3D Structural Bioinformatics of Proteins and Antibodies: State of the Art Perspectives and Challenges

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ABSTRACT

Proteins are an important class of biochemical molecules, as the structural components of animal and human tissue are based on them. Antibodies are proteins that play a crucial role in the preservation of life since they are produced by the body’s immune system as a response to harmful substances. The modelling of proteins and antibodies in particular is a vibrant research field which facilitates the design of drugs, a process otherwise demanding in terms of time and resources. A variety of computational methods and tools are being developed towards that goal, among which are hybrid quantum chemical/molecular mechanical methods and three-dimensional antibody modelling. In this review the authors discuss the knowledge concerning proteins and antibodies, as well as the use of quantum mechanics in the simulation of molecular systems and the three-dimensional antibody modelling.

Keywords: Antibodies, Biochemical Molecules, Proteins, Quantum Mechanics, Three-Dimensional Antibody Modelling

STRUCTURAL ORGANIZATION OF PROTEINS

Proteins are polymers that consist of one or more chains of amino acids, which are linked with peptide bonds. Proteins are the basis of living organisms since they perform a huge range of functions, such as catalyzing metabolic reactions and replicating DNA. When placed in the appropriate conditions, proteins can be prompted to form crystals, which means that individual protein molecules arrange themselves in an ordered pattern extending in all three spatial dimensions.

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The backbone or main chain of a protein is the linked series of the carbon, nitrogen, and oxygen atoms of the amino acids that participate in the protein’s peptide bonds. The conformation of the backbone can be described by the torsion angles around the Ca-N bond (φ) and the Ca-C bond (ψ) of each residue (Branden & Tooze, 1991; Chothia & Finkelstein, 1990).

The primary structure of a protein is the linear sequence of the amino acids of its backbone, as well as the cross-linking atoms, if they exist. The secondary structure of a protein refers to the way the backbone atoms of a protein are arranged spatially, without regard to the residues of its side chains. The geometric shape of the secondary structural elements and the side chains of a protein take after the protein has folded consists its tertiary structure. When a protein is composed by more than one chains, its quaternary structure is defined by the grouping of those chains into a final conformation.

The α helix and the β sheet are two prevalent forms of regular protein secondary structure, in which all possible hydrogen bonds are formed. They are composed of sequences of residues with repeating φ and ψ values that fall in the allowed regions of the Ramachandran plot. The amino acids in an α helix are arranged in a right-handed helical structure whose core atoms are in Van der Waals contact. The residues of the backbone are arranged such that the peptide C=O bond of the nth residue points toward the peptide N-H group of the (n + 4)th residue along the helix axis, resulting in a strong hydrogen bond between them. The structural units of a β sheet are pieces of polypeptide chain, called β strands, that form hydrogen bonds with other β strands. A β sheet can be parallel, which means that its neighboring polypeptide chains run in the same direction, or antiparallel, which means that its neighboring polypeptide chains have opposite directions (Creighton, 1993; Darby & Creighton, 1993; Kyte, 1995).

Fibrous proteins are one of the three main classes of proteins, the other two being globular proteins and membrane proteins. Their role in living organisms is often protective, connective, or supportive. Keratin, silk fibroin and collagen are three kinds of fibrous proteins which have molecules dominated by a single type of secondary structure. Keratin is a protein that occurs in all higher vertebrates. Keratins have been classified as either α keratins, which occur in mammals, or β keratins, which occur in birds and reptiles. The secondary structure of α keratin resembles that of an α helix, although the helix of α keratin has smaller spacing than the α helix. The structural pattern of β Keratin is similar to that of a β sheet. Silk fibroin consists of antiparallel β sheets whose chains extend parallel to the fiber axis. It has been shown that the six-residue pattern (Gly-Ser-Gly-Ala-Gly-Ala)n is repeated in long stretches of silk fibroin. Collagen is the most abundant protein in vertebrates. Three polypeptide chains in helical form compose a collagen molecule. The pattern Gly-X-Y, where X is often Pro, and Y is often Hyp, is prevalent at the amino acid sequence of a collagen polypeptide (Bella et al., 1994; Kaplan et al., 1994; Prokop & Kivirikko, 1995).

The structure of globular proteins consists of the main secondary structural elements in varying proportions and combinations, unlike fibrous proteins. A significant portion of a globular protein’s structure may be irregular or unique, yet no less ordered than α helices or β sheets are. The regular conformations of secondary structural elements can be distorted by variations in amino acid sequence as well as the overall structure of the folded protein, such as the β bulge and the helix capping. In addition, segments with regular secondary structure are typically joined by stretches of polypeptide that abruptly change direction, such as reverse turns, b bends and Ω loops.

The tertiary structure of globular proteins can be described by a variety of phenomena. First of all, the amino acid side chains of globular proteins are spatially distributed according to their polarities. For example, the nonpolar hydrophobic residues Val, Leu, Ile, Met, and Phe are found mostly in the interior of a protein, out of contact with the hydrous solvent. In contrast, the charged polar residues Arg, His, Lys, Asp, and Glu are usually located on the surface of a protein in contact with the aqueous solvent,
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