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Badu, S., Melnik, R., and Prabhakar, S.

Proceedings of the 4th International Conference on Computational and Mathematical Biomedical Engineering CMBE2015, France, 29 June - 1 July , 2015, Eds. P. Nithiarasu et al, ISBN: 978-0-9562914-3-1, pp. 630–633, 2015.

CMBE15

4th International Conference on Computational & Mathematical Biomedical Engineering

29th June - 1st July 2015
École Normale Supérieure de Cachan
Cachan (Paris) France

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Published by CMBE
Zeta Computational Resources Ltd.
Charter Court, Phoenix Way
Enterprise Park, SA7 9FS
Swansea, United-Kingdom

First Edition, 2015
Printed in the United Kingdom for CMBE

ISBN: 978-0-9562914-3-1
ISSN: 2227-3085 (print)
ISSN: 2227-9385 (electronic)

4th International Conference on Computational and Mathematical Biomedical Engineering - CMBE2015
29 June-1 July 2015, France
P. Nithiarasu and E. Budyn (Eds.)

MULTISCALE MODELING OF RNA NANOTUBE PROPERTIES

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SUMMARY

We analyze biological nanostructures with essential coupling components in the form of nanorings. Such nanostructures are important in a wide range of current and potential bio-nanotechnological and medical applications. Our main attention is devoted to a class of RNA-based nanostructures, in particular RNA nanotubes which consist of a series of around 20 nm in diameter nanorings. Multiscale properties of these RNA nanostructures are studied with the molecular dynamics (MD) method using CHARM force field implemented in the NAMD package. Structural and thermal behaviours of these important objects are discussed in the context of physiological solutions typical for their practical applications.

Key words: *Multiscale biological systems, RNA nanotubes, Molecular Dynamics Simulation*

1 INTRODUCTION

Among many complex biological macromolecular systems, RNA-based molecular systems stand out due to their flexibility and other unique properties. RNA bio-nanotechnological and medical applications are among most important applications of such systems [1, 2].

The key to such applications lies with our ability to built self assembling RNA building blocks. Our study here focuses on RNA nanoclusters which have been created by using the RNAI/II building blocks [3, 4]. More specifically, firstly the six helical segments have been constructed from RNAI and RNAII building blocks to model a typical RNA nanoring. Then, the nanorings have been connected via the links built from the RNA strands (usually of 22 nucleotides). Finally, we embed the resulting RNA nanotubes into physiological solutions to better reflect the situation in applications [5]. The interest to studies of such RNA nanostructures has been growing dramatically over the recent years [6, 7]. However, studies of such structure properties and the development of efficient numerical procedures are at the beginning of their advancement.

2 MATHEMATICAL MODEL AND COMPUTATIONAL METHODOLOGY

The CHARM force field that we use in molecular dynamics simulations is expressed as follows:

$$V_{total} = \sum_{bond} K_b(r-r_0)^2 + \sum_{angle} K_\theta(\theta-\theta_0)^2 + \sum_{dihedral} K_\phi(1+cos(n\phi-\gamma)) + \sum_{Hbond}(\frac{C_{ij}}{r_{ij}^{12}} - \frac{D_{ij}}{r_{ij}^{10}}) + \sum_{Vanderwaals}(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{10}}) + \sum \frac{q_i q_j}{\varepsilon r_{ij}}, \quad (1)$$

where the first term corresponds to bonds, second corresponding to angle parameters, the third term corresponds to the potential energy and interactions raised from the dihedral angles in the molecular system, the fourth term defines the interaction coming from the hydrogen bonds which includes the base pairing as well as the hydrogen bonding between the RNA and the water molecules. Finally, the last term in the potential expression represents the long distance interactions known as the van der Waals' interactions. The other notations in the Equation 1 have the following meanings:
K_b is the intra chain force constant corresponding to bonds,

r_0 is the inter atomic bond distance at equilibrium,
K_θ is the intra chain force constant corresponding to angles,
θ_0 is the bond angle at equilibrium,
K_ϕ is the intra chain force constant corresponding to dihedral angles,
C_{ij} and D_{ij} are two empirical constants for hydrogen bonding,
A_{ij} and B_{ij} are two coefficients corresponding to the repulsive and the attractive interactions between i-th and j-th atom that are determined experimentally,
q_i and q_j are the charges of the i-th and j-th atoms,
ε is the electrostatic permeability, and
r_{ij} is the distance between the i-th and j-th atoms.
From the expression (1) for the total potential energy of the biological system at hand, it is clear that the energy is a function of the positions of particles. The next step is standard, that is if the position of the particle at a time t is known, its value after the time step δt i.e $t+\delta t$ can be calculated by using the Taylor series expansion as follows:

$$x(t) = x_0 + v_0 t + a_0 \frac{t^2}{2} + ..., \tag{2}$$

where the x_0, v_0 and a_0 are the initial positions, velocities and acceleration of the atom at the initial time t_0, and

$$x(t+\delta t) = x(t) + v(t)\delta t + \frac{F(t)}{m}\frac{\delta t^2}{2} + ... \tag{3}$$

The velocity of an atom at times t and $t+\delta t$ can also be calculated using the acceleration of the atom, similar to the way how the position is calculated from the velocity based on Equations 2 and 3. From the potential energy of the system the acceleration of the k-th particle can also be calculated from the Newton's equation of motion as

$$a_k(t) = -\frac{1}{m_k}\frac{dV_{total}}{dr_k(t)}, \tag{4}$$

where m_k is mass of kth atom. Alternatively, the force of an atom during MD simulations can be expressed as

$$F_k(t) = m_k \frac{d^2 r_k(t)}{dt^2} = \frac{dV}{dr}, \tag{5}$$

where the $r_k(t)$ is characterised by the coordinates $(x_k(t), y_k(t), z_k(t))$ in three dimensions. For the pair potential the force can be calculated as:

$$F_k = -\sum_{j\neq k}\frac{\delta V(r_{kj})}{\delta x_k} = \sum_{j\neq k}(-\frac{\delta V}{\delta r}\mid_{r=r_{kj}})\hat{x_{kj}} = \sum_{j\neq k}(-\frac{1}{r}\frac{\delta V}{\delta r}\mid_{r=r_{kj}})x_{kj} \tag{6}$$

with the unit vector

$$\hat{x_{kj}} = \frac{x_{kj}}{r_{kj}} \quad \text{and} \quad x_{kj} = x_k - x_j. \tag{7}$$

The force F_k in the above equation is the net force on the k-th particle. Force on the k-th particle due to j-th particle is given by

$$F_{kj} = (-\frac{1}{r}\frac{\delta V}{\delta r}\mid_{r=r_{kj}})x_{kj}. \tag{8}$$

We note that several studies on the development of coarse graining (CG) methodologies that may be useful in the current context have been recently presented [8, 9] . Here, for the coarse-graining modeling we use the Boltzmann Inversion Method (BIM) in a way similar we initiated in our earlier work [10].

The BIM has been used to fit the CG parameters for the RNA nanotubes. This method was originally developed for simple liquid systems, but it was shown that it can be efficiently applied to organic polymers and biological systems such as RNA nanostructures. In this technique the coarse graining potential is calculated from the pairwise potential:

$$U_{CG}(R) = \sum_{i<j} u_{CG}(R_{ij}), \tag{9}$$

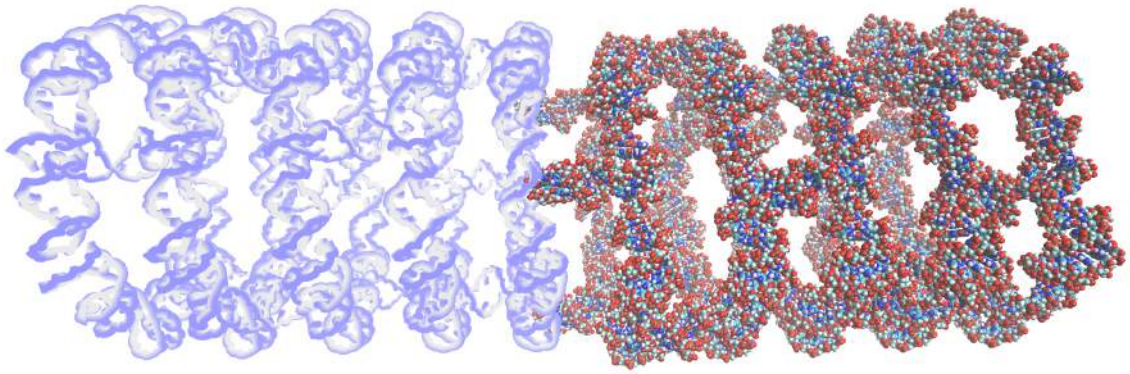

Figure 1: RNA nanotube modeled from 10 nanorings

where U_{CG} is the effective energy function and $u_{CG}(R_{ij})$ pair wise potential between two atoms. This idea is based on the famous Henderson uniqueness theorem which states that for a given pair of radial distribution function there exists a pairwise potential. The Boltzmann inversion method to calculate the coarse graining potential in the context of our biological structures has been implemented with the following algorithm [3]:

- Carry out all atom MD simulation;
- Convert all atom simulation trajectory into the corresponding coarse-graining model and then calculate the radial distribution function for this CG pseudoatom;
- Using these pseudoatomic radial distribution functions, calculate pairwise potential for each pair of the CG pseudoatoms by the following formalism:

$$u_{CG}(R) = -k_B T \ln g_A(R), \tag{10}$$

  where $g(R)$ is the radial distribution function, k_B is the Bolzman coefficient, and T is the temperature;
- Then, carry out the NVT MD simulation for the resulting CG system by using the computed pairwise potentials, and measure the radial distribution function for the pseudoatoms in CG ensemble;
- Now, update the potential using the relation:

$$u_{CG}(R) = u_{CG}(R) - k_B T ln(g_R/g_{CG}) \tag{11}$$

- Repeat the CG simulation according to the above step with the NVT MD simulation until the value of u_{CG} converges.

3 RESULTS AND CONCLUDING REMARKS

The molecular dynamics simulations of a class of the RNA nanotubes have been performed in the simulation box for the time period 1ns at a constant temperature 310K. The energy and temperatures have been saved at every 1ps. Among other investigations, variations of energy and the temperature during molecular dynamics simulations of the RNA nanotube with 10 RNA nanorings in the magnesium chloride solution have been studied in details. The significant change in the energy has been observed in the minimization region of the molecular dynamics simulation. The latter part of the simulation is known as the production region around which the calculation of the properties of the RNA nanocluster in the MgCl2 (as well as NaCl solutions) is done.

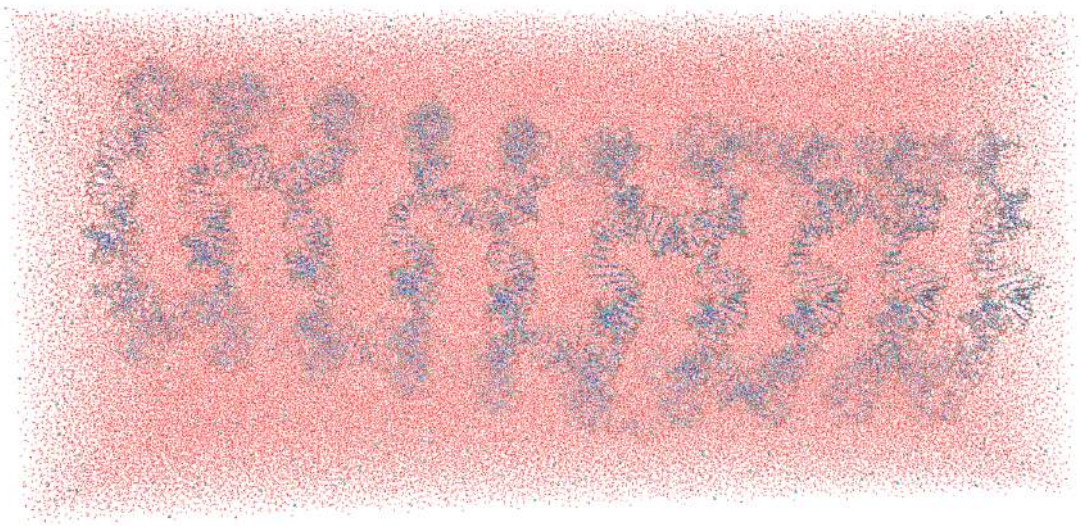

Figure 2: 10 ring RNA nanotube in physiological solution

By using the developed molecular dynamics multiscale strategy we have been able to model a large class of the RNA nanotubes described here. As an example, the optimized geometry of the 10 ring RNA nanotube and the tube in the physiological solution are shown in Figures 1 and 2, respectively.

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