Advanced Simulations of RNA-based Biological Nanostructures

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***Abstract*—We present a methodology and the results of numerical simulations of complex biological polymeric molecular nanostructures, whose major components consist of ribonucleic acids (RNAs). The case where such nanostructures are considered in fluids, e.g. physiological solutions, is also reported. The developed methodology is based on molecular dynamics and our efficient coarse graining algorithms applied to such structures. We discuss such important characteristics as the radius of gyration, root mean square deviation, and radial distribution function in the application to RNA nanotubes, consisting of a number nanorings, studied in the previous works. Among other things, we provide insight into typical distributions of various ions around the RNA nanotubes as a function of time within a distance of a few angstroms from their surface.**

Keywords–Coarse-Graining Algorithms; Ribonucleic Acid Nanostructures; Molecular Dynamics; Scaffolding; Medical Biology; High Performance Computing.

I. INTRODUCTION

Modelling complex systems such as biological polymers is necessarily closely connected with advanced high performance computing. The task is becoming even more challenging when biological polymeric nanostructures are considered. Such structures have a range of current and potential therapeutic and other biomedical applications [1]. By now we know that the stability of the ribonucleic acid (RNA) assemblies is higher than that of the DNA self assembled nanoparticles in fluidic solutions [2], [3], and that different shape RNA molecules are available to form RNA building blocks and their complexes with other biomolecules [4], [5], [6]. Here our main focus is on such RNA nanostructures constructed with six helical building blocks of either one or two types (RNAI/RNAII). They consist of a number of nanorings linked together via base pairing hydrogen bonds, forming RNA nanotubes which may operate in the applications mentioned above in fluidic physiological solutions.

II. COMPUTATIONAL MODELS, METHODOLOGY, AND MAIN RESULTS

Given the computational complexity of the problem at hand and its multiscale character, it is necessary to develop efficient coarse-graining procedures for molecular dynamics simulations of these structures [7]. To do that, we use the Boltzmann inversion method. The force matching is based on the objective function of the parameter α:

$$Z(\alpha) = Z_F(\alpha) + Z_c(\alpha), \quad (1)$$

$$Z_F(\alpha) = \left(3\sum_{k=1}^{M} N_k\right)^{-1} \sum_{k=1}^{M}\sum_{i=1}^{N_k} |F_{ki}(\alpha) - F_{ki}^0|^2, \quad (2)$$

$$Z_C(\alpha) = \sum_{r=1}^{N_C} W_r |A_r(\alpha) - A_r^0|^2. \quad (3)$$

The parameters α defined in the above equations (1) -(3) are calculated by matching the forces obtained by using the first-principles calculations of the several configurations of the molecular system and the classical potentials. Notations in (1) - (3) are as follows: the integer M in Z_F (the force objective function) is the number of configurations, N_k is the number of atoms in the k-th configuration and $F_{ki}(\alpha)$ is the force on the ith atom in the kth configuration which is obtained from the parametrization of α, and the F_{ki}^0 is the corresponding reference force obtained from the first principles calculations. In the constraint objective function Z_C the quantities $A_r(\alpha)$ are also physical parameters obtained from parametrization, A_r^0 are experimental values or the values calculated from the first principles methods and W_r is the weight factor. The force objective function defined in equation (1) is minimized for given α to calculate the classical force parameters by using the force and physical quantities obtained from *ab initio* calculations.

The entire system is integrated in time where the potential uses the CHARMM force field. The compatibility of this force field for this type of biological system was tested earlier [8], [9], demonstrating that the results are close to experiments.

We have performed all-atom molecular dynamics simulations of RNA nanotubes by using the CHARMM27 force field implemented in the NAMD package as it was done for the nanoring [10], [11]. The modeling of the nanotube, visualization and the analysis of the simulation outputs have been performed using the software visual molecular dynamics (VMD).

