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Review

Hydration of proteins and nucleic acids: Advances in experiment and theory. A review

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ABSTRACT

Background: Most biological processes involve water, and the interactions of biomolecules with water affect their structure, function and dynamics.
Scope of review: This review summarizes the current knowledge of protein and nucleic acid interactions with water, with a special focus on the biomolecular hydration layer. Recent developments in both experimental and computational methods that can be applied to the study of hydration structure and dynamics are reviewed, including software tools for the prediction and characterization of hydration layer properties.
Major conclusions: In the last decade, important advances have been made in our understanding of the factors that determine how biomolecules and their aqueous environment influence each other. Both experimental and computational methods contributed to the gradually emerging consensus picture of biomolecular hydration.
General significance: An improved knowledge of the structural and thermodynamic properties of the hydration layer will enable a detailed understanding of the various biological processes in which it is involved, with implications for a wide range of applications, including protein-structure prediction and structure-based drug design.
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1. Introduction

Water is a ubiquitous element that is indispensable for all organisms. Life evolved in water for billions of years, during which biomolecules "learned" to utilize their aqueous surroundings in both structural and functional terms. Water constitutes ~50–70% of cell content and is therefore not only the native environment in which all biological processes occur but also an integral part of nearly all of biological processes [1–3]. The structural integrity of most bio-macromolecules depends on water, and their mutual interactions determine biomolecular dynamics and function. A certain critical level of hydration, usually estimated to $h \approx 0.2$ (g of water per g of protein) is required for the physiological function of most native proteins [4]. Water is sometimes described as the "twenty-first" amino acid [5], an "integral part of nucleic acids" [6] or a "biological" molecule [7]. However, while water is indispensable for the proper functioning of biological molecules, the functionality dominantly belongs to the biomolecule itself, and thus the term "biological water" should be avoided [8]. Regardless of terminology, it is now clear that water acts not only as a solvent for biological processes, but actively participates in most of them, influencing structure, dynamics and interactions of biomolecules. Thus, it is not surprising that the topic has attracted increasing attention as knowledge of biomolecular systems expands. Several reviews [9–12], books [13] and even special journal issues [14] have been dedicated to this subject. New techniques have been developed, and existing techniques have been improved and applied in novel ways. These developments are encouraging because different techniques can probe different properties and access different time and length scales, and each technique can thus contribute important details to the overall picture of biomolecular hydration.

In this article, we review recent developments in the study of biomolecular hydration. In the first part (Section 2), we provide a brief overview of the biophysical processes in which water is involved, focusing on the properties of surface hydration of native proteins and nucleic acids. Due to the breadth of this topic, many other important aspects of the role of water in biological processes, such as recognition, binding, and catalysis, are mentioned only briefly. The main focus of this review is recent developments in methods that can be applied to the study of hydration structure and dynamics, which are discussed in the second

Abbreviations: MD, molecular dynamics; PMF, potential of mean force; RDF, radial distribution function; SAXS, small-angle X-ray scattering; SANS, small-angle neutron scattering; EINS, elastic incoherent neutron scattering; QENS, quasi-elastic neutron scattering; NMR, nuclear magnetic relaxation; NOE, nuclear Overhauser effect; NMRD, nuclear magnetic relaxation dispersion; ODNP, Overhauser dynamic nuclear polarization; ESEEM, electron-spin echo envelope modulation; DRS, dielectric relaxation spectroscopy; DSC, differential scanning calorimetry; TDFSS, time-dependent fluorescent Stokes shift; QM, quantum mechanics; KITA, kinetic terahertz absorption; H/D, hydrogen/deuterium; 2D-IR, two-dimensional infrared vibrational echo spectroscopy; VSFG, vibrational sum frequency generation spectroscopy; PB/SA, Poisson–Boltzmann/surface area; GB/SA, generalized Born/surface area; IFST, inhomogeneous fluid solvation theory; GIST, grid inhomogeneous solvation theory; 3D-RISM, three-dimensional reference-interaction-site model; GCMC, grand canonical Monte Carlo method; CCG, Chemical Computing Group.

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part (Sections 3 and 4), including X-ray and neutron diffraction and scattering, NMR techniques, time-resolved fluorescence, terahertz spectroscopy, dielectric spectroscopy, and molecular dynamics (MD) simulations. For each method, we critically review its principles and inherent advantages and drawbacks and provide an overview of its contributions to our understanding of the properties of biomolecular hydration. We also compare experimental studies with computer simulations and theoretical models and discuss advances in computational methods and software tools for hydration-site prediction and analysis (Section 5).

2. Water as an indispensable component of biomolecular systems

At the molecular level, the interface at which water contacts macromolecules or molecular aggregates is of greatest interest both biologically and biophysically. Water participates in the folding of the three-dimensional structure of proteins [9,15–18] and nucleic acids [19]. Besides that, water also stabilizes the native structure of proteins [20,21] and nucleic acids [22] and contributes to protein thermal stability [23]. Lowering the relative humidity of DNA duplexes of certain sequences can induce their transition from the most stable B-form to another right-handed form, A, or even to left-handed Z-DNA [24].

The aqueous environment also influences protein binding. Water enhances the interactions between proteins and small ligands [25] as well as other biomolecules [9,26–28] and is involved in protein aggregation [29–31]. Water also mediates DNA-peptide recognition [32], and the interactions between DNA and minor-groove binders [33]. Water molecules often mediate sequence-specific recognition between proteins and DNA sites [34,35]; these interface water molecules are numerous and have specific dynamic properties [36]. Structured water molecules (with long residence times) in the active site are important for ligand recognition and selectivity [37], whereas the dynamics of water molecules determine ligand binding [38] and dissociation [39]. Whereas some water molecules directly mediate binding at the ligand-biomolecule interface, other water molecules are forced to leave the interface to enable ligand access, which contributes significantly to the overall thermodynamics of binding [27,40].

