Vertex Dynamics and Topology of Epithelial Tissue

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Abstract

This summer I have read many papers about epithelial tissue modeling, taken an online course in the CUDA programming langauge and become a proficient Python programmer, read the CHASTE source code, and worked through the CHASTE tutorials. I have a solid knowledge of a variety of epithelial tissue models, ability to work the leading modeling software, and a high level of proficiency in two languages which will be instruental in producing my own model.

Chapter 1

Why Study Epithelial Tissue?

And what is epithelial tissue, anyway? Epithelial tissue is the most prolific of the four types of tissue in the human body. The tissue covers the whole body, inside and out, as it is specialized to form the covering of internal and external surfaces. It is important to study this tissue as an intellectual activity in and of itself, but more importantly because once its behavior is understood coomputational models will become useful tools for biomedical research and animal-free experimentation. My primary interest in this modeling is because it offers an obviously parallel programming task and also because it promisesto enable medical researchers to run computational simulations where once they had to perfrom animal experiments.

Chapter 2

Overview of the Literature

Introduction

Lately, vertex dynamics models have acquired a great deal of attention for their ability to accurately simulate the morphogenesis of epithelial tissue. The models all agree that epithelial tissues can be approximated by a mesh of polygons. Where these models distinguish themselves, however, is in how they specify the forces which act upon the vertices of the mesh. Some models, such as the Weliky-Oster model, specify explicit forces which act upon the vertices. Others, such as the Honda-Nagai model, assume that the forces acting upon the vertices can be described as the gradient of the free energy function, which wants to minimize itself.

The Nagai-Honda Model

The Honda-Nagai model, studied since the 1980s by the researchers H. Honda and T. Nagai, asserts that the the vertices in the mesh are acted upon by the force given by the gradient of the free energy function, which tends to want to minimize itself. The free energy function for each cell in this model is given by:

1. The deformation energy term
   $U_D = \lambda(A - A_0)^2$
   where A_0 is a target area for a cell, and lambda is some positive constant.

2. The membrane surface energy
   $U_S = \beta(C - C_0)^2$
   where C is the cell perimiter, and C_0 is a target perimeter.

3. The cell-cell adhesion energy
   $U_A = \sum_{j=0}^{n-1} \gamma_j d_j$
   where n is the number of vertices in the cell, γ is some constant for the boundary in question between one cell and another, and d is the distance between one vertex and the next in a counter clockwise fashion.

As we have already mentioned, the *gradient* of this free energy is what gives us the force acting on each vertex i. As seen in [6], this force on each vertex i is given by:

$$F_i = -\sum_{l \in N_i} (2\lambda(A_l - A_{0_l})\nabla_i A_l + 2\beta(C_l - C_{0_l})(\nabla_i d_{l,I_l-1} + \nabla_i d_{l,I_l}) + \gamma_{l,I_l-1}\nabla_i d_{l,I_l-1} + \gamma_{l,I_l}\nabla_i d_{l,I_l} \quad (2.1)$$

where l is the lth cell containing vertex i, given a counter clockwise orientation. I_l is the local index of node i in element l.
Furthemore, we have to specify the area and vertex-distance gradients. They are given by:

$$\nabla_i A_l = \frac{1}{2} \begin{pmatrix} y^l_{I+1} - y^l_{I-1} \\ x^l_{I-1} - x^l_{I+1} \end{pmatrix} \tag{2.2}$$

where the superscrpits l denote that x, y are in cell l. The subscripts are local indices in the cell l. The orientation is once again anti-clockwise.

$$\nabla_i d_{l,j} = \frac{1}{d_{l,j}} \begin{pmatrix} x_i - x_j \\ y_i - y_j \end{pmatrix} \tag{2.3}$$

where the subscript j denotes the neighboring vertex.
The other consideration of this model are T1 and T2 switches. These switches change the topology of the tissue in such a way that the cells never become concave, and edges never cross. A T1 swap is one that occurs when two vertices become too close to one another. Then the edge containing these vertices is flipped ninety degrees and two new vertices are introduced at a prespecified distance from each other. A T2 swap is other wise known as element removal, when a triangular element in the mesh shrinks below some minimal area, and the three vertices are replaced by one single vertex.
The specified force, combined with these two elementary operations, constitute the Honda-Nagai model.

