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Is the Protein Folding Problem Solvable? The Structure of Tetrameric Impase from *T. Maritima* Shows Unusual Protein Plasticity. Boguslaw Stec¹, Kimberly A. Stieglitz², Mary F. Roberts, ¹ The Burnham Inst. for Medical Research, La Jolla CA 92307, ²Dept. of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill MA 02467.

The thermodynamic hypothesis of protein folding has become an important paradigm of modern biology. Substantial progress was made towards understanding the main factors influencing folding. However, recent developments question the general validity of this hypothesis. We will review the experimental and theoretical work aimed at defining the relation of the protein sequence to the protein structure. We also present an interesting example that questions the uniqueness of solution of this problem. In this work we present a structure of the first tetrameric inositol monophosphatase (IMPase) from *Thermotoga maritima*. The structure provides insights into evolutionary specialization of function and emergence of allosteric regulation by transition from dimeric IMPase fold to tetrameric FBPase fold. The tetrameric structure of this unregulated enzyme is similar in its quaternary assembly to the allosterically regulated tetramer of fructose 1,6 bisphosphatases (FBPase), while individual dimers are similar to human IMPase. It also offers a more detailed view into the protein folding problem by focusing on a fragment of the protein found in two seemingly opposing secondary structure arrangements. In the first crystal form the tetramer is symmetric, while in the second form it is asymmetric. In the asymmetric form the active site loop, adopts the β -structure in the upper dimer, while it takes on an α -helical conformation in the lower dimer.