Supporting Information

Accurate Prediction of Protein NMR Spin Relaxation by Means of Polarizable Force Fields. Application to Strongly Anisotropic Rotational Diffusion

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Structure of the UIM domain

Protein sequence of the UIM domain used in the present study along with its numbering and secondary structure representation.

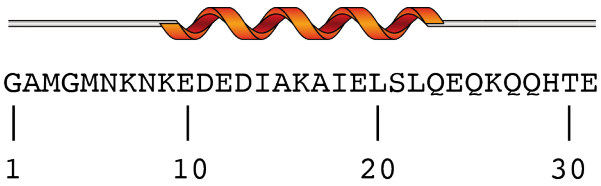
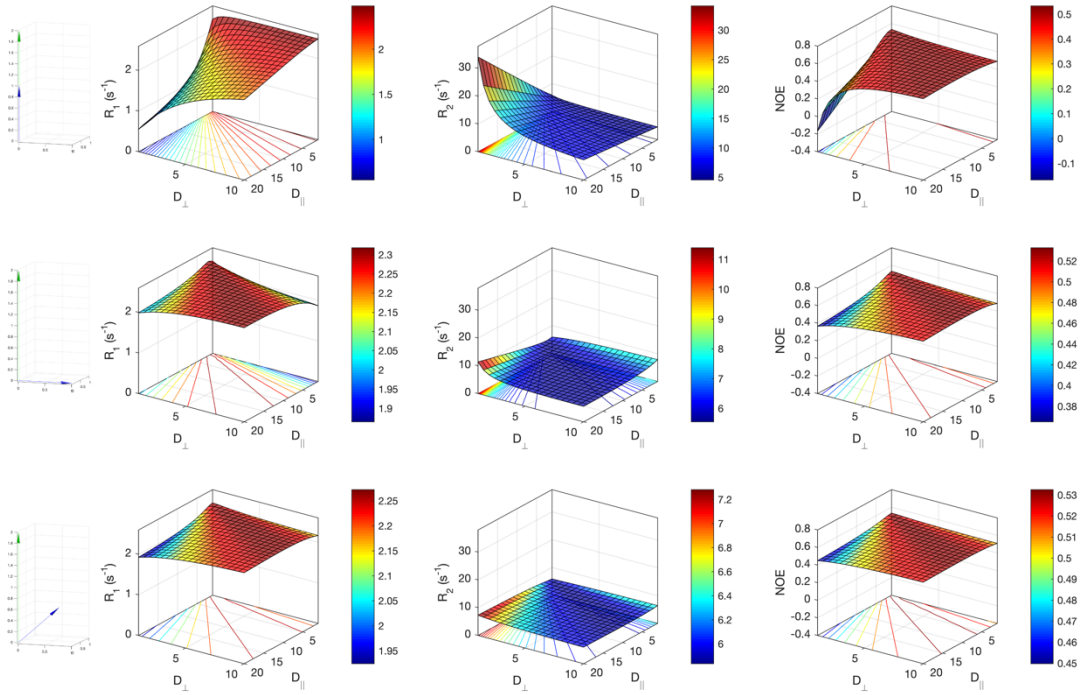


Figure S1A-B

Dependence of the NMR spin relaxation parameters R_1, R_2 and NOE as a function of various degrees of anisotropy ($D_\Delta = D_{||}/D_\perp$) and NH vector orientation with respect to the principal axis frame (PAF). On the left panel, the $D_{||}$ axis of the PAF axis is represented in green along the z axis of the laboratory frame and three NH unit vectors are presented with a 0° (top), 90° (middle) and 54° (bottom) orientation with respect to the $D_{||}$ axis of the PAF. The synthetic data were obtained by assuming local model-free combined with an axially symmetric molecular reorientation (see analytical expressions in materials and methods). In (A), we used the following parameters: S^2=0.84, a local motion τ_{loc}=200 ps, a global tumbling τ_c=4.0 ns for a ^{1}H frequency of 600MHz while in (B) we have used S^2=0.2, a local motion τ_{loc}=200 ps, a global tumbling τ_c=4.0 ns for a ^{1}H frequency of 600MHz. Plain lines represent the surface projection for a given anisotropy.

