How carcinogenic chemicals slip past DNA repair mechanisms
Transferri ng data to/from the clusters
Transferri ng data to/from Prince cluster using Globus
Submittin g jobs with sbatch
Available software
Licensed Software Available on the HPC Cluster
Building Software
Slurm Tutorial
Tutorials
FAQs
Scratch Area Cleanup
Programming for Biologists
Acknowle dge Statemen t
Research Gallery
HPC People
The B rookly n Res earch Cluste r provid es flexibl e comp uting, includi ng for NYU Tando n's Visuali zation, Imag i ng, and Data Analyt ics resear ch center.

* An app that transl ates sign langu age into spoke n Englis h using Brookl yn Res earch Cluste r Platfor m.
• An Event-Driven Model for Estimation of Phase-Amplitude Coupling at Time Scales of Cognitive Phenomena

• Drug design for treatment of heart attack and stroke - How the hSCA N-1 enzyme is activated

• How carcinogenic chemicals slip past DNA repair mechanisms

• Seeing below the resolution of MRI

• The link between Atlantic Ocean warming and Antarctic climate change
The Broyde Laboratory is concerned with determining how DNA lesions, including some that are derived from environmental chemical pollutants present in automobile exhaust, tobacco smoke, and broiled meats, can cause mutations that initiate cancer if they are not repaired. These types of pollutants are multi-ringed chemical compounds, such as the widely-studied benzo[a]pyrene, that are activated in the body so that they can attack our DNA and link to it. The repair mechanism that is responsible for excising these types of DNA damage is termed nucleotide excision repair (NER). The NER machinery operates through recognition of the lesion by a specific human protein known as XPC that detects destabilizing DNA damage. A complex of additional proteins is then assembled, which cut out a section of the DNA strand containing the damage and then restore the correct DNA sequence. Remarkably, the number and arrangement of the rings in the chemicals determine how well the NER process operates, with differences that vary over many orders of magnitude, and the origin of this phenomenon is not understood. Our work is elucidating the factors that are responsible for the differential repair rates. Lesions that are not repaired are the most harmful ones as they survive to be mutagenic, and identifying them for remediation through a combination of computational and experimental approaches is an overall goal.

We work closely with our collaborator Professor Nicholas E. Geacintov in the Chemistry Department, whose laboratory performs experimental investigations of NER for various lesions with differing repair susceptibilities using human HeLa cell extracts. These data provide benchmarks in our simulations of the structural, dynamic and energetic properties of the damaged DNA. We utilize molecular dynamics simulations employing the AMBER suite of programs on the NYU ITS HPC cluster. These resources are essential for efficiently obtaining, storing and analyzing the data from the long-timeframe simulations of large systems that are the current state-of-the-art. Because of the availability of the HPC resources to all postdoctoral researchers and graduate students in our group, we are able to carry out simultaneously a number of different projects that has resulted in 9 peer-reviewed publications in 2012-2013.

As an example, a recent publication in the journal Biochemistry (Mu, et al, 2013 Aug 20;52(33):5517-21) explained an intriguing data set obtained in the Geacintov Laboratory. They found that the identical bulky benzo[a]pyrene-derived lesion attached to the DNA base guanine could be excised or overlooked by the NER machinery depending on whether the base opposite the guanine was its normal partner cytosine or a mismatched adenine. Our simulations showed that the damaged DNA was dynamically destabilized with normal partner, while the mismatched adenine locally stabilized the duplex, preventing the lesion recognition protein from detecting the damage. This interpretation fits in well with our recent simulations indicating that have indicated that lesions which locally stabilize duplex DNA resist repair, while destabilizing ones are repaired. This work required simulating 16 systems whose size was ~ 12,000 atoms each including counterions and aqueous solvent for ~ 400 ns. The coordinates were collected every 1 ps, resulting in 64 GB of data that was accumulated over about 4 months. We analyzed how the structures evolved dynamically in time and the energetic interactions within each of the damaged DNAs, to interpret the experimental functional studies on structural, energetic and dynamic grounds.

In this first video, we see that the small normal partner C in the damaged DNA is dynamically unstable, which could trigger Nucleotide Excision Repair. Contrast the second video, in which the damaged G-base has mis-paired with an A-base rather than it's normal C-base partner. In this case, the larger partner A is stable, which could leave the lesion undetected.

Currently and in future work, we are investigating ER of lesioned-DNA when associated with histone proteins in the nucleosome, the next higher order of DNA packaging in the cell. The nucleosome system entails ~150,000 atoms when solvated and neutralized by counterions.

The HPC resources have enabled our group to carry out a series of computational projects that provide structural understanding of experimental data and thereby explain biological function. These published studies are featured at http://broyde.nyu.edu/.