Feedback Mechanisms and Proliferation

This model is limited in that includes neither mechanical nor chemical feedback, and does not specify how cells proliferate. These are two extensions which can and have been made to the model by certain researchers. On the other hand, the dynamics of some successful models such as [10] have the patterning of cells specified entirely by morphogens. In these models, chemicals called 'morphogens' are what drive cells to proliferate, and the low concentrations of the morphogen on the fringe of the tissue explain why the tissue eventually ceases to grow as the tissue reaches a certain size. Other models, such as those described in [1] are based upon the vertex dynamics models such as the Honda-Nagai model, but include additional mechanical feedback terms which limit the growth of cells.

Additional Curiosities

The vast majority of models assume that exactly three cells meet at any vertex, except vertices on the boundary. In the language of topology, one would say that all interior vertices in the tissue have degree three. Empirical observations show, however, that more more than three cells can meet at any junction under certain circumstances [5]. This means that models ought to be extended to include the formation of these 'rosettes'.

Chapter 3

Topological Considerations

The Euler Characeteristic and Its Results

Topological Changes to the Mesh

An Additional Topological Change, and the Effects

Biological Considerations

rosettes morphogens, modelling diffusion. A mechanical or a chemical process

Chapter 4

Numerical Methods for the Project

The Forward Euler Method

A Modified Runge Kutta Method

Chapter 5

Overview of the Literature

Introduction

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Appendix A

Valuable Programming Lessons Learned

GitHub

When you are working on a large project such as this one, it is a good idea to have some sort of version control system which tracks the changes you have made to your code, and to return to an earlier working version in case something gets terrribly broken. Many people who do not know about version control will do just this, except they will save as' every couple of days. Unfortunately, this method is very space inefficient, as each time you 'save as', you save your entire project. Roughly speaking, git saves only the small changes you have made between versions. Git is a popular version control tool, and github is a popular place to store you files online.

Get Your Files on GitHub

- Go to github.com and sign up for an account
- Make a new repo on github
- cd to the directory of your project on your machine.
- git init
- git add .
- git commit -m "some message"
- git remote add origin YOUR URL HERE (This url is given to you from github when you make the repo.)
- git pull origin master
- git push origin master

Access And Modify These Files Somewhere Else

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Bibliography

[1] Buchmann, A. Alber, M., Zartman, J. *Sizing it up: The mechanical feedback hypothesis of organ growth regulation.* Seminars in Cell and Developmental Biology, 2014.

[2] *Chaste Tutorial* `https://chaste.cs.ox.ac.uk/chaste/tutorials/release_2.1/UserTutorials.html`

[3] Drasdo, D. *Bucking Instabilities of One Layered Growing Tissues.* Physical Review Letters 84.

[4] *Epithelial Tissues* `http://www.botany.uwc.ac.za/sci_ed/grade10/mammal/epithelial.htm`

[5] Fletcher, A. , Osterfield, M., Baker, R., Shvartsman, S. *Vertex Models of E[ithelial Morphogenesis.* Biophysical Journal 106, June 2014.

[6] Fletcher, A., Osborne, J., Maini, P, Gavaghan, D. *Implementing vertex dynamics models of cell populations in biology within a consitent computational framework.* Prog. Biophys. Mol. Biol. 113: 299 - 326.

[7] Gibson, W., Gibson, M. *Cell Topology, Geometry, and Morphogenesis in Proliferating Epithelia.* Current Topics in Developmental Biology 89.

[8] Luebke, D. and Owens, J. *Intro to Parallel Programming* `https://www.udacity.com/course/cs344` 2013.

[9] Nagai, T. Honda, H. *A dynamic model for the formation of epithelial tissues.* Philisohpical Magazine, Pt. B. Vol 81, Issue 7, 2001.

[10] Restrepo, S., Zartman, J. , and Basler, K. *Coordination of Patterning and Growth by the Morphogen DPP* Current Biology 24, 245- 255.