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Rotational velocity rescaling of molecular dynamics trajectories for direct prediction of protein NMR relaxation

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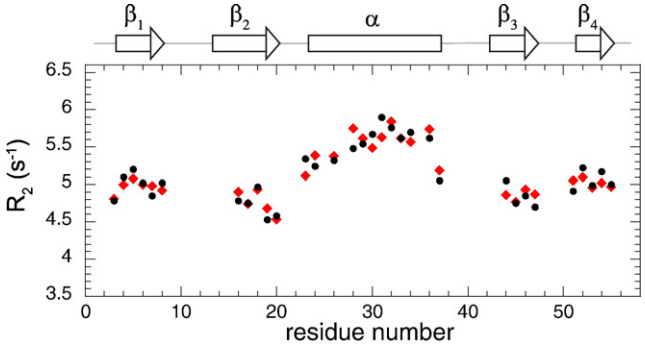
HIGHLIGHTS

- Rescaling of rotational velocity in molecular dynamics for the B3 domain of Protein G reproduces its anisotropic tumbling.
- The optimal rotational velocity rescaling factor closely matches that predicted from the self-diffusion rate of TIP3P water.
- ^{15}N relaxation data of GB3 can be predicted from the rescaled trajectories with no system-specific adjustable parameters.
- ^{15}N chemical shift anisotropy of −168 ppm predicts the field-dependent data better than reported residue-specific values.
- Sites for which observed and predicted relaxation markedly differ are assessed in terms of implied force field inadequacies.

GRAPHICAL ABSTRACT



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ABSTRACT

Rotational velocity rescaling (RVR) enables ^{15}N relaxation data for the anisotropically tumbling B3 domain of Protein G (GB3) to be accurately predicted from 1 μs of constant energy molecular dynamics simulation without recourse to any system-specific adjustable parameters. Superposition of adjacent trajectory frames yields the unique rotation axis and angle of rotation that characterizes each transformation. By proportionally scaling the rotation angles relating each consecutive pair of frames, the rotational diffusion in the RVR-MD trajectory was adjusted to correct for the elevated self-diffusion rate of TIP3P water. ^{15}N T_1 and T_2 values for 32 residues in the regular secondary structures of GB3 were predicted with an rms deviation of 2.2%, modestly larger than the estimated experimental uncertainties. Residue-specific chemical shift anisotropy (CSA) values reported from isotropic solution, liquid crystal and microcrystalline solid measurements less accurately predict GB3 relaxation than does applying a constant CSA value, potentially indicating structure-dependent correlated variations

Abbreviations: RVR, rotational velocity rescaling; GB3, B3 domain of Protein G; PDB, protein data bank; MD, molecular dynamics; rms, root mean square; RDC, residual dipolar coupling; NOE, nuclear Overhauser enhancement; CSA, chemical shift anisotropy; ROESY, rotating frame nuclear Overhauser enhancement spectroscopy.

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in $^{1}H-^{15}N$ bond length and ^{15}N CSA. By circumventing the quasi-static analysis of NMR order parameters often applied in MD studies, a more direct test is provided for assessing the accuracy with which molecular simulations predict protein motion in the ps–ns timeframe. Since no assumption of separability between global tumbling and internal motion is required, utility in analyzing simulations of mobility in disordered protein segments is anticipated.

1. Introduction

NMR relaxation measurements provide experimental monitors of protein conformational dynamics with an atomic level of detail that is unmatched by any other technique. As such, in principle, relaxation experiments offer the most stringent test available for assessing the accuracy with which molecular dynamics simulations model the rates of intramolecular motion that occurs in proteins and biomacromolecules in general. In practice, nearly all comparisons between MD predictions and observed protein NMR relaxation behavior reported to date have applied a quasi-static analysis. In this approach the dominant relaxation contribution arising from the overall tumbling of the molecule is removed from the simulation by superimposing each frame of the trajectory upon the initial frame. In the familiar case of ^{15}N amide relaxation measurements, the orientational autocorrelation for the individual $^{1}H-^{15}N$ bond vectors is then calculated as a function of time separation along the trajectory. Instead of transforming these modeled time dependent autocorrelation functions into frequency domain spectral densities to directly predict the observed T_1, T_2 and heteronuclear NOE data, "plateau" values are estimated from each bond vector autocorrelation function and compared to experimental S^2 order parameter values derived from the classical dynamical analysis of NMR relaxation data of Lipari and Szabo [1,2].

