Laboratory for Theoretical and Computational Molecular Biophysics

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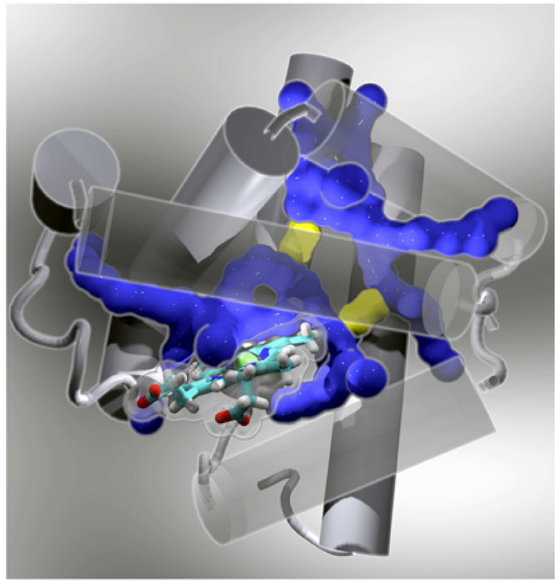
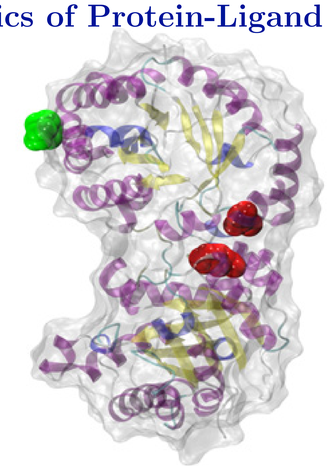
Wormholes in Proteins



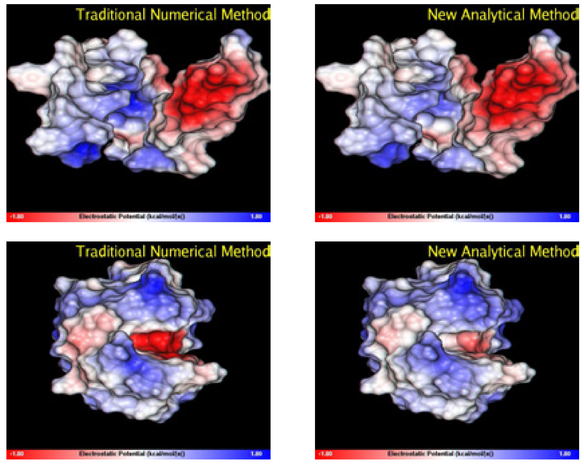
The structure of the small globular protein myoglobin, which is responsible for oxygen storage in cells, was determined more than 50 years ago. But a mystery remained: Exactly what paths does oxygen follow as it moves in and out of myoglobin? And what are the physical mechanism that force oxygen along the pathways? Our team used room-temperature molecular dynamics simulations to provide a complete atomic level picture of ligand migration in myoglobin. We find that there are two discrete dynamical pathways for ligand migration in myoglobin (blue tracks). Trajectory hops between these pathways are limited to two bottleneck regions (yellow tracks). Localized structural fluctuations are the primary physical origin of the simulated migration pathways inside the protein.

Physics of Protein-Ligand Binding



What happens in the protein when it binds a ligand? We know that its structure is likely to change, but will its charge also change? The answer to the question is critical for for many areas of both fundamental and applied sciences, including rational drug design. We use computational tools to address the issue: so far, our conclusions is that ionization state change upon ligand binding occurs in most proteins – an effect that has so far been ignored. The above image shows a protein with a ligand (green spheres) shifting the pKa values of two residues located 37 Å away (red spheres).

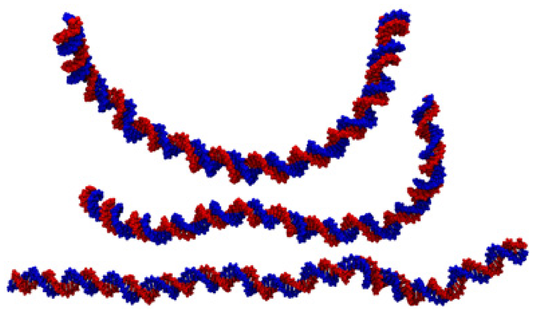
Electrostatic Potential for Macromolecules



Electrostatic interactions are the dominant long-range interactions in biomolecular systems. These need to be computed accurately and quickly for many biologically motivated problems including protein folding. We are developing an analytic approach that is several times faster than the numerical approaches while retaining most of their accuracy. The key is to use the exact solutions of the Poisson-Boltzmann equation for simple geometries, i.e. a sphere, to gain insights into the rigorous physics of the electrostatic interactions in realistic biomolecular systems.

