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Atomistic details of protein dynamics and the role of hydration water☆

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ABSTRACT

Background: The importance of protein dynamics for their biological activity is now well recognized. Different experimental and computational techniques have been employed to study protein dynamics, hierarchy of different processes and the coupling between protein and hydration water dynamics. Yet, understanding the atomistic details of protein dynamics and the role of hydration water remains rather limited.
Scoop of review: Based on overview of neutron scattering, molecular dynamic simulations, NMR and dielectric spectroscopy results we present a general picture of protein dynamics covering time scales from faster than ps to microseconds and the influence of hydration water on different relaxation processes.
Major conclusions: Internal protein dynamics spread over a wide time range from faster than picosecond to longer than microseconds. We suggest that the structural relaxation in hydrated proteins appears on the microsecond time scale, while faster processes present mostly motion of side groups and some domains. Hydration water plays a crucial role in protein dynamics on all time scales. It controls the coupled protein-hydration water relaxation on 10–100 ps time scale. This process defines the friction for slower protein dynamics. Analysis suggests that changes in amount of hydration water affect not only general friction, but also influence significantly the protein's energy landscape.
General significance: The proposed atomistic picture of protein dynamics provides deeper understanding of various relaxation processes and their hierarchy, similarity and differences between various biological macromolecules, including proteins, DNA and RNA.
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1. Introduction

It is now well accepted that dynamics of biological macromolecules such as protein, DNA and RNA play a key role in their biological activity. It is recognized that these macromolecules at physiological conditions are not rigid solids and fluctuate constantly between different conformational states. Their dynamics include many stochastic local and collective motions from bond vibrations to larger domain motions that span over an enormous time range. [1–11] Despite significant efforts over the past several decades, our microscopic understanding of protein dynamics remains rather limited [3,12,13]. It has been also realized that hydration water plays a crucial role in dynamics and biological activity of proteins, from enzyme activity, macromolecular recognition and ligand binding to participating in electron and proton transfer [4,14]. It has been demonstrated that not only protein surface, but also its interior dynamics are strongly affected by the hydration water [15–18].

Many experimental and computational methods have been applied to study protein dynamics at different time and length scale. Single molecular studies [19–25], e.g. fluorescence techniques, atomic force microscopy, optical and magnetic tweezers usually analyze dynamics on time scale longer than milliseconds and length scales of a few nm. Molecular dynamics (MD) simulations, Nuclear magnetic resonance (NMR) and neutron scattering are among the techniques to directly analyze atomic motions from faster than ps to nanoseconds and microseconds. MD simulations provide the most direct visualization of the atomic motions in proteins [7,8,10,26–29]. Many experimentally measured parameters can be directly calculated from MD simulated atomic trajectories. However, the results depend on the approximations used and it is essential to combine MD-simulations with experimental results to validate the simulations. NMR mainly provides local information on motions of specific groups and residues. [13,30–35] Neutron scattering provides analysis of local and collective dynamics, and reveals geometry of the underlying motions in a broad time and length scale [11,36–46]. Exceptionally high incoherent scattering cross section of hydrogen atom in comparison to other atoms (including deuterium) provides a unique labeling capability, which helps to disentangle complex structure and dynamics of biological macromolecules [36,42]. Moreover, in

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contrast to X-ray techniques, the milielectronvolt (meV) energy of neutrons used in this method is not destructive for biological systems. Broadband dielectric spectroscopy provides dynamic measurements in extremely broad frequency range with very high accuracy in relatively short experimental time. In this method reorientation motions of dipoles and translational motion of charges are measured. This technique, however, does not provide microscopic information on the different observed molecular motions and their origin. Combination of different experimental techniques, such as dielectric spectroscopy, NMR, neutron scattering and MD simulations, is a powerful approach to study details of molecular motions in a broad frequency (time) range [27,47–49]. In combining different experimental data one should keep in mind that motions of different molecular origins may appear at the same time scale. NMR and neutron scattering methods provide the option for selectively labeling protein or its solvent, which allows clear separation of their contributions to the overall dynamics on different time scales. However for a valid comparison the same environmental conditions, such as hydration level and temperature, should be used.

