Coarse-grained Modeling of *Saccharomyces cerevisiae* Physiology

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Project Goals: We have developed a coarse-grained, mechanistic, and dynamic model of yeast physiology that integrates key processes of metabolic, gene regulatory, and signaling networks underlying cellular metabolism. The proposed model describes the cell's dynamic resource partitioning (proteome allocation) under varying glucose-replete and glucose-limited conditions. The model successfully captures key metabolic characteristics of yeast, including the Crabtree effect and diauxic shift observed during batch growth and the critical dilution rate seen in chemostat cultures.

S. cerevisiae has proven itself to be an industrial workhorse, where metabolic engineering has turned it into a cell factory for sustainable production of biofuels, pharmaceuticals, and other valuable chemicals. However, there have been experimental challenges in reprogramming the cells for production of heterologous chemicals due to the complexity of the underlying metabolic network. Mathematical modeling provides a potential solution to this problem. Genome-scale models have guided previous engineering attempts by predicting how mutations of a specific gene target or a group of targets could alter chemical production. Here, we provide a complementary approach to genome-scale modeling. We propose a coarse-grained, mechanistic, and dynamic model of yeast physiology that describes global resource allocation under varying nutrient conditions. The model is simple but is still able to capture key characteristics of yeast metabolism.

As protein synthesis is one of the most energetically expensive cellular processes and because cellular growth rate is proportional to protein synthesis rate[1], we chose to investigate resource allocation at the level of the proteome. Based on previous work of coarse-grained modeling of *E. coli*[2], we categorize the approximately 6000 proteins of *S. cerevisiae* into nine major proteome sectors: R (including gene expression machinery), 8 E proteins (including proteins that promote forward metabolic flux), and Z (housekeeping proteins and the remainder of the proteome). We found this to be the minimal number of coarse-grained enzymes required to reproduce the correct phenotype. Next, we developed a biophysical model that combines transcription and translation processes to describe protein synthesis. This module describes resource partitioning through competition for ribosomes among the different proteins. We then consider the cell's resource partitioning among amino acids, energy (ATP), ethanol, and storage carbohydrates. We chose PKA and SNF1 as coarse-grained global regulators that adjust the fermentation and respiration rates in response to varying glucose levels and TORC1 as the global regulator that responds to amino acid levels. These regulators adjust the resource allocation between the R and E sectors to meet metabolic demands.

We see that the model successfully captures key characteristics of yeast metabolism. Simulations return different proteome partitions for varying nutrient compositions. This changing proteome allocation provides a possible mechanistic explanation for the Crabtree effect as well as the diauxic shift and critical dilution rate that are observed in our simulations of batch and chemostat cultures. Under good nutrient conditions (glucose-replete), PKA and TORC1 promote cell growth and synthesis of R proteins, which minimizes the resource allocation to the E sector proteins. However, once glucose is depleted or in glucose-limited conditions, SNF1 shifts the metabolism toward ATP generation through remodeling of the proteome.

This work advances the fundamental understanding of microbial physiology by capturing and providing a quantitative and mechanistic explanation of the metabolic characteristics of *S. cerevisiae*. With addition of specific metabolic pathways to this simple framework, it has the potential to predict the effects of perturbations of the network on cell growth and chemical production to offer insight into the rational design of metabolic pathways.

References

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