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Structural dynamics of bio-macromolecules by NMR: The slowly relaxing local structure approach

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Abbreviations: AK, adenylate kinase; AKeco, adenylate kinase from *Escherichia coli*; B.-O., Born–Oppenheimer approximation; CaM, Ca^{2+}-calmodulin; CSA, chemical shift anisotropy; 3D GAF, 3-dimensional Gaussian axial fluctuations; DNA, deoxyribonucleic acid; EDA, essential dynamics analysis; EMF, extended model-free; ESR, electron spin resonance; FPK, Fokker–Planck–Kramers; GB3, the B3 immunoglobulin-binding domain of streptococcal protein G; GNM, Gaussian network model; HP36, chicken villin headpiece subdomain protein; iRED, isotropic reorientational eigenmode dynamics; JAM, jumping among minima; LC, liquid crystal; MD, molecular dynamics; MF, model-free; MOMD, microscopic order macroscopic disorder; NCR, network of coupled rotators; NMA, normal mode analysis; NMR, nuclear magnetic resonance; *NOE*, nuclear Overhauser enhancement; PCA, principal component analysis; POMF, potential of mean force; protein *L*, the B1 immunoglobulin-binding domain of *Peptostreptococcal* protein *L*; RDC, residual dipolar coupling; RNA, ribonucleic acid; SLE, stochastic Liouville equation; SRLS, slowly relaxing local structure.

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1. Introduction

Protein dynamics by NMR has been reviewed extensively in recent years [1–10]. These surveys show decisively that information on structure should be complemented by information on motion both to properly characterize the protein, and to understand its function. The time scale accessible by NMR extends from picoseconds to days, with different methods accessing different parts of this time axis. Here we focus on heteronuclear NMR spin relaxation used to study *ps* to *ns* protein dynamics. The slow limit of this time regime is determined by the global tumbling of the protein, with the rates for internal motion of the probe being typically faster.

Based on experience gained over nearly a decade we came to the conclusion that the traditional method of NMR spin relaxation analysis in proteins and nucleic acids, called "model-free" (MF) [11–13], does not extract adequately and fully the information inherent in the experimental data largely because it is oversimplified. We have developed an approach that overcomes many of the MF deficiencies. This method, called the slowly relaxing local structure (SRLS) [14–20], may be regarded as a generalization of MF. SRLS predates the MF approach, and even provided derivations of the exact equivalents of the MF equations [15,21].

The primary issue is how to address the great complexity of protein dynamics, including global and restricted local motions. The typical probe for backbone motion in proteins is the ^{15}N–^{1}H bond, with ^{15}N relaxation observed [1–10]. The typical probe for side-chain motion is the uniformly ^{13}C-labeled, fractionally deuterated, $^{13}CDH_2$ methyl group, with deuterium relaxation observed [6,22–24]. A given probe might move independently of the protein or be coupled to it dynamically. Any general theoretical approach should account for the relationship between the global and local motions, for the local ordering, and for the relevant magnetic interactions. The respective tensorial properties should be realistically chosen within the scope of the data sensitivity. Thus, the model should include the appropriate parameter combinations. All of these features and capabilities are inherent to SRLS. Correlations along the protein backbone might well be important [3,25–27], but the local factors mentioned above must first be accounted for. That the latter are important was shown in theoretical studies [16,17], and confirmed experimentally [18–20]. Effects from statistical inter-dependence of the various motions we have referred to as "mode-coupling".

NMR spin relaxation in liquids pertains to the Redfield limit where only relaxation parameters can be measured [28,29]. The number of experimental data points is limited; one acquires typically three data points (^{15}N T_1, T_2, and ^{15}N–{^{1}H} *NOE*) for amide ^{15}N and two (^{2}H T_1 and T_2) for methyl ^{2}H at each magnetic field. Hence, it is not practical to treat explicitly the complex local motions coupled to the global motion and to account explicitly for correlations along the protein backbone. However, the latter can affect the analysis implicitly via the values of the parameters determined [20].

As currently implemented to treat NMR spin relaxation in proteins and nucleic acid fragments, SRLS is a stochastic two-body coupled-rotator diffusive approach [16–20]. It can be generalized to three (or more) bodies that are coupled, as well as the inclusion of inertial effects in these motions [16], as opposed to the purely