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Playing hard balls with RNA: fully automated *ab initio* RNA folding by discrete molecular dynamics

In the area of small-molecule drug discovery, we are witnessing an increased interest in the potential of RNA to act as a drug or to serve as a drug target [1–5]. To design both the RNA-based pharmaceuticals and the RNA-targeted drugs in a rational manner, the knowledge of RNA three-dimensional (3D) structure and folding dynamics is evidently of prime importance. All direct structural methods, however, like X-ray crystallography or NMR spectroscopy, are so time- and labor-consuming that there is an urgent need for fast and accurate prediction of 3D RNA folding by computational means.

Various approaches have been developed for this purpose [6]. Still, none of them was as efficient in reaching the goal as a recently developed method, called iFoldRNA, which is based on the simplified 'beads-on-a-string' RNA model and discrete molecular dynamics (DMDs) computerized simulations [7].

Indeed, this new method is at least ten times faster than the potent *in silico* RNA-folding methodology reported in the past year, which employs the fragment assembly of RNA (FARNA) using Monte Carlo sampling with a knowledge-based energy function to predict putative RNA conformations [8]. Compared to FARNA, iFoldRNA is also able to predict 3D folding for

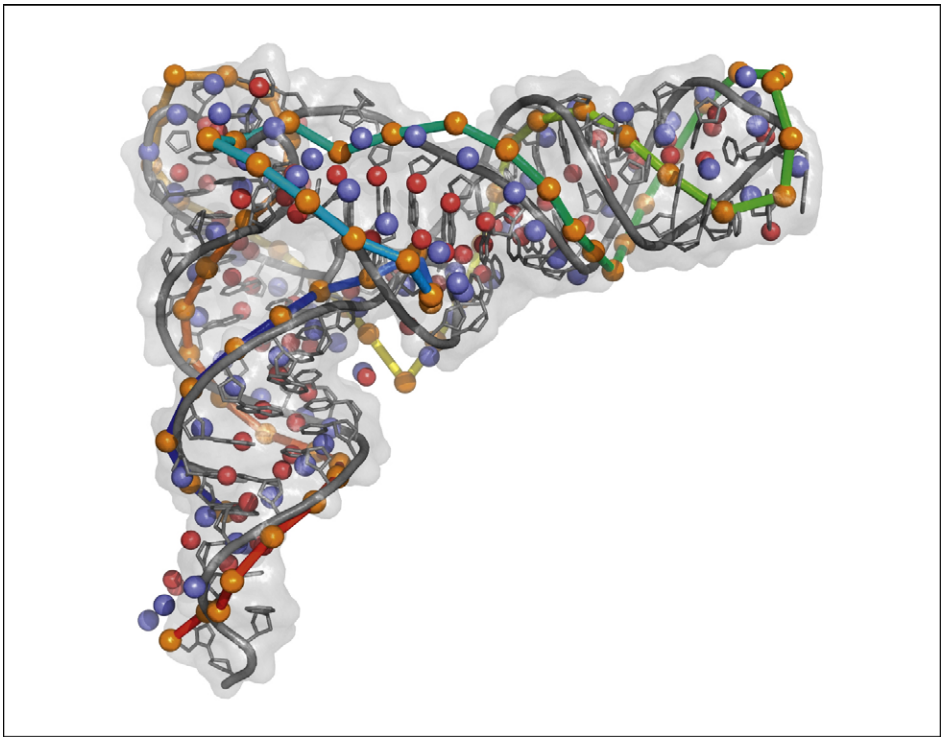

FIGURE 1

Superposition of the least root mean square deviations (RMSD) for the 'beads-on-a-string' model of a 76-nt-long transfer RNA (tRNA) against the corresponding crystal structure (Nucleic Acid DataBank: 1evv; colored gray). The three beads, sugar, phosphate and nucleobase in the 'beads-on-a-string' model, are colored blue, orange and magenta, respectively. The backbone trace of the model tRNA is colored from blue (N-terminus) to red (C-terminus). The RMSD between the model tRNA and the experimental structure is 7.1 Å (courtesy of Nikolay V. Dokholyan, University of North Carolina at Chapel Hill).

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longer RNA molecules and gives better agreement with corresponding known native structures (Fig. 1).

Another robust *in silico* RNA-folding methodology reported this spring employs the 'nucleotide cyclic motifs' RNA model and two computer algorithms, which are well known in the field: MC-Fold and MC-Sym [9]. It allows the accurate prediction of 3D RNA structures up to ~150 nucleotides long just from knowing only the RNA sequence, as does iFoldRNA. However, besides predicting the 3D RNA folding with near atomic resolution accuracy, the newest tool, iFoldRNA, also allows the detailed analysis of RNA-folding kinetics and thermodynamics.

RNA-folding parameters provided by iFoldRNA include specific heat, contact maps, calculated trajectories, gyration radii and root mean square deviations (RMSDs) from native state and fraction of native-like contacts. Each parameter can be determined at different temperatures. All these advantages of iFoldRNA are due to the fact that this new method truly mimics the natural RNA folding, starting from totally unfolded, linear-chain RNA conformations.

To understand how iFoldRNA works, imagine a flexible chain of hard balls, each representing a nucleobase or sugar, or phosphate residue of the corresponding nucleotide of known RNA sequence. The balls are allowed randomly to bump each other in the space of a specially designed force field with square well potentials. Then, RNA folding can be viewed as a set of successive collisions of the chain-linked hard balls that are progressively driven by a force field to adopt an arrangement with a lowest total energy or the least RMSD. It is thought that the real RNA molecule finds the most energetically favorable conformation namely this way.

The new methodology has been successfully validated on more than a dozen structurally diverse RNA molecules [7]. I believe, therefore, that iFoldRNA will serve as a useful resource for several molecular biotechnology and molecular biology related applications, including the area of RNA-based drug design. Importantly, this RNA-folding server is freely available on the web for not-for-profit users at http://iFoldRNA.dokhlab.org.

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