The RNA-nanotube was solvated in a water box where the distance from the surface of the nanocluster to the wall is slightly larger than the cut off radius used in the molecular dynamics simulation. In order to make the system neutral we have added ions, depending on the size of the nanotube (e.g., for a 4-ring nanotube we had 1254 ions). The resulting system has been first simulated at constant temperature and pressure using the NAMD software package. The temperature in the system has been controlled by using Langevin's method with

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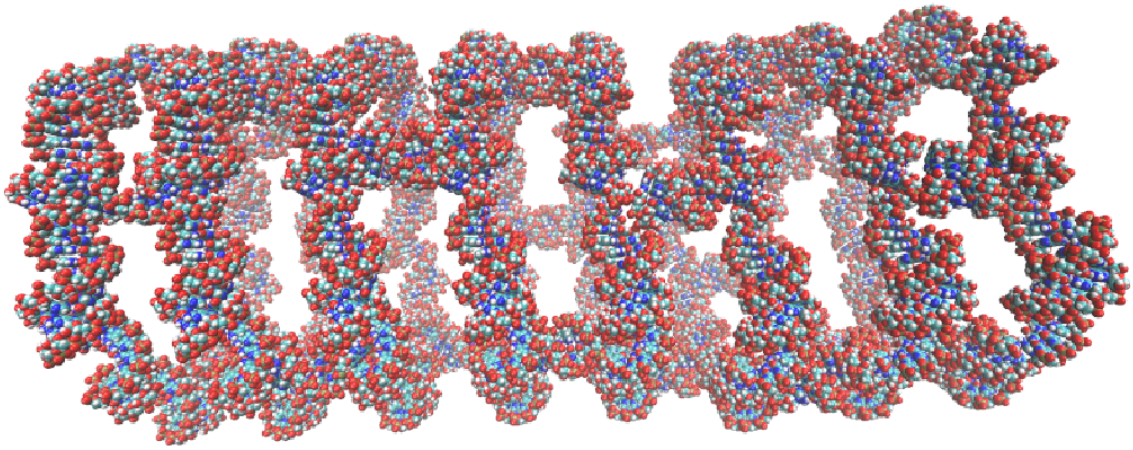

Figure 1. Three-dimensional structure on 8-ring nanotube modeled by using VMD

damping η = 5 ps^{-1}. For adding chemical bonds between the segments in the nanoclusters we have used the topotools available in the VMD. A typical RNA nanotube is shown in the figure above, where 8 nanorings were used (we modeled currently up to 20). The tails used to connect the RNA nanorings are the double strand RNAs with the length of 22 nucleotides. The chemical bonds between the ring and the links are mediated through the phosphorous of the phosphate group in the ring and the oxygen in the sugar ring of the corresponding link or vice versa. Using NAMD, we optimized the chemical bonds added between different segments of the RNA nanoclusters. We analyzed the obtained results for the variation of the energy and temperature as a function of simulation time, as well as the number of ions around the RNA nanotube within the distance of 5 $\AA$ at different temperatures, the number of bonds per basepairs, the radius of gyration and the root mean square deviation (RMSD) at two temperatures, 310K and 510K. The results corresponding to variations of the parameters are similar to the results obtained for the other nanoclusters described in our earlier studies [10], [11]. The radial distribution functions have been calculated for our RNA nanotubes for phosphorous-phosphorous, phosphorous-water, phosphorous-sodium and phosphorous-chlorine. For example, from the P-P RDF analysis, we have concluded that there are three well-pronounced peaks around the same positions at it was observed for other nanoclusters studied in our earlier paper [11]. These peaks actually show the first, second and third nearest neighbours of the phosphorous atom respectively. Similar analyses were carried out for other RDFs (e.g., P-OH2, etc). The results for larger RNA nanotubes have shown that the nature of solvation and the ionic distribution during the molecular dynamics simulation is similar to those found in the case of the smaller nanotubes (e.g., we studied earlier 3- and 4- ring nanotubes). Finally, it is worthwhile mentioning that the phenomenon of self stabilization, first reported in [10], has also been observed in this case.

III. Conclusion

Complex RNA-based biological nanostructures have been analyzed with molecular dynamics simulations based on the developed coarse-graining procedures. Main characteristics, such as the root mean square deviation, radius of gyration, number of hydrogen bonds per basepair, ion accumulation around the tube, and the radial distribution functions, have been calculated. The results may be useful for the development of new drug delivery procedures, scaffolding, and other biomedical applications.

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