RESEARCH ARTICLE

Atomistic to continuum model for studying mechanical properties of RNA nanotubes

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ABSTRACT
With rapid advancements in the emerging field of RNA nanotechnology, its current and potential applications, new important problems arise in our quest to better understand properties of RNA nanocomplexes. In this paper, our focus is on the modeling of RNA nanotubes which are important for many biological processes. These RNA complexes are also important for human beings, with their theurapeutical and biomedical applications discussed vigorously in the literature over the recent years. Here, we develop a continuum model of RNA nanotubes, originally obtained from self assembly of RNA building blocks in the molecular dynamics simulation. Based on the finite element method, we calculate the elastic properties of these nanostructures and provide a relationship between stress and strain induced in the RNA nanotube. We also analyze the variations in the displacement vector along the assembly axis for RNA nanotubes of different sizes. In particular, we show that oscillations in the amplitudes of strains and displacements significantly differ for such RNA nanotubes. These findings are discussed in the context of atomistic simulations and experimental results in this field.

KEYWORDS
RNA; Nanotubes; Mechanical Properties of RNA; Biomechanics; Computational modeling; Finite element analysis

1. Introduction

Ribonucleic acid (RNA) nanotechnology is based on nanometer-scale RNA architectures consisting of RNA nanoclusters or nanocomplexes (Jasinski et al. 2017; Grabow and Jaeger 2014). This emerging field has attracted immense interest in life sciences and engineering. It should not come as a surprise. Indeed, RNA molecules provide a key to cell regulation and RNA nanoparticles/nanoclusters can be used for gene expression regulation (Jedrzejczyk and Chworos 2019). The RNA-based technology, known as the RNA silencing, can protect the eukaryotic cells against viruses and transposons (e.g., (Yang et al. 2007) and references therein). RNA has both catalytic and genetic functions. It is a stable biopolymer with extraordinary potential as a building block in

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materials and life sciences. This includes also a series of novel ideas such as its usage for resistive biomolecular memory and tissue engineering, as well as its conjugation to graphene and other nanomaterials with biosensing and many other applications (Jasinski et al. 2017; Li et al. 2015). RNA molecules play a fundamental role in many biological processes, including regulation of gene expression (Ponce-Salvatierra et al. 2019). Nowadays, it is possible to use RNA nanoclusters to modulate immune behaviour (Chandler and Afonin 2019) and to tune the immunogenetic properties of synthetic RNA constructs for in vivo applications (Jasinski et al. 2017). The increasingly high interest to RNA-based technologies has been further amplified by several recent developments: (a) the discovery of hierarchical nanomaterials and nanostructures via biomolecular self-assembly and bio-inspiration and their new applications, not only in biomedicine, but also in energy and environmental applications (Gong et al. 2019), as well as (b) rapid advances in synthetic biology and nanobiotechnology with their constructions of various synthetic RNA nanoparticles and nanocomplexes with different functionalities and application areas (Ishikawa et al. 2013; Jedrzejczyk et al. 2017). RNA nanoclusters have tremendous potential for applications in nanobiomedicine, treatment of cancer cells and of other diseases due to their biological compatibility to the human beings (Jasinski et al. 2017; Shu et al. 2014). Indeed, since protein-free RNA molecules induce a minimal immune response, RNA nanoparticles and nanoclusters can be potentially used in long-term treatments of chronic diseases such as hepatitis B or AIDS (Yingling and Shapiro 2007).

The DNA nanoclusters have also potential interest for nanobiomedicine and other biological applications, but the main advantage of using RNA over DNA nanoclusters is that they possess the free energy smaller than corresponding DNA structures. Hence, the smaller free energy of RNA provides engineers more flexibility to make efficient devices out of RNA nanoclusters (Guo 2010; Sugimoto et al. 1995; Guo 2005; Osada et al. 2014; Simpson et al. 2000). To construct any kind of nanostructures of biomolecules, a detailed understanding of building blocks of self assembly of such molecules at the nanoscale is important. For example, the RNA has been used to build the higher order of self assembly devices in vitro and in vivo by assembling the multidimensional RNA structures (Cayrol et al. 2009; Delebecque et al. 2011). Hence, the modeling of the RNA nanotubes by self assembling their building blocks and calculating their physical properties show potential interest for researchers around the globe (Badu et al. 2014; Paliy et al. 2009; Yingling and Shapiro 2007). In order to construct the RNA nanotube, by using molecular dynamics simulations, one can first self assemble the RNA building blocks to make the rings and then connect these rings in series to build a RNA nanotube (Lee and Crothers 1998; Badu et al. 2014; Paliy et al. 2009; Tomizawa 1984, 1986).

