SUPPORTING INFORMATION

Long-Range Correlated Dynamics in Intrinsically Disordered Proteins

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Supporting Methods

NOE calculations. The sign of proton-proton NOEs depends on the magnitude of the reorientational correlation time. The presence of negative NOEs (same sign of cross peaks and diagonal peaks) is an indication of slow tumbling, while positive NOEs indicate that no contributions arise from long correlation times. The NOE intensities were calculated using the equation

$$\mathrm{NOE}=(6J(2\omega)-J(0))/(6J(2\omega)+3J(\omega)+J(0)) \quad \text{(S1)}$$

with $J(\omega) = S^2 \frac{\tau_R}{1+\omega^2\tau_R^2} + (1-S^2)\frac{\tau_{fast}}{1+\omega^2\tau_{fast}^2}$.

Ensemble generation and HYCUD calculations. Two ensembles of α-syn, each containing 5000 random structures, were used for the HYCUD calculations. The two ensembles were generated using the program Flexible-Meccano,[1] with or without introduction of a distance constraint between N- and C-terminal residues.[2] The long-range contact between N- and C-terminal residues of α-syn was defined as a distance < 15 Å between at least one of the C^β atoms of residues 1-20 from any C^β atom of residues 121-140. Addition of this long-range contact has been shown to improve the fit to experimental RDCs of α-syn.[2] An ensemble of 1000 random full-length tau (1-441) structures was generated by the Flexible-Meccano program. In addition, a random ensemble of 5000 poly-alanine (1-100) structures without any long-range distance constraint was generated. For all α-syn, tau and poly-alanine ensembles, side-chain atoms were added by the program SSCOMP. HYCUD calculations were performed as described in [3], using an in-house Python script. For HYCUD calculations, each member of the α-syn ensemble was split into non-overlapping fragments of 14 residues, and hydrodynamic calculation for the isolated fragments were made at 25 °C using the specified atomic effective radius (AER) of 2.9 or 3.3 Å. For full-length tau protein, each member of the protein ensemble was split into fragments of 14 or 15 residues each, defined as 1-15, 16-29, 30-43, 44-57, 58-71, 72-86, 87-100, 101-114, 115-128, 129-142, 143-157, 158-171, 172-185, 186-199, 200-213, 214-228, 229-242, 243-256, 257-270, 271-284, 285-299, 300-313, 314-327, 328-341, 342-355, 356-370, 371-384, 385-398, 399-412, 413-426 and

427-441. In case of poly-alanine (1-100), protein fragments were defined as residues 1-15, 16-29, 30-43, 44-57, 58-71, 72-85 and 86-100. The uncertainty of HYCUD-predicted τ_R for each fragment was estimated from the standard deviation of results obtained for 10 (two, in case of tau protein) sub-ensembles each containing 500 conformers.

Supporting Table

Table S1. Best-fit parameters obtained from the protein proton relaxation profiles of the tau protein using Lorentzian dispersion and either one or two correlation times

Tau protein (htau40) (441 AA)		
τ_{R1} (ns)	9.8±0.9	27±5
$S_{C(1)}^2$	0.12±0.01	0.023±0.004
τ_{R2} (ns)	-	4.3±0.8
$S_{C(2)}^2$	-	0.17±0.03
α (s^{-1})	8.9±0.7	5.9±1.0
quality of the fit: R^2	*0.982*	*0.997*
residuals	*0.0103*	*0.0016*