A)



B)

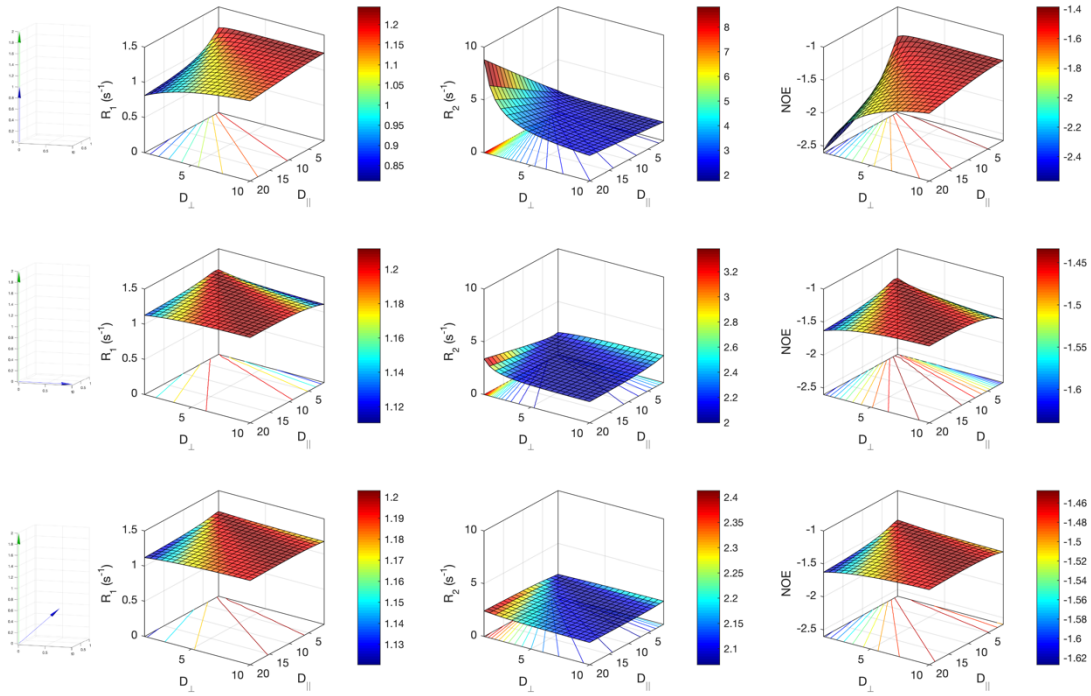


Figure S2
A) Cartoon representation of the UIM domain along with the orientation of the laboratory frame and the unique axis ($D_{\|}$) of the rotational diffusion tensor (in blue). (B) The distribution of NH unit vectors used to determine the rotational diffusion of the UIM domain. The laboratory frame is represented in red with the same orientation as in A), the unique axis of the rotational diffusion is represented in blue while the α-helix NH unit vectors are represented in green. One has to keep in mind that the relaxation parameters are not sensitive to the directionality (sign) of the NH-vector coordinates.[1]

