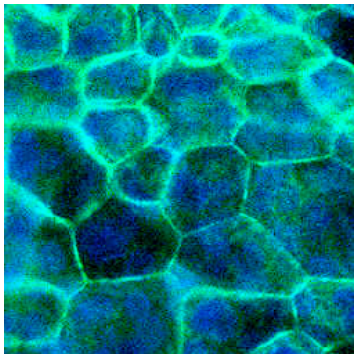
Modelling the Epidermis

Epithelial biology

Epithelial tissues form the boundary between 'inside' and 'outside'. The external surface of the body is covered by skin (the epidermis), and the luminal surfaces of all body cavities are lined with specialised epithelium - airway epithelium in the lungs, urothelium in the bladder, intestinal epithelia in the gut. All epithelia control transport across this interface. Skin and urothelium have tight junctions surrounding the cells in the outermost layer, and act primarily to limit transport across the boundary. In contrast to this, the primary function of intestinal and airway epithelia is to facilitate transport across the interface[1]. Internal epithelia vary from one to a few cells in thickness (e.g. one cell in the intestine and bladder, a few cells in airway epithelium). Skin has more layers, and the thickness depends on site - thin on the inner surface of the forearm, thick beneath the heel - but normally not exceeding about 0.5 mm in thickness.

All epithelial cells have a common developmental origin, and are defined by a set of common features which enable the barrier function. They are strongly polarised, with clearly differentiated apical (towards the 'outside'), basal (towards the 'inside') and lateral (towards neighbours in the same layer) surfaces. The form tight junctions between cells, so the cells form cohesive sheets with little extra-cellular space, and adhere tightly to the basement membrane (the collagen layer separating them from the supporting tissue). As a result, they appear cuboidal or rectangular on vertical section, and on-face are closely packed hexagons. The specialised structure and function is a result of localised physical and chemical signalling.



A surface view of normal urothelium, grown *in vitro*. The adhesion molecules forming the tight junctions between the cells have been labelled with a green fluorescent protein. Image courtesy of Professor Jenny Southgate, University of York.

Figure 1. En-face view of urothelium

Superficially, our skin appears to not change on a timescale of years - we are familiar with the ageing process causing a reduction in elasticity, with consequent wrinkling, but over shorter time periods there is no visible change. In practice, all epithelia are being constantly renewed - the skin over a period of about a month - and the generation of the appearance of stasis despite constant renewal (homeostasis) is a remarkable and little understood phenomenon which is central to a mechanistic understanding of the behaviour of epithelia. Understanding the control mechanisms which ensure that the structure and function are maintained despite constant renewal is essential for the understanding of epithelia-related disease. An example in skin is psoriasis, in which a failure of the homeostatic mechanism gives rise to hyper-proliferation of the epidermal cells.

Although there are different structures in different epithelial tissues, the renewal process appears to be similar at all locations. There is a stem-cell niche in which stem cells are localised - in intestinal crypts this is at the base of the crypt, in skin it is the bottom of the Rete ridges (which are actually conical depressions - the use of ridge as a descriptor is a result of viewing vertical cross-sections). The stem cells (and in some epithelia the progenitor cells as well) divide, there is one or more stages of differentiation and movement away from the stem cell niche, followed finally by shedding of the cells into the lumen or atmosphere. The epithelium in an intestinal crypt is one cell in thickness. The stem cells at the base of the crypt divide continuously, the cells differentiate as they are pushed up the side of the crypt by the dividing stem cells, and are eventually shed when they reach the luminal surface of the intestine. In skin, the stem cells divide to give rise to either more stem cells or to progenitor cells. If the progenitor cells remain attached to the basement membrane, they will continue to divide, but will stop dividing if they are pushed up into the next cell layer (cell signalling between the progenitor cell and the basement membrane is responsible for the change in behaviour). Cells are continuously pushed towards the surface by the dividing cells

[1] For a general introduction, the reader is referred to Alberts B, Johnson A, Lewis J, Raff M, Roberts K, et al. Molecular Biology of the Cell: Taylor and Francis; 2002, (particularly Chapter 19: Cell Junctions, Cell Adhesion and the Extracellular Matrix), available on the NCBI Bookshelf at http://www.ncbi.nlm.nih.gov/books/NBK21054/.

at the basement membrane, and differentiate as they approach the surface. In the final stage of differentiation (the corneocytes), the cells lose their nucleus and flatten, and are shed from the surface. Normally we do not notice the shedding of skin cells. In dandruff, the cells are shed as clumps of cells, not individually, and the clumps are large enough to be visible.

The extended area of epithelial sheets require very large numbers of cells (~10^{11} in skin), and renewal results in an extremely large number of cell divisions (~10^{12} divisions/per annum in skin). A very low probability of mutation at cell division can give rise to significant numbers of pre-cancerous cells, and indeed the majority of carcinomas originate in epithelial tissues. There is evidence that the presence of pre-cancerous cells in epithelial tissues is normal.

Epithelial cells can detect strain. Mechano-transduction at focal adhesions is common to many types of cell, as are strain-sensitive ion channels. Urothelial cells have been shown to act as strain sensors in the bladder, by releasing signalling molecules which are detected by nerve endings in the bladder wall. They can also produce signals which affect nociceptors, giving rise to pain sensation, a common factor in bladder pathology. It has been suggested that a buckling collapse of the airways in an acute asthma attack can result in the release cytokines from acutely stressed airway epithelial cells, provoking an immune response which exacerbates the attack.