The characterization of mechanical behavior of nanomaterials utilizing experimental techniques is in general quite challenging and very costly, partly due to associated limitations and complexities in handling the physical and mechanical aspects of such nanoscale dimensions (Cheng et al. 2009a). Thus, computational tools provide a more efficient and flexible alternative to such intricate experiments and have become a powerful means for studying the properties of nanomaterials. To date, different computational techniques have been used to study the mechanical performance of nanomaterials utilizing atomistic and continuum mechanics approaches. Atomistic molecular dynamics models have become quite popular but still are limited to a relatively small-scale model, while continuum models are certainly simplified as they largely neglect the atomistic representation and appropriate constitutive relations that govern material behavior at the nanoscale

(Wernik and Meguid 2010). Therefore, effective multiscale modeling has become quite popular in bridging the two scales and several such techniques have been presented in the past decade (Li and Urata 2016). The atomistic-based continuum multiscale modeling is one such novel technique that has become quite popular for predicting the elastic properties of carbon nanotubes (Rafiee and Moghadam 2014), which have similar physical structures as of RNA nanotubes. In the earlier studies, using atomistic and continuum modeling techniques, the mechanical properties of the collagen fibril proteins have also been studied (Buehler 2008; Depalle et al. 2015). Further, the continuum particle-based models for DNA systems utilizing a continuum rod-like model approximated by discrete base-pairs is well known in the literature for studying their mechanical properties (Manning et al. 1996). More recently, the principal structural features of the DNA double-helix along with their effects on its mechanical properties have been investigated utilizing the helical continuum model in Kim and Kim (2016). The continuum model approximation has also been previously applied for studying protein-protein interactions, protein-nucleic acid interactions and for quantifying the stability of A and B forms of DNA (Srinivasan et al. 1998; Carrillo et al. 2013; Picinbono et al. 2001; Sokkar et al. 2015). Also, an extensive study has been performed on the development of the atomistic to continuum model to calculate the mechanical properties of the microtubules found in the blood vessels (Sept and MacKintosh 2010) which can also be potentially used to study the mechanical properties of the systems at the macroscopic level. An atomistic-continuum model of microtubules was proposed in Xiang and Liew (2011), where the microtubule was modeled as a singular cylindrical nanostructure for predicting the elastic modulus and studying its global buckling under axial compression. The aforementioned works provide the initial foundation and motivation for our development of the atomistic to continuum model of RNA nanotubes with the aim of studying their mechanical properties, the task that has not been undertaken before. Thus, in this paper, we focus our study on the development of a continuum model of RNA nanotubes, accounting for necessary atomistic information. By using the finite element method, we investigate the mechanical properties, e.g. stress and strain, of RNA nanotubes. We approach the modeling strategy of RNA nanotubes based on the ideas similar to the modeling of carbon nanotubes and several other nanorods (Cheng et al. 2009b; Tserpes and Papanikos 2005; Odijk 1986; Kohji et al. 1978; Tashiro et al. 1978; Badu and Melnik 2017b; Fatehiboroujeni et al. 2018; Fang et al. 2013; Gupta and Kumar 2018; Fatehiboroujeni et al. 2018; Maghsoodi and Perkins 2018; Kumar et al. 2016; Schmidt et al. 2015; Gupta and Kumar 2017; Venkataiah et al. 2018; Badu and Melnik 2017a).

The rest of this paper is organized as follows. In section 2 we describe the theory behind the atomistic to continuum model and pertinent to our nanocluster, focusing on its elastic properties. In Section 3 we describe the computational methodologies used for calculations. The main results are presented and discussed in Section 4. Concluding remarks and an outlook are summarized in Section 5.

2. Theory of Atomistic to Continuum Modeling

The full atomistic modeling of RNA complexes including their surroundings and accounting for their heterogeneity and multiscale spatio-temporal nature is beyond the reach in the majority of practical cases. This brings the development of simplified models and approximations to the forefront of the current research in this field.

2.1. Multiscale Problems and Atomistic to Continuum Methodologies

RNA complexes provide a rich ground for applications of advanced numerical procedures developed for multiscale problems. In its general setting, we need to deal with different spatio-temporal scales. However, in most cases the application of such procedures is severely limited by extreme computational resources required for full atomistic simulations of such complexes. Moreover, "critical" regions for such simulations are not easily identifiable for RNA nanotubes, as soon as we consider realistic examples of their practical applications. A typical simplified procedure to handle multiscale problems, that has received popularity in the recent years, is based on considering two scale continuum-on-atomistic methods. They are usually classified (Ulz 2015) as those that are developed with a simultaneous implementation (concurrent) and those that are developed with a serial implementation (hierarchical). The first group couples "critical", atomistically-modelled regions (or a region) with their "continuum" surroundings has received close attention of numerical analysts and theoreticians for quite some time (e.g., (Zhang et al. 2010; Chen et al. 2015; Luskin and Ortner 2013) and references therein). There are many variants of these methods, ranging from the bridging-scale methods to various continuum-field theory methodologies, and from atomistic-scale finite element methods to matching multiscale simulations. Some of these methods, including multiscale multilevel method, have been applied to biomolecules, such as DNA (Chen et al. 2012), in a simplified setting, far from challenges represented by biological nanotube complexes. Until recently, the second group (hierarchical continuum-on-atomistic methods) has been less studied, with a new interesting results appearing in the literature (e.g., (Wurm and Ulz 2016) and references therein). Another relatively new class of multiscale models, principally derived from the concurrent methods, that has received increasing popularity in recent years are the adaptive resolution methods. These models address the common limitations of the concurrent models by providing the possibility of capturing the particle exchange in the fixed regions of systems that are treated at different resolutions, thereby enhancing the accuracy and required precision (Gooneie et al. 2017). In general, during the adaptive resolution simulations, also referred as double-resolution methods, the domain is divided into an all-atomistic and a coarse-grained region along with a linking transition region that connects the two regions. The novelty as well as the difficulty of these adaptive resolution schemes, developed by Kremer and co-workers (Praprotnik et al. 2007, 2011), tremendously depends on the properties of the transition regions. More details about such models along with other relevant multiscale models can be found in a recent review article by (Gooneie et al. 2017). In the spirit of this second group of methods, in what follows we develop a simple model for RNA nanotubes by using explicitly their geometric characteristics and combining the finite element methods with atomistic molecular dynamic simulations.

