Investigating the Selective Forces Driving Whole-genome Duplication in Cancer

Andrew Chan (Mentor: Dr. Khanh Dinh, 2023 IICD SRP)

Whole-genome duplication (WGD), the doubling of each chromosome in a cell, is found in over 30% of human tumors and is known to greatly change the fitness landscape of the tumor. However, despite its prevalence across cancer types and significant effect on the evolutionary trajectory of the tumor, the driving forces that select for WGD are still debated. Three possible hypotheses for the function of WGD in cancers are that (1) WGD protects cells against missegregations resulting in nullisomy; (2) WGD results in chromosomal instability, allowing for whole-genome doubled cells (WGD+ cells) to evolve more quickly than WGD– cells by accumulating large-scale chromosomal gains and losses; and (3) WGD leads to multipolar cell division, resulting in a rapid evolution of cells with an abnormal copy number landscape and potentially higher fitness over WGD– cells. We will test these various hypotheses by simulating their underlying assumptions in a model of cancer evolution, performing parameter sweeps of model variables, and validating our results using statistical testing with results from an analysis of cancer sequencing data. It is important to clarify which of these hypotheses most accurately reflects the forces selecting for WGD in certain environments so that we can better understand the specific role of WGD in shaping the fitness landscape of cancer evolution.