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RESOLVING THE STRUCTURE OF BACTERIOPHAGE HK97 WITH ATOMISTIC RESOLUTION

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EXECUTIVE SUMMARY

Viruses are omnipresent, diverse, and potentially lethal biological systems that our bodies encounter every day in copious quantities without us taking notice. The essence of each virus is its genome, a biological program written using letters of the genetic alphabet. The genome is protected from the outside world by a protein shell (a viral capsid) until the conditions are met for viral invasion, at which point the genome is released from its protective shell into a host cell, initiating a new cycle of infection. The ongoing adaptation of viruses to antiviral drugs currently in use necessitates development of the next generation of drugs that target viruses from a physical standpoint. By carrying out large-scale molecular dynamics simulations on Blue Waters, the research team has constructed the first atomically resolved model of a complete virus particle, including the 3D structure of its genome, an untapped resource of potential drug targets. The modeling approach demonstrated by this proof-of-principle simulation may be applied in the future to develop new antiviral drugs.

RESEARCH CHALLENGE

Atomistic structures of protein capsids have been resolved for many viral species, but the structural organization of their genomes still remains largely unclear. One such viral species is the HK97 bacteriophage, for which experiments have characterized the packaging mechanism and resolved its protein capsid with atomistic resolution [1]. Previous cryogenic electron microscopy and Small-Angle X-Ray Scattering experiments [2] have not yet elucidated the precise organization of the genome in individual virus particles. Previous computational efforts have addressed the dynamic behavior of the capsid [3,4], matrix [1], or outer envelope, but the structural assignment of nucleic acids inside viral capsids has not been explored comprehensively. Using Blue Waters, the research team has met the challenge of reconstructing the 3D structure of the HK97 bacteriophage genome, a double-stranded DNA molecule containing 39,732 base pairs.

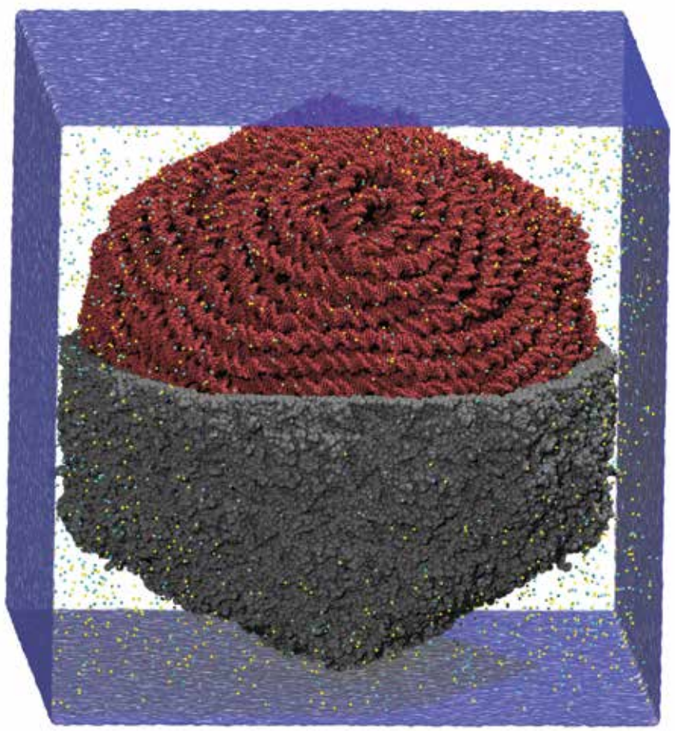

Figure 1: An all-atom model of a fully packaged HK97 bacteriophage. The DNA genome of the virus is shown in red, the icosahedral protein capsid in grey, water is shown as a blue semitransparent surface, and the ions are shown as colored spheres.

METHODS & CODES

To obtain microscopically correct structures of DNA inside viral capsids, the researchers employed a multiscale approach whereby the results of computationally inexpensive coarse-grained (*i.e.*, with reduced representation) molecular dynamics (MD) simulations were used to set up initial conditions for fully atomistic all-atom simulations of a virus particle loaded with DNA. With four base pairs of DNA represented as one coarse-grained particle, the 39,732-base-pair-long genome was packaged into a grid-based implicit protein capsid through a narrow portal that exerted a physiological packaging force [5]. Starting from the final packaged conformation, the team obtained an atomistic model of the genome from a series of simulations gradually increasing in resolution. Subsequently, water and ions were added to mimic conditions at DNA densities typical of pressurized viruses such as HK97 [6], yielding a fully atomistic model of the HK97 genome submerged in explicit solvent. The DNA structure was then placed inside the all-atom capsid through a set of all-atom simulations carried out in the presence of a confining potential. The final atomistic system was comprised of roughly 27 million atoms. All MD simulations were carried out using NAMD [7].

RESULTS & IMPACT

The research team validated the results of the coarse-grained simulations by comparing experimentally determined internal pressure inside a viral capsid [8] to the pressure exerted by the DNA genome on the confining potential. Small-Angle X-ray Scattering profiles generated from the atomic model of the genome were found to be in quantitative agreement with experimental data [2]. The team performed further simulations to characterize the effect of different packaging mechanisms and to determine the contribution of bending stress (attributed to confining a stiff polymer, DNA) to the internal pressure. For quantifying the geometry of the DNA inside the capsid, the scientists evaluated a toroidal order parameter that indicated a preferential organization of the packaged DNA about the axis along which the DNA was packaged into the capsid. Overall, the team found the outcome of the simulations matched experimental data extremely well, which validates the obtained structures of the HK97 genome. The simulation protocol developed through this project can now be applied to other viruses to predict their genomic structures, offering exciting avenues for designing new antiviral drugs.

WHY BLUE WATERS

Explicit-solvent all-atom MD simulation is needed to examine the fine details of DNA–capsid interactions and to accurately characterize the surrounding ionic environment. Given the large system of approximately 27 million atoms, such MD simulations are computationally demanding. The Blue Waters petascale system is one of only a few supercomputers in the world with the computational power sufficient to carry out fully atomistic MD simulations of viral particles containing packaged genomes. The large number of GPU-accelerated XK nodes and fast Gemini interconnect of Blue Waters make it one of the best publicly available systems for performing large-scale MD simulations of virus particles.