DESIGN OF NOVEL ENZYMED-CATALYZED REACTIONS LINKED TO PROTEIN SEQUENCES FOR FINDING ENZYME ENGINEERING TARGETS

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A key challenge in metabolic engineering is to find and to improve biosynthetic pathways that lead to the cellular production of a given industrial, pharmaceutical or specialty chemical compound. In many cases, the enzymatic reactions required for bio-production have not been observed in nature and need to be designed from scratch. Computational approaches are essential to predict possible novel biotransformation and to find enzymes that can potentially catalyze the proposed reactions.

In this work, we present two computational tools, BNICE.ch and BridgIT, and we demonstrate their concerted action to (i) predict hypothetical biotransformations and (ii) to link these novel reactions with well characterized enzymatic reactions and their associated genes. BNICE.ch reconstructs known reactions and generates novel reactions by applying its integrated, expert curated, generalized enzyme reaction rules on known metabolites. In order to find enzymes that potentially catalyze the biotransformation of these novel reactions, we assume that molecules with a similar reactive site and a similar atomic structure around the reactive site may be recognized and transformed by the same enzyme. Hence, BridgIT compares every predicted novel reaction to all known enzymatic reactions for which a protein sequence is available. Novel and known reactions are compared based on the reactive site of the substrates, the atoms surrounding the reactive site, and the breakage and formation of atomic bonds during the conversion of the substrate to the product. As a result, BridgIT reports a similarity score for each comparison of known reactions to novel reactions, thus giving an estimate of how possible it is that a given enzyme can catalyze a novel reaction.

The results are organized in a database of known and hypothetical reactions called the “ATLAS of Biochemistry”[1], where every hypothetical reaction is associated with its structurally most similar known enzymatic reactions, thus suggesting a plausible Gene-Protein-Reaction (GPR) association that can be used as a starting point for enzyme engineering. Our database currently spans more than 130’000 biochemically possible reactions between known metabolites from the Kyoto Encyclopedia of Genes and Genomes (KEGG). The ATLAS database and the BridgIT online tool are available on the web (http://lcsb-databases.epfl.ch/) and they can be used to extract potential reactions and pathways and to identify enzyme targets for metabolic and enzymatic engineering purposes.

[1]Hadadi, N., Hafner, J., Shajkofci, A., Zisaki, A., & Hatzimanikatis, V. (2016). ATLAS of Biochemistry: A repository of all possible biochemical reactions for synthetic biology and metabolic engineering studies. ACS Synthetic Biology, 2016.