In this review we overview experimental and computational studies of atomistic details of protein dynamics and the role of hydration water. We discuss the recently proposed general atomistic picture of protein dynamics [12], hierarchy of different processes [2,3,6], and the coupling between protein and hydration water dynamics [17]. We focus on discussion of the intra-molecular protein dynamics on time scales from sub-picosecond to microseconds studied mostly using neutron scattering, broadband dielectric spectroscopy, NMR and MD simulations results.

2. Hierarchical structure of internal protein dynamics

Protein explores many conformational states [7,12,50] and its internal dynamics at ambient conditions span over a wide time range from faster than picosecond to longer than microsecond, with atomic displacements ranging from smaller than 0.5 Å to ~10 Å. The recent review [12] proposed a general picture of internal protein dynamics (Fig. 1) and analyzed its similarity and differences with dynamics of other Soft Materials. This dynamic picture includes (i) fast dynamics; (ii) localized diffusion and (iii) conformational jumps, both dominated by motions of side groups; and (iv) segmental (structural) relaxation that is dominated by the backbone motions. Here we briefly present the general picture and its details can be found in [12].

Fast dynamics (faster than a few ps) present small scale conformational fluctuations reflecting 'rattling' of residues in a cage formed by the neighboring residues and solvent molecules. They have mean squared atomic displacement (MSD) ~0.2–0.4 Å^2, and low energy barriers ~2–5 kJ/mol [51–53]. Fast dynamics also includes low-frequency collective vibrations, the so-called boson peak [54,55], which appears

