PROCEEDINGS

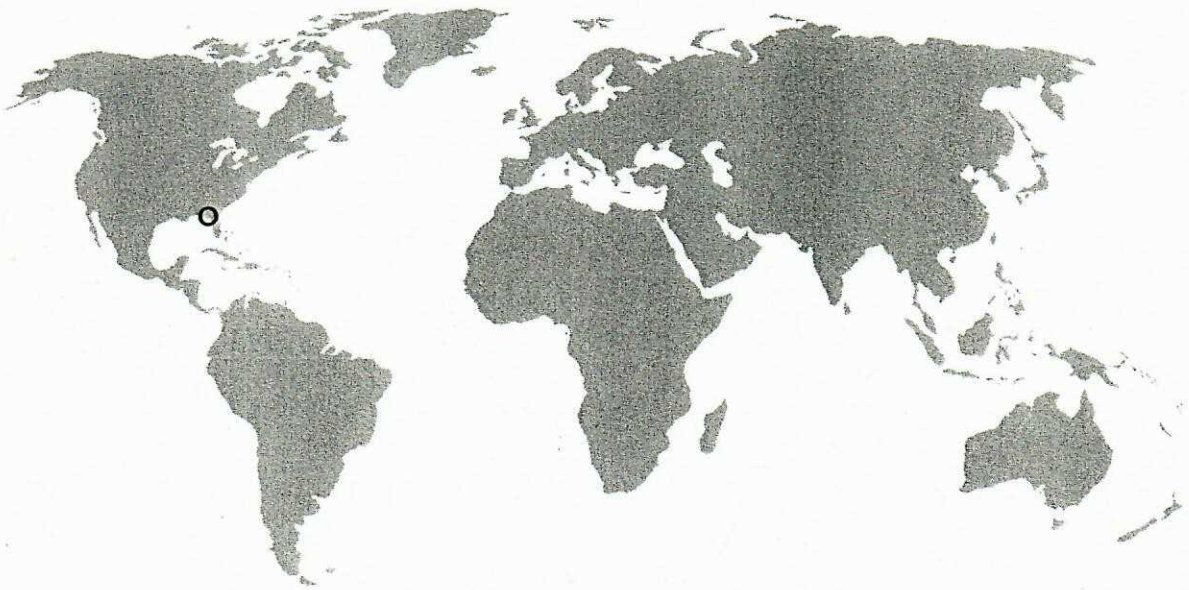
MMM 2008

Fourth International Conference

MULTISCALE MATERIALS MODELING

OCTOBER 27-31, 2008 • TALLAHASSEE, FLORIDA, USA

Tackling Materials Complexities via Computational Science



Hosted by the Department of Scientific Computing and Florida State University

DEPARTMENT OF
Scientific
COMPUTING

FLORIDA STATE UNIVERSITY • 1851 •

Forced Dynamics and Stability of RNA Nanostructures

Maxim Paliy[1], Roderick Melnik[1], Bruce Shapiro[2]

[1] M²NeT Lab, Wilfrid Laurier University, Waterloo, ON, Canada, N2L 3C5, http://www.m2netlab.wlu.ca, mpaliy@wlu.ca, rmelnik@wlu.ca
[2] Center for Cancer Research Nanobiology Program, National Cancer Institute, Frederick, MD 21702, bshapiro@ncifcrf.gov

ABSTRACT

We study the mechanical and thermodynamic properties of a hexagonal RNA nanoring structure [Y.G.Yingling, B.A.Shapiro, NanoLett. 7 (2007)] focusing on the following issues: (i) stability of the nanoring versus temperature; (ii) effect of the environment (solvent, counter-ions); (iii) conformations and dynamics under external force. Evaporation of the ions from the ring upon decrease of temperature has been observed, demonstrating a surprising feature - the uptake of ions by the ring grows with the temperature. Several key properties of the nanoring, such as elastic coefficient and damping coefficient in water, have been determined. A measure of the tensile elasticity of the ring against its uniform 2D in-plane compression yields the value of $K_{eff} < 0.013$ GPa, which is much lower than typical values found for soft matter other than RNA.

