Using NMR relaxation data to improve the dynamics of methyl groups in AMBER and CHARMM force fields

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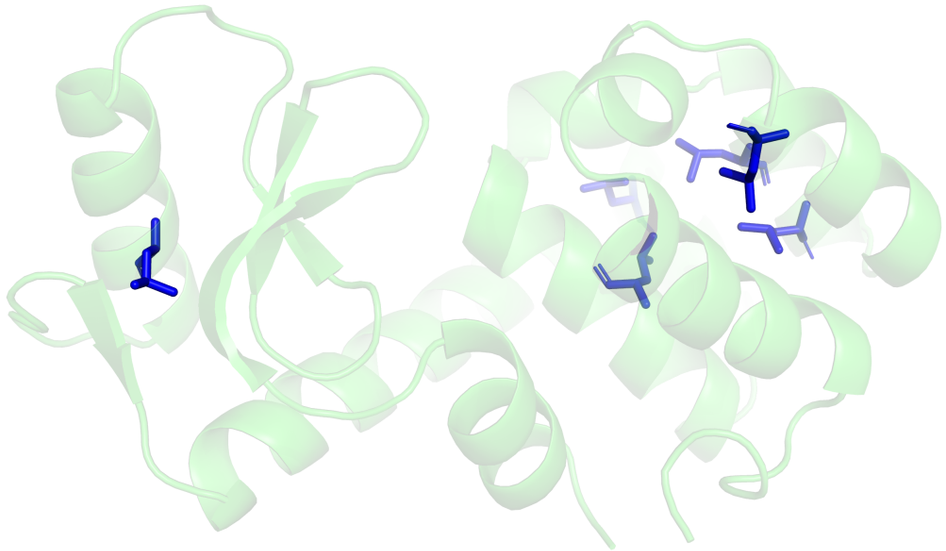
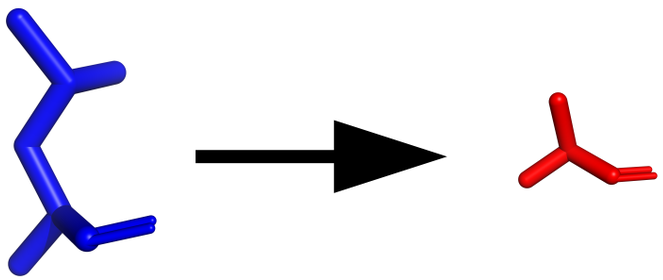
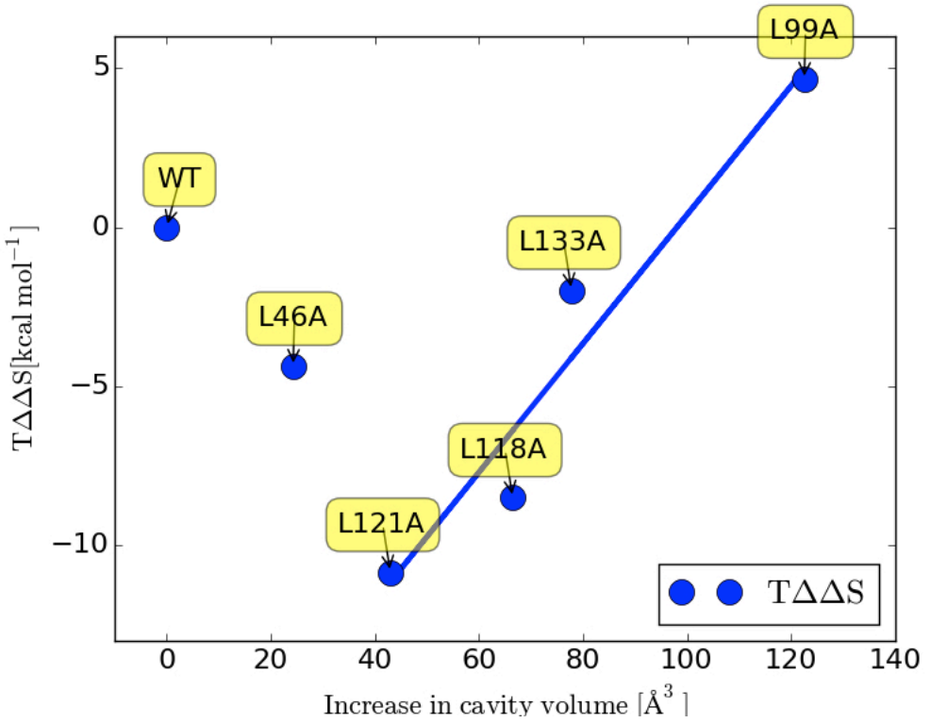
- Thermostability of T4 Lysozyme and configurational entropy
- Order parameter and relaxation rates
- Reparametrization of force fields
- Applicability of Lipari-Szabo model for methyl groups
- Force field evaluation

Thermostability of T4L mutants







Xue, Hoffmann, et al., in preparation

Configurational entropy from NMR relaxation

$$\Delta S_{tot} = \Delta S_{conf} + \underbrace{\Delta S_{rot+trans} + \Delta S_{solvent} + \Delta S_{other}}_{< \Delta S_{conf}}$$

$$\Delta S_{conf} = \Delta S_{bb} + \Delta S_{sc}$$

Changes in configurational entropy are connected to changes in dynamics

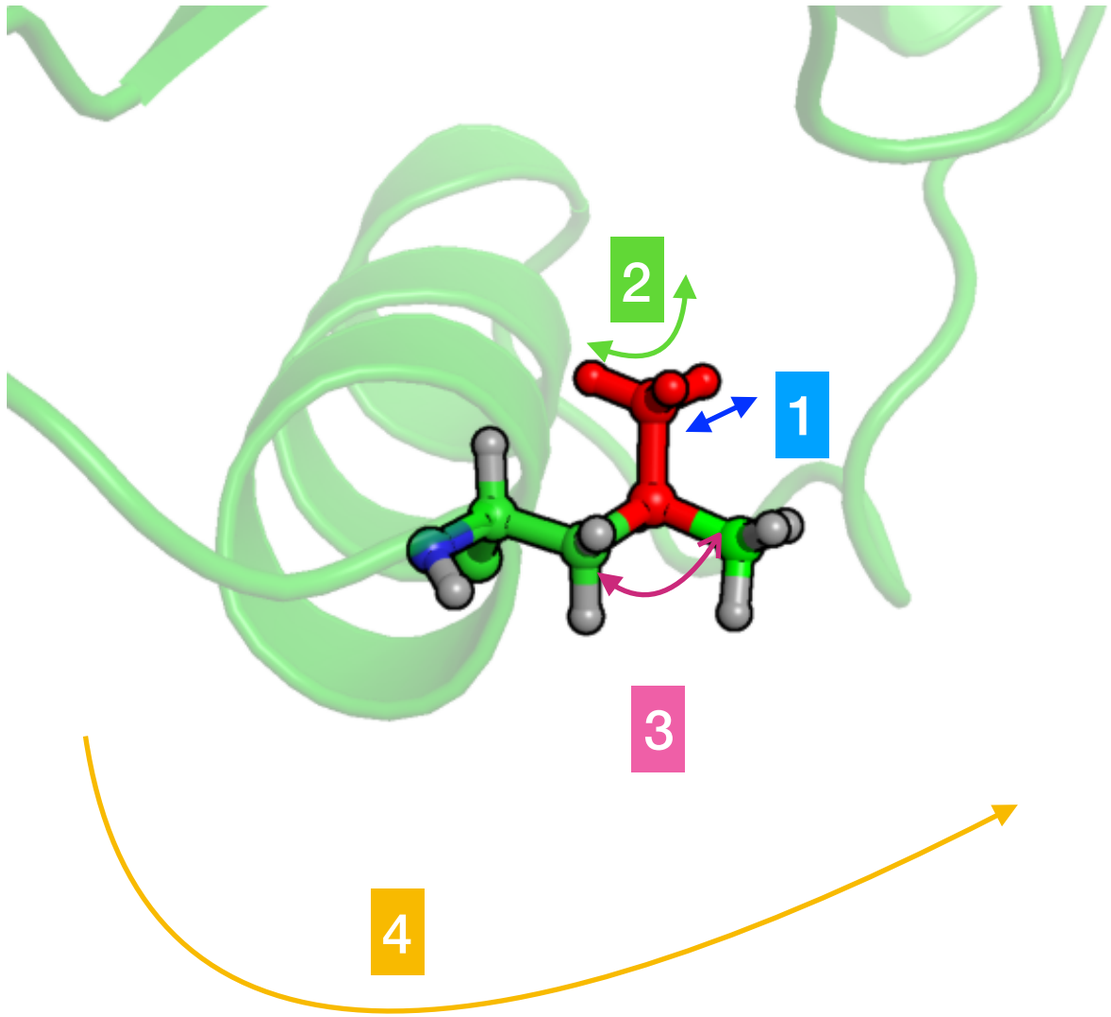
Dynamics can be represented by the orientational motions of representative (backbone and sidechain) bonds

