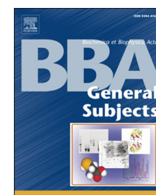
Biochimica et Biophysica Acta xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagen



Protein dynamics as seen by (quasi) elastic neutron scattering

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ARTICLE INFO

Article history:
Received 2 April 2016
Received in revised form 18 July 2016
Accepted 27 July 2016
Available online xxxx

Keywords:
Neutron scattering
Lamb-Mossbauer factor
Mean Square Displacement
Resolution elastic neutron scattering
Elastic incoherent scattering

ABSTRACT

Background: Elastic and quasielastic neutron scattering studies proved to be efficient probes of the atomic mean square displacement (MSD), a fundamental parameter for the characterization of the motion of individual atoms in proteins and its evolution with temperature and compositional environment.

Scope of review: We present a technical overview of the different types of experimental situations and the information quasi-elastic neutron scattering approaches can make available. In particular, MSD can crucially depend on the time scale over which the averaging (building of the "mean") takes place, being defined by the instrumental resolution. Due to their high neutron scattering cross section, hydrogen atoms can be particularly sensitively observed with little interference by the other atoms in the sample. A few examples, including new data, are presented for illustration.

Major conclusions: The incoherent character of neutron scattering on hydrogen atoms restricts the information obtained to the self-correlations in the motion of individual atoms, simplifying at the same time the data analysis. On the other hand, the (often overlooked) exploration of the averaging time dependent character of MSD is crucial for unambiguous interpretation and can provide a wealth of information on micro- and nanoscale atomic motion in proteins.

General significance: By properly exploiting the broad range capabilities of (quasi)elastic neutron scattering techniques to deliver time dependent characterization of atomic displacements, they offer a sensitive, direct and simple to interpret approach to exploration of the functional activity of hydrogen atoms in proteins. Partial deuteration can add most valuable selectivity by groups of hydrogen atoms. "This article is part of a Special Issue entitled "Science for Life" Guest Editor: Dr. Austen Angell, Dr. Salvatore Magazù and Dr. Federica Migliardo".
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1. Introduction

It is well established that the way protein molecules perform their functions has a fundamental dynamic dimension: fluctuations in the molecular configurations are prerequisites for the reactions to take place. A good example to visualize this is the binding of a Fe atom inside hemoglobin. For the Fe atom to physically access its binding locations inside the wound up protein macromolecule, the path only opens up from time to time by fluctuating deformations in the folded configurational shape. Since these molecular shape fluctuations are in practice most often determined by the temperature, the strong temperature dependence of protein functionality can be understood on the basis of the thermally excited shape/configuration fluctuations.

The thermally activated fluctuation motion of whole macromolecules or parts of them is relatively slow compared to the vibrations of atoms or small groups of atoms (such as an HO radical) or the rotational motion of small molecules around their center of gravity. These latter atomic scale motions (which for convenience we will call "microscopic" in the present review) happens on the 1–100 meV energy scale, which corresponds to about 0.005 to 0.5 ps in time. Phonon excitations prominently belong to this class. Motion related to the rearrangement of macromolecular configurations, fluctuations of parts/subunits of the molecule (so called secondary and ternary structure) are inherently slower processes due to the higher moving masses and lower forces involved (e.g. van der Waals forces as opposed to of chemical binding). They typically happen on time scales longer than about 0.5 ps and at low temperatures these type of motions actually can freeze out, unlike phonons and similar vibrations. For the current purpose the time domain 0.5 ps to 50 ns (i.e. 0.01 μeV to 1 meV in energy) will be called

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http://dx.doi.org/10.1016/j.bbagen.2016.07.030
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"mesoscopic" or "nanoscale" and longer times as "macroscopic" The somewhat arbitrary limit between "meso" and "macro" scale was selected to correspond to the order of magnitude of the lowest neutron energy change (longest time) that can be observed with neutron scattering spectroscopy, namely by Neutron Spin Echo (NSE). The upper end of the macroscopic time domain, of course, is infinity.

Full information on the dynamic behavior of a sample system (that can in principle be obtained by neutron scattering spectroscopy) would imply the observation of the scattering function $S(Q,\omega)$ over the energy transfer range $\hbar\omega$ covering both the microscopic and mesoscopic domains, i.e. 0.01 μeV to 100 meV and the momentum transfer Q domain from some practical resolution limit of 0.01 $Å^{-1}$ to the inverse of the smallest meaningful distance in the molecular structure, typically about 10 $Å^{-1}$.

Here already we have assumed a large practical limitation: we took the momentum transfer Q as a scalar. The sample volumes needed for detailed inelastic scattering studies are too large for producing good quality single crystals for biological matter, and what we can practically observe is the directional average produced by an isotropic polycrystalline (or amorphous) sample. In principle the scattering function for a single crystal $S(\mathbf{Q},\omega)$ cannot be uniquely inverted into the full atomic structure of the sample, which would contain all the atomic positions and motions much like an atom by atom movie. The reason for this is that, while the function $S(\mathbf{Q},\omega)$ delivered by scattering experiments (neutrons, X-rays, light, …) is the result of complex interference phenomena and it is related to the absolute value of the different $\mathbf{Q}$ scattering amplitudes without the complex phases. However, in practice for single crystalline samples in some complex way or another, and with a lot of computing power, the "phase problem" is at the end always solved (occasionally honored by a Nobel prize in one of the disciplines of physics, chemistry or biology). This means that we can get a full picture of what happens in a good single crystal without disorder, where the atomic motion always organizes itself into coherent phonon excitations (or in addition magnons, if the matter is magnetic).

