The interactions between proteins and nucleic acids guide the flow of genetic information between DNA, RNA, and protein. The reviews in this issue of Current Opinion in Structural Biology discuss some of the most fundamental aspects of RNA folding and dynamics, modes of nucleic acid recognition, and the assembly and structures of large protein–nucleic acid complexes including ribosomes, nucleosomes, and spliceosomes. Many recent advances in these fields stem from structural insights gained through a combination of X-ray crystallography, NMR, electron cryo-microscopy, small-angle X-ray scattering, and chemical and enzymatic probing. A recurrent theme in these reviews is the interplay between structure and the dynamics of macromolecular complex assembly, catalysis, and regulation.

New functions of noncoding RNA in biology continue to be discovered, underscoring the unique capabilities of RNA to both encode and act upon genetic information. As Hashimi and Walter describe in the first review, these functions often require dynamic changes in both the conformation and molecular partners of RNA. Recent studies suggest that many RNA molecules, though prone to kinetic trapping of locally misfolded structures, are designed to form correct secondary structural interactions during transcription. In some cases, the capacity for conformational change is directly relevant to biological function, as in the case of riboswitches. Both single-molecule and bulk solution experiments using fluorescently labeled RNAs have illuminated the dynamics of riboswitch conformational dynamics in response to ligand binding, providing exciting insight into this mode of RNA-mediated gene regulation. Future challenges include determining how large RNA–protein complexes assemble and harness conformational motion for functional purposes. Highlights of recent findings about ribozyme dynamics and the ordered conformational changes that are integral to ribosome function illustrate principles likely to crop up in other systems.

RNAs must struggle to fold to their most stable three-dimensional structure. Chu and Herschlag review the huge advances that have occurred in the study of RNA folding. Like proteins, RNAs must find their low-energy conformation, and many studies have highlighted the rugged nature of this folding landscape — RNAs often get stuck in misfolded states, which require traversal of large free-energy barriers to arrive at the correct state. The authors discuss recent mechanistic work into how a ubiquitous class of RNA helicase enzymes, the DEAH-DEAD box proteins, reorganizes RNA structures using the energy of ATP hydrolysis to create a correctly folded state. Helicases control key transactions in RNA metabolism, including splicing and noncoding RNA function, and highlight the intimate collaboration between RNA and protein structures. Chu and Herschlag also review a large body of biophysical and computational studies of RNA folding.
without the help of proteins. Electrostatics is a dominant force in RNA folding, but recent theoretical, computational, and experimental investigations have revealed the interplay of counterions, RNA structure and folding pathways. New structural methods, including time-resolved footprinting, small-angle X-ray scattering, NMR and X-ray crystallography, bode well for structural snapshots along an RNA folding pathway.

In the third review, we are aptly reminded that far from being dull, the classic RNA-recognition motif (RRM) continues to reveal new aspects of both form and function. Clery et al. point out that the abundance of this ~90-amino acid fold within vertebrate genomes — RRMs are found in an astounding 0.5–1% of human genes — correlates with its exceptional versatility as an RNA and protein interaction partner. Several recent structures, determined by X-ray crystallography and NMR, show how sequence specificity can be heightened or diminished depending on the amino acid composition of the beta-sheet and loop regions of the RRM. Multiple RRMs often occur within a single protein, where they can interact to enhance RNA-binding affinity, specificity, or both. In some cases such interacting RRMs bind to single-stranded DNA rather than RNA, or block nucleic acid binding altogether. RRMs can also bind uniquely to other non-RRM proteins, thereby altering the nucleic acid binding properties of the resulting complex. Future work to understand the contributions of RRMs to folding kinetics and dynamics of large ribonucleoproteins are eagerly anticipated.

