GA

DNA "BREATHING" CAPTURED IN ALL-ATOM DETAIL

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EXECUTIVE SUMMARY

Meters of human DNA are packaged with proteins into nucleosomes and ultimately form chromosomes within the micron-diameter nucleus. This genetic material must be unpackaged and the nucleosomes disrupted in order for essential biological processes such as transcription to occur. Transcription is the process by which the information in a strand of DNA is copied into a new molecule of messenger RNA. Cell stores its genetic material in the nucleus.

Through simulations performed on the Blue Waters supercomputer, we observed in atomistic detail how DNA "breathes" by unwrapping and rewrapping an individual nucleosome. This is of particular interest in medical research because the misregulation of nucleosome and chromosome dynamics is implicated in a number of diseases such as Coffin–Siris and Rett syndromes and can lead to the development of various types of cancer.

RESEARCH CHALLENGE

It is well-known that DNA provides the code for all living things. Evidence is now mounting that patterns in DNA sequencing as well as and in minor chemical modifications provide a structural roadmap for the global organization of genetic material within the nucleus and for determining how genes are expressed throughout the cell lifecycle. Single-molecule *in vitro* experiments [1] and bioinformatics analysis [2] have identified specific DNA motifs

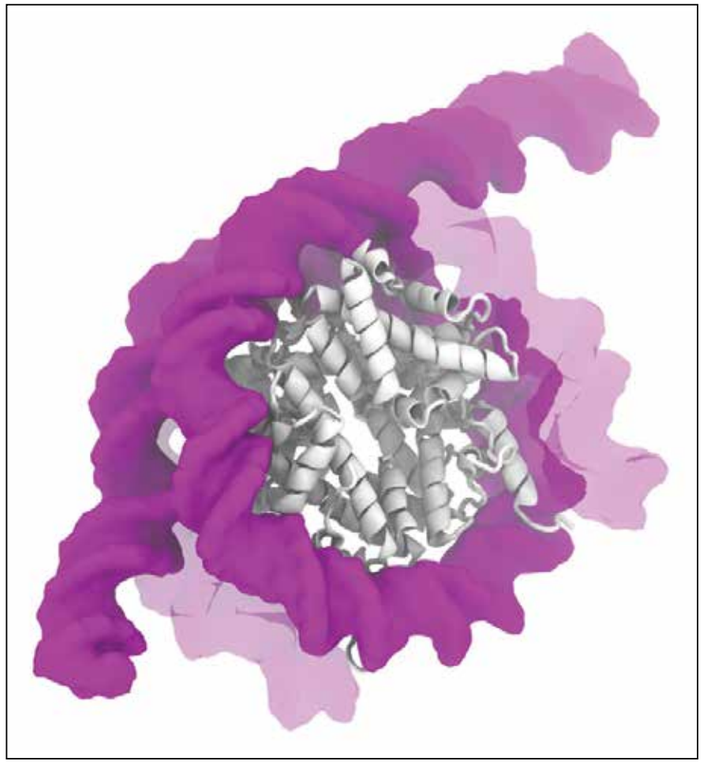

Figure 1: A nucleosome particle before and after undergoing spontaneous unwrapping. White and purple highlight the histone protein core and DNA, respectively. DNA's initial conformation is semitransparent; its final one is opaque.

and global features as important determinants of nucleosome stability. Through simulations performed on the Blue Waters supercomputer, we have observed, in atomistic detail, spontaneous and reversible unraveling of nucleosome particles, also known as "DNA breathing." Reaching the timescale and statistics needed to characterize this process with confidence presented a significant challenge.

Arrays of nucleosomes form chromatin fibers, which ultimately organize into chromosomes. Our project is important for the understanding of how fundamental biological processes occur, and it is medically relevant as well. The improper occurrence of nucleosome and chromatin unraveling in the cell can lead to several human diseases, including various forms of cancer, Coffin–Siris and Rett syndromes, and alpha thalassemia [3].

METHODS & CODES

We performed explicit-solvent all-atom molecular dynamics (MD) simulations with the latest version of NAMD2 of a set of individual nucleosomes in varying ionic conditions, DNA sequences, and DNA length surrounding the protein core [4,5]. We then confirmed a stepwise mechanism of nucleosomal DNA detachment by performing an additional set of simulations, shifting several identified protein residues away from the DNA and observing enhanced unwrapping.

RESULTS & IMPACT

We observed spontaneous and reversible detachment of the outer stretches of nucleosomal DNA in a set of all-atom molecular dynamics simulations performed at a condition of high ionic strength. The likelihood of observing such DNA breathing events was found to correlate with the coarse-grained (CG) content of the nucleosomal DNA, with higher CG content being associated with more stable nucleosomes. In contrast, the inner stretches of nucleosomal DNA were found to be more stably associated with the histone core by a greater abundance of nonspecific DNA–protein contacts. Analysis of the simulation trajectories revealed the stepwise character of the DNA detachment process orchestrated by the motion of several conserved histone residues.

The sensitivity of unwrapping to nucleosomal DNA CG content we observed may be enhanced when forces or torques are applied to the DNA endpoints *in vivo*. Furthermore, the mutation or chemical modification of specific highly conserved histone residues identified in this study as forming important interactions with DNA could increase the rate of unwrapping. Along with bioinformatics [2] and experimental [6] studies, our results support the possibility that AT (adenine–thymine)-rich segments of DNA form less stable nucleosomes and may signal the start of transcription

WHY BLUE WATERS

Explicit-solvent all-atom MD simulation is needed to examine the fine details of DNA–histone interactions and to accurately characterize the surrounding ionic environment. Because of the long time scale needed to observe spontaneous detachment, such MD simulations are computationally demanding. The large number of XK nodes on Blue Waters, with graphics processing unit accelerators connected by the fast Gemini interconnect, makes it one of the best publicly available systems for performing simulations studying DNA–protein and DNA–DNA interactions in atomistic detail. Over the past several years, our group has used Blue Waters to carry out a set of landmark simulations in the area of nucleosome and DNA dynamics, bringing high-performance simulations to the forefront of this research field.