2.2. Finite Element Method with Inter-atomic Interactions

For the continuum model of RNA nanotubes, we consider a cylindrical hollow shell and perform finite element simulations similar to those of a continuum model for carbon nanotubes (Cheng et al. 2009b; Tserpes and Papanikos 2005; Badu and Melnik 2017b). The idea to formulate a discrete to continuum model has been used for other biological systems as well (Kuzkin et al. 2016; Lacarbonara et al. 2015; Badu and Melnik 2017b). In order to study the properties of such biological systems, we develop the continuum model equations based on the properties of the inter-atomic interactions calculated

from the atomistic molecular dynamics simulations, where one can model the self-assembled RNA nanotubes (Hansson et al. 2002; Badu et al. 2014; Paliy et al. 2009). For example, in Refs (Badu et al. 2014; Paliy et al. 2009) for molecular dynamics simulations study of RNA nanotubes, the CHARMM27 force field (Phillips et al. 2005) implemented in the NAMD software package (MacKerell et al. 1998) has been used. The potential of the system used during the molecular dynamics simulations is expressed as:

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

where the first term corresponds to bonds, second corresponds to angle parameters, and so on. Also, the constants k_r, k_θ and k_ϕ are the bond stretching, bond bending, dihedral angle torsional force and $\mathbf{r}$ is the displacement vector.

Based on Eq. (1) of all atoms molecular dynamics simulations, one can develop a continuum model as follows. First, we express the motion of atoms in the molecule as a simple harmonic oscillator, where the potential energy is expressed in the bond stretching, bond bending and dihedral angle torsion as

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

$$V_\theta = \frac{1}{2} k_\theta r (\theta - \theta_0)^2, \quad (3)$$

and

$$V_\phi = \frac{1}{2} k_\phi (\phi - \phi_0)^2. \quad (4)$$

Now, let us take a small element of the RNA nanotube of length L and diameter d and suppose that ΔL, $\Delta\theta$, and $\Delta\phi$ are the stretch, bending and the torsional displacement in the cylindrical element of the tube. Then, the elastic energy due to stretching of the element is expressed as

$$U_A = \frac{1}{2} \frac{YA}{L} (\Delta L)^2, \quad (5)$$

where ΔL, Y, L and A are the infinitesimal change in length along the axial direction of the RNA nanotube, Young's modulus, length and the cross-sectional area of the RNA nanotube, respectively.

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

$$U_M = \frac{1}{2} \frac{YI}{L} (2\alpha)^2. \quad (6)$$

Finally, the energy corresponding to the rotational motion of the cylindrical element

is expressed as

$$U_A = \frac{1}{2}\frac{\mu J}{L}(\Delta\beta)^2, \tag{7}$$

where $\Delta\beta$ is the twisting angle of the tube due to the elastic torsion, J in the beam element of the cylindrical RNA nanotube and μ is the shear modulus. The quantities V_r, V_θ and V_ϕ are the energies associated to the bond stretching, bond bending and the torsional energies. From comparison of corresponding energies in two different formulations we find that

$$\frac{YA}{L} = k_r, \ \frac{YI}{L} = k_\theta, \ \frac{\mu J}{L} = k_\phi. \tag{8}$$