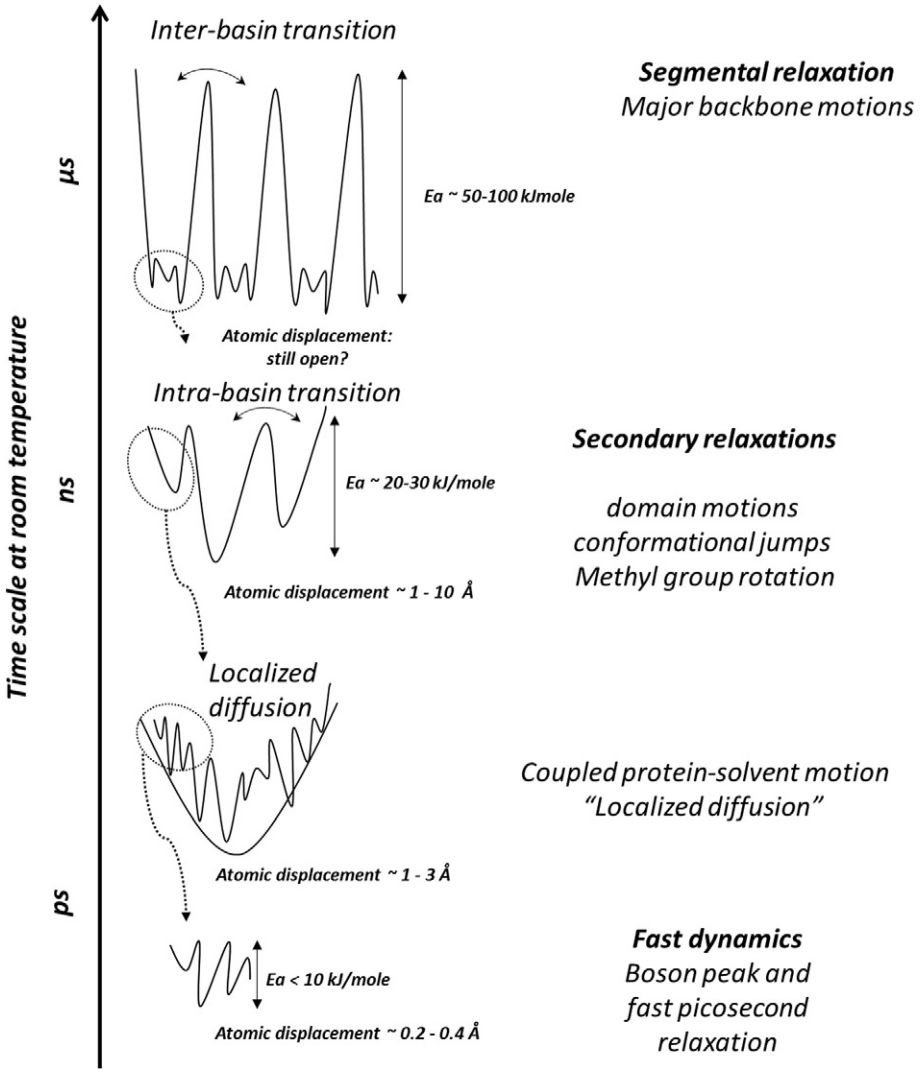

Fig. 1. Hierarchical picture of protein dynamics [12]: It includes (i) fast dynamics with rather low energy barriers ~3–5 kJ/mol and small atomic displacement; (ii) Coupled protein-solvent process that can be described as a localized diffusion (diffusion in a potential well); (iii) Intra-basin conformational jumps mostly ascribed to side group motions and some domain motions; and (iv) Inter-basin transitions that can be ascribed to structural (segmental) relaxation.

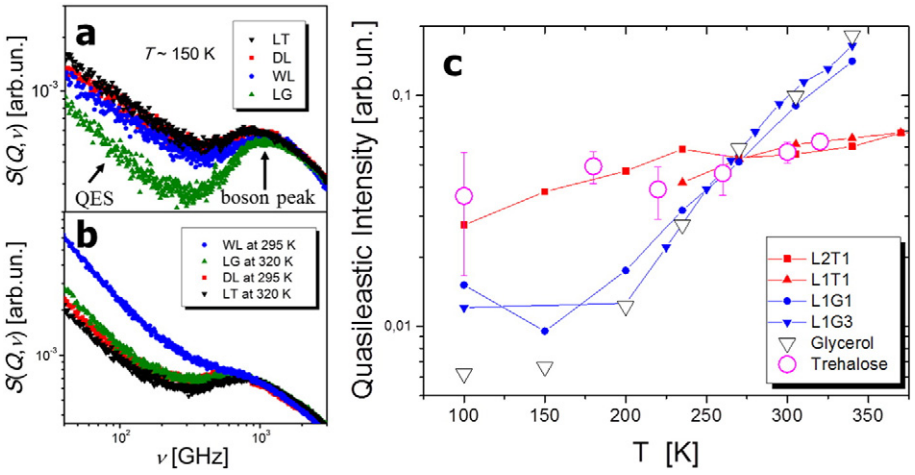

Fig. 2. (a) and (b) Dynamic structure factor S(Q,ν) of lysozyme as measured by neutron scattering technique at different temperatures and solvents (DL — dry lysozyme; WL — hydrated lysozyme; LG — lysozyme in glycerol; LT — lysozyme in trehalose) [46,61]. The boson peak appears as inelastic scattering, while fast relaxation appears as the quasielastic scattering (QES) at lower frequency. (c) Temperature dependence of the normalized quasielastic scattering intensity $I_n(\nu)$ for two samples of lysozyme in glycerol (L1G1 and L1G3, numbers indicate weight ratio), and in trehalose (L2T1 and L1T1), and pure glycerol and trehalose [62]. The similarity of the temperature dependence of the QES intensity in lysozyme (filled symbols) and in its solvents (open symbols) indicates that fast conformational fluctuation of the protein is strongly coupled to the fast dynamics of its solvent [61–63].

as inelastic scattering (Fig. 2). It presents excess of vibrational density of states compared to the Debye model for acoustic modes, is general for disordered solids and is usually ascribed to heterogeneity in elastic constants [56–59]or to soft modes [52,60].

Side group motions appear on longer time scales, that at ambient conditions span from ~10 ps to longer than ns. It includes several processes. Among them methyl group rotations with rather low energy barriers (E ~10–20 kJ/mol) [46] present conformational jumps active even at low hydration levels and low temperatures [28,33,34,64–67]. It has been revealed that the fastest methyl groups in lysozyme and myoglobin are placed around the active sites [28,34,46,65,68] which highlight the importance of methyl group dynamics in providing conformational flexibility and facilitation of protein dynamics [65].