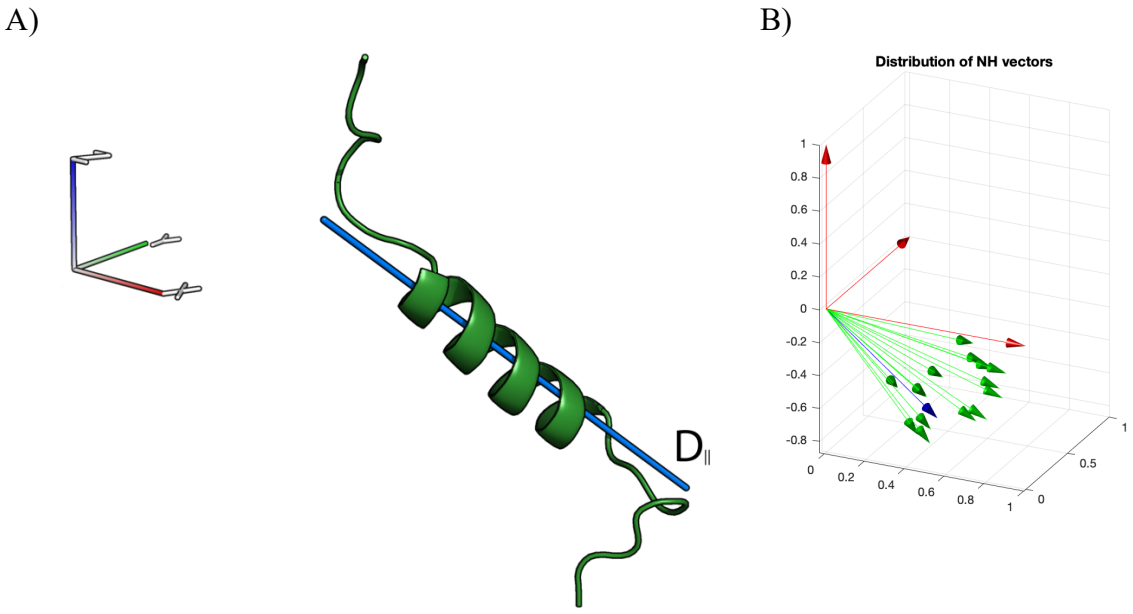
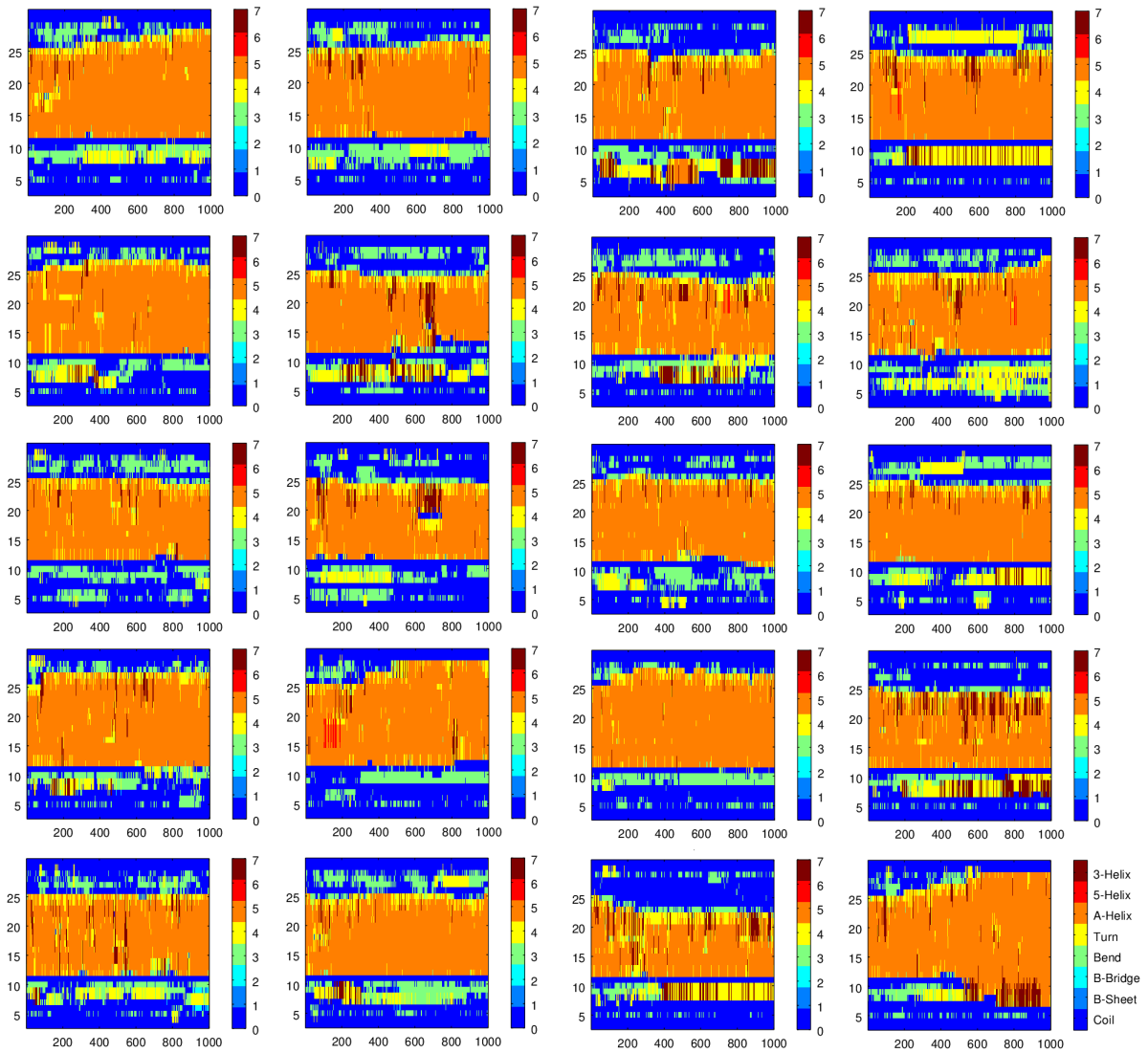
