Title:	Femtosecond Hydration Map of Intrinsically Disordered α-Synuclein
Authors:	Arya, S. (/jspui/browse?type=author&value=Arya%2C+S.) Bhasne, K. (/jspui/browse?type=author&value=Bhasne%2C+K.) Dogra, P. (/jspui/browse?type=author&value=Dogra%2C+P.) Mukhopadhyay, S. (/jspui/browse?type=author&value=Mukhopadhyay%2C+S.)
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Abstract:	Protein hydration water plays a fundamentally important role in protein folding, binding, assembly, and function. Little is known about the hydration water in intrinsically disordered proteins that challenge the conventional sequence-structure-function paradigm. Here, by combining experiments and simulations, we show the existence of dynamical heterogeneity of hydration water in an intrinsically disordered presynaptic protein, namely α-synuclein, implicated in Parkinson's disease. We took advantage of nonoccurrence of cysteine in the sequence and incorporated a number of cysteine residues at the N-terminal segment, the central amyloidogenic nonamyloid-β component (NAC) domain, and the C-terminal end of α-synuclein. We then labeled these cysteine variants using environment-sensitive thiol-active fluorophore and monitored the solvation dynamics using femtosecond time-resolved fluorescence. The site-specific femtosecond time-resolved experiments allowed us to construct the hydration map of α-synuclein. Our results show the presence of three dynamically distinct types of water: bulk, hydration, and confined water. The amyloidogenic NAC domain contains dynamically restrained water molecules that are strikingly different from the water molecules present in the other two domains. Atomistic molecular dynamics simulations revealed longer residence times for water molecules near the NAC domain and supported our experimental observations. Additionally, our simulations allowed us to decipher the molecular origin of the dynamical heterogeneity of water in α-synuclein. These simulations captured the quasi-bound water molecules within the NAC domain originating from a complex interplay between the local chain compaction and the sequence composition. Our findings from this synergistic experimental simulation approach suggest longer trapping of interfacial water molecules near the amyloidogenic hotspot that triggers the pathological conversion into amyloids via chain sequestration, chain desolvation, and entropic liberation of ordered water molecules.
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