Supporting Figures

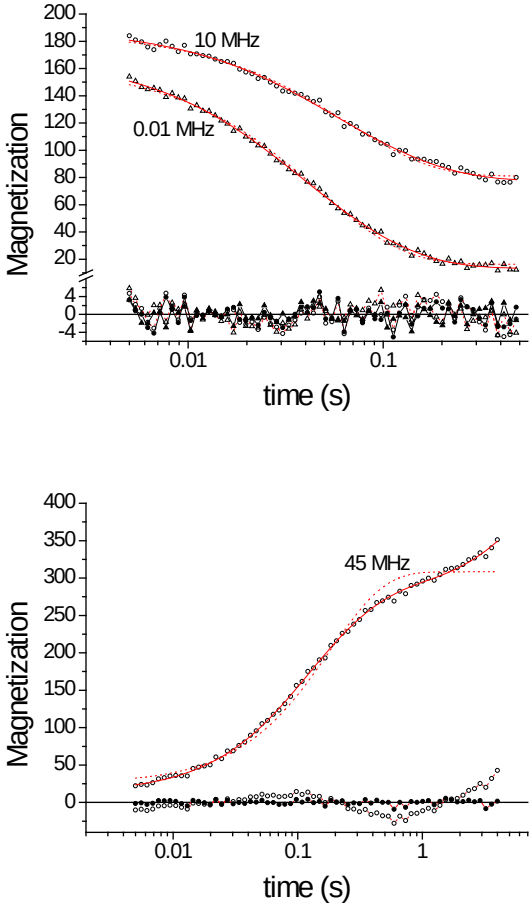

Figure S1. Protein proton relaxation rate measurements. Magnetization decays at 0.01 and 10 MHz (top panel) and magnetization recovery at 45 MHz (bottom panel) are shown. The monoexponential fits are shown as dotted lines, the three-exponential fits performed using eq. 1 as solid lines; the residuals for the different cases are also shown.

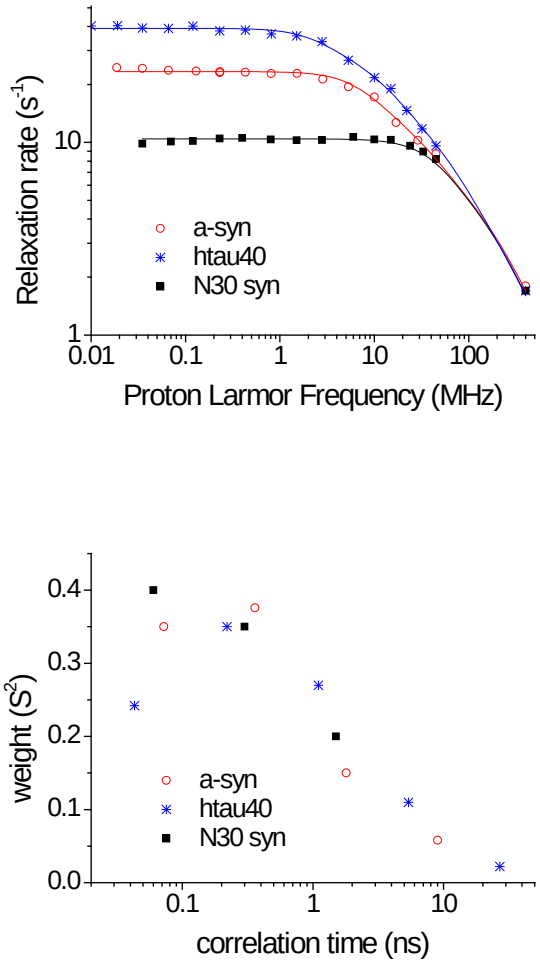

Figure S2. Best-fit analysis of the collective protein proton relaxation rates of α-synuclein (140 residues), of 441-residue Tau and of the peptide comprising the N-terminal 30 residues of α-synuclein, performed as a weighted sum of the relaxation rates calculated with different τ_{Ri} and S_{Ci}^2 values (eq. 4) (top panel) and the resulting parameters (bottom panel).