Localized diffusion appears as an extremely stretched relaxation process in hydrated proteins with characteristic relaxation time τ ~10–50 ps at room temperature (Fig. 1). [8,40,43,46,47,64,66,69–71] These conformational fluctuations involve the entire protein, its surface and core [27,72,73]. Extremely strong stretching of the relaxation spectrum reflects significant dynamic heterogeneity apparently caused by the difference in chemical structure and position of residues in proteins. Proteins "localized diffusion" present conformational fluctuations of residues, side groups and backbone with the amplitude of motion ~1–3 Å [8,46,64,71]. This process is associated with the dynamic transition observed as a sharp increase in MSD of hydrated proteins on the ns time scale at the so called dynamic transition temperature T_d ~220 K. It is important to emphasize that T_d essentially marks the temperature at which the dynamic process enters the energy window of the instrument in use, and therefore it can be shifted slightly depending on the instrument's energy resolution [74,75]. Strong correlations of behavior of the localized diffusion process with biochemical or enzymatic activity of proteins [40,74,76–78] suggest its importance for protein functionality. Although this process is much faster than characteristic time of biochemical reactions, it presents necessary precursor for slower protein dynamics, in particular, for motions directly involved in protein functions. It is important to emphasize that this process does not present jumps between well-defined conformational states, but rather a continuous diffusion in a restricted space [8,46,71], a kind of a friction controlled diffusion in a harmonic potential.

Similar relaxation process has been also observed in RNA and DNA dynamics [79,80], but it has significantly larger localization length ~7 Å in t-RNA [79]. This relaxation process in t-RNA exhibits stronger temperature dependence and is slower than in proteins like lysozyme and myoglobin. This process in DNA is even slower than in t-RNA [69].

Larger scale conformational jumps with displacements on the length scale ~1–10 Å [5,8,10,11,37,81] and characteristic activation energy of about 20–40 kJ/mol appear on the nanosecond time scale at ambient temperature [8,10,12,27,81,82] (Figs. 1,3). These conformational jumps in hydrated proteins are observed in NMR and neutron scattering, dielectric spectroscopy and MD-simulations [8,10,27,33,34,37,38,45,71,81,83]. Neutron scattering on protein solutions also detected intra-molecular relaxation processes on the time scale ~10–30 ns [10,81,82]. They present rather large atomic displacements ~8 Å, and were ascribed to domain-like motions [10,37,38,81]. Similar process has recently been reported for intrinsically disordered protein Myelin Basic Protein [11]. NMR and MD-simulation studies reveal strong contribution of side group motions in this time range [7,26,33,34,84]. The temperature dependence of these conformational jumps most probably is controlled by the behavior of the sub-nanosecond localized diffusion process that effectively defines a local friction for the slower dynamics.

Although backbone motions appear on various time scales, including localized diffusion and conformational jumps, they dominate dynamics on microsecond time scale [7,12,17] (Fig. 1). It is controlled by high energy barriers for torsional rotation of polypeptide backbone ~30–80 kJ/mol [88–90]. Although NMR studies confirmed the existence of backbone conformational dynamics at microsecond timescale [91,92], there are significant challenges in analyzing this process. This process is much slower than protein tumbling time in water (~10–100 ns) that complicates its studies in protein solutions. Moreover, current neutron scattering spectroscopy is limited to hundreds of ns and cannot reach this time scale, and current MD-simulations are usually limited to hundreds of ns. Nevertheless, a few simulations that reached millisecond times indeed identified protein relaxations in microsecond time scales [7,32]. MD simulations and NMR studies suggest that the microsecond process presents the main backbone motion, its rotation, and jumps between well-defined basins in potential energy landscape [7,32,91,92]. However the general microscopic picture of this relaxation remains unknown. This process has been also detected in dielectric spectra of hydrated protein powders and provided analysis suggests a direct connection of this process to the glass transition in hydrated protein system [85,93,94]. By definition, structural relaxation time in liquids reaches ~100 s at their glass transition temperature Tg. The characteristic relaxation time of this very slow process in hydrated proteins reaches ~100 s at T ~170–220 K (Fig. 3), depending on hydration level [85,94]. Calorimetric measurements on hydrated proteins revealed a broad glass transition with strong dependence on hydration around the same temperature range T ~160–200 K [95–101]. The inflection

