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Selection Driven Tumor Evolution Involving Non-Cell Autonomous Environmental Engineering Leads to Patterns of Clonal Expansion Consistent with Neutral Evolution

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INTRODUCTION: It is well known that tumors undergo somatic evolution, and there have been countless studies on the process [1]. However, many of these studies neglect the role of the environment and ecological interactions in evolution. The importance of these factors is still being studied, and as such, the role of space as an ecological resource within tumor development is a topic of great interest within the field of mathematical oncology. Agent-based models are excellent tools to study evolution within a spatial context and are well suited for multi-scale modeling. They algorithmically simulate individual agents based on pre-determined rules, which can lead to observation of population-level emergent behaviors.

METHODS: We introduce an agent-based model of tumor growth where space is the key growth-limiting resource and is controlled through non-cellular autonomous niche engineering. We examine this space as an ecological resource, where both the ability to create this resource through engineering, achieved by degrading extracellular matrix, and the ability to utilize this resource effectively through maximizing proliferation, are likely to be under strong selection within the model. Assuming the well-established principle of evolutionary tradeoff, we used our model to explore the interplay between engineering and consumption strategies in evolving populations of tumor cells, as well as the impact of this interplay on intratumor heterogeneity in space and time.

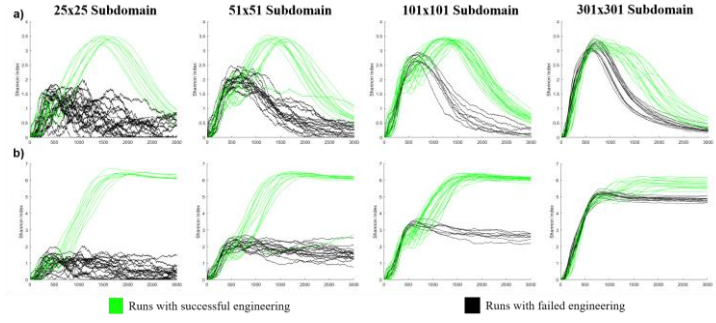

Figure 1: Heterogeneity plots from simulations in 25x25, 51x51, 101x101, and 301x301 subdomain sizes. Green lines represent simulations where engineering was a successful strategy and black lines represent runs where engineering failed. There are 30 simulations per plot, and each simulation ran for 3000 timesteps. **a)** Phenotypic heterogeneity within simulations as measured by the Shannon Index (y-axis from 0 to 4). **b)** Clonal heterogeneity within simulations as measured by the Shannon Index (y-axis from 0 to 7).

RESULTS: We found that simple rules for proliferation and turnover led to a consistent observation of phenotypic convergence and when engineering was successful, the creation and maintenance of intratumor heterogeneity (Fig. 1). These emergent behaviors from the model greatly resemble behaviors exhibited by patient tumors [2]. We also found that that this interplay results in ecological succession, enabling generation of large, heterogenous and highly proliferative populations. Visualizing clonal linages over time allowed us to qualitatively analyze the evolutionary dynamics over time. Different clonal frequency thresholds were used when creating visuals for the data to reflect different levels of sampling sensitivities for detection. Surprisingly, even though in our simulations both engineering and consumption strategies were under strong positive selection, their interplay led to sub-clonal architecture that could be interpreted as neutral evolution with sampling strategies commonly used in tumor genome analyses [3].

CONCLUSIONS: Our model was able to demonstrate that within a spatial context, simple rules for cell proliferation and mutation can lead to complex patterns of somatic evolution and ecological succession. This succession demonstrates how an ecological perspective can provide insight to key processes with the development of tumors, such as how phenotypic change occurs spatially throughout a tumor. Successful engineering in the model seemed to result in a rapid neutral expansion, yet our foundational rules within the model and more sensitive analysis of our data disproved neutrality within our model. Our results also warrant more careful interpretation of inferences from sequencing cancer genomes and highlight the importance of consideration of ecological aspects of somatic evolution.

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