The folding of a small protein

Leonor Cruzeiro
Depto. Física, Faculdade de Ciências e Tecnologia
Universidade do Algarve, Campus de Gambelas, 8005-139 Faro, (Portugal)
email: lhansson@ualg.pt
URL: http://w3.ualg.pt/lhansson

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.

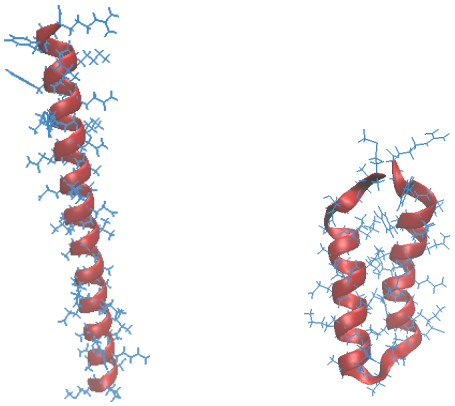

FIGURE 1. This figure shows the *same* protein in two conformations. The left panel shows the protein in a full α-helix conformation, assumed to be the structure the protein has immediately after synthesis, and the right panel shows the native state of the protein, obtained by solution nuclear magnetic resonance (NMR) methods [**5**].

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

Acknowledgements

This work received national funds from FCT - Foundation for Science and Technology, Portugal, through the project UID/Multi/04326/2013. The Laboratory for Advanced Computing at University of Coimbra is also acknowledged for HPC computing resources.

References

[1] C.B. Anfinsen. Principles that govern the folding of protein chains. *Science* 181:223–230, 1973.

[2] C. Levinthal. Are there pathways for protein folding? *J. Chim. Phys.* 65:44–45, 1968.

[3] L. Cruzeiro. Protein Folding. *Chemical Modelling: Applications and Theory*, Royal Society of Chemistry, London, volume 7, pp.89-114, 2010.

[4] L. Cruzeiro. A kinetic mechanism for in vivo protein folding. *Bio-Algorithms and Med-Systems* 10:117-127, 2014.

[5] J.M. Aramini *et al.* Solution NMR structure of the SOS response protein YnzC from Bacillus subtilis. *Proteins* 72:526–530, 2008.