Selection driven agent-based model with non-cell autonomous engineering produces clonal expansions consistent with neutral evolution

Jack Edwards*[1,2], Andriy Marusyk[1], David Basanta[1]
[1]Department of Integrated Mathematical Oncology, Moffitt Cancer Center, Tampa, FL
[2]Department of Physics, University of South Florida, Tampa, FL

Introduction

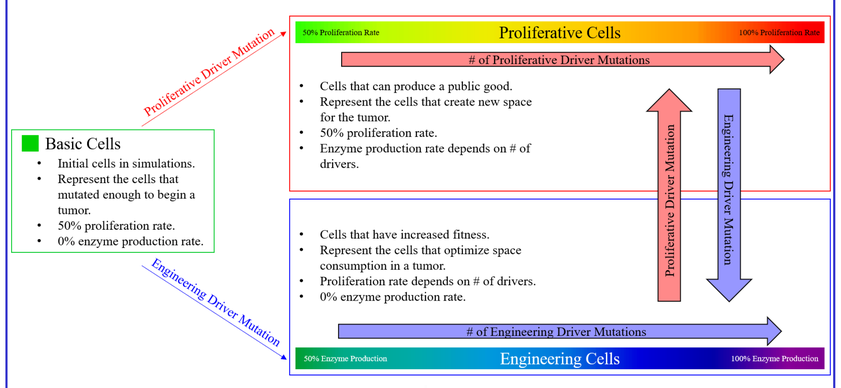
Cancer is a disease that starts when a cell in our body breaks away from the rules of cooperation and homeostasis imposed by multicellularity and starts acting as an independent evolutionary entity. As a cell that has lost homeostatic constraints divides, its progeny (clone) acquires genetic and epigenetic alterations generating novel phenotypic variants (subclones). This subclonal diversification enables a selection for more fit variants, which can lead to evolution of malignancy through selection-driven expansion of subpopulations that have acquired hallmarks of cancers. Sub-clonal diversification generates genetic and phenotypic Intratumor Heterogeneity (ITH), which correlates to poor prognosis and contributes to treatment failure. Understanding the basic rules that govern the somatic evolution and how ITH is maintained in the face of subclonal competition is the key to more effective tumor prevention and therapies.

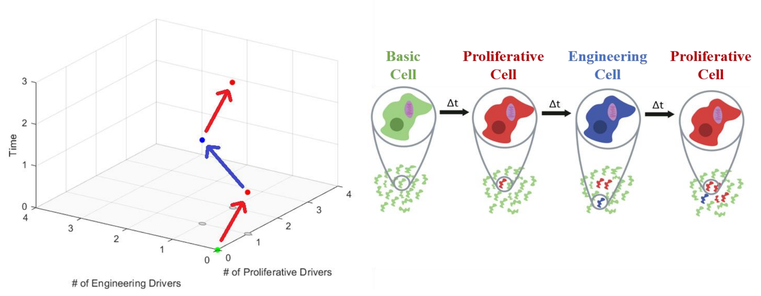
The purpose of this work is to examine how non-cellular autonomous engineering impacts the creation and maintenance of ITH by using an agent-based model of tumor growth.

