Integration of transcriptomics and metabolomics data to investigate metabolic heterogeneity in breast cancer cells

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Abstract:
Cancer cells must rewire cellular metabolism to support uncontrolled growth. Regrettably, this general characteristic develops from different mechanisms that result in a cancer phenotype. Understanding what features characterize this metabolic heterogeneity may support the development of ad-hoc therapeutic strategies. The progress of new and efficient omics techniques today allows obtaining a huge amount of measurements on an organism of interest. However, the quantification of biological components (genes, transcripts, proteins) with these techniques does not promptly translate into knowledge on the utilization of metabolic pathways. In fact, cellular utilization of metabolic pathways is the final downstream product of different regulatory layers and the most direct expression of the phenotype. Analysis and interpretation of data represent a major challenge for life scientists; therefore, it is necessary to build data integration strategies to support a better understanding of biological systems. To this end, Systems biology is an integrative research strategy that combines experimental and computational biology to obtain a quantitative description of a complex biological system. Genotype-phenotype relationship can be investigated with constraint-based models that represent mathematically the capabilities of a metabolic network. In particular, genome-scale models are a powerful tool that can link the genes to metabolic enzymes through a set of Boolean rules. In this work, we show that starting from our genome-scale model called ENGRO2, it is possible to represent the metabolism of four different breast cancer cell lines and one control breast cell line. For each cell line, we reduced the solution-space by integrating the medium, the spent medium composition data, and the expression profile of transcripts. Given constraints on the consumption/production ratios of the external metabolites, we sampled – with a randomized sampling method – the feasible solution space. Finally, we visualized on metabolic maps the difference in cells' intracellular flux profiles. Taken together these findings point out how metabolism could support the growth of different breast cancer cell lines in heterogeneous ways.