N-H → **Order parameter S^2**

CH_3 → **Order parameter S^2**

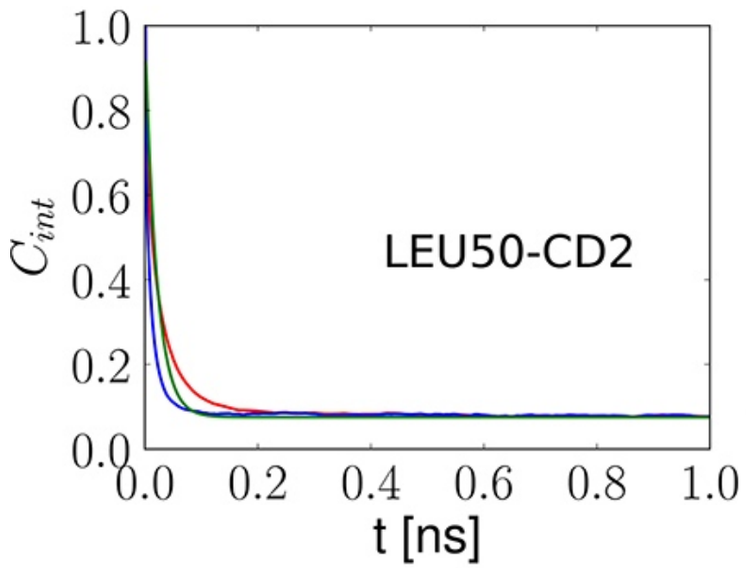
Methyl order parameter

$$S^2 = \lim_{t->\infty} C_{int}$$



1. Librational motions (fs)
2. Methyl rotation (several ps)
3. Rotamer jumps (ps-ns)
4. Global tumbling (~10ns)

Bond motions measured by NMR order parameter via internal time correlation function $C_{int}(t)$



$$\rightarrow \frac{1}{9} S^2_{axis}$$

NMR order parameter

Relaxation rates

↓

Spectral density points

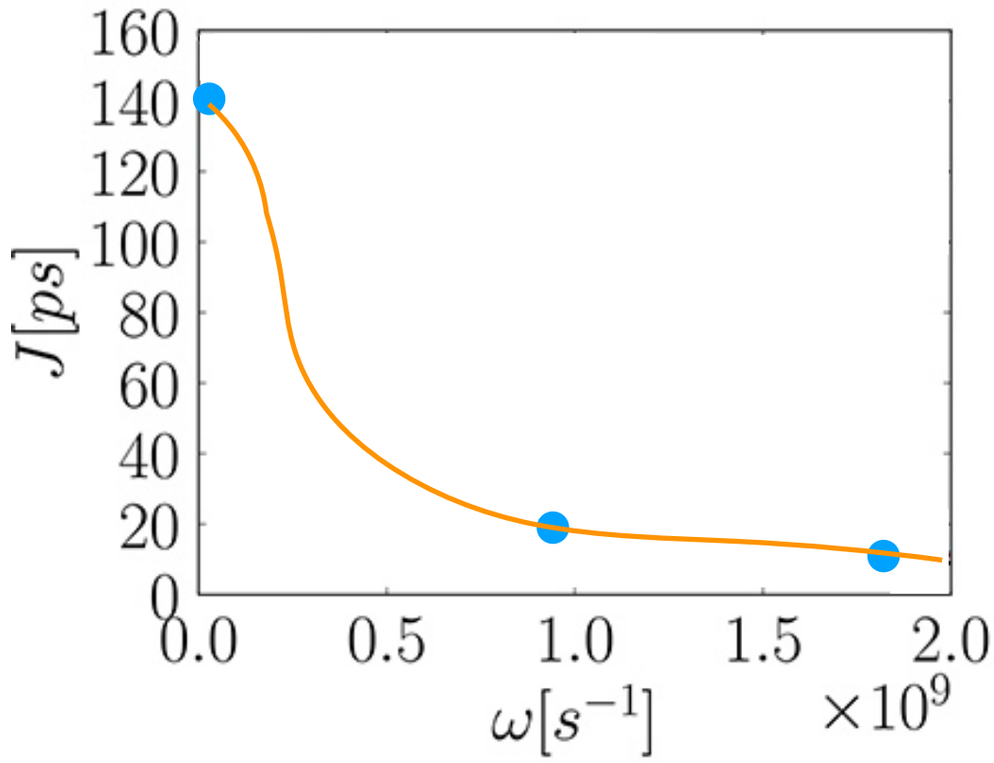
↓

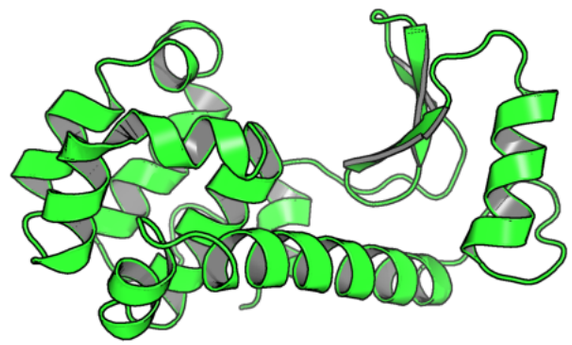
Lipari-Szabo (LS) model

$$C(t) = C_O C_{int}$$

$$C(t) = e^{-t/\tau_R}\left(\frac{1}{9}S^2_{axis} + (1-\frac{1}{9}S^2_{axis})e^{-t/\tau_f}\right)$$

$$J(\omega) = \int_0^\infty C(t)e^{-\omega t} = \frac{1}{9}S^2_{axis}\frac{\tau_R}{\omega^2+\tau_R{}^2} + (1-\frac{1}{9}S^2_{axis})\frac{\tau_{eff}}{\omega^2+\tau_{eff}{}^2}$$





