Title:	Direct Observation of the Intrinsic Backbone Torsional Mobility of Disordered Proteins
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Abstract:	The fundamental backbone dynamics of unfolded proteins arising due to intrinsic ϕ-ψ dihedral angle fluctuations dictate the course of protein folding, binding, assembly, and function. These internal fluctuations are also critical for protein misfolding associated with a range of human diseases. However, direct observation and unambiguous assignment of this inherent dynamics in chemically denatured proteins is extremely challenging due to various experimental limitations. To directly map the backbone torsional mobility in the ϕ-ψ dihedral angle space, we used a model intrinsically disordered protein, namely, α-synuclein, that adopts an expanded state under native conditions. We took advantage of nonoccurrence of tryptophan in α-synuclein and created a number of single-tryptophan variants encompassing the entire polypeptide chain. We then utilized highly sensitive picosecond time-resolved fluorescence depolarization measurements that allowed us to discern the site-specific torsional relaxation at a low protein concentration under physiological conditions. For all the locations, the depolarization kinetics exhibited two well-separated rotational-correlation-time components. The shorter, subnanosecond component arises due to the local mobility of the indole side chain, whereas the longer rotational-correlation-time component (1.37 ± 0.15 ns), independent of global tumbling, represents a characteristic timescale for short-range conformational exchange in the ϕ-ψ dihedral space. This correlation time represents an intrinsic timescale for torsional relaxation and is independent of position, which is expected for an extended polypeptide chain having little or no propensity to form persistent structures. We were also able to capture this intrinsic timescale at the N-terminal unstructured domain of the prion protein. Our estimated timescale of the segmental mobility is similar to that of unfolded proteins studied by nuclear magnetic resonance in conjunction with molecular dynamics simulations. Our results have broader implications for a diverse range of functionally and pathologically important intrinsically disordered proteins and disordered regions.
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