

Abstract Submitted
for the MAR11 Meeting of
The American Physical Society

Deciphering evolutionary instructions for specifying protein fold and function WALRAJ GOSAL, RAMA RANGANATHAN, UT Southwestern Medical Center — Classical studies show that proteins have evolved to fold into functional native states that are, at best, only marginally stable through weak non-covalent interactions encoded by their primary sequences. How such fold and functional information is stored in a single amino acid sequence remains elusive. Using the statistical analysis of covariation between pairs of amino acids at all positions in a protein, here we identify groups of a few key physically-interconnected residues, which we term sectors. What information about the fold and function is captured by sectors? Using simulated-annealing Monte Carlo, we introduce variation in the sequence of a single member of the PDZ family in a manner that either preserves or disrupts sector correlations. Experimentally we show that function is specifically retained in designed proteins that obey sector correlations, and strikingly, even in the absence of a native state. Thus, we suggest that native-state stability is not a fundamental requirement for function, and is encoded in the sequence in an idiosyncratic manner in the PDZ family.

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Date submitted: 19 Nov 2010

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