Spectral density mapping from Molecular Dynamics (MD) trajectories

MD simulations

↓ **Remove tumbling**

C_{int}

↓ **Fit**

Smooth TCF

↓ **Introduce tumbling**

$$C(t) = (\sum_{i=1}^{6} A_i e^{-t/\tau_i} + S^2_{long}) e^{-t/\tau_R}$$

↓

Spectral density

LS

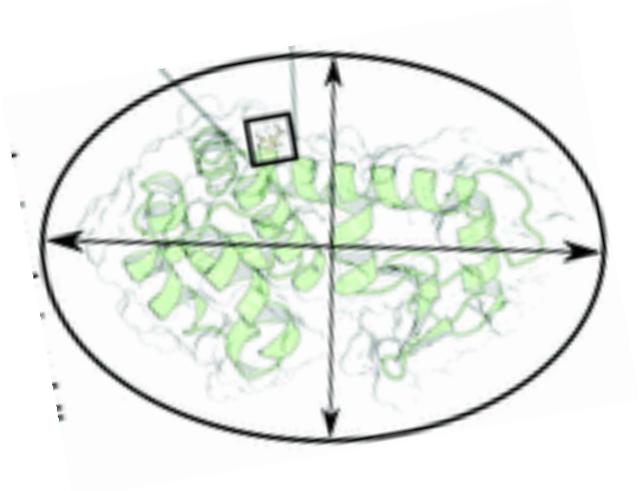
$$\frac{1}{9} S^2_{axis}, \tau_f \qquad R(D_x), R(D_y), R(3D_z^2 - 2)$$

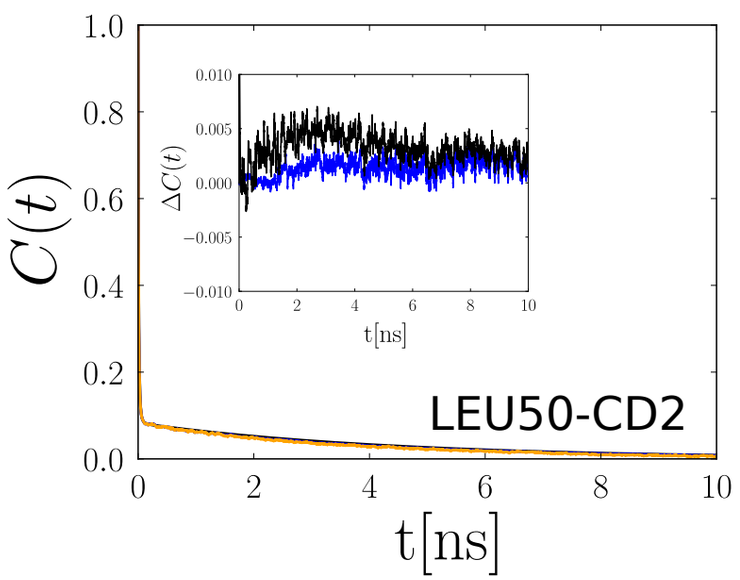
Introduce tumbling:

1) Lipari-Szabo for backbone (BB)

2) Anisotropy tensor from backbone

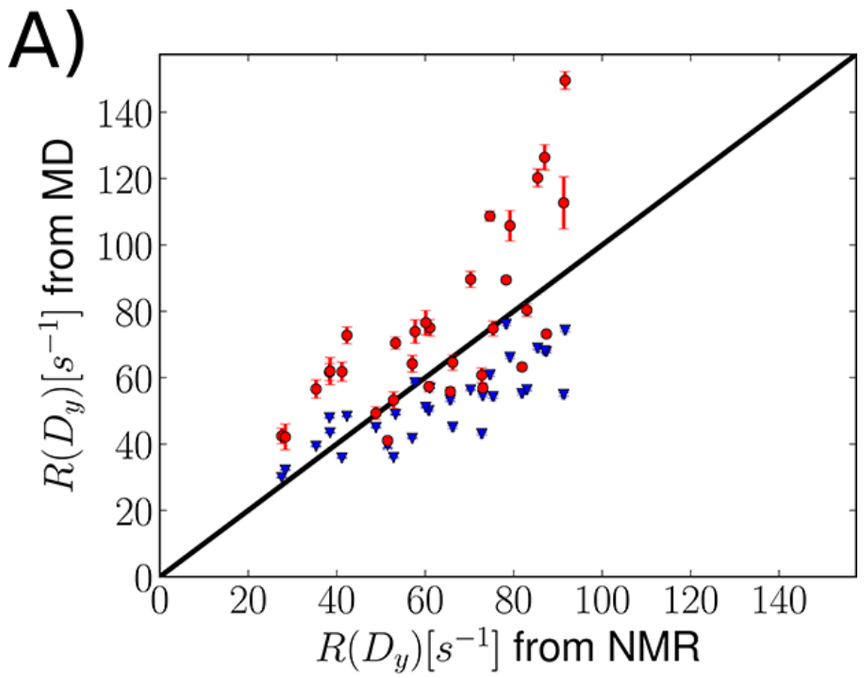
3) Relative BB-methyl orientation

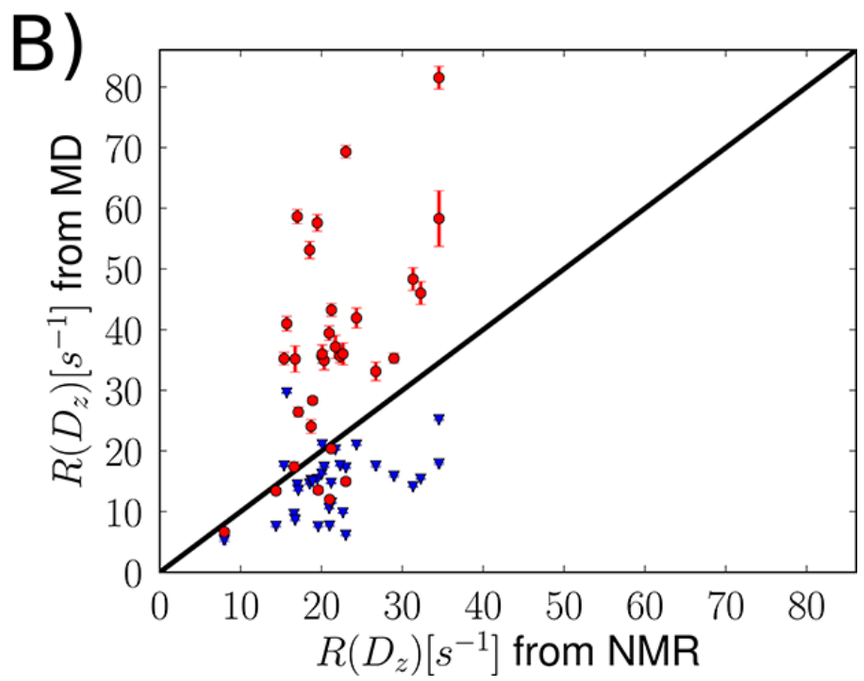


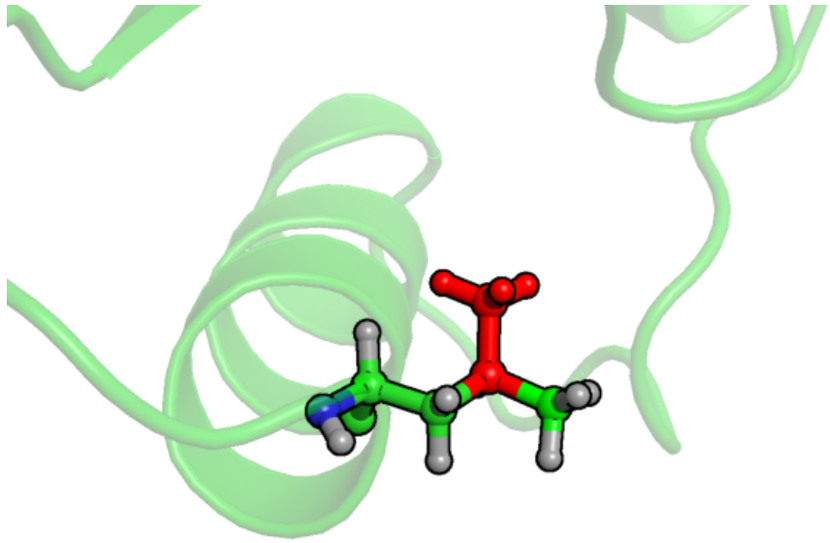


Hoffmann, Mulder, Schäfer, J. Phys. Chem. B 2018, 122, 19, 5038-5048
Hoffmann, Xue, Schäfer, Mulder, Phys. Chem. Chem. Phys., 2018, 20, 24577-24590

