CHEMO-MECHANICAL MODELS OF ACTIVE CELL FORCES IN GROWTH AND REMODELLING

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Background

Biological cells actively generate contractile and protrusive forces to probe their surrounding microenvironment, and mechanically communicate with other cells. In turn, cells continuously remodel their shape, size, and cytoskeleton in response to chemical and mechanical feedback which can stimulate active tissue growth and remodelling [1]. A growing field of research has evolved around theoretical mechanobiology and computational cell mechanics to provide fundamental insight into the biomechanisms that underlie dynamic cell activity and tissue reorganisation in disease.

Recent Advances

Remodelling of actomyosin, the force-generating machinery in cells, is stimulated by changes in cellular loading. Considering the chemical free energy of associated bound and unbound cytoskeletal proteins facilitates a natural coupling between stress/strain-rate dependent cytoskeletal remodelling and dynamic cellular contractility [2, 3]. We demonstrated that cell spreading and shape emerges from a competition between such chemical free energy and deformation of elastic cell constituents (Fig 1A), whereby cells assume low free energy states [4]. Extended to tissue-level, the model also provides a free-energy basis for heart failure [5] whereby increased cross-bridge cycling due to pathological loading can reduce the chemical potential of unbound proteins to drive muscle fibre assembly in hypertrophy. Active cell models can also provide insight into cancer progression and metastasis. We developed a theoretical model to uncover how gap junctions can amplify spatial variations in tumour cell volume by facilitating ion flow stimulated by growth-induced stress (Fig 1B), with implications for tumour invasion [6]. When tumour cells break away from a primary tumour, they may burrow though gaps in blood vessels which act as a superhighway to distant organs. In new work, we proposed a novel chemo-mechanical model to determine how the feedback between mechanosensitive signalling and active cell forces regulates endothelial gaps (Fig 1C). Combined with time-series imaging of junction remodelling, we determined that a critical balance between contractile and protrusive forces is required for stable adhesion [7]. Recently, we also developed a novel cell growth model to provide a biophysical explanation for stress-dependent growth in tumours and other tissue.

Future directions

An important future direction would be to explicitly couple active models for cytoskeletal contractility with size control for analysis of mechanosensitive feedback pathways in disease. Moving forward, such chemo-mechanical models could shed light on nuclear remodelling and epigenetics. Future research in this space should also explore the feedback between active forces and cellular metabolism in pathological growth.

Eoin is an Assistant Professor in Biomedical Engineering at the University of Galway. His research group focuses on the development of novel theoretical and computational models to explore the feedback between cell mechanics and tissue remodelling for the prediction of disease progression, with a specific interest in cancer mechanobiology and autoimmune disease. Eoin completed his PhD in cellular biomechanics at the University of Galway. He subsequently worked as a postdoctoral researcher at the University of Pennsylvania and the Center for Engineering Mechanobiology, investigating how the tumour microenvironment guides cancer metastasis.

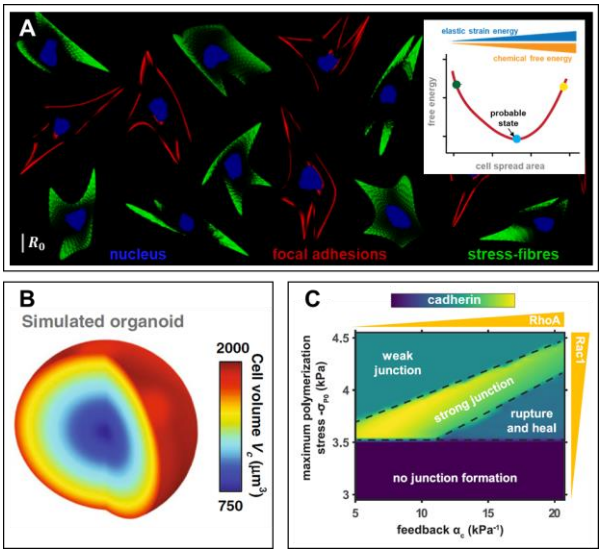

Figure 1: A) Simulated cell spreading as driven by free energy minimization [4]; B) Predicted spatial variance in tumour cell volume [6]; C) Endothelial gaps as regulated by competing active forces [7].

References

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