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Stronger, tighter and faster: designing improved protein functions

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PURPOSE OF THE ABSTRACT

The evolution of altered or improved function is constrained by stability-function tradeoffs, whereby mutations accumulated along an evolutionary trajectory increasingly reduce stability and functional expression. A further constraint is the epistatic relationships among the spatially close positions that make up an active site. To address these problems, we have developed a methodology that combines phylogenetic information and Rosetta atomistic simulations to stabilize proteins and to improve their function.

PROSS method stabilizes enzymes and other proteins without altering their functions. It was applied to several 'tough-nut' cases, resulting in improvement in bacterial expression and substantial increases in thermal resistance.

FuncLib method introduces combinations of mutations in the active site without impacting the core catalytic residues. Testing as few as several dozens of mutants can yield variants with various activity profiles, simultaneously increasing activity on several substrates. FuncLib designs epistatic active-site mutations that are likely to be inaccessible by natural and laboratory evolution, and opens the way to design highly efficient and diverse catalytic repertoires. In addition, our new method, HT-FuncLib (high throughput FuncLib) relies on machine learning and allows to sample large sequence spaces in an efficient way,

Our design algorithms are currently available as webserver and are being extensively used. The methods are fully automated, requiring only a structure or a model and a sequence alignment of homologues, and they can be applied to proteins, whether or not they are amenable to high-throughput screening.

I will describe several recent cases of protein stabilization and improvement of function, which were achieved using PROSS and FuncLib methods.

FIGURES

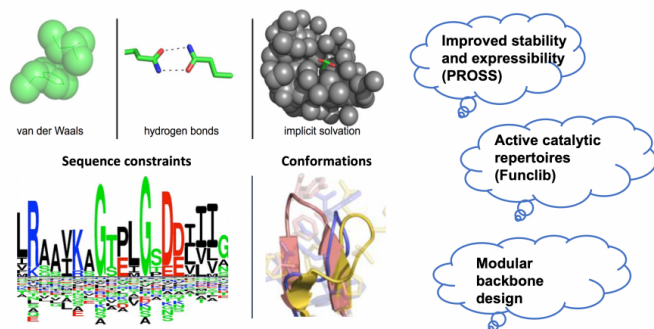


FIGURE 1

Computational design strategy

Our computational methods rely on the combination of phylogenetic data and native protein conformations with explicit energy calculations by Rosetta

FIGURE 2

KEYWORDS

protein stability | atomistic calculations | function design | phylogenetic information

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