Relaxation rates







Methyl rotation too slow

↓

Dihedral angle reparametrization

$$V_{dih} = k_{dih}(1 - \cos(\phi - \phi_0))$$

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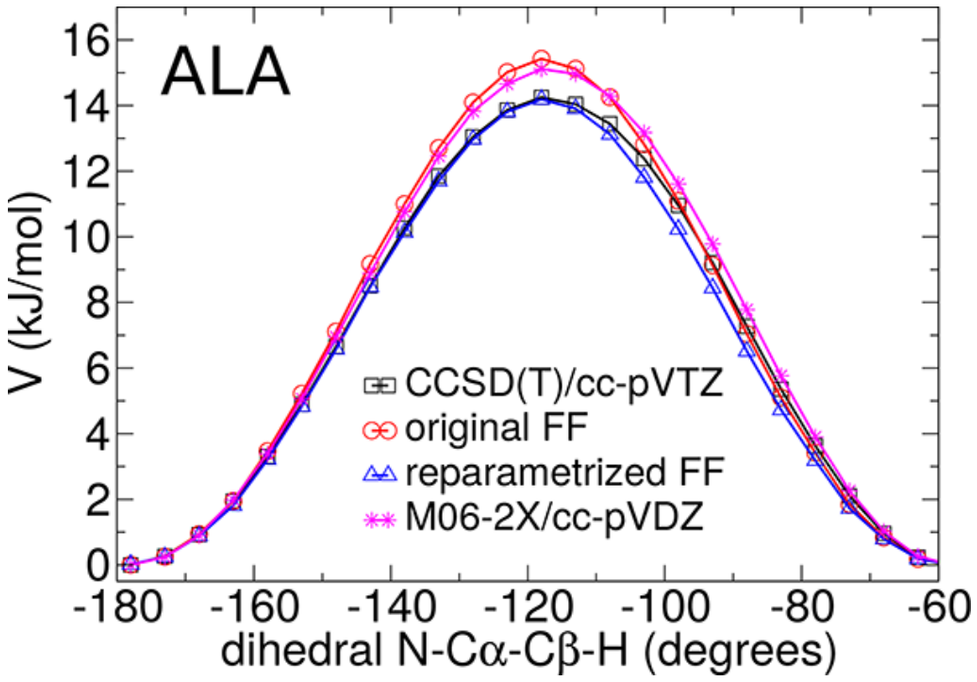
Reparametrization



methyl group	Δk_{dih} [kJ/mol]
ALA C^{β}	−0.06964
MET C^{ϵ}	−0.31380
VAL C^{γ}	−0.30220
LEU C^{δ}	−0.16270
ILE C^{γ}	−0.30220
ILE C^{δ}	−0.16270

$$V_{dih} = k_{dih}(1 - \cos(\phi - \phi_0))$$

	ALA	MET	THR	VAL	LEU	ILE
original FF	15.5	9.0	11.0	18.4/17.3	16.8/16.2	17.4/13.5
reparametrized FF	14.2	7.2	11.0	13.1/12.1	13.9/13.3	12.4/10.7
CCSD(T)	14.2	7.1	11.4	14.0/11.5	14.1/12.9	12.2/10.7

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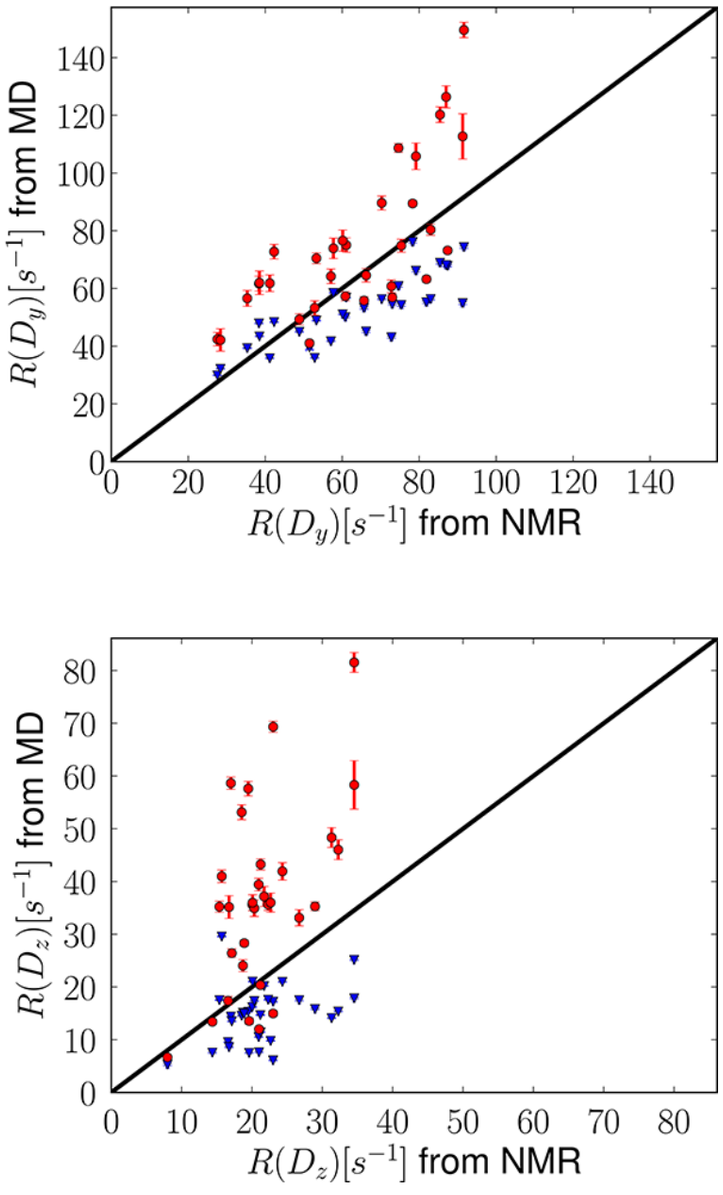
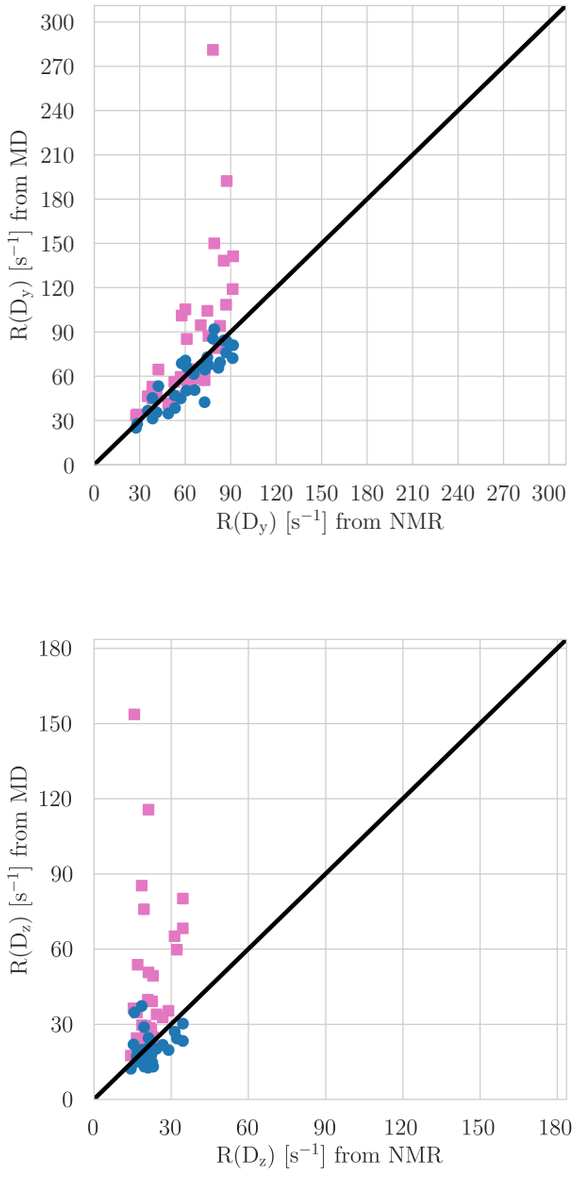
Reparametrization

