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Extending the CHASTE simulation library, comparing vertex dynamics and cellular Potts model

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Introduction

Many mathematical models of biological cells exist. Among the most powerful for modelling the detailed interactions and geometry of individual cells are vertex dynamics models, commonly used for epithelial sheets. In this project we develop extensions to CHASTE (Cancer, Heart and Soft Tissue Environment, http://www.cs.ox.ac.uk/chaste/), an open-source modelling software developed at the University of Oxford, that includes vertex dynamics models, to facilitate future simulations. We also compare qualitative and quantitative characteristics of the vertex dynamics models to the cellular Potts model.

CHASTE

CHASTE is a free and open-source library for simulating various biological scenarios, written in C++ with a test-driven development approach[6]. It has modules for cardiac electrophysiology and cell modelling, the latter of which we used for this project.

The Nagai–Honda vertex dynamics model

In this project we worked mainly with the two-dimensional Nagai–Honda model[7] of biological cells. Each cell consists of a set of vertices which make up its boundary, and the simulation proceeds by moving each vertex according to the gradient of a potential energy function (Hamiltonian). Typically, the energy for a single cell is [5, 3]

$$E = \lambda_p(p - P)^2 + \lambda_a(a - A)^2 + \sum_{\sigma'} J_{\sigma,\sigma'} p_{\sigma'} \tag{1}$$

where p is the cell perimeter, P is the target perimeter, a is the cell area, and A is the target area. The first two terms of the Hamiltonian are minimized when the cell is at its target perimeter and area. To model adhesion, each cell is assigned a type σ, and the third term of the Hamiltonian sums up over the contact perimeter between the cell and its neighbours of types σ'. Each pair of types (σ, σ') has an associated adhesion energy $J_{\sigma,\sigma'}$.

In CHASTE, the gradient of the Hamiltonian is computed at every vertex position, and then the vertex is moved by gradient descent (other implementations use different minimization procedures; see [2] for example). At equilibrium, therefore, each vertex is in its local energy minimum.

Cellular Potts model

The cellular Potts model (CPM) [4] is widely used in mathematical biology. Unlike vertex dynamics models, it has a coarser spatial resolution, being defined on a square lattice, where each lattice site belongs to a cell or the medium. A Monte Carlo algorithm attempts to transition lattice sites from one cell to another: the probability of a site (i, j) transitioning from cell c to cell c' is

$$P\left(c(i,j) \to c'(i,j)\right) = \begin{cases} e^{-\Delta E/kT} & \text{if } \Delta E > 0 \\ 1 & \text{if } \Delta E \leq 0 \end{cases}, \tag{2}$$

where E is a Hamiltonian similar to Equation (1) and k and T are constants (T is called the temperature, in analogy to the thermodynamic inspiration of the model).

New CHASTE features

To facilitate the comparison study, we added several new features to CHASTE. These have been released under an open-source license, and effort will be made to submit them upstream to the CHASTE development team. Among these are the ability to track some measurements of interest for cells (direct ancestor, generation number, pressure, perimeter, perimeter in contact with medium), XML data output, support for more than two cell types, the ability to apply an arbitrary force vector to a cell, force dependent on contact with medium, contact inhibition based on fraction of perimeter in contact with medium, support for a contractility term in the Hamiltonian (see Figure 6), a cell cycle model where cell division occurs upon reaching a threshold volume, λ_a and λ_p dependent on cell type, and random edge contractility forces.

Parameter sweeps

We developed code to greatly facilitate parameter sweeps in CHASTE, avoiding unnecessary compilation of simulation routines for different parameters, and automating the compilation, execution, and production of graphical output. As well, the sweeps are run in parallel, cutting down on simulation time.

The sweeps are run through a Python script. The script is given a dictionary (hash map) of parameters to be constant across simulations, as well as parameter values to be used in the sweeps. It then runs the simulation for each tuple in the cross product of the lists of values for each sweep parameter.

