DISCOVERY: Georgia State Honors College Undergraduate Research Journal

Volume 1 *DISCOVERY - Georgia State University Honors College Undergraduate Research Journal*

Article 15

2012

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Recommended Citation

Reid, Keon (2012) "Investigating the Solvation, Binding Mode, and Free Energy of a Minor Groove DNA Complex Using Atomistic Computer Simulations," *DISCOVERY: Georgia State Honors College Undergraduate Research Journal*: Vol. 1 , Article 15.
DOI: https://doi.org/10.31922/disc1.15
Available at: https://scholarworks.gsu.edu/discovery/vol1/iss1/15

Investigating the solvation, binding mode, and free energy of a minor groove DNA complex using atomistic computer simulations

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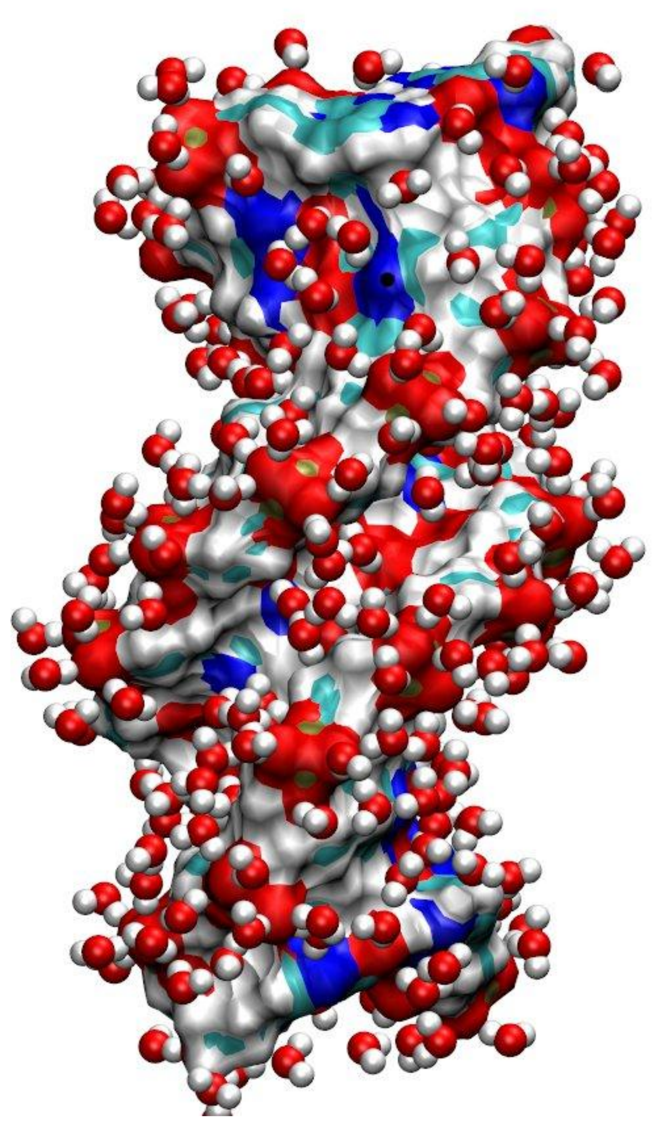
Abstract

Two helical (alpha and beta) strands form DNA. The DNA structural background provides grooves which may act as a binding site. The major groove is 22 Å wide whereas the minor groove is 12 Å wide. The minor groove of the double-stranded DNA can interact with many different classes of ligands in a sequence specific fashion. Netropsin is an oligopeptide with antibiotic and antiviral activity that binds tightly to an adenine-rich sequence of DNA. Atomic resolution x-ray crystal structures of the DNA-netropsin complex have been solvated and many experiments have been carried out over the year to understand the thermodynamics and kinetics of netropsin binding.