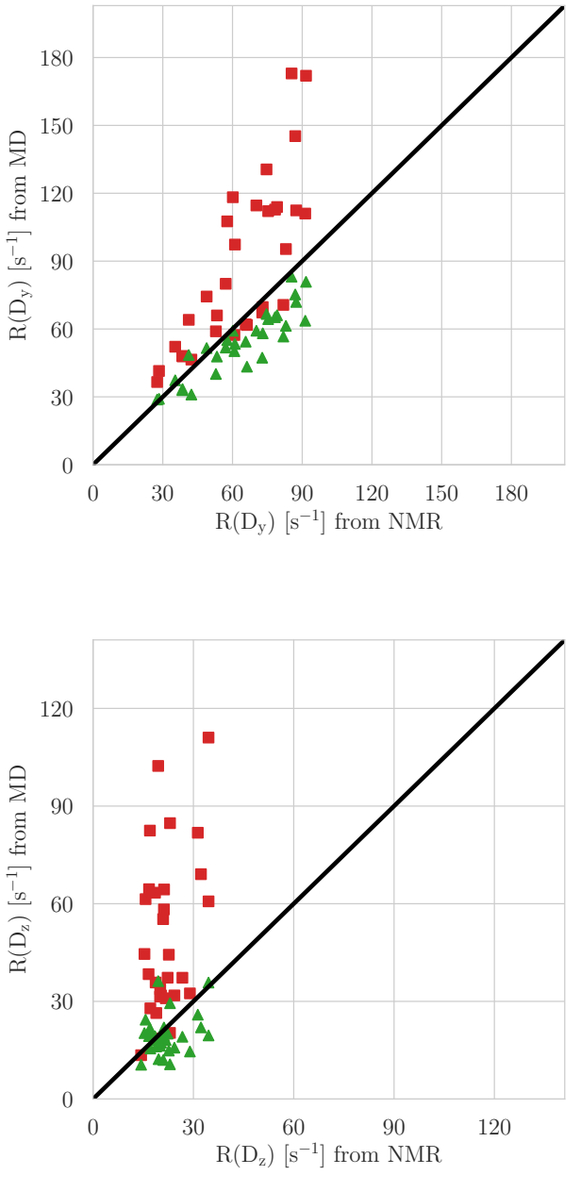
AMBER ff99SB*-ILDN



AMBER ff15IPQ



CHARMM36



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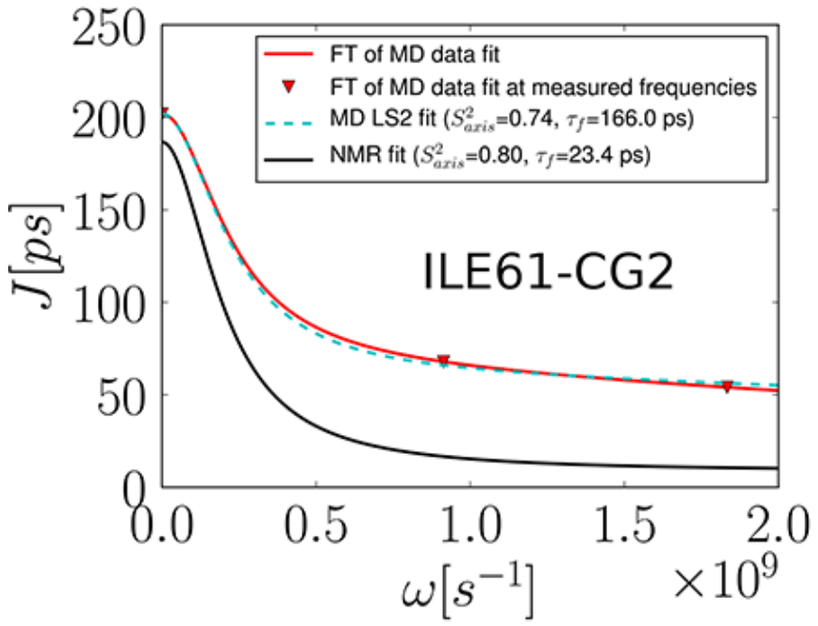
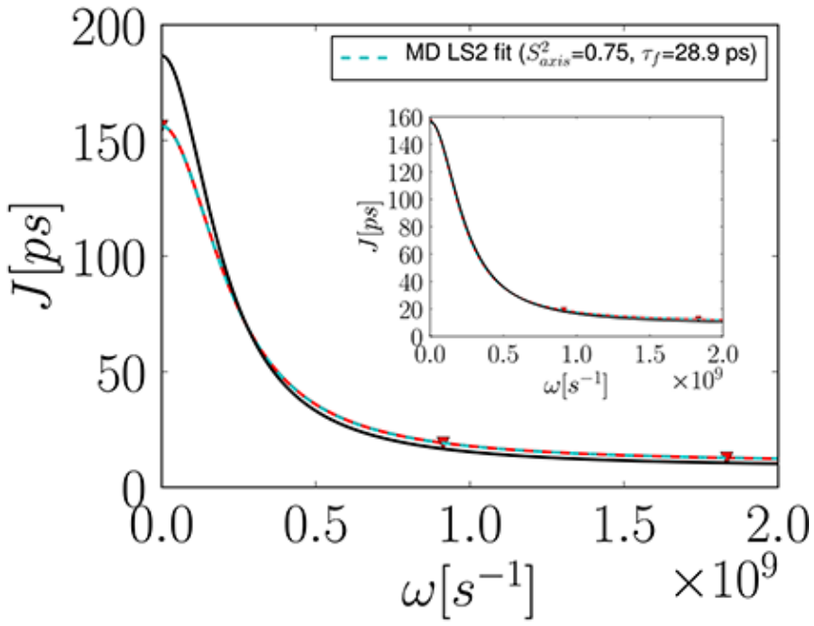
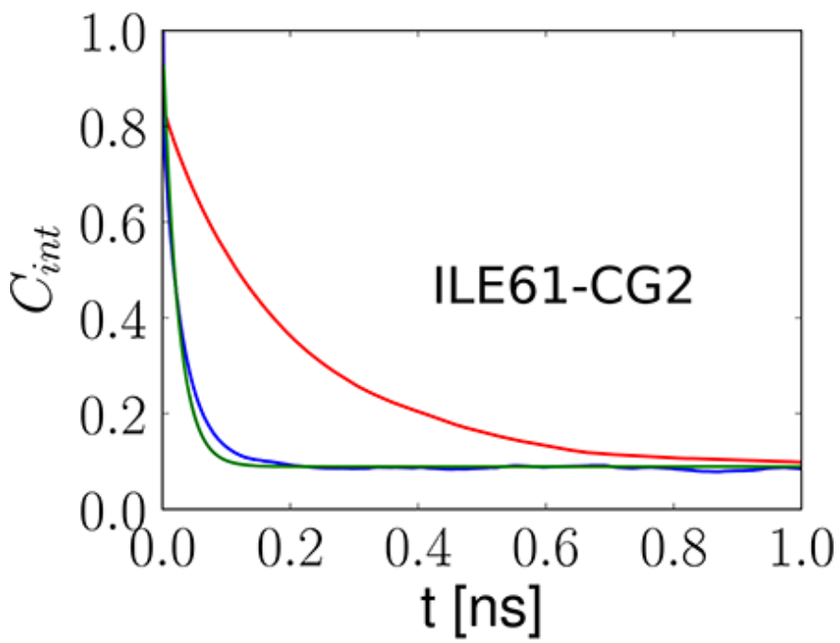
Hoffmann, Mulder, Schäfer, J. Phys. Chem. B, in revision