For example, the following invocation will run `TestSimulation` with the parameters in `single_parameters`, and sweep across `(adhesion02, adhesion12)` in $(0.5, 0.6, 0.7, 0.8) \times (0.6, 0.7, 0.8, 0.9)$.

```
run_simulation('TestSimulation',
               single_parameters={'cells_across': 20, 'cells_up': 10,
                                  'area_deformation_parameter': 60.0,
```

```
                            'perimeter_deformation_parameter': 20.0,
                            'type1_fraction':0.5, 'adhesion01': 5.0,
                            'diffusion_temperature': 100.0,
                            'end_time': 30.0, 'dt': 0.001},
        sweep_parameters={'adhesion02': (0.5, 0.6, 0.7, 0.8),
                          'adhesion12': (0.6, 0.7, 0.8, 0.9)})
```

Comparison

In order to compare vertex dynamics and cellular Potts model simulations, we calibrated parameters across the two models. [5] has shown that there exist parameter regions which define the equilibrium configurations for both models; we extended this work to look at other scenarios.

Anisotropy in the cellular Potts model

Calculating the perimeter of shapes on a square lattice by counting boundary edges is highly anisotropic, and has little relation to the "expected" perimeter (that is, the perimeter of a vector shape occupying the same region)[8]. In order to sensibly compare parameters between vertex-based models and CPM, an alternative method of measuring lengths must be used. [5] describe such a method, which involves counting, for every lattice site in a cell, the number of lattice sites not belonging to that cell in a certain neighbourhood of the lattice site. We developed a method of quantifying the anisotropy in CPM simulations by approximating cells as polygons (see Figure 2) and measuring the angle distribution of edges.

Cell sorting

In vertex-based models of epithelia, rearrangement of cells occurs only through vertex swaps, most significantly the T1 swap[1]. Cell sorting, therefore, is driven mostly through contraction of edges to zero length. Although adhesion terms in potential-based models can lead to edge contraction in some cases, isolated groups of homotypic cells will not tend to join. Thus cell sorting simulations in vertex-based models get very easily trapped in local energy minima.

We found that adding contractile forces on random edges in a vertex-based simulation, by inducing T1 swaps that are not energetically favourable and thus increasing exploration of the energy landscape, leads to lower-energy configurations (Figures 3, 4, and 5). Furthermore, we found that adding random forces to vertices, as in [3], is not sufficient to significantly affect sorting behaviour.

Acknowledgements

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Figure 1: A sheet of cells in the cellular Potts model. Each colour region corresponds to a different cell.

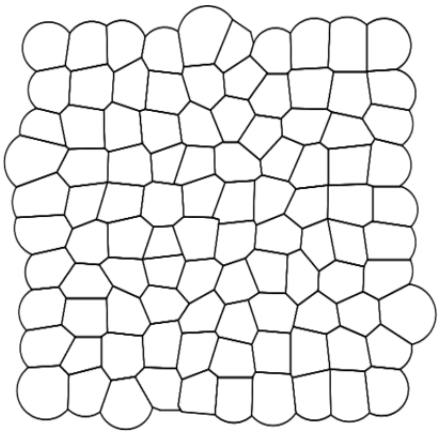

Figure 2: The polygonal approximation of the cells in Figure 1. On the boundary, circular arcs are used.

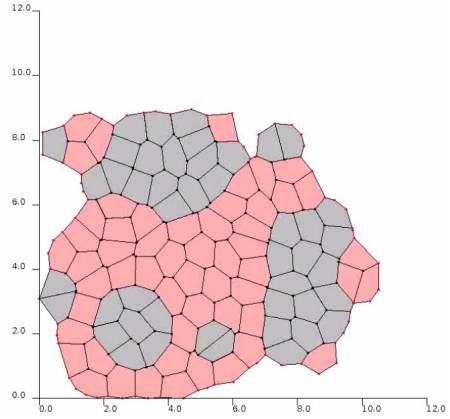

Figure 3: The final state of a cell sorting simulation with an edge contractility force applied for 60 timesteps

