabilities at different available sites in their anisotropic mitosis model. Piotrowska and Angus[43] applied a probabilistic overlay to determine the location for the daughter cells to avoid morphological artifact in their simulation of *in vitro* multicellular spheroid tumor growth. In their simulation of three-dimensional brain tumor growth, Kansal *et al.*[33] used the intercellular mechanical stress algorithm in which a daughter cell pushes an adjacent cell outward until the cell at the tumor edge fills the adjacent empty space. Ferreira *et al.*[16] enabled the cancer cells to pile up in a given lattice site in their simulation of avascular tumor growth. If the dividing cancer cell was inside the tumor, the daughter cell piled up at the site, and if the cell is on the tumor border, the daughter cell replaces the normal or necrotic cell at the nearest neighboring site.[16]

In case of cellular Potts model in which one biological cell occupies more than one lattice sites, half of the lattice sites in the parent cell can become a new cell.[1,32] In case of lattice-free models, the orientation of cell division can be determined by the direction of the total force the dividing cell experiences.[19] Galle *et al.*[19] included the effect of the substrate in the determination of the cell division orientation in their simulation of the growth of epithelial cell populations *in vitro*.

Cell growth can be modeled between the cell divisions in the models such as cellular Potts model or lattice-free model both of which can accommodate cell shape change. In their Potts model of avascular tumor growth, Jiang *et al.*[32] set a target volume which each cell tries to reach, and reaching the target volume is a condition for cell division. Galle *et al.*[19] modeled the cell growth such that the cell doubles its mass and volume during the interphase in their simulation of the growth of epithelial cell populations. When a cell is compressed by its neighbor cells and the resulting cell volume is less than a threshold value, the growth is inhibited.[19]

Migration

For random movement of cell, new location of the cell can be selected randomly from one of the neighboring sites.[9,23,42] The migration, however, can occur several times for each proliferation step because the time scales of the migration and the proliferation are different.[9,42] Contact inhibition is commonly used as in the case of cell division such that the cell cannot move if all the neighboring sites are occupied.[9,23,42] Cheng *et al.*[10] developed a tissue growth model in which cell migration is modeled as a persistent random walk. Each cell moves in one direction for a certain period of time until it changes its direction and continues to move. After the cell cycle time, the cell stops to divide. The two daughter cells resume their persistent random movements. When the two cells collide, they stop for some time and start moving again.[10] For directed movement of cell, Deisboeck and coworkers[36,54] chose the best location for migration among the neighboring sites based on the amount of nutrients, levels of toxicity, and mechanical confinement in their tumor model . In their simulation of cell movement in the prostate epithelium, Lao and Kamei[34] tested different movement behaviors of transit amplifying/intermediate cells and luminal cells in the prostate duct, and compared with experimental data.

In their model of avascular tumor growth, Ferreira *et al.*[16] used a probability of migration which increases with the number of tumor cells in the element. This probability also increases with the level of nutrient. In a similar model by Mallet and De Pillis[35] for tumor-immune system interactions, immune cells move randomly until they encounter a tumor cell. In the case study of their hybrid agent-based model for microbiological systems, Guo *et al.*[30] modeled the chemotactic displacement of cells such that it is proportional to the difference in newly bounded receptors at the front and rear of the cell. Robertson *et al.*[45] modeled the cell

migration based on the relative concentrations of fibronectin, integrin, and cadherin in their simulation of *Xenopus laevis* morphogenesis.

In case of lattice-free models, the movements of the cells are usually computed from the equations of motion which incorporate the forces acting on the cells.[18,46]

Apoptosis and Necrosis

When apoptosis occurs, cells are usually removed from the lattice, and the site can remain vacant until it is filled with other cells.[20] In their simulation of tissue differentiation, Checa and Prendergast[9] implemented apoptosis to the cells differentiated by a type of stimulus when the stimulus changed to other type. In the model of chronic chagasic cardiomyopathy after stem cell transplantation by Galvão *et al.*,[20] the apoptosis of inflammatory cell occurs if there is at least one bone marrow stem cell in the neighborhood of the inflammatory cell. In their simulation of the growth of epithelial cell populations *in vitro*, Galle *et al.*[18,19] made the cell undergo anoikis when the contact area to the substrate is smaller than a threshold value.