Modelling the epidermis

The structure, functional properties and behaviour of the epidermis is a result of cell-cell interaction, interactions between cells and the basement membrane, and locality-specific physical and biochemical signalling. In addition, there are influences external to the epidermis. Epidermal cell behaviour is strongly influenced by fibroblasts which reside in the dermis - a particular example is fibroblast behaviour in wound healing. If an immune response is triggered in the epidermis, it will involve migration of immune system components into the epidermis. In general (and this applies to all epithelia), the model will have to be based around the behaviour of individual cells and, because of the central role of homeostasis in epithelia, will have to include the cell cycle and its control (growth, triggers for differentiation etc)[2].

The first stage is to develop a *domain model*[3], that is, a description of the entities, relationships and mechanisms that constitute the biological problem. The *platform model* is a mathematical and computational representation of the biological problem described by the *domain model*. If the biological problem relates to the *in vitro* growth of properly structured and functional skin, we might need to know: the cell types and successive stages of differentiation (NHKs - normal human keratinocytes with the differentiation route stem cells -> transit amplifying cells -> committed cells -> corneocytes; fibroblasts); adhesion (cell-cell and cell-substrate) and its effect on cell behaviour); signalling pathways (cell-cell; diffusion through extra-cellular space; mechano-transduction); determinant of differentiation; etc. The 'model' is actually a set of models, as the modelling paradigm best suited to each component will be different (individually-based cell models; differential equation models of signalling processes; finite element model of physical behaviour), and the software framework used for instantiating the *platform model* will have to be able to accommodate these different modelling paradigms. A number of approaches to this are described elsewhere[4].

Validating the model(s)

How can be be assured that the model is an adequate representation of a complex system? Our approach has been to start with a *domain model* of an *in vitro* or *ex vivo* system, and use these laboratory systems to demonstrate that the behaviour predicted by the computational model is indeed the same as that produced by the laboratory model. However, one does need to take care

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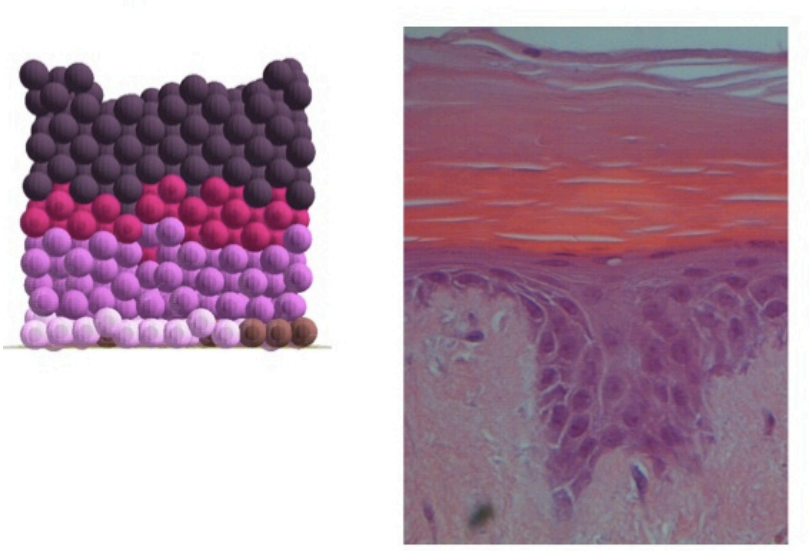
[2] A review of modelling approaches can be found in Smallwood R 2009 Computational Modelling of epithelial tissues. Wiley Interdisciplinary Reviews: Systems Biology and Medicine.

[3] I am grateful to Jon Timmis, University of York, for drawing my attention to this formal description of the process - see http://www.cs.york.ac.uk/ftpdir/reports/2010/YCS/453/YCS-2010-453.pdf, in particular figure 2.1 and the accompanying text.

[4] The approach we have used is described in Smallwood R 2011 Cell-Centred Modeling of Tissue Behaviour in Dubitzky W; Southgate J; Fuss H, Understanding the Dynamics of Biological Systems: Lessons Learned from Integrative Systems Biology 175-194. DOI: 10.1007/978-1-4419-7964-3_9



An individual-based model of normal epidermis (left), compared to a vertical cross-section of normal epidermis grown in vitro (right). The histological section has been H&E stained to reveal individual cells, and the cell colouring in the model corresponds to the H&E staining. Stem cells are brown, progenitor cells white, stratum spinosum cells purple, stratum granulosum cells pink, and corneocytes brown. For simplicity, this model represents the cells as spheroids and not with the biological aspect ratio. Model image courtesy of Shannon Li (University of Sheffield), H&E section courtesy of Anthony Bullock (Sheffield).

Figure 2. Individual-based computational model of epidermis v. H&E stained section of epidermis

that the behaviour represented by the computational model is not peculiar to the very simplified laboratory system. In particular, most *in vitro* laboratory models make use of immortalised cell lines, which by definition are not normal cells, and can have very different behaviour from normal lines[5]. In the VPH AirPROM project, we are using two *ex vivo* laboratory models for validation of the cellular-level model of airway remodelling as a result of exposure to allergens and irritants. The cells used in the *ex vivo* models are obtained from patients by airway brushing and bronchial biopsies, which provide populations of airway epithelial cells, fibroblasts and smooth muscle cells in different disease states.

Rod Smallwood
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[5] A comparison of normal and immortalised cells can be found in Walker D et al 2006 Modeling the effect of exogenous calcium on keratinocyte and HaCat cell proliferation and differentiation using an agent-based computational paradigm. Tissue Engineering 12:2301-2309.