

Statistical approach for quantifying the evolution of tumor heterogeneity in chronic lymphocytic leukemia (CLL)

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Intra-tumor heterogeneity, a significant challenge in targeted cancer therapy, is particularly pronounced in CLL. Clonal evolution, driven by VDJ recombination and somatic hypermutation, generates a heterogeneous population of subclones that can confer resistance. Thus, phylogenetic tree reconstruction is key to understanding this process.

Using the weighted uniform distribution [1], we present a probabilistic framework for clonal reconstruction, generating a phylogenetic graph to better account for biological noise and allow sampling of multiple evolutionary trajectories, offering a more flexible and realistic model of tumor evolution than tree-based methods [2, 3]. To further refine this construction, we developed a Variational Expectation-Maximization algorithm, which systematically adds an optimal number of unobserved clones. This improves resolution, leading to a more complete and accurate representation of tumor evolution.

Future work will integrate longitudinal cancer gene mutation data (VCF) into our existing VDJ-based evolutionary graphs, creating a unified graph. This will provide a more comprehensive model of clonal evolution, improving insights into tumor progression and resistance for precision oncology.

Keywords: Phylogenetic tree, VDJ sequencing, Somatic hypermutation, Leukemia, Intraclonal heterogeneity, Variational Expectation Maximization.

References

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