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Coarse-Grained Modeling Elucidates Differential Metabolism of *Saccharomyces cerevisiae* Under Varied Nutrient Limitations

Background/Objective

Microorganisms such as *S. cerevisiae* can natively adapt their metabolism to varying nutrient conditions. Understanding their responses to nutrient limitations is critical for decoding cellular physiology and designing strategies for metabolic engineering. While the influence of carbon (C) availability on yeast metabolism has been extensively studied, the role of nitrogen (N) availability remains relatively underexplored. Since metabolic dynamics are inherently complex, it is challenging to effectively compare the nutrient limitation conditions using existing mathematical models. Coarse-grained modeling addresses this by grouping enzymes and metabolites into representative units based on similar functions and patterns, thereby reducing modeling complexity and providing insights into complex metabolic regulation. In this work, we built on our previous coarse-grained kinetic model to analyze and compare the effects of C and N limitations on yeast metabolism.

Approach

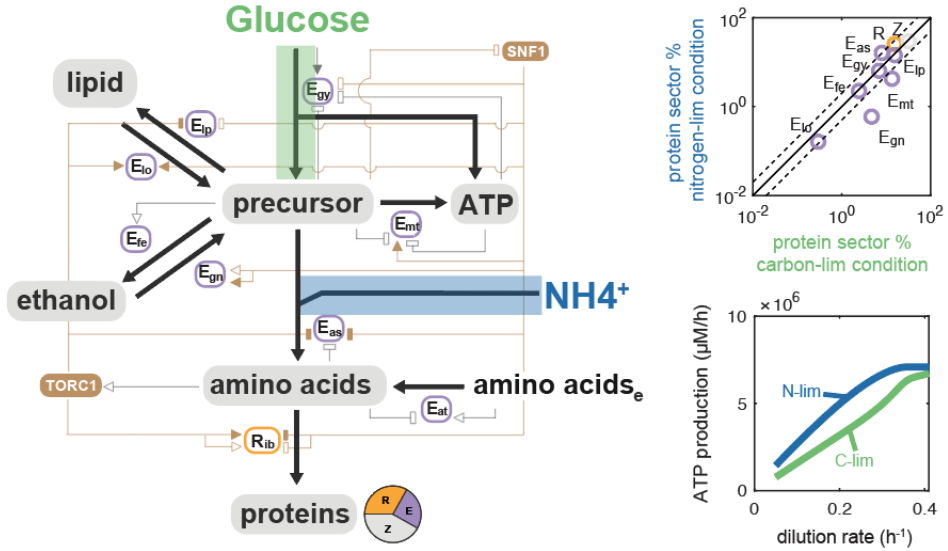
We expanded our previous *S. cerevisiae* kinetic model, which focused on glucose catabolism, to include ammonium-catabolism pathways. We added a lipid outlet to capture biomass composition changes driven by the C/N ratio in the medium and quantify the trade-off between C-rich biomass (lipids) and N-rich biomass (proteins) under different nutrient conditions. We then integrated additional pathways and regulatory mechanisms by introducing new equations and modifying parameters and assumptions. We further calibrated the model using proteomics and metabolomics datasets collected from published literature.

Results

Our model successfully showed the differential metabolic characteristics of *S. cerevisiae* under C- and N-limited chemostat conditions, highlighted protein activity regulation at varying C/N ratios, and elucidated distinct strategies employed to maintain ATP homeostasis.

Significance/Impacts

This model is a tool for investigating yeast physiology under nutrient limitations and offers quantitative and mechanistic insights into yeast metabolism.



Coarse-grained modeling of *S. cerevisiae* captures the metabolic network, signaling regulation, and proteome allocation under varying C/N ratios.

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