Model Description

Cell Phenotypes

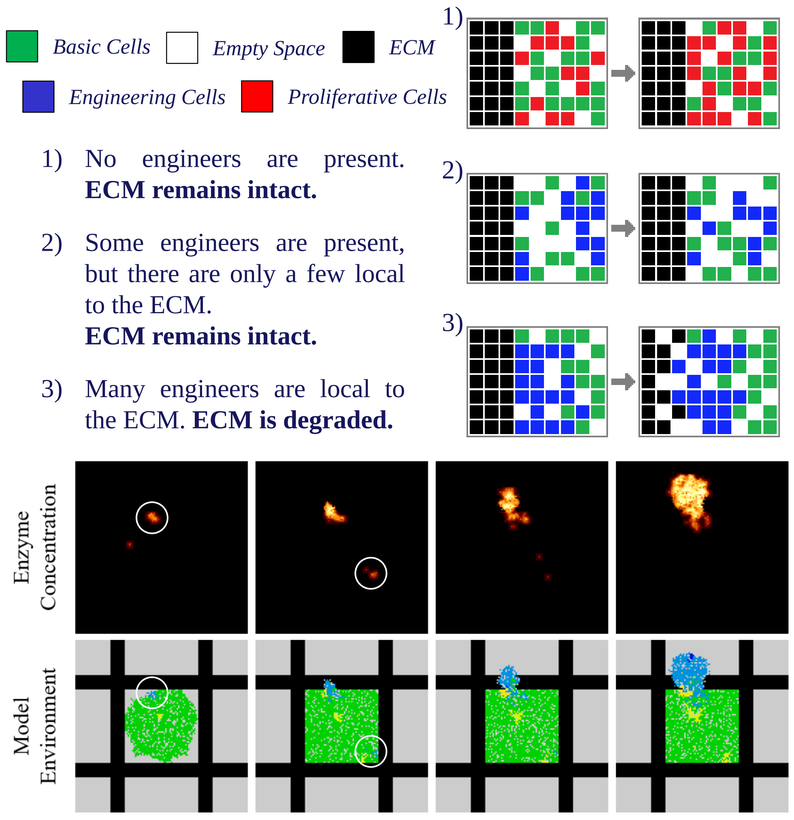
There are three cell phenotypes within the model, which can change via driver mutations. A sample phenotypic trajectory is shown below.





Rules of Engineering

Engineering cells can produce extracellular-matrix (ECM) degrading enzymes, allowing the tumor to access previously unavailable space.



1) No engineers are present. **ECM remains intact.**

2) Some engineers are present, but there are only a few local to the ECM. **ECM remains intact.**

3) Many engineers are local to the ECM. **ECM is degraded.**

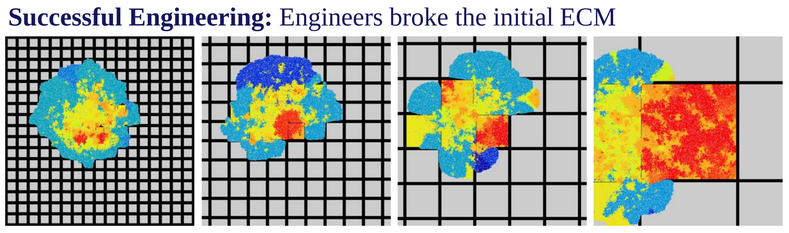
Circles highlight areas where engineers that produced insufficient enzyme to remove the nearby ECM are located.

Methods

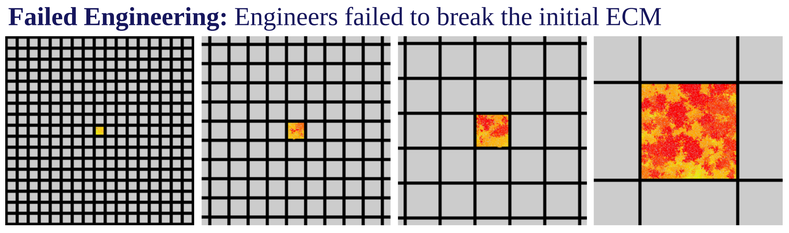
Characterization of Simulations

All simulations were run with the same parameters for mutation rate, death rate, ECM strength, ect. All simulations were run in 4 different subdomain sizes to examine the effects of engineering with different amounts of ECM present. Outcomes of the simulations were inherently stochastic, and characterized in the following manner:

Successful Engineering: Engineers broke the initial ECM

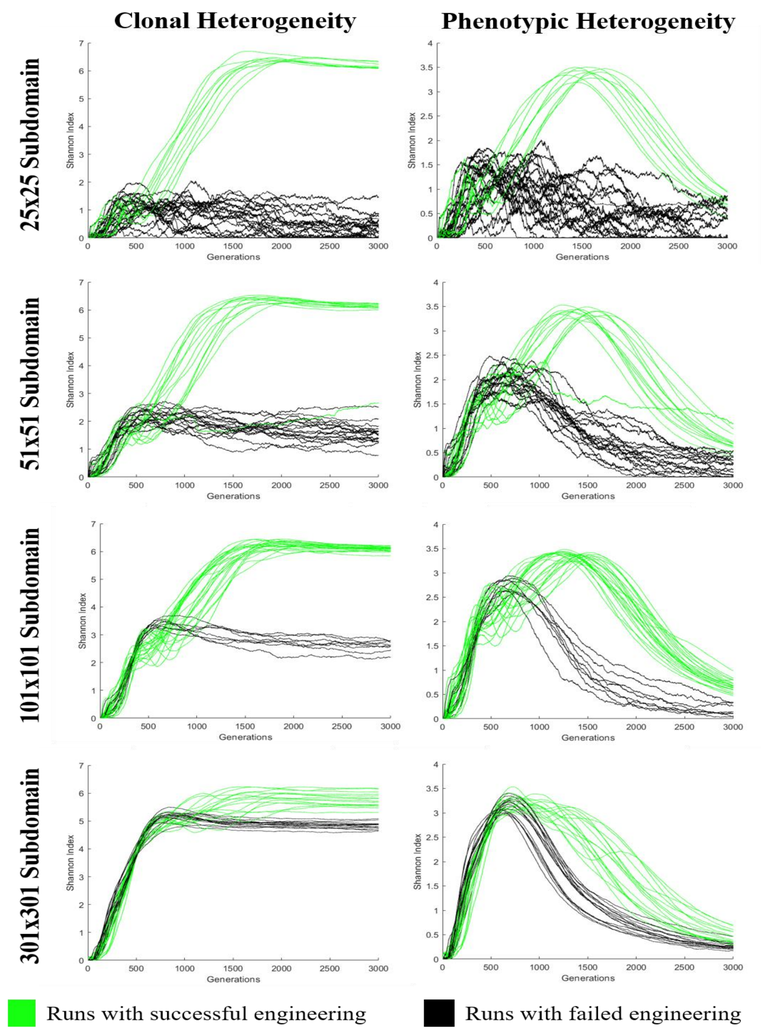


Failed Engineering: Engineers failed to break the initial ECM



Results

Tracking ITH within simulations

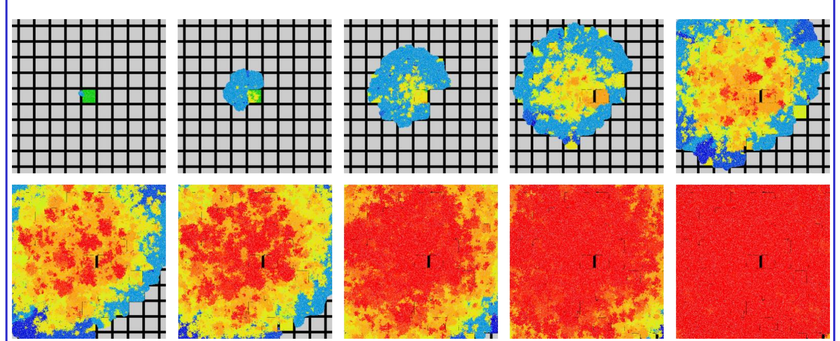


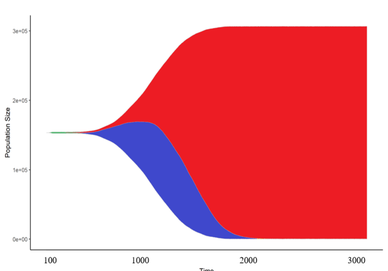
Runs with successful engineering

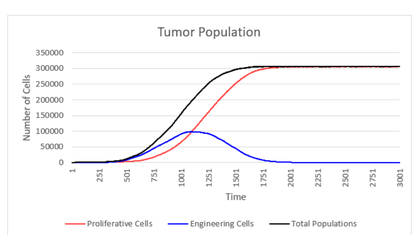
Runs with failed engineering

Selection Driven Phenotypic Succession

Patterns of ecological succession were observed within the model, which is an important emergent behavior, as it is another clear sign of the stringent selection within the model.