One of the common ways to model necrosis is to make it occur when local nutrient concentration is below a threshold value.[32,43] In case of tumor growth simulations, the necrotic cells usually do not vanish from the lattice but are added to the necrotic material inside the tumor.[12,32]

Differentiation

When a cell differentiates into other cell, the type of the cell in the lattice site can simply be changed. Checa and Prendergast[9] made a portion of the mesenchymal stem cells differentiate into fibroblasts, chondrocytes, or osteoblasts depending on the level of mechanical stimulus and local vascularity when the cells have reached the maturation age. Grant *et al.*[28] determined whether a cell would make a transition to a more differentiated form based on the arrangement of cell, matrix, and free space around the cell in the hexagonal grid system in their simulation of *in vitro* epithelial cell morphogenesis. They also included the de-differentiation of the cell in their simulation.

ENVIRONMENT

Cell behaviors are influenced by their interaction with the environment. Gerlee and Anderson[23] linked the environmental factors to the cell behaviors using a response network in their model of tumor growth. They consider the environmental factors such as neighbors, oxygen concentration, glucose concentration, and hydrogen ion concentration, and the cell behaviors such as proliferation, quiescence, apoptosis, metabolism, and movement. The cellular responses to those environmental factors are determined through the response network that each cell is equipped with.[23] In this section, modeling of extracellular matrix (ECM), chemicals, microvasculature, and forces are reviewed. Chemical concentrations and forces are usually computed in a different spatial scale from that of the cell, and this information from different spatial scale is projected to the cellular level for the cells to react to those factors.

Extracellular Matrix

Extracellular matrix (ECM) can be placed in the lattice sites which are available for cells as well.[9,28] Checa and Prendergast[9] let their lattice sites available for either cell or ECM in their simulation of tissue differentiation. They made the cells synthesize ECM after cell division so that the number of cells and matrix production can be in a proportional relation. Grant *et al.*[28] made the cells produce matrix depending on the arrangement of the surrounding elements in their simulation of *in vitro* epithelial cell morphogenesis. When matrix is generated by a cell, the cell moves to a neighboring site, and the resulting vacant site is filled with the produced matrix. Robertson *et al.*[45] enabled each pixel to have different amount of fibronectin, and affect the cell behavior.

Chemicals

One of the popular ways to determine the concentrations of the chemicals such as nutrients is solving the reaction-diffusion partial differential equations.[16,32] Finite difference method can be used for the computation of the equations,[23,30] and the grid system which cells occupy can be used for the numerical computation of the reaction-diffusion equations as well.[23,35] Mallet and De Pillis[35] gained sufficient accuracy in nutrient concentrations when they used the same grid system for cells and for the reaction-diffusion equations for nutrients in their simulation of tumor-immune system interactions. Their equations are based on the ones used by Ferreira *et al.*,[16] and for the boundary conditions, they assumed that the nutrients are constantly supplied from the blood vessels located at the top and bottom sides of the computational domain. Palsson[41] used a regular 3-D grid for the calculation of cAMP concentrations while letting the cells unrestricted to the grid points in his 3-D model of multicellular systems. As a result, the cAMP

concentrations are interpolated between the cells and the grid system where the cAMP concentrations are calculated.

Microvasculature

Incorporating microvasculature in the model provides the source for nutrients. In their modeling of the effects of vasculature evolution on early brain tumor growth, Gevertz and Torquato[25] modeled the microvasculature evolution on a triangular lattice overlaid on top of the lattice for cells (Fig. 5). The interaction between the microvasculature and the cells were simulated such that the interaction is mediated by the key proteins involved in the vessel growth and regression. The concentrations of the proteins were obtained from the numerical solution of the reaction-diffusion equations. Checa and Prendergast[9] modeled each capillary as a sequence of endothelial cells in their model for tissue differentiation. The growth of the vascular network on a regular lattice was simulated following their random walk model. High oxygen concentration was assumed within a distance from any blood vessel.

Peirce and coworkers[3,4] modeled the microvasculature consisting of endothelial cells and smooth muscle cells based on the confocal microscopy image of mouse muscle, and simulated circulating inflammatory cell trafficking[4] and adipose-derived stromal cell trafficking during ischemia.[3] Qutub and Popel[44] simulated capillary sprouting by applying local rules to the individual endothelial cells.

Forces

In their model for tissue differentiation, Checa and Prendergast[9] incorporated the interaction between mechanical stimuli and the cell behavior in the tissue. The mechanical stimuli affect the differentiation of precursor cells and angiogenesis, and in turn, the mechanical properties of the tissue change due to the resulting change of the tissue composition. They determined the level of mechanical stimuli using the following equation: $S = \gamma/a + \upsilon/b$ where S is a mechanoregulatory stimulus, γ is shear strain, υ is fluid/solid velocity, and a and b are constants. The mesenchymal stem cells were made to differentiate toward fibroblasts, chondrocytes, or osteoblasts according to different levels of the mechanical stimuli. The shear strain and fluid/solid velocity were obtained from finite element analysis. They also included the effect of oxygen such that, at low oxygen concentration, cartilage instead of bone forms. Ausk *et al.*[2] simulated the real-time signaling induced by mechanical stimuli in osteocytic networks. Bailey *et al.*[3,4] used the pressure differential calculated from network flow model to drive leukocyte movement in their microvasculature model. In lattice-free models, the forces that the cell experiences usually determine the direction and magnitude of the cell displacement.[18,46]

