Characterization of cancer evolution and intra-tumor heterogeneity from single-cell sequencing data

The increasing availability of multiple -omics data (e.g., genomics, transcriptomics, epigenomics, etc.) obtained from tumor samples may allow to generate explanatory and predictive models of the disease with unprecedented resolution and accuracy [1]. Single-cell sequencing data, in particular, allow one to dissect the high levels intra-tumor heterogeneity observed in most cases, and which often underlie drug resistance and relapse [2]. To this end, Artificial Intelligence (AI) and, in particular, machine learning methods can be effectively employed to develop comprehensive frameworks to process, denoise, analyze and integrate (big) heterogeneous single-cell data of cancer patients. Accordingly, this allows to deliver diagnostic and prognostic tools to support experimentalists and clinicians [3].

One notable example is provided by LACE (Longitudinal Analysis of Cancer Evolution), the first algorithmic framework that processes single-cell somatic mutation profiles from cancer samples collected at different time points and in distinct experimental settings, to produce longitudinal models of cancer evolution [4]. Such models can be effectively employed to assess the efficacy of therapies over time on the clonal composition of a tumor and to identify (rare) resistant subclones. Our approach solves a Boolean matrix factorization problem with perfect phylogenetic constraints, by maximizing a weighted likelihood function computed on multiple time points, and it outperforms state-of-the-art methods for both bulk and single-cell sequencing data.

Remarkably, as the results are robust with respect to high levels of data-specific errors, LACE can be employed to process single-cell mutational profiles as generated by calling variants from the increasingly available scRNA-seq data, thus obviating the need of relying on rarer and more expensive genome sequencing experiments. This also allows to investigate the relation between genomic clonal evolution and phenotype at the single-cell level.

Another important example is provided by scFBA (single-cell Flux Balance Analysis), a computational framework aimed at translating single-cell transcriptomes into single-cell fluxomes, for investigation of the deregulation of cancer metabolism. Our approach allows to: (i) reduce the space of feasible single-cell fluxomes; (ii) identify clusters of cells with different growth rates within the population; (iii) point out the possible metabolic interactions among cells via exchange of metabolites [5].

By exploiting high-resolution data at the single-cell level, the results delivered by such approaches may cast a light on the mechanisms underlying intra-tumor heterogeneity, thus paving the way for the development of patient-specific diagnostic, prognostic and therapeutic strategies.

References:


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