Computational analysis and synthesis of biochemical networks for sustainable processes

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The engineering of cells for the sustainable production of fuels and chemicals involves the identification of new routes for the production of industrial chemicals and the development of industrial biocatalysts that achieve simultaneously multiple objectives, such as specific productivity, extended substrate range and improved tolerance – all under a great degree of uncertainty. The achievement of these objectives under physiological and process constraints will be impossible without the use of mathematical modeling. However, the limited information and the uncertainty in the available information require new methods for modeling and simulation that will characterize the uncertainty and will quantify, in a statistical sense, the expectations of success of alternative metabolic engineering strategies. We discuss these considerations around the development of BNICE and ORACLE, two frameworks for the design and optimization of complex cellular systems.

BNICE is a computational framework for the discovery and the rational design of novel biosynthetic pathways for the production of industrial, man-made chemicals. The framework is based on computational methodologies developed in the area of chemical reaction engineering. Given a set of enzyme reaction rules and a set of starting chemicals, BNICE is able to identify every possible pathway to chemicals that can be produced by the application of the enzyme chemistry. The identified pathways are next evaluated with respect to their energetic feasibility. The final output of the framework is a set of novel, candidate routes for enzyme-based synthesis of chemical compounds that can be further evaluated by the biochemistry and organic chemistry experts. This approach will accelerate discovery, assist in evaluating new processes, identify competitive alternatives to existing processes, and provide guidance to the experts.

ORACLE addresses the problem of choosing targets for improving the performance of industrial biocatalysts. This is a very difficult problem due to the complex reaction networks that determine the performance of an organism and the incomplete information about these networks. Borrowing concepts and methods from risk analysis and decision-making under uncertainty, we are developing decision-making methods tailored to biochemical reaction networks. Moreover, ORACLE formulates the problem of optimizing industrial biocatalysts as a multiobjective optimization problem, and it considers the simultaneous optimization of multiple metabolic engineering objectives such as specific productivity, product selectivity, and biocatalyst tolerance to inhibitory medium components.

We will demonstrate the use of BNICE for the discovery of novel biochemical pathways for the synthesis of the industrial chemical 3-hydroxy-propionic acid, and we will show how ORACLE can be used for the identification of metabolic engineering targets for the production of ethanol from lignocellulosic biomass hydrolysates.