Spectral densities and TCFs







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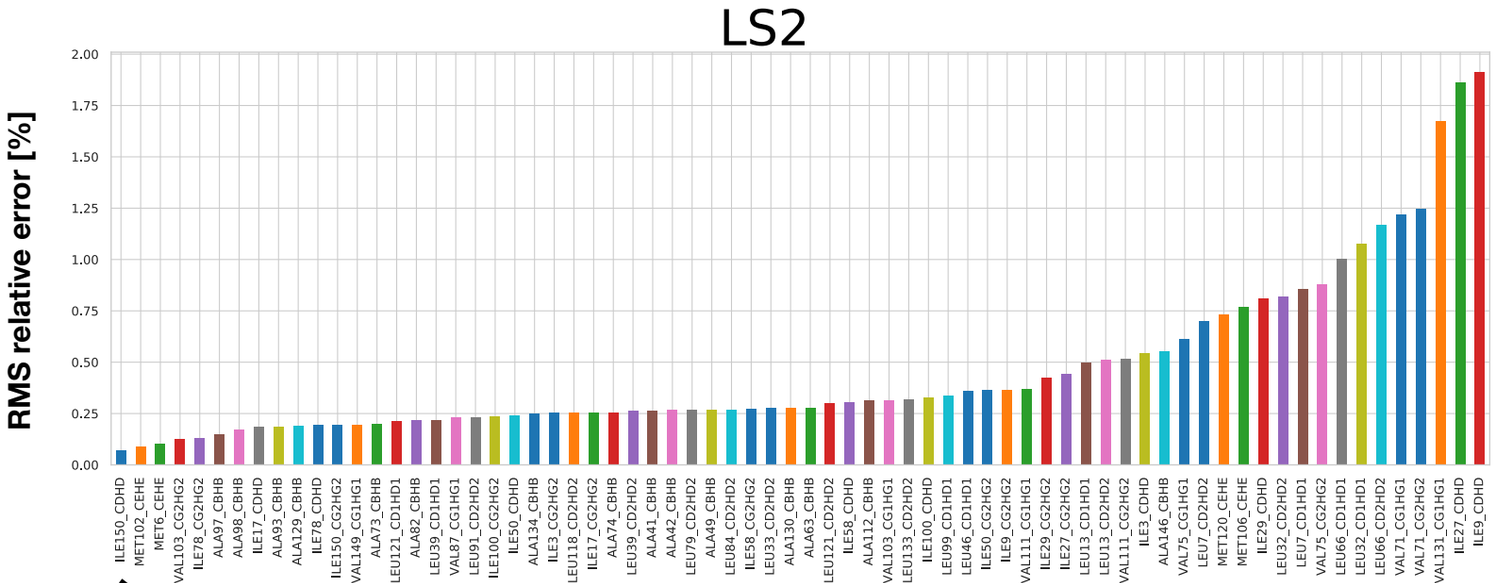
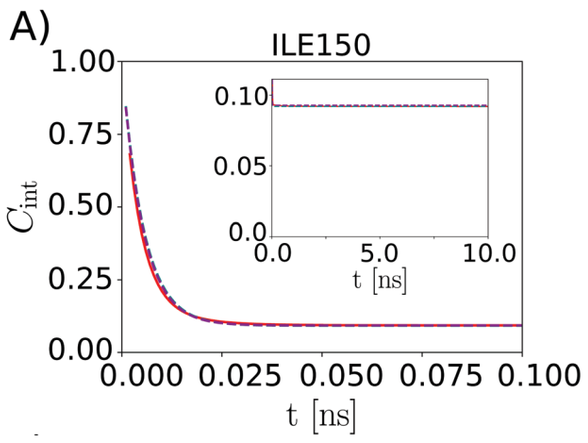
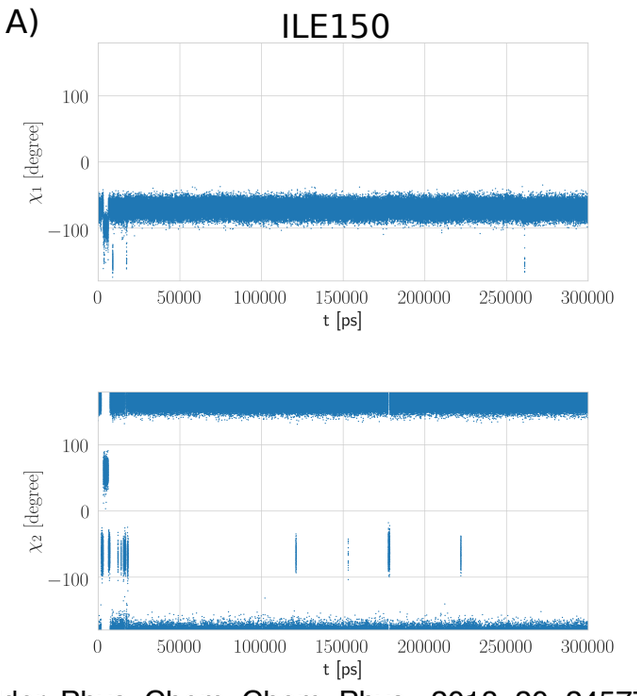
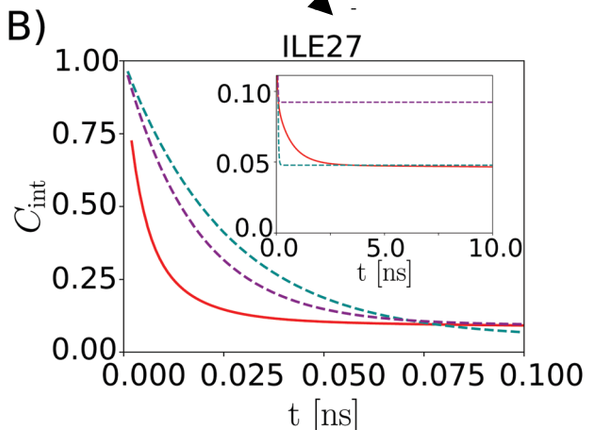
Applicability of LS for methyl groups

