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 (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

8. Acknowledgements
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