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COUPLED NANOSTRUCTURES OF RIBONUCLEIC ACIDS: DEVELOPING DISCRETE-CONTINUUM MODELS FOR LARGE TIME-SCALE SIMULATIONS

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Abstract. Continuing progress in the development of theoretical and computational techniques in the field of biomolecular systems involving Ribonucleic acids (RNA) has a very important impact in biomedicine and human health. Many essential biological phenomena in these systems are on the time scale longer then the time it is possible to simulate computationally using existing atomistic models. In this article we describe the development of a continuum model based on atomistic scale parameters. We also present initial results on the mechanical, as well as thermal properties of the RNA nanoclusters obtained by using the finite element methodology. Specifically, using the elastic constants available for the nucleic acid, we report the distributions of the displacement fields due to stress and thermal effects along typical RNA nanotubes that are important for biomedical applications.

1 Introduction

Since the ribonucleic acid (RNA) structures are flexible in nature, it is very easy to create RNA nanoclusters of different sizes and shapes via their self assembly. The motivation for self assembling these RNA nanoclusters is their potential application in the field of human health, biomedicine and bioengineering [1, 2, 3]. For these self assembled RNA nanoclusters it is very important to study their properties in different environments such as physiological solutions [4]. Studies of structural properties of RNA nanoclusters have been performed using molecular dynamics and coarse graining modeling techniques [5, 6, 7]. The building blocks used to model the RNA nanoclusters are the RNA strands such as RNAi/RNAii which are taken from the protein data bank [8]. Up to date the mechanical properties of these ribonucleic acid nanoclusters has not been studied in details.

Thermal stability of these nanoclusters is another issue of great importance. It is shown that the thermal stability of the proteins is increasing in presence of the sugar and polyols in aqueous solution [9]. The importance of such studies also follows from the fact that there can be a change in the molecular structure of the cell, cell membrane and the cell nucleus due to thermal effects. Based on the previous studies, in this paper we develop a discrete-to-continuum model for the analysis of mechanical and thermal properties of RNA nanoclusters. Studies on the mechanical properties have also been reported for soft materials such as collagen fabril protein and polymers [10, 11, 12, 13]. For carbon nanotubes (CNT), that have similar physical structures as RNA nanotubes, the atomistic to continuum modeling has been performed using the finite element method [14, 15] to calculate their elastic properties under stress.

The continuum and particle models of deoxy-ribonucleic acid (DNA) systems have been studied by using discrete base-pair results and approximating the properties for a continuum rod type model to analyze the mechanical properties [16]. The continuum model can also be used to study the protein-protein interaction and protein-nucleic acid interactions to understand the relative stability of A and B forms of deoxy-ribonucleic acids (DNA) [17, 18].

In what follows, we describe the development of a model to study the elastic properties of typical RNA nanoclusters and the effect of thermal change on them.

2 Theoretical Details

We consider the RNA nanotube as a cylindrical shell. This analogy is similar to the continuum approximations used for carbon nanotubes. Therefore, the application of the atomistic parameters of these systems in the development of continuum models can be done in a way similar to the CNT [14, 15]

At the molecular level of consideration, the energy of the entire system is due to the inter-atomic interaction of the atoms where the molecules perform a simple harmonic motion. Under this assumption the energy contribution from bond stretching, bond bending and dihedral angle torsion can be related to the energies of their equivalent continuum elements. From comparison we can relate the atomic parameters to the elastic parameters of the continuum model as follows,

$$V_r = \frac{1}{2}k_r(r - r_0)^2, \tag{1}$$

$$V_\theta = \frac{1}{2}k_\theta(\theta - \theta_0)^2, \tag{2}$$

and

$$V_\phi = \frac{1}{2}k_\phi(\phi - \phi_0)^2, \tag{3}$$

where k_r, k_θ and k_ϕ are the bond stretching, bond bending and the dihedral angle torsional force constant for the molecular system taken into consideration. In equations (1)-(3) r_0,

