Toward Quantitative Interpretation of Methyl Side-Chain Dynamics from NMR by Molecular Dynamics Simulations

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Introduction

Methyl groups are the dynamically best studied side-chain moieties of proteins. Advances in molecular dynamics (MD) force fields have recently allowed the nearly quantitative interpretation of protein backbone dynamics as measured by NMR spin relaxation and residual dipolar couplings. These improvements were solely due to modification of the backbone φ, ψ dihedral angle potential, as demonstrated for the AMBER99SB force field1 in our previous work.2,3 Because changes in side-chain motions are not necessarily correlated to changes in protein backbone mobility, it is unclear how these force-field modifications affect side-chain dynamics.

Experimental and Computation

Methyl side-chain dynamics of calbindin in its calcium-bound form have recently been reported.4 Computation was performed using the AMBER 8.0 software together with the AMBER99SB force field.

Results and Discussion

$^{13}$CH$_2$D-methyl relaxation measurements allow the unambiguous extraction of spectral densities $J(0)$, $J(\omega_D)$, and $J(2\omega_D)$, where $\omega_D$ is the Larmor frequency of deuterium. As shown here, these spectral densities lend themselves to direct comparison with computer simulations (Figure 1). The agreement for $J(\omega_D)$ and $J(2\omega_D)$ both at 500 MHz (black symbols) and 600 MHz (red symbols) field strengths (panels C,D) is excellent (correlation coefficients $r \geq 0.94$), and still remarkably good for $J(0)$ (panels A,B; $r = 0.86$).

Conclusions

These results demonstrate that the modified backbone potential of AMBER99SB considerably improves the description of amino-acid methyl side chain dynamics, suggesting a direct connection between the accurate representation of the structure (and dynamics) of the protein backbone and side-chain mobility.5

Figure 1. Comparison between experimental and MD back-calculated spectral densities $J(\omega)$ of Ca$^{2+}$-bound calbindin. (A) $J(0)$ color coded by residue type: Ala (black), Ile (red), Leu (blue), Met (magenta), Thr (cyan), Val (green). Correlation coefficient excludes Thr45. (B) $J(0)$ as a function of residue number from experiment (black) and MD (red). (C) $J(\omega_D)$ at 500 MHz (black) and 600 MHz (red). (D) $J(2\omega_D)$ at 500 MHz (black) and 600 MHz (red).

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References