# Algorithmic Deconstruction of Somatic Copy Number Alterations for Therapeutic Target Discovery in Cancer

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## Introduction

- Somatic copy number alterations (SCNAs) are changes in the number of copies of specific DNA segments in cells, which can lead to genetic abnormalities.
- SCNAs are among the most prevalent mutational events in cancer, driving tumor growth by modulating the dosage of key genes.[1]
- Despite their significance, the wide-ranging effects of SCNAs often make it difficult to identify their targets, presenting a major challenge for developing cancer therapies.[2]
- Our project aims to address this challenge by creating an advanced computer algorithm that leverages biological mechanisms behind SCNA formation.

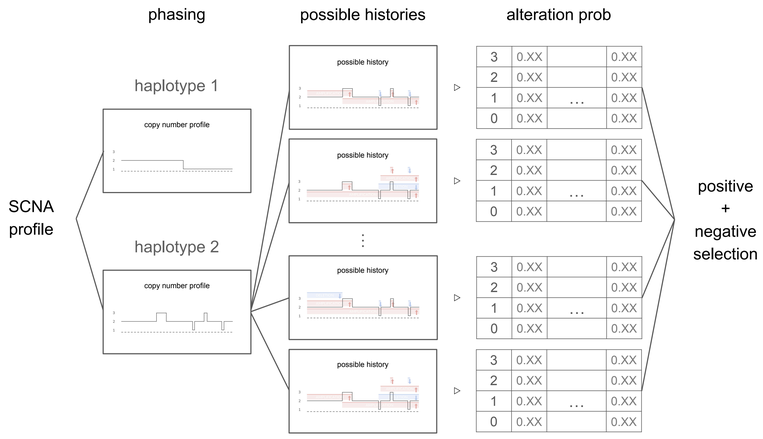
## Hypotheses

- We hypothesize that our algorithm will pinpoint genes whose lack or abundance is pivotal to cancer, providing valuable insights for drug discovery.

## Methods

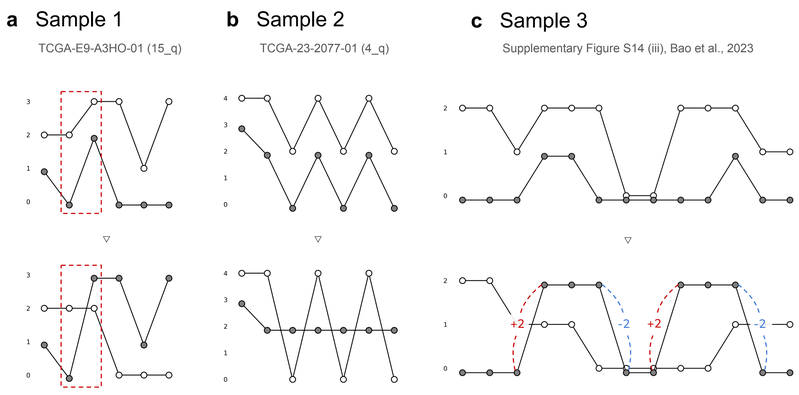
- We leverage a large-scale dataset of tumor samples curated from public consortiums, including The Cancer Genome Atlas (TCGA) and the Genomics England 100 000 Genomes Project.[3,4]
- Haplotype-specific SCNA patterns are inferred using a phasing algorithm based on experimental evidence from previous studies (**Fig. 2**).[5]
- We then apply a mathematical strategy to reconstruct all possible histories of duplications and deletions that could have resulted in a given SCNA profile (**Fig. 3**).
- An iterative algorithm evaluates the likelihood of different histories, which informs the downstream analysis of potential genetic targets.
- Through simulation of SCNA generation, we assess genomic regions that exhibit disproportionate alterations than expected under neutral conditions.
- We introduce the concept of relative fitness to quantify the impact of these alterations on cell survival (**Fig. 7**).

