



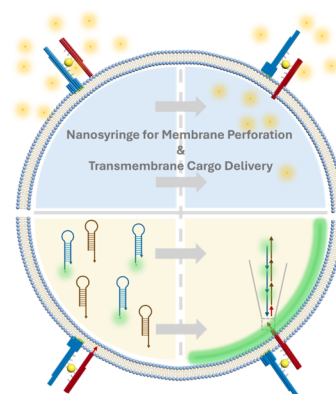
A DNA Origami Syringe for Programmable Membrane Translocation

Yifeng Shi

Department of Electrical Engineering and Computer Sciences, University of California, Berkeley, CA 94720, USA; yifengshi@berkeley.edu

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Abstract: Transmembrane cargo delivery plays an important role in biological processes and therapeutic applications, ranging from viral infection to engineered cell-penetrating systems. A recent report in *Nature Nanotechnology* demonstrates a novel approach to membrane perforation and cargo delivery through the controlled engineering of a DNA origami nanosyringe. The nanosyringe can physically penetrate the membrane and directly translocate cargo without relying on endocytosis or subsequent endosomal escape. At the same time, both needle insertion and retraction are precisely programmed through DNA strand-displacement reactions, enabling nanometer-scale and reversible mechanical motion. This programmable molecular machine provides a versatile platform for biological engineering, offering direct and spatially-controlled cargo translocation across lipid membranes.



Keywords: transmembrane delivery; nanosyringe; DNA origami; strand displacement; membrane perforation

1. Introduction

The cell membrane, as a selectively permeable interface, provides a natural barrier to separate the interior of the cell from the external environment. Penetrating this barrier enables transmembrane delivery for multiple therapeutic and biotechnological applications. Traditionally, endocytosis is one of the most common pathways for delivering large macromolecules, particles, and other types of extracellular cargos into cells. The cargo, however, often faces the challenge of escaping from the endosome after cellular internalization [1]. Nature has evolved more sophisticated systems, such as biological contractile injection systems (CIS), that use mechanically driven machinery to penetrate target membranes and deliver cargo without relying on endosomal uptake. However, reprogramming these sophisticated mechanical machines into synthetic devices that can perform similar functions at the nanoscale remains a grand challenge.

To develop a CIS-inspired nanodevice capable of membrane translocation, at least three steps need to be achieved with high precision: (i) membrane anchoring of the device, (ii) needle penetration across the membrane, and (iii) cargo translocation into the interior of the cell. Reported in *Nature Nanotechnology*, Liu and co-workers took advantage of the programmability of structural DNA nanotechnology to synthesize a DNA origami nanosyringe that can reproduce key functions of a molecular injection system [2]. Using giant unilamellar vesicles (GUVs) as biomimetic compartments for synthetic cells, the authors demonstrated successful membrane perforation and cargo translocation through mechanically actuated penetration. Furthermore, they showed that the physical penetration was reversible and could induce membrane resealing after needle retraction. The capability to directly transport cargo across the membrane allowed them to initiate several biological processes within synthetic cells, including membrane-localized hybridization chain reaction (HCR), RNA transcription, and catalytic RNA cleavage.

2. Result & Discussion

The basic design of the nanosyringe is shown in Figure 1. The syringe is composed of two 14-helix DNA origami bundles (blue and red) that are connected through a single scaffold. An additional multi-helix segment



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functionalized with cholesterol was attached to the blue bundle to anchor the syringe to the lipid bilayer. At the same time, a gold nanoparticle was positioned between the two helix bundles, functioning as a mechanical sliding component that allows the red helix bundle (the “needle”) to slide downward upon a DNA-strand-displacement reaction triggered by fuel strands. Such a “sliding” design has also been reported in Liu’s previous publication [3]. Upon membrane perforation, small molecules such as ions and fluorophores could diffuse across the membrane through the hollow channels inside the needle. In contrast, larger molecules such as DNA and RNA could be selectively conjugated to the tip of the needle and actively translocated through direct membrane penetration.

