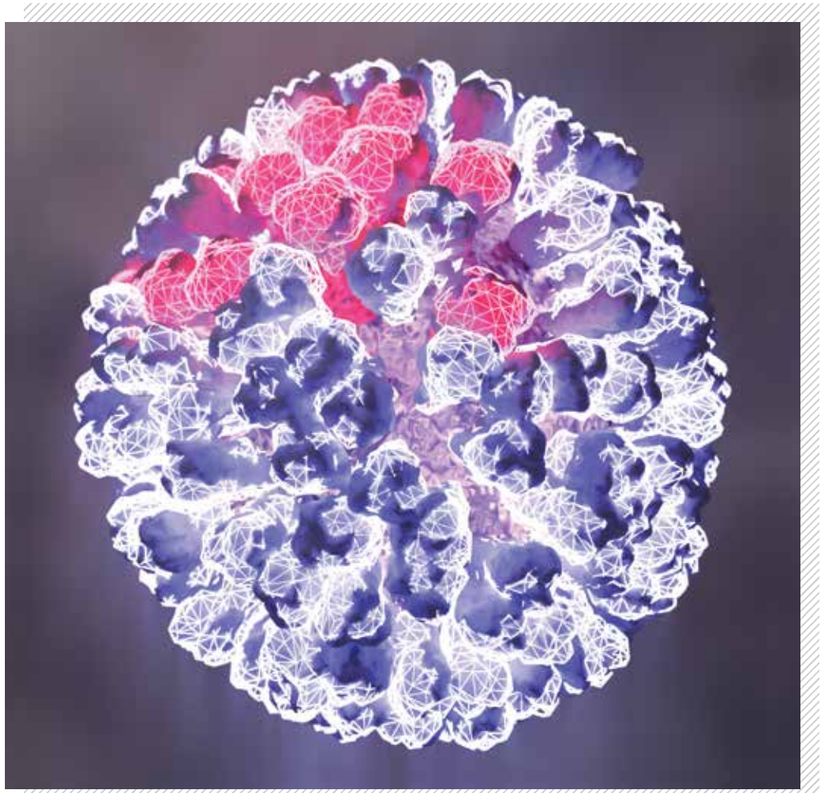

FIGURE 3: Surface-coat dynamics: the first and last frames of the whole-virion simulation. Neuraminidase and hemagglutinin are shown in red and blue, respectively. The glycoprotein conformations of the first and last frames are shown in solid and glowing-mesh representations, respectively. As expected for a simulation of this duration, glycoprotein diffusion through the lipid bilayer was limited. However, the atomic-resolution motions of individual glycoproteins were substantial because they were sampled over both simulated time and space, thanks to the multiple copies of each glycoprotein scattered across the model surface. Credit: Jacob D. Durrant.

motions of these residues permit conformations that have additional druggable hotspots beyond those of the sialic acid-binding and 150-loop regions. Furthermore, we are currently building Markov state models to explore the pharmacologically relevant kinetics of 150-loop opening and closing, and the neuraminidase conformations sampled by this large-scale simulation may prove useful for future virtual-screening efforts as well.

We are similarly analyzing the many hemagglutinin molecules included in the whole-virion-coat simulations. We are hopeful that Brownian dynamics simulations in the context of the whole viral particle will provide useful insights into the mechanism of broadly neutralizing antibodies.

The M2 channels of our model also sample many conformations, ranging from open to closed. We have characterized the volume distributions of these channels and hope to build a Markov state model to describe the opening/closing kinetics of this crucial surface-coat component. The many M2-channel conformations sampled may also prove useful in future small-molecule virtual screens.

WHY BLUE WATERS

Blue Waters has been critical for this project. To our knowledge, a molecular dynamics simulation on so grand a scale has **never before** been attempted. Very few supercomputers are capable of the petascale performance required. **Without Blue Waters, the current work would be impossible.**

These simulations are providing important information about the surface motions and electric fields that surround the viral particle. These "dynamics" and "electrostatics" govern not only the infection process, but also drug and vaccine/antibody binding.

MOLECULAR DYNAMICS OF SELF-ASSEMBLED DNA SYSTEMS

Allocation: Blue Waters Professor/240 Knh
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EXECUTIVE SUMMARY

DNA nanotechnology utilizes self-assembly for the high-throughput construction of sub-micron-size objects with nanometer precision. In comparison to conventional nanofabrication approaches, the DNA origami method is relatively low cost, easy to use, and has an infinite number of possible applications. Using Blue Waters, we have explored the ability of DNA nanostructures to function as membrane channels, carried out a **landmark simulation** of a DNA origami sculpture, and characterized the mechanical properties and ionic conductivity of DNA brick structures. The results of our simulations have contributed to the development of a web server for prediction of DNA origami structures and a web tool for designing nanostructures using the DNA brick methods.

