Efficient Simulation of Cellular Migration

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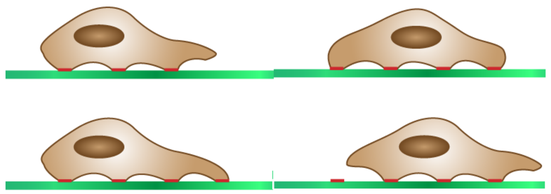
Problem Statement

The goal is to develop an efficient model of cellular migration, incorporating cytoskeletal influences that have effects over a distance, along with cell adhesion, haptotaxis, and chemotaxis. The movement of cells within an organism is central to the processes of embryogenesis, wound-healing and metastasis.

How Cells Move

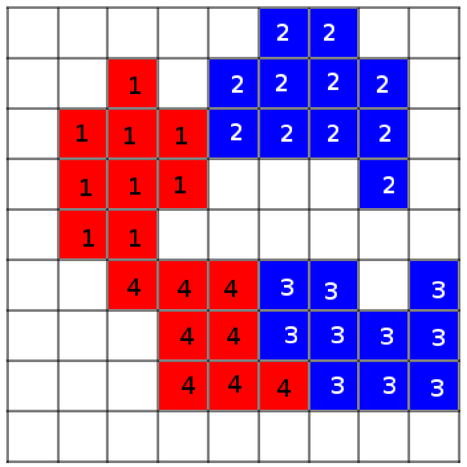
The cell sends projections from its leading edge. These projections are created by the extension of actin filaments under the cell's membrane. As the cell moves towards its leading edge, the cytoskeleton contracts, bringing the rear part of the cell forward, then back end of the cell releases from the substrate. The pulling of the back end forward suggests a model that can represent forces acting at a distance.



[2]

Modeling Background

CELLULAR POTTS MODEL (CPM). Models of cellular interactions can be classified as lattice-based or individual-based. One inspiration for this model is the CPM, a lattice-based model. In this model, cells are represented by contiguous, numbered elements in a lattice. All elements with the same number belong to a single cell. The image below represents four cells of two different types. In each time step, the algorithm tries to update the number (i.e. the identity) of randomly selected elements. For each lattice element it attempts to change the number to that of an adjacent element, determining the change in energy for that element by using using localized changes to the Hamiltonian energy defined by:



$E = E_{contact} + E_{vol} + E_{surf} + E_{chem}$

where $E_{contact}$ is energy from contact with adjacent cells, E_{vol} and E_{surf} are variations from target volume and surface area and E_{chem} is energy due to the cell's attraction to or repulstion from external chemical gradients. With the goal of minimizing total energy, the move is accepted if the change in energy is negative or with probability $e^{-\Delta E/kT}$ if the change is positive.[1]

Advantages: Simplicity, flexibility, efficiency.

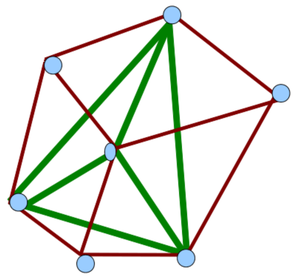
Disadvantages: Cellular structure not modeled, potential inefficiencies.

TENSEGRITY MODEL Ingber[3] has proposed a model for the cellular cytoskeleton based on *struts* and *cables*, where struts are rigid structures, having a minimum but no maximum length, and cables are flexible structures, having a maximum but no minimum length. This model shows how local forces can be transmitted globally around the cell.

Advantage: Simple model of structure.

Disadvantage: Discrete nature may make changes hard to compute.

Our Model



The cell is modeled as a collection of points (beads) connected by springs, which approximate both kinds of tensegrity components but with simple computations of changes. The parameters of the springs are the undeformed length and the elasticity; a strut has low elasticity, a cable high elasticity.

Our Approach

Although it is not lattice-based, our approach mimics that of the CPM as a Monte-Carlo simulation minimizing a Hamiltonian representing system energy. In each time step, a set of beads are randomly selected. For each of these beads, a random vector is generated and a move is proposed. Using a Hamiltonian approximation that includes the energy from the connected springs and struts, the change in energy is determined. The probability that the move is made uses the same function as that of the CPM.

If the cell's external surface stretches due to adhesion to a neighboring cell, new beads are added to allow the formation of membrane projections.

Challenges

When cells move, they may come into contact and adhere, but they cannot move through each other. Therefore the simulation must determine when the cells come in contact with each other. This requires finding collisions, not just between the beads, but also between the triangles that define the surfaces. Without a very efficient algorithm, collision detection could make the computation inefficient.

We will overcome this challenge by using methods from computer animation and video gaming for modeling moving objects. See "Kinetic Data Structure in Cell Movement Simulation" for more.

References

[1] Trevor M. Cickovski, Chengbang Huang, Rajiv Chaturvedi, Tilmann Glimm, H. George E. Hentschel, Mark S. Alber, James A. Glazier, Newman Stuart A., and Jesus A. Izaguirre. A framework for three-dimensional simulation of morphogenesis. *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, 2(3):1–16, 2005.

[2] Alexandre Saez. Four steps of cell migration. `http://upload.wikimedia.org/wikipedia/commons/3/35/Four_steps_of_cell_migration.png`, February 2011. [CC-BY-SA-3.0 or GFDL, via Wikimedia Commons.

[3] Dimitrije Stamenovic and Donald E. Ingber. Tensegrity-guided self assembly: From molecules to living cells. *Soft Matter*, 5(6):1137–1145, 2009.