

Molecular Dynamics of DNA Origami Nanostructures

*Annual Report for
Blue Waters Allocation*

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Executive summary

DNA origami is a rapidly emerging field that enables high-throughput construction of DNA-based sub-micron-size nanomachines with nanoscale accuracy. Similar to the computer-aided design (CAD) of macroscopic machines (*e.g.*, airplanes), our group is pioneering CAD for nanoscale machines made of DNA origami. To achieve accuracy high enough to predict both chemical and mechanical properties of DNA origami objects, we employ all-atom molecular dynamics (MD) simulations. The Blue Waters supercomputer is essential for achieving this goal due to the sheer size of the DNA origami objects and computationally demanding nature of the MD technique. In this report, we present our achievements using the JQ5 allocation for the year of 2016, including characterizing biomimetic DNA-origami channels, and the development of a simulation protocol for *de novo* DNA-origami structure prediction. We request 240,000 node hours for 2017 to expand our investigation of biomimetic ion channels and to design and characterize DNA-origami propellers with rotational motion controlled by an operator.

Confidentiality

This report includes confidential or restricted information. Please share its contents only with the Blue Waters team and the National Science Foundation.

Description of research activities and results

Key challenges

Self-assembly of DNA into complex three-dimensional objects has emerged as a new paradigm for practical nanotechnology [1, 2]. Among the methods that have been put forward that utilize self-assembly of DNA [2], DNA origami [3] stands out due to its conceptual simplicity and infinite range of possible applications [1, 2]. The basic principle of DNA origami is the programmed folding of a long (thousands of nucleotides) DNA strand into a custom two- or three-dimensional (3D) shape, guided by specially designed short oligonucleotides [3]. Since its first demonstration in 2006, the DNA origami method has advanced to encompass self-assembly of complex 3D objects with sub-nanometer precision [4] including static structures [1, 2, 5, 6] as well as objects that perform active functions [7, 8, 9]. Recent methodological advances [10] have made practical applications [10, 11, 12, 13] of DNA origami feasible.

Experimental characterization of DNA origami is essential for accurate design, but has been limited to rather qualitative techniques such as atomic force spectroscopy [7], small-angle X-ray scattering [7], and transmission electron microscopy (TEM) [4, 5]. Recently, super-resolution optical imaging [9], fluorescence resonance energy transfer (FRET) [12, 14] and magnetic tweezers [15] have been applied to DNA origami objects to infer information about their *in situ* structure and dynamics. The only atomic-level model of DNA origami *in situ* has been derived from cryo-electron microscopy (cryo-EM) [16], which revealed considerable deviations from the idealized design. The two fundamental challenges of the DNA origami field are (1) design of complex DNA origami objects that can form through self-assembly of relatively simple building blocks and (2) programming complex motion of such objects for specific functional purpose, for example, gating ionic current across biological membrane or delivery of a specific drug to a specific cell type. Our group uses computational approaches to advance methodology of programming DNA self-assembly and, in collaboration with leading experimental groups, develop novel DNA origami designs that function as desired.

Why it Matters

Predictive computational modeling of DNA origami objects is an important complement to experimental characterization procedures, which are expensive and time-consuming. It is already common practice for experimentalists to use the simplest available computational description of DNA—a continuum-based model—to validate their designs [17, 18]. In these models, DNA double helices are approximated as uniform cylinders with material properties set to reproduce the average bending rigidity of DNA helices. Unfortunately, this level of

description permits only semi-quantitative estimation of the overall structure [18]. There are also several coarse-grained models of DNA that are more sophisticated than continuum-based models and can represent the double-helical structure of DNA [19, 20, 21]. In a typical coarse-grained DNA model, each nucleotide is represented by 2–3 interaction beads. When the interaction parameters are properly optimized, such models have the potential to make realistic predictions. However, these models are new and their accuracy is not well-established.

Currently, the most accurate computational method that can realize our goal—prediction of structure and function of DNA origami objects—is the all-atom molecular dynamics (MD) method. In 2013, we reported the first MD simulations of several model DNA origami systems [22]. Subsequently, we have shown that the all-atom MD method can be used to predict the structure of realistic DNA origami objects [23] and has predictive power [24, 25, 26]. Our group continues to be a pioneer in the field of DNA origami systems, leading the computational exploration of self-assembled systems for applications in nanotechnology and medicine.