1. Introduction

Recently, RNA has been proposed as a promising alternative to DNA and proteins for the design of artificial self-assembled materials at a nanoscale [1,2]. RNA (as compared to DNA) offers (i) much greater variety of interactions, as well as (ii) enhanced conformational flexibility, that is not only already used by Nature via the ubiquitous catalytic function of RNA, but it also makes RNA an interesting material for use in the man-made molecular machines. That is why the study of the "functional behavior" of RNA nanostructures (externally controlled conformational changes, e.g. elbow-like motions in a "kink-turn motif" [3, p.320], or isomerisation of the "kissing-loop motif" [4]) is important. To date, only limited data about thermal stability/dynamics of such nanostructures are available [1-3] from experiments and simulations, while the "functional" aspect has been largely overlooked, and a complete picture of RNA nanostructures behavior (esp. under an external forcing) is required.

In this paper we present all-atom classical Molecular Dynamics (MD) results on the stability and dynamics of a simple RNA nanostructure (~13 nm in size) – hexagon-shaped RNA ring [2], composed of 6 "RNAIi/RNAIIi complexes", joined by "kissing loop" motifs (Fig. 1, left). Firstly, the behaviour of the nanoring upon the temperature change is determined. Secondly, the response of the nanostructure to the combined action of the temperature and applied external forces is studied in some detail. One of the emphases of this work is on the effect of the counter-ions and solvent [5]. Finally, dictated by the slowness of MD simulations, the development a coarse-grained model [6], suitable for the description of RNA nanostructures, is in progress.

2. Model and Methods

We use NAMD/VMD packages [7] for all-atom MD simulation/visualisation of the RNA nanoring with the CHARMM27 force field. For the purposes of this study, the RNA nanoring is solvated in 88664 TIP3P water molecules (box ~180x180x90 Angstroms), together with a varied number of ions - 330 Na^+ or 165 Mg^{2+} ions are added to neutralize 330 phosphates, and some extra Na^+, Mg^{2+}, and Cl^- ions are added in order to represent a range of solutions from "physiological" to "sea water". The system is simulated at constant temperature T (via Langevin method) and pressure P=1 atm (via Nose-Hoover Langevin piston) with periodic boundary conditions in all 3D. The time step is 2 fs and non-bonded interactions cutoff is 12 Angstroms.

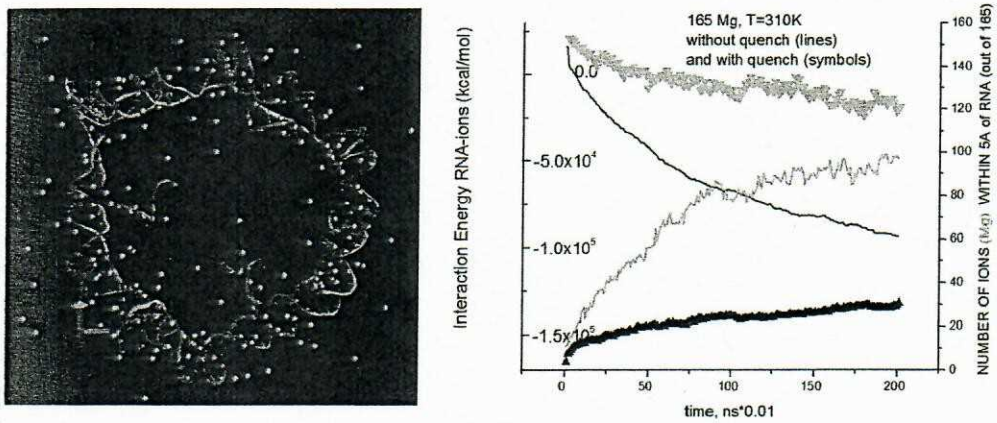
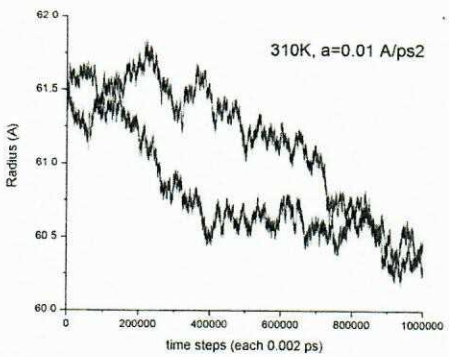


