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Applications Note

Systems biology

BioSynther: a customized biosynthetic potential explorer

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Abstract

Motivation: One of the most promising applications of biosynthetic methods is to produce chemical products of high value from the ready-made chemicals. To explore the biosynthetic potentials of a chemical as a synthesis precursor, biosynthetic databases and related chemoinformatics tools are urgently needed. In the present work, a web-based tool, BioSynther, is developed to explore the biosynthetic potentials of precursor chemicals using BKM-react, Rhea, and more than 50 000 in-house RxnFinder reactions manually curated. BioSynther allows researchers to explore biosynthetic potentials, through so far known biochemical reactions, step by step interactively, which could be used as a useful tool in metabolic engineering and synthetic biology.

Availability and implementation: BioSynther is available at: http://www.lifemodules.org/BioSynther/.

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Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

Biosynthesis has important applications in producing bulk chemicals (Hermann *et al.*, 2007; Shin *et al.*, 2013), biofuels (Atsumi *et al.*, 2008; Lee *et al.*, 2008) or natural products (Paddon *et al.*, 2013). There are some biosynthesis informatics tools (Copeland *et al.*, 2012; MacDonald *et al.*, 2011; Medema *et al.*, 2012; Mienda and Shamsir, 2015; Moura *et al.*, 2013), such as BNICE (Hatzimanikatis *et al.*, 2005), RetroPath (Carbonell *et al.*, 2011), DESHARKY (Rodrigo *et al.*, 2008) and FMM (Chou *et al.*, 2009), to design biosynthesis pathways from a start molecule to a target molecule.

In industrial biotechnology applications, researchers usually plan to get value-added chemicals from the ready-made molecules. That is, how to automatically explore the biosynthetic potentials of simple chemical precursors? In the present work, BioSynther is developed to assist researchers to get comprehensive biosynthesis target molecules based on the BKM-React reactions (Lang *et al.*, 2011), Rhea reactions (Alcantara *et al.*, 2012) and in-house RxnFinder (Hu *et al.*, 2011) reactions (www.rxnfinder.org).

2 Methods

Data: The reaction data used in BioSynther is BKM-React (Lang *et al.*, 2011), Rhea (Alcantara *et al.*, 2012) and in-house RxnFinder Reactions. BioSynther contains all BKM-react reactions which integrated Brenda, KEGG and MetaCyc reactions. However, the structure information is not provided in BKM-react, so we have downloaded from Brenda, KEGG, MetaCyc websites respectively and converted or generated structure information into smiles format (Weininger, 1988). That is, BioSynther contains 11 860 Brenda reactions, 9121 KEGG Reactions, 13 416 MetaCyc reactions. We removed 8005 Rhea master reactions (Alcantara *et al.*, 2012) from 32 020 Rhea reactions, so BioSynther contains 24 015 rhea reactions. What's more, BioSynther contains more than 50 000 in-house RxnFinder reactions manually

curated from 120 000 scientific publications related to biosynthesis and metabolism. We apply PubChem Compound database to unify compound synonyms.

Algorithms: In our research, we need search reaction pathways in a reaction network. The pathway search algorithm is a customized version of Dijkstra's algorithm implemented in C++, which was compiled to a dynamic library to be called by BioSynther web server.

In BioSynther, user-customized pathway search engines are implemented by removing some nodes and/or edges to find the biosynthesis pathways so that researchers can explore step by step interactively.

Visualization: JavaScript library D3.js (http://d3js.org) is used for manipulating web documents based on search data. Software package RDKit (http://www.rdkit.org) is implemented in our web-based chemical structure display system using chemical name or smiles.

3 Results

In BioSynther, there are three different kinds of display view options to explore biosynthetic potentials interactively. For example, after users input a starting molecule, vanillin, three different view options (that is, tree, circle or plain page) are available. Figure 1A displays the biosynthetic potentials of vanillin, in which each node or edge is clickable. When the computer mouse moves on a node, the related chemical structure is shown on the computer screen. Each edge represents a biosynthetic reaction converting the starting molecule to a target molecule.

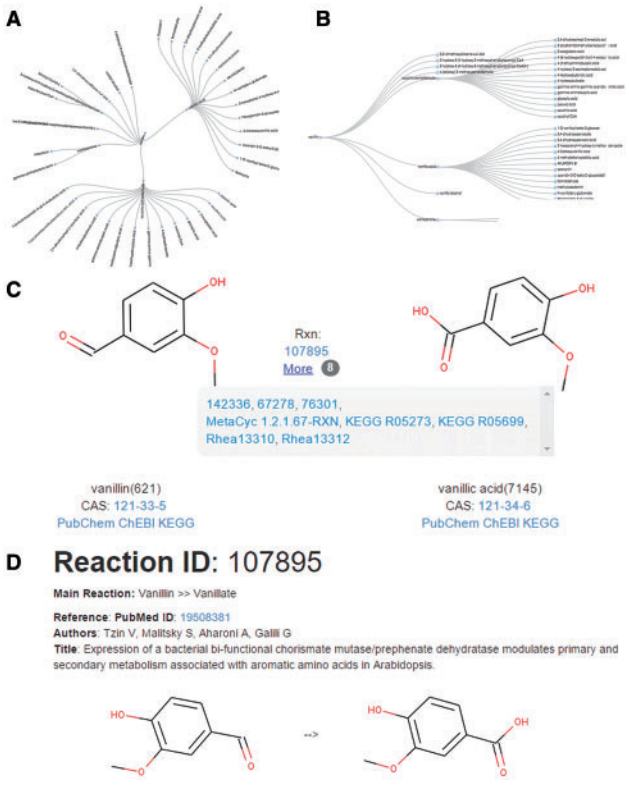

Fig. 1. Biosynthesis potentials of a starting molecule. (**A**) Circle view for molecule 'vanillin' in two steps; (**B**) Tree view for 'vanillin'. (**C**) One reaction example from the vanillin possibilities. (**D**) Reference information of the example reaction

When an edge is clicked, the biosynthetic reactions of this edge are displayed with its original references.

In another view option such as Tree view, after users input 'vanillin' as a biosynthesis precursor, eight possible chemicals in one reaction step is retrieved. Each tree node is clickable to explore its biosynthetic potentials according to researcher's interest interactively.

In order to explore the biosynthetic potentials of precursor chemicals, a novel web-based tool, BioSynther, is developed using BKM-react, Rhea, and in-house RxnFinder reactions. BioSynther applies an interactive interface for researchers to explore biosynthetic potentials step by step. BioSynther could be used as a useful tool in metabolic engineering.

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