World Academy of Science, Engineering and Technology
International Journal of Biomedical and Biological Engineering
Vol:17, No:08, 2023

Modeling Competition Between Subpopulations with Variable DNA Content in Resource-Limited Microenvironments

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Abstract : Resource limitations shape the outcome of competitions between genetically heterogeneous pre-malignant cells. One example of such heterogeneity is in the ploidy (DNA content) of pre-malignant cells. A whole-genome duplication (WGD) transforms a diploid cell into a tetraploid one and has been detected in 28-56% of human cancers. If a tetraploid subclone expands, it consistently does so early in tumor evolution, when cell density is still low, and competition for nutrients is comparatively weak – an observation confirmed for several tumor types. WGD+ cells need more resources to synthesize increasing amounts of DNA, RNA, and proteins. To quantify resource limitations and how they relate to ploidy, we performed a PAN cancer analysis of WGD, PET/CT, and MRI scans. Segmentation of >20 different organs from >900 PET/CT scans were performed with MOOSE. We observed a strong correlation between organ-wide population-average estimates of Oxygen and the average ploidy of cancers growing in the respective organ (Pearson R = 0.66; P= 0.001). In-vitro experiments using near-diploid and near-tetraploid lineages derived from a breast cancer cell line supported the hypothesis that DNA content influences Glucose- and Oxygen-dependent proliferation-, death- and migration rates. To model how subpopulations with variable DNA content compete in the resource-limited environment of the human brain, we developed a stochastic state-space model of the brain (S3MB). The model discretizes the brain into voxels, whereby the state of each voxel is defined by 8+ variables that are updated over time: stiffness, Oxygen, phosphate, glucose, vasculature, dead cells, migrating cells and proliferating cells of various DNA content, and treat conditions such as radiotherapy and chemotherapy. Well-established Fokker-Planck partial differential equations govern the distribution of resources and cells across voxels. We applied S3MB on sequencing and imaging data obtained from a primary GBM patient. We performed whole genome sequencing (WGS) of four surgical specimens collected during the 1st and 2nd surgeries of the GBM and used HATCHET to quantify its clonal composition and how it changes between the two surgeries. HATCHET identified two aneuploid subpopulations of ploidy 1.98 and 2.29, respectively. The low-ploidy clone was dominant at the time of the first surgery and became even more dominant upon recurrence. MRI images were available before and after each surgery and registered to MNI space. The S3MB domain was initiated from 4mm^3 voxels of the MNI space. T1 post and T2 flair scan acquired after the 1st surgery informed tumor cell densities per voxel. Magnetic Resonance Elastography scans and PET/CT scans informed stiffness and Glucose access per voxel. We performed a parameter search to recapitulate the GBM's tumor cell density and ploidy composition before the 2nd surgery. Results suggest that the high-ploidy subpopulation had a higher Glucose-dependent proliferation rate (0.70 vs. 0.49), but a lower Glucose-dependent death rate (0.47 vs. 1.42). These differences resulted in spatial differences in the distribution of the two subpopulations. Our results contribute to a better understanding of how genomics and microenvironments interact to shape cell fate decisions and could help pave the way to therapeutic strategies that mimic prognostically favorable environments.

Keywords : tumor evolution, intra-tumor heterogeneity, whole-genome doubling, mathematical modeling
Conference Title : ICCR 2023 : International Conference on Cancer Radiology
Conference Location : London, United Kingdom
Conference Dates : August 17-18, 2023