MOLECULAR DYNAMICS SIMULATION AND NEUTRON SCATTERING FROM PROTEINS

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1 Introduction

Since the early days of Rahman's historic simulation of liquid argon [1], Molecular Dynamics (MD) simulations have become a standard tool for the investigation of the structure and dynamics of condensed matter. The best experimental reference for MD simulation are neutron scattering experiments, since both methods cover the same time and space domains (approximately 0.1 *fs* – 10 *ns*, and 1 – 100 Å), and neutrons "see" the atomic nuclei, which are the basic objects in MD simulations.Once agreement between simulated and experimental spectra is found, the simulated trajectories can be analyzed in detail and information not accessible to experiments can be extracted from simulations. This approach is particularly useful for the study of complex molecular systems, such as biological macromolecules. Over the last ten years programs have been developed which allow to simulate and analyze the structure and dynamics of molecular systems an the basis of MD simulation [2, 3].

2 C-phycocyanine

The first example concerns hydrated C-phycocyanin, a light-conducting protein in cyanobacteria. MD simulation and an analytical model have been used to model diffusive motions in this protein. Since the simulation-derived scattering function was found to be in good agreement with experiment, a further analysis was undertaken to find the essential contributions. It is found that the geometry of the atomic motions can be modeled as diffusion in spheres with a distribution of radii that is different for backbone (average radius = 1.1 Å) and side chains (average radius = 2.0 Å). The time dependence follows a stretched exponential behavior, reflecting a distribution of relaxation times. With this description, the average side-chain and backbone dynamics are quantified and compared. The dynamical parameters are also shown to present a smooth variation with distance from the core of the protein. This is reflected in a progressive increase of the mean sphere size of diffusion and in the narrowing and shift to shorter times of the relaxation time distribution. This smooth, "depth-dependent" dynamics may have important consequences for protein function. It may allow local reorganization of the structure for efficient ligand binding without affecting the internal stability [4, 5].

3 Simulation-based modeling

An essential point that should be retained from the last example is that internal protein dynamics is characterized by multi-scale relaxation processes. A model process that is still simpler than diffusion in a sphere, and which describes confined motions as well, is diffusion in a multidimensional harmonic well. Multiscale relaxation is obtained by coupling harmonic oscillators with friction. Such models can give quantitative agreement with full MD simulations, if one considers a coarse-grained scale where each residue is represented by a point [6, 7]. The parameters of the model (force constants and friction coefficients) are obtained from conventional protein force fields and short simulations [7]. Another method to describe multiscale relaxation in proteins is to use the concept of memory functions [8]. Each correlation function, and in particular the intermediate scattering function,

$$I_{coh}(\mathbf{q},t) = \sum_{\alpha,\beta} \overline{b_\alpha b_\beta} \left\langle e^{i\mathbf{q}^T \cdot [\mathbf{R}_\beta(t) - \mathbf{R}_\alpha(0)]} \right\rangle \qquad (1)$$

obeys an integral equation of the form

$$\partial_t I(\mathbf{q},t) = -\int_0^t d\tau \xi(\mathbf{q},t-\tau) I(\mathbf{q},\tau). \qquad (2)$$

Here $\xi(\mathbf{q},t)$ is the *memory function* which can be interpreted as a generalized friction coefficient. In case of confined motion the memory function equation (2) is applied to $I'(\mathbf{q},t) = I(\mathbf{q},t) - EISF(\mathbf{q})$, where $EISF(\mathbf{q}) = \lim_{t \to \infty} I(\mathbf{q},t)$ is the Elastic Incoherent Structure Factor. When the memory kernel is short-ranged compared to the correlation function $I(\mathbf{q},t)$, the latter becomes a simple exponential. Internal protein dynamics is known to span an enormous range of time scales, ranging from sub-picoseconds to seconds. There is no characteristic time scale for the decay $I'(\mathbf{q},t)$,