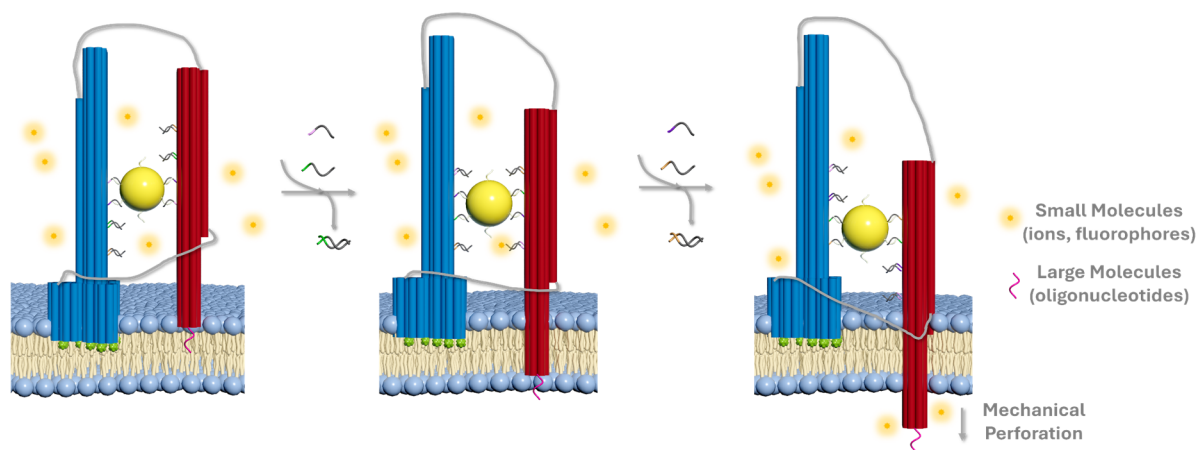


Figure 1. Schematic illustration of the DNA origami nanosyringe. The needle (red helix bundle) can slide up and down upon the addition of DNA strands with specific sequences. Small molecules could diffuse across the membrane through the hollow channels within the needle, while large cargos could be conjugated onto the tip of the syringe and get across the membrane through mechanical perforation.

Through single-channel current recordings, the authors confirmed successful membrane perforation by the nanosyringe. The hollow channels within the needle provide pathways for ions to diffuse across the membrane, generating detectable ionic currents. Similarly, fluorescence microscopy was used to monitor the diffusion of the fluorescent dye sulforhodamine B from the exterior of the membrane into the interior of the GUV. It is worth pointing out that the honeycomb design, which leaves part of the interior of the needle hollow, was essential for providing these diffusion pathways. Negative-control experiments showed that when the needle was switched from a honeycomb to a hexagonal lattice, leaving the needle tip more densely packed, the membrane became nearly impermeable to small molecules. These results indicate that the transportation of small molecules primarily occurred through the internal channels of the needle rather than through nonspecific membrane disruption around the device. As such, the nanosyringe also exhibited a degree of size selectivity, as demonstrated by the observation that the perforated membrane became nearly impermeable when the diffusing molecule was changed from sulforhodamine B (~0.7 nm) to 3-kDa dextran-Cy3 (~3 nm).

Another unique feature of the nanosyringe is its operational reversibility. Unlike some previously reported DNA transmembrane structures in which hydrophobic groups were directly introduced into the channel to promote membrane insertion [4], the needle of the nanosyringe was free of cholesterol modification and could therefore be mechanically retracted by adding fuel strands in reverse order. Similar current recordings and fluorescence recovery after photobleaching (FRAP) experiments provided evidence that the membrane could reseal after needle retraction. This reversible operation is particularly important because it suggests that the nanosyringe can transiently establish a membrane-spanning pathway without requiring the membrane pore to remain permanently open.

Beyond diffusion driven primarily by concentration gradients, DNA origami also provides the nanosyringe with the capability to directly translocate a selected cargo into the interior of the synthetic cell. Due to its high programmability, different oligonucleotides can be attached to the tip of the needle to initiate specific biological functions. In this work, the nanosyringe was used to initiate a membrane-localized HCR, a DNA-based signal amplification method that is triggered by the presence of an initiator strand. The nanosyringe not only exposed the initiator strand to the interior of the GUV, but also spatially confined the autocatalytic HCR reaction to the vicinity of the membrane. As a result, the original uniformly-distributed fluorescent signals from the free-floating hairpins became concentrated near the inner periphery of the GUV, forming a ring-shaped fluorescent cortex that could be readily visualized by fluorescence microscopy. The versatility of DNA origami also allowed the authors to apply

the same platform to other biological functions, including RNA transcription and catalytic RNA cleavage, through modifications of the GUV environment and the oligonucleotides conjugated to the needle tip.

3. Conclusion & Outlook

The nanosyringe developed in this paper differs fundamentally from many previously reported membrane-translocation devices because it tackles one of the major challenges in intracellular cargo delivery: direct physical translocation across the membrane. By bypassing endocytic uptake, the system avoids the subsequent challenge of endosomal escape that accompanies many cellular uptake approaches. At the same time, further engineering will be needed before this platform can be translated from proof-of-concept model membranes to more complex biological environments. First, as the authors also noted, the penetration efficiency decreases with increasing membrane mechanical resistance. The lipid membranes used in the current study are simplified model systems and do not fully reproduce the mechanical complexity of biological cell membranes, which can vary substantially in lipid composition, cholesterol content, membrane tension, and interactions with the cytoskeleton. To address this challenge, one possible strategy could be to selectively increase the mechanical robustness of the needle tip through approaches such as silicification or metallization [5]. Such modifications could potentially improve penetration while retaining the programmability of the DNA scaffold for cargo conjugation, although their effects on membrane interaction and mechanical actuation would need to be carefully evaluated. At the same time, the stability of DNA origami in physiological fluids remains a longstanding challenge that has motivated numerous stabilization strategies. Surface coatings such as oligolysine may improve the structural stability of DNA origami under physiological conditions [6], although additional strategies would likely be needed to control protein adsorption and the formation of a protein corona.

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