Multicellular computational and in-vitro models to uncover the mechanisms underlying mechanosensitive tumour growth

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Abstract

Introduction

Tumour growth is a complex mechanosensitive process guided by feedback between cells and the extracellular matrix (ECM). Sensitivity to mechanical cues can influence tumour progression and impact disease outcomes (1). Critically, the underlying biomechanisms by which external loading impacts tumour growth remain unknown. In this study, we first develop an in-vitro culture system for heterogeneous tumour spheroids to identify key biomechanical factors that restrict spheroid growth. We then propose a novel framework consisting a novel hydromechanical cell growth model, a 3D deformable cell framework and a deep-neural network (DNN)-accelerated finite element (FE) solver to uncover the mechanisms underlying mechanosensitive growth.

Methods

In-vitro spheroids: Murine breast cancer (4T1) cells were cultured, isolated and propagated to obtain distinct phenotypes (epithelial-like, amoeboid-like). Tumour spheroids were generated by either seeding cells within gelatin hydrogels of varying stiffness to investigate stress-dependent responses, or into 96-well plates layered with agarose cryogels (formed by freeze/thawing of solid agarose hydrogels) to determine how mixing ratios govern growth. Hydromechanical cell model: A mathematical model was developed to predict cell growth as driven by a competition between hydrostatic pressure arising from active cell stress and external loading, and osmotic pressure arising from biomolecule synthesis and ion fluxes (2). Biomolecules are synthesized during the G1 growth phase, which drives a fluid influx and growth through entropic osmotic forces. Multicellular growth: The hydromechanical model was integrated with MPacts (3), a discrete element method platform for multicellular mechanics, where cells are described as foam-like fluid-filled membranes. Cell growth is achieved by predicting the internal pressure required to attain the target cell volume with a proportional integrated controller. Coupled with tractions from cell and matrix contact interfaces, there is feedback in turn to govern the cell growth rate, and we consider that mitosis is subject to surpassing a critical volume checkpoint for which the underlying mechanisms are characterised. DNN-FE acceleration: The deformable cell model is embedded in a 3D finite element model of a hyperelastic matrix. To efficiently simulate this matrix deformation, a deep neural network (DNN) framework was developed. Synthetic training data for a diverse range of loading scenarios was generated using Abaqus and subsequently provided to a fully connected DNN comprised of 4 layers with 8,192 neurons per layer to obtain a converged

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solution.

Results and Discussion

Analysis of the in-vitro spheroids reveals that tumour spheroid size reduces with increasing gel stiffness. Importantly, there was a significant reduction in the number of cells per spheroid and lower number of proliferative cells as determined by Ki-67 immunofluorescence. 4T1 spheroids developed from predominantly amoeboid-like cells were observed to have 2-3 fold larger diameters than epithelial-like spheroids. Our computational models predict that cell growth increases with biomolecule synthesis and the subsequent increase in osmotic pressure, which deforms surrounding matrix. Standard simulation of multicellular growth with matrix contact carries a significant computational cost (203s per FE increment). Although there is a relatively high one-time up-front computational cost for synthetic training data generation and model training, our trained NN models can predict highly non-linear material behaviour with a negligible computational cost (133