Why Blue Waters

DNA origami nanostructures can be larger than 30 nm on each side [7, 11, 16]. Although rough estimation of their structures can be done using simpler models [17], accurate structure prediction requires an all-atom approach [22]. Furthermore, all-atom MD simulation is the only computational method that can treat DNA origami objects enhanced by non-standard functional groups and characterize the transport phenomena in simulations of DNA origami channels.

Capturing the effect of the surrounding water and ions is necessary to accurately describe the structural fluctuations and electrical properties of DNA origami objects. Explicit solvent all-atom MD simulations of such large-scale systems require an amount of computational resources that can only be afforded by a supercomputer on the scale of Blue Waters. Over the past several years, our group used Blue Waters to carry out a set of landmark simulations in the area of DNA nanotechnology, bringing high-performance simulations to the forefront of this research field.

Accomplishments

In 2016, we used Blue Waters to study a range of exemplary DNA origami systems leading to the publication of four manuscripts [23, 25, 26, 27]. In collaboration with the experimental Keyser lab (U. Cambridge), we characterized the structure and transport properties of two biomimetic DNA origami channels: the largest [26] and the smallest [25] DNA channels ever made. Building on our landmark simulation of the DNA origami sculpture [23], we developed ENRG MD, a webserver for *de novo* DNA origami structure prediction with similar accuracy as costly state-of-the-art high-resolution cryo-electron microscopy (cryo-EM). We used a small fraction of the allocation for simulations of other DNA systems, which resulted in three additional publications [28, 29, 30]. The outcome of Blue Waters simulations were featured in ten invited talks and three poster presentations at the major DNA nanotechnology meetings.

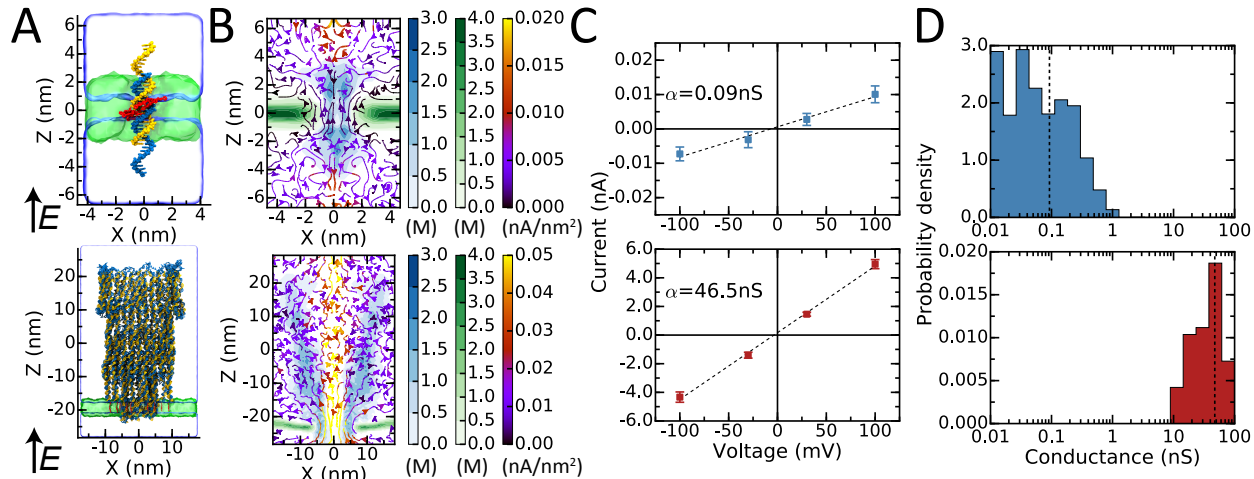


Figure 1: **Biomimetic DNA membrane channels.** (A) All-atom models of the DNA duplex [25] (top) and DNA porin [26] (bottom). The DNA channels (blue and yellow) with cholesterol tags (red) embedded in a lipid membrane (green) are shown prior to equilibration. The system contains magnesium ions in an amount sufficient to neutralize the electrical charge of the DNA porin and 1 M KCl solution (not shown). The total system sizes are $\sim 140,000$ atoms (top) and $\sim 8,000,000$ atoms (bottom). The electric field, E , in the direction of positive transmembrane bias is indicated. (B) Steady-state local densities of lipid chain (carbon atoms, green), DNA (phosphorus atoms, blue), and ionic current (streamlines) in the corresponding DNA duplex (top) and DNA porin (bottom) simulations. The arrows indicate the direction of the local ionic current flux and the colors show the flux’s magnitude. (C) The simulated current–voltage characteristics in the DNA duplex (top) and DNA porin (bottom). The dashed lines represent linear fits. (D) All-point conductance histograms with logarithmic binning in the DNA duplex (top) and DNA porin (bottom). The dashed lines indicate the mean conductance values.

