PENNSTATE

Technology Available for Licensing
Office of Technology Management - The Pennsylvania State University
113 Technology Center, University Park, PA 16802
814.865.6277 phone; 814.865.3591 fax

Non-Confidential Description - PSU No. 4127
"*OptZyme*: Computational Enzyme Redesign Using Transition State Analogues"

Keywords/Field of Invention:

Computational Design, *In silico*, protein engineering, molecular mechanics, interaction energy

Inventors:

Costas Maranas, *et al.*

Background

Enzymes are highly-specific, biomolecular catalysts that enhance the economical production of numerous industrial bioproducts such as biofuels and therapeutics. In recent years, computational tools utilizing primary, secondary, and/or tertiary protein structural information have been tested to discover promising enzyme redesigns. As the degree of complexity increases, accuracy improvements occur often at the expense of greater computational time. Consequently, the computational design of enzymes remains a formidable as task with only isolated commercial successes.

Invention Description

The invention represents a novel computation method to discover promising enzyme redesigns that can be experimentally tested. Unlike competing, computationally intense techniques, this method does not necessitate complete quantum mechanics analysis. Rather, the invention's software utilizes known transition state analogue (TSA) compounds/structures, as proxies for the typically unknown rate-limiting transition state (TS) structures. TSAs manage to interfere with the enzyme catalytic activity by mimicking the geometry of the TS and preferentially binding with the enzyme over the substrate, thus preventing the reaction from proceeding. The inventors have shown that mutations that minimize the interaction energy (IE) of the enzyme with its TSA, rather than with its substrate, allows for the identification of lower transition state formation energy barrier. Although the TS structure of the limiting reaction step is often unavailable, TSAs of the reaction are frequently known. TSAs mimic the structural and partial charge environment of the TS. This invention, OptZyme, identified three libraries of mutants that were computationally predicted to enhance enzyme catalytic parameters relative to the wild type control. The observed mutants seemed to lower the relevant IE predominantly through improving flexibility in the active site, increasing solvation stabilization, or improving the electrostatic IE (including hydrogen bonding). Using this computational method to improve the binding affinity of a TSA, the inventors identified E. coli enzymatic mutants with improved K_M, K_{cat}, and K_{cat}/K_M for a new substrate. The inventors demonstrated that Optzyme is sensitive enough to detect even minor structural variances between substrates.

Commercial Applications

The invention has the potential to become a (in)valuable tool in the design of new commercial enzymes, providing a strong starting point before using experimental approaches such as directed evolution. OptZyme is bested suited for systems where the solute entropy change upon binding is assumed to be negligible relative to other terms, substrate binding is not a consequence of "induced fit", and equilibrium following the rate-limiting step strongly favors product release. OptZyme allows for the construction of a library of mutants with improved enzyme catalytic parameters for a similar substrate by identifying novel contacts with the ligand that were absent from other established libraries.

A prototype demonstration of OptZyme can be accessed at http://maranas.che.psu.edu/submission/OptZyme.htm.

Contact: **Matthew D. Smith**
Sr. Technology Licensing Officer
The Pennsylvania State University

Phone: (814) 865-6277
Direct: (814) 863-1122
E-mail: mds126@psu.edu