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A combined in silico – in vitro framework for modelling three-dimensional cancer growth

Dominic M. Giles[1]*, Bogdan Elefteriu[1], Bushra Khan[1], William McLean[1], Judith Pape[1], Claire Walsh[1], Umber Cheema[1], Simon Walker-Samuel[1], Vasileios Vavourakis[1,2], Peter A. Wijeratne[1]

[1] University College London, London WC1E 6BT [dominic.giles.15@ucl.ac.uk, bogdan.elefteriu.15@ucl.ac.uk, bushra.khan.15@ucl.ac.uk, william.mclean.14@ucl.ac.uk, judith.pape.15@ucl.ac.uk, c.walsh.11@ucl.ac.uk, u.cheema@ucl.ac.uk, simon.walkersamuel@ucl.ac.uk, p.wijeratne@ucl.ac.uk]
[2] University of Cyprus, Nicosia 1678, Cyprus [vavourakis.vasileios@ucy.ac.cy]

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In silico cancer models are increasingly used to gain insight into the biophysical processes governing inception, growth and metastasis, and as potential tools in diagnosis and therapy. However, they often involve simplifying assumptions and require experimental data to give their predictions biological meaning. Conversely, in vitro cancer models facilitate biologically relevant observations, but the underlying biophysical processes can be difficult to infer from the data alone. As such, there is demand for combined in silico – in vitro models, whereby experimental data are used to specify bespoke computational models and hence generate hypotheses and guide future in vitro model development.

Here we propose an in silico – in vitro modelling framework, which has three main components: i) three-dimensional in vitro cancer models, comprised of colorectal cancer cells embedded in a collagen matrix [1]; ii) in vitro imaging, using High-Resolution Episcopic Microscopy [2] to obtain detailed three-dimensional images; and iii) three-dimensional in silico models, which mathematically describe in vitro tumouroids growing into a collagen matrix.

A simple multi-species continuum-based model of neoplastic growth is proposed, which models the concentration of oxygen and population balance of normoxic, hypoxic and apoptotic cells in terms of coupled partial differential equations. The model equations also include the effects of extracellular matrix density and chemotaxis on growth. Initial and boundary conditions, domain geometry, and oxygen gradient are completely specified by in vitro model data. We utilise High Resolution Episcopic Microscopy to acquire three-dimensional images of in vitro tumouroids at different time points, and use machine learning techniques to segment the tumour volume in post-processing. This provides longitudinal information, such as volume, surface area and number of cells, which is used to further specify the in silico model. The model equations are solved using finite element analysis with an explicit Total Lagrangian integration scheme, and implemented in our open-source software FEB3 [3]. We use the specified in silico model to perform a parametric analysis, and to investigate potential mechanisms for different invasion patterns observed in our in vitro experiments.

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