

Ribonucleic acid (RNA) has been postulated as the essence of the origins of life on Earth. On the most basic level of chemical structure, RNA resembles DNA. Like DNA, it is a linear polymer of nucleotide residues, Adenine (A), Cytosine (C), Guanine (G), and Uracil (U), bound together into a sequence, like beads on a string. RNA molecules can store genetic information similar to DNA and mediate catalysis, similar to protein enzymes. Therefore, the 'RNA World Hypothesis' suggests that the most primitive forms of life may have relied solely on RNA for both to store genetic information and to catalyze chemical reactions. Even the most modern cells in all kingdoms of life contain different classes of RNAs, that perform a plethora of activities from information processing to catalysis that is of utmost importance for cellular function and development. To understand how RNA molecules work, determining their three-dimensional (3D) atomic structures is necessary.

Experimental determination of RNA structures at atomic detail is laborious and difficult, and therefore the majority of known RNAs remain structurally uncharacterized. Predictive computational methods were developed to address this problem. However, all theoretical methods suffer from various limitations, and they are generally unable to accurately predict structures for RNA sequences longer than 100 nucleotide residues unless aided by additional experimental data.

Therefore, I propose an approach to model the 3D structure of RNAs that combines the advantages of theoretical structure prediction methods with experimental data analysis. The proposed software will build on a successful modeling package, SimRNA, developed in my home laboratory. I will develop new algorithms to use data from X-ray crystallography, cryo-electron microscopy, and/or small-angle X-ray scattering. These experimental data will be used as restraints to guide the computational simulation to the best solution, thereby achieving a synergistic effect. The new software will make the experimental determination of RNA structures easier and less laborious. It will extend the range of RNA structures that we can model. As a result, we will be able to learn the mechanistic details about RNA molecules, speeding up both fundamental research on their function and analyses leading to their practical applications.