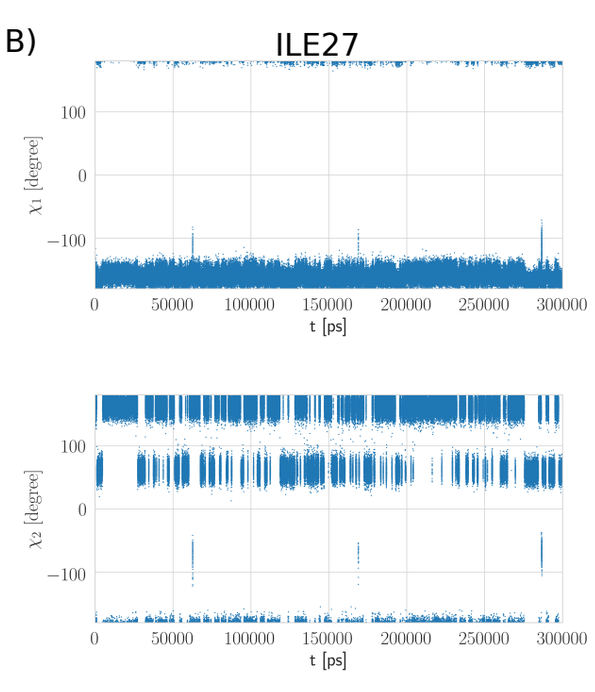


$$RMSRE = \frac{1}{N}\sqrt{\sum_{N}\left(\frac{C_{int,LS}(t) - C_{int}(t)}{C_{int}(t)}\right)^2}$$









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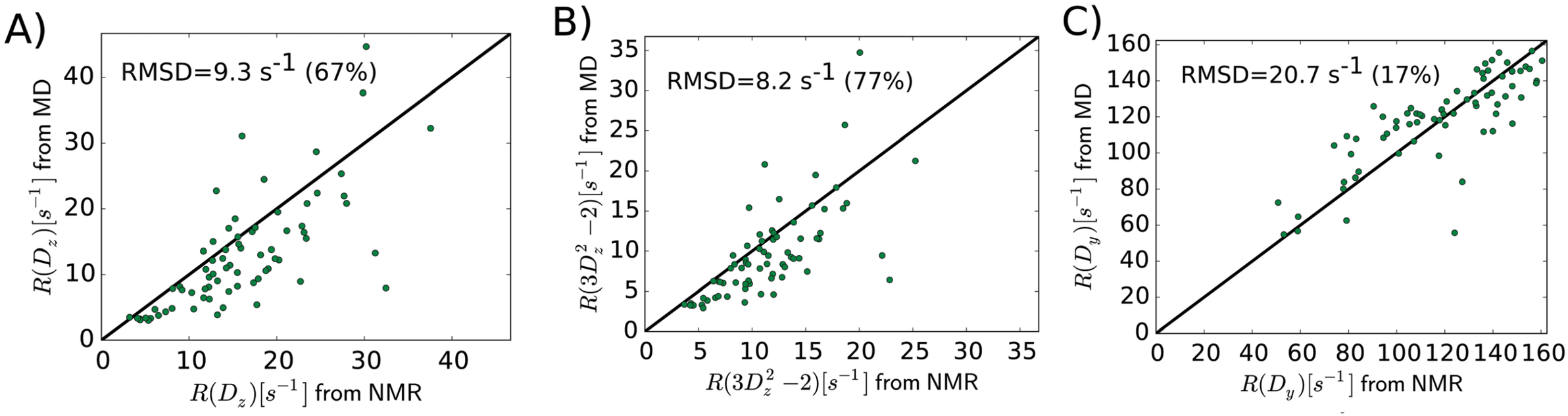
Relaxation rates



Relaxation rate	R_P	R_S	RMSD $[s^{-1}]$	Relative RMSD
$R(D_z)$	0.72	0.78	9.3	0.67
$R(3D_z^2-2)$	0.73	0.77	8.2	0.77
$R(D_y)$	0.77	0.82	20.7	0.17

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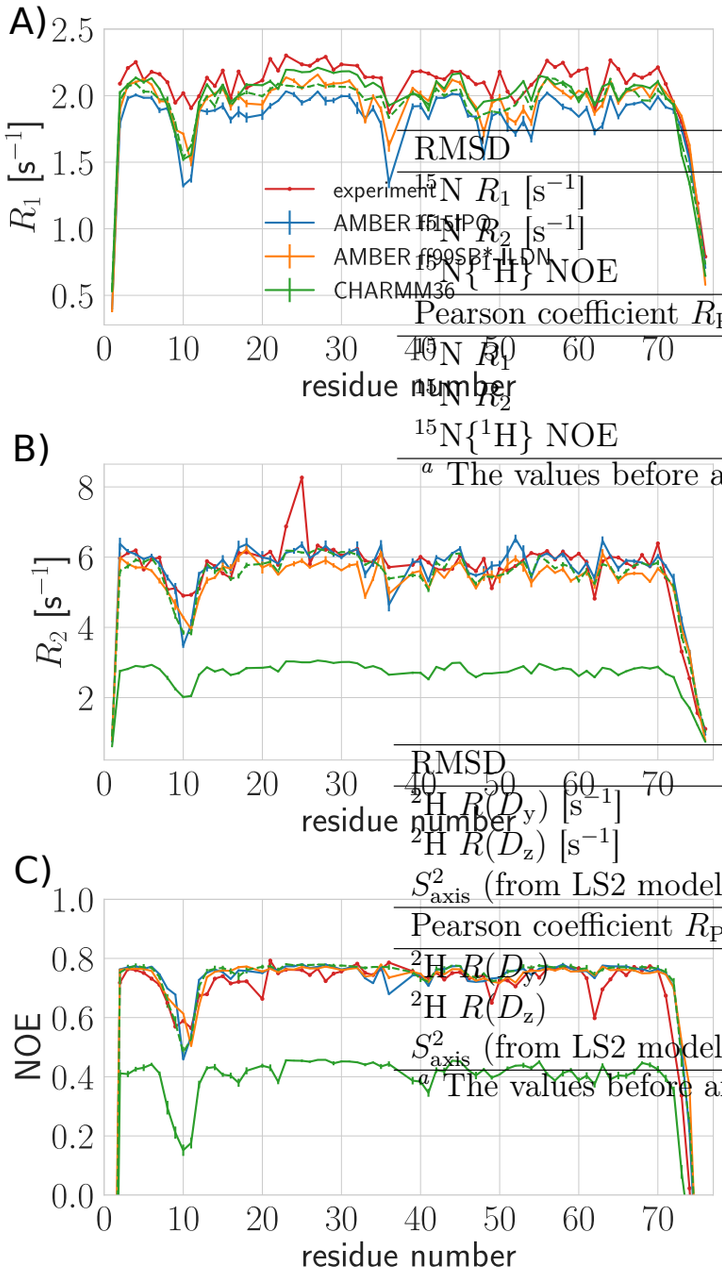
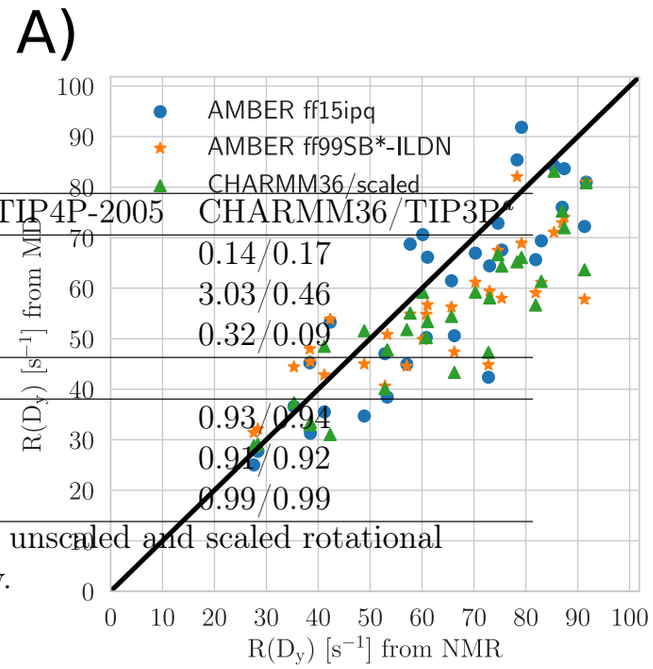
FF evaluation