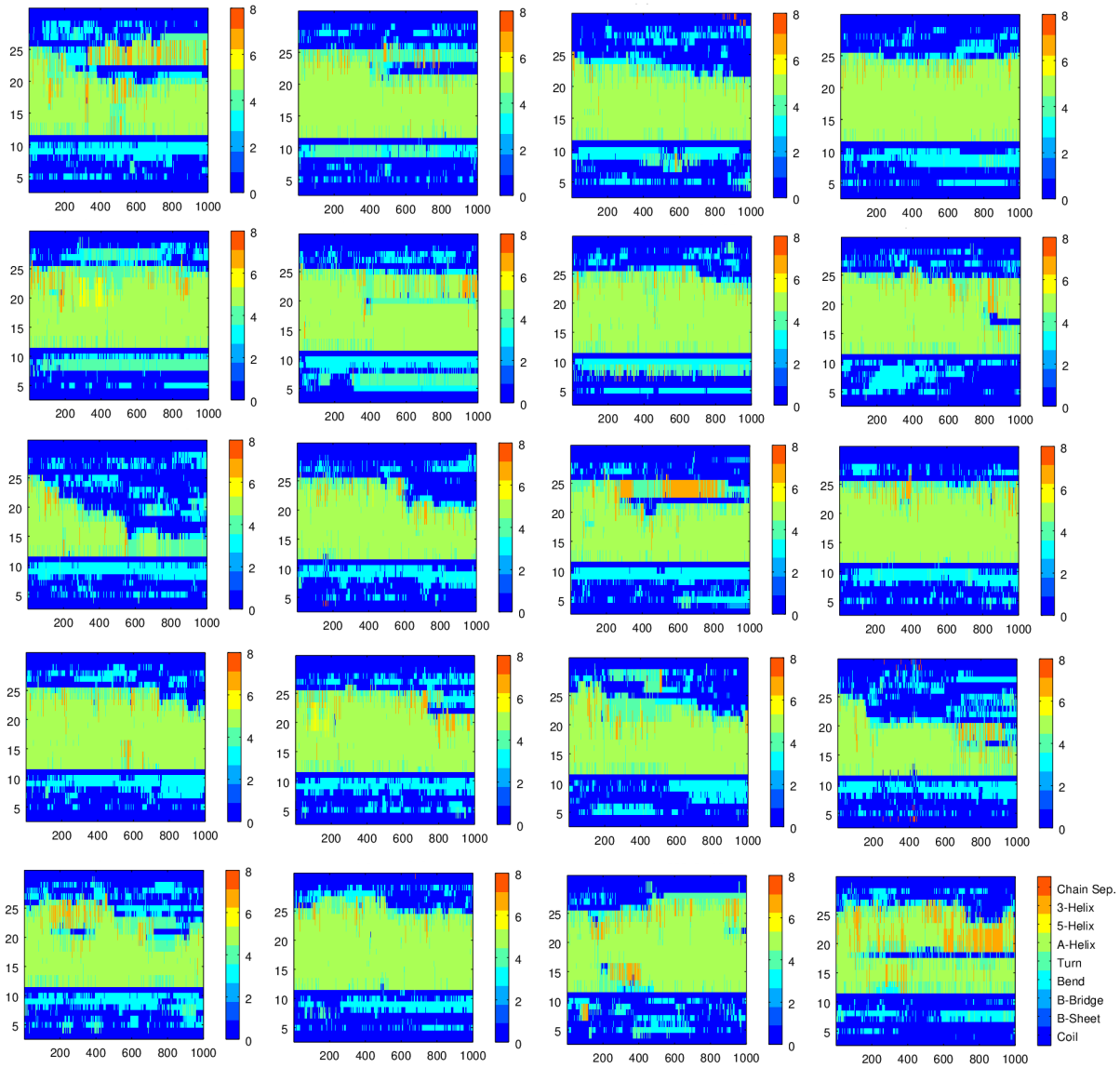