The first sizable compromise we have to accept for the exploration of dynamics of biological matter is that we do not have single crystals to study (neither for looking at nor to function in natural objects), and hence many details of the experimental information get lost in the isotropic averaging. What this means in practice is that the isotropic averaging of information cannot be mathematically inverted in order to get the full picture in space. However, if we have a detailed mathematical model, its isotropic average can be compared in great detail with the experimental data and we will have a most sensitive microscopic and mesoscopic benchmark of our model, which can prove it compatible or incompatible with the experiments down to the atomic scale. As a matter of fact, in natural sciences this kind of information is the only one we really can obtain: is our model compatible with the experimental data (together with an infinite number of other possible models), or not. Experiments can never prove that a model is the only right one. People still write volumes about alternatives to relativity theory, and some of these alternatives cannot be objectively proven wrong.

2. Determination of Lamb–Mossbauer factors and Mean Square Displacements

2.1. Incoherent scattering

In natural biological matter the neutron scattering information is further blurred by the dominant strength of the incoherent scattering cross section of the H atom. This is a bit more subtle averaging than that over all possible orientations of crystalline and non-crystalline local structures. The nuclear spin of proton nucleus is what the neutrons "see" most strongly from a H atom, and under ordinary conditions in the absence of huge or complexly modulated magnetic fields (magnetic resonances) it is randomly oriented. Once the averaging is performed over all possible combinations of orientations of the nuclear spin of all H nuclei in a sample, all effects of correlations between atoms (e.g. preferred distances and geometrical arrangements, moving together as a molecule or by flow, etc.) average to zero and what remains in the resulting incoherent scattering signal is just the motion (if any) of each H atom alone, without any correlation of and with its neighbors. The corresponding incoherent scattering function $S_i(\mathbf{Q},\omega)$ (or $S_i(Q,\omega)$ after averaging to all directions in not single crystalline matter) depends on and reveals the correlation of an individual H atom with itself, i.e. its trajectory of motion $\mathbf{r}(t)$ among its invisible neighbors.

There is one practical situation (outside fancy magnetic conditions) where there is a long lived correlation between the nuclear spins of H atoms: the H_2 molecule, a rather rare object in biological studies. The proton nuclear spins are either parallel or anti-parallel to each other for macroscopic times at ordinary temperatures in H_2 molecules (ortho and para states, respectively). Since the nuclear spin orientations between different H_2 molecules are fully random under ordinary conditions, the H_2 molecules will act as incoherent scattering object (with ortho-H_2 having a much larger scattering cross section than para), so we can trace the motion of the molecule by "incoherent" neutron scattering in this particular case. In reality the scattering is coherent within the H_2 molecules – leading to a Q dependent atomic structure factor in contrast to atomic H. The same phenomenon can actually also exist with water molecules (ortho- and para-water have been indeed recently successfully separated [1]), but under the conditions of atomic densities in biological matter the conversion time between the two nuclear spin isomers of water is shorter than the microscopic time domain we are concerned with.

The dominating incoherent character of H scattering in biological matter is an important simplification: above a rather small and/or well identifiable background (e.g. Bragg peaks) we can extract information on the motion of H atoms without being mixed to or masked by signal from a large number of other, differently behaving atoms and structures in the sample. We can address the interpretation of the experimental observations by models of the H dynamics (i.e. ensemble of trajectories) as the only visible objects in a much more complex mix with a lot more unknown details and degrees of freedom. For example, to start with, if all H atoms would be immobile on micro- and mesoscopic time scales, their incoherent scattering signal would be

$$S_i(Q,\omega) = \sigma_i\,\delta(\omega) \tag{1}$$

where the scattering intensity constant σ_i is simply proportional to the density of H atoms in the sample. Any deviation from this simple form is a signature of motion of the H atoms.

Deviations from Eq. (1) can be considered in terms of the following parametrical form:

$$S_i(Q,\omega) = \sigma_i\,[A(Q)\delta(\omega) + B(Q)F(Q,\omega)] \tag{2}$$

Here for convenience we assume for the spectral shape function F that

$$\int_{-\infty}^{\infty} F(Q,\omega)d\omega = 1. \tag{3}$$

Under this condition $A(Q) + B(Q) = 1$ is to be expected for model assumptions, which is on the other hand hard to precisely verify experimentally since the accessible range of energy transfers ω is experimentally limited. For the conversion of measured neutron scattering intensities/cross sections to scattering functions $S(Q,\omega)$ the reader is referred to general textbooks, e.g. [2].

2.2. Lamb-Mossbauer factor and Mean Square Displacement (MSD)

In order to examine the practicalities of using Eq. (2), let us start with the example of phonons and similar vibrations. The H particle trajectories can be viewed as a random sum at any time of

Please cite this article as: S. Magazù, et al., Protein dynamics as seen by (quasi) elastic neutron scattering, Biochim. Biophys. Acta (2016), http://dx.doi.org/10.1016/j.bbagen.2016.07.030

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