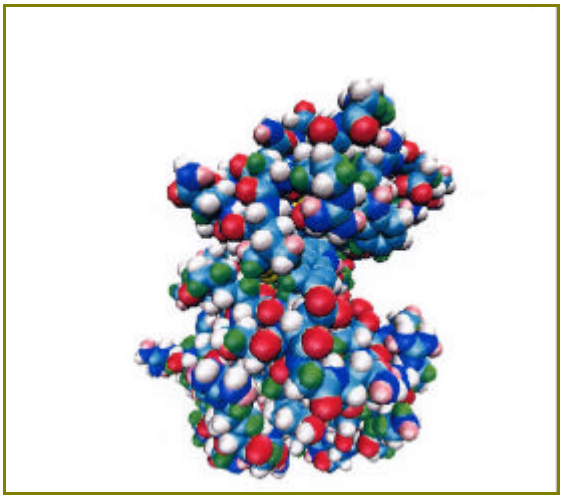

Figure 1. The lysozyme molecule. Each atom is represented by a sphere with the corresponding van derWaals radius.

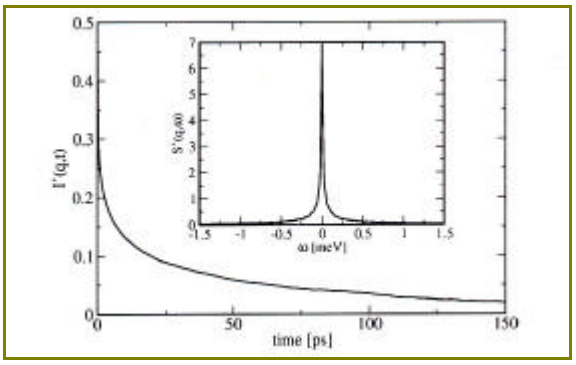

Figure 2. Simulated incoherent intermediate scattering function, $I'(\mathbf{q},t)$, of lysozyme, averaged over 30 momentum transfer vectors with q = 15 nm^{-1}. The corresponding dynamic structure factor, $S'(\mathbf{q},\omega)$, is shown in the inset.

since all internal protein motions are coupled due to the high atomic density which can be higher than in solids. This leads to a non-exponential decay of $I'(\mathbf{q},t)$, and the corresponding dynamic structure factor, $S'(\mathbf{q},\omega)$, is not a Lorentzian. Fig. 2 shows the simulated incoherent intermediate scattering function of lysozyme (see Fig. 1) at 300 K and normal pressure and the corresponding dynamic structure factor. All functions have been computed from a 1 *ns* trajectory, using autoregressive modelling of time series [3, 9]. The corresponding memory function is shown in Fig. 3. It can be seen that $x(\mathbf{q},t)$ has an algebraic long-time tail of the form

$$\xi(\mathbf{q},t) \propto (\beta - 1)\left(\frac{t}{\tau}\right)^{\beta-2}, \quad (3)$$

where $\tau > 0$ and $0 < \beta < 1$. This is a characteristic feature of "fractal dynamics" with long-time memory [10, 11]. We note that the short-time behavior of $\xi(\mathbf{q},t)$ is not well resolved since a coarse-grained autoregressive model with a sampling interval of Δt = 0.4 *ps* has been used.

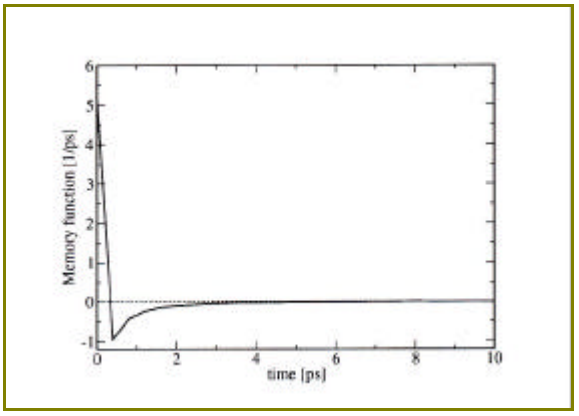

Figure 3. Memory function corresponding to $I'(\mathbf{q},t)$ depicted in Fig. 2.

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