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Type	Oral communication
Session	Structural Bioinformatics
Title	New computational insights on enzyme stability-activity trade-off
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Motivation

Enzymes play a fundamental role in a wide range of biotechnological processes such as the transformation of biomass into biofuels, in biopharmaceutical processes such as drug manufacturing and also in clinics where they are used for diagnosing a wide range of diseases. Many efforts have been devoted in the last decades to better understand enzyme stability and activity with the aim of improving enzyme design and optimization. However, the complex interplay between these two key enzymatic properties is still far from being elucidated. Indeed, while we know that there is a stability-activity trade-off that leads to catalytic regions that are not optimized for stability, it is not yet quantitatively clear how this trade-off is tuned in catalytic sites, their periphery or in the rest of the enzyme. The picture is further complicated by the fact that environmental conditions shape such complex interplay. For example, enzymes from organisms that live in cold environments need to be accurately tuned in terms of stability to maintain their activity at low temperature conditions.

Methods

We first created a well curated dataset of 551 enzymes with known 3D X-ray crystallographic structure with a resolution of at most 2.5˚A and with a maximum sequence identity of 25%. We collected the annotations from the Catalytic Site Atlas to determine the catalytic residues of the 551 enzymes. For each residue i in the dataset we computed:
(1) The per-residue folding free energy ΔGi, i.e. the contribution of the given residue i to the overall enzyme stability. We computed four different types of per-residue folding free energy contributions using our in-house method SWOTein to which we refer for further details.
(2) The distance between the residue i and the closest catalytic residue, measured as the distance between their closest atoms.
Positive values of the per-residue folding free energy ΔGi indicate that the residue is a stability weakness, which means it is not optimized in terms of stability. The term ”frustrated residues” has also been used by others in the literature to describe these types of residues. Conversely, residues with a negative ΔGi value indicate that they are a stability strength, and therefore contribute significantly to the global protein stability.

Results

The main results of this investigation are the following :
(1) Catalytic regions are energetically characterized by stability compensations. For all enzymes we observe that catalytic residues are generally stability weaknesses. On the other hand, the first shell of neighboring residues are stability strengths or at least less weak. In the second shell the residues are again stability weaknesses. This behavior is well illustrated in the figure in which we plot the per-residue folding free energy as a function of the residue distance from the closest catalytic site, averaged over all enzymes in our dataset. We carefully checked that this trend is independent on the solvent accessibility of the residues and from the EC class of the enzymes.
(2) Stability strength and weakness as environmental adaptation mechanisms. We repeated the analysis focusing only on enzymes belonging to psycrophilic and thermophilic organisms. We found that psycrophilic enzymes have catalytic sites as well as 3D structures that are weaker in terms of stability than thermophilic ones. The increased amount of stability weaknesses in psycrophilic enzymes can be seen as environmental adaptation mechanism to low temperature conditions.
(3) Hints for enzyme design. Taking as an example the phosphatase and tensin homolog (PTEN) enzyme and using available experimental fitness data, we identified some common characteristics of mutations that improve the fitness. For example, these mutations are inserted in regions that are not conserved, that are stability weaknesses, that are far from the active site and are usually exposed to the solvent.

Info

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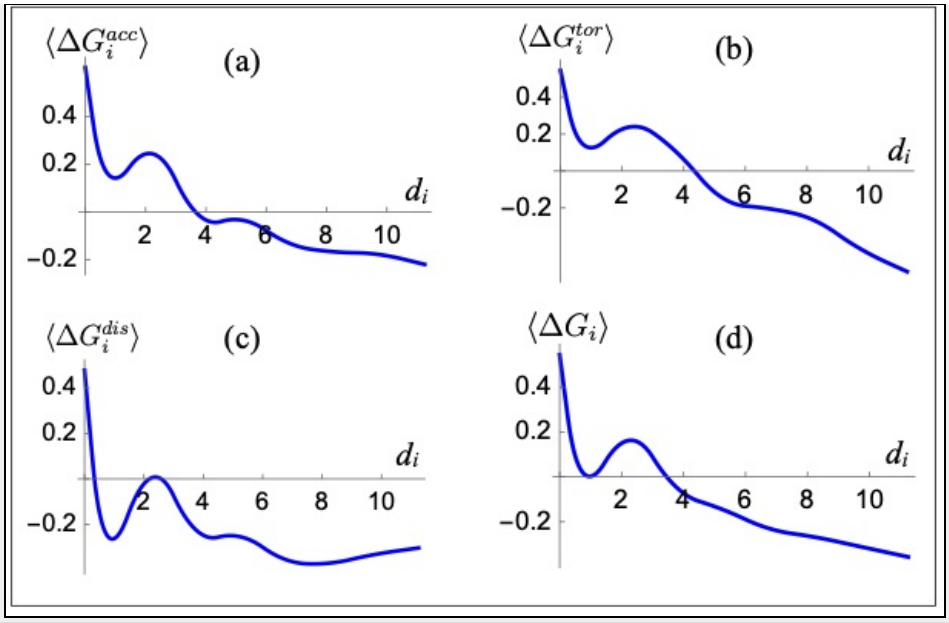
Figure



Availability	-

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