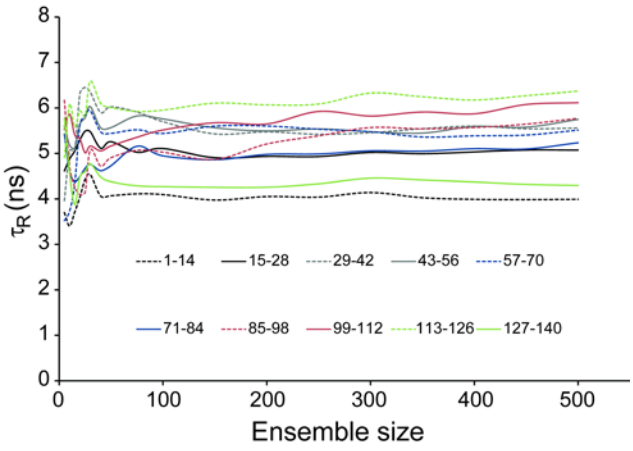

Figure S3. Influence of ensemble size on τ_R of different fragments of α-syn, as predicted by HYCUD. Fragments are named by their constituting residues (1-14, 15-28 etc.). Convergence of HYCUD calculations is achieved with 500 structures.

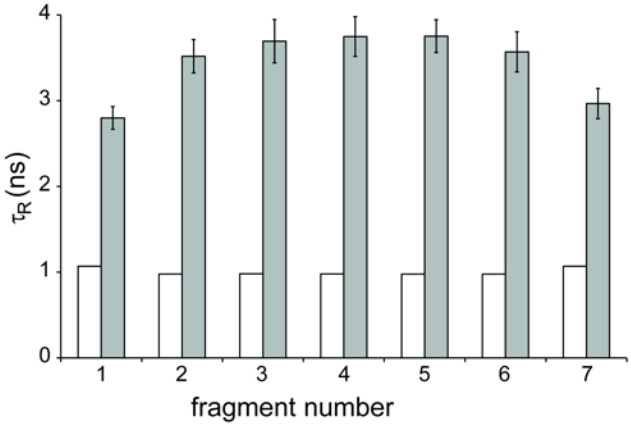

Figure S4. HYCUD calculations for an ensemble of 5000 random poly-alanine structures. The ensemble-average τ_R predicted by HYCUD for protein fragments in isolation (white columns) or in the context of full-length poly-alanine(1-100) molecules (gray columns) are shown. An AER of 2.9 Å was used. Fragments 1-7 were defined as residues 1-15, 16-29, 30-43, 44-57, 58-71, 72-85 and 86-100 of poly-alanine(1-100).

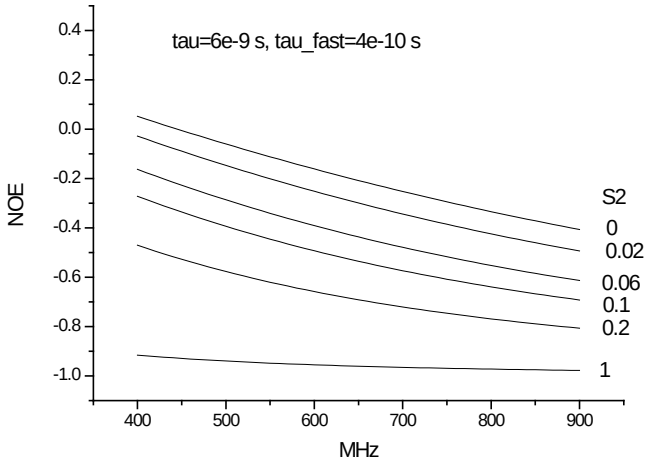

Figure S5. NOE intensities as a function of the applied magnetic field for a protein with an overall correlation time of 6 ns (corresponding to the reorientation time of a rigid globular protein of about 100 amino acids at 298 K) and local motions with correlation time of 0.4 ns, for different squared order parameters.

