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Digging deep into nucleic acid structure and nucleic acid protein recognition

Joseph D Puglisi and

Department of Structural Biology, Stanford University School of Medicine, Stanford, CA
94305-5126, USA

James R Williamson

Department of Molecular Biology & Chemistry, The Skaggs Institute for Chemical Biology, The
Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

The field of nucleic acid structural biology has both expanded its horizons and refocused on unanswered fundamental questions, as outlined in this *Current Opinion in Structural Biology*. The diverse topics spanned by these reviews include relatively old questions from new perspectives, such as ion binding, base modifications or RNA–protein interactions, and new, exciting areas such as riboswitches. The pace of solving new and interesting RNA structures and RNA–protein complexes is rapidly accelerating, and general principles of recognition are beginning to emerge. A wide variety of approaches to understand nucleic acid structure and protein recognition, using a continually evolving range of techniques. The structural biology of nucleic acids continues to surprise and provides a context to understand their ever richer biology. The reviews in this issue span structure, dynamics, modeling, and protein recognition, using diverse approaches including crystallography, NMR, SAXS, computation, and single-molecule techniques.

Base modifications in nucleic acids have been a mystery since their discovery. However, over the past decade, the field of epigenetics has revealed a central role for modified DNA in both bacteria and higher organisms. Recently, a new modified DNA base 5-hydroxymethyl-cytosine has been discovered, with roles in stem cell biology and development. The challenge around modified bases is their detection on a genome wide scale. Korlach & Turner provide a timely review of how a variety of direct methods have been developed to detect the presence of distinct modified bases in DNA. These approaches use real time interactions of polymerases or nanopores to discriminate unmodified and distinctly modified bases. The future application of these approaches, which harness biophysical and structural knowledge, is exciting.

Divalent ions are essential to stabilize and modulate nucleic acid structures. This was first appreciated in classic studies on the folding of tRNAs in the 1960s and 70s. The recent explosion in crystal structures of RNAs has presented a rich compendium of ion–RNA interactions, leading to new general views of how ions stabilize nucleic acid structures.

The Puglisi lab studies the role of RNA structure and dynamics in cellular processes and disease.

The Williamson lab uses biophysical approaches to study RNA structure and RNA–protein interactions, including ribosome assembly.

Bowman, Lenx, Hud and Williams present a cogent review of divalent ion interactions with RNAs that summarize recent viewpoints. The review presents a summary of the fundamental chemistry of magnesium ions, and shows structural evidence for common motifs of Mg–RNA contact, that go beyond simple electrostatic contacts. The evolving structural and theoretical treatments of ion–RNA interactions will be essential for our understanding of RNA biology.

The field of RNA structural biology has lagged the developments in protein structural biology, and so too has the application of molecular modeling to RNA. This is in part due to the lack of a sufficient database of structures to provide information for developing energy potentials to describe nucleic acid structure. Sim, Minary and Levitt provide an excellent overview of the developments in the area of RNA modeling. Depending on the application, nucleic acids can be readily modeled at a varying level of detail, from all-atom representations to residue or helix-based coarse grain representations. Models can be developed using a wide variety of degrees of freedom and methods for conformational sampling. This is an important area that is undergoing rapid development to meet the challenge of understanding RNA structure and function computationally.

RNA continues to surprise in terms of function. Riboswitches were discovered about 10 years ago as RNA elements in bacterial mRNAs that bind directly to small-molecule metabolites. The binding of the metabolite leads to RNA conformational changes that change transcription or translation rates. These relatively small (<100 nt) RNA elements have been excellent targets for structural biology. Serganov and Patel summarize the remarkable progress in understanding the diversity of ligand–RNA interactions, and coupling with RNA folding in riboswitches. The field has blossomed, as high-resolution structure has merged with both biophysical and biological results.

There is rapid development in the structural biology of RNA–protein complexes, and numerous structures are emerging each year. One clear principle that is emerging is that there are changes in the structure and dynamics of both the RNAs and the proteins. Dynamics localized within domains are modulated upon complex formation, and flexible linkers between RNA binding domains can become ordered upon complex formation. The contribution from Mackereth and Sattler provides an insightful overview of the developments in this area, as well as a summary of the diverse experimental approaches that can be used to assess changes in structure and dynamics upon complex formation.

One particularly exciting example of the role of conformational changes and dynamic changes is the area of recognition of double-stranded RNA by RIG-I like receptors, involved in the immune response to viral infections. A series of recent structures are reviewed by Leung and Amarasinghe, describing the mechanism of dsRNA recognition and proposing a model for activation of the receptor. Binding of the dsRNA is effectively competitive with the signaling domains that are *in cis* with the RNA binding domains. These structures provide a striking example of how dynamics and conformational flexibility are exploited in signaling pathways.

The application of novel single-molecule approaches has revolutionized our ability to probe and manipulate nucleic acids. Using trapping methods, with either magnetic or optical control, nucleic acids can be placed under either mechanical (stretching) or torsional stress. Conversely, the stress induced by protein action or conformational changes can be measured. Bryant, Oberstrass and Basu review the exciting recent advances in measuring DNA mechanics. In particular, the ability to monitor torsional movements and torque in DNAs, using various rotational assays, has allowed investigation of the mechanisms of topoisomerases and gyrases, which manipulate DNA topology. While structures of these enzymes are known, the mechanistic details of how DNA topology is changed remains an open question. The new single-molecule approaches outlined in this review promise deeper insights into mechanism, and will be useful in the budding field of DNA nanotechnology.

The structural biology of nucleic acids is in a dynamic phase. Many landmark structures, such as tRNAs, Group I and Group II self splicing introns, the ribosome, and RNase P have been solved, providing a remarkably rich set of structural motifs as a basis set. The current forefront is interaction of nucleic acids with diverse ligands, including ions, metabolites, and proteins. The latter problem of specific recognition of diverse RNA sequences by relatively few RNA binding domains is a current area of active development. The genomic era is providing an avalanche of information about sequences that interact, resulting in a combinatorial explosion of complexes to understand in terms of specificity. The Future of nucleic acid structural biology is bright, so return here as the Future becomes Current for exciting new developments in this area.