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RNA Structural Variability and Functional Versatility Challenge RNA Structural Modeling and Design

RNA's rising stardom is well-justified by its structural variability and functional versatility. Indeed, besides RNA's key role in the translational machinery, RNA is instrumental for the manipulation and regulation of genetic information. Because regulatory errors and altered RNA functions can trigger abnormal cellular events, RNA has also emerged as a strong drug target for treating a variety of human diseases. Of course, fundamental mechanistic knowledge of RNA folding, energetics, and kinetics is essential for understanding RNA's pathways into its many functional states and how these states are affected by ions, proteins, and other nucleic acid entities in the cellular milieu. Such information is important for deploying RNA features into targeted therapy using nucleic acid targets rather than proteins and other compounds.

Our understanding of these fundamental aspects of RNA activity has advanced in recent years due to significant improvements in experimental structural determination of RNAs as well as focused computational efforts that explore RNA structure and motion. The combined knowledge has led to many efforts in RNA design, with applications in medicine and technology.

This special volume in Biophysical Journal celebrates the many innovative approaches in RNA science, while also presenting the challenges in RNA structural modeling and design. Papers were invited by scientists who are advancing the field on both genomic and molecular levels of RNA using novel experimental, mathematical, statistical, and computational approaches.

In our perspective article (Schlick and Pyle), we provide an overview of current RNA topics and point to open questions, including RNA structural assemblies (hierarchical folding, multiple conformational states and their clustering), RNA motifs, and chemical reactivity of RNA, as used for structural prediction and functional inference.

We also discuss the software and database issues associated with RNA structures: motif annotation, database updating, and quality control of RNA structures. We mention various modeling approaches for structure prediction, mechanistic analysis of RNA reactions, and RNA design. In particular, we highlight the complementary roles that both atomistic and coarse-grained approaches play in such simulations.

Among the research articles in this collection, many deal with the complex landscapes and structural assemblies of RNA, and RNA's conformational variability.

Four papers, in particular, focus on the effect divalent ions and/or other molecular components for the assembly of RNA complexes. Falkenberg and colleagues (Carson et al.) develop an innovative deterministic-stochastic-statistical modeling approach to study RNA granules, ensembles of specific RNA, and proteins; their work offers mechanistic insight into the function of RNA granules in eukaryotic transcription.

Mitra and co-workers (Halder et al.) use density functional quantum-mechanical computations to study the modes of magnesium ion binding in RNAs containing reverse Watson-Crick base pairs. They find that the ions can modulate the base pair geometries in a variety of sequence contexts.

Bergonzo and Cheatham show by classical molecular dynamics simulations how divalent ions can stabilize geometries within the Varkud Satellite ribozyme so that the RNA junction in the structure acts a scaffold.

With Roy and Onuchic, Sanbonmatsu similarly uses large-scale atomic molecular dynamics simulations of the SAM riboswitch RNA to reveal the importance of divalent ions in coordinating a pseudoknot motif motion that is significant to transcription regulation.

The separate groups of Mathews (Tan et al.), Heitsch (Rogers et al.), and Laederach (Woods et al.) present new approaches to predict or assess the conformational landscape of RNA secondary structural elements. Although secondary-structure (2D) prediction algorithms have improved in recent years through the incorporation of experimental data from chemical probing and cross-linking methods like SHAPE (Selective 2′-OH acylation by primer extension), for example, challenges arise in evaluating the complex landscape of 2D structures, since many local minima may be biologically relevant.

Tan et al. present an algorithm for 2D structure prediction that uses comparative sequence analysis and chemical mapping data called TurboFold II.

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Rogers et al. present a numerical analysis model that helps measure the conditioning and robustness of the Boltzmann ensemble of minimum-free-energy states in the 2D landscape of RNAs. Woods et al. describe a robust approach for visualizing the conformational ensemble of RNAs based on clustering and evaluating ensembles for a family of mutant sequences; their application to an RNA riboswitch generates profiles that correlate with structural rearrangements consistent with the RNA's function.

The theme of structural variability is also exemplified in the cluster analysis work of Lindorff-Larsen and Botaro, who reveal the versatility of sequence and tertiary interactions involved defining RNA tetraloops.

A different theme of RNA structural assemblies is the focus of two experimental works from the groups of Lanier (Roy et al.) and Knobler (Beren et al.).

Roy et al. explore ribosomal RNA (rRNA) interactions with protein factors to determine the extent by which rRNA folds independently of the proteins with which it binds in the complex. Their results highlight the folding autonomy of rRNA, whereby the protein cofactors act as co-chaperones, providing evidence for the RNA-world hypothesis.

Beren et al. use various experimental techniques to analyze the assembly of the cowpea chlorotic mottle virus (CCMV). They show that the structure of the capsid protein of CCMV formed during the self-assembly of the CCMV virus-like particles depends critically on the 2D structure of the RNA molecule and its absence, highlighting the importance of RNA's 2D structures in biological structure and activity.

Besides atomic models, lower-resolution (or coarse-grained) models have been successful at modeling RNA, specifically for predicting tertiary structures and for pursuing design applications.

Pasquali and co-workers explore how human intuition might play a role in problem solving by employing their group's coarse-grained model for RNA combined with experience in open software they developed for students. Their study suggests that human instinct could be deployed to fold simple but non-trivial tertiary RNA topologies. Such studies open the way for further scientific discovery by open source scientific games that started for proteins (like "folding at home").

A new coarse-grained model for RNA, focused on studying RNA interactions, is presented by Marrink and colleagues.

As this collection shows, scientists from varied disciplines are increasingly drawn into RNA's unique challenges, which are benefitting from the growing experimental information on RNA structural variability and function, along with the various mathematical, statistical, and kinetic approaches for RNA investigations. We can only anticipate more exciting research and discoveries on RNA, as well as applications to human disease treatment in the coming years. We hope you will enjoy these papers.

Tamar Schlick,[1,3] and Anna Pyle[2]
[1]*New York University, New York, New York;*
[2]*Yale University and the Howard Hughes Medical Institute, New Haven, Connecticut; and*
[3]*Associate Editor, Nucleic Acids and Genome Biophysics*