A1. Biomimetic DNA channels of small and large conductances.

Membrane protein channels involved in cellular signal transduction are fascinating biological sensors with high selectivity and efficiency. Recently, it was demonstrated that DNA origami-based channels could mimic the ionic conductance and transport properties of membrane protein channels [11, 31, 32, 33, 34, 35]. A typical DNA channel is made by arranging a few parallel DNA double helices as a polygon. The central cavity of the polygon is the transmembrane pore. The inner diameter of the DNA channel depends on the arrangement and number of DNA double helices. To stabilize the DNA channels in a lipid bilayer membrane, the DNA channel has to be “anchored” to the lipid bilayer membrane by means of hydrophobic groups covalently connected to the channel, such as ethylthiolate [31], cholesterol [11, 34, 35] or porphyrin [32, 33]. Until recently, all DNA channel designs featured either four [34] or six [11, 31, 32, 33, 35] parallel DNA double helices arranged as a square or a hexagon, with the inner pore diameter of 1–2.5 nm. In collaboration with the Keyser group (U. Cambridge), we considerably expanded the design space of DNA channels by building and characterizing the smallest and the largest DNA channels ever made.

The smallest DNA channel, Fig. 1A (top), was built using a single DNA duplex. Through all-atom MD simulations, we have shown that a membrane-spanning DNA duplex decorated with six porphyrin-tags can provide an ion pathway across the lipid membrane despite the lack of an internal physical channel. Lipid molecules were found to rearrange around the transmembrane part of the duplex, forming a narrow water-filled passage at its circumference,

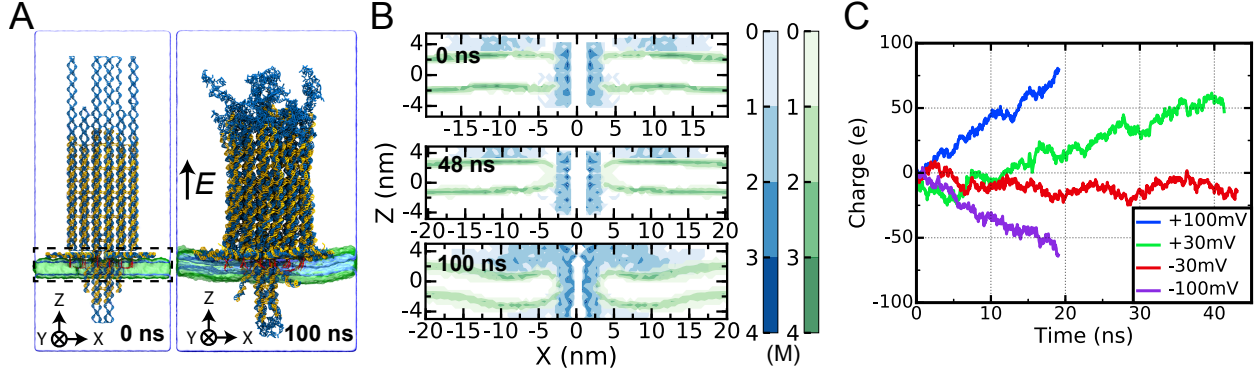


Figure 2: **MD simulation of a large honeycomb-lattice DNA channel.** (A) The idealized [11] (left) and equilibrated (right) structures of the honeycomb-lattice DNA channel. The DNA channel (blue and yellow) with cholesterol tags (red) is embedded in a lipid membrane (green). The system contains magnesium ions in an amount sufficient to neutralize the total electrical charge of the DNA backbone and 1 M KCl solution (not shown). The system contains $\sim 12,000,000$ atoms. The electric field, E , in the direction of positive transmembrane bias is indicated. The dashed box on the left image indicates the region featured in panel B. (B) Snapshots of the local concentration of lipid head group (phosphorus atoms, green) and DNA (phosphorus atoms, blue) during equilibration simulation. (C) The integrated ionic current (in units of elementary charge, e) passing through the DNA channel in MD simulations performed under a transmembrane bias of specified polarity and magnitude.

allowing ions and water molecules to pass through the membrane, Fig. 1B (top). The simulated average conductance of such a channel (~ 0.09 nS) was in excellent agreement with the average experimental value (~ 0.1 nS), Fig. 1C (top). The simulations also characterized the structural fluctuation at the DNA duplex–lipid bilayer interface, providing a microscopic explanation for the variation of the ionic conductance (Fig. 1D) observed both in simulation and experiment. The results of this work were published in *Nano Letters* [25].