θ_0 and ϕ_0 are the distance, angle, and dihedral angle at equilibrium. In the continuum model, let us take a small element of the RNA nanotube of length L and diameter d. Suppose that ΔL, $\Delta\theta$, and $\Delta\phi$ are the stretch, bending and the torsional displacement in the cylindrical element of the tube. Now the corresponding types of energies in the continuum model for this cylindrical shell can be expressed based on the following arguments. Firstly, the energy due to the lateral stretching ΔL of the element of length L , with Young's modulus Y and cross-sectional area A, is given by

$$U_A = \frac{1}{2}\frac{YA}{L}(\Delta L)^2. \tag{4}$$

Next, to account for bending phenomena with moment of inertia I and with bending angle α, the expression for the elastic energy is given by

$$U_M = \frac{1}{2}\frac{YI}{L}(2\alpha)^2. \tag{5}$$

Finally, the energy corresponding to the rotational motion of the cylindrical element can be expressed as

$$U_T = \frac{1}{2}\frac{GJ}{L}(\Delta\beta)^2, \tag{6}$$

where $\Delta\beta$ is the twisting angle due to the elastic torsion, of the RNA nanotube, J is the angular momentum, and G is the shear modulus.

The above values for the energy terms, V_r, V_θ and V_ϕ are the bond stretching energy, bond bending energy and the torsional energies corresponding to the atomistic interactions coming from the harmonic motion of the atoms. These quantities are similar to the energy terms U_A, U_M and U_T derived for a finite element representation of the RNA nanotube under the continuum approximation. From comparison of the corresponding energies at these two kind of formulations we find that

$$\frac{YA}{L} = k_r, \qquad \frac{YI}{L} = k_\theta, \qquad \frac{GJ}{L} = k_\phi. \tag{7}$$

Using relations (7), the parameters of the atomistic scale can be used to determine the parameters to be built in into the continuum model. It is possible to calculate the quantities k_r, k_θ, and k_ϕ using the atomistic molecular dynamics simulation technique.

For most of the materials of interest, there is a linear relationship between the strain and stress. The components of the stress tensor in terms of the elastic coefficients and the stress tensor for the linear and isotropic continuum systems can be expressed as [19]

$$\begin{bmatrix}\sigma_{11}\\ \sigma_{22}\\ \sigma_{33}\\ \sigma_{23}\\ \sigma_{13}\\ \sigma_{12}\end{bmatrix} = \frac{Y}{(1+\nu)(1-2\nu)}\begin{bmatrix}1-\nu & \nu & \nu & 0 & 0 & 0\\ \nu & 1-\nu & \nu & 0 & 0 & 0\\ \nu & \nu & 1-\nu & 0 & 0 & 0\\ 0 & 0 & 0 & \frac{1-2\nu}{2} & 0 & 0\\ 0 & 0 & 0 & 0 & \frac{1-2\nu}{2} & 0\\ 0 & 0 & 0 & 0 & 0 & \frac{1-2\nu}{2}\end{bmatrix}\begin{bmatrix}\epsilon_{11}\\ \epsilon_{22}\\ \epsilon_{33}\\ 2\epsilon_{23}\\ 2\epsilon_{13}\\ 2\epsilon_{12}\end{bmatrix} + \frac{Y\alpha\Delta T}{(1-2\nu)}\begin{bmatrix}1\\ 1\\ 1\\ 0\\ 0\\ 0\end{bmatrix} \tag{8}$$

which in tensor form can be written as follows

$$\sigma_{ij} = \frac{Y}{(1+\nu)}\left(\epsilon_{ij} + \frac{\nu}{(1-2\nu)}\epsilon_{kk}\delta_{ij}\right) - \frac{Y\alpha\Delta T}{(1-2\nu)}\delta_{ij} \qquad i,j,k = 1,2,3, \tag{9}$$

where Y is Young's modulus, α is the coefficient of thermal expansion, ΔT is the increase in temperature of the system, and ν is the Poisson ratio, given by the relations

$$\nu = \frac{3K - 2\mu}{(3K + \mu)}. \tag{10}$$

The rate-dependent phenomena can be described for the biosystems such as RNA nanoclusters by introducing viscoelasticity terms. In the constitutive relation described above we can introduce the extra term of the stress that is proportional to the rate of change of the strain as