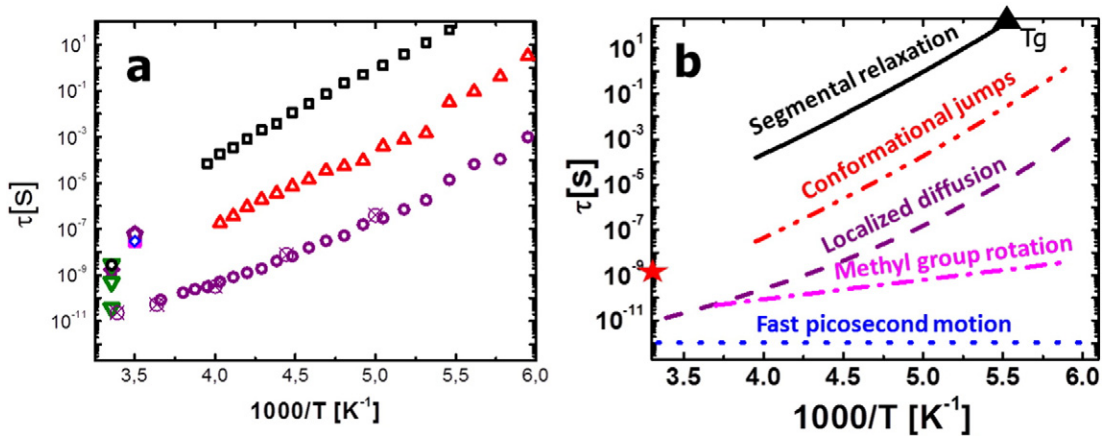

Fig. 3. (A) Temperature dependence of the relaxation times observed by dielectric spectroscopy for hydrated lysozyme powder (h ~0.4; open symbols). Neutron scattering data for hydrated lysozyme (h ~0.4) are shown as crossed circles (data taken from [47,85]). Circles are localized diffusion (coupled protein-solvent motion), triangles are side group motions (conformational jumps) and squares are segmental relaxation. For comparison the dielectric relaxation times in protein solutions at 298 K are also included: RNase A (open triangles [86] and star [87]), lysozyme [87] (open circle). Characteristic τ of the domain motions estimated from neutron spin echo measurements are also shown: Alcohol Dehydrogenase [37] (open diamond); PGK bounded (open square) and unbounded to substrate (open pentagon) at 283 K (data from [81]). (B) Schematic of temperature dependence of different internal motions of protein including: (i) Main structural (segmental) relaxation reaching τ ~100 s at glass transition temperature T_g of hydrated proteins; (ii) Domain and side group motions, conformational jumps with nanosecond relaxation times at room temperature (indicated by the star); (iii) Coupled protein-solvent motions, present "localized diffusion" of residues and side group motions with relaxation time of tens of picosecond at room temperature; (iv) Methyl group rotation with Arrhenius temperature dependence; and (v) Fast picosecond relaxation with a rather weak temperature dependence of its characteristic relaxation time.

point observed in temperature dependence of characteristic relaxation time of the coupled protein-water process also appears in the same temperature range and was assigned to the underlying glass transition [102]. Thus there are several evidences connecting the microsecond process to the glass transition of hydrated proteins. In that case the microsecond relaxation presents the main structural relaxation of hydrated proteins (Fig. 3). This connection makes it especially intriguing to understand the microscopic nature of the microsecond process. Moreover, this process appears on time scale usual for many biochemical processes and might be directly connected to the proteins function. Advanced MD-simulations, NMR and complementary scattering and spectroscopic studies might provide detailed microscopic information on mechanism of the microsecond relaxation.

