Poster Session

Rational Modular Design of Yeast Strains Towards Overproduction of Industrially Relevant Products

Lopes, H., University of Minho
Maia, P., - Computational Biology Solutions for the Life Sciences
Patil, K. R., EMBL
Rocha, I., University of Minho

Despite some progress over the last years, the development of optimized yeast strains for the production of chemicals and other materials is still a costly and time-consuming process. The availability of suitable chassis cells, pre-optimized for the overproduction of different compounds, can contribute to reduce this cost/time burden. Among several eukaryotic organisms that can be exploited in industrial biotechnology, Saccharomyces cerevisiae is uniquely positioned as a well-established, robust and scalable industrial production platform for a large portfolio of products, due to its high tolerance to harsh industrial conditions and available knowledge.

Following this rationale, we herein propose a conceptual framework for the design of platform S. cerevisiae strains towards enhanced production of families of industrially relevant compounds, through the identification of gene deletions to improve the production of the desired targets. The framework includes two main stages: i) Optimization stage, where an OptGene-based [1, 2] multi-objective metaheuristic approach is applied for all targets in a given family and ii) Chassis analysis, where the occurrence of each gene in each of the targeted metabolites’ solution set is accounted for. Candidate genes for deletion are sorted based on a computed score that favors genes occurring for multiple targets. Top scoring genes are then selected for chassis generation. Afterwards, all the solutions are organized in groups with common chassis. Case studies include the production of metabolites that have found widespread applications in the food, chemical and pharmaceutical industries, namely C4-dicarboxylic acids derived from the TCA cycle (succinate, fumarate and L-malate) and a set of heterologous products derived from the shikimate pathway.

Several chassis strains containing a common backbone of non-intuitive gene deletions to the selected targeted metabolites, along with additional genetic targets to guarantee the desired phenotype, were generated and characterized in terms of their biological feasibility. Candidate solutions were ranked based on computed metrics resembling productivity and number of associated gene knockouts. Although experimental validation is still lacking, there is support in the literature for some of the proposed candidate strategies.

This work establishes a proof-of-concept showing that it is possible to generate pre-optimized platform strains for enhanced production of different metabolites derived from the same metabolic pathways. Furthermore, we foresee that this model-driven modular design concept may constitute an important step towards realizing the full potential for economical and sustainable production of other families of industrially relevant chemicals.