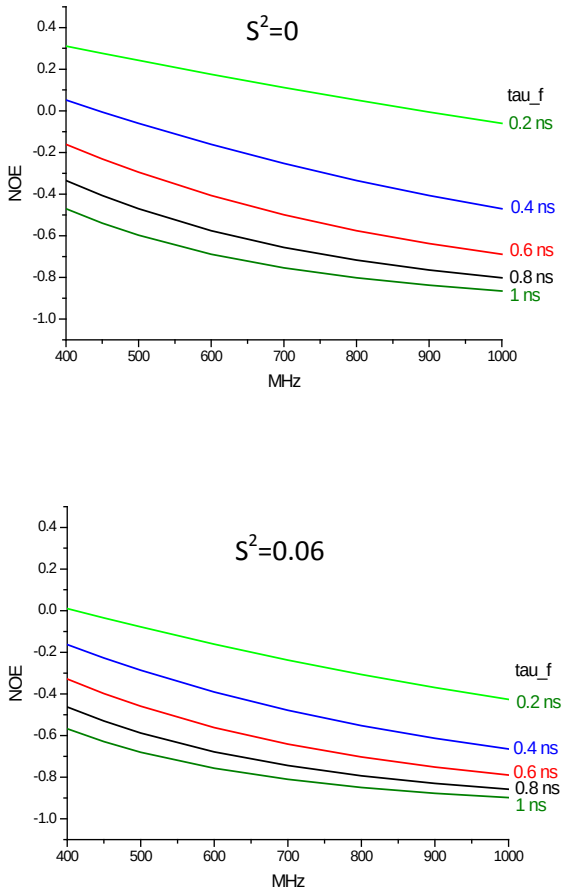

Figure S6. NOE intensities as a function of the applied magnetic field for a protein with an overall correlation time of 6 ns, $S^2 = 0$ (top panel) or 0.06 (bottom panel), and correlation times for fast internal motions ranging from 0.2 to 1 ns.

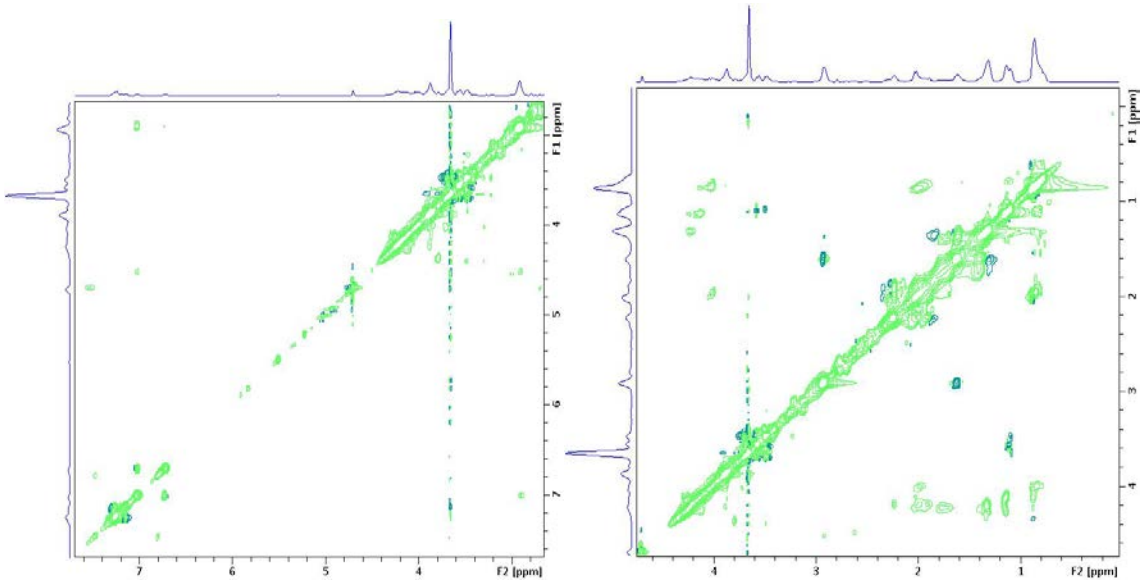

Figure S7. ^{1}H, ^{1}H NOESY spectrum of the truncated α-synuclein protein (1-108) at 400 MHz