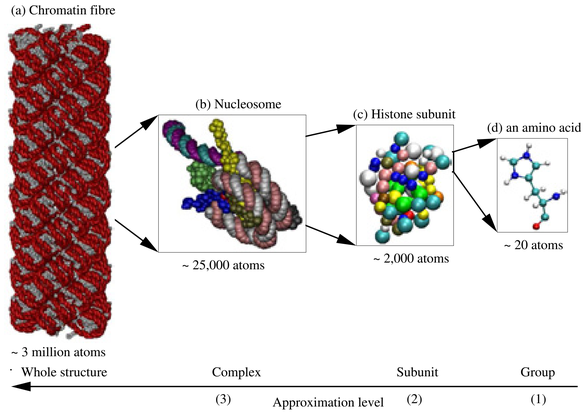
As a test of the scalability of our method, we calculated the electrostatic potential at the surface of a tobacco ringspot virus in an all-atom model (∼500,000 atoms) on a desktop PC – something that would require a multi-node supercomputer to calculate using the numerical solvers.

How Flexible is the DNA?



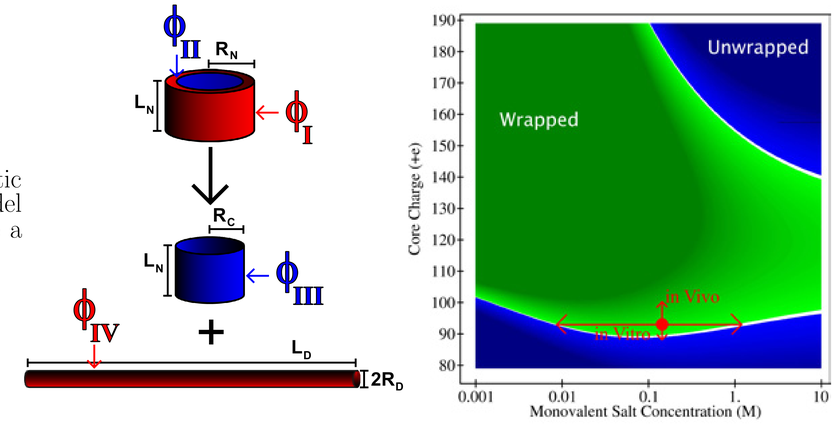
Most of the DNA found in biological systems is very tightly bent. And while the physics of weak bending of this most important polymer in the Hook's law regime is well-understood, what happens to the DNA when it bends sharply is still unclear. We are using coarse-grained models of the double-helix along with simulations to address the issue..

Novel Techniques for Molecular Modeling



"... everything that living things do can be understood in terms of the jiggling and wiggling of atoms," Richard Feynman. Molecular dynamics can be used to simulate the "jiggling and wiggling" of atoms so we can "understand how living things work". We have developed a novel method (based on the natural partitioning of biomolecules) to speed up computation of long-range interactions that is simple and accurate. Using this method and Virginia Tech System X supercomputer, we hope to extend the size and duration of such simulations beyond anything achieved before, such as the folding of medium to large proteins and microsecond timescale simulation of very large structures.

Physics of DNA Compaction



The exact mechanisms involved in wrapping and unwrapping the DNA of the Nucleosome, which is vital for many cellular functions, are not fully known. Experiments have explored many physical parameters that affect the stability of the Nucleosome; however, there are some aspects of the stability that still elude experiments. We developed a two-state model of the wrapping and unwrapping of the DNA that is fully consistent with the available experimental evidence. Our model suggests that controlled changes to the charge of the system is one mechanism the cell utilizes to control the state of the nucleosome *in vivo*.

For more information about research opportunities, please contact Dr. Alexey Onufriev: alexey"at"cs.vt.edu.