SUMMARY AND CONCLUSION

Rule-based modeling approach is suited for MCBS simulation in that it models the behavior of each individual cell and the interaction among the cells and with the environment. Emergent system behaviors can be observed by applying local rules to individual cells. The rules are situation-dependent, that is, different rules have to be implemented depending on the type of MCBS. Although many cell behaviors and environmental factors have been discussed in the previous sections, not all of the factors have equal effects on the system behavior in an application. The factors that have greater effects have to be selected depending on the specific application. The rules including the parameters used in the simulation can be determined based on the knowledge obtained from wet lab experiment or from the literature. When the information is not available, appropriate level of simplification and assumption can be made, and the simulation results have to be interpreted accordingly. Parameter sensitivity analysis is one way of testing the influence of the variability of the parameter on the system behavior.[49]

These models can be used to test scientific hypothesis, plan experiments, and elucidate the connection between emerging properties of complex system and micro-scale simplistic rules. Different rules can be tested by examining the resulting system behavior. The effect of each component in the system can be investigated by changing the rules for the components. This enables the identification of the more dominant factors contributing to the global behavior.

As mentioned in the previous sections, continuum models can be combined into the cell-based models, and some components such as chemical distribution in MCBS are modeled more conveniently with the continuum models. Appropriate mixture of both approaches would predict more accurate system behavior of MCBS.

Most of CA and ABM in biology are so called *ad hoc* models. Their main purpose is to understand and extract key mechanisms behind apparent emergent complexity. Although their outcomes are usually qualitative and may explain the underlying biological mechanism, it is not impossible that, in the future, some of these models could be predictive and possibly patient specific with the increasing amount of biologic knowledge and computing power.

ACKNOWLEDGMENT

This work was supported by NIH (R01-HL095508-01).

REFERENCES

[1]Alber, M. S., M. A. Kiskowski, J. A. Glazier, and Y. Jiang. On cellular automaton approaches to modeling biological cells. In: Mathematical Systems Theory in Biology, Communications, Computation, and Finance, edited by J. Rosenthal, and D. S. Gilliam. New York: Springer-Verlag, 2003, pp. 1–40.

[2]Ausk, B. J., T. S. Gross, and S. Srinivasan. An agent based model for real-time signaling induced in osteocytic networks by mechanical stimuli. *J. Theor. Biol.* 39:2638–2646, 2006.

[3]Bailey, A. M., M. B. Lawrence, H. Shang, A. J. Katz, and S. M. Peirce. Agent-based model of therapeutic adipose-derived stromal cell trafficking during ischemia predicts ability to roll on P-selectin. *PLoS Comput. Biol.* 5:e1000294, 2009.

[4]Bailey, A. M., B. C. Thorne, and S. M. Peirce. Multi-cell agent-based simulation of the microvasculature to study the dynamics of circulating inflammatory cell trafficking. *Ann. Biomed. Eng.* 35:916–936, 2007.

[5]Bartha, K., and H. Rieger. Vascular network remodeling via vessel cooption, regression and growth in tumors. *J. Theor. Biol.* 241:903–918, 2006.

[6]Bonabeau, E. Agent-based modeling: methods and techniques for simulating human systems. *Proc. Natl Acad. Sci. USA* 99:7280–7287, 2002.

[7]Byrne, H., and D. Drasdo. Individual-based and continuum models of growing cell populations: a comparison. *J. Math. Biol.* 58:657–687, 2009.

[8]Chavali, A. K., E. P. Gianchandani, K. S. Tung, M. B. Lawrence, S. M. Peirce, and J. A. Papin. Characterizing emergent properties of immunological systems with multicellular rule-based computational modeling. *Trends Immunol.* 29:589–599, 2008.

[9]Checa, S., and P. J. Prendergast. A mechanobiological model for tissue differentiation that includes angiogenesis: A lattice-based modeling approach. *Ann. Biomed. Eng.* 37:129–145, 2009.

[10]Cheng, G., B. B. Youssef, P. Markenscoff, and K. Zygourakis. Cell population dynamics modulate the rates of tissue growth processes. *Biophys. J.* 90:713–724, 2006.