A DNA channel of large conductance was designed by anchoring 19 cholesterol tags to a megadalton funnel-shaped DNA origami porin, Fig. 1A (bottom). The conductance of this funnel-shaped channel (~ 46.5 nS) was an order of magnitude larger than of any previous man-made channel, whereas its cross section was similar to that of a nuclear pore complex, Fig. 1C-D (bottom). Consistent with the results of the DNA duplex simulation, the ion current was found to flow through both the central pore of the channel ($\sim 80\%$ of the total current) and along the channel’s walls ($\sim 20\%$ of the total current), Fig. 1B (bottom). Such large membrane-spanning DNA structures can find applications in biosensing and drug delivery systems. The results of this work were published in *ACS Nano* [26].

Following last year’s proposal, we have applied our approach to other previously reported DNA channels, including a 4-helix channel [34], a 6-helix channel [35] and a large honeycomb channel [11]. In addition, we also investigated two unpublished designs, including one 4-helix channel and one 6-helix channel. In all simulations, the equilibrated structure was observed to deviate from its idealized design. The lipid molecules around the transmembrane part of the channels were found to rearrange themselves around the DNA channel to minimize the exposure of the charged group to the hydrophobic environment of the bilayer. The conductance of the channels was found to depend on the size of the pore and the structure of the DNA-lipid interface. One particularly interesting system was the large honeycomb channel, Fig. 2A, which was the first experimentally demonstrated DNA

channel [11]. Upon equilibration, the single-stranded regions at the top and the bottom of the channel formed unstructured loops, Fig. 2A, while a toroidal pore formed at the DNA-lipid interface, Fig. 2B. MD simulations of the channel under applied electric field revealed its asymmetric current-voltage dependence, reflecting the asymmetric shape of the channel. The results of these simulations, along with the planned work (see Section P1) will be described in two manuscripts that are being prepared for publication.

A2. ENRG MD: DNA origami structure prediction made simple.

Characterization of DNA origami structure is essential for accurate design, but has been limited experimentally to low resolution and qualitative techniques such as atomic force spectroscopy [7], small-angle X-ray scattering [7], and transmission electron microscopy (TEM) [4, 5]. In 2012, a high-resolution 3D reconstruction of the “pointer,” a asymmetric DNA origami object [16], was obtained by the Dietz group using cryo-electron microscopy (cryo-EM). Years later, this reconstruction remains the only DNA origami model derived from experiment in atomic detail.

The lack of computational methods for high-resolution DNA origami structure prediction prompted us to explore how MD simulations could be used for this purpose. As we reported previously, *de novo* all-atom MD simulations of the pointer provided structural agreement with the cryo-EM reconstruction to within the reported resolution of the experiment [23]. We were then able to develop a simulation protocol, called elastic network of restraints-guided (ENRG) MD, that predicted similar structures to our all-atom MD simulations at a small fraction of the computational cost.

In the past year, we developed a web service to simplify the ENRG MD procedure, Fig. 3 A. Using our service, an experimentalist can simply upload their caDNAno design files to obtain an archive containing the files needed for an ENRG MD simulation. The archive also

