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Modelling the effects of cell-cycle heterogeneity on tumour response to chemotherapy: Biological insights from a hybrid multi-scale cellular automaton model

The therapeutic control of a solid tumour depends critically on the responses of the individual cells that constitute the entire tumour mass. A particular cells spatial location within the tumour and intracellular interactions, including the evolution of the cell cycle within each cell, has an impact on their decision to grow and divide. They are also influenced by external signals from other cells, and oxygen and nutrient concentrations. Hence, it is important to take these into account when modelling tumour growth and the response to various cell-kill therapies, including chemotherapy.

In order to address this multi-scale nature of tumour growth, we propose a hybrid, individual-based approach that analyses spatio-temporal dynamics at the level of cells, linking individual cell behaviour with the macroscopic behaviour of cell organisation and the microenvironment. The individual tumour cells are modelled by using a cellular automaton (CA) approach, where each cell has its own internal cell cycle, modelled using a system of ODEs. The internal cell-cycle dynamics determine the growth strategy in the CA model, making it more predictive and biologically relevant. It also helps to classify the cells according to their cell-cycle states and to analyse the effect of various cell-cycle dependent cytotoxic drugs. Moreover, we have incorporated the evolution of oxygen dynamics within this hybrid model in order to study the effects of the microenvironment in cell-cycle regulation and tumour treatments. An important factor from the treatment point of view is that the low concentration of oxygen can result in a hypoxia-induced quiescence (G0/G1 arrest) of the cancer cells, making them resistant to key cytotoxic drugs. Using this multi-scale model, we investigate the impact of oxygen heterogeneity on the spatio-temporal patterning of the cell distribution and their cell-cycle status. We demonstrate that oxygen transport limitations result in significant heterogeneity in HIF-1 alpha signalling and cell-cycle status, and when these are combined with drug transport limitations, the efficacy of the therapy is significantly impaired.