[11]Deutsch, A., and S. Dormann. Cellular Automaton Modeling of Biological Pattern Formation. Boston: Birkhäuser, 2005.

[12]Dormann, S., and A. Deutsch. Modeling self-organized avascular tumor growth with a hybrid cellular automaton. *In Silico Biol.* 2:0035, 2002.

[13]Elliott, E., and L. D. Kiel. Agent-based modeling in the social and behavioral sciences. *Nonlinear Dynam., Psych., Life Sci.* 8:121–130, 2004.

[14]Engelberg, J. A., G. E. P. Ropella, and C. A. Hunt. Essential operating principles for tumor spheroid growth. *BMC Syst. Biol.* 2:110, 2008.

[15]Ermentrout, G. B., and L. Edelstein-Keshet. Cellular automata approaches to biological modeling. *J. Theor. Biol.* 160:97–133, 1993.

[16]Ferreira, Jr., S. C., M. L. Martins, and M. J. Vilela. Reaction-diffusion model for the growth of avascular tumor. *Phys. Rev. E* 65:021907, 2002.

[17]Frisch, U., B. Hasslacher, and Y. Pomeau. Lattice-gas automata for the Navier-Stokes equation. *Phys. Rev. Lett.* 56:1505–1508, 1986.

[18]Galle, J., M. Hoffmann, and G. Aust. From single cells to tissue architecture—a bottom-up approach to modelling the spatio-temporal organisation of complex multi-cellular systems. *J. Math. Biol.* 58:261–283, 2009.

[19]Galle, J., M. Loeffler, and D. Drasdo. Modeling the effect of deregulated proliferation and apoptosis on the growth dynamics of epithelial cell populations in vitro. *Biophys. J.* 88:62–75, 2005.

[20]Galvão, V., J. G. V. Miranda, and R. Ribeiro-dos-Santos. Development of a two-dimensional agent-based model for chronic chagasic cardiomyopathy after stem cell transplantation. *Bioinformatics* 24:2051–2056, 2008.

[21]Garbey, M., C. Mony, and M. Smaoui. Fluid flow-agent based hybrid model for the simulation of virtual prairies. Proceedings of the Conference of Parallell CFD, Lyon, 2008, to appear.

[22]Gardner, M. Mathematical games: the fantastic combinations of John Conway's new solitaire game "Life". *Sci. Am.* 223:120–123, 1970.

[23]Gerlee, P., and A. R. A. Anderson. An evolutionary hybrid cellular automaton model of solid tumour growth. *J. Theor. Biol.* 246:583–603, 2007.

[24]Gerlee, P., and A. R. A. Anderson. A hybrid cellular automaton model of clonal evolution in cancer: the emergence of the glycolytic phenotype. *J. Theor. Biol.* 250:705–722, 2008.

[25]Gevertz, J. L., and S. Torquato. Modeling the effects of vasculature evolution on early brain tumor growth. *J. Theor. Biol.* 243:517–531, 2006.

[26]Gilbert, N. Agent-Based Models. Los Angeles: Sage Publications, 2008.

[27]Grabe, N., and K. Neuber. A multicellular systems biology model predicts epidermal morphology, kinetics and Ca^{2+} flow. *Bioinformatics* 21:3541–3547, 2005.

[28]Grant, M. R., K. E. Mostov, T. D. Tisty, and C. A. Hunt. Simulating properties of in vitro epithelial cell morphogenesis. *PLoS Comput. Biol.* 2:e129, 2006.

[29]Grimm, V., and S. F. Railsback. Individual-Based Modeling and Ecology. Princeton: Princeton University Press, 2005.

[30]Guo, Z., P. M. A. Sloot, and J. C. Tay. A hybrid agent-based approach for modeling microbiological systems. *J. Theor. Biol.* 255:163–175, 2008.

[31]Holland, J. H. Hidden Order, How Adaptation Builds Complexity. Helix Books, 1995.

[32]Jiang, Y., J. Pjesivac-Grbovic, C. Cantrell, and J. P. Freyer. A multiscale model for avascular tumor growth. *Biophys. J.* 89:3884–3894, 2005.

[33]Kansal, A. R., S. Torquato, G. R. Harsh IV, E. A. Chiocca, and T. S. Deisboeck. Simulated brain tumor growth dynamics using a three-dimensional cellular automaton. *J. Theor. Biol.* 203:367–382, 2000.

[34]Lao, B. J., and D. T. Kamei. Investigation of cellular movement in the prostate epithelium using an agent-based model. *J. Theor. Biol.* 250:642–654, 2008.

[35]Mallet, D. G., and L. G. De Pillis. A cellular automata model of tumor-immune system interactions. *J. Theor. Biol.* 239:334–350, 2006.

