
Preface

Research in the last 30 years has revealed that an unexpectedly large fraction of genomic DNA is transcribed into RNA [1]. Moreover, many new functions of RNA are being discovered [2]. This has provided a need for ways to rapidly translate sequence into structural information.

The twenty-first century witnessed many advances in modeling and determining RNA structures. Secondary structure prediction on the basis of sequences alone is increasingly accurate. New methods have been developed for experimentally probing secondary structure to identify paired and unpaired nucleotides for restraining predictions. Multiple methods are being developed to model three-dimensional structure. At the same time, more and more three-dimensional structures are being determined. The new structures are providing benchmarks for improving predictions of three-dimensional structure from sequence.

Twenty-First Century Advances

Secondary structure prediction improved in accuracy as a result of several innovations. New parameter sets were derived to quantify structure quality [3–5]. New algorithms were invented to consider folding of structural ensembles, rather than only most likely structures [4, 6–10]. Additionally, new approaches are available to determine the conserved secondary structure for multiple homologous sequences, thus increasing accuracy relative to single sequence structure prediction [11–17].

Probing structure by enzymatic and chemical methods is a cornerstone of determining RNA secondary structure [18–20]. New methods for probing structure were developed. In particular, a new class of chemical probing agents, based on selective 2'-hydroxyl acylation and primer extension readout (SHAPE), was developed to identify RNA nucleotides in flexible regions of the structure. The most reactive nucleotides tend to be in loops [21–23]. Unlike base-specific agents, SHAPE attacks flexible 2'-hydroxyl groups and thus interrogates all nucleotides. SHAPE was also coupled with quantification of the reactivity per nucleotide, and these data provide restraints that dramatically improve the accuracy of secondary structure prediction [24–27]. At the same time, traditional probing agents were applied in new ways. Enzymatic cleavage was coupled with next-generation sequencing to probe structure across the transcriptome [28, 29]. The extent of dimethyl sulfate (DMS) reactivity was quantified and also used as restraints for structure prediction [30]. SHAPE reagents were shown to be effective at *in vivo* mapping [31, 32], as previously shown for DMS [33]. Finally, DMS and SHAPE were coupled with next-generation sequencing to probe RNA structure *in vivo* across the transcriptome [34–36].

Modeling of three-dimensional RNA structure has also advanced. As for protein structure prediction [37], RNA structure prediction uses blind modeling to assess advances in the field by employing new benchmarks, called RNA Puzzles [38, 39]. A number of groups participate in the blind predictions, using approaches ranging from physics-based to knowledge-based [40–49]. The second RNA Puzzles comparison concluded that overall

topologies are correctly modeled, but that noncanonical pair interactions are not yet well predicted [39].

At the start of the century, x-ray crystal structures of ribosomes were solved. Since that time, ongoing advances in x-ray crystallography [50–52], nuclear magnetic resonance (NMR) [53–55], and cryo-electron microscopy (cryo-EM) [56–58] have all led to the determination of more complex and higher resolution structures. Small angle x-ray scattering (SAXS) is being applied to RNA to determine molecular envelopes in solution [59, 60]. The advances extend to new approaches to consider ensembles and structural flexibility [61, 62]. Importantly, this work was enabled by development of new modeling methods, including improved methods for validating structures [63].

Organization of the Book

This book provides protocols for RNA structure modeling and determination. The first chapters provide protocols for RNA secondary structure prediction. Chapters 1 and 2 discuss single sequence modeling with the software packages, Crumple [64] and RNAstructure [65], respectively. Chapter 3 discusses using RNAstructure to model conserved secondary structures with multiple homologs. The prediction of bimolecular secondary structures with RNAstructure is presented in Chapter 4 and with Vfold [42] in Chapter 5. Chapter 6 presents STarMir [66], an application of secondary structure prediction to miRNA target prediction.

Chapters 7, 8, and 9 provide protocols for structure mapping, with traditional chemical agents [18], with enzymatic mapping across the transcriptome [29], and with SHAPE reagents [67], respectively. Chapter 10 provides protocols for using mapping data to constrain or restrain RNA secondary structure prediction with RNAstructure. Chapter 11 gives the protocol for using unassigned NMR resonances to improve secondary structure prediction and to provide initial assignments of some resonances to start solving a three-dimensional structure [68].

The book concludes with protocols focusing on three-dimensional structure. Chapters 12, 13, 14, and 15 provide modeling protocols for FARFAR [43], RNAComposer [40], ModeRNA [41], and MC-Fold [46], respectively. Chapter 16 provides an introduction to structure determination by NMR. Chapter 17 provides a protocol for x-ray crystallography determination of RNA structure.

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Methods and Protocols

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