Journal of Proteomics and Bioinformatics

OPEN ACCESS Freely available online

Commentary

Protein Folding: A Polypeptide Chain Folds to Become a Biologically Active Protein in its Native 3D Structure

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DESCRIPTION

Protein folding is the physical process of translating a protein chain to its native three-dimensional structure, which is often a "folded" conformation that allows the protein to operate biologically. A polypeptide folds into its characteristic three-dimensional structure from a random coil in a quick and repeatable process. After being translated from mRNA to a linear chain of amino acids, each protein exists as an unfolded polypeptide or random coil. The polypeptide has no stable three-dimensional structure at this point. The linear polypeptide chain begins to fold into its three-dimensional form as it is generated by a ribosome.

Many proteins begin folding even as the polypeptide chain is being translated. Amino acids interact with one another to form a well-defined three-dimensional structure called the native state, which is a folded protein. The amino acid sequence, or primary structure, determines the three-dimensional structure that results. Protein dynamics are vital because the right three-dimensional structure is required for function, even though some sections of functioning proteins may remain unfolded. In most cases, proteins that fail to fold into their original structure are inert, however misfolded proteins might have altered or harmful functions. The aggregation of amyloid fibrils created by misfolded proteins, infectious variants of which are known as prions, is thought to cause several neurodegenerative and other disorders. Because the immune system does not develop antibodies for specific protein shapes, many allergies are caused by improper protein folding.

The length of time it takes for a protein to fold varies substantially depending on the protein. Outside of the cell, the slowest folding proteins take many minutes or hours to fold, owing to proline isomerization, and must pass through a number of intermediate states, such as checkpoints, before the process is finished. Very small single-domain proteins with lengths of up to a hundred amino acids, on the other hand, usually fold in a single step. Millisecond time scales are common, with the fastest known protein folding operations taking only a few microseconds to complete. A protein's folding time scale is determined by its size, contact order, and circuit topology. Since the late 1960s, understanding and simulating the protein folding process has been a major issue for computational biology.

Driving forces of protein folding

Folding is a natural process governed primarily by hydrophobic contacts, intramolecular hydrogen bond formation, van der Waals forces, and conformational entropy. Co-translational folding occurs when the N-terminus of a protein begins to fold while the C-terminus of the protein is still being synthesised by the ribosome; however, a protein molecule can fold spontaneously during or after production. While these macromolecules may appear to "fold themselves," the process is influenced by the solvent, salt concentrations, pH, temperature, and the presence of cofactors and molecular chaperones. Because of the limited bending angles or conformations that proteins can take, their folding abilities will be limited. In order for protein folding to be a spontaneous reaction, it must be thermodynamically advantageous within a cell. Protein folding must have a negative Gibbs free energy value since it is a spontaneous reaction. Enthalpy and entropy are directly proportional to Gibbs free energy in protein folding.

A major driving force behind the folding process is reducing the number of hydrophobic side-chains exposed to water. The hydrophobic effect is a phenomenon in which a protein's hydrophobic chains collapse into the protein's centre. Water molecules tend to congregate around the hydrophobic sections or side chains of proteins in an aqueous environment, forming water shells of ordered water molecules. An increase in order in a system due to the ordering of water molecules around a hydrophobic region adds to a negative change in entropy. The hydrophobic collapse, or inward folding of the hydrophobic groups, is caused by the water molecules being locked in these water cages.

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Received: 01-Feb-2022, Manuscript No. JPB-22-16165; **Editor assigned:** 03-Feb-2022, PreQC No. JPB-22-16165 (PQ); **Reviewed:** 17-Feb-2022, QC No. JPB-22-16165; **Revised:** 22-Feb-2022, Manuscript No. JPB-22-16165 (R); **Published:** 02-Mar-2022, DOI: 10.35248/0974-276X.22.15.569

Citation: Galperin M (2022) Protein Folding: A Polypeptide Chain Folds to Become a Biologically Active Protein in its Native 3D Structure. J Proteomics Bioinform.15:569.