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OUTPERFORMING NATURE: SYNTHETIC ENZYME BUILT FROM DNA FLIPS LIPIDS OF BIOLOGICAL MEMBRANES AT RECORD RATES

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EXECUTIVE SUMMARY

Mimicking enzyme function and increasing the performance of naturally evolved proteins is one of the most challenging and intriguing aims of nanoscience [1,2]. Here, we employ DNA nanotechnology to design a synthetic enzyme that substantially outperforms its biological archetypes. Consisting of only eight strands, our DNA nanostructure spontaneously inserts into biological membranes by forming a toroidal pore that connects the membrane's inner and outer leaflets. The membrane insertion catalyzes spontaneous transport of lipid molecules between the bilayer leaflets, rapidly equilibrating the lipid composition. Through a combination of microscopic simulations and fluorescence measurements we found the lipid transport rate catalyzed by the DNA nanostructure to exceed 10^7 molecules per second—three orders of magnitude higher than the rate of lipid transport catalyzed by biological enzymes. Furthermore, we showed that our DNA-based enzyme can control the composition of human cell membranes, which opens new avenues for applications of membrane-interacting DNA systems in medicine.

RESEARCH CHALLENGE

The development of customizable synthetic enzymes will have significant impacts on the fields of biology and medicine but is challenging because the function of an enzyme depends sensitively on its atomic-scale structure and dynamics. This sensitivity to the atomic scale makes all-atom molecular dynamics (MD) the computational method of choice for prototyping designer enzymes. In this work, we simulated a synthetic enzyme made from DNA and demonstrated that it substantially outperforms its biological equivalents.

METHODS & CODES

We used the latest version of NAMD [3,4] to perform explicit-solvent all-atom MD simulations of a synthetic scramblase—an enzyme that transports lipids from one leaflet of a bilayer to the other—that was made from eight DNA strands and was embedded in a lipid bilayer membrane through two covalently attached cholesterol anchors. Microsecond-timescale simulations allowed for the direct observation of lipid-scrambling activity. Our simulations were complemented by the experimental work of our collaborators in the Keyser Lab in Cambridge, UK.

RESULTS & IMPACT

Through all-atom MD simulations, we have shown that a membrane-spanning single DNA helix decorated with chemical tags forms a toroidal pore that provides a pathway for lipid molecules to cross from one leaflet of the bilayer to the other leaflet. We found a very small (~2 k_BT) barrier to lipid crossing at the toroidal pore, indicating that lipids could move at near diffusion-limited rates. The average lipid transfer rate calculated from simulation exceeded 10^7 molecules per second and was found to be in good agreement with experiment. The simulations provided a microscopic description of the mechanism of lipid transport, while experiments demonstrated that the enzyme was also active in cancer cells. Results of this study have been published in *Nature Communications*.

This work exemplifies the potential of DNA nanotechnology for creating synthetic enzymes with biological functionality. The specific outcomes of this work may have direct biomedical applications. As rapid scrambling of a cell membrane's composition can activate programmed cell death, DNA nanostructures decorated with cell surface recognition factors can be developed to insert and scramble the membranes of only the target cells, opening new avenues for development of cancer therapeutics.

WHY BLUE WATERS

Explicit-solvent all-atom MD simulation is the only computational method that can treat objects built with DNA nanotechnology that are enhanced by nonstandard functional groups. It is the only method that can accurately characterize their structural fluctuations and transport properties [5]. Because of the size of the DNA structures, such MD simulations are computationally demanding. The large number of GPU-accelerated nodes and fast Gemini interconnect of Blue Waters make it one of the best publicly-available systems for performing DNA nanotechnology simulations. Over the past several years, our group has 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 [6–8].

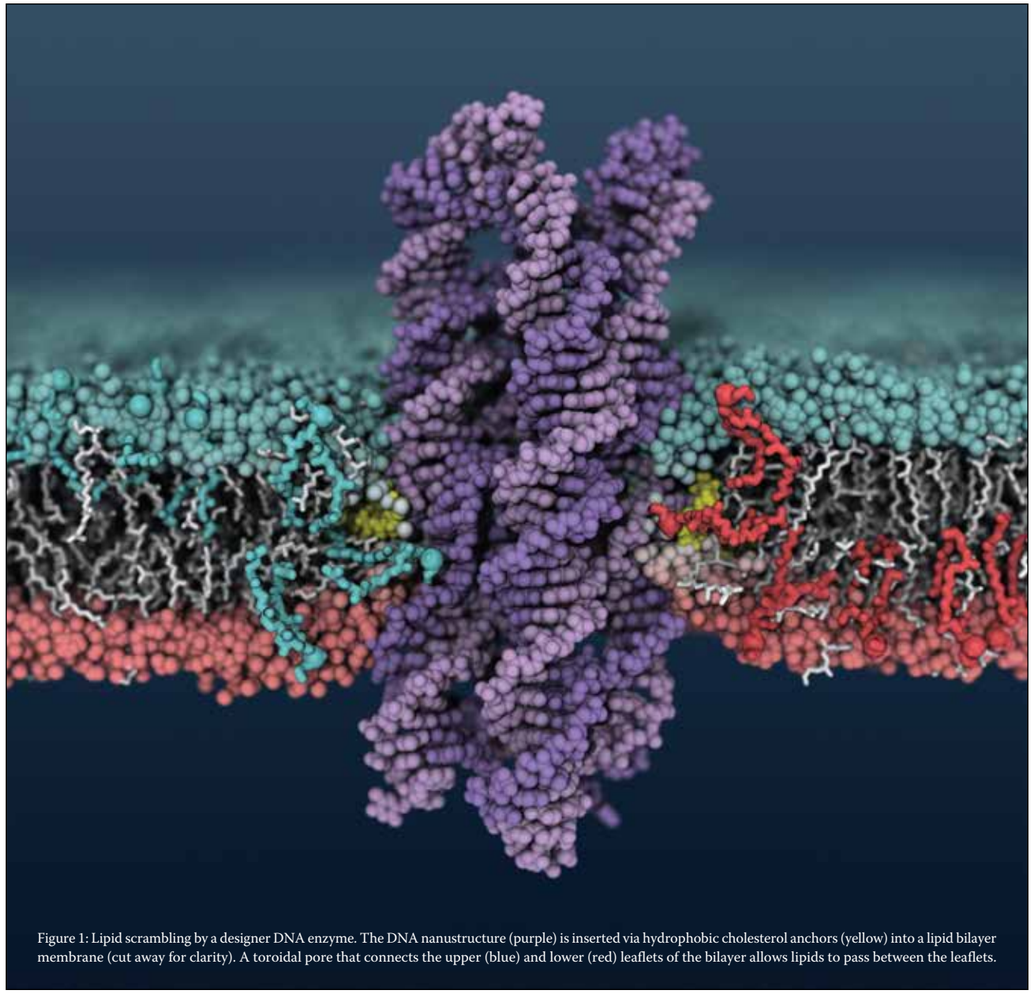

Figure 1: Lipid scrambling by a designer DNA enzyme. The DNA nanustructure (purple) is inserted via hydrophobic cholesterol anchors (yellow) into a lipid bilayer membrane (cut away for clarity). A toroidal pore that connects the upper (blue) and lower (red) leaflets of the bilayer allows lipids to pass between the leaflets.

PUBLICATIONS & DATA SETS

[1] Ohmann, A., et al., Outperforming nature: synthetic enzyme built from DNA flips lipids of biological membranes at record rates. *Nature Communications*, 9 (2018), DOI:10.1038/s41467-018-04821-5.