From the above relations, one can implement the elastic parameters in the continuum model, which can be originally obtained from the atomistic calculations. Specifically, one can find the quantities k_r, k_θ, and k_ϕ by using molecular dynamics simulations. For example, assuming hysteresis effects in the nucleic acid nanotube are negligibly small, for a 5 ring RNA nanotube, we can predict an approximate volume of the cluster as $V = 4.42 \times 10^{-24} m^3$ and mass is $M = 8.5 \times 10^{-22} kg$, so that the density is $\rho = 0.190 g/cm^3$. These parameters were used in the continuum model simulations of the RNA nanotube. Also, by applying an external force in the all atoms molecular dynamics simulations of RNA nanotube, we ensure that there is an infinitesimal change in the bond stretching, bond bending and dihedral angle torsional. Then, one can calculate the Young modulus and Poisson ratio of RNA nanotube, which can be used as material parameters for continuum model simulations. Since in this manuscript we are not formally focusing on any molecular dynamics simulations, but instead developing a continuum model for RNA nanotubes, where we use the Poisson ratio and Young modulus as 0.40 and 300 MPA, respectively (Marko and Cocco 2003). For the mathematical modeling based on a continuum model for RNA nanotube, the components of the stress tensor in terms of the elastic coefficients and the strain tensor for the linear and isotropic continuum system are written as

$$(\sigma_{11}, \sigma_{22}, \sigma_{33}, \sigma_{23}, \sigma_{13}, \sigma_{12})^T = \frac{Y}{(1+\nu)(1-2\nu)} A(\epsilon_{11}, \epsilon_{22}, \epsilon_{33}, \epsilon_{23}, \epsilon_{13}, \epsilon_{12})^T, \tag{9}$$

where A is given by

$$\begin{aligned} A = [a_{ij}], i, j = 1, 2, 3, 4, 5, 6, \\ a_{ii} = 1 - \nu, i = 1, 2, 3, \\ a_{jj} = \frac{1-2\nu}{2}, j = 4, 5, 6, \\ a_{12} = a_{13} = a_{21} = a_{31} = \nu, \end{aligned} \tag{10}$$

with the rest of elements being zero. ν is the Poisson ratio defined as

$$\nu = \frac{3K - 2\mu}{(3K + \mu)}, \tag{11}$$

where the quantities K and μ are the bulk modulus and the shear modulus, respec-

tively. For the continuum system of RNA nanotube, the elastic deformations are found from

$$\partial_j \sigma_{ik} = 0, \tag{12}$$

with the Cauchy strain-displacement relationship:

$$u_{ik} = \frac{1}{2}\left(\frac{\partial u_i}{\partial x_k} + \frac{\partial u_k}{\partial x_i}\right), \tag{13}$$

where $u_{i,j}$ is the strain and u_i is the displacment. From the above relations one can derive elastic strain-stress equations once the elastic parameters like the Poisson ratio and the elastic moduli of the system are calculated from atomistic modeling.

3. Computational Details

The developed computational procedure consists of two parts, connected in a hierarchical manner, as it is described in Section 2.1. The first part of the procedure is based on the molecular dynamics simulation. This part is based on the methodology developed earlier in Paliy et al. (2009) for an RNA nanoring, and its further development in Badu et al. (2014). In particular, we have performed all-atom molecular dynamics simulations of RNA nanotubes by using the CHARMM27 force field (Phillips et al. 2005) implemented in the NAMD package (MacKerell et al. 1998). Further, the VMD tool (Humphrey et al. 1996) and topotool (to connect the bonds between the fragments) have been used during the modeling of the system. The building blocks for the RNA nanotube are the small double strand RNA complexes RNAIi/RNAIIi taken from the protein data banks with the pdb code (2bj2.pdb) (Lee and Crothers 1998) and the assembling of the fragments is done via tcl scripting in the VMD. The second part of the procedure is based on finite element computations. Both parts have standard limitations, such as inherent physical limitations of the atomistic force fields in the MD simulations (see, e.g., recent reviews in Sponer et al. (2018); Pokorna et al. (2018)). Some of the recently developed software tools (Bottaro et al. 2019; Stasiewicz et al. 2019) could be useful for the analysis of some parts of such complex structures as ours, although their applicability is not straightforward. It is also worthwhile noting the importance of coarse-grained model development in this field. For the fundamental part of RNA nanotubes, the nanoring, this development has been pioneered in Paliy et al. (2010). Some recent developments in the field of coarse-grained modeling of RNA systems can be found in Sponer et al. (2018); Šulc et al. (2014) and references therein. The first initial steps in developing the approach described and applied here were made in Badu and Melnik (2017b,a), where challenges for large time-scale simulations of RNA complexes were also discussed. The details of the second part of our computational procedure are as follows.

In order to study the mechanical properties of the RNA nanocluster, we have used the finite element method implemented in the COMSOL software (www.comsol.com). First, we have used the Dirichlet boundary conditions at both ends of the tubes in such a way that one end of the tube is displaced by certain distance and the other end is fixed, e.g., u_i =0 at z=0 and $u_1 = 0.1$ nm, $u_2 = u_3 = 0$ at the other end. For example, RNA nanotubes with the length of z=20, 40, 80 and 120 nm correspond to 5, 10, 20 and 30 RNA rings connected in series. A fixed displacement has been imposed

at one end of the RNA nanotube, while at the cylindrical surfaces, the Neumann boundary conditions have been imposed i.e. $n \cdot \sigma = 0$. We also present our results for mixed boundary conditions, which have been implemented at different boundaries of the continuum structures of the analyzed RNA nanotubes. Based on the developed discrete to continuum model, we find the density of the RNA cluster as the ratio of the total mass to the approximate volume of the cluster.

