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Modelling the Effect of the Actin Basket and Basement Membrane in the Deformation of the Colonic Crypt

The role of the basement membrane is vital in maintaining the integrity and structure of an epithelial layer, acting as both a mechanical support and forming the physical interface between epithelial cells and the surrounding connective tissue. The function of this membrane is explored here in the context of the epithelial monolayer that lines the colonic crypt, a test tube shaped gland responsible for renewing the intestinal surface through a coordinated sequence of cell division, migration and death. It is believed that in the first step in colorectal carcinogenesis, crypts acquire genetic mutations that disrupt the normal patterns of cell proliferation and migration, which can lead to crypt buckling and fission. To identify mechanisms responsible for this, a model of the crypt with a realistic, deformable geometry is required, which takes into account the role of the surrounding tissue stroma in maintaining crypt homeostasis throughout these cell events.

A model is proposed here to directly address these criteria. An off-lattice cell-centre modelling approach is adopted, with cell-cell connectivity defined by a Delaunay triangulation, and polygonal cell shapes realistically prescribed by the dual Voronoi tessellation. As such, cell centres are defined by nodes that are free to move in space, which are connected to neighbouring cells along the lines of the triangulation. A novel method for modelling the role of the basement membrane beneath a growing epithelium is presented, which subsequently allows the desired crypt geometry to develop, rather than to be imposed. Further to this, the model takes into account the continuous meshwork of actin that forms a basket below each crypt base, and which provides stability to this region.

Results from *in silico* simulations show that homeostasis of the growing epithelial monolayer can be achieved and sustained within this modelling framework, and the necessary balance of interactive cell forces, cell migration and cell death are presented. This work forms the basis for investigation of the deformation of the crypt structure that can occur due to proliferation of cells exhibiting mutant phenotypes, experiments that would not be possible *in vivo* or *in vitro*.

This model is proposed as the foundation of a realistic representation of growth of an epithelial sheet in a deformable environment. Whilst it is applied here specifically to the colonic crypt, the basic principles extend to other biological epithelia, such as the interfollicular epidermis, or the olfactory mucous membrane. Thus, this work and the results presented, hold potential for future research in other biological contexts.