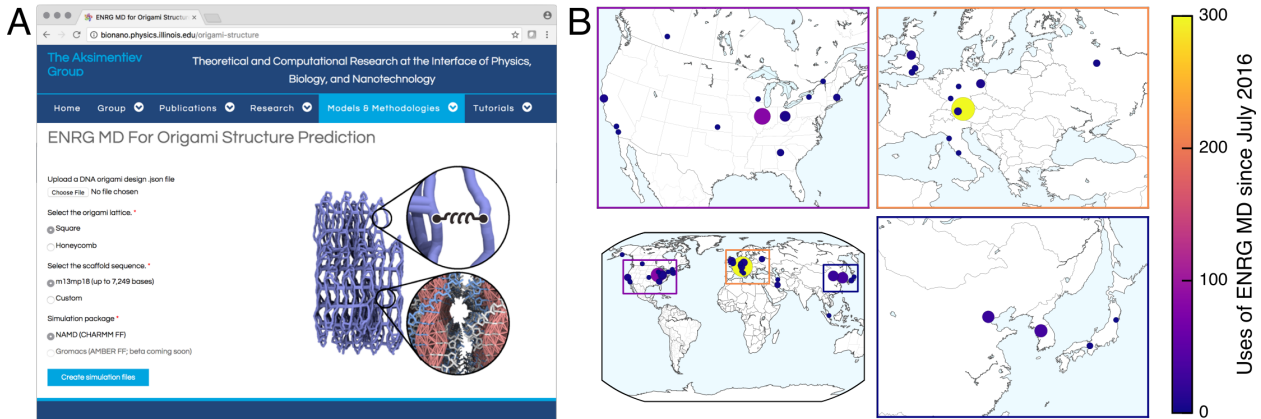


Figure 3: **The ENRG MD web service.** (A) The web page at bionano.physics.illinois.edu/origami-structure includes simple webforms that allow a user to upload a DNA origami design file and download an archive suitable for simulation. (B) Map showing all uses of the ENRG MD web service. When the service is used, the user’s IP address is converted to a latitude and longitude that is recorded in a database. Each circle on the map corresponds to a unique latitude and longitude. The area of the circle and its color indicate the number of uses from the given location. Please note that some dots are located very close and overlap on the map.

contains detailed instructions to make it easy for any user to perform the simulations, even if they have no prior computational modeling experience. Since July, the service has been used over 600 times, averaging about 3 uses per day. Our users are located at the top DNA nanotechnology centers, Fig. 3 B.

Although the ENRG MD protocol worked very well for square-lattice origami designs, the protocol caused strong right-handed twisting of honeycomb-lattice objects that was inconsistent with both experimentally obtained transmission electron microscopy images and atomistic MD simulations [5, 22]. As a result, the ENRG MD service supported only square-lattice origami designs during its first months.

We have since performed a series of ENRG MD simulations to optimize the spring constants and rest lengths in the elastic network to remove the twist in honeycomb-lattice objects. The optimization procedure was performed as follows. First, we performed an ENRG MD simulation of a reference structure until the object fully relaxed. Each spring constant was then updated by a small value multiplied by the strain of the spring. In this way, highly stretched springs in the elastic network were relaxed, resulting in a structure closer to the unstretched idealized object. As a result of this work, we extended the ENRG MD webserver to support honeycomb-lattice designs.

List of publications and presentations associated with this work

- K. Göpfrich, C. Li, M. Ricci, S. P. Bhamidimarri, J. Yoo, B. Gyenes, A. Ohmann, M. Winterhalter, A. Aksimentiev, and U. F. Keyser. Large-Conductance Transmembrane Porin Made from DNA Origami *ACS Nano*, 10:8207-8214, 2016.
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- C. Maffeo, J. Yoo, and A. Aksimentiev. *De novo* prediction of DNA origami structures through atomistic molecular dynamics simulation. *Nucleic Acids Research*, 44:3013-3019, 2016.
- S. Slone, J. Yoo, C.-Y. Li, and A. Aksimentiev. Molecular mechanics of DNA bricks: *In situ* structure, mechanical properties and ionic conductivity. *New Journal of Physics*, 18:05512, 2016.
- M. Belkin and A. Aksimentiev. Molecular Dynamics Simulation of DNA Capture and Transport in Heated Nanopores. *ACS Applied Materials & Interfaces*, 8:12559-13180 (2016). Cover.
- K. Decker, M. Page, A. Boyd, I. MacAllister, M. Ginsberg, and A. Aksimentiev. Selective Permeability of Truncated Aquaporin 1 in Silico. *ACS Biomaterials Science & Engineering*, Published online: 10.1021/acsbiomaterials.6b00583, 2017.