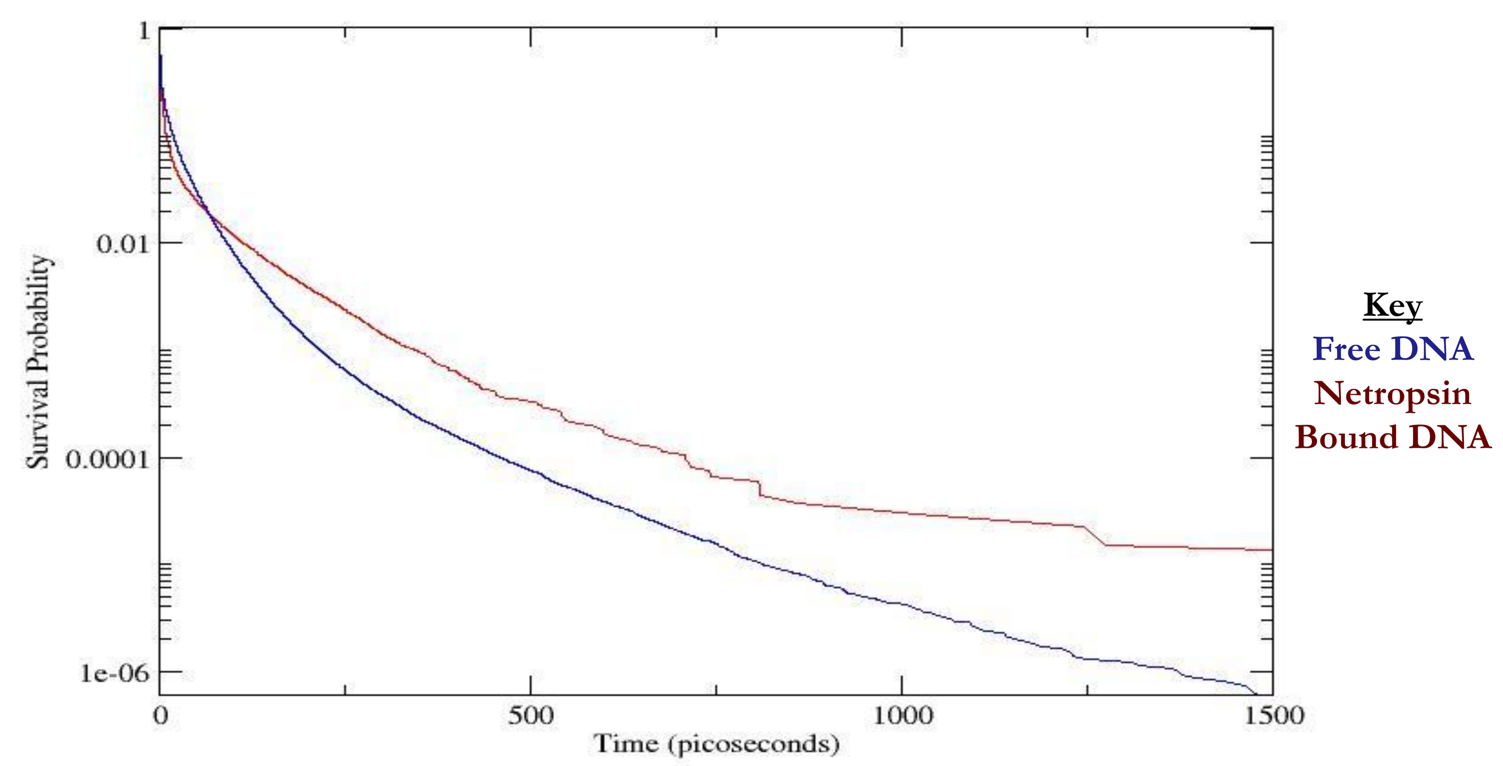
However, the experimental biophysics community disagrees on the exact nature of the different binding modes in solution and the role water molecules play in ligand recognition. Here, we carried out molecular dynamic simulations on the free DNA, free netropsin, and DNA-netropsin complex in explicit water, in order to gain insights on the subtleties of the DNA-netropsin complex at atomistic detail. We studied the different conformational states of netropsin in the minor groove of the DNA. We also analyzed the population and dynamics of the water molecules upon complex formation and calculated the free energy of binding. Results show an affinity for holding water molecules in the binding site rather than on the surface of DNA or complex. These results provide atomistic insights into DNA minor groove recognition that will be beneficial in the development of novel drug candidates.