Figure S3: Secondary structure of the UIM domain as a function of time for the different trajectories and FFs used in the present study. Each panel represents a trajectory length of 50 ns (1000 steps of 50 ps) and describes the secondary structure for each amino acids (1-31). The bar plot numbering indicates the corresponding fold and is shown on the last plot.

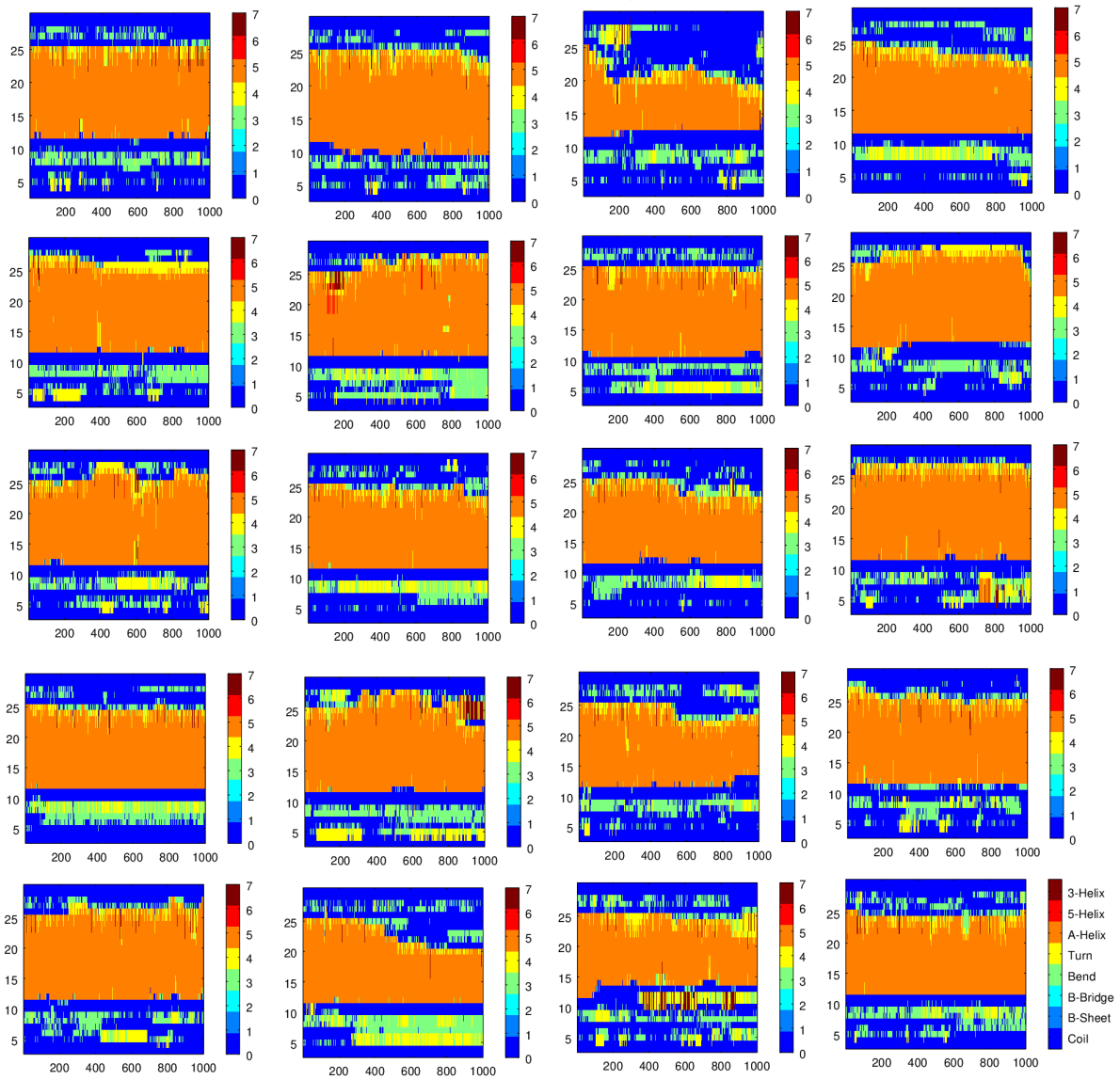
ff99SB-disp



ff15ipq


Chain Sep.
3-Helix
5-Helix
A-Helix
Turn
Bend
B-Bridge
B-Sheet
Coil

C36m



AMOEBA

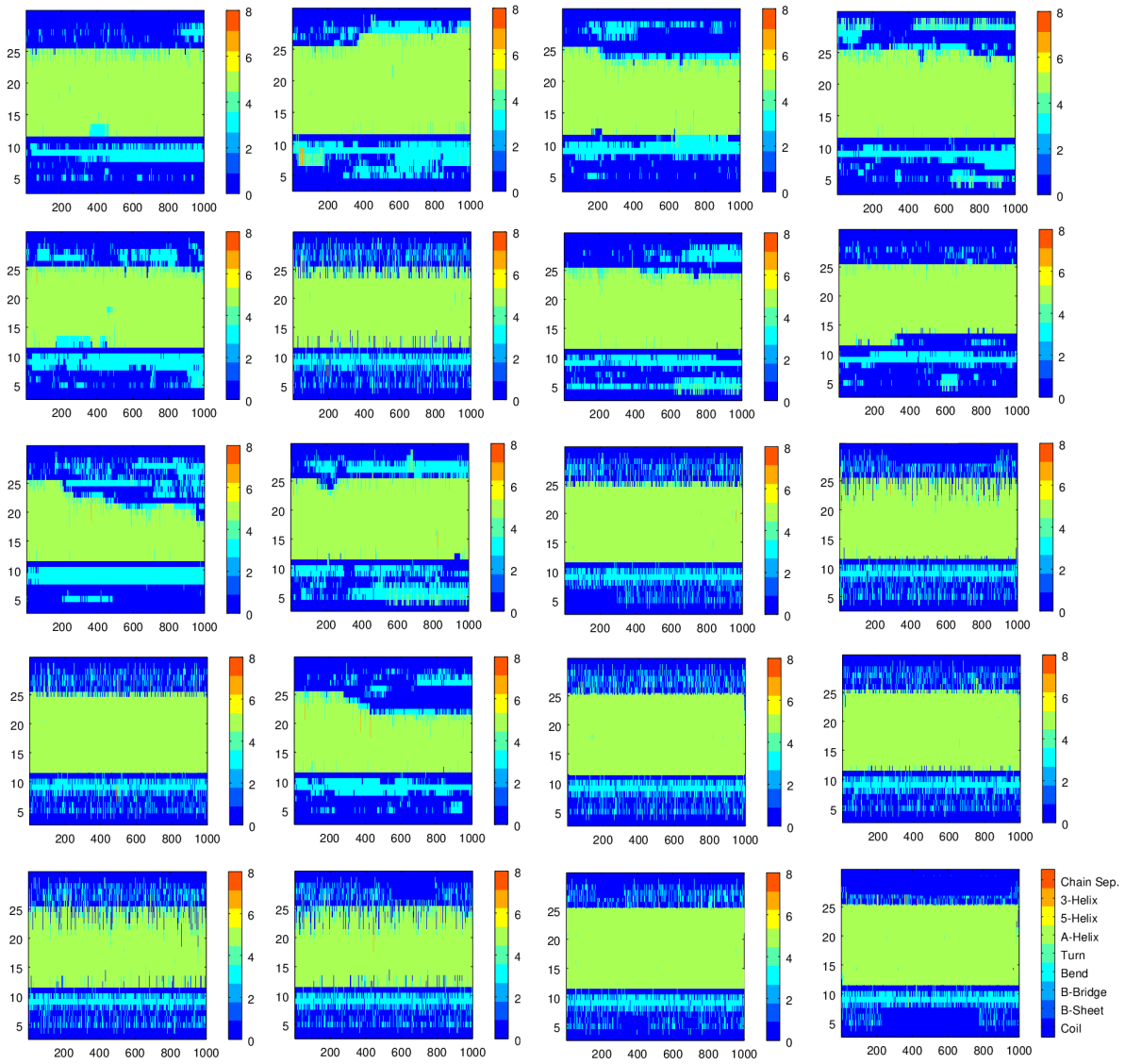

Chain Sep.
3-Helix
5-Helix
A-Helix
Turn
Bend
B-Bridge
B-Sheet
Coil

Table S1: Average radii of gyration of UIM along with their respective coordinates computed in the full ensemble of simulations for each FF. According to these results, the UIM domain clearly shows an axially symmetric tumbling.

Force Field	Rg (nm)	R_g^x (nm)	R_g^y (nm)	R_g^z (nm)
ff99SB-disp	1.40 ± 0.11	0.57 ± 0.08	1.31 ± 0.13	1.36 ± 0.12
ff15ipq	1.27 ± 0.18	0.58 ± 0.07	1.20 ± 0.20	1.22 ± 0.19
C36m	1.29 ± 0.15	0.58 ± 0.07	1.19 ± 0.17	1.25 ± 0.16
AMOEBA	1.36 ± 0.11	0.50 ± 0.06	1.30 ± 0.12	1.34 ± 0.12

Correlation functions analysis

Relaxation parameters are expressed as a linear combination of spectral densities *J(w)* operating at different Larmor frequencies that are the Fourier transforms of the heavy atom-proton vector autocorrelation functions *C(t)* that expresses the rotational motion of a NH bond (v_{NH}).[2-3] The v_{NH} motions measured in experiments can be classified into three distinct sources: global tumbling of the host domain $C_O(t)$, its local motions $C_I(t)$, as well as QM zero-point vibrations described by a constant correction factor ζ[4] initially set as $(1.02/1.041)^6 \sim 0.89$.

