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Current Opinion in Structural Biology

Understanding enzyme function evolution from a computational perspective

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In this review, we will explore recent computational approaches to understand enzyme evolution from the perspective of protein structure, dynamics and promiscuity. We will present quantitative methods to measure the size of evolutionary steps within a structural domain, allowing the correlation between change in substrate and domain structure to be assessed, and giving insights into the evolvability of different domains in terms of the number, types and sizes of evolutionary steps observed. These approaches will help to understand the evolution of new catalytic and non-catalytic functionality in response to environmental demands, showing potential to guide *de novo*enzyme design and directed evolution experiments.

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Current Opinion in Structural Biology 2017, **47**:131–139

This review comes from a themed issue on **Catalysis and regulation**

Edited by **Christine Orengo** and **Janet Thornton**

http://dx.doi.org/10.1016/j.sbi.2017.08.003

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Introduction

Enzymes are the product of billions of years of evolution giving us molecular machines that are critical for life. Across the vast space of protein structure, evolution has settled upon a limited number of structural folds that support an incredibly diverse chemistry acting on a multitude of substrates. Enzymes have evolved substrate and function specificity to improve the organism's overall fitness in response to environmental demands, but enzymes can have multiple substrates and functions, contradicting the traditional view of one enzyme one reaction and the high specificity implied in the lock and key and induced-fit paradigms. Furthermore, it is advantageous for organisms to be able to adapt quickly to a changing environment which manifests itself at the molecular level in the inherent promiscuity present in many enzymes.

Exploiting enzyme promiscuity to develop novel functionality has been the focus of much recent research effort, where directed evolution techniques can improve the catalytic performance of even very weakly active starting points to become commercially relevant enzymes. In this review, we discuss the biochemical role of enzymes in terms of specificity and functionality, and then focus on recent developments in the application of structural bioinformatics methods to understand the evolution of specificity and guide *de novo* enzyme design.

Functional changes in enzyme evolution

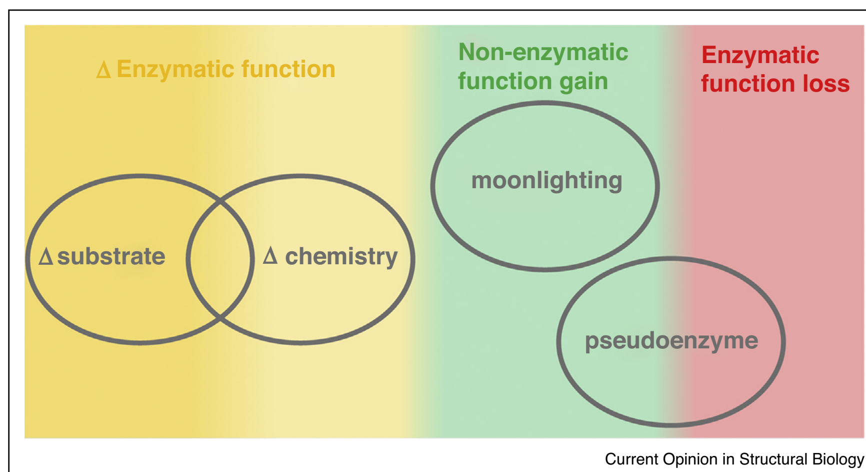
Evolution is a random generator of possible improvements in the face of the environmental challenges an organism experiences, where survival of the fittest ensures the retention of successful solutions into future generations. Evolution is powerful and has produced enzymes with varying degrees of substrate and function specificity where beneficial to the organism. Figure 1 shows the various types of functional changes observed in enzyme evolution, where more common changes in chemistry and substrates are supplemented with rarer gain or loss of function in the form of moonlighting and pseudo-enzymes respectively. These rarer functional changes will be considered briefly first, before the discussion moves to the more common evolutionary pathways.

Gain and loss of enzyme function: moonlighting and pseudo-enzymes

The acquisition of new functionality within an enzyme family as a result of gene duplication and mutation is commonly observed, see [1•] for some selected examples, but some enzymes can exhibit secondary, markedly different non-enzymatic functionality, when an enzyme with exactly the same chemical structure can moonlight to perform different roles in different cell compartments or environments [2,3]. These moonlighting enzymes, although rare, are being increasingly documented, where secondary function may be controlled by the varying ligand concentrations, by local phosphorylation levels and their different homo/hetero oligomeric states.

The additional functionality from moonlighting enzymes usually arises from a different site in the same structure and is distinct from gene fusions, multiple RNA splice variants or pleiotropic effects (where one gene influences two or more seemingly unrelated phenotypic traits), which can all affect enzyme catalysis. The evolution of secondary functional sites on an enzyme and the

Figure 1



Different types of functional changes in enzymes.

regulation of expression are active research questions [4] and demonstrate that multi-functional proteins are a design possibility, opening up opportunities for multi-functional polypeptide drugs and synthetic pathways. Researchers are becoming increasingly aware of the contribution of moonlighting enzymes but it is challenging to identify moonlighting functionality with bioinformatics methods [5] where small changes in structure or context can have dramatic effects on functionality [6]. Most discoveries of moonlighting occur from observation and serendipity and a database of moonlighting enzymes with approaching 300 entries has recently been curated from the literature [7], where one example is alpha-crystallin, the structural protein in the lens of the eye, that also has lactate dehydrogenase and argininosuccinate lyase activity.

Pseudo-enzymes are proteins that closely resemble an active enzyme, but at some point have lost their catalytic functionality and are retained in a genome for the beneficial new functionality that they have acquired [8], such as roles in regulatory and signaling pathways. Pseudo-enzymes are considered in more detail elsewhere in this edition, and the discussion here will move on to on the evolution of different functionality from the same binding pocket giving changes in substrate specificity and chemistry.

Different types of enzyme substrate specificity

Enzymes are able to give many orders of magnitude speed-up in essential reactions such as respiration, digestion and photosynthesis by stabilising transition states, thereby reducing activation energies and enabling reactions to proceed on timescales that can support life [9]. At a fundamental level, catalytic residues must be positioned around substrates in the correct orientations to stabilise transition states [10]. However, the specificity of the binding event between enzyme and substrate can vary depending on the extent to which the pocket has been optimised over evolutionary time [11]. An enzyme only needs to offer selectivity over detrimental side-reactions on potential substrates it is likely to encounter in its expressed location, where it becomes beneficial for evolution to deliver greater specificity. Indeed, some enzymes have evolved group or bond specificity such as those acting on some proteins and carbohydrates (see Figure 2 for trypsin and amylase examples), a more efficient solution then having to evolve a set of highly specific enzymes for every occurrence of each bond or group.

Enzyme specificity, defined according to the range of substrates and their similarity either for an individual enzyme or family of enzymes, exists on a continuum between highly specific and highly unspecific (promiscuous), demonstrating the concept that enzymes only evolve specificity when it is advantageous for the organism. It is challenging to define mutually exclusive categories to characterise the varied specificity observed, but despite this four categories of enzyme specificity have emerged [12]:

a) high specificity (an enzyme catalyzes one reaction at one site in one substrate to produce one product)
b) group specificity (an enzyme acts on a specific group (i. e. a given bond (cleaving or ligating) in a defined and restricted molecular environment))
c) bond specificity (an enzyme acts on a specific bond regardless of molecular environment)
d) low specificity (an enzyme can act at multiple sites in multiple substrates where site of reaction is influenced but not dictated by reactivity and accessibility considerations).

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