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Exploration of the Structural and Energetic Landscape of Glycol Nucleic Acids

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1. Introduction

•Glycol nucleic acid (GNA) is a non-natural analog of DNA
•In place of the deoxyribose unit of DNA, GNA has an acyclic ethylene glycol unit (Fig. 1) [1]

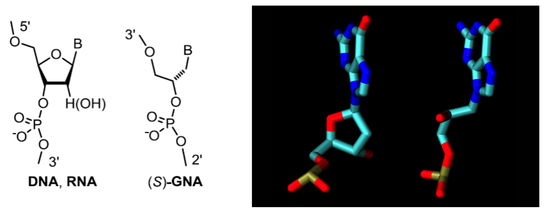

Fig. 1- Left: side by side comparison of DNA and GNA nucleotides. Right: A different representation, DNA nucleotide on left and GNA nucleotide on right.

•The differences between DNA and GNA are evident in the duplex structure (Fig. 3) [1]
•Instead of a major and minor groove, GNA has one large groove (Fig. 3) [1]
•The base pairs of GNA wrap around the single groove like a ribbon on a spool (Fig. 3) [1]
•GNA has primarily intra-strand base stacking, with each base stacking on top of a base of the opposite strand, as opposed to the inter-strand base stacking of DNA (Fig. 2) [2]

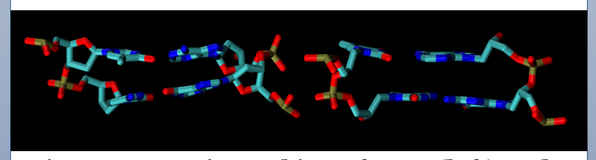

Fig. 2- Base pair stacking of DNA (left) and GNA (right).

•GNA has a higher stability than DNA, as shown by its melting point being, on average, 20 degrees Celsius higher than DNA [2]
•The stability of GNA appears to be due to entropic factors, not enthalpic factors [2]
•Due to its stability and unique shape, GNA is of interest for its use in place of DNA as a molecular scaffold
•Molecular dynamics (MD) uses classical laws of motion to follow the movement of atoms or molecules in computer simulations [3]
•MD can be used to explore the properties of nucleic acids
•Studies comparing MD simulations to atomic force microscopy have found that the results of simulated pulling of nucleic acids are accurate and realistic [4]

2. Objectives

•Measure forces of extension and separation of GNA relative to identical sequences of DNA
•Explore structure, flexibility, and energetics of GNA and how these may relate to its stability
•Explore the usefulness of Steered Molecular Dynamics simulations in investigations of GNA

3. Methods

•Models were prepared for simulation by addition of sodium ions to balance the negative charges of the phosphate backbones, as these charges can make simulations unstable (Fig. 3)
•Charge-balanced models were then submerged in a water box slightly longer than twice the length of the molecule as determined from crystal structures (Fig. 3)

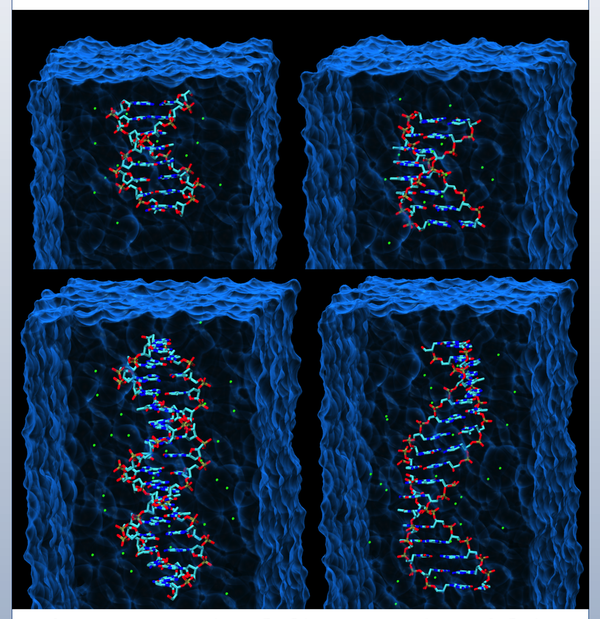

Fig. 3- DNA-8 (top left), GNA-8 (top right), DNA-16 (bottom left), and GNA-16 (bottom right) models in simulated water boxes. Green dots are sodium ions. The bottom halves of the boxes are not pictured.

•An oxygen atom at the 2' end (equivalent to the 5' end of DNA) of one strand was fixed to remain stationary (Fig. 4)
•An oxygen atom at the 2' end of the other strand was set to be pulled (Fig. 4)

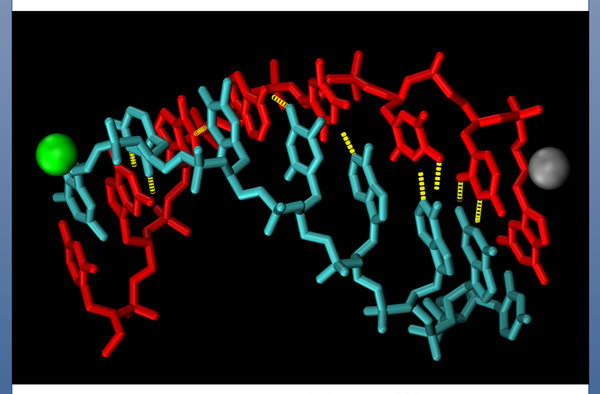

Fig. 4- GNA-8 prepared for pulling. Hydrogen bonds are shown in yellow. The atom that is fixed in place is highlighted in green; the atom to be pulled is in silver.

