Nature vs nurture in cancer initiation in hierarchical cell populations: a computational model.

Jacob G Scott[1,2†] and David Basanta[1]
1. Integrative Mathematical Oncology, H. Lee Moffitt Cancer Center and Research Institute
2. Centre for Mathematical Biology, Oxford University

The cancer stem cell hypothesis states that tumors are sustained by an immortal, stem-like (pluripotent) side population of cells that are capable of recapitulating the entire tumor bulk and associated heterogeneity. The existence of cells with these properties have been shown in a wide variety of fluid and solid malignancies and there has been significant work done to elucidate the importance of these cells from a therapeutic and biological standpoint without much success. While there is no doubt that cells with this sort of capacity can be found in tumors, further understanding of this hypothesis through experimental means remains extremely difficult - leaving the onus largely on theoreticians at this time.

To this end, we have built a hybrid cellular automaton model of a stem hierarchical tissue designed to represent a glioblastoma, the most common primary tumor of the brain with no known cure. This model represents the cells as discrete agents with specific, rule based activity and interactions and represents the milieu in which the agents live by a continuously defined space defined by oxygen. Cells of three types - glioma stem cells (GSCs), transient amplifying cells (TACs) and terminally differentiated cells (TDs) - make up the cellular population, and the microenvironment is described fully by a vascular architecture of varying density and oxygen which diffuses in a Fickian manner from these vessels and is consumed by the cells.
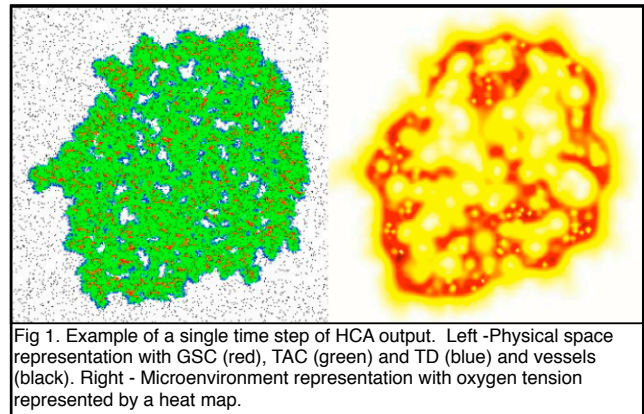

Fig 1. Example of a single time step of HCA output. Left -Physical space representation with GSC (red), TAC (green) and TD (blue) and vessels (black). Right - Microenvironment representation with oxygen tension represented by a heat map.

We present results germane to tumor initiation and progression with specific attention paid to stem cell phenotypes that promote these events. Specifically, we have found that there is a small band in the TAC phenotype governing rounds of division that promotes tissue overgrowth (tumorigenesis) that is conserved across other values for symmetric division and vascular density, suggesting the critical role that these TACs play (Fig 2.). Further, we have found that the microenvironment, in this case defined by vascular architecture, seems to play little role in cancer initiation and progression in the tissue size ranges considered ($<10^6$ cells) and that the stem cell phenotype governing symmetric/asymmetric division is only important when the TACs can divide less than 12 times.

We will also present pilot biological experiments designed and carried out to parameterize this model as well as several novel hypotheses concerning tumor vasculature and the role of stem cells in its creation.
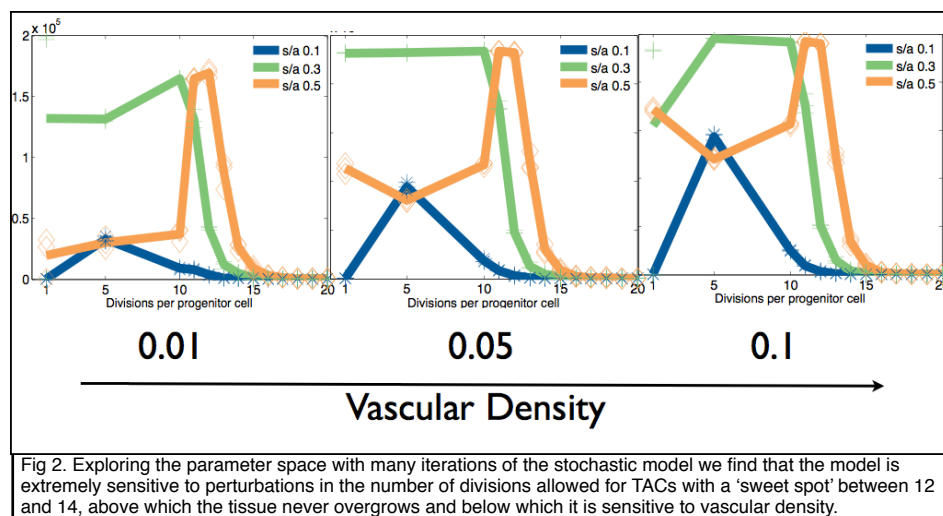

Fig 2. Exploring the parameter space with many iterations of the stochastic model we find that the model is extremely sensitive to perturbations in the number of divisions allowed for TACs with a 'sweet spot' between 12 and 14, above which the tissue never overgrows and below which it is sensitive to vascular density.

†jacob.g.scott@gmail.com