A Bioinformatics Approach To Study Convergent Evolution In Cancer

Paniz Tayebi[1], Dr. Ryan Gregory[2], Dr. Geoffrey Wood[3], Dr. Arijit Chakravarty[4]

[1] Master of Bioinformatics , University of Guelph, Ontario, Canada

[2] Department of Integrative Biology, University of Guelph, Ontario, Canada

[3] Department of Pathobiology, University of Guelph, Ontario, Canada

[4] Fractal Therapeutics, Cambridge, Massachusetts, United States

Background & Objectives

The Fundamental Challenge in Cancer Treatment: Cancer progression involves critical phenotypic changes that enable tumor survival and treatment resistance. Understanding how these changes occur is essential for developing effective therapies. The key question is: Do tumors achieve resistance through single genetic pathways or multiple evolutionary routes?

Traditional Oncogene Addiction Model:

- ❑ Cancer behavior is controlled by driver genes[1]
- ❑ Single genetic pathway leads to specific phenotype[1,2]
- ❑ Treatment targets one gene/pathway ("one gene, one drug" approach)[3]
- ❑ **Limitation:** Ignores cancer's adaptive, heterogeneous nature and evolutionary dynamics[4,5]

Convergent Evolution Model:

- ❑ Different genetic changes can lead to identical phenotypic outcomes
- ❑ Multiple pathways can produce the same result (e.g., drug resistance)
- ❑ Tumors exploit various genetic routes to survive treatment
- ❑ Requires adaptive therapeutic strategies

Research Objectives

Goal: Develop a computational model to simulate tumor evolution, comparing oncogene addiction versus convergent evolution paradigms.

Key Hypothesis: Tumors may exploit multiple genetic pathways to achieve the same survival advantage, requiring evolution-guided treatment approaches rather than single-target therapies.

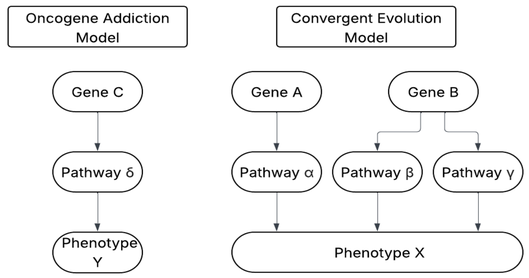


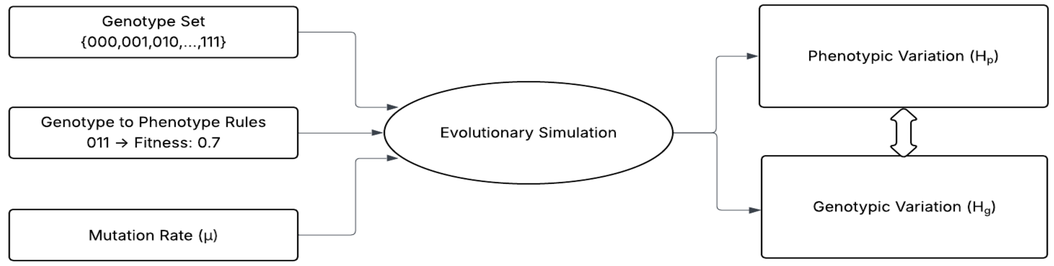
Figure 1. Schematic comparison of oncogene addiction vs. convergent evolution in cancer. In the oncogene addiction paradigm (left), phenotype Y depends exclusively on gene C and pathway delta. In contrast, convergent evolution (right) demonstrates how phenotype X can arise via multiple genetic routes (genes A or B) and divergent pathways (alpha, beta, or gamma), highlighting the flexibility of tumor evolution.