The hydration level influences the dynamics of biomolecules. At low temperatures (below ~200 K), hydration water was reported to suppress protein dynamics, whereas at higher temperatures it facilitates protein fluctuations [41], as shown by neutron scattering measurements of the differences in atomic mean-squared displacements between dry and hydrated proteins. The sharp increase in the mean-squared atomic displacement in proteins at temperatures above ~200–230 K, the so-called dynamic transition, is often ascribed to liquid-glass transition of hydration water [42,43], however, the exact nature of the coupling between these phenomena is still debated. This dynamic crossover has been observed only in hydrated biomolecules (globular proteins [44], intrinsically disordered proteins [45], and RNA [46]) and is absent in dry molecules. The strong influence of solvent translational motion and hydrogen-bonding lifetimes on biomolecule dynamics observed in these studies suggested that the dynamics of biomolecules are controlled by, or "slaved" to, solvent motions [15,47]. However, subsequent experiments revealed significant differences in the dynamics of various proteins, RNA, and DNA and their hydration water [41,48], indicating that the simple picture of slaved dynamics is incomplete. An interdependence between biomolecules and their hydration water is now accepted, but the exact mechanism by which protein and hydration water dynamics are coupled is not yet fully understood [49].

The plasticizing and lubricating effects of hydration water are also an integral component of the biological function of native biomolecules. While some enzymes remain active in organic solvents, they typically retain a hydration layer on the surface, and only a few examples of enzymes that are active below this level of hydration exist [50,51]. Generally, the catalytic function of most enzymes decreases seriously as the hydration level is reduced [4,52,53]. In addition to facilitating the larger conformational transitions necessary for catalysis and allostery [3], water also assists substrate binding [25,54] and is directly involved in the chemical process of hydrolysis reactions. Hydration influences enzyme kinetics [55] and enantioselectivity [56] and affects the electrochemical potential of an enzyme [57]. A hydration funnel of modified solvent dynamics has been proposed to contribute to net enzyme reactivity [58]. Solvent dynamics also plays a role in the catalytic function of ribozyme [59]. The water structure at biomolecular surfaces and the specific interactions of water molecules are key determinants of important cellular processes, such as water transport through aquaporin channels [60], hydrophobic gating of ion permeation in ion channels [61], and mechanogating of the mechanosensitive channel MscL [62].

While playing an important role in the processes mentioned above, the structure and dynamics of water itself are greatly perturbed by the presence of solute biomolecules [11]. This is because of both specific effects, such as the interactions of water molecules with the solute, and nonspecific effects, in which the solute poses boundary restrictions on the H-bonded network of water molecules [3,63]. The structural and dynamic properties of biomolecule-associated water, or water in the hydration layer, thus differ significantly from the properties of bulk water. Nevertheless, the detailed knowledge of these differences continues to be fragmentary, and thus the intensity and the cause of this effect at the molecular level continue to be active topics of investigation [64], as discussed later in this review (particularly in Sections 4.4.1 and 4.4.2). Several factors hinder the characterization of this perturbation: the complicated nature of liquid water, the heterogeneous water/biomolecule interface, and the unclear boundary between bulk water and the hydration shell associated with the biomolecule, as discussed below.

First, although water is a rather simple molecule, comprising only one oxygen and two hydrogens, the structure of water in the liquid phase is surprisingly complicated. Water, due to its small size, tetrahedral shape and capacity to form up to four hydrogen bonds gives rise to a dynamic, three-dimensional network that can readily rearrange in contact with solutes [3,13,65]. Despite great efforts, the multifaceted properties of water structure have not yet been fully described even for pure water. This complicated nature of liquid water confers on it its specific and unique characteristics and undoubtedly contributes to its many anomalous properties, e.g. the most well known density anomaly, in which the liquid phase has higher density than the crystal phase [66], or the vigorously debated liquid water polymorphism [67]. However, the molecular-level origins of these anomalies are not yet fully understood.

Second, water interacting with biomolecules occupies a complex, heterogeneous environment. Some water molecules are buried inside the core of globular proteins, representing an integral component of protein structure by interacting with the unsaturated hydrogen-bonding capacities of main-chain polar groups not involved in secondary structures and of buried polar side-chain atoms [68–70]. Other water molecules are located in confined regions such as internal cavities and active sites. The hydrophobic enclosure of these sites can lead to anomalous entropic and enthalpic penalties of hydration, contributing to ligand binding affinity [25], whereas the distinct dynamic properties of water at the active site have been suggested to contribute to efficient catalysis [71]. The environment of water at the surface of a protein or nucleic acid, which is the main focus of this review, is equally complex. The structure and dynamics of the water molecules in the hydration layer are affected by the complex topography (surface clefts, grooves, pockets and protrusions) [72–74] and varied chemical composition (hydrophobic, polar or charged groups) [64,75] of the biomolecule's solvent-exposed surface. This picture is further complicated by intermolecular interactions with other solvent molecules [9,28,76] and the effect of crowding [77,78].

Third, there is no universal definition of hydration water, and the interpretation of what actually constitutes the hydration layer of a biomolecule typically depends on the nature of the technique used to

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