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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

[1] R. Lyons, Y. Peres, *Probability on Trees and Networks*, Cambridge University Press, 2016.

[2] L. Jeusset, N. Abdollahi, T. Verny, M. Armand, A. L. De Septenville, F. Davi, J. S. Bernardes, ViCloD, an interactive web tool for visualizing B cell repertoires and analyzing intraclonal diversities: application to human B-cell tumors, *NAR Genomics and Bioinformatics*, 5:lqad064, 2023.

[3] S. Malikic, K. Jahn, J. Kuipers, S. C. Sahinalp, N. Beerenwinkel, Integrative inference of subclonal tumour evolution from single-cell and bulk sequencing data, *Nature Communications*, 10:2750, 2019.