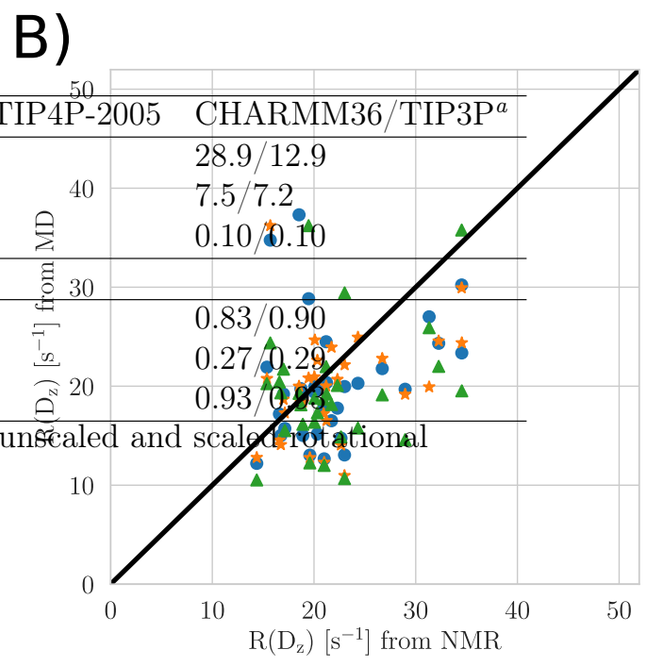
RMSD	ff15ipq/SPCE$_b$	ff99SB*-ILDN/TIP4P-2005	CHARMM36/TIP3P[a]
^{15}N R_1 [s^{-1}]	0.28	0.17	0.14/0.17
^{15}N R_2 [s^{-1}]	0.47	0.54	3.03/0.46
^{15}N{^{1}H} NOE	0.07	0.06	0.32/0.09
Pearson coefficient R_P			
^{15}N R_1	0.88	0.93	0.93/0.94
^{15}N R_2	0.89	0.90	0.91/0.92
^{15}N{^{1}H} NOE	0.99	0.98	0.99/0.99

[a] The values before and after the slash correspond to the unscaled and scaled rotational diffusion times, respectively.



RMSD	ff15ipq/SPCE$_b$	ff99SB*-ILDN/TIP4P-2005	CHARMM36/TIP3P[a]
^{2}H $R(D_y)$ [s^{-1}]	11.1	13.5	28.9/12.9
^{2}H $R(D_z)$ [s^{-1}]	7.2	6.5	7.5/7.2
S^2_{axis} (from LS2 model)	0.13	0.12	0.10/0.10
Pearson coefficient R_P			
^{2}H $R(D_y)$	0.86	0.83	0.83/0.90
^{2}H $R(D_z)$	0.26	0.32	0.27/0.29
S^2_{axis} (from LS2 model)	0.85	0.89	0.93/0.93

[a] The values before and after the slash correspond to the unscaled and scaled rotational diffusion times, respectively.



Hoffmann, Mulder, Schäfer, J. Phys. Chem. B, in revision

Consequences for future FF developments

- Similar chemistry does not give similar FF parameters

- Different rotamer states lead to slightly different energy barriers of methyl rotation

- Backbone dynamics is well captured with modern FFs

- Side-chain dynamics has to be improved, especially for fast dynamics (ps)

Summary

- Reparametization of methyl group rotation leads to better NMR deuterium relaxation rates and spectral densities

- Truncation of time correlation function at rotational tumbling time of protein leads to better methyl order parameter

- Lipari-Szabo model does not describe dynamics of all methyl groups correctly

- MD force fields capture amplitude of motions better than their time scales

Hoffmann, Xue, Schäfer, Mulder, Phys. Chem. Chem. Phys., 2018, 20, 24577-24590

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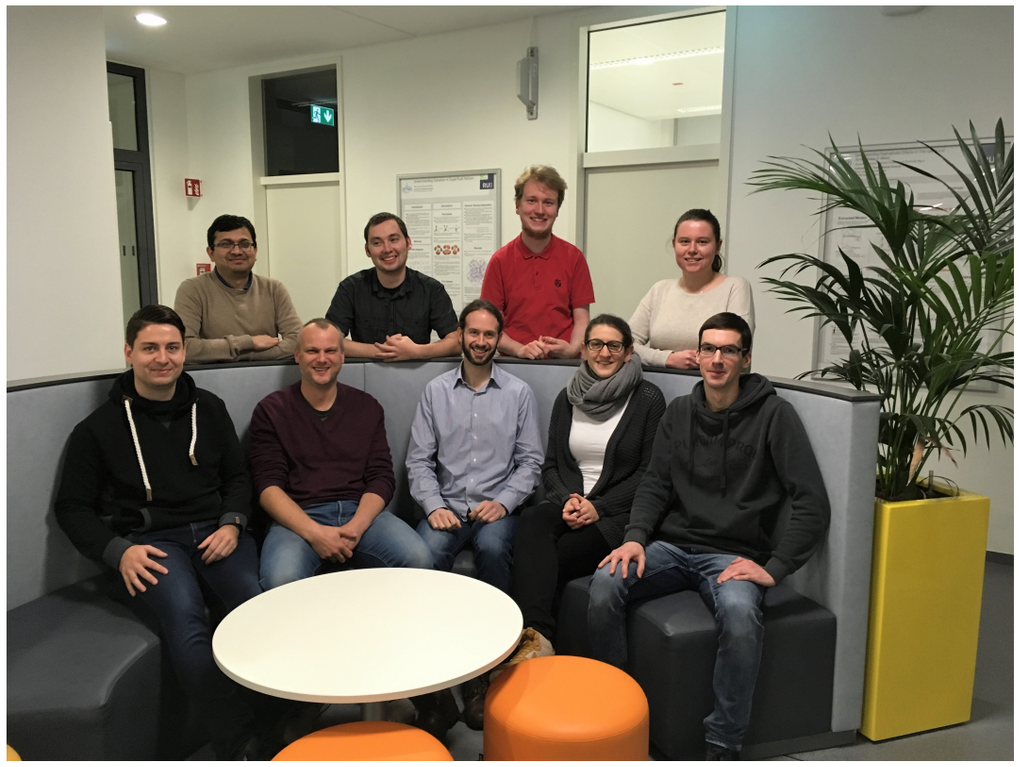

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Code availability:
www.molecular-simulation.org/downloads
https://github.com/fahoffmann (soon)