Cell-based models

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Summary

Cell-based models are theoretical models of biological systems in which cells are represented explicitly, as individual units. They are typically used for modeling systems that require cellular resolution, where the complex behavior or geometry of the cells is intrinsic to the system's behavior, or when the cells themselves become the focus of study, not just the larger system they compose. In these situations, it is either not possible or not desirable to reduce cells to elemental "atoms", in which case a more compact mathematical description of the system as a whole might be possible.

Cell-based models are particularly interesting because they combine two orthogonal aspects of biological cells, the physical – membranes, cytoskeleton, etc. – and the logical – cell regulation, control. Cells can move, grow, change shape and modify their structure over time, yet they are also equipped with extremely sophisticated information processing, control and regulation mechanisms.

In this thesis focus is given to modeling basic cell mechanics, with only very simple programs for cell behavior. Cell-based models can be divided into two broad categories: lattice-based and lattice-free models. In lattice-based models, space is divided into a regular grid (or lattice) such that spatial coordinates can be given as whole numbers, much like a chessboard. A virtual cell in the model may consist of single site, or a collection of adjacent sites, and any movement in space occurs in discrete jumps from one grid site to another. Lattice-based models are often in the form of cellular automata, in which each lattice site is in some discrete state, such as "occupied" or "free", and at each time step sites transition to a new state based on the states of their neighbors according to a fixed set of rules. The system evolves in time by applying the rules over and over again, forming a sequence of snapshots

of the system state, like a motion picture where each frame is generated by applying a set of rules to the previous frame. The rules are chosen to provide a rough approximation of the behavior of the real system and can be chosen ad hoc. However, in many cases the Cellular Potts model (CPM), where the rules are chosen such that the system evolves to a state of minimum potential energy, has proven a popular choice for cell-based modeling, particularly for systems where cell-cell adhesion is the dominant driving force.

In lattice-free models, space is continuous and model elements have a true velocity and acceleration. There are many types of lattice-free model and they differ chiefly on how the cells are represented geometrically. The simplest models represent cells as spheres or ellipsoids, and are well suited to systems of proliferating and actively motile cells. Compact epithelia are well captured by simple polygon models, in which each cell is a convex polygon (or polyhedron) attached to its neighbors. The most general models are the complex polygon models that can potentially represent any cell geometry, albeit at a high computational cost. In each case the geometry of the cells evolves over time due to the strain involved in growth, collision, deformation and other mechanical processes according to the assumed material properties of the cell, which are typically some combination of elasticity, viscosity and surface tension, leading to both liquid and solid like behavior.

In this thesis, we explore cell-based models for the embryogenesis of the sea anemone *Nematostella vectensis* and pattern formation in cultures filamentous cyanobacteria. Despite being far removed from each other biologically, these two systems can be modeled effectively using similar cell-based techniques. For *Nematostella*, a two-dimensional complex polygon model is used to model a cross-section of the blastula-stage embryo. Each virtual cell consists of an eighty-four vertex polygon, allowing the model to capture characteristic cell shapes, such as bottle cells. By programming a subpopulation of the cells to use filopodia for motility and undergo apical constriction, we are able to simulate the first stages of gastrulation, where the embryo contorts itself to form the gut. For the second system, filamentous cyanobacteria, a two-dimensional complex polygon model is used to represent the typically long and flexible trichomes of gliding, filamentous cyanobacteria. The trichomes are programmed with a simple light-seeking strategy called photophobia for optimizing their irradiance exposure. Using this model we are able to recreate the "cyanograph" experiments of D.-P. Häder, in which a photographic projection onto a Petri dish can become imprinted onto the

culture through the movements of the cyanobacteria. We also show how the extensive length and relatively fast speeds of the trichomes can be a significant advantage in optimizing exposure. Finally, we explore the formation of reticulate patterns in cultures of *Anabaena variabilis*, thought to be analogous to fossilized patterns dating to the earliest periods of life on Earth. We use a three-dimensional version of the cyanograph model to study the formation of these patterns under varying parameters such as trichome density and cohesiveness. We find that by randomly gliding backwards and forwards the trichomes can self-organize into stable channels when weakly cohesive and sufficiently packed, as was observed in experiments.

We conclude with thoughts on the future of cell-based modeling and suggest research directions. With desktop computing power now well passed the teraflop mark, full scale cell-based models of simple organisms such as the slime mold or the roundworm are within reach. Given the amount of experimental research and funding pouring into these model organisms, it is both a feasible and exciting new avenue of research that could pay large dividends in the future. It is also my personal hope that computer science and biology become increasingly synergetic as increasing recognition is given to the logical aspects of biological systems, while inspiration is drawn from biology for new computational paradigms. In any case, if biology is truly at the crossroads of physics and computer science, then by integrating these distinct natures, cell-based models will surely play a significant role in future research.