The ribosome is the archetypal of a ribonucleoprotein assembly. Williamson reviews how the ribosomal particle is assembled. Structural studies during the past eight years have revealed the architecture of the ribosomal particles in several organisms. These structures have shown the intimate interactions of RNAs and proteins to form the ribosomal particles; these structures have also propelled mechanistic investigations of ribosomal assembly. In bacteria, the prior work of Nomura and others mapped the equilibrium assembly pathway of the ribosome. New approaches have provided fresh perspectives on ribosomal assembly. Mass spectrometry of ribosomal proteins using isotope pulse labeling has allowed dynamic investigation of the assembly pathway. Computational power has also been brought to bear on this interrelated RNA–protein assembly process. The field is now poised to move beyond in vitro investigations toward understanding cotranscriptional assembly and its regulation in vivo.

RNA modifications add chemical diversity to the homogeneity of four nucleotides. A large number of RNA modification enzymes exist to add simple to complex chemical modifications to RNA. Ishitani, Yokoyama, and Nureki review the stunning progress in our structural knowledge of how RNA modification enzymes recognize their targets. A large number of crystal structures of modification enzymes with their target RNAs have now been solved. Transfer RNAs (tRNAs) contain a large number of modifications that assist in stabilizing the overall tertiary structure and modulating molecular recognition by proteins or RNAs. Structures of unmodified tRNAs with modification enzymes show that these enzymes distort the tRNA fold to allow proper chemistry on the target nucleotide to occur. In some regards, this is the RNA version of the base-flipping mechanism seen in DNA modification enzymes. The RNA modification enzymes use various strategies to recognize the overall fold of the RNA to impart specificity on which nucleotide is modified. Other noncoding RNAs, such as those in the ribosome and splicesome, are also modified. In higher organisms, small nucleolar RNAs guide modification, and several structures have revealed how RNA–protein assemblies might target specific sites in ribosomal RNA. The future is clear: RNA modifications and their synthesis machinery are essential features of the evolving biology of RNA.

The nucleosome core particle (NCP), consisting of 146 bp of DNA wound twice around an octameric core of four histone proteins, is the fundamental building block of packaged DNA or chromatin in eukaryotic cells. As Park and Lugerdiscuss, histones within these structures are not static but instead are turned over or exchanged independent of DNA replication in vivo. Histone chaperones, previously thought to simply bind to histones, have emerged as central players in chromatin dynamics through their ability to coordinate the delicate balance between nucleosome assembly and re-assembly during transcription. Recent structural studies of histone chaperones and a chaperone–histone dimer complex have suggested mechanisms by which this may be accomplished. The recruitment of ATP-dependent chromatin remodeling factors enables histone chaperones to function catalytically to incorporate histone variants into nucleosomes, with diverse effects on nucleosome structure and stability. Histone variants also influence the ability of nucleosomal arrays to condense into higher order chromatin structures. These studies lay the foundation for investigating how such structural changes correlate with changes in transcription initiation, recombination, transposition, and other aspects of genome regulation.

In the last review in this issue, Jurica discusses recent structural insights into an equally fascinating complex, the spliceosome, which is responsible for removing introns from pre-mRNAs in eukaryotic cells. Because of its size, composition, and conformational plasticity, combinations of methods are being used to tackle the structure of the spliceosome. Whereas atomic resolution structures of individual splicing factors are steadily emerging, electron cryo-microscopy has been useful for...
revealing the overall architecture of the intact spliceosome and its component small nuclear ribonucleoprotein (snRNP) particles. On the horizon are X-ray crystallographic structures of snRNPs, which together with computational approaches will provide unprecedented insights into the organization and functional core of the eukaryotic splicing machinery.

The field of nucleic acid–protein interactions has exploded in recent years, driven by our expanding view of RNA in biology. Structural studies have come in rapid succession, revealing the basic architectures of many key systems, including the ribosome and transcription machinery. The resulting detailed understanding of nucleic acids from a structural, biophysical, and biochemical standpoint has enhanced our foundation to probe novel biological functions. The future will require complementary studies of molecular dynamics to merge structure and mechanism, and the patience to grasp the breathless pace of biological discovery.