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Multiscale models of somatic evolution in ductal carcinomas

An important precursor of invasive breast cancer, a leading cause of cancer mortality in women, is ductal carcinoma *in situ*. This is characterized by abnormal proliferation of epithelial cells within the mammary duct without the basement membrane being breached, confining the neoplasm to the duct. Tissue in the duct is not directly vascularized; metabolite exchange occurs with the blood vessels in the stroma surrounding the duct. If cells proliferate abnormally away from the basement membrane, vascular exchange becomes less efficient due to the distance that metabolites must diffuse. Cells that are adapted to these conditions will have a greater chance of survival. Cells within a neoplasm acquire different genetic changes, and thus different phenotypic characteristics. Therefore, a neoplasm can be regarded as being composed of interacting and competing populations of heterogeneous cells. The fitness of a neoplastic cell is determined by its interactions with other nearby cells and with factors in the microenvironment. Thus the development and progression of cancer can be described as somatic evolution.

Previous work has modelled somatic evolution in the mammary duct using a cellular automaton (Gatenby *et al.*, Brit. J. Canc., 2007). In this model, the epithelial cells can become hyperplastic (no longer subject to typical growth constraints thus able to proliferate away from the basement membrane into the ductal space), glycolytic (no longer require oxygen to produce cellular energy, however this has the effect of acidifying the microenvironment), and acid-resistant (able to survive at lower pH than normal cells). The results of this model show that the effects of local metabolite concentrations increase the fitness of neoplastic cells which have acquired all three phenotypic adaptations. Due to their increased fitness, these cells outcompete other cell types present. Moreover, this phenotype has acquired the properties to make it highly invasive. This model has provided a useful initial investigation, however it has a number of limitations. Individual-based models are computationally expensive. This limits the number of cells that can be modelled, and the parameter space which can be explored. Using a continuum model to average over the cell populations would be more computationally and analytically tractable, however there is the risk that the behaviour at the cellular level will be lost.

We are developing continuum models of somatic evolution which will link the cellular and tissue-level behaviour. Most partial different equation (PDE) models of tissue behaviour are phenomenological and a linear diffusion coefficient is chosen. However, PDE representations using non-linear diffusivities often agree more closely with experimental results, and such non-linearities can arise from cellular constraints at the micro-level. Therefore it is essential to develop evidence-based methodologies linking the behaviour at the two scales. The long-term aim of this work is to derive PDE approximations directly from the cellular automaton representation of somatic evolution, thus more accurately representing the microscopic details whilst modelling at the macroscopic level. We will present preliminary results obtained thusfar.