Predicting Novel Biosynthetic Pathways with Generalized Enzymatic Reaction Rules

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Project Goals: Curate a set of generalized enzymatic reaction rules that can predict the entire space of possible metabolic reactions, and create a cheminformatics framework to predict novel biosynthetic pathways leading to bioproduction of valuable molecules

Enzyme promiscuity, where enzymes may catalyze a range of side reactions in addition to its main reaction, is a widely recognized yet still largely unexplored phenomenon in biological systems. This could open up vast possibilities for bioproduction of valuable chemicals, where novel biosynthetic pathways leading to molecules of interest can be constructed based on enzymes with desired promiscuous reactions. In order to design these biosynthetic pathways, we curated a set of generalized enzymatic reaction rules capable of describing most enzymatic transformations, which can be applied in the Biochemical Network Integrated Computational Explorer (BNICE) platform to predict the entire space of possible metabolic reactions. We have created a minimum number of these rules verified to 1) comprehensively cover known reactions across metabolic databases, 2) describe reactions with the maximum level of promiscuity, and 3) represent unique enzymatic transformations. Based on these rules, a cheminformatics workflow is developed to efficiently predict and prune novel biosynthetic pathways towards molecules of interest, and systematically identify the most promising ones for experimental validation. By leveraging the entire knowledge of possible metabolic reactions through enzymatic reaction rules, we are able to accelerate novel pathway design and enable bioproduction towards a wide range of new molecules.

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