- S. Pud, S. Chao, M. Belkin, D. Verschueren, T. Huijben, C. van Engelenburg, C. Dekker and A. Aksimentiev. Mechanical Trapping of DNA in a Double-Nanopore System. *Nano Letters*, 16:8021-8028, 2016.
- (Invited talk) A. Aksimentiev. “The Structure and Ionic Conductance of DNA Membrane Channels.” 2nd Functional DNA Nanotechnology Workshop. Rome, Italy. June 2016.
- (Invited talk) A. Aksimentiev. “Making Sence of DNA Channels.” The 22nd International Conference on DNA Computing and Molecular Programming. Munich, Germany. September 2016.
- (Invited talk) J. Yoo. “A novel epigenetic mechanism of DNA compaction and atomistic simulations of DNA origami.” Michigan Technological University, Department of Physics, 2016.
- (Invited talk) J. Yoo. “A novel epigenetic mechanism of DNA compaction and atomistic simulations of DNA origami.” Korea Institute for Advanced Study (KIAS), 2016.
- (Invited talk) J. Yoo. “A novel epigenetic mechanism of DNA compaction and atomistic simulations of DNA origami.” Ulsan National Institute of Science and Technology (UNIST), 2016.
- (Invited talk) J. Yoo. “The Physics of Chromosomes: From DNA Loops to Nucleus-Scale Structures.” University of Tennessee, Knoxville, Department of Chemistry, 2016.
- (Invited talk) J. Yoo. “The Physics of Chromosomes: From DNA Loops to Nucleus-Scale Structures.” North Carolina State University, Department of Physics, 2016.
- (Invited talk) J. Yoo. “The Physics of Chromosomes: From DNA Loops to Nucleus-Scale Structures.” Arizona State University, Department of Physics, 2016.
- (Invited talk) J. Yoo. “Molecular Driving Forces in the Self-assembly of Chromosomes and DNA Nano-machines.” Institute for Basic Science, 2016.
- (Invited talk) J. Yoo. “Molecular Driving Forces in the Self-assembly of Chromosomes and DNA Nano-machines.” Sungkyunkwan University, Department of Chemistry, 2016.
- (Poster) J. Yoo, C.-Y. Li, and A. Aksimentiev. “Membrane-Spanning DNA Ion Channels: Conductance Mechanism, Electro-Osmotic Transport and Mechanical Gating.” Biophysical Society Annual Meeting. Los Angeles, California. February 2016.
- (Poster) J. Yoo and A. Aksimentiev. Improved Parameterization of Amine-Carboxyate, Amine-Phosphate, and Aliphatic Carbon-Carbon Interactions for Molecular Dynamics Simulations using the Charmm and Amber Force Fields. Biophysical Society Annual Meeting. Los Angeles, California. February 2016.

- (Poster) C. Maffeo, J. Yoo, and A. Aksimentiev. *De novo* Reconstruction of DNA origami structures through atomistic molecular dynamics simulation. FNANO2016. Snowbird, Utah. April 2016.

Plan for the next year

Next year, we plan to focus our efforts on completing our characterization of DNA nanochannels by extending our work to a recently published design [36] and develop a new kind of DNA nanostructures that can undergo rotational motion subject to an external electrical field.

Using the latest version of the NAMD package [37, 38], we have found that a 1 ns (NS) simulation of a 1-million-atom (MA) system requires 80 node hours (NH). We will use the 80 NH/MANS factor to estimate the requested allocation for each subproject. As detailed below, projects P1 and P2 will require 80,000 and 160,000 node hours, respectively, resulting in the **total requested allocation of 240,000 node hours**. P1 will be performed during Q1 and Q2, and P2 will be performed during Q3 and Q4. We estimate our Blue Waters Professor allocation usage schedule throughout the year to be (Q1: 15%, Q2: 15%, Q3: 35%, Q4: 35%).

P1. T-shaped biomimetic DNA pore.

Recently, a DNA channel of novel structures— a T-shaped DNA channel— was experimentally characterized [36]. Building on our successful studies of DNA channels [25, 26, 39] and complementing our unpublished results, we will apply the MD method to this novel DNA channel system to complete characterization of all possible membrane channel architectures. The dimensions of the entire T-channel are 51 nm \times 46 nm \times 27 nm. Since we are predominantly interested in the structure of the DNA-lipid interface and the ionic conductance, we