Methodology

Model Framework: Discrete-time Moran process simulates tumor evolution [6]

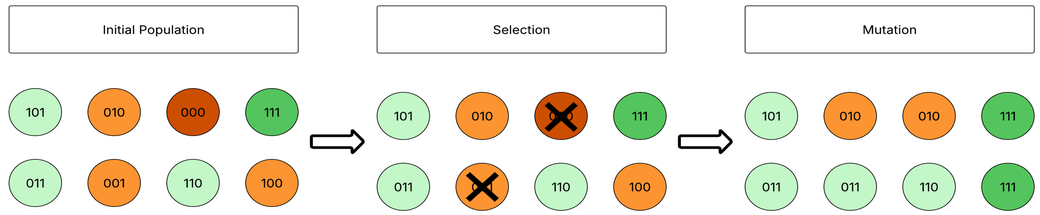
Key Components:

- ❑ **Population:** Grid of tumor cells with 3-bit genotypes (e.g., 000, 110, 101)
- ❑ **Fitness Mapping:** Genotype-to-phenotype relationships determining cell survival
- ❑ **Selection Pressure:** Treatment conditions favoring resistant phenotypes
- ❑ **Mutation Process:** Random bit-flips generating genetic diversity
- ❑ **Diversity Metrics:** Shannon's entropy for genotypic (Hg) and phenotypic (Hp) diversity [7]



Simulation Process

- ❑ **Stage 1 - Initial Population:** Random distribution of genotypes across cell grid
- ❑ **Stage 2 - Selection:** Least-fit cells die based on treatment pressure; fittest cells selected for reproduction
- ❑ **Stage 3 - Mutation:** Offspring undergo random bit-flip mutations, potentially altering fitness landscapes
- ❑ **Stage 4 - Measurement:** Calculate diversity metrics integrating genotype-phenotype mappings with population parameters



$$H(x) = -\sum_{i=1}^{n} p(x_i) \log_2 p(x_i)$$

final entropy · probability of an event · logarithm of event's probability

Expected Findings & Variance Patterns

Under Oncogene Addiction Model:

- ❑ **Genetic Variance:** Low (single pathway dominates) [1,2]
- ❑ **Phenotypic Variance:** Low (tightly coupled to genetics)
- ❑ **Pattern:** Strong correlation between genetic and phenotypic diversity - both decrease together
- ❑ **Clinical Evidence:** Predictable resistance mechanisms through dominant pathway

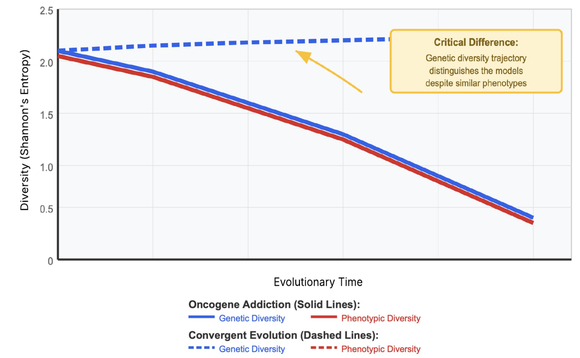
Under Convergent Evolution Model:

- ❑ **Genetic Variance:** High (multiple pathways remain active)
- ❑ **Phenotypic Variance:** Low (same adaptive outcome via different routes)
- ❑ **Pattern:** Decoupled genetic and phenotypic diversity - genetic stays high while phenotypic decreases
- ❑ **Clinical Evidence:** Tumors achieve identical phenotypes (e.g., drug resistance) through distinct genetic pathways [5,8]

Model Validation:

- ❑ Simulation reproduces observed clinical patterns of treatment resistance
- ❑ Demonstrates how genetic heterogeneity can coexist with phenotypic consistency
- ❑ Multiple fitness peaks in genetic landscape leading to same survival advantage

Anticipated Results & Implications



Clinical Implications:

- ❑ **Challenges:** Traditional "one gene, one drug" approaches insufficient for heterogeneous tumors [3,4]
- ❑ **Solution:** Evolution-guided, adaptive combination therapies targeting multiple pathways simultaneously[9,10]
- ❑ **Personalization:** Treatment selection based on tumor's evolutionary potential, not just current genetics
- ❑ **Resistance Prediction:** Identify likely evolutionary escape routes before they emerge
- ❑ **Combination Optimization:** Design drug cocktails that close multiple evolutionary pathways
- ❑ **Treatment Timing:** Sequence therapies to prevent rather than react to resistance

Future Directions:

- ❑ Incorporate spatial tumor structure and microenvironment effects [11]
- ❑ Add epigenetic modifications and non-genetic inheritance mechanisms [12]
- ❑ Integrate real patient genomic data for validation
- ❑ Develop decision-support tools for oncologists
- ❑ Design clinical trials testing evolution-guided therapy protocols
- ❑ Create biomarkers predicting convergent evolution potential

References

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