4. Results and Discussion

In what follow, we provide details of the numerical experiments and main findings, along with a discussion on relevant experimental results and their availability in the context of RNA nanostructures analyzed here.

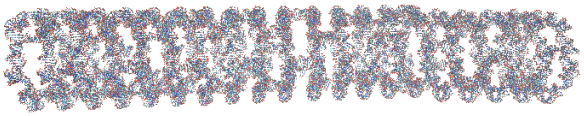
4.1. Analysis of RNA Nanotubes with Different Architectures

As mentioned earlier, first we perform molecular dynamics simulations to obtain the optimized structure of RNA nanotubes, so that we can use material parameters for continuum model simulations. As an example, in Fig. 1(a), we present the optimized structure of 20 rings of RNA nanostructures connected in series by using molecular dynamics simulations. In Fig. 1(b), we present the cylindrical structure that mimics Fig. 1(a) in the continuum modeling framework. Using the strain-stress constitutive relations, we have visualized the stress and strain in the cylindrical shells of 20 nm, 40 nm, 80 nm and 120 nm RNA nanotubes which are equivalent to the 5 rings, 10 rings, 20 rings and 30 rings RNA nanotubes in the atomistic approximation. The diameter of all nanotubes is around 10 nm, which is approximately the same to that found in molecular dynamics simulations (see Figs. 1(a)-(b)). The results for the displacement in the entire volume of the RNA nanotubes with the length of 20 nm, 40 nm and 80 nm are presented in Figs. 2(a), 2(b) and 2(c), respectively. Here we have used the Dirichlet boundary conditions at both ends in such a way that one end is fixed and the other end is displaced by the same length for all the tubes. It can be seen that the variation of displacements in the entire volume of RNA nanotubes of different sizes has a similar pattern, i.e., vanishes at the left end and achieves its maximum at the right end.

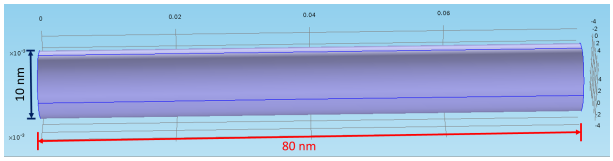
We have analyzed the distribution of displacement in the RNA nanotube for different sets of boundary conditions in Fig. 3(a). Here we chose Dirichlet boundary conditions at one end and the Neumann boundary conditions at the other end of the RNA nanotube. The force at the atomic scale is chosen in such a way that one atom experiences the acceleration of $0.01 \times Aps^{-2}$, which is equivalent to 10 N force in the whole structure of 5 ring RNA nanotube.

In Fig. 3(b) we present the variation of the displacements with respect to stress for the case of 10 ring RNA nanotube, which is equivalent to the 40 nm RNA nanotube in the continuum model. Here we chose Neumann boundary conditions at one end and kept the other end to be fixed via Dirichlet boundary conditions. Furthermore, in Fig. 4(a) we have also presented the cross sectional plot of the displacements along the assembly axis of the tube. Here we see that the displacements achieve their maximum at one end and decrease as we move towards the other end.

Finally, we have also plotted the distribution of strain and stress along the assembly axis of the RNA nanotubes for different sizes in Figs. 4(b) and 5, respectively. Here we use a combination of Dirichlet and Neumann boundary conditions. We find that



(a)



(b)

Figure 1. Schematic of (a) atomistic representation of RNA nanotube with 20 nanorings, and (b) continuum model of 20 ring RNA nanotube in the form of hollow cylindrical shell.

