Molecular simulations of IDPs: from exploring their structures to understanding their aggregation leading to diseases

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About half of the human proteome are intrinsically disordered proteins (IDPs) or proteins that contain disordered regions. By definition these proteins differ from natively folded proteins and do not adopt a properly folded structure in solution. However, these IDPs also systematically differ in amino acid composition and uniquely often become folded upon binding to an interaction partner. These factors impede the determination of IDP structures. The same applies to the protein aggregation problem, since this meta-folding process can give rise to different and short-lived aggregate sizes and structures. An alternative method is provided by molecular dynamics (MD) simulations that already successfully explored the energy landscapes of IDP conformational switching and protein aggregation in multiple cases. These energy landscapes are very different from those of ‘simple’ protein folding, where one energy funnel leads to a unique protein structure. Instead, the energy landscapes of IDP conformational switching and protein aggregation feature a number of minima for different competing low-energy structures. In this presentation, I discuss the characteristics of these multifunneled energy landscapes in detail for some disease-relevant proteins, illustrated by MD simulations that elucidated the underlying conformational transitions and aggregation processes.