For the purpose of defining atoms associated with the reference frame, we included the similar atoms used to analyze NMR data. The computation of the rotational diffusion D_{rot} using our PLUMED-fork (https://github.com/zharmad/plumed2) is based on the autocorrelation of the molecular orientation expressed as a quaternion Q, whose vector components contain information on the axial elements of D_{rot} after appropriate frame transformations[5]. The numerical resolution of $C_I(t)$ and $C_O(t)$ was set to every 5 ps, which implicitly assumes that fast motions < 5 ps in $C_I(t)$ were effectively collapsed into S_{fast} not visible in *J(w)*. Our current implementation of spin relaxation computation workflow is publicly available (https://github.com/zharmad/SpinRelax). In this work, we have approximated the $C_O(t)$ correlation function with the global tumbling of an axially symmetric top where the rotational diffusion tensor D_{rot} is comprised of axial components $D_{\parallel}$ and $D_{\perp}$ or equivalently isotropic tumbling D_{iso} and axial anisotropy D_{Δ}, where $D_{\Delta} = D_{\parallel}/D_{\perp}$ and $D_{iso} = (2\ D_{\perp} + D_{\parallel})/3$.[6]

Figure S4. Internal correlation function analysis $C_I(t)$ for selected residues mentioned in the main text in the four FFs, colored according to the legend. Fitted autocorrelation is shown in color, and the raw simulated data is shown in grey. The residue and local secondary structure are mentioned above each plot.

