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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 contrast to X-ray techniques, the milielectronvolt (meV) energy of neutrons used in this method is not destructive for biological systems.

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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 as inelastic scattering (Fig. 2). It presents excess of vibrational density

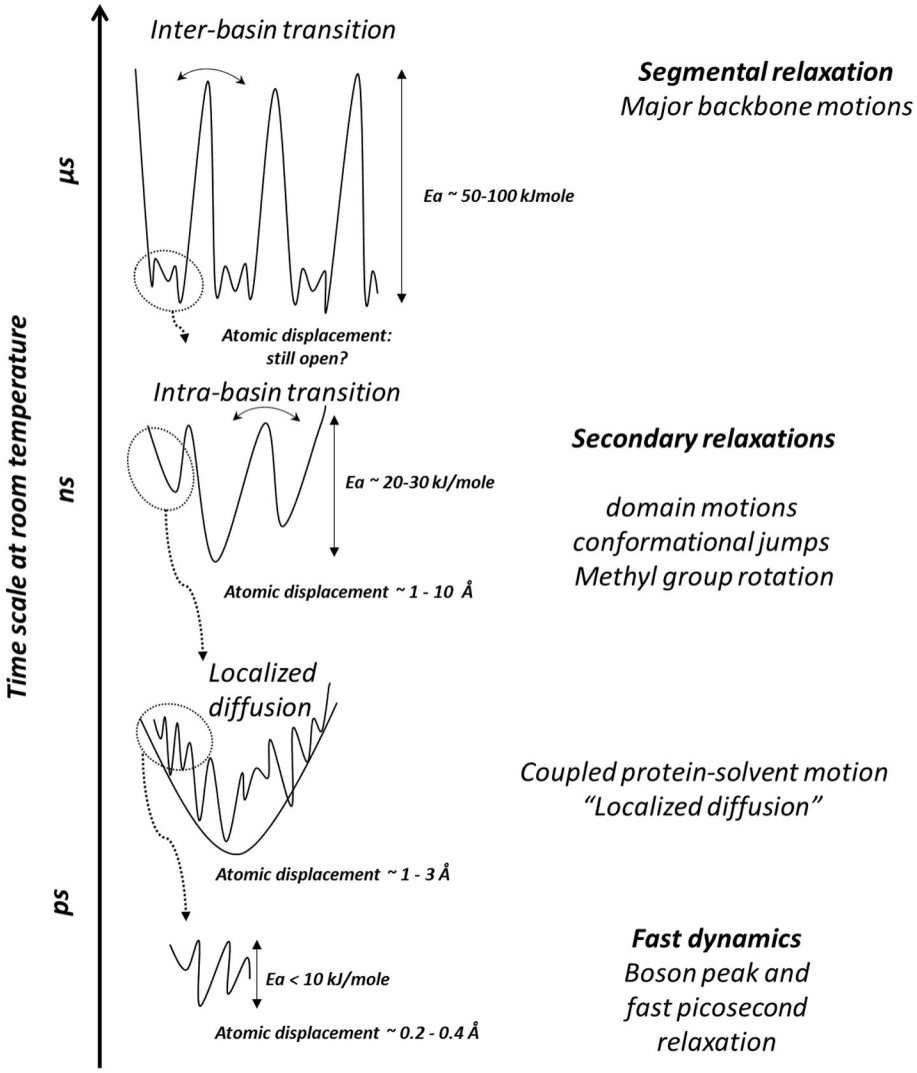

Fig. 1. Hierarchical picture of protein dynamics [12]: It includes (i) fast dynamics with rather low energy barriers ~3–5 kJ/mol and small atomic displacement; (ii) Coupled protein-solvent process that can be described as a localized diffusion (diffusion in a potential well); (iii) Intra-basin conformational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

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