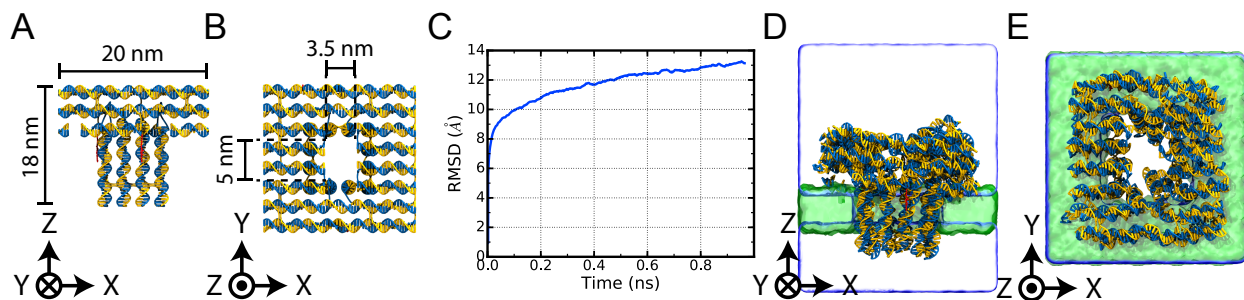


Figure 4: **The all-atom model of the T-pore.** (A & B) The side-view (A) and top-view (B) of the idealized structure of the T-pore. The T-pore is colored in blue and yellow and cholesterol tags are colored in red. The dimension of the idealized structure is 20 nm \times 20 nm \times 18 nm. The cross-section of the pore is 5 nm \times 3.5 nm. (C) The root-mean-square deviation (RMSD) trace during the ENRG MD. (D & E) The side-view (D) and top-view (E) of the relaxed structure of the T-pore after ENRG MD. The lipid membrane is shown as a green semi-transparent surface. The system contains magnesium ions in an amount sufficient to neutralize the electrical charge of the T-pore and 1 M KCl solution (not shown).

will explicitly simulate only the pore region (T-pore) of the T-channel. We have already built an all-atom model of the T-pore, Fig. 4 A, B and applied our ENRG MD method to relax the structure, Fig. 4 C. The final solvated system will measure $26\text{ nm} \times 26\text{ nm} \times 29\text{ nm}$ and contain ~ 1.96 million atoms. We will follow our previously established simulation protocol and perform constrained 50 ns equilibration of the system to observe rearrangement of lipid molecules, followed by 15 ns of gradual relaxation of the elastic network restraints and the subsequent 50 ns free equilibration. For ionic current simulations, we estimate 100 ns will be needed per voltage bias to obtain sufficient statistics of ion permeation events.

In total, this project will require **(1.96 M atom systems) \times (constrained equilibration 50 ns + gradual relaxation of an elastic network of restraints 15 ns + free equilibration 50 ns + (100 ns \times 4 bias)) = 1000 MANS \times (80 node hours/MANS) = 80,000 Node hours** on Blue Waters.

P2. DNA origami nanorotors for induced-flow-modulated rotation.

Biological systems commonly utilize complex macromolecular machines for transport and catalysis, such as the bacterial flagellar motor [40] and the F_o subunit in ATP synthase [41]. Both machines are examples of nanorotors, which are usually powered by a concentration or a pressure gradient. Similar mechanisms can, in principle, drive the rotation of artificial nanorotors in a controllable manner. DNA origami is a suitable method for creating such structures as it offers rapid and simple prototyping of nanostructures that exist in biological conditions. Our experimental collaborators have already realized structures that are able to rotate by Brownian motion [42], but they have not yet been able to control the rotation.

Working in collaboration with the experimental labs of C. Dekker (TU Delft) and H. Dietz (TU Munich), we aim to model and construct DNA nanostructures that mimic macroscale turbines, Fig. 5 A and B. In a preliminary study, we found that flow induced by either an applied electric field or a hydrostatic pressure gradient caused the rotation of a nanostructure, Fig. 5 C. However, the nanorotor experienced large deformations depending heavily on the chosen driving mechanism. Our simulations clearly show that an induced flow can produce rotation and control the angular velocity.

In our preliminary study, we used DNA origami designed with extra crossovers to ensure the stability of the structure in our high-flow simulations. However, this design cannot be realized in the experiment because the added crossovers drastically reduce the yield of self-assembled structures. We also simulated just the rotating portion of the nanorotor, using harmonic restraints to mimic a fixed portion of the rotor to save computational resources. To facilitate direct comparison with experiment, we must use a more typical origami design of crossovers and simulate both the fixed and rotating parts of the rotor. We have developed a new nanorotor design that integrates these necessary features and contains ~ 1.34 M atoms, Fig. 5D–F. Here we propose to use all-atom MD simulations to simulate rotation under experimentally achievable conditions (1 M KCl solution, a transmembrane bias of 0.1 and 0.5 V or a hydrostatic pressure gradient of 0.1 and 0.5 bar/nm), iteratively optimizing the designs to enhance rotational efficiency and control.