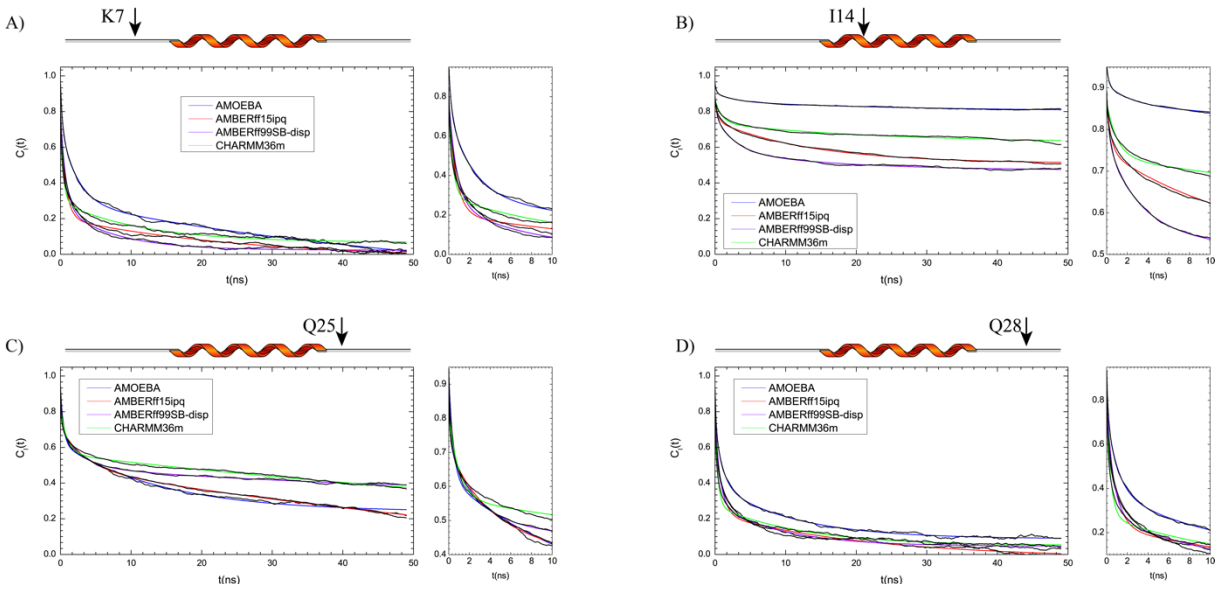
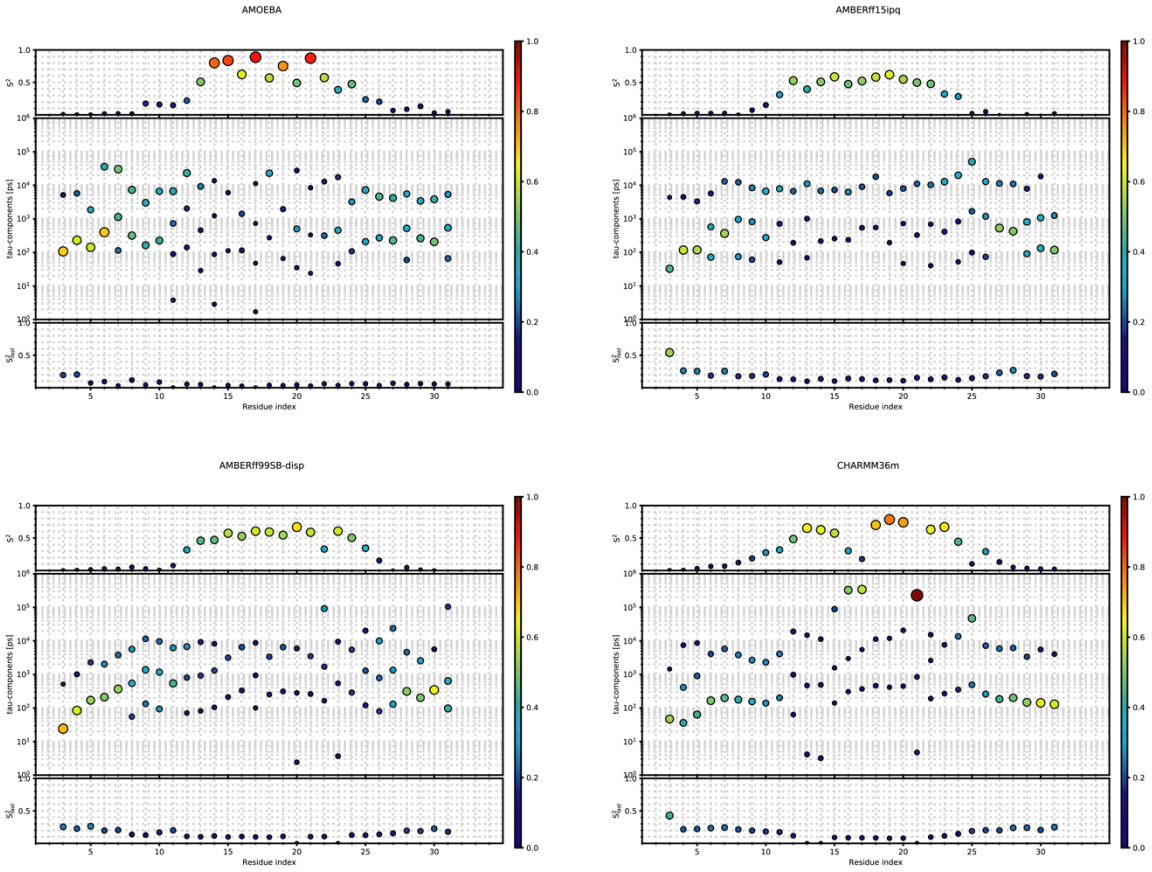


Figure S5. Fitted parameters of $C_I(t)$ to curves computed from molecular dynamics trajectories of UIM. The results are presented for the four FFs used in the present work. The three subplots respectively record the order parameters S^2, the set of motional parameters each containing a time-scale τ_j and a magnitude α_j, and the fast motions S^2_{fast} that have timescales below the resolution of $C_I(t)$. All values are shaded according to the relative magnitude of contributions such that $S^2 + \sum_j \alpha_j + S^2_{fast} = 1$.



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2. Palmer, A. G., NMR characterization of the dynamics of biomacromolecules. *Chem Rev* **2004,** *104* (8), 3623-3640.
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4. Case, D. A., Calculations of NMR dipolar coupling strengths in model peptides. *Journal of Biomolecular NMR* **1999,** *15* (2), 95-102.

5. Chen, P.-c.; Hologne, M.; Walker, O., Computing the Rotational Diffusion of Biomolecules via Molecular Dynamics Simulation and Quaternion Orientations. *J Phys Chem B* **2017,** *121* (8), 1812-1823.
6. Fushman, D.; Varadan, R.; Assfalg, M.; Walker, O., Determining domain orientation in macromolecules by using spin-relaxation and residual dipolar coupling measurements. *Prog Nucl Magn Reson Spectrosc* **2004,** *44* (3), 189-214.