DINUCLEOTIDE BINDING ROSSMANN DOMAIN: ANALYSIS AND DESIGN

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Introduction. Proteins involve a notable structure-function relationship at the molecular level, which is coded in their single chain of aminoacid residues. The identification of critical residues for the proper fold and function of a protein domain is an approach for the subsequent protein design with desired capabilities.
We used Statistical Coupling Analysis (SCA) [(1)] to identify coevolving residues in the Rossmann domain of the *Escherichia coli* shikimate dehydrogenase (AroE) and then used this information to recreate the Rossmann domain in fold and function (binding of NADP dinucleotide) with a very different peptide sequence.

Methods. Blast search for the AroE Rossmann domain homologs were retrieved and aligned. This alignment was filtered to reduce redundancy at 80% as maximum. The alignment was submitted to Statistical Coupling Analysis and the information generated was used to design a Rossmann domain keeping coupled and conserved residues using Rosetta[(2)] with the original coordinates of AroE Rossmann domain as template. We designed the inverse case (antiSCA) sequence and also a random Rossmann sequence using the same template. After all, Molecular dynamics[(3)] of designs binding NADP were made with the three desings and the wild type AroE Rossmann domain.

Results. The identified coupled residues tend to group around the NADP binding pocket.
The antiSCA RMSD spectrum is the least similar to the wild type than any other; it is even more different than the Random design. This is in agreement with the results for WW domains[(3)]. However, the random design seems to lose the NADP binding during dynamics (data not shown).

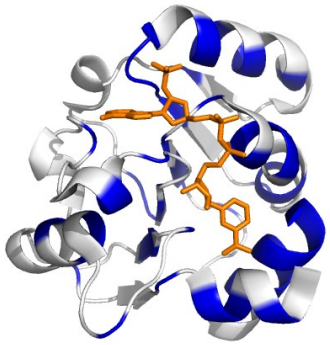

Fig.1 AroE Rossmann domain. The residues identified as coupled by SCA are colored blue. NADP is in sticks representation and colored orange.

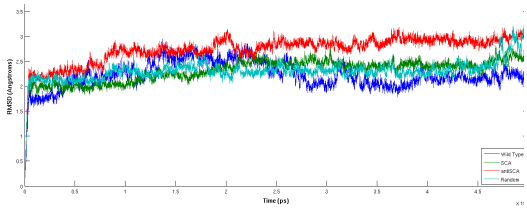

Fig. 2 Molecular dynamics. Different designs were used to compare to the original AroE Rossmann domain.

Conclusions. All these results highlight the sensitiveness of the SCA algorithm to detect the most important residues necessary to maintain the essential fold, movement and function of the AroE Rossmann domain.

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