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Mathematical Modelling of Mutation Initiation and Acquisition in Stem Cell Driven Cancers

Most tissues consist of three classes of cells: stem cells, transit-amplifying progenitor cells, and differentiated cells. Many tumors also have a hierarchical organization, with the bulk of the tumor composed of relatively differentiated short-lived cells with a limited replicative potential. Tumors are thought to be maintained by a small subpopulation of cancer stem cells (CSC), which have the capacity to proliferate indefinitely, and drive tumor growth. It is unclear whether CSCs originate from stem cells or from de-differentiated mature cells. We consider a hybrid stochastic deterministic model of mutation acquisition in stem cells and their progeny. We study the effects of competition between cells both at the stem cell level (in a stochastic model) and the progenitor level (in an age structured PDE model), as well as the effects of de-differentiation of progenitor cells to stem-cell like state. We give estimates on the necessary division and mutation rates to maintain a stable cohort of mutant transit-amplifying cells due to progenitor mutations alone. However, to obtain unlimited growth, de-differentiation from progenitor to stem cell state is essential. Interestingly, effects of de-differentiation only become important once homeostasis, which limits the number of cells in the stem cell pool, is lost.