INTRODUCTION

DNA origami is an experimental technique that allows folding of a long DNA molecule into an arbitrary three-dimensional shape [1]. Over the past ten years, the DNA origami method has **advanced** to encompass self-assembly of complex 3D objects with sub-nanometer precision including static structures [2], as well as objects that perform active functions [3].

Predictive computational modeling of DNA origami is an attractive alternative to experimental characterization of such self-assembled objects. Currently, the most accurate computational method is all-atom molecular dynamics (MD). In 2013, we reported the **first** MD study of several model DNA origami systems [4]. Last year, we explored the possibility of using DNA origami in nanopore sensing applications [5]. Our most recent work includes a study of a DNA-based channel embedded in a lipid bilayer, a **landmark** simulation of a DNA sculpture that demonstrates the predictive power of the MD method, and a detailed comparison between DNA origami and an alternative self-assembly approach known as DNA bricks.

METHODS & RESULTS

In living cells, membrane protein channels control the transport of molecules across the cell membrane. Recently, several experimental groups demonstrated assembly and insertion of DNA channels into lipid bilayer membranes [6]. A typical DNA channel is made by arranging several parallel DNA double helices to form a polygon. The central cavity of the polygon is the transmembrane pore. Using

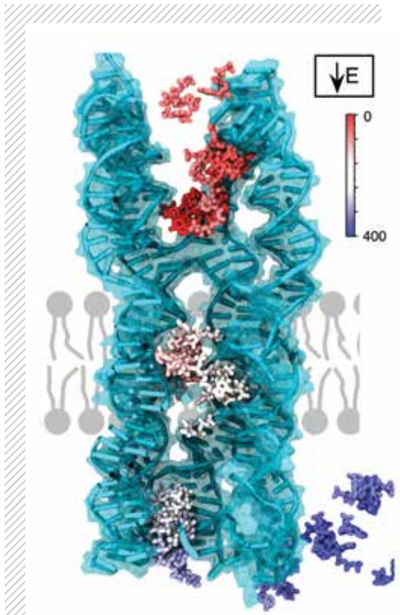

FIGURE 1: A time-lapse illustration of the MD trajectory showing an ATP molecule passing from one side of the DNA channel to the other. The color indicates the progress of the simulation using the red (beginning)–white–blue (end) scheme. Because of the electro-osmotic flow, the ATP molecule moves in the direction of the electric field, opposite to the direction prescribed by its negative charge.

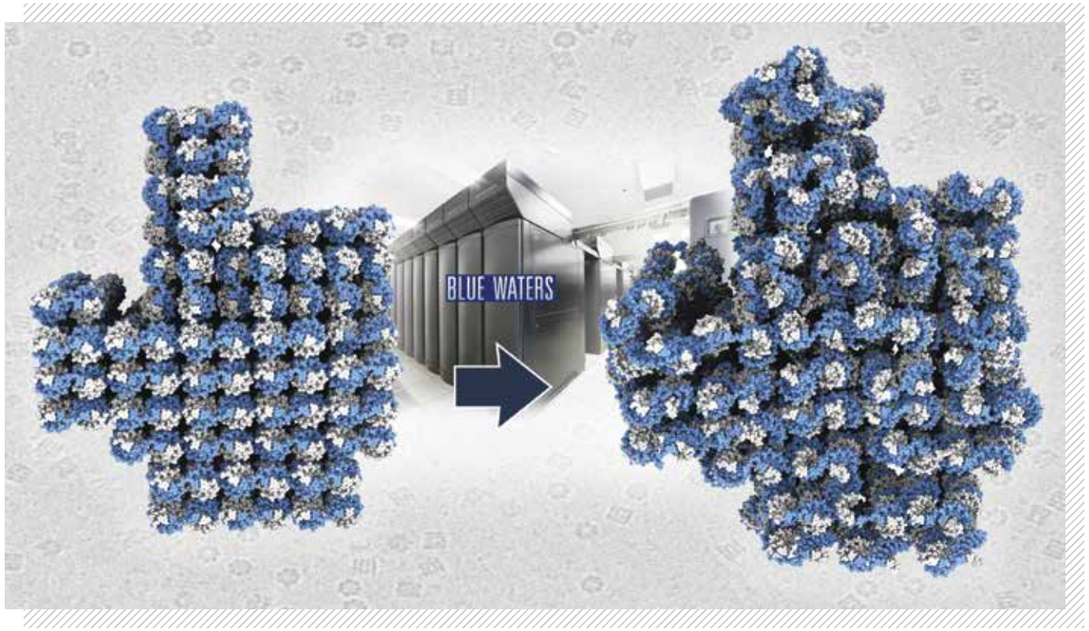

FIGURE 2: Molecular dynamics simulation predicts the solution structure of a 5 megadalton DNA origami object. The background image was adapted from "CryoEM GroEL" by Vossman under a Creative Commons license.