There are many relaxation processes at even longer time scales, e.g. at ms — seconds and longer times. Some of them can be studied with fluorescence and several other single molecular techniques [19–25, 103]. On this longer time scale atomistic details of the biomolecular structure become less important and more coarse-grained models can be applied. It is similar to the situation in synthetic polymers, where details of chemical structure become less important on time scale longer than segmental dynamics and coarse-grained theories, such as Rouse and reptation, describe dynamics reasonably well. Discussion of these long time processes, including folding/unfolding is out of the scope of the current paper.

3. Role of hydration water in protein dynamics

Water as an integral part of protein structure plays a key role in protein folding, stability and activity at physiological conditions. Therefore many efforts are focused on studies of coupling between dynamics of proteins and their hydration water. [18,44,69] It was shown that hydration water strongly affects fast dynamics [41,62,63]. It increases the amplitude of the fast picosecond fluctuations in biological macromolecules at ambient temperature, but strongly suppresses it at lower temperatures (Fig. 2). [66,80,104] Analysis of the fast dynamics in proteins placed in various solvents revealed strong correlations between the amplitude of the fast relaxation in proteins and in pure solvents [62, 63] (Fig. 2). These results suggest a strong coupling between fast picosecond fluctuations of biomolecules and surrounding solvent, and have been used for rational design of formulations (solvents) for long-term biopreservation [61,105,106]. It was speculated that suppression of the fast dynamics maybe the key to long-term stabilization of biological macromolecules [61,62,105–107]. It remains a puzzle to understand how the suppression of dynamics on ps time scale can affect biomolecular stability on time scale of months. But this problem is analogous to much longer standing puzzle related to the connection of fast ps and slow structural dynamics in glass forming liquids known for more than two decades [55,108–110].

Methyl group rotation appears to be rather independent on hydration water, and remains fast even at low hydrations, and for proteins placed in various solvents [28,33,34,46,64,65,111]. This can be explained by hydrophobicity of methyl groups that are mostly buried in the protein core. Similar behavior is expected for other hydrophobic side groups. Due to rather low energy barriers for rotation, methyl groups might be considered as internal plasticizers that facilitate protein dynamics even at extreme conditions (e.g. at low temperatures or at low hydration levels) [65].

One of the most intriguing questions is the coupling between protein 'localized diffusion' and structural dynamics of hydration water. Not only they occur on the same time scale (~10–50 ps at ambient temperature, Fig. 4), but they also show similar temperature dependence (Fig. 5) [12,69]. It has been suggested that this process is actually coupled protein-hydration water relaxation [47,69,75]. There is, however, a significant difference in dynamics of hydration water and protein at this time scale: water has diffusive like motion, while motions in protein are localized (Fig. 4) [8,66]. It has been shown that dynamics of protein hydration water is slowed down relative to bulk water by a factor of 2–4 (Fig. 4) [66,112]. Its characteristic relaxation time shows strong Q-dependence exemplifying complex non-Fickian diffusion (Fig. 4) [8, 66]. In contrast to hydration water, characteristic relaxation time of protein dynamics is essentially Q-independent reflecting localized nature of the dynamics on time scale ~10–100 ps (Fig. 4). Analysis of neutron scattering data and MD-simulations estimated characteristic localization length to be ~1–3 Å [8,46,64,71]. This is the reason that this process can be ascribed to a localized diffusion. It presents a kind of diffusive motions in a harmonic potential [8,12,66].

