BITS :: Call for Abstracts 2022 - Oral communication

Type	Oral communication
Session	Multi-omics data analysis and integration
Title	Knowledge-based multi-omics data integration to unveil the many facets of metabolic variation and regulation
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Motivation

Knowledge of the metabolic flux distribution of a given tumor, that is, the rate of turnover of metabolites through each metabolic reaction, is the starting point to identify specific metabolic drug targets. Yet, fluxomic techniques are far from being high-throughput, especially at the single-cell and sub-cellular levels. On the contrary, transcriptomics and metabolomics datasets are increasingly available, but provide static profiles of a cell’s metabolic state and do not capture dynamic features.
Therefore, to face these challenges efficient methodologies to integrate different omics data must be developed.

Methods

We defined the INTEGRATE computational pipeline to reconstruct metabolic fluxes and to identify their regulation level, from transcriptomic (and/or proteomics) and metabolomics data.
INTEGRATE uses RNA levels to constrain the metabolic fluxes, i.e. the rate of metabolic reactions of a metabolic network reconstruction. To link the level of one or more genes to the flux over a specific metabolic reaction, it relies on Gene-Protein-Reaction (GPRs) logical formulas included in current metabolic network reconstructions. GPRs link gene products, namely enzymes, to the metabolic reaction that concurs to catalysis. The OR operation joins genes that code for isoforms of the catalyzing enzyme, whereas the AND operator joins genes coding for subunits of the same enzyme. INTEGRATE assigns to each reaction in the network a continuous Reaction Activity Score (RAS), taking the minimum RNA level for AND-joined genes, the sum for OR-joined genes.
INTEGRATE uniformly sample the feasible region of the admitted fluxes of each sample under study. The feasible region is delimited by the constraints on the reaction stoichiometry, mass balance, exchange of metabolites with the environment computed from exo-metabolomics measurements, and the RAS-derived constraints on admitted flux values. The mass balance constraint is represented by the equation $S*v=0$, where S is the stoichiometric matrix and v is the vector of metabolic fluxes. INTEGRATE assigns an upper bound to each component of v, i.e. each metabolic flux, as a function of the relative RAS value of each sample.
In parallel, INTEGRATE uses intracellular metabolomics data to compute a Reaction Propensity Score (RPS) for each reaction, based on substrate availability.
INTEGRATE finally analyzes the concordance between variations in the predicted metabolic fluxes and in the RASs or in the RPS scores to discriminate fluxes regulated at the substrate level only (metabolic control), from fluxes controlled by enzyme expression (transcriptional control).

Results

As a proof of concept, we applied the pipeline to five human cell lines, including four breast cancer cell lines and one non tumorigenic breast cell line. We showed that the sampled flux distributions well discriminate the five cell lines.
Remarkably, we identified reactions for which there is a good agreement between flux variations and variations in RPSs, even if the two datasets are fully independent.
We demonstrated that INTEGRATE can complement information on the differential propensity of reactions derived from metabolomics, with information on the compartment in which the reaction occurs. For instance, INTEGRATE indicated that the aconitase reaction is regulated by the substrate located in the cytosol compartment rather than in the mitochondrion.
Metabolomics data alone would not have allowed us to differentiate between the two scenarios. Notably, this information was complemented by transcriptomics data even though the aconitase flux itself is not regulated at the transcriptional level, thanks to the indirect regulation captured by INTEGRATE.
Knowing the level of regulation of a reaction is fundamental to properly identify candidate drug targets.

Info

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Availability	https://zenodo.org/badge/latestdoi/352613136

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Submitted on	28.04.2022