O-17.5 Short talk

An efficient coarse-grained method to unravel conformational pathways in large proteins and protein-nucleic acid complexes

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With the advance of cryoEM we now have huge amounts of data for large proteins and protein-nucleic acid complexes, often captured in distinct conformational states. Understanding how these systems interconvert their conformation during the functional cycle is pivotal to get mechanistic insights into their biological behavior. However, their large size and often-large-scale nature of their conformational change hinders the applicability of gold-standard computational methods such as Molecular Dynamics (MD). Here, we show that our new coarse-grained algorithm, eBDIMS2, can efficiently simulate large-scale pathways in gigantic proteins. It outperforms existing path-sampling methods for large systems (> 300 kDa), generates realistic on-path conformers that agree with experimental intermediates, and is consistent with MD simulations. We recently extended the method to DNA and RNA, so that we can also simulate conformational changes for large complexes such as ribosomal subunits. eBDIMS2 conformers can be successfully used for atomistic analyses, which opens new opportunities for enhanced sampling applications, mutation studies, and drug design.