Molecular Simulations of DNA Nanosystems

Reports for the Blue Waters allocation 2021

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Accomplishments

We used our 2020 allocation on Blue Waters to perform molecular dynamics simulations of biomimetic nanoscale systems and to explore their biophysical applications. Previously, we have shown that membrane-spanning DNA nanostructures are capable of scrambling lipids of bilayer membranes 10,000 faster than any known biological enzyme. In order to optimize the design of DNA nanostructures further, this year we studied the interactions between DNA, its hydrophobic modifications and the lipids. By combining our all-atom MD simulations with experiments performed by the Keyser lab at Cambridge University, UK we successfully demonstrated control over the rate of interleaflet lipid transfer induced by a modified DNA enzyme. A manuscript describing this work was published in *Nano Letters* (2020). In our ongoing simulations studies, we are examining the effect of divalent ions on lipid-DNA interactions and how those interactions affect the rate of lipid scrambling.

In another umbrella of projects, we are collaborating with several leading experimental labs across the world to develop new types of synthetic water and ion channels for potential applications in desalination, molecular sensing and medicine. In the report submitted last year, we presented a new class of artificial water channels, peptide-appended hybrid[4] arenes, PAH[4], which at that time was under review in Nature Nanotechnology. Prompted by the comments from the reviewers, we analyzed the hydrogen bond pattern in the simulations trajectories performed on Blue Waters and found the transmembrane transport of water through clusters of PAH[4] channels to be similar to that in a biological water channel aquaporin. Our analysis also revealed the molecular origin of the high water-to-ion permselectivity in cluster-forming PAH[4] channels, pushing forward a new design paradigm. The results of our work were published in *Nature Nanotechnology* (2020).

In parallel to the above efforts, we collaborated with the Zeng group from the A*STAR University of Singapore to build and characterize a synthetic iodide channel. Our all-atom simulations uncovered the molecular mechanisms responsible for the overall anion selectivity of the synthetic channels and their specific preference for iodide ions. A manuscript describing our findings was published in *Angewandte Chemie* (2020). Since then, we have extended our simulation work to investigate water transport through variants of the synthetic membrane channels synthetized by the Zeng group. That work resulted in another manuscript that is presently being revised for publication in *Nature Nanotechnology*.

Key challenges

Previous experimental and simulation studies, including our own work, have shown that self-assembled DNA nanostructures can form stable channels in lipid bilayer membranes and mimic the function of naturally occurring membrane proteins. However, to fully control the function of a membrane spanning DNA channel, we need to know how exactly such a channel inserts into a lipid membrane and how various chemical modifications at the channel surface affect the structure of such an assembly. In collaboration with several leading experimental labs (Ulrich Keyser, Cambridge University and Stefan Howorka, University College London), our group has been investigating the interactions between modified DNA and lipid membranes. Next year, we will focus our investigations on determining how various ions, in particular divalent ions, modulate the affinity of DNA to lipid membranes. In particular, we aim to determine how the phase state of a membrane (gel or fluid) and the presence of defects, such as at the interface of two lipid phases, affects DNA insertion. We will also examine what influence different types of hydrophobic

modifications have on the DNA structure inserted in a lipid membrane. The overarching goal of these simulations is to computationally elucidate the mechanism of DNA nanopore insertion, which is essential to practical applications of such nanostructures in molecular sensing and medicine.

Plan for the next year

(P1) Self-assembled DNA nanopores decorated with lipid anchors facilitate the transmembrane permeation of water and ions and lipid scrambling by forming water-filled channels through lipid bilayer membranes. Our recent studies have shown that the rate of lipid scrambling can be tailored by modifying the chemical design of the DNA. Lipid anchors, such as cholesterol, are usually conjugated to the membrane-spanning DNA nanostructure by extending the backbone of the DNA, which creates nicks in the DNA duplex. Our previous simulations have shown that such nicks can play an important role in the structure of the DNA channels and, hence, can affect the rate of lipid scrambling and water/ion transport. In collaboration with the Keyser lab (Cambridge University, UK), we will systematically study the effect of nicks on the structure and transport of DNA channels. For this purpose, we will create several all-atom models of the DNA scramblase nanopores differing by the pattern of nicks and the attachment sites for the cholesterol anchors. The designs will be simulated in a lipid bilayer membrane and electrolyte solution for 1μs each, which will be sufficient to quantitatively characterize the rate of lipid scrambling and structural changes in the DNA constructs produced by the membrane embedment.

(P2) The binding of the DNA to the lipid bilayer membrane is the crucial first step preceding DNA insertion into a membrane. We will computationally assess the binding affinity of DNA to a lipid bilayer membrane in different physical phases (gel *vs* liquid), lipid headgroup compositions and concentration of electrolyte solution. Each system will contain a two-turn DNA duplex, a patch of a lipid bilayer, water and ions, about 150,000 atoms in total. The binding affinity will be characterized by calculating the potential of mean force between the DNA and the membrane using 40 sampling windows, each simulation spanning approximately 100 ns. A larger system will be constructed to feature an interface between two membrane phases. The simulations are expected to identify specific molecular interactions that favor DNA binding to the lipid membrane and the role of magnesium and calcium ions in modulating the binding affinity.

Using the latest version of the NAMD package, 1 ns (NS) simulation of a one-million atom (MA) system requires 80 node hours (NH) on Blue Waters. We will use the 80 NH/MANS factor to estimate the requested allocation for each subproject. Carrying out projects P1 and P2 will require approximately 128,000 and 112,000 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 Q2, Q3 and Q4. We estimate our Blue Waters Professor allocation usage schedule throughout the year to be Q1: 15%, Q2: 35%, Q3: 35%, Q4: 15%.

Data migration

We have recently purchased a storage system congaing 197 terabytes (TBs) of free space. Overall, our lab has five main data storage servers, each containing ~ 175, 117, 115, 98 and 197 terabytes (TBs) of space. We are also in the process of purchasing new data storage systems and local workstations. Hence, we will have sufficient storage space to copy and back up all the data generated on the Blue Waters supercomputer.