By construction, the order parameter provides a time-independent characterization of the diversity of bond vector orientations within a conformational distribution. The original Lipari–Szabo analysis, as well as the subsequent three parameter extension [3], also includes a time constant to characterize how rapidly the assumed stable conformational distribution is sampled. In practice, these derived time constants are often poorly constrained by the experimental data and are rarely used for quantitative structural interpretation [4,5]. By relating the S^2 order parameters to the spectral density values required for prediction of the NMR relaxation rates, the Lipari–Szabo formalism largely avoids the need for detailed modeling of the underlying conformational dynamics which are necessarily severely underdetermined by the available experimental data. One key assumption of this model-free approach is the independence of internal motion from the global tumbling of the macromolecule. Although factorization of the internal and global autocorrelation functions cannot be exact when the overall rotation is anisotropic [1], to a useful approximation the original assumption of isotropic tumbling can be expanded to molecular rotation according to a time-independent diffusion tensor that is either axially symmetric (4 adjustable parameters) or fully asymmetric (6 adjustable parameters) [6]. The approximation of a time-independent diffusion tensor for a conformationally dynamic macromolecule is generally believed to yield only modest errors for well-ordered single domain proteins [7], although it can more significantly fail in the presence of interdomain mobility [8].

One approach for moving beyond the assumption of independent internal and global motion is the slowly relaxing local structure approach of Freed and colleagues [9–11]. A recent implementation by Zerbetto, Buck, Meirovitch and Polimeno [12] utilized CHARMM27 [13] molecular dynamics simulations to provide estimates for the coupling potentials between global tumbling and the various sites of local motion in a two-body coupled-rotator stochastic model. The global tumbling dynamics were estimated by a hydrodynamics modeling approach. The experimental T_1, T_2 and NOE data were then used to optimize the rate of local motion and the orientation of each local frame relative to the global diffusion frame. The problem of achieving a proper Boltzmann probability distribution was resolved by postulating that the potential of mean force is adequately represented by a phenomenological equation relating the MD-derived coupling potentials and the local diffusion frames.

To adequately model global molecular tumbling in an isotropic solution, an MD trajectory needs to be long enough so that every orientation of each bond vector is approximately equally probable. Significant errors in the derived correlation function can be anticipated for trajectories that are less than 100-fold longer than the molecular tumbling time [14]. To help mitigate the effects of undersampling, Prompers and Brüschweiler [15] proposed isotropic reorientational eigenmode dynamics (iRED) covariance analysis in which the averaging over the correlated bond vector orientations within an MD trajectory is then isotropically averaged over all orientations in space. Since this analysis removes the time dependence of the bond vector correlations, correlation time information is reconstructed by projecting the reorientational eigenmodes onto the MD trajectory vectors. Analysis of a 5 ns explicit solvent simulation of ubiquitin, yielded nine largest eigenmodes with derived correlation times ranging from 368 ps to 660 ps. The top five eigenmodes were assigned to global tumbling modes, and their correlation times were then rescaled by an average factor of 7-fold to obtain values near the experimental τ_c value of 4.03 ns [16]. The correlation times of the second set of five largest eigenmodes were then rescaled by factors ranging from 1.7 to more than 4000 to achieve an optimal fit to the experimental ^{15}N relaxation data.

More recently, as microsecond long simulations have become more generally feasible, the intrinsic limitation of undersampling of molecular tumbling in simulations of modestly sized proteins has become less severe. However, an additional complication to the direct prediction of NMR relaxation values from MD simulations is that the widely used nonpolarizable water models all predict self-diffusion coefficients that are markedly higher than the experimental value. Self-diffusion for the original TIP3P model is 2.35-fold too high, while for the CHARMM-modified TIP3P model the prediction is 2.57-fold above the experimental value [17]. In this regard, the SPC model is modestly better (1.83-fold), and the SPC/E model approaches the experimental result (1.17-fold) [17]. Since for most protein backbone amide nitrogens, global tumbling provides the dominant contribution to relaxation, accurate modeling of the overall rotational diffusion is essential for robust predictions. Despite a similar issue of inaccurately modeled solvent self-diffusion, Peter, Daura and van Gunsteren [18] demonstrated that the ROESY buildup curves for various $^{1}H-^{1}H$ interactions of a heptapeptide of β-amino acids in methanol at 298 K could be reasonably reproduced from a GROMOS96 simulation. Using a 1.2 μs OPLS-AA force field simulation of ubiquitin, Shaw and colleagues [19] have extracted ^{15}N order parameters directly from the unscaled trajectory by fitting to the extended Lipari–Szabo model [3] with the molecular tumbling time optimized to 1.98 ns, reflecting the elevated self-diffusion rate of the SPC water model used in that study.

Direct prediction of experimental relaxation data offers several advantages over the more familiar comparisons with derived order parameter values. Particularly in the case of internal motion occurring on the ns timescale, there are ambiguities as to how to best extract an effective order parameter, with a resultant loss in the information content resident in the original experimental data. Full atom molecular simulations represent the current best predictions for the conformational