This 'localized diffusion' in proteins depends strongly on hydration. It has been shown in simulations that restrictions of hydration water translational motions lead to strong suppression of the protein dynamics on time scale ~10–100 ps [113]. These results are consistent with assignment of this process to a strongly coupled protein-hydration water relaxation. It has been shown that similar process exists also in

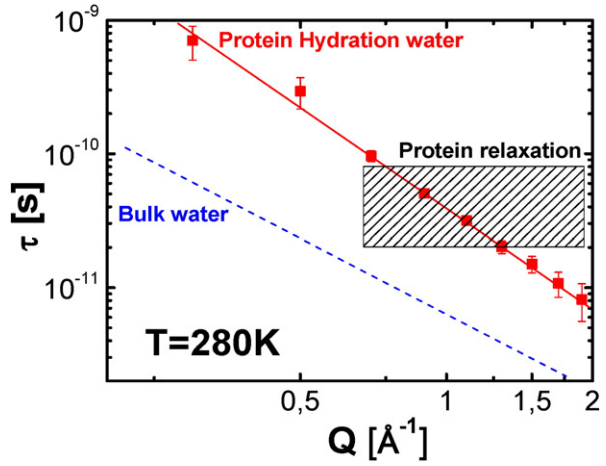

Fig. 4. Wave-vector, Q, dependence of relaxation time at T = 280 K in protein hydration water (symbols) and bulk water (dashed line) [66], and characteristic relaxation of the protein dynamics for lysozyme [75], GFP [66] and myoglobin [64]. Bulk water shows normal diffusion behavior with $\tau \sim Q^{-2}$, while hydration water shows stronger Q dependence and is ~4 times slower than bulk water on local length scale (Q ~1.5–2 Å^{-1}). In contrast, proteins exhibit very broad and Q-independent relaxation spectra (shaded area), indicating localized nature of the relaxation process.

nucleic acids, but it is a bit slower and has stronger temperature dependence [69]. It appears that dynamics of hydration water are also slower in the case of nucleic acids, confirming strong coupling between dynamics of hydration water and this process in biomolecules [69]. Slight difference in behavior of hydration water was also found when water soluble proteins were compared to intrinsically disordered and membrane proteins [44]. Moreover, recent neutron scattering studies combined with MD simulations demonstrated how hydration water dynamics around the surface of the tau amyloid fibers are enhanced in comparison to its monomer [114]. All these results indicate that it is not just hydration water controlling (slaving) the biomolecular dynamics, also biomolecules affect the dynamics of hydration water leading to a coupled biomolecule-hydration water process. We speculate that hydration water plasticizes protein (works as a lubricant) and facilitates its dynamics. But protein dynamics then require displacements of hydration water molecules (translational motions) to provide space for residue motions. This leads to the coupled protein-hydration water

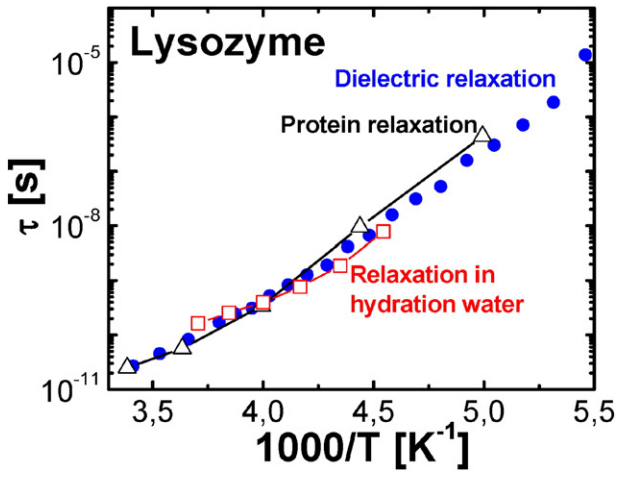

Fig. 5. Temperature dependence of characteristic relaxation times in hydrated lysozyme for coupled protein-hydration water dynamics: Dielectric relaxation process (filled circles) is usually ascribed to hydration water dynamics (data from [85]); neutron scattering data on lysozyme hydrated with D_2O present protein relaxation process (data from [47]), and neutron scattering data for hydration water in lysozyme (data from [112]). These data clearly reveal coupled protein-hydration water process.

process that is localized in nature, but involves entire protein, its surface and the core [72]. Apparently, this process defines the friction coefficient for all slower relaxation processes as they all have essentially the same temperature dependence (Fig. 3).