[36]Mansury, Y., and T. S. Deisboeck. The impact of "search precision" in an agent-based tumor model. *J. Theor. Biol.* 224:325–337, 2003.
[37]Mi, Q., B. Rivière, G. Clermont, D. L. Steed, and Y. Vodovotz. Agent-based model of inflammation and wound healing: insights into diabetic foot ulcer pathology and the role of transforming growth factor-β1. *Wound Repair Regen.* 15:671–682, 2007.
[38]N'Dri, N. A., W. Shyy, and R. Tran-Son-Tay. Computational modeling of cell adhesion and movement using a continuum-kinetics approach. *Biophys. J.* 85:2273–2286, 2003.
[39]Neumann, J. V. Theory of Self-Reproducing Automata, edited and completed by A. W. Burks. Urbana: University of Illinois Press, 1966.
[40]O'Sullivan, D. Graph-cellular automata: a generalised discrete urban and regional model. *Environ. Plann. B* 28:687–705, 2001.
[41]Palsson, E. A 3-D model used to explore how cell adhesion and stiffness affect cell sorting and movement in multicellular systems. *J. Theor. Biol.* 254:1–13, 2008.
[42]Pérez, M. A., and P. J. Prendergast. Random-walk models of cell dispersal included in mechanobiological simulations of tissue differentiation. *J. Biomech.* 40:2244–2253, 2007.
[43]Piotrowska, M. J., and S. D. Angus. A quantitative cellular automaton model of *in vitro* multicellular spheroid tumour growth. *J. Theor. Biol.* 258:165–178, 2009.
[44]Qutub, A. A., and A. S. Popel. Elongation, proliferation & migration differentiate endothelial cell phenotypes and determine capillary sprouting. *BMC Syst. Biol.* 3:13, 2009.
[45]Robertson, S. H., C. K. Smith, A. L. Langhans, S. E. McLinden, M. A. Oberhardt, K. R. Jakab, B. Dzamba, D. W. DeSimone, J. A. Papin, and S. M. Peirce. Multiscale computational analysis of *Xenopus laevis* morphogenesis reveals key insights of systems-level behavior. *BMC Syst. Biol.* 1:46, 2007.
[46]Schaller, G., and M. Meyer-Hermann. A modelling approach towards epidermal homoeostasis control. *J. Theor. Biol.* 247:554–573, 2007.
[47]Simpson, M. J., A. Merrifield, K. A. Landman, and B. D. Hughes. Simulating invasion with cellular automata: connecting cell-scale and population-scale properties. *Phys. Rev. E* 76:021918, 2007.
[48]Smaoui, M., M. Garbey, and C. Mony. Volunteer computing for ecology: the virtual prairie BOINC project. IEEE Asia-Pacific Services Computing Conference (IEEE APSCC 2008), Taiwan, 2008, accepted for publication.
[49]Thorne, B. C., A. M. Bailey, D. W. DeSimone, and S. M. Peirce. Agent-based modeling of multicell morphogenic processes during development. *Birth Defects Res. C Embryo Today* 81:344–353, 2007.
[50]Thorne, B. C., A. M. Bailey, and S. M. Peirce. Combining experiments with multi-cell agent-based modeling to study biological tissue patterning. *Brief Bioinform.* 8:245–257, 2007.
[51]Tran-Son-Tay, R., M. Hwang, M. Garbey, Z. Jiang, C. K. Ozaki, and S. A. Berceli. An experiment-based model of vein graft remodeling induced by shear stress. *Ann. Biomed. Eng.* 36:1083–1091, 2008.
[52]Walker, D. C., J. Southgate, G. Hill, M. Holcombe, D. R. Hose, S. M. Wood, S. Mac Neil, and R. H. Smallwood. The epitheliome: agent-based modelling of the social behaviour of cells. *BioSystems* 76:89–100, 2004.
[53]Wolfram, S. A New Kind of Science. Champaign: Wolfram Media, 2002.
[54]Zhang, L., C. A. Athale, and T. S. Deisboeck. Development of a three-dimensional multiscale agent-based tumor model: simulating gene-protein interaction profiles, cell phenotypes and multicellular patterns in brain cancer. *J. Theor. Biol.* 244:96–107, 2007.
[55]Zhang, L., Z. Wang, J. A. Sagotsky, and T. S. Deisboeck. Multiscale agent-based cancer modeling. *J. Math. Biol.* 58:545–559, 2009.
[56]Zygourakis, K., G. Cheng, and P. Markenscoff. Dynamic behavior of heterogeneous cell populations growing under mass transport limitations. *Biophys. J.* 96:317a, 2009.