Blue Waters, we carried out the **first** all-atom MD study of the DNA membrane channels. We showed that, while overall remaining stable, the local structure of the channels undergoes considerable fluctuations, departing from the idealized design. The transmembrane ionic current flows both through the central pore of the channel as well as along the DNA walls and through the gaps in the DNA structure. Surprisingly, we found the conductance of DNA channels to depend on the membrane tension, making them potentially suitable for force-sensing applications. Finally, we showed that electro-osmosis governs the transport of drug-like molecules through the DNA channels.

To test the accuracy of our all-atom MD method, we carried out a **landmark** simulation of a DNA origami sculpture whose 3D structure was determined through cryo-electron microscopy [7]. Over the course of the all-atom explicit solvent simulation, the structure was observed to depart from its ideal design, changing its shape toward the experimentally determined structure. Next, we showed that elastic network-guided simulations performed without solvent could yield similarly accurate structural models at a **fraction** of the computational cost, making them suitable for **prototyping** and validation of self-assembled DNA nanostructures. A web-server implementation of our elastic network-guided methods has made it available to a **broader** scientific community.

In contrast to DNA origami, the DNA bricks [8] method produces custom three-dimensional objects using only short DNA fragments. As a result of their design, the assembled DNA brick structures have fewer inter-helical connections than equivalent DNA origami structures. Using the MD method, we directly compared the structure, mechanical properties and ionic conductivity of DNA brick and DNA origami structures. In comparison to equivalent DNA origami structures, the DNA brick structures were found to be less rigid and less dense. Subject to an external electric field, a DNA brick plate was found to be more permeable to ions than an equivalent DNA origami plate because of its lower density and larger cross-section area. Based on the results of this study, we have developed a web tool that considerably **simplifies** the design of DNA brick structures.

WHY BLUE WATERS

Explicit solvent all-atom MD simulation is the only computational method that can treat DNA origami objects enhanced by non-standard functional groups and characterize their transport properties. Because of the size of the DNA origami structures, 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 DNA origami simulations.

NEXT GENERATION WORK

Using the next-generation Track-1 system, we hope to apply our all-atom MD method to dynamic and externally actuated DNA nanostructures, exploring their applications in nanoscale engineering.

PUBLICATIONS AND DATA SETS

Yoo, J., and A. Aksimentiev, Molecular dynamics of membrane-spanning DNA channels: conductance mechanism, electro-osmotic transport, and mechanical gating. *J. Phys. Chem. Lett.*, 6:23 (2015), pp. 4680—4687.

Maffeo, C., J. Yoo, and A. Aksimentiev, De Novo Reconstruction of DNA Origami Structures through atomistic molecular dynamics simulation. *Nucleic Acids Res.*, 44:7 (2016), pp. 3013—3019.

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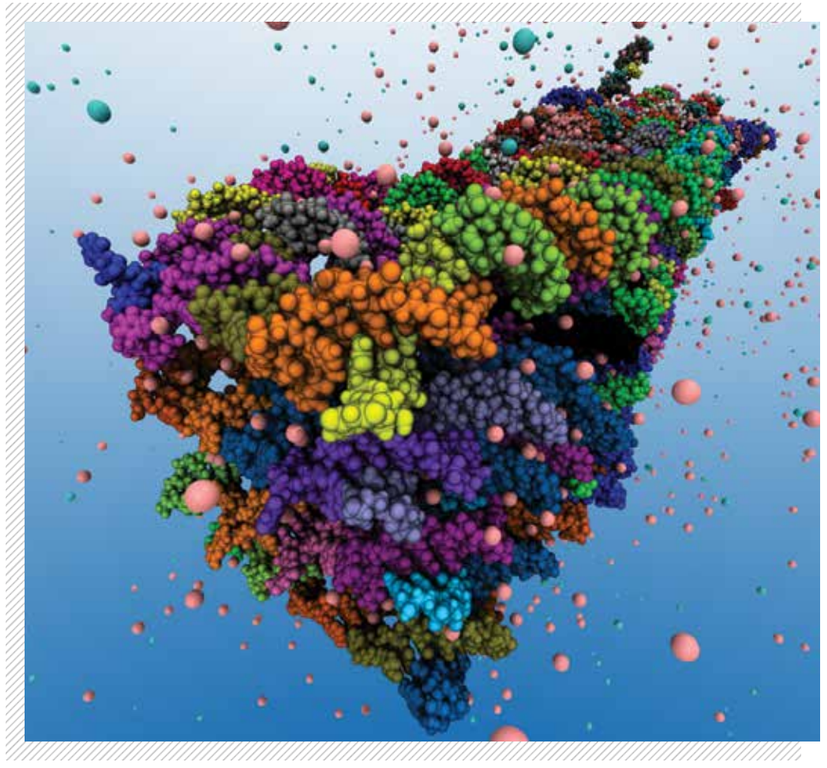

FIGURE 3: The microscopic conformation of a DNA brick structure at the end of a molecular dynamics simulation. Individual DNA strands are shown in distinct colors; magnesium and chloride ions are shown as green and pink spheres, respectively, water is not shown.