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Modelling evolutionary adaptation of cancer cells to fluctuating oxygen levels

Abstract

A major challenge in malignant tumours is cell heterogeneity, which has been proposed to arise due to temporal variations in nutrient supply caused by highly irregular vasculature. Such variability requires cells to adapt to potentially lethal variations in environmental conditions. Risk spreading ("bet-hedging") through spontaneous phenotypic variations is an evolutionary strategy that allows species to survive in temporally varying environments. Individuals within a species diversify their phenotypes ensuring that at least some of them can survive in the face of sudden environmental change. We aim to investigate whether cancer cells may adopt this strategy when dealing with rapidly changing levels of nutrient due to temporally-varying blood flow.

Here, we present a system of nonlocal partial differential equations modelling the evolutionary dynamics of phenotype-structured cancer cell populations exposed to fluctuating oxygen levels. In this model, the phenotypic state of every cell is described by a continuous variable that provides a simple representation of its metabolic phenotype, ranging from fully oxidative to fully glycolytic. The cells are grouped into two competing populations that undergo heritable, spontaneous, phenotypic variations at different rates. A combination of analysis and numerical simulations indicates that under certain conditions the cell-oxygen dynamics can lead to regions of chronic hypoxia (low oxygen level) and cycling hypoxia. Moreover, the model shows that under chronic-hypoxic conditions lower rates of phenotypic variation lead to a competitive advantage, whereas higher rates of phenotypic variation can confer a competitive advantage under cycling-hypoxic conditions. In the latter case, bet-hedging evolutionary strategies, whereby cells switch between oxidative and glycolytic phenotypes, can spontaneously emerge. These results shed light on the evolutionary processes that may underpin the emergence of phenotypic heterogeneity in vascularised tumours, and suggest potential therapeutic strategies.