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Inference of lineage hierarchies and growth mechanisms in cell populations without tracking

Lineage inference largely relies on single-cell tracking techniques, which are notoriously difficult in complex biological models. Furthermore, while modern genomic approaches do allow to identify the different composing phenotypes, resolving the dynamics and inferring the interactions among the different lineages in a small group of cells still remains a difficult task. Mathematically, a lineage dynamics can be simulated and investigated using braching process models and we developed a set of methods to infer which phenotypic transitions are active in a small multi-lineage tumor or clone and to evaluate their likelihood solely based on counting the abundance of lineages. To this end, we developed two approaches that leverage multi-lineage discrete branching processes for Bayesian inference: one within a fully analytical framework and another using a numerical method with a Gibbs sampler. Finally, we developed a maximum-likelihood approach that employs Monte Carlo Expectation-Maximization with multi-lineage branching processes for cases where the previous methods cannot be applied. We demonstrate the applicability of our approaches to cancer cell plastiticy and to a set of diverse experimental contexts, showcasing its effectiveness. Overall, our approaches enable the identification of death, phenotypic switch, and proliferation rates, uncovering the relevant mechanisms underlying lineage plasticity and the feedback loops driving subpopulation dynamics.

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