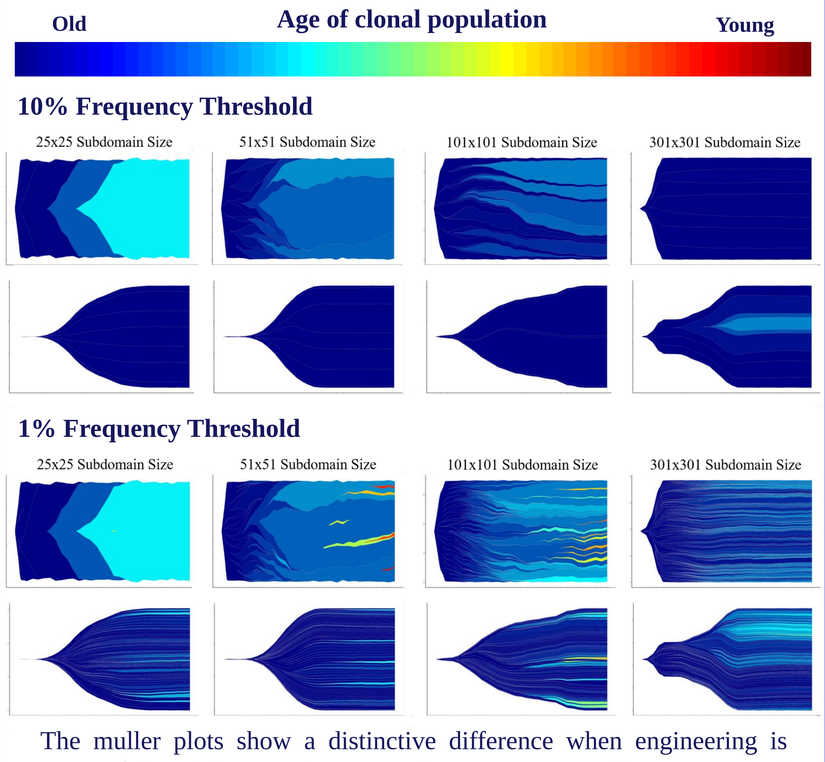




Analysis of ITH

Non-cellular Autonomous Engineering Promotes Neutral-like Expansions

Analysis of the clonal heterogeneity over time was done by creating muller plots using Evo Freq. The plots were visualized with a clonal frequency threshold of 10%, corresponding to ~20x genome sequencing depth of bulk sequencing (assuming near diploid genome), and 1%, reflecting higher resolution analysis. Top row in each panel is failed engineering, bottom row is successful engineering.



The muller plots show a distinctive difference when engineering is successful, and the growth patterns share a great resemblance to neutral clonal expansions.

Discussion/Conclusions

Our results show that even though the model used is one founded on the principle of natural selection and it exhibits emergent phenomenon such as phenotypic succession due to selection, analysis of clonal frequencies over time still suggests that non-cellular autonomous engineering causes neutral-like clonal expansions. This suggests that sampling approaches that are often limited to a single time point with limited resolution may miss key evolutionary dynamics within the tumor.

By tracking heterogeneity in simulations, we were able to observe the following for successful engineering:

- **An increased peak in phenotypic heterogeneity**
- **The maintenance of clonal heterogeneity over time, even in simulations with small subdomains.**

These observations are consistent with results found in a mouse-model of non-cell autonomous driver of tumor growth, providing more insight on these types of effects.

References

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