Public Abstract

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Title: Statistical Thermodynamics for RNA Structures with Simple Tertiary Contacts and Pseudoknots

Ribonucleic acids (RNAs) are polymer molecules which play a variety of roles in processes of transmission, expression, and conservation of genetic information. The RNA molecules are able to play these roles largely due to their ability to form different structures and to interact with other molecules. The availability of an accurate RNA folding model is essential for our understanding of RNA functions and in RNA-targeted drug discovery. Despite the widespread importance of RNA folding for cellular function, understanding of the principle of the RNA folding, especially of the tertiary structure folding, is very limited. Reliable prediction for tertiary structural stability and folding pathways is not possible, even for the simplest tertiary folds. In this thesis, we develop statistical mechanical models for the folding of simple RNA tertiary structures.

One of the bottlenecks to model RNA tertiary folding is the entropy problem. In the tertiary structures, different structural subunits (loops, base stacks) are strongly dependent on each other due to the long-range intrachain contacts that form the tertiary structure. Therefore, unlike secondary structures, the entropy of tertiary structure is non-additive, i.e. cannot be calculated as a sum of the entropies of structural subunits. As a result, a major challenge in the theory is how to account for the nonlocal correlations between different parts of the tertiary structures. Our principle approach is "dividing and conquering": to divide the structure into conformational subunits and to treat the inter-subunit interactions by focusing on the local interactions near the inter-subunit interfaces. The theory is developed based on a two-dimensional lattice model. Extensive tests against exhaustive computer lattice enumerations show that the model is accurate and reliable.

The model developed in this thesis enables predictions for stability and pathways for thermally facilitated folding-unfolding of tertiary structures and pseudoknots. The theory has been applied to study the mechanical unfolding (in the single molecule pulling experiments) of model RNA H-pseudoknots. The information about structural transitions in the unfolding process has been obtained from force-extension curves, computed using the force-dependent partition functions.

The theory developed in this thesis may provide paradigms for modeling complex RNA tertiary structure folding thermodynamics. It permits the use of arbitrary chain representation, can be generalized to any off-lattice models, and can be developed to treat more complex tertiary structures.