PREFACE

It is clear from the Encyclopedia of DNA Elements (ENCODE) project that a significant portion in the transcriptome does not translate into protein sequences. Many of these sequences function through the formation of specific RNA structures. Riboswitches represent an important class of noncoding RNAs. Riboswitches perform functions as genetic "switches" that regulate when and where genes are expressed. To understand the structure and function of riboswitches requires computational models that can predict stable and metastable structures, their folding stabilities, kinetic pathways, transition states, and rate constants for the conformational switches, in addition to the effects of metal ions and ligand binding on RNA folding, all from the nucleotide sequence.

This book represents a state-of-the-art collection of advanced computational methods for modeling RNA riboswitch structure, thermal stability, dynamics, and kinetics. Given the fact that riboswitches have been extensively studied experimentally, yet currently the accuracy of computational prediction for riboswitch remains generally inconsistent, this volume is particularly timely. We believe that this volume will excite future more radical advances in computational modeling for riboswitches and other noncoding RNAs.

One of the major scientific challenges for RNA modeling relates to how we use the knowledge derived from limited information about known RNA structures. Effective structure prediction methods often involve integration of knowledge-based algorithm and physics-based or experimental data-based models. Several chapters present methods along this line: Purzycka et al. and Cheng et al. developed motif library-based and fragment-based methods, respectively; Sloma and Mathews developed methods that incorporate high-throughput structure probing data into secondary structure prediction; Kirmizialtin et al. employed selective 2′-hydroxyl acylation by primer extension (SHAPE) data and developed a new force field for molecular dynamics simulation; and Krokhotin and Dokholyan incorporated SHAPE into discrete molecular dynamics to predict RNA structure.

Another major challenge for the computational modeling of riboswitches comes from conformational sampling due to the large conformational space of the molecule and the flexibility of RNA structure.

To enhance the quality of conformational sampling, Krokhotin and Dokholyan developed a three-bead coarse-grained structure model in molecular dynamics simulation and Kim et al. developed a graph-theoretic approach to efficient sampling of RNA motif structures. These methods offer very interesting new tools for modeling RNA folding.

Kinetics are intrinsic to RNA folding and conformational switching. Riboswitches can fold cotranscriptionally into the conformations that correspond to ON and OFF states. The kinetics of RNA folding and conformational switching are critical for understanding riboswitch structure and function. This volume contains several chapters that address the methods to model riboswitch kinetics. Badelt et al. developed a cotranscriptional kinetics model by integrating RNA secondary structure with the dynamic energy landscape. Lin et al. developed a three-dimensional coarse-grained self-organized polymer model to predict riboswitch dynamics under force. Using a steered molecular dynamics-based method, Di Palma et al. developed an all-atom model to predict ligand-induced riboswitch stability and structure changes at atomic resolution. Hanke and Gohlke presented a critical analysis for the performances of the different force fields, including the Mg^{2+} ion effects, in riboswitch simulations. In addition to the physical models, informatics-based approaches have been highly successful in predicting riboswitch structures and finding riboswitch genes. Clote presented a comprehensive introduction for the different computational methods with particular emphasis on informatics-based approaches for riboswitch structure and kinetics.

Conformational changes in riboswitches can be induced by ligands or ions. It is thus important to have a reliable tool to predict the binding sites and binding modes. This volume contains two chapters on this issue. Using knowledge-based scoring functions, Philips et al. developed novel methods ("LigandRNA" and "MetalionRNA") for the prediction of riboswitch binding. Panteva et al. presented a multiscale method for modeling conformational switching, metal ion binding, and enzymatic reactions. In these chapters, the related computational methods are discussed, as well as their limitations and pitfalls.

RNA conformational switching can also be induced by the presence of other RNA or DNA molecules. Afonin et al. presented a thermodynamic model for predicting association and dissociation of RNA/DNA hybrids containing a novel split functionality. The results demonstrate the great promise of using RNA structure and conformational switches in RNA nanotechnology.

Finally, we would like to thank the fabulous team of authors, who have put together high-quality chapters. Without the phenomenal works of the authors, it is simply impossible to publish such a quality volume.

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SECTION I

RNA Structure Prediction