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Editorial overview: Molecular interactions that drive folding and binding: new challenges and opportunities

Shachi Gosavi and Benjamin Schuler

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Shachi Gosavi

National Centre for Biological Sciences, Tata Institute of Fundamental Research, Bellary Road, Bangalore 560065, India
e-mail: shachi@ncbs.res.in

Shachi Gosavi obtained her PhD in Theoretical Physical Chemistry from the California Institute of Technology, Pasadena, USA. After a postdoctoral stint at the Centre for Theoretical Biological Physics, University of California San Diego, USA, she started her own research group at the National Centre for Biological Sciences, TIFR, Bangalore, India in 2010. Her group currently studies protein self-assembly, conformational transitions, folding dynamics, and related matters using primarily computational approaches with help from some experimental structural biology.

Benjamin Schuler

Molecular Biophysics, Department of Biochemistry and Department of Physics, University of Zurich, Zurich, Switzerland
e-mail: schuler@bioc.uzh.ch

Ben Schuler obtained his PhD in Physical Biochemistry from the University of Regensburg, Germany, and did his postdoctoral research in the Laboratory of Chemical Physics at the National Institutes of Health in Bethesda, USA. He then headed an independent research group at the University of Potsdam in Germany supported by the Emmy Noether Program of the Deutsche Forschungsgemeinschaft. In 2004, he joined the faculty of the University of Zurich, where he investigates the structure, dynamics, and interactions of proteins using single-molecule spectroscopy integrated with a broad range of biochemical, biophysical, and computational techniques.

The structure, dynamics, and interactions of proteins, tuned by evolution, are at the heart of biomolecular function. Even after decades of discovery, new concepts and surprises keep emerging in the understanding of protein structure and dynamics, often enabled by new methods or ideas from neighboring fields of science. In the past decades, many of the basic textbook notions of folding and binding have had to be extended considerably, such as the competition between protein folding and the formation of diverse morphologies of aggregates and amyloids; the functional roles of intrinsically disordered proteins (IDPs); and liquid–liquid phase separation as an important organizing principle in the cell. The articles in this issue review recent developments in these and other exciting areas and illustrate the remarkable range of mechanisms and complexity that can emerge from intramolecular and intermolecular interactions in biology.

All these mechanisms are a result of evolution within the constraints of physics and chemistry. Consequently, we observe many compromises between antagonistic contributions, such as enthalpy and entropy, or stability and function. Bigman and Levy describe the different types of such trade-offs, their connections and interdependencies, and biological mechanisms that have emerged as a consequence. An interesting case of the compromise between chain topology and foldability is discussed by Joanna Sulkowska: the presence of knots and related non-trivial topologies in proteins, such as the ones formed due to the presence of disulfide bonds. Of particular interest is the role of topological frustration in such knotted structures, and how efficient folding can still be achieved. Another remarkable phenomenon that has only recently been discovered is the extreme mechanical stability of some protein-protein interactions, with rupture forces up to the nanonewton range in some pathogen-host interactions. Milles and Gaub summarize the systems known so far, how these extreme stabilities are achieved, and how they can be studied based on recent developments in force spectroscopy.

The enabling power of methodological advances is also illustrated by several other articles. Alderson and Kay outline the latest developments in NMR spectroscopy for characterizing the structural and dynamic properties of sparsely populated conformations in protein folding and misfolding, and how advanced NMR methods can be used to study the details of the folding energy landscape and the underlying molecular mechanisms of protein folding. De Souza and Picotti show how mass spectrometry-based proteomics has taken the investigation of protein folding, stability, aggregation, and molecular interactions to a new level where these properties can be probed on a proteome-wide scale in cell lysates and even in intact cells, a major step towards a systematic structural view of the cell. Not only

experimental but also theoretical methods continue to make important contributions to many aspects of biomolecular science. Noé, De Fabritiis, and Clementi summarize how developments in machine learning have begun to open new perspectives and opportunities in many areas of protein folding and dynamics, including protein structure prediction, force-field development, enhanced sampling, and data analysis.

The investigation of amyloids has been transformed by innovations in method development as well, especially in cryo-electron microscopy, electron diffraction, and solid-state NMR, as explained by Gallardo, Ranson, and Radford. As a result, it has now become possible to determine not only the high-resolution structures of amyloid fibrils generated *in vitro* but even directly from patient samples, which together have revealed an unexpected diversity in amyloid folds, illustrating the subtle balance of non-native interactions in proteins. Reddy, Muttathukattil, and Mondal address the effects of cosolvents on amyloid formation. They demonstrate that coarse-grained models and enhanced sampling can bridge the timescale gap between simulations and experiments to help understand the opposing effects of denaturants and osmolytes on the aggregation mechanisms of both foldable proteins and IDPs. Cosolvents have also played an important role in understanding the dimensions of unfolded and disordered proteins as a function of solvent quality. As outlined by Robert Best, recent advances in experiments, simulations, and data analysis have revealed increasingly detailed insights into the degree of compaction of unfolded polypeptide chains in water and the dependence of this compaction on amino acid composition, which has helped to reconcile seemingly disparate experimental results.

Both the physical properties of IDPs and their biological roles have been of great recent interest because of the large number of previously unexpected and far-reaching implications for cellular regulation. One important characteristic of IDPs is the prevalence of posttranslational modifications in disordered regions. Phillips and Kriwacki highlight the role of these diverse reversible modifications in IDPs for cellular signaling, the resulting effects on biomolecular recognition, and the emerging opportunities for the design of synthetic regulatory circuits. A surprising recent result has been the identification of electrostatically driven high-affinity interactions of highly charged IDPs that do not form secondary or tertiary structure upon binding. Schuler, Borgia, Borgia, Heidarsson, Nettels, and Sottini summarize the increasing evidence for such biological polyelectrolyte interactions, the underlying molecular mechanisms, and how these potentially widespread complexes may have important consequences for regulatory processes in the cell.

Over the past decade, it has become clear that IDPs are also key drivers for the formation of cellular condensates by liquid–liquid phase separation and gelation. These large membraneless assemblies are increasingly recognized as a functionally important feature of the complex cellular architecture, but elucidating the structural and dynamic properties of the constituting proteins and nucleic acids poses new challenges. Peran and Mittag review the existing views on the roles of folded domains, disordered low-complexity regions, and amyloid-type cross-β structure in mediating condensate formation and the open questions in this rapidly growing field.

In summary, many topics in biomolecular folding and binding have seen remarkable recent progress, ranging from new insights into long-standing questions to unexpected types of assemblies and binding mechanisms. In many cases, crucial prerequisites for discovery and understanding have been new developments in biophysical methodology, the integration of experimental data with theory and simulation, and knowledge transfer from neighboring scientific fields, such as soft matter and polymer physics, or machine learning. We hope that this collection of reviews will not only provide a helpful overview of the latest developments in the field but also convey the challenges we are facing and the exciting new opportunities that arise from them.