Free Hydrated DNA

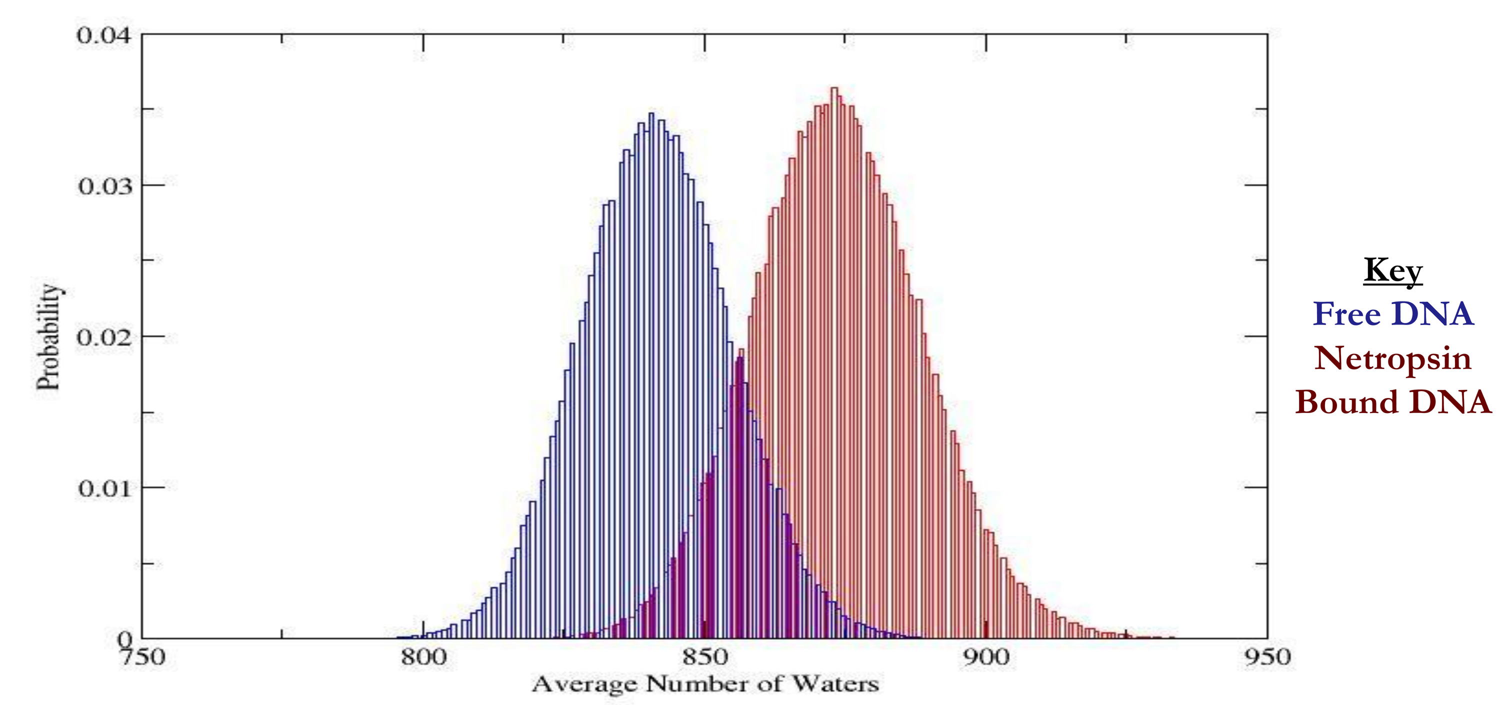


Results

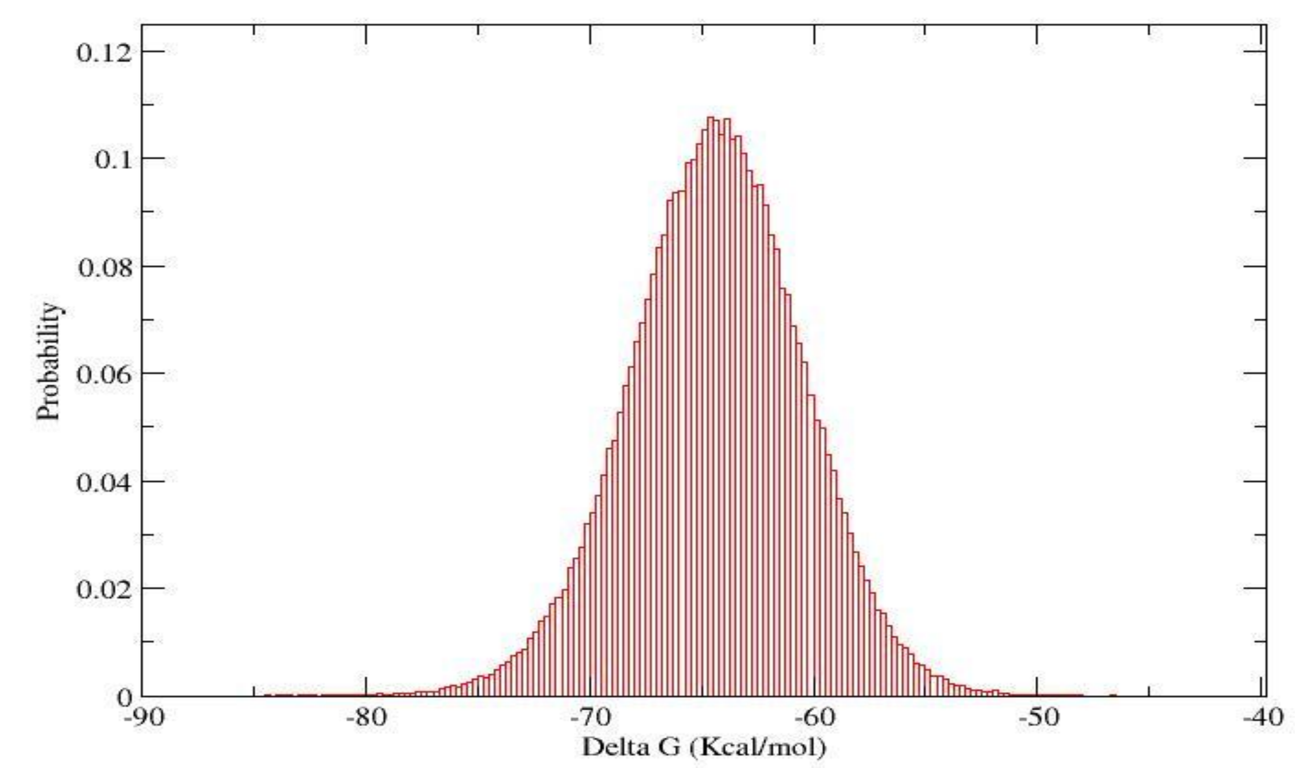
Lifetime Analysis of Water Molecules



Water Distribution in Complex

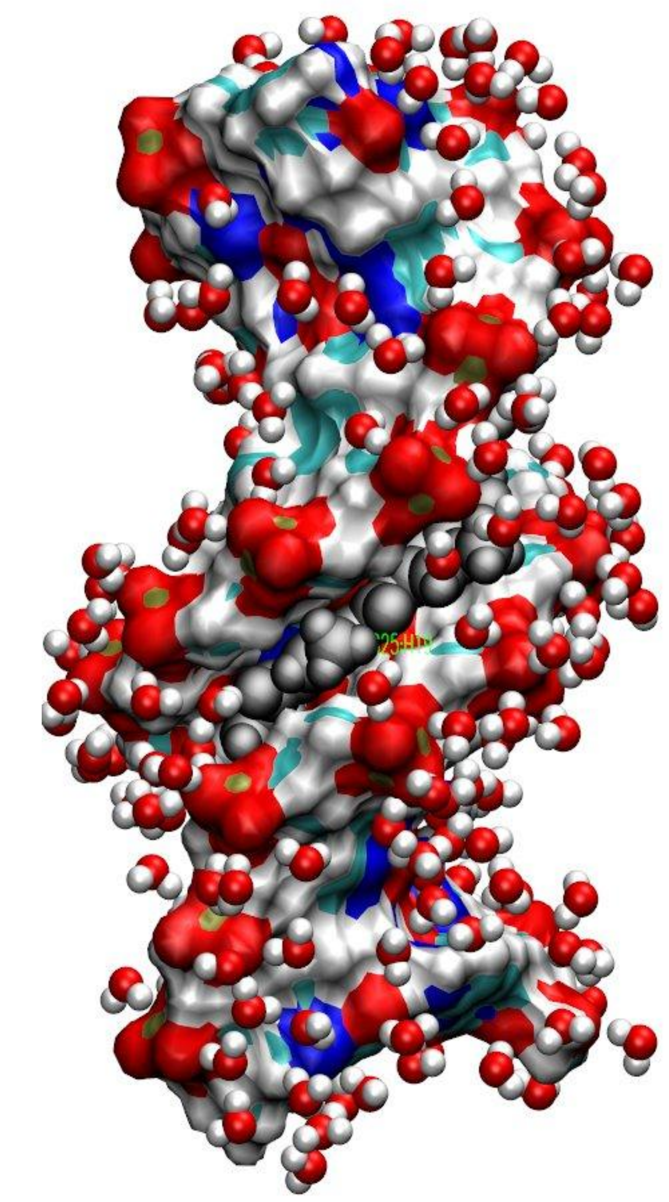


Free Energy Distribution



Results

Hydrated DNA Complex



Conclusion

Key Observations:

- There is affinity for water in minor groove.
- It is evident that some of the water molecules act as a bridge to aid the binding of the DNA to the ligand.
- The lifetime of most water molecules attached to DNA are are short-lived.
  - There is a spine of hydration in the binding pocket where some water molecules exhibit a longer lifetime.
  - Once the ligand is bound to the water, no long lasting binding of the water molecule is evident.

References

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