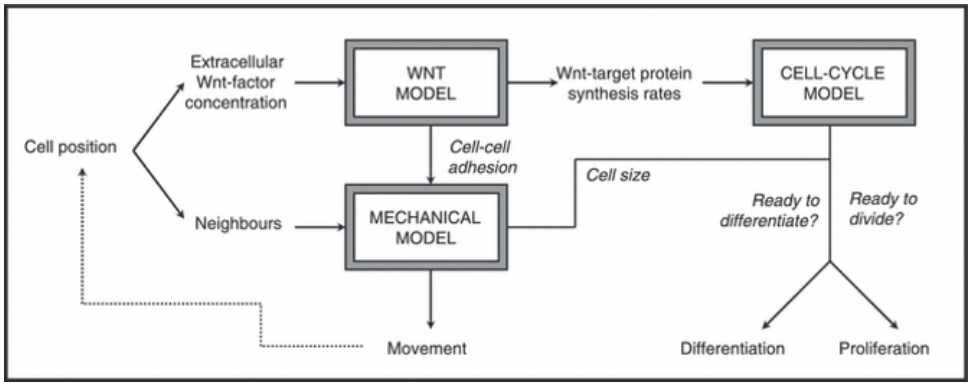

Figure 1: Schematic of the multiscale model for the dynamics of a colonic crypt. During a model simulation, the occurrence of cellular events (proliferation, differentiation, migration) is monitored at discrete time steps, t_n. By coupling Wnt signalling, cell cycle, and mechanical models, the spatio-temporal behaviour of every cell is predicted at time t_{n+1}, given the state of the system at time t_n (e.g. intracellular protein levels, cell position, Wnt stimulus, location of neighbouring cells) and the system parameters. Figure from [4]

1 Model

These simulations of the intestinal crypt are performed using cell based models in CHASTE [2], discussed in [4]. A cylindrical approximation to the crypt is modelled using a 2D rectangle with periodic boundary condtions on the left and right and sides. A gradient of Wnt signalling factor (highest at the bottom of the crypt) is imposed on a subcellular Wnt signalling model, which provides input to the cell cycle model [3]. This model is then coupled to the Meineke *et al* model [1], see Figure 1, which deals with the multicellular interactions, including cell division, differentiation and cell migration.

1.1 Meineke *et al* Model

The model is populated with stem, transit and differentiated cells, which can undergo cellular proceses at discrete times t_n:

Cell Division Stem and transit cells undergo division, with a new cell cycle time being assigned to each daughter cell. The direction of division is stochastic, with one daughter cell placed at the site of the mother cell, the other a fixed distance away.

Cell Differentiation Stem cells divide such that one daughter cell remains a stem cell, the other becoming a transit cell. After a fixed number of generations transit cells undergo terminal differenation

Cell Death Cells above the top layer of the crypt are considered to have undergone cell death

Cell Migration Stem cells are non mobile, whereas transit and differianted cells move due to forces exerted due to cell division. The movement is modelled by overdamped springs, see figure 2. Cell shape is determined by the cell centre ans Voronoi Tessellation.

1.2 Wnt Signalling

The Wnt concentration gradient is set to be a linear function with a higher concentration at the bottom of the crypt. Each cell detects the Wnt concentration at the cell centre, the Wnt pathway is modelled by a system of nonlinaer ODEs [5]. The Wnt model returns the intracellular gene expression level for target proteins and the cellular adhesion potential.

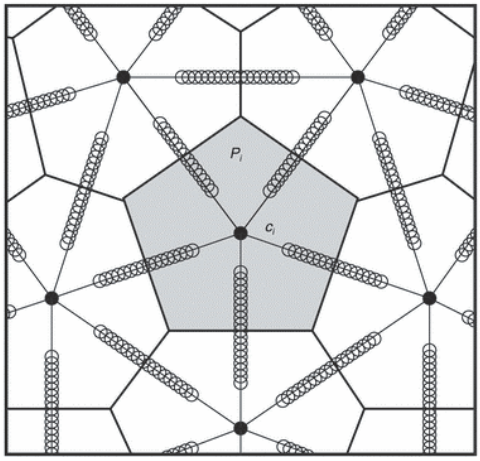

Figure 2: Black points correspond to cell centres. Each pair of neighbouring cells (identified using a Delaunay triangulation) is attached by a spring. Solid lines represent the associated Voronoi tessellation, which is a partition of two-dimensional space that assigns a polygon Pi to each cell centre ci such that all points in P_i are closer to c_i than to any other cell centre. Five neighbouring cells surround the central cell i, highlighted in grey. Figure from [4]

1.3 Cell Cycle model

The cell cycle model is dependent on Wnt concentration, and thus cell cycle duration is positionally dependent. The cell cycle can be halted at G_1/S checkpoint, when Wnt levels are too low. These are considered differentiated cells, which can only become active if by local cell rearrangement they pass to a higher Wnt concentration region lower in the crypt.

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