Figure 1. Left: *RNA nanoring solvated in a water box (not shown) together with the Mg^{2+} counter-ions (green spheres).* Right: *The energy of interaction "RNA - ions" (black) and the number of Mg ions found within 5 Angstroms of RNA (green) versus time at 310K. The "quenched" dependencies (as explained in Sec. 3) are shown with the symbols, while those for the runs that started from an initial non-solvated configuration are shown with solid lines.*

3. The effect of the temperature and the ions on the nanoring

We study the thermal stability of the RNA nanoring in the range of temperatures (310K to 510K). Our results demonstrate the intricate role of the ions in a series of "quenched" runs (i.e. when the ring, equilibrated at higher temperature of 510K, is subsequently subjected to a lower temperature of 310K). Surprisingly, the quench leads to the evaporation of the ions from the ring into the solution, as illustrated in Fig.1, right (such evaporation occurs for both Mg and Na ions). From Fig.1 and similar data for Na, one can estimate that at higher T=510K the ring takes up more ions (e.g. 0.8 Na per phosphate or 0.88 Mg per 2 phosphates), as compared to T=310K (0.6 Na or 0.66 Mg, respectively). Since the counter-ions are known to be an important factor in stabilization of the native folds of the biopolymers, *the observed higher uptake of ions by the RNA ring at higher temperature may mean that the RNA ring demonstrates, in a sense, a mechanism of "self-stabilization" upon increase of temperature.*

However, the origin of this phenomenon remains rather puzzling to us. It contradicts (i) simple chemical equilibrium ideas (van't'Hoff equation); and (ii) Manning condensation theory describing the adsorption of ions onto charged polymers in the solutions (the latter is not applicable directly, because of circular instead of linear geometry, and the ring thickness comparable to the Debye length). One may speculate that the thermal contraction of the ring leads to the evaporation of the ions (in the range 510-310K the ring contracts about 5%, or 10%-15% in terms of volume, roughly the same as pure water); however, the percentage of ions evaporated is higher (17% - 27%). Other hypotheses should be explored, e.g. some (yet to be identified) structural change in the RNA ring with temperature (the changes of the hydration state of the solutes, in particular biological ones [8], are known to modify also their solubility).



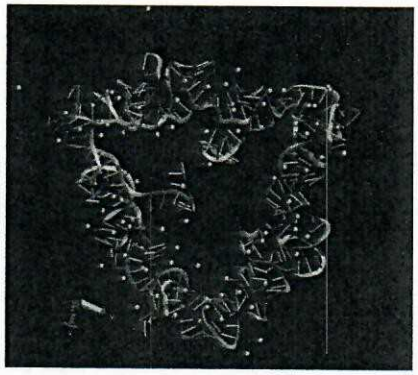


Figure 2. Left: *Gyration radius R(t) of the RNA ring subjected to a small constant compressive force a = 0.01 A/ps^2. Two independent runs are shown.* Right: *Snapshot of the RNA ring subjected to extreme compression by quasi-linearly increasing force, at a = 1.7 A/ps^2.*

4. Forced dynamics of the nanoring

"Steered MD" functionally of NAMD has been used to apply uniform compressive/expansive force, that is directed towards the centre of mass of the RNA ring, to 2130 atoms of its nucleic acid backbone (this setup, dictated by geometry, allows one to estimate average properties of the ring). Since the strength of the ring is mainly determined by hydrogen bonding, the total force applied to the ring should not exceed ~100 pN, i.e. ~0.05 pN per atom (~0.02 A/ps^2 in the units of acceleration used). However, the response of the ring to such weak forcing is expected to be extremely slow, ~μs, which cannot be achieved in our MD simulations. In attempts to circumvent this difficulty, we studied the dynamics of the ring within a range of forces, 10^{-2} - 1 A/ps^2. The evolution of the gyration radius of the ring *R(t)* has been monitored.

