Thesis Defense:

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Understanding Tumor Composition and Evolution Through Geometric Models

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7101 GHC

Abstract

Despite rapid progress in the understanding and treatment of disease over the course of the past 100 years, diagnosis and treatment of cancer has become a focal point for basic science research. As a result, advances have been made in quantifying the myriad changes in tumor genomes, transcriptomes, epigenomes, andmetagenomes as compared to healthy tissue. Specific to the work of this thesis, technical advances have led to more robust quantification of RNA expression states via RNA-seq, and DNA copy number quantification via DNA-seq. These approaches allow for the measurement of the state of tens of thousands of genes in a sample. Moreover, the enhanced quantification has led to understanding the existence of heterogeneity among tumors.

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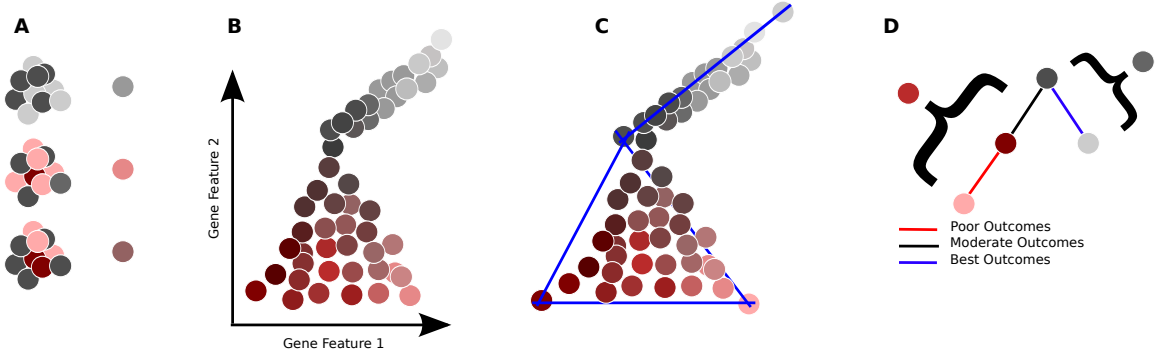
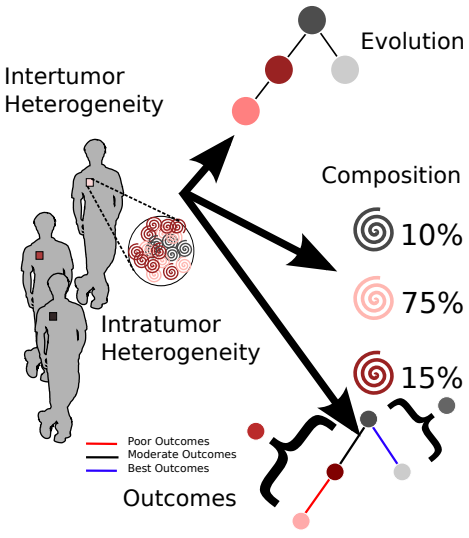


Bulk sequencing leads to condensed molecular measurements not representative of subpopulations (A). However, evolution and heterogeneity constrain the geometry of point clouds of quantified abberations (B). We find the optimal fits for these point clouds (C), which carry implications for tumor composition and can be related to outcomes (D).



The thesis aims to improve understanding of intratumor heterogeneity and intratumor heterogeneity. Intertumor heterogeneity means tumors become manifest in different individuals in different ways, exhibited by molecular measurement. Intratumor heterogeneity means that in a bulk sample, many cells that have substantial variability are pooled and sequenced together. The resulting measurement is a weighted average of the genomes of all cells. This work uses intertumor heterogeneity, embodied by the geometry of quantified measurements across patient panels, coupled with general constraints imposed by evolution, to learn the specifics of evolution in the patient panel, as well as the intratumor heterogeneity, in terms of the genomes of subpopulations, as well as composition. The work of the thesis then combines these inferences of evolution and composition to make predictions on patient outcomes.