AN INTEGRATED FINITE ELEMENT AND AGENT-BASED MODEL TO ANALYSE MECHANOSENSITIVE TUMOUR GROWTH

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Introduction

Tumour growth is a force-sensitive process, regulated in part by mechanical feedback from surrounding tissue [1]. Such mechano-responsiveness can govern tissue-specific risk and progression of cancer, ultimately impacting disease outcomes. However, the underlying biomechanisms by which mechanical loading influences cellular growth and proliferation have not yet been uncovered. In this study, we integrate custom finite element (FE) and agent-based (AB) models to determine how the feedback between single tumour cell growth and mechanical loading could restrict proliferation.

Methods

Model development: Cell size is regulated by an interplay between mechanosensitive ion channels, pumps, actomyosin tension, and cytosolic proteins that coordinate to manipulate cellular osmolarity and subsequently cell volume V [2]. We propose that growth is induced by feedback between electro-osmotic ion fluxes $dc(\phi)/dt$ and biomass synthesis dX/dt, such that the osmotic pressure difference across the cell membrane is given by $\Delta\Pi = RT(\sum \Delta c + X/V)$. Cell growth may then be written as $dV/dt = -L_{p,m}(\Delta P - \Delta\Pi)$, where the hydrostatic pressure ΔP depends on active cell stress and external mechanical loading.

Computational analysis: To consider chemo-mechanical cell-matrix interactions, a custom FE model was developed and integrated with AB modelling platform PhysiCell [3]. Cell migration and cycling are dependent on forces induced by adhesion, repulsion, and motility. Our framework also exhibits high performance owing to extensive GPU acceleration. Integrating our novel cell growth model, we aim to quantify the external pressure required to inhibit cell division by restricting growth below a critical mitotic volume V_{crit} (Fig 1A).

Results

Our model predictions for osmotic control of division suggest that cell cycle synthesis drives growth, and that compressive loading can limit the potential for a cell to surpass the size checkpoint for division (Fig 1B). Our integrated FE-AB modelling framework can further characterize multicellular interactions and matrix loading. Simulations reveal that increasing matrix stiffness reduces the rate of cell proliferation in tumour spheroids (Fig 1C), due to the emergent stress-sensitivity of cell growth and division. Mean cell pressure is predicted to converge to a critical value, independent of matrix stiffness, at which proliferation is inhibited (Fig 1D). Cells at the tumour core are revealed to experience higher stress than peripheral cells, as supported by data from excised tumours [4]. Overall, simulations suggest that tumour spheroid size reduces with increasing matrix stiffness in a stress-dependent manner (Fig 1E), in agreement with recent findings [5].

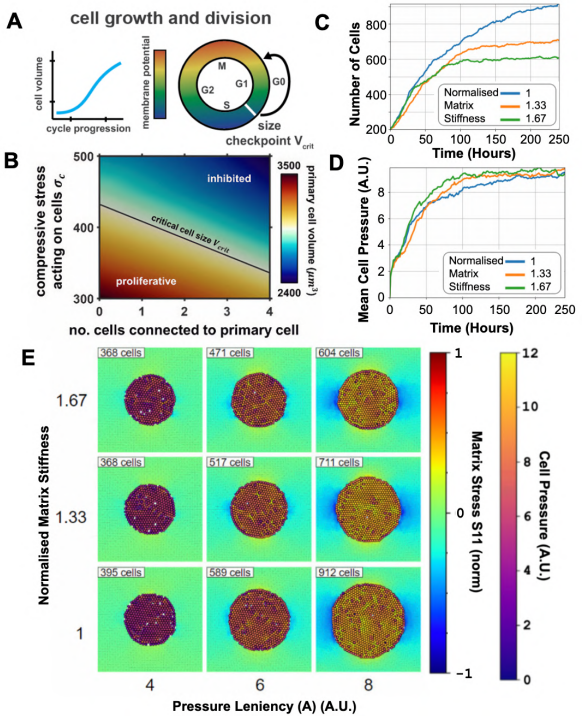

Figure 1: (A) Cells increase in volume during their cycle due to biomass synthesis; (B) Model predictions for cell growth suggest that mitosis can be restricted by stress; Predicted (C) cell proliferation and (D) pressure over time as dependent on matrix stiffness; (E) Tumour spheroid size reduces with increasing matrix stiffness due to mechanosensitive feedback.

Discussion

Our analyses suggests that stress-dependent tumour growth emerges from a constraint on osmotically-regulated cell growth, whereby cells cannot obtain a critical mitotic volume due to external loading. Simulation of multicellular proliferation using coupled finite element and agent-based models provides unique insight into the evolution of such macro-scale tissue behavior and mechanosensitive growth, with broad applications to patient-specific cancer diagnosis.

References

[1] M. Kalli and T. Stylianopoulos. Front. Oncol. 8 (2018)
[2] E. McEvoy et al. Nat. Commun. 11 (2020)
[3] A. Ghaffarizadeh, et al. PLOS Comput. Biol. 14 (2018)
[4] H.T. Nia, et al. Nat. Biomed. Eng. 1 (2017).
[5] V. Kumar et al. BioRxiv. (2022)

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