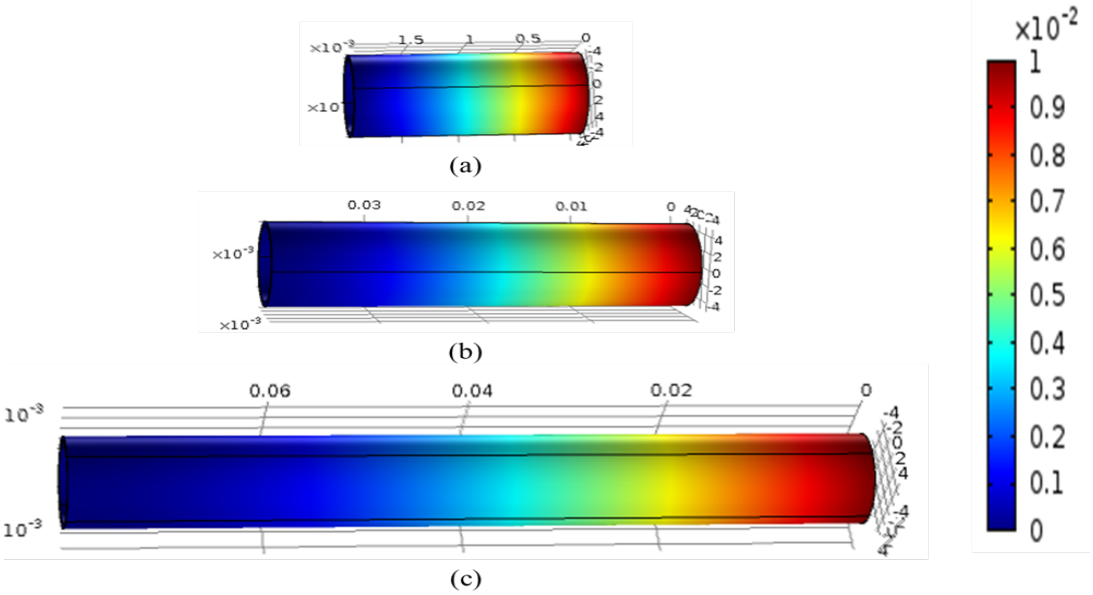


Figure 2. Distribution of displacements (in μm) of RNA nanotube with Dirichlet boundary conditions along (a) 5 rings, (b) 10 rings, and (c) 20 rings.

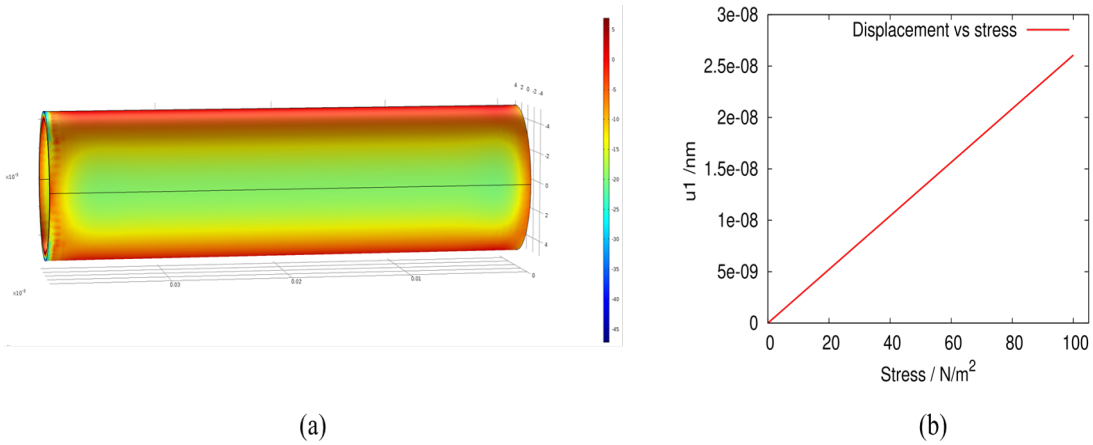


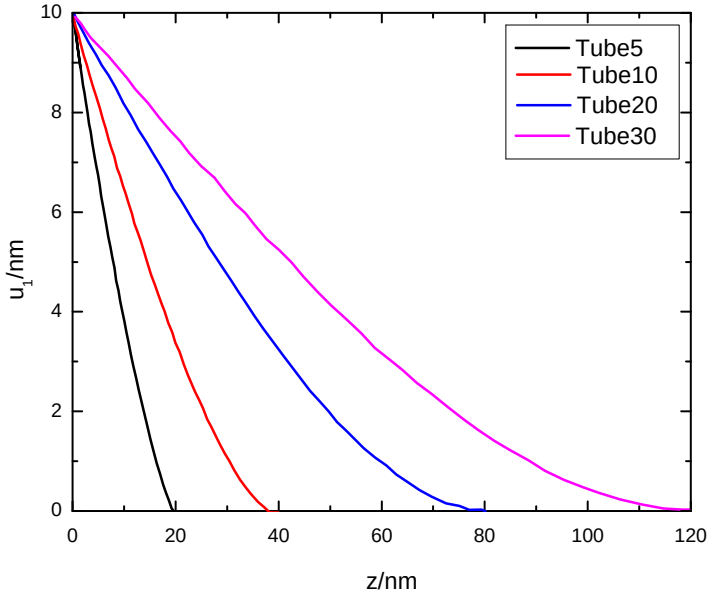
Figure 3. (a) Distribution of displacements (in nm), and (b) variation of displacement with stress for the 10 ring RNA nanotube subjected to combination of Dirichlet and Neumann boundary conditions.

the amplitude of variation in strain decreases as we increase the size of the tube. This is consistent with the characteristics found in the variations in the displacements in Figs. 2(a), 2(b) and 2(c).