$$\sigma_{ij}^{v} = \eta\frac{\partial\epsilon_{ij}}{\partial t}, \tag{11}$$

where η is the coefficient of viscosity Therefore the general elastic constitutive equation including rate-dependent term can be expressed as,

$$\sigma_{ij} = \frac{Y}{(1+\nu)}\left(\epsilon_{ij} + \frac{\nu}{(1-2\nu)}\epsilon_{kk}\delta_{ij}\right) - \frac{Y\alpha\Delta T}{(1-2\nu)}\delta_{ij} + \eta\frac{\partial\epsilon_{ij}}{\partial t} \qquad i,j,k = 1,2,3. \tag{12}$$

In (12) the quantities K and μ are the bulk modulus and the shear modulus respectively. Under the underlined assumptions, for the systems like our RNA nanotube the steady state elastic equations can be expressed as

$$\sigma_{ij,j} = 0 \qquad i,j = 1,2,3. \tag{13}$$

with the Cauchy relationship connecting the displacement and strain:

$$u_{ik} = \frac{1}{2}\left(\frac{\partial u_i}{\partial x_k} + \frac{\partial u_k}{\partial x_i}\right) \qquad i,k = 1,2,3. \tag{14}$$

The strain-stress relationships are fully determined once the elastic parameters such as Poisson's ratio and the elastic moduli of the system are available. In our case we use the elastic moduli calculated from the atomistic modeling and the experimental techniques available in literature.

While in the general case (13) is augmented to account for time-dependency, in the current study we calculate the steady-state elastic properties and the thermal effect on them. In order to study the mechanical properties of the RNA nanoclusters in the presence of thermal effect, we have used the finite element method implemented via COMSOL multiphysics. The general partial differential equation representation has been used. We have used the Dirichlet boundary condition at one end of the tube and the Neumann boundary condition at the other end, i.e at z=40nm we set $n \cdot \sigma = 0$.

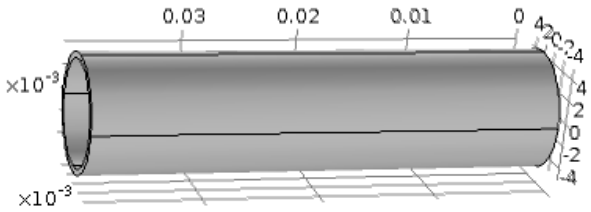


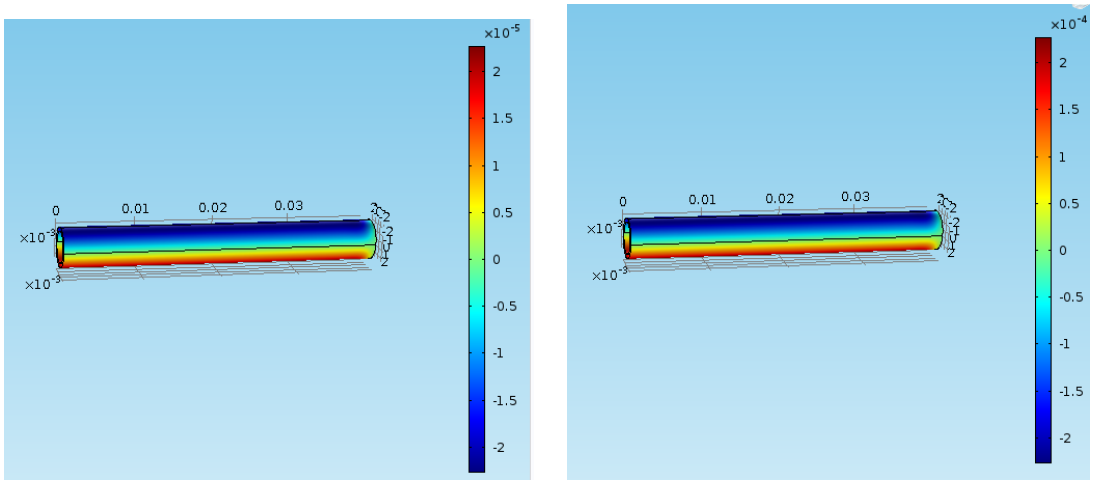
Figure 1: Approximated continuum geometry of the RNA nanotube as a hollow cylinder generated by using COMSOL

