STICKING TOGETHER: COMPUTATIONAL MODELLING OF CELL-CELL AND CELL-MATRIX INTERACTIONS

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Background

Within tissues, cells interact with each other (e.g., through cell–cell adhesion) and their matrix (e.g., through cell–matrix adhesion) at the same time, and these physical interfaces are integrated into biochemical signals that influence their behaviour. Although cell-cell and cell-matrix have been studied extensively in isolation, it is not completely understood 1) how cells sense the individual signals, 2) how cells integrate these, including potential regulating factors. Given the small size and dynamic nature (e.g., short lifetimes) of adhesions, the use of conventional microscopic and experimental techniques can be challenging and computational modelling can be a valuable resource to simulate and explore various "what if?" scenarios *in silico* and defining the key molecular components and mechanisms to be explored further.

Recent Advances

Many computational models of cell-matrix and cell-cell interactions, with the integrin and cadherin protein families as essential transmembrane links respectively, have been developed at different scales (tissue, cell, subcellular) to help understand the dynamical signalling and sensing mechanisms. At the subcellular scale, we and others have modelled cadherin binding and clustering [1], including the influence of the actin cytoskeleton and force [2-4] as well as signalling crosstalk [5-6]. Regarding integrin signalling, computational models have shown that the number of ligand-bound integrins increases with the number ligands [7], which was extended to include ligand competition [8]. Simulations have also identified that ligand spacing exceeding 60 nm leads to a decrease in clustering [9-10]. To explain the mechanical aspects of cell-matrix interactions, molecular clutch models were developed [11-13] and extended to include for example Rho signalling [14]. We have developed a mechanochemical model to capture the biochemical and mechanical changes during the focal adhesion maturation process, including force-dependent talin unfolding and vinculin reinforcement and show that disassembly dynamics play a crucial role in stiffness sensing (work under review). In addition, we are developing a stochastic agent-based model to understand how YAP-based mechanosensing arises from the dynamics of integrin clustering, disassembly and nuclear translocation (unpublished data). Subcellular clutch models have been integrated to capture cell scale behaviour such as mechanical homeostasis [15] and cell motility [16-19], providing evidence for 'negative durotaxis' [20]. At the tissue scale, mechanical models including cadherin signalling have been, for example, used to understand the dynamic nature of gap formation in the endothelium [21].

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Future directions

Considering that both integrin and cadherin families form bidirectional signaling linkages and transmit microenvironmental information across the cell membrane, including common effector molecules in the cascading signaling pathways, future work should focus on integrating cadherin and integrin computational models in order to elucidate the adhesive crosstalk. Moreover, further advances in experimental techniques will enable cell-specific calibration of the above models, allowing to elucidate cell-specific physiological and pathological mechanisms of adhesive crosstalk and ultimately contributing to improved biomaterial design and regenerative medicine strategies.

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