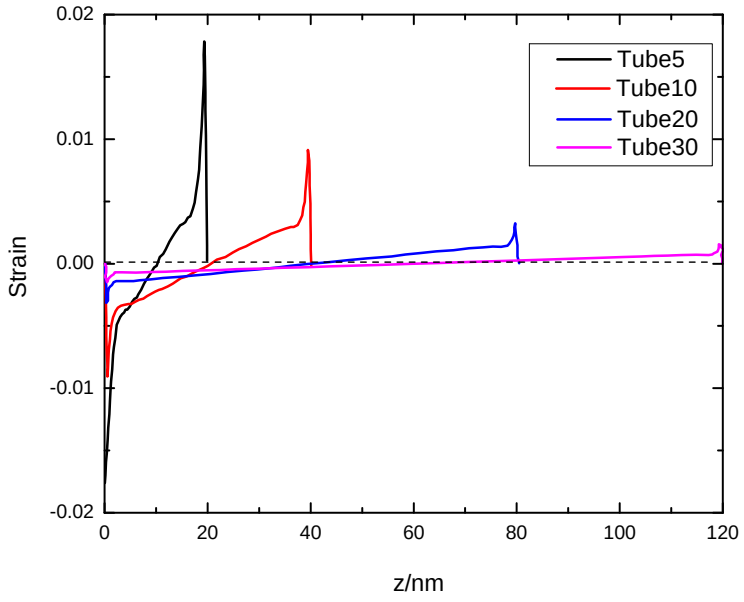
Analysis of mechanical strain mentioned above has significant influence on utilizing drugs into the RNA nanotube (Huang et al. 2013). More precisely, the orientation of drug molecules in the RNA nanotubes, that have different strain configurations, diffuses into the blood vessels with different rates. Hence, these drugs reach the target, e.g. cancer cells, at different rates from different directions, that has significantly different effects on the entire process of cancer therapy. For example, choosing Dirichlet boundary conditions in Figs. (2(a), 2(b), 2(c)) have different impact on the orientation of drugs in the RNA nanotube and thus has different rate of flow of the drugs to the target cells if one choose Neumann boundary condition in Figs. (3(a), 3(b)). Note that different boundary conditions in the RNA nanotube modeling provide different mechanical strains and thus lead to different influences on utilization of the drugs with the RNA nanotube. For example, strain distribution vanishes at the center of the RNA nanotube, which means that drugs in the RNA nanotube are mostly unaffected at the center of the RNA nanotube. Hence, in a small size strained RNA nanotube (< 5 rings RNA nanotube), the large influence of strain at the boundary would force the RNA nanotube to release the drugs more rapidly than in the case of larger RNA nanotubes (> 30 rings RNA nanotubes).

4.2. Availability of Experimental Results and Coupled Problem

In the previous sections we developed and applied a new atomistic-to-continuum type model for RNA nanotubes. For these systems, such a model has been developed in detail for the first time. While the accuracy of biomolecular simulations has been continuously expanding, many systems, such as RNA complexes considered in this paper, remain out of reach for such simulations. Therefore, although the final goal remains to be an increasingly tight integration of experiments and simulations (Bottaro and Lindorff-Larsen 2018), it is too early to say that such an integration can be easily achieved for the systems we consider here. At this stage, there are several serious



(a)



(b)

Figure 4. Variation of (a) displacement, and (b) strain, as a function of position along the axial direction of the RNA nanotube with 5, 10, 20, and 30 rings.

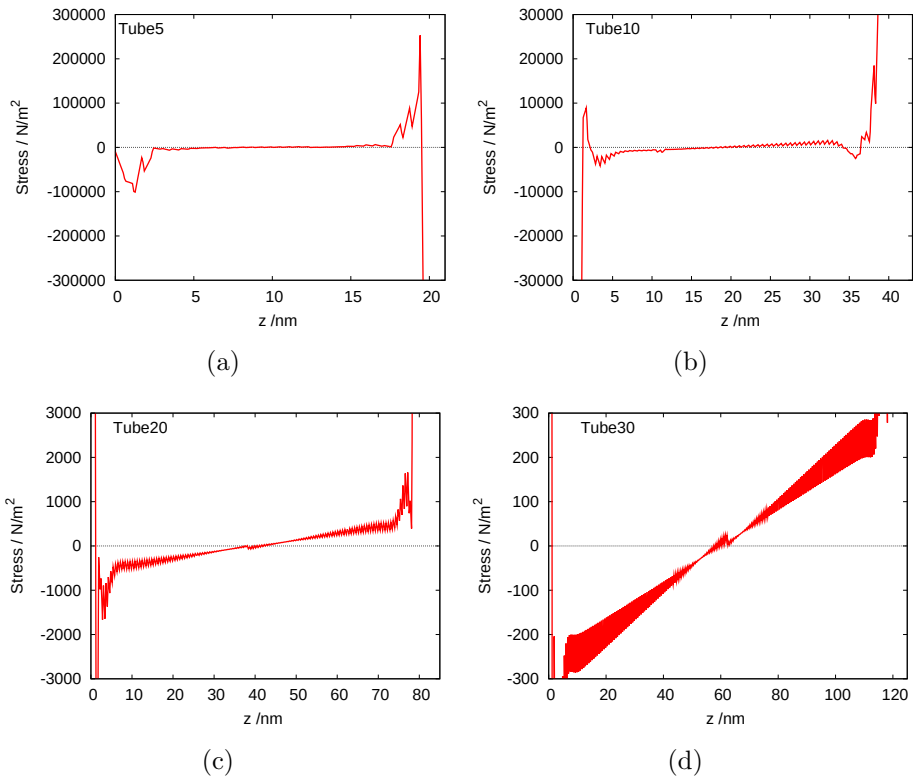


Figure 5. Variation of stress along the axial direction in the RNA nanotube with (a) 5 rings, (b) 10 rings, (c) 20 rings, and (d) 30 rings, as a function of position.