Under the application of an intermediate dc force, a=0.1 A/ps^2, the *R(t)* dependencies are linear, i.e. the ring shows a behaviour compatible with a drift of an overdamped non-interacting particle subjected to a constant force. Namely, *R(t)* can be found from $m\eta_{eff}\dot{R} = ma$, where η_{eff} is an effective damping for RNA fragments in water, that can be determined from the slope of a *R(t)* dependence, $\eta_{eff} \approx 56\,\mathrm{ps}^{-1}$ at T=310K, and $\eta_{eff} \approx 29\,\mathrm{ps}^{-1}$ at T=510K. One can further estimate

the activation energy from the Arrhenius formula $\eta_{eff} = \eta_0 \exp(E_a / k_B T)$, as $E_a \approx 450K$. We tried to elucidate the ring elasticity in this regime, by collecting the energies E of the configurations obtained during the "compression drift", and plotting them against R, but the resulting $E(R)$ turned out to be non-parabolic, and therefore an elastic coefficient could not be determined, probably because the used configurations are not at equilibrium.

A series of longer (*2* ns) runs have been carried out at a small force, $a=0.01\ A/ps^2$ (~ two times less the one needed to break hydrogen bonds in our setup). Fig. 2, left, shows that even if the equilibrium is not yet achieved after *2 ns*, the system spends a long time (> *200 ps*) in the plateaux of $R(t)$ dependence, before jumping to a next plateau, and the hypothesis of a free forced drift no longer applies. From the data of Fig. 2, left, one can give an *upper* estimate for the elasticity of the RNA ring in the following way. In the plane of the ring, the 2D equation analogous to the one for the bulk modulus in 3D, reads: $dP = -K_{2D} dS / S$, where dS is the change in ring's surface upon the change in "2D pressure", $dP = aM/(2\pi R)$, where M is the total mass of the nucleic acid backbone. Since from Fig. 2, left, one can judge that $dR_g \geq 1.3A$, and $dS/S = 2dR/R$, one obtains an estimate, $K_{2D} \leq 0.04$ N/m. In order to compare it with a 3D measure of elasticity, one can divide K_{2D} by the (approximately constant) thickness of the ring in a normal direction, *~30 A*, to obtain $K_{eff} \leq 0.013 GPa$. This is a much lower value compared to those for soft matter other than RNA (typical values for DNA Young modulus are *~0.1 GPa*).

Finally, under the action of a very strong compressive force, the ring starts to fold into a triangular shape (Fig. 3, right), where three of the six "kissing loops" form the angles and three remaining ones belong to the sides of the triangle.

Ackno□ledgements

M.P. and R.M. are grateful to the NSERC and the CRC Program for the support and to Sarah Woodson for helpful comments. This work was made possible by the facilities of the Shared Hierarchical Academic Research Computing Network (SHARCNET: www.sharcnet.ca), and was supported in-part by the intramural research program of the NIH, National Cancer Institute, Center for Cancer Research.

References

[1] Luc Jaeger and Arkadiusz Chworos, Curr. Opinion Struct. Biol., 16 (4), 531-543, 2006.
[2] Y. G. Yingling, B. A. Shapiro, Nano Letters, 7, 2328-2334, 2007.
[3] Computational studies of RNA and DNA. Series: Challenges and Advances in Computational Chemistry and Physics , Vol. 2, Šponer, Jirí; Lankaš, Filip (Eds.) 2006, XI, 638 p.
[4] Xianglan Li, Satoru Horiya, and Kazuo Harada, J. Am. Chem. Soc., 128, 4035-4040, 2006.
[5] M.Paliy, R. Melnik, B.Shapiro, to be submitted (2008).
[6] V.Tozzini, Curr. Opinion Struct. Biol. 15,144-150, 2006.
[7] W. Humphrey, A. Dalke and K. Schulten, J. Mol. Graphics 4 (1996), pp. 33-38; James C. Phillips et al. , Journal of Comp. Chemistry, 26:1781-1802, 2005.
[8] Peter. J. Mikulesky and Andrew L. Feig, Biopolymers, 82 (1), 38 (2006).