Microsoft Research
Computational Science Lab

Multiscale Cell Based Modelling of Tissue Development

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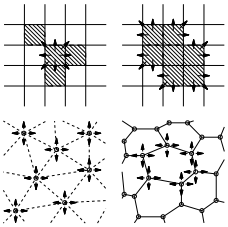
When investigating the development and function of tissues it is not enough to only consider the behaviour of individual cells in isolation. How cells interact, both mechanically and biochemically, influences the resulting tissues form and function. Utilising the natural structural unit of the cell we have developed a multiscale modelling framework for simulating the development and function of tissues. The cell level is central to the framework and cells are modelled as discrete interacting entities using one of a number of possible mechanically based modelling paradigms. The sub-cellular level concerns numerous metabolic and biochemical processes represented by interaction networks rendered stochastically or into ODEs. Tissue level behaviour is represented, for example, by field equations for nutrient or messenger concentration, with cells functioning as sinks and sources. The modular approach taken enables more realistic behavior to be considered at each scale. The framework has been used to investigate the how tissues form and what happens when things go wrong.

Framework

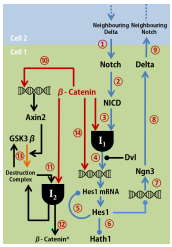
The modelling and simulation framework consists of three main scales: the tissue level (macro-scale); the cell level (meso-scale); and the sub-cellular level (micro-scale), with multiple interactions occurring between all scales.

Cell based modelling



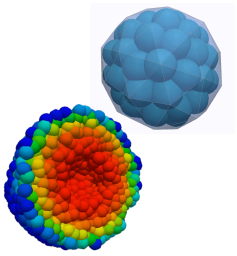
The cell level is central to the framework and cells are modelled as discrete interacting entities using one of a number of possible mechanically based modelling paradigms. These fall in to two categories, on lattice models (such as the Cellular Automota model, top left, or the Cellular Potts model, top right), where cells are restricted to lie in a fixed lattice and cell dynamics is controlled by stochastic simulation, or off lattice models (such as a cell centre model, bottom left, or the cell vertex/ finite element model, bottom right) where cells are represented as points (or collections of points) free to move in space, and cell dynamics is derived though stochastic simulation or by mechanical conservation laws.

Subcellular dynamics



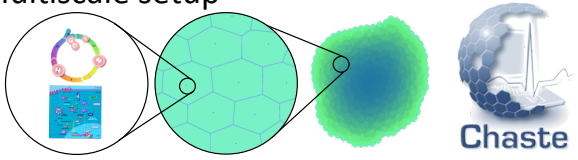
Cells respond to their environment (internal and external) by processing information. This processing can be represented in many ways. The most common being a coupled system of Ordinary Differential Equations (ODEs).
We further separate this component into the processes which influence the cell cycle, cell cycle models, and those that don't, subcellular reaction networks. This approach allows us to combine models in multiple configurations to easily test different competing hypotheses.

Tissue level factors



Cells do not exist in isolation, they interact with each other and the surrounding environment. The simplest of these interactions is that cells secrete or uptake a substrate which subsequently diffuses about the growing tissue (left). More detailed models, for example deformable membranes (right) or vasculatures can be considered. These models influence processes at both the cellular and subcellular scale

Multiscale setup

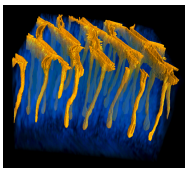


This framework has been implemented in the Open Source Chaste library, http://chaste.cs.ox.ac.uk. Depending on the application being investigated, and the question of interest, appropriate models can be chosen at each scale. Due to the modular nature of the framework additional models can be easily added.

Example simulations

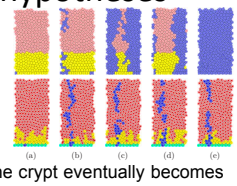
This framework is being used to study the development (and disease) of tissues and structures, with applications including tissue engineering, C. elegans development, Biofilms, and protein interactions. A key application thus far has been the colorectal crypt. Some of these results are presented here.

The Crypt



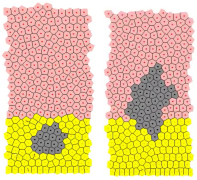
The lining of the gut is made up of millions of small test tube shaped invaginations known as crypts (the Crypts of Lieberkühn). In humans each crypt contains around 700 cells which renew every 3-5 days. Cells proliferate towards the base of the crypt, migrate up the walls of the crypt differentiating as they go, when the cells reach the top of the crypt they are removed through a mixture of apoptosis and sloughing.

Testing stem cell division hypotheses



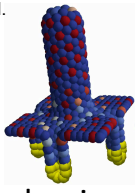
By developing a computational model for the crypt we are able to test competing hypotheses, for example to see how cells regulate proliferation. On the right we see the different patterns of cells we get using a position based (top) verses a generation based (bottom) model for proliferation.
We see that using the position based model the crypt eventually becomes monoclonal (something that is observed experimentally) which does not occur in the pedigree model.

Modelling mutations



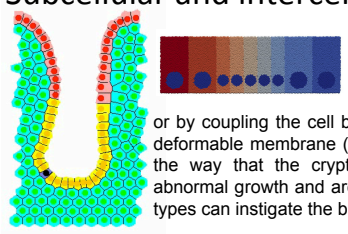
Being the site of the onset of colorectal cancer it is important to be able to model mutations within the crypt. By altering the behaviour of a subset of (or individual) cells we are able to model the spread of a mutation in the tissue. We see that in order for a mutation to overtake the crypt we need to not only modify the regulation of proliferation but we also need to change the mechanical properties of the cell.

Subcellular biochemistry



By introducing cell-cell (juxtacrine and paracrine) signalling we are able to identify regions of the crypt (and neighbouring villus) where patterns in signalling molecules can develop leading to cell fate specification.

Subcellular and intercellular mechanics



By using a more detailed model for individual cells (where cells are composed of a collection of points, right), or by coupling the cell based model with a model of a deformable membrane (left) we are able to investigate the way that the crypt deforms under healthy and abnormal growth and are able to see how differing cell types can instigate the buckling of the epithelial layer.

This is me.
I should be around somewhere nearby. I would be very happy to discuss this work with you, just come find me…
If not feel free to email me
James.Osborne@cs.ox.ac.uk

Refs:
[1] A two-dimensional model of the colonic crypt accounting for the role of the basement membrane and pericryptal fibroblast sheath. Dunn, *et al*. (2012). *PLoS Computational Biology*. No. 5. Pages e1002515. doi:10.1371/journal.pcbi.1002515.
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