**Fig. 1 | Schematic overview of the framework**



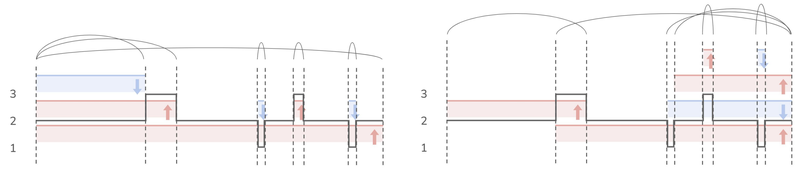

Genomic regions that promote (positive selection) or inhibit (negative selection) cancer growth are identified by integrating results from all possible histories, haplotypes, and tumor samples.

**Fig. 2 | Strategies of haplotype inference**



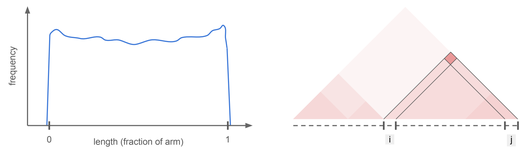

The top panels display the raw data, while the bottom panels show the inferred haplotypes. Experimental observations include minimal breakpoints in copy number (**a**), multiple changes likely accumulating within a single haplotype (**b**), and copy level changes often occurring in pairs (**c**).[5]

**Fig. 3 | Reconstruction of underlying events**



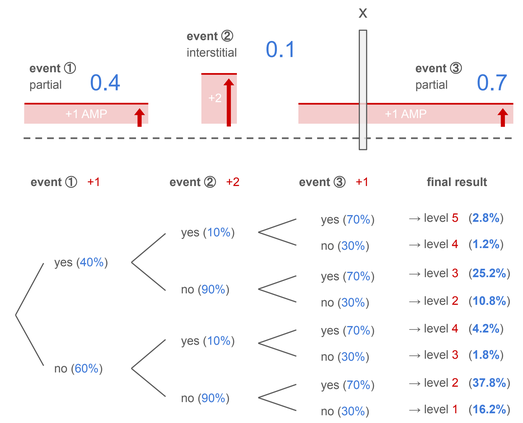
Every possible set of duplication and deletion events is generated by permuting breakpoint pairings within a given profile.

**Fig. 4 | Length distribution of events**



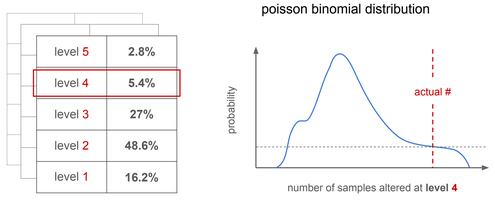

Different event types (**a**, **b**) show distinct probability distributions of extending to specific lengths.[2,6]

**Fig. 5 | Expected alteration levels**




Alteration probabilities are determined by simulating different combinations of events extending to location *x*.

**Fig. 6 | Integration**




Results across tumor samples are integrated using a poisson binomial distribution.

**Fig. 7 | Relative fitness**

$$\frac{\textbf{level } \textit{n} \text{ reality} \,/\, \textbf{level } \textit{n} \text{ expectation}}{\textbf{level } \textit{ref} \text{ reality} \,/\, \textbf{level } \textit{ref} \text{ expectation}}$$

The fitness advantage of level *n* alteration is assessed by comparing observed survival rates to expected ones, relative to the reference level.

## Results

- Our work introduces four novel algorithms, each tackling a central component of the methodology, forming a comprehensive and sophisticated workflow.
- This method overcomes the limitations of previous tools (e.g., GISTIC and BISCUT) by incorporating information from all SCNA event types and detecting regions under both positive and negative selection.[2,7]

## Conclusion

- Preliminary analyses show that these algorithms are effective in identifying candidate genomic regions of interest.
- We anticipate this work to uncover previously undiscovered targets of SCNAs, contributing to the advancement of personalized therapies that are tailored to the unique genetic composition of each patient's cancer.
- Furthermore, it will serve as a vital resource for researchers studying the underlying causes of different tumors.

## References

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