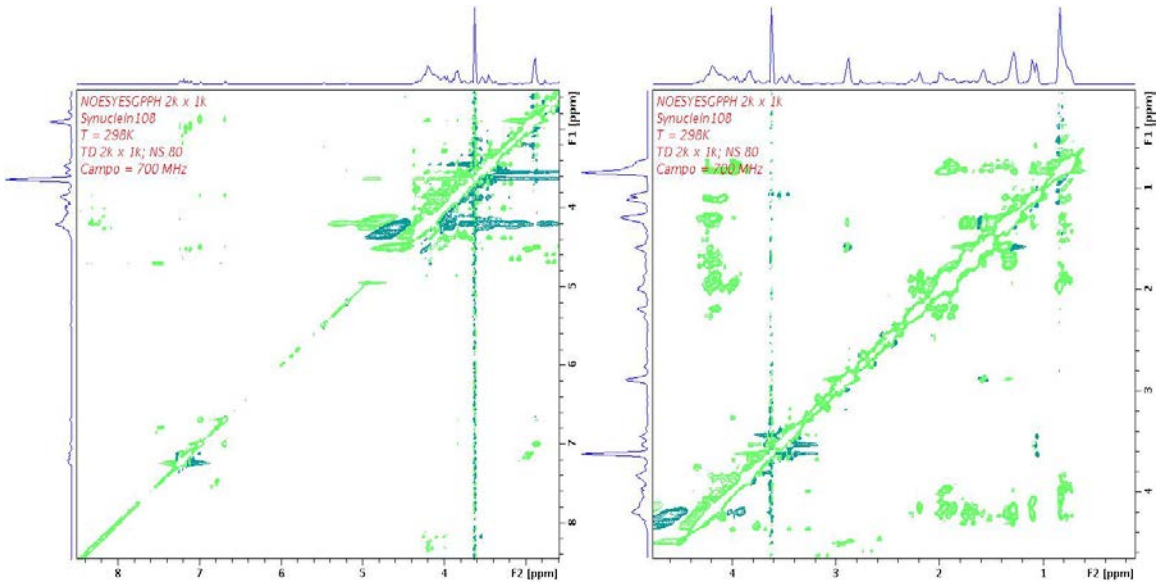

Figure S8. ^{1}H, ^{1}H NOESY spectrum of the truncated α-synuclein protein (1-108) at 700 MHz

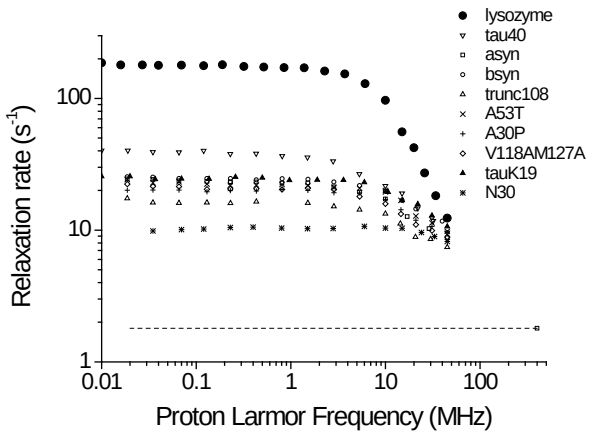

Figure S9. Comparison of collective protein proton relaxation rates for folded lysozyme at pH* 3.5 (black starts) and for the unfolded proteins and mutants investigated in this study.

References

(1) Ozenne, V.; Bauer, F.; Salmon, L.; Huang, J. R.; Jensen, M. R.; Segard, S.; Bernado, P.; Charavay, C.; Blackledge, M. *Bioinformatics* **2012**, *28*, 1463.

(2) Bernado, P.; Bertoncini, C. W.; Griesinger, C.; Zweckstetter, M.; Blackledge, M. *J. Am. Chem. Soc.* **2005**, *127*, 17968.

(3) Rezaei-Ghaleh, N.; Klama, F.; Munari, F.; Zweckstetter, M. *Angew. Chem. Int. Ed. Engl.* **2013**, *52*, 11410.