The Evolution of Enzyme Function.


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Introduction

With sequenced genomes, the full complement of enzymes in an organism can be defined. To help assign accurate functions to these new sequences, we need to understand how enzyme families evolve functional diversity.

Objective

To map how enzymes evolve new functions.

Materials & Methods

We developed two new software tools to explore the evolution of enzyme function. EC-BLAST performs quantitative similarity searches between enzyme reactions. FunTree integrates a wide range of data to unravel the evolution of novel enzyme functions. We have applied these methods to analyse a large number of families comprising very diverse relatives.

Discussion and Results

Clustering the universe of biochemical reactions - We derived a network of the 5,073 representative reactions, connected according to the similarity of their reactions. Most clusters contain enzymes with the same primary EC number, but a few (~7.6%) contain a mixture of reactions from different primary classes, highlighting cases of shared chemistry between these enzymes.

The chemistry and classification of the isomerases - As a test case, we have explored the ability of EC-BLAST to capture the overall chemistry of the isomerases (EC 5) and to reproduce their EC classification. Our results revealed that isomerase reactions are chemically diverse and difficult to classify automatically from first principles.

Evolution in 276 enzyme families - An analysis of 276 enzyme superfamilies revealed that almost all enzyme families perform multiple reactions. Most changes of function relate to substrate changes, whilst maintaining the enzyme chemistry. The molecular mechanisms involved in changing function include sequence variations, indels and domain composition changes. Although the catalytic residues are the most conserved of all residues, they do change both their type and position along the sequence in most families.

Conclusions
Our study highlights the complexity of enzymatic catalysis and the need for well-structured, accurate databases of enzyme reactions. There is no simple relationship between changes in enzyme function and sequence during evolution.