New and Notable

Atomistic Glimpse of the Orderly Chaos of One Protein

Jianhan Chen[1,*]

[1]Biochemistry and Molecular Biophysics, Kansas State University, Manhattan, Kansas

Intrinsically disordered proteins (IDPs) are a fascinating class of newly recognized proteins that can exist as dynamic and heterogeneous ensembles of disordered structures under physiological conditions (1). They are highly prevalent in biology, frequently play crucial roles in cell signaling and regulation, and are associated with numerous human diseases (2). Many concepts have been proposed on how intrinsic conformational disorder may offer functional advantages, such as structural plasticity for binding multiple partners and inducibility by posttranslational modifications (3). Establishing the physical basis of these phenomena requires not only detailed characterization of the disordered conformational ensembles, but also mechanistic understanding of the roles of various ensemble properties in IDP interaction and regulation. Importantly, the heterogeneous ensembles of IDPs do not lend themselves to description using traditional high-resolution methods that are geared toward describing a coherent set of similar structures (4). Reliable atomistic simulations have an important and transformative role to play in terms of describing IDP ensembles and interactions. At the same time, atomistic simulations of IDPs have been very challenging, pushing the limits on both the accuracy of existing protein force fields and one's ability to sufficiently sample the broad accessible conformation space.

A particularly interesting concept is that the intrinsic thermodynamic instability of IDPs could provide a robust mechanism for allosteric regulation (5). Many IDPs involved in cellular signaling and regulation appear to exist near the stability/instability boundary. They are thus poised to respond sensitively to one or multiple signals ranging from cellular environmental conditions (e.g., pH and temperature) and posttranslational modifications to association with various cofactors such as ions, small ligands, proteins, nucleic acids, and membranes. Such disorder-mediated allostery is nicely illustrated in the article by Pang and Zhou (6) published in this issue of the *Biophysical Journal*. Using state-of-the-art molecular simulations, they were able to calculate the atomistic disordered ensembles of the active-site loop of enzyme sortase A in apo form as well as when bound with a sorting signal peptide or calcium or both. The results demonstrate that binding of either calcium at the C-terminal region or a sorting signal peptide at the N-terminal leads to partial collapse of the accessible conformational space of the active-site loop, preorganizing the binding pocket for binding the second ligand. The atomistic simulations thus provide a detailed mechanism for how the intrinsic conformational equilibrium of the disordered active-site loop mediates the allosteric activation of sortase A by calcium.

The success of Pang and Zhou's work (6) was made possible by significant recent advances in enhanced sampling techniques, specifically, replica exchange with solute tempering (REST) in the work of Wang et al. (7). Enhanced sampling aims to yield statistically meaningful conformational ensembles with much less computation, generally by accelerating the crossing of various energy barriers. Even with recent breakthroughs that greatly extend the reach of traditional all-atom explicit solvent simulations, enhanced sampling is often preferred, even if not entirely necessary, for atomistic simulation of IDPs due to the critical need for achieving sufficient convergence in the simulated ensembles (4). REST in particular allows one to selectively enhance the sampling of selected (protein) regions of interest, and reduces the number of replicas required for covering the appropriate temperature range. This has been essential for Pang and Zhou (6) to achieve a sufficient level of convergence in the simulated ensembles to assess the molecular mechanism of allosteric activation in sortase A. Nonetheless, it should be noted that the temperature replica exchange class of sampling techniques (including REST) can be limited for sampling cooperative transitions such as local or global folding (8). There remains a need for further development of more efficient sampling strategies for general atomistic simulation of disordered proteins.

Besides exciting breakthroughs in computer hardware and molecular simulation methodologies, substantial progresses are also being made in addressing many imperfections in contemporary explicit and implicit solvent protein force fields (9,10). There is great hope that an atomistic view of the orderly chaos of proteins will become more readily accessible, even for larger and more complex IDPs. When properly integrated with experiments, such simulation capability is opening up exciting opportunities for understanding the functional mechanisms of numerous biologically important IDPs and for rational exploration of these IDPs as novel drug targets.

AUTHOR CONTRIBUTIONS

J.C. designed and performed research, and wrote the article.

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*Correspondence: jianhanc@ksu.edu

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