challenges on the way. Firstly, given that the RNA nanotechnology is an emerging field, some of the structures have only been generated computationally so far, with no experimental results obtained up to date. Even if we take a small part of the structures we are analyzing here - an RNA nanoring - it is well known that designing such self-assembled objects is a highly non-trivial task and it is still a subject of intense discussions in the literature (Sharan et al. 2017). While the coupling of such nanorings and the simulations of the resulting structures are of very recent origin (Badu et al. 2015b, 2014). Secondly, it is also well-known that in designing RNA complexes, chemical modifications may change the identity of RNA nucleotides, as well as their characteristics (Tanzer et al. 2018), although with recent advances the role of this factor has been decreasing (Jasinski et al. 2017). Nevertheless, for some applications, in particular biomedical, it is still critical as these modifications will lead to an alteration of genetic and structural information. Other related challenges have recently been highlighted in Schroeder (2018). Thirdly, even the determination of the structure of RNA molecules themselves is seriously restricted by their size and flexibility, making consistent experimental results difficult to obtain (Dans et al. 2018). Despite the rapid progress in the field, as of today, RNA structural characterization is lagging substantially behind the progress for other biomolecules such as proteins, and there is a general consensus that the experimental data should be more comprehensive. However, given that RNA functions are intimately linked to its structure and dynamics (Sponer et al. 2018), it is not easy to achieve. As a result, on the two-way road, where experiments being used to refine simulations and simulations used to interpret the experiments (Bottaro and Lindorff-Larsen 2018), in the context of RNA nanotubes we hope that

our results here will assist in interpreting future experiments in this field. In the meantime, we would like to point out several recent papers where RNA-based experiments were used to refine theoretical models and simulations. As we already mentioned in Section 3, much effort in this direction has been devoted to various fitting corrections to RNA force fields (e.g., (Cesari et al. 2019)). Calibration procedures may also become more prominent in the future, when more data become available, while the current situation is such that the majority of known RNAs remain structurally uncharacterized (Ponce-Salvatierra et al. 2019). Hence, it is expected that new theoretical and computational models can assist in setting up the experiment and in guiding it. It should also be noted that the stability of RNA nanoparticles and nanoclusters in the bloodstream and nonspecific cellular uptakes, which may pose a requirement of high dosage (Yingling and Shapiro 2007), has not been studied yet in its natural setting as a coupled solid-fluid interaction problem. At the same time, the consideration and analysis of the dynamics of RNA nanostructures in the bloodstream and physiological solutions, as well as transport properties of these nanostructures, is essential (Badu et al. 2015a). The model developed in this paper can provide an important step in such studies. Moreover, a nonlinear atomistic-based continuum model integrating the Modified Morse potential at the atomistic scale for carbon nanotubes has been reported in Wernik and Meguid (2010). More recently, Palacios and Ganesan (2019) reported an atomistic-continuum model to study the dynamic response of carbon nanotubes reinforced polymer incorporating the Mooney-Rivlin strain energy for computing the non-linear response. In another recent study (Adnan et al. 2018), an atomistic-based continuum viscoelastic model of microtubules was reported based on the interatomic potential for protein and continuum homogenization method. Such modeling frameworks can be easily adopted and incorporated in the proposed model of RNA nanotubes to further enhance model accuracy and predictions.

5. Conclusions and Outlook

In this paper, we have studied the mechanical properties of the RNA nanoclusters based on the developed discrete to continuum model. First, we have modeled self assembled RNA nanoclusters by using the molecular dynamics simulation technique. Then, we have approximated the RNA nanotube by considering a cylindrical hollow shell for continuum model calculations. This has allowed us to mimic the RNA nanostructures of atomistic scale simulations. The elastic properties of the system have then been studied based on the linear constitutive relation between strain and stress. Using the Dirichlet and Neumann boundary conditions, we have studied the distribution of the displacements and strain for RNA nanotubes of different sizes. We have shown that the amplitude of oscillations in the strain and displacement differs significantly for different sizes of RNA nanotubes. Our study should be useful for building RNA nanotubes that have applications in biomedicine, where one can assemble drugs into the RNA nanotube for treatment of cancer cells as well as for treatment plans of other diseases. While a linear model has been used in this work, the study of the systems with more complicated non-linear relations, as well as those accounting for the influence of thermal and electrical properties on the RNA nanotubes, may be useful for performing experiments at the device level.

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