Conformational jumps in proteins that appear on ns time scale at ambient conditions show even stronger hydration dependence than the localized diffusion. It has been shown that in lysozyme the ratio of characteristic times of the ns-process to the localized diffusion is ~10^3 times at hydration level h ~0.37 (g of water per g of protein), and increases to ~10^5 times (i.e. 100 times) when the hydration level is reduced to h ~0.23 [47]. Thus these conformational jumps, assigned mostly to motions of side groups and also some domain-like motions [12], appear to be even more sensitive to hydration than the localized diffusion.

The influence of hydration water on the relaxation process in microsecond time range has not been studied in details yet. A few studies based on dielectric spectroscopy [85,94] suggest also very strong dependence of this process on hydration that follows shift of the glass transition temperature in the hydrated protein powders. This result is the major argument in assigning this process to the main structural relaxation of hydrated proteins. It has been demonstrated that this process slows down by 5–6 orders when the hydration level of protein is reduced from h ~0.4 to h ~0.1 [94]. All these results demonstrate that hydration water is not only crucial part of the protein structure, but also plays the key role in dynamics of biological macromolecules. Only methyl group dynamics (and maybe dynamics of some other hydrophobic side groups) appear to be independent of hydration. The rest of the dynamics, starting from fast ps fluctuations all the way to structural relaxation on microsecond and longer time scales, are extremely sensitive to the hydration water. Moreover, it seems that the slower the protein relaxation process is, the more sensitive it is to the amount of available hydration water. Apparently the hydration water not only affects the friction of the atomic motions, but also influences the energy barriers between conformational states.

4. Conclusions

We present here an overview of atomistic details of protein dynamics and their dependence on hydration. On ps–ns time scale the dynamics is dominated by motions of side groups, although motions of backbone, and even some domains motions also appear in this time range. Backbone motions start to dominate on microsecond time scale and provide the main structural relaxation in hydrated proteins. It seems that coupled protein-hydration water process that appears on time scale ~10–50 ps (localized diffusion) defines the friction for all other slower relaxation modes, as is evident from their similar temperature dependence (Fig. 3). However, the slower processes seem to be more sensitive to hydration water than the localized diffusion, reflecting significant change in the energy landscape of proteins with change in its hydration.

There are certainly even slower relaxation processes in protein dynamics. One of the slowest probably will be the unfolding process. Here it is interesting to comment on the recent paper by Smith and coworkers [115] suggesting that protein might remain non-ergodic (non-equilibrated) through its entire life. The authors clearly demonstrated that the protein dynamics change with the simulations waiting time all the way to microseconds. Taking into account that structural (segmental) relaxation in proteins happens on time scale ~10 μs and longer [7,12], this observation is consistent with the expected aging process. Usually to reach equilibrium in glass forming liquids (including synthetic polymers) requires aging (annealing) time ~10 times the equilibrium structural relaxation time. This analogy suggests that protein dynamics are expected to become ergodic only for ms simulations. It would be interesting to verify this prediction.

Overall, we expect that dynamics on time scale longer than microseconds can be well addressed with coarse-grained models where

detailed atomistic structure is hidden in friction coefficients, chain rigidity and amplitude of displacements. This approach will help to bridge the gap between atomistically detailed studies discussed above and single molecular studies performed on time scale ms and longer.

In this review we only discussed the role of hydration water and its dynamical coupling to different types of protein motions, and did not touch the subject of biomolecules placed in other solvents. This is another important topic that is directly related to the field of bio-preservation. Experimental and computation studies revealed a strong coupling of fast dynamics and localized diffusion process to the dynamics of solvents, such as water, glycerol and sugars [61,62,105,111,116–119]. Understanding the role of the solvents in protein dynamics, activity and stability remains a great challenge mainly due to the complex dynamical coupling of different motions combined with the complex structure of the protein itself. Many questions on dynamical coupling between protein and its solvent, especially when it comes to additives and co solvents, intrinsic protein's dynamical heterogeneity and how to separate different dynamical processes and their contribution to biochemical activity remain to be explored. Developing a general concept for protein dynamics and its dynamical coupling with the environment might be one of the key approaches to address this challenge.

Transparency document

The Transparency document associated with this article can be found, in online version.

Acknowledgments

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