ABSTRACT

Title: Yeast Genome-Scale Metabolic Models as a Framework for Multi-Omics Integration and Metabolomics Interpretation

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Abstract content:
Metabolomics is the omics discipline devoted to the comprehensive study of metabolites, the small molecules that act as substrates and products of metabolic reactions within biological systems. As the metabolome reflects intracellular biochemical processes and environmental influences, it represents a key link between genotype and phenotype, capturing interactions among molecular layers, including the genome, transcriptome, and proteome. Within the framework of systems biology, metabolomics plays a crucial role in providing a holistic understanding of cellular functions through the integration of multi-omics data. Untargeted metabolomics approaches allow the large-scale detection of metabolites in biological samples. However, the complete identification and characterization of detected compounds remain a challenge, and no cellular metabolome has yet been fully experimentally characterized. In this context, artificial intelligence (AI) is emerging as a promising strategy to support metabolite annotation and improve the interpretation of complex metabolomics datasets. Focusing on the model organism *Saccharomyces cerevisiae*, this study evaluates recent community-supported AI-informed approaches for metabolomics data analysis, including global optimization methods, reference data-driven strategies, and machine learning–based metabolite annotation. However, the effectiveness of AI in metabolomics is constrained by limited curated datasets and heterogeneous annotation resources. Integrating metabolomics within systems biology frameworks, including genome-scale metabolic models, may therefore provide a more robust strategy for data interpretation. Accordingly, we optimized a workflow based on the genome-scale metabolic model Yeast9 to facilitate the integration of metabolomics data within a multi-omics framework. This workflow highlights the importance of well-curated, species-specific genome-scale metabolic models for supporting metabolomics interpretation within systems biology studies.