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Type	Oral communication
Session	Multi-Omics
Title	Leveraging high-throughput data to characterize cancer metabolic heterogeneity
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Motivation

Alteration of metabolism plays a role in many multi-factorial diseases, including cancer and neurodegenerative disorders. Metabolism has been reported to be highly heterogeneous across cancer patients and within the tumor microenvironment. Understanding the metabolic program of each tumor or cell population ideally requires measurements of the metabolic fluxome, i.e. the net between the forward and backward rate of each metabolic reaction. However, fluxes can be inferred only indirectly with current experimental techniques and just for a limited set of reactions. The procedure is expensive, laborious, and can hardly be applied at a single-cell or spatial resolution. To overcome these limitations, many attempts have been made to predict metabolic fluxes from other high-throughput data, especially from gene expression data, either bulk or single-cell.

A major challenge of proposed methodologies is the lack of a ground truth to demonstrate their validity and to assess their performance with respect to other methods.

We are exploring the possibility of using bulk intracellular-metabolomics datasets to benchmark the results of main state-of-the-art methods to predict metabolic fluxes from bulk transcriptomics datasets. Once the methodologies have been tested they can be extended to single-cell or spatial datasets.

Methods

We exploited data in the Cancer Cell Line Encyclopedia (CCLE), which includes paired omics datasets for several human cancer cell lines, as well as some metadata about samples. To avoid confounding factors due to different culturing conditions, we considered a subset of 512 cell lines in the CCLE database that were cultured in the same growth medium (namely, RPMI 1640), and for which both transcriptomics and metabolomics data were available.

To computationally derive the fluxomics of each cell line, we integrated the transcriptomics into a metabolic network, focused on central carbon metabolism (462 reactions, 391 metabolites and 501 genes), using different strategies, such as INTEGRATE, GIMME, INIT, iMAT, COMPASS, RIPTIDE, with the aim to provide one specific network for each cell line. Then, we performed flux sampling of each network, using two approaches: the Coordinate Hit-and-Run with Rounding (CHRR) and a corner-based sampling strategy.

Finally, we performed an extensive cluster analysis of each omic separately (i.e., simulated fluxomics, transcriptomics, and metabolomics) aiming at exploring the degree of concordance between their results. To do this, we considered different clustering algorithms (including k-Means, Hierarchical clustering, Louvain, and DBSCAN) and different parameter settings.

Results

As the first evaluation of the results of flux clustering, we verified that the flux distributions sampled from the same cell line model tend to cluster together. Then, we studied if there is any relationship between clustering of any omic and some prior information about cell lines. Finally, we investigated if there is any relationship between the clusters obtained from fluxomics and the ones obtained from transcriptomics and metabolomics. To this aim, we used both the silhouette index and the v-measure, assuming as possible ground truth, the cluster labels provided by transcriptomics or metabolomics.

As preliminary results, we found that metabolomics and transcriptomics divide the cell lines in two main clusters, whereas the clustering provided by fluxomics is more complex and fragmented, with a moderate homogeneity with the clusters provided by the transcriptomics data.

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