Carrying out project P2 will require **(1.34 M atom system) \times (3 iterations: initial test, addressing issues, refinement of properties) \times (5 conditions: 1 equilibration run + 2 applied biases + 2 pressure gradients) \times (100 ns/condition) = 2000**

$\text{MANS} \times (80 \text{ node hours/MANS}) = 160,000 \text{ Node hours}$ on Blue Waters.

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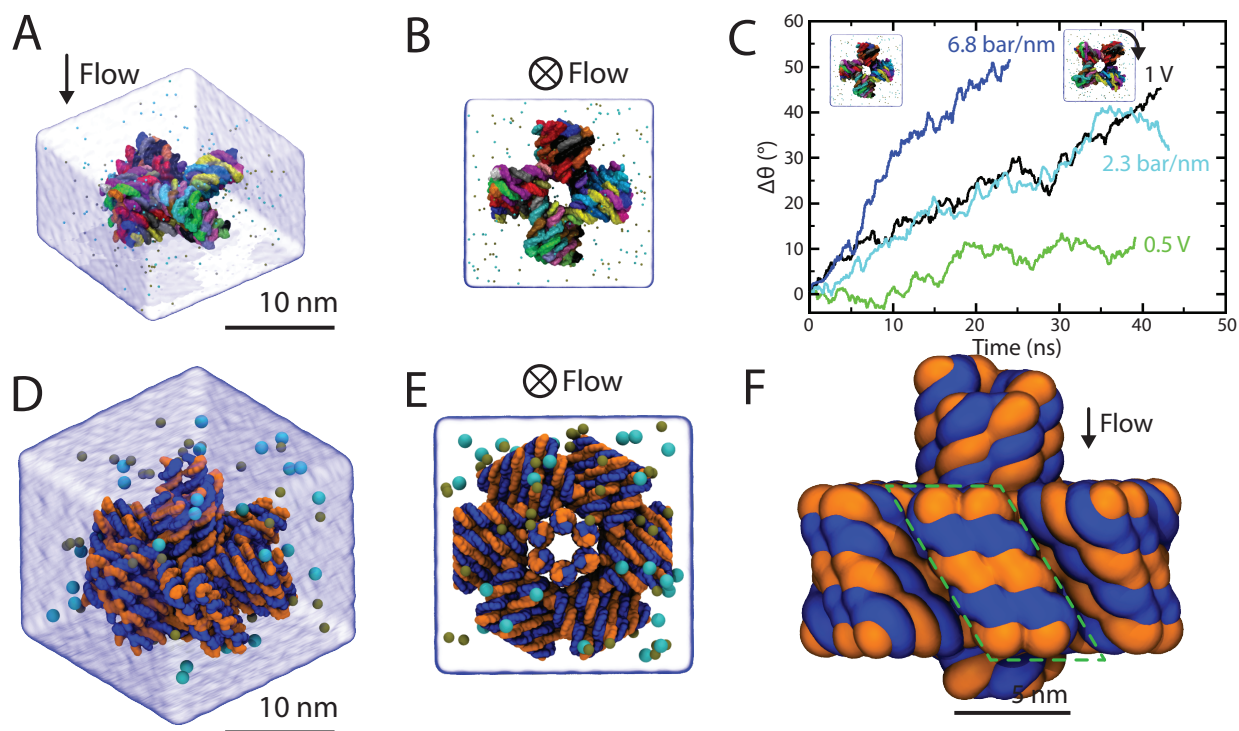


Figure 5: DNA propellers with controlled rotational motion. (A & B) Square-lattice propeller composed of four fins built from DNA helices viewed at an angle (A) and in the direction of flow (B); the systems are submerged in 1 M KCl solution. DNA strands are colored individually. K^+ and Cl^- ions are shown as brown and green spheres. Water is represented as a blue semitransparent surface. (C) The angular displacement of the nanorotor in response to the applied electric bias (V) or a hydrostatic pressure gradient (bar/nm). The angular displacement is defined as the rotation that brings the propellers in their initial configuration into alignment with the configuration at a later time. (D & E) Hex-lattice propeller composed of six fins using DNA origami method and integrating a central axis. Scaffold and staple strands are shown as blue and orange molecular surfaces, respectively. The ion concentration is the same as in panels A & B. (F) Ideal Hex-lattice propeller. DNA is represented as in panels D & E but with the surface smoothed to show the fin shape. The fin is highlighted by the dashed green outline.

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