3 Results and Discussion

In our current study under the above assumptions, we study the RNA nanotube as a continuous system with the length and the radius equivalent to the size of the RNA nanocluster modeled using the atomistic molecular dynamics simulation. The continuum model of the RNA nanotube of the size 40nm with the 10 rings is presented in Figure 1. Here for calculations of the elastic properties of RNA nanotube, we use the finite element method. For these calculations we use the constitutive relations between strain and stress accounting for the thermal effect in the system. Poisson's ratio and Young's modulus for the nucleic acid system were 0.42 and 300 MPA i.e $3 * 10^8$ PA respectively. They were taken from the literature and obtained by using experimental and atomistic calculations [20]. The results for the displacement field at different positions for the entire volume of the RNA nanotube of size equivalent to 10 rings, i.e 40 nm in length, obtained by using the finite element method at 10 degree and 100 degree K are presented in Figure 2. Corresponding displacements of the points along a line in the direction of the axis of the 10 ring RNA nanotube at these two temperatures are presented in Figure 3. Since the values for the thermal expansion coefficient are not yet available for the bionanosystems like RNA nanoclusters, we have used the average value of the coefficient calculated for the protein system using the molecular dynamics simulation for a wide range of its densities [21]. From our results for the displacement along the RNA nanotube, it is clear that the displacement is increasing as the temperature is increased. During calculation of the displacement field, due to stress and thermal effects in the RNA nanotube, we have fixed one end by Dirichlet boundary condition and on the other end a force via Neumann's boundary condition has been applied. From the obtained results it is clear that there is an increase in the displacement as the temperature is increases.

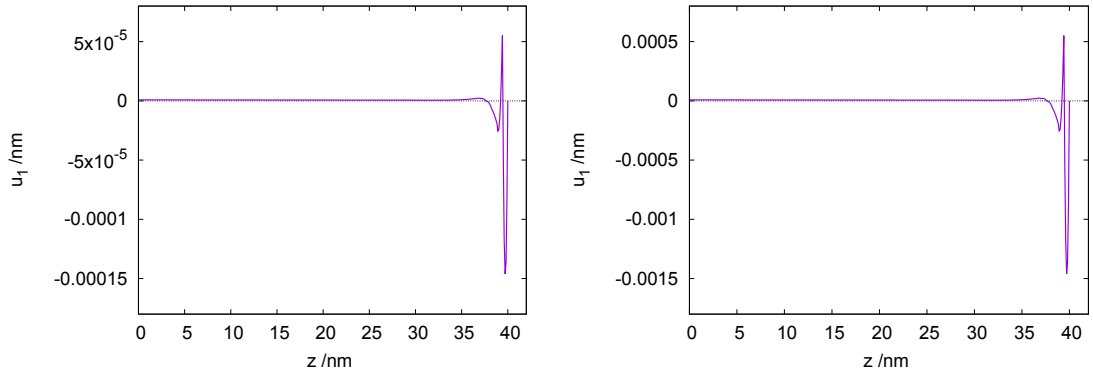
4 Conclusions and Outlook

We have studied the elastic properties and the effect of thermal changes on them in earlier developed RNA nanotubes by using the finite element method. We have also studied the effect of stress as a function of the temperature change along the entire volume of the RNA nanotube. For calculating these properties of RNA nanoclusters we have used



(a) (b)

Figure 2: Distribution of the displacement at different points along 10 ring RNA nanotube at (a) 10 K and (b) 100K using finite element method.



(a) (b)

Figure 3: Displacement along the line in the direction of the axis of the 10 ring RNA nanotube at (a) 10 K and (b) 100K using finite element method.

a cylindrical shell representation of the size equivalent to the size of the RNA nanocluster. The elastic and thermal coefficients have been taken from the literature and calculated for the nucleic acid molecules and the protein systems. The experimental results of such physical quantities are not yet available and we expect that our computational studies will motivate experimentalists to shed new light on underlying problems for RNA nanoclusters.

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