•The atom set for pulling was pulled at a rate of 1 angstrom/ps for 120 ps
•Slower speeds are needed for more accurate data, but quicker pulls were done to gain a rough understanding of the behavior of GNA when stretched

4. Results

•Stretching simulations went mostly as planned
•Molecules began to unwind as forces were applied
•Hydrogen bonds broke, beginning near the end being pulled (Fig. 5)

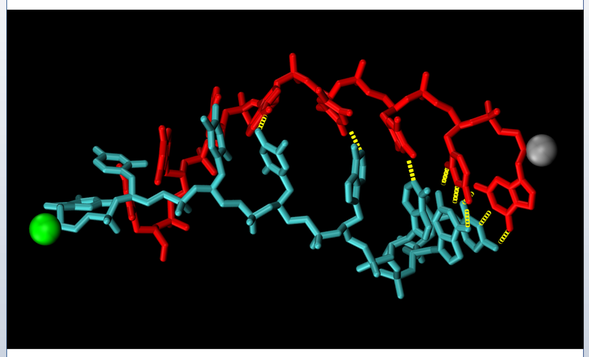

Fig. 5- GNA-8 being stretched. Note broken hydrogen bonds between base pairs (yellow) relative to Fig. 5.

•After more pulling, strands fully separated
•No hydrogen bonds were remade after separation had been completed (Fig. 6)

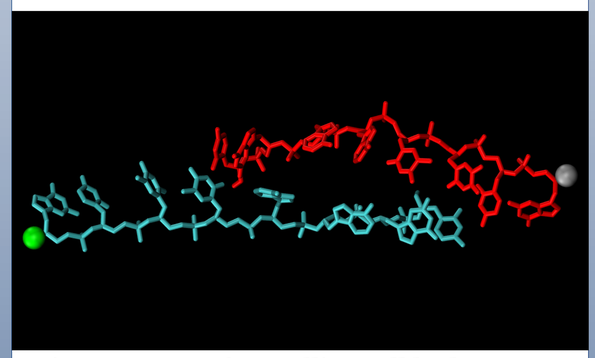

Fig. 6- GNA-8 after pulling. All hydrogen bonds have been broken, and none are reformed after this point in the simulation.

•From preliminary stretches, force data was extracted from the output files of the simulations using a VMD script
•For 8 base-pair duplexes, GNA stretched less and separated more quickly with a lower force peak than DNA (Fig. 7)

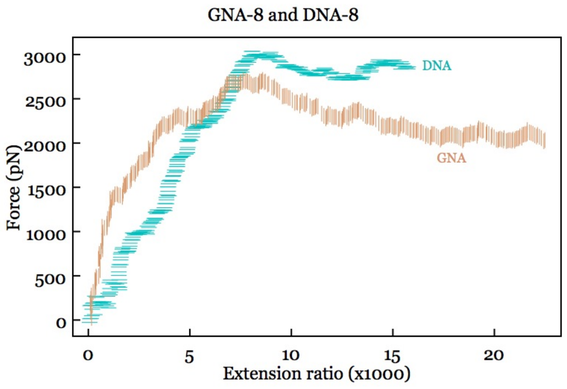

Fig. 7- DNA-8 and GNA-8 extension ratio (extended length/equilibrium length) vs. calculated pulling force.

•For 16 base-pair duplexes, the same relationship seems to occur as in the 8 base-pair duplexes (Fig. 8)
•Initial simulations were on too short of a time scale to fully separate strands, but it is expected that both curves will peak and fall similarly to the 8 base-pair duplexes once further data is collected

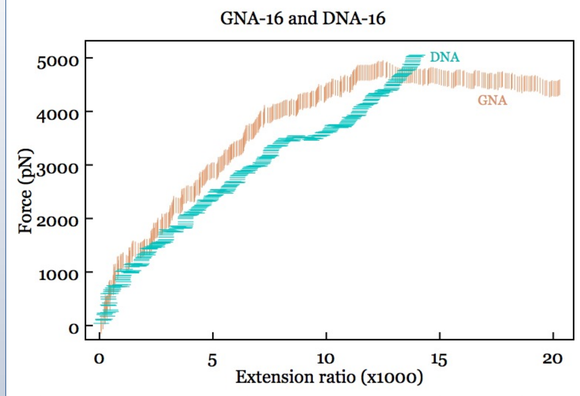

Fig. 8- DNA-16 and GNA-16 extension ratio (extended length/equilibrium length) vs. calculated pulling force.

5. Discussion

•Force measurements appear to differ significantly between GNA and DNA, though further research is needed to clarify details
•Molecular dynamics appears to be a promising method of study GNA
•Since GNA appears to move randomly in a spring-like motion[2], the GNA models in this simulation may not have been in their most compact conformations; more research is needed to see what effect this may have

6. Current & Future Research

•Further pulling at much slower speeds for more accurate measurements
•Adaptive biasing force simulations to collect data for free energy calculations
•Extracting helicoidal parameters of GNA

7. References

[1] Megger, E., & Zhang, L. (2012). *Accounts of Chemical Research*.
[2] Johnson, A. T. (2011). Computational studies of natural and nonnatural nucleic acids. Doctoral dissertation, University of Notre Dame.
[3] Ercolessi, F. (1997). A molecular dynamics primer.
[4] MacKerell, A. D., & Lee, G. U. (1999). *European Biophysics Journal*.

8. Acknowledgements

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