Evolutionary Design of Proteins

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Proteins can fold spontaneously into well-defined three-dimensional structures and can carry out complex biochemical reactions such as molecular recognition, catalysis, and allosteric communication. The precision required for these properties is somehow achieved while also preserving evolvability – the capacity for adaptive variation in response to ever-changing selection pressures. How are proteins built in Nature to support all of these properties? To address this question, we have taken a statistical genomics approach – deducing the pattern of constraints on amino acid residues in proteins through analysis of amino acid coevolution a protein family[1,2,14]. This approach reveals a novel decomposition of proteins into sparse groups of co-evolving amino acids termed "protein sectors"[9]. The sectors comprise physically connected networks in the tertiary structure that often connect functional surfaces and can be modular – with different sectors in a single protein delivering different functional properties. Experiments demonstrate the connection of sectors to protein function[1-2,5-11] and importantly, this pattern was shown to be necessary and sufficient to design functional artificial proteins without the use of any direct structural or chemical information[3,4]. These results suggest that sectors are the conserved units of folding, function, and adaptability in natural proteins. We are now working on two key problems: (1) understanding the physics of sectors[12], and (2) defining how the dynamics of the evolutionary process controls the emergence of this structural architecture in proteins[11].

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