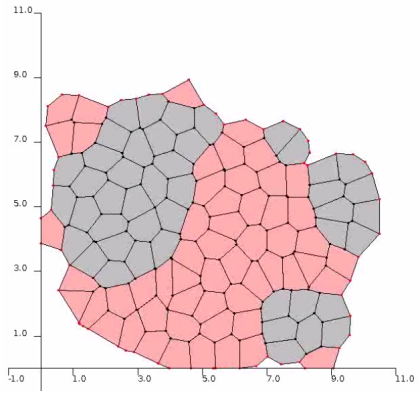

Figure 4: The final state of a cell sorting simulation with an edge contractility force applied for 120 timesteps

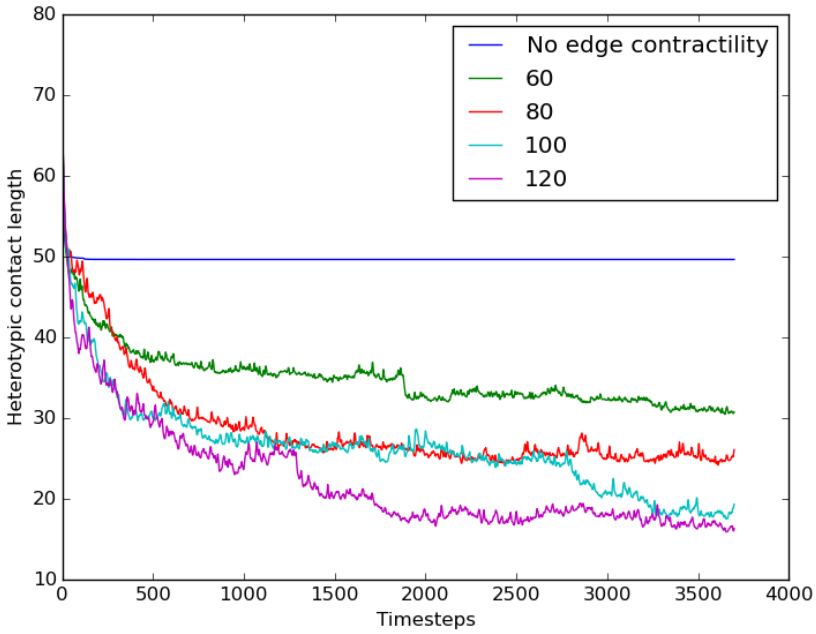

Figure 5: The total amount of perimeter shared by different types of cells over time, for varying durations of edge contractility force

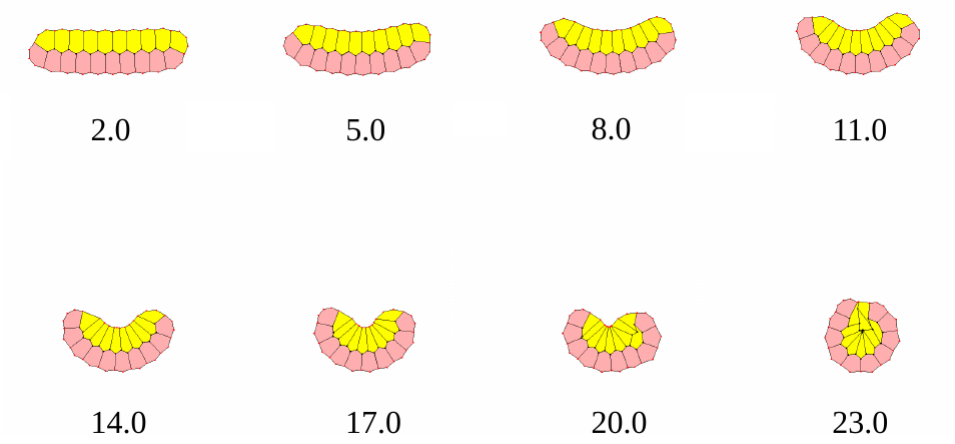

Figure 6: Tissue folding implemented solely by increasing contractility of yellow cells

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