Proteins are the macromolecules that mediate most of the processes that occur in living cells. In order to function properly, after being synthesized, they must reach a well-defined average structure, known as the native state, which is quite specific for each protein. According to Anfinsen’s thermodynamic hypothesis [1], protein folding is an equilibrium process and the native state of a protein is uniquely defined by its amino acid sequence. However, in spite of more than four decades of study, the protein folding problem, i.e., the problem of determining the protein structure from its amino acid sequence alone, remains unsolved. In the first part of the lecture, results will be presented that suggest that one main reason for this lack of success is that each protein can assume many, very different structures that are as thermodynamically stable as the native state, as first proposed by Levinthal [2]. Indeed, following Levinthal, it has been suggested [3, 4] that protein folding is a non-equilibrium, kinetic process in which the initial structure for all proteins is helical, as shown in the left panel of figure 1.

In the second part of the lecture, the idea that the initial structure of all proteins is helical is applied to the folding of PDB2HEP [5], a small protein with just 42 amino acids whose native structure is constituted by two α-helices joined by a loop, as seen in the right panel of figure 1. Molecular dynamics (MD) simulations will be presented, in which the initial structure of the protein is the helix in the left panel of figure 1. The aim of these MD simulations is to fold this protein. The ultimate aim of these investigations is to solve the protein folding problem by determining the conditions under which the native state of all proteins can be obtained, in a reproducible manner, from such an initial condition.

Keywords: Protein Folding, VES hypothesis, Molecular Dynamics

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